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Synthesis of (−)-neplanocin A with the highest overall yield via an efficient Mitsunobu coupling

Benoît Y. Michel and Peter Strazewski*

Laboratoire de Synthèse de Biomolécules (UMR 5246, ICBMS), Bâtiment Eugène Chevreul (5ième étage), Université Claude Bernard Lyon 1, 43 boulevard du 11 novembre 1918, 69622 Villeurbanne, France

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Abstract—Neplanocin A was synthesized in very high isolated yield and purity, in 10 steps from D-ribose via an efficient Mitsunobu coupling using N^6-bis-Boc-protected adenine. In fact, this synthesis is a short pathway to enantiopure neplanocin A giving the highest published overall yield.

1. Introduction

Originally isolated from the culture filtrate of the soil fungus *Ampulliariella regularis*,[1] (−)-neplanocin A (**1**), a carbocyclic nucleoside (Fig. 1), showed potent antiviral and antitumor activities.[2] Its effects have been attributed to the inhibition of *S*-adenosyl-L-homocysteine (AdoHcy) hydrolase,[1] which in turn affects the viral mRNA capping methylation. Unfortunately, this antibiotic is not suitable for the clinical use because of its cytotoxicity, which would be largely due to a potential 5′-phosphorylation. Because of the absence of a true glycosidic bond, this naturally occurring carbocyclic analogue of adenosine is chemically more stable and not subject to the action of the enzymes that break this linkage in conventional nucleosides.[3]

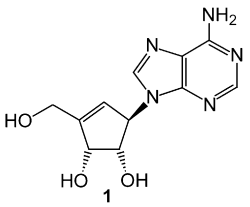

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Figure 1. Neplanocin A.

Each synthesis of the neplanocin A[4] or other carbocyclic[5] nucleosides presents the same drawback, the low yield and N7/N^6/N9 regioselectivity of the Mitsunobu coupling when adenine was used to attach the *N*-heterocyclic base.[4g,5] Indeed, the main invoked reasons were the low solubility of adenine in THF, which is the favorite solvent of this coupling, and the free amino group at C6 of adenine, which is responsible for sides effects. Several alternatives were proposed to make up for this problem. The most interesting idea was to use 6-chloropurine for the coupling followed by the substitution of Cl by ammonia. However, this amination step requires somewhat extreme conditions (high pressure and temperature), which contributed to the reduced overall yield obtained.[6] Recently, Schneller and co-workers developed a procedure with bis-Boc adenine,[7,8] which enables them to circumvent the previous worries. Indeed, this di-protected base was perfectly soluble in THF, consequently the rate of the reaction was considerably accelerated. We have optimized the conditions of the Mitsunobu reaction, in particular the order of addition of the reactants and the elimination of the hydrazine derived from DIAD, which is often difficult to separate.[9] Both measures enabled us to obtain quasi-quantitatively the coupled product in a high purity.

Among several syntheses of carbocyclic moieties,[4e,10] we chose the one of Jeong and coworkers[11] that lead to D-cyclopentenone derivative **8** using olefin ring closing metathesis (RCM) as one of the key steps. This protected triol **8** is an important synthetic precursor not only of **1**, but also its analogues and other cyclopentenoids.[12] This synthesis presents several assets, first, its short stereoselective route with a high overall yield, moreover the possibility to work on a large scale. However, we replaced the second generation Grubbs catalyst[13] with Fürstner's new metathesis catalyst[14] Neolyst dichloride™. It is commercially available, six times cheaper and it works just as well.

Keywords: Antiviral; Antitumor; Carbocyclic nucleosides; Mitsunobu coupling; Metathesis; Fürstner's catalyst.
* Corresponding author. Tel.: +334 72 44 82 34; fax: +334 72 43 13 23; e-mail: strazewski@univ-lyon1.fr

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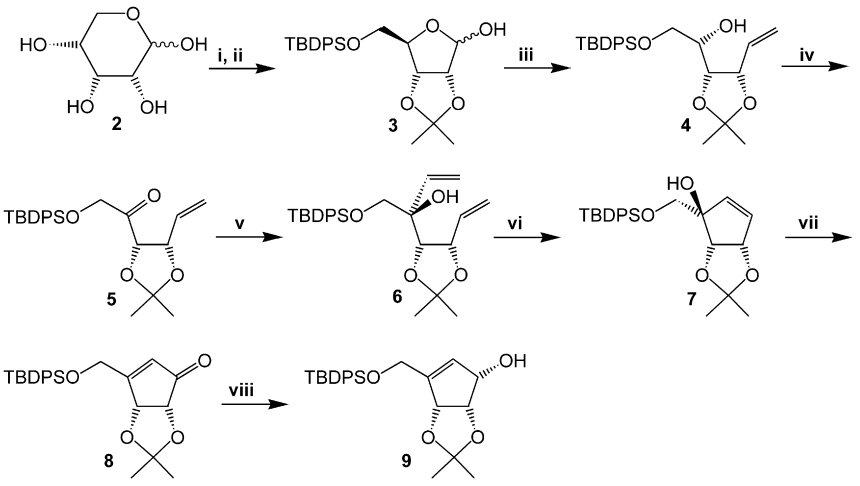
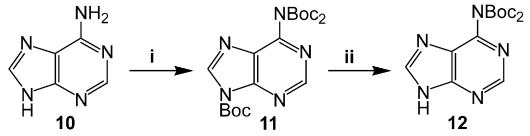


