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LEWIS ACID MEDIATED ALDOL CONDENSATIONS USING THIOESTER SILYL KETENE ACETALS

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Abstract- BF_3-OEt_2 mediated thioester silylketene acetal additions to aldehydes are stereoconvergent and give high anti-syn ratios and good chemical yields. An acyclic transition state model was hypothesized in order to account for the observed selectivity. Theoretical methods (MNDO) were used to evaluate the ground-state conformations of thioester silylketene acetals and to model the acyclic transition states. Lewis acid mediated additions of thioester silylketene acetals to 2-phenylpropionaldehyde (BF_3-OEt_2), O-benzyl lactic aldehyde ($SnCl_4$), 2,3-O,O-dibenzyl glyceraldehyde ($SnCl_4$), and 3-benzyloxy-2-methylpropionaldehyde ($TiCl_4$) were found to be highly diastereoface selective so that three contiguous stereocenters could be established. With α-, β-, or α,β-alkoxy aldehydes, relative stereoselection (chelation) effectively controls internal stereolection. The ground state conformations of the chiral aldehydes were studied using molecular mechanics (MM2).

Since its discovery, the Lewis acid catalyzed reaction of enolsilanes with aldehydes (Mukaiyama reaction)[1] has attracted the interest of synthetic organic chemists and has provoked considerable research and interpretation.[2-6]

The major drawback of this reaction has been the low level or the complete lack of 2,3-stereoselectivity (internal stereoselectivity): except for two single cases (Z enolsilane derived from ethyl tert-butyl ketone addition to benzaldehyde, >95:5 anti-syn;[6] E enolsilane derived from ethyl propionate addition to isobutyraldehyde,[5a] 93:7 anti-syn) the anti-syn ratios are uniformly low (1:1 - 4:1).[1-6]

On the contrary the Lewis acid mediated enolsilane additions to chiral aldehydes are often highly diastereoface-selective,[7] and in the case of a few ketone enol silyl ethers 3,4-stereoselection (relative) effectively controls 2,3-stereoselection (internal).[8-14]

Unfortunately the latter part of the above does not apply to ester silylketene acetals,[8,9] and thus the synthetic utility of the process is restricted.

We have recently shown that thioester silylketene acetals solve both the internal and the relative stereoselection problems, and are therefore useful synthetic reagents.[15,16,17]

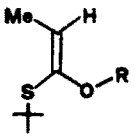
Here we report additional examples of this selectivity and propose mechanistic explanations together with the conformational analysis of the ground state of the reagents (thioester silylketene acetals and the chiral aldehydes).

THIOESTER SILYLKETENE ACETALS. SYNTHESIS AND ADDITIONS TO ACHIRAL ALDEHYDES.

Thioesters have attracted the interest of organic chemists since the discovery that in nature they are used in enzymatic acylation processes. The relative weakness of the overlapping of the C(2p) and S(3p) orbitals in carbon-sulfur double bond $\geq C=\overset{+}{S}-R$, when compared with $\geq C=\overset{+}{O}-R$, makes the contribution to the stability of thioesters of the resonance form depicted below much less important than in the corresponding esters.

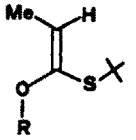
As a result, the α-hydrogen acidity is enhanced and processes like enolate formation and Claisen condensations are favored.[18] Thioesters are therefore electronically more similar to ketones than esters, and this aspect is particularly important as it permits the extention to thioesters of the selectivity shown by ketone enolsilylethers and enolates. Thioester enolates have been extensively used in stereoselective aldol condensations[19] and in the synthesis of complex natural products.[20] Moreover thioesters offer relevant synthetic opportunities: they can be easily transformed to acids (Hg^{++},H_2O), esters (Hg^{++},ROH), aldehydes (H_2/Ra-Ni), alcohols (LAH or H_2/Ra-Ni), ketones (R_2CuLi) under mild conditions and in high yield. Thioester silylketene acetals are easily prepared from thiopropionates in high stereoisomeric purity.

