→ 3.443, 2.435; 1.419 → 6.961, 2.435, 1.910; 0.623 → 5.951, 5.164, 5.030.

Acknowledgment. This research was supported by Grant No. CHE 83-03996 from the National Science Foundation.

Registry No. 1, 92219-95-9; 3, 109217-15-4; 4, 109217-16-5; 5, 109217-17-6; 6, 109281-38-1; 7, 109217-18-7; 8, 109217-19-8; 9, 102045-13-6; 10, 101968-76-7; 11, 106865-63-8.

Synthesis of C-Glycosides of 3-Deoxy-D-*manno*-2-octulosonic Acid. Stereoselectivity in an Enolate Reaction

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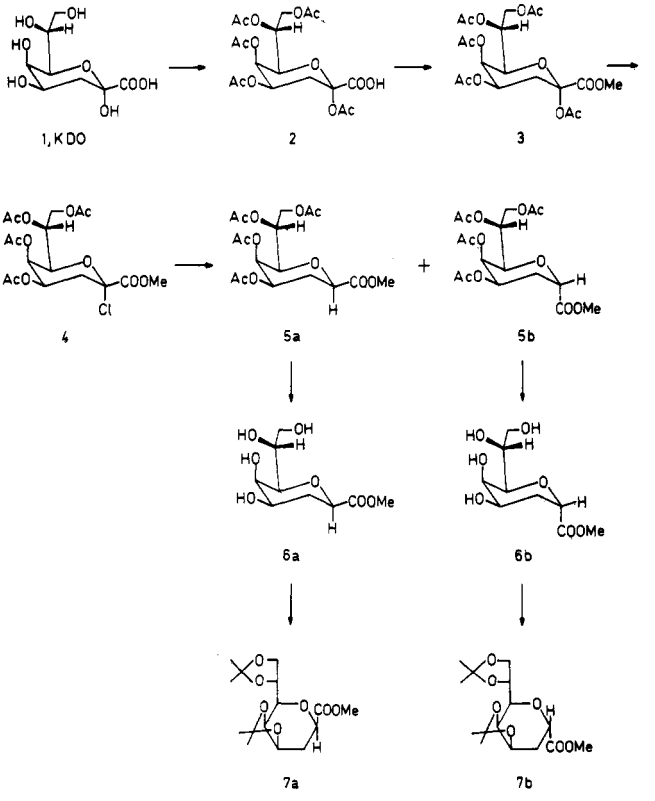
Eight different C-glycosidic derivatives of 3-deoxy-D-*manno*-2-octulosonic acid (KDO) were prepared by reacting the enolate of methyl or ethyl 2,6-anhydro-3-deoxy-4,5:7,8-di-*O*-isopropylidene-D-*glycero*-D-*talo*-(or *galacto*)octonate (**7a,b** and **22**) with the electrophiles cyanogen, formaldehyde, carbon dioxide, acetic anhydride, acetyl chloride, phenyl acetate, iodomethane, 3-bromopropyne, benzyl bromide, *tert*-butyl 2-bromoacetate, and methyl acrylate. All C-glycosides were formed with the β-configuration predominating; the β to α ratio varied from 70:30 (formaldehyde, phenyl acetate) to ≥95:5 (alkyl halides). Total yields varied from 30% to 67%. The key intermediates in the synthesis, i.e., the acetonide-protected 2-deoxy-KDO derivatives **7a,b**, were prepared by hydrogenolysis of 4,5,7,8-tetra-*O*-acetyl-2-chloro-2-deoxy-KDO (**4**) followed by deacetylation and acetonide formation. α,β-Configurations were assigned on the basis of chemical correlation with the nitrile **9b**, which has been studied by X-ray crystallography, and of the three-bond coupling constants between the C-glycosidic carbon and the deoxyprotons at C-3. Labeling with $^{13}CO_2$ was used in one instance.

Introduction

The biosynthesis of the lipopolysaccharide (LPS) of Gram-negative bacteria has recently attracted interest in connection with developing novel antibacterial agents with specificity for Gram-negative bacteria.[2] Our work has focused on the inhibition[3] of the enzyme CTP:CMP-3-deoxy-2-octulosonate cytidylyl-transferase (CMP-KDO synthetase) which catalyzes the formation of the nucleotide derivative CMP-KDO from KDO (**1**)[4] and cytidine triphosphate. It has recently been shown by ^{13}C NMR spectroscopy that the enzyme utilizes the β-pyranose form of KDO as a substrate.[5] This was also indicated by our earlier observation that only the β-2-deoxy and not the α-2-deoxy analogue of KDO is an inhibitor of the enzyme.[3a]

In order to further investigate the inhibitory activity of structural analogues of KDO, we have synthesized C-glycosides of KDO, a class of compounds that are unknown in the literature.[3c] The new carbon–carbon bond was formed in a straightforward way by an enolate reaction (eq 1) of compounds **7a** and **7b** separately or as a mixture or of a mixture of the corresponding ethyl esters (**22**).

Scheme I



Knowledge of the stereochemistry of the enolate reaction[7] was of crucial importance for the applicability of the

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(2) (a) Allen, N. E. *Annu. Rep. Med. Chem.* **1985**, *20*, 155–162. (b) Ray, P. H.; Kelsey, J. E.; Bigham, E. C.; Benedict, C. D.; Miller, T. A. *Bacterial Lipopolysaccharides* (Eds. Andersson, L., Unger, F. M. Eds.; ACS Symposium Series 231, 1983; pp 141–170.

(3) (a) Claesson, A.; Luthman, K.; Gustafsson, K.; Bondesson, G. *Biochem. Biophys. Res. Commun.* **1987**, *143*, 1063–1068. (b) Luthman, K.; Claesson, A.; Jansson, A.; Pring B. G. *Carbohydr. Res.* **1987**, in the press. (c) **Note added in proof**: Abbott workers have also prepared C-glycosides of KDO: Norbeck, D. W.; Kramer, J. B.; Lartey, P. A. *J. Org. Chem.* **1987**, *52*, 2174–2179.

(4) 3-Deoxy-D-*manno*-2-octulosonic acid. For a review on the chemistry and biochemistry of KDO, see: Unger, F. M. *Adv. Carbohydr. Chem. Biochem.* **1981**, *38*, 323–388.

(5) Kohlbrenner, W. E.; Fesik, S. W. *J. Biol. Chem.* **1985**, *260*, 14695–14700.

(6) Claesson, A. *J. Org. Chem.*, in press.

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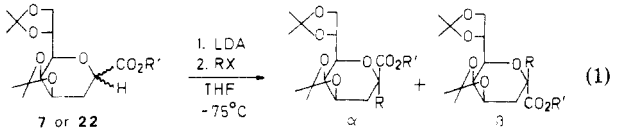


(1)

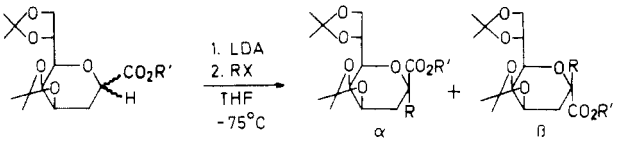
reaction to the synthesis of C-glycosides of KDO with the β-configuration at C-2. Determination of the stereochemistry of alkylation of enolate anions of several substituted cyclic carboxylic esters has been reported.[8] During recent years several reports on α-heterosubstituted carboxylate derivatives have also been published.[9a-g] Very recently Deslongchamps[9h,i] reported studies on alkylation of an enolate derived from a tetrahydropyran-3-carboxylic acid ester. However, to our knowledge nothing has been published on enolates from tetrahydropyran-2-carboxylic ester systems. It is known that both steric and stereoelectronic[9h,10] effects are important for the stereoselectivity in enolate reactions, normally with the steric effects dominating.[7] The observation[8] that heteroatoms in an enolate can affect the stereochemical course is of special relevance to the present system; the cause is probably to be found in their ability to affect the conformation by chelating inter- or intramolecularly with the metal countercation. Influences of base,[11] solvent,[12] and countercation[13] in addition to the above factors make it difficult to predict the stereochemistry in many enolate reactions.

Results

Compounds **7a** and **7b** were obtained according to Scheme I; the known pentaacetate **2**[14] was converted to the methyl ester **3** by reaction with cesium carbonate and iodomethane in *N,N*-dimethylformamide (DMF), thus avoiding the somewhat hazardous diazomethane procedure used by others.[14]

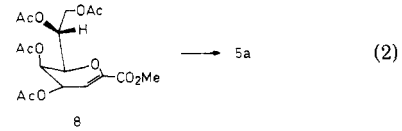
Hydrogenolysis of the chloride **4**,[15] obtained from **3**, proceeded well when pyridine was used as an acid scavenger;[16] a mixture of the epimers **5b** and **5a** in a 11:1 ratio was obtained in high yield.[17] The epimers could be separated by silica gel chromatography. The structures assigned to **5a** and **5b** were deduced from a comparison with the hydrogenation product obtained from the glycal **8**[18] (eq 2).

Table I. Products and α/β Ratios of the Enolate Reactions of Compounds 7a, 7b, and 22



R	R'	Cpd. no.	% α	Cpd. No.	% β	Total yield %
-CN	Me	9a	< 5	9b	> 95	47
-CN	Et	15a	10	15b	90	55
$-CH_2OH$	Et	14a	25[a]	14b	75	46
$-CH_2OH$	Et	14a	10[b]	14b	90	47
$-COCH_3$	Et	16a	30[c]	16b	70	60
$-COCH_3$	Et	16a	5[d]	16b	95	62
$-COCH_3$	Et	16a	15[e]	16b	85	55
-Me	Et	17a	< 5	17b	> 95	50
$-CH_2C{\equiv}CH$	Et	18a	10	18b	90	50[f]
$-CH_2CO_2t$-Bu	Et	19a	< 5	19b	> 95	30
$-CH_2Ph$	Me	20a	5	20b	95	67
$-CH_2CH_2CO_2Me$	Et	21a	25	21b	75	27[f]

[a] From (1) CO_2; (2) Vilsmeier reagent; (3) $NaBH_4$ (Scheme III). [b] From CH_2O. [c] From phenyl acetate. [d] From acetic anhydride. [e] From acetyl chloride. [f] GC yield.