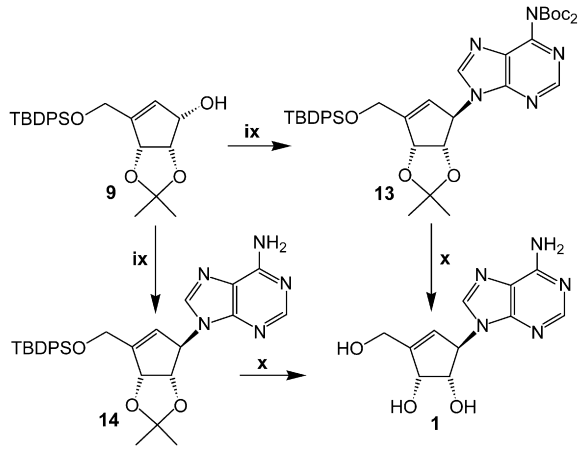
Scheme 1. Reagents and conditions: (i) acetone, H_2SO_4 cat., rt, 3 h, 88%; (ii) TBDPSCl, Et_3N, DMAP, CH_2Cl_2, rt, 3 h, 100%; (iii) Ph_3PMeBr, ^tBuOK, THF, 0 °C to rt, 8 h, 86%; (iv) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to rt, 2 h, 30, 99%; (v) CH_2═$CHMgBr$, THF, −78 °C, 1 h, 96%; (vi) Neolyst dichloride™, CH_2Cl_2, rt, 2 days, 95%; (vii) PDC, 4 Å MS, DMF, rt, 36 h, 90%; (viii) $CeCl_3\cdot 7H_2O$, $NaBH_4$, MeOH, 0–5 °C, 30 min, 99%.

2. Results and discussion

We began the synthesis with the protection of the 2′ and 3′ positions (Scheme 1). D-Ribose (**2**) was converted to the acetonide.[10c] The 5′ position was then quantitatively protected as *tert*-butyldiphenylsilyl ether **3**, which underwent Wittig reaction followed by Swern oxidation to afford **5**. During the Grignard reaction the bulky protecting group plays an important role. In fact, the steric hindrance enforced the vinylmagnesium bromide to add itself preferentially on one of the faces, following Felkin–Anh's model, and yielded stereoselectively the tertiary allylic alcohol **6**. RCM was carried out on diene **6** using Neolyst dichloride™ to furnish the *tert*-β-allylic alcohol **7** in the same yield as after RCM with Grubbs II catalyst.[10] An oxidative rearrangement of **7** with PDC in DMF afforded D-cyclopentenone **8**, which underwent a quantitative Luche reduction to give the allylic alcohol **9**.



Scheme 2. Reagents and conditions: (i) $(Boc)_2O$, DMAP, THF, rt, overnight, 87%; (ii) $NaHCO_3$ satd, rt, overnight, 93%.



Scheme 3. Reagents and conditions: (ix) PPh_3, DIAD, adenine or N^6-bis-Boc-adenine, 0 °C to rt, overnight, 74–98%; (x) TFA, $ClCH_2CH_2Cl$/MeOH, rt, 3 h, 99%.

In order to carry out the Mitsunobu coupling, bis-Boc-adenine was first prepared according to the Garner procedure (Scheme 2).[8] With the desired di-protected heterocyclic base in hand, an almost quantitative coupling was achieved to give **13**, which was totally deprotected under acidic conditions (Scheme 3). Thanks to a special eluant system EtOAc/MeOH/H_2O, flash chromatography of this highly polar compound afforded neplanocin A with a high purity in an overall yield reaching 59%. In comparison, the Mitsunobu reaction using adenine gave **14** in only 74% yield.

3. Conclusion

This optimized 10-step procedure enabled us to obtain a naturally occurring carbocyclic nucleoside, neplanocin A, in an overall yield of 59% from D-ribose. The pathway called in a highly stereoselective Grignard addition, followed by a RCM using an unsolicited cheap catalyst and ended on a quasi-quantitative Mitsunobu coupling. The scale-up, the restricted number of steps and the mildness of reaction conditions render this synthetic route very interesting for future works on more complex carbocyclic nucleosides as, for example, methanocarba nucleosides. Indeed, the introduction of Simmons–Smith reaction just after the Luche reduction followed by a quantitative Mitsunobu coupling leads to (*N*)-methanocarba analogues on a substantial scale.

