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Diastereoselection in the Addition of Enolates to Chiral α,β-Epoxyaldehydes

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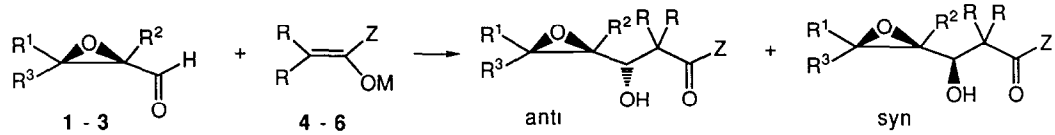
Abstract : *The stereochemistry of addition of lithium enolates to the α,β-epoxyaldehydes 1-3 has been investigated. Moderate to high diastereoselectivity (up to 13.1) is obtained in favour of the anti isomer, which is explained by the Felkin-Anh model for asymmetric induction.*

Diastereogenic addition to α- or β-alkoxy carbonyl compounds has received wide attention [1-5]. Although some rationalization can be proposed when discussing the results in terms of chelation or non-chelation controlled asymmetric induction, no general rule can predict the selectivity encountered in these reactions [3]. Among them, the condensation of lithioacetates with α- or β-alkoxyaldehydes was found poorly selective and inefficient for the synthesis of polyols or polyoxygenated molecules [2,5].

As an alternative route to chiral functionnalized polyols [6,7], the stereoselective addition of lithioenolates to epoxyaldehydes was examined (fig. 1, table 1) ; α,β-epoxyaldehydes **1-3** are obtained in high yield and optical purity (ee > 96 %) [8] by oxidation [9a] of the corresponding epoxide alcohols readily available by the Sharpless enantioselective epoxidation [9b].

Figure 1 :



	R^1	R^2	R^3		R	Z
1	H	H	CH_2OBn	4	H	OtBu
2	H	H	CH_2OSiPh_2tBu	5	Me	OEt
3	Ph	Me	H	6	H	tBu

Table 1 - Reaction of aldehydes **1** - **3** with esters **4**, **5** and ketone **6** [a]

Entry	Aldehyde	Reagent	% Yield [b]	anti : syn
1	**1**	**4**	87	82 : 18
2	**1**	**5**	47	79 :21
3	**1**	**6**	64	82 : 18
4	**2**	**4**	90	80 : 20
5	**3**	**4**	75	71 : 29

[a] Experimental conditions : 0.4 M in Et_2O, -78°C, 30 min, acidic hydrolysis (NH_4Cl)

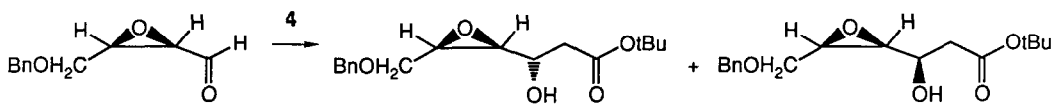
[b] Isolated yields from effectively reacted aldehyde

When aldehydes **1**, **2** are condensed with tertiobutyl lithioacetate **4** a fairly good diastereoisomeric ratio is obtained (anti : syn ~ 4 : 1) in contrast to the reaction of lithioacetates with α- or β-alkoxy aldehydes (anti . syn ~ 1 : 1) [2, 5].

The same diastereoface preference occurs in the addition of lithioisobutyrate **5** or lithiopinacolone with aldehyde **1** (anti : syn ~ 4 : 1), while reaction of lithioacetate with aldehyde **3** (entry 5) gave a modest diastereoisomeric excess. These results are in agreement with those reported in the litterature for the condensation of epoxyaldehydes with methyllithium Grignard reagents and alkylstannanes [10].

In order to improve the selectivity we surveyed a variety of experimental conditions for the reaction of α,β-epoxyaldehyde **1** with enolate **4** (fig. 2, table 2).

Figure 2 :



1 **7** (anti) **8** (syn)

