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Practical Synthesis of Enantiopure Spiro[4.4]nonane *C*-(2′-Deoxy)ribonucleosides

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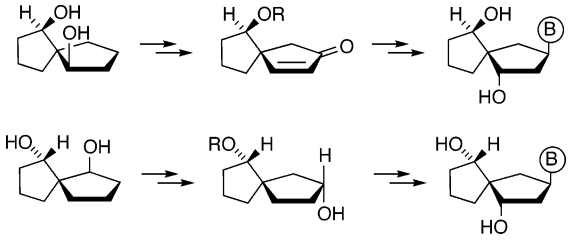
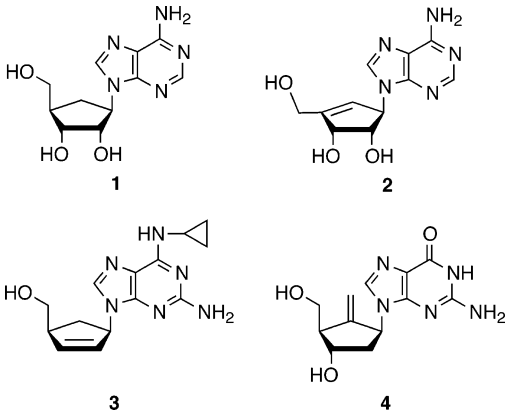


The levorotatory diol **7** has been sequentially monosilylated, dehydrated, and oxidized at the allylic methylene group to provide (+)-**12**. The enantiomeric dextrorotatory diol **7** has been directed down a different sequence of steps involving monosilylation, dehydration, hydroboration, Swern oxidation, and regioselective introduction of a conjugated double bond to generate (−)-**33**. The novel feature of these transformations is that two key deoxycarbospironucleoside intermediates of the proper absolute configuration have been made available from enantiomerically related precursors. Also reported is a highly practical and reliable means for the formation of novel 2′-deoxyribonucleosides of novel structural type from these spirocyclic cyclopentenones.

The considerable attention that has been focused on the capacity of carbocyclic nucleosides to function as potent inhibitors of viral infection has been rewarded with a number of striking successes. Aristeromycin (**1**)[1] and neplanocin A (**2**)[2] were among the early discoveries, to be followed by the potent anti-HIV agent abacavir (**3**).[3] Presently in advanced stages of clinical trial for chronic hepatitis B virus infection is entecavir (**4**).[4] Rounding out the picture at this time are other carbocyclic nucleosides active against the smallpox, monkeypox, and West Nile viruses.[5] An intriguing and persistent question surrounds structure−activity relationships in this compound class. Despite the significant effort made in recent years, the design of analogues having predictable biological and chemical profiles persists as a significant unmet challenge.



1 **2** **3** **4**

In continuation of our efforts to explore the feasibility of synthesizing enantiopure spirocyclic nucleoside building blocks containing oxygen,[6] sulfur,[7] and carbon[8] at the apical position,[9] we have turned attention to the elaboration of nucleoside analogues of DNA of the general type **5** and **6**. The impetus underlying this undertaking was to evaluate this type of conformational restriction while

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(5) (a) Song, G. Y.; Paul, V.; Choo, H.; Morrey, J.; Sidwell, R. W.; Schinazi, R. F.; Chu, C. K. *J. Med. Chem.* **2001**, *44*, 3958. (b) Chu, C. K.; Jin, Y. H.; Baker, R. O.; Huggins, J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 9.

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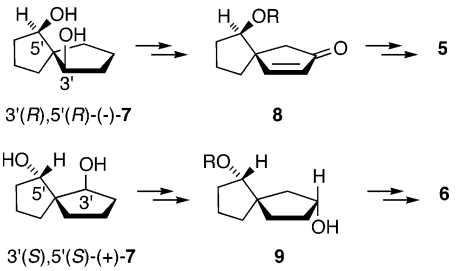
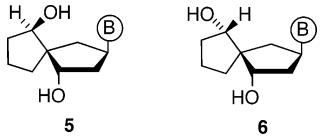
SCHEME 1



simultaneously guarding against possible enzymatic degradation under physiological conditions.



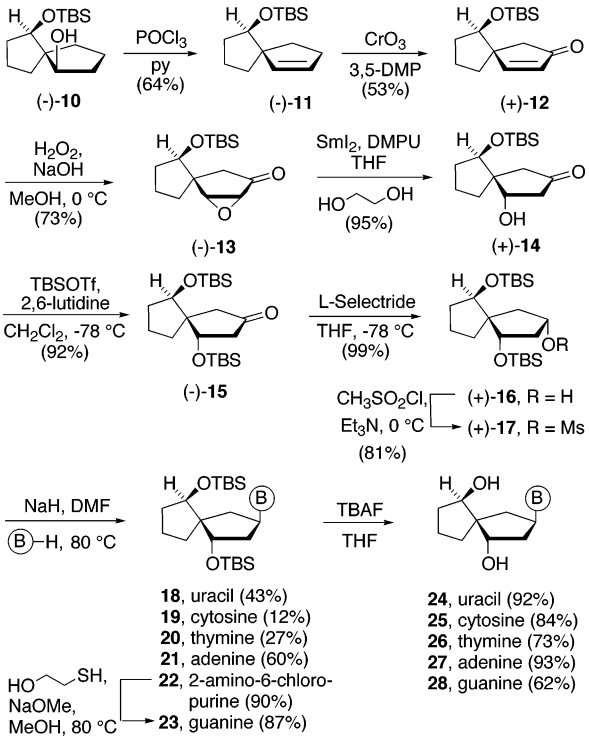
Results and Discussion

Retrosynthetic considerations led us back to the report by Nieman and Keay that describes the resolution of racemic *cis,cis*-spiro[4.4]nonane-1,6-diol via ketalization with (1*R*)-(+)-camphor.[10] So efficient is their process that appreciable quantities of both (−)-**7** and (+)-**7** can be generated. As seen in Scheme 1, the levorotatory enantiomer was anticipated to serve as a suitable precursor to **5** in light of their closely related absolute configurations. Several stereocontrolled steps must be developed to proceed from (−)-**7** to **8** and onward from that point. Fruitful deployment of (+)-**9** as the progenitor of **6** would require a different series of transformations to attain this objective.

As expected, the nonbonded steric constraints resident in **7** were found to impede the more advanced silylation of **10** (Scheme 2) while complicating its dehydration to give **11**. Nevertheless, operation of a Wagner-Meerwein ring expansion was minimized when recourse was made to phosphorus oxychloride in pyridine at 0 °C.[11] Conversion to spirocyclopentene **11** was repeatedly achieved in 64% yield.

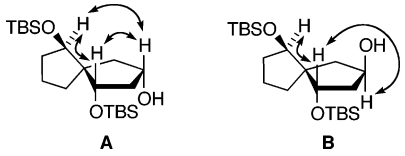
Exposure of **12** to alkaline hydrogen peroxide[12] resulted in clean conversion to a single oxirane formulated as **13**. Past experience has shown that the bulky OTBS substituent directs the entry of reagents to the α-face in related spirononanes,[6] and no stereochemical crossover should be operational here. More direct evidence was secured following the reductive cleavage of **13** with

SCHEME 2



samarium diiodide in anhydrous THF containing ethylene glycol and DMPU.[13] α-Deoxygenation in this manner gave rise efficiently to **14**, thereby setting the stage for arrival at **15** by means of conventional silylation under mild conditions. Were the hydroxyl group in **14** on the *β*-face of this intermediate, its protection would be strongly impeded as is the case with **10**.

Ketone **15** was readily reduced with L-Selectride in THF at −78 °C, these conditions giving rise quantitatively to the α-alcohol **16**. Other hydride reagents did not perform with comparably high stereoselectivity. For example, Dibal-H dissolved in CH_2Cl_2 led, at the same low temperature, to a chromatographically separable 3:1 mixture of **16** and its epimer. The availability of both stereoisomers in pure condition allowed for confirmation of stereochemical configuration by NOE methods (see **A** and **B**).



This accomplished, **16** was transformed in turn into mesylate **17** to prepare for direct S_N2 displacement involving a series of nucleoside bases. The protected pyrimidine deoxycarbospironucleosides **18**−**20** were obtained with modest efficiency by direct condensation of **17** with the sodium salts of uracil, cytosine, and thymine.[14] For the two related purines **21** and **22**, the closely comparable protocol developed by Robbins involving

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(10) Nieman, J. A.; Keay, B. A. *Synth. Commun.* **1999**, *29*, 3829.

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(12) (a) Bunton, C. A.; Minkoff, G. J. *J. Chem. Soc.* **1949**, 665. (b) House, H. O.; Ro, R. S. *J. Am. Chem. Soc.* **1958**, *80*, 2428.