4. Experimental section

4.1. General

^1H NMR spectra (300 MHz) were obtained from solutions in $CDCl_3$, with the residual protonated solvent signal as internal reference (7.26 ppm for $CHCl_3$). The chemical shifts δ_H are given in parts per million; the coupling constants *J* are

given in hertz (Hz); the signals are described as follows: ps=pseudo, br=broad, s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet. ^{13}C NMR spectra (75 MHz) were measured in $CDCl_3$; δ_C (central signal)=77.0 ppm. The assignments of ^1H and ^{13}C NMR signals were achieved with the help of D/H exchange, COSY, HSQC, HMBC, and DEPT experiments. All fully interpreted NMR spectra are available in Supplementary data. Mass spectra (MS and HRMS) were obtained using fast atom bombardment (FAB from CH_2Cl_2 or H_2O/MeOH 9:1) and electro spray ionization (ESI, from CH_2Cl_2 or DMSO). Mp: melting points were taken in a Büchi apparatus and are uncorrected. Thin layer chromatography (TLC) was performed on pre-coated silica gel F_{254} plates with fluorescent indicator. The compounds were visualized using UV light (254 nm). Free amines were visualized on TLC plates by spraying with 20% ninhydrin solutions in ethanol, followed by heating. Nucleosides were visualized on TLC plates by subsequent spraying with concentrated H_2SO_4 followed by 2% naphthoresorcinol (for the ribose intermediates) or phosphomolybdic acid solutions in ethanol, followed by heating. Column chromatography was performed with flash silica gel (0.04–0.063 mm).

4.2. Optimized synthetic procedures

4.2.1. 2,3-*O*,*O*-Isopropylidene-5-(*tert*-butyldiphenylsilyl)-D-ribose (3). To a stirred suspension of D-ribose (10.05 g, 66.6 mmol) in acetone (125 mL) was added dropwise concd H_2SO_4 (0.3 mL) at room temperature and the reaction mixture was stirred at this temperature for 3 h. The mixture was neutralized with solid $NaHCO_3$, filtered and evaporated under reduced pressure to give a colorless syrup. The residue was purified by silica gel column chromatography using petroleum ether and ethyl acetate (1:2) as the eluent to afford the acetonide **2** as a colorless syrup (11.15 g, 88%): $C_8H_{14}O_5$ (190.19). R_f (petrol ether/EtOAc 1:2)=0.40. ^1H NMR (MeOH-d_4): δ=1.31 (s, 3H, CH_3); 1.44 (s, 3H, CH_3); 3.58 (dd, 1H, ^3J=5.1, ^2J=11.7, H_A5); 3.63 (dd, 1H, ^3J=4.5, ^2J=11.7, H_B5); 4.19 (irregular t=dd, 1H, ^3J=4.5, 5.1, H4); 4.52 (d, 1H, ^3J=6.0, H2); 4.77 (d, 1H, ^3J=6.0, H3); 5.26 (s, 1H, H1). ^{13}C NMR (MeOH-d_4): δ=25.00 (CH_3); 26.79 (CH_3); 64.35 (C5); 83.46 (C3); 87.93 (C2); 88.61 (C4); 103.98 (C1), 113.20 (C-isopropylidene). MS (ESI^+): m/z=213.0 $[M+Na]^+$.

To a stirred solution of the acetonide (6.75 g, 35.5 mmol) in CH_2Cl_2 (150 mL) were added triethylamine (10.0 mL, 71.0 mmol), *tert*-butylchlorodiphenylsilane (9.9 mL, 37.3 mmol), and DMAP (44 mg, 0.36 mmol) and the mixture was stirred at room temperature for 3 h. After the solvent was removed, the residue was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (petrol ether/EtOAc 7:1) to yield **3** (15.21 g, 100%) as a colorless oil as a 4:1 anomeric mixture according to ^1H NMR integrals: $C_{24}H_{32}O_5Si$ (428.59). R_f (petrol ether/EtOAc 7:1)=0.33. ^1H NMR ($CDCl_3$): δ=1.05 (s, 1.8H, Si–C(CH_3)$_3$); 1.09 (s, 7.2H, Si–C(CH_3)$_3$); 1.32 (s, 2.4H, CH_3); 1.40 (s, 0.6H, CH_3); 1.48 (s, 2.4H, CH_3); 1.56 (s, 0.6H, CH_3); 3.64 (m, 1H, H_A5); 3.82 (m, 1H, H_B5); 3.95 (d, 0.2H, ^3J=11.4, OH); 4.15 (t, 0.2H, ^3J=2.4, H4); 4.29 (t, 0.8H, ^3J=2.4, H4); 4.53 (s, 0.8H, OH); 4.61 (d, 0.8H, ^3J=5.7, H3); 4.67 (dd, 0.2H, ^3J=4.2, 6.3, H3); 4.72 (d, 0.8H, ^3J=6.0, H2); 4.78 (d, 0.2H, ^3J=6.0, H2); 5.35 (d, 0.8H, ^3J=10.8, H1); 5.63 (dd, 0.2H, ^3J=3.9, ^3J=11.2, H1); 7.40–7.70 (m, 10H, H-Ar). ^{13}C NMR ($CDCl_3$): δ=19.45, 19.53 (Si–*C*(CH_3)$_3$); 25.08, 25.36 (CH_3); 26.56, 26.87 (CH_3); 27.25, 27.30 (Si–C(*C*H_3)$_3$); 65.90, 66.49 (C5); 79.89 (C3); 81.66 (C4); 82.03, 82.7 (C2); 87.47 (C4), 87.76 (C3); 112.52, 113.38 (C-isopropylidene); 128.31, 128.46, 128.52 (4C, C–*m*-Si–Ph); 130.35, 130.43, 130.65, 130.84 (4C, C–*p*-Si–Ph); 131.90, 132.00, 132.78, 133.03 (4C, C–*i*-Si–Ph); 135.95, 136.14 (4C, C–*o*-Si–Ph). MS (ESI^+): m/z=878.9 $[2\cdot M+Na]^+$.

