Diastereoselectivity in Organometallic Additions to the Carbonyl Group of Protected Erythrulose Derivatives

J. Alberto Marco,*[,1a] Miguel Carda,*[,1b] Florenci González,[1b] Santiago Rodríguez,[1b] Encarna Castillo,[1b] and Juan Murga[1b]

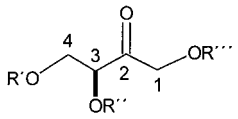
Departamento de Química Orgánica, Universidad de Valencia, E-46100 Burjassot, Valencia, Spain, and Departamento de Química Inorgánica y Orgánica, Universidad Jaume I, E-12080 Castellón, Spain

Received September 9, 1997

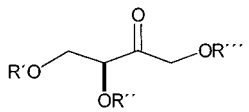
We have investigated a number of nucleophillic additions to L-erythrulose derivatives (**4**−**12**) bearing protective *O*-silyl, *O*-benzyl, and *O*-trityl groups in various relative positions. The results are discussed in the frame of chelated vs nonchelated transition states with additional support of previously published theoretical calculations. Sound evidence appears to exist for the formation of α-chelates as the key intermediates in nucleophillic additions to these α,*β*-dioxygenated ketones. Since such evidence is still lacking in the case of *β*-chelates, proposals of their intermediacy have been relegated in favor of the more solid Felkin−Anh model, which predicts the same stereochemical result. The behavior of these highly functionalized ketones does not always match that of structurally similar aldehydes.

Introduction

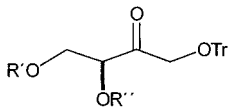
Carbohydrates, very particularly monosaccharides, represent one of the most convenient chiral sources in the synthesis of enantiopure compounds.[2] The ketotetrose L-(*S*)-erythrulose and derivatives[3] of general formula **1** (R′, R″, R‴ = protecting groups) are useful additions to the list of chiral precursors of this type. The carbonyl group of **1** is a prominent site for the appendage of additional carbon fragments via nucleophillic addition. The selection of suitable protecting groups is important, as they will exert a control on the steric course of nucleophillic additions.[4] The literature contains a great deal of studies on stereoselective additions of carbon nucleophiles to polyoxygenated aldehydes.[5] However, the corresponding behavior of highly functionalized ketones such as **1** is known with much less detail.[3d,6] In two preliminary reports, we have described the stereochemical outcome of organometallic additions to the carbonyl groups of 1-*O*-silylated erythrulose 3,4-acetonides[7a] (**1**, R′, R″ = CMe_2; R‴ = silyl) and 3,4-di-*O*-benzyl derivatives[7b] (**1**, R′, R″ = benzyl, Bn; R‴ = silyl). More recently, the diastereoselective additions to erythrulose 1,3-*O*-ethylidene acetals[7c] have also been reported. The diastereoselectivity of these reactions proved dependent on the type of hydroxyl protecting group. In the present paper, we describe in full[7d] the results of the diastereoselective reactions of several nucleophillic reagents with a range of variously protected L-erythrulose derivatives **1**. The



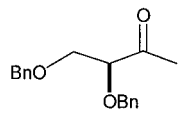
1



2 R′=R″=R‴=H
3 R′,R″=CMe_2, R‴=H
4 R′,R″=CMe_2, R‴=TPS
5 R′=R″=Bn, R‴=TPS
6 R′=R‴=TPS, R″=Bn
7 R″=R‴=TPS, R′=Bn
8 R′=R″=R‴=TPS



9 R′,R″=CMe_2
10 R′=R″=Bn
11 R′=Tr, R″=Bn



12

(1) (a) Universidad de Valencia. (b) Universidad Jaume I, Castellón.

(2) (a) Vasella, A. In *Modern Synthetic Methods 1980*; Scheffold, R., Ed.; Salle & Sauerländer Verlag: Frankfurt, 1980; pp 173−267. (b) Fraser-Reid, B.; Anderson, R. C. *Prog. Chem. Org. Nat. Prod.* **1980**, *39*, 1−61. (c) Hanessian, S. *Total Synthesis of Natural Products: the Chiron Approach*; Pergamon Press: Oxford, 1983. (d) Inch, T. D. *Tetrahedron* **1984**, *40*, 3161−3213. (e) Lichtenthaler, F. W. In *Modern Synthetic Methods 1992*; Scheffold, R., Ed.; VHCA.-VCH: Basel, 1992; pp 273−376. (f) Ferrier, R. J.; Middleton, S. *Chem. Rev.* **1993**, *93*, 2779−2831. (g) Monneret, C.; Florent, J.-C. *Synlett* **1994**, 305−318. (h) Collins, P.; Ferrier, R. J. *Monosaccharides. Their Chemistry and Their Roles in Natural Products*; John Wiley and Sons: New York, 1995. (i) Bols, M. *Carbohydrate Building Blocks*; John Wiley and Sons: New York, 1996.

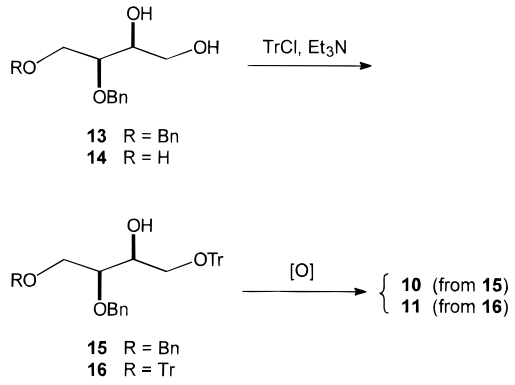
(3) (a) De Wilde, H.; De Clercq, P.; Vandewalle, M.; Röper, H. *Tetrahedron Lett.* **1987**, 4757−4758. (b) Van der Eycken, E.; De Wilde, H.; Deprez, L.; Vandewalle, M. *Tetrahedron Lett.* **1987**, 4759−4760. (c) Marco, J. L. J. *Chem. Res.* (S) **1988**, 276, (M) 2013−2016. (d) Nagano, H.; Ohno, M.; Miyamae, Y.; Kuno, Y. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 2814−2820. (e) Dequeker, E.; Compernolle, F.; Toppet, S.; Hoornaert, G. *Tetrahedron* **1995**, *51*, 5877−5890.

(4) Chen, X.; Hortelano, E. R.; Eliel, E. L.; Frye, S. V. *J. Am. Chem. Soc.* **1992**, *114*, 1778−1784.

(5) (a) Jurczak, J.; Pikul, S.; Bauer, T. *Tetrahedron* **1986**, *42*, 447−488. (b) Huryn, D. M. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Schreiber, S. L., Eds.; Pergamon Press: Oxford, 1991; Vol. 1, pp 49−75. (c) Lipshutz, B. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Schreiber, S. L., Eds.; Pergamon Press: Oxford, 1991; Vol. 1, pp 107−138. (d) Ferreri, C.; Palumbo, G.; Caputo, R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Schreiber, S. L., Eds.; Pergamon Press: Oxford, 1991; Vol. 1, pp 139−172. (e) Saccomano, N. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Schreiber, S. L., Eds.; Pergamon Press: Oxford, 1991; Vol. 1, pp 173−209. (f) Knochel, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Schreiber, S. L., Eds.; Pergamon Press: Oxford, 1991; Vol. 1, pp 211−229. (g) Imamoto, T. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Schreiber, S. L., Eds.; Pergamon Press: Oxford, 1991; Vol. 1, pp 231−250. (h) Shambayati, S.; Schreiber, S. L. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Schreiber, S. L., Eds.; Pergamon Press: Oxford, 1991; Vol. 1, pp 283−324. (i) Yamaguchi, M. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Schreiber, S. L., Eds.; Pergamon Press: Oxford, 1991; Vol. 1, pp 325−353.

