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Enantioselective Synthesis of Bicyclo[3.1.0]hexane Carbocyclic Nucleosides via a Lipase-Catalyzed Asymmetric Acetylation. Characterization of an Unusual Acetal Byproduct

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The bicyclo[3.1.0]hexane scaffold can lock the conformation of a carbocyclic nucleoside into one of the two antipodal (north or south) conformations typical of conventional nucleosides that normally exist in a rapid, two-state equilibrium in solution. In a recent brief communication, we reported a practical method to access the requisite bicyclo[3.1.0]hexane pseudosugar for the north antipode via an intramolecular olefin−ketocarbene cycloaddition. The most attractive features of this synthesis was that a relatively complex synthon was obtained from simple and inexpensive starting materials and that the resulting racemic mixtures of purine nucleosides could be successfully resolved by adenosine deaminase (ADA) hydrolysis. In this work, we describe the development of a more general, lipase-catalyzed double-acetylation reaction, which could successfully resolve an earlier precursor, 4-(*tert*-butyldiphenylsilamethoxy)-1-(hydroxymethyl)bicyclo[3.1.0]hexan-2-ol [(±)-**7**], into enantiomerically pure (+)-diacetate **8** and (−)-monoacetate **9**. The former diacetate was converted to the conformationally locked (north)-carbocyclic guanosine (+)-**17** identical to the one obtained previously by ADA resolution. The present method represents a more general and efficient process applicable to the synthesis of all classes of (north) bicyclo[3.1.0]hexane nucleosides, including pyrimidine analogues. During the lipase-catalyzed resolution, we were able to demonstrate the presence of an unusual acetal-forming reaction that consumed small amounts of the unreactive monoacetate (−)-**9**. This side reaction was also enzyme-catalyzed and was triggered by the byproduct acetaldehyde generated during the reaction.

Introduction

In nucleosides, the ability of the furanose ring to adopt multiple forms represents a formidable challenge to our understanding of the relationship between shape and function. Normally, a conformationally unrestricted furanose ring can adopt a number of envelope (E) or twist (T) forms, which can be conveniently described by the value of *P* in the pseudorotational cycle (Figure 1).[1−3] The value of *P* depends on the five endocyclic sugar torsion angles (ν_0−ν_4) of the furanose ring and, by convention, a phase angle $P = 0°$ corresponds to an absolute north conformation possessing a symmetrical twist form $^3T_2$, whereas its south antipode, $_3T^2$, is represented by $P = 180°$.[1−3] Conventional nucleosides or nucleotides equilibrate rapidly in solution between these two extreme forms of ring pucker: (1) The north conformation with *P* ranging between 342° and 18° ($_2E \rightarrow {}^3T_2 \rightarrow {}^2E$) and (2) the antipodal south conformation with values of *P* between 162° and 198° ($^2E \rightarrow {}^2T_3 \rightarrow {}_3E$).[1−3] Preference for any of these specific conformations in solution is determined by the interplay of important interactions resulting from anomeric and gauche effects.[2] However, when a nucleoside or nucleotide binds to its target enzyme, only one of these forms is present at the active site. Thus, to query these enzymes for their conforma-

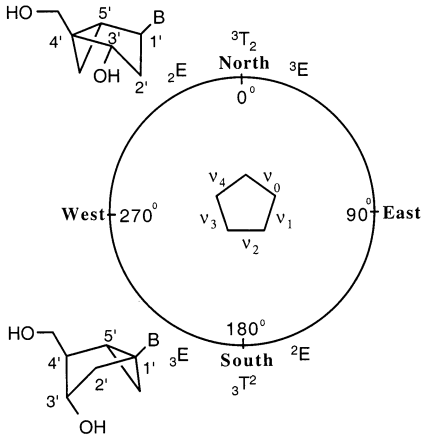

FIGURE 1. Fixed location of the bicyclo[3.1.0]hexane templates in the pseudorotational cycle.

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(1) Saenger, W. *Principles in Nucleic Acid Structure*; Springer-Verlag: New York, NY, 1984.

(2) Thibaudeau, C.; Chattopadhyaya, J. *Stereoelectronic Effects in Nucleosides and Nucleotides and Their Structural Implications*; Uppsala University Press: Uppsala, Sweden, 1999.

(3) Altona, C.; Sundaralingam, M. *J. Am. Chem. Soc.* **1972**, *94*, 8205−8212.

10.1021/jo020249u CCC: $22.00
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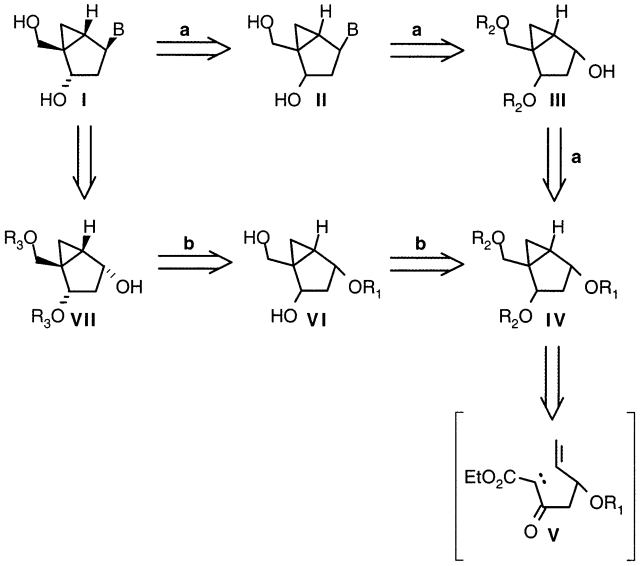
tional preference, we have embarked on a program aimed at systematically synthesizing conformationally locked nucleosides that would reside strictly in the normal range of either north or south conformations.[4]

For the generation of such nucleoside analogues in which both solution and solid-state conformations are the same, we and others have used the bicyclo[3.1.0]hexane system as a convenient pseudosugar template.[4,5] This sugar surrogate exhibits a rigid pseudoboat conformation such that carbanucleosides constructed with it can adopt a fixed conformation that mimics the ring pucker of a true sugar moiety in a specific north or south conformation, depending on the pattern of substitution.[4,5] Because of the exclusive pseudoboat conformation of this template, a rigid north envelope $_2$E conformation can be constructed when the cyclopropane ring is fused between carbons C4′ and C5′. Conversely, fusion of the cyclopropane ring between carbons C1′ and C5′ provides a rigid south $_3$E envelope conformation (Figure 1). Since a specific form of ring pucker is known to be the strongest determinant in controlling the value of the other conformational parameters, namely the glycosyl torsion angle (χ) and the hydroxymethyl torsion angle (γ), the most valuable asset of conformationally constrained nucleosides is that the entire molecular ensemble is completely defined.

The use of bicyclo[3.1.0]hexane templates has already allowed us to determine conformational preference for

SCHEME 1



enzymes such as adenosine deaminase (ADA),[4f,g] HIV reverse transcriptase,[4c,d] DNA (cytosine-C5) methyl transferase,[4k,n] and several subtypes of adenosine receptors.[4h,i,l,m,o] The conformationally locked antipodes of thymidine, north-methanocarba-T and south-methanocarba-T, represent yet another example of clear conformational discrimination, with the final outcome being that only the north antipode is endowed with activity against herpes infections caused by HSV-1 and HSV-2 herpes viruses.[4b,r]

The structural complexity of the bicyclo[3.1.0]hexane template is inextricably linked to its unique biological properties, and unfortunately, some of the synthetic approaches utilized thus far appear lengthy and complicated.[4,5] Since accessibility to these compounds is key to their successful development as potential drugs, our criteria in searching for alternative syntheses was to design a simple and convenient method for the requisite racemic bicyclo[3.1.0]hexane template and to rely on a practical and efficient enantioselective enzymatic resolution of the products at some point of the synthesis. We have recently implemented this approach and reported on the synthesis of chiral, north-methanocarba adenosine and guanosine analogues through an efficient olefin−ketocarbene cycloaddition (V → IV, Scheme 1).[5i] After reaching the target nucleoside II [IV → III → II (path a), Scheme 1], a chiral enzymatic resolution of the final product with ADA provided the desired purine analogues in the D-form [II → I, (path a), B = adenine or 2,6-diaminopurine, Scheme 1].[5i] Although, the procedure worked well and it served as a proof of the concept, the method was still not satisfactory for two reasons. First, it delayed the resolution of enantiomers toward the end of the synthesis, and second, the method was applicable only to purine nucleosides. In this paper, we wish to report a highly convenient approach toward north-methanocarba nucleosides based on the same efficient and inexpensive olefin−ketocarbene cycloaddition, coupled to an equally efficient and economical lipase-catalyzed resolution performed at an earlier stage of the synthesis [VI → VII (path b) Scheme 1] applied soon after the construction of the bicyclo[3.1.0]hexane template.