(2)

Hydrogen is expected to be added from the sterically less hindered side, thus giving epimer **5a** as the major product. The main product (>90%) isolated from the hydrogenation mixture was shown to be identical with the minor product from the hydrogenolysis reaction, thus allowing structural assignments as shown. Unger et al. also have briefly reported the synthesis of **5a** from **8** by the hydrogenation procedure.[18b] Compounds **5a** and **5b** were deacetylated by treatment with sodium methoxide in methanol, giving compounds **6a** and **6b**, respectively. These compounds were converted to the diacetonides **7a** and **7b** by an exchange reaction with 2,2-dimethoxypropane in anhydrous acetone catalyzed by *p*-toluenesulfonic acid.[19]

A great difference in reactivity between **6a** and **6b** was observed in these reactions. Compound **7b** was readily formed from **6b** in high yields (>80%) while compound **7a** under the same reaction conditions was formed in yields

(7) General review, see; e.g.: (a) Evans, D. A. In *Asymmetric Synthesis*; Academic Press: New York, Morrison J. D., Ed.; 1984; Vol. 3, Chapter 1. (b) Jackman, L. M.; Lange, B. C. *Tetrahedron* **1977**, *33*, 2337–2769. (c) d'Angelo, J. *Tetrahedron* **1976**, *32*, 2979–2990.

(8) Krapcho, A. P.f Dundulis, E. A. *J. Org. Chem.* **1980**, *45*, 3236–3245.

(9) (a) Touzin, A. M. *Tetrahedron Lett.* **1975**, 1477–1480. (b) Naef, R.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 1030–1031. (c) Seebach, D.; Naef, R. *Helv. Chim. Acta* **1981**, *64*, 2704–2708. (d) Seebach, D., Boes, M.; Naef, R. *J. Am. Chem. Soc.* **1983**, *105*, 5390–5398. (e) Seebach, D.; Aebi, J. D. *Tetrahedron Lett.* **1983**, *24*, 3311–3314. (f) Seebach, D.; Weber, T. *Tetrahedron Lett.* **1983**, *24*, 3315–3318. (g) Seebach, D.; Naef, R.; Calderari, G. *Tetrahedron* **1984**, *40*, 1313–1324. (h) Caron, M.; Kawamata, T.; Ruest, L.; Soucy, P.; Deslongchamps, P. *Can. J. Chem.* **1986**, *64* 1781–1787. (i) Ndibwami, A.; Deslongchamps, P. *Can. J. Chem.* **1986**, *64*, 1788–1794.

(10) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Baldwin, J. E., Ed.; Pergamon Press: New York, 1983; pp 274–284 and references therein.

(11) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066.

(12) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868–2877.

(13) Heathcock, R. M. In *Asymmetric Synthesis*; Academic Press: Morrison, J. D., Ed.; 1984; Vol. 3, Chapter 2.

(14) (a) Ghalambor, M. A.; Levine, E. M.; Heath, E. C. *J. Biol. Chem.* **1966**, *241*, 3207. (b) Unger, F. M.; Stix, D.; Schultz, G. *Carbohydr. Res.* **1980**, *80*, 191. (c) Charon, D.; Szabo, L. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2369.

(15) Bhattacharjee, A. K.; Jennings, H. J.; Kenny, C. P. *Biochemistry* **1978**, *17*, 645–651.

(16) Triethylamine could also be used as an acid scavenger but was found to give a lower ratio of **5b** to **5a**, 3:1 (A. Jansson, personal communication). This might be due to facilitated elimination of HCl from **4**, giving the glycal **8** which gives **5a** upon hydrogenation.

(17) Compound **5b** is thermodynamically more stable than **5a** due to the anomeric effect of the carboxymethyl group which has been found to be 0.6 kcal/mol: Franck, R. W. *Tetrahedron* **1983**, *39*, 3251–3252. The present reaction is not, however, thermodynamically controlled.

(18) (a) Claesson, A.; Luthman, K. *Acta Chem. Scand., Ser. B* **1982**, *B36*, 719–720. (b) Unger, F. M.; Stix, D.; Schwarzinger, E.; Schulz, G. Communication at the 9th International Symposium on Carbohydrate Chemistry, London, 1978, Abstract No. B-49.

(19) Initially the intention was to use the tetra-*O*-benzyl derivatives of **6a** and **6b** as starting materials in the enolate reactions. However, attempts to synthesize these derivatives, e.g., by treatment of **6a** and **6b** with sodium hydride and benzyl bromide in DMF or in dimethyl sulfoxide were not satisfactory since the yields were lower than 20%. Silver oxide mediated reactions with benzyl bromide in DMF likewise proved to be unsatisfactory.

(20) Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879.

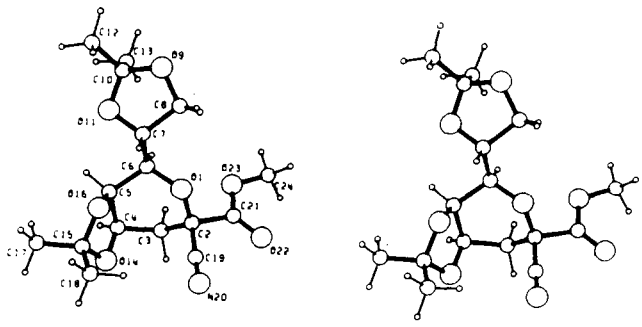


Figure 1. X-ray structure of the nitrile **9b**.[21]

lower than 40%. Increase in temperature or use of 2-methoxypropene instead of 2,2-dimethoxypropane did not affect the yield. However, the yields were improved by using freshly distilled 2,2-dimethoxypropane and adding magnesium sulfate to the reaction mixture.

An alternative synthesis of **22** from 2,3:5,6-di-*O*-isopropylidenemannose has been carried out.[6]

The lithium enolate from **7a** and **7b**, separately or as a mixture, or from **22** was formed by treatment with lithium diisopropylamide (LDA) in THF at −75 °C. The enolates appeared to be unstable at slightly higher temperatures, since the reaction mixtures started to turn yellow at −55 to −50 °C. In addition, very little material could be recovered when reactions were run at these temperatures even when the product yields were low. It was possible, however, to run the reaction at −75 °C by using reactive electrophiles (Table I).

In some enolate reactions both C-2 epimers of the products could be isolated and identified. When this was not possible, the structural assignment was based on NMR of mixtures; the regular behavior of the analogous epimers on TLC and GC was also helpful. The epimeric ratio was not altered by using the epimers **7a** and **7b** separately as opposed to mixing them or by using the ethyl esters **22**. The product ratio was also unaffected by the metalation time and the amount of LDA used.

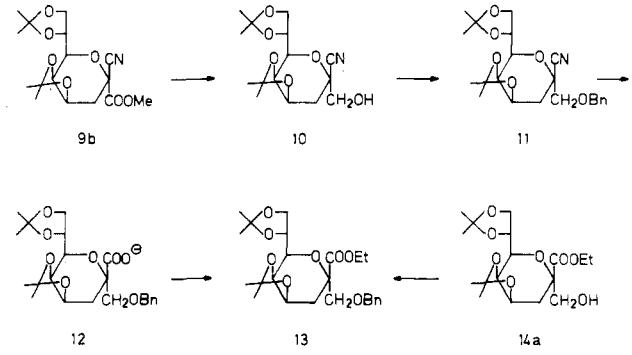
Recovered **7a** or **7b** was often found to have undergone epimerization with compound **7b** being the predominant epimer. The equilibrium ratio was determined in a separate experiment by treatment of the pure epimers **7a** and **7b** with 1 equiv of sodium methoxide in dry methanol at room temperature under a nitrogen atmosphere. The epimerization equilibrium was established instantaneously with a ratio of **7b** to **7a** of 4:1 according to GC. Some decomposition could be observed after a reaction time of several hours.

The reaction of the enolate derived from a mixture of **7a** and **7b** with cyanogen as the electrophile gave a 95:5 mixture of epimeric nitrile esters **9b** and **9a** in a yield of 47%. The ethyl esters **22** gave a very similar result (Table I). The product **9b** was studied by X-ray crystallography[21] whereby the C-2 configuration was shown to be β (Figure 1).

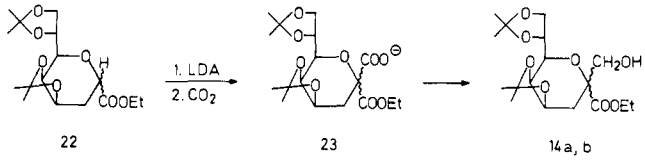
Synthesis of the 2-hydroxymethyl analogues of KDO, compounds **14a** and **14b**, was performed by passage of gaseous formaldehyde through a solution in THF of the enolate from **22**.[22] **14b** and **14a** were formed in a 90:10 ratio.

