in hexane (126 μL, 0.315 mmol) dropwise at -78 °C. After the resulting dark red solution was stirred at -78 °C for 15 min, 200 μL of HMPA and 150 μL of the aldehyde **2** were added successively. The reaction mixture was stirred at -78 °C for 40 min, then warmed to -20 °C, and stirred at that temperature for 30 min. After the temperature was slowly raised to 25 °C, the reaction mixture was poured into ice-water. The aqueous phase was extracted by 3 × 2 mL of ether. The combined extracts were washed with brine, filtered through 1 g of deoxygenated silica gel, and dried over $MgSO_4$. After concentrating in vacuo, the yellow oily residue was chromatographed over 4 g of silica gel. Elution with hexane-ethyl acetate (10:1) resulted in a crude product (**24**) (30%) containing 5:1 Z-E mixture and some impurities.

Further purification of the *Z* isomer was effected by either repeated flash column chromatography (silica gel; 20:1 hexane-ethyl acetate; *E* isomer, R_f 0.09; *Z* isomer, R_f = 0.06; on TLC plate) or HPLC (Alltech, 10 μPorsail, length 50 cm, i.d. 9.4 mm column; 988:2:10 hexane-ethyl acetate-Et_3N; flow rate 3 mL/min; retention time of *E* isomer = 17.7 min; *Z* isomer = 19.8 min) gave 32 mg (15%) of pure **24**: TLC (5:1 hexane-ethyl acetate) R_f 0.56; $[\alpha]^{25}_D$ +205° (*c* 2.1, $CDCl_3$); UV $(MeOH)_{max}$ 262, 272, 284 nm; IR ($CDCl_3$) 3000 (w), 2960 (m), 2930 (m), 2850 (m), 1740-1710 (s), 1450-1425 (w), 1310 (w), 1270 (s), 1105 (s), 1065 (w), 1020 (w), 990 (m), 700 (s) cm^{-1}; ^1H NMR δ 0.88 (t, 3 H), 1.10 (s, 9 H), 1.10-1.40 (m, 8 H), 1.76 (m, 4 H), 2.29 (m, 4 H), 3.60 (s, CH), 4.18 (m, 2 H), 5.28 (m, 2 H), 5.63-6.38 (m, 6 H), 7.30, (7.60, and 7.92 (m, 15 H).

Methyl 5(*S*)-(Benzoyloxy)-12(*R*)-hydroxy-6(*Z*),8,10-(*E*),14(*Z*)-eicosatetraenoate (25). To a stirred solution of 32 mg (0.046 mmol) of the silyl ether **24** in 0.6 mL of THF was added 400 μL of tetra-*n*-butylammonium fluoride at 25 °C. After the mixture was stirred for 5 h, 1.5 mL of water was added. The aqueous phase was extracted with ether (3 × 1 mL). The combined extracts were washed with water and concentrated in vacuo to yield 31 mg of crude product, which was chromatographed over 1.4 g of silica gel. Elution of the column with hexane-ethyl acetate (5:1) afforded 10 mg (48%) of the alcohol **25**: TLC (5:1 hexane-ethyl acetate) R_f 0.29; $[\alpha]^{25}_D$ +288.7° (*c* 0.75, $CDCl_3$); UV $(CH_3OH)_{max}$ 262, 271, 282; ^1H NMR δ 0.88 (t, 3 H), 1.30 (m, 8 H), 1.70 (m, 4 H), 2.00 (m, 2 H), 2.35 (m, 4 H), 3.68 (s, 3 H), 4.18 (m, 1 H), 5.28 (m, 2 H), 5.63-6.38 (m, 6 H), 7.92 and 7.60 (m, 5 H).

LTB_4 (1). A 1-mL reaction vial was charged with a solution of 10 mg (0.022 mmol) of the ester **25** in 200 μL of CH_3OH, 50 μL of water, and 24 mg (0.24 mmol) of K_2CO_3 at room temperature under argon. The reaction progress was monitored by TLC. After the starting material **25** was completely hydrolyzed (12 h), 200 μL of water was added. The pH was adjusted to pH 4 with 10% acetic acid and the aqueous phase was then extracted with ethyl acetate (5 × 300 mL). After concentration of the extracts, the residue was purified by column chromatography over 1 g of deoxygenated silica gel. The column was eluted with hexane-ethyl acetate (1:1) with 1% acetic acid, to yield 5 mg (68%) of LTB_4 (1). RP-HPLC (reversed-phase HPLC, using a C_{18} partisil 10/50 ODS Whatman column; 3:1 methanol-water, containing 0.01% acetic acid) showed ≥98% purity for the final product, 1: TLC (ethyl acetate), R_f 0.31; $[\alpha]^{25}_D$ +12.6° (*c* 0.46, $CDCl_3$); UV (CH_3OH) λ_{max} 260 270.5, 281 nm, (ε 43 000, 52 000, 42 000); ^1H NMR δ 0.91 (t, 3 H), 1.30 (m, 8 H), 1.69 (m, 4 H), 2.03 (m, 2 H), 2.35 (m, 4 H), 4.25 (m, 1 H), 4.66 (m, 1 H), 5.25-5.55 (m, 4 H), 5.68-5.98 (m, 1 H), 6.10-6.40 (m, 4 H).

Acknowledgment. This work was supported by the National Institutes of Health, Grant AM09688.

Synthesis of 9-[5-(Alkylthio)-5-deoxy-β-D-*erythro*-pent-4-enofuranosyl)adenines as Potential Inhibitors of Transmethylation†

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Received November 6, 1985

Various methods have been examined for the conversion of suitably protected nucleoside 5'-aldehydes into the previously undescribed dithioacetals. Treatment with (alkylthio)trimethylsilanes in the presence of trimethylsilyl triflate and/or zinc iodide is effective in various series, and sequential formation of mixed dithioacetals can be achieved. Treatment of thioacetals of fully benzoylated adenosine derivatives with bromine and DBU leads to efficient elimination to provide, e.g., 9-[5-deoxy-5-(isobutylthio)-β-D-*erythro*-(*Z*)-pent-4-enofuranosyl]adenine (**20a**), a compound containing structural features of both the sinefungin analogue A9145C and SIBA. A comparable elimination in the uridine series can be accomplished with mercuric trifluoroacetate and lithium carbonate.

The importance of *S*-adenosylmethionine (AdoMet) mediated transmethylation in diverse biochemical processes has made this system an attractive target for medicinal intervention.[2] The byproduct of such transmethylation, *S*-adenosylhomocysteine (AdoHcy), is itself a potent inhibitor of the methyl transferases and plays a key regulatory role. The levels of AdoHcy are regulated by the enzyme AdoHcy hydrolase (EC 3.3.1.1), and the latter species has become a central target in the development of specific methylation inhibitors.[3]

Amongst the many compounds that have proved to suppress transmethylation via inhibition of AdoHcy hydrolase are the natural products sinefungin (1),[4] a recent synthetic target within this Institute,[5] and the related unsaturated nucleoside A9145C (**2**).[4] Also, a wide range of biological effects have been recorded by using 5'-deoxy-5'-(isobutylthio)adenosine (SIBA, **3**)[3a] a compound

† Contribution 222 from the Institute of Bio-Organic Chemistry, Syntex Research, Palo Alto, CA.

(1) Syntex Postdoctoral Fellow.

(2) See, e.g.: (a) "Transmethylations"; Usdin, E., Borchardt, R. T., Creveling, C. R., Eds.; Elsevier: New York, 1969. (b) "The Biochemistry of *S*-Adenosylmethionine and Related Compounds"; Usdin, E., Borchardt, R. T., Creveling, C. R., Eds.; Macmillan Press: London, 1982.

(3) See, e.g.: (a) Ueland, P. M. *Pharmacol. Rev.* **1982**, *34*, 223. (b) Houston, D. M.; Dolence, E. K.; Keller, B. T.; Patel-Thombre, U.; Borchardt, R. T. *J. Med. Chem.* **1985**, *28*, 467 and references therein.

