An Allylic Azide Route to 4′-Azido Carbocyclic Nucleosides. Synthesis of (±)-(1′α,2′α,3′β)- and (±)-(1′α,2′β,3′β)-1-[1-Azido-2-hydroxy-1-(hydroxymethyl)-3-cyclopentyl]thymine[1]

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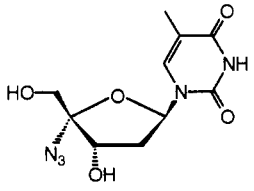
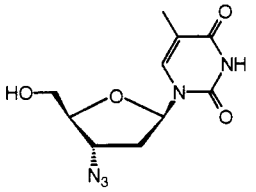
Treatment of (±)-1-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-3-methoxycyclopent-1-ene (**17**) with azidotrimethylsilane under Lewis acid catalyzed conditions gave an equilibrium mixture of allylic azides **18** and **19**. Epoxidation of this mixture with peroxybenzimidic acid gave key epoxide (±)-(1α,2α,5α)-2-azido-2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-6-oxabicyclo[3.1.0]hexane (**5**). Alternate routes designed to give tertiary azide precursors to **5** led to unanticipated products which are described. Title compound **28** was prepared by ring opening of **5** under Vorbrüggen conditions followed by deprotection. Inversion of configuration at C-6′ to give compound **30** was effected via O^2,6′-cyclic intermediates **31** and **32**. The relative stereochemistry of compounds in this series was suggested by NOE data for bromohydrins **23** and **26** and was confirmed by preparation of the fused oxetane **34**.

Introduction

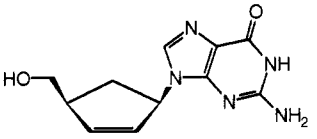
Recently, the preparation and anti-HIV activity of 4′-substituted-2′-deoxynucleosides such as 4′-azidothymidine (ADRT, **1**) were documented.[2] These compounds are inhibitors of reverse transcriptase as well as DNA chain terminators, with a mechanism of action which appears to be distinct from that of other reverse transcriptase inhibitors such as 3′-azido-3′-deoxythymidine (AZT, **2**).[3,4] Thus no cross-resistance to ADRT was observed in cell lines infected with strains of HIV-1 which were resistant to AZT.[2] The structure–activity relationship (SAR) found among members of this series has been reviewed[5] and serves to highlight the possibilities inherent in the modification of nucleosides at C-4′. Relatively few examples of this type of modification are reported in the literature.[6-9]



ADRT (**1**)



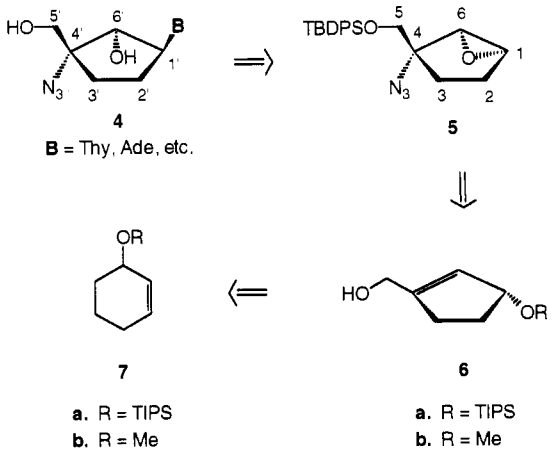
AZT (**2**)



Carbovir (**3**)

Carbocyclic sugar analogs of nucleosides have often been sought for their metabolic stability, since the furanose oxygen in nucleosides weakens the N–$C_{1'}$ bond, making glycosidic cleavage by phosphorylases or under hydrolytic conditions a relatively facile process.[10] The same effect may impart a certain instability to the nitrogen substituent in the other anomeric position, the 4′-azido group in 4′-azido-2′-deoxynucleosides. Therefore carbocyclic analogs of such compounds, expected to benefit from the increased stability, are an attractive proposition in this case. Furthermore, the role of the methylene group as a bioisostere of oxygen has been justified in theory on the basis of

Scheme I



semiempirical calculations[11] as well as in fact by the observed antiviral efficacies of compounds such as carbovir (**3**).[12] Evidence to support the intriguing possibility that the activity of carbocyclic nucleosides may be attributed to factors other than simple metabolic stability was obtained by the synthesis of the carbocyclic analog of 2′-deoxy-2′-fluoro-*ara*-guanosine, which has anti-HSV activity 800 times greater than its oxa equivalent.[13]

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(1) Contribution 359 from the Institute of Bio-Organic Chemistry.
(2) Maag, H.; Rydzewski, R. M.; McRoberts, M. J.; Crawford-Ruth, D.; Verheyden, J. P. H.; Prisbe, E. J. *J. Med. Chem.* **1992**, *35*, 1440.
(3) Chen, M. S.; Suttmann, R.; Bach, C.; Wu, J. C.; Prisbe, E. J.; McRoberts, M. J.; Crawford-Ruth, D. Fourth International Conference on Antiviral Research, New Orleans, LA, 21–26 April, 1991, Poster 87.
(4) Chen, M. S.; Suttmann, R. T.; Wu, J. C.; Prisbe, E. J. *J. Biol. Chem.* **1992**, *267*, 257.
(5) Prisbe, E. J.; Maag, H.; Verheyden, J. P. H.; Rydzewski, R. M. Structure-Activity Relationship of HIV Inhibitory, 4′-Substituted Nucleosides. In *Nucleosides and Nucleotides as Antitumor and Antiviral Agents*; Chu, C. K., Baker, D. C., Eds.; Plenum Publishing Corp.: New York, in press.
(6) Reference 2, and references therein.
(7) O-Yang, C.; Wu, H. Y.; Fraser-Smith, E. B.; Walker, K. A. M. *Tetrahedron Lett.* **1992**, *33*, 37.
(8) O-Yang, C.; Kurz, W.; Eugui, E. M.; McRoberts, M. J.; Verheyden, J. P. H.; Kurz, L. J.; Walker, K. A. M. *Tetrahedron Lett.* **1992**, *33*, 41.
(9) Lipschutz, B. H.; Sharma, S.; Dimock, S. H.; Behling, J. R. *Synthesis* **1992**, 191.
(10) Jones, M. F. *Chem. Br.* **1988**, 1122.
(11) Hodgkin, E. E.; Richards, W. G. *J. Chem. Soc., Chem. Commun.* **1986**, 1342.
(12) Vince, R.; Hua, M. *J. Med. Chem.* **1990**, *31*, 17.
(13) Borthwick, A. D.; Kirk, B. E.; Biggadike, K.; Exall, A. M.; Butt, S.; Roberts, S. M.; Knight, D. J.; Coates, J. A. V.; Ryan, D. M. *J. Med. Chem.* **1991**, *34*, 907.

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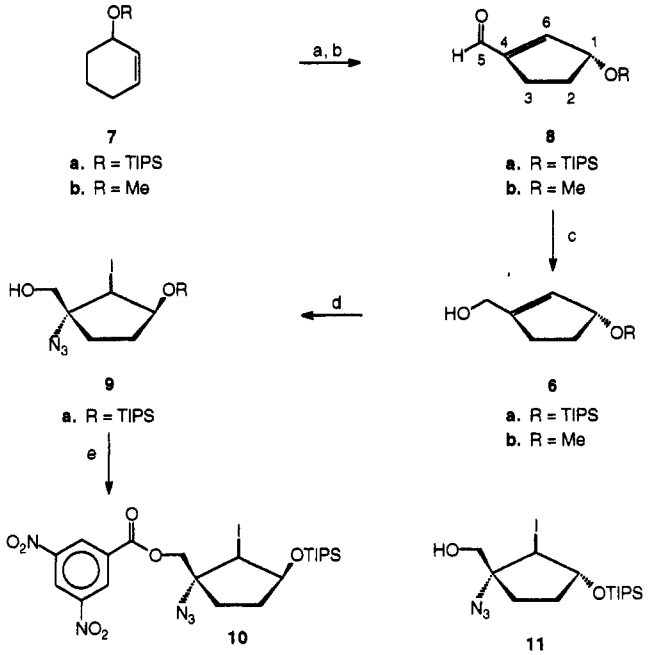
Scheme II[a]



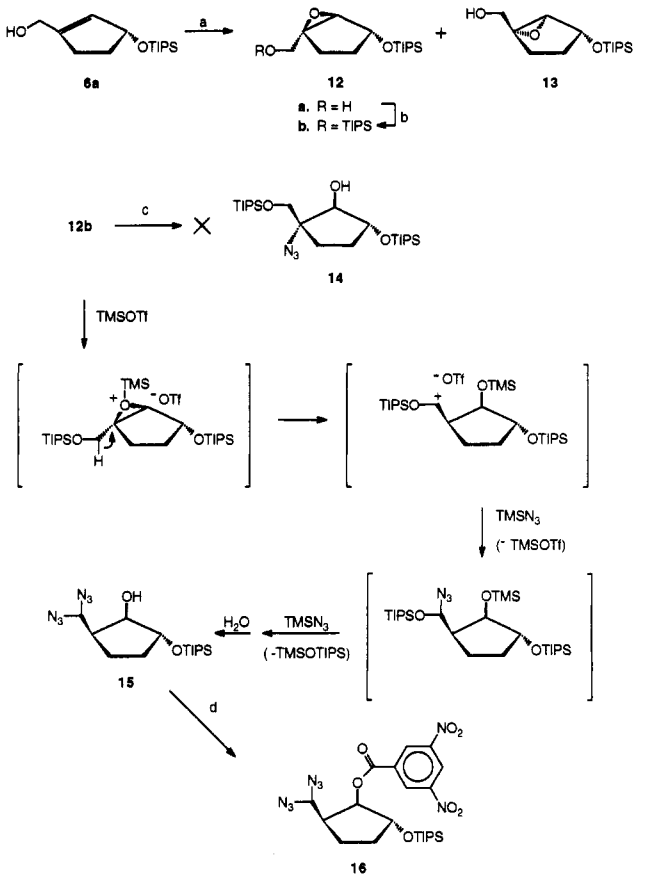
[a] Key: (a) O_3, MeOH, −70 °C, then $P(OMe)_3$, −70 °C to rt; (b) $(PhCH_2)_2NH_2OCOCF_3$, THF, 0 °C; (c) $NaBH_4$, EtOH; (d) IN_3, CH_3CN; (e) 3,5-dinitrobenzoyl chloride, pyridine.

In order to determine if the substitution of a methylene group for the furanose oxygen would provide therapeutic advantages in the 4′-substituted nucleoside series, these compounds became the focus of our efforts. Few members of this class of compounds have been reported.[14] The diversity of synthetic approaches to carbocyclic nucleosides in general testifies to the challenges involved in their preparation.[15,16] In many cases, lengthy synthetic routes which are not readily amenable to the drug development process have been required. In order to avoid this problem, we sought a straightforward and concise entry into a series of racemic carbocyclic analogs of 4′-azido-2′-deoxynucleosides. Such a synthesis is described herein.

