Synthesis of Neplanocin A and Its 3'-Epimer via an Intramolecular **Baylis-Hillman Reaction**

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ABSTRACT: The key cyclopentenyl intermediate 11b was synthesized in 4 steps from D-ribose in 41% overall yield via an efficient intramolecular Baylis-Hillman reaction. This novel key intermediate can be modified easily and transformed to neplanocin A (1a) and its 3'-epimer (1b).

INTRODUCTION

Carbocyclic nucleosides are nucleoside analogues that have attracted the interest of medicinal chemists due to their potential applications as antivirals¹ and anticancer agents.² Their structural similarity to conventional nucleosides suggest that they are likely to bind and inhibit the same protein targets, and the lack of a glycosidic linkage confers on them an increased stability toward enzymatic degradation.³ Fivemembered-ring carbocyclic nucleosides are found in both natural and synthetic compounds and have gained much interest due to their potent biological properties. The natural products neplanocin A $(1a)^4$ and aristeromycin (2) (Figure 1) are potent antivirals, while synthetic derivatives such as deazaneplanocin A (3) have recently been shown to be global histone methyl transferase inhibitors.⁵ The majority of carbocyclic nucleosides have been synthesized via coupling of



1a X = N, R₁ = OH, R₂ = H, Neplanocin A



3 X = CH, R₁ = OH, R₂ = H,3-Deazaneplanocin A

Figure 1. Structures of carbocyclic nucleosides: aristeromycin, 3deazaneplanocin A, and neplanocin A and its 3'-epimer.

the appropriately functionalized five-membered carbocycle with a purine or pyrimidine heterocycle. Not surprisingly, much effort has been invested in the efficient synthesis of these functionalized cyclopentenes from sugars: for example, through ring-closing metathesis,⁶ an intramolecular Wittig reaction,⁷ the Ramberg–Bäcklund reaction,⁸ or C–H insertion of a methylidene carbene.⁹ Despite these efforts, the preparation of enantiopure functionalized carbocycles is tedious, necessitating long reaction sequences.¹⁰ To date, there have been several reports on the total synthesis of neplanocin A. Of note, the report by Michel and Strazewski^{4q} gives the highest published overall yield to date. The key step is an improvement in the Mitsunobu coupling of the carbocyclic core with N6-bis-BOCadenine. The carbocyclic core was obtained using a ring-closing metathesis reaction which in turn utilized Neolyst dichloride as catalyst. In this paper, we report an expedient route to a densely functionalized cyclopentenol using an intramolecular Baylis-Hillman (BH) reaction^{11,12} as the key step in the formation of the cyclopentene ring. This approach is atom economical and simultaneously installs the desired stereocenters in a single step. The utility of the methodology is demonstrated in the formal synthesis of neplanocin A and synthesis of its 3'-epimer 1b.

RESULTS AND DISCUSSION

The retrosynthetic analysis of neplanocin A and its 3'-isomer is summarized in Scheme 1. Neplanocin A (1a) and its 3'-epimer

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1b can be accessed from the key intermediate cyclopentenol **4** through coupling reactions with adenine **5**. Cyclopentenol **4** can in turn be derived from the Baylis–Hillman adduct **6** through functional group manipulation. We intend to effect an intramolecular BH reaction from the precursor 7, which will be derived from readily available D-ribose.

The synthesis of (*Z*)-enoate 7 was completed in 3 steps from D-ribose in 57% overall yield following the procedure reported by the Argyropoulos group.¹³ Interestingly, as noted by the authors, the *Z* stereoisomer was obtained. This is in contrast with the report by Wightman et al.,¹⁴ where the *E* isomer was reported as the major product. However, closer examination of the data reported by Wightman (*J* values of 12 Hz for the olefinic protons) suggests that the *Z* isomer was also obtained in their studies. The synthesis of the *E* isomer **10** was achieved by refluxing alkene **9**¹⁵ with ethyl acrylate in DCM in the presence of 20 mol % of Hoveyda–Grubbs second-generation catalyst to give **10** as a single cross-coupling isomer in 46% yield.¹⁶ The coupling constants for the vicinal alkene protons of 7 and **10** were found to be $J_{2,3} = 11.5$ and 15.6 Hz, respectively (Scheme 2).^{13,17}





"Reagents and conditions: (a) concentrated H_2SO_4 , acetone, room temperature, 3 h, 95%; (b) (i) ethyl 2-(triphenylphosphoranylidene)acetate, cat. PhCO₂H, DCM, room temperature, 16 h, (ii) NaIO₄, DCM/H₂O, room temperature, 1 h, 60% for two steps; (c) ref 15; (d) ethyl acrylate, 20 mol % Hoveyda–Grubbs II catalyst, DCM, reflux, 8 h, 46%.

With the two enoates 7 and **10** in hand, the key intramolecular BH reaction was attempted. Two protocols had previously been developed by Keck et al.:^{12j} one used catalytic amounts of trimethylphosphine in dichloromethane (Morita-BH reaction), while another utilized 1 equiv of DMAP and 0.25 equiv of DMAP·HCl as promoters in refluxing ethanol. Our initial experiments were carried out with 7 using

the former protocol, and no reaction ensued despite increasing the catalyst loading to stoichiometric amounts (Table 1, entries 2 and 3). With the latter protocol, the expected BH products **11a,b** were obtained, but in poor yields (total of 12%), along with 18% of the side product **12** (Table 1, entry 1), which was formed by a competing oxa-Michael reaction.^{12j,18} Other promoters were explored in attempts to improve the yields of the desired BH adducts. However, treatment of 7 with tertiary amines such as DABCO and DBU (Table 1, entries 4 and 5) in chloroform gave the oxa-Michael adducts **12** as the only major product. Secondary amines and phosphines (piperidine, pyrrolidine, and tributylphosphine) were also screened but did not result in any reaction, and so the DMAP/DMAP·HCl combination remains the best (Table 1).

