STEREOSELECTIVE TRANSFORMATIONS OF INTRAMOLECULAR CYCLOADDITION PRODUCTS

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ABSTRACT

In this work, the intramolecular cycloaddition of furan dienes was investigated. At equilibrium, amide-tethered substrates form acyclic precursor : cycloadduct mixtures. Higher portion of cycloadduct proved to be favoured by bulky nitrogen-groups, polar solvents, higher temperature and the presence of some Lewis acids. It was demonstrated that the equilibrium can be displaced by coupling a reversible Diels-Alder cycloaddition to an irreversible and chemoselective reaction, such as Pd-catalysed hydrogenation or *m*CPBA epoxidation, resulting in the complete transformation of the mixture starting material to the functionalised cycloadduct. A range of asymmetric transformations were also investigated to resolve the racemic mixture derived from the Diels-Alder reaction. The Sharpless dihydroxylation showed a high level of chemoselectivity but it was not able to discriminate between the cycloadduct enantiomers. The Jacobsen epoxidation was not chemoselective but, in absence of Diels-Alder starting material, produced cycloadduct epoxides in modest enantioselectivity via kinetic resolution and dynamic kinetic resolution. Non-symmetrical transformation of the olefin, by asymmetric hydroboration-oxidation, provided regioisomeric alcohols in good enantiomeric excess by regiodivergent resolution.

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Word count: 39699

ABBREVIATIONS

$(DHQ)_2PHAL$	Hydroquinine 1,4-phthalazinediyl diether
$(DHQD)_2PHAL$	Hydroquinidine 1,4-phthalazinediyl diether
4-PPNO	4-Phenylpyridine N-oxide
Ac	acetyl
AD	asymmetric dihydroxylation
BINAP	(2,2′-bis(diphenylphosphino)-1,1′-binaphthyl)
Bn	benzyl
***n*-BuLi**	butyllithium
COSY	Correlated spectroscopy
DA	Diels-Alder
DABCO	1,4-diazabicyclo[2.2.2]octane
DCC	*N*,*N*'-Dicyclohexylcarbodiimide
DCE	1,2-Dichloroethane
DCM	dichloromethane
DET	Dithioerythritol
DKR	dynamic kinetic resolution
DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*'-dimethylformamide
DMP	Dess–Martin periodinane
DMSO	dimethyl sulfoxide
dosp	*N*-(*p*-dodecylphenylsulfonyl)prolinato
dr	diastereomeric ratio
dtbpf	1,1′-Bis(di-*tert*-butylphosphino)ferrocene
***i*Pr-DUPHOS**	1,2-Bis(2,5-diisopropylphospholan-1-yl)benzene
EDC, EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
EDG	Electron donating group
ee	enantiomeric excess
er	enantiomeric ratio
Et	ethyl
EWG	electron withdrawing group

FMO	frontier molecular orbital
FTIR	Fourier transform infrared spectroscopy
HBpin	4,4,5,5-Tetramethyl-1,3,2-dioxaborolane
HMF	5-(hydroxymethyl)furfural
HOMO	highest occupied molecular orbital
HPLC	High-performance liquid chromatography
IMDA	intramolecular Diels-Alder reaction
IMDAF	intramolecular Diels-Alder reaction of furan dienes
IPC	isopinocampheyl
IR	infrared
KR	Kinetic resolution
LA	Lewis acid
LUMO	lowest unoccupied molecular orbital
***m*CPBA**	*meta*-Chloroperoxybenzoic acid
Me	Methyl
MOM	Methoxymethyl
Ms, mesyl	methanesulfonyl
NMO	*N*-Methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
NOE	Nuclear Overhauser effect
NOESY	Nuclear Overhauser Spectroscopy
Ph	phenyl
PKR	Parallel kinetic resolution
rDA	Retro-Diels-Alder
Rf	retention factor
rt	room temperature
SAD	Sharpless asymmetric dihydroxylation
SM	starting material
taniaphos	1-[(Dimethylamino)[2-(diphenylphosphino)phenyl]methyl]-2-(diphenylphosphino)ferrocene
TBAF	Tetrabutylammonium fluoride
TBDPS	*tert*-Butyldiphenylsilyl

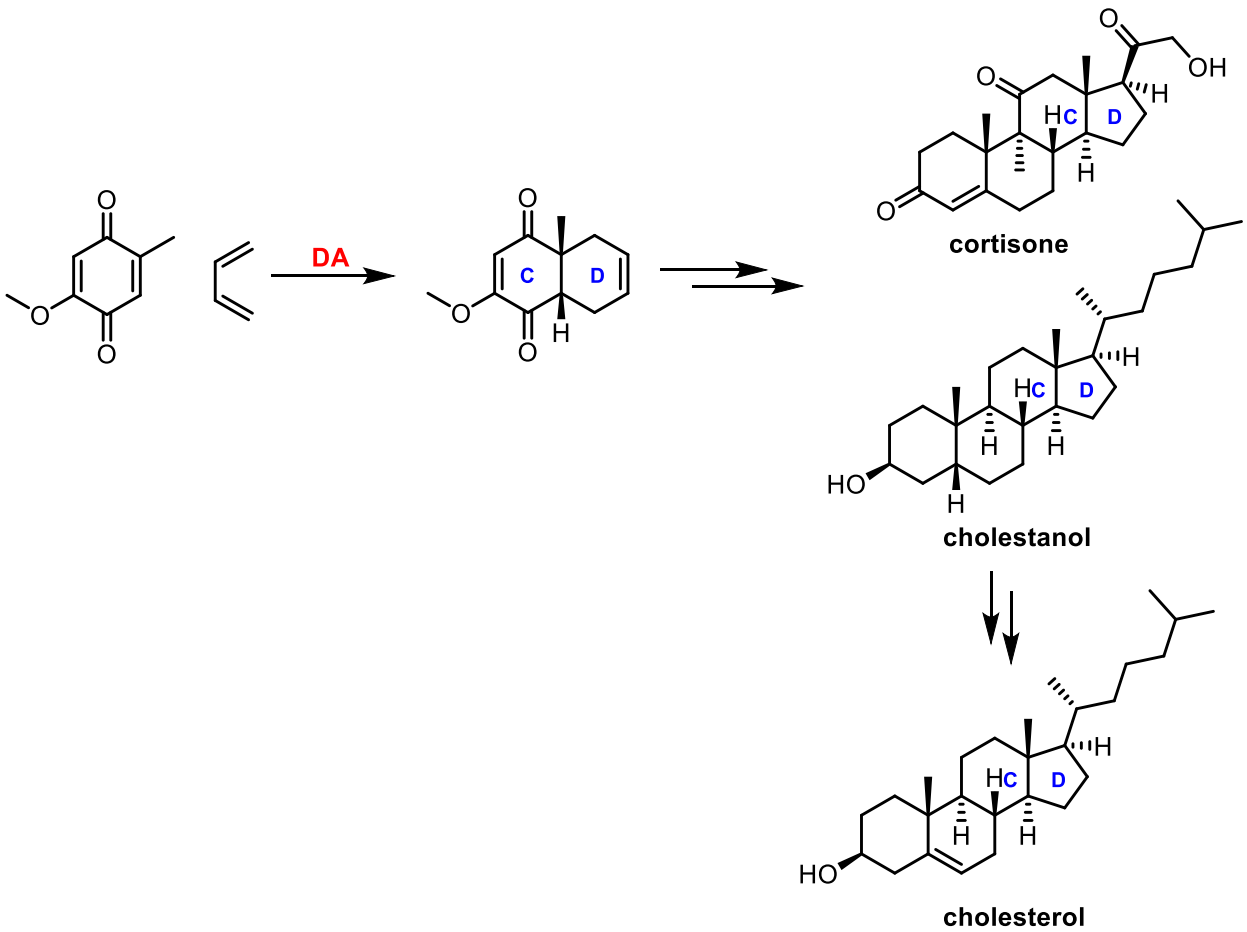
TBHP	*tert*-Butyl hydroperoxide
TBS	*tert*-Butyldimethylsilyl
***t*Bu**	*tert*-butyl
TC	thiophene-2-carboxylate
Tf, triflate	trifluoromethanesulfonate
TFA	Trifluoroacetic acid
THF	tetrahydrofuran
TLC	Thin-layer chromatography
TMEDA	*N*,*N*,*N*′,*N*′-Tetramethylethylenediamine
Tol	*p*-tolyl
TS	Transition state

CHAPTER 1: INTRODUCTION

1.1 DIELS-ALDER CYCLOADDITION

1.1.1 The Intermolecular Diels-Alder Cycloaddition

The Diels-Alder (DA) reaction, described for the first time in 1928 by Otto Diels and Kurt Alder[1], represents a milestone in organic chemistry and in the synthesis of natural products. One of the first applications dates back to 1952, when Woodward published a synthetic route to steroid hormones cortisone and cholesterol employing a Diels-Alder reaction between methoxytoluquinone and butadiene as a key step (Scheme 1),[2] and it is still one of the most frequently employed reactions in total synthesis thanks to its efficiency, versatility, scope and ability to create molecular complexity.



Scheme 1: Synthesis of cortisone and cholestanol by Woodward employing a DA reaction

The success of the Diels-Alder reaction is due to the high complexity generated in a single synthetic step: two new carbon-carbon bonds, a six-membered ring and up to four new contiguous stereocenters are generated at the same time. Also, the reaction is stereospecific and usually shows high level of regio- and diastereoselectivity. These characteristics can be explained in terms of symmetry of the frontier molecular orbitals (FMOs) involved in the reaction (Figure 2). The Diels-Alder reaction belongs to the class of [4+2]-cycloaddition: a 4π electron system (diene) interacts with a 2π electron system (dienophile) to form a cyclohexene in a concerted but asynchronous step.[3] To have an effective overlapping of the highest occupied molecular orbital (HOMO) of one reactive species and the lowest unoccupied molecular orbital (LUMO) of the other reactive species, the two orbitals must have similar energy and same symmetry. According to the Woodward-Hoffmann rules about the conservation of orbital symmetry, the reacting species involved in a thermal cycloaddition must satisfy the Equation 1 to allow *supra-supra* attack with respect to both components and equation 2 to allow *supra-antara* attack (Figure 1). *p* and *q* are the numbers of electrons of the two π-systems, and n can be any positive integer number (n = 1 in the DA reaction). The second type of interaction is not possible for small rings because of geometric constraints on the transition state.

$$p+q = (4n+2) \qquad \text{(Eq. 1)}$$

$$p+q = 4n \qquad \text{(Eq. 2)}$$

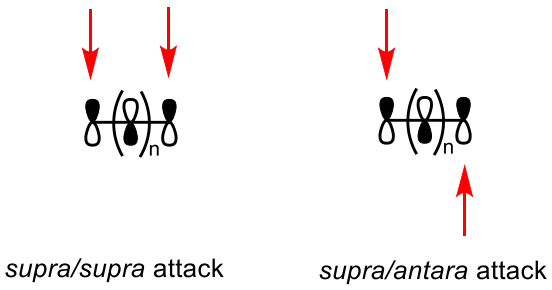


Figure 1: Suprafacial and antarafacial interaction

Electron donating substituents (EDG) increase the energy levels while the energy levels are lowered by electron withdrawing substituents (EWG). In case of reactions occurring with normal electron demand, EDGs on the diene and EWGs on the dienophile facilitate the reaction. The opposite is true for reactions occurring with inverse electron demand (Figure 2).

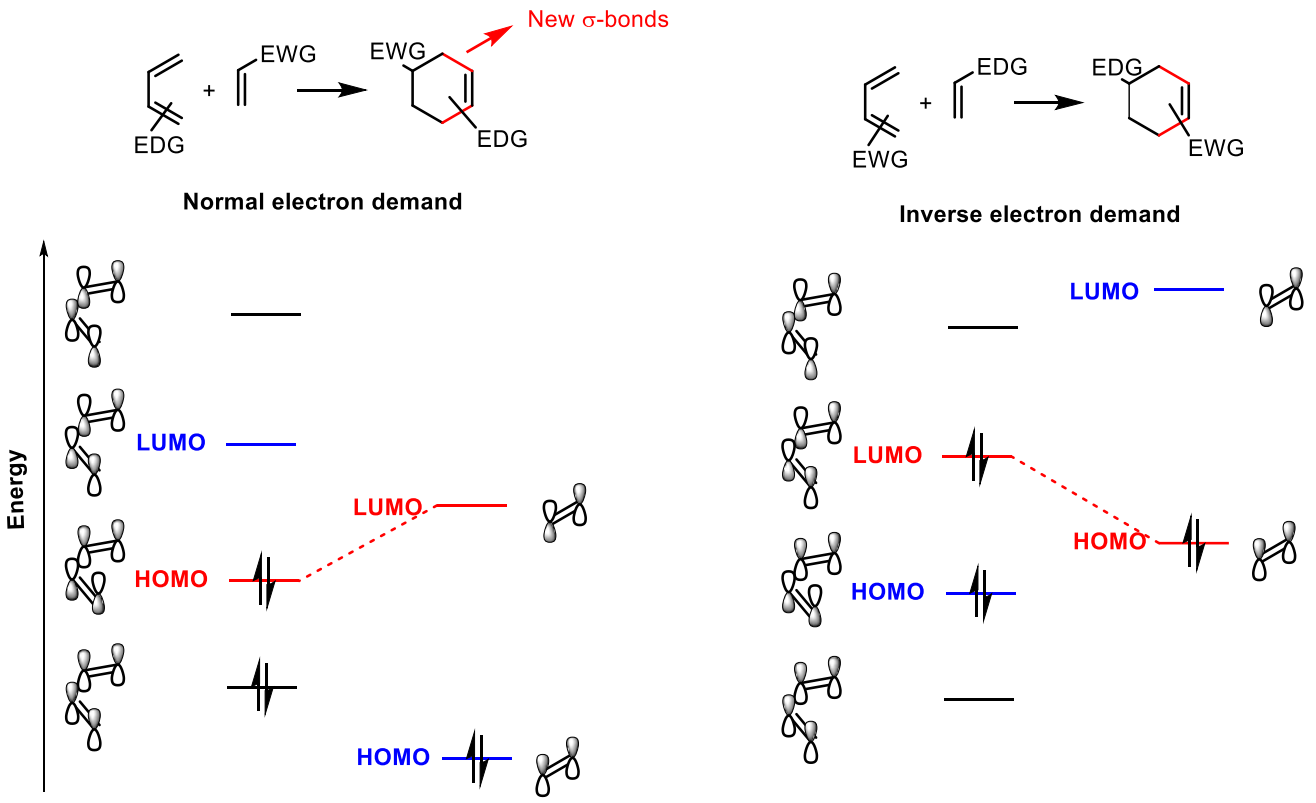


Figure 2: molecular orbitals involved in DA reaction

As the two π-systems approach each other to form two new σ bonds, the HOMO of one component and the LUMO of the other component ($HOMO_{(diene)}$-$LUMO_{(dienophile)}$ or $HOMO_{(dienophile)}$-$LUMO_{(diene)}$) must have the orbitals of the terminal carbons with matching phase to generate a favourable bonding interaction. The diene must adopt a *cisoid* conformation to interact with the dienophile. If the diene is locked in the s-*cis* conformation because it is part of a ring (e.g. cyclopentadiene) the reaction is much faster than in case of an acyclic system. If the diene is locked in an s-*trans* conformation, no DA reaction can occur. During the reaction, the relative stereochemistry of the substituents on the diene and on the dienophile is preserved (stereospecificity) and in case of unsymmetrical dienophiles the *endo* product is often kinetically favoured (diastereoselectivity) because of secondary orbital interactions between the π-system of the substituent on the dienophile and the π-system of the diene. This is known as "endo rule" (Figure 3)[3] .

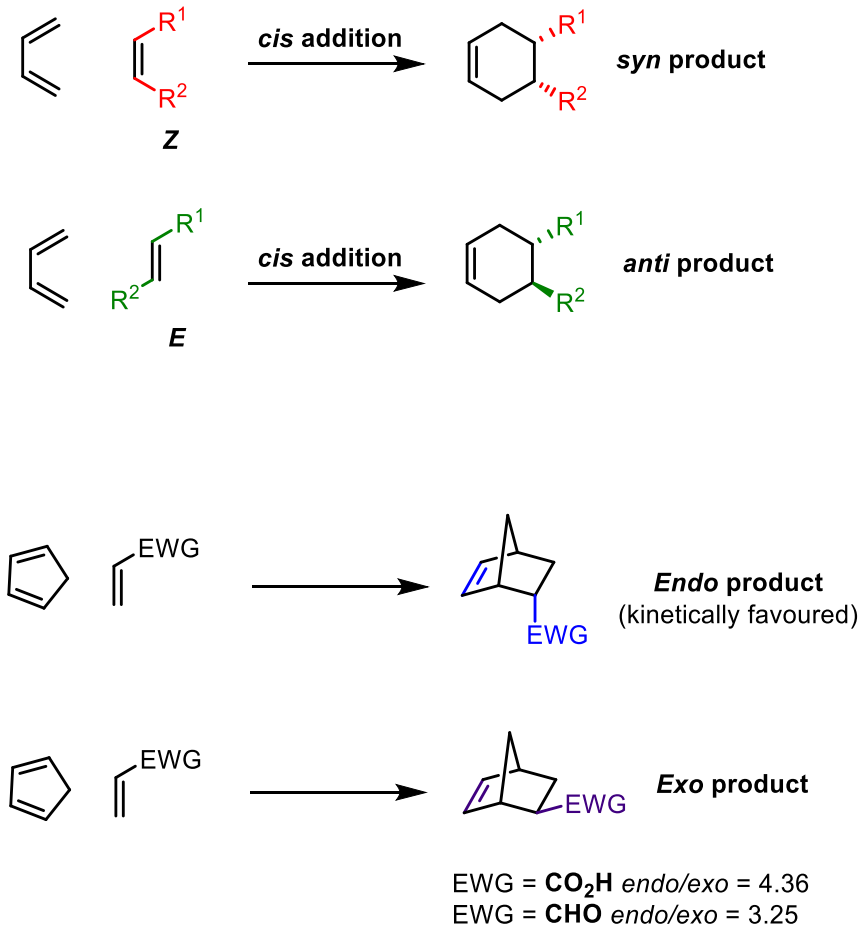


Figure 3: Stereoselectivity of DA cycloaddition

1.1.2 The Intramolecular Diels-Alder reaction

The intramolecular Diels-Alder (IMDA) reaction has been known for more than 50 years[4-7] and it has become an effective and widely used method in the synthesis of complex polycyclic molecules. IMDA reactions present some advantages with respect to the intermolecular reaction: they are often faster and require milder condition thanks to less negative activation entropies (the initial system is in a more ordered state than the bimolecular reaction because diene and dienophile moieties are part of the same molecule) and the constraint due to the connecting chain leads to a more pronounced regio- and stereo-selectivity. The entropy advantage declines with the length of the connecting chain and is almost insignificant for chains containing more than 5 atoms.

IMDA reactions can be divided into two main groups: Type I and type II, depending on whether the tether is attached to the 1- or 2- position of the diene (Figure 4). In both cases two rings are formed in one single step:

the 6-membered ring derived from the [4+2]-cycloaddition and a second ring whose size depends on the number of atoms present in the chain connecting diene and dienophile (Figure 5).

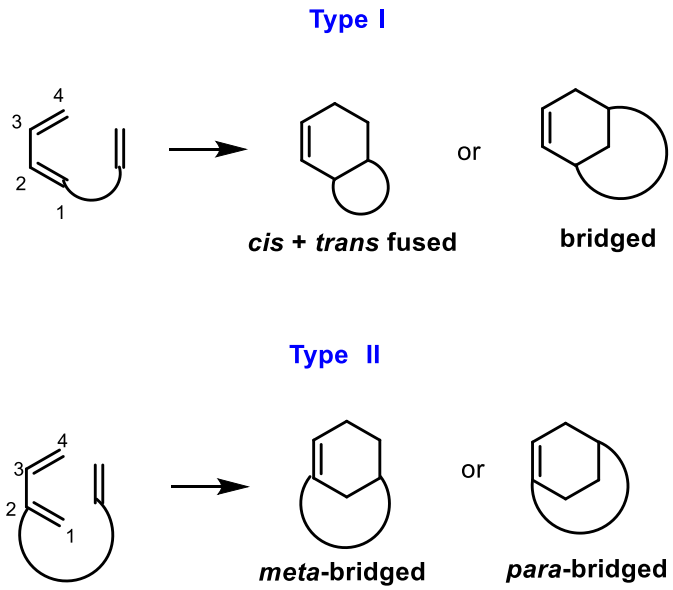


Figure 4: IMDA: type I and type II

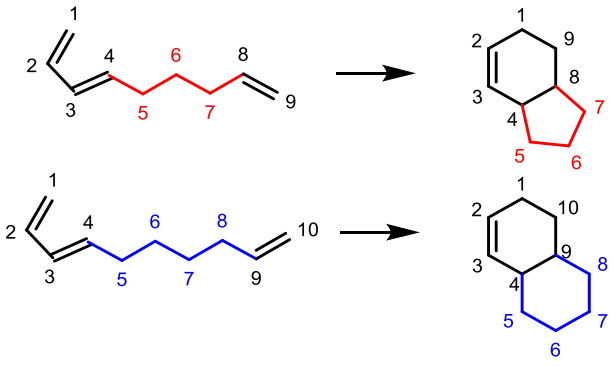


Figure 5: The size of the second ring in the IMDA reaction depends on the number of atoms in the connecting chain

When unsymmetrical dienes and dienophiles are involved, there are two possible regiochemical outcomes, deriving from *syn* and *anti* transition states respectively. The type II IMDA mechanism can provide *meta*-bridged or *para*-bridged products. The former is the only possible product in case of short chains (≤ 5 atoms). In the case

of type I IMDA, both fused and bridged rings are possible, but fused products are much more common and bridged systems are observable only in case of long tethers (> 9 atoms) (Figure 3). Calculations on ester- and amide-tethered substrates show that, in the transition state, boat-like conformations are preferred over chair-like conformations (the amide is nearly planar in the TS), and *endo* geometries are favoured over the *exo* ones (Figure 6).[8]

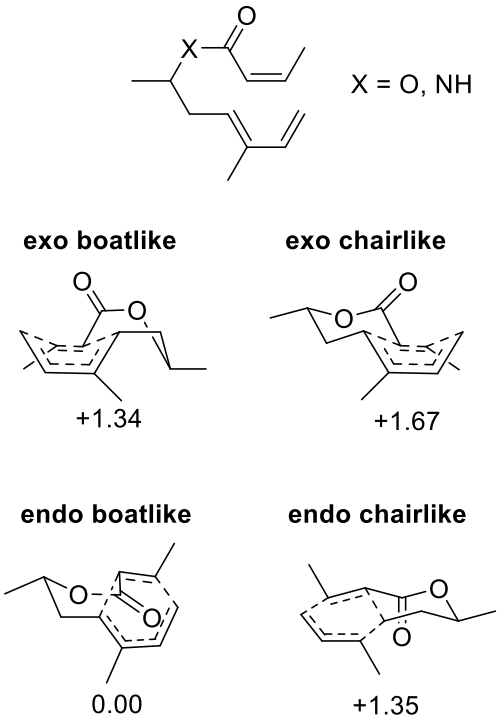


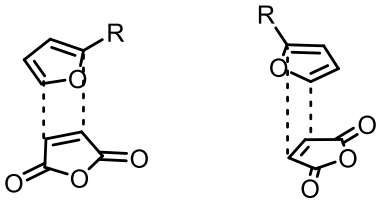
Figure 6: Possible transition states for an intramolecular Diels-Alder reaction with ester tether and calculated free energies (kcal/mol).

1.1.3 Furans as diene in Diels-Alder reactions

Heterocycles such as furan, pyrrole and thiophene are interesting compounds that potentially allow incorporation of heteroatoms in organic structures through the DA reaction. Their tendency to undergo cycloaddition is limited by their aromaticity. Referring to aromaticity in terms of uniformity of the bonds lengths of the π-system, furan is the less uniform (average deviation from uniformity = 0.258) and therefore the most likely of the three heterocycles to react as conjugated diene, followed by thiophene (average deviation from uniformity = 0.196) and then pyrrole (average deviation from uniformity = 0.162).[9] There are other ways to describe aromaticity and different experiments suggest a different order.[10-11] The different reactivity is reflected

in the number of furan Diels-Alder reported compared to the few examples of pyrrole[12-16] or thiophene[17-18] employed in the same reaction.

The Diels-Alder reaction of furans is known to proceed with normal electron demand because of the electron-rich nature of the furan ring.[9, 19] The frontier orbital interaction is $HOMO_{furan}$–$LUMO_{dienophile}$, and the reaction is expected to be favoured by substituents on the furan ring which increase the HOMO energy level (electron-donating substituents), and substituents on the dienophile moiety which lower the LUMO energy level (electron-withdrawing substituents). The *exo*/*endo* selectivity (Figure 7) is affected by temperature, solvent of the reaction and substituents on furan and dienophile.[20] The reaction of furan derivatives with maleic anhydride has been used by Qiu to calculate the activation energies for *endo* and *exo* transition states.[21] Results in Table 1 show both *exo* and *endo* TS energies increasing when EWG are present in the diene suggesting a normal electron demand reaction. In case of the unsubstituted furan (entry 4), the *endo* TS is slightly favoured. A strong preference for the *exo* TS is observed for furan-2-ol (entry 1) and the *endo* TS is favoured mostly with 2-(trifluoromethyl)furan (entry 7).



***Exo* TS** ***Endo* TS**

Figure 7: *Exo* and *endo* TS for DA between 2-substituted furan and maleic anhydride

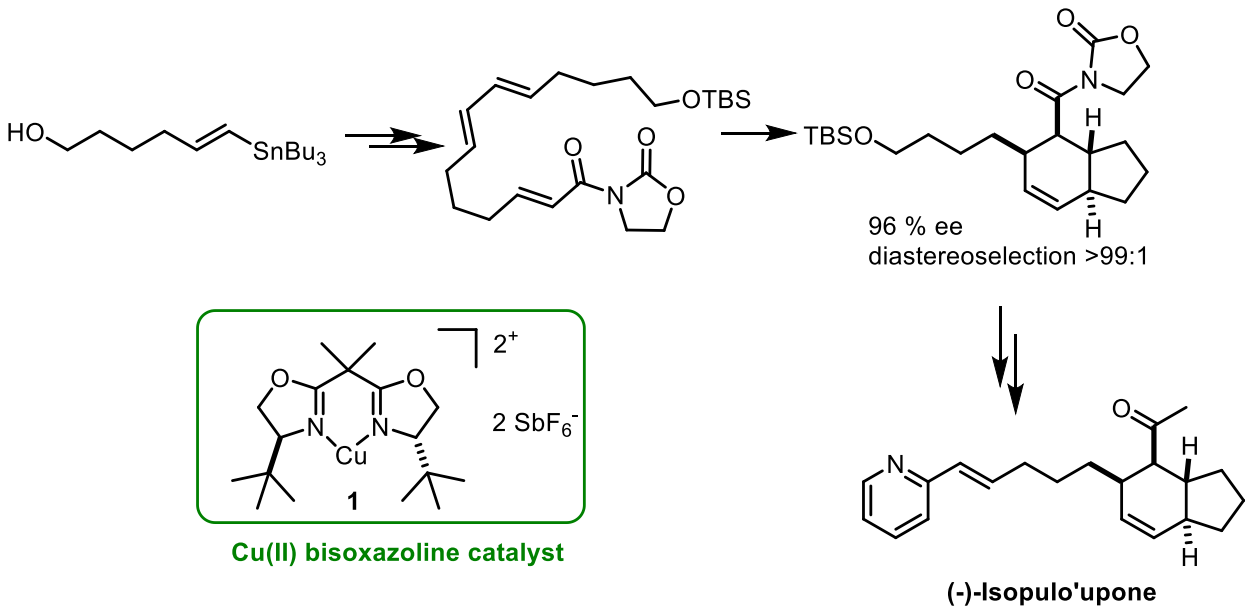
Table 1: Activation free energies calculated for *exo* and *endo* TS in furan DA by the M06-2X/6-31G(d) method.

		ΔG_{act} (Kcal/mol)	
Entry	**R**	***Exo***	***Endo***
1	OH	17.03	22.37
2	OMe	20.64	20.56
3	Me	22.19	24.92
4	H	24.23	24.19
5	Cl	26.44	25.27
6	CHO	27.99	28.86
7	CF_3	27.82	25.98
8	CN	30.96	29.48
9	NO_2	28.75	28.09

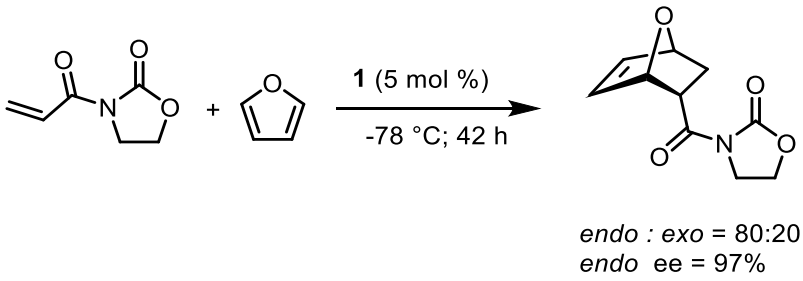
ΔG_{act}= free energy difference between TS and dienophile and diene.

1.1.4 Asymmetric Diels-Alder reaction

The development of asymmetric variants of the intramolecular Diels-Alder reaction is a topic of great interest. There are many examples of asymmetric induction obtained with chiral auxiliaries or catalysts. Evans has undertaken extensive work on the subject using oxazolidinones as chiral auxiliaries[22-24] and C_2-symmetric Cu(II) *tert*-butylbis(oxazoline) complexes as catalysts.[25-27] Scheme 2 shows the synthesis of marine toxin (-)-Isopulo'upone, obtained by an intramolecular Diels Alder with high enantiocontrol thanks to asymmetric cationic Cu(II) complex **1**.[26] For a long time, despite the value as synthetic intermediates of 7-oxabicyclo[2.2.1]hept-2-enes, there were very few examples of furans employed in asymmetric cycloadditions. Evans reported an enantioselective intermolecular furan Diels-Alder reaction, realised with the same chiral Lewis acid **1** (Scheme 3).[25]

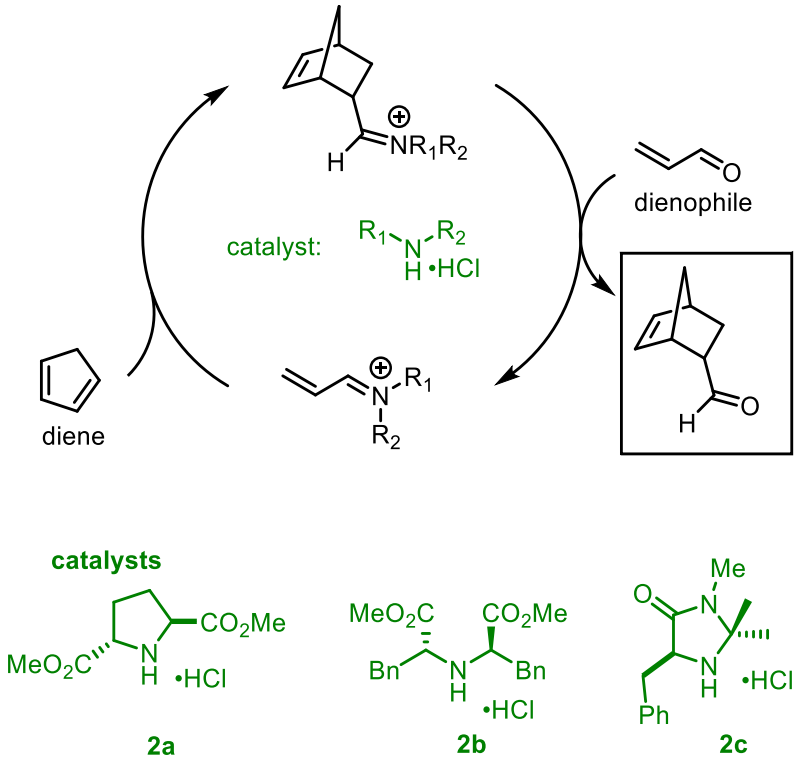


Scheme 2: Synthesis of (-)-Isopulo'upone



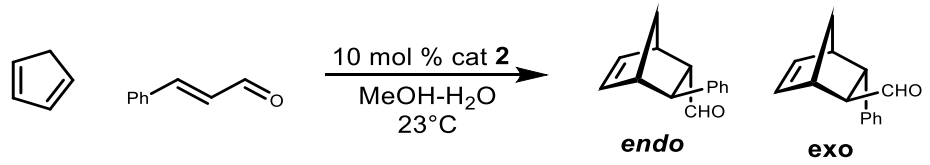
Scheme 3: Enantioselective intermolecular Diels-Alder reaction of furan diene

More recently, MacMillan published a highly enantioselective organocatalytic Diels-Alder reaction realized with iminium activation (Scheme 4, Table 2).[28-30] The iminium ion facilitates the reaction by lowering the LUMO of the dienophile, and through iminium geometry control it is possible to increase the enantioselectivity of the reaction. A number of dienes and dienophiles were used to probe the scope of the reaction which appear to be tolerant to change of structure and the presence of aromatic groups on the dienophile. A few years later they also reported an intramolecular version of the reaction, obtaining a precursor of Solanapyrone D in 90% ee (Scheme 5).[31]



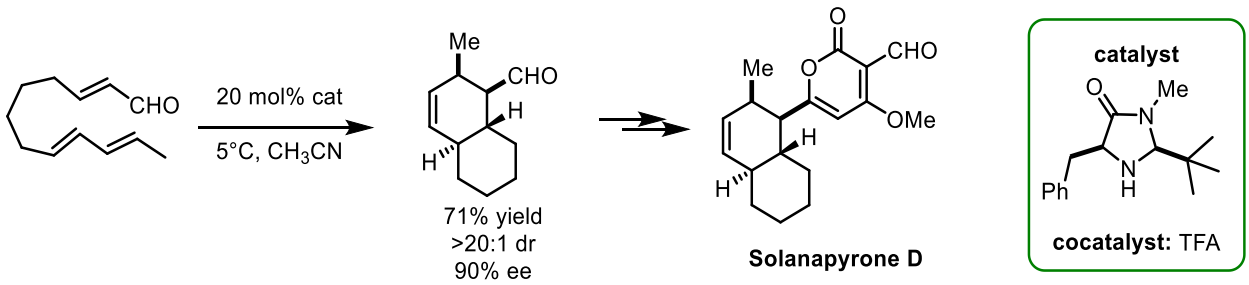
Scheme 4: Iminium activation of DA reaction

Table 2: Organocatalysed DA reaction between Cinnamaldehyde and Cyclopentadiene



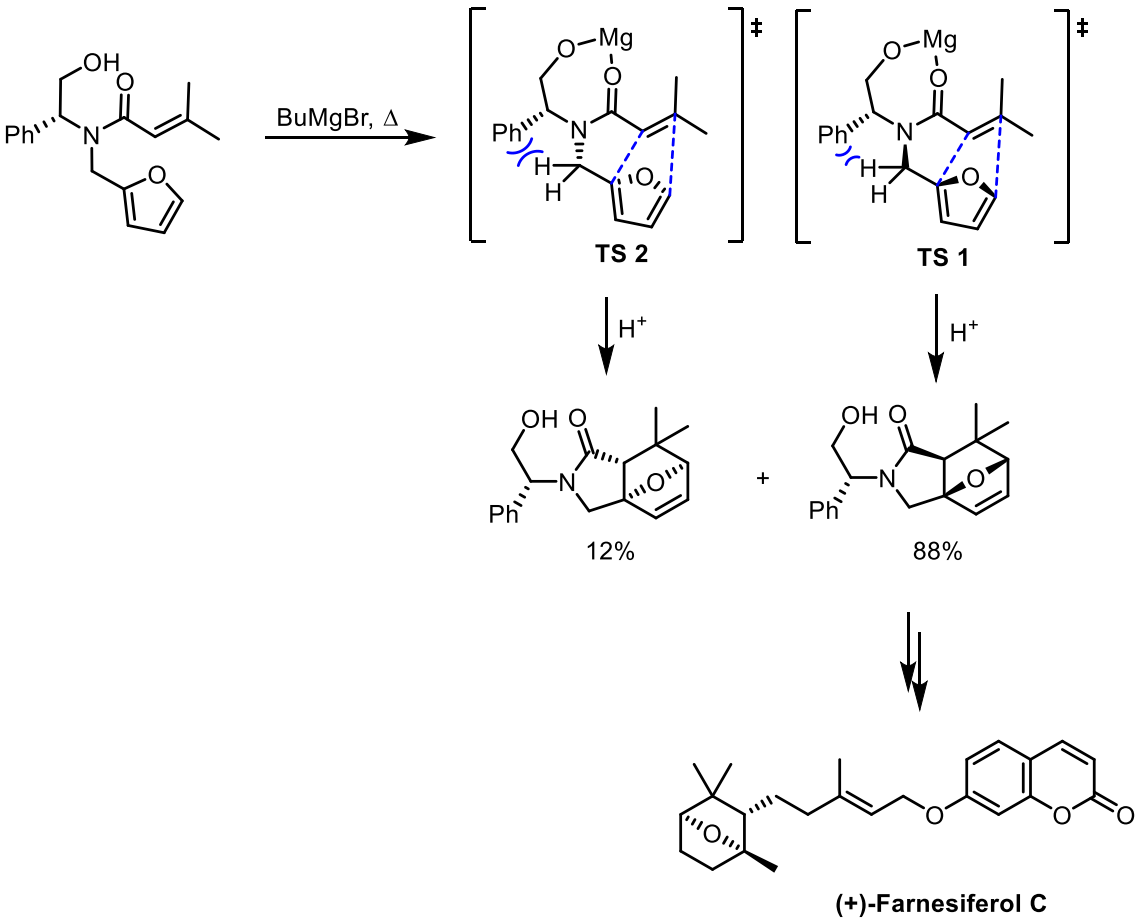
Catalyst 2	time (h)	yield (%)	*endo : exo*	*exo* ee (%)
a	23	92	2.6:1	57
b	84	82	3.6:1	74
c	8	99	1.3:1	93[a]

a. Using 5 mol % of catalyst



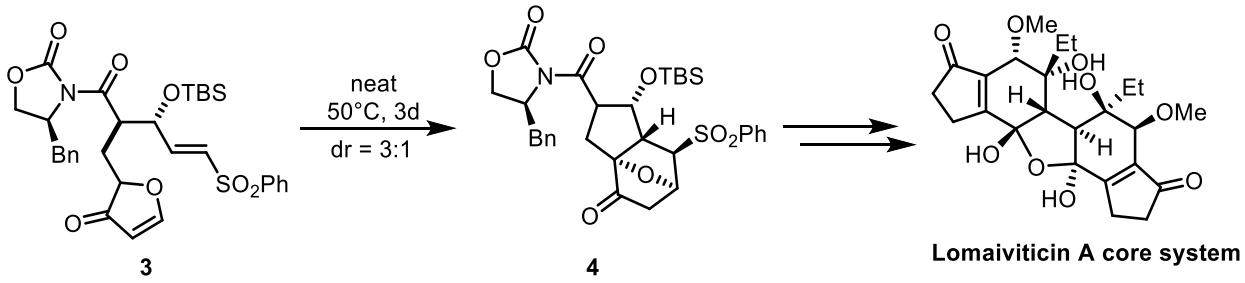
Scheme 5: Enantioselective organocatalytic IMDA reaction as key-step in the synthesis of Solanapyrone D

For IMDAF reactions, the background retrocyclization generally precludes an asymmetric variant, with some exceptions. Mukaiyama and Iwasawa used an internal chiral auxiliary to secure stereoinduction in the cycloaddition process, a key-step in the synthesis of (+)-farnesiferol C.[32] The stereochemical outcome is explained in terms of steric repulsion between the benzene ring and the methylene next to the furan ring in the chelate transition state. To minimize this interaction the furan attacks from the top face (Scheme 6, **TS 1**).



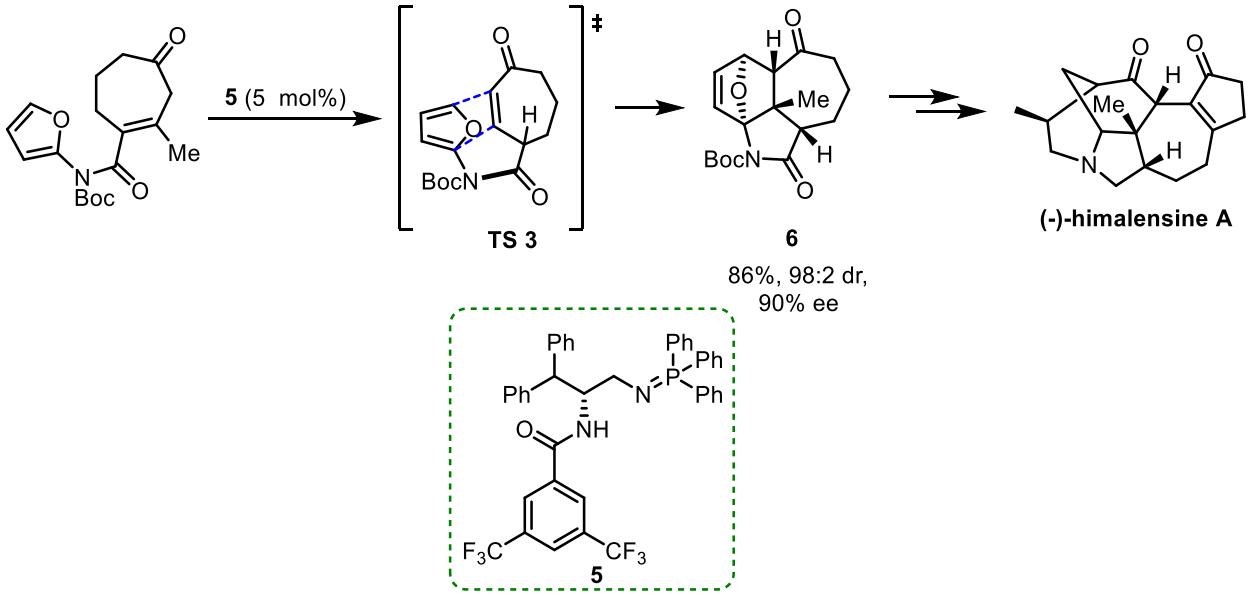
Scheme 6: Diastereoselective IMDAF in the synthesis of Farnesiferol C (top) and TS to explain the stereochemical outcome.

An asymmetric IMDAF was also employed to make the central ring system of Lomaiviticin A using an oxazolidinone as chiral auxiliary (Scheme 7).[33] Compound **3** tautomerises to form the diene component that promptly reacts to yield the corresponding cycloadduct, which then undergoes a second enol tautomerisation preventing retrocyclization. The *endo* product **4** is the only one observed, instead of the thermodynamically more stable *exo* product normally obtained from reversible IMDAF reactions.



Scheme 7: Sysnthesis of lomaiviticin A core system by asymmetric tautomerisation/IMDA in presence of a chiral auxiliary

The first example of an enantioselective catalytic prototropic shift/IMDAF reaction was reported by Dixon *et al.* as key step for the synthesis of (-)-Himalensine A (Scheme 8).[34] From computational calculations, the *exo* cycloadduct was predicted to be kinetically and thermodynamically more stable than the *endo* product, and 8 kcal/mol more stable than the starting material, indicating irreversibility of the reaction. Enantiomerically pure bifunctional iminophosphorane **5** was used to catalyse the first part of the [1,3]-prototropic shift/furan Diels-Alder cascade, resulting in a 90% ee of the desired product **6**.



Scheme 8: Synthesis of (-)-himalensine A by enantioselective prototropic shift/IMDAF reaction

1.1.5 Intramolecular Diels-Alder Reaction of Furan Dienes

1.1.5.1 Regio- and Stereoselectivity

The intramolecular Diels-Alder reaction of furan dienes (IMDAF) leads to the formation of 7-oxabicyclo-[2.2.1]-5-heptene (or 7-oxanorbornene) systems with high regio- and stereo control. The length of the chain of most IMDAF precludes the formation of bridged cycloadducts, and the reduced freedom of the intramolecular system results in almost exclusive formation of thermodynamically more stable *trans*-fused products with the tether in *exo*-position with respect to the oxygen bridge. The examples found in literature (≤ 4 atoms tethers) and theoretical calculations confirm the formation of only one regio- and diastereomer (Figure 8).[35-39]

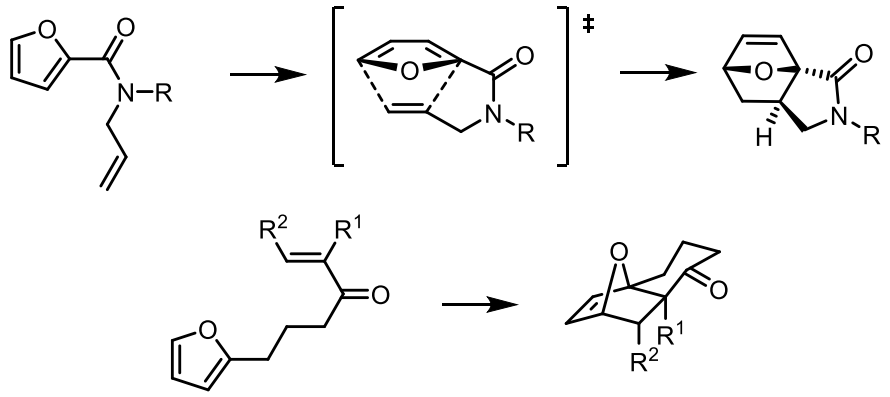


Figure 8: Stereochemistry for IMDAF possessing short tethers

Structures of cycloadducts were confirmed by NMR experiments (Figure 9)[36, 40-45] or by X-ray crystallography.[46-48] The values of the coupling constants measured for the structures in Figure 9 are consistent with the drawn structures.[49] The coupling constant between H_a and H_b suggests a dihedral angle of 40°, and no coupling between H_a and $H_{b'}$ was observed, in agreement with a 90° dihedral angle (in the *endo* isomer this angle would be 120°). In *endo* compounds, coupling between protons H_b and H_c would be about 9 Hz because they are on the same side of the molecule and $J_{Hc\text{-}Hb'} \approx 4$ Hz because they are on opposite sides[50]. The values of $J_{Hc\text{-}Hb'}$ observed in IMDAF cycloadducts agree with the *trans*-fused geometry.

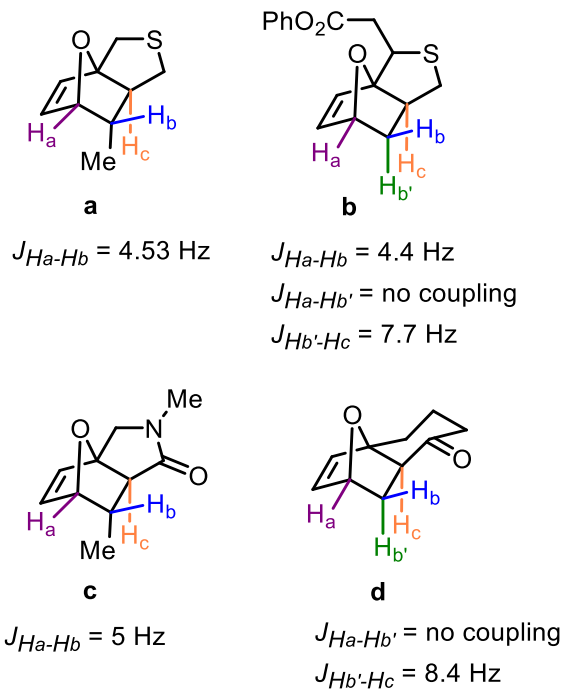
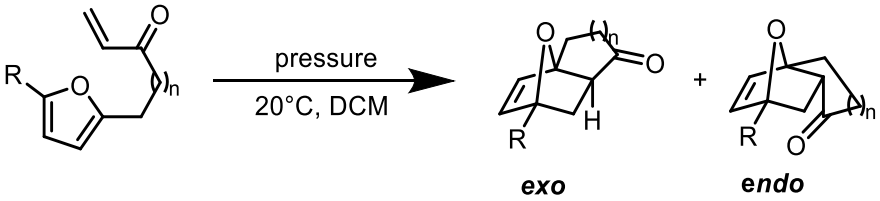


Figure 9: IMDAF produces exclusively trans-fused products.

The strong preference for *exo*-products observed in IMDAF reactions does not applied to reactions conducted at high pressure. Harwood *et al.* reported the formation of the *endo*-adduct by IMDAF reaction from 2-substituted furans.[51-52] The *exo*:*endo* ratio depends on the pressure applied and the reaction time, with the *exo* isomer (kinetic product) favoured in the early stages of the reaction (Table 3).

Table 3: *Endo*:*exo* ratio for IMDAF reaction at high pressure[52]



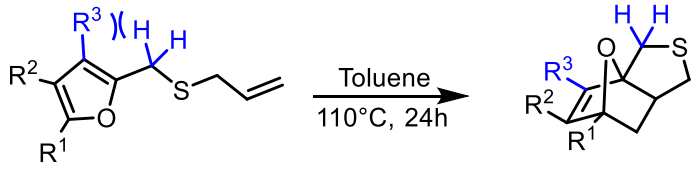
exo **e*ndo***

Entry	n	R	conditions	SM	Ratio *Exo*	*Endo*
1	2	H	10 Kbar, 10 min	0	95	5
2	2	Me	10 kbar, 10 min	0	100	0
3	3	H	12 Kbar, 24 h	0	50	50
4	3	Me	12 Kbar, 24 h	10	40	50

1.1.5.2 Substituent activation

Modification of the length of the linking chain and incorporation of heteroatoms and various functionalization allows the formation of a series of different scaffolds but it also affects rate and conversion. The effect of the substituents on diene and dienophile is not always what would be expected for a normal electron demand Diels-Alder. FMO energies are not the main factor in controlling IMDAF reactions, as it appears from the work of Klein,[40] Babbington[53] and Klepo.[54] Klein, working on cycloaddition of furfuryl allyl sulfides, noticed that some of the results could not be explained only in terms of electronic effects of the substituents but steric effects also contributed (Table 4). It was hypothesised that the cycloaddition was favoured by the decrement of steric strain between the R groups and the protons of the adjacent methylene of the side chain, which are farther away in the cycloadduct, especially in case of 3-substituted furans. This would explain the higher conversion of the 3-methylfuran, and the even higher conversion of the 3-bromofuran, despite the higher donating effect of the methyl compared to the halogen.

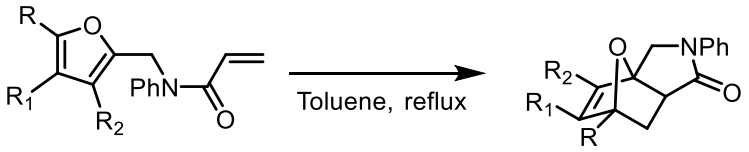
Table 4: Effect of substituents on cycloaddition of furfuryl allyl sulfides[40]



Entry	R^1	R^2	R^3	Yield (%)
1	Me	H	H	18
2	H	Me	H	40
3	H	H	Me	77
4	H	H	Br	83

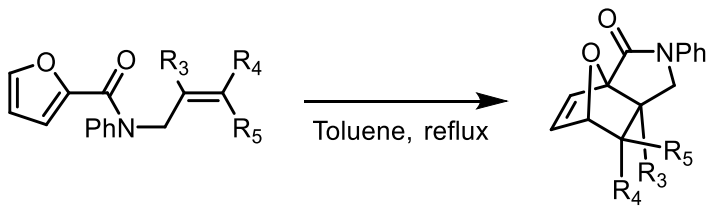
The behaviour of halo-substituted furans in IMDAF reactions was investigated in more details by Padwa,[55] Bebbington and Paterson *et al.*[53] Some of their results are summarised in Table 5, Table 6 and Table 7. The presence of a halogen in 5-position promotes the DA reaction, particularly with bromine (Table 5 and Table 7, entry 2). The authors attribute this effect to the polarization of the substituents. According to theoretical calculation,[55-56] halogen substitution increases the exothermicity and decreases the activation enthalpy of the reaction, which has the double effect of facilitating the DA reaction and make the retro-DA more difficult. This is true regardless of the position of the halogen in the furan ring or the length of the tether. Reactions with haloalkene dienophiles on the other hand, proved to be more difficult than the non-halogenated equivalents (Table 6), particularly when a *Z*-dienophile is involved (Entry 3).

Table 5: Effect of furan substituents on conversion in IMDAF reactions[53]



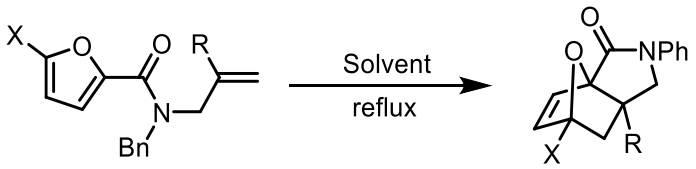
Entry		Yield (%)
1	R = H; R_1 = H; R_2 = H;	62
2	**R = Br**; R_1 = H; R_2 = H;	70
3	R = H; **R_1 = Br**; R_2 = H;	76
4	R = H; R_1 = H; **R_2 = Br**;	83

Table 6: Effect of dienophile substitution in IMDAF reaction[53]



Entry		Yield (%)
1	**R_3 = Cl**; R_4 = H; R_5 = H;	27
2	**R_3 = Br**; R_4 = H; R_5 = H;	44
3	R_3 = H; R_4 = H; **R_5 = Cl**;	7
4	R_3 = H; **R_4 = Cl**; R_5 = H;	28

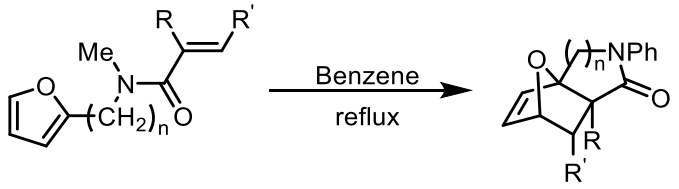
Table 7: Effect of halogen substituents on furan in IMDAF reaction [55]



Entry	R	X	Yield (%)	Conditions
1	**H**	H	48	Toluene, 48 h
2	H	Br	100	Toluene, 48 h
3	H	Cl	92	Toluene, 48 h
4	H	I	94	Toluene, 48 h
5	Me	H	40	Benzene, 6 d
6	Me	Br	82	Benzene, 36 h

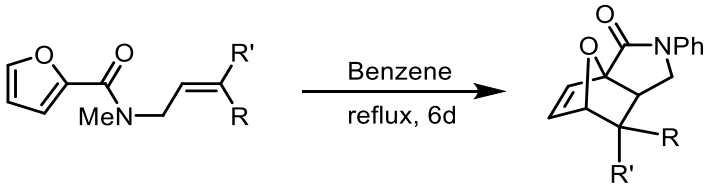
IMDAF reactions are highly dependent on substitution (on both diene and dienophile) and tether (length and type of atoms). In general, when the connecting chain contains an ester or a secondary amide no cycloaddition is observed. Only a few exceptions have been reported.[48, 57] This is probably due to the preference of the molecules for a conformation which prevents the effective overlap of diene and dienophile moieties.[36] Conversions of tertiary amides are reported in Table 8 and Table 9.[36] The reaction is higher-yielding when a 5-membered ring is formed (Table 8, compare entry 3 with entries 5 and 7) and, as seen for halo-substituted dienophiles, non-terminal alkenes give lower yields (Table 8, entries 2 and 3 and Table 9).

Table 8: Effect of number of atoms in the connecting chain and substituents on the dienophile in IMDAF reaction [36]



Entry	n	R	R’	Conversion (%)
1	1	H	H	100 (6d)
2	1	Me	H	100 (5d)
3	1	H	Me	40 (14d)
4	2	H	H	100 (4d)
5	2	H	Me	12
6	3	H	H	45 (6d)
7	3	H	Me	0

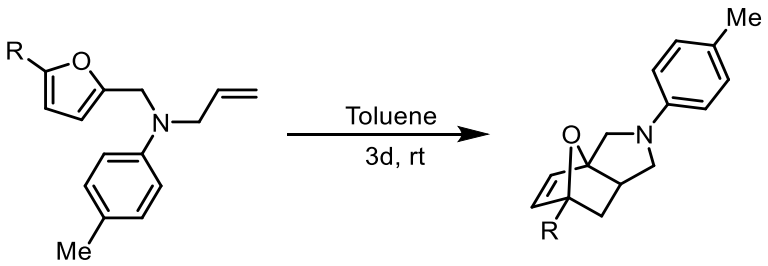
Table 9: Effect of substituents at the terminal position of the dienophile[36]



Entry	R	R’	Conversion (%)
1	H	H	100
2	Me	H	0
3	H	Me	0

The effect that substituents on the furan ring have on the reaction has been extensively studied.[35, 53-56, 58] Amine-tethered furans rarely undergo cycloaddition, unless activated by an appropriate *N*-protective group[59] or by substitution on the furan (Table 10). The electron-donating methyl group on the diene decreases the reaction rate (entry 6), while electron-withdrawing groups facilitate the reaction, particularly in case of nitro-substituted furan (entry 5).[54]

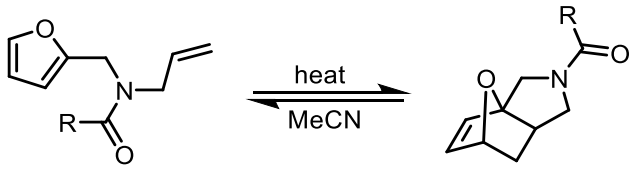
Table 10: Electronic effect of EWG and EDG on the furan ring [54]



Entry	R	Yield (%)
1	H	7
2	Br	54
3	Cl	48
4	I	34
5	NO_2	73
6	CH_3	5
7	OCH_3	37

The nature of the *N*-substituents influences the reactivity of furan amides considerably. Secondary amides do not cyclize, and it was observed that the rate of the reaction increases with the size of the N-substituent and, to a lesser extent, its electronegativity (Table 11).[39, 60-63]

Table 11: Effect of the size of substituents on the nitrogen in IMDAF reaction with amide tethers



Entry	R	Conversion (%)[a]	Yield (%)[a]
1	CF_3	91 (42)	88 (39)
2	CCl_3	100 (80)	99 (76)
3	$C(CH_3)_3$	100 (47)	98 (44)
4	$CHCl_2$	100 (41)	97 (39)
5	$CH(CH_3)_2$	62 (9)	60 (8)
6	$C(CH_3)Cl_2$	100 (52)	98 (47)
7	$C(C_2H_5)Cl_2$	100 (61)	98 (57)
8	CH_2Cl	43 (6)	40 (5)

[a] At 80°C (30 h) and in parenthesis at 60°C (20 h)

The electronic effect of the substituents was explained by Ghelfi in terms of resonance between the two hybrid structures shown in Figure 10. The electron-withdrawing effect increases the contribution of the structure with the sp^3-nitrogen (on the left) which will make the resonance hybrid undergo the cycloaddition more easily (angle C-N-C 109° (left) instead of 120°(right)).[60]

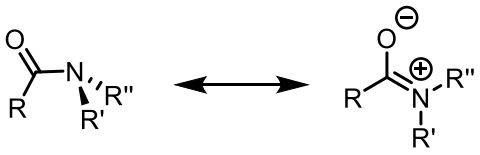


Figure 10: Resonance structures of amides

Unlike what was originally thought, the effect of the bulkiness of the nitrogen substituent on the reaction rate is not due to rotational isomerism (the *Z*/*E*-geometry interconversion is faster than the DA reaction), but is now explained in terms of decrement of steric strain during the cycloaddition.[63] Kitagawa *et al.* calculated activation

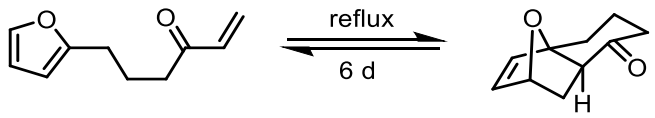
energies and enthalpies of the reaction and suggested that bulky substituents increase the exothermicity and, as explained for the halo-substitution effect, promote the reaction and prevent the retro-Diels-Alder.[63]

1.1.5.3 Equilibrium

Some IMDAF reaction substrates are known to cyclize giving mixtures of starting material and product.[39, 45, 57, 64-65] The degree of conversion at the equilibrium is known to be influenced by solvent and temperature (Table 12 - Table 14). As expected, higher temperature gives higher conversion (Table 12, entries 1 and 3). The effect of the solvent of the reaction on the conversion was first reported by De Clercq and Van Royen with all-carbon connecting chain substrates (Table 12).[44] An increment in cycloaddition was observed going from benzene (80°, 45%, entry 4) to DCM (40°, 82%, entry 1) even though the temperature of the reaction is higher in benzene. In ethanol, despite the higher polarity and temperature, conversion was lower than in DCM (entries 1 and 2). Jung and Gervay studied the equilibrium of IMDA reactions of substituted 2-furfuryl methyl fumarates[57] and obtained rate constants for the forward and reverse reaction in different solvents (Table 13): the reaction is faster in DMSO (6.6×10^{-6} s^{-1}, entry 1) and acetonitrile (1.1×10^{-6} s^{-1}, entry 2) and it is two orders of magnitude slower in toluene (3.6×10^{-8} s^{-1}, entry 6). The rate constants for the reverse reaction are in a much smaller range, from 7.7×10^{-3} s^{-1} in DMSO (entry 1) to 1.6×10^{-3} s^{-1} in acetone (entry 3). While k_{-1} is relatively insensitive to solvent change, k_1 varies in accordance with the polarity, more precisely with the dielectric constant (ε) more than the solvent polarity parameter E_T. They are both indicator of polarity but ε is a measure of the ability of a substance to insulate charges from each other, while $E_T(30)$, defined as the molar electronic transition energy of betaine 30, is an empirical parameter determined using the frequency of the absorption maximum of dye betaine 30.[66] More polar solvents facilitate the reaction by stabilizing the net dipole moment of the TS (Figure 11). The less polar TS of amide-tethered furans makes the cycloaddition rate relatively insensitive to change of solvent polarity. The reaction in Figure 12 was found to have the same conversion in toluene-d_8, CD_2Cl_2, acetone-d_6, CD_3CN and DMSO-d_6.

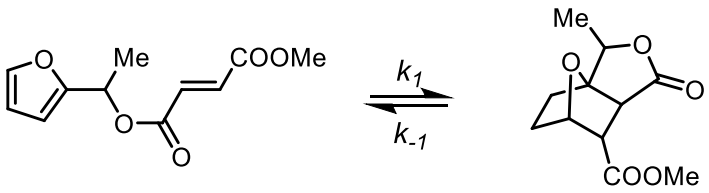
Although the solvent effect is generally expressed in terms of polarity, Sternbach and Rossana noticed that the yield of cycloadduct obtained from their reaction roughly increased with the viscosity of the solvent (Table 14),[67] suggesting that reactions with high negative entropy of activation are favoured by highly ordered solvents.

Table 12: Solvent and temperature effect in IMDAF [44]



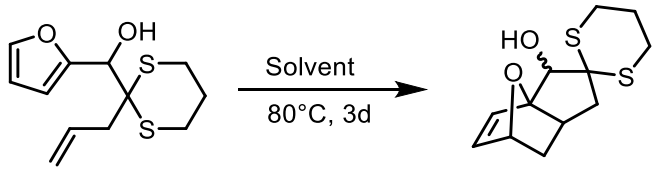
		Composition at the equilibrium	
Entry	**Conditions**	**SM**	**Product**
1	CH_2Cl_2, 40°C	18	82
2	Ethanol, 78°C	36	64
3	CH_2Cl_2, rt	45	55
4	Benzene, 80°C	56	45

Table 13: Rate of DA in relation to solvent polarity [57]



Entry	**Solvent**	**ε**	**E_T**	***k_1*** **(s^{-1})**	***k_{-1}*** **(s^{-1})**
1	d_6-DMSO	48.9	45.0	6.6×10^{-6}	7.7×10^{-7}
2	CD_3CN	37.9	46.0	1.1×10^{-6}	2.0×10^{-7}
3	Acetone-d_6	20.5	42.2	5.5×10^{-7}	1.6×10^{-7}
4	CD_2Cl_2	8.9	41.1	3.0×10^{-7}	2.7×10^{-7}
5	$CDCl_3$	4.7	39.1	4.3×10^{-7}	4.1×10^{-7}
6	Toluene-d_8	2.38	33.9	3.0×10^{-8}	2.6×10^{-7}

Table 14: Solvent effect in IMDAF [67]



Entry	Solvent	Yield (%)	Entry	Solvent	Yield (%)
1	Water/ethanol (5:2)	93	**6**	Ethanol	68
2	Ethylene glycol	89	**7**	1,2-dichloroethane	51
3	Neat	75	**8**	Diisopropyl ether	45
4	Methylcyclohexane	68	**9**	Acetonitrile	45
5	Benzene	63	**10**	Water	45

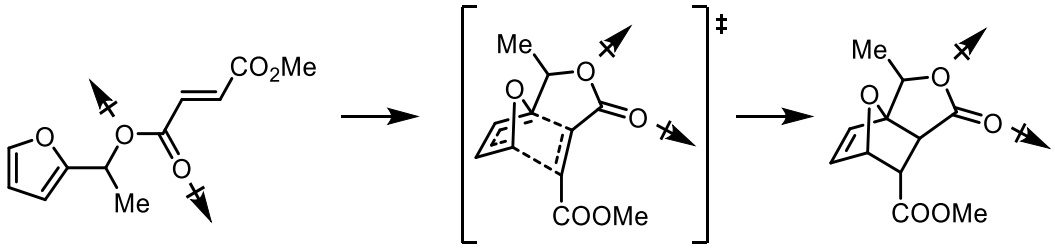


Figure 11: Change of dipole moment during cyclization of ester-tethered furans

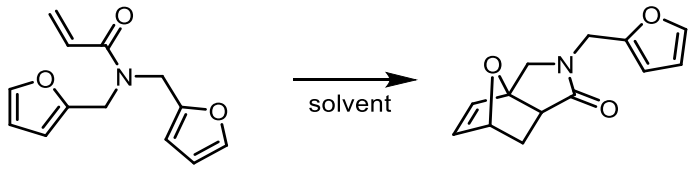
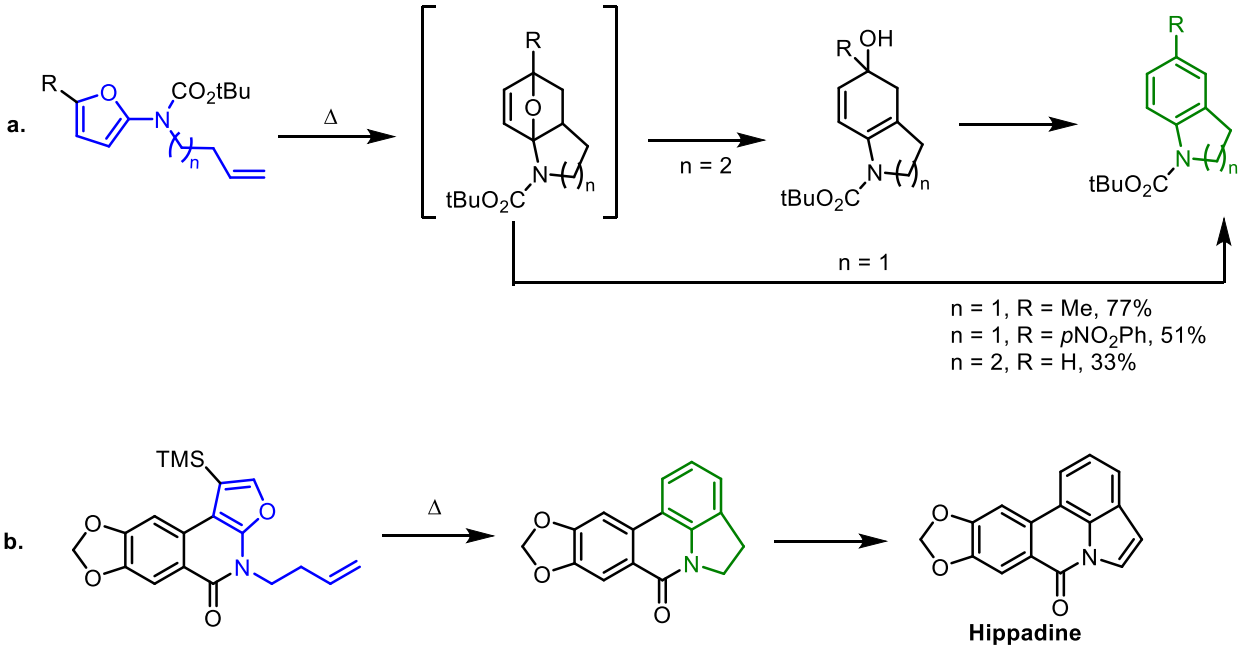


Figure 12: cycloaddition of amide-tethered furan

1.1.5.4 Applications in total synthesis

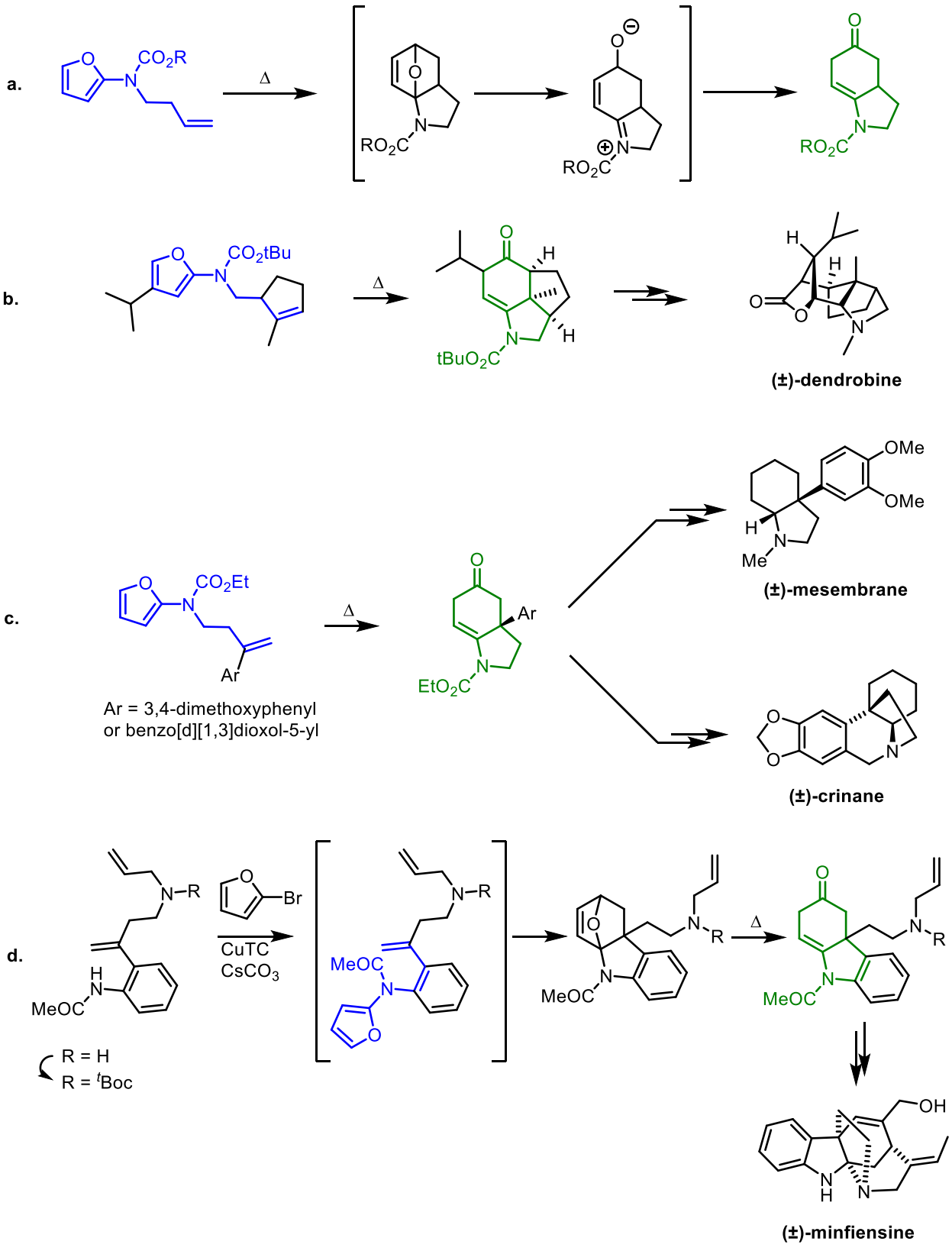
Oxanorbornene systems are valuable synthetic intermediates that can easily provide a range of derivatives by manipulation of the olefin functionality, the tether or the bridged C-O bond. Consequently, IMDAF reactions have been used as key step in many syntheses of drugs and natural products.[68] The Padwa group have made a significant contribution to the total synthesis of alkaloids employing IMDAF reaction. 2-substituted amidofurans

were used to prepare alkaloids containing indoline and tetrahydroquinoline rings, which show a broad range of biological activities.[69] An initial IMDAF reaction, followed by ring-opening and dehydration provided the desired compounds in variable yields depending on the substituents present (Scheme 9a). The reactions sequence was applied to the synthesis of pyrrolophenanthridone alkaloid Hippadine (Scheme 9b).



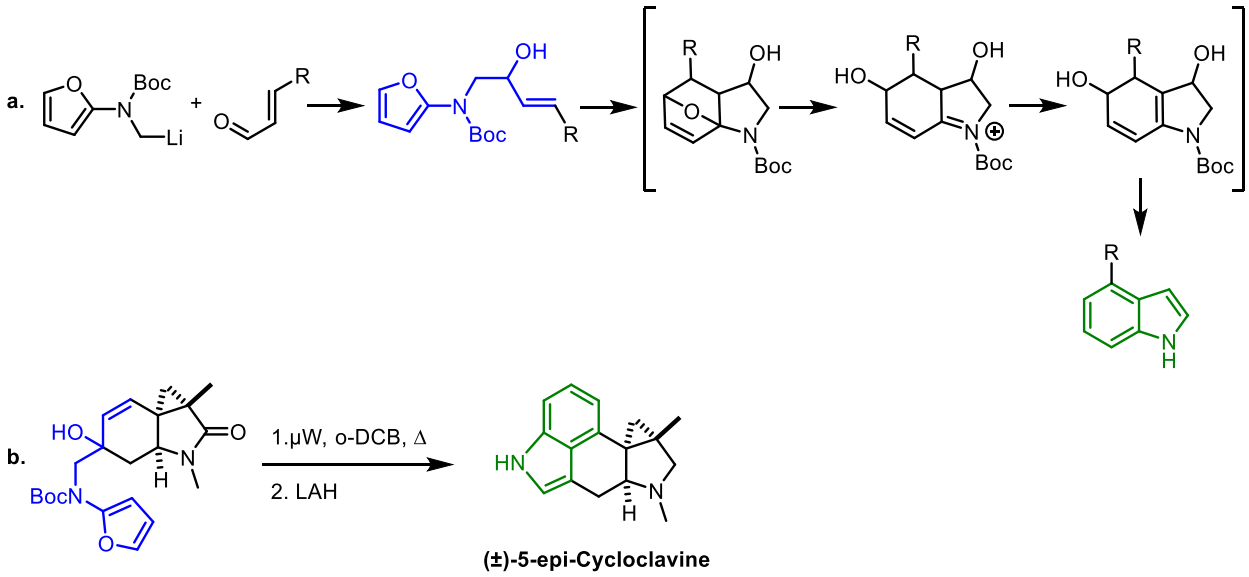
Scheme 9: IMDAF based strategy for the synthesis of indoline and tetrahydroquinoline rings (a), applied to the synthesis of alkaloid Hippadine (b).

An IMDAF-nitrogen-assisted ring opening cascade of amido- or imidofurans was used to generate tetra- and hexahydroindolinones (Scheme 10a),[69] intermediates in the synthesis of alkaloids like (±)-crinane, (±)-mesembrane,[70] (±)-dendrobine[71] and (±)-minfiensine[72] (Scheme 10b-d).



Scheme 10: IMDAF approach in total synthesis of alkaloids

Wipf developed a method to obtain 4-mono- and 3,4-disubstituted indoles by reaction of α-lithiated amidofurans and α,β-unsaturated carbonyl compounds, *in-situ* IMDAF reaction, ring-opening and aromatisation[73] (Scheme 11a). The methodology was used as the last stage in the synthesis of alkaloid 5-*epi*-cycloclavine (Scheme 11b).[74]



Scheme 11 Application of IMDAF strategy to the synthesis of 5-epi-cycloclavine

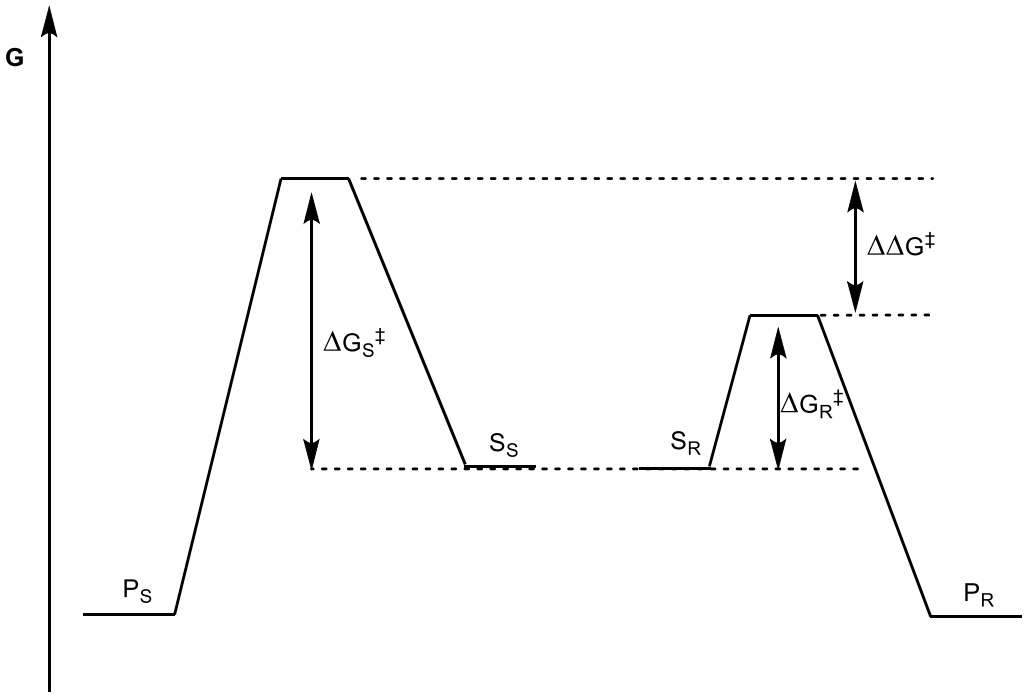
1.2 Kinetic Resolution

1.2.1 Standard kinetic resolution

Kinetic resolution is an effective method to obtain enantiomerically enriched compounds from a racemate. It is based on the different reaction rates of the two enantiomers of a racemic mixture when in the presence of an enantiomerically pure chiral reagent or catalyst. In its standard version, ideally only one substrate enantiomer is completely converted to an enantiomerically pure product (if chiral), while the other is recovered unreacted. (Figure 14). The maximum theoretical yield allowed in this process is 50%. The optical purity of the unreacted substrate is a function of the conversion and it reaches its maximum theoretical value when half of the racemic substrate is transformed. Beyond 50% conversion, reaction of the less reactive enantiomer will lower the optical purity of the product. A requirement for KR is that the reaction rate of one of the enantiomers is much greater than the other ($k_S \gg k_R$ or $k_R \gg k_S$). The parameter used to indicate the relative reaction rate of a racemic

substrate is the relative constant (k_{rel}) or selectivity factor (s) (eq. 1), and it derives from the difference in activation energies of the two diastereomeric transition states (Figure 13).

$$s = k_{rel} = k_{fast}/k_{slow} = e^{\Delta\Delta G^{\ddagger}/RT} \qquad \text{Eq. 1}$$



$P_{S/R}$ = S and R enantiomer of the product, $S_{S/R}$ = S and R enantiomer of the substrate, $\Delta G^{\ddagger}_{S/R}$= free energy of the reaction relative to enantioers S or R, $\Delta\Delta G^{\ddagger}$ = Difference of activation energies for the two enantiomeric transition states

Figure 13: Potential energy diagram of a kinetic resolution process

In most real KR, k_{rel} is not big enough to give perfect selectivity. Besides, approaching 50% conversion, the relative concentration of the less reactive enantiomer increases, and with it, also its relative reaction rate. To prevent degradation of optical purity of the starting material, conversion must be pushed enough to consume all the more reactive enantiomer. Lower selectivity factors require higher conversions at the expense of the yield. For example, even with s = 10, the starting material can still be recovered in 99% ee if the racemic mixture reaches 72% conversion.[75] The optical purity of the product on the other hand, depends on the selectivity and decreases further with higher degree of conversion.

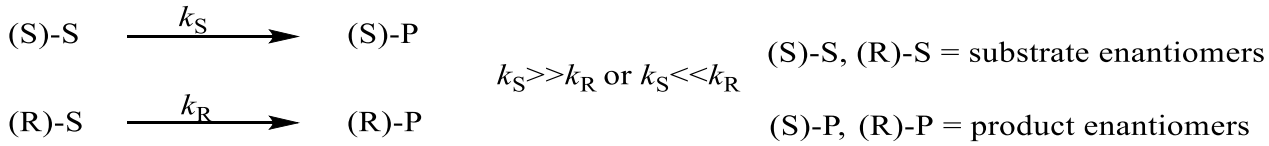
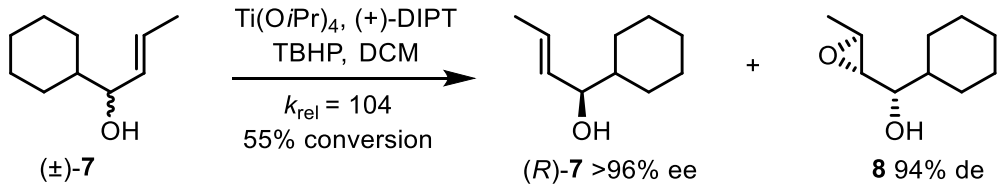


Figure 14: Standard kinetic resolution

A very well-known example of Kinetic resolution is the resolution of chiral secondary allylic alcohols by asymmetric epoxidation described by Sharpless.[76-77] Racemic mixtures of allylic alcohols, in presence of the titanium alkoxide tartrate catalyst system, show high k_{rel} values, that increase with the size of R group of the tartrate ester $Ti(OR)_4$. In Scheme 12 is the kinetic resolution of (*E*)-cyclohexylbutenol **7** by asymmetric epoxidation. (*S*)-**7** reacts much faster (k_{rel} = 104) to give epoxide **8**, and (*R*)-**7** is recovered unreacted in >96% ee.



Scheme 12: KR by Sharpless epoxidation

1.2.2 Dynamic kinetic resolution

The limit of 50% yield in standard kinetic resolution is overcome in the dynamic kinetic resolution (DKR), thanks to racemization of the unreacted enantiomer that can provide up to 100% yield of enantiomerically pure product (Figure 15). The conditions to obtain DKR are: fast racemization of the substrate (faster than the rate constant of the resolution step), k_{rel} >20, an irreversible resolution step and no racemisation of the desired product.

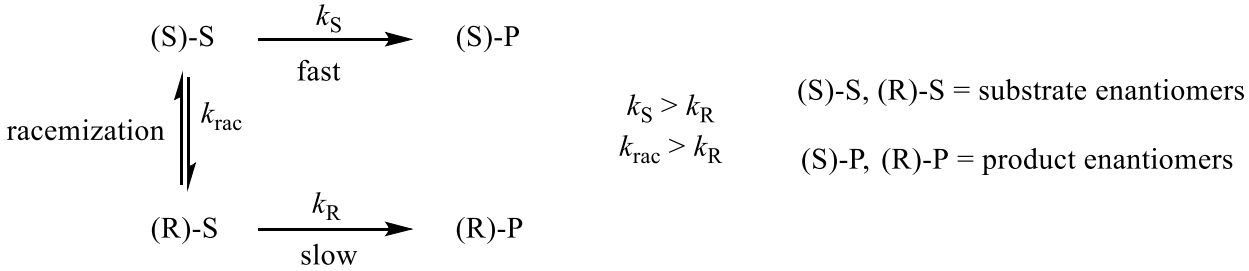
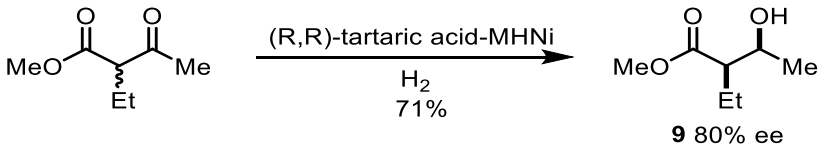


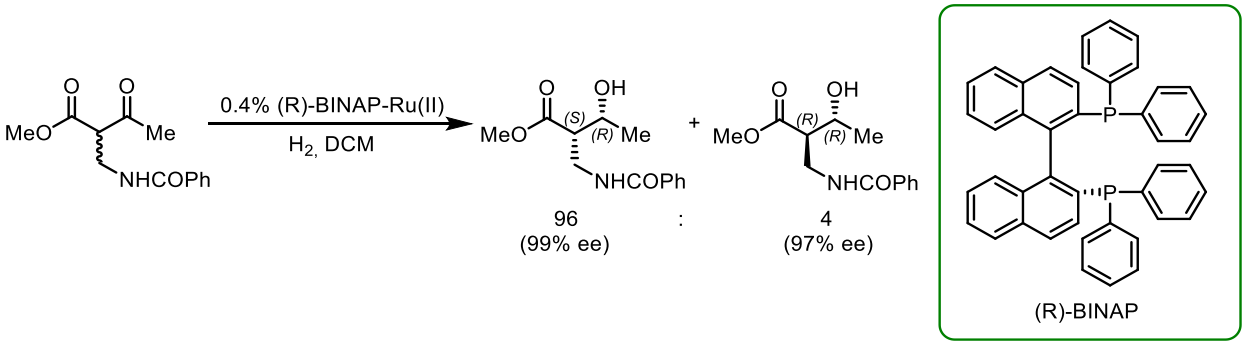
Figure 15: Dynamic kinetic resolution

The first DKR was reported by Tai in 1979.[78] Reducing methyl 2-ethyl-3-oxobutanoate in presence of (*R,R*)-Tartaric acid and a Nickel catalyst, they observed formation of product **9** with unusually high ee which can only be explained by fast interconversion of the SM enantiomers (Scheme 13).



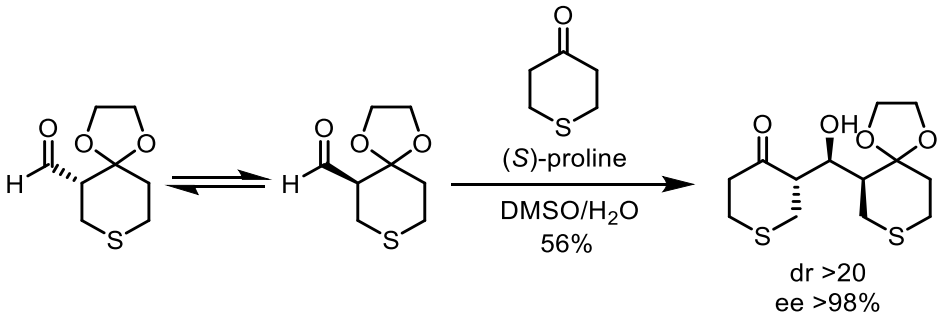
Scheme 13: DKR in β-keto ester reduction

The same reaction was also studied by Noyori, who used his BINAP-Ru(II) complex to obtain a ruthenium-catalysed DKR. In Scheme 14 is one of the many examples of DKR performed by Noyori using asymmetric hydrogenation as resolving reaction.[79] The chemical outcome is due to the interaction of the ester function of the substrate with the metal of the ruthenium-BINAP complex in a way to minimize the interaction with the phosphine phenyl groups, leaving only one side of the keto ester exposed to attack.



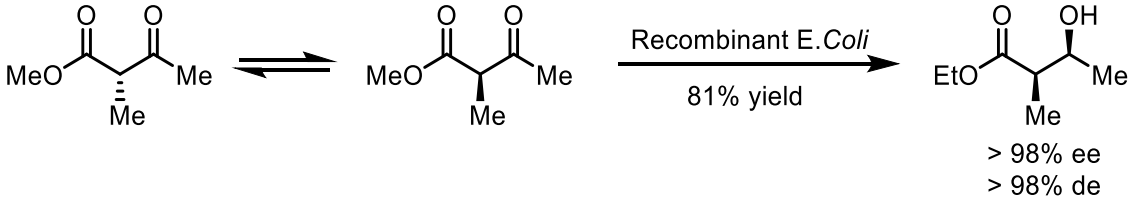
Scheme 14: Noyori asymmetric hydrogenation

A more environmentally friendly option is the organocatalysed DKR. Natural compounds such as *Cinchona* alkaloids or amino acids are now becoming a popular choice as catalyst.[80-81] In Scheme 15 is an example of DKR process which involves a *L*-proline catalysed Aldol reaction.[82-83]



Scheme 15: DKR with organocatalysed Aldol reaction

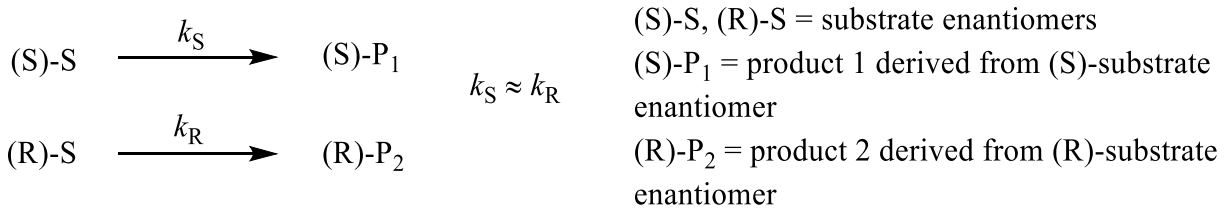
Resolution of racemic mixtures are also possible by biocatalytic DKR. In Scheme 16 is the asymmetric reduction of a α-substituted β-keto ester by reductase enzymes expressed in recombinant *E. coli*.[84]



Scheme 16: Enzymatic DKR

1.2.3 Parallel kinetic resolution and divergent reactions on a racemic mixture

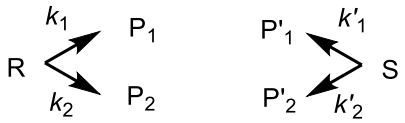
A third and more unusual type of resolution is the parallel kinetic resolution (PKR).[85-86] A pair of enantiomers can in some cases react at a comparable rate but generate two different products. Unlike what happens with standard and dynamic kinetic resolutions, the different reactivity towards a chiral reagent or catalyst transforms the enantiomers of the starting material into non-enantiomeric products (Scheme 17).



Scheme 17: Parallel kinetic resolution

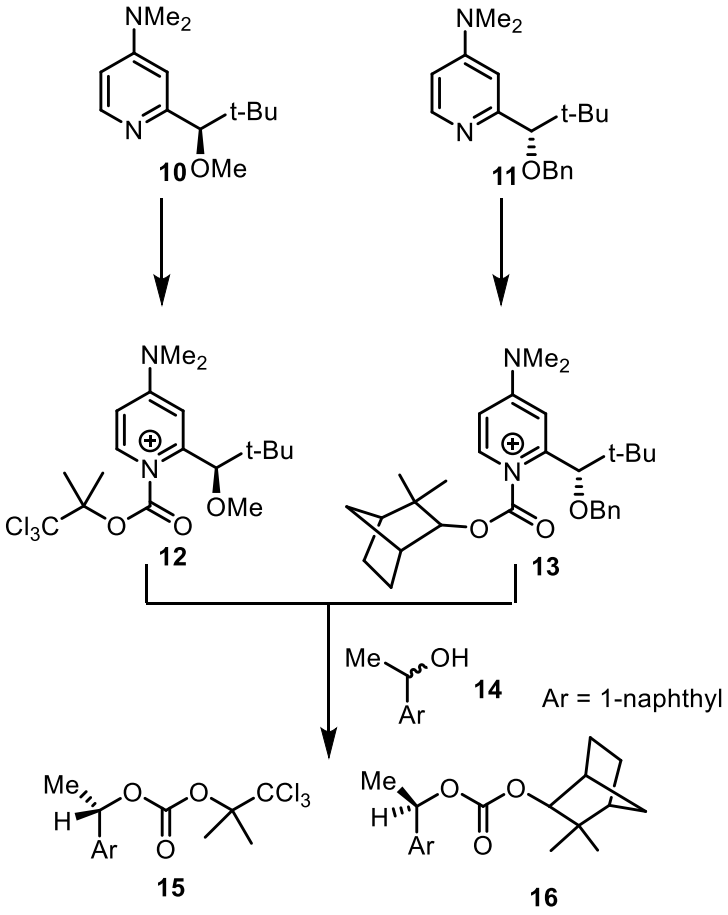
The simultaneous reaction of the substrate enantiomers avoids the problem of optical purity degradation found in standard kinetic resolution due to increasing relative concentration of the less reactive enantiomer with the evolution of the reaction. The starting material enantiomers have a similar reaction rate and consequently are always present in very similar concentration. The maximum yield is still 50% for each product of the reaction but high ee are accessible even with low selectivity factors. For example, to obtain a product in 50% yield and 96% ee with standard kinetic resolution, k_{rel} = 200 is necessary. The same result requires k_{rel} = 49 in PKR (each product isolated in 49% yield).[85] To have a good PKR, the reactions involved must produce two different and easily separable products with complementary enantioselectivity and similar rate. The process can be classified as chemo-, regio- or stereodivergent. In the first case the two enantiomers produce two entirely different compounds, in the second and third case constitutional isomers and diastereomers are generated respectively.

The term parallel kinetic resolution was coined by Vedejs and Chen in 1997.[87] More recently, Kagan suggested tthe use of the term kinetic resolution only when one enantiomer reacts faster than the other (k_1+k_2> k'_1+k'_2) (Scheme 18). If enantiomer *R* produces mostly product P_1 and enantiomer *S* produces mostly product P'_2, we can deduce that k_1>>k_2 and k'_2>>k'_1, but k_1 and k'_2 are not necessarily different. For this type of reactions, Kagan suggested the name "divergent reactions on a racemic mixture".[88] In this context, we are going to describe as parallel kinetic resolution every process in which an enantiomeric mixture reacts to form two non-enantiomeric products.



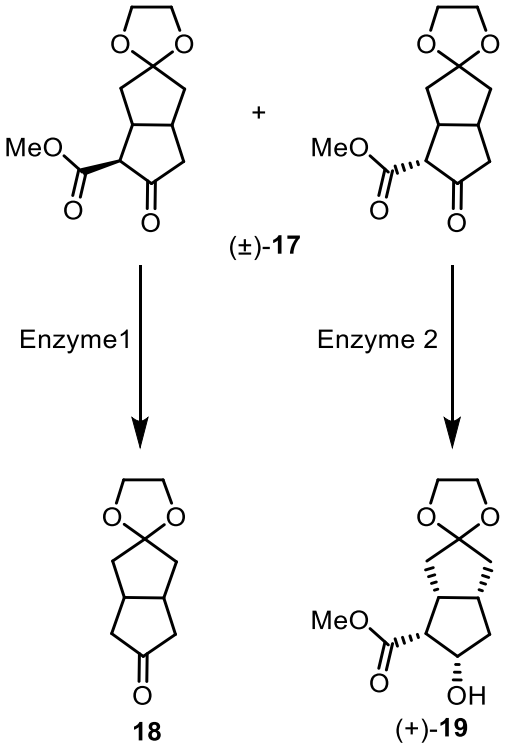
Scheme 18 Divergent reactions on a racemic mixture

In Vedejs' experiment,[87] resolution of racemic 1-(1-naphthyl)ethanol **14** was achieved by reaction with DMAP derived salts **12** and **13**, prepared from quasienantiomers **10** and **11** to ensure similar reaction rate and complementary stereoselectivity. Selectivity was calculated to be **s** = 42. Enantiomer (*S*)-**14** reacts selectively with **12** to give trichloro-*tert*-butyl carbonate **15** in 88% ee and 46% yield. (*R*)-**14** reacted with **13** yielding fenchyl carbonate **16** in 95% ee and 49% yield. This last result agrees with an ideal PKR process with s = 41-42 but it would require s > 125 in a standard KR process for the same level of enantioselectivity.



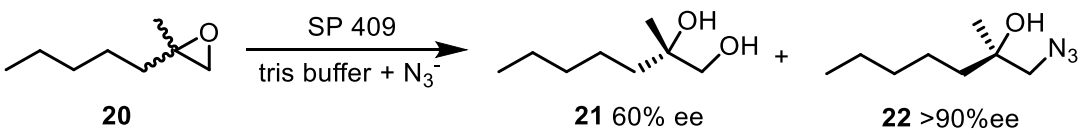
Scheme 19: PKR using quasienantiomers

Even though the PKR process was defined for the first time by Vedejs, examples of this type of resolution can be found before 1997.[89-96] One of the first examples reported was the simultaneous transformation of keto ester (±)-**17** into **18** and (+)-**19** by Baker's yeast (Scheme 20).[89] One enzyme promotes the enantioselective reduction of 1*R*,5*S*-**17**, while 1*S*,5*R*-**17** is hydrolysed by a second enzyme type and then decarboxylated to afford ketone **18**.



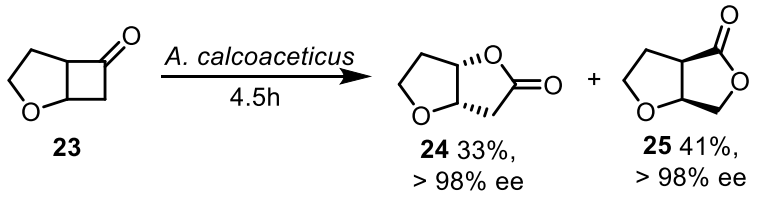
Scheme 20: Enzyme-catalysed PKR

Another example of biocatalytic chemodivergent process was described by Mischitz and Faber in 1994.[93] They found that, in the presence of enzyme preparation SP 409, racemic epoxide **20** reacted to form diol **21** in modest yield and enantiomeric excess, but if nucleophile N_3^- was added to the solution, a second product, azido alcohol **22**, was formed at the same time, considerably improving the ee. They noted that the product had opposite configuration at the chiral centre and analysis of enantiomeric purity of the starting material and the two products during the reaction, led them to the conclusion that the products derived from two independent and simultaneous enantiodivergent enzyme-catalysed processes.



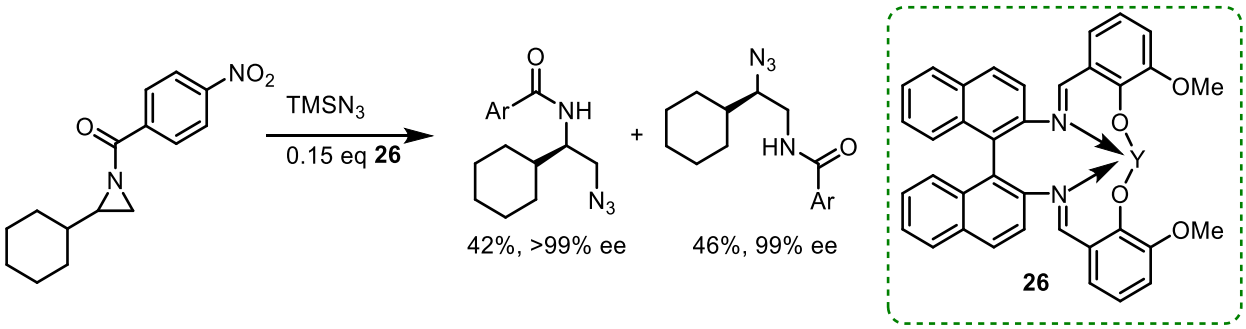
Scheme 21: PKR of substituted epoxides

The second type of PKR is the regiodivergent. Furstoss *at al*. described the first example of regiodivergent PKR by enzymatic Baeyer-Villiger of bicyclic ketones, which provides regioisomeric lactones in high optical purity.[90-91] An example is in Scheme 22. The enantiomer of **23** with *S* configuration at the tertiary carbon α- to the carbonyl formed the expected Baeyer-Villiger product **24**, and its enantiomer formed the unexpected regioisomer **25**.



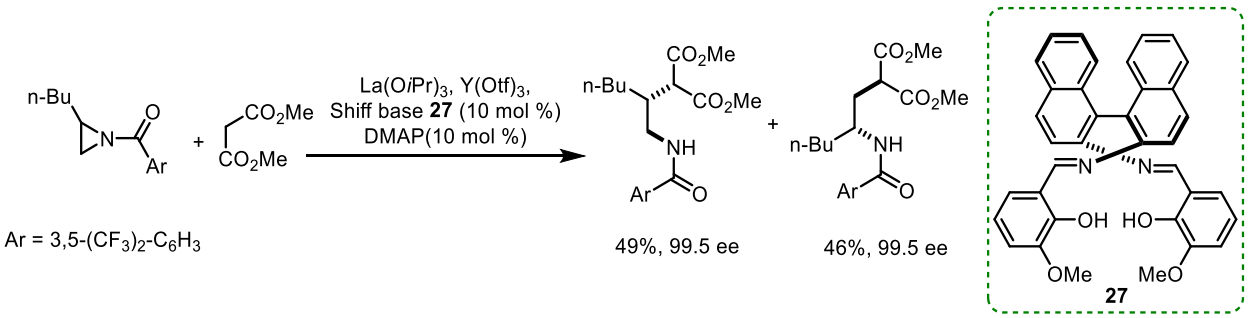
Scheme 22: Regiodivergent PKR

A regiodivergent kinetic resolution strategy was also used in the catalytic resolution of racemic mono- and disubstituted aziridines by ring-opening reaction.[97-98] Parquette and RajanBabu demonstrated that a dimeric yttrium-salen complex **26** can discriminate between the two enantiomers of racemic aziridines inducing complementary enantio-dependent regioselectivity (Scheme 23). It was hypothesised that the complementary selectivity is due to the different orientation of the enantiomers bound to the catalyst, leaving them each with a different carbon exposed for attack.[97]



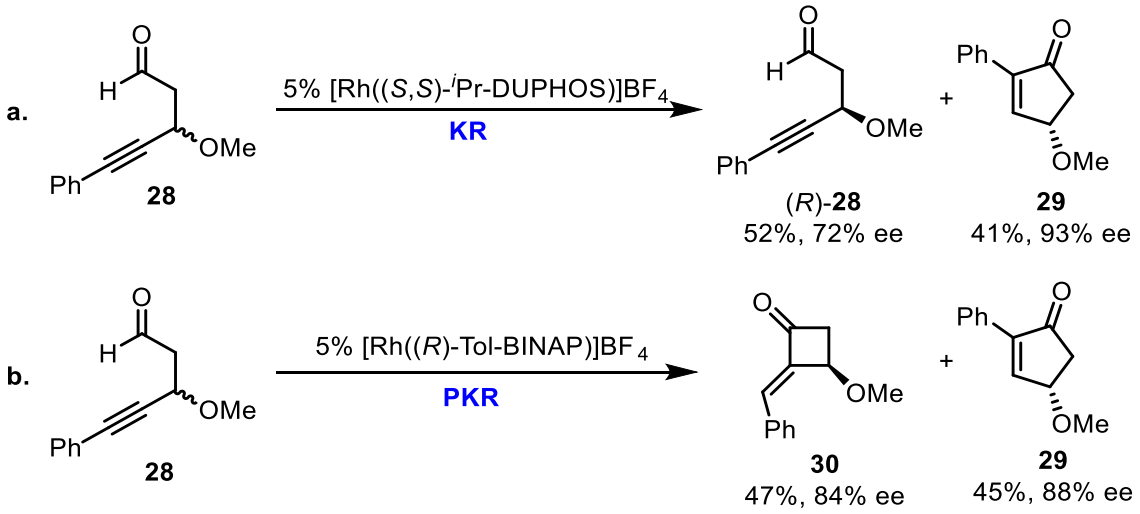
Scheme 23: Regiodivergent kinetic resolution of aziridine

Shibasaki, Matsunaga *et al*. expanded the scope of the convergent kinetic resolution of aziridines with malonates, using an equimolar amount of a Brønsted acid, Lewis acid and Schiff base (Scheme 24).



Scheme 24: Regioconvergent kinetic resolution of aziridines

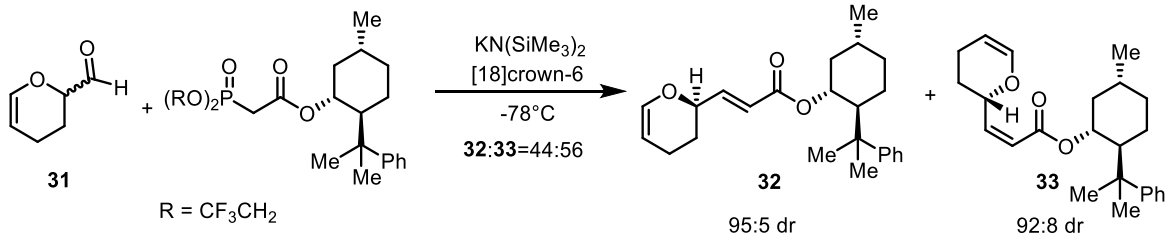
In the case of metal-ligand complex-catalysed reactions, the role of the ligand can be very important for the success of the PKR process.[99-100] There are examples of reactions where both standard KR or PKR are possible depending on the ligand choice. Cyclisation of **28** with Rh(I)/((*S*,*S*)-*i*-Pr-DUPHOS) yielded product **29** in 41% yield and 93% ee from starting material (*S*)-**28**, while enantiomerically enriched (*R*)-**28** was recovered via KR process, (Scheme 25a). With Rh(I)/((*R*)-Tol-BINAP), (*R*)-**28** forms cyclobutanone **30** via PKR process (Scheme 25b).[99]



Scheme 25: KR vs PKR: effect of ligands in cyclisation of alkynes

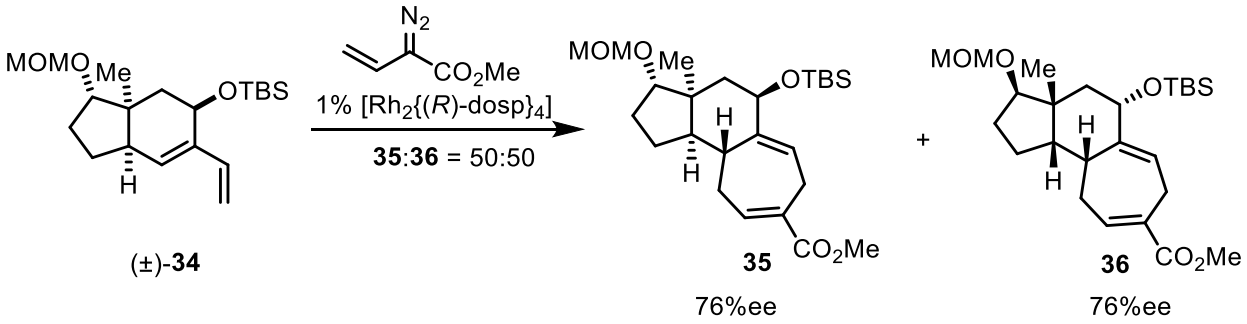
Reaction of pure (*R*)-**27** with [Rh((*R*)-Tol-BINAP)]BF_4 and [Rh((*S*)-Tol-BINAP)]BF_4 gives almost exclusively **29** and **30** respectively, suggesting that a matched or mismatched interaction of the catalyst with the substrate determines the regiochemical outcome of the reaction.