Tert-butyl thiopropionate[21] was enolized to give either the kinetic (LDA, -78°C,THF)[22] or the thermodynamic enolate (LDA,-78°C, THF-HMPA).[23] The kinetic enolate was then trapped with $Me_2tBuSiOTf$ or Me_3SiCl to give compound (1)(Z-E > 95:5) and (2)(Z-E 90:10), while the thermodynamic enolate was trapped with $Me_2tBuSiCl$ or Me_3SiCl to give compound (3)(E-Z > 95:5) and (4)(E-Z 93:7).



(1) R = $SiMe_2Bu^t$

(2) R = $SiMe_3$



(3) R = $SiMe_2Bu^t$

(4) R = $SiMe_3$

Unlike the corresponding ester silylketene acetals, which show a complete lack or low levels of stereoselectivity, depending on the starting double bond geometry,[2,5a,6] the thioester analogs are stereoconvergent: they give anti aldols independent of the starting configuration of the double bond. BF_3-OEt_2 proved to be better than other Lewis acids, including $TiCl_4$, BCl_3, $SnCl_4$, ethylenechloroboronate ($C_2H_4O_2BCl$) in promoting high anti-syn ratios and good chemical yields (Table 1).

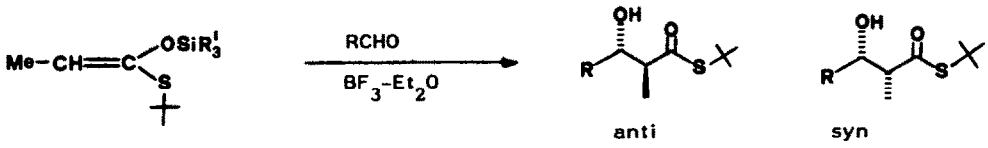


Table 1. BF_3-OEt_2 mediated aldol additions to achiral aldehydes.

Entry	Reagent	Aldehyde	%Yield[a]	Anti-syn ratio
1	(1)	PhCHO	95	21 : 1
2	(3)		93	26 : 1
3	(2)		96	19 : 1
4	(1)	n-C_5H_{11}CHO	90	8 : 1
5	(3)		92	7 : 1
6	(2)		95	11 : 1
7	(3)	i-PrCHO	93	10 : 1
8	(2)		95	10 : 1
9	(3)	t-BuCHO	15[b]	8 : 1
10	(3)	Ph 	85	13 : 1

a Isolated yield. Compounds were purified by flash-chromatography (see experimental).

b The reaction was warmed up to -10 °C, and stirred 2hr at -10 °C before quenching.

CONFORMATIONAL ANALYSIS OF THE THIOESTER SILYLKETENE ACETALS AND TRANSITION STATE MODELS.

A "pinwheel" shape for the ground state conformers of silylketene acetals has recently been proposed.[24] In order to gain a deeper insight into the reaction mechanism we decided to employ theoretical methods (MNDO) to evaluate the ground state conformations of thioester silylketene acetals and to model the acyclic transition states. The calculations were performed on thioester silylketene acetals (2) and (4) by the MNDO-SCF method[25] (QCPE n.353). A full minimization of the geometries of these compounds was carried out by the DFP technique.[26] Selected values of the obtained geometrical parameters for the ground state conformations are reported in the table below.

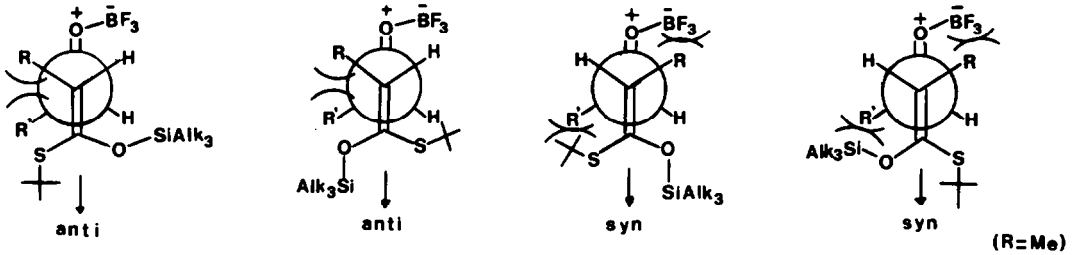
Table

	(2)	(4)		(2)	(4)
r C=C	1.363 Å	1.362 Å	ϑ C=C-Me	127.7°	127.5°
r C-Me	1.494 Å	1.495 Å	ϑ C=C-H	118.8°	118.5°
r C-S	1.724 Å	1.727 Å	ϑ C=C-S	121.8°	121.1°
r C-O	1.327 Å	1.325 Å	ϑ C=C-O	122.9°	124.0°
r S-CBu^t	1.785 Å	1.785 Å	ϑ C-O-Si	132.4°	132.8°
r O-Si	1.740 Å	1.740 Å	ϑ C-S-C	114.3°	113.4°
			ω C=C-O-Si	81.6°	109.1°
			ω C=C-S-C	110.3°	86.2°

