Enantiospecific Total Synthesis of L-2′,3′-Dideoxyisonucleosides via Regioselective Opening of Optically Active C_2-Symmetric 1,4-Pentadiene Bis-epoxide[1]

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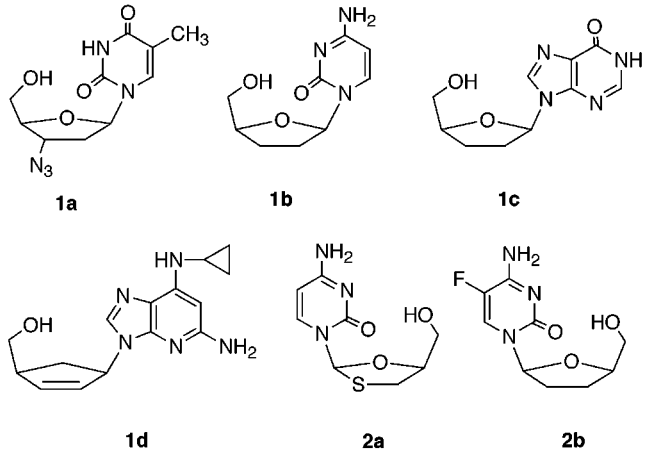
A new method for the synthesis of L-2′,3′-dideoxyisonucleosides is described. The readily available, optically active C_2-symmetric bis-epoxide (2*S*,4*S*)-1,2:4,5-diepoxypentane (**5**) was prepared by a short route from readily available starting materials. The key step of the new synthesis is the opening of **5** with nucleophiles, which proceeds highly regioselectively; e.g., reaction with sodium sulfide affords a 5:1 mixture of the tetrahydrothiophenediol **9a** and the tetrahydrothiopyrandiol **14**, and reaction with sodium hydroxide gives exclusively the tetrahydrofurandiol **9b** via a preferred 5-exo cyclization. These five-membered diols **9a**,**b** can be converted in only four steps into the modified dideoxyuridine and adenosine isonucleosides **4a**−**c**, one of which (**4c**) has shown good antiviral activity. In addition, we have examined the opening of the analogous six-carbon bis-epoxide, (2*S*,5*S*)-1,2:5,6-diepoxyhexane (**23**), which affords a 3:1 mixture of the hexahydrothiepinediol **24** and the tetrahydrothiopyrandiol **25** with sodium sulfide via a preferred 7-endo cyclization. An alternate route to these two optically active bis-epoxides **5** and **23** was also examined, namely the asymmetric dihydroxylation of 1,4-pentadiene and 1,5-hexadiene followed by selective sulfonylation and epoxide formation. The asymmetric reaction produces a nearly 1:1 mixture of optically active and meso tetrols, e.g., **28**−**9** and **32**−**3**. Unfortunately, the tetrols, their simple derivatives, and the final sulfonates and epoxides could not be readily separated by any simple means.

Introduction

For several years, the preferred treatment for AIDS has been the use of modified nucleosides for inhibition of HIV reverse transcriptase (RT).[3] Thus, compounds such as AZT (**1a**), ddC (**1b**), ddI (**1c**), and BW-1685 (**1d**) have shown potent activity against HIV RT and, in some cases, have been used as the first line of defense against AIDS.[3] Recently, it has been found that certain modified nucleosides in the enantiomeric L-series, e.g., L-3-TC (**2a**) and L-5-F-ddC (**2b**), have also shown activity against HIV RT.[4] In general, these compounds exhibit much lower toxicity and, therefore, have better therapeutic indices. In addition to these modified nucleoside analogues, all of which have the heterocyclic base at the normal anomeric position, there is another class of modified nucleosides, called isonucleosides, which have the base attached to a nonanomeric carbon, usually C2. Examples of these compounds that show antiviral activity are both the D- and the L-dideoxyadenosines,[5] e.g., **3a**, and the methylene-expanded oxetanocin thymidine in the L-series **3b**[6] (here the D and L designations refer to the stereochemistry at C4, namely the center designated in the pentoses). We now report the efficient total synthesis of



(1) Presented in part at the 2nd AFMC International Medicinal Chemistry Symposium (AIMECS 97), Seoul, Korea, July 1997.

(2) Deutsche Forschungsgemeinschaft Fellow, 1996−1997.

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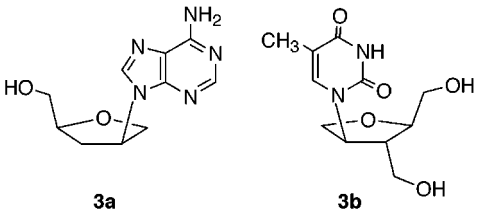
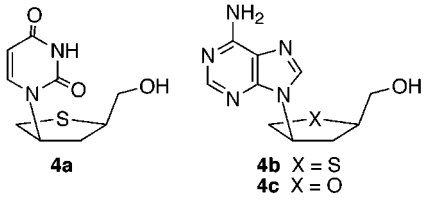


3a **3b**

the L-enantiomers of several isonucleosides containing both oxygen and sulfur substitution in the ring, namely the isonucleosides **4a**−**c**.[7] Our route is a very efficient enantiospecific one beginning with the readily available C_2-symmetric bis-epoxide of 1,4-pentadiene.[8]



4a **4b** X = S **4c** X = O

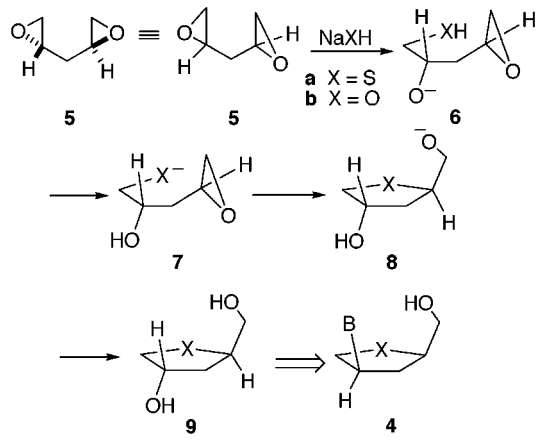
Results and Discussion

Our proposed route to the isonucleosides **4** involved the regioselective opening of either of the two epoxide bonds in the optically active bis-epoxide **5** with either sodium sulfide or sodium hydroxide at the less-hindered primary end of the epoxide to generate the alkoxide **6** (Scheme 1). Since the starting epoxide is C_2-symmetric, opening of either epoxide produces the same intermediate **6**. Internal proton transfer would afford the isomeric heteroanion **7**. For the thiol **6a**, this proton transfer to give **7** should be energetically quite favorable since thiols are much more acidic than the corresponding alcohols. For the alcohol **6b**, this equilibrium would only slightly favor **7b**, because primary alcohols generally have pK_a's about one unit lower than secondary alcohols. Internal opening of the remaining epoxide by the nucleophile of **7** would then generate the tetrahydrothiophene or the tetrahydrofuran alkoxides **8a** and **8b**, respectively, which after protonation would give the diols **9ab**. Final conversion of the diols **9ab** into the isonucleosides **4a**−**c** would follow known procedures.

