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SYNTHETIC AND SPECTROSCOPIC STUDIES OF 2-*C*-METHYL-ERYTHRITOL AND 2-*C*-METHYL-THREITOL

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Key Word Index—*Convolvulus glomeratus*; Convolvulaceae; branched chain alditol; 2-*C*-methyl-D-erythritol; 2-*C*-methyl-D,L-threitol; acetates; isopropylidene derivatives.

Abstract—The synthesis of 2-*C*-methyl-D,L-threitol and two isopropylidene derivatives of 2-*C*-methyl-D-erythritol is described. ^1H and ^{13}C NMR spectra of these and several related compounds are discussed.

INTRODUCTION

Branched chain carbohydrates constitute a rare group of naturally occurring compounds found in plants and micro-organisms. The best known examples of branched aldoses are apiose [3-*C*-(hydroxymethyl)-D-*glycero*-aldotetrose] (**1**) [1], hamamelose [2-*C*-(hydroxymethyl)-D-ribose] (**2**) and those which are components of antibiotics such as mycarose (**3**) and cladinose (**4**). In addition, aldonic acids with branching are also present in plants, e.g. 2-*C*-methylerythronic acid (**5**) [2, 3] and a 2-*C*-(hydroxymethyl)-pentonic acid (**6**) [2]. The only naturally occurring branched alditol is 2-*C*-methyl-D-erythritol (**7**) [4, 5]. It is also noteworthy that branched chain *N*-nucleosides have biological activity [6].

RESULTS AND DISCUSSION

The biosynthesis of the branch methyl in mycarose (**3**) and cladinose (**4**) has been established to take place through methylation by *S*-adenosyl-L-methionine [7]. UDP-D-apiose is biosynthesized from UDP-D-glucuronic acid via decarboxylation and rearrangements [8]. Similar rearrangements have been proposed for the synthesis of 2-*C*-methyl-D-erythronic (**5**) and 2-*C*-methyl-D-threonic acids from 1-deoxy-D-*glycero*-2,3-pentadiulose (**8**) [9]. Moreover, it has been shown that both 2-*C*-methyl-D-erythronic (**5**) and 2-*C*-methyl-D-threonic acids are formed in base-catalysed rearrangements of D-xylose and D-fructose [10].

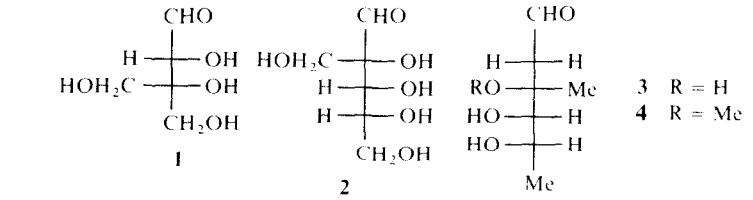
Although branched chain carbohydrates constitute a rather small group of natural products, apiose itself is not rare. It occurs in a wide variety of plants, including morning glory *Convolvulus minor* [1]. It may be of chemotaxonomic interest to note that the only naturally occurring branched chain alditol, 2-*C*-methyl-D-erythritol (**7**), was isolated from *Convolvulus glomeratus* [4].

Inspired by the isolation of this alditol, we have studied the possibilities of synthesis of branched alditols through addition of diazomethane and sulfur ylides to the oxo group in suitable aldehydes and ketones [11, 12]. Reactions with diazomethane under the influence of media of varying polarity were studied and we have concluded that the stereoselectivity of the reactions decreases with increasing amounts of methanol in the reaction medium.

Studies of reactions with 1-deoxy-3,4-*O*-isopropylidene-D-*glycero*-tetrulose (**9**) led to the synthesis of natural 2-*C*-methyl-D-erythritol (**7**) [12]. Addition of dimethyloxosulfonium methylide to **9** furnished a mixture of epimeric epoxides in the ratio 65:35. The mixture was, in our hands, inseparable. However, it was shown that the dominant epoxide was the *erythro* isomer. Base hydrolysis of the mixture gave a mixture of diols from which 2-*C*-methyl-3,4-*O*-isopropylidene-D-erythritol (**10**) was crystallized. Acid hydrolysis of **10** gave a tetritol which was identical with natural **7**.