4.2.2. (1*S*,4*R*,5*S*)-(−)-1-(2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-2-(*tert*-butyldiphenylsilyloxy)ethan-1-ol (4). To a stirred suspension of methyl phosphonium bromide (3.66 g, 10.0 mmol) in THF (30 mL) was added potassium *tert*-butoxide (1.16 g, 9.8 mmol) at 0 °C and the reaction mixture was stirred at room temperature for 1 h. After the mixture was cooled to 0 °C, a solution of lactol **3** (2.00 g, 4.67 mmol) in THF (5 mL) was added and the reaction mixture was stirred at 0 °C for 3 h, then at room temperature for 4 h. The reaction mixture was divided between water and ethyl acetate and the organic layer was washed with brine, dried over anhydrous magnesium sulfate, filtered, and evaporated. The residue was purified by silica gel column chromatography (petrol ether/EtOAc 10:1) to give **4** as a colorless oil (1.71 g, 86%): $C_{25}H_{34}O_4Si$ (426.63). R_f (petrol ether/EtOAc 8:1)=0.37. ^1H NMR ($CDCl_3$): δ=1.08 (s, 9H, Si–C(CH_3)$_3$); 1.35 (s, 3H, CH_3); 1.38 (s, 3H, CH_3); 2.58 (d, 1H, ^3J=4.2, OH); 3.72 (m, 1H, H1); 3.80 (dd, 1H, ^3J=5.3, ^2J=10.4, H_A2); 3.87 (dd, 1H, ^3J=3.5, ^2J=10.4 Hz, H_B2); 4.15 (dd, 1H, ^3J=6.3, 9.0, H4); 4.70 (t, 1H, ^3J=6.3, H5); 5.28 (dt, 1*H*, ^3J=10.5, ^2J=1.5, CH=CH_2 *cis*); 5.41 (dt, 1H, ^3J=17.1, ^2J=1.5, CH=CH_2 *trans*); 6.01 (ddd, 1H, ^3J=6.8, 10.4, 17.1, C*H*=CH$_2$); 7.36–7.71 (m, 10H, H-Ar). ^{13}C NMR ($CDCl_3$): δ=19.29 (Si–*C*(CH_3)$_3$); 25.41 (CH_3); 26.82 (Si-C(*C*H_3)$_3$); 27.74 (CH_3); 65.22 (C2); 69.78 (C1); 77.46 (C4); 78.79 (C5); 108.72 (C-isopropylidene), 117.71 (CH=*C*H_2); 127.72, 127.77 (4C, C–*m*-Si–Ph); 129.79, 129.83 (4C, C–*p*-Si–Ph), 132.92, 133.05 (4C, C–*i*-Si–Ph); 133.98 (*C*H=CH$_2$); 135.51, 135.57 (4C, C–*o*-Si–Ph). MS (ESI^+): m/z=449.1 $[M+Na]^+$.

4.2.3. (4*S*,5*S*)-(−)-1-(2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-2-(*tert*-butyldiphenylsilyloxy)ethan-1-one (5). To a stirred solution of oxalyl chloride (1.75 mL, 20.29 mmol) in CH_2Cl_2 (70 mL) was added a solution of DMSO (3.2 mL, 44.38 mmol) in CH_2Cl_2 (10 mL) at −78 °C, and the reaction mixture was stirred at the same temperature for 30 min. After a solution of alcohol **4** (5.41 g, 12.68 mmol) in CH_2Cl_2 (10 mL) was added, the reaction mixture was stirred at −78 °C for 1 h. Triethylamine (11.8 mL, 83.7 mmol) was added at −78 °C and then the reaction mixture was allowed to warm up to room temperature and stirred for 1 h. After saturated NH_4Cl solution was carefully added at 0 °C, the reaction mixture was partitioned between CH_2Cl_2 and water, and the organic layer was dried over anhydrous magnesium sulfate, filtered and evaporated. The residue was purified by silica gel column chromatography (CyHex/EtOAc 8:1) to give the ketone **5** as a colorless

oil (5.35 g, 99%): $C_{25}H_{32}O_4Si$ (424.62). R_f (petrol ether/EtOAc 8:1)=0.40. ^{1}H NMR ($CDCl_3$): δ=1.10 (s, 9H, Si-C(CH_3)$_3$); 1.36 (s, 3H, CH_3); 1.49 (s, 3H, CH_3); 4.24 (d, 1H, ^2J=18.8, H_A2); 4.49 (d, 1H, ^2J=18.8, H_B2); 4.86 (m, 2H, H4, H5); 5.12 (dt, 1H, ^3J=10.2, ^2J=1.5, CH=CH_2 *cis*); 5.32 (dt, 1H, ^3J=16.5, ^2J=1.5, CH=CH_2 *trans*); 5.43 (m, 1H, C*H*=CH_2); 7.37–7.66 (m, 10H, H-Ar). ^{13}C NMR ($CDCl_3$): δ=19.22 (Si–*C*(CH_3)$_3$); 24.81, 26.75 (CH_3); 26.75 (Si–C(*C*H_3)$_3$); 69.00 (C2); 78.31 (C5); 81.75 (C4); 110.30 (C-isopropylidene), 119.03 (CH=*C*H_2); 127.77, 128.82 (4C, C-*m*-Si–Ph); 129.94 (4C, C–*p*-Si–Ph); 132.36 (*C*H=CH_2); 132.55 (4C, C-*i*-Si–Ph); 135.52, 135.56 (4C, C–*o*-Si–Ph); 205.59 (C1). MS (ESI$^+$): *m*/*z*=447.2 [M+Na]$^+$.