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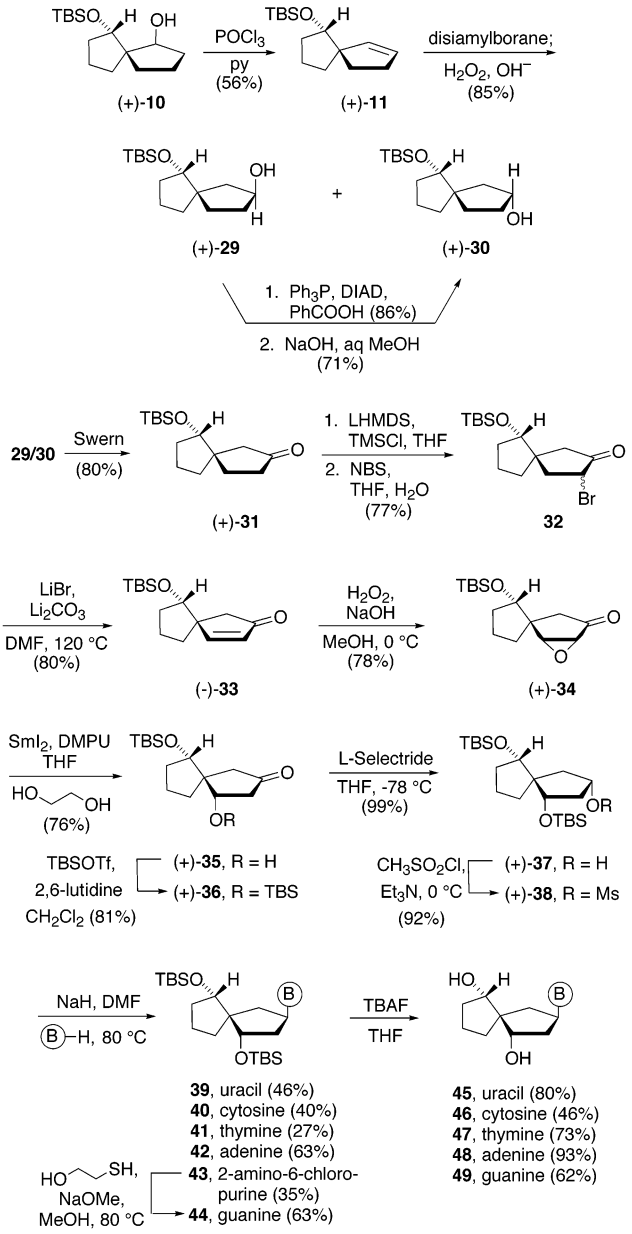
adenine and 2-amino-6-chloropurine was adapted.[15] Hydrolytic removal of the Cl substituent required for the conversion of **22** into the guanine relative **23** was accomplished without complication[6d,16] with 2-mercaptoethanol in hot aqueous methanol.[14a,17] Finally, global deprotection of intermediates from the group **18**−**23** with TBAF led efficiently to the targeted 2′-deoxy spironucleosides **24**−**28**.

Preparation of members of the α subset of carbocyclic spironucleosides began with the dehydration of **10**, although now in the form of its dextrorotatory enantiomer. This transformation resulted in the formation of (+)-**11** (Scheme 3). The next important step concerned proper regiodirected hydration of the cyclopentene double bond. The steric shielding provided by the structural scaffold resident in **11** served to guide hydroboration in the proper direction. From among a number of organoboranes examined, disiamylborane emerged as a reasonable compromise in that **29** and **30** were isolated in 19% and 51% yield, respectively. Although not needed for the present purposes, it proved possible to maximize the availability of **30** by means of the Mitsunobu reaction.[19]

To develop the synthetic route, the **29/30** mixture was directly subjected to Swern oxidation. The ketone **31**, so generated in 80% yield, proved in turn to be amenable to regiodirected α-deprotonation in view of the steric shielding existent at the alternative neighboring site. Direct treatment of the silyl enol ether with *N*-bromosuccinimide[19] resulted in formation of a diastereomeric mixture of the α-bromo ketones **32**. The dehydrobromination of **32** with lithium bromide and lithium carbonate in DMF at 120 °C[20] led smoothly to **33**. It is pertinent to underscore that "migration" of the double bond from its original position in **11** to its ultimate location along the leading edge constitutes a practical crossover into the series diastereomeric to **12**. The brevity of steps allows for the conversion of very reasonable quantities of (+)-**10** into **33**, whose elaboration into **45**−**49** was subsequently accomplished in a manner similar to that developed earlier. Attention is called in particular to the parallel behavior of **15** and **36** to reduction with L-Selectride, which occurs totally from the *β*-face in both series and is therefore independent of the configuration at the carbon atom bearing the −OTBS substituent. These and related results form the basis of the structural assignments given in Scheme 3.

In summary, the unique characteristics of (−)-**7** and (+)-**7** permit their development as starting materials for the synthesis of stereoisomeric deoxycarbospironucleosides. The adoption of two different reaction pathways allows for the direct conversion of the two enantiomers into the key enone intermediates **12** and **33**. This "merger of chirality" illustrates a principle that should find application in a variety of contexts.

SCHEME 3



Experimental Section

(−)-Monoprotected Diol 10. To a solution of (−)-**7** (2.77 g, 17.7 mmol), DMAP (0.43, 3.5 mmol), and imidazole (1.81 g, 26.6 mmol) in CH_2Cl_2 (94 mL) was added TBSCl (3.99 g, 26.6 mmol), and the solution was brought to reflux for 12 h. The reaction mixture was quenched with saturated $NaHCO_3$ solution, transferred to a separatory funnel, and extracted with ether (3 × 50 mL). The combined organic phases were dried, concentrated in vacuo, and purified by chromatography on silica gel (10:1 hexanes:ethyl acetate) to give 4.69 g (98%) of **10** as a yellowish oil: IR (neat, cm^{-1}) 3483, 1471, 1252; ^1H NMR (300 MHz, $CDCl_3$) δ 4.21 (s, 1H), 4.15−4.09 (m, 2H),

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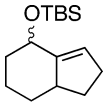
1.90−1.53 (series of m, 10H), 1.31−1.26 (m, 2H), 0.90 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 80.7, 78.9, 56.5, 34.2, 33.7, 33.5, 32.9, 25.7 (3C), 20.8, 19.9, 17.7, −4.3, −5.2; ES HRMS *m/z* calcd 293.1907, obsd 293.1925; $[\alpha]^{25}_D$ −54 (*c* 1.2, $CHCl_3$). Anal. Calcd for $C_{15}H_{30}O_2Si$: C, 66.61; H, 11.18. Found: C, 66.48; H, 11.10.

(−)-Unsaturated Silyl Ether 11. A solution of (−)-**10** (2.71 g, 10.0 mmol) in pyridine (68 mL) was cooled to 0 °C, and $POCl_3$ (1.87 mL, 20.07 mmol) was added dropwise. The reaction mixture was stirred for 8 h at 0 °C, allowed to warm to rt overnight, transferred to a separatory funnel, diluted with 270 mL of 10% HCl, and extracted with ether (4 × 75 mL). The combined ether layers were washed with 10% HCl (1 × 100 mL), dried, and concentrated. The residue was purified by chromatography on silica gel (petroleum ether) to give 1.80 g (64%) of **11** and 0.70 g (25%) of **i**.

For **11**: IR (neat, cm^{-1}) 1461, 1358, 1250; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.38 (d, J = 2.1 Hz, 1H), 4.52 (t, J = 2.7 Hz, 1H), 2.79 (m, 1H), 2.33−1.22 (series of m, 10H), 0.92 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 121.9, 99.8, 67.4, 41.5, 35.9, 35.8, 31.0, 30.2, 25.8 (3C), 22.6, 20.2, −4.6, −5.1; ES HRMS *m/z* $(M)^+$ calcd 252.1909, obsd 252.1891; $[\alpha]^{25}_D$ −73 (*c* 1.05, $CHCl_3$).



i

For **i**: IR (neat, cm^{-1}) 1461, 1358, 1250; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.38 (d, J = 2.1 Hz, 1H), 4.52 (t, J = 2.7 Hz, 1H), 2.79 (m, 1H), 2.33−1.22 (series of m, 10H), 0.92 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 121.9, 99.8, 67.4, 41.5, 35.9, 35.8, 31.0, 30.2, 25.8 (3C), 22.6, 20.2, −4.6, −5.1; ES HRMS *m/z* $(M)^+$ calcd 252.1909, obsd 252.1891.

