A Straightforward Stereoselective Synthesis of D- and L-5-Hydroxy-4-hydroxymethyl-2-cyclohexenylguanine

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A novel and facile synthesis of 5-hydroxy-4-hydroxymethyl-2-cyclohexenylguanine **1** is described. The key steps involve a Diels−Alder reaction of ethyl (2*E*)-3-acetyloxy-2-propenoate **2** as dienophile with Danishefsky's diene **3** to build up the six-membered ring skeleton, a Fraser-Reid reductive rearrangement of the adduct using $LiAlH_4$, and base-moiety introduction using a Mitsunobu reaction. Optically pure D- and L-**1** were obtained via resolution of intermediate **7** with (*R*)-(−)-methylmandelic acid. The synthetic procedure toward racemic **1** consists of only five steps and has proven to be highly efficient toward the synthesis of cyclohexenyl nucleosides.

Introduction

Recently, we have demonstrated[1] that both D- and L-cyclohexenylguanine (**1**) (Figure 1) are highly potent and selective anti-herpes virus (HSV-1, HSV-2, VZV, CMV) agents. Their activity profile is similar to that of the known antiviral drugs acyclovir and ganciclovir, and they represent the most potent antiviral nucleosides containing a six-membered carbohydrate mimic that have ever been reported. Remarkably, the antiviral activity profiles of both enantiomers are very similar.

We have described an enantioselective synthesis of the D- and L-enantiomers of **1** starting from (*R*)-carvone.[1,2] However, the synthesis is long and time-consuming, and it is not suited for the preparation of large amounts of the final products that are needed for full biological evaluation.

We hereby report a short and facile synthesis of **1** and its two enantiomers (Schemes 1−3). The key step is a Diels−Alder reaction[3] of ethyl (2*E*)-3-acetyloxy-2-propenoate **2** with Danishefsky's diene **3** to construct the six-membered ring skeleton (**4**) with the desired trans orientation of the substituents in positions 4 and 5. Simultaneous reduction and rearrangement using lithium aluminum hydride (LAH) leads to triol **6**. After protection as benzylidene acetal **7**, the base moiety is introduced using a Mitsunobu reaction.

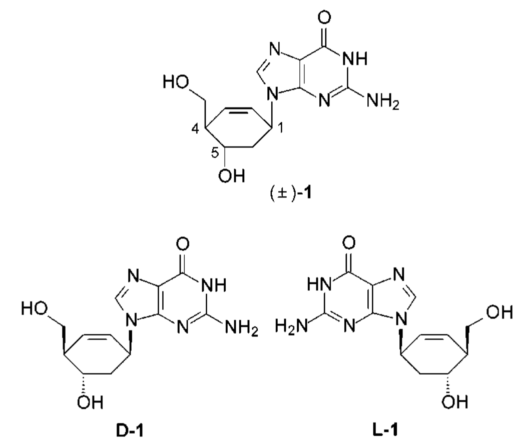

Figure 1. Structure of (±)-cyclohexenyl G and assignment of D- and L-nomenclature.

Results and Discussion

The preparation of dienophile (*E*)-**2** and diene **3** for the Diels−Alder reaction is presented in Scheme 4. Ethyl (2*E*)-3-acetyloxy-2-propenoate **2**[4] can easily be obtained on a multigram scale by formylation of ethyl acetate and acetylation of the sodium salt of the α-formyl ester using acetyl chloride. A mixture of (*E*)-**2** and (*Z*)-**2** was obtained when the temperature during reaction and distillation was not well controlled. However, the (*Z*)-**2** isomer can easily be converted quantitatively into (*E*)-**2** via treatment of the mixture of (*Z*)-**2** and (*E*)-**2** with thiophenol in the presence of 2,2′-azobis(2-methylpropionitrile) (AIBN). Danishefsky's diene **3**[5] was readily obtained (50 g scale) by silylation of (*E*)-4-methoxy-3-buten-2-one (TMSCl, $ZnCl_2$, Et_3N) followed by distillation.

The Diels−Alder reaction was carried out by heating a mixture of neat **2** and **3** in the presence of hydroquinone at 180 °C for 1.5 h (Scheme 1). After removal of the volatiles, the residue was distilled under high vacuum and the adduct was obtained in 71% yield as a 4:1

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(1) Wang, J.; Froeyen, M.; Hendrix, C.; Andrei, G.; Snoeck, R.; De Clercq, E.; Herdewijn, P. *J. Med. Chem.* **2000**, *43(4)*, 736−745. References of related six-membered carbocyclic nucleosides are cited therein.

(2) (a) Wang, J.; Herdewijn, P. *J. Org. Chem.* **1999**, *64*, 7820−7827. (b) Wang, J.; Busson, R.; Blaton, N.; Rozenski, J.; Herdewijn, P. *J. Org. Chem.* **1998**, *63*, 3051−3058.