(4) (a) Jeong, L. S.; Marquez, V. E.; Yuan, C.-S.; Borchardt, R. T. *Heterocycles* **1995**, *41*, 2651−2656. (b) Marquez, V. E.; Siddiqui, M. A.; Ezzitouni, A.; Russ, P.; Wang, J.; Wagner, R. W.; Matteucci, M. *J. Med. Chem.* **1996**, *39*, 3739−3747. (c) Marquez, V. E.; Ezzitouni, A.; Russ, P.; Siddiqui, M. A.; Ford, H., Jr.; Feldman, R. J.; Mitsuya, H.; George, C.; Barchi, J. J., Jr. *Nucleosides Nucleotides* **1998**, *17*,1881−1884. (d) Marquez, V. E.; Ezzitouni, A.; Russ, P.; Siddiqui, M. A.; Ford, H., Jr.; Feldman, R. J.; Mitsuya, H.; George, C.; Barchi, J. J., Jr. *J. Am. Chem. Soc.* **1998**, *120*, 2780−2789. (e) Jeong, L. S.; Buenger, G.; McCormack, J. J.; Cooney, D. A.; Hao, Z.; Marquez, V. E. *J. Med. Chem.* **1998**, *41*, 2572−2578. (f) Marquez, V. E.; Russ, P.; Alonso, R.; Siddiqui, M. A.; Shin, K. J.; George, C.; Nicklaus, M. C.; Dai, F.; Ford, H., Jr. *Nucleosides Nucleotides* **1999**, *18*, 521−530. (g) Marquez, V. E.; Russ, P.; Alonso, R.; Siddiqui, M. A.; Hernandez, S.; George, C.; Nicklaus, M. C.; Dai, F.; Ford, H., Jr. *Helv. Chim. Acta* **1999**, *82*, 2119−2129. (h) Nandanan, E.; Jang, S.-Y.; Moro, S.; Kim, H.; Siddiqui, M. A.; Russ, P.; Marquez, V. E.; Busson, R.; Herdewijn, P.; Harden, T. K.; Boyer, J. L.; Jacobson, K. A. *J. Med. Chem.* **2000**, *43*, 829−842. (i) Jacobson, K.A; Ji, X; Li, A.; Melman, N.; Siddiqui, M. A.; Shin, K. J.; Marquez, V. E.; Ravi, R. G. *J. Med. Chem.* **2000**, *43*, 2196−2203. (j) Prota, A.; Vogt, J.; Perozzo, R.; Pilger, B.; Wurth, C.; Marquez, V. E.; Russ, P.; Schultz, G. E.; Folkers, G.; Scapozza, L. *Biochemistry* **2000**, *39*, 9597−9603. (k) Wang, P.; Nicklaus, M. C.; Marquez, V. E.; Brank, A. S.; Christman, J. K.; Banavali, N. K.; MacKerell, A. D., Jr. *J. Am. Chem. Soc.* **2000**, *122*, 12422−12434. (l) Lee, K.; Ravi, R.; Ji, X. D.; Marquez, V. E.; Jacobson, K. A.; *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1333−1337. (m) Ravi, G.; Lee, K.; Ji, X. D.; Kim, H. S.; Soltysiak, K. A.; Marquez, V. E.; Jacobson, K. A. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2295−2300. (n) Marquez, V. E.; Wang, P.; Nicklaus, M. C.; Maier, M.; Manoharan, M.; Christman, J. K.; Banavali, N. K.; MacKerell, A. D., Jr. *Nucleosides, Nucleotides Nucleic Acids* **2001**, *20*, 451−459. (o) Kim, H. S.; Ravi, R. G.; Marquez, V. E.; Maddileti, S.; Wihlborg, A.-K.; Erlinge, D.; Malsmjo, M.; Boyer, J. L.; Harden, T. K.; Jacobson, K. A. *J. Med. Chem.* **2002**, *45*, 208−218. (p) Choi, Y. S.; George, C.; Strazewski, P.; Marquez, V. E. *Org. Lett.* **2002**, *4*, 589−592. (q) Zalah, L.; Huleihel, M.; Manor, E.; Konson, A.; Ford, H., Jr.; Marquez V. E.; Johns, D. G.; Agbaria, R. *Antiviral Res.* **2002**, *55*, 63−75. (r) Hernandez, S.; Ford H., Jr.; Marquez, V. E. *Bioorg. Med. Chem.* **2000**, *10*, 2723−2730.

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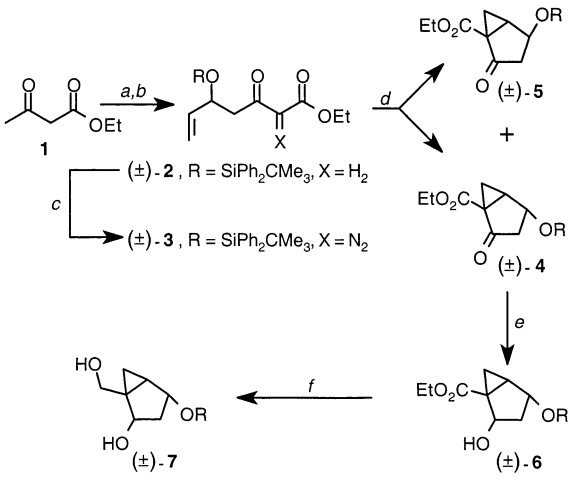
SCHEME 2



(a) LDA, THF, 0 °C/acrolein, −78 °C, 20 min; (b) TBDPSCl, imidazole, CH_2Cl_2, rt, 1 h; (c) TsN_3, Et_3N, CH_3CN, rt, 17 h; (d) $CuSO_4$, cyclohexane, reflux, 35 h, (±)-**4** (61%), (±)-**5** (23%); (e) $NaBH_4$, CH_2Cl_2, MeOH, −25 °C, 30 min; (f) $LiAlH_4$, Et_2O, 0 °C, 10 min.

In the present work, we demonstrate the successful use of this combined approach to generate first a rather complex molecular scaffold from simple starting materials and with remarkable chemical diastereoselectivity. Second, we demonstrate that this chemistry can be conveniently combined with an efficient lipase-catalyzed resolution step,[6] which provides a versatile process applicable for the synthesis of *all* target bases (VII → I, Scheme 1) with a natural D-like stereochemistry. While investigating this lipase-catalyzed resolution we also discovered the unusual formation of an acetal resulting from the unwanted L-like enantiomer during the lipase-mediated asymmetric acetylation. This minor product, which could be an important source of contamination unless appropriate steps are taken for its efficient removal, provided some additional insight into the mechanism of lipase-catalyzed asymmetric acetylation.

Results and Discussion

The intermediate for the olefin−ketocarbene cycloaddition was prepared from ethyl acetoacetate (**1**) and acrolein in three steps, as illustrated in Scheme 2. The dianion of **1**, which was generated by treatment with LDA in THF at 0 °C, was treated with acrolein at −78 °C. The resulting alcohol was immediately protected as a silyl ether to give (±)-**2** in 53% yield as a mixture of keto−enol tautomers. After diazo transfer with *p*-toluenesulfonyl azide, diazo compound (±)-**3** was obtained from (±)-**2** quantitatively. Intramolecular cyclopropanation of (±)-**3**, which presumably proceeds via a copper-carbenoid intermediate under thermolysis, generated a chromatographically separable mixture of (±)-**4** (61%) and (±)-**5** (23%). It was unambiguously confirmed that the major product (±)-**4** had the desired relative trans stereochemistry between the ester and the silylated alcohol after its conversion to an identical compound

(6) For a recent review of biocatalytic modifications applied to nucleoside chemistry, see: Ferrero, M.; Gotor, V. *Chem. Rev.* **2000**, *100*, 4319−4347.

