# Total Synthesis of (−)-Neplanocin A by Using Lithium Thiolate-Initiated Michael−Aldol Tandem Cyclization Reaction

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(−)-Neplanocin A (**1**), *S*-adenosylhomocystein hydrolase inhibitor, was synthesized. The characteristic of this synthesis is a stereoselective construction of five-membered ring of neplanocin A by intramolecular aldol reaction of the lithium enolate that was generated by conjugate addition of lithium thiolate. TBS-protected chiral *ω*-oxo-α,*β*-unsaturated ester **16**, which was prepared from D-mannitol, was treated with 1.2 equiv of lithium benzylthiolate in THF at −20 °C to give three separable cyclization products in good yields and stereoselectivity. After conversions of protective groups, the benzylsulfanyl part of **21** was removed by oxidation to sulfoxide and subsequent thermal elimination to give the requisite double bond. Through the functional group transformations of **30**, total synthesis of (−)-neplanocin A (**1**) was accomplished.

## Introduction

(−)-Neplanocin A (**1**) is a carbonucleoside[1] isolated from *Ampullariella regularis* in 1981[2] and has *S*-adenosylhomocystein hydrolase inhibitory activity.[3] To date, several resourceful examples of the total synthesis of neplanocin A have been reported. In these approaches, the characteristics were chemoenzymatic desymmetrization of bicyclic Diels−Alder adducts derived from cyclopentadiene;[4] palladium-mediated rearrangement[5] or desymmetrization reaction of cyclopentene derivatives;[6] construction of five-membered ring by intramolecular Horner−Wadsworth−Emmons or Wittig reaction,[7] or C−H insertion reaction,[8] respectively. However, there is no precedent of ring construction by intramolecular aldol reaction.

As an extension of asymmetric addition reaction of lithium thiolate with α,*β*-unsaturated esters,[9] we have already developed a lithium thiolate-initiated Michael−aldol tandem reaction of α,*β*-unsaturated esters with aldehydes and its application to intramolecular cyclization reaction of *ω*-oxo-α,*β*-unsaturated esters.[10] The latter reaction constructs five-, six-, and seven-membered rings in good yields with excellent stereoselectivity. This cyclization is constituted by formation of a transient lithium enolate, which is generated by conjugate addition of lithium thiolate, followed by its intramolecular aldol reaction. Since the sulfur functional groups can be easily removed, this cyclization reaction seems to be useful for the chemical synthesis of carbosugars and cyclitols.[11] To verify the usefulness of this cyclization reaction, we chose (−)-neplanocin A (**1**) as a synthetic target.

Our strategy is as follows: (1) stereoselective ring construction by tandem Michael−aldol cyclization of **4** initiated by conjugate addition of lithium thiolate, (2) thermal elimination of sulfide moiety in **3** affording an olefin **2**, and (3) functional group transformations to provide (−)-neplanocin A (Scheme 1).

## Results and Discussion

We started our synthesis from an acetonide-protected chiral diol **5**, which is readily available from D-mannitol in large scale[12] (Scheme 2).

One of the hydoxy groups in **5** was protected by treating with *p*-methoxybenzyl chloride and KOH in

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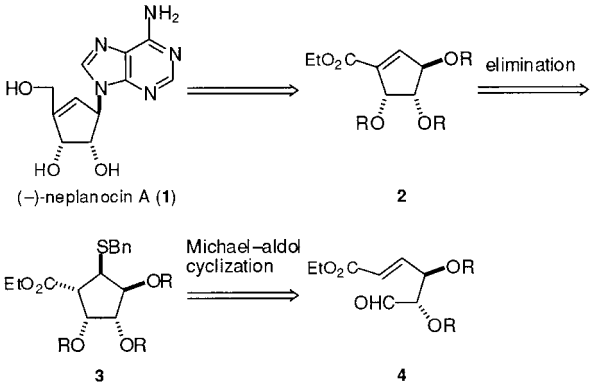
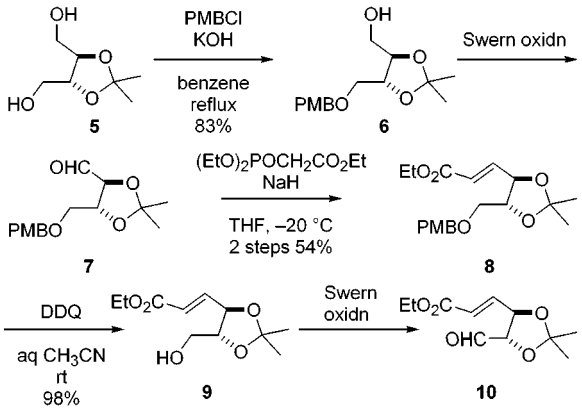
**Scheme 1. Retrosynthetic Analysis of (−)-Neplanocin A**

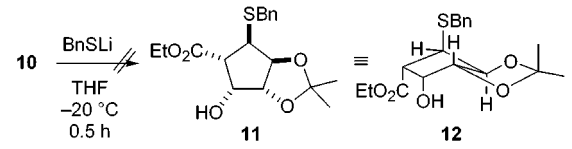



R = H or protective groups.

