Diastereoselective Grignard Additions to *O*-Protected Polyhydroxylated Ketones: A Reaction Controlled by Groundstate Conformation?

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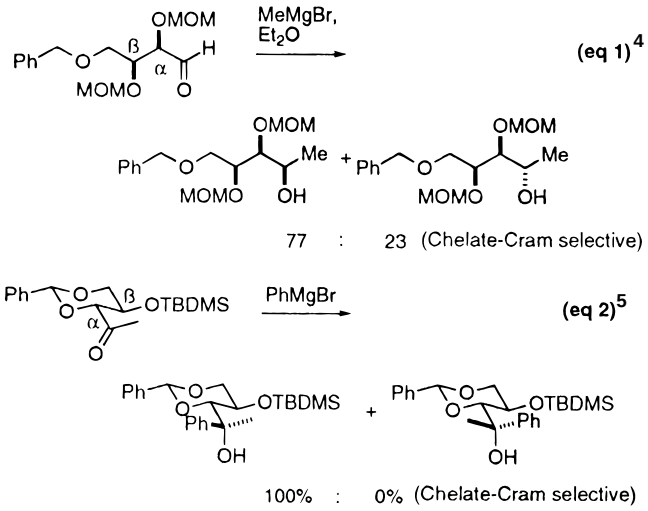
The *O*-protected polyhydroxy ketones **9**−**14** and **39**, **42** add σ-type Grignard reagents with >90:10 stereoselectivity to give the 3,4-*syn*-adducts **17**−**22** and **43**, **45**, respectively, as the major diastereomers (Tables 1 and 2). The stereoselectivity is interpreted in terms of early transition states which are very close to the groundstate conformations shown in Figure 6 and 7. These demonstrate that the "top face" of the carbonyl group is much less shielded than the "bottom" face. Complexation phenomena are of minor importance. It is also shown that the classical transition state models (Felkin−Anh or chelate Cram) are not applicable to polyoxygenated ketones.

Organometallic additions to acyclic chiral α-alkoxy ketones are of central importance in organic synthesis.[1] Various empirical transition state models have been devised over the past four decades to describe the stereochemical course of such additions, among which the chelate Cram (CC) or the Felkin−Anh (FA) model are the most prominent ones.[2] However, most mechanistic studies have been confined to substrates which bear only one alkoxy-substituted stereogenic center in α-position to the carbonyl group.[3] When two such stereogenic centers were present they were located on the same side of the carbonyl, as for instance in eqs 1 and 2 of Scheme 1.

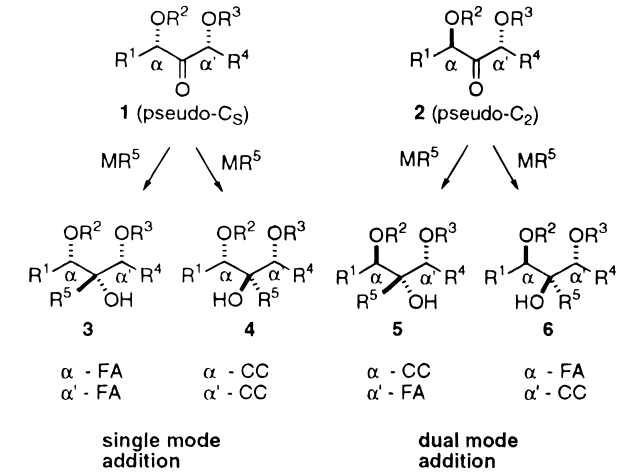
To our knowledge there is no systematic study on acyclic ketones in which the carbonyl group is *flanked* by stereogenic carbinol centers as represented by compounds **1** and **2** in Scheme 2.

The stereodirecting effect of each one of these α/α′-stereocenters may then be described via one of the established transition state models, for instance the Felkin−Anh (FA) or chelate Cram (CC) model. Formally, we have the possibility of a single or a dual mode addition. For instance, if ketone **1** is converted into adduct **3**, this corresponds to a Felkin-Anh type addition with respect to both the α and α′ center, and, hence, a single mode process. Similarly, the formation of adduct **4** from **1** corresponds to a chelate Cram addition with respect to the α and α′ centers, and, therefore this also represents a single mode addition case. By contrast, ketone **2** can only react via dual mode additions, either via an α-CC-α′-FA-process, which gives diastereomer **5**, or an α-FA-α′-CC-process, which gives diastereomer **6**

Scheme 1



Scheme 2



(Scheme 2). However, this is only a formalistic description of the addition, which does not tell us anything about the actual diastereoselectivity. This one in turn is determined by the stereoreinforcing or stereo-non-reinforcing effects[6] the α and α′ centers may have on each other. Therefore, both the single mode and the dual

