An Enantioselective Synthesis of *cis*-4-*tert*-Butoxycarbamoyl-1-methoxycarbonyl-2-cyclopentene—A Useful, General Building Block

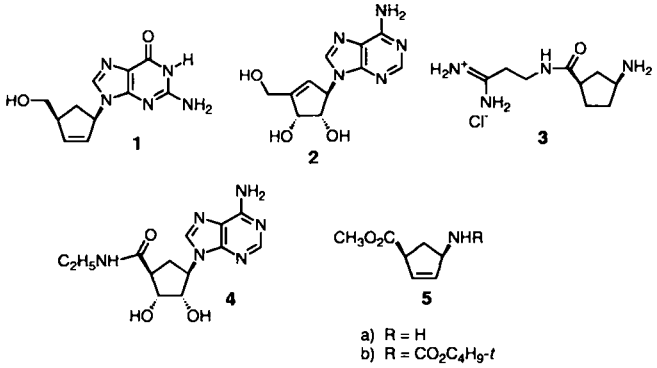
Barry M. Trost,* Dirk Stenkamp, and Shon R. Pulley

Abstract: The amino acid derivative in the title represents an important building block for the synthesis of a number of biologically important targets such as the antiviral carbanucleosides and amidinomycin. By using asymmetric palladium-catalyzed desymmetrization of *meso*-2-ene-1,4-diols, *cis*-1,4-dibenzoyloxy-2-cyclopentene can be converted to the enantiomerically pure title compound in only four steps. Chemoselective ester reduction allows entry into the domain of carbanucleosides, whereas double-bond reduction provides the precursor for amidinomycin. In an ancillary study, a facile diastereoselective *cis*-hydroxylation provides aminocyclopentitols, compounds that have proven to be potent glycosidase inhibitors.

Keywords
allylic substrates · amidinomycin · asymmetric syntheses · carbanucleosides · palladium catalysts

Introduction

Carbocyclic analogues of nucleosides, highlighted by carbovir (**1**)[1, 2] and aristeromycin (**2**)[3] as antiviral agents,[4] have stimulated synthetic efforts for asymmetric syntheses of amino cyclopentyl derivatives.[5] The antiviral agent amidinomycin (**3**)[5g, 6, 7] and the coronary vasodilator C-NECA (**4**)[8] led us to



focus on a simple asymmetric synthesis of *cis*-4-amino-1-methoxycarbonyl-2-cyclopentene (**5a**), which could be a common intermediate towards all of these compounds. In this paper, we report a simple solution to this important problem by effecting an asymmetric synthesis of the Boc derivative **5b**.

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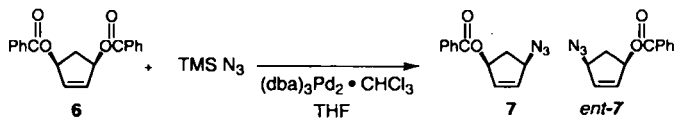
Results and Discussion

Desymmetrization of *meso*-2-cycloalkene-1,4-diols has frequently centered on enzymatic protocols involving either hydrolysis of diesters or acylation of diols.[9] In such cases, the desymmetrization step must be performed as an additional step in a sequence to effect net asymmetric substitution. Our development of asymmetric allylic alkylation provides the opportunity to combine these two events in a single step.[10, 11] The versatility of an azide group and the mild conditions for its conversion to an amine group led us to explore the asymmetric substitution with azide of the dibenzoate of *cis*-cyclopent-2-ene-1,4-diol (**6**) (Scheme 1),[10] which is readily available in two



Scheme 1. dba = dibenzylidene acetone.

steps from cyclopentadiene.[12] Palladium(0)-catalyzed reaction of trimethylsilyl azide in the presence of triphenylphosphine gave the racemic mixture of azides **7** and *ent*-**7**. To develop an analytical protocol to establish the *ee* and sense of chirality, the racemate was reduced to the racemic amine by triphenylphosphine,[13] and the crude amine derivatized with (*S*)-*O*-methylmandelic acid to give diastereomers **8** and **9** in 90% yield (Scheme 2). Based upon the analysis we previously presented,[14] the (1*S*,4*R*) amide **8** has an upfield shift for H_a ($\delta = 6.01$ vs 6.15) and a downfield shift for H_b ($\delta = 2.96$ vs 2.88) as compared to the (1*R*,4*S*) amide **9**. These signals establish the absolute stereochemistry and provide a method to quantify *ee* as well.

