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A Formal Total Synthesis of (±)-Neplanocin A

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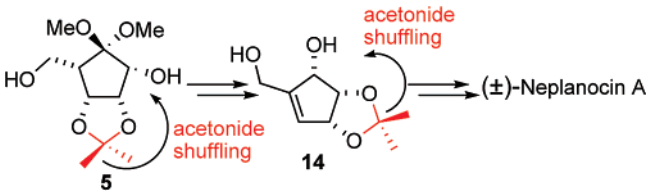
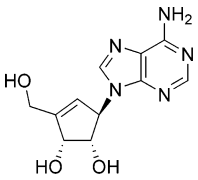
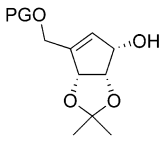


Stereoselective formal synthesis of (±)-neplanocin A from a cyclopentane derivative employing an elegant strategy involving reiterative usage of an already existing acetonide protecting group is reported. The acetonide protecting group that is carried forward intact right from the starting adduct to an advanced intermediate is shuffled around twice as in a "relay race" through the synthetic sequence, thus avoiding unnecessary employment of additional protecting groups.

Neplanocin A (**1**) is a naturally occurring carbocyclic nucleoside[1] isolated from the culture filtrate of soil fungus *Ampullariella regularis* in 1981.[2] It inhibits cellular *S*-adenosyl methionine dependent methyltransferases[3] and is a potent antitumor and antiviral agent.[4] The promising biological activity of **1** stimulated several synthetic endeavors.[5] The protected tetrol **2** had long been recognized as a convenient advanced precursor[5f] wherein a Mitsunobu inversion of the secondary hydroxyl group with adenine followed by deprotection of hydroxyl groups furnished **1**. A recent report by Schneller and co-workers[6] on improved Mitsunobu reaction of **2** with N-6 amino bis-Boc-protected adenine makes this strategy further attractive.



1 Neplanocin A



2 PG = Protecting group

We envisioned that **1** could be crafted from the polyhydroxylated cyclopentane derivative **4** reported recently by us,[7] starting from **3**. We herein report the conversion of **4** to **2** (PG = TBS), thus completing the formal total synthesis of **1**.

A two-step protocol involving glycol cleavage with $NaIO_4$ followed by reduction of the resulting ketone with $NaBH_4$ allowed us to stereoselectively remove one of the hydroxymethyl groups in **4** to obtain **5** (Scheme 1). Conversion of **5** to dibenzyl protected **6** followed by treatment with acid catalyst in moist acetone furnished cyclopentenone **7**. Fortunately, elimination occurred regioselectively furnishing the double bond carrying the hydroxymethyl moiety in the desired position. Suitable protection of the secondary hydroxyl group in **7** prior to carbonyl reduction was essential to install the adenine group at this position at a later stage. Thus, TBS protected **8** was stereoselectively reduced to **9** in high yield with DIBAL-H. It was then transformed to tribenzyl derivative **10** followed by TBS group removal to obtain **11**. The stage is now set for the final coupling with adenine. Finally, orchestration of a global deprotection strategy would lead to **1**. Mitsunobu inversion, generally employed for the installation of the adenine unit, was attempted on **11**. Unfortunately, no coupling product **12** was observed both at room temperature and at prolonged refluxing.

We then retracted to intermediate **5**, which has an acetonide protecting group between two of the three secondary hydroxyl groups. We thought that if the acetonide protecting group is shuffled such that the free secondary hydroxyl group in **5** is now engaged as acetonide, it would release the one intended for elimination. If the reaction conditions are fashioned in such a way that a concomitant ketal hydrolysis occurred, then generation of an α,β-unsaturated enone moiety would be the driving force for the instantaneous elimination of the released hydroxyl group, thus constituting an elegant strategy.