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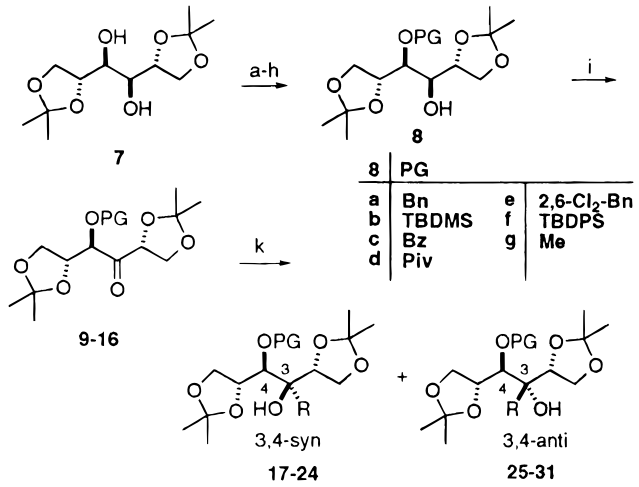
Scheme 3[a]



8	PG		
a	Bn	e	2,6-Cl_2-Bn
b	TBDMS	f	TBDPS
c	Bz	g	Me
d	Piv		

[a] (a) NaH, BnCl, DMF, 0 °C, (mono:di = 5:1), 48% mono (**8a**); (b) BDMSiCl, imidazole, DMF, 40 °C, (mono:di = 11:1), 81% mono (**8b**); (c) BzCl, pyridine, DMAP, 0 °C, (mono:di = 3.6:1), 54% mono (**8c**); (d) PivCl, pyridine, DMAP, 0 °C, (mono:di = 8.5:1) 68% mono (**8d**); (e) NaH, 2,6-$C_6H_3Cl_2$-CH_2Cl, DMF, 0 °C, (mono:di = 5:1), 41% mono (**8e**); (f) TBDPSiCl, imidazole, CH_2Cl_2, 0 °C, 63% (**8f**); (g) NaH, MeI, DMF, 0 °C, (mono:di = 3:1), 46% mono (**8g**); (h) oxalyl chloride, DMSO, TEA, CH_2Cl_2, −68 °C, 86% **9**, 91% **10**, 94% **11**, 89% **12**, 88% **13**, 92% **14**, 88% **15**, 83% **16**; (i) 3−4 equiv RMgX (iPrMgBr, vinylMgCl, EtMgBr, allylMgBr), THF, 0 °C, 15 min, 42−89%.

Table 1. Diastereomeric Ratio of Grignard Additions to the Ketones 9−16

		R			
ketone	PG	isopropenyl	ethyl	vinyl	allyl
9	Bn	**17a**:**25a** >98:2	**17b**:**25b** 91:9	**17c**:**25c** 96:4	**17d**:**25d** 67:33
10	TBDMS	**18a**:**26a** 95:5	**18b**:**26b** >98:2	−	**18d**:**26d** 57:43
11	Bz	**19a**:**27a** >98:2	**19b**:**27b** >98:2	**19c**:**27c** >98:2	**19d**:**27d** >98:2
12	Piv	**20a**:**28a** >98:2	**20b**:**28b** >98:2	**20c**:**28c** >98:2	**20d**:**28d** >98:2
13	2,6-Cl_2-Bn	**21a**:**29a** >98:2	**21b**:**29b** >98:2	**21c**:**29c** >98:2	**21d**:**29d** >98:2
14	TBDPS	**22a**:**30a** >98:2	**22b**:**30b** >98:2	−	−
15	Me	**23a**:**31a** **56**:**44**	**23b**:**31b** **67**:**33**	**23c**:**31c** **78**:**22**	**23d**:**31d** **67**:**33**
16	Ac	adducts **24** and **32** are partially deacetylated			

mode combination had to be tested for its stereoreinforcing qualities. We started with the dual mode possibility; as a model for ketone **2** we prepared ketones **9**−**16** from the protected D-mannitol derivative **7** as shown in Scheme 3.

The Grignard additions were performed under standard conditions to give the adducts **17**−**31** in almost quantitative yields. Substitution patterns and diastereomeric ratios are listed in Table 1. In terms of the general considerations given in Scheme 2, ketones **9**−**16** belong to type **2**, and the major adducts **17**−**31**, which are formed with high selectivity in most cases, are of type **6**, so that the dual mode α-FA-α′-CC-combination appears

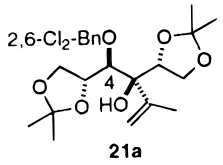


Figure 1. Crystal structure of **21a**.