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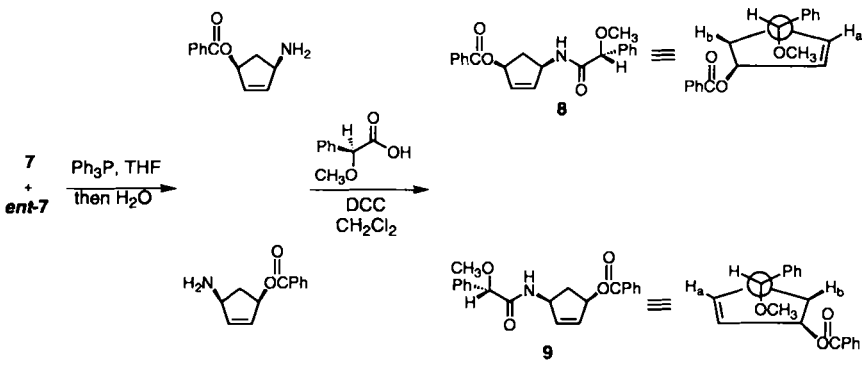
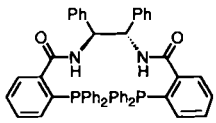


Scheme 2. DCC = 1,3-dicyclohexylcarbodiimide.

When the substitution was performed with the chiral ligand **10**[10] at 0 °C, **7** was obtained in 71% yield at 80–90% *ee*. A decrease in temperature to −20 or −78 °C gave **7** in 68 and 62% (77% based upon recovered starting material) yields, respectively. In both cases, NMR analysis as described above showed only one diastereomer; this indicates that **7** was formed with >98% *ee*.



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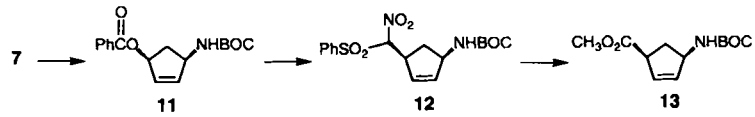
Conversion of **7** to the BOC-protected amine **11** was performed in a single step by reduction with triphenylphosphine in wet THF followed by addition of di-*tert*-butyl dicarbonate and potassium carbonate at room temperature (Scheme 3). The crystalline urethane **11** was obtained in 88% yield.

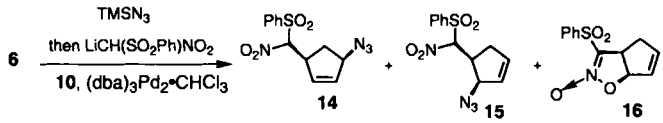
Installation of the methoxycarbonyl group *cis* to the amine requires replacement of the benzoate with retention of configuration. In order to employ palladium-catalyzed allylic alkylations to effect this stereochemical transformation, we utilized phenylsulfonylnitromethane as our surrogate for a methoxycarbonyl group.[2] With 0.5 mol% $(dba)_3Pd_2 \cdot CHCl_3$ and 4 mol% triphenylphosphine, a 96% yield of the alkylation product **12** was obtained as a single regio- and diastereoisomer with respect to the cyclopentene ring, but as a diastereomeric mixture at the sulfone-bearing carbon.

The final step requires an oxidative Nef reaction to give the acylsulfone, which solvolyzes in methanol to the desired ester **13**.[2] Previously, this sequence involved ozonolysis, which fails in this case due to competitive double-bond cleavage. Use of singlet oxygen should avoid this problem but the yield of ester **13** was an unacceptable 17%.[15] Among the oxidants explored, tetra-*n*-butylammonium oxone (TBA oxone)[16] proved most efficacious. Conversion to the nitronate salt with sodium hydride in methanol followed by addition of TBA oxone buffered with cesium carbonate at room temperature gave a 45% yield of ester **13**. Use of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) instead of sodium hydride gave a somewhat cleaner product in 47% yield, and this proved to be the method of choice.



Scheme 3. BOC = *tert*-butoxycarbonyl.

Since both benzoates are ultimately replaced in the palladium-catalyzed substitutions, a one-pot introduction of both the nitrogen and carbon nucleophiles was envisioned (Scheme 4).



Scheme 4.