Results and Discussion

A 6′-hydroxy carbocyclic nucleoside such as **4** (Scheme I) was desired both as a target molecule and as a starting point for further modifications at C-6′. A versatile approach to such a compound would involve the stereo- and regioselective ring opening of epoxide **5**. Many carbocyclic nucleoside syntheses have made use of epoxide opening by the azide anion.[15,17] Subsequent reduction furnishes the amine which is used to "build up" the heterocyclic moiety.[18] This type of methodology would require selective reduction of a bis-azido compound in our case, and was consequently not employed. The alternative, epoxide opening by the heterocycle itself, is also well-precedented, both under basic[17,19] and Lewis acid catalyzed[20] conditions.

Scheme III[a]



[a] Key: (a) mCPBA, hexane; (b) triisopropylchlorosilane, imidazole, CH_2Cl_2; (c) $TMSN_3$, TMSOTf, −78 °C; (d) 3,5-dinitrobenzoyl chloride, pyridine.

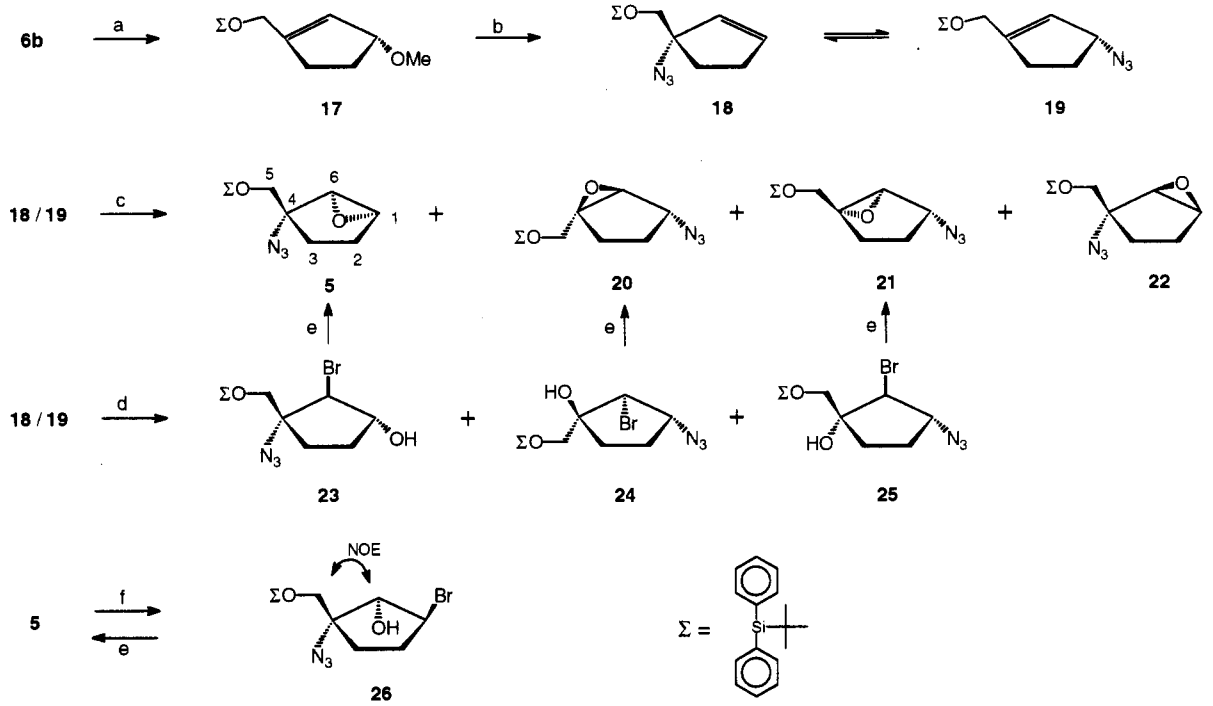
Retrosynthetic analysis suggests that key intermediate **5** may be obtained from cyclopentenes **6** by one of several routes. Tertiary azides, although infrequently encountered, have been prepared by IN_3 addition to olefins[21,22] and by the Lewis acid catalyzed reaction of hydrazoic acid with tertiary alcohols or olefins.[23,24] Subsequent experimentation, reported herein, confirmed the suitability of **6** as precursors of azide **5**, albeit by an unexpected route. The straightforward, multigram synthesis of cyclopentenes **6**, beginning with the ozonolysis of cyclohexenes **7** according to the method of Jommi,[25] highlights the simplicity of this overall approach.

As shown in Scheme II, olefin **7a**, prepared by silylation of 2-cyclohexen-1-ol, was ozonized at low temperature. Reductive workup followed by intramolecular aldol reaction/dehydration catalyzed by dibenzylammonium trifluoroacetate[25] afforded **8a**, which could be used without purification. Reduction of this material with sodium borohydride gave alcohol **6a** in a yield of 51% from **7a**.

The next crucial step, namely introduction of the tertiary azide, was then attempted by IN_3 addition to **6a**. Here the regiochemistry of the addition was never in doubt; opening of the intermediate iodonium species at the tertiary carbon was expected and observed. The expected stereochemistry of this reaction was, however, less clear. Speculation that the bulky (triisopropylsilyl)oxy substit-

(14) Biggadike, K.; Borthwick, A. D. *J. Med. Chem.* **1990**, *33*, 1380.
(15) Marquez, V. E.; Lim, M.-I. *Med. Chem. Res. Rev.* **1986**, *6*, 1.
(16) Borthwick, A. D.; Biggadike, K. *Tetrahedron* **1992**, *48*, 571.
(17) Madhavan, G. V. B.; McGee, D. P. C.; Rydzewski, R. M.; Boehme, R.; Martin, J. C.; Prisbe, E. J. *J. Med. Chem.* **1988**, *31*, 1798.
(18) Shealey, Y. F.; O'Dell, C. A.; Thorpe, M. C. *J. Heterocycl. Chem.* **1981**, *18*, 383.
(19) Biggadike, K.; Borthwick, A. D.; Exall, A. M. *J. Chem. Soc., Chem. Commun.* **1990**, 458.
(20) Matsumura, F.; Nishiyama, Y.; Matsubara, K.; Nagahata, T.; Hoshino, H.; Seki, J. Eur. Pat. Appl. EP 0330992 1989; *Chem. Abstr.* **1990** *112*, 235073w.
(21) Hassner, A.; Dehaen, W. *J. Org. Chem.* **1990**, *55*, 2243.
(22) Hassner, A. *Acc. Chem. Res.* **1971**, *4*, 9.
(23) Hassner, A.; Fibiger, R.; Andisik, D. *J. Org. Chem.* **1984**, *49*, 4237.
(24) Marquez, V. E.; Bodenteich, M. *Tetrahedron Lett.* **1990**, *31*, 5977.
(25) Canonica, S.; Ferrari, M.; Jommi, G.; Sisti, M. *Synthesis* **1988**, 697.

Scheme IV[a]



[a] Key: (a) $Ph_2(t\text{-Bu})SiCl$, imidazole, CH_2Cl_2; (b) $TMSN_3$, TMS triflate, −78 °C; CH_2Cl_2; (c) $PhCN/H_2O_2$, $KHCO_3$, MeOH, 50 °C; (d) *N*-bromoacetamide, aqueous dioxane; (e) KOH, EtOH; (f) HBr, acetone.

uent (TIPSO) would ensure the formation of adduct **11**, where this group and the iodine atom are trans-disposed, proved to be unfounded. Instead, the only major product obtained upon treatment of **6a** with IN_3 was the cis-disposed **9a**, the stereochemistry of which was determined by its conversion to the crystalline 3,5-dinitrobenzoyl derivative **10** and subsequent X-ray crystallography. A search of the literature then revealed that the addition of IN_3 to 3-*tert*-butylcyclohexene also resulted in the product arising from ring opening of the *cis*-iodonium intermediate.[26]

The conversion of desired adduct **11** to the 1,6-epoxide **5**,[27] at least conceptually, would only involve a simple desilylation/epoxide formation step. However, the cis-disposition of the iodo and (triisopropylsilyl)oxy substituents in **9a** implied that its transformation to **5** would require inversion of configuration at the carbon bearing the silyloxy substituent along with protection and deprotection steps. Due to the length of such a route, a different approach to the conversion of **6a** to **5** was attempted, as shown in Scheme III.

Olefin **6a** was epoxidized with mCPBA in hexane to afford a 2:1 mixture of the desired epoxide **12a** and its isomer **13**, easily separable by chromatography.[28] Identification of the relative stereochemistry of these isomers, neither of which displayed any diagnostic NOE effects, took advantage of the C-1, C-6 proton coupling constants, 0 Hz for **12** indicating the trans-disposition, while the corresponding *J* value for **13** was 1.2 Hz. Silylation of **12a** afforded the bis-protected **12b**.

An attempt was made to open epoxide **12b** by azide attack at C-4 under Lewis acid catalyzed conditions, thus introducing the tertiary azide and providing **14**, a suitable precursor of **5**. The "abnormal" ring opening of epoxides by azide anion at the more highly substituted carbon has been reported to proceed in certain instances where highly stabilized carbocation-like transition states were involved.[29] However, under the reaction conditions employed in this case (−78 °C, 2.2 equiv of azidotrimethylsilane, 1.0 equiv of TMS triflate, dichloromethane) the epoxide was opened in an unexpected way by a facile 1,2-hydride shift, producing the silyloxy-stabilized carbocation. This, after quenching by azide ion to afford a silylated *gem*-azidohydrin,[30] displacement of the silyloxy group of the azidohydrin by another azide ion, and hydrolysis of the TMS ether, gave the interesting *gem*-diazido compound **15**.[31] The structure of **15** was unambiguously determined by X-ray crystallographic analysis of its 3,5-dinitrobenzoyl derivative, **16**. It should be noted that although the hydride shift leading to the production of **15** was not anticipated, a 1,2-hydride shift which produces a stabilized α-silyloxy carbocation has previously been observed in carbocyclic nucleoside chemistry.[32]

At this point, a closer examination of the structure of **6** revealed a potential for allylic substitution. Prior work established the utility of allylic halides or sulfonates in nucleophilic azidations[33,34] as well as the use of allylic carbonates and acetates for palladium-catalyzed azidations.[35,36] Our successful route for the synthesis of **5**,

(26) Cambie, R. C.; Rutledge, P. S.; Smith-Palmer, T.; Woodgate, P. D. *J. Chem. Soc., Perkin Trans. 1* **1978**, 997.

(27) For the sake of consistency, the numbering scheme shown in Scheme I is used throughout including for all NMR assignments in the Experimental Section. This numbering scheme is derived from the one generally used for carbocyclic nucleosides, see ref 17. However, the compound names and numbering in the titles of the Experimental Section are derived from IUPAC rules.

(28) The product ratio proved remarkably sensitive to the solvent used. For example, in CH_2Cl_2, the same reaction afforded epoxides **12a** and **13** in a 1:2 ratio.

(29) VanderWerf, C. A.; Heisler, R. Y.; McEwen, W. E. *J. Am. Chem. Soc.* **1954**, *76*, 1231.