To our delight, employment of Amberlyst-15 in acetone at room temperature indeed transformed **5** directly to **13** in 56% yield (Scheme 2). The sensitivity of the enone system to acidic conditions is perhaps responsible for the modest yield. A

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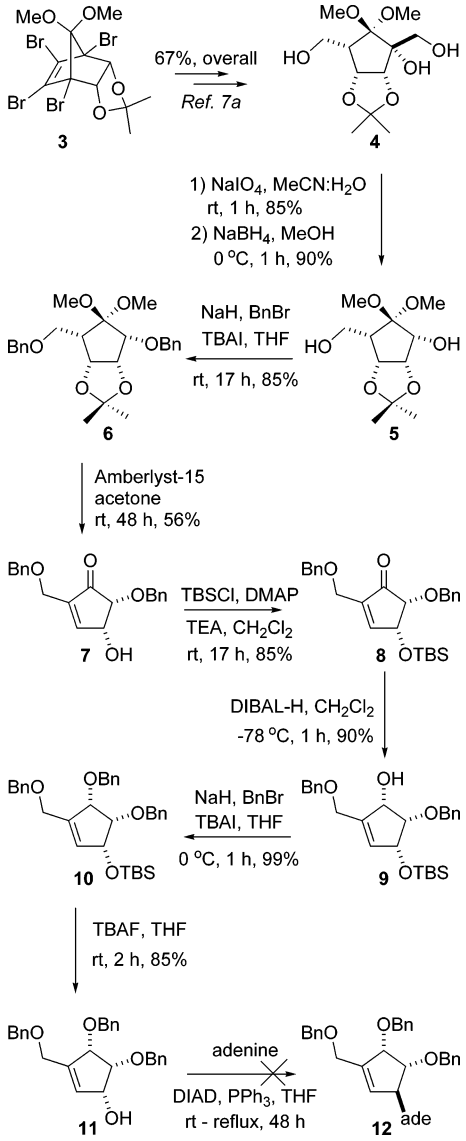
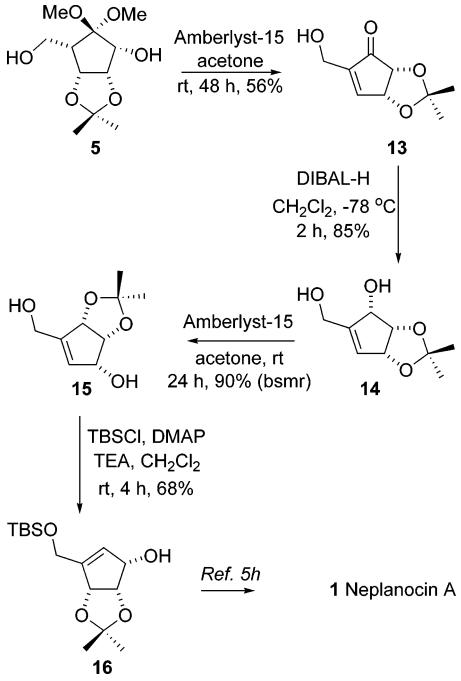
SCHEME 1. Synthesis of 11



stereoselective reduction of the carbonyl group in **13** from the sterically accessible convex face by using DIBAL-H furnished **14**.[8] The deprotected triol (1*S*,2*S*,3*R*)-4-hydroxymethylcyclopent-4-ene-1,2,3-triol, an antipode of **14**, is itself a natural product isolated from *Streptomyces citricolor* and was shown to be an intermediate in the biosynthesis of **1**.[9]

Once again, the newly formed secondary hydroxyl group in **14** must be protected while releasing one of the acetonide protected allylic hydroxyl groups. We were fortunate to have this wish fulfilled with the same set of reagents as before, furnishing **15** in 90% yield (50% conversion).[10,11] Thus the

SCHEME 2. Formal Synthesis of Neplanocin A



acetonide group originally present in our starting material could be successfully shuffled twice in the desired direction in a "relay race" manner, making the usage of additional protecting groups redundant. Finally, TBS protection of the primary hydroxyl group in **15** gave **16** (Scheme 2). The identity of alcohol **16** was unambiguously established by comparison of ^{1}H and ^{13}C NMR spectra with the reported one.[5k,11] The conversion of **16** to neplanocin A through Mitsunobu inversion of the secondary hydroxyl group with adenine followed by deprotection of all the hydroxyl groups with HCl/MeOH has already been reported in the literature,[5h] thus completing a formal synthesis.

In summary, a stereoselective formal total synthesis of (±)-neplanocin A from **4** was achieved in eight steps in 17% overall yield. The acetonide group already present in **4** is shuffled twice, such that each time it traverses in the direction of the newly created vicinal *cis* secondary hydroxyl group setting free the first one on the preceding bond for further reaction, thus minimizing protection−deprotection steps significantly.