**Scheme 2. Preparation of Acetonide-Protected *ω*-Oxo-α,*β*-unsaturated Ester 10**




**Scheme 3. Attempted Michael−Aldol Tandem Cyclization Reaction of 10 with BnSLi (Failed)**




refluxing benzene to give alcohol **6**. Swern oxidation of **6** afforded an aldehyde **7**, which was then converted, without purification, to α,*β*-unsaturated ester **8** by Horner−Wadsworth−Emmons reaction. Deprotection of the PMB group by DDQ,[13] giving **9**, followed by Swern oxidation gave the desired *ω*-oxo-α,*β*-unsaturated ester **10**. Because **10** was too unstable to purify, the crude product was used directly in the next step.

We examined the cyclization reaction of **10** with lithium thiolate (Scheme 3). However, the reaction of **10** with 1.2 equiv of lithium benzylthiolate in THF at −20 °C for 0.5 h resulted in the formation of a complex mixture, and the desired cyclization product **11** was not detected. High distortion of the *trans*-bicyclo[3.3.0] structure **12** of **11** prevents the aldol cyclization of **10**.[14]

To overcome the above problem, we changed substrate **10** to **16**, which has two silyl protective groups instead of acetonide, and does not form a *trans*-bicyclo[3.3.0] ring after cyclization (Scheme 4).

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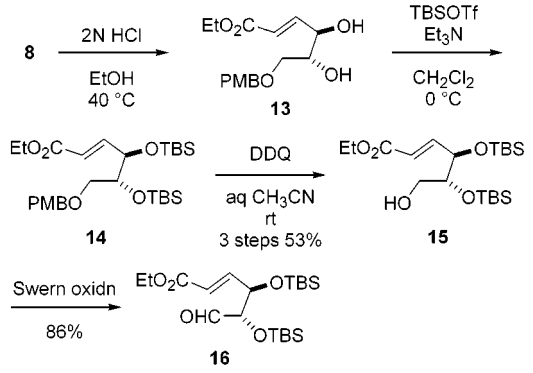
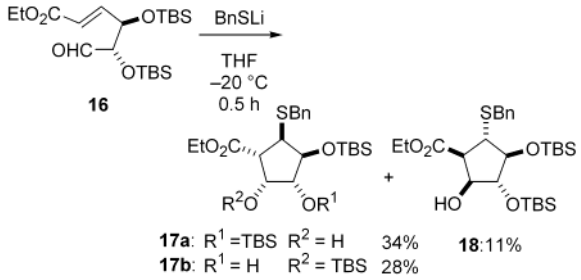
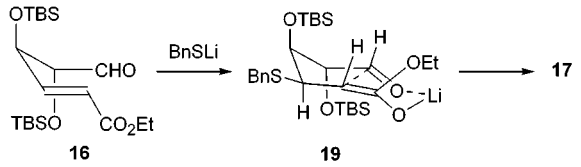
**Scheme 4. Preparation of TBS-Protected *ω*-Oxo-α,*β*-unsaturated Ester 16**




**Scheme 5. Stereoselective Michael−Aldol Tandem Cyclization Reaction of 16 with BnSLi**




**Scheme 6. Plausible Diastereoselection in Michael−Aldol Tandem Cyclization of 16 with BnSLi**




The acetonide protection in **8** was removed by acid hydrolysis giving diol **13**, which was then protected by TBS groups to afford **14**. Deprotection of PMB group with DDQ gave alcohol **15**. Swern oxidation of **15** gave the desired *ω*-oxo-α,*β*-unsaturated ester **16**, which was stable and could be purified by bulb-to-bulb distillation.

As a second trial, we examined a key cyclization reaction of **16** with lithium thiolate (Scheme 5). The best result was obtained in a reaction of **16** with 1.2 equiv of lithium benzylthiolate in THF at −20 °C. The reaction proceeded smoothly within 0.5 h giving, after silica gel column chromatography, three cyclization products **17a**,**b** and **18** in 34%, 28%, and 11% isolated yields, respectively (47:38:15).

The stereochemistry of **17** and **18** was determined by NOE spectra. Since **17b** is a silyl-migrated product from **17a**, the selectivity of thiolate conjugate addition in the first step was estimated to be 85:15. Furthermore, the selectivity of aldol cyclization in the second step was perfect. The stereoselectivity of the addition of lithium thiolate and subsequent aldol cyclization could be explained by the model shown in Scheme 6.

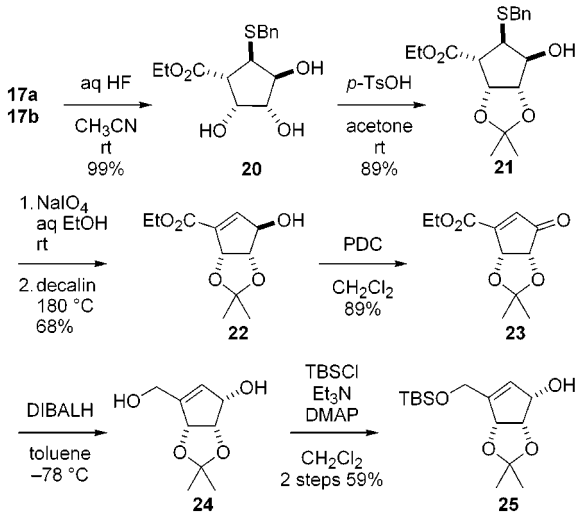
The unsaturated ester **16** has two bulky *tert*-butyldimethylsiloxy groups in the vicinal position. These TBSO groups take an anti orientation to avoid mutual steric repulsion as shown in Scheme 6.[15] The addition of lithium thiolate took place from the face opposite the terminal aldehyde moiety to generate the transient lithium enolate

