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ON THE STERIC COURSE OF THE ADDITION OF SOME ORGANOMETALLIC REAGENTS TO (R)-2,3-ISOPROPYLIDENE GLYCERALDEHYDE. SYNTHESIS OF OPTICALLY ACTIVE α-BENZYLOXY ALDEHYDES, ALCOHOLS, CARBOXYLIC ACIDS AND 1,2-DIOLS.

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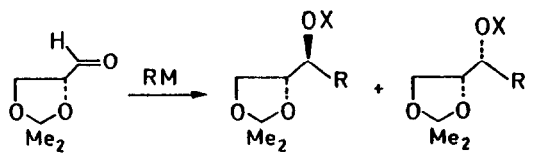
Summary. Organo-titanium and organo-zinc reagents were added stereoselectively to (R)-2,3-isopropylidene glyceraldehyde (1) to give the alcohols 2/3, which were converted into the optically active derivatives 4-11.

Several recent communications[1] prompt us to give a preliminary report on our related work concerning the steric course of organometallic additions to (R)-isopropylidene glyceraldehyde (1)[2]. The rationale behind this project was the fact that the 1,2-di-O-moiety occurs in a multitude of natural products, among which there are pheromones (e.g. brevicomine[3]), macrolides (e.g. colletodiol[4]), fungicides (e.g. canadensolide[5]), toxines (e.g. muscarine[6]) and all carbohydrates. So it seemed worth-while to look for a flexible connective method which allows the construction of this structural feature in a diastereo- and enantioselective manner[7]. Moreover, the degradation of 2/3 without affecting the newly created asymmetric center promised an easy access to a number of useful chiral building blocks like 7-10.
Specifically, we reacted 1 with a variety of organometallic agents (RM) and obtained the alcohols 2/3 in satisfactory yields (Table 1). To determine the diastereomeric ratio the distilled product mixture was benzylated (NaH in tetrahydrofurane (THF) and dimethylsulfoxide, 3h reflux, then 2 mole equivalents of benzyl chloride, 2h reflux, aqueous workup) to give 4/5 quantitatively. The 60 MHz ^{1}H-NMR spectrum of this mixture in $CDCl_3$ or benzene showed base line separated singlets or AB-systems for the benzyl CH_2-group, which were evaluated by machine integration (estimated accuracy ca. 5%). Gravity column chromatography (silicagel, ether-pentane 1:1) furnished isomerically pure 4b,c,d and 5a,b,respectively.



1 2 3 (X=H)
4 5 (X=CH2Ph)
erythro threo

2 - 11	R
a	Ph
b	Me
c	n-butyl
d	allyl

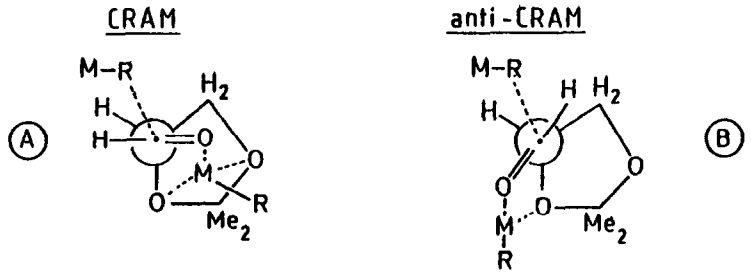
Table 1. Stereochemistry and Yields for Various RM-Additions to 1.

Run	R	M	2,3	Ratio 2:3 (=4:5)	Addition Mode[a]	Yield 2+3 (%)	Solvent/Temp. (°C)/ Time (h)
1	Ph	Li	a	48:52	AC	88	Et_2O/-78/2
2	"	MgBr	a	48:52	AC	85	"
3	"	$Zn_{1/2}$	a	79:21	C	46	Et_2O/-40/2
4	"	$Ti(OiPr)_3$	a	24:76	AC	82	Et_2O/-78/2
5	"	"	a	9:91	AC	79	THF/-78/2
6	Me	Li	b	60:40	C	60	Et_2O/-70/2
7	"	MgBr	b	67:33	C	57	Et_2O/-50/2
8	nBu	Li	c	69:31	C	83	Et_2O/-78/2
9	"	MgBr	c	75:25	C	86	"
10	"	$Ti(OiPr)_3$	c	90:10	C	40	Et_2O/+22/12
11	allyl	MgBr	d	60:40	C	89	Et_2O/-78/2
12	"	$Ti(OiPr)_3$	d	71:29	C	72	THF/-100/2
13	"	$Cr_{1/2}$[b]	d	70:30	C	56	THF/+25/2
14	"	$Zn_{1/2}$	d	84:16	C	60	Et_2O/-78/2
15	"	"	d	91: 9	C	65	THF/-78/2

[a] C= Cram, AC= Anti-Cram. [b] prepared according to T.Hyiama, Y.Okude, K.Kimura, H.Nozaki, Bull.Chem.Soc.Japan 1982, 55, 561.