The configuration at C-2 of the major product, compound **14b**, was determined by a chemical method described in Scheme II. The ester functionality was reduced selectively with sodium borohydride[23] to give the nitrile alcohol **10**. The alcohol was converted to a benzyl ether by treatment with benzyl bromide and sodium hydride to give **11**. The cyano group was then hydrolyzed with potassium hydroxide and hydrogen peroxide and the resulting carboxylate **12** was esterified with iodoethane and cesium carbonate in DMF to give **13**. Attempts to hydrolyze the cyano group of **10** gave very low yields of the carboxylate. The strong alkaline conditions used probably catalyzed a retro-aldol-like reaction leading to decomposition. Compound **13** isolated from this reaction sequence was compared (GC) and found to be identical with the compound obtained when the minor product from the enolate reaction with formaldehyde (compound **14a**) was converted to its benzyl ether derivative. It has thus been demonstrated that formaldehyde also attacks the enolate, predominantly from the β-face.

Scheme II



Scheme III

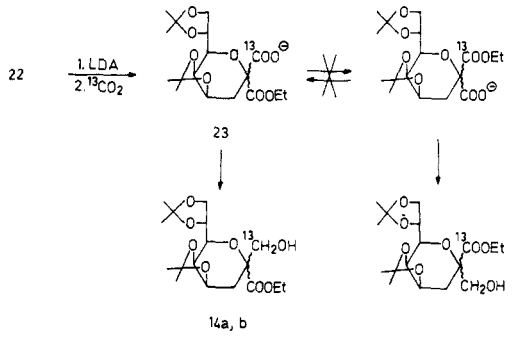


The hydroxymethyl analogues **14a,b** were also synthesized by another reaction pathway (Scheme III). Gaseous carbon dioxide was passed through a solution of the enolate at −75 °C.[24] The resulting carboxylate esters **23** were treated with *N,N*-dimethylchloromethyleneiminium chloride, prepared from DMF and oxalyl chloride according to Fujisawa et al.[25] The carboxymethyleneiminium salt thus formed was reduced with sodium borohydride to the alcohols **14a** and **b**. Also in this reaction compound **14b** was the major product and the total yield was similar to the direct hydroxymethylation reaction (Table I).

It was subsequently determined that carbon dioxide also reacts at the β-face of the enolate. However, it was not possible to determine this directly due to a potential intra- or intermolecular transesterification reaction of **23**. This possibility was inferred from an observation that carboxylation of the enolate generated from **7b** results in a 50:50 mixture of epimeric carboxylate ester analogues of **23** (^{1}H NMR), which was believed to be a result of a transesterification during the workup procedure.[3b] Experiments to determine whether a scrambling process might occur

(21) Additional crystallographic data on compound **9b** will be published elsewhere by Dr. I. Csöregh.
(22) Grieco, P. A.; Hiroi, K. *J. Chem. Soc., Chem. Commun.* **1972**, 1317–1318.
(23) Hanaya, K.; Koga, Y.; Yamagughi, A.; Kudo, H.; Chow, Y. L. *Nouv. J. Chim.* **1982**, *6*, 149–154.
(24) Reiffers, S.; Wynberg, H.; Strating, J. *Tetrahedron Lett.* **1971**, 3001–3004.
(25) Fujisawa, T.; Mori, T.; Sato, T. *Chem. Lett.* **1983**, 835–838.

Scheme IV



before workup, even at the low temperatures used, were done by reacting the enolate from **22** with ^{13}C-labeled carbon dioxide, formed from $K_2{}^{13}CO_3$ and sulfuric acid (Scheme IV). Subsequent reaction with the iminium salt and borohydride reduction as in Scheme III gave a product mixture that could be analyzed by ^1H and ^{13}C NMR spectroscopy. According to NMR spectra the ^{13}C label was only found in the hydroxymethyl groups of both epimers **14a** and **14b**.

If a transesterification reaction had occurred, the ^{13}C-label should have been found in both the carboxylate ester group and the hydroxymethyl group as indicated in Scheme IV. After having established that no scrambling occurred, it was possible from the known configurations of **14a** and **14b** to deduce the β-selectivity of the carbon dioxide reaction (cf. above and Table I).

Measurements of the three-bond coupling constants[26] from ^{13}C in the hydroxymethyl group to the deoxy protons at C-3 gave further proof of the configuration. The hydroxymethyl group in **14b** is supposed to occupy an axial or a pseudoaxial position (cf. Figure 1), which results in a gauche relationship to one of the two deoxy protons at C-3 and a trans relationship to the other. Larger values of the coupling constants are thus expected in **14b** than in **14a** where the hydroxymethyl group occupies an equatorial or pseudoequatorial position. The coupling constants in **14b** were found to be $^3J_{3ax,C'} = 6.2$ Hz and $^3J_{3eq,C'} = 5.4$ Hz and in the epimer **14a** 5.3 Hz and <1 Hz, respectively (Figure 2). Measurements of the corresponding coupling constants in the completely deprotected products from **14a** and **14b** corroborated these assignments.[27a]

Alkylation of the enolate was performed by using four different halides, benzyl bromide, 3-bromo-1-propyne, iodomethane, and *tert*-butyl 2-bromoacetate (Table I).

The benzylated epimers **20a** and **20b** gave remarkably different responses to UV light on TLC plates. The α-epimer **20a** was not detectable under UV light while the β-epimer **20b** was easy to detect. Both compounds responded equally well on TLC when charred with sulfuric acid.

The reaction of the enolate from **22** with iodomethane led in 50% yield to a product ratio of **17b** to **17a** greater than 65:5, while use of other alkyl iodides (1-iodohexane, 2-(2-(benzyloxy)ethoxy)-1-iodoethane), met with complete failure. Attempts to promote the latter reactions by addition of hexamethylphosphoramide also proved unsuccessful. The C-2 configuration of **17b** was determined by proton-coupled ^{13}C NMR spectroscopy of the deprotected compound and was shown to be β.[27b] Similarities in ^1H

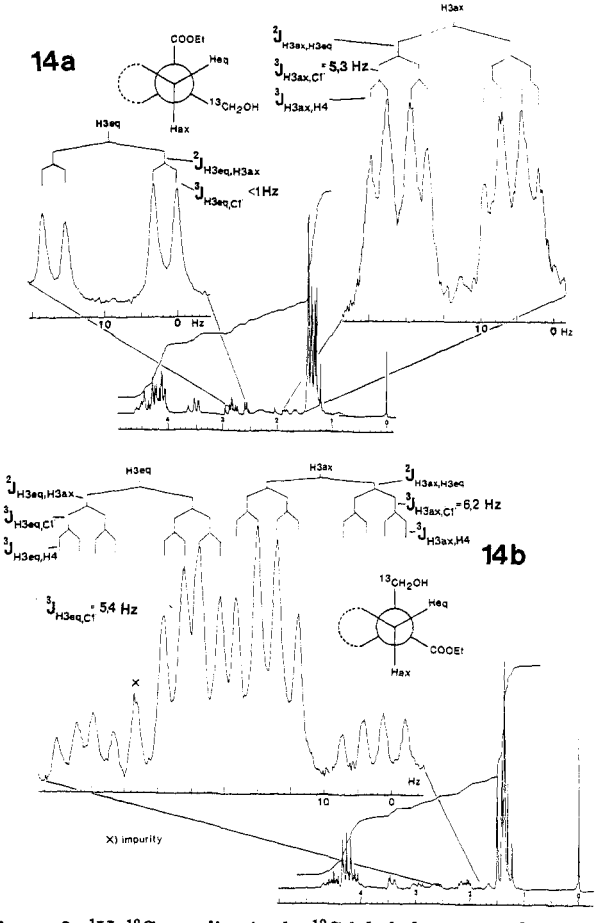


Figure 2. ^1H–^{13}C coupling in the ^{13}C-labeled compounds **14a** and **14b** ($^3J_{H,C'}$).

NMR spectra of **17b** and of the major product from each of the other three alkylation reactions suggest that these also have the β-configuration. In reactions using ethyl 2-bromoacetate as the alkylating agent, it was found that the products were very difficult to separate from starting material by silica gel chromatography. In order to increase the lipophilicity of the products formed, octyl 2-bromoacetate was used as an electrophile in the reaction. However, a careful examination of the product mixture from this reaction revealed that the enolate attacked the electrophile not only at the 2-position but also to a lesser extent at the carbonyl carbon. This side reaction was eliminated by using *tert*-butyl 2-bromoacetate, which gave the products **19** in a low yield (30%) and a ratio β to α of 95:5.

Methyl acrylate was used in a Michael reaction with the enolate which gave products **21a,b**. The stereoselectivity in this reaction was lower than in most of the other alkylation reactions with a product ratio β to α of 75:25.

Acetylation of the enolate from **22** was performed with three different acetylating agents, i.e., acetyl chloride, acetic anhydride, and phenyl acetate. The epimeric ratios are given in Table I. In the reaction using acetyl chloride, two byproducts were isolated, which, according to ^1H and ^{13}C NMR, appeared to result from *O*-acetylation of the enolate (*E* and *Z* isomers). Traces of these byproducts were also detected in the reactions with acetic anhydride but could not be found in reactions with phenyl acetate as an electrophile.

The β-selectivity in the methyl acrylate reaction and the acylation reactions was presumed in accordance with the results from the reactions with cyanogen, formaldehyde, and carbon dioxide.

(26) Haverkamp, J.; Spoormaker, T.; Dorland, L.; Vliegenthart, J. F. G.; Schauer, R. *J. Am. Chem. Soc.* **1979**, *101*, 4851–4853.
(27) (a) Orbe, M., unpublished results. (b) Wåglund, T., unpublished results.

Discussion

The present results establish the enolate reaction of diacetonide-protected KDO esters as a useful synthetic method for β-C-glycosides. The simple derivatives obtained can then be further elaborated to provide potential enzyme inhibitors.