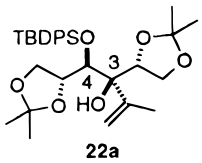
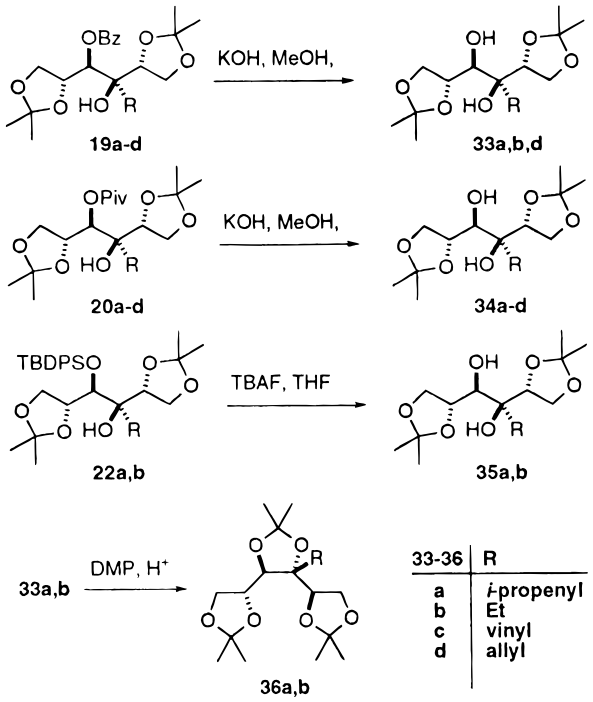


Figure 2. Crystal structure of **22a**.

Scheme 4



33-36	R
a	*i*-propenyl
b	Et
c	vinyl
d	allyl

to be the stereoreinforcing one. Specifically, isopropenyl and ethylmagnesium bromide show the highest stereoselectivity, irrespective of the protective group (PG). Vinylmagnesium bromide is similarly selective, whereas allylmagnesium bromide reacts unselectively with ketones **9** and **10**. With respect to the protective groups, Bz, Piv, and 2,6-dichlorobenzyl are the best, followed by Bn. Me leads to unselective additions in all cases, and Ac is unstable under the Grignard conditions. The configurations of the newly created stereogenic centers in **21a** and **22a** were determined by X-ray single crystal analysis (Figures 1 and 2).[11]

From adducts **19a**−**d**, **20a**−**d**, and **22a,b** the *O*-protective groups were removed (Scheme 4). Among the alcohols thus obtained the following ones were identical: **33a** ≡ **34a** ≡ **35a**, **33b** ≡ **34b** ≡ **35b**, **33c** ≡ **34c**, **33d** ≡ **34d**. The vinyl adduct **33c** was transformed into the ethyl derivative **33b** by catalytic hydrogenation. The relative configurations of **33a** and **33b** were established by ^{1}H-NOESY of the corresponding triacetonide **36a**,**b**. The allyl adducts **33d** were not assigned.

The resemblance of the conformations of the 3-isopropenyl-hexaol derivatives **21a**, **22a**, and **33a** (Figures 1−3) is remarkable. All three compounds are characterized

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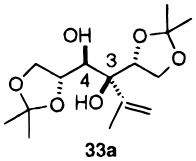
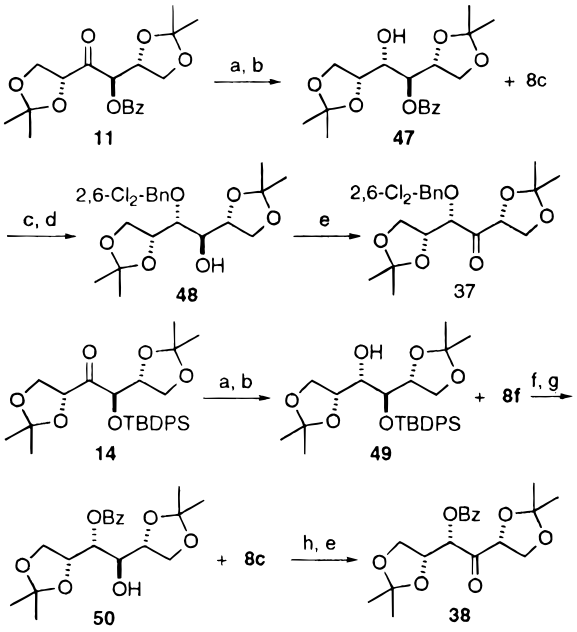


Figure 3. Crystal structure of **33a**.

Scheme 5. Synthesis of Model Compounds 39/42[a]



[a] (a) $Zn(BH_4)_2$, ether, −15 °C, 4−5 h, 53% **37**, 26% **8c**, respectively, 45% **40**, 55% **8f**; **8c** and **8f** are recycled. (b) HPLC, eluent: 3% 2-propanol/hexane (for **37**), 1% 2-propanol/hexane (for **40**); (c) NaH, 2,6-$C_6H_3Cl_2$-CH_2Cl, DMF, 0 °C, 44%; (d) 30% KOH solution, CH_2Cl_2, 15 min, 92% (e) DMSO, oxalyl chloride, TEA, CH_2Cl_2, −68 °C, 1 h, 85% **35**, respectively, 58% **42**.

by an *anti*-arrangement of *O*-2 and *O*-3, and a *syn*-arrangement of *O*-3, *O*-4, and *O*-5. These conformations are obviously adopted to minimize 1,3-repulsions between *O*-2/4 and *O*-3/5. The presence or nature of the protective groups has almost no influence on the overall conformation.