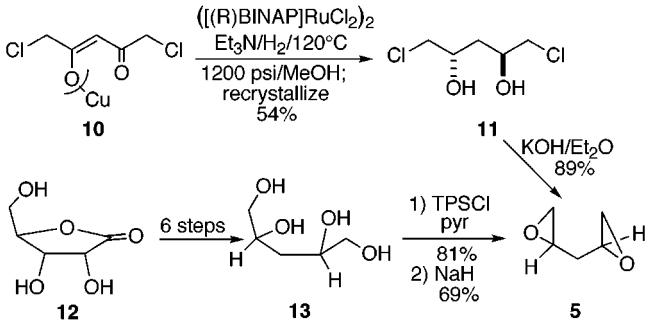
The bis-epoxide **5** can be easily prepared by either of two literature routes (Scheme 2).[8] Asymmetric reduction of the copper salt of 1,5-dichloropentane-2,4-dione (**10**) using Noyori's catalyst gave in 54% yield the diol **11** (>97% ee after recrystallization), which was cyclized in base to give **5** in 89% yield.[8a] Alternatively, D-ribonic acid γ-lactone **12** can be converted in six steps to the optically active tetrol **13**.[8bc] Sulfonylation of the primary alcohols of **13** with 2,4,6-triisopropylbenzenesulfonyl chloride (TPSCl) followed by treatment with sodium hydride afforded **5** in good yield. Both of these methods produce useful quantities of **5** for further reactions.

Addition of sodium sulfide to **5** in aqueous ethanol at 0 °C for several hours afforded the desired tetrahydrothiophenediol **9a** in excellent yield along with the

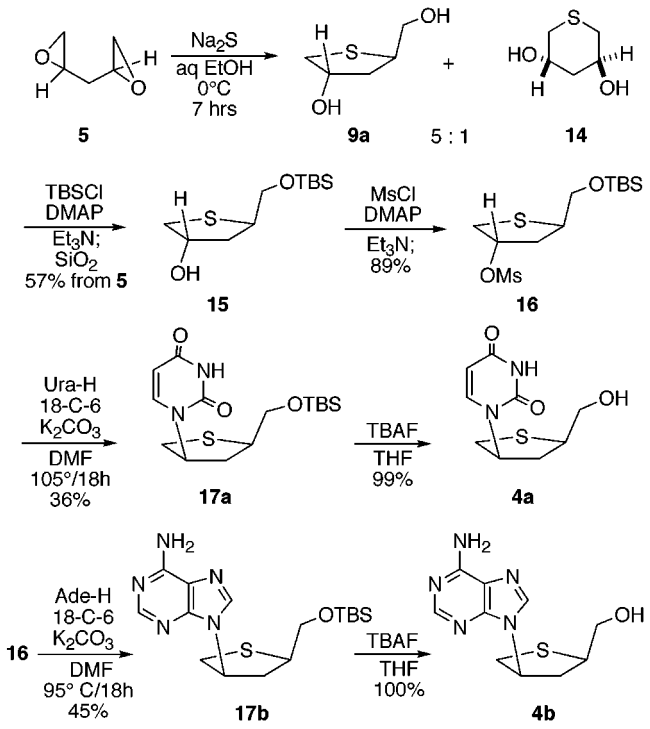
Scheme 1



Scheme 2



Scheme 3



undesired tetrahydrothiopyrandiol **14** as a 5:1 mixture (Scheme 3). The structure of the major and minor components of this crude diol mixture were easily assigned by their proton and, especially, carbon NMR, since the C_2-symmetric diol **14** has only three carbon resonances and a fairly simple proton NMR spectrum while the unsymmetric diol **9a** has five carbon resonances and a much more complex proton NMR spectrum. Silylation

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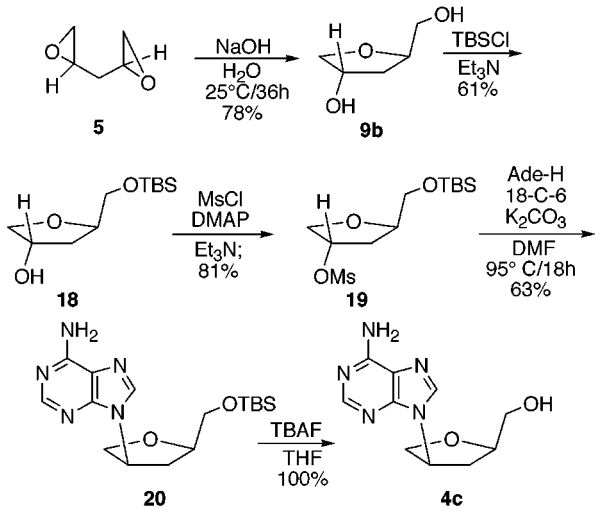
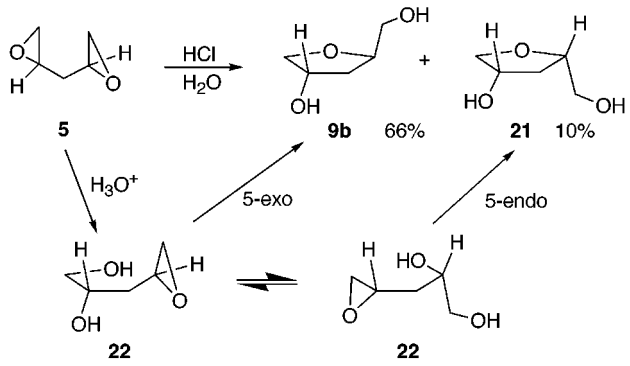
Scheme 4