(+)-Spiro Enone 12. A solution of CrO_3 (10.17 g, 101.8 mmol) and 3,5-dimethylpyrazole (9.77 g, 101.8 mmol) in CH_2Cl_2 (30 mL) was stirred at 0 °C for 20 min, cooled to −15 °C, and treated with a solution of (−)-**11** (1.71 g, 6.8 mmol) in CH_2Cl_2 (30 mL). The reaction mixture was stirred for 7 h, quenched with ether, filtered through a pad of silica gel, and concentrated. The residue was purified by chromatography on silica gel (10:1 hexanes/ethyl acetate) to give 0.96 g (53%) of **12** as a yellowish oil: IR (neat, cm^{-1}) 1716, 1462, 1252; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (dd, J = 5.7, 0.8 Hz, 1H), 7.26 (dd, J = 5.6, 1.5 Hz, 1H), 3.90 (m, 1H), 2.09−1.51 (series of m, 8H), 0.86 (s, 9H), 0.01 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.1, 170.1, 133.0, 81.8, 57.3, 46.8, 35.2, 34.3, 25.7 (3C), 21.6, 18.0, −4.9, −5.0; ES HRMS *m/z* $(M + Na)^+$ calcd 289.1594, obsd 289.1571; $[\alpha]^{25}_D$ +32.6 (*c* 1.35, $CHCl_3$).

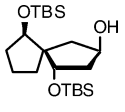
(−)-Epoxy Ketone 13. Methanol (0.2 mL), (+)-**12** (0.163 g, 0.61 mmol), and 30% H_2O_2 (0.13 mL, 1.84 mmol) were combined and cooled to 0 °C. Aqueous 1 M NaOH (0.2 mL, 0.31 mmol) was added dropwise via syringe. The reaction mixture was allowed to warm to rt, stirred for 4 h, and diluted with ether (5 mL) and saturated $NaHCO_3$ solution. The separated aqueous phase was extracted with ether (3 × 25 mL), and the combined organic phases were dried and concentrated. The residue was purified by chromatography on silica gel (10:1 hexanes/ethyl acetate) to yield **13** as a colorless oil (125 mg, 73%): IR (neat, cm^{-1}) 1751, 1471, 1408; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.87−3.84 (m, 2H), 3.36 (d, J = 2.5 Hz, 1H), 2.31−1.62 (m, 8H), 0.84 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.8, 803, 61.5, 56.5, 50.2, 42.1, 32.7, 31.1, 25.6 (3C), 19.9, 17.7, −4.5, −5.3; ES HRMS *m/z* $(M + Na)^+$ calcd 305.1543, obsd 305.1545; $[\alpha]^{20}_D$ −50.2 (*c* 1.1, $CHCl_3$).

(+)-β-Hydroxy Ketone 14. Into a flame-dried 10 mL pear-shaped flask equipped with a magnetic stirring bar was introduced a 0.1 M solution of SmI_2 in THF (2.82 mL, 0.282 mmol), THF (2 mL), DMPU (0.18 mL), ethylene glycol (0.1 mL), and (−)-**13** (26.5 mg, 0.095 mol). The reaction mixture was stirred for 1.5 h, diluted with petroleum ether, filtered through a pad of Celite, and concentrated. The residue was purified by chromatography on silica gel (3:1 hexanes/ethyl acetate) to give **14** as a yellowish oil (18.3 mg, 95%); IR (neat, cm^{-1}) 3390, 1745, 1244; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.58 (t, J = 7.6 Hz, 1H), 3.99 (m, 1H), 2.83 (s, 1H), 2.69−1.60 (m, 1H), 2.32−2.21 (m, 3H), 2.02−1.62 (m, 4H), 1.37−1.26 (m, 1H), 0.92 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.9, 82.7, 72.1, 55.1, 49.7, 45.5, 34.7, 27.4, 25.8 (3C), 21.2, 17.9, −4.4−4.9; ES HRMS *m/z* $(M + Na)^+$ calcd 307.1699, obsd 307.1708; $[\alpha]^{20}_D$ +36.9 (*c* 1.1, $CHCl_3$).

***O*-Silylation of (+)-14.** A solution of (+)-**14** (56 mg, 0.2 mmol), CH_2Cl_2 (5 mL), and 2,6-lutidine (114 μL, 0.98 mmol) was blanketed with N_2, cooled to −78 °C, treated with TBSOTf (90 μL, 0.39 mmol), and stirred for 45 min. The reaction mixure was warmed to rt, quenched with saturated $CuSO_4$ solution, stirred for 15 min, and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried and concentrated to leave a residue that was purified by chromatography on silica gel (10:1 hexanes:ethyl acetate) to give **15** as a yellowish oil (72 mg, 92%): IR (neat, cm^{-1}) 1750, 1472, 1257; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.55 (t, J = 2.2 Hz, 1H), 3.76 (t, J = 5.5 Hz, 1H) 2.57 (dd, J = 18.3, 5.3, 1H), 2.34−1.49 (m, 9H), 0.92 (s, 9H), 0.91 (s, 9H), 0.11 (s, 3H), 0.08 (s, 6H), 0.05 (s, 3H);^{13}C NMR (75 MHz, $CDCl_3$) δ 217.9, 79.4, 72.3, 57.0, 48.5, 47.7, 33.8, 31.1, 26.19 (3C), 26.17 (3C), 20.6, 18.3 (2C), −3.8, −4.0, −4.4, −4.6; ES HRMS *m/z* $(M + Na)^+$ calcd 421.2564, obsd 421.2576; $[\alpha]^{20}_D$ −44.8 (*c* 1.12, $CHCl_3$).

Hydride Reduction of (−)-15. A. With L-Selectride. A cold (−78 °C) solution of (−)-**15** (100 mg, 0.24 mmol) in THF (3.2 mL) was treated with L-Selectride (260 μL, 0.26 mmol, 1.1 equiv) and stirred for 10 min. The reaction mixture was quenched with saturated $NaHCO_3$ solution and extrated with ether (3 × 30 mL). The combined organic layers were dried and concentrated to leave a residue that was purified by chromatography on silica gel (20:1 hexanes:ethyl acetate) to give **16** (99 mg, 99%) as a colorless oil: IR (neat, cm^{-1}) 3384, 1471, 1463; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.40 (m, 1H), 4.24−4.22 (m, 1H) 3.55−3.54 (m, 1H), 2.16−2.13 (m, 1H), 1.92−1.28 (series of m, 9H), 0.93 (s, 9H), 0.91 (s, 9H), 0.14 (s, 3H), 0.12 (s, 3H), 0.06 (s, 3H), 0.04 (m, 3H);^{13}C NMR (75 MHz, $CDCl_3$) δ 80.8, 74.5, 74.0, 60.1, 47.6, 43.9, 26.5, 26.3, 26.1 (3C), 25.9 (3C), 20.9, 18.3 (2C), −3.9, −4.0, −4.4, −4.5; ES HRMS *m/z* $(M + Na)^+$ calcd 423.2721, obsd 423.2752; $[\alpha]^{20}_D$ −1.4 (*c* 1.02, $CDCl_3$).

With Dibal-H. A solution of (−)-**15** (42 mg, 0.106 mmol) in CH_2Cl_2 (4 mL) was blanketed with N_2, cooled to −78 °C, and treated with a 1M solution of Dibal-H in hexanes (127 μL, 0.13 mmol) in dropwise fashion. The reaction mixture was stirred for 45 min, quenched at −78 °C with saturated sodium potassium tartrate solution, and warmed to rt. After 30 min, the products were extracted into CH_2Cl_2 (3 × 25 mL), the combined organic phases were dried and concentrated, and the residue was purified by chromatography on silica gel (10:1 hexanes/ethyl acetate) to give (31 mg, 71%) of **16** and (10 mg, 26%) of **ii**, both as colorless oils.



ii

For **ii**: IR (neat, cm^{-1}) 3355, 1472, 1360; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.47 (t, J = 6.0 Hz, 1H), 4.32−4.30 (m, 1H), 3.91 (t, J = 7.2 Hz, 1H), 2.15−1.27 (m, 10H), 0.95 (s, 9H), 0.91 (s, 9H), 0.11 (s, 6H), 0.088 (s, 3H), 0.086 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 80.6, 73.3, 71.6, 57.1, 46.0, 45.9, 33.3, 31.0, 26.3 (3C), 26.2 (3C), 20.3, 18.4, 18.3, −3.74, −3.75, −4.3, −4.5; ES HRMS *m/z* $(M + Na)^+$ calcd 423.2721, obsd 423.2752; $[\alpha]^{20}_D$ +2.0 (*c* 0.8, $CHCl_3$).