The third type of PKR is the stereodivergent resolution: a racemic mixture of starting material generates diastereomeric products. This can be the result of the formation of geometric isomers deriving from opposite enantiomers of the starting material. Condensation of racemic Diels-Alder product of acrolein **31** with a chiral phosphonate formed geometric isomers **32** and **33**. Mosher ester analysis shows that (*E*)-isomer **33** and (*Z*)-isomer **34** derive from the two opposite enantiomers of the starting material (Scheme 26).[101]



Scheme 26 Stereodivergent resolution of 31

Sarpong *et al.* used a stereodivergent strategy to generate diastereomers **35** and **36**, that they identified as useful scaffolds to potentially employ in total synthesis of cyathane and cyanthiwigin diterpenes (Scheme 27).[102] Cyclopropanation of racemic diene **34** by Davies' dirhodium tetraprolinate catalysis, followed by stereospecific divinylcyclopropane rearrangement yielded products **35** and **36**.

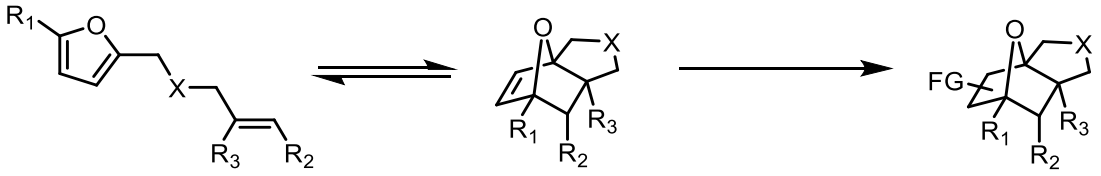


Scheme 27: Stereodivergent resolution as potential key step in the total synthesis of diterpenes

CHAPTER 2: RESULTS AND DISCUSSION

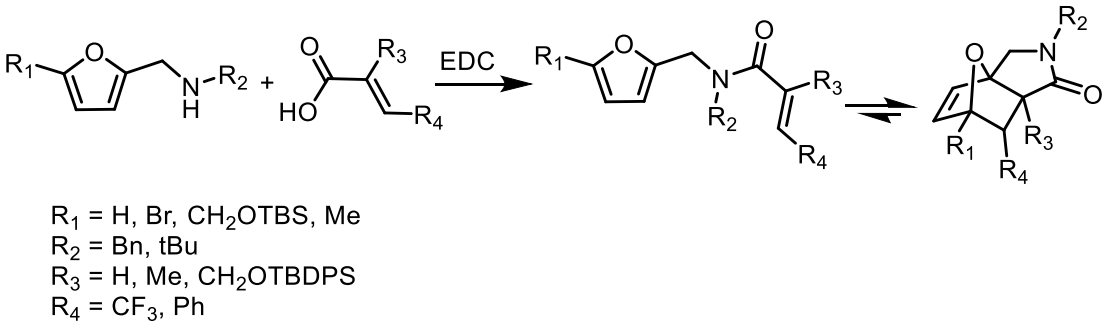
2.1 AIM OF THE PROJECT

IMDAF reactions often show reversible kinetics that lead to the formation of mixtures of starting material (SM) and cycloadducts in variable ratios. Application of a catalytic asymmetric IMDAF cycloaddition to generate optically pure cycloadducts is limited by the known propensity towards retro-cyclisation. The factors that influence the SM:cycloadduct equilibrium and how to displace it were investigated by coupling the cycloaddition with a chemoselective irreversible reaction based on the different electronic nature of the double bonds of cycloadduct and acyclic precursor (Scheme 28). Removal of the cycloadduct from the equilibrating mixture results in equilibrium displacement in favour of the more reactive species, and removal of the cycloadduct olefin precludes retro-cycloaddition. The possibility to use chiral reagents or catalysts to discriminate between the enantiomers starting material was envisaged. A systematic investigation of asymmetric olefin transformations using electrophilic reagents was carried out. The reaction chosen for this purpose are: epoxidation, dihydroxylation, hydroboration, hydrogenation and reductive Heck. Catalytic asymmetric version of some of the reactions were also investigated. Other reactions that could potentially be employed were identified: cyclopropanation, ring opening cross-metathesis, hydroformylation and hydroamination.



Scheme 29: General scheme for Diels-Alder cyclisation and subsequent functionalisation

Knowing that the structure of substrate, solvents and presence of Lewis acid can influence the rate of forward and reverse Diels-Alder reaction, the investigation commence by preparing a number of substrates with different characteristics (electronic and structural). The work mainly focused on amide-tethered structures, as they often cyclise even when in presence of substituents that deactivate the substrate towards the DA reaction (Scheme 30).

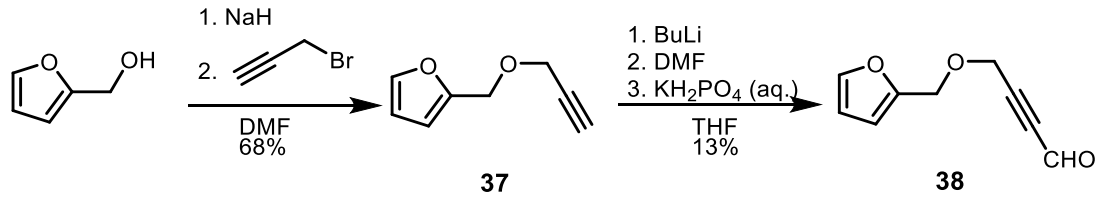


Scheme 30: General route to synthesize cycloadducts

2.2 Synthesis of Acyclic Substrates and Cycloaddition Reactions

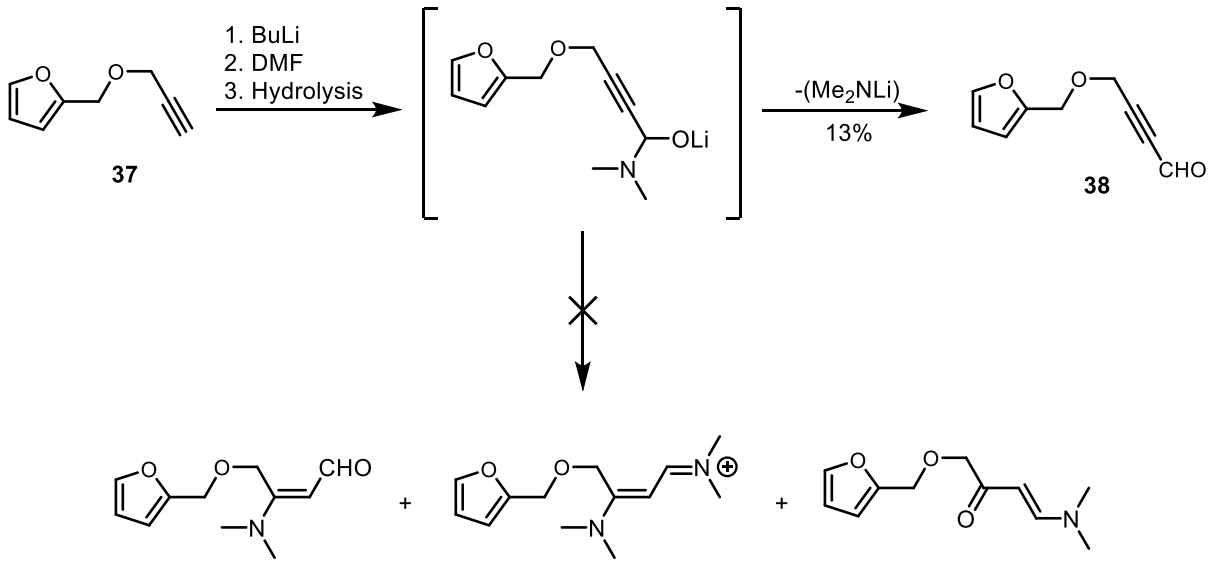
2.2.1 2-[(Prop-2-yn-1-yloxy)methyl]furan 38

Alkynes have been successfully employed in thermal IMDAF reactions as dienophile.[103-104] α,β-acetylenic aldehyde **38** was prepared in two steps from furfuryl alcohol. Following a literature procedure[105], furfuryl alcohol was transformed into terminal alkyne **37** by reaction with propargyl bromide. Formylation of **37** gave the desired product **38** in 13% yield (Scheme 31).



Scheme 31: Synthesis of substrate 38

Formylation of terminal alkynes with DMF is the shortest way to obtain α,β-acetylenic aldehydes. Reaction of an alkyne with ^{n}BuLi generates lithium acetylide, which readily reacts with DMF. The critical part of the process is the hydrolysis, where side reactions may occur. Journett *et al.* identified three by-products, derived from conjugated addition of dimethylamine.[106] Their formation depends on the hydrolysis conditions and can be avoided by using a phosphate buffer (Scheme 32).

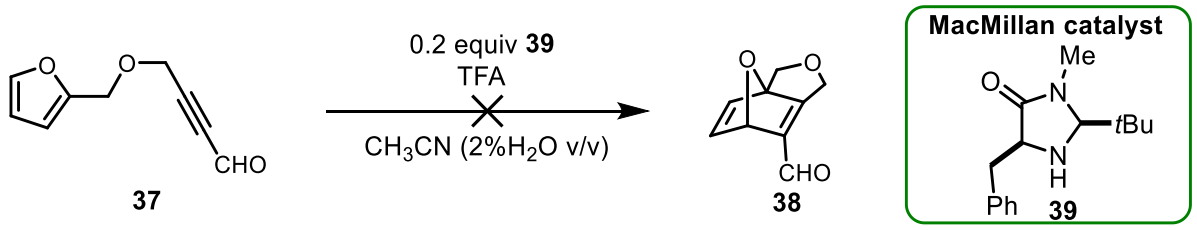


Byproducts derived from conjugated addition of the dimethylamine.
Their generation depends on the hydrolysis conditions

Scheme 32 Formylation of terminal alkyne

The low yield of the reaction is not due to the hydrolysis conditions (no side-products derived from conjugated addition were observed) but to low conversion (~25%) and instability of the product. Isolation of the product has proved to be difficult, as **38** is unstable in silica gel and alumina, and is stable only for a short time at room temperature

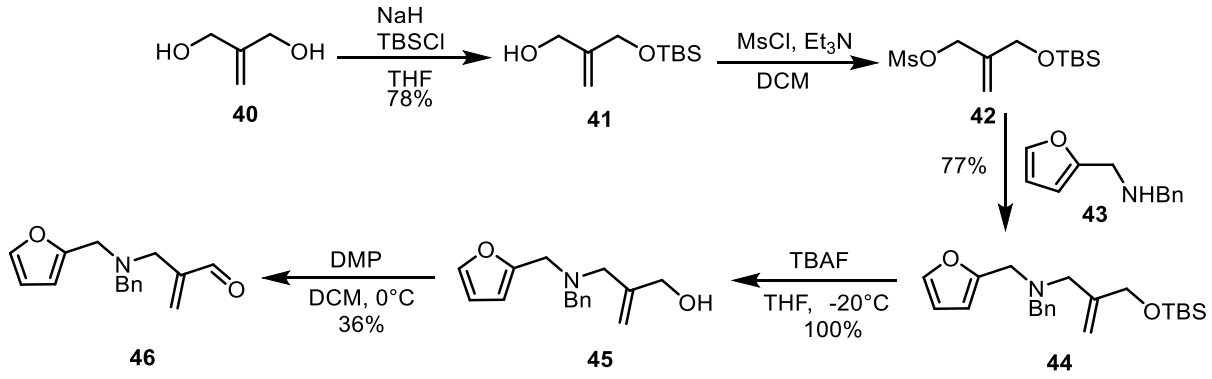
Substrate **38** did not produce any cycloadduct at room temperature and it was not possible to heat because of its instability at elevated temperature. Following the methodology developed by MacMillan *et al.*, Diels-Alder cycloaddition was attempted with substrate **38** in presence of 0.2 equiv. of imidazolidinone **39** and TFA as co-catalyst at -20 °C in the hope that acceleration of the cyclisation by the catalyst would yield cycloadduct faster than the rate of decomposition.[31] After 1 h, the substrate was completely decomposed into unidentifiable products and no cycloadduct was observed (Scheme 33).



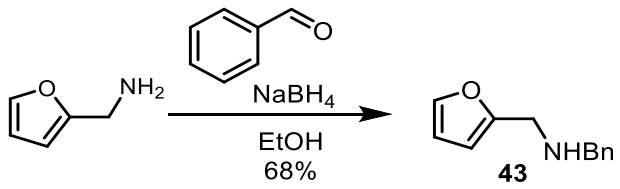
Scheme 33: Attempted catalytic Diels-Alder with substrate 38

2.2.2 4-(Furan-2-ylmethoxy)but-2-ynal 46

Synthesis of tertiary amine **46** (Scheme 34) started with monoprotection of diol **40** with TBS chloride following a known procedure.[107] Alcohol **41** was treated with mesyl chloride and triethylamine in DCM to obtain mesylate **42**. Purification of the product was not necessary and decreased the yield considerably: **42** was obtained in only 18% yield after column chromatography. Also transformation of mesylate **42** into the corresponding bromide by addition of lithium bromide, resulted in lower yields of **44** (34%-62%). Furfuryl benzyl amine **43** was prepared by reductive amination of furfurylamine and benzaldehyde (Scheme 35).[108] Tertiary amine **44** was obtained by neat reaction of secondary amine **43** and mesylate **42** in 77% yield. Deprotection of silyl ether **44** was quantitative and provided alcohol **45** which was then oxidized to **46** using DMP. DMP is well tolerated by substrates containing furan rings, and the hydroxyl functionality is oxidized to aldehyde leaving the furan moiety unchanged.[109] Performing the oxidation at 0°C, **46** was obtained in 36% yield, against the 25% conducting the reaction at -20 °C. Compound **46**, after 24 h at 50 °C did not show any cycloadduct **47**, confirming the expected low tendency of amines towards cycloaddition.

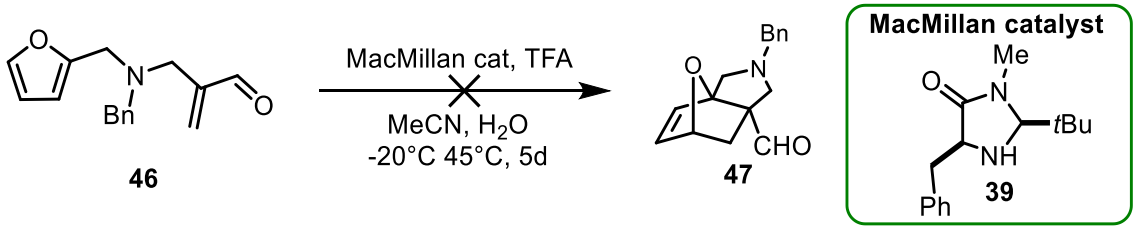


Scheme 34: Synthesis of substrate 46



Scheme 35: Reductive amination to synthesise furfurylamine 43

After treatment of substrate **46** with MacMillan catalyst in presence of TFA, it was not possible to isolate any cycloadduct (Scheme 36). Analysis of the reaction mixture by ^{1}H NMR indicated the presence of a new aldehyde but the compound was not isolated nor identified. After work-up of the reaction, the starting material **46** was the only compound seen. Increase in temperature from -20 °C to 45 °C did not have any effect on the reaction outcome.

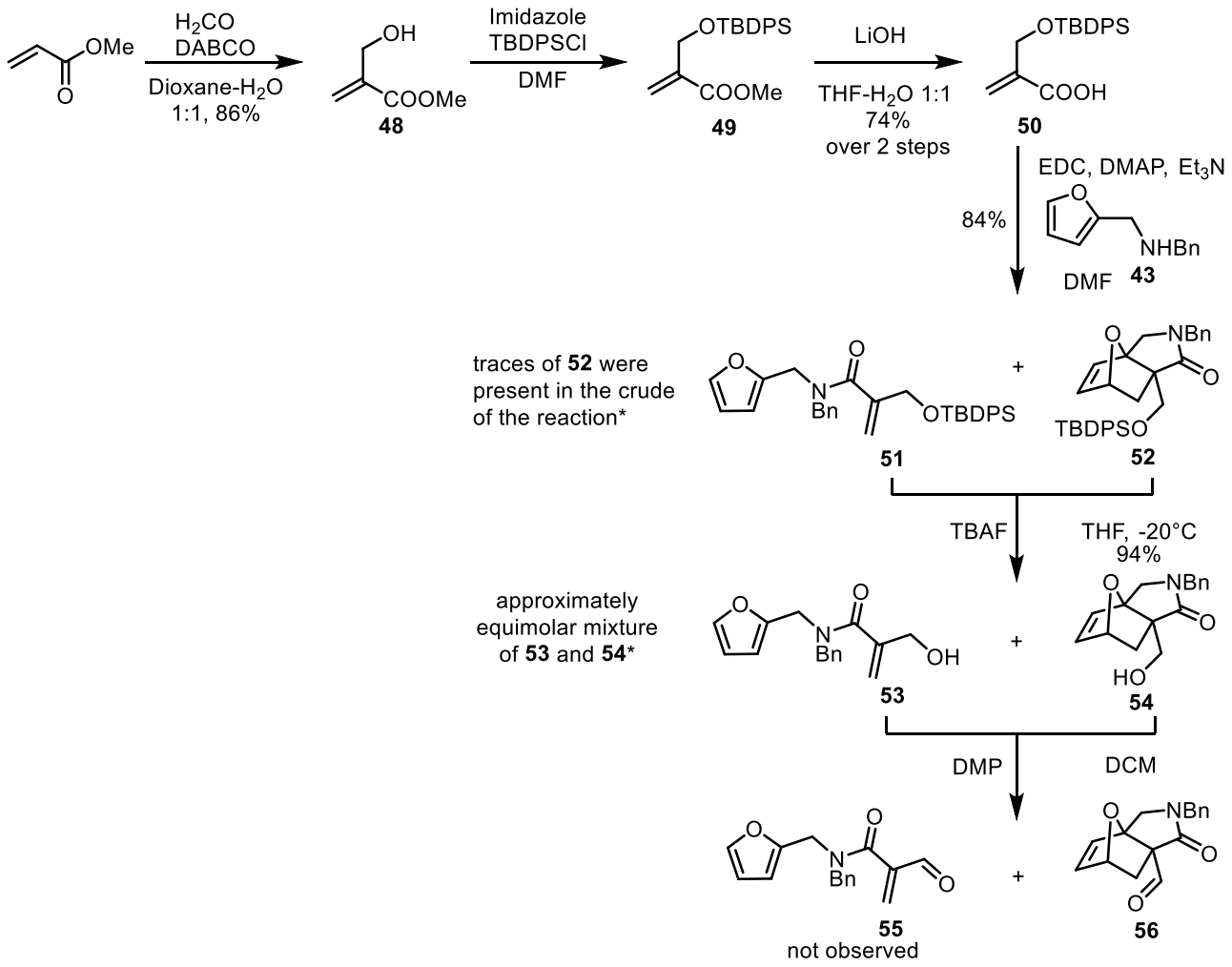


Scheme 36: Attempted Diels-Alder reaction with substrate 46

2.2.3 *N*-Benzyl furfurylamides 51, 53 and 55

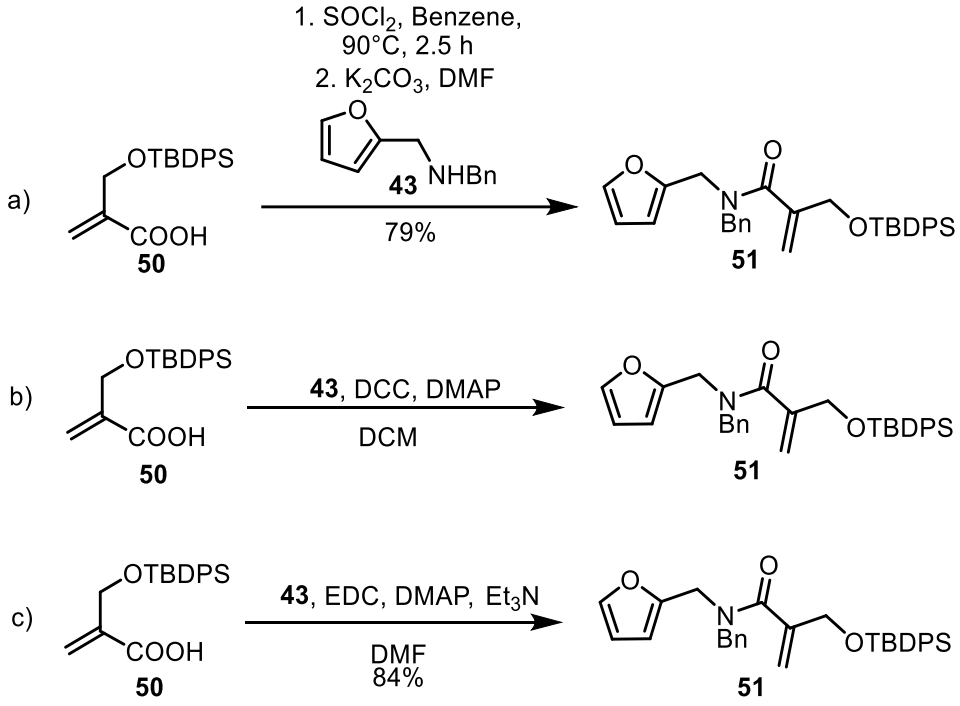
N-benzyl amides **51**, **53** and **55** were susceptible to cycloaddition and they were always obtained as mixtures of Diels-Alder starting material and cycloadduct. The ratio of the two species depends on the substituent on the dienophile and increases in the series **51** < **53** < **55**. The least reactive (R = CH_2OTBDPS) is still reactive enough to cyclize even at -20 °C, where it formed an equilibrating mixture **51**:**52** = 83:17. Isolation of pure silyl ether **51** or alcohol **53** was not possible, as the DA product started forming soon after the coupling reaction. Both inter and intra-molecular DA reactions are known to be accelerated by alumina or silica gel[44, 110-111]

The synthesis of amides **51**, **53**, **55** (Scheme 37) started from hydroxymethyl acrylate **48**, easily obtained from methyl acrylate through a Baylis-Hillman reaction.[112-114] The hydroxyl group was then protected by reaction with TBDPS chloride, necessary as less stable silyl ethers (such as the TBS analogue) proved to be unstable in the following hydrolysis and related work-up steps.



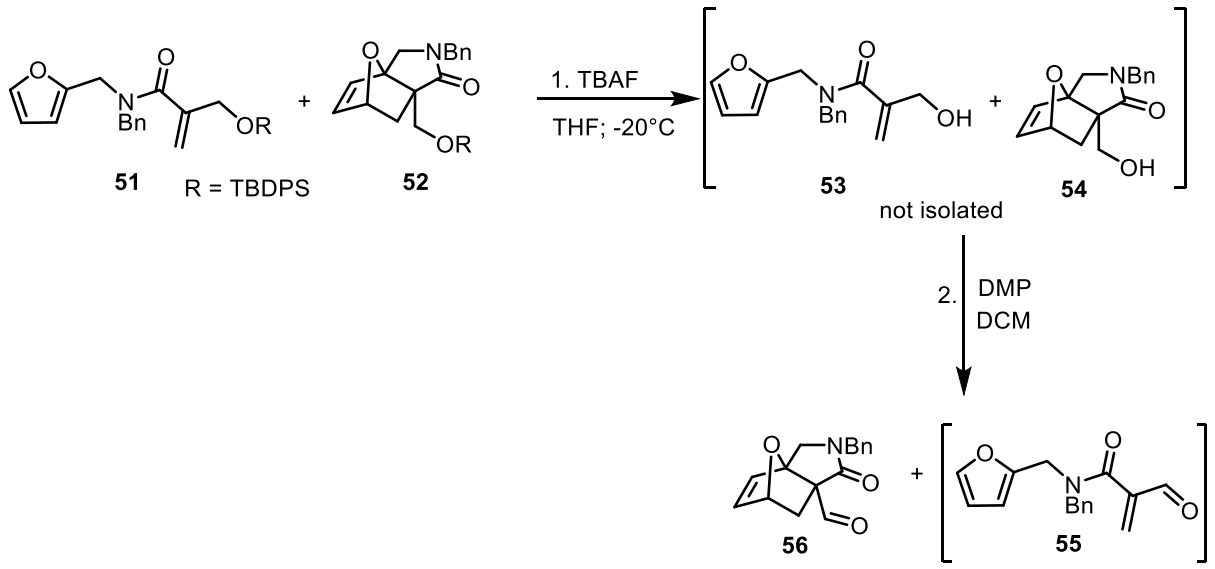
Scheme 37: Synthesis of substrates 51, 53 and 55. Composition of mixtures was determined by ^{1}H NMR

Synthesis of 2-furanyl amide **51** was realized with 3 different methods (Scheme 38): via acid chloride (a), via coupling with DCC (b) and via EDC hydrochloride coupling (c). With DCC (b), the purification process was complicated by the low solubility of the product, which did not allow a good separation from by-product dicyclohexylurea. Treating carboxylic acid **50** with thionyl chloride to generate the corresponding acid chloride, followed by reaction with amine **43** in presence of a base gave good results (b), but coupling with EDCI hydrochloride allowed generation of amide **51** in one step, and with a slightly better yield (84%) (c).



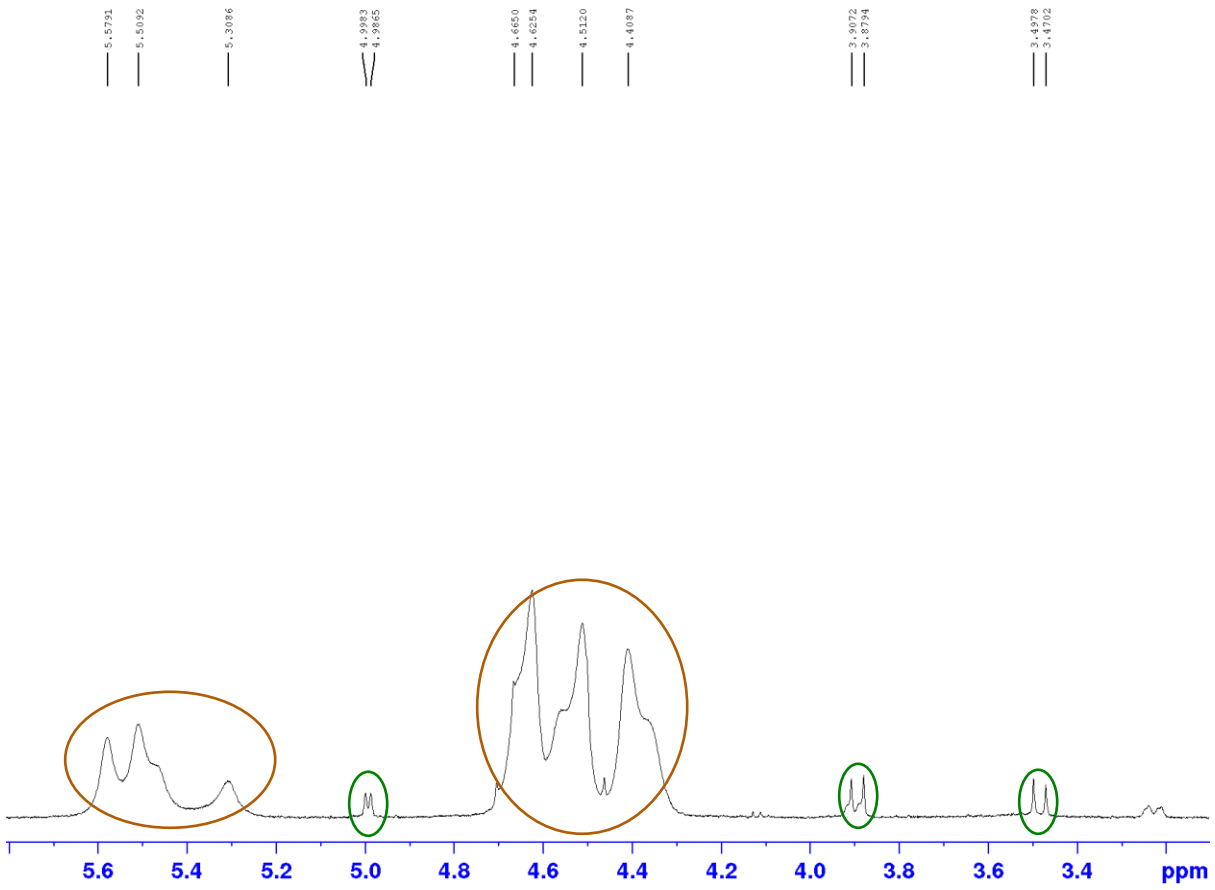
Scheme 38: Synthesis of furanyl amide 51

Because of the high reactivity towards cyclisation, deprotection and oxidation reactions to prepare final compound **55** were performed by deprotection and oxidation from crude product **51** without purification (Scheme 39). After DMP oxidation of alcohols **53** and **54**, the only product present was cycloadduct **56**. Aldehyde **56** was not stable during the conventional method of purification (column chromatography on silica gel or alumina) and it was not possible to calculate the yield of the reaction.



Scheme 39: Attempted synthesis of aldehyde 55 and cyclisation to 56

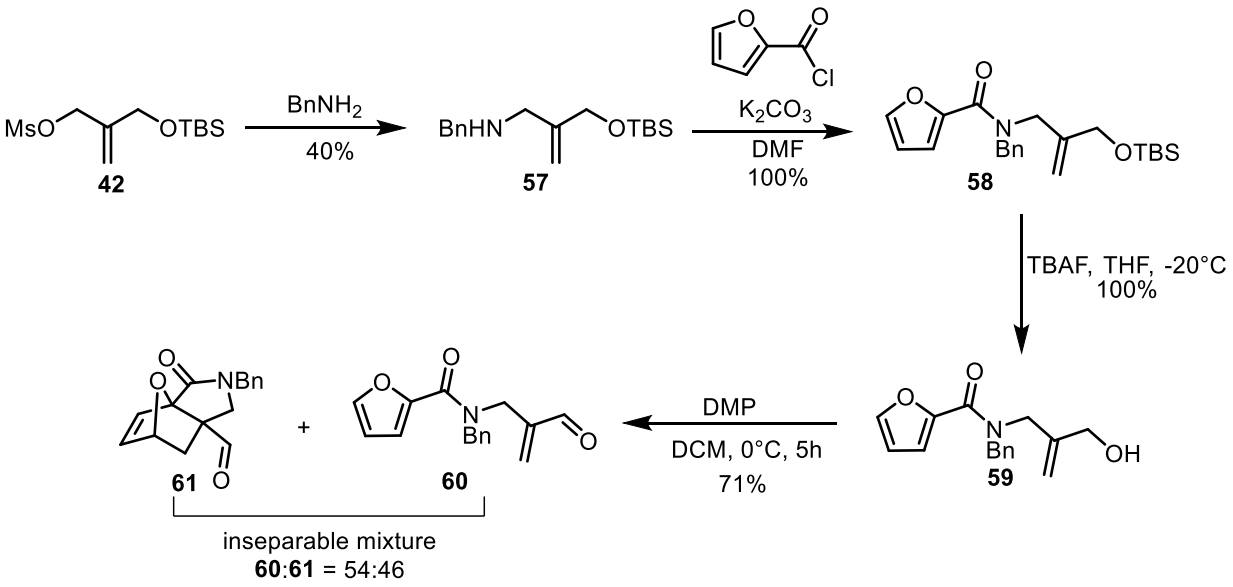
^{1}H NMR signals relative to amide precursors or DA products are easily recognisable, as the amides give broad signals poorly resolved (NMR 1, blue signals corresponding to compound **53**) whilst the cycloadducts produce sharp and well-resolved peaks (NMR 1, green signals corresponding to compound **54**).



NMR 1 Comparison between amide precursor (53) and cycloadduct (54) ^{1}H NMR

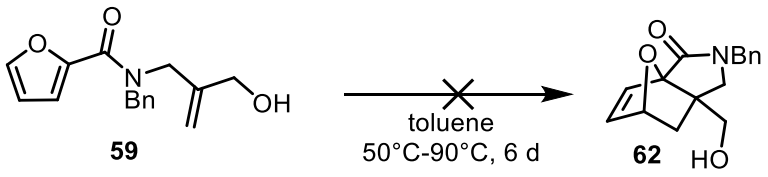
2.2.4 *N*-Benzyl-*N*-(2-formylallyl)furan-2-carboxamide 60

Consideration of the molecular orbitals involved in the Diels-Alder reaction suggests that substrates where an electron-withdrawing group is present in the diene moiety are less activated. Scheme 40 represents the route used to prepare compounds **58**-**60,** analogous to **51**-**55** but less activated because of the carbonyl of the amide group is next to the furan ring (diene).

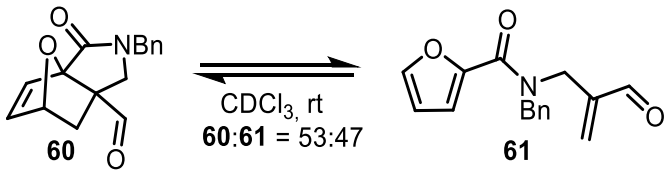


Scheme 40: Synthesis of substrate 60

In this case mesylate **42** reacted with a primary amine, and to reduce the possibility of multiple substitution, 10 equivalents of benzylamine were used. Secondary amine **57** was isolated in 40% yield after purification by column chromatography on silica gel. Reaction of amine **57** with furoyl chloride in presence of potassium carbonate gave amide **58** quantitatively. This compound, regioisomeric with **15**, is stable at room temperature and after several days no formation of DA product was observed. Alcohol **59**, obtained from deprotection of **58** with TBAF, was heated for several days without observing any DA reaction (Scheme 41). This change in reactivity is in line with a normal electron-demand Diels-Alder reaction. After oxidation of the alcohol, a mixture of aldehydes **60** and **61** was obtained. The ratio of the two species **60** and **61** in chloroform was monitored and was constant at 54:46 for several weeks (Scheme 42). After 6 months at rt and no solvent, the ratio **60**:**61** was unchanged.



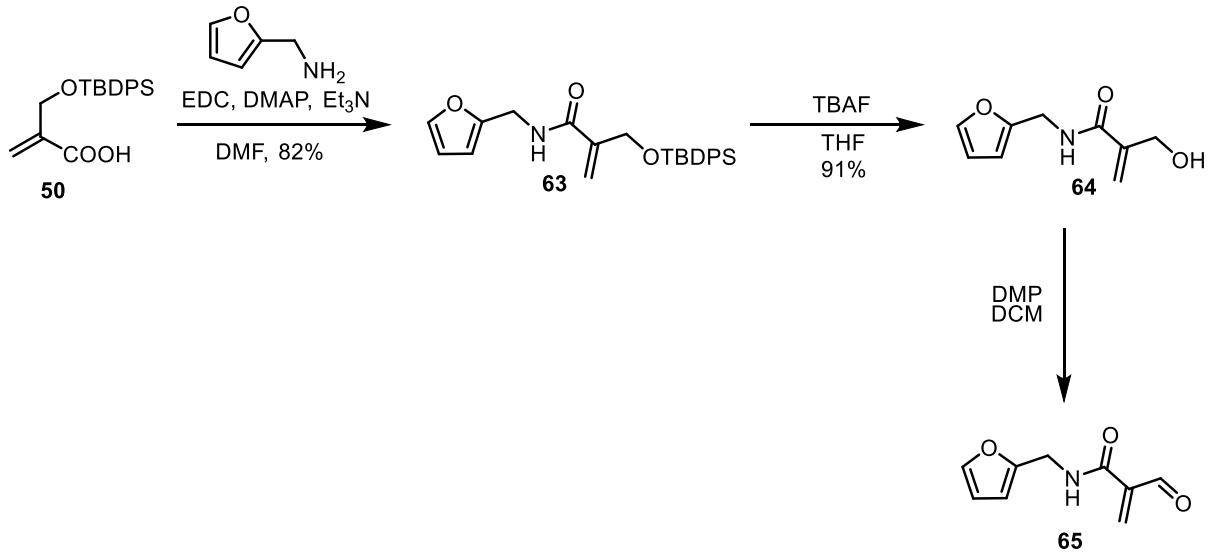
Scheme 41: Attempted cyclisation of alcohol 59



Scheme 42: Equilibrium between 60 and 61 species at rt in $CDCl_3$

2.2.5 Secondary furfurylamide 65

The work of Kitagawa and others[60-63] on the effect of *N*-substituents on amide tethered intramolecular Diels-Alder reactions clearly indicates that a bulkier group facilitates the reaction whereas a smaller group slows it down. They also suggest secondary amides cannot undergo DA cycloaddition because the activation energies and reaction enthalpies associated with the process are too high. Despite the high reactivity of compound **55** and analogues, substitution of the benzyl group with a hydrogen did not give any DA product (Scheme 43). The scheme of reaction to obtain **65** is similar to the one previously discussed for the synthesis of **55** (Scheme 37). Coupling of carboxylic acid to **50** with furfurylamine in presence of EDC gave TBDPS-protected secondary amide **63**. Treatment with TBAF in THF yielded the corresponding alcohol **64**. Upon treatment with DMP, alcohol **64** was not converted to aldehyde **65**, and only unidentifiable products of decomposition were observed.

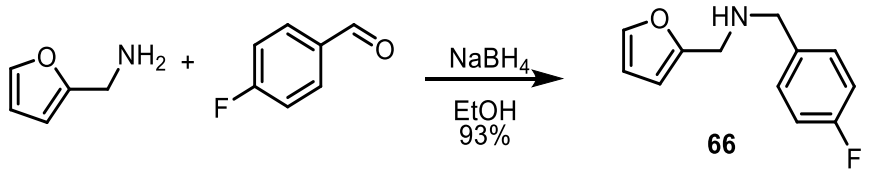


Scheme 43: Synthesis of substrate 65

2.2.6 *N*-Fluorobenzyl furfurylamides 67 and 69

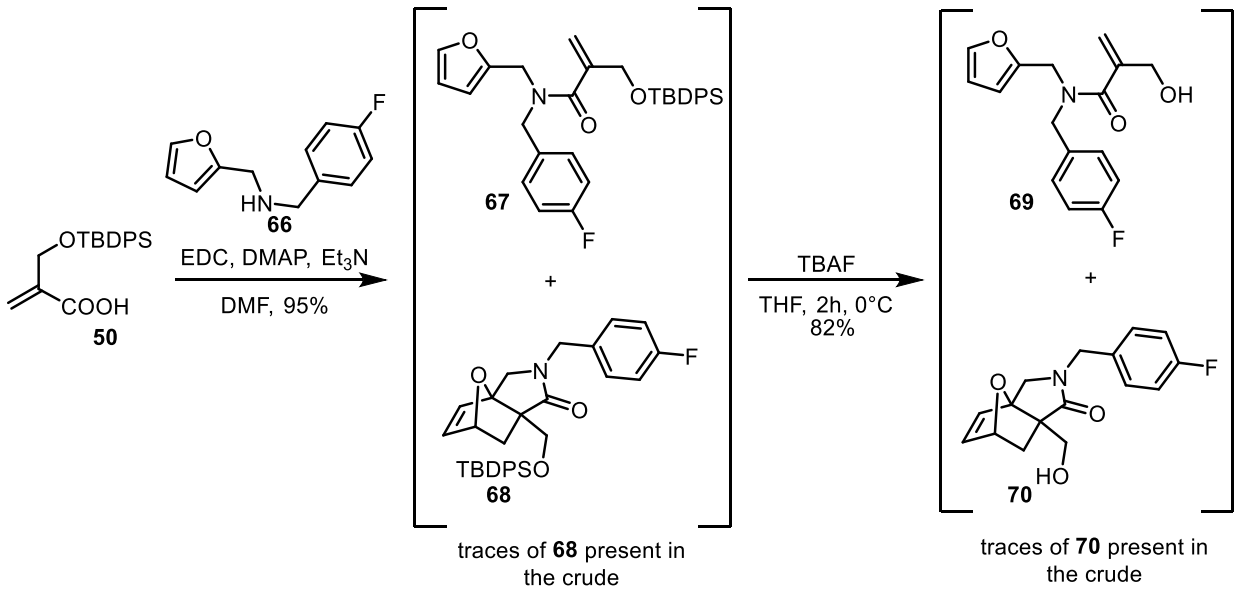
Quantification of the ratio of SM and cycloadduct present in the reactions is challenging. Precise integration of proton NMR was not possible due to the rotational barrier of amides which causes broad overlapping peaks that were difficult to integrate. We therefore targeted the analogous *p*-fluoro benzyl compounds, in the expectation that ^{19}F NMR would enable accurate quantitation of substrate:product ratios, without significantly perturbing the reactivity.

Amine **66** was obtained in 93% yield by condensation of furfurylamine and 4-fluorobenzaldehyde followed by reduction of the resulting imine with $NaBH_4$ (Scheme 44).



Scheme 44: Synthesis of fluorinated amine 66

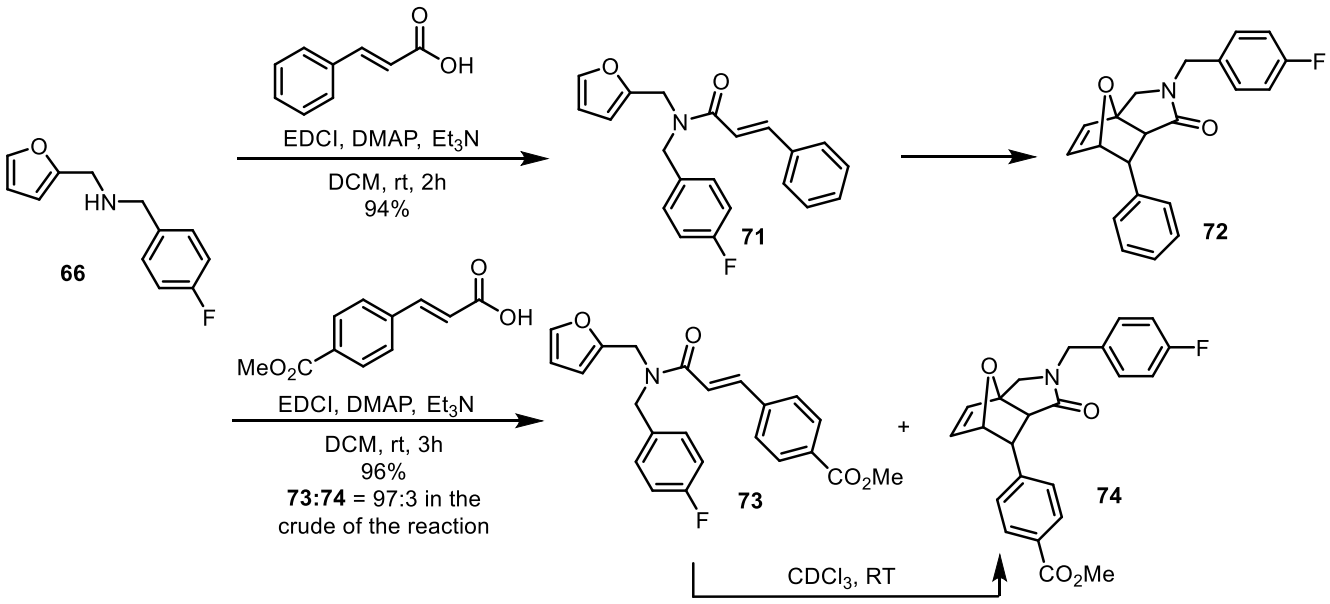
Scheme 45 shows the synthesis of **67** and **69**, fluorinated analogues of **51** and **53** respectively. EDC coupling between carboxylic acid **50** and amine **66** gave the corresponding amide **67** in 95% yield. After purification, traces of DA product **68** were observed together with the desired product. Deprotection of **67** with TBAF provided **69** in 82% yield. Also in this case, **69** cyclized spontaneously and an increasing amount of **70** was always present.



Scheme 45: Synthesis of substrates 67 and 69

2.2.7 Cinnamic acid derivatives 72 and 74

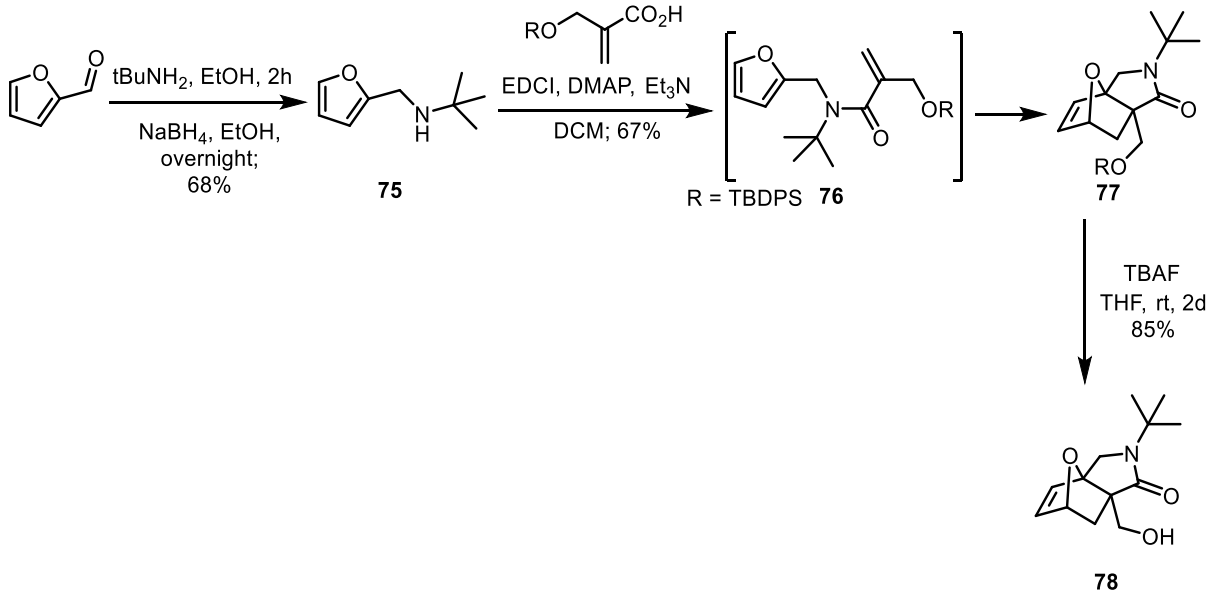
EDCI coupling between fluorobenzyl amine **66** (Scheme 46) and cinnamic acid or its derivative, produced DA substrates **71** and **73** in high yield. EWGs on the dienophile are expected to promote the reaction by lowering the LUMO of the dienophile and ERG are expected to slow it down increasing the LUMO energy. This was confirmed experimentally: ester-substituted cycloadduct **74** was already present in the crude of the reaction (3%), whereas **72** was only detectable by ^{1}H NMR after 6 days in $CDCl_3$ at RT.



Scheme 46: Cinnamic acid derivatives

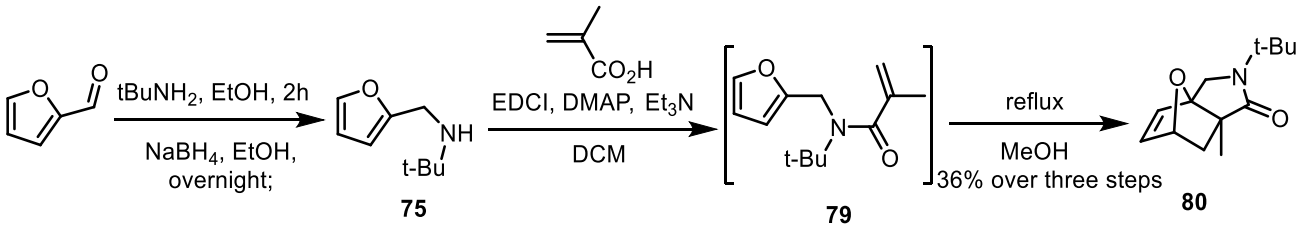
2.2.8 *N-tert*-butyl furfurylamides and correspondent cycloadducts 76, 78, 80 and 82

Bulkier groups on the nitrogen are known to facilitate the cycloaddition. For this reason, analogues of **68** and **70** with a *tert*-butyl nitrogen substituent were made. Reductive amination of furfural and *tert*-butylamine in ethanol produced secondary amine **75** in 68% yield. The amine, in the presence of carboxylic acid **50** and coupling reagent EDCI gave cycloadduct **77** in 67% yield. No Diels-Alder starting material **76** was recovered from the purification process. Deprotection of **77** with TBAF provided **78** in 85% yield (Scheme 47).

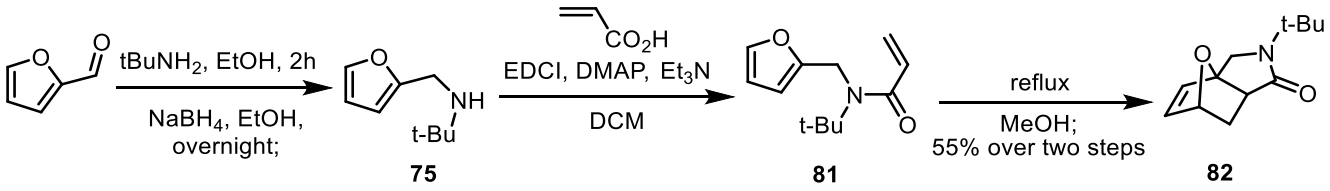


Scheme 47 Synthesis of 77 and 78

EDC coupling of amine **75** with acrylic and methacrylic acids provided cycloadduct **80** (Scheme 48) and **82** (Scheme 49) respectively. It was found that heating a mixture of DA precursor and cycloadduct at reflux in methanol, drove the reactions to completion. This strategy was applied to the synthesis of products **80** and **82** to ensure that the DA precursor was completely transformed into cycloadducts. The desired products were purified by trituration, a quicker method than column chromatography but that has as downside a lower yield of reaction (**80** was obtained in 36 % yield and **82** in 55% yield).



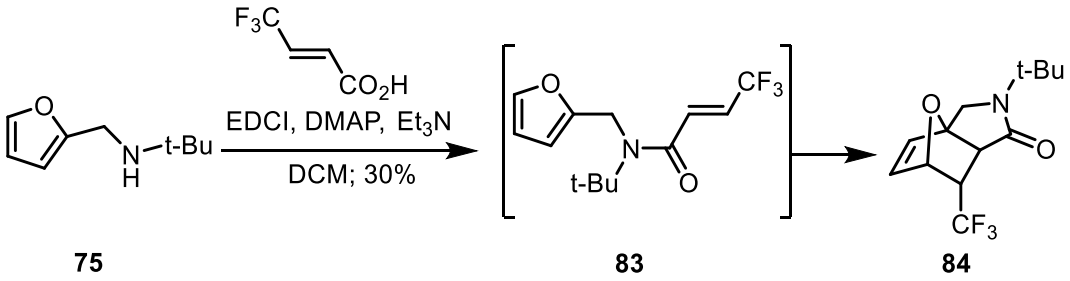
Scheme 48: Synthesis of methacrylic acid derivative 80



Scheme 49: Synthesis of acrylic acid derivative 82

2.2.1 Trifluoromethyl-substituted substrate 84

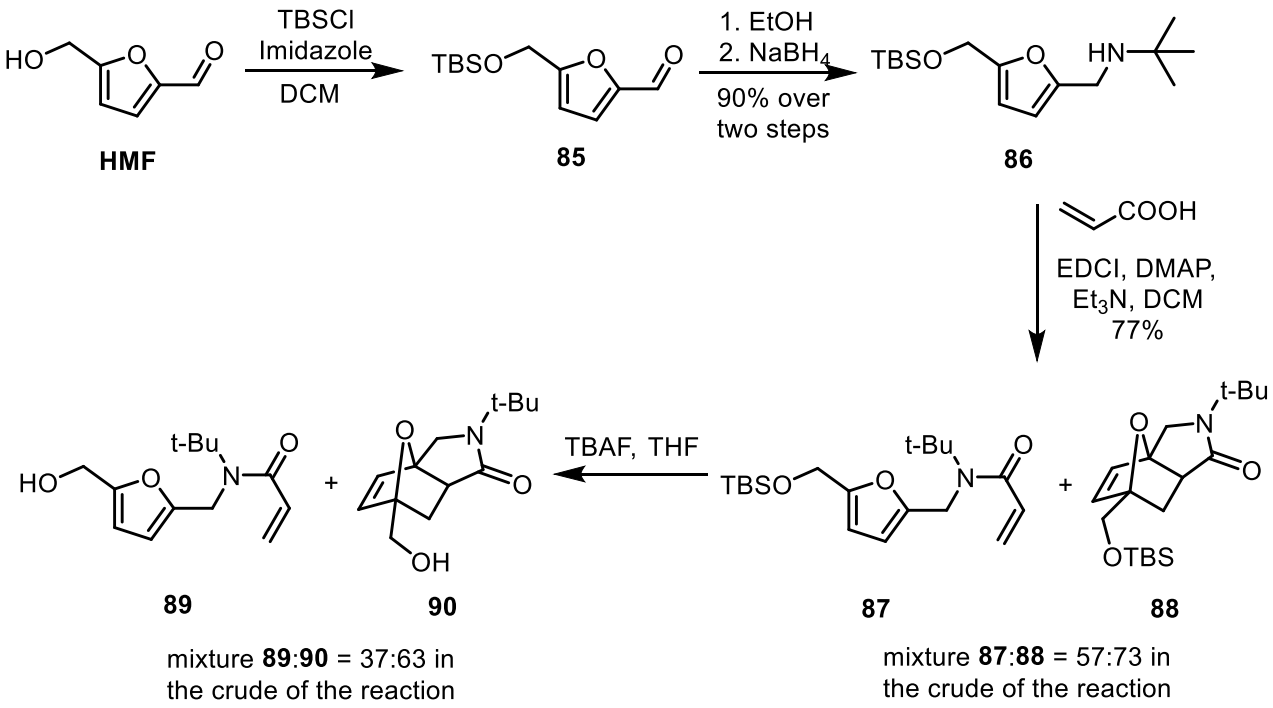
Coupling of amine **75** with trifluorocrotonic acid gave 7-substituted cycloadduct **84** in 30 % yield after column chromatography. No acyclic precursor **83** was observed in the crude of the reaction. Extensive decomposition accompanied the reaction but it was not possible to isolate any product other than **84**.



Scheme 50: Synthesis of 7-trifluoromethyl substituted cycloadduct

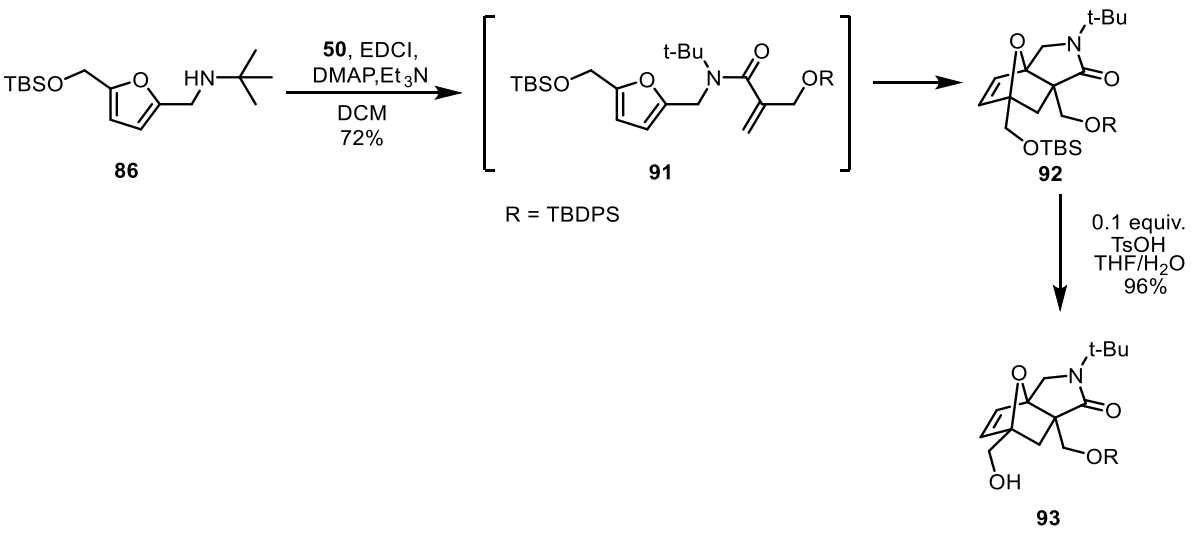
2.2.2 6-CH_2OTBS-substituted cycloadducts 88, 90 and 92 and 93 from 5-CH_2OTBS substituted furan

Some olefin transformations, such as the epoxidation reaction, require a directing group on the substrate to facilitate the reaction, or to impart a stereochemistry different from the one derived from steric control.[103] 6-hydroxy methyl analogue **90** was prepared to enable study of such directed reactions. Synthesis of **89** and **90** started with commercially available 5-(hydroxymethyl)furfural (HMF) and followed the same steps used to make compound **78**: after protection of the hydroxyl group by transformation in TBS-ether, **85** was transformed in secondary amine **86** by reductive amination with t-butylamine in 90% yield. Coupling with acrylic acid in presence of EDCI, DMAP, Et_3N in DCM gave a mixture of **87** and **88** in 77% yield overall. In the crude product of the reaction 57% of amide **87** and 43% of **88** were obtained. After purification, the two species were isolated but, as expected, **87** was unstable and reacted further to give more DA product **88**. A mixture of the two silyl ethers underwent deprotection by treatment with TBAF in THF to provide a mixture of **89** and **90** (**89**:**90** = 37 :63)(Scheme 51).



Scheme 51: Synthesis of substrates 87 and 89 and corresponding DA products. Composition of mixtures was determined by ^{1}H NMR

Coupling of amine **86** with carboxylic acid **50**, yielded cycloadduct **92** as only product (Scheme 52). The result indicates that substitution on the dienophile favours the cyclisation (**90** formed a mixture with precursor **89**) and the $TBSOCH_2$ group on the diene disfavours it (crude of coupling reaction to make unsubstituted **81** contained almost exclusively cycloadduct **52**). Chemoselective removal of the TBS group provided a useful scaffold to test directed reactions.

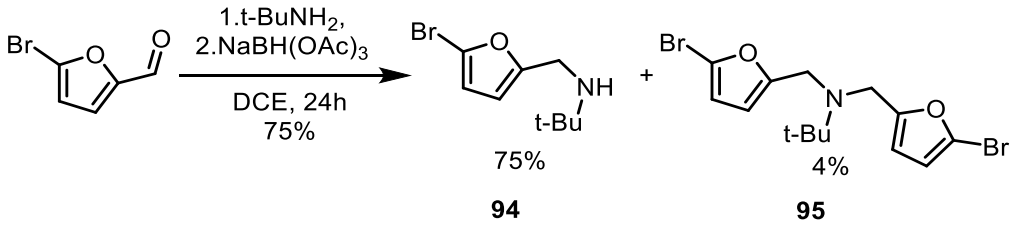


Scheme 52: Synthesis of cycloadducts 92 and 93

2.2.3 Cycloadducts 97 and 100 from 5-substituted furans

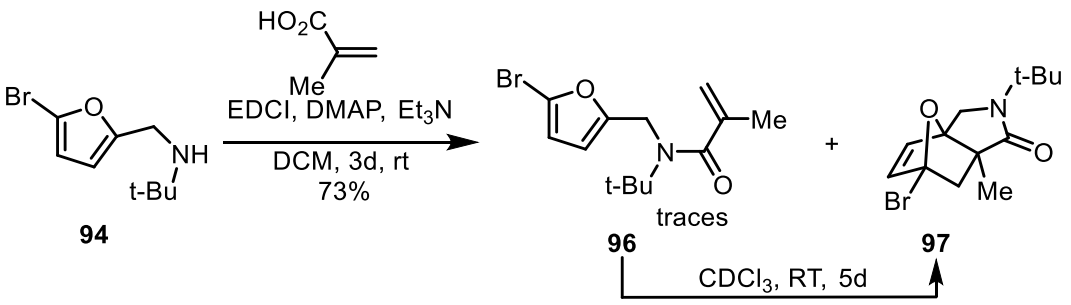
Halogen substituents on the furan are known to decrease the tendency of IMDAF reactions toward retro-cycloaddition. To a lesser extent, the same effect is also observed with other types of substituents.[55-56] Bromine and methyl groups were chosen to investigate the effect of furan substituents on the reactions.

Amine **94** was prepared by reductive amination with sodium triacetoxyborohydride following a literature procedure.[115] Formation of tertiary amine **95** was also observed (Scheme 53).



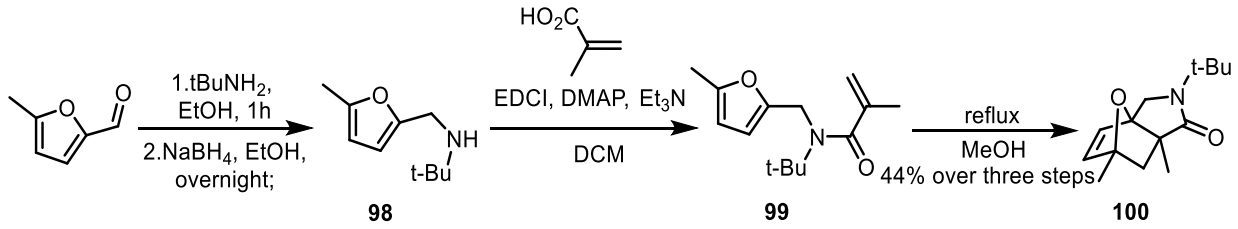
Scheme 53: Reductive amination of 5-Bromofurfural and *tert*-butylamine

Cycloadduct **97** was obtained from EDC coupling between 5-bromofurfurylamine **94** and methacrylic acid (Scheme 54). Only traces of precursor **96** were observed.



Scheme 54: Synthesis of 6-Bromo cycloadduct 97

5-Methylfuraldehyde was used as starting material to obtain a cycloadduct with a methyl group in the bridged carbon. The usual reductive amination with sodium borohydride, followed by EDC coupling strategy was used. Heating the crude of the reaction in methanol was necessary to convert all **99** into cycloadduct **100**. The initial ratio **99**:**100** was 63:37. Purification of the cycloadduct by trituration provided product **100** in 44% yield.



Scheme 55: Synthesis of 6-methyl cycloadduct 100

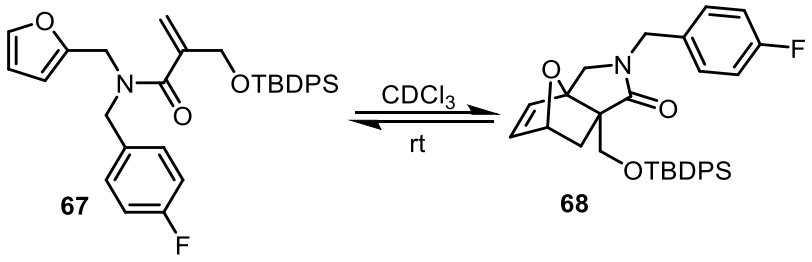
2.3 Investigation of DA Equilibria

A strategy to obtain enantiomerically pure cycloadduct derivatives by DKR was envisaged, taking advantage of the known reversibility of IMDAF reactions. As a means of racemisation, the parameters of the reaction that can influence the equilibrium of the two species, acyclic precursor and cycloadduct, present at equilibrium were investigated. Firstly, the investigation focused on how this ratio is influenced by solvent, temperature and presence of Lewis acids, then it was demonstrated that chemoselective reactions of the cycloadduct can be used to completely displace the equilibrium.

2.3.1 Temperature and Solvent Effect

Relative concentration of Diels-Alder products **68** and **70** was monitored via ^{19}F NMR and reported in Chart 1 and Chart 2.

Chart 1: Cycloadduct 68 rate to equilibrium



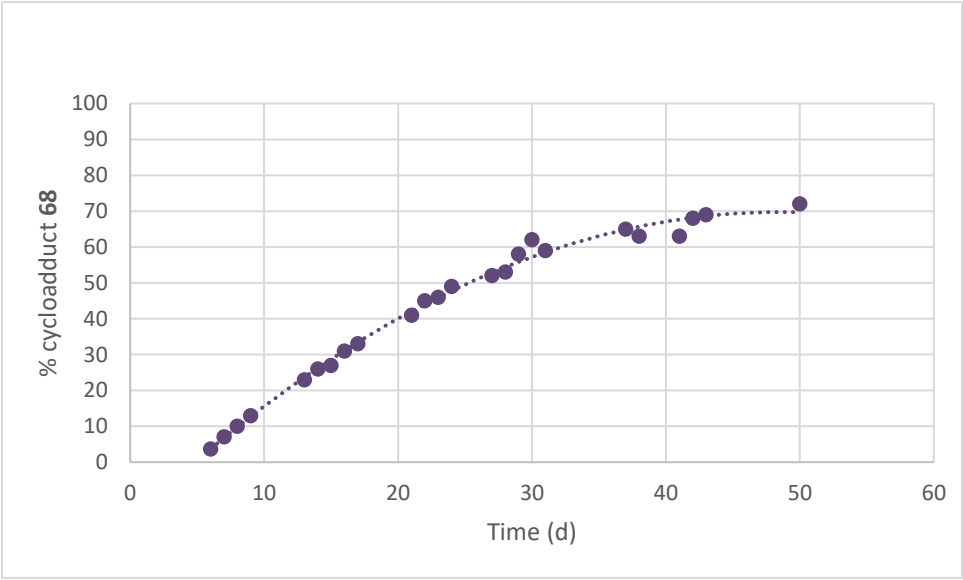
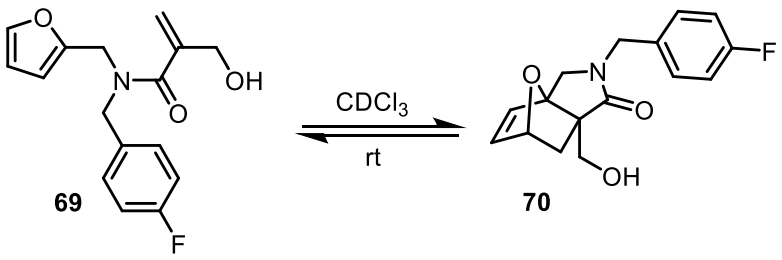
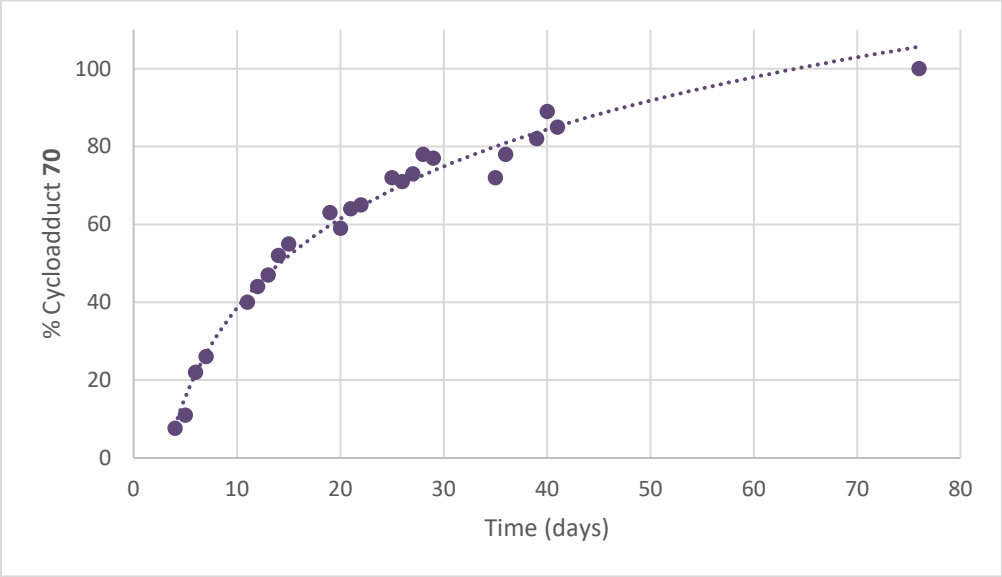


Chart 2: Cycloadduct 70 rate to equilibrium





On the basis of the examples reported by Jung and Gervay for ester-tethered substrates,[57] the DA examined likely follow reversible first-order kinetics. For this type of kinetic, plotting $\ln \frac{[A]-[Aeq]}{[Ao]-[Aeq]}$ vs time, a linear curve should be obtained,[116] however, for compounds **67** this was not the case. Moreover, compound **69** did reach completion and did not fit a linear plot of ln A vs time. Over this extended time period other processes may have been involved ([A]= concentration of A, $[A_{eq}]$= concentration of A at the equilibrium, $[A_0]$= concentration of A at the beginning of the reaction).

N-fluoro benzyl compounds **67** and **69** showed similar reactivity to *N*-benzyl analogues **51** and **53**, cyclising spontaneously even at -20°C. DA reaction is highly dependent on solvent and temperature. Chart 3 and Chart 4 show how the concentration of DA product changes in deuterated chloroform, DCM, Toluene, Acetonitrile, methanol, THF and a 1:1 mixture of water and t-butanol at room temperature. The data was obtained by ^{19}F NMR, except for substrate **67** in MeCN and MeOH. In this case the peaks of the TBDPS group from ^{1}H NMR spectra

were used instead. DA product **68** is favoured the most in methanol-d_4, whereas **70** is obtained in higher concentration in the mixture 1:1 *tert*-butanol-d_{10}/D_2O.

Chart 3: Cycloadduct 68 rate at rt in organic solvents

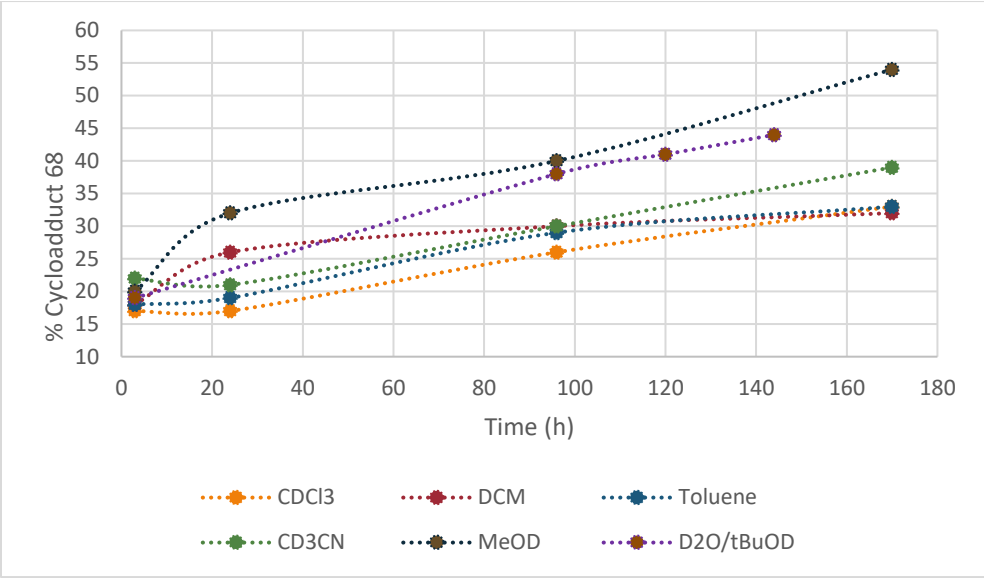


Chart 4: Cycloadduct 70 rate at rt in organic solvents

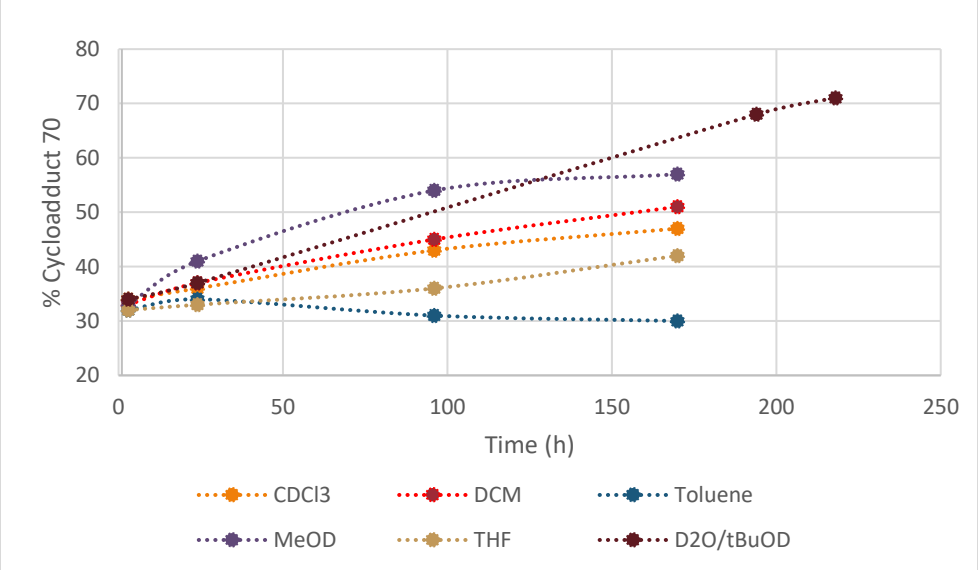
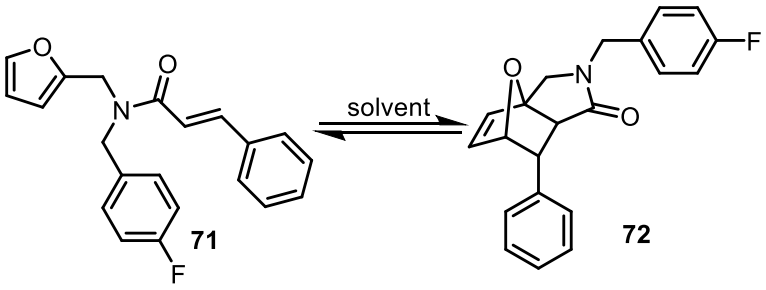


Chart 5 and Chart 6 show the dependence of the cycloaddition rate of cinnamic acid derivatives **71** and **73** on solvent and temperature. In both cases, the mixtures rapidly reach an equilibrium when heated at 80 °C in acetonitrile. At rt equilibration is slower but it favours cycloadduct **73** over a long period of time (Chart 6). After 10 days at rt the percentage of cycloadduct present in the mixture **73**/**74** in acetonitrile was superior than the one heated at 80 °C. When the mixtures **71**/**72**, and **77** /**74** are dissolved in the less polar chloroform, as expected the DA reaction is slower than in acetonitrile at the same temperature.

Chart 5: Substrate 71 rate to equilibrium in $CDCl_3$ and MeCN-d_3 at rt and 80°C



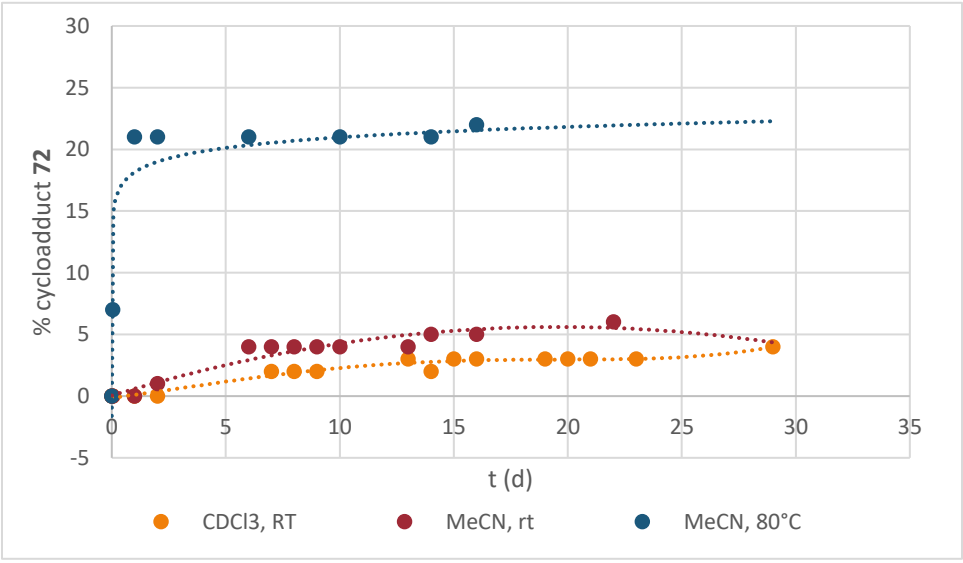
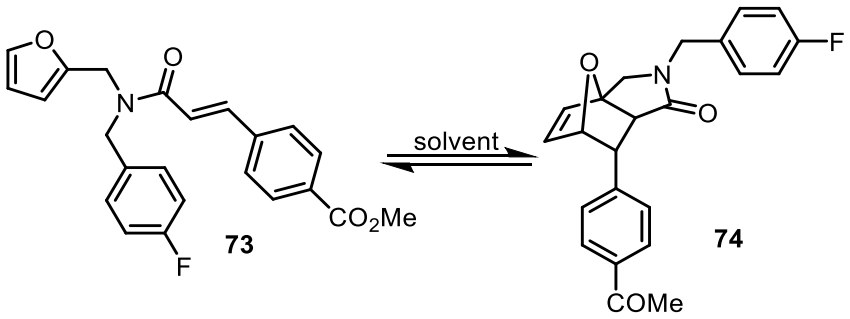
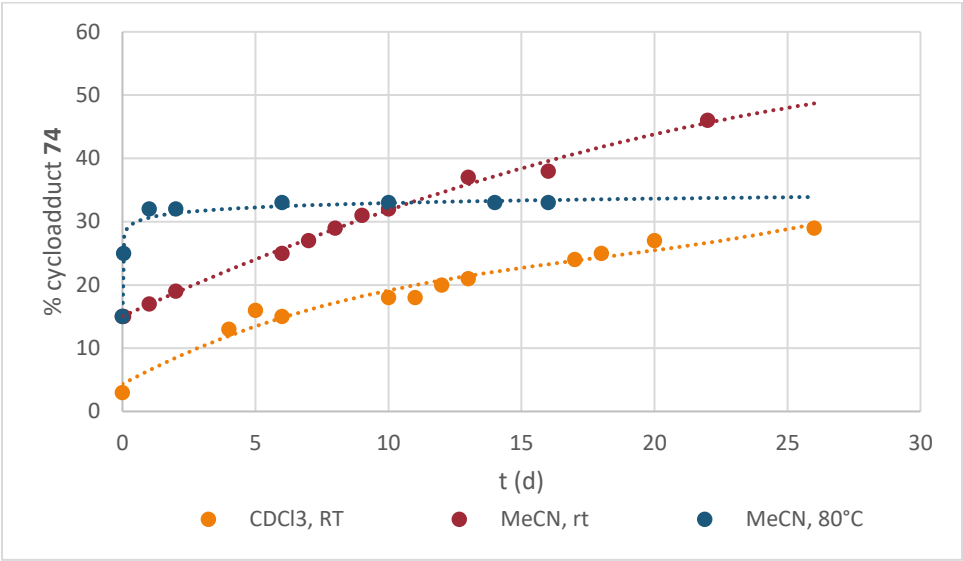


Chart 6: Substrate 73 rate to equilibrium in $CDCl_3$ and MeCN-d_3 at rt and 80°C

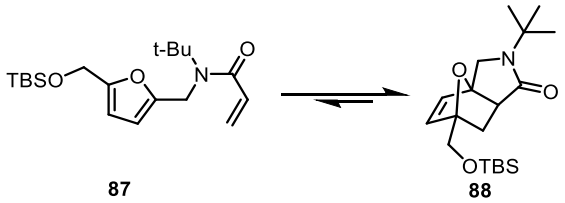




The trend of the curves for 6-substituted compounds **87** and **99** are in Chart 7 and Chart 8.

All the substrates analysed (**68**, **70**, **72** and **74**) showed a strong dependence of the rate of cycloaddition with the polarity of the solvent, contrary to what was observed by Jung and Gervay for amide-tethered substrates.[57]

Chart 7: DA precursor 87 rate to equilibrium in $CDCl_3$ at RT



87 **88**

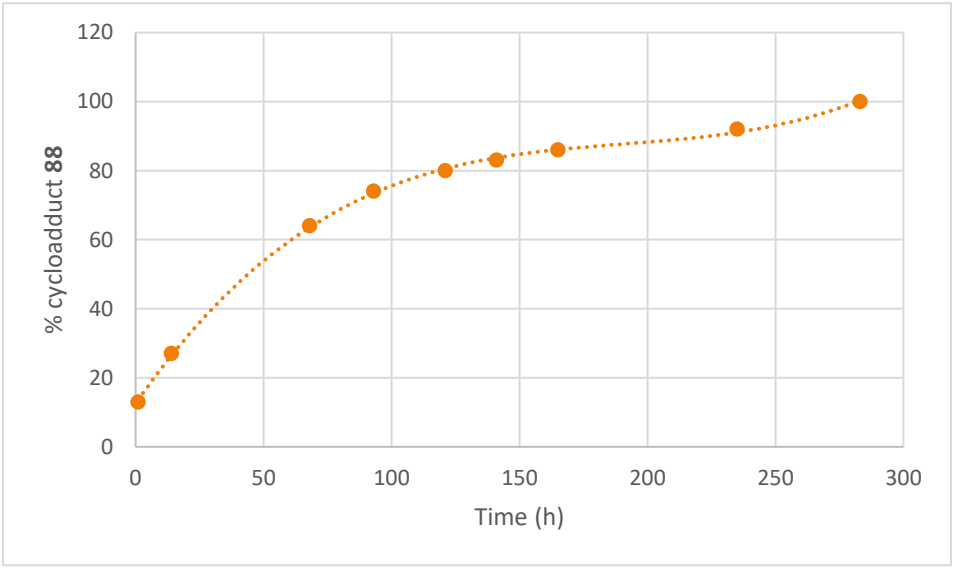
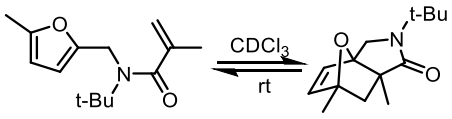
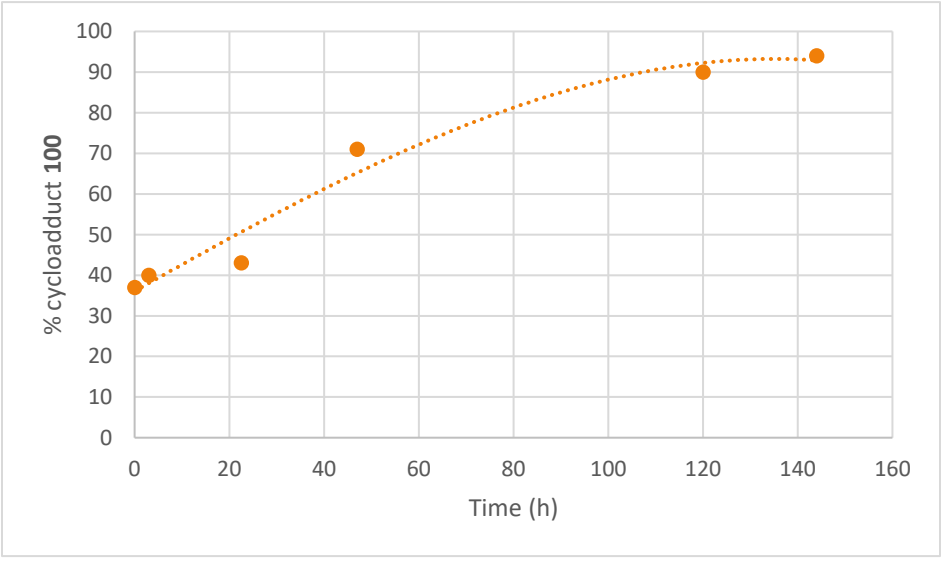


Chart 8: Substrate 99 rate to equilibrium in $CDCl_3$ at RT



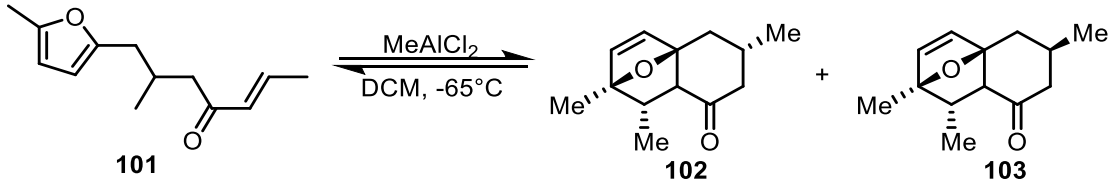
99 **100**



2.3.2 Lewis Acids

A possible strategy to lower the activation energy of forward and reverse DA reaction involves the use of Lewis acids. Using this approach, high temperature to promote retro cyclisation are not necessary and this opens up the possibility of using Lewis acids in combination with an appropriate asymmetric catalyst of a resolving reaction (if compatible). The rate of racemisation would be increased and DKR promoted even at low temperature, which is preferable for asymmetric reactions. Lewis acids are widely used in inter- and intramolecular Diels-Alder reaction, included IMDAF.[37, 117] Their application to DA reactions has usually the target to facilitate the forward reaction by the increased electron deficiency caused by the Lewis acid interacting with the LUMO of the dienophile. There are also examples where LA enhanced the tendency to the reverse reaction: methyl aluminium dichloride is known to promote retro Diels-Alder (rDA) reactions on norbornene derivatives of type I, and has been successfully applied to the synthesis of natural products without additional thermal activation.[118] Keay reported $MeAlCl_2$ promoted retro IMDAF at -65 °C both using 1.1 equiv. or 0.1 equiv. of Lewis acid, still accelerating also the forward reaction (Table 15):[119] with 1.1 equiv. of LA, starting material **101** increases over time, whereas with 0.1 equiv. of LA, concentration of starting material **101** decreases but so does diastereomer **103**, transformed into product **102** through retrocyclisation / forward cyclisation.

Table 15: Keay's experiments on Lewis acid-catalysed rDA[119]



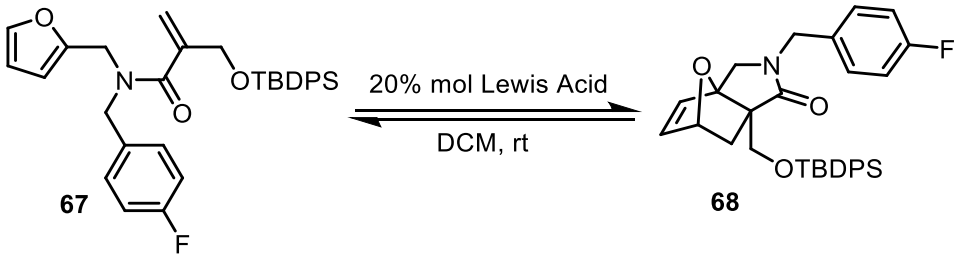
101 **102** **103**

Entry	Time	1.1 equiv. $MeAlCl_2$ (101:102:103)	0.1 equiv. $MeAlCl_2$ (101:102:103)
1	5 min	61:39:0	72:14:14
2	2h	72:28:0	11:67:2
3	4h	70:30:0	17:77:6

In light of this, we tested the effect of Lewis acids on the composition of an equilibrating mixture of **67** and **68**. Zinc iodide, titanium (IV) chloride, dimethylaluminum chloride, boron trifluoride diethyl etherate and Scandium (III) triflate were tested (Table 16). After one hour, the composition of the mixture was roughly the same with and without LA and no sign of degradation of the substrates was observed. After 6h, the sample with no LA had

still the same composition (82% of **67** and 18% of **68** (Entry 1)), whereas in most cases, in presence of LA the ratio changed in favour of **68** with the exception of $TiCl_4$ (Entry 3) and $Sc(OTf)_3$ (Entry 6). The sample containing $BF_3{\cdot}Et_2O$ showed some decomposition after 6h. (Entry 5). ZnI_2 and Me_2AlCl produced an increment of **68** from 18% to 25% and 27% respectively (Entries 2 and 4). The modest increase in cycloadduct conversion suggests that acceleration is possible. **67**/**68** is one of the more hindered systems studied (bulky OTBDPS) so it is possible that other substrates will show a more pronounced effect.

Table 16: Effect of LA on DA equilibrium



67 **68**

Entry	Lewis Acid	% of cycloadduct		
		1h	**6h**	**2d**
1	/	18	18	22
2	ZnI_2	18	25	
3	$TiCl_4$	17	18	
4	Me_2AlCl	17	27	
5	$BF_3{\cdot}Et_2O$	18	26	
6	$Sc(OTf)_3$	18		22

% of cycloadduct over time determined by ^1H NMR experiments

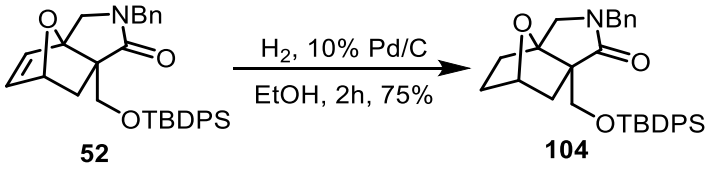
2.3.3 Equilibrium Displacement by Chemoselective Reaction

Exploitation of the electron-rich double bond functionality on the cycloadduct allows a variety of electrophilic transformations both on pure cycloadducts and on mixtures of cycloadduct/starting material. Racemic reactions were first used to test the substrate reactivity.

2.3.3.1 Hydrogenation

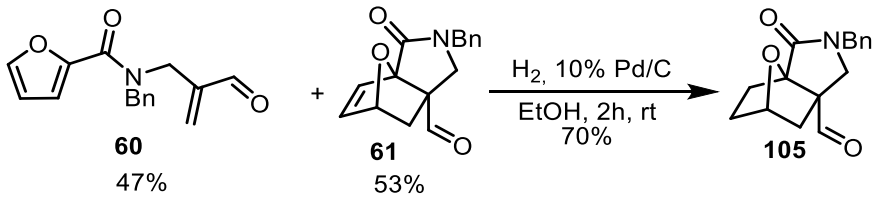
Catalytic hydrogenation of olefins is a widely used reaction in both its racemic and asymmetric variant. Hydrogenation of IMDAF products delivers oxanorbornane systems, which have found application for drug-delivery[120-121] and for the synthesis of natural products, some of which show interesting biological activity.[122]

To demonstrate that hydrogenation of cycloadducts works effectively, compound **52** was treated with hydrogen in presence of palladium on charcoal in ethanol to yield 75% of isolated compound **104** (Scheme 56).

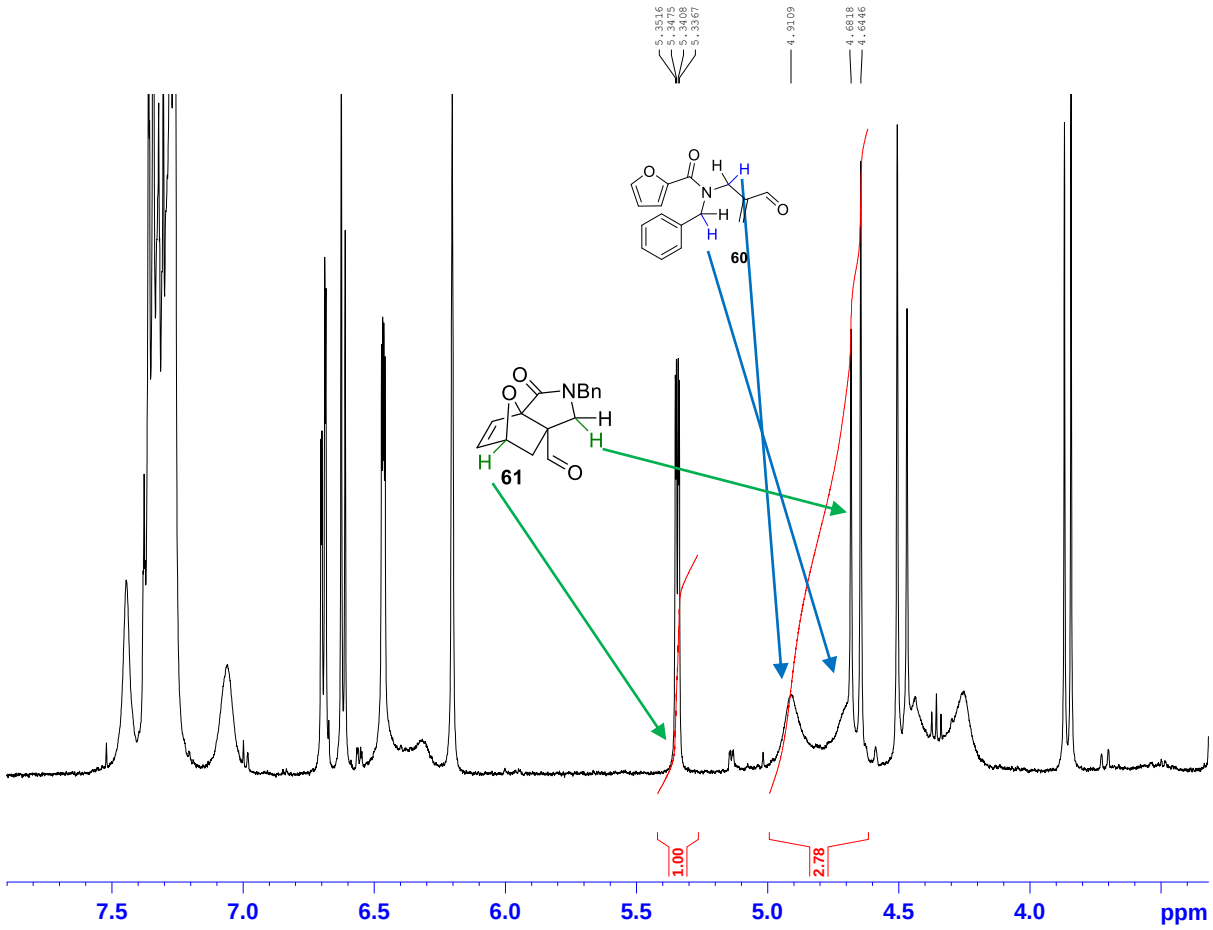


Scheme 56: Hydrogenation on cycloadduct 52

An equilibrating mixture of cycloadduct **61** and precursor **60** was then hydrogenated under similar conditions. After 2 h, complete consumption of both **60** and **61** was observed. Hydrogenated cycloadduct **105** was obtained in 70% yield after purification by column chromatography. No other product was present in the crude of the reaction. The composition of the **60**/**61** mixture was monitored for weeks in deuterated chloroform at rt and the amount of cycloadduct was 53% of the total mass without any significant change. The ratio of **60** and **61** in the initial equilibrating mixture was determined by integration of the ^{1}H NMR spectrum, comparing the integrals of the alkene protons of adduct **61** (δ 6.7 and 6.6) and the methyl protons of the internal standard 1,3,5-trimethoxybenzene (δ 3.8) and by direct comparison of the areas of the protons of the two species in equilibrium (NMR 2).



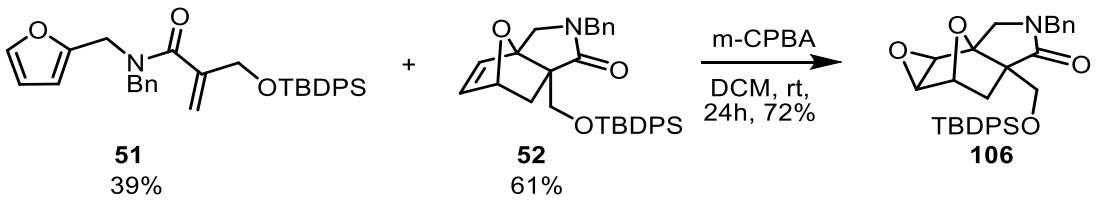
Scheme 57: Hydrogenation of 60/61 aldehyde mixture



NMR 2: Aldehydes 60 and 61

2.3.3.2 Epoxidation

meta-chloroperbenzoic acid (*m*CPBA) is expected to oxidise preferentially the cycloadduct double-bond in the presence of the electron-poor substrate olefin because of the electrophilic properties of the peracid. This hypothesis was tested on an equilibrating mixture of **51** and **52** (Scheme 58). 3.0 equiv. of *m*CPBA were added to the **51**/**52** mixture (39:61) in DCM at rt and the stirred for 24h. The SM:cycloadduct ratio (**51**:**52**) was determined by integration of the ^{1}H NMR 3 spectrum comparing the integrals of the proton on the bridged 6-carbon of adduct **52** (δ 4.93) and the two protons of the terminal alkene of the acyclic precursor **51** (δ 5.58-5.25). Results were confirmed by integration relative to internal standard 1,3,5-trimethoxybenzene. The ratio of the two equilibrating species changes over time, similarly to compounds **67** and **68** (Chart 1). Epoxide **106** was isolated after purification by column chromatography in 72% yield. Other by-products isolated derived from the purification process (flash chromatography on silica gel) and not from the reaction. No **51** or **52** was present in the crude.

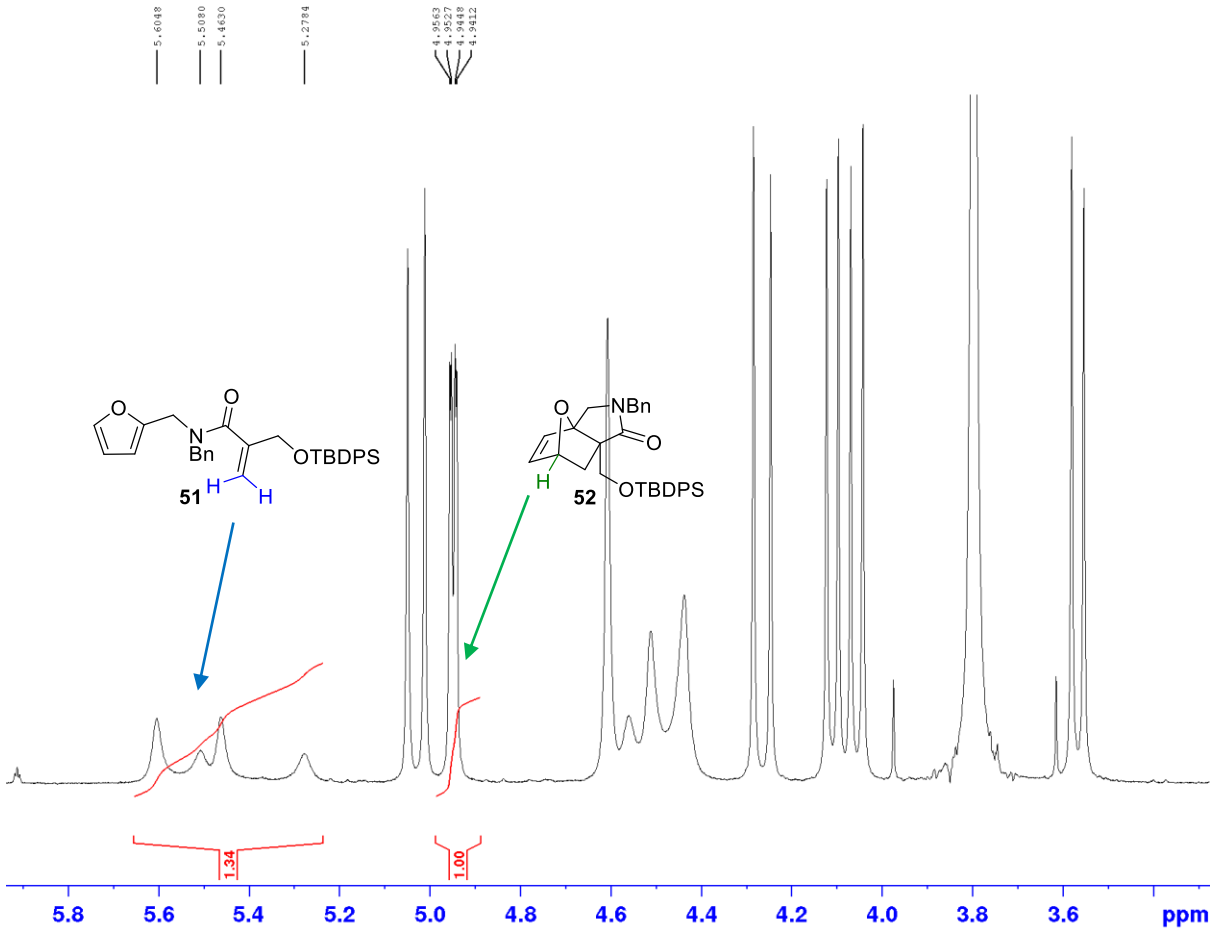


51
39%

52
61%

106

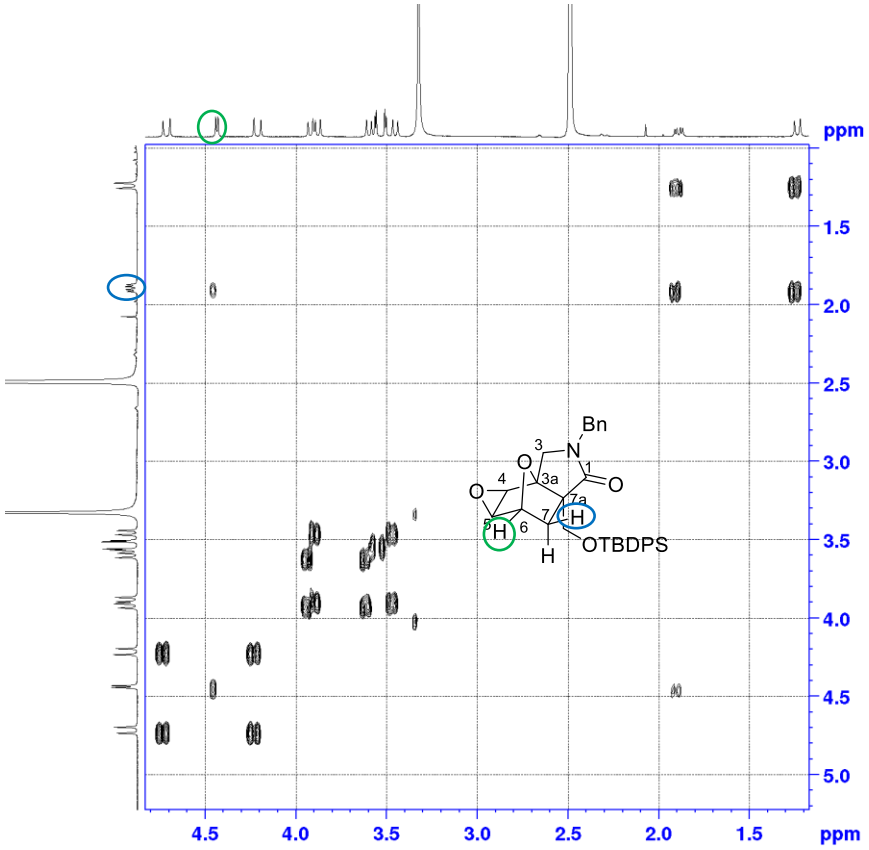
Scheme 58: Epoxidation of silyl ether mixture



NMR 3: mixture of 51 and 52

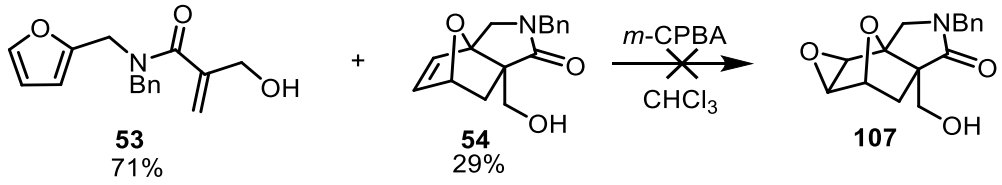
The cycloadduct reacted exclusively on the *exo*-face with *m*-CPBA. The stereochemistry of the epoxide was confirmed by NMR experiments. As showed by previous studies, in norbornene derivatives the proton in 6-position and the adjacent *endo* proton form a 90° dihedral angle and no coupling is possible between them. In

epoxide **106**, the proton in 6-position is a doublet, as it only couples with the *exo* 4-H. This can also be seen in the COSY experiment (NMR 4).



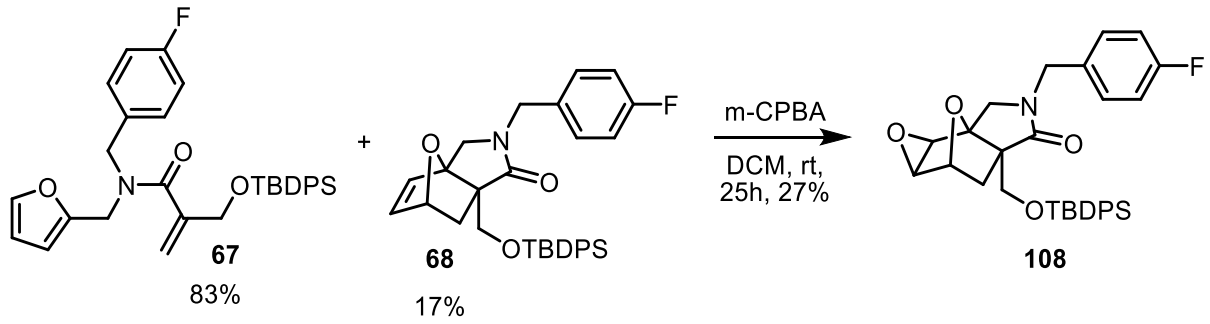
NMR 4 COSY experiment of compound 106

The same reaction was performed on mixture of alcohols **53** and **54**, but the crude of the reaction showed high level of decomposition of the starting materials and, despite **107** being observed by NMR, its attempted purification resulted in complete loss of the product (Scheme 59).