**Table 1. Optimization of Reaction Conditions in Stereoselective Michael−Aldol Tandem Cyclization of 16 with BnSLi (Scheme 5)[a]**

| entry | solvent | *T* (°C) | time (h) | **17a**[b] (%) | **17b**[b] (%) | **18**[b] (%) |
|---|---|---|---|---|---|---|
| 1 | DME | −20 | 0.5 | 25 | 19 | 0 |
| 2 | THF | −20 | 0.5 | 34 | 28 | 11 |
| 3 | $CH_3CN$ | −20 | 0.5 | 23 | 26 | 0 |
| 4 | dioxane | rt | 0.5 | 41 | 4 | 17 |

[a] The reaction was carried out with 1.2 equiv of BnSLi. [b] Isolated yield.

**Scheme 7. Conversion of Cyclization Products 17 to 25**

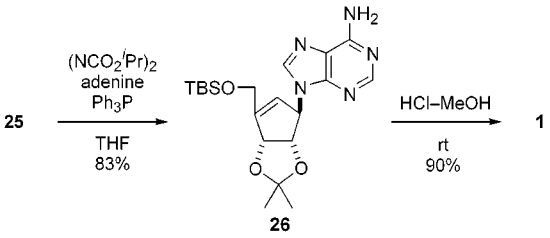



**19**. Both conformational control of the enolate **19** by allylic strain[16] and coordination of an aldehyde oxygen to lithium produce the cyclization product **17** selectively.

The results of examinations of reaction conditions are summarized in Table 1. In nonpolar solvents such as toluene, ether, and dichloromethane, the reaction did not proceed. In polar solvents such as DME, THF, acetonitrile, and dioxane, bearing a heteroatom available for coordination to lithium, the reaction proceeded to afford cyclization products in moderate to good yields and stereoselectivities (Table 1, entries 1−4).

The TBS groups in cyclization products **17a** and **17b** were deprotected with aqueous HF in acetonitrile to afford the same triol **20** in 99% yields, respectively (Scheme 7). The cis vicinal hydroxyl groups in **20** were selectively protected by treating with acetone in the presence of *p*-TsOH giving **21**. Oxidation of sulfide to sulfoxide with sodium metaperiodinate in aqueous ethanol, followed by thermal syn elimination of the sulfoxide in decalin at 180 °C, gave the olefin **22**. The hydroxyl group in **22** was converted to ketone **23** by PDC oxidation. Both the ketone and ester of **23** were simultaneously reduced to alcohols by treating with DIBALH in toluene at −78 °C, giving diol **24**, in which the configuration of a secondary alcohol was inverted.

**Scheme 8. Completion of Total Synthesis of (−)-Neplanocin A**




Selective protection of primary alcohol by TBS group afforded the mono alcohol **25** that is a synthetic intermediate in the total synthesis of neplanocin A developed by Ogasawara's group,[4b] and the $^1$H NMR spectrum of **25** agreed with those kindly provided from Ogasawara's group.

The remaining transformations to (−)-neplanocin A followed Ogasawara's route (Scheme 8). Thus, the hydroxyl group in **25** was substituted with adenine by Mitsunobu reaction,[17] and subsequent deprotection of both an acetonide and a TBS group completed the total synthesis of (−)-neplanocin A (**1**).

In conclusion, we have accomplished a total synthesis of (−)-neplanocin A in 3% overall yield over 16 steps from D-mannitol-derived chiral diol **5** by using lithium thiolate-initiated stereoselective intramolecular Michael−aldol tandem cyclization as a key reaction. This work demonstrates the usefulness of this cyclization reaction in organic synthesis.

## Experimental Section

**(4*R*,5*R*)-5-(4-Methoxybenzyloxymethyl)-2,2-dimethyl-1,3-dioxolan-4-ylmethanol (6).** A mixture of diol **5** (4.86 g, 30 mmol), KOH (1.88 g, 85%, 28.5 mmol), and 4-methoxybenzyl chloride (3.28 mL, 23.6 mmol) in benzene (50 mL) was heated under reflux for 9 h. After cooling, the whole was filtered and the filtrate was dried over $Na_2SO_4$. Concentration followed by silica gel chromatography (hexane/EtOAc = 2/1) gave **6** as a colorless oil (5.5 g, 83%): $^1$H NMR ($CDCl_3$) $\delta$ 1.41 (6H, s), 2.31 (1H, dd, $J$ = 4.3, 8.2 Hz), 3.51 (1H, dd, $J$ = 5.8, 9.8 Hz), 3.66 (1H, dd, $J$ = 5.2, 9.8 Hz), 3.68 (1H, ddd, $J$ = 4.3, 8.2, 11.6 Hz), 3.75 (1H, ddd, $J$ = 4.3, 4.6, 11.6 Hz), 3.80 (3H, s), 3.92 (1H, ddd, $J$ = 4.3, 4.6, 8.2 Hz), 4.02 (1H, ddd, $J$ = 5.2, 5.8, 8.2 Hz), 4.51 (2H, s), 6.88 (2H, m), 7.26 (2H, m); $^{13}$C NMR ($CDCl_3$) $\delta$ 26.9, 55.2, 62.4, 70.0, 73.3, 76.7, 79.8, 109.3, 113.8, 129.4, 129.5, 159.3; IR (neat) 3440, 1610, 1585 cm$^{-1}$; MS *m*/*z* 282 ($M^+$), 121; $[\alpha]^{25}_D$ −10.6 (*c* 1.05, $CHCl_3$). Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 64.10; H, 7.82.

