Total synthesis of carbocyclic nucleoside (+)-neplanocin A

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1. Introduction

Carbocyclic nucleosides, in which an oxygen atom in a furanose ring of ribonucleosides is replaced by a methylene group, are among the most interesting discoveries in the field of natural products. Due to the absence of a true glycosidic bond, carbocyclic nucleosides are more chemically stable and not involved in the action of the enzymes that cleave the N-glycosidic linkage in conventional nucleosides. Thus, carbocyclic nucleosides have been the focus of much attention in the development of new therapeutic agents.

(+)-Neplanocin A (1), an unsaturated analogue of (-)-aristeromycin (2), is a naturally occurring carbocyclic nucleoside isolated from the culture filtrate of the soil fungus Ampullariella regularis in 1981 (Fig. 1). The absolute structures of 1 and 2 were established by X-ray analysis. Other natural neplanocin analogs, e.g., (+)-neplanocin B (3), (+)-neplanocin C (4), (+)-neplanocin D (5), and (+)-neplanocin F (6), were also identified. Among neplanocin family, (+)-neplanocin A has received great attention due to its interesting biological properties such as potent antiviral and antitumor activities. (+)-Neplanocin A efficiently inhibits cellular S-adenosylmethionine hydrolase in cells, which results in the accumulation of S-adenosylhomocysteine, thus inhibiting cell and viral methyltransferases involved in messenger RNA maturation and the synthesis of other macromolecules.

The protected tetrol 7 has been widely used as a convenient precursor wherein a Mitsunobu inversion of a secondary hydroxyl group with adenine followed by deprotection of hydroxyl groups provided (+)-neplanocin A (Scheme 1). The formation of 7 and its enantiomer is achieved from optically active ribonolactone derivatives via the palladium-catalyzed rearrangement of the acetate moiety, construction of a carbocyclic ring by intramolecular Horner–Wadsworth–Emmons or Wittig reactions, intramolecular aldol reaction, C–H insertion reaction of allyldiene-carbenes, and ring-closing metathesis reaction using Grubbs catalysts. Another approach for the preparation of 1 includes
a palladium-catalyzed desymmetrization of cyclopentenes with 6-chloropurine,14 chemoenzymatic desymmetrization of bicyclic Diels–Alder adducts,15 intramolecular nitrene cycloaddition,16 zirconocene-mediated ring construction,17 and intramolecular Baylis–Hillman reaction.18

As part of an ongoing research program aimed at developing asymmetric total synthesis of biologically active compounds through a chlorosulfonyl isocyanate-mediated stereoselective amination,19 we herein describe the asymmetric total synthesis of \( (+)-\)neplanocin A (ent-1) starting from commercially available \( \beta \)-galactose via the highly regioselective and diastereoselective allylic amination of cyclic polybenzyl ethers using chlorosulfonyl isocyanate (CSI) and intramolecular olefin metathesis as the key steps.

2. Results and discussion

Our initial investigation focused on the efficient construction of carbocyclic polybenzyl ether 12, which can be subjected to our amination methodology to give the protected amino alcohol 13. Thus, the total synthesis of \( (+)-\)neplanocin A began with the protected lactol 8 derived from \( \beta \)-galactose according to the reported literature (Scheme 2).20 Wittig reaction of 8 and subsequent Swern oxidation of a secondary alcohol afforded the ketone 10 in high yields. Second Wittig reaction of 10 was subjected under NaHMDS as a base to give the diene 11, which was treated with second-generation Grubbs catalyst in refluxing CH2Cl2 to provide the carbocyclic polybenzyl ether 12 in 90% yield. Next, after the screening of various reaction conditions for the coupling between 12 and CSI, we found that the reaction in methylene chloride at 0 °C gave the desired product 13 with an excellent level of diastereoselectivity (anti/syn = 50:1) in 91% yield. The origin of stereochemistry can be explained by competition between \( S_N1 \) mechanism and \( S_N1 \) mechanism.19c In general, \( S_N1 \) mechanism leads to retention of stereochemistry via a four-centered transition state by the formation of a tight ion pair. Another plausible \( S_N1 \) mechanism may cause the generation of a carbocation intermediate, which can provide the racemization of products. However, in the case of \( \text{anti-dibenzyl ether 12, anti-amino alcohol 13} \) can be exclusively obtained due to the facile approach of \( \text{\text{NCO}_2\text{Bn}} \) species to the less sterically hindered face in a carbocation intermediate.

