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Diastereoselectivity in the *Lewis* Acid Mediated Aldol Reaction of Chiral α, β-Epoxyaldehydes with a Ketene Silyl Acetal

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Summary. The Lewis acid mediated aldol reaction of chiral α, β-*cis* and *trans* epoxyaldehydes **1** and **2** with *tert*-butyl ketene silyl acetal proceeds mainly with *anti* diastereofacial preference. The best results were obtained for *cis* epoxyaldehyde **1** in the presence of catalytic amounts of $BiCl_3 \cdot 1.5$ eq. ZnI_2 (*anti*:*syn* ~ 13:1), whereas the poorest stereoselectivity was observed when an excess of $LiClO_4$ was used (*anti*:*syn* ~ 1:1). The more stable epoxyaldehyde conformers were determined and the diastereofacial preference was found to be in agreement with a nucleophilic attack on the energetically more favoured conformers.

Keywords. Diastereoselection; Epoxyaldehydes; Enolate, Optically active γ, δ-epoxy-β-hydroxyesters.

Diastereoselektivität der *Lewis*-Säure-katalysierten Aldolreaction zwischen chiralen α, β-Epoxyaldehyden und einem Ketensilylacetal

Zusammenfassung. Die *Lewis*-Säure-katalysierte Aldolreaktion der chiralen α, β-*cis*- und -*trans*-Epoxyaldehyde **1** und **2** mit *tert*-Butylketensilylacetal verläuft stereoselektiv *anti*. Die besten Ergebnisse wurden für den *cis*-Epoxyaldehyd **1** in Gegenwart katalytischer Mengen BiCl3·1.5 eq. ZnI_2 erhalten (*anti*:*syn* ~ 13:1). Die geringste Stereoselektivität trat auf, wenn $LiClO_4$ im Überschuß eingesetzt wurde (*anti*:*syn* ~ 1:1). Das beobachtete Verhalten steht mit einem nucleophilen Angriff am energetisch günstigeren Konformeren im Einklang.

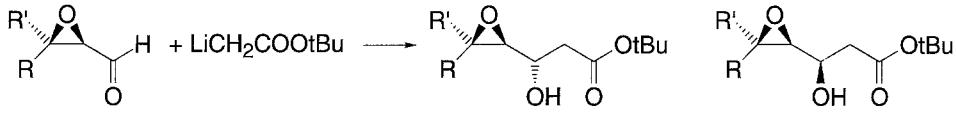
Introduction

Asymmetric aldol reactions are of great potential value of synthetic chemists [1]. The search for catalysts, solvents, and reaction conditions which optimize the diastereofacial selectivity of addition reactions to carbonyl compounds has been a very active field for many years and continues to stimulate much thought from a synthetic and mechanistic point of view [2–4].

This reaction has been largely applied to syntheses of optically active compounds with a 1,2, 1,3, or 1,2,3 polyhydroxylated frame which are useful synthons for the synthesis of natural products or their analogues that may possess interesting

biological activities [5, 6]. Among the most useful methods is that of the aldol reaction of metal enolates with chiral α-, β-, or α,β-alkoxyaldehydes. Numerous studies describe the 1,2 or 1,3 asymmetric induction by metal assisted aldol condensations [7, 8] and analyze the results of the stereochemistry observed by the concept of chelation (*Cram* cyclic model) or non-chelation control (*Felkin-Anh* model); nevertheless, only a few reports on the diastereofacial selectivity of α, β-epoxyaldehydes are known [9], although these compounds can be considered as synthetic equivalents to α-, β-, or α,β-alkoxyaldehydes.

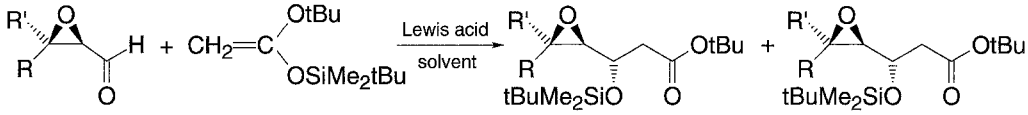
We have recently described the aldolization reaction of lithium ester enolates with chiral α,β-epoxyaldehydes [10]. The reaction proceeds with diastereofacial preference in favour of the *anti* diastereoisomer. When *trans* α, β-epoxyaldehydes are condensed with lithium *tert*-butyl acetate, the diastereoisomers were obtained in ~3:1 ratio, whereas *cis* α, β-epoxyaldehydes reacting under the same conditions give a 4:1 mixture of diastereoisomers in favour of the *anti* adduct. Under certain experimental conditions (synergetic effect of temperature and excess enolate), the diastereofacial preference in the case of *cis* α,β-epoxyaldehydes can be greatly enhanced (*anti*:*syn* ~ 13:1). The *Felkin-Anh* model was used to explain the results.