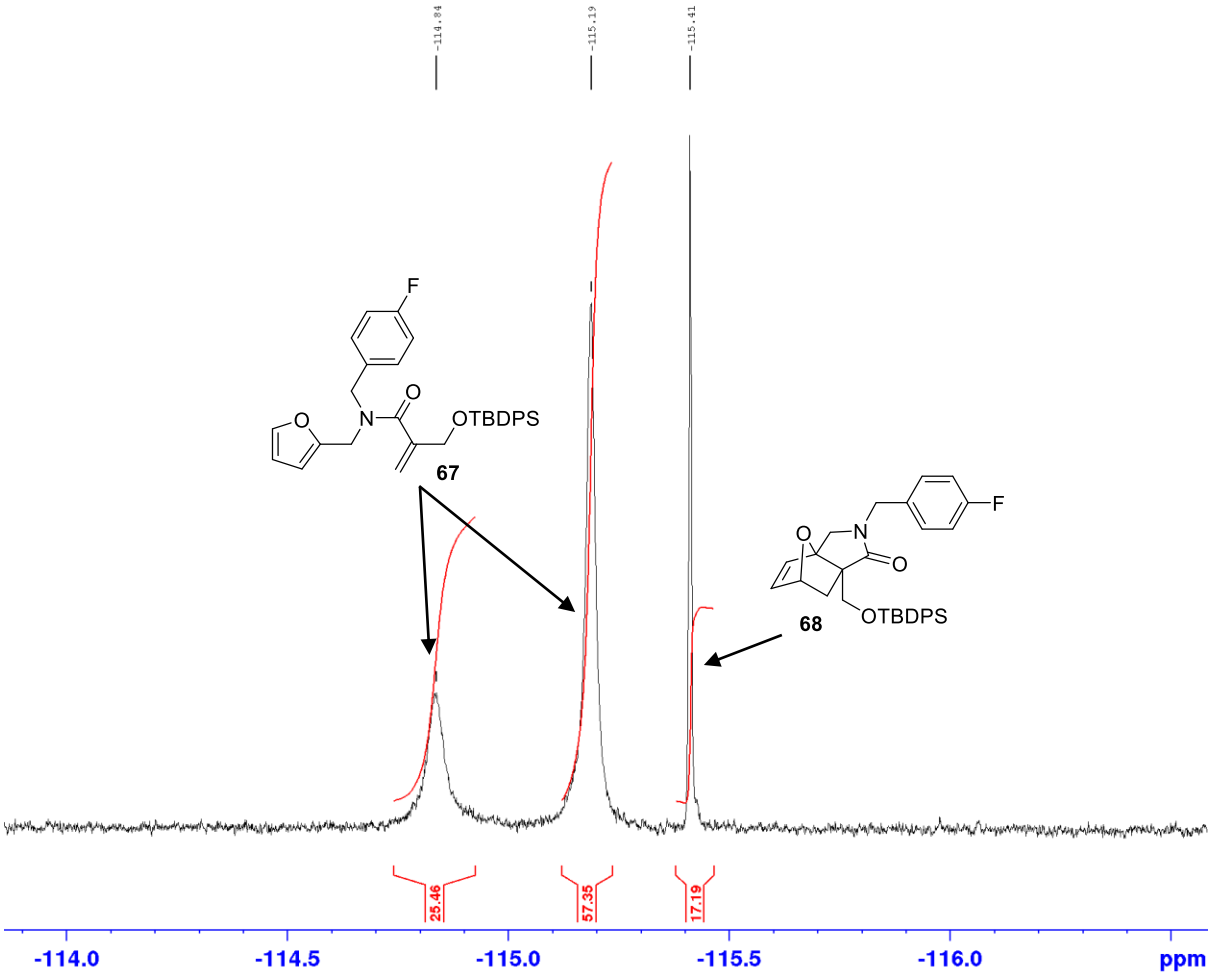


Scheme 59: Attempted epoxidation of 53/54 alcohol mixture

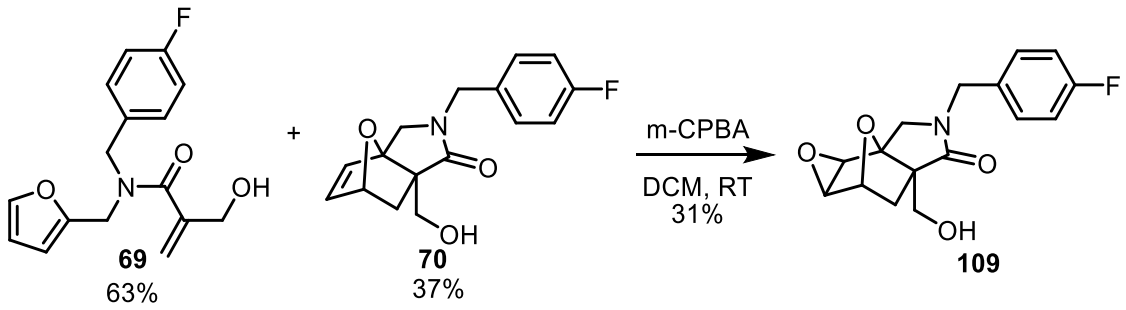
Epoxidation of mixtures **67**/**68** (Scheme 60, NMR 5) and **69**/**70** (Scheme 61, NMR 6) was performed with *m*CPBA in DCM at rt. The NMR of the crude of the reactions showed a high level of decomposition in both cases. Starting materials were not observed in the reaction crudes. The ratio of acyclic precursor and cycloadduct **67**/**68** and **69**/**70** in the mixtures were determined by ^{19}F NMR. Epoxides **108** and **109** were isolated after purification by column chromatography in 27% and 31% yield respectively.



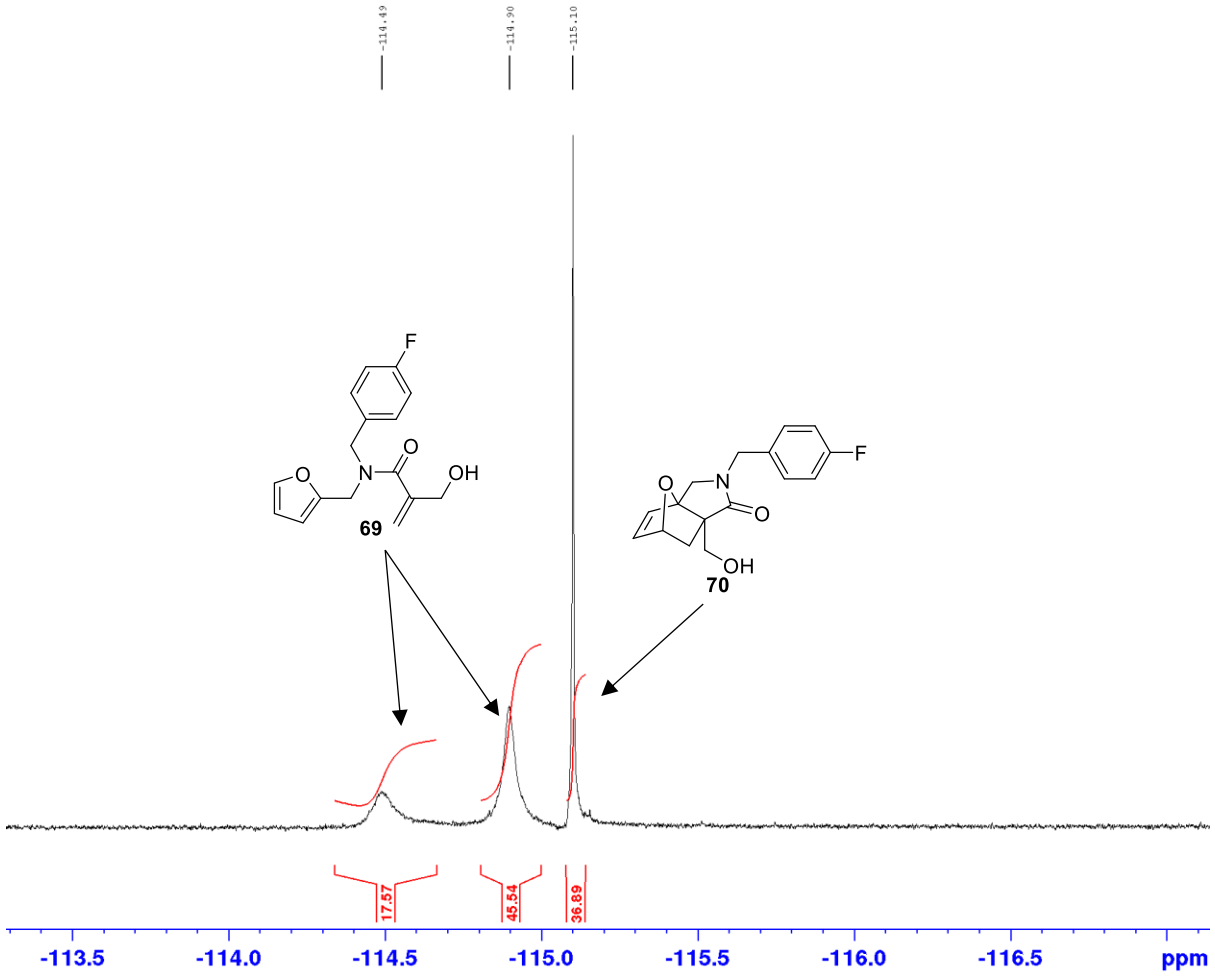
Scheme 60 Epoxidation mixture of 67 and 68



NMR 5: ^{19}F NMR of 67 and 68



Scheme 61: Epoxidation of mixture of 69 and 70

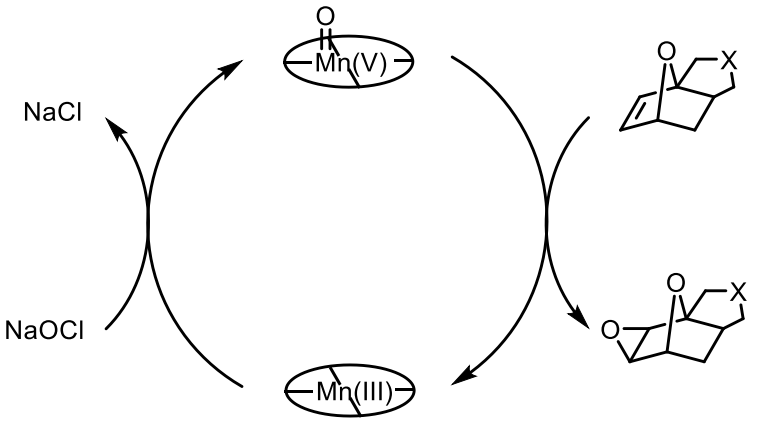


NMR 6: ^{19}F NMR of 69 and 70

2.4 Asymmetric Transformation of 7-Oxanorbornene Derived from IMDAF Reaction: Kinetic Resolution

2.4.1 Epoxidation

In the early 1990's Jacobsen and Katsuki independently reported application of optically active Mn-salen catalysts in epoxidation of olefins in high enantioselectivity[123-127] and with a broad substrate scope.[128-130] The reaction proceeds by oxidation of the Mn(III)-salen precatalyst to Mn(V)-oxo catalyst, followed by oxygen transfer to the olefin and recycle of the Mn(III)-species (Scheme 62). The more common oxidation conditions are: NaOCl and PhIO at room temperature, and *m*CPBA at -78 °C.



Scheme 62: General Jacobsen-Katsuki epoxidation mechanism

The Mn-salen complexes used have C_2-symmetry, chiral sp^3 carbons in the chain connecting the imine nitrogens and a *tert*-butyl or chiral phenylpropyl group in *ortho* of the phenyl rings (Figure 16). First generation catalysts were very efficient with *cis* di- and trisubstituted olefins. Modifications to their structure were introduced later to increase enantioselectivity and to broaden substrate scope.[131] Electron-donating substituents in the *para* position of the phenyl groups were found to improve the facial selectivity by stabilisation of the Mn(V)-oxo species.[124] For the same reason donor ligands, such as 4-phenylpyridine *N*-oxide, are often used as co-ligands.[132-133]

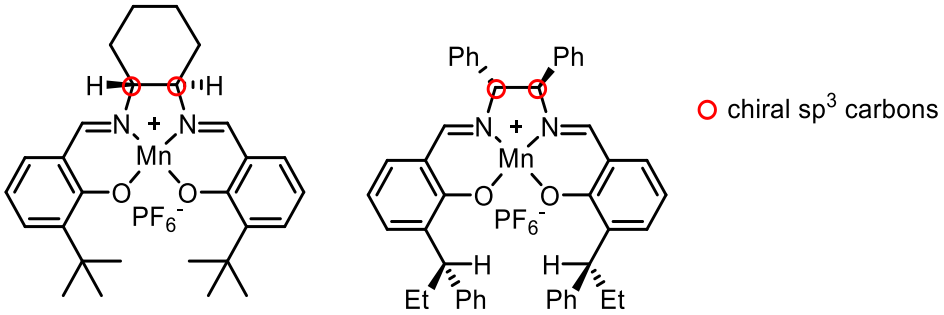


Figure 16: First catalyst utilised by Jacobsen (left) and Katsuki (right)

Jacobsen proposed an attack of the double bond parallel to the salen ligand from the diimine bridge, with the smaller substituent on the same side of the axial hydrogen (Figure 17, path a). Katsuki suggested an attack that minimises the interaction between the smaller substituent of the olefin and the substituents in *para* position of

the phenyl ring (Figure 17, path b). The outcome is the same in both suggested paths. Both steric and electronic effects are responsible for the induction of asymmetry.[131, 134]

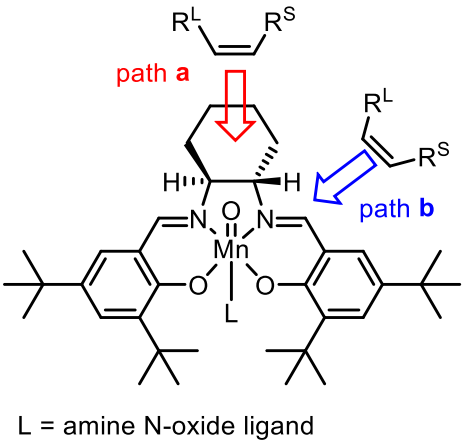
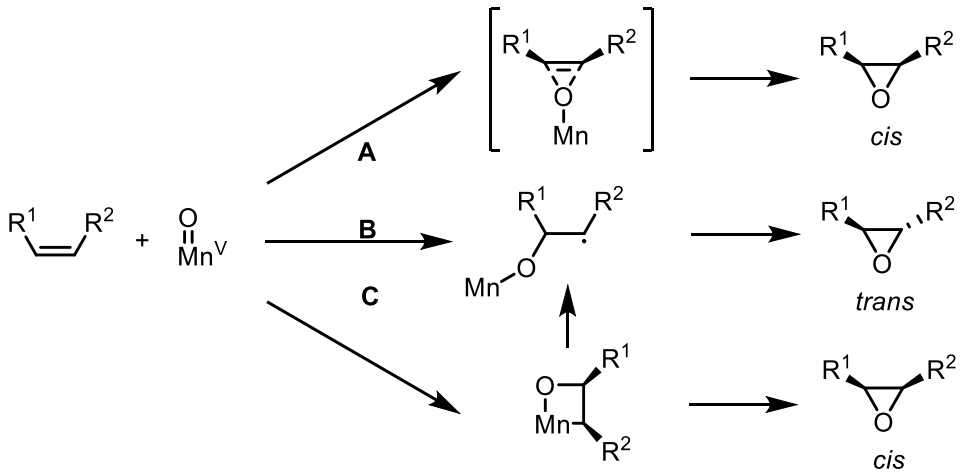
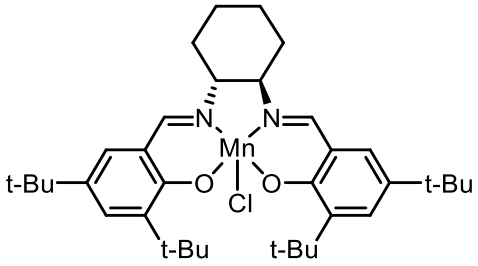


Figure 17: Proposed direction of approach of the diene according to Jacobsen (path a) and Katsuki (path b)

The mechanism of the reaction is still debated and there are results that suggests that epoxidation of different olefins or in different reaction conditions, occurs by different mechanisms (Scheme 63).[134]



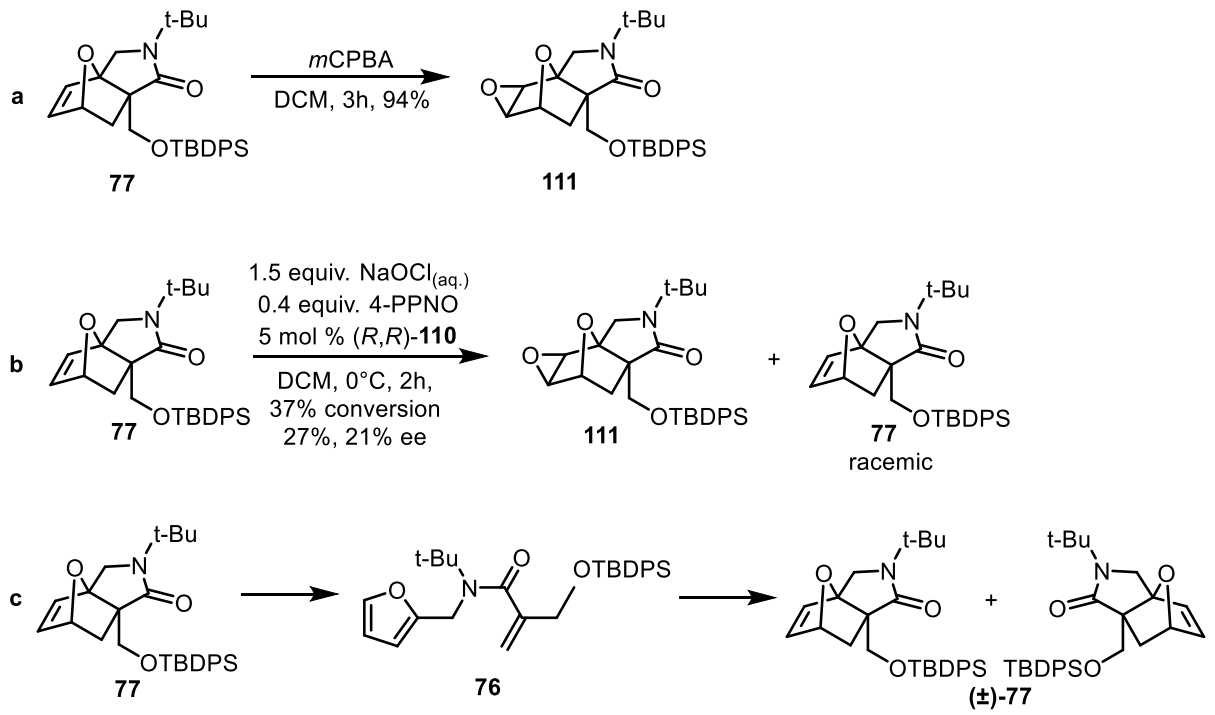
Scheme 63: proposed mechanism for the oxidation step in the Jacobsen-Katsuki epoxidation reaction



110

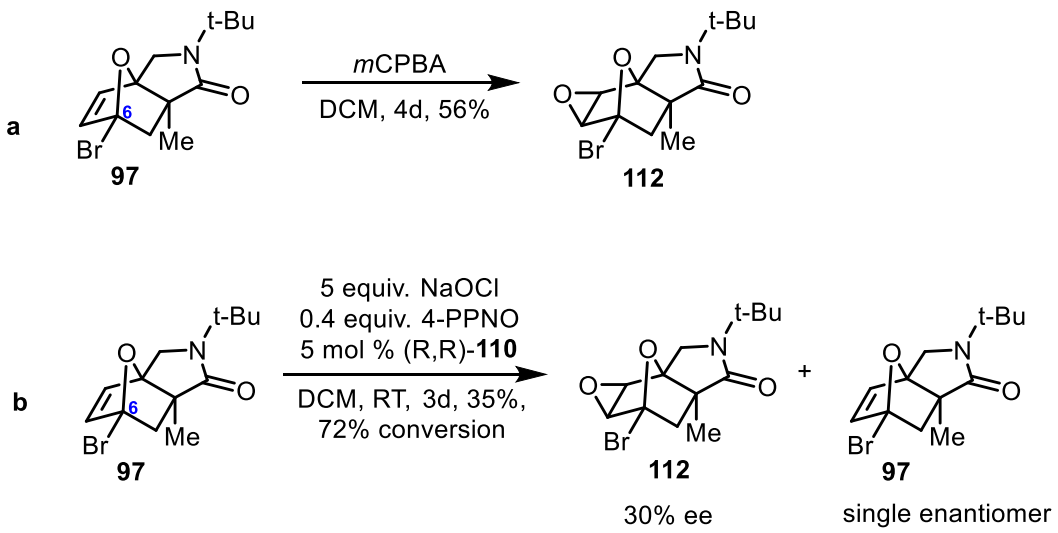
Figure 18: Jacobsen's catalyst

Treatment of pure cycloadduct **77** with mCPBA provided epoxide **111** as racemic mixture in 94% yield. Under Jacobsen epoxidation conditions (Salen-Mn(III) catalyst 3, NaOCl, 4-PPNO) at 0°C, **111** was obtained in 27% isolated yield (Scheme 64). The reaction was stopped after 2h, before complete conversion of the starting material. After work-up, in the crude of the reaction, SM **77** and product **111** were present in a ratio 62:32. HPLC analysis of compound **111** showed an enantiomeric ratio of 39:61. Although one enantiomer of **77** reacts faster than the other, the unreacted cycloadduct starting material was racemic, which implies that racemization via acyclic precursor took place (Scheme 64c). The acyclic precursor was not observed in the crude of the reaction, proof that the cycloaddition is much faster than the reverse Diels-Alder reaction, as already observed during preparation of the substrate (Section 2.2, Scheme 46). Racemization rate is likely to be too slow to allow an efficient DKR.



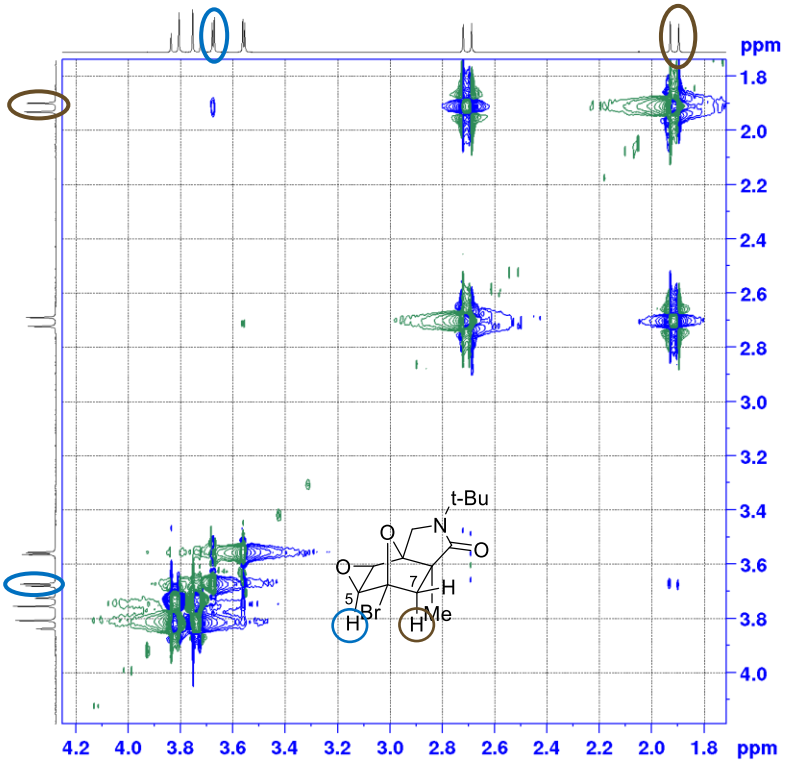
Scheme 64: Racemic (a) and asymmetric (b) epoxidation of 77. Racemisation pathway of cycloadduct 77 (c). ee values were determined by chiral HPLC.

Epoxidation was performed on substrate **97** bearing a bromo substituent in position 6. Reaction of **97** with *m*CPBA provided racemic product **112** in 56% isolated yield. The reaction rate was much lower (4d) than with substrate **77** (3h). Also the Jacobsen epoxidation was slower, and after 3d there was still unreacted starting material (SM:product = 28:72). Epoxide **112** was isolated in 65:35 enantiomeric ratio, obtained from chiral HPLC. Interestingly, analysis of the starting material by chiral HPLC showed that only one enantiomer of **97** was recovered unreacted from the crude of the reaction. The results suggest that it is a case of standard kinetic resolution: the more reactive enantiomer of alkene **97** reacted faster and was completely converted to one enantiomer of product **112**, then the less reactive enantiomer also started to react (22% of it) decreasing the enantiomeric purity of the product. Unlike substrate **77**, cycloadduct **97** is not reversible under the reaction conditions and it is therefore recovered enantiomerically pure. Calculations by Jacobsen and co-workers indicates that kinetic resolution with selectivity factor of 10 allows will give starting material in optical purity higher than 99% ee at 72% conversion,[75] suggesting that a similar or grater selectivity factor was observed here.



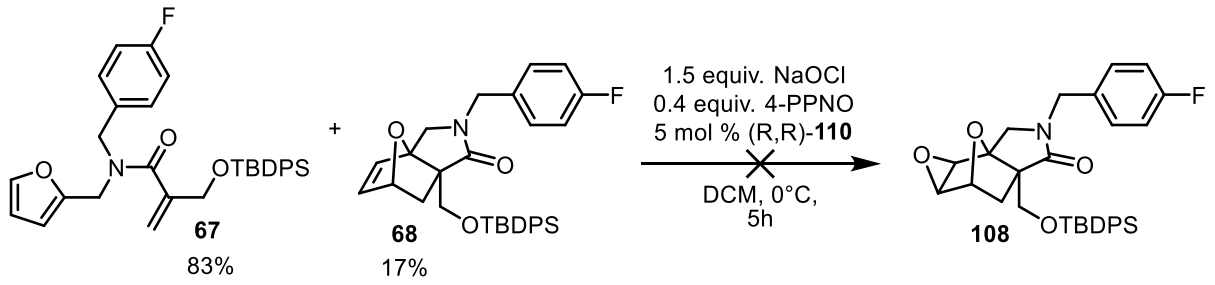
Scheme 65: Racemic (a) and asymmetric (b) epoxidation of substrate 97. ee values were determined by chiral HPLC.

The epoxide structure was deduced by 2D NMR: A weak NOE correlation appears in the NMR 7 between the 5-H and the *endo* 7-H.



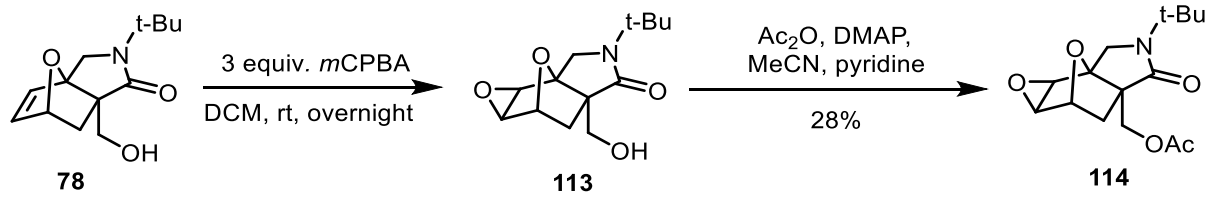
NMR 7 NOESY experiment of epoxide 112

The foregoing mixture of **67** and **68** provided the opportunity to investigate the chemoselectivity of the asymmetric reaction, as done with the racemic reaction (Scheme 58). Asymmetric epoxidation using Jacobsen's catalyst **110** (Figure 18) was attempted on mixture **67**/**68** using NaOCl as oxidising agent and 4-PPNO as co-catalyst. The reaction conditions caused fast decomposition of **67** and no **108** was isolated. The NMR of the crude of the reaction showed the presence of **68** (Scheme 66) which was consumed slower than **67**. It was not possible to isolate or identify any side-product produced by the reaction. Also under racemic epoxidation conditions the DA precursor underwent rapid decomposition, and epoxidation of the cycloadduct was slow (Scheme 60).

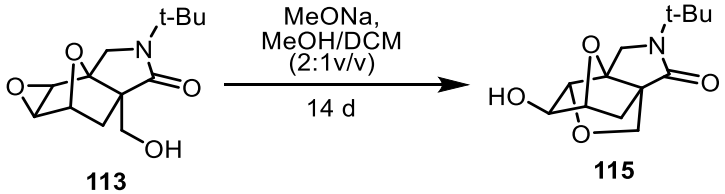


Scheme 66 Jacobsen epoxidation of 67 and 68 mixture

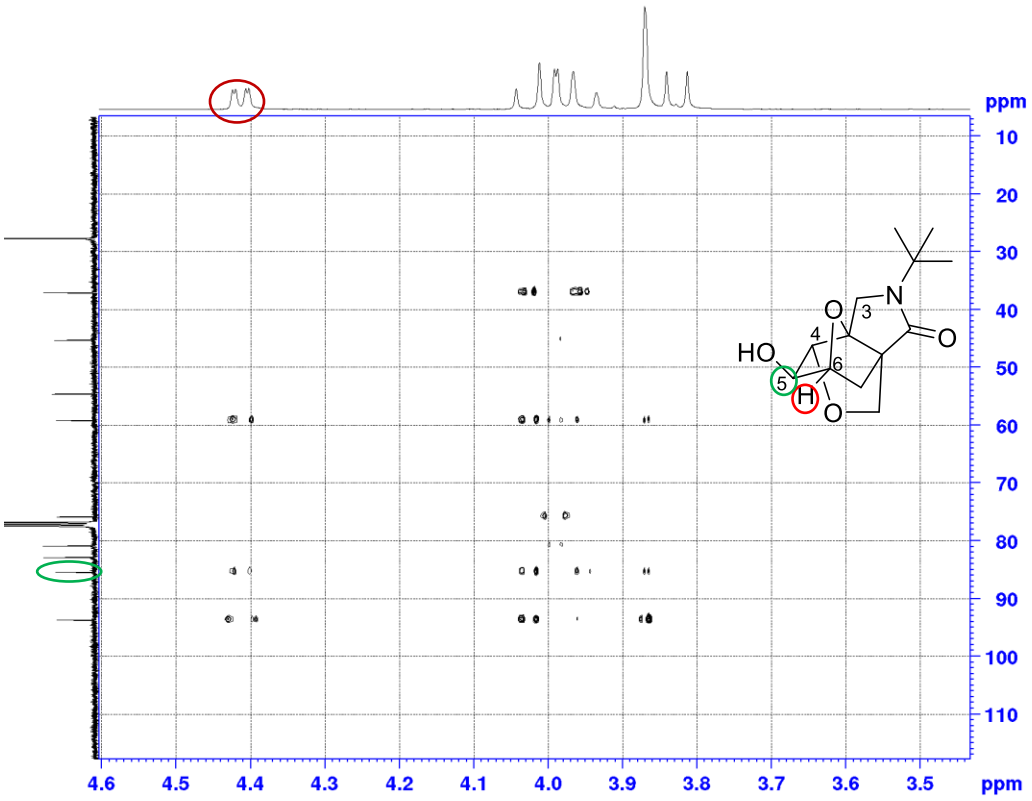
Racemic epoxide **113** was obtained from cycloadduct **78** by treatment with *m*CPBA in DCM. Acetylation of the product was performed to decrease the polarity of the compound and facilitate its extraction and purification (Scheme 67). To confirm attack on the *exo* face, epoxide **113** was dissolved in methanol in presence of a strong base (NaOMe) to induce epoxide ring-opening by attack of the alkoxide. The molecule is not flexible enough to allow attack of the alkoxide from the top face. Therefore, in case of *endo* epoxide no product would be produced. After 14 days in presence of 0.15 equiv. of base, 35% of epoxide **113** was converted into product **115**, confirming the expected facial selectivity of the substrate. Complete conversion to product **115** was observed using 1.0 equiv. of base (Scheme 68). The 2D ^{13}C–^{1}H HMBC experiment (NMR 8) shows a long-range correlation between 6-H and the carbon bearing the hydroxyl functionality, which is therefore identified as 5-C, and not 4-C, confirming the attack from the alkoxide to the epoxide ring at the carbon in 4-position.



Scheme 67 Racemic epoxidation and acetylation of substrate 78

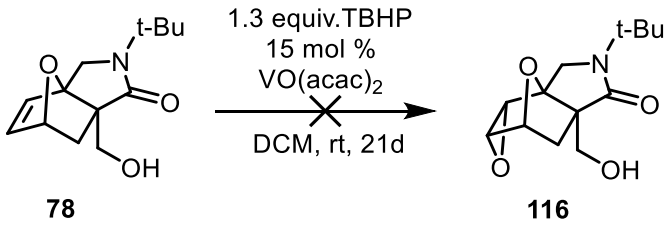


Scheme 68: Ring opening of epoxide 113



NMR 8 ^{1}H, ^{13}C-HMBC experiment of compound 115

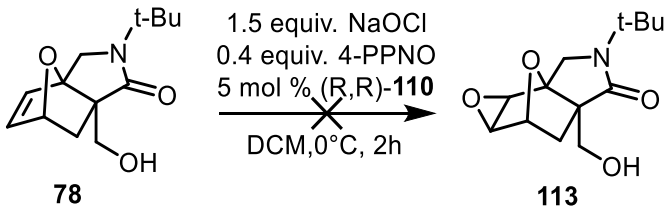
Attempt to direct the epoxidation on the *endo* face was made by using the hydroxyl group in the tether of **78** to direct the vanadium-catalysed epoxidation in Scheme 69. Alcohol **78** was treated with 1.3 equiv. of TBHP in presence of 15 mol % of $VO(acac)_2$ in DCM at rt. After 21 days, no *endo* epoxide **116** was detected and starting material **78** was recovered unreacted.



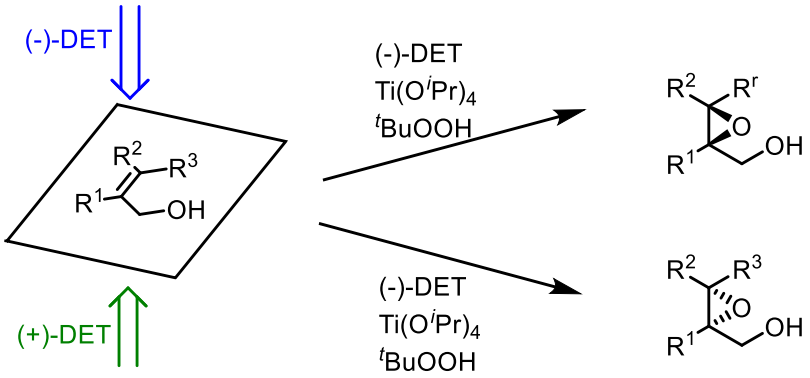
78 **116**

Scheme 69: Attempted epoxidation on the *endo* face cycloadduct 78

Treatment of alcohol **78** under Jacobsen epoxidation conditions was not successful and only SM (57%) and decomposition products were observed after 2 h at rt (Scheme 70).

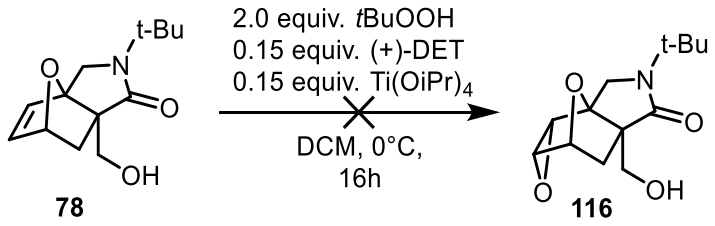


Scheme 70: Attempted Jacobsen epoxidation on substrate 78



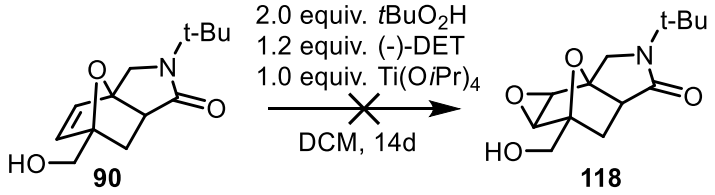
Scheme 71: Sharpless asymmetric epoxidation

Alcohol **78** was also used as substrate for the Sharpless epoxidation (Scheme 71).[76] The reaction is known to proceed with very high stereoselection in presence of allylic alcohols[77, 135] and with moderate results with of homoallylic alcohols.[136] In spite of **78** not being the classic substrate, the rigidity of the structure was expected to provide epoxide **116** by directing the attack of the oxygen on the lower face. Unfortunately, after 16 h only unreacted starting material was recovered (Scheme 72).

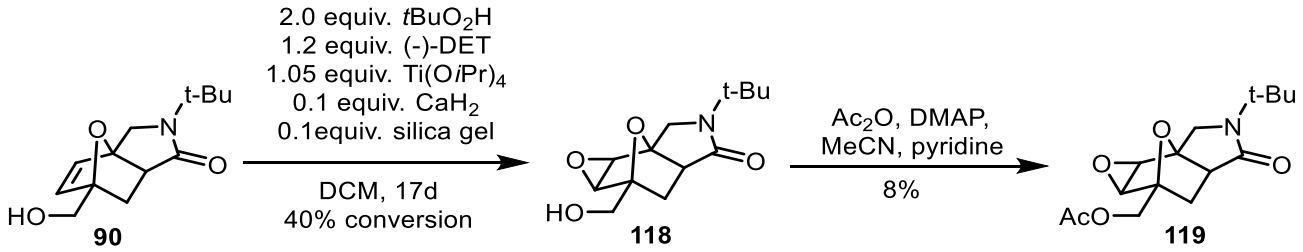


Scheme 72: Attempted Sharpless epoxidation on substrate 78

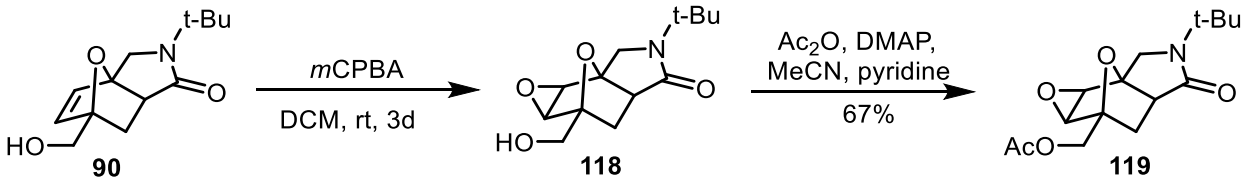
Also homoallylic alcohol **90** was unreactive under Sharpless epoxidation conditions. A modified procedure where calcium hydride and silica gel are added in the reaction mixture[137] allowed 40% conversion (8% isolated yield of **119**) after 17 days at rt (Scheme 74). Compound **119** was found to be racemic by chiral HPLC. *m*CPBA was used in the racemic reaction to obtain epoxide **118**, then converted to ester **119** (67%) to facilitate the extraction and purification process.



Scheme 73: Standard Sharpless epoxidation reaction on substrate 90

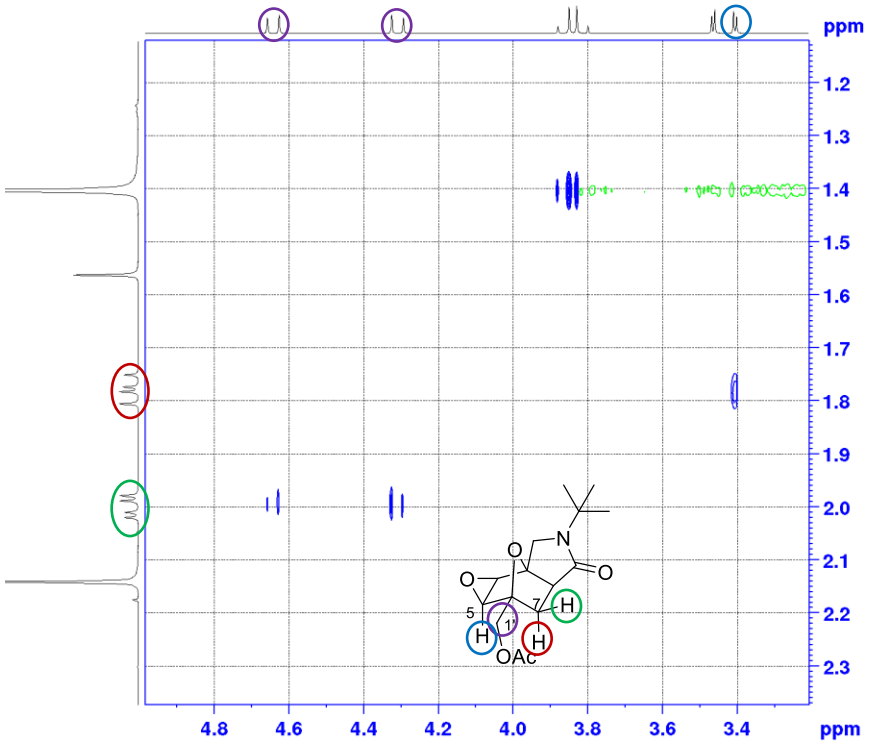


Scheme 74: Modified Sharpless epoxidation reaction on homoallylic alcohol 90



Scheme 75: Racemic epoxidation of homoallylic alcohol 90

The *exo* stereochemistry of epoxide **119** was confirmed by NMR experiments. In the NMR 9, NOE correlation can be observed between the 5-H and the *endo* 7-H, and between the 1'-CH_2 and the *exo* 7-H.

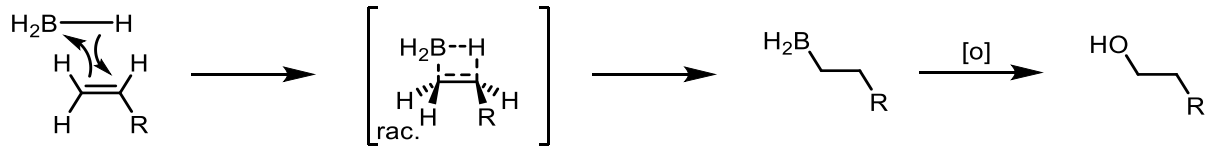


NMR 9 NOESY experiment on substrate 119

2.4.2 Hydroboration-Oxidation Reaction

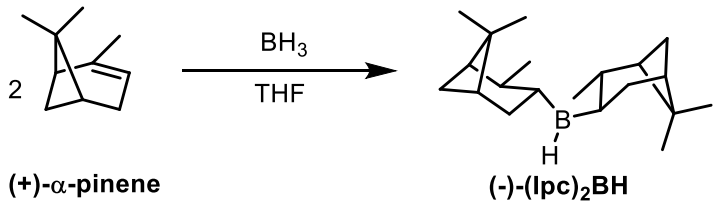
Addition of borane to a double or triple bond is called Brown hydroboration reaction. The reaction is highly regioselective and stereospecific: it proceeds via *syn* addition of the B-H bond to the olefin, to form the *anti*-Markovnikov product (the hydrogen is delivered to the most substituted carbon). The addition of the borane

proceeds through a concerted 4-membered TS. Oxidation of the resulting organoborane results in formation of the corresponding alcohol with complete retention of configuration (Scheme 76).



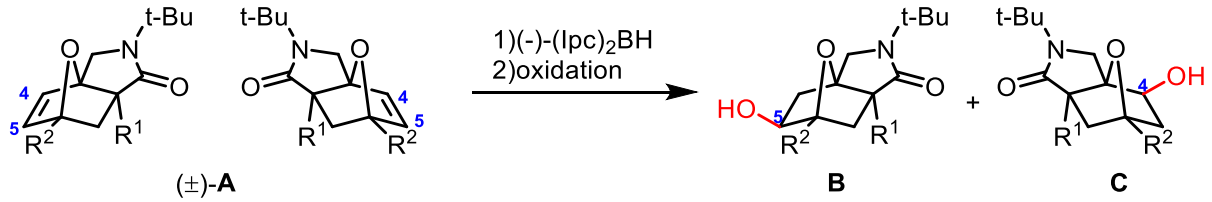
Scheme 76: Hydroboration-oxidation - general scheme

Hydroboration can be conducted in an enantioselective fashion by using boron reagent bearing enantiomerically pure chiral substituents. Many useful reagents for enantioselective synthesis derive from α-pinene. Among these, monoisopinocampheylborane $IpcBH_2$ and diisopinocampheylborane $(Ipc)_2BH$ have been widely used as hydroborating agent.[138] $IpcBH_2$ is most suitable in case of more hindered compounds, such as trisubstituted and/or *trans*-olefins.[139-141] With $(Ipc)_2BH$ very high enantiomeric excess have been reached with *cis*-disubstituted alkenes.[142-144] In the present work, (-)-$(Ipc)_2BH$ was used, which was synthesised for the first time by Brown and Zweifel in 1961 by treatment of (α)-pinene with sodium borohydride and BF_3-Et_2O in diglyme.[145] The downside of the first synthesis was that the optical purity of the organoborane was limited to the optical purity of the starting material. Subsequent modifications allowed (-)-(diisopinocampheyl)borane in 92.7 % ee to be obtained from 84% ee (+)-α-pinene, and 99.1% ee from 92% ee (+)-(α)-pinene after a certain equilibration time.[139, 142, 146-147] One of the advantages of using $(Ipc)_2BH$ is the availability of both enantiomer of α-pinene, which give access to alcohols of opposite configuration. In our experiments, $(Ipc)_2BH$ was prepared *in situ* by addition of 1 equiv. of BH_3-DMS and 2.30 equiv. of (α)-pinene (Scheme 77) to avoid formation of monoisopinocampheylborane ($IpcBH_2$) that induces opposite chirality in the product.[148] No equilibration time was necessary as the α-pinene starting material was bought in 97% ee.



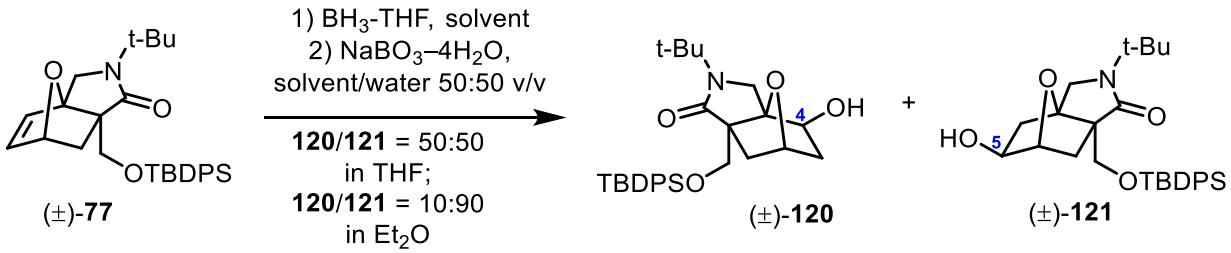
Scheme 77: Synthesis of (-)-$(Ipc)_2BH$

Treatment of enantiomeric mixtures of oxanorbornene substrates, with both achiral BH_3 and chiral Ipc_2BH, gave mixtures of isomeric product and that differ for the position of the substitution (4 and 5). By Mosher ester analysis, we proved that in the asymmetric reaction the two products **B** and **C** derive from opposite enantiomers of starting material **A**, in a process known as regiodivergent parallel kinetic resolution (Scheme 78).

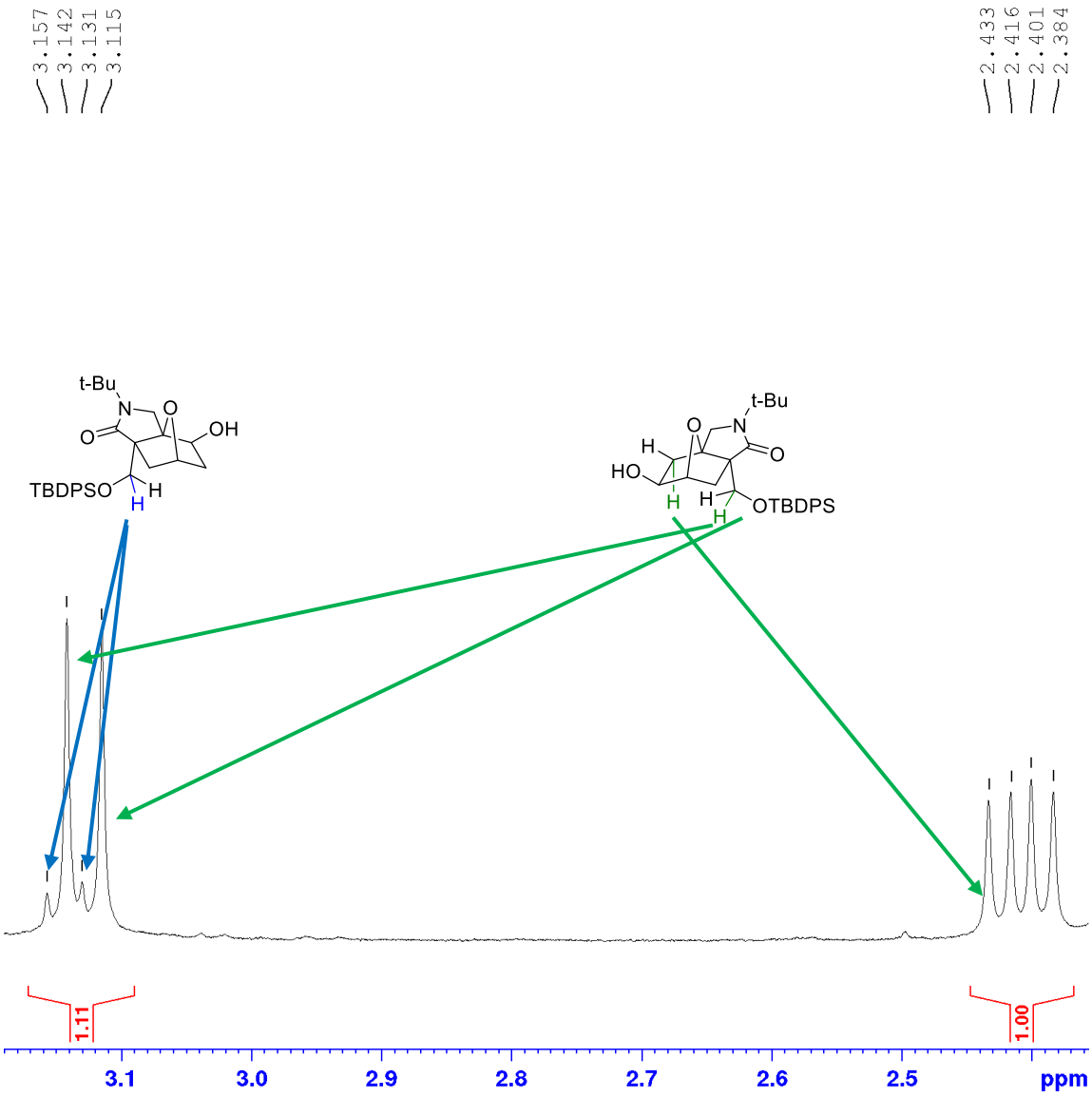


Scheme 78 regiodivergent kinetic resolution

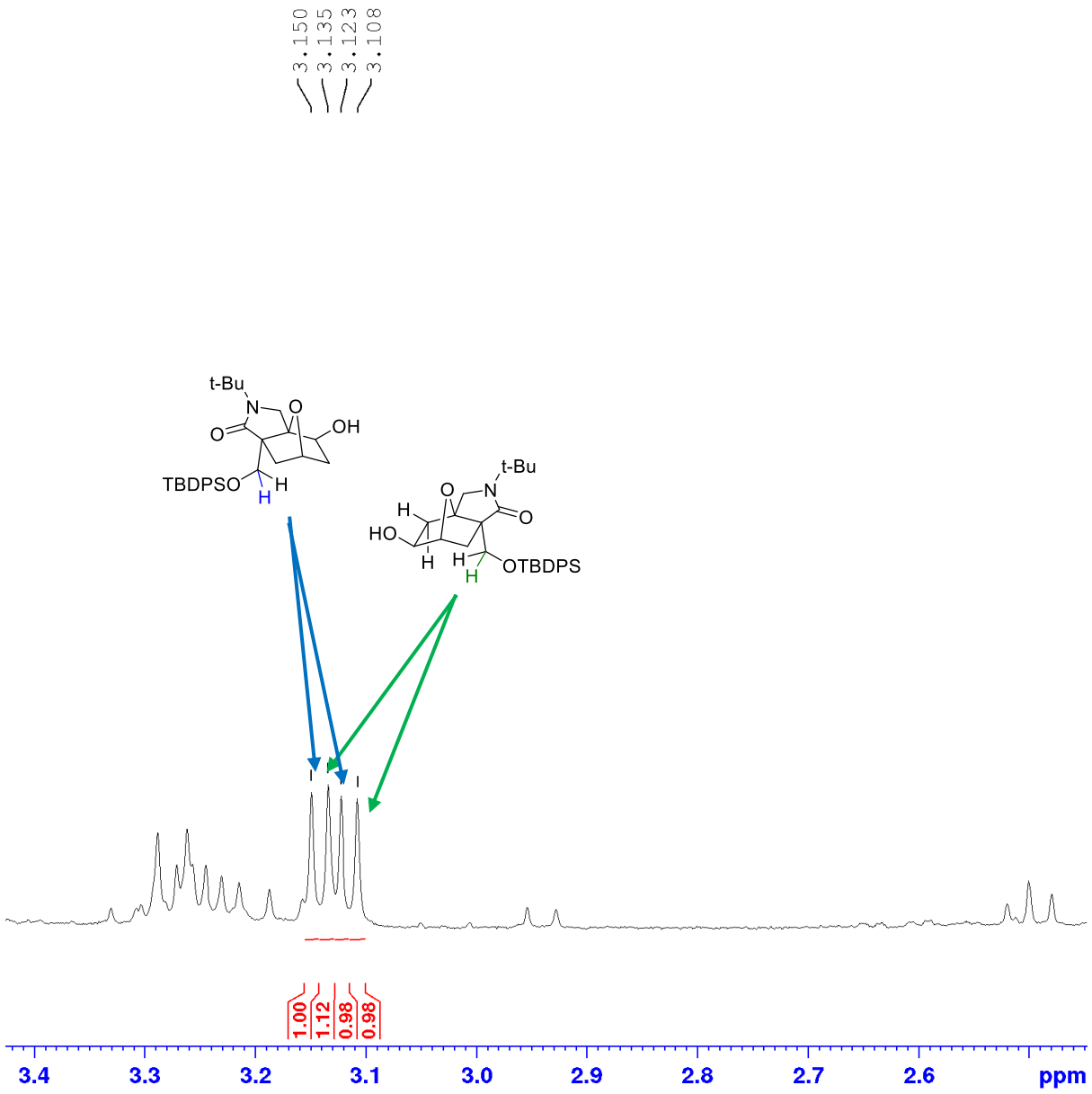
Reaction of substrate **77** with BH_3-THF complex in THF, yielded a 50:50 mixture of regioisomer organoborane, then transformed into **120** and **121** by oxidative workup with sodium perborate in water/THF (1:1 v/v) (Scheme 79 and NMR 11). Equimolar quantities of substrate and borane were used in all the reactions. Changing the solvent of the reaction to Et_2O (together with the THF derived from the reagent BH_3-THF 1M in THF), affects both the reaction rate (reaction completed after 23 h), and the ratio of the two products, found in 90:10 ratio in favour of 5-substituted **121** (NMR 10). Regardless of the solvent used, the asymmetric reaction with substrate **77** provided always a mixture close to 50:50 enantiomerically enriched **120** and **121** (Table 17). Change in temperature has only a minor effect on the regioselectivity (Table 17, Entry 2). Complete consumption of the starting material was observed in all reactions, except at -78 °C where only unreacted SM was found in the crude of the reaction.



Scheme 79 Racemic hydroboration-oxidation reaction of substrate 77



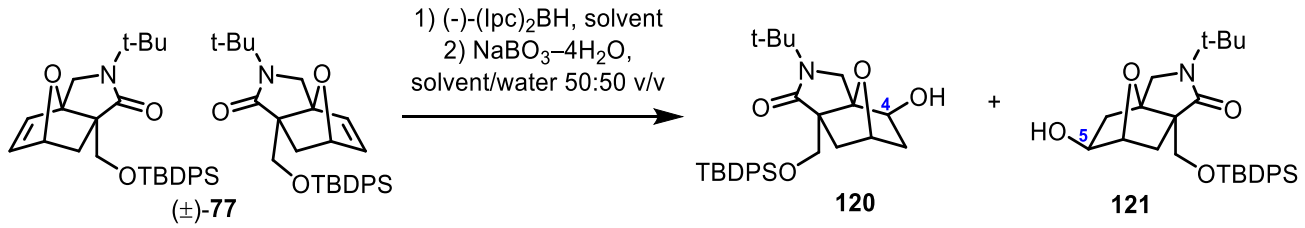
NMR 10: Racemic hydroboration-oxidation of substrate 77 in diethyl ether



NMR 11: Racemic hydroboration-oxidation of substrate 77 in tetrahydrofuran

Assignment of the 4-OH and 5-OH regioisomers was made by 1D and 2D NMR experiments. The multiplicity of the protons in 6-position (a triplet in **120** and a doublet in **121**) was useful, as it allowed us to identify the compounds.

Table 17: Asymmetric hydroboration-oxidation of substrate 77

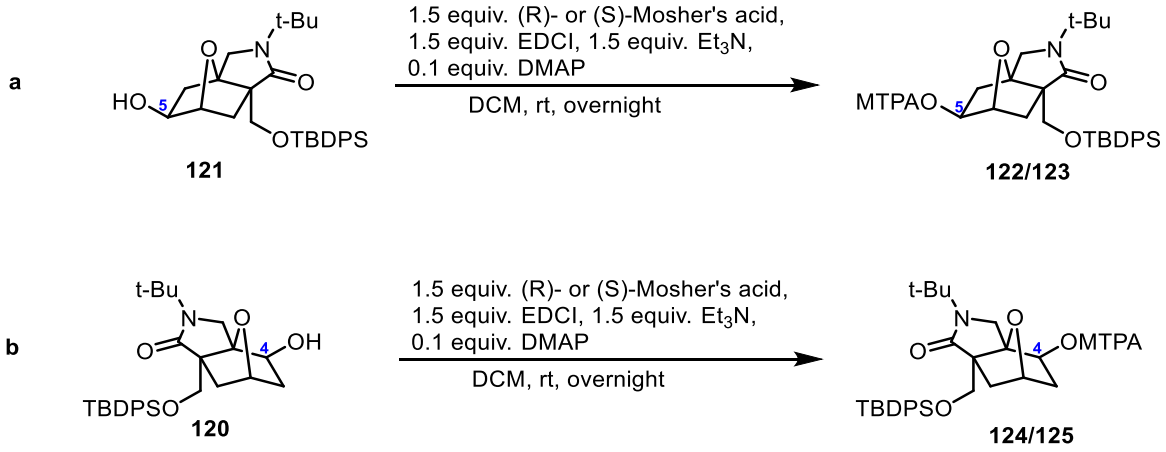


(±)-**77** **120** **121**

Entry	Conditions	Ratio 120:121	er 120[a]	er 121[a]	Isolated yield (%)
1	THF, 0°C	50:50	75:25	76:24	64
2	THF, -40°C	55:45	76:24	94:6	67
3	THF, -78°C	/	/	/	/
4	Et_2O/THF 6:1, -20 to -10°C	50:50	97:3	95:5	75[b]

[a]Determined by chiral HPLC; [b]Isolated yield of *p*-bromobenzoate ester derivatives obtained following the general procedure L

Absolute configuration of alcohols **120** and **121** was determined by Mosher's esters analysis[149] Esters **122** and **123** were prepared by EDCI coupling reaction of **121** with (*S*)-(-)- and (*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid (MTPA-OH) respectively (Scheme 80a). Esters **124** and **125** were obtained from alcohol **120** in an analogous way (Scheme 80b). Moshers's esters assume a conformation in which the trifluoromethyl, the carbonyl ester, and the proton of the carbinol are *syn*-coplanar (Figure 19). Protons on the same side of the phenyl group experience a stronger magnetic shielding effect that results in more upfield chemical shifts. The sign of the difference of chemical shift $\Delta\delta^{SR}$ of the pair of diastereomers obtained with (+)- and (-)-Mosher acid (or acid chloride), let us deduce conformation of the carbinol. Analysis of the data collected indicates absolute configuration of the carbinol 4-C of **120** as (*S*) and carbinol 5-C of **121** as (*S*).



Scheme 80: Synthesis of Mosher's esters from 121 (a) and 120 (b)

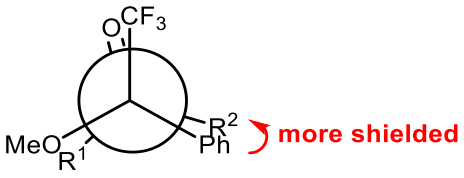
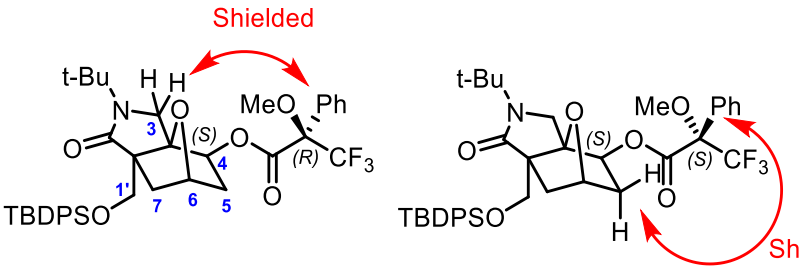


Figure 19: Configuration adopted by Mosher's esters

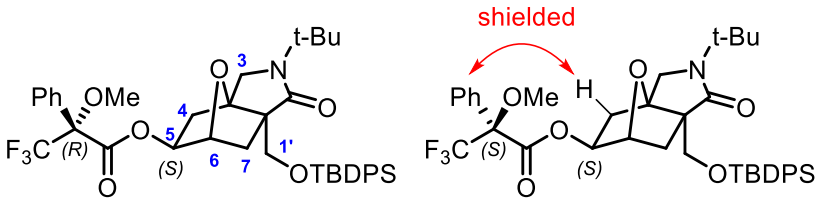
Table 18: Chemical shifts obtained by analysis of Mosher's esters of 120



$\Delta\delta^{SR}$ (=δS-δR)

proton	ppm	Hz (400 MHz)
4	-0.02	-7
6	-0.03	-13
1'	0.014	5.76
1'	0.0008	3.09
3	0.157	78.51
3	0.168	83.98
5	-0.08	-31
5	-0.026	-12.76
7	0	0
7	0	0
N-*t*Bu	0.042	21.24

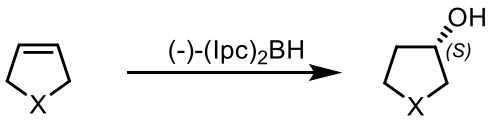
Table 19: Chemical shifts obtained by analysis of Mosher's esters of 121



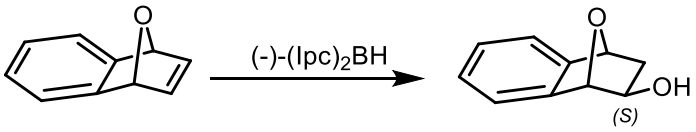
$\Delta\delta^{SR}$ (=δS-δR)

proton	ppm	Hz (400 MHz)
6	0.08	33
5	0	0
1'	0	0
1'	-0.01	-3
4 *exo*	-0.07	-28
4 *endo*	-0.07	-28
7 *exo*	0.013	5.31
7 *endo*	0.012	4.95

The absolute stereochemistry obtained in our study agrees with previous examples reported by Brown (Scheme 81).[150]

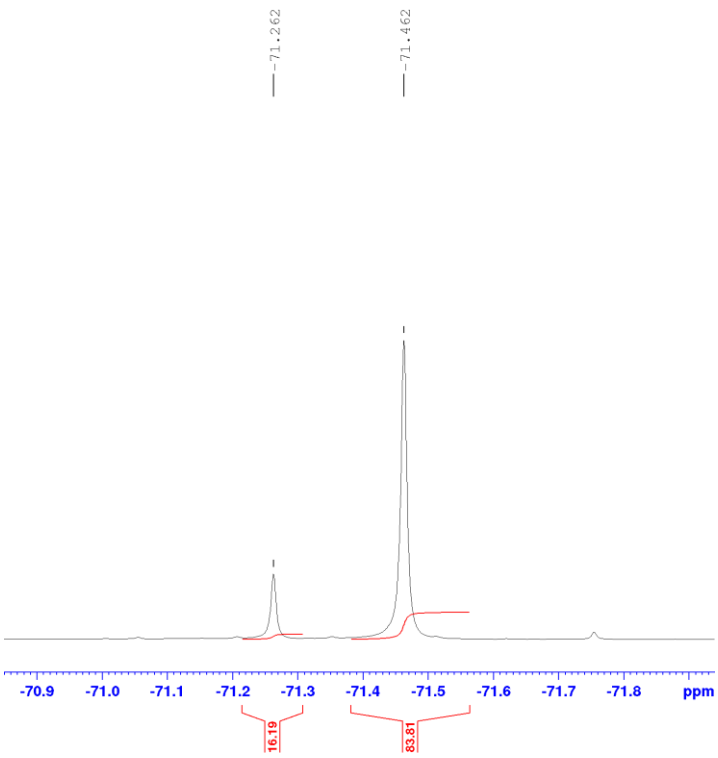


X = O, N-$CH_2C_6H_5$, N-$CO_2CH_2C_6H_5$

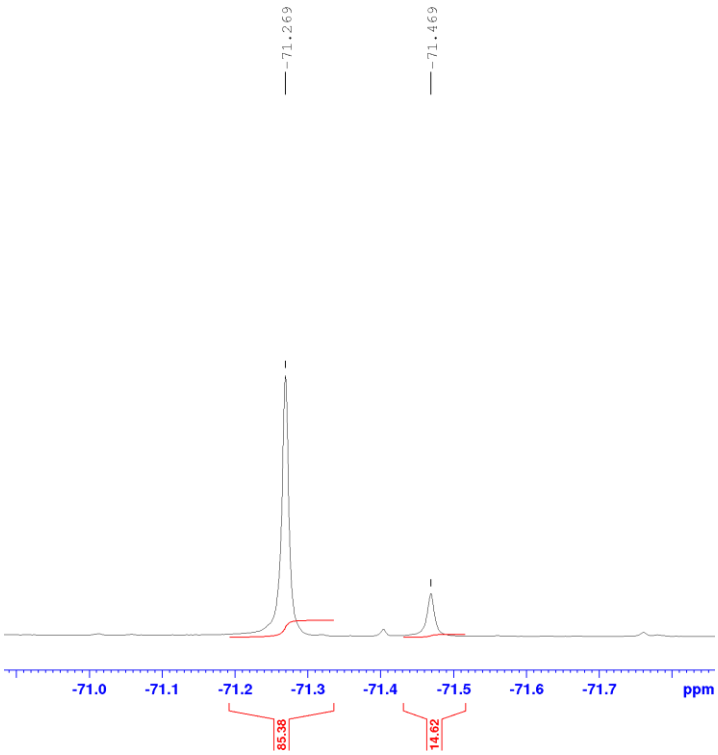


Scheme 81: Absolute stereochemistry of alcohols obtained from heterocycles with $(Ipc)_2BH$

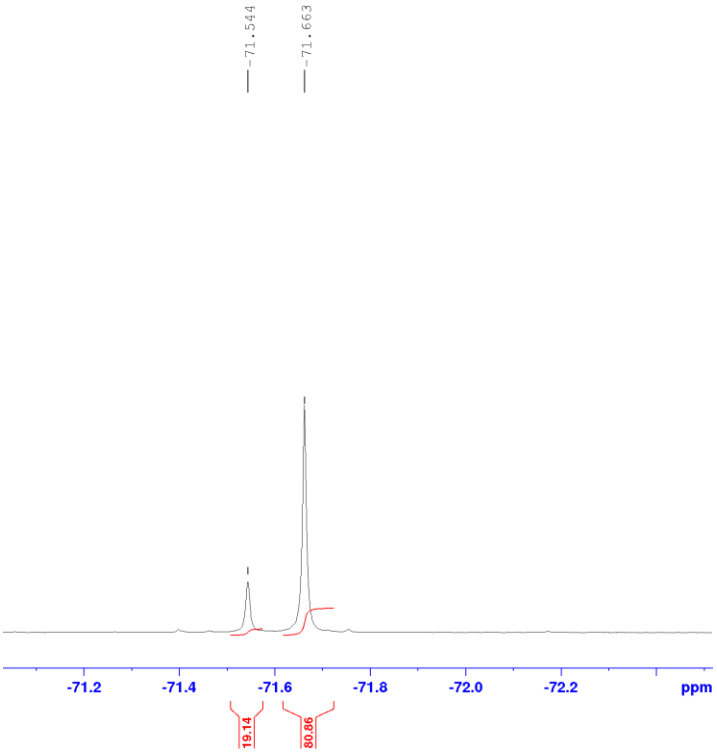
^{19}F NMR of Mosher's esters was also used to determine the enantiomeric ratio of **120** and **121** by integration of the pairs of diastereomers **122**-**123** and **124**-**125**. Data indicates an enantiomeric ratio of 85:15 for compound **120** (NMR 12, NMR 13) and 81:19 for **121** (NMR 14, NMR 15). This is in contrast with the results obtained from analysis by chiral HPLC of samples obtained under the same conditions (Entry 2, Table 17).



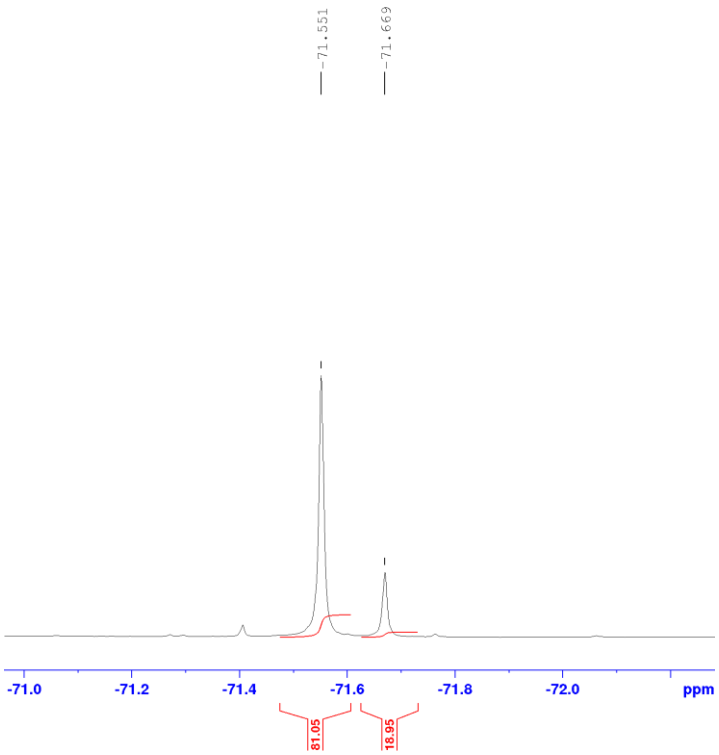
NMR 12: ^{19}F of (+)-Mosher ester from 120



NMR 13: ^{19}F of (-)-Mosher ester from 120



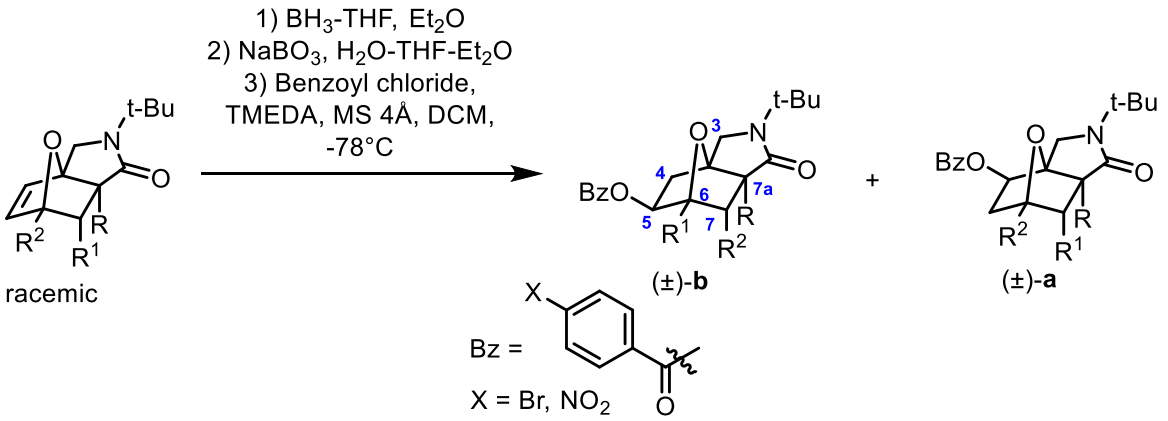
NMR 14: ^{19}F of (+)-Mosher ester from 121



NMR 15: ^{19}F of (-)-Mosher ester from 121

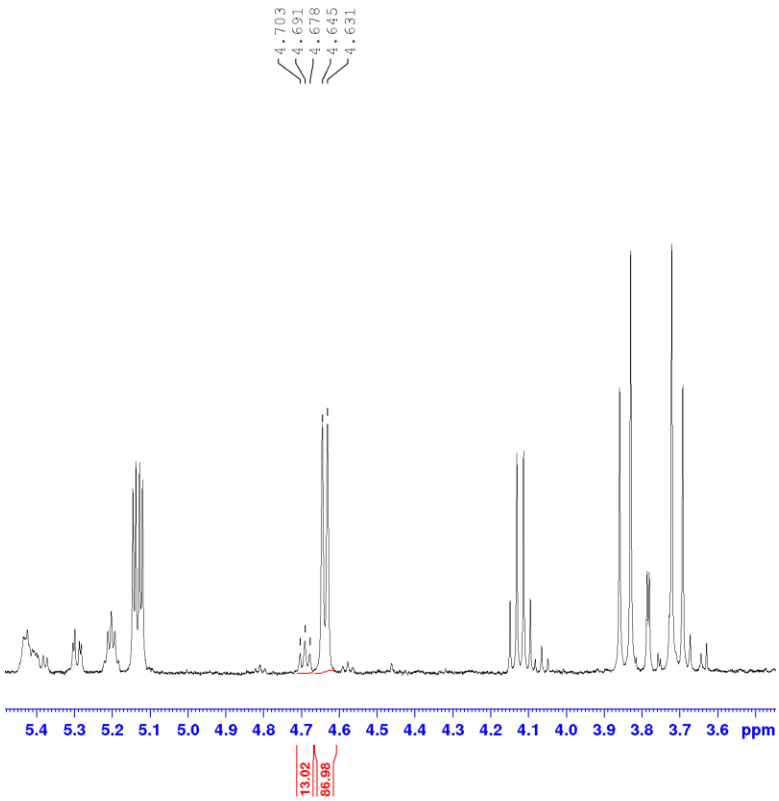
The substituent effect on the ratio of the two products was investigated (Table 20): when no substituent is present in positions 6 and 7, a mixture of the two regioisomers, with the 5-substituted strongly favoured, is obtained (entries 1 and 2). 6-bromo cycloadduct was not reactive and only starting material was present in the crude of the reaction after 5 days at rt (entry 5). When R^2 = Methyl, the substrate favours the 4-substituted product and the ratio shift to **130**:**131** = 68:32 (entry 3). 7-trifluoromethyl cycloadduct **84** gave the product of attack by boron exclusively at the 5-position (entry 6). Structures were confirmed by 2D NMR experiments.

Table 20: Racemic hydroboration

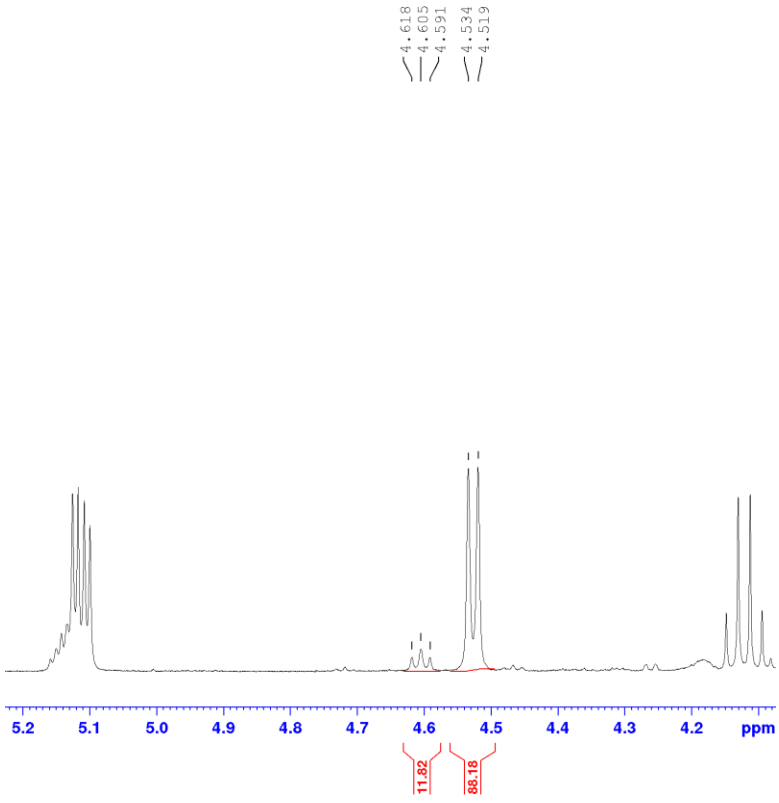


					Ratio[a]		Total Yield	
Entry	**SM**	**R**	**R^1**	**R^2**	**a (4-OR)**	**b (5-OR)**	**(%)**	**Ref**
1	**82**	H	H	H	13 (**126**)	87 (**127**)	11	NMR 16
2	**80**	Me	H	H	12 (**128**)	88 (**129**)	Not isolated	NMR 17
3	**100**	Me	H	Me	68 (**130**)	32 (**131**)	47	NMR 18
5	**97**	Me	H	Br	/	/	0	/
6[b]	**84**	H	CF_3	H	0	100 (**132**)	/	/

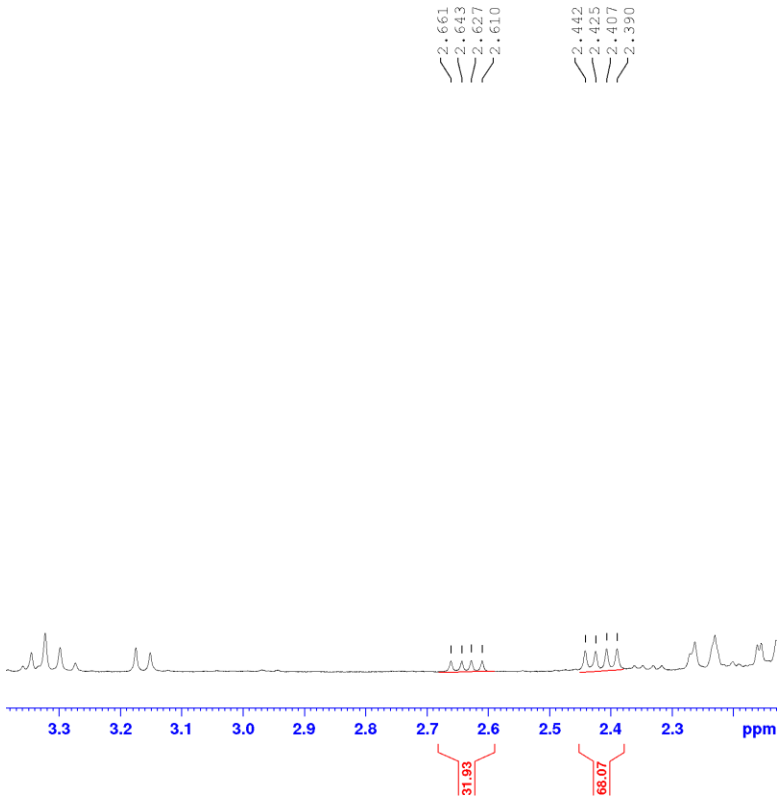
[a]Determined by ^{1}H NMR; [b]Compound derived from hydroboration-oxidation without derivatisation to ester.



NMR 16: Ratio of 126/127 obtained with BH_3



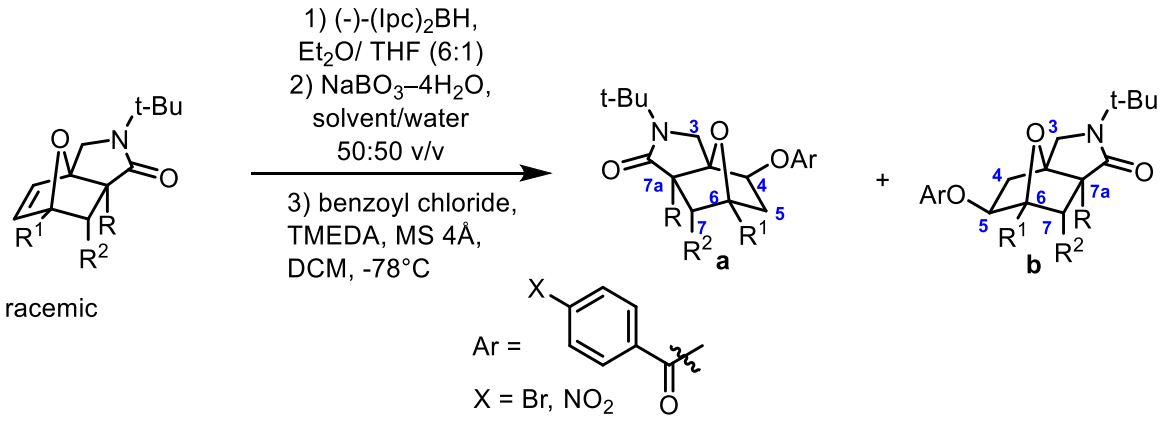
NMR 17: Ratio of 128/129 obtained with BH_3



NMR 18: Ratio of 130/131 obtained with BH_3

An interesting fact that emerged from asymmetric hydroboration with (-)-$(Ipc)_2BH$, is that the rate of the reaction increased with the bulkiness of the substituent R (Table 21). As seen in Entry 2 of Table 17, when R =$CH_2OTBDPS$, the reaction proceeds smoothly at -40°C. At -20°C, substrate with R = methyl shows a conversion of only 28% (Table 21, entry 3), and without any substituent (R = H), no product was obtained at -20 °C (entry 1). As seen also for the racemic reaction, 6-bromo cycloadduct **97** does not react under the hydroboration conditions (entry 6). Compounds with substituents in 6-position showed lower reactivity, and higher temperature and longer reaction time were necessary (entries 4-6). Also, ratio of the regioisomeric products is perturbed in favour of the 4-substituted alcohol (entry 4). Recovered starting material **100** showed an enantiomeric ratio of 98:2, suggesting a different reactivity of the cycloadduct enantiomers.

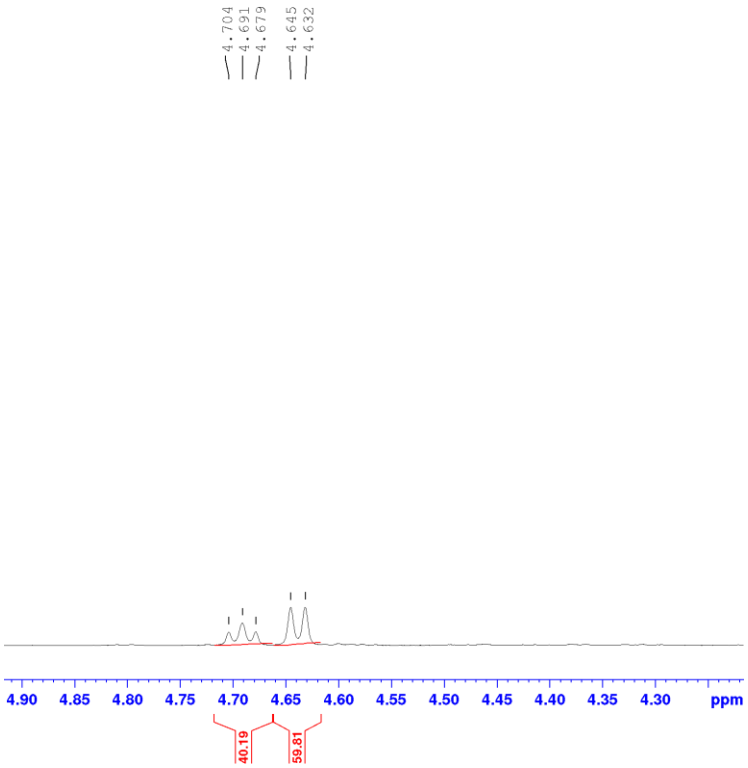
Table 21: Asymmetric hydroboration-oxidation reaction



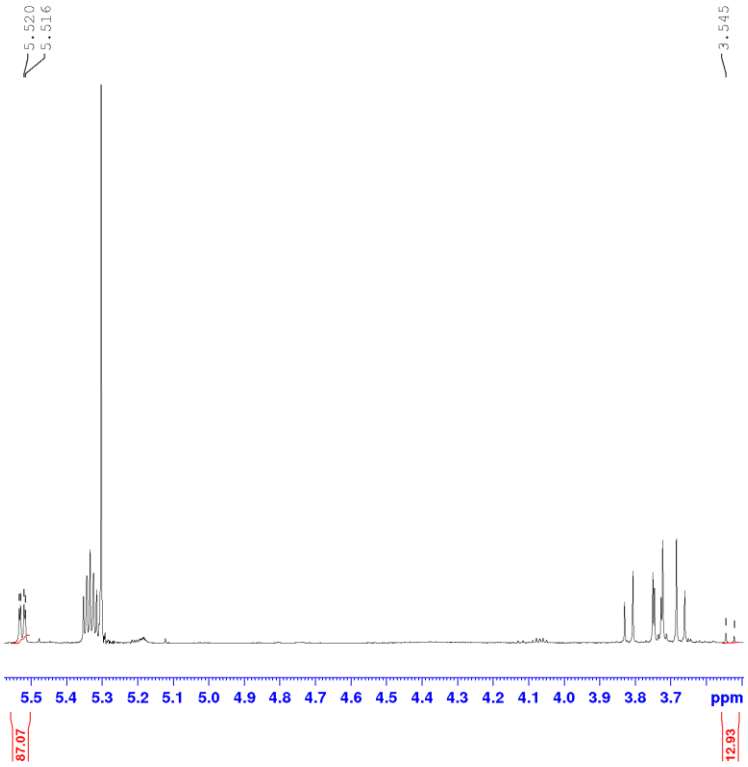
Entry	SM	R	R^1	R^2	Time	T (°C)	Ratio[a] a	Ratio[a] b	Conversion (%)	Total yield (%)	ee[b] (%)	Ref
1	**82**	H	H	H	7h	-20			0			
2	**82**	H	H	H	18h	20	40	60	100	40	84 **a** 60 **b**	NMR 19
3	**80**	Me	H	H	7h	-20			28			
4	**100**	Me	H	Me	4d	-15	87	13	65	38	74 **a** 40 **b**	NMR 20
5	**92**[c]	OTBDPS	H	OTBS	7h	-40			0			
6	**97**[c]	Me	H	Br	7.5h	-20			0			

[a]Determined by ^{1}H NMR; [b] Determined by chiral HPLC; [c] Reaction performed in THF

Analysis of the product composition derived from cycloadduct **82** showed that products derived from each cycloadduct enantiomer are in a 49:51 ratio, suggesting that no DKR took place. Analysis of the product composition derived from **100** and the enantiomeric composition of the recovered starting material, showed that little DKR took place (ratio of species derived from each enantiomer = 47:53).

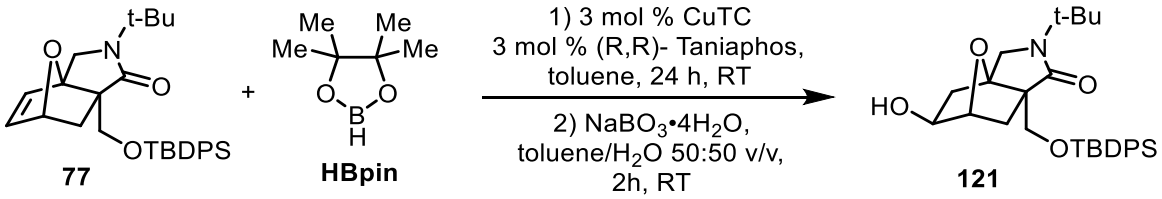


NMR 19: Ratio of 126/127 obtained with (-)-(Ipc)$_2$BH



NMR 20: Ratio of 130/131 obtained with (-)-(Ipc)$_2$BH

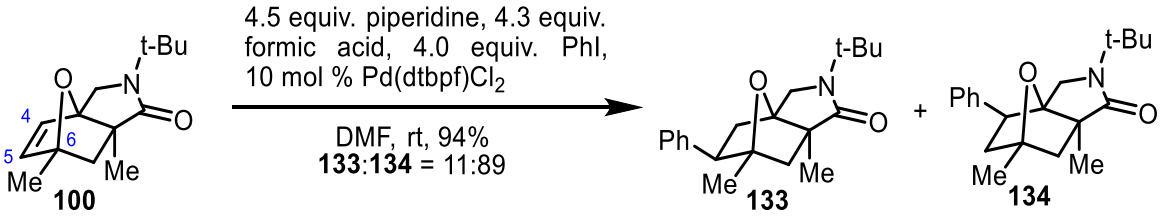
Catalytic enantioselective hydroboration is an efficient method to obtain optically enriched organoboron compounds. Yun *et al.*, recently developed a method for metal-catalysed asymmetric hydroboration of bicyclic alkenes, including oxanorbornene derivatives.[151] Following their protocol, substrate **77** was treated in presence of 3 mol % of CuTC, 3 mol % of ligand Taniaphos and 1.2 equiv. of HBpin in toluene. Unfortunately, oxidative work-up after 24 h at rt, provided only traces of 5-substituted product **121** (Scheme 82).



Scheme 82: Catalytic asymmetric hydroboration

2.4.3 Reductive Heck

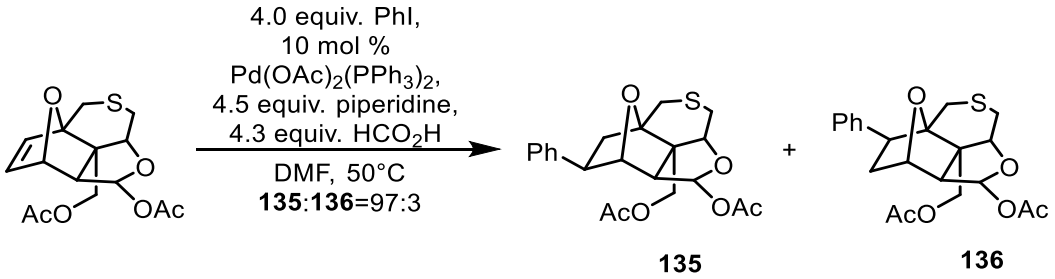
Reductive Heck is an efficient method to form new carbon-carbon bonds between olefins and aryl or alkenyl halides. The reaction has been successfully applied to bicyclo[2.2.1]hept-2-ene, aza- and oxabicyclo[2.2.1]hept-2-ene derivatives.[152-155] In all reported cases complete *exo*-stereoselectivity was observed, but only a few examples of regioisomeric products from asymmetric norbornenes were reported.[156-158]



Scheme 83: Reductive Heck coupling of substrate 100

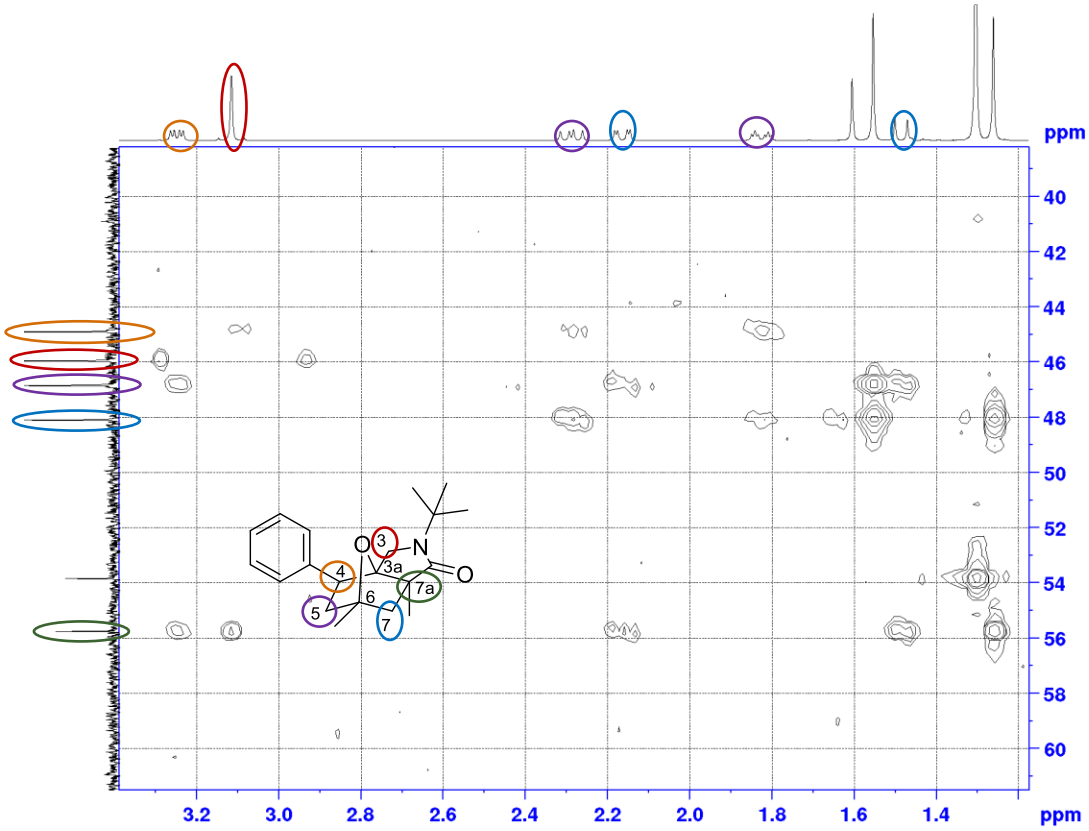
Reductive Heck coupling was performed on substrate **100** and benzyl iodide using 10% of precatalyst Pd(dtbpf)Cl_2, 4.5 equiv. of piperidine, 4.3 equiv. of formic acid in DMF at rt. After 20 h starting material **100** was completely consumed and no other products other than **133** and **134** were present in the crude of the reaction (Scheme 83). After column chromatography, the two products were isolated in 94% total, but it was not possible to completely

separate them. As seen with the hydroboration reaction, mono-substitution of the cycloadduct double-bond generates a mixture of two regioisomers. A previous example reported by Wållberg and Magnusson of reductive Heck on oxanorbornene strongly favoured the 5-substituted product (Scheme 84). In our case, the presence of the methyl at the bridged position, is likely to bias the steric environment of the two sp^2 carbons in favour of the carbon in 4-position, from which derives the major product (89% in the crude).



Scheme 84: Reductive Heck reaction with preference for attack to 5-position

Compound **134** was identified as the 4-substituted regioisomer by 2D NMR experiments. In NMR 21 is the 1H, 13C-HMBC spectrum of compound **134** in which are shown the correlations between the carbon bearing the phenyl ring and the 3-H_2, and between 5-H_2 and 7-C.



NMR 21 ^{1}H, ^{13}C-HMBC spectrum of compound 134

2.4.4 Dihydroxylation

The third resolving reaction examined is the Sharpless asymmetric dihydroxylation (SAD) reaction.[159] There are examples of cyclic olefins that underwent SAD reaction with good enantioselectivity,[160] and the polar water/alcohol solvent mixture necessary for the reaction is desirable for our reactions as it increases the rate of the cycloaddition in case of SM:cycloadduct mixtures. It is a catalytic, stereospecific and enantioselective process, used for the formation of vicinal diols by oxidation of an olefin with osmium tetroxide in presence of chiral ligands. The presence of the ligand is crucial in this reaction, not only for the induction of enantioselectivity, but also because they are known to significantly accelerate the reaction. The ligands used are Cinchona alkaloids, and the more common are $(DHQ)_2PHAL$ and $(DHQD)_2PHAL$ (Figure 20). The two alkaloids are pseudoenantiomers: diastereomers that behave like enantiomers in the reaction, inducing opposite configuration in the product (Figure 21).

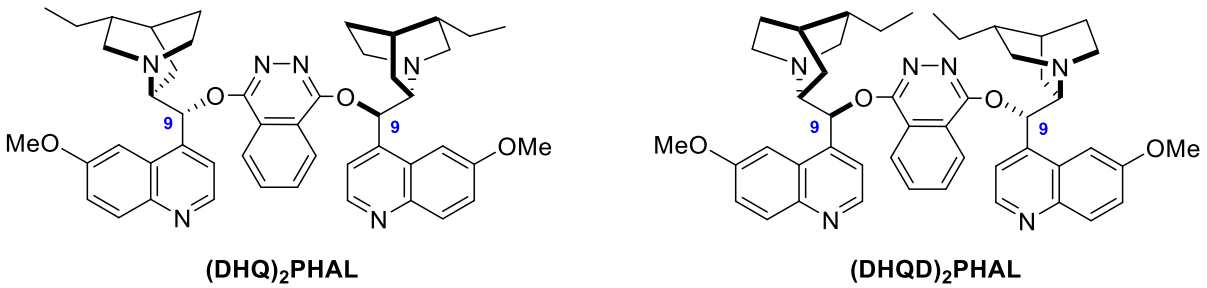


Figure 20: $(DHQ)_2PHAL$ and $(DHQD)_2PHAL$

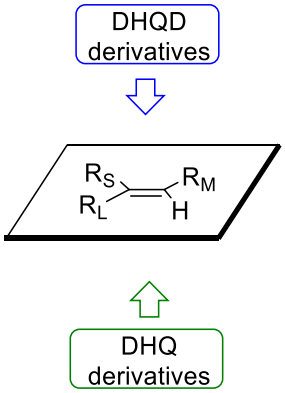
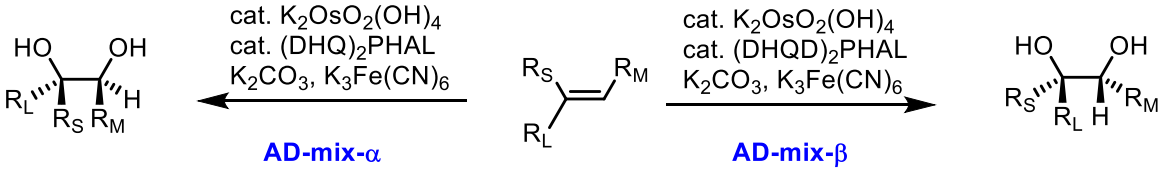


Figure 21: Opposite facial attack from pseudoenantiomers $(DHQ)_2PHAL$ and $(DHQD)_2PHAL$

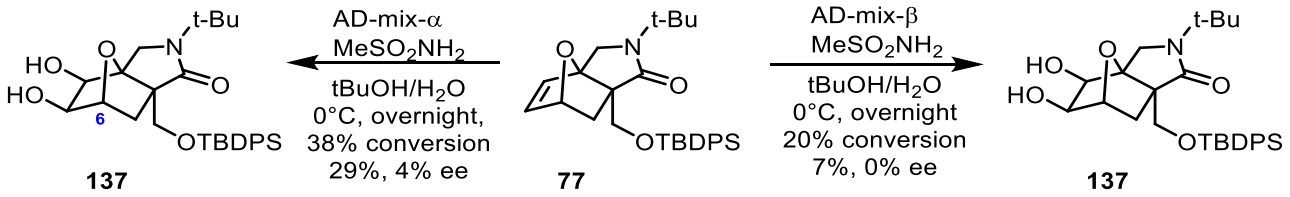
The reaction can be conveniently carried out using a premix (AD-mix-α or AD-mix-β) that contain non-volatile $K_2OsO_2(OH)_4$ as osmium(VI) source, chincona alkaloid ligand ($(DHQ)_2PHAL$ or $(DHQD)_2PHAL$), K_2CO_3 and oxidant $K_3Fe(CN)_6$ (Scheme 85).



Scheme 85: AD-mix

With the exception of terminal alkenes, addition of $MeSO_2NH_2$ to the reaction accelerate considerably the dihydroxylation, especially with sterically hindered substrates. Its addition allows the reactions to be performed at lower temperature, increasing the enantioselectivity.[161]

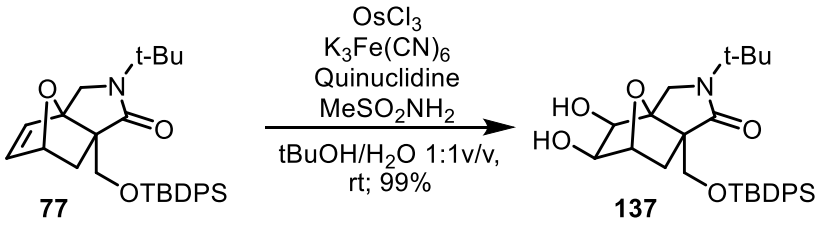
Treatment of cycloadduct **77** with AD-mix and methanesulfonamide in a 50:50 v/v mixture of water and *tert*-butyl alcohol at 0 °C overnight, produced diol **137** in 29% yield and 4% ee when using AD-mix α, and racemic diol in 7% yield with AD-mix β (Scheme 86). The difference in enantioselectivity of the two reactions is not uncommon when employing cinchona alkaloid derivatives, as they are not real enantiomers even if they induce opposite configuration in the products.[162] The enantiomeric excesses were measured by chiral HPLC.



Scheme 86: SAD reaction on substrate 77 using AD-mix α and AD-mix β

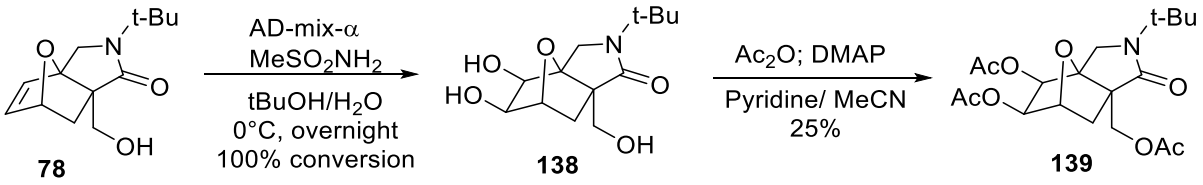
Analysis by ^1H NMR of diol **138** showed that the proton in 6-position was a doublet, suggesting an *exo* stereochemistry of the product.

The Upjohn method caused extensive decomposition of the substrates. For this reason, the racemic reactions were performed using the Sharpless-like protocol reported by Warren and Wyatt.[163] Oxidation relies on the accelerating effect of the ligand, which in this case is the achiral quinuclidine. Under these conditions (cat. $OsCl_3$, cat. quinuclidine, $K_3Fe(CN)_6$, $MeSO_2NH_2$, K_2CO_3, 50:50 H_2O/*t*BuOH), substrate **77** was converted into diol **137** in 99% yield (Scheme 87).



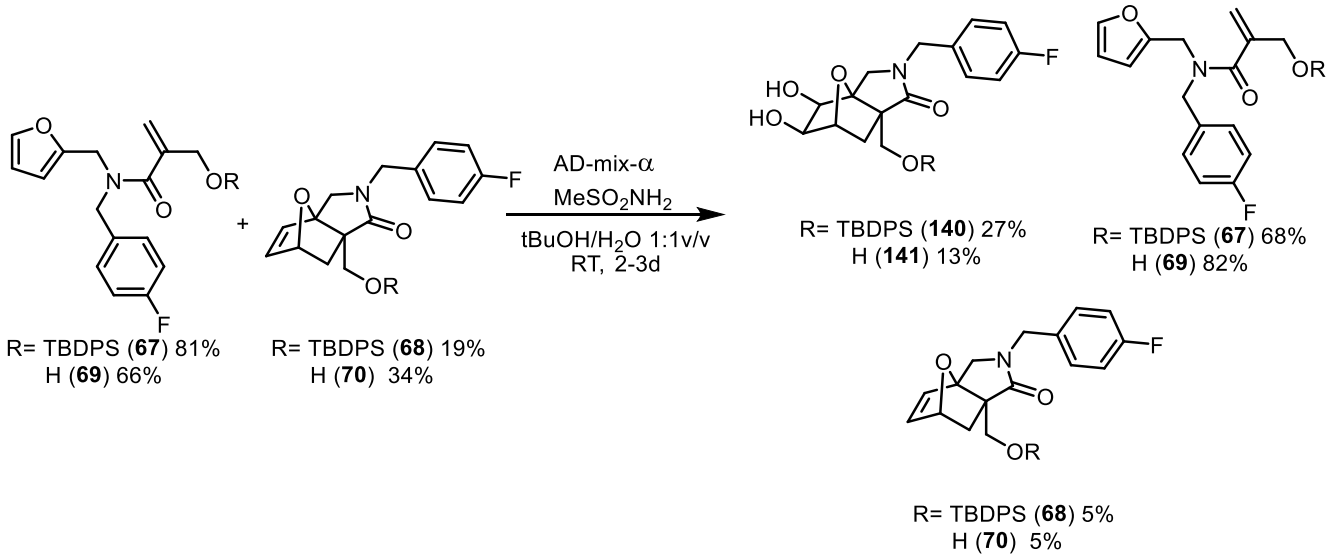
Scheme 87: Racemic dihydroxylation of cycloadduct 77

Reaction of cycloadduct **78** under SAD conditions, followed by treatment with acetic anhydride, provided compound **139** (Scheme 88). It was not possible to determine the enantiomeric ratio by chiral HPLC with UV detector because the product is not UV active.

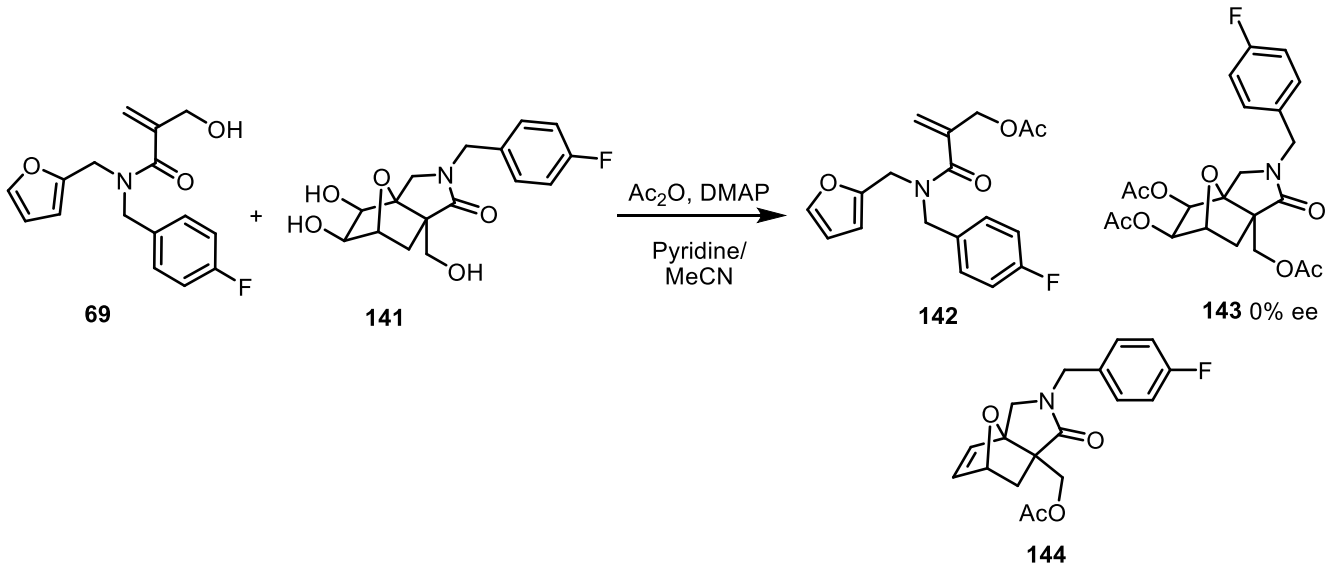


Scheme 88 SAD on substrate 78

Dihydroxylation was also attempted on mixtures SM:cycloadduct **67**/**68** and **69**/**70** with AD-mix α, to obtain compounds **140** and **141** respectively (Scheme 89). After work-up, the crude of the reaction from mixture **67**/**68** had the following composition: 68% of DA starting material **67**, 5% of DA product **68**, 27% of diol **140**. The crude of the SAD reaction from mixture **69**/**70** consisted of 82% of amide **69**, 5% of cycloadduct **70** and 13% of diol **141**. The composition of the mixtures suggests chemoselectivity of the reaction in favour of the cycloadduct, as the acyclic precursor is found unreacted after the oxidation. The small amount of cycloadducts **68** and **70** are expected to be always present as they derive from cycloaddition of unreacted **67** and **68**. Alcohol **69** was high to purify due to its high polarity so it was treated with acetic anhydride and DMAP in pyridine/acetonitrile (Scheme 90). The products obtained were triester **143**, acetylated Diels-Alder starting material **142**, and acetylated oxanorbornene **144** derived from **142** (the NMR shows the presence of DA starting material and its product which increases over time: 7% after isolation and 17% after 24 h). The ee measured by chiral HPLC indicated that Sharpless dihydroxylation was not stereoselective.