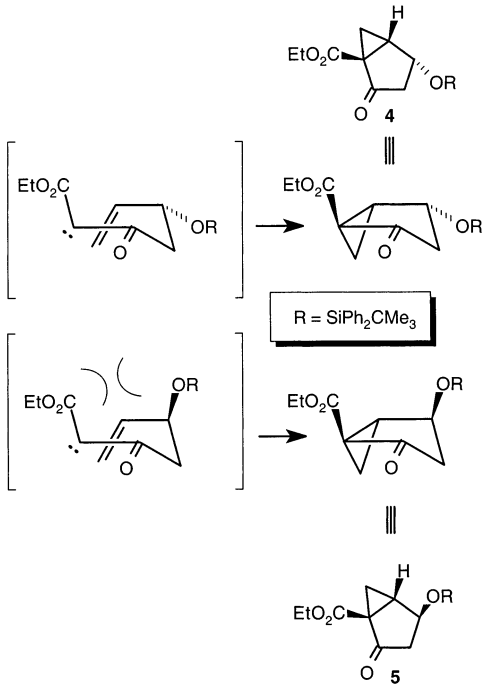
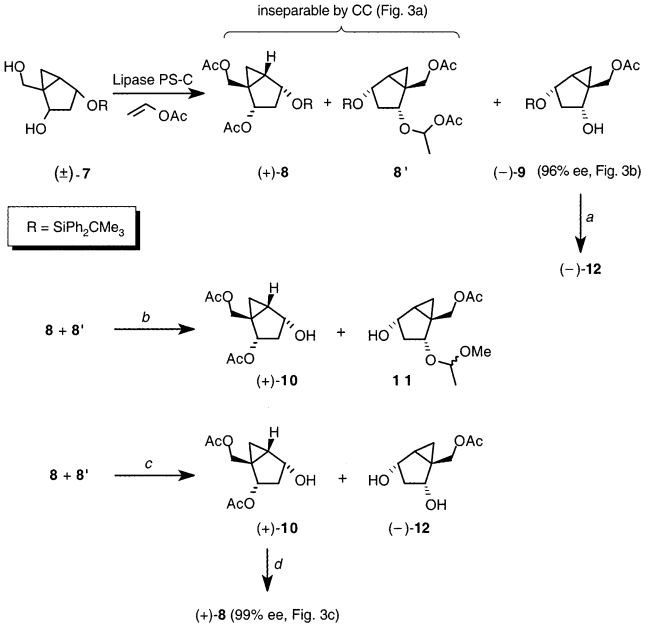


FIGURE 2. Proposed pseudoboat transition state for the intramolecular olefin−ketocarbene cycloaddition to explain the favorable formation of **4** over **5** on steric grounds. Only the transition states for the D-like diastereoisomers are shown.

previously synthesized from an enantiomerically pure starting material by a different route (vide infra). A tentative explanation for the preferred formation of (±)-**4** over (±)-**5** can be surmised by assuming that the transition states adopt a product-like pseudoboat conformation. Using the D-like diastereoisomers as an example (Figure 2), when the bulky *tert*-butyldiphenylsilyl group is in the pseudoequatorial orientation, the transition-state for the trans-intermediate is less sterically encumbered than in the case of the cis-intermediate with the *tert*-butyldiphenylsilyl group in the pseudoaxial orientation. Compound (±)-**4** was reduced in a stepwise fashion by first reducing the keto group with sodium borohydride to give exclusively compound (±)-**6**, which resulted from the selective attack of hydride from the less hindered convex face of the bicyclo[3.1.0]hexane system. This step was followed by reduction of the ester with lithium aluminum hydride to give diol (±)-**7** in 79% yield (Scheme 2). Surprisingly, the simultaneous reduction of both ester and keto functions of (±)-**4** with diisobutylaluminum hydride resulted in a mixture of epimeric alcohols, suggesting that perhaps the ester group played an important role in directing hydride attack.

Commercially available lipases PS-C and AK were selected and used for the asymmetric acetylation of alcohol (±)-**6** in the presence of vinyl acetate. Unfortunately, use of lipase PS-C gave the corresponding acetate only in low yield, even after 6 days, and lipase AK did not react at all (data not shown). Diol (±)-**7** did react with lipase PS-C in the presence of 2 equiv of vinyl acetate in *tert*-butyl methyl ether, leading to the formation of a monoacetylated product and trace amounts of the diacetate (data not shown). From this result, it was clear that the enzyme had failed to discriminate between enantiomers as a monoacetylating reagent of the primary

SCHEME 3



(a) HF−pyridine/pyridine, rt, overnight; (b) NH_4F, MeOH, 50 °C, overnight; (c) $(NH_4)HF_2$, DMF, H_2O, 50 °C, 17 h; (d) TBDPSCl, imidazole, CH_2Cl_2, rt, 2 h.

alcohol function. When enantiomeric discrimination was attempted at the level of the diacetylated products by employing a large excess of vinyl acetate (10 equiv), we observed a clear separation of products corresponding to diacetate (+)-**8** and monoacetate (−)-**9**, which were obtained in 57% and 42% yields, respectively, after 64 h (Scheme 3). To determine enatiomeric purity, both (+)-**8** and (−)-**9** were analyzed by HPLC using Chiralcel. The enantiomeric excess of monoacetate (−)-**9** was estimated to be 96% (Figure 3b), and although the enantiomeric excess of (+)-**8** should have been over 98%, it contained 13% of an impurity (**8′**, vide infra) of unknown structure (Figure 3a). The presence of this impurity was also evidenced in the ^{1}H NMR spectrum of (+)-**8**.

The removal and structural elucidation of this impurity took center stage after it was confirmed that diacetate (+)-**8** corresponded to the enantiomer with the desired D-like configuration. To determine the absolute stereochemistry of this enantiomer, we synthesized tribenzoate (+)-**15** from (+)-**8** and from a known chiral compound (+)-**13**[7] to compare their optical rotations (Scheme 4). In an ongoing related project and using chemistry already developed in this laboratory,[4f,g] compound (+)-**13** was converted to the *O-tert*-butyldiphenylsilyl-protected bicyclo-[3.1.0]hexane derivative (+)-**14**.[8] From this compound, tribenzoate (+)-**15** was readily obtained after deprotection of the silyl ether group and subsequent benzoylation. Meanwhile, diacetate (+)-**8** was fully deprotected by sequential treatment with ammonium fluoride in methanol and sodium methoxide, and the resulting triol was esterified with benzoyl chloride to give the identical tribenzoate (+)-**15** in 79% yield from (+)-**8** (Scheme 4). As shown later, deprotection of (+)-**8** permitted the

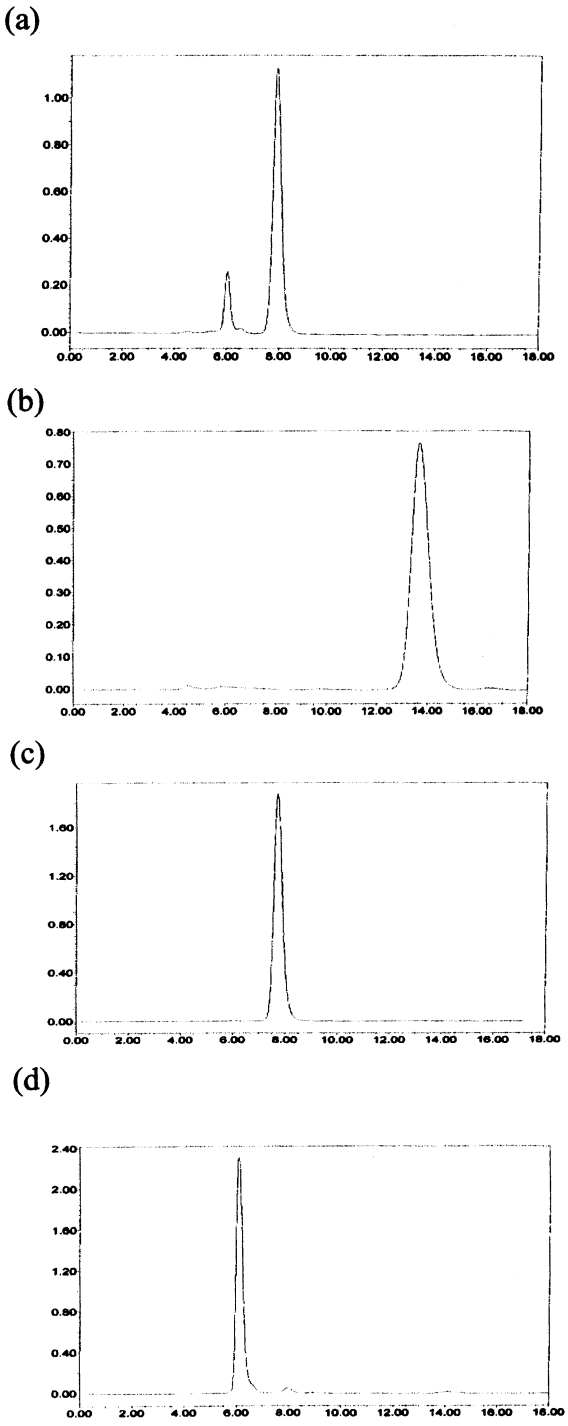
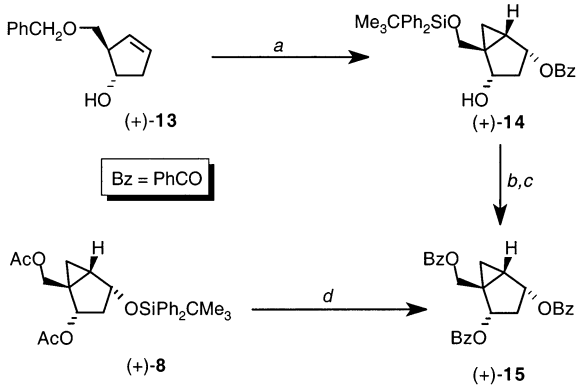