1 R = $CH_2OSitBuPh_2$, R' = H — **1a** — **1b**
2 R = H, R' = $CH_2OSitBuPh_2$ — **2a** — **2b**

Results and Discussion

In this paper we describe our investigations on the diastereoselectivity of the reaction of a ketene silyl acetal in the presence of three different *Lewis* acids, *i.e.* Eu(*fod*)$_3$, $BiCl_3MX_2$, and $LiClO_4$, with the *cis* and *trans* epoxyaldehydes **1** and **2** (Tables 1, 2). We postulate that in the presence of the selected *Lewis* acids the reactivity of the aldehyde function will prevail over the oxirane ring opening.



1 **5** **3a** **3b**
2 **4a** **4b**

Europium complexes and lanthanides in general have served as *Lewis* acids in many synthetic reactions [11] and particularly provided efficient catalysis for the aldol reactions of aldehydes with ketene silylacetals. Bismuth chloride, although a weak *Lewis* acid, is a potential catalyst for the reactions of enoxysilanes; it was recently shown to present a drastically increased catalytic activity when it is used in combination with a metallic iodide [12] and thus can catalyze efficiently the *Mukaiyama* aldol and *Michael* reaction. Finally, $LiClO_4$ (in excess or catalytically)

Table 1. *Lewis* acid mediated aldol reaction of aldehyde **1** with ketene silyl acetal **5**; [a]total yield of silylated and desilylated (8–20%) aldol products; [b]yield calculated from analytical liquid chromatography

Entry	*Lewis* acid	Solvent	Temperature	Reaction time (h)	Yield[a] (%)	Diastereoselectivity (*anti*:*syn*)	
a	Eu(*fod*)$_3$ cat.	CH_2Cl_2	20	3	nd	83:17	5:1
b	Eu(*fod*)$_3$ cat.	CH_2Cl_2	20	24	69	89:11	8:1
c	Eu(*fod*)$_3$ cat.	CH_2Cl_2	0	1	58[b]	83:17	5:1
d	Eu(*fod*)$_3$ 1 eq.	CH_2Cl_2	20	7	70	87:13	6,5:1
e	$BiCl_3 \cdot 3NaI$ cat.	CH_2Cl_2	20	3	nd	91:9	10:1
f	$BiCl_3 \cdot 3NaI$ cat.	CH_2Cl_2	20	90	38	90:10	10:1
g	$BiCl_3 \cdot 1.5\ ZnI_2$ cat.	CH_2Cl_2	20	12	77	93:7	13:1
h	$BiCl_3 \cdot 1.5\ ZnI_2$ cat.	CH_2Cl_2	20	12	73[b]	93:7	13:1
i	$BiCl_3 \cdot 1.5\ ZnI_2$ cat.	CH_2Cl_2	0	2	32[b]	94:6	15:1
j	$LiClO_4$ cat.	CH_2Cl_2	20	17	77	87:13	6,5:1
k	$LiClO_4$ cat.	Et_2O	20	90	21	87:13	6,5:1
l	$LiClO_4$ 1.5 eq.	CH_2Cl_2	20	2	66	58:42	1,4:1

has been used by *Reetz et al.* [13] as an effective *Lewis* acid which induces chelation controlled group transfer *Mukaiyama* aldol reaction of aldehydes with silyl ketene acetals).

First, condensed the aldehydes **1** and **2** with lithium *tert*-butylacetate by a procedure described before [10]. The purified aldol adducts were subjected to silylation. Best results were obtained using *tert*-butyldimethylsilyl chloride in presence of *DMAP* (catalyst) in *DMF*, whereas reaction of *tert*-butyldimethylsilyl triflate in anhydrous methylene chloride lead to a poor yield of protected aldol compounds along with degradation products.

Ketene silyl acetal **5** was obtained in high yield (93%) by reacting lithium *tert*-butylacetate with *tert*-butyldimethylsilyl chloride in *THF* at 0 °C in the presence of *HMPA* [14], and condensed with the epoxyaldedydes **1** and **2**.

The results obtained for the reaction of *cis* epoxyaldehyde **1** are summarized in Table 1.