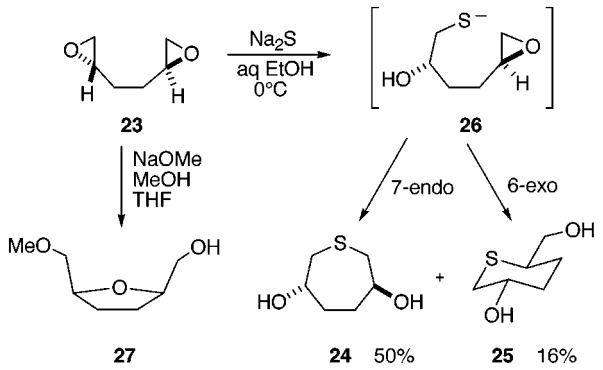
of this mixture of diols, **9a** and **14**, with *tert*-butyldimethylsilyl chloride followed by silica gel chromatography afforded the desired protected tetrahydrothiophene alcohol **15** in 57% yield for the two steps. Thus, the hypothesis that intermolecular ring opening at the primary end of the epoxide followed by selective 5-exo-epoxy opening (in preference to 6-endo-epoxy opening) would occur has been demonstrated. Activation of the secondary alcohol of **15** for S_N2 displacement as the mesylate **16** was accomplished under the usual conditions in 89% yield. Reaction of **16** with the anion of uracil (prepared from uracil, potassium carbonate, and 18-crown-6) in DMF at 95 °C for 18 h afforded in 36% yield the desired product **17a**, which was desilylated to give the modified dideoxyuridine isonucleoside analogue **4a** in 99% yield. The dideoxyadenosine isonucleoside analogue **4b** could also be prepared from the mesylate **16** in 45% overall yield by alkylation with the anion of adenine and desilylation of the intermediate product **17b**. Thus, in only five steps from the C_2-symmetrical bis-epoxide **5**, both dideoxy thioisonucleosides **4a**,**b** are available in 18% and 23% overall yields, respectively.

We next examined the preparation of the oxygen analogues of these isonucleosides as exemplified by the adenine analogue **4c** (Scheme 4). Reaction of the bis-epoxide **5** with aqueous sodium hydroxide produced the desired (hydroxymethyl)tetrahydrofuranol **9b** in 78% yield with only traces of other byproducts being produced. Thus, in this case, the 5-exo cyclization is very highly regioselective with almost none of the product of 6-endo cyclization being observed. This difference between the oxygen and sulfur cases is probably due to the shorter C−O bonds as compared to C−S bonds, which favor the 5-exo process at the expense of the 6-endo one. The cyclization of **5** to give **9b** could also be carried out under acidic conditions (Scheme 5) to produce a mixture of the two (hydroxymethyl)tetrahydrofuranols **9b** and **21** in yields of 66% and 10%, respectively. These are formed by two competing cyclizations of the initially formed intermediate **22**: opening of the epoxide at the secondary center by the primary hydroxyl (a 5-exo process) to give **9b** vs opening of the epoxide at the primary end by the secondary hydroxyl (a 5-endo process) to give **21**. Here again, the 5-exo process is favored presumably because of the relatively short C−O bond. Returning to the synthesis of **4c** (Scheme 4), selective protection of the

Scheme 5



Scheme 6



primary alcohol of the diol **9b** gave the monosilyl ether **18** in 61% yield. Mesylation of the remaining secondary alcohol of **18** afforded in 81% yield the mesylate **19**, which was displaced by the anion of adenine in hot DMF to give the desired product **20** in 63% yield. Final desilylation of **20** furnished the dideoxyadenosine isonucleoside **4c** in quantitative yield. Thus, this active antiviral isonucleoside **4c**[7] is available in only five steps and 24% overall yield from **5**. Obviously, by starting with the enantiomer of **5**,[8a] one could prepare the D-enantiomers of these isonucleosides by the identical sequence.

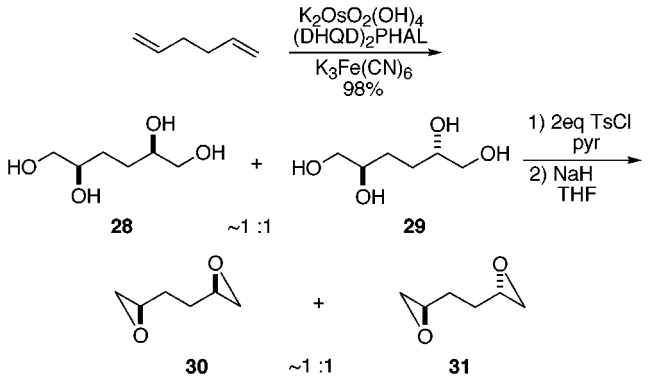
Even though modified nucleosides having six-membered rings have not shown good antiviral properties, we decided to look at nucleophilic opening of the analogous six-carbon bis-epoxide **23** (Scheme 6). This compound was prepared by slight modifications of the known seven-step route from D-mannitol.[9,10] Treatment of this bis-epoxide **23** with sodium sulfide in aqueous ethanol afforded two products in good yield that were easily separated by column chromatography. The major product, isolated in 50% yield, was hexahydrothiepine-3,5-diol (**24**), while the minor product was the tetrahydrothiopyranol **25**, isolated in 16% yield. Thus, cyclization of the initially formed intermediate **26** proceeds mainly via a 7-endo process rather than a 6-exo one. These compounds were not pursued further. One additional opening of the bis-epoxide **23** was attempted, namely treatment with sodium methoxide in a mixture of methanol and THF, which furnished the monoprotected *cis*-tet-

(9) Machinaga, N.; Kibayashi, C. *Synthesis* **1992**, 989; *J. Org. Chem.* **1991**, *56*, 1386; **1992**, *57*, 5178.

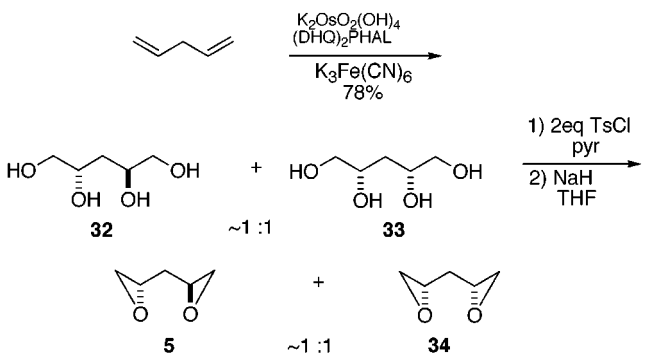
(10) (a) For an almost identical approach to the bis-epoxides **23** and **30**, see: Maier, M. E.; Reuter, S. *Liebigs Ann./Receuil* **1997**, 2043. (b) For a similar route to chiral heptane-1,2,6,7-tetrols, see: Takahata, H.; Kouno, S.-i.; Momose, T. *Tetrahedron: Asymmetry* **1995**, *6*, 1085.

(11) Kakuchi, T.; Satoh, T.; Kanai, H.; Umeda. S.; Hatakeyama, T.; Hashimoto, H.; Yokota, K. *Macromolecules* **1996**, *29*, 4490.

Scheme 7



Scheme 8



rahydrofuran-bis-methanol **27**,[11] the expected product of initial opening of the epoxide at the primary carbon followed by a 5-exo cyclization.

