Synthesis of (+)-Neplanocin A from a Chromium−Carbene Complex-Derived Optically Active Butenolide

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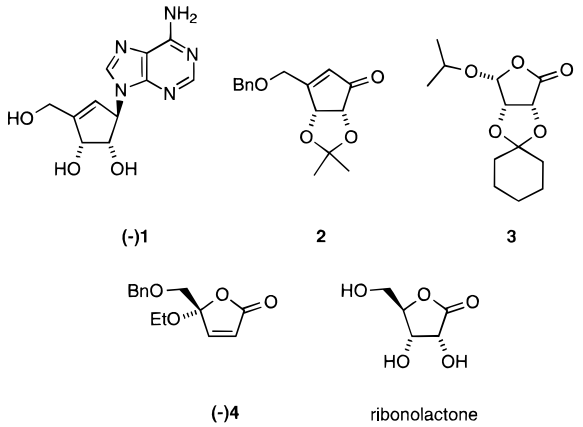
Introduction

(−)-Neplanocin A (**1**)[1] is a cyclopentenyl analogue of adenosine with potent antitumor and antiviral activity and is a powerful inhibitor of *S*-adenosylhomocysteine hydrolase.[2] A number of asymmetric syntheses of neplanocin A have been reported.[3] Several rely on chemoenzymic processes to provide optically active intermediates,[4] while others start with optically active materials from the "chiral pool" such as D-ribonolactone,[5] D-ribose,[6] or L-tartaric acid.[7] Optically active cyclopentenone **2** is a key intermediate in the synthesis of a number of carbocyclic nucleosides, in addition to neplanocin A.[3] It has been synthesized from ribonolactone by ring opening of the lactone with the lithium anion of dimethyl methylphosphonate, followed by oxidation of the released γ-hydroxy group and Wadsworth−Emmons cyclization onto the thus-formed ketone.[5] With ribonolactone, this multistep process suffered from modest yields and partial racemization. However, with simpler lactones (e.g., **3**) having an alkoxide leaving group geminal to the lactone ring oxygen, this ring opening/cyclization occurred in a one-pot, cascade process without detectable racemization, providing an efficient approach to neplanocin analogues.[8]

Recently, an efficient synthesis of optically active butenolide **4**, a potential precursor to nucleoside analogues, has been reported from these laboratories.[9] Both enantiomers are equally available in enantiomerically pure form in overall ≈60% yield (from chromium hexacarbonyl and α-benzyloxymethyl acetyl chloride), by starting with the appropriate enantiomer of the phenyl glycine-derived chiral auxiliary.[10] Butenolide **4** has structural features (the double bond that might be cis hydroxylated and a leaving group geminal to the ring oxygen) that make it an attractive precursor to neplanocin A, utilizing the above phosphonate anion/intramolecular ylide process. Studies to convert **4** to neplanocin A are described below.



Results and Discussion

cis-Hydroxylation of (±)-**4** with potassium permanganate/dicyclohexano-18-crown-6 produced a single cis diol in 72% yield at 70% conversion (50% isolated yield of **5**). The use of sodium periodate in the presence of a catalytic amount of ruthenium(III) chloride[11] produced a 3:1 mixture of cis diols in overall 65% yield, at 80% conversion (40% and 12% isolated yields of diastereomers of **5**, respectively). The major diol from the periodate oxidation corresponded to the product from the permanganate oxidation (Scheme 1). Attempts to establish the stereochemistry of these diols using NOESY measurements failed, as is often the case in five-membered ring systems. COSY established that the proton β to the carbonyl group for the *major* diastereomer appeared at δ 4.6 while the α proton appeared at δ 4.31. The situation was reversed for the minor isomer, with the β proton appearing at δ 4.32 and the α proton at δ 4.62. The β proton of *both* isomers showed a substantial NOE interaction with the CH_2OBn group, making stereochemical assignments impossible.

