Carbocyclic Nucleoside Analogs. 1. Concise Enantioselective Synthesis of Functionalized Cyclopentanes and Formal Total Synthesis of Aristeromycin

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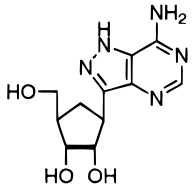
An enantioselective synthesis of functionalized cyclopentanes has been used to access carbocyclic nucleoside analogs. This pathway allows access to carbocyclic *C*- or carbocyclic *N*-nucleosides from a common intermediate, ester **16**. Additionally, (1*R*,2*R*,3*S*,4*R*)-4-amino-2,3-dihydroxy-1-cyclopentanemethanol (**18**), an intermediate in the total synthesis of aristeromycin, has been prepared as a single enantiomer in eight isolated steps from cyclopentadiene. Progress toward the synthesis of novel carbocyclic *C*-nucleosides is also discussed.

Introduction

Nucleoside analogs form the basis of several medicinally important therapies,[1] including antiviral[2] and anticancer[3] treatments. For example, compounds such as acyclovir[4] and AZT[5] are currently in widespread clinical use as antiherpetic and anti-AIDS medications. Given the considerable amount of research currently underway toward the development of novel nucleosides, synthetic methods that allow access to multiple classes of compounds are decidedly valuable. In this paper, we will discuss a formal total synthesis of the carbocyclic *N*-nucleoside aristeromycin (**2**) and progress made toward the synthesis of carbocyclic *C*-nucleoside **1**.



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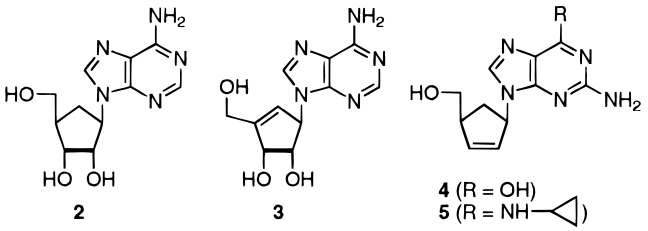
One important class of modified nucleosides is the carbocyclic nucleosides[6] in which the furanose ring has been replaced by a cyclopentane. The natural product aristeromycin (**2**), obtained from *Streptomyces citricolor*, is a prominent member of this family[7] and has demonstrated a high degree of cytotoxicity in cell cultures.[8] Neplanocin A (**3**) is an olefinic analog of **2** isolated from *Actinoplanacea ampullariella* that possesses pronounced *in vivo* antileukemic activity and low toxicity.[9] Carbovir (**4**)[10] and 1592U89 (**5**)[11] are synthetic cyclopentenoid nucleosides, both of which are actively being studied in the clinic against HIV. Based on their notable biological activities, it is not surprising that these targets have drawn substantial synthetic interest.[6]



Another alteration to the nucleoside structure that has resulted in profound biological effects is modification of the heterocyclic base. 9-Deazaadenosine (**6**), isolated from the cyanobacterium *Anabaena affinis* strain VS-1, is an example of a *C*-nucleoside, where the site of the glycosidic linkage is carbon rather than nitrogen.[12] These compounds, which are very stable to both chemical and enzymatic cleavage, also possess remarkable bioactivity. Formycin (**7**)[13] and pyrazofurin (**8**)[14] are two naturally occurring *C*-nucleosides that exhibit antitumor properties, and **8** also has notable antiviral properties.

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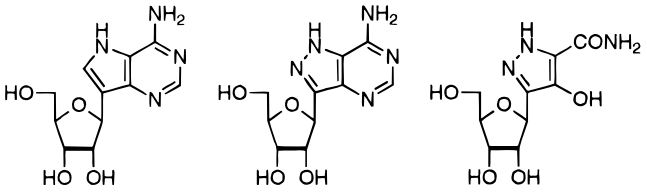

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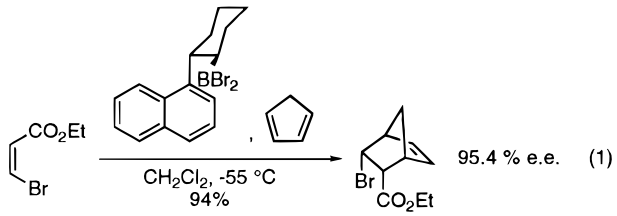
Results and Discussion

We have embarked on a project aimed at the development of a versatile pathway that would allow access to a diverse array of carbocyclic analogs, including unnatural carbocyclic *C*-nucleosides such as **1**.[15] Since the biological activity of a nucleoside analog typically resides in one enantiomer,[16] an enantioselective synthesis is critical. Recent reports have described several L-nucleosides that possess activity comparable to that of D-nucleosides;[17] thus, we are interested in accessing either enantiomer of an analog. Also, since we are interested in a pathway that allows maximum flexibility, the approach should branch from a common intermediate to provide either carbocyclic *C*- or carbocyclic *N*-nucleosides.