Originally the constitution of natural **7** was based mainly upon ^1H and ^{13}C NMR [4] while the absolute stereochemistry was deduced from CD spectra [5]. 2-*C*-Methyl-D-erythritol was characterized also by a tri- (**11**) and a tetra-acetate (**12**). Racemic 2-*C*-methyl-D,L-erythritol was obtained synthetically from citraconic acid (**13**). Dihydroxylation with potassium permanganate of its dimethyl ester (**14**) furnished dimethyl 2-*C*-methyl-*erythro*-tartrate (**15**) which was reduced with $LiAlH_4$ to give 2-*C*-methyl-D,L-erythritol.

In addition we have now synthesized 2-*C*-methyl-D,L-threitol (**16**) in a similar manner from mesaconic acid (**17**). The dimethyl ester (**18**) of this acid was *cis*-dihydroxylated with osmium tetroxide to yield dimethyl 2-*C*-methyl-D,L-*threo*-tartrate (**19**). Reduction of this diester gave a water-soluble product which was acetylated to yield a tri- (**20**) and a tetra-acetate (**21**). The two acetates were separated chromatographically and both gave racemic 2-*C*-methyl-threitol (**15**) on hydrolysis. From 2-*C*-methyl-D-erythritol (**7**), two isopropylidene derivatives, one mono and one di, were also obtained. The mono derivative was different from the one (**10**) synthesized earlier (see above) and was shown by ^1H and ^{13}C spectroscopy to be 2-*C*-methyl-2,3-*O*-isopropylidene-D-erythritol (**22**). The other was obviously 2-*C*-methyl-1,2: 3,4-di-*O*-isopropylidene-D-erythritol (**23**). Another monoisopropylidene derivative of the threitol, 2-*C*-methyl-3,4-*O*-isopropylidene-D-threitol (**24**), has been prepared before [12].



1 2

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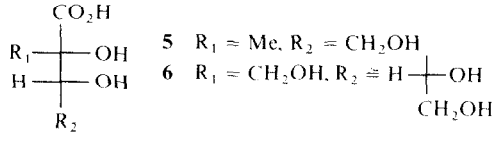
4 R = Me



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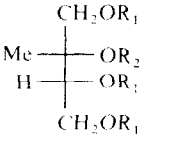
6 R_1 = CH_2OH, R_2 = H



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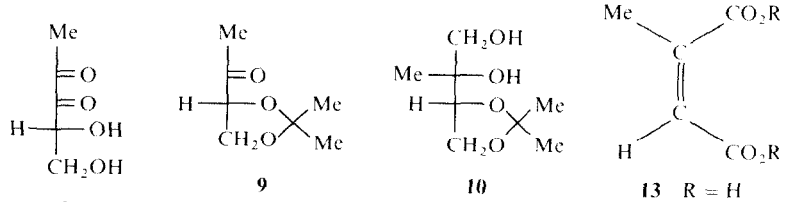
11 R_1 = Ac, R_2 = H
12 R_1 = R_2 = Ac



8 9 10

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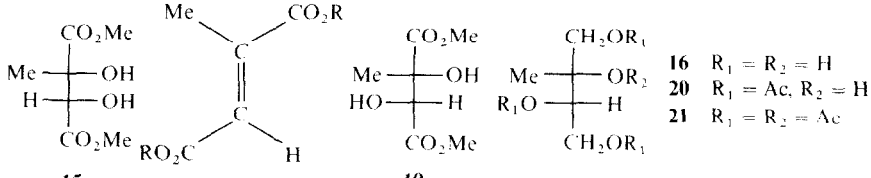
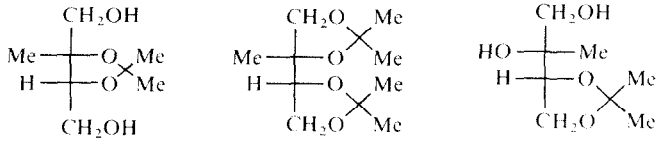


