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METHYLENATION OF ALDONOLACTONES

RENÉ CSUK AND BRIGITTE I GLÄNZER+

PHARMAZEUTISCH-CHEMISCHES INSTITUT, UNIVERSITAT HEIDELBERG,
Im Neuenheimer Feld 364, D-6900 Heidelberg, F R G

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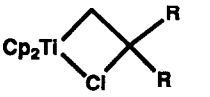
Summary.- Convenient access to carbohydrates possessing an *exo*-methylene group adjacent to the ring oxygen at C-1 can be achieved by direct methylenation of aldonolactones with dicyclopentadienyldimethyltitanium

Introduction.- Carbon-carbon bond forming reactions at the anomeric center of carbohydrates have attracted considerable attention during the last decade due to an increasing interest in the synthesis of biologically active *C*-glycosides [1] 1-Methylene sugars are *C*-glycoside congoners of particular interest and there have been several attempts for their synthesis, *e g* by multistep-sequences from glycosylbromides[2-4], a selenium based cyclisation-oxidation-elimination sequence [5], as well as metal carbene-mediated methylenation of aldonolactones [6-8] In search of inhibitors of glycosidases and a project dealing with the total synthesis of certain natural products we became interested in an easy protocol for the synthesis of pyranoid as well as furanoid carbohydrates having an *exo*-methylene group adjacent to the ring-oxygen at C-1

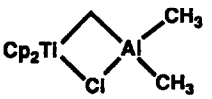
Results and Discussion.- Dichloromethylenation [9, 10] as well as difluoromethylenation [11, 12] of carbohydrate lactones have been achieved by concise and short sequences whereas methylenation of aldonolactones was performed by more [2] or less [5] lengthy sequences or by the use of metal-carbene [6, 7, 13] based transformations Difficulties and problems, however, are encountered with the use of the titanocene methylidene complex [$Cp_2Ti{=}CH_2$] generated either from *Grubb's* titanocyclobutanes **1** [14] or from *Tebbe's* [15] reagent, μ-chloro-bis(cyclopentadienyl) (dimethylaluminium)-μ-methylenetitanium (**2**) The short shelf life of the latter reagent associated with the need for special techniques due to its extreme sensibility to air and moisture, tedious preparation as well as high costs of commercially available *Tebbe's* reagent called for an alternative procedure which should allow access to the target compounds in a more efficient, less expensive and more convenient way Although the use of crude *Tebbe's* reagent has been suggested [16] and recently introduced into the carbohydrate field [7], the applicability of this approach to 1-methylene sugars is limited since furanoid aldonolactones afforded only low yields of desired 1-methylenated products [7]
Very recently dicyclopentadienyldimethyltitanium (**3**) has been introduced as an alternative to the titanocene methylidene complex for the methylenation of carbonyl compounds [17] **3** is a reasonable stable compound which

+present address Deutsches Krebsforschungszentrum, Im Neuenheimer Feld 280, D-6900 Heidelberg, F R G

can be prepared in large quantities [18], exposed to air during handling and it can be stored at -20°C in the dark for extended periods of time without any significant decomposition



1



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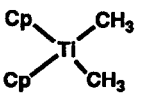

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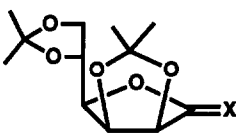
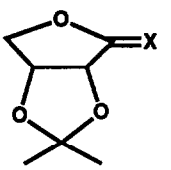
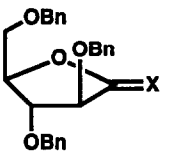


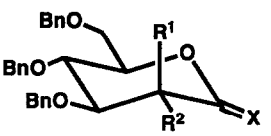
4 X = O
5 X = CH_2



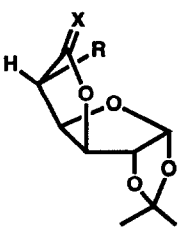
6 X = O
7 X = CH_2



10 X = OH, H
11 X = O
12 X = CH_2



17 R^1 = H, R^2 = OBn, X = O
18 R^1 = H, R^2 = OBn, X = CH_2
19 R^1 = OBn, R^2 = H, X = O
20 R^1 = OBn, R^2 = H, X = CH_2