**(4*S*,5*R*)-5-(4-Methoxybenzyloxymethyl)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (7).** To a solution of oxalyl chloride (6.98 mL, 80 mmol) in $CH_2Cl_2$ (100 mL) was added DMSO (6.81 mL, 96 mmol) in $CH_2Cl_2$ (30 mL) at −60 °C. After the mixture was stirred for 3 min, a solution of alcohol **6** in $CH_2Cl_2$ (40 mL) was added, and the whole was further stirred for 15 min. Triethylamine (28 mL, 200 mmol) was added to the reaction mixture, and then the cooling bath was removed. After the mixture was warmed to room temperature, the reaction was quenched with saturated aqueous $NH_4Cl$, and the aqueous layer was extracted with $CHCl_3$. The combined organic layers were washed with brine and then dried over $MgSO_4$. Concentration gave a crude **7** (14.1 g) as an oil.

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**(*E*)-Ethyl 3-[(4*R*,5*R*)-5-(4-Methoxybenzyloxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl]prop-2-enoate (8).** To a suspension of NaH (2.4 g, 60% oil dispersion, 60 mmol) in THF (60 mL) was added triethyl phosphonoacetate (11.9 mL, 60 mmol) at −20 °C. After the mixture was stirred for 1 h, a solution of crude aldehyde **7** (14.1 g) in THF (40 mL) was added. The whole was stirred for 1 h at −20 °C. The reaction was quenched with water, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine and then dried over $Na_2SO_4$. Concentration followed by silica gel chromatography (hexane/EtOAc = 9/1) gave **8** as a yellow oil (7.49 g, 54% from **5**): $^1$H NMR ($CDCl_3$) $\delta$ 1.29 (3H, t, $J$ = 7.0 Hz), 1.43 (3H, s), 1.45 (3H, s), 3.58 (1H, dd, $J$ = 4.6, 10.5 Hz), 3.61 (1H, dd, $J$ = 4.6, 10.5 Hz), 3.81 (3H, s), 3.94 (1H, ddd, $J$ = 4.6, 4.6, 8.2 Hz), 4.20 (2H, q, $J$ = 7.0 Hz), 4.40 (1H, ddd, $J$ = 1.5, 5.5, 8.2 Hz), 4.52 (2H, s), 6.08 (1H, dd, $J$ = 1.5, 15.6 Hz), 6.88 (3H, m), 7.26 (2H, m); $^{13}$C NMR ($CDCl_3$) $\delta$ 14.2, 26.7, 26.9, 55.2, 60.5, 69.0, 73.3, 77.5, 79.6, 110.2, 113.8, 122.5, 129.8, 129.8, 144.1, 159.3, 166.0; IR (neat) 1720, 1660 cm$^{-1}$; MS *m*/*z*: 350 ($M^+$), 121; $[\alpha]^{25}_D$ +27.3 (*c* 1.43, $CHCl_3$). Anal. Calcd for $C_{19}H_{26}O_6$: C, 65.13; H, 7.48. Found: C, 64.96; H, 7.41.

**(*E*)-Ethyl (4*R*,5*R*)-4,5-Dihydroxy-6-(4-methoxybenzyloxy)hex-2-enoate (13).** To a solution of **8** (6.0 g, 17.1 mmol) in EtOH (34.2 mL) was added 2 N HCl (34.2 mL) at 0 °C, and the mixture was stirred for 1.5 h at 40 °C. EtOH was removed by evaporation. Brine was added to the mixture, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine successively and then dried over $Na_2SO_4$. Concentration gave a crude **13** (4.87 g) as an oil.

**(*E*)-Ethyl (4*R*,5*R*)-4,5-Bis(*tert*-butyldimethylsiloxy)-6-(4-methoxybenzyloxy)hex-2-enoate (14).** To a solution of crude **13** (4.87 g) in $CH_2Cl_2$ (50 mL) were added triethylamine (19.0 mL, 136 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (15.6 mL, 68 mmol), and the mixture was stirred for 0.5 h at 0 °C. The mixture was diluted with ether, and water was added. The organic layer was separated and washed with saturated aqueous $NaHCO_3$ and brine successively and then dried over $MgSO_4$. Concentration gave crude **14** (14.7 g) as an oil.

