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THE SYNTHESIS OF METHYL 3-*O*-ETHYL-α-D-GLUCOPYRANOSIDE

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ABSTRACT

Two syntheses of methyl 3-*O*-ethyl-α-D-glucopyranoside (**6**) are described A comparison of the n m r spectra of a series of substituted methyl α-D-glucopyranosides in methyl sulfoxide-d_6 allows the assignment of chemical shifts and coupling constants to the hydroxyl protons in substituted methyl α-D-glucopyranosides

INTRODUCTION

During an investigation of the products obtained by the vinylation of methyl α-D-glucopyranoside[2], methyl 3-*O*-ethyl-α-D-glucopyranoside was required Several syntheses have been described for the homologous methyl 3-*O*-methyl-α-D-glucopyranoside[3–6] and the parent sugar, 3-*O*-ethyl-D-glucose[7,8]

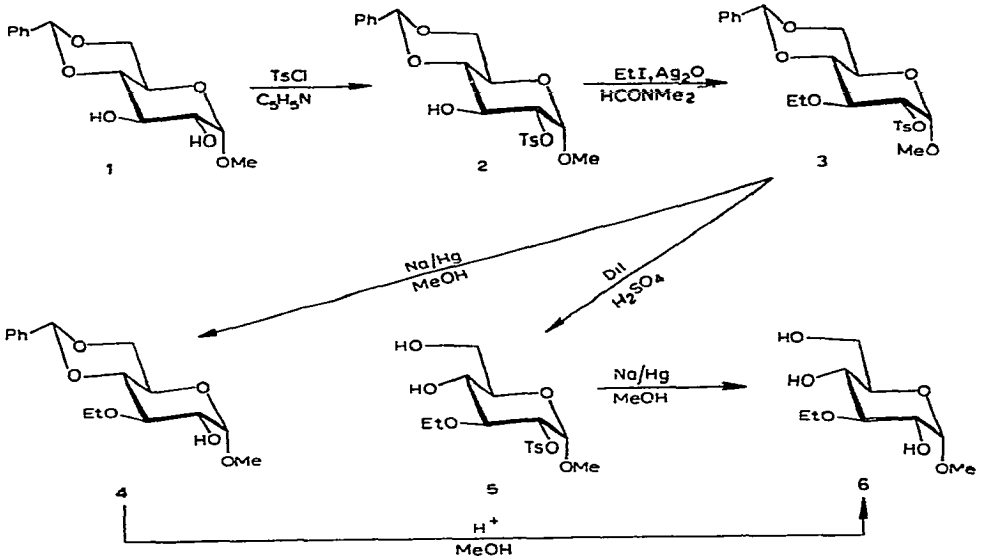
The first of two synthetic methods used in this study was selected because of interest in the relation of n m r spectra and structures of the intermediate methyl D-glucopyranosides The second confirmatory method was chosen for its simplicity

DISCUSSION

Synthesis — In the first approach (see Scheme 1) methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**1**) was *p*-toluenesulfonylated[3 6 9] to yield methyl 4,6-*O*-benzylidene-2-*O*-*p*-tolylsulfonyl-α-D-glucopyranoside (**2**) The n m r spectrum of ester **2** in chloroform-*d* shows the H-2 signal as a multiplet, apparently overlapped by the signals of H-3 and H-5 Confirmation of the structure is provided by the spectrum in methyl sulfoxide-d_6 (see Table I) Ethylation of compound **2** gave methyl 4,6-*O*-benzylidene-3-*O*-ethyl-2-*O*-*p*-tolylsulfonyl-α-D-glucopyranoside (**3**) Ethylation of the 3-hydroxyl group causes the H-3 signal to be moved upfield[10], exposing the quartet due to H-2 These compounds show only two of the three characteristic[11] α-glucopyranoside bands in their i r spectra (see Table II)

Desulfonylation, or removal of the benzylidene group, from **3** was accomplished by established methods[3]. When removal of the benzylidene group was performed before desulfonylation, the intermediate methyl 3-*O*-ethyl-2-*O*-*p*-tolylsulfonyl-α-D-glucopyranoside (**5**) was obtained as a glass that has not yet been crystallized

