Carbohydrate Research, 164 (1987) 229–240
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

1,3,5-TRIDEOXY-3,5-DI-*C*-METHYL-L-TALITOL: A CHIRON FOR THE C-33–C-37 SEGMENT OF AMPHOTERICIN B*,†

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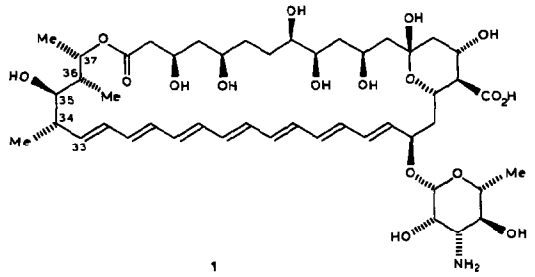
(Received September 22, 1986; accepted for publication, November 5th, 1986)

ABSTRACT

1,3,5-Trideoxy-3,5-di-C-methyl-L-talitol is a potential chiron for the C-33–C-37 segment of amphotericin B. This hexitol has been synthesized from 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose by a route in which a *C*-methylene derivative at C-5 is hydroborated, to give a single C-5 epimer. The extent of stereoselectivity has been found to be dependent on the substitution patterns at C-3 and C-6.

INTRODUCTION

There are approximately 100 members of the family of polyene macrolides[1], some of which have been in world-wide clinical use for over thirty years, primarily for the treatment of yeast *e.g. Candida* infections[2–4]. Although the gross structural features of most of the members have been determined, the absolute stereo-



1

Amphotericin B

*Dedicated to the memory of Burckhardt Helferich on the hundredth anniversary of his birth.
†Taken, in part, from the Ph.D. Theses of D. L. (Duke University, 1985) and A.D.S. (University of Maryland, 1985).
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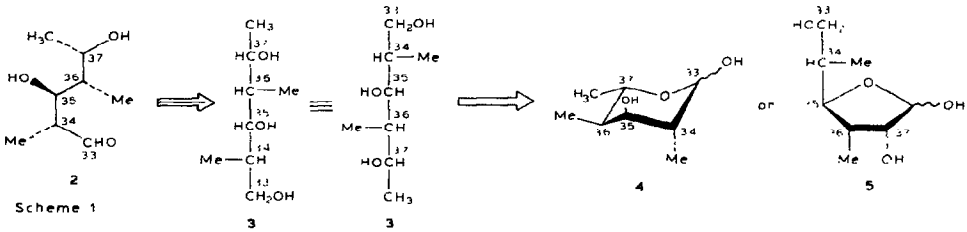


Scheme 1

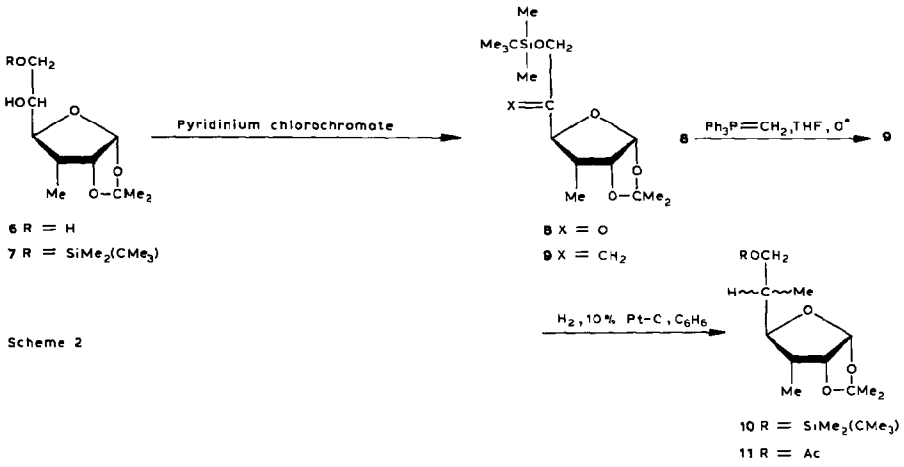
chemistry has been assigned to only one member, namely amphotericin B (**1**), through X-ray analysis[5]. However, these antibiotics are, in general, amorphous, and their sensitivity to a wide variety of chemical reagents, as well as to light, renders chemical proof of their structures very difficult.

Our laboratory has been developing a general program on the polyene macrolides, which should facilitate proof of their structures, both relative and absolute, by a combination of degradative and synthetic studies[6,7]. Of interest is the propanoate-derived C-33–C-37 segment, which is shown as **2**. A similar array, albeit of unknown absolute stereochemistry, occurs in nystatin, candidin, and mycoheptin[8], and it is conceivable that the absolute stereochemistry is the same in all four antibiotics. Accordingly, a route to an optically pure precursor, such as **2** or **3**, should facilitate correlation of these antibiotics through a combination of degradation and synthesis. Three non-carbohydrate routes to this segment have recently been reported by Brooks and Kellogg[9], Masamune *et al.*[10], and McGarvey *et al.*[11]. Herein, we describe a route to **3**, in which D-glucose is the ultimate starting-material.

RETROSYNTHETIC CONSIDERATIONS

The hexose **2** and hexitol **3** can respectively be correlated with 2,4,6-trideoxy-2,4-di-*C*-methyl-L-altropyranose (**4**) and 3,5-dideoxy-3,5-di-*C*-methyl-L-talofuranose (**5**). The former (**4**) was the target in the work of Brooks and Kellog[9], and, although a sugar-based approach to this chiron is conceivable, the alternative, namely, **5**, emerged as the favored candidate for our studies.

