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An asymmetric approach to 2-deoxynucleosides *via* organosulfur building blocks as chemical chameleons

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ABSTRACT

An asymmetric synthesis of 6-*N*-benzoyl-5′-*O*-benzyl-2′-deoxyadenosine and its *α* anomer from non-carbohydrate building blocks is achieved in 7 steps. The sequence builds the basic structures using bis(methylthio)methane and methylthiomethyl phenyl sulfone as both nucleophilic and electrophilic building blocks, a feature that suggests their behavior as chemical chameleons. The asymmetric induction is achieved utilizing a kinetic resolution based upon catalytic asymmetric epoxidation.

INTRODUCTION

The obvious importance of 2-deoxynucleosides in molecular biology and of analogues thereof as potential therapeutic agenst (for example, AZT) makes the development of simple syntheses an important goal. With the explosion of new synthetic methods, the possibility of building upon them to create new routes to various carbohydrates and their important derivatives, especially the nucleic acids, becomes an intriguing venture.

Organosulfur chemistry has contributed extensively to the evolving synthetic revolution. Among the various programs in sulfur chemistry underway in our laboratories, the combination of two of them appeared to offer an opportunity to obtain nucleosides using a reasonably simple protocol. The first program considers thionium ions (thiocarbocations) as "super carbonyl groups"[1*]. For example, a sulfur equivalent of a Schmidt rearrangement was developed[3] according to Eq. *1*. The ability to generate the reactive intermediate 1 chemoselectively, and the high electrophilicity of this fully charged species, inverts the role of a thioacetal from its normal behavior as a carbonyl protecting-group to one of its being a functionality that can become more reactive than a carbonyl group.

Combining the ability of a sulfur substituent to become a leaving group with its anion-stabilizing properties[4] (see ref. 4 for reviews) imparts tremendous diversity to the synthetic applications of organosulfur compounds as building blocks. For example, a novel ring-expansion is available[5,6] through the use of sulfones as both an anion-stabilizing group and a leaving group, as shown in Eq. *2*. A ring enlargement of lactones

* Also see ref. 2 for non-acylthionium ions.

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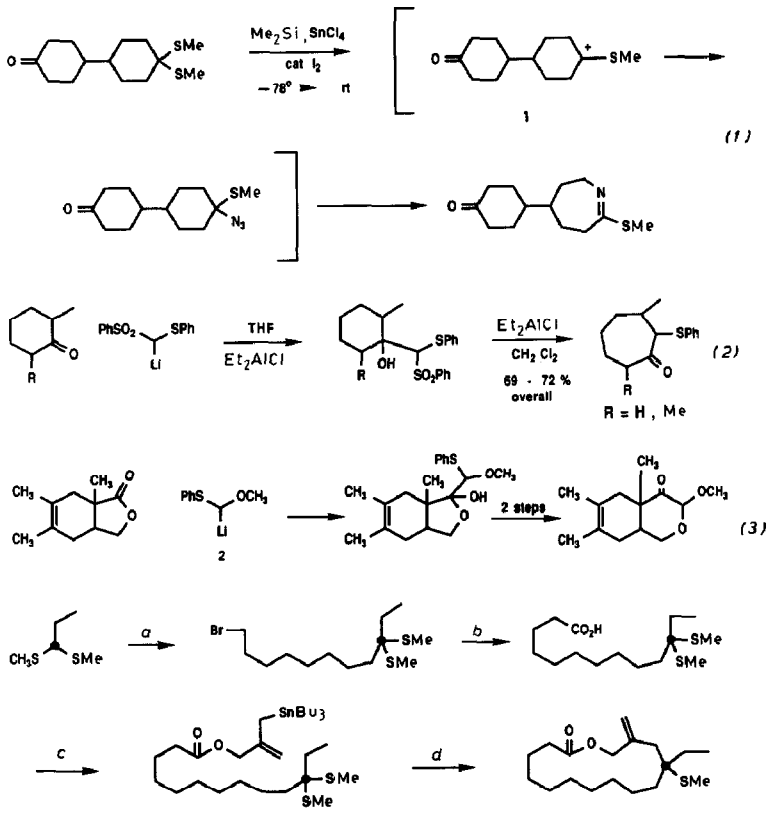
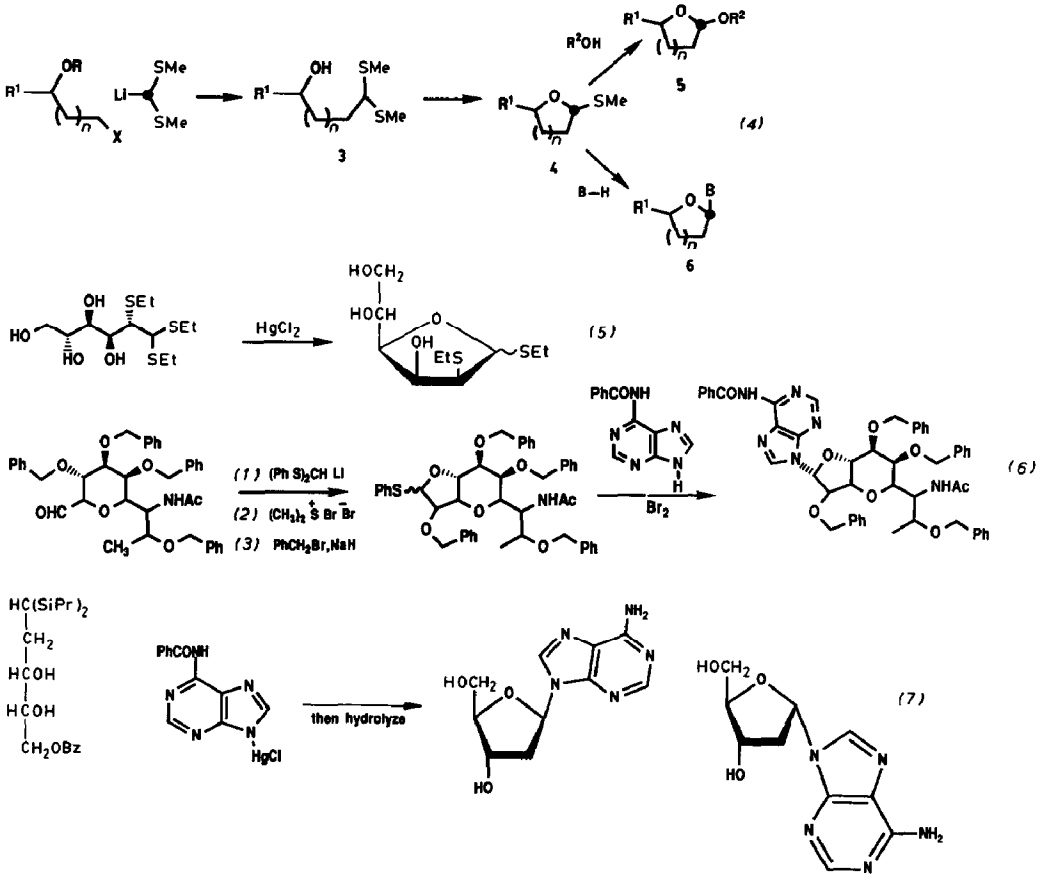


