column contained a white solid (0.25 g), which was shown by ^1H NMR to be a 70:30 mixture of **24** and **25**. The total yields of **24** and **25** were 0.45 g (10%) and 0.10 g (3%), respectively.

3,6-Dichloro-β,β-dimethyl-4-pyridazineethanol (24) from Aldehyde and No Silver Catalysis. To an 80 °C solution of concentrated H_2SO_4 (0.33 mL, 0.006 mol) in H_2O (10 mL) were added 3-hydroxy-2,2-dimethylpropionaldehyde (**27**) (2.55 g, 0.025 mol) and **1** (0.75 g, 0.005 mol). A solution of ammonium persulfate (5.7 g, 0.025 mol) in H_2O (15 mL) was added dropwise over 10 min. Gas evolution and a temperature increase to 100 °C accompanied the addition. After 1 h at 90 °C, TLC showed **1** still present, so additional **27** (0.51 g, 0.005 mol) and ammonium persulfate (1.1 g, 0.005 mol) were added, and the reaction mixture was stirred at 90 °C for 1 h. The reaction mixture was cooled and extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were washed with H_2O (20 mL) and saturated $NaHCO_3$ (20 mL), dried (Na_2SO_4), and evaporated to an orange oil. Flash chromatography on silica gel (100 g) with 70/30 hexane–EtOAc gave a white solid (0.43 g, 40%), which was shown by ^1H NMR spectroscopy to be an 80/20 mixture of **24** and **25**.

3,6-Dichloro-4-(2-chloro-1,1-dimethylethyl)pyridazine (3). To a stirred solution of alcohol **24** (11.05 g, 0.05 mol), dry pyridine (5.4 mL, 0.067 mol), and toluene (60 mL) was added $SOCl_2$ (4.9 mL, 0.067 mol) over 1 min. The solution was heated at 75 °C under N_2 for 16 h and cooled to 25 °C; 1 N HCl (30 mL) and toluene (20 mL) were added. The layers were separated, the toluene layer was washed with H_2O (30 mL) and brine (30 mL) and dried (Na_2SO_4), and the toluene was removed under vacuum to leave yellow crystals (9.62 g). Recrystallization from *i*-PrOH gave white crystals of **3** (8.57 g, 76%, 2 crops), mp 68–70 °C, identical with that obtained earlier.

3,6-Dichloro-β,β-dimethyl-4-pyridazineethanol, 4-Methylbenzenesulfonate Ester (29). T a stirred slurry of *p*-toluenesulfonyl chloride (10.48 g, 0.055 mol) in dry pyridine (5 mL) was added a solution of **24** (11.05 g, 0.050 mol) in pyridine (40 mL) over 10 min. The reaction mixture was stirred under N_2 at 25 °C for 17 h. CH_2Cl_2 (50 mL) was added, and the mixture was cooled to 0 °C. Concentrated HCl (45 mL) was added dropwise, while the temperature was kept below 25 °C. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (50 mL). The combined organic layers were washed with H_2O (2 × 50 mL) and brine (50 mL) and dried over Na_2SO_4. Solvent evaporation gave a light yellow oil (17.76 g), which crystallized upon standing. Recrystallization from *i*-PrOH (65 mL) gave **29** as white crystals (14.95 g, 80%), mp 111–113 °C: IR (KBr) 2920, 1595, 1560, 1485, 1358, 1350, 1310, 1190, 1146, 978, 847, 818 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.59 (dd, J_1 = 9 Hz, J_2 = 2 Hz, 2 H), 7.36 (s, 1 H), 7.28 (dd, J_1 = 9 Hz, J_2 = 2 Hz, 2 H), 4.34 (s, 2 H), 2.44 (s, 3 H), 1.45 (s, 6 H). Anal. Calcd for $C_{15}H_{16}Cl_2N_2O_3S$: C, 48.01; H, 4.30; N, 7.46; S, 8.54. Found: C, 48.09; H, 4.31; N, 7.47; S, 8.74.

3,6-Dichloro-4-(2-bromo-1,1-dimethylethyl)pyridazine (30). Oven-dried LiBr (13.92 g, 0.16 mol) and **29** (37.5 g, 0.10 mol) were added to dry DMSO (100 mL). The mixture was heated at 110 °C under N_2 for 2 h and cooled to 25 °C. H_2O (100 mL) was added dropwise, and a solid was collected and washed with H_2O (3 × 50 mL). Vacuum drying at 45 °C gave 27.74 g (97%). Recrystallization from *i*-PrOH (55 mL) gave white crystals (25.92 g, 91%) of **30**, mp 86.5–88.5 °C: IR (KBr) 1560, 1390, 1372, 1354, 1310, 1248, 1158, 1140, 1107 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.48 (s, 1 H), 3.95 (s, 2 H), 1.63 (s, 6 H). Anal. Calcd for $C_8H_9BrCl_2N_2$: C, 33.84; H, 3.19; Br, 28.14; Cl, 24.97; N, 9.86. Found: C, 33.89; H, 3.10; Br, 29.12; Cl, 25.43; N, 9.80.

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Total Synthesis of (–)-Neplanocin A

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An efficient synthesis of neplanocin A, which is easily adaptable for the preparation of other cyclopentenyl containing nucleoside isosteres, has been developed. This enantioselective synthesis provides control of two of the three chiral centers of neplanocin A by constructing the carbocyclic ring portion of the molecule (compound **10a**) from optically pure D-ribonolactone (**9**). The last chiral center is constructed by the regiospecific reduction of the intermediate cyclopentenone **10a** to the α allylic alcohol **8a**, followed by the inversion of this center to the required β stereochemistry by S_N2 displacement with LiN_3 or the sodium salt of 6-chloropurine. The resulting cyclopentenyl azide (**15**) and the cyclopentenyl purine (**17a**) were both converted to (–)-neplanocin A.

