Pure & Appl. Chem., Vol.53, pp.113-128.
Pergamon Press Ltd. 1981. Printed in Great Britain.
©IUPAC
0033-4545/81/0101-0113$02.00/0

STEREOSELECTIVE SYNTHESES OF BRANCHED-CHAIN SUGAR DERIVATIVES

Juji Yoshimura

Laboratory of Chemistry for Natural Products, Faculty of Science, Tokyo Institute of Technology, Nagatsuta, Midoriku, Yokohama 227, Japan

Abstract - Stereoselectivities in reactions for the introduction of an α hydroxyethyl group to 4-uloses via 4-C-vinyl and 4-C-ethylidene derivatives were examined, and the results were used for the stereoselective synthesis of methyl 6-deoxy-4-C-(hydroxymethyl)-5-O-methyl-2,3-O-methylene-L-idonate which was obtained by methanolysis of everninomicin B and D. In addition, the configuration of methyl eurekanate (methyl 4-C-acetyl-6-deoxy-2,3-O-methylene-hexonate) from flambamycin was determined to be D-galacto by synthesis.

As an extension of knowledge in the chemistry of branched-chain sugars to chiral syntheses of natural products, 4-amino-2-(hydroxymethyl)-tetrahydrofuran-4-carboxylic acid found in acid hydrolysate of diabetic urine, and thiazole-4-carboxylic acids having an optically active substituent at C-2 found in thiostrepton and nosiheptide were studied.

INTRODUCTION

Significant parts of over thirty kinds of naturally occurring branched-chain sugars have been synthesized during the last two decades, mainly by the nucleophilic 1,2-addition to uloses. The development of newer methods (Ref. 1) and accumulated data for prediction of the stereoselectivity in this field accelerated recent advances in chiral syntheses of natural products of widely diverse structures by the use of carbohydrates as intermediates (Ref. 2-4). However, in spite of strong demands for higher stereoselectivities and higher yields, the control of absolute stereochemistry at the branching point remains as the crucial problem, even in such simple molecules as cyclohexanone derivatives (Ref. 5-7). Starting point of our research in this field was to discover the factors controlling the complementary stereoselectivities between diazomethane and the Grignard reactions. In addition to the well-known non-bonded interaction, an attractive electrostatic interaction between the diazomethyl cation and a neighbouring axial oxygen in the transition state of the diazomethane reaction (Ref. 8 & 9), and thermodynamic control in such an equilibration reaction as the nitromethane reaction (Ref. 10 & 11) were shown to be important factors.

Recently, our keen interest has been in the synthesis of five new branched-chain sugars found in oligosaccharide antibiotics of the orthosomycin family, everninomicins (Ref. 12) and flambamycin (Ref. 13). Thus, we have reported on synthesis of three of them; D-evermicose (Ref. 14), D-evalose (Ref. 15), and L-evernitrose (Ref. 16). In the present lecture I would like to present the synthesis of the remaining two at first, and then of a few non-sugar natural products from sugar precursors.

SYNTHESIS OF BRANCHED-CHAIN SUGARS

The configuration of terminal 6-deoxy-4-C-(hydroxymethyl)-5-O-methyl-2,3-O-methylene-hexono-1,4'-lactone in everninomicin B and D, which links with a characteristic orthoester interlinkage, was determined to be (1R)-L-ido by the X-ray analysis of the partially hydrolyzed pentasaccharide, olgose (Ref. 17). This lactone was chemically characterized as the corresponding methyl L-idonate (1) (Ref. 18). Besides, a similar lactone (4-acetyl-6-deoxy-2,3-O-methylene-hexono-1,5-lactone) is included in flambamycin, and the corresponding aldonate was named as "methyl eurekanate" of unknown configuration (2) (Ref. 13). In this section synthesis of (1) and configurational determination of (2) by synthesis are described.

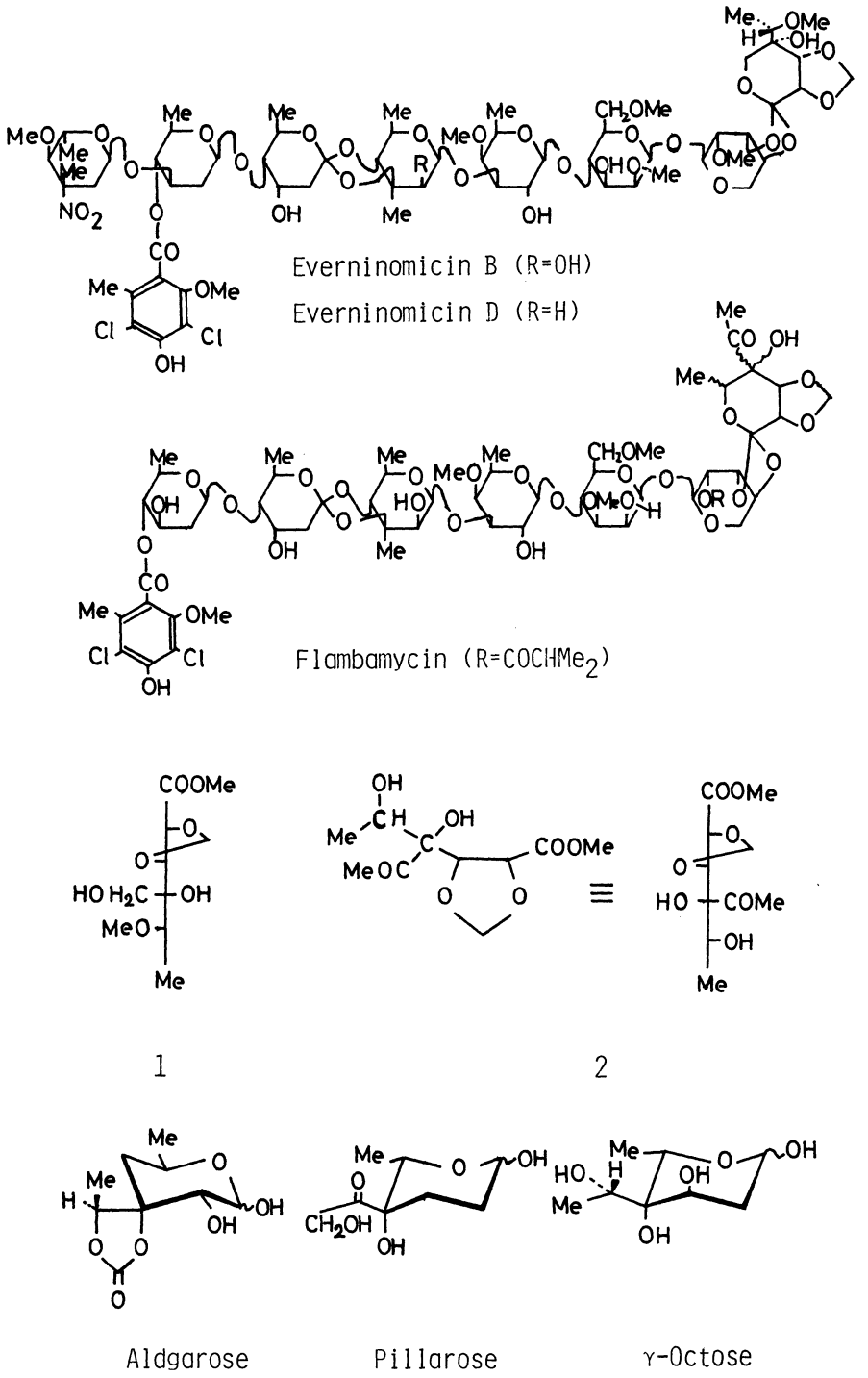


Fig. 1 Oligosaccharide antibiotics and branched-chain sugars.

The above compounds,(1) and (2), are of a branched-chain sugar kind having a two-carbon branch. To date, two-carbon branched sugars such as aldgarose (Ref. 19 & 20) from aldgamycin E and pillarose (Ref. 21 & 22) from pillaromycin A have been synthesized via the corresponding C-vinyl or C-(2-methyl- or 2-hydroxymethyl-1,3-dithian-2-yl) derivatives, and L-γ-octose from quinocyclin B via the corresponding C-vinyl derivative (Ref. 23). From these results, it was deduced that the 1,2-addition of carbanions to 3- or 4-uloses gave preponderantly equatorially C-substituted products and osmium tetroxide oxidation of C-alkylidene derivatives obtained from a 4-ulose gave predominantly axially 4-C-substituted products (Ref. 22). However no proper methods for the stereoselective introduction, and also for the

determination of the chirality in the branched carbon (for example in the case of the 3-C-α-hydroxyethyl group of aldgarose) are known (Fig. 1).

As shown in Fig. 2, it was considered that the comparison of the diols obtained from the corresponding C-vinyl derivatives by epoxidation and reduction (route A) with those obtained from the corresponding C-ethylidene derivative by osmium tetroxide oxidation or epoxidation followed by alkaline ring-opening in dimethyl sulfoxide (route B or C) should give the unambiguous configuration of the branched carbon, when the configuration of the ethylidene group is obvious. By the use of this principle the configurations of most of the diols synthesized were determined, and the stereoselectivities in reactions used were examined. Moreover, it was shown that the simultaneous inversion of the configurations at the branching point and the branching α-carbon in diols via the corresponding epoxides were possible.

