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PROOF OF THE STRUCTURE OF RISTOTETRAOSE: SYNTHESIS OF PROPYL α-RISTOTETRAOSIDE*

DAMIR MEDAKOVIC†, GYULA BATTA, FERENC SZTARICSKAI‡,
Research Group for Antibiotics of the Hungarian Academy of Sciences, Institute of Chemistry, Lajos Kossuth University, P.O. Box 70, H-4010 Debrecen (Hungary)

AND JÁNOS HARANGI
Department of Biochemistry, Lajos Kossuth University, P.O. Box 55, H-4010 Debrecen (Hungary)

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ABSTRACT

A definitive synthesis of the propyl glycoside (**1**) of ristotetraose, the heterotetrasaccharide component of the antibiotic ristomycin A (ristocetin A) is described.

INTRODUCTION

Of the members of the glycopeptide-type vancomycin group of antibiotics[1], ristomycin A (ristocetin A) is the only representative in which a branched heterotetrasaccharide (ristotetraose) that contains L-rhamnose, D-glucose, D-mannose, and D-arabinose is attached to the heptapeptide aglycon. Earlier investigations[2,3] of reducing disaccharides (rutinose and ristobiose) and trisaccharides (ristotriose and ristriose), obtained[2] by mild acid hydrolysis or acetolysis of the antibiotic, revealed a β-D-arabinopyranosyl unit in ristotetraose.

Mild reductive-alkaline degradation of the antibiotic yielded[4a,b] a fragment (**1**; ϕ_3–S_4) that contained an α-D-arabinofuranosyl unit in the heterotetrasaccharide moiety. Since the conversion of a terminal D-arabinofuranosyl unit into the thermodynamically more stable D-arabinopyranosyl analogue cannot be excluded under the conditions of the acid-catalyzed reaction, the propyl glycoside (**2**) of ristotetraose was synthesized, in which the D-arabinose component is in the α-furanosyl form. Apart from the clarification of the ring size of the arabinosyl unit in ristotetraose, the present work also represents the first, definitive synthesis of this branched heterotetrasaccharide.

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†Present address: Institute of Chemistry, University of Novi Sad, P.O. Box 7, Novi Sad, Yugoslavia.
‡Author for correspondence.

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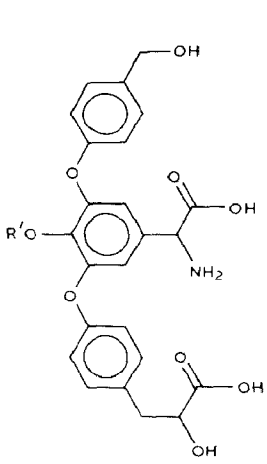
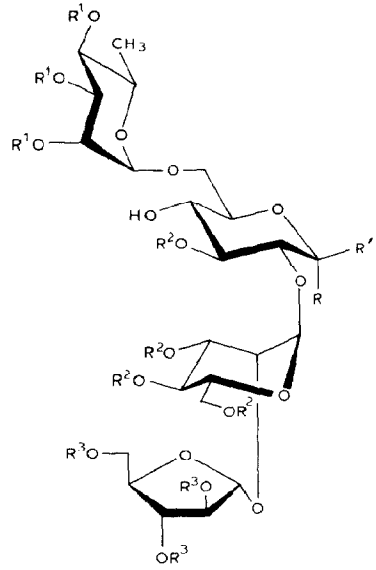


1 R = ristotetraosyl—



2 R = ^{n}PrO, R′ = R¹ = R² = R³ = H

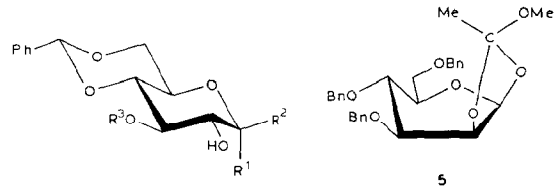
3 R = ^{n}PrO, R′ = H, R¹ = Ac, R² = Bn, R³ = Bz

RESULTS AND DISCUSSION

The target tetrasaccharide **1** was synthesized by a "step-by-step" strategy in 23 stages.

Allyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside[5] (**4**) was used as the first glycosyl acceptor. The glycosyl donor 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl chloride (**6**) was synthesized from the orthoester **5** by a modification of the literature procedure[6], and used, without further purification, for the glycosylation of **4** with silver triflate as the promoter[7]. The disaccharide derivative **9** was isolated in good yield after chromatography. Zemplén saponification of **9** gave **10** with HO-2′ unsubstituted. Glycosylation of **10** with 2,3,5-tri-*O*-benzoyl-α-D-arabinofuranosyl bromide[8] (**8**) in dichloromethane and in the presence of silver triflate gave, after chromatography, the trisaccharide derivative **11** in excellent yield. That the D-Man*p* and D-Glc*p* residues in **9** and **10** were α was proved by the $J_{1,2}$ values of 2–3 Hz. The C-1 signals of the D-Glc*p* and D-Man*p* residues in **11** were assigned by means of ^{1}H–^{13}C correlations. The H-1 signal of the D-Ara*f* unit was a singlet.

The final step in the construction of **2** was the formation of a (1→6) linkage between L-Rha*p* and D-Glc*p*. Although the dioxolane ring of the D-glucose residue of **11** could not be cleaved regioselectively, even with the borane–trimethylamine–aluminium chloride system[9] in toluene or dichloromethane, it could be removed readily by treatment with trifluoroacetic acid in dichloromethane, to give **12**. Owing to the expected low reactivity of HO-4 as compared to that of HO-6, **12** was



4 R^1 = allyloxy, R^2 = H, R^3 = Bn

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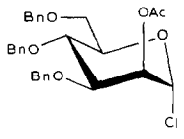

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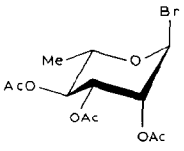

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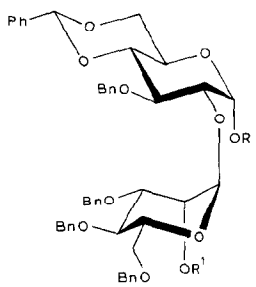
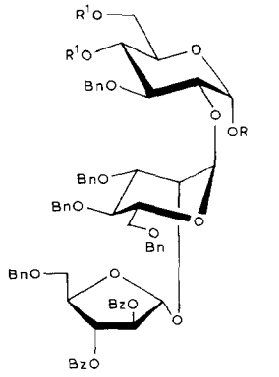


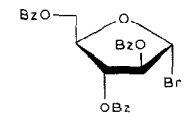
9 R = allyl, R^1 = Ac

10 R = allyl, R^1 = H



11 R = allyl, R^1 = R^1 = PhCH<

12 R = allyl, R^1 = H



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glycosylated with tri-*O*-acetyl-α-L-rhamnopyranosyl bromide[10] (**7**) under Koenigs–Knorr conditions, to obtain the tetrasaccharide derivative **3** (50%). The acetyl groups of **3** were removed under Zemplén conditions and the benzyl groups by hydrogenolysis (Pd/C), affording, with simultaneous saturation of the allyl function, propyl *O*-α-D-Ara*f*-(1→2)-*O*-α-D-Man*p*-(1→2)-*O*-[α-L-Rha*p*-(1→6)]-α-D-Glc*p* (**2**). The sequence, ring-size, and configuration of the glycosidic linkages in **2** were identical with those of the tetrasaccharide present in ristomycin A. Differences were found only in the nature of the aglycon moiety and the configuration of the linkage between the aglycon and the D-Glc*p* residue.

The n.m.r. data for **2** and **3** are given in the Experimental. The assignments were based on COSY[11] and HETCOR[12] methods. Comparison of the ^{13}C-n.m.r. spectra of **2** and the ristotetraose moiety in the antibiotic (Table I) led to the following conclusions.