Based on these criteria, we envisioned that a practical starting point would be an asymmetric Diels–Alder reaction. We selected Hawkins' catalyst, the chiral dibromoborane shown in eq 1. The dichloro analog of this



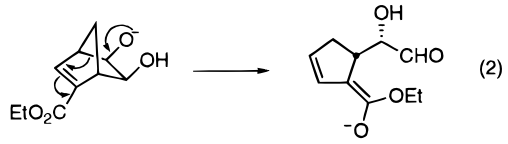
CH_2Cl_2, -55 °C, 94%; 95.4 % e.e. (1)

9 (–) 10

compound has been previously reported as an efficient enantioselective Diels–Alder catalyst.[18] Subsequent to the initial communication, Hawkins has demonstrated that the dibromoborane is a more selective catalyst.[19] In our hands, the *(Z)*-bromopropenoate **9**[20] underwent cyclization with cyclopentadiene in the presence of Hawkins' catalyst (10 mol %) to provide the bicyclic adduct **10** in excellent yield and with high enantioselectivity.[21] This reaction could be conveniently performed on a large scale and demonstrates the utility of the catalyst in reactions with functionalized dienes.

With either antipode of **10** now readily available in large quantities, we turned our attention to the functionalization of the norbornene skeleton. The Diels–Alder product **10** was dihydroxylated with osmium tetroxide/NMO[22] from the least hindered face of the bicyclic system to afford diol **11**, which was recrystallized to a constant optical rotation (Scheme 1). Elimination of the bromide with DBU then proceeded smoothly to give **12**. We found that the order of the dihydroxylation and the elimination steps was crucial. While dehydrobromination of **10** was easily accomplished, dihydroxylation of the subsequent norbornadiene occurred exclusively on the conjugated olefin.[23]

Although protection of **12** as an acetonide has previously been reported,[24] the acid sensitivity of the isopropylidene made it an unsuitable protecting group for our purposes.[25] Intermediates available directly from acetonide protected **12**[26] could not be successfully converted to the tri-*O*-benzyl ether **16**.[27] Therefore, we sought to introduce the necessary functionality at an earlier point in the synthesis. The formation of the bisbenzyl ether of diol **12** proved to be challenging. Under standard basic protection conditions, the substrate decomposed, most likely via a retrograde aldol pathway driven by relief of ring strain (eq 2).[28] Although protection with benzyl



(2)

trichloroacetimidate provided **13**, purification proved difficult. Silver oxide-promoted ether formation in the presence of 3 Å molecular sieves cleanly afforded the desired product in good yield.

With a suitably protected intermediate in hand, we turned to functionalization of the olefin. Ozonolytic cleavage of **13** followed by reductive workup and periodate oxidation generated labile aldehyde **14**. During chromatographic purification, the benzyl ether at the 2-position of **14** underwent elimination to form the corresponding α,β-unsaturated aldehyde. Thus, the aldehyde was immediately oxidized to ester **15** with bromine in methanol.[29] In practice, the direct transformation of α,β-unsaturated ester **13** into **15** was performed without any intermediate purification in 66% overall