When aldehyde **1** reacted with a catalytic amount of Eu(*fod*)$_3$, fairly good yields of aldol products were obtained. Changes in the reaction time (entries a, b) and temperature (entries a, c) or *Lewis* acid equivalent (entries b, d) did not alter the *anti* diastereoface preference of the reaction (*anti*:*syn* 5:1, 7:1). Bismuth(III) chloride has been activated by 3 eq. of NaI or 1.5 eq. ZnI_2 according to *Dubac* [12] to obtain a species with greater catalytic activity. In the presence of $BiCl_3 \cdot 3$ NaI as *Lewis* acid catalyst, the reaction was very slow and never went to completion. After 90 h of reaction, only 38% of aldol products were obtained with an *anti* diastereoface preference of 9:1 (entry f). Again no change of diastereoselectivity was observed with time (entries e, f). The *Mukaiyama* aldol reaction with a catalytic amount of $BiCl_3 \cdot 1.5\ ZnI_2$ was much more efficient, leading to the aldol products in $\sim 75(\pm 2)\%$ yield, in addition to 8% of unreacted aldehyde (after 12 h) and with a very good *anti*

Table 2. *Lewis* acid medicated aldol reaction of aldehyde **2** with ketene silyl acetal **5** (r.t., CH_2Cl_2)

Entry	*Lewis* acids	Reaction time (h)	Yield (%)	Diastereoselectivity *anti*:*syn*	
a	Eu (*fod*)$_3$ cat.	12	66	68:32	2:1
b	$BiCl_3 \cdot 1.5\ ZnI_2$ cat.	12	62	75:25	3:1
c	$LiClO_4$ cat.	24	78	61:39	1.5:1
d	$LiClO_4$ 1.5 eq.	1.5	54	52.48	~1:1

diastereoselectivity (~ 13:1, entries g, h). The same *anti* diastereoface preference was obtained when the reaction was carried out at 0 °C and stopped after 2 h (*anti*:*syn* > 15:1; 40% of unreacted aldehyde was detected by analytical liquid chromatography). Finally, when a catalytic amount of lithium perchlorate was used as *Lewis* acid in methylene chloride, the reaction went to completion after 17 h to give 77% yield of aldol products with a 7:1 *anti* diastereoselectivity (entry j). An ethereal solution of lithium perchlorate reacted much slower (42% of unreacted aldehyde after 90 h of reaction, entry k). In diethylether, $LiClO_4$ is able to form soluble etherates so that the solvent competes with the substrate for coordination to the lithium cation, whereas in methylene chloride no such phenomenon exists. Surprisingly, the aldol products were obtained with almost no diastereoselectivity when 1.5 eq. of $LiClO_4$ were used (entry 1, *anti*:*syn* ~ 3:2).

Other attempts with $SnCl_4$ or $Et_2O \cdot BF_3$ as *Lewis* acid catalysts were found unsuccessful. $TiClO_4$, known to reverse the stereocontrol in the *Mukaiyama* aldol addition to chiral α- or β-thioaldehydes [15], was unsuitable for the epoxyaldehydes.

Trans epoxyaldehyde **2** was also subjected to a *Mukaiyama* aldol type reaction (Table 2).

Little *anti* diastereoface preference (1.5:1 to 3:1) was obtained with all three *Lewis* acids present in catalytic amounts, the best results being obtained with $BiCl_3 \cdot 1.5\ ZnI_2$ (entry b, 3:1), whereas again using 1.5 eq. of $LiClO_4$ resulted in aldol products without any diastereoselectivity (entry d).

The *Lewis* acid catalyzed silyl ketene acetal additions to the chiral γ-alkoxy α, β-epoxyaldehydes **1** and **2** are shown to exhibit mainly *trans* diastereofacial selection except for reactions carried out in presence of 1.5 eq. of lithium perchlorate instead of a catalytic amount where almost no diastereoselectivity was observed. An analogous effect of *Lewis* acid stoichiometry on the stereoselectivity of the aldol reaction has also been observed by *Heathcock* [16] with the reaction of chiral boron enolates with prochiral aldehydes in the presence of different amounts of $SnCl_4$. Although there is no direct proof, the possibility of the existence of different complexes varying with the *Lewis* acid: aldehyde ratio may explain the results obtained. A marked difference in diastereoselectivity has also been observed recently [17] when using catalytic or no quantities of *Lewis* acids in the intramolecular *Diels-Alder* reaction with a furan diene.

