(1*S*,2*R*)-[(Benzyloxy)methyl]cyclopent-3-enol. A Versatile Synthon for the Preparation of 4′,1′a-Methano- and 1′,1′a-Methanocarbocyclic Nucleosides

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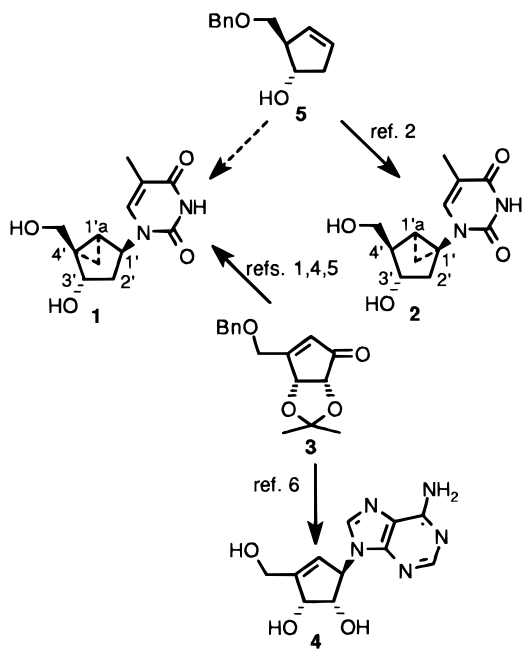
Introduction

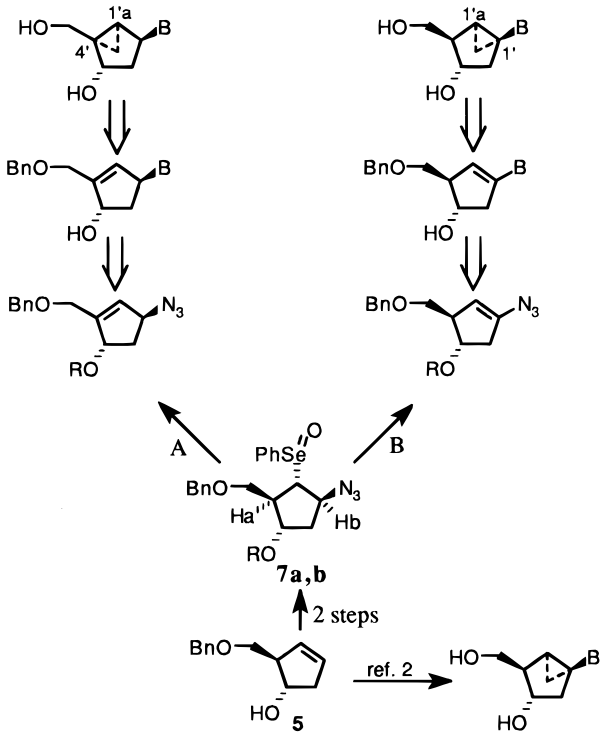
4′,1′a-Methanocarbocyclic thymidine (**1**, Scheme 1) is a recently discovered potent anti-herpes virus agent that showed better *in vitro* activity against HSV-1 and HSV-2 than acyclovir.[1] The structurally related and conformationally distinct 1′,1′a-methanocarbocyclic thymidine (**2**), however, was totally devoid of antiviral activity.[1,2] We have recently suggested that the difference between **1** and **2** might be related to their antipodal pseudosugar conformation imposed by the rigid bicyclo[3.1.0]hexane system.[1] In the case of **1**, the conformation of the pseudosugar mimics that of a 2′-deoxysugar locked in the northern hemisphere of the pseudorotational cycle, whereas in **2** the pseudosugar mimics a 2′-deoxysugar locked in the southern hemisphere.[3]

In an effort to prepare additional quantities of **1** for further biological testing, we decided to investigate an alternative approach to the already published methods.[1,4,5] These methods begin with the same chiral cyclopentenone precursor **3** (Scheme 1) that was first employed for the synthesis of neplanocin A (**4**).[6] In these methodologies, a two-step deoxygenation protocol to remove the extra hydroxyl group was necessary, and thus, the development of a method that circumvented these steps was desirable. For that reason, we considered the possibility of using the readily accessible cyclopentenol synthon, (1*S*,2*R*)-2-[(benzyloxy)methyl]cyclopent-3-enol (**5**), as a starting material for the preparation of **1** and other 4′,1′a-methanocarbanucleosides. Compound **5** was developed by Roberts et al.[7,8] for the synthesis of 2′-deoxycarbanucleosides, and recently, we have utilized it for the synthesis of 1′,1′a-methano carbocyclic nucleosides, including **2**.[2] If successful, the same homochiral compound could then serve as a common precursor to both series of conformationally locked nucleosides.