Since reaction of the dibenzoate with phenylsulfonylnitromethane leads directly to double alkylation with formation of isoxazoline *N*-oxides (e.g., **16**),[2] the sequence requires introduction of the nitrogen nucleophile before the carbon nucleophile. Sequential addition of trimethylsilylazide (at −78 °C to RT) and lithiophenylsulfonylnitromethane (at RT) in the presence of chiral ligand **10** with a palladium(0) source gave a mixture of the desired doubly alkylated product **14**, as well as **15** and **16**. Allylic azides are known to undergo thermal [3,3] sigmatropic rearrangements,[17] but neither isomerization to **15** nor elimination to **16** occurred when **14** was heated to 50 °C. On the other hand, subjecting **14** to $(dba)_3Pd_2 \cdot CHCl_3$ and triphenylphosphine induced its conversion to both **15** and **16**. This observation strongly suggests that azide serves as a leaving group in Pd^0-catalyzed reactions, in which addition of the eliminated N_3^- to regenerate **14** or its allylic isomer **15** competes with formation of the nitronate anion, which cyclizes to **16**. Since both **15** and **16** begin to form before all of dibenzoate **6** is consumed, azide appears to be only somewhat less active as a leaving group at

Editorial Board Member:[*] *Born in Philadelphia, Pennsylvania, in 1941, where he obtained his BA (1962) at the University of Pennsylvania, Barry M. Trost completed his Ph.D. degree in Chemistry at the Massachusetts Institute of Technology in 1965 under Professor Herbert O. House. He moved immediately to the University of Wisconsin where he was promoted to Professor of Chemistry in 1969 and subsequently became Vilas Research Professor in 1982. He joined the faculty at Stanford as Professor of Chemistry in 1987 and became Tamaki Professor of Humanities and Sciences in 1990. In addition, he has been visiting professor in Germany (Universities of Marburg, Hamburg, Munich), France (Universities of Paris VI and Paris South), Italy (University of Pisa), Denmark (University of Copenhagen), and Spain (University of Barcelona). In 1994 he was presented with an honorary doctorate from the Université Claude-Bernard (Lyon I), France. He has received numerous awards for both teaching and research, the most recent being the Roger Adams Award from the ACS (1995), and was elected a member of the U. S. National Academy of Sciences (1980) and a fellow of the American Academy of Sciences (1982).*

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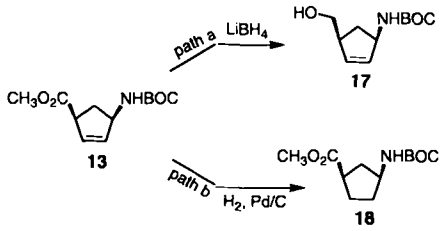
room temperature than benzoate. Because room temperature is required for the second alkylation, this one-pot sequence is not a viable alternative to the two-step process.

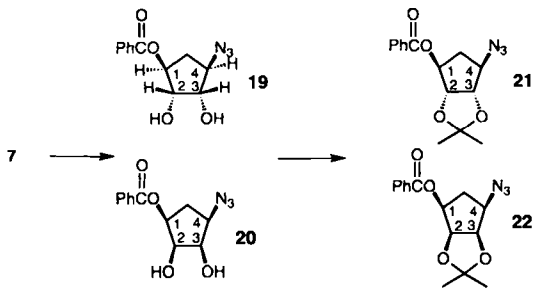
With some of our targets in mind, we explored some simple transformations. Chemoselective reduction of the ester to generate the carbovir precursor **17** occurred in 73% yield with lithium borohydride (Scheme 5).[18] Catalytic hydrogenation generated the amidinomycin precursor **18** in 90% yield.



Scheme 5.

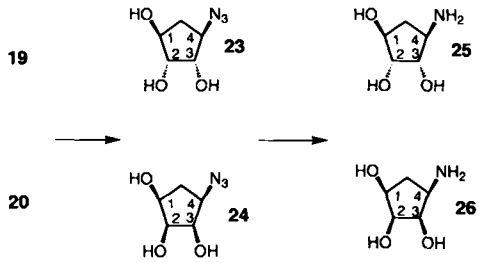
For a number of applications, dihydroxylation of the double bond is an important transformation. Besides carbanucleosides, a number of potent inhibitors of glycoside-processing enzymes are polyhydroxylated cyclopentanes. Dihydroxylation of cyclopentenes with osmium tetroxide has led to mixed results in terms of diastereoselectivity.[2, 19] Exposing **7** to catalytic dihydroxylation with osmium tetroxide and NMO (4-methylmorpholine *N*-oxide) under typical conditions in aqueous THF gave a mixture of the diols **19**/**20** in an 8:1 ratio, from which the major isomer was isolated upon simple column chromatography, but only in 35% yield. Remarkably, the reaction time of 24 h could be dramatically shortened to 0.5 h, the ratio increased to 15:1, and the yield increased to 70% by performing the reaction in moist methylene chloride with NMO hydrate. We have found that use of methylene chloride containing a small amount of water generally significantly increases the rate, and frequently the yield, of this dihydroxylation.[20]