Finally, an alternate route to both of the bis-epoxides **5** and **23** and their enantiomers were briefly examined.[10] Thus, 1,5-hexadiene (prepared by reaction of allyl chloride with magnesium) was subjected to the Sharpless asymmetric dihydroxylation process using $(DHQD)_2PHAL$ (AD mix β) to produce an excellent yield of an approximately 1:1 mixture of the optically active tetrol **28** and the *meso*-tetrol **29** (Scheme 7). These compounds, and several of their simple derivatives, could not be separated by any simple means (crystallization, distillation, or chromatography). They were converted via their bis-tosylates into the optically active bis-epoxide **30** (the enantiomer of **23**) and the meso bis-epoxide **31**. Unfortunately, neither the bis-epoxides **30** and **31** nor their precursor bis-tosylates were separable by normal means. Thus, until a method of separation of these diastereomers is developed, it is best to prepare **23** from D-mannitol. In like fashion, 1,4-pentadiene was converted into a roughly 1:1 mixture of the corresponding tetrols **32** and **33** via a Sharpless asymmetric dihydroxylation process using $(DHQ)_2PHAL$ (AD mix α) and then converted into the epoxides **5** and **34** by an identical route to that described above (Scheme 8). Again, nearly none of the intermediates could be easily separated by any simple means. Since we had already prepared the two bis-epoxides **5** and **23** by different routes that gave optically pure material and had studied the regioselectivity of their opening reactions, we abandoned all work on this approach.

Conclusion

The optically active bis-epoxides (2*S*,4*S*)-1,2:4,5-diepoxypentane (**5**) and (2*S*,5*S*)-1,2:5,6-diepoxyhexane (**23**) have been prepared by short routes from readily available starting materials. Their opening with nucleophiles has been examined with the following results: (a) the five-carbon bis-epoxide **5** affords a 5:1 mixture of the tetrahydrothiophenediol **9a** and the tetrahydrothiopyrandiol **14** with sodium sulfide and exclusively the tetrahydrofurandiol **9b** with sodium hydroxide via a preferred 5-exo cyclization; (b) these five-membered diols **9a**.**b** can be converted in only four steps into the modified dideoxyuridine and adenosine isonucleosides **4a**−**c**, one of which (**4c**) has shown good antiviral activity; (c) the six-carbon bis-epoxide **23** affords a 3:1 mixture of the hexahydrothiepinediol **24** and the tetrahydrothiopyrandiol **25** with sodium sulfide via a preferred 7-endo cyclization. An alternate route to these two optically active bis-epoxides **5** and **23** was also examined, namely the asymmetric dihydroxylation of 1,4-pentadiene and 1,5-hexadiene followed by selective sulfonylation and epoxide formation. The asymmetric reaction produces a nearly 1:1 mixture of optically active and meso tetrols, e.g., **28**−**9** and **32**−**3**. Unfortunately, the tetrols, their simple derivatives, and the final sulfonates and epoxides could not be readily separated by any simple means. The use of these optically active bis-epoxides, **5** and **23**, in the synthesis of other natural products is under active investigation.

Experimental Section

General Methods. All solvents were distilled prior to use: tetrahydrofuran (THF) from sodium/benzophenone; dichloromethane, triethylamine, pyridine, and DMSO from calcium hydride; and methanol from magnesium methoxide. All reactions were conducted under an inert atmosphere of argon.

(2*S*,4*S*)-1,2:4,5-Diepoxypentane 5. The bis(2,4,6-triisopropylbenzenesulfonate) was prepared from the tetrol **13**[8b] by the known route.[8c] To a stirred solution of 5.00 g (7.47 mmol) of this bis-sulfonate in 200 mL of THF was added portionwise 3.00 g (37.35 mmol) of sodium hydride (60% dispersion in oil). Vigorous stirring was required to overcome the precipitation of the sodium sulfonates formed. The mixture was stirred for an additional 30 min and filtered through magnesium sulfate and the THF removed under reduced pressure in an ice bath to give a yellowish oil, which was purified by column chromatography (SiO_2, 1:3 diethyl ether/pentane) to yield 505 mg (5.0 mmol, 69%) of the bis-epoxide **5** as a colorless oil: R_f 0.45 (diethyl ether); $[\alpha]^{20}_D = -51.3°$ (*c* 0.37, $CHCl_3$).

(3*S*,5*R*)-5-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-methyl]tetrahydrothiophene-3-ol, 15. To an ice-cold solution of 505 mg (5.04 mmol) of the *S*,*S*-bis-epoxide **5** in 150 mL of ethanol was added dropwise a solution of 1.20 g (5.00 mmol) of sodium sulfide nonahydrate in 42 mL of ethanol and 14 mL of water within 2 h. The mixture was then stirred for an additional 5 h at 0 °C and subsequently allowed to warm to room temperature overnight. After neutralization with 1 M HCl, 3 mL of silica gel was added, and the solvents were removed in vacuo. Column chromatography (SiO_2, 20:1 $CHCl_3$/MeOH) yielded 619 mg (4.61 mmol) of a 5:1 mixture (5-exo/6-endo) of diols **9a** and **14** as a colorless oil. The mixture of diols was dissolved in 30 mL of CH_2Cl_2 and 5 mL of Et_3N, treated with 1.04 g (6.89 mmol) of *tert*-butyldimethylsilyl chloride (TBSCl) and 140 mg (1.15 mmol) of DMAP, and stirred for 12 h. After dilution with 70 mL water, the mixture was extracted two times with 30 mL of CH_2Cl_2, and the combined organic phases were washed with brine and dried over magnesium sulfate. Removal of solvent and column chromatography on silica gel (1:4 ethyl acetate/hexanes) yielded 710 mg (2.86 mmol, 57% over two steps) of the alcohol **15** as a colorless oil: R_f 0.19 (ethyl acetate/hexanes = 1/4); ^1H NMR (400 MHz, C_6D_6) δ 0.08 (s, 6H), 0.10 (s, 9H), 1.36 (d, br, J = 4.4 Hz, 1H), 1.43 (ddd, J = 13.0, 8.0, 4.0 Hz, 1H), 1.94 (dddd, J = 13.0, 6.4, 3.4, 1.5 Hz, 1H), 2.51 (ddd, J = 11.2, 4.2, 1.5 Hz,

1H), 2.68 (dd, J = 11.2, 4.1 Hz, 1H), 3.53−3.68 (m, 3H), 4.14 (m, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ −5.3, −5.2, 18.5, 26.0, 39.9, 41.2, 47.7, 67.8, 74.8; IR (neat) 3346, 2954, 2857, 1472, 1256, 1111, 1076, 837, 777 cm^{-1}; HRMS (EI) calcd for $C_{11}H_{25}O_2SSi$ 249.1345, found 249.1354 (M + H); $[\alpha]^{20}_D$ = −62.0° (*c* 0.40, $CHCl_3$). Data for compound **14**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.79 (m, 2H), 2.48 (dd, J = 13.1, 7.3 Hz, 2H), 2.70 (dd, J = 13.1, 2.1 Hz, 2H), 4.17 (m, 2H) (OH protons appear at 2.56 ppm together with those of **9b**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.1, 41.5, 65.5. Under less dilute conditions, up to 10% of the minor biproduct, (2*S*,4*S*)-1,5-diethoxypentane-2,4-diol, was formed and could be isolated from the major products by column chromatography (SiO_2, 20:1 $CHCl_3$/MeOH) as a colorless oil.

