Tetrahedron. Asymmetry Vol. 3, No. 12, pp. 1511-1514, 1992
Printed in Great Britain

0957-4166/92 $5.00+.00
Pergamon Press Ltd

Diastereoselective Synthesis of Enantiomeric Tertiary Alcohols via Nucleophilic Additions to Protected D- and L-Erythrulose Derivatives

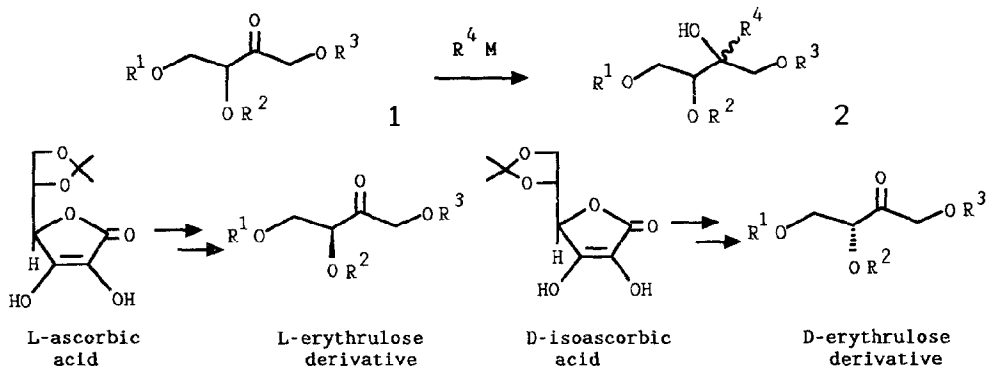
Miguel Carda,[a] Florenci González,[a] Santiago Rodríguez[a] and J. Alberto Marco[b,*]

[a]*Departamento de Ciencias Experimentales, Universitat Jaume I, E-12080 Castellón, Spain, and*
[b]*Departamento de Química Orgánica, Facultad de Químicas, Universidad de Valencia, E-46100 Burjassot, Valencia, Spain.*

(*Received in UK* 2 *October* 1992; *accepted* 2 *November* 1992)

Abstract: The diastereoselectivity of the addition of several organometallic reagents to the carbonyl group of protected D- and L-erythrulose derivatives has been investigated. Tertiary alcohols are stereoselectively formed, the diastereomeric ratio being markedly dependent on the reagent type, solvent and temperature.

Protected erythrulose derivatives of general formula 1 and related chirons[1,2] may display a considerable utility in the synthesis of various oxygenated, chiral natural products like carbohydrates and macrolide antibiotics. Diastereoselective additions of organometallic reagents R^4M to the carbonyl group of **1** will yield tertiary alcohols **2** bearing additional functionality, which may be then further manipulated in a selective way with the use of appropriate protective groups R^1, R^2 and R^3. Since there are few methods to synthesize such tertiary alcohol fragments in a stereoselective way,[3] we decided to explore the stereoselectivity of the reactions of both enantiomers of **1** with various nucleophilic reagents.



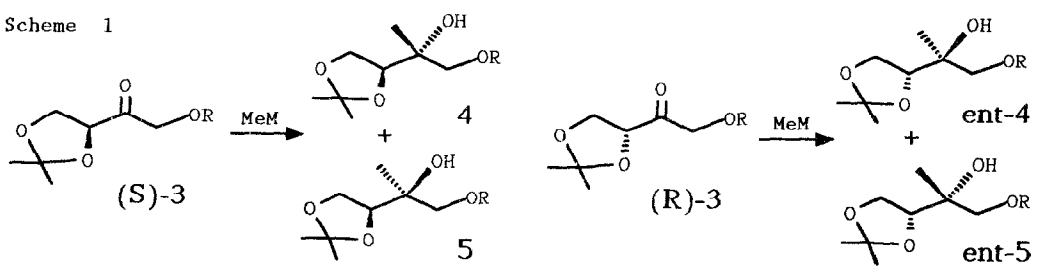
Protected L-erythrulose derivatives (S)-**3** were synthesized from L-ascorbic acid through a described reaction sequence.[4] The enantiomeric D-erythrulose derivatives (R)-**3** were prepared via a similar sequence from D-isoascorbic acid.[5] We have studied the nucleophilic addition of several organometallic reagents MeM (M = metal) to both enantiomeric erythrulose acetonides (Scheme 1, R = protective group). As reflected in Table 1, a mixture of the two possible diastereomeric adducts, **4** and **5**, was obtained from (S)-**3**, with predominance of either one or the other adduct