Compound **5** has two *C*-methyl groups and the sequence in which these are introduced proved to be of crucial importance. Thus, 3-deoxy-1,2-*O*-isopropylidene-3-*C*-methyl-α-D-allofuranose (**6**), readily obtained by the procedure of Rosenthal and Sprinzt[12], seemed a logical starting-material. Indeed, 6-*O*-(*tert*-butyldimethylsilyl)-3,5-dideoxy-1,2-*O*-isopropylidene-3-*C*-methyl-5-*C*-methylene-α-D-*ribo*-hexofuranose (**9**) was obtained from **6** by routine procedures. Hydrogenation gave a product, **10**, whose ^{1}H-n.m.r. spectrum was too complex to be analyzed. However, the corresponding acetate, **11**, showed acetyl signals at 2.03 and 2.02 p.p.m.in the ratio of 2.3:1. As might have been expected, stereocontrol at C-5 was very poor and emerged as a major problem.

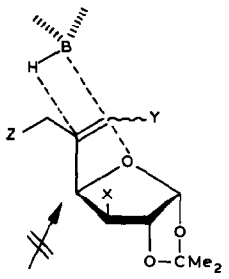


Scheme 2

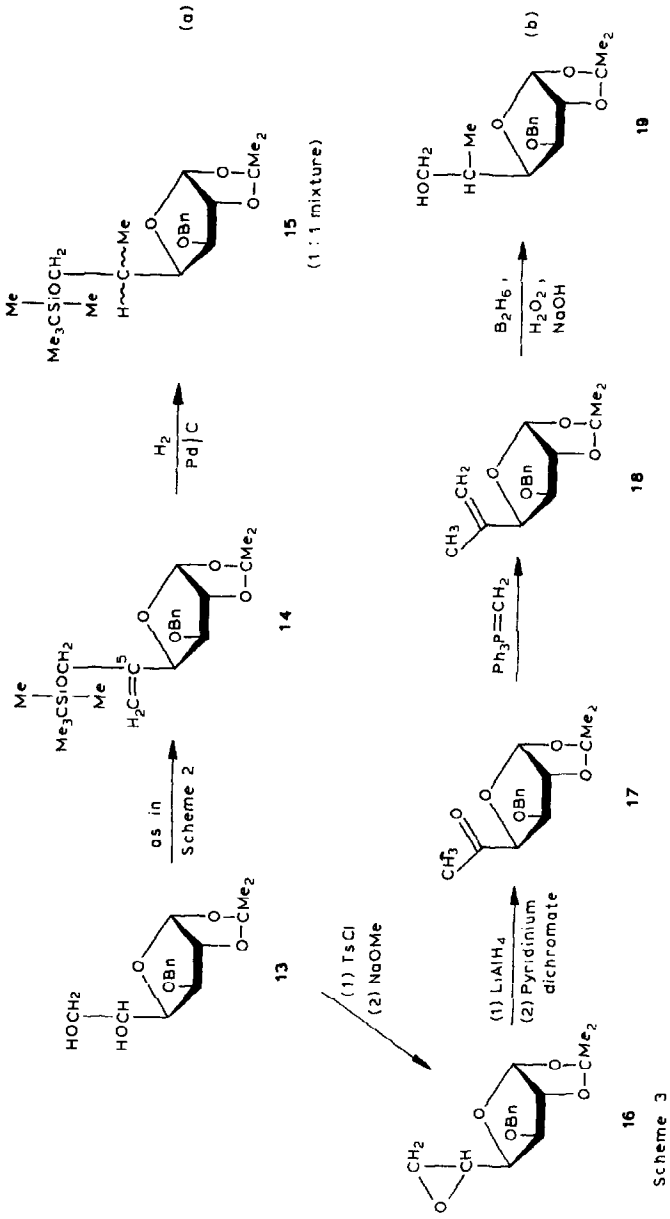
We addressed this issue by making use of the pioneering work of Redlich and Neumann[13] for controlling the facial selectivity at trigonal centers at C-5 of furanose systems by means of a bulky substituent[13,14] at C-3. This result was rationalized by postulating that the favored rotamer for such systems is as shown for **12**, with the larger group (in this case, CH_3) pointing away from the ring. Steric hindrance by the substituent X then forces reagents to approach from "behind", that is, from the *re*-face of the double bond. Indeed, this rationalization was upheld in our recent synthesis[6] of the hemiacetal moiety of amphotericin B and in an approach to sesquisterpene lactones[15].

Two avenues to the desired C-5 stereocenter are then conceivable, depending on the substituents at C-6: (*i*) for **12** (Y = H; Z = OR), hydrogenation would be required; (*ii*) alternatively, for **12** (Y = Z = H), hydroboration would be needed.