The reactions with *cis*-expoxyaldehyde **1** provided the aldol products in the same yield and with better diastereoselectivity than when a 1:1 molar ratio of aldehyde and lithium *tert*-butylacetate was used (*anti*:*syn* 4:1) [10]. It is also noteworthy that

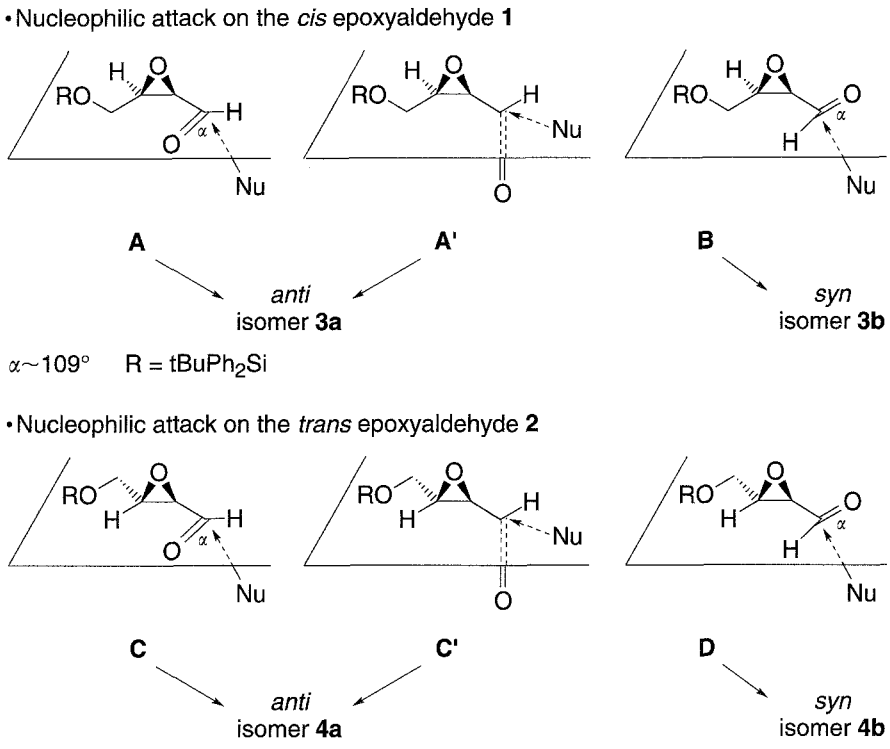


Fig. 1. **A**, **B**, **C**, **D**: *Felkin-Anh* type models; **A'**, **C'**: *Cornforth* type models

in situ use of *Lewis* acids during the lithium enolate reaction did not improve the results. Activated bismuth(III) chloride with 1.5 eq. of ZnI_2 gave the best *anti* diastereoselectivity (*anti*:*syn* ~ 13:1) which is the same as that observed for lithium enolate reaction under the optimum experimental conditions (2 eq. of enolate, $-78 \rightarrow 25\,^{\circ}C$; [10]).

No variation in the stereoselectivity was observed with the temperature or the time of the aldol addition reaction which leads to the silylated aldol adducts. Thus, the diastereoselectivity will be considered to result from a kinetic control in the nucleophilic attack on the aldehyde.

The *anti* diastereofacial preference obtained with the *cis* epoxyaldehyde **1** can be analyzed according to the *Felkin-Anh* [18] or *Cornforth* [19] type models. In the first one (**A**), a preferential, non perpendicular nucleophilic attack (Nu) on the carbonyl will occur antiperiplanar to the epoxide C–O bond. In the second conformer (**A'**), the carbonyl function is oriented nearly antiperiplanar to the epoxide C–O bond and the nucleophilic attack will preferentially take place on the sterically less hindered Si face of the carbonyl (almost antiperiplanar to the C_2–C_3 bond) and lead to the **3a** isomer Fig. 1.

In the same way, the enolate addition to the *trans* epoxyaldehyde in the conformation **C** (or **C'**) will favour in *anti* aldol product **4a** whereas the conformer **D** will give preferentially the *syn* product **4b**.

The energetically more favoured conformers have been calculated by the MMX program [20] for the two aldehydes. The three conformational minima predicted

Table 3. Conformational energy minima and dihedral angle values calculated for the *cis* and *trans* epoxyaldehydes **1** and **2**; [a]the values are given as an average; the position of the minimum on the rotational energy profile was less marked than for the other conformers reported

			dihedral angle values (°)			
		ΔE(kcal·mol^{-1})	$O{=}C_1C_2C_3$	$O{=}C_1C_2O$	$SiOC_4C_3$	$OC_4C_3C_2$
	A	22.7	48	115	−176	−91
cis	**A′**	22.7	97	164	167	−82
	B	23.7	−126	−59	−172	−83
	C	22.3	22(5)	89	−168	98
trans	**C′**	22.3	118	−176	−169	96
	D[a]	22.9	168	−140	−169	101

from the calculated rotational profile (**A**, **A′**, **B** for the *cis* aldehyde **1**, **C**, **C′**, **D** for the *trans* aldehyde **2**) are reported in Table 3.

