

Published in final edited form as:

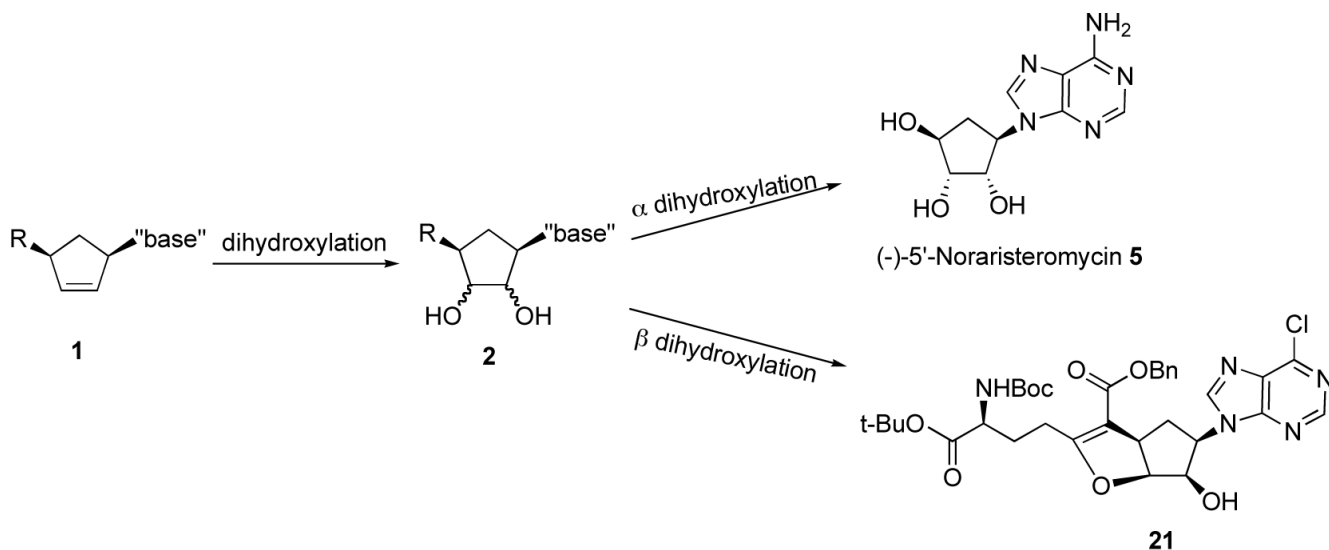
*J Org Chem.* 2006 May 26; 71(11): 4164–4169. doi:10.1021/jo060224l.

## Substrate-Dependent Dihydroxylation of Substituted Cyclopentenes: Towards the Syntheses of Carbocyclic Sinefungin and Noraristeromycin

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### Abstract



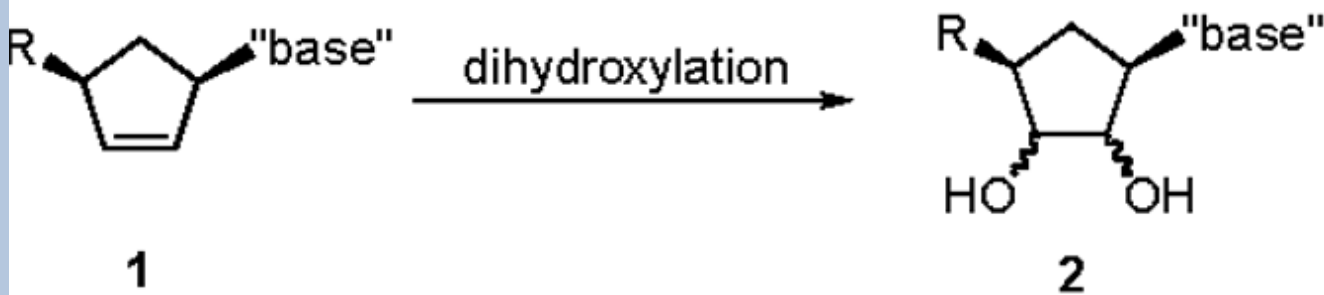
Carbocyclic nucleosides are of considerable interest for the development of new therapeutic agents. A key reaction in the preparation of many such nucleoside analogs is dihydroxylation of appropriately substituted cyclopentenes. While often considered a routine reaction, in this paper we report the dramatic influence of substituents on the facial selectivity of dihydroxylations. The substituted cyclopentene substrates are derived from acylnitroso cycloaddition reactions of cyclopentadiene, followed by N-O reduction and efficient enzymatic resolution. The results are directly utilized in a very efficient asymmetric synthesis of an antiviral carbocyclic nucleoside, noraristeromycin **5**. Extensions towards synthesis of carbocyclic sinefungin **7** document the importance of realizing the substituent dependence of the dihydroxylation reaction.

Infectious diseases are posing increasingly severe health risks, as evidenced by the recent SARS flu epidemic and the rapid spread of AIDS in developing countries. Accordingly, extensive research has been directed at finding effective therapeutic agents for the treatment of viral

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Supporting Information Available: General methods and procedures for compounds **15**, **16**, **17**, **28**, **29** and spectral data for all new compounds, and details for the crystal structures of **21** and **25**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

infections as well as cancers. To that end, carbocyclic nucleosides have received considerable attention.<sup>1</sup> As with normal nucleosides, many carbocyclic nucleosides contain *syn*-2',3'-dihydroxyl groups. Most often this important functionality is introduced by osmium-mediated reactions of the corresponding cyclopentene precursors (eq 1). For steric reasons it might be anticipated that such *syn*-dihydroxylations would occur *trans* relative to the other substituents on the cyclopentene ring. However, the electrophilic nature of OsO<sub>4</sub> may alter the facial selectivity of this reaction. Trost and others have reported on the competition of stereoelectronic and steric effects in related important dihydroxylation reactions.<sup>2</sup> In this paper we report that the facial selectivity of key dihydroxylation reactions of cyclopentene precursors of carbocyclic nucleoside analogs depends markedly on the additional substituents. The results dramatically influence the efficiency of syntheses of several biologically important carbocyclic nucleosides, including carbocyclic sinefungin and noraristeromycin.



(eq 1)

The natural carbocyclic nucleosides, neplanocin A **3** and aristeromycin **4** have potent antiviral activities (Figure 1).<sup>3</sup> Aristeromycin (-)-**4** is a carbocyclic analog of adenosine that terminates viral growth by inhibiting *S*-adenosyl-L-homocysteine (AdoHcy) hydrolase.<sup>4</sup> However, the high cytotoxicity of aristeromycin, presumably caused by the metabolism of **4** to its 5'-phosphates, has greatly hindered its therapeutic application.<sup>5</sup> In the search for a less toxic analog of aristeromycin, Schneller and coworkers found that the 5'-nor compound ( $\pm$ )-**5** had improved antiviral activity with no cytotoxicity.<sup>6</sup> Subsequently, the same workers found the (-)-enantiomer of **5** was more active than the (+)-enantiomer.<sup>7</sup> Sinefungin **6** is a natural nucleoside first isolated from *Streptomyces griseolus* in 1973 and *S. incarnatus* in 1976.<sup>8</sup> Since its isolation from natural sources, sinefungin has been synthesized by several groups.<sup>9</sup> Preliminary bioassays showed that it inhibited the growth of several fungi<sup>8</sup> and viruses<sup>10</sup>, and that it showed significant antiparasitic<sup>11</sup> activity *in vitro*. There are two key features of the biological activity profile of sinefungin that stand out, one of which is its antiviral activity due to inhibition of methyltransferase.<sup>12</sup> Chemotaxis, neurosecretions, membrane receptor interactions, DNA modification-restriction, gene expression and cellular differentiation are among the diverse processes that methylation of biomolecules affects.<sup>13</sup> Sinefungin and derivatives have been tested against both *vaccinia*- and Newcastle disease virus- (guanine-7) methyltransferases.<sup>10</sup> The elucidation of structure-activity-relationships for sinefungin and its derivatives was attempted with these studies. Several features were found to be necessary in order to retain methyltransferase inhibition: (1) the L configuration of the side chain (2) both terminal amino and carboxyl groups as well as a three-carbon linker between the S-atom and the terminal amino/carboxyl groups and (3) either the 2' or 3' hydroxyl groups on the ribosyl unit. Few modifications of the heterocyclic base were tolerated. Isosteric replacement of the ribosyl oxygen for a methylene unit was tolerated. Sinefungin has also been co-crystallized into the active site of *thermus aquaticus* DNA methyltransferase by Schluckebier.<sup>14</sup> The structural requirements that appear to be necessary for biological activity from this study (based on binding within the active site) generally agree with the SAR study published by Pugh &

Borchardt.<sup>10</sup> One point of disparity between the studies is the necessity of both hydroxyl groups for biological activity.