The major isomer was thought to be that from attack of the α face of the butenolide, resulting in the stereoisomer required for conversion to neplanocin A, on the basis of previous studies with simpler analogues.[12] However when the cis diol from (−)-**4** was carried through the synthetic sequence in Scheme 1, (+)-*neplanocin A* was produced rather than the expected (−) enantiomer. Since

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(10) The chiral ene carbamate was made in one step and 78% yield from phenyl glycinol and (ethoxy)(methyl)carbene chromium pentacarbonyl. The chiral oxazolidinone auxiliary was recovered in >80% yield in the elimination step generating enone **4**. Miller, M.; Hegedus, L. S. *J. Org. Chem.* **1993**, *58*, 6779.

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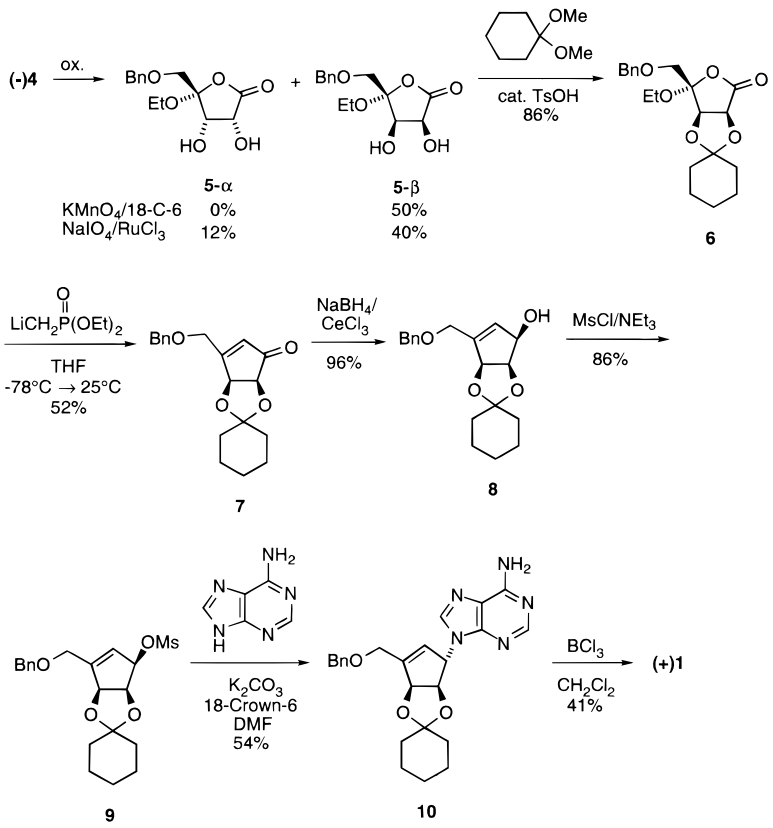
Scheme 1



it is the cis-hydroxylation step that sets all of the stereo centers, the major diol resulted from cis-hydroxylation of the β-face of the butenolide, the face opposite the alkoxy group. To confirm that the major diol was indeed **5**-β and not **5**-α, it was converted to its acetonide, which had an $[\alpha]_D$ of +8° (c = 0.06, $CHCl_3$), in comparison to the reported $[\alpha]_D$ of −7.2° (c = 1.1, $CHCl_3$) reported for the α-isomer.[5] (−)-Neplanocin A should be available by the same chemistry by starting with the (+) enantiomer of **4**, which is readily available from *S*-phenyl glycine.[10]

The synthesis of (+)-neplanocin A from (−)-**4** is outlined in Scheme 1. cis-Hydroxylation of (−)-**4** ($KMnO_4$/dicyclohexano-18-crown-6) proceeded in only 50% yield, somewhat lower than that observed with the model butenolide (having a butyl group in place of the benzyloxymethyl group).[12] In this case, the formation of diol **5**-β is in competition with the decomposition of both butenolide **4** and diol **5**-β under the reaction conditions. The reaction was monitored and quenched when the undesired side products began to form, making it possible to recycle **4**. Care was also required to prevent hydrolysis of the lactone during the acid hydrolysis of the manganate ester.