To aid in the assignment of stereochemistry, a number of derivatives were made. Thus, the major diol (**19** or **20**) was converted to the corresponding acetonide (**21** or **22**, Scheme 6),



Scheme 6.

to rigidify the ring by making it bicyclic. Hydrolysis of the major diol (**19** or **20**) to the polyol (**23** or **24**) and catalytic hydrogenation to the amine (**25** or **26**) provided the types of substitution desired for glycosidase inhibitors (Scheme 7). Table 1 summarizes the observed coupling constants $J(1,2)$ and $J(3,4)$ for these compounds. Molecular mechanics calculations for **23** indicate that $J(1,2)$ should be 2–4 Hz (dihedral angle of 122°) and $J(3,4)$ should be 0.5–1.5 Hz (dihedral angle of 109°). The same calculations for **24** suggest that $J(1,2)$ should be 8–14 Hz (dihedral angle of 2°) and $J(3,4)$ should be 5–10 Hz (dihedral angle of 36°). The observed coupling constants (Table 1, entry 3) are best in accord with the *trans*-hydroxylation stereochemistry, that is, **23**. On this basis, the major stereoisomers can be assigned the structures **19**, **21**, and **25**.



Scheme 7.

Table 1. Observed coupling constants for the dihydroxylated products.

Entry	Compound	$J(1,2)$/Hz	$J(3,4)$/Hz
1	**19** or **20**	3.9	4.0
2	**21** or **22**	<1	<1
3	**23** or **24**	4.7	<1
4	**25** or **26**	3.4	6.7

Conclusion

This method constitutes a convenient synthesis of an important building block, which delivers the *cis* amino ester **13** of >98% *ee* in four steps and 31% overall yield from the symmetric ester **6**. This synthesis compares quite favorably to all the other enantioselective syntheses reported to date. Since we have shown that the catalysts used apply equally well to five-, six-, and seven-membered rings,[21] similarly substituted compounds should be available in all of these ring sizes. This application highlights the utility of asymmetric palladium-catalyzed desymmetrization of *meso*-2-ene-1,4-diols.

Experimental Section

General: All manipulations of compounds and solvents were carried out under a nitrogen atmosphere. All glassware was flame-dried and purged with nitrogen prior to use. Solvents, tetrahydrofuran (THF), dichloromethane, and methanol were degassed and purified by distillation under nitrogen from standard drying agents. NMR spectra were recorded on Varian Gemini 200, 300, and 400 MHz NMR spectrometers. Chemical shifts are reported in ppm vs. tetramethylsilane, and the $CDCl_3$ resonance in ^{13}C NMR spectra is assigned to be at $\delta = 77.23$. Infrared spectra were recorded on a Nicolet 205 FTIR spectrophotometer. Optical rotations were determined on a JASCO DIP-360 in 50 mm cells. Column chromatography was performed with ICN 32-63 mm, 60 A silica gel with flash-column techniques. Elemental analyses were obtained from M-H-W Laboratories, Phoenix, AZ. High resolution mass spectra (HRMS) were obtained from the Mass Spectrometry Resource, School of Pharmacy, University of California-San Francisco, on a Kratos MS9. Melting points were determined on a Thomas-Hoover melting-point apparatus in open capillaries and are uncorrected. $Pd_2(dba)_3 \cdot CHCl_3$ [22], $Pd(PPh_3)_2Cl_2$ [23], (+)-(1*S*,2*S*)-bis[2-(diphenylphosphino)benzamido]-1,2-diphenylethane, (phenylsulfonyl)nitromethane [24], and TBA oxone [16] were prepared by literature procedures. Trimethylsilyl azide [25] was purchased from Petrarch System and distilled (b.p. 95–99 °C) prior to use.

Preparation of (1*S*,4*R*)-4-azido-1-benzoyloxycyclopent-2-ene (7): A solution of $Pd_2(dba)_3 \cdot CHCl_3$ (16.8 mg, 0.016 mmol) and (+)-**10** (51.2 mg, 0.065 mmol) in THF (4 mL), which had been stirred for 15 min at RT and cooled to −78 °C, was added through a cannula to a solution of (1*S**,4*R**)-1,4-di(benzyloxy)cyclopent-2-ene (**6**) [10] (500 mg, 1.62 mmol) in THF (4 mL), precooled to −78 °C. Trimethylsilyl azide (0.22 mL, 1.62 mmol) was added at once. When the reaction had gone to completion (1.5 h), the organic layer was washed with saturated $NaHCO_3$