Other workers have encountered similar difficulties[6]. The specific rotation of the crude product 5, $[\alpha]_D^{22}$ +70° (*c* 0.99, chloroform), is congruous with that reported for its



Scheme 1

TABLE I

N M R SPECTRA OF SUBSTITUTED METHYL α-D-GLUCOPYRANOSIDES IN[a] METHYL SULFOXIDE-d_6

Compound	*Aromatic protons*		*PhCH H-1*		*Ring protons*	*OMe*	*2-OR*	*3-OR′*	*4-OR″*	*6-OR‴*
	Ts	*Ph*								
1[b]		2 54	4 42	5 34d (3 2)	5 57–6 75	6 68	4 86d (4 8)	5 12d (6 6)		
2[c]	2.10d (8 6) 2 52d	2 58	4 45	5 33d (3 5)	5 57–6 92	6 82	CH_3Ar 7 65	4 37d (6 5)		
3[c]	2 13d (8 1) 2 53d	2 62	4 42	5 26d (3 4)	5 57–6 90	6 95	CH_3Ar 7 68	CH_3CH_2- 9 28t (7 0)		
4[b]		2 55	4 36	5 35d (2 2)	5 74–6 74	6 69	4 98d (4 6)	CH_3-CH_2- 8 98t (7 0)		
6[b]				5 46d (2 2)	6 10–6 90	6 71	5 11d (4 8)	CH_3-CH_2 8 98t (7 0)	5 38d (5 5)	5 58t (5 8)
(methyl α-D-glucopyranoside)[b]				5 43d (3 4)	6 15–6 90	6 67	5 18d (4 7)	5 29d (5 2)	5 38d (5 9)	5 56t (5 8)

[a]Chemical shifts given as τ values, *J* values are given in Hz and are enclosed in parentheses, external standard Me_4Si at τ = 10 0 checked before and after each measurement, d, doublet, m, multiplet, q, quartet, t, triplet [b]Spectrum obtained at 100 MHz [c]Spectrum obtained at 60 MHz.

3-*O*-methyl homolog, $[\alpha]_D^{20}$ +79 5° (*c* 1 11, chloroform)[6] Compound **5** was converted into methyl 3-*O*-ethyl-α-D-glucopyranoside (**6**) by treatment with sodium amalgam in methanol

TABLE II

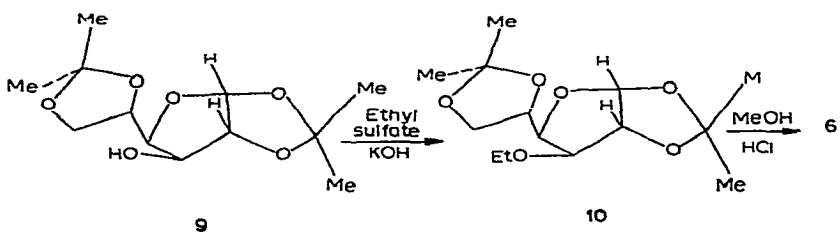
TYPES 1 AND 2a BANDS IN THE INFRARED SPECTRA OF CERTAIN METHYL α-D-GLUCOPYRANOSIDES

Compound	*Solvent or dispersant*	*Type 1* (cm^{-1})	*Type 2a* (cm^{-1})
1	$CHCl_3$	918[a]	845
2	$CHCl_3$	918	838
3	$CHCl_3$	918	840
4	$CHCl_3$	918	837
5	CCl_4	915	835
6	KBr	910	840
8	CCl_4	905	937

[a]Polystyrene showed a band at 1603 cm^{-1} in all cases

When desulfonylation was effected prior to removal of the benzylidene group, crystalline methyl 4,6-*O*-benzylidene-3-*O*-ethyl-α-D-glucopyranoside (**4**) was obtained The i r. spectrum of **4** is in accord with the replacement of a *p*-tolylsulfonyloxy substituent by a hydroxyl group, and the n m r spectrum confirms the substitution pattern (see Table I) Hydrolysis of **4** gave a product (**6**) identical with that obtained from **5** The identity of **6** was confirmed by its hydrolysis[7,8] to 3-*O*-ethyl-D-glucose (**7**)