15 17 18 19

16 R_1 = R_2 = H
20 R_1 = Ac, R_2 = H
21 R_1 = R_2 = Ac



22 23 24

During work with branched chain carbohydrates, ^{13}C NMR has been an excellent tool for the analysis of mixtures of epimers. ^{13}C NMR may be used for quantitative purposes when the spin-gitter relaxation times (T_1) for the nuclei to be compared are of similar magnitude. We have measured the ^{13}C T_1s for the alditols **7** and **16** by the inversion recovery technique at 25.1 MHz. The values for **7** (in sec) were: 0.72 (C-1), 12.78 (C-2), 1.29 (C-3), 0.78 (C-4) and 1.08 (Me). The corresponding values for **16** were: 0.77, 12.64, 1.33, 1.01 and 1.21.

^{13}C chemical shifts for 12 compounds are given in Table 1. Some assignments were done by selective heteronuclear decoupling in Eu and Pr-shifted spectra.

EXPERIMENTAL

Chromatography. A Perkin Elmer F-11 instrument equipped with FI detector and a 5′ × 1/8″ column packed with 5% OV-17 was used for GLC; N_2 flow rate 5 ml/min. At 160° the retention times of the acetates were: triacetates (**11** and **20**): 12 min, tetraacetates (**12** and **21**): 18 min. The retention times for the dimethyl esters at 120° were: **15**: 11.5 min, 19: 13.5 min. TLC was performed on 'Merck Fertigplatten' 0.25 mm Si gel GF 254.

Spectroscopy. NMR spectra were recorded on Jeol FX-100, a pulse-Fourier transform instrument, at 99.6 MHz for ^1H and 25.1 MHz for ^{13}C. The solvents were $CDCl_3$ containing 1% TMS and D_2O with MeOH as internal reference (δ $^{13}CH_3OH$ = 49.9 ppm). MS were recorded with AEI MS 902 and optical rotations with a Perkin Elmer 241 polarimeter.

Synthesis and spectroscopic properties of compounds **7**, **9**, **10–12**, **14**, **15** and **24** have been described earlier [4, 10, 11].

Dimethyl mesaconate (**18**). A mixture of mesaconic acid (**17**) (20 g), MeOH (20 g), dry C_6H_6 (70 ml) and conc H_2SO_4 (3.3 ml) was refluxed for 30 hr and then poured into ice cold water. The C_6H_6 layer was separated and the aq. layer extracted with Et_2O. The combined organic phases were washed with aq. $NaHCO_3$ and H_2O, dried and evapd to dryness. The residual oil was distilled (12 mm, 137–139°) to yield the oily dimethyl ester (**18**) (19 g). $M^{+\cdot}$ 158.0574, calc. for $C_7H_{10}O_4$ 158.0579. ^1H NMR: δ 3.77 and 3.81 (both 3H and *s*, two methoxyls), 2.28 and 6.76 (3H *d* and 1H *q*, J = 1.5 Hz, Me—C=CH group), cf. [4] for **14**: 2.04 and 5.89. ^{13}C NMR: 13.7, 51.1 and 52.0 (all *q*, one olefinic and two ester methyls), 125.9 (*d*) and 143.3 (*s*) (two olefinic carbons), 165.6 and 166.9 (two carbonyls). The corresponding shifts for the *cis* isomer (**14**) are: 19.8, 51.1, 51.7, 120.1, 145.2, 164.7 and 168.7.

Table 1. ^{13}C chemical shifts for branched sugars

Compound	C-1	C-4	C-2	C-3	(Me)
7	67.3	63.0	75.0	75.9	19.4
10	67.2	64.9	72.3	79.0	20.0
11	68.1	62.8	71.9	72.7	19.9
12	63.5	62.4	81.3	70.7	21.7
15	174.7	171.7	76.7	75.6	22.6
16	67.2	62.9	74.9	76.0	20.4
19	174.6	171.5	77.0	75.3	21.7
20	68.0	62.5	72.3	73.8	21.4
21	64.5	62.5	81.0	72.5	21.1
22	67.2	64.9	72.5	78.8	19.9
23	72.8	65.3	80.9	78.3	19.2
24	69.4	64.8	70.7	80.5	19.9