(30) Birkofer, L.; Müller, F.; Kaiser, W. *Tetrahedron Lett.* **1967**, 2781.

(31) Kirchmeyer, S.; Mertens, A.; Olah, G. A. *Synthesis* **1983**, 500.

(32) Biggadike, K.; Borthwick, A. D.; Evans, D.; Exall, A. M.; Kirk, B. E.; Roberts, S. M.; Stephenson, L.; Youds, P. *J. Chem. Soc., Perkin Trans. 1* **1988**, 549.

(33) Askin, D.; Angst, C.; Danishefsky, S. *J. Org. Chem.* **1985**, *50*, 5005.

(34) Rosen, T.; Guarino, K. J. *Tetrahedron* **1991**, *47*, 5391.

(35) Murahashi, S.-I.; Tanigawa, Y.; Imada, Y.; Taniguchi, Y. *Tetrahedron Lett.* **1986**, *27*, 227.

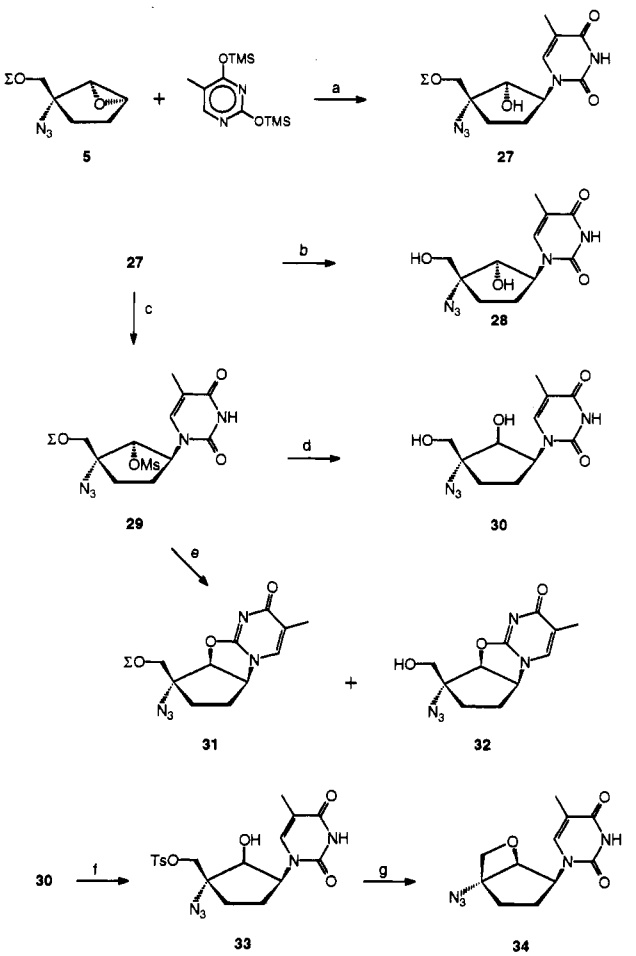
shown in Scheme IV, takes advantage of the latent allylic carbocation present in **17**. The synthesis began with **6b**, prepared by analogy to **6a** and subsequently silylated to afford **17**. Azidation in the presence of a Lewis acid might be expected to give products arising from elimination to the cyclopentadiene or another 1,2-hydride shift to afford geminally disubstituted compounds. In practice, using an excess of azidotrimethylsilane and a catalytic amount of TMS triflate at −78 °C, little (<1%) and none of such products were obtained, respectively. Instead, a 1:3 equilibrium mixture of allylic azides **18** and **19** was obtained in good yield. This ratio is typical for equilibrating allylic azides, the rearrangement of which was first described by Winstein.[37] Although equilibration did not allow for the separation of these two compounds, their identities and relative abundance were easily ascertained by comparison of the integrations of their exocyclic methylene protons, which appear as an AB quartet centered at δ 3.56 for **18** and a broad singlet at δ 4.20 for the allylic **19**.

The synthetic challenge then became selective functionalization of the double bond of **18**, the less highly substituted alkene isomer. The epoxidation of olefins is known to occur preferentially at the most electron-rich site.[38] Thus, most epoxidations attempted gave similar product distributions favoring **20** and **21**. Typical of these was mCPBA in dichloromethane, which gave isolated yields of 43% of **20**, 22% of **21**, 2.4% of desired epoxide **5**, and little or no **22**. Similar results were obtained, for example, using *tert*-butyl hydroperoxide/$Mo(CO)_6$.[39] Only one set of reaction conditions gave a significant improvement in the yield of **5**, the Payne reagent,[40,41] in which an excess of aqueous hydrogen peroxide is added slowly to the substrate, benzonitrile, and $KHCO_3$ in methanol.[42] This gave isolated yields of 18% of **5**, 18% of **20**, 15% of **21**, and 0.6% of the fourth possible epoxide, **22**. These results are consistent with previous studies by Carlson which indicated the general lack of sensitivity to the degree of alkene substitution observed with the Payne reagent relative to peracids.[43,44] This was attributed to a transition state reached at an earlier point along the reaction coordinate, and hence less subject to thermodynamic control. Thus, the very lack of selectivity that makes peroxybenzimidic acid "not the reagent of choice for selective epoxidation of polyunsaturated substrates",[44] made it the reagent of choice for the epoxidation of mixture **18**/**19**. Although the yield was low (18% overall, or 72% based on the minor component of the 1:3 mixture) and chromatography was required, this epoxidation afforded a viable route to multigram quantities of **5**.

The assignment of structures to epoxides **5**, **20**, **21**, and **22** was not trivial. Structures **20** and **21** were assigned by analogy to **12** and **13** in their proton NMR spectra. Determination of the relative stereochemistry of **5** and **22**, however, was more difficult, as no NOE effect between the C-6 and the exocyclic methylene protons could be observed in either product. These structures were therefore derived from spectral data for the related bromohydrins. Treatment of the **18**/**19** mixture with *N*-bromoacetamide in aqueous dioxane afforded bromohydrins **23**, **24**, and **25**. TLC indicated that under basic conditions these could be converted to epoxides **5**, **20**, and **21**, respectively. Another bromohydrin which also gave rise to **5** upon treatment with base, **26**, was obtained upon ring opening of **5** with HBr. No significant NOE effect between the C-6 proton and the exocyclic methylene protons was observed for **23**, while **26** displayed a strong enhancement of exocyclic methylene proton resonance upon irradiation at H-6. This established the trans relationship between the silyloxymethyl group and the hydroxyl group of **26**. If the correct structure for the epoxide which both **23** and **26** give rise to had been **22** instead of **5**, this type of NOE would have been observed for the bromohydrin produced from the olefin and not in the one produced by HBr ring opening of the epoxide, where the C-6 and the exocyclic methylene protons would necessarily be trans-disposed. Hence, the structures for products **5** and **22** must be as depicted.

Epoxide **5** was treated with bis(trimethylsilyl)thymine[45] under Lewis acid catalyzed conditions to afford **27** in good yield (Scheme V). This reaction proved remarkably

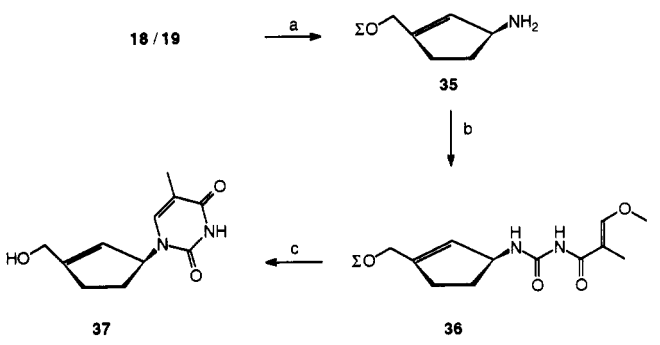
Scheme V[a]



[a] Key: (a) $BF_3{\cdot}Et_2O$, CH_3CN, 60 °C; (b) CsF, DMF; (c) MsCl, pyridine; (d) 0.1 N NaOH, H_2O/EtOH, 60 °C; (e) DBU, DMF, 55 °C; (f) pTsCl, pyridine, 50 °C; (g) 0.1 N NaOH, H_2O/EtOH.

(36) Murahashi, S.-I.; Taniguchi, Y.; Imada, Y.; Tanigawa, Y. *J. Org. Chem.* **1989**, *54*, 3292.
(37) Gagneux, A.; Winstein, S.; Young, W. G. *J. Am. Chem. Soc.* **1960**, *82*, 5956.
(38) Hudlicky, M. *Oxidations in Organic Chemistry*; ACS Monograph 186; American Chemical Society: Washington, D.C., 1990; p 61.
(39) Sharpless, K. B.; Verhoeven, T. R. *Aldrichimica Acta* **1979**, *12*, 63.
(40) Payne, G. B.; Deming, P. H.; Williams, P. H. *J. Org. Chem.* **1961**, *26*, 659.
(41) Payne, G. B. *Tetrahedron* **1962**, *18*, 763.
(42) This slow peroxide addition required the use of a syringe pump. It was found that stainless steel fittings (or corrosion therein) catalyzed the slow but premature decomposition of the 30% H_2O_2. Best results were therefore obtained using an all-plastic setup.
(43) Carlson, R. G.; Behn, N. S. *J. Org. Chem.* **1967**, *32*, 1363.
(44) Carlson, R. G.; Behn, N. S.; Cowles, C. *J. Org. Chem.* **1971**, *36*, 3832.
(45) Garner, P.; Park, J. M. *J. Org. Chem.* **1990**, *55*, 3772.

Scheme VI[a]



[a] Key: (a) PPh_3, THF/H_2O; (b) 3-methoxy-2-methylacryloyl isocyanate,[18] benzene; (c) 4 N H_2SO_4, *n*-PrOH, 70 °C.

sensitive to the catalyst and solvent employed, in agreement with earlier observations by Vorbrüggen on this type of reaction.[46,47] For example, a change in the solvent from acetonitrile to dichloromethane reduced the yield from 71% to 8%, and the use of TMS triflate in place of boron trifluoride etherate afforded only trace amounts of **27**. Desilylation of **27** afforded the first target compound in this series, **28**.

Inversion of configuration at C-6′ was accomplished by mesylation of **27** followed by treatment of crude mesylate **29** with aqueous base to give the deprotected diol **30**. The reaction undoubtably proceeds via the O^2,6′-anhydronucleoside **31** or **32** (both of which were produced and isolated upon treatment of **29** under milder conditions, using DBU as the base[48]) and subsequent ring opening via attack of the hydroxyl group at C-2.[49] Indeed, analysis of the reaction mixture by TLC implicates **31** and **32** as intermediates in the conversion of **29** to **30**. TLC analysis also was used to demonstrate the transformation of isolated products **31** and **32** to **30** with aqueous base. Interestingly, tricyclic **31** could not be obtained from **27** using diphenyl carbonate under conditions often used to prepare O^2,2′-anhydronucleosides and related compounds.[19]

Decisive confirmation of the stereochemistry of compounds in this series was obtained by selective monotosylation of **30** to give **33** followed by formation of fused oxetane **34**. The proton NMR spectrum of this compound displayed the unusually large downfield shift of the C-5′ protons (δ 4.59 and δ 4.66) as well as coupling of the C-5′-exo proton with the C-3′-exo proton via a W-effect. The formation of **34** fixes the relative positions of the hydroxymethyl group at C-4′ and the adjacent hydroxyl group in **30** as being cis. Thus, the corresponding stereochemistry of epimer **28** must indeed be trans and, by extension, the structure of epoxide **5** which gave rise to it was again confirmed.