FIGURE 3. Chiral HPLC evaluation of optical purity of products obtained by lipase-catalyzed asymmetric acetylation: (a) diacetate (+)-**8** contaminated with **8′**; (b) monoacetate (−)-**9**; (c) diacetate (+)-**8** from (+)-**10**; (d) compound **8′** obtained by the reaction of (−)-**9** with lipase, vinyl acetate, and acetaldehyde. All experiments were conducted using Chiralcel OD column with hexane:isopropyl alcohol (95:5) as eluant; flow rate 3.0 mL/min; UV detection at 220 nm. Retention times (*x*-axis): **8′**, 6.0 min; (+)-**8**, 7.8 min; (−)-**9**, 14.5 min.

separation and removal of the impurity, and thus the obtained tribenzoate (+)-**15** was considered to be optically pure. Since the optical rotation of (+)-**15**, obtained from both (+)-**8** and (+)-**13**, showed almost identical values [+70.6° from (+)-**13** and +69.1° from (+)-**8**] it was

(7) Ezzitouni, A.; Russ, P.; Marquez, V. E. *J. Org. Chem.* **1997**, *62*, 4870−4873.
(8) Marquez, V. E. and Choi, Y. S. Unpublished results.

SCHEME 4



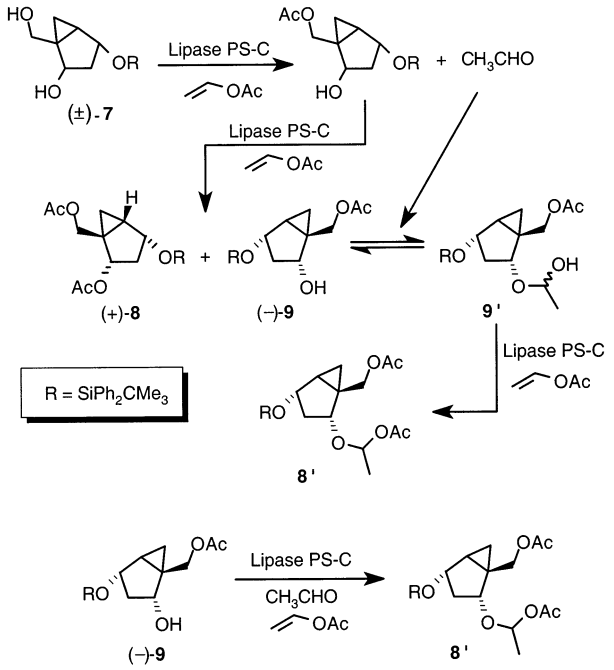
(a) Refs 4f,g,8; (b) NH_4F, MeOH, 60 °C, 5 h; (c) PhCOCl, pyridine, reflux; (d) (i) NH_4F, MeOH, 60 °C, 17 h; (ii) NaOMe, rt, 2 h; (iii) PhCOCl, pyridine, reflux.

unequivocally determined that diacetate (+)-**8** was the enantiomer with the desired D-like configuration. This experiment also validated the above claim that the major product (±)-**4** had the requisite trans stereochemistry between the ester and the silylated alcohol.

Judging from the isolated yields of (+)-**8** and (−)-**9**, it was plausible that the impurity could have arisen from the unreacted L-like enantiomer, a presumption that was later confirmed. To eliminate the impurity **8′** from (+)-**8**, removal of the silyl group with HF−pyridine was first attempted. However, when the isolated product expected to be pure alcohol (+)-**10** was converted back to (+)-**8** with *tert*-butyldiphenylsilyl chloride (TBDPSCl), HPLC analysis revealed the presence of the same contaminant in ca. 10% (data not shown). Desilylation with ammonium fluoride in methanol also gave (+)-**10** but still contaminated with a small amount of an unknown secondary product (8%). The ^{1}H NMR spectrum of this secondary product showed a pattern similar to the spectrum of (+)-**10**, except for several important changes, which included a missing acetate group, the appearance of a methoxy group at δ 3.27, and an extra quartet at δ 4.68 (1 H) coupled to a doublet at δ 1.30 (3 H). These features suggested structure **11** for this compound (Scheme 3), an assignment also supported by FAB MS and elemental analyses (see Experimental Section). Considering these results, the structure of **8′** was assigned to the corresponding acetal (Scheme 3). Since the separation of (+)-**10** and **11** was difficult, deprotection of (+)-**8** was finally attempted under acidic conditions. Use of ammonium hydrogen fluoride (ammonium bifluoride) in aqueous DMF (50 °C, overnight) gave easily separable (+)-**10** and diol (−)-**12** in 79% and 11% yields, respectively. The optical purity of (+)-**10** was estimated to be 99% ee by HPLC after its conversion to (+)-**8** (Scheme 3, Figure 3c). The structure of (−)-**12** was also unambiguously determined after matching its identity to that of the compound obtained from (−)-**9** following treatment with HF−pyridine (Scheme 3). Indeed, the optical rotation of (−)-**12** obtained from **8′** and (−)-**9** were, respectively, −41.9° and −43.7°, thus confirming that **8′** had been generated from (−)-**9**, as originally hypothesized.

The formation of **8′** is proposed to proceed according to Scheme 5. Since the enzyme does not discriminate as a monoacetylating reagent, the first products of the

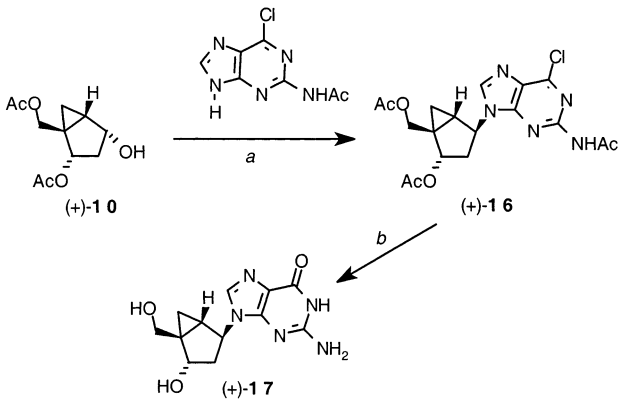
SCHEME 5



reaction are the racemic monoacetate plus acetaldehyde. Additional acetaldehyde byproduct is also produced as the (+)-enantiomer is gradually converted to diacetate (+)-**8**. Normally, the unrecognized enantiomer, such as (−)-**9**, remains unreacted in the mixure. However, in the presence of acetaldehyde, a significant amount of hemiacetal **9′** was produced and slowly acted upon by lipase PS-C to give acetal **8′**. Even though the reaction equilibrium does not favor hemiacetal formation, it appears that only one hemiacetal diastereoisomer is recognized as substrate for further lipase acetylation and that this provides the driving force to shift the reaction equilibrium toward forming more hemiacetal. As a result, acetal **8′** was generated as shown in Scheme 5. This hypothesis was supported by chiral HPLC analysis, which showed that the generated **8′** corresponded to a single diastereoisomer (Figure 3d). To validate our hypothesis, we modified the reaction conditions to favor acetal formation. Thus, compound (−)-**9** was treated with lipase PS-C in the presence of vinyl acetate and acetaldehyde. All the conditions except for the added acetaldehyde were identical. As expected, the reaction produced higher levels of acetal **8′** (32%) together with recovered unreacted (−)-**9** (67%). The resulting **8′** showed the same retention time on HPLC (Figure 3d) and its NMR spectrum matched all the minor peaks present in the original spectrum of the originally contaminated sample of (+)-**8**.