The β-stereoisomer could be identified as the major product in all reactions. Pure **7a** and **7b** gave the same stereochemical result on alkylation, indicating that the same enolate intermediate is involved in both reactions.

The pyranose ring system in compounds **7a**, **7b**, and **22** has a rigid geometry due to the dioxolane ring at the 4,5-positions and for **7b** has been shown to adopt a conformation in solution that is intermediate between a skew-boat and a boat.[3b] The conformation of the epimer **7a** is not known. The twisted boat form is also the preferred conformation for the alkylation products presented here (cf. Figure 1). As to the conformation of the enolate, it does not seem possible to conclude from molecular models which is the preferred one.

Of the electrophiles used only cyanogen is worthy of a comment. Interestingly, this gas does not appear to have been used as a source of "positive cyanide" in enolate reactions although its reactions with Grignard reagents have been known for a long time.[28] Tosyl cyanide has been recommended[29] instead but this reagent was not as efficient as cyanogen in the present enolate reaction.

There is not a readily apparent trend regarding the variability in stereoselectivity among the electrophiles. It is conspicuous, however, that alkyl halides give greater than 90% β-selectivity whereas the distinctly different formaldehyde only gives 70%. This distinction is interesting to note in reference to the reversal of stereoselectivity observed in a similar reaction when going from alkyl halides to acetone.[9b]

Experimental Section

General. Melting points were determined in open capillary tubes and are uncorrected. Optical rotations were measured with a Perkin-Elmer 241 polarimeter at ambient temperature. NMR spectra were recorded with JEOL FX90Q or JEOL FX200 instruments. Tetramethylsilane (Me_4Si) was used as internal standard in $CDCl_3$ and *tert*-butyl alcohol (δ_H 1.23 and δ_C 32.2) in D_2O. Coupling constants are measured in hertz. GC analyses were performed on a Varian 2700 chromatograph equipped with a 2.7-m glass column packed with 3% OV-25 on Varaport 30 (80/100 mesh) at temperatures between 200 and 295 °C. TLC was performed on Merck silica gel 60 F_{254} aluminum sheets and spots on chromatograms were detected by UV light and/or by spraying with sulfuric acid and heating. Column chromatography was performed on Merck silica gel 60 (0.040–0.063 mm). Tetrahydrofuran (THF) was obtained dry and free from oxygen by distillation from a solution of ketyl (benzophenone and sodium). *n*-Butyllithium in hexane was titrated prior to use.[20] Diisopropylamine was kept over potassium hydroxide for 24 h and was then distilled. Elemental analyses were carried out at Mikrokemi AB, Uppsala.

Methyl 2,4,5,7,8-Penta-*O*-acetyl-3-deoxy-α-D-*manno*-2-octulosonate (3). Cs_2CO_3 (2.6 g, 8.0 mmol) followed by iodomethane (0.5 mL, 8.0 mmol) were added to a solution of **2** (3.0 g, 6.7 mmol) in DMF (40 mL) and the mixture was stirred overnight at room temperature. After evaporation of the volatiles and addition of ethyl acetate, the product precipitated in a yield of 45%. The mother liquor was concentrated and the residue was chromatographed on silica gel with ethyl acetate/hexane (5:2) as eluent, affording compound **3** in a total yield of 82%: mp 159–160 °C (lit.[14b] mp 155–156 °C); $[\alpha]_D$ +105.8° (*c* 3.2, $CHCl_3$).

Methyl 4,5,7,8-Tetra-*O*-acetyl-2-chloro-2,3-dideoxy-α-D-*manno*-2-octulosonate (4). $TiCl_4$ (0.9 mL, 8.2 mmol) was added to a stirred solution of **3** (2.5 g, 5.4 mmol) in dichloromethane (30 mL). After 4 h at room temperature the mixture was concentrated. The yellowish solid was triturated several times with ether and the combined ether extracts were concentrated. The residue was chromatographed on silica gel with ether as eluent, affording pure semicrystalline **4** in a yield of 82%: $[\alpha]_D$ +132.4° (*c* 2.4, $CHCl_3$) (lit.[15] $[\alpha]_D$ +138°).

Methyl 4,5,7,8-Tetra-*O*-acetyl-2,6-anhydro-3-deoxy-D-*glycero*-D-galacto- and -D-*talo*-octonate (5a and 5b). A suspension of **4** (2.0 g, 4.6 mmol), pyridine (1 mL), and Pd on charcoal (10%, 1 g) in toluene (25 mL) was hydrogenated in a Parr apparatus at 40 psi for 8 h. The reaction mixture was then filtered through Celite and the solvent evaporated. The syrupy residue was purified on a silica gel column with ether/pentane (2:1) as eluent, affording **5a** (0.11 g, 6%) and **5b** (1.25 g, 68%), respectively. **5a**: mp 113–115 °C (lit.[18b] mp 118–120 °C); $[\alpha]_D$ +41.6° (*c* 2.2, $CHCl_3$) (lit.[18b] $[\alpha]_D$ +41.8°);[18b] ^1H NMR ($CDCl_3$) δ 2.0–2.15 (m, 14 H, acetyls, H3ax, H3eq), 3.79 (s, 3 H, OMe), 3.80 (dd, 1 H, $J_{6,7}$ = 9.8, $J_{6,5}$ = 0.6, H6), 4.12–4.20 (m, 2 H, H8, H8′), 4.54 (dd, 1 H, $J_{2,3ax}$ = 12.5, $J_{2,3eq}$ = 2.6, H2), 5.08 (ddd, 1 H, $J_{4,3ax}$ = 11, $J_{4,3eq}$ = 6, $J_{4,5}$ = 3.1, H4), 5.22 (ddd, 1 H, $J_{7,8}$ = 4.3, $J_{7,8'}$ = 2.4, H7), 5.30 (d, 1 H, H5); ^{13}C NMR ($CDCl_3$) δ 20.60, 20.68 (acetyls), 28.63 (C3), 52.37 (OMe), 62.42 (C8), 64.54, 67.67, 69.10, 74.63, 74.78 (C2, C4, C5, C6, C7), 169.24, 169.30, 169.50, 170.32, 170.44 (C1, acetyls). Anal. Calcd for $C_{17}H_{24}O_{11}$: C, 50.50; H, 5.98. Found: C, 50.5; H, 6.2. **5b**: mp 102–104 °C; $[\alpha]_D$ +108.8° (*c* 2.2, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.99, 2.01, 2.10, 2.11 (4s, 12 H, acetyls), 2.13–2.39 (m, 2 H, H3ax, H3eq), 3.78 (s, 3 H, OMe), 4.23–4.31 (m, 2 H, H8, H8′), 4.43 (dd, 1 H, $J_{8,8'}$ = −12.2, $J_{8,7}$ = 2.4, H8), 4.66 (dd, 1 H, $J_{2,3ax}$ = 6.1, $J_{2,3eq}$ = 1.5, H2), 4.96 (ddd, 1 H, $J_{4,3ax}$ = 12.2, $J_{4,3eq}$ = 5.2, $J_{4,5}$ = 2.7, H4), 5.09 (ddd, 1 H, $J_{7,6}$ = 9.5, $J_{7,8'}$ = 4.7, H7), 5.32 (d, 1 H, H5); ^{13}C NMR ($CDCl_3$) δ 20.77, 20.86 (acetyls), 26.36 (C3), 52.38 (OMe), 62.54 (C8), 64.92, 66.72, 67.99, 70.47, 72.22 (C2, C4, C5, C6, C7) 169.63 (overlapping signals), 170.12, 170.41, 170.65 (C1, acetyls). Anal. Calcd for $C_{17}H_{24}O_{11}$: C, 50.50; H, 5.98. Found: C, 50.4; H, 6.2.

Hydrogenation of Compound 8. An Alternative Synthesis of Compound 5a. Compound **8**[18] (2.5 g, 6.2 mmol) in ethyl acetate (25 mL) was hydrogenated with Pd on charcoal (10%, 1 g) in a Parr apparatus at 40 psi for 12 h. The workup procedure was the same as described for **5a** and **5b**. Compound **5a** was isolated in a yield of 93%.

Methyl 2,6-Anhydro-3-deoxy-D-*glycero*-D-*galacto*-octonate (6a). Compound **5a** (0.5 g, 1.2 mmol) was treated with sodium methoxide (from 65 mg of Na) in methanol (20 mL) for 1 h. Neutralization with methanol-washed Dowex H^+ ion exchange resin, filtration, and concentration gave **6a** (290 mg, 100%): mp 170–171 °C (lit.[18b] mp 152–158 °C); $[\alpha]_D$ +49.0° (*c* 2.4, MeOH) (lit.[18b] $[\alpha]_D$ +49.6°); ^1H NMR (D_2O) δ 1.77 (ddd, 1 H, $J_{3ax,3eq}$ = −12.2, $J_{3ax,2}$ = 12.2, $J_{3a,4}$ = 12.2, H3ax), 2.88 (ddd, 1 H, H3eq), 3.42 (d, 1 H, $J_{6,7}$ = 8.8, H6), 3.66 (dd, 1 H, $J_{8,8'}$ = −12.2, $J_{8',7}$ = 5.8, H8′), 3.76 (s, 3 H, OMe), 3.79–3.95 (m, 3 H, H4, H7, H8), 3.99 (br s, 1 H, H5), 4.22 (dd, 1 H, $J_{2,3eq}$ = 2.4, H2); ^{13}C NMR (D_2O) δ 31.11 (C3), 53.64 (OMe), 63.78 (C8), 66.91 (C5), 69.43 (C4), 69.87 (C7), 75.04 (C2), 78.19 (C6), 173.61 (C1). Anal. Calcd for $C_9H_{16}O_7$: C, 45.76; H, 6.83. Found: C, 45.3; H, 6.8.