(4) was calculated ($\Delta\Delta H_f$) to be 1.2 Kcal/mol more stable that (2).

The observed anti preference independent of the silyl ether geometry of this BF_3-OEt_2 catalyzed condensation is in accord with an acyclic extended transition state.[4,5c,6,15]

Three different interactions should be considered to explain the observed selectivity: the "gauche" steric interaction (R-R'), the "Lewis acid" interaction (R-BF_3), and the "pinwheel" steric interaction (R'-Bu^t or R'-SiAlk$_3$). On the assumption that the reaction starts with the coordination of the Lewis acidic boron to the aldehyde carbonyl group, the complexes shown in the figure should be formed with the dihedral angle φ(C-C=O-B)=180°.[27,28] The "gauche" steric repulsion between R and R', which disfavors the transition states leading to the anti isomer in related models,[29] is usually overwhelmed by the "Lewis acid" repulsion (R-BF_3), and the result is the normal, moderate anti-preference encountered in the Mukaiyama aldol reaction (2-4:1).[1,6]



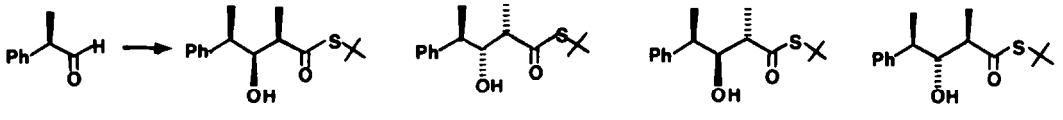
In our thioester chemistry, preliminary MNDO calculations suggest that the deviation from planarity of the bulky -Bu^t and -$SiAlk_3$ groups determines an increase of the C=C-R bond angle (~130°) due to the R-Bu^t or R-$SiAlk_3$ steric interaction. As a consequence the interaction between R and BF_3 in the transition states leading to the syn isomer becomes more important. Moreover the R-BF_3 Lewis acid interaction cannot be released by a rotation of the aldehyde because of the R'-$SiAlk_3$ (R'-Bu^t) "pinwheel" steric repulsion. The result is the observed dramatic enhancement of the selectivity (10-26:1 anti-syn).

Using ketene bis(trimethylsilyl)acetals, an inversion from the anti to the syn preference was reported when bulky substituents (R=Bu^t) were used in the silyl ether moiety.[3] According to our model this is explained by the "gauche" steric repulsion between R and R', which becomes determining. In our reaction, it is interesting to observe that using pivalaldehyde (R=Me; R'=Bu^t) the reaction product was obtained in a very low yield (Table 1, entry 9). In our model both the transition states leading to the syn and to the anti isomer are disfavored by the bulkiness of R', and the reaction is likely to become sluggish.

ADDITION TO CHIRAL ALDEHYDES. RESULTS AND DISCUSSION.

R,S-2-Phenylpropionaldehyde.

BF_3-Mediated enolsilane additions to 2-phenylpropionaldehyde are known to be highly diastereoface-selective in the Cram sense.[7,10c] 2-Phenylpropionaldehyde (5) is readily available, ideally in the resolved form,[30] and its phenyl group, after the condensation, can be easily converted (O_3,H_2O_2) to a carboxylic acid without eroding the stereointegrity of the α-chiral center.[10c] Using our thioester chemistry with aldehyde (5), it is possible to selectively establish three contiguous stereocenters with a single reaction (Table 2).

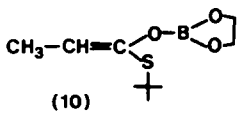


(5) (6) Cram-syn (7) antiCram-syn (8) Cram-anti (9) antiCram-anti

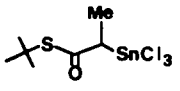
Table 2. Additions to 2-phenylpropionaldehyde.