We therefore shifted our attention into studying the effect of different solvents on the BH reaction with the DMAP and DMAP·HCl promoter system. Several solvents were screened (Table 2), and significantly improved results were obtained when polar aprotic solvents such as DMSO, MeCN, and DMF were used (Table 2, entries 5-7). These solvents gave the desired products 11a,b in moderate to good yields without the formation of 12, with DMF as solvent giving the best diastereoselectivity of 11a:11b (5:1). The diastereoselectivity of the reaction was further improved to 9:1 when the (Z)enoate 7 was added dropwise to the mixture of DMAP/DMAP. HCl at 0 °C (Table 2, entry 8). The stereochemistry of 11a was consistent with the measured coupling constant of 1.5 Hz between H-2 and H-3, while a larger coupling constant (5.8 Hz) was observed for 11b. Next, we shifted our attention to the development of a catalytic version of the BH reaction. After extensive studies, we found that heating of (Z)-enoate 7 at 60 °C in DMF for 18 h in the presence of 20 mol % of DMAP and 5 mol % of DMAP·HCl was the most optimal condition in terms of yield and diastereoselectivity. This gave 65% and 6% of isomers 11a,b, respectively, on gram-scale synthesis. Intriguingly, even under these optimized conditions the BH reaction of the corresponding E isomer 10 only led to the formation of numerous unidentified products.

With the key intermediate cyclopentenol 11a in hand, the synthesis of neplanocin A (1a) and its epimer 1b can be demonstrated. For the synthesis of neplanocin A, inversion of the stereochemistry of the hydroxyl group at C-3' is needed. Treatment of 11a under Mitsunobu conditions using diisopropyl azodicarboxylate (DIAD) and triphenylphosphine at 0 °C in the presence of benzoic acid gave benzoate 13 (instead of the expected Mitsunobu product 14) in 64% yield (Scheme 3). This suggests that a $S_N 2'$ attack¹⁹ is the dominant reaction pathway under these reaction conditions for this substrate.

Table 1. Screening of Promoters for the Baylis-Hillman Reaction



entry	promoter ^a	solvent	temp, time (h)	result
1	DMAP (1 equiv), DMAP·HCl (0.25 equiv)	EtOH	reflux, 24	11a:11b:12 (7%:5%:18%) ^b
2	PMe ₃	DCM	room temp, 24	recovery of 7
3	PMe ₃ (1 equiv)	DCM	room temp, 24	recovery of 7
4	DABCO	CHCl ₃	room temp, 24	12 ^c
5	DBU	CHCl ₃	room temp, 24	12 ^c
6	piperidine	CHCl ₃	room temp, 24	recovery of 7
7	pyrrolidine	CHCl ₃	room temp, 24	recovery of 7
8	<i>n</i> -Bu ₃ P	CHCl ₃	room temp, 24	recovery of 7

"Unless indicated otherwise, 0.2 equiv of promoter was used and the substrate concentration was 0.1 M. "Based on isolated yield. "Yield not determined.

Table 2. Study of Solvent Effects on the Baylis-Hillman Reaction

		$\xrightarrow{\text{EtO}_2C} \qquad \qquad$	CO ₂ Et
	7	11a $R_1 = H, R_2 = OH$ 12 11b $R_1 = OH, R_2 = H$	
entry	solvent	conditions ^a	yield (%) ^b 11a:11b:12
1	EtOH	А	7:5:18
2	DCM	В	30:20:17
3	CHCl ₃	В	12:18:20
4	THF	В	recovery of 7
5	DMSO	В	50:16:0
6	MeCN	В	54:20:0
7	DMF	В	58:12:0
8	DMF	С	68:8:0

^{*a*}1 equiv of DMAP and 0.25 equiv of DMAP·HCl were used as promoters, and the substrate concentration was 0.1 M. Conditions: (A) reflux, 24 h; (B) room temperature, 48 h; (C) addition at 0 $^{\circ}$ C and then room temperature for 48 h. ^{*b*}Based on isolated yield.

Scheme 3. $S_N 2'$ Reaction of 11a under Mitsunobu Conditions^{*a*}



^aReagents and conditions: (a) BzOH, DIAD, PPh₃, THF, room temperature, 18 h, 64%.

An alternative strategy to invert the chiral center at the C-3' position involved the oxidation of the allylic alcohol **11a** to the enone followed by stereoselective reduction to the secondary alcohol. Although oxidation of **11a** with Dess–Martin periodinane (DMP) followed by Luche reduction gave an excellent yield of the desired alcohol, no stereoselectivity was observed (Scheme 4). In contrast, we found that high selectivities and yields of the Luche reduction can be achieved when enone **1**7 was utilized instead.²⁰ In this route, DIBAL-H reduction of **11a** at -78 °C gave the diol **15** in 60% yield, which was used

without further purification (Scheme 5). Selective silylation of the primary alcohol yielded **16**, and subsequent DMP oxidation of the free secondary alcohol furnished the enone **17**. To our delight, Luche reduction of **17** gave **18** as the only stereoisomer with an excellent yield of 97%. This was followed by acetonide shuffling^{4p} to yield cyclopentenol **19** in 97% yield based on starting material recovery (bsmr) with 50% conversion. This constitutes the formal synthesis of neplanocin A **1a**, as neplanocin A can be accessed from **19** in two additional steps.^{4q} Scheme 4. Inversion of the Chiral Center at the C-3' Position^a



"Reagents and conditions: (a) DMP, room temperature, 18 h; (b) NaBH₄, CeCl₃:7H₂O, DCM, 0 $^{\circ}$ C, 2 h, 98% in two steps.

