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STEREOSELECTIVITY IN THE ELECTROPHILE-MEDIATED CYCLIZATION OF 2,3,5-TRI-*O*-BENZYL-1,2-DIDEOXY-D-*arabino*-HEX-1-ENITOL. A STEREOCONTROLLED SYNTHESIS OF 1-AMINO-2,5-ANHYDRO-3,4,6-TRI-*O*-BENZYL-1-DEOXY-D-GLUCITOL

FILLMORE FREEMAN* AND KIRK D. ROBARGE
Department of Chemistry, University of California at Irvine, Irvine, California 92717 (U.S.A.)
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ABSTRACT

Cyclization of 2,3,5-tri-*O*-benzyl-1,2-dideoxy-D-*arabino*-hex-1-enitol (**2**) with mercuric acetate, mercuric trifluoroacetate, iodine, and *N*-bromosuccinimide gave preponderantly the *allo* isomer of the *C*-arabinofuranosyl structure. 1-Amino-2,5-anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-D-glucitol, which is a key intermediate in the synthesis of 3-(β-D-arabinofuranosyl)pyrazole[4,3-*d*]pyrimidine-5,7-dione (β-D-*arabino* epimer of oxoformycin B), was stereoselectively prepared in 48% overall yield from **2** in three steps. The stereochemical outcome of the cyclizations is also discussed.

INTRODUCTION

In 1974, Acton *et al.*[1] synthesized the α- and β-D-*arabino* (**6**) epimers of the naturally occurring *C*-nucleoside oxoformycin B. We wish to report a stereoselective synthesis of Acton's key intermediate, 1-amino-2,5-anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-D-glucitol (**5**), in three steps (from **2**) *with excellent control* of the anomeric center to give preponderantly the β-D-*arabino* epimer. During this study, it was observed that electrophile-mediated cyclizations of 2,3,5-tri-*O*-benzyl-1,2-dideoxy-D-*arabino*-hex-1-enitol[2] (**2**) were highly stereoselective, with a strong preference for formation of *C*-arabinofuranosyl derivatives which have the *cis* arrangements of substituents at C-2 and C-3.

RESULTS AND DISCUSSION

The synthesis of **5** was accomplished by reaction of methylidenetriphenylphosporane (2.0 equiv. from the phosphonium bromide and butyllithium)[2,3] with 2,3,5-tri-*O*-benzyl-D-arabinose[4] (**1**) in oxolane to give hydroxyolefin **2** in 94% yield. Cyclization with iodine[3–6] gave a mixture of *allo* and *altro* in 79% yield, which was

*To whom correspondence should be addressed.

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TABLE I

ELECTROPHILE-MEDIATED CYCLIZATIONS OF 2,3,5-TRI-*O*-BENZYL-1,2-DIDEOXY-D-*arabino*-HEX-1-ENITOL (2)

Electrophile	*Ref.*	*Reaction conditions*	*Yield (%)*		allo *(β)-to-* altro *(α) ratio*	*^{13}C-N.m.r. (δ)*[a]	
			Crude	*Pure*		allo	altro
I_2	2, 3	10 eq. sat'd $NaHCO_3$, 5 eq. I_2–oxolane; 24°, 4 h	85	79	82:18[b]	0.68	7.14
Br_2	9	*N*-Bromosuccinimide (1.5 eq.)–$HCONMe_2$; 24°, 2 h	85	75	84:16[b](89:11)	28.26(28.20)	32.37(32.30)
$Hg(OAc)_2$	10	(a) $Hg(OAc)_2$ (1.5 eq.)–oxolane; 24°, 3 h (b) sat'd KCl	100	87	89:11[c,d](87:13)	28.33	35.45
$Hg(OCOCF_3)_2$	11	(a) $Hg(OCOCF_3)_2$ (1.5 eq.)–oxolane; 24°, 3 h (b) sat'd KCl	83	63	89:11[c,d]	28.33	35.45
PheSeCl	12	PheSeCl (1.5 eq.)–oxolane; −78→24°, 8 h	100	46	40:60[b]	25.47	29.98
PheSeCl	12, 14	PheSeCl (1.5 eq.)–oxolane–K_2CO_3 (2.0 eq.)	100	48	85:15[b]	25.47	29.98
3-Chloro-peroxybenzoic acid	8	3-Chloroperoxybenzoic acid (1.2 eq.)–$(CH_2)Cl_2$;16, 18 h, reflux		33	50:50[e](55:45)	61.71	62.73