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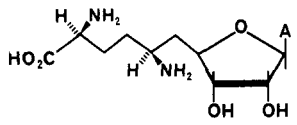

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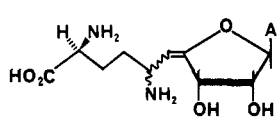

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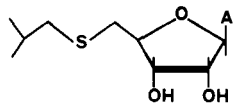

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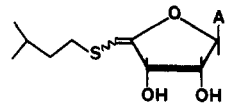
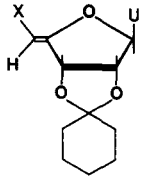


4

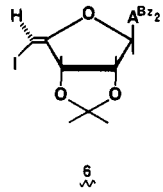
originally prepared by Hildesheim, et al.[6] In view of the many interesting activities shared by the above types of molecule, it occurred to us that 9-[5-deoxy-5-(isobutylthio)-β-D-*erythro*-pent-4-enofuranosyl)adenine (**4**), a molecule incorporating structural features of both SIBA and A9145C, might be an interesting target. This paper records a pathway suitable for the synthesis of **4** and its alkyl congeners.

We have previously had considerable experience in the synthesis of simple 4-,5'-unsaturated nucleosides in both the pyrimidine[7] and purine[8] series via base or silver fluoride promoted elimination reactions of suitably protected 5'-deoxy-5'-iodo nucleosides. Similar base-induced eliminations of 5'-*O*-sulfonyl moieties have also been used,[9] as have thermal eliminations of selenoxides[10a] and sulfoxides.[10b]

While the above methods are well suited for the preparation of simple 4',5'-olefins, they are not readily adapted to the synthesis of substituted vinyl derivatives such as **4**. Previously both enol acetate (e.g., **5a**)[11a] and enamine derivatives[11b] have been prepared from appropriately protected nucleoside 5'-aldehydes. Also, the vinyl iodide



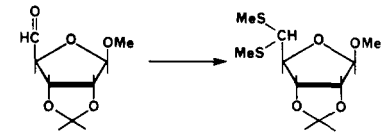
5 (a) X = OAc
(b) X = N(CH$_2$)$_4$



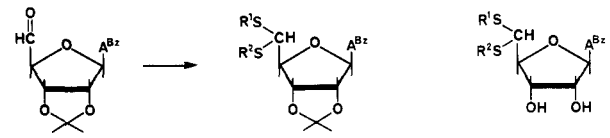
6

6 was previously obtained in our work,[9b] but methods for the alkylation of this interesting species have not been explored. On the basis of NMR considerations presented later in this paper, the *E* configuration assigned to **6** may well be in question. The chemical stability of **4** was also something of an uncertainty since it is a monothio enediol derivative, and even the simple, unsubstituted 4',5'-unsaturated nucleosides are known to be quite acid labile.[7-9]

A consideration of the varied methods available for the synthesis of vinyl sulfides[12] suggested that an elimination reaction upon an appropriate dithioacetal derived from a nucleoside 5'-aldehyde would be attractive. While we have had much experience in the synthesis of such aldehydes[13,14] using the carbodiimide–sulfoxide method,[15] we are unaware of any preparation of the corresponding dithioacetals. Preliminary experiments on BF_3·OEt_2-catalyzed condensation of N^6-benzoyl-2',3'-*O*-isopropylideneadenosine-5'-aldehyde (**9**)[13b] with 2-methylpropanethiol were unpromising under conditions that readily led to thioacetal formation from *n*-hexanal. TLC analysis showed the formation of the less polar presumed hemithioacetal, which reverted to the parent aldehyde. The use of titanium tetrachloride[16] or sulfur dioxide[17] was no more promising. Accordingly, we turned to the methods of Evans[18] and Noyori[19] using (alkylthio)trimethylsilanes in the presence of zinc iodide or trimethylsilyl triflate. Reaction of methyl 2,3-*O*-isopropylidene-β-D-*ribo*-pentodialdo-1,4-furanoside (**7**)[20] with (methylthio)trimethylsilane in the presence of a catalytic amount of trimethylsilyl triflate gave the crystalline dithioacetal **8** in 50% yield (unoptimized). The corresponding reaction using the protected adenosine 5'-



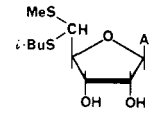
7 8



9

10 (a) R^1, R^2 = Me
(b) R^1 = *i*-Bu, SR^2 = OTMS
(c) R^1, R^2 = *i*-Bu
(d) R^1 = *i*-Bu, R^2 = Me

11 (a) R^1, R^2 = Me
(b) R^1, R^2 = *i*-Bu
(c) R^1 = *i*-Bu, R^2 = Me



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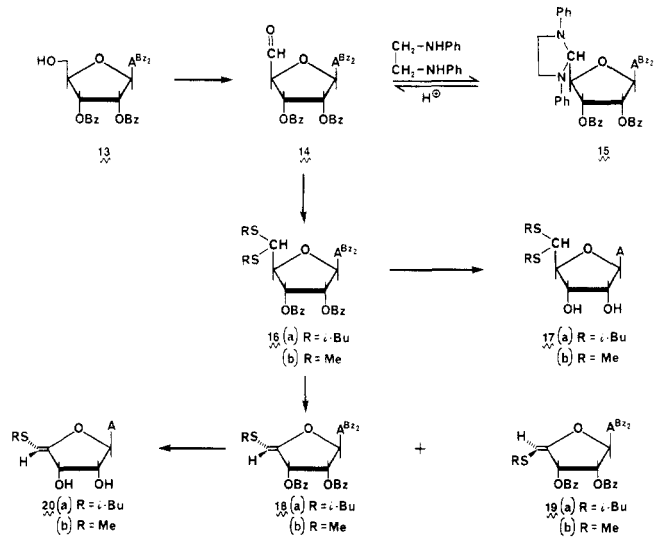
aldehyde **9** was also successful and gave the only slightly impure thioacetal **10a** in 52% yield. Selective removal of the acetonide with trifluoroacetic acid then gave the highly crystalline diol **11a** which showed the expected magnetic nonequivalence of the methylthio groups in its NMR spectrum.

Attempted extension of this reaction using (isobutylthio)trimethylsilane and either trimethylsilyl triflate or zinc iodide was, however, not satisfactory and led, even after prolonged reaction times, only to the trimethylsilyl ether of the hemithioacetal **10b**. Accumulation of this much less polar product was apparent upon TLC analysis, but aqueous workup rapidly regenerated the known hydrate of the parent aldehyde **9**.[13b] Such compounds have previously been obtained and studied by Evans et al.[18] and by Chan et al.[21] It was noted, however, that addition of a catalytic amount of triflic acid to the above reactions led to formation of the desired isobutyl thioacetal **10c** (18%) together with the corresponding diol **11b** (43%) resulting from partial hydrolysis of the isopropylidene group. The relative proportions of **10c** and **11b** varied considerably in different reactions. Accumulation of the intermediate, **10b**, permitted the preparation of mixed thioacetals. Thus **9** was reacted with (isobutylthio)trimethylsilane and trimethylsilyl triflate, and then all volatile components were removed in vacuo. The resulting **10b** was then reacted with (methylthio)trimethylsilane and a catalytic amount of triflic acid giving two major and three minor products. Careful TLC analysis showed only a small amount of the dimethyl thioacetal **10a** and none of the diisobutyl thioacetal **10c**. Isolation of the two major products led to their identification as the mixed thioacetal **10d** and the corresponding diol **11c** in yields of 21% and 26%, respectively. Debenzoylation of **11c** by treatment with methanolic ammonium hydroxide gave the free mixed thioacetal **12** in essentially quantitative yield. The 300-MHz NMR spectra of **10d**, **11c**, and **12** were very clean and showed that each was an essentially 1:1 mixture of thioacetal diastereomers containing equal amounts of methylthio and isobutylthio groups. The chemical ionization mass spectra of each also confirmed the molecular structures and showed the absence of symmetrical thioacetals.