The synthesis of the 3'-epimer of neplanocin A (Scheme 6), the xylo analogue of 1b, commenced with the DIBAL-H reduction of 11a followed by benzoylation to give the dibenzovlated 20 in 73% vield over two steps. Deprotection of the acetal group of 20 under acidic conditions gave the diol 21 in 70% yield. Subsequent silvlation with 1.1 equiv of tertbutyldiphenylchlorosilane (TBDPSCl) gave monosilylated products 22a,b (3:2) in 85% combined yield along with a small amount of the disilylated product. The structure of 22b was confirmed by X-ray analysis (see the Supporting Information, Figure S1), which unambiguously validated the suitability of our synthetic approach to construct xylo carbocyclic nucleosides. The alcohol 22b was then subjected to a Mitsunobu coupling reaction with N6-bis-BOC-adenine²¹ to afford the coupling product 23 in 57% yield. Without further optimization, treatment of 23 with sodium methoxide followed by global deprotection in the presence of 2 N HCl afforded the xylo analogue 1b as a hydrochloride salt in 51% yield. To our knowledge, this is the first reported synthesis of the 3'-epimer of neplanocin A.

CONCLUSION

In summary, a stereoselective formal total synthesis of neplanocin A was achieved in 11 steps with 17% overall yield while the hitherto unknown xylo analogue **1b** was synthesized for the first time in 11 steps. We have presented here a simple and practical method for the construction of an enantiopure cyclopentenol ring in gram scale from the readily available Dribose via a catalytic Baylis—Hillman reaction. This cyclopentenol ring should provide a good starting point to access many novel carbocyclic nucleosides.

EXPERIMENTAL SECTION

General Methods. All chemicals were used as received from commercial sources. Dried solvents (MeCN, DCM, DMF, THF, diethyl ether, and toluene) were drawn from a Glass Contour Solvent Dispensing System. Anhydrous DMSO was purchased and used

without further purification. All reactions requiring anhydrous conditions were carried out under an argon atmosphere using ovendried glassware. Reaction progress was monitored by TLC plates (silica gel 60F254), and spots were visualized by UV or phosphomolybdic acid stain. Flash column chromatography was carried out using silica gel 60 (70–230 mesh). NMR spectra were recorded on a 400 MHz spectrometer using standard pulse sequences. ¹H and ¹³C NMR chemical shifts are reported on the δ scale (ppm) relative to residual nondeuterated solvent as the internal standard. HRMS were recorded by a TOF-MS spectrometer.

(3aR,6R,6aR)-6-(Hydroxymethyl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-ol (8). To a stirred suspension of D-ribose (20.0 g, 0.13 mol) in acetone (250 mL) was added dropwise concentrated H_2SO_4 (0.6 mL, 11.2 mmol) at room temperature. The suspension was stirred for 3 h at room temperature until a clear solution was obtained. The solution was then treated with NaHCO₃ (10.0 g, 120 mmol) and was stirred for an additional 1 h. The reaction mixture was filtered and concentrated in vacuo. The residue was absorbed onto silica gel and filtered through a pad of silica gel (with 50/50 to 100/0 EtOAc/hexanes as eluent) to give 1 in 95% yield as a colorless syrup. The spectroscopic data obtained are identical with those previously reported: $R_f = 0.39$ (80/20 EtOAc/hexanes).¹⁵

(Z)-Ethyl 3-((4S,5S)-5-Formyl-2,2-dimethyl-1,3-dioxolan-4yl)acrylate (7). To a solution of 8 (8.00 g, 42.1 mmol) in DCM (250 mL) was added the ylide ethyl 2-(triphenylphosphoranylidene)acetate (19.0 g, 54.5 mmol) at room temperature. This was followed by the addition of benzoic acid as catalyst (250 mg, 2.0 mmol). The reaction mixture was stirred for 16 h, following which it was cooled to 0 °C. Aqueous NaIO₄ (11.0 g, 51.2 mmol, 100 mL of water) was added, and the reaction mixture was stirred for a further 1 h at room temperature, before it was filtered through a pad of Celite. The filtrate was extracted with DCM and washed with water. The combined organic layers were dried, filtered, and concentrated in vacuo. The bulk of the triphenylphosphine oxide was removed by washing with diethyl ether and filtered. The filtrate was concentrated in vacuo, and purified by silica gel column chromatography (with 3/97 to 10/90 EtOAc/ hexanes as eluent) to give 7 in 60% yield as a colorless oil: $R_{\rm f} = 0.52$ (40/60 EtOAc/hexanes); $[\alpha]_{D}^{24.9}$ = +116.0° (c = 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 9.47 (d, J = 2.8 Hz, 1H), 6.22 (dd, J = 11.6, 6.8 Hz, 1H), 5.96 (dd, J = 11.6, 1.8 Hz, 1H), 5.81 (ddd, J = 7.8, 6.9, 1.8 Hz, 1H), 4.79 (dd, J = 7.8, 2.8 Hz, 1H), 4.19 (qd, J = 7.2, 1.8 Hz, 2H), 1.60 (s, 3H), 1.43 (s, 3H), 1.29 (t, J = 7.2 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 199.5, 165.6, 143.6, 123.3, 111.6, 82.1, 75.9, 61.0, 27.4, 25.3, 14.3; FTIR (cm⁻¹) 3455, 1716, 1649; HRMS (ESI; m/z) [M + H]⁺ calcd for C₁₁H₁₇O₅ 229.1076, found 229.1068.

(E)-Ethyl 3-((45,55)-5-Formyl-2,2-dimethyl-1,3-dioxolan-4-yl)acrylate (10). To a solution of 9 (400 mg, 2.6 mmol) in anhydrous DCM (50 mL) was added ethyl acrylate (2.8 mL, 26.0 mmol) in one portion under an argon atmosphere. The stirred mixture was heated to reflux before the Hoveyda–Grubbs II catalyst (80 mg, 0.13 mmol) was added in a single portion. The reaction mixture was refluxed for 8 h, following which it was cooled to room temperature, concentrated in vacuo, and purified by silica gel column chromatography (with 0/100 to 30/70 EtOAc/hexanes as eluent) to give 10 in 46% yield (270 mg, 1.2 mmol) as a colorless oil: $R_{\rm f} = 0.21$ (40/60



^aReagents and conditions: (a) DIBAL-H, DCM, -78 °C to room temperature, 3 h, 60%; (b) TBDPSCl, imidazole, cat. DMF, DCM, 0 °C, 4 h, 85%; (c) DMP, room temperature, 18 h, 98%; (d) NaBH₄, CeCl₃·7H₂O, DCM, 0 °C, 2 h, 97%; (e) cat. *p*-TsOH, acetone, room temperature, 18 h, 97% (bsmr); (f) ref 4q, two steps to 1a.