The same energy values have been found for the more stable conformers **A** and **A′**, whereas the value for the **B** conformer is greater by 1 kcal·mol^{-1}.

According to *Reetz* [21] and *Wuts* [22], the hypothesis that π facial diastereoselectivity in nucleophilic addition reactions could be primarly dictated by the aldehyde structures and their conformational energies in the two transition states can be considered in our examples. An energy difference of 1 kcal·mol^{-1} between **A**, **A′**, and **B** is correctly correlated to the *anti* diastereofacial preference observed when the *cis* α, β-epoxyaldehyde is condensed with lithiated or silylated *tert*-butylacetates (*anti*:*syn* 4:1 [10] and 5:1 to 13:1, respectively) or other nucleophiles.

The same interpretation holds for the reaction with the *trans* epoxyaldehyde **2**; the more stable conformers **C**, **C′** will favor the formation of the *anti* aldol **4a** over the *syn* **4b**. The energy difference between **C**, **C′**, and **D** ($\sim$ 0.7 kcal·mol^{-1} compared to 1 kcal·mol^{-1} for the *cis* aldehydes) agrees with a weaker *anti* preference in the aldol condensation with the *trans* α, β-epoxyaldehyde.

The participation of the *Lewis* acids in the *Mukaiyama* type aldol reaction can proceed by activation of the carbonyl function and formation of mono- or bidentate chelates which could change the relative population of the predominating conformers. Chelation controlled additions to chiral alkoxyaldehydes have been described. Whereas α-alkoxyaldehydes lead preferentially to *syn* aldol products through chelation control, α, α-O-isopropylidene aldehydes are known to give the *anti* products in good to excellent diastereoselectivity. *Mukaiyama et al.* [22] have published a series of papers concerning the *anti* stereoselectivity of the reaction of 2,3-O-isopropylidene-*D*-glyceraldehydes with nucleophiles in presence of *Lewis* acids. An *anti* stereocontrol in the reaction of glyceraldehyde acetonide with ketene silyl acetal in presence of catalytic amounts of chiral europium (III) compounds has also been reported [24].

The *Lewis* acid in the presence of the aldehyde can chelate the epoxide oxygen function or (and) the carbonyl; the participation of the bulky *tert*-butyl diphenyl silyl ether function is unlikely, as has been shown by *Keck* [25], *Eliel*, and *Frye* [26] for some other silyloxy protected groups.

Lithium is the smaller cation in the series, and $LiClO_4$ appeared to be a harder *Lewis* acid than europium or bismuth catalysts which can more easily coordinate with the carbonyl function. The participation of bidentate or more complex association states with the aldehyde and $LiClO_4$ is possible, especially when the salt is added in a stoichiometric amount. The size of europium or bismuth salts might render such bi(poly)dentate associations more difficult. The carbonyl activation by these two catalysts will probably occur on the same preferential conformers as previously described (Fig. 1, Table 3); finally, even if the *anti* diastereoselection is the main tendency in these *Lewis* acid catalyzed aldol reactions, the differences observed in the *anti*:*syn* ratio could result from slight changes in the steric interactions between the incoming nucleophile and the activated carbonyl, dependent of the presence (with the *cis* epoxyaldehyde) or not (*trans* epoxyaldehyde) of the bulky $CH_2OSitBuPh_2$ group.

Experimental

Products were purified by medium pressure liquid chromatography on a Jobin-Yvon Moduloprep apparatus using Amicon 6–35 µm or Merck 15 µm silica. Analytical liquid chromatography was performed with a Spectroflow 400 Kratos pump equipped with an UV 759A Applied Biosystems detector, a D-2000 Merck integrator, and a silica Novapack (15 cm) column (pressure: 19 bars). IR spectra were recorded with a Perkin Elmer 883 spectrometer. For NMR spectra, a Bruker AC-250 spectrometer was used (250 MHz for ^1H, 62.9 MHz for ^{13}C). Chemical shifts were referenced to *TMS*. Optical rotations were measured at 25 °C with a Perkin-Elmer 141 apparatus. Mass spectra were recorded on a Nermag R10-10. All solvents were distilled and dried before use. α, β-Epoxyaldehydes **1** and **2** and the aldol products **1a**, **1b**, **2a**, and **2b** were synthesized as reported previously [10].