Scheme 1



Scheme 2



As illustrated in Scheme 2, *syn*-elimination of the intermediate selenoxides **7a,b** generated from **5** could in theory proceed in two directions, giving the allylic azide (path A) or the vinyl azide (path B), respectively. Retrosynthetically, path A should provide access to the 4′,1′a-methanocarbanucleoside series, whereas path B would lead to the 1′,1′a-methanocarbanucleoside series, after performing hydroxyl-directed cyclopropanations on each olefin. The preferred pathway for the *syn*-elimination would be determined by the ease of abstraction of the hydrogens (Ha vs Hb), the stability of the five-membered Ei transition state, and the stability of the resulting

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(5) Siddiqui, M. A.; Ford, H., Jr.; George, C.; Marquez, V. E. *Nucleosides Nucleotides* **1996**, *15*, 235.
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(8) 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.

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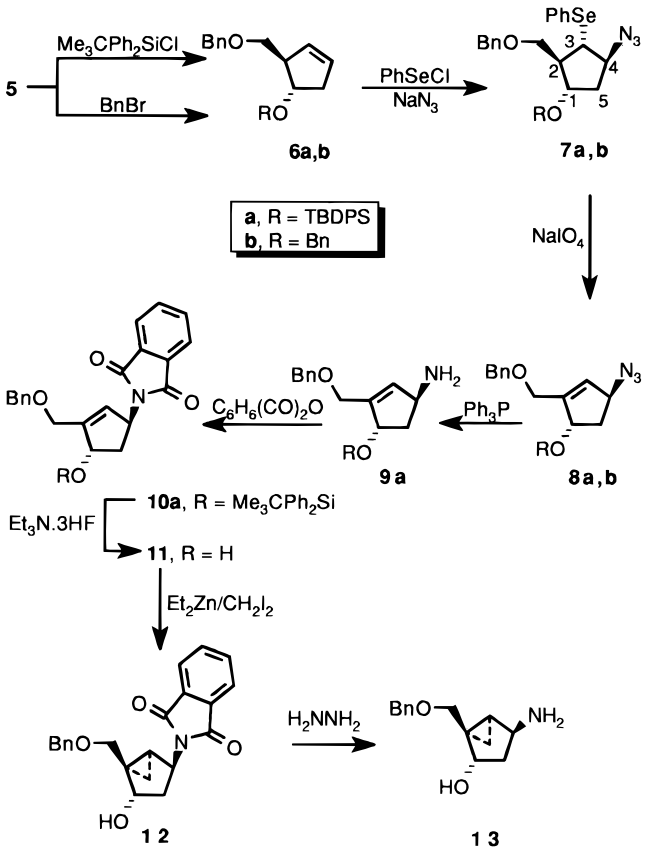
Scheme 3

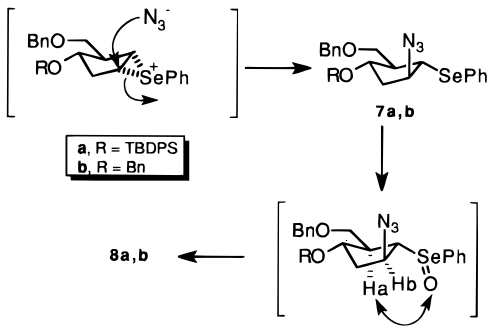


olefin, among other factors.[9] Experimentally, the allylic azide (path A) overwhelmingly predominated over the vinyl azide (path B), despite the inductive polarization associated with the azido group, which could have facilitated removal of Hb. Therefore, since we already have used compound **5** for the effective synthesis of the 1′,1′a-methanocarbanucleoside series,[2] we now wish to report the use of the same precursor for the synthesis of the antipodal 4′,1′a-methanocarbanucleosides by capitalizing on the regioselectivity of the *syn*-elimination of the selenoxide intermediates **7a,b** (path A). As an illustration, the synthetic method for the preparation of the biologically important thymidine analogue **1** is herein described.