S0022-3263(97)01674-5 CCC: $15.00
Published on Web 01/22/1998

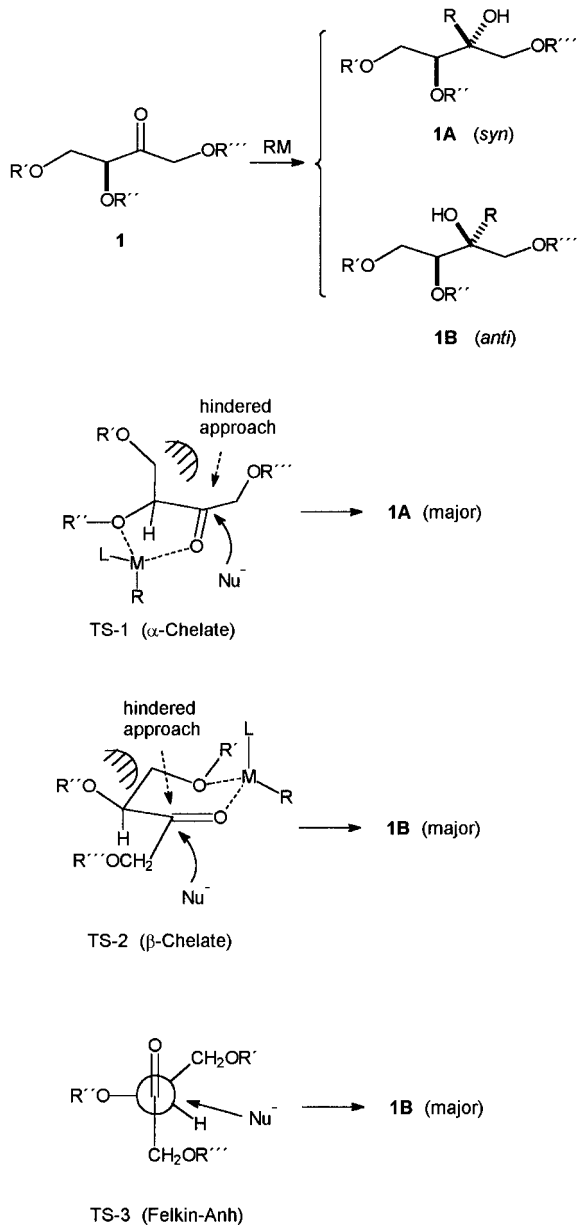
Scheme 1. Synthesis of Erythruloses 10 and 11



protecting groups were selected as to either favor (Bn) or to disfavor (*tert*-butyldiphenylsilyl, TPS, and trityl, Tr) the formation of metal chelates,[4] thus directing the process toward either a cyclic Cram chelation or to a nonchelation Felkin−Anh pathway.[8] The preparation of 1-*O*-silylated L-erythrulose derivatives **4**−**8** has recently been described.[9a] Ketones **9**−**11**, which bear a 1-*O*-trityl group (see comments below), have been obtained as reported in the literature[3c] or as depicted in Scheme 1 from the known compounds **13**[9a] and **14**.[10]

Aside from the carbonyl group, molecules **1** contain three additional, potentially complexing oxygen atoms in α, α′, and *β* positions. Our purpose was to determine to which extent the stereoselectivity of nucleophillic additions would be controlled by either Cram type chelation mechanisms involving any of these oxygen atoms or by transition states of the Felkin−Anh type. If either the α- or α′-oxygen atom enters complex formation, a five-membered chelate is formed (see Scheme 2), whereas involvement of the *β*-oxygen atom leads to the formation of a six-membered chelate. The α-chelate is predicted to react from the less hindered *Si* side of the carbonyl group (TS-1), leading predominantly to stereoisomer **1A**, which we here will arbitrarily name the syn stereoisomer.[11] The alternative anti stereoisomer **1B**, derived from attack to the *Re* side, is expected to be the major product when a *β*-chelate is the key intermediate (TS-2). When a Felkin−Anh transition state is traversed, stereoisomer **1B** should also be preferentially formed (TS-3, Scheme 2).

Scheme 2. Stereoselective Addition of Organometallic Reagents to Erythrulose Derivatives and Possible Transition States



Results and Discussion

It was clear from the beginning of the present work that, if a highly stereoselective addition was desired, the oxygen atom of the primary alcohol at C-1 should be prevented from complexation with the metal atom of the reagent. Examples of low stereoselectivities due to competitive complexation at both sides of ketone carbonyl groups are known,[5b,12] and in fact, we found that a very bulky protecting silyl group[12b,c] at the C-1 hydroxyl was necessary for having a high stereoselectivity.[7] The

(6) Chikashita, H.; Nakamura, Y.; Uemura, H.; Itoh, K. *Chem. Lett.* **1992**, 439−442.

(7) (a) Carda, M.; González, F.; Rodríguez, S.; Marco, J. A. *Tetrahedron: Asymmetry* **1992**, *3*, 1511−1514. (b) Carda, M.; González, F.; Rodríguez, S.; Marco, J. A. *Tetrahedron: Asymmetry* **1993**, *4*, 1799−1802. (c) Carda, M.; Casabó, P.; González, F.; Rodríguez, S.; Domingo, L. R.; Marco, J. A. *Tetrahedron: Asymmetry* **1997**, *8*, 559−577. (d) González, F., Ph.D. Thesis, University Jaume I, Castellón, 1995.

(8) (a) Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145−162. (b) Reetz, M. *Top. Curr. Chem.* **1982**, *106*, 1−54. (c) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556−569. (d) Reetz, M. T. *Acc. Chem. Res* **1993**, *26*, 462−468. For the importance of chelation in ketone reductions, see, for example: Oishi, T.; Nakata, T. *Acc. Chem. Res* **1984**, *17*, 338−344. Iida, H.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* **1986**, *51*, 3769−3771. Taniguchi, M.; Fujii, H.; Oshima, K.; Utimoto, K. *Tetrahedron* **1993**, *49*, 11169−11182. Sarko, C. R.; Guch, I. C.; DiMare, M. *J. Org. Chem.* **1994**, *59*, 705−706. Sarko, C. R.; Collibee, S. E.; Knorr, A. L.; DiMare, M. *J. Org. Chem.* **1996**, *61*, 868−873. For the role of chelation in other synthetically important processes, see: Kauffmann, T. *Synthesis* **1995**, 745−755.

(9) (a) Marco, J. A.; Carda, M.; González, F.; Rodríguez, S.; Murga, J. *Liebigs Ann. Chem.* **1996**, 1801−1810. (b) Part of the present results have been taken from the projected Ph.D. Thesis of E. Castillo.

(10) Steuer, B.; Wehner, V.; Lieberknecht, A.; Jäger, V. *Org. Synth.* **1997**, *74*, 1−11.

(11) The scope of this syn/anti nomenclature is limited to the present work and has no relation to the use of the same prefixes in other instances: Heathcock, C. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Schreiber, S. L., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, pp 181−238.

(12) (a) Annunziata, R.; Cinquini, M.; Cozzi, F.; Fuchicello, A. *Tetrahedron* **1991**, *47*, 3853−3868. (b) Frye, S. V.; Eliel, E. L. *J. Am. Chem. Soc.* **1988**, *110*, 484−489. (c) Bai, X.; Eliel, E. L. *J. Org. Chem.* **1992**, *57*, 5166−5172.

Table 1. Stereoselective Additions of Nucleophillic Reagents to Erythrulose Derivatives 4−8[a]

entry	compd	RM	solvent	*T* (°C)/*t* (h)	% yield	**1A**:**1B**[b]
1	**4**	MeLi	Et_2O	−78/1	86	86:14
2	**4**	allylLi	THF	−78/1	85	22:78
3	**4**	MeMgBr	Et_2O	0/1	88	75:25
4	**4**	vinylMgBr	THF	−78/1	93	80:20
5	**4**	allylMgBr	Et_2O	−78/1	90	20:80
6	**4**	Me_2CuLi	Et_2O	−78/2	80	88:12
7	**4**	$MeTi(OiPr)_3$	neat	25/60	67	9:91
8	**4**	$AlMe_3$	C_6H_6	25/1	80	60:40
9	**4**	$LiCH_2COOtBu$	Et_2O	−78/1	78	10:90
10	**5**	MeLi	Et_2O	−78/1	86	26:74
11	**5**	$MeLi/TiCl_4$	Et_2O	0/1	69	81:19
12	**5**	allylLi	THF	−78/2	87	30:70
13	**5**	MeMgBr	Et_2O	−78/1	95	>95:5
14	**5**	EtMgBr	THF	−78/1	94	>95:5
15	**5**	vinylMgBr	THF	−78/1	90	>95:5
16	**5**	ethynylMgBr	Et_2O	0/1	80	93:7
17	**5**	allylMgBr	Et_2O	−78/1	86	67:33
18	**5**	$allylSiMe_3/SnCl_4$	CH_2Cl_2	−78/6	80	>95:5
19	**5**	Me_2CuLi	Et_2O	−78/2	80	88:12
20	**5**	$MeTi(OiPr)_3$	neat	25/48	48	81:19
21	**5**	$AlMe_3$	C_6H_6	25/2	94	50:50
22	**5**	$Me_2Zn/TiCl_4$	CH_2Cl_2	−78/0.5	85	>95:5
23	**5**	$LiCH_2COOtBu$	Et_2O	−78/1	95	20:80
24	**5**	$LiCH_2CN$	THF	−78/1	70	24:76
25	**6**	MeLi	Et_2O	−78/1	83	15:85
26	**6**	MeMgBr	THF	−78/1	72	>95:5
27	**6**	EtMgBr	THF	−78/1	81	>95:5
28	**6**	vinylMgBr	THF	−78/1	76	>95:5
29	**6**	ethynylMgBr	THF	0/1	90	91:9
30	**6**	Me_2CuLi	Et_2O	−78/2	46	57:43
31	**6**	$MeTi(OiPr)_3$	neat	25/48	51	62:38
32	**7**	MeLi	Et_2O	−78/1	88	14:86
33	**7**	MeMgBr	Et_2O	−78/1	60	58:42
34	**7**	Me_2CuLi	Et_2O	−78/2	71	58:42
35	**7**	$MeTi(OiPr)_3$	neat	25/48	52	14:86
36	**8**	MeLi	Et_2O	−78/1	80	16:84
37	**8**	MeMgBr	Et_2O	−40/5	88	20:80
38	**8**	Me_2CuLi	Et_2O	−40/5	73	15:85