The problems associated with the formation of the diisobutyl thioacetal **10c**, together with indications that the isopropylidene group was leading to side reactions during conversion to the desired vinylthioethers (as in **4**), led us to redirect our efforts toward 2′,3′-acylated thioacetals. Our overall approach is outlined in Scheme I. Oxidation of N^6,N^6,$O^{2'}$,$O^{3'}$-tetrabenzoyladenosine (**13**)[8a,22] using the Me_2SO–DCC method[15] with either dichloroacetic or methylphosphonic acid as the proton source readily gave the 5′-aldehyde as judged by TLC analysis. The crystalline N^1,N^3-diphenylimidazolidine derivative **15** could be isolated in 57% yield following addition of 1,2-dianilinoethane, but regeneration of the free aldldehyde **14** or its hydrate proved to be more difficult than in other series we have studied.[13] The use of an acidic ion-exchange resin appeared to be very slow, but treatment with *p*-toluenesulfonic acid in methylene chloride–acetone led to rapid hydrolysis with precipitation of the 1,2-dianilinoethane tosylate. Nevertheless, even by use of extreme care, traces of impurities accompanied the desired aldehyde, and for most purposes we have found that crude **14** directly obtained from the oxidation reaction was preferable for

Scheme I



subsequent reactions. In view of the potential for β-elimination of the 3′-benzoyl group to generate an α,β-unsaturated aldehyde,[23] considerable care should be taken with this compound, and manipulations should be minimized. Because of this we have tended to use the crude aldehyde, presumably as its hydrate, without attempting dehydration via azeotropic drying as was used in the 2′,3′-acetal series.[13] Reaction of such crude **14** with either (isobutylthio)trimethylsilane or (methylthio)trimethylsilane, trimethylsilyl triflate, and a trace of anhydrous zinc iodide in tetrahydrofuran followed by chromatography on silica gel led to the isolation of the crystalline thioacetals **16a** and **16b** in overall yields of 51% and 56%, respectively, from **13**.

Complete debenzoylation of these compounds was readily achieved by treatment with methanolic ammonium hydroxide giving the free adenosine 5′-thioacetals **17a,b** in yields of 85% and 88%. The same compounds were obtained by debenzoylation of **11a** and **11b**.

It has been known since the pioneering works of Fischer[24] that carbohydrate dithioacetals undergo oxidative hydrolysis with bromine, and this has been extended to useful methods for hydrolysis of thioacetals using *N*-bromosuccinimide[25] and to the preparation of 1-(alkylthio)-1-bromo-1-deoxy alditols as precursors of acyclic nucleosides.[26] It was our contention that the intermediate bromosulfonium salt **21a**, or the related bromo sulfide **21b**, would readily lose a proton from $C_{4'}$ under basic conditions with subsequent elimination of sulfenyl bromide or bromide ion to generate the desired vinyl sulfide (**18**, **19**).

In practice, the dithioacetals **16a,b** were reacted with 1 equiv of bromine in methylene chloride at −78 °C and then allowed to warm to room temperature with the addition of 1 equiv of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Chromatography of the reaction products on silica gel gave in each case a roughly 95% yield of a slightly more polar product that was shown by ^1H NMR to be a roughly 9:1 mixture of isomers of the desired vinyl sulfides. A

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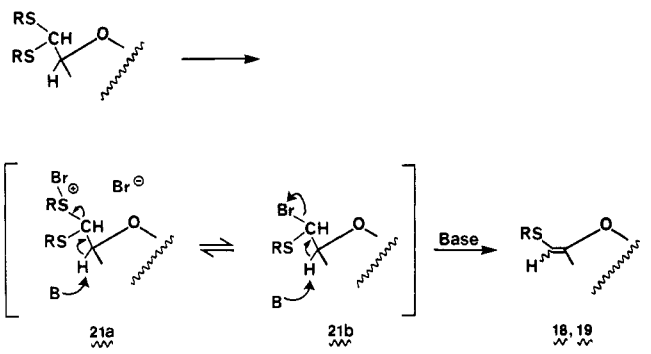


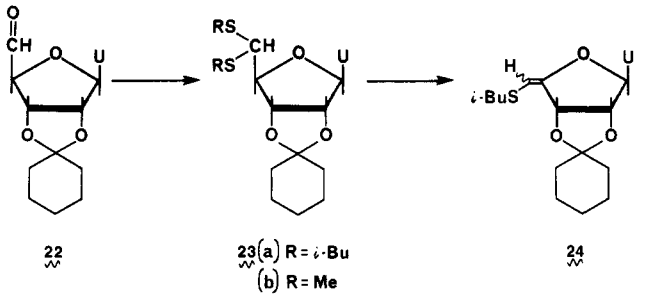
single crystallization of the mixture derived from **16a** from ether–hexane gave pure **18a** in a yield of 78%. Almost identical results were obtained in the preparation of the methylthio analogue **18b**.

On the basis of NMR studies we have assigned the *Z* stereochemistry to the major products of these reactions. This has been possible only through examination of both the 300-MHz ^{1}H and ^{13}C NMR spectra of the 9:1 mixture of isomers **18b** and **19b** prior to crystallization since complete assignments could be deduced for both compounds. With respect to the ^{1}H NMR spectra, the assignments must be somewhat tenuous since the relative magnitudes of *cis*- and *trans*-allylic couplings are not unequivocal. In acyclic systems it has generally been accepted that *cis*-allylic couplings are larger than the trans counterparts.[27a,b] In exocyclic systems, however, the opposite is true, allylic J_{trans} usually being larger than J_{cis},[27c,d] although this is still subject to variation depending upon the particular geometry of the system.[27e] In our case the observed value of $J_{3',5'}$ for the major isomer was 0.65 Hz, while that of the minor isomer was 0.89 Hz, suggesting the *Z* configuration (**18b**) for the major component. This assignment is supported by the ^{13}C NMR spectrum of the mixture, in which $C_{3'}$ of the major isomer appears 1.11 ppm downfield of this carbon in the minor component.[28] Further independent support was provided by examination of the NOE difference spectra obtained from the mixed isomers. Here, distinct nuclear Overhauser enhancement was observed between $H_{3'}$ and $H_{5'}$ in the major, but not the minor, isomer. An NOE effect was not seen between $H_{3'}$ and the SMe group in either isomer. A similar result has been used by Cook and Secrist[11a] to assign the *Z* configuration to the enol acetate **5a**. These combined results give us confidence that the major product has the *Z* configuration (**18b**), while the minor component is the *E* isomer (**19b**). In the *S*-isobutylthio series (**18a**, **19a**), it was not possible to precisely measure the very small allylic couplings, but the $C_{3'}$ and $C_{5'}$ protons in the major isomer showed precisely the same 0.26 and 0.18 ppm upfield shift relative to those of the minor isomer, and hence *Z* stereochemistry is once again indicated.

Complete deprotection of both **18a** and **18b** by treatment with methanolic ammonium hydroxide led to the crystalline 9-[5-(alkylthio)-5-deoxy-β-D-*erythro*-(*Z*)-pent-4-enofuranosyl]adenines **20a,b** in high yield. It is interesting to note that the ultraviolet spectra of these compounds in methanol show maxima at 258 nm (ε 19 000), which are considerably more intense than those of simple adenosine derivatives [λ_{max} 259 (ε 15 000)]. Simple 1-alkoxy-2-(alkylthio)ethylenes, however, are known to have UV maxima at 252–256 nm (ε 3000–5000),[29] which readily explains the observed results.

While we have not examined the chemical stability of compounds such as **20a,b** in any detail, we have made some general observations based only upon TLC examination following various acidic treatments. Thus, both **20a** and **20b** appear to be completely stable in 20% acetic acid at room temperature for 16 h. In 20% trifluoroacetic acid, however, they are roughly 50% hydrolyzed to adenine in 5 h and in 50% trifluoroacetic acid, adenine is the sole product after 2 h. Similarly, in 0.1 N hydrochloric acid there is essentially complete hydrolysis within 90 min. It is interesting to note that since adenine is the product of hydrolysis of **20** and nucleoside 5′-aldehydes are reasonably stable to acid, it appears that selective cleavage of the *O*-vinyl rather than the *S*-vinyl bond is occurring.