Carbocyclic nucleosides are biologically interesting materials that sometimes display important antitumor or antiviral activities.[1–4] Because of the absence of a true glycosidic bond, carbocyclic nucleosides are chemically more stable and not subject to the action of the enzymes that cleave this linkage in conventional nucleosides.[1–4] A remarkable change in the biological activity of some of these pseudonucleosides occurs when the cyclopentane ring is modified into a cyclopentene ring. This structural change is usually accompanied by an increase in the biological potency and specificity of the unsaturated compounds when compared to the corresponding saturated carbocyclic analogues. Such phenomenon was first observed after the isolation and evaluation of neplanocin A, which proved to have superior antitumor and antiviral properties compared with its saturated counterpart aristeromycin (Figure 1).[5–8] Since the isolation of neplanocin

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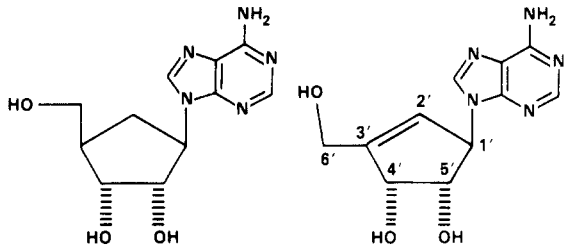
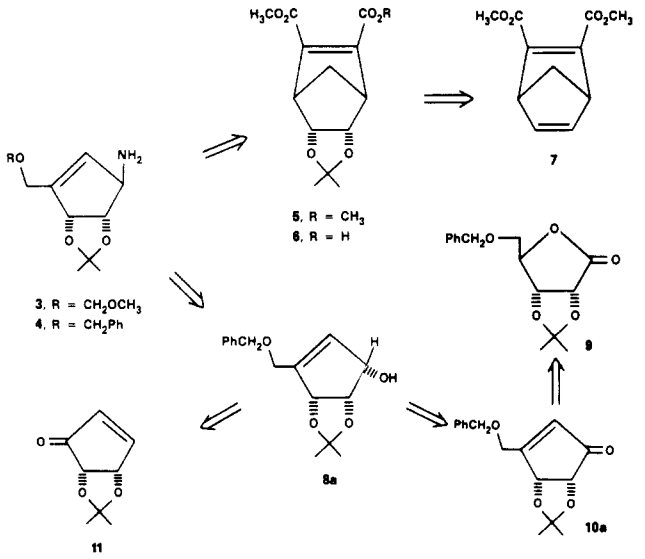


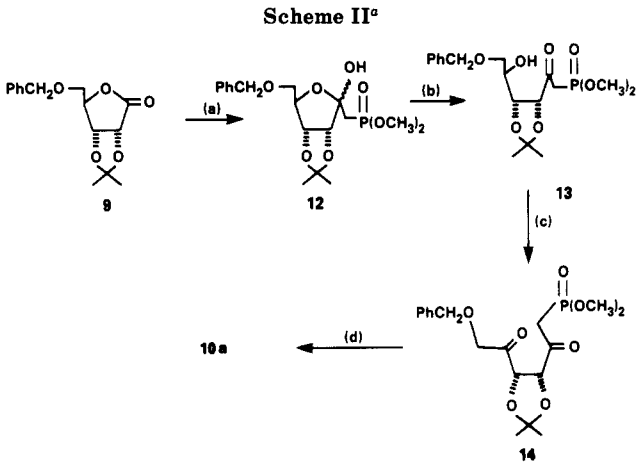
Figure 1. Structures of (−)-aristeromycin (1) and (−)-neplanocin A (2).

Scheme I



A,[5] numerous studies have been performed in which the unique activity of this substance has been confirmed.[9-21] Moreover, the incorporation of the same unsaturated carbocyclic "sugar" has been extended to other non-naturally occurring carbocyclic nucleosides with similar results in terms of pharmacological selectivity and potency.[14,22-28]

Scheme II[a]



[a] (a) $LiCH_2P(O)(OCH_3)_2$; (b) $NaOCH_3$; (c) CrO_3/pyridine; (d) K_2CO_3/18-crown-6.

The unusual presence of the double bond in neplanocin A, as expected, attracted also a great deal of interest from synthetic organic chemists. Thus far, four total syntheses of neplanocin A have been reported, three of which are enantioselective.[29-32]

The first enantioselective synthesis, developed by Ohno and co-workers in Japan[29] originated from the known diester **5**, which was constructed via cis hydroxylation of the Diels–Alder adduct **7** (Scheme I). The success of Ohno's approach was based on the selective hydrolysis of **5** by pig liver esterase, which generated the half-ester **6** in optically active form. By a series of steps this half-ester intermediate was converted to the cyclopentenylamine **3**, which served as a direct precursor of neplanocin A (Scheme I).

The second enantioselective synthesis of neplanocin A was developed in our laboratory and was reported in brief in a previous communication.[30] In the present paper, we report the detailed methodology of this approach, which has the additional advantage of being simpler and easily adaptable to large-scale syntheses of neplanocin A and other cyclopentene-containing carbocyclic nucleosides. Our strategy was conceptually different from that of Ohno et al. in that we utilized a chiral carbohydrate precursor to gain control of the three stereochemical centers of the molecule. The success of our approach hinged upon an efficient synthesis of **10a**, from either D-ribose or the protected D-ribonic acid lactone (**9**), from which the cyclopentenylamine **4** was to be stereoselectively generated (Scheme I).

The last and most recently reported enantioselective synthesis of neplanocin A was reported by Johnson and co-workers.[32] This synthesis converged with ours at the

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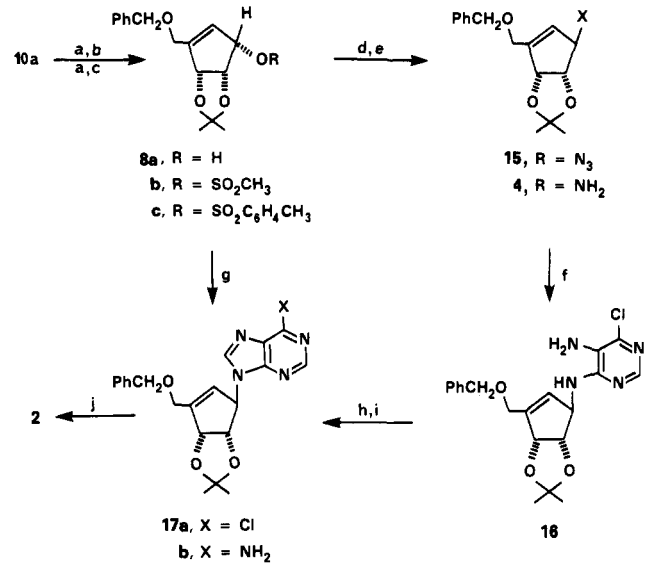
same cyclopentenol intermediate **8a**, which was generated from cyclopentenone **11** (Scheme I).