Although the D-Glc*p* residues have opposite anomeric configurations and the aglycons are different, most of the chemical shifts of the ^{13}C resonances for **2** correspond (±1 p.p.m., Table I) to those for the monosaccharide units of the ristotetraosyl side-chain of ristomycin. The exceptions were C-1 and C-4 of the α-D-Man*p* residue, since, in previous papers[4a,13], the assignments of C-1 of the β-D-Glc*p* and α-D-Man*p* residues were exchanged. In addition, the α-D-Man*p* residue in **2** is linked to an alkyl α-D-glucopyranoside, which is reflected in the chemical shift of the C-1 resonance of the α-D-Man*p* residue. In contrast to the reported[4a,b] $J_{C\text{-}1,H\text{-}1}$

TABLE I

^{13}C-N.M.R. DATA (INTERNAL 1,4-DIOXANE, δ 67.3) FOR RISTOMYCIN AND **2** (δ IN P.P.M., $J_{C\text{-}1,H\text{-}1}$ VALUES IN Hz)

Carbohydrate unit	*Carbon*	*Ristomycin*[4a] *(D_2O)*	*Ristomycin*[13] *(D_2O)*	**2** *(D_2O + CD_3OD)*
α-L-Rha*p*	1	102.3 (174 Hz)	102.3	101.5 (170 Hz)
	2	71.2	71.3	(71.2)
	3	71.2	71.3	(71.5)
	4	73.7	73.2	(72.7)
	5	69.6	69.7	69.7
	6	17.8	17.7	17.7
β-D-Glc*p*	1	102.3 (166 Hz)	100.1	96.1 (169 Hz)
	2	78.9	78.6	(75.7)
	3	76.0	76.0	(73.1)
	4	70.7	71.3	(71.1)
	5	76.0	76.0	(71.8)
	6	68.3	68.3	67.5
α-D-Man*p*	1	100.1 (175 Hz)	102.3	97.5 (172 Hz)
	2	77.9	78.1	78.6
	3	71.2	70.8	70.8
	4	67.6	70.8	67.9
	5	72.9	73.8	(73.9)
	6	62.1	62.1	62.2
α-D-Ara*f*	1	110.3 (172 Hz)	110.3	110.6 (174 Hz)
	2	82.1	82.1	82.4
	3	77.9	77.8	(77.7)
	4	85.2	85.3	84.7
	5	61.9	62.5	63.6

α-D-Glc*p* (**2**): 97.5 (172 Hz), 78.6, 70.8, 67.9, (73.9), 62.2

value of 166 Hz for the β-D-Glc*p* residue of fragment **1**, a value of 169 Hz was found for the α-D-Glc*p* residue of **2**. Since a 3-Hz difference in the $J_{C\text{-}1,H\text{-}1}$ values for α and β anomers is unexpected in the light of the reported[14] 10-Hz values, re-determination of the coupling constants is advisable. Nevertheless, according to the chemical shift values[4a,4b,13], the presence of the β-D-Glc*p* residue in ristomycin A (ristocetin A) is not questionable.

EXPERIMENTAL

General. — $[\alpha]_D$ values were measured with a Perkin–Elmer 241 polarimeter. The ^{1}H- and ^{13}C-n.m.r. spectra were recorded with a Bruker WP 200 SY instrument at 200 and 50.3 MHz, respectively, for solutions in $CDCl_3$ and D_2O by using Me_4Si and 1,4-dioxane (67.3 p.p.m.) as internal standards. Whenever the 200-MHz ^{1}H-n.m.r. spectra were not interpretable as first order, the "fingerprint" ^{13}C- and ^{1}H-n.m.r. chemical shift values and coupling constants are given for characterization of the spectra. Dichloromethane was distilled from phosphorus pentaoxide

and kept over 4 Å molecular sieves. T.l.c. was performed on Silica Gel 60 F_{254} (Merck) and column chromatography on Silica Gel 60 (0.2–0.5 mm) with *A*, 3:1 toluene–ethyl acetate; *B*, 9:1 toluene–ethyl acetate; *C*, 98:2 dichloromethane–methanol; *D*, 8:2 toluene–ethyl acetate; *E*, 1:3:1 chloroform–methanol–aq. 25% ammonium hydroxide; *F*, 7:3 chloroform–ethyl acetate; *G*, 2:1 toluene–ethyl acetate; and detection with u.v. light or charring with sulfuric acid. Evaporations were carried out under diminished pressure at <40°.

