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Synthetic Studies on the Validamycins. III. Bromination of DL-Tri-*O*-acetyl-(1,3/2)-4-methylene-5-cyclohexene-1,2,3-triol. Preparation of Several Branched-chain Unsaturated Cyclitols Related to Valienamine[1]

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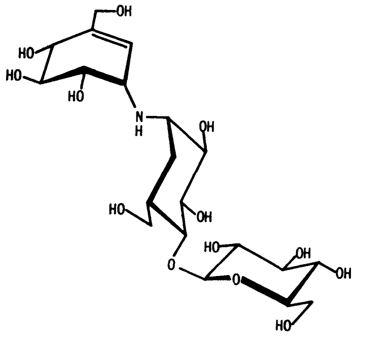
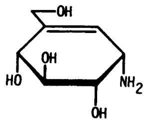
Bromination of DL-tri-*O*-acetyl-(1,3/2)-4-methylene-5-cyclohexene-1,2,3-triol with bromine in an appropriate solvent yielded mainly two 1,4-addition products, from which several branched-chain unsaturated cyclitols, related to biologically interesting valienamine, were selectively prepared. Reaction courses are discussed for the bromination of the diene and the debromination of the bromo(bromomethyl)cyclohexenetriol triacetates obtained under various conditions.

Validamycin A (**1**)[2] is the major and most active component of the antibiotic validamycins, produced by *Streptomyces hygroscopicus* var. *limoneus* and widely used in order to control sheath blight in rice plants. Microbial degradation of validamycin A with a cell suspension of *Pseudomonas denitrificans* gave, besides validamine,[3] a branched-chain unsaturated aminocyclitol, valienamine (**2**), which is a common building block of validamycins and the structure of which was assigned to 1D-(1,3,6/2)-6-amino-4-hydroxymethyl-4-cyclohexene-1,2,3-triol on the basis of ^{1}H NMR spectroscopy.[4]

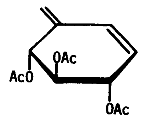
In recent years, some biologically active branched-chain unsaturated cyclitols such as glyoxalase I inhibitor[5] and rancinamycins I—IV[5] have been discovered. Very recently, the valienamine moiety linked to D-glucose or 6-deoxy-D-glucose *via* an imino linkage has been found as an essential unit in a homologous series of pseudo-oligosaccharides such as acarboses,[7] trestatins,[8] and adiposins,[9] all of which show a marked inhibitory effect against α-glucosidases in mammals.[10] Furthermore, valienamine itself has been found to show both the α-glucosidase inhibition and the antibiotic activity against *Bacillus* species.[11]



Validamycin A (1)



Valienamine (2)



3

In connection with our synthetic studies on the validamycins,[12] we now report the synthesis of several branched-chain unsaturated cyclitols related to valienamine. The synthetic route involved the preferential 1,4-addition of bromine to the conjugated diene, DL-tri-*O*-acetyl-(1,3/2)-4-methylene-5-cyclohexene-1,2,3-triol (**3**),[13] assembling all the carbon atoms present in valienamine, and the stereocontrolled syntheses of the branched-chain unsaturated cyclitols by utilization of the different reactivities of the allylic primary and secondary bromine atoms and the neighboring group participation of acetoxyl groups in the replacement process. This synthetic approach may be extended to the synthesis of other analogs of this kind as well. Some intermediates obtained in this study are also important precursors of amino analogs including valienamine.

By consideration of the transition state analogous theory,[14] the synthetic branched-chain unsaturated cyclitols are expected to display some glucosidase inhibitory activity similarly to valienamine.

Results and Discussion

*Bromination of Conjugated Diene **3** with Bromine. Synthesis of Bromo(bromomethyl)cyclohexenetriol Triacetates **5** and **6**:* Since electrophilic addition to conjugated diene often gives 1,4-addition product in much larger amount than 1,2-addition product, we have undertaken the bromination of readily available **3** with bromine in order to construct the carbon skelton of valienamine.

Treatment of **3** with a molar equiv. of bromine produced preferentially the 1,4-addition products **5** and **6**. In the ^{1}H NMR spectrum, the signal due to the olefinic proton (H-5) of **5** appeared as a doublet (J=5.5 Hz) at δ 6.19, indicating that the C-6 bromine atom is situated at a pseudoaxial position in a favored half-chair conformation,[15] whereas that of **6** appeared as a broad singlet at δ 6.13, supporting that **6** is the C-6 epimer of **5**. Therefore, the structures of **5** and **6** were assigned to DL-(1,3,6/2)- and DL-(1,3/2,6)-6-bromo-4-bromomethyl-4-cyclohexene-1,2,3-triol triacetates, respectively.

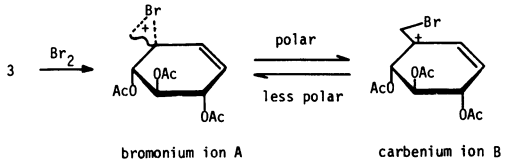
Of interest here is the fact that the product-distribution was affected by the polarity of the solvent used and by reaction temperature. Table 1 gives a summary of the results of the bromination of **3**. When the reaction was carried out in carbon tetrachloride, **6** was produced predominantly over **5** at −15 °C, whereas at room temperature the reverse was the case. On the other hand, the reaction in acetic acid at room temperature resulted in preferential formation of **6**. Both **5** and **6** were found to be interconvertible in the presence of a trace of bromine, but the interconversion took place so slowly that it would be negligible during the following work-up.

The above results can be interpreted by assuming the

Table 1. Bromination of **3** with an equimolar amount of bromine

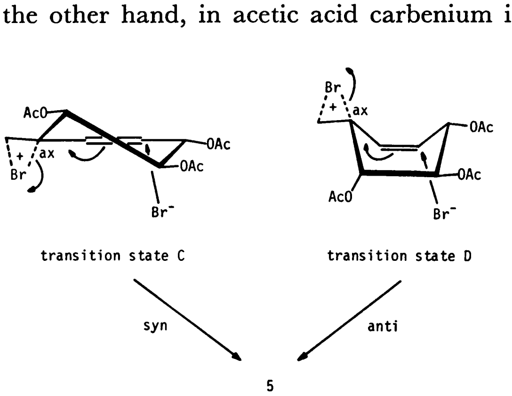
Solvent	Temp/°C	Isolated yield/%[a]		Total yield/%	Product ratio[b]
		5	**6**		**5/6**
	−15	18	40	79	1.6
CCl_4	−4	33	29	90	0.7
	r.t.	48	17	89	0.4
AcOH	r.t.	10	43	72	3.4
50%aq AcOH[c]	r.t.	7	18	49[d]	2.1

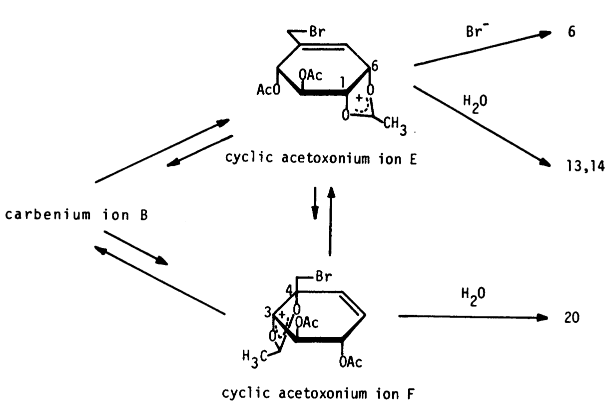
a) After silica-gel column chromatography. b) Determined by ^{1}H NMR analysis of the mixture. c) The resulting product was successively acetylated with acetic anhydride containing a trace of sulfuric acid. d) In addition to **5** and **6**, bromo tetraacetate **7** was obtained in 22% yield.



reaction course, which involves the equilibrium between bromonium ion **A** and carbenium ion **B**.[16] The observed solvent dependence of the bromination may be the result of differential solvation requirement of the bromonium ion **A** and carbenium ion **B** in their equilibrium, leading to more bromonium ion character in nonpolar solvent. Therefore, in carbon tetrachloride at room temperature the equilibrium lies to the bromonium ion **A**. The 1,4-addition product is known to be formed by opening of a bromonium ion by an S_N2' attack by at bromide ion.[17] Although a most theoretical analysis of S_N2' reactions has indicated a preference for syn attack by nucleophile, Toromanoff[18] has recently reported that, if the leaving group departs from an axial position in a half-chair conformation, S_N2' reaction is of syn stereochemistry, and that, if the leaving group is of an axial orientation in a boat form, anti stereochemistry is important. Thus, if bromine approaches from below, the reaction will proceed *via* the transition state **C** (half-chair), resulting in S_N2' attack by a bromide ion in syn stereochemistry, whereas if bromine approaches from above, the reaction will proceed *via* the transition state **D** (boat), resulting in S_N2' attack in anti stereochemistry. Both pathways give **5**.