To obtain an essential precursor 14 for the formation of \( (+)-\)neplanocin A, we then screened a chemoselective removal of the Cbz protection of 13 under various reaction conditions. After
several failed attempts such as BF₃·OEt₂/SMet₂, BBr₃, 40% KOH/MeOH, and Pd(OAc)₂/Et₃SiH/Et₃N, the chemoselective removal of the Cbz protection of 13 was successfully achieved under basic hydrolysis conditions (LiOH·H₂O, 1,4-dioxane/water (3:1), 120 °C, 48 h) to give the primary amine 14 in high yield (89%).

To construct the remaining adenine heterocycle, compound 14 was subjected to the three-step sequence as reported in the literature (Scheme 3). The condensation of 14 with 5-amino-4,6-dichloropyrimidine in n-butyl alcohol at 120 °C afforded our desired product 15 in low yield (20%) (Table 1, entry 1). The yield of 15 was improved to 61% when DMF was employed (Table 1, entry 4), however, the reaction required 48 h to go to completion. The best result was realized when 14 was exposed to 5-amino-4,6-dichloropyrimidine in isoamyl alcohol, which produced the pyrimidine compound 15 in high yield (89%) within 24 h (Table 1, entry 5). Intramolecular ring formation of 15 and subsequent amination reaction using methanolic ammonia afforded the adenine 17 in high yields. Finally, debenzylation of 17 under the standard reaction condition (BCl₃ in anhydrous CH₂Cl₂) proceeded cleanly to afford (+)-neplanocin A (ent-1) with specific rotation and spectral data (¹H and ¹³C NMR) identical to those reported in the literature.¹⁵e

### 4. Experimental

#### 4.1. General

Commercially available reagents were used without additional purification, unless otherwise stated. All reactions were performed under an inert atmosphere of nitrogen or argon. Nuclear magnetic resonance spectra (¹H and ¹³C NMR) were recorded on a Bruker Unity 300 MHz and Varian Unit 500 MHz spectrometer for CDCl₃ solutions, and chemical shifts are reported as parts per million (ppm) relative to, respectively, residual CHCl₃ δH (7.26 ppm) and CDCl₃ δC (77.0 ppm) as internal standards. Resonance patterns are reported with the notations s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). In addition, the notation br is used to indicate a broad signal. Coupling constants (J) are reported in hertz (Hz). IR spectra were recorded on a Bruker Infrared spectrophotometer and are reported as cm⁻¹. Optical rotations were measured with a Jasco P1020 polarimeter. Thin layer chromatography was carried out using plates coated with Kieselgel 60F₂₅₄ (Merck). For flash column chromatography, E. Merck Kieselgel 60 (230–400 mesh) was used. LC/mass spectra (LC/MS) were recorded on a Waters 2767 LCMS system. High-resolution mass spectra (HRMS) were recorded on a JEOL JMS-600 spectrometer.

#### 4.2. (2R,3S,4R,5S)-1,3,4,5-Tetrakis(benzyloxy)hept-6-en-2-ol (9)

To a stirred solution of MePPh₃Br (17.6 g, 49.3 mmol) in THF (54 mL) was carefully added n-BuLi (37.1 mL, 59.4 mmol in 1.6 M solution) at 0 °C under N₂ atmosphere. The reaction mixture was stirred for 2 h at room temperature to generate ylide. To a reaction mixture was added a solution of 8 (6.78 g, 12.5 mmol) in THF (7.5 mL) at −78 °C. The resulting mixture was warmed to room temperature and further stirred for 4 h. The reaction was quenched with water (30 mL) and the aqueous layer was extracted with EtOAc (100 mL x 2). The organic layer was washed with water and brine, dried over MgSO₄, and concentrated in vacuo. The residue was purified by flash column chromatography (n-hexane/EtOAc=5:1) to afford 5.07 g (9.41 mmol, 75%) of 9 as yellow syrup. Rf=0.30 (n-hexane/EtOAc=5:1); [α]D²⁵ = -3.4 (c 0.5, CHCl₃); IR (neat) ν 3030, 2867, 1497, 1454, 1210, 1095, 1067, 1028, 736, 698, 477, 419 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.37−7.16 (m, 20H), 5.87 (ddd, J=17.5, 10.0, 8.0 Hz, 1H), 5.36−5.30 (m, 2H), 4.76 (d, J=12.0 Hz, 2H), 4.65 (d, J=10.0 Hz, 2H).