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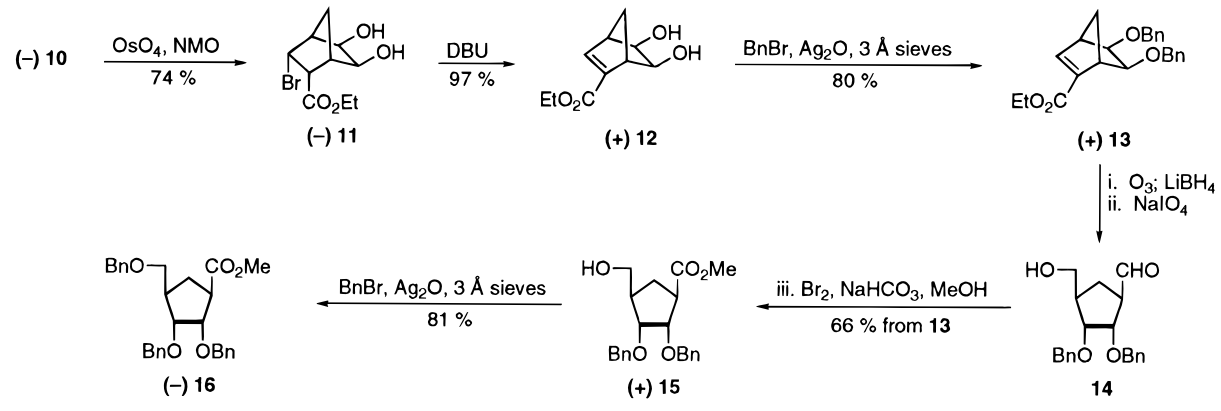
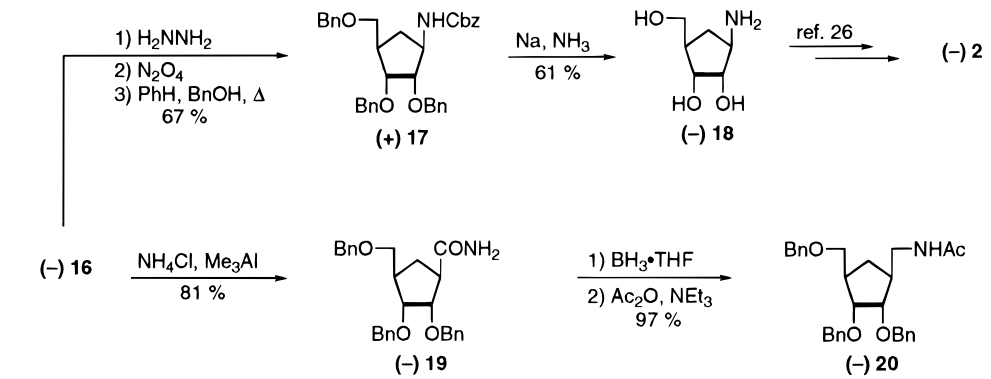
Scheme 1



Scheme 2



yield. Protection of the primary alcohol of **15** occurred under the neutral silver oxide conditions previously described in order to avoid β-elimination similar to that experienced during purification of aldehyde **14**.

The viability of this synthetic route as an approach to carbocyclic nucleosides was demonstrated by the preparation of amine **18** (Scheme 2). Ester **16** was converted into the corresponding acyl azide via standard protocol, and Curtius rearrangement in the presence of benzyl alcohol yielded fully protected cyclopentane **17**. Complete deprotection with sodium in ammonia provided the known amino triol **18**. The optical rotation of the product, $[\alpha]^{23}_D = -10.5$ (*c* 0.62, H_2O), compares favorably with the previously reported value of $[\alpha]^{23}_D = -10.3$ (*c* 1.52, H_2O).[26] Since **18** has previously been converted into aristeromycin (**2**),[7b,26] synthesis of the amino triol constitutes a formal total synthesis of the natural product.

To establish the feasibility of using **16** as a versatile intermediate for the generation of carbocyclic *C*- or carbocyclic *N*- nucleosides, we explored additional functionalization of the ester. Although it has been demonstrated that esters such as **16** can be transformed into a variety of *C*-nucleoside bases such as those contained in tiazofurin[15a] and showdomycin,[15d] carbocyclic pyrazolo[4,3-*d*]pyrimidines such as **1** have never previously been synthesized. Since 1,3-dipolar cycloadditions have proven useful in generating this type of heterocycle,[30] we chose to investigate the possibility of converting **16** into an appropriate diazoalkane precursor, acetamide **20**. Treatment of **16** under Weinreb conditions[31] provided amide **19**, which was subjected to borane reduction and acetylation to give **20**. Work toward the use of **20** in the preparation of carbocyclic *C*-nucleosides is underway, and will be reported in due course.

Conclusions

We have accomplished a concise, enantioselective synthesis of the versatile ester **16** that can be used for the preparation of both carbocyclic *C*- and carbocyclic *N*-nucleosides. The known aminotriol **18**, which has previously been converted into aristeromycin, has been prepared from cyclopentadiene in eight isolated steps (overall 12% yield). The synthetic pathway provides novel, robust intermediates which cannot be obtained using previous approaches. For example, selective deprotection of carbamate **17** would afford the corresponding tri-*O*-benzyl amine, which could withstand a wide variety of reaction conditions in the preparation of novel nucleoside analogs. Additionally, a pathway toward an array of carbocyclic *C*-nucleosides from ester **16** has also been discussed.