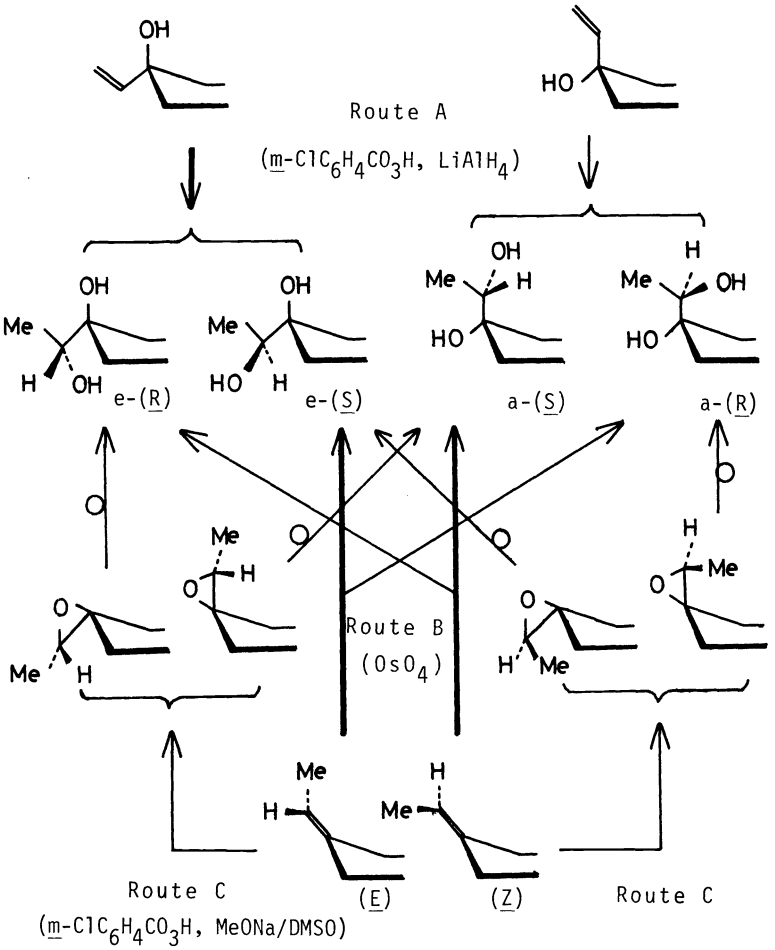
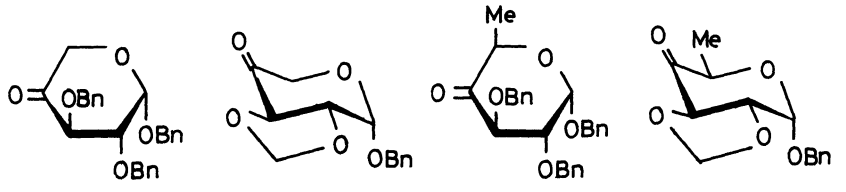


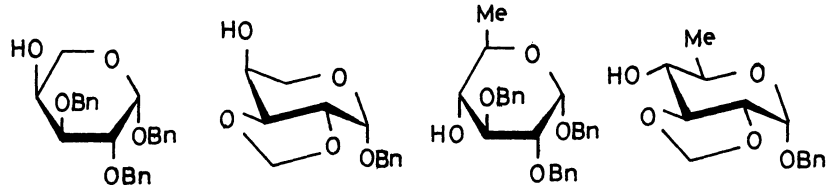
Fig. 2 The principle for the determination of the configuration of the α-hydroxyethyl group.

Preparation of 4-C-ethylidene and 4-C-vinyl derivatives for syntheses of (1) and (2). For the synthesis of (1), two pathways; i.e. the introduction of an equatorially oriented two-carbon unit to benzyl 2,3-O-methylene-L-threo-pentopyranosid-4-ulose (4) and that of an axially oriented one-carbon unit into benzyl 6-deoxy-2,3-O-methylene-L-xylo-hexopyranosid-4-ulose, were considered. However, the former was chosen because of the difficulty in the preparation of the latter. In addition, benzyl-6-deoxy-2,3-O-methylene-α-D-xylo-hexopyranosid-4-ulose (6) and the corresponding 2,3-di-O-benzyl derivatives (3 and 5) of (4) and (6) were synthesized as the substrates for the examination of stereoselectivities in reactions to be used here.

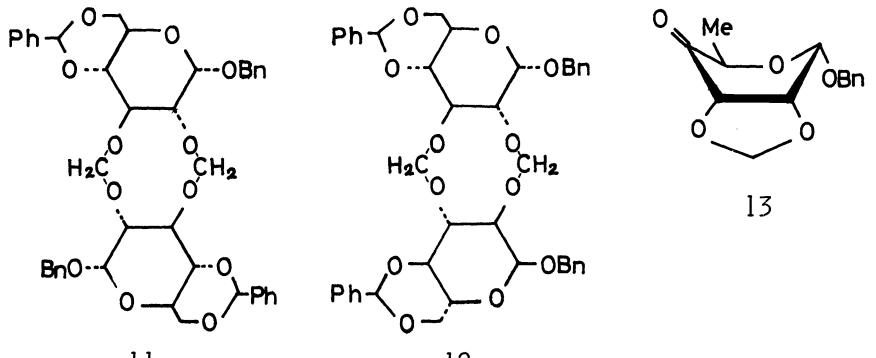
The precursors (7-10) of 4-uloses were synthesized as follows. Protection of the 4-hydroxyl group of benzyl 2,3-di-O-benzoyl-β-L-arabinopyranoside (Ref. 24) with the (methylthio) methyl group by the method of Pojer and Angyal (Ref. 25) followed by de-O-benzoylation gave



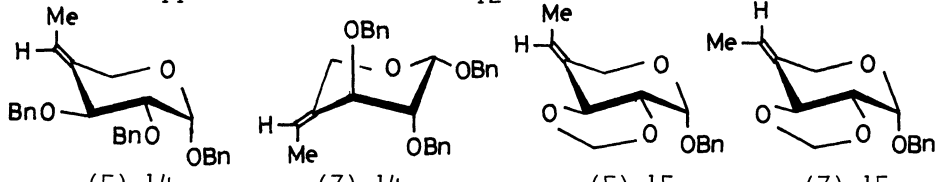
3 4 5 6



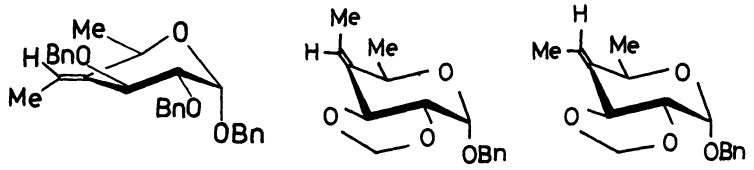
7 8 9 10



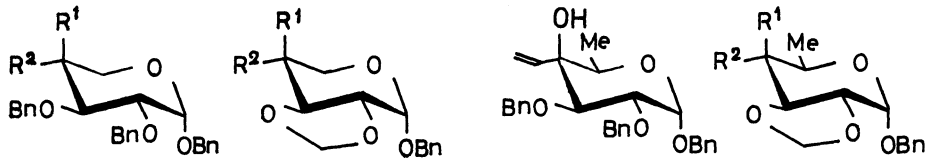
11 12 13



(E)-14 (Z)-14 (E)-15 (Z)-15



(Z)-16 (E)-17 (Z)-17



18 R^1=OH, R^2=vinyl
19 R^1=vinyl, R^2=OH
20 R^1=OH, R^2=vinyl
21 R^1=vinyl, R^2=OH
22
23 R^1=OH, R^2=vinyl
24 R^1=vinyl, R^2=OH
25 R^1=OH, R^2=2-methyl-1,3-dithian-2-yl

Fig. 3 Syntheses of 4-C-ethylidene and 4-C-vinyl derivatives.

benzyl 4-O-(methylthio)methyl-β-L-arabinopyranoside in 50% overall yield. The free hydroxyl groups at C-2 and C-3 of the above product were protected with benzyl and methylene groups (Ref. 26). De-O-(methylthio)methylation with mercuric chloride and calcium carbonate gave benzyl 2,3-di-O-benzyl- (7) and 2,3-O-methylene-β-L-arabinopyranoside(8) in 81% and 29% overall yields, respectively. On the other hand, partial tosylation of benzyl 2,3-di-O-benzyl-α-D-glucopyranoside (Ref. 26) followed by reduction with lithium aluminium hydride gave benzyl 2,3-di-O-benzyl-6-deoxy-α-D-glucopyranoside (9) in 38% yield. Benzyl 4,6-O-benzylidene-α-D-glucopyranoside (Ref. 27) was converted into benzyl 6-deoxy-2,3-O-methylene-α-D-glucopyranoside (10) by successive reactions (2,3-O-methylenation (Ref. 27), de-O-benzylidenation, 6-O-tosylation, reductive 6-deoxygenation) in 26% overall yield. It is noteworthy that in the first reaction in these conversions, two dimers (11 and 12) are formed each in ca.7% yield. The configurations of these compounds were determined from the 2,3-O-methylene signals (11: AB quartet, indicating two magnetically non-equivalent protons of two equivalent methylene groups; 12: two singlets, each indicating two equivalent protons of two non-equivalent methylene groups) in the n.m.r. spectra.