Mesylate (+)-17. A solution of (+)-**16** (60 mg, 0.15 mmol) and Et_3N (63 μL, 0.45 mmol) in CH_2Cl_2 (5 mL) was cooled to 0 °C and treated dropwise with MsCl (24 μL, 0.3 mmol). The reaction mixture was stirred for 3 h, allowed to warm to rt, quenched with saturated $NaHCO_3$ solution, and extracted with Et_2O (3 × 25 mL). The combined organic phases were dried and concentrated. The residue was purified by chromatography on silica gel (10:1 hexanes/ethyl acetate) to give 60 mg (81%) of **17** as a colorless oil: IR (neat, cm-1) 1472, 1359, 1256; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.11−5.06 (m, 1H), 4.27 (dd, J = 5.0, 0.9 Hz, 1H), 3.71 (t, J = 6.8 Hz, 1H), 3.00 (s, 3H), 2.46−2.40 (m, 1H), 2.22−2.16 (m, 1H), 2.04−1.41 (series of m, 8H), 0.93 (s, 9H), 0.92 (s. 9H), 0.09 (s, 6H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 80.8, 79.2, 72.8, 57.5, 42.6, 42.5, 38.8, 26.2 (3C), 26.1 (3C), 20.4, 18.37, 18.33, −3.85, −3.86, −4.5, −4.6; ES HRMS *m/z* $(M + Na)^+$ calcd 501.2496, obsd 501.2508; $[\alpha]^{20}_D$ +10.4 (*c* 1.4, $CHCl_3$).

Incorporation of Uracil. To a mixture of NaH (6 mg, 0.25 mmol) and uracil (28 mg, 0.25 mmol) in DMF (5.2 mL) was added (+)-**17** (80 mg, 0.16 mmol) dissolved in DMF (1 mL). The reaction mixture was brought to 80 °C, stirred for 12 h, allowed to cool to rt, quenched with saturated $NaHCO_3$ solution, and extracted with ether (3 × 30 mL). The combined ether layers were dried and concentrated to leave a residue that was purified by chromatography on silica gel (3:1 hexanes: ethyl acetate) to give **18** (13 mg, 16%, 43% brsm) as a white solid: mp 118 °C; IR (neat, cm^{-1}) 1684, 1464, 1257; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.47 (s, NH), 7.20 (d, J = 8.1 Hz, 1H), 5.73 (dd, J = 7.0, 2.3 Hz, 1H), 5.07−5.04 (m, 1H), 4.46 (t, J = 5.5 Hz, 1H), 3.85 (t, J = 7.0 Hz, 1H), 2.18−1.26 (series of m, 10H), 0.94 (s, 9H), 0.91 (s, 9H), 0.09 (s, 6H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.8, 150.6, 1411, 102.4, 78.9, 72.0, 56.6, 54.1, 40.6, 39.6, 32.7, 30.3, 25.9 (3C), 25.7 (3C), 19.3, 18.0, 17.8, −4.2 (2C), −4.81, −4.83; ES HRMS *m/z* $(M + Na)^+$ calcd 517.2888, obsd 517.2871; $[\alpha]^{20}_D$ −10.7 (*c* 1.0, $CHCl_3$).

Incorporation of Cytosine. From 124 mg (0.26 mmol) of (+)-**17**, adaptation of the preceding conditions in the presence of cytosine afforded 15 mg (12%) of **19** as a colorless oil: IR (neat, cm^{-1}) 1635, 1591, 1559; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, J = 5.7 Hz, 1H), 6.09 (d, J = 5.6 Hz, 1H), 5.44−5.40 (m, 1H), 4.86 (s, NH_2), 4.45 (t, J = 5.2 Hz, 1H), 4.15 (t, J = 7.1 Hz, 1H), 2.24−1.28 (series of m, 10H), 0.93 (s, 9H), 0.92 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.9, 164.2, 157.9, 99.3, 78.8, 76.6, 74.5, 58.5, 42.4, 41.7, 26.2 (6C), 20.8, 18.4, 18.3, −3.9 (2C), −4.3, −4.4; ES HRMS *m/z* $(M + Na)^+$ calcd 516.3054, obsd 516.2900; $[\alpha]^{20}_D$ −7.8 (*c* 1.1, $CHCl_3$).

Incorporation of Thymine. When 80 mg (0.16 mmol) of (+)-**17** was processed in analogous fashion with thymine, there was isolated 20 mg (25%, 27% brsm) of **20** as a colorless oil: IR (neat, cm^{-1}) 1689, 1666, 1471; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.46 (s, NH), 6.99 (s, 1H), 5.08−5.05 (m, 1H), 4.47 (t, J = 5.9 Hz, 1H), 3.85 (t, J = 7.1 Hz, 1H) 2.19−1.28 (series of m, 10H), 1.94 (s, 3H), 0.95 (s, 9H), 0.91 (s, 9H), 0.09 (s, 6H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.4, 150.7, 136.9, 111.0, 78.7, 71.9, 56.3, 53.3, 40.7, 39.6, 32.6, 30.1, 25.9 (3C), 25.7 (3C), 19.7, 18.0, 17.8, 12.6, −4.1, −4.2, −4.8, −4.9; ES HRMS *m/z* $(M + Na)^+$ calcd 531.3044, obsd 531.3023; $[\alpha]^{20}_D$ −25.2 (*c* 1.0, $CHCl_3$).

Incorporation of Adenine. A mixture of **17** (39 mg, 0.08 mmol), adenine (16.5 mg, 0.122 mmol), and NaH (3 mg, 0.122 mmol) in 3 mL of DMF was heated to reflux for 18 h, allowed to cool to rt, quenched with saturated $NaHCO_3$ solution, and extracted with Et_2O (3 × 25 mL). The combined organic phases were dried and concentrated. The residue was purified by chromatography on silica gel (2:1 hexanes/ethyl acetate) to give 25 mg (60%) of **21** as a colorless oil: IR (neat, cm^{-1}) 1650, 1598, 1471; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.87 (s, 1H), 5.14−5.10 (m, 1H), 4.62 (dd, J = 5.4, 3.9 Hz, 1H), 4.07 (t, J = 6.1 Hz, 1H), 2.50−1.42 (series of m, 10H), 0.96 (s, 9H), 0.94 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H), 0.10 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.4, 152.2, 150.4, 139.7, 120.6, 79.4, 73.5, 58.3, 53.8, 42.6, 41.0, 33.4, 31.3, 26.3 (3C), 26.2 (3C), 20.5, 18.4, 18.3, −3.8 (2C), −4.3, −4.4; ES HRMS *m/z* $(M + Na)^+$ calcd 518.3341, obsd 518.3326; $[\alpha]^{20}_D$ −10.6 (*c* 1.0, $CHCl_3$).

Incorporation of 2-Amino-6-chloropurine. A mixture of NaH (16 mg, 0.65 mmol) and 2-amino-6-chloropurine (107 mg, 0.63 mmol) in DMF (9 mL) was treated with (+)-**17** (100 mg, 0.21 mmol) in DMF (1 mL), brought to 80 °C, stirred for 12 h, allowed to cool to rt, quenched with saturated $NaHCO_3$ solution, and extracted with ether (3 × 30 mL). The combined ether layers were dried and concentrated. The residue was purified by chromatography on silica gel (3:1 hexanes:ethyl acetate) to give **22** (31 mg, 27%, 90% brsm) as a white solid: mp > 300 °C; IR (neat, cm^{-1}) 1609, 1566, 1456; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (s, 1H), 5.06 (s, NH), 4.98−4.95 (m, 1H), 4.59 (t, J = 8.7 Hz, 1H), 4.26 (t, J = 4.3 Hz, 1H), 2.40−1.39 (series of m, 10H), 0.94 (s, 9H), 0.93 (s, 9H), 0.10 (s, 3H), 0.09 (s, 6H), 0.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.6, 153.6, 151.2, 141.1, 126.0, 79.0, 72.8, 57.6, 53.3, 41.6, 40.3, 32.9, 30.7, 25.9 (3C), 25.8 (3C), 20.0, 18.0, 17.9, −4.2, −4.3, −4.7 (2C); ES HRMS *m/z* $(M + Na)^+$ calcd 574.2770, obsd 574.2780; $[\alpha]^{20}_D$ −2.5 (*c* 0.8, $CHCl_3$).