Although sinefungin showed strong bioactivity against viruses and parasites, it caused fatalities, probably resulting from its nephrotoxic side effects, when tested *in vivo* with larger mammals.<sup>15</sup> Methyltransferases are important for many biological functions in humans and other animals. Inhibition of this important enzyme in order to affect some desirable therapeutic activity may be difficult because of the toxicity. Thus, the development of selective methyltransferase inhibitors continues to be of considerable interest.<sup>16</sup> However, it has also been noted in earlier literature that sinefungin possesses antiviral activity that is, partly due to an alternate unknown biological mechanism.<sup>10</sup> It may be prudent then to pursue sinefungin derivatives that are not good methyltransferase inhibitors in the hope that the other biological mechanism(s) responsible for its antiviral activity will lead to new antiviral therapeutic agents without toxic side effects to humans.

As a starting point for the synthesis of sinefungin analogs for biological testing, we set as a goal the synthesis of carbocyclic sinefungin **7** which contains an isosteric replacement of the ribosyl oxygen for a methylene unit. The synthesis of carbocyclic sinefungin **7** is envisioned to arise from functionalized cyclopentene **8** after the key stereoselective dihydroxylation followed by decarboxylation, diastereoselective reductive amination and full deprotection (Scheme 1). Highly functionalized **8** would be available via a Pd(0)-mediated nucleophilic addition of  $\beta$ -keto ester **10** to the carbocyclic core **9** containing an allylic acetate. The carbocyclic core **9** would be synthesized from enantiomerically pure aminocyclopentenol derivative **11** and compound **11** is derived from a hetero Diels-Alder cycloadduct **12** after N-O bond reduction followed by enzymatic resolution as previously described.<sup>17</sup>  $\beta$ -Keto ester side chain **10** can be synthesized from L-pyroglutamic acid **13**.

The synthesis of the  $\beta$ -keto ester **15**, a specific example of **10**, is shown in Scheme 2. L-Pyroglutamic acid **13** was first reacted with *t*-butyl acetate in 70% perchloric acid and the resulting *t*-butyl pyroglutamate was treated with Boc<sub>2</sub>O to give fully protected pyroglutamate **14**.<sup>18</sup> The nucleophilic attack of carbonyl of compound **14** by the *in situ* generated anion of benzyl acetate followed by ring opening gave the linear  $\beta$ -keto ester **15** in quantitative yield.

Previously we have reported<sup>17</sup> that enantiomerically pure compound **11** can be derived from nitroso-Diels-Alder cycloadduct after N-O bond reduction followed by enzymatic resolution. With compound **11** in hand, the adenine base and side chain **15** were installed sequentially as shown in Scheme 3. After compound **11** was treated with TFA, the resulting amine salt was coupled with 5-amino-4,6-dichloropyrimidine in *n*-butanol and NEt<sub>3</sub> at 110 °C to give compound **16** in 79% yield for the two steps. The cyclized product **17** was obtained in 91% yield by the reaction of compound **16** with CH(OEt)<sub>3</sub> in the presence of a catalytic amount of 10-camphorsulfonic acid. Side chain **15** was successfully added to the carbocyclic core **17** by an intermolecular Pd(0) catalyzed  $\pi$ -allyl nucleophilic reaction to give **18** in 80% yield. Treatment of compound **18** with Na<sub>2</sub>S•9H<sub>2</sub>O in aqueous solution gave decarboxylated product **19** in 71% yield.

The dihydroxylation reaction was first attempted on compound **18** (Scheme 4). The reaction was carried out in THF with a catalytic amount of OsO<sub>4</sub> and excess NMO at room temperature for 30 minutes to give unexpected  $\beta$ -dihydroxylated product **20** in 70% yield. Using 2D NMR, attempts were made to determine the stereochemistry of the newly introduced diol relative to the other substituents of **20**, but it was found that the compound was not stable in CDCl<sub>3</sub> and it slowly converted to compound **21**. Thus, compound **21** was fully characterized and its structure was confirmed by X-ray analysis.

Though examples of non-selective dihydroxylation reactions of substituted cyclopentenes have been discussed,<sup>2</sup> *exclusive*  $\beta$  face dihydroxylation reaction of compound **18** to give  $\beta$ -dihydroxylated product **20** was unexpected since many reported syntheses of dihydroxylated carbocyclic nucleosides have employed similar conditions to give predominantly the opposite facial selectivity.<sup>19,20</sup> Suspecting that the unusually high  $\beta$ -face selectivity might be due to this specific substrate, we decided to examine a series of substitutionally related cyclopentenes. Thus, the dihydroxylation reaction was next attempted on substrate **19**, which was derived from decarboxylation of compound **18** (Scheme 4). The same facial selectivity was observed in this reaction and only  $\beta$ -dihydroxylated product **22** was obtained in 59% yield. Product **22** also was not stable and was slowly transformed to compound **23** upon standing.

Since both advanced intermediates **18** and **19** which had the core carbon structure of carbocyclic sinefungin gave only  $\beta$ -dihydroxylated products **20** and **22**, respectively, the dihydroxylation reaction was attempted on the simpler intermediate **17** in which the side chain **15** was not yet installed (Scheme 5). The reaction was carried out under similar conditions and this time the desired  $\alpha$  face dihydroxylated product was obtained. After the protection of the two hydroxyl groups, product **24** was obtained as a single stereoisomer in 64% yield over two steps. 1D NOE and 2D ROSEY spectra of compound **24** confirmed the stereochemistry of these two newly generated OH groups. The ultimate proof of exclusive  $\alpha$  dihydroxylation of compound **17** came from the X-ray analysis of product **25**, which was derived from the removal of the acetyl group from compound **24**. As a consequence of the exclusive  $\alpha$  face dihydroxylation selectivity of **17** to give **26**, the asymmetric synthesis of noraristeromycin could be achieved by replacement of the chloro group with ammonia and removal of the acetate (Scheme 6). Aminolysis of **26** accomplished both steps and afforded (-)-5'-noraristeromycin **5** in 82% yield.

Compounds **18** and **19** that had side chains installed and compound **17** that had no side chain installed gave completely different face selected dihydroxylation products, which suggested that the side chain might play some role in the face selectivity of dihydroxylation reactions. To further test the effect of the side chain on the face selectivity of dihydroxylation reactions, compound **28** which had the side chain installed but an incompletely formed nucleobase, was synthesized for further studies (Scheme 7). The synthesis of compound **28** started from enantiomerically pure compound **11** which was directly accessible from our enzymatic resolution process. Compound **28** was obtained after the side chain **15** was added to compound **11** by Pd(0) catalyzed intermolecular nucleophilic addition followed by decarboxylation. The dihydroxylation reaction was carried out under similar conditions and only a mixture of hemiacetals **29** derived from  $\beta$ -dihydroxylated product were obtained in 87% yield.