One further structural modification was made possible by the availability of allylic azide mixture **18/19** (Scheme VI). Staudinger-type reduction[36] of this mixture gave allylic amine **35**, which was converted via standard chemistry[18] to **36**. The acid-catalyzed cyclization of **36** to the thymine (**37**) was beset by problems most likely due to fragmentation of **36** to give the stabilized cyclopentenyl carbocation. Thus, only a 6.2% yield of **37** was obtained. The 4′,6′-unsaturated **37** is formally the thymine analog of 2′,3′-dideoxy Neplanocin A.[50] Although no antiviral activity against HIV-1, HSV-1, or HSV-2 was exhibited by carbocyclic nucleosides **28**, **30**, or **37**, the effects of further structural modifications on the antiviral activity of compounds in this series awaits exploration.

Experimental Section

General Procedure. Glassware was oven-dried (140 °C, 2 h), and all reactions were performed with magnetic stirring under a positive pressure of dry nitrogen. Acetonitrile, benzene, DMF, CH_2Cl_2, and pyridine were dried over activated 3-Å molecular sieves. THF was freshly distilled from sodium metal/benzophenone under nitrogen. Solvents were removed at 40 Torr using a rotary evaporator. Solutions were dried over anhydrous Na_2SO_4. Flash chromatography was done under nitrogen pressure using silica gel 60 Å (230–400 mesh), and preparative TLC plates (20 × 20 cm) precoated with a 1-mm silica gel layer with a 254-nm fluorescent indicator were purchased from Analtech, Inc., Newark, DE. Melting points were determined on either a Fischer-Johns apparatus or a hot stage microscope and are corrected. GC analyses employed a J&W Scientific DB-5 (30-m × 0.25-mm-i.d.) capillary column and a flame ionization detector. IR are reported in wavenumbers (cm^{-1}). ^1H NMR spectra and ^{13}C NMR spectra were obtained at 300 and 125 MHz, respectively, unless otherwise noted.[27] J values are reported in hertz. Mass spectra were obtained by electron impact at 70 eV unless otherwise noted.

3-[(Triisopropylsilyl)oxy]cyclohexene (7). A solution of 2-cyclohexen-1-ol (5.00 g, 50.9 mmol), triisopropylchlorosilane (11.8 g, 61.1 mmol), imidazole (6.93 g, 102 mmol), and CH_2Cl_2 (150 mL) was stirred at rt overnight. After washing twice with water and once with brine, the organic phase was dried. Filtration and evaporation of the filtrate gave a residue (15.1 g) that was flash chromatographed (5% EtOAc/hexane) to give **7a** (12.7 g, 98%) as a colorless oil: ^1H NMR (90 MHz, $CDCl_3$) δ 5.76 (br s, 2 H, H1, H2), 4.23–4.49 (br m, 1 H, H3), 1.40–2.16 (m, 9 H, H4, H5, H6, SiCH), 1.12 (m, 18 H, CH_3); IR (neat) 3029 m, 2943 s; MS *m/z* 254 (M^+).

Anal. Calcd for $C_{15}H_{30}SiO \cdot {}^1/_4H_2O$: C, 69.56; H, 11.87. Found: C, 69.73; H, 11.70.

(±)-3-[(Triisopropylsilyl)oxy]- and (±)-3-Methoxycyclopent-1-ene-1-carboxaldehydes (8a and 8b).[27] *Caution! This reaction proceeds via potentially explosive peroxide intermediates. The reaction should therefore be carried out in a hood using a safety shield, and all appropriate safety precautions should be observed.* A stream of 4% ozone in oxygen was bubbled through a stirred solution or suspension of the appropriate cyclohexene (50.0 mmol) in MeOH (500 mL) at −70 °C until a blue solution resulted. After the solution was purged thoroughly with nitrogen, trimethyl phosphite (9.31 g, 75.0 mmol) was added dropwise, and the solution was gradually allowed to reach rt. Evaporation of the solvent was followed by addition of dibenzylammonium trifluoroacetate (3.12 g, 10.0 mmol) and THF (50 mL). Storage at 0 °C overnight followed by evaporation gave a residue which was partitioned between ether and water. After separation and further ether extractions, the combined organic phase was washed with water and brine and dried. Solvent evaporation afforded the crude product which decomposed over the course of several weeks at 0 °C. The freshly prepared material was used without purification for the subsequent reaction. A sample was purified for analytical purposes.

Data for 8a: UV (MeOH) λ_{max} 232 nm (4960); ^1H NMR ($CDCl_3$) δ 9.84 (s, 1 H, CHO), 6.71–6.74 (m, 1 H, H6), 5.12–5.18 (m, 1 H, H1), 2.63–2.73 (m, 1 H, CH), 2.30–2.43 (m, 2 H, CH_2), 1.79–1.91 (m, 1 H, CH), 1.19–1.02 (m, 3 H, SiCH), 1.09 (m, 18 H, CH_3); IR (neat) 2945 vs, 1690 s; MS *m/z* 268 (M^+); capillary GC purity 96.7%.

Data for 8b: ^1H NMR (500 MHz, $CDCl_3$) δ 9.86 (s, 1 H, CHO), 6.83 (dd, *J* = 3.8, 1.9, 1 H, H6), 4.63 (m, 1 H, H1), 3.39 (s, 3 H, OCH_3), 2.63–2.69 (m, 1 H, CH), 2.39–2.44 (m, 1 H, CH), 2.29–2.38 (m, 1 H, CH), 1.84–1.91 (m, 1 H, CH); IR (neat) 1680 s; MS *m/z* 126 (M^+).

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(51) Characteristic of carbocyclic O^2,6′-anhydronucleosides in this series was TLC polarity greater than that of the corresponding starting material in $MeOH/CH_2Cl_2$ solvents systems ($\Delta R_f \approx 0.1$), but much greater in water-saturated EtOAc ($\Delta R_f > 0.5$), possibly owing to the zwitterionic nature of these compounds.

(±)-1-(Hydroxymethyl)-3-[(triisopropylsilyl)oxy]- and (±)-1-(Hydroxymethyl)-3-methoxy-1-cyclopentenes (6a and 6b). To a stirred solution of the crude aldehyde **8a** or **8b**, respectively (40.2 mmol), in EtOH (75 mL) was added $NaBH_4$ (0.53 g, 14.0 mmol) in portions. After 10 min, 20% aqueous NH_4Cl (2 mL) was added dropwise. The solvent was evaporated and the residue partitioned between ethyl acetate (EtOAc) and water. After separation and further extraction of the aqueous phase (EtOAc), the combined organic phase was washed with brine and dried. Filtration, solvent evaporation, and flash chromatography (EtOAc/hexane) gave the pure alcohol.

Data for 6a (6.76 g, 51% from **7a**): ^1H NMR ($CDCl_3$) δ 5.67 (apparent q, J = 1.8, 1 H, H6), 4.97–5.02 (m, 1 H, H1), 4.14–4.28 (ABX, 2 H, OCH_2), 2.40–2.51 (m, 1 H, CH), 2.29–2.39 (m, 1 H, CH), 2.15–2.27 (m, 1 H, CH), 1.74–1.85 (m, 1 H, CH), 1.50 (t, J = 6.1, 1 H, OH), 1.17–1.03 (m, 3 H, SiCH), 1.08 (m, 18 H, CH_3); IR (neat) 3330 br, s; MS m/z 270 (M^+).

Anal. Calcd for $C_{15}H_{30}SiO_2 \cdot {}^1/_4H_2O$: C, 65.51; H, 11.18. Found: C, 65.20; H, 10.98.

Data for 6b (3.31 g, 52% from 3-methoxycyclohexene): ^1H NMR (500 MHz, $CDCl_3$) δ 5.79 (m, 1 H, H6), 4.44 (m, 1 H, H1), 4.23 and 4.19 (AB, J = 14.7, 1 H, OCH_2), 3.32 (s, 3 H, OCH_3), 2.44–2.48 (m, 1 H, CH), 2.19–2.24 (m, 2 H, CH_2), 1.82–1.87 (m, 2 H, CH, OH); IR (neat) 3410 vs; MS m/z 127 $(M - H)^+$.

Anal. Calcd for $C_7H_{12}O_2 \cdot {}^1/_2H_2O$: C, 61.29; H, 9.55. Found: C, 61.22; H, 9.15.

(±)-(1α,2β,3β)-1-Azido-1-(hydroxymethyl)-2-iodo-3-[(triisopropylsilyl)oxy]cyclopentane (9a). To a vigorously stirred suspension of NaN_3 (1.54 g, 23.6 mmol) in CH_3CN (50 mL) was added ICl (1.50 g, 9.24 mmol) in CH_3CN (10 mL). After 15 min, the suspension was transferred to an addition funnel and introduced over 20 min to a stirred solution of **6a** (2.00 g, 7.39 mmol) in CH_3CN (50 mL). After 2 h, the mixture was filtered and the filtrate evaporated in vacuo. The residue was partitioned between Et_2O and water, the aqueous phase was separated and extracted twice more with Et_2O, and the combined organic phase was washed with 5% $Na_2S_2O_3$ and brine and dried. Filtration, solvent evaporation, and flash chromatography of the residue (7.5% → 10% EtOAc/hexane) gave the major product, **9a**, as a colorless oil (1.17 g, 36%): ^1H NMR ($CDCl_3$) δ 4.42 (d, J = 4.7, 1 H, H6), 4.07 (m, J = 6.2, 1 H, H1), 3.96 (d, J = 6.4, 2 H, OCH_2), 2.37 (t, J = 6.4, 1 H, OH), 2.02–2.23 (m, 2 H, CH_2), 1.85–2.01 (m, 1 H, CH), 1.67–1.78 (m, 1 H, CH), 1.05–1.18 (m, 3 H, SiCH), 1.10 (m, 18 H, CH_3); IR (neat) 3419 br m, 2103 s; MS m/z 396 $(M - iPr)^+$.

Anal. Calcd for $C_{15}H_{30}IN_3O_2Si$: C, 41.00; H, 6.88; N, 9.56. Found: C, 40.72; H, 6.84; N, 9.37.

