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ON THE STERIC COURSE OF THE ADDITION OF CROTYL METALS ONTO (2S,3S) 2,3-ISOPROPYLIDENEDIOXY BUTYRALDEHYDE AND (3S,4S) 3,4-ISOPROPYLIDENEDIOXYPENTANONE. SYNTHESIS OF 2,6-DIDEOXY-2-C METHYL BRANCHED SUGARS OF THE L-SERIES

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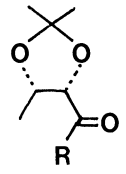
The mode of addition and the synthetic applications of the products obtained in the reaction of $BrMgCH_2CH=CHCH_3$ and $BrCH_2CH=CHCH_3/CrCl_2$ with α,β-dialkoxy carbonyl compounds are reported.

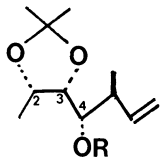
Recently,[1] we reported on the direction and the extent of the α-induction (Cram/anti Cram selectivity)[2] in the addition of allyl metals onto the carbonyl carbon of the C_4 and C_5 chiral compounds 1 and 2, bearing in the α and β-positions two oxygen functions embedded in a pentacyclic ketal framework. The remarkable selectivity observed under certain conditions and the usefulness of the C_7 homoallylic alcohols obtained in the reaction as starting materials alternative to carbohydrates in the synthesis of enantiomerically pure forms of natural products[3] suggested an extension of the investigations to the mode of addition onto 1 and 2 of crotyl metals.[4] A recent report[5] on the addition of a Z-γ-methoxyallyl boronic ester onto the threo isomer of 1 (cyclohexylidene instead of isopropylidene), proceeding with anti-Cram selectivity, induced us to present results on the addition of crotyl metals onto 1 and 2, including the reaction of 1 with $BrCH_2CH=CHCH_3/CrCl_2$ to give the Cram-type adduct 3 almost exclusively.

Thus, reaction of 2 mol equiv. of $BrCH_2CH=CHCH_3/CrCl_2$[6] (the E-isomer of $BrCH_2=CHCH_3$ containing ca. 13% $CH_2=CHCHBrCH_3$ was used in this case) with 1 in THF at 10 °C gave a mixture of two isomeric materials in 96:4 ratio (GLC) (55% yield). These materials were assigned structural formulas 3 and 4, respectively, on the basis of the follwing evidences. Acid hydrolysis (30% AcOH, 50 °C, 6 h 80%) of the above reaction mixture afforded a triol fraction which on sequential treatment with O_3 in MeOH at -40 °C and Me_2S gave rise, after SiO_2 column chromatography, to the 2-C-methyl-2,6-dideoxysugar 12, oil, $[\alpha]_D^{20}$ -5.4° (c 1, EtOH) (75% yield) and a mixture of 12 and of the C-2 epimer 13 (80:20), as shown by NMR studies (see Table 1). When the aldehyde 1 was allowed to react with 2 mol equiv. of $BrMgCH_2CH=CHCH_3$ in ether at -78 °C the adducts 3 and 4 were obtained along with the isomers 5 and 6 in 40:20:28:12 ratio, respectively, and 45% yield. SiO_2 chromatography allowed separation of 3 + 4 and 5 + 6. The latter mixture, once submitted to the above mentioned

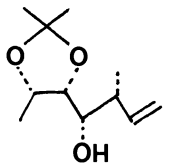
sequence, afforded an inseparable mixture (ca. 70:30) of the 2-C-methylbranched 2,6-dideoxysugars 14 and 15, later converted into the methylglycosides for NMR studies (see Table 1). These results allow the assignement of the precursors of 14 and 15 structural formulas 5 and 6, respectively. The methyl ketone 2 behaves towards the reaction with $BrMgCH_2CH=CHCH_3/CrCl_2$ in similar ways. With the former reagent a ca. 55:45 mixture of isomeric materials was obtained in 70% yield.