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(2 × 20 mL), brine (10 mL), and dried over $MgSO_4$. The solvent was removed in vacuo to produce a yellow oil (560 mg). Purification by flash chromatography (silica gel, 2.2 × 19 cm, 10% EtOAc/hexane) afforded 229.2 mg (62%, 77% including recovered starting material) as a colorless oil, $R_f = 0.28$ in 10% EtOAc/hexane; $[\alpha]_D^{25} = +50.3$ ($c = 2.8$, CH_2Cl_2). IR (neat): $\tilde{\nu} = 3075, 2955, 2097, 1718, 1599, 1450, 1265, 1106\ cm^{-1}$. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.07$ (d, $J = 7$, 2H), 7.57 (t, $J = 7.5$ Hz, 1H), 7.45 (t, $J = 7.6$ Hz, 2H), 6.26 (m, 1H), 6.11 (m, 1H), 5.86 (m, 1H), 4.28 (m, 1H), 2.9 (dt, $J = 15$, 7.5 Hz, 1H), 2.0 (dt, $J = 15$, 3.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 166.2, 134.4, 134.3, 133.1, 129.9, 129.7, 128.4, 77.1, 64.4, 36.9$. Anal. calcd for $C_{12}H_{11}N_3O_2$: C, 62.86; H, 4.84; N, 18.34. Found: C, 62.63; H, 5.00; N, 18.29.

Preparation of (1*S*,4*R*)-1-benzoyloxy-4-*tert*-butyloxycarbamoylcyclopent-2-ene (11): To a solution of **7** (600 mg, 2.62 mmol) in THF (8.8 mL) and water (0.55 mL) was added triphenylphosphine (894 mg, 3.41 mmol) at RT. After 14 h, di-*tert*-butyl dicarbonate (858 mg, 3.93 mmol), potassium carbonate (724 mg, 5.24 mmol), and water (3 mL) were added to form a milky solution, which was stirred for 24 h. The mixture was diluted with ether. The organic layer washed with saturated $NaHCO_3$ (20 mL) and brine (20 mL), and dried over $MgSO_4$. The solvent was removed in vacuo to produce a white solid (1.9 g). Purification by flash chromatography (silica gel, 2.5 × 20 cm, 10% EtOAc/hexane) gave 697 mg (88%) of the product as a white solid, $R_f = 0.29$ in 20% EtOAc/hexane; m.p. = 118–119 °C; $[\alpha]_D^{25} = -100.7$ ($c = 5.41$, CH_2Cl_2). IR (neat): $\tilde{\nu} = 3360, 2978, 1712, 1518, 1367, 1270, 1173, 1113, 1070\ cm^{-1}$. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.03$ (d, $J = 7.1$ Hz, 2H), 7.57 (appt, $J = 7.3$, 1H), 7.44 (appt, $J = 7.8$ Hz, 2H), 6.06 (brs, 2H), 5.78 (m, 1H), 4.71 (m, 2H), 2.95 (dt, $J = 14.8$, 7.41 Hz, 1H), 1.68 (dt, $J = 14.6$, 4.3 Hz, 1H), 1.46 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 166.33, 155.19, 137.34, 133.22, 132.35, 130.34, 129.78, 128.55, 79.81, 78.30, 54.63, 39.04$. Anal. calcd for $C_{17}H_{21}NO_4$: C, 67.29; H, 6.98; N, 4.62. Found: C, 67.08; H, 6.76; N, 4.57.

