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Highly Diastereoselective Additions of Organometallic Reagents to 1-O-Silylated 3,4-Di-O-Benzyl-L-Erythrulose Derivatives

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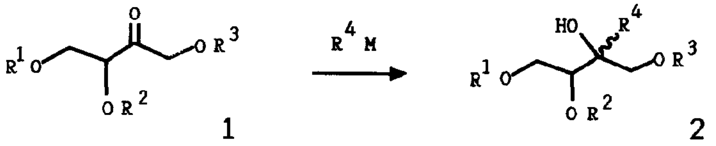
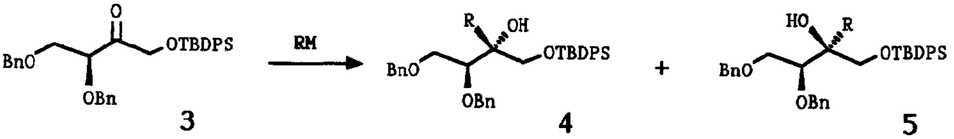
Abstract: The diastereoselectivity of the addition of several organometallic reagents to the carbonyl group of the title compounds has been investigated. Some organomagnesium reagents display high diastereoselectivities (90-99%) and the major products are those predicted by the α-chelation model.

Protected erythrulose derivatives of general formula **1** may be very useful for the synthesis of chiral natural products. We have recently shown[1] that various organometallic reagents of general formula $MeML_n$ (ML_n = metal + ligands) undergo diastereoselective addition to the carbonyl group of protected erythrulose acetonides **1** (R^1,R^2= CMe_2, R^3= silyl group). Tertiary alcohols **2** (R^4 = Me) were obtained with diastereomeric excesses (de's) ranging from 0 to ca. 80%. With the aim of improving the diastereoselectivity of the process, we have investigated the effect of the replacement of the acetonide moiety by two more strongly chelating O-benzyl groups.[2] In fact, the reaction of several organometallic reagents with L-erythrulose derivative **3**[3,4] yielded two diastereomeric adducts, **4** and **5**. Product ratio was dependent on the reaction conditions (Table 1), very high de's (>90 %) being observed with some organomagnesium reagents. The *t*-butyldiphenylsilyl group was selected for the protection of the primary alcohol group, as it gave better de's than the *t*-butyldimethylsilyl or the tri*iso*propylsilyl group.[1,5,6]





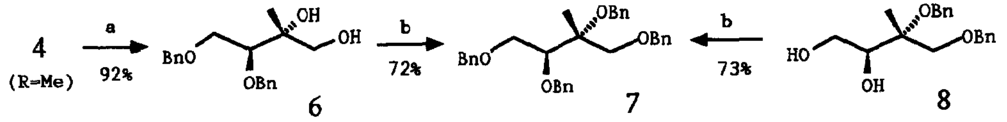
(TBDPS = t-butyldiphenylsilyl   Bn = benzyl)

Table 1. Diastereoselectivity in nucleophilic additions to **3**.