Scheme 1. "Chemical chameleons" in the synthesis of macrolides. (*a*) BuLi, THF, $Br(CH_2)Br$. (*b*) $LiCH_2CO_2Li$, THF. (*c*) $(Im)_2CO$, THF, $Bu_3SnCH_2C(CH_2OH)=CH_2$. (*d*) DMTSF, CH_2Cl_2

using the sulfide **2** introduced[7] the latter as a very useful acyl anion equivalent (Eq. *3*), a theme subsequently extensively developed by Otera and others[8]. This dual reactivity of organosulfur compounds led us to dub them "chemical chameleons", since they change their chemical reactivity from a nucleophile to an electrophile depending upon their environment.

Intramolecular trapping of the thionium ions made thioacetals key building blocks using this principle in the synthesis of macrolides, as outlined[9,10] in Scheme 1. The stability of the thioacetal towards many transformations and its extreme lability with certain activating agents highlighted by the use of dimethylthiosulfonium fluoroborate (DMTSF) enhances the utility of this strategy. The high chemoselectivity towards sulfur associated with DMTSF led one of us to propose to Prof. H. Paulsen, during a stay as a Senior Humboldt Awardee in Hamburg, that such a reagent should provide an excellent approach for glycoside-bond formation using glycosyl sulfides. The subsequent work of the groups of Paulsen[11], and Garegg[12,13] with the trifluoromethanesulfonate rather than fluoroborate salt (namely DMTST) has established the validity of the proposal.

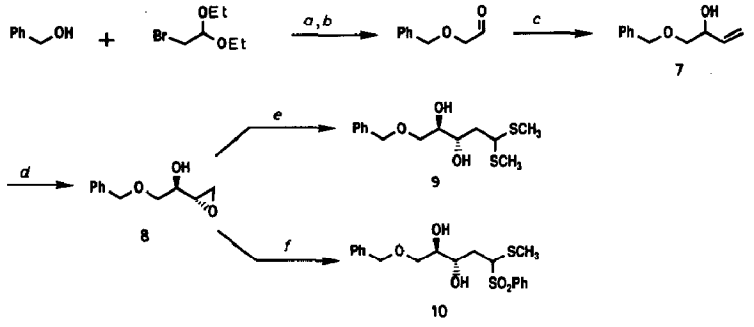
We examined the use of thioacetals for the synthesis of the basic sugar ring system in terms of their ability to function as chemical chameleons to Eq. *4*. This application



invokes both sulfur substituents as leaving groups – the first to form the glycosyl sulfide **4** and the second to form the glycosidic bond (namely **5**) or to replace the sulfur with a purine or pyrimidine to form a nucleoside **6**. A potential defect in this proposal is the relative reactivity of the α-thioether **4** towards the same reagents required to ionize the thioacetal **3**. A major uncertainty of this sequence is the question of the effectiveness of an oxygen nucleophile to capture a thionium ion. The propensity of thionium ions to suffer deprotonation to generate vinyl sulfides, and the mismatch of a hard oxygen nucleophile with a soft carbocation heightened the improbabitity of this proposal. Nevertheless, the potential ready accessibility of the requisite substrates in enantiomerically pure form led us to attempt the sequence.