For synthetic purposes, protection as the cyclohexanone ketal **6** was more efficient than conversion to the acetonide. Treatment of **6** with the lithium salt of dimethyl methylphosphonate produced cyclopentenone **7** in good yield in the one-pot lactone ring-opening, intramolecular Wadsworth−Emmons process. This step was quite sensitive to reaction conditions. It was critical that the phosphonate anion be completely consumed in the ring lactone-opening step prior to formation of any of the enone **7**, since this compound can also react with the phosphonate anion. Reduction of ketone **7** with $NaBH_4/CeCl_3$[5] occurred exclusively from the face opposite the protected diol, giving **8** in virtually quantitative yield.

A number of approaches for the direct introduction of adenine into allylic alcohols such as **8** have been reported. Mitsunobu coupling[4c] seemed the most direct approach. However, at room temperature in THF, no reaction occurred, perhaps because of the very low solubility of adenine in the reaction medium. Heating to 100 °C in a pressure tube resulted in extensive decomposition.

Similarly, conversion of alcohol **8** to the tosylate[6] met with limited success because of difficulty in the separation from excess tosyl chloride and the intolerance of the next step to tosyl chloride. In contrast, mesylation of **8**[13] proceeded in excellent yield without complications. Coupling of **9** (adenine/K_2CO_3/18-crown-6)[13] took place in 54% yield accompanied by small amounts (~4%) of the N-7 isomer, results comparable to other reported direct couplings with adenine.[5,9b] Removal of the two protecting groups in a single step with BCl_3[5] in 41% yield completed this synthesis of (+)-neplanocin A. The natural enantiomer should be available by this same route from (+)-**4**. Since cyclopentenone **7** has served as the key intermediate in the synthesis of a number of carbocyclic nucleoside analogues,[3] its asymmetric synthesis by this route may streamline syntheses of these compounds as well.

Experimental Section

General Methods. THF was distilled from sodium−benzophenone ketyl, and CH_2Cl_2, DMF, and Et_3N were distilled from CaH_2. Commercially available reagents were used as received except as indicated, and the dimethyl methylphosphonate was stored in a desiccator. ^1H NMR, NOE, COSY (300 MHz), ^{13}C

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NMR (75 MHz), and HSQC (400 ^{1}H MHz) spectra were recorded in $CDCl_3$ unless otherwise noted, and chemical shifts are given in ppm relative to $CDCl_3$ (7.24 ppm). Column chromatography was performed with ICN 32−66 nm, 60 Å silica gel using flash column techniques. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ. FAB−High-Resolution Mass Spectrometry (HRMS) was obtained with a Fisons VG AutoSpec mass spectrometer with a Cs ion gun, *m*-nitrobenzyl alcohol was used for the matrix, and the resolution was set to 10,000. All reactions were performed in flame-dried glassware under an atmosphere of Ar unless otherwise noted.

(3*S*,4*R*,5*R*)-5-Benzyloxymethyl-5-ethoxy-3,4-dihydroxy-dihydro-furan-2-one (5-*β*). (−)-5-Benzyloxymethyl-5-ethoxy-5*H*-furan-2-one (**4**)[9] (0.900 g, 3.62 mmol) was dissolved in 30 mL of CH_2Cl_2, and *cis*-dicyclohexano-18-crown-6 (0.135 g, 0.362 mmol) was added. The solution was cooled to −40 °C in a dry ice/acetonitrile bath, and $KMnO_4$ (0.744 g, 4.71 mmol) was added in five portions over 45 min. The mixture was stirred at −40 °C until side products were visible (ca. 2−3 h) by TLC (silica gel, hex/ETOAc, 3:1). Solid $NaHSO_3$, H_2O, and two drops of 1 M H_2SO_4 were added, and the mixture was transferred to a separatory funnel. The mixture was shaken vigorously and additional solid $NaHSO_3$ was added until the solution decolorized upon shaking. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude yellow oil was purified by flash column chromatography (5:1 → 3:1 hex/Et_2O → 100% Et_2O gradient elution) to yield diol **5**-*β* as a clear oil (0.514 g, 1.82 mmol, 50%) and recovered butenolide **4** (0.256 g). **5-*β***: $[\alpha]^{25}_D$ −17° (*c* = 1.83, EtOH); ^{1}H NMR *δ* 7.35 (m, 5H), 4.63 (m, 1H), 4.60 (s, 2H), 4.29 (dd, *J* = 2.7 Hz, *J* = 4.8 Hz, 2H), 3.87 (d, *J* = 11.1 Hz, 1H), 3.75 (d, *J* = 10.8 Hz, 1H), 3.63 (q, *J* = 7.1 Hz, 2H), 2.93 (m, 2H), 1.15 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR *δ* 175.4, 136.9, 128.5, 128.1, 128.0, 107.4, 73.7, 71.9, 69.4, 64.2, 59.1, 15.3; IR (neat) 3421, 1793 cm^{-1}; FAB−HRMS calcd for $C_{14}H_{18}O_6$ (M + H) 283.1182, found 283.1174.

