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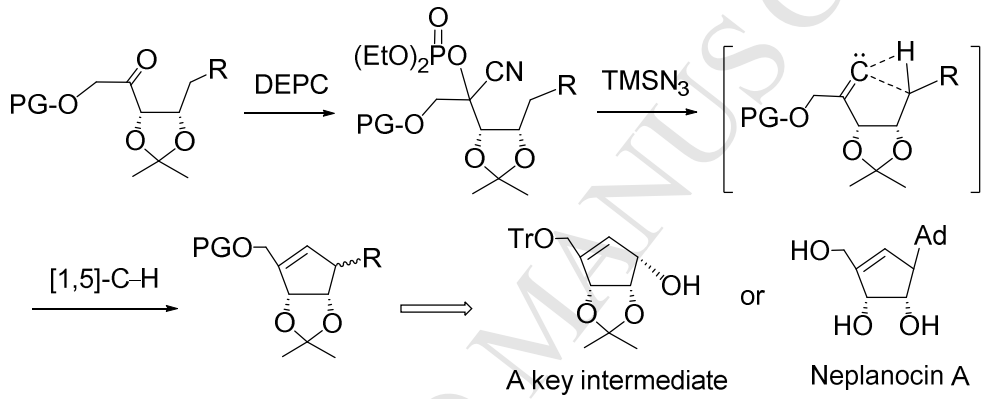
Graphical Abstract



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Syntheses of cyclopentyl nucleoside (−)-neplanocin A through tetrazole-fragmentation from cyanophosphates

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ABSTACT

We recently reported a novel synthetic method for five-membered unsaturated cyclic compounds from ketones involving cyanophosphates (CPs) under neutral conditions, in which alkylidene carbenes generated through tetrazole-fragmentation undergo [1,5]-C–H insertions to produce the target compounds. The present paper describes the use of the tetrazole-fragmentation from CPs for the efficient and practical syntheses of (−)-neplanocin A and a protected tetrol, the latter of which is an important synthetic precursor of both (−)-neplanocin A and its analogues. Furthermore, formation of an unusual dihydropyran derivative was observed during the synthetic study of the tetrol.

Keywords:
Neplanocin A
Carbocyclic nucleoside
Cyanophosphate
Neutral condition
[1,5]-C–H insertion
Alkylidene carbene

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(−)-Neplanocin A (NPA: **1**) is a naturally occurring carbocyclic nucleoside that was first isolated from the culture filtrate of the soil fungus *Ampullariella regularis* in 1981.[1] NPA and other natural analogues have received great attention owing to their interesting biological properties, such as their potent antiviral and antitumor properties (Fig. 1).[2] (−)-NPA, one of the most potent *S*-adenosylhomocysteine hydrolase inhibitors, has broad-spectrum antiviral activity.[3] However, NPA itself is apparently cytotoxic to host cells[2c,4] and is also rapidly deaminated by adenosine deaminase to a chemotherapeutically inactive inosine congener,[5] which may account for its reduced therapeutic potency. Therefore, the chemical synthesis and structural modification of NPA have been investigated extensively,[2c,6] and several total syntheses have been achieved. In these approaches, the key steps were palladium-catalyzed rearrangement of the acetate moiety,[7] the construction of a carbocyclic ring through intramolecular Horner–Wadsworth–Emmons or Wittig reactions,[8] an intramolecular aldol reaction,[9] or a ring-closing metathesis reaction using Grubbs catalysis.[10] Other approaches for the preparation of **1** have included a palladium-catalyzed desymmetrization of cyclopentenes with 6-chloropurine,[11] chemoenzymatic desymmetrization of bicyclic Diels-Alder adducts,[12] intramolecular nitrone cycloaddition,[13] zirconocene-mediated ring constraction,[14] and an intramolecular Baylis-Hillman reaction.[15]