In the cases of (7) and (9), oxidations into the corresponding 4-uloses proceeded even with dimethyl sulfoxide (DMSO)-acetic anhydride, however, those of (8) and (10) gave only the corresponding 4-O-(methylthio)methyl derivatives in low yields. Oxidation of (8) and (10) with Jones' reagent were accompanied with epimerization at C-3, indicating the strained state of the 2,3-O-methylene ring. Configuration of the product (13), benzyl 6-deoxy-2,3-O-methylene-α-D-*ribo*-hexopyranosid-4-ulose, from (6) was confirmed by a separate synthesis. The oxidation with DMSO-trifluoroacetic anhydride (Ref. 28) generally proceeded smoothly to give the corresponding 4-uloses in 72-100% yields. Examination by n.m.r. spectroscopy of 4-uloses synthesized here indicated that (4) and (6) have the $B_{3,0}$ ($J_{1,2}$=3.0, $J_{2,3}$=10.8, $J_{3,5}$=1.0 Hz) conformation (Ref. 23), and (13) has the $^{1,4}B$($J_{1,2}$=3.6, $J_{2,3}$=7.2, $J_{3,5}$=0.8 Hz) conformation.

On the other hand, the above uloses (3-6) were converted into the corresponding 4-C-ethylidene derivatives by the reaction with ethyltriphenylphosphonium bromide and butyllithium in ether. In the case of (3), (E)- and (Z)-isomers (14) were obtained in 22% and 25% yields, respectively. Their configurations could be clearly assigned from their $^{1}C_{1}$($J_{1,2}$=3.0, $J_{2,3}$= 9.0 Hz) and ^{1}C ($J_{1,2}$=1.5, $J_{2,3}$=4.0 Hz) conformations. The conformation of (Z)-16 obtained from (5) was deduced to be flattened $^{1}C_{1}$ ($J_{1,2}$=3.0, $J_{2,3}$=6.0 Hz), and the configuratinal determination will be described in the following paragraph, together with those of other ethylidene derivatives from (4) and (6). It is interesting that (E)-isomers showed commonly larger dextro-rotational values than (Z)-isomers.

The results in the synthesis of 4-C-vinyl derivatives are summarized in Table 1. The configurations of products were determined from the chemical shifts of branched α-carbons in ^{13}C n.m.r. spectra (Ref. 29-32). The complemental stereoselectivity in the reaction of (3) with methylmagnesium iodide and methyllithium in ether at a lower temperature is the same that reported by Miljkovic *et al.* in the reaction of methyl 2,3-di-O-methyl-6-O-triphenylmethyl-α-D-*xylo*-hexopyranosid-4-ulose (Ref. 33). It is interesting that the tendency to give an equatorially substituted product is stronger in the reaction of hexos-4-uloses (5,6) than (4), though the axial attack product predominates in the case of (3).

TABLE 1. Addition of nucleophiles to 4-uloses

4-Uloses	Nucleophiles	Conditions Solvent	Temp.(°C)	Products* and ratio of axial/equatorial attack	Yields(%)
(3)	MeMg I	ether	-80	1 / 2.6	98
	"	ether-THF	20	2.5 / 1	84.5
	MeLi	ether	20	1 / 0	42
	CH_2=CHMgBr	THF	20	(19) 2.5 / 1 (18)	52
	2-methyl-2-lithio-1,3-dithiane	THF	-30	2.5 / 1	40
(4)	CH_2=CHMgBr	THF	20	(21) 1 / 4.8 (20)	59
(5)	CH_2 = CHMgBr	THF	20	0 / 1 (22)	52
(6)	CH_2=CHMgBr	THF	20	(24) 1 / 16 (23)	56
	2-methyl-2-lithio-1,3-dithiane	THF	-30	0 / 1 (25)	40
(13)	MeMg I	ether-THF	20	1 / 0	95

* only the products mentioned in the text are numbered.

Stereoselectivities in reactions for the introduction of 4-C-(α-hydroxyethyl) group

From 4-C-ethylidene derivatives (14-17) and 4-C-vinyl derivatives (18-24) shown in Fig. 3, 4-C-(α-hydroxyethyl) derivatives were synthesized (Fig. 5), and the stereoselectivities in reactions used were examined (Table 2). First of all, determination of the configurations of 4-C-(α-hydroxyethyl) groups by the principle shown in Fig. 2 were ascertained by use of (18), (19), (E)-14 and (Z)-14 (Fig. 4). Peracid oxidation of (18) and (19) gave a mixture of the corresponding epoxides in the ratios of 1:14 and 1.2:1, respectively. Reduction of each epoxide with lithium aluminium hydride gave the corresponding diols (26-29) in good yields (route A). Oxidation of (E)-14 and (Z)-14 with osmium tetroxide and N-methylmorpholine-N-oxide gave a 1:4.8 mixture of (27) and (29) and a 1:2 mixture of (26) and (28), respectively (route B). These interrelations were further confirmed by the route C. Peracid oxidation of (E)-14 and (Z)-14 gave the corresponding epoxides in the ratios of 2.3:1 and 1:1.5, respectively. Treatment of the former and the latter epoxides with 2M potassium hydroxide in dimethyl sulfoxide gave reversely a mixture of (26) and (28) and a mixture of (27) and (29), respectively. Thus, the configurations of α-hydroxyethyl groups in (26), (27), (28) and (29) were unambiguously determined to be (R), (S), (S) and (R) respectively. The similar relationships between diols (30-37) and 4-C-vinyl(20-21, 23-24) or 4-C-ethylidene derivatives (15 and 17) were also examined by the routes A and B, and (E)- and (Z)-configurations of (15) and (17) were determined. In the case of (Z)-16, the minor product (38) in the osmium tetroxide oxidation was identical with that obtained by the reduction of (R)-epoxide from (22), whose configuration was deduced on the supposition of a similar stereoselectivity in the epoxidation of (22) and (23), and consequently, the configuration of major product (40) was also determined.

In Table 2, it is characteristic that osmium tetroxide oxidation of 4-C-ethylidene derivatives gave predominantly 4-C-axial derivatives in good yields. The exclusive formation of equatorial-attack products in cases of hexose derivatives (17) indicates a decisive effect of steric hindrance. Thus, the selectivity in the reaction of (Z)-16, was reversed, reflecting the respective presence of two and one axial substituents in α- and β-positions of the olefinic function. Besides, epoxidation with peracids does not usually proceed selectively (Ref. 37), except for cis-epoxidation of cyclohexenols. However, the results in Fig. 4 and Table 2 indicate that equatorial 4-C-vinyl groups in pentose derivatives (18 and 20) and in

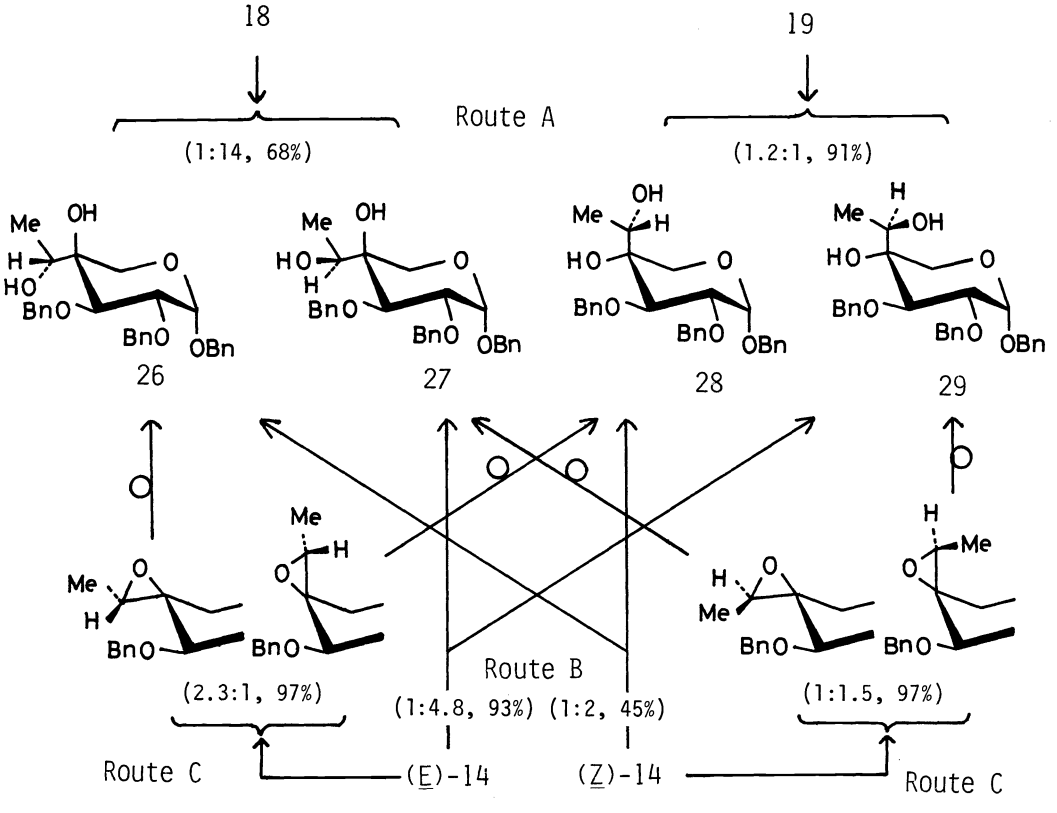


Fig. 4 Configurational determination of 4-C-(α-hydroxyethyl) groups.