On the other hand, in acetic acid carbenium ion **B** can be stabilized by allylic rearrangement with an assistance of the C-1 acetoxyl group, producing the 1,6-cyclic acetoxonium ion **E**, which is then opened by attack by a bromide ion from the back side at C-6 to give **6**. Carbenium ion **B** may also be stabilized by an assistance of the C-3 acetoxyl group, resulting in the formation of the 3,4-cyclic acetoxonium ion **F**, but this participation must be unfavorable because of the steric hindrance at C-4. Bromo triacetates **13**, **14**, and **20** were obtained as side-products in trace amounts. Compounds **13** and **14** could result from the opening of the cyclic acetoxonium **E** by attack by a trace of water present, and **20** from a similar opening of **F**. Furthermore, when the reaction was run in 50% aqueous acetic acid, bromotetraacetate **7** was obtained in 22% yield, after acetylation with acetic anhydride containing a trace of sulfuric acid. These findings substantiated the proposed mechanism for the bromination in acetic acid.[19]



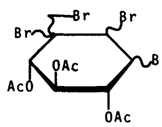


Compound **6** could be readily available by crystallization of the bromination products in acetic acid–acetic anhydride[20] from ethanol. From the mother liquor, an inseparable mixture of **7** and **8** was obtained by fractionation by a silica-gel column. These were considered to be formed, respectively, by subsequent acetylation of **13** and **14** under the reaction conditions and by the opening of the acetoxonium ion **E** by an acetate ion from the back side at C-6.

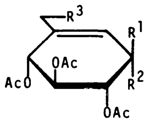
When an excess bromine was used for the bromination in carbon tetrachloride at 0—5 °C, tetrabromides, presumably consisting of two isomers **4a** and **4b**, were obtained as crystals in 91% yield. Recrystallization from ethanol gave one of the isomers **4a** in a pure form in 59% yield. Monitoring of the reaction by TLC indicated the reaction to proceed *via* **5** and **6**, but the structures of the tetrabromides could not definitively be determined by analysis of the ^{1}H NMR spectral data. Hydrogenolysis of **4a** in ethyl acetate with Raney nickel T-4[21] in the presence of Amberlite IR-45 (OH^-) gave a mixture of tri-*O*-acetyl-DL-deoxyvalidatol and its 4-epimer, identical with authentic samples.[13]

Debromination of **5** and **6** was attempted with tributyltin(IV) hydride or with lithium aluminium hydride but, instead of desired debrominated product, **3** was regenerated in a good yield. Compounds **5** and **6** were expected to be potential intermediates for the present synthetic study.

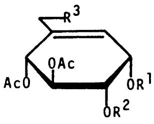
Hydrobromination of Conjugated Diene 3. Hydro-



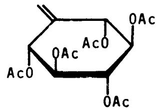
4a,b



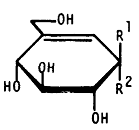
	R1	R2	R3
5	H	Br	Br
6	Br	H	Br
7	H	OAc	Br
8	OAc	H	Br
9	H	Br	OAc
10	Br	H	OAc
11	H	OAc	OAc
12	OAc	H	OAc



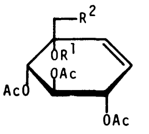
	R1	R2	R3
13	Ac	H	Br
14	H	Ac	Br
15	Ac	H	OAc
16	H	Ac	OAc



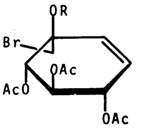
17



	R1	R2
18	H	OH
19	OH	H



	R1	R2
20	H	Br
21	H	OMe
22	Ac	OMe
23	H	OAc
24	Ac	OAc



	R
25	H
26	Ac

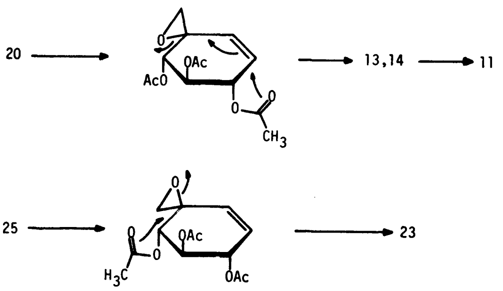
bromination of **3** using *N*-bromoacetamide (NBA) or *N*-bromosuccinimide (NBS) resulted in the preferential formation of 1,2-addition products in contrast to the bromination of **3** with a molar equiv. of bromine.

Treatment of **3** with a molar equiv. of NBA in aqueous acetone buffered with sodium acetate at room temperature for 5 d, followed by acetylation, gave a mixture of products from which 1,2-addition products **20** (9%), **23** (21%), and **26** (trace), and 1,4-addition product **11** (10%) were isolated by a silica-gel column chromatography. On the other hand, when **3** was treated with 1.5 molar equiv. of NBS in aqueous dimethyl sulfoxide for 5 h below 10 °C, 1,2-addition products **20** (36%) and **25** (12%), and 1,4-addition products **13** and **14** (5%) were obtained after chromatography.

The structures of **11**, **13**, **14**, and **20** were confirmed by comparison of their ^{1}H NMR spectra with those of authentic samples prepared later *via* unambiguous routes. In the ^{1}H NMR spectrum of **23**, the signals due to the olefinic protons (H-5 and H-6) appeared as a two-proton singlet at δ 5.37. The facts that acetoxymethyl protons of **23** appeared as AB-quartet (J=12 Hz) at δ 3.84 and 4.02 and that no signal changed upon deuteration except the disappearance of the signal at δ 2.57 due to the hydroxyl proton, indicated that **23** has a tertiary hydroxyl group. Further acetylation of **23** with acetic anhydride and pyridine for 7 d yielded pentaacetate **24** quantitatively. In the ^{1}H NMR spectrum of **24** the H-3 signal appeared as a doublet of doublets (J=9 Hz, 10.5 Hz) at δ 5.19, whereas in that of **23** it appeared in the vicinity of δ 5.33—5.62, partly overlapping with the H-4 signal. This observation suggested that the C-1 hydroxyl group of **23** would occupy a 1,3-diaxial position with respect to H-3, and hence the orientation of the acetoxymethyl group of **23** was assumed to be pseudoequatorial in a favored half-chair conformation. The structure of **25** was tentatively assigned by the elemental analysis and by comparing its ^{1}H NMR spectrum with that of **20**. The spectrum of **25** exhibited two olefinic protons as two doublets (J=10 Hz) at δ 6.00 and 6.09. The ^{1}H NMR spectrum of **26** resembled that of **25** in the region for the ring protons (H-2, H-3, and H-4), except that signals for the bromomethyl protons appearing as a AB-quartet (J=11 Hz) shifted down-field by *ca.* 0.13 ppm, supporting the assigned structure of **26**.

The reaction products suggested that the hydrobromination of **3** using NBA in aqueous conditions would not differ fundamentally from the aforementioned bromination of **3** with bromine in acetic acid. Therefore, the reaction is thought to proceed *via* the carbenium ion **B**. Since solvents such as dimethyl sulfoxide[22] and water are known to serve as nucleophiles, the carbenium ion **B** might be attacked by solvents to give the 1,2-addition products preferentially.

Compounds **11** and **23** were probably derived from the corresponding intermediate spiro-epoxides formed by the dehydrobromination of **20** and **25**, respectively, during subsequent acetylation. Compound **11** seemed to be yielded by the replacement of the remaining allylic bromine atom in **13** and **14** with an acetate ion present followed by acetylation. When the mixture of **13**, **14**, **20**, and **25**, obtained by the hydrobromination of **3** with NBS in aqueous dimethyl sulfoxide, was acetylated, the formation of **7**, **11**, **20**, **23**, and **26** was observed by TLC, supporting partly the above assumption.