The use of thioacetals in the synthesis of sugars and nucleosides has been previously noted, as exemplified[14–16*] in Eq. *5–7*. In all cases, starting materials were carbohydrate-based. The efficacy of the process varied depending upon the presence

* See ref 15(b) for a recent paper on oxocene synthesis *via* thionium ions.



Scheme 2. Synthesis of cyclization substrates. (*a*) NaH, THF, reflux, 70%. (*b*) 2M HCL, H_2O, acetone, 83%. (*c*) CH_2=CHMgBr, THF, reflux, 100%. (*d*) D-(−)-DIT, $Ti(OC_3H_7\text{-}i)_4$, Bu^tOOH, MS-3Å, CH_2Cl_2, −20°, 41% (82% based upon theoretical yield of 50%). (*e*) $CH_2(SMe)_2$, BuLi, THF, −70°, 83%. (*f*) $CH_3SCH_2SO_2Ph$, nBuLi, THF, −78°, 91%.

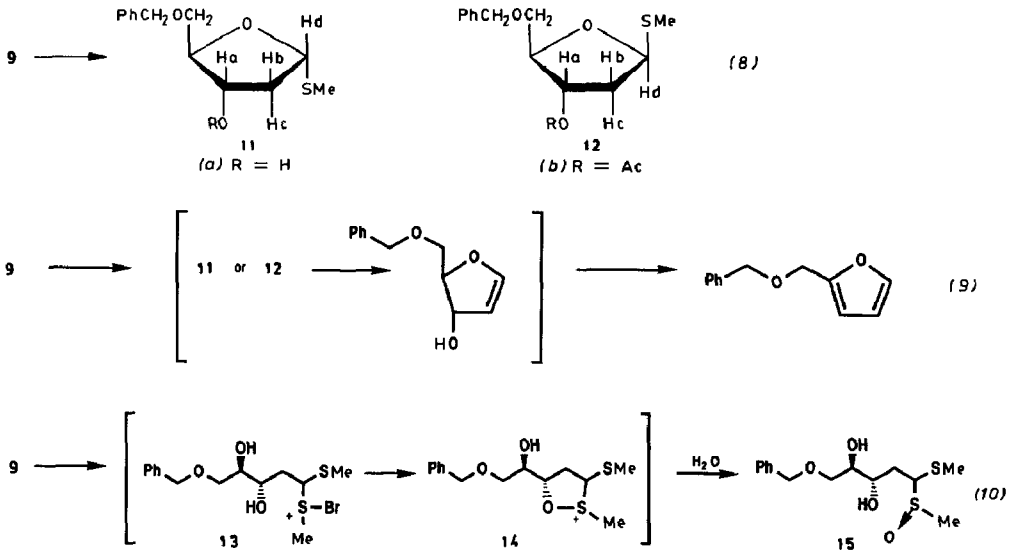
(Eq. *5* and *6*) or absence (Eq. *7*) of a 2-substituent in the resultant nucleoside derivative. We undertook a study of a *de novo* synthesis of a deoxynucleoside from a non-carbohydrate precursor utilizing a formaldehyde thioacetal as a key lynchpin.

RESULTS

An enantiocontrolled synthesis of the substrates. — Scheme 2 outlines the synthesis of the cyclization substrates directed towards 2-deoxyfuranoses. The allyl alcohol **7** is available following classical procedures[17]. The key for asymmetric synthesis is the kinetic resolution of **7**. Applying the Sharpless kinetic-resolution protocol[18] using D-(−)-diisopropyl tartrate provides epoxyalcohol **8** with 94% d.e. and >95% e.e., as determined by both g.l.c. and ^{13}C-n.m.r. analysis of the corresponding Mosher ester[19] in 82% yield, based upon a maximum conversion of 50%. Opening of the epoxide with the lithium salts of either bis(methylthio)methane[20] or methylthiomethyl phenyl sulfone[21] proceeds normally to the key cyclization precursors **9** or **10**, respectively. While we do not claim to have optimized the yields, the efficiency of the sequence appears evident by the current 40% overall yield from benzyl alcohol.

Cyclization studies. — As anticipated, the cyclization proved troublesome. DMTSF-initiated cyclization under various conditions of solvent, temperature, time, and quench leads, at best, only to 13% of the desired cyclized product, isolated as its acetates **11b** and **12b** (Eq. *8*). The fact that the methylthio group transfers reversibly apparently precludes the chemoselectivity required, leading to decomposition of the product concomitant with sulfur activation.

