A Novel and Stereospecific Synthesis of (±)- and (−)-Aristeromycin[1,2]

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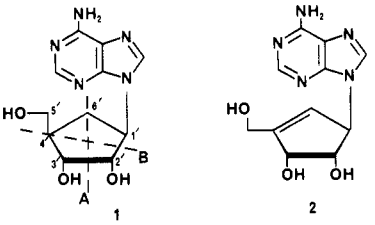
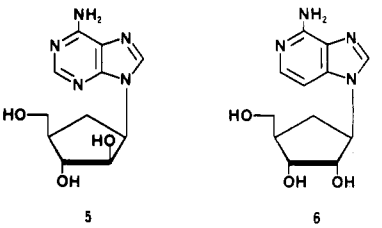
A new, efficient synthetic route to (±)- and (−)-aristeromycin (1) has been developed which has as its key feature the cycloaddition of singlet oxygen to 5-[(phenylmethoxy)methyl]-1,3-cyclopentadiene (8) followed by in situ reduction to give ene diol 10. This reaction has been optimized and scaled-up to give 197 g (60%) of partially purified 10. The key intermediate azide 15 was prepared from the partially purified 10 in 56% yield by a three-step sequence of epoxidation to give 13, reaction with NaN_3, and acetonation. Azide 15 was converted by standard chemistry via adenine intermediate 22 to (±)-aristeromycin (1) in 31% overall yield. Intermediate 22 was also prepared in 25% yield by a novel and shorter sequence which involved the reaction of epoxide 13 with the sodium salt of adenine and then acetonation. Alternatively, azide 15 was resolved by conversion to its naproxen ester 26, and the (−)-isomer of 15 was converted to the known amino triol 31, thus constituting a formal synthesis of (−)-aristeromycin.

Aristeromycin (1) is a carbocyclic analogue of adenosine which was first synthesized in racemic form by Shealy and Clayton in 1966[5] and later isolated as a natural product, (−)-enantiomer, from *S. citricolor* n.s.p.[6] Since the early synthesis, this class of compounds has attracted considerable synthetic interest.[7] More recently, another natural



product neplanocin A (2) was isolated from *Actinoplanacea ampullariella* s.p. and shown to exhibit selective antitumor activity, L1210 leukemia.[8] The neplanocins, such as A, B (3), and C (4),[9] are the first examples of carbocyclic nucleosides in which all five of the cyclopentane carbons are functionalized, and syntheses of neplanocin A have been reported.[7h,10]

In addition to the natural products, some important biologically active carbocyclic analogues have been synthesized. Foremost among these are the carbocyclic araadenosine (5)[7b] and the carbocyclic 3-deazaadenosine (6)[7i] which have been shown to exhibit antiviral activity. Analogue 6 apparently exerts an antiviral effect by interfering with the methylation capping of messenger RNA mediated by *S*-adenosylmethionine.



To date, most of the syntheses of carbocyclic nucleosides have utilized a strategy which takes into account an inherently obvious plane of symmetry (line A, 1) in a cyclopentane precursor which divides the C-2′, C-3′ bond and intersects C-6′.[11] These syntheses commenced from norbornene precursors. Most recently, this type of an approach has culminated in an elegant chemicoenzymatic synthesis by Ohno and co-workers of enantiomerically pure (−)-aristeromycin and (−)-neplanocin A.[7h] This first chiral synthesis of (−)-aristeromycin, however, proceeds in a questionable overall yield because the enzymatic enantiomeric excess is only 80%. In order to obtain enantiomerically pure material, one of the intermediates was purified from the undesired isomer by recrystallization, and the yield for this step was not reported.

We now report our studies in this class of compounds which culminates in syntheses of (±)- and (−)-aristeromycin. In designing a synthesis of aristeromycin we desired a synthetic route that would satisfy two requirements. First, the approach should be flexible enough to

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(2) Presented in part at 189th National Meeting of the American Chemical Society, Miami Beach, FL, May 1, 1985; CARB 41.
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(4) Current address: Bristol-Myers Company, Pharmaceutical Research and Development Division, Wallingford, CT 06492-7660.
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(11) The numbering system shown on the structure of aristeromycin (1) is consistent with that for adenosine. We also use this numbering system in the Experimental Section to facilitate comparison of the NMR spectra.

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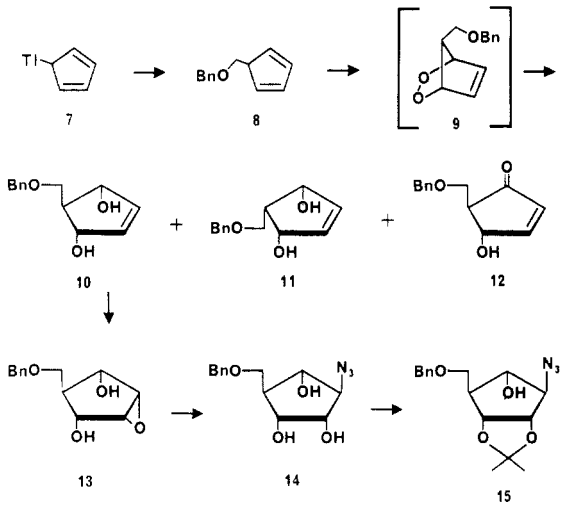
Scheme I



allow for the straightforward synthesis of other natural products and analogues. Secondly, the synthesis should be practical in that the number of synthetic steps be limited and easy to scale-up and that potential common intermediates for other analogues come late in the sequence. We chose as a strategy to this class of nucleosides an approach which would allow for the functionalization of all five cyclopentane positions early in the synthetic route.

Results and Discussion

Our synthetic strategy has as its key initial steps the $^1O_2$ addition to substituted cyclopentadiene **8** with in situ reduction to give ene diol **10** followed by stereospecific epoxidation to give the symmetrical epoxy diol **13** (Scheme I). This approach is the first to recognize a "hidden" plane of symmetry in a carbocyclic nucleoside precursor which bisects the C-1′, C-2′ bond and intersects C-4′ (line B, 1). *This chemistry is expected to have general synthetic utility because it allows for an efficient stereospecific functionalization for all five carbons of cyclopentane.*

The alkylation of thallium(I) cyclopentadienide (**7**) was first reported by Corey and co-workers in a prostaglandin synthesis.[12] They found that the thallium derivative **7** was superior to the lithium or sodium derivatives since it minimized the isomerization of the initially formed product **8** to more stable cyclopentadiene isomers. For our first step, we chose to alkylate **7** with benzyl chloromethyl ether to give **8**.[13] Although thallium cyclopentadienide is commercially available (Alfa), this material needed to be purified by sublimation in order to give a clean reaction. However, freshly prepared **7** gave a clean reaction even on a large scale without the need for sublimation. The alkylation was carried out at −20 °C and the product kept at below −5 °C at all times to prevent isomerization.

The alkylation product **8** was treated with photochemically generated $^1O_2$ using Rose Bengal as the sensitizer, and the intermediate endo peroxide **9** was reduced in situ with thiourea by the method of Kaneko et al.[14] to give ene diol **10**. This reaction was carefully studied, and the disappointing initial yields of around 10% were improved to 60% to give 197 g of partially purified **10** following filtration through silica gel. One essential factor was to keep the photolysis reaction solution below −5 °C to prevent isomerization of **8** to more stable isomers. The light source for this reaction was a cooled 400-W mercury immersion lamp. Potassium dichromate was used in the cooling water to completely screen out UV light. By screening out the UV light and therefore avoiding photochemical side reactions, it was possible to carry out the reaction more concentrated than recommended.[14] This increase in concentration greatly improved the yield presumably by increasing the rate of the bimolecular reduction with thiourea over that of the rate of the thermal decomposition of the endo peroxide **9**.