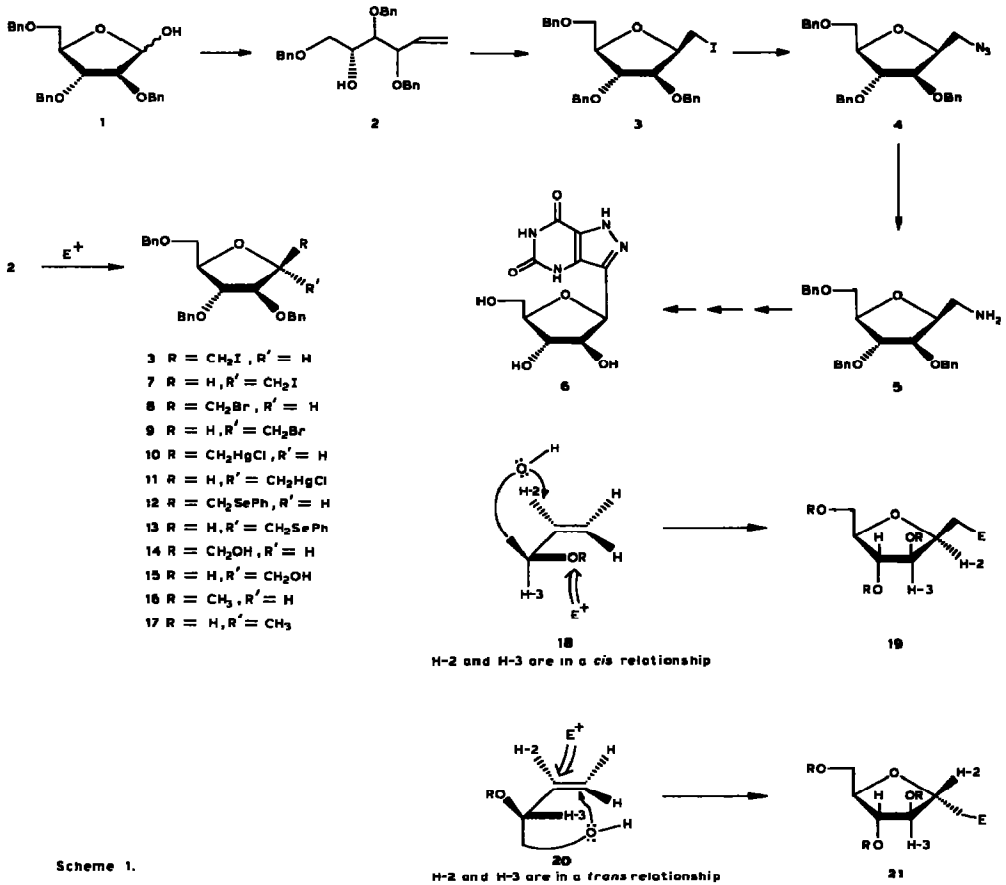
[a] ^{13}C-Chemical shifts are referenced to the signal of $CDCl_3$ at δ 77.27. All ^{13}C-spectra were taken for solutions in $CDCl_3$. $J_{2,3}$ in compound **3** = 3.6 Hz. The numbers in parentheses are those reported by Reitz *et al.*[8]. [b] The *allo*-to-*altro* ratio was determined by reduction (azoisobutyronitrile–Bu_3SnH–C_6H_6; 45 min)[11] of *crude* cyclization products and analysis of the *crude* methyl compound by ^{1}H-n.m.r. (250 MHz) in C_6D_6. Integration of the two sets of anomeric methyl doublets gave the *allo*-to-*altro ratios*. [c] The *allo*-to-*altro* ratio was determined by reduction [$NaBH_4$ (excess)-$BnEt_3NCl$(10 eq.)–10% NaOH; 0°, 2 min)] of the crude organomercurial and ^{1}H-n.m.r. (250 MHz) analysis of a solution in C_6D_6. [d] $HgBr_2$ or $HgCl_2$[11] did not effect cyclization. Only quantitative recovery of starting material resulted. [e] The *allo*-to-*altro* ratio was determined by ^{1}H-n.m.r. (250 MHz) integration of the two OH triplets.

highly enriched in the *allo* anomer (Table I). Flash column chromatography gave the anomerically pure *allo* isomer (**3**). Reaction of **3** with 1,1,3,3 tetramethylguanidinium azide in *N,N*-dimethylmethanamide at 80° for 1 h (71%), followed by lithium aluminum hydride reduction at 0° in diethyl ether, gave the desired amine[7] **5** (90%). This short, stereocontrolled synthesis of **5** took advantage of a highly stereoselective, electrophile-mediated cyclization to control the stereochemistry at the anomeric center.

The stereoselectivity shown by the cyclization of **2** with iodine prompted us to study this reaction further with a series of electrophiles. Though the method to quantify *allo*-to-*altro* ratios in the cyclized products differs from that used by Reitz *et al.*[8], these results are in excellent agreement with their report[9–14] (Table I). The steric structure of the cyclization products was determined by the relative positions and intensities in the ^{13}C-n.m.r. of the C-1 signals[8]. The 1:1 mixture of **14** and **15** was converted into the iodo compounds by the procedure of Ho and Davies[15] (triphenylphosphine, diethyl azodicarboxylate, zinc iodide, 30%). Two ^{13}C resonances were observed for the iodomethyl carbon atoms at δ 7.14 and 0.68. The ^{13}C-n.m.r. spectrum of the crude reaction mixture from the cyclization of **2** with iodine showed a major resonance for the iodomethyl carbon atom at δ 0.68 and another smaller resonance (*ca.* one-fifth the height) at δ 7.14. Ohrui *et al.*[16] have shown that for furanoses the ^{13}C-chemical shift of a carbon atom bonded to the anomeric center in the 2,3-*cis* isomer [*allo* (β) isomer in this case] is 3–4 p.p.m. *upfield* of that for the corresponding 2,3-*trans* isomer [*altro* (α) isomer in this case].