1 R= H
2 R= Me



3 R= H
7 R= $CH_2C_6H_5$



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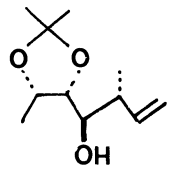

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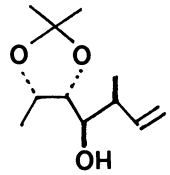

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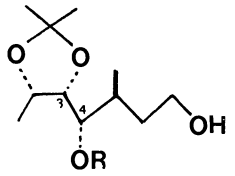
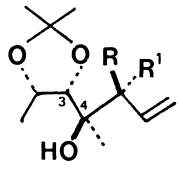
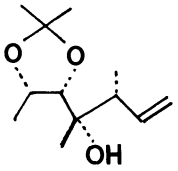


8 R= $CH_2C_6H_5$



9 R= H; R^1= Me
10 R= Me; R^1= H



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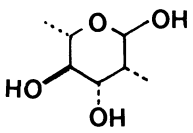
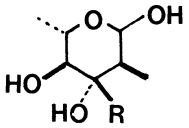
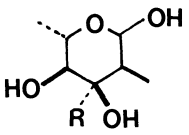


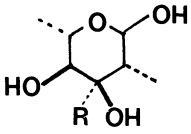
12



13 R= H
16 R= Me



14 R= H
17 R= Me



15 R= H
18 R= Me

These pruducts were assigned to structures 9 and 10 because of their conversion, via the above reported procedure, into the 2,3-di-C-methyl-2,6-dideoxysugars 17 and 18, inseparable by chromatography, in 60% yield, subsequently converted into the methylglycodides for NMR studies (see Table 1). Using $BrCH_2CH=CHCH_3/CrCl_2$ as reagent, from 2 we obtained 9, 10 and a third material of structure 11 in ca. 55:40:5 ratio and 55% yield. Indeed the whole mixture afforded products 17 + 18 and 16, separated by SiO_2 column chromatography and obtained in minute amount (NMR, see Table 1).

The present results thus indicate the expected lack[4] of stereocontrol between the allylic and homoallylic positions in the sddition of the above crotyl metals onto the methyl ketone 2, but a precise control of the mode of addition, relative to positions 3 and 4 of 9 and 10 (anti-Cram selectivity). Conversely, a rather strict control at both sites of the educt occurs in the addition of $BrCH_2CH=CHCH_3/CrCl_2$ onto 1: anti diastereoselectivity[4] in the allylic/homoallylic positions and Cram-type mode of reaction, relative to position 3 and 4 of 3.[7] A general lack of control is observed in the reaction of 1 with $BrMgCH_2CH=CHCH_3$, although a moderate anti

Table 1. ^{1}H NMR data for compounds 12-18[a)]

compound	12[b)]	13[b)]	14[c)]	15[c)]	16[d)]	17[e)]	18[e)]	18[f)]
H-1	4.92	4.97	4.35	4.75	4.26	4.49	4.51	4.28
H-2	2.10	1.65	1.71	2.17	1.40	1.78	2.01	1.50
H-3	3.94	3.49	3.88	3.88	-	-	-	-
H-4	3.19	2.98	3.30	3.49	2.88	2.93	3.10	3.00
H-5	3.80	3.85	3.71	3.70	3.20	3.55	3.55	3.55
Me-2	0.96	1.02	1.05	1.00	0.83	1.06	1.02	1.01
Me-3	-	-	-	-	0.91	1.20	1.20	1.25
Me-5	1.17	1.18	1.31	1.33	1.12	1.33	1.33	1.31
OMe	-	-	3.48	3.47	-	3.38	3.40	3.47
J(1,2)	1.2	3.4	8.6	2.5	8.7	3.2	1.2	8.7
J(2,3)	5.3	10.5	2.6	3.6	-	-	-	-
J(3,4)	9.4	8.7	3.2	3.3	-	-	-	-
J(4,5)	9.2	9.2	9.5	8.9	9.5	9.7	9.6	9.4
J(2,Me)	7.0	6.7	6.8	7.0	6.9	7.2	7.2	6.8
J(5,Me)	6.1	6.1	6.1	6.1	6.0	6.2	6.2	6.2