O-tert-Butyl-O-tert-butyldimethylsilyl ketene acetal (**5**)

A 50 ml round-bottomed flask equipped with magnetic stirring was charged with *n*-butyllithium (7.6 ml of 1.6 *M* solution in hexane, 12.1 mmol) and a solution of diisopropylamine (1.7 ml, 12.1 mmol) in *THF* (11.6 ml) at 0°C under N_2. After 15 min, the mixture was cooled to −78 °C and *tert*-butyl acetate (1.6 ml, 11.9 mmol) was added dropwise. The solution was warmed to 0 °C after 15 min of stirring, and hexamethylphosphoramide (1.2 ml, 6.9 mmol), followed by a solution of *tert*-butyldimethylsilyl chloride (3.2 ml, 3.7 *M* in petroleum ether, 12.2 mmol), were added dropwise. The reaction mixture was allowed to react for 20 min and was then quenched with aqueous acetic acid (2.2 ml, 1 *M* solution, 13.2 mmol). The organic phase was extracted, dried over $MgSO_4$, and evaporated to leave 3.23 g (11 mmol) of the desired product (yield 93%).

IR (film): $\nu = 3140$, 3176 (C=CH); 2958, 2860 (CH); 1651 (C=C); 1285, 1246 (C–O; $SiCH_3$); 1047 (Si-O) cm^{-1}; ^1H NMR (250 MHz, C_6D_6): $\delta = 3.68$ and 3.60 (AB system, 2 H, $J = 11.6$ Hz, CH_2=C); 1.27 (s, 9 H, *t*BuO); 0.97 (s, 9 H, *t*BuSi); 0.16 (s, 6 H, CH_3Si) ppm; ^{13}C NMR (62.9 MHz, C_6D_6): $\delta = 158.2$; 77.8, 73.2; 28.5; 26.0; 18.3; −4.54 ppm.

Lewis acid mediated aldol reactions. General procedure

To a stirred solution of aldehyde (1 mmol, 0.1 *M*) in anhydrous methylene chloride or ether, a catalytic amount (2–5%) of *Lewis* acid, or 1.5 eq. of lithium perchlorate were added at r.t. under N_2. After 15 min, O-*tert*-butyl-O-*tert*-butyldimethylsilyl ketene acetal **5** (1 eq.) was added dropwise. The reaction was monitored by TLC or liquid analytical chromatography on aliquots of the reaction mixture recuperated at different intervals of time. When no further transformation was observed, the mixture was

quenched with saturated aqueous NH_4Cl, extracted with ether, dried over $MgSO_4$, and evaporated. The crude product was separated by chromatography on silicagel (eluant: petroleum ether:methylene chloride:ethyl acetate 90:8:2) to give the non-reacted aldehyde **1** (or **2**), the mixture of the two silylated diastereoisomers **3a**, **3b** (**4a**/**4b**), and the two desilylated diastereoisomers which can be separated by another chromatographic run (petroleum ether:methylene chloride:ethyl acetate 70:24:6) to obtain the desilylated aldol products.

Analytical chromatography was performed on each one of these solutions in order to determine the diastereoface preference of the reaction before separation, identification, and yield calculation of the products.

(3S,4R,5R)-tert-Butyl-(6-(tert-butyldiphenylsilyloxy)-4,5-epoxy-3-(tert-butyldimethylsilyloxy))-hexanoate (**3a**)

IR (film): $\nu = 3074$, 3060 (=CH); 2934, 2860 (CH); 1735 (C=O); 1254 (C–O); 1158, 1114 (Si-O) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): $\delta = 7.71$–7.67 (m, 4 H, phenyl); 7.42–7.38 (m, 6 H, phenyl); 3.96 and 3.72 (AB part of an ABX system, 2 H, $J = 3.91$; 6.24; 11.11 Hz, CH_2OSi); 3.91 (m, 1 H, $J = 3.74$; 7.50; 7.97 Hz, CH-OSi); 3.20 (ddd, 1 H, $J = 3.91$; 4.00; 6.24 Hz, CH_{ep}-CH_2OSi); 2.95 (dd, 1 H, $J = 4.00$; 7.50 Hz, CH_{ep}-CHOSi); 2.50 and 2.46 (AB part of an ABX system, 2 H, $J = 3.74$; 7.97; 15.58 Hz, $CH_2COOtBu$); 1.43 (s, 9 H, *t*BuOCO); 1.08 (s, 9 H, *t*BuPh$_2$Si); 0.80 (s, 9 H, *t*BuMe$_2$Si); −0.01 (s, 3 H, Me$_2$Si); −0.05 (s, 3 H, Me$_2$Si) ppm; ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 170.1$; 135.6; 133.3 and 133.1; 129.8 and 127.8; 80.6; 66.1; 62.4; 58.6 and 58.1; 42.2; 28.1; 26.6; 25.7; 19.2; 17.9; −4.6 and −4.9 ppm; MS (DCI, NH_3): $m/e = 588$ (100%, M + 18); 532 (20.5%); 437 (66.5%); 359 (41.1%); Analysis (calculated/found): %C (67.32/67.95); %H (8.83/8.99); $[\alpha]_{25}^{D} = +5.0°$ ($c = 1.07$; $CHCl_3$). Analytical liquid chromatography; eluant isooctane:methylene chloride:ethyl acetate 95:4:1; retention time: 7.09 min.