In addition to **10**, biproducts **11** and **12** were also isolated, each of which comprised less than 3% of the reaction product. The isolation of **11**, the product of addition of $^1O_2$ to the more hindered face of diene **8**, permitted the assignments of the structures of the isomeric diols **10** and **11**. The tertiary hydrogen of **10** which is cis to the two hydroxy groups exhibited an ^1H NMR absorbance upfield (δ 2.12) of that of isomer **11** (δ 2.53). This result is consistent with Sable's studies which showed that the proton cis to a hydroxy group in cyclopentane systems absorbs upfield from the trans proton.[15]

The formation of hydroxy eneones such as **12** from endo peroxides is precedented, and the base-catalyzed decomposition of an endo peroxide to give a hydroxy eneone has been used preparatively in a prostaglandin synthesis.[16]

Partially purified **10** was then epoxidized utilizing *m*-chloroperoxybenzoic acid. This epoxidation was directed by the alcohol functionalities to give only one isomer as predicted by the Henbest rule.[17] The reaction was carried out as a concentrated solution in dichloromethane, and both the epoxide **13** and *m*-chlorobenzoic acid crystallized from the solution. The epoxide is very water soluble and could not be separated from the acid by simple extraction. An analytical sample was obtained by recrystallization from dichloromethane/ethyl acetate. On larger scales to reduce material loss, the crude crystalline product mixture was isolated simply by filtration, and the purification was achieved in the subsequent step. On the largest scale, 324 g of crude product was obtained, which was estimated by its ^1H NMR spectrum to contain 127 g (62% yield) of **13**.

The crude epoxide **13** was next treated with sodium azide in DMF to give racemate **14**. Interestingly, the azido triol **14** was much less soluble in water than epoxide **13**. Thus, the *m*-chlorobenzoic acid impurity was easily removed at this stage by extraction with aqueous $NaHCO_3$. The conversion of **13** to **14** resulted in the formation of five chiral centers. Because the precursor **13** is meso, this reaction was completely stereospecific, and thus only one diastereomer **14** was formed.

Next, **14** was converted to acetonide **15** by treatment with 2,2-dimethoxypropane. On larger scales **15** was the first intermediate that was obtained in pure form. The overall yield of **15** from crude epoxide **13** was 56% following a simple chromatographic purification. The ability to proceed through these steps without purification greatly simplifies this chemistry.

Azido alcohol **15** was envisioned as a key intermediate with protected functionalities for the synthesis of carbocyclic nucleoside analogues. However, in order to synthesize aristeromycin, the hydroxy group of **15** needed to be removed. In order to attempt this deoxygenation, **15** was converted to thioimidazolide **16** by reaction with

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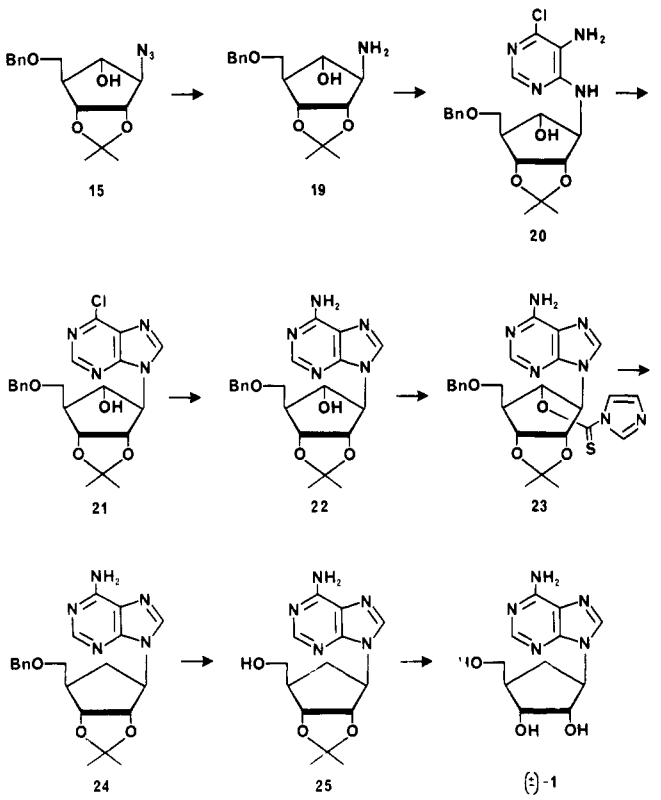
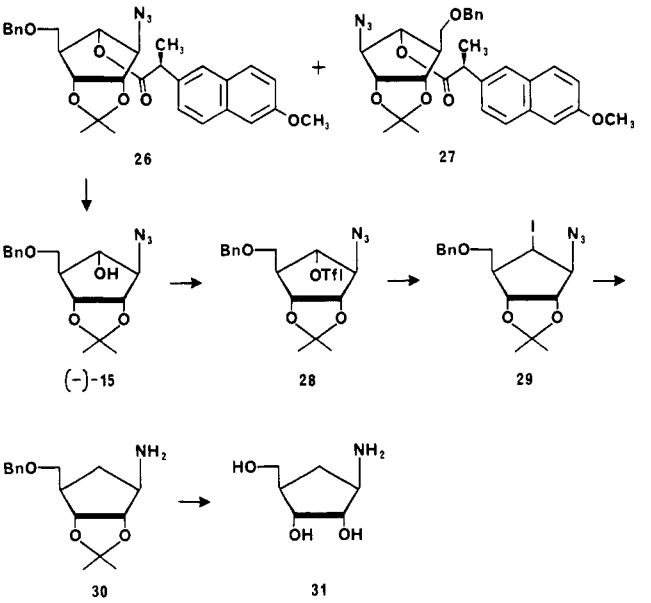
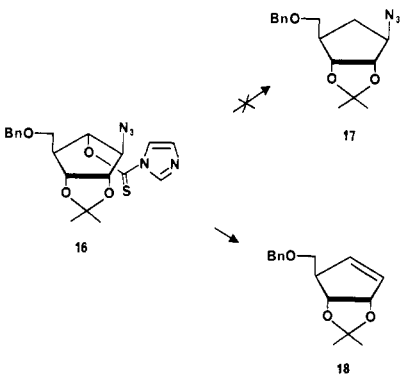
Scheme II



Scheme III



N,N-thiocarbonyldiimidazole.[18] However instead of affording **17**, tri-*n*-butyltin hydride (generated in situ)[19] reduction of **16** gave the elimination product **18**. This type



of elimination to olefins has been noted before for sulfides[20] and halides[21] but not azides. This result was surprising because iodo azides are known to be dehalogenated along with reduction to the amine by tri-*n*-butyltin hydride treatment.[22]

Deoxygenation β to a 9-adeninyl functionality is known;[23] therefore, an alternative approach to aristeromycin was investigated whereby the azido functionality of **15** was converted to a 9-adeninyl substituent before deoxygenation was effected. This approach proved successful (Scheme II).

Reduction of **15** with H_2 over Lindlar catalyst cleanly gave amine **19** in 88% yield with no benzyl ether hydrogenolysis.[24] The 9-adeninyl substituent was elaborated by a known three-step sequence.[5,25] Reaction of **19** with 5-amino-4,6-dichloropyrimidine in *N*-methylpyrrolidinone at 180 °C for 12 h have a 68% yield of **20**. Cyclization of **20** with diethoxymethyl acetate furnished purine derivative **21** in 90% yield, which in turn was reacted with methanolic ammonia (60 °C, 48 h) to give a 75% yield of **22**. Alternatively, **22** was prepared in 25% overall yield by treatment of purified epoxide **13** with the sodium salt of adenine followed by acetonation. This yield, although low, is comparable to that of the longer sequence to **22** via azide **15**.

Reaction of **22** with *N,N'*-thiocarbonyldiimidazole furnished **23**, which in turn was treated with tri-*n*-butyltin hydride to give an 83% yield of **24**. Starting alcohol **22** was also recovered in 5% yield. Straightforward deprotection of **24** by catalytic transfer hydrogenation[26] to give intermediate **25** and then hydrolysis with aqueous acetic acid gave a 91% yield of (±)-aristeromycin, which was identical in melting point and ^{13}C NMR spectrum with the data reported in the literature.[27]

The key intermediate **15** also served for the preparation of (−)-aristeromycin (Scheme III). The alcohol was first resolved by esterification with naproxen[28] to give diastereomers **26** and **27**. These diastereomers were not crystalline and, therefore, were isolated as oils following chromatographic purification. Saponification of **26** with NaOH gave the desired alcohol (−)-**15**.