We have also attempted to extend this work to the pyrimidine series. To this end, 2′,3′-*O*-cyclohexylideneuridine 5′-aldehyde (**22**)[13a] was reacted with (isobutylthio)trimethylsilane in the presence of trimethylsilyl triflate and zinc iodide to give the pure thioacetal **23a** as a foam in 45% yield. A comparable reaction between **22** and (methylthio)trimethylsilane gave the corresponding thioacetal **23b** in 55% yield, using only a catalytic amount of zinc iodide in the absence of trimethylsilyl triflate. Thus, with this less basic nucleoside, the demands for acid catalysis are less stringent. An alternative, and much more efficacious, synthesis of **23** will be described elsewhere.[30] Attempts to effect elimination by treatment of **23a,b** with bromine at a low temperature were unsuccessful, presumably due to competitive bromination of the uracil ring. Some indication of the desired reaction was chromatographically observed upon treatment of **23a** with cupric chloride and diisopropylethylamine in benzene under reflux.[12b] The method of Trost and Lavoi[31] using mercuric trifluoroacetate and lithium carbonate was more satisfactory and led to the isolation of the vinyl thioethers **24** in 38% yield, together with 10% of the regenerated aldehyde **22**. The 300-MHz ^{1}H NMR spectrum of the product showed it to be a roughly 4:1 mixture of *Z* and *E* isomers, the major product having $J_{3',5'}$ = 0.9 Hz. The resolution of the minor isomer was not adequate for determination of the allylic coupling constant, and hence the stereochemistry of **24** remains uncertain. As in the adenosine series, the ultraviolet spectrum of **24** shows a shift to shorter wavelengths and an elevated extinction coefficient [λ_{max} 256 nm (ε 14 300)] relative to other uridine derivatives due to the monothioendiol chromophore. Since cleavage of the cyclohexylidene group would be expected to result in concomitant vinyl ether hydrolysis, further work in the uridine



(27) (a) Whipple, E. B.; Goldstein, J. H.; Mandell, L. *J. Am. Chem. Soc.* **1960**, *82*, 3010. (b) Jackman, L. M.; Sternhell, S. "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed.; Pergamon Press: New York, 1969; pp 316–328. (c) Newsoroff, G. P.; Sternhell, S. *Tetrahedron Lett.* **1968**, 6117. (d) Newsoroff, G. P.; Sternhell, S. *Aust. J. Chem.* **1972**, *25*, 1669. (e) Spear, R. J.; Sternhell, S. *Tetrahedron Lett.* **1973**, 1487.

(28) See, e.g.: Stothers, J. B. "Carbon-13 NMR Spectra"; Academic Press: New York, 1972; Chapter 3.

(29) Tureček, F.; Prochazka, M. *Collect. Czech. Chem. Commun.* **1975**, *40*, 2099.

(30) Craig, G. W.; Moffatt, J. G., unpublished work in preparation.

(31) Trost, B. M.; Lavoi, A. C. *J. Am. Chem. Soc.* **1983**, *105*, 5075.

series must await preparation of an appropriately acylated aldehyde.

Finally, some preliminary studies on the biological properties of **20a** have been carried out by others at Syntex.[32] Thus, **20a** was shown to have only very modest in vitro antiviral activity with ED_{50}'s of 10 and 32 μg/mL against the SA-11 strain of rotavirus and the C-243 strain of parainfluenza-3. Other DNA and RNA viruses were inhibited even less. These results are similar to those observed with SIBA (**3**), although the relative specificities differed. Antiviral studies with SIBA have previously been reported.[33] Both SIBA and **20a** were also shown to be roughly equipotent in inhibition of retroviral transformation of murine 3T3 fibroblasts by Moloney sarcoma virus, 60–80% inhibition being observed with 10^{-4} M **20a**. Details of this work will be published elsewhere.

The methods developed in this paper make the somewhat unusual hybrid compounds such as **20** quite easily available. While they retain the essential biological activities of SIBA, they are considerably less potent than sinefungin or A9145C.[3]

Experimental Section

General Methods. Thin-layer chromatography (TLC) was conducted with 0.25-mm layers of silica gel GF from Analtech Corp. and column chromatography with Merck silica gel with 0.05–0.20-mm particles. Chromatotron chromatography used an apparatus from Harrison Research, Palo Alto, CA, coupled with a Gilson micro fraction collector. 300-MHz ^{1}H NMR spectra were obtained with a Bruker WM-300 spectrometer and are reported in ppm downfield of an internal standard of tetramethylsilane. ^{13}C NMR spectra were recorded using a Bruker WH-90 spectrometer operating at 22.62 MHz. Chemical ionization (NH_3) and electron impact mass spectra were recorded with a Varian MAT 112S instrument. Other analytical services were provided by the Analytical Research staff of Syntex Research, to whom we express our thanks. We are particularly grateful to Dr. M. L. Maddox and J. Nelson for their continual help with NMR spectroscopy, and to Drs. T. R. Matthews and D. A. Eppstein for preliminary biological studies.

Methyl 5-Deoxy-2,3-*O*-isopropylidene-5,5-bis(methylthio)-β-D-ribofuranoside (8). Trimethylsilyl triflate (10 μL) was added to a solution of **7** (150 mg, 0.74 mmol)[20] and (methylthio)trimethylsilane (280 mg, 2.3 mmol) in methylene chloride (5 mL) at −78 °C. The mixture was allowed to warm to room temperature and kept overnight after addition of a further 10 μL of Me_3Si-Tf. The solution was then washed with dilute aqueous ammonium hydroxidie, dried ($MgSO_4$) and chromatographed on silica gel (60 g) with 1% ethyl acetate in chloroform, giving 100 mg (48%) of **8** with mp 49.5–50.0 °C from hexane: $[\alpha]^{25}_D$ −8.0° (*c* 0.7, CH_2Cl_2); NMR (300 MHz, $CDCl_3$) 1.32, 1.48 (s, 3, CMe_2), 4.14 (s, 6, SMe), 3.71 (d, 1, $J_{2',3'}$ = 11.5 Hz, C_2H), 4.07 (dd, 1, $J_{3,4}$ = 1.1 Hz, C_3H), 4.58 (d, 1, $J_{4,5}$ = 6 Hz, C_5H), 5.01 (s, 1, C_1H), 5.06 (dd, 1, C_4H) ppm; MS, *m/e* 280 (M^+). Anal. Calcd for $C_{11}H_{20}O_4S_2$ (280.27): C, 47.14; H, 7.19. Found: C, 46.83; H, 6.95.

(Isobutylthio)trimethylsilane. Butyllithium (165 mmol) was added over 20 min to a solution of 2 methylpropanethiol (13.5 g, 150 mmol) in ether (160 mL) at −78 °C. Chlorotrimethylsilane (17.9 g, 165 mmol) was then added and the mixture was warmed to room temperature and stirred for 2 h. Following addition of hexane (100 mL) and evaporation to dryness several times, the mixture was filtered, and the filtrate was distilled, giving 11.9 g (49%) of (isobutylthio)trimethylsilane with bp 60 °C (40 mm): MS (70 eV), *m/e* 147 (M − 15). Anal. Calcd for $C_7H_{18}SSi$ (162.37): C, 51.78; H, 11.17. Found: C, 51.83; H, 11.19.