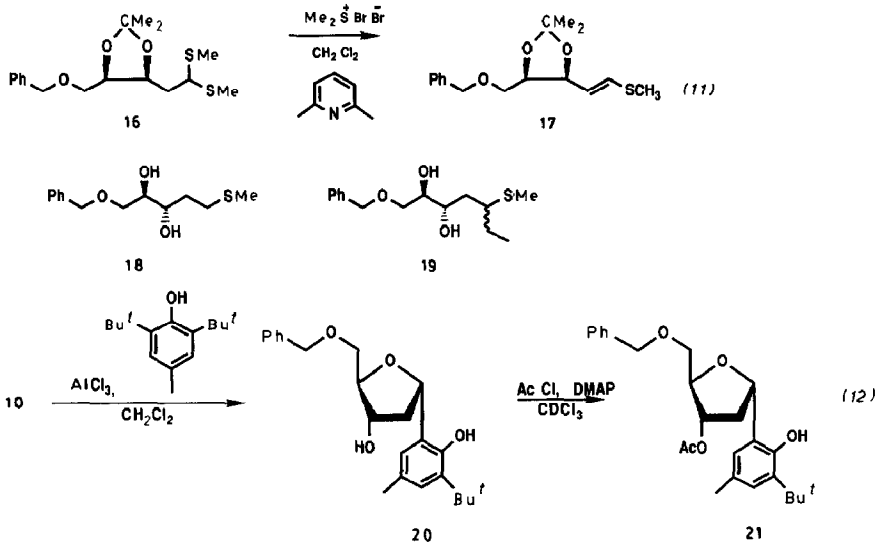
Procedures for irreversible sulfur activation at temperatures low enough to prevent ionization of the activated thioacetal were sought. Methylation[22] with dimethyl sulfate, trimethyloxonium fluoroborate, dimethoxycarbonium fluoroborate, or even methyl triflate leads mostly to black tars. In the case of dimethyl sulfate, the n.m.r. spectrum suggested the presence of some 2-benzyloxymethylfuran (δ 6.35 and 7.42) — a



fact indicating that the separation of the activation and ionization steps has not been achieved (Eq. *9*). Use of bromodimethylsulfonium bromide in dichloromethane[15] also forms a black tar. Addition of 2,6-lutidine to this latter reaction, however, generates a 79% yield of a new product identified as the monosulfoxide **15**. Eq. *10* outlines a possible source of the monosulfoxide wherein participation of one of the neighboring hydroxyl groups in the first-formed intermediate **13** forms a stable sulfoxonium ion **14** which hydrolyzes during work-up. To encourage ionization from **14**, the temperature was allowed to increase prior to quenching, but only an uncharacterized mixture was obtained. To minimize premature participation of the hydroxyl group, the corresponding acetal **16** was subjected to the same conditions. Unfortunately, all oxygen participation ceased and only the elimination product **17** was observed (Eq. *11*).

The use of thiophilic metals proved more promising. While ferric and stannic chlorides, triflates of zinc, cadmium, and cobalt, various mercury (II) and copper salts, as well as phenylboronic acid and molybdenum hexacarbonyl proved unrewarding, silver salts[23] led to successful cyclization. Treatment of thioacetal **9** with silver tetrafluoroborate in dichloromethane at room temperature gave a 63% yield of a ~10:1 ratio of cyclized products **11** and **12** at 69% conversion. Assignment of **11a** as the major diastereomer derives from the 6.5% n.O.e. between H_b and H_a and 6.7% n.O.e. between H_b and H_d, indicating that they are all on the same face of the tetrahydrofuran as in **11** and not **12**. Addition of 2,6-lutidine stopped the reaction.

Differentiating the two sulfur substituents as in substrate **10** provides a possible avenue to enhance the reactivity difference between the cyclization substrate and the methyl 1-thiofuranoside[2]. Our previous work on sulfones established the utility of aluminum salts as Lewis acids[24]. A mixture of **10** and 4–5 eq. of diethylaluminum chloride[25] in dichloromethane at −78 to −10° gave a 46% yield of a 1:1.4 ratio of reduced and ethylated products **18** and **19**. Switching to ethylaluminum dichloride