(3*S*,5*R*)-5-(Hydroxymethyl)tetrahydrothiophene-3-ol, 9a. To a stirred solution of 16 mg (60 μmol) **15** in 5 mL of THF was added dropwise 120 μL of a solution of TBAF in THF (1.0 molar) and the resulting solution stirred for 2 h. After addition of 1 mL of silica gel and evaporation to dryness, the residue was subjected to column chromatography (SiO_2, ethyl acetate) to yield 7.6 mg of **9a** (57 μmol, 95%) as a colorless oil: R_f 0.23 (ethyl acetate); ^{1}H NMR (400 MHz, C_6D_6) δ 1.19 (d, J = 6.0 Hz, 1H), 1.43 (ddd, J = 13.0, 8.5, 3.9 Hz, 1H), 1.51 (t, J = 6.0 Hz, 1H), 1.73 (dddd, J = 13.0, 6.7, 3.2, 1.5 Hz, 1H), 2.42 (ddd, J = 11.2, 2.6, 1.5 Hz, 1H), 2.56 (dd, J = 11.2, 4.0 Hz, 1H), 3.23−3.48 (m, 3H), 4.10 (s, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ 40.2, 40.6, 48.6, 65.0, 75.1; IR (neat) 3357, 2932, 1643, 1428, 1325, 1196, 1018 cm^{-1}; HRMS (EI) calcd for $C_5H_{10}O_2S$ 134.0402, found 134.0399; $[\alpha]^{20}_D$ = −61.5° (*c* 0.16, $CHCl_3$).

(3*S*,5*R*)-5-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-methyl]-3-[(methylsulfonyl)oxy]tetrahydrothiophene, 16. The alcohol **15** (560 mg, 2.26 mmol) and DMAP (70 mg, 0.57 mmol) were dissolved in 9 mL of CH_2Cl_2 and cooled to 0 °C. After addition of 1 mL of triethylamine and 350 μL (4.52 mmol) of mesyl chloride, the mixture was allowed to warm to room temperature and stirred for 12 h. Addition of SiO_2, removal of volatile compounds in vacuo, and chromatography on silica gel (1:4 ethyl acetate/hexanes) afforded 654 mg (2.00 mmol, 89%) of **16** as a colorless oil: R_f 0.19 (ethyl acetate/hexanes = 1/4); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.06 (s, 6H), 0.89 (s, 9H), 1.95 (ddd, J = 13.6, 7.8, 4.2 Hz, 1H), 2.44 (ddd, J = 13.6, 9.2, 5.1 Hz, 1H), 3.05 (s, 3H), 3.10−3.30 (m, br, 2H), 3.68 (m, 3H), 5.43 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.4 (2), 18.3, 25.8, 37.0, 38.8, 39.3, 47.0, 66.8, 82.8; IR (neat) 2955, 2857, 1472, 1360, 1258, 1169, 837, 777 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{27}O_4S_2Si$ 327.1120, found 327.1126 (M + H); $[\alpha]^{20}_D$ = −60.3° (*c* 0.87, $CHCl_3$).

1-[(3*R*,5*R*)-5-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]-methyl]tetrahydrothiophen-3-yl]pyrimidine-2,4-dione, 17a. To a solution of the mesylate **16** (154 mg, 0.472 mmol) in 13 mL of DMF were added 260 mg (1.881 mmol) of K_2CO_3, 250 mg (0.946 mmol) of 18-crown-6, and 159 mg (0.472 mmol) of uracil. The mixture was then warmed to 105 °C and stirred at that temperature for 18 h. After removal of the solvent under reduced pressure, the residue was taken up in 5 mL of MeOH, and 2 mL of silica gel was added. Evaporation to dryness and column chromatography (SiO_2, 1:2 ethyl acetate/hexanes) gave after recrystallization from ethanol 59 mg (0.172 mmol, 36%) of the protected isonucleoside **17a** as colorless prisms: mp 149−151 °C (ethanol); R_f 0.20 (ethyl acetate/hexanes = 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.08 (s, 6H), 0.90 (s, 9H), 1.88 (ddd, J = 12.4, 10.8, 9.3 Hz, 1H), 2.48 (dt, J = 12.4, 6.4 Hz, 1H), 2.88 (dd, J = 10.8, 9.9 Hz, 1H), 3.12 (dd, J = 10.8, 6.8 Hz, 1H), 3.58 (ddd, J = 12.6, 9.1, 6.2 Hz, 1H), 3.71 (m, 2H), 5.18 (m, 1H), 5.76 (dd, J = 8.1, 2.3 Hz, 1H), 7.38 (d, J = 8.1 Hz, 1H), 8.49 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.3 (2), 18.3, 25.8, 33.8, 36.5, 46.1, 58.0, 66.9, 102.8, 140.2, 150.5, 162.4; IR (KBr) 3193, 2928, 2859, 1705, 1686, 1464, 1371, 1289, 1102, 841, 777 cm^{-1}; HRMS (FAB$^+$ on NBA) calcd for $C_{15}H_{27}N_2O_3SSi$ 343.1514, found 343.1512 (M + H); $[\alpha]^{20}_D$ = −5.4° (*c* 0.15, $CHCl_3$).

1-[(3*R*,5*R*)-5-(Hydroxymethyl)tetrahydrothiophen-3-yl]pyrimidine-2,4-dione, 4a. A stirred solution of 20 mg (58 mmol) of **17a** in THF was treated with 120 μL (120 μmol) of a 1.0 M solution of TBAF in THF at room temperature and stirred for 30 min. Addition of 1 mL of silica gel, evaporation to dryness, and column chromatography (SiO_2, 10:1 $CHCl_3$/MeOH) yielded 13 mg (57 μmol, 99%) of the dideoxyuridine isonucleoside **4a** as a colorless hygroscopic gum: R_f 0.10 ($CHCl_3$/MeOH = 10/1); ^{13}C NMR (100 MHz, DMSO-d_6) δ 31.7, 35.1, 45.7, 57.8, 65.7, 101.4, 142.0, 150.9, 163.1; $[\alpha]^{20}_D$ = −4.4° (*c* 0.20, DMSO-d_6) [lit.[7] $[\alpha]^{23}_D$ = −8.7° (*c* 0.23, DMSO)].