With these results in hands we turned to the single mode case and, as representatives for ketone **1**, we synthesized ketones **37/38** via nonstereocontrolled but efficient routes as outlined in Scheme 5. The Grignard additions were performed as before: for better characterization the adducts from ketone **38** were deprotected to give the corresponding diols **53/54a**−**c**.

To our surprise ketones **37/38** showed the same diastereofacial preference in the Grignard reaction as ketones **9**−**16**, and adducts **51, 53** were formed with still high, yet clearly diminished, stereoselectivity (Scheme 6, Table 2). In terms of Scheme 1 this addition corresponds to the transformation of ketone **1** to adduct **4**, i.e. which is a single mode α-CC-α′-CC addition and should now represent the *stereo-non-reinforcing* combination. As the stereoselectivity is about the same as for the reinforcing combination, this can be only mean that one of the two stereocenters (*C*-2) has a much higher directing influence than the other one (*C*-4)! To get more insight into the stereochemical situation we analyzed the ground state conformation of two representative ketones, i.e. ketone **11** for the pseudo C_s-type **1** and ketone **38** for the pseudo C_2-type (Figures 4, 5).

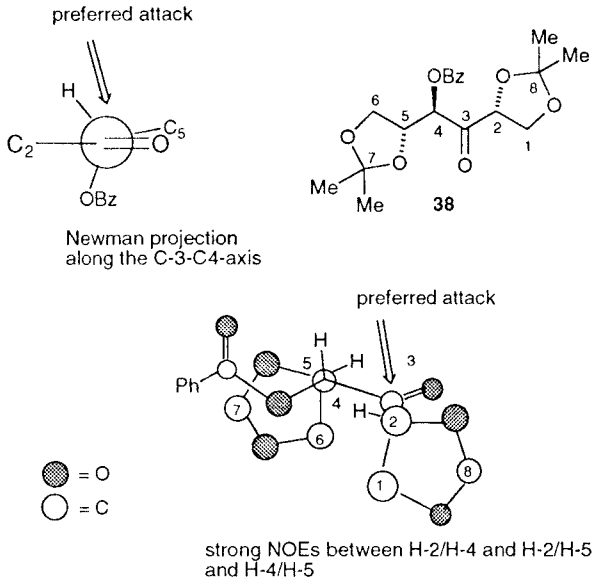
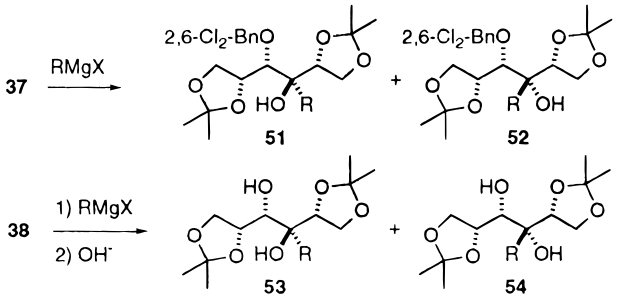


Figure 4. Conformational analysis of ketone **11**.

Scheme 6



Ketone	R = *i*-Propenyl	Ethyl	Vinyl
37	**51a**:**52a** >90:10	**51b**:**52b** -	**51c**:**52c** 75:25
38	**53a**:**54a** >98: 2	**53b**:**54b** 95: 5	**53c**:**54c** 90:10

Table 2. Diastereomeric Ratios of Grignard Additions to Ketones 39−42

	R		
ketone	isopropenyl	ethyl	vinyl
37	**51a**:**52a** >90:10	**51b**:**52b** –	**51c**:**52c** 75:25
38	**53a**:**54a** >98:2	**53b**:**54b** 95:5	**53c**:**54c** 90:10

For ketone **11** the crystal structure (Figure 6) served as a basis for the conformational analysis, and in fact, ^{1}H-NOESY experiments confirmed that the same conformation was adopted also in solution.

As shown in Figure 4, *O*-2 and *O*-3 are almost ecliptic *without* having a complexing metal ion between them. This conformation is surprising in view of the Coulomb repulsion it implies; on the other hand, the Coulomb repulsion between *O*-2 and *O*-4 and the steric congestion between the *C*-2 and *C*-4 substituents are minimized. The 3,4-axis roughly adopts a Felkin-Anh conformation with the OBz-substituent *syn* to *C*-2. A similar conformation is adopted by ketone **13** in the crystalline state (Figure 6). Overall, the "bottom face" of the carbonyl is much more shielded than the top face is, and this fact nicely explains the stereochemical course of the addition. Unfortunately, ketone **42** is not crystalline, so that the

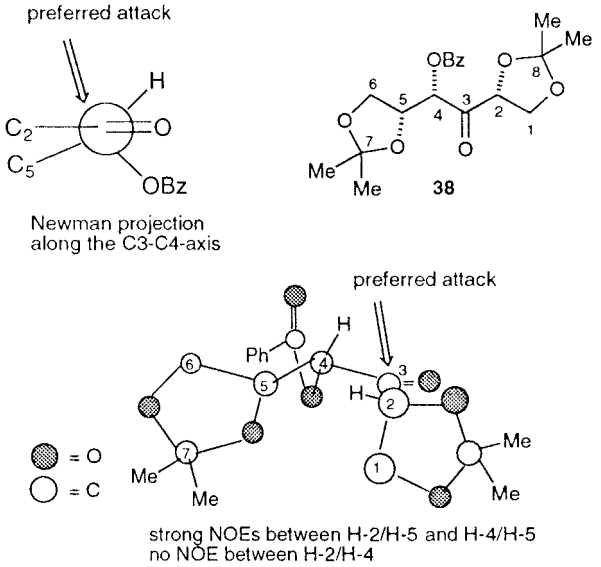


Figure 5. Conformational analysis of ketone **42**.