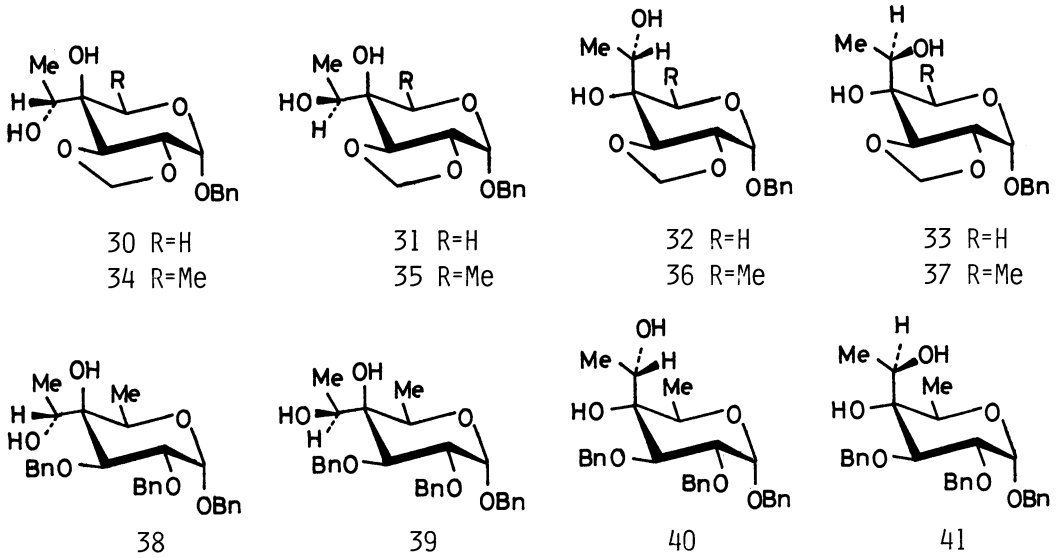


Fig. 5 4-C-(α-Hydroxyethyl) derivatives.

TABLE 2. Stereoselectivities in reactions for the introduction of 4-C-(α-hydroxyethyl) group

substrate (Route B)	4-C-(α-hydroxyethyl) derivs., and ratio of axial/equatorial attack			Yield(%)	substrate (Route A)	3-C-(α-hydroxyethyl) derivs., and ratio of (S)/(R)			Yield(%) Total epoxide(diol)**
(E)-15	(31)	1/7.8	(33)	87	20	(31)	4.5/1	(30)	91 (80, 75)
(Z)-15	(30)	1/17	(32)	89	21	(32)	2/1	(33)*	64 (37, 20)
(E)-17	(35)	0/1	(37)	73	23	(35)	1/2	(34)*	45 (30, 60)
(Z)-17	(34)	0/1	(36)	73	24	(36)	2/1	(37)	59 (86, 87)
(Z)-16	(38)	1/13	(40)	73	22	(39)	1/1.5	(38)	75 (32, 47)

*The ratio of (S) to (R) was determined after conversion into 4-C-(α-hydroxyethyl) derivatives, and others were determined by the separation of epoxides.
**These yields indicate (S) and (R) diols, respectively.

hexose derivatives (22 and 23) gave preferentially (S)- and (R)-epoxides (namely, (S)- and (R)-α-hydroxyethyl derivatives), respectively, but, axial 4-C-vinyl groups gave (S)-epoxides regardless of pentose or hexose derivatives (19,21 and 24). These results will be explained by deductions that the conformation of an equatorial vinyl group shown in (A) of Fig. 6 is preferable in cases of pentosides (R=H) but not hexosides (R=CH_3) and that the conformation of an axial one shown in (B) is commonly preferable by the electrostatic repulsion between electrons of the ring-oxygen and vinyl group.

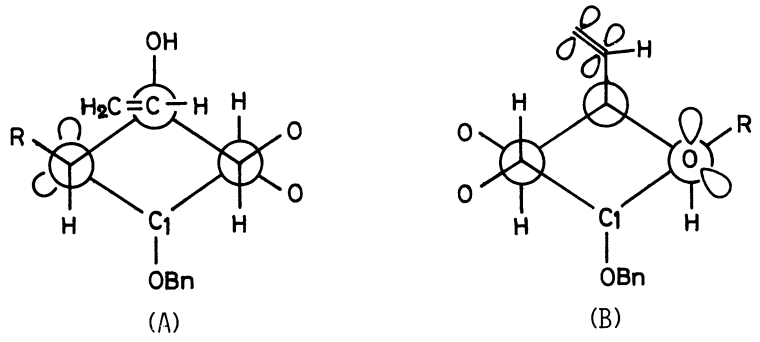
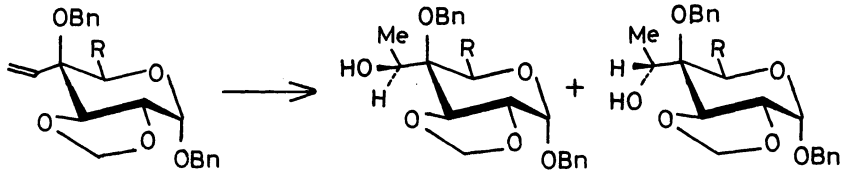


Fig. 6 Possible conformations of 4-C-vinyl groups.

The weak effect of tertiary hydroxyl group in the peracid oxidation of 4-C-vinyl derivatives was noticed in the following experiments (Fig. 7). Conversion of 4-O-benzyl derivatives (42 and 43) of (20) and (23) into the corresponding diols by the route A gave (S)- (44 and 46) and (R)-diols (45 and 47) in the ratios of 1:1 and 1:2, respectively.



42 R=H
43 R=Me

44 R=H
46 R=Me

45 R=H
47 R=Me

Fig. 7

In the next experiment, a simultaneous inversion of the configurations of 4-C and branched α-carbon was examined (Fig. 8). Acetylation of the secondary hydroxyl group of (29) followed by mesylation of tertiary hydroxyl group with methanesulfonyl chloride gave the corresponding diester in 46% yield. Treatment of the diester in dimethyl sulfoxide with sodium methoxide at 80°C for 18 hours gave 4'-O-methyl derivative of (27), which was also prepared by the partial O-methylation of (27), in 82% yield. In a similar manner, (28) was converted into 4'-O-methyl derivative of (26).

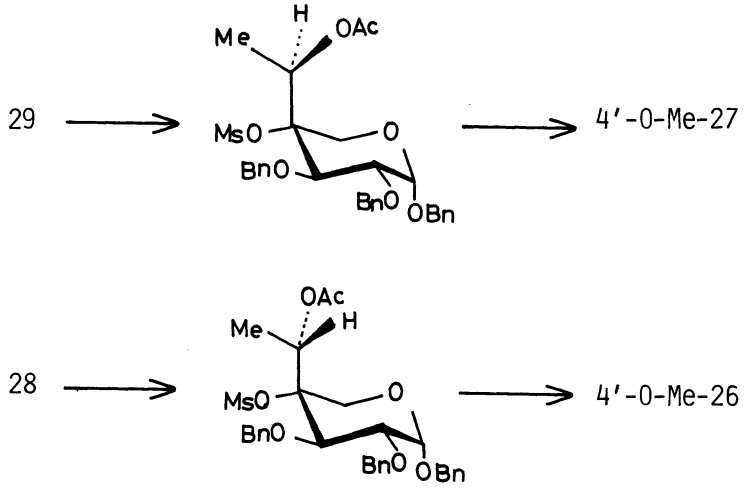


Fig. 8 Simultaneous inversion of the configurations of C-4 and branching α-carbon of 4-C-(α-hydroxyethyl) derivatives.

Synthesis of (1) and (2)

Compound (1) can be synthesized from (4) by successive conversions; i) introduction of an equatorial 4-C-[(S)-α-hydroxyethyl] group, ii) selective methylation of the hydroxyl group in the branch, and iii) conversion of the obtained glycoside into the corresponding methyl aldonate. Compounds (44) or (45) obtained above are the suitable intermediates for ii). However, their configurations are ambiguous. The configurations of (44) and (45) were deduced from the analogy of the rotational values of (31) and (30),respectively. Compounds (44) and (45) were converted into 4-C-[(S)-α-methoxyethyl]- (48) and 4-C-[(R)-α-methoxyethyl] -2,3-O-methylene-α-L-arabinose (49) in 60 and 69% overall yields, respectively, by O-methylation with sodium hydride and methyl iodide followed hydrogenolysis in the presence of palladium-charcoal (Fig. 9). Oxidation of (48) and (49) in 85% aqueous methanol with bromine, treatment of the reaction mixture with silver oxide, and separation of the products by preparative t.l.c. gave respectively (1) and the corresponding D-gluco isomer (50) in low yields, together with the dimethyl acetals (51 and 52) of the parent free sugars (48 and 49).

As was expected, rotational value ($[\alpha]_D$-26.1°) and ^{1}H n.m.r. parameters of (1) were consistent with those reported ($[\alpha]_D$-28°)(Ref. 38).

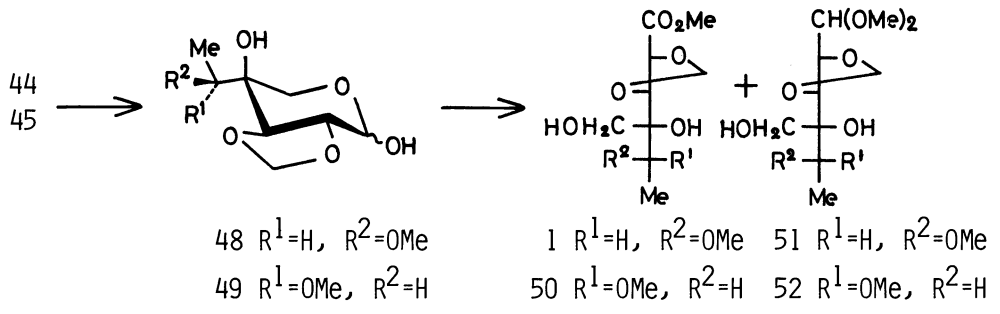


Fig. 9 Synthesis of (1) and its 4-epimer.