4.2.4. (1*R*,4*S*,5*S*)-(+)-1-(2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-1-(*tert*-butyldiphenylsilyloxymethyl)-2-propen-1-ol (6). To a stirred solution of **5** (8.69 g, 20.47 mmol) in THF (90 mL) was added dropwise vinylmagnesium bromide (40.93 mL, 40.93 mmol, 1 M in THF) at −78 °C, and the reaction mixture was stirred for 1 h at the same temperature. It was quenched by saturated ammonium chloride solution and brine and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered and evaporated under reduced pressure. The resulting oil was purified by silica gel column chromatography (CyHex/EtOAc 12:1) to give the allylic alcohol **6** (8.90 g, 96%) as a colorless oil: $C_{27}H_{36}O_4Si$ (452.67). R_f (CyHex/EtOAc 12:1)=0.33. ^{1}H NMR ($CDCl_3$): δ=1.08 (s, 9H, Si-C(CH_3)$_3$); 1.40 (s, 3H, CH_3); 1.50 (s, 3H, CH_3); 2.81 (s, 1H, OH); 3.48 (d, 1H, ^2J=9.9, H_A6); 3.80 (d, 1H, ^2J=9.9, H_B6); 4.47 (d, 1H, ^3J=6.9, H4); 4.68 ('t'=dd, 1H, ^3J=7.5, 7.8, H5); 5.14 (dt, 1H, ^3J=9.9, ^2J=1.2, CH=CH_2 *cis*); 5.25 (dd, 1H, ^3J=11.7, ^2J=1.5, H3 *cis*); 5.26 (dt, 1H, ^3J=16.8, ^2J=1.2, CH=CH_2 *trans*); 5.44 (dd, 1H, ^3J=17.4, ^2J=1.5, H3 *trans*); 6.11 (m, 2H, H2, C*H*=CH_2); 7.36–7.70 (m, 10H, H-Ar). ^{13}C NMR ($CDCl_3$): δ=19.32 (Si–*C*(CH_3)$_3$); 24.89 (CH_3); 26.81 (Si–C(*C*H_3)$_3$); 27.27 (CH_3); 68.44 (C6); 75.46 (C1); 78.67 (C4); 79.35 (C5); 108.19 (C-isopropylidene), 115.95 (C3); 117.76 (CH=*C*H_2); 127.66, 127.72 (4C, C-*m*-Si–Ph); 129.77, 129.82 (4C, C-*p*-Si–Ph), 132.81, 132.87 (2C, C-*i*-Si–Ph); 135.11 (*C*H=CH_2); 135.59, 135.61 (4C, C–*o*-Si–Ph); 138.17 (C2). MS (ESI$^+$): *m*/*z*=475.2 [M+Na]$^+$.

4.2.5. (1*R*,4*S*,5*S*)-(+)-4,5-*O*,*O*-Isopropylidene-1-(*tert*-butyl-diphenylsilyloxymethyl)-2-cyclopenten-1-ol (7). To a stirred solution of **6** (8.90 g, 19.66 mmol) in CH_2Cl_2 (65 mL) was added Neolyst dichloride™ (364 mg, 0.39 mmol) and the reaction mixture was stirred at room temperature for 2 days. The volatiles were removed under reduced pressure and the residue was purified by silica gel column chromatography (CyHex/EtOAc 7:1, 6:1, 5:1) to give the allylic alcohol **7** (7.88 g, 95%) as a colorless oil: $C_{25}H_{32}O_4Si$ (424.62). R_f (CyHex/EtOAc 6:1)=0.30. ^{1}H NMR ($CDCl_3$): δ=1.10 (9H, Si-C(CH_3)$_3$); 1.28 (s, 3H, CH_3); 1.34 (s, 3H, CH_3); 3.29 (s, 1H, OH); 3.71 (d, 1H, ^2J=10.1, H_A6); 4.03 (d, 1H, ^2J=10.1, H_B6); 4.55 (d, 1H, ^3J=5.4, H5); 5.34 (dt, 1H, ^3J=1.2, 5.4, H4); 5.75 (dt, 1H, ^3J=0.9, 5.7, H2); 5.99 (dd, 1H, ^3J=1.7, 5.7, H3); 7.36–7.76 (m, 10H, H-Ar). ^{13}C NMR ($CDCl_3$): δ=19.30 (Si-C(CH_3)$_3$); 26.09 (CH_3); 26.79 (Si-C(CH_3)$_3$); 27.39 (CH_3); 65.69 (C6); 84.60 (C4); 84.81 (C5); 85.04 (C1); 111.97 (C-isopropylidene); 127.62, 127.75 (4C, C-*m*-Si–Ph); 129.78, 129.81 (4C, C-*p*-Si–Ph); 132.73, 132.95 (2C, C-*i*-Si–Ph); 134.44 (C2); 135.52, 135.71 (4C, C-*o*-Si–Ph); 135.77 (C3). MS (ESI$^+$): *m*/*z*=447.2 [M+Na]$^+$.