(3) Reviews: (a) Danishefsky, S. *Acc. Chem. Res.* **1981**, *14*, 400. (b) Danishefsky, S.; DeNinno, M. P. *Angew. Chem., Int. Ed. Engl.* **1987**, *15*. (c) Danishefsky, S. *Chemtracts: Org. Chem.* **1989**, *2*, 273.

(4) (a) Wislicenus, W. *Chem. Ber.* **1887**, *20*, 2930−2934. (b) Von-Pechman, H. *Chem. Ber.* **1892**, *25*, 1040−1045. For the use of ethyl (2*E*)-3-acetyloxy-2-propenoate as a dienophile, see: Ranganathan, S.; Ranganathan, D.; Mehrota, A. K. *Synthesis* **1976**, 620−621. (c) Blancou, H.; Casadevall, E. *Tetrahedron* **1976**, *32*, 2907−2913.

(5) Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, *96*, 7807−7808.

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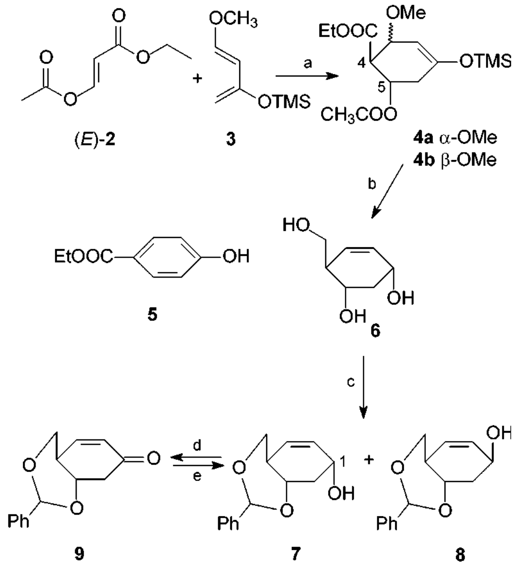
Scheme 1. Synthesis of the Cyclohexenyl Precursor[a]



[a] Key: (a) 180 °C, hydroquinone, 1.5 h, 62%; (b) $LiAlH_4$, THF, 0 °C, 66%; (c) $PhCH(OMe)_2$, PTSA, 1,4-dioxane, rt, 24 h, 70%; (d) MnO_2, CH_2Cl_2, rt, 21 h, 83%; (e) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, rt, 2 h, 90%.

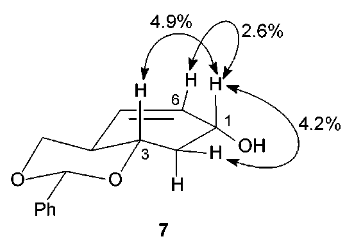


Figure 2. Assignment of the α-configuration of 1-OH using NOE experiments.

mixture of the endo and exo adducts **4a** and **4b**, respectively (as determined by ^{1}H NMR analysis). During the distillation, the temperature should be carefully controlled to avoid the formation of phenol derivative **5** as the major product. The highly functionalized adduct **4** is sensitive to acid and moisture and is best reduced immediately. The stereochemical ambiguity in the adduct is removed during the next reaction. Reduction of the mixture **4a/4b** with excess $LiAlH_4$, according to the procedure of Fraser-Reid,[6] gave triol **6** in 64% yield. This reaction involves the reduction of two ester groups and concomitant rearrangement of the silyloxyenol ether to the enone intermediate, which is then further reduced to **6**.

Reaction of triol **6** with benzaldehyde dimethyl acetal[7] in the presence of PTSA at room temperature for 1 day gave rise to benzylidene acetal **7** (70% yield). Prolongation of the reaction time (2 days) gave rise to a mixture of **7** and **8** (ranging from 6:1 to 3:1). As separation of **7** and **8** proved difficult, the mixture was oxidized to enone **9**, which was then reduced using $NaBH_4$ in the presence of $CeCl_3{\cdot}7H_2O$.[8] In this way, only **7** was obtained in 74% yield over the two steps. The α-configuration of the 1-OH substituent of **7** was established by an NOE experiment (Figure 2): irradiation of the proton at C1 gave enhanced signals of H2β, H3, and H6.