The spectra of the alditols **7** and **16** were recorded in D_2O solution with MeOH as internal reference ($^{13}CH_3OH$ = 49.9 ppm). The isopropylidene derivatives **10**, **22**, **23** and **24** showed peaks around 109 and in the region 24.6–27.1 ppm due to the quaternary carbon and the methyl groups, respectively. The acetates **11**, **12**, **20** and **21** showed carbonyl resonances at 169.3–170.9 and acetyl methyls at 18.9–20.7 ppm. Assignments were done by off resonance proton-decoupled spectra. To distinguish between C-1 and C-4 which are both triplets in off resonance spectra, selective decouplings were performed in Eu and Pr-shifted spectra of the alditols **7** and **16**. For the rest of the compounds the low-field peaks were assigned to C-1.

Dimethyl 2-C-*methyl*-threo-*tartrate* (**19**). A soln of OsO_4 (2 g) in dry pyridine (15 ml) was added dropwise to an ice cold soln of dimethyl mesaconate (**18**) (1.2 g) in pyridine (15 ml) during 5 min whereby a brown ppt. appeared. The mixture was stirred for 1 hr at 0–5° and then for another 2 hr at room temp. To the cold mixture was added with stirring a mixture of $NaHSO_3$ (3.6 g), H_2O (60 ml) and pyridine (40 ml). The ppt. dissolved, the soln turned brown and then red after stirring for 1 hr. The soln was extracted with $CHCl_3$ (100 ml × 4) and then with CH_2Cl_2 (50 ml × 3). The combined extracts were dried and evapd to dryness. The residue was distilled (0.05 mm, 125–145°) to yield **19** (1.2 g) as a colourless oil; ^1H NMR: δ 1.49 (3H, *s*, quat. methyl), 3.82 (6H, *s*, two methoxyls), 3.8 (2H, *s*, two hydroxyls), 4.39 (1H, *s*, methine H); ^{13}C NMR see Table 1.

1,3,4-*Tri*-O-*acetyl*-2-C-*methyl*-D,L-*threitol* (**20**) *and* 1,2,3,4-*tetra*-O-*acetyl*-2-C-*methyl*-D,L-*threitol* (**21**). A soln of **19** (1 g) in dry Et_2O (100 ml) was added dropwise to a soln of $LiAlH_4$ (2.5 g) in dry Et_2O (200 ml) during 30 min with vigorous stirring and under N_2. The mixture was stirred and refluxed for 5 hr and excess $LiAlH_4$ was decomposed by addition of EtOAc (12 ml). After addition of HOAc (10 ml), the mixture was evapd to dryness, and the crude product acetylated with Ac_2O (50 ml) in pyridine (50 ml). After heating on a water bath with intermediate shaking for 6 hr, the ppt. was removed by centrifugation. The soln was evapd *in vacuo* and traces of Ac_2O removed by repeated addition and evapn of toluene. The dry residue was extracted with $CHCl_3$ and filtered to yield an oily mixture (1.54 g). TLC showed an approximate ratio of tri- and tetra-acetates of 3:1. Prep. TLC (35% hexane in Et_2O) yielded pure triacetate **20** (0.77 g). MS: M^+ 262 (absent), *m/e* 189 (8%, M − CH_2OAc, calc. for $C_8H_{13}O_5$ 189.0765, found 189.0771. ^1H NMR: δ 1.28 (3H, *s*, quat. methyl), 2.04, 2.10 and 2.11 (all 3H and *s*, acetyl methyls), 2.80 (*br. s*, OH), AB system 3.99 and 4.08 J_{AB} = 11.7 Hz (2H-1), ABX system, ν_A = 4.16, ν_B = 4.50 and ν_X = 5.20, J_{AB} = 12.2, J_{AX} = 8.3, J_{BX} = 3.4 Hz (H-3 and 2H-4). ^{13}C NMR, see Table 1.