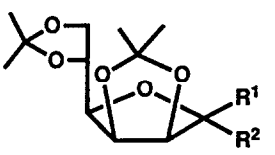


13 R = OBn, X = O
14 R = H, X = O
15 R = OBn, X = CH_2
16 R = H, X = CH_2

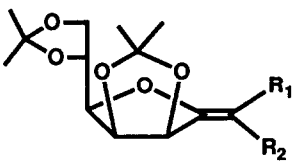
Thus reaction of 2,3,5,6-di-*O*-isopropylidene-D-mannono-1,4-lactone (**4**) with two equivalents of **3** in toluene at 65°C for 24 hours afforded 85% of 2,5-anhydro-1-deoxy-3,4,6,7-di-*O*-isopropylidene-D-manno-hept-1-enitol (**5**) Due to the pronounced hydrolytic instability of such furanoid enol ethers as compared to their pyranoid counterparts aqueous work-up has to be ommitted during the isolation of these compounds A somewhat lower yield of 64% of **7** was achieved when 2,3-*O*-isopropylidene-D-erythrono-1,4-lactone (**6**) [19] was used As a byproduct due to hydratation of the double bond during chromatography the formation of 1-deoxy-3,4,6,7-di-*O*-isopropylidene-α-D-manno-hept-2,5-furanosulose (**8**) and of 1-deoxy-3,4-*O*-isopropylidene-β-D-erythro-pent-2,5-furanosulose (**9**) has been observed in *ca* 5-7% and 15%, respectively 2,3,5-Tri-*O*-benzyl-D-arabinono-1,4-lactone (**11**) [20], easily available in 86% by the pyridinium chlorochromate mediated oxidation of 2,3,5-tri-*O*-benzyl-D-arabinose (**10**) in the presence of anhydrous sodium acetate and 4Å molecular sieves, afforded after reaction with **3** at 65°C for 2 days 84% of 2,5-anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-D-arabino-hex-1-enitol (**12**) In order to investigate the scope and limitations of reagent **3** base labile 1,2-*O*-isopropylidene-5-O-benzyl-α-D-glucofuranurono-6,3-lactone (**13**) [21] and 5-deoxy-1,2-*O*-isopropylidene-α-D-xylo-hexofuranurono-6,3-lactone (**14**) [22] have been reacted each with 2 equivalents of **3** for 48 hours **13** afforded 87 % of 3,6-anhydro-5-*O*-benzyl-1,2-*O*-isopropylidene-6-*C*-methylene-α-D-glucofuranose (**15**) and with **14** 89 % of 3,6-anhydro-5-

deoxy-1,2-*O*-isopropylidene-6-*C*-methylene-α-D-xylohexofuranose (**16**) was obtained These results clearly evidence the broader applicability of **3** as compared to *Tebbe's* reagent since the latter reagent was shown to afford upon reaction with such bicyclic furanoid systems mainly lactols instead of the corresponding olefins [7] Similar good results have been obtained with δ-lactones. Thus, 2,3,4,6-tetra-*O*-benzyl-D-glucono-1,5-lactone (**17**) [23] afforded upon treatment with **3** 89% of the corresponding 2,6-anhydroheptenitol **18** [5, 7, 24], 2,3,4,6-tetra-*O*-benzyl-D-mannono-1,5-lactone (**19**) [25] gave 86 % of **20** The yields obtained with δ-lactones are as high as those compared by others working with pure [24] or crude [7] *Tebbe's* reagent.

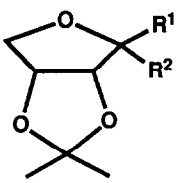
Concerning the synthesis of functionalized C-1 alkylidene elongated sugars a different synthetic scheme had to be applied [26] Since Wittig reagents [27-29] have only scarcely been used for the successful olefination of lactone carbonyls [30, 31] a different route had to be envisaged As an alternative the reaction of alkyl lithiotrimethylsilyl acetate [32] or of nitrile α-anions [33] with lactones has been proposed Unfortunately, reaction of aldonolactones **4** or **3** with ethyl lithiotrimethylsilyl acetate afforded only insignificant yields of desired olefins, instead 30-40% of known lactols **21** and **22** [34, 35] were isolated, the formation of which can either be explained by a deprotonation/reprotonation sequence *via* a carbohydrate derivate enolate or by assuming a *Brook* rearrangement As exemplified for two cases, these lactols **21** and **22**, alternatively obtained in good yields by the *Reformatzky*-type reaction of the corresponding lactons with ethyl bromoacetate and the zinc-silver graphite surface compound [34] or by a organosilicon-reagent based approach [35], are readily eliminated to the desired alkenes by simple treatment with methanesulphonyl chloride / triethylamine at 0°C [36, 37] Thus, from **21** or from **22** separable mixtures of the corresponding (*E*) **23** and (*Z*) **24** or (*E*) **25** and (*Z*) **26** configurated alkenes were obtained in good yields



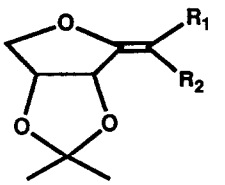
8 $R^1 = CH_3$, $R^2 = OH$
21 $R^1 = CH_2CO_2Et$, $R^2 = OH$
27 $R^1 = CH_3$, $R^2 = Cl$
29 $R^1 = CH_2Cl$, $R^2 = OH$