Reaction of Dibromocyclohexenes ***5*** *and* ***6****: Synthesis of Branched-chain Unsaturated Cyclitols.* With **5** and **6** in hand in which two kinds of allylic bromine atoms are present at C-6, we initiated a stereocontrolled synthesis of branched-chain unsaturated cyclitols by taking advantage of different reactivities of the bromine atoms.

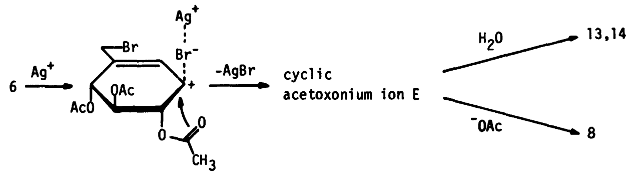
With Sodium Acetate: Preferential replacement of the primary allylic bromine atoms in both **5** and **6** by an acetate ion was effected by the reaction with a molar equiv. of sodium acetate in *N*,*N*-dimethylformamide (DMF) at room temperature for 24 h, and a *ca.* 3.5 : 1 mixture of the bromo tetraacetates **9** and **10** was obtained in both cases, from which **9** was easily isolated in 47—49% yield by crystallization from ethanol. The structure of **9** was confirmed by the ^{1}H NMR spectrum which revealed a down-field shift of the signal due to the C-7 methylene group, resulting from the replacement of the bromine atom by an acetoxyl group, and an olefinic proton (H-5) present as a broad doublet (*J*=*ca.* 5 Hz) at δ 6.07. A comparison of the ^{1}H NMR spectrum of the mixture of **9** and **10** with that of **9** showed that **10** is the C-6 epimer of **9**. The H-5 signal of **10** appeared as a singlet at δ 5.99.

Interestingly, the product-distribution was almost independent of starting from either **5** or **6**. The C-6 bromine atom seems to be readily exchangeable upon an S_N2 attack of a bromide ion generated in course of the reaction.

When both **5** and **6** reacted with an excess of sodium acetate in DMF at room temperature for 2 d, a 2—3 : 1 mixture of pentaacetates **11** and **12** was obtained.

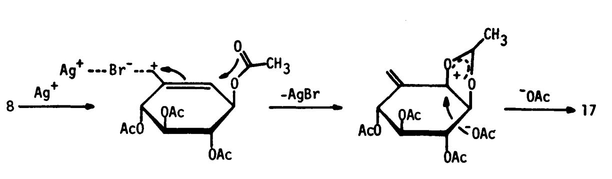
With Silver Acetate: In the presence of silver ion, alkyl halides, even primary, react *via* and S_N1-like mechanism, and the participation of neighboring acetoxyl group in replacement reactions has been extensively studied by Winstein and Buckles.[23]

According to their results, some branched-chain unsaturated cyclitols were expected to be selectively prepared by the following reaction sequences. Treatment of **6** with a molar equiv. of silver acetate in 90% aqueous acetic acid at room temperature for 2 h gave a 3 : 1 mixture of **13** and **14** as crystals in 73% yield, together with a 3 : 1 mixture of tetraacetates **15** and **16** in 13% yield. The latter was readily obtainable from **6** in 56% yield by using 4 molar equiv. of silver acetate in a similar condition at 90 °C for 1 h. On the other hand, treatment of **6** with 1 or 4 molar equiv. of silver acetate in acetic acid–acetic anhydride[20] at 80 °C gave **8** (63%) or **12** (73%). The *exo*-olefin **17**[24] was produced concomitantly by the reaction when 4 molar equiv. of silver acetate was used. Compound **12** was also obtained selectively by the reaction of **8** with sodium acetate at room temperature for 24 h.



In both conditions, acetoxonium ion **E** is considered to be formed as an intermediate by the participation of the neighboring C-1 acetoxyl group either simultaneously with or very short after the removal of the C-6 bromine atom by a silver ion. The cyclic intermediate is then opened by attack of water in the case of the former condition to give a mixture of **13** and **14**, which is further converted into a mixture of **15** and **16**, whereas under the latter condition it is opened by a back-side attack of an acetate ion at C-6 to give **8**, which is then converted into **12**. Compound **17** seemed to be formed from **8** *via* the intermediate **G**. Isolations of **13** and **14** and of **15** and **16** were unsuccessful because of their similar chromatographic mobilities on silica gel.

The structures of **13** and **14** were tentatively assigned by the elemental analysis and ^{1}H NMR spectral data.



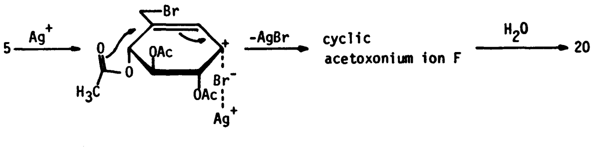
The fact that the signal due to the H-2 proton appeared as a doublet of doublets (*J*=5 Hz, 11 Hz) at δ 3.91 for **13** and as a doublet of doublets (*J*=3 Hz, 10 Hz) at δ 4.93 for **14**, indicated that the hydroxyl group of **13** was located at C-2, whereas that of **14** is at C-1. Similarly, the H-2 signals of **15** and **16** appeared as a doublet of doublets (*J*=4 Hz, 11 Hz) at δ 3.87 and a doublet of doublets (*J*=5 Hz, 11 Hz) at δ 4.91, respectively, being consistent with the assigned structures.

Acetylation of a mixture of **13** and **14** gave the bromotetraacetate **7**, which was convertible into the pentaacetate **11** by the reaction with sodium acetate in aqueous DMF. Compound **11** was also obtainable either by acetylation of a mixture of **15** and **16** or by treatment of a mixture of **13** and **14** with sodium acetate followed by acetylation.

The structures of **11** and **12** were assigned by the ^{1}H NMR spectra in which the olefinic protons (H-6) of **11** and **12** appeared as a doublet of doublets (*J*=2 Hz, 6 Hz) at δ 5.94 and a broad singlet at δ 5.82 partly overlapping with the H-4 signal, respectively.

O-Deacetylation of **11** and **12** with methanolic sodium methoxide gave crystalline pentols **18** and **19**, respectively.

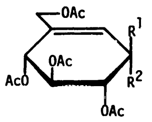
When **5** reacted with 1.1 molar equiv. of silver acetate in 90% aqueous acetic acid at room temperature for 24 h, **20** was obtained in 52% yield. Since in the case of **5** the C-1 acetoxyl group and C-6 bromine atom are cis to each other, any neighboring group participation of the C-6 acetoxyl group is unfavorable. Therefore, the reaction is presumed to involve successively an allylic rearrangement (S_N1') with an assistance of the C-3 acetoxyl group, the formation of the 3,4-cyclic acetoxonium ion **F**, and its cleavage by water.



The structure of **20** was assigned on the basis of the appearance of the two-proton singlet at δ 5.83 attributable to two olefinic protons.

An attempt failed to remove the remaining bromine atom in **20** by further treatment with excess silver acetate at 90 °C, presumably because of the low reactivity of C-7 bromine atom under the S_N1-like conditions. On the other hand, reaction of **20** with sodium methoxide in methanol gave a crystalline methyl ether **21**, which was converted into the tetraacetate **22** by acetylation with acetic anhydride in pyridine at room temperature for 9 d. The reaction is considered to proceed *via* a spiro-epoxide, which is subsequently opened by a methoxide ion. The ^{1}H NMR spectrum of **22** showed the presence of four acetoxyl groups and two olefinic protons (H-5 and H-6); for H-5, a doublet of doublets (J=2 Hz, 10 Hz) at δ 5.76 and for H-6, a doublet of doublets (J=1 Hz, 10 Hz) at δ 6.33.