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

Entry	R	Reagent	Solvent	T / t[a]	Yield (%)	Ratio **4/5**[b]
1	H	MeLi	Et_2O	-78/1	53	50:50
2	$SiMe_3$	MeLi	Et_2O	-78/1	65	50:50
3	$SiEt_3$	MeLi	Et_2O	-78/1	75	61:39
4	$SiMe_2tBu$	MeLi	Et_2O	-78/1	85	63:37
5	$SiiPr_3$	MeLi	Et_2O	-78/1	85	75:25
6	$SiPh_2tBu$	MeLi	Et_2O	-78/1	86	86:14
7	$SiPh_2tBu$	MeLi	Et_2O	0/1	80	78:22
8	$SiPh_2tBu$	MeLi	THF	-78/1	86	67:33
9	$SiPh_2tBu$	MeLi	DME	-78/1	85	57:43
10	$SiPh_2tBu$	MeLi	Tol	-78/1	83	77:23
11	$SiPh_2tBu$	Me_2CuLi	Et_2O	-78/1	80	88:12
12	$SiPh_2tBu$	$MeLi/ZnCl_2$	Et_2O	-20/1	–[c]	–
13	H	MeMgBr	Et_2O	-78/1	30	50:50
14	$SiMe_3$	MeMgBr	Et_2O	-78/1	38	25:75
15	$SiEt_3$	MeMgBr	Et_2O	-78/1	73	21:79
16	$SiMe_2tBu$	MeMgBr	Et_2O	-78/1	65	34:66
17	$SiiPr_3$	MeMgBr	Et_2O	-78/1	86	43:57
18	$SiPh_2tBu$	MeMgBr	Et_2O	-78/1	90	50:50
19	$SiPh_2tBu$	MeMgBr	Et_2O	0/1	88	75:25
20	$SiiPr_3$	$AlMe_3$	C_6H_6	25/1	80	60:40
21	$SiiPr_3$	$AlMe_3$	Et_2O	0/1	–[d]	–
22	$SiPh_2tBu$	$MeTi(OiPr)_3$	neat	25/60	67	9:91
23	$SiPh_2tBu$	$MeLi/CeCl_3$	THF	-78/2	78	42:58
24	$SiPh_2tBu$	$MeLi/YbCl_3$	THF	-78/2	25	37:63
25	$SiPh_2tBu$	$MeMgBr/YbCl_3$	THF	-78/2	63[e]	58:42

[a]Temp. (°C) / time (hours). [b]Determined by ^1H and ^{13}C NMR. [c]After work-up, we isolated a mixture of **3** (ca. 50%) and **4/5** (3:1, ca. 35%). [d]No reaction. [e]Ca. 25% of starting product was recovered.

Scheme 1

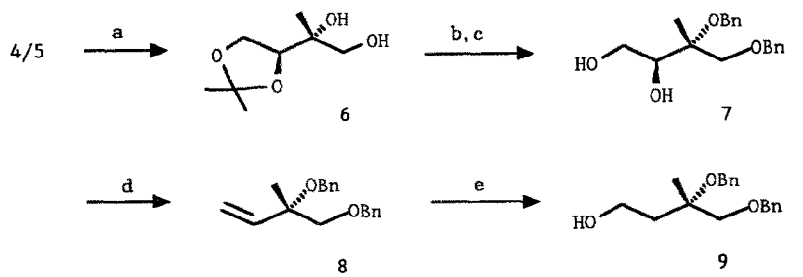


according to the reaction conditions (Scheme 1). In the same way, the enantiomers of **4** and **5** were obtained from (R)-**3**. The diastereomeric excess (de) was markedly dependent on the nature of the metal atom, protective group, solvent and temperature. For instance, when methyl lithium was used (entries 1-10), diastereomer **4** (or ent-**4**) was found to be the major reaction product. The highest