Discussion

The successful completion of the synthesis of **1** according to path A (Scheme 2) required the regio and stereoselective generation of the *trans*-3-(phenylselenyl)-4-azidocyclopentane intermediate **7a,b** (Scheme 3). Remarkably, azido-phenylselenylation of protected olefin **5** (**6a** or **6b**) proceeded with complete stereochemical control, possibly due to the preferred pseudoequatorial disposition of both substituents in the cyclopentene ring, which biased formation of the episelenonium intermediate from the bottom face of the ring to give a stable chairlike transition-state intermediate (Scheme 4). Regioselective opening of the episelenonium ion was followed by azide attack at the carbon atom farthest from the (benzyloxy)methyl group to give the desired compounds **7a** and **7b**. Equal stereo- and regioselectivity was achieved when the 1-hydroxyl group was protected either as a *tert*-butyldiphenylsilyl ether (**6a**) or as a benzyl ether

Scheme 4



(**6b**). However, a better yield was obtained with the more sterically demanding *tert*-butyldiphenylsilyl group (87% yield after column chromatography). On the other hand, the ^{1}H NMR spectrum of **7b** was more diagnostic due to the isolated appearance of the H-3 signal as nearly symmetric triplet at δ 3.15 ($J \approx 9$ Hz). The *tert*-butyldiphenylsilyl ether was ultimately preferred because it allowed the selective liberation of the 1-hydroxyl moiety required for the hydroxyl-directed cyclopropanation step (*vide infra*). Subsequently, the *in situ* oxidation of the phenylselenide group in **7a** triggered the anticipated *syn*-elimination, giving almost exclusively the allylic azide **8a** with only an observable trace of the alternate vinyl azide. In the case of **7b**, the isolated yield of the allylic azide **8b** was lower, and several unidentified side products were detected (see the Experimental Section). Such overwhelming preference for the abstraction of Ha (Schemes 2 and 4) over Hb was intriguing; however, there is precedent in the literature for the predominance of the allylic azide under similar oxidative eliminations.[9,10]

The allylic azide **8a** was efficiently reduced (Scheme 3), and the resulting carbocyclic amine **9a** was protected as the phthalimide derivative **10a** before removing of the *tert*-butyldiphenylsilyl group. Complete protection of the amine was necessary to allow the allylic hydroxyl group in **11** to direct the course of cyclopropanation in the succeeding Simmons−Smith reaction. Indeed, we have shown previously that in the identical system an acyl−NH group takes precedence over a hydroxyl group in directing delivery of the incoming methylene group in the Simmons−Smith reaction.[11] Therefore, after full protection of the amine, the allylic alcohol was able to control delivery of the methylene group, and compound **12** was obtained exclusively in 96% yield following column chromatography. Hydrazinolysis of the phthalimido group afforded the required bicyclo[3.1.0]hexane amine **13**, which was used without further purification for the construction of the base.

Pyrimidine bases are normally prepared by reacting the corresponding amine with 3-methoxy-2-methylacryloyl isocyanate.[12] Use of this reagent, however, would have required reprotection of the alcohol function in **13**. Therefore, we chose to use carbamate **14**,[13,14] which selectively reacted with the carbocyclic amine **13** to give the intermediate acryloylurea **15** (Scheme 5). Acid-catalyzed cyclization of **15** provided the protected thy-

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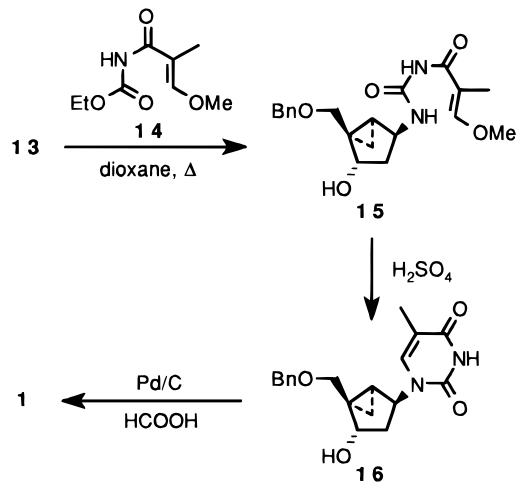
Scheme 5



midine analogue **16**, and following the removal of the benzyl ether group, the intended target **1** was obtained. The physical and spectral properties of this compound were identical with those of an authentic sample.[1,4]

In summary, we have developed a new approach for the preparation of the potent antiviral agent 4′,1′a-methanocarbocyclic thymidine (**1**). The starting material is the readily accessible chiral cyclopentenol **5**, which also serves as starting material for the synthesis of the complementary 1′,1′a-methanocarbocyclic nucleoside series. The remarkable efficiency of the process appears to depend on (a) the stereo- and regioselective azidophenylselenylation of protected olefin **5** (**6a** or **6b**), (b) the regiospecific *syn*-elimination of the transient selenoxide generated *in situ* from **7a** or **7b**, and (c) the hydroxyl-directed cyclopropanation of **11** under Simmons−Smith conditions after full protection of the amine function. The resulting carbocyclic amine **13** obtained by this method represents an advanced common intermediate for the synthesis of **1** and other 4′,1′a-methanocarbocyclic nucleosides.