Methyl 2,6-Anhydro-3-deoxy-D-*glycero*-D-*talo*-octonate (6b). The same procedure as above for compound **5b** (1.25 g, 3.1 mmol) and sodium methoxide (from 100 mg of Na) gave crystalline **6b** (730 mg, 100%): mp 74–75 °C; $[\alpha]_D$ +75.9° (*c* 2.4, MeOH); ^1H NMR (D_2O) δ 2.07–2.28 (m, 2 H, H3ax, H3eq), 3.53 (d, 1 H, $J_{6,7}$ = 8.8, H6), 3.63–3.89 (m, 7 H, H4, H7, H8, H8′, including OMe δ 3.78), 3.97 (br s, 1 H, H5), 4.67 (dd, 1 H, $J_{2,3ax}$ = 5.9, $J_{2,3eq}$ = 2.0, H2); ^{13}C NMR (D_2O) δ 28.38 (C3), 53.58 (OMe), 64.29 (C8), 66.96 (C5), 67.16 (C4), 70.25 (C7), 73.36 (C6), 75.60 (C2), 174.40 (C1). Anal. Calcd for $C_9H_{16}O_7$: C, 45.76; H, 6.83. Found: C, 45.4; H, 7.1.

Methyl 2,6-Anhydro-3-deoxy-4,5:7,8-di-*O*-isopropylidene-D-*glycero*-D-*galacto*-octonate (7a). Compound **6a** (1.5 g, 6.3 mmol) was dissolved in a mixture of freshly distilled 2,2-dimethoxypropane (5 mL) and anhydrous acetone (15 mL), *p*-toluenesulfonic acid (10 mg), and $MgSO_4$ (1.5 g) were added. After

(28) Grignard, V.; Bellet, E.; Courtot, C. *Ann. Chim. (Paris)* **1919**, *12*, 364–393.

(29) Kahne, D.; Collum, D. B. *Tetrahedron Lett.* **1981**, *22*, 5011. Tosyl cyanide is now commercially available (Aldrich).

3 h at room temperature the mixture was concentrated and the residue was chromatographed on silica gel with ether/hexane (3:1) as eluent, affording **7a** as a crystalline compound (1.6 g, 80%): mp 73–74 °C; $[\alpha]_D$ +30.4° (*c* 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.33, 1.42, 1.48 (3s, 12 H, isopropylidene methyls), 1.9–2.25 (m, 2 H, H3ax, H3eq), 3.52 (dd, 1 H, $J_{6,7}$ = 8, $J_{6,5}$ = 2, H6), 3.76 (s, 3 H, OMe), 4.0–4.52 (m, 6 H, H2, H4, H5, H7, H8, H8′); ^{13}C NMR ($CDCl_3$) δ 25.38, 25.94, 27.05, 27.30 (isopropylidene methyls), 30.39 (C3), 52.19 (OMe), 66.96 (C8), 71.03, 71.34, 72.33, 74.18, 75.67 (C2, C4, C5, C6, C7), 109.27, 109.58 ($C(CH_3)_2$), 171.28 (C1). Anal. Calcd for $C_{15}H_{24}O_7$: C, 56.95; H, 7.64. Found: C, 57.2; H, 7.9.

Methyl 2,6-Anhydro-3-deoxy-4,5:7,8-di-*O*-isopropylidene-D-*glycero*-D-*talo*-octonate (7b). The same procedure as above starting with compound **6b** (1.5 g, 6.3 mmol) afforded **7b** as a colorless syrup (1.7 g, 87%): $[\alpha]_D$ −45.9° (*c* 2.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.37, 1.38, 1.42, 1.49 (4s, 12 H, isopropylidene methyls), 1.86 (ddd, 1 H, $J_{3ax,3eq}$ = −14.9, $J_{3ax,2}$ = 11.8, $J_{3ax,4}$ = 2.5, H3ax), 2.31 (ddd, 1 H, $J_{3eq,2}$ = 5.9, $J_{3eq,4}$ = 3.2, H3eq), 3.51 (dd, 1 H, $J_{6,7}$ = 7.8, $J_{6,5}$ = 1.5, H6), 3.75 (s, 3 H, OMe), 4.10–4.25 (m, 3 H, H7, H8, H8′), 4.35 (dd, 1 H, $J_{5,4}$ = 8, H5), 4.52–4.63 (dd, H2; ddd, H4); ^{13}C NMR ($CDCl_3$) δ 24.89, 25.08, 26.19, 26.99 (isopropylidene methyls), 26.75 (C3), 51.95 (OMe), 67.20 (C8), 68.31 (C2), 69.74 (C4), 72.21 (C5), 75.82 (C6), 73.69 (C7), 109.20, 109.33 ($C(CH_3)_2$), 173.32 (C1). Anal. Calcd for $C_{15}H_{24}O_7$: C, 56.95; H, 7.64. Found: C, 57.2; H, 7.8.

Epimerization of Compounds 7a and 7b. Freshly prepared sodium methoxide solution (1 mL from 37 mg of sodium in 10 mL of methanol) was added to a solution of **7a** or **7b** (50 mg, 0.16 mmol) in dry methanol (3 mL). The mixture was stirred at room temperature for 12 h under a N_2 atmosphere. GC monitoring after 2 min indicated an epimeric ratio of 4:1 for **7b** and **7a**, which did not subsequently change.

General Procedure for Enolate Formation. *n*-Butyllithium in hexane (1.4 mmol) was added by means of a syringe to a solution of diisopropylamine (1.5 mmol) in 50 mL anhydrous THF at −20 °C under a nitrogen atmosphere. After 10 min the solution was cooled to −75 °C. After stirring for 15 min, compound **7a**, **7b**, or **22** (1.2 mmol) dissolved in 5 mL of anhydrous THF was added dropwise from a syringe. The metalation proceeded during 30 min at −75 °C before the electrophile was added.

Methyl 2,6-Anhydro-2-cyano-3-deoxy-4,5:7,8-di-*O*-isopropylidene-D-*glycero*-D-*talo*-octonate (9b). Cyanogen was bubbled for 5 min through a solution of the enolate (prepared from 1.2 g of **7b**; 3.8 mmol) at −75 °C. The dark brown solution was allowed to reach room temperature and 5 mL of saturated NH_4Cl solution was added. After concentration, the mixture was fractionated between ether and water. The ether fraction was dried (Na_2SO_4) and after concentration the crude mixture was chromatographed on silica gel with ether/hexane (2:1) as eluent, affording crystalline **9b** (0.6 g, 47%): mp 138–138.5 °C; $[\alpha]_D$ −7.3° (*c* 0.72, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.36, 1.40, 1.60 (3s, 12 H, isopropylidene methyls), 2.13 (dd, 1 H, $J_{3ax,3eq}$ = −15.9, $J_{3ax,4}$ = 2.4, H3ax), 2.68 (dd, 1 H, $J_{3eq,4}$ = 2.9, H3eq), 3.50 (dd, 1 H, $J_{6,7}$ = 8.2, $J_{6,5}$ = 1.7, H6), 3.89 (s, 3 H, OMe), 4.09–4.43 (m, 4 H, H5, H7, H8, H8′), 4.67 (ddd, 1 H, $J_{4,5}$ = 8.3, H4); ^{13}C NMR ($CDCl_3$) δ 24.56, 24.90, 25.48, 26.94 (isopropylidene methyls), 30.69 (C3), 53.88 (OMe), 66.72 (C8), 68.52 (C4), 69.30 (C2), 70.91, 72.90 (C5, C7), 73.63 (C6), 109.33, 110.01, ($C(CH_3)_2$), 116.77 (CN), 167.10 (C1). Anal. Calcd for $C_{16}H_{23}NO_7$: C, 56.30; H, 6.79; N, 4.10. Found: C, 56.4; H, 6.8; N, 4.0.

Ethyl 2,6-Anhydro-2-cyano-3-deoxy-4,5:7,8-di-*O*-isopropylidene-D-*glycero*-D-*galacto*- and -D-*talo*-octonate (15a and 15b). Cyanogen was bubbled for 5 min through a solution of the enolate (prepared from 300 mg of **22**; 1.5 mmol) at −75 °C. Workup as described for **9b** afforded **15a** as a colorless syrup (15 mg, 5%) and crystalline **15b** (160 mg, 50%). **15a**: ^1H NMR ($CDCl_3$) δ 1.27–1.44 (3s, 15 H, isopropylidene methyls, ester methyl), 2.30 (dd, 1 H, $J_{3ax,3eq}$ = −15.0, $J_{3ax,4}$ = 3.1, H3ax), 2.73 (dd, 1 H, $J_{3eq,4}$ = 5.0, H3eq), 3.71 (dd, $J_{6,7}$ = 7.7, $J_{6,5}$ = 1.5, H6), 4.03–4.55 (m, 7 H, H4, H5, H7, H8, H8′, ester methylene); ^{13}C NMR ($CDCl_3$) δ 14.21 (ester methyl), 25.20, 26.00, 26.93 (isopropylidene methyls), 63.50 (ester methylene), 66.96 (C8), 69.18, 71.09, 72.27, 73.38, 74.43 (C2, C4, C5, C6, C7), 109.39, 110.07 ($C(CH_3)_2$), 116.43 (CN), 164.86 (C1). **15b**: mp 120–121 °C; $[\alpha]_D$ −5.5° (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.28–1.60 (3s, 15 H, isopropylidene methyls, ester methyl), 2.11 (dd, 1 H, $J_{3ax,3eq}$ = −15.5, $J_{3ax,4}$ = 2.4, H3ax), 2.69 (dd, 1 H, $J_{3eq,4}$ = 3.1, H3eq), 3.50 (dd, 1 H, $J_{6,7}$ = 8.1, $J_{6,5}$ = 1.5 H6), 4.06–4.44 (m, 6 H, H5, H7, H8, H8′, ester methylene), 4.63 (ddd, 1 H, $J_{4,5}$ = 8.3, H4); ^{13}C NMR ($CDCl_3$) δ 14.02 (ester methyl), 24.71, 25.02, 25.63, 27.05 (isopropylidene methyls), 30.76 (C3), 63.62 (ester methylene), 66.83 (C8), 68.75 (C4), 69.67 (C2), 71.16, 73.19 (C5, C7), 73.75 (C6), 109.70, 110.32 ($C(CH_3)_2$), 117.17 (CN), 167.19 (C1). Anal. Calcd for $C_{17}H_{25}NO_7$: C, 57.46; H, 7.09; N, 3.94. Found: C, 57.5; H, 7.1; N, 4.0.