(±)-(1α,2β,3β)-1-Azido-1-[[(3,5-dinitrobenzoyl)oxy]methyl]-2-iodo-3-[(triisopropylsilyl)oxy]cyclopentane (10). To a solution of **9a** (250 mg, 0.569 mmol) in pyridine (3 mL) was added 3,5-dinitrobenzoyl chloride (244 mg, 1.06 mmol). After 1 h the solvent was removed in vacuo, and the residue was partitioned between EtOAc and water. After separation and reextraction of the aqueous layer (EtOAc), the combined organic phase was washed with brine and dried. Filtration and solvent evaporation followed by flash chromatography of the residue (7% EtOAc/hexane) gave **10** (321 mg, 89%), which upon recrystallization from hexane three consecutive times, gave platelets (mp 89–90 °C) suitable for X-ray structural determination: ^1H NMR ($CDCl_3$) δ 9.26 (m, 1 H, ArH), 9.19 (m, 2 H, ArH), 4.93 and 4.86 (AB, J = 11.7, 1 H, OCH_2), 4.41 (d, J = 4.5, 1 H, H6), 4.12 (q, J = 6.1, 1 H, H1), 2.09–2.31 (m, 2 H, CH_2), 1.85–2.08 (m, 2 H, CH_2), 1.04–1.20 (m, 3 H, SiCH), 1.11 (m, 18 H, CH_3); MS m/z 590 $(M - iPr)^+$.

Anal. Calcd for $C_{22}H_{32}IN_5O_7Si$: C, 41.71; H, 5.09; N, 11.05. Found: C, 41.52; H, 4.94; N, 11.15.

(±)-(1β,2α,5β)-5-(Hydroxymethyl)-2-[(triisopropylsilyl)oxy]-6-oxabicyclo[3.1.0]hexane (12a) and (±)-(1α,2α,5α)-5-(Hydroxymethyl)-2-[(triisopropylsilyl)oxy]-6-oxabicyclo[3.1.0]hexane (13). A mixture of **6a** (2.50 g, 9.24 mmol), 60% *m*-chloroperbenzoic acid (2.92 g, 10.1 mmol), and hexane (125 mL) was stirred for 2 h. The mixture was filtered, and the precipitate was washed with hexane. The combined filtrate and 50 mL of Et_2O were washed with saturated Na_2SO_3, saturated $NaHCO_3$, and brine and then dried. Filtration and solvent evaporation followed by flash chromatography (25% EtOAc/hexane) gave, as the higher R_f product, **12a**, a colorless oil (1.58 g, 60%): ^1H NMR ($CDCl_3$) δ 4.40 (d, J = 4.4, 1 H, H1), 4.02 and 3.85 (AB, J = 12.6, 1 H, OCH_2), 3.41 (s, 1 H, H6), 1.64–1.95 (m, 5 H, OH, CH_2), 1.01–1.29 (m, 3 H, SiCH), 1.06 (m, 18 H, CH_3); MS m/z 243 $(M - iPr)^+$.

Anal. Calcd for $C_{15}H_{30}SiO_3 \cdot {}^1/_4H_2O$: C, 61.91; H, 10.56. Found: C, 61.94; H, 10.65.

Eluting later was **13**, also a colorless oil (0.811 g, 31%): ^1H NMR ($CDCl_3$) δ 4.38 (dt, J = 7.6, 1.2, 1 H, H1), 3.89 (dd, J = 12.5, 4.5, 1 H, OCH_2) and 3.76 (dd, J = 12.5, 8.3, 1 H, OCH_2), 3.46 (d, J = 1.2, 1 H, H6), 1.94–2.06 (m, 1 H, CH), 1.82–1.92 (m, 1 H, CH), 1.75 (dd, J = 8.3, 4.5, 1 H, OH), 1.46–1.66 (m, 2 H, CH_2), 1.02–1.17 (m, 3 H, SiCH), 1.08 (m, 18 H, CH_3); IR (neat) 3405 br m; MS m/z 243 $(M - iPr)^+$.

(±)-(1β,2α,5β)-2-[(Triisopropylsilyl)oxy]-5-[[(triisopropylsilyl)oxy]methyl]-6-oxabicyclo[3.1.0]hexane (12b). A solution of **12a** (1.00 g, 3.49 mmol), triisopropylchlorosilane (0.808 g, 4.19 mmol), and imidazole (0.475 g, 6.98 mmol) in CH_2Cl_2 (20 mL) was stirred overnight, diluted with CH_2Cl_2 (20 mL), and washed with water. The aqueous phase was back-extracted twice with CH_2Cl_2. The combined organic phase was washed with brine and dried. Filtration and solvent evaporation gave an oil (2.1 g) which was flash chromatographed (2% → 3% EtOAc/hexane) to give **12b** (1.43 g, 92%) as an oil: ^1H NMR ($CDCl_3$) δ 4.37 (d, J = 4.7, 1 H, H1), 4.03 and 3.93 (AB, J = 11.4, 1 H, OCH_2), 3.31 (s, 1 H, H6), 1.87–2.00 (m, 2 H, CH_2), 1.60–1.75 (m, 2 H, CH_2), 1.01–1.18 (m, 42 H, $SiCH,CH_3$); MS m/z 399 $(M - iPr)^+$.

Anal. Calcd for $C_{24}H_{50}Si_2O_3$: C, 63.80; H, 11.38. Found: C, 63.98; H, 11.75.

(±)-(1β,2β,3α)-1-(Diazidomethyl)-3-[(triisopropylsilyl)oxy]cyclopentan-2-ol (15). To a solution of **12b** (300 mg, 0.678 mmol) in CH_2Cl_2 (10 mL) at −78 °C were added azidotrimethylsilane (172 mg, 1.49 mmol) and a solution of trimethylsilyl trifluoromethanesulfonate (151 mg, 0.678 mmol) in CH_2Cl_2 (2 mL). After 2 h, saturated $NaHCO_3$ (3 mL) was added and the stirred mixture allowed to reach rt. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic phase was dried and filtered, and the solvent was evaporated. Flash chromatography (7% EtOAc/hexane) of the residue (366 mg) gave **15** (150 mg, 68%), a colorless oil: ^1H NMR ($CDCl_3$) δ 4.78 (d, J = 9.6, 1 H, $CH(N_3)_2$), 4.11–4.15 (m, 1 H, H1), 4.01–4.08 (br m, 1 H, H6), 2.45 (dddd, J = 9.6, 4.4, 4.4, 4.4, 1 H, H4), 2.06–2.20 (m, 1 H, CH), 1.88–2.02 (m, 1 H, CH), 1.68 (d, J = 3.7, 1 H, OH), 1.43–1.68 (m, 2 H, CH_2), 1.01–1.17 (m, 21 H, $SiCH,CH_3$); ^{13}C NMR ($CDCl_3$) δ 79.16 (C1 or C6), 79.08 (C1 or C6), 78.68 ($CH(N_3)_2$), 45.85 (C4), 32.32 (CH_2), 23.92 (CH_2), 17.93 (CH_3), 12.13 (SiCH); IR (CH_2Cl_2) 2104 vs.

(±)-(1β,2β,3α)-1-(Diazidomethyl)-2-[(3,5-dinitrobenzoyl)oxy]-3-[(triisopropylsilyl)oxy]cyclopentane (16). To a solution of **15** (87 mg, 0.245 mmol) in pyridine (1.0 mL) was added 3,5-dinitrobenzoyl chloride (110 mg, 0.477 mol). After 1 h, the solvent was evaporated and the residue was triturated with EtOAc. After filtration through a short plug of cotton, the volume of the filtrate was reduced to 1 mL and the material chromatographed on preparative silica plates. **16** (113 mg, 84%) was obtained, which after two consecutive recrystallizations from hexane gave colorless platelets, mp 104.5–105.5 °C, suitable for X-ray structural determination: ^1H NMR δ 9.26 (m, 1 H, ArH), 9.10 (m, 2 H, ArH), 5.37 (br d, J = 3.0, 1 H, H6), 4.73 (d, J = 9.2, 1 H, $CH(N_3)_2$), 4.39 (m, 1 H, H1), 2.74–2.90 (m, 1 H, H4), 2.08–2.25 (m, 2 H, CH_2), 1.76–1.90 (m, 2 H, CH_2), 1.02–1.20 (m, 21 H, SiCH, CH_3); MS m/z 505 $(M - HN_3)^+$.

Anal. Calcd for $C_{22}H_{32}N_8O_7Si$: C, 48.16; H, 5.88; N, 20.42. Found: C, 47.97; H, 5.75; N, 20.16.

(±)-1-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-3-methoxycyclopent-1-ene (17). To a stirred solution of **6b** (2.00 g, 15.6 mmol) and imidazole (1.59 g, 23.4 mmol) in CH_2Cl_2 (20 mL) was added *tert*-butylchlorodiphenylsilane (5.14 g, 18.7 mmol). After 1 h, the mixture was diluted with CH_2Cl_2, washed with water and brine, and dried. Solvent evaporation followed by flash chromatography (5% EtOAc/hexane) gave 4.40 g of **17** (77%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 7.66–7.70 (m, 4 H, ArH), 7.35–7.45 (m, 6 H, ArH), 5.87 (dd, J = 3.5, 1.8, 1 H, H6), 4.47 (m, 1 H, H1), 4.27 and 4.22 (AB, J = 14.6, 1 H, OCH_2), 3.32 (s, 3 H, OCH_3), 2.35–2.46 (m, 1 H, CH), 2.12–2.26 (m, 2 H, CH_2), 1.79–1.89 (m, 1 H, CH), 1.06 (s, 9 H, *t*-Bu); IR (neat) 3072 m, 1082 s; MS m/z (DCI) 384 $(M + NH_4)^+$.

(±)-1-Azido-1-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-cyclopent-2-ene (18) and (±)-3-Azido-1-[[(*tert*-butyldiphenylsilyl)oxy]methyl]cyclopent-1-ene (19). To a solution of **17** (3.00 g, 8.18 mmol) in CH_2Cl_2 (100 mL) at −70 °C was added first azidotrimethylsilane (1.89 g, 16.4 mmol) and then trimethylsilyl trifluoromethanesulfonate (91 mg, 0.409 mmol). The solution was allowed to warm to 0 °C and stirred for 1 h. Saturated $NaHCO_3$ (25 mL) was then added and the mixture transferred to a separatory funnel. The organic phase was separated, and the aqueous was extracted twice more (CH_2Cl_2). The combined organic phase was washed with brine and dried. Evaporation followed by flash chromatography of the residue (2% EtOAc/hexane) gave 2.69 g of an equilibrium mixture of **18** and **19**, in approximately a 1:3 ratio (87%): ^{1}H NMR ($CDCl_3$) δ 7.58–7.63 (m, 4 H, ArH), 7.28–7.39 (m, 6 H, ArH), 6.01–6.05 (m, $^1/_4$ H, H6 [18]), 5.70–5.75 (m, 1 H, H1 [18], H6 [19]), 4.25–4.35 (m, $^3/_4$ H, H1 [19]), 4.20 (br s, $^6/_4$ H, OCH_2 [19]), 3.59 and 3.53 (AB, J = 10.2, $^1/_4$ H, OCH_2 [18]), 2.52–1.84 (m, 4 H, CH_2 [18], CH_2 [19]), 1.00 (s, 9 H, *t*-Bu [18], *t*-Bu [19]); ^{13}C NMR ($CDCl_3$) δ 150.78 (C4 [19]), 136.79 (C6 [18]), 135.65 (Ar), 133.40 (Ar), 129.65 (Ar), 127.72 (Ar), 121.92 (C6 [19]), 119.90 (C1 [18]), 78.21 (C4 [18]), 69.15 (OCH_2 [18]), 67.17 (C1 [19]), 62.74 (OCH_2 [19]), 32.07 (CH_2 [18]), 31.68 (CH_2 [18]), 31.33 (CH_2 [19]), 30.58 (CH_2 [19]), 26.78 (*t*-BuCH_3 [18], *t*-BuCH_3 [19]), 19.27 (*t*-BuC [18], *t*-BuC [19]); IR (neat) 2093 vs; MS m/z 320 (M − C_4H_9)$^+$.