Experimental Section

All chemical reagents were commercially available. Reported melting points are uncorrected. Column chromatography was performed on silica gel 60, 230−400 mesh (E. Merk), and analytical TLC was performed on Analtech Uniplates silica gel GF. Infrared and ^{1}H NMR spectra were recorded using standard methods. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA.

(1*S*,2*R*)-1-*O*-(*tert*-Butyldiphenylsilyl)-2-[(benzyloxy)-methyl]cyclopent-3-enol (6a). A stirred solution of (1*S*,2*R*)-2-[(benzyloxy)methyl]cyclopent-3-enol (**5**, 2.2.4 g, 10.8 mmol) and imidazole (1.61 g, 23.7 mmol) in dry DMF (30 mL) was treated dropwise with *tert*-butyldiphenylsilyl chloride (3.1 mL, 11.9 mmol) at room temperature. After 14 h, the reaction mixture was cooled over ice, treated with water (50 mL), and extracted with CH_2Cl_2 (3 × 50 mL). The organic solution was washed with saturated aqueous NaCl (2 × 50 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 25% benzene/hexane) gave **6a** (3.70 g, 76%) as a viscous oil: ^{1}H NMR ($CDCl_3$) δ 7.65−7.20 (m, 15 H), 5.62 (s, 2 H), 4.30 (s, 2 H), 4.25 (m, 1 H), 3.15 (dd, J = 8.9, 3.4 Hz, 1 H), 3.02 (dd, J = 8.9, 6.7 Hz, 1 H), 2.92 (m, 1 H), 2.42 (dd, J = 15.5, 6.6 Hz, 1 H), 2.30 (dd, J = 15.5, 3.8 Hz, 1 H), 1.10 (s, 9 H). Anal. Calcd for $C_{29}H_{34}O_2Si$: C, 78.68; H, 7.74. Found: C, 78.44; H, 7.73.

(1*S*,2*R*)-1-*O*-Benzyl-2-[(benzyloxy)methyl]cyclopent-3-enol (6b). A stirred solution of (1*S*,2*R*)-2-[(benzyloxy)methyl-]cyclopent-3-enol (**5**, 0.414 g, 2.03 mmol) in dry THF (8 mL) was cooled to 0 °C under argon. Sodium hydride (0.122 g, 60%, 3.04 mmol) was immediately added, and after 15 min at 0 °C, tetrabutylammonium iodide (0.037 g, 0.10 mmol) and benzyl bromide (0.36 mL, 3.04 mmol) were added. The reaction mixture was stirred for 4.5 h after it was allowed to reach ambient temperature. Volatiles were removed under reduced pressure, and the crude material was purified by flash column chromatography (silica gel, step gradient: hexane, 3% EtOAc/hexane, and 5% EtOAc/hexane) to give **6b** (0.206 g, 35%) as a colorless liquid: ^{1}H NMR ($CDCl_3$) δ 7.40−7.20 (m, 10 H), 5.75 (m, 1 H), 5.65 (m, 1 H), 4.56 (s, 2 H), 4.51 (s, 2 H), 4.08 (irregular quintuplet, 1 H), 3.45 (dd, J = 9.2, 5.7 Hz, 1 H), 3.33 (dd, J = 9.2, 7.2 Hz, 1 H), 3.05 (br m, 1 H), 2.70 (m, 1 H), 2.42 (m, 2 H). Anal. Calcd for $C_{22}H_{22}O_2$·0.25H_2O: C, 80.37; H, 7.58. Found: C, 80.15; H, 7.58.

(1*S*,2*R*,3*S*,4*S*)-1-*O*-(*tert*-Butyldiphenylsilyl)-2-[(benzyloxy)methyl]-3-(phenylselenyl)-4-azidocyclopentane (7a). Under an atomosphere of argon, phenylselenium chloride (2.31 g, 12.1 mmol) was added to a stirred solution of **6a** (2.67 g, 6.04 mmol) in DMSO (75 mL) at room temperature. After the reaction mixture appeared completely homogeneous, sodium azide (1.57 g, 24.2 mmol) was added, and stirring was continued overnight. The reaction mixture was poured into ether (150 mL), and the organic layer was washed with water (3 × 100 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 25% benzene/hexane) gave **7a** (3.34 g, 87%) as a viscous oil: IR (neat) 2200 (N_3) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.70−7.10 (m, 20 H), 4.25 (m, 3 H), 3.98 (dd, J = 15.5, 8.3 Hz, 1 H), 3.35 (dd, J = 9.4, 3.9 Hz, 1 H), 3.15 (m, 2 H), 2.08 (m, 1 H), 1.95 (m, 1 H), 1.59 (m, 1 H), 1.05 (m, 9 H). Anal. Calcd for $C_{29}H_{34}N_3O_2SeSi$: C, 65.61; H, 6.14; N, 6.56. Found: C, 65.49; H, 6.16; N, 6.52.