Entry	Reagent	%Yield	Ratios (%)			
			(6)	(7)	(8)	(9)
1	(3)/BF_3-OEt_2	75	7.0	-	91.0	2.0
2	(10)	68	90.6	7.5	1.9	-
3	(11)	59	90.5	2.0	7.5	-

Using (3) and BF_3-OEt_2, the anti-syn ratio was 13:1 and the Cram-antiCram ratio was 49:1 (entry 1). Using enolborate (10)[15,19f,g] the syn-anti ratio was 52:1 and the Cram-antiCram ratio 12:1 (entry 2). By treating trimethylsilyl ketene acetals (2) or (4) with $SnCl_4$ in methylene chloride at -78 °C for 1 hr, the α-trichlorostannylthioester (11) was obtained in good yield. Following the transformation by ^{1}H-NMR (CD_2Cl_2, -50 °C), the vinyl proton of both (2) (5.16, q) and (4) (5.12, q) disappeared with the clean formation of (11) (4.48, q, J=7.81 Hz).[31] The α-stannylthioester reacted with 2-phenylpropionaldehyde to give a 12:1 syn-anti ratio and a 49:1 Cram-antiCram ratio (entry 3).



(10)



(11)

(S)(+) O-Benzyl lactic aldehyde.

$SnCl_4$ mediated aldol additions of thioester silylketene acetals to achiral aliphatic aldehydes are only slightly anti-selective (see, for example, Table 3, entries 1,2). On the contrary the additions to O-benzyl lactic aldehyde are highly selective: no Felkin-type product was obtained, and the syn-anti ratio was >30:1 (Table 4, entry 3).

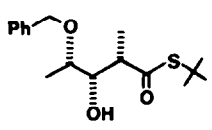
Table 3. Comparison data. Addition to achiral aldehydes.

Entry	Reagent	Aldehyde	%Yield	Syn-anti ratio
1	(4)/$SnCl_4$[a]	i-PrCHO	86	1 : 1.4
2	(2)/$SnCl_4$[a]	i-PrCHO	80	1 : 1.4
3	(11)[b]	i-PrCHO	45	72 : 1
4	(4)/Bu_4NF[c]	PhCHO	91	18 : 1
5	(2)/Bu_4NF[c]	PhCHO	42	1.3 : 1

a To a mixture of aldehyde (1.0 mol.equiv.) and silyl ether (1.5 mol.equiv.) in methylene chloride at -78 °C, $SnCl_4$ (1.0 mol.equiv.) was added. After 20 min at -78 °C the mixture was quenched and worked-up as usual.

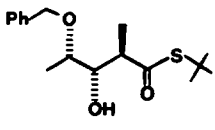
b $SnCl_4$ (1.0 mol.equiv.) was added to the silyl ether (2) or (4) (1.0 mol.equiv.) in methylene chloride at -78 °C. After 1 hr the aldehyde (1.0 mol.equiv.) was added. The mixture was slowly warmed up to 0 °C, quenched and worked-up as usual.

c To a solution of aldehyde (1.0 mol.equiv.) and silyl ether (1.5 mol.equiv.) in THF at -78 °C, nBu_4NF (0.06 mol.equiv.) was added. After 20 min at -78 °C, the mixture was quenched and worked-up as usual.



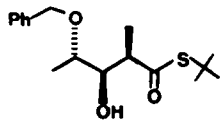
(12)

chelated-syn



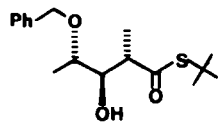
(13)

chelated-anti



(14)

Felkin-syn



(15)

Felkin-anti

Table 4. Additions to (S)(+)-O-benzyl lactic aldehyde.[a]