In addition, upon decoupling of H-1A,B in **3**, the H-2 signal collapsed to a *doublet* with a $J_{2,3}$ value of 3.6 Hz. Similarly, decoupling of the anomeric methyl group of its reduction product gave a $J_{2,3}$ value of 3.7 Hz. These values are indicative of a *cis* relationship between H-2 and H-3. This, in conjunction with the relative positions of the iodomethyl carbon atom signals in the ^{13}C-n.m.r. spectrum allowed the assignment of the *allo* (β) structure to the major product of the cyclization with iodine. The configurations of the other cyclization products were assigned accordingly. With the exception of the selenium-mediated cyclization, this observed stereoselectivity was in accord with the selectivity reported by other investigators[8,10,13,17–19].

Unlike the cyclization of 6-*O*-benzyl-1,2-dideoxy-3,4-*O*-isopropylidene-D-*ribo*-hex-1-enitol[3], the stereochemical outcome of the cyclization in alkene **2** is dependent upon the electrophile. Iodine, bromine, mercury(II) acetate and mercury(II) trifloroacetate, all showed a stereoselective preference for *C*-arabinofuranosyl derivatives that have a *cis* arrangement of H-2 and H-3 (*allo* isomer). 3-Chloroperbenzoic acid showed no selectivity and with phenylselenyl chloride the *altro* isomer was slightly preferred. Although the reversal of stereochemistry shown by the selenium-induced cyclization is not clear, it may be due to an acid-catalyzed equilibration of the epimers, since the *allo* isomer is the major product in the presence of base*. Lancelin *et al.*[21] have reported a selenium-induced cyclization in which the stereochemical result is consistent with these



Scheme 1.

observations. For this kinetically controlled reaction[8], it appears as though the allylic ether oxygen atom is again controlling the stereochemical outcome of the cyclization[3]. There seems to be a preference to cyclize through a "transition state" in which the OR residue (Scheme 1) is in the plane of the prochiral olefin. In this conformation, the internal nucleophile is positioned to trap from above, as depicted in Scheme 1. Electrophile approach from the least hindered side (below, **18**), followed by trapping by the internal nucleophile leads to H-2 and H-3 in a *cis* relationship to one another (*i.e.*, the *β-arabino* epimer). Cyclization through conformation **20**, in which the hydrogen atom eclipses the prochiral olefin, leads to the *α-arabino* product (*altro* isomer).

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*The modest yield of products (46%) suggests possible competing-side reactions. For example, there may be decomposition of the products at differing rates under the experimental conditions which would effect the final *allo* to *altro* ratio. The stereochemical outcome of the selenium mediated cyclization of **2** is dependent on the reaction conditions. Use of camphorsulfonic acid and N-(phenylseleno)phthalimide in refluxing benzene gave a 2:1 *allo*-to-*altro* ratio[20].

In the absence of any steric bias, the preference for reactions of this type to cyclize *via* a "reactive conformer" resembling **18** may be very general. For example, the stereoselectivity observed in iodolactonizations of allylic alcohols[22] and iodoetherifications[23,24] to form functionalized oxolanes can be rationalized accordingly. This "working model" is useful for predicting *a priori* the stereochemical outcome for these cyclizations in which there is a preference for a *cis* relationship between the substituents at C-2 and C-3 in the newly formed oxolane ring.

EXPERIMENTAL

General methods. — Melting points were determined in open capillary tubes with a Thomas–Hoover apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer 241 polarimeter in an unthermostatted 10-cm glass cell at the sodium D line. I.r. spectra were obtained with a Perkin–Elmer 283 spectrophotometer for dilute solutions in CCl_4, neat films, or KBr disks. Medium-resolution mass spectra were obtained with a Finnigan 9610 g.l.c.–c.i. mass spectrometer with a Nova 3 data system operating at an ionization potential of 70 or 100 eV. Chemical-ionization mass spectra were obtained by use of 2-methylpropane as the reactant gas. Peaks greater than ~10% relative intensity are generally reported. ^{1}H-N.m.r. spectra were recorded at 250 MHz (Bruker WM-250) with the solvent(s) noted. Chemical shifts (δ) are reported downfield from the internal Me_4Si signal (~0.5% for Fourier transform) at δ 0.00 (Abq, ab quartet; br, broad; d, doublet; m, multiplet; q, quartet; s, singlet; and t, triplet). Apparent coupling-constants (J) are reported in hertz (Hz). Because of the data digitization with the F.t. instrument, J values are ±0.40 Hz maximum, but normally are accurate to ±0.20 Hz. ^{13}C-N.m.r. data were obtained with a Bruker WM-250 spectrometer. Silica gel 60 (230–400 mesh) was used for flash column chromatography. T.l.c. was performed on Merck Silica gel 60 F-254 (0.25 mm, precoated on glass). Solvents used for extraction and chromatography were nanograde quality or distilled. Oxolane and ether were distilled from sodium benzophenone anion prior to use. Dichloromethane was distilled from CaH_2 prior to use. *N,N*-Dimethylmethanamide was predried over BaO, and then distilled under diminished pressure from CaH_2 in the dark and stored over 4A sieves. Other reagents were used as supplied or purified as noted. Butyllithium in hexane (Alfa) was titrated at 24° in oxolane with (2,5-dimethoxyphenyl)methanol. All reactions were carried out in oven- or flame-dried glassware under Ar with magnetic stirring, unless noted otherwise. Solutions and liquids were delivered by syringe or cannula through rubber septa or by pressure-equalizing dropping funnels where appropriate. Elemental analyses were performed by Robertson Laboratory, Florham Park, NJ.