23 $R^1 = H$, $R^2 = CO_2Et$
24 $R^1 = CO_2Et$, $R^2 = H$
30 $R^1 = Cl$, $R^2 = H$



9 $R^1 = OH$, $R^2 = CH_3$
22 $R^1 = OH$, $R^2 = CH_2CO_2Et$
28 $R^1 = Cl$, $R^2 = CH_3$



25 $R^1 = H$, $R^2 = CO_2Et$
26 $R^1 = CO_2Et$, $R^2 = H$

As for simple alkyl α(tetrahydro-2-furylidene or pyrylidene)acetates [32] the (*E*) and (*Z*) isomers were found to isomerize on standing Configurational assignment for **23-26** was established by NMR spectroscopy As for the model compounds [32], the allylic hydrogen H-C(4) and the olefinic hydrogen H-C(2) appear at lower chemical shifts in the corresponding (*E*) isomers As expected, the lactols **8** and **9** having been obtained as the byproducts of the methylenation step afforded upon treatment with methane sulfonylchloride/ triethylamine instead of the alkenes the corresponding 2,5-anhydro-2-chloro-2-deoxy-alditols **27** and **28** in 88% and 78% yield, respectively, whereas **29** [38] gave under the same conditions (*Z*) 2,5-anhydro-1-chloro-1-deoxy-1-deoxy-3,4 6,7-di-*O*-isopropylidene-D-manno-hept-1-enitol (**30**) in 78% yield

Acknowledgment.- We are indebted to *Professor Dr R Neidlein*, Pharmazeutisch-Chemisches Institut, Universitat Heidelberg, for his encouragement and to *Boehringer Ingelheim* for support

Experimental.- Melting points are uncorrected (*Tottoli*), optical rotations were obtained using a *Perkin-Elmer* 241 polarimeter, NMR spectra for solutions in $CDCl_3$ (internal Me_4Si) were recorded using a *Bruker* AM250 instrument (δ given in ppm, *J* in Hz), IR spectra (3% solution in $CHCl_3$) on a *Perkin-Elmer* 298 TLC was performed on silica gel (*Merck* 5554, detection by spraying with a 5 % solution of vanillin in concentrated sulfuric acid followed by heating to 150 °C) All reactions were performed under argon

Dicyclopentadienyl-dimethyltitanium **3** --To a 10°C cold solution of titanocene dichloride (Aldrich, 10 0 g, 40 16 mmol) in absolute diethylether (200 mL) a solution of methyl lithium (60 mL, 96 mmol, 1 6 M in diethylether) was added carefully under argon in the dark After completion of the addition, the reaction mixture was allowed to warm to room temperature, stirred for another 10 min, then cooled to 0-5°C and at this temperature ice water (15 mL) was added dropwise to destroy the excess of methyl lithium The layers were separated, the organic layer extracted twice with diethylether (50 mL each), the combined organic layers were dried (Na_2SO_4) and the solvent was evaporated in the dark at 20°C to yield of **3** (7 1 g, 85 %) as orange needles, dec p 93-96°C (Lit 97° [18])

General procedure for the methylenation of aldonolactones - A toluene solution (5 mL/mmol of lactone) and **3** (2 1 mmol/mmol lactone) was stirred in the dark for 48h at 65-70°C under argon until TLC (hexanes/ethyl acetate 3 1) showed disappearance of the starting material The brownish reaction mixture was concentrated and the remaining syrup after dilution with a minimum amount of toluene subjected to column chromatography on silica gel (column and eluent containing 1 % of triethylamine, gradient hexanes(b p 60-80°)/ethyl acetate 20 1 to 5 1 (*v/v*)) to afford the methylenated products

2,5-Anhydro-1-deoxy-3,4,6,7-di-O-*isopropylidene*-α-D-*manno-hept-1-enitol* (**5**) and *1-deoxy-3,4,6,7-di*-O-*isopropylidene*-α-D-*manno-hept-2,5-furanosulose* (**8**)-- From **4** (0 26 g, 1 01 mmol) and **3** (0 45 g, 2 16 mmol) 0 22 g (85 3 %) of **5** were obtained as an oil $[\alpha]_D^{25}$ = +153 5° (*c* 1 04, $CHCl_3$), IR 1680 cm^{-1} (C=C), ^{1}H-NMR 5 0 (*td*, *J* = 1 0, 5 8, H-C(3)), 4 69 (*dd*, *J* = 3 8, 5 8, H-C(4)), 4 41 (*dd*, *J* = 1 0, 2 0, H_A(=CH_2), 4 36 (*ddd*, *J* = 4 8, 6 0, 7 3, H-C(6)), 4 19 (*dd*, *J* = 1 0, 2 0, H_B(=CH_2)), 4 07 (*dd*, *J* = 6 0, 8 5, H_A-C(7), 4 03 (*dd*, *J* = 4 8, 8 5, H_B-C(7)), 3 97 (*dd*, *J* = 3 8, 7 3, H-C(5)), 1 42 (*s*, 3H, CH_3), 1 39 (*s*,

