Diastereoselective Reduction of Hemiacetals Derived from 2,3-*O*-Isopropylidene Derivatives of Carbohydrate Lactones

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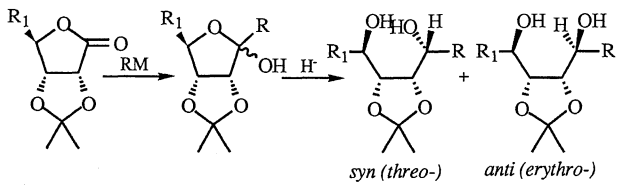
Reactions of organomagnesium and/or organolithium reagents with 2,3-*O*-isopropylidene-D-erythronolactone and 5-*O*-*tert*-butyldiphenylsilyl-2,3-*O*-isopropylidene-D-ribonolactone gave good yields of the corresponding hemiacetals which, by choice of hydride reagents, can be reduced stereoselectively to give products with a *syn*-(*threo*-) relationship between the new chiral centre and that at C-2 of the lactone.

A frequently employed strategy in organic synthesis for diastereoselective chain extension of carbohydrates was the addition of organometallic reagents to suitably protected carbohydrate hemiacetals.[1] When the substrates were the 2,3-*O*-isopropylidene derivatives of carbohydrates, their reaction with organometallic reagents afforded predominantly the *anti-(erythro-)*[2] products, often with moderate to good diastereoselectivities,[3] which could be accommodated by the Felkin-Anh transition model.[4] However, there is a lack of method that allows for the preparation of the *syn-(threo-)* products.[5] We envisaged that the addition of organometallic reagents to 2,3-*O*-isopropylidene derivatives of carbohydrate lactones would give the hemiacetals whose newly created anomeric centre can then be reduced stereoselectively to afford the *syn*-products, the preliminary results of which are reported here.



1 **2A-E** **3** **4**
5 **6A-E** **7** **8**

For **1**, 2A-E, **3** and **4**, R_1 = H
For **5**, 6A-E, **7** and **8**, R_1 = $CH_2OSiPh_2{}^tBu$

Treatment of 2,3-*O*-isopropylidene-D-erythronolactone **1**[6] with organomagnesium reagents (Table 1, Entries A to D) and lithium trimethylsilylacetylide (Entry E) afforded the corresponding hemiacetals which were recrystallised to give single crystalline anomers, whose stereochemistry at the anomeric centre have not yet been determined, althouth we believe from the ^1H and ^{13}C NMR data, in particular the ^{13}C NMR data of the anomeric carbons, that they were all β anomers in the crystalline form. With ribonolactone **5**,[7] we found that use of organolithium reagents gave better results in certain cases (Entries A, B and E), whereas use of methylmagnesium bromide and phenylmagnesium bromide gave recovered starting material (Entries A and B), and all these hemiacetals obtained were oils and existed as anomeric mixtures.

With these hemiacetals in hand we investigated their reduction initially with both sodium borohydride and DIBAL (Table 2). Reduction of these with sodium borohydride resulted in the formation of equal amounts of the two diastereoisomers in both series with the exception of the lithium trimethylsilylacetylide adducts (Entries 5 and 15) where their reduction resulted in almost exclusively the *syn*-products.[8] In the series of reactions where DIBAL was employed as the reducing agent increased stereoselectivity for the *syn*-products was observed except for Entry 7 (substrate **2**B, R=Ph). With substrates **6**A, C and D (R=Me, vinyl and allyl) derived from ribonolactone **5**, their reduction with DIBAL (Entries 16, 18 and 19) afforded almost exclusively the *syn*-products. However in the Entries 10 and 20 where the R substituent contains an alkyne group hydroalumination of the alkynes occurred as a side reaction.

All the *syn*- and *anti*-products of the reduction were fully

Table 1.

Entry	RM[a]	2A-E, Yield,	6A-E, Yield,
A	MeMgBr[b]/MeLi	82%,	73%,
B	PhMgBr[b]/PhLi	73%,	95%,
C	Vinyl MgCl	81%,	84%,
D	Allyl MgCl	76%,	87%,
E	Li TMS-Acetylide	83%,	63%

[a] Reactions were conducted at -78 °C in THF with 1.2 equiv. of organometallic reagents; [b] No reaction occurred with **5**.

Table 2.