The resolved alcohol (−)-**15** could clearly be elaborated to aristeromycin by the procedure detailed above. However, at this point, we chose to investigate an alternative approach to the deoxygenation of the azido alcohol (−)-**15**. The alcohol (−)-**15** was converted to the unstable triflate **28**, which in turn was immediately treated with LiI to give iodide **29** in 70% overall yield. Reduction of **29** with H_2

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(20 psi) over 10% Pd/C gave amine **30** as its HI salt in 55% yield. Aqueous acetic acid hydrolysis of **30** followed by Na/NH_3 hydrogenolysis gave a 92% yield of aminotriol **31** in analytically pure form after ion-exchange chromatography. This compound exhibited the same rotation (−10°) as previously reported and was used by Ohno and co-workers to synthesize (−)-aristeromycin.[7h] Thus the preparation of **31** constitutes a formal synthesis of (−)-**1**.

In summary, efficient syntheses of racemic and chiral aristeromycin have been completed from the easily prepared azido alcohol **15**. Although **15** contains a hydroxy functionality which needed to be removed to complete the aristeromycin syntheses, this group provided a convenient functionality to effect a resolution. Moreover, **15** is a versatile intermediate because the hydroxy group provides us a convenient synthetic handle for potential syntheses of other carbocyclic nucleosides such as the neplanocins. These syntheses and studies directed at the asymmetric opening of epoxide **13** to give an enantiomeric excess of (−)-**15** are currently under investigation.

Experimental Section

Nuclear magnetic resonance spectra were recorded on a Bruker WH-90 (^{13}C NMR, 22.62 MHz) and a Bruker WM-300 instrument (^1H NMR, 300 MHz; ^{13}C NMR, 75.453 MHz), and chemical shifts are reported in parts per million downfield from internal tetramethylsilane.[11] Spectroscopic data and elemental analyses were obtained by Syntex Analytical Research. Unless otherwise stated chromatographic purifications were carried out on silica gel. Melting points were determined on a hot stage microscope and are corrected.

Thallium(I) Cyclopentadienide (7). Thallium sulfate (450 g, 0.89 mol) was added with stirring to a solution of KOH (200 g, 3.56 mol) in water (3 L) at room temperature. The suspension was warmed to 40 °C to effect complete dissolution and then cooled back to room temperature. A precipitate was removed by filtration. Freshly distilled cyclopentadiene (500 mL) was added with stirring over 40 min to the filtrate. After an additional 30 min, the precipitate was isolated by filtration, washed with water (1 L, 0 °C), methanol (1 L, −78 °C), and ether (1 L, −78 °C), and then thoroughly dried under vacuum to give 475 g (98%) of **7**.

(1α,2β,3α)-2-[(Phenylmethoxy)methyl]-4-cyclopentene-1,3-diol (10). Benzyl chloromethyl ether (208 mL, 1.48 mol) was added dropwise over 30 min to a mechanically stirred suspension of **7** (475 g, 1.76 mmol) in ether (450 mL). The resulting suspension was mechanically stirred at −20 °C for an additional 18 h and then filtered with the filtrate flask precooled to −20 °C. The filtrate was evaporated at 0 °C (1 torr) to give **8** as a clear oil. A solution of **8** in methanol was transferred to a −5 °C solution of thiourea (126 g, 1.66 mol), sodium acetate (2.8 g, to prevent decolorization of the Rose Bengal), and Rose Bengal (2.8 g) in methanol (22 L, saturated with oxygen). The solution was then irradiated at −5 °C for 9 h with a 400-W mercury immersion lamp with continuous bubbling of oxygen into the solution. The lamp was cooled with a 0 °C solution of aqueous $Na_2Cr_2O_7$. The resulting solution was evaporated to a brown oil, which was dissolved in ethyl acetate, washed with water and evaporated to a brown oil. The oil was chromatographed over silica gel (2 kg) with a gradient of 1:1 to 9:1 of ethylacetate/hexane to give 197 g (60%) of purified **10** as a brown oil. An analytical sample was obtained by crystallization from ethyl acetate/hexane: mp 47–48 °C; ^1H NMR ($CDCl_3$) 7.25–7.40 (m, 5 H, phenyl), 5.87 (s, 2 H, olefinic), 4.56 (s, 2 H, benzylic), 4.38 (d, J = 4 Hz, 2 H, CHO), 3.66 (d, J = 6 Hz, 2 H, CH_2O), 2.12 (m, 1 H, CH); ^{13}C NMR (22.62 MHz, $CDCl_3$) 138.20 (phenyl), 135.53 (olefinic), 128.50, 127.86 (phenyl), 77.86 (CHOH) 73.47 (benzylic), 70.51 (CH_2O), 59.04 (CH). Anal. Calcd for $C_{13}H_{16}O_3$ (220.27): C, 70.89; H, 7.32. Found: C, 70.57; H, 7.96.

By careful chromatography of the photolysis reaction product, byproducts **11** and **12** were isolated as clear oils.

(1α,2α,3α)-2-[(Phenylmethoxy)methyl]-4-cyclopentene-1,3-diol (11): ^1H NMR ($CDCl_3$) 7.26–7.38 (m, 10 H, phenyl), 6.06 (s, 2 H, olefinic), 4.61 (d, J = 5 Hz, 2 H, CHO), 4.53 (s, 2 H, benzylic), 3.85 (d, J = 6 Hz, 2 H, OCH_2), 2.53 (p, J = 6 Hz, 1 H, CH); ^{13}C NMR (22.62 MHz, $CDCl_3$) 137.77 (phenyl), 136.67 (olefinic), 128.74, 128.12, 127.98 (phenyl), 76.04 (CHO), 73.60 (benzylic), 67.26 (CH_2O), 45.68 (CH). Anal. Calcd for $C_{13}H_{16}O_3$ (220.27): C, 70.89; H, 7.32. Found: C, 70.74; H, 7.33.

(±)-(4α,5β)-4-Hydroxy-5-[(phenylmethoxy)methyl]-2-cyclopenten-1-one (12): ^1H NMR ($CDCl_3$) 7.53 (dd, J = 3, 6 Hz, 1 H, olefinic β to carbonyl), 7.26–7.38 (m, 5 H, phenyl), 6.20 (dd, J = 1, 6 Hz, 1 H, olefinic α to carbonyl), 4.96 (m, 1 H, CHO), 4.51 (s, 2 H, benzylic), 3.86 and 3.71 (ABX, J_{AB} = 10 Hz, J_{AX} = 4 Hz, J_{BX} = 6 Hz, 2 H, CH_2O), 2.49 (m, 1 H, CH); ^{13}C NMR (22.62 MHz, $CDCl_3$) 205.23 (CO), 162.35 (C β to CO), 137.94 (phenyl), 134.69 (C α to CO), 128.57, 127.83 (phenyl), 74.58 (CHO), 73.54 (benzylic), 67.36 (CH_2O), 56.24 (CH). Anal. Calcd for $C_{13}H_{14}O_3$ (218.25): C, 71.54; H, 6.47. Found: C, 71.35; H, 6.24.

(1α,2α,3β,4α,5α)-2,4-Dihydroxy-3-[(phenylmethoxy)methyl]-6-oxabicyclo[3.1.0]hexane (13). *m*-Chloroperoxybenzoic acid (308 g, 1.52 mol) was added portionwise to a stirred solution of **10** (197 g, 0.89 mol) in dichloromethane (3 L) at 0 °C. The resulting suspension was stirred for 48 h at room temperature and then filtered and dried to give 324 g of the crude product, which by ^1H NMR was shown to be a 7:3 molar mixture of chlorobenzoic acid and **13** (127 g, 62%). An analytical sample was obtained by recrystallization from ethyl acetate/dichloromethane: mp 170–171 °C; ^1H NMR ($CDCl_3$–Me_2SO-d_6) 7.25–7.35 (m, 5 H, phenyl), 4.53 (s, 2 H, benzylic), 3.98 (d, J = 8 Hz, 2 H, CHO), 3.67 (d, J = 4 Hz, 2 H, CH_2O), 3.47 (s, 2 H, epoxide H), 3.18 (br s, 2 H, OH), 1.66 (m, 1 H, CH); ^{13}C NMR (75.453 MHz, $CDCl_3$–Me_2SO-d_6) 138.74, 128.39, 127.60 (phenyl), 73.30 (benzylic), 71.93 (CHOH), 68.25 (CH_2O), 56.95 (epoxide C), 46.64 (CH). Anal. Calcd for $C_{13}H_{16}O_4$ (236.27): C, 66.09; H, 6.83. Found: C, 65.91; H, 7.05.