Hydrolysis of 22 to Guanine Derivative 23. To a solution of **22** (12 mg, 0.022 mmol) in MeOH (5.0 mL) was added 2-mercaptoethanol (30 μL, 0.43 mmol) and a 5.25 M solution of NaOMe in MeOH (87 μL, 0.45 mmol). The reaction mixture was heated to 60 °C for 4 h, cooled, and concentrated. Purification of the residue by chromatography on silica gel (9:1 dichlromethane/methanol) gave **23** as a white solid: mp > 300 °C (10 mg, 87%); ^{1}H NMR (500 MHz, CD_3OD) δ 7.67 (s, 1H), 5.00−4.93 (m, 1H), 4.66−4.64 (m, 1H), 4.01 (t, J = 5.9 Hz, 1H), 2.38−1.46 (series of m, 10H), 0.96 (s, 9H), 0.95 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H), 0.12 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.6, 155.3, 152.3, 134.3, 114.4, 79.0, 73.1, 57.5, 51.9, 42.0, 40.1, 32.7, 30.5, 25.0 (3C), 24.9 (3C), 19.5, 17.5, 17.4, −5.3, −5.5, −5.8, −5.9; ES HRMS *m/z* $(M + Na)^+$ calcd 556.3109, obsd 556.3080; $[\alpha]^{20}_D$ −2.5 (*c* 0.8, $CHCl_3$).

General Procedure for the Global Deprotection of 18−23. A solution of **18** (11 mg, 0.02 mmol) and 1M TBAF in THF (0.13 mL, 0.13 mmol) in THF (1 mL) was stirred at rt for 32 h. The reaction mixture was concentrated and the crude product was purified by chromatography on silica gel (9:1 dichloromethane/methanol) to give **24** (5.4 mg, 92%) as a white solid: mp 179 °C; IR (neat, cm^{-1}) 3415, 1687, 1463, 1382; ^{1}H NMR (500 MHz, CD_3OD) δ 7.69 (d, J = 8.0 Hz, 1H), 5.70 (d, J = 8.0 Hz, 1H), 5.06−5.03 (m, 1H), 4.50 (t, J = 5.6 Hz, 1H), 3.93 (t, J = 5.0 Hz, 1H), 2.22−1.36 (series of m, 10H); ^{13}C NMR (125 MHz, CD_3OD) δ 164.8, 151.3, 143.1, 101.2, 79.6, 72.2, 56.4, 54.3, 39.9, 37.9, 32.5, 28.8, 19.9; ES HRMS *m/z* $(M + Na)^+$ calcd 289.1158, obsd 289.1169; $[\alpha]^{20}_D$ −9.8 (*c* 1.0, $CHCl_3$).

For **25**: white solid; mp 164−165 °C; 84% yield; IR (neat, cm^{-1}) 3335, 3206, 1632, 1596; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, J = 6.0 Hz, 1H), 6.13 (d, J = 5.9 Hz, 1H), 5.43−5.38 (m, 1H), 4.45 (t, J = 5.9 Hz, 1H), 3.94 (t, J = 2.6 Hz, 1H), 2.21−1.37 (series of m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 164.6, 155.5, 98.9, 79.4, 75.8, 74.1, 57.5, 42.5, 40.8, 33.3, 29.8, 20.7; EI HRMS *m/z* (M^+) calcd 265.1420, obsd 265.1393; $[\alpha]^{20}_D$ −17.3 (*c* 0.6, MeOH).

For **26**: colorless oil; 73% yield; ^{1}H NMR (500 MHz, C_5D_5N) δ 7.50 (d, J = 1.2 Hz, 1H), 5.05−5.02 (m, 1H), 4.51 (t, J = 6.7 Hz, 1H), 3.94 (t, J = 5.3 Hz, 1H), 2.23−1.39 (series of m, 10H), 1.95 (3H); ^{13}C NMR (125 MHz, C_5D_5N) δ 165.0, 151.5, 138.8, 110.2, 79.6, 72.1, 56.3, 53.9, 39.9, 37.8, 32.5, 28.7, 19.5, 12.6; ES HRMS *m/z* $(M + Na)^+$ calcd 303.1315, obsd 303.1296; $[\alpha]^{20}_D$ −12.3 (*c* 0.70, C_5H_5N).

For **27**: white solid; mp > 300 °C; 93% yield; IR (neat, cm^{-1}) 3321, 1478, 1415; ^{1}H NMR (500 MHz, CD_3OD) δ 8.20 (s, 1H), 5.20−5.15 (m, 1H), 4.58 (m, 1H), 4.06 (t, J = 5.0 Hz, 1H), 2.61−2.55 (m, 1H), 2.28−2.19 (m, 3H), 2.04−1.94 (m, 2H), 1.84−1.80 (m, 1H), 1.72−1.65 (m, 2H), 1.54−1.49 (m, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 156.3, 152.2, 149.4, 140.5, 119.7, 80.2, 72.9, 57.5, 53.7, 41.6, 40.2, 32.6, 29.7, 20.2; EI HRMS *m/z* (M^+) calcd 289.1533, obsd 289.1502; $[\alpha]^{20}_D$ −3.0 (*c* 1.0, MeOH).

For **28**: white solid; mp > 300 °C; 62% yield; ^{1}H NMR (500 MHz, C_5D_5N) δ 8.10 (s, 1H), 5.16 (t, J = 5.6 Hz, 1H), 4.72 (t, J = 5.4 Hz, 1H), 4.25−4.24 (m, 1H), 2.71−1.30 (series of m, 10H);^{13}C NMR (125 MHz, C_5D_5N) δ 158.5, 157.2, 154.5, 143.4, 119.0, 79.9, 72.7, 57.6, 52.3, 42.5, 41.6, 33.8, 29.8, 20.9; ES HRMS *m/z* $(M + Na)^+$ calcd 328.1380, obsd 328.1395; $[\alpha]^{20}_D$ −5.7 (*c* 0.2, C_5H_5N).

Dehydration of (+)-10. A procedure identical to those utilized above for the levorotatory enantiomer furnished 56% of (+)-**11** and 25% of **i**. The ^{1}H and ^{13}C NMR of (+)-**11** are identical to those of (−)-**11**: ES HRMS *m/z* $(M + H)^+$ calcd 253.1982, obsd 253.1992; $[\alpha]^{23}_D$ +89 (*c* 1.2, $CHCl_3$).

Hydroboration of (+)-11. A cold (0 °C) 1 M solution of BH_3.THF (8.37 mL, 8.37 mmol) was treated with 2-methyl-2-butene (1.79 mL, 16.76 mmol), allowed to warm to rt during 30 min, returned to 0 °C, and treated with a solution of (+)-**11** (0.70 g, 2.8 mmol) in 1 mL of THF. The reaction mixture was stirred for 12 h with warming to rt, treated with 3 M NaOH solution (2.29 mL) and 30% H_2O_2 (7.34 mL), washed with saturated $NaHCO_3$ solution, and extracted with ether (3 × 25 mL). The combined organic solutions were dried and concentrated to leave a residue that was purified by chromatography on silica gel (10:1 hexanes:ethyl acetate) to give 500 mg (66%) of **30** and 140 mg (19%) of **29**, both as colorless oils.

For **29**: IR (neat, cm^{-1}) 3378, 1471, 1254; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.22 (s, 1H), 3.81 (t, J = 7.7 Hz, 1H), 3.04−3.01 (m, 1H), 1.97−1.47 (series of m, 12H), 0.91 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 80.8, 73.8, 52.8, 45.1, 42.3, 37.6, 35.5, 32.9, 31.7, 25.9 (3C), 19.4, −4.2, −4.7; ES HRMS *m/z* $(M + Na)^+$ calcd 293.1907, obsd 293.1919; $[\alpha]^{20}_D$ +30 (*c* 0.82, $CHCl_3$).

For **30**: IR (neat, cm^{-1}) 3372, 1471, 1255; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.30−4.32 (m, 1H), 3.66 (t, J = 5.4 Hz, 1H), 2.25 (dd, J = 7.5, 6.5 Hz, 1H), 1.90−1.24 (series of m, 11H), 0.88 (s, 9H), 0.03 (s, 6H);^{13}C NMR (75 MHz, $CDCl_3$) δ 80.2, 74.2, 53.2, 41.4, 37.5, 35.3, 34.5, 32.9, 25.8 (3C), 20.1, 17.9, −4.3, −4.9; ES HRMS *m/z* $(M + Na)^+$ calcd 293.1907, obsd 293.1913; $[\alpha]^{20}_D$ +38 (*c* 1.47, $CHCl_3$).