[a] In most cases, 3 equiv of the organometallic reagent was added to the appropriate ketone under the indicated conditions (see Experimental Section for more specific details). [b] Determined by ^1H and ^{13}C NMR (dr > 95:5 means that NMR signals from the minor isomer are not visible).

voluminous TIPS and TPS groups gave rise to the highest diastereoisomeric ratios (dr's),[7a] but the latter was preferred because of several convenient features such as its UV absorbance, which facilitated TLC analysis, and its more desirable ^1H NMR properties (no blurring multiplets around δ 1 ppm). With all these ideas in mind, erythruloses **4**−**8**, which contain various combinations of acetonide, TPSO, and BnO groups at C-3/C-4, were prepared in enantiopure form[9] and submitted to reaction with a series of different nucleophiles, mainly organometallic reagents. Several organolithium,[5b,13a] organomagnesium,[5b,13d] organocopper[5c,13c] and organotitanium[5d,13b] derivatives were examined for this purpose. In ketones **4** and **5**, the organoaluminum reagent $AlMe_3$ and allyltrimethylsilane/Lewis acid were also assayed. The organozinc reagent Me_2Zn was found to be reactive only in the presence of Lewis acids. The main results are presented in Table 1. The particular reaction conditions indicated for each reagent are those giving rise to the best results in terms of yield and stereoselectivity. Detrimental changes in the former or in the latter were consistently observed with deviations from these conditions (changes in temperature or solvent). Other changes such as addition of Lewis acids (BF_3, $TiCl_4$, Me_3SiCl, with the aforementioned exceptions),[5h,i] cation-sequestering agents (12-crown-4),[5i] and metal salts (LiCl, $LiClO_4$, $ZnCl_2$)[5i] proved in most cases unproductive or even deleterious,[7] as did prior metal exchange of either organolithium or organomagnesium reagents with trivalent lanthanide salts.[5g,13e]

Ketone **4** showed dr's which ranged from good to mediocre.[7a] Among the reagents assayed, only MeLi and the cuprate Me_2CuLi gave good dr's of **1A** (entries 1 and 6). In contrast, magnesium reagents (entries 3−5) behaved here in an erratic way and displayed unsatisfactory dr's. The allyl derivatives of lithium and magnesium displayed stereoselectivities which are opposite to those of non-allyl counterparts. The titanium reagent $MeTi(OiPr)_3$ gave a quite good dr (entry 7) with predominant formation of **1B**. It is worth mentioning here that all ketones assayed showed a very low reactivity toward this sterically crowded reagent (reaction times 2−3 d), which had to be used without solvent in great excess at room temperature. It is interesting to note that the stereoselectivity of **4** in all the aforementioned reactions does not match that of the structurally close 2,3-*O*-isopropylidene glyceraldehyde.[5a,14a]

Ketone **5** was, as previously reported,[7b] more diastereoselective than **4** toward organometallic reagents, most particularly with Grignard derivatives. With these, very high dr's were observed, the major product being **1A**, predicted by Cram's α-chelation model (entries 13−16). With $Me_2Zn/TiCl_4$ (entry 22) the stereoselectivity was also very high and had the same sense. In contrast, the sense of stereoselectivity with organolithium reagents corresponds to a non-α-chelate pathway (entries 10 and 12) and is thus opposite to that observed with **4**. Allylmetal derivatives showed here low stereoselectivities, except for allyltrimethylsilane/$SnCl_4$ (entry 18), where practically only one diastereomer is formed. This result is extremely interesting from the preparative point of view, since the allyl group can be transformed later into a broad range of carbon appendages. Contrary to **4**, ketone **5** reacted with $MeTi(OiPr)_3$ to give mainly the syn isomer **1A** (entry 20), expected for an α-chelated transition state. As for **4**, ketone **5** differs in its behavior from the structurally close 2,3-di-*O*-benzylglyceraldehyde.[14a]

In relation to one of our research projects,[9b] we also investigated the reactions of **4** and **5** with the lithium enolate of *tert*-butyl acetate (entries 9 and 23) and the reaction of **5** with the carbanion formed by deprotonation of acetonitrile (entry 24). Stereoisomer **1B** was in all cases the major product. Chiral α-alkoxy aldehydes have been shown to react with lithium enolates in a very unselective way whereas their β-alkoxy counterparts often show useful levels of stereoselectivity.[8c] It is difficult, however, to say whether chelation may be involved in the present case, as both mechanistic alternatives have been reported.[11]

(13) (a) Schlosser, M. In *Organometallics in Synthesis*; Schlosser, M., Ed.; John Wiley and Sons: New York, 1994; Chapter 1. (b) Reetz, M. T. In *Organometallics in Synthesis*; Schlosser, M., Ed.; John Wiley and Sons: New York, 1994; Chapter 3. (c) Lipshutz, B. H. In *Organometallics in Synthesis*; Schlosser, M., Ed.; John Wiley and Sons: New York, 1994; Chapter 4. (d) Wakefield, B. J. *Organomagnesium Methods in Organic Synthesis*; Academic Press: London, 1995; Chapter 6. (e) Imamoto, T. *Lanthanides in Organic Synthesis*; Academic Press: London, 1994; pp 80−97.

(14) (a) Mead, K.; Macdonald, T. L. *J. Org. Chem.* **1985**, *50*, 422−424. (b) Reetz, M. T.; Kesseler, K. *J. Org. Chem.* **1985**, *50*, 5434−5436. These results should be compared with those observed for a sterically encumbered glyceraldehyde derivative, where the nonchelation mode appears to be the main mechanistic pathway: Ley, S. V.; Woods, M.; Zanotti-Gerosa, A. *Synthesis* **1992**, 52−54.

Table 2. Stereoselective Additions of Nucleophillic Reagents to Erythrulose Derivatives 9−11[a]

entry	compd	RM	solvent	*T* (°C)/*t* (h)	% yield	**1A**:**1B**[b]
1	**9**	MeLi	Et_2O	−78/1	84	78:22
2	**9**	MeMgBr	THF	−78/1	95	77:23
3	**9**	vinylMgBr	THF	−78/1	85	78:22
4	**10**	MeLi	THF	−78/1	92	45:55
5	**10**	MeMgBr	THF	−78/1	86	>95:5
6	**10**	EtMgBr	THF	−78/1	87	90:10
7	**10**	vinylMgBr	THF	−78/1	95	>95:5
8	**10**	ethynylMgBr	Et_2O	0/1	80	93:7
9	**10**	allylMgBr	Et_2O	−78/1	95	60:40
10	**10**	allylLi	Et_2O	−78/1	90	40:60
11	**11**	vinylMgBr	THF	−78/1	90	>95:5

[a,b] See footnotes to Table 1.

Ketone **6**, where the β-OBn group of **5** is replaced by a TPSO group, was prepared with the idea that its structure would allow the formation of an α-chelate but, because of the bulky silyl moiety, not a β-chelate.[8c,d] In the event, **6** behaved in essentially the same way as **5** toward lithium and magnesium reagents (entries 25−29), with Me_2CuLi and $MeTi(OiPr)_3$ being, however, much less stereoselective (entries 30 and 31). In general terms, this behavior is similar to, but not completely coincident with, that of the structurally close 2-*O*-benzyl-3-*O*-(*tert*-butyldimethylsilyl)glyceraldehyde,[14b] where $MeTi(OiPr)_3$ gave very predominantly the nonchelation-controlled product.

In comparison with **6**, ketone **7** represents the alternative situation in which the α-chelate pathway has been blocked via protection of the corresponding hydroxyl with a bulky silyl group, leaving the possibility of a β-chelation still open. Indeed, anti isomer **1B** was the major isomer with both MeLi and $MeTi(OiPr)_3$ (entries 32 and 35) but Me_2CuLi reacted with a unexpectedly[5c] low stereoselectivity (entry 34).

Erythrulose derivative **8** represents a limiting case as it has its three hydroxyl functions protected with voluminous TPS groups. This excludes any mechanistic pathway involving chelates. In line with this, the anti stereoisomer **1B** was the major product in the cases essayed (entries 36−38), in agreement with a Felkin−Anh transition state. The reactions of **8** were more sluggish than those of the other ketones and required higher temperatures and/or reaction times to completion. This obviously reflects the high steric hindrance of the carbonyl group in this molecule. For instance, the bulky reagent $MeTi(OiPr)_3$ did not react at all with **8**.

The somewhat high price of TPS chloride led us to test alternative protecting groups such as the cheaper trityl group,[15] which displays a comparable steric size. We then synthesized erythruloses **9**,[3c] **10**, and **11** (Scheme 1) and tested their reactions with several key organometallic reagents (Table 2). It was very satisfactory to find that the dr's of these reactions were quite similar to those of their 1-O-silylated counterparts. The reactions with **9** gave similar results as those previously found.[3d] The higher sensitivity of the trityl group toward acidic reagents, however, showed up in extensive decomposition when **9**−**11** were allowed to react in the presence of Lewis acids such as $TiCl_4$.