^aReagents and conditions: (a) (i) DIBAL-H, DCM, -78 °C to room temperature, 3 h, (ii) BzCl, Et₃N, 18 h, 73% for two steps; (b) 2 N HCl, THF, 65 °C, 16 h, 70%; (c) TBDPSCl, imidazole, 0 °C, DCM, 5 h, 85%; (d) N6-bis-BOC-adenine, DIAD, PPh₃, toluene, room temperature, 16 h, 57%; (e) NaOMe, MeOH, room temperature, 14 h, 78%; (f) 2 N HCl, MeOH, room temperature, 48 h, 65%.

EtOAc/hexanes); $[\alpha]^{22.6}_{D} = +12.3^{\circ}$ (c 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 9.51 (d, J = 3.0 Hz, 1H), 6.81 (dd, J = 15.6, 5.2 Hz, 1H), 6.14 (dd, J = 15.6, 1.7 Hz, 1H), 4.98 (ddd, J = 7.6, 5.2, 1.7 Hz, 1H), 4.50 (dd, J = 7.7, 3.0 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 1.62 (s, 3H), 1.44 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 200.3, 165.5, 139.8, 124.0, 112.1, 82.1, 76.8, 60.9, 27.4, 25.4, 14.3; FTIR (cm⁻¹) 3443, 1719, 1659; HRMS (ESI; m/z) [M + Na]⁺ calcd for C₁₁H₁₆O₅Na 251.0890, found 251.0887.

General Procedure for Study of Solvent Effects on the Baylis–Hillman Reaction (Table 2). *Methods A and B.* To a stirred solution of compound 7 (114 mg, 0.5 mmol) in 5.0 mL of solvent were added 4-(dimethylamino)pyridine (60 mg, 0.5 mmol) and 4-(dimethylamino)pyridine hydrochloride (20 mg, 0.125 mmol) at room temperature. The reaction mixture was heated at 78 °C for 24 h for method A or stirred at room temperature for 48 h for method B. The reaction mixture was concentrated in vacuo and purified by silica gel column chromatography.

Method C. A solution of 4-(dimethylamino)pyridine (60 mg, 0.5 mmol) and 4-(dimethylamino)pyridine hydrochloride (20 mg, 0.125 mmol) in DMF (1.0 mL) was added to a solution of compound 7 (114 mg, 0.5 mmol) in DMF (4 mL) at 0 °C. The mixture was warmed to room temperature and stirred for 48 h. The reaction mixture was concentrated in vacuo and purified by silica gel column chromatography.

Catalytic Baylis–Hillman Reaction. The catalysts 4-(dimethylamino)pyridine (0.37 g, 3.08 mmol) and 4-(dimethylamino)pyridine hydrochloride (120 mg, 0.77 mmol) were dissolved in anhydrous DMF (20 mL) at room temperature. To this solution was added compound 7 (3.50 g, 15.4 mmol) in anhydrous DMF (180 mL). The reaction mixture was heated at 60 °C for 18 h. The reaction mixture was concentrated in vacuo and purified by silica gel column chromatography (with 10/90 to 30/70 EtOAc/hexanes as eluent) to give the titled compound **11a** in 65% yield (2.28 g) as a colorless oil and **11b** in 6% yield (218 mg) as a colorless oil.

(3aR,4S,6aS)-Ethyl 4-hydroxy-2,2-dimethyl-4,6a-dihydro-3aHcyclopenta[d][1,3]dioxole-5-carboxylate (11a): Waters Preparative LC-MS initial A 20% acetonitrile, and B 80% water, final A 60% and B 40%, gradient 30 min, flow rate 20 mL/min, UV@254 nm, column Phenomenex Luna C18, 10 μ m, 250 × 21.20 mm, product retention time 11.45 min; $R_f = 0.45$ (80/20 diethyl ether/hexanes); $[\alpha]^{22.5}_{D} =$ +57.3° (c = 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 6.76 (d, J =1.6 Hz, 1H), 5.32 (dt, J = 5.6, 1.6 Hz, 1H), 4.96 (d, J = 1.6 Hz, 1H), 4.62 (d, J = 5.6 Hz, 1H), 4.26 (q, J = 7.2 Hz, 2H), 1.39 (s, 3H), 1.35 (s, 3H), 1.32 (t, J = 7.2 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 164.6, 143.0, 138.7, 112.1, 85.1, 83.1, 79.2, 61.3, 27.4, 25.6, 14.3; FTIR (cm⁻¹) 3431, 1717; HRMS (ESI; m/z) [M + Na]⁺ calcd for C₁₁H₁₆O₅Na 251.0890, found 251.0905. Anal. Calcd for C₁₁H₁₆O₅: C, 57.88; H, 7.07; O, 35.05. Found: C, 57.47; H, 7.10; O, 35.34.

(3*aR*,4*R*,6*aS*)-Ethyl 4-hydroxy-2,2-dimethyl-4,6*a*-dihydro-3*a*H-cyclopenta[*d*][1,3]dioxole-5-carboxylate (11*b*): Waters Preparative LC-MS: initial A 20% acetonitrile and B 80% water, final A 60% and B 40%, gradient 30 min, flow rate 20 mL/min, UV@254 nm, column Phenomenex Luna C18, 10 μm, 250 × 21.20 mm, product retention time 9.5 min; R_f = 0.39 (80/20 diethyl ether/hexanes); $[\alpha]^{21.8}_{D}$ = +35.2° (*c* = 0.36, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 6.68 (*s*, 1H), 5.04 (dd, *J* = 5.6, 2.0 Hz, 1H), 4.84 (t, *J* = 5.6 Hz, 1H), 4.79 (d, *J* = 6.4 Hz, 1H), 4.26 (m, 2H), 1.45 (*s*, 3H), 1.41 (*s*, 3H), 1.32 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 164.3, 140.1, 139.8, 113.1, 81.5, 77.8, 72.5, 61.1, 27.6, 26.4, 14.3; FTIR (cm⁻¹) 3496, 1720; HRMS (ESI; *m*/*z*) [M + Na]⁺ calcd for C₁₁H₁₆O₃Na 251.0890, found 251.0903.