4.2.6. (4*R*,5*R*)-(+)-3-*tert*-Butyldiphenylsilyloxymethyl-4,5-*O*,*O*-isopropylidene-2-cyclopentenone (8). A solution of allylic alcohol **7** (940 mg, 2.21 mmol), 4 Å molecular sieves (1.82 g), and pyridinium dichromate (2.55 g, 6.64 mmol) in DMF (8 mL) was stirred at room temperature for 2 days. The reaction mixture was directly purified by silica gel column chromatography (CyHex/EtOAc 8:1, 7:1, 6:1) to give the cyclopentenone **8** (7.88 g, 90%) as a colorless oil: $C_{25}H_{30}O_4Si$ (422.59). R_f (CyHex/EtOAc 7:1)=0.25. $[\alpha]_D^{27}$ 6.2 (*c* 2.29, CH_2Cl_2).[11] ^{1}H NMR ($CDCl_3$): δ=1.09 (s, 9H, Si-C(CH_3)$_3$); 1.33 (s, 3H, CH_3); 1.35 (s, 3H, CH_3); 4.49 (dd, 1H, ^3J=1.2, ^2J=18.9, H_A6); 4.49 (d, 1H, ^3J=5.6, H5); 4.69 (dd, 1H, ^3J=1.8, ^2J=18.9, H_B6); 4.98 (d, 1H, ^3J=5.6, H4); 6.33 (s, 1H, H2); 7.36–7.73 (m, 10H, H-Ar). ^{13}C NMR ($CDCl_3$): δ=19.18 (Si–*C*(CH_3)$_3$); 26.18 (CH_3); 26.66 (Si–C(*C*H_3)$_3$); 27.36 (CH_3); 62.37 (C6); 77.63 (C4); 77.97 (C5); 115.33 (C-isopropylidene); 127.80 (C2); 127.86 (4C, C-*m*-Si–Ph); 129.99 (4C, C-*p*-Si–Ph); 132.48, 132.55 (2C, C-*i*-Si–Ph); 135.38 (4C, C-*o*-Si–Ph); 176.77 (C3); 201.67 (C1). MS (ESI$^+$): *m*/*z*=866.9 [2M+Na]$^+$.

4.2.7. (1*S*,4*R*,5*S*)-4,5-*O*,*O*-Isopropylidene-3-(*tert*-butyldiphenylsilyloxymethyl)-2-cyclopenten-1-ol (9). Sodium borohydride (220 mg, 5.82 mmol) was added portionwise to a solution of cyclopentenone **8** (1.585 g, 3.75 mmol) and cerium(III) chloride heptahydrate (1.198 g, 3.15 mmol) in methanol (7 mL), while the temperature was maintained between 0 and 5 °C. After 30 min, acetic acid was carefully added to adjust to pH 5. Water (7 mL) was added and the reaction mixture was extracted with ether. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. The solvents were removed under reduced pressure and the residue was purified by silica gel column chromatography (CyHex/EtOAc 9:1) to give the allylic alcohol **9** (1.61 g, 99%) as a colorless oil: $C_{25}H_{32}O_4Si$ (424.62). R_f (CyHex/EtOAc 9:1)=0.25. ^{1}H NMR ($CDCl_3$): δ=1.07 (s, 9H, Si–C(CH_3)$_3$); 1.33 (s, 3H, CH_3); 1.35 (s, 3H, CH_3); 2.68 (d, 1H, ^3J=9.9, OH); 4.28 (d, 1H, ^2J=15.2, H_A6); 4.38 (d, 1H, ^2J=15.2, H_B6); 4.56 (m, 1H, H1); 4.75 (ps t, 1H, ^3J=4.8, 5.9, H5); 4.86 (d, 1H, ^3J=5.9, H4); 5.84 (d, 1H, ^3J=1.8, H2); 7.34–7.69 (m, 10H, H-Ar). ^{13}C NMR ($CDCl_3$): δ=19.22 (Si–*C*(CH_3)$_3$); 26.68 (CH_3); 26.77 (Si–C(*C*H_3)$_3$); 27.58 (CH_3); 60.77 (C6); 73.25 (C1); 77.94 (C5); 82.77 (C4); 112.44 (C-isopropylidene); 127.66 (4C, C-*m*-Si–Ph); 129.26 (C2); 129.71 (4C, C-*p*-Si–Ph); 133.26 (2C, C–*i*-Si–Ph); 135.50 (4C, C–*o*-Si–Ph); 145.23 (C3); HRMS (ESI$^+$): *m*/*z*=447.1968 (calculated for [M+Na]$^+$: 447.1967).