Mitsunobu Inversion of (+)-29. A solution of DIAD (86 μL, 0.45 mmol) and triphenylphosphine (118 mg, 0.45 mmol) in cold (0 °C) THF (2 mL) was stirred for 10 min prior to the addition of a solution of (+)-**29** (61.4 mg, 0.23 mmol) and $PhCO_2H$ (55 mg, 0.45 mmol) in 0.5 mL of THF at rt. The reaction mixture was stirred for 12 h and concentrated. The residue was purified by chromatography on silica gel (10:1 hexanes:ethyl acetate) to give 0.36 g (86%) of inverted benzoate as a yellowish oil; IR (neat, cm^{-1}) 1710, 1421, 1264; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, J = 8.2 Hz, 2H), 7.55 (t, J = 6.2 Hz, 1H), 7.46−7.41 (m, 2H), 5.47−5.40 (m, 1H), 3.77 (t, J = 5.8 Hz, 1H), 2.39 (dd, J = 7.8, 6.5 Hz, 1H), 2.16−2.04 (m, 1H), 1.95−1.12 (series of m, 10H), 0.91 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 132.5, 130.9, 129.4 (2C), 128.2 (2C), 80.2, 77.9, 53.4, 38.3, 36.8, 34.8, 33.1, 32.5, 25.8 (3C), 20.2, 17.9−4.3, −4.9; ES HRMS *m/z* $(M + Na)^+$ calcd 397.2169, obsd 397.2185; $[\alpha]^{20}_D$ −2 (*c* 1.23, $CHCl_3$).

A 5.25 M solution of NaOMe in MeOH (36 μL, 0.19 mmol) was added to the above benzoate (599 mg, 0.16 mmol) dissolved in MeOH (0.5 mL). The reaction mixture was stirred for 30 min, quenched with saturated $NaHCO_3$ solution, transferred to a separatory funnel, and extracted with ether (3 × 10 mL). The combined ether layers were dried and concentrated to leave a residue that was purified by chromatography on silica gel (10:1 hexanes/ethyl acetate) to give 30 mg (71%) of (+)-**30** as a colorless oil. The spectral features of this product were identical to those reported above.

Swern Oxidation of 29/30. A solution of oxalyl chloride (17 μL, 0.195 mmol) in CH_2Cl_2 (1 mL) was brought to −78 °C where DMSO (28 μL, 0.39 mmol) was added dropwise. After 15 min, a mixture of **39** and **40** (35.1 mg, 0.13 mmol) in 1 mL of CH_2Cl_2 was introduced dropwise. After an additional hour, Et_3N (54 μL, 0.39 mmol) was added, and the solution was allowed to come to rt prior to quenching with saturated $NaHCO_3$ solution, transferred to a separatory funnel, and extracted 3 times with ether. The combined organic phases were dried and concentrated. Purification of the residue by chromatography on silica gel (10:1 hexanes:ethyl acetate) gave **31** as a colorless oil (27.9 mg, 80%): IR (neat, cm^{-1}) 1745, 1472, 1406; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.83 (t, J = 6.9 Hz, 1H), 2.54−2.48 (m, 1H), 2.26−223 (m, 2H), 1.93−1.52 (series of m, 9H), 0.85 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 219.8, 79.4, 51.1, 45.0, 37.6, 34.8, 32.8, 32.6, 25.6 (3C), 19.5, 17.8, −4.3, −5.1; ES HRMS *m/z* $(M + Na)^+$ calcd 291.1750, obsd 291.1770; $[\alpha]^{20}_D$ +43.1 (*c* 1.22, $CHCl_3$).

Regioselective Bromination of (+)-31 A solution of (+)-**31** (67 mg, 0.25 mmol) in THF (1.5 mL) was cooled to −78 °C. A 1M solution of lithium hexamethyldisilazide in THF (300 μL, 0.3 mmol) was added and the mixture was stirred for 1 h. TMSCl (44 μL, 0.35 mmol) was introduced and stirring was maintained for an additional hour with warming to rt. The reaction mixture was quenched with saturated $NaHCO_3$ solution and extracted with ether (3 × 15 mL). The combined organic solutions were dried and concentrated. The crude product was redissolved in a mixture of THF and H_2O (5:1, 3 mL), at which point NBS (134 mg, 0.75 mmol) was added. After 4 h of stirring, the reaction mixture was quenched with saturated $NaHCO_3$ solution and extracted with ether (3 × 15 mL). The combined organic solutions were dried and concentrated to leave a residue that was purified by chromatography on silica gel (hexanes:ethyl acetate 10:1) to give **32** as a mixture of diastereomers; colorless oil (67 mg, 77%): IR (neat, cm^{-1}) 1750, 1471, 1257; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.40 (s, 1H), 4.00 (t, J = 6.9 Hz, 1H), 2.41−1.54 (series of m, 10H), 0.84 (s, 9H), 0.24 (s, 3H), 0.15 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.5, 81.0, 57.3, 34.4, 33.4, 32.0, 28.1, 26.1 (3C), 22.7, 20.2, 18.3, −3.9, −4.7; ES HRMS *m/z* $(M + Na)^+$ calcd 369.0855, obsd 369.0862.

Unsaturated Ketone (−)-33. A solution of **32** (1.12 g, 3.23 mmol), LiBr (489 mg, 5.49 mmol), and Li_2CO_3 (597 mg, 8.07 mmol) in DMF (62 mL) was heated to 120−130 °C for 2h, quenched with saturated $NaHCO_3$ solution, and extracted with ether (3 × 15 mL). The combined organic phases were dried and concentrated. The residue was purified by chromatography on silica gel (hexanes:ethyl acetate 10:1) to give **33** as a colorless oil (680 mg, 80%): IR (neat, cm^{-1}) 1716, 1472, 1401; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (d, J = 5.6 Hz, 1H), 6.12 (d, J = 5.6 Hz, 1H), 4.02 (t, J = 8.1 Hz, 1H), 2.79 (d, J = 18.1 Hz, 1H), 2.20−1.52 (series of m, 6H), 1.94 (d, J = 18.1 Hz, 1H), 0.84 (s, 9H), 0.03 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 210.4, 169.9, 134.1, 77.9, 57.1, 42.1, 35.3, 33.4, 26.0 (3C), 20.2, 18.3, −4.2, −4.5; ES HRMS *m/z* $(M + Na)^+$ calcd 289.1594, obsd 289.1604; $[\alpha]^{20}_D$ −94.6 (*c* 0.89, $CHCl_3$).

Epoxy Ketone (+)-34. Methanol (0.2 mL), (−)-**33** (0.163 g, 0.61 mmol), and 30% H_2O_2 (0.13 mL, 1.84 mmol) were combined and cooled to 0 °C. 1 M NaOH (0.2 mL, 0.31 mmol) was added dropwise via syringe. The reaction mixture was allowed to warm to rt, stirred for 4 h, quenched with saturated $NaHCO_3$ solution, and extracted with ether (3 × 15 mL). The combined organic solutions were dried and concentrated. The residue was purified by chromatography on silica gel (hexanes/ethyl acetate 10:1) to give **34** as a colorless oil (130 mg, 78%): IR (neat, cm^{-1}) 1720, 1445, 1360; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.03 (t, J = 7.8 Hz, 1H), 3.56 (d, J = 2.3 Hz, 1H), 3.36 (d, J = 2.4 Hz, 1H), 2.40−1.59 (series of m, 8H), 0.87 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.7, 142.0, 77.3, 66.2, 38.9, 32.8, 32.0, 29.7, 25.9 (3C), 20.1, 18.2, −4.0, −4.7; ES HRMS *m/z* $(M + Na)^+$ calcd 305.1543, obsd 305.1519; $[\alpha]^{20}_D$ +8.4 (*c* 0.5, $CHCl_3$).

Samarium Iodide-Promoted Reduction of (+)-34. Ethylene glycol (4.13 mL, 74.1 mmol), DMPU (7.82 mL, 64.8 mmol) and (+)-**34** (1.1 g, 3.9 mmol) were dissolved in THF (83 mL). The solution was degassed with argon, at which point a 0.1 M solution of SmI_2 in THF (117 mL, 11.7 mmol) was added. The reaction mixture was stirred for 1 h, quenched with saturated $NaHCO_3$ solution, transferred to a separatory funnel, and

extracted with Et_2O (3 × 100 mL). The combined organic solutions were dried and concentrated. The residue was purified by chromatography on silica gel (2:1 hexanes/ethyl acetate) to give **35** as a colorless oil (0.84 g, 76%): IR (neat, cm^{-1}) 3434, 1735, 1466; ^1H NMR (500 MHz, $CDCl_3$) δ 4.16−4.09 (m, 1H), 3.97 (t, J = 7.8 Hz, 1H), 2.70−1.43 (series of m, 10H), 0.84 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H);^{13}C NMR (125 MHz, $CDCl_3$) δ 217.7, 77.2, 74.8, 55.8, 47.4, 43.5, 33.6, 29.5, 26.1 (3C), 19.7, 18.2, −3.8, −4.7; ES HRMS *m/z* $(M + Na)^+$ calcd 307.1699, obsd 307.1722; $[\alpha]^{20}_D$ +22.0 (*c* 1.3, $CHCl_3$).