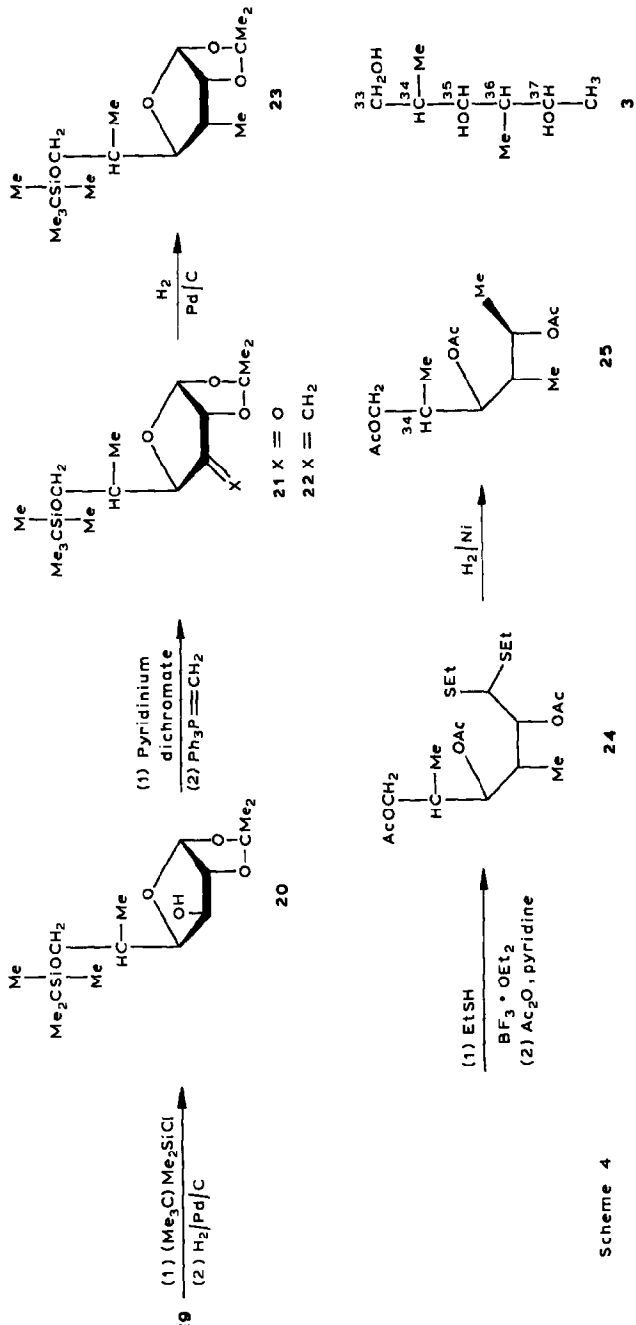
We first examined the hydrogenation of 3-*O*-benzyl-6-*O*-(*tert*-butyldimethylsilyl)-5-deoxy-1,2-*O*-isopropylidene-5-*C*-methylene-α-D-*xylo*-hexofuranose (**14**), which was obtained from 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose[16] (**13**) by routine steps. However, upon hydrogenation, the reaction gave a 1:1



12


(a)
(b)
as in Scheme 2
H2 Pd/C
(1) TsCl (2) NaOMe
(1) LiAlH4 (2) Pyridinium dichromate
Ph3P=CH2
B2H6, H2O2, NaOH
OBn
O—CMe2
13
14
15
(1 : 1 mixture)
16
17
18
19

Scheme 3


19
(1) (Me3C)Me2SiCl
(2) H2/Pd/C
20
(1) Pyridinium dichromate
(2) Ph3P=CH2
21 X = O
22 X = CH2
H2
Pd/C
23
(1) EtSH
BF3 • OEt2
(2) Ac2O, pyridine
24
H2/Ni
25
3

Scheme 4

mixture of the C-5 epimers **15** (see Scheme 3a), implying that compound **14** did not react from any favored conformation.

The alternative substrate **18** is closer to those studied by Redlich and Neumann[13,14], and the compound was prepared by the operations outlined in Scheme 3b. Hydroboration of **18** gave a single product, whose structure was assigned as **19**, in keeping with the trends observed by Redlich and Neumann[13,14].

The second *C*-methyl group was now introduced by the procedure of Rosenthal and Sprinzt[12]. Thus, after appropriate protecting-group adjustments, the alcohol **20** was obtained, and was processed to give alkene 6-*O*-(*tert*-butyldimethylsilyl)-3,5-dideoxy-1,2-*O*-isopropylidene-5-*C*-methyl-3-*C*-methylene-β-L-*lyxo*-hexofuranose (**22**). As expected, hydrogenation gave the L-*talo* derivative **23** as the sole detectable product.

The final steps of the sequence involved treating **23** with ethanethiol in the usual way; this cleaved the acetal linkages, and gave the dithioacetal **24** in excellent yield. Desulfurization of **24** gave the desired product in the form of the triacetate **25** of **3**.

EXPERIMENTAL

General. — Melting points were determined in capillary tubes, using a Büchi Model 510 apparatus and are uncorrected. Elemental analyses were performed either by M-H-W-Laboratories (Phoenix, AZ), or by Dr. F. Kasler (Department of Chemistry, University of Maryland). Optical rotations were determined with a Perkin–Elmer 241 polarimeter. T.l.c. was performed on silica gel HF-254 (0.2-mm layers) containing a fluorescent indicator (Merck, 5539), using the following solvent systems: ethyl acetate–hexane mixtures (*A* 5:95, *B* 15:85, *C* 25:75, and *D* 50:50). Detection was by u.v. (254 nm) or charring with sulfuric acid. Column chromatography was effected on Silica gel (Merck 70–230 mesh A.S.T.M. or 230–400 mesh A.S.T.M.). ^{1}H-N.m.r. spectra were recorded for solutions in $CDCl_3$ (internal Me_4Si), unless otherwise stated, with a Varian EM-360A, Varian XL-100, Bruker WP-80, or Bruker WM-250 spectrometer. Coupling constants were measured directly from the spectra, or calculated from the peak listing. I.r. spectra for films or solutions were determined using either a Beckman IR-10 or a Perkin–Elmer 298 spectrometer. High-resolution mass spectra (h.r.m.s.) were obtained with a VG 7070F instrument.