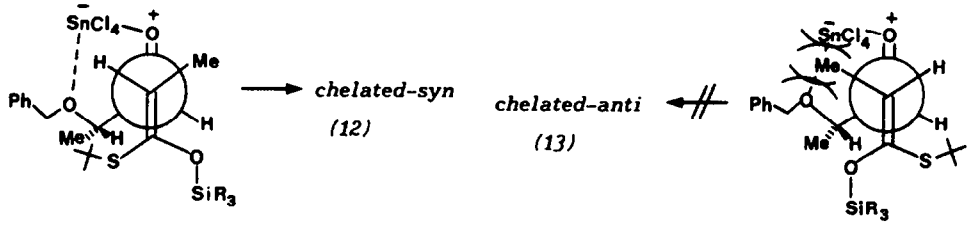
Entry	Reagent	%Yield[b]	Ratios (%) (12)	(13)	(14)	(15)
1	(4)/$SnCl_4$	90	95	5	-	-
2	(2)/$SnCl_4$	87	85	15	-	-
3	(3)/$SnCl_4$	89	97	3	-	-
4	(1)/$SnCl_4$	90	76	24	-	-
5	(4)/$TiCl_4$	85	94	6	-	-
6	(2)/$TiCl_4$	82	83	17	-	-
7	(11)	75	10	90	-	-
8	(4)/Bu_4NF	72	16	3	73	8
9	(2)/Bu_4NF	68	13	3	72	12
10	(4)/BF_3-OEt_2	57	6	22	12	60

a Prepared from (S)(+)-ethyl lactate according to the following references: K. Mislow,et al., J.Am.Chem.Soc., 1962, 84, 1940; C.H. Heathcock, et al., J.Org.Chem. 1981, 46, 2298.

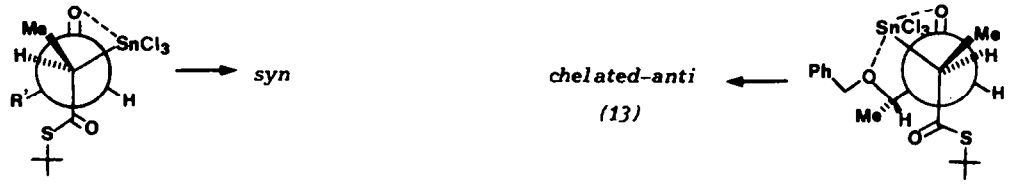
b Isolated yields. Compounds were purified by flash chromatography (see experimental)

A reversal of the internal selectivity (from anti to syn) determined by the relative stereoselection (chelation control) had already been observed for ketone enolsilylethers.[8,9]

In terms of the proposed acyclic extended transition state, the "Lewis acid" repulsion is here reversed because of the opposite coordination site of $SnCl_4$, and cooperates with the gauche steric repulsion to disfavor the transition state leading to the anti isomer.



On the contrary α-stannylthioester (11), which reacts with aliphatic aldehydes to give the syn adduct with excellent selectivity (72:1; Table 3, entry 3), gave with O-benzyl lactic aldehyde the chelated-anti product (13) as the major isomer (9:1; Table 4, entry 7). Assuming that the carbon-tin bond cleavage occurs with retention of stereochemistry, relative stereoselection (chelation) here again effectively controls internal stereoselection, as suggested by the transition state models shown below.

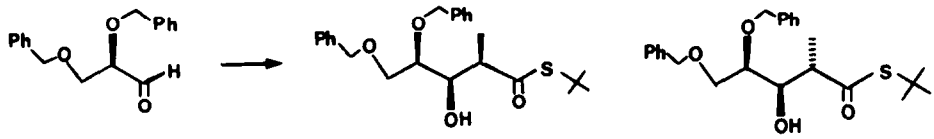


Selectively synthesizing the Felkin-type compounds (14) and (15) is more problematic: some success was obtained using a fluoride induced reaction to obtain the Felkin-syn adduct (14) (Table 4, entries 8,9)[12,32] and a BF_3-OEt_2-mediated reaction to give the Felkin-anti

adduct (15) (Table 4, entry 10).

(R)-2,3-O,O-dibenzyl glyceraldehyde.

The same kind of selectivity described above can be extended to α,β-dialkoxy aldehydes. Although 2,3-O,O-dibenzyl glyceraldehyde could in principle react through either the α- or β-chelated transition state,[33] the products derived from α-chelation (16,17) were obtained exclusively. The $SnCl_4$ promoted silylketene acetal (3) addition gave the α-chelated-syn compound (16) with excellent selectivity (>95:5), while the trichlorostannylthioester (11) gave the α-chelated-anti compound (17) as the major isomer (86:14) (Table 5).