6-Amino-9-[(3*R*,5*R*)-5-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]tetrahydrothiophen-3-yl]purine, 17b. To a solution of the mesylate **16** (70 mg, 214 mmol) in 6 mL of DMF was added 118 mg (857 μmol) of K_2CO_3, 113 mg (429 μmol) of 18-crown-6, and 87 mg (643 μmol) of adenine. The mixture was then warmed to 95 °C and stirred at that temperature for 18 h. After removal of the solvent under reduced pressure, the residue was taken up in 5 mL of MeOH, and 2 mL silica gel were added. Evaporation to dryness and column chromatography (SiO_2, 10:1 $CHCl_3$/MeOH) gave 35 mg (96 μmol, 45%) of the protected isonucleoside **17b** as a colorless solid: R_f 0.44 ($CHCl_3$/MeOH = 9/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.06 (s, 6H), 0.87 (s, 9H), 2.27−2.60 (m, 1H), 2.70 (m, 1H), 3.31 (m, 2H), 3.60−3.73 (m, 3H), 5.14 (m, 1H), 6.03 (s, br, 2H), 7.94 (s, 1H), 8.34 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.4, −5.3, 18.2, 25.8, 34.9, 37.7, 46.4, 57.9, 67.2, 119.8, 138.3, 150.0, 152.9, 155.6; IR (KBr) 3294, 3180, 2953, 2855, 1667, 1607, 1122, 1109, 841, 779 cm^{-1}; HRMS (FAB$^+$ on NBA) calcd for $C_{16}H_{28}N_5OSSi$ 366.1801, found 366.1784 (M + H); $[\alpha]^{20}_D$ = −17.1° (*c* 0.13, $CHCl_3$).

6-Amino-9-[(3*R*,5*R*)-5-(hydroxymethyl)tetrahydrothiophen-3-yl]purine, 4b. A stirred solution of 16 mg (44 μmol) of the protected isonucleoside **17b** in THF was treated with 132 μL (132 μmol) of a 1.0 molar solution of TBAF in THF at room temperature and stirred for 30 min. Addition of 1 mL of silica gel, evaporation to dryness, and column chromatography (SiO_2, 9:1 $CHCl_3$/MeOH) yielded 11 mg (44 μmol, quant) of the dideoxyadenosine isonucleoside **4b** as a colorless solid: R_f 0.17 ($CHCl_3$/MeOH = 9/1); ^{13}C NMR (100 MHz, DMSO-d_6) δ 33.2, 36.7, 46.4, 57.5, 65.9, 119.0, 139.4, 149.4, 152.3, 156.0; $[\alpha]^{20}_D$ = −3.9° (*c* 0.16, MeOH) [lit.[7] $[\alpha]^{23}_D$ = −1.3° (*c* 1.13, MeOH)].

(3*S*,5*R*)-5-(Hydroxymethyl)tetrahydrofuran-3-ol, 9b. A vigorously stirred suspension of 100 mg (1.00 mmol) of the *S*,*S*-bis-epoxide **5** in 20 mL of water was treated dropwise with 1 mL of 1 M NaOH at 0 °C. After being warmed to ambient temperature, the mixture was stirred for additional 36 h, neutralized with 1 mL of 1 M hydrochloric acid, and after addition of 2 mL of silica gel, evaporated to dryness. The residue was subjected to column chromatography (SiO_2, 6:1 ethyl acetate/MeOH) to afford 92 mg (0.779 mmol, 78%) of the diol **9b** as a colorless oil along with some unreacted starting material: R_f 0.37 (ethyl acetate/MeOH = 3/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.89 (ddd, J = 13.4, 9.1, 4.9 Hz, 1H), 1.93 (dddd, J = 13.4, 6.6, 2.0, 1.0 Hz, 1H), 2.30 (s, br, 2H), 3.51 (dd, J = 11.9, 5.4 Hz, 1H), 3.75 (dd, J = 11.9, 3.0 Hz, 1H), 3.78 (dd, J = 9.8, 2.0 Hz, 1H), 3.94 (dd, J = 9.8, 4.0 Hz, 1H), 4.30 (m, 1H), 4.52 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.7, 64.2, 72.6, 75.6, 78.4; IR (neat) 3359, 2934, 2876, 1658, 1439, 1331, 1233, 1063, 976, 820 cm^{-1}; HRMS (EI) calcd for $C_5H_{11}O_3$ 119.0708, found 119.0706 (M + H); $[\alpha]^{20}_D$ = −14.7° (*c* 0.40, $CHCl_3$).

(3*S*,5*R*)-5-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-methyl]tetrahydrofuran-3-ol, 18. The diol **9b** (85 mg, 0.720 mmol) was dissolved in 10 mL of CH_2Cl_2 and 1 mL of Et_3N, treated with 163 mg (1.08 mmol) of TBSCl and 22 mg (0.180 mmol) of DMAP, and stirred for 12 h. After the mixture was diluted with 10 mL of CH_2Cl_2 and 10 mL of water, the mixture was extracted twice with 15 mL of CH_2Cl_2, and the combined organic phases were washed with brine and dried over $MgSO_4$. Removal of the solvents and column chromatography on silica gel (1:3 ethyl acetate/hexanes) yielded 100 mg (0.430 mmol, 60%) of the alcohol **18** as a colorless oil: R_f 0.20 (ethyl acetate/hexanes = 1/2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 6H), 0.87 (s, 9H), 1.90 (m, 2H), 2.64 (s, br, 1H), 3.58 (dd, J = 10.9, 4.5 Hz, 1H), 3.65 (dd, J = 10.9, 4.0 Hz, 1H), 3.75 (d, br, J = 9.6 Hz, 1H), 3.88 (dd, J = 9.6, 4.0 Hz, 1H), 4.20 (m, 1H), 4.45 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.5, −5.4, 18.3, 25.8, 37.1,

65.3, 72.5, 75.6, 78.4; IR (neat) 3424, 2953, 2859, 1651, 1472, 1256, 1136, 1088, 1001, 839, 777 cm^{-1}; HRMS (EI) calcd for $C_{11}H_{25}O_3Si$ 233.1573, found 233.1573 (M + H); $[\alpha]^{20}_D = -5.2°$ (*c* 1.15, $CHCl_3$).