5-Benzyloxymethyl-5-ethoxy-3,4-dihydroxy-dihydro-furan-2-one (5-α and 5-*β*). (−)-Butenolide **4** (52.5 mg, 0.211 mmol) was dissolved in 2 mL of ETOAc and 2 mL of CH_3CN, and the mixture was cooled to 0 °C. $RuCl_3{\cdot}xH_2O$ (3.1 mg, 0.015 mmol) and $NaIO_4$ (67.8 mg, 0.317 mmol) were dissolved in 0.75 mL of H_2O and added to the butenolide solution via syringe. The reaction was stirred vigorously for 5 min and then poured into saturated aqueous $Na_2S_2O_3$. The organic layer was extracted with ETOAc, combined, dried over $MgSO_4$, filtered, and concentrated. The crude brown residue was purified by flash column chromatography (4:1−3:1 hex/ETOAc gradient elution) to yield diol **5**-α (7 mg, 0.02 mmol, 12%) and **5**-*β* (24 mg, 0.085 mmol, 40%) as clear oils and recovered butenolide **4** (11 mg). **5-α**: ^{1}H NMR (400 MHz) *δ* 7.31 (m, 5H), 4.61 (m, 1H), 4.57 (d, *J* = 12.4 Hz, 1H), 4.49 (d, *J* = 11.6 Hz, 1H), 4.30 (d, *J* = 5.6 Hz, 1H), 3.90 (m, 1H), 3.73 (d, *J* = 9.6 Hz, 1H), 3.68 (m, 1H), 3.66 (d, *J* = 10.4 Hz, 1H), 3.17 (s, 1H), 2.96 (d, *J* = 8.4 Hz, 1H), 1.24 (t, *J* = 7.2, 3H); ^{13}C NMR *δ* 174.0, 136.4, 128.7, 128.3, 128.0, 127.8, 103.6, 74.0, 70.8, 70.2, 69.5, 61.0, 15.4.

(3*S*,4*R*,5*R*)-5-Benzyloxymethyl-5-ethoxy-3,4-*O*-cyclohexylidene-dihydro-furan-2-one (6). A flask, equipped with reflux condensor and Soxhlet extractor containing 4 Å molecular sieves, was charged with diol **5** (27 mg, 0.096 mmol) and 8 mL of benzene. The solution was warmed to reflux, and then a few crystals of TsOH were added. The mixture was kept at reflux for until no starting material was present (∼30 min) by TLC (silica gel, hex/ETOAc, 4:1). The mixture was cooled to room temperature and quenched with saturated aqueous Na_2CO_3. The separated organic layer was washed with saturated aqueous Na_2CO_3 and water. The organic layer was then dried over $MgSO_4$, filtered, and concentrated by rotary evaporation. The crude oil (37 mg) was purified by flash column chromatography (25:1 hex/ETOAc) to yield protected diol **6** as a clear oil (30 mg, 0.083 mmol, 86%): $[\alpha]^{25}_D$ −15° (*c* = 1.38, EtOH); ^{1}H NMR *δ* 7.30 (m, 5H), 4.87 (d, *J* = 4.8 Hz, 1H), 4.65 (d, *J* = 12.3 Hz, 1H), 4.60 (d, *J* = 12.6 Hz, 1H), 4.56 (d, *J* = 5.1 Hz, 1H), 3.84 (d, *J* = 10.8 Hz, 1H), 3.71 (d, *J* = 10.5 Hz, 1H), 3.68 (m, 2H), 1.57 (m, 10H), 1.16 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR *δ* 173.8, 137.3, 128.3, 127.8, 115.1, 106.4, 78.9, 75.5, 73.6, 64.2, 59.0, 36.5, 35.6, 24.7, 23.8, 15.2; IR (neat) 1801 cm^{-1}; FAB−HRMS calcd for $C_{20}H_{26}O_6$ (M + H) 363.1808, found 363.1804.