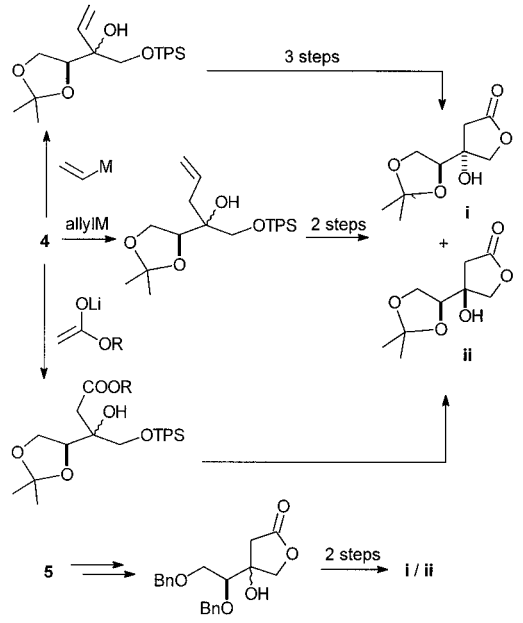
The configurations of the diastereoisomers formed in these reactions have been established with the aid of chemical correlations, described in part in our previous communications (Scheme 3).[7] In the case of the products derived from **4** and **5**, additional evidence of the correctness of our configurational assignments comes from their conversion into some naturally occurring compounds.[16] For ketones **6**−**8** and **9**−**11**, the configurations of the addition products have been determined by chemical correlation with the known products **20**, **25**, and their epimers,[7,9b] which were identified either pure or as stereoisomeric mixtures by ^1H and ^{13}C NMR spectroscopy.[17]

Taking the results of Tables 1 and 2 as a whole, some general conclusions may be drawn. Isomer **1A**, predicted only by Cram's α-chelation model, is formed with a very high dr in several cases, mainly with Grignard reagents and ketones **5** and **6**, where α-chelation is not sterically impeded by O-substitution (entries 13−16 and 26−29). It is thus likely that α-chelates are formed in these cases. There is presently a great deal of experimental evidence[4,8d] of the real existence of α-chelates as intermediates in carbonyl additions, particularly with organomagnesium reagents.[5b] A further aspect deserves mention. Although we have not performed kinetic measurements, we have observed that these highly stereoselective reactions were also particularly fast. In most cases, all reactions were complete within 1 h. We observed, however, that the reactions corresponding to entries 13−15 and 26−28 were already complete after only 2 min at −78 °C. The addition of 3 equiv of Grignard reagent was necessary, however, for the reaction to occur in such a fast way. With addition of only 1 equiv, 30% of unreacted ketone was recovered after 1 h. Furthermore, addition of chelation-disrupting HMPA to the Grignard reaction mixture *caused both a strong decrease in the reaction rate (10% unreacted ketone after 7 h at 0 °C) and an almost complete disappearance of the stereoselectivity* (dr ∼ 1.1:1). It is

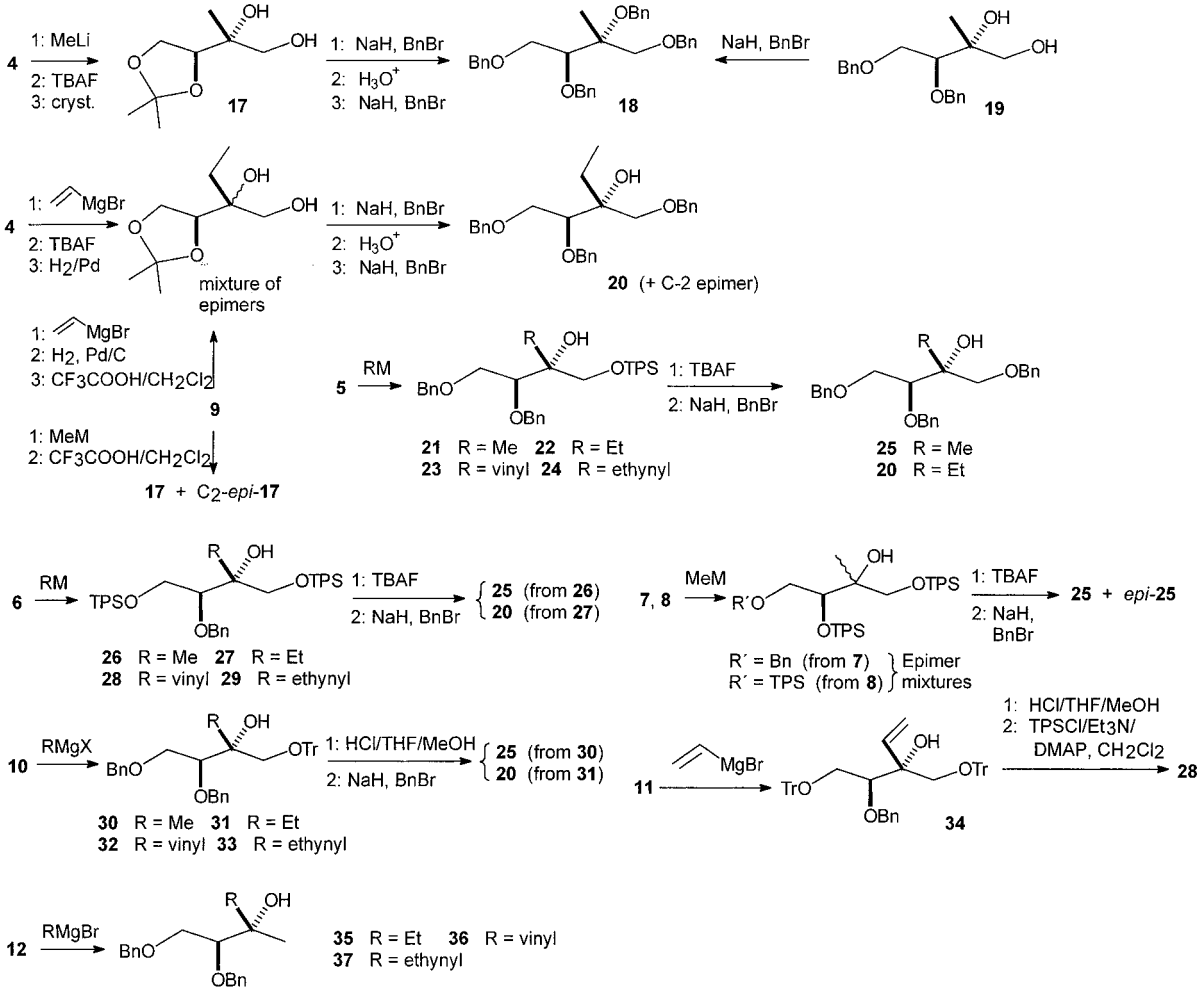
(15) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; John Wiley and Sons: New York, 1991; pp 60−62.

(16) (a) Marco, J. A.; Carda, M.; González, F.; Rodríguez, S.; Murga, J.; Falomir, E. *An. Quím.* **1995**, *91*, 103−112. (b) Marco, J. A.; Carda, M.; González, F.; Rodríguez, S.; Murga, J. J. *Chem. Res.* (S) **1996**, 1, (M) 201−205.

(17) The configurations of the products formed after addition of allylmetal derivatives, acetonitrile, and *tert*-butyl acetate enolates to ketone **4** were determined by conversion into lactone **i** and its epimer **ii**, as either the pure compounds or mixtures thereof. Addition products to ketone **5** were subjected to an analogous sequence of reactions, and the obtained lactones were then converted into **i** and/or **ii**. These results constitute a part of the projected Ph.D. Thesis of E.C.