(3*S*,5*R*)-5-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-methyl]-3-[(methylsulfonyl)oxy]tetrahydrofuran, 19. The alcohol **18** (74 mg, 0.318 mmol) and DMAP (10 mg, 80 μmol) were dissolved in 10 mL of CH_2Cl_2 and cooled to 0 °C. After addition of 200 μL of triethylamine and 50 μL (648 μmol) of mesyl chloride, the mixture was allowed to warm to room temperature and stirred for 12 h. Addition of SiO_2, removal of the volatile compounds in vacuo, and chromatography on silica gel (1:3 ethyl acetate/hexanes) afforded 80 mg (0.258 mmol, 81%) of the mesylate **19** as a colorless oil: R_f 0.29 (ethyl acetate/hexanes = 1/2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.87 (s, 9H), 2.15 (ddd, J = 13.9, 8.5, 5.7 Hz, 1H), 2.22 (dd, J = 13.9, 6.5 Hz, 1H), 3.02 (s, 3H), 3.61 (dd, J = 11.0, 3.8 Hz, 1H), 3.73 (dd, J = 11.0, 3.7 Hz, 1H), 4.00 (d, br, J = 10.7 Hz, 1H), 4.05 (dd, J = 10.7, 4.1 Hz, 1H), 4.21 (m, 1H), 5.31 (ddd, br, J = 7.4, 3.8, 1.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.5, −5.4, 18.2, 25.8, 34.7, 38.6, 64.7, 73.2, 78.6, 81.5; IR (neat) 2932, 2857, 1474, 1360, 1256, 1173, 1090, 955, 899, 837, 777 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{27}O_5SSi$ 311.1348, found 311.1344 (M + H); $[\alpha]^{20}_D = -10.1°$ (*c* 1.40, $CHCl_3$).

6-Amino-9-[(3*R*,5*R*)-5-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]tetrahydrofuran-3-yl]purine, 20. To a solution of 63 mg (0.203 mmol) of the mesylate **19** in 7 mL of DMF were added 112 mg (0.812 mmol) of K_2CO_3, 107 mg (0.405 mmol) of 18-crown-6, and 82 mg (0.609 mmol) of adenine. The mixture was then warmed to 95 °C and stirred at that temperature for 18 h. After removal of the solvent under reduced pressure, the residue was taken up in 5 mL of MeOH, and 2 mL of silica gel was added. Evaporation to dryness and column chromatography (SiO_2, 20:1 $CHCl_3$/MeOH) gave 45 mg (0.129 mmol, 63%) of the protected isonucleoside **20** as a colorless solid: R_f 0.37 ($CHCl_3$/MeOH = 9/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.08 (s, 6H), 0.89 (s, 9H), 2.18 (ddd, J = 13.8, 8.1, 4.1 Hz, 1H), 2.63 (dt, J = 13.8, 8.3 Hz, 1H), 3.76 (dd, J = 11.2, 3.9 Hz, 1H), 3.94 (dd, J = 11.2, 3.4 Hz, 1H), 4.01 (dd, J = 10.0, 5.6 Hz, 1H), 4.05−4.13 (m, 2H), 5.31 (m, 1H), 6.20 (s, br, 2H), 8.18 (s, 1H), 8.32 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.4, −5.3, 18.5, 25.9, 34.6, 53.9, 64.0, 73.5, 79.8, 119.2, 138.9, 149.7, 152.8, 155.6; IR (neat) 3303, 3146, 2955, 2928, 2855, 1678, 1603, 1482, 1416, 1329, 1304, 1254, 1136, 843, 777 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{28}N_5O_2Si$ 350.2012, found 350.2007 (M + H); $[\alpha]^{20}_D = +35.3°$ (*c* 0.71, $CHCl_3$).

6-Amino-9-[(3*R*,5*R*)-5-(hydroxymethyl)tetrahydrofuran-3-yl]purine, 4c. A stirred solution of 42 mg (0.120 mmol) of the protected isonucleoside **20** in THF was treated with 200 μL (200 μmol) of a 1.0 M solution of TBAF in THF at room temperature and stirred for 30 min. Addition of 1 mL of silica gel, evaporation to dryness, and column chromatography (SiO_2, 9:2 $CHCl_3$/MeOH) yielded 28 mg (0.120 mmol, quant) of the dideoxyadenosine isonucleoside **4c** as a colorless solid: R_f 0.11 ($CHCl_3$/MeOH = 9/1); ^{13}C NMR (100 MHz, DMSO-d_6) δ 33.9, 53.9, 62.4, 71.9, 79.6, 118.7, 138.9, 149.3, 152.3, 156.0; $[\alpha]^{20}_D$ = +30.5° (*c* 0.78, MeOH) [lit.[7] $[\alpha]^{22}_D$ = +31.9° (*c* 1.05, MeOH)].

(3*S*,5*R*)-5-(Hydroxymethyl)tetrahydrofuran-3-ol, 9b, and (3*S*,5*S*)-5-(Hydroxymethyl)tetrahydrofuran-3-ol, 21. A vigorously stirred suspension of 50 mg (0.50 mmol) of the *S*,*S*-bis-epoxide **5** in 10 mL of water was treated dropwise with 0.5 mL of 1 M HCl at room temperature, stirred for 24 h, and neutralized with 0.5 mL of 1 M NaOH. After addition of 1 mL of silica gel, the mixture was evaporated to dryness. The residue was subjected to column chromatography (SiO_2, 6:1 ethyl acetate/MeOH) to afford 45 mg (0.38 mmol, 76%) of a mixture of diols **21** (5-endo, 10%) and **9b** (5-exo, 66%) as a colorless oil and some unreacted starting material. Compound **21**: R_f 0.37 (ethyl acetate/MeOH = 3/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.88 (m, 1H), 2.26 (ddd, J = 14.0, 9.8, 5.7 Hz, 1H), 3.54 (dd, J = 11.8, 2.6 Hz, 1H), 3.68 (dd, J = 9.6, 3.2 Hz, 1H), 3.84 (dd, J = 11.8, 2.4 Hz, 1H), 4.18 (m, br, 1H), 4.33 (m, 2H), OH protons overlap with the OH protons of **9b** at ~3.0 ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.6, 64.1, 71.5, 76.7, 78.3.