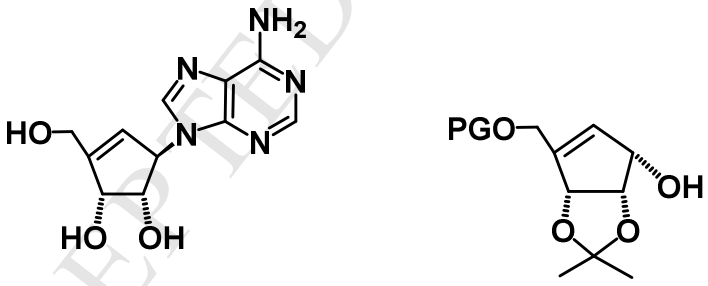


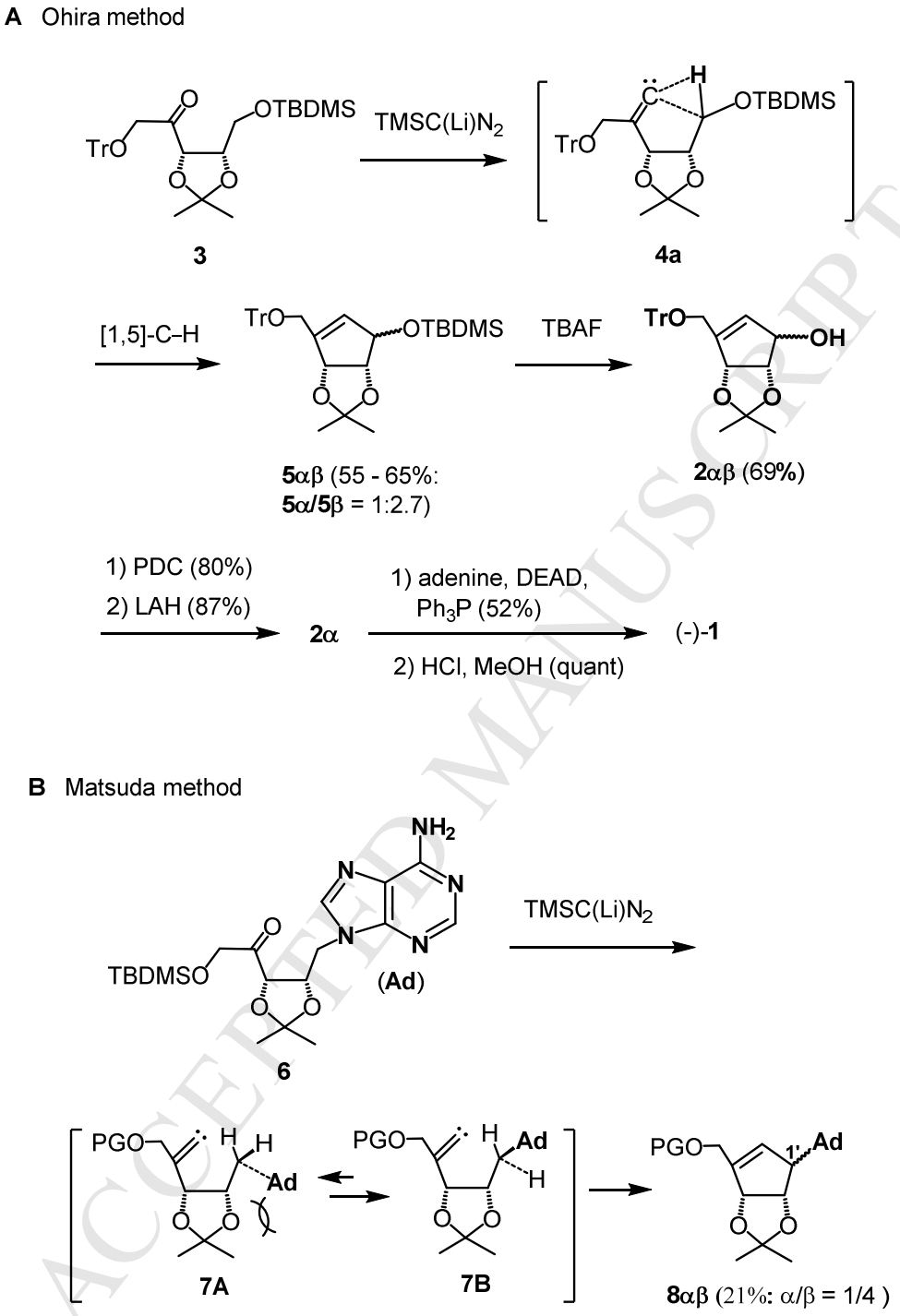
Figure 1. (−)-Neplanocin A (**1**) and important synthetic precursor **2α** for neplanocin derivatives.

Protected cyclopentenyl tetrol **2** has been widely used as a synthetic precursor not only for (−)-**1**, but also its analogues.[6-15] The shortest method thus far was reported by Ohira and co-workers, who synthesized of (−)-**1** from **2α** [PG = triphenylmethyl (Tr)] by employing a C–H insertion reaction of alkylidene-carbene **4** (Scheme 1–A)[16]. With this method, ketone **3** derived from D-ribose is reacted with lithium

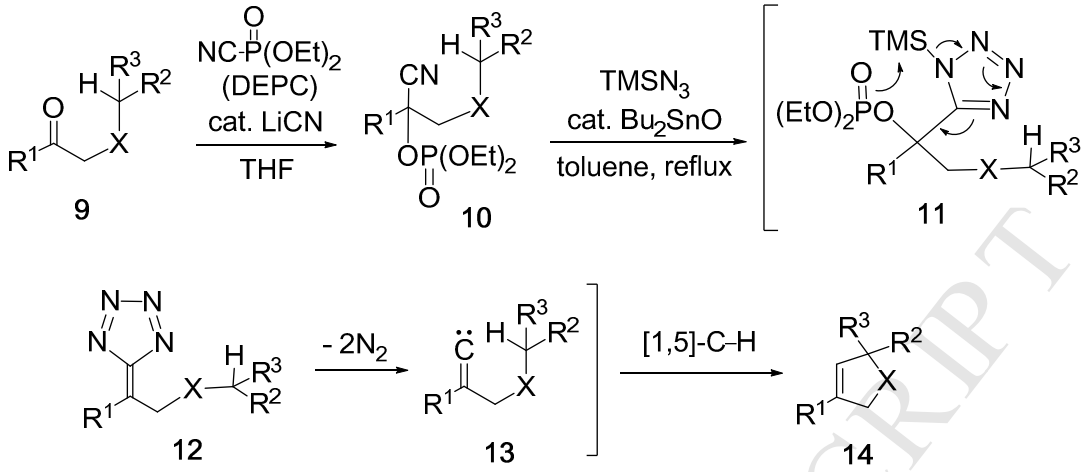
trimethylsilyldiazomethane [TMSC(Li)N_2],[17] affording cyclopentene derivative **5αβ** in 55–65% yield (**5α/5β** = 1:2.7).[16] Removal of the *tert*-butyldimethylsilyl (TBDMS) group of **5αβ** with tetrabutylammonium fluoride (TBAF) furnished protected tetrol **2αβ** (69%). Subsequent pyridinium dichromate (PDC) oxidation (80%) of **2αβ** followed by lithium aluminum hydride (LAH) reduction (87%) provided desired tetrol **2α** as a single stereoisomer. Then, Mitsunobu reaction of **2α** with adenine using the Nokami procedure[18] followed by deprotection of the hydroxy groups afforded (−)-**1**. On the basis of the Ohira method, Liao and co-workers also described the syntheses of 2'-β-C-methyl-neplanocin derivatives.[19]

Alternatively, Matsuda and co-workers employed ketone **6** derived from adenosine for the C–H insertion reaction of alkylidene-carbene **7** using TMSC(Li)N_2 (Scheme 1–B).[20] Reaction of ketone **6** with TMSC(Li)N_2 afforded a 1:4 epimeric mixture (**8αβ**) of **8α** and **8β** at the 1'-position in only 21% yield. Generated carbene **7** has two conformers, **7A** and **7B**. Steric repulsion between the isopropylidene and adenine groups in conformer **7A** could lead preferentially to the adoption of conformer **7B**, which would afford desired β-diastereomer **8β** (Scheme 1–B). However, desired isomer **8β** was unfortunately not isolated from epimeric mixture **8αβ**, presumably owing to the difficulty of separation through column chromatography on silica gel. As a result, this second synthetic study employing a C–H insertion reaction of an alkylidene-carbene could not be accessed.[20]