Experimental Section

General. All solvents were reagent grade quality and distilled immediately prior to use: acetonitrile and methylene chloride from calcium hydride, ether from sodium and benzophenone. All reagents were obtained from commercial suppliers and were used as received. Further purification was conducted according to known procedures.[32] Cyclopentadiene

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was obtained from thermally cracked dicyclopentadiene and was stored neat at −78 °C. Ozone was generated on a Wellsbach T-816 ozone generator. Merck Kieselgel 60 F-254 silica gel plates were used for thin layer chromatography. Flash column chromatography was carried out with EM Science 60 (230−300 mesh) silica gel according to the method of Still.[33] Unless otherwise noted, ^{1}H NMR spectra were recorded at 400 MHz, ^{13}C{H} NMR spectra were obtained at 100 MHz, and spectra were taken of compounds dissolved in $CDCl_3$. Elemental analyses were performed by MHW Laboratories, Phoenix, AZ.

(1*R*,2*R*,3*S*,4*S*)-2-Bromo-3-carbethoxybicyclo[2.2.1]hept-5-ene (10). To a stirred solution of the dienophile **9** (47.1 g, 263.2 mmol) and Hawkins' catalyst (10.0 g, 26.3 mmol) in 280 mL of methylene chloride cooled to −55 °C was slowly added cyclopentadiene (104 g, 1.28 mol). The mixture was stirred for 41.5 h, and the reaction was stopped with the addition of 150 mL of saturated aqueous $NaHCO_3$. After slowly being warmed to rt, the two layers were separated, and the organic layer was washed with saturated aqueous $NaHCO_3$. The organic layer was dried ($MgSO_4$), filtered, and concentrated to provide a yellow oil. Distillation under reduced pressure yielded the adduct **10** (60.6 g, 94%, 95.4% e.e.) as a colorless oil: bp 83−85 °C/0.35 Torr; $[\alpha]^{23}_D = -53.3$ (*c* 1.33, $CHCl_3$); IR (neat) 2990, 1745 cm^{-1}; ^{1}H NMR δ 1.22 (t, 3H, J = 7.2), 1.34 (d, 1H, J = 9.1), 1.59 (d, 1H, J = 9.1), 3.05 (s, 1H), 3.14 (d, 1H, J = 3.0), 3.17 (m, 1H), 4.08 (q, 2H, J = 7.1), 4.59 (dd, 1H, J = 9.2, 3.6), 6.06 (dd, 1H, J = 5.5, 3.0), 6.49 (dd, 1H, J = 5.6, 3.0); ^{13}C NMR δ 14.1, 44.6, 47.2, 49.6, 49.6, 51.0, 60.4, 133.8, 136.6, 170.9. Anal. Calcd for $C_{10}H_{13}BrO_2$: C, 49.00; H, 5.35. Found: C, 49.36; H, 5.61.

(1*R*,2*R*,3*S*,4*S*,5*S*,6*R*)-2-Bromo-3-carbethoxy-5,6-dihydroxybicyclo[2.2.1]heptane (11). To a solution of the ester **10** (60.6 g, 247.1 mmol) in 500 mL of acetone/water (4:1 v/v) warmed to 40 °C was added *N*-methylmorpholine *N*-oxide (31.8 g, 271.8 mmol), followed by a 4 wt % solution of osmium tetroxide in water (7.08 mL, 282.8 mg, 1.11 mmol). The solution was stirred for 13 h, at which point solid $NaHSO_3$ (5 g) was added. After stirring for an additional 2 h, the mixture was cooled to rt and partitioned between saturated aqueous NH_4Cl and CH_2Cl_2. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined extracts were dried (Na_2SO_4), filtered, and concentrated to provide an oily solid. Recrystallization of the product to a constant optical rotation from diethyl ether provided the diol **11** (50.9 g, 74%) as colorless white plates: mp 86.3−86.9 °C; $[\alpha]^{23}_D = -30.0$ (*c* 1.20, $CHCl_3$); IR (NaBr pellet) 3330, 2990, 1745 cm^{-1}; ^{1}H NMR δ 1.28 (t, 3H, J = 6.8), 2.09 (d, 1H, J = 11.1), 2.39 (s, 1H), 2.54 (d, 1H, J = 3.9), 3.08 (d, 1H, J = 3.9), 3.10 (d, 1H, J = 3.9), 3.23 (s, 1H), 4.15 (q, 2H, J = 7.2), 4.51−4.47 (m, 2H), 4.89 (d, 1H, J = 5.6); ^{13}C NMR δ 14.2, 32.8, 46.2, 47.7, 48.3, 50.5, 60.8, 68.1, 71.3, 170.4.