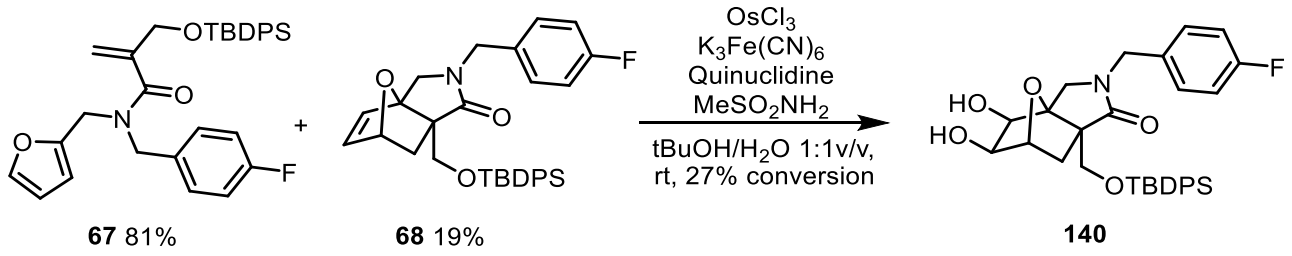


Scheme 89: Sharpless AD and acylation of AD products

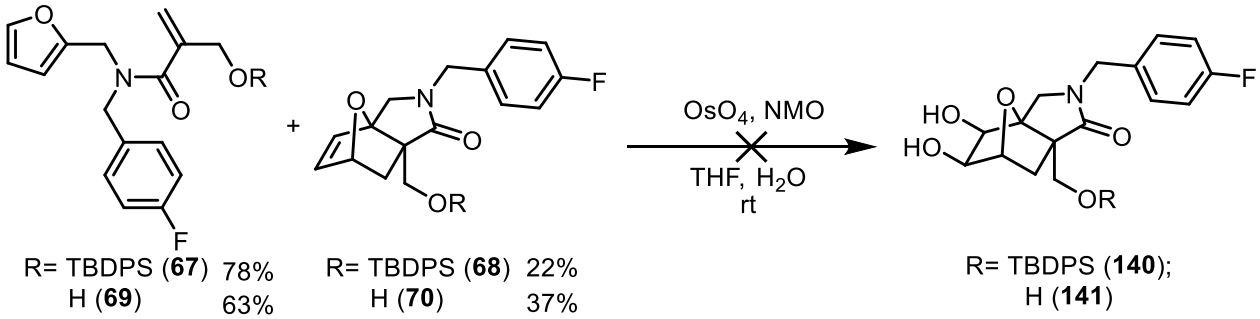


Scheme 90: Acetylation of triol 141

The Upjohn method brought about extensive decomposition also with mixtures **67**/**68** and **69**/**70**, and no product was observed with the conditions indicated in Scheme 92. Under racemic Sharpless-like conditions, from **67**/**68** (91:19) mixture, 27% was converted into diol product **140**. Only 7% was isolated after column chromatography purification (Scheme 91).



Scheme 91: Racemic dihydroxylation of 31/32 mixture



Scheme 92: Upjohn dihydroxylation

2.5 CONCLUSION

It has been demonstrated that equilibrium displacement is possible coupling an equilibrating cycloaddition to an irreversible chemoselective reaction, and resolution of the cycloaddition can be achieved employing an asymmetric transformation. Substituents at the 6-position have a positive effect on the selectivity factor of the resolving reaction, and 6-substituted cycloadducts were obtained in excellent enantiomeric enrichment by Jacobsen epoxidation and asymmetric hydroboration. Asymmetric hydroboration delivered regiochemical alcohols with absolute configuration (*S*) at the carbinol by regiodivergent resolution. The tether of the substrate does not affect the regiochemical outcome, but it was observed a strong preference for one regioisomer when in presence of 6-substituted cycloadducts. It was also observed that the reversibility of the uncatalysed retro-cycloaddition is too slow for an effective dynamic resolution. Future work will focus on combining asymmetric transformations to a Lewis acid capable of promoting retro- (and forward) cycloaddition.

CHAPTER 3: EXPERIMENTAL

Chemicals were purchased from Sigma Aldrich, Fisher Scientific or Fluorochem and were used as received. Deuterated solvents were purchased from Goss Scientific. CH_2Cl_2 and $CHCl_3$ were distilled from CaH_2 under nitrogen and THF was distilled from Na/benzophenone under nitrogen. Et_2O and DMF were purchased anhydrous. Glassware used in moisture-sensitive reactions was oven dried (120°C) or flame dried under a stream of nitrogen.

Column chromatography was performed using silica gel (60Å, 230-400 mesh) or alumina (50-200 µm, 60 Å, neutral) obtained from Sigma-Aldrich. Thin layer chromatography (TLC) was performed using plates coated with silica gel or aluminium oxide 60 and fluorescent indicator F_{254} from Merck Millipore. Visualization on TLC was achieved using UV-light (254 nm), potassium permanganate solution or phosphomolybdic acid solution in ethanol.

Nuclear magnetic resonance (NMR) data were acquired using a Bruker Advance 400 MHz spectrometer. Multiplicity is tabulated as s for singlet, d for doublet, t for triplet, q for quadruplet, dd for doublet of doublet, dt for doublet of triplet, ddd for doublet of doublets of doublets, m for multiplet, bs for broad singlet, bm for broad multiplet. COSY, HMQC, HMBC and NOESY experiments were used for the NMR spectral assignment.

HPLC data was obtained using Agilent 1100 Series, G1311A Pump with chiral IB-3, OD-3 and IE-3 columns. Samples were run at 20 °C or 30 °C with an injection volume of 5µL and 1 mL/min flow rate.

Melting points were determined on a Stuart SMP10 melting point apparatus and are uncorrected.

Fourier transform infrared (FTIR) data was acquired as thin film using a Thermo Electron Corporation Nicolet 380 FTIR with Smart Orbit diamond window instrument and data is reported in cm^{-1}.

Mass spectra (MS) were obtained using an Agilent 6530 Q-TOF MS high resolution spectrometer by electrospray ionization (ESI) method.

3.1 GENERAL PROCEDURES

General procedure A: Acetylation of alcohols

Alcohol starting material (1 equiv.), DMAP (0.1 equiv.) and acetic anhydride (2 equiv. for each -OH) were dissolved in dry acetonitrile/pyridine (4:1, 4-10 mL per 1 mmol substrate) and stirred at rt under an atmosphere of nitrogen. After completion of the reaction, it was concentrated and purified by silica gel column.

General procedure B: Alcohol deprotection

TBAF (1M in THF, 2.0 equiv.) was added dropwise to an ice cold solution of silyl ether (1.0 equiv.) in dry THF (10 mL per 1 mmol substrate) and stirred under an atmosphere of nitrogen at 0 °C. The reaction was monitored by TLC and after consumption of the starting material it was quenched with a saturated aqueous solution of NH_4Cl. The product was extracted 3 times with EtOAc and the combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*.

General procedure C: Reductive amination

Amine (1.0 equiv.) was added to a solution of aldehyde (1.1 equiv.) in anhydrous ethanol (1 mL per 1 mmol substrate). After complete formation of the imine (followed by TLC), $NaBH_4$ (2 equiv.) was added in portions at 0 °C and the reaction mixture was stirred under an atmosphere of nitrogen at rt overnight. The solvent was then removed in *vacuo*. Water was added and the product was extracted 3 times with EtOAc. The combined organic extracts were washed with water, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography provided the secondary amine.

General procedure D: Amide formation by EDC coupling

EDC·HCl (1.5 equiv.) was added to a stirred solution of carboxylic acid (1.0-1.2 equiv.), DMAP (0.1 equiv.) and amine **7** (1.0-10 equiv.) in dry DMF or DCM (2-2.5 mL per 1 mmol limiting reagent). After 5 min Et_3N (1.2 equiv.) was added and the reaction mixture was stirred at rt under an atmosphere of nitrogen until completion. A saturated solution of NH_4Cl was added and the mixture was extracted three times with Et_2O. The combined organic extracts were washed three times with brine, dried over Na_2SO_4 and concentrated *in vacuo*.

General procedure E: DMP oxidation of alcohol to aldehyde

DMP (1.5 equiv.) was added to an ice-cold solution of alcohol (1 equiv.) in dry DCM (9 mL per 1 mmol substrate). The reaction mixture was stirred at 0 °C under an atmosphere of nitrogen until complete consumption of the starting material (TLC). The reaction was quenched by addition of saturated aqueous solutions of $NaHCO_3$ and $Na_2S_2O_3$ and stirred for other 30 min. The product was extracted three times with DCM and the combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*.

General procedure F: Racemic epoxidation

*m*CPBA (3 equiv.) was added to a solution of silyl ether (1 equiv.) in DCM (10-20 mL per 1 mmol substrate) and stirred overnight at rt. The reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$ and the

product was extracted 3 times with DCM or EtOAc. The combined organic extracts were washed with water, dried over Na_2SO_4 and concentrated *in vacuo*.

General procedure G: Jacobsen epoxidation

To a solution of alkene (0.201 g, 0.423 mmol) and 4-PPNO (0.4 equiv.), Jacobsen catalyst (0.04 equiv.) was added. A second solution of buffered NaOCl (pH= 11.3) was prepared and about 5 equiv. of this solution was added to the first solution and stirred at 0°C for until complete consumption of the SM (TLC). The mixture was then extracted 3 times with DCM. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*.

General procedure H: Racemic dihydroxylation[163]

Racemic dihydroxylation of alkenes was performed following the procedure reported by Warren, Wyatt *et al*.:[163] Potassium ferricyanide (3 equiv.), potassium carbonate (3 equiv.), osmium(III) chloride hydrate (0.0135 equiv.), quinuclidine (0.03 mmol) and methanesulfonamide (1 equiv.) were added to water/*t*BuOH (1:1, 10 mL per 1 mmol substrate) and stirred for 1h. Alkene (1.03 equiv.) was added and stirred at rt. Anhydrous sodium sulphite (12 equiv.) was added and the reaction mixture was stirred for 1h. The product was extracted three times with DCM. The combined organic extracts were washed with an aqueous solution of KOH 2M, dried over Na_2SO_4 and concentrated *in vacuo*.

General procedure I: Asymmetric dihydroxylation with AD-mix

For the asymmetric dihydroxylation of alkene was followed the procedure reported by Sharpless:[162] A mixture of AD-mix-α or AD-mix-β (1.4 g/1mmol alkene) and $MeSO_2NH_2$ (1.0 equiv.) in H_2O/*t*BuOH (1:1 v/v, 10 mL per 1 mmol alkene) was stirred at rt until all solids were dissolved, then cooled to 0°C and added to the alkene (1 equiv.). The reaction mixture was stirred until complete consumption of the SM (TLC), quenched by addition of sodium sulfite (12 equiv., stirred for 1 h) and extracted several times with EtOAc. The organic phase was washed with KOH 2M, dried over Na_2SO_4 and concentrated *in vacuo*.

General procedure J: Racemic hydroboration

Racemic hydroboration of alkenes was performed by addition of BH_3-THF complex (1M in THF, 1 equiv.) to a solution of alkene (1 equiv.) in dry THF or Et_2O (5 mL per 1 mmol substrate) and stirred under an atmosphere of nitrogen until complete consumption of the SM (TLC). $NaBO_3 \cdot 4H_2O$ (6 equiv.) and water were added and the reaction mixture was stirred for 2 h. EtOAc and brine were added and separated. The product was extracted 3 times with EtOAc, dried over Na_2SO_4, concentrated *in vacuo* and purified by column chromatography.

General procedure K: Asymmetric hydroboration with IPC_2BH[164]

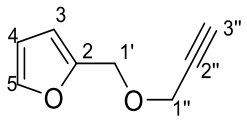
α-Pinene (2.3 equiv.) was added dropwise to a solution of BH_3-SMe_2 (1.0 equiv.) in dry THF (1-2 mL per 1 mmol substrate) at 0°C under an atmosphere of nitrogen. A temperature probe was used to monitor the temperature during the addition. The reaction mixture was stirred for 2h at the same temperature and refrigerated overnight to induce crystallisation. The supernatant was removed by syringe and a solution of alkene starting material (1.0 equiv.) in dry THF or THF/Et_2O (1.3-6 mL per 1 mmol substrate) was added dropwise. The reaction was monitored by TLC and quenched by addition of $NaBO_3 \cdot H_2O$ (3 equiv.) and water (same amount of the organic solvent in the mixture) and stirred for 2h. The layers were separated and the product was extracted 3 times with EtOAc. The combined organic extracts were dried over Na_2SO_4, concentrated *in vacuo* and purified by column chromatography.

General procedure L: Acylation of alcohols with benzyl chloride derivatives

Esterification of alcohols derived from the hydroboration-oxidation reaction was performed following the procedure reported by Oriyama and co.:[165] The alcohol starting material (1.0 equiv.) was dissolved in DCM and added at rt to a solution of TMEDA (0.6 equiv.) in DCM under argon atmosphere in presence of MS 4Å. The reaction mixture was cooled to -78 °C and a solution of 4-bromobenzoyl chloride or 4-nitrobromobenzoyl chloride in DCM was added. After stirring for 3 hours, a phosphate buffer solution (pH = 7, 1 mL buffer solution per 1 mL of DCM used) was added and the product was extracted 3 times with DCM. The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo.*

3.2 Experimental Data

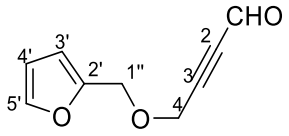
2-[(prop-2-yn-1-yloxy)methyl]furan (37)[105]



A dispersion of NaH (60% in mineral oil, 1.1 equiv., 2.24 g, 55.00 mmol) in dry DMF (60 mL) was cooled to 0 °C and furfuryl alcohol (1.0 equiv., 4.4 mL, 49.95 mmol) was added dropwise. After 15 min propargyl bromide (80% in toluene) was added and the mixture was stirred overnight. Water (100 mL) was added and the product was extracted with Et_2O (3 X 100 mL). The combined organic extracts were washed with water (3 X 150 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by chromatography (6:1 Petrol/Et_2O) provided compound **37** as a yellow oil (4.65 g, 34.15 mmol, 68%).

Rf 0.5 (SiO_2, Petrol/Et_2O 6:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.42–7.43 (m, 1H, 5-H), 6.38–6.35 (m, 2H, 3-H and 4-H), 4.57 (s, 2H, 1'-H_2), 4.16 (d, *J* = 2.4 Hz, 2H, 1''-H_2), 2.47 (t, *J* = 2.4 Hz, 1H, 3''-H); ^{13}C (100 MHz, $CDCl_3$) δ 150.79 (C2), 143.11 (C5), 110.32, 110.09 (C3-C4), 79.29 (C2''), 74.80 (C3''), 63.04 (C1'), 56.74 (C1''); *m/z* (ESI+) calculated for $C_8H_8O_2$ $[M+H]^+$ 137.0597, observed 137.0594 (error 2.57 ppm). ν_{max} (oil, cm^{-1}): 3294 (m, C≡C-H stretch), 2856, 2359, 1502, 1349, 1224, 1149, 1070 (vs, asym C–O stretch), 1010, 918, 736, 636, 599.

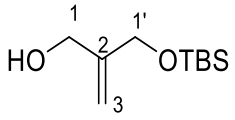
4-(furan-2-ylmethoxy)but-2-ynal (38)



Furfuryl propargyl ether **37** (1.0 equiv., 0.25g, 1.84 mmol) was dissolved in dry THF (5 mL) and cooled to -78 °C before the addition of *n*-BuLi (1.0 equiv., 1.6 M in hexanes, 1.1 mL, 1.84 mmol) and dry DMF (2.0 equiv., 0.29 mL, 3.67 mmol). The reaction was stirred at room temperature overnight and then poured into an ice cold biphasic solution prepared from 10% aqueous solution of KH_2PO_4 (4 equiv., 7.344 mmol, 1 g/10 mL) and EtOAc (10 mL) and stirred for 30 min. The product was extracted with EtOAc (3 X 10 mL) and the combined organic extracts were washed with brine (30 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (4:1 Petrol/Et_2O) afforded **38** as an orange oil (39 mg, 0.24 mmol, 13%).

Rf 0.43 (SiO_2, Petrol/Et_2O 4:1); ^1H NMR (400 MHz, $CDCl_3$) δ 9.24 (s, 1H, -CHO), 7.44-7.43 (m, 1H, 5'-H), 6.40–6.36 (m, 2H, 3'-H and 4'-H), 4.57 (s, 2H, 1''-H_2), 4.35 (s, 2H, 4-H_2); ^{13}C (100 MHz, $CDCl_3$) δ 176.18 (CHO), 150.14 (C2'), 143.41 (C5'), 110.69 and 110.49 (C3' and C4'), 91.84 (C3), 85.71 (C2), 63.74 (C1''), 56.55 (C4); *m/z* (ESI+) calculated for $C_9H_8O_3$ $[M+H]^+$ 165.0546, observed 165.0548 (error +1.04 ppm).

2-(((*tert*-butyldimethylsilyl)oxy)methyl)prop-2-en-1-ol (41)[107]

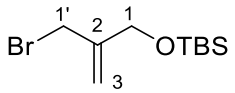


2-Methylenepropane-1,3-diol **40** (1.0 equiv., 45.40 mmol, 4 g) was added dropwise to an ice-cold suspension of NaH (60% in mineral oil, 1.0 equiv., 49.94 mmol, 2 g) in dry THF (100 mL). The reaction mixture was stirred for 45 min at rt before addition of TBSCl (1.1 equiv., 49.94 mmol, 7.53 g) at 0 °C. The stirring was continued for 100 min at rt. The reaction was quenched with water and the product was extracted with EtOAc (3 X 50 mL). The combined organic extracts were washed with brine (150 mL), dried over Na_2SO_4 and concentrated *in vacuo*.

Purification by column chromatography (4:1 Petrol/Et_2O) afforded **41** as a colourless oil (7.14 g, 35.28 mmol, 78%).

Rf 0.39 (SiO_2, Petrol/Et_2O 3:1); ^1H NMR (400 MHz, $CDCl_3$) δ 5.10 (s, 1H, 3-H), 5.08 (s, 1H, 3-H), 4.25 (s, 2H, 1'-H_2), 4.17 (d, *J* = 6.2 Hz, 2H, 1-H_2), 1.94 (bs, 1H, OH), 0.91 (s, 9H, SiC(CH_3)$_3$), 0.09 (s, 6H, Si-(CH_3)$_2$); ^{13}C (100 MHz, $CDCl_3$) δ 147.43(C2), 111.17 (C3), 65.17 (C1'), 64.77 (C1), 25.87 (SiC($\underline{C}H_3$)$_3$), 18.30 (Si-$\underline{C}$(CH_3)$_3$), -5.43 (Si-($\underline{C}H_3$)$_2$); *m/z* (ESI+) calculated for $C_{10}H_{22}O_2Si$ $[M+H]^+$ 203.1462, observed 203.1465 (error -1.62 ppm). ν_{max} (oil, cm^{-1}): 3309 (broad, OH stretch), 2955, 2929, 2885, 2857, 1471, 1463, 1389, 1361, 1252, 1081, 1006, 832 (vs, C=$\underline{C}$-H vibration), 772 (vs), 667.

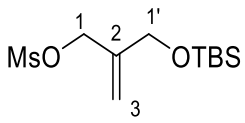
((2-(bromomethyl)allyl)oxy)(*tert*-butyl)dimethylsilane (42.1)[166]



Et_3N (2 equiv., 7.90 mmol, 1.1 mL) and MsCl (1.5 equiv., 5.92 mmol, 0.47 mL) were added dropwise to a solution of alcohol **41** (1.0 equiv., 3.95 mmol, 0.800 g) in dry THF (10 mL) at -78 °C. After stirring for 2 h at this temperature, it was warmed at 0 °C and LiBr (5 equiv., 19.75 mmol, 4.9 mL) was added dropwise and the stirring was continued for 45 min. The reaction was then quenched with a saturated aqueous solution of $NaHCO_3$ and the product was extracted with Et_2O (2 X10 mL). The combined organic extracts were washed with water (30 mL), dried over Na_2SO_4 and concentrated *in vacuo* to afford **41.1** (80%) as a yellow oil.

^1H NMR (400 MHz, $CDCl_3$) δ 5.24 (d, *J* = 6.1 Hz, 2H, 3-H_2), 4.27 (s, 1H, 1-H_2), 4.01 (s, 2H, 1'-H_2), 0.92 (s, 9H, SiC-(CH_3)$_3$), 0.09 (s, 6H, Si-(CH_3)$_2$); ^{13}C (100 MHz, $CDCl_3$) δ 144.83 (C2), 114.82 (C3), 63.49 (C1), 32.80 (C1'), 25.88 (SiC-($\underline{C}H_3$)$_3$), 18.35 (Si-$\underline{C}$-(CH_3)$_3$), -5.40 (Si-($\underline{C}H_3$)$_2$);

2-(((*tert*-butyldimethylsilyl)oxy)methyl)allyl methanesulfonate (42)

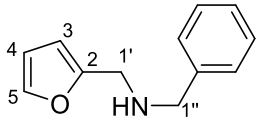


Et_3N (1.6 equiv., 54.4 mmol, 7.6 mL) and MsCl (1.3 equiv., 54.2 mmol, 3.4 mL) were added dropwise to a solution of alcohol **41** (1.0 equiv., 34 mmol, 6.88 g) in dry DCM (70 mL) at 0 °C. After stirring for 2 h at the same temperature, the reaction was quenched with a saturated aqueous solution of Na_2CO_3 and the product was

extracted with DCM (3 X 50 mL). The combined organic extracts were washed with brine (100 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The compound obtained was used in the next step without purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.35 (s, 1H, 3-H), 5.27 (s, 1H, 3-H), 4.74 (s, 2H, 1-H_2), 4.20 (s, 2H, 1'-H_2), 3.02 (s, 3H, SO_2CH_3), 0.91 (s, 9H, SiC-$(CH_3)_3$), 0.08 (s, 6H, Si-$(CH_3)_2$); ^{13}C (100 MHz, $CDCl_3$) δ 141.55 (C2), 115.86(C3), 70.02 (C1), 63.31 (C1'), 37.83 (SO_2CH_3), 25.83 (SiC-($\underline{C}H_3)_3$), 18.31 (Si-$\underline{C}$-$(CH_3)_3$), -5.43 (Si-($\underline{C}H_3)_2$); *m/z* (ESI+) calculated for $C_{11}H_{24}O_4SSi$ $[M+Na]^+$ 303.1057, observed 303.1059 (error -0.83 ppm); ν_{max} (oil, cm^{-1}): 2954, 2930, 2857, 1463, 1353 (s, S=O stretching), 1253, 1173 (s, S=O stretching), (s), 1115, 1083, 927, 833 (s, C=$\underline{C}$-$\underline{H}$ vibration), 775 (s), 527.

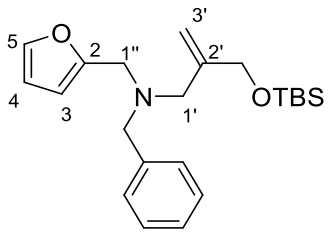
_N_-benzyl-1-(furan-2-yl)methanamine (43)[108]



Furfurylamine (1.0 equiv., 154 mmol, 15 g) was added to a solution of benzaldehyde (1.1 equiv., 170 mmol, 18 g) in anhydrous ethanol (150 mL). After 45 min $NaBH_4$ (2 equiv., 11.68 g, 309 mmol) was added in three portions at 0 °C. The reaction mixture was stirred for 3 h at rt and then diluted with water (100 mL), acidified with HCl to pH 1 and extracted with DCM (3 X 200 mL). The aqueous layer was basified to pH 10 with NaOH 2M and extracted again with DCM (3 X 200 mL). The organic extracts were dried over Na_2SO_4 and concentrated *in vacuo* to yield pure **43** (21.3 g, 105 mmol, 68%).

Rf 0.39 (SiO_2, Petrol/Et_2O 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.23 (m, Ph and 5-H), 6.32–6.33 (m, 1H, 4-H), 6.18 (d, *J* = 3.03 Hz, 1H, 6-H, 3-H), 3.79 (s, 4H, 1'-H_2 and 1''-H_2), 1.66 (s, 1H, NH); ^{1}H NMR (400 MHz, DMSO) δ 7.56 (d, *J* = 0.8 Hz, 1H, 5-H), 7.32-7.21 (m, 5H, Ph), 6.39-6.38 (m, 1H, 4-H), 6.24 (d, *J* = 2.9 Hz, 1H, 3-H), 3.67 (s, 2H, 1''-H_2), 3.64 (s, 2H, 1'-H_2); ^{13}C (100 MHz, $CDCl_3$) δ 153.87 (C2), 141.183 (C5), 139.93 (quaternary Ph), 128.47 (Ph), 128.26 (Ph), 127.02 (Ph), 110.10 (C4), 107.02 (C3), 52.83 (C1''), 45.40 (C1'); *m/z* (ESI+) calculated for $C_{12}H_{13}NO$ $[M+H]^+$ 188.1070, observed 188.1070 (error 0.00 ppm); ν_{max} (oil, cm^{-1}): 3026 (N-H stretc), 2826, 1453, 1146, 1007, 729.

***N*-benzyl-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-*N*-(furan-2-ylmethyl)prop-2-en-1-amine (44)**



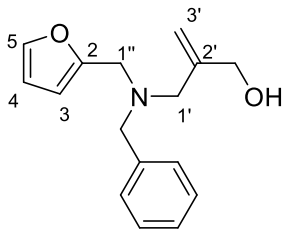
Method 1: A solution of amine **43** (1.2 equiv., 0.300 g, 1.48 mmol) and Cs_2CO_3 (3.0 equiv., 1.20 g, 3.69 mmol) in dry DMF (5 mL) was stirring at rt for 45 min under an atmosphere of nitrogen. Bromide **41.1** (1.0 equiv., 0.328 g, 1.23 mmol) was added and the reaction was stirred for 4 h. Water (5 mL) was added and the product was extracted with Et_2O (3 X 10 mL). The combined organic extracts were washed with water (3 X 20 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (10:1 Petrol/Et_2O) afforded **44** as a yellow oil (0.15 g, 0.40 mmol, 34%).

Method 2: A solution of amine **43** (1.0 equiv., 133 mg, 0.66 mmol) and K_2CO_3 (3.0 equiv., 274 mg, 1.98 mmol) in DMF (3 mL) was stirred at rt for 45 min under an atmosphere of nitrogen. Bromide **41.1** (2.0 equiv., 350 mg, 1.32 mmol) was added and the reaction was stirred overnight. Water (5 mL) was added and the product was extracted with Et_2O (3 X 10 mL). The combined organic extracts were washed with water (3 X 20 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (10:1 Petrol/Et_2O) afforded **44** (0.15 g, 0.40 mmol, 62%).

Method 3: Mesylate **42** (1.0 equiv., 1.2 g, 4.28 mmol) was added dropwise to a stirring neat amine **7** (1.5 equiv., 1.30 g, 6.42 mmol) at 0 °C. The reaction mixture was stirred at rt for 20 h and purified by column chromatography (SiO_2, 10:1:0.1 Petrol/Et_2O/Et_3N) to afford **44** (1.22g, 3.28 mmol, 77%).

Rf 0.89 (SiO_2, Petrol/Et_2O 10:1); ^{1}H NMR (400 MHz , $CDCl_3$) δ 7.38–7.7.21 (m, Ph and 5-H), 6.32–6.31 (m, 1H, 4-H), 6.16 (d, *J* = 3.3 Hz, 1H, 3-H), 5.22 (s, 1H, 3'-H), 5.11 (s, 1H, 3'-H), 4.19 (s, 2H, C$\underline{H_2}$OTBS), 3.58 (s, 2H, PhC$\underline{H_2}$), 3.55 (s, 2H, 1''-H_2), 3.06 (s, 2H, 1'-H_2), 0.91 (s, 9H, SiC$(CH_3)_3$), 0.06 (s, 6H, Si-$(CH_3)_2$); ^{1}H NMR (400 MHz , DMSO-d_6) δ 7.60 (d, *J* = 1.0 Hz, 1H, 5-H), 7.34-7.22 (m, 5H, Ph), 6.41-6.40 (m, 1H, 4-H), 6.27 (d, *J* = 3.0 Hz, 1H, 3-H), 5.14 (s, 1H, 3'-H), 5.01 (s, 1H, 3'-H), 4.11 (s, 2H, C$\underline{H_2}$OTBS), 3.51 (s, 2H, Ph$\underline{CH_2}$), 3.49 (s, 2H, 1''-H_2), 3.00 (s, 2H, 1'-H_2), 0.86 (s, 9H, SiC$(CH_3)_3$), 0.02 (s, 6H, Si-$(CH_3)_2$); ^{13}C (100 MHz, $CDCl_3$) δ 152.76 (C2), 146.28 (C2'), 141.80 (C5), 139.43 (quaternary Ph), 128.73 (Ph), 128.19 (Ph), 126.83 (Ph), 111.55 (C3'), 109.98 (C4), 108.48 (C3), 64.57 (TBS$\underline{C}H_2$), 57.36 (C1'), 56.75 (Ph$\underline{C}H_2$), 49.07 (C1''), 25.95 (SiC-($\underline{C}H_3)_3$), 18.42 (Si-$\underline{C}$-$(CH_3)_3$), -5.37 (Si-($\underline{C}H_3)_2$); *m/z* (ESI+) calculated for $C_{22}H_{33}NO_2Si$ $[M+H]^+$ 372.2353, observed 372.2355 (error -0.14 ppm); ν_{max} (oil, cm^{-1}): 2954, 2927, 2855, 1252, 1103, 834, 775, 730.

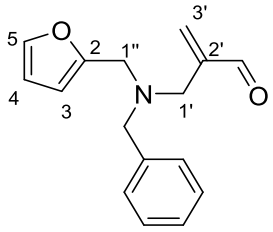
2-((benzyl(furan-2-ylmethyl)amino)methyl)prop-2-en-1-ol (45)



Deprotection of silyl ether **44** (1.0 equiv., 3.23 mmol, 1.20 g) with TBAF (1M in THF, 2.0 equiv., 6.46 mmol, 6.5 mL) in THF (30 mL) was performed as described in general procedure B. Purification by column chromatography (2:1 Petrol/Et_2O) afforded **45** as a yellow oil (0.83 g, 3.23 mmol, 100%).

Rf 0.2 (SiO_2, Petrol/Et_2O 3:1); ^{1}H NMR (400 MHz , $CDCl_3$) δ 7.42 (s, 1H, 5-H), 7.34–7.25 (m, Ph), 6.34–6.33 (m, 1H, 4-H), 6.22 (d, *J* = 3.2 Hz, 1H, 3-H), 5.13 (s, 1H, 3'-H), 5.03 (s, 1H, 3'-H), 4.35 (bs, 1H, OH), 4.18 (s, 2H, $\underline{CH_2}OH$), 3.64 (s, 2H, $Ph\underline{CH_2}$), 3.60 (s, 2H, 1''-H_2), 3.20 (s, 2H, 1'-H_2); ^{1}H NMR (400 MHz , DMSO-d_6) δ 7.62 (d, *J* = 1.1 Hz, 1H, 5-H), 7.36–7.22 (m, 5H, Ph), 6.42–6.41 (m, 1H, 4-H), 6.28 (d, *J* = 3.1 Hz, 1H, 3-H), 5.14 (s, 1H, 3'-H), 5.01 (s, 1H, 3'-H), 4.75 (t, *J* = 5.4 Hz, 1H, OH), 3.94 (d, *J* = 5.4 Hz, 2H, $\underline{CH_2}OH$), 3.53 (s, 2H, $Ph\underline{CH_2}$), 3.50 (s, 2H, 1''-H_2), 2.99 (s, 2H, 1'-H_2); ^{13}C (100 MHz, $CDCl_3$) δ 151.60 (C2), 144.56 (C2'), 142.31 (C5), 138.14 (quaternary Ph), 129.08 (*m*-Ph), 128.50 (*o*-Ph), 127.33 (*p*-Ph), 115.35 (C3'), 110.13 (C4), 109.27 (C3), 67.29 ($\underline{C}H_2OH$), 58.77 (C1'), 57.78 ($Ph\underline{C}H_2$), 49.02 (C1''); *m/z* (ESI+) calculated for $C_{16}H_{19}NO_2$ $[M+H]^+$ 258.1489, observed 258.1488 (error 0.32 ppm); ν_{max} (oil, cm^{-1}): 3326 (br, OH), 3028, 2922, 2826, 1773 (w), 1651 (w), 1600 (w), 1452, 1147, 1011, 908, 732, 697.

2-((benzyl(furan-2-ylmethyl)amino)methyl)acrylaldehyde (46)

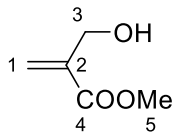


Oxidation of alcohol **45** (1.0 equiv., 0.29 mmol, 74 mg) was performed by addition of DMP (1.5 equiv., 185 mg, 0.44 mmol) in DCM (3 mL) as described in general procedure E. The reaction was stirred for 5 h. Purification by column chromatography (Et_2O/Petrol 1:2 then 1:1) afforded **46** as a colourless oil (26 mg, 0.10 mmol, 35%).

Rf 0.71 (SiO_2, Petrol/Et_2O 3:1); ^{1}H NMR (400 MHz , $CDCl_3$) δ 9.62 (s, 1H, CHO), 7.42–7.26 (m, Ph and 5-H), 6.66 (s, 1H, 3'-H), 6.36 (t, *J* = 2.2 Hz, 1H, 4-H), 6.23 (d, 1H, *J* = 3.1 Hz, 3-H), 6.18 (s, 1H, 3'-H), 3.64 (s, 2H, Ph-$\underline{CH_2}$), 3.63 (s,

2H, 1''-H_2) 3.38 (s, 2H, 1'-H_2); ^{13}C (100 MHz, $CDCl_3$) δ 194.29 (CHO), 152.41 (C2), 147.07 (C6), 142.05 (C5), 139.06 (quaternary Ph), 135.03 (C3'), 128.68 (Ph), 128.35 (Ph), 127.10 (Ph), 110.13 (C4), 108.72 (C3), 58.04 (Ph<u>C</u>H_2), 50.49 (C1'), 49.83 (C1''); *m/z* (ESI+) calculated for $C_{16}H_{17}NO_2$ $[M+H]^+$ 256.1332, observed 256.1332 (error 0.03 ppm); ν_{max} (oil, cm^{-1}): 3027, 2926, 2820, 1687 (s, CHO stretch), 1495, 1453, 1366, 1147, 1012, 732 (s), 697 (s).

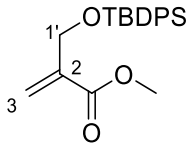
methyl 2-(hydroxymethyl)acrylate (48)[114]



A solution of formaldehyde (37% w/w, 77.4 mmol, 5.8 mL) and methyl acrylate (3 equiv., 232.3 mmol, 20 g) in water/1,4-dioxane (1:1 v/v, 80 mL) was stirred in the presence of DABCO (77.4 equiv., 8.69 g). The reaction was stirred for 23 h at room temperature and quenched with brine. The product was extracted with Et_2O (3 X 60 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo* to afford **48** as a colourless oil (5.2 g, 44.8 mmol, 58%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.26 (s, 1H, 1-H), 5.84 (s, 1H, 1-H), 4.33 (s, 2H, 3-H_2), 3.79 (s, 3H, $COOCH_3$); ^{13}C (100 MHz, $CDCl_3$) δ 166.79 (C=O), 139.25 (C2), 125.95 (C1), 62.60 (C3), 51.95 (COO<u>C</u>H_3); *m/z* (ESI+) calculated for $C_5H_8O_3$ $[M+H]^+$ 117.0546, observed 117.0548 (error -1.40 ppm); ν_{max} (oil, cm^{-1}): 3411 (br, OH), 2954, 1713 (s, C=O ester), 1635, 1438, 1307, 1272, 1197, 1154, 1052.

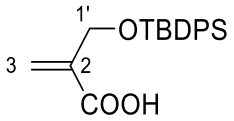
methyl 2-(((*tert*-butyldiphenylsilyl)oxy)methyl)acrylate (49)[167]



Imidazole (1.1 equiv., 3.1g, 46.3 mmol) and TBDPSCl (1.1 equiv., 11.8 mL, 46.3 mmol) were added to a solution of methyl 2-(hydroxymethyl)acrylate **48** (4.89 g, 42.1 mmol) in dry DMF (40 mL) at 0 °C. The mixture was stirred at rt under an atmosphere of nitrogen for 19 h. A saturated solution of ammonium chloride was added and the product was extracted with EtOAc (3 X 50 mL). The combined organic extracts were washed with brine (3 X 150 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The product was used in the next step without any purification.

^{1}H NMR (400 MHz , $CDCl_3$) δ 7.73–7.65 (m, 4H, Ph), 7.45–7.37 (m, 6H, Ph), 6.34 (d, *J* = 1.8 Hz, 1H, 3-H), 6.12 (d, *J* = 1.9 Hz, 1H, 3-H), 4.42 (t, *J* = 1.8 Hz, 2H, 1'-H_2), 3.70 (s, 3H, CH_3) 1.08 (s, 9H, $C(CH_3)_3$); ^{13}C (100 MHz, $CDCl_3$) δ 166.25 (C=O), 139.32 (C2), 135.46 (Ph), 134.81 (Ph), 133.23 (Ph), 129.78 (Ph), 127.76 (Ph), 127.73 (Ph), 124.09 (C3), 62.20 (C1'), 51.63 ($\underline{C}H_3$), 26.81 ($C(\underline{C}H_3)_3$), 19.30 ($\underline{C}(CH_3)_3$); *m/z* (ESI+) calculated for $C_{21}H_{26}O_3Si$ $[M+Na]^+$ 377.1543, observed 377.1548 (error -0.14 ppm); ν_{max} (oil, cm^{-1}): 3071, 2931, 2892, 2857, 1718 (C=O ester), 1637, 1427, 1274, 1088 (s), 819, 699.

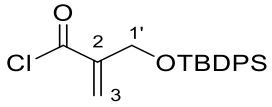
2-(((*tert*-butyldiphenylsilyl)oxy)methyl)acrylic acid (50)



LiOH·H_2O (2 equiv., 74.64 mmol, 3.13 g) was added to a solution of ester **49** (37.32 mmol, 13.2 g) in THF/H_2O (1:1 v/v, 100 mL). The reaction mixture was stirred overnight at 50 °C, then acidified with HCl 10% to pH 1 and extracted with Et_2O (2 X 50 mL). The organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The solid obtained was triturated with Et_2O/hexane (1:10, v/v) to yield **50** as a white solid (9.4g, 27.61 mmol, 74%).

Mp: 120-123 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66–7.64 (m, 4H, Ph), 7.45-7.36 (m, 6H, Ph), 6.42 (d, *J*= 1.8 Hz, 1H, 3-H), 6.16 (d, *J* = 1.6 Hz, 1H, 3-H), 4.41 (s, 2H, 1'-H_2), 1.08 (s, 9H, $C(CH_3)_3$); ^{13}C (100 MHz, $CDCl_3$) δ 170.9 (COOH), 138.7 (C2), 135.4 (Ph), 133.1 (Ph), 129.8 (Ph), 127.8 (Ph), 126.5 (C3), 61.9 (C1'), 26.8 ($C(\underline{C}H_3)_3$), 19.3 ($\underline{C}(CH_3)_3$); *m/z* (ESI+) calculated for $C_{20}H_{24}O_3Si$ $[M+Na]^+$ 363.1387, observed 363.1390 (error 0.03 ppm); ν_{max} (solid, cm^{-1}): 2960, 2861, 2363, 1688 (C=O carboxylic acid), 1633, 1428, 1099 (s), 961, 823, 697.

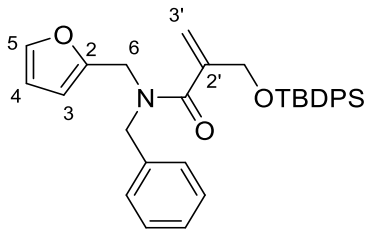
2-(((*tert*-butyldiphenylsilyl)oxy)methyl)acryloyl chloride (50.1)



To a stirred solution of acrylic acid **50** (5.47g, 16.06 mmol) in benzene (80 mL) was added $SOCl_2$ at rt. The reaction mixture was stirred at 90 °C for 2.5 h and then concentrated in vacuo. The crude of the reaction was utilized in the next step without purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65-7.63 (m, 4H, Ph), 7.47-7.37 (m, 6H, Ph), 6.70 (t, *J* = 1.7 Hz, 1H, 3-H), 6.16 (t, *J* = 2.0 Hz, 1H, 3-H), 4.42 (s, 2H, 1'-H_2), 1.09 (s, 9H, $C(CH_3)_3$).

***N*-benzyl-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)-*N*-(furan-2-ylmethyl)acrylamide (51)**



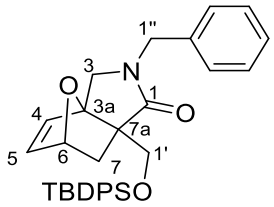
Method 1: To a stirred ice-cold solution of acrylic acid **50** (1.5 equiv., 3.78g, 11.12 mmol) in dry DCM (100 mL), amine **43** (1.0 equiv., 1.5 g, 7.41 mmol) and DMAP (0.1 equiv., 0.09 g, 0.74 mmol) were added. After 15 min DCC (2.0 equiv., 3.06 g, 14.82 mmol) was added. The reaction mixture was stirred at rt under an atmosphere of nitrogen for 2 h, then filtered through a fritted funnel and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 3:1 Petro/Et_2O) afforded **51** as a colourless oil (2.62 g, 5.14 mmol, 46%).

Method 2: To a stirred solution of acrylic acid 50 (5.47g, 16.06 mmol) in benzene (80 mL) was added $SOCl_2$ at rt. The reaction mixture was stirred at 90 °C for 2.5 h and then concentrated in vacuo. The acyl chloride formed was added to a solution of amine **43** (1.2 equiv., 3.76 g, 18.6 mmol) and K_2CO_3 (3.0 equiv., 6.43 g, 46.5 mmol) in dry DMF (50 mL), previously stirred for 30 min. The reaction mixture was stirred overnight at rt. Water (30 mL) was added and the product was extracted with Et_2O (3 X 50 mL) and the combined organic extracts were washed with brine (3 X 100 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Column chromatography (SiO_2, 4:1 Petrol/Et_2O) afforded compound **51** as a colourless oil (6.25 g, 12.26 mmol, 76%).

Method 3: Coupling of carboxylic acid **50** (1.0 equiv., 2.0 g, 5.87 mmol) and amine **43** (1.23 equiv., 1.42 g, 7.04 mmol) was performed as described in general procedure D by addition of EDC·HCl (1.5 equiv., 1.69 g, 8.80 mmol), DMAP (0.1 equiv., 0.071 g, 0.587 mmol) Et_3N (1.2 equiv., 0.98 mL, 7.04 mmol) in DMF (10 mL). The reaction mixture was stirred for 20 h. Column chromatography (SiO_2, 2:1, 1:1 Petrol/Et_2O) afforded compound **51** as a colourless oil (2.52 g, 4.94 mmol, 84%).

Rf 0.52 (SiO_2, Petrol/Et_2O 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67–7.65 (m, 5H, Ph and 5-H), 7.43–7.17 (m, Ph), 6.32-6.30 (m, 1H, 4-H), 6.16 (bs, 1H, 3-H), 5.58–5.26 (m, 2H, 3'-H_2), 4.58–4.42 (m, 6H, TBDPSO$\underline{CH_2}$, NCH_2, Ph$\underline{CH_2}$), 1.04 (s, 9H, $C(CH_3)_3$); ^{1}H NMR (400 MHz, DMSO-d_6) 7.61–7.19 (m, 16H, Ph and 5-H), 6.40–6.24 (m, 2H, 2-H, 3-H), 5.58-5.20 (m, 2H, 3'-H_2), 4.46-4.31 (m, 6H, TBDPSO$\underline{CH_2}$, NCH_2, Ph-CH_2), 0.98 (s, 9H, $C(CH_3)_3$); *m/z* (ESI+) calculated for $C_{32}H_{35}NO_3Si$ $[M+H]^+$ 510.2459, observed 510.2462 (error 0.01 ppm); ν_{max} (oil, cm^{-1}): 2929, 2856, 1651, 1624 (C=O amide), 1427, 1105, 1074, 737, 699 (s).

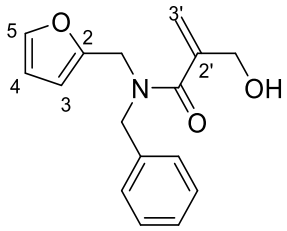
2-benzyl-7a-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2,3,7,7a-tetrahydro-3a,6-epoxyisoindol-1(6*H*)-one (52)



Diels-Alder product **52** is formed by spontaneous cyclization of **51** as a white solid. Pure **52** was isolated by column chromatography of **51**.

Mp: 100-102°C; Rf 0.80 (Alumina, Petrol/EtOAc 1:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65–7.61 (m, 4H, Ph), 7.49–7.38 (m, 6H, Ph), 7.30–7.23 (m, Ph), 6.36–6.32 (m, 2H, 4-H and 5-H), 5.03 (d, *J* = 15.2 Hz, 1H, 1''-H), 4.95 (dd, J_1 = 4.7 Hz, J_2 = 1.5 Hz, 1H, 6-H), 4.26 (d, *J* = 15.2 Hz, 1H, 1''-H), 4.11 (d, *J* = 10.4 Hz, 1H, 1'-H), 4.05 (d, *J* = 10.6 Hz, 1H, 3-H), 3.56 (d, *J* = 10.7 Hz, 1H, 3-H), 3.07 (d, *J* = 10.6 Hz, 1H, 1'-H), 2.31 (dd, J_1 = 11.9 Hz, J_2 = 4.6 Hz, 1H, *exo*-7-H), 1.03 (s, 9H, $C(CH_3)_3$), 0.82 (d, *J* = 11.9 Hz, 1H, *endo*-7-H); ^{1}H NMR (400 MHz , DMSO-d_6) δ 7.58–7.56 (m, 4H, Ph), 7.50–7.43 (m, 6H, Ph), 7.26-7.20 (m, Ph), 6.48–6.44 (m, 2H, 4-H and 5-H), 4.93 (d, *J* = 4.2 Hz, 1H, 6-H), 4.78 (d, *J* = 15.2 Hz, 1H, 1''-H), 4.25 (d, *J* = 15.2 Hz, 1H, 1''-H), 4.02 (d, *J* = 10.9 Hz, 1H, 1'-H), 3.85 (d, *J* = 10.4 Hz, 1H, 3-H), 3.54 (d, *J* = 11.2 Hz, 1H, 3-H), 3.04 (d, *J* = 10.4 Hz, 1H, 1'-H), 2.00–1.96 (m, 1H, *exo*-7-H), 0.94 (s, 9H, $C(CH_3)_3$), 0.81 (d, *J* = 11.9 Hz, 1H, *endo*-7-H); ^{13}C (100 MHz, $CDCl_3$) δ 175.65 (C1), 136.67 (Ph), 136.17 (C4), 135.65 (Ph), 135.53 (Ph), 132.94 (Ph), 132.30 (Ph), 132.09 (C5), 129.92 (Ph), 129.90 (Ph), 128.66 (Ph), 127.93 (Ph), 127.83 (Ph), 127.81 (Ph), 127.35 (Ph), 91.26 (C3a), 78.16 (C6), 68.09 (C1'), 58.43 (C7a), 49.66 (C3), 46.73 (C1''), 31.94 (C7), 26.83 ($C(\underline{C}H_3)_3$), 19.12 ($\underline{C}(CH_3)_3$); *m/z* (ESI+) calculated for $C_{32}H_{35}NO_3Si$ $[M+Na]^+$ 532.2278, observed 532.2277 (error -0.08 ppm); ν_{max} (solid, cm^{-1}): 3010, 2930, 2857, 1681 (s, C=O lactone), 1470, 1427, 1357, 1069, 750, 670.

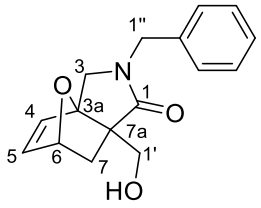
***N*-benzyl-*N*-(furan-2-ylmethyl)-2-(hydroxymethyl)acrylamide (53) and 2-benzyl-7a-(hydroxymethyl)-2,3,7,7a-tetrahydro-3a,6-epoxyisoindol-1(6*H*)-one (54)**



Deprotection of silyl ether **51** (1.0 equiv., 6.87 mmol, 3.50 g) with TBAF (1M in THF, 2.0 equiv., 3.73 mmol, 14 mL) in THF (70 mL) was performed as described in general procedure B. The reaction mixture was stirred for 4 h.

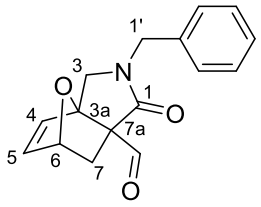
Purification by column chromatography (SiO_2, EtOAc/Petrol 3:1) afforded **53** as a clear oil and **54** as a white solid. **54** is formed by spontaneous cyclization of **53**. The combined yield of the two compounds was 94% (1.76 g, 6.49 mmol).

Rf 0.42 (SiO_2, Petrol/EtOAc 1:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.24 (m, Ph), 6.33 (s, 1H, 3-H), 6.21 (d, *J* = 3.0 Hz, 1H, 4-H), 5.58-5.31 (bm, 2H, 3'-H_2), 4.66-4.41 (bm, 6H, Ph$\underline{CH_2}$, NCH_2, $\underline{CH_2}$OH), 2.50 (bs, 1H, -OH).



Rf 0.10 (SiO_2, Petrol/EtOAc 1:3); mp: 147–149 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.25 (m, Ph), 6.48 (d, *J* = 5.9 Hz, 1H, 4-H), 6.44 (d, *J* = 5.9 Hz, 1H, 5-H), 4.99 (d, *J* = 4.5 Hz, 1H, 6-H), 4.65 (d, *J* = 15.2 Hz, 1H, 1''-H), 4.52 (d, J= 15.1 Hz, 1H, 1''-H), 3.94 (d, *J* = 8.4 Hz, 1H, 3-H), 3.91 (d, *J* = 8.3 Hz, 1H, 1'-H), 3.48 (d, *J* = 11.1 Hz, 1H, 3-H), 3.18 (d, *J* = 10.9 Hz, 1H, 1'-H), 2.32 (dd, J_1 = 12.0 Hz, J_2 = 4.6 Hz, 1H, *exo*-7-H), 1.00 (d, *J* = 11.9 Hz, 1H, *endo*-7-H); ^{1}H NMR (400 MHz , DMSO-d_6) δ 7.32–7.21 (m, 5H, Ph), 6.50 (d, *J* = 5.8 Hz, 1H, 4-H), 6.43 (dd, J_1 = 1.6 Hz, J_2 = 5.8Hz, 1H, 5-H), 4.99 (t, *J* = 4.7 Hz, 1H, 3-H), 4.90 (dd, J_1 = 1.6 Hz, J_2= 4.7 Hz, 1H, 6-H), 4.54 (d, *J* = 15.5 Hz, 1H, 1'-H), 4.37 (d, *J* = 15.6 Hz, 1H, 1'-H), 3.85 (d, *J* = 10.8 Hz, 1H, 3-H), 3.65 (dd, J_1 = 5.2 Hz, J_2 = 10.8 Hz 1H, 1''-H), 2.89 (dd, J_1= 1.6 Hz, J_2 = 4.1 Hz, 1H, 1''-H), 1.97–1.93 (m, 1H, *exo*-7-H), 0.79 (d, *J* = 11.7 Hz, 1H, *endo*-7-H); ^{13}C (100 MHz, $CDCl_3$) δ 176.28 (C1), 136.79 (C5), 136.04 (Ph), 132.18 (C4), 128.70 (Ph), 127.79 (Ph), 127.447 (Ph), 90.98 (C3a), 78.33 (C6), 66.83 (C1), 58.68 (C7a), 49.61 (C3), 46.78 (C1''), 31.78 (C7); *m/z* (ESI+) calculated for $C_{16}H_{17}NO_3$ $[M+Na]^+$ 294.1101, observed 294.1100 (error ppm -0.05); ν_{max} (solid, cm^{-1}): 3296 (br, OH), 2925, 2860, 1652 (vs, C=O lactam), 1454, 1362, 1257, 1204, 1050, 861, 831, 724.

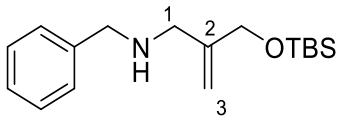
2-benzyl-1-oxo-2,3,6,7-tetrahydro-3a,6-epoxyisoindole-7a(1*H*)-carbaldehyde (56)



Deprotection of silyl ether **53** (1.0 equiv., 3.79 mmol, 1.9 g) with TBAF (1M in THF, 2.0 equiv., 7.57 mmol, 7.6 mL) in THF (40 mL) was performed as described in general procedure B. The reaction mixture was stirred for 2 h. The crude of the reaction was dissolved in DCM (30 mL) and treated with DMP (1.5 equiv., 2.4 g) as described in procedure E. Purification by column chromatography (SiO_2 deactivated with Et_3N, Et2O as eluent) afforded **56** as yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.30 (s, 1H, CHO), 7.38–7.28 (m, Ph), 6.57 (dd, 1H, J_1 = 5.9 Hz, J_2 = 1.7 Hz, 1H, 5-H), 6.37 (d, J = 5.7 Hz, 1H, 4-H), 5.22 (dd, 1H, J_1 = 4.6 Hz, J_2 = 1.7 Hz, 1H, 6-H), 4.74 (d, J = 15.0 Hz, 1H, 1'-H), 4.51 (d, J = 15.0 Hz, 1H, 1'-H), 3.93 (d, J = 11.8 Hz, 1H, 3-H), 3.56 (d, J = 11.8 Hz, 1H, 3-H), 2.65 (dd, 1H, J_1 = 12.2 Hz, J_2 = 4.6 Hz, 1H, *exo*-7-H), 1.98 (d, J = 12.2 Hz, 1H, *endo*-7-H); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.18 (s, 1H, CHO), 7.39-7.28 (m, 5-H, Ph), 6.59 (dd, 1H, J_1 = 5.7 Hz, J_2 = 1.7 Hz, 1H, 5-H), 6.52 (d, J = 5.7 Hz, 1H, 4-H), 5.20 (dd, 1H, J_1 = 4.6 Hz, J_2 = 1.6 Hz, 1H, 6-H), 4.60 (d, J = 15.0 Hz, 1H, 1'-H), 4.44 (d, J = 15.3 Hz, 1H, 1'-H), 4.05 (d, J = 12.0 Hz, 1H, 3-H), 3.55 (d, J = 12.0 Hz, 1H, 3-H), 2.21 (dd, 1H, J_1 = 12.2 Hz, J_2 = 4.6 Hz, 1H, *exo*-7-H), 1.92 (d, J = 12.2 Hz, 1H, *endo*-7-H); ^{13}C (100 MHz, $CDCl_3$) δ 197.53 (CHO), 170.45 (C1), 138.70 (C5), 135.54 (Ph), 131.47 (C4), 128.85 (Ph), 127.83 (Ph), 127.75 (Ph), 92.29 (C3a), 79.77 (C6), 69.39 (C7a), 48.35 (C3), 46.99 (C1'), 30.61 (C7); *m/z* (ESI+) calculated for $C_{16}H_{15}NO_3$ $[M+H]^+$ 270.1125, observed 270.1125 (error 0.32 ppm); ν_{max} (oil, cm^{-1}): 2921, 1717 (C=O aldehyde), 1667 (s, C=O lactam), 1426, 1355, 1261, 1196, 1102, 1066, 852, 698.

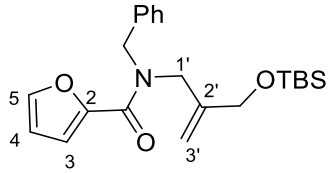
***N*-benzyl-2-(((*tert*-butyldimethylsilyl)oxy)methyl)prop-2-en-1-amine (57)[168]**



Mesylate **42** (1.0 equiv., 24.70 mmol) was added dropwise to stirring neat benzylamine (10 equiv., 25.79 g, 240.7 mmol) at 0 °C. The reaction mixture was stirred at rt for 20 h and then the crude was purified by column chromatography (SiO_2, 10:1:0.1 Petrol/Et_2O/Et_3N) to afford **57** (2.89 g, 9.91 mmol, 40%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 4.4 Hz, 4H, Ph), 7.27–7.22 (m, Ph), 5.15 (s, 1H, 3-H_2), 5.03 (s, 1H, 3-H_2), 4.19 (s, 2H, TBSO$\underline{CH_2}$), 3.77 (s, 2H, Ph$\underline{CH_2}$), 3.27 (s, 2H, 1-H_2), 1.41 (bs, 1H, NH), 0.91 (s, 9H, SiC$(CH_3)_3$), 0.07 (s, 6H, Si$(CH_3)_2$); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.30–7.19 (m, 5H, Ph), 5.05 (s, 2H, 3-H_2), 4.98 (s, 1H, 3-H_2), 4.13 (s, 2H, TBSO$\underline{CH_2}$), 3.63 (s, 2H, Ph$\underline{CH_2}$), 3.10 (s, 2H, 1-H_2), 2.22 (bs, 1H, NH), 0.87 (s, 9H, SiC$(CH_3)_3$), 0.04 (s, 6H, Si$(CH_3)_2$); ^{13}C (100 MHz, $CDCl_3$) δ 146.83 (C2), 140.45 (Ph), 128.36 (Ph), 128.15 (Ph), 126.88 (Ph), 110.40 (C3), 65.11 (TBSO$\underline{C}H_2$), 53.22 (CPh$\underline{C}H_2$), 51.40 (C1), 25.92 (SiC-($\underline{C}H_3)_3$), 18.37 (Si$\underline{C}$-$(CH_3)_3$), -5.36 (Si-($\underline{C}H_3)_2$); *m/z* (ESI+) calculated for $C_{17}H_{29}NOSi$ $[M+H]^+$ 292.2091, observed 292.2092 (error 0.16 ppm); ν_{max} (oil, cm^{-1}): 2954, 2928, 2855, 1454, 1251, 1078, 840 (s), 774 (s), 696.

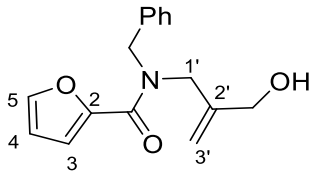
_N_-benzyl-_N_-(2-(((*tert*-butyldimethylsilyl)oxy)methyl)allyl)furan-2-carboxamide (58)



Potassium Carbonate (3.0 equiv., 26.76 mmol, 3.70 g) was added to a solution of amine **57** (8.92 mmol, 2.6 g) in DMF (30 mL) and stirred at rt for 1 h before the addition of 2-Furoyl chloride (1.3 equiv., 11.59 mmol, 1.2 mL). The reaction mixture was stirred overnight. Water (20 mL) was added and the product was extracted with Et_2O (3 X 50 mL). The combined organic extracts were washed with brine (3 X 150 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Column chromatography (SiO_2, 1:1 Petrol/EtOAC) afforded compound **58** as a colourless oil (3.44g, 8.92 mmol, 100%).

Rf 0.49 (SiO_2, Petrol/EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (s, 1H, 5-H), 7.36–7.28 (m, Ph), 7.08 (bs, 1H, 3-H), 6.47–6.46 (m, 1H, 4-H), 5.29 (s, 1H), 5.02–4.75 (m, 3H), 4.15 (s, 4H), 0.91 (s, 9H, SiC$(CH_3)_3$), 0.07 (s, 6H, Si$(CH_3)_2$); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.82 (s, 1H, 5-H), 7.37–7.26 (m, 5H, Ph), 7.00 (bs, 1H, 3-H), 6.60–6.59 (m, 1H, 4-H), 5.19 (s, 1H, 3'-H), 4.89 (s, 1H, 3'-H), 4.62 (bs, 2H), 4.09 (s, 4H), 0.84 (s, 9H, SiC$(CH_3)_3$), 0.02 (s, 6H, Si$(CH_3)_2$); ^{13}C (100 MHz, $CDCl_3$) δ 144.09 (C4), 137.00 (C2), 128.67 (Ph), 127.49 (Ph), 116.33, 111.27, 64.58, 49.12, 25.85 (SiC-($\underline{C}H_3)_3$), 18.331 (Si$\underline{C}$-$(CH_3)_3$), -5.41 (Si-($\underline{C}H_3)_2$); *m/z* (ESI+) calculated for C22H31NO_3Si $[M+Na]^+$ 408.1965, observed 408.1965 (error -0.04 ppm); ν_{max} (oil, cm^{-1}): 2953, 2928, 2886, 1623 (m, C=O amide), 1421, 1252, 1075, 834, 750.

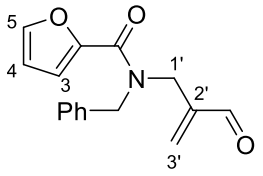
***N*-benzyl-*N*-(2-(hydroxymethyl)allyl)furan-2-carboxamide (59)**



Deprotection of silyl ether **58** (1.0 equiv., 8.4 mmol, 3.0 g) with TBAF (1M in THF, 2.0 equiv., 16.7 mmol, 16.7 mL) in THF (30 mL) was performed as described in general procedure B. The reaction mixture was stirred for 4 h. Purification by column chromatography (2:1 Petrol/Et_2O) afforded **59** as a colourless oil (2.3 g, 8.4 mmol, 100%).

Rf 0.16 (SiO_2, Petrol/Et_2O 1:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 0.8 Hz, 1H, 5-H), 7.41–7.31 (m, Ph), 7.10–7.09 (m, 1H, 3-H), 6.50–6.49 (m, 1H, 4-H), 5.21 (bs, 1H, 3'-H), 4.97 (bs, 1H, 3'-H), 4.80 (s, 2H, PhC$\underline{H_2}$), 4.14 (s, 2H, 1'-H_2), 4.07 (s, 2H, C$\underline{H_2}$OH); ^{13}C (100 MHz, $CDCl_3$) δ 144.68 (C5), 143.46 (C2), 128.92 (Ph), 127.74 (Ph), 127.05 (Ph), 117.65 (C3), 116.07 (C3'), 111.59 (C4), 63.50 (C$\underline{H_2}$OH), 50.47 (Ph$\underline{C}H_2$), 47.69 (C1'); *m/z* (ESI+) calculated for $C_{16}H_{17}NO_3$ $[M+Na]^+$ 294.1101, observed 294.1102 (error -0.47 ppm); ν_{max} (oil, cm^{-1}): 3411.6 (br, OH), 2918, 1604 (s, C=O amide), 1565, 1483 (s), 1422 (s), 1269, 1176, 1016, 750 (s), 701.

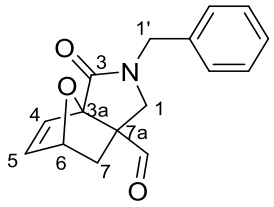
***N*-benzyl-*N*-(2-formylallyl)furan-2-carboxamide (60)**



Oxidation of alcohol **59** (8.1 mmol, 2.2 g) was performed by addition of DMP (1.5 equiv., 12.3 mmol, 5.2 g) in DCM (70 mL) as described in general procedure E. The reaction was stirred for 6 h. Purification by column chromatography (SiO_2 deactivated with Et_3N, Et_2O as eluent) afforded a mixture of **60** and **61** (1.6 g, 5.8 mmol, 72%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.63 (bs, 1H, CHO), 7.44 (bs, 1H, 5-H), 7.35–7.26 (m, Ph), 7.05 (bs, 1H, 3-H), 6.46–6.31 (m, 2H, 4-H and 3'-H), 6.20 (s, 1H, 3'-H), 4.90 (bs, 1H, 1'-H), 4.69 (bs, 1H, C$\underline{H_2}$Ph), 4.43 (bs, 1H, 1'-H), 4.25 (bs, 1H, C$\underline{H_2}$Ph).

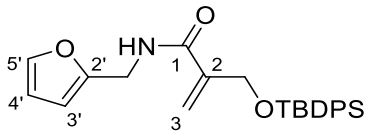
2-benzyl-3-oxohexahydro-3a,6-epoxyisoindole-7a(1*H*)-carbaldehyde (61)



Cycloadduct **61** was obtained by cyclisation of Diels-Alder starting material **60**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.12 (s, 1H, CHO), 7.46–7.08 (m, Ph), 6.69 (dd, J_1 = 5.9 Hz, J_2 = 1.53 Hz, 1H, 5-H), 6.61 (d, J = 5.9 Hz, 1H, 4-H), 5.33 (dd, J_1 = 4.2 Hz, J_2 = 1.5 Hz 1H, 6-H), 4.66 (d, J = 15.0 Hz, 1H, 1'-H), 4.48 (d, J = 15.0 Hz, 1H, 1'-H), 3.85 (d, J = 10.0 Hz, 1H, 1-H), 3.28 (d, J = 10.0 Hz, 1H, 1-H), 2.19 (dd, J_1 = 12.4 Hz, J_2 = 4.3 Hz, 1H, *exo*-7-H), 1.81 (d, J = 12.5 Hz, 1H, *endo*-7-H);

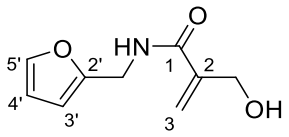
2-(((*tert*-butyldiphenylsilyl)oxy)methyl)-*N*-(furan-2-ylmethyl)acrylamide (63)



Coupling of carboxylic acid **50** (1.0 equiv., 2.0 g, 5.87 mmol) and furfurylamine (1.5 equiv., 0.85 g, 8.80 mmol) was performed as described in general procedure D by addition of EDC·HCl (1.5 equiv., 1.69 g, 8.80 mmol), DMAP (0.1 equiv., 0.071 g, 0.59 mmol), Et_3N (1.2 equiv., 0.98 mL, 7.04 mmol) in DMF (10 mL). The reaction mixture was stirred for 16 h. Column chromatography (SiO_2, 1:1 Petrol/Et_2O) afforded compound **63** as a colourless oil (2.03 g, 4.84 mmol, 82%).

Rf 0.52 (SiO_2, Petrol/Et_2O 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64–7.61 (m, 4H, Ph), 7.46–7.35 (m, 8H, Ph, 5'-H and NH), 6.33–6.32 (m, 1H, 4'-H), 6.26 (d, J = 3.1 Hz, 1H, 3'-H), 6.05 (s, 1H, 3-H), 5.34 (d, J = 1.1 Hz, 1H, 3-H), 4.54 (d, J = 5.4 Hz, 2H, NH-CH_2), 4.38 (s, 2H, TBDPSOC$\underline{H_2}$), 1.00 (s, 9H, C(CH_3)); ^{13}C (100 MHz, $CDCl_3$) δ 166.45 (C1), 151.11 (C2'), 142.29 (C5'), 140.69 (C2), 135.55 (Ph), 132.49 (Ph), 130.02 (Ph), 127.85 (Ph), 123.03 (C3), 110.44 (C4'), 107.74 (C3'), 64.74 (TBDPSO$\underline{C}H_2$), 36.51 ($\underline{C}H_2$NH), 26.61 (C($\underline{C}H_3)_3$), 19.08 ($\underline{C}(CH_3)_3$); *m/z* (ESI+) calculated for $C_{25}H_{29}NO_3Si$ $[M+Na]^+$ 442.1809, observed 442.1813 (error -0.70 ppm); ν_{max}(oil, cm^{-1}): 3335 (NH), 3070, 2930, 2857, 1661 (m, C=O amide), 1617, 1530, 1427, 1106, 739, 699.

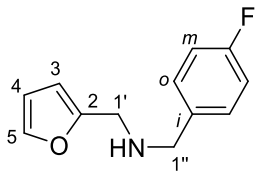
***N*-(furan-2-ylmethyl)-2-(hydroxymethyl)acrylamide (64)**



Deprotection of silyl ether **63** (1.0 equiv., 4.53 mmol, 1.90 g) with TBAF (1M in THF, 2.0 equiv., 9.0 mmol, 9.0 mL) in THF (50 mL) was performed as described in general procedure B. Purification by column chromatography (SiO_2, Et2O) afforded **64** as a yellow solid (0.75 g, 4.14 mmol, 91%).

Mp: 97-100 °C; Rf 0.40 (SiO_2, Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.35 (m, 1H, 5'-*H*), 9.91 (bs, 1H, NH), 6.32–6.31 (m, 1H, 4'-H), 6.25–6.24 (m, 1H, 3'-H), 5.92 (s, 1H, 3-H), 5.54 (d, *J* = 0.58 Hz, 1H, 3-H), 4.50 (d, *J* = 5.72 Hz, 2H, C$\underline{H}_2$NH), 4.35 (d, *J* = 5.02 Hz, 2H, C$\underline{H}_2$OH), 2.76 (bs, 1H, OH); ^{13}C (100 MHz, $CDCl_3$) δ 167.06 (C1), 150.99 (C2'), 142.31 (C5'), 141.89 (C2), 121.98 (C3), 110.48 (C4'), 107.61 (C3'), 63.84 ($\underline{C}H_2$OH), 36.49 ($\underline{C}H_2$NH); *m/z* (ESI+) calculated for $C_9H_{11}NO_3$ $[M+H]^+$ 182.0812, observed 182.0811 (error 0.08 ppm); ν_{max} (solid, cm^{-1}): 3377 (NH), 3248 (OH), 2930, 2881, 1657 (C=O amide), 1609, 1537, 1312, 1201, 1143, 1029, 952, 920, 806, 738.

***N*-(4-fluorobenzyl)-1-(furan-2-yl)methanamine (66)**

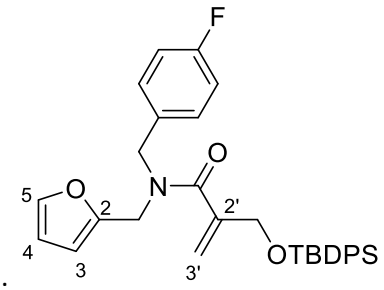


Reductive amination of furfurylamine (1.00 equiv., 51 mmol, 5. 0 g) and 4-fluorobenzaldehyde (1.2 equiv., 61.8 mmol, 7.7 g) in ethanol (50 mL) was performed following the general procedure C by addition of $NaBH_4$ (2 equiv., 3.9 g, 103 mmol) after 4 h. Purification by column chromatography (SiO_2, 3:1 Et_2O/Petrol) gave amine **66** as a colourless oil (9.8 g, 47.7 mmol, 93%).

Rf 0.46 (SiO_2, Petrol/Et_2O 1:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 1.2 Hz, 1H, 5-H), 7.31–7.26 (m, 2H, *o*Ph), 7.04–6.98 (m, 2H, *m*Ph), 6.33–6.32 (m, 1H, 4-H), 6.18 (d, *J* = 3.0 Hz, 1H, 3-H), 3.77 (s, 2H, 1'-H_2), 3.75 (s, 2H, 1''-H_2), 1.63 (s, 1H, NH); ^{19}F NMR (400 MHz, $CDCl_3$) δ 15.97 (d, *J* = 1.92 Hz); ^{13}C (100 MHz, $CDCl_3$) δ 161.96 (d, *J* = 244 Hz, C-F), 153.74 (C2), 141.89 (C4), 135.62 (*i*Ph), 129.79 (d, *J* = 7.96 Hz, *o*Ph), 115.18 (d, *J* = 21.24 Hz, *m*Ph), 110.13 (C5), 107.09 (C3), 52.03 (C1''), 45.31 (C1'); *m/z* (ESI+) calculated for $C_{12}H_{12}FNO$ $[M+H]^+$ 206.0976, observed 206.0969 (error 3.61 ppm); ν_{max} (oil, cm^{-1}): 2831, 1601, 1507 (s), 1451, 1357, 1218 (s), 1146, 1008, 821, 732 (s), 599, 554, 501.

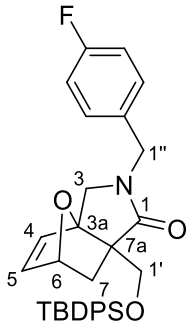
2-(((*tert*-butyldiphenylsilyl)oxy)methyl)-*N*-(4-fluorobenzyl)-*N*-(furan-2-ylmethyl)acrylamide (67) and

7a-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-(4-fluorobenzyl)-2,3,7,7a-tetrahydro-3a,6-epoxyisoindol-1(6*H*)-one (68)



Coupling of carboxylic acid **50** (1.2 equiv., 6.0 g, 17.6 mmol) and amine **66** (1.0 equiv., 3.0 g, 14.7 mmol) was performed as described in general procedure D by addition of EDC·HCl (1.5 equiv., 4.2 g, 22.0 mmol), DMAP (0.1 equiv., 0.81g, 1.47 mmol), Et_3N (1.2 equiv., 17.6 mmol, 1.78 g) in DMF (30 mL). The reaction mixture was stirred for 4 h. Column chromatography (SiO_2, 3:1 Petrol/EtOAc) afforded compound **67** as a colourless oil (7.38 g, 14.0 mmol, 95%). Cycloadduct **68** was obtained by spontaneous cycloaddition of amide **67**.

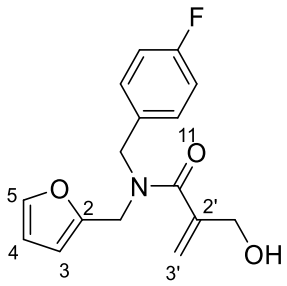
Rf 0.74 (SiO_2, Petrol/EtOAc 2:1); ^{1}H NMR (400 MHz , $CDCl_3$) δ 7.73–7.59 (m, 4H, Ar), 7.45–7.34 (m, 7H, Ar and 5-H), 7.22–6.92 (m, 4H, Ar), 6.32-6.33 (m, 1H, 4-H), 6.16 (s, 1H, 3-H), 5.56–5.24 (m, 2H, 3'-H_2), 4.54 (s, 2H), 4.48 (s, 2H), 4.41 (s, 2H), 1.03 (s, 9H, $C(CH_3)_3$); ^{19}F NMR (400 MHz, $CDCl_3$) δ -114.84, -115.19;



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60–7.59 (m, 4H, Ar), 7.47–7.37 (m, 6H, Ar), 7.26–7.21 (m, 2H, Ar), 6.94–6.90 (m, 2H, Ar), 6.34 (dd J_1 = 5.8 Hz, J_2 = 1.6 Hz, 1H, 5-H), 6.31 (d, J = 5.8 Hz, 1H, 4-H), 4.92 (dd J_1 = 4.9 Hz, J_2 = 1.5 Hz, 1H, 6-H), 4.92 (d, J = 15.1 Hz, 1H, 1''-H), 4.23 (d, J = 15.1 Hz, 1H, 1''-H), 4.08 (d, J = 10.4 Hz, 1H, 1'-H), 4.03 (d, J = 10.6 Hz, 1H, 3-H), 3.52 (d, J= 10.6 Hz, 1H, 3-H), 3.06 (d, J= 10.4 Hz, 1H, 1'-H), 2.27 (dd, J_1 = 12.0 Hz, J_2 = 4.7 Hz, 1H, *exo*-7-H), 1.01 (s, 9H, *t*Bu), 0.80 (d, J= 12.0 Hz, 1H, *endo*-7-H); ^{13}C (100 MHz, $CDCl_3$) δ 175.70 (C1), 162.16 (d, J = 245

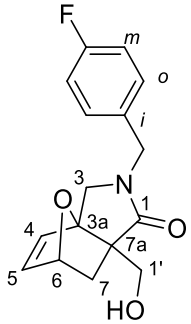
Hz, C-F), 136.76 (C5), 135.60 (Ar), 135.51 (Ar), 132.85 (Ar), 132.29 (C4), 131.98 (Ar), 131.95 (Ar), 131.92 (Ar), 129.97 (Ar), 129.94 (Ar), 129.62 (Ar), 129.54 (Ar), 127.85 (Ar), 115.62 (Ar), 115.41 (Ar), 91.25 (C3a), 78.17 (C6), 68.06 (C1'), 58.42 (C7a), 49.66 (C3), 46.03 (C1''), 31.92 (C7), 26.81 ($C(CH_3)_3$), 19.14 ($C(CH_3)_3$); ^{19}F (400 MHz, $CDCl_3$) δ -115.4; *m/z* (ESI+) calculated for $C_{32}H_{34}FNO_3Si$ $[M+K]^+$ 566.1924, observed 566.1921 (error 0.89 ppm).

_N_-(4-fluorobenzyl)-_N_-(furan-2-ylmethyl)-2-(hydroxymethyl)acrylamide (69) and 2-(4-fluorobenzyl)-7a-(hydroxymethyl)-2,3,7,7a-tetrahydro-3a,6-epoxyisoindol-1(6*H*)-one (70)



Deprotection of silyl ether **67** (1.0 equiv., 5.6 mmol, 3.0 g) with TBAF (1M in THF, 2.0 equiv., 11.3 mmol, 11.3 mL) in THF (55 mL) was performed as described in general procedure B. Cycloadduct **70** was obtained by spontaneous cyclization of compound **69**. Purification by column chromatography (SiO_2, EtOAc) afforded **69** (with **70**) as a colourless oil (1.38 g, 4.77 mmol, 82%).

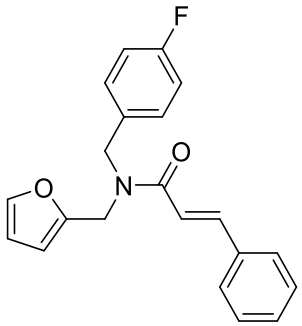
Rf 0.41 (SiO_2, Petrol/EtOAc 1:3); ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (s, 1H, Ar), 7.26–7.20 (m, 2H, Ar), 7.03–7.00 (m, 2H, Ar), 6.33 (s, 1H, 3-H), 6.21 (d, *J* = 3.1 Hz, 1H, 4-H), 5.57–5.28 (bm, 2H, 3'-H_2), 4.62 (s, 2H), 4.51 (s, 2H), 4.40 (s, 2H, Ar-C$\underline{H_2}$), 2.54 (bs, 1H, -OH); ^{19}F NMR (400 MHz, $CDCl_3$) δ -114.49, -114.89.



Rf: 0.25 (SiO_2, EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 7.29–7.26 (m, *o*Ph), 7.05-7.01 (m, 2H, *m*Ph), 6.49-6.45 (m, 2H, 4-H, 5-H), 5.01 (dd, J_1= 1.1 Hz, J_2= 4.6 Hz, 1H, 6-H), 4.62 (d, *J* = 15.2 Hz, 1H, 1''-H), 4.50 (d, *J* = 15.2 Hz, 1H, 1''-H), 3.94 (d, *J* = 5.9 Hz, 1H, 1'-H), 3.91 (d, *J* = 6.0 Hz, 1H, 3-H), 3.48 (d, *J*= 11.0 Hz, 1H, 3-H), 3.23 (d, *J* = 11.0 Hz, 1H, 1'-H), 2.34 (dd, J_1 = 11.9 Hz, J_2 = 4.7 Hz, 1H, *exo*-7-H), 1.03 (d, *J* = 11.9 Hz, 1H, *endo*-7-H); ^{13}C (100 MHz, $CDCl_3$) δ

176.05 (C1), 162.21 (d, *J* = 246 Hz, C-F), 136.94 (C4), 132.05 (C5), 131.83 (d, *J* = 3.2 Hz, *i*Ph), 129.46 (d, *J* = 8.2 Hz, *o*Ph), 115.58 (d, *J* = 21.4 Hz, *m*Ph), 90.91 (C7a), 78.36 (C6), 66.97 (C1'), 58.50 (C3a), 49.47 (C3), 46.05 (C1''), 31.82 (C7); ^{19}F (400 MHz, $CDCl_3$) δ -115.1; *m/z* (ESI+) calculated for $C_{16}H_{16}FNO_3$ $[M+Na]^+$ 312.1006, observed 312.1007 (error -0.07 ppm); ν_{max} (solid, cm^{-1}): 3324 (br, OH), 2944, 2903, 1651 (C=O lactame), 1514, 1474, 1371, 1217, 1073, 832, 565.

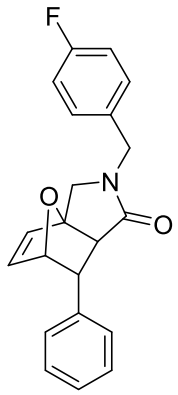
_N_-(4-fluorobenzyl)-_N_-(furan-2-ylmethyl)cinnamamide (71)



Coupling of cinnamic acid (1.3 equiv., 1.9 g, 12.7 mmol) and amine **66** (1.0 equiv., 2.0 g, 9.7 mmol) was performed as described in general procedure D by addition of EDC·HCl (1.5 equiv., 2.80 g, 14.61 mmol), DMAP (0.1 equiv., 0. 12 g, 0.974 mmol, Et_3N (1.3 equiv., 1.8 mL, 12.7 mmol) in DMF (25 mL). The reaction mixture was stirred for 3 h. Column chromatography (SiO_2, 1:2 Petrol/Et_2O) afforded compounds **71** as a white solid (3.07 g, 9.15 mmol, 94%).

Mp: 71-74 °C; Rf 0.46 (SiO_2, 2:1 Et_2O/Petrol, EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82–7.78 (m, 1H), 7.55–6.79 (m, 11H), 6.34–6.20 (m, 2H, 3-H, 4-H), 4.68 (s, 2H), 4.58 (d, *J* =71.5 Hz, 2H); ^{1}H NMR (400 MHz, CD_3CN) δ 7.69–6.95 (m, 12H), 6.35 (s, 1H), 6.29 (s, 1H), 4.73 (s, 1H), 4.63 (s, 3H); ^{19}F NMR (400 MHz, $CDCl_3$) δ -114.68, -115.09; ^{19}F NMR (400 MHz, CD_3CN) δ -117.25, -117.46; ^{13}C (100 MHz, $CDCl_3$) δ 166.99, 166.81, 163.47, 161.03, 150.78, 150.16, 144.13, 143.70, 142.82, 142.32, 135.21, 135.06, 133.08, 130.12, 130.04, 129.80, 128.84, 128.23, 128.16, 127.92, 117.40, 116.90, 115.98, 115.77, 115.58, 115.37, 110.49, 109.04, 108.30, 50.00, 48.18, 43.71, 41.87; *m/z* (ESI+) calculated for $C_{21}H_{18}FNO_2$ $[M+H]^+$ 336.1394, observed 336.1386 (error 2.89ppm); ν_{max} (solid, cm^{-1}): 1648 (C=O amide), 1598 (s), 1506, 1438, 1412, 1220, 1186, 818, 765, 740.

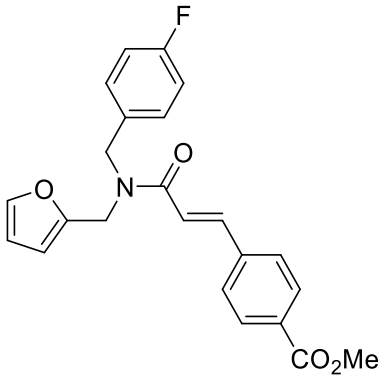
7-benzyl-2-(4-fluorobenzyl)-2,3,7,7a-tetrahydro-3a,6-epoxyisoindol-1(6*H*)-one (72)



Little amount of compound **72** was observed by spontaneous cyclization of compound **71**.

^{19}F NMR (400 MHz, $CDCl_3$) δ -114.80; ^{19}F NMR (400 MHz, CD_3CN) δ -117.13;

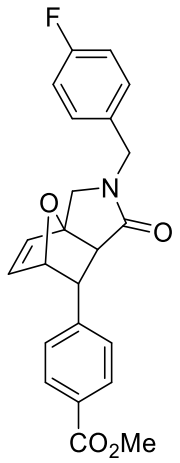
Methyl (*E*)-4-(3-((4-fluorobenzyl)(furan-2-ylmethyl)amino)-3-oxoprop-1-en-1-yl)benzoate (73)



Coupling of (*E*)-3-(4-(methoxycarbonyl)phenyl)acrylic acid (1.3 equiv., 0.65 g, 3.2 mmol), and amine **66** (1.0 equiv., 0.50 g, 2.4 mmol) was performed as described in general procedure D by addition of EDC·HCl (1.5 equiv., 0.70 g, 3.6 mmol), DMAP (0.1 equiv., 30 mg, 0.24 mmol) Et_3N (1.3 equiv., 0.4 mL, 3.2 mmol) in DMF (5 mL). The reaction mixture was stirred for 3 h. Column chromatography (SiO_2, 1:2 Petrol/Et_2O) afforded compound **73** and **74** (97:3) as a pale yellow oil (0.92 g, 2.3 mmol, 96%).

Rf 0.55 (SiO_2, 2:1 Et_2O/Petrol); ^{1}H NMR (400 MHz , $CDCl_3$) δ 8.05-6.87 (m, 11H), 6.35-6.21 (m, 2H), 4.68 (s, 2H), 4.67 (s, 1H), 4.50 (s, 1H), 3.92 (d, *J* =6.34 Hz, 3H, CH_3); ^{19}F NMR (400 MHz , $CDCl_3$) δ -114.44, -114.91; ^{19}F NMR (400 MHz , CD_3CN) δ -117.16, -117.38; ν_{max} (solid, cm^{-1}): 2951, 1716 (C=O ester), 1650 (C=O amide), 1508, 1434, 1408, 1274, 1220, 1179, 1105, 1011, 842, 820, 771, 716, 494.

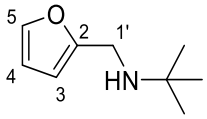
methyl 4-((2-(4-fluorobenzyl)-1-oxo-1,2,3,6,7,7a-hexahydro-3a,6-epoxyisoindol-7-yl)methyl)benzoate (74)



Compound **74** was observed by spontaneous cyclization of compound **73**.

^{19}F NMR (400 MHz, $CDCl_3$) δ -114.67 ; ^{19}F NMR (400 MHz, CD_3CN) δ-117.09;

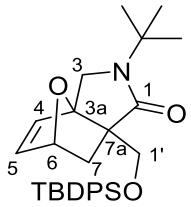
***N*-(furan-2-ylmethyl)-2-methylpropan-2-amine (75)**



Reductive amination of *tert*-butylamine (1.00 equiv., 48.3 mmol, 3.53 g) and furfural (1.1 equiv., 52 mmol, 5.0 g) in ethanol (120 mL) was performed following the general procedure C by addition of $NaBH_4$ (2 equiv., 3.8 g, 100 mmol) after 1 h. Purification by column chromatography (SiO_2, 4:1 Et_2O/Petrol) gave *N*-furfuryl-*t*-butylamine **75** as a colourless oil (5.02 g, 32.8 mmol, 68%).

Rf 0.11 (SiO_2, 2:1 EtOAc/Petrol); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.34 (m, 1H, 5-H), 6.30–6.29 (m, 1H, 4-H), 6.16–6.15 (m, 3-H), 3.75 (s, 2H, 1'-H), 1.16 (s, 9H, $C(CH_3)_3$); ^{13}C (100 MHz, $CDCl_3$) δ 154.64 (C2), 141.62 (C5), 110.15 (C4), 106.18 (C3), 50.53 ($\underline{C}(CH_3)_3$), 40.06 (C1'), 28.95 ($C(\underline{C}H_3)_3$); *m/z* (ESI+) calculated for $C_9H_{15}NO$ $[M+H]^+$ 154.1226, observed 154.1229 (error 1.99 ppm); ν_{max}(oil, cm^{-1}): 2961, 1599, 1506, 1478, 1446, 1362, 1218, 1146, 1074, 1010, 918, 803, 728 (s), 599.

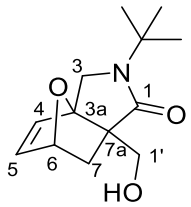
2-(*tert*-butyl)-7a-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2,3,7,7a-tetrahydro-3a,6-epoxyisoindol-1(6*H*)-one (77)



Coupling of carboxylic acid **50** (1.0 equiv., 3.3 g, 9.7 mmol) and amine **75** (1.2 equiv., 1.8 g, 11.6 mmol) was performed as described in general procedure D by addition of EDC·HCl (1.5 equiv., 2.8 g, 14.5 mmol), DMAP (0.1 equiv., 118 mg, 0.97 mmol), Et_3N (1.3 equiv., 1.7 mL, 12.6 mmol) in DMF (20 mL). The reaction mixture was stirred overnight. Column chromatography (SiO_2, 1:2 Petrol/EtOAc) afforded compound **77** as a white solid (3.08 g, 6.47 mmol, 67%).

Mp: 139-143 °C; Rf 0.86 (SiO_2, 3:1 EtOAc/Petrol); ^{1}H NMR (400 MHz , $CDCl_3$) δ 7.64–7.60 (m, 4H, Ph), 7.43–7.37 (m, 6H, Ph), 6.30 (s, 2H, 4-*H* and 5-H), 4.86 (d, *J* = 4.6 Hz, 1H, 6-H), 4.16 (d, *J* = 10.8 Hz, 1H, 3-H), 4.02 (d, *J* = 10.3 Hz, 1H, 1'-H), 3.77 (d, *J* = 10.6 Hz, 1H, 3-H), 2.94 (d, *J* = 10.3 Hz, 1H, 1'-H), 2.18 (dd, J_1 = 11.9 Hz, J_2 = 4.7 Hz, 1H, *exo*-7-H), 1.45 (s, 9H, N-C(CH_3)$_3$), 1.07 (s, 9H, Si-C(CH_3)$_3$), 0.69 (d, *J* = 11.9 Hz, 1H, *endo*-7-H); ^{13}C (100 MHz, $CDCl_3$) δ 175.66 (C1), 136.46 (C4/C5), 135.63 (Ph), 135.57 (Ph), 132.44 (Ph), 132.24 (C4/C5), 129.93 (Ph), 129.78 (Ph), 127.81 (Ph), 127.75 (Ph), 90.50 (C3a), 78.00 (C6), 68.18 (C1'), 58.97 (C7a), 54.35 (N-C(CH_3)$_3$), 48.89 (C3), 32.33 (C7), 27.86 (N-C(CH_3)$_3$), 26.95 (Si-C(CH_3)$_3$), 19.14 (Si-C(CH_3)$_3$); *m/z* (ESI+) calculated for $C_{29}H_{37}NO_3Si$ $[M+Na]^+$ 498.2435, observed 498.2436 (error -0.39 ppm); ν_{max} (solid, cm^{-1}): 2979, 2956, 2857, 1674 (m, C=O lactam), 1468, 1428, 1349, 1111, 1066, 824, 741, 702 (s), 616, 505, 464.

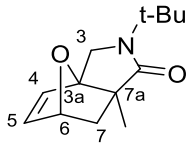
2-(*tert*-butyl)-7a-(hydroxymethyl)-2,3,7,7a-tetrahydro-3a,6-epoxyisoindol-1(6*H*)-one (78)



Deprotection of silyl ether **77** (1.0 equiv., 4.1 mmol, 1.9 g) with TBAF (1M in THF, 2.0 equiv., 8.2 mmol, 8 mL) in THF (40 mL) was performed as described in general procedure B. Purification by silica gel chromatography (100% EtOAc) afforded **78** (0.91 g, 3.8 mmol, 94%) as a white solid.

Rf 0.18 (SiO_2, EtOAc); Mp: 193–195 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.43 (s, 2H, 4-H and 5-H), 4.94 (d, *J* = 4.5 Hz, 1H, 6-H), 3.97 (d, *J* = 11.10 Hz, 1H, 3-H), 3.75 (d, *J* = 11.10 Hz, 1H, 3-H), 3.74 (d, *J* = 10.9 Hz, 1H, 1'-H), 3.21 (dd, J_1 = 10.9 Hz, J_2 = 5.1 Hz, 1H, 1'-H), 2.27 (dd, J_1 = 11.9 Hz, J_2 = 4.7 Hz, 1H, *exo*-7-H), 1.91 (t, 1H, OH), 1.44 (s, 9H, *N*-$C(CH_3)_3$), 0.98 (d, *J* = 11.9 Hz, 1H, *endo*-7-H); ^{13}C (100 MHz, $CDCl_3$) δ 176.18 (C1), 136.99 (C5), 132.16 (C4), 89.80 (C3a), 78.32 (C6), 67.15 (C1'), 59.10 (C7a), 54.48 ($\underline{C}(CH_3)_3$), 48.20 (C3), 32.15 (C7), 27.78 ($C(\underline{C}H_3)_3$); *m/z* (ESI+) calculated for $C_{13}H_{19}NO_3$ $[M+Na]^+$ 238.1438, observed 238.1443 (error 2.33 ppm); ν_{max} (solid, cm^{-1}): 3344 (br, OH), 2977, 2946, 2870, 2359, 1651 (s, C=O lactam), 1456, 1412, 1359, 1213, 1040, 868, 704, 572.

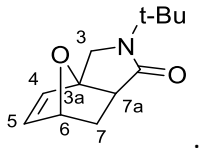
2-(*tert*-butyl)-7a-methyl-2,3,7,7a-tetrahydro-3a,6-epoxyisoindol-1(6*H*)-one (80)



Coupling of methacrylic acid (1.0 equiv., 0.93 g, 10.87 mmol) and amine **75** (1.2 equiv., 3.00 g, 13.0 mmol) was performed as described in general procedure D by addition of EDC·HCl (3.12 g, 16.3 mmol), DMAP (133 mg, 1.1 mmol) Et_3N (1.2 equiv., 2.0 mL, 14.1 mmol) in DCM (20 mL). The reaction mixture was stirred for 3 days. The crude of the reaction was heated at reflux in MeOH for 2 h and concentrated. The oil obtained was passed through a pad of silica. Compound **80** crystallised into white crystals (1.06 g, 4.78 mmol, 44%), then washed with heptane.

Mp: 92-93 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.42 (dd, J_1 = 5.8, J_2 = 1.7 Hz, 1H, 5-H), 6.33 (d, *J* = 5.8 Hz, 1H, 4-H), 4.91 (dd, J_1 = 4.8, J_2 = 1.6 Hz, 1H, 6-H), 3.85 (d, *J* = 11.7 Hz, 1H, 3-H), 3.75 (d, *J* = 11.7 Hz, 1H, 3-H), 2.40 (dd, J_1 = 11.7, J_2 = 4.8 Hz, 1H, *exo*-7-H), 1.40 (s, 9H, *t*Bu), 1.01 (d, *J* = 11.7 Hz, 1H, *endo*-7-H), 0.99 (s, 3H, Me); ^{13}C (100 MHz, $CDCl_3$) δ 178.14 (C=O), 137.45 (C5), 131.71 (C4), 90.24 (C3a), 78.75 (C6), 53.85 ($\underline{C}Me_3$), 52.86 (C7a), 46.28 (C3), 36.08 (C7), 27.69 ($C\underline{Me}_3$), 20.59 (Me); *m/z* (ESI+) calculated for $C_{13}H_{19}NO_2$ $[M+Na]^+$ 244.1308, observed 244.1307 (error 0.60 ppm); ν_{max} (solid, cm^{-1}):2960, 2868, 1667 (C=O lactam), 1352, 1256, 1215, 1079, 1024, 914, 854, 697.

2-(*tert*-butyl)-2,3,7,7a-tetrahydro-3a,6-epoxyisoindol-1(6*H*)-one (82)



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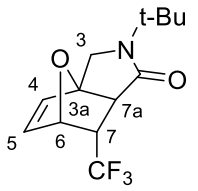
Coupling of acrylic acid (1.0 equiv., 0.78 g, 10.87 mmol) and amine **75** (1.2 equiv., 3.00 g, 13.0 mmol) was performed as described in general procedure D by addition of EDC·HCl (3.12 g, 16.3 mmol), DMAP (133 mg, 1.1 mmol) Et_3N (1.2 equiv., 2.0 mL, 14.1 mmol) in DCM (20 mL). The reaction mixture was stirred for 3 days. The crude of the reaction was heated at reflux in MeOH for 2 h and concentrated. The oil obtained was passed through a pad of silica. Compound **82** crystallised into white crystals, then washed with heptane to provide pure **82** as a white solid (1.25 g, 6.03 mmol, 55%).

Mp: 71-73 °C; ^{1}H NMR (400 MHz , $CDCl_3$) δ 6.35 (s, 2H, 4-H and 5-H), 5.01 (d, *J* = 4.4 Hz, 1H, 6-H), 3.96 (d, *J* = 11.7 Hz, 1H, 3-H), 3.81 (d, *J* = 11.7 Hz, 1H, 3-H), 2.39 (dd, J_1 = 8.7, J_2 = 3.3 Hz 8.7, 1H, 7a-H), 2.15 (dq, *J* = 11.8, 4.0 Hz, 1H, *exo*-7-H), 1.50 (dd, J_1 = 11.8, J_2 = 8.7 Hz, 1H, *endo*-7-H), 1.41 (s, 9H, *t*Bu); ^{13}C (100 MHz, $CDCl_3$) δ 174.31 (C=O), 137.06 (C5), 133.43 (C4), 88.15 (C3a), 78.95 (C6), 54.16 (<u>C</u>Me_3), 48.57 (C7a), 47.81 (C3), 28.27 (C7), 27.72 (C<u>Me</u>$_3$); *m/z* (ESI+) calculated for $C_{12}H_{17}NO_2$ $[M+Na]^+$ 230.1151, observed 230.1153 (error -0.7 ppm); ν_{max} (solid, cm^{-1}): 2972, 1666 (C=O lactam), 1475, 1358, 1255, 1223, 898, 868, 725.

2-(*tert*-butyl)-7-(trifluoromethyl)-2,3,7,7a-tetrahydro-3a,6-epoxyisoindol-1(6H)-one (84)

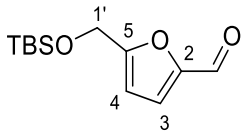


Coupling of 4,4,4-trifluorocrotonic acid (1.2 equiv., 2.52 g, 18.0 mmol) and amine **75** (1.0 equiv., 2.30 g, 15.0 mmol) was performed as described in general procedure D by addition of EDC·HCl (4.31 g, 22.5 mmol), DMAP (0.18 g, 1.50 mmol) Et_3N (1.2 equiv., 2.5 mL, 18.0 mmol) in DCM (30 mL). The reaction mixture was stirred overnight. Column chromatography (SiO_2, Petrol/EtOAc 1:4) afforded compounds **84** as a white solid (1.24 g, 4.50 mmol, 30%).

Rf 0.58 (SiO_2, 3:1 EtOAc/Petrol); Mp = 120 °C (dec.), ^{1}H NMR (400 MHz , $CDCl_3$) δ 6.55 (d, 1H, *J* = 5.8 Hz, 4-H), 6.39 (dt, 1H, J_1 = 5.8 Hz, J_2 = 1.7 Hz, 5-H), 5.13 (dd, 1H, J_1 = 4.3 Hz, J_2 = 1.6 Hz, 6-H), 4.01 (d, 1H, *J* = 12.0 Hz, 3-H),

3.80 (d, 1H, *J* = 12.0 Hz, 3-H), 3.26-3.17 (m, 1H, 7-H), 2.56 (d, 1H, *J* = 4.1 Hz, 7a-H), 1.42 (s, 9H, *t*Bu); ^{13}C (100 MHz, $CDCl_3$) δ 171.47 (C=O), 135.25 (C4), 134.63 (C5), 125.05 (d, *J* = 277 Hz, CF_3), 89.59 (C3a), 78.66 (C6), 54.60 ($\underline{C}Me_3$), 51.23 (C7a), 47.73 (C3), 45.90 (q, C7), 27.62 ($C\underline{Me_3}$); ^{19}F NMR (400 MHz , $CDCl_3$) δ -65.59; *m/z* (ESI+) calculated for $C_{13}H_{16}F_3NO_2$ $[M+Na]^+$ 298.1025, observed 298.1029 (error 1.10 ppm); ν_{max} (solid, cm^{-1}): 2984, 1674 (C=O lactam), 1357, 1277, 1204, 1163, 1133, 732, 688.

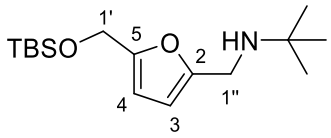
5-(((*tert*-butyldimethylsilyl)oxy)methyl)furan-2-carbaldehyde (85)[169]



Imidazole (1.1 equiv., 47.28 mmol, 3.22 g) was added to a solution of 5-hydroxymethylfurfural (1 equiv., 42.98 mmol, 5.42 g) in DCM (85 mL). The mixture was stirred at rt for 15 min and TBSCl (1.1 equiv., 47.28 mmol, 7.13 g) was added. The flask containing the reaction was covered with aluminium foil. The reaction mixture was stirred overnight at rt. Water (80 mL) was added and the organic phase was separated. The water was extracted with DCM (2 X 80 mL) and the combined organic phase was dried over Na_2SO_4 and concentrated *in vacuo* to give **85** as a yellow oil. The crude product was used without purification.

Rf: 0.44 (SiO_2, 1:5 EtOAc/Petrol); ^{1}H NMR (400 MHz , $CDCl_3$) δ 9.57 (s, 1H, CHO), 7.20 (d, *J* = 3.6 Hz, 1H, 3-H), 6.47 (d, *J* = 3.6 Hz, 1H, 4-H), 4.74 (s, 2H, 1'-H), 0.92 (s, 9H, Si-C$(CH_3)_3$), 0.11 (s, 6H, Si-$(CH_3)_2$); ^{13}C (100 MHz, $CDCl_3$) δ 177.56 (CHO), 161.48 (C5), 152.18 (C2), 122.52 (C3), 109.42 (C4), 58.63 (C1'), 25.78 ((Si-C($\underline{C}H_3)_3$), 18.34 (Si-$\underline{C}(CH_3)_3$), -5.37 (Si-C($\underline{C}H_3)_2$); *m/z* (ESI+) calculated for $C_{12}H_{20}O_3Si$ $[M+NH_4]^+$ 258.152, observed 258.1524 (error -2.09 ppm);

***N*-((5-(((*tert*-butyldimethylsilyl)oxy)methyl)furan-2-yl)methyl)-2-methylpropan-2-amine (86)**

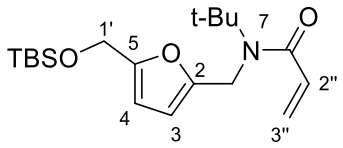


Reductive amination of *tert*-butylamine (1.0 equiv., 20.5 mmol, 1.5 g) and TBS-furfural (1.1 equiv., 22.5 mmol, 5.4 g) in ethanol (50 mL) was performed following the general procedure C by addition of $NaBH_4$ (2 equiv., 1.5 g,

41.0 mmol) after 1 h. Purification by column chromatography (SiO_2, 2:1 Et_2O/Petrol) gave *N*-furfuryl-*tert*-butylamine **86** as a colourless oil (5.5 g, 18.4 mmol, 90%).

^{1}H NMR (400 MHz , $CDCl_3$) δ 6.13 (d, *J* = 3.1 Hz, 1H, 4-H), 6.09 (d, *J* = 3.1 Hz, 1H, 3-H), 4.60 (s, 2H, 1'-H_2), 3.73 (s, 2H, 1''-H_2), 1.15 (s, 9H, NC$(CH_3)_3$), 0.90 (s, 9H, SiC$(CH_3)_3$), 0.08 (s, 6H, Si-$(CH_3)_2$); ^{13}C (100 MHz, $CDCl_3$) δ 154.29 (C2), 153.32 (C5), 107.92 (C4), 106.75 (C3), 58.28 (C1'), 50.54 (N-C$(CH_3)_3$), 4.14 (C1''), 28.97 (N-C$(CH_3)_3$), 25.92 (Si-C$(CH_3)_3$), 18.45 (Si-C$(CH_3)_3$), -5.16 (Si$(CH_3)_2$); *m/z* (ESI+) calculated for $C_{16}H_{31}NO_2Si$ $[M+H]^+$ 298.2204, observed 298.2197 (error 2.35 ppm); ν_{max} (oil, cm^{-1}): 2956, 2928, 2857, 1472, 1361, 1253, 1073, 833, 775.

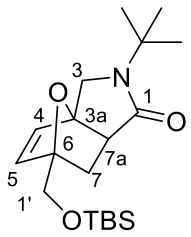
_N_-(*tert*-butyl)-N-((5-(((*tert*-butyldimethylsilyl)oxy)methyl)furan-2-yl)methyl)acrylamide (87)



Same procedure used for **88**.

Rf 0.86 (SiO_2, 2:1 Et_2O/Petrol); ^{1}H NMR (400 MHz , $CDCl_3$) δ 6.58 (dd, J_1 = 8.7 Hz, J_2 = 3.3 Hz, 1H, 2''-H), 6.25 (dd, J_1 = 16.7 Hz, J_2 = 2.0 Hz, 1H, 3''-H), 6.17 (d, *J* = 3.1 Hz, 1H, 4-H), 6.11 (d, *J* = 3.1 Hz, 1H, 5-H), 5.56 (dd, J_1 = 16.7 Hz, J_2 = 2.0 Hz, 1H, 3''-H), 4.59 (s, 2H, 1'-H_2), 4.51 (s, 2H, N-CH_2), 1.46 (s, 9H, N-C$(CH_3)_3$), 0.89 (s, 9H, Si-C$(CH_3)_3$), 0.08 (s, 6H, Si-$(CH_3)_2$); ^{13}C (100 MHz, $CDCl_3$) δ 168.31 (C=O), 153.76 (C5), 152.49 (C2), 131.62 (C2''), 126.84 (C3''), 108.21 (C4), 107.66 (C3), 58.09 (C1'), 57.70 (N-CH_2)$_3$), 42.94 (N-C$(CH_3)_3$, 28.54 (N-C$(CH_3)_3$), 25.9 (Si-C$(CH_3)_3$), 18.41 (Si-C$(CH_3)_3$), -5.18 (Si-$(CH_3)_2$);

2-(*tert*-butyl)-6-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,3,7,7a-tetrahydro-3a,6-epoxyisoindol-1(6*H*)-one (88)



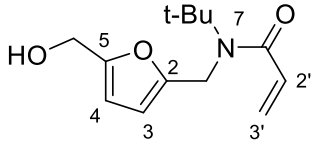
Coupling of acrylic acid (1.3 equiv., 0.83 g, 11.5 mmol) and amine **86** (1.0 equiv., 2.5 g, 8.9 mmol) was performed as described in general procedure D by addition of EDC·HCl (2.55 g, 13.32 mmol), DMAP (0.11g, 0.89 mmol), Et_3N (1.3 equiv., 1.6 mL, 11.5 mmol) in DCM (20 mL). The reaction mixture was stirred overnight. Column

chromatography (SiO_2, 1:2 Petrol/Et_2O) afforded compounds **87** and **88** as a pale yellow oils (1.36 g, 3.87 mmol of **88** and 1.04 g, 2.96 mmol of **87**, 77% in total).