(1*S*,2*R*,3*S*,4*S*)-1-*O*-Benzyl-2-[(benzyloxy)methyl]-3-(phenylselenyl)-4-azidocyclopentane (7b). In the same manner as described for **7a**, a solution of **6b** (0.200 g, 0.68 mmol) in dry DMSO (10 mL) was treated with phenylselenium chloride (0.260 g, 1.36 mmol) and NaN_3 (0.177 g, 2.72 mmol). The crude product was purified by flash column chromatography (silica gel, step gradient: 25% benzene/hexane and 50% benzene/hexane) to give **7b** (0.231 g, 71%) as a pale orange liquid that was used directly in the following step: ^{1}H NMR ($CDCl_3$) δ 7.40−7.20 (m, 10 H), 4.45 (s, 2 H), 4.38 (s, 2 H), 3.95 (m, 2 H), 3.55 (AB d, 2 H), 3.15 (t, J = 9.0 Hz, 1 H), 2.10 (m, 2 H), 1.80 (m, 1 H).

(1*S*,4*S*)-1-*O*-(*tert*-Butyldiphenylsilyl)-2-[(benzyloxy)-methyl]-4-azidocyclopent-2-enol (8a). A solution of **7a** (4.23 g, 6.61 mmol) and sodium metaperiodate (2.83 g, 13.2 mmol) in methanol:water (9:1) was stirred at room temperature for 36 h. The reaction mixture was concentrated under reduced pressure, and the residue was stirred with benzene. Removal of the insolubles by filtration and concentration of the filtrate under vacuum gave an orange oily residue. Purification by flash column chromatography (silica gel, step gradient: hexane, 30% benzene/hexane, and 50% benzene/hexane) afforded the desired compound **8a** (2.42 g, 76%) as a viscous oil: IR (neat) 3500 (OH), 2200 (N_3) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.70−7.20 (m, 15 H), 5.80 (br s, 1 H), 5.00 (br t, 1 H), 4.45 (s, 2 H), 4.42 (m, 1 H), 4.10 (d, J = 14.4 Hz, 1 H), 3.90 (d, J = 14.4 Hz, 1 H), 2.08 (ddd, J = 14.2, 7.3, 4.2 Hz, 1 H), 1.89 (ddd, J = 14.2, 6.7, 2.8 Hz, 1 H), 1.03 (br s, 9 H). Anal. Calcd for $C_{29}H_{33}N_3O_2Si$: C, 72.01; H, 6.88; N, 8.69. Found: C, 71.98; H, 6.93; N, 8.63. A small amount of a less polar compound was isolated and characterized by NMR as (1*R*,2*S*)-1-*O*-(*tert*-butyldiphenylsilyl)-2-[(benzyloxy)methyl]-4-azidocyclopent-3-enol: ^{1}H NMR ($CDCl_3$) δ 7.70−7.20 (m, 15 H), 5.65 (s, 1 H), 4.32 (s, 2 H), 4.25 (m, 1 H), 3.15 (dd, J = 8.9, 5.4 Hz, 1 H), 3.02 (dd, J = 8.9, 6.6 Hz, 1 H), 2.93 (m, 1 H), 2.42 (ddd, J = 15.5, 6.6, 1.5 Hz, 1 H), 2.30 (dd, J = 15.5, 3.8 Hz, 1 H), 1.03 (s, 9 H).

(1*S*,4*S*)-1-*O*-Benzyl-2-[(benzyloxy)methyl]-4-azidocyclopent-2-enol (8b). In the same manner as described for **8a**, a mixture of **7b** (0.214 g, 0.45 mmol) and sodium metaperiodate (0.192 g, 0.90 mmol) in 10 mL of methanol:water (9:1) was allowed to react. Purification by flash column chromatography (silica gel, step gradient: 25% benzene/hexane, 50% benzene/hexane, and 75% benzene/hexane) gave **8b** (0.082 g, 54%) as a pale yellow liquid. This reaction was not as clean as the previous one and required a second purification under the same chromatographic conditions to afford 0.079 g (52%) of **8b** as a colorless liquid: ^{1}H NMR ($CDCl_3$) δ 7.40−7.20 (m, 10 H), 5.92 (br s, 1 H), 4.75 (br m, 1H), 4.55 (m, 4 H), 4.20 (s, 2 H), 2.25 (m, 1 H), 2.19 (m, 1 H). Anal. Calcd for $C_{20}H_{21}N_3O_2$: C, 71.62; H, 6.31; N, 12.53. Found: C, 71.68; H, 6.34; N, 12.56.