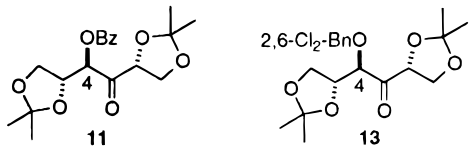
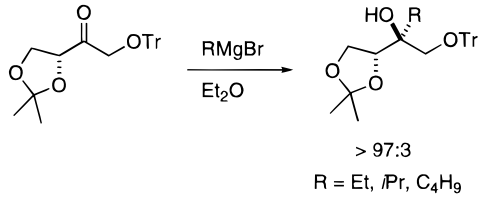


Figure 6. Crystal structure of ketones **11** and **13**.

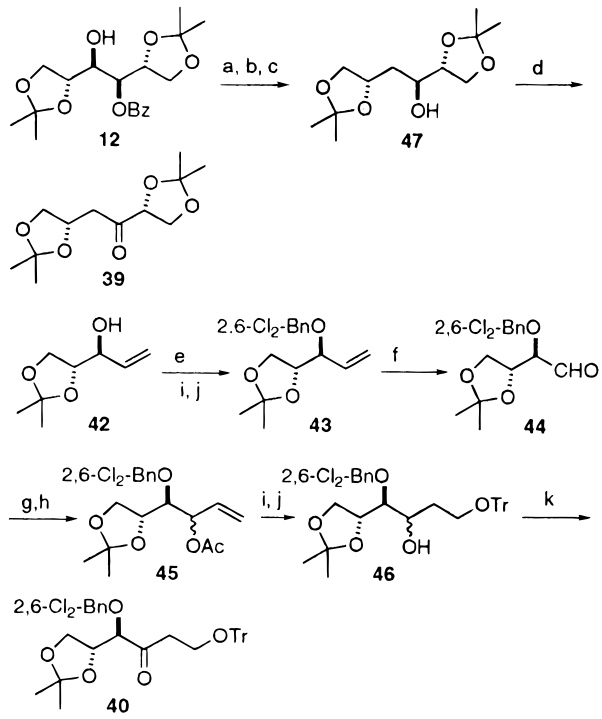
Scheme 7



conformational analysis is solely based on ^{1}H-NOESY experiments (Figure 5). The situation with respect to *O*-2 and *O*-3 is the same as for **11**, except that the conformation around the *C*-3/*C*-4 axis is different: *C*-2 and *C*-5 are nearly ecliptic in **42** and *anti*-periplanar in **11**. The overall shielding of the "bottom-face" of the carbonyl, however, is very similar for both ketones **42** and **11**. So apparently, we have a situation where the ground state conformation could also serve as the reactive conformation: at least the stereochemical outcome could be well interpreted by assuming that an ecliptic arrangement of *O*-2 and the carbonyl-*O* is the dominating feature, whereas the substitution around *C*-4 plays a minor role. This raises the question whether the presence of a *C*-4 stereocenter is necessary at all. At least, the literature example shown in Scheme 7 indicates that high selectivities may be obtained in absence of such a center.[7]

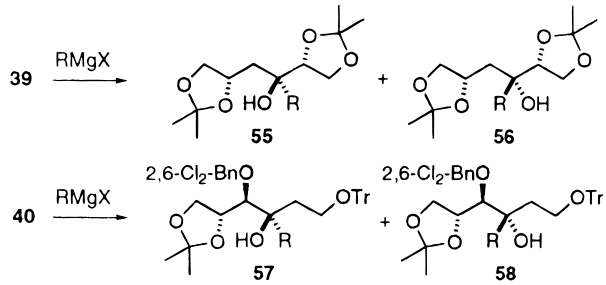
We thus prepared ketones **39** and **40** (Scheme 8) via obvious routes. The usual Grignard additions furnished **55/56** and **57/58** with low diastereoselectivity (Scheme 9), which shows that the presence of a stereogenic carbinol center at *C*-4, irrespective of its configuration, is required for highly diastereoselective Grignard additions to *C*-3. The 4-OR-residue probably has an anchoring effect on the overall conformation and contributes to the shielding of the bottom face of the carbonyl group. This reemphasizes the requirement to have stereogenic carbinol centers on *both* sides of the carbonyl.