α-Cyanophosphates (CPs) have been widely utilized as synthetic intermediates in organic synthesis.[21] In continuation of our program on the utilization of the CPs, we recently reported a novel synthetic method for five-membered unsaturated cyclic compounds from ketones based on the reactions of CPs with trimethylsilylazide ($TMSN_3$) in the presence of Bu_2SnO as a catalyst, as shown in Scheme 2.[22] In this two-step transformation, CPs **10** may form tetrazolylphosphates **11**, which subsequently undergo successive fragmentation to generate alkylidene carbenes **13**,[23] which undergo [1,5]-C–H insertions to produce five-membered cyclic compounds **14**.[22] The scope of these reactions that occur under neutral conditions could be extended towards a variety of cyclopentenes and heterocyclic products that are not usually accessible from the corresponding carbonyl compounds through the TMSC(Li)N_2 procedure, which requires basic conditions.[17,22] In addition, Postel and co-workers have reported the preparation of cyclopentene derivatives as the intermediates for the syntheses of NPA stereoisomers from D-mannose using similar [1,5]-C–H insertions of alkylidene carbenes generated from α-cyanomesylates.[24]



Scheme 1. (A) Synthesis of neplanocin A (**1**) from synthetic precursor **2α** using the Ohira method, (B) Synthesis of epimeric mixture **8αβ** at the 1'-position using the Matsuda method



Scheme 2. Synthesis of five-membered unsaturated cyclic compounds **14** from ketones **9** through CPs **10**.

On the basis of these reports, to demonstrate the synthetic utility of the alkylidene carbenes generated under neutral condition from CPs (CP method),[22] we attempted to apply the CP method to ketones **3** and **6** employed by Ohira and Matsuda, respectively.[16,20] Herein, we report the efficient and practical syntheses of protected tetrol **2α** and (−)-**1** using CPs **16** and **21**, respectively, in which the intramolecular [1,5]-C–H insertion reactions of the alkylidene carbenes generated via tetrazole-fragmentation were the key synthetic transformations. Furthermore, in the synthesis of tetrol **2α**, formation of an unusual dihydropyran derivative **17** was newly observed.[23]

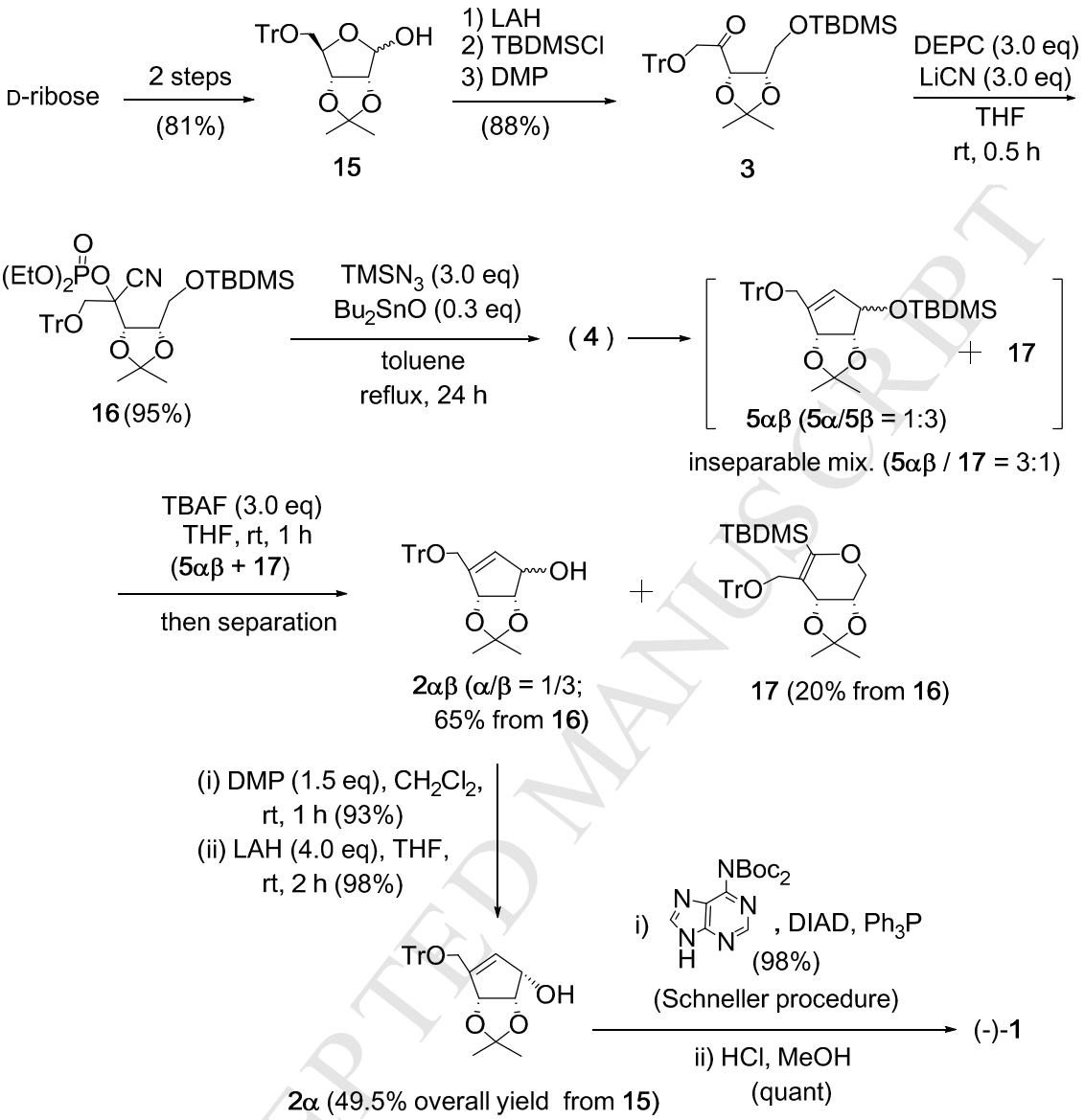
1. Synthesis of (−)-neplanocin A from CP 16