Entry	Reagent RM	Solvent	T / t[a]	Yield (%)	Ratio **4**/**5**[b]
1	MeLi	Et_2O	-78/1	86	26:74
2	MeLi/12-crown-4	Et_2O	-78/1	70	34:66
3	$MeLi/ZnCl_2$	Et_2O	0/1	–[c]	–
4	$MeLi/LiClO_4$	Et_2O	-78/1	94	50:50
5	$MeLi/Me_3SiCl$	Et_2O	-78/1	86	27:73
6	$MeLi/TiCl_4$	Et_2O	0/1	69	81:19
7	$MeLi/BF_3.Et_2O$	Et_2O	-78/1	73	40:60
8	$MeTi(O$*i*$Pr)_3$	neat	25/48	48	81:19
9	$AlMe_3$	C_6H_6	25/2	94	50:50
10	MeMgCl	Et_2O	-78/1	89	>99:1[b,d]
11	MeMgBr	Et_2O	-78/1	95	>99:1[b,d]
12	MeMgBr	THF	-78/1	87	>99:1[b,d]
13	$MeMgBr/BF_3.Et_2O$	Et_2O	-78/1	75	>99:1[b,d]
14	EtMgBr	Et_2O	-78/1	98	88:12
15	EtMgBr	Et_2O	0/1	93	89:11
16	EtMgBr	THF	-78/1	94	97:3
17	EtMgBr	THF	0/1	92	97:3
18	$CH_2=CHMgBr$	Et_2O	-78/1	87	98:2[b,d]
19	$CH_2=CHMgBr$	Et_2O	0/1	84	96:4
20	$CH_2=CHMgBr$	THF	-78/1	90	98:2[b,d]
21	$CH_2=CHMgBr$	THF	0/1	91	96:4
22	$CH\equiv CMgBr$	Et_2O	0/1	80	93:7 (94:6)[e]
23	$CH\equiv CMgBr$	THF	0/1	93	86:14
24	$CH_2=CHCH_2MgBr$	Et_2O	-78/1	86	67:33[f]
25	$CH_2=CHCH_2MgBr$	Et_2O	0/1	87	50:50[f]
26	$CH_2=CHCH_2MgBr$	THF	-78/1	85	34:66[f]
27	$CH_2=CHCH_2MgBr$	THF	0/1	82	40:60[f]

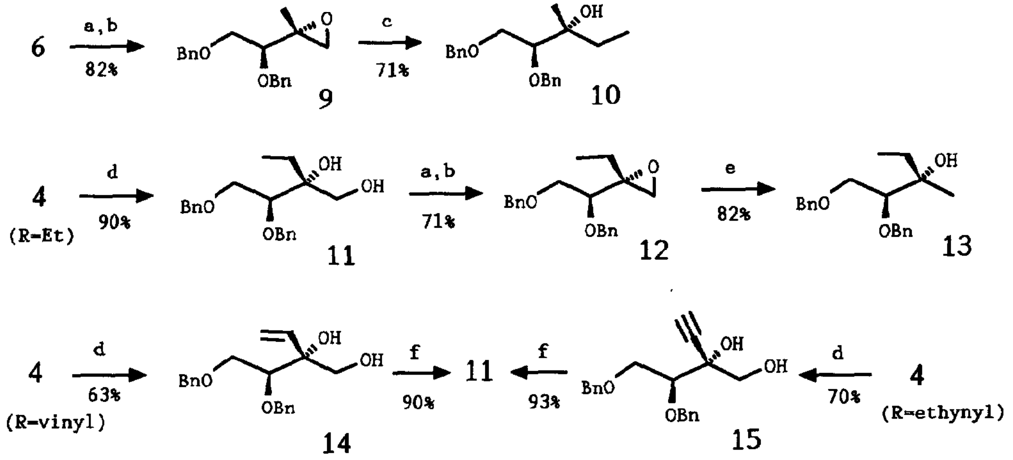
[a] Temp. (°C) / time (hours). In entries 6, 8, 9, 22 and 23, the reaction was too slow at temperatures significantly lower than the indicated one. [b] Determined by ^1H and ^{13}C NMR. [c] No reaction. [d] Confirmed by GC. [e] Determined by GC. [f] The configurations of the products were not determined.

The absolute configurations of the obtained products were assigned chemically as depicted in Schemes 1 and 2. Compound **4** (R = Me) was transformed *via* **6** into perbenzylated tetraol **7**, identical with the product obtained from the previously described **8**[1] (Scheme 1). Furthermore, compound **4** (R = Et) was transformed into tertiary alcohol **13** (Scheme 2), which was different of its diastereomer **10**, obtained from **6** as depicted. Finally, both **14** and **15** were hydrogenated to the same compound **11**, an intermediate in the sequence **4** → **13**. The configuration of the reaction products with allylmagnesium bromide, which showed a poor diastereoselectivity (entries 24-27), was not established.



Scheme 1

a: TBAF (1 eq)/THF, r.t., 15 min. b: BnBr (4 eq), HNa (4 eq), cat. am. nBu_4NI, DME, 90 °C, 4 h.