(16) *(17)*

Table 5. Additions to (R)-2,3-O,O-dibenzyl glyceraldehyde.

Entry	Reagent	%Yield	Ratios (%)[a] (16)	(17)
1	(3)/SnCl4	75	>95	<5
2	(11)	80	14	86

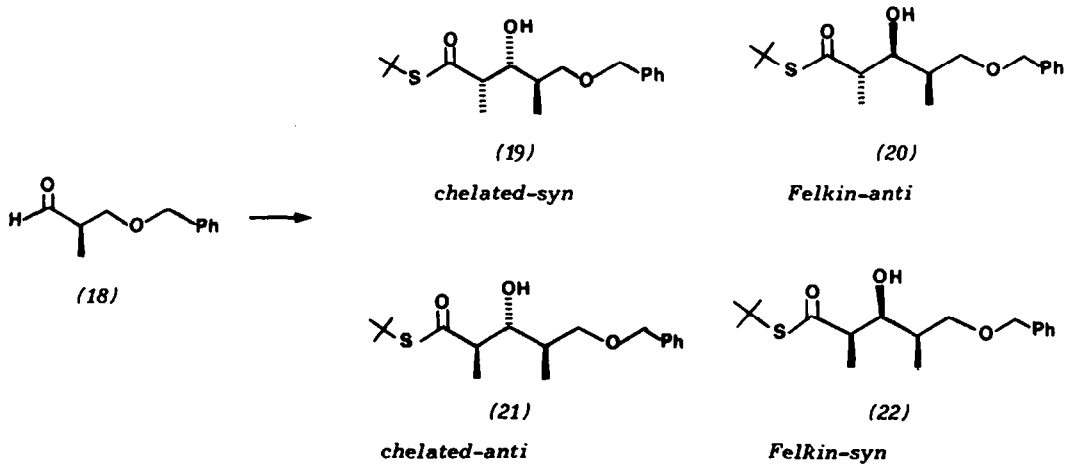
a Ratios were determined on the crude reaction mixtures by ^{13}C-NMR.

We had previously obtained the Felkin-type of addition with syn internal selectivity using the enolborate (10) and isopropylideneglyceraldehyde.[19g]

(R)(-)-3-benzyloxy-2-methylpropionaldehyde.

Due to its structural features (chirality and the possibility of β-chelation) 3-benzyloxy-2-methylpropionaldehyde (18) has been extensively used in organic synthesis, and its optically active forms are important intermediates in the total synthesis of natural products. Both enantiomers have usually been prepared from β-hydroxyisobutyric acid, and more recently by asymmetric synthesis.[17]

Reaction of (18) with the thioester ketene acetal (1) or (3) and $TiCl_4$ (CH_2Cl_2,-78°C) gave the chelated-syn compound (19) in 67% isolated yield and >99% stereoselectivity (Table 5, entries 1,2).



(18)

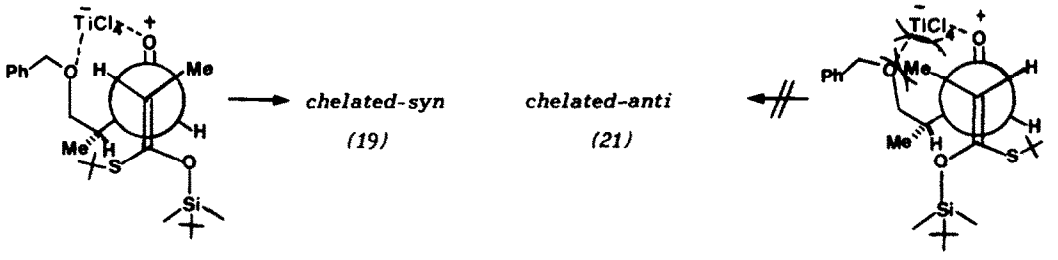
(19) *chelated-syn*

(20) *Felkin-anti*

(21) *chelated-anti*

(22) *Felkin-syn*

As shown by the transition state models depicted below, the same kind of steric interactions discussed above for O-benzyl lactic aldehyde and $SnCl_4$ are responsible for the exclusive formation of the chelated-syn isomer.



Using a non-chelating Lewis acid (BF_3-OEt_2) three stereoisomers were obtained (Table 5, entries 5,6), and the more predominant was characterized as the Felkin-anti compound (20).