Entry	Substrate	Reducing Agent[a]	Product Ratio (*syn:anti*)[f]	Yield (%)[f] (combined)
1	**2**A	$NaBH_4$	58 : 42	37[b]
2	**2**B	$NaBH_4$	42 : 58	92
3	**2**C	$NaBH_4$	57 : 43	56[b]
4	**2**D	$NaBH_4$	60 : 40	77
5	**2**E	$NaBH_4$	86 : 14[c]	38[b, d]
6	**2**A	DIBAL	73 : 27	57[b]
7	**2**B	DIBAL	45 : 55	74
8	**2**C	DIBAL	78 : 22	41[b]
9	**2**D	DIBAL	84 : 16	85
10	**2**E	DIBAL	-[e]	-[e]
11	**6**A	$NaBH_4$	58 :42	88
12	**6**B	$NaBH_4$	64 : 36	83
13	**6**C	$NaBH_4$	80 : 20	71
14	**6**D	$NaBH_4$	53 : 47	89
15	**6**E	$NaBH_4$	100 : 0	70
16	**6**A	DIBAL	98 : 2	75
17	**6**B	DIBAL	86 : 14	85
18	**6**C	DIBAL	100 : 0	73
19	**6**D	DIBAL	100 : 0	88
20	**6**E	DIBAL	-[e]	-[e]

[a] Reactions with sodium borohydride (5.0 equiv.) were conducted in MeOH at 0 °C; those with DIBAL (5.0 equiv.) were conducted in toluene as solvent at 0 °C for substrates 2A-E and at -78 °C for substrates 6A-E. [b] The low yields reflected the labile nature of the isopropylidene group in the erythronolactone series where the DIBAL reduction had to be quenched with saturated aqueous ammonium chloride while use of aqueous hydrochloric acid (which was used for quenching the DIBAL reduction of substrates 6A-E) resulted in complete deprotection of the products. [c] An inseparable mixture resulted and the ratio was determined by ^1H NMR calculation. [d] The trimethylsilyl group was lost during work-up when partitioning between water and ethyl acetate. [e] Hydroalumination of the alkynes occurred. [f] Unless indicated all yields and ratios refer to isolated pure products by flash chromatography on silica gel.

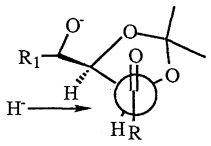


Figure 1. R_1 = H or $CH_2OSiPh_2{}^tBu$

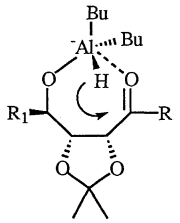


Figure 2.

characterised[9] and stereochemically assigned by correlating to the previously known structures. *Syn*-**3** and *anti*-**4** (where R=Me, Ph, vinyl and allyl) were correlated to the isolated compounds from the Grignard reactions of 2,3-*O*-isopropylidene-L-erythrose, the stereochemistry of which were fully established by cyclization on treatment with methanesulphonyl chloride in pyridine.[3d] *Syn*-**3** and *anti*-**4** (R=ethynyl) were partially hydrogenated over Lindlar catalyst to give *syn*-**3** and *anti*-**4** (R=vinyl). *Syn*-**7** and *anti*-**8** (R=Me and Ph) were degraded by a sequence of desilylation (Bu_4NF), $NaIO_4$ cleavage and $NaBH_4$ reduction to be correlated to *syn*-**3** and *anti*-**4** (R=Me and Ph). The stereochemistry of *anti*-**8** (R=vinyl and allyl) were confirmed by selective silylation of 1,2,3-trideoxy-5,6-*O*-isopropylidene-D-*allo*-oct-1-enitol[10] and 1,2-dideoxy-4,5-*O*-isopropylidene-D-*allo*-hept-1-enitol.[11] *Syn*-**7** (R=TMS-ethynyl) was selectively desilylated (K_2CO_3, MeOH) to remove the TMS group and then hydrogenated over Lindlar catalyst to give *syn*-**7** (R=vinyl).

The *syn*-products that predominate in the reduction correspond formally to the Felkin-Anh transition state model (Figure 1).[4] The high diastereoselectivity in the reduction of substrates **6**A-D with DIBAL may be due to a more defined trajectory for the incoming nucleophile with increased steric interactions. The seven-membered cyclic chelate model (Figure 2) proposed below would also favour the formation of the *syn*-products.

We have found that the reduction of hemiacetals derived from carbohydrate lactones proceeds in high degree of diastereoselectivity with DIBAL and in some cases (Entries 5 and 15) with sodium borohydride to give the *syn*-products to be of use for further synthetic elaboration. Further studies on other reducing agents and lactone substrates, and the application of this methodology in natural product synthesis will be reported in due course.

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References and Notes

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7 We conveniently prepared **5** by silylation of 2,3-*O*-isopropylidene-D-ribose and subsequent oxidation with potassium permanganate to give analytically pure colourless prisms, mp 97-99 °C; $[\alpha]_D$ -17.3° (c 1.04, $CHCl_3$). Its mp was previously reported as 68 °C, see: J. A. Piccirilli, T. Krauch, L. J. MacPherson, and S. A. Benner, *Helv. Chim. Acta*, **74**, 397 (1991).