Experimental Section

Synthesis of Alcohol 5. To a stirred solution of triol **4** (500 mg, 1.8 mmol) in acetonitrile (7 mL) was added sodium metaperiodate (769 mg, 3.6 mmol) dissolved in distilled water (7 mL) at room temperature. After 1 h, the reaction mixture was diluted with water (7 mL) and extracted with ethyl acetate (15 mL) three times. The combined organic layer was washed with brine (3 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the crude reaction mixture was purified on silica gel column chromatography by eluting with EtOAc/ hexane (1:1) to give keto alcohol as a colorless viscous liquid (376 mg, 85%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (3H, s), 1.45 (3H, s), 2.42 (1H, br, OH), 2.71−2.76 (1H, m), 3.16 (3H, s), 3.35 (3H, s), 3.62 (2H,

(8) For an alternative synthesis of **14** from 2,3-isopropylidene-D-ribose, see: van Boggelen, M. P.; van Dommelen B. F. G. A.; Jiang, S.; Singh, G. *Tetrahedron* **1997**, *53*, 16897−16910. Also, an inseparable mixture of **14** and **15** (2:1) along with two other ketals were obtained when (1*S*,2*S*,3*R*)-4-hydroxymethylcyclopent-4-ene-1,2,3-triol, a natural product isolated from *Streptomyces citricolor*, was treated with 2,2-dimethoxypropane.[9]

(9) Roberts, S. M.; Thorpe, A. J.; Turner, N. J.; Blows, W. M.; Buss, A. D.; Dawson, M. J.; Noble, D.; Rudd, B. A. M.; Sidebottom, P. J.; Wall, W. F. *Tetrahedron Lett.* **1993**, *34*, 4083−4086.

(10) The mixture of **14** and **15**, although homogeneous on TLC, was quantitatively separated by using JAI LC-908W preparative HPLC equipped with a JAIGEL-OA4100 column (Japan Analytical Industry Co).

(11) Cyclopentenol derivative **15** is also an intermediate in the total synthesis of neplanocin A by Tomioka, which was directly transformed into TBS protected **16** without isolation.[5k] The authors have provided ^{1}H and ^{13}C NMR data of **16** in the Experimental Section and a scanned copy of the ^{1}H NMR spectrum (obtained from Ogasawara's group) in the Supporting Information.[5k]

d, $J = 6.3$ Hz), 4.58 (1H, d, $J = 7.5$ Hz), 4.87 (1H, t, $J = 7.2$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.2, 25.7, 45.6, 50.4, 50.5, 58.7, 74.4, 76.7, 104.0, 114.0, 203.0; IR (neat, cm^{-1}) 3250, 2850, 1720, 1450. Anal. Calcd for $C_{11}H_{18}O_6$: C, 53.65; H, 7.37. Found: C, 53.78; H, 7.32.

To a stirred solution of the above keto alcohol (376 mg, 1.5 mmol) in methanol (7 mL) was added sodium borohydride (84 mg, 2.3 mmol) at 0 °C. After 1 h, the reaction mixture was quenched with water (14 mL) at 0 °C and extracted with ethyl acetate (20 mL) three times. The combined organic layer was washed with brine (3 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the crude reaction mixture was purified on silica gel column chromatography with EtOAc/hexane (1/1) to give a colorless viscous liquid **5** (347 mg, 90%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (3H, s), 1.50 (3H, s), 2.45 (1H, br, OH), 2.57−2.62 (1H, m), 3.18 (3H, s), 3.35 (3H, s), 3.45 (1H, s), 3.79−3.90 (3H, m), 4.54 (1H, dd, $J = 5.3$, 7.1 Hz), 4.68 (1H, t, $J = 7.3$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.4, 25.6, 45.9, 48.3, 50.4, 50.8, 58.8, 78.1, 78.9, 110.3, 113.0; IR (neat, cm^{-1}) 3350, 2900, 1350, 1050. Anal. Calcd for $C_{11}H_{20}O_6$: C, 53.22; H, 8.12. Found: C, 53.28; H, 8.32.

α,β-Unsaturated Keto Alcohol 13. The reaction was performed as described in the procedure for α,β-unsaturated keto alcohol **7**, with **5** (347 mg, 1.4 mmol) and amberlyst-15 (250 mg). The crude product was purified by column chromatography (silica gel, EtOAc/hexane = 2/3) to furnish **13** (144 mg, 56%) as a colorless viscous liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (3H, s), 1.38 (3H, s), 2.14 (1H, br, OH), 4.36 (2H, d, $J = 1.2$ Hz), 4.51 (1H, d, $J = 5.3$ Hz), 5.25 (1H, dd, $J = 1.2$, 5.3 Hz), 7.42 (1H, dd, $J = 1.7$, 3.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.9, 27.4, 57.3, 77.6, 115.6, 145.8, 153.0, 202.4; IR (neat, cm^{-1}) 3220, 2900, 1700, 1620, 1350. Anal. Calcd for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.87; H, 6.23.