It was clear that the side chain **15** had a significant influence on the facial selectivity of the dihydroxylation process. While more detailed studies are warranted, these studies further illustrate the need for considerable attention to the effects of peripheral substitution on the core carbocycle during syntheses of important dihydroxylated carbocyclic nucleosides. One possible explanation for the dramatic effects observed is that the compounds may adopt favored conformations in which large lipophilic side chains block the approach of the dihydroxylation reagent. Support for this is provided by the X-ray structure of compound **21** which indicated that one of the methyl groups from the NHBoc substituent was only 3.6 Å away from one of the carbons of the cyclopentene double bond. The investigation of the diastereoselectivity of related dihydroxylation reactions merits further study because of the importance of this reaction for the syntheses of carbocyclic nucleosides and other biologically useful compounds.

## Experimental

### (S)-1-Benzyl 7-*tert*-butyl 6-(*tert*-butoxycarbonyl)-2-((1*S*, 4*R*)-4-(6-chloro-9*H*-purin-9-yl)cyclopent-2-enyl)-3-oxoheptanedioate (18)

To a solution of keto ester **15** (1.09 g, 2.5 mmol) in THF (4 mL) was added NaH (0.10 g, 2.51 mmol) and the resultant mixture was stirred for 20 min. In a separate flask, palladium acetate (80 mg, 0.35 mmol) was dissolved in THF (2 mL), followed by addition of PPh<sub>3</sub> (0.37 g, 1.43 mmol). The resulting canary yellow solution was stirred for 5 min, acetate **17** (0.50 g, 1.79 mmol) was added and the reaction was stirred for another 10 min. The enolate was transferred to the  $\pi$ -allyl complex *via* cannulation. This mixture was allowed to stir at 40°C for 2h while monitoring the progress of the reaction by TLC. After completion of the reaction, water (5 mL) was added and the biphasic mixture was extracted thoroughly with EtOAc (4×20 mL). The combined organic extracts were dried with NaSO<sub>4</sub>. After filtration and concentration, the residue was purified by column chromatography eluting with hexanes: EtOAc from 5:1 to 1:1 to afford 1.05 g (80%) compound **18** as a 1:1 mixture of diastereoisomers. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  1.31 (s, 9H), 1.39 (s, 18H), 1.41 (s, 9H), 1.52-2.13 (m, 6H), 2.42-2.70 (m, 4H), 2.85-3.03 (m, 2H), 3.55-3.57 (m, 2H), 3.66-3.71 (m, 2H), 4.04-4.06 (m, 2H), 4.96-4.99 (m, 2H), 5.12 (AB, *J* = 17.4, 12Hz, 1H), 5.124 (AB, *J* = 13.8, 13.8 Hz, 1H), 5.69-5.76 (m, 2H), 5.83-5.87 (m, 2H), 6.05-6.12 (m, 2H), 7.24-7.33 (m, 10H), 8.10 (s, 1H), 8.13 (s, 1H), 8.69 (s, 2H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  26.2, 26.8, 27.75, 27.78, 28.0, 28.1, 35.6, 36.3, 38.0, 38.6, 43.5, 43.8, 52.5, 53.1, 52.5, 53.1, 59.9, 62.4, 62.6, 67.3, 79.5, 79.6, 82.0, 128.3, 128.4, 128.5, 128.6, 129.0, 129.2, 131.7, 134.66, 134.73, 138.2, 138.5, 143.6, 150.65, 150.68, 151.3, 151.5, 155.3, 155.4, 167.8, 167.9, 171.05, 171.13, 202.1, 202.5; IR (neat)  $\nu$  3332, 2886, 1667, 1641, 1245 cm<sup>-1</sup>; MS (*m/e*, rel. int.) 654 (25), 326 (20), 189 (25), 136 (100); HRMS calcd. for C<sub>33</sub>H<sub>41</sub><sup>35</sup>Cl N<sub>5</sub>O<sub>7</sub> (M+H)<sup>+</sup>: 654.2695, found 654.2670.

### (S)-*tert*-Butyl 2-(*tert*-butoxycarbonyl)-6-((1*R*, 4*R*)-4-(6-chloro-9*H*-purin-9-yl)cyclopent-2-enyl)-5-oxohexanoate (19)

To a solution of compound **18** (0.37 g, 0.57 mmol) in THF (3 mL)-H<sub>2</sub>O (3 mL) was added Na<sub>2</sub>S•9H<sub>2</sub>O (1.1 g, 4.53 mmol). The mixture was stirred for 60 h and extracted with EtOAc. The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration and concentration, the residue was purified by column chromatography eluting with 2:3 to 1:2 hexanes: EtOAc to afford 0.21 g (71%) of compound **19** as a colorless oil. [ $\alpha$ ]<sub>D</sub> = +3.4° (*c* = 0.45, CHCl<sub>3</sub>). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  1.37 (s, 9H), 1.42 (s, 9H), 1.50-1.59 (m, 1H), 1.74-1.79 (m, 1H), 2.08-2.13 (m, 1H), 2.37-2.75 (m, 5H), 3.02 (dt, *J* = 13.8, 8.4 Hz, 1H), 3.26-3.31 (m, 1H), 5.05 (d, *J* = 7.8 Hz, 1H), 5.73-5.78 (m, 1H), 5.85-5.88 (m, 1H), 6.17-6.21 (m, 1H), 8.15 (s, 1H), 8.72 (s, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  26.8, 27.9, 28.3, 38.5, 38.6, 40.0, 48.0, 53.1, 60.5, 79.7, 82.1, 127.8, 131.9, 141.1, 143.4, 150.9, 151.5, 151.7, 155.4, 171.4, 207.6; IR (CH<sub>2</sub>Cl<sub>2</sub>)  $\nu$  2980, 2927, 1713, 1590, 158, 1480, 1367, 1260 cm<sup>-1</sup>; HRMS calcd. for C<sub>25</sub>H<sub>35</sub><sup>35</sup>ClN<sub>5</sub>O<sub>5</sub> (M+H)<sup>+</sup>: 520.2327, found 520.2347.

### (3*aR*,5*R*,6*R*,6*aS*)-Benzyl 2-((*S*)-4-*tert*-butoxy-3-(*tert*-butoxycarbonyl)-4-oxobutyl)-5-(6-chloro-9*H*-purin-9-yl)-6-hydroxy-4,5,6,6*a*-tetrahydro-3*aH*-cyclopenta[*b*]furan-3-carboxylate (21)

To a solution of compound **18** (66 mg, 0.1 mmol) in THF (1 mL) was added NMO (24 mg, 0.2 mmol) followed by an OsO<sub>4</sub> solution in 2-methyl-2-propanol (0.13 mL, 0.01 mmol) dropwise. The mixture was stirred at room temperature for 4 h and the reaction was monitored by TLC. The reaction was quenched with 10% Na<sub>2</sub>S<sub>2</sub>O<sub>5</sub> solution (2 mL) and the mixture was stirred for 10 min. It was diluted with H<sub>2</sub>O, extracted with EtOAc. The organic layer was washed with H<sub>2</sub>O and brine and dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration and concentration, the residue was purified by column chromatography eluting with 1:1 hexanes: EtOAc to afford 48 mg (70%) of compound **20** as an oil. Compound **20** was not stable and it was slowly transformed

to compound **21**. Compound **21** was characterized. Mp=118-120°C. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 1.41 (s, 9H), 1.46 (s, 9H), 1.89-1.96 (m, 1H), 2.14-2.21 (m, 1H), 2.43-2.49 (m, 1H), 2.51-2.59 (m, 1H), 2.65-2.70 (m, 1H), 3.16-3.21 (m, 1H), 3.72-3.78 (m, 1H), 4.24-4.28 (m, 1H), 4.48 (t, J = 4 Hz, 1H), 4.95-5.00 (m, 1H), 5.09-5.24 (m, 4H), 5.28-5.30 (m, 1H), 7.32-7.35 (m, 5H), 8.62 (s, 1H), 8.73 (s, 1H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 24.1, 27.9, 28.3, 29.8, 36.5, 43.0, 52.7, 55.0, 65.7, 71.8, 80.5, 82.5, 85.6, 107.3, 127.9, 128.1, 128.6, 128.7, 136.2, 145.8, 150.7, 151.6, 151.9, 155.9, 164.8, 171.5, 171.6; IR (neat) ν 3332, 2979, 1702, 1639, 1591, 1565, 1368, 1153, 755 cm<sup>-1</sup>; HRMS calcd. for C<sub>33</sub>H<sub>41</sub><sup>35</sup>ClN<sub>5</sub>O<sub>8</sub> (M+H)<sup>+</sup>: 670.2644, found 670.2690. The structure of this compound was confirmed by X-ray analysis.