Scheme 8. Synthesis of Model Compounds 48/54[a]



[a] (a) PhOCSCl, DMAP, pyridine, CH_2Cl_2, 24 h reflux, 95%; (b) nBu_3SnH, AIBN, toluene, 90 min reflux, 85%; (c) 30% KOH solution, CH_2Cl_2, 30 min, 98%; (d) DMSO, oxalyl chloride, TEA, CH_2Cl_2, −68 °C, 90 min, 89%; (e) NaH, 2,6-$C_6H_3Cl_2$-CH_2Cl, DMF, 0 °C, 76%; (f) O_3, CH_2Cl_2, $(Ph)_3P$, −78 °C, 30 min; (g) (vinyl)MgCl, THF, 0 °C, 15 min, 54%; (h) Ac_2O, pyridine, DMAP, 22 °C, 24 h, 93%; (i) BH_3·THF, THF, 22 °C, 1−2 d, 51%; (j) $(Ph)_3CCl$, DMAP, pyridine, 22 °C, 2 d, 95%; (k) DMSO, oxalyl chloride, TEA, CH_2Cl_2, −78 °C, 1 h, 95%.

Scheme 9. Grignard Additions to Ketones 65−67



Ketone	R = *i*-Propenyl	Ethyl	Vinyl
39	**55a**:**56a** 50:50	**55b**:**56b** 60:40	**55c**:**56c** 85:15
40	**57a**:**58a** 67:33	**57b**:**58b** 55:45	**57c**:**58c** 78:22

The configurations of the newly created stereogenic centers in the Grignard adducts were determined by X-ray single crystal analysis (**53a**, Figure 7)[11] or by chemical correlations (**55a**−**c**, Scheme 10).

For instance, on treatment with allylmagnesium bromide the readily available ketones **59a,b** gave diastereomeric mixtures of adducts **60a,b** and **61a,b**, which were separated by HPLC. The adducts **60a,b** were converted into the acetonides **62a,b**, whose relative configurations at *C*-2/3 were assigned by ^{1}H-NOESY. Osmylation of **60a,b** gave a mixture of the diols **63/64**, which were separated and transformed into the acetonides **65a**,**b** and **66a**,**b**. On catalytic hydrogenation adduct **55a** gave **65a**,

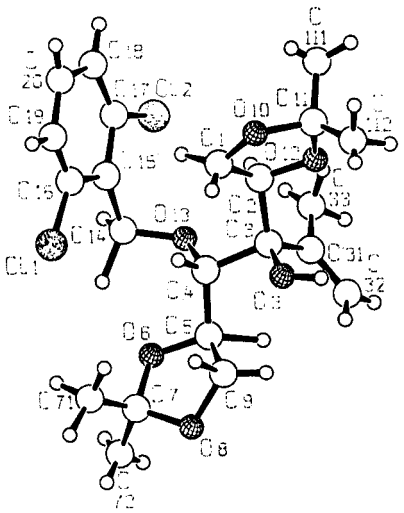
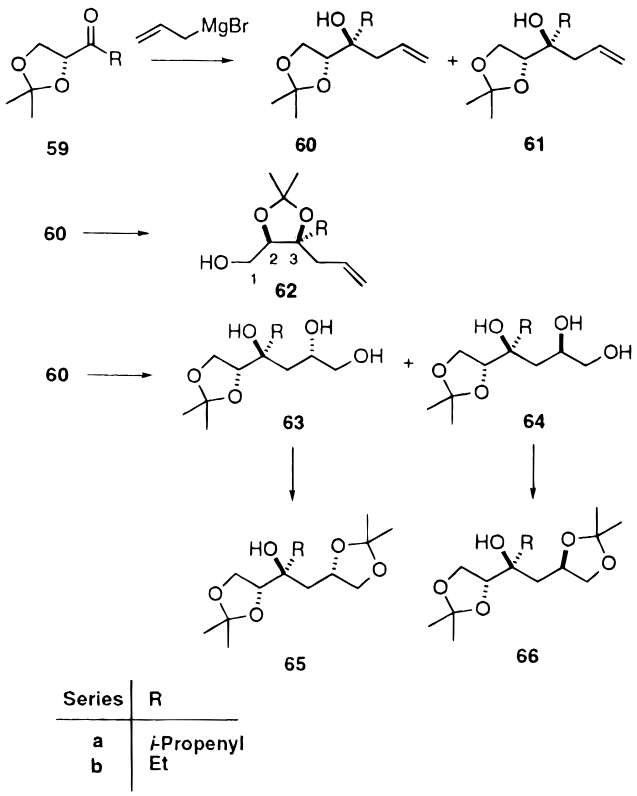


Figure 7. Crystal structure of **43a**.