Ketone **3**, which was prepared via triphenylmethyl (Tr) ether **15**[25] from D-ribose in five steps (71% overall yield),[26] was subjected to the CP method, as illustrated in Scheme 3. Reaction of ketone **3** with diethyl phosphorocyanidate (DEPC, 3.0 equiv.)[21] in the presence of LiCN (3.0 equiv.) easily afforded CP **16** in 95% yield.[27] Reaction of CP **16** with $TMSN_3$ (3.0 equiv.) in the presence of Bu_2SnO (0.3 equiv.) in refluxing toluene for 24 h afforded an inseparable mixture of epimeric cyclopentenes **5αβ**,[22] which was the result of the C–H insertion reaction of alkylidene-carbene **4**, along with unexpected compound **17**. The ratio of **5αβ** to **17** was 3:1 according to ^{1}H-NMR (TLC on silica gel: R_f = 0.7, 20% EtOAc in hexane). After the mixture was subsequently treated with TBAF to remove the TBDMS group, deprotected cyclopentenes **2αβ** (**2α**/**2β** = 1/3) and

compound **17** were separated using column chromatography on silica gel and obtained in 65% and 20% yields, respectively, from CP **16**. Compound **17** was determined to be a dihydropyran derivative and the stereochemical assignment was concluded using NOESY analysis, as illustrated in Figure 2–A. The unexpected formation of **17** may have been due to [1,6]-O–Si bond insertion of the carbene **4a** or 1,2-TBDMS shift of ylide **4b** (Figure 2–B),[28a] as opposed to common [1,5]-O–Si insertions that generate dihydrofuran derivatives.[23,28b]

Ohira and co-workers reported only the formation of **5αβ** in the reaction of ketone **3** with TMSC(Li)N_2 and did not mention the production of dihydropyran **17**, as shown in Scheme 1–A[16] The unusually broad yield range (55–65%) of **5αβ** reported by Ohira may be a combined yield of **5αβ** and **17** owing to the difficulty of their separation. Indeed, when we attempted to reproduce Ohira's result [reaction of ketone **3** with TMSC(Li)N_2 (3 equiv) in THF for 1 h at 0 ^{o}C],[16] an inseparable mixture of **5αβ** (**5α** / **5β** = 1/3) and **17** was produced in 61% combined yield (see experimental section).

Transformation of **2αβ** into desired cyclopentenol **2α** using Dess-Martin periodinane (DMP) oxidation (93%) and subsequent LAH reduction (98%) was more effective than the corresponding reactions in the Ohira method (Scheme 1–A). Cyclopentenol **2α** was obtained in 49.5% overall yield in eight steps from protected D-ribose **15**. This result is superior to that achieved by Ohira method (18–23% overall yield of **2α** from **15**): the overall yield was more than two times higher. Alchohol **2α** can be converted to to (–)-**1** through efficient Mitsunobu coupling with *N*-6 amino bis-Boc-protected adenine using the Schneller procedure[29] followed by deprotection under acidic condition.



Scheme 3. Synthesis of (−)-neplanocin A from CP **16**

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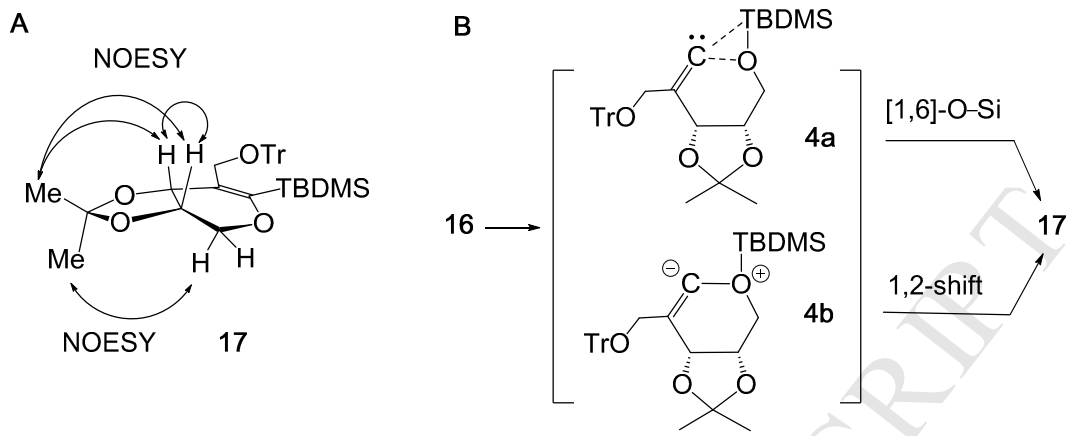
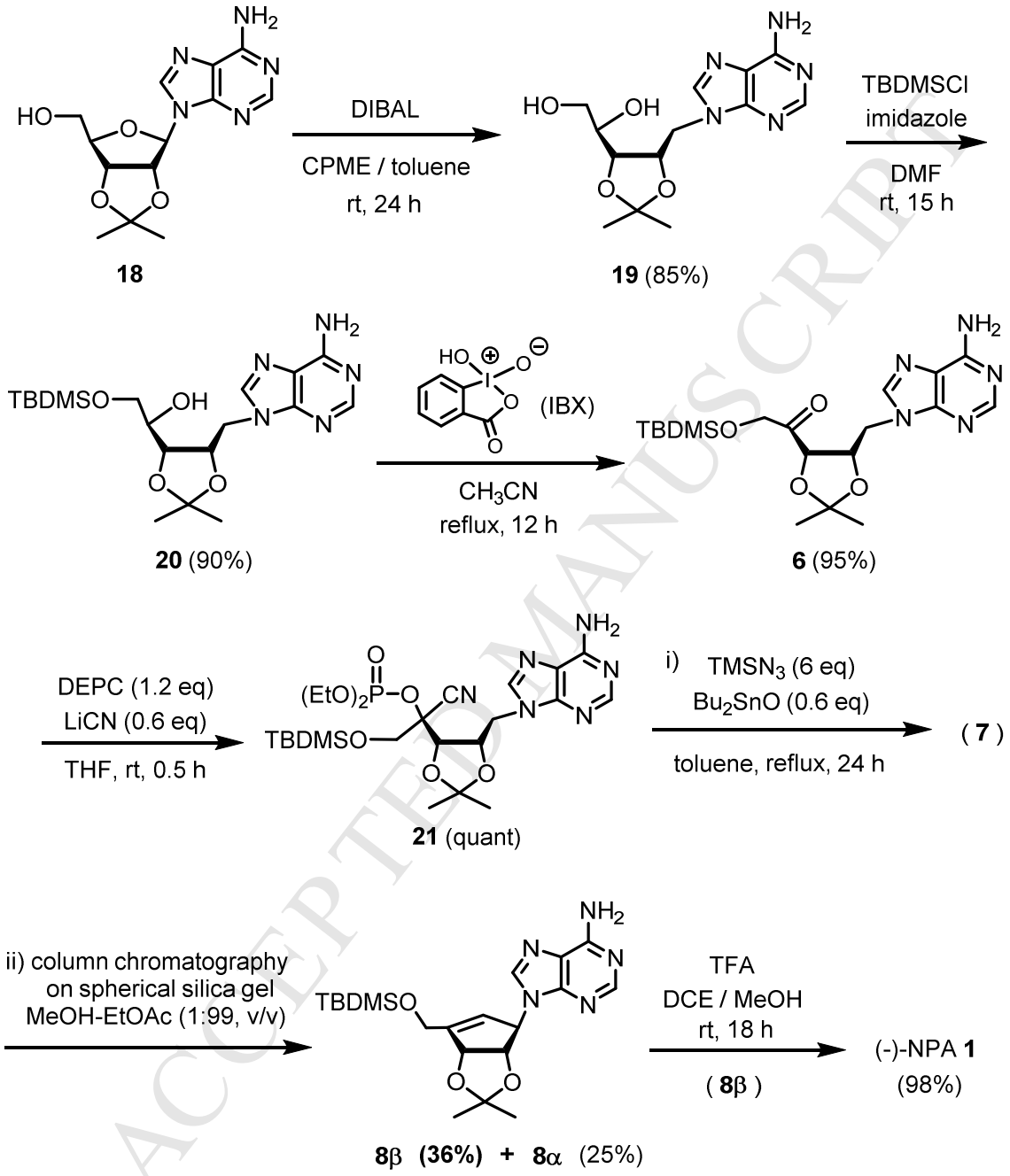