N^6-Benzoyl-5′-deoxy-5′,5′-bis(methylthio)adenosine (11a). Trimethylsilyl triflate (0.1 mL) was added to a solution of azeotropically dehydrated **9** (105 mg, 0.24 mmol)[13b] (and (methylthio)trimethylsilane (0.1 mL) in 1,2-dichloroethane (5 mL). After 2 h at room temperature the mixture was washed with aqueous bicarbonate and water, dried ($MgSO_4$), and evaporated to dryness. Crystallization from ether–hexane gave 61 mg (52%) of slightly impure **10a** with mp 79–85 °C: λ_{max} 280 nm (ϵ 19 400); NMR ($CDCl_3$) 1.43, 1.64 (s, 3, Ip), 2.05, 2.19 (s, 3, Ip), 2.05, 2.19 (s, 3, SMe), 3.93 (d, 1, $J_{4',5'}$ = 8 Hz, C_5H), 3.39 (dd, 1, $J_{3',4'}$ = 3.4 Hz, C_4H), 5.28 (dd, 1, $J_{2',3'}$ = 6.4 Hz, C_3H), 5.41 (dd, 1, $J_{1',2'}$ = 2.4 Hz, C_2H), 6.22 (d, 1, C_1H), 8.26, 8.82 (s, 1, C_2H, C_8H) ppm; MS, *m/e* 487 (M^+), 472 (M−CH_3). Anal. Calcd for $C_{22}H_{25}N_5O_4S_2$ (487.48): C, 46.83; H, 6.95. Found: C, 47.14; H, 7.14.

This material was treated with 90% trifluoroacetic acid at room temperature for 10 min and evaporated to dryness. The residue was treated with solid potassium carbonate in methylene chloride, filtered, evaporated, and crystallized from methanol–ether to give **11a** with mp 161.5–163.5 °C: λ_{max} (MeOH) 280 nm (ϵ 20 300), 230 (14 000); NMR ($CDCl_3$) 2.14, 2.20 (s, 3, SMe), 4.12 (d, 1, $J_{4',5'}$ = 5.3 Hz, C_5H), 4.34 (dd, $J_{3',4'}$ = 4.4 Hz, C_4H), 4.58 (dd, 1, $J_{2',3'}$ = 5.4 Hz, C_3H), 4.85 (dd, 1, $J_{1',2'}$ = 5.5 Hz, C_2H), 6.16 (d, 1, C_1H), 7.5–8.1 (m, 5, Bz), 8.63, 8.73 (s, 1, C_2H, C_8H) ppm. Anal. Calcd for $C_{19}H_{21}N_5O_4S_2$ (447.40): C, 51.00; H, 4.73; N, 15.65. Found: C, 50.85; H, 4.77; N, 15.56.

N^6-Benzoyl-5′-deoxy-5′,5′-bis(isobutylthio)adenosine (11b) and Its Acetonide (10c). A solution of **9** (105 mg, 0.24 mmol), (isobutylthio)trimethylsilane (0.14 mL), and trimethylsilyl triflate (0.14 mL) in 1,2-dichloroethane (5 mL) was stored at room temperature for 48 h. Triflic acid (45 μL) was then added and after 1 h the solution was washed with 10% bicarbonate and water, dried ($MgSO_4$), and separated by chromatotron chromatography using methylene chloride–methanol (19:1). The more polar band contained 55 mg (43%) of diol **11b** as a homogeneous foam: NMR ($CDCl_3$) 0.98 (m, 12, CMe_2), 1.8 (m, 2, $CHMe_2$), 2.6 (m, 4, SCH_2), 4.00 (d, 1, $J_{4',5'}$ = 4.4 Hz, C_5H), 4.48 (dd, 1, $J_{3',4'}$ = 4 Hz, C_4H), 4.57 (dd, 1, $J_{2',3'}$ = 5.3 Hz, C_3H), 4.79 (dd, 1, $J_{1',2'}$ = 6 Hz, C_2H), 6.12 (d, 1, C_1H), 7.5–8.1 (m, 5, Bz), 8.39, 8.62 (s, 1, C_2H, C_8H), ppm; CI/MS *m/e* 532 (MH^+).

The less polar band gave 24 mg (18%) of acetonide **10c** as a foam: NMR ($CDCl_3$) 1.00 (m, 12, CMe_2), 1.42, 1.65 (s, 3, Ip), (m, 2, $CHMe_2$), 2.6 (m, 4, SCH_2e, 4.01 (d, 1, $J_{4',5'}$ = 7.3 Hz, C_5H), 4.43 (dd, 1, $J_{3',4'}$ = 3.0 Hz, C_4H), 5.27 (dd, 1, $J_{2',3'}$ = 6.6 Hz, C_3H), 5.36 (dd, 1, $J_{1',2'}$ = 2.7 Hz, C_2H), 6.24 (d, 1, C_1H), 7.5–8.1 (m, 5, Bz), 8.31, 8.82 (s, 1, C_2H, C_8H) ppm; CI/MS *m/e* 572 (MH^+).

N^6-Benzoyl-5′-deoxy-5′-(isobutylthio)-5′-(methylthio)-adenosine (11c) and Its Acetonide (10d). A solution of dehydrated **9** (240 mg, 0.56 mmol), (isobutylthio)trimethylsilane (0.20 mL), and trimethylsilyl triflate (40 μL) in methylene chloride (5 mL) was stored overnight at room temperature and then evaporated to dryness and kept under vacuum for 1 h. The residue was dissolved in methylene chloride (7 mL) together with (methylthio)trimethylsilane (0.30 mL) and triflic acid (150 μL) was added in 30 μL portions over 1 h. The solution was washed with aqueous bicarbonate and water, dried, and evaporated leaving a foam that contained two major and three minor components by TLC using THF–CCl_4 (1:1) that were largely separated by chromatotron chromatography using a 1% to 5% gradient of methanol in methylene chloride. The least polar fraction contained 62 mg (21%) of **10d** as a ~1:1 mixture of diastereomers uncontaminated by either **10a** or **10c** and containing equal amounts of SMe (2.05 and 2.19 ppm) and $CHMe_2$ (4 doublets at 0.83, 0.89, 1.00, and 1.03 ppm) by 300-MHz NMR in $CDCl_3$; CI/MS *m/e* 530 (MH^+). The second fraction (34 mg, 10%) was a mixture of **10d** and **10a**, while fraction 3 contained 71 mg (26%) of the mixed thioacetal diol **11c** that was free of symmetrical acetals by TLC and NMR analysis and contained SMe (s, 2.17, 2.20 ppm) and $CHMe_2$ (m, 1.00 ppm) groups.

Treatment of this material with methanolic ammonium hydroxide (1:1) for 2 days at 4 °C and 4 h at room temperature gave the deprotected mixed thioacetal **12** in 95% yield following chromatotron purification. The 300-MHz NMR (MeOH-d_4) of this compound was extremely clean and showed only a 1:1 mixture of diastereomers of **12**: CI/MS, *m/e* 386 (MH^+). Anal. Calcd for $C_{15}H_{23}N_5O_3S_2{\cdot}H_2O$ (403.37): C, 44.66; H, 6.22; N, 17.37. Found: C, 45.06; H, 5.83; N, 16.85.

N^6,N^6,$O^{2'}$,$O^{3'}$-Tetrabenzoyl-5′-deoxy-5′-(N^1,N^3-diphenylethylenediamino)adenosine (15). Methylphosphonic acid (110

(32) We are most grateful to Dr. T. R. Matthews and Dr. D. A. Eppstein and their staffs for this assistance.