3H, CH_3), 1 32 (*s*, 6H, 2x CH_3), ^{13}C-NMR 161 31 (*s*, C(2)), 113.25 (*s*, C_q of isopropylidene), 109 07 (*s*, C_q of isopropylidene), 86 15 (*t*, C(1)), 82 09 (*d*), 79 81 (*d*), 78 31 (*d*), 73 07 (*d*), 66 93 (*t*, C(7)), 26 68 (*q*, CH_3), 26 59 (*q*, CH_3), 25 61 (*q*, CH_3), 25 05 (*q*, CH_3)

Anal calcd for $C_{13}H_{20}O_5$ (256 30) C, 60 92, H, 7 87 Found C, 61 19, H, 7 93

Further elution afforded **8** (19 3 mg, 7 %) m p 100-102° (lit 102-104° [38]), $[\alpha]_D^{25}$ = +10 4° (*c* 0 9, $CHCl_3$) (lit 10 5° (*c* 0 8, $CHCl_3$))

*2,5-Anhydro-1-deoxy-3,4-*O*-isopropylidene-*D*-erythro-pent-1-enitol* (**6**) and *1-deoxy-3,4-*O*-isopropylidene-*ß*-D-erythro-pent-2,5-furanosulose* (**9**)-- From **7** (0 63 g, 4 0 mmol) and **3** (1 66 g, 7 97 mmol) 0 4 g (64 1 %) of **6** were obtained as an oil $[\alpha]_D^{25}$ = -135 8° (*c* 0 2, $CHCl_3$), IR 1660 cm^{-1} (C=C), ^{1}H-NMR 4 92 (*ddd*, *J* = 0 5, 1 0, 6 0, H-C(3)), 4 72 (*ddd*, *J* = 1 4, 4 5, 6 0, H-C(4)), 4 41 (*dd*, *J* = 1 0, 2 0 H_A(=CH_2)), 4 19 (*dd*, *J* = 0 5, 2 0, H_B(=CH_2)), 4 16 (*dd*, *J* = 1 4, 10 4, H_A-C(5)), 4 0 (*dd*, *J* = 4 5, 10 4, H_B-C(5)), 1 43 (*s*, 3H, CH_3), 1 31 (*s*, 3H, CH_3), ^{13}C-NMR 162 04 (*s*, C(2)), 113 20 (*s*, C_q of isopropylidene), 85 81 (*t*, C(1)), 79 50 (*d*), 78 55 (*d*), 74 23 (*t*, C(5)), 27 02 (*q*, CH_3), 25 76 (*q* CH_3)

Anal calcd for $C_8H_{12}O_3$ (156 18) C, 61 52, H, 7 74 Found C, 61 68, H, 7 65

Further elution afforded **9** (0 106 g, 15 2%) as an oil $[\alpha]_D^{25}$ = -65 0° (*c* 0 5, $CHCl_3$) (lit [38] -65 4° (*c* 1, $CHCl_3$))

*2,5-Anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-*D*-arabino-hex-1-enitol* (**12**)--From **11** (0 42 g, 1 0 mmol) and **3** (0 45 g , 2 16 mmol) **12** (0 35 g, 83 7 %) was obtained as an oil $[\alpha]_D^{25}$ = +15 9°, IR 1680 cm^{-1} (C=C), ^{1}H-NMR 7 12-7 24 (*m*, 15H, aromat), 4 59 (*d*, *J* = 11 4, OBn), 4 51 (*d J* = 10 2, OBn), 4 47 (*dd*, *J* = 1 0, 2 0, H_B-(=CH_2)), 4 46 (*s*, 2H, OBn), 4 42 (*d*, *J* = 11 4, OBn), 4 40 (*d*, *J* = 10 2, OBn), 4 35 (*dt*, *J* = 3 0, 6 0, H-C(5)), 4 31 (*dt*, *J* = 1 0, 3 0, H-C(3)), 4 09 (*dd*, *J* = 1 0, 2 0, H_A-(=CH_2)), 3 97 (*t*, *J* = 3 0, H-C(4)), 3 55 (*dd*, *J* = 6 0, 10 4, H_A-C(6)), 3 52 (*dd*, *J* = 6 0, 10 4, H_B-C(6)), ^{13}C-NMR 159 03 (*s*, C(2)), 137 83 (*s*), 137 60 (*s*), 137 39 (*s*), 128 29 (*d*), 128 20 (*d*), 127 69 (*d*), 127 60 (*d*), 127 52 (*d*) each of Bn, 85 58 (*t*, C(1)), 83 38 (*d*), 81 98 (*d*), 81 46 (*d*), 73 17 (*t*), 71 56 (*t*), 70 63 (*t*), 69 58 (*t*) of OBn and C(6)

Anal calcd for $C_{27}H_{28}O_4$ (416 52) C, 77 86, H, 6 78 Found C, 77 99, H, 6 57