The tetra-acetate **21** (0.40 g) was isolated pure from the same TLC plates as **20**. MS: M^+ 304 (absent), *m/e* 231 (3.8%, M − CH_2OAc, calc. for $C_{10}H_{15}O_6$ 231.0870, found 231.0865). ^1H NMR: δ 1.56 (3H, *s*, quat. methyl), 2.03, 2.03, 2.06 and 2.09 (all 3H and *s*, acetyl methyls), AB system, 4.37 and 4.53, ABX system, ν_A = 4.11, ν_B = 4.50 and ν_X = 5.49. Coupling constants and assignments as for **20**. ^{13}C NMR, see Table 1.

2-C-*Methyl*-D,L-*threitol* (**16**). A soln of **21** (1 g) in EtOH (50 ml) was heated with 1N NaOH (75 ml). After 5 hr at 70° the mixture was cooled, neutralized with Amberlite IR-120 cation exchanger, followed by Amberlite IR-45 anion exchanger until the solution was neutral. The mixture was evapd *in vacuo* to yield oily **16** (0.38 g, 85.4%). MS: M^+ 136 (absent), *m/e* 105 (22%, M − $^{\cdot}CH_2OH$, calc. for $C_4H_9O_3$ 105.1257, found 105.1260), *m/e* 76 (100%, $C_3H_8O_2^+$). ^1H NMR: δ 1.13 (3H, *s*, quat. methyl), 3.4–3.9 (5H, *m*, 2H-1, H-3, 2H-4). ^{13}C NMR, see Table 1.

2-C-*Methyl*-1,2:3,4-*di*-O-*isopropylidene*-D-*erythritol* (**23**). To a soln of $ZnCl_2$ (9 g) in 2-propanone (45 ml) was added 2-C-methyl-D-erythritol (**7**) (0.8 g). The mixture was stirred vigorously for 3 hr, poured into a soln of K_2CO_3 (11 g) in water (20 ml) and Et_2O (45 ml) was added. After stirring for 45 min, the mixture was filtered and the water layer extracted with Et_2O (20 ml × 3). The combined Et_2O extracts were dried and evapd *in vacuo* to yield a semi-crystalline solid (1.1 g) which was applied to a Si gel column. Elution with 30% Et_2O in hexane gave **23** (0.38 g), mp 63°, $[\alpha]_{578}$ 7.35° (*c* = 0.49, $CHCl_3$). MS *m/e* (rel. int.): 216 ($M^{\cdot+}$ absent), 201 (13, M − 15) (obs. 201.1121, calc. for $C_{10}H_{17}O_4$ 201.1127), 143 (15, $C_7H_{11}O_3^+$), 115 (90, $C_6H_{11}O_2^+$), 101 (20, $C_5H_9O_2^+$), 43 (100, $MeC{\equiv}O^+$). ^1H NMR: δ 1.27 (3H, *s*, quat. methyl), 1.32, 1.39, 1.39 and 1.42 (all 3H and *s*, isopropyl methyls), 3.71 and 4.04 (AB system, J_{AB} = 12.5 Hz, 2H-1), 3.85–4.15 (*m*, ABC system, 2H-4 and H-3). ^{13}C NMR, see Table 1.

2-C-*Methyl*-2,3-O-*isopropylidene*-D-*erythritol* (**22**). The previous Si gel column was eluted with Et_2O to yield **22** (0.27 g), mp 95°, $[\alpha]_{578}$ + 7.92° (*c* = 0.48, $CHCl_3$). MS *m/e* (rel. int.): 176 ($M^{\cdot+}$, absent), 161 (**14**, M − 15) (obs. 161.0812, calc. for $C_7H_{13}O_4$ 161.0814), 101 (38, $C_5H_9O_2^+$), 87 (7, $C_4H_7O_2^+$), 43 (100, $MeC{\equiv}O^+$). ^1H NMR: δ 1.16 (3H, *s*, quat. methyl), 1.36 and 1.44 (both 3H and *s*, isopropyl methyls), 2.87 (2H, *br. s*, hydroxyls), 3.43 and 3.61 (AB system, J_{AB} = 12.5 Hz, 2H-1), 3.90–4.20 (*m*, ABC system, 2H-4 and H-3). ^{13}C NMR, see Table 1.

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