2,3,5-Tri-O-*benzyl-1,2-dideoxy*-D-arabino-*hex-1-enitol* (**2**). — To a stirred solution of methyltriphenylphosphonium bromide (2.80 g, 7.92 mmol; Aldrich, predried at 140°, 18 h) in dry oxolane (25 mL) at 25° under Ar was added dropwise

2.4M butyllithium in hexane (2.97 mL, 7.13 mmol) over 8 min. A color change from yellow to red occurred. The mixture was stirred for 15 min at 24° and a solution of 2,3,5-tri-*O*-benzyl-D-arabinose[4] (**1**) (1.5 g, 3.57 mmol) in oxolane (10 mL) was added over 3 min. Solids began to form in the cream-colored suspension. The mixture was stirred for 18 h at 24° under Ar and the reaction quenched by the addition of wet ether (100 mL). The mixture was extracted several times with ether, and the combined organic layers were washed with saturated aqueous NaCl (35 mL), and dried (K_2CO_3). Removal of solvent under reduced pressure and flash-column chromatography of the residue on silica (60 g) with 3:1:1 petroleum ether-(35–60°)–ether–dichloromethane afforded **2** (1.40 g, 94%), $[\alpha]_D^{26}$ +4.6° (*c* 1.15, chloroform), R_F 0.30 (3:1:1 petroleum ether–ether–dichloromethane); ν_{max}^{film} 3540–3460 (br, OH), 3100, 3080, 3040 (alkene, arom.), 2920, 2880 (CH_2,CH), 1500, 1460 (arom. ring), 1400, 1350, 1225, 1080, 930 (vinyl), 740, and 700 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 7.35–7.24 (m, 15 H, Ph), 5.97 (ddd, 1 H, $J_{1,2(trans)}$ 16.5, $J_{1,2(cis)}$ 11.3, $J_{2,3}$ 7.5 Hz, H-2, X part of ABX), 5.33 (m, 2 H, H_2-1), 4.60 (ABq, 2 H, $\Delta\nu_{AB}$ 18.4, J_{AB} 11.5 Hz, OCH_2Ph), 4.52 (s, 2 H, OCH_2Ph), 4.51 (ABq, 2 H, $\Delta\nu_{AB}$ 69.5, J_{AB} 12.0 Hz, OCH_2Ph), 4.09 (dd, 1 H, $J_{2,3}$ 7.5, $J_{3,4}$ 4.0 Hz, H-3), 4.03 (m, 1 H, H-5), 3.64 (dd, 1 H, $J_{3,4}$ 4.0, $J_{4,5}$ 7.0 Hz, H-4), 3.61 (d, 2 H, $J_{5,6}$ 4.0 Hz, H_2-6), and 2.84 (d, 1 H, $J_{5,OH}$ 5.0 Hz, OH); ^{13}C-n.m.r. ($CDCl_3$): δ 138.47, 138.38, 138.17 (s, C quat., OCH_2Ph), 135.40 (d, C-2), 128.61–127.91 (m, OC$H_2C_6H_5$), 119.31 (t, C-1), 80.89 (d, C-3), 80.48 (d, C-4), 74.35 (t, OCH_2Ph), 73.62 (t, C-6), 71.22 (t, OCH_2Ph), 70.95 (d, C-5), and 70.65 (t, OCH_2Ph); m.s. (c.i.): *m/z* 419 (MH^+), 219, 181, 129, 107, and 91.

Anal. Calc. for $C_{27}H_{30}O_4$: C, 77.48; H, 7.22. Found: C, 77.42; H, 7.37.

*2,5-Anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-1-iodo-*D*-allitol* (**3**). — Alkene **2** (3.34 g, 7.99 mmol) was cyclized with iodine as described previously[3,6]. Work-up as usual[3], followed by flash-column chromatography on silica (175 g) in 9:1:1 petroleum ether (35–60°)–ether–dichloromethane yielded the anomerically pure iodo compound **3** (3.43 g, 79%), $[\alpha]_D^{28}$ +41.1° (*c* 1.78, chloroform), R_F 0.30 (9:1:1 petroleum ether–ether–dichloromethane); ν_{max}^{film} 3080, 3060, 3020 (alkene, arom.), 2910, 2860, (CH_2, CH), 1500, 1450 (arom. ring), 1370, 1210, 1100, 740, and 697 cm^{-1} (monosubst. arom.); ^{1}H-n.m.r. ($CDCl_3$): δ 7.39–7.24 (m, 15 H, Ph), 4.62–4.43 (m, 6 H, 3 OCH_2Ph, no ABq's could be determined), 4.35 (ddd, 1 H, $J_{2,3}$ 3.6, $J_{1,2}$ 6.0, $J_{1,2}$ 5.5 Hz, H-2, collapsed to d upon irradiating H-1A,B and a dd upon irradiating H-3), 4.24 (dt, 1 H, $J_{4,5}$ 2.0, $J_{5,6}$ 6.0 Hz, H-5), 4.05 (br. d, 1 H, $J_{2,3}$ 3.6 Hz, H-3), 3.96 (br. d, 1 H, $J_{4,5}$ 2.0 Hz, H-4), 3.60 (dd, 1 H, $J_{6A,B}$ 10, $J_{6,5}$ 6.0 Hz, H-6A or 6B), 3.49 (dd, 1 H, $J_{6A,B}$ 10, $J_{6,5}$ 7.0 Hz, H-6A or 6B), and 3.34 (m, 2 H, H_2-1); ^{13}C-n.m.r. ($CDCl_3$): δ 138.28, 137.85, 137.72 (s, C quat., OCH_2Ph), 128.64–127.79 (m, OC$H_2C_6H_5$), 83.97 (d, C-2), 83.33 (d, C-5), 82.74 (d, C-3), 82.18 (d, C-4), 73.48, 72.27, 71.62 (t, OCH_2Ph), 70.65 (t, C-6), and 0.68 (t, C-1); m.s. (c.i.): *m/z* 545 (MH^+), 453, 181, 107, and 91.