In the second synthetic method (see Scheme 2), 3-*O*-ethyl-1,2 5,6-di-*O*-isopropylidene-α-D-glucofuranose (**10**), a known compound[7,8], was treated with methanolic hydrochloric acid to yield **6**, identical with methyl 3-*O*-ethyl-α-D-glucopyranoside prepared by the first method

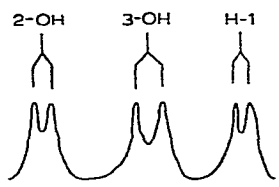


9 10

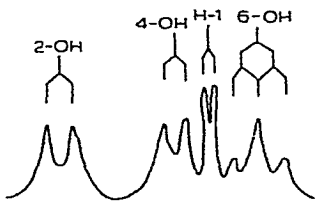
Scheme 2

The n m r. spectra in methyl sulfoxide-d_6 — The usefulness of highly purified and neutral solvents for the detection of vicinal H-O-C-H splittings has been recorded in a number of publications[12–22] Chapman and King have shown that primary, secondary, and tertiary hydroxyl protons can be easily and conclusively differentiated by n m.r. when methyl sulfoxide-d_6 is used as the solvent[16] Variance in the coupling constants of different alcohols has been recorded[16–22], and it is likely that the Karplus

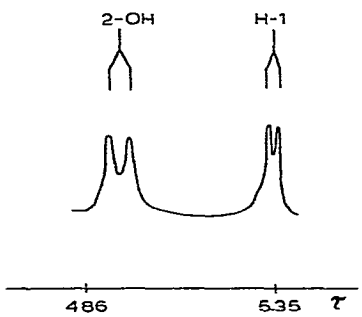
equation[23] should hold qualitatively for the H-O-C-H system[18,21] The advantage of this solvent for n m r. studies on saccharides has been utilized by Casu *et al.*[17,19,21], who have been able to assign, conclusively, the 1-OH, H-1, and 6-OH protons for α-D-glucopyranose, and assign tentatively, the 2-OH, 3-OH, and 4-OH protons for methyl α-D-glucopyranoside The 2-OH proton was assigned the largest coupling constant on the assumption[21] that "this hydroxyl would be most affected by the changes in the stereochemistry at C-1" The 3-OH and 4-OH protons have been assigned on the basis of Perlin's work[22] Perlin reported that double-resonance experiments confirmed these assignments for α-D-glucopyranose, that is, the signals of the 1-OH, C-1, 4-OH, 3-OH, 2-OH, and 6-OH protons appear at progressively higher field Based on these assignments, the results of the present investigation suggest that, proceeding from α-D-glucose to the α-D-glucopyranoside, a change in the order of the 2-OH and 4-OH signals occurs (see Table I) Perlin and Casu and co-workers have shown that analysis of the hydroxyl region of n m r spectra of saccharides gives valuable information concerning the substitution patterns of the sugars The present investigation extends this approach



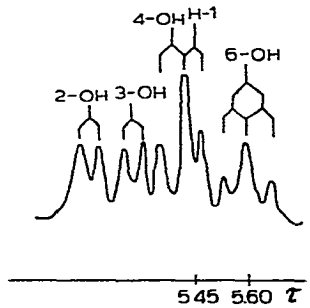
Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (1)



Methyl 3-*O*-ethyl-α-D-glucopyranoside



Methyl 4,6-*O*-benzylidene-3-*O*-ethyl-α-D-glucopyranoside (4)



Methyl α-D-glucopyranoside

Fig 1a N m r spectra of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (1) and methyl 4,6-*O*-benzylidene-3-*O*-ethyl-α-D-glucopyranoside (4) in methyl sulfoxide-d_6 at 100 HMz

Fig 1b N m r spectra of methyl 3-*O*-ethyl-α-D-glucopyranoside (6) and methyl α-D-glucopyranoside in methyl sulfoxide-d_6 at 100 MHz