(±)-(1α,2α,3β,4α,5β)-3-Azido-5-[(phenylmethoxy)methyl]-1,2,4-cyclopentanetriol (14). A solution of crude epoxide **13** (45.1 g contains 17.7 g of **13**, 75 mmol) and sodium azide (19.5 g, 0.3 mol) in DMF (200 mL) was heated at 110 °C for 12 h and then evaporated to dryness. The residue was partitioned between ethyl acetate and water. The organic phase was washed with saturated $NaHCO_3$, dried over Na_2SO_4, and then evaporated to dryness to give 21 g quantitative of **14**. An analytical sample was obtained as an oil by purification by chromatography (8:2 ethyl acetate/hexane): IR (neat) 2290 cm^{-1}; ^1H NMR ($CDCl_3$) 7.25–7.38 (m, 5 H, phenyl), 4.52 (s, 2 H, benzylic), 4.34 (d, J = 5 Hz, 1 H, OH), 4.15 (d, J = 5 Hz, 1 H, OH), 3.95 (d, J = 5 Hz, 1 H, OH), 3.70–3.90 (m, 4 H, H-1′, H-2′, H-3′, H-6′), 3.60 (d, J = 5 Hz, 2 H, H-5′), 2.12 (m, 1 H, H-4′); ^{13}C NMR (75.453 MHz, $CDCl_3$) 137.73, 128.57, 127.95, 127.74 (phenyl), 75.05 (C-1′), 74.20 (C-6′), 73.55 (benzylic), 71.97 (C-2′), 71.68 (C-3′), 70.21 (C-5′), 51.81 (C-4′). Anal. Calcd for $C_{13}H_{17}N_3O_4$ (279.30): C, 55.91; H, 6.14; N, 15.04. Found: C, 56.00; H, 6.16; N, 14.96.

(±)-(1α,2β,3α,4α,5β)-2-Azido-3,4-(dimethylmethylenedioxy)-5-[(phenylmethoxy)methyl]-1-cyclopentanol (15). A solution of **14** (21 g, 75 mmol), 75% $HClO_4$ (1 mL), and 2,2-dimethoxypropane (18 mL) in acetone (75 mL) was kept at room temperature for 1 h, and then concentrated NH_4OH was added dropwise until the solution was neutralized (pH 7). The solution was evaporated to dryness. The residue was dissolved in ethyl acetate, washed with water, dried over Na_2SO_4, and evaporated to dryness. The residue was purified by chromatography (7:3 ethyl acetate/hexane) to give 22.0 g (92%) of **15** as an oil: IR (neat) 2100 cm^{-1}; ^1H NMR ($CDCl_3$) 7.28–7.40 (m, 5 H, phenyl), 4.54 (s, 2 H, benzylic), 4.28 (m, 2 H, H-2′, H-3′), 3.92 (m, 1 H, H-6′), 3.55–3.82 (m, 3 H, H-1′, H-5′), 2.85 (br s, 1 H, OH), 2.28 (m, 1 H, H-4′), 1.52 (s, 3 H, CH_3), 1.28 (s, 3 H, CH_3); ^{13}C NMR (75.453 MHz, $CDCl_3$) 137.76, 128.57, 127.96, 127.76 (phenyl), 113.12 (OCO), 81.30 (C-2′), 77.87 (C-3′, C-6′), 73.58 (benzylic), 72.23 (C-1′), 69.54 (C-5′), 50.28 (C-4′), 27.25 (CH_3), 24.86 (CH_3), Anal. Calcd for $C_{16}H_{21}N_3O_4$ (319.36): C, 60.18; H, 6.63; N, 13.16. Found: C, 60.22; H, 6.84; N, 13.06.

(±)-(1β,2α,3α,4β,5α)-2,3-(Dimethylmethylenedioxy)-5-[(1-imidazolylthiocarbonyl)oxy]-4-[(phenylmethoxy)methyl]-1-cyclopentyl Azide (16). A solution of **15** (0.638 g, 2.0 mmol) and *N,N′*-thiocarbonyldiimidazole (0.712 g, 4.0 mmol) in DMF (10 mL) was kept at room temperature for 5 h and then evaporated to dryness. The residue was dissolved in ethyl acetate, washed with water, dried over Na_2SO_4, and evaporated to dryness to give

0.82 g (95%) of **16** as an oil: IR (neat) 2110 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$), 8.33 (s, 1 H, imidazole), 7.62 (m, 1 H, imidazole, 7.27–7.34 (m, 5 H, phenyl), 7.03 (m, 1 H, imidazole), 5.85 (t, J = 5 Hz, 1 H, H-6′), 4.57 (dd, J = 3, 6 Hz, 1 H, H-3′), 4.53 (s, 1 H, benzylic), 4.48 (dd, J = 4, 6 Hz, 1 H, H-2′), 4.24 (t, J = 4 Hz, 1 H, H-1′), 3.59 (d, J = 6 Hz, 2 H, H-5′), 2.75 (m, 1 H, H-4′), 1.52 (s, 3 H, CH_3), 1.31 (s, 3 H, CH_3).

(±)-(1β,2α,3α)-2,3-(Dimethylmethylenedioxy)-1-[(phenylmethoxy)methyl]-4-cyclopentene (18). A solution of **16** (0.43 g, 1.0 mmol), 2,2′-azobis(2-methylpropionitrile) (0.05 g, 0.3 mmol), polymethylhydrogen siloxane (2.38 g), and dibutyltin oxide (2.38 g, 4 mmol) in toluene (80 mL) was heated at reflux for 2 h and then evaporated to an oil. The residue was taken up in acetonitrile, washed with hexane, and evaporated to dryness. The residue was purified by preparative TLC (1:1 ethyl acetate/hexane) to give 0.18 g (60%) of **18** as a clear oil: ^1H NMR (300 MHz, $CDCl_3$) 7.26–7.35 (m, 5 H, phenyl), 5.86 (m, 1 H, H-1′), 5.78 (m, 1 H, H-6′), 5.14 (d, J = 6 Hz, 1 H, H-2′), 4.54 (d, J = 6 Hz, 1 H, H-3′), 4.52 (s, 2 H, benzylic), 3.37 and 3.50 (ABX, J_{AB} = 9 Hz, J_{AX} = 6 Hz, J_{BX} = 5 Hz, 2 H, H-5′), 3.06 (m, 1 H, H-4′), 1.42 (s, 3H, CH_3), 1.35 (s, 3 H, CH_3); ^{13}C NMR (22.62 MHz, $CDCl_3$) 138.36 (phenyl), 134.07 (C-6′), 132.38 (C-1′), 128.45, 127.67 (phenyl), 110.12 (OCO), 85.12 (C-2′), 81.52 (C-3′), 73.20 (benzylic), 71.21 (C-5′), 52.69 (C-4′), 27.43 (CH_3), 25.64 (CH_3). Anal. Calcd for $C_{16}H_{20}O_3$ (260.33): C, 73.85; H, 7.69. Found: C, 73.64; H, 7.76.