*6-O-(*tert*-Butyldimethylsilyl)-3,5-dideoxy-1,2-O-isopropylidene-3-C-methyl-5-C-methylene-α-*D*-ribo-hexofuranose* (**9**). — A solution of 3-deoxy-1,2-*O*-isopropylidene-3-*C*-methyl-α-D-allofuranose (**6**; 4.60 g, 21 mmol) and 4-(dimethyl amino)pyridine (0.005 g) in pyridine (105 mL) was treated at 0° with *tert*-butylchlorodimethylsilane (3.80 g, 25.0 mmol). The mixture was allowed to warm to room temperature and then stirred for 4.5 h, poured into H_2O (300 mL) and extracted with dichloromethane. The extracts were combined, washed with H_2O, dried (Na_2SO_4), and evaporated. Purification by flash chromatography gave the

silyl ether **7** as a colorless liquid (5.31 g, 85%); R_F 0.50 (*C*); ^{1}H-n.m.r. (60 MHz, $CDCl_3$): δ 5.68 (d, 1 H, *J* 4.0 Hz, H-1), 4.77 (t, 1 H, *J* 4.0 Hz, H-2), 3.60–3.80 (m, 4 H, H-4,5,6,6'), 2.50 (br s, 1 H, O*H*, exchanges with D_2O), 1.63–2.21 (m, 1 H, H-3), 1.42 [s, 3 H, $C(CH_3)_2$], 1.28 [s, 3 H, $C(CH_3)_2$], 1.12 (d, 3 H, *J* 7.0 Hz, 3-C-CH_3), 0.83 [s, 9 H, $(CH_3)_3C$], and 0.02 [s, 6 H, $Si(CH_3)_2$]. A solution of the alcohol **7** (0.333 g, 1.0 mmol) in dry dichloromethane (2 mL) was added to a suspension of pyridinium chlorochromate[7] (0.644 g, 3.0 mmol), Celite (0.84 g), and anhydrous sodium acetate (0.065 g, 0.70 mmol) in dichloromethane (8 mL). The mixture was stirred for 19 h at room temperature, ether (10 mL) was added, and the suspension filtered through a pad of Celite. The filtrate was evaporated *in vacuo*, and the residue purified by flash chromatography, to give ketone **8** as a colorless, unstable liquid (0.18 g, 54% yield), which was used directly. The methylenation reagent was prepared by addition of 1.7M butyllithium–hexane solution (0.36 mL, 0.61 mmol) to a suspension of methyltriphenylphosphonium bromide (0.216 g, 0.61 mmol) in dry tetrahydrofuran (2 mL) at 0° under N_2. The yellow solution was stirred for 10 min at 0°, warmed to room temperature, and stirred for 25 min, cooled to −52° (diethyl malonate–Dry Ice), and a solution of ketone **8** (0.100 g, 303 μmol) in dry tetrahydrofuran (5 mL) was added dropwise. The mixture was stirred for 1 h at −52° and then for 31 h at room temperature. Water (8 mL) was added, and the mixture was extracted with diethyl ether. Drying (Na_2SO_4) and customary processing gave a residue which was purified by flash column chromatography, to afford alkene **9** as a clear, colorless syrup (0.070 g, 70%); R_F 0.24 (*A*); $[\alpha]_D^{23}$ −68.5° (*c* 1.3, chloroform); ^{1}H-n.m.r. (100 MHz, $CDCl_3$): δ 5.78 (d, 1 H, *J* 4.0 Hz, H-1), 5.26 (m, 1 H, 5-*C*-methylene), 5.07 (m, 1 H, 5-*C*-methylene), 4.53 (t, 1 H, *J* 4.0 Hz, H-2), 4.09–4.26 (m, 3 H, H-4,6,6'), 1.79–2.15 (m, 1 H, H-3), 1.49 [s, 3 H, $C(CH_3)_2$], 1.31 [s, 3 H, $C(CH_3)_2$], 1.00 (d, 3 H, *J* 7.6 Hz, 3-C-CH_3), 0.89 [s, 9 H, $(CH_3)_3C$], and 0.04 [s, 6 H, $Si(CH_3)_2$].

Anal. Calc. for $C_{17}H_{32}O_4Si$: C, 62.15; H, 9.92. Found: C, 62.11; H, 10.10.

***Hydrogenation of compound* 9. — A solution of alkene 9 (0.070 g, 0.20 mmol) in ethanol (25 mL) was subjected to catalytic hydrogenation in the** presence of 0.070 g of 5% (w/w) Pd–C and at a pressure of 345 kPa of H_2 for 26 h. The catalyst was removed by filtration, and the filtrate was evaporated *in vacuo*, to give a yellow liquid. Purification by flash chromatography afforded the product **10** as a colorless liquid (0.060 g, 90%); R_F 0.78 (*D*). Treatment with 0.5M tetrabutylammonium fluoride solution in tetrahydrofuran (12 mL, 6.0 mmol) for 45 min caused desilylation, and the product was dissolved in acetic anhydride (0.60 mL, 0.66 g, 6.0 mmol) and dry pyridine (0.60 mL, 0.60 g, 7.5 mmol), and stirred for 15 h at room temperature. The mixture was evaporated *in vacuo*, and the residue purified by flash chromatography, to give the acetate **11** as a colorless liquid (0.013 g, 97%); R_F 0.50 (*A*); ^{1}H-n.m.r. (200 MHz, $CDCl_3$): δ 5.72 (d, 1 H, *J* 4.2 Hz, H-1), 4.50 (t, 1 H, *J* 4.2 Hz, H-2), 3.63–4.20 (m, 3 H, H-4,6,6'), 2.02 and 2.03 (2 s, 3 H, –COCH_3, peak integral ratio 1:2.3), 1.78–2.03 (m, 2 H, H-3,5), 1.48 [s, 3 H, $C(CH_3)_2$], 1.30 (s, 3 H, $C(CH_3)_2$], and 0.82–1.10 (m, 6 H, 3-C-CH_3, 5-C-CH_3).