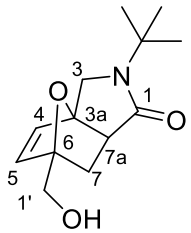
Rf 0.38 (SiO_2, 2:1 Et_2O/Petrol); Mp: 54-56 °C; ^{1}H NMR (400 MHz , $CDCl_3$) δ 6.36 (d, *J* = 5.8 Hz, 1H, 4-H), 6.33 (d, *J* = 5.8 Hz, 1H, 5-H) 4.00 (s, 2H, 1'-H_2), 3.91 (d, *J* = 11.7 Hz, 1H, 3-H), 3.79 (d, *J* = 11.7 Hz, 1H, 3-H), 2.47 (dd, J_1 = 8.7 Hz, J_2 = 3.3 Hz, 1H, 7a-H), 2.00 (dd, J_1 = 11.7 Hz, J_2 = 3.4 Hz, 1H, 7-H), 1.55 (dd, J_1 = 11.7 Hz, J_2 = 8.7 Hz, 1H, 7-H), 1.40 (s, 9H, N-C(CH_3)$_3$), 0.88 (s, 9H, Si-C(CH_3)$_3$), 0.06 (s, 6H, Si-(CH_3)$_2$); ^{13}C (100 MHz, $CDCl_3$) δ 174.37 (C1), 137.94 (C5), 133.86 (C4), 90.80 (C6), 88.28 (C3a), 63.39 (C1'), 54.14 (N-C(CH_3)$_3$), 50.96 (C7a), 48.00 (C3), 30.36 (C7), 27.73 (N-C(CH_3)$_3$), 25.91 (Si-C(CH_3)$_3$), 18.39 (Si-C(CH_3)$_3$), -5.30 (Si-(CH_3)$_2$); *m/z* (ESI+) calculated for $C_{19}H_{33}NO_3Si$ $[M+Na]^+$ 374.2126, observed 374.2126 (error -1.41 ppm); ν_{max} (solid, cm^{-1}): 2953, 2928, 2856, 1668 (s, C=O lactam), 1470, 1410, 1356, 1253, 1097, 837, 773.

_N_-(_tert_-butyl)-_N_-((5-(hydroxymethyl)furan-2-yl)methyl)acrylamide (89) and 2-(_tert_-butyl)-6-(hydroxymethyl)-2,3,7,7a-tetrahydro-3a,6-epoxyisoindol-1(6_H_)-one (90)

Deprotection of silyl ether **87** and **88** (3.85 mmol, 1.35 g) with TBAF (7.70 mmol, 8 mL) in THF (40 mL) was performed as described in general procedure B. The reaction mixture was allowed to warm to rt and stirred overnight. Purification by column chromatography (SiO_2, EtOAc/Petrol 3:1 then EtOAc/MeOH 9:1) afforded **6.47a** (0.12 g, 0.51 mmol, 13%) as a pale yellow oil and **90** (0.67 g, 2.82 mmol, 73%) as a white solid.



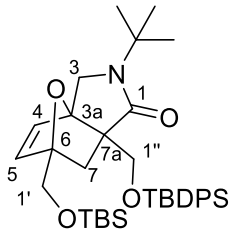
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.57-6.50 (m, 1H), 6.25-6.20 (m, 2H), 6.11 (bs, 1H), 4.55 (s, 2H), 4.51 (s, 2H), 1.44 (s, 9H).



Rf 0.26 (SiO_2, EtOAc); ^{1}H NMR (400 MHz , $CDCl_3$) δ 6.43 (d, *J* = 5.8 Hz, 1H, 5-H), 6.36 (d, *J* = 5.8 Hz, 1H, 4-H), 4.08 (d, *J* = 12.4 Hz, 1H, 1'-H), 4.00 (d, *J* = 12.4 Hz, 1H, 1'-H), 3.95 (d, *J* = 11.8 Hz, 1H, 3-H), 3.81 (d, *J* = 11.8 Hz, 1H, 3-H), 2.53 (dd, J_1 = 8.6 Hz, J_2 = 3.3 Hz, 1H, 7a-H), 2.00 (dd, J_1 = 11.7 Hz, J_2 = 3.3 Hz, 1H, 7-H), 1.85 (s, 1H, OH), 1.52

(dd, J_1 = 11.7 Hz, J_2 = 8.7 Hz, 1H, 7-H), 1.42 (s, 9H, *t*Bu); ^{13}C (100 MHz, $CDCl_3$) δ 174.10 (C1), 137.40 (C5), 134.83 (C4), 91.42 (C6), 88.48 (C3a), 62.93 (C1'), 54.27 ($\underline{C}(CH_3)_3$), 51.02 (C7a), 47.92 (C3), 29.66 (C7), 27.75 ($C(\underline{C}H_3)_3$); *m/z* (ESI+) calculated for $C_{13}H_{19}NO_3$ $[M+H]^+$238.1438, observed 238.1443 (error -2.16 ppm); ν_{max} (solid, cm^{-1}): 3415 (br, OH), 2970, 2927, 1663 (s, C=O lactam), 1410, 1353, 1255, 1229, 1049, 1002, 857, 748.

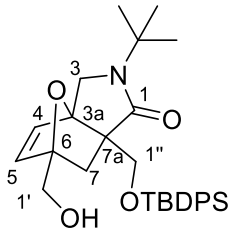
2-(*tert*-butyl)-6-(((*tert*-butyldimethylsilyl)oxy)methyl)-7a-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2,3,7,7a-tetrahydro-3a,6-epoxyisoindol-1(6*H*)-one (92)



Coupling of carboxylic acid **50** (1.2 equiv., 3.9 g, 11.5 mmol) and amine **86** (1.0 equiv., 2.5 g, 8.9 mmol) was performed as described in general procedure D by addition of EDC·HCl (2.55 g, 13.32 mmol), DMAP (0.11 g, 0.89 mmol) Et_3N (1.3 equiv., 1.6 mL, 11.54 mmol) in DCM (20 mL). The reaction mixture was stirred overnight. Column chromatography (SiO_2, Petrol/Et_2O 7:1, 5:1, 2:1) afforded compounds **92** as a white solid (3.99 g, 6.44 mmol, 72%).

Rf 0.26 (SiO_2, 1:5 Et_2O/Petrol); Mp: 106-107 °C; ^{1}H NMR (400 MHz , $CDCl_3$) δ 7.64–7.60 (m, 4H, Ph), 7.44–7.37 (m, 6H, Ph), 6.31 (d, *J* = 5.7 Hz, 1H, 4-H), 6.27 (d, *J* = 5.7 Hz, 1H, 5-H), 4.10 (d, *J* = 10.7 Hz, 1H, 3-H), 4.00 (d, *J* = 10.4 Hz, 1H, 1''-H), 3.93 (d, *J* = 11.1 Hz, 1H, 1'-H), 3.89 (d, *J* = 11.1 Hz, 1H, 1'-H), 3.75 (d, *J* = 10.7 Hz, 1H, 3-H), 2.98 (d, *J* = 10.4 Hz, 1H, 1''-H), 2.04 (d, *J* = 11.8 Hz, 1H, 7-H), 1.44 (s, 9H, N-$C(CH_3)_3$), 1.06 (s, 9H, $SiC(CH_3)_3$), 0.86 (s, 9H, $SiC(CH_3)_3$), 0.74 (d, *J* = 11.9 Hz, 1H, 7-H), 0.04 (s, 6H, Si-$(CH_3)_2$); ^{13}C (100 MHz, $CDCl_3$) δ 175.73 (C1), 137.35 (C5), 135.63 (Ph), 135.57 (Ph), 132.77 (Ph), 132.64 (C4), 132.49 (Ph), 129.91 (Ph), 129.75 (Ph), 127.81 (Ph), 127.74 (Ph), 90.61 (C3a), 89.56 (C6), 68.01 (C1''), 63.40 (C1'), 61.29 (C7a), 54.33 (N-$\underline{C}(CH_3)_3$), 49.05 (C3), 34.24 (C7), 27.86 (N-$C(\underline{C}H_3)_3$), 26.95 (Si-$C(\underline{C}H_3)_3$), 25.89 (Si-$C(\underline{C}H_3)_3$), 19.14 (Si-$\underline{C}(CH_3)_3$), 18.37 (Si-$\underline{C}(CH_3)_3$), -5.31 (Si-$(CH_3)_2$); *m/z* (ESI+) calculated for $C_{36}H_{53}NO_4Si_2$ $[M+H]^+$ 620.3586, observed 620.3584 (error 0.06 ppm); ν_{max} (solid, cm^{-1}): 2958, 2926, 2853, 1677 (C=O lactam), 1428, 1346, 1111, 1075, 816, 708, 507.

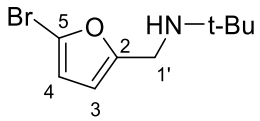
2-(*tert*-butyl)-7a-(((*tert*-butyldiphenylsilyl)oxy)methyl)-6-(hydroxymethyl)-2,3,7,7a-tetrahydro-3a,6-epoxyisoindol-1(6*H*)-one (93)



TsOH monohydrate (0.1 equiv., 0.52 mmol, 99 mg) was added to a solution of silyl ether **90** (5.21 mmol, 3.23 g) in THF (50 mL) and water (2.5 mL). The solution was stirred at rt for 2 days and quenched with Et_3N (2.5 mL). The solvent was removed *in vacuo* and the product was purified by column chromatography (SiO_2, EtOAc/Petrol 4:1) to obtain **93** as a white solid (2.53 g, 5.00 mmol, 96%).

Rf 0.38 (SiO_2, 3:1 EtOAc/Petrol); Mp: 57-63°C; ^{1}H NMR (400 MHz , $CDCl_3$) δ 7.64–7.60 (m, 4H, Ph), 7.44–7.36 (m, 6H, Ph), 6.34 (d, *J* = 5.7 Hz, 1H, 4-H), 6.29 (d, *J* = 5.7 Hz, 1H, 5-H), 4.13 (d, *J* = 10.8 Hz, 1H, 3-H), 4.00 (d, *J* = 10.4 Hz, 1H, 1''-H), 3.97-3.87 (m, 2H, 1'-H_2), 3.76 (d, *J* = 10.7 Hz, 1H, 3-H), 2.98 (d, *J* = 10.4 Hz, 1H, 1''-H), 2.00 (d, *J* = 11.8 Hz, 1H, 7-H), 1.45 (s, 9H, N-C$(CH_3)_3$), 1.07 (s, 9H, SiC$(CH_3)_3$), 0.70 (d, *J* = 11.7 Hz, 1H, 7-H); ^{13}C (100 MHz, $CDCl_3$) δ 175.46 (C1), 136.72 (C5), 135.64 (Ph), 135.56 (Ph), 133.67 (C4), 132.63 (Ph), 132.39 (Ph), 129.98 (Ph), 129.81 (Ph), 127.84 (Ph), 127.77 (Ph), 90.80 (C3a), 90.12 (C6), 67.99 (C1''), 62.95 (C1'), 61.45 (C7a), 54.42 (N-C$(CH_3)_3$), 49.97 (C3), 33.58 (C7), 27.88 (N-C$(CH_3)_3$), 26.96 (Si-C$(CH_3)_3$), 19.13 (Si-C$(CH_3)_3$); *m/z* (ESI+) calculated for $C_{30}H_{39}NO_4Si$ $[M+Na]^+$ 528.2541, observed 528.2547 (error 1.63 ppm); ν_{max} (solid, cm^{-1}): 3429 (br, OH), 2931, 2857, 1658 (C=O lactam), 1459, 1427, 1351, 1240, 1214, 1112, 1063, 820, 741, 701, 503.

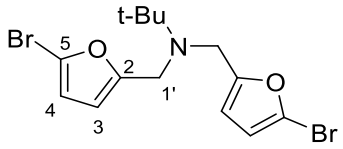
***N*-((5-bromofuran-2-yl)methyl)-2-methylpropan-2-amine (94)[35]**



Amine **94** was prepared following the procedure reported by Padwa *et al.*[35] by addition of 5-Bromo-2-furfural (1.0 equiv., 28.57 mmol, 5.00 g), *t*$BuNH_2$ (1.0 equiv., 28.57 mmol, 3.0 mL) and $NaBH(OAc)_3$ (1.5 equiv., 42.85 mmol, 9.08 g) in DCE (100 mL). Purification by column chromatography (SiO_2, EtOAc/Petrol/Et_3N 1:1:0.01, EtOAc/Et_3N 1:0.01) provided **94** as an orange oil (5.00 g, 21.54 mmol, 75%).

Rf 0.18 (SiO_2, 1:1:0.01 EtOAc/Petrol/ Et_3N); ^1H NMR (400 MHz , $CDCl_3$) δ 6.20 (d, 1H, *J* = 3.20 Hz, 4-*H*), 6.15 (d, 1H, *J* = 3.20 Hz, 3-*H*), 3.71 (s, 2H, 1'-H_2), 1.15 (s, 9H, *t*Bu); ^{13}C (100 MHz, $CDCl_3$) δ 156.91 (C2), 120.25 (C5), 111.81 (C4), 109.03 (C3), 50.62 ($\underline{C}Me_3$), 40.12 (C1'), 28.95 ($C\underline{Me}_3$); *m/z* (ESI+) calculated for $C_9H_{14}BrNO$ $[M+H]^+$ 232.0332, observed 232.0341 (error 3.78 ppm); ν_{max} (oil, cm^{-1}): 2962, 1508, 1362, 1229, 1206, 1124, 1011, 921, 781.

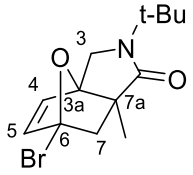
_N_,_N_-bis((5-bromofuran-2-yl)methyl)-2-methylpropan-2-amine (95)



Tertiary amine **95** was obtained following the procedure reported by Padwa *et al.*[35] for the preparation of **94**. It was obtained as a yellow oil (0.50 g, 1.28 mmol, 4%).

Rf 0.75 (SiO_2, 1:1:0.01 EtOAc/Petrol/ Et_3N); ^1H NMR (400 MHz , $CDCl_3$) δ 6.17 (d, 1H, *J* = 3.1 Hz, 4-H), 6.09 (d, 1H, *J* = 3.1 Hz, 3-H), 3.73 (s, 2H, 1'-H_2), 1.13 (s, 9H, *t*Bu); ^{13}C (100 MHz, $CDCl_3$) δ 156.67 (C2), 119.91 (C5), 111.75 (C4), 110.40 (C3), 54.85 ($\underline{C}Me_3$), 45.05 (C1'), 27.38 ($C\underline{Me}_3$); *m/z* (ESI+) calculated for $C_{14}H_{17}Br_2NO_2$ $[M+H]^+$ 389.9699, observed 389.9626 (error -3.44 ppm); ν_{max} (oil, cm^{-1}): 2970, 1503, 1196, 1123, 1009, 948, 920, 780.

6-bromo-2-(*tert*-butyl)-7a-methyl-2,3,7,7a-tetrahydro-3a,6-epoxyisoindol-1(6*H*)-one (97)

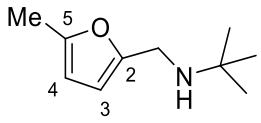


Coupling of methacrylic acid (1.2 equiv., 1.11 g, 12.9 mmol) and amine **94** (1.0 equiv., 2.50 g, 10.8 mmol) was performed as described in general procedure D by addition of EDC·HCl (3.09 g, 16.1 mmol), DMAP (130 mg, 1.1 mmol) Et_3N (1.2 equiv., 1.8 mL, 12.9 mmol) in DCM (20 mL). The reaction mixture was stirred for 3 days. Column chromatography (SiO_2, Petrol/EtOAc 1:3) afforded compounds **97** as a white solid (2.35 g, 7.83 mmol, 73%).

Rf 0.41 (SiO_2, 3:1 EtOAc/Petrol); Mp: 128–130°C; ^1H NMR (400 MHz, $CDCl_3$) δ 6.48 (d, 1H, *J* = 5.6 Hz, 5-H), 6.36 (d, 1H, *J* = 5.6 Hz, 4-H), 3.82 (dd, 2H, J_1 = 17.9 Hz, J_2 = 11.9 Hz, 3-H_2), 2.74 (d, 1H, *J* = 11.9 Hz, 7-H), 1.68 (d, 1H, *J* = 11.9 Hz, 7-H), 1.41 (s, 9H, *t*Bu), 1.02 (s, 3H, Me); ^{13}C (100 MHz, $CDCl_3$) δ 176.51 (C=O), 141.28 (C5), 132.91 (C4), 89.90 (C3a), 88.88 (C6), 56.41 (C7a), 54.19 ($\underline{C}Me_3$), 46.82 (C7), 45.99 (C3), 27.68 ($C\underline{Me}_3$), 19.84 (CH_3); *m/z* (ESI+)

calculated for $C_{13}H_{18}BrNO_2$ $[M+H]^+$ 300.0594, observed 300.0603 (error 3.03 ppm); ν_{max} (solid, cm^{-1}): 2966, 1670 (C=O lactam), 1351, 1231, 1069, 981.

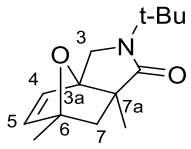
2-methyl-*N*-((5-methylfuran-2-yl)methyl)propan-2-amine (98)



Reductive amination of *tert*-butylamine (1.1 equiv., 49.95 mmol, 4.2 mL) and 5-methylfurfural (1.0 equiv., 45.4 mmol, 5.0 g) in ethanol (50 mL) was performed following the general procedure C by addition of $NaBH_4$ (2 equiv., 90.8 mmol, 3.4 g) after 6 h. Amine **98** was used without purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.02 (d, *J* = 3.0 Hz, 1H, 3-H), 5.85 (dd, J_1 = 2.9 Hz, J_1 = 0.9 Hz, 1H, 4-H), 3.68 (s, 2H, CH_2), 2.25 (s, 3H, Me), 1.15 (s, 9H, *t*Bu); ^{13}C (100 MHz, $CDCl_3$) δ 152.73 (C2), 151.24 (C5), 106.98 (C3), 105.96 (C4), 50.53 ($\underline{C}(CH_3)_3$), 40.09 (CH_2), 28.93 ($C(\underline{CH_3})_3$), 13.61 (Me).

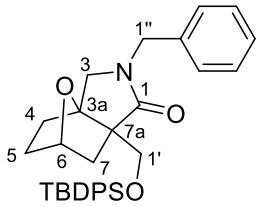
2-(*tert*-butyl)-6,7a-dimethyl-2,3,7,7a-tetrahydro-3a,6-epoxyisoindol-1(6*H*)-one (100)



Coupling of methacrylic acid (1.2 equiv., 2.44 mL, 28.8 mmol) and amine **98** (1.0 equiv., 4.00 g, 24.0 mmol) was performed as described in general procedure D by addition of EDC·HCl (6.90 g, 36.0 mmol), DMAP (293 mg, 2.4 mmol) Et_3N (1.3 equiv., 4.35 mL, 31.2 mmol) in DCM (50 mL). The reaction mixture was stirred for 1 d. The crude of the reaction was heated at reflux in MeOH for 4 h and concentrated. The oil obtained was passed through a pad of silica. Compound **100** crystallised into white crystals (2.71 g, 11.52 mmol, 48%), then washed with heptane.

Mp: 81–83 °C; ^{1}H NMR (400 MHz , $CDCl_3$) δ 6.33 (d, *J* = 5.7 Hz, 1H, 4-H), 6.27 (d, *J* = 5.7 Hz, 1H, 5-H), 3.81 (d, *J* = 11.6 Hz, 1H, 3-H), 3.73 (d, *J* = 11.6 Hz, 1H, 3-H), 2.15 (d, *J* = 11.7 Hz, 1H, 7-H), 1.56 (s, 3H, 6-Me), 1.42 (s, 9H, *t*Bu), 1.12 (d, *J* = 11.7 Hz, 1H, 7-H), 0.99 (s, 3H, 7a-Me); ^{13}C (100 MHz, $CDCl_3$) δ 178.39 (C=O), 140.70 (C5), 132.29 (C4), 90.04 (C3a), 86.70 (C6), 56.14 (C7a), 53.87 ($\underline{C}Me_3$), 46.54 (C3), 42.21 (C7), 27.73 ($C\underline{Me}_3$), 20.35 (7a-$\underline{Me}$), 18.93 (6-$\underline{Me}$); *m/z* (ESI+) calculated for $C_{14}H_{21}NO_2$ $[M+Na]^+$ 258.1465, observed 258.1578 (error -2.52 ppm); ν_{max} (solid, cm^{-1}): 2960, 1675 (C=O lactam), 1348, 1241, 861, 707.

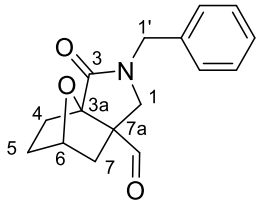
2-benzyl-7a-(((*tert*-butyldiphenylsilyl)oxy)methyl)hexahydro-3a,6-epoxyisoindol-1(4*H*)-one (104)



Cycloadduct **52** (0.39 mmol, 198 mg) was dissolved in dry EtOH (3 mL) and 10% Pd/C was added (15 mg). The flask was washed with nitrogen to replace all the oxygen, then a balloon containing hydrogen was attached and the reaction mixture was stirred for 2 h. The mixture was filtered through celite and washed with EtOH. The filtrate was evaporated under reduced pressure to yield **104** as a white solid (0.15 g, 0.29 mmol, 74%).

Mp= 127–128 °C; Rf 0.65 (SiO_2, Petrol/EtOAc 1:2.5); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66–7.63 (m, 4H, Ph), 7.49–7.40 (m, 6H, Ph), 7.31–7.22 (m, 5H, Ph), 4.95 (d, *J* = 15.1 Hz, 1H, 1''-H), 4.50 (t, *J* = 5.1 Hz, 1H, 6-H), 4.27 (d, *J* = 15.0 Hz, 1H, 1''-H), 4.22 (d, *J* = 10.5 Hz, 1H, 1'-H), 3.71 (d, *J* = 10.6 Hz, 1H, 3-H), 3.49 (d, *J* = 10.6 Hz, 1H, 3-H), 3.40 (d, *J* = 10.6 Hz, 1H, 1'-H), 2.22–2.18 (m, 1H, *endo*-7-H), 2.00–1.95 (m, 1H, 4-H), 1.93–1.88 (m, 1H, 5-H), 1.74–1.67 (m, 1H, 4-H), 1.43–1.37 (m, 1H, 5-H), 1.15 (d, *J* = 12.3 Hz, 1H, *endo*-7-H), 1.03 (s, 9H, -SiC$(CH_3)_3$); ^{13}C (100 MHz, $CDCl_3$) δ 176.42 (C1), 136.21 (Ph), 135.69 (Ph), 135.61 (Ph), 132.90 (Ph), 132.24 (Ph), 129.95 (Ph), 129.89 (Ph), 128.65 (Ph), 127.95 (Ph), 127.85(Ph), 127.83(Ph), 127.34 (Ph), 89.04 (C7a), 75.94 (C6), 66.83 (C1'), 59.21 (C3a), 49.75 (C3), 46.73 (1''), 39.80 (C7), 29.68 (C5), 26.82 (-SiC(<u>C</u>$H_3)_3$), 25.47 (C4), 19.13 (-Si<u>C</u>$(CH_3)_3$); *m/z* (ESI+) calculated for $C_{32}H_{37}NO_3Si$ $[M+H]^+$ 512.2615, observed 512.2612 (error 0.28 ppm); ν_{max} (solid, cm^{-1}): 2965, 2875, 2857, 1682 (C=O lactam), 1471, 1427, 1354, 1259, 1068, 1049, 809, 728.

2-benzyl-1-oxohexahydro-3a,6-epoxyisoindole-7a(1*H*)-carbaldehyde (105)

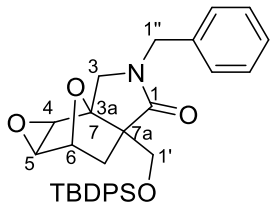


A mixture of aldehydes **60** and **61** (1.41 mmol, 380 mg) was dissolved in dry EtOH (9 mL) and 10 % Pd/C was added (53 mg). The flask was washed with Nitrogen to replace all the oxygen, then a balloon containing Hydrogen was attached and the reaction mixture was stirred for 2 h. The mixture was filtered through celite and washed

with EtOH. The filtrate was evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/Petrol 1:1) afforded **105** as a yellow oil (0.27 g, 0.99 mmol, 70%).

Rf 0.24 (SiO_2, Petrol/EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.45 (s, 1H, CHO), 7.38–7.26 (m, Ph), 4.88 (t, *J* = 4.9 Hz, 1H, 6-H), 4.57 (dd, J_1 = 18.0 Hz, J_2 = 14.9 Hz, 2H, 1'-H_2), 3.61 (d, *J* = 10.2 Hz, 1H, 1-H), 3.21 (d, *J* = 10.2 Hz, 1H, 1-H), (d, *J* = 5.9 Hz, 1H, 4-H), 2.22 (d, *J* = 12.6 Hz, 1H, 7-H), 2.18–2.05 (m, 2H, 4-H_2 and 5-H_2), 1.97–1.92 (m, 1H, 7-H), 1.76–1.65 (m, 2H, 4-H_2 and 5-H_2); ^{13}C (100 MHz, $CDCl_3$) δ 198.73 (CHO), 167.59 (C3), 135.47 (Ph), 128.89 (Ph), 128.06 (Ph), 127.90 (Ph), 91.22 (C3a), 81.17 (C6), 61.47 (C7a), 50.91 (C1), 47.10 (C1'), 40.00 (C1), 28.87 (C4), 25.40 (C5); *m/z* (ESI+) calculated for $C_{16}H_{17}NO_3$ $[M+H]^+$ 272.1281, observed 272.1281 (error 0.14 ppm); ν_{max} (oil, cm^{-1}): 2925, 1693 (vs, C=O amide), 1485, 1433, 1280, 950, 736, 699 (s).

5-benzyl-3a-(((*tert*-butyldiphenylsilyl)oxy)methyl)hexahydro-2,6a-epoxyoxireno[2,3-*e*]isoindol-4(2*H*)-one (106)

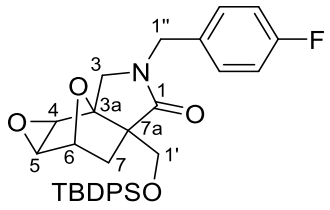


Epoxide **106** was obtained from a mixture of silyl ethers **51** and **52** (99 mg, 0.195 mmol) in DCM (2 mL) by addition of *m*CPBA (72%, 0.60 mmol, 0.14 mL) following the general procedure F. Purification by column chromatography (SiO_2, EtOAc/Petrol 1:4) afforded **106** as colourless oil (74 mg, 0.14 mmol, 72%).

Rf 0.19 (SiO_2, Petrol/EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65–7.61 (m, 4H, Ph), 7.50–7.40 (m, 6H, Ph), 7.28–7.26 (m, Ph), 4.97 (d, *J* = 15.1 Hz, 1H, 1''-H), 4.50 (d, *J* = 5.1 Hz, 1H, 6-H) 4.24 (d, *J* = 15.0 Hz, 1H, 1''-H), 4.20 (d, *J* = 10.7 Hz, 1H, 1'-H), 3.93 (d, *J* = 10.8 Hz, 1H, 3-H), 3.59 (d, *J* = 10.8 Hz, 1H, 3-H) 3.52–-3.49 (m, 2H, 1'-H and 4-H), 3.33 (d, *J* = 3.2 Hz, 1H, 5-H), 2.26 (dd, J_1 = 12.8 Hz, J_2 =5.2 Hz 1H, *exo*-7-H), 1.16 (d, *J* = 12.8 Hz, 1H, *endo*-7-H), 1.05 (s, 9H, -SiC(CH_3)$_3$); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.60- 7.41 (m, 10H, Ph), 7.23–7.22 (m, 5H, Ph), 4.71 (d, *J* = 15.1 Hz, 1H, 1''-H), 4.43 (d, *J* 5.1z, 1H, 6-H), 4.21 (d, *J* = 15.3 Hz, 1H, 1''-H), 3.92 (d, *J* = 10.8 Hz, 1H, 1'-H), 3.88 (d, *J* = 11.1 Hz, 1H, 3-H), 3.59 (d, *J* = 10.8 Hz, 1H, 1'), 3.56 (d, *J* = 3.2 Hz, 1H, 4-H), 3.50 (d, *J* = 3.3 Hz, 1H, 5-H), 3.45 (d, *J* = 11.1 Hz, 1H, 3-H), 1.89 (dd, J_1 = 12.7 Hz, J_2 =5.2 Hz 1H, 1H, *exo*-7-H), 1.23 (d, *J* = 12.7 Hz, 1H, *endo*-7-H), 0.94 (s, 9H, -Si(CH_3)$_3$); ^{13}C (100 MHz, $CDCl_3$) δ 174.79 (C1), 135.69 (Ph), 135.64 (Ph), 135.52 (Ph), 132.50 (Ph), 131.80 (Ph), 130.19 (Ph), 130.08 (Ph), 128.74 (Ph), 128.01 (Ph), 127.98 (Ph), 127.94 (Ph), 127.51 (Ph), 85.66 (C3a), 74.68 (C6), 65.00 (C1'), 61.58 (C7a), 49.42 (C5), 48.44 (C3), 47.90 (C4), 46.83 (C1''), 34.88 (C7), 26.85 (-SiC(CH_3)$_3$),

19.08 (-Si<u>C</u>$(CH_3)_3$); *m/z* (ESI+) calculated for $[M+H]^+$ 526.2408, observed 526.2409 (error -0.36 ppm); ν_{max} (solid, cm^{-1}): 2930, 2857, 1687 (C=O amide), 1471, 1427, 1073, 740, 700.

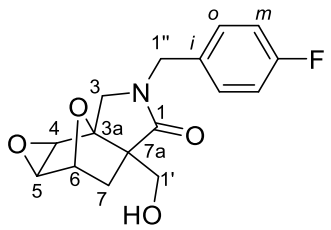
3a-(((*tert*-butyldiphenylsilyl)oxy)methyl)-5-(4-fluorobenzyl)hexahydro-2,6a-epoxyoxireno[2,3-*e*]isoindol-4(2*H*)-one (108)



Epoxide **108** was obtained from a mixture of silyl ethers **67** and **68** (374 mg, 0.71 mmol) in DCM (7 mL) by addition of *m*CPBA (72%, 2.1 mmol, 0.51 g) following the general procedure F. Purification by column chromatography (SiO_2, EtOAc/Petrol 1:2 then 1:1) afforded **108** as colourless oil (103 mg, 0.19 mmol, 27%).

Rf 0.39 (SiO_2, Petrol/EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62–7.57 (m, 5H, Ar), 7.44–7.38 (m, 7H, Ar), 7.26–7.21 (m, 2H, Ar), 4.88 (d, *J* = 14.6 Hz, 1H, 1''-H), 4.48 (d, *J* = 4.7 Hz, 1H, 6-H) 4.23–4.17 (m, 2H, 1''-H and 1'-H), 3.92 (d, *J* = 11.0 Hz, 1H, 3-H), 3.55 (d, *J* = 10.7 Hz, 1H, 3-H) 3.51–3.48 (m, 2H, 1'-H and 4-H), 3.32 (d, *J* = 3.2 Hz, 1H, 5-H), 2.26 (dd, J_1 = 5.1 Hz, J_2 = 12.8 Hz, 1H, *exo*-7-H), 1.15 (d, *J* = 12.9 Hz, 1H, *endo*-7-H), 1.02 (s, 9H, -SiC$(CH_3)_3$); ^{19}F NMR (400 MHz, $CDCl_3$) δ -115.08; ^{13}C (100 MHz, $CDCl_3$) δ 174.96 (C1), 169.73 (C-F), 135.58 (Ar), 135.50 (Ar), 133.79 (Ar), 130.25 (Ar), 130.12 (Ar), 129.85 (Ar), 129.69 (Ar), 129.61 (Ar), 128.30 (Ar), 128.03 (Ar), 127.95 (Ar), 85.65 (C3), 74.68 (C6), 64.96 (C1'), 61.61 (C7a), 49.41 (C5), 48.50 (C3), 47.82 (C4), 46.15 (C1''), 34.87 (C7), 26.83 (-SiC(<u>C</u>$H_3)_3$), 19.08 (-Si<u>C</u>$(CH_3)_3$); *m/z* (ESI+) calculated for $C_{32}H_{34}FNO_4Si$ $[M+H]^+$ 544.2314, observed 544.2316 (error -0.01 ppm); ν_{max} (oil, cm^{-1}): 2928, 2857, 1689 (C=O amide), 1509, 1427, 1299, 1220, 1105, 1074, 746, 700.

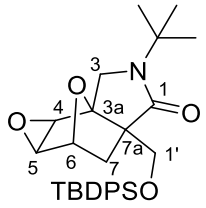
5-(4-fluorobenzyl)-3a-(hydroxymethyl)hexahydro-2,6a-epoxyoxireno[2,3-*e*]isoindol-4(2*H*)-one (109)



Epoxide **109** was obtained from a mixture of alcohols **69** and **70** (366 mg, 1.26 mmol) in DCM (25 mL) by addition of *m*CPBA (72%, 3.80 mmol, 0.93 g) following the general procedure F. Purification by column chromatography (SiO_2, EtOAc) afforded **109** as white solid (0.12 g, 0.39 mmol, 31%).

Mp: 162-164°C; Rf 0.10 (SiO_2, EtOAc); ^{19}F NMR (400 MHz, $CDCl_3$) δ -114.86; ^{19}F NMR (400 MHz, DMSO) δ -115.82; ^{1}H NMR (400 MHz , DMSO-d_6) δ 7.34–7.30 (m, 2H, *o*Ph), 7.17–7.13 (m, 2H, *m*Ph), 4.49 (d, *J* = 15.5 Hz, 1H, 1''-H), 4.41 (d, *J* = 5.0 Hz, 1H, 6-H), 4.34 (d, *J* = 15.7 Hz, 1H, 1''-H), 3.77–3.70 (m, 3H, 1'-H, 3-H, 4-H), 3.56 (d, *J* = 3.4 Hz, 1H, 5-H), 3.48 (dd, J_1 = 11.2 Hz, J_2 = 4.3 Hz, 1H, 1'-H), 3.27 (d, *J* = 10.9 Hz, 1H, 3-H), 1.90 (dd, J_1 = 12.4 Hz, J_2 = 5.1 Hz 1H, *exo*-7-H), 1.24 (d, *J* = 12.5 Hz, 1H, *endo*-7-H); ^{13}C (100 MHz, DMSO) δ 175.53 (C1), 161.80 (d, *J* = 242.6 Hz, C-F), 133.30 (d, *J* = 3.0 Hz, *i*Ph), 129.74 (d, *J* = 8.2 Hz, *o*Ph), 115.61 (d, *J* = 21.3 Hz, *m*Ph), 85.64 (C3a), 74.58 (C6), 62.81 (C1'), 61.68 (C7a), 49.32 (C5), 48.54 (C3), 47.69 (C4), 45.32 (C1''), 34.72 (C7); *m/z* (ESI+) calculated for $C_{16}H_{16}FNO_4$ $[M+H]^+$ 306.1136, observed 306.1136 (error -0.12 ppm); ν_{max} (solid, cm^{-1}): 3307 (br, OH), 2903, 1660 (vs, C=O amide), 1604, 1508, 1220, 1037, 836.

5-(*tert*-butyl)-3a-(((*tert*-butyldiphenylsilyl)oxy)methyl)hexahydro-2,6a-epoxyoxireno[2,3-*e*]isoindol-4(2*H*)-one (111)

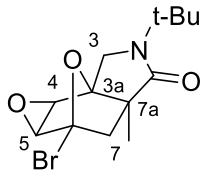


With m-CPBA: Epoxide **111** was obtained from silyl ether **77** (0.2 g, 0.42 mmol) in DCM (4 mL) by addition of *m*CPBA (72%, 1.3 mmol, 0.30 g) following the general procedure F. Purification by column chromatography (SiO_2, EtOAc/petrol 1:1 +1% Et_3N) afforded **111** as white solid (0.19 g, 0.40 mmol, 94%).

With Jacobsen catalyst: Epoxide **111** was obtained from silyl ether **77** (0.20 g, 0.42 mmol) following the general procedure G by addition of 4-PPNO (30 mg), Jacobsen catalyst (0.017 mmol, 11 mg) and 5 mL of $NaOCl_{(aq)}$. The reaction mixture was stirred for 2 h. Purification by silica gel column (1:1:0.1 petrol/EtOAc/Et_3N) afforded **111** as white solid (56 mg, 0.11 mmol, 27%).

Rf: 0.52 (SiO_2, 1 :1 :0.01 EtOAc/Petrol/Et_3N); Mp: 166–167 °C; ^{1}H NMR (400 MHz , $CDCl_3$) δ 7.66–7.59 (m, 4H, Ph), 7.47–7.38 (m, 6H, Ph), 4.42 (d, *J* = 5.1 Hz, 1H, 6-H), 4.10 (d, *J* = 10.8 Hz, 1H, 1'-H), 4.03 (d, *J* = 10.9 Hz, 1H, 3-H), 3.78 (d, *J* = 10.9 Hz, 1H, 3-H), 3.46 (d, *J*= 3.2 Hz, 1H, 4-H), 3.37 (d, *J* = 10.8 Hz, 1H, 1'-H), 3.26 (d, *J* = 3.3 Hz, 1H, 5-H), 2.16 (dd, J_1 = 12.8 Hz, J_2 = 5.1 Hz, 1H, *exo*-7-H), 1.44 (s, 9H, N*t*Bu), 1.09 (s, 9H, Si*t*Bu), 1.02 (d, *J* = 12.8 Hz, 1H, *endo*-7-H); ^{13}C (100 MHz, $CDCl_3$) δ 174.77 (C1), 135.61 (Ph), 135.55 (Ph), 132.34 (Ph), 131.89 (Ph), 130.21 (Ph), 129.96 (Ph), 128.03 (Ph), 127.86 (Ph), 84.87 (C7a), 74.51 (C6), 65.00 (C1'), 62.06 (C3a), 54.61 (N-$\underline{C}(CH_3)_3$), 49.52 (C5), 48.05 (C4), 47.55 (C3), 35.28 (C7), 27.81 (N-C($\underline{C}H_3)_3$), 26.97 (Si-C($\underline{C}H_3)_3$), 19.09 (Si-$\underline{C}(CH_3)_3$); *m/z* (ESI+) calculated for $C_{29}H_{37}NO_4Si$ $[M+H]^+$ 492.2565, observed 492.2550 (error 3.56 ppm); ν_{max} (solid, cm^{-1}): 2945, 2864, 2364, 1676 (C=O lactam), 1471, 11427, 1339, 1223, 1112, 1068, 865, 814, 741, 708, 623, 502.

2-bromo-5-(*tert*-butyl)-3a-methylhexahydro-2,6a-epoxyoxireno[2,3-*e*]isoindol-4(2*H*)-one (112)



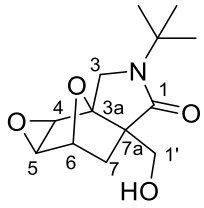
With m-CPBA: Epoxide **112** was obtained from alkene **97** (0.40 g, 1.33 mmol) in DCM (15 mL) by addition of *m*CPBA (72%, 4.0 mmol, 0.96 g) following the general procedure F. Purification by column chromatography (SiO_2, EtOAc/petrol 4:1 +1% Et_3N) afforded **112** as white solid (0.24 g, 0.76 mmol, 56%).

With Jacobsen catalyst: Epoxide **112** was obtained from silyl alkene **97** (304 mg, 1.01 mmol) following the general procedure G by addition of 4-PPNO (70 mg), Jacobsen catalyst (0.04 mmol, 26 mg) and 13 mL of $NaOCl_{(aq)}$. The reaction mixture was stirred for 3 d. Purification by silica gel column (EtOAc/petrol 4:1 +1% Et_3N) afforded **112** as a white solid (111 mg, 0.35 mmol, 35%).

Rf 2.6 (SiO_2, EtOAc); MP: 210–213 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84 (d, 1H, *J* = 12.1 Hz, 3-H), 3.76 (d, 1H, *J* = 12.1 Hz, 3-H), 3.70 (d, 1H, *J* = 3.1 Hz, 5-H), 3.58 (d, 1H, *J* = 3.1 Hz, 4-H), 2.73 (d, 1H, *J* = 12.9 Hz, 7-H), 1.93 (d, 1H, *J* = 12.9 Hz, 7-H), 1.45 (s, 9H, *t*Bu), 1.25 (s, 3H, Me); ^{13}C (100 MHz, $CDCl_3$) δ 175.64 (C=O), 86.24 (C-Br), 85.24 (C3a), 57.98 (C7a), 54.46 ($\underline{C}Me_3$), 53.78 (C5), 50.19 (C4), 48.16 (C7), 44.96 (C3), 27.64 ($C\underline{Me_3}$), 16.82 (Me); *m/z* (ESI+)

calculated for $C_{13}H_{18}BrNO_3$ $[M+H]^+$ 316.0543, observed 316.0549 (error 1.74 ppm); ν_{max} (solid, cm^{-1}): 3066, 2974, 1677 (C=O lactam),1226, 1010, 874.

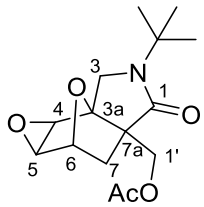
5-(*tert*-butyl)-3a-(hydroxymethyl)hexahydro-2,6a-epoxyoxireno[2,3-*e*]isoindol-4(2*H*)-one (113)



Epoxide **113** was obtained from alkene **78** (225 mg, 0.95 mmol) in DCM (1 mL) by addition of *m*CPBA (2.8 mmol, 680 mg) following the general procedure F. The solid obtained was washed with EtOAc and filtrated to obtain white solid **113**.

Rf 0.11 (SiO_2, 100% EtOAc); ^{1}H NMR (400 MHz , $CDCl_3$) δ 4.50 (d, *J* = 5.1 Hz, 1H, 6-H), 4.00 (d, *J* = 11.0 Hz, 1H, 1'-H), 3.88 (d, *J* = 11.1 Hz, 1H, 3-H), 3.76 (d, *J* = 11.1 Hz, 1H, 3-H), 3.61 (d, *J* = 11.0 Hz, 1H, 1'-H), 3.61 (d, *J* = 3.3 Hz, 1H, 4-H), 3.42 (d, *J* = 3.2 Hz, 1H, 5-H), 2.24 (dd, J_1 = 12.8 Hz, J_2 = 5.1 Hz, 1H, *exo*-7-H), 1.42 (s, 9H, *t*Bu), 1.27 (d, *J* = 12.8 Hz, 1H, *endo*-7-H); ^{13}C (100 MHz, $CDCl_3$) δ 175.27 (C1), 84.47 (C3a), 74.76 (C6), 64.00 (C1'), 62.18 (C7a), 54.72 ($\underline{C}Me_3$), 49.51 (C5), 48.07 (C4), 47.09 (C3), 35.07 (C7), 27.73 ($C\underline{Me_3}$); *m/z* (ESI+) calculated for $C_{13}H_{19}NO_4$ $[M+Na]^+$ 279.1206, observed 279.1210 (error 1.87 ppm); ν_{max} (solid, cm^{-1}): 2978, 1655 (C=O lactam), 1450, 1384, 1217, 1043, 886, 576.

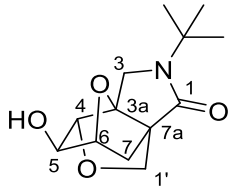
5-(*tert*-butyl)-4-oxohexahydro-2,6a-epoxyoxireno[2,3-*e*]isoindol-3a(4*H*)-yl)methyl acetate (114)



Epoxide **114** was obtained from alkene **78** (137 mg, 0.58 mmol) in DCM (6 mL) by addition of *m*CPBA (1.7 mmol, 415 mg) following the general procedure F. The crude of the reaction was dissolved in MeCN/Pyridine (11.6 mL) and treated with Ac_2O (1.7 mmol, 0.15 mL) and DMAP (0.06 mmol, 7 mg) following the general procedure A. After 2 h the reaction mixture was concentrated under reduced pressure and purified by column chromatography (SiO_2, EtOAc) to provide compound **114** as a white solid (48 mg, 0.16 mmol, 28%).

Rf 0.44 (SiO_2, 100% EtOAc); Mp: 128–131°C; ^{1}H NMR (400 MHz , $CDCl_3$) δ 4.51 (d, *J* = 5.1 Hz, 1H, 6-H), 4.41 (d, *J* = 11.7 Hz, 1H, 1'-H), 4.08 (d, *J* = 11.7 Hz, 1H, 1'-H), 3.77 (s, 2H, 3-H_2), 3.50 (d, *J* = 3.2 Hz, 1H, 4-H), 3.44 (d, *J* = 3.2 Hz, 1H, 5-H), 2.33 (dd, J_1 = 11.9 Hz, J_2 = 5.1 Hz, 1H, *exo*-7-H), 1.44 (s, 3H, Ac), 1.41 (s, 9H, *t*Bu), 1.31 (d, *J* = 12.9 Hz, 1H, *endo*-7-H); ^{13}C (100 MHz, $CDCl_3$) δ 173.58 (C1), 169.84 (Me<u>C</u>=O), 84.24 (C3a), 74.68 (C6), 64.42 (C1'), 59.50 (C7a), 54.69 (N<u>C</u>Me_3), 49.44 (C5), 47.74 (C4), 46.85 (C3), 35.37 (C7), 27.71 (C(<u>C</u>H_3)$_3$), 20.74 (<u>Me</u>-C=O); *m/z* (ESI+) calculated for $C_{15}H_{21}NO_5$ $[M+Na]^+$ 318.1312, observed 318.1315 (error 1.23 ppm); ν_{max} (solid, cm^{-1}): 2364, 2173, 2030, 1970, 1749 (C=O ester), 1664 (C=O lactam), 1221, 1037, 865.

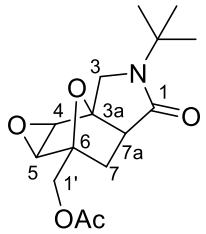
7-(*tert*-butyl)-3-hydroxytetrahydro-2*H*,5*H*,6*H*-2,5a-methanofuro[3',2':2,3]furo[3,4-*c*]pyrrol-6-one (115)



Epoxide **113** (1.0 equiv., 0.10 mmol, 25 mg), was dissolved in MeOH/DCM (2:1 v/v, 6 mL) and NaOMe (1.0 equiv., 0.10 mmol, 6 mg) in MeOH (1 mL) was added. After 14 days SiO_2 (1 g) was added and the mixture was filtered through celite and concentrated. The crude of the reaction was purified by column chromatography (SiO_2, EtOAc) to afford **113** as a white solid (21 mg, 0.08 mmol, 80%).

Rf 0.21 (SiO_2, 100% EtOAc); ^{1}H NMR (400 MHz , $CDCl_3$) δ 4.41 (dd, J_1 = 5.3 Hz, J_2 = 1.2 Hz, 1H, 6-H), 4.02 (d, *J* = 9.4 Hz, 1H, 1'-H), 3.98 (d, *J* = 1.1 Hz, 1H, 5-H), 3.94 (d, *J* = 9.4 Hz, 1H, 1'-H), 3.86 (d, *J* = 1.8 Hz, 2H, 3-H_2), 3.82 (d, *J* = 8.4 Hz, 1H, 4-H), 2.41 (dd, J_1 = 13.2 Hz, J_2 = 5.3 Hz, 1H, *exo*-7-H), 1.76 (d, *J* = 13.2 Hz, 1H, *endo*-7-H), 1.41 (s, 9H, *t*Bu); ^{13}C (100 MHz, $CDCl_3$) δ 172.78 (C1), 93.64 (C3a), 85.32 (C5), 82.77 (C6), 80.80 (C4), 75.73 (C1'), 59.06 (C7a), 54.46 (N<u>C</u>Me_3), 45.14 (C3), 36.89 (C7), 27.57 (NC<u>Me</u>$_3$); *m/z* (ESI+) calculated for $C_1H_1NO_5$ $[M+H]^+$ 254.1387, observed 254.1389 (error 0.44 ppm).

5-(*tert*-butyl)-4-oxohexahydro-2,6a-epoxyoxireno[2,3-*e*]isoindol-2(3*H*)-yl)methyl acetate (119).

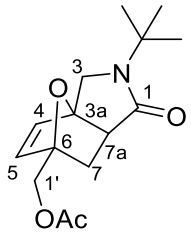


Racemic: Epoxide **119** was obtained from alkene **90** (143 mg, 0.603 mmol) in DCM (6 mL) by addition of *m*CPBA (1.8 mmol, 430 mg) following the general procedure F. The crude of the reaction was dissolved in MeCN/Pyridine (12 mL) and treated with Ac_2O (1.8 mmol, 0.17 mL) and DMAP (0.06 mmol, 7 mg) following the general procedure A. After 2 h the reaction mixture was concentrated under reduced pressure and purified by column chromatography (SiO_2, EtOAc) to provide compound **119** as a white solid (120 mg, 0.41 mmol, 67%).

Modified Sharpless epoxidation: A solution of titanium isopropoxide (1.05 equiv., 0.88 mmol, 0.27 mL), CaH_2 (0.1 equiv., 0.08 mmol, 3 mg) and silica gel (0.1 equiv., 0.08 mmol, 5 mg) in dry DCM (5 mL) was stirred at -20 °C under inert atmosphere for 10 min before the addition of alcohol **90** (1.0 equiv., 0.84 mmol, 180 mg). The stirring continued for further 10 min and then TBHP (2.0 equiv., 1.68 mmol, 0.31 mL) was added. The reaction mixture was stirred at rt for 17 days. A solution of 25% $NaOH_{(aq)}$ (5 mL) was added and stirred for 30 min. The product was then extracted with EtOAc (3 X 15 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was dissolved in MeCN/pyridine 4:1 (17 mL) and treated following the general procedure A by addition of DMAP (0.1 equiv., 10 mg, 0.08 mmol) and Ac_2O (3 equiv., 0.24 mL, 2.53 mmol). Purification by column chromatography (SiO_2, EtOAc) provided compound **119** as a white solid (19 mg, 0.064 mmol, 8%).

Rf 0.26 (SiO_2, 100% EtOAc); Mp: 123–125 °C; ^{1}H NMR (400 MHz , $CDCl_3$) δ 4.64 (d, *J* = 5.1 Hz, 1H, 6-H), 4.30 (d, *J* = 12.6 Hz, 1H, 1'-H), 4.08 (d, *J* = 12.6 Hz, 1H, 1'-H), 3.84 (dd, J_1 = 19.9 Hz, J_2 = 11.9 Hz 2H, 3-H_2), 3.46 (d, *J* = 3.4 Hz, 1H, 4-H), 3.40 (d, *J* = 3.4 Hz, 1H, 5-H), 2.67 (dd, J_1 = 9.1 Hz, J_2 = 3.9 Hz, 1H, 7a-H) 2.00 (dd, J_1 = 12.6 Hz, J_2 = 3.9 Hz, 1H, 7-H), 2.14 (s, 3H, Ac), 1.77 (dd, J_1 = 12.6 Hz, J_2 = 9.1 Hz, 1H, 7-H), 1.40 (s, 9H, *t*Bu); ^{13}C (100 MHz, $CDCl_3$) δ 172.71 (C1), 170.85 (Me<u>C</u>=O), 84.66 (C6), 84.55 (C3a), 62.20 (C1'), 54.55 (N<u>C</u>Me_3), 51.16 (C5), 50.92 (C7a), 49.67 (C4), 46.61 (C3), 33.07 (C7), 27.66 (C(<u>C</u>H_3)$_3$), 20.79 (<u>Me</u>-C=O); *m/z* (ESI+) calculated for $C_{15}H_{21}NO_5$ $[M+H]^+$ 296.1492, observed 296.1487 (error 2.13 ppm); ν_{max} (solid, cm^{-1}): 1741 (C=O ester), 1683 (C=O lactam), 1376, 1250, 1220, 1047, 978, 891, 877, 746.

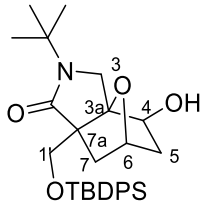
2-(*tert*-butyl)-1-oxo-2,3,7,7a-tetrahydro-3a,6-epoxyisoindol-6(1*H*)-yl)methyl acetate (119.1)



Obtained from unreacted **90** during acetylation to obtain **119**, as a white solid (27 mg).

Rf 0.39 (SiO_2, 100% EtOAc); Mp: 116–122 °C; ^{1}H NMR (400 MHz , $CDCl_3$) δ 6.43 (d, *J* = 5.8 Hz, 1H, 5-H), 6.27 (d, *J* = 5.8 Hz, 1H, 4-H), 4.71 (d, *J* = 12.6 Hz, 1H, 1'-H), 4.33 (d, *J* = 12.6 Hz, 1H, 1'-H), 3.89 (dd, J_1 = 37.6 Hz, J_2 = 11.8 Hz, 2H, 3-H_2), 2.51 (dd, J_1 = 8.6 Hz, J_2 = 3.3 Hz, 1H, 7a-H), 2.10 (s, 3H, Ac), 2.03 (dd, J_1 = 11.7 Hz, J_2 = 3.3 Hz, 1H, 7-H), 1.56 (dd, J_1 = 11.7 Hz, J_2 = 8.7 Hz, 1H, 7-H), 1.41 (s, 9H, *t*Bu); ^{13}C (100 MHz, $CDCl_3$) δ 173.81 (C1), 170.89 ($CH_3\underline{C}$=O)), 136.71 (C4), 134.88 (C5), 88.76 (C6), 88.64 (C3a), 63.40 (C1'), 54.30 (N$\underline{C}Me_3$), 50.66 (C7a), 47.87 (C3), 30.24 (C7), 27.72 (NC$\underline{Me}_3$), 20.84 ($\underline{CH_3}$C=O); *m/z* (ESI+) calculated for $C_{15}H_{21}NO_4$ $[M+H]^+$ 280.1543, observed 280.1533 (error 3.53 ppm); ν_{max} (solid, cm^{-1}): 1739 (C=O ester), 1677 (C=O lactam), 1351, 1243, 1218, 1030, 905, 869, 731.

2-(*tert*-butyl)-7a-(((*tert*-butyldiphenylsilyl)oxy)methyl)-4-hydroxyhexahydro-3a,6-epoxyisoindol-1(4*H*)-one (120)

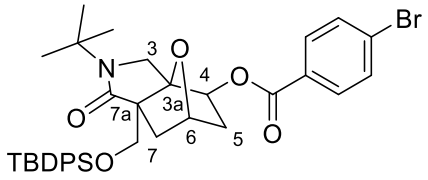


Racemic hydroboration of alkene **77** (306 mg, 0.64 mmol) was performed following the general procedure J by addition of BH_3-THF (0.63 mg, 0.63 mmol) in THF (3 mL). The reaction mixture was stirred at rt for 24 h before addition of sodium perborate (300 mg, 2 mmol). Purification by column chromatography (EtOAc/Pterol 1:1) provided **120** and **121** (45 mg, 0.091 mmol, 14%).

Asymmetric hydroboration of alkene **77** (3.15 mmol, 1.51 g) was performed following the general procedure K by addition of BH_3-DMS (0.30 mL, 3.15 mmol), (-)-α-pinene (7.25 mmol, 1.15 mL) THF (4 mL). Reaction stirred at -40 °C for 7 h and quenched with sodium perborate (9.45 mmol, 1.45 g). Purification by column chromatography (3:1 EtOAc/petrol) afforded compounds **120** and **121** in 67% yield total.

Rf 0.47 (SiO_2, 2:1 EtOAc/Petrol); Mp: 63–69 °C; ^{1}H NMR (400 MHz , $CDCl_3$) δ 7.68–7.61 (m, 4H, Ph), 7.45–7.38 (m, 6H, Ph), 7.47 (t, 1H, *J* = 5.3 Hz, 6-H), 4.21 (m, 1H, 4-H), 4.07 (d, 1H, *J* = 10.7 Hz, 1'-H), 3.94 (d, 1H, *J* = 11.1 Hz, 3-H), 3.71 (d, 1H, *J* = 11.1 Hz, 3-H), 3.14 (d, 1H, *J* = 10.7 Hz, 1'-H), 3.14 (ddd, 1H, J_1 = 1.9 Hz, J_2 = 4.7 Hz, J_3 = 12.3 Hz, *exo*-7-H), 1.86 (dd, 1H, J_1 = 13.9 Hz, J_2 = 6.4 Hz, *exo*-5-H), 1.76 (d, 1H, *J* = 10.6 Hz, *endo*-5-H), 1.45 (s, 9H, Si-*t*Bu), 1.08 (s, 9H, N-*t*Bu), 0.96 (d, 1H, *J* = 12.4 Hz, *endo*-7-H); ^{13}C (100 MHz, $CDCl_3$) δ 175.40 (C1), 135.69 (Ph), 135.57 (Ph), 132.40 (Ph), 132.13 (Ph), 130.11 (Ph), 129.86 (Ph), 127.96 (Ph), 127.81 (Ph), 90.7 (C3a), 74.65 (C6), 70.43 (C4), 65.88 (C1'), 57.96 (C7a), 54.45 (N<u>C</u>Me$_3$), 46.97 (C3), 43.43 (C5), 38.19 (C7), 27.84 (NC<u>Me</u>$_3$), 26.95 (Si<u>C</u>Me$_3$), 19.13 (SiC<u>Me</u>$_3$); *m/z* (ESI+) calculated for $C_{29}H_{39}NO_4Si$ $[M+H]^+$ 494.2721, observed 494.2715 (error 1.03 ppm); ν_{max} (solid, cm^{-1}): 2929, 2857, 1659 (C=O lactam), 1471, 1427, 1362, 1240, 1218, 1105, 1077, 1055, 1013, 811, 741, 702.

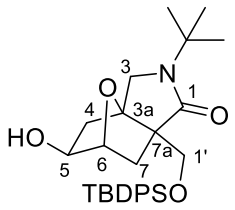
(3a*R*,4*S*,6*S*)-2-(*tert*-butyl)-7a-(((*tert*-butyldiphenylsilyl)oxy)methyl)-1-oxooctahydro-3a,6-epoxyisoindol-4-yl 4-bromobenzoate (120.1)



For procedure see compound **121.1**.

Rf 0.20 (SiO_2, 3:1 Heptane/EtOAc); Mp: 66–68°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89–8.01 (m, 2H, Ph), 7.75–7.73 (m, 2H, Ph), 7.55–7.71 (m, 4H, Ph), 7.46-7.39 (m, 6H, Ph), 5.66 (dd, J_1 = 6.6, J_2 = 1.6 Hz, 1H, 4-H), 4.49–4.62 (m, 1H, 6-H), 4.10 (d, *J* = 11.0 Hz, 1H, 1'-H), 3.92 (d, *J* = 11.0 Hz, 1H, 3-H), 3.79 (d, *J* = 10.9 Hz, 1H, 3-H), 3.30 (d, *J* = 10.9 Hz, 1H, 1'-H), 2.02–2.16 (m, 2H, 7-H + 5-H), 1.97 (ddd, J_1 = 14.0, J_2 = 4.0, J_3 = 1.8 Hz, 1H, 5-H), 1.44 (s, 9H, NCMe$_3$), 1.12 (d, *J* = 12.3 Hz, 1H, *endo*-7-H), 1.05 (s, 9H, SiCMe$_3$); ^{13}C (126 MHz, $CDCl_3$) δ 174.79 (NC=O), 164.88 (OC=O), 135.47 (Ph), 135.27 (Ph), 131.89 (Ph), 131.83 (Ph), 131.52 (Ph), 131.02 (Ph), 129.81 (Ph), 129.54 (Ph), 128.54 (Ph), 128.12 (Ph), 127.75 (Ph), 127.55 (Ph), 89.08 (C3a), 74.68 (C6), 73.01 (C4), 65.43 (C1'), 58.57 (C7a), 54.24 (N<u>C</u>Me$_3$), 46.32 (C3), 40.69 (C5), 37.79 (C7), 27.54 (NC<u>Me</u>$_3$), 26.62 (Si<u>C</u>Me$_3$), 18.81 (SiC<u>Me</u>$_3$); *m/z* (ESI+) calculated for $C_{36}H_{42}BrNO_5Si$ $[M+H]^+$ 676.2088, observed 676.2104 (error -2.42 ppm); ν_{max} (solid, cm^{-1}): 2956, 2857, 1719 (C=O ester), 1685 (C=O lactam), 1267, 1102, 812, 756, 702.

2-(*tert*-butyl)-7a-(((*tert*-butyldiphenylsilyl)oxy)methyl)-5-hydroxyhexahydro-3a,6-epoxyisoindol-1(4*H*)-one (121)

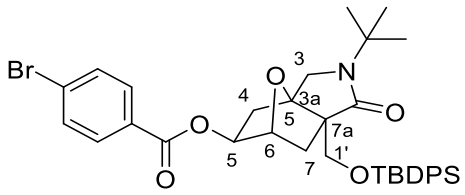


Racemic hydroboration of alkene **77** (306 mg, 0.64 mmol) was performed following the general procedure J by addition of BH_3-THF (0.63 mg, 0.63 mmol) and THF (3 mL). The reaction mixture was stirred at rt for 24 h before addition of sodium perborate (300 mg, 2 mmol). Purification by column chromatography (EtOAc/Petrol 1:1) provided **120** and **121** (48 mg, 0.097 mmol, 15%)

Asymmetric hydroboration of alkene **77** (3.15 mmol, 1.51 g) was performed following the general procedure K by addition of BH_3-DMS (0.30 mL, 3.15 mmol), (-)-α-pinene (7.25 mmol, 1.15 mL) and THF (4 mL). The reaction was stirred at -40 °C for 7 h and quenched with sodium perborate (9.45 mmol, 1.45 g). Purification by column chromatography (3:1 EtOAc/petrol) afforded compounds **120** and **121** in 67% yield total.

Rf 0.40 (SiO_2, 2:1 EtOAc/Petrol); Mp: 60–65 °C; ^{1}H NMR (400 MHz , $CDCl_3$) δ 7.64–7.59 (m. 4H, Ph), 7.46–7.40 (m, 6H, Ph), 7.20 (d, 1H, *J* = 5.6 Hz, 6-H), 4.05 (d, 1H, *J* = 10.7 Hz, 1'-H), 3.90 (td, J_1 = 7.3 Hz, J_2 = 3.0 Hz, 1H, 5-H), 3.77 (dd, 2H, J_1 = 21.3 Hz, J_1 = 11.7 Hz, 3-H_2), 3.12 (d, 1H, *J* = 10.7 Hz, 1'-H), 2.41 (dd, 1H, J_1 = 13.0 Hz, J_2 = 6.8 Hz, , 4-H), 2.05 (dd, 1H, J_1 = 12.8 Hz, J_2 = 5.6 Hz, *exo*-7-H), 1.80 (d, 1H, *J* = 8.0 Hz, OH), 1.52 (dd, 1H, J_1 = 13.0 Hz, J_2 = 2.8 Hz, 4-H), 1.44 (s, 9H, Si-*t*Bu), 1.05 (s, 9H, N-*t*Bu), 0.95 (d, 1H, *J* = 12.9 Hz, *endo*-7-H); ^{13}C (100 MHz, $CDCl_3$) δ 175.70 (C1), 135.66 (Ph), 135.56 (Ph), 132.45 (Ph), 132.12 (Ph), 130.12 (Ph), 129.86 (Ph), 127.96 (Ph), 127.81 (Ph), 88.05 (C3a), 83.25 (C6), 75.17 (C5), 66.23 (C1'), 58.57 (C7a), 54.34 (N<u>C</u>Me_3), 48.44 (C3), 38.44 (C4), 34.64 (C7), 27.82 (NC<u>Me</u>$_3$), 26.93 (Si<u>C</u>Me_3), 19.11 (SiC<u>Me</u>$_3$); *m/z* (ESI+) calculated for $C_{29}H_{39}NO_4Si$ $[M+H]^+$ 494.2721, observed 494.2704 (error 3.30 ppm); ν_{max} (solid, cm^{-1}): 3406 (br, OH), 2928, 2857, 1659 (C=O lactam), 1427, 1348, 1110, 1075, 1058, 809, 740, 702, 615, 504.

(3a*R*,5*S*,6*R*)-2-(*tert*-butyl)-7a-((*(tert*-butyldiphenylsilyl)oxy)methyl)-1-oxooctahydro-3a,6-epoxyisoindol-5-yl 4-bromobenzoate (121.1)

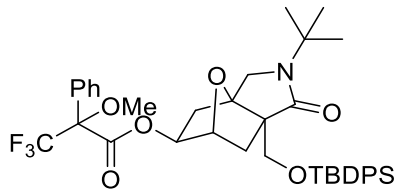


Racemic hydroboration of alkene **77** (210 mg, 0.44 mmol) was performed following the general procedure J by addition of BH_3-THF (0.44 mg, 0.44 mmol) and Et_2O (3 mL). The reaction mixture was stirred at rt for 24 h before addition of sodium perborate (203 mg, 1.32 mmol). The crude of the reaction was treated with 4-bromobenzoyl chloride (105 mg, 0.48 mmol) and TMEDA (39 µL, 0.26 mmol) in DCM (5 mL) as described in the general procedure L. Purification by column chromatography provided **120.1** and **121.1** in 60% yield total.

Asymmetric hydroboration of alkene **77** (1.12 mmol, 532 mg) was performed following the general procedure K by addition of BH_3-DMS (106 µL, 1.12 mmol), (-)-α-pinene (2.58 mmol, 0.409 mL), Et_2O (6mL) and THF (1 mL). The reaction was stirred at -10 °C for 2 d and quenched with sodium perborate (3.36 mmol, 517 mg). The crude of the reaction was treated with 4-bromobenzoyl chloride (782 mg, 3.56 mmol) and TMEDA (0.302 mL, 2.02 mmol) in DCM (5 mL) as described in the general procedure L. Purification by column chromatography provided **120.1** and **121.1** in 75 % yield total.

Rf 0.26 (SiO_2, 3:1 Heptane/EtOAc); Mp: 77–78°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.5 Hz, 2H, Ph), 7.51–7.73 (m, 6H, Ph), 7.43 (m, 6H, Ph), 4.96 (dd, *J* = 7.1, 3.4 Hz, 1H, 5-H), 4.46 (d, *J* = 5.6 Hz, 1H, 6-H), 4.12 (d, *J* = 10.8 Hz, 1H, 1'-H), 3.82 (dd, *J* = 28.0, 10.8 Hz, 2H, 3-H_2), 3.26 (d, *J* = 10.8 Hz, 1H, 1'-H), 2.55 (dd, *J* = 13.1, 7.1 Hz, 1H, 4-H), 2.16 (dd, *J* = 12.9, 5.7 Hz, 1H, *exo*-7-H), 1.90 (dd, *J* = 13.1, 3.3 Hz, 1H, 4-H), 1.44 (s, 9H, $NCMe_3$), 1.18 (d, *J* = 13.0 Hz, 1H, *endo*-7-H), 1.08 (s, 9H, $SiCMe_3$); ^{13}C (100 MHz, $CDCl_3$) δ 175.17 (NC=O), 165.26 (OC=O), 135.35 (Ph), 135.25 (Ph), 132.01 (Ph), 131.82 (Ph), 131.47 (Ph), 130.91 (Ph), 129.90 (Ph), 129.61 (Ph), 128.29 (Ph), 128.15 (Ph), 127.75 (Ph), 127.54 (Ph), 87.78 (C3a), 80.30 (C6), 77.39 (C5), 65.90 (C1'), 58.55 (C7a), 54.15 (N<u>C</u>Me_3), 47.92 (C3), 34.69 (C4, C7), 27.52 (NC<u>Me</u>$_3$), 26.65 (Si<u>C</u>Me_3), 18.8 (SiC<u>Me</u>$_3$); *m/z* (ESI+) calculated for $C_{36}H_{42}BrNO_5Si$ $[M+H]^+$ 676.2088, observed 676.2100 (error -2.55 ppm); ν_{max} (solid, cm^{-1}): 2959, 2857, 1717 (C=O ester), 1680 (C=O lactam), 1268, 1103, 1066, 1011, 810, 701, 504.

(3a*R*,5*S*,6*R*)-2-(*tert*-butyl)-7a-(((*tert*-butyldiphenylsilyl)oxy)methyl)-1-oxooctahydro-3a,6-epoxyisoindol-5-yl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (122 and 123)



Mosher esters **(-)-122** and **(+)-123** were obtained by reaction of alcohol **121** (1.0 equiv., 0.27 mmol, 0.13 g) with EDCI (3.0 equiv., 0.81 mmol, 155 mg), DMSP (3.0 equiv., 0.81 mmol, 190 mg), Et_3N (3.0 equiv., 0.81 mmol, 133 µL) following the general procedure D. The crude of the reaction was passed through a pad of silica and concentrated.

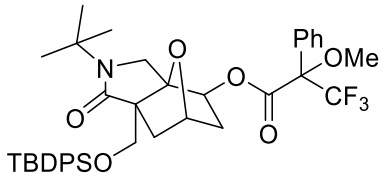
122:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68–7.65 (m, Ph), 7.62–7.60 (m, Ph), 7.51–7.38 (m, Ph), 4.92 (dd, J_1 = 7.0 Hz, J_1 = 3.4 Hz, 1H, 5-H), 4.33 (d, J = 5.6 Hz, 1H, 6-H), 4.09 (d, J = 10.8 Hz, 1H, 1'-H), 3.77 (dd, J_1 = 18.4 Hz, J_2 = 10.8 Hz, 2H, 3-H_2), 3.53 (s, 3H, OMe), 3.22 (d, J = 10.8 Hz, 1H, 1'-H), 2.50 (dd, J = 13.1, 7.1 Hz, 1H, 4-H), 2.12 (dd, J_1 = 12.9, J_2 = 5.7 Hz, 1H, *exo*-7-H), 1.78 (dd, J_1 = 13.1, J_2 = 3.4 Hz, 1H, 4-H), 1.41 (s, 9H, $NCMe_3$), 1.14 (d, J = 12.9 Hz, 1H, *endo*-7-H), 1.07 (s, 9H, $SiCMe_3$);

123:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67–7.65 (m, Ph), 7.62–7.60 (m, Ph), 7.52–7.40 (m, Ph), 4.92 (dd, J_1 = 7.0 Hz, J_1 = 3.4 Hz, 1H, 5-H), 4.41 (d, J = 5.6 Hz, 1H, 6-H), 4.09 (d, J = 10.8 Hz, 1H, 1'-H), 3.76 (d, J = 6.45 Hz, 2H, 3-H_2), 3.54 (s, 3H, OMe), 3.22 (d, J = 10.8 Hz, 1H, 1'-H), 2.43 (dd, J_1 = 13.1, J_2 = 7.1 Hz, 1H, 4-H), 2.13 (dd, J_1 = 12.9, J_2 = 5.7 Hz, 1H, *exo*-7-H), 1.71 (dd, J_1 = 13.1, J_2 = 3.4 Hz, 1H, 4-H), 1.42 (s, 9H, $NCMe_3$), 1.15 (d, J = 13.0 Hz, 1H, *endo*-7-H), 1.06 (s, 9H, $SiCMe_3$); ^{13}C (100 MHz, $CDCl_3$) δ 175.25 (NC=O), 166.37 (OC=O), 135.66, 135.55, 132.31, 132.10, 131.88, 130.20, 129.92, 129.71, 128.52, 128.03, 127.83, 127.29, 87.99 (C3a), 80.13 (C6), 79.01 (C5), 66.08 (C1'), 58.79 (C7a), 55.41 (N<u>C</u>Me_3), 54.44 (OMe), 48.06 (C3), 34.99 (C7), 34.56 (C4), 27.78 (NC<u>Me</u>$_3$), 26.96 (SiC<u>Me</u>$_3$), 19.12 (Si<u>C</u>Me_3).

(3a*R*,4*S*,6*S*)-2-(*tert*-butyl)-7a-(((*tert*-butyldiphenylsilyl)oxy)methyl)-1-oxooctahydro-3a,6-epoxyisoindol-4-yl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (124, 125)



Mosher esters **(-)-124** and **(+)-125** were obtained by reaction of alcohol **120** (1.0 equiv., 0.33 mmol, 0.16 g) with EDCI (3.0 equiv., 1.0 mmol, 192 mg), DMSP (3.0 equiv., 1.0 3 mmol, 234 mg), Et_3N (3.0 equiv., 1.0 mmol, 139 µL) following the general procedure D. The crude of the reaction was passed through a pad of silica and concentrated.

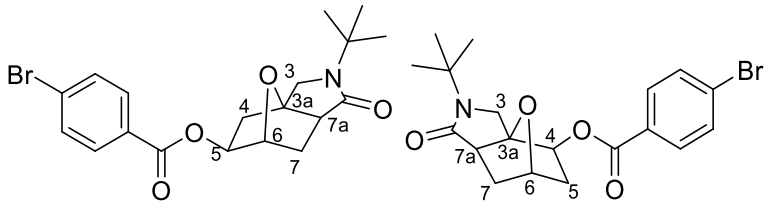
124:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73–7.71 (m, 2H, Ph), 7.64–7.62 (m, 2H, Ph), 7.58–7.56 (m, 4H, Ph), 7.47-7.39 (m, 6H, Ph), 7.57 (m, 4H, Ph), 7.46-7.39 (m, 6H, Ph), 5.57 (d, *J* = 6.3 Hz, 1H, 4-H), 4.52 (t, *J* = 5.2 Hz, 1H, 6-H), 4.08 (d, *J* = 11.0 Hz, 1H, 1'-H), 3.63 (d, *J* = 11.0 Hz, 1H, 3-H), 3.59 (s, 3H, OMe), 3.42 (d, *J* = 11.0 Hz, 1H, 3-H), 3.20 (d, *J* = 11.0 Hz, 1H, 1'-H), 2.06 (m, 2H, 7-H and 5-H), 1.90 (dd, J_1 = 14.0, J_2 = 5.6, 1H, 5-H), 1.35 (s, 9H, $NCMe_3$), 1.07 (s, 10H, $SiCMe_3$ and 7-H); ^{13}C (100 MHz, $CDCl_3$) δ 174.78 (NC=O), 165.90 (OC=O), 135.72, 135.50, 132.31, 132.02, 131.94, 130.18, 129.87, 129.67, 128.53, 128.47, 128.11, 127.86, 127.19 , 89.10 (C3a), 74.82 (C4), 74.62 (C6), 65.85 (C1'), 58.52 (C7a), 55.46 (Me), 54.48 ($NCMe_3$), 46.27 (C3), 40.66 (C5), 38.01 (C7), 27.69 ($NCMe_3$), 26.94 $SiCMe_3$), 19.04 ($SiCMe_3$);

125:

^{1}H NMR (400 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73–7.71 (m, 2H, Ph), 7.64–7.62 (m, 2H, Ph), 7.57–7.55 (m, 4H, Ph), 7.46-7.40 (m, 6H, Ph), 5.55 (dd, J_1 = 6.4, J_2 = 1.2, 1H, 4-H), 4.49 (t, *J* = 5.3 Hz, 1H, 6-H), 4.10 (d, *J* = 10.8 Hz, 1H, 1'-H), 3.79 (d, *J* = 10.8 Hz, 1H, 3-H), 3.59 (d, *J* = 11.0 Hz, 1H, 3-H), 3.53 (s, 3H, OMe), 3.21 (d, *J* = 10.9 Hz, 1H, 1'-H), 2.08–2.01 (m, 2H, 7-H and 5-H), 1.82 (dd, J_1 = 14.0, J_2 = 5.7, 1H, 5-H), 1.39 (s, 9H, $NCMe_3$), 1.06 (s, 10H, 7-H and $SiCMe_3$);

2-(*tert*-butyl)-1-oxooctahydro-3a,6-epoxyisoindol-5-yl 4-bromobenzoate (127) and 2-(*tert*-butyl)-1-oxooctahydro-3a,6-epoxyisoindol-4-yl 4-bromobenzoate (126)



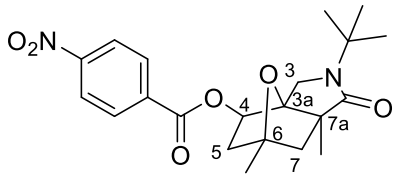
Racemic hydroboration of alkene **6.55** (251 mg, 1.21 mmol) was performed following the general procedure J by addition of BH_3-THF (1.21 mg, 1.21 mmol) and Et_2O (7 mL). The reaction mixture was stirred at rt for 18 h before addition of sodium perborate (558 mg, 3.63 mmol). The crude of the reaction was treated with 4-bromobenzoyl chloride (292 mg, 1.33 mmol) and TMEDA (109 µL, 0.73 mmol) in DCM (5 mL) as described in the general procedure L. Purification by column chromatography provided **126** and **127** in 12% yield.

Asymmetric hydroboration of alkene **6.55** (1.65 mmol, 342 mg) was performed following the general procedure K by addition of BH_3-DMS (156 µL, 1.65 mmol), (-)-α-pinene (602 µL, 3.79 mmol), Et_2O (6mL) and THF (1 mL). The reaction was stirred at rt for 18 h and quenched with sodium perborate (4.95 mmol, 760 mg). The crude of the reaction was treated with 4-bromobenzoyl chloride (1.32 g, 5.98 mmol) and TMEDA (489 µL, 3.26 mmol) in DCM (5 mL) as described in the general procedure L. Purification by column chromatography provided **126** and **127** in 40% yield.

127:

^{1}H NMR (400 MHz , $CDCl_3$) δ 7.90–7.88 (m, 2H, Ar), 7.59-7.57 (m, 2H, Ar), 5.13 (dd, J_1 = 7.0 Hz, J_2 = 3.1 Hz, 1H, 5-H), 4.64 (d, J = 5.5 1H, 6-H), 3.84 (d, J = 11.6, 1H, 3-H), 3.71 (d, J = 11.6, 1H, 3-H), 2.58 (dd, J_1 = 9.3 Hz, J_2 = 4.2 Hz, 1H, 7a-H), 2.35 (dd, J_1 = 12.8 Hz, J_2 = 7.1 Hz, 1H, 4-H), 2.17-2.12 (m, 1H, 7-H), 1.91-1.86 (m, 2H, 4-H and 7-H), 1.42(s, 9H, *t*Bu); *m/z* (ESI+) calculated for $C_{19}H_{22}BrNO_4$ $[M+H]^+$ 408.0805, observed 408.0810 (error -2.29 ppm).

2-(*tert*-butyl)-6,7a-dimethyl-1-oxooctahydro-3a,6-epoxyisoindol-4-yl 4-nitrobenzoate (130)

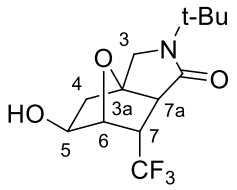


Racemic hydroboration of alkene **100** (500 mg, 2.12 mmol) was performed following the general procedure J by addition of BH_3-THF (2.12 mL, 2.12 mmol) and Et_2O (10 mL). The reaction mixture was stirred at rt for 16 h before addition of sodium perborate (1.00 g, 6.50 mmol). The crude of the reaction was treated with 4-nitrobenzoyl chloride (433 mg, 2.33 mmol) and TMEDA (191 µL, 1.27 mmol) in DCM (10 mL) as described in the general procedure L. Purification by column chromatography provided **130** and **131** in 47% yield.

Asymmetric hydroboration of alkene **100** (4.25 mmol, 1.00 g) was performed following the general procedure K by addition of BH_3-DMS (403 µL, 4.25 mmol), (-)-α-pinene (9.8 mmol, 1.54 mL), Et_2O (6 mL) and THF (1.5 mL). The reaction was stirred at -15 °C for 4 d and at rt for 1 d, and quenched with sodium perborate (17.0 mmol, 2.6 g). The crude of the reaction was treated with 4-nitrobenzoyl chloride (2.60 g, 14.02 mmol) and TMEDA (1.15 mL, 7.65 mmol) in DCM (24 mL) as described in the general procedure L. Purification by column chromatography provided **130** and **131** in 38% yield.

RF 0.57 (2:1 EtOAc/Heptane); ^{1}H NMR (400 MHz , $CDCl_3$) δ 8.31–8.30 (m, 2H, Ar), 8.23–8.20 (m, 2H, Ar), 5.52 (dd, J_1 = 6.7 Hz, J_2 = 1.69 Hz, 1H, 4-H), 3.73 (d, J = 11.7, 1H, 3-H), 3.66 (d, J = 11.7, 1H, 3-H), 2.41 (dd, J_1 = 14.0 Hz, J_2 = 6.8 Hz, 1H, 5-H), 2.14 (dd, J_1 = 12.3 Hz, J_2 = 2.5 Hz, 1H, 7-H), 1.77 (dt, J_1 = 14.0 Hz, J_2 = 2.0 Hz, 1H, 5-H), 1.52 (s, 3H, 6-Me), 1.44 (d, J = 12.2 Hz, 1H, 7-H), 1.40 (s, 9H, *t*Bu), 1.26 (s, 3H, 7a-Me); ^{13}C (100 MHz, $CDCl_3$) δ 177.56 (NC=O), 164.44 (OC=O), 135.01 (Ar), 130.91 (Ar), 123.65 (Ar), 89.38 (C7a), 83.93 (C6), 75.78 (C4), 54.43 (C3a), 54.18 ($\underline{C}(CH_3)_3$), 46.86 (C7), 46.43 (C5), 44.73 (C3), 27.69 ($C(\underline{C}H_3)_3$), 20.67 (6-Me), 19.22 (7a-Me); *m/z* (ESI+) calculated for $C_{21}H_{26}N_2O_6$ $[M+H]^+$ 403.1864, observed 403.1869 (error -0.79 ppm).

2-(*tert*-butyl)-5-hydroxy-7-(trifluoromethyl)hexahydro-3a,6-epoxyisoindol-1(4*H*)-one (132)

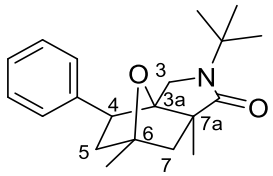


With BH_3-THF: Racemic hydroboration of alkene **84** (200 mg, 0.73 mmol) was performed following the general procedure J by addition of BH_3-THF (1M in THF, 0.7 mL) in Et_2O (3 mL). The reaction mixture was stirred at rt for 24 h before addition of sodium perborate (300 mg, 2 mmol). Purification by column chromatography (EtOAc/Petrol 3:1) provided **132.**

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.51–4.48 (m, 2H, 5-H, 6-H), 3.80 (d, 1H, *J* = 11.9 Hz, 3-H), 3.70 (d, 1H, *J* = 11.9 Hz, 3-H), 3.13-3.03 (m, 1H, 7-H), 2.58 (d, 1H, *J* = 4.4 Hz, 7a-H), 2.29 (dd, 1H, J_1 = 13.2 Hz, J_2 = 6.6 Hz, 4-H), 1.97 (d, 1H, *J* = 8.5 Hz, -OH), 1.69 (d, 1H, *J* = 13.2 Hz, 4-H), 1.40 (s, 9H, *t*Bu); ^{13}C (100 MHz, $CDCl_3$) δ 171.80 (C=O), 126.70 (CF_3), 123.64 (CF_3), 86.90 (C3a), 83.40 (C6), 71.25 (d, C5), 54.59 ($\underline{C}Me_3$), 51.62 (C7a), 47.67 (C3), 46.75 (q, C7), 41.66 (C4), 27.58 ($C\underline{Me}_3$); ^{19}F (400 MHz, $CDCl_3$) δ -65.03; *m/z* (ESI+) calculated for $C_{13}H_{18}F_3NO_3$ $[M+Na]^+$ 316.1131, observed 316.1136 (error -2.68 ppm);ν_{max} (solid, cm^{-1}): 3498 (OH), 2977, 1672 (C=O, lactame), 1351, 1410, 1262, 1157, 1103, 980.

2-(*tert*-butyl)-6,7a-dimethyl-4-phenylhexahydro-3a,6-epoxyisoindol-1(4*H*)-one (134) and 2-(*tert*-butyl)-6,7a-dimethyl-5-phenylhexahydro-3a,6-epoxyisoindol-1(4*H*)-one (133)

134:

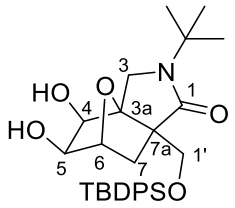


Cycloadduct **100** (1.0 equiv., 0.85 mmol, 200 mg), Pd-118 (0.1 equiv., 0.085 mmol, 55 mg) and iodobenzene (4.0 equiv., 3.40 mmol, 381 µg) were dissolved in dry DMF. Piperidine (4.5 equiv., 3.82 mmol, 378 µL) and formic acid (4.3 equiv., 3.65 mmol, 138 µg) were added and the reaction mixture was stirred under nitrogen at rt for 20 h. The reaction mixture was diluted with EtOAc (10mL) and was washed with brine (10 mL). The aqueous phase was extracted with EtOAc (3X10 mL). The combined organic phases were washed with water (3X20 mL) and dried

(MgSO4). Purification by column chromatography (heptane/EtOAc) afforded 250 mg (94%) of products **133** and **134** as white solids.

1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.23 (m, 5H, Ph), 3.25 (dd, *J* = 8.8, 3.6 Hz, 1H, 4-H), 3.12 (s, 2H, 3-H_2), 2.29 (dd, *J* = 12.9, 8.8 Hz, 1H, 5-H), 2.16 (dd, *J* = 12.1, 2.7 Hz, 1H, 7-H), 1.82 (dt, *J* = 12.9, 3.2 Hz, 1H, 5-H), 1.55 (s, 3H, 6-Me), 1.48 (d, *J* = 12.1 Hz, 1H, 7-H), 1.30 (s, 9H, *t*Bu), 1.26 (s, 3H, 7a-Me); 13C (101 MHz, $CDCl_3$) δ 178.88 (C=O), 142.66 (Ph), 128.41 (Ph), 128.23 (Ph), 126.77 (Ph), 91.21 (C3a), 83.54 (C6), 55.74 (C7a), 53.82 (CMe_3), 48.07 (C7), 46.82 (C5), 45.93 (C3), 44.87 (C4), 27.67 (CMe_3), 21.07 (6-Me), 19.96 (7a-Me); *m/z* (ESI+) calculated for $C_{20}H_{27}NO_2$ $[M+Na]^+$ 336.1934, observed 336.1941 (error -2.34 ppm);

2-(*tert*-butyl)-7a-(((*tert*-butyldiphenylsilyl)oxy)methyl)-4,5-dihydroxyhexahydro-3a,6-epoxyisoindol-1(4*H*)-one (137)



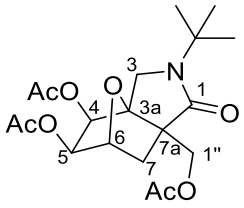
Asymmetric: Diol **137** was obtained by treatment of alkene **77** (0.20 g, 0.43 mmol) in H_2O/*t*BuOH (7 mL) with AD-mix-α (0.59 g) and $MeSO_2NH_2$ (0.43 mmol, 30 mg) following the general procedure I. The reaction mixture was stirred for 19 h. Purification by silica gel column (3:1 EtOAc/ Petrol) to afforded **137** as a white solid (63 mg, 0.12 mmol, 29%).

Racemic: Diol **137** was obtained following the general procedure H stirring $OsCl_3$ hydrate (0.007 mmol, 2 mg), $K_3Fe(CN)_6$ (1.22 mmol, 0.40 g), quinuclidine (0.018 mmol, 2 mg), $MeSO_2NH_2$ (0.41 mmol, 40 mg), K_2CO_3 (1.22 mmol, 0.17 g) and alkene **77** (0.42 mmol, 0.20 g) in *t*BuOH/H_2O (4mL) overnight. 0.6 g of Na_2SO_3 were used to quench the reaction. The reaction provided product **137** (0.22 g, 0.43 mmol, 99%). No purification was necessary.

Mp: 70°C (dec.); Rf 0.21 (SiO_2, 3:1 EtOAC/Petrol); ^{1}H NMR (400 MHz , $CDCl_3$) δ 7.64–7.60 (m, 4H, Ph), 7.48–7.39 (m, 6H, Ph), 4.17 (d, 1H, *J* = 5.3 Hz, 6-H), 4.13 (d, 1H, *J* = 5.6 Hz, 4-H), 4.05 (d, 1H, *J* = 10.9 Hz, 1'-H), 3.90 (d, 1H, *J* = 11.3 Hz, 3-H), 3.85 (d, 1H, *J* = 5.6 Hz, 5-H), 3.71 (d, 1H, *J* = 11.2 Hz, 3-H), 3.14 (d, 1H, *J* = 10.8 Hz, 6-H), 2.05-2.01 (m, 1H, *exo*-7-H), 1.43 (s, 9H, Si-*t*Bu), 1.08 (s, 10H, N-*t*Bu and *endo*-7-H),. ^{13}C (100 MHz, $CDCl_3$) δ 175.01 (C1), 135.67 (Ph), 135.57 (Ph), 132.32 (Ph), 131.98 (Ph), 130.20 (Ph), 129.96 (Ph), 128.00 (Ph), 127.85 (Ph), 90.16 (C3a), 82.58 (C6), 75.87 (C5), 70.42 (C4), 65.15 (C1'), 58.07 (C7a), 54.55 (Si$\underline{C}(CH_3)$), 46.61 (C3), 34.48 (C7), 27.77 (SiC($\underline{C}H_3$)), 26.95 (N-C($\underline{C}H_3$)), 19.13 (N-$\underline{C}(CH_3)$). *m/z* (ESI+) calculated for $C_{29}H_{37}NO_5Si$ $[M+Na]^+$ 530.2333, observed

532.2495 (error 0.01 ppm); ν_{max} (solid, cm^{-1}): 3372 (br, -OH), 2933, 2858, 1651 (C=O lactam), 1471, 1427, 1362, 1235, 1112, 1076, 1053, 1014, 807, 702, 616, 504.

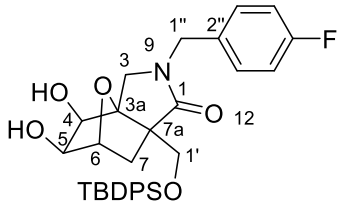
7a-(acetoxymethyl)-2-(*tert*-butyl)-1-oxooctahydro-3a,6-epoxyisoindole-4,5-diyl diacetate (139)



Compound **139** was obtained by treatment of **78** (0.2 mmol, 47 mg) in H_2O/*t*BuOH (2 mL) with AD-mix-α (0.27 g) and $MeSO_2NH_2$ (0.2 mmol, 19 mg) following the general procedure I (2 d). The crude of the reaction was dissolved in MeCN/Pyridine (4 mL) and treated with Ac_2O (1.2 mmol, 0.10 mL) and DMAP (0.02 mmol, 3 mg) following the general procedure A. Purification by silica gel column (4:1 EtOAc/ Petrol) afforded **139** as a white solid (20 mg, 0.051 mmol, 25%).

Rf: 0.66 (SiO_2, 4 :1 EtOAc/Petrol); mp: 156–161 °C (dec.); ^{1}H NMR (400 MHz , $CDCl_3$) δ 5.30 (d, *J* = 6.0 Hz, 1H, 4-H), 5.00 (d, *J* = 6.0 Hz, 1H, 5-H), 4.44 (d, *J* = 5.4 Hz, 1H, 6-H), 4.40 (d, *J* = 12.0 Hz, 1H, 1'-H), 3.97 (d, *J* = 11.9 Hz, 1H, 1'-H), 3.71 (d, *J* = 11.3 Hz, 1H, 3-H), 3.62 (d, *J* = 11.3 Hz, 1H, 3-H), 2.28 (d, J_1 = 13.1 Hz, J_2 = 5.5 Hz, 1H, *exo*-7-H), 2.13 (s, 3H, Ac), 2.08 (s, 6H, Ac), 1.50 (d, *J* = 13.2 Hz, 1H, *endo*-7-H), 1.40 (s, 9H, *t*Bu); ^{13}C (100 MHz, $CDCl_3$) δ 173.21 (C1), 170.07 (COMe), 169.93 (COMe), 169.85 (COMe), 88.70 (C3a), 80.35 (C6), 77.23 (C5), 71.41 (C4), 64.46 (C1'), 55.88 (C7a), 54.77 ($C(CH_3)$), 45.38 (C3), 34.51 (C7), 27.65 ($C(CH_3)$), 20.64 ($CO\underline{C}H_3$), 20.49 ($CO\underline{C}H_3$); *m/z* (ESI+) calculated for $C_{19}H_{27}NO_8$ $[M+Na]^+$ 420.1629, observed 420.1626 (error 1.94 ppm); ν_{max} (solid, cm^{-1}): 2981, 1736 (C=O ester), 1751 (C=O ester), 1686 (C=O lactam), 1376, 1227, 1038, 968, 876.

7a-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-(4-fluorobenzyl)-4,5-dihydroxyhexahydro-3a,6-epoxyisoindol-1(4*H*)-one (140)



Asymmetric: Diol **140** was obtained by treatment of a alkene mixture **67**/**68** (1 equiv., 0.41 mmol, 0.21 g) in H_2O/*t*BuOH (4 mL) with AD-mix-α (0.57 g) and $MeSO_2NH_2$ (0.41 mmol, 39 mg) following the general procedure I. Purification by column chromatography (SiO_2, Petrol/EtOAc 5:1 then 2:1) afforded **140** as white solid (29% calculated yield from ^{19}F NMR of the crude).

Racemic: (±)-**140** was prepared following the general procedure I by addition of potassium ferricyanide (1.1 mmol, 0.36 g), potassium carbonate (1.1 mmol, 0.15 g), osmium(III) chloride hydrate (7 µmol, 2 mg), quinuclidine (18 µmol, 2 mg), methanesulfonamide (0.37 mmol, 35 mg) and alkene mixture **67**/**68** (0.40 mmol, 0.20 g) water/*t*BuOH (4 mL). The reaction mixture was stirred at rt for 1 d before the addition of sodium sulphite (4.4 mmol, 0.56 g). Purification by column chromatography (SiO_2, Petrol/EtOAc 1:2) afforded 15 mg of **140** (15 mg, 0.03 mmol, 7%).

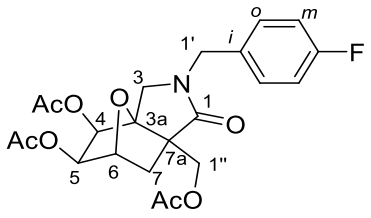
Rf 0.46 (SiO_2, EtOAc/Petrol 2:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.62–7.57 (m, 4H, Ph), 7.48–7.38 (m, 6H, Ph), 7.24–7.20 (m, 2H, Ar), 6.96–6.92 (m, 2H, Ar), 4.82 (d, *J* = 15.0 Hz, 1H, 1''-H), 4.25–4.21 (m, 2H, 1''-H and 6-H), 4.17 (t, *J* = 6.1 Hz, 1H, 5-H), 4.12 (d, *J* = 10.8 Hz, 1H, 1'-H), 3.89 (t, *J* = 5.3 Hz, 1H, 4-H), 3.77 (d, *J* = 11.1 Hz, 1H, 3-H) 3.45 (d, *J* = 11.1 Hz, 1H, 3-H), 3.25 (d, *J* = 10.8 Hz, 1H, 1'-H), 2.61 (d, *J* = 5.9 Hz, 1H, -OH), 2.46 (d, *J* = 7.6 Hz, 1H, -OH), 2.10 (dd, J_1 = 12.8 Hz, J_2 = 5.4 Hz, 1H, *exo*-7-H), 1.17 (d, *J* = 12.9 Hz, 1H, *endo*-7-H), 1.01 (s, 9H, $C(CH_3)_3$). ^{13}C (100 MHz, $CDCl_3$) δ 175.23 (C1), 162.13 (d, *J* = 245 Hz, C-F), 135.60 (Ar), 135.56 (Ar), 132.39 (Ar), 131.85 (Ar), 131.55 (Ar), 131.52 (Ar), 130.20 (Ar), 130.10 (Ar), 129.76 (Ar), 129.68 (Ar), 128.01 (Ar), 127.93 (Ar), 115.73 (Ar), 115.51 (Ar), 91.08 (C3a), 82.67 (C6), 75.77 (C4), 70.27 (C5), 65.12 (C1'), 57.62 (C7a), 47.61 (C3), 46.23 (C1''), 34.08 (C7), 26.80 (-SiC($\underline{C}H_3)_3$), 19.11 (-Si$\underline{C}(CH_3)_3$); ^{19}F NMR (400 MHz, $CDCl_3$) δ -115.04; *m/z* (ESI+) calculated for $C_{32}H_{36}FNO_5Si$ $[M+Na]^+$ 584.2239, observed 584.2223 (error 2.72 ppm); ν_{max} (solid, cm^{-1}): 3344 (br, OH), 2930, 2857, 1667 (C=O amide), 1510, 1472, 1222, 1111, 1078, 805, 701.

7a-(acetoxymethyl)-2-(4-fluorobenzyl)-1-oxooctahydro-3a,6-epoxyisoindole-4,5-diyl diacetate (143) and 2-(4-fluorobenzyl)-1-oxo-2,3,6,7-tetrahydro-3a,6-epoxyisoindol-7a(1*H*)-yl)methyl acetate (144)

Asymmetric: Compound **143** was obtained by treatment of a mixture of alcohols **69/70** mixture (0.73 mmol, 0.21 g) in H_2O/*t*BuOH (7 mL) with AD-mix-α (0.98 g) and $MeSO_2NH_2$ (0.73 mmol, 69 mg) following the general procedure I. The crude of the reaction was dissolved in MeCN/Pyridine (7 mL) and treated with Ac_2O (3.5 mmol, 0.33 mL) and DMAP (0.03 mmol, 4 mg) following the general procedure A. After 3 days the reaction mixture was concentrated and purified by silica gel column (3:1 EtOAc/ Petrol) to afford **142**, **143** and **144** not completely separated.

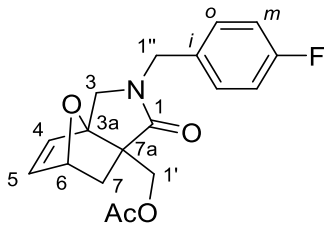
Racemic: (±)-**143** was prepared following the general procedure I by addition of potassium ferricyanide (1.5 mmol, 0.50 g), potassium carbonate (1.5 mmol, 0.2 g), osmium(III) chloride hydrate (7 µmol, 2 mg), quinuclidine (18 µmol, 2 mg), methanesulfonamide (0.50 mmol, 48 mg) and alkene mixture **69**/**70** (0.40 mmol, 0.20 g) water/*t*BuOH (5 mL). The reaction mixture was stirred at rt for 1 d before the addition of sodium sulphite (6.0 mmol, 0.76 g). The crude of the reaction was dissolved in MeCN/Pyridine (10 mL) and treated with Ac_2O (3.2 mmol, 0.3 mL) and DMAP (0.05 mmol, 7 mg) following the general procedure A. Purification by silica gel column (3:1 EtOAc/ Petrol) afforded **142**, **143** and **144**. 15 mg of **143** were obtained from a second column chromatography with silica gel impregnated with $AgNO_3$ used to separate **143** and **144**.

143:



Rf 0.35 (SiO_2, EtOAc/Petrol 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23–7.21 (m, 2H, *o*Ph), 7.03-6.99 (m, 2H, *m*Ph), 5.29 (d, *J* = 5.9 Hz, 1H, 4-H), 5.02 (d, *J* = 5.8 Hz, 1H, 5-H), 4.63 (d, *J* = 15.0 Hz, 1H, 1'-H), 4.49 (d, *J* = 5.4 Hz, 1H, 6-H), 4.45 (d, *J* = 12.0 Hz, 1H, 1''-H), 4.34 (d, *J* = 15.0 Hz, 1H, 1'-H), 4.04 (d, *J* = 12.0 Hz, 1H, 1''-H), 3.53 (d, *J* = 11.2 Hz, 1H, 3-H), 3.44 (d, *J* = 11.2 Hz, 1H, 3-H), 2.33 (dd, J_1 = 13.1 Hz, J_2 = 5.5 Hz, 1H, *exo*-7-H), 2.08 (s, 3H, *endo*-7-H), 2.06 (s, 3H, Ac, 1.94 (s, 3H, Ac), 1.58 (d, *J* = 12.8 Hz, 1H, -7-H); ^{13}C (100 MHz, $CDCl_3$) δ 173.32 (C1), 169.91 (C=OCH_3), 169.80 (C=OCH_3), 162.32 (d, *J* = 246 Hz, C-F), 131.38 (d, *J* = 3.2 Hz, *i*Ph), 129.73 (d, *J* = 8.2 Hz, *o*Ph), 115.73 (d, *J* = 21.5 Hz, *m*Ph), 89.78 (C3a), 80.40 (C6), 76.85 (C5), 71.13 (C4), 64.53 (C1''), 55.13 (C7a), 46.87 (C3), 46.32 (C1'), 34.56 (C7), 20.46 (C=OCH_3), 20.39 (C=OCH_3); ^{19}F NMR (400 MHz, $CDCl_3$) δ -114.35;

144:



Mp: 163-167 °C; Rf 0.37 (SiO_2, 3:1 EtOAc/Petrol, EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.29 (m, 2H, *o*Ph), 7.07–7.02 (m, 2H, *m*Ph), 6.49 (dd, J_1 = 5.8 Hz, J_2 = 1.1 Hz, 1H, 5-H), 6.37 (d, *J* = 5.8 Hz, 1H, 4-H), 5.04 (dd, J_1 = 5.6 Hz, J_2 = 1.6 Hz, 1H, 6-H), 4.86 (d, *J* = 14.9 Hz, 1H, 1''-H), 4.34 (d, *J* = 11.2 Hz, 1H, 1'-H), 4.25 (d, *J* = 15.0 Hz, 1H, 1''-H), 3.81 (d, *J* = 11.2 Hz, 1H, 3-H), 3.66 (d, *J* = 11.2 Hz, 1H, 1'-H), 3.52 (d, *J* = 11.2 Hz, 1H, 3-H), 2.43 (dd, J_1 = 12.0 Hz, J_2 = 4.7 Hz, 1H, *exo*-7-H), 1.11 (d, *J* = 12.2 Hz, 1H, *endo*-7-H); ^{19}F NMR (400 MHz, $CDCl_3$) δ -114.67; ^{13}C (100 MHz, $CDCl_3$) δ 174.31 (C1), 169.88 ($CH_3\underline{C}$=O), 161.09 (C-F), 137.41 (C5), 132.01 (d, *J* = 3.3Hz, *i*Ph), 131.67 (C4), 129.95 (d, *J* = 8.1 Hz, *o*Ph), 115.60 (d, *J* = 21.4 Hz, *m*Ph), 90.74 (C3a), 78.44 (C6), 67.73 (C1'), 55.59 (C7a), 49.49 (C3), 46.30 (C1''), 32.34 (C7), 20.56 ($\underline{C}H_3$C=O); *m/z* (ESI+) calculated for $C_{18}H_{18}FNO_4$ $[M+H]^+$ 332.1293, observed 332.1281 (error 3.41 ppm); ν_{max} (solid, cm^{-1}): 2916, 1737 (C=O ester), 1667 (C=O amide), 1513, 1477, 1219, 1034, 849, 566.