Preparation of (1*S*,4*R*)-4-*tert*-butoxycarbamoyl-1-[nitro(phenylsulfonyl)methyl]cyclopent-2-ene (12): To a solution of **11** (289 mg, 0.95 mmol) and the lithium salt of (phenylsulfonyl)nitromethane (257 mg, 1.24 mmol) in degassed THF (5 mL) was added, through a cannula, a prestirred (30 min) solution of $Pd_2(dba)_3 \cdot CHCl_3$ (4.9 mg, 4.7 μmol, 0.5 mol%) and triphenylphosphine (10 mg, 0.038 mmol, 4 mol%) in THF (0.5 mL) at RT. After 30 min, a white precipitate formed, and the solution changed from orange to yellow. The reaction was complete after 2 h. The organic layer was washed with saturated NH_4Cl (10 mL), saturated $NaHCO_3$ (10 mL), brine (10 mL), and dried with $MgSO_4$. The solvent was removed in vacuo to give a yellow oil (401 mg). Purification by flash chromatography (silica gel, 2 × 20 cm, 20% EtOAc/hexane) afforded 348 mg (96%) as a colorless oil, consisting of a 1:1 mixture of side-chain diastereomers. $R_f = 0.17$ in 20% EtOAc/hexane. IR (neat): $\tilde{\nu} = 3409, 3336, 2977, 1689, 1556, 1510, 1450, 1337, 1244, 1158\ cm^{-1}$. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.92$ (m, 4H), 7.78 (m, 2H), 7.63 (m, 4H), 6.11 (brd, $J = 5.5$ Hz, 1H), 5.94 (dt, $J = 5.7$, 2.7 Hz, 1H), 5.89 (dt, $J = 5.7$, 2.2 Hz, 1H), 5.61 (d, $J = 9$ Hz, 1H), 5.52 (m, 2H), 4.87–4.7 (m, 4H), 3.58–3.46 (m, 2H), 2.79 (dt, $J = 14.2$, 8.2 Hz, 1H), 2.58 (dt, $J = 14.0$, 8.2 Hz, 1H), 1.77 (dt, $J = 14.1$, 6.5 Hz, 1H), 1.6–1.5 (m, 1H), 1.44 (s, 9H), 1.42 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 155.16, 137.04, 136.91, 135.80, 134.49, 130.22, 130.08, 129.78, 129.65, 104.80, 104.61, 79.93, 56.49, 55.50, 44.14, 43.92, 35.35, 34.91, 28.52$. HRMS calcd for $C_{13}H_{13}N_2O_6S$ ($M^+ - C_4H_9$): 325.0494. Found: 325.0493.

Preparation of (1*S*,4*R*)-4-*tert*-butoxycarbamoyl-1-methoxycarbonylcyclopent-2-ene (13): Cyclopentene **12** (36.3 mg, 0.094 mmol) was dissolved in anhydrous methanol (0.75 mL) to which DBU (13.5 μL, 0.09 mmol) was added at RT. After 30 min, TBA oxone (513 mg, 51% active reagent as determined by titration, ca. 0.74 mmol) and cesium carbonate (239.8 mg, 0.74 mmol) in dichloromethane (0.75 mL) were added, and the heterogenous solution sonicated for 4 h and then stirred for 40 h at RT. The mixture was diluted with ether, and the organic layer washed with saturated NH_4Cl (10 mL), and brine (10 mL), and dried over $MgSO_4$. The solvent was removed in vacuo to give a yellow oil. Purification by flash chromatography (silica gel, 1 × 20 cm, 20% EOAc/hexane) afforded 10.7 mg (47% of product) as a colorless oil. ($R_f = 0.42$ in 30% EtOAc/hexane), $[\alpha]_D^{25} = -53.2$ ($c = 4.75$, $CHCl_3$). IR (neat): $\tilde{\nu} = 3363, 2976, 1730, 1713, 1507, 1366, 1243, 1162\ cm^{-1}$. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 5.9-5.84$ (m, 2H), 4.8 (m, 2H), 3.72 (s, 3H), 3.48 (dd, $J = 8.64$, 4.38, 1H), 2.51 (dt, $J = 14.0$, 8.5 Hz, 1H), 1.86 (dt, $J = 14.0$, 4.1 Hz, 1H), 1.45 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 175.13, 155.34, 135.07, 131.32, 79.50, 56.00, 52.36, 49.38, 34.78, 28.62$. HRMS: calcd for $C_8H_{11}NO_4$ ($M^+ - C_4H_9$): 185.0688. Found: 185.0687. Anal. calcd for $C_{12}H_{19}NO_4$: C, 59.72; H, 7.94; N, 5.81. Found: C, 59.03; H, 7.51; N, 5.45.

Preparation of (1*S*,4*R*)-4-*tert*-butoxycarbamoyl-1-hydroxymethylcyclopent-2-ene (17): To a solution of **13** (9.4 mg, 0.039 mmol) in ether (0.2 mL) was added a solution of 95% lithium borohydride (1.1 mg, 0.049 mmol) in ether (0.2 mL) at RT. After completion of the reaction (2 h), the mixture was diluted with ether, and the organic layer washed with saturated NH_4Cl (5 mL) and brine (5 mL), and dried over $MgSO_4$. The solvent was removed in vacuo to give a yellow oil. Purification by flash chromatography (silica gel, pasteur pipette, 50% EtOAc/hexane) afforded 6.1 mg (73%) as a colorless oil, $R_f = 0.31$ in 50% EtOAc/hexane: $[\alpha]_D^{25} = 19.0$ ($c = 1.39$, chloroform). IR (neat): $\tilde{\nu} = 3336, 2977, 1682, 1516, 1364, 1251, 1171, 1038\ cm^{-1}$. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 5.82$ (d, $J = 5.5$ Hz, 1H), 5.77 (d, $J = 5.5$ Hz, 1H), 4.89 (brs, 1H), 4.7 (brs, 1H), 3.66 (dd, $J = 4.0$, 10.3 Hz, 1H), 3.57 (brd, $J = 10$ Hz, 1H), 2.83 (m, 1H), 2.5 (dt, $J = 3.7$, 13.7 Hz, 1H), 1.44 (s, 9H), 1.44–1.41 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 155.47, 134.32, 134.07, 79.39, 65.23, 56.11, 47.06, 34.80, 28.65$. HRMS: calcd for $C_7H_{11}NO_3$ ($M^+ - C_4H_8$): 157.0739. Found: 157.0739. Anal. calcd for $C_{11}H_{19}NO_3$: C, 61.93; H, 8.98; N, 6.57. Found: C, 61.90; H, 9.08, N, 6.43.