Anal. Calc. for $C_{27}H_{29}IO_4$: C, 59.57; H, 5.37; I, 23.31. Found: C, 59.40; H, 5.48; I, 23.04.

Compound **3** could also be prepared by the addition of solid iodine (until the red color persisted) to an oxolane solution of the corresponding organomercurial compound[3]. Work-up as usual, followed by flash chromatography, gave a product identical in all respects with the one obtained by cyclization with iodine.

2,5-Anhydro-1-azido-3,4,6-tri-O-*benzyl-1-deoxy*-D-*allitol* (**4**). — Compound **3** (284.3 mg, 0.52 mmol) was dissolved in *N,N*-dimethylmethanamide (5 mL) and solid 1,1,3,3-tetramethylguanidinium azide (Alfa) (165.0 mg, 1.04 mmol) was added quickly. The mixture was heated to 80° and stirred at 80° for 20 min. The color changed from clear to golden upon heating. The starting material was completely consumed at this time as determined by t.l.c. (3:1:1 petroleum ether–ether–dichloromethane). The mixture was heated an additional 20 min, cooled, and evaporated under vacuum (50°, 4 kPa) to leave a crude yellow oil. Flash chromatography on silica (10 g) in 9:1:1 petroleum ether–ether–dichloromethane gave pure azide (**4**) (170.4 mg, 71%), $[\alpha]_D^{26}$ +7.7° (*c* 0.78, chloroform), R_F 0.30 (9:1:1 petroleum ether–ether–dichloromethane); ν_{max}^{film} 3100, 3075, 3040 (alkene arom.), 2930, 2870 (CH_2, CH), 2100 (N_3), 1500, 1455 (arom. ring), 1370, 1160–1050 (br. OR), 740 and 695 cm^{-1} (monosubst. arom.); ^{1}H-n.m.r. ($CDCl_3$): δ 7.40–7.22 (m, 15 H, Ph), 4.7–4.39 (m, 6 H, 3 OC*H*$_2$Ph, no ABq's could be deermined), 4.23–4.15 (m, 2 H, H-2,5), 4.0 (m, 2 H, H-3,4), and 3.70–3.40 (m, 4 H, H-1, H-6); ^{13}C-n.m.r. ($CDCl_3$): δ 138.37, 137.91, 137.68 (s, C quat., OCH_2Ph), 128.70–127.85 (m, O$CH_2C_6H_5$), 83.35 (d), 83.14 (d), 82.94 (d), 79.74 (d), 73.56 (t), 71.81 (t), 70.53 (t), and 50.27 (t, C-1); m.s. (c.i.): *m/z* 460 (MH^+), 432 (MH^+ −28), 205, 181, 120, 107, and 91.

Anal. Calc. for $C_{27}H_{29}N_3O_4$: C, 70.57; H, 6.36; N, 9.14. Found: C, 70.44; H, 6.43; N, 9.01.

1-Amino-2,5-anhydro-3,4,6-tri-O-*benzyl-1-deoxy*-D-*allitol*[7] (**5**). — Compound **4** (86.4 mg, 0.190 mmol) was dissolved in dry diethyl ether (5 mL). The reaction vessel was cooled in an ice–water bath to 0–5°. Excess $LiAlH_4$ (36.0 mg, 0.95 mmol) was added and the reaction stirred at 0–5° for 30 min. The mixture was diluted to 15 mL with diethyl ether and solid $Na_2SO_4 \cdot 10\ H_2O$ was added in small portions at 0° until effervescence ceased. Water (1.0 mL) was then added cautiously to ensure that $LiAlH_4$ was fully quenched. The liquid was then decanted from the fine granular precipitate and evaporated to give 81.0 mg (100%) of a yellow oil. Flash-column chromatography on silica (3.5 g) with 10:0.5:0.25 chloroform–methanol–NH_4OH yielded the pure *allo* epimer **5** (73.6 mg, 90%), $[\alpha]_D^{23.5}$ +88.0° (*c* 2.09, chloroform), R_F 0.30 (10:0.5:0.25 chloroform.methanol–NH_4OH; stains red with ninhydrin spray followed by charring); ν_{max}^{film} 3380 (NH_2), 3320 (NH_2), 3100, 3080, 3040 (alkene arom.), 2920, 2880 (CH, CH_2), 1500, 1460 (arom. ring), 1370, 1220, 1150–1080 (br, OR), 740 and 698 cm^{-1} (monosubst. arom.); ^{1}H-n.m.r. ($CDCl_3$): δ 7.34–7.20 (m, 15 H, Ph), 4.58–4.30 (m, 6 H, 3 OC*H*$_2$Ph, but no ABq's could be determined), 4.06 (m, 1 H, H-5), 3.93 (m, 3 H, H-2,3,4), 3.57 (dABq, 2 H, $\Delta\nu_{AB}$ 16.2, J_{AB} 10.0, $J_{5,6}$ 6.0 Hz, H-6A,B), and 2.94 (m, 2 H, H-1); ^{13}C-n.m.r. ($CDCl_3$): δ 138.28, 137.97, 137.90 (s, C quat., OCH_2Ph), 128.55–127.75 (m,