(1*S*,4*R*,5*S*,6*R*)-3-Carbethoxy-5,6-dihydroxybicyclo[2.2.1]-hept-2-ene (12). To a solution of the diol **11** (7.58 g, 27.2 mmol) in 135 mL of ether was added 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) (10.4 g, 67.9 mmol). The mixture was stirred at rt for 24 h, diluted with ether, and washed with 2 N HCl. The combined aqueous layers were extracted with CH_2Cl_2, and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated to a yellow oil. Flash column chromatography (hexanes/EtOAc 50:50) provided the unsaturated ester **12** (5.19 g, 97%) as a colorless oil: bp 97 °C/12 mmHg; $[\alpha]^{23}_D = +91.2$ (*c* 1.0, $CHCl_3$); IR (neat) 3380, 2990, 1710 cm^{-1}; ^{1}H NMR δ 1.29 (t, 3H, J = 7.1), 1.76 (d, 1H, J = 9.6), 1.99 (d, 1H, J = 9.0), 2.89 (d, 1H, J = 1.2), 3.07 (s, 1H), 3.73−3.76 (m, 1H), 3.79 (bs, 2H), 3.88 (d, 1H, J = 4.5), 4.18 (q, 2H, J = 7.2), 6.90 (d, 1H, J = 3.2); ^{13}C NMR δ 14.2, 42.2, 48.0, 49.9, 60.6, 68.2, 68.4, 141.4, 146.9, 164.4. Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.32; H, 6.91.

(1*S*,4*R*,5*S*,6*R*)-3-Carbethoxy-5,6-(benzyloxy)bicyclo-[2.2.1]hept-2-ene (13). To a flask fitted with a mechanical stirrer and argon inlet was introduced 2.4 g of crushed, activated 3 Å sieves. The diol **12** (5.19 g, 26.4 mmol) was added as a solution in 52 mL of benzene, followed by benzyl bromide (22.6 g, 132 mmol). The flask was covered with aluminum foil, and the mixture was cooled to 0 °C. To the rapidly stirring suspension was added silver oxide (31.0 g, 132 mmol) portionwise. The mixture was allowed to warm to rt over 23 h, at which point the suspension was filtered through a pad of Celite. The black solid was thoroughly washed with hexanes/EtOAc (90:10 v/v), and the filtrate was concentrated to a yellow oil. Flash column chromatography (hexanes/EtOAc 90:10) furnished the protected diol **13** (7.95 g, 80%) as a colorless oil: $[\alpha]^{23}_D = +84.2$ (*c* 1.0 in $CHCl_3$); IR (neat) 3028, 2982, 1710 cm^{-1}; ^{1}H NMR δ 1.26 (t, 3H, J = 7.2), 1.78 (d, 1H, J = 9.2), 2.27 (d, 1H, J = 9.1), 2.98 (s, 1H), 3.26 (s, 1H), 3.53 (d, 1H, J = 1.29), 3.57 (d, 1H, J = 1.36), 4.15 (q, 2H, J = 7.1), 4.58 (d, 1H, J = 12.0), 4.66 (d, 1H, J = 12.0), 4.67 (d, 1H, J = 12.1), 4.70 (d, 1H, J = 12.1), 6.84 (d, 1H, J = 3.1), 7.25−7.39 (m, 10H); ^{13}C NMR δ 14.2, 43.7, 45.4, 47.8, 60.2, 72.1, 72.4, 76.0, 76.1, 127.4, 127.7, 127.9, 128.2, 138.4, 141.9, 146.8, 164.0. Anal. Calcd for $C_{24}H_{26}O_4$: C, 76.16; H, 6.92. Found: C, 76.36; H, 7.11.

Methyl (1*R*,2*R*,3*S*,4*R*)-4-(Hydroxymethyl)-2,3-bis(benzyloxy)cyclopentanecarboxylate (15). To a solution of the unsaturated ester **13** (7.95 g, 21.0 mmol) in 215 mL of CH_2Cl_2/CH_3OH (38:1 v/v) at −78 °C was bubbled ozone until a blue color persisted. Nitrogen was bubbled through the solution to remove excess ozone, lithium borohydride (3.20 g, 147 mmol) and 21 mL of THF were added, and the reaction was warmed to 0 °C. The mixture was subsequently allowed to warm to rt over 20 h. After cooling the solution to 0 °C, 50 mL of CH_3OH was added dropwise, the mixture was concentrated to a white paste that was used immediately for the following transformation.