4.2.8. N^6,N^6,9-*N*-Tris-(*tert*-butoxycarbonyl)adenine (11). To a stirred suspension of adenine (300 mg, 2.22 mmol) and DMAP (82 mg, 0.67 mmol) in THF (11 mL) was added Boc_2O (2.00 g, 8.88 mmol). After 20 min, the solution became clear yellow. The reaction mixture was stirred overnight at room temperature. Then, the volatiles were

removed under reduced pressure and the residue was purified by silica gel column chromatography (CyHex/EtOAc 9:1, 4:1, 7:3) to give the tri-protected product **11** (840 mg, 87%) as a colorless oil: $C_{20}H_{25}N_5O_6$ (435.47). R_f (CyHex/EtOAc 7:3)=0.48. ^{1}H NMR ($CDCl_3$): δ=1.36 (s, 18H, N^6Boc_2); 1.65 (s, 9H, N9Boc); 8.46 (s, 1H, H8); 8.94 (s, 1H, H2). ^{13}C NMR ($CDCl_3$): δ=27.54, 27.73 (N(C(O)OC(CH_3)$_3$)); 83.74, 87.31 (N(C(O)OC(CH$_3$)$_3$)); 129.39 (C5); 143.04 (C8); 145.45, 151.01, 152.27 (C4, C6, N(C(O)O^{t}Bu); 149.83 (N(C(O)O^{t}Bu)$_2$); 153.85 (C2).

4.2.9. N^6,N^6-Bis-(*tert*-butoxycarbonyl)adenine (12). To a stirred solution of tris-Boc-adenine (**11**) (3.080 g, 7.07 mmol) in MeOH (70 mL) was added a saturated solution of $NaHCO_3$ (35 mL) and the reaction mixture became cloudy. Then, the solution is warmed at 50 °C for 1 h 15 min. The evolution of the reaction is followed by TLC. When the conversion is quantitative, MeOH was removed under reduced pressure. Water (70 mL) was added and the aqueous layer was extracted with 3×$CHCl_3$. The organic layer was dried over anhydrous magnesium sulfate and filtered. The solvents were removed under reduced pressure and the residue was purified by silica gel column chromatography (CyHex/EtOAc 3:7, 1:4, 1:9, 0:1) to give the bis-Boc-adenine (**12**) (2.21 g, 93%) as a white solid: $C_{15}H_{21}N_5O_4$ (335.36). Mp: 149–150 °C.[8] R_f (EtOAc)=0.36. ^{1}H NMR ($CDCl_3$): δ=1.36 (s, 18H, N^6Boc_2); 8.63 (s, 1H, H8); 8.81 (s, 1H, H2); 13.68 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ=27.23 (N(C(O)OC(CH_3)$_3$)$_2$); 83.12 (N(C(O)OC(CH$_3$)$_3$)$_2$); 145.61 (C8); 149.86 (N(C(O)O^{t}Bu)$_2$); 151.36 (C2).

4.2.10. (l*R*,4*R*,5*S*)-9-*N*-[3-(*tert*-Butyl-diphenylsilyloxymethyl)-4,5-*O*,*O*-isopropylidene-2-cyclopenten-L-yl]-N^6,N^6-bis-(*tert*-butoxycarbonyl)adenine (13). To a stirred solution of triphenylphosphine (563 mg, 2.12 mmol) in THF (5 mL) at 0 °C was added dropwise the DIAD (436 μL, 2.12 mmol) and the yellow reaction mixture was stirred at this temperature for 30 min. After that, a solution of the allylic alcohol **9** (403 mg, 0.92 mmol) in THF (5 mL), beforehand coevaporated with toluene (3×5 mL), was added and the reaction mixture was stirred at 0 °C for 10 min. Then, the cold bath was removed and the yellow solution was stirred for 30 min at room temperature. Bis-Boc adenine (710 mg, 2.12 mmol) was added finally and the solution became clear after 2 min. The reaction mixture was stirred overnight at room temperature. The volatiles were removed under reduced pressure and the residue was purified by silica gel column chromatography (CyHex/EtOAc 6:1, 4:1, 3:1). The desired product was still contaminated by a large amount of the hydrazine derivated from DIAD. To eliminate it, the product was dissolved in a minimum volume of EtOAc, then added dropwise to a large volume of petroleum ether. The solution was put in the freezer at −22 °C for 2 h, afterwards filtered and eventually the volatiles were removed under reduced pressure to yield **13** (669 mg, 98%) as a colorless oil: $C_{40}H_{51}N_5O_7Si$ (741.97). R_f (CyHex/EtOAc 2:1)=0.33. ^{1}H NMR ($CDCl_3$): δ=1.08 (s, 9H, Si–C(CH$_3$)$_3$); 1.33 (s, 3H, CH$_3$); 1.43 (s, 3H, CH$_3$); 1.48 (s, 18H, NBoc$_2$); 4.45 (d, H, ^2J=13.2, H$_A$6′); 4.52 (d, H, ^2J=13.2, H$_B$6′); 4.72 (d, 1H, ^3J=5.9, H4′); 5.28 (d, 1H, ^3J=5.9, H5′); 5.65 (s, 1H, H1′); 5.87 (s, 1H, ^3J=6.9, H2′); 7.32–7.68 (m, 10H, H-Ar), 7.86 (s, 1H, H8); 8.89 (s, 1H, H2). ^{13}C NMR ($CDCl_3$): δ=19.17 (Si–C(CH$_3$)$_3$); 25.85 (CH$_3$); 26.71 (3C, Si–C(CH$_3$)$_3$); 27.27 (CH$_3$); 27.73 (6C, N(C(O)OC(CH$_3$)$_3$)$_2$); 61.10 (C6′); 64.81 (C1′); 83.61 (C5′); 83.73 (2C, N(C(O)OC(CH$_3$)$_3$)$_2$); 84.47 (C4′); 112.72 (C-isopropylidene); 120.69 (C2′); 127.74 (4C, C-*m*-Si–Ph); 129.20 (C5); 129.87 (2C, C-*p*-Si–Ph); 132.93 (2C, C-*i*-Si–Ph); 135.36 (4C, C-*o*-Si–Ph); 142.95 (C8); 150.28 (C6); 150.47 (2C, N(C(O)O^{t}Bu)$_2$); 152.21 (C2); 152.52 (C3′); 152.89 (C4). HRMS (ESI$^+$): m/z=742.3641 (calculated: 742.3636).