Scheme 10

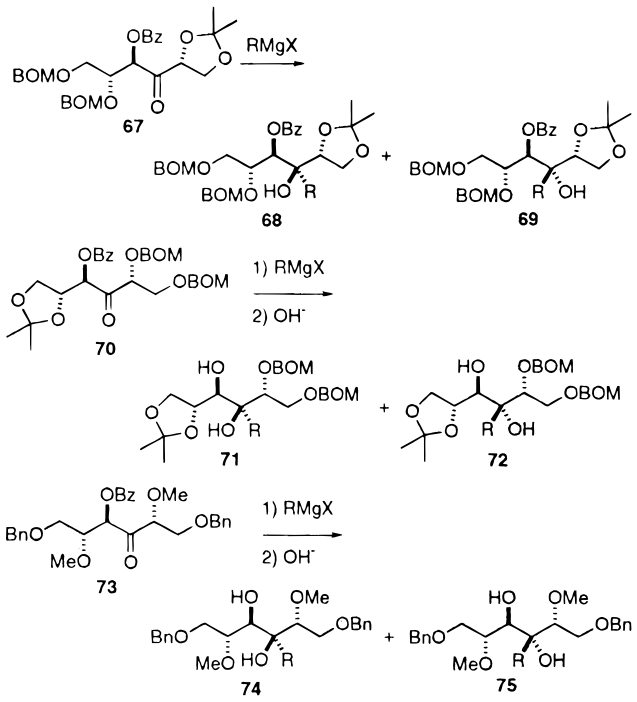


and **56c** gave **65b**. Compounds **55b** and **65b** are identical. The isomers **66a**,**b** were clearly different from **65a**,**b**.

To test the question whether chelate complexes are formed as intermediates, some of the additions to ketones **13** and **48** were repeated in the presence of complex-destroying (DMPU or HMPA) or -inducing ($ZnCl_2$ or $MgBr_2$) additives (Table 3).

For ketone **13** there is no significant change in the presence of HMPA or DMPU, which is consistent with our assumption of an unchelated ground state conformation controlled reaction. For ketone **48**, the presence of $ZnCl_2$ or $MgBr_2$ does have a strong effect. Thus, isopropenylmagnesium bromide shows enhanced chelate Cram selectivity, whereas the reverse is true for ethylmagnesium bromide. It is difficult to interpret these contradictory results; possibly competing 1,2- and 1,3-complex formation compete with each other.

Scheme 11



	R	68 : 69	71 : 72	74 : 75
a	*i*-propenyl	> 90:10	> 95:5	> 95:5
b	Et	> 85:15	> 95:5	55:45
c	vinyl	> 95:5	> 95:5	80:20
d	allyl	75:25	67:33	67:33

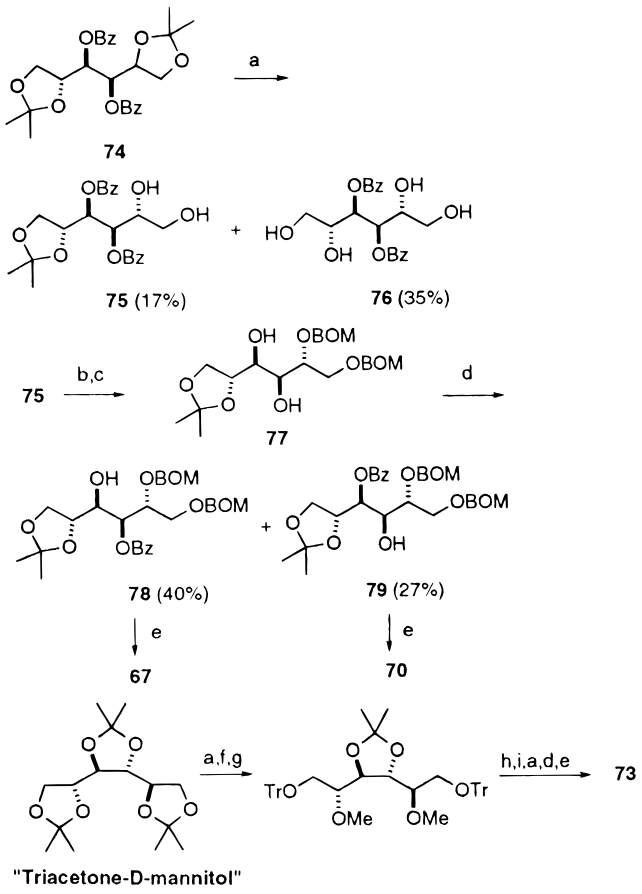
Table 3. Diastereomeric Ratios of Grignard Additions to Ketones 13 and 48 with Additives

	R			
ketone/additive	isopropenyl	ethyl	vinyl	allyl
13	**21a**:**29a**	**21b**:**29b**	**21c**:**29c**	**21d**:**29d**
	>98:2	>98:2	>98:2	>98:2
+ DMPU	>98:2	>98:2	>98:2	>98:2
48	**55a**:**56a**	**55b**:**56b**	**55c**:**56c**	**55d**:**56d**
	50:50	60:40	85:15	73:27
+ $ZnCl_2$	80:20	20:80!	33:67!	82:18
+ $MgBr_2$–Et_2O	>95:5	>9:91!	88:22	82:18

Effect of the Acetonide Rings. To test the influence of cyclic vs acyclic protective groups for the terminal diol moieties, model compounds **67, 70, 73** were prepared (Scheme 12) and submitted to the usual Grignard additions (Scheme 11). The diastereomeric ratios are listed in Scheme 11. It is surprising to see that the loss of one acetonide moiety on either side of the carbonyl groups does not significantly diminish the stereochemical course of the reaction: ketones **67** and **70** add isopropenyl, ethyl, and vinyl Grignard reagents with still high selectivity. The totally acyclic system **73**, however, shows a significantly lower selectivity. So apparently, the reactive conformation and possibly also the ground state conformation are highly influenced by the presence of acetonide protective groups, as mentioned before (Figures 4, 5).