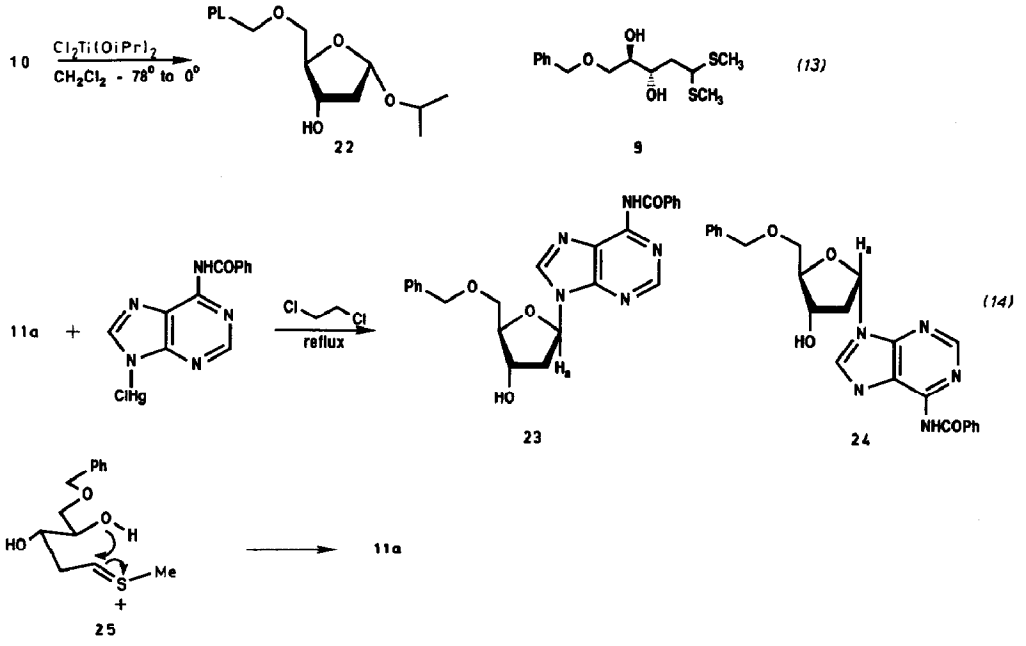


eliminated the ethylated product **19**, but gave mainly the reduced product **18** and only 15% of the cyclized products **11** and **12** in a 1:2.8 ratio. Reduction product **18** could be totally suppressed by use of dimethylaluminum chloride or methylaluminum dichloride, but the desired cyclization products were obtained in only low yields.

Aluminum chloride in nitromethane for 30 min at −78° gave 8% of **11a** and 11% of **12a** with substantial recovery of starting material. The yield increased to 26% total after 2.5 h, but an appreciable amount of the 5-benzyl ether of 2-deoxy-D-*erythro*-pentose was being generated simultaneously. In an attempt to modulate the reactivity of aluminum chloride, it was first treated with 2,6-di-*tert*-butyl-4-methylphenol (BHT), followed by the sulfone **10**. Surprisingly, the arylated tetrahydrofuran **20** was obtained as the exclusive observed product in 39% yield, and was further characterized as the corresponding acetate **21** (Eq. *12*).

In contrast to the foregoing, titanium-based Lewis acids proved more effective. Exposing the sulfone to 5 eq. of titanium tetrachloride in dichloromethane at −78° gave a 56% yield of a 1:1 mixture of the desired cyclization products **11a** and **12a** at 60% conversion. A milder catalyst, dichlorodiisopropoxytitanium, was examined in an attempt to minimize decomposition at higher coversions. In this case, acetal–thioacetal exchange gave a 34% yield of the cyclized acetal **22**, and a 42% yield of the uncyclized thioacetal **9** accompanied cyclization (Eq. *13*).

Conversion of hemithioacetal into nucleoside. — Having established an enantiocontrolled approach to the 2-deoxy-D-*erythro*-pentose system, the final substitution of the remaining methylthio group by a purine was briefly examined. Attempts to effect purination of the hemithioacetal activated with DMTSF or with bromine in DMF gave only low yields of the desired coupled-product in very unsatisfactory reactions. On the other hand, the reaction of the chloromercury salt of *N*-benzoyladenine[26,27] with hemithioacetal **11a** gave a 1:1.4 mixture of the β and α anomers **23** and **24** respectively (Eq.



14). Assignment of stereochemistry derives from n.m.r. comparisons. Quite diagnostic is the appearance of H_a as a triplet (J 6.4 Hz) in **23**, but[28] as a double doublet (J 9.0, 2.2 Hz) in **24**.

DISCUSSION

The capture of a thionium ion by an oxygen nucleophile appears less efficacious compared to carbon nucleophiles. The sensitivity of the success of the cyclization to the exact conditions attests to the correctness of this statement. Nevertheless, silver fluoroborate did successfully induce the proper cyclization to predominantly a single isomer at the anomeric center. Based upon **25** as the reactive conformer, the observed *a* anomer is the expected kinetic product.

The difference in ease of cyclization as reported herein, compared to previous cyclizations of thioacetals in the carbohydrate field, is striking[14,15]. Previous examples where good yields were obtained involved cyclizations to furanoses or pyranoses bearing an additional heteroatom substituent at the carbon adjacent to the anomeric center. In examples lacking such a substituent, very low yields were obtained. In the case reported herein, the absence of such a substituent can lead competitively to deprotonation to a vinyl sulfide prior to cyclization, or to consumption of the initial products under many of the cyclization conditions. The presence of an adjacent oxygen or sulfur substituent appears to inhibit both of these side processes. Nevertheless, reasonable yields are obtained with the use of silver salts.

Thus, thioacetals may be employed as chemical chameleons in the construction of 2-deoxynucleosides. The ability of sulfur to facilitate anion formation utilizes the nucleophilic properties of the building block which then are electronically inverted to electrophilic in order to allow sequential replacement of the sulfur by an alcohol (intramolecularly) and a purine (intermolecularly). Combining the versatility of the sulfur chemistry with the accessibility of the requisite epoxide in enantiomerically pure form then constitutes a very convenient and rapid entry to 2-deoxy sugars and, ultimately, 2'-deoxynucleosides from totally non-cabohydrate building-blocks.

EXPERIMENTAL

General methods. — Flash chromatography employed E. Merck silica gel (Kieselgel 60, 200–400 mesh). Analytical t.l.c. was performed using 0.2 mm coated commercial silica gel plates (E. Merck, DC-Plastikofien, Kieselgel 60 F_{254}). Melting points, obtained on a Thomas–Hoover apparatus in open capillary tubes, and boiling points, are uncorrected. N.m.r. spectra were obtained on a Varian XL-400 (100 MHz for ^{13}C) or Gemini 300 (75 MHz for ^{13}C) instrument, and are reported in p.p.m. relative to Me_4Si. Drying of organic layers utilized a mixture of anhydrous magnesium and sodium sulfates. Benzyloxyacetaldehyde diethyl acetal (b.p. 88–92° at 0.2 mm; lit.[17] 132–140° at 10 mm) and benzyloxyacetaldehyde (b.p. 76–80° at 0.3 mm; lit.[17] 108–114° at 10 mm) were prepared according to the procedure of Grob and Reber[17].