The first and most critical part of our synthetic approach is outlined in Scheme II. Commercially available D-ribono-1,4-lactone was sequentially protected with the isopropylidene and benzyl moieties in essentially the same manner as reported in the literature.[33] Treatment of the resulting (−)-5-*O*-benzyl-2,3-*O*-isopropylidene-D-ribonolactone (**9**) with lithium dimethyl methylphosphonate in THF gave a quantitative yield of the hemiketal **12**. Subsequent opening of this hemiketal intermediate to the keto phosphonate **13** was accomplished with sodium methoxide in methanol. Compound **13** is simply the open-chain tautomer of **12** which under acidic conditions can recyclize back to the hemiketal. For this reason, the reaction mixture was carefully neutralized to pH 7 before proceeding with the extraction of **12** into ethyl acetate. Oxidation of **13** with modified Collins reagent produced the diketo phosphonate **14**, which underwent intramolecular cyclization to the desired cyclopentenone **10a**. When this reaction was examined more closely, a partial base catalyzed epimerization of carbons 3 and 4 in the starting diketone **14**, which accounted for an observed partial racemization of the cyclopentenone product, was uncovered. Fortunately, the racemic material (**10b**) crystallized preferentially from a mixture of ether and petroleum ether, while the pure enantiomer **10a** remained in solution. The enantiomerically pure cyclopentenone (**10a**), which was eventually converted to (−)-neplanocin A, was isolated as a yellow oil in 35% yield. Despite the low yield of the final cyclization step, kilogram amounts of the cyclopentenone **10a** have been prepared by this procedure. Two years after our initial report was communicated, Altenbach et al. in West Germany published an identical approach to cycloalkenones from γ and δ lactone precursors.[34]

The stereochemistry of the starting ribonolactone **9** insured that the stereochemistry of carbons 4 and 5 of this cyclopentenone **10a** was the same as that of neplanocin A (see Figure 1). On the other hand, the remaining chiral center of neplanocin A was to be determined by the outcome of the reduction of the prochiral enone carbonyl in **10a**. In order to achieve the desired chirality at this center, the reduction of this carbonyl had to proceed both regioselectively (1,2 reduction rather than 1,4 reduction) and stereoselectively to the α-allylic alcohol. In practice, as shown in Scheme III, the stereoselective reduction of the cyclopentenone **10a** proceeded as desired due to the concave–convex nature of its bicyclic [3.3.0] ring system. This molecule allowed the incoming hydride to approach exclusively from the less congested convex β face to give a single product (**8a**). In fact, when the same reduction was performed with a cyclopentenone substrate whose 4- and 5-hydroxyl groups were protected with acetyl groups, rather than with the isopropylidene moiety, the two possible epimeric alcohols were obtained. The presence of $CeCl_3$ in the reaction promoted the required 1,2 addition in this concave–convex molecule in agreement with results obtained with other systems.[35,36] The desired α epimeric alcohol **8a** was readily mesylated, and the mesyl group was nucleophilically displaced with lithium azide to give the inverted allylic azide **15** with the required β stereochemistry. Reduction of the azide functionality was initially

Scheme III[a]



[a] (a) $NaBH_4/CeCl_3$; (b) CH_3SO_2Cl; (c) p-CH_3PhSO_2Cl; (d) LiN_3; (e) Lindlar catalyst/H_2; (f) 5-amino-4,6-dichloropyrimidine; (g) 6-chloropurine sodium salt; (h) $HC(OEt)_3/HCl$; (i) $NH_3/MeOH$; (j) BCl_3/CH_2Cl_2.

performed with 1,3-propanedithiol;[30] however, it was more conveniently accomplished by hydrogenation over Lindlar catalyst, which did not affect the double bond. As the resulting cyclopentenylamine **4** was not very stable, it was used immediately in the construction of the purine ring of neplanocin A by a standard three-step sequence (Scheme III).[37] Condensation of **4** with 5-amino-4,6-dichloropyrimidine, ring closure with triethyl orthoformate, and ammonolysis afforded protected neplanocin A. Simultaneous removal of benzyl and isopropylidene groups with BCl_3 in dichloromethane at −78 °C, followed by neutralization with ammonia, afforded synthetic neplanocin A, identical with natural neplanocin A (^1H NMR, ^{13}C NMR, FAB-MS, IR, UV, and TLC analyses and specific rotation). The synthetic material likewise displayed the expected cytotoxicity (ID_{50} 6.5 μM) against P388 cells in culture.

In a simpler approach, the direct alkylation of the sodium salt of 6-chloropurine with either the mesylate (**8b**) or the corresponding tosylate (**8c**) afforded a 30% yield of the cyclopentenyl-6-chloropurine **17a** (Scheme III).[38] Small amounts of either unreacted or degraded tosylate were isolated as part of the reaction mixture, and the amount of N-7 isomer detected by TLC was insignificant.[38] Treatment of the resulting **17a** with methanolic ammonia and deprotection of the resulting product with BCl_3 afforded neplanocin A in essentially the same overall yield as with the previous approach, but with the additional economy of time and reagents.