Anal. Calcd for $C_{22}H_{27}N_3OSi$: C, 69.99; H, 7.21; N, 11.13. Found: C, 70.29; H, 7.46; N, 11.00.

(±)-(1α,2α,5α)-2-Azido-2-[[(*tert*-butyldiphenylsilyl)oxy]-methyl]-6-oxabicyclo[3.1.0]hexane (5), (±)-(1β,2α,5β)-2-Azido-5-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-6-oxabicyclo-[3.1.0]hexane (20), (±)-(1α,2α,5α)-2-Azido-5-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-6-oxabicyclo[3.1.0]hexane (21), and (±)-(1β,2α,5β)-2-Azido-2-[[(*tert*-butyldiphenylsilyl)oxy]-methyl]-6-oxabicyclo[3.1.0]hexane (22). Benzonitrile (10.7 g, 104 mmol) and $KHCO_3$ (0.80 g, 7.99 mmol) were added to a solution of the **18**/**19** mixture (11.2 g, 29.7 mmol) in MeOH (200 mL). To the solution at 50 °C was added 30% H_2O_2 (34.0 mL, 333 mmol) over 24 h using a syringe pump equipped with a plastic syringe, fittings, and tubing.[42] The reaction mixture was stirred at 50 °C for another 4 h, then cooled to rt, quenched with saturated Na_2SO_3 (20 mL), and filtered. Evaporation of the filtrate was followed by partitioning of the syrup between 5% Na_2SO_3 and hexane. Separation of the organic phase and three further hexane extractions afforded a combined organic phase which was washed with brine and dried. Filtration and solvent evaporation gave 11.45 g of residue that was flash chromatographed (4% → 6% EtOAc/hexane).

Unreacted starting material (0.656 g, 1.74 mmol) was eluted first, followed by (in order of elution) **20** (2.00 g, 18%): mp 53–4 °C; ^{1}H NMR ($CDCl_3$) δ 7.66–7.70 (m, 4 H, ArH), 7.36–7.46 (m, 6 H, ArH), 4.00 (d, J = 3.3, 1 H, H1), 3.96 and 3.88 (AB, J = 11.8, 1 H, OCH_2), 3.39 (s, 1 H, H6), 1.99–2.06 (m, 1 H, CH), 1.77–1.93 (m, 3 H, CH, CH_2), 1.06 (s, 9 H, *t*-Bu); IR (CH_2Cl_2) 2105 vs; MS m/z 336 (M − C_4H_9)$^+$.

Anal. Calcd for $C_{22}H_{27}N_3O_2Si$: C, 67.14; H, 6.91; N, 10.68. Found: C, 66.95; H, 6.94; N, 10.57.

Overlapping fractions gave 2.03 g of a mixture containing approximately equal amounts of **20** and **21** as major products and a small amount of the intermediate R_f **22**.

21 (1.71 g, 15%): oil; ^{1}H NMR ($CDCl_3$) δ 7.64–7.67 (m, 4 H, ArH), 7.36–7.47 (m, 6 H, ArH), 3.85 (s, 2 H, OCH_2), 3.63 (m, 1 H, H1), 3.36 (d, J = 1.2, 1 H, H6), 2.07–2.15 (m, 1 H, CH), 1.91–2.00 (m, 1 H, CH), 1.73–1.83 (m, 1 H, CH), 1.52–1.65 (m, 1 H, CH), 1.06 (s, 9 H, *t*-Bu); IR (CH_2Cl_2) 2100 s; MS m/z 336 (M − C_4H_9)$^+$.

Anal. Calcd for $C_{22}H_{27}N_3O_2Si$: C, 67.14; H, 6.91; N, 10.68. Found: C, 67.14; H, 6.96; N, 10.70.

5 (2.06 g, 18%): mp 45–7 °C; ^{1}H NMR ($CDCl_3$) δ 7.65–7.69 (m, 4 H, ArH), 7.37–7.49 (m, 6 H, ArH), 3.61 (s, 2 H, OCH_2), 3.54 (d, J = 2.7, 1 H, H6), 3.40 (d, J = 2.7, 1 H, H1), 2.07–2.13 (m, 1 H, CH), 1.56–1.68 (m, 3 H, CH, CH_2), 1.09 (s, 9 H, *t*-Bu); ^{13}C NMR ($CDCl_3$) δ 135.67 (Ar), 132.58 (Ar), 129.99 (Ar), 127.86 (Ar), 71.10 (C4), 66.78 (OCH_2), 59.27 (C6), 55.60 (C1), 26.75 (CH_3C), 26.36 (C2 or C3), 26.32 (C2 or C3), 19.25 (SiC); IR 2105 vs; MS m/z 336 (M − C_4H_9)$^+$.

Anal. Calcd for $C_{22}H_{27}N_3O_2Si$: C, 67.14; H, 6.91; N, 10.68. Found: C, 67.16; H, 6.92; N, 10.61.

The overlapping material mentioned above was flash chromatographed, carefully eluting with 5% EtOAc/hexane, the crude intermediate R_f product then being chromatographed on silica plates, eluting twice with this same solvent system. Finally, **22** (75.0 mg, 0.64%) was obtained as an oil: ^{1}H NMR ($CDCl_3$) δ 7.69–7.73 (m, 4 H, ArH), 7.37–7.48 (m, 6 H, ArH), 3.86 and 3.81 (AB, J = 10.5, 1 H, OCH_2), 3.57–3.60 (m, 2 H, H1, H6), 2.02–2.09 (m, 1 H, CH), 1.80–1.91 (m, 1 H, CH), 1.58–1.65 (m, 1 H, CH), 1.21–1.32 (m, 1 H, CH), 1.10 (s, 9 H, *t*-Bu); MS m/z 336 (M − C_4H_9)$^+$.

(±)-(1α,2β,3α)-1-Azido-2-bromo-1-[[(*tert*-butyldiphenylsilyl)oxy]methyl]cyclopentan-3-ol (23), (±)-(1β,2α,3α)-3-Azido-2-bromo-1-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-cyclopentan-1-ol (24), and (±)-(1α,2β,3α)-3-Azido-2-bromo-1-[[(*tert*-butyldiphenylsilyl)oxy]methyl]cyclopentan-1-ol (25). To a solution of the **18**/**19** mixture (0.200 g, 0.53 mmol) in 10% water in dioxane (5.0 mL) was added *N*-bromoacetamide (0.102 g, 0.74 mmol). After the mixture was stirred at rt overnight, solid Na_2SO_3 (50 mg) was added and the solvent was removed. The residue was partitioned between water and Et_2O, the aqueous phase being separated and extracted twice more (Et_2O). The combined organic phase was washed with brine and dried. Filtration and evaporation of the filtrate was followed by chromatography of the residue on preparative silica plates (7.5% EtOAc/hexane). The three major products isolated were as follows (in order of decreasing R_f).

24 (0.100 g, 40%): oil; ^{1}H NMR ($CDCl_3$) δ 7.63–7.73 (m, 4 H, ArH), 7.38–7.49 (m, 6 H, ArH), 4.33–4.42 (m, 2 H, OCH_2), 4.13 (d, J = 10.2, 1 H, H6), 3.63 (d, J = 10.2, 1 H, H1), 3.17 (br s, 1 H, OH), 1.82–2.21 (m, 3 H, CH, CH_2), 1.66–1.70 (m, 1 H, CH), 1.09 (s, 9 H, *t*-Bu); MS m/z 458 (M − CH_3)$^+$. Treatment of **24** with ethanolic KOH gave a product which cospotted with **20** upon TLC (5% EtOAc/hexane).

25 (0.030 g, 12%): oil; ^{1}H NMR ($CDCl_3$) δ 7.63–7.74 (m, 4 H, ArH), 7.35–7.49 (m, 6 H, ArH), 4.09–4.15 (m, 2 H, OCH_2), 3.91 (d, J = 10.1, 1 H, H6), 3.67 (d, J = 10.1, 1 H, H1), 2.90 (br s, 1 H, OH), 2.12–2.22 (m, 2 H, CH_2), 1.86–1.97 (m, 2 H, CH_2), 1.09 (apparent d, J = 6.8, 9 H, *t*-Bu); MS m/z 416 (M − C_4H_9)$^+$. Treatment of **25** with ethanolic KOH gave a product which cospotted with **21** upon TLC (5% EtOAc/hexane).

23 (0.018 g, 7.2%): oil; ^{1}H NMR ($CDCl_3$) δ 7.68–7.73 (m, 4 H, ArH), 7.38–7.49 (m, 6 H, ArH), 4.31–4.40 (m, 1 H, H1), 4.11 (d, J = 5.0, 1 H, H6), 3.93 and 3.80 (AB, J = 10.8, 1 H, OCH_2), 2.44 (d, J = 6.6, 1 H, OH), 1.92–2.24 (m, 3 H, CH, CH_2), 1.69–1.81 (m, 1 H, CH), 1.10 (s, 9 H, *t*-Bu); NOE irradiation at H6 (δ 4.11) resulted in no enhancement of resonance at OCH_2 (δ 3.93, 3.80); IR (CH_2Cl_2) 2105 vs; MS m/z 416 (M − C_4H_9)$^+$. Treatment of **23** with ethanolic KOH gave a product which cospotted with **5** upon TLC (5% EtOAc/hexane).

(±)-(1α,2α,3β)-1-Azido-3-bromo-1-[[(*tert*-butyldiphenylsilyl)oxy]methyl]cyclopentan-2-ol (26). To a solution of **5** (50.0 mg, 0.127 mmol) in acetone (1 mL) was added 48% aqueous HBr (43 μL, 0.381 mmol). After 0.5 h, excess acid was neutralized (saturated $NaHCO_3$), and the solvent was evaporated. The residue was triturated with 6% EtOAc/hexane and the supernatant chromatographed on silica plates using the same solvent system to afford **26** (55.0 mg, 92%) as an oil: ^{1}H NMR ($CDCl_3$) δ 7.64–7.72 (m, 4 H, ArH), 7.39–7.51 (m, 6 H, ArH), 4.08–4.18 (m, 1 H, H1), 3.97 (dd, J = 8.2, 6.6, 1 H, H6), 3.84 and 3.77 (AB, J = 10.4, 1 H, OCH_2), 2.39–2.50 (m, 1 H, CH), 2.39 (d, J = 6.6, 1 H, OH), 1.88–2.10 (m, 3 H, CH, CH_2), 1.09 (s, 9 H, *t*-Bu); NOE irradiation at H6 (δ 3.97) produces an enhancement of resonance at OCH_2 (δ 3.84, 3.77); IR (CH_2Cl_2) 2105 vs; MS m/z 416 (M − C_4H_9)$^+$.