(3R,4R,5R)-6-tert-Butyl-(6-(tert-butyldiphenylsilyloxy)-4,5-epoxy-3-(tert-butyldimethylsilyloxy))-hexanoate (**3b**)

IR (film): $\nu = 3074$, 3061 (=CH); 2934, 2893, 2860 (CH); 1733 (C=O); 1255 ($C–O_{epoxide}$); 1153 (C–O, Si-C_{arom}); 1107 (Si-O-C_{aliph}) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): $\delta = 7.73$–7.68 (m, 4 H, phenyl); 7.46–7.39 (m, 6 H, phenyl); 3.82 and 3.75 (AB part of an ABX system, 2 H, $J = 11.42$; 6.14; 5.51 Hz, CH_2OSi); 3.87 (m, 1 H, $J = 6.00$; 8.20 Hz, CHOSi); 3.21 (m, 1 H, $J = 6.14$; 5.51; 4.50 Hz, $CH_{ep}CH_2OSi$); 3.07 (dd, 1 H, $J = 4.50$; 8.20 Hz, CH_{ep}CHOSi); 2.47 (d, 2 H, $J = 6.00$ Hz, $CH_2COOtBu$); 1.43 (s, 9 H, *t*BuOCO); 1.08 (s, 9 H, *t*BuPh$_2$Si); 0.91 (s, 9 H, *t*BuMe$_2$Si); 0.14 and 0.07 (s, 3 H, *t*Bu*Me*$_2$Si) ppm; ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 169.8$; 135.6; 133.1 and 133.0; 129.9 and 127.9; 80.6; 69.0; 62.6; 60.0 and 56.5; 41.6; 28.2; 26.8; 25.9; 19.2; 18.1; −4.4 and −5.1 ppm; MS (DCI, NH_3): $m/e = 588$ (89.6%, M + 18); 571 (1.1%, M + 1); 532 (100%); 437 (33.3%); 359 (83.7%). Analysis (calculted/found): %C(67.32/67.77); %H (8.83/8.80); $[\alpha]_{25}^{D} = +6.1°$ ($c = 0.23$; $CHCl_3$). Analytical liquid chromatography: eluant isooctane:methylene chloride:ethyl acetate 95:4:1; retention time: 5.28 min.

(3S,4R,5S)-6-tert-Butyl-(6-(tert-butyldiphenylsilyloxy)-4,5-epoxy-3-(tert-butyldimethylsilyloxy))-hexanote (**4a**)

IR (film): $\nu = 3075$–3060 (=CH); 2934, 2861 (CH); 1732 (C=O); 1254 ($C–O_{epoxide}$); 1160 (C–O + Si-C_{arom}); 1.11 (Si-O-C_{aliph}) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): $\delta = 7.70$–7.66 (m, 4 H, phenyl); 7.44–7.36 (m, 6 H, phenyl); 4.02 (ddd, 1 H, $J = 4.50$; 7.58; 5.10 Hz, CHOSi); 3.69 and 3.87 (AB part of an ABX system, 2 H, $J = 2.90$; 4.70; 11.91 Hz, CH_2OSi); 3.08 (ddd, 1 H, $J = 2.90$; 4.70; 2.50 Hz, $CH_{epoxide}CH_2OSi$); 2.96 (dd, 1 H, $J = 2.50$; 5.10 Hz, $CH_{epoxide}$CHOSi); 2.45 and 2.50 (AB part of an ABX system, 2 H, $J = 4.50$; 7.58; 15.28 Hz, $CH_2COOtBu$); 1.45 (s, 9 H, *t*BuOCO); 1.05 (s, 9 H, *t*BuPh$_2$Si); 0.86 (s, 9 H, *t*BuMe$_2$Si); 0.07 (s, 6 H, Me$_2$Si) ppm; ^{13}C NMR (62.9 MHz, $CDCl_3$), $\delta = 170.2$; 135.6; 133.2; 129.8 and 127.8; 80.6; 68.6; 63.5; 57.6 and 57.2; 41.6; 28.2; 26.8; 25.8; 19.3; 18.1; −4.41 and −5.01 ppm; MS