*3-O-Benzyl-6-O-(*tert*-butyldimethylsilyl)-5-deoxy-1,2-O-isopropylidene-5-C-methyl-α-*D*-gluco- and β-*L*-idofuranose* (**15**). — A mixture of alkene **14** (42 mg, 0.1 mmol) and a catalytic amount of 5% palladium on activated carbon in ethanol (1 (270 mg, 88%) by using the procedure described for **9**. Compound **14** showed the following characteristics: t.l.c. R_F 0.50 (*B*); $[\alpha]_D^{23}$ −39.8° (*c* 1.0, chloroform); ^{1}H-n.m.r. (80 MHz, $CDCl_3$): δ 0.03 [s, 6 H, Si(CH_3)$_2$], 0.88 [s, 9 H, (CH_3)$_3$CSi], 1.32, 1.50 [s, s, 6 H, C(CH_3)$_2$], 3.96 (d, 1 H, $J_{3,4}$ 3.4 Hz, H-3), 4.15 (s, 1 H, H-6), 4.56 (d, 2 H, *J* 1.7 Hz, PhCH_2), 4.61 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-2), 4.77 (m, 1 H, H-4), 5.26 (m containing d, 2 H, *J* 1.1 Hz, C=CH_2), 5.96 (d, 1 H, *J* 3.7 Hz, H-1), and 7.28 (s, 5 H, C_6H_5).

Anal. Calc. for $C_{23}H_{36}O_5Si$: C, 65.68; H, 8.63. Found: C, 65.73; H, 8.68.

*3-O-Benzyl-6-O-(*tert*-butyldimethylsilyl)-5-deoxy-1,2-O-isopropylidene-5-C-methyl-α-*D*-gluco- and β-*L*-idofuranose* (**15**). — A mixture of alkene **14** (42 mg, 0.1 mmol) and a catalytic amount of 5% palladium on activated carbon in ethanol (1 mL) was stirred at room temperature under a hydrogen atmosphere. After 3 h, the mixture was filtered, the solid rinsed with ethanol, and the filtrate evaporated *in vacuo*. Flash chromatography of the residue gave two products (20 mg each). Use of 10% platinum on activated carbon, platinum oxide, or 5% rhodium on alumina powder as the catalyst gave the same results. The less-polar product showed the following characteristics: t.l.c. R_F 0.60 (1:5 ethyl ether–petroleum ether); $[\alpha]_D^{23}$ −32.0° (*c* 1.1 chloroform); ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ 0.02 [2 s, 6 H, Si(CH_3)$_2$], 0.82 (d, 3 H, *J* 4.2 Hz, 5-C-CH_3), 0.86 [s, 9 H, (CH_3)$_3$Si], 1.29, 1.48 [s, s, 6 H, C(CH_3)$_2$], 2.08 (m, 1 H, H-5), 3.63, 3.71 (2 dd, 2 H, *J* 5.1, *J* 4.3, J_{gem} 9.4 Hz, 2 H-6), 3.81 (d, 1 H, $J_{3,4}$ 3.0 Hz, H-3), 3.95 (dd, 1 H, *J* 3.0, $J_{4,5}$ 10.7 Hz, H-4), 4.56 (ABq, 2 H, *J* 11.6 Hz, Δδ 0.23 p.p.m., PhCH_2), 4.59 (d, 1 H, $J_{1,2}$ 4.2 Hz, H-2), 5.88 (d, 1 H, *J* 4.2 Hz, H-1), and 7.32 (m, 5 H), C_6H_5).

Anal. Calc. for $C_{23}H_{38}O_5Si$: C, 65.42; H, 9.07. Found: C, 65.48; H, 9.12.

Data for the more-polar product: t.l.c. R_F 0.53 (1:5 ethyl ether–petroleum ether); ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ 0.01 [2 s, 6 H, Si(CH_3)$_2$], 0.85 [s, 9 H, (CH_3)$_3$Si], 1.09 (d, 3 H, *J* 8.6 5-C-CH_3), 1.37, 1.47 [s, s, 6 H, C(CH_3)$_2$], 2.13 (m, 1 H, H-5), 3.40 (2 dd, 2 H, *J* 5.1, *J* 4.3, J_{gem} 10.7 Hz, 2 H-6), 3.83 (d, 1 H, $J_{3,4}$ 3.0 Hz, H-3), 4.01 (dd, 1 H, *J* 3.0, $J_{4,5}$ 9.9 Hz, H-4), 4.57 (ABq, 2 H, *J* 12.8 Hz, Δδ 0.24 p.p.m., PhCH_2), 4.61 (d, 1 H, $J_{1,2}$ 4.2 Hz, H-2), 5.90 (d, 1 H, *J* 4.2 Hz, H-1), and 7.32 (m, 5 H, C_6H_5).

*5,6-Anhydro-3-O-benzyl-1,2-O-isopropylidene-α-*D*-glucofuranose* (**16**). — 3-*O*-Benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose (**13**; 6.5 g, 21 mmol) was converted into compound **16** (5.3 g, 86%) by formation of the 6-*p*-toluenesulfonate, and cyclization thereof as described recently[7]. Compound **16** showed the following characteristics: t.l.c. R_F 0.87 (*C*); ^{1}H-n.m.r. (80 MHz, $CDCl_3$): δ 1.30, 1.43 [s, s, 6 H, C(CH_3)$_2$], 2.75 (dd, 1 H, $J_{5,6a}$ 2.5, $J_{6a,6b}$ 5.0 Hz, H-6a), 2.91 (dd, 1 H, $J_{5,6b}$ 4.0, *J* 5.0 Hz, H-6b), 3.29 (ddd, 1 H, *J* 2.5, *J* 4.0, $J_{4,5}$ 7.0 Hz, H-5), 4.07 (d, 1 H, *J* 3.0 Hz, H-3), 4.62 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-2), 4.68 (s, 2 H, PhCH_2), 5.95 (d, 1 H, *J* 4.0 Hz, H-1), and 7.32 (s, 5 H, C_6H_5).