A comparison of the n.m r spectra of compounds **1**, **4**, and **6** (Figs 1a and 1b) leads to the assignments indicated for the hydroxyl protons Although these assignments are not unequivocal, it seems unlikely that both the line-position and coupling constant of the 2-OH would shift in compounds **4** and **6** Inspection of Corey–Pauling and Buchi–Dreiding models revealed that the environment of the 2-OH is very similar in these two compounds. Although the precise spatial position of the 1-OMe group cannot be thus determined, the regular effect of the axial O-1 atom on the H-3 and H-5 axial protons in α-D-glucopyranosides[10] indicates that an electron pair on this oxygen atom is so oriented as to be approximately equidistant between the two, and, therefore, the methoxyl group may also have a favored orientation The effect of an oriented 1-OMe group would be to limit the environment of the 2-OH group Positioning of a 3-OEt group as in compounds **4** and **6** would further limit the environment of the 2-OH group, and a very obvious decrease in the H-1–H-2 coupling constant for compounds **4** and **6** can be seen The assignments for the hydroxyl groups of methyl α-D-glucopyranoside (see Fig 1b) are consistent with the above pattern The i r spectra of these compounds have the same characteristics in the 3600–3400 cm^{-1} region as have been reported previously[17 19 21]

EXPERIMENTAL

General — Melting points are uncorrected T l c was performed on silica gel G (E Merck, Germany) with benzene–ethanol or benzene–butyl alcohol mixtures The plates were developed by spraying the dried chromatogram with a 10% (w/v) solution of phosphomolybdic acid, followed by heating for 5 min at *ca* 100°. I r spectra were recorded with a Perkin–Elmer Infracord spectrometer, model 137, and optical rotations were measured with a Bendix Automatic polarimeter or a Rudolph polarimeter Model 80 N m r spectra were recorded with Varian Associates A-60 and HA-100 spectrometers (60 and 100 MHz), with tetramethylsilane (τ = 10 00) as the internal or external standard Methyl sulfoxide-d_6 and chloroform-*d* were obtained from Merck, Sharp and Dohme, Ltd , Canada, and were used without purification Most of the samples for n m r studies were degassed The assignment of all hydroxyl peaks was confirmed by deuterium oxide exchange Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, New York

Methyl 4,6-O-benzylidene-α-D-glucopyranoside (**1**) — The preparation of this compound has been described[24], m p 161°, $[\alpha]_D^{25}$ +95° (*c* 1, ethanol)

Methyl 4,6-O-benzylidene-2-O-p-tolylsulfonyl-α-D-glucopyranoside (**2**) — This compound was prepared by the method of Bolliger and Prins[3], m p 153–154°, $[\alpha]_D^{15}$ +61° (*c* 2 75, chloroform) Its i r spectrum showed $\nu_{max}^{CHCl_3}$ 3600 (OH), 1370, 1145 cm^{-1} (sulfonic ester), and other characteristic bands given in Table II

Methyl 4,6-O-benzylidene-3-O-ethyl-2-O-p-tolylsulfonyl-α-D-glucopyranoside (**3**) — A solution containing 50 ml of *N*,*N*-dimethylformamide, 2 0 g (4 6 mmoles) of **2**, and 2.0 ml (25 mmoles) of ethyl iodide was stirred with 4 2 g (18 mmoles) of silver oxide for 28 h at room temperature The mixture was filtered and the filtrate evaporated to dryness The crude product, yield 1 4 g (66%), was recrystallized to

TABLE III

N.M R SPECTRA OF SUBSTITUTED METHYL α D-GLUCOPYRANOSIDES IN CHLOROFORM-*d* OR PYRIDINE[a]