(33) See, e.g.: Robert-Gero, M.; Pierre, A.; Vedel, M.; Enouf, J.; Lawrence, F.; Raies, A.; Lederer, E. In "Enzyme Inhibitors"; Brodbeck, U., Ed.; Verlag Chemie: Weinheim, 1980; p 61 and references therein.

mg, 1.14 mmol) was added to a solution of $N^6,N^6,O^{2'},O^{3'}$-tetrabenzoyladenosine (**13**, 790 mg, 1.1 mmol)[8a] and dicyclohexylcarbodiimide (716 mg, 3.5 mmol) in anhydrous dimethyl sulfoxide. After 3 h at room temperature a solution of oxalic acid dihydrate (104 mg, 0.8 mmol) in methanol (2 mL) was added, and after 30 min the mixture was filtered and the dicyclohexylurea washed with a little cold methanol. The filtrate was diluted with ethyl acetate, washed three times with water, dried, and evaporated to dryness. 1,2-Dianilinoethane (285 mg, 1.3 mmol) and acetic acid (0.23 mL) were added to a solution of the residue in methanol, and after storage overnight crystalline **15** (560 mg, 57%) was collected with mp 130–131 °C: $[\alpha]^{25}_D$ −76.1° (*c* 0.22, $CHCl_3$); λ_{max} (MeOH) 239 nm (ε 55 100), 249 (52 800), 280 (sh, 24 100); NMR ($CDCl_3$) 3.5–3.9 (m, 4, NCH_2), 4.96 (d, 1, $J_{3',4'}$ = 4.6 Hz, C_4'H), 5.94 (s, 1, C_5'H), 6.12 (dd, 1, $J_{2',3'}$ = 5.9 Hz, C_3'H), 6.12 (dd, 1, $J_{1',2'}$ = 5.7 Hz, C_2'H), 6.42 (d, 1, C_1'H), 6.7–8.0 (m, 30, Ar), 7.85, 8.55 (s, 1, C_2H, C_8H) ppm. Anal. Calcd for $C_{52}H_{41}N_7O_7H_2O$ (893.91): C, 69.86; H, 4.84; N, 10.97. Found: C, 69.36; H, 4.75; N, 11.11.

***N*⁶,*N*⁶,*O*²',*O*³'-Tetrabenzoyladenosine 5'-Aldehyde (14).** A solution of *p*-toluenesulfonic acid monohydrate (54 mg, 0.28 mmol) in acetone (5 mL) was added to a solution of **15** (106 mg, 0.12 mmol) in methylene chloride (10 mL) at 0 °C. A precipitate of dianilinoethane tosylate separated immediately, and after 30 min the mixture was filtered and the filtrate carefully evaporated to dryness. A solution of the residue in methylene chloride was washed twice with water, dried ($MgSO_4$), and evaporated to leave essentially pure **14** as a foam in quantitative yield.

For most purposes the crude oxidation product prior to preparation of the imidazolidine derivative was used for subsequent reactions.

***N*⁶,*N*⁶,*O*²',*O*³'-Tetrabenzoyl-5'-deoxy-5',5'-bis(isobutylthio)adenosine (16a).** Trimethylsilyl triflate (0.28 mL) was added under nitrogen to a solution of crude **14** (350 mg, 0.47 mmol), (isobutylthio)trimethylsilane (177 mg, 1.1 mmol), and anhydrous zinc iodide (0.5 mg) in dry tetrahydrofuran (5 mL). After 2 h at room temperature TLC (19:1 methylene chlloride–methanol) showed the reaction to be complete and the mixture was diluted with chloroform, washed with aqueous potassium acetate and water, dried (Na_2SO_4), and evaporated. The residue was purified by using chromatotron chromatography on silica gel using a gradient of methylene chloride–hexane (1:1) to methylene chloride, and the major band was crystallized from methylene chloride–hexane, giving 203 mg (51%) of **16a** with mp 178–180 °C: $[\alpha]^{25}_D$ −76.2° (*c* 0.49, $CHCl_3$); λ_{max} (MeOH) 231 nm (ε 42 200), 272 (21 900); NMR ($CDCl_3$) 1.00 (m, 12, $CHMe_2$), 1.85 (m, 2, $CHMe_2$), 2.6 (m, 4, SCH_2), 4.31 (d, 1, $J_{4',5'}$ = 3.8 Hz, C_5'H), 4.78 (dd, 1, $J_{3',4'}$ = 3.7 Hz, C_4'H), 6.03 (d, 1, $J_{2',3'}$ = 6.2 Hz, C_3'H), 6.14 (dd, 1, $J_{1',2'}$ = 6.2 Hz, C_2'H), 6.61 (d, 1, C_1'H), 7.3–8.0 (m, 20, Bz), 8.63, 8.66 (s, 1, C_2H, C_8H) ppm. Anal. Calcd for $C_{46}H_{45}N_5O_7S_2$ (843.99): C, 65.46; H, 5.37; N, 8.29; S, 7.58. Found: C, 65.27; H, 5.18; N, 8.01; S, 7.60.

***N*⁶,*N*⁶,*O*²',*O*³'-Tetrabenzoyl-5'-deoxy-5',5'-bis(methylthio)adenosine (16b).** The reaction of **14** (500 mg, 0.73 mmol), (methylthio)trimethylsilane (0.23 mL, 1.6 mmol), zinc iodide (0.7 mg), and trimethylsilyl triflate (2 mg) was worked up as for **16a** after 2 h, giving 311 mg (56%) of **16b** with mp 99–101 °C from methylene chloride–hexane: $[\alpha]^{25}_D$ −73.0° (*c* 0.27, $CHCl_3$); λ_{max} (MeOH) 230 nm (ε 48 300), 272 (sh, 25 400); NMR ($CDCl_3$) 2.23, 2.24 (s, 3, SMe), 4.21 (d, 1, $J_{4',5'}$ = 4.2 Hz, C_5'H), 4.80 (dd, 1, $J_{3',4'}$ = 4.1 Hz, C_4'H), 6.10 (d, 1, $J_{2',3'}$ = 6.0 Hz, C_3'H), 6.17 (dd, 1, $J_{1',2'}$ = 5.8 Hz, C_2'H), 6.56 (d, 1, C_1'H), 7.3–8.0 (m, 20, Bz), 8.55, 8.67 (s, 1, C_2H, C_8H) ppm. Anal. Calcd for $C_{40}H_{33}N_5O_7S_2$ (759.83): C, 63.22; H, 4.38; N, 9.22. Found: C, 63.28; H, 4.23; N, 8.94.

5'-Deoxy-5',5'-bis(isobutylthio)adenosine (17a). (a) A solution of **16a** (200 mg, 0.24 mmol) in methanol (2 mL) and concentrated ammonium hydroxide (2 mL) was stirred overnight at room temperature. After evaporation of the solvents the residue was chromatographed on silica by using methylene chloride–methanol (19:1) and crystallized from methanol, giving 87 mg (85%) of **17a** with mp 80–85 °C (dec: $[\alpha]^{25}_D$ 23.1° (*c* 0.54, MeOH); λ_{max} (MeOH) 259 nm (ε 14 000); NMR ($CDCl_3$–MeOH-d_4) 1.00 (m, 12, $CHMe_2$), 1.84 (m, 2, $CHMe_2$), 2.60 (m, 4, SCH_2), 4.03 (d, 1, $J_{4',5'}$ = 1.9 Hz, C_5'H), 4.46 (m, 3, C_2'H, C_3'H, C_4'H), 6.01 (d, 1, $J_{1',2'}$ = 3.9 Hz, C_1'H), 8.26, 8.29 (s, 1, C_2H, C_8H) ppm. Anal. Calcd for $C_{18}H_{29}N_5O_3S_2$ (427.44): C, 50.56; H, 6.84; N, 16.38; S, 15.00. Found: C, 50.45; H, 7.03; N, 16.20; S, 15.07.

(b) Hydrolysis of **11b** with methanolic ammonium hydroxide essentially as above gave an 85% yield of **17a** identical with that in a.

5'-Deoxy-5',5'-bis(methylthio)adenosine (17b). (a) Hydrolysis of **16b** (250 mg, 0.33 mmol) with methanolic ammonium hydroxide as for **17a** gave an 88% yield of **17b** with mp 115–117 °C: $[\alpha]^{25}_D$ 20.6° (*c* 0.41, $CHCl_3$); λ_{max} (MeOH) 259 nm (ε 13 800); NMR (CCl_3) 2.23, 2.24 (s, 3, SMe), 3.96 (d, 1, $J_{4',5'}$ = 3.9 Hz, C_5'H), 4.47 (br s, 3, C_2'H, C_3'H, C_4'H), 5.99 (d, 1, $J_{1',2'}$ = 2.4 Hz, C_1'H), 8.23, 8.26 (s, 1, C_2H, C_8H) ppm; MS, *m/e* 343 (M^+), 328 ($M^+ - CH_3$). Anal. Calcd for $C_{12}H_{17}N_5O_3S_2$ (343.40): C, 41.98; H, 4.99. Found: C, 41.60; H, 5.32.