diastereomeric ratios were observed with bulky R groups (entries 2-6), low temperatures and solvents with low chelating power (entries 6-10). Lithium dimethylcuprate gave comparable results (entry 11). Addition of Lewis acids to the reaction medium caused a decrease in reaction rate without improving the diastereoselectivity (entry 12). Interestingly, the results of the reactions with methylmagnesium bromide clearly differ of those with methyl lithium (entries 13 to 19). Whereas no diastereoselectivity was observed in the absence of protective group, introduction of silyl groups of increasing steric bulk gave rise to an initial increase in the diastereoselectivity followed by a sharp fall. In these cases, the major diastereomer was **5** (or ent-**5**), the opposite one to that obtained with methyllithium. The effect of temperature is noteworthy: while increasing the temperature from -78° to 0° C increases the percentage of stereoisomer **4** in the case of MeMgBr, the opposite effect is observed with MeLi.

Further organometallic reagents were assayed. While trimethylaluminum gave unsatisfactory results (entries 20 and 21), the titanium reagent[6-9] $MeTi(OiPr)_3$ reacted only when used in a great excess as the solvent (entry 22). A good diastereoselectivity was indeed observed, with **5** being now the major reaction product. The lantanide reagents[10] $MeLi/CeCl_3$, $MeLi/YbCl_3$ and $MeMgBr/YbCl_3$ led to rather disappointing chemical yields and de's (entries 23-25).[11]

The results detailed in Table 1 can be discussed in terms of competition between chelated and nonchelated transition states.[6-9,12-14] In the reactions with methyl lithium, the observed decrease of the de's with increasing chelating power of the solvent agrees well with a chelation mechanism,[14] as does the effect of the size increase of the silyl group, which inhibits the competitive, stereochemically unproductive chelation with the CH_2OR side of the carbonyl group.[13] In these particular examples, Cram's cyclic model involving α-chelation is able to explain the observed results. The situation is less straightforward with other metal atoms. While $MeTi(OiPr)_3$ is usually assumed to react via unchelated Felkin-Anh transition states,[6,12] which are expected to lead here to adduct **5**, the rather variable results observed with MeMgBr and other reagents may be explained by assuming a competition between an α-chelation and a Felkin-Anh mechanism, without excluding β- or even α,β- chelation modes, which also yield predominantly compound **5**.[2,12,14]



Scheme 2

a: i) TBAF (1 eq)/THF, r.t., 15 min; ii) crystallize from hexane-Et_2O, 50% overall. **b**: BnBr (4 eq), HNa (4 eq), cat. am. nBu_4NI, DME, reflux, 4 h, 96%. **c**: 80% aq HOAc, r.t., 18 h, 95%. **d**: Ph_2PCl (2.2 eq), imidazole (4 eq), I_2 (2.2 eq), toluene, reflux, 2 h, then Zn (10 eq), reflux, 1h, 38 % (ref 17) **e**: i) BH_3/SMe_2 (0 5 eq), THF, r t., 2 h ii) H_2O_2, NaOH, r t., 1 h, 20%.

Desilylation of the diastereomeric mixture **4/5** enriched in **4** (entries 6 or 11) and crystallization from hexane-Et_2O allowed the isolation of compound **6** (**4**, R = H, see Scheme 2) as a single diastereomer.[15] Its absolute configuration was established as depicted in the Scheme by chemical correlation with the known dibenzylated triol **9**.[16] The potential applications of all these chiral compounds for the synthesis of other natural products are currently being explored in our group.

Acknowledgements- The authors thank the DGICYT (Spanish Ministry of Education and Science) for financial support (project PB89-0523). They also thank Prof. M. Vandewalle, from the State University of Gent, Belgium, for the access to unpublished information of his group.