(±)-(1β,2α,3β,4α,5α)-4,5-(Dimethylmethylenedioxy)-2-hydroxy-3-[(phenylmethoxy)methyl]-1-cyclopentanamine (19). A mixture of **15** (0.32 g, 1.0 mmol) and Lindlar catalyst (0.08 g) in methanol (15 mL) was stirred under H_2 (1 atm) for 12 h and then filtered with additional hot methanol. The filtrate was evaporated to dryness and the residue was purified by chromatography (ethyl acetate) to give 0.26 g (88%) of **19** as an oil: ^1H NMR ($CDCl_3$) 7.25–7.40 (m, 5 H, phenyl), 4.54 (s, 2 H, benzylic), 4.31 (t, J = 5 Hz, 1 H, H-3′), 4.11 (t, J = 5 Hz, 1 H, H-2′), 3.55–3.78 (m, 3 H, H-5′, H-6′), 3.17 (dd, J = 5, 9 Hz, 1 H, H-1′), 2.22 (m, 1 H, H-4′), 1.50 (s, 3 H, CH_3), 1.27 (s, 3 H, CH_3); ^{13}C NMR (22 MHz, $CDCl_3$) 138.04 128.61, 127.83 (phenyl), 112.54 (OCO), 84.65 (C-2′), 79.58 (C-6′), 78.25 (C-3′), 73.54 (benzylic), 70.25 (C-5′), 64.17 (C-1′), 50.68 (C-4′), 27.34 (CH_3), 24.93 (CH_3). Anal. Calcd for $C_{16}H_{23}NO_4$ (293.37): C, 65.51; H, 7.90; N, 4.77. Found: C, 65.80; H, 7.80; N, 5.08.

(±)-(1α,2β,3α,4α,5β)-2-[(5-Amino-6-chloro-4-pyrimidinyl)amino]-5-[(phenylmethoxy)methyl]-3,4-(dimethylmethylenedioxy)-1-cyclopentanol (20). A solution of **19** (0.29 g, 1.0 mmol), 5-amino-4,6-dichloropyrimidine (0.16 g, 1.0 mmol), and pyridine (0.08 g, 1.0 mmol) in *N*-methylpyrrolidinone (15 mL) was heated under N_2 at 180 °C for 12 h. The solution was evaporated to a brown oil. The residue was dissolved in ethyl acetate, washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4, and evaporated to dryness. The residue was purified by chromatography (1:1 ethyl acetate/hexane) to give 0.29 g (68%) of **20**. An analytical sample was prepared by recrystallization from ethyl acetate/hexane: mp 107–108 °C; ^1H NMR ($CDCl_3$ + D_2O) 7.99 (s, 1 H, H-2), 7.26–7.40 (m, 5 H, phenyl), 4.57 (m, 3 H, H-3′, benzylic), 4.47 (t, J = 5 Hz, 1 H, H-1′), 4.03 (t, J = 6 Hz, 1 H, H-6′), 3.72 (m, 2 H, H-1′), 2.41 (m, 1 H, H-4′), 1.54 (s, 3 H, CH_3), 1.31 (s, 3 H, CH_3); ^{13}C NMR (75.453 MHz, Me_2SO-d_6) 152.06 (C-4), 145.32 (C-2), 138.47 (phenyl), 137.11 (C-6), 128.16, 127.41, 127.31 (phenyl), 123.37 (C-5), 111.02 (OCO), 81.38 (C-2′), 76.98 (C-6′), 74.15 (C-3′), 72.24 (benzylic), 67.66 (C-5′), 63.11 (C-1′), 50.68 (C-4′), 27.42 (CH_3), 25.07 (CH_3). Anal. Calcd for $C_{20}H_{25}ClN_4O_4$ (420.90): C, 57.14; H, 5.95; N, 13.33. Found: C, 56.94; H, 6.06; N, 13.04.

(±)-(1α,2β,3α,4α,5β)-2-(6-Chloro-9*H*-purin-9-yl)-3,4-(dimethylmethylenedioxy)-5-[(phenylmethoxy)methyl]-1-cyclopentanol (21). A solution of **20** (0.21 g, 0.50 mmol) and diethoxymethyl acetate (5 mL) was heated at reflux for 12 h and then evaporated to dryness. A solution of the residue and *p*-toluenesulfonic acid (5 mg) in toluene (10 mL) was kept at room temperature for 1 h and then evaporated to dryness. The residue was purified by chromatography (1:9 methanol/dichloromethane) to give 0.22 g (90%) of **21**: mp 190–191 °C; ^1H NMR (300 MHz, Me_2SO-d_6 + D_2O) 8.90 (s, 1 H, H-2), 8.79 (s, 1 H, H-8), 7.28–7.35 (m, 5 H, phenyl), 5.02 (t, J = 7 Hz, 1 H, H-2′), 4.71 (dd, J = 7, 10 Hz, 1 H, H-3′), 4.61 (m, 1 H, H-1′), 4.57 (s, 2 H, benzylic), 4.46 (t, J = 10 Hz, 1 H, H-6′), 3.59 and 3.68 (ABX, J_{AB} = 10 Hz, J_{AX} = 6 Hz, J_{BX} = 4 Hz, 2 H, H-5′), 2.20 (m, 1 H, H-4′), 1.51 (s, 3 H, CH_3), 1.24 (s, 3 H, CH_3); ^{13}C NMR (75.453 MHz, Me_2SO-d_6) 152.07 (C-4), 151.35 (C-2), 149.50 (C-4), 146.81 (C-8), 138.38 (phenyl), 131.40 (C-5), 128.20, 127.42, 127.36 (phenyl), 112.08 (OCO), 78.52 (C-2′), 77.42 (C-6′), 72.79 (C-3′), 72.21 (benzylic), 68.10 (C-5′), 67.90 (C-1′), 50.06 (C-4′), 27.26 (CH_3), 24.92 (CH_3). Anal. Calcd for $C_{21}H_{23}ClN_4O_4$ (430.89): C, 58.54; H, 5.38; N, 13.00. Found: C, 58.50; H, 5.44; N, 12.90.

(±)-(1α,2β,3α,4α,5β)-2-(6-Amino-9*H*-purin-9-yl)-3,4-(dimethylmethylenedioxy)-5-[(phenylmethoxy)methyl]-1-cyclopentanol (22). A solution of **21** (0.22 g, 0.51 mmol) in methanolic ammonia (10 mL, saturated at 0 °C) was heated in a Parr bomb at 60 °C for 48 h. The solution was evaporated to dryness and the residue recrystallized from methanol/ethyl acetate to give 0.15 g (75%) of **22**: mp 242–243 °C; UV λ_{max} (methanol) 260 nm (ε 14 000); ^1H NMR (300 MHz, Me_2SO-d_6) 8.23 (s, 1 H, H-2), 8.13 (s, 2 H, H-8), 7.28–7.43 (m, 5 H, phenyl), 7.20 (br s, 2 H, NH_2), 5.50 (d, J = 6 Hz, 1 H, OH), 5.00 (t, J = 7 Hz, 1 H, H-2′), 4.38–4.61 (m, 5 H, H-1′, H-3′, H-6′, benzylic), 3.58 and 3.68 (ABX, J_{AB} = 10 Hz, J_{AX} = 7 Hz, J_{BX} = 3 Hz, 2 H, H-5′), 2.15 (m, 1 H, H-4′), 1.49 (s, 3 H, CH_3), 1.23 (s, 3 H, CH_3); ^{13}C NMR (75.453 MHz, Me_2SO-d_6) 155.99 (C-6), 152.14 (C-2), 149.54 (C-4), 140.55 (C-8), 138.38, 128.17, 127.40, 127.32 (phenyl), 119.50 (C-5), 111.80 (OCO), 78.56 (C-2′), 77.37 (C-6′), 72.70 (C-3′), 72.14 (benzylic), 68.05 (C-5′), 67.48 (C-1′), 50.24 (C-4′), 27.26 (CH_3), 24.89 (CH_3). Anal. Calcd for $C_{21}H_{25}N_5O_4$ (411.46): C, 61.30; H, 6.12; N, 17.02. Found: C, 61.54; H, 5.85; N, 16.76.