Anal. Calcd for $C_{22}H_{28}BrN_3O_2Si$: C, 55.69; H, 5.95; N, 8.86. Found: C, 55.98; H, 5.85; N, 8.64.

Treatment of **26** with ethanolic KOH gave a product which cospotted with **5** upon TLC (5% EtOAc/hexane).

(±)-(1′α,2′α,3′β)-1-[1-Azido-1-[[(*tert*-butyldiphenylsilyl)-oxy]methyl]-2-hydroxy-3-cyclopentyl]thymine (27). To a solution of **5** (0.444 g, 1.13 mmol) in CH_3CN (20 mL) were added bis(trimethylsilyl)thymine[45] (1.22 g, 4.51 mmol) and BF_3·Et_2O (0.321 g, 2.26 mmol). After the mixture was stirred under nitrogen at 60 °C (bath temperature) for 4 h, more BF_3·Et_2O (0.160 g, 1.13 mmol) was added. Warming and stirring were continued for 4

h. The mixture was cooled to rt, stirred with saturated $NaHCO_3$ (15 mL), and then filtered, the solids being rinsed with more CH_3CN. Evaporation of the filtrate afforded a residue which produced an apparent emulsion upon addition of CH_2Cl_2 and water. Filtration through a sintered-glass frit resulted in phase separation. Three further extractions of the aqueous phase with cold CH_2Cl_2 were followed by washing of the combined organic phase with brine and drying. Filtration and concentration in vacuo afforded a residue (0.864 g) which was purified by flash chromatography (5% MeOH/CH_2Cl_2) to give **27** (0.417 g, 71%): mp 221–2 °C dec (EtOAc/hexane); UV (EtOH) λ_{max} 271 nm (10900); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.75 (br s, 1 H, NH), 7.56–7.64 (m, 4 H, ArH), 7.31–7.41 (m, 6 H, ArH), 6.87 (br s, 1 H, H6), 4.36 (apparent q, J = 9.0, 1 H, H1′), 4.25 (apparent t, J = 7.6, 1 H, H6′), 3.83 and 3.74 (AB, J = 10.4, 1 H, H5′), 2.67 (br d, J = 7.5, 1 H, OH), 2.13–2.18 (m, 1 H, CH), 2.00–2.07 (m, 1 H, CH), 1.89–1.94 (m, 1 H, CH), 1.81 (br s, 3 H, 5CH_3), 1.80–1.87 (m, 1 H, CH), 1.02 (s, 9 H, t-Bu); NOE irradiation at H-6′ (δ 4.25) produces an enhancement of resonance at H6 (δ 6.87); ^{13}C NMR ($CDCl_3$) δ 163.74 (C4), 150.86 (C2), 139.35 (C6), 135.60 (Ar), 132.40 (Ar), 130.09 (Ar), 127.89 (Ar), 110.83 (C5), 76.76 (C6′), 70.78 (C4′), 67.76 (C5′), 65.41 (C1′), 28.17 (C2′ or C3′), 26.80 (CH_3C), 23.38 (C2′ or C3′), 19.20 (SiC), 12.40 (5CH_3); IR (KBr) 2113 s; MS m/z 462 (M − C_4H_9)$^+$.

Anal. Calcd for $C_{27}H_{33}N_5O_4Si$: C, 62.40; H, 6.40; N, 13.48. Found: C, 62.16; H, 6.39; N, 13.34.

(±)-(1′α,2′α,3′β)-1-[1-Azido-2-hydroxy-1-(hydroxymethyl)-3-cyclopentyl]thymine (28). A solution of **27** (0.160 g, 0.308 mmol) and CsF (0.061 g, 0.400 mmol) in DMF (4 mL) was stirred at rt for 2 h. HOAc (23 μL, 0.400 mmol) was added, and the reaction mixture was evaporated. The residue was purified by chromatography on preparative silica plates (10% MeOH/CH_2Cl_2) to give **28** (0.61 g, 70%) as a foam: UV (0.1 N HCl) λ_{max} 273 nm (9810), (0.1 N NaOH) λ_{max} 271 nm (7970); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.20 (br s, 1 H, NH), 7.58 (br s, 1 H, H6), 5.50 (d, J = 5.6, 1 H, 6′OH), 5.18 (t, J = 5.4, 1 H, 5′OH), 4.63 (apparent q, J = 9.0, 1 H, H1′), 4.17 (dd, J = 9.7, 5.6, 1 H, H6′), 3.72 and 3.56 (ABX, J = 11.1, 5.4, 1 H, H5′), 1.89–2.00 (m, 2 H, CH_2), 1.78 (br s, 3 H, 5 CH_3), 1.58–1.68 (m, 2 H, CH_2); NOE irradiation at H6′ (δ 4.17) produces an enhancement of resonance at H6 (δ 7.58); ^{13}C NMR (DMSO-d_6) δ 163.73 (C4), 151.12 (C2), 138.79 (C6), 108.82 (C5), 75.42 (C6′), 70.51 (C4′), 63.80 (C5′), 60.77 (C1′), 27.98 (C2′ or C3′), 23.01 (C2′ or C3′), 11.92 (5CH_3); IR (KBr) 2112 s; MS m/z 281 M$^+$.

Anal. Calcd for $C_{11}H_{15}N_5O_4$: C, 46.97; H, 5.38; N, 24.90. Found: C, 47.17; H, 5.46; N, 24.66.

(±)-(1′α,2′α,3′β)-1-[1-Azido-1-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-2-[(methanesulfonyl)oxy]-3-cyclopentyl]thymine (29). To a stirred solution of **27** (0.410 g, 0.79 mmol) in pyridine (5 mL) was added methanesulfonyl chloride (92 μL, 1.18 mmol). After 3 h, the solvent was removed, and the residue was partitioned between EtOAc and cold water. After separation and four further extractions (EtOAc), the combined organic phase was washed with brine and dried. Filtration and solvent evaporation afforded **29** (0.456 g, 97%) as a brittle foam which was used without purification: ^{1}H NMR ($CDCl_3$) δ 8.41 (br s, 1 H, NH), 7.62–7.69 (m, 4 H, ArH), 7.38–7.49 (m, 6 H, ArH), 6.91 (apparent d, J = 1.0, 1 H, H6), 5.61 (d, J = 8.5, 1 H, H6′), 4.59–4.66 (m, 1 H, H1′), 3.84 and 3.81 (AB, J = 10.5, 1 H, H5′), 2.88 (s, 3 H, SCH_3), 2.27–2.41 (m, 2 H, CH_2), 1.87–2.16 (m, 2 H, CH_2), 1.91 (br s, 3 H, 5 CH_3), 1.11 (s, 9 H, t-Bu).

(±)-(5aα,8α,8aα)-8-Azido-8-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-3-methyl-5a,7,8,8a-tetrahydro-2*H*,6*H*-cyclopent[4,5]oxazolo[3,2-*a*]pyrimidin-2-one (31) and (±)-(5aα,8α,8aα)-8-Azido-8-(hydroxymethyl)-3-methyl-5a,7,8,8a-tetrahydro-2*H*,6*H*-cyclopent[4,5]oxazolo[3,2-*a*]pyrimidin-2-one (32). A solution of crude **29** (0.158 g, 0.264 mmol) and DBU (0.204 g, 1.34 mmol) in DMF (2 mL) was stirred at 55 °C for 4 h. The solvent was removed, and the residue was partitioned between CH_2Cl_2 and 0.2 N HCl. Phase separation was followed by reextraction of the aqueous layer twice with CH_2Cl_2, the combined organic phase then being washed with brine and dried, while the aqueous phase was reserved for later use. Filtration and solvent evaporation gave a residue (103 mg) which was chromatographed on preparative silica plates (5% MeOH/CH_2Cl_2) to give **31**[51] (38 mg, 28%): mp 167–9 °C; UV (EtOH) λ_{max} 259 nm (6730); ^{1}H NMR ($CDCl_3$) δ 7.66–7.73 (m, 4 H, ArH), 7.38–7.45 (m, 6 H, ArH), 7.05 (apparent d, J = 1.3, 1 H, H6), 5.00 (d, J = 7.0, 1 H, H6′), 4.86 (apparent t, J = 6.7, 1 H, H1′), 4.06 and 3.91 (AB, J = 11.0, 1 H, H5′), 2.22–2.31 (m, 1 H, CH), 2.00–2.11 (m, 2 H, CH_2), 1.98 (d, J = 0.7, 3 H, 5 CH_3), 1.58–1.68 (m, 1 H, CH), 1.09 (s, 9 H, t-Bu); IR (KBr) 2108 vs; MS m/z 444 (M − tBu)$^+$.

Anal. Calcd for $C_{27}H_{31}N_5O_3Si\cdot H_2O$: C, 62.40; H, 6.40; N, 13.48. Found: C, 62.08; H, 6.13; N, 13.41.

Evaporation of the aqueous phase from above was followed by trituration with 5% MeOH/CH_2Cl_2 and filtration through a short plug of glass wool. Washing the precipitate with more solvent and evaporation of the filtrate gave a yellow oil (413 mg) which was flash chromatographed (7.5% MeOH/CH_2Cl_2). A yellow solid (29 mg) was obtained and recrystallized from CH_3CN to give **32** (16 mg, 23%): mp 238–9 °C dec; UV (EtOH) λ_{max} 259 (8380); ^{1}H NMR (DMSO-d_6) δ 7.71 (apparent d, J = 1.1, 1 H, H6), 5.46 (t, J = 5.0, 1 H, OH), 5.04 (br s, 2 H, H1′,H6′), 3.85 and 3.76 (dd, J = 5.0, 11.6, 1 H, H5′), 2.05–2.11 (m, 2 H, CH_2), 1.83–1.88 (m, 1 H, CH), 1.82 (br s, 3 H, 5 CH_3), 1.58–1.71 (m, 1 H, CH); IR (KBr) 2110 vs; MS m/z 263 (M)$^+$.

Anal. Calcd for $C_{11}H_{13}N_5O_3$: C, 50.19; H, 4.98; N, 26.60. Found: C, 50.25; H, 4.98; N, 26.57.