Introduction of the purine base moiety was performed according to our previously reported procedure;[2] i.e., **7** was reacted with 2-amino-6-chloropurine under Mitsunobu reaction conditions to generate the chloropurine **10a** with inversion of the configuration at C1 (Scheme 2). The N_7-isomer (14%) **10b** was also isolated. Finally, acidic hydrolysis of **10a** gave the racemic (±)-**1** in 27% overall yield starting from **7**. The spectral data of (±)-**1** are identical to those of the previously reported enantiomer(s).[1,2]

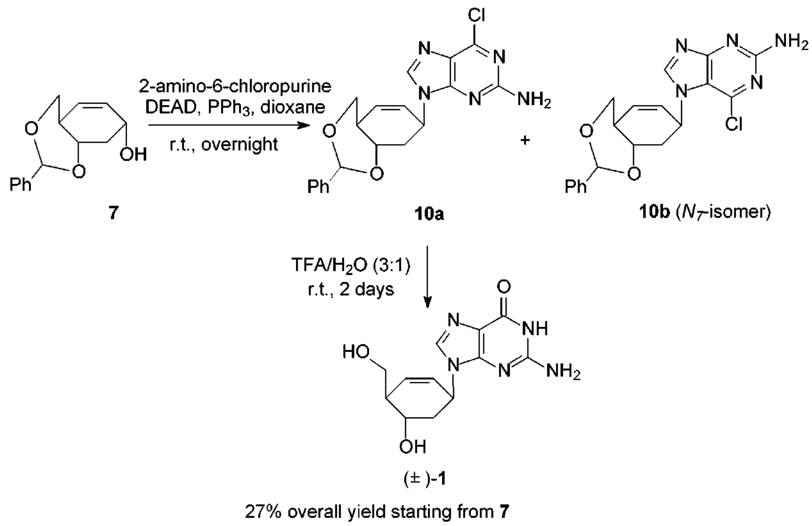
The synthesis of optically pure D-**1** and L-**1** was achieved via resolution of intermediate **7** followed by introduction of the base moiety on the enantiopure cyclohexene precursor using a Mitsunobu reaction (Scheme 3). Several methods for resolving **7** could be envisaged, i.e., kinetic resolution using Sharpless epoxidation,[9] enzymatic methods such as enantioselective esterification using a lipase,[10] or formation of diastereomeric esters.[11] Sharpless epoxidation has the disadvantage that half of the material will be lost because conversion of the resulting epoxide back to the double bond is rather tedious. In a first experiment, esterification of **7** using vinyl acetate and Lipase PS (Amano) gave only 33% of enantiomeric excess. As both enantiomers of **7** were needed, we preferred to synthesize the diastereomeric esters of **7** using a chiral acid. The use of the cheap and commercially available pyroglutamic acid **11** for this purpose was not satisfactory due to the difficult separation of the resulting diastereomeric esters. The use of (+)-naproxene **12** was also attempted. However, the best result with this chiral acid was 38% of diastereomeric excess because only partial separation of its esters on silica gel could be obtained. Finally, we retained (*R*)-(−)-*O*-methylmandelic acid, which has been applied earlier to resolve the diastereomeric esters of cyclohexanyl nucleosides.[11]

Acylation of **7** was carried out with (*R*)-(−)-methylmandelic acid in the presence of DCC and DMAP in 79% yield. Careful separation of the two diastereoisomers **13a** and **13b** by chromatography with a gradient of hexane and EtOAc gave pure **13a** (eluting first) and **13b**, respectively. The diastereomeric purity of **13a** and **13b** was checked by HPLC and found to be 97% for **13a** and 98% for **13b**. Hydrolysis of the ester group of **13a** or **13b** with KOH/MeOH provided D-**7a** and L-**7b** in good yields. The enantiomeric purity D-**7a** and L-**7b** was examined by chiral chromatography, and was 97% and 98%, respectively.

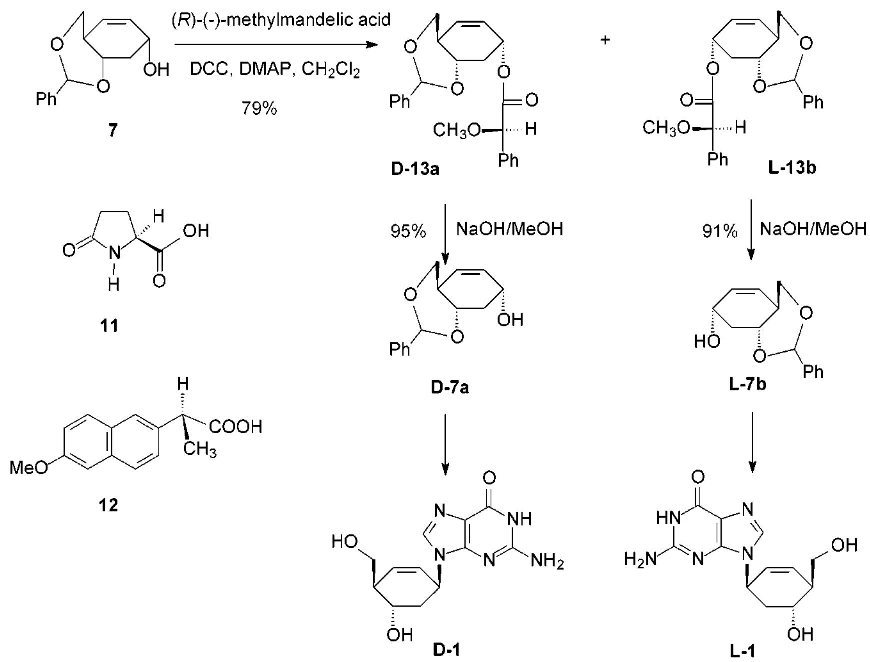
Conversion of D-**7a** into D-**1** and of L-**7b** into L-**1** was accomplished according to the same procedure as for (±)-**1**. The enatiomeric purity of D-**1** and L-**1** was 99% and