Anal. Calc. for $C_{16}H_{20}O_5$: C, 65.73; H, 6.90. Found: C, 65.80; H, 6.95.

*3-O-Benzyl-6-deoxy-1,2-O-isopropylidene-α-*D*-xylo-hexofuranos-5-ulose* (**17**). — To a solution of the anhydro sugar **16** (5.26 g, 18 mmol) in dry tetrahydrofuran (100 mL) was added lithium aluminum hydride (1.37 g, 36 mmol) at 0° in small portions during 5 min. After stirring the mixture for 4 h at room temperature, the reaction was quenched by the addition of water (1.4 mL), followed by 15% aqueous sodium hydroxide (1.4 mL) and water (4.2 mL) at 0°. The suspension was stirred for 30 min, filtered, and the solid rinsed with diethyl ether. The filtrates were combined, dried (anhydrous magnesium sulfate), filtered, and the filtrate evaporated *in vacuo*, to give an alcohol (5.1 g, 96%) which was oxidized with pyridinium dichromate by the procedure of Andersson and Samuelsson[17], to afford the ketone **17** (4.5 g, 91%). Compound **17** showed the following characteristics: t.l.c. R_F 0.56 (*C*); $[\alpha]_D^{23}$ −47.8° (*c* 1.4, methanol); ν_{max}2980, 2940, 1720 (C=O), 1380, 1210, and 1160 cm^{-1}; ^{1}H-n.m.r. (80 MHz, $CDCl_3$): δ 1.32, 1.48 [s, 6 H, $C(CH_3)_2$], 2.22 (s, 3 H, 6-CH_3), 4.28 (d, 1 H, $J_{1,2}$ 3.9 Hz, H-2), 4.53 (ABq, 2 H, *J* 11.3 Hz, Δδ 0.17 p.p.m., PhCH_2), 4.62 (dd, 2 H, $J_{3,4}$ 2.2 Hz, H-3,4), 6.08 (d, 1 H, *J* 3.9 Hz, H-1), and 7.25 (s, 5 H, C_6H_5).

Anal. Calc. for $C_{16}H_{20}O_5$: C, 65.73; H, 6.90. Found: C, 65.80; H, 6.93.

*3-O-Benzyl-5,6-dideoxy-1,2-O-isopropylidene-5-C-methyl-α-*D*-xylo-hex-5-enofuranose* (**18**). — Olefination of the ketone **17** (2.7 g, 9.3 mmol) was carried out by using the standard procedure (as for **9**), to afford compound **18** (2.2 g, 82%). Compound **18** showed the following characteristics: t.l.c. R_F 0.66 (*C*); $[\alpha]_D^{23}$ −46.5° (*c* 0.71, $CHCl_3$); ν_{max} 2980, 2930, 1450, 1380, 1260, 1220, 1160, 1080, 1030, 900, 860, 740, and 700 cm^{-1}; ^{1}H-n.m.r. (80 MHz, $CDCl_3$): δ 1.32, 1.52 [s, s, 6 H, $C(CH_3)_2$], 1.70 (s, 3 H, 5-C-CH_3), 3.95 (d, 1 H, $J_{3,4}$ 3.4 Hz, H-3), 4.58 (m, containing ABq, 4 H, *J* 11.5 Hz, Δδ 0.19 p.p.m., PhCH_2, H-2,4), 5.00, 5.19 (dd, m, 2 H, *J* 1.5, *J* 2.5 Hz, 2 H-6), 6.00 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-1), and 7.30 (s, 5 H, C_6H_5).

Anal. Calc. for $C_{17}H_{22}O_4$: C, 70.31; H, 7.64. Found: C, 70.36; H, 7.70.

*3-O-Benzyl-5-deoxy-1,2-O-isopropylidene-5-C-methyl-β-*L*-idofuranose* (**19**). — Hydroboration of the alkene **18** (2.3 g, 7.9 mmol) was carried out by a standard procedure, as described recently[7]. The product was isolated by flash chromatography, to give compound **19** (2.2 g, 89%); t.l.c. R_F 0.52 (*D*); $[\alpha]_D^{23}$ −17.6° (*c* 2.8, methanol); ν_{max} 3450 (OH), 2950, 2860, 1470, 1380, 1220, 1170, 1080, and 1020 cm^{-1}; ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ 0.73 (d, 3 H, *J* 6.9 Hz, 5-C-CH_3), 1.30, 1.48 [s, 6 H, $C(CH_3)_2$], 2.25 (m, 1 H, H-5), 2.80 (br s, 1 H, OH, D_2O exchange), 3.64, 3.66 (s, 2 H, *J* 3.0 Hz, 2 H-6), 3.83 (d, 1 H, $J_{3,4}$ 3.0 Hz, H-3), 3.94 (dd, 1 H, *J* 3.0, $J_{4,5}$ 10.0 Hz, H-4), 4.56 (ABq, 2 H, *J* 11.8 Hz, Δδ 0.25 p.p.m., PhCH_2), 4.59 (d, 1 H, $J_{1,2}$ 3.9 Hz, H-2), 5.90 (d, 1 H, *J* 3.9 Hz, H-1), and 7.30 (m, 5 H, C_6H_5).

Anal. Calc. for $C_{17}H_{24}O_5$: C, 66.20; H, 7.85. Found: C, 66.31; H, 7.91.