*Reaction of Bromo Tetraacetate **9** with Alcohol.* Nucleophilic substitution of **9** with an alcohol such as methanol, ethanol, or 2-propanol in the presence of silver perchlorate proceeded predominantly with inversion at C-6 leading to the corresponding alkyl ether derivative **28**, **30**, or **32**, respectively (Table 2). This result can be derived as a consequence of either S_N2 attack by alcohol at C-6 or heterolysis of C-6 bromine atom leading to an allyl cation that is stabilized by neighboring group participation of C-1 acetoxyl group, followed by opening of the 1,6-cyclic acetoxonium ion by back-side attack of alcohol. In each case **15**, **16**, and **23** as a mixture were separated in 15% yield as side-products. This fact indicated that both 1,6- and 3,4-cyclic intermediate acetoxonium ions are formed during the course of reaction.



	R¹	R²
27	H	OCH_3
28	OCH_3	H
29	H	OC_2H_5
30	OC_2H_5	H
31	H	$OC(CH_3)_2$
32	$OC(CH_3)_2$	H

TABLE 2. REACTION OF **9** WITH ALCOHOL CATALYZED BY SILVER ION

Alcohol	Time/min	Yield/%[a)]	Product ratio[b)]
Methanol	60	25	Only **28**
Ethanol	70	21	**29**/**30**=1/4
2-Propanol	50	17	**31**/**32**=1/4

a) After silica-gel column chromatography. b) Determined by ^{1}H NMR analysis of the mixture.

When **9** was treated with methanolic sodium methoxide at room temperature or with ethanol containing a trace of hydrogen bromide, a 1 : 1 mixture of **27** and **28** in 71% yield or a 1 : 1 mixture of **29** and **30** in 64% yield was obtained, respectively, after acetylation with acetic anhydride and pyridine.

Though each pair of C-1 epimers, **27** and **28**, **29** and **30**, and **31** and **32**, could not be separated because of their similar chromatographic mobilties, **28** was selectively formed by the reaction of **9** with methanol in the presence of silver perchlorate. Their structures were easily assigned by the ^{1}H NMR spectral data, which showed olefinic protons at δ 6.02 (broad d, J=6 Hz), 5.99 (broad d, J=6 Hz), and 5.90 (broad d, J=5 Hz) for **27**, **29**, and **30** and δ 5.82 (broad s), 5.82 (broad s), and 5.75 (broad s) for **28**, **30**, and **32**.

Experimental

General. Melting points were determined on a Büchi 510 capillary melting point apparatus and uncorrected. Unless otherwise noted, ^{1}H NMR spectra were taken on a Varian EM-390 (90 MHz) in chloroform-*d* ($CDCl_3$) with reference to tetramethylsilane as an internal standard. The peak positions were given in terms of δ-values and values given for coupling constants were of first-order. TLC was performed on a precoated silica gel 60 F-254 plaques (Merck, Darmstadt; 0.25 mm thickness), and the spots were visualized by heating above 150 °C after spraying concd sulfuric acid. The silica gel used for the column chromatography was Wakogel C-300 (Wako Pure Chemical Industries, Ltd.). Solutions were dried over anhydrous sodium sulfate and evaporated under reduced pressure at 40—50 °C. Acetylation was conventionally carried out with acetic anhydride in anhydrous pyridine at room temperature overnight and the reaction mixture was evaporated to remove the excess of reagents. Crude syrupy products (acetates) were usually purified preliminarily by rapid passage through a short column of active alumina with chloroform. Catalytic hydrogenations were carried out in a Parr shaker type apparatus at initial hydrogen pressure of 3.2 kg/cm^2.

*Bromination of Conjugated Diene **3** with Bromine. With Excess Bromine: Tetrabromides **4a**,**b**.* To a stirred solution of **3** (0.5 g) in carbon tetrachloride (8 ml) was added dropwise bromine (0.35 ml, *ca.* 3.5 molar equiv.) at 0—5 °C, and the mixture was stirred at the same temperature overnight. After removal of the solvent, the residual solid was crystallized from ethanol to give a mixture of **4a**, **b** (1g, 91%) as crystals, (Found: C, 26.32; H, 2.73; Br, 54.65%). Recrystallization from ethanol gave **4a** (0.65 g, 59%), one of the isomers, in a pure forms: mp 147—148 °C; ^{1}H NMR δ=1.96 (3H, s), 2.04 (3H, s), and 2.07 (3H, s) (OAc), 3.58 and 4.02 (AB-quartet, J=11.7 Hz, CH_2Br), 4.68—5.03 (2H, m, H-5 and H-6), and 5.36—5.59 (3H, m, H-1, H-2, and H-3).

Found: C, 26.47; H, 2.85; Br, 54.52%. Calcd for $C_{13}H_{16}Br_4O_6$: C, 26.56; H, 2.74; Br, 54.37%.

From the mother liquor, a mixture of **4a**,**b** was obtained. The other isomer **4b** could not be isolated because of their similar chromatographic mobilities on silica gel. The ^{1}H NMR spectrum of the mixture showed the signal for the bromomethyl protons of **4b** at δ 3.95 and 4.34 as an AB-quartet (J=7.5 Hz).

With an Equimolar Amount of Bromine: Synthesis of DL-*(1,3,6/2)-(**5**) and* DL-*(1,3/2,6)-6-Bromo-4-bromomethyl-4-cyclohexene-1,2,3-triol Triacetate (**6**)*: The results are summarized in Table 1.

General Procedure. a) In Carbon Tetrachloride: To a stirred solution of **3** (0.3 g) in carbon tetrachloride (15 ml) was added dropwise over a period of 15 min 5% bromine solution in the same solvent (1.5 ml, a molar equiv.) at various temperatures, and stirring was continued at the same temperature for 30 min. The mixture was then diluted with carbon tetrachloride (15 ml), washed thoroughly with aqueous sodium hydrogencarbonate solution and water, dried, and evaporated to give a syrup, which was shown by TLC (1: 5 2-butanone–toluene) to contain two major components (R_f 0.65 and 0.62). Chromatography of the products on a silica-gel column (30 g) with 1 : 20 2-butanone–toluene as an eluent gave **5** (R_f 0.65) as a syrup and **6** (R_f 0.62) as crystals (mp 109—110 °C): ^{1}H NMR (60 MHz)[25)] for **5**, δ=2.04 (3H, s), 2.09 (3H, s), and 2.11 (3H, s) (OAc), 3.75 and 3.97 (AB-quartet, J=11 Hz, $C\underline{H}_2Br$), 4.75—5.06 (2H, m, H-1 and H-6), 5.62 (1H, dd, J=7 and 10 Hz, H-2), 6.00 (1H, d, J=7 Hz, H-3), and 6.19 (1H, broad d, J=5.5 Hz, H-5), and for **6**, δ=2.04 (3H, s) and 2.11 (6H, s) (OAc), 3.81 and 4.09 (AB-quartet, J=11 Hz, $C\underline{H}_2Br$), 4.67 (1H, m, H-6), 5.10 (1H, dd, J=7 and 10 Hz, H-1), 5.55 (1H, dd, J=8 and 10 Hz, H-2),) 5.85—6.08 (1H, m, H-3), and 6.13 (1H, broad s, H-5).

Found: for **5**, C, 36.64; H, 3.83; Br, 37.47%, and for **6**, C, 36.29; H, 3.75; Br, 37.42%. Calcd for $C_{13}H_{16}Br_2O_6$: C, 36.48; H, 3.77; Br, 37.33%.

When the reactions were carried out at −4 °C and at

−15 °C, trace amounts of **13**, **14**, and **20** were produced as side-products. *b) In Acetic Acids*: The reaction was carried out in the same way as in *a*), except that the reaction mixture was diluted with ethyl acetate (30 ml). Similar to the reaction in carbon tetrachloride at low temperature, **13**, **14**, and **20** were obtained in trace amounts as side-products.

c) In 50% Aqueous Acetic Acid. After the reaction had been carried out in a similar way as described above, the reaction mixture was evaporated below 30 °C, without dilution or washing of the mixture, because TLC analysis (1: 5 2-butanone–toluene) revealed the presence of a large amount of slower-moving components in addition to a small amount of the desired products **5** and **6**. The yellow syrupy residue was treated with acetic anhydride (2 ml) in the presence of a trace of concd sulfuric acid at room temperature overnight and then neutralized with saturated aqueous sodium hydrogencarbonate solution. The mixture was diluted with ethyl acetate (30 ml), and the organic layer was washed with water and dried. Evaporation of the solvent left a syrup which was chromatographed similarly on a silica-gel column. After **5** and **6** had been eluted, tetraacetate **7** was obtained in 22% yield: mp 109—111 °C. The ^{1}H NMR spectrum of **7** is described later. In all cases, tetrabromides **4a**,**b** were detected by TLC analysis.