LITERATURE

1. De Wilde, H., De Clercq, P., Vandewalle, M., Roper, H., *Tetrahedron Lett.* **1987**, 4757, 4759.
2. Jurczak, J., Pikul, S., Bauer, T., *Tetrahedron* **1986**, *42*, 447.
3. Heathcock, C.H., Pirrung, M.C., Young, S.D., Hagen, J.P., Jarvi, E.T., Badertscher, U., Marki, H.-P., Montgomery, S.H., *J.Am.Chem.Soc.* **1984**, *106*, 8161.
4. Marco, J.L., *J.Chem.Res. (S)*, **1988**, 276. While commercial L-erythrulose is rather expensive, its enantiomer D-erythrulose is not commercially available.
5. Abushanab, E., Vemishetti, P., Leiby, R.W, Singh, H.K., Mikkilineni, A.B., Wu, D.C.-J., Saibaba, R., Panzica, R.P., *J.Org.Chem.* **1988**, *53*, 2598.
6. Reetz, M.T., *Top.Curr.Chem.* **1982**, *106*, 1.
7. Weidmann, B., Seebach, D., *Angew.Chem.* **1983**, *95*, 12; *Angew.Chem.Int.Ed.Engl.* **1983**, *22*, 31.
8. Reetz, M.T., *Angew.Chem.* **1984**, *96*, 542; *Angew.Chem.Int.Ed.Engl.* **1984**, *23*, 556.
9. Reetz, M.T., Hüllmann, M., *J.Chem.Soc.Chem.Commun* **1986**, 1600
10. Molander, G.A., *Chem.Rev.* **1992**, *92*, 29.
11. Other nucleophilic reagents or conditions assayed were: MeLi/LiX (X = Cl, ClO_4): decreased reactivity or stereoselectivity; MeLi/$TiCl_4$, $MeSCH_2Li$, 2-lithio-1,3-dithiane, $(MeS)_3CLi$: almost complete decomposition; $(MeS)_3CLi/ZnCl_2$, $(MeS)_3CLi/CeCl_3$: partial decomposition.
12. Anh, N.T., *Top.Curr.Chem.* **1980**, *88*, 145.
13. Chen, X., Hortelano, E.R., Eliel, E.L., Frye, S.V., *J.Am.Chem.Soc.* **1992**, *114*, 1778. See also: Guanti, G., Banfi, L., Narisano, E., *Tetrahedron Lett.* **1991**, 6939.
14. Mead, K., Macdonald, T.L., *J.Org.Chem.* **1985**, *50*, 422.
15. All new compounds gave satisfactory microanalytical (C,H, ±0.4%) and spectral data. Selected physical data of compounds **6-9** (optical rotations at 23 °C).

    6: White needles, mp 100-101 °C (from hexane-Et_2O), $[\alpha]_D = -6.7$ (c, 3; $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$), δ 4.15-4.00 (m, 2H), 3.91 (1H, dd, J = 8 and 6.5 Hz), 3.63 (1H, d, J = 11.3 Hz), 3.46 (1H, d, J = 11.3 Hz), 1.43 (3H, s), 1.35 (3H, s), 1.16 (3H, s).

    Ent-**6**: $[\alpha]_D = +6.6$ (c, 0.76; $CHCl_3$).

    7: Colourless oil, $[\alpha]_D = +6.4$ (c, 3.1; $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$), δ 7.40-7.20 (10H, m), 4.56 (4H, s), 3.90-3.70 (3H, m), 3.65 (1H, d, J = 10 Hz), 3.57 (1H, d, J = 10 Hz), 3.00 (2H, br s, OH), 1.32 (3H, s).

    8: Colourless oil, $[\alpha]_D = -7.1$ (c, 3.4; $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$), δ 7.40-7.20 (10H, m), 5.93 (1H, dd, J = 17.6 and 10.7 Hz), 5.30 (2H, m), 4.61 (2H, s), 4.46 (2H, s), 3.52 (1H, d, J = 10 Hz), 3.48 (1H, d, J = 10 Hz), 1.42 (3H, s).

    9: Colourless oil, $[\alpha]_D = +10.5$ (c, 1.4; $CHCl_3$), lit.[7] $[\alpha]_D = +10.1$ (c, 1.77; $CHCl_3$).
16. Sugai, T., Watanabe, N., Ohta, H., *Tetrahedron: Asymmetry* **1991**, *2*, 371.
17. Liu, Z., Classon, B., Samuelsson, B., *J.Org.Chem.* **1990**, *55*, 4273.