*3,6-Anhydro-5-*O*-benzyl-1,2-*O*-isopropylidene-6-*C*-methylene-*α*-*D*-glucofuranose* (**15**)-- From **13** (0 3 g, 0 97 mmol) and **3** (0 5 g, 2 4 mmol) **15** (0 26 g, 87%) was obtained as a solid mp 118-120 °C $[\alpha]_D^{25}$ = +102 3° (*c* 1 7, $CHCl_3$), IR 1685 cm^{-1} (C=C), ^{1}H-NMR 7 31-7 43 (*m*, 5H, aromat), 6 02 (*d*, *J* = 3 7, H-C(1)), 4 86 (*d*, *J* = 12 1, OBn) 4 80 (*m*, 2H), 4 70 (*d*, *J* = 3 7, H-C(2)), 4 66 (*d*, *J* = 12 1, OBn), 4 63 (*d*, *J* = 2 9, H-C(3)), 4 37-4 44 (*m* 1H, H_A-C(7)), 4 25 (*m*, 1H, H_B-C(7)), 1 51 (*s*, 3H, CH_3), 1 33 (*s*, 3H, CH_3) ^{13}C-NMR 159 15 (*s*, C(6)), 137 07 (*s*, of Bn), 128 32 (*d*), 127 71 (*d*), 127 73 (*d*) each of OBn, 112 30 (*s*, C_q of isopropylidene), 106 99 (*t*, C(1)), 85 08 (*d*), 83 58 (*d*), 82 99 (*t*, C(7)), 78 53 (*d*), 77 61 (*d*), 72 05 (*t*, of OBn), 26 92 (*q*, CH_3), 26 39 (*q*, CH_3)

Anal calcd for $C_{12}H_{20}O_5$ (304 35) C, 67 09, H, 6 62. Found C, 67 31, H, 6 69

3,6-Anhydro-5-deoxy-1,2-O-isopropylidene-6-C-methylene-α-D-xylo-hexofuranose (**16**)-- From **14** (0 4 g, 1 99 mmol) and **3** (0 85 g, 4 08 mmol) 0 352 g (88 9 %) of **16** were obtained as a solid after refrigeration for 24 h at -20°C mp· 51-54°C $[\alpha]_D^{25}$ = +62 3° (*c* 1 3, $CHCl_3$), IR 1680 cm^{-1} (C=C), ^{1}H-NMR 4 85-4 90 (*m*, 1H, H-C(4)), 4 73 (*d*, *J* = 3 8, H-C(2)), 4 67 (*d*, *J* = 2 9, H-C(3)), 4 25-4 30 (*m*, 1H, H_A-C(7)), 3 92 (*m*, 1H, H_B-C(7)), 2 78 (*d*, *J* = 16 7, H_A-C(5)), 2 68 (*ddt*, *J* = 2 2, 4 2, 16 7, H-C_B(5)), 1 50 (*s*, 3H, CH_3), 1 33 (*s*, 3H, CH_3), ^{13}C-NMR. 160 87 (*s*, C(6)), 111 96 (*s*, C_q of isopropylidene), 106 41 (*t*, C(1)), 88 31 (*d*), 83 21 (*d*), 81 89 (*t*, C(7)), 81 29 (*d*), 35 82 (*t*, C(5)), 26 91 (*q*, CH_3); 26 44 (*q*, CH_3)

Anal calcd. for $C_{10}H_{14}O_4$ (198 22) C, 60 59, H, 7 12 Found C, 60 76, H, 7 23

2,6-Anhydro-3,4,5,7-tetra-O-*benzyl-1-deoxy*-D-*gluco-hept-1-enitol* (**18**)-- From **17** (0 27 g, 0 5 mmol) and **3** (0 25 g, 1 2 mmol) **18** (0 24g, 89 2 %) was obtained mp 65-68°C (lit 68-68 5°C [24] or 65°C [5]) $[\alpha]_D^{25}$ = +58 4° (*c* 1, CH_2Cl_2) (lit 60° ± 0 8° (*c* 1, CH_2Cl_2)[24] or 45 5° (*c* 0 33, $CHCl_3$) [5]), IR 1665 cm^{-1} (C=C), ^{1}H-NMR 7 19-7 42 (*m*, 20H, aromat), 4 84 (*d*, *J* = 11 6, OBn), 4 79 (*d*, *J* = 12 0, OBn), 4 78 (*bs*, 1H, H_A-C(1)), 4 66 (*bs*, 1H, H_B-C(1)), 4 61 (*d*, *J* = 11 9, OBn), 4 60 (*d*, *J* = 11 9, OBn), 4 59 (*d*, *J* = 12 1, OBn), 4 46 (*d*, *J* = 11 6, OBn), 4 45 (*d*, *J* = 12 0, OBn), 4 33 (*d*, *J* = 12 1, OBn), 3 97 (*d*, 1H, *J* = 9 8), 3 67-3 86 (*m*, 5H), ^{13}C-NMR 156 29 (*s*, C(2)), 138 31 (*s*), 138 07 (*s*), 138 00 (*s*), 137 03 (*s*), 129 65 (*d*), 128 97 (*d*), 128 92 (*d*), 128 39 (*d*), 128 29 (*d*), 127 81 (*d*), 127 71 (*d*), 127 61 (*d*), 94 64 (*t*, C(1)), 84 69 (*d*), 78 89 (*d*), 78 48 (*d*), 77 49 (*d*), 74 38 (*t*), 74 32 (*t*), 73 46 (*t*), 72 68 (*t*), 68 72 (*t*, C(7))