(b) This compound was also obtained by methanolic ammonium hydroxide treatment of **11a**.

***N*⁶,*N*⁶,*O*²,*O*³-Tetrabenzoyl-9-[5-deoxy-5-(isobutylthio)-β-D-*erythro*-(*Z*)-pent-4-enofuranosyl]adenine (18a).** Bromine (1.73 mmol as a 1.1 M solution in methylene chloride) was added over 5 min to a solution of **16a** (1.46 g, 1.73 mmol) in methylene chloride (25 mL) at −78 °C. After 10 min the cooling bath was removed and stirring was continued for 35 min, at which point DBU (0.65 mL, 1.73 mmol) was slowly added, the color of the reaction fading from orange to pale yellow and then becoming pale brown at the very end. TLC (4:1 CCl_4–EtOAc) showed formation of a single slightly more polar product. The mixture was filtered through a pad of silica and the filtrate chromatographed on a column of silica gel by using a gradient of 0–10% ethyl acetate in methylene chloride, and the major band was crystallized from ether–hexane, giving 1.01 g (78%) of **18a** with mp 171–172 °C: $[\alpha]^{25}_D$ −86.8° (*c* 0.43, $CHCl_3$); λ_{max} (MeOH) 233 nm (ε 47 400), 250 (sh, 41 000), 270 (sh, 27 300); NMR ($CDCl_3$) 0.96 (d, 6, *J* = 6.8 Hz, $CHMe_2$), 1.86 (m, 1, $CHMe_2$), 2.60 (d, 1, *J* = 6.9 Hz, CH_2S), 5.66 (s, 1, C_5'H), 6.35 (dd, 1, $J_{1',2'}$ = 6.3 Hz, $J_{2',3'}$ = 5.4 Hz, C_2'H), 6.45 (d, 1, C_3'H), 6.77 (d, 1, C_1'H), 7.3–8.1 (m, 20, Bz), 8.29, 8.68 (s, 1, C_2H, C_8H) ppm; MS, *m/e* 600 ($Me^+ - Bz_2$). Anal. Calcd for $C_{42}H_{35}N_5O_7S$ (753.77): C, 66.92; H, 4.68; N, 9.29; S, 4.24. Found: C, 66.78; H, 4.73; N, 9.27; S, 4.20.

***N*⁶,*N*⁶,*O*²,*O*³-Tetrabenzoyl-9-[5-deoxy-5-(methylthio)-β-D-*erythro*-(*Z*)-pent-4-enofuranosyl]adenine (18b).** The reaction of **16b**, bromine, and DBU was carried out exactly as for **18a**. Following chromatography on silica gel, vinyl sulfide **18b** contaminated with ~10% of the *E* isomer **19b** was obtained in 94% yield. A single crystallization from ether–hexane gave pure **19b** (75%) with mp 116–117 °C: $[\alpha]^{25}_D$ −90.5° (*c* 0.46, $CHCl_3$); λ_{max} (MeOH) 223 nm (ε 46 800), 250 (sh, 37 100), 270 (sh, 26 500); ^1H NMR ($CDCl_3$) 2.32 (s, 3, SMe), 5.64 (d, 1, $J_{3',5'}$ = 0.65 Hz, C_5'H), 6.36 (dd, 1, $J_{1',2'}$ = 5.7 Hz, $J_{2',3'}$ = 5.5 Hz, C_2'H), 6.48 (d, 1, C_3'H), 6.76 (d, 1, C_1'H), 7.3–8.05 (m, 20, Bz), 8.29, 8.69 (s, 1, C_2H, C_8H) ppm; ^{13}C NMR ($CDCl_3$) 17.38 (SMe), 70.18 (C_3'), 73.45 (C_2'), 86.97 (C_5'), 104.89 (C_1'), 147.11 (C_4') ppm; MS, *m/e* 712 (M^+). Anal. Calcd for $C_{39}H_{29}N_5O_7S{\cdot}0.5H_2O$ (720.77): C, 64.98; H, 4.19; N, 9.71. Found: C, 65.00; H, 4.13; N, 9.42.

NMR analysis of the crude product prior to crystallization clearly showed signals for the minor *E* isomer (**19b**) as follows: 2.33 (s, 3, SMe), 5.85 (d, 1, $J_{3',5'}$ = 0.89 Hz, C_5'H), 6.76 (dd, 1, $J_{2',3'}$ = 5.4 Hz, C_3'H), 6.55 (dd, 1, $J_{1',2'}$ = 6.4 Hz, C_2'H), 6.70 (d, 1, C_1'H) ppm; ^{13}C NMR 69.07 (C_3'), 72.38 (C_2'), 87.22 (C_5'), 103.89 (C_1') ppm.

9-[5-Deoxy-5-(isobutylthio)-β-D-*erythro*-(*Z*)-pent-4-enofuranosyl]adenine (20a). A solution of **18a** (700 mg, 0.93 mmol) in methanol (5 mL), tetrahydrofuran (1 mL), and concentrated ammonium hydroxide (5 mL) and kept overnight at room temperature and then evaporated to dryness. Crystallization of the residue from ethanol gave 255 mg (76%) of **20a** with mp 106.5–108 °C: $[\alpha]^{25}_D$ 9.9° (*c* 0.35, MeOH); λ_{max} (MeOH) 258 nm (ε 19 300); NMR ($CDCl_3$–MeOH-d_4) 1.01 (d, 6, *J* = 6.6 Hz, $CHMe_2$), 1.86 (m, 1, $CHMe_2$), 2.58 (d, 2, *J* = 6.8 Hz, CH_2S), 4.64 (dd, 1, $J_{1',2'}$ = 4.6 Hz, $J_{2',3'}$ = 5.3 Hz, C_2'H), 4.73 (dd, 1, C_3'H), 5.34 (d, 1, $J_{3',5'}$ = 0.86 Hz, C_5'H), 6.21 (d, 1, C_1'H), 7.98, 8.27 (s, 1, C_2H, C_8H) ppm; MS, *m/e* 337 (M^+). Anal. Calcd for $C_{14}H_{19}N_5O_3S{\cdot}0.5EtOH$ (360.36): C, 49.99; H, 6.15; N, 19.44; S, 8.87. Found: C, 50.09; H, 6.00; N, 19.51; S, 8.95.

9-[5-Deoxy-5-(methylthio)-β-D-*erythro*-(*Z*)-pent-4-enofuranosyl]adenine (20b). Hydrolysis of **18b** (250 mg, 0.35 mmol) in methanolic ammonium hydroxide was done as for **20a** above. Crystallization from ethanol gave 91 mg (78%) of **20b** with mp 117–118 °C: λ_{max} (MeOH) 258 nm (ε 19 000) NMR ($CDCl_3$–MeOH-d_4) 2.31 (s, 3, SMe), 4.64 (dd, 1, $J_{1',2'}$ = 4.5 Hz, $J_{2',3'}$ = 5.2

Hz, C_2H), 4.75 (dd, 1, C_3H), 5.33 (d, 1, $J_{3',5'}$ = 0.9 Hz, C_5H), 6.22 (d, 1, C_1H), 7.98, 8.27 (s, 1, C_2H, C_8H) ppm; MS, *m/e* 295 (M^+). Anal. Calcd for $C_{11}H_{13}N_5O_3S$·0.5EtOH (335.03): C, 42.02; H, 4.81; N, 20.90; S, 9.55. Found: C, 42.06; H, 4.80; N, 21.38; S, 9.36.