**(S)-tert-Butyl 2-(tert-butoxycarbonyl)-4-(3aR,5R,6R,6aS)-5-(6-chloro-9H-purin-9-yl)-2,6-dihydroxy-hexahydro-2H-cyclopenta[b]furan-2-yl)butanoate (23)**

The compound was prepared using the same procedure for the synthesis of compound **21**. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.41 (s, 9H), 1.42 (s, 9H), 1.44 (s, 9H), 1.45 (s, 9H), 1.84-2.61 (m, 14H), 2.81-2.93 (m, 1H), 3.06 (dd, J = 13.5, 9.9 Hz, 1H), 4.16-4.27 (m, 4H), 4.51 (dd, J = 9.9, 3.9 Hz, 1H), 4.88-4.97 (m, 2H), 8.50 (s, 1H), 8.67 (s, 1H), 8.68 (s, 1H), 8.82 (s, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 26.0, 26.7, 27.9(2C), 28.21, 28.24, 35.2, 36.3, 37.9, 38.0, 39.3, 40.3, 40.6, 43.2, 57.9, 58.1, 60.9, 61.6, 70.1, 71.3, 80.5, 81.1, 81.2, 81.4, 81.5, 86.1, 105.2, 105.4, 131.1 (2C), 145.5, 146.0, 150.56, 150.63, 151.4, 151.6, 151.7, 151.8, 152.8, 153.1, 171.2, 171.7; IR (neat, CH<sub>2</sub>Cl<sub>2</sub>) ν 3361, 2978, 2934, 1740, 1697, 1591, 1368, 1158 cm<sup>-1</sup>; HRMS (FAB) calcd. for C<sub>25</sub>H<sub>35</sub><sup>35</sup>ClN<sub>5</sub>O<sub>6</sub> (M-H<sub>2</sub>O), 536.2276, found 536.2270.

**(3aR,5R,6R,6aS)-6-(6-Chloro-9H-purin-9-yl)-2,2-dimethyl-tetrahydro-3aH-cyclopenta[d][1,3]dioxol-4-yl acetate (24)**

To a solution of compound **17** (0.24 g, 0.86 mmol) in THF (8 mL) was added NMO (0.2 g, 1.72 mmol) followed by OsO<sub>4</sub> solution in 2-methyl-2-propanol (1.08 mL, 0.086 mmol) dropwise. The mixture was stirred at room temperature for 1 h and was monitored by TLC. The reaction was quenched with 10% Na<sub>2</sub>S<sub>2</sub>O<sub>5</sub> solution (4 mL) and the mixture was stirred for 10 min. It was diluted with H<sub>2</sub>O, extracted with EtOAc. The organic layer was washed with H<sub>2</sub>O and brine and dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration and concentration, the residue was dissolved in 2,2-dimethoxypropane followed by *p*TSA•H<sub>2</sub>O (16 mg, 0.086 mmol). The reaction was stirred at room temperature overnight. The reaction was quenched with NaHCO<sub>3</sub> solution and extracted with EtOAc. The organic layer was washed with H<sub>2</sub>O and brine and dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration and concentration, the residue was purified by column chromatography eluting with 1:1 hexanes: EtOAc to afford 0.13 g (64% for two steps) of compound **24** as a colorless oil. [α]<sub>D</sub> = - 8.0° (c = 0.5, CHCl<sub>3</sub>). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.32 (s, 3H), 1.54 (s, 3H), 2.02 (s, 3H), 2.39-2.44 (m, 1H), 2.85-2.95 (m, 1H), 4.77-4.79 (m, 1H), 5.07-5.10 (m, 2H), 5.28-5.30 (m, 1H), 8.22 (s, 1H), 8.77 (s, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 20.9, 24.2, 26.5, 34.5, 61.2, 77.9, 84.1, 84.2, 112.6, 131.8, 143.9, 151.7, 152.0, 169.4; IR (CH<sub>2</sub>Cl<sub>2</sub>) ν 1746, 1591, 1562, 1235 cm<sup>-1</sup>; HRMS calcd. for C<sub>15</sub>H<sub>18</sub><sup>35</sup>ClN<sub>4</sub>O<sub>4</sub> (M+H)<sup>+</sup>: 353.1017, found 353.1015.

**(3aR,5R,6R,6aS)-6-(6-Chloro-9H-purin-9-yl)-2,2-dimethyl-tetrahydro-3aH-cyclopenta[d][1,3]dioxol-4-ol (25)**

To a solution of compound **24** (0.18 g, 0.51 mmol) in CH<sub>3</sub>OH (5 mL) was added Bu<sub>2</sub>SnO (13 mg, 0.051 mmol). The mixture was stirred at 70°C overnight under an Ar atmosphere. The solvent was removed under reduced pressure and the residue was purified by column chromatography eluting with 1:3 hexanes: EtOAc to afford 135 mg (85%) of compound **25** as a white crystalline solid. Mp=152-153°C. [α]<sub>D</sub> = - 20° (c = 0.75, CH<sub>3</sub>OH). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.31 (s, 3H), 1.52 (s, 3H), 2.22-2.28 (m, 1H), 2.85-2.95 (m, 1H), 3.59 (bs, 1H), 4.53-4.54 (m, 1H), 4.71 (d, J = 5.7 Hz, 1H), 4.91 (d, J = 5.7 Hz, 1H), 5.06-5.09 (m, 1H), 8.49

(s, 1H), 8.76 (s, 1H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  24.2, 26.7, 36.9, 62.6, 76.1, 86.2, 87.0, 111.8, 131.5, 145.8, 151.0, 151.3, 151.8; IR ( $\text{CH}_2\text{Cl}_2$ )  $\nu$  3339, 1592, 1562, 1338, 1211  $\text{cm}^{-1}$ ; HRMS calcd. For  $\text{C}_{13}\text{H}_{16}^{35}\text{ClN}_4\text{O}_3$  ( $\text{M}+\text{H}$ ) $^+$ : 311.0911, found 311.0926.