1-Benzyloxybut-3-en-2-ol (**7**). — Dropwise addition of a solution of benzyloxyacetaldehyde (7.5 g, 50 mmol) in 50 mL of anhydrous THF to a 0.83M solution of vinylmagnesium bromide in THF (72 mL, 60 mmol) caused the temperature to rise to 60°. After 30 min at reflux and subsequent cooling, addition of saturated aq. NH_4Cl, followed by decanting of the organic layer and washing the precipitate with additional THF, led to a crude oil after evaporation *in vacuo*. The residue was dissolved in 300 mL of ether and dried. Removal of solvent *in vacuo* and flash chromatography elution with 2:1 hexane–ether gave 9.14 g (quantitative) of the title compound, identical to a literature sample[29] prepared by a different route.

(+)-(2R,3S)-1-Benzyloxy-3,4-epoxy-2-butanol (**8**). — Titanium tetraisopropoxide (2.27 g, 8.0 mmol) was added to a −20° mixture of the foregoing allyl alcohol **7** (14.23 g, 80.0 mmol), D-(−)-diisopropyl tartrate (2.81 g, 12 mmol) and powdered 3Å molecule sieves (4.3 g, 25 wt.% based on alcohol) in 300 mL of CH_2Cl_2. After stirring for 30 min at −20°, a 3.0M solution of *tert*-butyl hydroperoxide in isooctane (16 mL, 48 mmol, dried over 3Å molecular sieves for 30 min prior to addition) was added and the mixture stirred for 14 days at −15°. A solution of ferric sulfate heptahydrate (26.4 g) and citric acid hydrate (8.8 g) in 80 mL of water was added at −15° and the mixture stirred for 30 min at ambient temperature. After separation of the phases and extraction of the aqueous phase with CH_2Cl_2, the combined organic layers were stirred vigorously for 1 h with 30% aq. NaOH–NaCl. Filtration through Celite, extraction of the aq. phase with ether, drying of the combined organic layers, and evaporating of the organic

solvent *in vacuo* gave a crude oil which was purified by column chromatography eluting with 1:1 hexane–ether to provide 6.3 g (41%, 82% based upon 50% theoretical yield) of the title compound identical to the literature sample[30] prepared from tartaric acid; $[\alpha]_D^{25}$ −11.23° (*c* 1.3, $CHCl_3$); lit.[30] $[\alpha]_D^{25}$ −11° (*c* 0.93, $CHCl_3$).

(2 R,3S)-1-Benzyloxy-2,3-dihydroxy-5,5-bis(methylthio)pentane (**9**). — A solution of the foregoing epoxide **8** (1.84 g, 9.5 mmol) in 4 mL of anhydrous THF was added slowly at −70° to a suspension of bis(methylthio)methyllithium[20] prepared from bis-(methylthio)methane (4.1 g, 38 mmol) and BuLi (25 mL, 1.5M in hexane, 37.5 mmol) in 12 mL of anhydrous THF. After 30 min, at < −50°, the reaction was allowed to warm during 2 h to 0°, poured into 50 mL of saturated brine, and extracted with ether. The organic layer was dried and then evaporated, and the crude oil that was purified by chromatography, eluting with 1:2 hexane–ether, to give 2.38 g (83%) of an oil which slowly solidified; m.p. 55–56° (10:1 hexane–ether), $[\alpha]_D^{28}$ −10.1° (*c* 0.82, $CHCl_3$); $\nu_{max}^{CHCl_3}$: 3650–3300, 1460, 1440, 1110 cm^{-1}; ^{1}H-n.m.r. (400 MHz, $CDCl_3$); δ 7.37–7.30 (m, 5 H), 4.56 (s, 2 H), 4.02 (m, 1 H), 3.94 (dd, 1 H, *J* 8.9, 5.5 Hz), 3.71 (m, 1 H), 3.63 (m, 2 H), 2.76 (d, 1 H, *J* 5.6 Hz, D_2O-exchange), 2.61 (d, 1 H, *J* 5.1 Hz, D_2O-exchange), 2.13 (d, 3 H, 2.08 (s, 3 H), and 1.95 (m, 2 H).

Anal. Calc. for $C_{14}H_{22}O_3S_2$: C, 55.63; H, 7.28. Found: C, 55.68; H, 7.37.