$OCH_2C_6H_5$), 83.83 (d), 83.40 (d), 82.39 (d), 73.42 (t), 71.68 (t), 71.60 (t), 70.66 (t), and 41.56 (t, C-1); m.s. (c.i.): *m/z* 434 (MH^+), 205, 181, 107, and 91.

Anal. Calc. for $C_{27}H_{31}NO_4 \cdot 0.5\ H_2O$: C, 73.27; H, 7.29; N, 3.16. Found: C, 73.43; H, 6.99; N, 3.10.

*2,5-Anhydro-3,4,6-tri-*O*-benzyl-1-bromo-1-deoxy-*D*-allitol* (**8**) *and -*D*-altritol*[9] (**9**). — An *N,N*-dimethylmethanamide solution (3.75 mL) of *N*-bromosuccinimide (75.0 mg, 0.45 mmol) was added at 24° to a stirred solution of alkene **2** (150 mg, 0.36 mmol) in *N,N*-dimethylmethanamide (0.75 mL). The mixture was stirred for 2 h at 24° at which time all starting material had been consumed (t.l.c. assay). The mixture was diluted with ethyl acetate (25 mL) and washed successively with saturated $NaHCO_3$ (10 mL), water, and saturated NaCl. The organic layer was dried ($MgSO_4$), filtered, and evaporated under reduced pressure to give a clear oil (152 mg, 85%). The crude product could be purified by flash chromatography in 9:1:1 petroleum ether-(35–60°)–ether–dichloromethane leading to >95% enrichment in the *allo* epimer (**8**) (75% purified); $[\alpha]_D^{23}$ +32.3° (*c* 2.52, chloroform), R_F 0.30 (9:1:1 petroleum ether–ether–dichloromethane); ν_{max}^{film} 3100, 3075, 3040 (alkene, arom.), 2920, 2870 (CH_2,CH), 1500, 1450 (arom. ring), 1100, 740, and 697 cm^{-1} (monosubst. arom.); ^{1}H-n.m.r. ($CDCl_3$): δ 7.37–7.25 (m, 15 H, Ph), 4.61–4.47 (m, 6 H, 3 OCH_2Ph, no ABq's could be determined), 4.32 (m, 1 H, H-2), 4.21 (dt, 1 H, $J_{4,5}$ 2.0, $J_{5,6}$ 6.0 Hz, H-5), 4.03 (br. d, 1 H, $J_{2,3}$ 3.6 Hz, H-3), 3.96 (br. d, 1 H, $J_{4,5}$ 2.0 Hz, H-4), and 3.61–3.47 (m, 4 H, H_2-6, H_2-1); ^{13}C-n.m.r. ($CDCl_3$): δ 138.20, 137.72, 137.64 (s, C quat., OCH_2Ph), 128.56–127.79 (m, $OCH_2C_6H_5$), 83.65 (d, C-2), 83.17 (d, C-5), 82.21 (d, C-3), 81.47 (d, C-4), 73.39, 72.06, 71.53 (t, OCH_2Ph), 70.42 (t, C-6), and 28.26 (t, C-1); m.s. (c.i.): *m/z* 499 (MH^+, ^{81}Br), 497 (MH^+, ^{79}Br), 271, 181, and 91.

Anal. Calc. for $C_{27}H_{29}BrO_4$: C, 65.32; H, 5.89; Br, 15.89. Found: C, 65.03; H, 6.13; Br. 15.73.

*2,5-Anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-1-mercuriochloro-*D*-allitol* (**10**). — The general cyclization procedure and work-up described by Nicotra *et al.*[10] was used. Mercuric acetate and mercuric trifluoroacetate gave cyclized product in 100 and 83% crude yields, respectively. HgCl and HgBr[11] did not effect cyclization. The compound could be purified by flash-column chromatography in 3:1:1 petroleum ether-(35–60°)–ether–dichloromethane to yield the anomerically pure *allo* isomer **10**, $[\alpha]_D^{28}$ −20.3° (*c* 1.76, chloroform), R_F 0.27 (3:1:1 petroleum ether–ether–dichloromethane); ν_{max}^{film} 3090, 3075, 3040 (alkene, arom.), 2920, 2875 (CH_2, CH), 1610, 1590, 1500, 1460 (arom. ring), 1365, 1210, 1100–1040, 740 and 697 cm^{-1} (monosubst. arom.); ^{1}H-n.m.r. ($CDCl_3$): δ 7.36–7.24 (m, 15 H, Ph), 4.63–4.33 (m, 7 H, 3 OCH_2Ph and H-2, no ABq's could be determined), 4.11 (m, 1 H, H-5), 3.92 (d, 1 H, $J_{4,5}$ 2.70 Hz, H-4), 3.74 (d, 1 H, $J_{2,3}$ 3.5 Hz, H-3), 3.53 (dABq, 2 H, $\Delta\nu_{AB}$ 28.4, J_{AB} 9.8, $J_{5,6}$ 6.0 Hz, H-6A,B), 2.18 (dd, 1 H, $J_{1A\text{ or }1B,2}$ 5.6, $J_{1A,B}$ 12.5 Hz, H-1A or B), and 1.80 (dd, 1 H, $J_{1A\text{ or }1B,2}$ 2.8, $J_{1A,B}$ 12.5 Hz, H-1A or B); ^{13}C-n.m.r. ($CDCl_3$): δ 138.26, 137.79, 137.02 (s, C quat., OCH_2Ph), 128.73–127.91 (m, $OCH_2C_6H_5$), 83.92 (d, C-2), 83.44 (d, C-5), 83.20 (d, C-4), 79.27 (d, C-3), 73.61,