**(*E*)-Ethyl (4*R*,5*R*)-4,5-Bis(*tert*-butyldimethylsiloxy)-6-hydroxyhex-2-enoate (15).** To a solution of crude **14** (14.7 g) in $CH_2Cl_2$ (170 mL) and $H_2O$ (8.9 mL) was added DDQ (5.82 g, 26.6 mmol). After the mixture was stirred for 80 min at room temperature, saturated aqueous $NaHCO_3$ was added, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine successively and then dried over $Na_2SO_4$. Concentration followed by silica gel chromatography (benzene/ether = 9/1) gave **15** as a pale yellow oil (3.79 g, 53% from **8**): $^1$H NMR ($CDCl_3$) $\delta$ 0.08 (3H, s), 0.11 (3H, s), 0.12 (3H, s), 0.13 (3H, s), 0.92 (9H, s), 0.93 (9H, s), 1.30 (3H, dd, $J$ = 7.0, 7.0 Hz), 2.02 (1H, dd, $J$ = 5.5, 7.0 Hz), 3.46 (1H, ddd, $J$ = 5.7, 7.0, 11.6 Hz), 3.65 (1H, ddd, $J$ = 5.5, 5.5, 11.6 Hz), 3.85 (1H, ddd, $J$ = 5.5, 5.5, 5.5 Hz), 4.18 (1H, dq, $J$ = 7.0, 11.0 Hz), 4.22 (1H, dq, $J$ = 7.0, 11.0 Hz), 4.41 (1H, ddd, $J$ = 1.8, 3.7, 5.5 Hz), 6.14 (1H, dd, $J$ = 1.8, 15.6 Hz), 7.12 (1H, dd, $J$ = 3.7, 15.6 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ −5.1, −5.0, −4.7, −4.7, 14.2, 18.0, 18,1, 25.7, 60.4, 63.5, 74.1, 74.2, 121.3, 146.6, 166.3; IR (neat) 3460, 1725, 1655 cm$^{-1}$; $[\alpha]^{25}_D$ +27.3 (*c* 1.43, $CHCl_3$). Anal. Calcd for $C_{20}H_{42}O_5Si_2$: C, 57.37; H, 10.11. Found: C, 57.44; H, 10.09.

**(*E*)-Ethyl (4*R*,5*S*)-4,5-Bis(*tert*-butyldimethylsiloxy)-6-oxohex-2-enoate (16).** By the same procedure for oxidation of **6**, treatment of **15** (836 mg, 2 mmol) with oxalyl chloride (0.36 mL, 4 mmol), DMSO (0.36 mL, 4.8 mmol), and triethylamine (2.4 mL) in $CH_2Cl_2$ (45 mL) gave, after bulb-to-bulb distillation (200 °C, 0.3 mmHg), **16** as a pale yellow oil (716 mg, 86%): $^1$H NMR ($CDCl_3$) $\delta$ 0.05 (3H, s), 0.06 (3H, s), 0.08 (6H, s), 0.92 (18H, s), 1.29 (3H, t, $J$ = 7.3 Hz), 4.02 (1H, dd, $J$ = 1.6, 4.9 Hz), 4.16−4.25 (2H, m), 4.56 (1H, ddd, $J$ = 1.8, 4.9, 4.9 Hz), 6.05 (1H, dd, $J$ = 1.8, 15.5 Hz), 7.05 (1H, dd, $J$ = 4.9, 15.5 Hz), 9.60 (1H, d, $J$ = 1.6 Hz).

**Stereoselective Michael−Aldol Cyclization of 16 with BnSLi.** To a solution of benzylthiol (0.03 mL, 0.24 mmol) in THF (3.5 mL) was added BuLi (0.15 mL, 1.60 M in hexane, 0.24 mmol) at 0 °C. To the solution above was added a solution of **16** (83 mg, 0.2 mmol) in THF (1.5 mL) at −20 °C. The whole was stirred for 0.5 h at −20 °C, and the reaction was quenched with saturated aqueous $NH_4Cl$. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine and then dried over $Na_2SO_4$. Concentration followed by silica gel chromatography (hexane/MTBE = 20/1) gave **17a** (37 mg, 34%), **17b** (30 mg, 28%), and **18** (12 mg, 11%), respectively.

**(1*R*,2*R*,3*S*,4*R*,5*R*)-Ethyl 2-benzylsulfanyl-3,4-bis(*tert*-butyldimethylsiloxy)-5-hydroxycyclopentanecarboxylate (17a):** colorless oil; $^1$H NMR ($CDCl_3$) $\delta$ 0.01(3H, s), 0.03 (3H, s), 0.06 (3H, s), 0.10 (3H, s), 0.86 (9H, s), 0.87 (9H, s), 1.29 (3H, dd, $J$ = 7.3,7.3 Hz), 2.85 (1H, d, $J$ = 10.4 Hz), 3.21 (1H, dd, $J$ = 9.8, 9.8 Hz), 3.62 (1H, dd, $J$ = 3.7, 9.8 Hz), 3.67 (1H, d, $J$ = 13.4 Hz), 3.73 (1H, d, $J$ = 13.4 Hz), 3.73 (1H, dd, $J$ = 1.8, 3.7 Hz), 3.86 (1H, dd, $J$ = 1.8, 4.9 Hz), 4.17 (1H, dq, $J$ = 7.3, 10.7 Hz), 4.18 (1H, dq, $J$ = 7.3, 10.7 Hz), 4.50 (1H, ddd, $J$ = 4.9, 9.8, 10.4), 7.19−7.37 (5H, m); $^{13}$C NMR ($CDCl_3$) $\delta$ −5.1, −4.7, −4.6, −4.5, 14.2, 17.9, 18.0, 25.6, 25.7, 36.4, 49.5, 54.7, 60.7, 71.9, 77.3, 79.0, 126.8, 128.4, 128.9, 139.0, 171.9; IR (neat) 3500, 1730 cm$^{-1}$; MS *m*/*z* 541 ($MH^+$); $[\alpha]^{25}_D$ −14.8 (*c* 1.01, $CHCl_3$); HRMS calcd for $C_{27}H_{49}O_5SSi_2$ 541.2839, found 541.2834.