The white solid obtained from the ozonolysis was dissolved in 420 mL of THF/water (3:1 v/v), the solution pH was adjusted carefully to 5 with 12 N HCl, sodium periodate (13.5 g, 63.0 mmol) was added, and the mixture stirred at rt for 2 h. Removal of the volatiles by rotary evaporation yielded a white slurry that was extracted with CH_2Cl_2. The combined organics were dried overnight (Na_2SO_4), filtered, and concentrated to provide the unstable aldehyde **14** as a light yellow oil, which was carried on without further purification.

To a suspension of $NaHCO_3$ (35.3 g, 420 mmol) in 42 mL of CH_3OH/water (9:1 v/v) containing the aldehyde **14** obtained above was added a 2 M solution of bromine in CH_3OH/water (9:1 v/v) (52.5 mL, 16.8 g, 105 mmol) dropwise over 30 min. The mixture was stirred at rt for 1 h, at which point excess bromine was quenched by addition of $Na_2S_2O_4$ (10 g). The solution was diluted with 200 mL water and was extracted with CH_2Cl_2. The combined organics were dried (Na_2SO_4), filtered, and concentrated to a yellow oil. Flash column chromatography (hexanes/EtOAc 60:40) yielded the methyl ester **15** (5.13 g, 66%) as a colorless oil: $[\alpha]^{23}_D = +17.7$ (*c* 1.0, $CHCl_3$); IR (neat) 3455, 2948, 1731 cm^{-1}; ^{1}H NMR δ 1.48 (dt, 1H, J = 13.3, 4.5), 2.14 (dt, 1H, J = 13.4, 4.3), 2.37−2.47 (m, 2H), 3.04−3.10 (m,1H), 3.54−3.62 (m, 2H), 3.67 (s, 3H), 3.69 (dd, 1H, J = 8.0, 4.9), 4.07 (t, 1H, J = 4.9), 4.45 (d, 1H, J = 11.8), 4.53 (d, 1H J = 12.0), 4.56 (d, 1H, J = 11.8), 4.59 (d, 1H, J = 12.0), 7.23−7.35 (m, 10H); ^{13}C NMR δ 26.5, 43.5, 46.7, 51.9, 64.4, 71.3, 71.5, 80.3, 81.3, 127.6, 127.7, 127.8, 128.2, 128.3, 128.7, 137.8, 138.0, 175.0. Anal. Calcd for $C_{21}H_{26}O_5$: C, 70.37; H, 7.31. Found: C, 70.55; H, 7.25.

Methyl (1*R*,2*R*,3*S*,4*R*)-4-[(Benzyloxy)methyl]-2,3-bis-(benzyloxy)cyclopentanecarboxylate (16). Alcohol **15** (7.28 g, 19.7 mmol) was treated with benzyl bromide (11.8 g, 68.8 mmol) and silver oxide (15.9 g, 68.8 mmol) in the same manner as diol **11**. Flash column chromatography (hexanes/EtOAc 90:10) furnished the trisbenzyl ether **16** (7.30 g, 81%) as a colorless oil: $[\alpha]^{23}_D = -15.3$ (*c* 1.04, $CHCl_3$); IR (neat) 3029, 1732 cm^{-1}; ^{1}H NMR δ 1.50−1.58 (m, 1H), 2.17−2.24 (m, 1H), 2.44−2.52 (m, 1H), 3.10 (dt, 1H, J = 9.2, 2.5), 3.40 (dd, 2H, J = 6.1, 2.7), 3.66 (s, 3H), 3.73 (t, 1H, J = 5.2), 4.04 (dd, 1H, J = 6.7, 5.0), 4.48 (s, 2H), 4.50 (d, 1H, J = 12.1), 4.51 (d, 1H, J = 12.5), 4.55 (d, 1H, J = 12.2), 4.56 (d, 1H, J = 12.1), 7.24−7.34 (m, 15H); ^{13}C NMR δ 27.5, 42.3, 46.8, 51.8, 71.3, 71.6, 72.9, 79.7, 81.1, 127.4, 127.5, 127.8, 128.0, 128.2, 128.3, 128.4,

(33) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

128.8, 138.1, 138.3, 138.4, 175.1. Anal. Calcd for $C_{29}H_{32}O_5$: C, 75.63; H, 7.00. Found: C, 75.67; H, 6.95.