Cyclopentenol Derivative 14. The reaction was performed as described in the procedure for alcohol **9**, with **13** (144 mg, 0.8 mmol) and DIBAL-H (1.4 mL, 1.6 mmol). The crude product was purified by column chromatography (silica gel, EtOAc/hexane = 4/1) to furnish **14** (123 mg, 85%) as a colorless viscous liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (3H, s), 1.42 (3H, s), 2.35 (1H, br, OH), 2.86 (1H, d, $J = 9.3$ Hz, OH), 4.33 (2H, t, $J = 14.8$ Hz), 4.52 (1H, t, $J = 7.1$ Hz), 4.75 (1H, t, $J = 5.7$ Hz), 4.99 (1H, dd, $J = 1.5$, 3.9 Hz), 5.74 (1H, t, $J = 1.4$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.4, 27.6, 59.9, 73.9, 77.4, 82.3, 112.3, 125.9, 148.2; IR (neat, cm^{-1}) 3200, 1610, 1360, 1200, 1000. Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 58.32; H, 7.62.

Cyclopentenol Derivative 15. The reaction was performed as described in the procedure for α,β-unsaturated keto alcohol **7**, with **14** (123 mg, 0.66 mmol) and amberlyst-15 (75 mg). The crude product was purified by column chromatography (silica gel, EtOAc) to furnish a viscous liquid (116 mg). The viscous liquid was further purified in preparative HPLC using OA-4100 column with EtOH/hexane (1/9) as solvent with the other parameters $\lambda_{max} = 230$ nm, absorbance = 0.05, R.I. = 50 giving a viscous liquid **14** (61 mg) and a white viscous liquid **15** (55 mg, 90% based on starting material recovery): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (3H, s), 1.42 (3H,s), 1.88 (1H, br, OH), 2.71 (1H, br, OH), 4.3 (2H, q, $J = 14.2$ Hz), 4.55 (1H, s), 4.76 (1H, t, $J = 5.4$ Hz), 4.96 (1H, d, $J = 5.6$ Hz), 5.72 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.4, 27.5, 59.8, 73.2, 77.8, 83.2, 112.6, 130.2, 144.4; IR (neat, cm^{-1}) 3250, 2850, 1610, 1360, 1020. ESI-HRMS calcd for $C_9H_{14}O_4$ 186.0892, found 186.0847.

Alcohol 16. To a stirred solution of diol **15** (55 mg, 0.3 mmol) in CH_2Cl_2 (2 mL) was added triethylamine (50 mg, 0.5 mmol), DMAP (18 mg, 0.15 mmol), and *tert*-butyldimethylsilyl chloride (45 mg, 0.3 mmol) sequentially at 0 °C. After being stirred for 4 h at room temperature, the mixture was diluted with CH_2Cl_2 (10 mL) and washed with water (3 mL). The aqueous layer was extracted with CH_2Cl_2 (5 mL) three times. The combined organic layer was washed with brine (3 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the crude reaction mixture was purified on silica gel column chromatography with EtOAc/hexane (1/5) to give **16** (69 mg, 68%) as a colorless liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.00 (3H, s), 0.00 (3H, s), 0.83 (9H, s), 1.32 (3H, s), 1.35 (3H, s), 2.61 (1H, d, $J = 10.1$ Hz), 4.16 (1H, d, $J = 15.3$ Hz), 4.27 (1H, d, $J = 15.3$ Hz), 4.48 (1H, br), 4.69 (1H, dd, $J = 5.5$, 5.5 Hz), 4.82 (1H, d, $J = 5.5$ Hz), 5.65 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.5, −5.4, 18.4, 25.8, 26.6, 27.7, 59.9, 73.2, 77.9, 82.7, 112.5, 129.2, 145.6.[5k]

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Supporting Information Available: General experimental details and procedures, as well as spectral data for compounds **6**−**11** and copies of ^{1}H and ^{13}C NMR spectra of **5** to **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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