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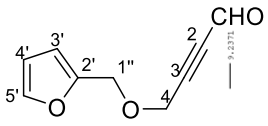
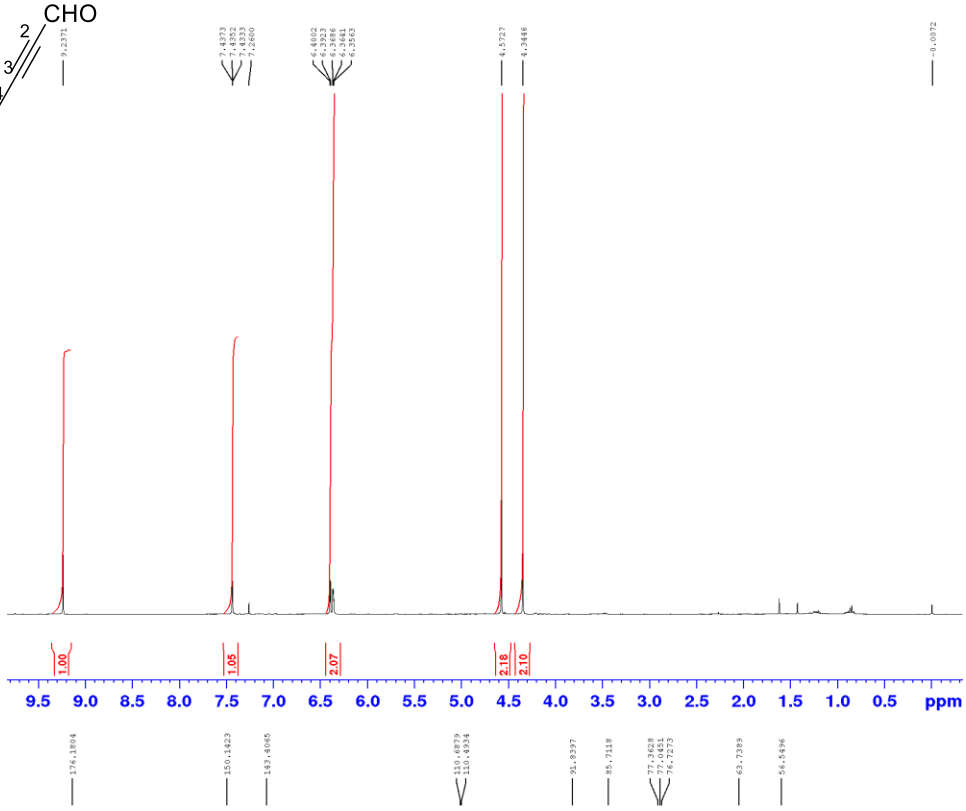
APPENDIX

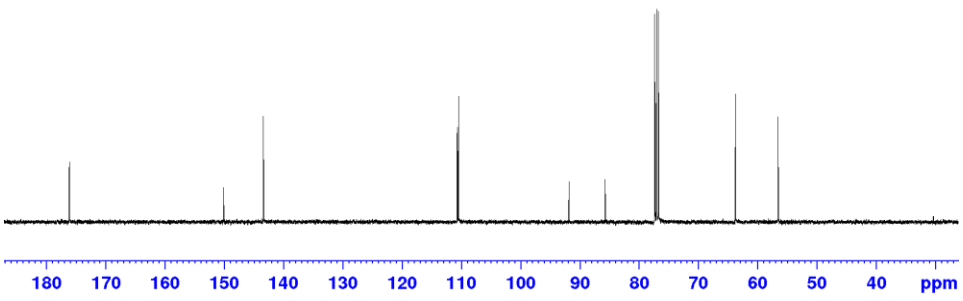
NMR DATA

Diels-Alder starting materials and products

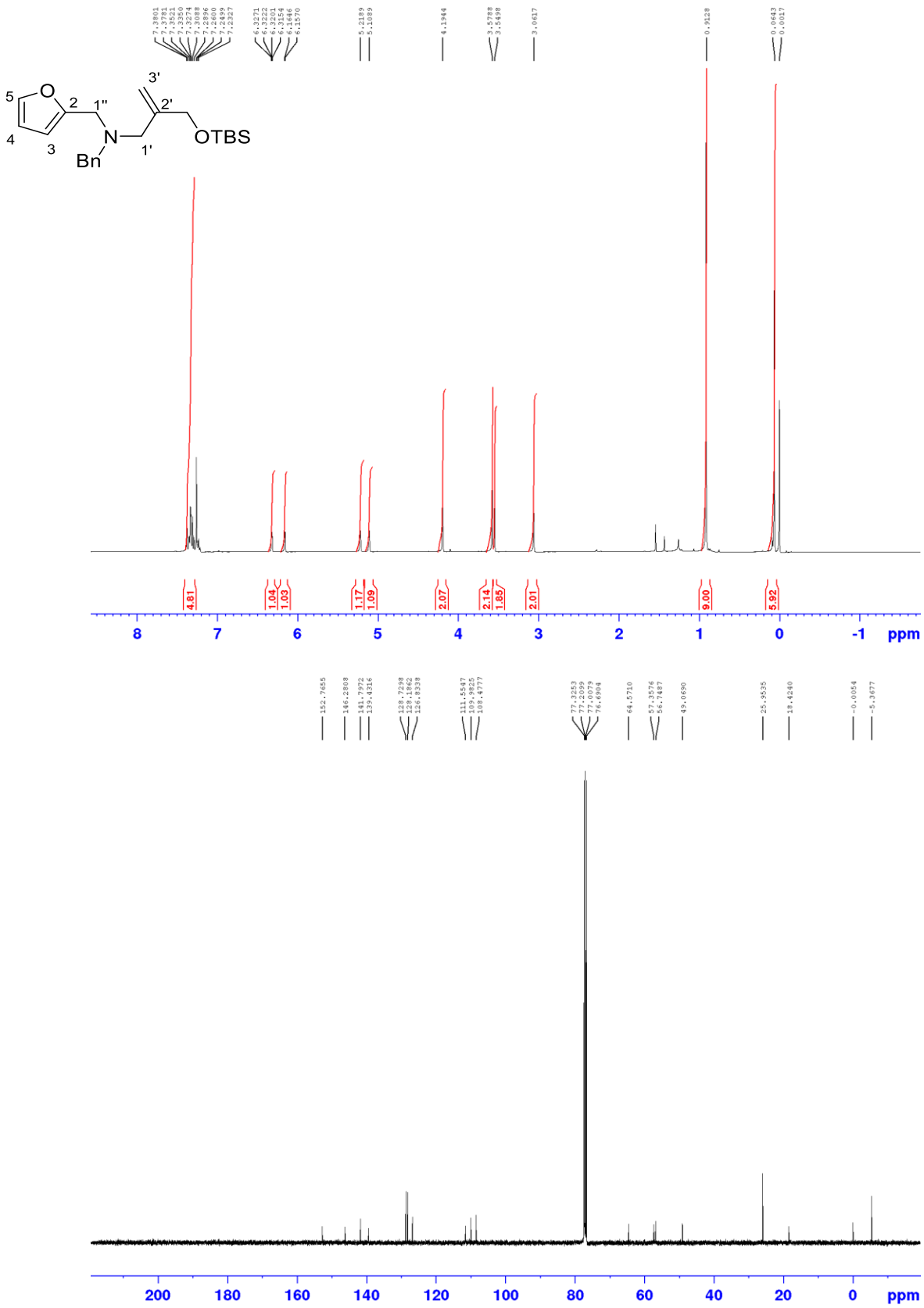
Compound **38**







Compound **44**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7.3521
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7.3274
7.3098
7.2986
7.2600
7.2499
7.2327
6.3271
6.3222
6.3201
6.3154
6.1646
6.1570
5.2199
5.1989
4.1944
3.5788
3.5498
3.0617
0.9128
0.0643
0.0017
O
2
1"
3'
2'
5
4
3
N
1'
OTBS
Bn
4.81
1.04
1.03
1.17
1.09
2.07
2.14
1.85
2.01
9.00
5.92
8
7
6
5
4
3
2
1
0
-1
ppm
152.7655
146.2808
141.7972
139.4316
128.7298
128.1862
126.8338
111.5547
109.9925
108.4977
77.3253
77.2099
77.0945
76.8904
64.5710
57.3576
56.7487
49.0690
25.9535
18.4240
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160
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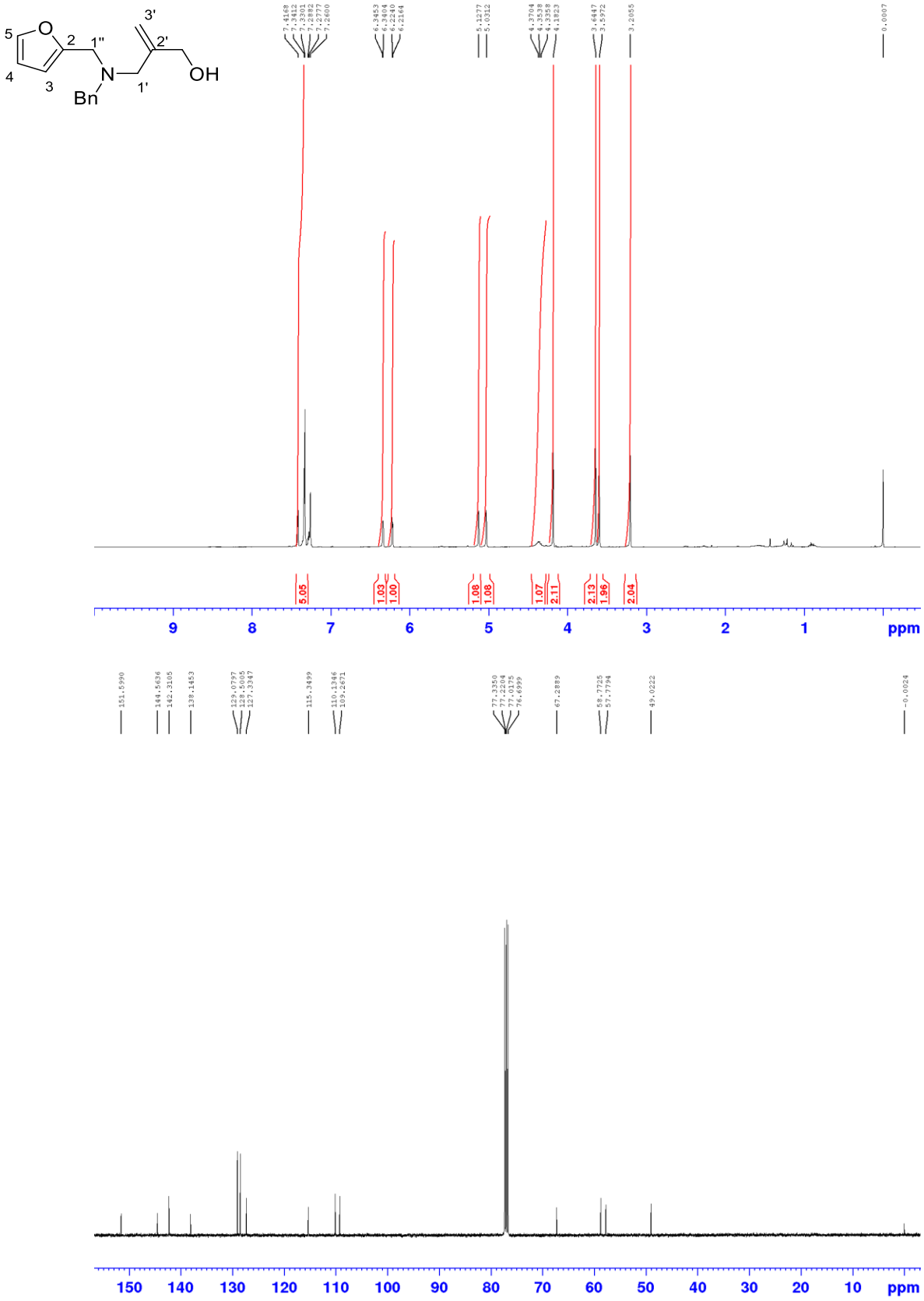
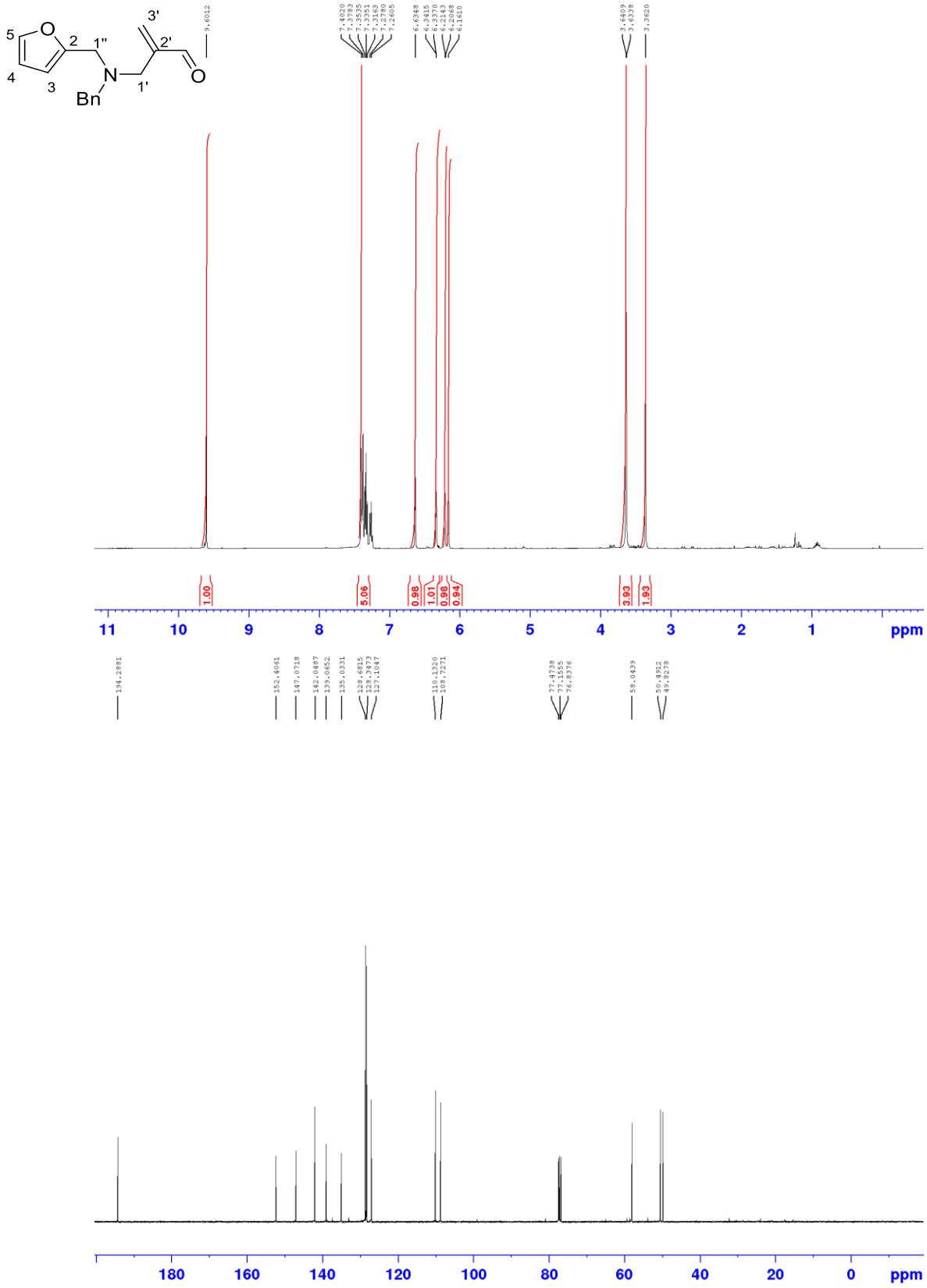
120
100
80
60
40
20
0
ppm

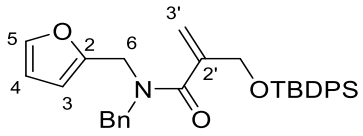
Compound **45**

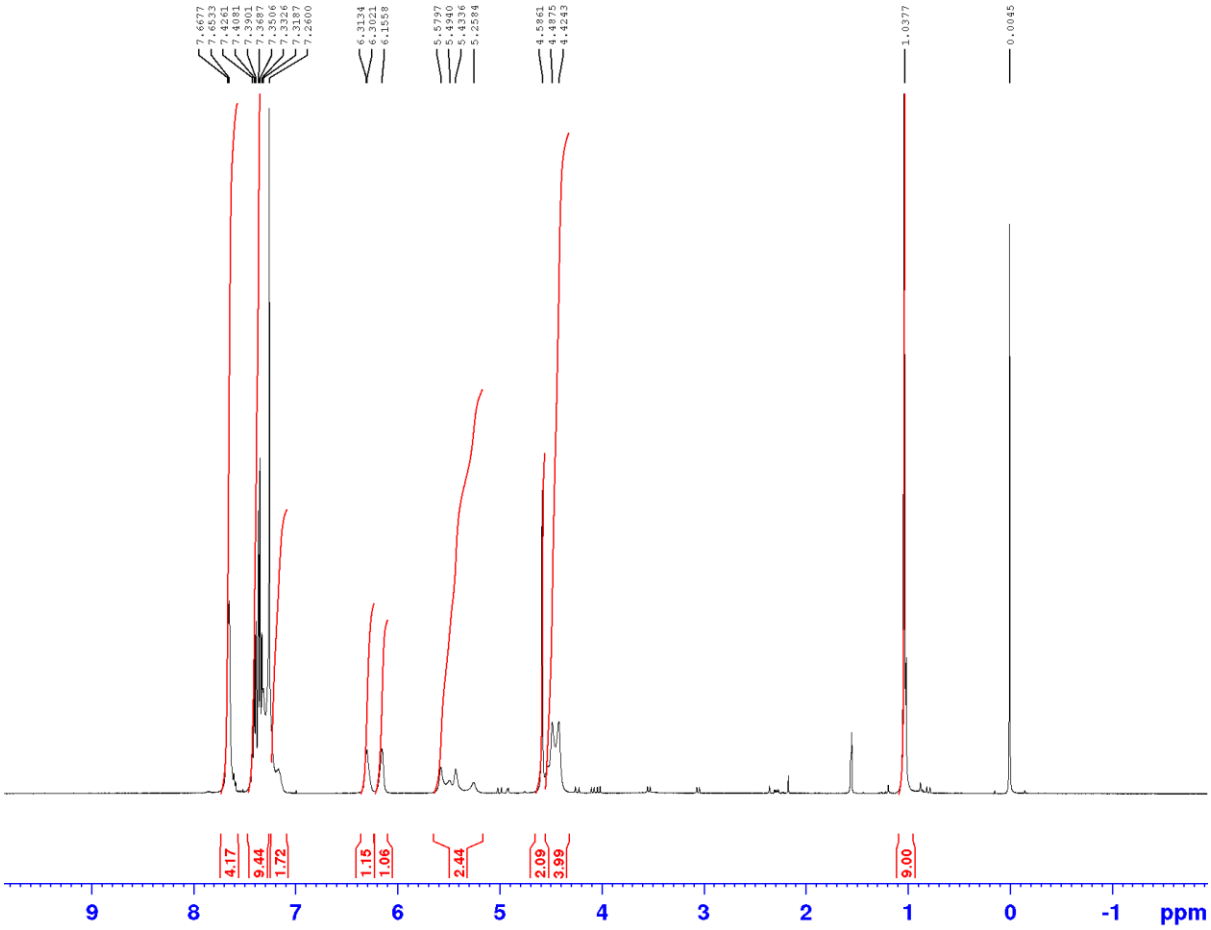


Compound **46**

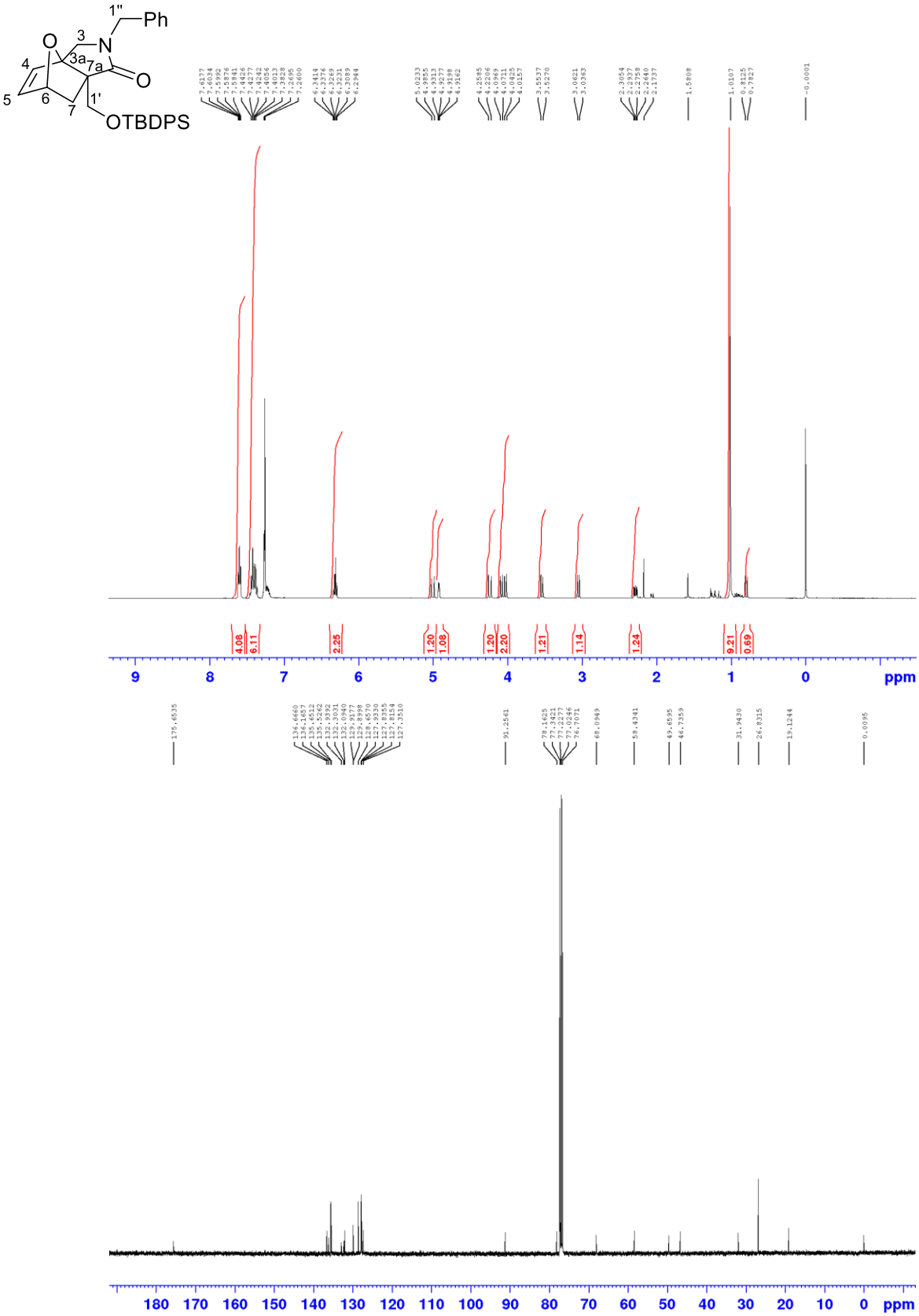

O
5
2
1"
3'
2'
4
3
N
1'
O
Bn
9.6012
7.4020
7.3789
7.3535
7.3351
7.3183
7.2790
7.2605
6.6348
6.3415
6.3370
6.2143
6.2088
6.1650
3.6409
3.6338
3.3620
1.00
5.06
0.98
1.01
0.98
0.94
3.93
1.93
11
10
9
8
7
6
5
4
3
2
1
ppm
194.2881
152.4061
147.0718
142.0487
139.0652
135.0331
128.6815
128.3473
127.1047
110.1320
108.7271
77.4738
77.1555
76.8376
58.0439
50.4912
49.2278
180
160
140
120
100
80
60
40
20
0
ppm

Compound **51**

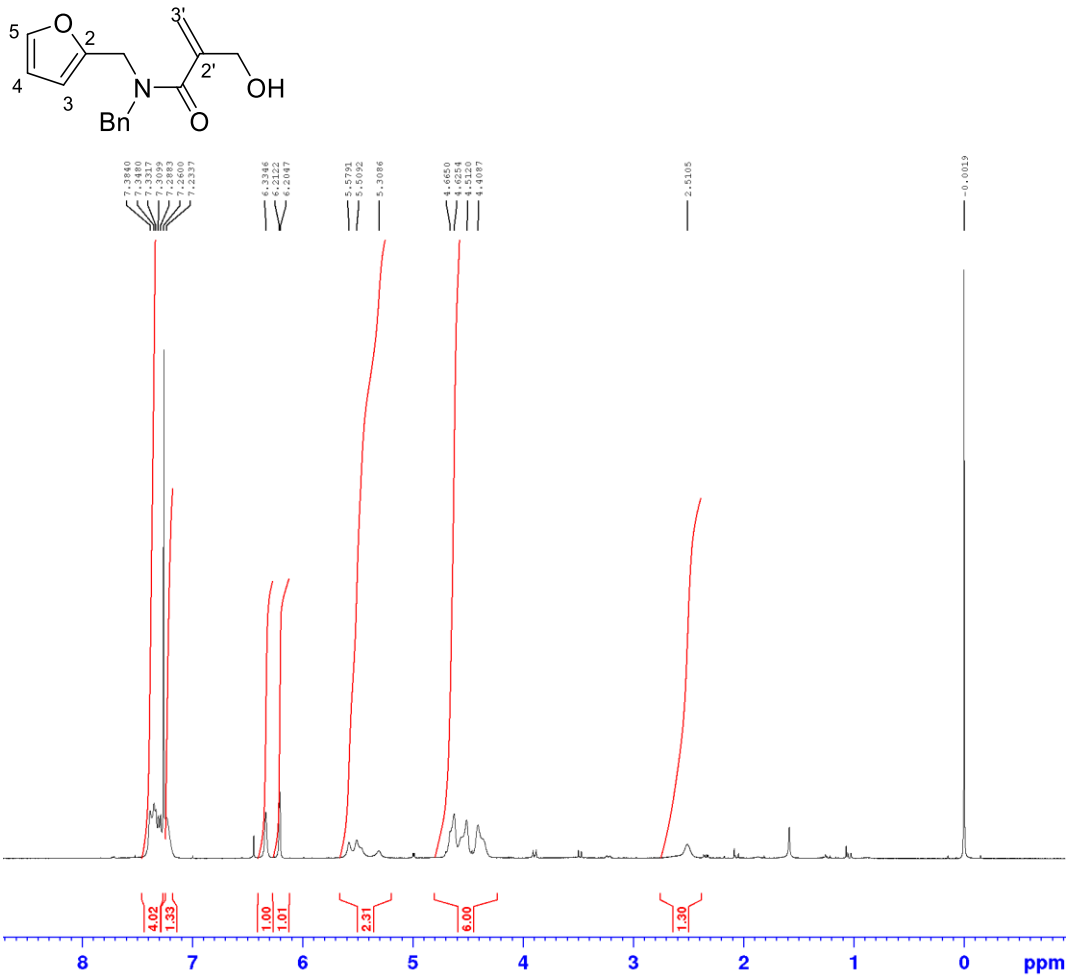

3'
5
O
2
6
2'
4
N
OTBDPS
3
Bn
O


7.6677
7.6533
7.4661
7.4481
7.3901
7.3687
7.3506
7.3326
7.3187
7.2600
6.3134
6.3021
6.1558
5.5797
5.4940
5.4336
5.2584
4.5861
4.4875
4.4243
1.0377
0.0045
4.17
9.44
1.72
1.15
1.06
2.44
2.09
3.99
9.00
9
8
7
6
5
4
3
2
1
0
-1
ppm

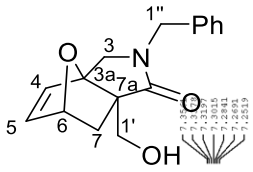
Compound **52**

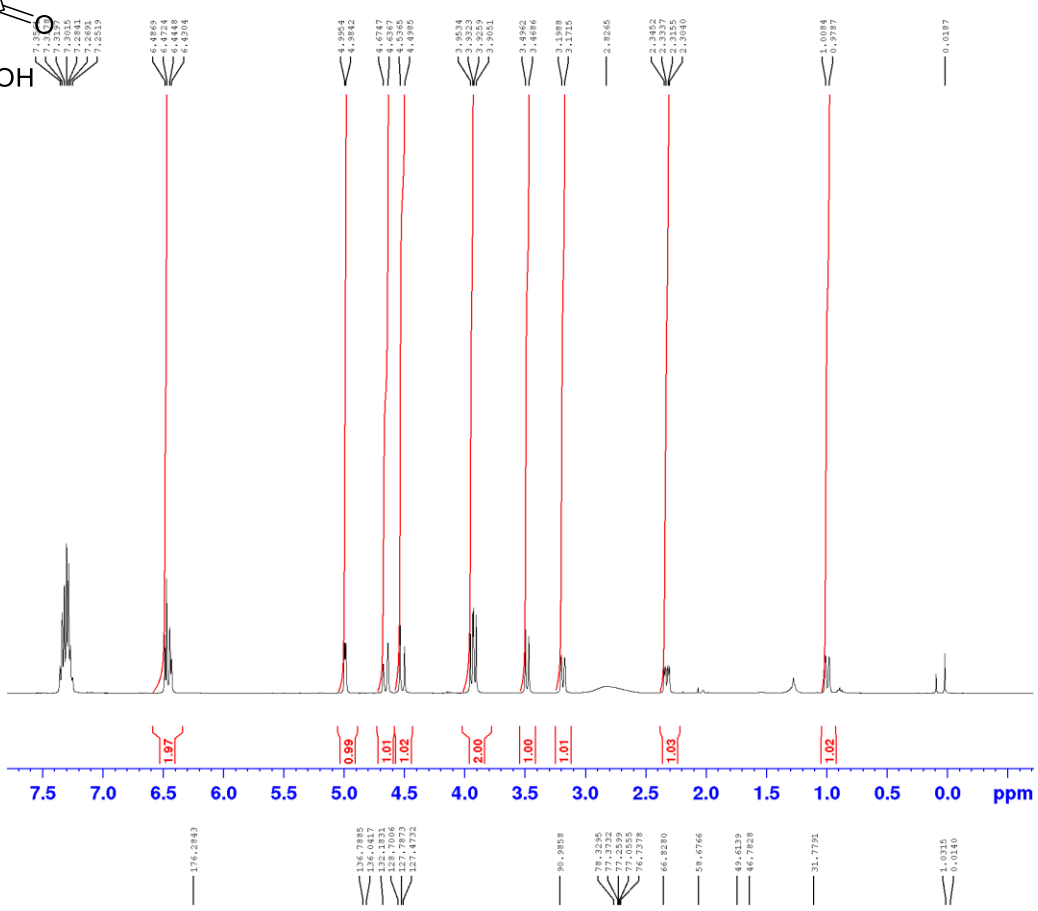


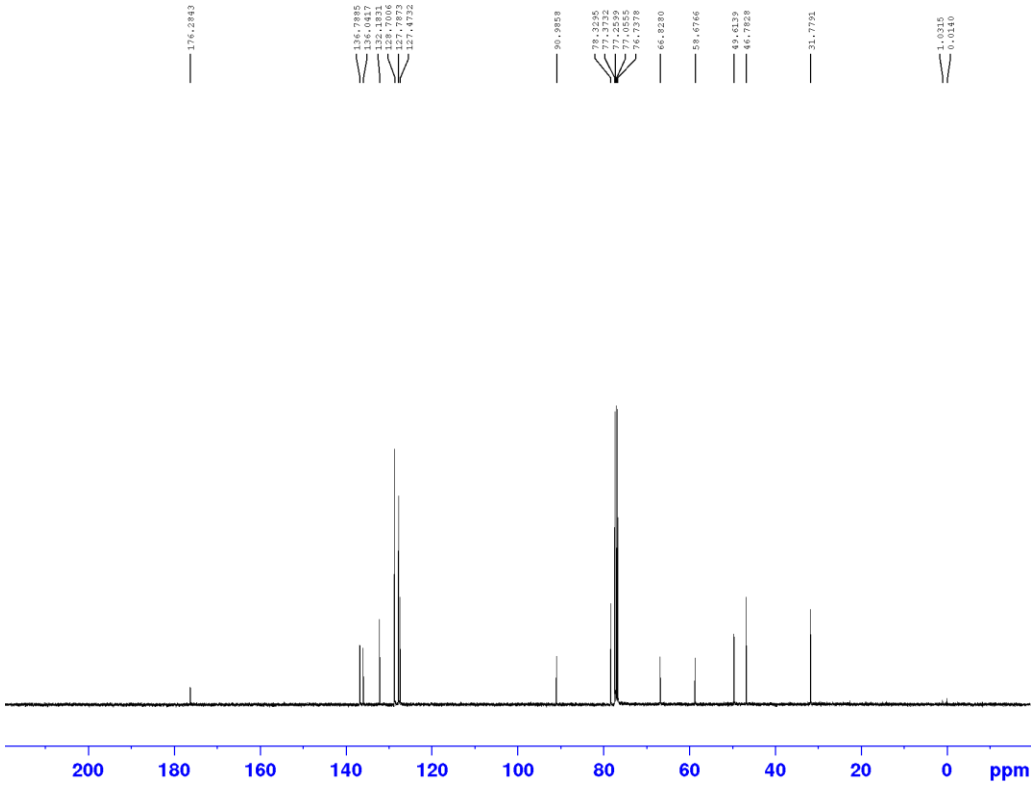
Compound **53**


5
O
2
3'
4
2'
3
N
OH
Bn
O
7.3840
7.3480
7.3317
7.3096
7.2883
7.2600
7.2337
6.3346
6.2122
6.2047
5.5791
5.5092
5.3086
4.6650
4.6254
4.5970
4.4087
2.5105
-0.0019
4.02
1.33
1.00
1.01
2.31
6.00
1.30
8
7
6
5
4
3
2
1
0
ppm

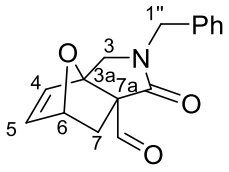
Compound **54**

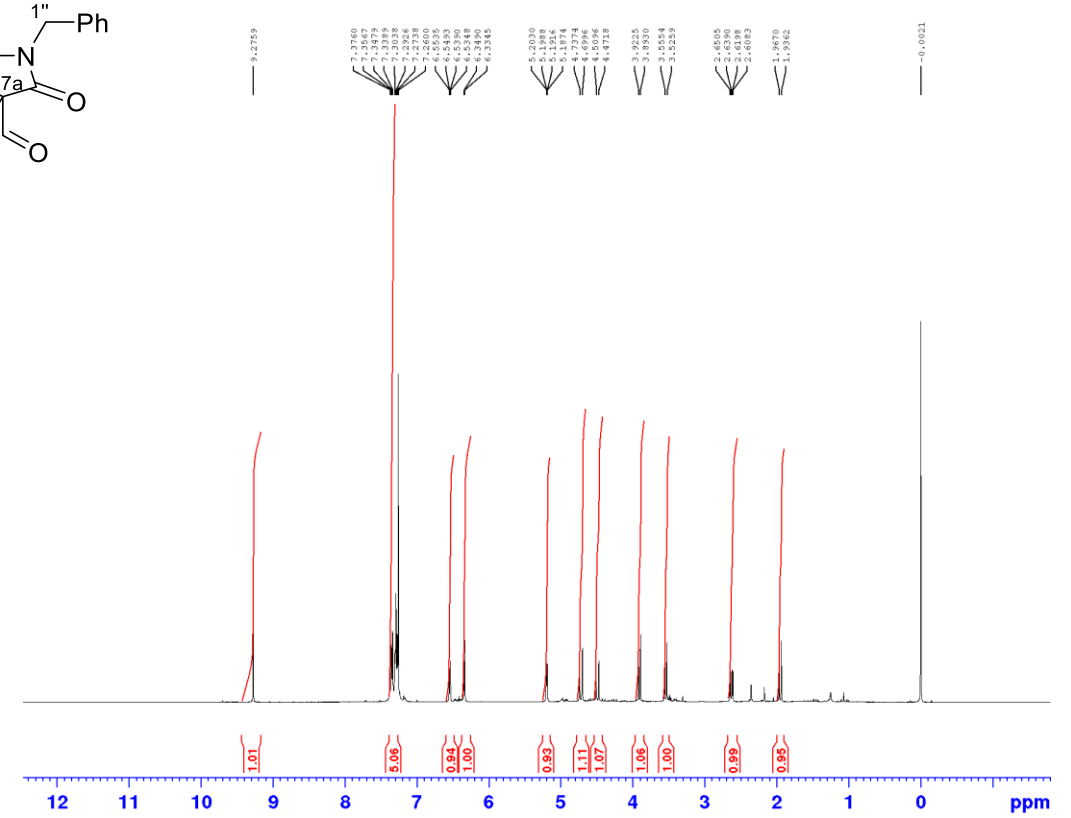

1"
Ph
3
N
O
3a
7a
4
O
5
6
7
1'
OH

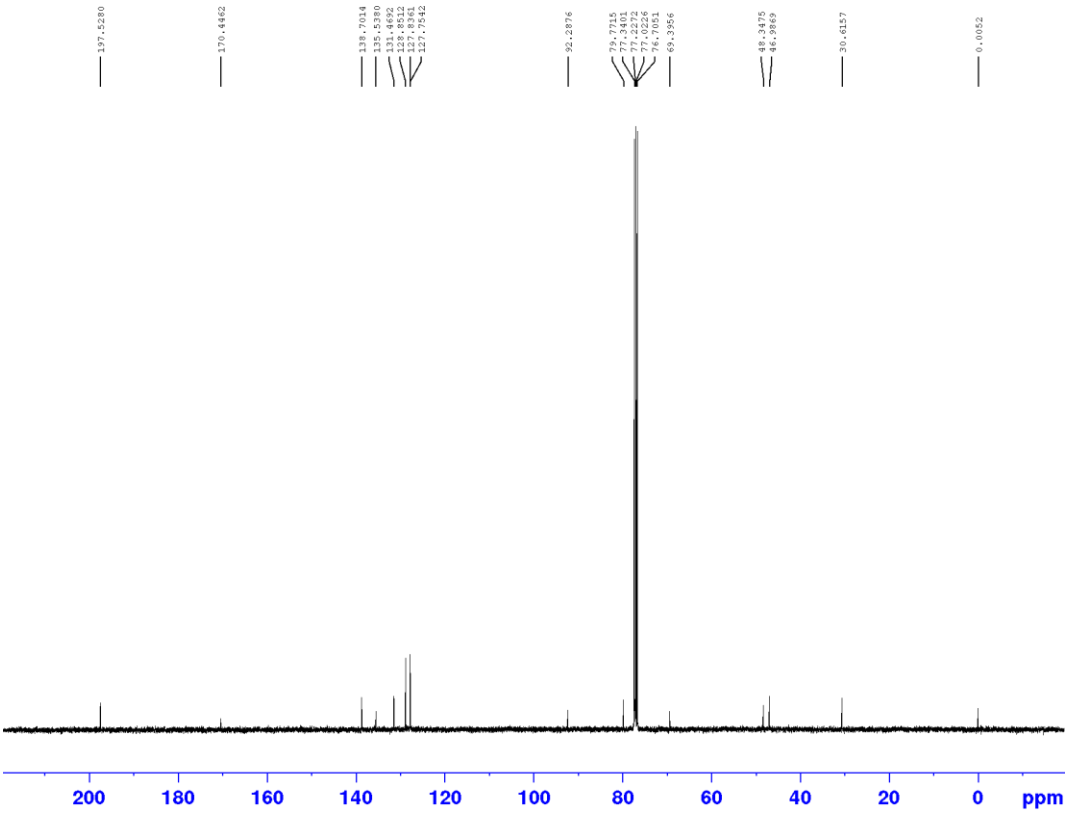

6.4869
6.4724
6.4448
6.4304
4.9964
4.9842
4.6747
4.6586
4.6385
4.4985
3.9534
3.9323
3.9259
3.9051
3.4962
3.4686
3.1988
3.1715
2.8265
2.3452
2.3337
2.3115
2.1040
1.0084
0.9787
0.0187
1.97
0.99
1.01
1.02
2.00
1.00
1.01
1.03
1.02
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm


176.2843
136.7885
136.0417
132.1831
129.7906
127.7872
127.4732
90.9858
78.3295
77.3732
77.2599
77.0465
76.7378
66.8280
58.6766
49.6139
46.7828
31.7791
1.0315
0.0140
200
180
160
140
120
100
80
60
40
20
0
ppm

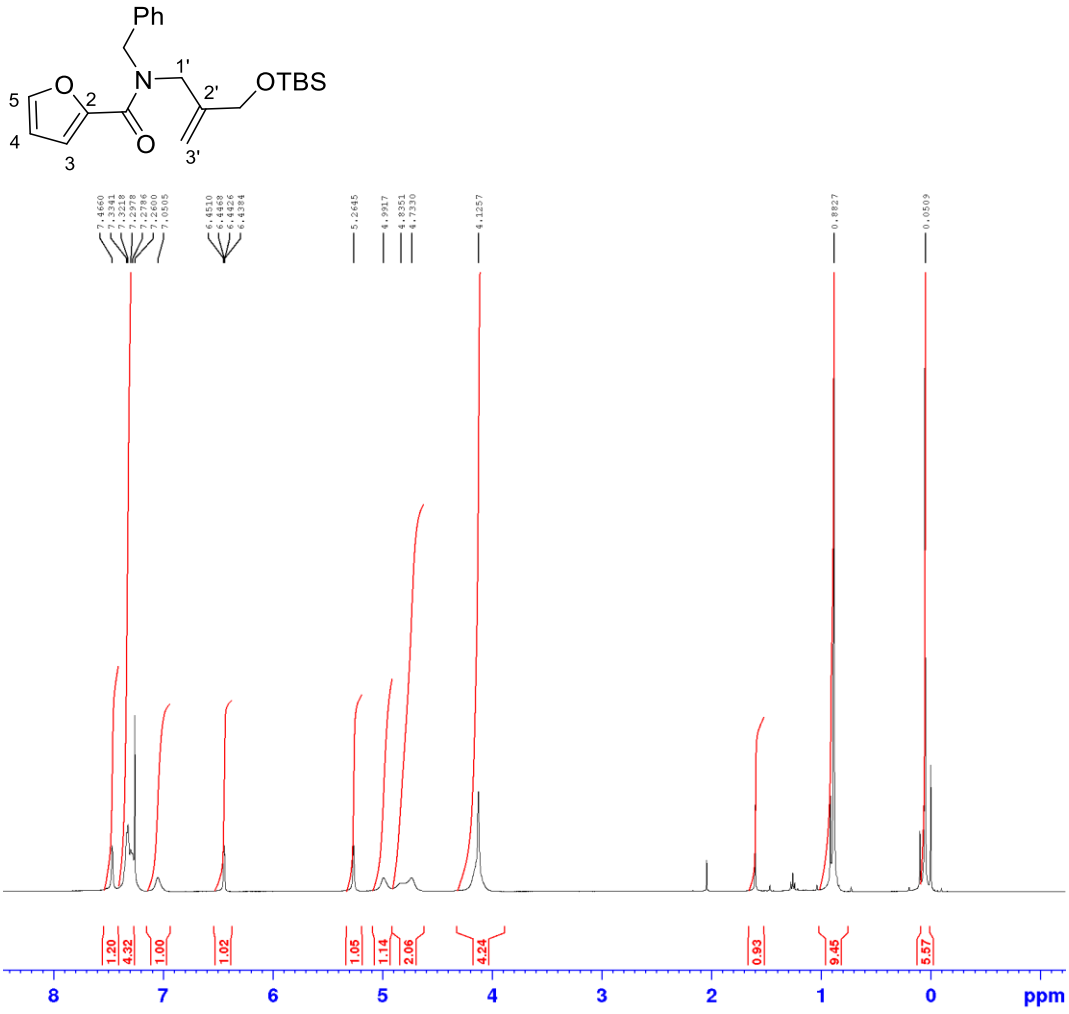
Compound **56**


1"
Ph
3
N
O
4
3a
7a
O
5
6
7
O

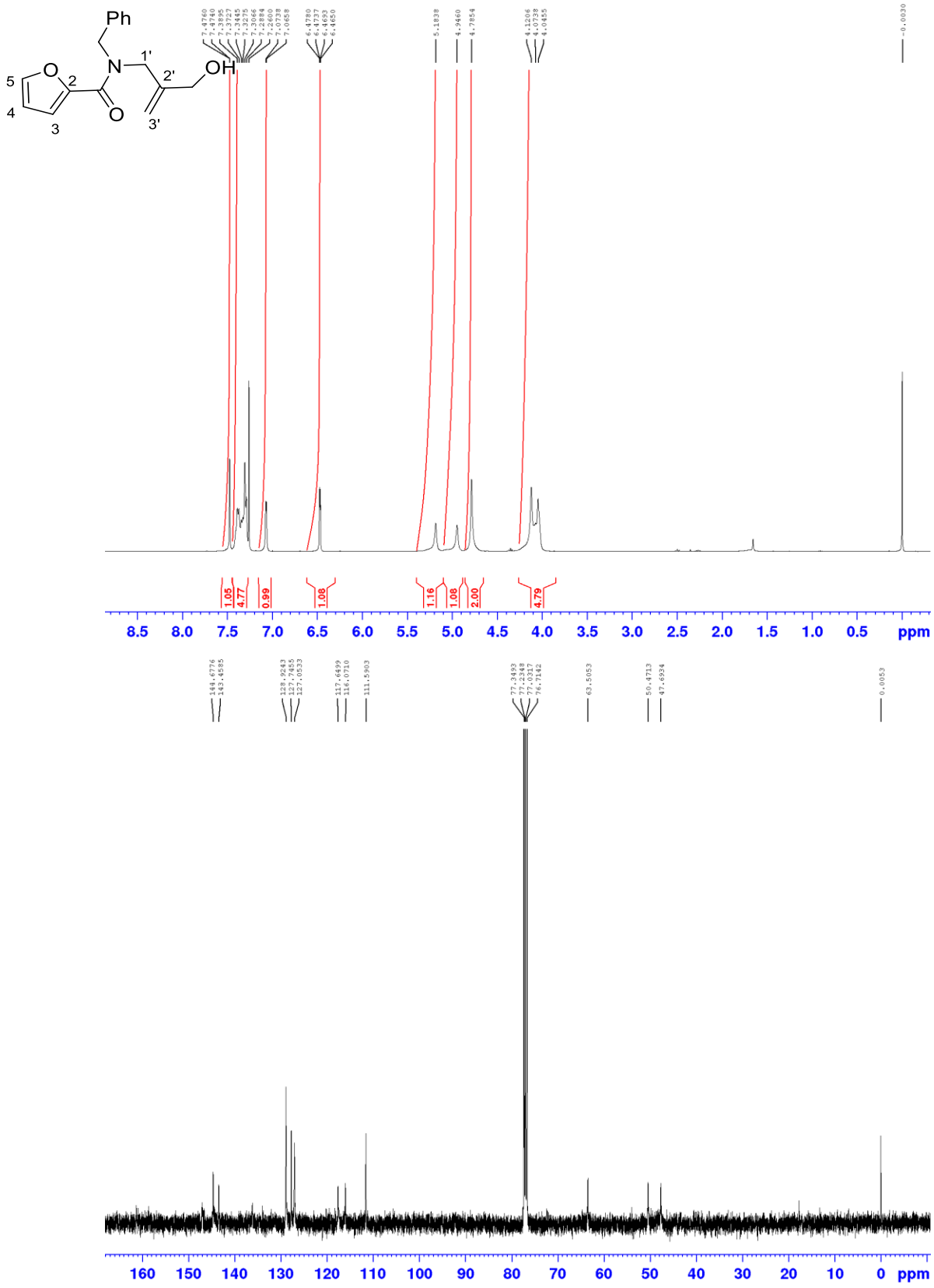

9.2759
7.3760
7.3597
7.3479
7.3389
7.3038
7.2936
7.2738
7.2600
6.5435
6.5303
6.5390
6.5348
6.4240
6.3345
5.2030
5.1988
5.1916
5.1874
4.6974
4.6996
4.5096
4.4718
3.9225
3.8930
3.5584
3.5259
2.6506
2.6390
2.6198
2.6083
1.9670
1.9362
0.0021
1.01
5.06
0.94
1.00
0.93
1.11
1.07
1.06
1.00
0.99
0.95
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


197.5280
170.4462
138.7014
135.6380
134.4662
128.8512
127.8361
127.7542
92.2876
79.7715
77.3401
77.2272
77.0226
76.7051
69.3956
48.3475
46.0869
30.6157
0.0052
200
180
160
140
120
100
80
60
40
20
0
ppm

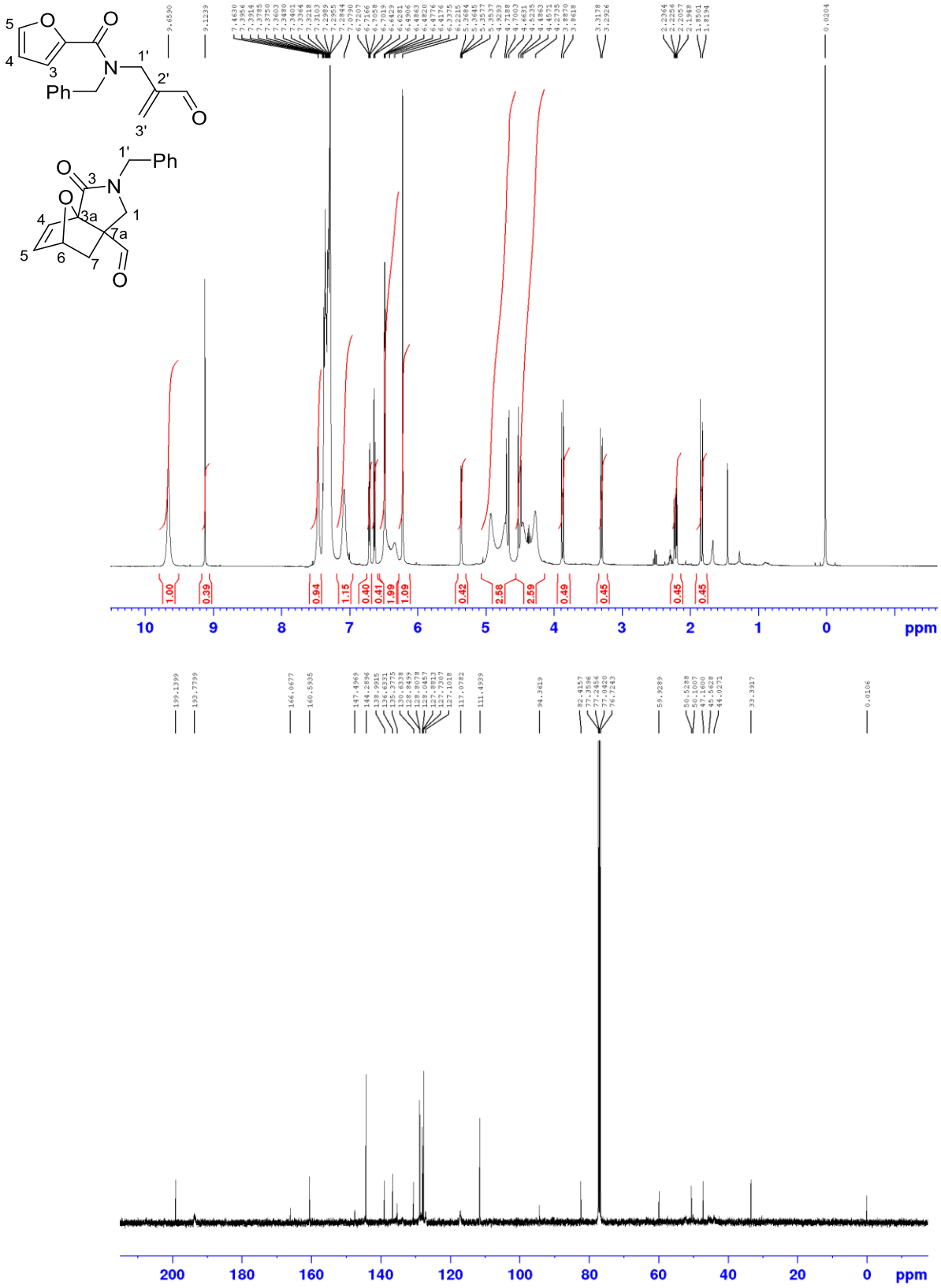
Compound **58**


Ph
N
1'
2'
OTBS
O
2
5
4
3
O
3'
7.4660
7.3341
7.3218
7.2978
7.2788
7.2600
7.0505
6.4510
6.4488
6.4326
6.4304
5.2645
4.9917
4.8351
4.7330
4.1257
0.8827
0.0509
1.20
4.32
1.00
1.02
1.05
1.14
2.06
4.24
0.93
9.45
5.57
8
7
6
5
4
3
2
1
0
ppm

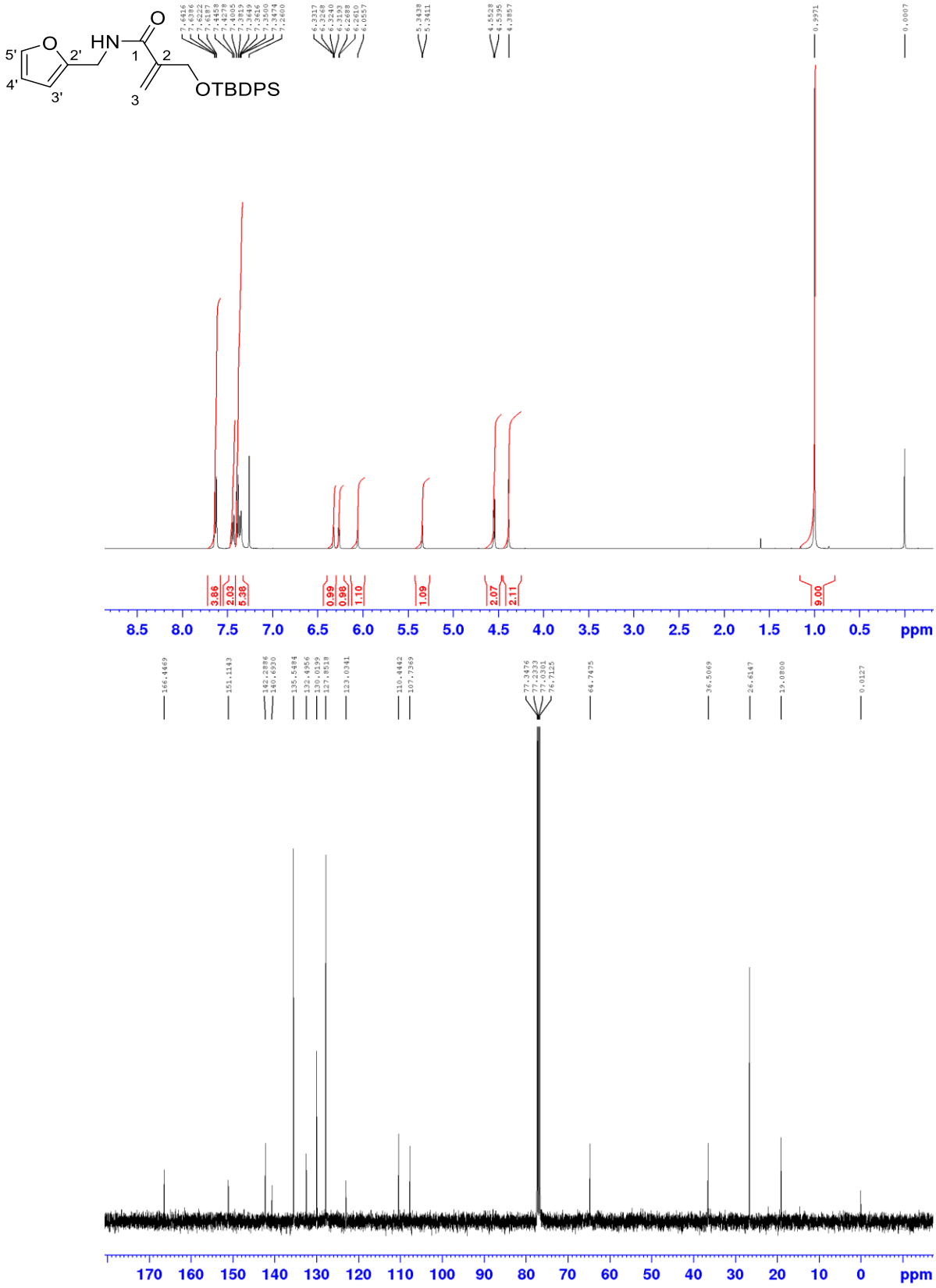
Compound **59**


Ph
N
1'
2'
OH
O
2
5
4
3
O
3'
7.4760
7.4740
7.3855
7.3727
7.3445
7.3275
7.3066
7.2884
7.2600
7.0738
7.0658
6.4780
6.4737
6.4693
6.4650
5.1838
4.9460
4.7854
4.1256
4.0738
4.0455
-0.0030
1.05
4.77
0.99
1.08
1.16
1.08
2.00
4.79
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
144.6776
143.4585
128.9243
127.7455
127.0533
117.6439
116.0710
111.5903
77.3493
77.2368
77.0317
76.7142
63.5053
50.4713
47.6934
0.0053
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

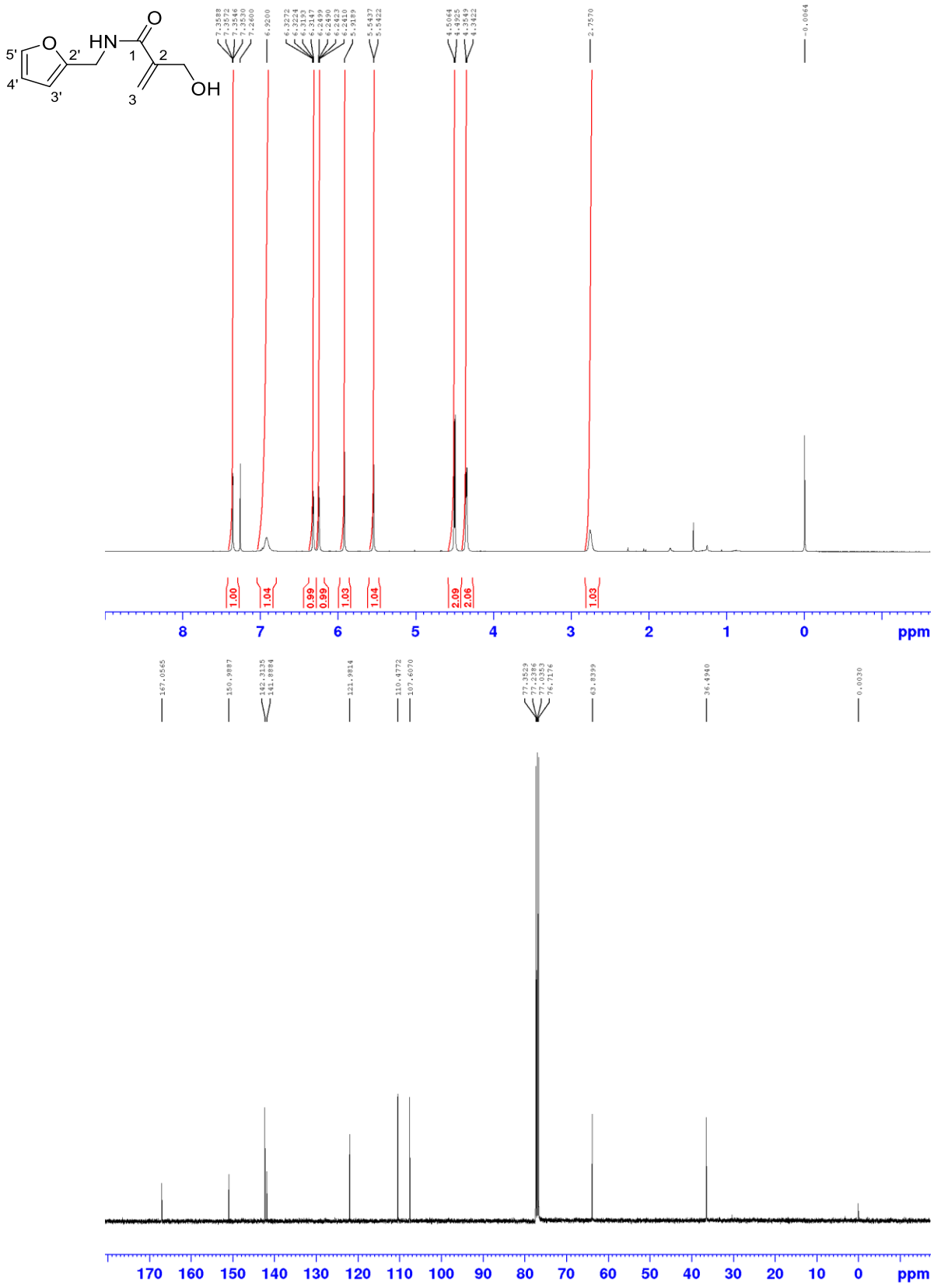
Compounds **60** and **61**



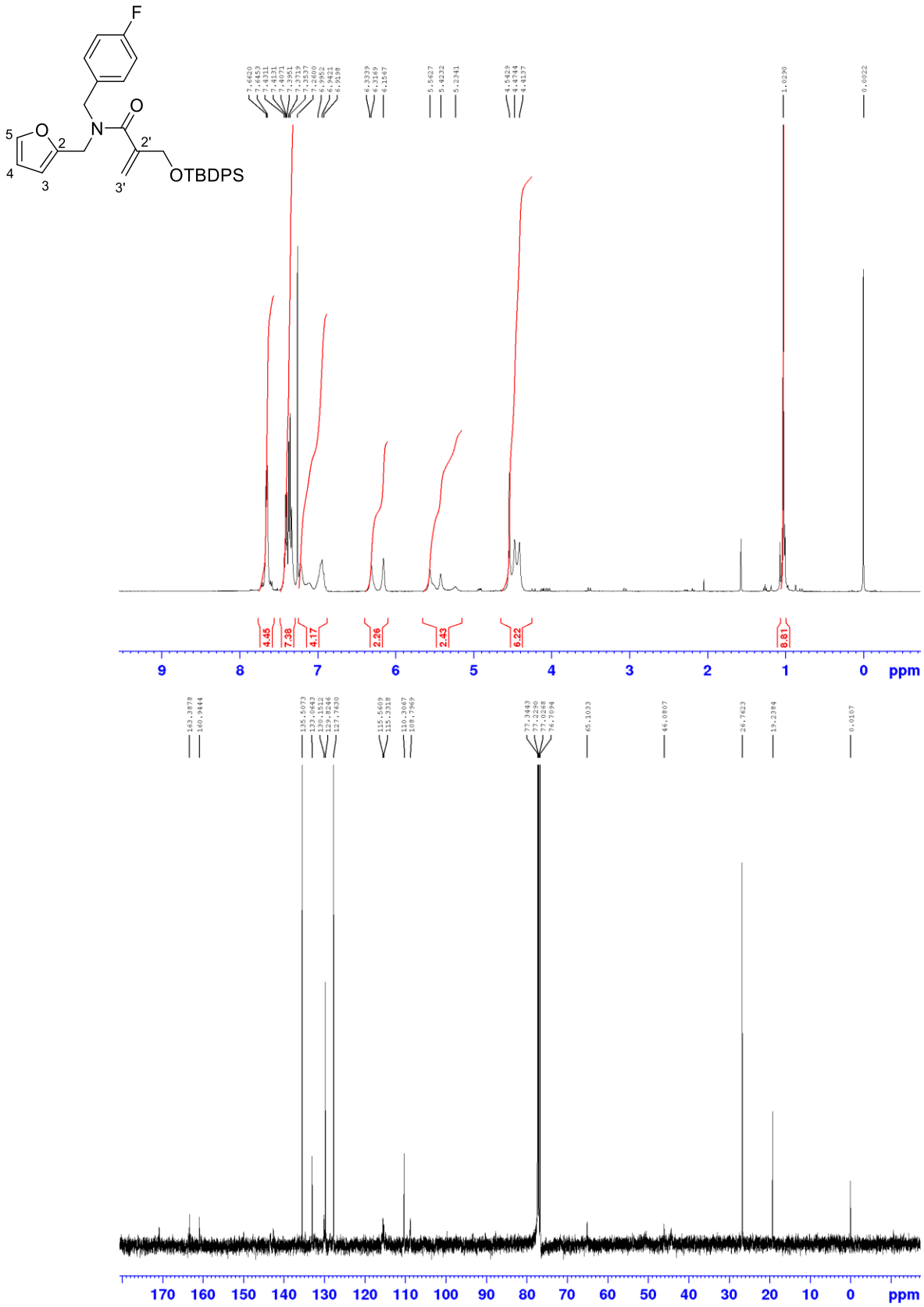
Compound **63**


O
HN
1
2
3
2'
5'
4'
3'
OTBDPS
7.6416
7.6386
7.6222
7.6192
7.4458
7.4278
7.4005
7.3805
7.3649
7.3656
7.3500
7.3478
7.2600
6.3317
6.3268
6.3140
6.3038
6.2888
6.2610
6.0557
5.3438
5.3411
4.5528
4.5396
4.3857
0.9971
0.0007
3.86
2.03
5.38
0.99
0.98
1.10
1.09
2.07
2.11
9.00
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
166.4469
151.1143
140.2886
140.6930
135.5484
132.4956
130.0199
127.8518
123.0341
110.4442
107.7369
77.3476
77.2323
77.0301
76.7125
64.7475
36.5069
26.6147
19.0800
0.0127
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

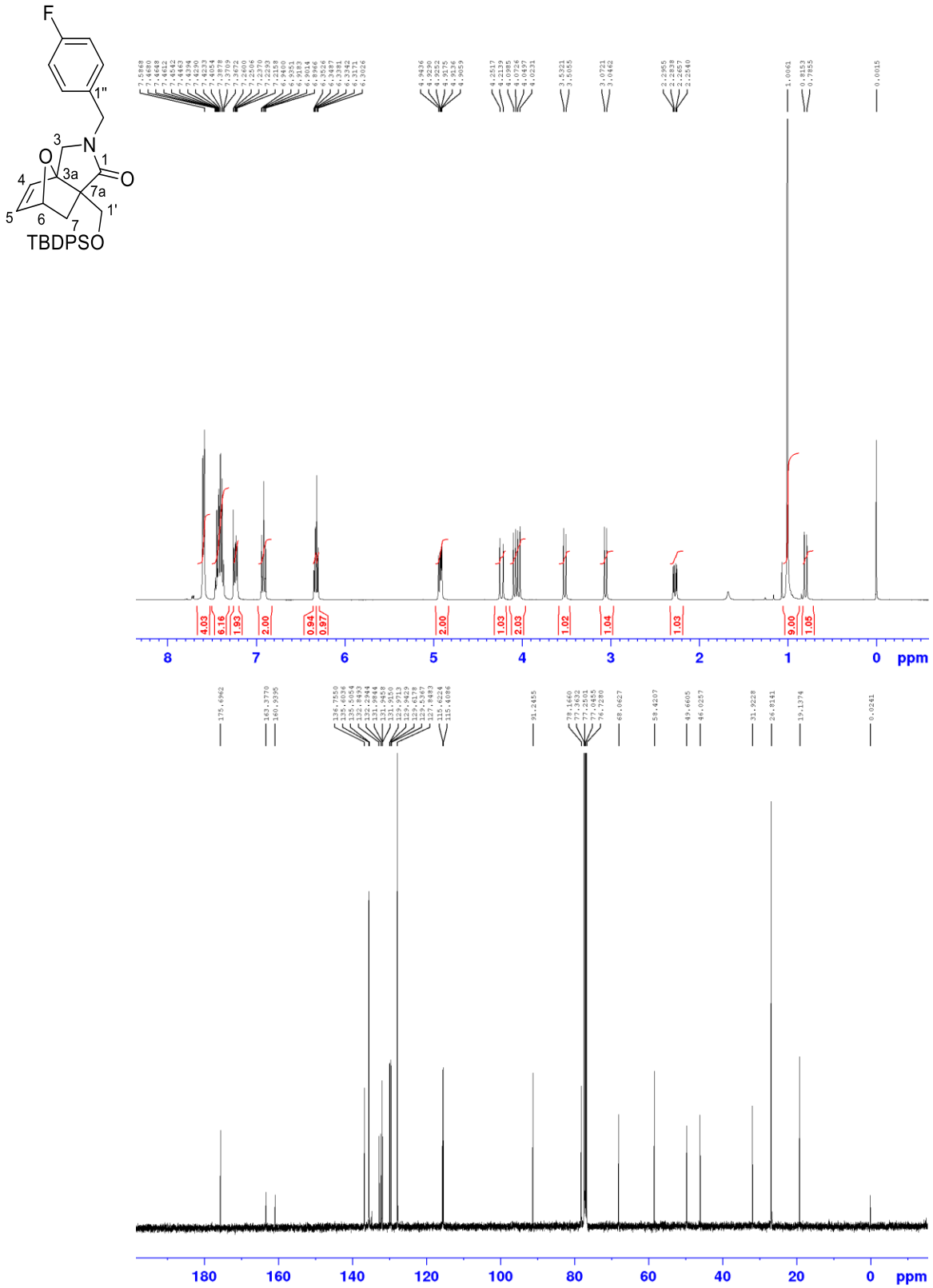
Compound **64**


O
HN
1
2
OH
3
2'
5'
4'
3'
7.3588
7.3572
7.3546
7.3530
7.2600
6.9200
6.3272
6.3224
6.3193
6.3147
6.2499
6.2460
6.2423
6.2410
5.9189
5.5437
5.5422
4.5064
4.4925
4.3549
4.3422
2.7570
0.0064
1.00
1.04
0.99
0.99
1.03
1.04
2.09
2.06
1.03
8
7
6
5
4
3
2
1
0
ppm
167.0565
150.9887
142.3135
141.8894
121.9814
110.4772
107.6070
77.3539
77.2386
77.0353
76.7176
63.8399
36.4940
0.0030
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

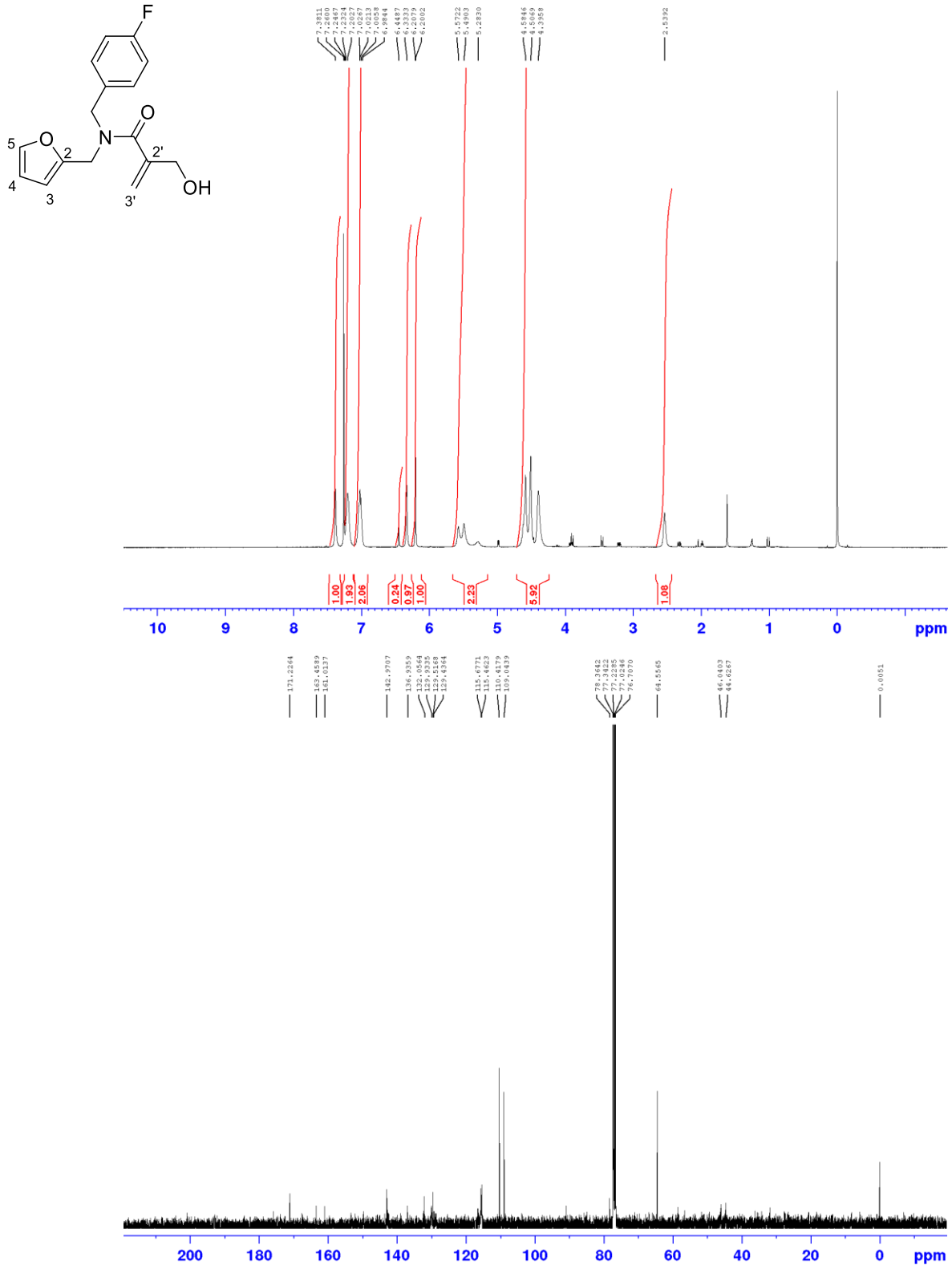
Compound **67**


F
O
N
O
5
O
2
2'
4
3
3'
OTBDPS
7.6620
7.6453
7.4311
7.4131
7.4071
7.3961
7.3739
7.3537
7.2600
6.9952
6.9821
6.9198
6.3339
6.3169
6.1167
5.5627
5.4232
5.2341
4.6409
4.4744
4.4137
1.0290
0.0022
4.45
7.38
4.17
2.26
2.43
6.22
8.81
9 8 7 6 5 4 3 2 1 0 ppm
163.3878
160.9444
135.5073
133.0643
130.1152
129.8246
127.7630
115.5609
115.3338
110.3067
108.7969
77.3443
77.2230
77.0268
76.7094
65.1033
46.0807
26.7623
19.2384
0.0107
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

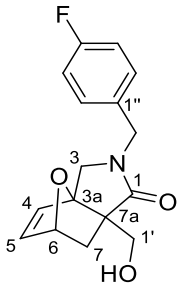
Compound **68**

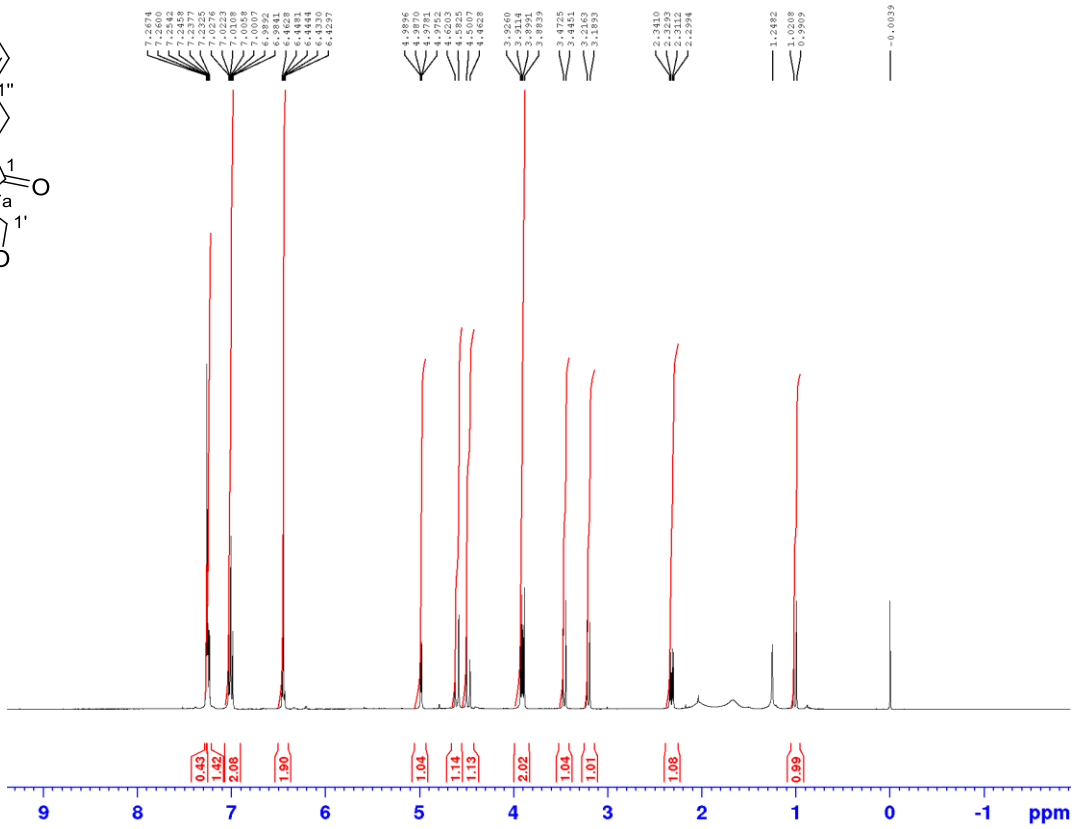


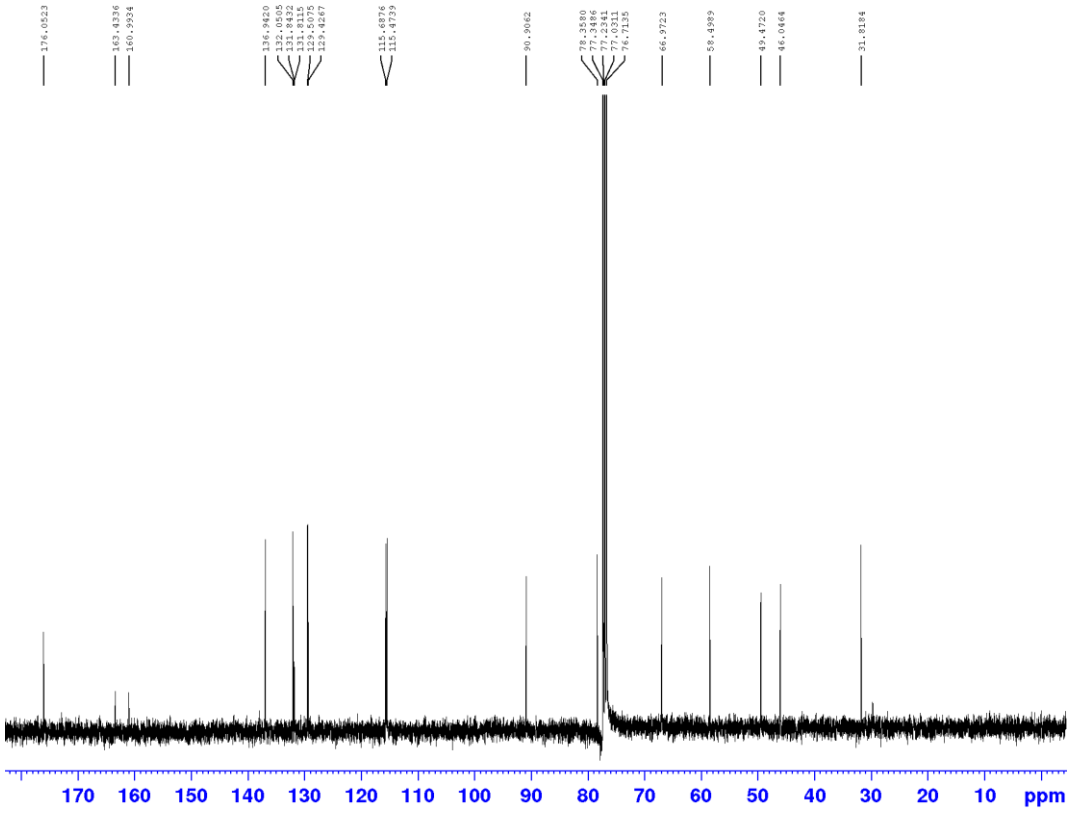
Compound **69**


F
O
N
O
5
O
2
2'
4
3
3'
OH
7.3911
7.2600
7.2467
7.2324
7.2202
7.0267
7.0213
7.0058
7.0004
6.4497
6.3333
6.2079
6.2002
5.5722
5.4903
5.2830
4.5846
4.5686
4.3958
2.5392
1.00
1.93
2.06
0.24
0.97
1.00
2.23
5.92
1.08
10
9
8
7
6
5
4
3
2
1
0
ppm
171.2264
163.4589
161.0137
142.9707
136.9359
132.0564
129.9335
129.5168
129.4964
115.6771
115.4623
110.4179
109.0439
78.3642
77.3422
77.2285
77.0848
76.7070
64.5565
46.0403
44.6267
0.0051
200
180
160
140
120
100
80
60
40
20
0
ppm

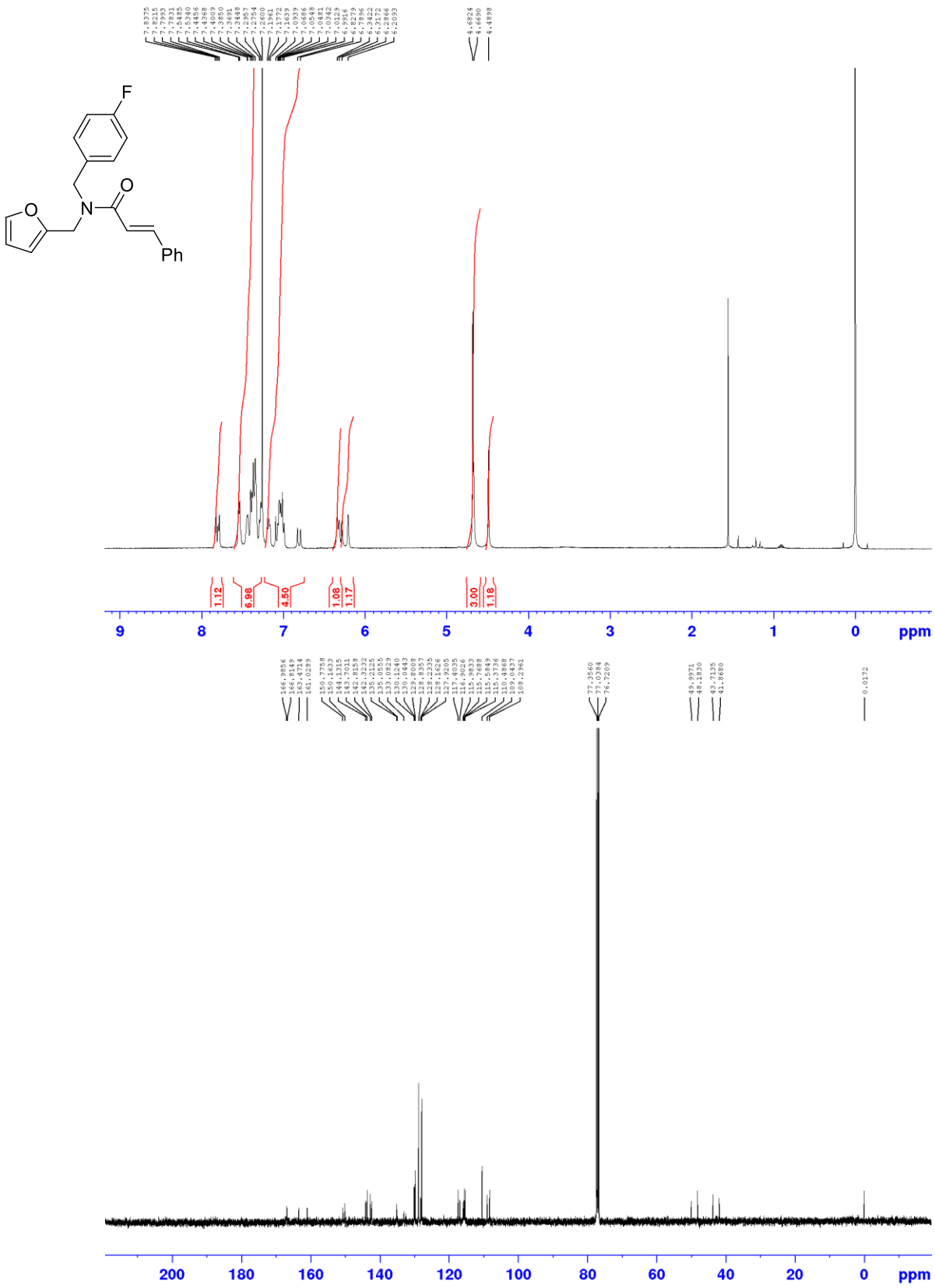
Compound **70**


F
1''
3
N
1
O
O
4
3a
7a
1'
5
6
7
HO

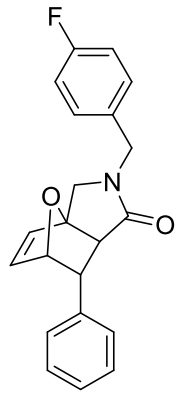

7.2674
7.2600
7.2458
7.2377
7.2325
7.2226
7.0223
7.0108
7.0058
7.0007
6.9992
6.9841
6.4628
6.4481
6.4444
6.4330
6.4297
4.9896
4.9870
4.9781
4.9703
4.6210
4.5825
4.5007
4.4628
3.9260
3.9114
3.8991
3.8839
3.4725
3.4451
3.2163
3.1893
2.3410
2.3293
2.3112
2.2994
1.2492
1.0208
0.9909
-0.0039
0.43
1.42
2.06
1.90
1.04
1.14
1.13
2.02
1.04
1.01
1.08
0.99
9
8
7
6
5
4
3
2
1
0
-1
ppm

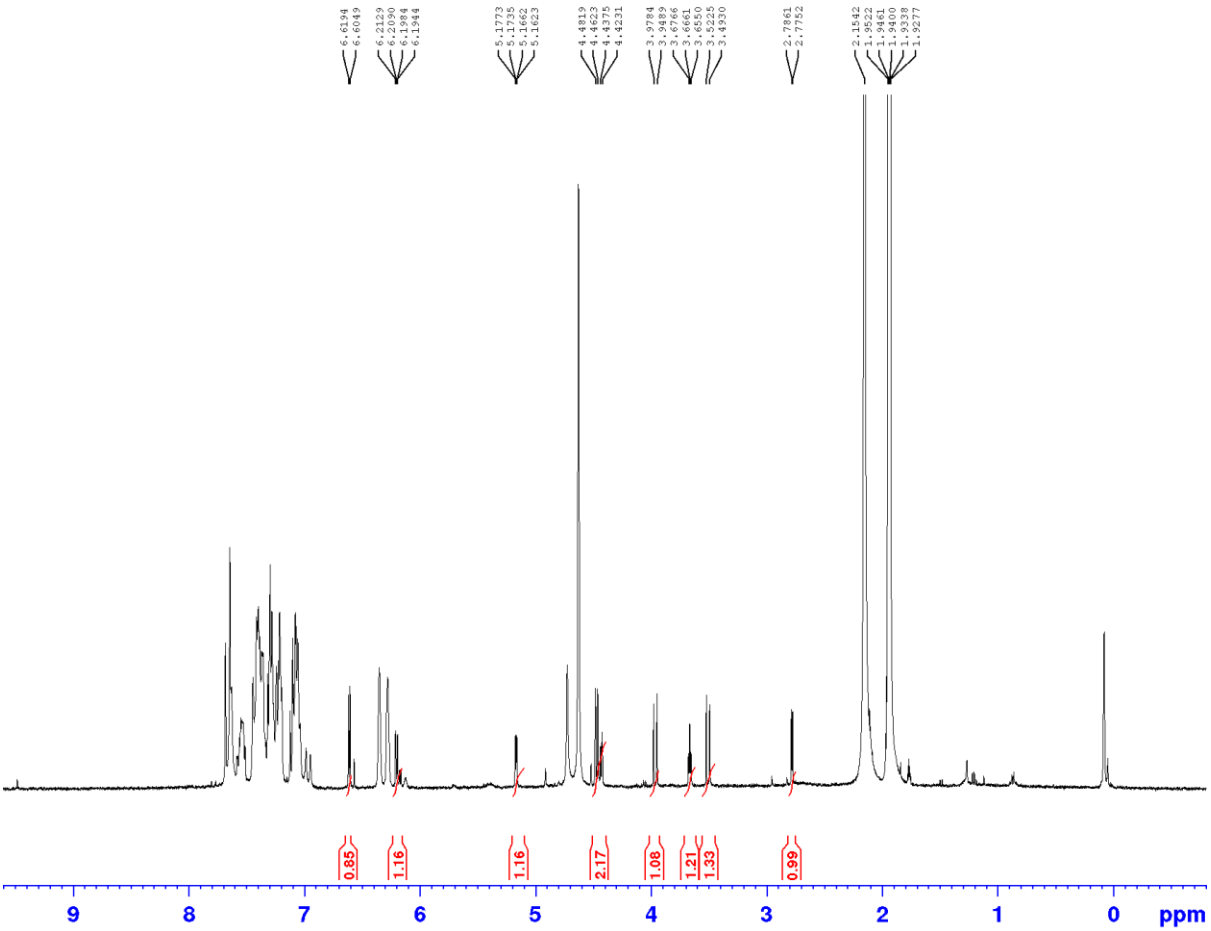

176.0523
163.4336
160.9934
136.9420
132.0565
131.8432
131.8115
129.5075
129.4267
115.6876
115.4739
90.9062
78.3580
77.3486
77.2341
77.0201
76.7135
66.9723
58.4989
49.4720
46.0464
31.8184
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

Compound **71**

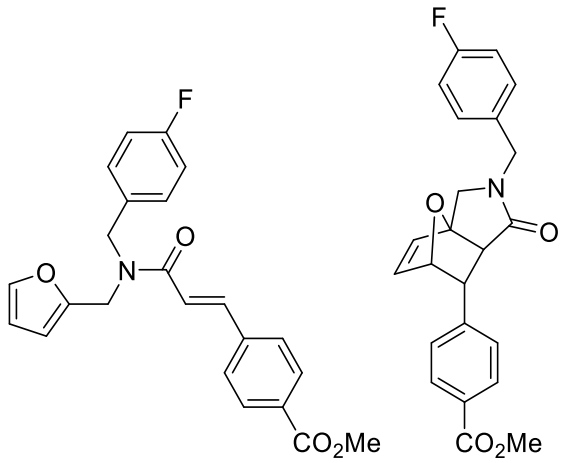

F
O
N
O
Ph
1.12
6.98
4.50
1.08
1.17
3.00
1.18
9
8
7
6
5
4
3
2
1
0
ppm
200
180
160
140
120
100
80
60
40
20
0
ppm

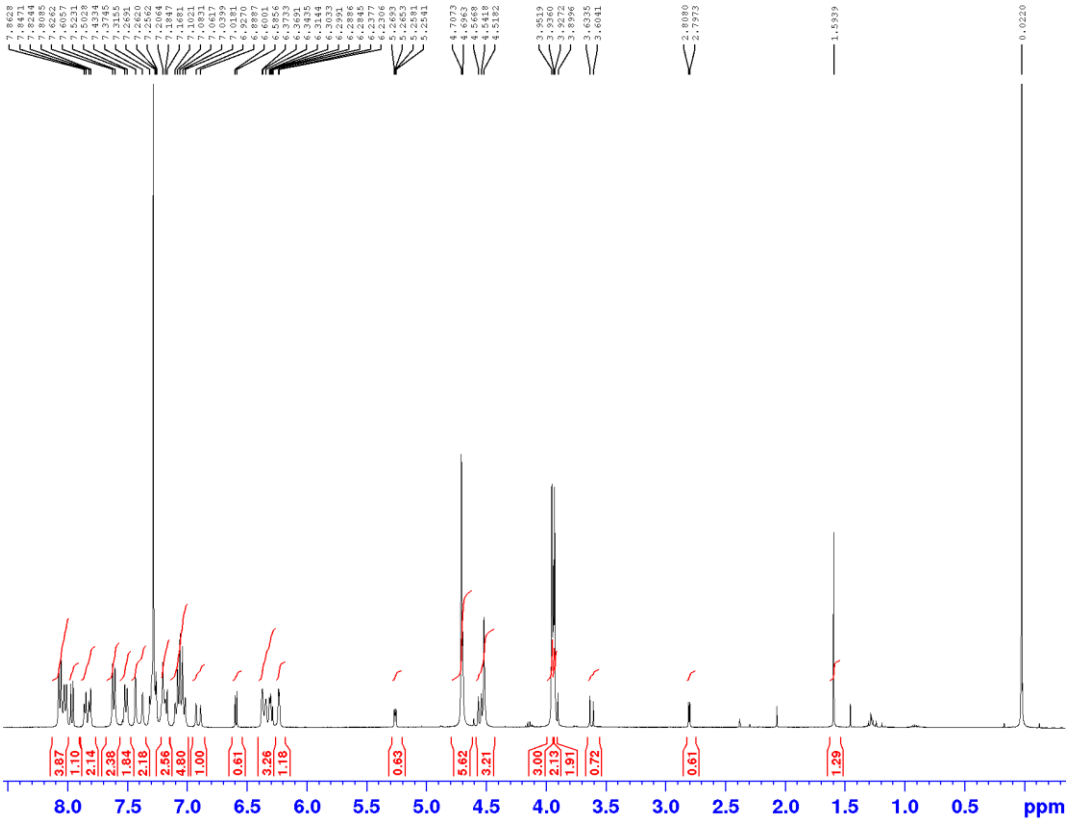
Compound **72** (MeCN-d_3) (+**71**)



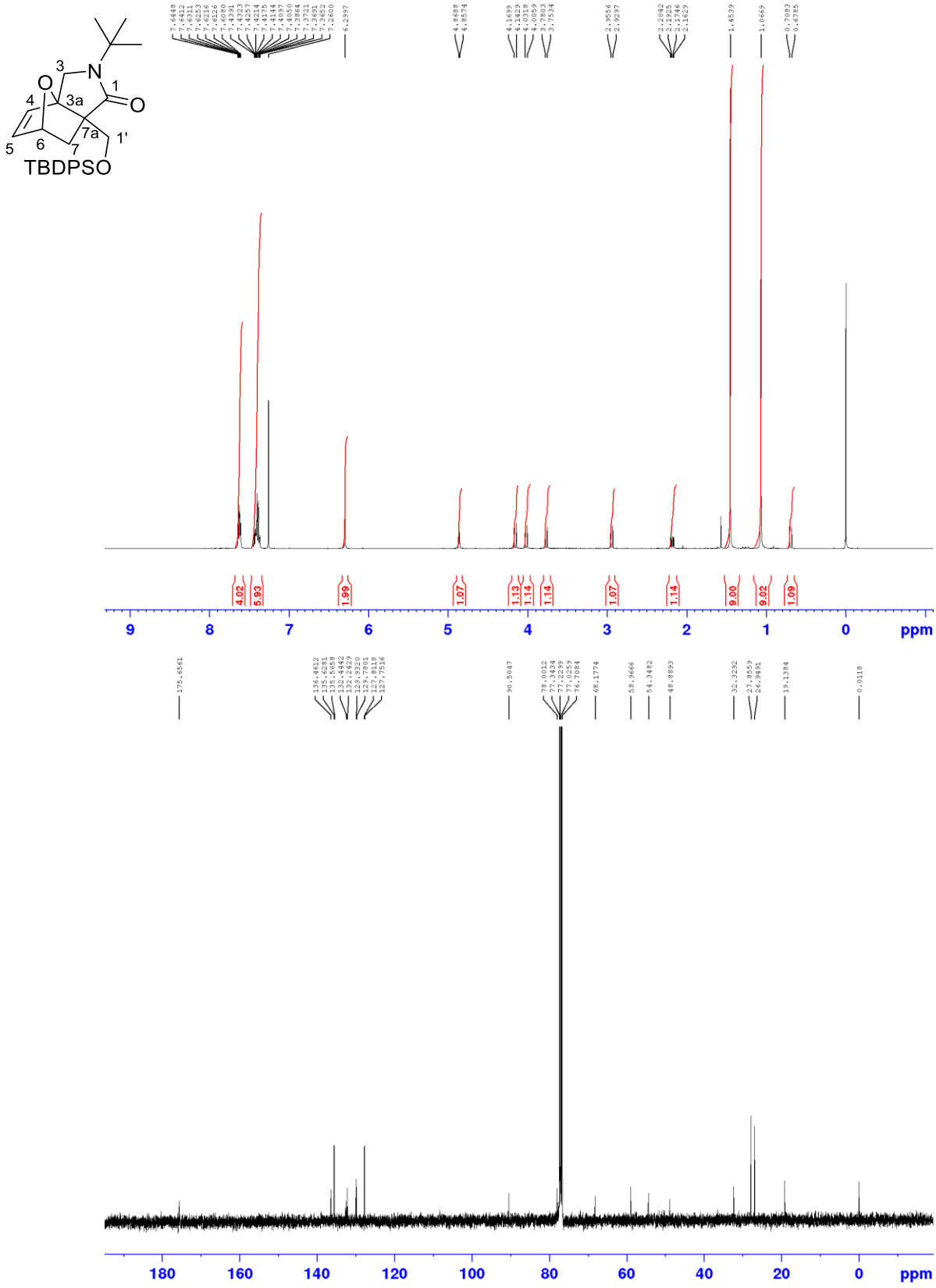


Compunds **73** and **74**

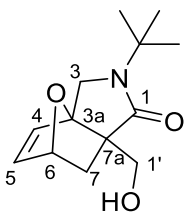


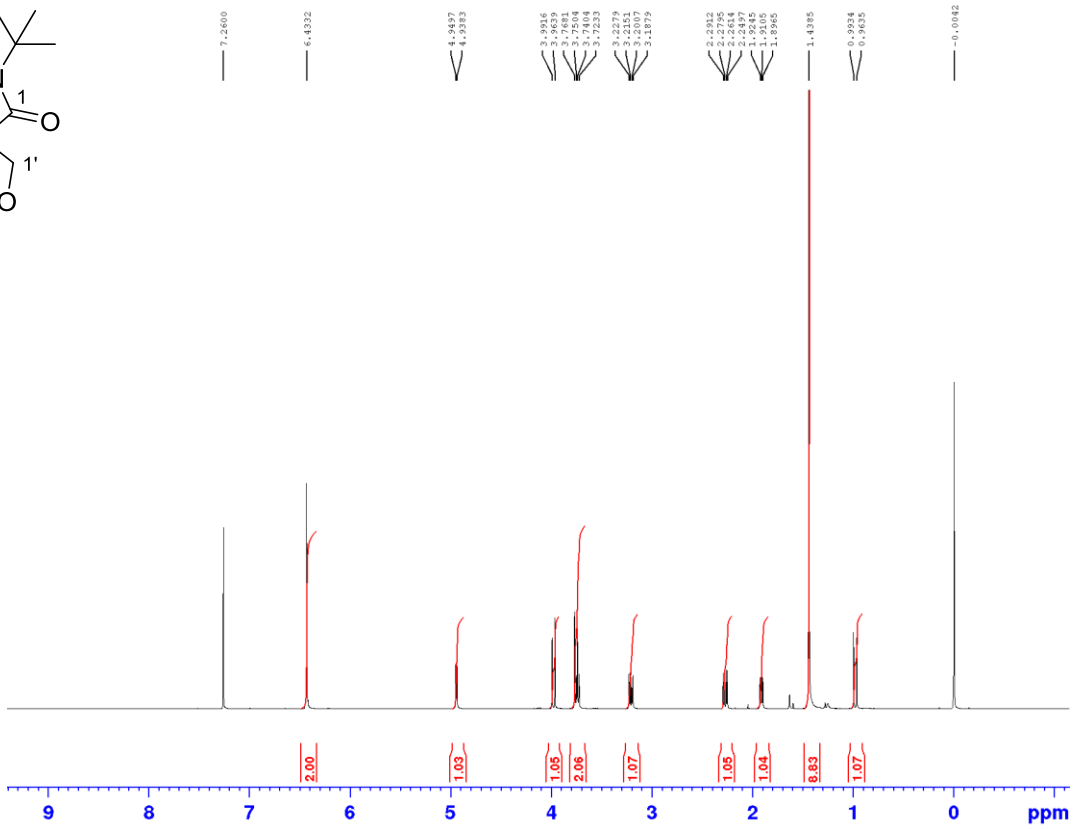


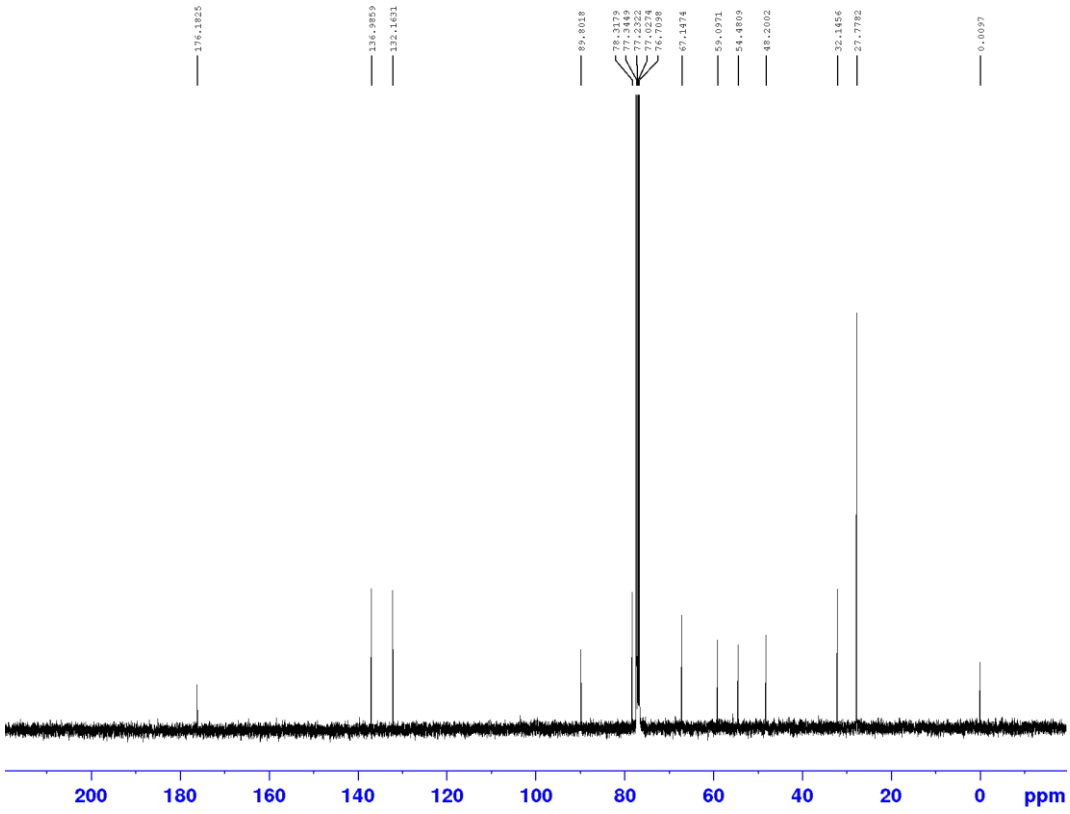
Compound **77**



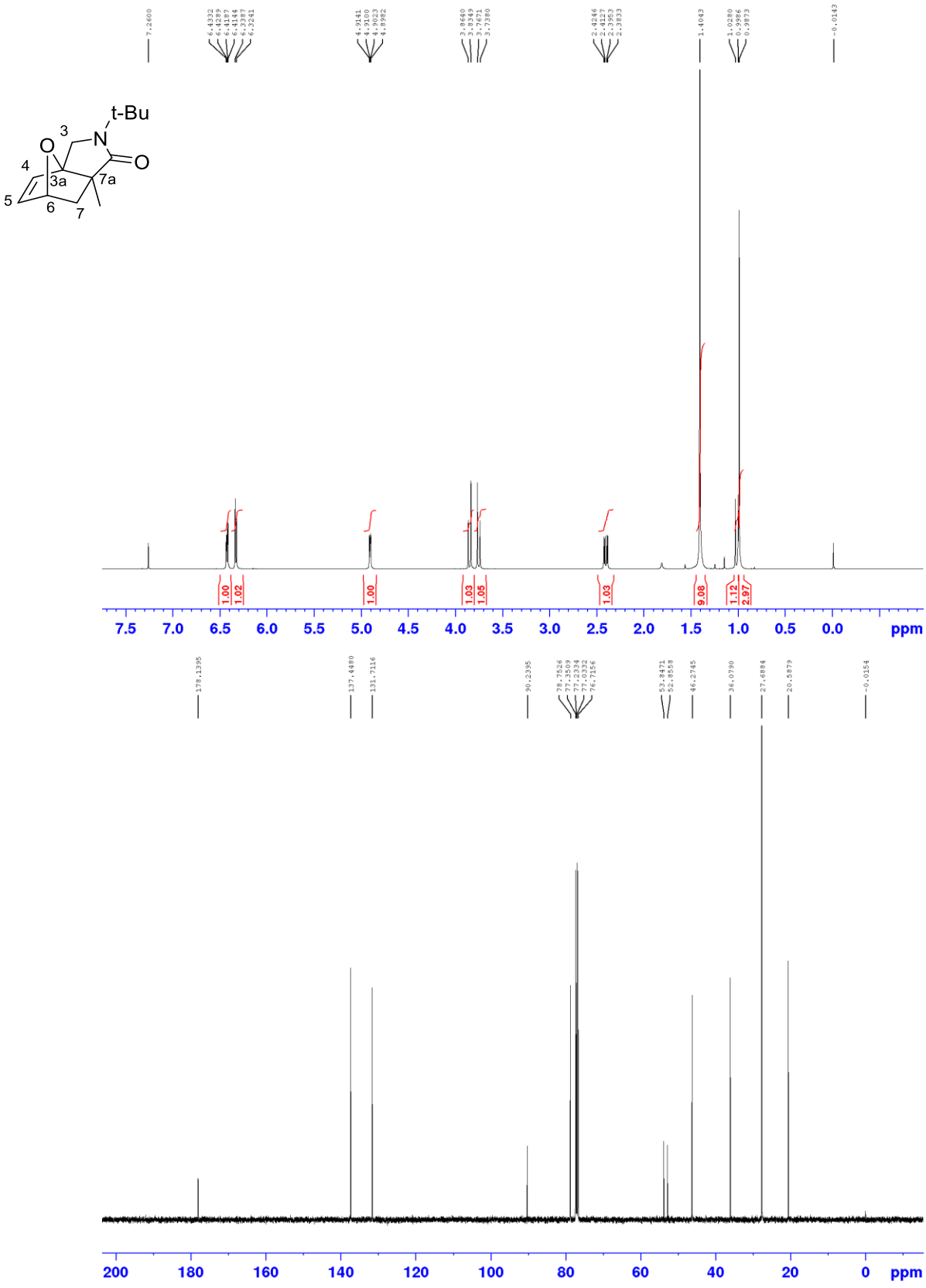
Compound **78**


3
N
1
O
O
4
3a
7a
1'
5
6
7
HO

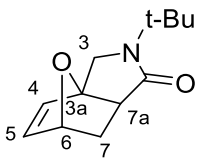

7.2600
6.4332
4.9497
4.9383
3.9916
3.9639
3.7681
3.7508
3.7404
3.7233
3.2279
3.2151
3.2007
3.1879
2.2912
2.2795
2.2654
2.2497
1.9245
1.9105
1.8965
1.4385
0.9934
0.9635
-0.0042
2.00
1.03
1.05
2.06
1.07
1.05
1.04
8.83
1.07
9
8
7
6
5
4
3
2
1
0
ppm

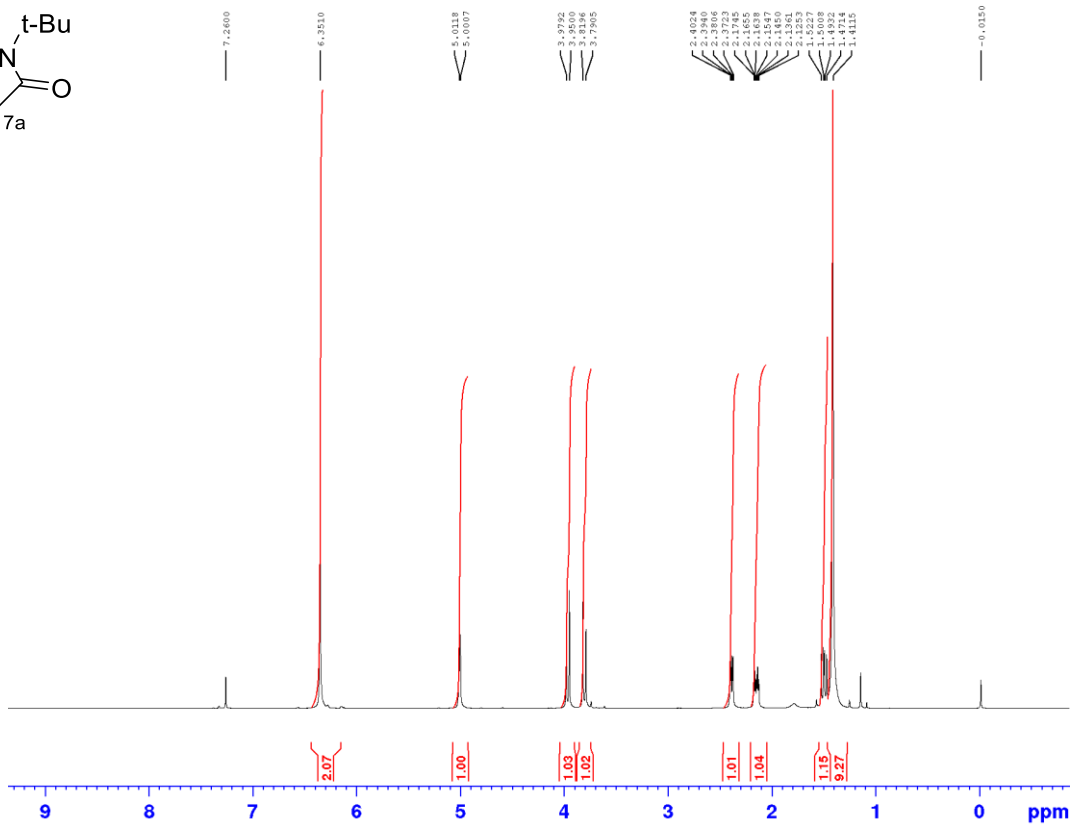

176.1825
136.9859
132.1631
89.8018
78.3179
77.3449
77.2322
77.0274
76.7098
67.1474
59.0971
54.4809
48.2062
32.1456
27.7782
0.0097
200
180
160
140
120
100
80
60
40
20
0
ppm