The key features of our methodology can be summarized as follows: (1) the ready access of cyclopentenone **10a** from an abundant chiral precursor, such as D-ribose or its ribonolactone, to secure the stereochemistry at carbons 4′ and 5′ on neplanocin A; (2) the stereo- and regioselective reduction of the enone carbonyl system in **10a** to provide the means of controlling the third chiral center of neplanocin A; and (3) the use of the unsaturated mesylate or tosylate **8b,c** to introduce directly and stereospecifically

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either a preformed purine ring system or a functional group that permitted the ready construction of the aglycon.

Experimental Section

All chemical reagents were commercially available. Melting points are uncorrected. Proton and ^{13}C NMR spectra were recorded at 200 and 50 MHz, respectively. The ^{13}C NMR peak positions were determined by reference to dioxane (δ 67.3). Positive-ion fast atom bombardment (FAB) mass spectra were obtained by using samples dissolved in a glycerol matrix, and ionization was effected by a beam of xenon atoms derived by neutralizing xenon ions accelerated through 8.6 kV. Normal-phase column chromatography was run on silica gel (J. T. Baker 60–200 mesh), and analytical TLC was performed on Analtech Uniplates silica gel GF with the solvents indicated for the individual experiments.

2,3-*O*-Isopropylidene-D-ribono-1,4-lactone. This compound was prepared in 75% yield according to the procedure of Hough, Jones, and Mitchell, mp 133–136 °C (lit.[39] mp 138–139 °C).

(−)-5-*O*-Benzyl-2,3-*O*-isopropylidene-D-ribono-1,4-lactone (9). A solution of 2,3-*O*-isopropylidene-D-ribono-1,4-lactone (35 g, 186 mmol) in THF (280 mL) was cooled to 0 °C, and a 50% sodium hydride dispersion (10.71 g, 223 mmol) was added to it portionwise over 15 min. Benzyl bromide (26.5 mL, 223 mmol) was then added slowly over 1 h, while the temperature was maintained between 0 and 2 °C. After such time, the mixture was warmed slowly to room temperature (1 h) and allowed to stir overnight. Ice was added slowly to destroy the excess of hydride, and the mixture was then poured into ice–water. After a methylene chloride extraction, the organic layer was washed with 10% brine and water and finally dried ($MgSO_4$) and reduced to dryness. The residue was chromatographed (flash) over silica gel with petroleum ether and ethyl acetate (5:1) as eluants. The product-containing fractions were combined and concentrated to give 30.14 g (58%) of compound **9** as an oil: $[\alpha]^{24}_D$ −44° (*c* 1.7, $CHCl_3$) [lit.[33] $[\alpha]^{24}_D$ −50° (*c* 0.8, $CHCl_3$)]. Both IR and ^1H NMR spectra agreed exactly with the published data.[33] Anal. Calcd for $C_{15}H_{18}O_5$: C, 64.74; H, 6.52; O, 28.74. Found: C, 64.89; H, 6.77; O, 28.46.

(−)-6-*O*-Benzyl-1-deoxy-1-(dimethylphosphono)-3,4-*O*-isopropylidene-D-*ribo*-hexofuranose (12). Dimethyl methylphosphonate (52 mL, 484 mmol) was dissolved in anhydrous THF (250 mL), and the stirred solution was cooled to −70 °C under a nitrogen atmosphere. *n*-Butyllithium (250 mL, 403 mmol, 1.6 M solution in hexane) was added to the above solution over a 0.5-h period, while the temperature was maintained at −70 °C. A solution of **9** (44.9 g, 161 mmol) in THF (100 mL) was then added dropwise to the resulting mixture over a 40-min period at the same temperature. After the addition was complete, the reaction mixture was allowed to warm to 0 °C over a period of 2 h, and the pH was adjusted to 7 with glacial acetic acid. The resulting mixture was partitioned between 10% brine and ethyl acetate, and the organic layer was then washed twice with water and dried ($MgSO_4$). The residue obtained from the organic phase was chromatographed (flash) over silica gel with petroleum ether and ethyl acetate (3:1), followed by methylene chloride and methanol (20:1), to give 64 g (98.6%) of the hemiketal **12** as a yellow syrup. A second chromatography afforded a purer product, which solidified on standing. This solid was dissolved in ether and cooled to −40 °C to produce crystalline **12**: mp 54–56 °C; $[\alpha]^{24}_D$ −14.0° (*c* 0.93, $CHCl_3$); IR (neat) 3350 (broad, m), 3000 (m), 2950 (m), 2850 (m), 1450 (m), 1380 (m), 1200 (broad, s), 1060 (broad, s), 870 (m), 820 (m), 740 (m), and 700 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 and 1.40 (s, 3 H, CH_3), 2.41 (m, 2 H, $CH_2PO(OCH_3)_2$), 3.64 (br d, 2 H, H-6a,b), 3.75 (d, J = 11 Hz, 3 H, $PO(OCH_3)$), 3.83 (d, J = 11 Hz, 3 H, $PO(OCH_3)$), 4.30 (t, J = 6 Hz, 1 H, H-4), 4.55 (d, J = 5 Hz, 1 H, H-5), 4.60 (br d, 2 H, OCH_2Ph), 4.80 (d, J = 6 Hz, 1 H, H-3), 5.60 (s, 1 H, OH), 7.38 (br s, 5 H, Ph). Anal. Calcd for $C_{18}H_{27}O_8P$: C, 53.73; H, 6.73; P, 7.69. Found: C, 53.79; H, 6.93; P, 7.79.