Scheme 3. Chemical Correlations between the Addition Products of Nucleophiles to Ketones 4−12



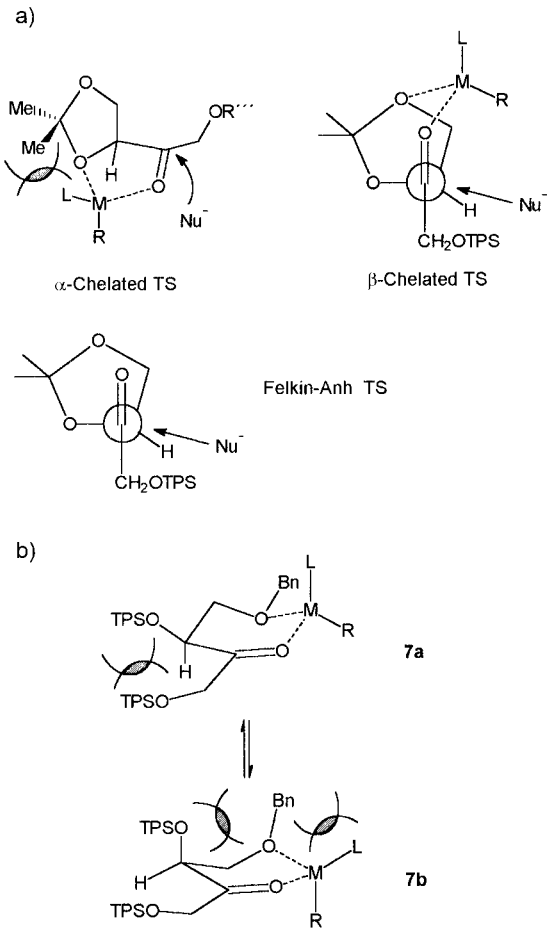
pertinent remembering here the observations of Eliel and co-workers[4] on organometallic additions to ketones bearing α-OR groups. They found that these ketones reacted not only much faster when R was a small alkyl group than when R was a bulky silyl group but also with a higher diastereoselectivity.[18] The same authors did not find rate enhancements in ketones bearing *β*-OR groups, which reacted with similar rates as substrates where chelation was not possible.[4] It thus appears that formation of **1A** through the α-chelate represents the reaction channel with the lowest activation barrier on both electronic and steric reasons. The fact that **6** gives essentially the same dr's as **5** toward Grignard reagents further indicates that the *β*-chelate pathway, even if feasible, does not participate in these cases to a noticeable extent. It may be concluded therefore that ketones **5** and **6**, which bear α-chelating groups, will react with organomagnesium reagents exclusively through the α-chelate, whether or not additional chelation points are offered. MeLi reacts with a lower stereoselectivity and in the opposite sense to that displayed by magnesium reagents, a not unprecedented behavior.[5b,12b] Whether the reasons of this apparent absence of an α-chelate involving the lithium cation are of thermodynamic (low stability) or kinetic (slow formation) nature remains unknown.

The behavior of **4** is surprising. The selectivities of Grignard reagents were lower than expected and not always predictable. Allylmagnesium bromide, for instance, gave mainly **1B**, opposite to that predicted by the α-chelation model. This may be due to the fact that many allyl-type organometallics react in most instances with allylic inversion through cyclic transition states of the metallo-ene type, which do not involve chelation.[19] MeLi gave a high dr of the α-chelation isomer **1A**, a not anticipated result with organolithium derivatives.[5b] These findings should be considered in the light of the previous observations on nucleophillic additions of 2,3-*O*-isopropylideneglyceraldehyde[5a,14a] and its 2,3-di-*O*-benzyl analogue.[14a] In all cases examined, the acetonide was clearly the less diastereoselective compound, with the major stereoisomer being opposite to that predicted by the α-chelation model. To explain this, it has been proposed[14a] that glyceraldehyde acetonide reacts mainly under nonchelation control because of (a) a too high chelate energy contents due to appreciable ring strain and to nonbonded interactions of the acetonide geminal methyl groups with metal ligands (cf. Scheme 4a), and/or (b) a depressed donor ability of the acetonide oxygens

(18) A parallel increase of reactivity and enantioselectivity has also been observed in some addition reactions: Zhang, H.; Xue, F.; Mak, T. C. W.; Chan, K. S. *J. Org. Chem.* **1996**, *61*, 8002−8003.

(19) (a) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Schreiber, S. L., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, pp 1−53. (b) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207−2293. (c) Yamamoto, Y.; Shida, N. In *Advances in Detailed Reaction Mechanisms*; Coxon, J. M., Ed.; JAI Press Inc.: Greenwich, CT, 1994; pp 1−44.

Scheme 4. (a) Structure of Chelates of Ketone 4 and Possible Transition States. (b) Temptative Conformations of the Putative β-Chelates of Erythrulose Derivative 7



owing to mutual electron-withdrawing inductive effect.[20] In the case of **4**, however, these proposals do not explain why some organolithium and organomagnesium reagents (entries 1 and 3−4) give predominantly **1A** (Scheme 4a). Rational explanations for these findings are still lacking.

No regular trends are recognizable in the behavior of the Gilman reagent Me_2CuLi. It showed a fairly good stereoselectivity toward **4** and **5**, with **1A** being predominantly formed. In contrast, it proved quite unselective in its reactions with **6** and **7**. Much work has been reported on stereoselective additions to polyoxygenated aldehydes, most particularly those having α- and β-alkoxy/silyloxy groups.[5c] Addition of the nucleophile to the corresponding cyclic α- or β-chelate has been invoked in such cases to explain the stereochemical outcome of the alkoxy derivatives, whereas the silyloxy compounds were postulated to react through Felkin−Anh transition states. Unfortunately, there is almost no precedent concerning structurally related ketones. Furthermore, it appears that the way of preparing these copper reagents may have an influence on the stereoselectivity of their addition reactions. For instance, Mead and Macdonald[14a] found that cuprates prepared by metal exchange from organolithium reagents did not give the same results as those similarly prepared from Grignard reagents. It is likely that the lithium and magnesium cations, which constitute a part of the reagent structure[21] and display different chelation abilities, are in these cases the ionic species actually involved in chelate formation.[5c]

The case of allyltrimethylsilane is especially interesting. In the presence of tin tetrachloride as a Lewis acid, this reagent added to ketone **5** (entry 18) to yield essentially pure stereoisomer **1A** (dr > 95:5). With $TiCl_4$ the stereoselectivity was equally high but the yield was lower. This is consistent with TS-1 in Scheme 2, where either of these bidentate Lewis acids forms the α-chelate and the nucleophile (CH_2=$CHCH_2SiMe_3$) adds subsequently to the less hindered carbonyl side. Similar considerations apply for $Me_2Zn/TiCl_4$ (entry 22). In the presence of these Lewis acids, however, ketone **4** gave a mixture of ill-defined products which still had a carbonyl group but lacked the acetonide moiety. Most likely, a Sakurai-type[22] reaction took place between the electrophillic acetal carbon and the allylsilane. Substitution of $SnCl_4$ or $TiCl_4$ for BF_3 only led to recovery of the starting ketone, even in the presence of an excess of the Lewis acid. In all probability, the complex between the ketone carbonyl oxygen and the monodentate Lewis acid BF_3 is not stable enough for steric reasons.

Methyltitanium trisisopropoxide is a further reagent which displays contrasting behavior toward ketones **4**−**7**. Since this weakly Lewis-acidic reagent is not very prone to form chelates,[5d,13b] the formation of **1B** from **4** (entry 7) is most likely explained through a Felkin−Anh transition state. However, **1A** is the major product with **5** and, to a lesser extent, with **6** (entries 20 and 31), which strongly suggests reaction through an α-chelate. This is not the usual outcome with this reagent but precedent has been reported.[8c,23] In the case of **5**, the reagents combination $MeLi/TiCl_4$ (entry 11) yields essentially the same stereoisomeric mixture as $MeTi(OiPr)_3$. Most likely, initial transmetalation of MeLi and $TiCl_4$ to yield $MeTiCl_3$ takes place, with the latter reagent thus reacting via chelate formation.[5d,13b] This constitutes the opposite result to that observed with MeLi alone (entry 10). The reaction of **4** with the same reagents mixture would have been meaningful, but unfortunately, the compound decomposed under these conditions, perhaps due to sensitivity of the acetal ring to strong Lewis acids (see above).

Ketone **7**, where β-chelation is the only possible chelation mode, reacted with an organocopper reagent in an almost stereorandom way (entry 34). Grignard reagents were also unselective. It is possible that the β-chelate, *if formed to any extent*, has a weak diastereofacial preference in the present case. This might be due to a higher flexibility of the six-membered chelate, when compared with the more compact and conformationally constrained five-membered α-chelate. Indeed, the structures of chelates formed between β-alkoxy aldehydes and Lewis acid such as $TiCl_4$ or $MgBr_2$ have been studied by

(20) There is some experimental basis which lends support to this proposal. In the reactions of Grignard reagents with 2-acyltetrahydrofurans, which only have an oxygen atom in the ring, high stereoselectivities are often observed: Eliel, E. L. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 2, Chapter 5. For a further example structurally very close to **4**, see: Rao, A. V. R.; Gurjar, M. K.; Devi, T. R.; Kumar, K. R. *Tetrahedron Lett.* **1993**, 1653−1656.

(21) Krause, N.; Gerold, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 187−204.

(22) Weber, W. P. *Silicon Reagents for Organic Synthesis*; Springer-Verlag, Berlin, 1983; pp 173−205.

(23) Reetz, M. T.; Hüllmann, M. *J. Chem. Soc., Chem. Commun.* **1986**, 1600−1602.

Table 3. Stereoselective Additions of Grignard Reagents to 12[a]

entry	RM	solvent	*T* (°C)/*t* (h)	% yield	**1A**:**1B**[b]
1	EtMgBr	THF	−78/1	87	>95:5
2	vinylMgBr	THF	−78/1	85	>95:5
3	ethynylMgBr	THF	−78/1	84	87:13

[a,b] See footnotes of Table 1.