Allyl O-(2-O-acetyl-3,4,6-tri-O-benzyl-α-D-mannopyranosyl)-(1→2)-3-O-benzyl-4,6-O-benzylidene-α-D-glucopyranoside (**9**). — To a mixture of **4**[5] (300 mg, 0.75 mmol), silver triflate (920 mg, 3.60 mmol), and powdered 4 Å molecular sieves (1.0 g) in dichloromethane at −40° was added dropwise under argon a solution of **6**[6] (750 mg, 1.46 mmol) in dry dichloromethane (5 mL). The mixture was stirred at −40° for 2 h, pyridine (1 mL) was added, and the mixture was allowed to attain room temperature, diluted with dichloromethane, and filtered through Celite. The filtrate was washed successively with aq. 10% sodium hydrogencarbonate, aq. 10% sulfuric acid, and aq. 10% sodium hydrogencarbonate, dried (Na_2SO_4), and concentrated. Column chromatography (96:4 toluene–ethyl acetate) of the residue gave **9** (513 mg, 78%), $[\alpha]_D^{20}$ +40° (*c* 0.8, chloroform), R_F 0.50 (solvent *A*). N.m.r. data ($CDCl_3$ + CCl_4): ^{13}C, δ 169.9 (C=O), 138.9, 138.5, 138.1, 138.0, 137.5 (5 aromatic quaternary carbons), 118.6 (=CH_2), 101.3 (*C*HO_2Ph), 94.9 (C-1 of D-Glc*p*), 94.5 (C-1 of D-Man*p*), 75.3, 75.1, 74.4, 71.8 (4 *C*H_2Ph), 68.7, 68.6 (3 OCH_2); ^1H, δ 5.01 (d, 1 H, $J_{1,2}$ 3 Hz, H-1 of D-Glc*p*), 4.95 (d, 1 H, $J_{1,2}$ 2 Hz, H-1 of D-Man*p*), 2.15 (s, 3 H, OAc).

Anal. Calc. for $C_{52}H_{56}O_{12}$ (872.97): C, 71.55; H, 6.46. Found: C, 71.70; H, 6.48.

Allyl O-(3,4,6-tri-O-benzyl-α-D-mannopyranosyl)-(1→2)-3-O-benzyl-4,6-O-benzylidene-α-D-glucopyranoside (**10**). — A mixture of **9** (160 mg, 0.18 mmol), methanol (8 mL), and methanolic 0.1M sodium methoxide (0.5 mL) was kept overnight at room temperature, then neutralized with Bio-Rad AG 50W-X12 (H^+) resin, filtered, and concentrated. Column chromatography (solvent *D*) of the residue gave **10** (124 mg, 82%), $[\alpha]_D^{20}$ +56° (*c* 0.6, chloroform), R_F 0.47 (solvent *F*). N.m.r. data ($CDCl_3$): ^1H, δ 5.09 (d, 1 H, $J_{1,2}$ 3 Hz, H-1 of D-Glc*p*), 5.04 (d, 1 H, $J_{1,2}$ 2 Hz, H-1 of D-Man*p*), 2.66 (s, 1 H, OH); ^{13}C, δ 138.8–137.5 (5 overlapping aromatic quaternary carbons), 118.7 (=CH_2), 101.2 (*C*HO_2Ph), 95.9 (C-1, D-Man*p*), 95.0 (C-1, D-Glc*p*).

Anal. Calc. for $C_{50}H_{54}O_{11}$ (830.93): C, 72.27; H, 6.55. Found: C, 72.13; H, 6.62.