Compound	*Aromatic protons*		*Benzylic proton*	*H-1*	*H-2*	*H-3*	*H 4, H-5, H 6e, H-6a*	*1-OMe*	*2-OR*	*2-OR'*
	Ts	*Ph*								
2[b]	1 98d (J = 8 4) 2 51d	2 46	4 38	5 03d ($J_{1,2}$ = 3 4)	5 52m	5 61–6 60	5 61–6 60	6 57	CH_3Ar, 7 50	7 37
3[b]	1.98d (J = 8 5) 2 53d	2 50	4 41	5 00d ($J_{2,3}$ = 3 9)	5 57q ($J_{2,3}$ = 8 8)	5,80–6 70	5,80–6 70	6 56	CH_3Ar, 7 54	CH_3CH_2, 9 03t (J = 7)
8[b]	2,03d (J = 8 4) 2 56d 2.24d (J = 8 2) 2 95d	2 58	4 62	4 88d ($J_{1,2}$ = 3 9)	5 55q ($J_{2,3}$ = 9 6)	4 77t ($J_{3,4}$ ~ 9 8) ($J_{2,3}$ ~ 9 8)	5 60–6 50	6 56	CH_3Ar, 7 52 or 7 71	7 52 or 7 71
1[c]		3 03	4 88	5 59d ($J_{1,2}$ = 3 5)	6 10–6 45	6 10–6 45	6 50–6 70	7 27	3 68	3 68

[a]All spectra obtained at 60 MHz, chemical shifts given as τ values, J values are given in Hz and are enclosed in parentheses, d, doublet, m, multiplet, q, quartet; t, triplet [b]Spectrum obtained in chloroform *d* [c]Spectrum obtained in pyridine, external standard Me_4Si at τ = 10 0 checked before and after each measurement

constant rotation from ether containing a few drops of petroleum ether (b p 40–60°), m p 108–109°, $[\alpha]_D^{22}$ +45° (*c* 1, chloroform) On t l c. with 49.1 butyl alcohol-benzene, the product showed one spot having an R_F value much greater than that of **2** The i r. spectrum showed $\nu_{max}^{CHCl_3}$ 1370 and 1160 cm^{-1} (sulfonic ester), but no OH absorption at 3600 cm^{-1} (see Table II)

Anal Calc for $C_{23}H_{28}O_8S$ C, 59 48; H, 6 03, S, 6 90 Found C, 59 79; H, 6 14; S, 6 92

Methyl 4,6-O-benzylidene-3-O-ethyl-α-D-glucopyranoside (**4**) — To a stirred solution of 25 ml of methanol containing 500 mg (1 1 mmoles) of **3** was added, in five equal portions, 20 g of 2 5% sodium amalgam during 4 h. The solution was decanted from the mercury, mixed with water, and rendered neutral with carbon dioxide After evaporation of the aqueous methanol, the residue was extracted with chloroform The extract was washed with water, dried (sodium sulfate), and evaporated Addition of ether to the resulting syrup caused formation of a precipitate which was recrystallized from chloroform–ether to yield 281 mg (84%) of crystals, m p 168–169°, $[\alpha]_D^{22}$ +111 1° (*c* 0 99, chloroform) It showed one spot having an R_F value much smaller than that of **3** on t l c with 1 49 butyl alcohol–benzene Its i r spectrum showed $\nu_{max}^{CHCl_3}$ 3600 cm^{-1} (OH), and other characteristic bands given in Table II

Anal Calc for $C_{16}H_{22}O_6$ C, 61 94, H, 7 97 Found C, 61 86, H, 8 08

Methyl 3-O-ethyl-2-O-p-tolylsulfonyl-α-D-glucopyranoside (**5**) — A mixture of 1 0 g (2 2 mmoles) of **3** with 8.5 ml of 0 005M sulfuric acid in 8 5 ml of methanol was stirred for 1 h at room temperature After neutralization of the acid with barium carbonate, and filtration, the solution was evaporated, starting material (0 2 g) was recovered. The filtrate was evaporated to dryness under diminished pressure to yield 0 45 g of product (69%, based on starting material recovered) as a glass, $[\alpha]_D^{22}$ +70° (*c* 0 99, chloroform) Its i r spectrum showed $\nu_{max}^{CCl_4}$ 3550 (OH), 1380, 1182 cm^{-1} (sulfonic ester), and other characteristic bands given in Table II The product showed only one spot on t l c with 1 19 butyl alcohol–benzene