(6) Fraser-Reid, B.; Rahman, M.-D. A.; Kelly, D. R.; Srivastava, R. M. *J. Org. Chem.* **1984**, *49*, 1835−1837.
(7) Crimmins, M. T.; Hollis, W. G., Jr.; Lever, G. J. *Tetrahedron Lett.* **1987**, *28*, 3647−3650.
(8) Gemal, A. L.; Luche, J. L. *J. Am. Chem. Soc.* **1981**, *103*, 5454−5459.
(9) (a) Trost, B. M.; Fleming, I. *Comprehensive Organic Synthesis*, **1991**, Vol. 7, 389−436. (b) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, B. *J. Am. Chem. Soc.*, **1981**, *103*, 6237−6240.
(10) (a) Johnson, C. R.; Golebiowski, A.; Steensma, D. H. *J. Am. Chem. Soc.* **1992**, *114*, 9414−9418. (b) Pearson, A. J.; Lai, Y. S.; Lu, W.; Pinkerton, A. *J. Org. Chem.* **1989**, *54*, 3882−3893. (c) Tsuji, T.; Onishi, T.; Sakata, K. *Tetrahedron*: *Asymmetry* **1999**, *10*, 3819−3825.
(11) Maurish, Y.; Rosemeyer, H.; Esnouf, R.; Medvedovici, A.; Wang, J.; Ceulemans, G.; Lescrinier, E.; Hendrix, C.; Busson, R.; Sandra, P.; Seela, F.; Van Aerschot, A.; Herdewijn, P. *Chem. Eur. J.* **1999**, *5*, 2139−2150.

Scheme 2. Synthesis of (±)-Cyclohexenyl G



Scheme 3. Separation of Enantiomers of (±)-Cyclohexenyl G



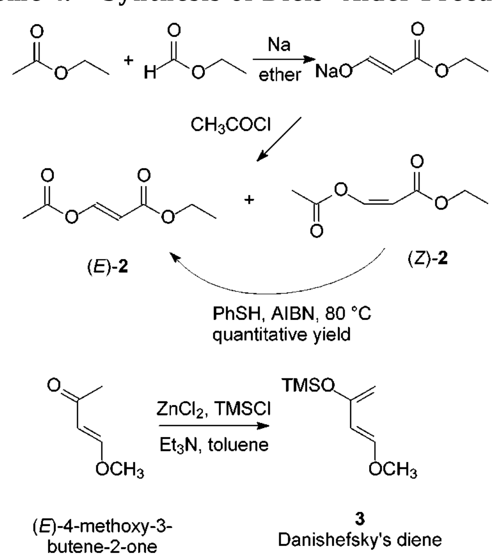
97%, respectively, according to chiral chromatographical analysis (Figure 3). The absolute configuration of D-**1** and L-**1** was established via comparison with an authentic sample of D-**1** that was obtained via the enantioselective synthesis starting from (*R*)-carvone.[1] By analogy, the absolute configuration of the intermediates **13a**/**13b** and **7a**/**7b** were also established.

In summary, we have developed a short and facile synthesis for the preparation of racemic **1** and its two enantiomers. The key steps involve a Diels–Alder reaction of enone **2** with Danishefsky diene **3** and the reductive rearrangement of the adduct **4**. The synthesis consists of only 5 steps (for (±)-**1**) and it represents a highly efficient approach toward the preparation of cyclohexenyl nucleosides.

Experimental Section

General Methods. All air-sensitive reactions were carried out under nitrogen. THF and Et_2O were distilled from sodium/benzophenone, 1,4-dioxane from CaH_2, and CH_2Cl_2 from P_2O_5.