In conclusion, the high stereoselectivities with which σ-type Grignard reagents add to most of the polyoxygenated ketones described in this article cannot be interpreted in terms of Felkin-Anh or chelate Cram models, as naively attempted in Scheme 1. Rather, as a working hypothesis, early transition states can be assumed for Grignard additions,[8] and, thus, ground state conforma-

Scheme 12[a]



[a] (a) 70% AcOH, 22 °C, 3−4 h; (b) BOM-Cl, $(iPr)_2NEt$, CH_2Cl_2, 0 °C, 24 h, 80%; (c) 30% KOH/MeOH, CH_2Cl_2, 22 °C, 30 min, 82%; (d) BzCl, DMAP, pyridine, 0 °C, 20 h, 67%, HPLC; (e) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, −68 °C, 93−97%; (f) TrCl, DMAP, pyridine, 22 °C, 2 d, 97%; (g) NaH, DMF, MeI, 0−22 °C, 20 h, 80%; (h) HCO_2H, CH_2Cl_2, 22 °C, 4 h, 65%; (i) NaH, DMF, BnBr, 0 °C, 92%.

tions may serve as a basis for interpreting the stereochemical course of the addition. Furthermore, there is no need to postulate metal chelate complexes as reactive intermediates, which is surprising in view of the multitude of oxygen functions available in the substrates. In summary, it appears that the diastereoselectivity of Grignard carbonyl additions is much less understood than one might have thought, 45 years after the formulation of Cram's rule.[2a]

Experimental Section

Di-*O*-isopropylidene-D-mannitol **7** was prepared from D-mannitol by a well-known procedure.[9] The protected alcohols **8a**−**h** were prepared via routine operations.[10] The ^1H and ^{13}C NMR spectra were recorded on a 250 or 500 MHz Brucker machine.

Typical Procedure. A. Swern-Oxidation: (2*R*,4*R*,5*R*)-4-*O*-Benzoyl-1,2:5,6-di-*O*-isopropylidene-1,2,4,5,6-pentahydroxy-3-hexanone (11). To a solution of oxalyl chloride (17.16 g, 135 mmol, 1.1 mol equiv) in dry methylene chloride (250 mL) was added slowly dry DMSO (23.05 g, 295 mmol, 2.4 mol equiv, dissolved in 100 mL of methylene chloride) at −78 °C. The mixture was stirred strongly for 15 min. Then alcohol **8c** (45 g, 123 mmol, 5 mol equiv) was added. The mixture was placed into an ice bath, and the reaction was quenched by addition of an ether/water mixture (4:1, 400 mL). The organic layer was separated, washed with water, and dried ($MgSO_4$). After concentration of the organic layer in vacuo the crude product was purified by column chromatography (hexane/ethyl acetate 2:1) to give **11** (42.1 g, 94%).

B. Grignard Reaction. To a solution of the ketone in dry THF (2−4 mL/mmol) were added slowly 3−4 mol equiv of the Grignard compound (1 M THF solution) at 0 °C. After stirring for 15 min (monitored by TLC) the reaction was stopped by adding saturated ammonium chloride solution drop by drop. The precipitated salts were removed by filtration and carefully washed with THF. The filtrate was concentrated in vacuo, and the residue was dissolved in ether and washed three times with water and one time with brine. The organic phase was dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by column chromatography (hexane/ethyl acetate 2:1).

All other experiments are analogous to the typical procedures or routine operations. Characteristic analytical data of the products are described in Supporting Information.

Supporting Information Available: Analytical data of compounds **8c,d,e,g,h, 11**−**16**, **19a-d**, **20a-c**, **21a-d**, **22a**,**b**, **23a**,**c**, **31c**, **33a**,**b**,**d**, **37**, **38**, **40**, **47**, **50**, **51a**,**c**, **53a-c**, **55a/56a**, **55b/56b**, **55c**, **57a/58a**, **57b/58b**, **57c/58c**, **59a**,**b**, **60a**,**b** **61a**,**b**, **62a**, **63a**, **63b/64b**, **65a**,**b**, **66a**,**b**, **67**, **68a-c**, **68d/69d**, **70**, **71a-d**, **73**, **74a**, **74b/75b**, **74c**, **74d/75d**, **77**, **78**, **79** (48 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.

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(11) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.