To complete the synthesis of a nucleoside target, we chose to make the same guanosine analogue previously obtained from ADA-catalyzed hydrolysis.[5i] Thus, according to Scheme 6, compound (+)-**10** was coupled with 2-acetamido-6-chloropurine under Mitsunobu conditions to give the corresponding purine derivative (+)-**16** (N^9-isomer) in 85% yield. Compound (+)-**16** was fully deprotected in one step after treatment with 2 N HCl in THF at 80 °C for 6 h to give the identical, conformationally locked north carbocyclic guanosine **17**[5i] in 64% yield after reversed-phase ODS column chromatography.

SCHEME 6



(a) PPh_3, DEAD, THF, rt, 2 h; (b) 2 N HCl, THF, 80 °C, 6 h.

In conclusion, we have developed a highly convenient method to obtain a versatile synthon for the construction of conformationally locked carbocyclic nucleosides built on a bicyclo[3.1.0]hexane system. The most practical aspect of the synthesis is that a relatively complex bicyclo[3.1.0]hexane synthon can be obtained as a racemate from simple and inexpensive starting materials. The lipase-mediated resolution of enantiomers of this important synthon was realized, thus expanding the approach to both purine and pyrimidine targets, which can be easily accessed in a convergent fashion from the Mitsunobu coupling of synthon (+)-**10** with suitable purine or pyrimidine bases. During our studies on the lipase-catalyzed reaction, we have discovered an unusual acetal formation reaction catalyzed by the enzyme. The identity of the product was confirmed and the mechanism of formation reproduced after the enzymatic reaction was modified utilizing acetaldehyde as a coreactant to enhance its formation.

Experimental Section

General Procedures. All chemical reagents were commercially available. Melting points are uncorrected. Column chromatography was performed on silica gel 60 (230−400 mesh) and analytical TLC was performed on plates coated with silica gel GF. Routine IR and ^1H and ^{13}C NMR spectra were recorded using standard methods. For positive fast-atom bombardment mass spectra (FABMS), nitrobenzyl alcohol was used as the sample matrix and ionization was effected by a beam of xenon atoms. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA.

Ethyl 5-(2,2-Dimethyl-1,1-diphenyl-1-silapropoxy)-3-oxohept-6-enoate [(±)-2]. A stirred solution of LDA (1.9 M in THF, 49.5 mL) in anhydrous THF (150 mL) was treated dropwise with ethyl acetoacetate (5 mL, 39.2 mmol) at 0 °C. After 20 min the reaction mixture was cooled to −78 °C, and acrolein (2.9 mL, 43.1 mmol) was added while stirring continued for 20 min at −78 °C. Following quenching with saturated NH_4Cl (40 mL), the reaction mixture was extracted with diethyl ether (3 × 150 mL). The organic extracts were combined, dried ($MgSO_4$), and concentrated under vacuum to give a crude product (10.02 g), which was used in the next step without further purification. A stirred solution of this product and imidazole (3.97 g, 58.24 mmol) in methylene chloride (60 mL) was maintained at 0 °C and treated with TBDPSCl (8.0 mL, 30.76 mmol). After stirring for 1 h and allowing the temperature of the bath to reach ambient temperature, water (100 mL) and methylene chloride (200 mL) were added. The organic layer was separated, washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography with EtOAc in hexanes (2%→4%) as eluant to give (±)-**2** (8.89 g, 53%) as a clear oil: IR (neat) 1746, 1719 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.63−7.68 (m, 4 H), 7.34−7.43 (m, 6 H), 5.81 (ddd, 1 H, J = 17.2, 10.5, 6.2 Hz), 5.03 (dt, 1 H, J = 17.2, 1.4 Hz), 4.96 (dt, 1 H, J = 10.1, 1.4 Hz), 4.64 (irregular q, 1 H), 4.15 (q, 2 H, J = 7.2 Hz), 3.33 (s, 2 H), 2.70 (dd, 1 H, J = 13.4, 5.9 Hz), 2.66 (dd, 1 H, J = 13.4, 6.2 Hz), 1.24 (t, 3 H, J = 7.2 Hz), 1.05 (s, 9 H); FAB MS *m*/*z* (relative intensity) 135 (39.8), 169 (71.2), 199 (25.4), 295 (34.5), 367 (20.8), 425 (16.9, MH^+). Anal. Calcd for $C_{25}H_{32}O_4Si$: C, 70.72; H, 7.60. Found: C, 71.10; H, 7.79.

Ethyl 5-(2,2-Dimethyl-1,1-diphenyl-1-silapropoxy)-2-diazo-3-oxohept-6-enoate [(±)-3]. A stirred solution of β-keto ester (±)-**2** (8.46 g, 19.94 mmol) and tosyl azide (3.94 g, 19.97 mmol) in CH_3CN (40 mL) was treated with triethylamine (5.57 mL, 39.96 mmol) at 0 °C. After 2 h of stirring at 0 °C, the reaction mixture was allowed to reach room temperature and stirring was continued for 19 h. Diethyl ether (260 mL) and 2 N aqueous NaOH solution (135 mL) were added. After 10 min, the organic layer was separated, dried ($MgSO_4$), filtered, and concentrated under vacuum. The residue was purified by flash column chromatography with EtOAc in hexanes (4%) to give diazo compound (±)-**3** (8.89 g, 99%) as a clear oil: IR (neat) 2135, 1716, 1657 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.70−7.80 (m, 4 H), 7.36−7.55 (m, 6 H), 5.94 (ddd, 1 H, J = 17.1, 10.3, 6.7), 5.07 (d, 1 H, J = 18.5 Hz), 5.01 (d, 1 H, J = 10.5 Hz), 4.81 (irregular q, 1 H), 4.32 (q, 2 H, J = 7.1 Hz), 3.26 (dd, 1 H, J = 15.1, 7.1 Hz), 3.07 (dd, 1 H, J = 15.1, 5.6 Hz), 1.38 (t, 3 H, J = 7.1 Hz), 1.11 (s, 9 H); FAB MS *m*/*z* (relative intensity) 135 (100), 195 (72.5), 199 (84.1), 423 (12.5), 451(25.5, MH^+). Anal. Calcd for $C_{25}H_{30}N_2O_4Si$: C, 66.64; H, 6.71; N, 6.22. Found: C, 66.76; H, 6.70, N, 6.28.

Ethyl 4-(2,2-Dimethyl-1,1-diphenyl-1-silapropoxy)-2-oxobicyclo[3.1.0]hexanecarboxylate [(±)-4 and (±)-5]. To a stirred solution of diazo compound **3** (8.89 g, 19.74 mmol) in cyclohexane (184 mL) was added $CuSO_4$ (3.46 g, 21.71 mmol) at room temperature. The reaction mixture was heated to reflux for 35 h. After cooling to room temperature, the reaction mixture was filtered through a pad of Celite, which was then washed with diethyl ether. The organic solvent was concentrated under vacuum and the residue was purified by flash column chromatography with EtOAc in hexanes (10%→15%) to give the desired intermediate **4** (5.07 g, 61%) and the minor C-4 epimer **5** (1.91 g, 23%).

Compound (±)-**4** (less polar material): oil; IR (neat) 1744, 1719 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.65−7.85 (m, 4 H), 7.40−7.55 (m, 6 H), 4.72 (irregular q, 1 H), 4.23 (q, 2 H, J = 7.1 Hz), 2.65 (m, 1 H), 2.44 (dd, 1 H, J = 18.3, 8.6 Hz), 2.32 (dd, 1 H, J = 18.8, 7.4 Hz), 2.10 (m, 1 H), 1.91 (irregular t, 1 H), 1.32 (t, 3 H, J = 7.1 Hz), 1.16 (s, 9 H); FAB MS *m*/*z* (relative intensity) 135 (65.1), 199 (74.3), 219 (38.6), 273 (23.2), 377 (87.0), 423 (100, MH^+). Anal. Calcd for $C_{25}H_{30}O_4Si$: C, 71.05; H, 7.16. Found: C, 71.11; H, 7.10.