Scheme 4. Synthesis of Diels–Alder Precursors



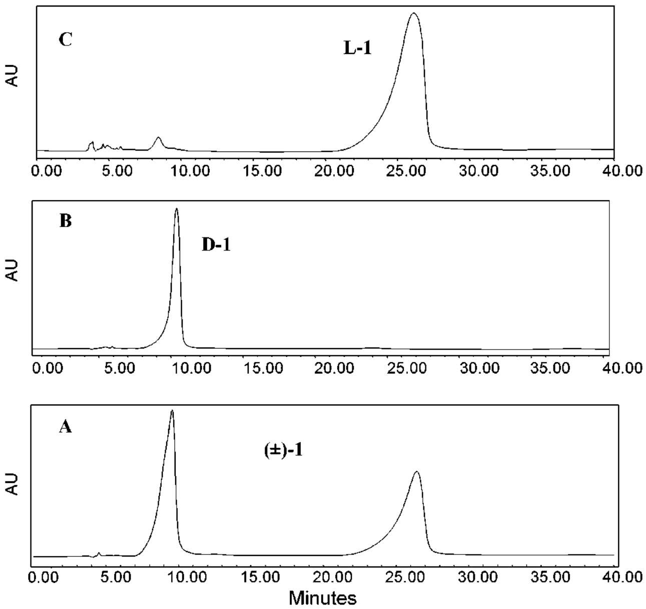


Figure 3. Chiral HPLC analysis of the racemate **1** (A) and its enantiomers D-**1** (B) and L-**1** (C) (see the Experimental Section for HPLC conditions).

Ethyl (2*E*)-3-acetyloxy-2-propenoate **2**[4] and Danishefsky's diene **3**[5] were prepared according to the literature procedures. HPLC analysis was performed on a Merck-Hitachi L-6200 A liquid chromatograph equipped with a Merck-Hitachi L-4000 UV detector, using a Bio-Sil D90-10 column (250 × 10 mm). Eluent: hexane−diisopropyl ether 65:35, flow: 3.5 mL/min, detection: 225 nm. Chiral HPLC analysis was performed on a Waters 6000 controller liquid chromatograph equipped with a Waters 2487 UV detector, using a Chiralpak AD column (250 × 4.6 mm). Eluent A: hexanes−EtOH 95:5, flow: 1.0 mL/min, detection: 200 nm; Eluent B: hexanes−EtOH 70:30 containing 0.2% TFA, flow: 1.0 mL/min, detection: 260 nm.

Isomerization of the *Z/E* Mixture 2 to Ethyl (2*E*)-3-Acetyloxy-2-propenoate (2). A mixture of (*Z*)-**2** and (*E*)-**2** (39:100, 52.5 g, 332 mmol) was treated with thiophenol (16.3 mL, 17.5 g, 159 mmol) and 2,2′-azobis(2-methylpropionitrile) (AIBN, 8.31 g, 50.6 mmol) at 80 °C for 2.5 h. The reaction mixture was cooled to rt and taken up in ethyl acetate (400 mL) that was washed with an 0.01 N NaOH aqueous solution (400 mL). The organic layer was dried over Na_2SO_4 and concentrated to leave a pale yellow oil. Distillation under vacuum (53 °C, 0.5−1.0 mmHg) afforded pure (*E*)-**2** (55.8 g, quantitative yield), slightly contaminated with aromatic thiol product: ^{1}H NMR ($CDCl_3$) δ 1.30 (t, 3H, J = 7.2 Hz), 2.22 (s, 3H), 4.21 (q, 2H, J = 7.2 Hz), 5.72 (d, 1H, J = 12.6 Hz), 8.30 (d, 1H, J = 12.6 Hz).

(±)-Ethyl (1*R,6*R**)-6-Acetoxy-2-methoxy-4-(trimethylsilyl)oxy-3-cyclohexene-1-carboxylate (4).** A mixture of **2** (55.8 g, 353 mmol) and **3** (72.9 g, 423 mmol) in the presence of a small amount of hydroquinone (372 mg) was heated at 180 °C for 1.5 h. The reaction mixture was distilled under vacuum (130 °C/0.18 mmHg) to afford **4** as a light-yellow oil (72 g, 62%) and as a 4:1 mixture of **4a** and **4b** (according to ^{1}H NMR). Data for major compound **4a**: ^{1}H NMR ($CDCl_3$) δ 0.21 (s, 9H), 1.27 (t, 3H, J = 7.3 Hz), 2.01 (s, 3H), 2.19 (m, 1H), 2.55 (dd, 1H, J = 16.7, 5.5 Hz), 2.77 (dd, 1H, J = 11.4, 8.4 Hz), 3.31 (s, 3H), 4.20 (m, 2H), 4.35 (dm, 1H, J = 8.4 Hz), 4.94 (t, 1H, J = 2.2 Hz), 5.13 (ddd, 1H, J = 11.0, 9.2, 5.9 Hz); ^{13}C NMR ($CDCl_3$) δ 0.06 (q), 14.2 (q), 20.8 (q), 35.4 (t), 51.1 (t), 55.4 (q), 60.9 (t), 68.8 (d), 76.5 (d), 103.3 (d), 149.3 (s), 170.0 (s), 172.2 (s).