(4*S*,5*S*)-3-Benzyloxymethyl-4,5-*O*-cyclohexylidene-cyclopent-2-enone (7). Following the general procedure of Borcherding et al.,[6] a two-necked flask was flame-dried and charged with freshly distilled dimethyl methylphosphonate (37 *μ*L, 0.35 mmol) and 2.2 mL of THF. The solution was cooled to −78 °C with an acetone/dry ice bath, and *n*-butyllithium (0.2 mL, 0.35 mmol) was added down the sidearm of the flask, to precool the solution, via syringe over a 15 min period. The solution was stirred for an additional 15 min after the addition was complete. Protected diol **7** (125 mg, 0.345 mmol), dissolved in a minimal amount of THF, was added down the sidearm via syringe. The solution was stirred at −78 °C for 2.5 h. The acetone/dry ice bath was removed, and the solution was warmed to room temperature (∼1 h). The solution was partitioned between Et_2O and brine. The organic layer was separated, and the aqueous layer was extracted with Et_2O. The combined etheral layers were dried over $MgSO_4$, filtered, and concentrated by rotary evaporation. The crude oil was purified by flash column chromatography (25:1 → 10:1 hex/EtOAc gradient elution) to yield enone **7** as a yellow oil (56 mg, 0.18 mmol, 52%) and some recovered starting material **6** (17.5 mg). **7**: $[\alpha]^{25}_D$ +7° (*c* = 0.855, EtOH); ^{1}H NMR *δ* 7.38 (m, 5H), 6.16 (m, 1H), 5.05 (d, *J* = 5.7 Hz, 1H), 4.64 (d, *J* = 11.7 Hz, 1H), 4.60 (d, *J* = 12.0 Hz, 1H), 4.50 (dd, *J* = 1.8 Hz, *J* = 17.4 Hz, 1H), 4.46 (d, *J* = 6.0 Hz, 1H), 4.33 (dd, *J* = 1.2 Hz, *J* = 17.7 Hz, 1H), 1.58 (m, 10H); ^{13}C NMR *δ* 201.7, 173.9, 137.1, 128.5, 128.3, 128.0, 127.6, 116.2, 77.6, 77.4, 73.3, 67.6, 37.3, 35.8, 25.0, 23.9, 23.6; IR (neat) 1724 cm^{-1}; FAB−HRMS calcd for $C_{19}H_{22}O_4$ (M + H) 315.1596, found 315.1600. Anal. Calcd for $C_{19}H_{22}O_4$: C, 72.56; H, 7.05. Found: C, 72.32; H, 6.91.