Ethyl (3aR,4R,6aR)-4-(Benzoyloxy)-2,2-dimethyl-3a,6a-dihydro-4H-cyclopenta[d][1,3]dioxole-5-carboxylate (13). To a solution of 11a (456 mg, 2 mmol), benzoic acid (366 mg, 3 mmol), and Ph₃P (1.05 g, 4 mmol) in 30 mL of anhydrous THF was added DIAD (0.8 mL, 4 mmol) at 0 °C under an argon atmosphere, and the mixture was stirred for 18 h at room temperature. The reaction mixture was adsorbed onto silica gel and then purified by silica gel column chromatography (2/98 to 10/90 EtOAc/hexanes) to give the corresponding coupled compound in 64% yield as a white amorphous solid: ¹H NMR (400 MHz, CDCl₃) δ 8.06-7.95 (m, 2H), 7.61-7.51 (m, 1H), 7.49–7.38 (m, 2H), 7.01 (s, 1H), 6.15 (s, 1H), 5.39 (d, J = 5.5 Hz, 1H), 4.70 (d, J = 5.5 Hz, 1H), 4.30-4.10 (m, 2H), 1.45 (s, 3H), 1.36 (s, 3H), 1.22 (t, J = 7.1 Hz, 3H); ¹³C NMR (101 MHz, $CDCl_3$) δ 165.9, 163.3, 146.5, 135.8, 133.3, 129.9, 128.5, 112.8, 83.9, 83.2, 80.8, 61.2, 27.4, 25.8, 14.2; FTIR (cm⁻¹) 2986, 2937, 2360, 2341, 1723; HRMS (ESI; m/z) [M + Na]⁺ calcd for C₁₈H₂₀O₆Na 355.1152, found 355.1161.

(3a*R*,45,6a*S*)-5-(Hydroxymethyl)-2,2-dimethyl-4,6a-dihydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-ol (15). To a solution of 11a (1.00 g, 4.4 mmol) in DCM (50 mL) was added dropwise a solution of DIBAL-H (1.0 M solution in hexanes) (17.6 mL, 17.6 mmol) at -78°C. The reaction mixture was then warmed to room temperature and stirred for 3 h. The reaction was quenched by addition of Celite (1 g) followed by dropwise addition of 5 mL saturated NH₄Cl solution at 0 °C. The mixture was then filtered through a pad of Celite and washed with EtOAc. The filtrates were concentrated in vacuo and purified by silica gel column chromatography (80/20 EtOAc/hexanes) to give **15** in (490 mg) 60% yield as a colorless oil: $R_f = 0.22$ (80/20 EtOAc/hexanes); $[\alpha]^{25.4}_{D} = +39.0^{\circ}$ (c = 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 5.86 (s, 1H), 5.25 (d, J = 5.7 Hz, 1H), 4.77 (s, 1H), 4.56 (d, J = 5.7 Hz, 1H), 4.34 (s, 2H), 1.40 (s, 3H), 1.34 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 146.6, 129.8, 111.8, 86.7, 83.5, 81.8, 61.1, 27.5, 25.7; FTIR (cm⁻¹) 3390; HRMS (ESI; m/z) [M + Na]⁺ calcd for C₉H₁₄O₄Na 209.0784, found 209.0788.

(3aR,4S,6aS)-5-(((tert-Butyldiphenylsilyl)oxy)methyl)-2,2-dimethyl-4,6a-dihydro-3aH-cyclopenta[d][1,3]dioxol-4-ol (16). To a solution of 15 (80 mg, 0.43 mmol) in THF (12 mL) was added 1 drop of DMF, imidazole (293 mg, 4.3 mmol), and tertbutyldiphenylchlorosilane (TBDPSCl; 355 mg, 1.3 mmol) sequentially, and the mixture was stirred at room temperature for 4 h. The reaction mixture was concentrated in vacuo. Then 10 mL of water was added to the reaction mixture and 3×10 mL of DCM was used to extract the desired product. The combined organic layers were dried, filtered, and concentrated in vacuo and purified by silica gel column chromatography (with 0/100 to 20/80 EtOAc/hexanes as eluent) to give 16 in 85% yield (156 mg) as a colorless oil: $R_{\rm f} = 0.25$ (20:80 EtOAc/hexanes); $[\alpha]^{247}_{D} = +33.6^{\circ}$ (c = 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.77–7.59 (m, 4H), 7.52–7.34 (m, 6H), 5.84 (s, 1H), 5.27 (d, J = 5.6 Hz, 1H), 4.74 (d, J = 3.2 Hz, 1H), 4.57 (d, J = 5.6 Hz, 1H), 4.36 (q, J = 13.9 Hz, 2H), 1.39 (s, 3H), 1.35 (s, 3H) 1.08 (s, 9H); ¹³C NMR (101 MHz, CDCl₃) δ 146.4, 135.7, 132.9, 130.1, 129.3, 128.0, 111.5, 86.4, 83.6, 81.3, 62.35, 27.6, 26.9, 25.9, 19.3; FTIR (cm^{-1}) 3439; HRMS (ESI; m/z) $[M + Na]^+$ calcd for $C_{25}H_{32}O_4SiNa$ 447.1962, found 447.1964.