Preparation of 22 from 13. A mixture of hexane prewashed sodium hydride (0.052 g, 50%, 1.1 mmol) and adenine (0.204 g, 1.5 mmol) in DMF (10 mL) was stirred at room temperature for 15 min. The epoxide **13** (0.24 g, 1.0 mmol) was added, and the resulting mixture was heated at 105 °C for 12 h and then evaporated to dryness. The residue was treated with 70% $HClO_4$ (one drop) and 2,2-dimethoxypropane (8 mL) in acetone (15 mL) for 45 min, and then concentrated NH_4OH was added dropwise until the solution was neutralized (pH 7). The solution was evaporated to dryness and the residue purified by chromatography (1:9 methanol/dichloromethane) to give 0.10 g (25%) of **22** as a crystalline solid.

(±)-(1β,2α,3β,4α,5α)-1-(6-Amino-9*H*-purin-9-yl)-4,5-(dimethylmethylenedioxy)-2-[(1-imidazolylthiocarbonyl)oxy]-3-[(phenylmethoxy)methyl]cyclopentane (23). A solution of **22** (190 mg, 0.46 mmol) and *N,N′*-thiocarbonyldiimidazole in DMF (1.5 mL) was heated at 70 °C for 2 h and then evaporated to dryness. The residue was purified by chromatography (1:14 methanol/dichloromethane) to give 0.2 g (quantitative) of **23** as a clear oil. An analytical sample was crystallized from ethyl acetate: mp 163–165 °C; UV λ_{max} (methanol) 263 nm (ε 15 800); ^1H NMR (300 MHz, Me_2SO-d_6) 8.42 (s, 1 H, imidazole), 8.29 (s, 1 H, H-2), 8.09 (s, 1 H, H-8), 7.71 (s, 1 H, imidazole, 7.25 (s, 5 H, Ar), 7.01 (s, 1 H, imidazole) 6.49 (t, J = 9 Hz, 1 H, H-6′), 5.20–5.35 (m, 2 H, H-1′, H-2′), 4.74 (t, J = 6 Hz, 1 H, H-3′), 4.50 (AB, J = 12 Hz, 2 H, benzylic), 3.71 (m, 2 H, H-5′), 3.92 (m, 1 H, H-4′), 1.58 (s, 3 H, CH_3), 1.29 (s, 3 H, CH_3); ^{13}C NMR (75.453 MHz, Me_2SO-d_6) 183.19 (CS), 155.96 (C-6), 152.38 (C-2), 149.60 (C-4), 139.95 (C-8), 137.97 (phenyl), 136.97 (imidazole, C-2), 130.66 (imidazole, C-4), 128.00, 127.25, 127.19 (phenyl), 119.26 (C-5), 118.61 (imidazole, C-5), 112.78 (OCO), 84.04 (C-6′), 78.73 (C-2′), 77.16 (C-3′), 72.14 (benzylic), 67.75 (C-5′), 64.03 (C-1′), 47.55 (C-4′), 27.21 (CH_3), 25.03 (CH_3). Anal. Calcd for $C_{25}H_{27}N_7O_4S$ (521.60): C, 57.57; H, 5.22; N, 18.80. Found: C, 57.36; H, 5.20; N, 18.68.

(±)-(1β,2α,3α,4β)-1-(6-Amino-9*H*-purin-9-yl)-2,3-(dimethylmethylenedioxy)-4-[(phenylmethoxy)methyl]cyclopentane (24). A solution of **23** from above (0.2 g, 0.46 mmol), 2,2′-azobis(2-methylpropionitrile) (5 mg, 0.03 mmol), polymethylhydrogen siloxane (1.7 mL), and dibutyltin oxide (1.7 mL) in dioxane (8 mL) was heated at reflux for 1.5 h. The resulting solution was diluted with methanol and washed with hexane. The methanol phase was evaporated to dryness, and the residue was purified by chromatography (1:16 methanol/dichloromethane). After recrystallization of selected fractions from ethanol/dichloromethane, 10.3 mg (5%) of starting alcohol **21** was recovered. The less polar **24** was isolated in 83% yield (151.1 mg) following recrystallization from ethyl acetate: mp 174–175 °C; UV λ_{max} (methanol) 261 nm (ε 13 300); ^1H NMR (300 MHz, Me_2SO-d_6) 8.24 (s, 1 H, H-2), 8.13 (s, 1 H, H-8), 7.32 (m, 5 H, phenyl), 7.20 (br s, 2 H, NH_2), 5.04 (t, J = 7 Hz, 1 H, H-2′), 4.82 (dt, J = 7, 11 Hz,

1 H, H-1'), 4.56 (dd, J = 5, 7 Hz, 1 H, H-3'), 4.52 (s, 2 H, benzylic), 3.54 (m, 2 H, H-5'), 2.20–2.45 (m, 3 H, H-4', H-6'); ^{13}C NMR (75.453 MHz, Me_2SO-d_6) 155.99 (C-6), 152.25 (C-2), 149.32 (C-4), 139.71 (C-8), 138.33, 127.41, 127.37, 127.33 (phenyl), 119.17 (C-5), 112.58 (OCO), 82.95 (C-2'), 81.08 (C-3'), 72.00 (benzylic), 70.74 (C-5'), 60.21 (C-1'), 43.16 (C-4'), 33.85 (C-6'), 27.37 (CH_3), 25.07 (CH_3). Anal. Calcd for $C_{21}H_{25}N_5O_3$ (395.46): C, 63.78; H, 6.37; N, 17.71. Found: C, 63.79; H, 6.52; N, 17.81.

(±)-Aristeromycin ((±)-1). A mixture of **24** (90 mg, 0.23 mmol) and 20% $Pd(OH)_2$/C (30 mg) in cyclohexene (1 mL) and ethanol (2 mL) was heated at reflux for 8 h and then filtered through Celite. The filtrate was evaporated to dryness, and the residue was purified by chromatography (1:6 methanol/dichloromethane) to give 70 mg (100%) of **25**. A solution of **25** (70 mg, 0.23 mmol) in 80% aqueous acetic acid was heated at 80 °C for 2 h and then evaporated to dryness. The residual oil was crystallized from ethanol/ethyl acetate to give 54.7 mg (91%) of (±)-1: mp 240–241 °C (lit. mp 241–243 °C); UV λ_{max} (0.1 N HCl) 260 nm (ϵ 13600), (0.1 N NaOH) 262 (13800); ^{1}H NMR (300 MHz, Me_2SO-d_6 + D_2O) 8.18 (s, 1 H, H-2), 8.12 (s, 1 H, H-8), 4.70 (q, J = 9 Hz, 1 H, H-1'), 4.34 (dd, $J_{1',2'}$ = 9 Hz, $J_{2',3'}$ = 5 Hz, 1 H, H-2'), 3.86 (dd, $J_{2',3'}$ = 5 Hz, $J_{3',4'}$ = 3 Hz, 1 H, H-3'), 3.40 (m, 2 H, H-5'), 2.25 (m, 1 H, H-6'), 2.05 (m, 1 H, H-4'), 1.74 (m, 1 H, H-6'); ^{13}C NMR (75.453 MHz, Me_2SO-d_6) 155.90 (C-6), 151.95 (C-2), 149.66 (C-4), 139.94 (C-8), 119.25 (C-5), 74.50 (C-2'), 71.61 (C-3'), 62.95 (C-5'), 59.26 (C-1'), 45.29 (C-4'), 29.21 (C-6'); ^{13}C NMR (Me_2SO-d_6)[27] 155.96, 152.01, 149.75, 140.00, 119.35, 74.62, 71.71, 62.98, 59.41, 45.39, 29.28.