(1*S*,4*S*)-1-*O*-(*tert*-Butyldiphenylsilyl)-2-[(benzyloxy)-methyl]-4-aminocyclopent-2-enol (9a). A mixture of **8a** (1.81 g, 3.77 mmol) and triphenylphosphine (2.45 g, 9.37 mmol) in 70 mL of wet THF (4% water) was refluxed for 4 h and then concentrated under reduced pressure. The crude amine was first purified by rapid flash column chromatography (silica gel) using $CHCl_3$ and a step gradient of MeOH/$CHCl_3$ solutions (1% → 2% → 5% MeOH). Pure amine **9a** (1.54 g, 90%) was obtained as a viscous oil after a second chromatography under the same conditions: ^{1}H NMR ($CDCl_3$) δ 7.70−720 (m, 15 H), 5.78 (br s, 1 H), 5.00 (m, 1 H), 4.42 (s, 2 H), 4.05 (m, 2 H), 3.92 (d, J = 13.5 Hz, 1 H), 2.13 (ddd, J = 13.9, 7.3, 3.1 Hz, 1 H), 1.40−1.60 (m, 3 H), 1.03 (s, 9 H). Anal. Calcd for $C_{29}H_{35}NO_2Si\cdot0.3H_2O$: C, 75.22; H, 7.74; N, 3.02. Found: C, 75.25; H, 7.71; N, 2.92.

(1*S*,4*S*)-1-*O*-(*tert*-Butyldiphenylsilyl)-2-[(benzyloxy)-methyl]-4-phthalimidocyclopent-2-enol (10a). Under an atmosphere of argon, a mixture of **9a** (0.87 g, 1.91 mmol) and phthalic anhydride (0.84 g, 5.73 mmol) was heated in dry pyridine (2 mL) at 90 °C for 2 h. Acetic anhydride (2 mL) was added to the dark-colored reaction mixture, and heating was continued for 2 h. The reaction mixture was cooled to room temperature, reduced to dryness, dissolved in toluene (15 mL), and reconcentrated. The residue was purified by flash column chromatography (silica gel) using hexane and 10% EOAc/hexane as eluants to give **10a** (0.86 g, 77%) as a viscous oil: ^{1}H NMR ($CDCl_3$) δ 7.80−7.20 (m, 19 H), 5.65 (br s, 1 H), 5.50−5.30 (m, 2 H), 4.45 (AB q, J = 11.8 Hz, 2 H), 4.12 (d, J = 14.3 Hz, 1 H), 4.00 (d, J = 14.3 Hz, 1 H), 2.15 (t, J = 5.8 Hz, 2 H), 1.05 (s, 9 H). Anal. Calcd for $C_{37}H_{37}NO_4Si$: C, 75.61; H, 6.35; N, 2.38. Found: C, 75.87; H, 6.51; N, 2.31.

(1*S*,4*S*)-2-[(Benzyloxy)methyl]-4-phthalimidocyclopent-2-enol (11). Under an atmosphere of argon, a stirred solution of **10a** (0.985 g, 1.61 mmol) in dry acetonitrile (50 mL) was treated with triethylamine trihydrofluoride (98%, 1.6 mL) and refluxed overnight. After the mixture was cooled to room temperature, water (50 mL) was added, and stirring was continued for 0.5 h. The reaction mixture was reduced to dryness, dissolved in toluene (50 mL), and reconcentrated. The residue was purified by flash chromatography (silica gel) using hexane and EtOAc. The product was eluted with EtOAc to give **11** (0.505 g, 90%) as a solid: mp 94−95 °C; ^{1}H NMR ($CDCl_3$) δ 7.90−7.20 (m, 9 H), 5.70 (br s, 1 H), 5.55 (m, 1 H), 5.30 (m, 1 H), 4.55 (AB q, J = 11.7 Hz, 2 H), 4.29 (br AB m, 2 H), 2.55 (ddd, J = 14.2, 7.25, 4.1 Hz, 1 H), 2.27 (ddd, J = 14.2, 8.7, 3.4 Hz, 1 H). Anal. Calcd for $C_{21}H_{19}NO_4$: C, 72.19; H, 5.48; N, 4.01. Found: C, 72.09; H, 5.56; N, 3.97.