(3aS,6aS)-5-(((tert-Butyldiphenylsilyl)oxy)methyl)-2,2-dimethyl-3aH-cyclopenta[d][1,3]dioxol-4(6aH)-one (17). To a solution of 16 (146 mg, 0.34 mmol) in DCM (11 mL) was added Dess-Martin periodinane (DMP; 173 mg, 0.41 mmol), and the reaction mixture was stirred at room temperature for 4 h. Diethyl ether (20 mL) was then added, and the mixture was filtered through a pad of Celite. The filtrate was concentrated in vacuo and purified with silica gel column chromatography (0/100 to 10/90 EtOAc/hexanes as eluent) to give 17 in 98% yield (143 mg) as a white amorphous solid: $R_{\rm f} = 0.72 \ (20/80 \ {\rm EtOAc/hexanes}); \ [\alpha]^{24.8} = +12.4^{\circ} \ (c = 1.0, \ {\rm CHCl}_3);$ ¹H NMR (400 MHz, CDCl₃) δ 7.63–7.621 (m, 4H), 7.55 (dd, J = 4.1, 2.0 Hz, 1H), 7.50-7.30 (m, 6H), 5.22 (br s, 1H), 4.49 (d, J = 5.4 Hz, 1H), 4.41 (t, J = 1.8 Hz, 2H), 1.42 (s, 3H), 1.40 (s, 3H), 1.09 (s, 9H); ¹³C NMR (101 MHz, CDCl₃) δ 201.6, 152.7, 147.2, 135.6, 133.0, 132.9, 130.1, 128.0, 115.5, 78.2, 58.9, 27.7, 27.0, 26.4, 19.4; FTIR (cm^{-1}) 1723; HRMS (ESI; m/z) $[M + Na]^+$ calcd for $C_{25}H_{30}O_4SiNa$ 445.1805, found 445.1797.

(3aR,4R,6aS)-5-(((tert-Butyldiphenylsilyl)oxy)methyl)-2,2-dimethyl-4,6a-dihydro-3aH-cyclopenta[d][1,3]dioxol-4-ol (18). To a solution of 17 (70 mg, 0.17 mmol) in MeOH (10 mL) were added CeCl₃·7H₂O (93 mg, 0.26 mmol) and NaBH₄ (11 mg, 0.27 mmol) sequentially at 0 °C, and the mixture was stirred for 2 h. The reaction mixture was quenched with water and concentrated in vacuo. The residue was purified with silica gel column chromatography (with 0/100 to 10/90 EtOAc/hexanes as eluent) to give 18 in 97% yield (68 mg) as a colorless oil: $R_{\rm f} = 0.62$ (20/80 EtOAc/hexanes); $[\alpha]^{25.3}_{\rm D} =$ +12.5° (c = 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.76–7.60 (m, 4H), 7.52-7.31 (m, 6H), 5.89 (s, 1H), 5.12-4.94 (m, 1H), 4.75 (t, J = 5.6 Hz, 1H), 4.37 (dt, J = 16.1, 10.6 Hz, 3H), 1.42 (d, J = 13.6 Hz, 6H), 1.08 (s, 9H); ¹³C NMR (101 MHz, CDCl₃) δ 149.4, 135.7, 133.6, 129.9, 127.8, 125.2, 112.4, 82.6, 77.9, 73.6, 61.2, 27.9, 27.0, 26.8, 19.4; FTIR (cm⁻¹) 3526; HRMS (ESI; m/z) [M + Na]⁺ calcd for C₂₅H₃₂O₄SiNa 447.1962, found 447.1961.

(3aS,4S,6aR)-6-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-2,2-dimethyl-4,6a-dihydro-3aH-cyclopenta[d][1,3]dioxol-4-ol (19). To a solution of 18 (30 mg, 0.07 mmol) in anhydrous acetone (10 mL) was added *p*-TsOH·H₂O (4.0 mg, 0.02 mmol), and the reaction mixture was stirred at room temperature for 18 h. The mixture was concentrated in vacuo, redissolved in DCM, and washed with saturated NaHCO₃ solution. The organic layer was dried, filtered, and concentrated in vacuo. The crude residue contained both 18 and **19** in a 10:9 ratio (from the ¹H NMR spectrum). The title compound **19** was isolated by silica gel column chromatography (with 10/90 to 20/80 EtOAc/hexanes as eluent) in 97% yield (14 mg) as a colorless oil based on starting material recovery (bsmr) (15.5 mg of **18**). The spectral data of **19** matched the data reported previously.^{4q}

((3aS,4S,6aS)-4-(Benzoyloxy)-2,2-dimethyl-4,6a-dihydro-3aH-cyclopenta[d][1,3]dioxol-5-yl)methyl Benzoate (20). DIBAL-H (60 mL, 1 M solution in hexanes, 59.2 mmol) was added slowly to a solution of ester 11a (3.00 g, 13.2 mmol) in DCM (120 mL) under argon at -78 °C. After the mixture was stirred at room temperature for 3 h, MeOH (25 mL) and water (10 mL) were sequentially added. After the mixture was stirred at room temperature for 30 min, Na₂SO₄·7H₂O (25 g) was added. The mixture was diluted with DCM (100 mL), and stirring was continued for 18 h. When a crystalline precipitate had fully formed, the mixture was filtered through Celite and washed with DCM (3 × 20 mL). The solvent was removed under reduced pressure to give diol 15 as a colorless oil. The compound was used without further purification.