### Acetic acid 4-(6-chloro-purin-9-yl)-2,3-dihydroxy-cyclopentyl Ester (26)

To a solution of compound **17** (127 mg, 0.456 mmol) in  $t\text{-BuOH-H}_2\text{O}$  (1:1, 4 mL) was added  $\text{K}_3\text{Fe}(\text{CN})_6$  (570 mg, 1.7 mmol),  $\text{K}_2\text{CO}_3$  (328 mg, 2.37 mmol) followed by an  $\text{OsO}_4$  solution in 2-methyl-2-propanol (99  $\mu\text{L}$ , 0.009 mmol) dropwise. The mixture was stirred at room temperature for 44 h and was monitored by TLC. The reaction was quenched with 10%  $\text{Na}_2\text{S}_2\text{O}_5$  solution (4 mL) and the mixture was stirred for 10 min. It was diluted with  $\text{H}_2\text{O}$  and extracted with  $\text{EtOAc}$ . The organic layer was washed with  $\text{H}_2\text{O}$  and brine and dried over  $\text{Na}_2\text{SO}_4$ . After filtration, removal of solvent under reduced pressure gave 106 mg (74%) of **26** as a colorless oil.  $[\alpha]_{\text{D}} = +53.2^\circ$  ( $c = 3.6$ , MeOH).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  2.14 (s, 3H), 2.39 (m, 1H), 3.07 (m, 1H), 3.39 (m, 1H), 4.30 (m, 1H), 4.56 (d,  $J = 5$  Hz, 1H), 4.66 (m, 1H), 4.85 (q,  $J = 8$  Hz, 1H), 5.10 (m, 1H), 8.18 (s, 1H), 8.76 (s, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  20.9, 32.5, 60.7, 74.8, 75.2, 77.1, 132.2, 144.3, 151.5, 151.6, 151.7, 170.9; HRMS calcd. for  $\text{C}_{12}\text{H}_{14}^{35}\text{ClN}_4\text{O}_4$  ( $\text{M}+\text{H}$ ) $^+$ : 313.0704, found 313.0681.

### (-)-5' Noraristeromycin (5)

A solution of compound **26** (21.8 mg, 0.0698 mmol) in MeOH (1 mL) in a sealable tube was cooled to  $-78^\circ\text{C}$ . Liquid ammonia (1 mL) was added via a condenser. The clear solution was then sealed and heated to  $43^\circ\text{C}$  for 2 d. Solvent was removed under reduced pressure. Flash chromatography ( $\text{CHCl}_3$ : MeOH, 10:1, 2:3) gave 14.4 mg (82%) of compound **5** as a white solid.  $[\alpha]_{\text{D}} = -45.7^\circ$  ( $c = 0.18$ , DMF) [lit. $^{21}$   $[\alpha]_{\text{D}} = -40.7^\circ$  ( $c = 1.16$ , DMF)]. Mp =  $251\text{-}252^\circ\text{C}$  [lit. $^{21}$   $250^\circ\text{C}$  (dec.)];  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO-d}_6$ )  $\delta$  1.80 (m, 1H), 2.59 (m, 1H), 3.76 (m, 1H), 3.89 (m, 1H), 4.50 (m, 1H), 4.68 (q,  $J = 9.5$  Hz, 1H), 4.94 (d,  $J = 3$  Hz, 1H), 5.07 (d,  $J = 6.5$  Hz, 1H), 5.41 (d,  $J = 4.5$  Hz, 1H), 7.24 (bs, 2H), 8.11 (s, 1H), 8.18 (s, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{DMSO-d}_6$ )  $\delta$  36.6, 58.4, 73.7, 75.4, 76.8, 119.2, 140.0, 149.4, 152.0, 156.0; HRMS calcd. for  $\text{C}_{10}\text{H}_{14}\text{N}_5\text{O}_3$  ( $\text{M}+\text{H}$ ) $^+$ : 252.1097, found 252.1078.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgment

The authors thank Eli Lilly and Co. and NIH (R01 GM68012) for the support of this research. We acknowledge Dr. Jaroslav Zajicek for NMR assistance and Dr. Bruce Noll for X-ray analysis as well as Nonka Sevova for Mass Spectroscopy. We thank Theresa Bollinger for help with manuscript preparation.