Ethyl 2,6-Anhydro-3-deoxy-2-(hydroxymethyl)-4,5:7,8-di-*O*-isopropylidene-D-*glycero*-D-*galacto*- and -D-*talo*-octonate (14a and 14b). Gaseous formaldehyde (from 1.0 g of paraformaldehyde) was passed through a solution of the enolate (prepared from 300 mg of **22**; 0.91 mmol) at −75 °C. The reaction mixture was allowed to reach room temperature before saturated NH_4Cl solution (5 mL) was added. The mixture was fractionated between ether and water and the ether fraction was dried (Na_2SO_4). Column chromatography on silica gel with ether/pentane (4:1) as eluent gave **14a** (10 mg, 4%) and **14b** (145 mg; 43%). **14a**: mp 99–104 °C; $[\alpha]_D$ −16.7° (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.20–1.43 (15 H, isopropylidene methyls, ester methyl), 1.76 (dd, 1 H, $J_{3ax,3eq}$ = −15.0, $J_{3ax,4}$ = 2.3, H3ax), 2.67 (dd, 1 H, $J_{3eq,4}$ = 3.2, H3eq), 3.50 (dd, 1 H, $J_{6,7}$ = 6.7, $J_{6,5}$ = 1.5, H6), 3.65 (br s, 2 H, hydroxymethyl), 4.07–4.38 (m, 6 H, H5, H7, H8, H8′, ester methylene), 4.57 (ddd, 1 H, $J_{4,5}$ = 8.2, H4); ^{13}C NMR ($CDCl_3$) δ 14.22 (ester methyl), 24.60, 25.09, 25.40, 26.88 (isopropylidene methyls), 27.99 (C3), 61.47 (ester methylene), 66.85 (C8), 67.46 (hydroxymethyl), 69.87 (C4), 72.28, 72.46, 74.44 (C5, C6, C7), 109.09, 109.71 ($C(CH_3)_2$), 169.01 (C1). Anal. Calcd for $C_{17}H_{28}O_8$: C, 56.65; H, 7.83. Found: C, 56.5; H, 7.9. **14b**: ^1H NMR ($CDCl_3$) δ 1.31 (t), 1.37, 1.42, 1.51 (s) (15 H, isopropylidene methyls, ester methyl), 1.96 (dd, 1 H, $J_{3ax,3eq}$ = −15.7, $J_{3ax,4}$ = 3.3, H3ax), 2.26 (dd, 1 H, $J_{3eq,4}$ = 3.1, H3eq), 2.73 (dd, 1 H, $J_{OH,H'}$ = 8, $J_{OH,H''}$ = 4, OH), 3.45 (dd, 1 H, $J_{6,7}$ = 7.7, $J_{6,5}$ = 2.0, H6), 3.8–4.45 (m, 8 H, H5, H7, H8, H8′, hydroxymethyl, ester methylene), 4.55 (ddd, 1 H, $J_{4,5}$ = 7.8, H4); ^{13}C NMR ($CDCl_3$) δ 14.21 (ester methyl), 24.83, 25.08, 26.25, 27.18 (isopropylidene methyls), 27.80 (C3), 61.46 (ester methylene), 66.77 (C8), 68.44 (hydroxymethyl), 70.04, 71.65, 73.69 (C5, C6, C7), 73.81 (C4), 78.88 (C2), 109.14, 109.33 ($C(CH_3)_2$), 172.95 (C1).

Enolate Reaction with Carbon Dioxide according to Scheme III. An Alternative Synthesis of Compounds 14a and 14b. Gaseous carbon dioxide was passed for 5 min through a solution of the enolate (prepared from 300 mg of **22**; 0.91 mmol) in anhydrous THF at −75 °C. After 30 min excess carbon dioxide was removed by a stream of N_2 for 5 min. A solution of *N*,*N*-dimethylchloromethyleneiminium chloride in acetonitrile, prepared from oxalyl chloride (0.5 mL, 5.7 mmol) and *N*,*N*-dimethylformamide (DMF) (0.17 mL, 2.2 mmol),[25] was added. After 1 h at −75 °C sodium borohydride (100 mg, 2.6 mmol) in DMF (5 mL) was added. The mixture was stirred overnight, while the temperature rose to room temperature. Saturated NH_4Cl solution (5 mL) was added. After drying (Na_2SO_4) and concentration, the residue was chromatographed on a silica gel column with ether/pentane (4:1) as eluent, affording **14a** (35 mg, 10%) and **14b** (110 mg, 36%).

Ethyl 2,6-Anhydro-3-deoxy-2-([^{13}C]hydroxymethyl)-4,5:7,8-di-*O*-isopropylidene-D-*glycero*-D-*galacto*- and -D-*talo*-octonate ([^{13}C]-14a and [^{13}C]-14b). [^{13}C]Carbon dioxide, prepared from $K_2{}^{13}CO_3$ (0.50 g, 3.5 mmol, 90% [^{13}C]) and concentrated H_2SO_4 (10 mL), was passed through a solution of the enolate (prepared from 265 mg of **22**; 0.80 mmol). The experimental procedure was the same as described above and afforded [^{13}C]-**14a** (36 mg, 12%) and [^{13}C]-**14b** (100 mg, 34%). [^{13}C]-**14a**: ^1H NMR ($CDCl_3$) is identical with that of unlabeled **14a** except for δ 1.76 (ddd, 1 H, $J_{3ax,3eq}$ = −15.4, $J_{3ax,C1'}$ = 5.3, $J_{3ax,4}$ = 2.3, H3ax), 2.67 (dd, $J_{3eq,4}$ = 3.2, $J_{3eq,C1'}$ < 1, H3eq), 3.76 (d, 2 H, $J_{C1',H1'}$ = 145.3, hydroxymethyl); ^{13}C NMR ($CDCl_3$) is identical with that of unlabeled **14a** except for δ 28.09 (d, $J_{C3,C1'}$ = 2.8, C3), 69.90 (d, $J_{C4,C1'}$ = 2.7, C4), 77.48 (d, $J_{C2,C1'}$ = 41.0, C2). [^{13}C]-**14b**: $[\alpha]_D$ −2.4° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) is identical with that of unlabeled **14b** except for δ 1.96 (ddd, 1 H, $J_{3ax,3eq}$ = −15.8, $J_{3ax,C1'}$ = 6.2, $J_{3ax,4}$ = 3.1, H3ax), 2.26 (ddd, 1 H, $J_{3eq,C1'}$ = 5.4, $J_{3eq,4}$ = 3.1, H3eq), 3.85 (ddd, 2 H, $J_{H1',C1'}$ = 147, $J_{H1',H1'}$ = −15.4, $J_{H1',OH}$ = 7.7, hydroxy methyl); ^{13}C NMR ($CDCl_3$) is identical with that of unlabeled **14b** except for δ 27.76 (s, $J_{C3,C1'} \leq 0.6$, C2), 73.86 (d, $J_{C4,C1'}$ = 2.1, C4), 78.91 (d, $J_{C2,C1'}$ = 40.4, C2). Anal. Calcd for

$C_{16}{}^{13}CH_{28}O_8$: C, 56.77; H, 7.81. Found: C, 56.5; H, 7.8.

Configurational Determination of C-2 in 14a and 14b by Conversion of Compound 9b to Compound 13. 2,6-Anhydro-3-deoxy-2-(hydroxymethyl)-4,5:7,8-di-*O*-isopropylidene-D-*glycero*-D-*galacto*-octanenitrile (10). Compound **9b** (500 mg, 1.5 mmol) was dissolved in THF (10 mL) containing 5% methanol at −10 °C. Sodium borohydride (100 mg, 2.6 mmol) was added and the mixture was stirred for 2 h; 2 mL of water was added and the mixture was fractionated between ether and water. After drying (Na_2SO_4) and concentration of the ether fraction, the crude product was filtered through a silica gel column with ether as eluent. Evaporation of the volatiles afforded crystalline **10** (0.42 g, 91%): mp 148–150 °C; $[\alpha]_D$ +4.8° (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.37, 1.38, 1.41, 1.61 (4s, 12 H, isopropylidene methyls), 2.08 (dd, 1 H, $J_{3ax,3eq}$ = −15.5, $J_{3ax,4}$ = 2.6, H3ax), 2.39 (dd, 1 H, $J_{3eq,4}$ = 2.8, H3eq), 2.60 (t, 1 H, OH), 3.51 (dd, 1 H, $J_{6,7}$ = 6.8, $J_{6,7}$ = 1.7, H6), 3.75 (br s, hydroxymethyl), 4.0–4.4 (m, 4 H, H5, H7, H8, H8′), 4.67 (ddd, 1 H, $J_{4,5}$ = 8.3, H4); ^{13}C NMR ($CDCl_3$) δ 23.23, 24.13, 24.23, 25.77, 27.82 (isopropylidene methyls, C3), 65.36 (C8), 66.80 (hydroxymethyl), 67.90 (C4), 69.24 (C2), 70.14, 72.98 (C5, C7), 71.74 (C6), 108.28, 108.93 ($C(CH_3)_2$), 118.80 (CN). Anal. Calcd for $C_{15}H_{23}NO_6 \cdot {}^1/_4H_2O$: C, 56.68; H, 7.45; N, 4.41. Found: C, 56.6; H, 7.5; N, 4.1.