Interconversion of 5 and 6: When **6** was treated with carbon tetrachloride containing a trace of bromine at room temperature overnight, formation of an equilibrium mixture of **5** and **6** was detected by TLC analysis. Without bromine no interconversion occurs.

Practical Synthesis of 6: To a stirred solution of **3** (1 g) in 3 : 1 acetic acid–acetic anhydride (40 ml)[20] was added dropwise over a period of 50 min 5% bromine solution in the same solvent (3.86 ml, a molar equiv.), and stirring was continued for 50 min. The reaction mixture was processed according to the general procedure and the product was directly crystallized from ethanol (8 ml) to give **6** (0.71 g, 45%): mp 108.5—109.5 °C.

From the mother liquor, an inseparable mixture (0.23 g, 15%) of **7** and **8** was obtained by chromatography on silica gel. The ^{1}H NMR spectrum showed it to be a *ca.* 1 : 1 mixture of **7** and **8**.

Reduction of Tetrabromide 4a with Raney Nickel. A solution of **4a** (0.25 g) in ethyl acetate (10 ml) was hydrogenolyzed with Raney nickel T-4[21] (5 ml) and Amberlite IR-45 (OH^-) (7 ml) at room temperature overnight. After removal of the catalyst and resin by filtration, the filtrate was evaporated to a syrup, which was purified by passage through a short column of alumina with chloroform to give an inseparable syrupy mixture (114 mg, 99%) of tri-*O*-acety-DL-deoxyvalidatol and its 4-epimer[13] (*ca.* 1 : 1).

Reduction of 5 and 6. With Tributyltin(IV) Hydride: A solution of **5** (0.17 g) in dry toluene (10 ml) was treated with tributyltin(IV) hydride (0.22 ml) at room temperature overnight under a nitrogen atmosphere. Evaporation of the mixture left an oil, which was purified by passage through a silica-gel column with 1 : 10 2-butanone–toluene to give **3** (87 mg, 80%) as needles: mp 66.5—68 °C.

Similar treatment of **5** with tributyltin(IV) hydride gave **3** in 89% yield: mp 66—67 °C.

With Lithium Aluminium Hydride: A suspension of **5** (0.26 g) and lithium aluminium hydride (0.14 g) in tetrahydrofuran (10 ml) was refluxed gently for 7 h. The mixture was then diluted with water carefully, and the precipitates were removed by filtration. Evaporation of the filtrate left a syrup, which was acetylated in the ususl way. The mixture was evaporated and the residue was purified by an alumina column and crystallized from ethanol to give **3** (0.11 g, 63%) as needles: mp 67—68.5 °C.

Similar treatment of **6** with lithium aluminium hydride gave **3** in 60% yield: mp 67—68 °C.

Hydrobromination of Conjugated Diene 3. With N*-Bromoacetamide (NBA)*: To a stirred solution of NBA (0.25 g, a molar equiv.) and sodium acetate (0.23 g) in water (10 ml) was added dropwise over a period of 10 min a solution of **3** (0.5 g) in acetone (20 ml), and stirring was continued at room temperature for 5 d. The aqueous mixture was then extracted with ether (40 ml + 30 ml × 2) and the organic layer was dried and evaporated. The residue was acetylated in the usual way, during which time the mixture became orange. Evaporation of the mixture left a yellow syrup, which was chromatographed on a silica-gel column 1 : 8 2-butanone–toluene as an eluent. The first and second fractions gave **11** (0.10 g, 10%) and **20** (61 mg, 9%), respectively. They were identical with the samples of which preparations *via* unequivocal routes are to be described later.

The third fraction gave DL-2,3,4,7-tetra-*O*-acetyl-(1,2,4/3)-1-*C*-hydroxymethyl-5-cyclohexene-1,2,3,4-tetrol (**23**) (0.14 g, 21%) as a homogeneous syrup: ^{1}H NMR δ=2.00 (3H, s), 2.04 (6H, s), and 2.08 (3H, s) (OAc), 2.57 (1H, s, OH, caused to disappear on deuteration), 3.84 and 4.02 (AB-quartet, J=12 Hz, C$\underline{H}_2$OAc), 5.13 (1H, broad d, J=*ca.* 10 Hz, H-2), 5.33—5.62 (2H, relatively sharp m, H-3 and H-4), and 5.37 (2H, s, H-5 and H-6).

Found: C, 52.43; H, 5.85%. Calcd for $C_{15}H_{20}O_9$: C, 52.32; H, 5.85%.

Acetylation of **23** in the usual way for 7 d gave DL-penta-*O*-acetyl-(1,2,4/3)-1-*C*-hydroxymethyl-5-cyclohexene-1,2,3,4-tetrol (**24**) as a syrup quantitatively: ^{1}H NMR δ=2.00 (3H, s), 2.02 (3H, s), 2.05 (3H, s), and 2.07 (6H, s) (OAc), 4.15 and 4.51 (AB-quartet, J=11 Hz, C$\underline{H}_2$OAc), 5.19 (1H, dd, J=9 and 10.5 Hz, H-3), 5.29—5.64 (2H, m, H-2 and H-4), 5.73 (1H, dd, J=2 and 10 Hz, H-5), and 6.33 (1H, dd, J=1 and 10 Hz, H-6).

Found: C, 53,12; H, 5.72%. Calcd for $C_{17}H_{22}O_{10}$: C, 52.85; H, 5.74%.

A trace amount of the other product was isolated from the faster moving component. The structure was tentatively assigned as DL-tetra-*O*-acetyl-(1,3/2,4)-1-*C*-bromomethyl-5-cyclohexene-1,2,3,4-tetrol (**26**): ^{1}H NMR (60 MHz)[25] δ=2.04 (6H, s), 2.06 (3H, s), and 2.10 (3H, s) (OAc), 3.58 and 3.82 (AB-quartet, J=11 Hz, C$\underline{H}_2$Br), 5.20—5.84 (3H, m, H-1, H-2, and H-3), and 6.00 (1H, d, J=10 Hz) and 6.09 (1H, d, J=10 Hz) (olefinic proton).

Found: C, 43.98; H, 4.52; Br, 19.98%. Calcd for $C_{15}H_{19}BrO_8$: C, 44.24; H, 4.70; Br, 19.62%.

With N*-Bromosuccinimide (NBS)*: To a stirred mixture of **3** (0.5 g), dimethyl sulfoxide (10 ml), and water (0.1 ml) was added NBS (0.5 g, 1.5 molar equiv.) as one portion, and then stirring was continued for 5 h below 10 °C. The reaction mixture was then quenched by addition of water (40 ml) and extracted with ether (20 ml × 4). The extracts were dried and evaporated to give a yellow syrup, which was chromatographed on a silica-gel column (50 g) with 1 : 4 2-butanone–toluene. The first fraction gave a syrup (78 mg, 12%), of which structure was tentatively assigned as DL-2,3,4-tri-*O*-acetyl-(1,3/2,4)-1-*C*-bromomethyl-5-cyclohexene-1,2,3,4-tetrol (**25**): ^{1}H NMR (60 MHz)[24] δ=2.04 (6H,s) and 2.11 (3H, s) (OAc), 3.30—3.72 (1H, broad m, O$\underline{H}$, caused to disappear on deuteration), 3.46 and 3.68 (AB-quartet, J=11 Hz, C$\underline{H}_2$Br), 5.10—5.55 (3H, m, H-2, H-3, and H-4), and 5.60 (1H, dd, J= 1 and 11 Hz) and 5.87 (1H, dd, J=0.8 and 11 Hz) (olefinic proton).

Found: C, 42.84; H, 4.59; Br, 21.73%. Calcd for

$C_{13}H_{17}BrO_7$: C, 42.76; H, 4.69; Br, 21.88%.

The second fraction gave **20** (0.25 g, 36%) as a syrup.