On the configuration of methyl eurekanate, it was postulated that the structure of the characteristic 2,3-O-methylene ring of the trans-diequatorial diols is the same as (1), and D-galacto (57) and D-gluco isomers (58) were synthesized as follows (Fig. 10). Oxidation of (34) or (35) with N-chlorosuccinimide and dimethyl sulfide (Ref. 39) gave benzyl 4-C-acetyl-6-deoxy-2,3-O-methylene-D-galactopyranoside (53) in a good yield. This compound was also obtained from (25) by treatment with mercuric oxide and mercuric chloride in aqueous methanol in 50% yield. Besides, the gluco isomer (54) of (53) was obtained from (36) or (37) by a similar oxidation. Hydrogenation of (53) and (54) in the presence of palladium-charcoal gave the free sugars (55 and 56) each in 96% yield. Oxidation of (55) and (56) with bromine and barium carbonate in water followed by deionization in methanol with ion-exchanger (IR 120) gave the corresponding methyl aldonates (57); $[\alpha]_D$ -52.1° and (58); $[\alpha]_D$ -39.8°) in 37% and 36% yields, respectively. Comparison of ^{1}H and ^{13}C n.m.r. parameters (Table 3) of (57) and (58) with those of methyl eurekanate ($[\alpha]_D$ -55.2°) indicated fortunately that natural methyl eurekanate and (57) of D-galacto configuration are identical (Ref. 40). In conclusion, it can be said that two carbon branches in naturally occurring branched-chain sugars known so far have an equatorial orientation in pyranoses such as in aldgarose, pillarose, and γ-octose and that (1) and (2) seem to originate from such branched-chain sugars.

TABLE 3. Comparison of NMR parameters of (57) and (58) with those of methyl eurekanate reported

positions	^{1}H n.m.r.(δ, $CDCl_3$)			^{13}C n.m.r.(ppm, $CHCl_3$)		
	reported	(57)	(58)	reported	(57)	(58)
1	3.78(s)	3.79(s)	3.76(s)	52.8	52.8	52.5
2	-	-	-	171.7	171.6	171.1
3	4.68(d) J=6	4.69(d) J=5.8	4.68(d) J=5.4	81.5	81.5	80.2
4	4.66(d)	4.67(d)	4.38(d)	74.6	74.6	73.8
5	-	-	-	84.2	84.2	83.8
6	4.18(q) J=6.5	4.16(q) J=6.6	4.14(q) J=6.6	68.4	68.4	69.9
7	1.03(d)	1.04(d)	1.22(d)	17.4	17.3	17.7
8	5.10(s) 4.89(s)	5.11(s) 4.90(s)	5.24(s) 5.06(s)	95.9	95.9	95.9
9	-	-	-	207.2	207.1	209.5
10	2.28(s)	2.29(s)	2.40(s)	26.1	26.1	27.1

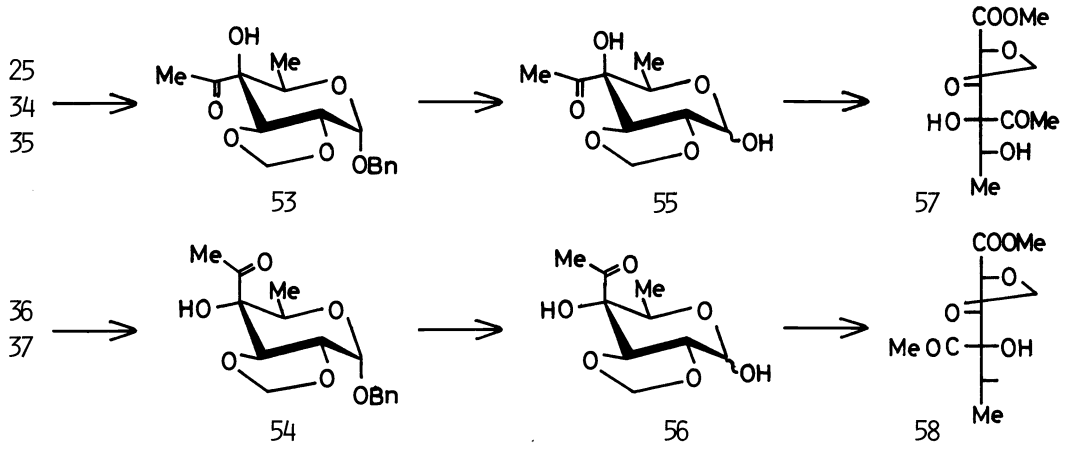
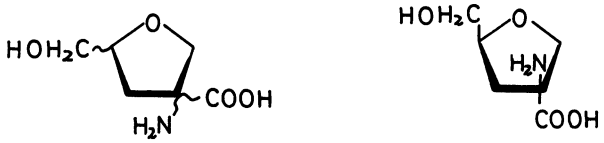


Fig. 10 Synthesis of methyl eurekanate.

SYNTHESES OF BRANCHED-CHAIN SUGAR DERIVATIVES

Synthesis of (2S,4S)-4-amino-2-(hydroxymethyl)tetrahydrofuran-4-carboxylic acid

An optically active 4-amino-2-(hydroxymethyl)tetrahydrofuran-4-carboxylic acid (59) was isolated first in 1974 from the acid hydrolysate of diabetic urine by Mizuhara et al. (Ref. 41), and its planar structure was determined by ^{1}H and ^{13}C n.m.r. data (Ref. 42). Although the interest in the physiological meaning of this unique amino acid (59) flagged with the finding that it was also formed from D-hexose and urea under the same conditions used for the acid hydrolysis, indicating (59) to be an artefact, a different question concerning the path of its formation arose. In the present work all four possible stereoisomers of (59) were synthesized from D-ribose and D-glucose and the configuration of (59) isolated from the urine was determined to be (2S,4S) (Fig. 11) as reported previously in brief (Ref. 43).



59 (2S,4S)-59

Fig. 11

Among a few synthetic methods generally used for α-alkyl-α-amino acids the application of a modified Bucherer reaction (Ref. 44) to (2R)-hydroxymethyl-4-oxotetrahydrofuran derivatives (74 and 80) was chosen. This method was used successfully for preparing the corresponding amino acid derivative of pentofuranos-3-ulose (Ref. 45). It was planned to prepare the two enantiomers (74 and 80) by changing the cyclization method properly via a common acyclic intermediate such as (69) or (71), which can be derived from 5-O-benzyl-3-deoxy-2-O-methyl-D-glycero-pent-2-enofuranose (61). This compound was prepared by two different routes from D-glucose and D-ribose, respectively. In the first route methyl 5-O-benzyl-2,3-di-O-methyl-D-xylofuranoside (Ref. 46) prepared as an anomeric mixture from D-glucose in 8 steps was hydrolyzed with 0.05 M sulfuric acid to give 5-O-benzyl-2,3-di-O-methyl-D-xylofuranose (60) in 90% yield. Alkaline β-elimination reaction of (60) using calcium hydroxide (Ref. 47) gave 2-enofuranose derivative (61) in 76% yield, whose structure was ascertained by i.r. absorption at 1690 cm^{-1}, n.m.r. signal at δ 4.68 (doublet) due to the enol ether olefinic proton, and further by the succeeding chemical conversion. The second and shorter route started by simultaneous isopropylidenation and glycosidation of D-ribose followed by benzylation with sodium hydride and benzyl chloride in N,N-dimethylformamide to give methyl-5-O-benzyl-2,3-O-isopropylidene-D-ribofuranoside (62) in a good yield. The ratio of α- to β-anomers was about 1:7. Acid hydrolysis of (62) in 0.7% aqueous hydrochloric acid at 100°C for 2 h gave de-O-isopropylidenated derivative (63) in 86% yield together with small amount of 5-O-benzyl-D-ribose, which was reconverted into (63) by treatment with methanol containing 0.2% sulfuric acid. Usual methylation of (63) with sodium hydride and methyl iodide afforded the corresponding 2,3-di-O-methyl derivative (64) in 54% yield, which was then hydrolyzed with

0.05M sulfuric acid under reflux for 5 h to give 5-O-benzyl-2,3-di-O-methyl-D-ribose (65) in 90% yield. The same β-elimination reaction of (65) afforded (61) also in a good yield.

At first, conversion of (61) into a furan derivative keeping the enol ether function was attempted. Sodium borohydride reduction of (61) gave the corresponding pent-2-enitol derivative (66) in quantitative yield. The structure was confirmed by disappearance of the anomeric protons in its n.m.r. spectrum and by i.r. absorption at 1670 cm^{-1}. Acetylation of (66) with acetic anhydride in pyridine afforded unexpectedly a mixture of 1-O-acetyl derivative (67) and (E)-1-acetoxy-5-benzyloxy-3-pentene-2-one (68). The structure of (67) was deduced the intensity of acetyl signal and the down-field shift of methylene protons at C-1 in the n.m.r. spectrum, and that of (68) from the i.r. absorption at 1740 cm^{-1} (acetyl), and 1690 and 1640 cm^{-1} (α,β-unsatured ketone) as well as the large coupling constant (16 Hz) between two olefinic protons. Aiming at a intramolecular cyclization, selective 1-O-tosylation of (66) with tolysulfonyl chloride in pyridine was performed but failed because of rapid conversion into 5-O-benzyl-3-deoxy-D-glycero-2-pentulose (69), which was also obtained directly from (61) by sodium borohydride reduction followed by treatment with weak acidic ion-exchange resin, in 45% yield together with 3-penten-2-one derivative (70, ca. 10% yield).The structure of (69) could be ascertained by i.r. absorption at 1720 cm^{-1} and C-3 deoxymethylene signals at δ 2.45 and 2.68 in the n.m.r. spectrum. Selective 1-O-tosylation again and direct dehydrolytic cyclization of (69) at high temperature and by orthophosphoric acid failed due to the instability of (69). Thus it became clear that cyclization of the acyclic compound having an enol ether or carbonyl function was not possible.