(±)-(1*R,3*S**,6*R**)-6-Hydroxymethyl-4-cyclohexene-1,3-diol (6).** To a mixture of $LiAlH_4$ (25 g, 658 mmol) in dry THF (220 mL) at 0 °C under nitrogen was added dropwise a solution of **4** (21.49 g, 70.6 mmol) in dry THF (85 mL). After the mixture was stirred at 0 °C for 2 h, the reaction was continued at room temperature for 19 h. The viscous reaction mixture was diluted with dry THF (110 mL). The mixture was cooled in an ice bath and carefully treated with water (25 mL) for 15 min, a 15% aqueous NaOH solution (25 mL) for 15 min, and finally water (75 mL). After being stirred at room temperature for 0.5 h, the resulting mixture was filtered and the slurry was washed with water (5 × 100 mL) and EtOAc (3 × 100 mL). The layers were separated, and the aqueous layer was washed with ethyl acetate (3 × 100 mL). The aqueous layer was evaporated to dryness to give a brown gummy residue, which was chromatographed on silica gel (EtOAc/MeOH 91:9) to give **6** (6.74 g, 66%) as a light yellow syrup: ^{1}H NMR (DMSO-d_6) δ 1.37 (td, 1H, J = 11.7, 9.9 Hz), 1.92−2.10 (m, 2H), 3.24−3.45 (m, 2H), 3.63 (dt, 1H, J = 10.2, 4.4 Hz), 4.07 (m, 1H), 4.49 (t, 1H, J = 5.3 Hz, OH), 4.63 (d, 1H, J = 5.1 Hz, OH), 4.70 (d, 1H, J = 5.9 Hz, OH), 5.52 (d, 1H, J = 11.0 Hz), 5.57 (d, 1H, J = 11.0 Hz); ^{13}C NMR (DMSO-d_6) δ 42.0 (t), 47.2 (d), 62.2 (t), 65.9 (d), 66.3 (d), 127.7 (d), 132.8 (d); HRMS *m/z* calcd for $C_7H_{12}O_3Na$ (M + Na^+) 167.0684, found 167.0675.

(±)-(4a*R,7*S**,8a*R**)-2-Phenyl-4a,7,8,8a-tetrahydro-4*H*-1,3-benzodioxin-7-ol (7).** Compound **6** (4.49 g, 31.1 mmol) was treated with benzaldehyde dimethyl acetal (6.2 mL, 41.2 mmol) in the presence of *p*-toluenesulfonic acid monohydrate (PTSA, 300 mg, 1.58 mmol) in dry 1,4-dioxane (140 mL) at r.t. for 24h. Ice was added, the mixture was stirred at r.t. for 0.5 h and extracted with EtOAc (3x). The combined organic layers were washed with water and brine, dried over sodium sulfate and concentrated. The residue was purified on silica gel (hexanes−EtOAc 1:1) to afford **7** (5.06 g, 70% yield) as a white crystalline solid. A total of 600 mg (13%) of **6** was recovered: mp 105−106 °C; ^{1}H NMR ($CDCl_3$) δ 1.78 (td, 1H, J = 12.1, 9.9 Hz), 2.17 (br-s, 1H, OH), 2.44−2.66 (m, 2H), 3.61 (t, 1H, J = 10.8 Hz), 3.67 (ddd, 1H, J = 11.1, 9.2, 2.9 Hz), 4.26 (dd, 1H, J = 10.8, 4.6 Hz), 4.49 (m, 1H), 5.41 (dt, 1H, J = 9.9, 1.6 Hz), 5.60 (s, 1H), 5.72 (dm, 1H, J = 9.9 Hz), 7.36−7.55 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 38.4 (t), 39.9 (d), 67.7 (d), 70.6 (t), 77.7 (d), 102.1 (d), 124.9 (d); HRMS *m/z* calcd for $C_{14}H_{16}O_3Na$ (M + Na^+) 255.0997, found 255.0995. Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.07; H, 6.82.

When the reaction time was prolonged for 2 days, a mixture of **7** and **8** (ratio ranging from 3:1 to 6:1) was obtained.

(±)-(4a*R,8a*R**)-2-phenyl-4,4a,8,8a-tetrahydro-4*H*-1,3-benzodioxin-7-one (9).** A mixture of **7**/**8** (3:1, 415 mg, 1.79 mmol) and activated manganese dioxide (MnO_2, 1.56 g, 17.9 mmol, 10 equiv) in dry CH_2Cl_2 (15 mL) was stirred at rt for 21 h. The black reaction mixture was diluted with CH_2Cl_2 and filtered through Celite. The filtrate was concentrated, and the residue was chromatographed on silica gel (hexanes−EtOAc 2:1) to afford **9** (340 mg, 83%) as a white solid: mp 92−93 °C; ^{1}H NMR ($CDCl_3$) δ 2.65 (dd, 1H, J = 16.4, 13.1 Hz), 2.83 (m, 1H), 2.95 (dd, 1H, J = 16.4, 4.8 Hz), 3.79 (t, 1H, J = 11.1 Hz), 4.04 (ddd, 1H, J = 13.1, 9.2, 4.8 Hz), 4.45 (dd, 1H, J = 11.1, 4.8 Hz), 5.63 (s, 1H), 6.13 (dd, 1H, J = 9.9, 2.9 Hz), 6.58 (dd, 1H, J = 9.9, 1.8 Hz), 7.39 (m, 3H), 7.51 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 39.9 (d), 44.3 (t), 69.2 (t), 77.4 (d), 101.7 (d), 126.1 (d), 128.4 (d), 129.2 (d), 132.1 (d), 137.5 (s), 144.9 (d), 196.8 (s); HRMS *m/z* calcd for $C_{14}H_{14}O_3Na$ (M + Na^+) 253.0841. found 253.0855. Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.03; H, 6.13. Found: C, 72.75; H, 5.98.