### 3. Conclusion

We described a concise total synthesis of (+)-neplanocin A starting from readily available D-galactose via the highly regioselective and diastereoselective amination of carbocyclic polybenzyl ether with retention of stereochemistry using chlorosulfonyl isocyanate and intramolecular olefin metathesis. It is believed that this synthetic strategy can be applied to the preparation of a broad range of biologically active compounds containing a chiral amine moiety.
was carefully quenched with water (10 mL) and the aqueous layer was further stirred for 4 h at 78 °C. The resulting mixture was carefully quenched with water (10 mL) and the aqueous layer was extracted with CH₂Cl₂ (20 mL×2). The organic layer was washed with water and brine, dried over MgSO₄, and concentrated in vacuo. The residue was purified by flash column chromatography (n-hexane/EtOAc=4:1) to afford 1.1 g (2.2 mmol, 88%) of 10 as yellow syrup. ¹H NMR (300 MHz, CDCl₃) δ 7.39–7.16 (m, 20H), 5.99 (d, J=1.5 Hz, 1H), 4.80–4.75 (m, 1H), 4.73 (d, J=11.8 Hz, 1H), 4.65 (d, J=2.7 Hz, 1H), 4.62–4.60 (m, 4H), 4.53 (d, J=1.8 Hz, 1H), 4.49 (d, J=3.9 Hz, 2H), 4.07 (s, 2H), 4.00 (d, J=6.8 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 142.5, 138.9, 138.6, 138.5, 130.5, 128.9, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.5, 127.2, 86.7, 84.6, 79.1, 72.9, 72.5, 72.1, 71.7, 67.5; HRMS (EI) calcd for C₃₅H₃₂O₄ [M⁺] 506.2457, found 506.2456.

4.6. Benzyl (15,45,5R)-4,5-bis(benzyloxy)-3-(benzyloxymethyl)cyclopenten-2-encarbamate (13)

To a stirred solution of 12 (0.13 g, 0.26 mmol) in anhydrous CH₂Cl₂ (2.6 mL) were added Na₂CO₃ (0.25 g, 2.3 mmol) and chlorosulfonyl isocyanate (0.18 mL, 2.0 mmol) at 0 °C under N₂ atmosphere. The reaction mixture was stirred for 24 h at room temperature. The resulting mixture was washed with water and brine, dried over MgSO₄, and concentrated in vacuo. The residue was extracted with EtOAc (10 mL×2). The organic layer was added to a solution of aqueous 25% Na₂SO₃ (5 mL), and the reaction mixture was further stirred for 24 h at room temperature. The organic layer was washed with water and brine, dried over MgSO₄, and concentrated in vacuo. The residue was purified by flash column chromatography (n-hexane/EtOAc=5:1) to afford 0.13 g (0.236 mmol, 91%) of 13 as white solid. ¹H NMR (300 MHz, CDCl₃) δ 7.37–7.24 (m, 20H), 5.81 (s, 1H), 5.17–5.12 (m, 2H), 4.87 (br s, 1H), 4.73 (s, 2H), 4.65 (d, J=11.4 Hz, 2H), 4.55 (d, J=5.0 Hz, 1H), 4.53–4.48 (m, 3H), 4.08 (s, 2H), 4.77 (d, J=4.5 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 143.4, 138.7, 138.2, 129.7, 128.8, 128.6, 128.5, 128.4, 128.2, 127.9, 127.8, 127.5, 127.5, 127.3, 127.2, 126.9, 84.6, 83.0, 82.3, 80.9, 75.0, 74.7, 73.3, 72.9, 70.9; HRMS (EI) calcd for C₃₅H₃₂O₅ [M⁺] 549.2515, found 549.2516.

4.7. (15,45,5R)-4,5-Bis(benzyloxy)-3-(benzyloxymethyl)cyclopenten-2-ename (14)