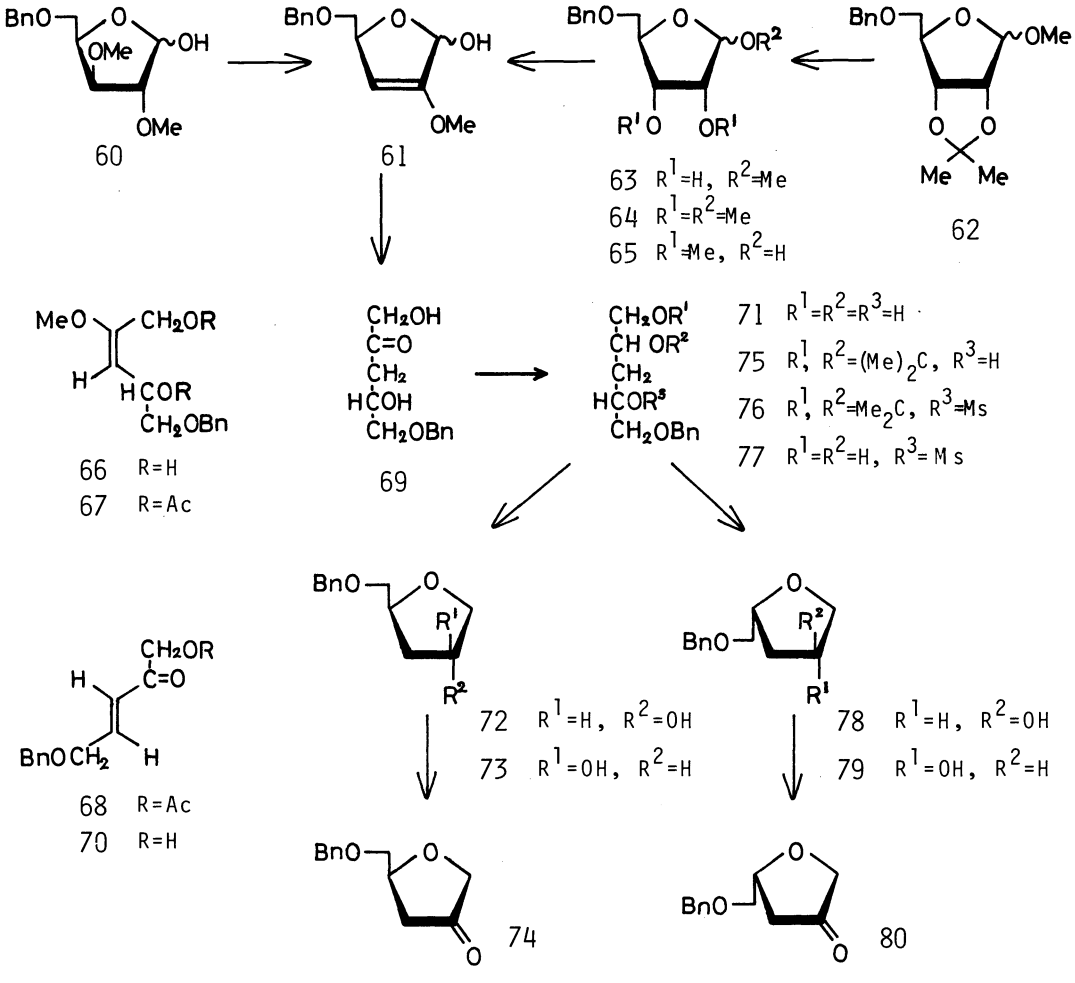


Fig. 12 Synthesis of (2S)- and (2R)-(benzyloxy)methyl-4-oxotetrahydrofuran as key intermediates.

The cyclization was then attempted after the reduction of the carbonyl group in (69). Sodium borohydride reduction of (69) gave a epimeric mixture of 3-deoxypentitol derivatives (71) in good yield, which was characterized as a 1,2,4-tri-O-acetyl-derivative mixture. For preparation of (74) selective 1-O-tosylation of (71) with tosyl chloride in pyridine at -15°C followed by addition of triethylamine gave cyclized compounds (72 and 73), which were separated by preparative t.l.c. in 74% and 18% yields, respectively. In the latter cyclization reaction the complete formation of (72) took 3 days after the addition of triethylamine, while (73) was formed quickly. The intermediate 1-O-tosyl derivative mixture was observed on t.l.c. butits isolation in a pure state could not be done, presumably due to its easy conversion to (72) and (73). Then the mixture of (72) and (73) was oxidized with dimethyl sulfoxide-trifluoroacetic anhydride to give the 4-oxo derivative (74) in 86% yield.

On the other hand, the enantiomer of (74) was prepared also from (71) in the following manner. Treatment of (71) with acetone and anhydrous cupric sulfate afforded 1,2-O-isopropylidene derivative mixture (75) in 81% yield, and its 4-O-mesyl derivative mixture (76) was obtained in the usual manner in quantitative yield. The down-field shift of H_4 in the n.m.r. spectrum of (76) confirmed the position of mesyl as well as isopropylidene groups. Hydrolysis of (76) gave de-O-isopropylidenated product (77) which was cyclized with sodium methoxide (accompanied by inversion at C-4) to give a mixture of (78) and (79). The mixture was successfully converted into the corresponding ketone (80), the enantiomer of (74), in the same manner as described above.

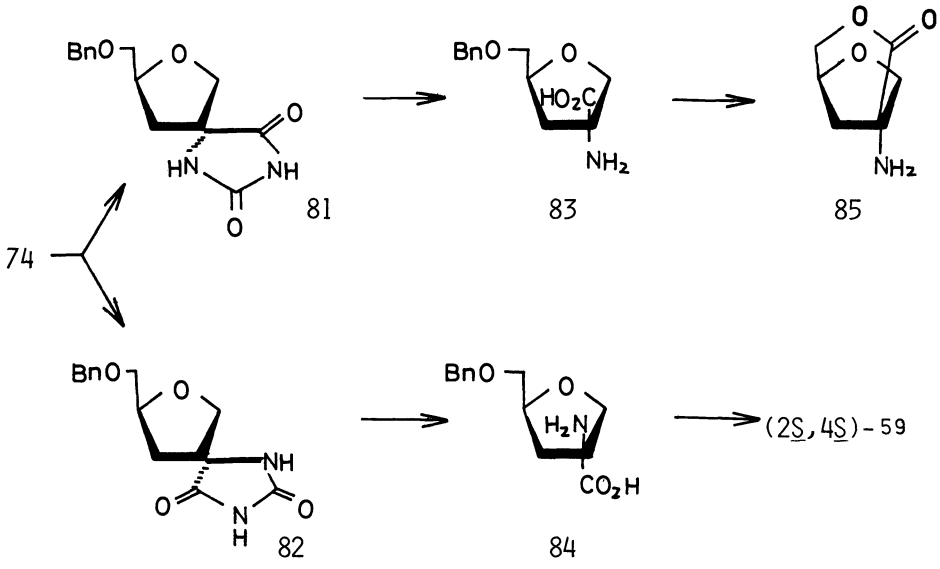


Fig. 13 Synthesis of (2S,4S)-59

The (2S)-4-oxo-derivative (74) was treated with potassium cyanide and ammonium carbonate in methanol at 50°C under 50 atm pressure of carbon dioxide (Ref. 45) to afford two epimers (81 and 82) of a hydantoin derivative in the ratio of 6:1 in 53% total yield. These epimers, separated by preparative t.l.c. show typical carbonyl absorption of hydantoin at 1740 and 1780 cm^{-1} in their i.r. spectra. Although a little difference was observed between n.m.r. data, a definite conclusion on the stereochemistry of the spiro-carbon could not be drawn. However, the succeeding chemical conversion ascertained the structure. Both epimers hydrolyzed in barium hydroxide solution under reflux for 1 day gave the corresponding amino acid derivatives (83 and 84) in 68% and 65% yield, respectively. Hydrogenolysis of (83) and (84) in methanol in the presence of palladium-carbon and acetic acid gave an aminolactone derivative (85) and an amino acid [(2S,4S)-59] both in quantitative yield. The former shows a six-membered lactone absorption at 1740 cm^{-1} in the i.r. spectrum. In the same manner the enantiomers of (85) and (2S,4S)-59 were synthesized from the (2R)-4-oxo-derivative (80). As shown in Table 4, (2S,4S)-59 was identical with the amino acid isolated from the acid hydrolysate of diabetic urine in most respects including n.m.r. spectrum and behaviour on liquid chromatography, but not in the magnitude of the optical rotation value.