(1*R*,2*S*,4*S*,5*S*)-1-[(Benzyloxy)methyl]-2-hydroxy-4-phthalimido-bicyclo[3.1.0]hexane (12). A stirred solution of **11** (0.657 g, 1.88 mmol) in dry CH_2Cl_2 (20 mL) was cooled over an ice/salt bath and treated dropwise with an Et_2Zn solution in hexane (1 M, 2.1 mL). After the addition, the reaction mixture was stirred for 15 min. Separately, CH_2I_2 (0.350 mL, 4.2 mmol) was dissolved in dry CH_2Cl_2 (10 mL), and 5 mL of this solution was added rapidly to the reaction mixture. After 5 min, additional Et_2Zn/hexane (2.1 mL) was added dropwise followed by the remaining 5 mL of the CH_2I_2 solution. The reaction mixture was stirred cold for about 10 h and then gradually allowed to reach room temperature as the bath warmed overnight. The reaction mixture was again cooled over ice and poured into 40 mL of aqueous saturated NH_4Cl. Extraction with EtOAc followed (3 × 50 mL), and the combined organic extract was washed twice with aqueous saturated NH_4Cl, dried ($MgSO_4$), filtered, and concentrated to dryness under reduced pressure. Purification by flash column chromatography (silica gel, step gradient: hexane, 25% EtOAc/hexane and 50% EtOAc/hexane) afforded a pure fraction of **12** (0.660 g, 96%) as a viscous oil (Note: the R_f values of starting material and product are identical in different mixtures of hexane/EtOAc): ^{1}H NMR ($CDCl_3$) δ 7.85−720 (m, 9 H), 5.15 (t, J = 8.1 Hz, 1 H), 4.75 (d, J = 8.3 Hz, 1 H), 4.60 (AB q, J = 12 Hz, 2 H), 4.28 (d, J = 9.3 Hz, 1 H), 3.29 (d, J = 9.3 Hz, 1 H), 2.15 (dd, J = 15.0, 8.4 Hz, 1 H), 1.82 (dd, J = 15.0, 7.7 Hz, 1 H), 1.28 (dd, J = 8.4, 3.9 Hz, 1 H), 0.97 (br t, $J \approx$ 4.5 Hz, 1 H), 0.75 (dd, J = 8.3, 5.8 Hz, 1 H). Anal. Calcd for $C_{22}H_{21}NO_4\cdot0.3H_2O$: C, 71.64; H, 5.90; N, 3.80. Found: C, 71.46; H, 5.72; N, 3.75.

(1*R*,2*S*,4*S*,5*S*)-1-[(Benzyloxy)methyl]-2-hydroxy-4-aminobicyclo[3.1.0]hexane (13). A solution of **12** (0.728 g, 2 mmol) was dissolved in 150 mL of 0.2 M methanolic hydrazine and stirred at room temperature for 30 min. Although TLC (silica gel, hexane:EtOAc 1:1) showed total disappearance of starting material, complete hydrolysis required heating at 50 °C for 3.5 h. The reaction mixture was concentrated under reduced pressure, dissolved in ethanol (3 × 50 mL), and reconcentrated three times. Finally, the residue was triturated with $CHCl_3$ (3 × 50 mL), and the insolubles were discarded. The chloroform solution was evaporated to dryness to give **13** (0.47 g, 100%) as a viscous oil. This crude product was used directly in the following condensation step.

***N*-(Ethoxycarbonyl)-(*E*)-2-(methoxymethylene)propanamide (14).** A solution of 3-methoxy-2-methylacryloyl chloride (3.94 g, 29.3 mmol) in toluene (100 mL) was refluxed with silver cyanate (6.62 g, 43.9 mmol) under argon for 1.5 h. The solution was cooled and rapidly decanted from the silver salt, which was washed three times with small portions of toluene. The combined organic solution was reduced to dryness under reduced pressure to give the isocyanate intermediate as a solid. The solid was immediately dissolved in dry dioxane (100 mL) and stirred with ethanol (100 mL) at room temperature for 20 min. The reaction mixture was reduced to dryness and purified by flash column chromatography (silica gel, step gradient: hexane, 25% EtOAc/hexane, 50% EtOAc/hexane, and EtOAc) to give **14** (3.07 g, 56%) as a white solid: mp 95 °C (begins to soften at 73 °C) (lit.[14] mp 103 °C); ^{1}H NMR ($CDCl_3$) δ 1.30 (t, J = 7.1 Hz, 3 H), 1.75 (s, 3 H), 3.82 (s, 3 H), 4.25 (q, J = 7.1 Hz, 2 H), 7.30 (s, 1 H), 7.40 (br s, 1 H). Anal. Calcd for $C_8H_3NO_4\cdot0.1H_2O$: C, 50.87; H, 6.99; N, 7.42. Found: C, 50.75; H, 6.93; N, 7.59.