To a stirred solution of 13 (0.16 g, 0.28 mmol) in 1,4-dioxane (5.4 mL) was added LiOH·H₂O (0.14 g, 3.4 mmol) in water (1.8 mL) at room temperature. The reaction mixture was stirred at 120 °C for 48 h, and then cooled to room temperature. The resulting mixture was evaporated to dryness, and the residue was partitioned between water (20 mL) and CH₂Cl₂ (10 mL). The aqueous layer was extracted with CH₂Cl₂ (10 mL×2). The organic layer was washed with water, dried over MgSO₄, and concentrated in vacuo. The residue was purified by flash column chromatography (CH₂Cl₂/MeOH=20:1) to afford 0.103 g (0.248 mmol, 89%) of 14 as yellow syrup. ¹H NMR (300 MHz, CDCl₃) δ 7.36–7.25 (m, 15H), 5.58–5.49 (m, 2H), 4.84–4.79 (m, 1H), 4.66 (s, 1H), 4.62 (d, J=11.0 Hz, 2H), 4.54 (d, J=11.0 Hz, 2H), 4.50 (d, J=2.5 Hz, 1H), 4.40 (d, J=2.5 Hz, 1H), 4.29 (d, J=11.9 Hz, 1H), 4.18–4.04 (m, 4H), 3.57 (dd, J=7.9, 3.5 Hz) 1H; ¹³C NMR (125 MHz, CDCl₃) δ 138.7, 138.6, 138.5, 136.5, 128.6, 128.4, 128.3, 128.2, 127.9, 127.7, 127.6, 127.5, 118.4, 115.7, 83.8, 80.4, 79.8, 75.1, 72.8, 70.8, 70.7, 70.5; HRMS (EI) calcd for C₃₅H₃₂O₅ [M⁺] 535.2851, found 535.2848.

4.5. (1S,2R,3S)-4-(Benzyloxymethyl)cyclopenten-4-ene-1,2,3-triyli(trioxy)tris(phenylethyl)tribenzen (12)

To a stirred solution of 11 (1.11 g, 2.08 mmol) in CH₂Cl₂ (21 mL) was added second-generation Grubbs catalyst (0.35 g, 0.41 mmol). The reaction mixture was refluxed for 8 h. The solution was evaporated to dryness and the residue was purified by flash column chromatography (n-hexane/EtOAc=8:1) to afford 1.01 g (1.99 mmol, 95%) of 12 as brown syrup. ¹H NMR (300 MHz, CDCl₃) δ 7.50–6.16 (m, 10H), 4.99 (s, 2H), 4.18–4.06 (m, 2H), 3.96–3.83 (m, 5H), 3.57 (dd, J=7.9, 3.5 Hz) 1H; ¹³C NMR (125 MHz, CDCl₃) δ 138.7, 138.6, 138.5, 136.5, 128.6, 128.4, 128.3, 128.2, 127.9, 127.7, 127.6, 127.5, 118.4, 115.7, 83.8, 80.4, 79.8, 75.1, 72.8, 70.8, 70.7, 70.5; HRMS (EI) calcd for C₃₅H₃₂O₅ [M⁺] 535.2851, found 535.2848.
4.9. 9-((15S,4S,R)-4,5-bis(benzoxyl)-3-(benzoxymethyl)cyclo-
cept-2-enyl)-6-chloro-9H-purine (16)

To a stirred solution of 15 (0.542 g, 0.998 mmol) in isomyl alcohol (25 mL) was added triethyl orthoformate (1.1 mL, 6.61 mmol) at room temperature under N2 atmosphere. The reaction mixture was stirred at 120°C for 12 h. The resulting mixture was evaporated to dryness and the residue was purified by flash column chromatography (n-hexane/EtOAc=1:1) to afford 0.66 g (1.22 mmol, 89%) of 15 as yellow syrup. Rf=0.50 (n-hexane/ 

EtOAc=1:1); [α]25D +32.9 (c 0.4, CHCl3); IR ( neat) ν 3357, 3030, 2585, 1576, 1496, 1455, 1420, 1360, 1210, 1097, 749, 768, 746, 419 cm-1; 1H NMR (500 MHz, CDCl3) δ 8.12 (s, 1H), 7.36–7.27 (m, 15H), 5.91 (d, J=1.5 Hz, 1H), 5.32 (dd, J=3.5, 1.5 Hz, 1H), 4.86 (d, J=12.0 Hz, 1H), 4.72 (d, J=12.5 Hz, 1H), 4.66 (d, J=12.0 Hz, 1H), 4.47 (d, J=11.5 Hz, 1H), 4.51–4.59 (m, 4H), 4.13 (s, 3H), 3.88 (dd,J=4.5, 4.4 Hz, 1H), 3.21 (s, 2H); 13C NMR (125 MHz, CDCl3) δ 154.8, 150.0, 144.1, 143.9, 138.6, 138.4, 132.9, 129.5, 128.7, 128.6, 128.4, 128.1, 120.8, 127.9, 127.8, 121.9, 82.6, 79.3, 73.4, 72.0, 67.3, 60.3; HRMS (EI) calcd for C31H21ClNO3 [M+H]+ 543.2163, found 543.2163.

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Supplementary data

1H NMR and 13C NMR copies of all compounds. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2014.12.093.

References and notes


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