The differences in the absolute values of specific rotation between enantiomers of (59) and (85) may imply the presence of S_N1 mechanism to some extent in the S_N2 cyclization of (77). It is not known whether (85) exists in the acid hydrolysate of diabetic urine, probably due to much different behaviour of (85) from (59) on liquid chromatography. The evidence of this point will be an important clue in the elucidation of the formation pathway of (59).

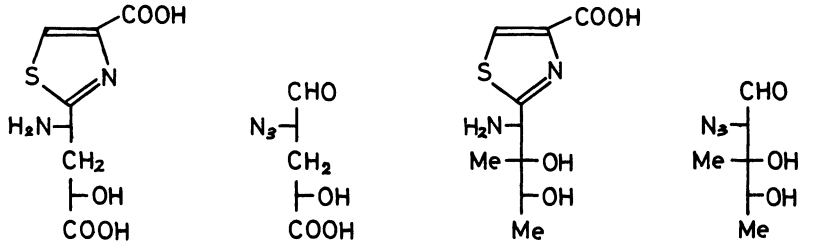
TABLE 4. Comparison of physical properties

Compound	(2S,4S)-59	(2R,4R)-59	(2S,4R)-85	(2R,4S)-85	Reported*
Mp, °C(dec.)	250-253	252-255	180-185	182-185	251-255
$[\alpha]_D$(solvent)	+35°(H_2O)	-28°(H_2O)	+18°(MeOH)	-21°(MeOH)	+38°(H_2O)
$\nu_{C=O}$ cm^{-1}	1645	1650	1735	1740	1640

* for the amino acid isolated from urine.

Synthesis of optically active 2-substituted-thiazole-4-carboxylic acids

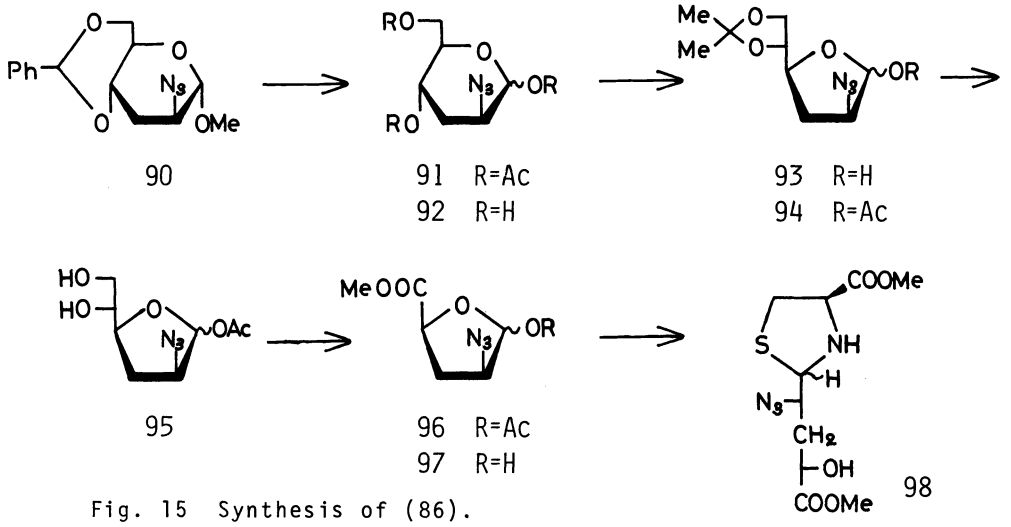
Recently, several thiazole-4-carboxylic acids having an optically active substituent at C-2 have been found as components of such polypeptide antibiotics as thiostrepton (Ref. 48), althiomycin (Ref. 49), micrococcin A (Ref. 50), and nosiheptide (ref. 51). The biosynthetic pathway of the thiazole-4-carboxylic acid unit from L-cysteine in peptides via the ring-formation into Δ^2-thiazoline was actually applied to the synthesis of the partial structure of bleomycin B_2 (Ref. 52). Besides, it is well known in carbohydrate chemistry that aldoses react with cysteine to give thiazolidine derivatives. Therefore, we have examined at first the direct oxidation of thiazolidines to thiazols with manganese dioxide, and as the challenging problems, adopted two optically active thiazole-4-carboxylic acids [86 and 87 (thiostreptin)] found in nosiheptide and thiostrepton (Fig. 14). It was considered that 2-azido-2,3-dideoxy-D-threo penturonic acid (88) and 2-azido-2,5-dideoxy-3-C-methyl-D-arabino-pentose (89) are key intermediates for synthesis of (86) and (87) respectively.



86 88 87 89

Fig. 14

Synthesis of (86). The protecting groups of methyl 2-azido-4,6-O-benzylidene-2,3-dideoxy- -D-arabino-hexopyranoside (90, Ref. 53) were removed via the corresponding acetolysis product (91) to give (92) in 67% yield. The usual acetonation of (92) gave the 5,6-O-isopropylidene derivative (93) in 88% yield. Acetylation of (93) to (94) followed by acid hydrolysis gave an α, β-mixture of de-O-isopropylidenated product (95) in 90% yield. Compound (95) was



90

91 R=Ac
92 R=H

93 R=H
94 R=Ac

95

96 R=Ac
97 R=H

98

Fig. 15 Synthesis of (86).

converted into methyl 1-O-acetyl-2-azido-2,3-dideoxy-D-threo-pentofuranuronate (96) by successive reactions (periodate oxidation, permanganate oxidation, and esterification with diazomethane) in 55% overall yield. De-O-acetylation of (96) in methanol with sodium methoxide gave (97), methyl ester of (88), quantitatively. Condensation of (97) with methyl L-cysteinate proceeded smoothly to give the corresponding thiazolidine derivative (98) in 60% yield (Ref. 54), and the structure was confirmed by n.m.r. spectra of derivatives. Analogous derivatives from (92) and (93) were also obtained. Conversion of (98) into (86) is under investigation.

Attempted synthesis of (89). Reaction of methyl 2,3-anhydro-6-deoxy-α-D-allopyranoside (99, Ref. 23) with sodium azide gave two products, which were separated on a silica gel column after acetonation to give methyl 3-azido-3,6-dideoxy-α-D-glucopyranoside (100) and methyl 2-azido-2,6-dideoxy-3,4-O-isopropylidene-α-D-altropyranoside (101) in 60% and 27% yields, respectively. The next step is the introduction of axial 4-C-methyl group into (100) via the corresponding 4-ulose. However, the selective protection of the 2-hydroxyl group of (100) with the benzoyl group (102, 80%) followed by oxidation with dimethyl sulfoxide-trifluoroacetic anhydride gave the corresponding enolone (103) in 92% yield (Ref. 55). Therefore, (100) was hydrolyzed to (104) followed by acetonation with dimethoxypropane to give the corresponding 1,2-O-isopropylidene derivative (105) in 87% yield. Oxidation of (105) with dimethyl sulfoxide-trifluoroacetic anhydride was unexpectedly accompanied by the epimerization of the 3-azido group to give 3-azido-3,6-dideoxy-1,2-O-isopropylidene-α-D-ribo-hexopyranos-4-ulose (106) in 87% yield. The configuration of (106) was confirmed from the n.m.r. spectrum of 1,2,3-tri-O-acetyl-3-azido-3,6-dideoxy-α,β-D-allopyranose (107) obtained by reduction of (106) with sodium borohydride followed by acetolysis. The reason for epimerization of the equatorial 3-azido group is attributed to a twist-boat conformation ($J_{1,2}$= 5.0, $J_{2,3}$=5.5, $J_{3,4}$=7.0 Hz) of (105) or the expected 4-ulose, caused by the formation of 1,2-O-isopropylidene ring. Because it became clear that a reasonable introduction of C-methyl group into the pyranose ring of (100) is impossible, other pathways via a ketonic thiazole derivative (108) and a pentofuranosid-3-ulose (109) are under investigation.

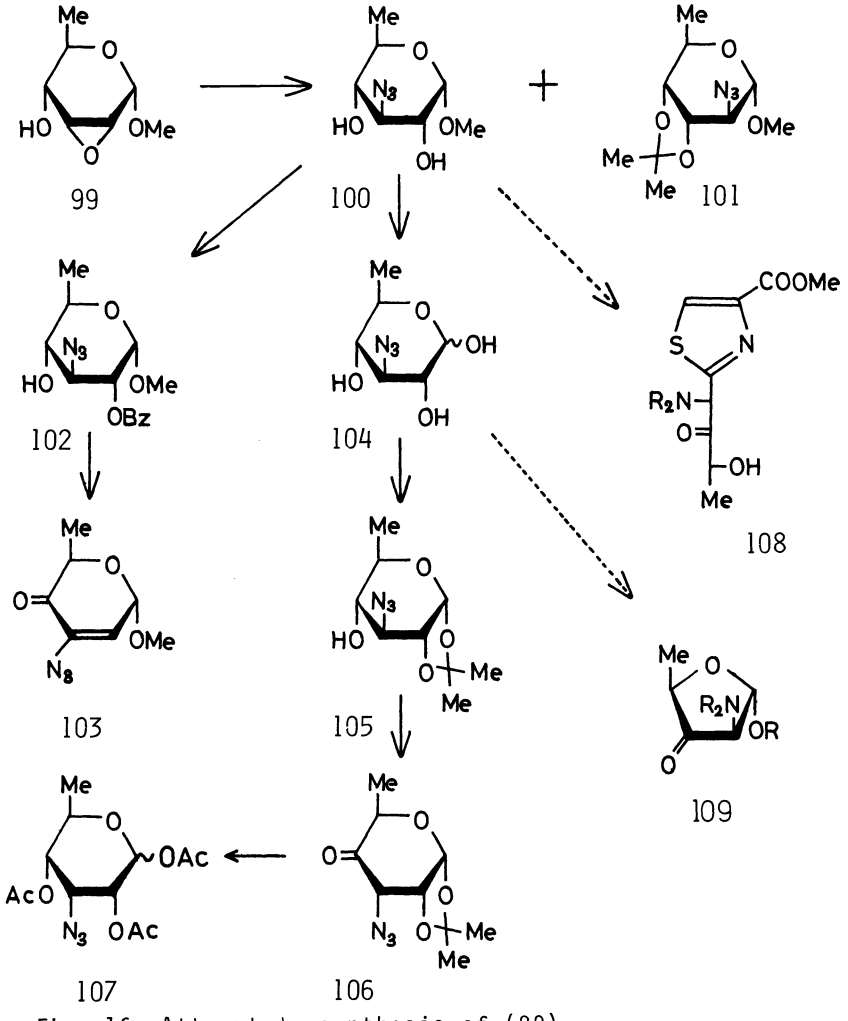


Fig. 16 Attempted synthesis of (89).