NMR.[24] The authors found that 1:1 complexes of 2-methyl-3-(benzyloxy)propanal with either of these Lewis acids are conformationally rigid, with the methyl group occupying a pseudoequatorial position in a flattened half-chair. However, when these concepts are translated to ketone **7**, important differences immediately appear (Scheme 4b). One of the half-chair conformations (**7a**) may be destabilized by a strong torsional gauche interaction between the bulky α-OTPS and CH_2OTPS groups (this interaction is negligible in aldehydes, where a hydrogen atom replaces the latter group). In the alternative conformation **7b**, similar destabilizing interactions are expected to arise between the OBn group and, depending of the spatial orientation of the benzyl moiety, either the pseudoaxial α-OTPS group or one of the magnesium ligands. The *β*-chelate therefore may not be formed at all here by either thermodynamic (insufficient stability) or kinetic reasons (too slow formation).[4,25a] Moreover, if actually formed, it may not have a marked diastereofacial bias.

MeLi and MeTi(OiPr)$_3$ reacted with **7** to show the same dr, with **1B** being the major isomer. Similar dr values are also observed in the reactions of ketone **8**, where chelation cannot take place. It is likely that these reactions take place through a Felkin−Anh transition state.

The diastereoselectivities of hydride reductions of the protected 1-deoxyerythrulose **12** have already been investigated.[14a] To make mechanistic comparisons with erythrulose **5**, we have now tested some additions of *carbon* nucleophiles. Since, in comparison with **5**, only the bulky nonchelating group OR‴ at C-1 has been removed, the stereoselectivities should be similar to those of the latter ketone. This assumption has actually been borne out in practice in the case of Grignard reagents. Ketone **12** was allowed to react with ethyl-, vinyl-, and ethynylmagnesium bromide, to yield **1A** with high dr values than the stereoisomer, expected from addition to the α-chelate (Table 3). The configurations of the addition products were established in each case by chemical correlation with the known product **35** (Scheme 3).[7b,d]

Some of the questions discussed above have also been addressed with the aid of computational methods. In a recently published ab initio study,[25a] the additions of Me_2-Mg to several α- and *β*-alkoxy carbonyl compounds have been investigated. The authors relied upon the aforementioned kinetic measurements of Eliel's group on the reactions of Me_2Mg with α-alkoxy ketones,[4] where an overall second-order kinetics (first order in both substrate and Grignard reagent) was established. They then postulated an initial, fast and exothermic chelation step, followed by 1,3 magnesium-to-carbon migration of the nucleophillic methyl group within the chelate. An energetically favored intervention of α-chelates was predicted for the α-alkoxy carbonyl compounds, with the observed stereochemical outcome being in a good agreement with theoretical conclusions. In contrast, the situation with *β*-chelates was much less clear-cut. While the bare existence of *β*-chelates seems to be confirmed by various experimental procedures,[4,24] their *actual* intervention in addition processes is still dubious. Alternative pathways not involving chelation may likely become competitive or even faster in such cases. A particularly interesting conclusion of this theoretical study is that C−C bond formation must not necessarily be the rate-limiting step of the whole process.[25a]

Still more recently,[25b] ab initio studies on the additions of the organomagnesium species $MeMg^+$ and MeMgCl (1 or 2 equiv) to some α-alkoxy and α,*β*-dialkoxy carbonyl compounds have been made. A particularly interesting example of the latter compound type was 3,4-di-*O*-methyl-1-*O*-(trimethylsilyl)-L-erythrulose, which is a suitable model for the compounds under discussion. In addition, the organometallic species selected as model reagents corresponded more closely to those we actually used. As in the previous instance, the authors found that an initial exothermic α-chelate formation takes place without any noticeable energy barrier (solvation was not considered in this study). Under assumption of a 1:1 ketone/Grignard reagent stoichiometry, rate-limiting C−C bond formation occurs subsequently via magnesium to carbon 1,3-methyl transfer. Interestingly, the authors also found that inclusion of a second molecule of the Grignard reagent into the reactive complex, i.e., intermolecular methyl transfer from one molecule of MeMgCl to a preformed MeMgCl/carbonyl chelate, causes a decrease of the predicted energy barrier. This suggests a second-order kinetics in the organomagnesium reagent and may be qualitatively in line with the fact that 3 equiv of the organomagnesium reagent are necessary for a fast reaction to occur at −78 °C (see above).[26] The stereofacial outcome predicted by this model (attack from the *Si* side of the carbonyl group)[25] nicely agrees with our experimental observations. This lends an additional support to our assumption of the intermediacy of α-chelates in these additions.

In summary, α,*β*-dioxygenated ketones will undergo very rapid and stereoselective organometallic additions to the carbonyl group provided that (a) the α-oxygen atom is not prevented by its substituent[4,24] from forming a five-membered chelate and (b) the organometallic reagent contains a Lewis acidic[5h] metal atom (e.g., magnesium, titanium) capable of forming sufficiently stable chelates of this ring size. Under these conditions, attack by the nucleophile will take place from the less hindered face of the chelated molecule, leading in most cases to high stereoselectivities. No conclusive evidence has been gathered in the present case, however, to substantiate the participation of six-membered *β*-chelates, which may even not be stable enough to be formed here. Despite the fact that *β*-chelates have often been invoked to explain the stereochemical outcome of nucleophillic additions in 1,3-difunctional compounds such as *β*-oxo

(24) (a) Keck, G.; Castellino, S. *J. Am. Chem. Soc.* **1986**, *108*, 3847−3849. (b) Keck, G.; Castellino, S.; Wiley, M. R. *J. Org. Chem.* **1986**, *51*, 5478−5480.

(25) (a) Mori, S.; Nakamura, M.; Nakamura, E.; Koga, N.; Morokuma, K. *J. Am. Chem. Soc.* **1995**, *117*, 5055−5065. (b) Safont, V. S.; Moliner, V.; Oliva, M.; Castillo, R.; Andrés, J.; González, F.; Carda, M. *J. Org. Chem.* **1996**, *61*, 3467−3475.

(26) It should be remembered, however, that the complex composition of Grignard reagent mixtures makes the interpretation of kinetic measurements a very difficult issue: Ashby, E. C.; Laemmle, J.; Neumann, H. M. *Acc. Chem. Res* **1974**, *7*, 272−280.

sulfoxides,[27] β-oxo amides,[28] β-oxygenated aldehydes,[29] β-hydroxy ketones,[30] β-oxo phosphine oxides,[31a] β-silyloxy ketones,[31b] etc., their actual participation in addition processes of β-oxygenated carbonyl compounds is still an object of discussion.[4,25a] It has recently been proposed that the stereochemical outcome of nucleophillic additions to polyalkoxy carbonyl compounds may be controlled by conformational factors in the ground state.[32] Of course, this stereochemical model might be considered here for those cases where α-chelation may be excluded. However, it is difficult to understand on this basis how the same molecule reacts with different reagents under similar temperature and solvent conditions to yield very different dr values. Additional kinetic measurements as well as high-level theoretical studies will thus be necessary for a deeper understanding of this complex mechanistic frame.

Experimental Section

General. Column chromatography (CC) was performed on silica gel Süd-Chemie AG (50−200 μm) with the mixture of solvents indicated in each case. Experiments which required an inert atmosphere were carried out under dry argon (Ar) in a flame-dried glass system. THF and benzene were freshly distilled from sodium/benzophenone ketyl and sodium wire, respectively, and were transferred via syringe. Methylene chloride was distilled from P_2O_5 and stored over 4 Å molecular sieves. DMSO was dried and stored on 4 Å molecular sieves. Triethylamine was distilled from CaH_2. Other commercially available reagents (Aldrich or Fluka) were used as received: organometallic reagents were used as solutions in Et_2O (MeLi, MeMgBr), THF (other magnesium reagents), benzene ($AlMe_3$), or toluene (Me_2Zn). Allyllithium was prepared immediately prior to use by reaction of lithium with allyl phenyl ether.[13a] If not detailed otherwise, the workup of the reactions was consistently performed in the following manner: the reaction mixture was poured into brine and extracted twice with solvent (Et_2O or CH_2Cl_2), the organic layer was washed with diluted acid or base (depending on whether the reaction conditions were basic or acid, respectively) and then washed again with brine, the organic layer was dried over anhydrous $MgSO_4$ or Na_2SO_4, and the solvent was eliminated with a rotary evaporator at aspirator pressure.

(*S*)-1-*O*-Trityl-3,4-*O*-isopropylidene-1,3,4-trihydroxybutan-2-one (9) was prepared according to ref 3c.

(2*S*,3*S*)-4-*O*-Trityl-1,2-di-*O*-benzylbutane-1,2,3,4-tetrol (15). 1,2-Di-*O*-benzyl-L-threitol (**13**)[9a] (3.024 g, 10 mmol) was dissolved in dry CH_2Cl_2 (40 mL) and treated under Ar with Et_3N (2.1 mL, 15 mmol), DMAP (15 mg), and TrCl (3.067 g, 11 mmol). The reaction mixture was stirred at room temperature for 18 h. Workup (CH_2Cl_2) and CC (hexane/EtOAc 9:1) afforded **15** (3.812 g, 70%).