2,6-Anhydro-3,4,5,7-tetra-O-*benzyl-1-deoxy*-D-*manno-hept-1-enitol* (**20**)-- From **19** (0 27 g, 0 5 mmol) and **3** (0 3 g, 1 44 mmol) **20** (0 23 g, 85 5 %) was obtained as an oil $[\alpha]_D^{25}$ = +16 5° (*c* 1 2, $CHCl_3$), IR 1660 cm^{-1} (C=C), ^{1}H-NMR 7 15-7 46 (*m*, 20H, aromat), 4 95 (*d*, *J* = 10 8, OBn), 4 91 (*bs*, 1H, H_A-C(1)), 4 78 (*d*, *J* = 12 4, OBn); 4 69 (*d*, *J* = 12 4, OBn), 4 50-4 65 (*m*, 4H), 4 44 (*d*, *J* = 12 4, OBn), 4 39 (*bs*, 1H, H_B-C(1)), 4 19 (*t*, 1H, *J* = 9 0), 4 09 (*d*, 1H, *J* = 3 2), 3 77-3 89 (*m*, 2H), 3 36-3 74 (*m*, 2H), ^{13}C-NMR 154 79 (*s*, C(2)), 138 29 (*s*), 138 19 (*s*), 138 09 (*s*), 137 92 (*s*), 128 22 (*d*), 128 02 (*d*), 127 87 (*d*), 127 68 (*d*), 127 61 (*d*), 127 51 (*d*), 127 42 (*d*), 99 41 (*t*, C(1)), 81 39 (*d*), 80 11 (*d*), 74 94 (*t*), 73 99 (*d*), 73 55 (*d*), 73 31 (*t*), 71 27 (*t*), 71 27 (*t*), 69 26 (*t*), 69 25 (*t*)

Anal calcd for $C_{35}H_{36}O_5$ (536 67) C, 78 22, H, 6 76 Found C, 78,57, H, 6 70

(E) *Ethyl 3,6-anhydro-2-deoxy-4,5,7,8-di*-O-*isopropylidene*-D-*manno-oct-2-enonate* (**23**) and (Z) *Ethyl 3,6-anhydro-2-deoxy-4,5,7,8-di*-O-*isopropylidene*-D-*manno-oct-2-enonate* (**24**)-- To a solution of **21** (0 4 g, 1 15 mmol) in dry dichloromethane (10 mL) containing triethylamine (0 17 g, 1 48 mmol) a solution of methane sulfonylchloride (0 15 g, 1 48 mmol) in dichloromethane (2 mL) was slowly added at 0°C - After completion of the reaction (10 min) ice water (1 mL) was added *via* a syringe, and the reaction mixture was diluted with dichloromethane (50 mL) After extraction with ice water and brine (5 mL each), drying over Na_2SO_4 and

evaporation the remaining syrup was subjected to flash chromatographgy (gradient hexanes/ethyl acetate 5 1 to 3 1 (*v/v*)) to result in oily **23** (0 1 g, 26 4 %) and oily **24** (0 21 g, 55 4 %)

Data for **23** $[\alpha]_D^{25}$ = +145 0° (*c* 1 8, $CHCl_3$) IR 1655 (C=C), 1710 (C=O) cm^{-1}, ^{1}H-NMR 5 74 (*d*, *J* = 6 0, H-(C4)), 5 40 (*d*, *J* = 1 1, H-C(2)), 4 84 (*dd*, *J* = 4 1, 6 0, H-C(5)), 4 45 (*ddd*, *J* = 4 7, 6 3, 6 9, H-C(7)), 4 16 (*dd*, *J* = 4 1, 6 9, H-C(6)), 4 16 (*q*, 2H, *J* = 7 1, CH_2 of ester), 4.13 (*dd*, *J* = 6 3, 8 9, H_A-C(8)), 4 04 (*dd*, *J* = 4.7, 8 9, H_B-C(8)), 1 44 (*s*, 3H, CH_3), 1 43 (*s*, 3H, CH_3), 1 40 (*s*, 3H, CH_3), 1 37 (*s*, 3H, CH_3), 1 25 (*t*, 3H, *J* = 7 1, CH_3 of ester), ^{13}C-NMR 171 48 (*s*), 166 62 (*s*, C(3)), 113 22 (*s*, C_q of isopropylidene), 109 39 (*s*, C_q of isopropylidene), 95 07 (*d*), 83 25 (*d*), 79 69 (*d*), 77 31 (*d*), 72 85 (*d*), 66 18 (*t*), 59 73 (*t*), 52 57 (*d*),, 26 73 (*q*), 26 42 (*q*), 25 27 (*q*), 25 05 (*q*), 14 18 (*q*), MS (CI, isobutane) 329 (M+1)