Allyl O-(2,3,5-tri-O-benzoyl-α-D-arabinofuranosyl)-(1→2)-O-(3,4,6-tri-O-benzyl-α-D-mannopyranosyl)-(1→2)-3-O-benzyl-4,6-O-benzylidene-α-D-glucopyranoside (**11**). — A mixture of **10** (112 mg, 0.13 mmol), silver triflate (190 mg, 0.74 mmol), and powdered 4 Å molecular sieves (0.60 g) in dichloromethane (10 mL) was stirred at room temperature under argon for 30 min, then cooled to −40°. A solution of 2,3,5-tri-*O*-benzoyl-α-D-arabinofuranosyl bromide[8] (**8**; 150 mg, 0.28

mmol) in dichloromethane (2.5 mL) was added dropwise with continuous stirring. Reaction was at −40° for 2 h, then pyridine (2.0 mL) was added; the mixture was allowed to attain room temperature and was then worked-up as described for the preparation of **9**. Column chromatography (96:4 toluene–ethyl acetate) of the product gave **11** (158 mg, 92%), $[\alpha]_D^{20}$ +25° (*c* 0.8, chloroform), R_F 0.46 (solvent *B*). N.m.r. data ($CDCl_3$): ^1H, δ 5.64 (s, 1 H, H-1 of D-Ara*f*), 5.10 (d, 1 H, $J_{1,2}$ 1.7 Hz, H-1 of D-Man*p*), 5.01 (d, 1 H, $J_{1,2}$ 3.0 Hz, H-1 of D-Glc*p*); ^{13}C, δ 165.7–165.1 (3 C=O), 118.5 (=CH_2), 106.8 (C-1, D-Ara*f*), 101.2 (*C*HO_2Ph), 95.6 (C-1, D-Man*p*), 94.7 (C-1, D-Glc*p*), 75.5, 75.0, 72.6, and 72.2 (4 *C*H_2Ph).

Anal. Calc. for $C_{76}H_{74}O_{18}$ (1275.35): C, 71.57; H, 5.85. Found: C, 71.42; H, 6.06.

Allyl O-*(2,3,5-tri-*O*-benzoyl-α-*D*-arabinofuranosyl)-(1→2)-*O*-(3,4,6-tri-*O*-benzyl-α-*D*-mannopyranosyl)-(1→2)-3-*O*-benzyl-α-*D*-glucopyranoside* (**12**). — To a solution of **11** (165 mg, 0.13 mmol) in dichloromethane (22.5 mL) was added trifluoroacetic acid containing 3% of water (2.5 mL). After 5 min, the mixture was concentrated and toluene was evaporated three times from the residue. Column chromatography (solvent *A*) of the residue gave **12** (132 mg, 85%), $[\alpha]_D^{20}$ +44° (*c* 0.4, chloroform), R_F 0.51 (solvent *C*). N.m.r. data ($CDCl_3$): ^1H, δ 5.68 (s, 1 H, H-1 of D-Ara*f*), 5.16 (d, 1 H, $J_{1,2}$ 1.7 Hz, H-1 of D-Man*p*), 5.04 (d, 1 H, $J_{1,2}$ 3 Hz, H-1 of D-Glc*p*); ^{13}C, δ 166.1–165.1 (3 COPh), 118.3 (=CH_2), 106.7 (C-1, D-Ara*f*), 95.5 (C-1, D-Man*p*), 94.0 (C-1, D-Glc*p*), 75.8, 74.9, 72.8, and 72.1 (4 *C*H_2Ph), 68.0 (C-6, D-Man*p*), 63.7 (C-5, D-Ara*f*), 62.4 (C-6, D-Glc*p*).

Anal. Calc. for $C_{69}H_{70}O_{18}$ (1187.25): C, 69.80; H, 5.94. Found: C, 69.87; H, 6.12.