(3*R*,4*R*)-(−)-6-*O*-Benzyl-1-deoxy-1-(dimethylphosphono)-3,4-*O*-isopropylidene-D-*ribo*-hexulose (13). The hemiketal intermediate **12** (143 g, 355 mmol) was dissolved in anhydrous methanol (400 mL). A solution of sodium methoxide (50.5 g, 935 mmol) was added portionwise while the temperature was maintained below 30 °C. Stirring was continued at room temperature for 24 h. The reaction mixture was then cooled to 20 °C and neutralized to pH 7 with glacial acetic acid, and the solvent was removed under reduced pressure. The residual gum was partitioned between ethyl acetate and water, and the organic phase was washed successively with 5% brine and water. After the organic phase was dried ($MgSO_4$), it was treated with charcoal and filtered through Celite. Following the removal of the solvent, the residue was dried under vacuum, and the desired compound **13** (135 g, 95%) was obtained as a yellow syrup; $[\alpha]^{24}_D$ −8.2° (*c* 1.02, $CHCl_3$); IR (neat) 3350 (broad, s), 3000 (m), 2950 (m), 2850 (m), 1720 (s, C=O), 1600 (w), 1580 (w) 1450 (m), 1380 (m), 1260 (broad, s), 1060 (broad, s), 860 (m), 800 (m), 740 (w), and 700 (w) cm^{-1}; ^1H NMR ($CDCl_3/D_2O$) δ 1.38 and 1.46 (s, 3 H, CH_3), 3.22–4.00 (m, 4 H, H-6a,b and $COCH_2PO(OCH_3)_2$), 3.76 (d, J = 11 Hz, 6 H, $PO(OCH_3)_2$), 4.25 (t, J = 6 Hz, 1 H, H-4), 4.56 (s, 2 H, OCH_2Ph), 4.62 (d, J = 6 Hz, 1 H, H-3), 7.32 (s, 5 H, Ph). Anal. Calcd for $C_{18}H_{27}O_8P$: C, 53.73; H, 6.73; P, 7.69. Found: C, 53.79; H, 6.76; P, 8.02.

(3*R*,4*S*)-(−)-6-*O*-Benzyl-1-deoxy-1-(dimethylphosphono)-3,4-*O*-isopropylidene-D-*erythro*-2,5-hexodiulose (14). Powdered chromium trioxide (20.58 g, 206 mmol) was added to a magnetically stirred solution of pyridine (33.3 mL, 412 mmol) in methylene chloride (300 mL), which was maintained at 14 °C over an ice–water bath. The resulting burgundy solution was treated with a solution of the hydroxy ketone **13** (13.8 g, 34.3 mmol) in methylene chloride (20 mL) and stirred for 1 h while the temperature was maintained between 14 and 25 °C. The reaction mixture was then filtered through a silica gel pad with the aid of ethyl acetate and acetone (2:1), and the collected organic solvents were removed under reduced pressure. The residue was chromatographed (flash) over silica gel with methylene chloride and methanol (30:1) as eluant. The product-containing fractions were collected to afford the diketone **14** (11.0 g, 80%) as a colorless oil: $[\alpha]^{24}_D$ −14.1° (*c* 1, $CHCl_3$); IR (neat) 3300 (broad, w), 3000 (m), 2950 (m), 2850 (m), 1730 (s, C=O), 1600 (w), 1450 (m), 1380 (m), 1260 (m), 1210 (w), 1030 (broad, s), 860 (m), 740 (m), and 700 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (s, 6 H, CH_3), 3.10–3.60 (m, 2 H, $COCH_2P$), 3.70 (d, J = 11 Hz, 6 H, $PO(OCH_3)_2$), 4.35 (d, J = 18 Hz, 1 H, H-6a), 4.50 (d, J = 18 Hz, 1 H, H-6b), 4.63 (s, 2 H, OCH_2Ph), 4.70 (m, 2 H, H-3 and H-4), 7.25 (br s, 5 H, Ph). This material was used in the next step without further purification.

(4*R*,5*R*)-(−)-3-[(Benzyloxy)methyl]-4,5-*O*-isopropylidene-2-cyclopentenone (10a) and (±)-3-[(Benzyloxy)methyl]-4,5-*O*-isopropylidene-2-cyclopentenone (10b). A stirred mixture of powdered potassium carbonate (8.3 g, 60 mmol) and 18-crown-6 ether (6.6 g, 35 mmol) in anhydrous benzene (300 mL) was placed under a nitrogen atmosphere and heated to 56 °C (internal). A solution of the diketone **14** (20 g, 50 mmol), previously azeotroped with benzene (2 × 40 mL), was dissolved in anhydrous benzene (50 mL) and added in one portion to the previous mixture and stirred for 40 min at the same temperature. After cooling, the mixture was filtered, and the filtrate was poured into ether (300 mL). The resulting mixture was washed with water (3 × 130 mL), and the organic phase was dried ($MgSO_4$) and filtered. The filtrate was concentrated under reduced pressure to give a greenish oil. Chromatography (flash) over silica gel with petroleum ether and ether (9:1, 8:2, 7:3, 4:6) as eluants gave pure, partially racemic cyclopentenone (8.4 g, 61%) as a yellow oil, which partially solidified on cooling.

Isomer Separation To Obtain 10a and Its Racemate 10b. The partially racemic compound (8.4 g) was stirred with a mixture of petroleum ether and ether (20 mL, 4:6) for 1 h with cooling over an ice–water bath. The solid that precipitated was collected by filtration, washed with cold petroleum ether, and dried to give pure racemic compound **10b** (2.6 g, 19%), mp 59–61 °C, zero optical rotation. The filtrate was concentrated, and the yellow oil obtained was dried under vacuum to constant weight to afford optically pure cyclopentenone **10a** (5.8 g, 42%): $[\alpha]^{24}_D$ −7.2° (*c* 1.1, $CHCl_3$); IR ($CHCl_3$) 2900 (m), 1720 (s), 1620 (s), 1440 (m), 1375 (s), 1220 (m), 1040 (s), 970 (m), and 880 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.39 (s, 6 H, CH_3), 4.32 (dd, J_{gem} = 17.5 Hz, J' = 1.5

(39) Hough, L.; Jones, J. K. N.; Mitchell, D. L. *Can. J. Chem.* **1958**, *36*, 1720.

Hz, 1 H, CHOCH$_2$Ph), 4.48 (dd, J_{gem} = 17.5 Hz, J' = 1.5 Hz, 1 H, CHOCH$_2$Ph), 4.50 (d, J = 5.5 Hz, 1 H, H-4), 4.61 (s, 2 H, OCH$_2$Ph), 5.08 (d, J = 5.5 Hz, 1 H, H-5), 6.18 (t, J = 1.5 Hz, 1 H, H-2), 7.34 (m, 5 H, Ph). Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.05; H, 6.61; O, 23.33. Found: C, 69.91; H, 6.59; O, 23.10.