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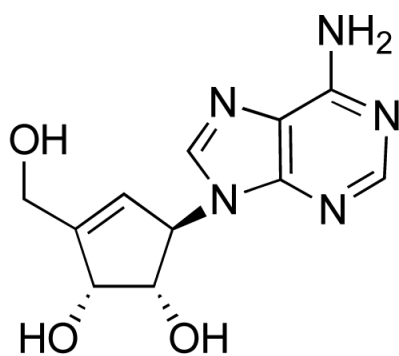
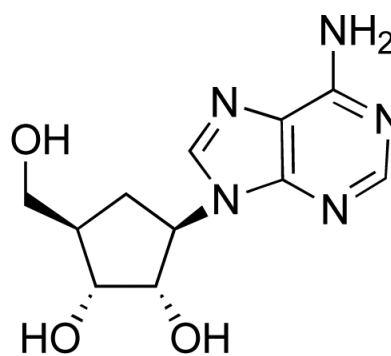
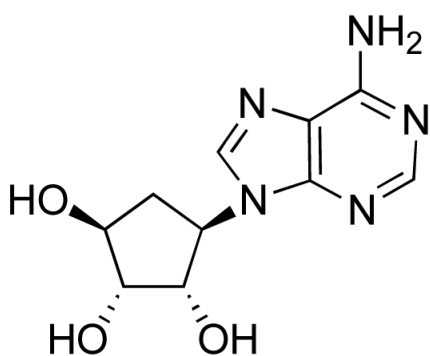
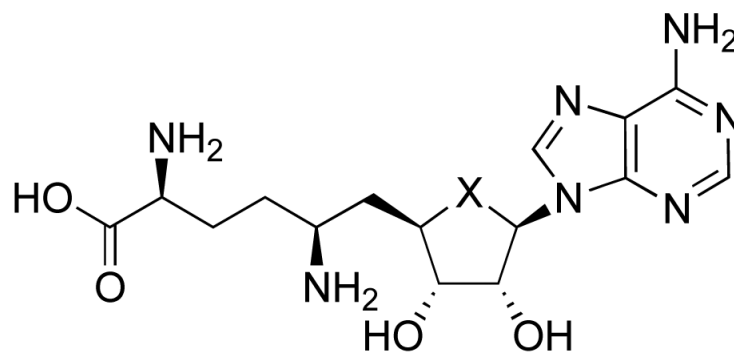
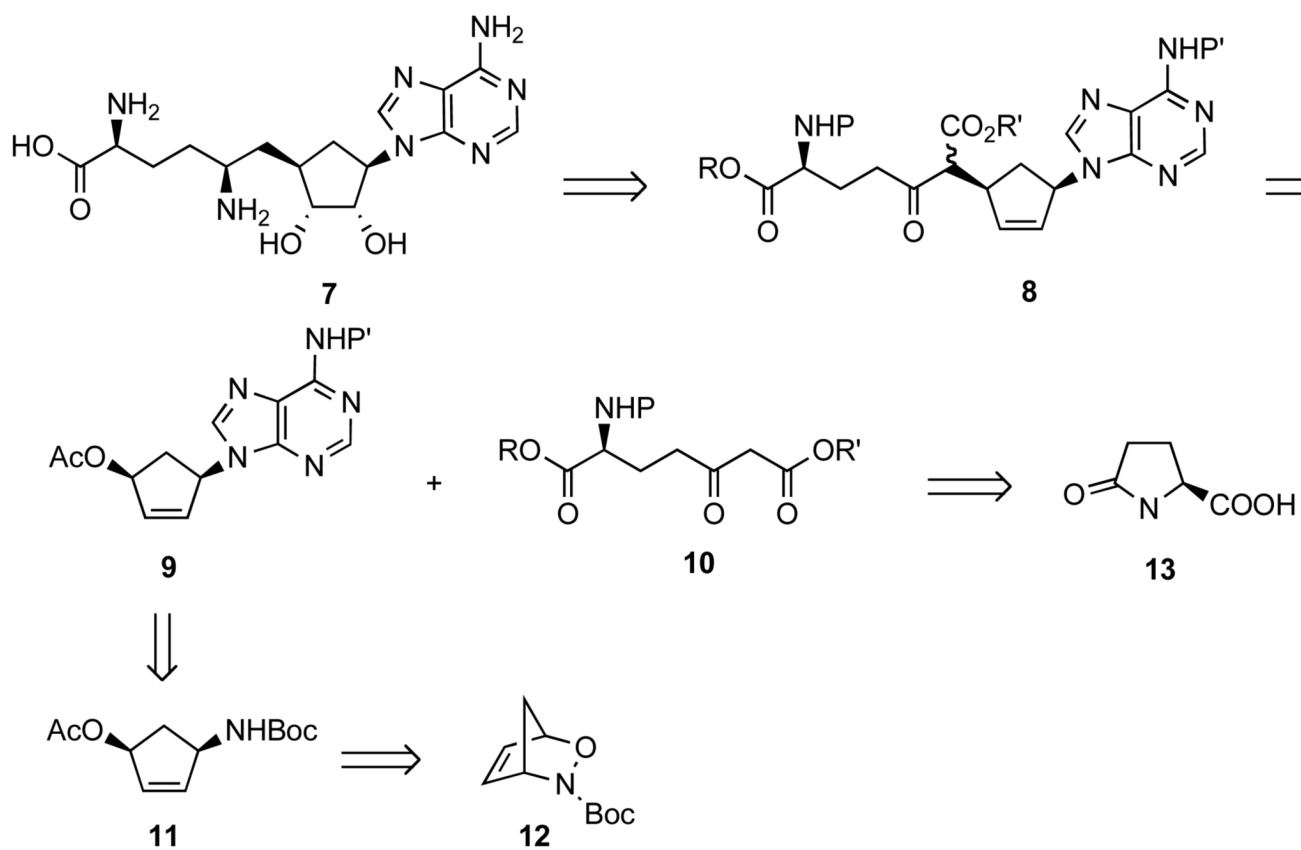