(*S*)-1-*O*-Trityl-3,4-di-*O*-benzyl-1,3,4-trihydroxybutan-2-one (10) by Swern Oxidation of 15. Dry DMSO (1.70 mL, 24 mmol) was added under Ar at −60 °C to a solution of oxalyl chloride (1.05 mL, 12 mmol) in dry CH_2Cl_2 (30 mL). After the mixture was stirred at this temperature for 2 min, a solution of **15** (3.268 g, 6 mmol) in dry CH_2Cl_2 (30 mL) was added dropwise. The stirring was further continued for 15 min, and then Et_3N (3.4 mL, 24 mmol) was added, with additional stirring at −60 °C for 15 min. The temperature was then increased to 25 °C and the reaction mixture was stirred for 1 h. Workup (CH_2Cl_2) and CC (hexanes/EtOAc 9:1) afforded **10** (2.54 g, 78%).

(2*S*,3*S*)-1,4-Di-*O*-trityl-2-*O*-benzylbutane-1,2,3,4-tetrol (16) was prepared from **14**[10] as described above for **15** but using a double amount of TrCl. Workup (CH_2Cl_2) and CC (hexane/EtOAc 9:1) afforded **16** in 70% yield.

(*S*)-1,4-Di-*O*-trityl-3-*O*-benzyl-1,3,4-trihydroxybutan-2-one (11) was obtained from **16** in 90% yield as described above for **10**.

(*S*)-3,4-Di-*O*-benzyl-3,4-dihydroxybutan-2-one (12). Diol **13**[9a] (3.024 g, 10 mmol) was dissolved in benzene (50 mL) and treated with lead tetraacetate (8.87 g, 20 mmol). After being stirred at room temperature for 30 min, saturated aqueous $NaHCO_3$ (25 mL) was added. The reaction mixture was then extracted with CH_2Cl_2 (4 × 10 mL), and the organic layer was filtered through Celite and evaporated *at reduced pressure*. This yielded crude 2,3-di-*O*-benzyl-L-glyceraldehyde, which was dried *at reduced pressure* and used immediately without purification for the next step.

The product obtained in the previous step was dissolved under Ar in dry THF (30 mL) and treated at −78 °C with a 1.6 M solution of MeLi in THF (20 mL, 32 mmol). The reaction mixture was stirred for 1 h at the same temperature. Workup (CH_2Cl_2) and solvent removal at reduced pressure afforded a crude dibenzylated triol (mixture of two epimers), which was filtered through a pad of silica gel (elution with hexanes/EtOAc 7:3). Evaporation of the solvent at reduced pressure provided an oily residue (1.174 g, 41% crude yield), which was used without further purification in the next step.

The mixture of epimeric alcohols obtained previously was oxidized as above (**15** → **10**) by the Swern procedure. Workup (CH_2Cl_2) and column chromatography on silica gel (elution with hexanes/EtOAc 8:2) furnished **12** (995 mg, 35% overall yield from **13**).

General Experimental Procedures for Organometallic Additions to Ketones 4−12. Substrate, solvent, temperature, reaction time, and yield are indicated in Tables 1−3. Careful exclusion of oxygen and moisture is assumed in all cases.

(a) For organolithium, Grignard reagents, and Me_3Al. A solution of the appropriate ketone (1 mmol) in the indicated solvent (4 mL) was cooled to the indicated temperature. The required organometallic reagent (3 mmol) was then added dropwise, and the reaction mixture was stirred for the indicated time. Workup (Et_2O) and column chromatography (hexane/EtOAc mixtures) yielded the desired product with the indicated yield and diastereoisomeric composition.

(b) For Organometallic Additions in the Presence of Lewis Acids ($TiCl_4$, $SnCl_4$, etc.). Method A. A solution of the appropriate ketone (1 mmol) in the indicated solvent (4 mL) was cooled to the indicated temperature. The Lewis acid (1 mmol) was then added dropwise at the same temperature, and the reaction mixture was stirred for 15 min. After this, the organometallic reagent (3 mmol) was added dropwise, followed by stirring for the indicated time. Workup (Et_2O or CH_2Cl_2) and column chromatography (hexane/EtOAc mixtures) yielded the desired product with the indicated yield and diastereoisomeric composition. **Method B.** Titanium tetrachloride (1 mmol) and MeLi (1 mmol) were dissolved in dry Et_2O (2 mL) at 0 °C. After 15 min of stirring, a solution of the ketone (0.5 mmol) in dry Et_2O (4 mL) was added dropwise. The reaction mixture was then stirred for 1 h at the same temperature. Workup and column chromatography as above.

(27) Bueno, A. B.; Carreño, M. C.; García-Ruano, J. L. *An. Quím.* **1994**, *90*, 442−451. See also: Page, P. C. B.; Purdie, M.; Lathbury, D. *Tetrahedron Lett.* **1996**, 8929−8932.

(28) (a) Taniguchi, M.; Fujii, H.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 2514−2521. (b) Taniguchi, M.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 645−653.

(29) (a) Marshall, J. A.; Perkins, J. F.; Wolf, M. A. *J. Org. Chem.* **1995**, *60*, 5556−5559. (b) Banfi, L.; Guanti, G.; Zannetti, M. T. *J. Org. Chem.* **1995**, *60*, 7870−7878. (c) De Kermadec, D.; Prudhomme, M. *New. J. Chem.* **1993**, *17*, 499−503. (d) Paquette, L. A.; Mitzel, T. M. *Tetrahedron Lett.* **1995**, 6863−6866. Nonchelation has been postulated in other cases: Braun, M.; Mahler, H. *Liebigs Ann. Chem.* **1995**, 29−40.

(30) García-Ruano, J. L.; Tito, A.; Culebras, R. *Tetrahedron* **1996**, 52, 2177−2186. Protection of the free hydroxyl group, however, seems to favor Felkin−Anh transition states in some cases: Guanti, G.; Banfi, L.; Riva, R. *Tetrahedron* **1995**, *51*, 10343−10360.

(31) (a) Bartoli, G.; Bosco, M.; Sambri, L.; Marcantoni, E. *Tetrahedron Lett.* **1996**, 7421−7424. (b) Bartoli, G.; Bosco, M.; Sambri, L.; Marcantoni, E. *Tetrahedron Lett.* **1997**, 3785−3788.

(32) (a) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322−4343. (b) Mulzer, J.; Pietschmann, C.; Buschmann; Luger, P. *J. Org. Chem.* **1997**, *62*, 3938−3943.

(c) For Me_2CuLi. CuI (228.5 mg, 1.2 mmol) was flame-dried under Ar until the appearance of a yellowish color. After the solution was cooled to 0 °C, Et_2O (3.5 mL) was added followed by MeLi (1.6 M in hexanes, 1.57 mL, 2.5 mmol). The mixture was then cooled to the indicated temperature and treated dropwise with a solution of the appropriate ketone (0.4 mmol) in Et_2O (2 mL). The reaction mixture was stirred at the same temperature for the indicated time. Workup (Et_2O) and column chromatography (hexane/EtOAc mixtures) yielded the desired product with the indicated yield and diastereoisomeric composition.

(d) For $MeTi(OiPr)_3$. A solution of $ClTi(OiPr)_3$ (1 M in hexanes, 7 mL, 7 mmol) was treated at −50 °C with MeLi (1.6 M in Et_2O, 4.4 mL, 7 mmol). The cooling bath was removed, and the mixture was stirred at room temperature for 2 h. After this, the solution was filtered under Ar with careful exclusion of moisture and poured directly into the flask containing the appropriate ketone (0.5 mmol). The solvent was then eliminated at reduced pressure, and the oily mixture was stirred at room temperature for the indicated time. Workup (Et_2O) and column chromatography (hexane/EtOAc mixtures) afforded the desired product with the indicated yield and diastereoisomeric composition.

(e) Acetonitrile and *tert*-Butyl Acetate Enolates. LDA was generated by dropwise addition of BuLi (620 μL of a solution ca. 1.6 M in hexanes, 1 mmol) to a solution of diisopropylamine (155 μL, 1.1 mmol) in dry Et_2O or THF (10 mL) under Ar at −78 °C. After 15 min of stirring at this temperature, dry *tert*-butyl acetate (135 μL, 1 mmol) or acetonitrile (52 μL, 1 mmol) was added dropwise via syringe at such a rate that the temperature of the mixture remained below −70 °C. After further stirring for 50 min, the appropriate ketone (0.4 mmol) dissolved in dry THF (3 mL) was slowly added dropwise via syringe. The reaction mixture was then stirred for 1 h at −78 °C. Workup (CH_2Cl_2) and column chromatography (hexane/EtOAc mixtures) yielded the desired product with the indicated yield and diastereoisomeric composition.

General Desilylation Procedure. A solution of the substrate (1 mmol) in dry THF (15 mL) was treated with solid tetra-*n*-butylammonium fluoride trihydrate (275 mg, 1.05 mmol) and stirred at room temperature for 30 min. After addition of water (1 mL), the volatiles were totally eliminated at reduced pressure. CC of the residue (hexane/EtOAc mixtures) provided the desilylation product. For compounds having two or three silyl groups, the relative proportion of TBAF was accordingly increased.