(1*S*,4*R*,5*S*)-(−)-3-[(Benzyloxy)methyl]-4,5-*O*-isopropylidene-2-cyclopenten-1-ol (8a). Sodium borohydride (2.3 g, 87 mmol) was added portionwise to a solution of **10a** (15.5 g, 56 mmol) and cerium(III) chloride heptahydrate (17.5 g, 47 mmol) in methanol (100 mL), while the temperature was maintained between 0 and 5 °C. After 10 min, acetic acid was added cautiously to adjust to pH 5. Water (100 mL) was added, and the mixture was extracted with ether (3 × 100 mL). The organic extract was washed with brine (3 × 50 mL) and dried ($MgSO_4$). The solvent was evaporated to give 15.2 g (97%) of the desired alcohol **8a** as an oil. On TLC (silica gel, chloroform/methanol, 9:1) the product was observed as a major spot (R_f = 0.61) with a slight trace of faster and slower moving impurities. This material was used as such in the next step.

(1*S*,4*R*,5*S*)-(−)-3-[(Benzyloxy)methyl]-4,5-*O*-isopropylidene-2-cyclopenten-1-ol Methanesulfonate (8b). Methanesulfonyl chloride (6.1 mL, 76 mmol) was added slowly to a solution of the carbinol **8a** (15 g, 54 mmol) and triethylamine (22 mL, 160 mmol) in methylene chloride (150 mL), while the temperature was maintained between −5 and 0 °C. After the addition was completed, the mixture was stirred for 10 min, washed with cold water (2 × 60 mL), washed with brine (2 × 60 mL), and dried ($MgSO_4$). The solvent was evaporated to give the mesylate **8b** (19.2 g, 100%) as a tan solid. On TLC (silica gel, ethyl acetate/petroleum ether, 1:2) the product was developed as one spot (R_f = 0.39) with a slight trace of faster and slower moving impurities. This material was used as such in the next step.

(1*S*,4*R*,5*S*)-(−)-3-[(Benzyloxy)methyl]-4,5-*O*-isopropylidene-2-cyclopenten-1-ol *p*-Toluenesulfonate (8c). Tosyl chloride (0.15 g, 0.787 mmol) was added at once to a solution of the carbinol **8a** (0.109 g, 0.394 mmol) and triethylamine (ca. 0.23 mL, 1.6 mmol) in methylene chloride (1 mL). The resulting reaction mixture was stirred at room temperature for 17 h and quenched by the addition of water (2 mL). The separated aqueous phase was washed with methylene chloride and the organic extracts were combined with the original organic solution. The resulting organic solution was purified by preparative silica gel TLC chromatography with hexane and ethyl acetate (3:2). The product (R_f = 0.53) was isolated as a single band and utilized immediately.

(1*R*,4*R*,5*S*)-(−)-1-Azido-3-[(benzyloxy)methyl]-4,5-*O*-isopropylidene-2-cyclopentene (15). Lithium azide (3.8 g, 78 mmol) was added to a solution of intermediate **8b** (19.2 g, 54 mmol) in dimethyl sulfoxide (62 mL) and hexamethylphosphorous triamide (6.2 mL). The suspension was stirred at ambient temperature overnight. Water (170 mL) was added, and the mixture was extracted into ether (4 × 300 mL). The combined organic extract was washed with brine (300 mL), dried ($MgSO_4$), and filtered. The solvent was evaporated to give 20 g of the correpsonding azide as a crude oil. Purification by column chromatography on silica gel (250 g, 50 × 250 mm, ethyl acetate/petroleum ether, 1:19) afforded the desired product **15** as a light yellow oil (12.1 g, 74%): $[\alpha]^{24}_D$ −145° (*c* 1.0, ethanol); IR ($CHCl_3$) 2120 cm^{-1} (N_3); ^{1}H NMR ($CDCl_3$) δ 1.34 and 1.38 (s, 3 H, CH$_3$), 4.16 (s, 2 H, H-6a,b), 4.35 (s, 1 H, H-1), 4.57 (m, 3 H, OCH$_2$Ph and H-5), 5.11 (d, J = 5.5 Hz, 1 H, H-4), 5.75 (s, 1 H, H-2), 7.34 (m, 5 H, Ph). On TLC (silica gel, ethyl acetate/petroleum ether, 1:19) the product was developed as one spot (R_f = 0.39). This product was used as such in the next step of the sequence.

(1*R*,4*R*,5*S*)-(−)-1-Amino-3-[(benzyloxy)methyl]-4,5-*O*-isopropylidene-2-cyclopentene (4). Lindlar's catalyst (4.8 g) was added to a solution of the azide **15** (11.9 g, 40 mmol) in 1-butanol (120 mL). The mixture was hydrogenated at 1 atm for 3 h during which time the mixture was purged with fresh hydrogen at 30-min intervals. The mixture was filtered, and the catalyst was washed with 1-butanol (40 mL). The butanolic solution of the amine **4** was immediately used in the next step without further purification. A small sample of **4** gave a consistent NMR spectrum: ^{1}H NMR ($CDCl_3$) δ 1.34 and 1.39 (s, 3 H, CH$_3$), 1.57 (br s, 2 H, NH$_2$), 3.93 (s, 1 H, H-1), 4.14 (s, 2 H, H-6a,b), 4.38 (d, J = 5.5 Hz, 1 H, H-5), 4.57 (s, 2 H, OCH$_2$Ph), 5.18 (d, J = 5.5 Hz, 1 H, H-4), 5.73 (s, 1 H, H-2), 7.34 (m, 5 H, Ph).