(1*R*,4*S*,5*R*)-3-Benzyloxymethyl-4,5-*O*-cyclohexylidene-cyclopent-2-enol (8). Enone **7** (67 mg, 0.21 mmol) was dissolved in 0.2 mL of MeOH (stored over 3 Å molecular sieves). The solution was cooled to 0 °C, and $CeCl_3{\cdot}7H_2O$ (66.7 mg, 0.179 mmol) was added. $NaBH_4$ (12.1 mg, 0.32 mmol) was added in three portions, and the reaction was stirred at 0 °C for 10 min. Glacial acetic acid was added via syringe until pH ∼5, brine was added, and the mixture was extracted with Et_2O. The combined etheral layers were dried over $MgSO_4$, filtered, and concentrated by rotary evaporation. The crude oil was purified by flash column chromatography (25:1 hex/EtOAc gradient elution) to yield alcohol **8** as a clear film (64 mg, 0.20 mmol, 96%): $[\alpha]^{25}_D$ −28° (*c* = 1.69, EtOH); ^{1}H NMR *δ* 7.28 (m, 5H), 5.77 (s, 1H), 4.95 (d, *J* = 5.4 Hz, 1H), 4.73 (t, *J* = 5.4 Hz, 1H), 4.54 (m, 2H), 4.13 (s, 2H), 2.76 (d, *J* = 9.9 Hz, 1H) 1.58 (m, 10H); ^{13}C NMR *δ* 173.8, 137.3, 128.3, 127.8, 115.2, 106.4, 78.9, 75.5, 73.6, 64.2, 59.0, 36.5, 35.7, 24.7, 23.8, 23.7, 15.2; IR (neat) 3540 cm^{-1}; FAB−HRMS calcd for $C_{19}H_{24}O_4$ (M + H) 317.1753, found 317.1740.

(1*R*,4*S*,5*R*)-Methanesulfonic Acid 3-Benzyloxymethyl-4,5-*O*-cyclohexylidene-cyclopent-2-enyl Ester (9). Alcohol **8** (40 mg, 0.126 mmol) was dissolved in 3 mL of CH_2Cl_2 and cooled to 0 °C. NEt_3 (0.02 mL, 0.164 mmol) and then MsCl (0.01 mL, 0.164 mmol) were added via syringe. The reaction was stirred at 0 °C for 10 min and quenched with water. The aqueous layer was separated and extracted with CH_2Cl_2. The combined organic layers were washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated by rotary evaporation. The crude oil was purified by flash column chromatography (4:1 hex/EtOAc) to yield mesylate **9** as a clear oil (43 mg, 0.109 mmol, 86%): $[\alpha]^{25}_D$ +15° (*c* = 1.96, EtOH); ^{1}H NMR (400 MHz) *δ* 7.30 (m, 5H), 5.78 (d, *J* = 0.8 Hz, 1H), 5.39 (dd, *J* = 2.0 Hz, *J* = 5.2 Hz, 1H), 4.94 (d, *J* = 5.6 Hz, 1H), 4.89 (t, *J* = 5.4 Hz, 1H), 4.57 (d, *J* = 12.0 Hz, 1H), 4.54 (d, *J* = 12.0 Hz, 1H), 4.20 (d, *J* = 14.0 Hz, 1H), 4.15 (d, *J* = 14.4 Hz, 1H), 3.12 (s, 3H), 1.54 (m, 10H); ^{13}C NMR (400 MHz) *δ* 147.3, 137.7, 128.4, 127.8, 127.6, 125.0, 114.2, 82.6, 80.9, 76.8, 73.0, 66.1, 39.0, 37.1, 36.4, 24.9, 23.9; IR (neat) 1350, 1175 cm^{-1}; FAB−HRMS calcd for $C_{20}H_{26}O_6S$ (M^+) 394.1450, found 394.1438.

(1S,4S,5R)-9-(3-Benzyloxymethyl-4,5-*O*-cyclohexylidene-cyclopent-2-enyl)-9*H*-purin-6-ylamine (10). K_2CO_3 (36.4 mg, 0.264 mmol) and 18-crown-6 (34.8 mg, 0.132 mmol) were dissolved in 1.8 mL of DMF. Adenine (35.6 mg, 0.264 mmol) was added, and the solution was stirred for 10 min. Mesylate **9** (52 mg, 0.13 mmol), dissolved in a minimal amount of DMF, was added dropwise to the solution. The solution was warmed to ∼70 °C for 18 h and then cooled to room temperature. The DMF was removed by rotary evaporation. The resulting tan residue was dissolved in CH_2Cl_2, filtered through Celite to remove any solid