Compound (±)-**5** (more polar material): oil; IR (neat) 1746 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.68−7.76 (m, 4 H), 7.43−7.55 (m, 6 H), 4.49 (d, 1 H, J = 4.6 Hz), 4.25−4.44 (m, 2 H), 2.68 (irregular dd, 1 H, J = 8.4, 5.7 Hz), 2.41 (ddd, 1 H, J = 18.8, 4.6, 2.0 Hz, 3), 2.29 (d, 1 H, J = 18.8 Hz), 1.94 (ddd, 1 H, J = 7.3, 5.4, 1.7 Hz), 1.40 (t, 3 H, J = 7.1 Hz), 1.18 (t, 1 H, J = 5.4 Hz), 1.14 (s, 9 H); FAB MS *m*/*z* (relative intensity) 135 (57.3), 199(51.6), 345 (32.5), 365 (74.3), 377 (45.1), 423 (100, MH^+). Anal. Calcd for $C_{25}H_{30}O_4Si$: C, 71.05; H, 7.16. Found: C, 71.20; H, 7.31.

Ethyl 4-(2,2-Dimethyl-1,1-diphenyl-1-silapropoxy)-2-hydroxybicyclo[3.1.0]hexanecarboxylate [(±)-6]. A stirred solution of bicyclo compound (±)-**4** (9.49 g, 22.4 mmol) in methanol (90 mL) and methylene chloride (45 mL) was cooled to − 25 °C and treated with $NaBH_4$ (0.934 g, 27.4 mmol). After further stirring between −25 and −15 °C for 30 min, the temperature was lowered to −20 °C and the reaction was quenched with 1 N aqueous H_2SO_4 solution (16 mL). Methyl-

ene chloride (500 mL) was added and the organic layer was separated, washed with brine (150 mL), dried ($MgSO_4$), filtered, and concentrated under vacuum. This compound could be used directly in the following step without further purification; however, an analytical sample was obtained following flash column chromatography with EtOAc in hexanes (30%) to give (±)-**6** as a clear oil: IR (neat) 3466, 1719 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.69−7.80 (m, 4 H), 7.41−7.55 (m, 6 H), 4.63 (m, 1 H, converted to a t after D_2O, $J \approx 8.6$ Hz), 4.38 (td, 1 H, J = 8.0, 4.9 Hz), 4.18 (m, 2 H), 2.12−2.23 (m, 2 H, reduced to 1 H after D_2O exchange), 2.07 (m, 1 H), 1.74 (irregular t, 1 H, $J \approx$ 5 Hz), 1.38−1.52 (m, 2 H), 1.29 (t, 3 H, J = 7.1 Hz), 1.13 (s, 9 H); FAB MS *m*/*z* (relative intensity) 135 (92), 169 (40.1), 199 (100), 321 (10.6), 367 (13.4), 407 (25.4), 425 (5.5, MH^+). Anal. Calcd for $C_{25}H_{32}O_4Si$: C, 70.72; H, 7.60. Found: C, 70.76; H, 7.70.

4-(2,2-Dimethyl-1,1-diphenyl-1-silapropoxy)-1-(hydroxymethyl)bicyclo[3.1.0]hexan-2-ol [(±)-7]. A stirred suspension of LAH (1.27 g, 33.6 mmol) in diethyl ether (250 mL) was treated dropwise with a solution of crude (±)-**6** (ca. 22.4 mmol) in diethyl ether (50 mL) at 0 °C After stirring for 10 min, water (1.4 mL), 15% aqueous NaOH solution (1.4 mL), and water (1.8 mL) were added dropwise successively at 0 °C. The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated under vacuum. The residue was purified by flash column chromatography using EtOAc in hexanes (60%) to give (±)-**7** (6.42 g, 75%) as a clear oil: IR (neat) 3348 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.70−7.80 (m, 4 H), 7.40−7.55 (m, 6 H), 4.31−4.44 (m, 2 H), 3.78 (d, 1 H, J = 11.2 Hz), 3.56 (d, 1 H, J = 11.2 Hz), 2.20 (m, 1 H), 2.01 (br s, 1 H, D_2O exchanged), 1.76 (br s, 1 H, D_2O exchanged), 1.38−1.48 (m, 3 H), 1.13 (s, 9 H), 0.63 (dd, 1 H, J = 8.8, 6.6 Hz); FAB MS *m*/*z* (relative intensity) 109 (29.6), 127 (19.5), 135 (95.4), 199 (100), 325 (12), 365 (28.1), 381 (5.0, $MH^+ - H_2$). Anal. Calcd for $C_{23}H_{30}O_3Si$: C, 72.21; H, 7.90. Found: C, 71.96; H, 8.13.

[(1*R*,2*S*,4*R*,5*S*)-[2-Acetoxy-4-(2,2-dimethyl-1,2-diphenyl-1-silapropoxy)bicyclo[3.1.0]hexyl]methyl Acetate [(+)-8] and [(1*S*,2*R*,4*S*,5*R*)-[4-(2,2-Dimethyl-1,1-diphenyl-1-silapropoxy)-2-hydroxybicyclo[3.1.0]hexyl]methyl Acetate [(−)-9]. To a suspension of diol (±)-**7** (6.10 g, 15.9 mmol) and Lipase PS-C "Amano" I (6.10 g) in *tert*-butyl methyl ether (250 mL) was added vinyl acetate (14.65 mL, 159 mmol). The mixture was stirred at room temperature for 64 h. The enzyme was removed by filtration through a pad of Celite and the solid cake was washed with EtOAc (200 mL) and CH_2Cl_2 (200 mL). The combined filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography with EtOAc in hexanes (5%→10%→20%). The less polar fractions were collected and concentrated to give diacetate (+)-**8** as a clear oil (4.26 g, >57%) which was contaminated with an inseparable byproduct (vide infra). The more polar fractions were combined and concentrated to give monoacetate (−)-**9** (2.83 g, 42%) as an oil: $[\alpha]^{25}_D = -35.0°$ (*c* 1.09, $CHCl_3$); IR (neat) 3445, 1736, 1714, 1056 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.61−7.68 (m, 4 H), 7.32−7.42 (m, 6 H), 4.29 (td, 1H, J = 8.1, 4.5 Hz), 4.10−4.15 (m, 2 H), 3.88 (d, 1H, J = 12.0 Hz), 2.07 (td, 1H, J = 13.3, 7.6 Hz), 2.00 (s, 3H), 1.26−1.38 (m, 3 H), 1.01 (s, 9 H), 0.53 (dd, 1H, J = 7.9, 5.4 Hz); FAB MS *m*/z (relative intensity) 135 (65.6), 169 (100), 199 (70.4), 347 (5.0), 365 (9.6), 367 (4.8), 407 (8.9, M^+-H_2O), 423 (3.4, $MH^+ - H_2$), 425 (0.7, MH^+). Anal. Calcd for $C_{25}H_{32}O_4Si$: C, 70.72; H, 7.60. Found: C, 70.43; H, 7.62.

(1*R*,2*S*,4*R*,5*S*)-(2-Acetoxy-4-hydroxybicyclo[3.1.0]hexyl)methyl Acetate [(+)-10] and (1*S*,2*R*,4*S*,5*R*)-[4-Hydroxy-2-(methoxyethoxy)bicyclo[3.1.0]hexyl]methyl Acetate (11). Compound (+)-**8** (contaminated with **8′**) (263 mg, 0.563 mmol) was added to a stirred solution of ammonium fluoride in MeOH (0.5 M, 11.26 mL) at room temperature. The temperature of the bath was raised to 60 °C and stirring was continued overnight. After cooling to room temperature, silica gel (ca 2 g) was added and the solvent was removed under reduced pressure. The solid with the adsorbed compound was placed on top of a short silica gel column and eluted with EtOAc in hexanes (40%). The fractions containing the inseparable mixture were combined and rechromatographed with the same solvent system (33%→40%) to give (+)-**10** (82 mg, 64%) and acetal **11** (11 mg, 8%) as separate diastereoisomers.

