CHEMISTRY LETTERS, pp. 335 - 338, 1984.

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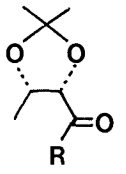
The mode of addition and the synthetic applications of the products obtained in the reaction of $BrMgCH_2CH=CHCH_3$ and $BrCH_2CH=CHCH_3/CrCl_2$ with α,β-dialkoxy carbonyl compounds are reported.

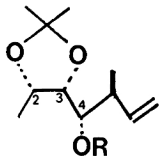
Recently,[1] we reported on the direction and the extent of the α-induction (Cram/anti Cram selectivity)[2] in the addition of allyl metals onto the carbonyl carbon of the C_4 and C_5 chiral compounds 1 and 2, bearing in the α and β-positions two oxygen functions embedded in a pentacyclic ketal framework. 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

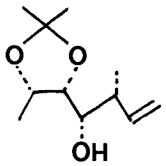
sequence, afforded an inseparable mixture (ca. 70:30) of the 2-C-methylbranched 2,6-dideoxysugars 14 and 15, later converted into the methylglycosides for NMR studies (see Table 1). These results allow the assignement of the precursors of 14 and 15 structural formulas 5 and 6, respectively. The methyl 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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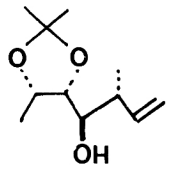

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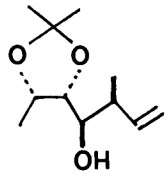
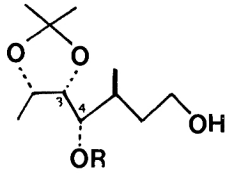
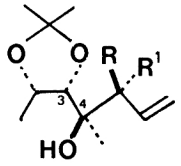


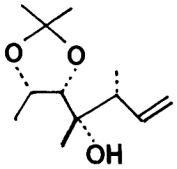
6



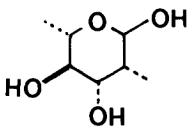
8 R= $CH_2C_6H_5$



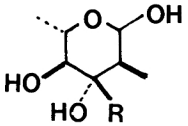
9 R= H; R^1= Me
10 R= Me; R^1= H



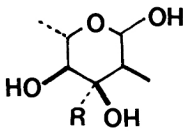
11



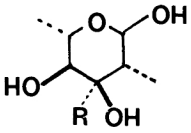
12



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).

We thank Farmitalia-C.Erba, Milano, for a grant (to C.Z.). This work has been supported by Piano Finalizzato CNR Chimica Fine e Secondaria.

References

1) G.Fronza, C.Fuganti, P.Grasselli, G.Pedrocchi-Fantoni, and C.Zirotti, Tetrahedron Lett., 1982, 4143.
2) M.N.Paddon-Row, N.Rondan, and K.N.Houk, J.Am.Chem.Soc., 104, 7162 (1982).
3) C.Fuganti, P.Grasselli, G.Pedrocchi-Fantoni, S.Servi, and C.Zirotti, Tetrahedron Lett., 1983, 3753; C.Fuganti, S.Servi, and C.Zirotti, Tetrahedron Lett.,1983, 5285.
4) Review: R.W.Hoffman, Angew. Chem., Int. Ed. Eng., 21, 555 (1982).
5) W.R.Roush, D.J.Harris, and B.M.Lesur, Tetrahedron Lett., 1983, 2227.
6) T.Hiyama, K.Kimura, and N.Nozaki, Tetrahedron Lett., 1981, 1037, and ref. therein.
7) W.C.Still and J.H.McDonald, Tetrahedron Lett., 1980, 1031; J.A.Schneider, ibid.,1980, 1035.
8) H.Akita, A.Furuichi, H.Koshiji, K.Horikoshi, and T.Oishi, Tetrahedron Lett., 1982, 4051; W.R.Roush, M.A.Adam, and S.M.Peseckis, Tetrahedron Lett., 1983, 1377.
9) Y.Yamamoto, N.Maeda, and K.Maruyama, J.Chem.Soc.,Chem.Commun., 1983, 774.
10) C.Altona and C.A.G.Haasnoot, Org.Magn.Reson., 13, 417 (1980).
11) B.Gillet, D.Nicole, J.J.Delpeuch, and B.Gross, Org. Magn. Reson., 17, 28 (1981).

(Received November 14, 1983)