Preparation of (1*S*,4*R*)-4-*tert*-butoxycarbamoyl-1-methoxycarbonylcyclopentane (18): A suspension of 10% Pd/C (4.6 mg) in a solution of **13** (10.5 mg, 43.5 mmol) in methanol (0.5 mL) was stirred for 3 h under a hydrogen atmosphere (1 bar). The mixture was filtered through Celite, and silica-gel chromatography (pasteur pipette) afforded 9.5 mg (90%) of **18** as a colorless oil, $R_f = 0.42$ in 30% EtOAc/hexane; $[\alpha]_D^{25} = -2.7$ ($c = 2.7$, chloroform). IR (neat): $\tilde{\nu} = 3375, 2970, 1710, 1519, 1370, 1251, 1174, 1031\ cm^{-1}$. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 4.97$ (brs, 1H), 4.06 (brs, 1H), 3.69 (s, 3H), 2.84 (m, 1H), 2.21 (ddd, $J = 7.4$, 8.8, 15.9 Hz, 1H), 1.92 (m, 3H), 1.73 (m, 2H), 1.44 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 177.59, 155.60, 79.30, 52.23, 52.13, 41.98, 36.63, 33.41, 28.64, 28.22$. HRMS: calcd for $C_8H_{13}NO_4$ ($M^+ - C_4H_8$): 187.0845. Found: 187.0843.

Preparation of (1*S*,2*R,3*R**,4*R*)-4-azido-1-benzoyloxycyclopentane-2,3-diol (19)**: To a solution of **7** (92 mg, 0.402 mmol) in methylene chloride (1 mL) and water (43 μL) was added NMO (141.2 mg, 1.205 mmol) and osmium tetroxide (3.1 mg, 12 μmol) at RT. The solution changed from colorless to bright yellow. The mixture was stirred for 30 min; sodium bisulfite was added, and after 15 min silica gel was added. The solvent was removed in vacuo to give a 15:1 mixture of diastereomers. Purification by flash chromatography (silica gel, 1 × 20 cm, 50% EtOAc/hexane) and by treatment with charcoal afforded 83 mg (79%) of a ca. 20:1 mixture of **19**:**20**. IR (neat): $\tilde{\nu} = 3417, 2937, 2105, 1748, 1452, 1273\ cm^{-1}$. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.03$ (d, $J = 7.1$ Hz, 2H), 7.64–7.44 (m, 3H), 5.11 (ddd, $J = 8.6$, 4.7, 3.9 Hz, 1H), 4.24 (dd, $J = 4.9$, 3.9 Hz, 1H), 4.12 (dd, $J = 4.9$, 4.0 Hz, 1H), 4.00 (ddd, $J = 7.1$, 5.0, 4.0 Hz, 1H), 3.77 (s, 1H, OH), 2.98 (s, 1H, OH), 2.82 (ddd, $J = 15.0$, 8.6, 7.1 Hz, 1H), 1.96 (dt, $J = 15.0$, 4.7, 5.0 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 167.54, 133.76, 129.92, 129.37, 128.69, 79.72, 76.72, 76.63, 64.25, 33.24$. HRMS: calcd for $C_{10}H_{11}N_3O_3$ ($M^+ - C_2H_2O$): 221.0800. Found: 221.0809.