(1*R*,2*S*,3*R*,4*R*)-4-[(Benzyloxy)methyl]-1-[(benzyloxycarbonyl)amino]-2,3-bis(benzyloxy)cyclopentane (17). To a solution of the methyl ester **16** (500 mg, 1.09 mmol) in 5.5 mL of 95% EtOH was added anhydrous hydrazine (285 mg, 8.9 mmol). The solution was heated at reflux for 46 h. After cooling to rt, the mixture was concentrated to a cloudy oil. The unstable hydrazide was dissolved in 6.8 mL of CH_2Cl_2 and cooled to −78 °C, and a 6 M solution of dinitrogen tetroxide in CCl_4 (0.75 mL, 411 mg, 4.47 mmol) was added. The mixture was stirred for 2 h and poured onto ice. The aqueous layer was extracted with CH_2Cl_2, and the combined organics were washed with saturated aqueous $NaHCO_3$ (30 mL), dried ($MgSO_4$), filtered, and concentrated to afford the acyl azide as an orange oil, which was submitted to the subsequent reaction conditions immediately.

A solution of the acyl azide in 4.4 mL of benzene was heated to reflux for 1 h, and benzyl alcohol was added (260 mg, 2.4 mmol). The mixture was heated at reflux for 36 h, and then was concentrated to an orange oil which was purified by flash column chromatography (hexanes/EtOAc 75:25) to afford the carboxybenzoyl-protected amine **17** (400 mg, 67%) as a glassy syrup: $[\alpha]^{23}_D = +78.1$ (*c* 0.85, $CHCl_3$); IR (neat) 3334, 3029, 2887, 1720 cm^{-1}; ^1H NMR δ 1.31 (bd, 1H, J = 12.4), 2.42−2.47 (bm, 2H), 3.44−3.51 (bm, 2H), 3.84 (bs, 1H), 3.85−3.86 (m, 1H), 4.1 (s, 1H), 4.27 (d, 1H, J = 11.8), 4.38−4.46 (bm, 3H), 4.63 (bd, 1H, J = 12.1), 4.70 (bd, 1H, J = 12.1), 4.99−5.07 (bm, 2H), 5.36 (bd, 1H, J = 7.0), 7.17−7.40 (m, 20H); ^{13}C NMR δ 30.1, 41.4, 53.3, 66.2, 70.3, 71.1, 71.4, 73.2, 79.3, 81.0, 127.4, 127.6, 127.7, 127.9, 128.0, 128.1, 128.2, 128.3, 128.8, 136.6, 137.7, 138.2, 138.3, 155.3. Anal. Calcd for $C_{35}H_{37}O_5N$: C, 76.20; H, 6.76; N, 2.54. Found: C, 76.02; H, 6.50; N, 2.50.

(1*R*,2*R*,3*S*,4*R*)-4-Amino-2,3-dihydroxy-1-cyclopentanemethanol (18). To a solution of sodium (160 mg, 7.39 mmol) in 9 mL NH_3 at −78 °C was added the fully protected amino triol **17** (76.4 mg, 0.138 mmol) as a solution in 2.6 mL THF/CH_3OH (20:1). The mixture was stirred at −78 °C for 2 h, at which point the reaction was quenched by the careful addition of NH_4Cl (250 mg). All of the volatiles were allowed to evaporate from the mixture. The resulting white solid was dissolved in water, the pH of the solution was adjusted to 7 with 2 N HCl, and the mixture was applied to a cation exchange column (Bio-Rad AG50W-X8). The column was washed thoroughly with water, and then was eluted with 0.5 N NH_4OH to provide the amine **18** (12.4 mg, 61%) as a colorless oil: $[\alpha]^{23}_D = -10.5$ (*c* 0.62, H_2O) [lit.[26] $[\alpha]^{23}_D = -10.3$ (*c* 1.52, H_2O)]; ^1H NMR (300 MHz, CD_3OD): δ 0.94 (dt, 1H J = 12.7, 8.5), 1.87−2.08 (m, 2H), 3.02 (dt, 1H, J = 7.2, 5.6), 3.21 (quint, 1H, J = 1.6), 3.37 (dd, 1H, J = 7.5, 7.0), 3.44 (dd, 1H, J = 5.9, 1.9), 3.72 (dd, 1H, J = 5.3, 4.1); ^{13}C NMR (75 MHz, CD_3OD): δ 33.1, 46.9, 57.0, 65.0, 74.5, 80.8.