(2 R,3S,5RS)-1-Benzyloxy-2,3-dihydroxy-5-methylthio-5-phenylsulfonylpentane(**10**). — A solution of the epoxide **8** (1.94 g, 10 mmol) in 10 mL of anhydrous THF was added dropwise to a −78° suspension of (methyl)(phenylsulfonyl)methyllithium in 40 mL of anhydrous THF prepared from (methylthio)methyl phenyl sulfone (6.06 g, 30 mmol) and BuLi (23.5 mL of 1.28 M solution in hexane, 30 mmol). The mixture was allowed to warm over 1.5 h to ambient temperature, poured into water, and extracted with CH_2Cl_2. After drying and evaporating the solvent *in vacuo*, column chromatography (elution with 4:1 ether–hexane) gave 3.6 g (91%) of the title compound as a 3:2 diastereomeric mixture which could be separated on small-scale chromatography; ν_{max}^{film} 3600–3200, 1440, 1350, 1290, 1140, and 1075 cm^{-1}; ^{13}C-n.m.r. (75 MHz, $CDCl_3$) of mixture: δ 137.39, 136.65, 134.22, 134.09, 129.93, 129.83, 129.02, 128.73, 128.69, 128.19, 128.12, 128.02, 73.66, 73.56, 72.16, 71.07, 70.95, 70.69, 69.36, 67.14, 66.68, 32.60, 30.25, 15.21, and 14.81; ^{1}H-n.m.r. (400 MHz, $CDCl_3$): (less-polar diastereomer): δ 7.94 (d, 2 H, *J* 7.3 Hz), 7.67 (t, 1 H, *J* 7.3 Hz), 7.55 (t, 2 H, *J* 7.3 Hz), 7.33 (m, 5 H), 4.54 (s, 2 H), 4.06 (dd, 1 H, *J* 7.7, 5.8 Hz), 3.99 (m, 1 H), 3.70 (m, 1 H), 3.62 (m, 2 H), 2.93 (d, 1 H, *J* 5.1 Hz, D_2O-exchange), 2.60 (d, 1 H, *J* 5.4 Hz), 2.49 (ddd, 1 H, *J* 15.0, 5.7, 4.3 Hz), 2.23 (s, 3 H), 1.89 (dd, 1 H, *J* 15.0, 7.9 Hz); (more-polar diastereomer): δ 7.94 (d, 2 H, *J* 7.6 Hz), 7.66 (t, 1 H, *J* 7.6 Hz), 7.56 (t, 2 H, *J* 7.6 Hz), 7.33 (m, 5 H), 4.54 (d, 1 H, *J* 11.8 Hz), 4.53 (d, 1 H, *J* 11.8 Hz), 4.11 (dd, 1 H, *J* 11.8, 2.6 Hz), 4.02 (m, 1 H), 3.72 (m, 1 H), 3.62 (m, 2 H), 2.61 (d, 1 H, *J* 5.5 Hz, D_2O-exchange), 2.51 (d, 1 H, *J* 7.2 Hz, D_2O-exchange), 2.29 (ddd, 1 H, *J* 14.0, 10.9, 2.8 Hz), 2.16 (s, 3 H), and 1.75 (ddd, 1 H, *J* 14.0, 12.0, 2.0 Hz).

(2S,4S,5R)-5-Benzyloxymethyl-4-hydroxy-2-methylthiotetrahydrofuran (**11a**) *and its 2R isomer* (**12a**). — A solution of 1.0 g (3.3 mmol) of thioacetal **9** in 20 mL of dry CH_2Cl_2 was added to silver fluoroborate (710 mg, 3.6 mmol, dried at 70°/0.5 mm) dissolved in 80 mL of dry CH_2Cl_2. After stirring for 3 h at ambient temperature, the

yellow suspension was poured into saturated aq. $NaHCO_3$ and the aq. phase extracted with ether. After drying and evaporating *in vacuo* the combined layers, the crude oil was chromatographed, eluting with 1:1 ether–hexane to give 328 mg (39%, 57% based upon recovered starting material) of **11a** and 345 mg of starting material containing a small quantity of **12a**; $[\alpha]_D^{25}$ +15.7° (*c* 0.52, $CHCl_3$); $\nu_{max}^{CCl_4}$ 3600–3400, 1445, 1430, 1355, and 1075 cm^{-1}; ^{1}H-n.m.r. (400 MHz, $CDCl_3$): δ 7.37–7.29 (m, 5 H), 5.41 (dd, 1 H, *J* 7.3, 2.5 Hz), 4.58 (d, 1 H, *J* 12.1 Hz), 4.54 (d, 1 H, *J* 12.1 Hz), 4.24–4.18 (m, 2 H), 3.63 (dd, 1 H, *J* 10.2, 4.4 Hz), 3.56 (dd, 1 H, *J* 10.2, 4.5 Hz), 2.60 (m, 1 H), 2.54 (d, 1 H, *J* 8.6, D_2O-exchange), 2.21 (s, 3 H), and 1.93 (dt, 1 H, *J* 13.9, 2.5 Hz);. ^{13}C-n.m.r. (75 MHz, $CDCl_3$): δ 138.03, 128.54, 127.87, 127.78, 84.83, 84.45, 73.45, 73.30, 70.01, 41.32, and 13.86; *m/z* calc. for $C_{13}H_{18}O_3S$: 254.0972, found: 254.0962.