DCI, NH_3): $m/e = 588$ (100%; M + 18); 532 (38.1%); 437 (62.0%); 359 (36.8%). Analysis (calculated/found): %C (67.32/67.54); %H (8.83/8.97); $[\alpha]_{25}^{D} = -17.1°$ ($c = 1.26$, $CDCl_3$). Analytical liquid chromatography; eluant isooctane:methylene chloride:ethyl acetate 95:4:1; retention time: 8.47 min.

(3R,4R,5S)-6-(tert-butyl-(6-(tert-butyldiphenylsilyloxy)-4,5-epoxy-3-(tert-butyldimethylsilyloxy))-hexanoate (**4b**)

IR (film): $\nu = 3075$–3060 (=CH); 2960, 2934, 2860 (CH); 1732 (C=O); 1255 ($C-O_{epoxide}$); 1158 ($C-O + Si_{Carom}$); 1111 ($Si-O-C_{aliph}$) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): $\delta = 7.69$–7.65 (m, 4 H, phenyl); 7.42–7.38 (m, 6 H, phenyl); 3.89 (ddd, 1 H, $J = 5.57$; 7.12; 6.25 Hz, CHOSi); 3.70 and 3.82 (AB part of an ABX system, 2 H, $J = 3.12$; 4.58; 11.78 Hz, CH_2OSi); 3.05 (m, 1 H, $J = 3.12$; 4.58; 2.20 Hz, $CH_{ep}CH_2OSi$); 2.97 (dd, 1 H, $J = 2.20$; 6.25 Hz, $CH_{ep}CHOSi$); 2.41 and 2.44 (AB part of an ABX system, 2 H, $J = 5.57$; 7.12; 15.53 Hz, $CH_2COOtBu$); 1.43 (s, 9 H, *t*BuOCO); 1.05 (s, 9 H, $tBuPh_2Si$); 0.89 (s, 9 H, $tBuMe_2Si$); 0.13 and 0.09 (s, 3 H, Me_2Si) ppm; ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 170.0$; 135.6; 133.3 and 133.2; 129.8 and 127.7; 80.7; 70.5; 63.5; 58.8 ad 56.3; 41.3; 28.1; 26.8; 25.8; 19.2; 18.1; −4.5 and −5.1 ppm; MS (DCI, NH_3): $m/e = 588$ (100%; M + 18); 571 (1.8%, M + 1); 532 (42.4%); 437 (86.8%); 359 (32.5%); $[\alpha]_{25}^{D} = +3.0°$ ($c = 0.50$; $CHCl_3$). Analytical liquid chromatography; eluant isooctane:methylene chloride:ethyl acetate 95:4:1; Retention time:6.11 min.

Analytical chromatography for aldehydes **1** and **2**: eluant isooctane:methylene chloride:ethyl acetate 95:4:1; retention time: 14.37 (**1**), 15.87 (**2**) min.

Analytical chromatography for desilylated products: eluant isooctane:methylene chloride:ethyl acetate 70:24:6; retention time: 4.60 (**1a**), 9.82 (**1b**), 2.95 (**2a**), 7.44 (**2b**) min.

Silylation of aldol products **1a**, **1b**, **2a**, **2b**. *General procedure*

To a solution of the aldol product in *DMF* (4 ml/mmol), a solution of imidazole (6 eq.), a catalytic amount of *DMAP* (2%), and *tert*-butyldimethylsilyl chloride (1.5 eq.) were added at r.t. and under N_2. After 16 h of stirring, the reaction mixture was quenched with aqueous saturated NH_4Cl and extracted with ether. The organic phases were dried over $MgSO_4$, evaporated, and the crude products were chromatographed under conditions describe above.

Compound **3a** (0.113 g, 0.2 mmol) was obtained from 0.1 g (0.2 mmol) of **1a** (yield 91%); **3b** (0.105 g, 0.18 mmol) from 0.1 g (0.22 mmol) of **1b** (yield 82%); **4a** (0.15 g, 0.26 mmol) from 0.21 g (0.47 mmol) of **2a** (yield 56%); **4b** (40 mg, 0.07 mmol) from 55 mg (0.12 mmol) of **2b** (yield 60%).

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