**(1*R*,2*R*,3*S*,4*R*,5*R*)-Ethyl 2-benzylsulfanyl-3,5-bis(*tert*-butyldimethylsiloxy)-4-hydroxycyclopentanecarboxylate (17b):** colorless oil; $^1$H NMR ($CDCl_3$) $\delta$ 0.06 (3H, s), 0.08 (3H, s), 0.10 (3H, s), 0.11 (3H, s), 0.88 (18H, s), 1.26 (3H, dd, $J$ = 7.3, 7.3 Hz), 3.06 (1H, d, $J$ = 3.7 Hz), 3.24 (1H, dd, $J$ = 9.2, 9.2 Hz), 3.70 (1H, d, $J$ = 13.2 Hz), 3.73 (1H, d, $J$ = 13.2 Hz), 3.75 (1H, ddd, $J$ = 1.5, 3.7, 4.6 Hz), 3.80 (1H, dd, $J$ = 4.0, 9.2 Hz), 4.01 (1H, dd, $J$ = 1.5, 4.0 Hz), 4.02 (1H, dq, $J$ = 7.3, 11.0 Hz), 4.18 (1H, dq, $J$ = 7.3, 11.0 Hz), 4.67 (1H, dd, $J$ = 4.6, 9.2 Hz), 7.20−7.36 (5H, m); $^{13}$C NMR ($CDCl_3$) $\delta$ −5.3, −5.2, −4.8, −4.8, 14.1, 18.0, 18.1, 25.6, 25.7, 36.7, 50.7, 55.5, 60.9, 73.1, 77.6, 78.7, 126.9, 128.4, 128.8, 138.7, 172.3; IR (neat) 3500, 1730 cm$^{-1}$; MS *m*/*z* 541 ($MH^+$); $[\alpha]^{25}_D$ −25.8 (*c* 1.36, $CHCl_3$); HRMS calcd for $C_{27}H_{49}O_5SSi_2$ 541.2839, found 541.2834.

**(1*S*,2*S*,3*S*,4*R*,5*S*)-Ethyl 2-benzylsulfanyl-3,4-bis(*tert*-butyldimethylsiloxy)-5-hydroxycyclopentanecarboxylate (18):** colorless oil; $^1$H NMR ($CDCl_3$) $\delta$ −0.01 (3H, s), 0.04 (3H, s), 0.10 (6H, s), 0.84 (9H, s), 0.90 (9H, s), 1.29 (3H, dd, $J$ = 7.0, 7.0 Hz), 3.19 (1H, d, $J$ = 11.0 Hz), 3.35 (1H, dd, $J$ = 5.2, 7.6 Hz), 3.55 (1H, dd, $J$ = 1.5, 7.6 Hz), 3.73 (1H, d, $J$ = 13.4 Hz), 3.77 (1H, d, $J$ = 13.4 Hz), 3.91 (1H, dd, $J$ = 1.5, 1.5 Hz), 3.95 (1H, ddd, $J$ = 1.5, 1.5, 1.5 Hz), 4.17 (1H, dddd, $J$ = 1.5, 1.5, 5.2, 11.0), 4.20 (1H, dq, $J$ = 7.3, 10.7 Hz), 4.21 (1H, dq, $J$ = 7.3, 10.7 Hz), 7.20−7.36 (5H, m); $^{13}$C NMR ($CDCl_3$) $\delta$ −5.1, −5.0, −4.8, −4.8, 14.2, 17.8, 17.9, 25.6, 25.7, 37.1, 51.1, 58.9, 60.9, 81.0, 81.0, 86.6, 126.9, 128.4, 129.0, 138.4, 172.0; IR (neat) 3480, 1735 cm$^{-1}$; MS *m*/*z* 541 ($MH^+$); $[\alpha]^{25}_D$ +21.7 (*c* 1.21, $CHCl_3$); HRMS calcd for $C_{27}H_{49}O_5SSi_2$ 541.2839, found 541.2813.

**(1*R*,2*R*,3*S*,4*R*,5*R*)-Ethyl 2-Benzylsulfanyl-3,4,5-trihydroxycyclopentanecarboxylate (20).** A solution of **17a** (5.0 mg, 0.009 mmol) and aqueous HF (0.05 mL, 47%) in acetonitrile (0.95 mL) was stirred for 3 h at 0 °C. Filtration of the mixture through a silica gel column (acetonitrile) gave **20** (2.8 mg, 99%) as a white solid of mp 73.5−74.5 °C. By the same procedure as described above, treatment of **17b** (4.0 mg, 0.007 mmol) with aqueous HF (0.05 mL, 47%) in acetonitrile (0.95 mL) gave **20** (2.2 mg, 99%) as a white solid: $^1$H NMR ($CD_3CN$) $\delta$ 1.20 (3H, t, $J$ = 7.3 Hz), 2.89 (1H, dd, $J$ = 7.3, 9.8 Hz), 3.08 (1H, s), 3.35 (1H, s), 3.37 (1H, s), 3.67 (1H, dd, $J$ = 5.2, 9.8 Hz), 3.77 (2H, s), 3.82 (1H, m), 3.83 (1H, m), 4.09 (2H, q, $J$ = 7.3 Hz), 4.31 (1H, m), 7.14−7.36 (5H, m); $^{13}$C NMR ($CD_3CN$) $\delta$ 14.6, 36.7, 49.0, 54.2, 61.5, 72.4, 76.7, 78.3, 128.0, 129.4, 129.8, 139.9, 172.0; IR (Nujol) 3400, 1725 cm$^{-1}$; MS (FAB) *m*/*z* 313 ($MH^+$), 267, 91; $[\alpha]^{25}_D$ +9.8 (*c* 0.5, EtOH); HRMS calcd for $C_{15}H_{21}O_5S$ 313.1110, found 313.1113.