6-O-*(tert-Butyldimethylsilyl)-5-deoxy-1,2-O-isopropylidene-5-C-methyl-β-*L*-idofuranose* (**20**). — Compound **19** (250 mg, 0.81 mmol) was silylated by reaction with 4-(dimethylamino)pyridine (15 g), triethylamine (0.33 mL) and *tert*-butylchlorodimethylsilane (122 mg, 0.81 mmol) in dichloromethane (25 mL) at room

temperature under an argon atmosphere. After 20 h, the mixture was poured into 100 mL of ice–water, extracted with dichloromethane, and the extract processed in the usual way[7]. The material (311 mg), a catalytic amount of 10% palladium on activated carbon and a few drops of 88% aqueous formic acid in 20 mL of methanol was stirred at room temperature under a hydrogen atmosphere. After 6 h, the mixture was filtered, and the filtrate evaporated *in vacuo*. Flash chromatography of the residue with 1:1 ethyl acetate–hexane afforded 225 mg (91%) of **20**, which showed the following characteristics: t.l.c. R_F 0.75 (*D*); $[\alpha]_D^{23}$ −13.08° (*c* 1.3, $CHCl_3$); $\nu_{max}^{CHCl_3}$ 3450 (OH), 2950, 2860, 1470, 1380, 1260, 1220, 1170, 1080, 1020, 840, and 780 cm^{-1}; ^{1}H-n.m.r. (80 MHz, $CDCl_3$): δ 0.03 [s, 6 H, $Si(CH_3)_2$], 0.88 [s, 9 H, $C(CH_3)_3$], 1.01 (d, 3 H, *J* 7.0 Hz, 5-C-CH_3), 1.28, 1.46 [s, s, 6 H, $C(CH_3)_2$], 2.05 (m, 1 H, H-5), 3.20 (br s, 1 H, O*H*, D_2O exchange), 3.52 (dd, 1 H, $J_{5,6a}$ 4.8, $J_{6a,6b}$ 9.8 Hz, H-6a), 3.78 (dd, 1 H, $J_{5,6b}$ 5.5, *J* 9.8 Hz, H-6b), 4.01 (m, 2 H, H-3,4), 4.48 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-2), and 5.87 (d, 1 H, *J* 4.0 Hz, H-1).

Anal. Calc. for $C_{16}H_{32}O_5Si$: C, 57.80; H, 9.71. Found: C, 57.69; H, 9.73.

*6-O-(tert-Butyldimethylsilyl)-5-deoxy-1,2-O-isopropylidene-5-C-methyl-β-*L-lyxo*-hexofuranos-3-ulose* (**21**). — Alcohol **20** (630 mg, 1.9 mmol) was oxidized by using pyridinium dichromate (1.5 mmol) and acetic anhydride (6 mmol) in dry dichloromethane (6 mL), to afford compound **21** (594 mg, 95%). Compound **21** showed the following characteristics: $[\alpha]_D^{23}$ +67.82° (*c* 1.1, $CHCl_3$); ν_{max} 2950, 2860, 1780 (C=O), 1470, 1380, 1260, 1160, 1090, 1020, 840, 790, and 760 cm^{-1}; ^{1}H-n.m.r. (80 MHz, $CDCl_3$): δ 0.03 [s, 6 H, $Si(CH_3)_2$], 0.88 [s, 9 H, $C(CH_3)_3$], 1.00 (d, 3 H, *J* 7.0 Hz, 5-C-CH_3), 1.45 [d, 6 H, $C(CH_3)_2$], 2.26 (m, 1 H, H-5), 3.45, 3.56 (s and d, 2 H, *J* 3.3 Hz, 2 H-6), 4.22 (m, 1 H, H-4), 4.43 (d, 1 H, $J_{1,2}$ 4.4 Hz, H-2), and 6.01 (d, 1 H, *J* 4.4 Hz, H-1).

Anal. Calc. for $C_{16}H_{30}O_5Si$: C, 58.15; H, 9.16. Found: C, 58.21; H, 9.17.

*6-O-*tert*-(Butyldimethylsilyl)-3,5-dideoxy-1,2-O-isopropylidene-5-C-methyl-3-C-methylene-β-*L-lyxo*-hexofuranose* (**22**). — Ketone **21** (884 mg, 2.68 mmol) was converted into compound **22** (738 mg, 84%) by using the standard procedure for Wittig olefination already described for **9**. Compound **22** showed the following characteristics: t.l.c. R_F 0.66 (*C*); $[\alpha]_D^{23}$ +118.75° (*c* 1.6, $CHCl_3$); $\nu_{max}^{CHCl_3}$ 2950, 2860, 1460, 1380, 1260, 1160, 1100, 1030, 840, and 780 cm^{-1}; ^{1}H-n.m.r. (80 MHz, $CDCl_3$): δ 0.03 [s, 6 H, $Si(CH_3)_2$], 0.88 [s, 9 H, $C(CH_3)_3$], 1.01 (d, 3 H, *J* 7.0 Hz, 5-C-CH_3), 1.37, 1.50 [s, s, 6 H, $C(CH_3)_2$], 1.92 (m, 1 H, H-5), 3.42 (dd, 1 H, $J_{5,6a}$ 7.1, $J_{6a,6b}$ 9.8 Hz, H-6a), 3.62 (dd, 1 H, $J_{5,6b}$ 5.9, *J* 9.8 Hz, H-6b), 4.78 (m, 2 H, H-2,4), 5.17 (t, 1 H, *J* 1.8 Hz, H-3'a), 5.40 (dd, 1 H, *J* 1.1 Hz, H-3'b), and 5.76 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-1).

Anal. Calc. for $C_{17}H_{32}O_4Si$: C, 62.16; H, 9.83. Found: C, 62.20; H, 9.86.