(+)-**10**: oil; $[\alpha]^{25}_D = +71.3°$ (*c* 0.79, $CHCl_3$); IR (neat) 3446, 1731, 1238 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.26 (t, 1 H, J = 8.3 Hz), 4.45−4.51 (m, 1 H), 4.24 (d, 1 H, J = 11.9 Hz), 3.90 (d, 1H, J = 11.9 Hz), 2.51 (td, 1H, J = 13.5, 7.8 Hz), 2.06, 2.05 (s, each 3 H), 1.68 (td, 1H, J = 8.3, 4.3 Hz), 1.58 (d, 1 H, J = 6.0 Hz, D_2O exchanged), 1.25 (dd, 1H, J = 5.6, 4.4, Hz), 1.17 (td, 1H, J = 13.5, 8.8 Hz), 0.71 (irregular t, 1H, $J \approx$ 6.9 Hz); FAB MS *m*/z (relative intensity) 91 (53.6), 109 (100), 169 (61.3), 211 (44.9, $MH^+ - H_2O$), 229 (11.1, MH^+). Anal. Calcd for $C_{11}H_{16}O_5 \cdot 0.2H_2O$: C, 56.99; H, 7.13. Found: C, 56.85; H, 7.23.

11: oil; IR (neat) 3451, 1738, 1258, 1024 cm^{-1}; ^1H NMR (major isomer, $CDCl_3$) δ 4.68 (q, 1 H, J = 5.3 Hz), 4.36−4.42 (m, 1 H), 4.36 (d, 1 H, J = 12.0 Hz), 4.18 (t, 1 H, J = 8.1 Hz), 3.89 (d, 1 H, J = 12.0 Hz), 3.27 (s, 3 H), 2.35 (td, 1 H, J = 13.4, 7.5 Hz), 2.07 (s, 3 H), 1.60 (td, 1 H, J = 8.2, 4.2 Hz), 1.51 (br s, 1 H, D_2O exchanged), 1.30 (d, 3 H, J = 5.3 Hz), 1.23−1.27 (m, 2 H), 0.63 (iregular t, 1 H, J = 7.6, 6.1 Hz); FAB MS *m*/z (relative intensity) 59 (100), 109 (20.8), 137 (5.2), 169 (23.1), 219 (7.9), 227 (4.5, $MH^+ - H_2O$). Anal. Calcd for $C_{12}H_{20}O_5 \cdot 0.5H_2O$: C, 56.90; H, 8.36. Found: C, 56.92; H, 8.30.

(1*R*,2*S*,4*R*,5*S*)-(2-Acetoxy-4-hydroxybicyclo[3.1.0]hexyl)methyl Acetate [(+)-10] and (1*S*,2*R*,4*S*,5*R*)-(2,4-Dihydroxybicyclo[3.1.0]hexyl)methyl Acetate [(−)-12]. A stirred solution of compound (+)-**8** (contaminated with **8′**) (1.10 g, 2.37 mmol) in DMF−H_2O (10:1, 16.5 mL) was treated with ammonium hydrogen fluoride (1.35 g, 23.7 mmol) at room temperature. The mixture was then kept at 50 °C for 17 h. After allowing the solution to reach room temperature, the insoluble materials were removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was coevaporated with toluene three times and then purified by silica gel column chromatography [50%→66% EtOAc in hexanes (system A), followed by 2%→4% MeOH in EtOAc (system B)]. The fractions obtained from system A were concentrated to give compound (+)-**10** as a clear oil (430 mg, 79%), whereas the fractions obtained from system B provided compound (−)-**12**. All the spectral data for compound (+)-**10** matched exactly with the material obtained before.

(−)-12: oil; $[\alpha]^{25}_D = -41.9°$ (*c* 1.99, $CHCl_3$); IR (neat) 3357, 1736, 1710, 1245, 1021 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.41 (m, 1 H), 4.34 (td, 1 H, J = 8.3, 4.0 Hz), 4.28 (d, 1 H, J = 11.9 Hz), 4.03 (d, 1 H, J = 12.0 Hz), 2.33 (td, 1 H, J = 13.3, 7.6 Hz), 2.10 (s, 3 H), 2.04 (d, 1 H, J = 4.8 Hz, D_2O exchanged), 1.64 (td, 1 H, J = 8.2, 4.1 Hz), 1.52 (d, 1 H, J = 5.4 Hz, D_2O exchanged), 1.22 (irregular t, 1 H, J = 5.9, 4.0 Hz), 1.19 (td, 1 H, J = 13.3, 8.9 Hz), 0.61 (t, 1 H, J = 6.8 Hz); FAB MS *m*/z (relative intensity) 59 (100), 109 (63.2), 117 (18.2), 169 (73.6, $MH^+ - H_2O$), 187 (17.4, MH^+). Anal. Calcd for $C_9H_{14}O_4 \cdot 0.4H_2O$: C, 55.89; H, 7.71. Found: C, 55.88; H, 7.77.

Synthesis of (+)-8 from Compound (+)-10. A stirred solution of (+)-**10** (60 mg, 0.262 mmol) and imidazole (32 mg, 0.472 mmol) in CH_2Cl_2 (2 mL) was treated with TBDPSCl (81 μL, 0.314 mmol) at room temperature for 2 h. Additional CH_2Cl_2 (20 mL) was added and the organic solution was extracted with water (15 mL), dried ($MgSO_4$), and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (5%→10% EtOAc in hexanes) to give (+)-**8** (113 mg, 92%) as a clear oil: $[\alpha]^{25}_D = +44.9°$ (*c* 0.82, $CHCl_3$); IR (neat) 1738, 1241, 1021 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.62−7.71 (m, 4 H), 7.36−7.46 (m, 6 H), 5.09 (t, 1 H, J = 8.3 Hz), 4.39 (td, 1 H, J = 8.0, 4.6 Hz), 4.14 (d, 1 H, J = 11.9 Hz), 3.78 (d, 1H, J = 12.0 Hz), 2.33 (td, 1 H, J = 13.5, 7.8 Hz), 2.04, 1.98 (s, each 3 H), 1.41 (td, 1 H, J = 8.3, 4.2 Hz), 1.29−1.37 (m, 2 H), 1.04 (s, 9 H), 0.67 (dd, 1H, J = 7.6, 5.9 Hz); FAB MS *m*/z (relative intensity) 91 (61.5), 135

(81.3), 169 (100), 347 (29.4), 407 (44.1), 467 (1.7, MH^+). Anal. Calcd for $C_{27}H_{34}O_5Si$: C, 69.49; H, 7.34. Found: C, 69.32; H, 7.40.

(1*S*,2*R*,4*S*,5*R*)-4-Phenylcarbonyloxy-5-(phenylcarbonyloxymethyl)bicyclo[3.1.0]hex-2-yl Benzoate [(+)-15]. Method A [from compound (+)-14]. Compound (+)-**14**[8] (129 mg, 0.265 mmol) was added to a methanolic solution of ammonium fluoride (0.5 M, 5.30 mL) and stirred at room temperature overnight. The following day the temperature was raised to 60 °C and the solution stirred further for 5 h. After cooling to room temperature, silica gel (ca 2 g) was added and the solvent removed under reduced pressure. The solid with the adsorbed compound was placed on top of a short silica gel column and eluted with of EtOAc in hexanes (33%→100%). The solvent was removed under reduced pressure to give crude desilylated product (46.3 mg, 0.186 mmol), which was immediately dissolved in pyridine (3 mL) and treated with benzoyl chloride (0.054 mL, 0.466 mmol) at room temperature. The solution was heated to reflux for 1 h, cooled to 70 °C, and quenched with methanol (0.2 mL). After 10 min, the solvent was removed under reduced pressure and the residue was partitioned between EtOAc (20 mL) and water (10 mL). The organic layer was washed with 1 N HCl (2 × 10 mL) and aqueous saturated $NaHCO_3$ solution (3 × 10 mL) and dried ($MgSO_4$). The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (5%→10% EtOAc in hexanes) to give tribenzoate (+)-**15** (63 mg, 52%) as a clear oil: $[\alpha]^{25}_D = +70.6°$ (*c* 3.15, $CHCl_3$); IR (neat) 1713, 1264 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.95−8.06 (m, 6 H), 7.30−7.59 (m, 9 H), 5.77 (t, 1 H, J = 8.1 Hz), 5.59 (td, 1 H, J = 8.3, 4.8 Hz), 4.53 (d, 1 H, J = 11.9 Hz), 4.40 (d, 1 H, J = 11.9 Hz), 2.92 (td, 1 H, J = 13.8, 8.1 Hz), 2.13 (td, 1 H, J = 8.4, 4.3 Hz), 1.67 (td, 1 H, J = 13.9, 8.6 Hz), 1.54 (dd, 1 H, J = 5.9, 4.4 Hz), 1.01 (irregular t, 1 H, J = 7.3, 6.7 Hz); FAB MS *m*/z (relative intensity) 105 (100), 335 (38.5), 457 (3.0, MH^+). Anal. Calcd for $C_{28}H_{24}O_6$: C, 73.67; H, 5.30. Found: C, 73.43; H, 5.28.