a) chemical shifts in ppm from internal TMS; J in Hz. b) α-anomer (acetone-d_6 + D_2O). c) β-methylglycoside ($CDCl_3$ + D_2O). d) β-anomer (DMSO-d_6 + D_2O). e) α-methylglycoside ($CDCl_3$); 17: OH-3 = 3.49 ppm, J(OH-H-2) 0.6 Hz; 18: OH-3 = 4.31 ppm. f) β-methylglycoside ($CDCl_3$); OH-3 = 2.13 ppm.

allylic/homoallylic diastereoselectivity is apparent.

Carbohydrate-like product 3, obtained in 96:4 ratio with the C-5 epimer 4, might hold some synthetic significance. Indeed, product 3 contains (carbon atoms 3-6), in a masked form, (2S,3R) 2-hydroxy-3-methyl-1,4-butanedial, in which the two carbonyl carbons may be revealed regioselectively, using different reagents. The synthesis of this type of unit has recently received attention.[8] Furthermore, product 3, once O-benzylated (NaH, DMF, $PhCH_2Cl$, 90%) to 7, $[\alpha]_D^{20}$ -15.3° (c 1, EtOH), gave rise, on hydroboration and H_2O_2/NaOH treatment, to the alcohol 8, $[\alpha]_D^{20}$ -25° (c 1, EtOH), in 45% yield. This material contains (carbon atoms 3-7) the chiral framework of 3-epi-verrucarinolactone.[9]

As far as the structural assignement of the above deoxysugars 12-18 is concerned, the following arguments have been used. The structure of the 2-C-methyl-2,6-dideoxysugars 12-15 was assigned from the values of the vicinal coupling constants. These values compare reasonably well with those predicted[10] for pyranose rings on the basis of the electronegativity and orientation of the substituents and are consistent with the $^1C_4$ (L) conformation of these rings. The 2,3-di-C-methyl-2,6-dideoxysugars 16-18 display a quaternary carbon at C-3, for which no vicinal coupling constants are available. In the case of compounds 17 and 18 the stereochemistry at C-3 may be

deduced from the chemical shifts of the OH-3 group. In fact, OH-3 resonates at much lower field for the α-methylglycosides 17 and 18 (3.49 and 4.31 ppm, respectively) than for the β-methylglycoside 18 (2.13 ppm), suggesting that an intramolecular hydrogen bonding occurs for the α-isomers between the OMe and OH-3 groups (axial orientation of OH-3). Moreover, compound 17 displays a long-range coupling constant J(OH-3,H-2) of 0.6 Hz, which is normally found in six-membered rings when the two interacting groups are in a trans diaxial orientation.[11)]

In order to substantiate the above observations the nuclear Overhauser effects were measured for compounds 16-18. The Me-3 group was irradiated using a subsaturating power of the decoupler to avoid any partial irradiation of the Me-2 and Me-5 groups. The technique of difference spectroscopy was employed, in which a control spectrum is subtracted from the irradiated spectrum, so that the changes in intensity appear allowing the measurements of small enhancements. Thus, the α-methyl glycosides 17 and 18 show enhancements for the H-4 (7%) and H-2 (5%) protons and no detectable enhancement for H-5, proving the equatorial orientation of the Me-3 group. Analogously, the β-methylglycoside 18 shows enhancements for H-4 (5%) and H-2 (7%) while H-5 and H-1 are not affected. On the contrary, compound 16 exhibits the enhancement of H-5 (7%) and H-1 (7%) protons and no intensity variation for protons H-4 and H-2 (Me-3 axial).

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