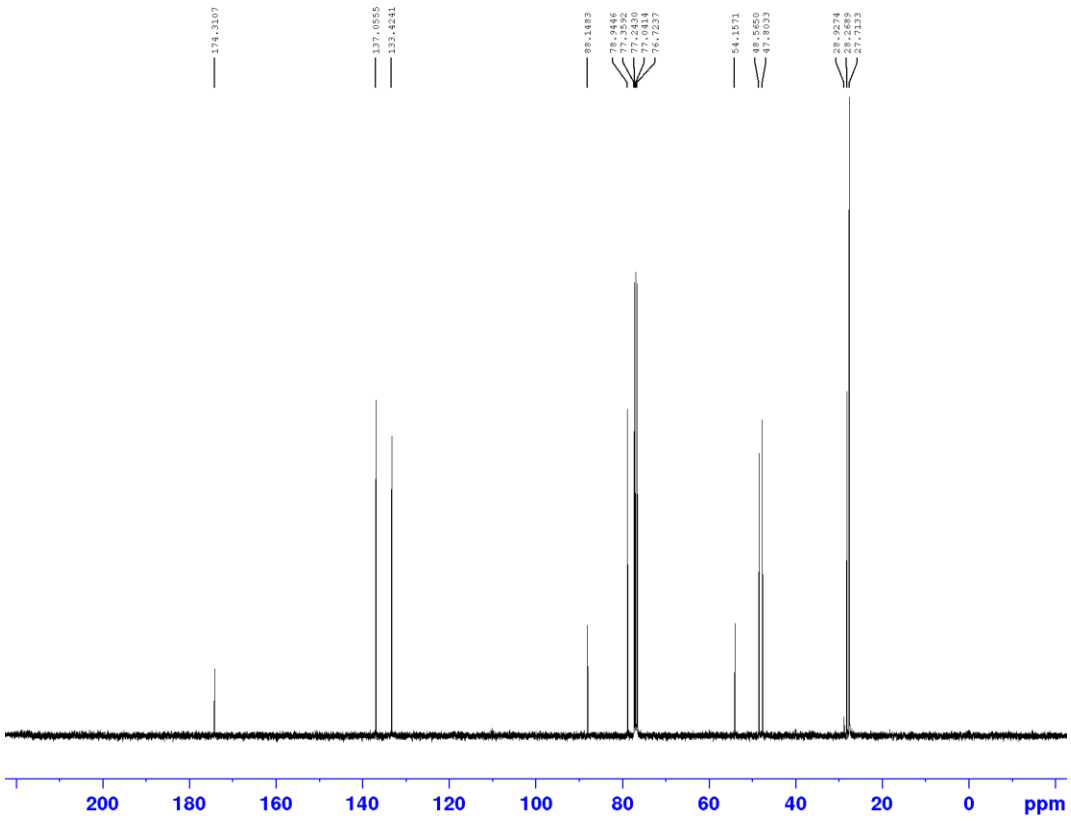
Compound **80**


t-Bu
O
N
O
3
4
3a
7a
5
6
7
7.2600
6.4332
6.4289
6.4187
6.4144
6.3387
6.3241
4.9141
4.9100
4.9023
4.8982
3.8640
3.8349
3.7671
3.7380
2.4246
2.4127
2.3953
2.3833
1.4043
1.0280
0.9986
0.9873
-0.0143
1.00
1.02
1.00
1.03
1.05
1.03
9.08
1.12
2.97
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
178.1395
137.4480
131.7116
90.2395
78.7526
77.3509
77.0334
76.7156
53.9471
52.9558
46.2745
36.0790
27.6884
20.5879
-0.0154
200 180 160 140 120 100 80 60 40 20 0 ppm

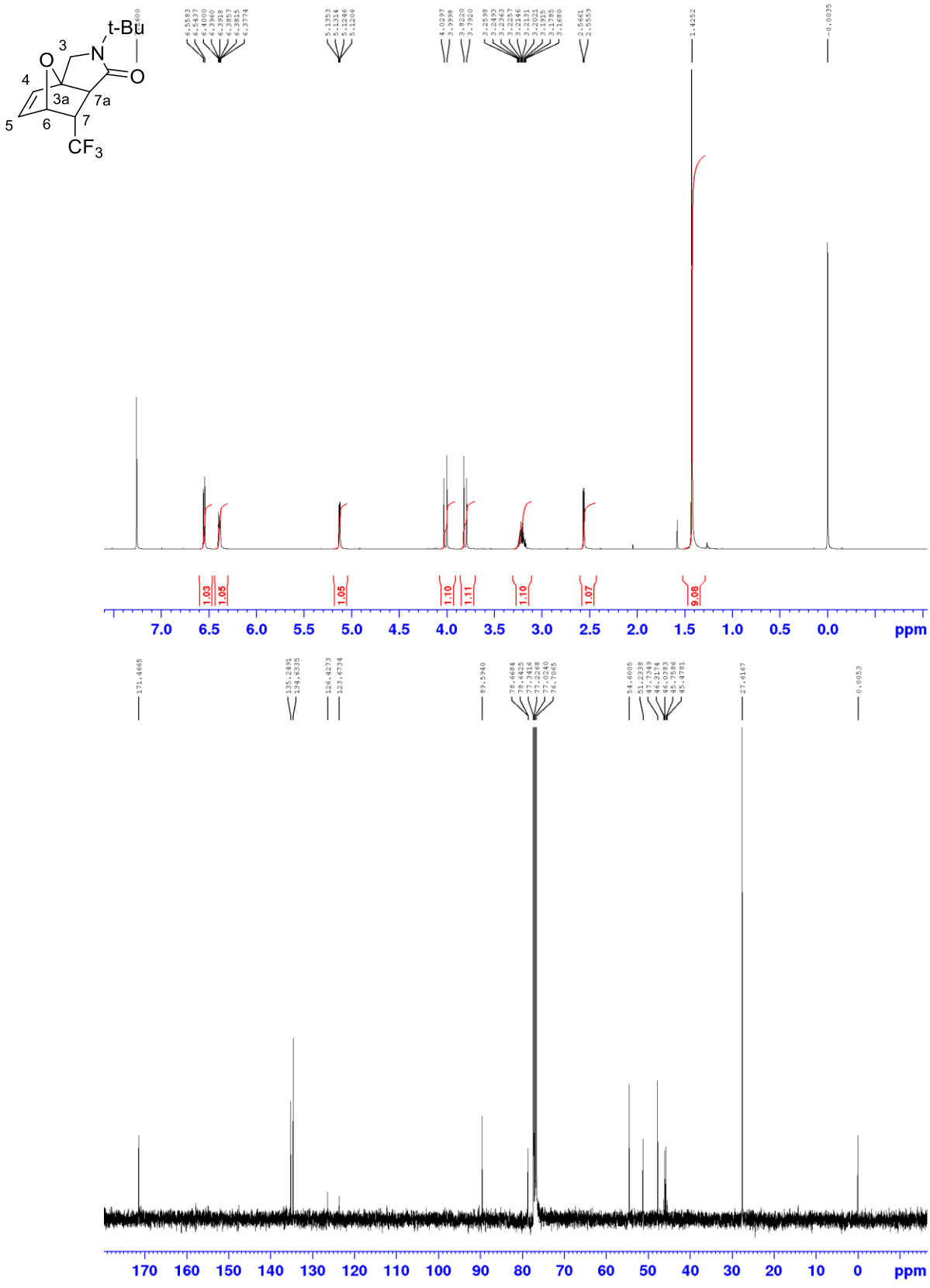
Compound **82**


t-Bu
3
N
O
O
4
3a
7a
5
6
7

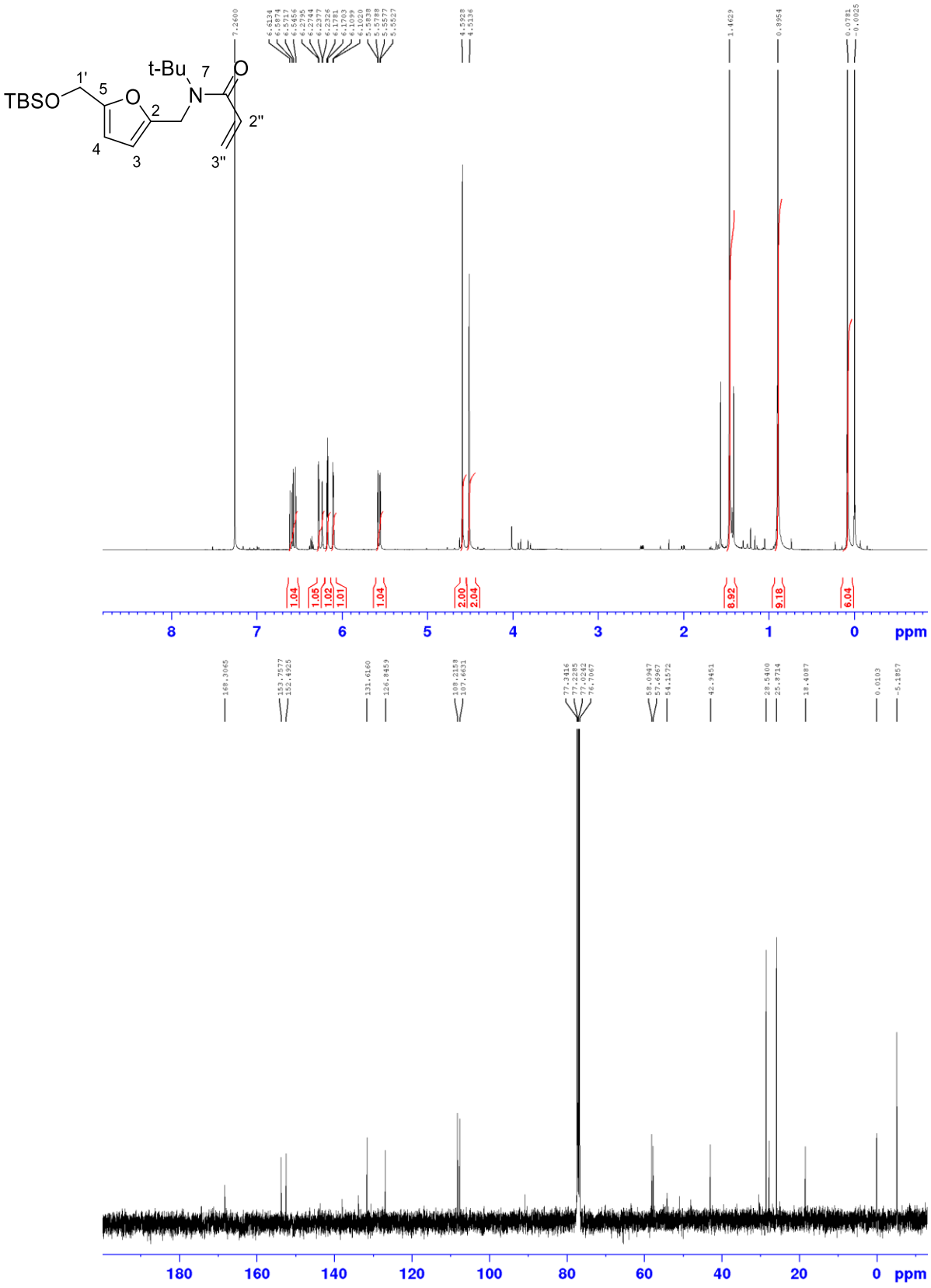

7.2600
6.3510
5.0118
5.0007
3.9792
3.9500
3.9196
3.7905
2.4024
2.3806
2.3723
2.1745
2.1655
2.1547
2.1450
2.1361
2.1225
1.5227
1.5008
1.4932
1.4734
1.4115
-0.0150
2.07
1.00
1.03
1.02
1.01
1.04
1.15
9.27
9
8
7
6
5
4
3
2
1
0
ppm


174.3107
137.0555
133.4241
88.1483
78.9446
77.3592
77.2430
77.0314
76.7217
54.1571
48.5650
47.9033
28.9274
28.2689
27.7133
200
180
160
140
120
100
80
60
40
20
0
ppm

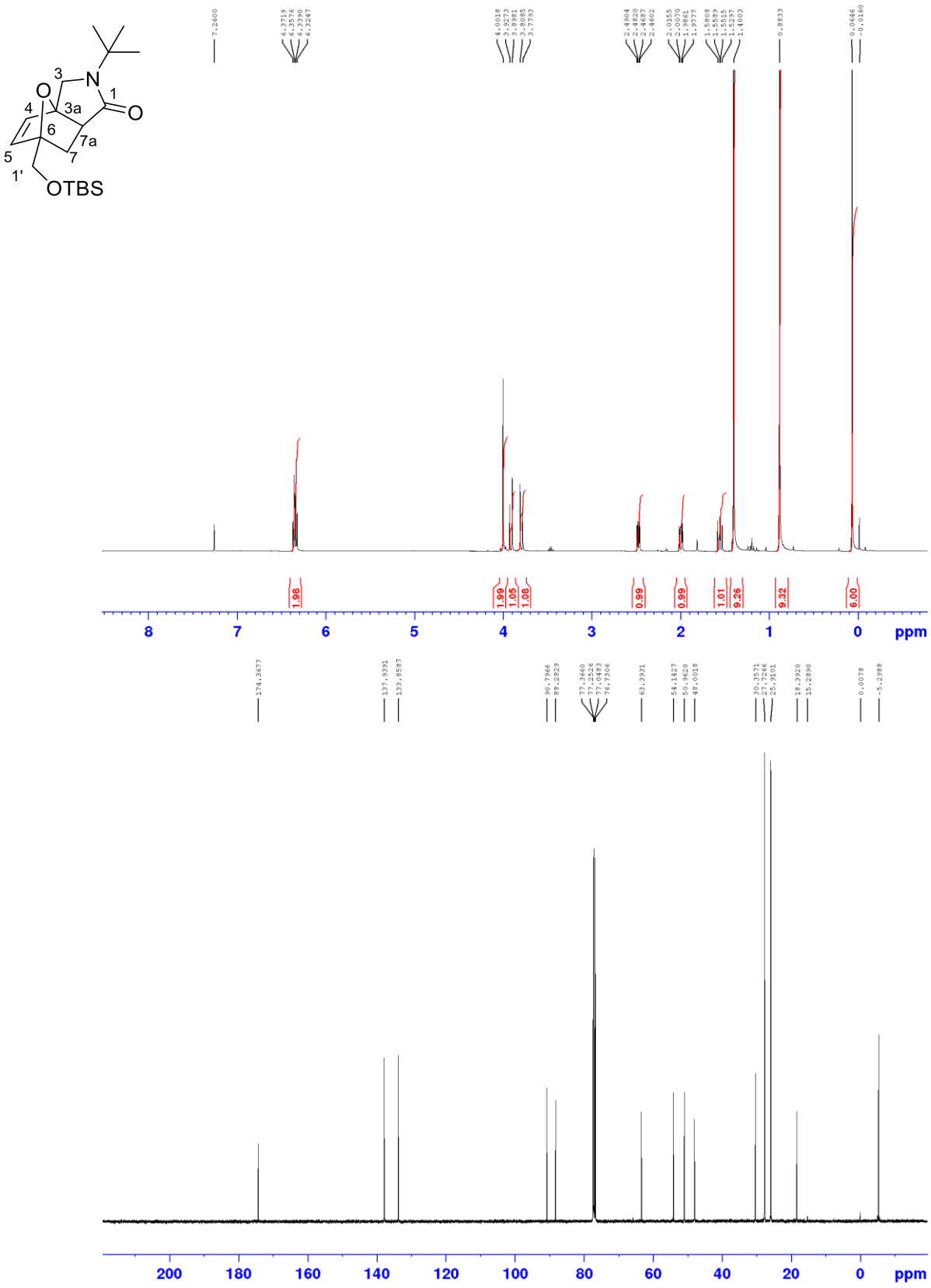
Compound **84**


t-Bu
N
O
O
3
4
3a
7a
5
6
7
CF3
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

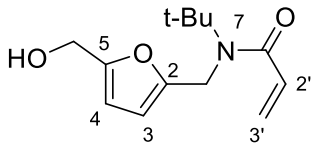
Compound **87**

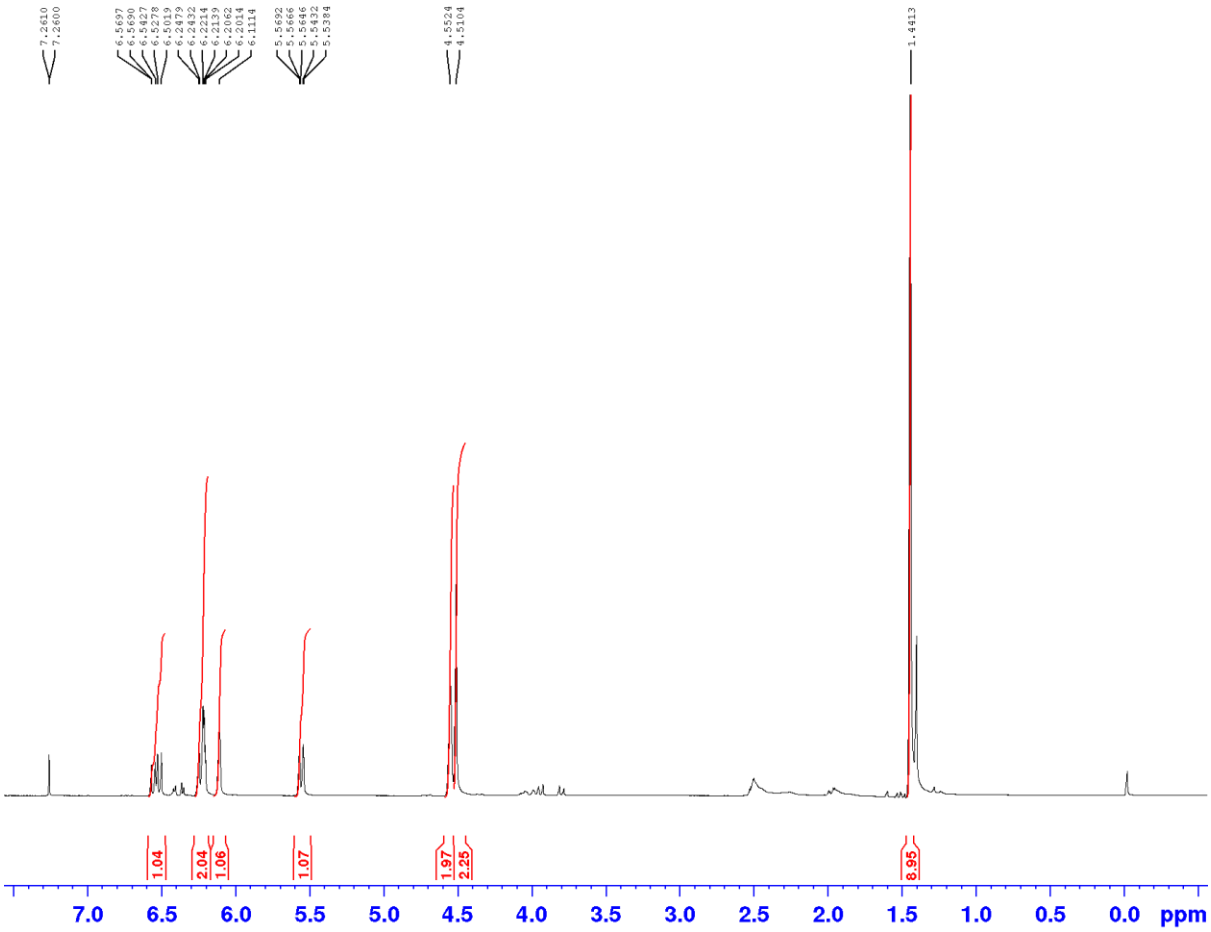

TBSO
1'
5
O
2
N
t-Bu
7
O
2"
3"
4
3
7.2600
6.6134
6.5874
6.5717
6.5456
6.2795
6.2744
6.2377
6.2116
6.1781
6.1703
6.1099
6.1039
5.5838
5.5788
5.5577
5.5527
4.5928
4.5136
1.4629
0.8954
0.0781
-0.0025
1.04
1.05
1.02
1.01
1.04
2.00
2.04
8.92
9.18
6.04
8
7
6
5
4
3
2
1
0
ppm
168.3065
153.7577
152.4925
131.6160
126.8459
108.2158
107.6631
77.3416
77.2285
77.0242
76.7067
59.0947
57.6967
54.1572
42.9451
28.5400
25.9714
18.4087
0.0103
-5.1857
180
160
140
120
100
80
60
40
20
0
ppm

Compound **88**

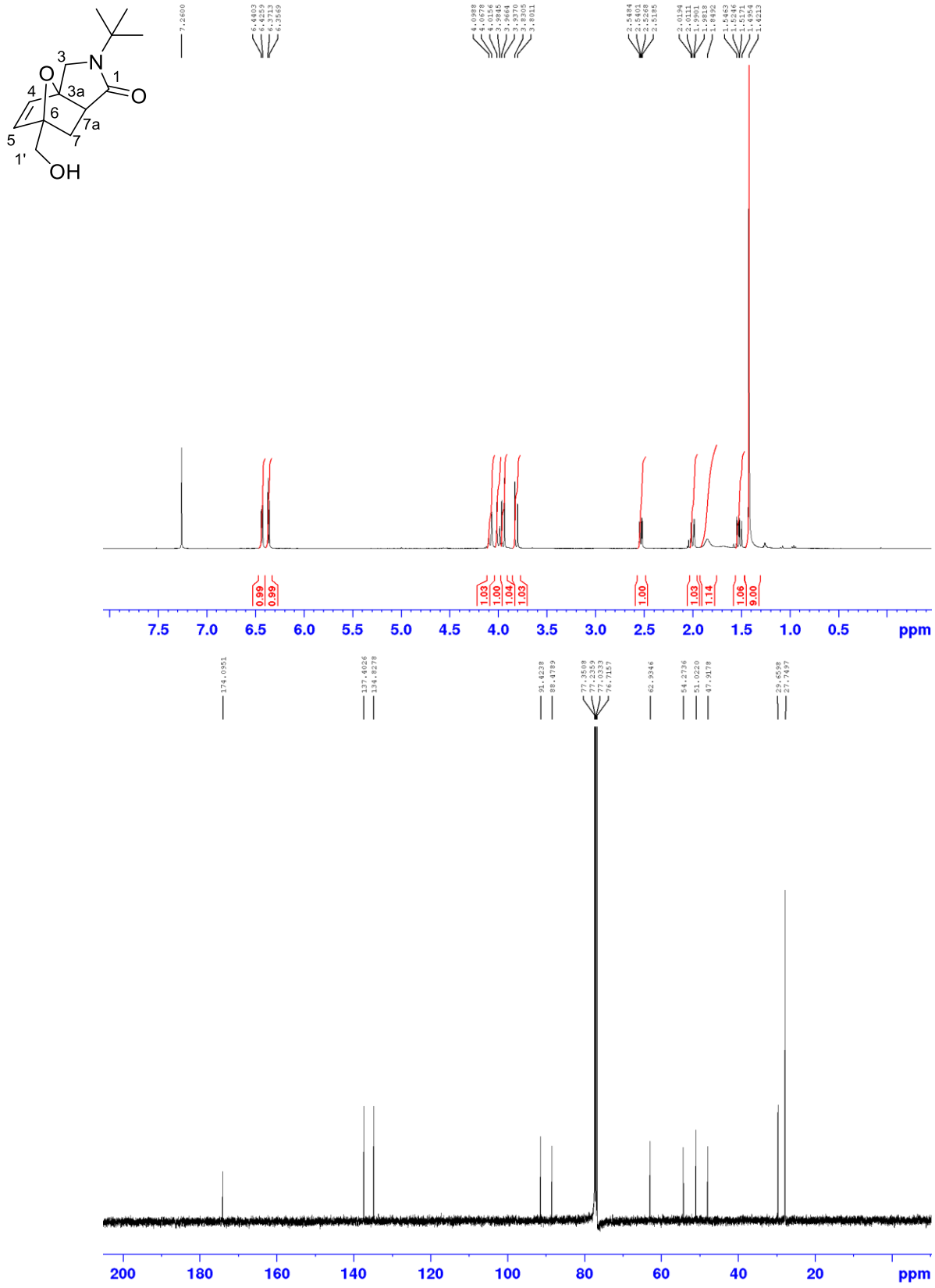

7.2600
6.3719
6.3576
6.3390
6.3247
4.0018
3.9273
3.8981
3.8805
3.7793
2.4904
2.4820
2.4677
2.4602
2.0155
2.0070
1.9861
1.9777
1.5808
1.5589
1.5515
1.5297
1.4003
0.8833
0.0646
-0.0160
1.98
1.99
1.05
1.08
0.99
0.99
1.01
9.26
9.32
6.00
8
7
6
5
4
3
2
1
0
ppm
174.3677
137.9391
133.8587
90.7966
88.2829
77.3660
77.2526
77.0393
76.7306
63.3931
54.1427
50.9620
48.4018
30.3571
27.7266
25.9101
18.3920
15.2890
0.0078
-5.2988
200
180
160
140
120
100
80
60
40
20
0
ppm

Compound **89**

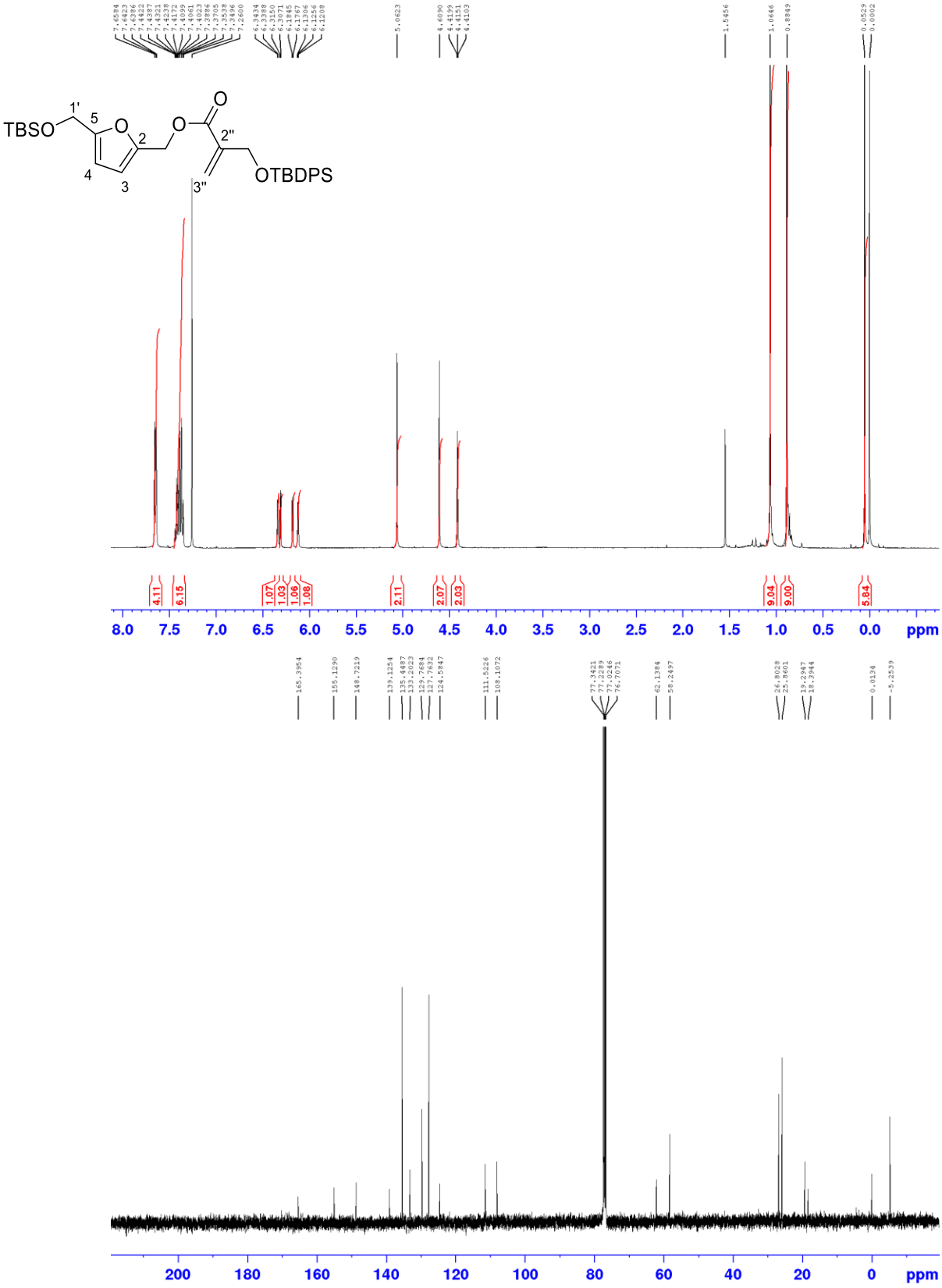

t-Bu
7
O
HO
5
O
2
N
2'
4
3
3'


7.2610
7.2600
6.5697
6.5690
6.5427
6.5278
6.5119
6.2479
6.2432
6.2214
6.2139
6.2062
6.2014
6.1114
5.5692
5.5666
5.5646
5.5432
5.5384
4.5524
4.5104
1.4413
1.04
2.04
1.06
1.07
1.97
2.25
8.95
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

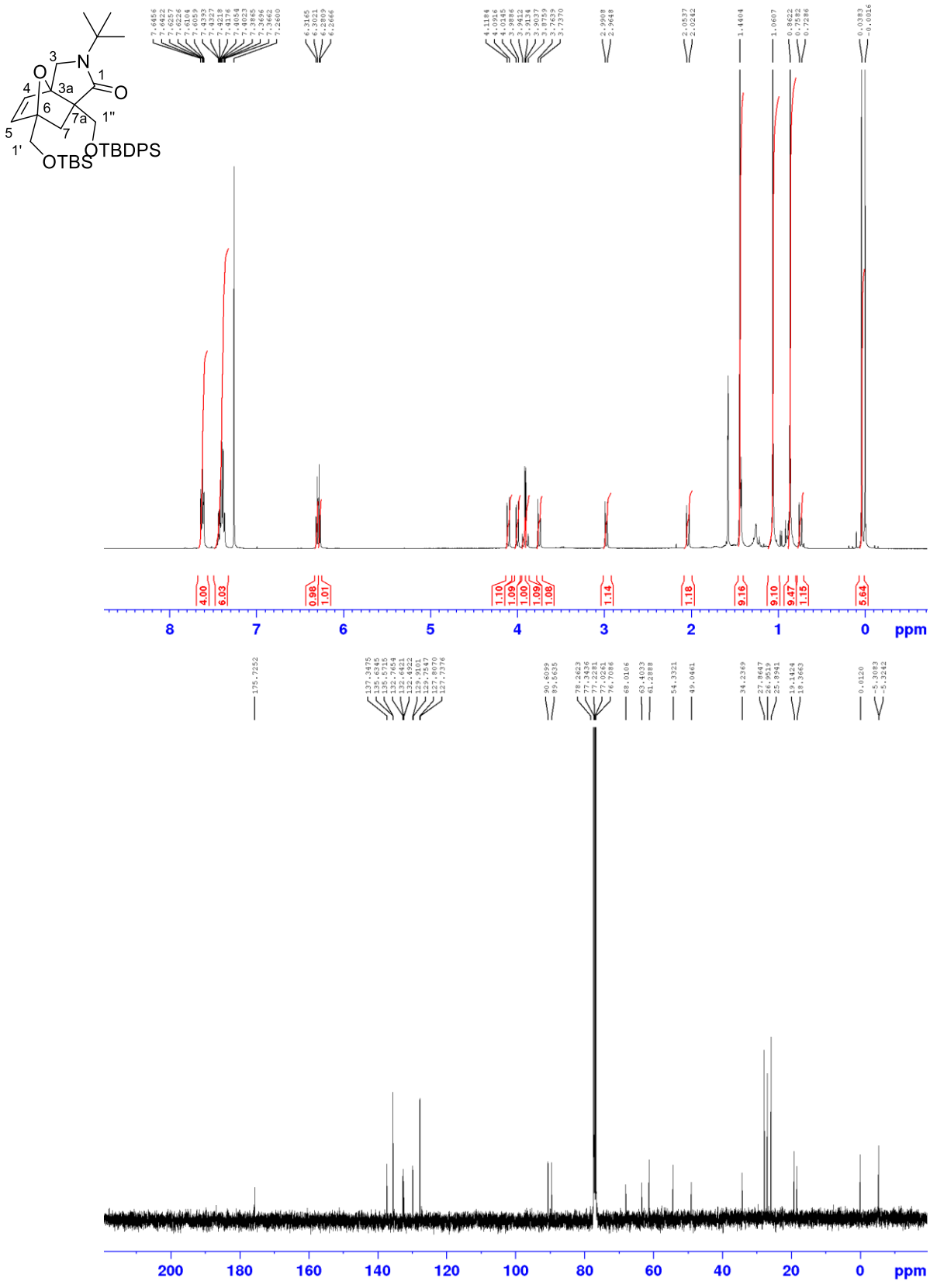
Compound **90**


O
N
O
OH
1
3
3a
4
5
6
7
7a
1'
7.2600
6.4403
6.4259
6.3713
6.3569
4.0988
4.0878
4.0156
3.9845
3.9664
3.9370
3.8306
3.8011
2.5484
2.5401
2.5308
2.5185
2.0194
2.0031
1.9901
1.9818
1.8492
1.5463
1.5246
1.5111
1.4954
1.4213
0.99
0.99
1.03
1.00
1.04
1.03
1.00
1.03
1.14
1.06
9.00
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
174.0951
137.4026
134.8278
91.4238
88.4789
77.3508
77.2353
77.1038
76.7157
62.9346
54.2736
51.0220
47.9178
29.4598
27.7497
200 180 160 140 120 100 80 60 40 20 ppm

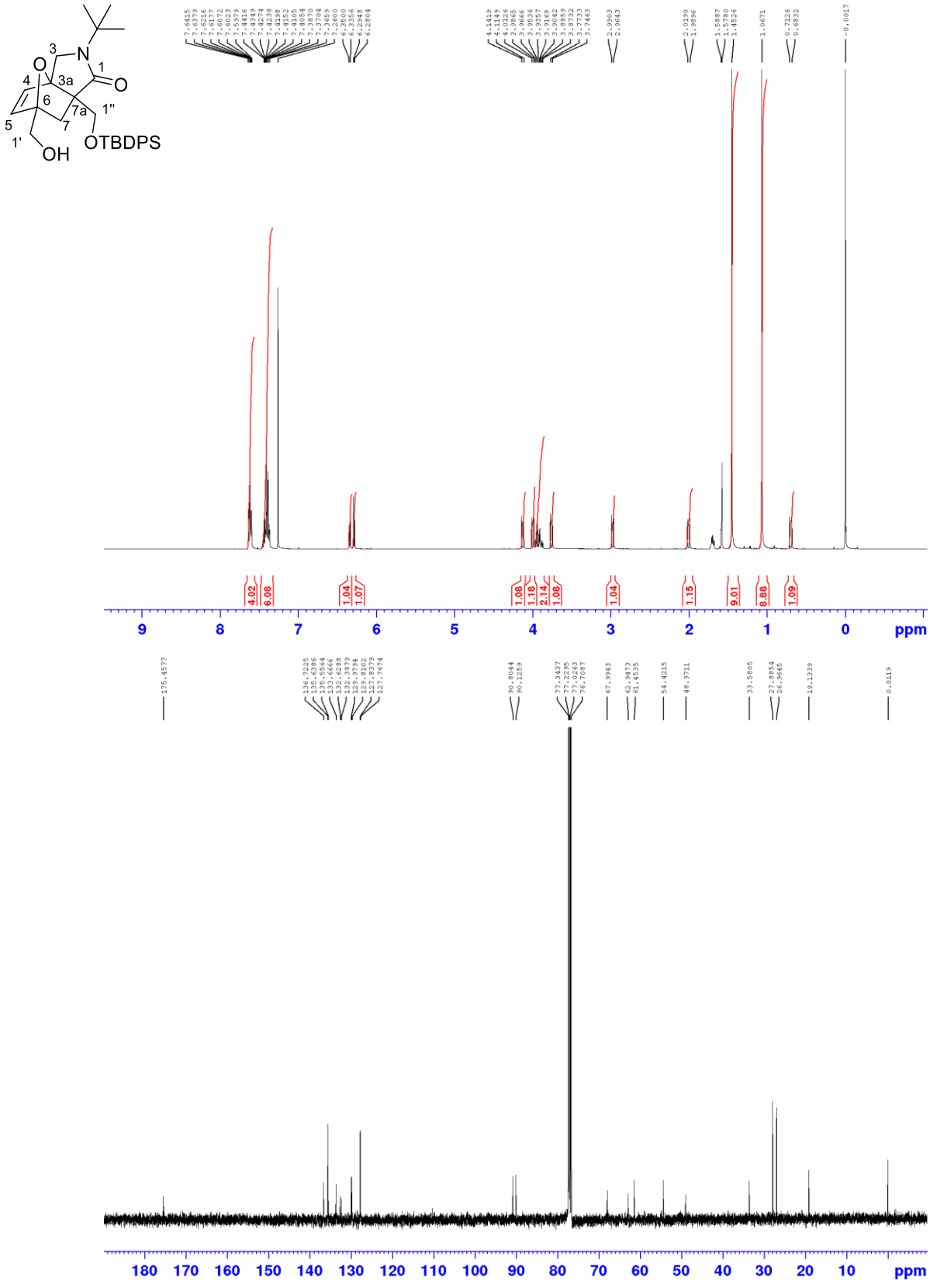
Compound **91**



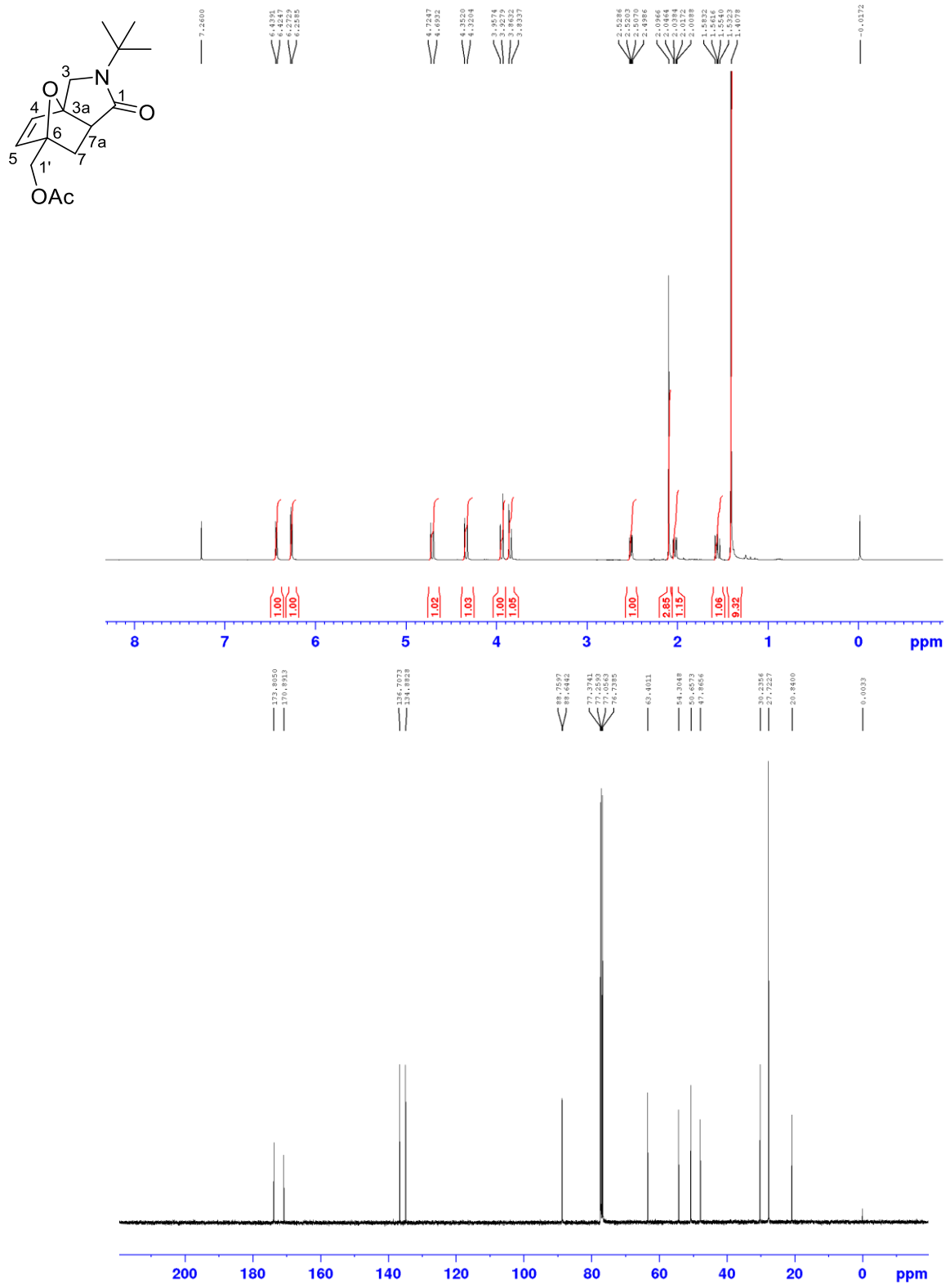
Compound **92**



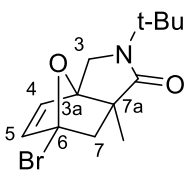
Compound **93**

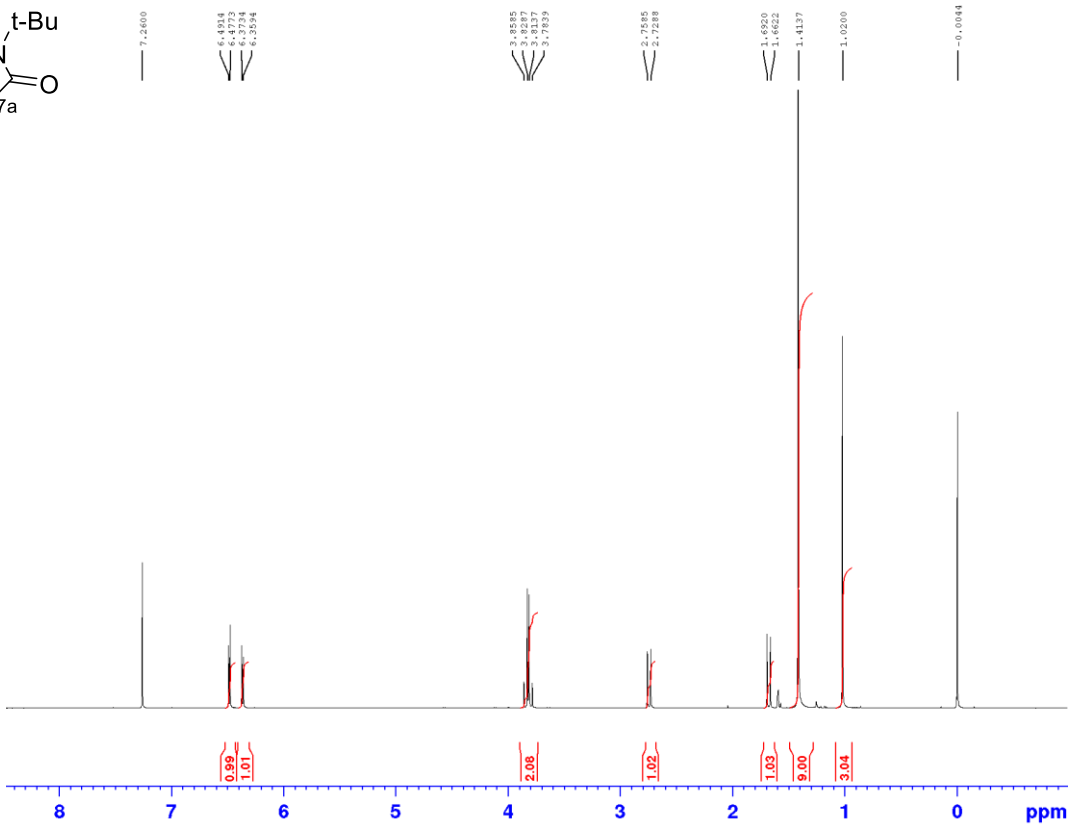

3
N
1
O
O
4
3a
6
7a
1"
5
7
1'
OH
OTBDPS
4.02
6.08
1.04
1.07
1.06
1.18
2.14
1.08
1.04
1.15
9.01
8.88
1.09
9
8
7
6
5
4
3
2
1
0
ppm
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

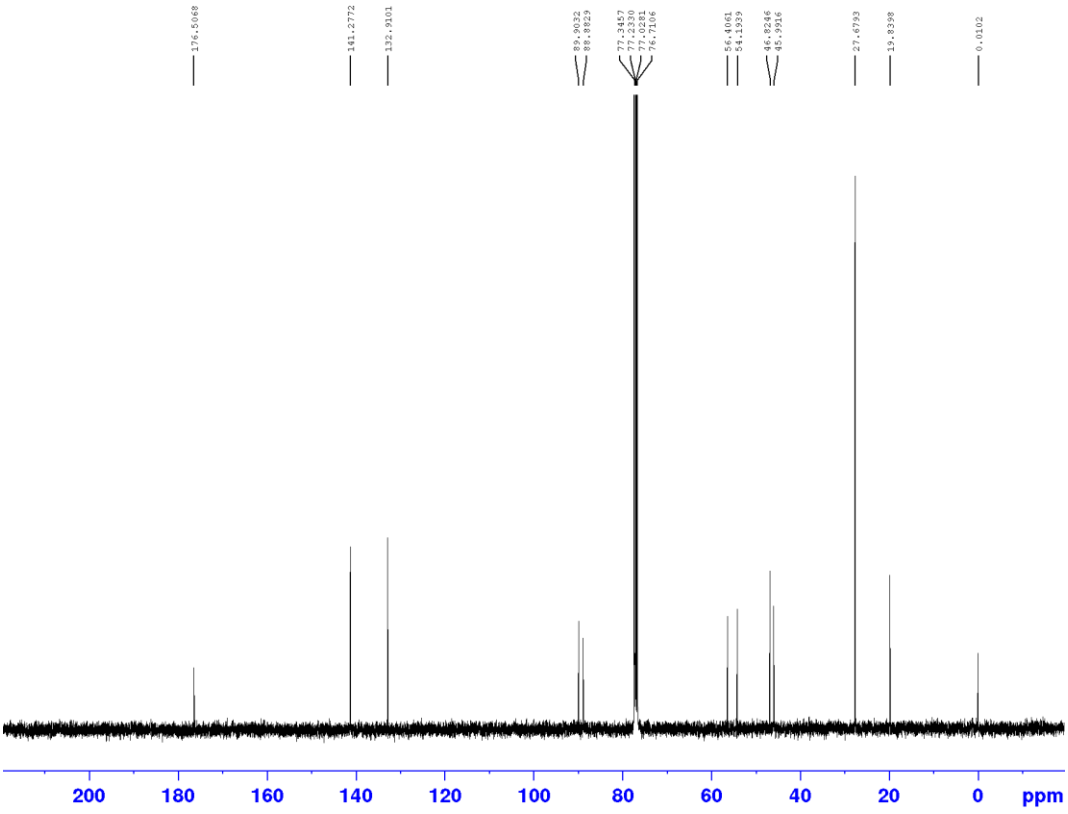
Compound **119.1**



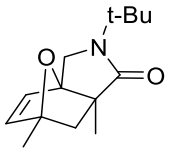
Compound **97**

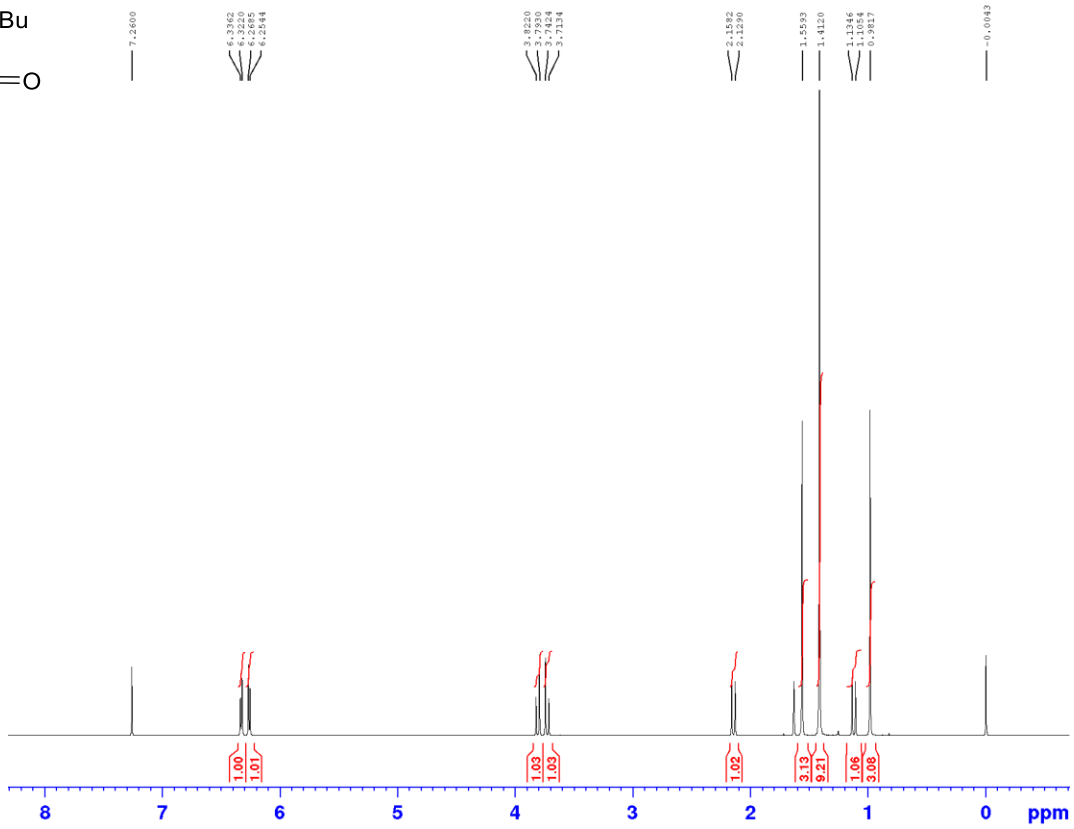

t-Bu
N
O
O
3
4
3a
7a
5
6
7
Br

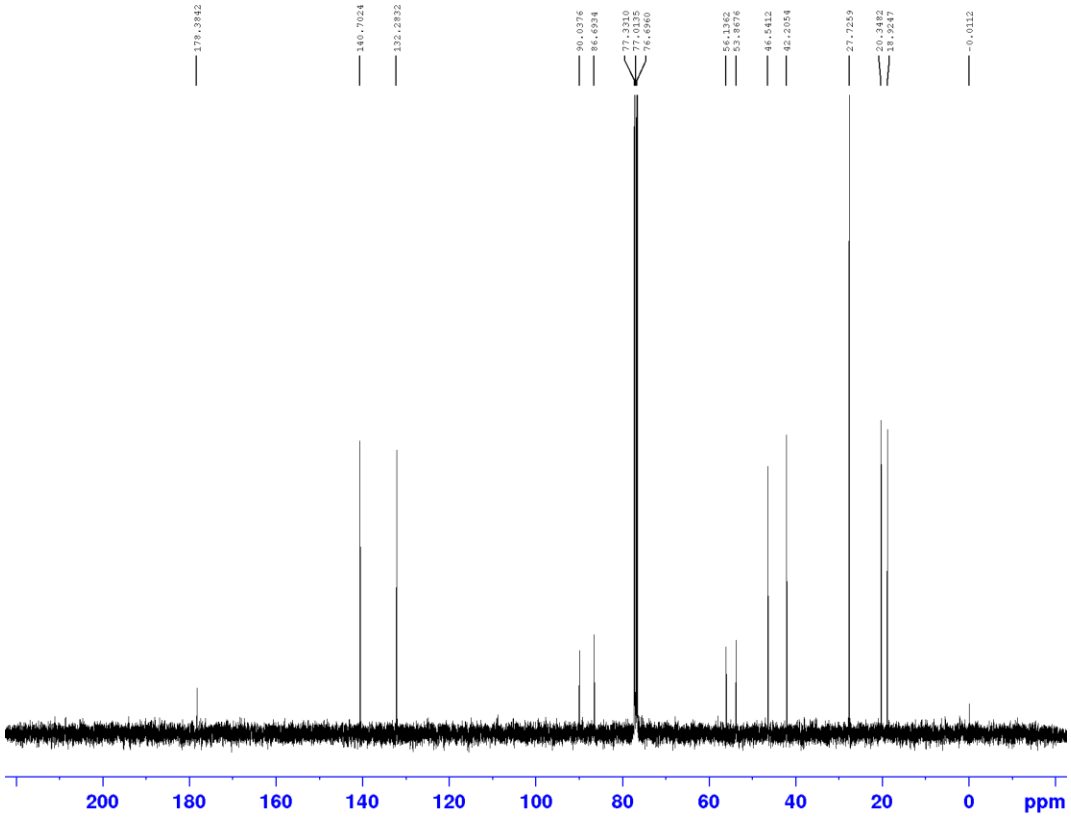

7.2600
6.4934
6.4773
6.3734
6.3594
3.8585
3.8287
3.7437
3.7039
2.7585
2.7288
1.6920
1.6622
1.4137
1.0200
-0.0044
0.99
1.01
2.08
1.02
1.03
9.00
3.04
8
7
6
5
4
3
2
1
0
ppm


176.5068
141.2772
132.9101
89.9032
89.8829
77.3457
77.2330
77.0203
76.7106
56.4061
54.2359
46.9246
45.9916
27.6793
19.8398
0.0102
200
180
160
140
120
100
80
60
40
20
0
ppm