Method B [from Compound (+)-8]: Compound (+)-**8** (183 mg, 0.392 mmol) was added to a methanolic solution of ammonium fluoride (0.5 M, 7.84 mL) and stirred at room temperature overnight. The following day the temperature was raised to 60 °C and the solution stirred for 12 h. After cooling to room temperature, a solution of sodium methoxide in methanol (0.5 M, 8.62 mL) was added and the mixture stirred for 2 h. After quenching the reaction with the addition of ammonium fluoride in methanol (0.5 M, 0.78 mL), silica gel (ca 3 g) was added and the solvent was removed under reduced pressure. The solid with the adsorbed compound was placed on top of a short silica gel column and eluted with MeOH in $CHCl_3$ (10%→15%). The solvent was removed under reduced pressure and the resulting crude triol was dissolved in pyridine (3 mL) and treated with benzoyl chloride (0.159 mL, 1.37 mmol) at room temperature. After a similar work up as in method A, tribenzoate (+)-**15** (142 mg, 79%) was obtained as a clear oil: $[\alpha]^{25}_D = +69.1°$ (*c* 1.00, $CHCl_3$). Anal. Calcd for $C_{28}H_{24}O_6$: C, 73.67; H, 5.30. Found: C, 73.88; H, 5.39.

Synthesis of (−)-12 from (−)-9. A stirred solution of **(−)-9** (141 mg, 0.332 mmol) in pyridine (1 mL) was treated with HF−pyridine (54 μL) at room temperature. The mixture was kept at room temperature overnight. The reaction was quenched with solid $NaHCO_3$, and the insoluble materials were removed by filtration. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (1%→2%→ 4%→ 8% MeOH in CH_2Cl_2) to give **(−)-12** (62 mg, 100%) as a clear oil: $[\alpha]^{25}_D = -43.7°$ (*c* 2.38, $CHCl_3$). Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 58.16; H, 7.79.

(1*S*,2*R*,4*S*,5*R*)-[1-(Acetoxymethyl)-4-(2,2-dimethyl-1,1-di-phenyl-1-silapropoxy)bicyclo[3.1.0]hex-2-yloxy]ethyl Acetate (8′). A solution of (−)-**9** (100 mg, 0.236 mmol), vinyl acetate (109 μL, 1.18 mmol), and acetaldehyde (66 μL, 1.18 mmol) in *tert*-butyl methyl ether (4 mL) was treated with Lipase PS-C "Amano" I (100 mg) and stirred at room temperature for 64 h. The enzyme was removed by filtration through a pad of Celite. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (10%→20%→40% EtOAc in hexanes). The less polar fractions were collected and concentrated to give **8′** (38.7 mg, 32%) as an oil: $[\alpha]^{25}_D = -50.8°$ (*c* 1.94, $CHCl_3$); IR (neat) 1739, 1244 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.63−7.71 (m, 4 H), 7.36−7.45 (m, 6 H), 5.80 (q, 1 H, J = 5.3 Hz), 4.30−4.34 (m, 1 H), 4.27 (d, 1 H, J = 11.9 Hz), 4.11 (1 H, t, J = 8.1 Hz), 3.76 (d, 1 H, J = 11.9 Hz), 2.18 (td, 1 H, J = 13.2, 7.6 Hz), 2.01, 1.98 (s, each 3 H), 1.36 (d, 3 H, J = 5.3 Hz), 1.29−1.36 (m, 3 H), 1.04 (s, 9 H), 0.60 (dd, 1 H, J = 7.2, 5.0 Hz); FAB MS *m*/z (relative intensity) 169 (100), 241 (80.1), 347 (21.8), 407 (42.7), 509 (0.9, $M^+ - 1$). Anal. Calcd for $C_{29}H_{38}O_6Si \cdot 0.2H_2O$: C, 67.73; H, 7.53. Found: C, 67.88; H, 7.63. The more polar fractions were concentrated to give the starting material (−)-**9** (67.2 mg, 67%).

(1*R*,2*S*,4*S*,5*S*)-{4-[2-(Acetylamino)-6-chloropurin-9-yl]-2-acetoxybicyclo[3.1.0]hexyl}methyl Acetate [(+)-16]. A suspension of alcohol (+)-**10** (388 mg, 1.70 mmol), triphenylphosphine (892 mg, 3.40 mmol), and 2-acetamido-6-chloropurine (719 mg, 3.40 mmol) in THF (50 mL) was treated dropwise with diethyl azodicarboxylate (0.535 mL, 3.40 mmol) at 0 °C. After 1 h of stirring at 0 °C, the mixture was stirred at room temperature for 2 h. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (50%→66%→80%→100% EtOAc in hexanes). The crude product, which contained trace amounts of triphenylphosphine oxide, was rechromatographed (50%→66%→80%→100% EtOAc in hexanes) to give nucleoside (+)-**16** as a white foam (610 mg, 85%): $[\alpha]^{25}_D = +64.7°$ (*c* 0.83, $CHCl_3$); IR (neat) 1735, 1371, 1235 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.36 (s, 1 H), 8.06 (br s, 1 H, D_2O exchanged), 5.68 (t, 1 H, J = 8.2 Hz), 5.14 (d, 1 H, J = 7.0 Hz), 4.66 (d, 1 H, J = 12.0 Hz), 3.90 (d, 1 H, J = 12.2 Hz), 2.52 (s, 3 H), 2.43 (dd, 1 H, J = 15.2, 7.9 Hz), 2.17, 2.09 (s, each 3H), 1.88 (ddd, 1 H, J = 15.4, 8.2, 7.1 Hz), 1.76 (dd, 1 H, J = 8.5, 4.1 Hz), 1.20 (dd, 1 H, J = 6.4, 4.1 Hz), 1.03 (t, 1 H, J = 7.2 Hz); FAB MS *m*/z (relative intensity) 91 (75.6), 109 (42.7), 170 (21.0), 211 (63.3), 212 (41.2), 362 (25.2), 422 (100, MH^+). Anal. Calcd for $C_{18}H_{20}ClN_5O_5$: C, 51.25; H, 4.78; N, 16.60. Found: C, 51.26; H, 4.75; N, 16.35.

(1*S*,2*S*,4*S*,5*R*)-2-Amino-9-[4-hydroxy-5-(hydroxymethyl)-bicyclo[3.1.0]hex-2-yl]hydropurin-6-one [(+)-17]. A stirred solution of nucleoside (+)-**16** (341 mg, 0.808 mmol) in a 1:1 mixture of 2 N HCl:THF (20 mL) was kept at 80 °C for 6 h. After allowing the solution to reach room temperature, it was neutralized with 15% aqueous NaOH. Following the removal of most of the THF under reduced pressure, the resulting suspension was diluted with water (total volume ca. 50 mL) and the resulting solution was chromatographed by reversed phase column chromatography (ODS) with 8%→12% MeOH in water). The fractions from the 12% MeOH eluant were concentrated to give the crystalline guanosine analogue (+)-**17** (143 mg, 64%): $[\alpha]^{25}_D = +19.6°$ (*c* 0.19, DMF); ^1H NMR (DMSO-d_6) δ 10.46 (br s, 1 H, D_2O exchanged), 7.95 (s, 1 H), 6.36 (br s, 2 H, D_2O exchanged), 4.85 (t, 1 H, D_2O exchanged, J = 4.8 Hz), 4.57−4.63 (m, 3 H, reduced to 2 H after D_2O addition), 4.00 (dd, 1 H, J = 11.2, 4.6 Hz), 3.12 (dd, 1 H, J = 11.4, 4.4 Hz), 1.74 (dd, 1 H, J = 14.3, 7.7 Hz), 1.56 (ddd, 1 H, J = 6.5, 8.5, 14.8 Hz), 1.41 (dd, 1 H, J = 3.4, 8.6 Hz), 0.80 (dd, 1 H, J = 5.3, 3.7 Hz), 0.54 (dd, 1 H, J = 8.2, 5.3 Hz). Anal. Calcd for $C_{12}H_{15}N_5O_3 \cdot H_2O$: C, 48.81; H, 5.80; N, 23.72. Found: C, 49.10; H, 5.82; N, 23.94.

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