**(3a*R*,4*R*,5*R*,6*S*,6a*S*)-Ethyl 5-Benzylsulfanyl-6-hydroxy-2,2-dimethyltetrahydro-3a*H*-cyclopenta[1,3]dioxole-4-carboxylate (21).** To a solution of **20** (2.0 mg, 0.006 mmol) in acetone (1 mL) was added *p*-toluenesulfonic acid monohydrate

(0.1 mg), and the mixture was stirred for 4 h at room temperature. $K_2CO_3$ was added to the solution, and the mixture was filtered. Concentration followed by silica gel chromatography (hexane/EtOAc = 1/1) gave **21** (2.0 mg, 89%) as a colorless oil: $^1$H NMR ($CDCl_3$) $\delta$ 1.24 (3H, s), 1.26 (3H, dd, $J$ = 7.0, 7.0 Hz), 1.36 (3H, s), 2.48 (1H, brs), 2.91 (1H, ddd, $J$ = 1.5, 6.4, 13.1 Hz), 3.65 (2H, m), 3.83 (2H, s), 4.17 (1H, dq, $J$ = 7.0, 10.7 Hz), 4.23 (1H, dq, $J$ = 7.0, 10.7 Hz), 4.53 (1H, d, $J$ = 5.8 Hz), 4.84 (1H, dd, $J$ = 5.8, 6.4 Hz), 7.25−7.40 (5H, m); $^{13}$C NMR ($CDCl_3$) $\delta$ 14.2, 24.2, 25.8, 36.6, 49.4, 52.0, 60.8, 73.8, 79.8, 83.4, 111.0, 127.4, 128.7, 128.8, 137.8, 169.3; IR (neat) 3450, 1730 cm$^{-1}$; MS $m/z$ 352 ($M^+$), 261, 185, 91; $[\alpha]^{25}_D$ +8.33 ($c$ 0.48, $CHCl_3$); HRMS calcd for $C_{18}H_{24}O_5S$ 352.1344, found 352.1349.

**(3a*R*,6*R*,6a*S*)-Ethyl 6-Hydroxy-2,2-dimethyl-6,6a-dihydro-3a*H*-cyclopenta[1,3]dioxole-4-carboxylate (22).** To a solution of **21** (30 mg, 0.09 mmol) in EtOH (0.5 mL) and water (0.5 mL) was added sodium metaperiodinate (36 mg, 0.017 mmol), and the mixture was stirred for 20 min at room temperature. Brine was added to the mixture, and the aqueous solution was extracted with ethyl acetate. The combined organic layers were dried over $Na_2SO_4$ and concentrated to give a crude sulfoxide as an oil. The oil was dissolved in decalin (1 mL), and the solution was heated for 20 min at 180 °C. After cooling, the mixture was directly applied to silica gel chromatography (hexane/ether = 1/2) to give **22** (14 mg, 68%) as a colorless oil: $^1$H NMR ($CDCl_3$) $\delta$ 1.32 (3H, dd, $J$ = 7.0, 7.0 Hz), 1.37 (3H, s), 1.41 (3H, s), 1.98 (1H, brs), 4.17 (1H, dq, $J$ = 7.0, 10.7 Hz), 4.23 (1H, dq, $J$ = 7.0, 10.7 Hz), 4.60 (1H, d, $J$ = 5.8 Hz), 4.88 (1H, s), 5.47 (1H, dd, $J$ = 1.5, 5.8 Hz), 6.70 (1H, d, $J$ = 1.5 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 14.2, 25.4, 27.1, 61.1, 80.3, 82.6, 86.3, 112.6, 139.3, 143.2, 163.8; IR (neat) 3470, 1725 1615 cm$^{-1}$; MS $m/z$ 228 ($M^+$); $[\alpha]^{25}_D$ +7.34 ($c$ 1.03, $CHCl_3$); HRMS calcd for $C_{11}H_{16}O_5$ 228.0998, found 226.0986.