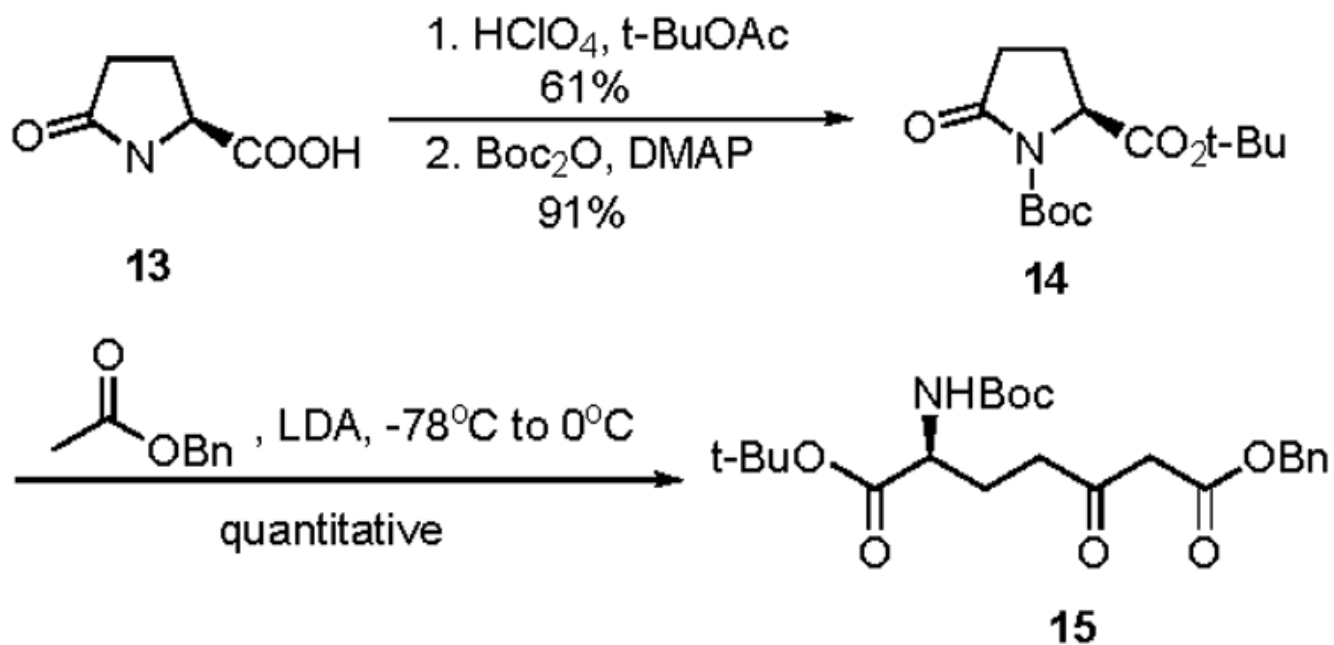
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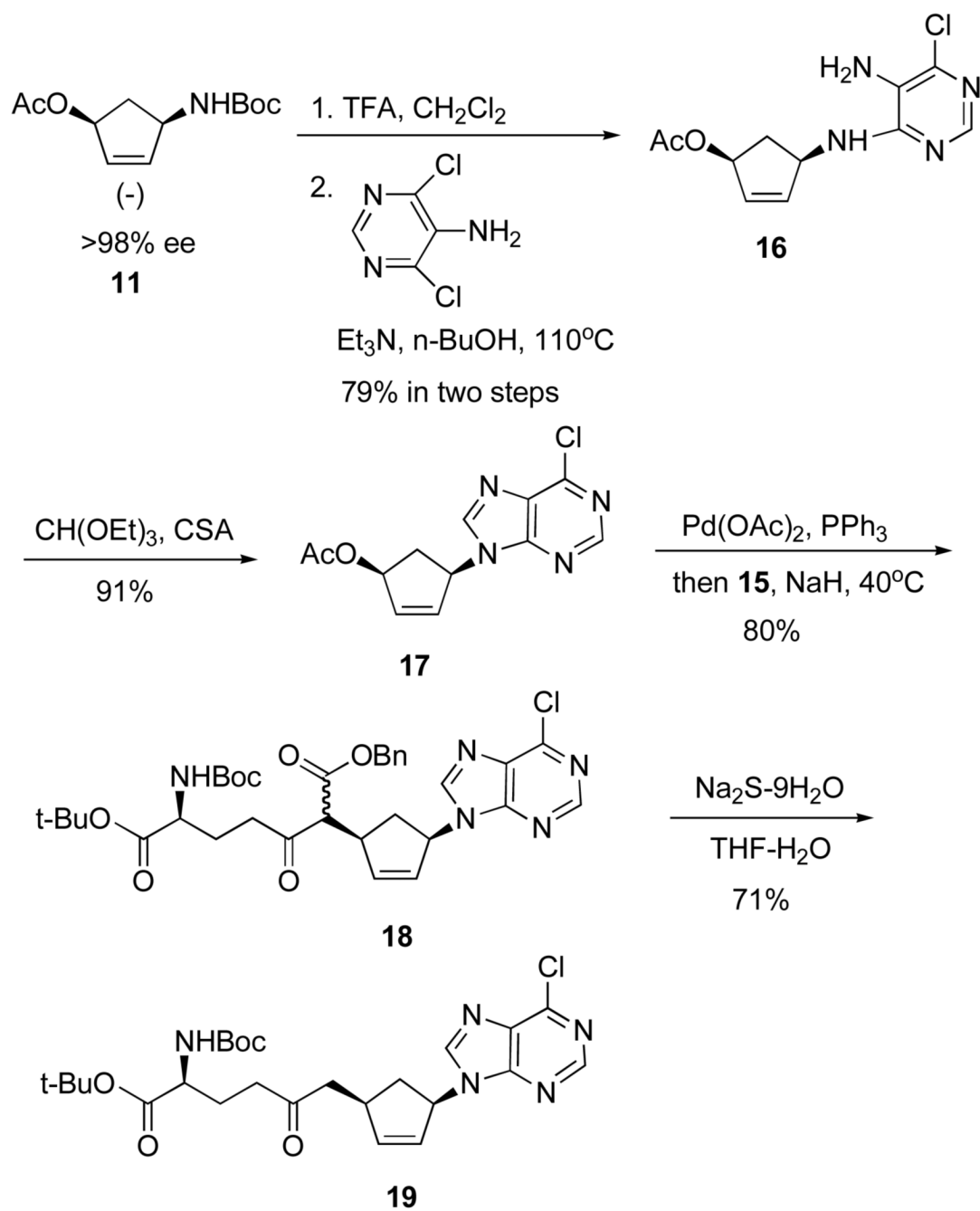
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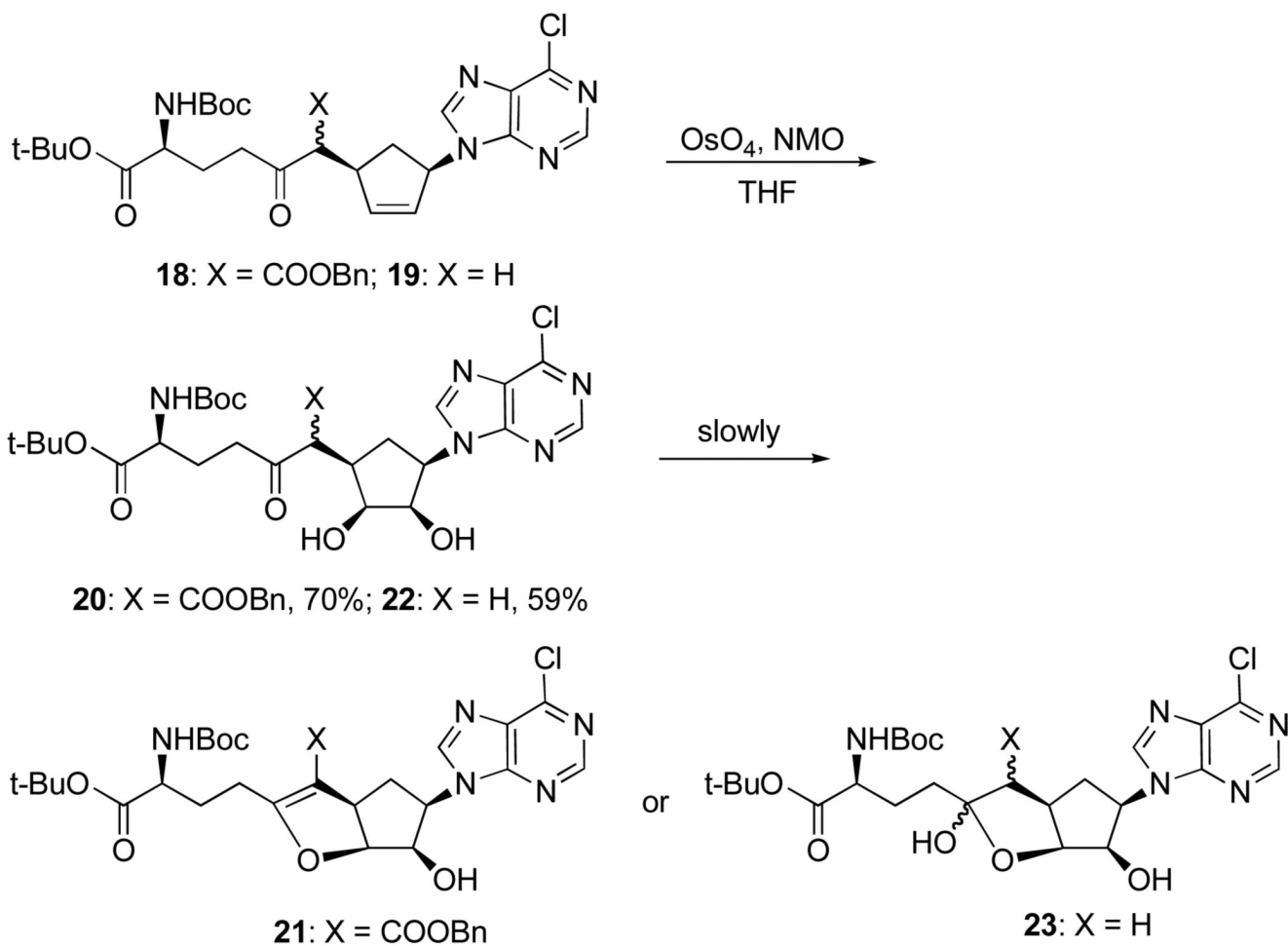
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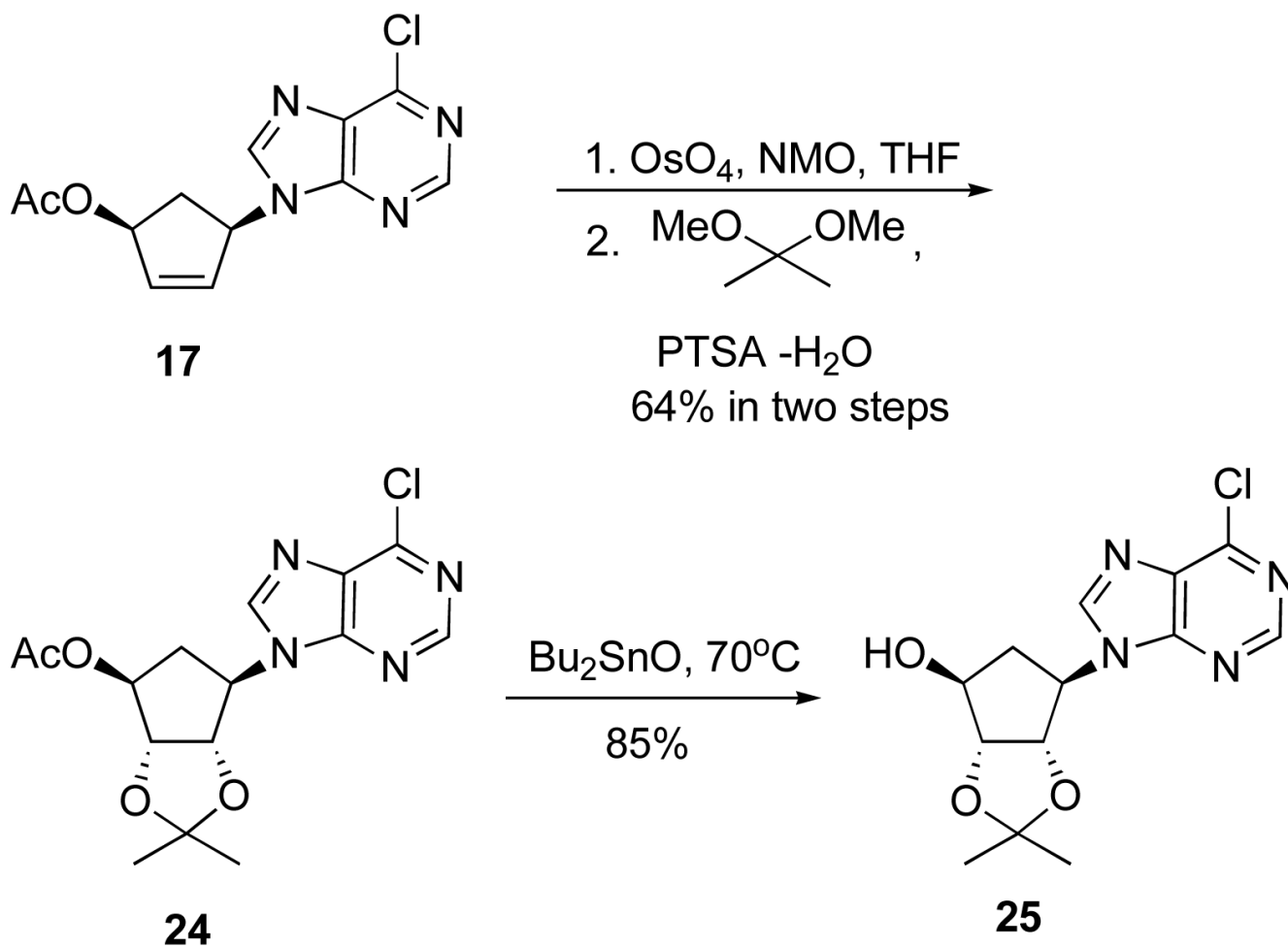