The third fraction gave an inseparable mixture (33 mg, 5%) of **13** and **14**, whose ^{1}H NMR spectrum indicated it to be a 3 : 1 mixture of **13** and**14**. The spectrum was superimposable on that of an authentic sample prepared later *via* an unequivocal route.

When the reaction products, without fractionation, were acetylated in the usual way, formation of **7**, **11**, **20**, **23**, and **26** was detected by TLC analysis.

DL-*Tetra-O-acetyl-(1,2,4/3)-5-bromomethyl-5-cyclohexene-1,2,3,4-tetrol (7).* A mixture of **6** (0.11 g), silver acetate (41 mg, a molar equiv.), and 90% aqueous acetic acid (10 ml) was vigorously stirred with protection from light at room temperature for 2 h. The precipitates were then removed by filtration and the filtrate was evaporated to give a syrup, which was chromatographed on a silica-gel column (3 g) with 1 : 3 2-butanone–toluene. Crystallization from ethanol gave an inseparable crystalline mixture (66 mg, 73%) of DL-1,3,4-(**13**) and DL-2,3,4-tri-*O*-acetyl-(1,2,4/3)-5-cyclohexene 1,2,3,4-tetrol (**14**): mp 110.5—111 °C; the ^{1}H NMR spectrum showed it to be a 3 : 1 mixture of **13** and **14**; ^{1}H NMR for **13**, δ=2.12 (6H, s) and 2.14 (3H, s) (OAc), 2.42—2.72 (1H, broad s, $O\underline{H}$), 3.78 and 3.99 (AB-quartet, J=11 Hz, $C\underline{H}_2Br$), 3.91 (1H, dd, J=5 and 11 Hz, H-2), 5.32 (1H, dd, J=7.5 and 11 Hz, H-3), 5.35—5.49 (1H,m, H-1), 5.82 (1H, broad d, J=8 Hz, H-4), and 6.15 (1H, J=5 Hz, H-6), and for **14**, δ=4.93 (1H, dd, J=3 and 10 Hz, H-2), and 5.42 (1H, dd, J=7 and 10 Hz, H-3).

Found: C, 42.48; H, 4.69; Br, 21.54%. Calcd for $C_{13}H_{17}BrO_7$: C, 42.76; H, 4.69; Br, 21.88%.

From the mother liquor a mixture of **15** and **16** was separated in 13% yield by chromatography.

The mixture of **13** and **14** (50 mg) was acetylated with acetic anhydride (5 ml) in the presence of a trace of concd sulfuric acid at room temperature overnight and then neutralized with saturated aqueous sodium hydrogencarbonate solution. The mixture was diluted with ethyl acetate, and the organic layer was washed with water and dried. Evaporation of the solvent gave crystals, which were recrystallized from ethanol to give **7** (55 mg, 98%): mp 134—135 °C; ^{1}H NMR (60 MHz)[25] δ=2.02 (3H, s), 2.04 (3H, s), and 2.08 (6H, s) (OAc), 3.80 and 4.01 (AB-quartet, J=11 Hz, $C\underline{H}_2Br$), 5.11 (1H, dd, J=3.5 and 10 Hz, H-2), 5.32—5.68 (2H, m, H-1 and H-3), 5.83 (1H, broad d, J=*ca.* 6.5 Hz, H-4), and 6.02 (1H, broad d, J=*ca.* 6 Hz, H-6).

Found: C, 44.04; H, 4.73; Br, 19.86%. Calcd for $C_{15}H_{19}BrO_8$: C, 44.24; H, 4.70; Br, 19.62%.

DL-*Tetra-O-acetyl-(1,3/2,4)-5-bromomethyl-5-cyclohexene-1,2,3,4-tetrol (8).* A mixture of **6** (0.42 g), silver acetate (0.17 g, a molar equiv.), and acetic acid–acetic anhydride (20 ml)[20] was heated to 80 °C with protection from light for 40 min. After cooling, the precipitates were removed by filtration and the filtrate was evaporated to give a syrup, which was purified by a short column of silica gel to give crystals. Recrystallization from ethanol gave **8** (0.25 g, 63%) as columns: mp 133.5—134 °C; ^{1}H NMR δ=2.01 (6H, s), 2.06 (3H, s), and 2.08 (3H, s) (OAc), 3.79 and 3.99 (AB-quartet, J=11 Hz, $C\underline{H}_2Br$), 5.25—5.68 (3H, m, H-1, H-2, and H-3), and 5.77—6.01 (2H, m, H-4 and H-6).

Found: C, 44.14; H, 4.65; Br, 19.87%. Calcd for $C_{15}H_{19}BrO_8$: C, 44.24; H, 4.70; Br, 19.62%.

DL-*Penta-O-acetyl-(1,2,4/3)-5-hydroxymethyl-5-cyclohexene-1,2,3,4-tetrol (11).* *a)*: A mixture of **6** (0.14 g), silver acetate (0.21 g, 4 molar equiv.), and 90% aqueous acetic acid (10 ml) was heated to 90 °C with protection from light for 1 h. The precipitates were removed by filtration and the filtrate was evaporated to give a syrup, which was chromatographed on a silica-gel column (5 g) with 1 : 3 2-butanone–toluene to give an inseparable mixture (61 mg, 56%) of DL-1,3,4,7- (**15**) and DL-2,3,4,7-tetra-*O*-acetyl-(1,2,4/3)-5-hydroxymethyl-5-cyclohexene-1,2,3,4-tetrol (**16**). The ^{1}H NMR spectrum indicated it to be a 3 : 1 mixture of **15** and **16**: ^{1}H NMR for **15**, δ=2.02 (3H, s), 2.04 (3H, s), 2.09 (3H, s), and 2.10 (3H, s) (OAc), 3.71—4.00 (1H, m, H-2, caused to change to dd with J=4 and 11 Hz at δ 3.87 on deuteration), 4.31 and 4.68 (AB-quartet, J=13 Hz, $C\underline{H}_2OAc$), 5.29 (1H, dd, J=8 and 11 Hz, H-3), 5.38 (1H, dd, J=4 and 6 Hz, H-1), and 5.65 (1H, broad d, J=8 Hz, H-4), 6.02 (1H, broad d, J=6 Hz, H-6), and for **16**, δ=4.91 (1H, dd, J=5 and 11 Hz, H-2).

Found: C, 52.56; H, 5.95%. Calcd for $C_{15}H_{20}O_9$: C, 52.32; H, 5.85%.

A trace of mixture of **13** and **14** was separated from the fast migrating component.

The mixture of **15** and **16** (76 mg) was acetylated in the usual way to give **11** (81 mg, 95%) as a homogeneous syrup: ^{1}H NMR (60 MHz)[25] δ=2.00 (3H, s), 2.03 (3H, s), 2.04 (6H, s), and 2.09 (3H, s) (OAc), 4.32 and 4.70 (AB-quartet, J=13 Hz, $C\underline{H}_2OAc$), 5.10 (1H, ddd, J=2, 4, and 10 Hz, H-2), 5.47 (1H, dd, J=7 and 10 Hz, H-3), 5.57 (1H, dd, J=4 and 6 Hz, H-1), 5.66 (1H, broad d, J=7 Hz, H-4), and 5.94 (1H, dd, J=2 and 6 Hz, H-6).

Found: C, 52.63; H, 5.69%. Calcd for $C_{17}H_{22}O_{10}$: C, 52.85; H, 5.74%.

b): The mixture of **13** and **14** (0.1 g) was treated with sodium acetate (24 mg, 1.1 molar equiv.) in 10% aqueous DMF (10 ml) at room temperature for 7 h. Evaporation of the mixture left a residue, which was purified by an alumina column to give a homogeneous syrup. The syrup was acetylated and the product was chromatographed on a silica-gel column (2 g) with 1 : 5 2-butanone–toluene to give **11** (0.9 g, 86%) as a homogeneous syrup.

c): A mixture of **7** (50 mg), sodium acetate (20 mg, 2 molar equiv.), and DMF (1 ml) was stirred at room temperature for 2 d. The mixture was then evaporated and the residue was purified by an alumina column to give **11** (33 mg, 70%) as a homogeneous syrup.