[1*S*-(1β,2α,3α,4β,5α)]-2,3-(Dimethylmethylenedioxy)-5-[(*S*)-(2-(6-methoxy-2-naphthyl)propionyl)oxy]-4-[(phenylmethoxy)methyl]-1-cyclopentyl Azide (26). A solution of oxalyl chloride (5.08 g, 40 mmol) in benzene (5 mL) was added to a stirred suspension of naproxen (9.92 g, 40 mmol) in DMF (5 mL) and benzene (20 mL). After 1 h at room temperature, the solution was evaporated to dryness. The residue as a solution in dichloromethane (25 mL) was added dropwise to a stirred solution of **15** (12.90 g, 40 mmol), pyridine (10 mL), and 4-(dimethylamino)pyridine (40 mg) in dichloromethane (100 mL). After 2 h at room temperature, the solution was washed with aqueous $NaHCO_3$ and water, dried over Na_2SO_4, and evaporated to give 17.0 g (80%) of the diastereomeric mixture of **26** and **27** as a brown oil. The mixture was resolved by chromatography (1:2:17 ethyl acetate/toluene/hexane) to give in order of elution 6.8 g (32%) of **27** and 6.8 g (32%) of **26** as clear oils. Also, 3.4 g (16%) of a mixture of **26** and **27** was recovered.

26: $[\alpha]^{25}_D$ −31.8° (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) 7.10–7.70 (m, 11 H, Ar), 5.18 (t, J = 8 Hz, 1 H, H-6'), 4.77 (s, 2 H, benzylic), 4.45 (dd, J = 3, 6 Hz, 1 H, H-3'), 4.26 (dd, J = 3, 6 Hz, 1 H, H-2'), 3.91 (s, 3 H, OCH_3), 3.82 (q, J = 7 Hz, 1 H, C*H*CH_3), 3.78 (dd, J = 3, 6 Hz, 1 H, H-1'), 3.40 and 3.49 (ABX, J_{AB} = 9 Hz, J_{AX} = 6 Hz, J_{BX} = 5 Hz, 2 H, H-5'), 2.35 (m, 1 H, H-4'), 1.55 (d, J = 7 Hz, 3 H, CHC*H*$_3$), 1.41 (s, 3 H, CH_3), 1.25 (s, 3 H, CH_3); ^{13}C NMR (75.453 MHz, $CDCl_3$) 173.75, 137.97, 156.20, 135.13, 133.81, 129.30, 129.03, 128.41, 127.78, 127.72, 127.28, 126.04, 119.01 (Ar), 112.83 (OCO), 105.72 (Ar), 81.71 (C-2'), 79.04 (C-3'), 77.20 (C-6'), 73.41 (benzylic), 70.76 (C-1'), 67.90 (C-5'), 55.32 (OCH_3), 49.16 (C-4'), 45.49 (*C*HCH$_3$), 27.11 (CH_3), 24.88 (CH_3), 18.39 (CH*C*H$_3$). Anal. Calcd for $C_{30}H_{33}N_3O_6$ (531.61): C, 67.78; H, 6.26; N, 7.90. Found: C, 68.10; H, 6.33; N, 7.82.

27: $[\alpha]^{25}_D$ 54.6° (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) 7.11–7.67 (m, 11 H, Ar), 5.22 (t, J = 8 Hz, 1 H, H-6'), 4.42 (dd, J = 3, 6 Hz, 1 H, H-3'), 4.30 (s, 2 H, benzylic), 4.28 (dd, J = 3, 6 Hz, 1 H, H-2'), 3.91 (s, 3 H, OCH_3), 3.85 (m, 2 H, H-1' and C*H*CH_3), 3.11 and 3.32 (ABX, J_{AB} = 9 Hz, J_{AX} = 6 Hz, J_{BX} = 5 Hz, 2 H, H-5'), 2.17 (m, 1 H, H-4'), 1.57 (d, J = 7 Hz, 3 H, CHC*H*$_3$), 1.46 (s, 3 H, CH_3), 1.25 (s, 3 H, CH_3); ^{13}C NMR (75.453 MHz, $CDCl_3$) 173.80 (CO), 157.97, 137.96, 135.39, 133.80, 129.28, 128.99, 128.36, 127.74, 127.66, 127.26, 126.10, 126.00, 119.06 (Ar), 81.29 (C-2'), 78.52 (C-3'), 76.40 (C-6'), 73.32 (benzylic), 70.45 (C-1'), 67.38 (C-5'), 55.33 (OCH_3), 49.06 (C-4'), 45.42 (*C*HCH$_3$), 27.18 (CH_3), 24.90 (CH_3), 18.31 (CH*C*H$_3$). Anal. Calcd for $C_{30}H_{33}N_3O_6$ (531.61): C, 67.78; H, 6.26; N, 7.90. Found: C, 68.10; H, 6.46; N, 7.94.

[1*S*-(1α,2β,3α,4α,5β)]-2-Azido-3,4-(dimethylmethylenedioxy)-5-[(phenylmethoxy)methyl]-1-cyclopentanol ((−)-15). A solution of **26** (5.0 g, 9 mmol) and NaOH (0.40 g, 100 mmol) in THF (50 mL) was heated at reflux for 4 h and then evaporated to dryness. The residue was dissolved in ethyl acetate, washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4, and evaporated to dryness. The residue was purified by chromatography (2:8 ethyl acetate/hexane) to give 1.90 g (91%) of (−)-**15** as a clear oil: $[\alpha]^{25}_D$ −26.0° (c 0.3, $CHCl_3$). Anal. Calcd for $C_{16}H_{21}N_3O_4$ (319.36): C, 60.18; H, 6.63; N, 13.16. Found: C, 60.30; H, 6.88; N, 13.04.

[1*S*-(1β,2α,3β,4α,5α)]-4,5-(Dimethylmethylenedioxy)-2-iodo-3-[(phenylmethoxy)methyl]-1-cyclopentyl Azide (29). A solution of (−)-**15** (1.76 g, 5.6 mmol), trifluoromethane sulfonic anhydride (1.68 g, 8.0 mmol), and pyridine (0.56 g, 8.0 mmol) in dichloromethane (15 mL) was kept at room temperature for 2 h. The solution was then washed with water and saturated aqueous $NaHCO_3$, dried over Na_2SO_4, and evaporated to give **28** as a brown oil. A solution of the residue and LiI (0.93 g, 7.0 mmol) in DMF (20 mL) was kept at room temperature for 1 h, then diluted with ethyl acetate, washed with water, dried over Na_2SO_4, and evaporated to dryness. The residue was purified by chromatography (2:8 ethyl acetate/hexane) to give 1.65 g (70%) of **29** as a yellow oil: $[\alpha]^{25}_D$ −32.9° (c 0.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$) 7.25–7.40 (m, 5 H, phenyl), 4.50–4.76 (m, 5 H, H-2', H-3', H-6', benzylic), 3.78 (dd, J = 4, 5 Hz, 1 H, H-1'), 3.63 (d, J = 7 Hz, 2 H, H-5'), 2.26 (m, 1 H, H-4'), 1.48 (s, 3 H, CH_3), 1.29 (s, 3 H, CH_3); ^{13}C NMR (75.453 MHz, $CDCl_3$) 138.01, 128.43, 127.82, 127.77 (phenyl), 113.00 (OCO), 83.50 (C-2'), 80.75 (C-3'), 73.35 (benzylic), 72.82 (C-5'), 70.30 (C-1'), 49.51 (C-4'), 33.08 (C-6'), 26.64 (CH_3), 24.34 (CH_3). Anal. Calcd for $C_{16}H_{20}IN_3O_6$ (429.26): C, 44.77; H, 4.70; N, 9.79. Found: C, 44.71; H, 4.84; N, 9.80.