Preparation of (1*R*,5*R,6*R**,8*S*)-6-azido-8-benzoyloxy-3,3-dimethyl-2,4-dioxabicyclo[3.3.0]octane (21)**: To a solution of **19** (32.1 mg, 0.122 mmol) in acetone (1 mL) was added TsOH (2.4 mg, 0.0122 mmol) and 2,2-dimethoxypropane (0.15 mL, 1.22 mmol). After 6 h at RT, the solution was diluted with ether, filtered through a Celite pad, washed with saturated $NaHCO_3$ (2 × 20 mL) and brine (1 × 10 mL), and dried over $MgSO_4$. The solvent was removed in vacuo to furnish a yellow oil. Purification by flash chromatography (silica gel, 2 × 9 cm, 5% ether/hexane and then 10% EtOAc/hexane) afforded a light yellow oil (36 mg, 97%), $R_f = 0.75$ in 50% EtOAc/hexane. IR (neat): $\tilde{\nu} = 2994, 2941, 2113, 1726, 1267, 1213, 1118, 1041, 713\ cm^{-1}$. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.06$ (d, $J = 7.1$ Hz, 2H), 7.58 (m, 1H), 7.45 (m, 2H), 5.36 (d, $J = 5.0$ Hz, 1H), 4.74 (dd, $J = 5.6$, 1.3 Hz, 1H), 4.6 (d, $J = 5.5$ Hz, 1H), 4.17 (d, $J = 5.6$ Hz, 1H), 2.51 (dt, $J = 15.5$ Hz, 5.6, 1H), 2.18 (dt, $J = 15.4$, 1.4 Hz, 1H), 1.47 (s, 3H), 1.31 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 165.57, 133.18, 129.65, 128.39, 111.20, 84.53, 84.36, 78.86, 65.48, 32.94, 26.22, 23.88$. HRMS: calcd for $C_{14}H_{14}N_3O_4$ ($M^+ - CH_3$): 288.0984. Found: 288.0975.

Preparation of (1*S*,2*S,3*R**,4*R*)-4-azido-cyclopentane-1,2,3-triol (23)**: To a solution of **19** (81 mg, 0.307 mmol) in methanol (0.9 mL) and THF (0.6 mL) was added potassium carbonate (8.5 mg, 0.062 mmol) at RT. The milky mixture was stirred for 3 h, silica gel added, and the solvent removed in vacuo. Purification by flash chromatography (silica gel, 1 × 15 cm, EtOAc) afforded 27.3 mg (56%) of **23**, $R_f = 0.26$ in EtOAc; $[\alpha]_D^{25} = -45.5$ ($c = 2.76$, ethanol). ^1H NMR (400 MHz, [D$_6$]acetone/D_2O): $\delta = 3.98$ (dd, $J = 6.6$, 4.8 Hz, 1H), 3.95 (ddd, $J = 7.2$, 4.6, 2.7 Hz, 1H), 3.76 (dd, $J = 4.7$, 2.7 Hz, 1H), 3.73 (dd, $J = 8.9$, 7.2 Hz, 1H), 3.53 (d, $J = 6.6$ Hz, 1H, OH), 3.51 (s, 1H, OH), 2.45 (ddd, $J = 14$, 8.9, 7.2 Hz, 1H), 1.36 (dddd, $J = 14$, 7.2, 4.6, 0.9 Hz, 1H). ^{13}C NMR (100 MHz, [D$_6$]acetone): $\delta = 78.29, 77.41, 74.80, 65.48, 36.40$. HRMS: calcd for $C_5H_9N_3O_3$: 159.0645. Found: 159.0649.

Preparation of (1*S*,2*S,3*R**,4*R*)-4-amino-cyclopentane-1,2,3-triol (25)**: A mixture of **19** (25.1 mg, 0.1577 mmol) in methanol (0.5 mL) and 10% Pd/C (16.8 mg) was stirred for 15 h under a hydrogen atmosphere (1 bar). The mixture was filtered through Celite. Ultrafiltration and concentration of the solution afforded 21 mg (100%) of **25** as a light yellow oil. $[\alpha]_D^{25} = -16.2$ ($c = 2.24$, methanol). IR (neat): $\tilde{\nu} = 3349, 2931, 1582, 1450, 1118, 1052\ cm^{-1}$. ^1H NMR (400 MHz, CD_3OD): $\delta = 3.93$ (ddd, $J = 7.3$, 6.0, 3.4, 1H), 3.78 (dd, $J = 5.4$, 3.3 Hz, 1H), 3.69 (dd, $J = 6.8$, 5.4 Hz, 1H), 3.09 (ddd, $J = 8.4$, 8.3, 6.7 Hz, 1H), 2.41 (ddd, $J = 13.6$, 8.2, 7.4 Hz, 1H), 1.22 (dddd, $J = 13.6$, 8.5, 5.9, 0.6 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD): $\delta = 79.80, 78.98, 76.14, 56.33, 39.06$. HRMS: calcd for $C_5H_{10}NO_2$ [$M^+ - OH$]: 116.0711. Found: 116.0711.

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