Figure 2. (A) NOESY analysis of **17**, (B) Formation of **17** through two possible pathways

2. Synthesis of (−)-neplanocin A from CP **21**

We next investigated the synthesis of (−)-**1** via CP **21** from adenine-containing ketone **6**, starting from 2',3'-*O*-isopropylidene-adenosine (**18**) using Matsuda's approach (Scheme 4). Matsuda used the reductive tetrahydrofuran-ring cleavage reaction reported by Maki.[30] Treatment of **18** with diisobutyl aluminum hydride (DIBAL) in THF afforded acyclic nucleoside **19** in 57% yield.[31] Meanwhile, we found that the use of cyclopentyl methyl ether (CPME)-toluene (1:1, v/v) solvent system for the ring-cleavage reaction of **18** led to improve yield of **19** to 85% owing to much easier extraction. After selective protection (90%) of the primary hydroxyl group of **19** with TBDMSCl, we oxidized (95%) secondary alcohol **20** with *o*-iodoxybenzoic acid (IBX) to furnish ketone **6**. The DMP oxidation of **20** reported by Matsuda gave a lower yield (71%).[20a] Cyanophosphorylation[27] (quant) of **6** with DEPC catalyzed by LiCN followed by treatment of CP **21** with $TMSN_3$ (6 eq) catalyzed by Bu_2SnO in refluxing toluene for 24 h afforded an epimeric mixture (**8αβ**) of carbocyclic nucleosides through a [1,5]-C–H insertion reaction of alkylidene carbene **7**.[23] Although desired product **8β** was not isolated successfully from mixture **8αβ** in the Matsuda approach,[20b] it was chromatographed over spherical silica gel[32] [MeOH-EtOAc (1:99, v/v)] and obtained in 36% yield in this study, with 25% yield of **8α**. Deprotection of thus obtained β-epimer **8β** under acidic conditions afforded (−)-**1** with a high purity in an overall yield of 25.6% in six steps from protected adenosine **18**.[8i] The physical and spectral properties of **1** were essentially identical to literature data {**1**: $[\alpha]_D$ −156.0 (c 0.5, H_2O) and mp 220–221

^{o}C; lit.[8i] $[\alpha]_D$ −156.6 (c 0.5, H_2O) and mp 220–222 ^{o}C}.



Scheme 4. Synthesis of (−)-neplanicin A from CP **21**

In conclusion, the efficient and practical syntheses of neplanocin A (**1**) and widely applicable intermediate **2α** were achieved using CPs through tetrazole-fragmentations under neutral conditions. The CP method gave **2α** in 49.5% overall yield in eight steps from protected D-ribose **15**, this yield was more than two times higher than that (18–23%) achieved by Ohira's approach. Furthermore, formation of the unusual dihydropyran derivative **17** was newly observed through two possible pathways in this study. In addition, the CP method was applied to the efficient synthesis of natural neplanocin A in 25.6% overall yield in six steps from protected adenosine **18** following successful isolation of cyclopentyl nucleoside **8β**. In contrast, the synthesis using the Matsuda approach was unfinished. We hope that the lessons learned in this undertaking can be applied fruitfully to other synthetic targets. In addition, the present study demonstrated the applicability of CPs as intermediates in organic synthesis.[21]

3. Experimental

3.1 General information

All reactions were carried out under an inert argon atmosphere. Anhydrous solvents (THF, toluene, CH_2Cl_2, DMF, CPME and MeCN) were purchased from Wako Chemical Company. During organic workup, solvent extracts were dried over Na_2SO_4 and subsequently removed in a rotary evaporator under reduced pressure. Fuji Silysia FL-60D silica gel was used for flash column chromatography. **8α** and **8β** were chromatographed over spherical silica gel (Fuji Silysia PSQ 100B silica gel). TLC was performed using precoated plates (Wako silica gel 70 F254). ^{1}H-NMR spectra were recorded on a Varian Mercury-300 or an Agilent 400-MR-DD2 spectrometer in $CDCl_3$ with tetramethylsilane (TMS) as an internal standard or CD_3OD with chemical shifts (δ) given relative to from CD_3OD (3.3 ppm). Coupling constants (*J*) are reported in Hertz (Hz). For multiplicities the following abbreviations were used: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad. ^{13}C-NMR spectra were recorded on a Varian Mercury-300 or an Agilent 400-MR-DD2 spectrometer in $CDCl_3$. Chemical shifts (δ) are given relative to $CDCl_3$ (77.0 ppm) or CD_3OD (49.0 ppm). High-resolution mass spectra were obtained using a JMS-700(2) double-focusing magnetic sector mass spectrometer (Jeol Ltd., Tokyo, Japan) operating in positive-ion mode, with 3-nitrobenzyl alcohol (NBA)-NaCl or triethanolamine (TEOA)-NaCl as matrices.[33]

*3.2. Synthesis of (-)-neplanocin A from CP**16***

*3.2.1. (2S,3S)-[4-(tert-Butyldimethylsilyloxymethyl)-2,3-isopropylidenedioxy-1-cyanobutyl diethyl phosphate (**16**)*

DEPC (831 mg, 5.1 mmol) and LiCN (168 mg, 5.1 mmol) were added to a solution of ketone **3** (944 mg, 1.7 mmol) in THF (20 mL) at rt. After it was stirred for 30 min, the reaction mixture was treated with water (60 mL), and then extracted with EtOAc-hexane (1:1, 100 mL). The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. Purification via silica gel column chromatography (EtOAc-hexane, 1:4) afforded CP **16** (1165 mg, 95%, oil).