DL-*Penta-O-acetyl-(1,3/2,4)-5-hydroxymethyl-5-cyclohexene-1,2,3,4-tetrol (12).* *a)* A mixture of **6** (1 g), silver acetate (1.56 g, 4 molar equiv.), and acetic acid–acetic anhydride (60 ml)[20] was treated similarly as described in the preparation of **8** for 3 h. The crystalline product was recrystallized from ethanol to give DL-penta-*O*-acetyl-(1,3,5/2,4)-6-methylene-1,2,3,4,5-cyclohexanepentol (**17**) (0.1 g, 12%): mp 188.5—189 °C (lit,[24] 189—190 °C); ^{1}H NMR δ=1.93 (9H, s) and 2.03 (6H, s) (OAc) and 4.72—5.67 (7H, m, H-1, H-2, H-3, H-4, H-5, and exocyclic methylene).

Found: C, 52.63; H, 5.62%. Calcd for $C_{17}H_{22}O_{10}$: C, 52.85; H, 5.74%.

Evaporation of the mother liquor and crystallization from ethanol gave **12** (0.59 g, 73%): mp 81.5—82.5 °C; ^{1}H NMR δ=2.03 (3H, s), 2.04 (3H, s), 2.05 (3H, s), 2.06 (3H, s), and 2.08 (3H, s) (OAc), 4.41 and 4.76 (AB-quartet, J=14 Hz, $C\underline{H}_2Br$), 5.16—5.72 (3H, m, H-1, H-2, and H-3), and 5.82 (2H, broad s, H-4 and H-6).

Found: C, 53.05; H, 5.76%. Calcd for $C_{17}H_{22}O_{10}$: C, 52.85; H, 5.74%.

b): A mixture of **8** (0.26 g), sodium acetate (79 mg, 1.5 molar equiv.), and DMF (5 ml) was stirred at room temperature for 24 h. The mixture was then evaporated and the residue was purified by an alumina column to give crystals. Recrystallization from ethanol gave **12** (0.26 g, 91%): mp 81—82 °C.

DL-*(1,2,4/3)-5-Hydroxymehthtyl-5-cyclohexene-1,2,3,4-tetrol*

(18). A solution of **11** (0.1 g) in methanol (10 ml) was treated with 1 M† methanolic sodium methoxide (0.2 ml) and allowed to stand at 0—5 °C overnight. The mixture was then neutralized with Amberlite IR-120 (H^+) and evaporated to give a syrup, which was crystallized from ethanol to give **18** (40 mg, 87%): mp 139.5—141 °C; ^{1}H NMR (90 MHz, D_2O)[26] δ=3.46—3.86 (2H, m, H-2 and H-3), 4.00—4.42 (4H, m, H-1, H-4, and $C\underline{H}_2OH$), and 5.88 (1H, dd, J=1.5 and 5 Hz).

Found: C, 47.65; H, 6.77%. Calcd for $C_7H_{12}O_5$: C, 47.72; H, 6.87%.

DL-*(1,3/2,4)-5-Hydroxymethyl-5-cyclohexene-1,2,3,4-tetrol (19).* Compound **12** (0.1 g) was treated with 1 M methanolic sodium methoxide in the same way as in the preparation of **18**. The crude product was recrystallized from aqueous ethanol to give **19** (45 mg, 98%): mp 150.5—151.5 °C; ^{1}H NMR (90 MHz, D_2O)[25] δ=3.26—3.70 (2H, m, H-2 and H-3), 4.05—4.36 (4H, m, H-1, H-4, and $C\underline{H}_2OH$), and 5.62 (1H, d, J=1.5 Hz).

Found: C, 47.66; H, 6.72%. Calcd for $C_7H_{12}O_5$: C, 47.72; H, 6.87%.

Reaction of 5 and 6 with Sodium Acetate. With an Equimolar Amount of Sodium Acetate: Synthesis of DL-*Tetra-O-acetyl-(1,3,6/2)-4-hydroxymethyl-6-bromo-4-cyclohexene-1,2,3-triol (9)*: A mixture of **5** (0.2 g), sodium acetate (37 mg, a molar equiv.), and DMF (10 ml) was stirred at room temperature for 24 h. The mixture was then diluted with ethyl acetate (20 ml), and the organic layer was washed with water and dried. Evaporation of the solvent left a syrup, which was crystallized from ethanol to give **9** (86 mg, 47%) as needles: mp 66—67.5 °C; ^{1}H NMR δ=2.02 (6H, s), 2.05 (6H, s), and 2.11 (3H, s) (OAc), 4.32 and 4.66 (AB-quartet, J=14 Hz, $C\underline{H}_2OAc$), 4.82 (1H, dd, J=4.5 and 10 Hz, H-1), 4.82—5.00 (1H, m, H-6), 5.58 (1H, dd, J=9 and 10 Hz, H-2), 5.81 (1H, d, J=9 Hz, H-3), and 6.07 (1H, broad d, J=*ca.* 5 Hz, H-5).

Found: C, 44.18; H, 4.69; Br, 19.73%. Calcd for $C_{15}H_{19}BrO_8$: C, 44.24; H, 4.70; Br, 19.62%.

From the mother liquor an inseparable 1.5 : 1 mixture (63 mg, 35%) of **9** and its C-6 epimer **10** was obtained. (Found: C, 43.97; H, 4.60; Br, 19.31%.) The ^{1}H NMR spectrum of **10** could be read in that of the mixture by elimination of the spectrum of **9**: ^{1}H NMR δ=4.32 and 4.66 (AB-quartet, J=14 Hz, $C\underline{H}_2OAc$), 5.11 (1H, dd, J=7.5 and 10 Hz, H-1), 5.46 (1H, dd, J=8 and 10 Hz, H-2), 5.79 (1H, broad d, J=8 Hz, H-3), and 5.99 (1H, broad s, H-5).

When **6** was used instead of **5**, **9** was similarly obtained in 49% yield.

With Excess Sodium Acetate: A mixture of **5** (90 mg), sodium acetate (0.7 g, 4 molar equiv.), and DMF (10 ml) was stirred at room temperature for 2 d. The mixture was worked up in a similar manner as above and the crude product was chromatographed on a silica-gel column (3 g) with 1 : 5 2-butanone–toluene to give an inseparable syrupy mixture (0.5 g, 60%) of **11** and **12**. Found: C, 52.60; H, 5.53%. From a comparison of the ^{1}H NMR spectrum with those of the authentic samples of **11** and **12**, it was found to be a 1 : 2—3 mixture of **11** and **12**.

When **6** was used instead of **5**, a similar result was obtained; a 1 : 2—3 mixture of **11** and **12** in 57% yield.

DL-*2,3,4-Tri-O-acetyl-(1,2,4/3)-1-C-bromomethyl-5-cyclohexene-1,2,3,4-tetrol (20).* A mixture of **5** (0.63 g), silver acetate (0.27 g, 1.1 molar equiv.), and 90% aqueous acetic acid (20 ml) was stirred with protection from light at room temperature for 24 h. The precipitates were then removed by filtration and the filtrate was evaporated to give a syrup, which was chromatographed on a silica-gel column (15 g) with 1 : 3 2-butanone–toluene to give **20** (0.28 g, 52%) as a homogeneous syrup: ^{1}H NMR (60 MHz)[25] δ=2.03 (3H, s), 2.06 (3H, s), and 2.13 (3H, s) (OAc), 2.78 (1H, s, $O\underline{H}$), 3.39 (2H, s, $C\underline{H}_2Br$), 5.21—5.66 (3H, m, H-2, H-3, and H-4), and 5.83 (2H, broad s, H-5 and H-6).

Found: C, 42.51; H, 4.72; Br, 21.60%. Calcd for $C_{13}H_{17}BrO_7$: C, 42.76; H, 4.69; Br, 21.88%.

When **20** was treated with an excess of silver acetate at 90 °C for a prolonged period, no further substitution reaction occurred.