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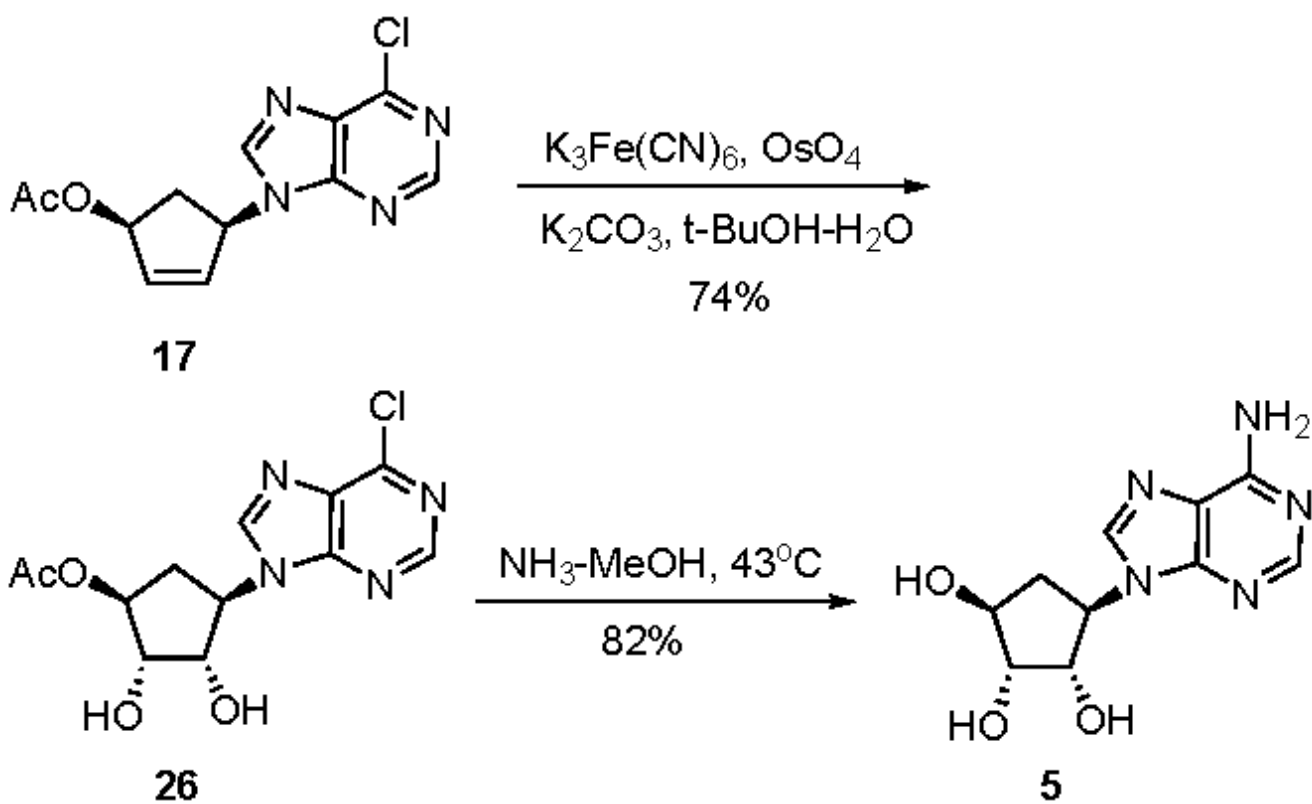
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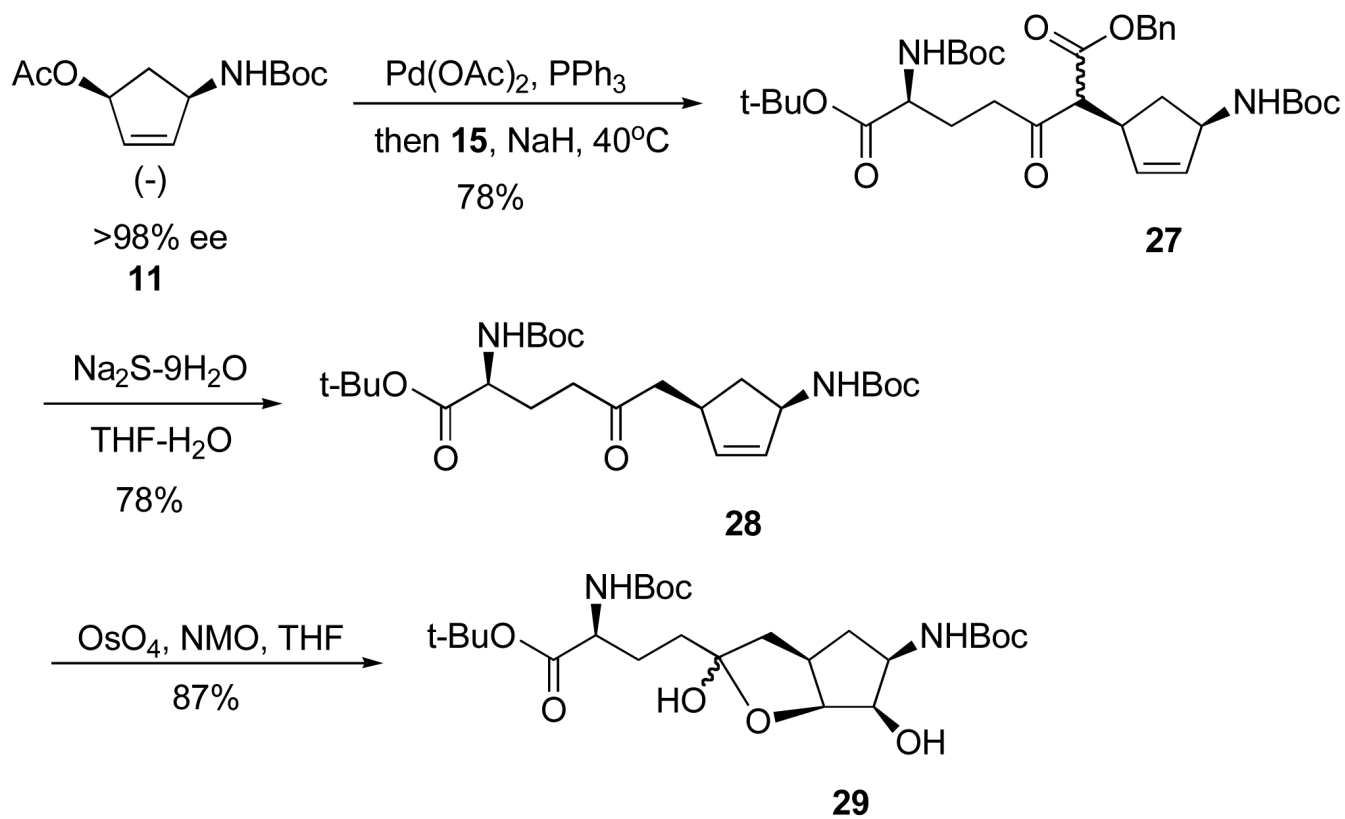
Scheme 4.



Scheme 5.



Scheme 6.



Scheme 7.