Anal Calc for $C_{16}H_{24}O_8S$ C, 51 05; H, 6 43, S, 8 52 Found C, 51 31, H, 6 25, S, 8 63

Methyl 3-O-ethyl-α-D-glucopyranoside (**6**) *from methyl 4,6-O-benzylidene-3-O-ethyl-α-D-glucopyranoside* (**4**) — A mixture of 0 75 g (3 4 mmoles) of **4** in 15 ml of 0 05M sulfuric acid in methanol was stirred for 1 h at room temperature After neutralization of the acid with barium carbonate, and filtration, concentration of the filtrate gave some unchanged starting material The filtrate was evaporated under diminished pressure to yield 0 35 g of product (70%, based on starting material recovered), m p 139–140°, $[\alpha]_D^{25}$ +152° (*c* 1, ethanol) The i r. spectrum showed ν_{max}^{KBr} 3450 (OH), 1000 cm^{-1}, and other characteristic bands given in Table II The product showed only one spot on t l c with 1 4 ethanol–benzene, and g l c of the *O*-(trimethylsilyl) derivative gave a single peak from each of several different columns[2]

Anal. Calc for $C_9H_{18}O_6$ C, 48 64, H, 8 16 Found. C, 48 55, H, 7 95.

Methyl 3-O-ethyl-α-D-glucopyranoside (**6**) *from methyl 3-O-ethyl-2-O-p-*

tolylsulfonyl-α-D-glucopyranoside (**5**) — Desulfonylation of **5** was accomplished by use of sodium amalgam as described for the preparation of **4** From 0 5 g (1.3 mmoles) of **5**, the syrup that resulted after evaporation of the methanol was crystallized from methanol–ether to yield 0 25 g (85%) of crystalline product, m p 137–140°, $[\alpha]_D^{25}$ +152° (*c* 1, ethanol) The products obtained from **4** and **5** were identical with each other, as shown by m p , mixed m p , i r and n m r spectra, and t l c and g l c

3-O-Ethyl-D-glucose (**7**) — A mixture of 0 1 g (0 5 mmole) of **6** and 15 ml of M sulfuric acid was stirred for two days at room temperature After neutralization of the acid with barium hydroxide, evaporation of the filtrate gave crude 3-*O*-ethyl-D-glucose, 0 06 g (67%) Recrystallization from ethanol yielded a crystalline product, m.p 156–157° (lit.[8] 155 5–157 5°), $[\alpha]_D^{25}$ +61° (equil , *c* 1, ethanol)

Methyl 4,6-O-benzylidene-2,3-di-O-p-tolylsulfonyl-α-D-glucopyranoside (**8**) — The preparation of this compound has been described[25], m p 147–148°, $\nu_{max}^{CHCl_3}$ 1370 and 1160 cm^{-1} (sulfonic ester), and other characteristic bands as given in Table II

1,2 5,6-Di-O-isopropylidene-α-D-glucofuranose (**9**) — The preparation of this compound has been described[26], m p 109–110°

3-O-Ethyl-1,2 5,6-di-O-isopropylidene-α-D-glucofuranose (**10**) — To a solution of 26 g (0 1 mole) of **9** in 300 ml of tetrahydrofuran was added 30 ml of ethyl sulfate and 25 g of powdered sodium hydroxide The mixture was boiled for 3 h under reflux with rapid stirring, and then cooled A second addition of 30 ml of ethyl sulfate and 25 g of powdered sodium hydroxide was made, followed by boiling for 3 h under reflux, with stirring After filtration, and the removal of tetrahydrofuran and ethyl sulfate by distillation, the residue was passed through an alumina column to yield 26 g (86%) of a liquid, $\nu_{max}^{CHCl_3}$ 2990 s, 2940 sh, 1475 m, 1440 m, 1405 s, 1380 s, 1365 s, 1340 m, 1285 m, 1250 s, 1215 s, 1195 s, 1165 s, 1122 s, 1080 vs, 1020 vs, 920 vs, 890 m, and 850 ms cm^{-1}