2,6-Anhydro-2-[(benzyloxy)methyl]-3-deoxy-4,5:7,8-di-*O*-isopropylidene-D-*glycero*-D-*galacto*-octanenitrile (11). Sodium hydride (25 mg, 1.04 mmol) was added to a solution of **10** (250 mg, 0.8 mmol) and benzyl bromide (120 μL, 0.8 mmol) in DMF/ether (3:1) at −10 °C. The suspension was stirred overnight at room temperature. Water (0.5 mL) was added dropwise. After addition of 5 mL of ether the solution was dried (Na_2SO_4), filtered, and concentrated. The residue was purified on a silica gel column with ether/pentane (3:1) as eluent, affording **11** as a colorless syrup (250 mg, 79%): ^1H NMR ($CDCl_3$) δ 1.34, 1.43 (2s, 12 H, isopropylidene methyls), 2.05–2.50 (m, 2 H, H3ax, H3eq), 3.50 (dd, 1 H, $J_{6,7}$ = 7.8, $J_{6,5}$ = 1.6, H6), 3.64–4.38 (m, 6 H, H5, H7, H8, H8′, -CH_2O-), 4.55–4.75 (ddd, 1 H, H4), 4.62 (s, 2 H, -CH_2Ph), 7.34 (s, 5 H, aromatic); ^{13}C NMR ($CDCl_3$) δ 24.46, 25.20, 25.45, 26.93 (isopropylidene methyls), 28.91 (C3), 66.77, 69.12, 69.24, 71.22, 73.57, 74.00, 74.92 (C4, C5, C6, C7, C8, -CH_2O-, -CH_2Ph), 109.39, 109.88 ($C(CH_3)_2$), 119.70 (CN), 127.80, 128.10, 128.35, 128.54, 137.00 (aromatic).

This compound was used in the next step without further characterization. Compound **11** (250 mg, 0.6 mmol) was heated under reflux in a mixture of 10 mL of 0.5 M KOH and 5 mL of 35% hydrogen peroxide for 24 h. After evaporation of the volatiles the residue (**12**) was redissolved in 5 mL of 50% EtOH and neutralized by addition of Dowex 50 H^+ ion exchange resin. After filtration and concentration the residue was redissolved in 5 mL of DMF. Cs_2CO_3 (230 mg, 0.7 mmol) followed by iodoethane (100 μL, 1.3 mmol) was added and the mixture was stirred overnight at room temperature. Purification on a silica gel column with ether/pentane (3:1) as eluent afforded **13**. Analysis of **13** by GC at 295 °C gave a single peak with retention time of 12.5 min. Conversions of **14a** and **14b** to their corresponding benzyl ethers were done according to the procedure described above. The benzyl ethers gave single peaks on GC analysis at 295 °C with retention times of 12.5 and 10.4 min, respectively.

Ethyl 2-Acetyl-2,6-anhydro-3-deoxy-4,5:7,8-di-*O*-isopropylidene-D-*glycero*-D-*galacto*- and -D-*galacto*-octonate (16a and 16b). To the enloate (prepared from 345 mg of **22**; 1.04 mmol) was added phenyl acetate (285 mg, 2.1 mmol). After 45 min at −75 °C, 5 mL of saturated NH_4Cl solution was added. After drying (Na_2SO_4) and evaporation of the volatiles, the residual mixture was purified on a silica gel column with ether/hexane (2:1) as eluent. The total yield was 60%. **16b**: $[\alpha]_D$ −38.5° (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.20–1.46 (15 H, isopropylidene methyls, ester methyl), 2.11 (dd, 1 H, $J_{3ax,3eq}$ = −15.5, $J_{3ax,4}$ = 2.5, H3ax), 2.29 (s, 3 H, acetyl), 2.96 (dd, 1 H, $J_{3eq,4}$ = 3.5, H3eq), 3.50 (dd, 1 H, $J_{6,5}$ = 1.8, $J_{6,7}$ = 8.1, H6), 4.06–4.38 (m, 6 H, ester methylene, H5, H7, H8, H8′), 4.54 (ddd, 1 H, $J_{4,5}$ = 7.7, H4); ^{13}C NMR ($CDCl_3$) δ 14.05 (ester methyl), 24.55, 25.14 (overlapping signals), 26.13, 27.02 (isopropylidene methyls, acetyl), 27.76 (C3), 62.14 (ester methylene), 66.83 (C8), 69.74, 71.74, 73.63, 74.37 (C4, C5, C6, C7), 83.76 (C2) 109.11, 109.42 ($C(CH_3)_2$), 169.24 (C1), 204.05 (acetyl). Anal. Calcd for $C_{18}H_{28}O_8$: C, 58.05; H, 7.58. Found: C, 58.2; H, 7.7.

Enolate Reaction with Acetyl Chloride. An Alternative Synthesis of Compounds 16a and 16b. Acetyl chloride (146 mg, 1.85 mmol) in THF (5 mL) was added to the enolate (prepared from 307 mg of **22**; 0.93 mmol). After 90 min at −75 °C, a saturated NH_4Cl (1 mL) solution was added. After drying (Na_2SO_4) and concentration, the mixture was purified on a silica gel column with ether/hexane (2:1) as eluent. The combined yield of **16a** and **16b** was 55%. According to GC, the two assumed O-acetylated products were formed in yields of approximately 25% and 10%. These were not unambiguously identified.

Enolate Reaction with Acetic Anhydride. An Alternative Synthesis of Compounds 16a and 16b. Acetic anhydride (0.17 mL, 1.8 mmol) in anhydrous THF (2 mL) was added to the enolate (prepared from 300 mg of **22**; 0.91 mmol) at −75 °C. After 30 min the mixture was allowed to reach room temperature and a saturated NH_4Cl (2 mL) solution was added. After purification as described above, impure **16a** (less than 10 mg) and compound **16b** (colorless glass, 210 mg; 62%) were isolated.

Ethyl 2,6-Anhydro-3-deoxy-4,5:7,8-di-*O*-isopropylidene-2-methyl-D-*glycero*-D-*talo*-octonate (17b). An excess of iodomethane was added to the enolate (prepared from 320 mg of **22**; 0.97 mmol) at −75 °C. The reaction mixture was stirred for 2 h before 2 mL of saturated NH_4Cl solution was added. The mixture was allowed to reach room temperature and dried (Na_2SO_4). After filtration and concentration the syrupy residue was purified on a silica gel column with ether/pentane (1:1) as eluent, giving 170 mg (50%) of pure **17b** and traces of the epimer: $[\alpha]_D$ −20.5° (*c* 1.7, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.23–1.52 (18 H, isopropylidene methyls, ester methyl, 2-methyl), 1.96–2.12 (m, 2 H, $J_{3ax,4}$ = 4.2, H3ax, H3eq), 3.36 (dd, 1 H, $J_{6,7}$ = 6.6, H6), 3.98–4.40 (m, 6 H, H5, H7, H8, H8′, ester methylene), 4.54 (ddd, 1 H, $J_{4,5}$ = 8.0, H4); ^{13}C NMR ($CDCl_3$) δ 14.21 (ester methyl), 25.17, 25.27, 26.72, 27.17, 32.25 (C3, 2-methyl, isopropylidene methyls), 61.12 (ester methylene), 67.00 (C8), 70.89, 71.49, 73.78, 73.93, 75.92 (C2, C4, C5, C6, C7), 109.12, 109.27 ($C(CH_3)_2$), 174.58 (C1). Anal. Calcd for $C_{17}H_{28}O_7$: C, 59.29; H, 8.20. Found: C, 59.0; H, 8.2.

Ethyl 2,6-Anhydro-3-deoxy-4,5:7,8-di-*O*-isopropylidene-2-propargyl-D-*glycero*-D-*galacto*- and -D-*talo*-octonate (18a and 18b). 3-Bromopropyne (160 mg, 1.3 mmol) dissolved in 1 mL of anhydrous THF was added to the enolate (prepared from 320 mg of **22**; 0.97 mmol) at −75 °C. The reaction mixture was stirred for 2 h before a saturated NH_4Cl solution (2 mL) was added. The mixture was allowed to reach room temperature and was thereafter dried (Na_2SO_4). After filtration and concentration the syrupy residue was purified on a silica gel column with ether/pentane (3:1) as eluent, giving 160 mg (45%) of pure **18b** and a fraction of epimeric **18a** mixed with starting material. **18b**: $[\alpha]_D$ −17.6° (*c* 2.9, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.24–1.50 (15 H, isopropylidene methyls, ester methyl), 2.00 (t, 1 H, *J* = 2.8, acetylenic), 2.04–2.44 (m, 2 H, $J_{3ax,4}$ = 3.8, H3ax, H3eq), 2.85 (d, 2 H, propargylic), 3.36 (dd, 1 H, $J_{6,5}$ = 1.8, $J_{6,7}$ = 9.9, H6), 4.05–4.38 (m, 6 H, H5, H7, H8, H8′, ester methylene), 4.58 (ddd, 1 H, $J_{4,5}$ = 7.5, H4); ^{13}C NMR ($CDCl_3$) δ 14.26 (ester methyl), 25.08, 25.17, 26.57, 27.12 (isopropylidene methyls), 29.01, 30.06 (C3, propargylic), 61.52 (ester methylene), 66.95, 70.69, 70.99, 71.64, 73.68, 74.08 (C2, C4, C5, C6, C7, C8), 77.56, 78.86 (acetylenic). Anal. Calcd for $C_{19}H_{28}O_7$: C, 61.94; H, 7.66. Found: C, 61.7; H, 7.6.