**(3a*R*,6a*R*)-Ethyl 2,2-Dimethyl-6-oxo-6,6a-dihydro-3a*H*-cyclopenta[1,3]dioxole-4-carboxylate (23).** To a solution of **22** (7 mg, 0.033 mmol) in $CH_2Cl_2$ (1 mL) was added PDC (46 mg, 0.12 mmol), and the mixture was stirred for 3 h at room temperature. The resultant suspension was diluted with ether, Celite was added to the mixture, and whole was filtered. Concentration of the filtrate, followed by silica gel chromatography (hexane/ether = 1/2), gave **23** (6.2 mg, 89%) as a pale yellow oil: $^1$H NMR ($CDCl_3$) $\delta$ 1.38 (3H, dd, $J$ = 7.0, 7.0 Hz), 1.42 (3H, s), 1.44 (3H, s), 4.37 (1H, dq, $J$ = 7.0, 11.0 Hz), 4.40 (1H, dq, $J$ = 7.0, 11.0 Hz), 4.59 (1H, d, $J$ = 5.8 Hz), 5.48 (1H, d, $J$ = 5.8 Hz), 6.72 (1H, s); $^{13}$C NMR ($CDCl_3$) $\delta$ 14.1, 26.0, 27.3, 62.2, 77.1, 78.1, 116.1, 137.2, 159.6, 163.1, 202.4; IR (neat) 1725 1615 cm$^{-1}$; MS $m/z$ 226 ($M^+$); $[\alpha]^{25}_D$ +7.34 ($c$ 1.03, $CHCl_3$); HRMS calcd for $C_{11}H_{14}O_5$ 226.0841, found 226.0846.

**(3a*S*,4*S*,6a*R*)-6-hydroxymethyl-2,2-dimethyl-4,6a-dihydro-3a*H*-cyclopenta[1,3]dioxol-4-ol (24).** To a solution of **23** (100 mg, 0.44 mmol) in toluene (10 mL) was added DIBALH (3.98 mL, 1.0 M in hexane, 3.98 mmol) at −78 °C. After being stirred for 1 h at −78 °C, the mixture was diluted with ether and the reaction was quenched with saturated aqueous $NH_4Cl$. The resulting mixture was stirred for 1 h at room temperature and then dried over $MgSO_4$. Filtration followed by concentration gave a crude **24** as an oil.

**(3a*S*,4*S*,6a*R*)-6-(*tert*-Butyldimethylsiloxymethyl)-2,2-dimethyl-4,6a-dihydro-3a*H*-cyclopenta[1,3]dioxol-4-ol (25).** To a solution of crude **24**, triethylamine (0.09 mL, 0.66 mL), and DMAP (5 mg, 0.04 mmol) in $CH_2Cl_2$ (3 mL) was added *tert*-butyldimethylsilyl chloride (99 mg, 0.66 mmol). After being stirred for 4 h at room temperature, the mixture was diluted with ether. The organic layer was washed with saturated aqueous $NaHCO_3$ and saturated aqueous $NH_4Cl$ successively and then dried over $Na_2SO_4$. Concentration followed by silica gel chromatography (hexane/EtOAc = 5/1) gave **25** (78 mg, 59% from **23**) as a colorless oil: $^1$H NMR ($CDCl_3$) $\delta$ 0.08 (3H, s), 0.08 (3H, s), 0.92 (9H, s), 1.40 (3H, s), 1.43 (s, 3H), 2.67 (1H, d, $J$ = 10.1 Hz), 4.24 (1H, d, $J$ = 15.3 Hz), 4.35 (1H, d, $J$ = 15.3 Hz), 4.56 (1H, m), 4.76 (1H, dd, $J$ = 5.5, 5.5 Hz), 4.90 (1H, d, $J$ = 5.5 Hz), 5.73 (1H, s); $^{13}$C NMR ($CDCl_3$) $\delta$ −5.6, −5.6, 18.2, 25.7, 26.5, 27.5, 59.8, 73.1, 77.8, 82.6, 112.3, 129.1, 145.5; IR (neat) 3480 cm$^{-1}$; $[\alpha]^{27}_D$ +22.4 ($c$ 0.66, $CHCl_3$).

**(3a*S*,4*R*,6a*R*)-9-[6-(*tert*-Butyldimethylsiloxymethyl)-2,2-dimethyl-4,6a-dihydro-3a*H*-cyclopenta[1,3]dioxol-4-yl]-9*H*-purin-6-ylamine (26):** $^1$H NMR ($CDCl_3$) $\delta$ 0.11 (6H, s), 0.93 (9H, s), 1.36 (3H, s), 1.49 (s, 3H), 4.41 (1H, d, $J$ = 16.2 Hz), 4.46 (1H, d, $J$ = 16.2 Hz), 4.72 (1H, d, $J$ = 5.8 Hz), 5.31 (1H, d, $J$ = 5.8 Hz), 5.60 (1H, s), 5.79 (1H, s), 5.99 (2H, s), 7.69 (1H, s), 8.39 (1H, s); $^{13}$C NMR ($CDCl_3$) $\delta$ −5.4, −5.4, 18.4, 25.9, 27.4, 60.4, 64.4, 83.6, 84.9, 112.7, 120.1, 121.1, 138.5, 149.9, 152.5, 153.3, 155.6; IR ($CHCl_3$) 3480, 3390, 1630, 1580 cm$^{-1}$; $[\alpha]^{29}_D$ −31.8 ($c$ 0.40, $CHCl_3$).

**(−)-Neplanocin A (1):** white solid; mp 214−216 °C dec; $^1$H NMR (DMSO-$d_6$) $\delta$ 4.10 (2H), 4.29 (1H), 4.42 (1H), 4.90 (1H), 4.94 (1H), 5.12 (1H), 5.32 (1H), 5.69 (1H), 7.16 (2H), 8.04 (1H), 8.11 (1H); $[\alpha]^{29}_D$ −145.4 ($c$ 0.11, $H_2O$).

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**Supporting Information Available:** General experimental procedure and spectroscopic data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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