(1*R*,2*R*,3*S*,4*R*)-4-[(Benzyloxy)methyl]-2,3-bis(benzyloxy)cyclopentanecarboxamide (19). To a suspension of ammonium chloride (1.59 g, 29.8 mmol) in 30 mL of benzene at 0 °C was added a 2.0 M solution of trimethylaluminum in toluene (14.9 mL, 29.8 mmol) dropwise. The mixture was warmed to rt and stirred for 2 h, at which point it was transferred to a flask containing the neat ester **16** (3.43 g, 7.74 mmol). After the ester solution was warmed to 50 °C and stirred for 19 h, the mixture was cooled to 0 °C and 2 N HCl (20 mL) was added. The aqueous and organic layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organics were dried (Na_2SO_4), filtered, and concentrated to an off-white solid. Flash column chromatography (hexanes/EtOAc 40:60) afforded the amide **19** (2.79 g, 81%) as a white solid: mp 104−105.7 °C; $[\alpha]^{23}_D = -80.2$ (*c* 1.70, $CHCl_3$); IR (CH_2Cl_2) 3508, 3394, 2986, 1686 cm^{-1}; ^1H NMR δ 1.53−1.88 (m, 1H), 2.05−2.13 (m, 1H), 2.42−2.46 (m, 1H), 3.00 (q, 1H, J = 9.3), 3.27 (t, 1H, J = 9.2), 3.41 (dd, 1H, J = 9.4, 5.2), 3.80−3.86 (m, 2H), 4.36 (d, 1H, J = 11.5), 4.44−4.51 (m, 4H), 4.59 (d, 1H, J = 12.0), 5.65 (bs, 1H), 6.20 (bs, 1H), 7.23−7.35 (m, 15H); ^{13}C NMR δ 25.8, 41.6, 47.2, 70.5, 71.8, 73.1, 78.7, 81.9, 127.6, 127.7, 127.8, 128.2, 128.3, 137.6, 138.1, 138.2, 175.9. Anal. Calcd for $C_{28}H_{31}NO_4$: C, 75.48; H, 7.01; N, 3.14. Found: C, 75.30; H, 6.86; N 3.02.

(1*S*,2*R*,3*R*,5*S*)-5-(*N*-Acetyl aminomethyl)-3-[(benzyloxy)methyl]-1,2-bis(benzyloxy)cyclopentane (20). To a 1.0 M solution of borane−THF (11.2 mL, 11.2 mmol) at 0 °C was added the amide **19** (1.0 g, 2.24 mmol) as a solution in THF (3.5 mL, 2 × 0.75 mL wash). The mixture was slowly warmed to reflux and heating continued for 19 h. After cooling the solution to 0 °C, 3 N HCl (8 mL) was slowly added, and the mixture was stirred for 2 h. The solution was saturated with solid KOH (1.5 g), and the aqueous and organic layers were separated. The aqueous layer was extracted with ether. The combined organics were dried (Na_2SO_4), filtered, and concentrated to provide the amine as a colorless oil, which was used without further purification.

To a solution of the crude amine in 13.4 mL of ether was added triethylamine (0.51 mL, 5.4 mmol), followed by acetic anhydride (1.25 mL, 8.96 mmol). The mixture was stirred at rt overnight and then washed with saturated aqueous $NaHCO_3$. The combined aqueous washes were extracted with CH_2Cl_2, and the combined organics were dried (Na_2SO_4), filtered, and concentrated to a yellow oil. Flash column chromatography (hexanes/EtOAc 30:70) yielded the amide **20** (1.03 g, 97%) as a white solid: mp 56.5−59.5 °C; $[\alpha]^{23}_D = -46.5$ (*c* 0.95, $CHCl_3$); IR (CH_2Cl_2) 3302, 3029, 2860, 1653 cm^{-1}; ^1H NMR δ 0.89−0.97 (m, 1H), 1.78 (s, 3H), 1.96−2.04 (m, 1H), 2.36−2.44 (m, 2H), 2.91−2.97 (m, 1H), 3.23 (t, 1H, J = 7.4), 3.38 (dd, 1H, J = 9.2, 4.9), 3.44 (dd, 1H, J = 9.6, 4.9), 3.54−3.60 (m, 1H), 3.83 (dd, 1H, J = 4.8, 2.1), 4.25 (d, 1H, J = 11.5), 4.44−4.56 (m, 4H), 4.64 (d, 1H, J = 12.1), 6.18 (s, 1H), 7.24−7.37 (m, 15H); ^{13}C NMR δ 23.0, 27.2, 40.4, 41.9, 43.3, 70.4, 71.6, 72.1, 73.1, 78.5, 84.4, 127.6, 127.9, 128.3, 128.4, 137.9, 138.2, 169.9. Anal. Calcd for $C_{30}H_{35}NO_4$: C, 76.08; H, 7.45; N, 2.96. Found: C, 75.98; H, 7.23; N 2.92.

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