Silylation of (+)-35. A solution of (+)-**35** (197 mg, 0.7 mmol), 2,6-lutidine (0.4 mL, 3.5 mmol), and CH_2Cl_2 (20 mL) was cooled to −78 °C, when TBSOTf (0.32 mL, 1.4 mmol) was added. The reaction mixture was stirred for 1 h, allowed to warm to rt, quenched with saturated $NaHCO_3$ solution, transferred to a separatory funnel, and extracted with Et_2O (3 × 50 mL). The combined organic phases were dried and concentrated to leave a residue that was purified by chromatography on silica gel (20:1 hexanes:ethyl acetate) to give **36** as a white solid: mp 58 °C (224 mg, 81%); IR (neat, cm^{-1}) 1748, 1472, 1255; ^1H NMR (500 MHz, $CDCl_3$) δ 4.10 (t, J = 5.8 Hz, 1H), 3.94 (t, J = 7.4 Hz, 1H), 2.57−1.42 (series of m, 10H), 0.88 (s, 9H), 0.85 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H), 0.03 (s, 6H);^{13}C NMR (125 MHz, $CDCl_3$) δ 216.7, 76.6, 74.4, 56.3, 47.8, 43.9, 34.0, 29.5, 26.14 (3C), 26.11 (3C), 19.8, 18.3, 18.2, −3.6, −3.9, −4.6, −4.64; ES HRMS *m/z* $(M + Na)^+$ calcd 421.2564, obsd 421.2582; $[\alpha]^{20}_D$ +40.0 (*c* 1.4, $CHCl_3$).

L-Selectride Reduction of (+)-36. A solution of (+)-**36** (30 mg, 0.08 mmol) in THF (1 mL) was cooled to −78 °C, treated with L-Selectride (83 μL, 0.08 mmol), stirred for 10 min, quenched with saturated $NaHCO_3$ solution, and extracted with ether (3 × 30 mL). The combined organic layers were dried and concentrated. The residue was purified by chromatography on silica gel (20:1 hexanes/ethyl acetate) to give **37** (30 mg, 99%) as a white solid: mp 65−66 °C; IR (CH_2Cl_2, cm^{-1}) 3394, 1472, 1256; ^1H NMR (500 MHz, $CDCl_3$) δ 4.22 (t, J = 6.2 Hz, 1H), 3.83 (t, J = 4.0 Hz, 1H), 3.71 (t, J = 7.0 Hz, 1H), 2.41−1.44 (series of m, 8H), 0.91 (s, 9H), 0.88 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H);^{13}C NMR (125 MHz, $CDCl_3$) δ 79.7, 78.2, 73.4, 58.1, 43.9, 40.7, 33.4, 31.5, 25.83 (3C), 25.82 (3C), 19.8, 18.0, 17.9, −4.1, −4.4, −5.0, −5.02; ES HRMS *m/z* $(M + Na)^+$ calcd 423.2721, obsd 423.2724; $[\alpha]^{20}_D$ 42.5 (*c* 1.0, $CHCl_3$).

Mesylate (+)-38. To a solution of (+)-**37** (335 mg, 0.84 mmol) in CH_2Cl_2 (29 mL) cooled to 0 °C was added Et_3N (0.35 mL, 2.5 mmol) followed by MsCl (0.2 mL, 2.5 mmol). The reaction mixture was allowed to warm to rt, where after 3 h it was quenched with saturated $NaHCO_3$ solution, and extracted with Et_2O (3 × 50 mL). The combined organic solutions were dried and concentrated. The residue was purified by chromatography on silica gel (10:1 hexanes/ethyl acetate) to give **38** as a white solid: mp 50 °C (0.37 g, 92%); IR (CH_2Cl_2, cm^{-1}) 1472, 1361, 1257; ^1H NMR (500 MHz, $CDCl_3$) δ 5.09−5.04 (m, 1H), 3.78−3.72 (m, 2H), 2.99 (s, 3H), 2.47−1.26 (series of m, 8H), 0.91 (s, 9H), 0.90 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H), 0.05 (s, 6H);^{13}C NMR (125 MHz, $CDCl_3$) δ 80.4, 76.6, 75.0, 41.8, 38.3, 36.8, 33.5, 29.1, 25.8 (3C), 25.7 (3C), 19.7, 17.9 (2C), −4.0, −4.2, −4.9 (2C); ES HRMS *m/z* $(M + Na)^+$ calcd 501.2496, obsd 501.2499; $[\alpha]^{20}_D$ +28 (*c* 1.1, $CHCl_3$).

Incorporation of Uracil. From 60 mg (0.13 mmol) of (+)-**38**, adaptation of the preceding conditions in the presence of uracil afforded 12 mg (19%, 46% brsm) of **39** as a colorless oil: IR (CH_2Cl_2, cm^{-1}) 1688, 1471, 1257; ^1H NMR (500 MHz, $CDCl_3$) δ 8.41 (s, NH), 7.37 (d, J = 8.1 Hz, 1H), 5.73 (dd, J = 8.0, 2.2 Hz, 1H), 5.21−5.18 (m, 1H), 4.06 (t, J = 6.6 Hz, 1H), 3.91 (t, J = 8.5 Hz, 1H), 2.06−1.26 (series of m, 8H), 0.92 (s, 9H), 0.90 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H);^{13}C NMR (125 MHz, $CDCl_3$) δ 162.8, 150.7, 141.3, 102.5, 75.1, 56.9, 52.8, 40.0, 34.5, 32.9, 28.8, 25.9 (3C), 25.7 (3C), 19.2, 18.1, 17.9, −4.0, −4.1, −4.6, −4.9; ES HRMS *m/z* $(M + Na)^+$ calcd 517.2888, obsd 517.2897; $[\alpha]^{20}_D$ +26 (*c* 1.0, $CHCl_3$).

Incorporation of Cytosine. When 74 mg (0.16 mmol) of (+)-**38** was processed in analogous fashion with cytosine, there was isolated 9 mg (12%, 40% brsm) of **40** as a colorless oil: IR (CH_2Cl_2, cm^{-1}) 3315, 3178, 1631; ^1H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, J = 5.7 Hz, 1H), 6.10 (d, J = 5.7 Hz, 1H), 5.34−5.30 (m, 1H), 4.93 (s, NH_2), 4.11 (t. J = 8.3 Hz, 1H), 3.88 (t, J = 7.0 Hz, 1H), 2.10−1.26 (series of m, 8H), 0.89 (s, 9H), 0.86 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H), 0.03 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.6, 157.0, 149.7, 139.3, 76.5, 74.7, 73.8, 56.6, 40.7, 36.2, 33.8, 28.3, 25.88 (3C), 25.84 (3C), 20.1, 18.0, 17.9, −4.0, −4.09, −4.8, −4.9; ES HRMS *m/z* $(M + Na)^+$ calcd 516.3048, obsd 516.3061; $[\alpha]^{20}_D$ +22.2 (*c* 0.9, $CHCl_3$).

Incorporation of Thymine. Reaction of 80 mg (0.16 mmol) of (+)-**38** with thymine under the predescribed conditions afforded 20 mg (25%, 27% brsm) of **41** as a white solid: mp 160−162 °C; IR (CH_2Cl_2, cm^{-1}) 1687, 1471, 1255; ^1H NMR (500 MHz, $CDCl_3$) δ 8.51 (s, NH), 7.07 (d, J = 1.1 Hz, 1H), 5.23−5.16 (m, 1H), 4.09 (t, J = 7.0 Hz, 1H), 3.91 (t, J = 7.3 Hz, 1H), 2.02−1.24 (series of m, 8H), 1.94 (s, 3H), 0.93 (s, 9H), 0.91 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H);^{13}C NMR (125 MHz, $CDCl_3$) δ 163.4, 150.8, 136.8, 111.1, 76.6, 74.6, 56.8, 52.2, 39.7, 34.3, 32.8, 28.2, 25.9 (3C), 25.8 (3C), 19.2, 18.0, 17.9, 12.5, −3.8, −4.1, −4.8, -4.9; ES HRMS *m/z* $(M + Na)^+$ calcd 531.3044, obsd 531.3070; $[\alpha]^{20}_D$ +26.2 (*c* 1.4, $CHCl_3$).