Methyl 3-O-ethyl-α-D-glucopyranoside (**6**) *from 3-O-ethyl-1,2 5,6-di-O-isopropylidene-α-D-glucofuranose* (**10**) — A solution of 26 g (0 1 mole) of **10** in 9 ml of conc hydrochloric acid and 300 ml of methanol was refluxed overnight After neutralization of the acid with sodium hydrogen carbonate, the suspension was filtered, and the filtrate was dried (magnesium sulfate), and evaporated to yield 19 g (95%) of a solid Repeated recrystallization from methanol gave a crystalline product, 14 g (70%), which was identical in all respects with **6** prepared as described previously

ACKNOWLEDGMENTS

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REFERENCES

1 Presented, in part, before the Division of Carbohydrate Chemistry, *151st National Meeting Amer Chem Soc* , Atlantic City, N J , Sept 12–17, 1965, Abstracts, p 4D

2 J W BERRY, J. T MARVEL, S K SEN, AND A J DEUTSCHMAN, JR, *Abstracts Papers, Winter Meeting Amer Chem Soc*, Phoenix, Arizona, Jan, 1966, 20c
3 H R BOLLIGER AND D A PRINS, *Helv Chim Acta*, 28 (1945) 465; *cf*, G J ROBERTSON AND C F GRIFFITH, *J. Chem Soc*, (1935) 1193
4 R W JEANLOZ AND M GUT, *J. Amer Chem. Soc*, 76 (1954) 5793
5 A F KRASSO, E WEISS, AND T. REICHSTEIN, *Helv Chim Acta*, 46 (1963) 2538
6 Some synthetic steps were reported by N K. KOCHETKOV AND A I USOV, *Tetrahedron Lett*, (1963) 519
7 J KENNER AND G N RICHARDS, *J Chem Soc*, (1957) 3019
8 W. L GLEN, G S MEYERS, AND G A GRANT, *J Chem Soc*, (1951) 2568
9 R W JEANLOZ AND D A JEANLOZ, *J Amer Chem Soc*, 79 (1957) 2579
10 R U LEMIEUX AND J D STEVENS, *Can J Chem*, 43 (1965) 2059.
11 K NAKANISHI, *Infrared Absorption Spectroscopy*, Holden-Day, Inc, San Francisco, 1962, p 34
12 J R HOLMES, D KIVELSON, AND W C BRINKHARD, *J. Chem Phys*, 37 (1962) 150
13 R J ABRAHAM, L D HALL, L HOUGH, AND K A. MCLAUCHLAN, *J Chem Soc*, (1962) 3699
14 D E MCGREER, R STEWARD, AND M M MOECK, *Can J Chem*, 41 (1963) 1024
15 D E. MCGREER AND M M MOECK, *J Chem Educ*, 40 (1963) 358
16 O L CHAPMAN AND R W KING, *J Amer Chem Soc*, 86 (1964) 1256
17 B CASU, M REGIANNI, G G GALLO, AND A VIGEVANI, *Tetrahedron Lett*, (1964) 2839
18 A A BOTHNER-BY, *Adv an Magn. Resonance*, 1 (1965) 307
19 B CASU, M REGIANNI, G G GALLO, AND A VIGEVANI, *Tetrahedron Lett*, (1965) 2253
20 C P RADER, *J Amer Chem Soc*, 88 (1966) 1713
21 B CASU, M REGIANNI, G G GALLO, AND A VIGEVANI, *Tetrahedron*, 22 (1966) 3061.
22 A S PERLIN, *Can J. Chem*, 44 (1966) 539
23 M KARPLUS, *J Chem Phys*, 30 (1959) 11
24 O T SCHMIDT, *Methods Carbohyd Chem*, 1 (1962) 351
25 S N DANILOV AND I S LISHANSKY, *J Gen Chem USSR* (Engl Transl), 25 (1955) 2063; *cf*, D S MATHERS AND G J ROBERTSON, *J Chem Soc*, (1933) 696
26 O T SCHMIDT, *Methods Carbohyd Chem*, 2 (1963) 321