DL-*Tetra-O-acetyl-(1,2,4/3)-1-C-methoxymethyl-5-cyclohexene-1,2,3,4-tetrol (22).* To a solution of **20** (0.11 g) in methanol (5 ml) was added 1 M methanolic sodium methoxide (1.3 ml, 4 molar equiv.), and the mixture was allowed to stand at room temperature overnight. After the mixture was neutralized by treatment with Amberlite IR 120 (H^+), it was evaporated and the residue was acetylated in the usual way. The product was chromatographed on a silica-gel column (5 g) with 1 : 3 2-butanone–toluene. The first fraction gave, after recrystallization from ethanol, **22** (7 mg, 6%): mp 130—130.5 °C; ^{1}H NMR (60 MHz)[25] δ=2.02 (3H, s), 2.04 (3H, s), and 2.09 (6H, s) (OAc), 3.29 (3H, s, $OC\underline{H}_3$), 3.39 and 3.83 (AB-quartet, J=5 Hz, $C\underline{H}_2OCH_3$), 5.17—5.61 (3H, m, H-2, H-3, and H-4), 5.76 (1H, dd, J=2 and 10 Hz, H-5), and 6.33 (1H, dd, J=1 and 10 Hz, H-6).

Found: C, 53.42; H, 6.08%. Calcd for $C_{16}H_{22}O_9$: C, 53.63; H, 6.19%.

The second fraction gave DL-2,3,4-tri-*O*-acetyl-(1,2,4/3)-1-*C*-methoxymethyl-5-cyclohexene-1,2,3,4-tetrol (**21**) (70 mg, 71%) as a homogeneous syrup: ^{1}H NMR (60 MHz)[25] δ=2.00 (3H, s), 2.03 (3H, s), and 2.06 (3H, s) (OAc), 3.02 (1H, s, $O\underline{H}$), 3.30 (5H, s, $OC\underline{H}_3$ and $C\underline{H}_2OCH_3$), 5.03—5.69 (3H, m, H-2, H-3, and H-4), and 5.81 (2H, s, H-5 and H-6).

Found: C, 53.29; H, 6.36%. Calcd for $C_{14}H_{20}O_8$: C, 53.16; H, 6.47%.

Further acetylation of **21** for 9 d gave **22** quantitatively.

Reaction of 9 with Alcohols in the Presence of Silver Ion. The results are summarized in Table 2.

General Procedure: To a vigorously stirred solution of **9** (0.3 g), alcohol (5 ml), and Drierite (0.5 g) in dry ether (8 ml) was added silver perchlorate (0.2 g) with ice-cooling under a nitrogen atmosphere, and stirring was continued with protection from light for an appropriate time. After the precipitates had been removed by filtration, the filtrate was washed with saturated aqueous sodium hydrogencarbonate solution and water, and then dried. Evaporation of the solvent left a yellow syrup, which was chromatographed on a silica-gel column (6 g) with 1 : 10 2-butanone–toluene to give the corresponding alkyl ether.

After the alkyl ether had been eluted from the column, a mixture of **15**, **16**, and **23** was separated in 13—15% yield. The ratio of (**15**, **16**) and **23** was estimated to be *ca.* 1 : 1.3 from the ^{1}H NMR spectrum.

With Methanol: DL-2,3,4,7-Tetra-*O*-acetyl-1-*O*-methyl-(1,3/2,4)-5-hydroxymethyl-5-cyclohexene-1,2,3,4-tetrol (**28**) only was formed as a syrup: ^{1}H NMR δ=1.96 (3H, s), 1.98 (3H, s), 2.01 (3H, s), and 2.02 (3H, s) (OAc), 3.34 (3H, s $C\underline{H}_3$), 3.92—4.14 (1H, m, H-1), 4.28 and 4.60 (AB-quartet, J=13 Hz, $C\underline{H}_2OAc$), 5.03—5.35 (2H, m, H-2 and H-3), 5.57—5.76 (1H, m, H-4), and 5.82 (1H, broad s, H-6).

Found: C, 53.48; H, 6.20%. Calcd for $C_{16}H_{22}O_9$: C, 53.63; H, 6.19%.

With Ethanol: A 1 : 4 mixture of DL-2,3,4,7-tetra-*O*-acetyl-1-*O*-ethyl-(1,2,4/3)-5-hydroxymethyl-5-cyclohexene-1,2,3,4-tetrol (**29**) and its C-1 epimer (**30**) was formed as a syrup: ^{1}H NMR for **29**, δ=1.17 (3H, t, J=7.5 Hz, $C\underline{H}_3CH_2$), 5.48 (1H,

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† 1 M=1 mol dm^{-3}.

t, $J=8$ Hz, H-3), 5.99 (1H, broad d, $J=6$ Hz, H-6), and for **30**, $\delta=1.16$ (3H, t, $J=7.5$ Hz, $\mathrm{C\underline{H}_3CH_2}$), 1.97 (3H, s), 2.01 (3H, s), and 2.04 (6H, s) (OAc), 3.57 (2H, q, $J=7.5$ Hz, $\mathrm{CH_3C\underline{H}_2}$), 4.01—4.20 (1H, m, H-1), 4.31 and 4.65 (AB-quartet, $J=14$ Hz, $\mathrm{C\underline{H}_2OAc}$), 5.13—5.33 (2H, m, H-2 and H-3), 5.65—5.78 (1H, m, H-4), and 5.82 (1H, broad s, H-6).

Found: C, 54.90; H, 6.41%. Calcd for $\mathrm{C_{17}H_{24}O_9}$: C, 54.83; H, 6.50%.

With 2-Propanol: A 1 : 4 mixture of DL-2,3,4,7-tetra-*O*-acetyl-1-*O*-isopropyl-(1,2,4/3)-5-hydroxymethyl-5-cyclohexene-1,2,3,4-tetrol (**31**) and its C-1 epimer (**32**) was obtained as a syrup: ^{1}H NMR for **31**, $\delta=5.90$ (1H, broad d, $J=5$ Hz, H-6), and for **32**, $\delta=1.10$ (3H, d, $J=6$ Hz) and 1.15 (3H, d, $J=6$ Hz) ($\mathrm{CMe_2}$), 1.97 (3H, s), 1.99 (3H, s), and 2.01 (6H, s) (OAc), 3.65 (1H, heptet, $J=6$ Hz, $\mathrm{\underline{H}CMe_2}$), 3.95—4.15 (1H, m, H-1), 4.25 (1H, d) and 4.59 (1H, broad d) (AB-quartet, $J=12$ Hz, $\mathrm{C\underline{H}_2OAc}$), 5.00—5.31 (2H, m, H-2 and H-3), 5.59—5.72 (1H, m, H-4), and 5.75 (1H, broad s, H-6).

Found: C, 56.25; H, 6.73%. Calcd for $\mathrm{C_{18}H_{25}O_9}$: C, 56.10; H, 6.54%.

*Treatment of **9** with Methanolic 1 M Sodium Methoxide.* To a solution of **9** (0.2 g) in methanol (5 ml) was added 1 M sodium methoxide (two drops with a syringe) with vigorous stirring at 0 °C, and the mixture was allowed to stand at room temperature for 3 d. At this time the pH of the mixture was 1. After neutralization with IRA 400 ($\mathrm{OH^-}$), the filtrate was evaporated to give a colorless syrup (79 mg), which showed a negative Beilstein test. The syrup was acetylated and the product was purified by an alumina column, giving a 1 : 1 syrupy mixture (125 mg, 71%) of **27** and **28**. Found: C, 53.43; H, 6.21%. The ^{1}H NMR spectrum of **27** could be read partly in that of the mixture by elimination of the spectrum of **28**: ^{1}H NMR $\delta=3.39$ (3H, s, $\mathrm{OC\underline{H}_3}$), 5.45 (1H, t, $J=9$ Hz, H-3), and 6.02 (1H, broad d, $J=6$ Hz, H-6).

*Treatment of **9** with Ethanol Containing a Trace of Hydrogen Bromide.* To a stirred solution of **9** (0.27 g) in ethanol (5 ml) was added 30% hydrogen bromide in acetic acid (0.06 ml) at 0 °C, and the mixture was allowed to stand at the same temperature for 5 d. After neutralization with IRA 400 ($\mathrm{OH^-}$), the filtrate was evaporated to give a colorless syrup (83 mg), which had a negative Beilstein test. The syrup was acetylated and the product was purified by an alumina column, giving a 1 : 1 syrupy mixture (155 mg, 64%) of **29** and **30**.

Found: C, 54.93; H, 6.31%. Calcd for $\mathrm{C_{17}H_{24}O_9}$: C, 54.83; H, 6.50%.

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