71.92, 71.75 (t, OCH_2Ph), 70.80 (t, C-6), and 28.37 (t, C-1); m.s. (c.i.): *m/z* 621 ($MH^+ - {}^{37}Cl$), 619 ($MH^+ - {}^{35}Cl$), 529, 181, 107, and 91.

Anal. Calc. for $C_{27}H_{29}ClHgO_4$: C, 49.62; H, 4.47. Found: C, 49.80; H, 4.60.

Typically, further manipulations of **10** were carried out on the crude organomercurial compound.

2,5-Anhydro-3,4,6-tri-O-*benzyl-1-deoxy-1-phenylseleno*-D-*allitol* (**12**) *and* -D-*altritol* (**13**). — Cyclization by the method of Nicolaou[3,12], followed by flash-column chromatography in 9:1:1 petroleum ether-(35–60°)–ether–dichloromethane, gave a 46% yield of a colorless oil. The product was an inseparable mixture of diastereomers (1.0:1.5 *allo*-to-*altro* ratio) as determined by ^{1}H- and ^{13}C-n.m.r. spectroscopy; $[\alpha]_D^{23}$ +7.5° (*c* 2.8, chloroform), R_F 0.20 (9:1:1 petroleum ether–ether–dichloromethane); ν_{max}^{film} 3100, 3070, 3040 (alkene, arom.), 2930, 2870 (CH_2, CH), 1585, 1500, 1455 (arom. ring), 1370, 1210, 1120–1050, 740, 695 cm^{-1} (monosubst. arom.); ^{1}H-n.m.r. ($CDCl_3$): δ 7.52–7.22 (m, 20 H, Ph), 4.60–4.44 (m, 6 H, 3 OCH_2Ph, no ABq's could be determined), 4.32–4.25 (m, 2 H, H-2,5), 4.13 (app. t, 1 H, $J_{3,4} \simeq J_{4,5}$ 2.5 Hz, H-4), 4.07 (br. d, 1 H, $J_{3,4}$ 2.5 Hz, H-3), and 3.64–3.51 (m, 4 H, H_2-1, H_2-6); ^{13}C-n.m.r. ($CDCl_3$): δ 29.98 (t, C-1 *altro*) and 25.47 (t, C-1 *allo*); m.s. (c.i.): *m/z* 575 (MH^+, ^{79}Se), 271, 181, and 91.

Anal. Calc. for $C_{33}H_{34}O_4Se$: C, 69.10; H, 5.97. Found: C, 69.34; H, 6.24.

2,5-Anhydro-3,4,6-tri-O-*benzyl*-D-*allitol* (**14**) *and* -D-*altritol*[8] (**15**). — Compound **1** (258.9 mg, 0.62 mmol) was dissolved in freshly distilled (from CaH_2) dichloroethane (6 mL). 3-Chloroperbenzoic acid (60 mg, 0.93 mmol) was added all at once. The mixture was refluxed for 19 h and cooled to 0°. The resulting solid was removed by filtration and the filtrate evaporated under reduced pressure. Crude ^{1}H-n.m.r. analysis showed ~15% of unreacted alkene present. Column chromatography in 1:1:1 petroleum ether–ether–dichloromethane gave a 1:1 mixture of *allo* (**14**) and *altro* (**15**) alcohols (as determined by ^{1}H-n.m.r. integration of the two OH triplets) as a colorless oil (90.2 mg, 34%); R_F 0.25 (1:1:1 petroleum ether–ether–dichloromethane); ν_{max}^{film} 3600–3300 (br. OH), 3085, 3060, 3030 (alkene, arom.), 2910, 2870 (CH_2,CH), 1600, 1580, 1450 (arom. ring), 1360, 1210, 1150–950 (br., OR), 735, and 690 cm^{-1} (monosubst. arom.); ^{1}H-n.m.r. ($CDCl_3$): δ 7.33–7.22 (m, 15 H, Ph), 4.62–4.41 (m, 6 H, 3 OCH_2Ph, no ABq's could be determined), 4.2–4.05 (m, 4 H, H-2,3,4,5), 3.84–3.64 (m, 2 H, sharpens to an app. t. at 3.83 and a dd at 3.70 upon addition of D_2O, H_2-1), 3.61 (m, 2 H, H_2-6), 2.55 (t, 1 H, $J_{1,OH}$ 6.5 Hz, D_2O exchange), and 2.10 (t, 1 H, $J_{1,OH}$ 6.5 Hz, D_2O exchange); ^{13}C-n.m.r. ($CDCl_3$): δ 138.05, 137.94, 137.85, 137.76, 137.67 (s, C quat., OCH_2Ph), 133.14–127.80 (m, $OCH_2C_6H_5$), 84.74, 84.33, 83.88, 83.42, 83.30, 81.92, 80.56, 73.46, 72.13, 72.00, 71.90, 70.27, 70.19, 62.73 (t, C-1 *altro*), and 61.71 (t, C-1 *allo*); m.s. (c.i.): *m/z* 435 (MH^+), 343, 371, 181, 145, 107, and 91.