Table 2 - Stereoselectivity of the reaction of aldehyde **1** with enolate **4**

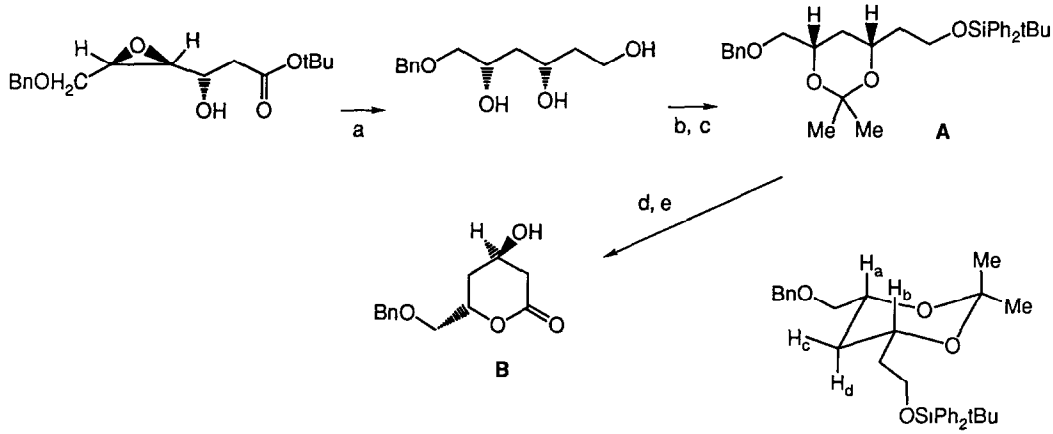
Entry	Metal	ald. : enolate	Temp (°C)	% Yield	anti : syn [b] **7** : **8**
1	Li	1 : 1	- 110	70 (83) [a]	81 : 19
2	Li	1 : 1	- 78	78 (87)	82 : 18
3	Li	1 : 1	- 20	71 (84)	81 : 19
4	Li	1 : 1	- 78 → 25	77 (81)	82 : 18
5	Li/BF_3	1 : 1	-78	45 (66)	79 : 21
6	Li	1 : 2	- 78	78 (78)	78 : 22
7	Li	1 : 2	- 78 → 25	82 (82)	93 : 7
8	Ti(OiPr)3	1 : 1	- 78	46 (60)	73 : 27
9	ZnBr	1 : 1	- 78	50 (57)	87 : 13

[a] Yield calculated from effectively reacted aldehyde

[b] the anti : syn ratio is determined by HPLC chromatography

No significant change of the diastereoisomeric excess with temperature or time reaction is observed when a 1 : 1 ratio of aldehyde and lithioenolate is used (entries 1-4) or when Lewis acids are added (entries 5, 8). The highest degree of asymmetric induction was obtained when two enolate equivalents were added to **1** at -78°C and the mixture was allowed to reach slowly the room temperature (entry 7, anti : syn 93 : 7).

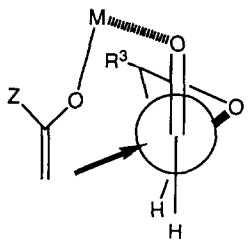
The relative stereochemistry of the two isomers has been established by proton NMR analysis of compound **A** [7] prepared by reduction of the corresponding epoxyester, primary hydroxyle protection and then acetalisation (scheme 1) [11]. Compound **A** is thus obtained in four steps and 60 % overall yield from **1**. The stereochemistry of the major isomer was further confirmed by selective deprotections, oxidation of the primary hydroxyle function and cyclisation to the mevinic lactone **B** [5] ($[\alpha]_D^{25}$ = +6.1° (c = 9.3.10^{-2} ; $CHCl_3$)).



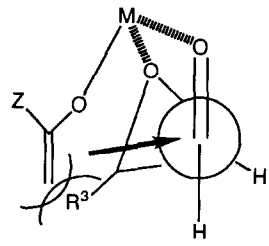
J_{ac} = 2.5 ; J_{bc} = 2.2 ; J_{ad} = 11.0 ; J_{bd} = 10.6 Hz

a : Red. Al, THF, 85 % ; b : imidazole, $ClSiPh_2tBu$, 95 % ; c : CSA, $(MeO)_2CMe_2$, 99 % ; d : n-Bu_4NF, THF, 90 % ; e : i) PDC, DMF ii) HCl, THF iii) H^+, toluene, 50 %

Assuming that the diastereoisomeric ratio observed at -78° (or -110°) is under kinetic control, the anti isomer preference can be explained by the Felkin-Anh model for asymmetric induction, the oxygen atom of the epoxide group playing the role of the "large" group. According to this model [12] there is a strong preference for transition states in which the entering nucleophile is antiperiplanar with the C-O bond of the epoxide.



Felkin-Anh model



Cram's cyclic model

The Cram's cyclic model for α alkoxy compounds is inoperative as this would predict that the major product would be the syn isomer.

Although the synergic effect of temperature and enolate excess on the final stereochemical issue is still not well understood, the high degree of asymmetric induction achieved, may be valuable for synthetic approaches to optically active polyols and polyhydroxylated compounds.