Anal calcd for $C_{16}H_{24}O_7$ (328 365) C, 58 53, H, 7 37 Found C, 58 80, H, 7 47

Data for **24** $[\alpha]_D^{25}$ = +106 1° (*c* 0 5, $CHCl_3$) IR 1665 (C=C), 1705 (C=O) cm^{-1}, ^{1}H-NMR 5 07 (*d*, *J* = 1 0, H-C(2)), 5 12 (*dd*, *J* = 1 0, 5 5, H-C(4)), 4 76 (*dd*, *J* = 3 5, 5 5, H-C(5)), 4 37 (*dd*, *J* = 3 5, 7 9, H-C(6)), 4 48 (*ddd*, *J* = 4 5, 5 5, 7 9, H-C(7)), 4 16-4 17 (m, 2H, H_2-C(8)), 4 12 (*q*, 2H, *J* = 7 1, CH_2 of ester), 1 45 (*s*, 3H, CH_3), 1 44 (*s*, 3H, CH_3), 1 38 (*s*, 3H, CH_3), 1 37 (*s*, 3H, CH_3), 1 12 (*t*, 3H, *J* = 7 1, CH_3 of ester) ^{13}C-NMR 168 88 (*s*), 165 22 (*s*), 114 12 (*s*), 109 51 (*s*), 92 36 (*d*), 84 52 (*d*), 81 51 (*d*), 76 66 (*d*), 72 73 (*d*), 66 28 (*t*), 59 43 (*t*), 27 02 (*q*), 26 76 (*q*), 25 95 (*q*), 25 17 (*q*), 14 16 (*q*), MS (CI, isobutane) 329 (M+1)

Anal calcd for $C_{16}H_{24}O_7$ (328 365) C, 58 53, H, 7 37 Found C, 58 76, H, 7 49

(E) *Ethyl 3,6-Anhydro-2-deoxy-4,5-*O*-isopropylidene-*D*-erythro-hex-2-enonate* (**25**) and (Z) *Ethyl 3,6-Anhydro-2-deoxy-4,5-*O*-isopropylidene-*D*-erythro-hex-2-enonate* (**26**) -- From **22** (0 3 g, 1 21 mmol) **25** (20 mg, 7 2 %) and **26** (200 mg, 71 9%) were obtained following the procedure given for **23** and **24** In addition, unchanged **22** (30 mg, 10 %) was recovered

Data for **25** $[\alpha]_D^{25}$ = -197 7° (*c* 0 2, $CHCl_3$), IR 1655 (C=C), 1700 (C=O) cm^{-1}, ^{1}H-NMR 5 66 (*dd*, *J* = 1 0, 6 2, H-C(4)), 5 36 (*d*, *J* = 1 0, H-C(2)), 4 82 (*ddd*, *J* = 1 4, 4 7, 6 2, H-C(5)), 4 30 (*dd*, *J* = 1 4, 10 6, H_A-C(6), 4 11 (*dd*, *J* = 4 7, 10 6, H_B-C(6)), 4 09 and 4 12 (*q*xAB, 2H, *J* = 1 3, 7 2, CH_2 of ester) 1 39 (*s*, 3H, CH_3), 1 35 (*s*, 3H, CH_3), 1 20 (*t*, 3H, *J* = 7 2, CH_3 of ester), ^{13}C-NMR 164 78 (*s*), 106 07 (*s*), 94 52 (*d*), 79 16 (*d*), 77 43 (*d*), 75 50 (*t*), 59 73 (*t*), 26 75 (*q*), 25 49 (*q*), 14 26 (*q*), MS (CI, isobutane) 229 (M+1)

Anal calcd for $C_{11}H_{16}O_5$ C, 57 89, H, 7 06 Found C, 57 98, H, 6 85

Data for **26** $[\alpha]_D^{25}$ = -190 4° (*c* 0 2, $CHCl_3$) IR 1670 (C=C), 1700 (C=O) cm^{-1}, ^{1}H-NMR 5 14 (*d*, *J* = 0 7, H-C(2)), 5 09 (*dd*, *J* = 0 7, 5 8, H-C(4)), 4 80 (*dd*, *J* = 4 2, 5 8, H-C(5)), 4 62 (*d*, *J* = 10 9, H_A-C(6)), 4 43 (*dd*, *J* = 4 2, 10 9, H_B-C(6)), 4 16 (*q*, 2H, *J* = 7 1, CH_2 of ester), 1 47 (*s*, 3H, CH_3), 1 39 (*s*, 3H CH_3), 1 26 (*t*, 3H, *J* = 7 1, CH_3 of ester), ^{13}C-NMR 169 36 (*s*), 165 35 (*s*), 113 74 (*s*), 92 04 (*d*), 81 17 (*d*), 76 59 (*t*), 76 52 (*d*), 59 39 (*t*), 27 03 (*q*), 25 77 (*q*), 14 16 (*q*), MS (CI, isobutane) 229 (M+1)