particles, and concentrated. The resulting yellow oil was purified by flash column chromatography (6:1 hex/ETOAc → 100% CH_2Cl_2 → 3% MeOH/CH_2Cl_2 gradient elution) to first yield a clear oil, which was triturated with CH_2Cl_2 to remove any inorganic impurities. Concentration of the triturating solvent gave **10** as a clear oil (31 mg, 0.072 mmol, 54%): $[\alpha]^{25}_D$ +102° (*c* = 1.34, EtOH); ^{1}H NMR δ 8.34 (s, 1H), 7.64 (s, 1H), 7.31 (m, 5H), 6.07 (bs, 2H), 5.78 (s, 1H), 5.55 (s, 1H), 5.38 (d, *J* = 4.2 Hz, 1H), 4.70 (d, *J* = 4.5 Hz, 1H), 4.63 (d, *J* = 9.3 Hz, 1H), 4.54 (d, *J* = 18.3 Hz, 1H), 4.50 (d, *J* = 18.6 Hz, 1H), 4.24 (d, *J* = 11.4 Hz, 1H), 1.59 (m, 10H); ^{13}C NMR (400 MHz) δ 155.3, 152.7, 149.8, 149.6, 138.9, 137.8, 128.4, 127.8, 127.6, 122.8, 120.1, 113.4, 83.9, 83.6, 72.9, 66.5, 64.7, 37.2, 35.6, 24.9, 24.0, 23.6; IR (neat) 3319, 3156, 1648, 1596 cm^{-1}; FAB−HRMS calcd for $C_{24}H_{27}N_5O_3$ (M + H) 434.2192, found 434.2195. The column then gave the N-7 isomer (2 mg, 0.005 mmol, 4%): ^{1}H NMR δ 8.49 (s, 1H), 7.85 (s, 1H), 7.34 (m, 5H), 6.02 (s, 1H), 5.76 (s, 1H), 5.53 (d, *J* = 1.5 Hz, 1H), 5.25 (d, *J* = 14.7 Hz, 1H), 4.72 (d, *J* = 6.0 Hz, 1H), 4.65 (s, 2H), 4.31 (d, *J* = 15.0 Hz, 1H), 4.26 (d, *J* = 15.0 Hz, 1H), 1.65 (m, 10H).

(+)-Neplanocin A (1). Protected (+)-neplanocin A **10** (20 mg, 0.0461 mmol) was dissolved in 0.5 mL of CH_2Cl_2, and the mixture was cooled to −78 °C. BCl_3 (0.5 mL, 0.461 mmol) was added slowly via syringe down the side of the flask to precool the solution. The mixture was stirred until no starting material was observed (∼10 min) by TLC (silica gel, 10% MeOH in CH_2Cl_2). The solution was warmed to room temperature, quenched with MeOH, and concentrated. MeOH (2 mL) was added, and the solution was concentrated. This addition/evaporation process was repeated twice more, followed by the addition of a solution of NH_3 in MeOH (1 mL, saturated at 0 °C), which was concentrated to provide a white solid. The crude solid was purified by flash column chromatography (10% EtOH/CH_2Cl_2 → 20% MeOH/CH_2Cl_2 gradient elution) to provide a white solid, which was triturated with ETOH to remove any inorganic impurities. Concentration of the triturating solvent gave (+)-**1** as a white solid (4.9 mg, 0.0186 mmol, 41%): $[\alpha]_D$ +35° (*c* = 0.5, H_2O). The ^{1}H, ^{13}C, and mass spectra of this compound were identical to those previously reported.[5a]

Supporting Information Available: ^{1}H and ^{13}C NMR spectra for compounds **5**-α, **5**-*β*, **6**, **7**, **8**, **9**, **10**, N-7 isomer of **10**, and **1**; DEPT ^{13}C NMR spectra for compounds **5**-*β* and **5**-α; NOE spectra for compounds **5**-*β* and **5**-α; ^{1}H−^{13}C 2D (HSQC) spectra for compounds **5**-*β* and **5**-α; ^{1}H−^{1}H 2D (COSY) spectra for compounds **5**-*β* and **5**-α (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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