Ethyl 2,6-Anhydro-2-[(*tert*-butyloxycarbonyl)methyl]-3-deoxy-4,5:7,8-di-*O*-isopropylidene-D-*glycero*-D-*talo*-octonate (19b). *tert*-Butyl 2-bromoacetate (230 mg, 1.18 mmol) dissolved in anhydrous THF (1 mL) was added to the enolate (prepared from 300 mg of **22**; 0.91 mmol) at −75 °C. The reaction mixture was stirred for 3 h before saturated NH_4Cl (2 mL) was added. The mixture was allowed to reach room temperature and dried (Na_2SO_4). After filtration and concentration the syrupy residue was purified on a silica gel column with ethyl acetate/pentane (1:2) as eluent, giving 120 mg (30%) of pure **19b**: $[\alpha]_D$ −22.5° (*c* 2.3, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.23–1.53 (24 H, isopropylidene methyls, ethyl ester methyl, *tert*-butyl ester methyls), 1.94 (dd, 1 H, $J_{3ax,3eq}$ = −15.7, $J_{3ax,4}$ = 3.2, H3ax), 2.20 (dd, 1 H, $J_{3eq,4}$ = 3.5, H3eq), 2.86 (d, 1 H, *J* = −14.7, 2-methylene), 3.15 (d, 1 H, 2-methylene), 3.51 (dd, 1 H, $J_{6,7}$ = 9.0, H6), 4.01–4.39 (m, 6 H, H5, H7, H8, H8′, ethyl ester methylene), 4.58 (ddd, 1 H, $J_{4,5}$ = 7.1, H4); ^{13}C NMR ($CDCl_3$) δ 14.16 (ethyl ester methyl), 25.03, 25.17, 26.22, 27.07, 27.92, 30.06 (C3, *tert*-butyl ester methyls, isopropylidene methyls), 45.81 (2-methylene), 61.12 (ethyl ester

methylene), 66.85, 70.74, 71.79, 73.43, 73.63, 75.82, (C2, C4, C5, C6, C7, C8), 80.61 ($C(CH_3)_3$), 109.32 ($C(CH_3)_2$), 168.85, 172.78 (carbonyls). Anal. Calcd for $C_{22}H_{36}O_9$: C, 59.44; H, 8.16. Found: C, 59.2; H, 8.2.

Methyl 2,6-Anhydro-2-benzyl-3-deoxy-4,5:7,8-di-*O*-isopropylidene-D-*glycero*-D-*galacto*- and -D-*talo*-octonate (20a and 20b). Benzyl bromide (0.25 mL, 2.1 mmol) in anhydrous THF (5 mL) was added to the enolate (prepared from 300 mg of a mixture of **7a** and **7b**; 0.95 mmol) at −75 °C. After 30 min the solution was warmed to room temperature and saturated NH_4Cl solution (5 mL) was added. The mixture was extracted with ether. The extract was dried (Na_2SO_4) and concentrated, yielding a syrup which was purified on a silica gel column with ether/pentane (2:1) as eluent. Syrupy **20a** (<10 mg) and crystalline **20b** (230 mg, 64%) were obtained. **20a**: ^1H NMR ($CDCl_3$) δ 1.20, 1.27, 1.35 (3s, 12 H, isopropylidene methyls), 1.78 (dd, 1 H, $J_{3ax,3eq}$ = −15.4, $J_{3ax,4}$ = 2.9, H3ax), 2.77 (dd, 1 H, $J_{3eq,4}$ = 4.7, H3eq), 2.88 (br s, 2 H, CH_2), 3.26 (dd, 1 H, $J_{6,7}$ = 9.4, $J_{6,5}$ = 2, H6), 3.48 (s, 3 H, OMe), 4.0–4.3 (m, H5, H7, H8, H8′), 4.45 (ddd, 1 H, $J_{4,5}$ = 7.7, H4), 7.18 (s, 5 H, aromatic). **20b**: mp 63–66 °C; $[\alpha]_D$ −18.0° (*c* 1.6, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.37, 1.55 (2s, 12 H, isopropylidene methyls), 1.88–2.28 (m, 2 H, $J_{3ax,4}$ = 4.5, $J_{3eq,4}$ = 4.5, H3ax, H3eq), 3.20 (dd, 2 H, methylene), 3.33 (dd, 1 H, $J_{6,7}$ = 8.2, $J_{6,5}$ = 1.2, H6), 3.53 (s, 3 H, OMe), 3.85–4.45 (m, 4 H, H5, H7, H8, H8′), 4.50 (ddd, 1 H, $J_{4,5}$ = 7.1, H4), 7.0–7.2 (m, 5 H, aromatic); ^{13}C NMR ($CDCl_3$) δ 25.32, 27.02 (isopropylidene methyls), 31.56 (C3), 46.56 (methylene), 51.75 (OMe), 67.10 (C8), 70.89, 71.69, 73.93, 74.03 (C4, C5, C6, C7), 79.36 (C2), 109.27 (overlapping signals, $C(CH_3)_2$), 126.77, 127.92, 130.26, 135.95 (aromatic), 173.53 (C1). Anal. Calcd for $C_{22}H_{30}O_7 \cdot {}^1/_4H_2O$: C, 64.30; H, 7.48. Found: C, 64.4; H, 7.5.

Ethyl 2,6-Anhydro-3-deoxy-4,5:7,8-di-*O*-isopropylidene-2-[2-(methoxycarbonyl)ethyl]-D-*glycero*-D-*galacto*- and -D-*talo*-octonate (21a and 21b). Methyl acrylate (95 mg, 1.11 mmol) dissolved in 1 mL of anhydrous THF was added to the enolate (prepared from 310 mg of **22**; 0.94 mmol) at −75 °C. The reaction mixture was stirred for 1 h before saturated NH_4Cl solution (1.5 mL) was added. The mixture was allowed to reach room temperature and dried (Na_2SO_4). After filtration and concentration the syrupy residue was purified on a silica gel column with ether/pentane (3:1) as eluent, giving 30 mg (8%) of pure **21a**, a mixture of **21b**, **22**, and an unidentified compound. **21a**: $[\alpha]_D$ −0.8° (*c* 1.3, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.20–1.50 (15 H, isopropylidene methyls, ethyl ester methyl), 1.71 (d, 1 H, $J_{3ax,3eq}$ = −15.1, $J_{3ax,4}$ = 2.6, H3ax) 1.85–2.96 (m, 4 H, -CH_2CH_2-), 2.79 (d, 1 H, $J_{3eq,4}$ = 2.6, H3eq), 3.34 (dd, 1 H, $J_{6,5}$ = 1.6, $J_{6,7}$ = 5.8, H6), 3.66 (s, 3 H, OMe) 3.85–4.40 (m, 6 H, H5, H7, H8, H8′, ethyl ester methylene), 4.51 (ddd, 1 H, $J_{4,5}$ = 8, H4); ^{13}C NMR ($CDCl_3$) δ 14.21 (ethyl ester methyl), 24.62, 25.02, 25.22, 26.97, 27.96, 32.40, 33.70 (-CH_2CH_2-, isopropylidene methyls, C3), 51.74 (OMe), 61.17 (ethyl ester methylene), 67.20 (C8), 69.89, 72.08, 72.33, 74.93, 75.77 (C2, C4, C5, C6, C7), 109.12, 109.52 ($C(CH_3)_2$), 172.78, 173.33 (carbonyls). Anal. Calcd for $C_{20}H_{32}O_9 \cdot H_2O$: C, 55.28; H, 7.92. Found: C, 55.3; H, 7.6.

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Practical Synthesis of Diastereomerically and Enantiomerically Pure 2-Methyl 1,3-Diols from (*R*)-2,3-*O*-Isopropylideneglyceraldehyde. Application to the C(1)–C(7) and C(9)–C(12) Fragments of Erythronolide B

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The synthesis of the homochiral 2-methyl 1,3-diol derivatives **1**, **2**, and **3** from (*R*)-2,3-*O*-isopropylideneglyceraldehyde via **4**/**5a–e** is described. **1** and **2** are prepared from **4**/**5b** via the epoxides **6**/**7**, which are opened regiospecifically by the Lipshutz methylcuprate reagent at C-2. **3** is obtained from **4e** via the epoxide **12**, which is converted into **13** by a Payne rearrangement and then treated with the cuprate. **1** corresponds to the C(9)–C(12) segment of erythronolide B; furthermore, **17b**, containing the C(1)–C(7) segment of erythronolides A and B, is prepared from **2c** via **18a**/**b** as intermediates.

The synthesis of propionate-derived macrolide antibiotics is one of the most attractive topics in current organic chemistry. In view of the notorious complexity of the target structures, the following three-step strategy appears to be appropriate.[1] (1) Construction of stereochemically defined 2-methyl 1,3-diol subunits (A) with differentiable functional groups FG^1 and FG^2 at both ends. (2) Elaboration of A into larger substructures. (3) Combining these substructures into the desired target molecule.

A wide variety of methods has been developed to prepare A in diastereomerically and frequently also in enantiomerically pure form, for instance, aldoltype condensations and variations thereof,[2] olefination–hydroboration[3]

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