(3*S*,5*S*)-Hexahydrothiepine-3,5-diol, 24, and (3*S*,6*R*)-6-(Hydroxymethyl)tetrahydro-2*H*-thiopyran-3-ol, 25. To an ice-cold solution of 100 mg (0.880 mmol) of the *S*,*S*-bisepoxide **23**[9] in 50 mL of ethanol was added dropwise a solution of 210 mg (0.870 mmol) of sodium sulfide nonahydrate in 6 mL of ethanol and 2 mL of water within 2 h. The mixture was then stirred for an additional 5 h at 0 °C and subsequently allowed to warm to room temperature overnight. After neutralization with 1 M HCl, 3 mL of silica gel was added, and the solvents were removed in vacuo. Column chromatography (SiO_2, 3:1 ethyl acetate/hexanes) yielded 65 mg (0.439 mmol, 50%) of the hexahydrothiepinediol **24** as a colorless solid and 20 mg (0.140 mmol, 16%) of the tetrahydrothiopyranol **25** as a colorless solid. Some highly polar baseline material was not isolated. The hexahydrothiepinediol **24** was recrystallized from chloroform to afford colorless needles. Compound **24**: mp 98 °C ($CHCl_3$); R_f 0.24 (ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.61 (m, 2H), 1.75 (s, br, 2H), 2.08 (m, 2H), 2.66 (ddd, J = 14.6, 6.4, 0.4 Hz, 2H), 2.91 (dd, J = 14.6, 4.3 Hz, 2H), 4.08 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.2, 41.7, 71.4; IR (neat) 3364, 2930, 1651, 1456, 1417, 1022, 760 cm^{-1}; HRMS (EI) calcd for $C_6H_{13}O_2S$ 148.0558, found 148.0560 (M + H); $[\alpha]^{20}_D = -51.2°$ (*c* 0.12, $CHCl_3$). Compound **25**: R_f 0.32 (ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (dddd, J = 13.2, 11.0, 9.5, 3.6 Hz, 1H), 1.66 (dddd, J = 13.2, 10.9, 9.5, 3.3 Hz, 1H), 1.71 (m, 1H), 1.98 (m, 1H), 2.01 (dddd, J = 13.3, 8.5, 6.7, 3.6 Hz, 1H), 2.18 (m, 1H), 2.55 (dd, J = 13.0, 9.0 Hz, 1H), 2.83 (m, 2H), 3.68 (m, 2H), 3.86 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.8, 33.1, 33.9, 43.7, 64.6, 67.9; IR (KBr) 3382, 3316, 2928, 2911, 1458, 1341, 1184, 1030, 976, 910, 772 cm^{-1}; HRMS (EI) calcd for $C_6H_{13}O_2S$ 148.0558, found 148.0559 (M + H); $[\alpha]^{20}_D = -42.8°$ (*c* 0.10, $CHCl_3$).

(2*S*,5*S*)-5-(Methoxymethyl)tetrahydrofuran-2-methanol, 27. To a refluxing solution of 100 mg (0.88 mmol) the *S*,*S*-bisepoxide **23** in 15 mL of THF was added 1 equiv of solid sodium methoxide and 5 mL of methanol. After being refluxed for 5 h, the mixture was neutralized with 1 M HCl. Addition of 1 mL of silica gel, removal of solvents, and column chromatography (SiO_2, ethyl acetate) yielded 55 mg (0.40 mmol, 43%) of the alcohol **27**[11] as a colorless oil: R_f 0.25 (ethyl acetate); $[\alpha]^{20}_D = -13.0°$ (*c* 0.60, $CHCl_3$).

(2*R*,5*R*)-1,2,5,6-Hexanetetrol, 28, and (2*R*,5*S*)-1,2,5,6-Hexanetetrol, 29. To a vigorously stirred mixture of potassium hexacyanoferrate (31.68 g, 96.0 mmol), potassium osmate dihydrate (44.8 mg, 0.122 mmol), potassium carbonate (13.5 g, 97.0 mmol), and $(DHQD)_2PHAL$ (250 mg, 0.320 mmol) in 80 mL of water was added 80 mL of 2-methyl-2-propanol and then the mixture cooled to 0 °C. After 1 h, 2 mL (16.8 mmol) of 1,5-hexadiene was added and the mixture kept at that temperature for 5 h. The mixture was then stirred at 6 °C for an additional 24 h before being quenched with 24 g of sodium metabisulfide. Adding 100 g of silica gel and evaporating to dryness afforded a gray powder, which was extracted with ethyl acetate by means of a Soxhlet apparatus for 4 d. After removal of ethyl acetate, the residue was submitted to column chromatography (SiO_2, 5:2 ethyl acetate/MeOH) to recover the chiral ligand quantitatively and to give 2.49 g (16.5 mmol, 98%) of a 1:1 mixture of the tetrols **28** and **29** as a colorless oil, which solidifies upon standing: R_f 0.21 (ethyl acetate/ methanol = 5:2); ^{1}H NMR (400 MHz, D_2O) δ 1.23−1.68 (m, 4H), 3.31−3.62 (m, 6H); ^{13}C NMR (100 MHz, D_2O) δ 28.2, 28.5, 65.2, 65.3, 71.5, 71.8.

(2*S*,4*S*)-1,2,4,5-Pentanetetrol, 32, and (2*S*,5*R*)-1,2,4,5-Pentanetetrol, 33. To a vigorously stirred mixture of potassium hexacyanoferrate (18.29 g, 56.0 mmol), potassium osmate dihydrate (25.9 mg, 70 μmol), potassium carbonate (9.15 g, 66.0 mmol) and $(DHQ)_2PHAL$ (144 mg, 0.185 mmol) in 50 mL of water was added 50 mL of 2-methyl-2-propanol and then the mixture cooled to 0 °C. After 1 h, 1 mL (9.7 mmol) of 1,4-pentadiene was added and the reaction kept at that temperature for 5 h. The mixture was then stirred at 6 °C for an additional 18 h before being quenched with 14 g of sodium metabisulfide. After addition 50 mL of silica gel and evaporation to dryness, the residue was submitted to column chromatography (SiO_2, 5:2 ethyl acetate/MeOH) to recover the

chiral ligand quantitatively and to give 1.03 g (7.6 mmol, 78%) of a mixture of the tetrols as a colorless solid: R_f 0.22 (ethyl acetate/methanol = 5:2); ^{1}H NMR (400 MHz, D_2O) δ 1.33−1.60 (m, 2H), 3.31−3.53 (m, 4H), 3.68−3.80 (m, 2H); ^{13}C NMR (100 MHz, D_2O) δ 35.5, 35.6, 65.1, 65.9, 68.3, 69.4.

(2*R*,5*R*)-1,2:5,6-Diepoxyhexane, 30, and (2*R*,5*S*)-1,2:5,6-Diepoxyhexane 31. The preparation of the tosylates and epoxides were carried out by essentially the method of ref 10 to give the inseparable mixture of epoxides **30** and **31**.

(2*S*,4*S*)-1,2:4,5-Diepoxypentane, 5, and (2*S*,4*R*)-1,2:4,5-Diepoxypentane, 34. The preparation of the tosylates and epoxides were carried out by essentially the method of ref 10 to give the inseparable mixture of epoxides **5** and **34**.

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Supporting Information Available: Copies of the ^{1}H and ^{13}C NMR spectra for all compounds described (34 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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