8 a) For a similar observation, see: J. G. Buchanan, A. D. Dunn, and A. R. Edgar, *J. Chem. Soc., Perkin Trans. 1*, **1975**, 1191. b) For another example, see: S. Mirza and A. Vasella, *Helv. Chim. Acta*, **67**, 1562 (1984).

9 Selected data: **3** (R=allyl): mp 33-34.5 °C; $[\alpha]_D$ +13.2° (c 0.95, $CHCl_3$); δ_H(200 MHz) 1.37 and 1.51 (each 3 H, s), 2.30-2.42 (2 H, m, 3-H_2), 2.60-2.74 (2 H, m, 2 OH), 3.70-3.86 (3 H, m, 7-H_2, 4-H), 4.10 (1 H, dd, *J* 6.8 and 2.8, 5-H), 4.22 (1 H, dt, *J* 6.8 and 4.8, 6-H), 5.07-5.21 (2 H, m, 1-H_2) and 5.85 (1 H, ddt, *J* 17.1, 10.2 and 7.0, 2-H); **3** (R=Ph): mp 77-78 °C; $[\alpha]_D$ -43.0° (c 1.05, $CHCl_3$); δ_H(200 MHz) 1.39 and 1.57 (each 3 H, s), 2.27 (1 H, dd, *J* 6.9 and 5.5, 4-OH), 3.11 (1 H, d, *J* 4.5, 1-OH), 3.58-3.82 (2 H, m, 4-H_2), 4.18 (1 H, ddd, *J* 6.6, 5.7 and 4.4, 3-H), 4.45 (1 H, dd, *J* 6.6 and 5.3, 2-H), 4.78 (1 H, ca t, *J* 4.8, 1-H) and 7.30-7.48 (5 H, m, Ph); **7** (R=Me): $[\alpha]_D$ -7.7° (c 0.91, $CHCl_3$); δ_H(200 MHz) 1.07 (9 H, s), 1.30 (3 H, d, *J* 6.4, 1-H_3), 1.32 and 1.35 (each 3 H, s), 2.48 (1 H, d, *J* 6.3, OH), 2.88 (1 H, d, *J* 4.4, OH), 3.76 (1 H, dd, *J* 10.3 and 5.3, 6-H_a), 3.88 (1 H, dd, *J* 10.3 and 2.7, 6-H_b), 3.94-4.09 (3 H, m, 2-H, 3-H, 4-H), 4.10-4.25 (1 H, m, 5-H), 7.33-7.50 (6 H, m, Ph) and 7.62-7.73 (4 H, m, Ph); **7** (R=TMS-ethynyl): $[\alpha]_D$ -5.3° (c 0.57, $CHCl_3$); δ_H(200 MHz) 0.16 and 1.08 (each 9 H, s), 1.32 and 1.43 (each 3 H, s), 3.05 (1 H, d, *J* 5.3, OH), 3.76 (1 H, dd, *J* 10.3 and 5.4, 7-H_a) 3.80 (1 H, d, *J* 9.1, OH), 3.90 (1 H, dd, *J* 10.3 and 3.0, 7-H_b), 4.24 (1 H, dd, *J* 9.3 and 6.2, 5-H), 4.34 (1 H, dd, J 6.2 and 4.3, 4-H), 4.38-4.50 (1 H, m, 6-H), 4.65 (1 H, dd, *J* 9.1 and 4.3, 3-H), 7.32-7.50 (6 H, m, Ph) and 7.60-7.74 (4 H, m, Ph) [Found(CI, NH_3): $MNH_4{}^+$, 544.2910. $C_{29}H_{46}NO_5Si$ requires MNH_4, 544.2914]; **8** (R=vinyl): mp 106.5-108 °C; $[\alpha]_D$ +9.4° (c 0.80, $CHCl_3$); δ_H(200 MHz) 1.08 (9 H, s), 1.24 and 1.26 (each 3 H, s), 3.39 (1 H, d, *J* 3.1, OH), 3.75 (1 H, dd, *J* 10.8 and 7.5, 7-H_a), 3.83-3.98 (1 H, m, 6-H), 3.93 (1 H, dd, *J* 10.8 and 2.9, 7-H_b), 4.03 (1 H, dd, *J* 8.8 and 5.2, 5-H), 4.11 (1 H, dd, *J* 9.1 and 5.2, 4-H), 4.22 (1 H, d, *J* 3.1, OH), 4.29-4.41 (1 H, m, 3-H), 5.25 (1 H, dt, *J* 10.6 and 1.7, 1-H_a), 5.44 (1 H, dt, *J* 17.3 and 1.7, 1-H_b), 6.03 (1 H, ddd, *J* 17.3, 10.6 and 5.3, 2-H), 7.33-7.50 (6 H, m, Ph) and 7.60-7.73 (4 H, m, Ph).

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