Anal calcd for $C_{11}H_{16}O_5$ C, 57 89, H, 7 06 Found C, 57 95, H, 6 93

2,5-Anhydro-2-chloro-1-deoxy-3,4,6,7-di-O-isopropylidene-D-*manno-heptitol* (**27**)-- From **8** (0 3 g, 1 09 mmol) **27** (0 28 g, 87 5%) was obtained following the procedure given for **23**, mp 137-139°C $[\alpha]_D^{25}$ = +50 3° (*c* 0 35, $CHCl_3$), ^{1}H-NMR 4 76 (*dd*, *J* = 3 8, 5 8, H-C(4)), 4 36 (*ddd*, *J* = 4 7, 6 3, 7 7, H-C(6)), 4 32 (*d*, *J* = 5 8, H-C(3)), 4 09 (*dd*, *J* = 6 3, 8 6, H_A-C(7)), 3 93 (*dd*, *J* = 4 7, 8 6, H_B-C(7)), 3 88 (*dd*, *J* = 3 8, 7 7, H-C(5)), 1 60 (*s*, 3H, H_3-C(1)), 1 47 (*s*, 3H, CH_3), 1 44 (*s*, 3H, CH_3), 1 37 (*s*, 3H, CH_3), 1 32 (*s*, 3H, CH_3), ^{13}C-NMR 112 57 (*s*, 109 14 (*s*), 109 05 (*s*), 86 97 (*d*), 80 01 (*d*), 79 52 (*d*), 73 01 (*d*), 66 85 (*t*), 22 87 (*q*), 25 90 (*q*), 25 20 (*q*), 24 62 (*q*), 18 92 (*q*)

Anal calcd for $C_{13}H_{21}ClO_5$ (292 76) C, 53 34, H, 7 23; Cl, 12 11 Found C, 53 53, H, 7 10, Cl, 12 30

2,5-Anhydro-2-chloro-1-deoxy-3,4-O-*isopropylidene*-D-*erythro-pentitol* (**28**)-- Obtained in 78 % yield from **9** as described for **27** mp 77-80°C; $[\alpha]_D^{25}$ = -63 3° (*c* 0 3, $CHCl_3$), ^{1}H-NMR 4 70 (*ddd*, *J* = 1 0, 3 4, 5 7, H-C(4)); 4 02 (*d*, *J* = 5 7, H-C(3)), 3 84 (*dd*, *J* = 1 0, 10 1, H_A-C(5)), 3 77 (*dd*, *J* = 3 4, 10 1, H_B-C(5)), 1 56 (*s*, 3H, CH_3), 1 40 (*s*, 3H, CH_3), 1 25 (*s*, 3H, CH_3), ^{13}C-NMR 112 33 (*s*), 109 63 (*s*), 86 68 (*d*), 80 54 (*d*), 71 37 (*t*), 26 36 (*q*), 25 13 (*q*), 18 77 (*q*)

Anal calcd for $C_8H_{13}ClO_2$ (176 64) C, 54 40, H, 7 42, Cl, 20.07 Found C, 54 52, H, 7 37, Cl, 20 17

(Z) *2,5-Anhydro-1-chloro-1-deoxy-3,4,6,7-di-O-isopropylidene*-D-*manno-hept-1-enitol* (**30**)-- Obtained from **29** in 78 % yield as described for **27** mp 59-60°C, $[\alpha]_D^{25}$ = +155 1° (*c* 0 3, $CHCl_3$), ^{1}H-NMR 5 28 (*d*, *J* = 1 0, H-C(1)), 5 05 (*dd*, *J* = 1 0, 5 8, H-C(3)), 4 76 (*dd*, *J* = 3 7, 5 8, H-C(4)), 4 40 (*dt*, *J* = 5 1, 7 9, H-C(6)), 4 10 (*dd*, *J* = 5 1, 10 2, H_A-C(7)), 4 08 (*dd*, *J* = 3 7, 7 9, H-C(5)), 4 08 (*dd*, *J* = 5 1, 10 2, H_B-C(7)), ^{13}C-NMR 155 53 (*s*), 113 99 (*s*), 109 58 (*s*), 92 96 (*d*), 83 13 (*d*), 79 63 (*d*), 78 84 (*d*), 73 01 (*d*), 66 56 (*t*), 26 89 (*q*), 26 79 (*q*), 25 86 (*q*), 25 29 (*q*)

Anal calcd for $C_{13}H_{19}ClO_5$ (290 75) C, 53 70, H, 6 59, Cl, 12 19 Found C, 53 92, H, 6 49, Cl, 12 24

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