To a solution of 15 (13.2 mmol) in DCM (180 mL) were added triethylamine (7.5 mL, 53.7 mmol) and BzCl (3.83 mL, 13.4 mmol) sequentially, and the mixture was stirred at room temperature for 18 h. The reaction mixture was quenched with saturated NH₄Cl solution (50 mL). Extraction of the mixture with DCM $(2 \times 50 \text{ mL})$ gave the combined organic layers, which were dried (MgSO₄), filtered, and concentrated in vacuo. The crude product was purified by silica gel column chromatography (with 0/100 to 10/90 EtOAc/hexanes as eluent) to give 3.81 g of 20 in (73% yield in two steps) as a white amorphous solid: $R_f = 0.35 (20/80 \text{ EtOAc/hexanes}); [\alpha]^{25.2} = +59.4^{\circ}$ $(c = 1.0, CHCl_3)$; ¹H NMR (400 MHz, CDCl₃) δ 8.07–7.93 (m, 4H), 7.53 (ddd, J = 9.0, 8.1, 0.7 Hz, 2H), 7.47-7.32 (m, 4H), 6.21 (d, J = 0.6 Hz, 1H), 5.97 (d, J = 0.6 Hz, 1H), 5.33 (d, J = 5.7 Hz, 1H), 4.97 (s, 2H), 4.75 (d, J = 5.8 Hz, 1H), 1.48 (s, 3H), 1.38 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 166.0, 139.8, 134.1, 133.3, 133.1, 129.8, 129.7, 129.5, 128.4, 112.5, 84.3, 83.2, 82.9, 61.1, 27.4, 25.8; FTIR (cm⁻¹) 1721; HRMS (ESI; m/z) [M + Na]⁺ calcd for C₂₃H₂₂O₆Na 417.1308, found 417.1309.

((3S,4S,5S)-5-(Benzoyloxy)-3,4-dihydroxycyclopent-1-en-1yl)methyl Benzoate (21). To a solution of 20 (3.80 g, 9.64 mmol) in THF (40 mL) was added 2 N HCl (16 mL), and the reaction mixture was stirred at 65 °C for 16 h. The reaction mixture was then cooled to room temperature and concentrated in vacuo. The residue was dissolved in EtOAc and washed with saturated NaHCO3 solution, water, and brine and then dried (MgSO₄). The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (50/50 EtOAc/hexanes) to give 21 (2.41 g, 70%) as a colorless oil: $R_{\rm f} = 0.16$ (40/60 EtOAc/hexanes); $[\alpha]^{25.1}_{\rm D}$ $= +43.6^{\circ}$ (c = 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 8.06–7.99 (m, 4H), 7.61–7.52 (m, 2H), 7.46–7.37 (m, 4H), 6.25 (s, 1H), 5.81 (s, 1H), 4.04 (q, J = 14.8 Hz, 2H), 4.78 (d, J = 5.2 Hz, 1H), 4.26 (br s, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 168.0, 166.2, 140.9, 133.8, 133.4, 132.9, 130.0, 129.8, 129.8, 129.3, 128.7, 128.6, 85.6, 72.7, 77.0, 61.0; FTIR (cm⁻¹) 3422, 1719; HRMS (ESI; m/z) [M + Na]⁺ calcd for C₂₀H₁₈O₆Na 377.0995, found 377.0994

22a,b. Imidazole (692 mg, 10.21 mmol) and *tert*-butyldiphenylchlorosilane (TBDPSCl; 2.05 g, 7.48 mmol) were added to a solution of diol **21** (2.40 g, 6.77 mmol) in anhydrous DCM (25 mL). After it was stirred at room temperature for 16 h, the reaction mixture was quenched with a saturated NH₄Cl solution (100 mL) and extracted with dichloromethane (2 \times 20 mL). The combined organic layers were washed with brine and then dried (MgSO₄). The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (5/95 EtOAc/hexanes) to give **22a** (2.02 g, 50%) as a colorless oil and **22b** (1.41 g, 35%) as a white crystalline solid.

((35,4R,55)-5-(Benzoyloxy)-3-((tert-butyldiphenylsilyl)oxy)-4-hydroxycyclopent-1-en-1-yl)methyl benzoate (**22a**): R_f = 0.65 (50/50 diethyl ether/hexanes); $[a]^{25.1}_{D}$ = +12.4° (*c* = 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 8.01–7.93 (m, 2H), 7.92–7.87 (m, 2H), 7.69 (d, *J* = 6.8 Hz, 4H), 7.57–7.49 (m, 2H), 7.48–7.31 (m, 10H), 6.03 (s, 1H), 5.63 (s, 1H), 5.04–4.65 (m, 3H), 4.26 (s, 1H), 1.10 (s, 9H); ¹³C NMR (101 MHz, CDCl_3) δ 166.2, 165.8, 140.6, 135.8, 135.7, 133.1, 133.0, 132.7, 132.3, 130.2, 130.1, 129.8, 129.7, 129.6, 128.3, 128.0, 127.8, 83.4, 76.3, 74.7, 61.1, 26.9, 19.3; FTIR (cm⁻¹) 3464, 1366; HRMS (ESI; m/z) [M + Na]⁺ calcd for C₃₆H₃₆O₆SiNa 615.2173, found 615.2143.

((35,45,55)-5-(Benzoyloxy)-4-((tert-butyldiphenylsilyl)oxy)-3-hydroxycyclopent-1-en-1-yl)methyl benzoate (**22b**): R_f = 0.48 (50/50 diethyl ether/hexanes); white crystalline solid, mp 93–94 °C (diethyl ether/hexane); $[\alpha]^{25.3}_{D}$ = +36.0° (*c* = 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.93–7.89 (m, 2H), 7.80–7.76 (m, 2H), 7.76–7.65 (m, 2H), 7.62–7.59 (m, 2H), 7.55–7.46 (m, 2H), 7.44–7.12 (m, 10H), 6.16 (d, *J* = 4.0 Hz, 1H), 6.11 (m, 1H), 4.83 (q, *J* = 14.8 Hz, 2H), 4.52–4.50 (m, 1H), 4.45 (br s, 1H), 1.10 (s, 9H); ¹³C NMR (101 MHz, CDCl₃) δ 165.9, 165.7, 141.1, 135.7, 135.6, 133.0, 132.9, 132.7, 132.6, 132.3, 130.2, 130.0, 129.8, 129.6, 128.2, 128.1, 128.0, 127.8, 82.5, 77.7, 72.4, 61.1, 26.9, 19.2; FTIR (cm⁻¹) 3233, 1272; HRMS (ESI; *m/z*) [M + Na]⁺ calcd for C₃₆H₃₆O₆SiNa 615.2173, found 615.2159.