Conversion of 9 to 7. To a solution of **9** (340 mg, 1.5 mmol) in MeOH (15 mL) at rt was addded $CeCl_3 \cdot 7H_2O$ (838 mg, 2.25 mmol, 1.5 equiv). After the mixture was stirred at rt for 1 h, $NaBH_4$ (68 mg, 1.8 mmol, 1.2 equiv) was added in portions. The reaction was stirred at rt for 2 h and quenched with crushed ice. The resulting mixture was stirred at rt for 0.5 h and concentrated. The residue was diluted with EtOAc, washed with water and brine, dried over sodium sulfate, and concentrated. The residue was chromatographed on silica gel (hexanes−EtOAc 5:1 and 1:1) to give **7** (307 mg, 90%) as a white solid.

(4a*R*,7*R*,8a*R*)-7-[(*R*)-(*O*-Methylmandelyl)oxy]-2-phenyl-4a,7,8,8a-tetrahydro-4*H*-1,3-benzodioxine (13a) and (4a*S*,7*S*,8a*S*)-7-[(*R*)-(*O*-methylmandelyl)oxy]-2-phenyl-4a,7,8,8a-tetrahydro-4*H*-1,3-benzodioxine (13b). To a mixture of **7** (3.48 g, 15 mmol), (*R*)-(−)-methylmandelic acid (2.73 g, 16.5 mmol) and DMAP (202 mg, 1.65 mmol) in dry CH_2Cl_2 (48 mL) at 0 °C was added DCC (3.42 g, 16.5 mmol) in portions. The reaction mixture was allowed to warm to rt over 1.5 h and was stirred for an additional 1.5 h at rt. CH_2Cl_2 (500 mL) was added, and the mixture was filtered. The filtrate was washed with an aqueous 1 M H_3PO_4 solution (90 mL), water (90 mL), and a saturated aqueous $NaHCO_3$ solution (45 mL), dried over Na_2SO_4, and concentrated. The crude product as white crystals (7.11 g) was subjected to chromatography on silica gel (35−70 nm) packed with hexane and eluting with a mixture of hexanes−EtOAc, slowly increasing the polarity. On elution with hexanes−EtOAc 71:29, 1.34 g of **13a** (93% de), a mixture of **13a** and **13b** (1.96 g), and 1.22 g of **13b** (79% de) were obtained (4.52 g, 79% yield). The diastereomeric excess was determined by HPLC.

The fractions containing **13a** and **13b** were again submitted to chromatographic purification yielding 589 mg (97% of diastereomeric purity) of **13a** and 426 mg (99% of diastereomeric purity) of **13b**.

Compound **13a**: mp 67−68 °C; ^{1}H NMR ($CDCl_3$) δ 1.91 (dt, 1H, J = 12.0, 10.2 Hz), 2.55 (ddd, 1H, J = 11.1, 7.5, 3.5 Hz), 2.60 (ddd, 1H, J = 10.9, 7.0, 3.9 Hz), 3.41 (s, 3H), 3.61 (t, 1H, J = 11.4 Hz), 3.71 (ddd, 1H, J = 11.4, 9.1, 3.1 Hz), 4.24 (dd, 1H, J = 11.0, 4.4 Hz), 4.78 (s, 1H,), 5.47 (s, 1H), 5.59 (s, 1H), 5.59−5.68 (m, 1H), 7.32−7.54 (m, 10H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 34.1 (t), 39.7 (d), 57.3 (q), 70.3 (t), 70.6 (d), 77.1 (d), 82.6 (d), 102.1 (d), 126.1 (d), 127.2 (d), 127.4 (d), 128.0 (d), 128.4 (d), 128.7 (d) 128.8 (d), 129.0 (d), 136.1 (s), 138.0 (s), 170.4 (s, CO). Anal. Calcd for $C_{23}H_{24}O_5$: C, 72.61; H, 6.36. Found: C, 72.64; H, 6.40.