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8. Enantiomeric purity of compounds **1-3** is determined by ^{1}H-NMR analysis using d-[camphorato]Eu as chiral shift reagent under conditions of resolution of the racemate :

   1 : $[\alpha]_D^{25}$ = +46.2 (c = 0.94, $CHCl_3$) ; **2** : $[\alpha]_D^{25}$ = +40.6 (c = 3.7,$CHCl_3$) ; **3** · $[\alpha]_D^{25}$ = -180 (c = 2 2, $CHCl_3$)
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11. ^{1}H and ^{13}C NMR spectra of selected compounds follow :

    1 : ^{1}H-NMR (200 MHz, $CDCl_3$) : δ 9.43 (d, 1H, J = 4 7 Hz, CHO), 7.33 (m, 5H, aromatic), 4.55 (s, 2H, CH_2Ph), 3.87-3.71 (AB part of an ABX(Y) system, 2H, J_{AB} = 11.5, J_{AX} = 3.5, J_{BX} = 4.5 Hz, O-CH_2), 3.52-3.46 (ddd, 1H, J = 3.5 ; 4.5 ; 4.7 Hz, O-CH_2-C<u>H</u>), 3.43-3.38 (dd = t, 1H, J = 4.7 ; 4.7 Hz, <u>CH</u>-CHO). ^{13}C-NMR (50 MHz, $CDCl_3$) : δ 197.8, 137.2, 128.6, 128.0, 127.7, 127.6,127.0 73.6, 66.3, 58.0, 57.4.

    7 : $[\alpha]_D^{25}$ = -19.3 (c = 0.8, $CHCl_3$). ^{1}H-NMR (200 MHz, $CDCl_3$) : δ 7.36-7.30 (m, 5H, aromatic), 4.62-4.54 (AB, 2H, J = 11.8 Hz, CH_2Ph), 3.80-3.68 (AB part of an ABX(Y) system, 2H, J_{AB} = 11.2, J_{AX} = 4.6, J_{BX} = 6.3 Hz, O-CH_2), 3.76 (m, 1H, <u>CH</u>-OH), 3.38 (m, 1H, OH), 3.28 (ddd, X of an ABXY system, 1H, J_{XA} = 4.6, J_{XB} = 6.3, J_{XY} = 4.3 Hz, OCH_2-<u>CH</u>), 2.98 (dd, 1H, J = 8.2 ; 4.3 Hz, <u>CH</u>-CHOH), 2.65-2.52 (A'B' part of an A'B'X'Y system, 2H, $J_{A'B'}$ = 16.3, $J_{A'X'}$ = 3.8, $J_{B'X'}$ = 8.2 Hz, CH_2-C=O), 1.46 (s, 9H, tBu). ^{13}C-NMR (50 MHz, $CDCl_3$) : δ 171.4, 137.5, 128.6, 128.0, 127.9, 81.6, 73.5, 68.3, 66.6, 57.2, 55.4, 40.3, 28.1.

    A : ^{1}H-NMR (200 MHz, $CDCl_3$) : δ 7.71-7.65 (m, 4H, aromatic), 7.43-7.35 (m, 11H, aromatic), 4.65-4.51 (AB, 2H, J = 12.2 Hz, CH_2Ph), 4.24-4.12 (m, 1H, J = 2.2, 10.6 Hz, H_b), 4.17-4.05 (m, 1H, J = 2.5, 11.0 Hz, H_a), 3.90-3.63 (m, 2H, J = 10.2 ; 7.4 ; 5.6 ; 5.5 ; 5.2 Hz, <u>CH_2</u>-O-$SiPh_2tBu$) ; 3.54-3.32 (AB part of an ABX(Y) system, 2H, J = 9.9, 5.8, 4.9 Hz, $BnOCH_2$), 1.76-1.62 (m, 2H, <u>CH_2</u>-CH_2-$OSiPh_2tBu$), 1.55-1.47 (m, 1H, J = 2.5, 2.2, 12 5 Hz, H_c), 1.47 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 1.35-1.20 (m, 1H, J = 11.0, 10.6, 12.5 Hz, H_d), 1.05 (s, 9H, tBu). ^{13}C-NMR (50 MHz, $CDCl_3$) : δ 138.4, 135.6, 134.0, 133.9, 129.7, 128.5, 127.9, 127.7, 98.7, 73.8, 73.5, 68 7, 65.4, 59.7, 39.5, 34.1, 30.3, 27.0, 19.9, 19.3.
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