((3R,4S,5S)-5-(Benzoyloxy)-3-(6-((bis-tert-butoxycarbonyl)amino)-9H-purin-9-yl)-4-((tert-butyldiphenylsilyl)oxy)-cyclopent-1-en-1-yl)methyl Benzoate (23). To a suspension of 22b (900 mg, 1.52 mmol), N6-bis-BOC-adenine²¹ (1.01 g, 3.04 mmol), and Ph₃P (797 mg, 3.04 mmol) in 20 mL of anhydrous toluene was added DIAD (600 μ L, 3.04 mmol) at 0 °C under an argon atmosphere. After the mixture was stirred at room temperature for 16 h, the solvent was evaporated and the residue was purified by flash column chromatography on silica gel (40/60 diethyl ether/hexanes) to give 23 (794 mg, 57%) as a foam: $R_f = 0.29$ (50/50 diethyl ether/ hexanes); $[\alpha]^{25.3}_{D} = -3.8^{\circ}$ (c = 1.0, CHCl₃); ¹H NMR (400 MHz, $CDCl_3$) δ 8.78 (s, 1H), 7.94 (d, J = 7.2 Hz, 2H), 7.82 (s, 1H), 7.78 (d, J = 7.2 Hz, 2H), 7.53 (dt, J = 15.1, 7.4 Hz, 2H), 7.43–7.27 (m, 10H), 7.21-7.02 (m, 4H), 6.19 (d, J = 4.1 Hz, 1H), 5.95 (s, 1H), 5.75 (br s, 1H), 5.10-4.94 (m, 1H), 4.89 (s, 1H), 4.83 (t, J = 4.6 Hz, 1H).1.47 (s, 18H), 0.95 (s, 9H); ¹³C NMR (101 MHz, CDCl₃) δ 165.8, 165.7, 153.1, 152.0, 150.6, 150.2, 143.0, 141.8, 135.3, 133.4, 133.2, 132.0, 131.7, 130.1, 129.8, 129.6, 129.4, 129.0, 128.4, 128.2, 127.7, 84.3, 83.7, 82.2, 63.9, 60.7, 27.8, 26.7, 19.0; FTIR (cm⁻¹) 1728, 1366; HRMS (ESI; m/z) [M + Na]⁺ calcd for C₅₁H₅₅N₅O₉SiNa 932.3661, found 932.3665

Bis-tert-butyl (9-((1R,4S,5S)-5-((tert-Butyldiphenylsilyl)oxy)-4-hydroxy-3-(hydroxymethyl)cyclopent-2-en-1-yl)-9H-purin-6yl)carbamate (24). Sodium methoxide (95 mg, 1.75 mmol) was added to a solution of 23 (800 mg, 0.88 mmol) in MeOH (10 mL) at room temperature. After it was stirred at room temperature for 14 h, the reaction mixture was quenched with a saturated NH₄Cl solution (10 mL) and the mixture was extracted with EtOAc (2×60 mL). The combined organic layers were washed with water and brine and then dried (MgSO₄). The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (75/25 EtOAc/hexanes) to give 24 (484 mg, 78%) as a foam: $R_{\rm f}$ = 0.23 (50/50 EtOAc/hexanes); $[\alpha]^{25.1}_{D} = -50.9^{\circ}$ (*c* = 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 8.70 (s, 1H), 7.62–7.56 (m, 2H), 7.51– 7.31 (m, 7H), 7.28-7.21 (m, 2H), 5.60 (s, 1H), 5.15 (s, 1H), 4.73 (s, 1H), 4.59 (s, 1H), 4.42 (q, J = 14.8 Hz, 2H), 1.45 (s, 18H), 1.04 (s, 9H); 13 C NMR (101 MHz, CDCl₃) δ 152.1, 151.4, 150.9, 150.3, 144.2, 135.5, 135.4, 132.1, 132.0, 130.2, 127.9, 122.3, 86.5, 84.1, 82.6, 66.8, 59.9, 27.8, 26.8, 19.0; FTIR (cm⁻¹) 3503, 1790, 1370; HRMS (ESI; m/z) $[M + H]^+$ calcd for $C_{37}H_{48}N_5O_7Si$ 702.3318, found 702.3330.

(15,25,5*R*)-5-(6-Amino-9*H*-purin-9-yl)-3-(hydroxymethyl)cyclopent-3-ene-1,2-diol Hydrochloride (1b). To a solution of 18 (200 mg, 0.28 mmol) in MeOH (5 mL) was added 2 N HCl (500 μ L), and the mixture was stirred at room temperature for 48 h. The reaction mixture was filtered through a plug of cotton wool and azeotroped with MeOH (3 × 10 mL) to remove water. The final product was purified by precipitation, in which the residue was washed with diethyl ether followed by DCM (2 × 5 mL) to afford pure 1b (49 mg, 65%) as a pale yellow solid: [α]²⁵³_D = -50.0° (*c* = 1.0, MeOH); ¹H NMR (400 MHz, CD₃OD) δ 8.38 (s, 1H), 8.34 (s, 1H), 5.79 (s, 1H), 5.37 (br s, 1H), 4.56 (br s, 1H), 4.41–4.22 (m, 3H); ¹³C NMR (101 MHz, CD₃OD) δ 152.2, 151.9, 150.4, 145.1, 144.0, 121.8, 120.1, 88.1, 80.7, 65.6, 59.7; FTIR (cm⁻¹) 3366, 1365; HRMS (ESI; *m/z*) [M + H]⁺ calcd for C₁₁H₁₄N₅O₃ 264.1091, found 264.1094.

ASSOCIATED CONTENT

S Supporting Information

Figures, tables, and a CIF file giving ¹H NMR and ¹³C NMR spectra of all compounds prepared and crystallographic data of **22b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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