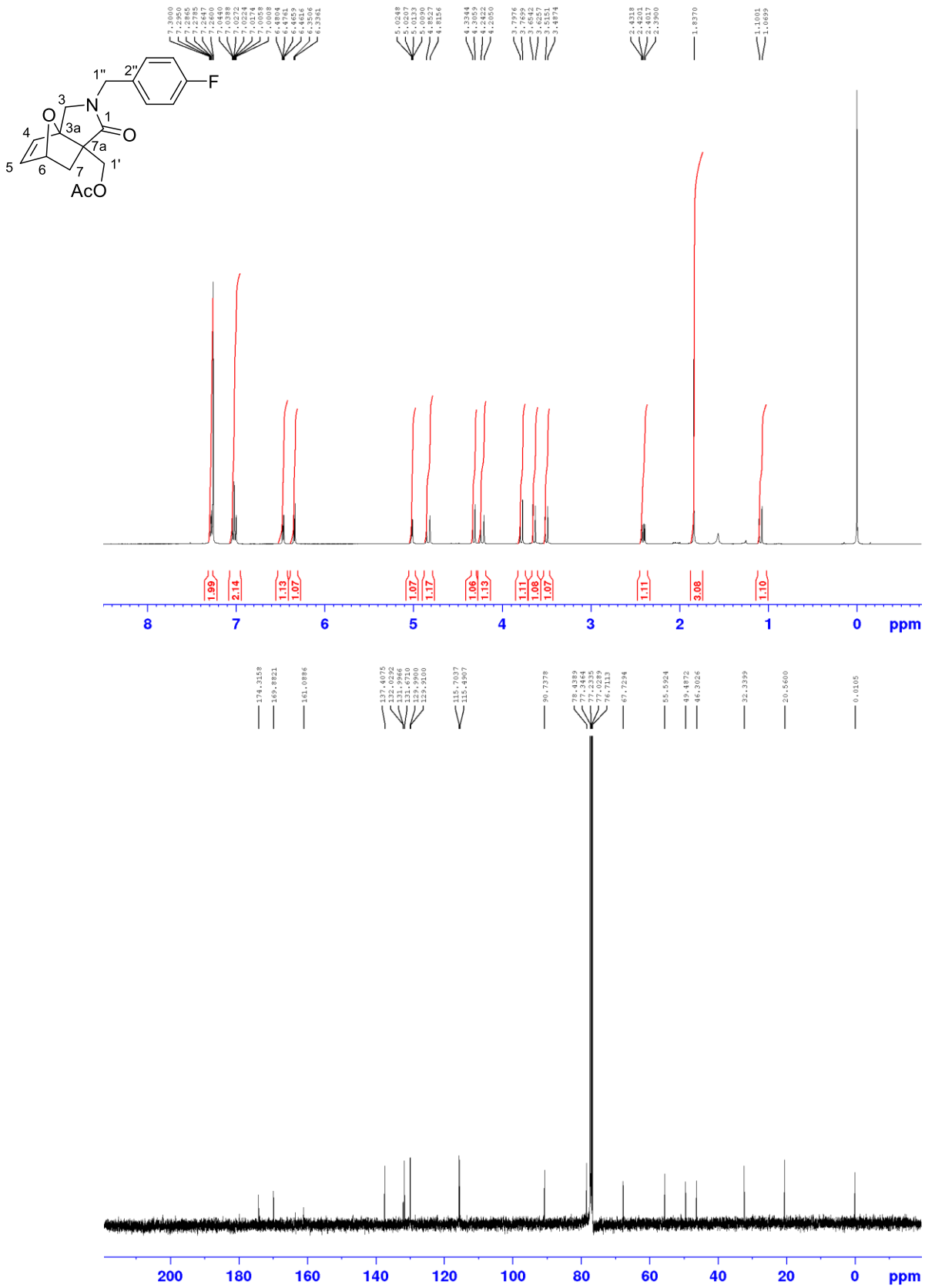
Compound **100**





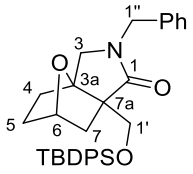


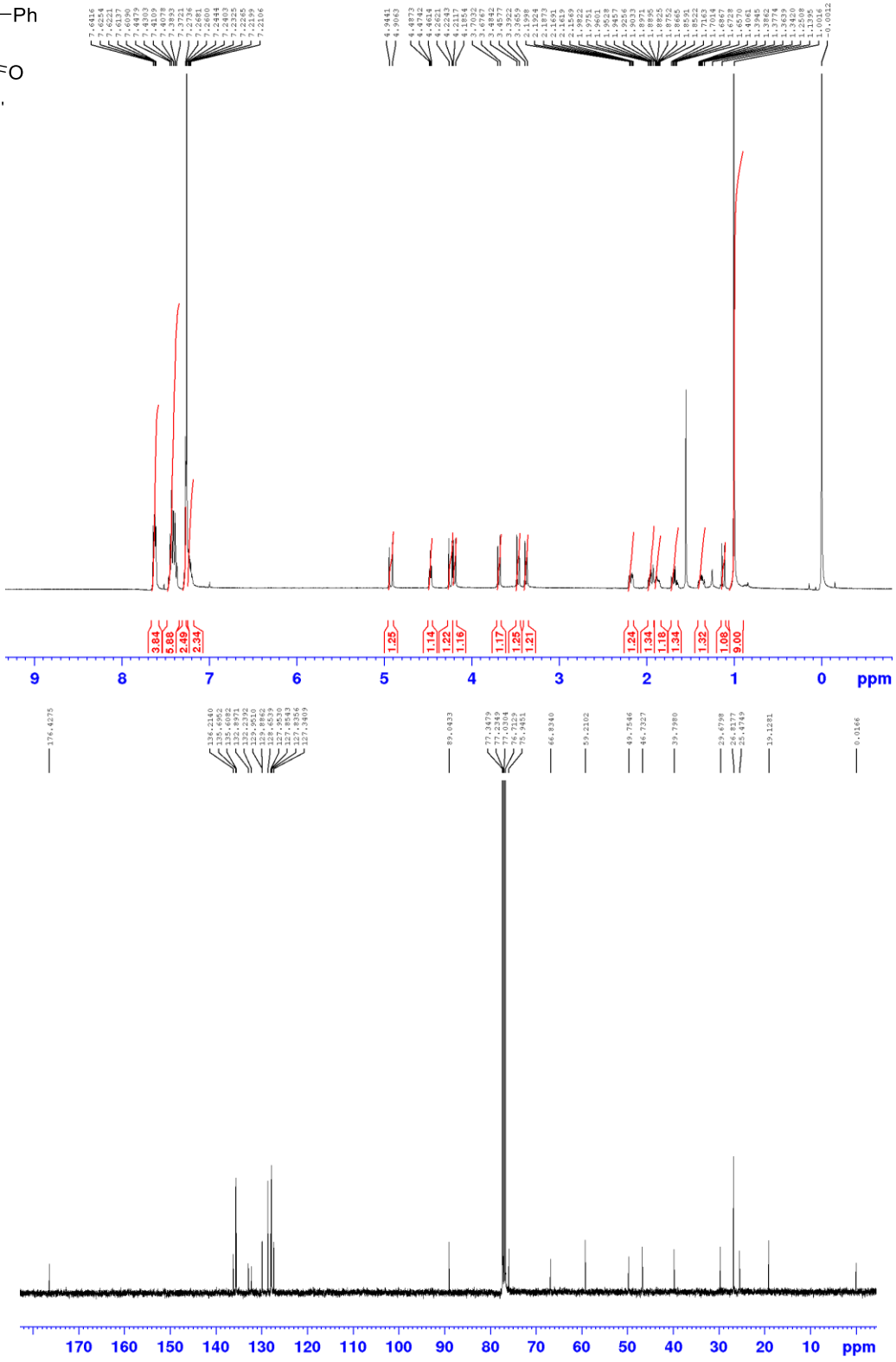
Compound **144**



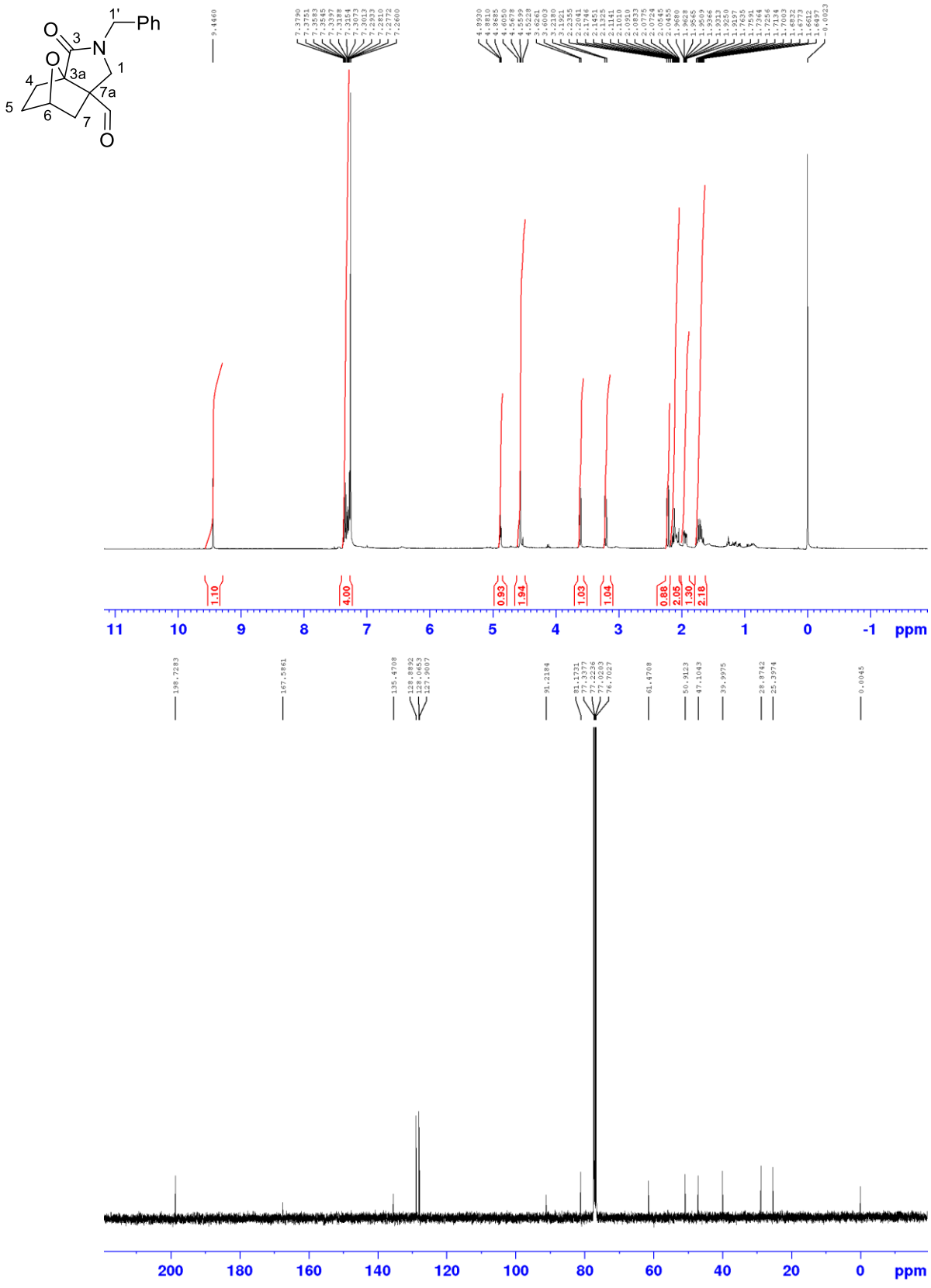
Hydrogenation products

Compound **104**



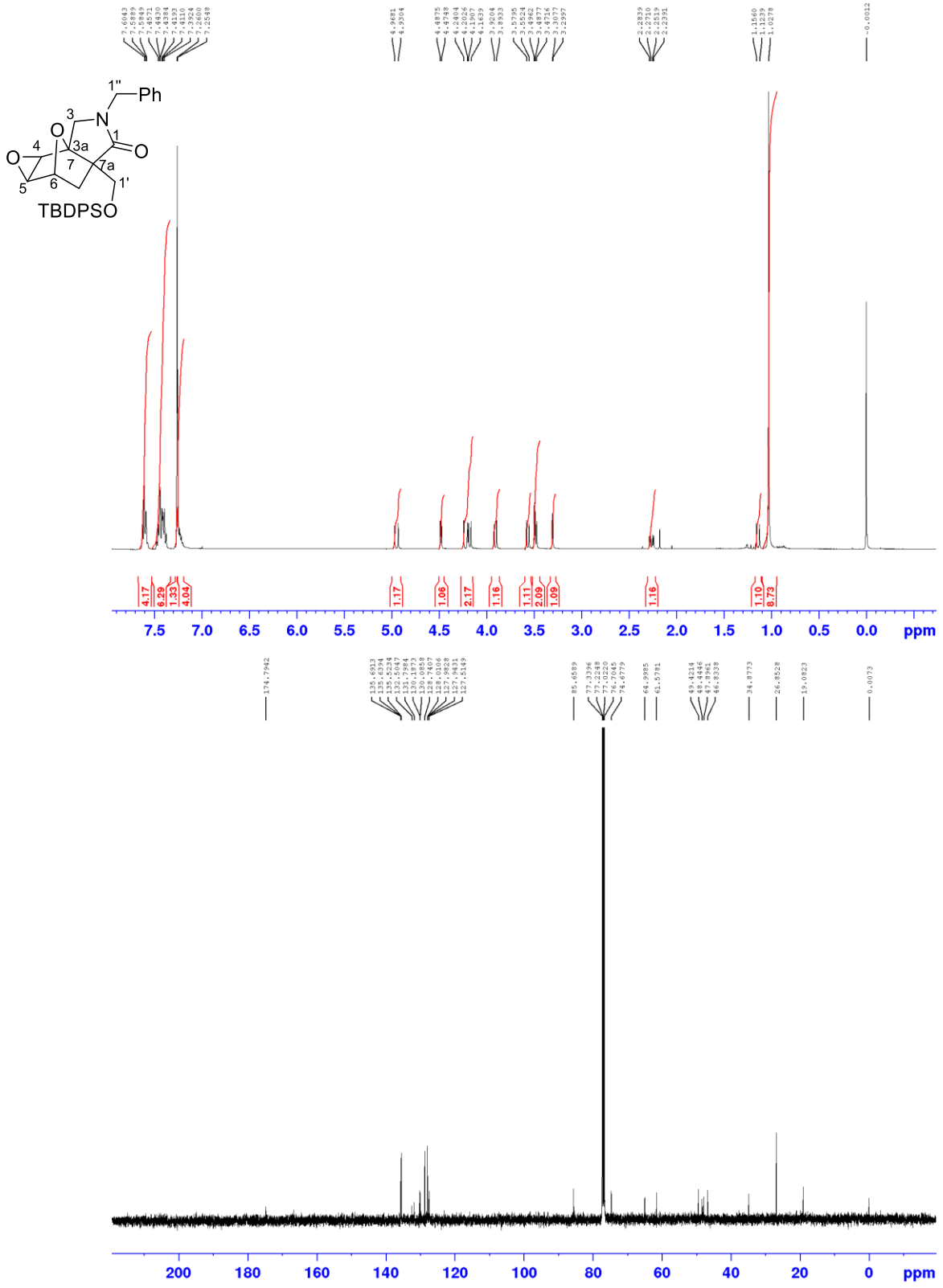


Compound **105**

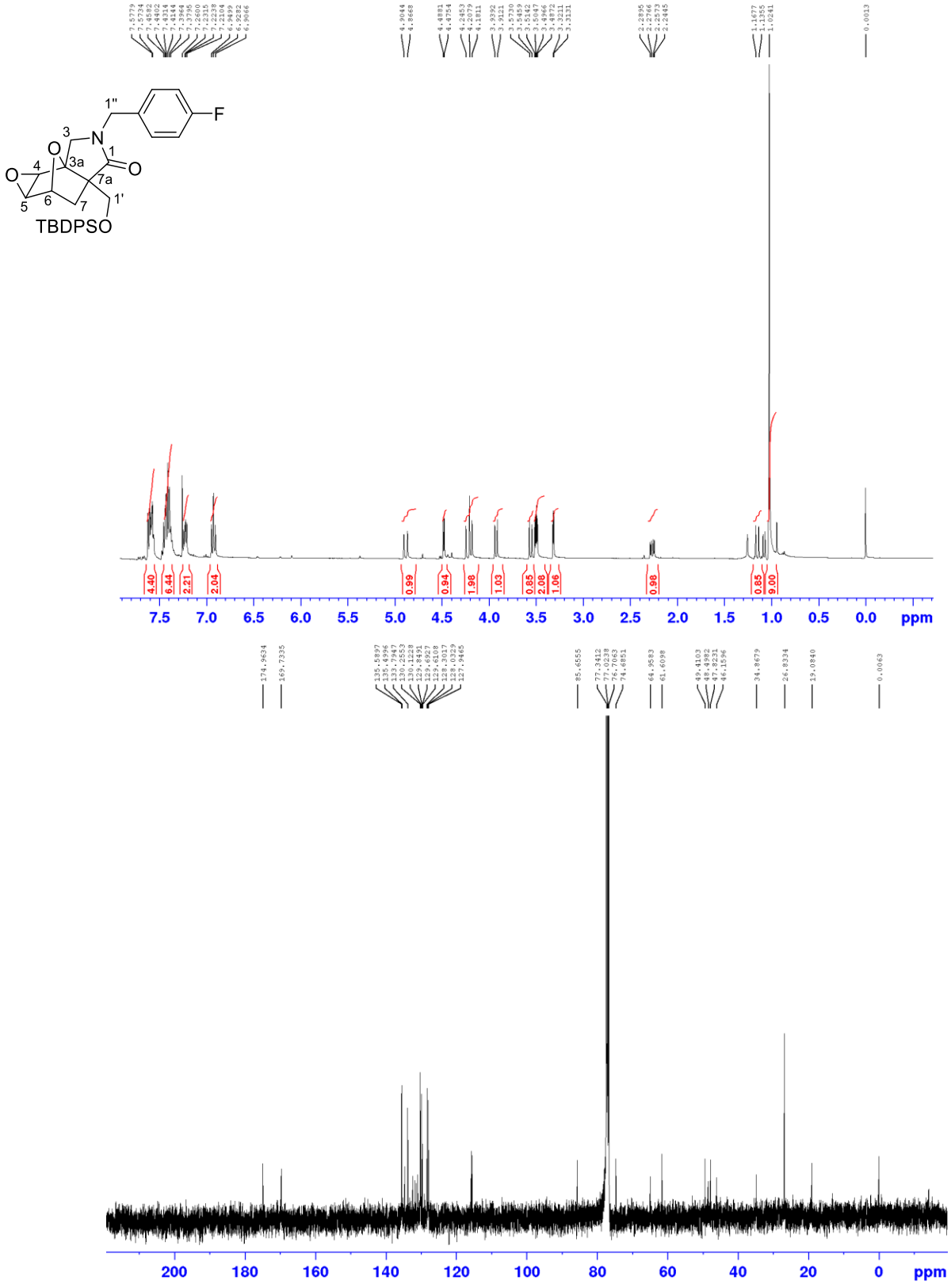


Epoxidation products

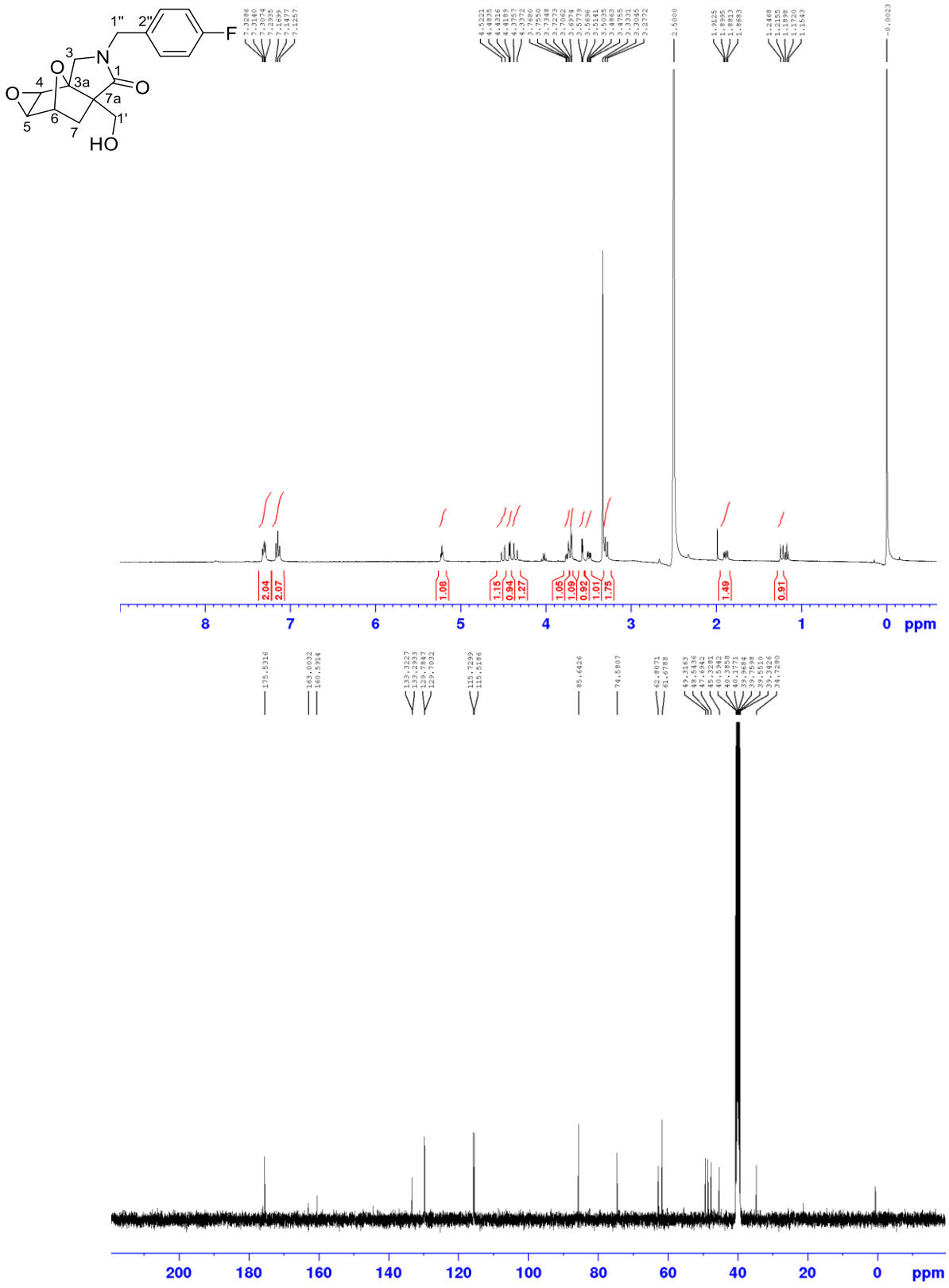
Compound **106**



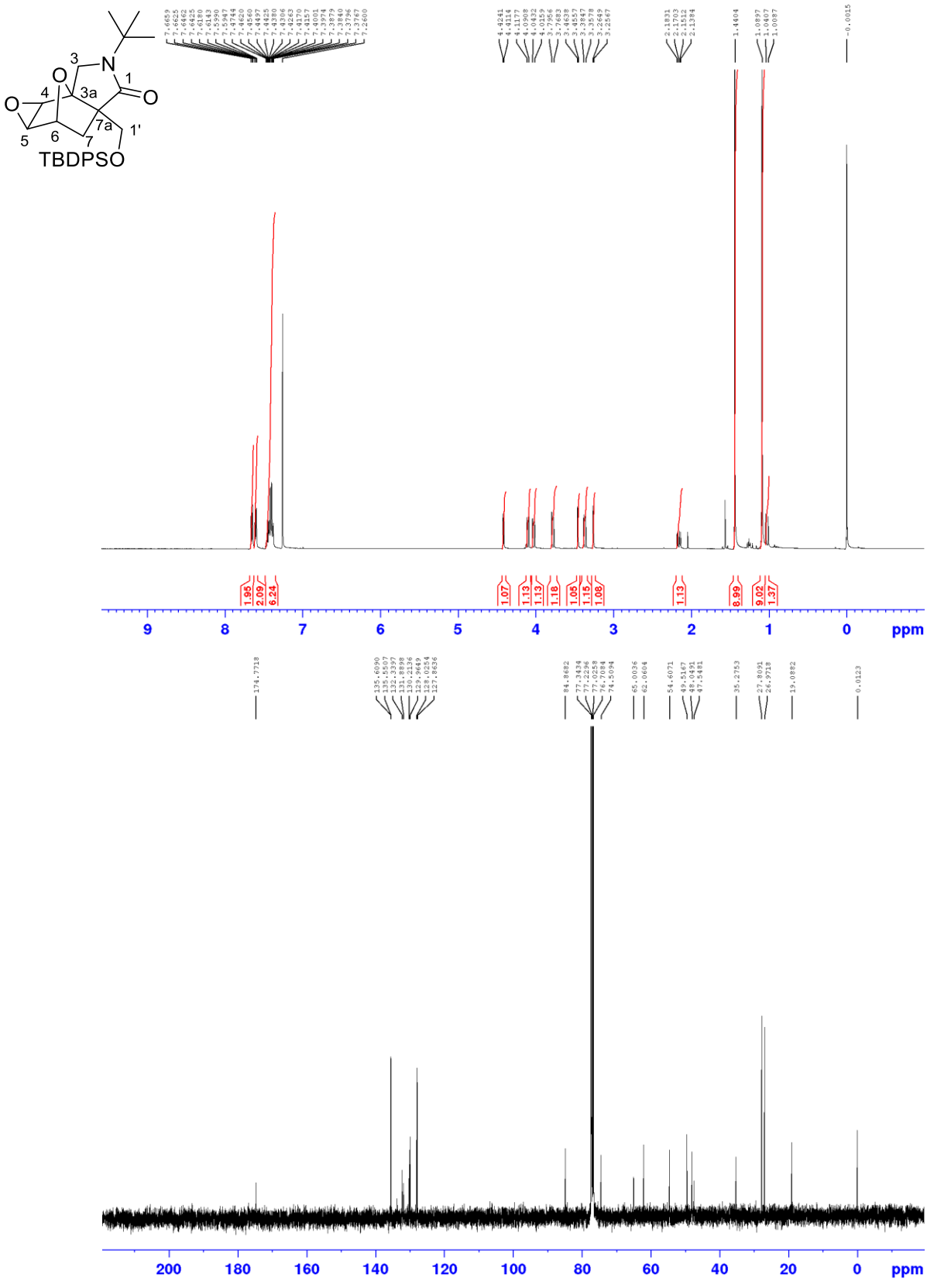
Compound **108**



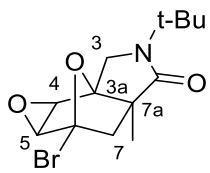
Compound **109**

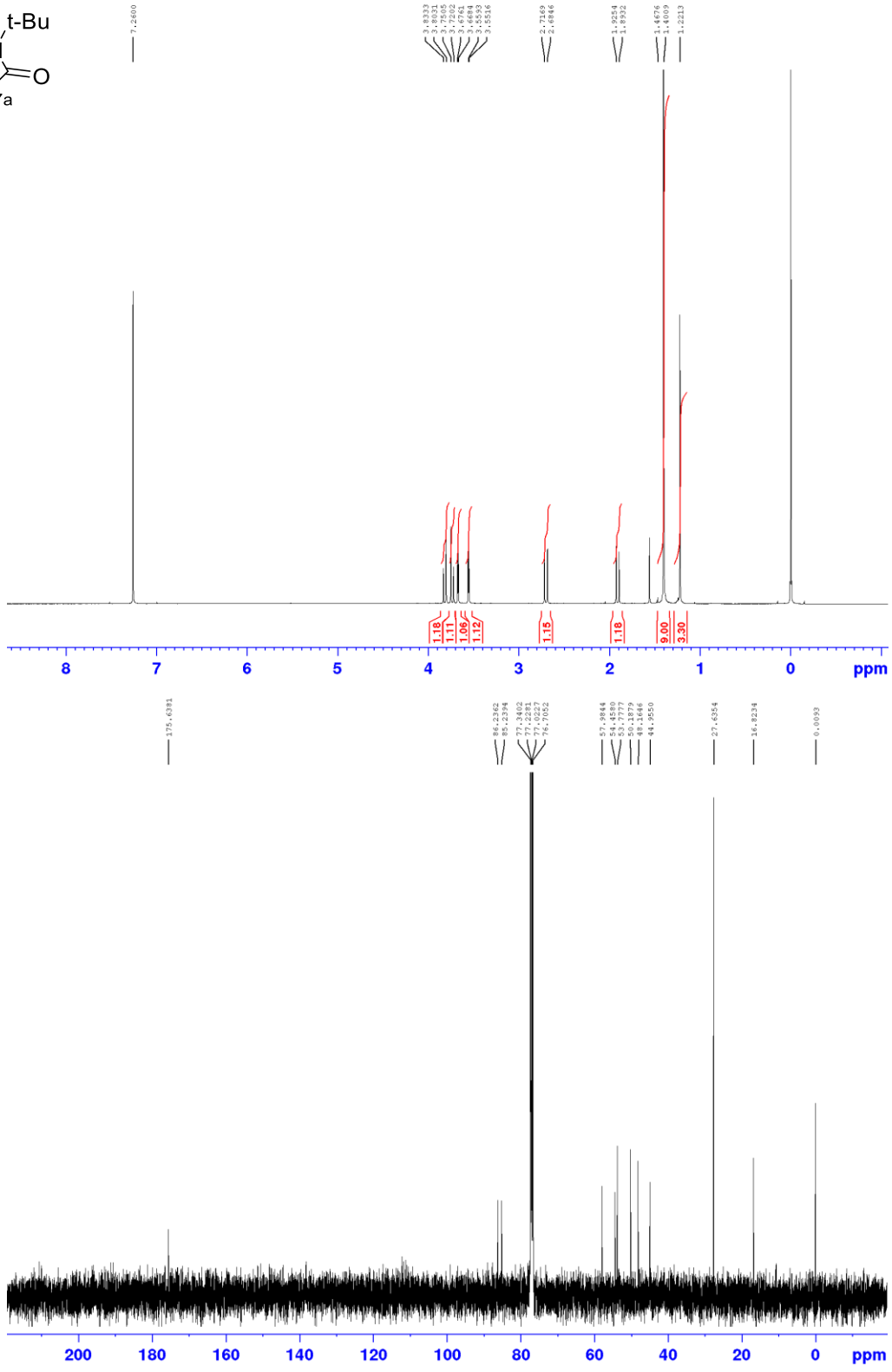


Compound **111**

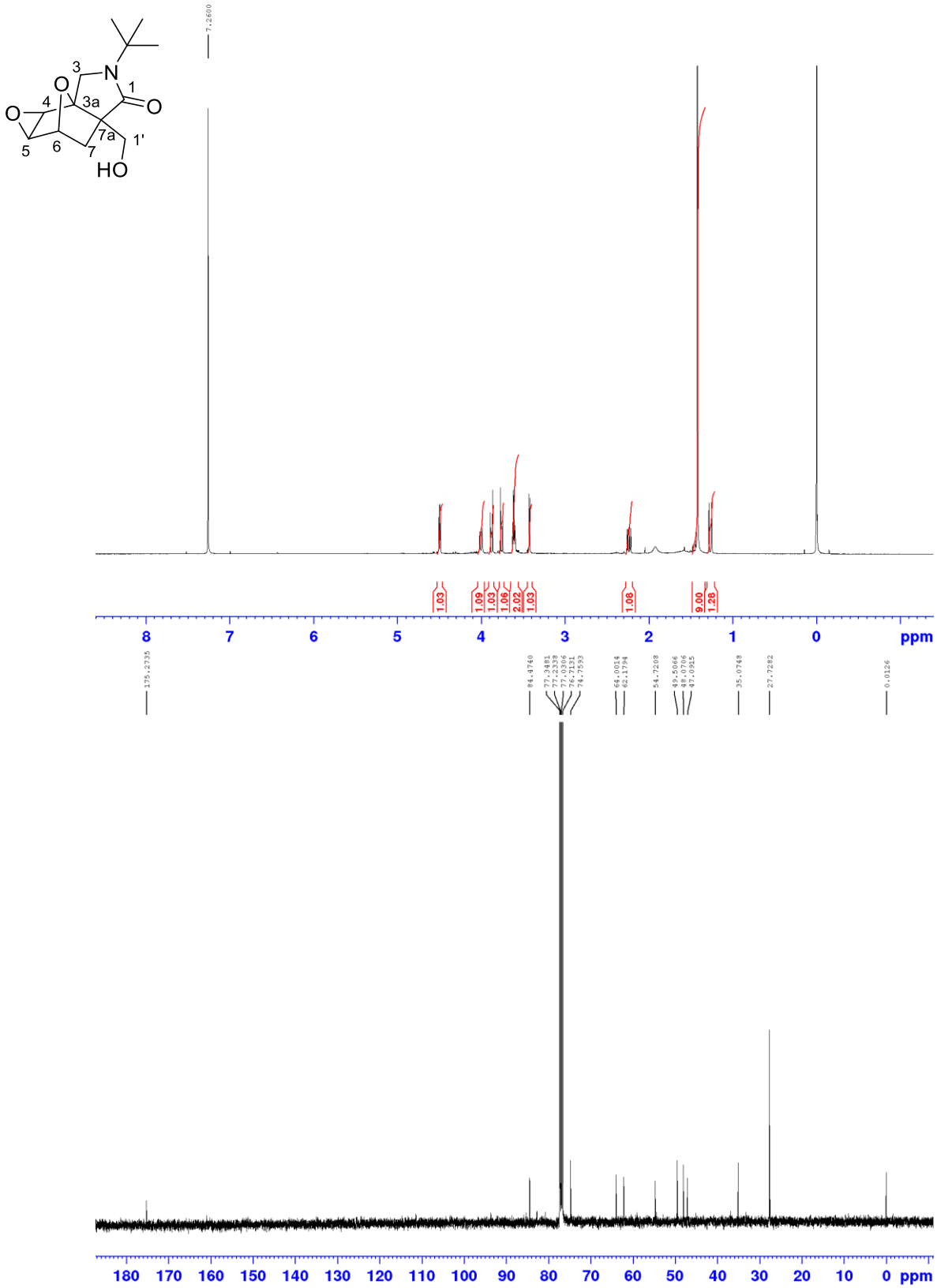


Compound **112**

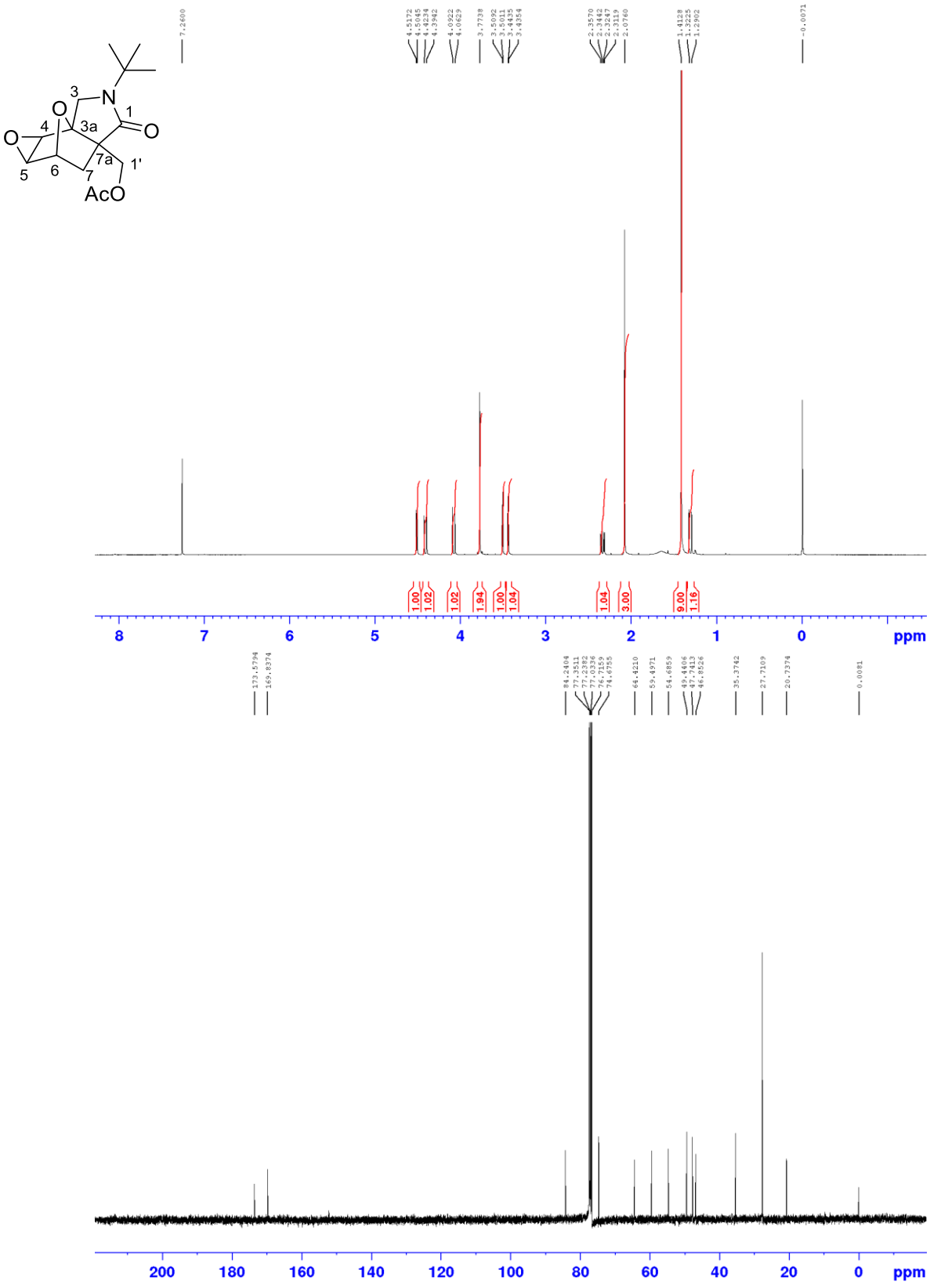




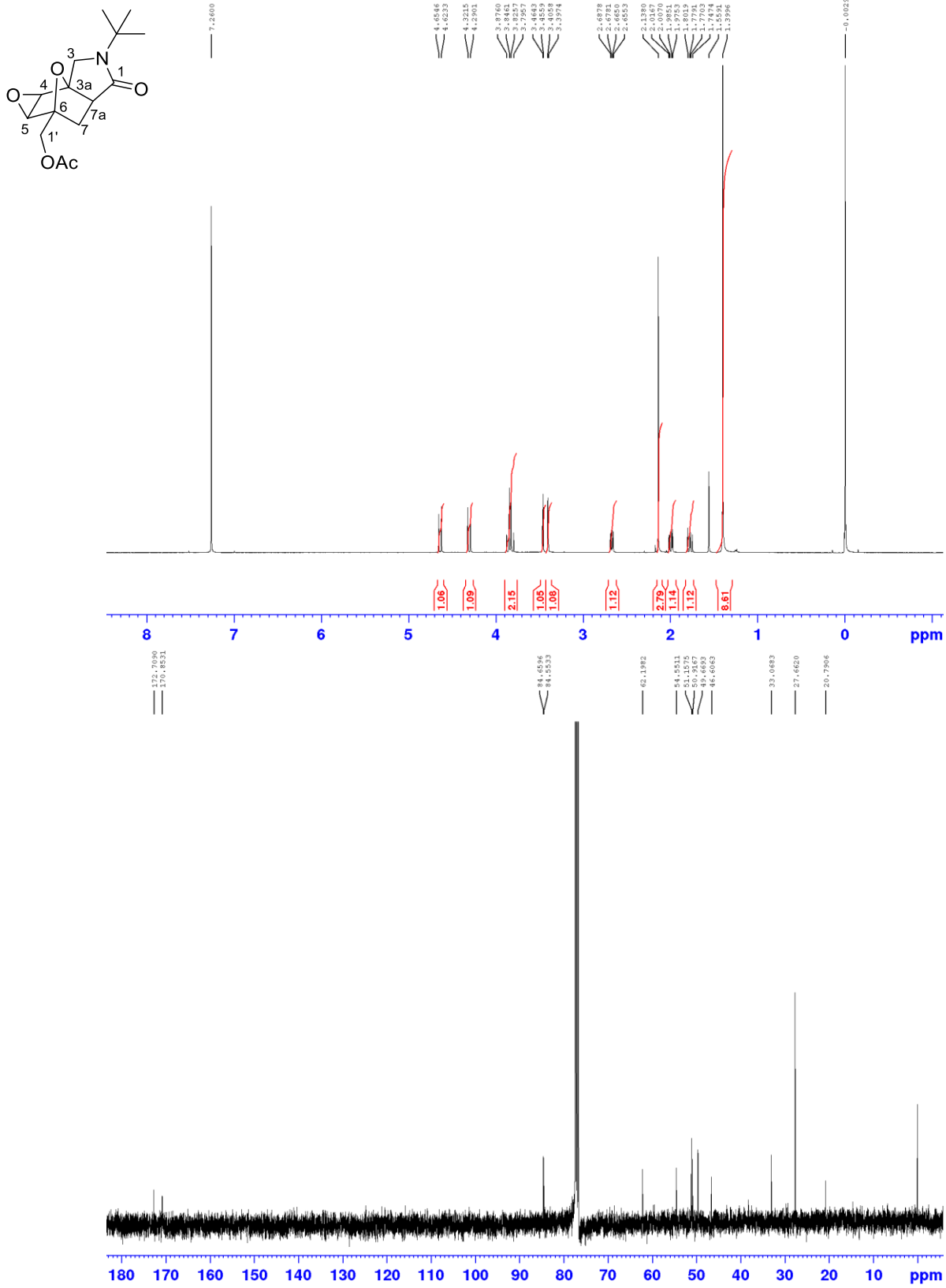
Compound **113**



Compound **114**

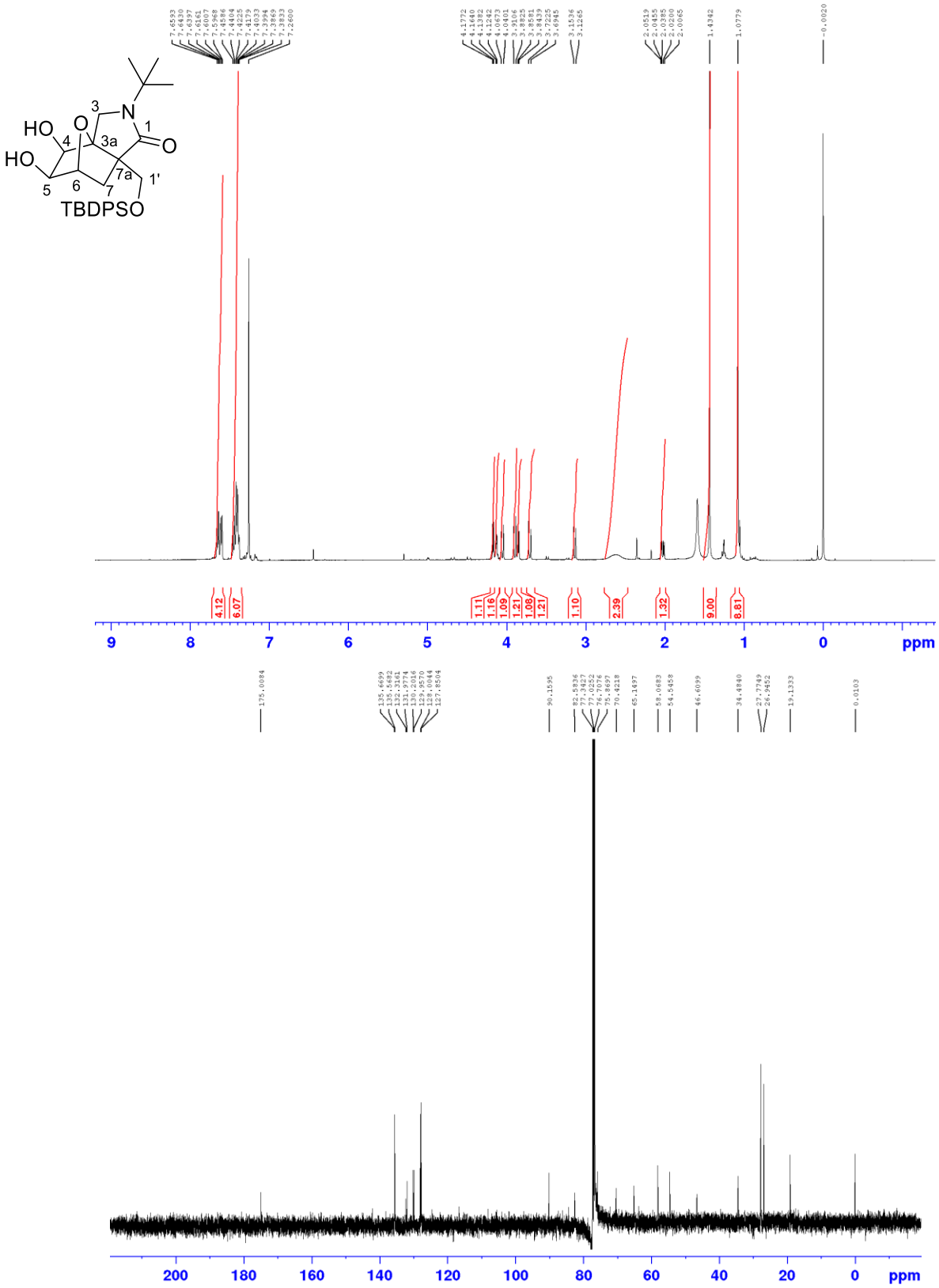


Compound **119**

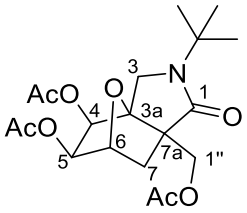


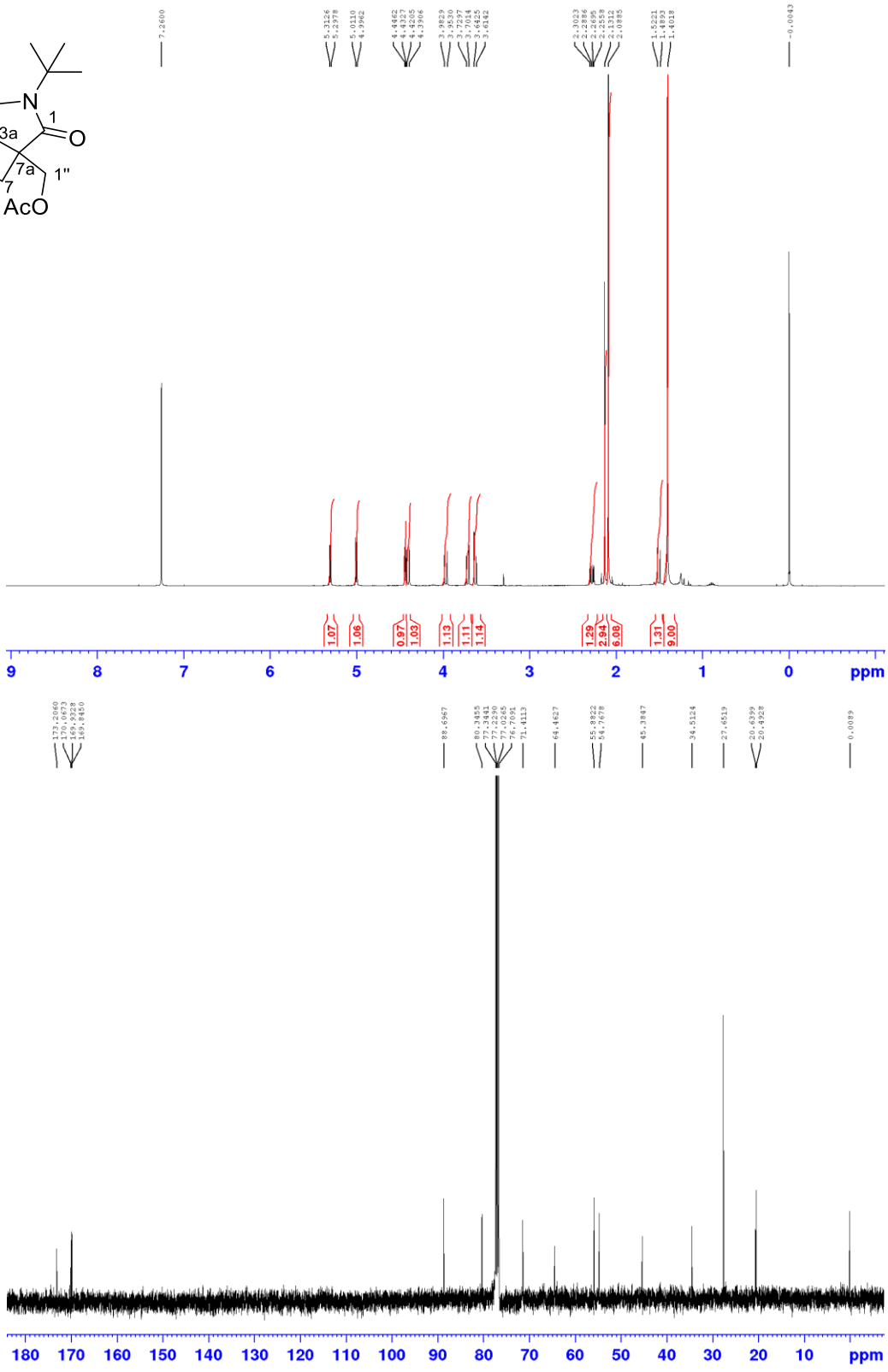
Dihydroxylation products

Compound **137**

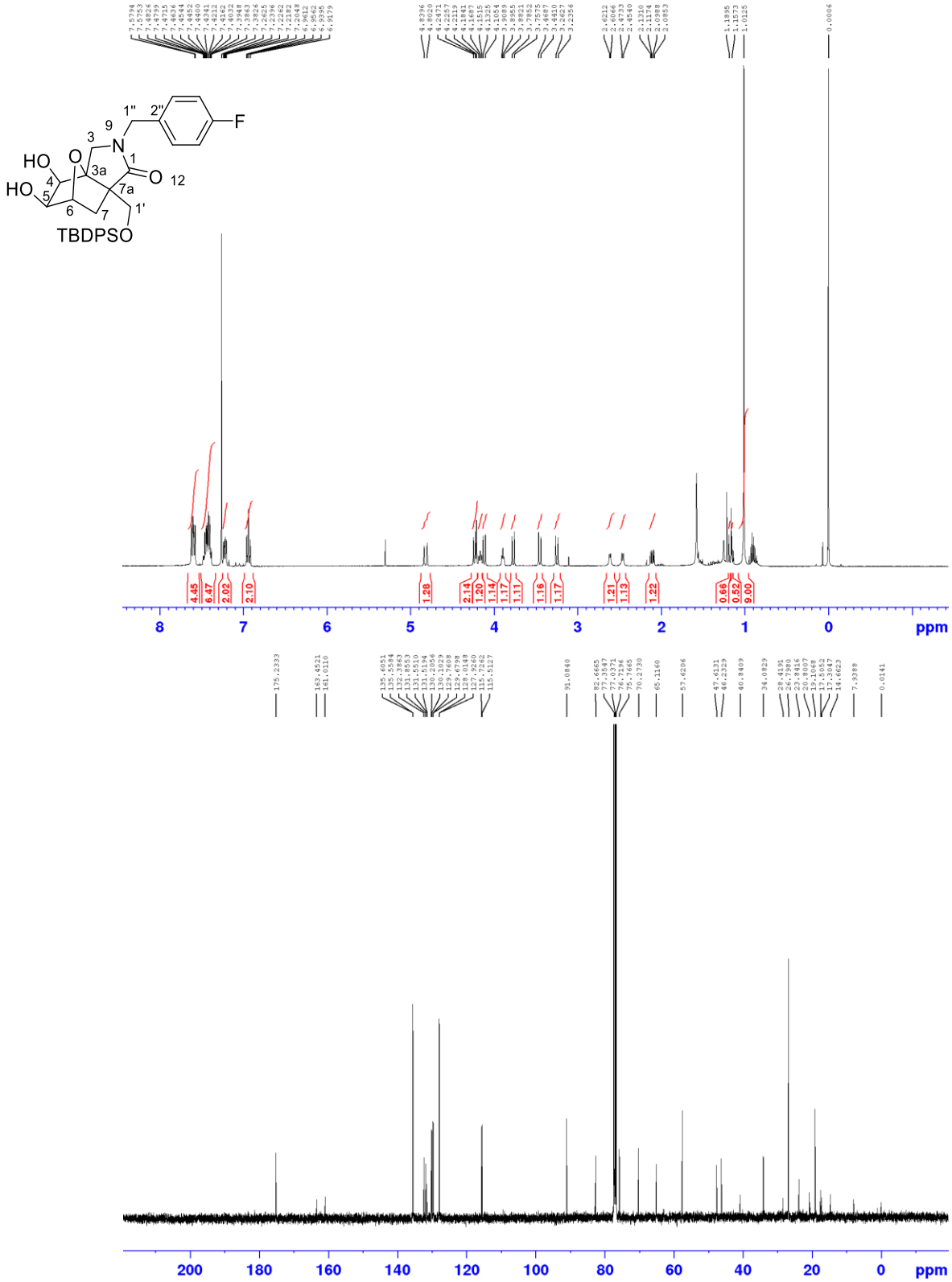


Compound **139**

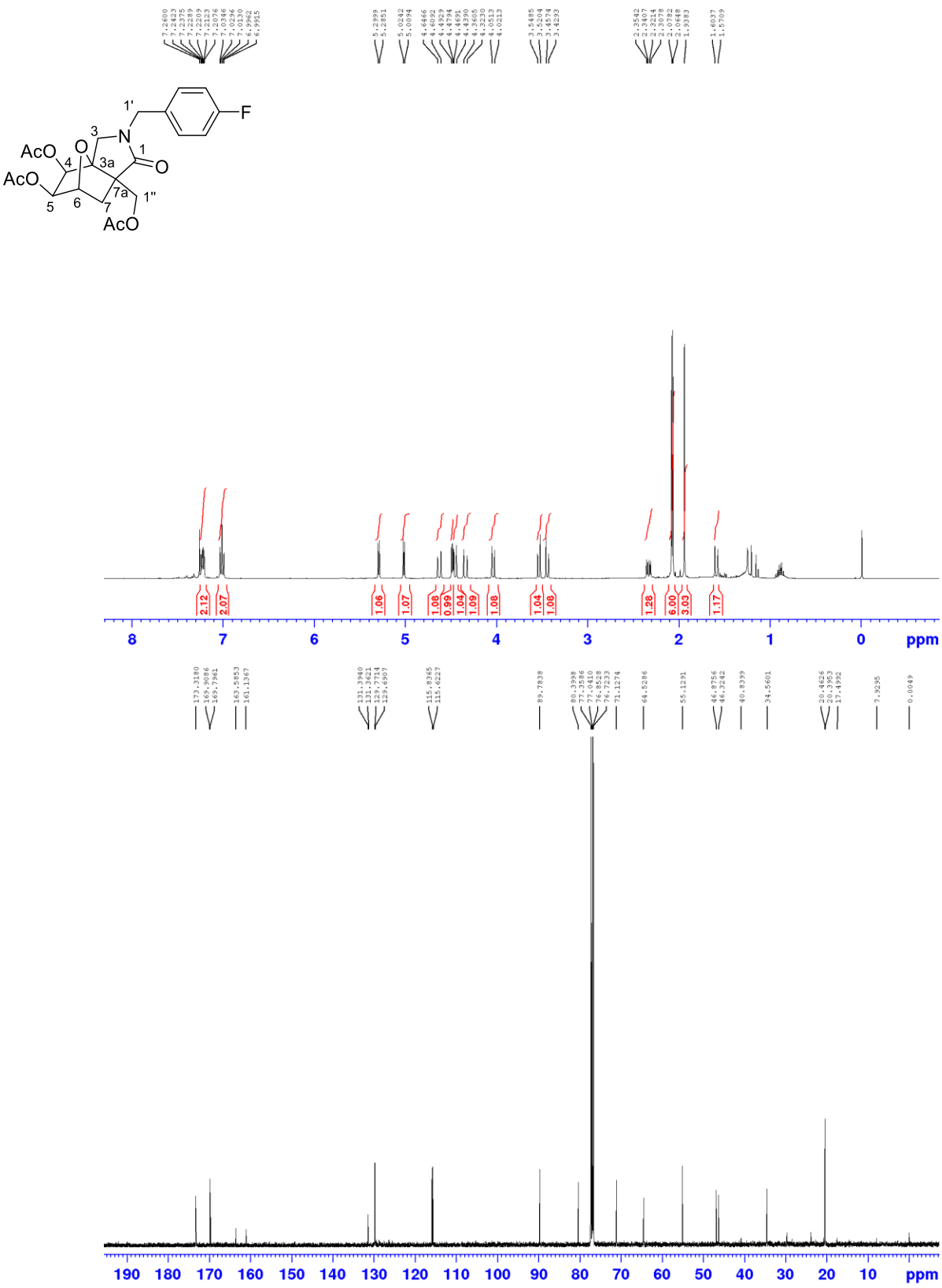




Compound **140**

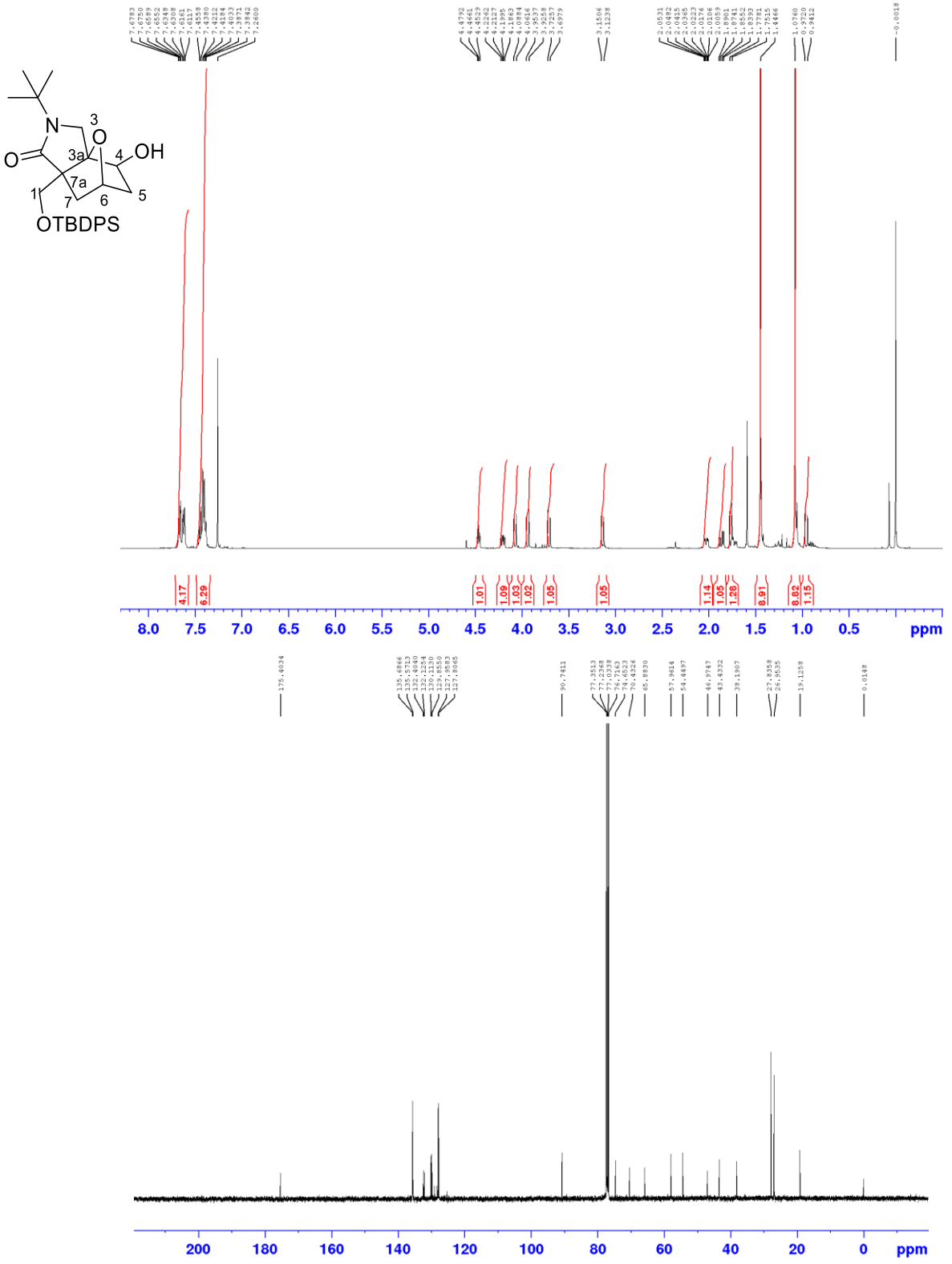


Compound **143**

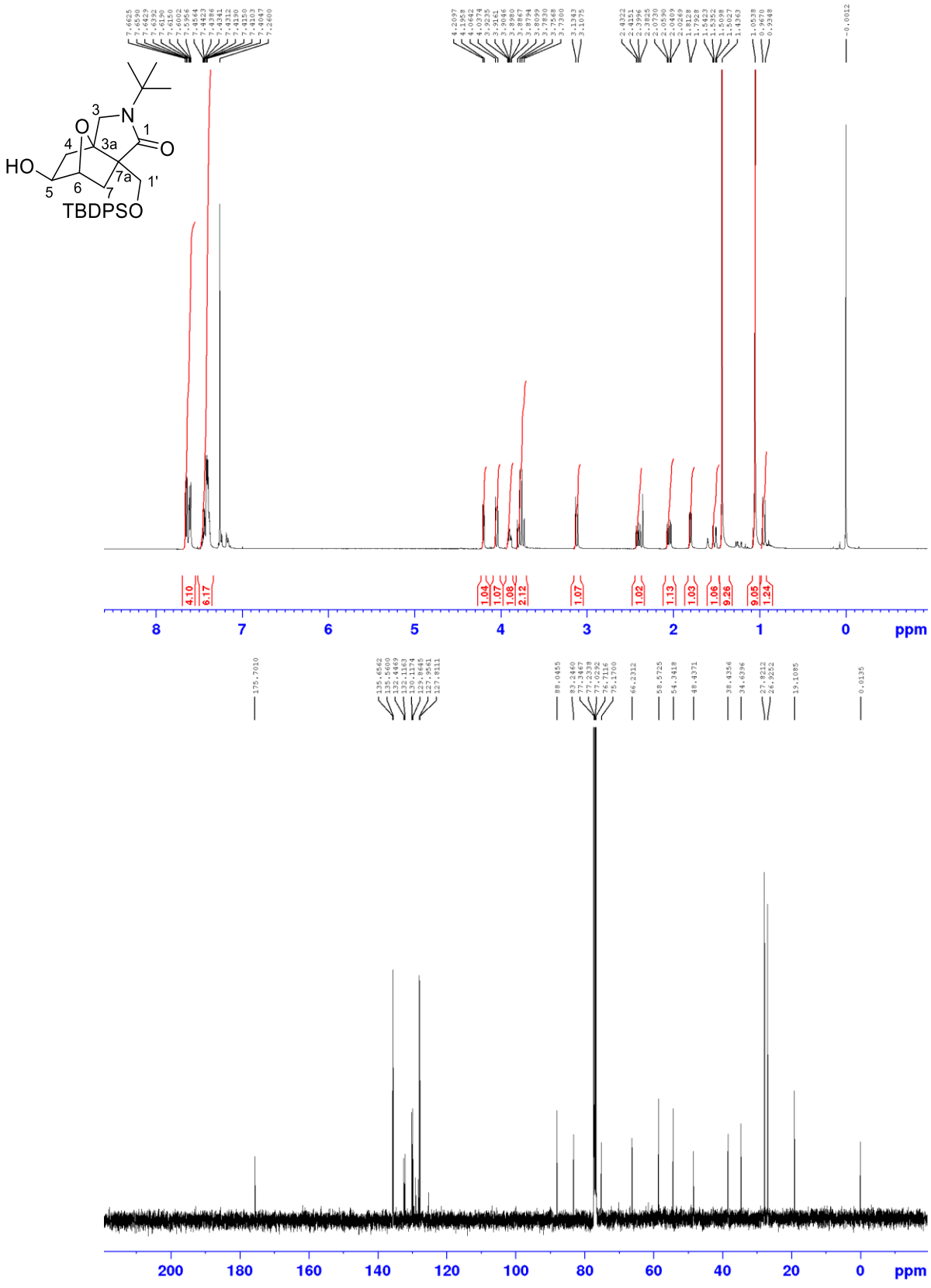


Hydroboration products

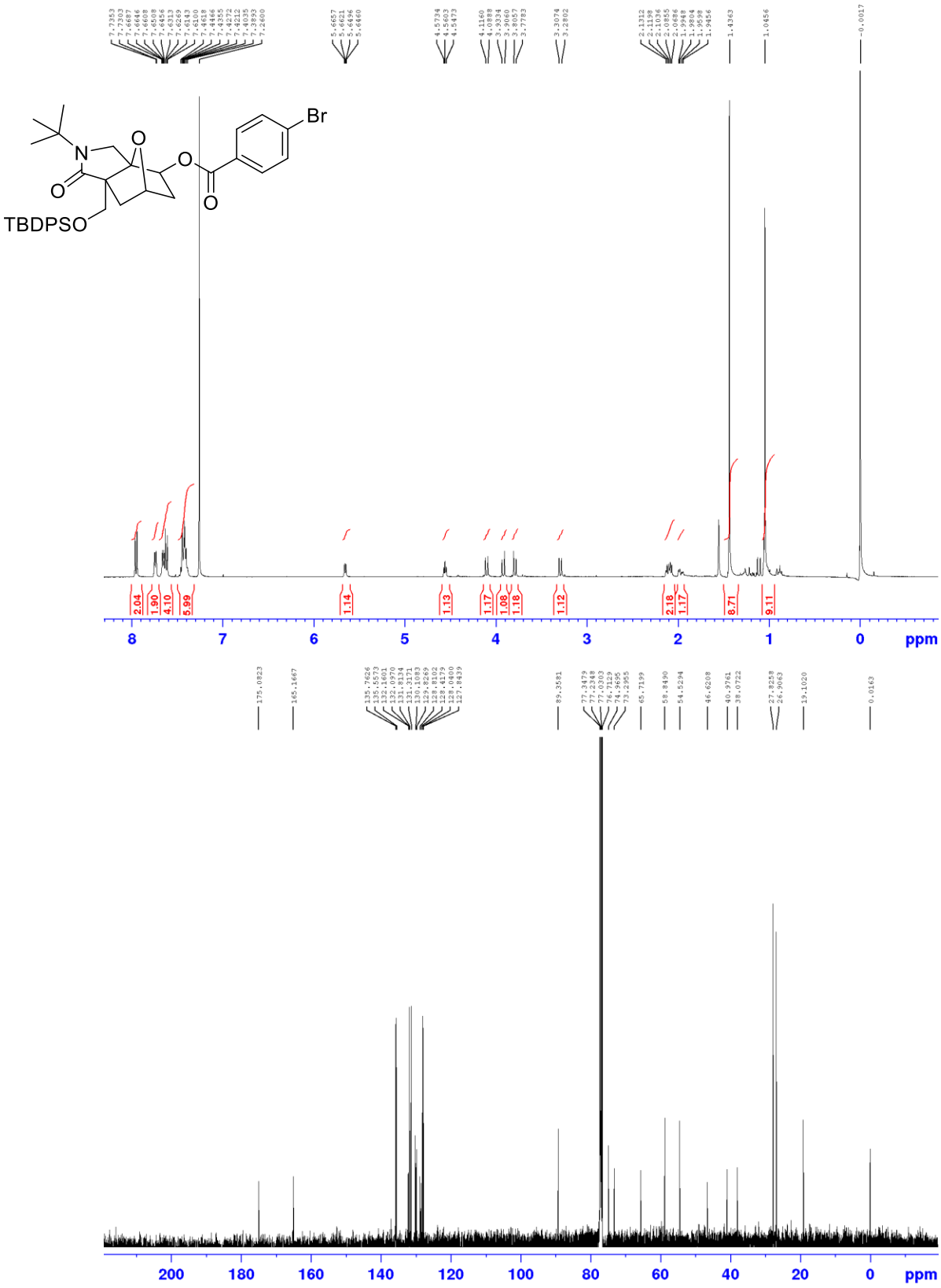
Compound **120**



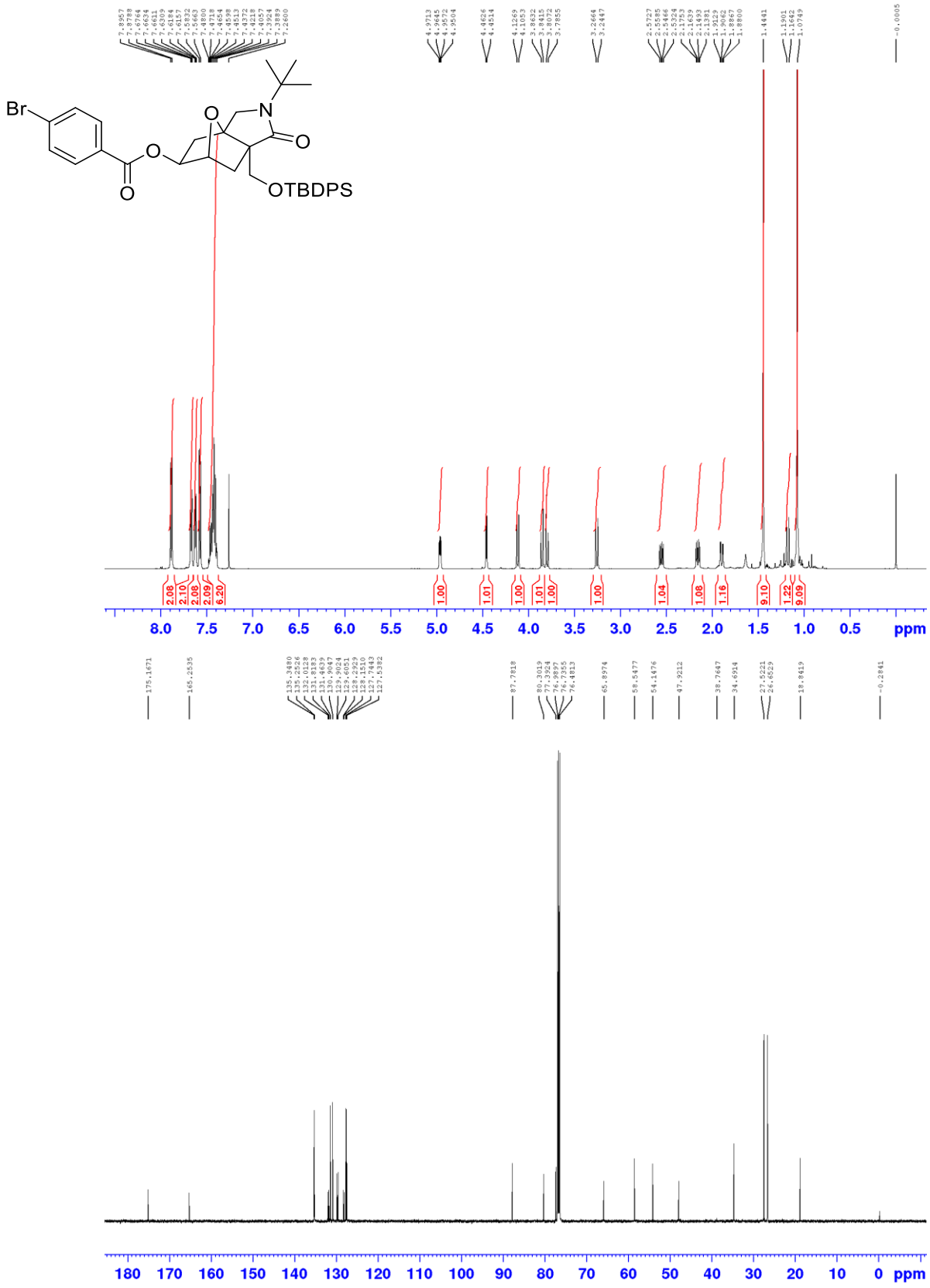
Compound **121**



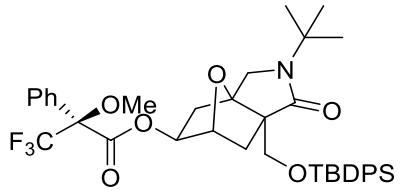
Compound **120.1**

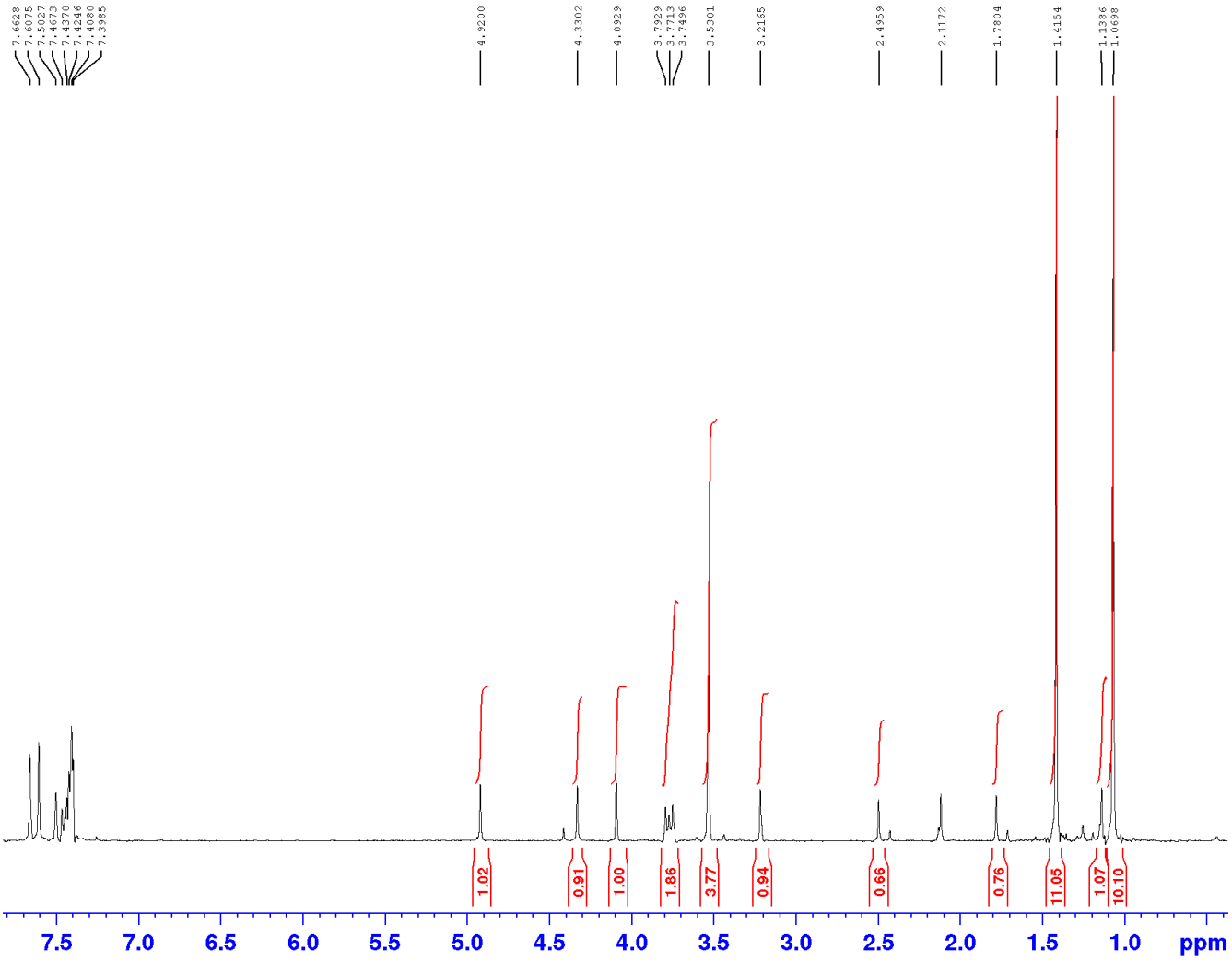


Compound **121.1**

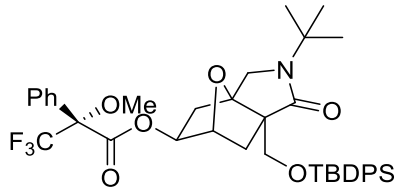


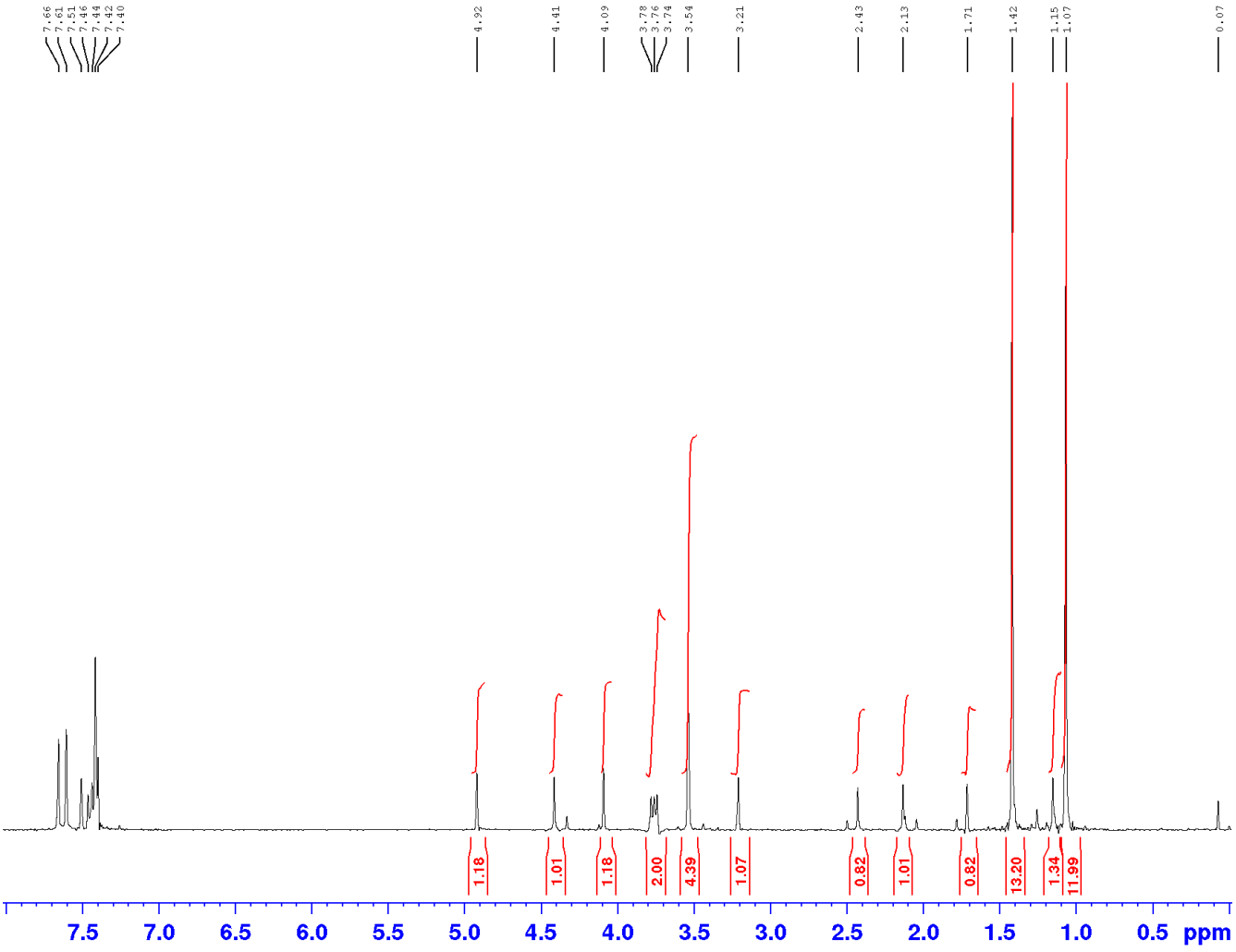
Compound **122** (^{1}H, Pure shift)



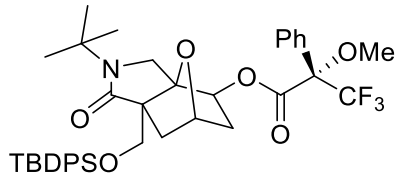


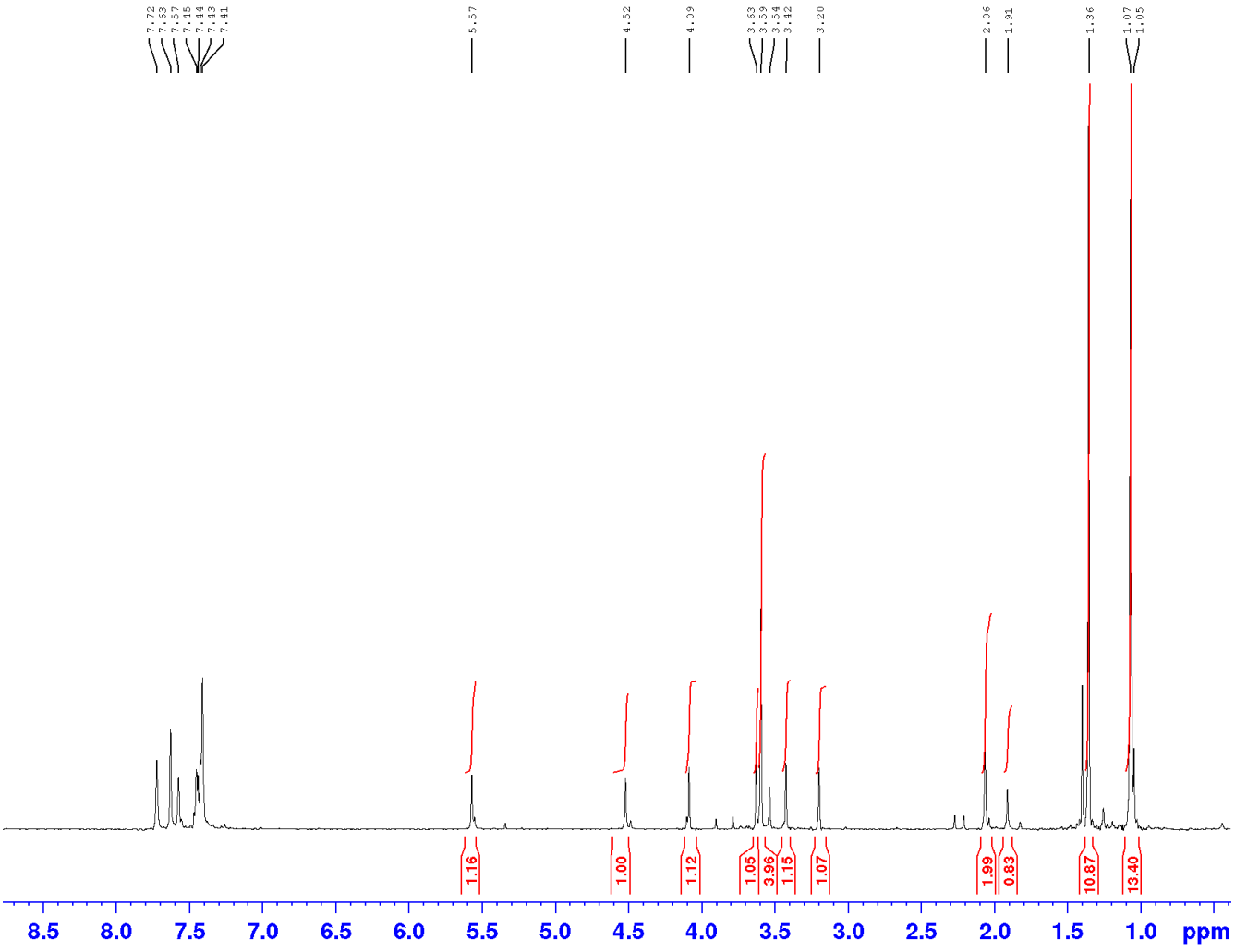
Compound **123** (^{1}H, Pure shift)



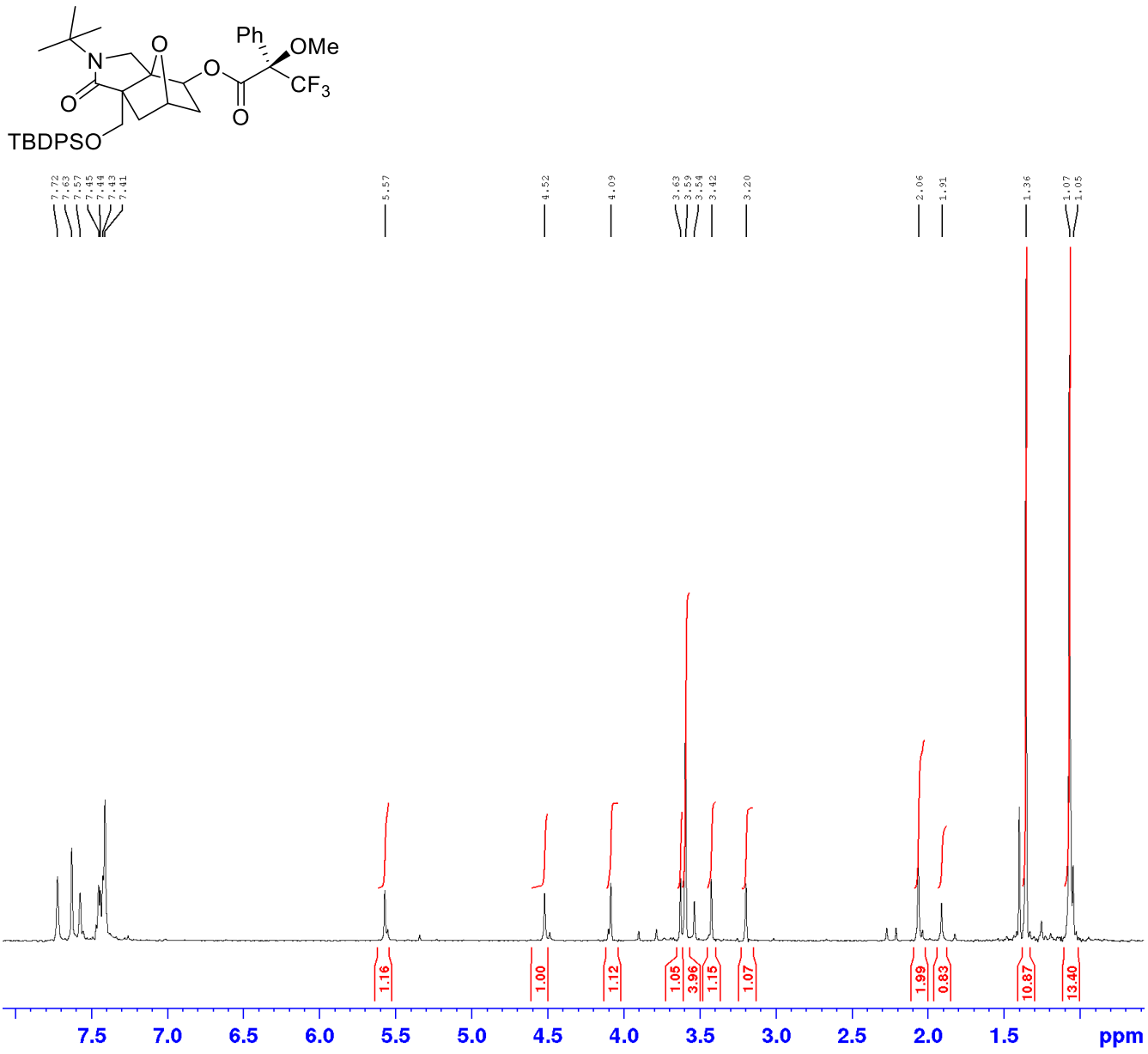


Compound **124** (^{1}H, Pure shift)

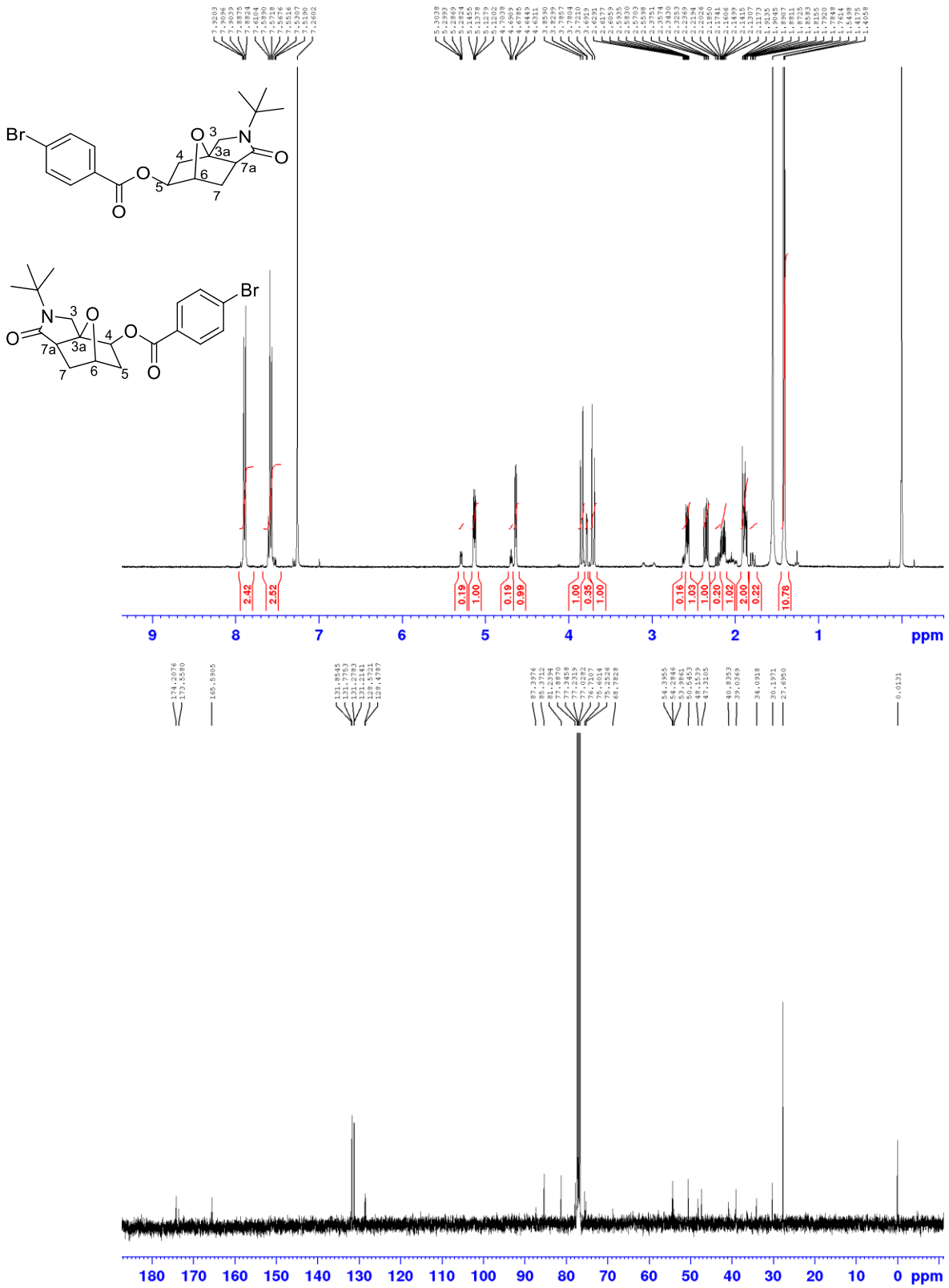




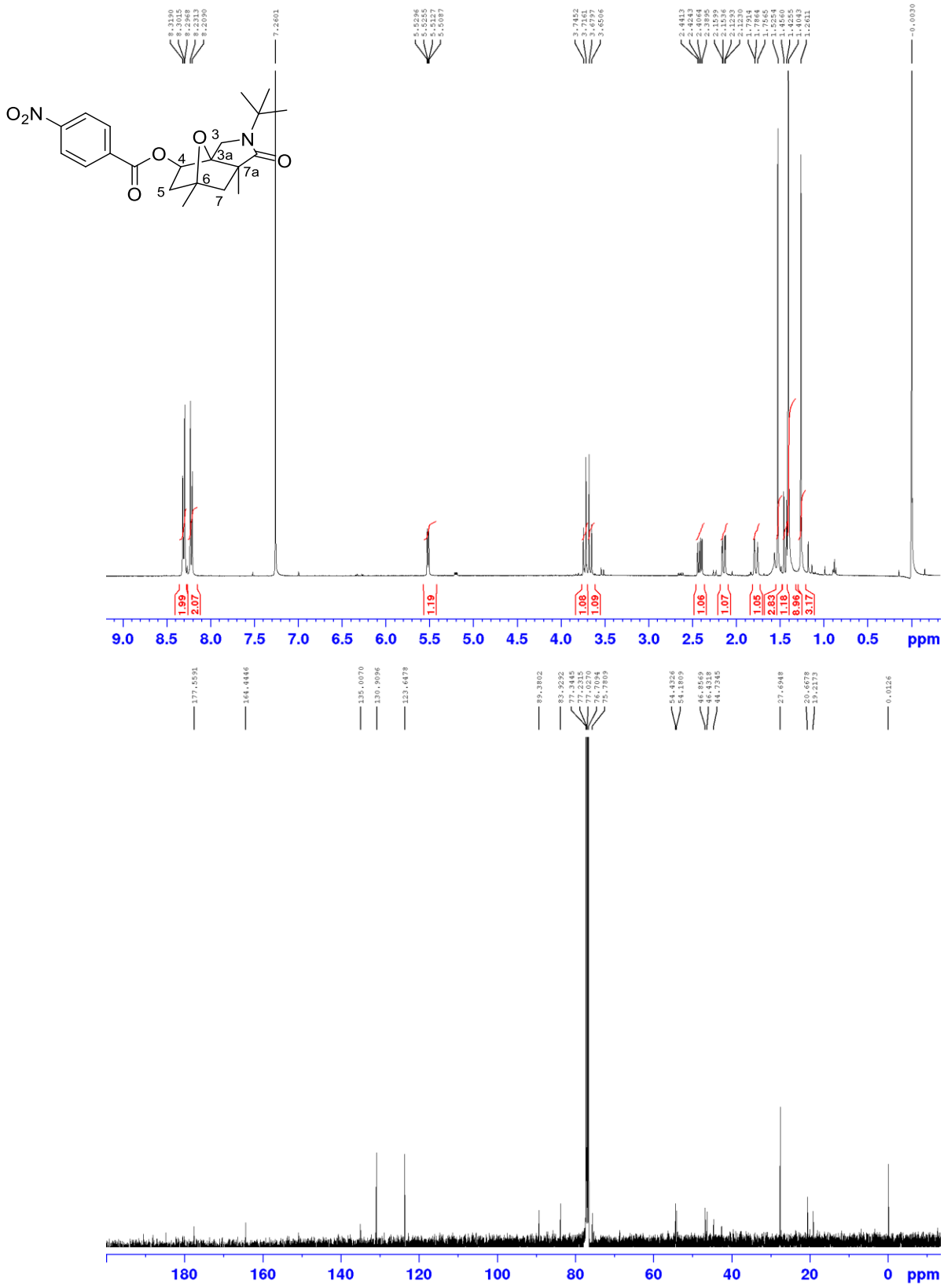
Compound **125** (^{1}H, Pure shift)



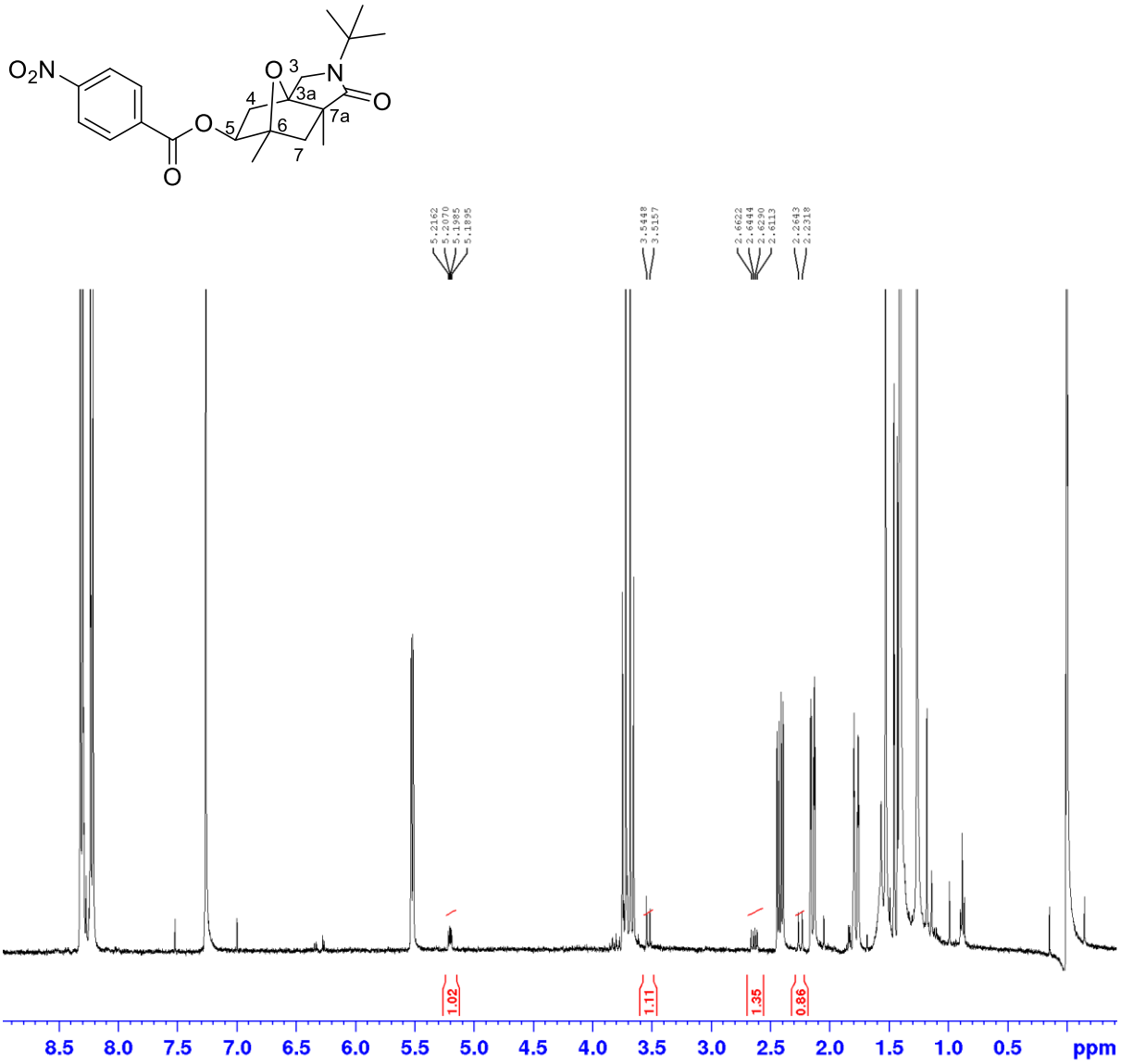
Compound **126** and **127**



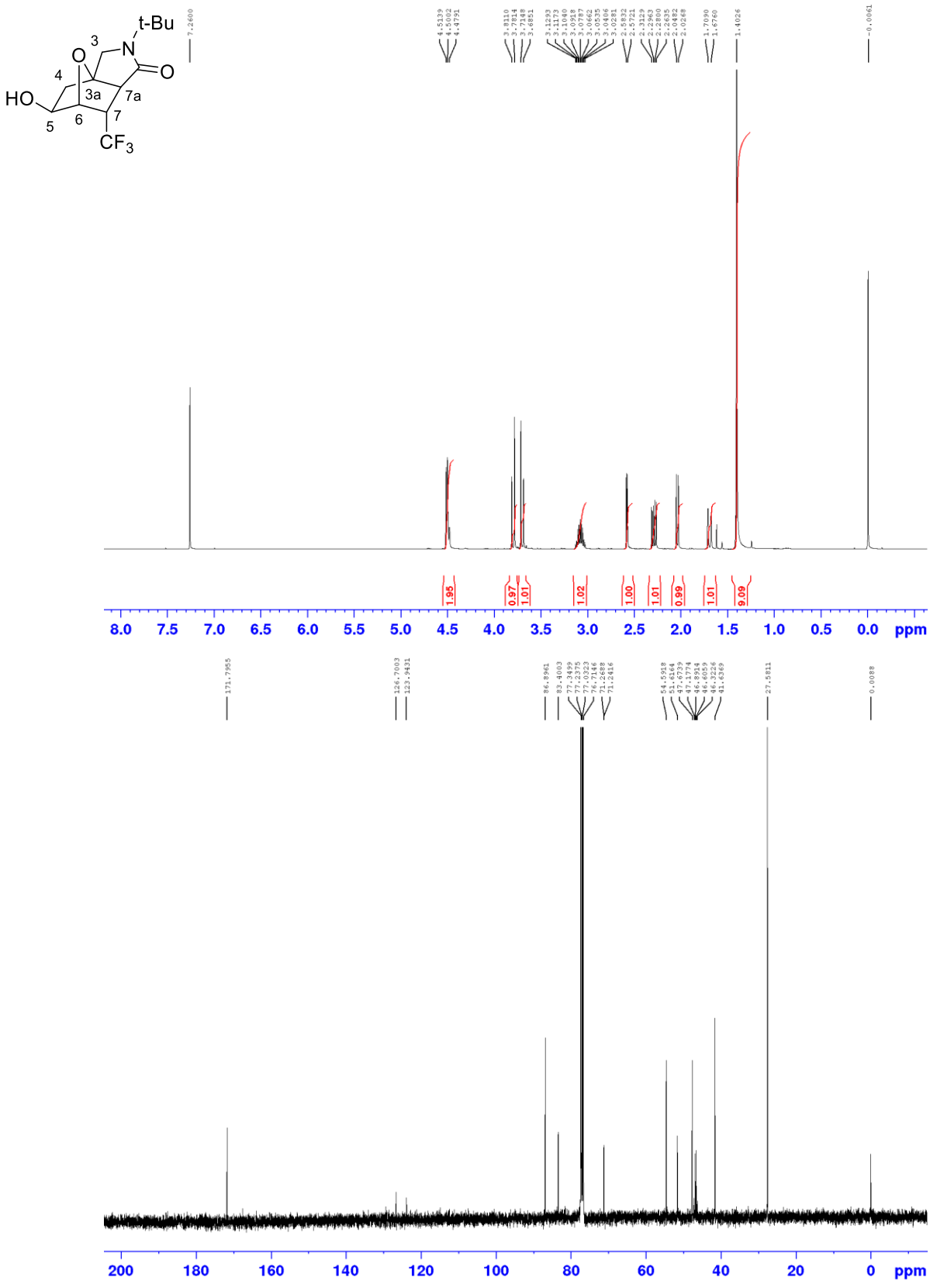
Compound **130**



Compound **131**

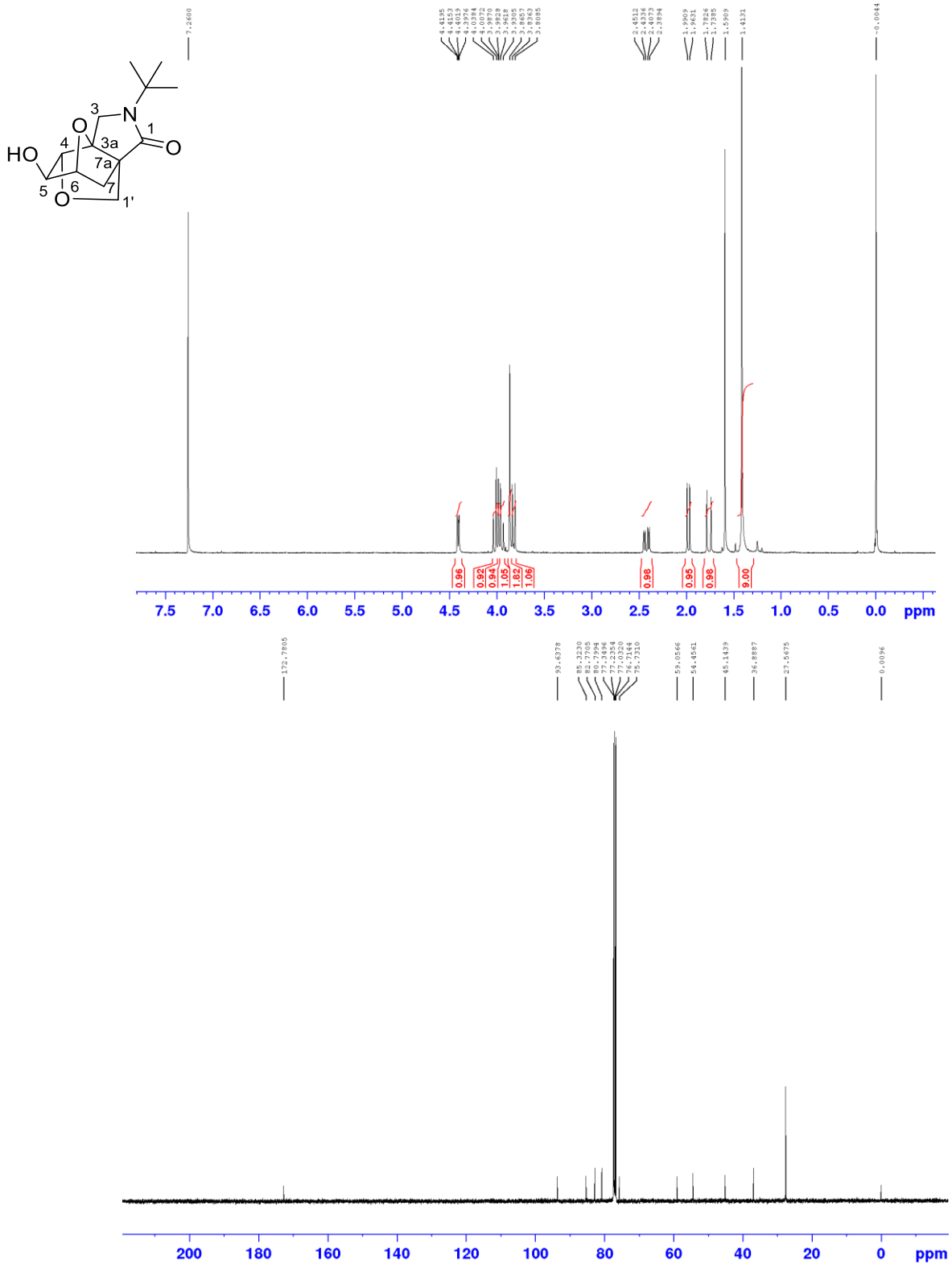


Compound **132**

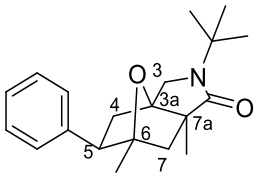


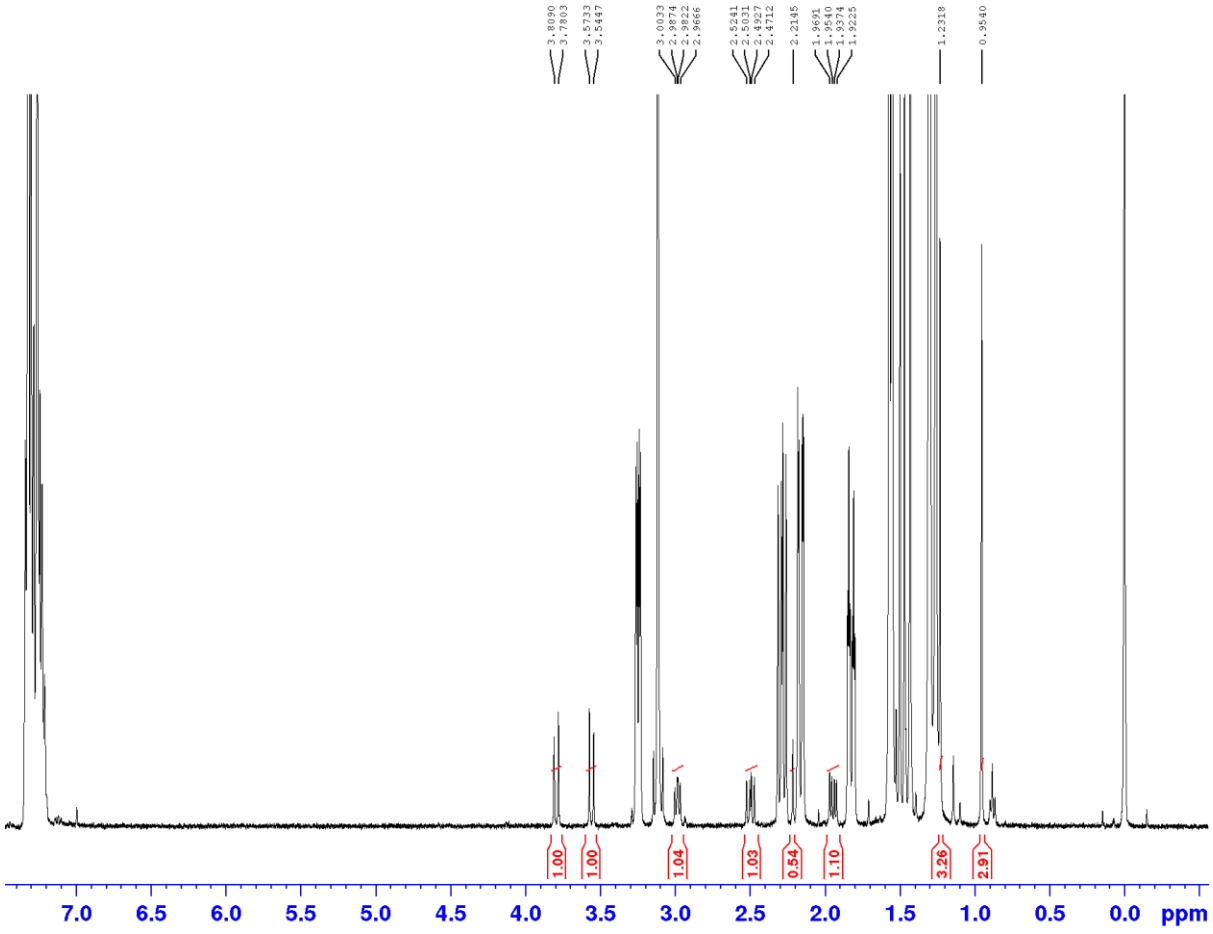
Others

Compound **115**

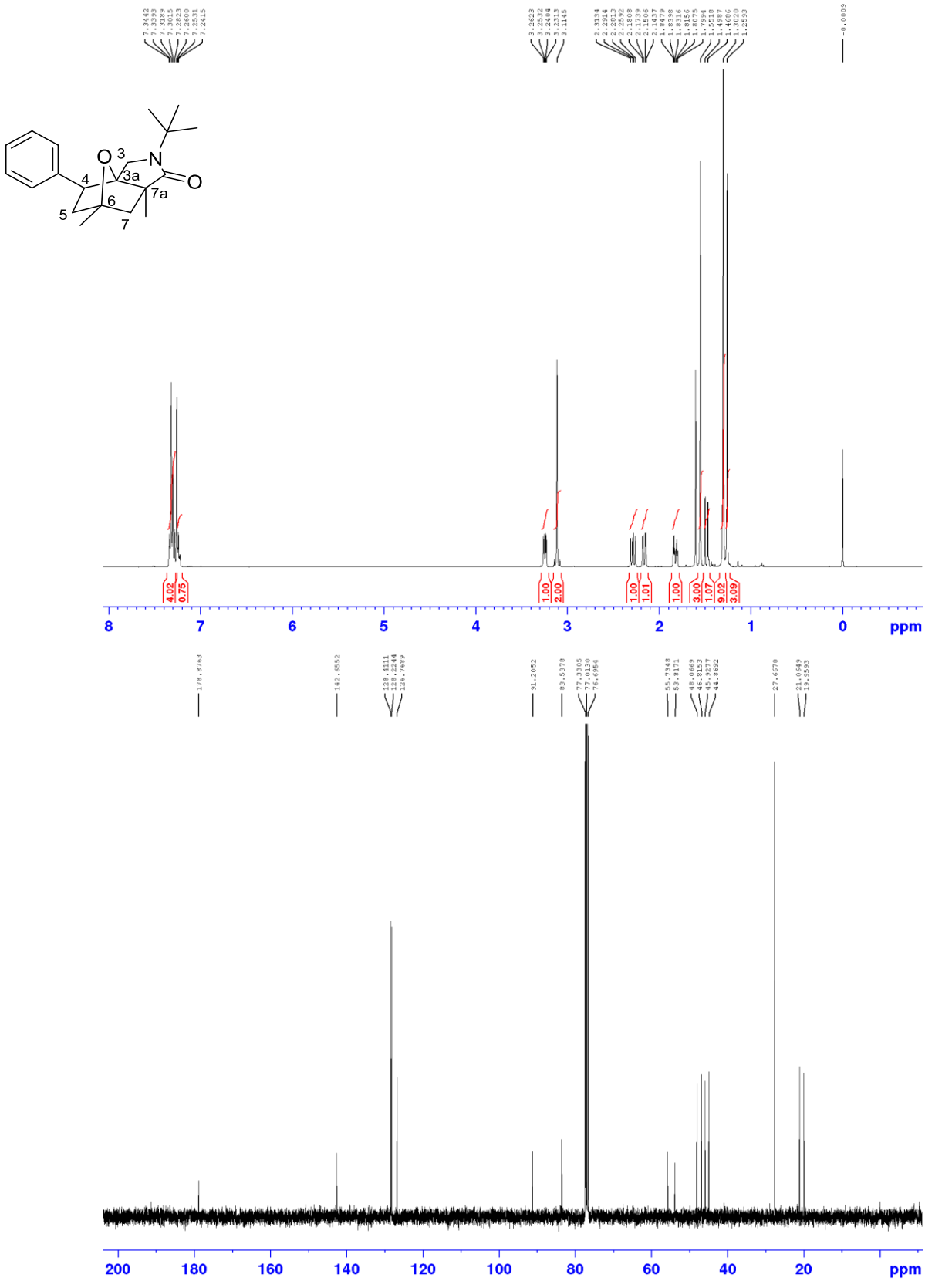


Compound **133**



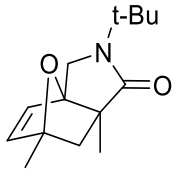


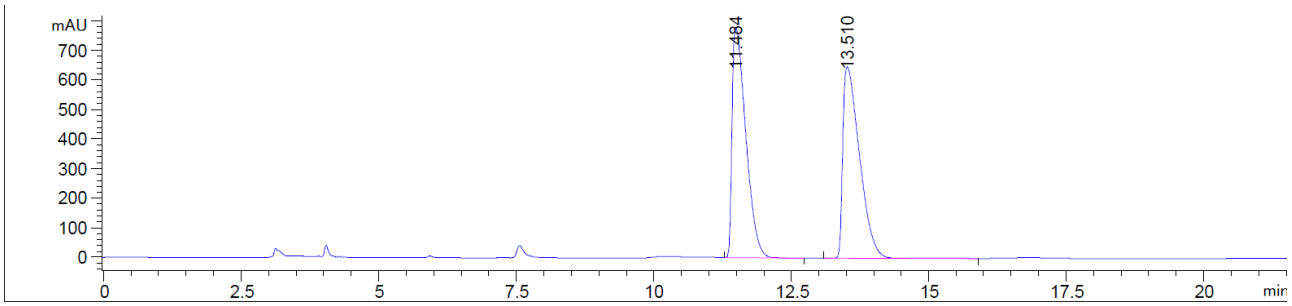
Compound **134**



HPLC DATA

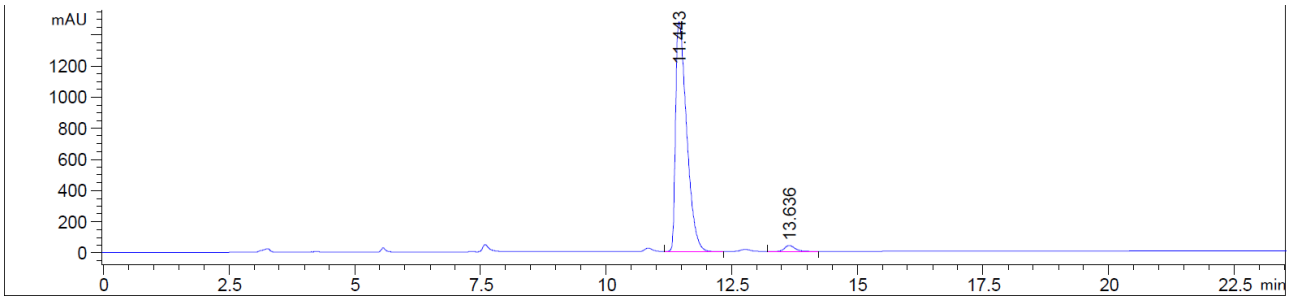
Compound **100**





Signal 3: DAD1 C, Sig=220,4 Ref=360,100

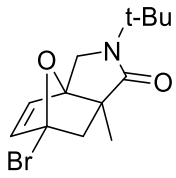
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.484	BB	0.2654	1.34582e4	779.73804	49.6942
2	13.510	BB	0.3235	1.36238e4	647.33862	50.3058

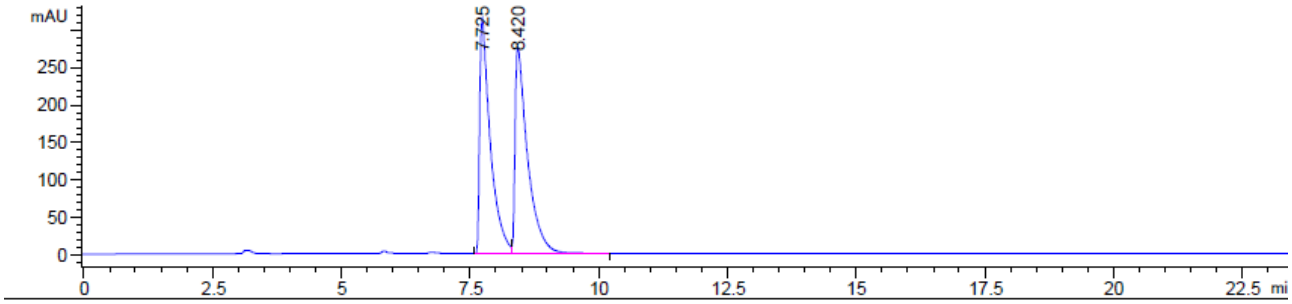


Signal 3: DAD1 C, Sig=220,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.443	VB	0.2300	7321.59814	490.93967	97.6835
2	13.636	BB	0.2132	173.62976	12.26374	2.3165

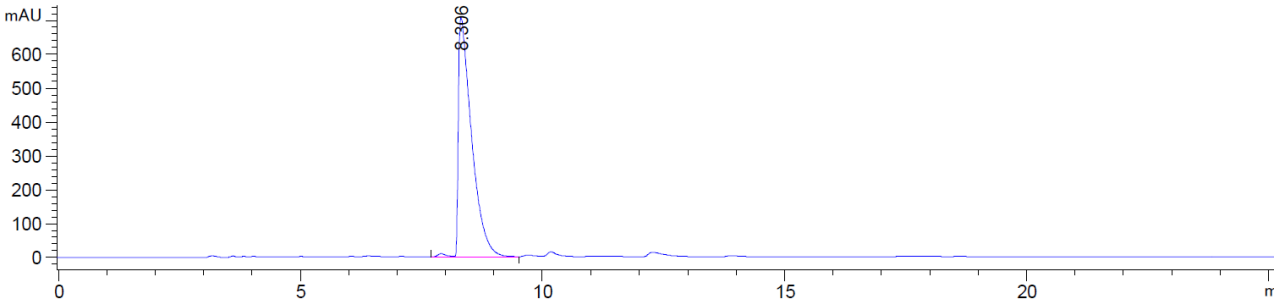
Compound **97**



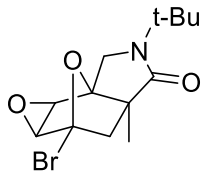


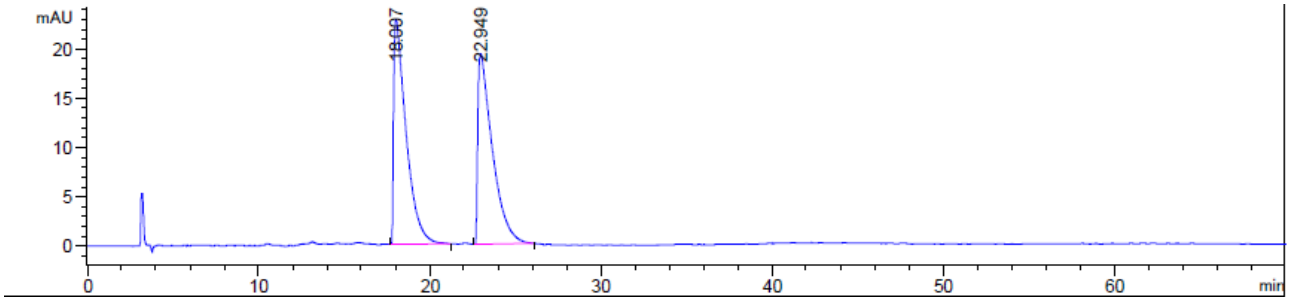
Signal 4: DAD1 D, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.725	BV	0.2034	1057.67297	73.73415	49.3455
2	8.420	VB	0.2384	1085.73218	64.49135	50.6545



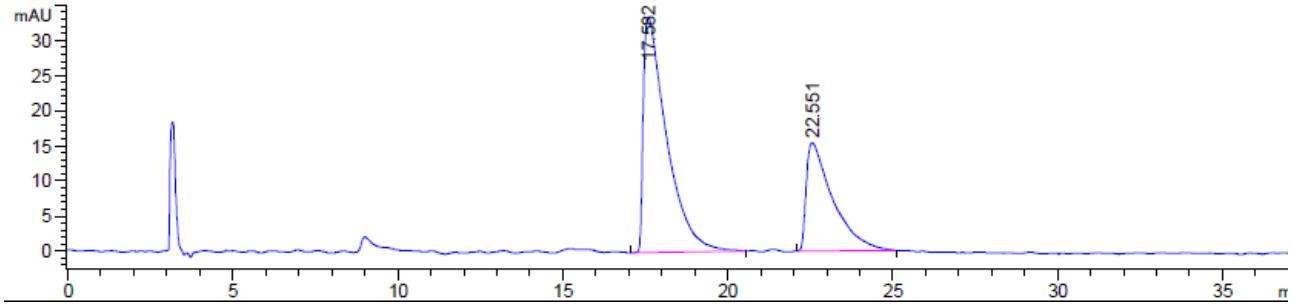
Compound **112**





Signal 2: DAD1 B, Sig=210,4 Ref=360,100

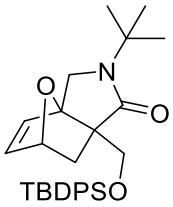
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.006	BB	0.7078	4091.97314	80.66919	49.9136
2	22.949	BB	0.8527	4106.13770	68.36921	50.0864

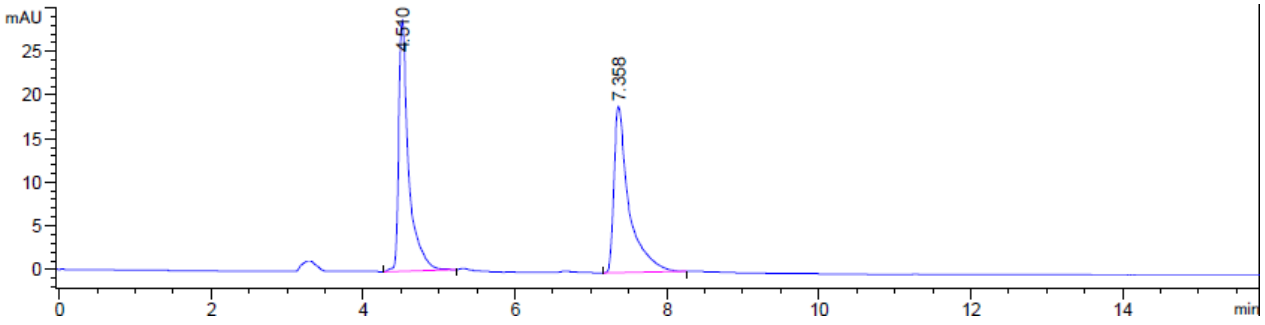


Signal 2: DAD1 B, Sig=210,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.582	BB	0.6923	1643.96960	33.51274	65.6948
2	22.551	BB	0.7492	858.46460	15.38049	34.3052

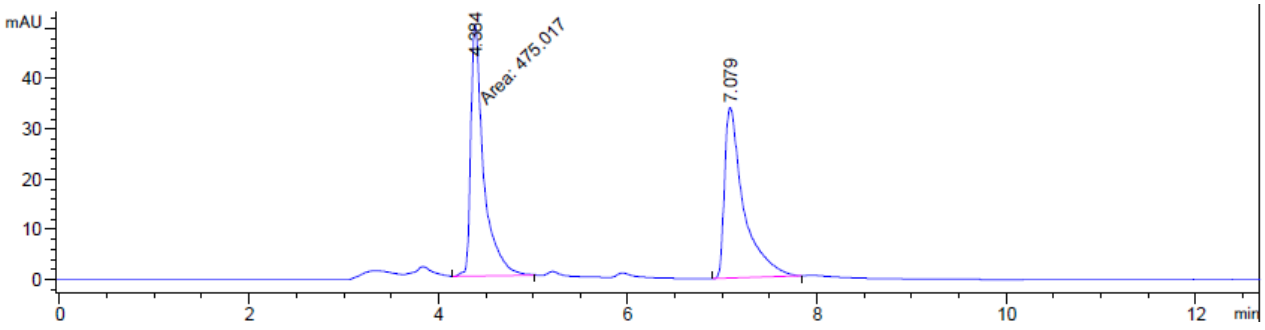
Compound **77**





Signal 5: DAD1 E, Sig=254,4 Ref=360,100

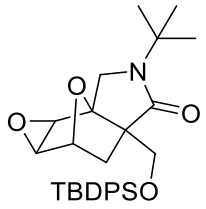
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.510	BB	0.1341	261.66006	28.77483	50.0842
2	7.358	BB	0.1958	260.78052	19.03772	49.9158

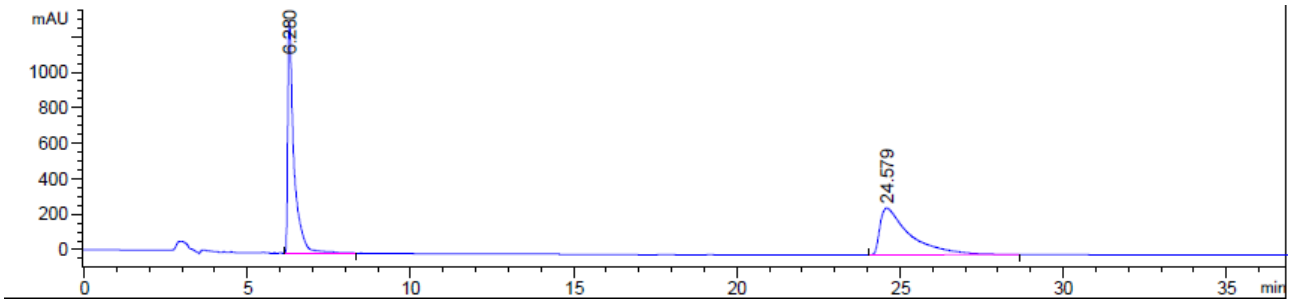


Signal 5: DAD1 E, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.384	MM	0.1577	475.01703	50.20908	49.9790
2	7.079	BB	0.2009	475.41693	34.04838	50.0210

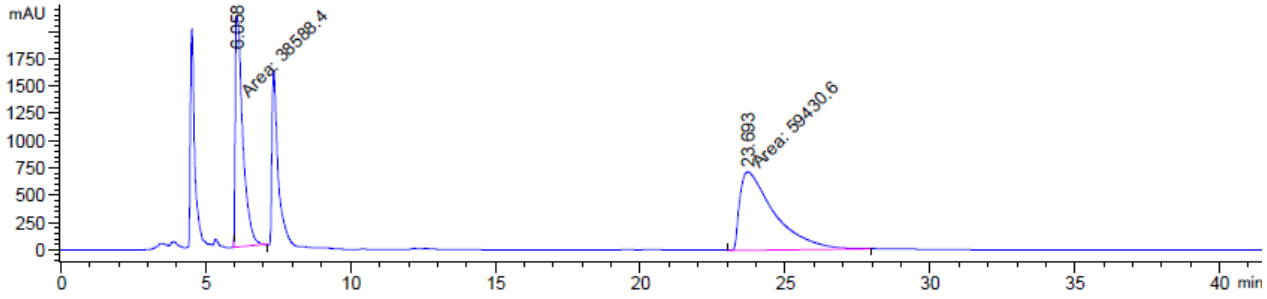
Compound **111**





Signal 3: DAD1 C, Sig=230,4 Ref=360,100

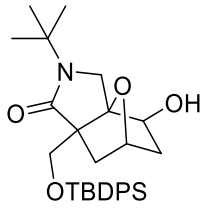
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.280	BV R	0.1851	1.72307e4	1309.92480	50.7714
2	24.579	BB	0.8957	1.67071e4	263.50009	49.2286

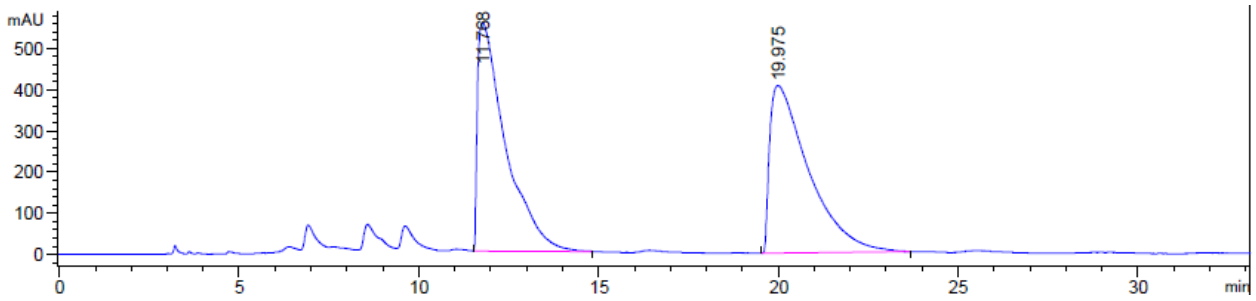


Signal 3: DAD1 C, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.058	MM	0.3037	3.85884e4	2117.46509	39.3683
2	23.693	MM	1.3808	5.94306e4	717.32843	60.6317

Compound **120**

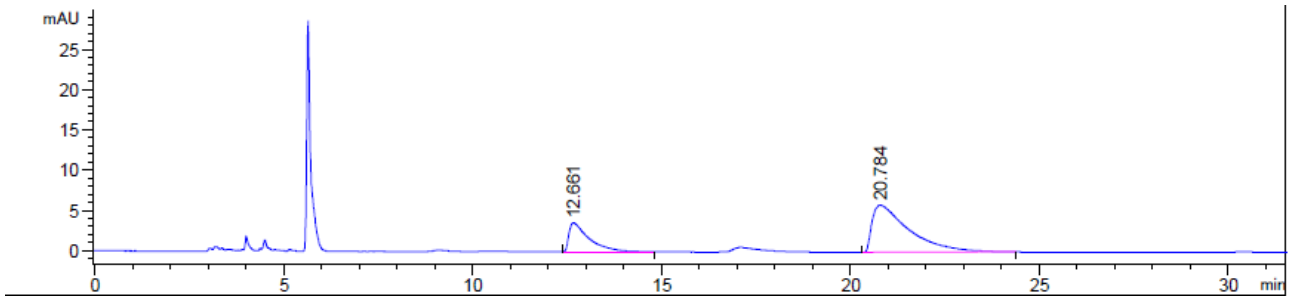




Signal 1: DAD1 A, Sig=200,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.768	BV R	0.7077	3.01232e4	556.30194	49.4349
2	19.975	BV R	0.9967	3.08119e4	408.14435	50.5651

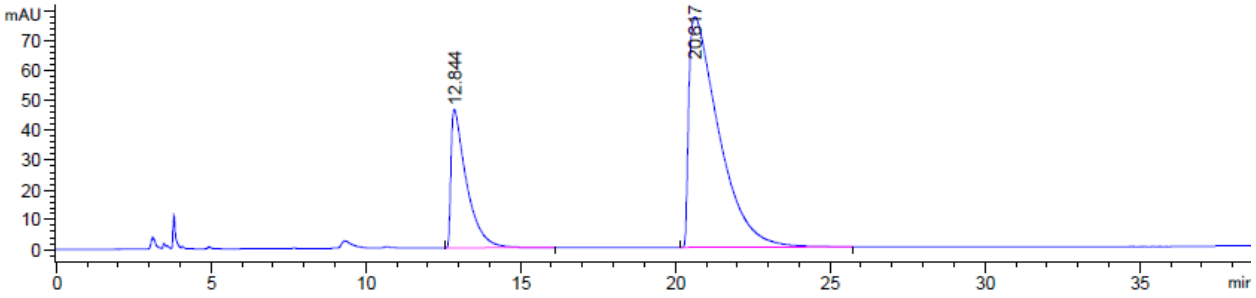
0°C



Signal 4: DAD1 D, Sig=240,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.661	BB	0.5106	133.27293	3.57761	25.1152
2	20.784	BB	0.9133	397.37283	5.82891	74.8848

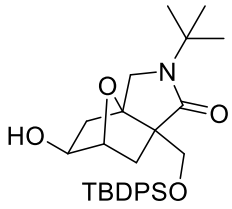
-40°C

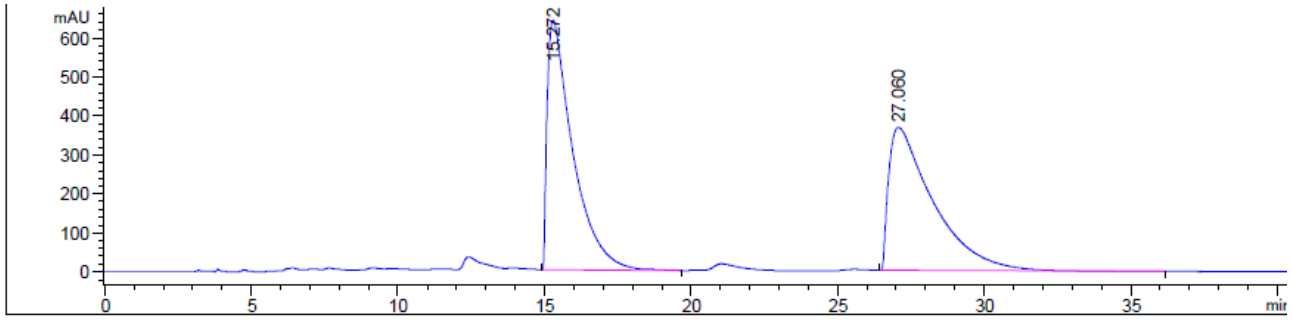


Signal 3: DAD1 C, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.844	BB	0.4994	1623.32227	46.26302	23.8260
2	20.617	BB	0.9689	5189.92383	77.13907	76.1740

Compound **121**

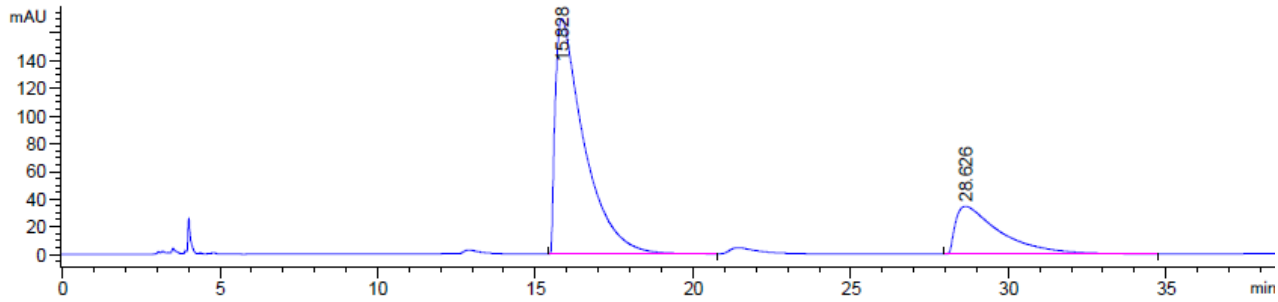




Signal 5: DAD1 E, Sig=220,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.272	BB	0.8794	3.87768e4	639.49164	50.0346
2	27.060	BB	1.4928	3.87231e4	367.05038	49.9654

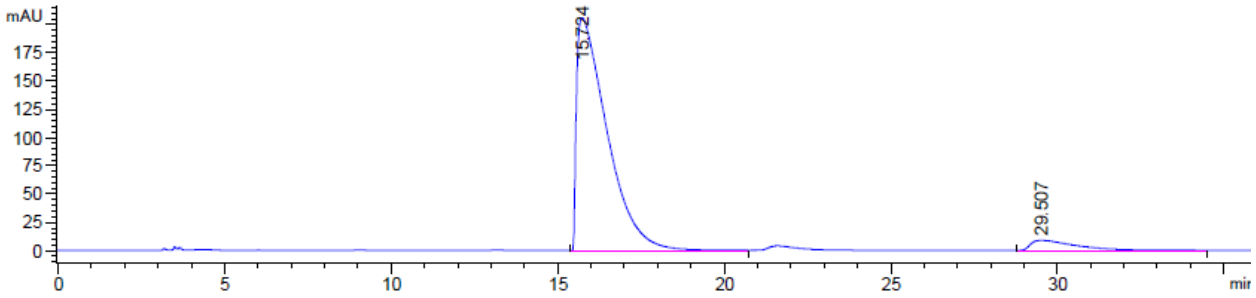
0°C



Signal 3: DAD1 C, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.828	BB	0.9193	1.07504e4	170.10013	76.0264
2	28.626	BB	1.3467	3389.93848	34.48981	23.9736

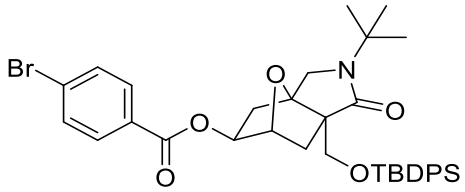
-40°C

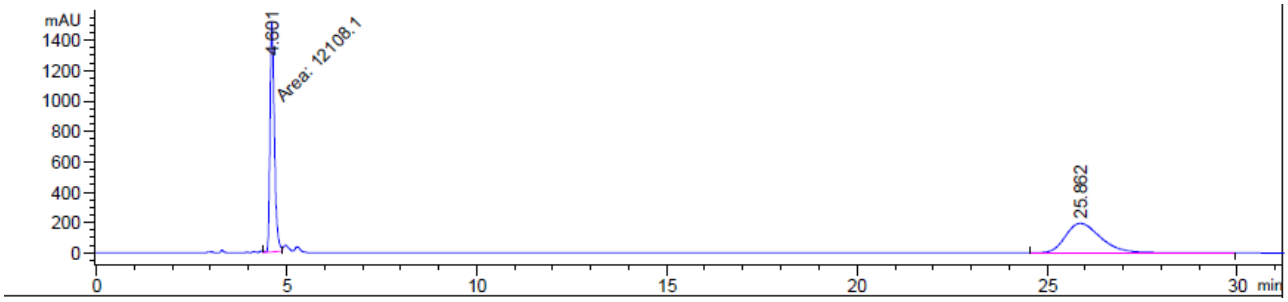


Signal 3: DAD1 C, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.724	BB	0.9644	1.30987e4	205.83115	93.9843
2	29.507	BB	1.2390	838.41455	8.94956	6.0157

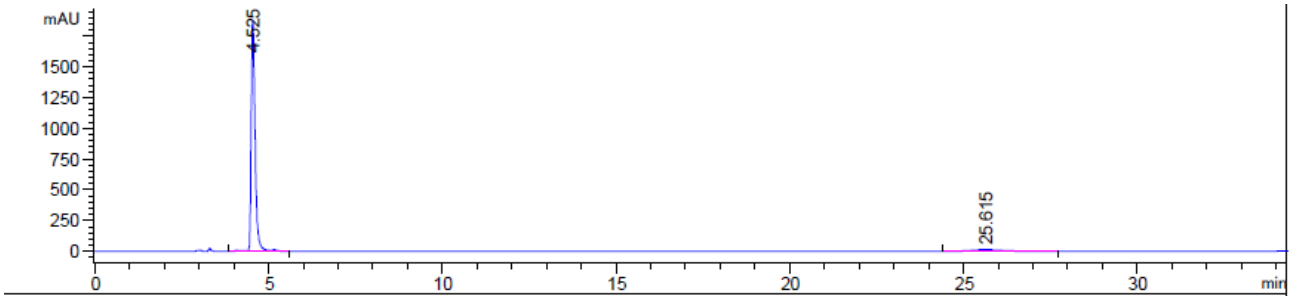
Compound **121.1**





Signal 3: DAD1 C, Sig=220,4 Ref=360,100

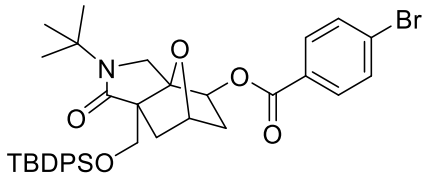
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.601	MM	0.1331	1.21081e4	1516.45178	49.3634
2	25.862	BB	0.9884	1.24204e4	194.14026	50.6366

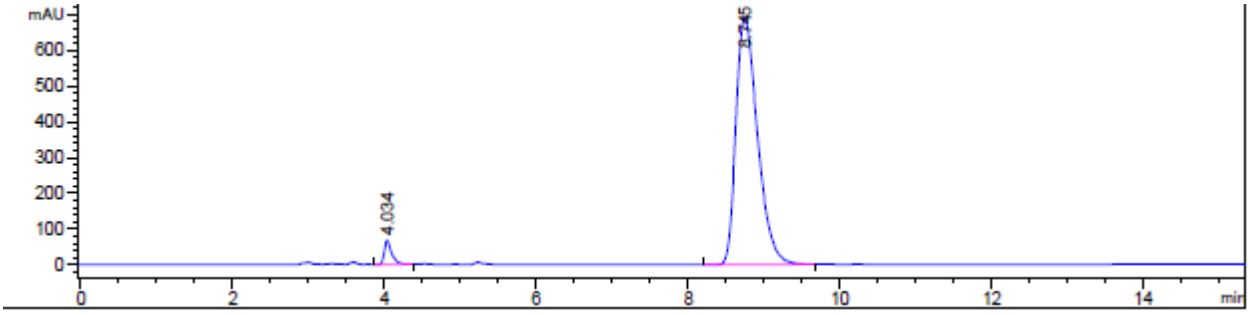


Signal 3: DAD1 C, Sig=220,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.525	VV R	0.1193	1.49063e4	1880.31909	94.9452
2	25.615	BB	0.9117	793.59467	12.72233	5.0548

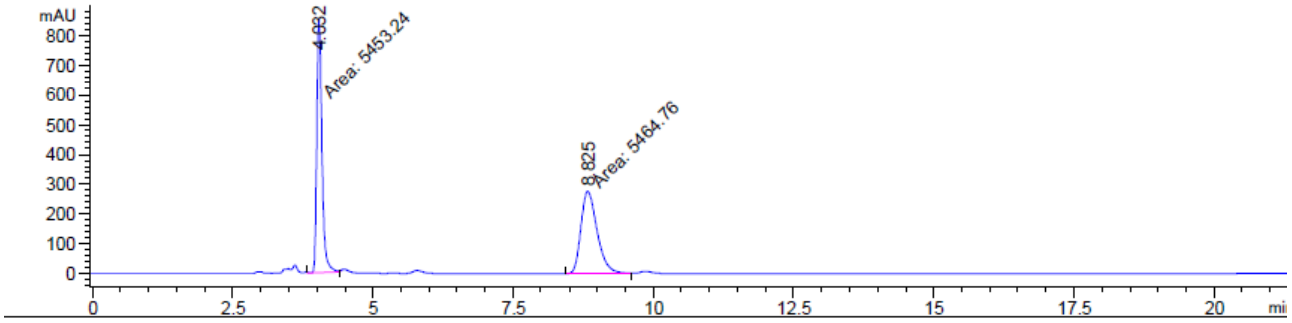
Compound **120.1**





Signal 5: DAD1 E, Sig=254,4 Ref=360,100

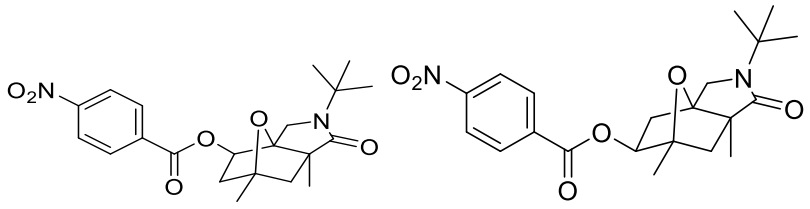
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.034	BB	0.1002	464.46783	67.57904	3.2851
2	8.745	BB	0.3051	1.36743e4	690.33905	96.7149

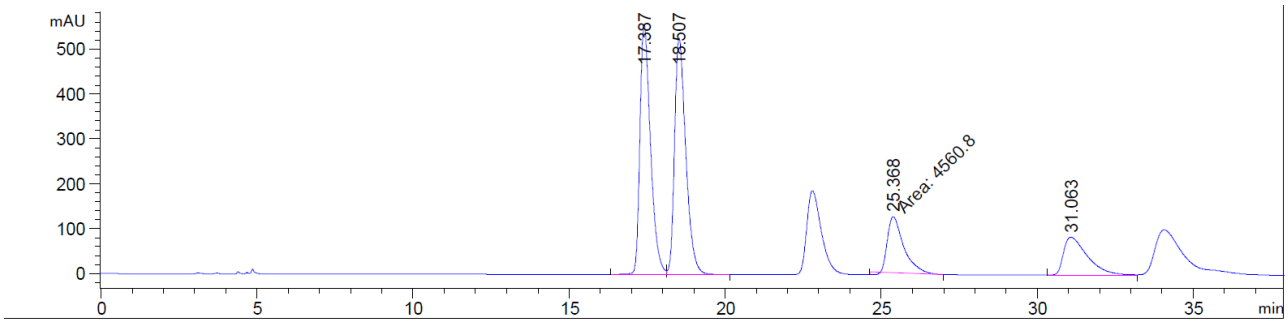


Signal 5: DAD1 E, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.032	MM	0.1064	5453.23779	854.33899	49.9472
2	8.825	MM	0.3317	5464.76270	274.59372	50.0528

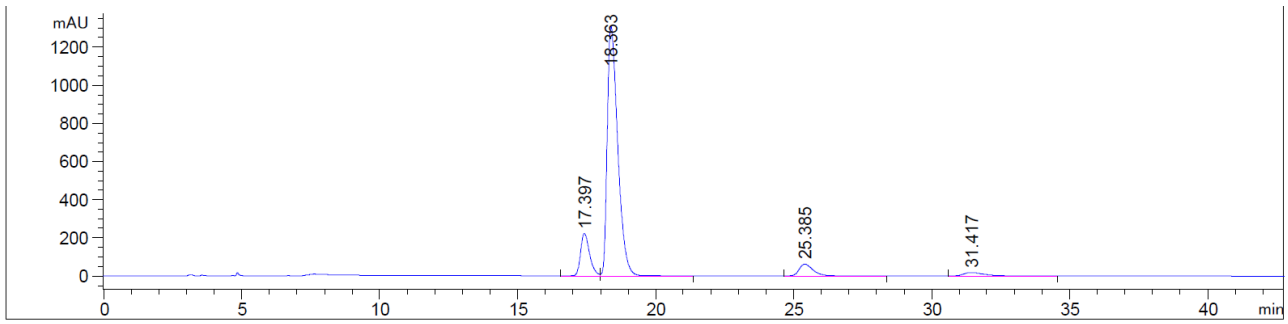
Compound **130** and **131**





Signal 5: DAD1 E, Sig=254,4 Ref=360,100

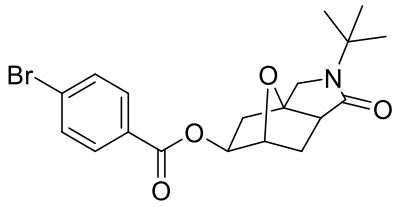
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.397	BV	0.3452	5017.31494	222.39696	11.8006
2	18.363	VB	0.4052	3.44845e4	1309.48926	81.1068
3	25.385	BB	0.5245	2114.40723	61.28453	4.9730
4	31.417	BB	0.7609	901.20508	17.55657	2.1196

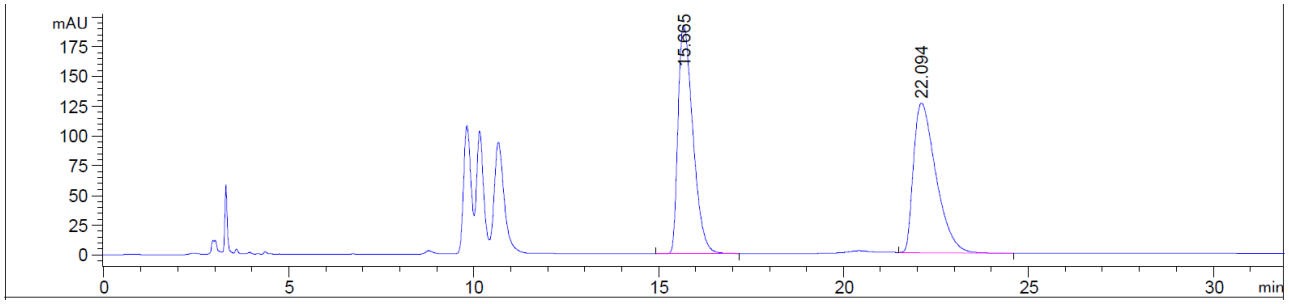


Signal 4: DAD1 D, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.397	BV	0.3443	1793.22888	79.75325	11.7113
2	18.363	VB	0.4016	1.24303e4	474.53833	81.1803
3	25.385	BB	0.5200	770.05426	22.45859	5.0291
4	31.408	BB	0.7014	318.38245	6.43268	2.0793

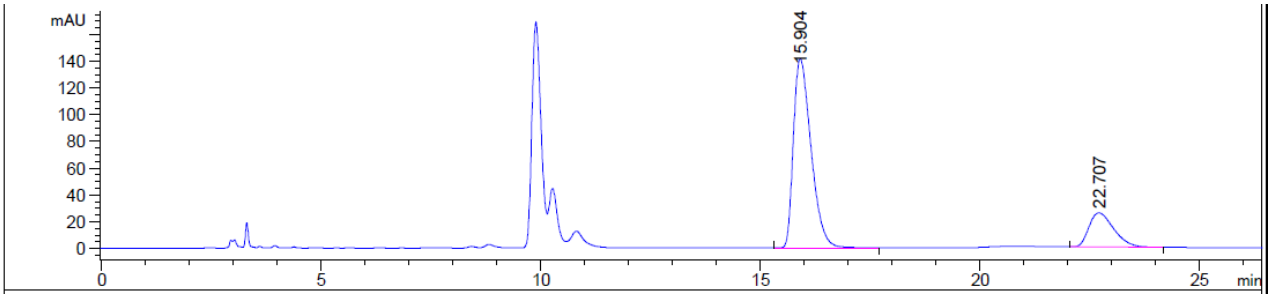
Compound **127**





Signal 3: DAD1 C, Sig=220,4 Ref=360,100

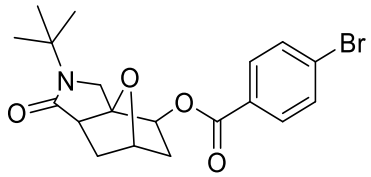
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.665	BB	0.4331	5353.95605	192.14481	50.2589
2	22.094	BB	0.6475	5298.79004	125.78265	49.7411

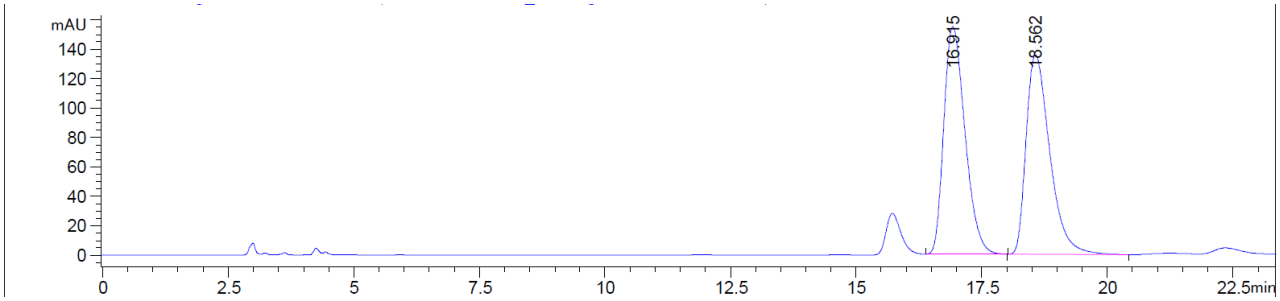


Signal 3: DAD1 C, Sig=220,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.904	BB	0.4310	3941.27832	141.49754	79.6557
2	22.707	BB	0.5992	1006.61218	25.57535	20.3443

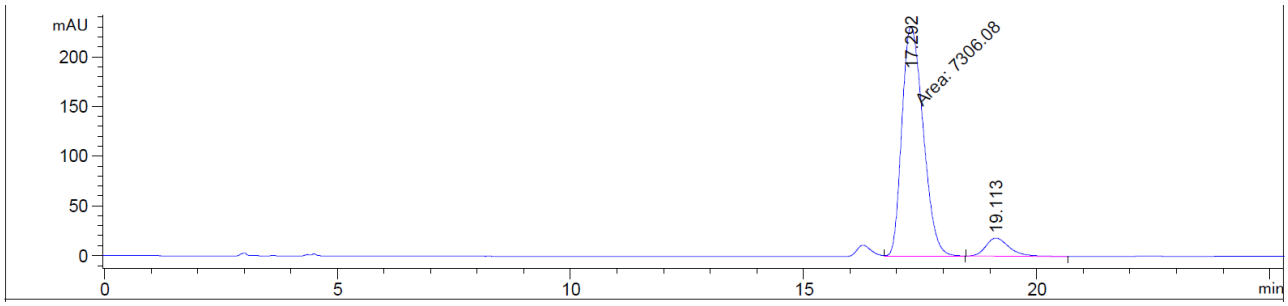
Compound **126**





Signal 2: DAD1 B, Sig=254,16 Ref=360,100

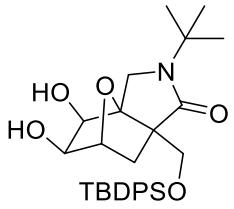
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.915	BB	0.4560	4534.93555	154.71587	50.4474
2	18.562	BB	0.5072	4454.50635	135.61868	49.5526

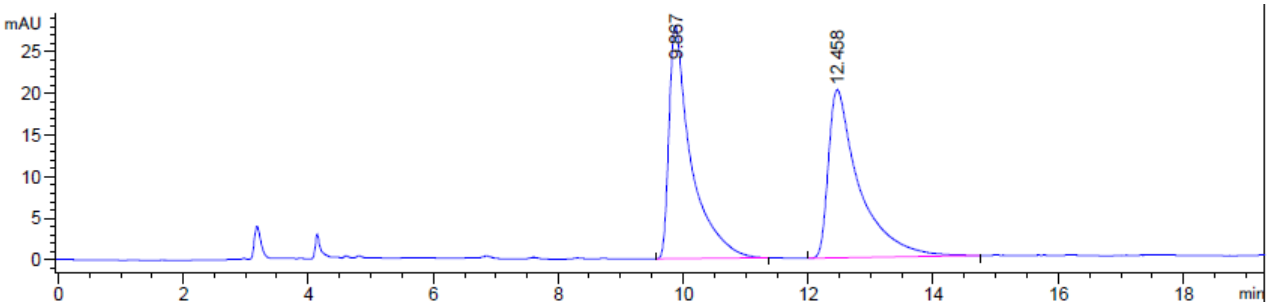


Signal 2: DAD1 B, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.292	MM	0.5271	7306.08008	230.99876	92.0761
2	19.113	BB	0.5246	628.75098	18.21836	7.9239

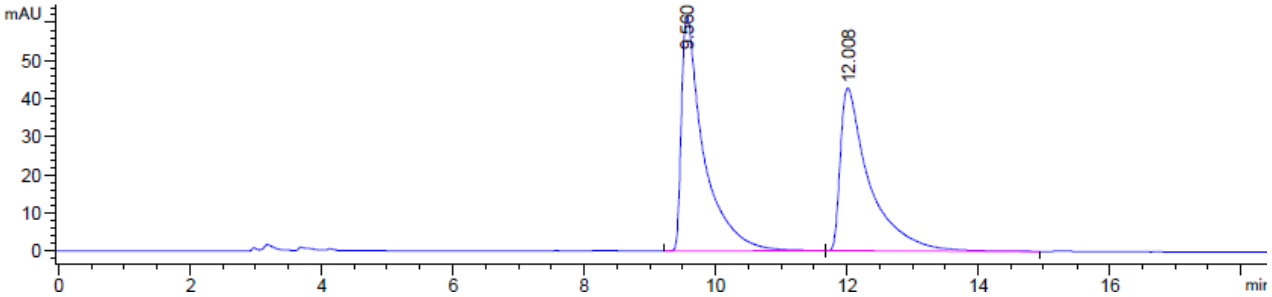
Compound **137**





Signal 2: DAD1 B, Sig=215,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.867	BB	0.3430	684.83356	28.03805	49.6374
2	12.458	BB	0.4828	694.84003	20.22608	50.3626



Signal 1: DAD1 A, Sig=200,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.560	VV R	0.3441	6178.08447	250.22588	52.0191
2	12.008	BV R	0.4295	5698.48535	180.91100	47.9809