The pioneering work on the chemistry of branched-chain sugars made easy the synthesis of those having a one-carbon branch, unless there are strict requirements for high stereoselectivity and yield. In connection with the synthesis of (1) having an optically active two-carbon branch, the possibilities of configurational control of not only the tertiary carbon but also the branching α- carbon by the proper use of three routes shown in Fig. 2 were indicated in the present work. As an addition to this work, the configuration of (2) could be determined by synthesis. Synthesis of four diastereomers of (59) illustrates that synthesis of optically active compounds having two asymmetric carbons is not too difficult. However, the results in the attempted synthesis of (87) indicate the shortage of knowledge on 4-uloses, in spite of their important role in biosynthesis of various sugars. The use of carbohydrates as sources for asymmetric synthesis of optically active compounds will become common in organic chemistry. Various other reactions will be applied to carbohydrates as organic substrates, and their selectivities will be disclosed.

Acknowledgements - The author is grateful to collaborators whose names appear in the list of references. Part of the present work was carried out with a Grant-in-Aid (no. 327023) from the Ministry of Education.

REFERENCES

1. H. Paulsen, Pure & Appl. Chem., 49, 1169-1186 (1977).
2. S. Hanessian and G. Rancourt, Pure & Appl. Chem., 49, 1201-1214 (1977).
3. J.P.H. Verheyden, A.C. Richardson, R.S. Bhatt, B.D. Grant, W.L. Fitch, and J.G. Moffatt, Pure & Appl. Chem., 50, 1363-1383 (1978).
4. S. Hanessian, Accounts of Chem. Res., 12, 159-165 (1979).
5. E.C. Ashby and J.T. Laemmle, Chem. Rev., 75, 521-546 (1975).
6. E.C. Ashby and S.A. Noding, J. Org. Chem., 44, 4371-4377 (1979).
7. M.-H. Rei, J. Org. Chem., 44, 2760-2767 (1979).
8. K. Sato and J. Yoshimura, Carbohydr. Res., 73, 75-84 (1979).
9. K. Sato and J. Yoshimura, Bull. Chem. Soc. Jpn., 51, 2116-2121 (1978).
10. K. Sato, K. Koga, H. Hashimoto, and J. Yoshimura, Bull.Chem.Soc.Jpn., 53, 2639-2641(1980).
11. K. Sato, J. Yoshimura, and C. Shin, Bull. Chem. Soc. Jpn., 50, 1191-1194 (1977).
12. A.K. Ganguly, Topics in Antibiotic Chemistry, Vol. 2, P.G. Sammes, Ed., pp.59-98, Wiley, New York (1978).
13. W.D. Ollis, C. Smith, and D.E. Wright, Tetrahedron, 35, 105-127 (1979).
14. M.Funabashi, N. Hong, H. Kodama, and J. Yoshimura, Carbohydr. Res., 67, 139-145 (1978).
15. J. Yoshimura, N. Hong, and K. Sato, Chem. Lett., 1263-1264 (1979).
16. J. Yoshimura, M. Matsuzawa, K. Sato, and Y. Nagasawa, Carbohydr. Res., 76, 67-78 (1979).
17. A.K. Ganguly, O.Z. Sarre, A.T. McPhail, R.W. Miller, J. Chem. Soc. Chem. Commun., 22-24 (1979).
18. A.K. Ganguly, O.Z. Sarre, D. Greeves, and J. Morton, J. Am. Chem. Soc., 97, 1982-1985 (1975).
19. H. Paulsen and H. Redlich, Chem. Ber., 107, 2992-3012 (1974).
20. J.S. Brimacombe, J. Minshall, and C.W. Smith, J. Chem. Soc. Perkin I, 682-686 (1975).
21. H. Paulsen, K. Roden, V. Sinnwell, and W. Koebernic, Chem. Ber., 110, 2146-2149 (1977).
22. D.L. Walker and B. Fraser-Reid, J. Am. Chem. Soc., 97, 6251-6253 (1975).
23. H. Paulsen and V. Sinnwell, Chem. Ber., 111, 869-878.(1978).
24. T. Sivakumaran and J.K.N. Jones, Can. J. Chem., 45, 2493-2500 (1967).
25. P.M. Pojer and S.J. Angyal, Tetrahedron Lett., 3067-3068 (1976).
26. J.S. Brimacombe, A.B. Foster, B.D. Jones, and J.J. Willard, J. Chem. Soc. (C), 2404-2407 (1967).
27. A. Lubineau, A. Thieffry, and A. Veyrières, Carbohydr. Res., 46, 143-148 (1976).
28. J. Yoshimura, K. Sato, and H. Hashimoto, Chem. Lett., 1327-1330 (1977).
29. M. Miljkovic, M. Gligorijević, T. Satoh, D. Glisin, and R.D. Pitcher, J. Org. Chem., 39, 3847-3850 (1974).
30. S. Omura, A. Nakagawa, A. Neszmelyi, S.D. Gero, A.-M. Sepulchre, F. Piriou, and G. Lukacs, J. Am. Chem. Soc., 97, 4001-4009 (1975).
31. P.M. Collins and V.R.N. Munashighe, Carbohydr. Res., 62, 19-26 (1978).
32. K. Sato, M. Matsuzawa, K. Ajisaka, and J. Yoshimura, Bull. Chem. Soc. Jpn., 53, 189-191 (1980).
33. M. Miljkovic, M. Gligorijevic, T. Satoh, and D. Miljkovic, J. Org. Chem., 39, 1379-1384 (1974).
34. W.G. Overend, A.C. White, and N.R. Williams, Carbohydr. Res., 15, 185-195 (1970).
35. B.M. Gough, S.W. Gunner, W.G. Overend, and N.R. Williams, Carbohydr. Res., 14, 173-180 (1970).
36. D. Horton and E.K. Just, Carbohydr. Res., 18, 81-94 (1971).
37. J. Yoshimura, K. Sato, and M. Funabashi, Bull. Chem. Soc. Jpn., 52, 2630-2634 (1979).
38. M. Matuszawa and J. Yoshimura, Carbohydr. Res., 81, C5-C9 (1980).
39. E.J. Corey and C.U. Kim, Tetrahedron Lett., 287-290 (1974).
40. J. Yoshimura and M. Matsuzawa, Carbohydr. Res., 85, to be printed.

41. S. Mizuhara, H. Kodama, S. Ohmori, K. Taketa, and M. Ueda, Physiol. Chem. & Physics, 6, 91-93 (1974).
42. S. Mizuhara, H. Kodama, Y. Ishimoto, M. Shimomura, T. Horita, and S. Ohmori, Physiol. Chem. & Physics, 7, 87-88 (1975).
43. J. Yoshimura, S. Kondo, M. Ihara, and H. Hashimoto, Chem. Lett., 819-820 (1979).
44. H.L. Hoyer and H. Barsch, J. Prakt. Chem., 140-151 (1934).
45. H. Yanagisawa, M. Kinoshita, S. Nakada, and S. Umezawa, Bull. Chem. Soc. Jpn., 43, 246-252 (1970).
46. P. Kovač and M. Patríková, Carbohydr. Res., 19, 249-251 (1971).
47. E.F.L.J. Anet, Carbohydr. Res., 2, 448-460 (1966).
48. B. Anderson, D.C. Hodgkin, and A. Viswamitra, Nature, 225, 233-235 (1970)..
49. H. Sakakibara, H. Naganawa, M. Ohno, K. Maeda, H. Umezawa, J. Antibiotics, 27, 897-899 (1974).
50. J. Walker, J. Chem.Soc., Chem. Commun., 121-122 (1975).
51. H. Depaire, J-P. Thomas, A. Brun, A. Olesker, and G. Lukacs, Tetrahedron Lett., 1403-1406 (1977).
52. D.A. McGowan, O. Jordis, D.K. Minster, S.M. Hecht, J. Am. Chem. Soc., 99, 8078-8079 (1977).
53. K. Kitahara, S. Takahashi, H. Shibata, N. Kurihara, and M. Nakajima, Agr. Biol. Chem., 33, 748-754 (1969).
54. R. Bognar, L. Somogyi, and Z. Gyovgydeak, Ann. Chem., 738, 68-78 (1970).
55. F.W. Lichtenthaler, Pure & Appl. Chem., 50, 1343-1362 (1978).