(1*R*,2*S*,4*S*,5*S*)-1-[(Benzyloxy)methyl]-2-hydroxy-4-[(3-methoxy-2-methylacryloyl)ureido]bicylo[3.1.0]-hexane (15). A stirred solution of the carbocyclic amine **13** (0.141 g, 0.605 mmol) and **14** (0.113 g, 0.605 mmol) in dry dioxane (10 mL) was heated to 100 °C under argon for 3 h. The reaction mixture was evaporated to dryness under reduced pressure, and the residue was purified by flash column chromatography (silica gel, packed with hexane and eluted with EtOAc) to give **15** (0.108 g, 50%) as a hygroscopic foam: ^{1}H NMR ($CDCl_3$) δ 8.81 (d, J = 7.0 Hz, 1 H), 8.28 (s, 1 H), 7.40−720 (m, 6 H), 4.73 (t, J = 8.4 Hz, 1 H), 4.55 (AB q, J = 12.1 Hz, 2 H), 4.20 (t, J = 6.7 Hz, 1 H), 3.83 (s, 3 H), 3.81 (d, J = 9.8 Hz, 1 H), 3.41 (d, J = 9.8 Hz, 1 H), 2.30 (br s, 1 H), 2.00 (dd, J = 14.3, 7.6 Hz, 1 H), 1.75 (s, 3 H), 1.51 (m, 1 H), 1.38 (dd, J = 8.3, 3.6 Hz, 1 H), 0.92 (br t, $J \approx$ 4.7 Hz, 1 H), 0.60 (distorted triplet, 1 H). Anal. Calcd for $C_{20}H_{26}N_2O_5\cdot0.2H_2O$: C, 63.62; H, 6.92; N, 7.42. Found: C, 63.86; H, 7.22; N, 7.17.

(1*R*,2*S*,4*S*,5*S*)-1-[(Benzyloxy)methyl]-2-hydroxy-4-[5-methyl-2,4-(1*H*,3*H*)-dioxopyrimidin-1-yl]bicyclo[3.1.0]hexane (16). In a Teflon-capped vial, compound **15** (0.028 g, 0.079 mmol) was dissolved in a mixture of ethanol (0.6 mL) and 2 N H_2SO_4 (0.6 mL) and heated in a heating block at 93 °C for 3.5 h. The ethanol was removed under reduced pressure, and the aqueous solution was neutralized to pH 6 with 1 N NaOH. Following neutralization, the solution was reduced to dryness, and the residue was dissolved in $CHCl_3$, dried ($MgSO_4$), and concentrated under reduced pressure to give **16** (0.019 g, 76%) as a white powder that was recrystallized from EtOAc/hexane: mp 192−193 °C; ^{1}H NMR ($CDCl_3$) δ 8.60 (s, 1 H), 7.70 (s, 1 H), 7.40−730 (m, 5 H), 5.00 (d, J = 7.2 Hz, 1 H), 4.87 (t, J = 8.5 Hz, 1 H), 4.55 (AB q, J = 11.5 Hz, 2 H), 4.08 (d, J =10.0 Hz, 1 H), 3.25 (d, J = 10.0 Hz, 1 H), 1.98 (dd, J = 15.2, 8.2 Hz, 1 H), 1.70 (m, 1 H), 1.58 (br s, 1 H), 1.52 (s, 3 H), 1.36 (dd, J = 8.6, 3.7 Hz, 1 H), 0.93 (dd, J = 5.9, 3.9 Hz, 1 H), 0.71 (distorted triplet, 1 H). Anal. Calcd for $C_{19}H_{22}N_2O_4$: C, 66.65; H, 6.48; N, 8.18. Found: C,66.72; H, 6.49; N, 8.11.

(1*R*,2*S*,4*S*,5*S*)-1-(Hydroxymethyl)-2-hydroxy-4-[5-methyl-2,4-(1*H*,3*H*)-dioxopyrimidin-1-yl]bicyclo[3.1.0]hexane (1). To a stirred suspension of Pd black (0.134 g) in MeOH (10 mL) was added a solution of **16** (0.096 g, 0.282 mmol) in MeOH (5 mL). Formic acid (96%, 0.34 mL) was added, and the reaction mixture was stirred at 50 °C for 1 h. The reaction mixture was filtered through Celite, concentrated under reduced pressure, and vacuum dried overnight to give a white solid. Recrystallization from 2-propanol/Et_2O gave **1** (0.066 g, 93%) as a white crystalline solid: mp 235−236 °C; $[\alpha]^{25}_D$ = +47.5° (*c* 0.16, MeOH) [lit.[1] $[\alpha]^{25}_D$ = +47° (c 0.28, MeOH)]. The rest of the spectral properties exactly matched those reported earlier for the identical compound synthesized by a different method.

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