General Benzylation Procedure: An 80% suspension of NaH in mineral oil (90 mg, ca. 3 mmol of sodium hydride) was washed three times under Ar with dry hexane. Dry THF (1 mL) was then added, followed by a solution of the substrate (1 mmol) in dry THF (3 mL). The solution was stirred at reflux for 30 min. Benzyl bromide (0.3 mL, 2.5 mmol) was then added dropwise, followed by $^nBu_4N^+ I^-$ (55 mg, 0.15 mmol). The reaction mixture was then heated at reflux for 90 min. Workup (Et_2O) and CC (hexanes/EtOAc mixtures) furnished the desired benzylation product. Two free hydroxyl groups are assumed. For compounds having three free hydroxyl groups, the proportions of NaH and benzyl bromide were increased to 4 and 3.5 equiv, respectively.

General Hydrogenation Procedure. A 5% Pd/C hydrogenation catalyst (20 mg) was suspended in EtOAc (1 mL) and stirred for 10 min under an H_2 atmosphere. The substrate (0.5 mmol) was dissolved in EtOAc (10 mL) and added via syringe to the catalyst suspension. The reaction mixture was then stirred for 3 h at room temperature. After this time, the mixture was filtered through Celite, the reaction flask and the Celite were washed two times with EtOH, and the organic layers were concentrated at reduced pressure. CC of the oily residue (hexanes/EtOAc mixtures) furnished the desired hydrogenation product.

General Acetonide Hydrolysis Procedure. The substrate (1 mmol) was dissolved in 80% aqueous HOAc (7 mL). The solution was then stirred at room temperature for 18 h. Workup (CH_2Cl_2) and CC (hexanes/EtOAc mixtures) afforded the desired hydrolysis product.

General Detritylation Procedure. Method A.[33] A 1.8 M solution of trifluoroacetic acid/trifluoroacetic anhydride was prepared by dissolving these reagents in the appropriate amount of dry CH_2Cl_2. The substrate (0.4 mmol) was then dissolved under Ar in dry CH_2Cl_2 (1 mL) and treated dropwise at room temperature with the aforementioned solution (0.65 mL, ca. 3 equiv). The reaction mixture turned yellow and was then cooled to 0 °C, followed by addition of triethylamine (0.5 mL, 3.6 mmol). After being stirred for 5 min, the reaction mixture was poured into MeOH (10 mL). Stirring was continued for 30 min at room temperature. After removal of all solvents at reduced pressure, the residue was chromatographed (hexane/EtOAc mixtures) to yield the desired detritylation product. **Method B.** The substrate (0.5 mmol) was dissolved in a 1:1 MeOH/THF mixture (5 mL) and treated with concentrated HCl (0.1 mL). The mixture was then stirred at room temperature for 18 h. Workup (Et_2O) and CC (hexanes/EtOAc mixtures) furnished the detritylation product.

(2*R*,3*S*)-3,4-*O*-Isopropylidene-2-methylbutane-1,2,3,4-tetrol (17). The addition product of MeLi or Me_2CuLi with ketone **4** was desilylated with TBAF. CC of the crude desilylation product (hexane/EtOAc 1:2) followed by crystallization from hexane/Et_2O provided **17** in 50% overall yield.

(2*R*,3*S*)-1,2,3,4-Tetra-*O*-benzyl-2-methylbutane-1,2,3,4-tetrol (18). Compound **17** was benzylated under the aforementioned conditions. Workup and CC (hexane/EtOAc 19:1) provided in 95% yield an oily dibenzyl derivative, which was then submitted to acetonide hydrolytic cleavage. Workup and CC (hexane/EtOAc 1:1) yielded an oily diol (95%), which was then benzylated as above. Workup and CC (hexane/EtOAc 9:1) afforded finally tetrabenzyl derivative **18** in 65% yield. The same product was obtained by benzylation of the known diol **19**.[16a]

(2*R*,3*S*)-1,3,4-Tri-*O*-benzyl-2-ethylbutane-1,2,3,4-tetrol (20) was obtained as depicted in Scheme 3 either as a mixture with its C-2 epimer (from the addition product of **4** with vinylmagnesium bromide, followed by five standard transformations) or as a stereoisomerically homogeneous compound from **22** by sequential desilylation and benzylation (50% overall yield).

(2*R*,3*S*)-1-*O*-(*tert*-Butyldiphenylsilyl)-3,4-di-*O*-benzyl-2-methylbutane-1,2,3,4-tetrol (21), (2*R*,3*S*)-1-*O*-(*tert*-butyldiphenylsilyl)-3,4-di-*O*-benzyl-2-ethylbutane-1,2,3,4-tetrol (22), (2*R*,3*S*)-1-*O*-(*tert*-butyldiphenylsilyl)-3,4-di-*O*-benzyl-2-vinylbutane-1,2,3,4-tetrol (23), and (2*R*,3*S*)-1-*O*-(*tert*-butyldiphenylsilyl)-3,4-di-*O*-benzyl-2-ethynylbutane-1,2,3,4-tetrol (24) were obtained by reaction of **5** with, respectively, methylmagnesium bromide, ethylmagnesium bromide, vinylmagnesium bromide, and ethynylmagnesium bromide. Compound **22** was also obtained by catalytic hydrogenation of **23** or **24**.

(2*R*,3*S*)-1,3,4-Tri-*O*-benzyl-2-methylbutane-1,2,3,4-tetrol (25) was obtained as a stereoisomerically homogeneous compound from **21** by sequential desilylation and benzylation (70% overall yield). The same product, either pure or as a mixture with its C_2-epimer, was also obtained from addition products of ketones **6**−**10** (Scheme 3).

(2*R*,3*S*)-1,4-Di-*O*-(*tert*-butyldiphenylsilyl)-3-*O*-benzyl-2-methylbutane-1,2,3,4-tetrol (26), (2*R*,3*S*)-1,4-di-*O*-(*tert*-butyldiphenylsilyl)-3-*O*-benzyl-2-ethylbutane-1,2,3,4-tetrol (27), (2*R*,3*S*)-1,4-di-*O*-(*tert*-butyldiphenylsilyl)-3-*O*-benzyl-2-vinylbutane-1,2,3,4-tetrol (28), and (2*R*,3*S*)-1,4-di-*O*-(*tert*-butyldiphenylsilyl)-3-*O*-benzyl-2-ethynylbutane-1,2,3,4-tetrol (29) were obtained by reaction of **6** with, respectively, methylmagnesium bromide, ethylmagnesium bromide, vinylmagnesium bromide, and ethynylmagnesium bromide. Compound **27** was also obtained by catalytic hydrogenation of **28** or **29**.

(33) Krainer, E.; Naider, F.; Becker, J. *Tetrahedron Lett.* **1993**, 1713−1716.

(2*R*,3*S*)-1-*O*-Trityl-3,4-di-*O*-benzyl-2-methylbutane-1,2,3,4-tetrol (30), (2*R*,3*S*)-1-*O*-trityl-3,4-di-*O*-benzyl-2-ethylbutane-1,2,3,4-tetrol (31), (2*R*,3*S*)-1-*O*-trityl-3,4-di-*O*-benzyl-2-vinylbutane-1,2,3,4-tetrol (32), and (2*R*,3*S*)-1-*O*-trityl-3,4-di-*O*-benzyl-2-ethynylbutane-1,2,3,4-tetrol (33) were obtained by reaction of **10** with, respectively, methylmagnesium bromide, ethylmagnesium bromide, vinylmagnesium bromide, and ethynylmagnesium bromide. Compound **31** was also obtained by catalytic hydrogenation of **32** or **33**.

(2*R*,3*S*)-1,4-Di-*O*-trityl-3-*O*-benzyl-2-vinylbutane-1,2,3,4-tetrol (34) was obtained by reaction of **11** with vinylmagnesium bromide. Detritylation of **34** (method B) and subsequent silylation (for reaction conditions, see ref 9a) afforded **28**.

(2*S*,3*S*)-1,2-Di-*O*-benzyl-3-methylpentane-1,2,3-triol (35), (2*S*,3*S*)-1,2-di-*O*-benzyl-3-methylpent-4-ene-1,2,3-triol (36), and (2*S*,3*S*)-1,2-di-*O*-benzyl-3-methylpent-4-yne-1,2,3-triol (37) were obtained by reaction of **12** with, respectively, ethylmagnesium bromide, vinylmagnesium bromide, and ethynylmagnesium bromide. Compound **35** was also obtained by catalytic hydrogenation of **36** or **37**.

Acknowledgment. Financial support for the project was provided through the Spanish Ministry of Education and Science (DGICYT projects PB92-0745 and PB95-1089) and by BANCAJA (project P1B95-21). E.C. thanks the Consellería de Cultura, Educaciò i Ciencia de la Generalitat Valenciana, for a predoctoral fellowship.

Supporting Information Available: Analytical and tabulated spectral data of compounds **10**−**12**, **15**−**18**, and **20**−**37** (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO9716744