*6-O-(tert-Butyldimethylsilyl)-3,5-dideoxy-1,2-O-isopropylidene-3,5-di-C-methyl-β-*L-*talofuranose* (**23**). — Hydrogenation of the alkene **22** (390 mg, 1.2 mmol) was carried out as described for the conversion of **14** into **15**, to yield compound **23** (350 mg, 89%): t.l.c. R_F 0.81 (*C*); $[\alpha]_D^{23}$ +27.36° (*c* 1.93, $CHCl_3$): $\nu_{max}^{CHCl_3}$ 2950, 2860, 1460, 1380, 1260, 1220, 1180, 1100, 1030, 840, and 780 cm^{-1};

^{1}H-n.m.r. (80 MHz, $CDCl_3$): δ 0.02 [s, 6 H, $Si(CH_3)_2$], 0.85 [s, 9 H, $C(CH_3)_3$], 1.01 (t, 6 H, *J* 7.0 Hz, 3-C-CH_3, 5-C-CH_3), 1.30, 1.48 [s, s, 6 H, $C(CH_3)_2$], 1.45–2.18 (m, 2 H, H-3,5), 3.40 (dd, 1 H, $J_{5,6a}$ 7.0, $J_{6a,6b}$ 11.0 Hz, H-6a), 3.70 (dd, 2 H, *J* 6.0, *J* 5.0 Hz, H-4,6b), 4.48 (dd, 1 H, $J_{1,2}$ 4.0, $J_{2,3}$ 5.0 Hz, H-2), and 5.71 (d, 1 H, *J* 4.0 Hz, H-1).

Anal. Calc. for $C_{17}H_{34}O_4Si$: C, 61.78; H, 10.38. Found: C, 61.72; H, 10.30.

2,4,6-Tri-O-*acetyl-1,3,5-trideoxy-3,5-di*-C-*methyl*-L-*talose diethyl dithioacetal* (**24**). — To a solution of compound **23** (10 mg, 0.03 mmol) and 3 drops of ethanethiol in dry dichloromethane (1 mL) was added boron trifluoride etherate (3 drops) at 0° under argon. After stirring the mixture at room temperature, the reaction was quenched with saturated sodium hydrogencarbonate (2 mL) and the mixture was extracted with dichloromethane (3 × 5 mL). The extracts were combined, dried (anhydrous magnesium sulfate), filtered, and the filtrate evaporated *in vacuo*. The residue was purified by flash chromatography, to give the triol (6 mg, 70%) which was treated with acetic anhydride and pyridine, to provide the triacetate **24** (9 mg). Compound **24** showed the following characteristics: t.l.c. R_F 0.71 (*D*); $[\alpha]_D^{23}$ +15.76° (*c* 0.85, $CDCl_3$); ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ 1.02, 1.05 (d, d, 6 H, *J* 6.8, *J* 7.0 Hz, 3-C-CH_3, 5-C-CH_3), 1.23 (ddd, 6 H, *J* 1.3, *J* 7.4 Hz, 2 SCH_2CH_3), 2.03, 2.04, 2.08 (3 s, 9 H, 3 $OCOCH_3$), 2.15 (m, 2 H, H-3,5), 2.63 (m, 4 H, 2 SCH_2CH_3), 3.86 (dd, 1 H, $J_{5,6a}$ 6.6, $J_{6a,6b}$ 11.0 Hz, H-6a), 3.96 (d, 1 H, $J_{1,2}$ 4.7 Hz, H-1), 4.05 (dd, 1 H, $J_{5,6a}$ 4.5, *J* 11.0 Hz, H-6b), 4.85 (dd, 1 H, *J* 5.0, *J* 6.6 Hz, H-4), and 5.12 (dd, 1 H, *J* 4.7, $J_{2,3}$ 6.8 Hz, H-2).

Anal. Calc. for $C_{18}H_{32}O_6S_2$: C, 52.92; H, 7.90; S, 15.67. Found: C, 52.92; H, 7.93; S, 15.71.

2,4,6-Tri-O-*acetyl-1,3,5-trideoxy-3,5-di*-C-*methyl*-L-*talitol** (**25**). — A mixture of the thioacetal **24** (6 mg, 15 μmol) and an excess of Raney nickel in 2-propanol (2 mL) was refluxed under a hydrogen atmosphere for 4 h. The mixture was filtered, and the solid washed with ethanol. The filtrates were combined, and evaporated *in vacuo*, and the residue was purified by flash chromatography, to give **25** (3 mg, 71%). Compound **25** showed the following characteristics: t.l.c. R_F 0.35 (*C*); ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ 0.96, 1.02, 1.22 (d, d, and d, *J* 7.0 Hz, 3 C–CH_3), 2.03, 2.06, 2.07 (3 s, 9 H, 3 $OCOCH_3$), 2.10–2.35 (m, 2 H, H-3,5), 3.88 (dd, 1 H, $J_{5,6a}$ 7.0, $J_{6a,6b}$ 11.5 Hz, H-6a), 4.07 (dd, 1 H, $J_{5,6b}$ 4.5, *J* 11.5 Hz, H-6b), 4.88 (t, 1 H, $J_{3,4} = J_{4,5}$ = 7.0 Hz, H-4), and 5.05 (dq, 1 H, $J_{2,3}$ 3.0, *J* 4.5 Hz, H-2); h.r.m.s. Calc. for $C_{14}H_{24}O_6$: M^+, 287.1494. Found: M^+ 287.1493.

ACKNOWLEDGMENTS

We are grateful to the University of Maryland and to the National Science Foundation (CHE 8304283) for financial support.

*Preferred name[18]: 1,3,5-tri-*O*-acetyl-2,4,6-trideoxy-2,4-di-*C*-methyl-L-altritol.

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