Incorporation of Adenine. To a mixture of NaH (9 mg, 0.32 mmol) and adenine (41 mg, 0.3 mmol) in DMF (4.5 mL) was added (+)-**38** (72 mg, 0.15 mmol) in DMF (1.5 mL). The reaction mixture was brought to 80 °C, stirred for 12 h, allowed to cool to rt, quenched with saturated $NaHCO_3$ solution, and extracted with ether (3 × 30 mL). The combined ether layers were dried and concentrated. The residue was purified by chromatography on silica gel (1:1 hexanes/ethyl acetate) to give **42** (28 mg, 37%, 63% brsm) as a white solid: mp 142 °C; IR (CH_2Cl_2, cm^{-1}) 3316, 3159, 1643; ^1H NMR (500 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.91 (s, 1H), 5.84 (s, NH_2), 5.13−5.10 (m, 1H), 4.29 (t, J = 7.0 Hz, 1H), 3.96 (t, J = 7.3 Hz, 1H), 2.37−1.41 (series of m, 8H), 0.91 (s, 9H), 0.90 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H), 0.07 (s, 3H), 0.05 (s, 3H);^{13}C NMR (125 MHz, $CDCl_3$) δ 155.3, 152.5, 150.0, 138.8, 119.9, 76.6, 74.5, 57.1, 51.5, 41.0, 36.0, 33.2, 28.4, 25.8 (6C), 19.5, 18.0, 17.9, −4.0, −4.1, −4.7, −4.9; ES HRMS *m/z* $(M + Na)^+$ calcd 540.3160, obsd 540.3154; $[\alpha]^{20}_D$ +40 (*c* 0.9, $CHCl_3$).

Incorporation of 2-Amino-6-chloropurine. To a mixture of NaH (7 mg, 0.29 mmol) and 2-amino-6-chloropurine (48 mg, 0.28 mmol) in DMF (4 mL) was added (+)-**38** (67 mg, 0.14 mmol) in DMF (1.4 mL). The reaction mixture was brought to 80 °C, stirred for 12 h, allowed to cool to rt, quenched with saturated $NaHCO_3$ solution, and extracted with ether (3 × 30 mL). The combined ether layers were dried concentrated to leave a residue that was purified by chromatography on silica gel (3:1 hexanes/ethyl acetate) to give **43** (15 mg, 20%, 35% brsm) as a white solid: mp 200 °C; IR (neat, cm^{-1}) 1609, 1566, 1456; ^1H NMR (500 MHz, $CDCl_3$) δ 7.88 (s, 1H), 5.06 (s, NH), 4.98−4.95 (m, 1H), 4.26 (t, J = 6.8 Hz, 1H), 3.96 (t, J = 7.3 Hz, 1H), 2.32−1.41 (series of m, 10H), 0.92 (s, 9H), 0.90 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H), 0.07 (3C); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.6, 153.6, 151.1, 141.1, 126.0, 76.6, 74.6, 57.1, 51.8, 40.6, 35.6, 33.2, 28.4, 25.9 (3C), 25.8 (3C), 19.5, 18.07, 18.01, −3.9, −4.1, −4.7, −4.8; ES HRMS *m/z* $(M + Na)^+$ calcd 574.2770, obsd 574.2795; $[\alpha]^{20}_D$ +29.9 (*c* 0.80, $CHCl_3$).

Hydrolysis of 43 to Guanine Derivative 44. To a solution of **43** (8.7 mg, 0.016 mmol) in MeOH (3.6 mL) was added 2-mercaptoethanol (27.4 μL, 0.31 mmol,) and a 5.25 M solution of NaOMe in MeOH (63 μL, 0.33 mmol). The reaction mixture was heated to 60 °C for 4 h and concentrated. The residue was chromatographed on silica gel (9:1 dichlromethane:methanol) to give **44** as a white solid: mp > 300 °C (5.3 mg, 63%); ^1H NMR (500 MHz, CD_3OD) δ 7.72 (s, 1H), 4.97−4.91 (m, 1H), 4.31 (t, J = 6.9 Hz, 1H), 4.02 (t, J = 7.2 Hz, 1H), 2.32−1.46 (series of m, 10H), 0.94 (s, 9H), 0.90 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.8, 153.5, 151.5, 135.9, 116.6, 77.0, 74.8, 57.2, 51.3, 39.9,

36.3, 33.3, 28.4, 25.0 (3C), 24.9 (3C), 19.4, 17.4 (2C), −5.2, −5.3, −5.8, −6.0; ES HRMS *m/z* $(M + Na)^+$ calcd 556.3109, obsd 556.3104; $[\alpha]^{20}_D$ +48.6 (*c* 0.5, MeOH).

Global Deprotection of 39−44. The procedure described earlier was adopted in all cases.

For **45**: white solid; mp 156 °C; 80% yield; ^{1}H NMR (500 MHz, CD_3OD) δ 7.83 (d, J = 8.1 Hz, 1H), 5.70 (d, J = 8.1, Hz, 1H), 5.17−5.13 (m, 1H), 4.07 (t, J = 5.5 Hz, 1H), 3.93 (t, J = 7.1 Hz, 1H), 2.14−1.40 (series of m, 8H); ^{13}C NMR (125 MHz, CD_3OD) δ 164.8, 151.4, 143.1, 101.2, 76.6, 75.1, 56.6, 53.7, 38.2, 34.4, 32.6, 29.3, 19.4; ES HRMS *m/z* $(M + Na)^+$ calcd 289.1158, obsd 289.1155; $[\alpha]^{20}_D$ 17 (*c* 0.7, $CHCl_3$).

For **46**: white solid; mp 156 °C; 86% yield; ^{1}H NMR (500 MHz, CD_3OD) δ 7.83 (d, J = 5.9 Hz, 1H), 6.13 (d, J = 5.9, Hz, 1H), 5.35−5.33 (m, 1H), 4.04 (t, J = 7.1 Hz, 1H), 3.89 (t, J = 5.8 Hz, 1H), 2.13−1.41 (series of m, 8H); ^{13}C NMR (125 MHz, CD_3OD) δ 165.8, 164.5, 155.5, 98.5, 76.0, 74.5, 73.7, 58.1, 40.2, 36.1, 32.4, 28.4, 19.7; ES HRMS *m/z* $(M + Na)^+$ calcd 288.1318, obsd 288.1313; $[\alpha]^{20}_D$ +15.3 (*c* 0.6, $CHCl_3$).

For **47**: white solid; mp 218 °C; 73% yield; ^{1}H NMR (500 MHz, CD_3OD) δ 7.67 (s, 1H), 5.16−5.13 (m, 1H), 4.09 (t, J = 5.5 Hz, 1H), 3.93 (t, J = 7.1 Hz, 1H), 2.12−1.53 (series of m, 8H), 1.90 (s, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 165.0, 151.6, 138.8, 110.2, 76.6, 75.0, 56.6, 53.3, 38.1, 34.3, 32.6, 29.3, 19.6, 11.0; ES HRMS *m/z* $(M + Na)^+$ calcd 303.1315, obsd 303.1325; $[\alpha]^{20}_D$ +23.5 (*c* 0.4, $CHCl_3$).

For **48**: white solid; mp 178−180 °C; 93% yield; ^{1}H NMR (500 MHz, CD_3OD) δ 8.30 (s, 1H), 8.20 (s, 1H), 5.23−5.20 (m, 1H), 4.15 (t, J = 5.1 Hz, 1H), 3.98 (t, J = 6.7 Hz, 1H), 2.43−1.41 (series of m, 8H); ^{13}C NMR (125 MHz, CD_3OD) δ 155.9, 151.9, 150.3, 140.1, 119.0, 76.6, 75.1, 57.3, 52.8, 39.9, 35.6, 32.8, 29.5, 19.8; ES HRMS *m/z* $(M + Na)^+$ calcd 312.1430, obsd 312.1428; $[\alpha]^{20}_D$ +31.1 (*c* 1.0, $CHCl_3$).

For **49**: white solid; mp > 300 °C; 62% yield; ^{1}H NMR (500 MHz, C_5D_5N) δ 7.88 (s, 1H), 5.18−5.15 (m, 1H), 4.18 (t, J = 5.1 Hz, 1H), 3.97 (t, J = 6.7 Hz, 1H), 2.33−2.01 (series of m, 8H); ^{13}C NMR (125 MHz, C_5D_5N) δ 158.0, 153.7, 151.4, 136.7, 116.5, 76.4, 74.8, 56.9, 51.8, 39.7, 35.8, 32.7, 29.1, 19.6; ES HRMS *m/z* $(M + Na)^+$ calcd 305.1488, obsd 305.1492; $[\alpha]^{20}_D$ +82 (*c* 0.1, C_5H_5N).

Supporting Information Available: High-field ^{1}H and ^{13}C NMR spectra for all compounds described herein. This material is available free of charge via the Internet at http://pubs.acs.org.

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