Allyl O-*(2,3,5-tri-*O*-benzoyl-α-*D*-arabinofuranosyl)-(1→2)-*O*-(3,4,6-tri-*O*-benzyl-α-*D*-mannopyranosyl)-(1→2)-*O*-[2,3,4-tri-*O*-acetyl-α-*L*-rhamnopyranosyl-(1→6)]-3-*O*-benzyl-α-*D*-glucopyranoside* (**3**). — A mixture of **12** (25 mg, 0.021 mmol), $HgBr_2$ (10 mg), HgO (100 mg), and powdered 4 Å molecular sieves (200 mg) in dichloromethane (3.0 mL) was stirred vigorously at room temperature under argon for 1 h. A solution of 2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl bromide[10] (50 mg, 0.14 mmol) in dry dichloromethane (1 mL) was added. The mixture was stirred for 2 h at room temperature, then diluted with dichloromethane, filtered, washed successively with aq. 10% sodium hydrogencarbonate and aq. 10% potassium iodide, dried (Na_2SO_4), and concentrated. Column chromatography (solvent *D*) of the residue yielded **3** (19 mg, 62%), $[\alpha]_D^{20}$ +21° (*c* 0.5, chloroform), R_F 0.44 (solvent *G*). N.m.r. data ($CDCl_3$): ^1H, δ 5.68 (s, 1 H, H-1 of D-Ara*f*), 5.15 (d, 1 H, $J_{1,2}$ 1.5 Hz, H-1 of D-Man*p*), 5.03 (d, 1 H, $J_{1,2}$ 3 Hz, H-1 of D-Glc*p*), 4.81 (d, 1 H, $J_{1,2}$ 1.7 Hz, H-1 of L-Rha*p*); ^{13}C, δ 169.95–169.75 [3 CO(OAc)], 166.1–165.1 (3 COPh), 118.2 (=CH_2), 106.7 (C-1, D-Ara*f*, $J_{C\text{-}1,H\text{-}1}$ 178 Hz), 97.9 (C-1, L-Rha*p*, $J_{C\text{-}1,H\text{-}1}$ 172 Hz), 95.6 (C-1, D-Man*p*, $J_{C\text{-}1,H\text{-}1}$ 171 Hz), 93.9 (C-1, D-Glc*p*, $J_{C\text{-}1,H\text{-}1}$ 166 Hz), 75.9, 74.9, 72.9, and 72.1 (4 *C*H_2Ph), 20.7–20.6 (3 *C*H_3CO), 17.3 (C-6, L-Rha*p*).

Anal. Calc. for $C_{81}H_{86}O_{25}$ (1459,50): C, 66.65; H, 5.94. Found: C, 66.59; H, 6.10.

Propyl O-α-D-*arabinofuranosyl-(1→2)*-O-α-D-*mannopyranosyl-(1→2)*-O-α-L-*rhamnopyranosyl-(1→6)*-α-D-*glucopyranoside* (**2**). — The pH of a solution of **3** (25 mg, 0.017 mmol) in methanol (15 mL) was adjusted to 8 by the addition of methanolic 0.1M sodium methoxide (1 mL). The mixture was stored overnight at room temperature, then neutralized with Bio-Rad AG 50W-X12 (H^+) resin, filtered, and concentrated. Methyl benzoate was extracted from the residue with 1:1 ether–hexane (3 × 1 mL). A solution of the amorphous residue in methanol was hydrogenolyzed at ambient pressure in the presence of 10% Pd/C (35 mg) for 18 h, then filtered through Celite which was washed with methanol and D_2O. The combined filtrate and washings were concentrated to give **2** as a colourless syrup (16.8 mg, ~99%), $[\alpha]_D^{20}$ +42° (*c* 0.6, water), R_F 0.50 (solvent *E*). N.m.r. data (D_2O + CD_3OD): ^1H, 5.13 (d, 1 H, $J_{1,2}$ 1.7 Hz, H-1 of D-Ara*f*), 5.12 (d, 1 H, $J_{1,2}$ 3.2 Hz, H-1 of D-Glc*p*), 5.10 (d, 1 H, $J_{1,2}$ 1.7 Hz, H-1 of D-Man*p*), 4.79 (d, 1 H, $J_{1,2}$ 1.8 Hz, H-1 of L-Rha*p*); ^{13}C, δ 110.3 (C-1, D-Ara*f*, $J_{C\text{-}1,H\text{-}1}$ 174 Hz), 101.2 (C-1, L-Rha*p*, $J_{C\text{-}1,H\text{-}1}$ 170 Hz), 97.3 (C-1, D-Man*p*, $J_{C\text{-}1,H\text{-}1}$ 172 Hz), 95.9 (C-1, D-Glc*p*, $J_{C\text{-}1,H\text{-}1}$ 169 Hz), 84.5 (C-4, D-Ara*f*), 82.1 (C-2, D-Ara*f*), 22.0 ($CH_3CH_2CH_2O$), 16.7 (C-6, L-Rha*p*), 10.2 ($CH_3CH_2CH_2O$).

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