(±)-(1′α,2′β,3′β)-1-[1-Azido-2-hydroxy-1-(hydroxymethyl)-3-cyclopentyl]thymine (30). To a solution of crude **29** (0.320 g, 0.535 mmol) in EtOH (35 mL) was added 0.2 N NaOH (35 mL). The solution was stirred at 60 °C overnight, cooled to rt, and brought to pH 5.5 by careful addition of Dowex 50X8-200 resin. The mixture was filtered, and the filtrate was evaporated. Crystallization of the resulting semisolid (290 mg) from EtOH gave microcrystalline **30** (114 mg, 75%): mp 223.5–225 °C dec; UV (MeOH) λ_{max} 272 nm (10700); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.21 (br s, 1 H, NH), 7.50 (apparent d, J = 0.8, 1 H, H6), 5.58 (d, J = 5.3, 1 H, OH), 5.07 (t, J = 5.3, 1 H, OH), 4.94 (d apparent t, J = 9.7, 4.3, 1 H, H1′), 3.76 and 3.64 (dd, J = 11.4, 5.3, 1 H, H5′), 3.75 (m, 1 H, H6′), 1.91–2.11 (m, 3H, CH_2, CH), 1.77 (d, J = 0.6, 3 H, 5 CH_3), 1.67–1.73 (m, 1 H, CH); ^{13}C NMR (75.4 MHz, DMSO-d_6) δ 164.41 (C4), 151.71 (C2), 140.25 (C6), 107.57 (C5), 74.59 (C4′), 73.68 (C6′), 64.20 (C5′), 56.36 (C1′), 28.81 (C2′ or C3′), 24.33 (C2′ or C3′), 12.45 (5 CH_3); IR (KBr) 2106 s; MS (LSIMS) m/z 282 (M + H)$^+$.

Anal. Calcd for $C_{11}H_{15}N_5O_4$: C, 46.97; H, 5.38; N, 24.90. Found: C, 46.91; H, 5.39; N, 24.91.

(±)-(1′α,2′β,3′β)-1-[1-Azido-2-hydroxy-1-[[[(4-methylphenyl)sulfonyl]oxy]methyl]-3-cyclopentyl]thymine (33). To a solution of **30** (20.0 mg, 0.071 mmol) in pyridine (2 mL) was added p-toluenesulfonyl chloride (29.8 mg, 0.156 mmol). After warming to 50 °C for 4 h, additional p-toluenesulfonyl chloride (29.8 mg, 0.156 mmol) was added and the solution was stirred at 50 °C overnight. The solvent was evaporated and the residue chromatographed on silica plates (10% MeOH/CH_2Cl_2). **30** (9.0 mg) was recovered and obtained as a foam was the less polar **33** (7.4 mg, 24%): ^{1}H NMR ($CDCl_3$) δ 9.88 (br s, 1 H, NH), 7.81 (d, J = 8.3, 2 H, ArH), 7.35 (d, J = 8.3, 2 H, ArH), 7.26 (s, 1 H, H6), 5.20 (d apparent t, J = 9.4, 4.2, 1 H, H1′), 4.38 and 4.27 (AB, J = 10.4, 1 H, H5′), 4.13 (d, J = 4.2, 1 H, H6′), 2.44 (s, 3 H, $ArCH_3$), 2.14–2.21 (m, 1 H, CH), 1.90–2.10 (m, 2 H, CH_2), 1.65–1.88 (m, 1 H, CH), 1.81 (s, 3 H, 5 CH_3); HRMS calcd for $C_{18}H_{21}N_5O_6S$ M$^+$ 435.1213, found M$^+$ 435.1206.

(±)-(1β,2β,5α)-5-Azido-(2-thymin-1-yl)-7-oxabicyclo[3.2.0]heptane (34). To a solution of **33** (6.0 mg, 0.014 mmol) in EtOH (0.25 mL) was added 0.2 N sodium hydroxide (0.25 mL). After the mixture was stirred for 1 h, HOAc (2.9 μL, 0.05 mmol) was added and the solvent was evaporated. The residue was chromatographed on a 250-μm 20- × 20-cm silica plate. Elution with 5% MeOH/CH_2Cl_2 gave **34** (1.8 mg, 50%): mp 156–7 °C; UV (EtOH) λ_{max} 270 nm; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.31 (br s, 1 H, NH), 7.65 (apparent d, J = 0.9, 1 H, H6), 4.98 (d, J = 3.5, 1 H, H6′), 4.69–4.74 (m, 1 H, H1′), 4.66 (dd, J = 7.2, 1.7, 1 H, H5′), 4.59 (d, J = 7.2, 1 H, H5′), 2.57–2.64 (m, 1 H, CH), 2.12–2.20 (m, 2 H, CH_2), 1.80–1.86 (m, 1 H, CH), 1.76 (br s, 3 H, 5 CH_3); ^{13}C NMR (DMSO-d_6) δ 163.58 (C4), 150.98 (C2), 138.79 (C6), 107.98 (C5), 87.43 (C6′), 78.13 (C5′), 65.20 (C4′), 56.26 (C1′), 30.41 (C2′ or C3′), 25.50 (C2′ or C3′), 12.08 (5CH_3); HRMS calcd for $C_{11}H_{13}N_5O_3$ M$^+$ 263.1018, found M$^+$ 263.1019.

(±)-3-Amino-1-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-cyclopent-1-ene (35). To a solution of the **18**/**19** mixture (1.25

g, 3.31 mmol) in dry THF (25 mL) were added water (89 μL, 4.96 mmol) and triphenylphosphine (0.868 g, 3.31 mmol). After 16 h, the solvent was removed, and the semisolid residue was triturated with ether (5 mL) and filtered. The precipitate was washed twice with 5-mL portions of ether, and the combined filtrate was evaporated. Flash chromatography of the residue (1.06 g) (20% → 25% MeOH/CH_2Cl_2), afforded **35** (0.473 g, 41%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.66–7.70 (m, 4 H, ArH), 7.34–7.45 (m, 6 H, ArH), 5.64 (m, 1 H, H6), 4.22 (br s, 2 H, OCH_2), 3.99 (br m, 1 H, H1), 2.27–2.38 (m, 2 H, CH_2), 2.14–2.20 (m, 1 H, CH), 1.82 (br s, 2 H, NH_2), 1.44–1.54 (m, 1 H, CH), 1.06 (s, 9 H, *t*-Bu); IR (CH_2Cl_2) 2970, 2865, 1111; MS *m/z* 351 M^+.

Anal. Calcd for $C_{22}H_{29}NOSi \cdot {}^1/_2H_2O$: C, 73.28; H, 8.39; N, 3.89. Found: C, 73.50; H, 8.35; N, 3.60.

(±)-*N*-[3-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1-cyclopent-2-enyl]-*N*^{1}-[(*E*)-3-methoxy-2-methylpropenoyl]-urea (36). To a stirred solution of **35** (440 mg, 1.25 mmol) in benzene (10 mL) was added dropwise a solution of 3-methoxy-2-methylacryloyl isocyanate[18] (220 mg, 1.50 mmol) in benzene (5 mL). After 1 h, the solvent was removed, and the residue (620 mg) was flash chromatographed (30% EtOAc/hexane) to give **36** (465 mg, 75%): foam; UV (EtOH) λ_{max} 254 nm, λ_{min} 229 nm; ^{1}H NMR ($CDCl_3$) δ 8.62 (br d, *J* = 7.6, 1 H, NH), 7.65–7.70 (m, 5 H, ArH, NH), 7.35–7.39 (m, 6 H, ArH), 7.32 (q, *J* = 1.1, 1 H, =CHOMe), 5.68 (q, *J* = 1.8, 1 H, H6), 4.91–5.02 (br m, 1 H, H1), 4.23 and 4.20 (AB, *J* = 15.2, 1 H, OCH_2), 3.86 (s, 3 H, OCH_3), 2.32–2.49 (m, 2 H, CH, CH), 2.14–2.27 (m, 1 H, CH), 1.78 (d, *J* = 0.9, 3 H, CH_3), 1.66–1.78 (m, 1 H, CH), 1.06 (s, 9 H, *t*-Bu).

(±)-1-[3-(Hydroxymethyl)cyclopent-2-en-1-yl]thymine (37). **36** (465 mg, 0.944 mmol), 4.0 N H_2SO_4 (10.0 mL), and 1-propanol (10.0 mL) were heated to 70 °C for 10 min, cooled to rt, and neutralized with $NaHCO_3$. The mixture was filtered and the precipitate washed with EtOH. Evaporation of the combined filtrate was followed by trituration of the residue with 5% MeOH/CH_2Cl_2 (5 mL) and filtration through a short plug of glass wool. The filtrate was evaporated and the residue (427 mg) chromatographed on preparative silica plates, eluting with 5% MeOH/CH_2Cl_2. The major band of lowest R_f afforded **37** (13 mg, 6.2%): mp 199–200 °C; UV (EtOH) λ_{max} 273 (7600); ^{1}H NMR (DMSO-d_6) δ 11.20 (br s, 1 H, NH), 7.14 (apparent d, *J* = 1.0, 1 H, H6), 5.45–5.53 (m, 2 H, H1′, H6′), 4.93 (t, *J* = 5.5, 1 H, OH), 4.07 (br s, 2 H, H5′), 2.25–2.52 (m, 3 H, CH_2, CH), 1.76 (d, *J* = 0.8, 3 H, 5 CH_3), 1.60–1.69 (m, 1 H, CH); ^{13}C NMR (DMSO-d_6) δ 163.88 (C4), 153.04 (C4′), 150.83 (C2), 137.01 (C6), 121.18 (C6′), 109.03 (C5), 60.36 (C1′), 59.89 (C5′), 30.88 (C3′), 30.24 (C2′), 12.14 (5CH_3); HRMS calcd for $C_{11}H_{14}N_2O_3$ M^+ 222.1004, found M^+ 222.1003.

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Supplementary Material Available: X-ray data for compounds **10** and **16**, including tables of atomic coordinates, thermal parameters, bond lengths, bond angles, and representations illustrating the computer-generated structures (9 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Inexpensive Reagents for the Synthesis of Amides from Esters and for Regioselective Opening of Epoxides

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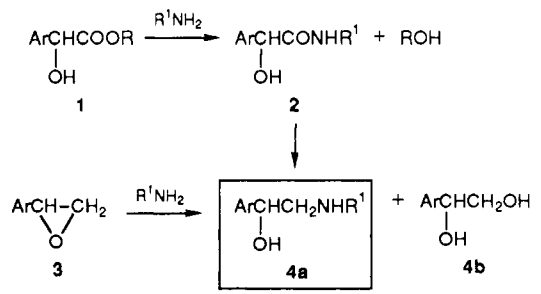
Lithium aluminum amides [$LiAl(NHR)_4$], **6a–6d**, easily prepared in Et_2O or THF from 1 equiv of $LiAlH_4$ and 5 equiv of amine, proved to be efficient reagents for the synthesis of secondary amides from esters (~100% with unhindered amines and 92% with $tBuNH_2$). They also open aryl epoxides with very high regioselectivity to give 97–98% of the β-amino-α-arylethanols (corresponding to the SN_2 mechanism).

During work on asymmetric synthesis of β-adrenergic compounds,[1] we became interested in the synthesis of secondary amides **2** from carboxylic esters **1** and the regioselective opening of aromatic epoxides **3** as short routes toward amino alcohols **4a**.



Since direct aminolysis of carboxylic esters with primary amines requires high temperatures and the use of an autoclave, more reactive reagents have been developed[2] such as alkali,[3] magnesium,[4] tin,[5] titanium,[6] and aluminum amides.[7] It is also well-known that the regioselectivity of the direct opening of aryl epoxides by primary amines is low and ranges between 60/40 and 85/15 in favor of regioisomer **a**.[8] Reagents such as aluminum,[9] magnesium,[10]

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