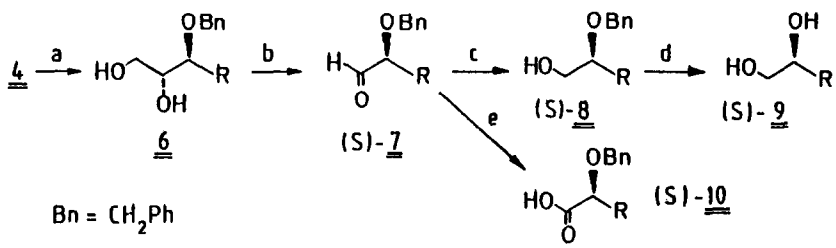
According to the current definition[8] 2 is the Cram and 3 the anti-Cram adduct. Table 1 shows that the ratio of 2:3 is highly dependent on RM. Low to moderate selectivity is observed for the organolithium and Grignard reagents (runs 1,2,6,7,8,9,11). For M= $Zn_{1/2}$ and $Ti(OiPr)_3$[9] the diastereomeric excesses are considerably higher (runs 3,4,5,10,14,15). Apart from $PhTi(OiPr)_3$ which favors the anti-Cram attack all other reagents prefer the Cram process if a stereoselective addition does occur at all. The solvent has a minor but significant effect; using THF instead of ether enhances the intrinsic selectivity of the reaction (runs 4 vs. 5, 14 vs. 15). In view of the familiar[10] chelate controlled anti-Cram additions to α-alkoxy carbonyl compounds the Cram preference observed for 1 is rather unexpected.[11] It may be attributed, as well as in related cases[1a,12], to the presence of the (additional) ß-alkoxy function which allows such an efficient complexation of M in the Cram-arrangement A that the system has nothing to gain from the anti-Cram chelate B which is so characteristic of the α-alkoxy carbonyl additions.[10]

By routine operations we converted 4b,c,d and 5a,b into the derivatives 6-11,



all of which were obtained in high yield and optical purity (Scheme 1). (R)-9c,d, (S)-8b, (R)-10a and (S)-10b are known[13] and allowed us to assign the configurations at the newly created chiral centers and, hence, to decide upon the Cram or anti-Cram direction of the organometallic additions.

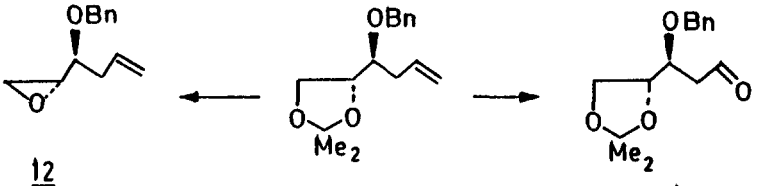
Scheme 1



a. 2N H_2SO_4,dioxane,110°C,2h.- b. $Pb(OAc)_4$,benzene,22°C,10 min.- c. $LiAlH_4$, ether,22°C,3h.- d. H_2-Pd,methanol + 1% HCl,22°C,2 atm.- e. CrO_3-acetone-H_2SO_4, 0°C,10 min.

Yields (based on 4/5) and $[\alpha]_D^{25}$ (in $CHCl_3$, unless specified otherwise) for 4-11: 4b: 40.5(c3.5); 4c: 14.4(c3.5); 4d: 60.9(c2); 5a: -83.4(c2); 5b: 14.1(c5.5); 6b: 79%, 38.3(c2); 6c: 96%, 10.7(c2); (R)-7a: 73%, -67.3(c4); (R)-7b: 65%, 53.5(c2.5); (S)-7b: 63%, -54.7(c2.5); (S)-7c: 85%, -66.0(c2); (S)-7d: 72%, -46.4(c2.5); (R)-8a: 70%, -53.9(c1.5); (R)-8b: 47%, -42.0(c3); (S)-8b: 51%, 43.1(c3); (S)-8c: 60%, 16.9(c1.7); (S)-8d: 51%, -33.0(c2); (S)-9c: 52%, -15.1 (c14,EtOH); (S)-9d (R=n-propyl): 45%, -16.1(c3,EtOH); (R)-10a: 40%, -117(c2); (S)-10b: 45%, -70.8(c9.5,benzene); 11a: 92%, -89.4(c5); 11b: 84%, -48.4(c2).

With regard to our initial objective, the allyl derivatives 2d/4d, which may be prepared with high diastereoselectivity (91:9, Table 1, run 15) in multigram quantities, are the most promising intermediates. In 4d, the functional



12 4d 13

groups on either side of the central 1,2-di-O-unit may be used for further elaboration. For example, 4d may be converted into 12, which undergoes nucleophilic ring openings of various kinds regioselectively at the terminal position. On the other hand, 4d may be ozonized to give 13, whose aldehyde group may be used for chain elongations and/or functionalization of the α-CH_2-position via enolate chemistry. By starting the whole sequence with (S)-1 [14], 4d is also available in the enantiomeric form. Furthermore, 2d may be transformed into 3d by the Mitsunobu inversion[15] thus providing an entry into the threo series as well. So, in conclusion, 2d/4d have to be considered as convenient precursors to a variety of compounds having a 1,2-diol moiety in any one of the four possible configurations. Experiments along these lines are under way in our laboratory directed towards the synthesis of some of the natural products mentioned in the introduction.

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