4.2.11. (l*R*,4*R*,5*S*)-9-*N*-[3-(*tert*-Butyl-diphenylsilyloxymethyl)-4,5-*O*,*O*-isopropylidene-2-cyclopenten-L-yl]adenine (14). To a stirred solution of triphenylphosphine (294 mg, 1.11 mmol) in THF (3 mL) at 0 °C was added dropwise the DIAD (228 μL, 0.39 mmol) and the reaction mixture was stirred at this temperature for 30 min. After that, a solution of the allylic alcohol **9** (204 mg, 0.48 mmol) in THF (3 mL) was added and the reaction mixture was stirred at 0 °C for 10 min. Then the cold bath was removed and the yellow solution was stirred 30 min at room temperature. Adenine (151 mg, 1.11 mmol) was added finally and the reaction mixture was stirred overnight at room temperature. The volatiles were removed under reduced pressure and the residue was purified by silica gel column chromatography (CyHex/EtOAc 1:1, 2:3, 3:7, 1:4) to give **14** (192 mg, 74%) as a colorless oil: $C_{30}H_{35}N_5O_3Si$ (541.73). ^{1}H NMR ($CDCl_3$): δ=1.08 (s, 9H, Si–C(CH$_3$)$_3$); 1.31 (s, 3H, CH$_3$); 1.41 (s, 3H, CH$_3$); 4.49 (2d, 2H, ^2J=18.6, H$_A$6′, H$_B$6′); 4.68 (d, 1H, ^3J=5.7, H4′); 5.25 (d, 1H, ^3J=5.7, H5′); 5.60 (s, 1H, H1′); 5.86 (s, 1H, H2′); 6.22 (s, 2H, NH_2); 7.35–7.70 (m, 10H, H-Ar); 7.58 (s, 1H, H8); 8.37 (s, 1H, H2). ^{13}C NMR ($CDCl_3$): δ=19.24 (Si–C(CH$_3$)$_3$); 25.92 (CH$_3$); 26.78 (Si–C(CH$_3$)$_3$); 27.35 (CH$_3$); 61.20 (C6′); 64.41 (C1′); 83.59 (C5′); 84.76 (C4′); 112.66 (C-isopropylidene); 119.99 (C5); 121.20 (C2′); 127.78 (4C, C–*m*-Si–Ph); 129.90 (4C, C–*p*-Si–Ph); 133.02, 133.11 (2C, C–*i*-Si–Ph); 135.43 (4C, C–*o*-Si–Ph); 138.49 (C8); 149.81 (C6); 152.08 (C3′); 153.14 (C2); 155.47 (C4). HRMS (ESI$^+$): m/z=542.2586 (calculated for [M+H]$^+$: 542.2587).

4.2.12. Neplanocin A: (1*S*,2*R*,5*R*)-5-(6-amino-9*H*-purin-9-yl)-3-(hydroxymethyl)cyclopent-3-ene-1,2-diol (1). To a stirred solution of **14** (224 mg, 0.41 mmol)—or an equimolar amount of **13**—in $ClCH_2CH_2Cl$/MeOH 1:1 (2 mL) was added dropwise TFA (1.18 mL, 15.38 mmol) and the reaction mixture was stirred at room temperature overnight. The volatiles were removed under reduced pressure and the residue was adsorbed on silica and purified by silica gel column chromatography (EtOAc/MeOH/H_2O 9:1:1, 8:1:1, 4:1:1) to yield neplanocin A (**1**) (108 mg, 99%) as a white solid. Mp: 220–222 °C.[1a] $C_{11}H_{13}N_5O_3$ (263.26). R_f (EtOAc/MeOH/H_2O 4:1:1)=0.33. $[\alpha]_D^{21}$ −156.6 (c 0.5, H_2O). ^{1}H NMR (DMSO-d_6): δ=4.10 (s, 2H, H6′); 4.26 (t, 1H, ^3J=5.6 Hz, H5′); 4.42 (d, 1H, ^3J=5.6 Hz, H4′); 5.38 (d, 1H, ^3J=2.7 Hz, H1′); 5.70 (d, 1H, ^3J=1.5 Hz, H(2′)); 8.25 (s, 1H, H8); 8.28 (s, 1H, H2). ^{13}C NMR (DMSO-d_6): δ=58.49 (C6′); 64.17 (C1′); 72.14 (C4′); 76.51 (C5′); 119.11 (C5); 123.32 (C2′); 139.52 (C8); 149.55 (C6); 150.03 (C3′); 152.05 (C2); 155.80 (C4). HRMS (ESI$^+$): m/z=286.0917 (calculated for [M+Na]$^+$: 286.0916).

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Supplementary data

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