^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.09 (s, 3H), 0.10 (s, 1.5H), 0.11 (s, 1.5H), 0.91 (s, 4.5H), 0.91 (s, 4.5H), 1.22-1.33 (m, 10.5H), 1.43 (s, 1.5H), 3.60 (d, 0.5H, *J* = 8.4 Hz), 3.61 (d, 0.5H, *J* = 10.2 Hz), 3.76 (d, 0.5H, *J* = 8.4 Hz), 3.89–4.27 (m, 6.5H), 4.40–4.48 (m, 1H), 4.59 (d, 0.5H, *J* = 6.3 Hz), 4.71 (dd, 0.5Hz, *J* = 6.3, 4.5 Hz), 7.24-7.34 (m, 9H), 7.45-7.49 (m, 6H); ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ -5.2, -5.0, 15.9, 16.0, 18.4, 24.9, 25.1, 25.9, 26.4, 26.8, 61.4, 61.5, 63.1, 63.9, 64.4, 64.5, 64.6, 64.7, 64.8, 64.9, 75.5, 75.6, 75.9, 76.0, 79.1, 79.3, 87.5, 87.7, 109.2, 109.4, 115.7, 115.8, 116.0, 127.3, 127.8, 127.9, 128.7, 128.8, 142.8, 142.9; HRMS (FAB+NaCl): *m/z* $[M+Na]^+$ calcd for $C_{38}H_{52}NO_8PSiNa$: 732.3098; found: 732.3099.

*3.2.2. (4R,5S)-4,5-O,O-Isopropylidene-3-(trityloxymethyl)-2-cyclopenten-1-ol (**2αβ**); (3aS,7aR)-2,2-dimethyl-7-(trityloxymethyl)-6-tert-butyldimethylsilyl-3a,7a-dihydro-4H-[1,3]dioxolo[4,5-c]pyran (**17**)*

$TMSN_3$ (0.20 mL, 1.50 mmol) and Bu_2SnO (37 mg, 0.15 mmol) were added to a solution of CP **16** (355 mg, 0.50 mmol) in toluene. After it was refluxed for 24 h, the reaction mixture was concentrated to give a residue, which was purified using silica gel column chromatography to give an inseparable 3:1 mixture of **5αβ** (**5α/5β =** 1/3) and **17** (210 mg). To a solution of the mixture in THF (5 mL), 1 M solution of TBAF in THF (1.2 mL, 1.20 mmol) was added. After 1 h, saturated aqueous NH_4Cl was added to the reaction mixture to quench it. After the mixture was extracted with EtOAc (30 mL), the organic layer was washed with H_2O and then brine, dried over Na_2SO_4, filtrated, and concentrated to give a residue, which was purified using silica gel column chromatography (EtOAc–hexane, 1:4) to give **2αβ** (139 mg, 65%, yellow amorphous) and **17** (54 mg, 20%, oil). In addition, **2β** could be partially resolved by use of the above solvent system.

2β: ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.30 (s, 3H), 1.33 (s, 3H), 2.06 (br, 1H), 3.70 (d, 1H,

J = 15.0 Hz), 3.89 (d, 1H, *J* = 15.0 Hz), 4.51 (d, 1H, *J* = 5.7 Hz), 4.78 (br, 1H), 5.08 (d, 1H, *J* = 5.7 Hz), 6.00 (br, 1H), 7.20–7.32 (m, 9H), 7.45–7.48 (m, 6H); ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 26.1, 27.4, 61.3, 76.6, 79.9, 83.7, 86.4, 111.8, 127.0, 127.8, 128.5, 143.8, 147.4; HRMS (EI): *m/z* [M^+] calcd for $C_{28}H_{28}O_4$: 428.1988; found: 428.1990.

17: ^{1}H-NMR (400 MHz, $CDCl_3$): δ -0.44 (s, 3H), -0.16 (S, 3H), 0.67 (s, 9H), 1.48 (s, 3H), 1.55 (s, 3H), 3.20 (dd, 1H, *J* = 10.0, 10.0 Hz), 3.52 (d, 1H, *J* = 10.0 Hz), 3.98 (dd, 1H, *J* = 10.0, 4.8 Hz), 3.99 (d, 1H, *J* = 10.0 Hz), 4.24 (ddd. 1H, *J* = 10.0, 6.0, 4.8 Hz), 5.00 (d, 1H, *J* = 6.0 Hz), 7.21–7.31 (m, 9H), 7.46–7.50 (m, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ -5.8, -5.4, 17.2, 26.0, 26.5, 28.5, 61.5, 64.9, 68.3, 70.4, 86.4, 107.7, 120.6, 126.9, 127.6, 129.0, 143.9, 161.2; HRMS (FAB+NaCl): *m/z* $[M+Na]^+$ calcd for $C_{34}H_{42}O_4SiNa$: 565.2750; found: 565.2753.

3.2.3. Conversion of ***2αβ*** *to* ***2α***

DMP (166 mg, 0.39 mmol) was added to a solution of **2αβ** (112 mg, 0.26 mmol) in CH_2Cl_2 at 0 °C. After the reaction mixture was stirred at rt for 1 h, saturated aqueous $NaHCO_3$ and aqueous $Na_2S_2O_3$ were added to quench it. The mixture was extracted with methyl *tert*-butyl ether (30 mL). The organic layer was washed with H_2O and then brine, dried over Na_2SO_4, filtered, and concentrated to give a residue, which was purified using silica gel column chromatography (EtOAc–hexane, 1:4) to give cyclopentenone derivative (**22**: 103 mg, 93%, white solid).