Cyclization of sulfone **10**. — Titanium tetrachloride (50 μL, 460 μmol) was added to a −78° solution of sulfone **10** (36.4 mg, 92 μmol) in 2 mL of CH_2Cl_2. After stirring for 4 h at −78°, the mixture was quenched at 78° with 3 drops of concentrated aq. ammonia. The reaction was filtered through a plug of cotton wool and the solvent evaporated. The resultant crude oil was purified by flash chromatography eluting with 3:1 ether–hexane to give 4 mg (17%, 29% based upon recovered starting material) of the foregoing cyclized product **11a**, 4 mg (17%, 29% based upon recovered starting material) of the epimer **12a**, and 40% recovered starting material. ^{1}H-N.m.r. of **12a** (300 MHz, $CDCl_3$): δ 7.34 (m, 5 H), 5.31 (t, 1 H, *J* 6.9 Hz), 4.58 (d, 1 H, *J* 12 Hz), 4.57 (d, 1 H, *J* 12 Hz), 4.42 (m, 1 H), 4.03 (m, 1 H), 3.66 (dd, 1 H, *J* 9.7, 5.1 Hz), 3.52 (dd, 1 H, *J* 9.7, 6.9 Hz), 2.30–2.15 (m, 2 H), 2.19 (s, 3 H), and 1.84 (d, 1 H, *J* 3.8 Hz, D_2O-exchange).

*9-(5-*O*-Benzyl-2-deoxy-β-*D*-*erythro*-pentofuranosyl)-6-*N*-benzoyladenine* **23** *and its α anomer* **24**. — A mixture of 31.3 mg (123 μmol) of thiofuranoside **11a** and 75.8 mg (160 μmol) of 6-*N*-benzoyl-9-chloromercuriadenine in 6 mL of 1,2-dichloroethane was heated at reflux for 5 h. After filtering through Celite and washing the precipitate with CH_2Cl_2, the filtrate was evaporated and the remaining oil was purified by flash chromatography eluting 2:1 CH_2Cl_2–acetone to give 11 mg (20%) of **23**, R_F 0.31, and 15 mg (28%) of **24**, R_F 0.48. For **23**: $\nu_{max}^{CHCl_3}$ 3500–3150; 1705, 1610, 1580, 1475, 1450, and 1400 cm^{-1}; ^{1}H-n.m.r. (400 Hz, $CDCl_3$): δ 9.09 (bs, 1 H, D_2O-exchange), 8.77 (s, 1 H), 8.33 (s, 1 H), 8.02 (d, 2 H, *J* 7.6 Hz), 7.60 (m, 1 H), 7.52 (m, 2 H), 7.36–7.26 (m, 5 H), 6.57 (t, 1 H, *J* 6.4 Hz), 4.72 (b, 1 H), 4.59 (d, 1 H, *J* 11.9 Hz), 4.53 (d, 1 H, *J* 11.9 Hz), 4.19 (m, 1 H), 3.73 (dd, 1 H, *J* 10.4, 3.9 Hz), 3.67 (dd, 1 H, *J* 10.4, 2.1 Hz), 2.79 (dt, 1 H, *J* 14.3, 6.4 Hz), 2.76 (s, 1 H, D_2O-exchange), and 2.57 (ddd, 1 H, *J* 14.3, 6.4, 3.3 Hz); ^{13}C-n.m.r. (100 MHz, $CDCl_3$): δ 164.73, 152.54, 151.41, 149.35, 141.61, 137.36, 133.63, 132.78, 128.83, 128.55, 127.99, 127.88, 127.77, 123.10, 86.10, 84.59, 73.63, 72.48, 69.94, and 41.01; *m/z* (f.a.b.): calc. for $C_{24}H_{23}N_5O_4 + H^+$: 446. found: 446. For **24**: $\nu_{max}^{CHCl_3}$ 3500–3150, 1705, 1610, 1585, 1495, 1475, 1450 cm^{-1}; ^{1}H-n.m.r. (400 MHz, $CDCl_3$): δ 9.08 (bs, 1 H, D_2O-exchange), 8.80 (s, 1 H), 8.14 (s, 1 H), 8.01 (d, 2 H, *J* 7.2 Hz), 7.61 (t, 1 H, *J* 7.4 Hz), 7.52 (t, 2 H, *J* 7.5 Hz), 7.39–7.29 (m, 5 H), 6.66 (d, 1 H, *J* 9.8 Hz, D_2O-exchange), 6.30 (dd, 1 H, *J* 9.0, 2.2 Hz), 4.59(d, 1 H, *J* 12.0 Hz), 4.53 (d, 1 H, *J* 12.0 Hz), 4.60–4.50 (m, 2 H), 3.63 (m, 2 H), 3.11 (ddd, 1 H, *J* 14.8, 9.0, 6.7 Hz), and 2.54 (bd, 1 H, *J* 14.8 Hz); ^{13}C-n.m.r. (100 MHz, $CDCl_3$): δ 164.58, 151.86, 150.02, (2C), 143.39, 137.72, 133.44, 132.87,

128.85, 128.50, 127.87, 127.77, 127.58, 124.04, 88.87, 86.86, 73.66, 73.27, 71.35, and 40.99; *m/z* (f.a.b.): calc. for $C_{24}H_{23}N_5O_4 + H^+$ 446; found: 446. Calc. for $C_{24}H_{23}N_5O_4$: 445.1745: found 445.1787.

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