Anal. Calc. for $C_{27}H_{30}O_5 \cdot H_2O$: C, 72.38; H, 7.09. Found: C, 72.52; H, 6.86.

2,5-Anhydro-3,4,6-tri-O-*benzyl-1-deoxy*-D-*allitol* (**16**) *and* -D-*altritol*[15] (**17**). — *Method A using the crude reaction mixture from the mercury-induced cyclization.* The crude organomercurials (153.2 mg, 0.23 mmol) were dissolved in dichloro-

methane (2.5 mL), and solid benzyltriethylammonium chloride (262 mg, 1.15 mmol) dissolved in 10% NaOH (1.5 mL) was added. The mixture was cooled to 0° and solid $NaBH_4$ (85.1 mg, 2.3 mmol) was added all at once. The reaction was quenched within 2 min by addition of water*. The reaction mixture was diluted with dichloromethane (20 mL), and the layers were separated. The organic layer was washed successively with water (5 mL), saturated NaCl (5 mL), and dried ($MgSO_4$). Filtration and evaporation under reduced pressure gave a yellow oil (48.2 mg, 49%) which, though homogeneous by t.l.c., was an inseparable mixture of diastereomers enriched in the *allo* (**16**) isomer, $[\alpha]_D^{26}$ +24.6° (*c* 1.46, chloroform), R_F 0.16 (9:1:1 petroleum ether–ether–dichloromethane); ν_{max}^{film} 3120, 3100, 3080, 3040 (alkene, arom.), 2940, 2920, 2880 (CH_2,CH,CH_3), 1500, 1450 (arom. ring), 1220, 1150–1050 (br., OR), 740 and 700 cm^{-1} (monosubst. arom.); ^{1}H-n.m.r. ($CDCl_3$): δ 7.39–7.27 (m, 15 H, Ph), 4.65–4.40 (m, 6 H, 3 OCH_2Ph, no ABq's could be determined), 4.15 (m, 1 H, H-2, collapses to a doublet having $J_{2,3}$ 3.7 Hz upon irradiation of CH_3), 4.05 (m, 1 H, H-5), 3.91 (app. d, 1 H, H-3), 3.78 (d, 1 H, $J_{4,5}$ 3.7 Hz, H-4), 3.60 (dABq, 2 H, ν_{AB} 20.94, J_{AB} 9.8, $J_{5,6}$ 6.2 Hz, H-6A,B), 1.35 (br. d, 3 H, $J_{1,2}$ 6.5 Hz, CH_3); ^{1}H-n.m.r. (C_6D_6): δ 1.42 (d, 3 H, $J_{1,2}$ 6.5 Hz, CH_3, *allo*), and 1.35 (d, 3 H, $J_{1,2}$ 6.5 Hz, CH_3, *altro*); ^{13}C-n.m.r. ($CDCl_3$): δ 138.49, 138.34, 138.14 (s, C quat., OCH_2Ph), 128.64–127.73 (m, O$CH_2C_6H_5$), 84.83 (d, C-2), 84.12 (d, C-5), 82.62 (d, C-3), 77.45 (d, C-4), 73.54, 71.71, 71.59 (t, OCH_2Ph), 71.01 (t, C-6), and 14.34 (q, C-1); m.s. (c.i.): *m/z* 419 (MH^+), 327, 181, 147, 133, 117, 107, and 91.

Anal. Calc. for $C_{27}H_{30}O_4$: C, 77.48; H, 7.22. Found: C, 77.21; H, 7.25.

Method B. General procedure for reduction of halogen (I_2, Br_2) and selenium-induced cyclization products. The crude cyclization product was dissolved in dry benzene (from CaH_2) to give a 0.06M solution. A catalytic amount of azoisobutyronitrile (0.05 eq.) was added, followed by excess tributyltin hydride (3.0 eq.). The mixture was refluxed for 45 min under an atmosphere of Ar. Benzene was removed *in vacuo* and the mixture diluted with acetonitrile. The acetonitrile layer was shaken with hexane (3 × 5 mL) and the combined hexane layers were discarded. The acetonitrile layer was dried ($MgSO_4$), filtered, and evaporated to give the crude reduction product (**16** and **17**) as a mixture of diastereomers. Yields were 70, 74, and 80% for reduction of the iodomethyl (**3**), bromomethyl (**8**), and phenylselenomethyl (**12**) compounds, respectively.

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*Longer reaction times or higher temperature gave **2** as the major product. These conditions minimized the β-elimination process (10–15%).

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