3.2.4. (4R,5R)-4,5-O,O-Isopropylidene-3-(trityloxymethyl)-2-cyclopentenone (**22**)

^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.34 (s, 6H), 3.94 (dd, 1H, *J* = 18.3, 1.2 Hz), 4.25 (dd, 1H, *J* = 18.3, 1.8 Hz), 4.47 (d, 1H, *J* = 5.7 Hz), 4.94 (d, 1H, *J* = 5.7 Hz), 6.44–6.46 (m, 1H), 7.23–7.36 (m, 9H), 7.40–7.47 (m, 6H); ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 26.3, 27.5, 62.5, 77.7, 78.1, 87.4, 115.4, 127.4, 128.0, 128.2, 128.4, 143.3, 174.6, 201.9; HRMS (EI+): *m/z* $[M]^+$ calcd for $C_{28}H_{26}O_4$: 426.1831; found: 426.1828.

3.2.5. (1S,4R,5S)-4,5-O,O-Isopropylidene-3-(trityloxymethyl)-2-cyclopenten-1-ol (**2α**)

A solution of **22** (81mg, 0.19 mmol) in THF (2 mL) was added dropwise to a suspension of LAH (36 mg, 0.96 mmol) in THF (2 mL) at 0 °C. After the reaction was stirred at rt for 2 h, H_2O (1 mL) was added to quench it. After the mixture was stirred at rt for 1 h, $MgSO_4$ was added, and the resulting mixture was filtered through Celite and concentrated to give a residue, which was purified using silica gel column chromatography (EtOAc–hexane 1:3) to give **2α** (79 mg, 98%, white solid).[16]

2α: ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.36 (s, 3H), 1.37 (s, 3H), 2.74 (d, 1H, *J* = 10.2 Hz),

3.65 (dt, 1H, *J* = 14.4, 1.8 Hz), 3.88 (d, 1H, *J* = 14.4 Hz), 4.59 (br, 1H), 4.75 (t, 1H, *J* = 5.4 Hz), 4.88 (d, 1H, *J* = 5.4 Hz), 6.00 (br, 1H), 7.20–7.32 (m, 9H), 7.44–7.48 (m, 6H).

*3.2.6. Reaction of ketone **3** with TMSC(Li)N_2*

A 1.6M solution of *n*-BuLi in hexane (1.1 mL, 1.71 mmol) was added dropwise to a solution of diisopropylamine (0.29 mL, 1.71 mmol) in THF (3mL) at -78 ^{o}C. After the mixture was stirred at -78 ^{o}C for 10 min, 0.6 M solution of $TMSCHN_2$ in hexane (2.8 mL, 1.71 mmol) was added dropwise. After 30 min at -78 ^{o}C, a solution of ketone **3** (315mg, 0.57 mmol) in THF (3 mL) was added dropwise at -78 ^{o}C. After the reaction mixture was stirred at 0 ^{o}C for 1 h, H_2O was added to quench it. The mixture was extracted twice with Et_2O (50 mL), and the combined organic layers were washed with H_2O and then brine, dried over Na_2SO_4, filtered, and concentrated to give a residue, which was purified by silica gel column chromatography (EtOAc–hexane 1:19) to give an inseparable mixture (188 mg, 61%) of **5αβ** (**5α/β** = 1/3) and **17**.

*3.3. Synthesis of (–)-neplanocin A from CP **21***

*3.3.1. 9-[(2S,3R,4R)-(5,4-Dihydroxy-2,3-isopropylidenedioxy)pentyl]adenine (**19**)*

A 1M solution of DIBAL-H in toluene (82 mL, 81.5 mmol) was added dropwise to a solution of 2',3'-*O*-isopropylideneadenosine **18** (5.0 g, 16.3 mmol) in CPME (80 mL) at 0 ^{o}C. After the reaction was stirred at rt for 24 h, aqueous potassium sodium tartrate (20 g/100 mL) was added at 0 ^{o}C to quench it. The mixture was stirred at rt for 24 h. After the mixture was extracted three times with BuOH (150 mL), the combined organic layers were concentrated to give a residue, which was purified using silica gel column chromatography (MeOH–CH_2Cl_2 1:4) to give **19** (4.3 g, 85%, amorphous).
^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.26 (s, 3H), 1.48 (s, 3H), 3.60–3.84 (m, 3H), 4.22 (dd, 1H, *J* = 9.2, 6.0 Hz), 4.30 (dd, 1H, *J* = 14.0, 10.8 Hz), 4.56–4.62 (m, 1H), 4.75 (dd, 1H, *J* = 14.0, 2.4 Hz), 8.12 (s, 1H), 8.19 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 25.7, 28.4, 45.6, 65.3, 70.9, 76.9, 77.4, 110.6, 119.7, 143.4, 150.7, 153.6, 157.2.

*3.3.2. 9-[(2S,3R,4R)-5-(tert-Butyldimethylsilyloxy-4-hydroxy-2,3-isopropylidenedioxy)-pentyl]adenine (**20**)*

TBDMSCl (2.11 g, 14.0 mmol) and imidazole (1.08 g, 15.9 mmol) were added to a solution of **19** (2.89 g, 9.35 mmol) in DMF (20mL). After the reaction mixture was stirred at rt for 15 h, EtOAc (200 mL) was added. The organic layer was washed twice with saturated aqueous $NaHCO_3$ and then brine, dried over Na_2SO_4, filtered, and

concentrated to give a residue, which was purified using silica gel column chromatography (MeOH–EtOAc 1:9) to give **20** (3.56 g, 90%, oil).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.11 (s, 6H), 0.92 (s, 9H), 1.29 (s, 3H), 1.50 (s, 3H), 3.29 (d, 1H, *J* = 6.0 Hz), 3.72–3.81 (m, 2H), 3.88 (dd, 1H, *J* = 9.6, 2.4 Hz), 4.14–4.21 (m, 2H), 4.57 (ddd, 1H, *J* = 10.0, 6.0, 2.4 Hz), 4.92 (dd, 1H, *J* = 14.4, 2.4 Hz), 6.06 (brs, 2H), 7.97 (s, 1H), 8.38 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ -5.5, -5.4, 18.3, 25.3, 25.8, 28.1, 44.2, 64.3, 69.1, 75.8 (75.76), 75.8 (75.82), 109.4, 119.3, 141.5, 150.1, 152.9, 155.5.