2',3'-*O*-Cyclohexylidene-5'-deoxy-5',5'-bis(isobutylthio)uridine (23a). Trimethylsilyl triflate (0.31 mL) was added to a solution of **22** (200 mg, 0.6 mmol),[13a] (isobutylthio)trimethylsilane (200 mg, 1.2 mmol), and anhydrous zinc iodide (0.6 mg) in methylene chloride–tetrahydrofuran (1:1, 5 mL). After 1 h at room temperature the mixture was worked up as for **16a** and chromatographed on silica gel using a gradient of 0.5% methanol in methylene chloride, giving 131 mg (45%) of **23a** as a homogeneous foam: λ_{max} (MeOH) 258 nm (ϵ 9800); NMR ($CDCl_3$) 1.00 (m, 12, CH*Me*$_2$), 1.3–1.9 (m, 12, cyclohexylidene + C*H*Me$_2$), 2.60 (m, 4, SCH_2), 3.99 (d, 1, $J_{4',5'}$ = 6.4 Hz, C_5H), 4.28 (dd, 1, $J_{3',4'}$ = 3.7 Hz, C_4H), 4.84 (dd, 1, $J_{1',2'}$ = 3.1 Hz, $J_{2',3'}$ = 6.6 Hz, C_2H), 4.95 (dd, 1, C_3H), 5.77 (d, 1, $J_{5,6}$ = 8 Hz, C_5H), 5.86 (d, 1, C_1H), 7.51 (d, 1, C_6H) ppm; MS, *m/e* 484 (M^+). Anal. Calcd for $C_{23}H_{36}N_2O_5S_2$ (484.52): C, 57.02; H, 7.44; N, 5.78. Found: C, 56.99; H, 7.40; N, 5.72.

2',3'-*O*-Cyclohexylidene-5'-deoxy-5',5'-bis(methylthio)uridine (23b). A solution of **22** (190 mg, 0.55 mmol), (methylthio)trimethylsilane (0.18 mL, 1.23 mmol), and anhydrous zinc iodide (0.6 mg) in tetrahydrofuran (5 mL) was stirred at room temperature for 2 h and then partitioned between chloroform and aqueous potassium acetate. The organic phase was washed with water, dried (Na_2SO_4), and evaporated, leaving a residue that was purified by chromatotron chromatography using a gradient of 0–5% methanol in methylene chloride, giving 126 mg (55%) of **23b** as a homogeneous foam: λ_{max} (MeOH) 258 nm (ϵ 10 000); NMR ($CDCl_3$) 1.3–1.8 (m, 10, cyclohexylidene), 2.19, 2.21 (s, 3, SMe), 3.93 (d, 1, $J_{4',5'}$ = 7.1 Hz, C_5H), 4.24 (dd, 1, $J_{3',4'}$ = 4.1 Hz, C_4H), 4.88 (d, 1, $J_{1',2'}$ = 2.6 Hz, $J_{2',3'}$ = 6.6 Hz, C_2H), 5.00 (dd, 1, C_3H), 5.76 (d, 1, C_1H), 5.76 (d, 1, $J_{5,6}$ = 8.0 Hz, C_5H), 7.40 (d, 1, C_6H), 8.80 (br s, 1, NH) ppm; MS, *m/e* 400 (M^+). Anal. Calcd for $C_{17}H_{24}N_2O_5S_2$·H_2O (418.51): C, 48.78; H, 6.26; N, 6.69. Found: C, 49.01; H, 5.83; N, 6.32.

1-(2,3-*O*-Cyclohexylidene-5-deoxy-5-(isobutylthio)-β-D-*erythro*-pent-4-enofuranosyl)uracil (24). A solution of **23a** (100 mg, 0.24 mmol) in n acetonitrile (2 mL) was stirred for 2 h at room temperature and at 40 °C for 1 h in the presence of lithium carbonate (103 mg, 1.4 mmol) and mercuric trifluoroacetate (100 mg, 0.24 mmol). TLC showed the presence of some unreacted **23a** together with more polar and less polar products. The mixture was filtered through silica gel, and the filtrate was evaporated to dryness and purified by chromatotron chromatography using a gradient of 0–5% methanol in methylene chloride. The more polar band contained 10 mg (10%) of **22**, while the less polar band gave 36 mg (38%) of **24** as a foam containing a roughly 4:1 mixture of geometric isomers: λ_{max} (MeOH) 256 nm (ϵ 14 300); NMR ($CDCl_3$, major isomer), 0.90 (m, 6, CH*Me*$_2$e, 1.2–1.8 (m, 10, cyclohexylidene), 1.85 (m, 1, C*H*Me$_2$), 2.55 (d, 2, *J* = 7 Hz, SCH_2), 4.98 (dd, 1, $J_{2',3'}$ = 6 Hz, $J_{3',5'}$ = 0.9 Hz, C_3H), 5.28 (d, 1, C_2H), 5.30 (s, 1, C_1H), 5.7 (m, 2, C_5H, C_5H), 7.20 (d, 1, $J_{5,6}$ = 8 Hz, C_6H). Anal. Calcd for $C_{19}H_{26}N_2O_5S$·1.5H_2O (421.49): C, 54.13; H. 6.93; N, 6.65. Found: C, 54.39; H, 6.40; N, 6.38.

Studies on the Synthesis of Side-Chain Hydroxylated Metabolites of Vitamin D. 2. Stereocontrolled Synthesis of 25-Hydroxyvitamin D_2[1]

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Received September 24, 1985

An efficient synthesis of 25-hydroxyvitamin D_2 is described. The chiral center at C-24 was introduced by the stereospecific and regioselective displacement of an allylic carbamate by a cuprate. The triene system was assembled by Horner–Wittig coupling of ketone **13** and the anion of phosphine oxide **14**.

The discovery of the fact that vitamin D_3 (**1a**) is metabolized in the living organism to a number of more polar substances that elicit a variety of biological responses has attracted continuing attention to the vitamin D dependent endocrine system during the last two decades.[2] The major metabolites of vitamin D_3 are the 25-hydroxyvitamin D_3 (25-OH-D_3, **1b**) and the 1α,25-dihydroxyvitamin D_3 (1,25-$(OH)_2$-D_3, **1c**), both of which bear a hydroxy group at C-25 that is known to be of great importance with regard to the biological activity of these metabolites.[2] 1,25-$(OH)_2$-D_3 (**1c**) is the most potent metabolite of vitamin D_3 known as regards calcium homeostasis and is considered a true steroid hormone.[2]

Progress in the knowledge of the vitamin D dependent endocrine system owes much to the efforts devoted to the synthesis of vitamin D_3 metabolites and analogues, since considerable amounts of synthetic material are needed to make a complete biological evaluation of every known metabolite. Furthermore, vitamin D_3 analogues (nonnaturally occurring compounds structurally related to vitamin D_3) have been used to characterize the protein receptors and carriers involved in vitamin D_3 metabolism.[3]

Structurally and metabolically related to vitamin D_3 (**1a**) is vitamin D_2 (**2a**), which differs from D_3 only in the nature of the side chain. The metabolism of vitamin D_2 is thought to be identical with that of vitamin D_3,[2,4] in support of which 25-hydroxyvitamin D_2 (25-OH-D_2, **2b**) and 1α,25-hydroxyvitamin D_2 (1,25-$(OH)_2$-D_2, **2c**) have been identified as its major metabolites.[5] Despite its clear relationship with vitamin D_3, the biological significance of vitamin D_2 and its metabolites remains largely unknown[4] due to the scarcity of synthetic metabolites of vitamin D_2, especially of the two major ones, 25-OH-D_2

(1) (a) For previous work with a model system see: Sardina, F. J.; Mouriño, A.; Castedo, L. *Tetrahedron Lett.* **1983**, *24*, 4477–4480. (b) A preliminary account of this work was presented at the Sixth Workshop on Vitamin D, Merano, Italy, 1985. (c) For the sake of consistency and clarity the steroidal numbering is maintained for the secosteroid compounds.

(2) (a) Norman, A. W. "Vitamin D: The Calcium Homeostatic Steroid Hormone"; Academic Press: New York, 1979. (b) DeLuca, H. F.; Paaren, H. E.; Schnoes, H. K. *Top. Curr. Chem.* **1979**, *83*, 1–65. (c) Jones, H.; Rasmusson, G. H. *Prog. Chem. Org. Nat. Prod.* **1980**, *39*, 63–121.

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