Scheme 2

a: TsCl (1.4 eq), Et_3N (1.8 eq), DMAP (cat.), CH_2Cl_2, r.t., 18 h. b: K_2CO_3 (2 eq), MeOH, r.t., 1 h. c: Me_2CuLi (5 eq), Et_2O, -30 °C, 2 h. d: TBAF (1 eq)/THF, r.t., 15 min. e: $LiAlH_4$ (4 eq), Et_2O, r.t., 5 h. f: H_2, 5% Pd/C, EtOAc, r.t., 3 h.

The results presented in Table 1 display a marked contrast with those observed by us with erythrulose acetonides.[1] In the present case, the additions of several organomagnesium reagents turn out to be highly diastereoselective (entries 10-23), with the major product being that expected from Cram's α-chelation model.[7] The reactions with MeLi showed here the opposite diastereofacial preference but de's were not satisfactory. Entry 1 represents the highest proportion obtained of diastereomer 5, which corresponds to either the non-chelation Felkin-Anh model or to β and/or α/β-chelation mechanisms.[6-8] Attempts at improving the diastereoselectivity by addition of certain reagents led to erratic effects (entries 1-7). It is noteworthy that addition of 12-crown-4 with the aim of preventing chelation via sequestering of Li^+, did not cause any relevant change in the diastereoselectivity. Reaction with $AlMe_3$ gave an excellent yield but was nonstereoselective (entry 9). On the other hand, $MeTi(O\textit{i}Pr)_3$ furnished mainly the product expected from α-chelation (entry 8), in line with other reports[9] but also in contrast to previous findings of ours[1] and others.[2] The low diastereoselectivity of the reactions with allylmagnesium bromide may be due to the occurrence of a metallo-Claisen-type mechanism, which does not involve chelation.[2]

Solvent and temperature effects have also been studied in the case of the more diastereoselective Grignard reagents. The latter factor seemingly plays a minor role in these cases, as no essential differences were noted between reactions conducted at 0 and -78 °C (see also footnote *a* in Table 1). On the other hand, MeMgBr and $CH_2=CHMgBr$ proved almost insensitive to the nature of the solvent whereas EtMgBr and $HC\equiv CMgBr$ were somewhat more diastereoselective in THF and Et_2O, respectively. These facts most likely reflect differences in the aggregation states[7] of the Grignard reagents but it is not easy to draw mechanistic conclusions of general value.

Very recently, Nagano *et al* have reported on the reaction of 1-O-benzoyl- and 1-O-trityl-L-erythrulose acetonide with various organolithium and organomagnesium derivatives.[10] While the former (MeLi, BuLi) showed poor diastereoselectivities, Grignard reagents gave high de's in some cases. A marked dependence on reagent structure, solvent and temperature was also observed. Most notably, methylmagnesium derivatives were the least diastereoselective among the assayed reagents. However, although the authors tried to explain their results within the classical frame of chelation vs. Felkin-Anh models,[2,6-8] no general trends with predictive value were established.

All the results above as well as their application to the synthesis of some natural products will be reported in full in due course.[11]

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3. Obtained from L-ascorbic acid by transformation into 1,2-O-isopropylidene-L-threitol[4] followed by O-benzylation, acetonide cleavage, selective silylation of the primary alcohol (TBDPSCl) and Swern oxidation. Experimental details will be published in a full paper.
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11. All new compounds gave satisfactory microanalytical (C,H, ±0.4%) and spectral data. Some optical rotation values in $CHCl_3$ at 23 °C are:

6: Oil, $[\alpha]_D = +23.6$ (c, 7.2). **7**: Oil, $[\alpha]_D = +5.3$ (c, 0.75).
9: Oil, $[\alpha]_D = +2.2$ (c, 3.6). **10**: Oil, $[\alpha]_D = +20.7$ (c, 3.5).
11: Oil, $[\alpha]_D = +17.2$ (c, 8.2). **12**: Oil, $[\alpha]_D = -8.1$ (c, 6).
13: Oil, $[\alpha]_D = +9.5$ (c, 3.7). **14**: Oil, $[\alpha]_D = -4.5$ (c, 4).
15: Oil, $[\alpha]_D = +10.9$ (c, 3.8).