[1*R*-(1β,2α,3α,4β)]-2,3(Dimethylmethylenedioxy)-4-[(phenylmethoxy)methyl]-1-cyclopentanamine Hydroiodide (30). A mixture of **29** (1.50 g, 3.5 mmol) and 10% Pd/C (0.15 g) in methanol (25 mL) was shaken on a Parr apparatus under H_2(20 psi) at room temperature for 6 h and then filtered through Celite. The filtrate was evaporated to dryness and the residue chromatographed (1:19 methanol/dichloromethane) to give 0.78 g (55%) of **30** as a yellow oil: $[\alpha]^{25}_D$ −2.9° (c 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$) 7.35–7.46 (m, 5 H, phenyl), 4.75 (d, J = 6 Hz, 1 H, H-2'), 4.58 and 4.74 (AB, J = 12 Hz, 2 H, benzylic), 4.50 (d, J = 6 Hz, 1 H, H-3'), 3.86 (d, J = 7 Hz, 1 H, H-1'), 3.52 and 3.61 (ABX, J_{AB} = 9 Hz, J_{AX} = J_{BX} = 3 Hz, 2 H, H-5'), 2.65 (dt, J = 14, 7 Hz, 1 H, H-6'), 2.48 (m, 1 H, H-4'), 1.97 (d, J = 14 Hz, 1 H, H-6'), 1.42 (s, 3 H, CH_3), 1.26 (s, 3 H, CH_3); ^{13}C NMR (22.62 MHz, $CDCl_3$) 135.66, 129.29, 128.8 (phenyl), 111.02 (OCO), 84.91 (C-3'), 84.78 (C-2'), 74.41 (benzylic), 71.46 (C-5'), 57.22 (C-1'), 45.51 (C-4'), 32.51 (C-6'), 26.53 (CH_3), 24.02 (CH_3). Anal. Calcd for $C_{16}H_{24}NO_3I$ (405.28): C, 47.42; H, 5.97; N, 3.46. Found: C, 47.36; H, 6.17; N, 3.30.

[1*R*-(1β,2α,3α,4β)]-2,3-Dihydroxy-4-(hydroxymethyl)-1-cyclopentanamine (31). A solution of **30** (0.60 g, 1.5 mmol) in 80% aqueous acetic acid (5 mL) was heated at 80 °C for 1 h and then evaporated to dryness to give **31** as an oil. A magnetically stirred solution of the residue in ammonia (15 mL) at −78 °C was treated with sufficient sodium so that the solution remained blue for 1 h. The reaction was then quenched with NH_4Cl and evaporated to dryness. Purification of the residue on a cation-exchange resin (Dowex AB 50W-X8, H^+ form) eluting with water and then 0.07 M NH_4OH gave 0.20 g (92%) of **31** as a clear oil: $[\alpha]^{25}_D$ −10.3° (c 0.3, H_2O) [lit. $[\alpha]^{25}_D$ −10.3° (c 1.52, H_2O)]; ^{1}H NMR (CD_3OD) 3.83 (dd, J = 4, 5 Hz, 1 H, H-3'), 3.54 (d, J = 6 Hz, 2 H, H-5'), 3.49 (dd, J = 5, 7 Hz, 1 H, H-2'), 3.13 (dt, J = 7, 9 Hz, 1 H, H-1'), 2.15 (m, 1 H, H-6'), 2.05 (m, 1 H, H-4'), 1.06 (m, 1 H, H-6'); ^{13}C NMR (75.453 MHz, CD_3OD) 80.59 (C-2'), 74.52 (C-3'), 64.96 (C-5'), 57.13 (C-1'), 46.99 (C-4'), 32.97 (C-6'). Anal. Calcd for $C_6H_{13}NO_3$ (147.18): C, 48.97; H, 8.90; N, 9.52. Found: C, 48.88; H, 9.00; N, 9.33.

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Registry No. (±)-1, 13190-75-5; (−)-1, 19186-33-5; **7**, 34822-90-7; **8**, 39939-07-6; **10**, 100021-11-2; **11**, 100021-12-3; **12**, 100021-13-4;

13, 100021-14-5; 14, 100021-15-6; 15, 100021-16-7; (-)-15, 100101-50-6; 16, 100021-17-8; 18, 100021-18-9; 19, 100021-19-0; 20, 100021-20-3; 21, 100021-21-4; 22, 100021-22-5; 23, 100021-23-6; 24, 100021-24-7; 25, 24587-86-8; 26, 100021-25-8; 27, 100101-49-3; 28, 100021-26-9; 29, 100021-27-0; 30, 100021-28-1; 31, 85026-59-1; cyclopentadiene, 542-92-7; benzyl chloromethyl ether, 3587-60-8; 5-amino-4,6-dichloropyrimidine, 5413-85-4; diethoxymethyl acetate, 14036-06-7; adenine, 73-24-5.

^{1}H NMR 2D Conformational Study of 2-Selenated 3-Substituted Cyclohexanones. Evidence of Trans Diaxial Conformers

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Syntheses of various cis and trans 2-phenylseleno 3-substituted cyclohexanones (**1–4**) are described as well as related ketals (**5–6**). The ^{1}H NMR 2D study shows that the 2-SePh group is located in axial position in both cis (**1–4c**) and trans (**1**, **2**, and **4t**) ketones, the cyclohexanone ring adopting a chair conformation; the two substituents lie in axial position in the trans isomer while a twist-boat is observed for the **3t** isomer. The stabilization of a single conformation was explained by a balance between electronic effect (π–σ^* interaction) and steric effects. On the contrary, in the trans ketals (**5–6t**) the 2-SePh moves to the equatorial position while in the corresponding cis isomers (**5–6c**) it remains in the axial position. The phenylseleno group elimination leading to α,β-unsaturated enones (**13–16**) was also examined.

In our previous work we have shown that conjugate addition of lithiated carbanionic species as a masked benzoyl group on 2-methyl-2-cycloalkenones led exclusively to cis 1,4 adducts.[1a] Moreover, under mild deprotection conditions we have been able to obtain the corresponding γ-diketones retaining the cis stereochemistry.

On the other hand, the trans 2,3-disubstituted cycloalkanones can be obtained by conjugate addition of benzoyl precursors followed by methyl iodide enolate trapping.[1b]

We now examine the influence of the phenylseleno group as the 2-substituent on the stereochemistry of these reactions. The choice of this group seemed particularly interesting from a synthetic point of view since it gives access to 3-substituted 2-cyclohexenones,[2,3] some of which were still unknown.

The unexpected conformational behavior of the obtained 2,3-disubstituted cyclohexanones led us to study compounds bearing a 3-alkyl or 3-aryl substituent and to examine the influence of the carbonyl group by protecting it as dioxolane.

The configurational and conformational analysis of the various cis and trans 2-phenylseleno 3-substituted cyclohexanones and corresponding ketals are made by ^{1}H 2D NMR. Furthermore, the structural information allows us to examine the phenylseleno group elimination.

Synthesis of the Various Compounds. 1,4-Adducts were prepared by conjugate addition of nucleophiles either to 2-(phenylseleno)-2-cyclohexenone (**7**) followed by protonation (method 1) or to 2-cyclohexenone (**8**), followed by enolate PhSeBr trapping (method 2)[4,5] (Scheme I). The structural assignments of the cis **1–6c** and trans **1–6t** isomers will be discussed later on. The ratios of isomers were determined by ^{1}H NMR 400-MHz integration of the H_2 signals.

According to the literature,[6] the addition of Me_2CuLi (**9**) to **7** has been realized in ether, followed by quenching with NH_4Cl saturated aqueous solution (method 1a). A mixture of compounds in which the trans isomer is highly predominent (**1t**/**1c** = 95/5) has been obtained. Use of $Me_2CuCNLi_2$ (**10**) and quenching with a solution of 10% NH_4OH/90% NH_4Cl (method 1b)[7] gave identical results. After simple preparative thin-layer chromatography on SiO_2 the obtained **1t**/**1c** mixture in a 35/65 ratio corresponds very likely to the thermodynamic equilibrium, since it remains unchanged after several chromatographies. Compounds **2** were obtained from $Ph_2CuCNLi_2$ (**11**): method 1 gives a **2c**/**2t** cis/trans mixture in a 45/55 ratio, while method 2 leads exclusively to the trans isomer **2t**. Attempts of purification of either the **2t**/**2c** mixture or **2t** alone by column chromatography on silica gel led to the same **2c**/**2t** = 60/40 mixture. This ratio corresponds to the thermodynamic equilibrium as it was mentioned above for compounds **1c** and **1t**.

The reaction of lithiated *N*-(dimethylamino)phenylacetonitrile **12** on **7** followed by protonation with saturated NH_4Cl solution leads exclusively to the cis isomer, in accordance with our previous results.[1] Our inability to epimerize **3c**, due to the known fragility of the amino nitrile group, led us to synthesize the trans isomer **3t** by method 2. It is well-known[1,8,9] that amino nitriles can be easily

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