(1*R*,4*R*,5*S*)-(−)-1-[(5-Amino-6-chloropyrimidinyl)-amino]-3-[(benzyloxy)methyl]-4,5-*O*-isopropylidene-2-cyclopentene (16). Triethylamine (59 mL, 420 mmol) was added to a mixture of the cyclopentenylamine **4** (from 11.9 g of azide, 40 mmol) and 5-amino-4,6-dichloropyrimidine (16.4 g, 100 mmol) in 1-butanol (200 mL). The solution was refluxed under nitrogen for 20 h. The solvent was evaporated, and the residue was partitioned between water (100 mL) and methylene chloride (600 mL). The organic layer was dried (K_2CO_3), and the solvent was evaporated. When the dark residue (25 g) was dissolved in warm methylene chloride (40 mL), part of the unreacted 2,4-dichloropyrimidine crystallized upon cooling to room temperature. This was separated and the dark mother liquor was concentrated to about 15 mL. This material was purified by column chromatography on silica gel (300 g, 50 × 350 mm) with ethyl acetate and petroleum ether (1:2) as the eluant mixture. Fractions containing the product were combined and evaporated to give 9 g of crystalline material. This material was recrystallized from a mixture of ethyl acetate and petroleum ether (1:2) to give compound **16** (8.6 g, 54%) as a colorless solid: mp 132–133 °C; $[\alpha]^{24}_D$ −68.6° (*c* 0.92, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.30 and 1.38 (s, 3 H, CH$_3$), 3.55 (br s, 2 H, NH$_2$), 4.10 (s, 2 H, H-6′a,b), 4.40 (d, J = 5 Hz, 1 H, H-5′), 4.45 (s, 2 H, OCH$_2$Ph), 5.05 (m, 2 H, H-1′, H-4′), 5.60 (s, 1 H, H-2′), 7.20 (m, 5 H, Ph), 7.95 (s, 1 H, H-2). Anal. Calcd for $C_{20}H_{23}ClN_4O_3$: C, 59.62; H, 5.76; Cl, 8.80; N, 13.91. Found: C, 59.42; H, 5.75; Cl, 8.87; N, 14.02.

(−)-9-[(1*R*,4*R*,5*S*)-3-[(Benzyloxy)methyl]-4,5-*O*-isopropylidene-2-cyclopenten-1-yl]-6-chloropurine (17a). Method A. A mixture of intermediate **16** (8.5 g, 21 mmol), triethyl orthoformate (75 mL), and concentrated hydrochloric acid (10 drops) was stirred at room temperature for 42 h. The reaction, while not complete, was terminated by adding triethylamine (4 mL). Excess orthoformate was evaporated (vacuum pump, 30 °C), and the residual product was purified by silica gel column chromatography with ethyl acetate and petroleum ether (1:2) as the eluant mixture. The early fractions contained both unreacted starting material and product (1.6 g). Fractions containing pure product (TLC silica gel, developed with a 10:1 mixture of methylene chloride and methanol, R_f = 0.68) were evaporated to give the desired purine **17a** (7 g) as a syrup. The mixture from the early fractions was dissolved in triethyl orthoformate (15 mL) and treated with concentrated HCl (5 drops). After 24 h at room temperature, the reaction was complete, and the product was isolated by column chromatography as described above. The combined yield of **17a** was 8.5 g (97%), which was used as such in the following step. A portion of this syrup (1.2 g) was dissolved in ether (10 mL), and the solution was diluted with petroleum ether (bp 30–60 °C, 15 mL). After the solution was stored in the freezer for several days, a white crystalline product was obtained, which was further recrystallized from a mixture of ether and petroleum ether (1:1) to give 700 mg of **17a**: mp 55–58 °C; $[\alpha]^{24}_D$ −51.3° (*c* 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.30 and 1.42 (s, 3 H, CH$_3$), 4.25 (m, 2 H, H-6′a,b), 4.55 (s, 2 H, OCH$_2$Ph), 4.65 (d, J = 5 Hz, 1 H, H-5′), 5.36 (d, J = 5 Hz, 1 H, H-4′), 5.55 (s, 1 H, H-1′), 5.78 (s, 1 H, H-2′), 7.20 (m, 5 H, Ph), 7.70 (s, 1 H, H-2), 8.45 (s, 1 H, H-8). Anal. Calcd for $C_{21}H_{21}ClN_4O_3$: C, 61.09; H, 5.15; Cl, 8.58; N, 13.57. Found: C, 60.96; H, 5.33; Cl, 8.69; N, 13.73.

Method B. A suspension of 6-chloropurine (0.63 g, 4.13 mmol) in anhydrous acetonitrile (10 mL, distilled over P_2O_5) was treated with 0.127 g (4.25 mmol) of NaH (80% suspension) at room temperature for 1 h. After such time, a white precipitate had formed, and the tosylate **8c** (0.51 g, 1.18 mmol) was added at once. The reaction was allowed to proceed at 50 °C for 42 h after which time TLC analysis (silica gel in a 1:1 mixture of ethyl acetate and hexane) indicated the presence of a major component (R_f = 0.38), which corresponded to the desired product. Other compounds visualized were unreacted tosylate **8c** (R_f = 0.75) and what appears to be a decomposed tosylate derivative (R_f = 0.83). After purification by preparative TLC, 0.152 g (31%) of **17a** was isolated. This material was identical in every respect with that obtained under method A.