*3.3.3. 9-[(2S,3S)-(5-tert-Butyldimethylsilyloxy-2,3-isopropylidenedioxy-4-pentanone)-1-yl]adenine (**6**)*

A solution of **20** (1.00 g, 2.36 mmol) in MeCN (20 mL) was added to a suspension of IBX (2.00 g, 7.08 mmol) in MeCN (70 mL). After it was refluxed for 12 h, the reaction mixture was filtered through Celite. The filtrate was concentrated to give a residue, which was purified using silica gel column chromatography (EtOAc) to give **6** (0.94 g, 95%, oil).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.14 (s, 3H), 0.15 (s, 3H), 0.94 (s, 9H), 1.34 (s, 3H), 1.64 (s, 3H), 3.90 (dd, 1H, *J* = 14.0, 9.6 Hz), 4.45 (d, 1H, *J* = 19.2 Hz), 4.56 (d, 1H, *J* = 19.2 Hz), 4.57 (dd, 1H, *J* = 14.0, 2.4 Hz), 4.83 (ddd, 1H, *J* = 9.6, 7.6, 2.4 Hz), 4.98 (d, 1H, *J* = 7.6 Hz), 6.47 (brs, 1H), 7.91 (s, 1H), 8.33 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ -5.6, -5.5, 18.3, 24.7, 25.7, 25.8, 27.2, 44.3, 68.7, 75.1, 79.7, 110.6, 119.0, 141.3, 149.8, 152.4, 155.3, 206.6.

*3.3.4. (2S,3S)-{4-(6-Amino-9H-purin-9-yl)-2-(tert-butyldimethylsilyloxymethyl)-2,3-isopropylidenedioxy-1-cyanobutyl diethyl phosphate (**21**)*

DEPC (20 mg, 0.12 mmol) and LiCN (2 mg, 0.06 mmol) were added to a solution of ketone **6** (42 mg, 0.10 mmol) in THF (1 mL) at rt. After it was stirred for 30 min, the reaction mixture was treated with EtOAc-hexane (1:1, 50 mL). The organic layer was washed with water and then brine, dried over Na_2SO_4, filtered, and concentrated. Purification using silica gel column chromatography (MeOH-EtOAc, 1:9) afforded CP **21** (59 mg, quant).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.13–0.17 (m, 6H), 0.92–0.95 (m, 9H), 1.26 (s, 1H), 1.26 (s, 2H), 1.34–1.44 (m, 6H), 1.50 (s, 2H), 1.62 (s, 1H), 4.04–4.14 (m, 1H), 4.20–4.35 (m, 5H), 4.54–4.82 (m, 3H), 4.93 (dd, 0.3H, *J* = 14.0, 2.0 Hz), 5.05 (dd, 0.7H, *J* = 14.0, 2.0 Hz), 6.00 (brs, 2H), 7.90 (s, 0.7H), 7.98 (s, 0.3H), 8.35 (s, 0.3H), 8.36 (s, 0.7H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ -5.7, -5.6, -5.5 (-5.52), -5.5 (-5.46), 16.0 (15.98),

16.0 (16.03), 16.1, 18.2, 18.3, 24.7, 25.1, 25.7, 26.5, 26.8, 43.2 (43.17), 43.2 (43.23), 63.1, 64.3, 64.8, 64.9, 65.0 (64.96), 65.0 (65.02), 65.1 (65.09), 65.1 (65.14), 65.4 (65.37), 65.4 (65.42), 74.2, 74.3, 75.0, 75.7, 75.8, 75.9, 76.0, 76.2, 77.2 (77.15), 77.2 (77.19), 77.5, 110.0, 110.3, 115.8, 115.9, 119.4 (119.40), 119.4 (119.41), 141.5, 141.9, 149.8, 149.9, 152.6, 152.7, 155.2, 155.3; HRMS (FAB): *m/z* $[M+H]^+$ calcd for $C_{24}H_{42}N_6O_7PSi$: 585.2621; found: 585.2618.

*3.3.5. (1R,4R,5S)-9-N-[3-(tert-Butyldimethylsilyloxymethyl)-4,5-O,O-isoprppylidene-2-cyclopenten-1-yl]adenine (**8β**)*

$TMSN_3$ (0.16 mL, 1.2 mmol) and Bu_2SnO (30 mg, 0.12 mmol) were added to a solution of **21** (116 mg, 0.2 mmol) in toluene (10 mL). After it was refluxed for 24 h, the reaction mixture was concentrated to give a residue, which was purified using silica gel column chromatography (PSQ100B silica gel, MeOH-EtOAc, 1:99) to give **8β** (30 mg, 36%)[20b] and **8α** (21 mg, 25%).

8β: ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.10 (s, 6H), 0.92 (s, 9H), 1.35 (s, 3H), 1.48 (s, 3H), 4.42 (brs, 2H), 4.71 (d, 1H, *J* = 5.7 Hz), 5.30 (d, 1H, *J* = 5.7 Hz), 5.60 (brs, 1H), 5.78-5.90 (brm, 3H), 7.67 (s, 1H), 8.38 (s, 1H).

*3.3.6. (-)-Neplanocin A: (1S,2R,5R)-5-(6-Amino-9H-purin-9-yl)-3-(hydroxymethyl)cyclopent-3-ene-1,2-diol (**1**)*

Trifluoroacetic acid (TFA) (0.5 mL, 6.8 mmol) was added to a solution of carbocyclic nucleoside **8β** (73 mg, 0.17 mmol) in $ClCH_2CH_2Cl$/MeOH (1/1; 4 mL). After it was stirred for 18 h, the reaction mixture was concentrated to give a residue, which was purified using silica gel column chromatography (MeOH-EtOAc-$H_2$0, 1:8:1) to give **1** (44 mg, 98%, white solid). Compound **1** thus obtained was recrystallized from MeOH to give colorless prisms.

$[\alpha]_D$ -156.0 (c 0.50, H_2O); m.p. 220–221 °C; ^{1}H-NMR (300 MHz, CD_3OD): δ 4.31 (brs, 2H), 4.38 (dd, 1H, *J* = 5.4, 5.4 Hz), 4.62 (d, 1H, *J* = 5.4 Hz), 5.45–5.55 (m, 1H), 5.91 (d, 1H, *J* = 1.8 Hz), 8.10 (s, 1H), 8.18 (s, 1H).

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