Compound **13b**: ^{1}H NMR ($CDCl_3$) δ 1.91 (dt, 1H, J = 12.0, 9.9 Hz), 2.37 (ddd, 1H, J = 10.8, 7.3, 2.9 Hz), 2.56 (m, 1 H), 3.39 (s, 3H), 3.57 (t, 1H, J = 11.4 Hz), 3.64 (ddd, 1H, J = 12.4, 9.2, 3.2 Hz), 4.24 (dd, 1H, J = 11.0, 4.6 Hz), 4.76 (s, 1H), 5.47 (s, 1H), 5.43−5.57 (m, 1H), 5.54−5.70 (m, 1H), 7.30−7.48 (m 10 H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 33.6 (t), 39.5 (d), 57.1 (q), 70.1 (t), 70.4 (d), 76.8 (d), 82.3 (d), 101.8 (d), 126.0 (d), 127.0 (d), 127.4 (d), 128.0 (d), 128.1 (d), 128.7 (d), 128.5 (d), 128.8 (d), 129.3 (s), 135.9 (s), 137.9 (s), 170.2 (s, CO); HRMS m/z calcd for $C_{23}H_{24}O_5Na$ (M + Na^+) 403, found 403. Anal. Calcd for $C_{23}H_{24}O_5$: C, 72.61; H, 6.36. Found: C, 72.44; H, 6.42.

Hydrolysis of 13a to D-7a and 13b to L-7b. A solution of **13a** (500 mg, 1.31 mmol, 97% de) in 20% aqueous NaOH (27 mL, 133 mmol), THF (27 mL), and MeOH (27 mL) was heated under reflux for 2 h. The organic solvent was evaporated under vacuum, and the remaining aqueous phase was diluted with water (30 mL) and extracted with CH_2Cl_2 (4 × 60 mL). The combined organic layers were washed with a saturated $NaHCO_3$ solution (60 mL) and brine (60 mL), dried over Na_2SO_4, and evaporated. The residue was chromatographed on silica gel (hexanes−EtOAc 2:1) to give D-**7a** (291 mg, 95% yield, 97% ee according to chiral HPLC analysis using eluent A) as a white solid: mp 95 °C. Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.33; H, 6.70.

The same procedure was followed for conversion of **13b** to L-**7b** (91% yield, 99% ee):mp 94−95 °C. Anal. Calcd for $C_{14}H_{16}O_3\cdot 0.5H_2O$: C, 69.69; H, 7.10. Found: C, 69.57; H, 6.94.

(±)-(1*S,4*R**,5*S**)-9-(5-Hydroxy-4-hydroxymethyl-2-cyclohexen-1-yl)guanine (1).** To a mixture of *7* (696 mg, 3 mmol), 2-amino-6-chloropurine (1.02 g, 6 mmol), and triphenylphosphine (PPh_3, 1.57 g, 6 mmol) in dry 1,4-dioxane (30 mL) was added slowly a solution of DEAD (945 mL, 6 mmol) in dry 1,4-dioxane (10 mL). The reaction was stirred at rt overnight and concentrated. The residue was absorbed on silica gel and chromatographed (CH_2Cl_2−MeOH 100:1 and 50:1) to afford crude **10a** (2 g) and the N_7-epimer **10b** (140 mg) as a white solid.

Crude **10a** (2 g) was treated with TFA−H_2O (3:1, 20 mL) at rt for 2 days. The reaction mixture was concentrated and coevaporated with toluene. The residue was chromatographed on silica gel (CH_2Cl_2−MeOH 50:1 and 10:1) to give (±)-**1** (220 mg, 27% overall yield starting from **7**). The physicochemical properties (^{1}H NMR, ^{13}C NMR, MS, UV) of **1** are identical to those previously reported.[1]

(1*S*,4*R*,5*S*)-9-(5-Hydroxy-4-hydroxymethyl-2-cyclohexen-1-yl)guanine (D-1). The same procedure as described for the preparation of (±)-**1** was used. The analytical sample was obtained by crystallization with a mixture of diisopropyl ether−MeOH (8:2). The enantiomeric excess (99% ee) was determined by Chiral HPLC analysis using eluent B): mp 275−280 °C dec. Anal. Calcd for $C_{12}H_{19}N_5O_3.2(H_2O)$: C, 46.00; H, 6.11; N, 22.35. Found: C, 46.30; H, 5.81; N, 22.18.

(1*R*,4*S*,5*R*)-9-(5-Hydroxy-4-hydroxymethyl-2-cyclohexen-1-yl)guanine (L-1). The same procedure as described for the preparation of (±)-**1** was used. The analytical sample (97% ee) was obtained by crystallization from a mixture of EtOAc−MeOH (4:3): mp 273−277 °C dec. Anal. Calcd for $C_{12}H_{19}N_5O_3.2(H_2O)$: C, 46.00; H, 6.11; N, 22.35. Found: C, 46.21; H, 5.86; N, 21.73.

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