(−)-9-[(1*R*,4*R*,5*S*)-3-[(Benzyloxy)methyl]-4,5-*O*-isopropylidene-2-cyclopenten-1-yl]adenine (17b). A solution of **17a** (3.5 g, 8.4 mmol) in dry methanol (20 mL) was placed in an

autoclave and cooled to -75 °C. Ammonia gas was bubbled through the cold solution until ca. 30 mL was condensed; the volume of the solution at this point was ca. 50 mL. The autoclave was sealed and heated at 60 °C for 18 h. The ammonia and methanol were evaporated, and the residue was dissolved in dichloromethane (150 mL). The brown solution was washed with water, dried (K_2CO_3), filtered, and evaporated to dryness. The off-white residue was dissolved in a mixture of ether (20 mL), containing dichloro methane (2 mL). Seed crystals were added, and the solution was stirred at room temperature for 2 h at which time most of the product had crystallized. The suspension was cooled to 5 °C and filtered. The white solid was washed with cold ether and air-dried to give crystalline product **17b** (2.6 g). This material was recrystallized from a mixture of dichloromethane (2.5 mL) and ether (20 mL) to give pure **17b** (2.3 g, 70%): mp 120–123 °C; $[\alpha]^{24}_D$ -57° (*c* 0.9, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.36 and 1.48 (s, 3 H, CH_3), 4.28 (s, 2 H, H-6'a,b), 4.63 (s, 2 H, OCH_2Ph), 4.74 (d, *J* = 5.5 Hz, 1 H, H-5'), 5.39 (d, *J* = 5.50 Hz, 1 H, H-4'), 5.58 (s, 1 H, H-1'), 5.83 (s, 1 H, H-2'), 6.61 (s, 2 H, NH_2), 7.34 (m, 5 H, Ph), 7.68 (s, 1 H, H-2), 8.35 (s, 1 H, H-8). Anal. Calcd for $C_{21}H_{23}N_5O_3$: C, 64.11; H, 5.89; N, 17.60. Found: C, 63.88, H, 6.13; N, 17.45.

(-)-Neplanocin A (2). The crystalline precursor **17b** (2 g, 5.1 mmol) was dissolved in dry dichloromethane (200 mL), and the solution was cooled with stirring to -75 °C. Boron trichloride in hexane (36 mL, 1 M solution) was added in one portion. The mixture was stirred at -75 °C for 2.5 h, after which time no starting material was observable by TLC. Methanol (40 mL) was added, and the clear solution was evaporated to dryness. The gummy residue was redissolved in methanol (20 mL), and the solution was evaporated; this procedure was repeated twice. The residual foam was refluxed with ether until a crystalline precipitate was obtained. After cooling, the supernatant was decanted, and the crystalline product was refluxed with a mixture of ethanol (5 mL) and ether (25 mL). The hot suspension was diluted with ether (25 mL) and cooled, and the crystalline (-)-neplanocin A hydrochloride was collected (1.8 g, a slightly hygroscopic solid). This material was dissolved in warm methanol (30 mL), and the cloudy solution was filtered through Celite. The clear filtrate was adjusted to pH 12 with ammonium hydroxide (10% aqueous solution), and the resulting solution was evaporated to dryness. The residue was refluxed with ethanol (20 mL), and crude (-)-neplanocin A (0.9 g) was separated after cooling. This material was recrystallized twice from boiling 75% aqueous ethanol to give 0.65 g (50%) of pure (-)-neplanocin A: mp 212–213 °C (lit.[5] mp 220–222 °C); $[\alpha]^{24}_D$ -153.8° (*c* 0.3, H_2O) [lit.[5] $[\alpha]^{23}_D$ - 157° (*c* 0.5, H_2O)]; ^1H NMR (Me_2SO-d_6/D_2O) δ 4.10 (s, 2 H, H-6'a,b), 4.22 (t, *J* = 5.5 Hz, H-5'), 4.40 (d, *J* = 5.5 Hz, 1 H, H-4'), 5.30 (br s, 1 H, H-1'), 5.67 (d, *J* < 1 Hz, 1 H, H-2'), 8.05 and 8.10 (s, 2 H, aromatic); ^{13}C NMR (Me_2SO-d_6/D_2O) δ 59.87, 65.88, 73.55, 78.27, 120.10, 126.30, 141.95, 150.20, 150.35, 153.62, 156.70; FAB MS, *m/z* (relative intensity) 356 (MH^+ glycerol, 10), 264 (MH^+, 100), 136 (b + 2H, 92). Anal. Calcd for $C_{11}H_{13}N_5O_3 \cdot 0.5H_2O$: C, 48.53; H, 5.18; N, 25.72. Found: C, 48.55; H, 5.13; N, 25.95.

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Electrochemical Oxidation of Polyfluoroalkyl Iodides: Direct Anodic Transformation of $C_8F_{17}CH_2CH_2I$ to Amides, Esters, and Ethers†

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The cyclic voltammetry of polyfluoroalkyl iodides of the type $R_fCH_2CH_2I$ (R_f = *n*-C_6F_{13}, *n*-C_8F_{17}, *n*-$C_{10}F_{21}$) and R_fI (R_f = *n*-C_4F_9, *n*-C_6F_{13}, *n*-C_8F_{17}, *n*-$C_{10}F_{21}$) was investigated in nonaqueous media. All the iodides exhibited one distinctive oxidation peak, but only $C_8F_{17}CH_2CH_2I$ was suitable for surveying preparative-scale electrosynthetic reactions because the other iodides either had poor solubility or caused severe filming of the anode. The direct anodic transformations of the iodide to the corresponding amides ($C_8F_{17}CH_2CH_2NHCOR$; R = CH_3, $CH{=}CH_2$, $C(Me){=}CH_2$), esters ($C_8F_{17}CH_2CH_2OCOR$; R = CH_3, CF_3, $CH{=}CH_2$, $C(Me){=}CH_2$, C_6H_5), ethers (mainly $C_8F_{17}CH_2CH_2OCH_2CF_3$), and alcohol ($C_8F_{17}CH_2CH_2OH$) were observed and a general mechanistic scheme involving a hypervalent iodanyl radical intermediate is proposed.

Introduction

Perfluoroalkyl and 2-(perfluoroalkyl)ethyl iodies, R_fI and $R_fCH_2CH_2I$, are important starting materials in organofluorine chemistry. Unconventional methods, however, often are required to replace the iodide with other functional groups since these fluoroalkyl iodides are prone to give elimination rather than substitution products. For example, 2-(perfluoroalkyl)ethanols $R_fCH_2CH_2OH$ cannot be made by displacement of the iodide with hydroxide ion since this produces almost exclusively the elimination products, $R_fCH{=}CH_2$. Instead, the alcohols are prepared by treatment of the corresponding iodide with oleum,[1-3] concentrated nitric acid,[4] heavy metal ions,[5] or amides.[6,7]

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