Using optically active aldehyde (R)(-)-(18), racemization during the Lewis acid mediated additions mentioned above was very small (<5%),[17] and therefore those reactions appear to be very useful for the synthesis of polyketide-derived natural products.

Table 6. Additions to 3-benzyloxy-2-methylpropionaldehyde.

Entry	Reagent	%Yield[a]	Ratios (%) (19)	(20)	(21)	(22)
1	(3)/$TiCl_4$	67	>99	-	<1	-
2	(1)/$TiCl_4$	65	>99	-	<1	-
3	(4)/$SnCl_4$	65	98	-	2	-
4	(2)/$SnCl_4$	69	49	51	3	-
5	(3)/2BF_3OEt_2	75	-	77	9	14
6	(1)/2BF_3OEt_2	71	-	77	7	16

a Isolated yields. Compounds were purified by flash-chromatography (see experimental).

ADDITIONS TO CHIRAL ALDEHYDES. CONFORMATIONAL ANALYSIS AND DISCUSSION OF THE DIASTEREOFACE SELECTIVITY.

We ran MM2 calculations on the chiral aldehydes in order to determine the ground state conformers.[34]

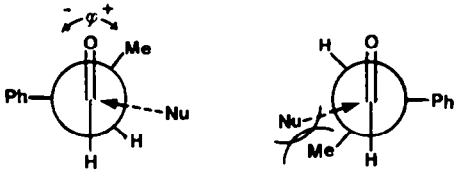
In light of the rapidity of the aldol condensation it is not unreasonable to assume a very early transition state so that the reaction stereochemistry is mainly controlled by the ground state conformers of the aldehyde. Our calculations support this assumption only in a qualitative sense: ground state conformational analysis of the chiral aldehydes can be useful to predict the diastereofacial preference but not the degree of preference. Even if the aldol reaction is diffusion controlled, and this would represent the maximum possible rate of the reaction, equilibration between the conformations should occur faster than the aldol condensation since the rotational barriers among the various conformations of the starting chiral aldehyde are relatively small,[35] and thus the Curtin-Hammett conditions are satisfied.[36] Therefore no quantitative prediction of the diastereofacial preference can be made using the energy difference among the ground state conformers.[37]

The results with 2-phenylpropionaldehyde are shown in Table 7.

Table 7. Ground state conformers of 2-phenylpropionaldehyde.

Conformer	O=C-C-Me Dihedral Angle ($\varphi°$)	Excess MM2-Energy (Kcal/mol)
A	0	0.0
B	-132	1.1
C	+144	1.7

The two lowest energy conformers (A,B) give rise to the Felkin transition state (D) and to the anti-Felkin transition state (E) respectively.[38] The degree of diastereofacial preference reflects the preference of D over E because of the Nu-CH_3 interaction.



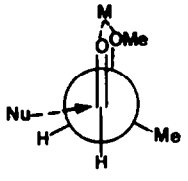
D ← A ⇌ B → E

This steric interaction is likely to become worse in the case of the Lewis-acid catalyzed reactions because of the change of the nucleophile trajectory (nucleophile closer to Me)[7] and the ratios are enhanced from 3-4:1 (lithium enolates)[39] to 10-50:1.

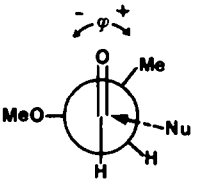
MM2 Calculations on O-methyl lactic aldehyde are shown in Table 8.

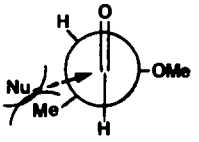
Table 8. Ground state conformers of O-methyl lactic aldehyde.

Conformer	O=C-C-Me Dihedral Angle ($\varphi°$)	Csp2-C-O-Me Dihedral Angle ($\omega°$)	Excess MM2 Energy (Kcal/mol)
A	-3	-168	0.0
B	-129	-75	0.2
C	-123	-167	0.7
D	-2	-88	0.9
E	+2	+74	1.1



F





G ← (A,D,E) ⇌ (B,C) → H

In this case there are two ground state conformations with very little energy difference (A,B). The first one is close to the reactive conformation (transition state G) which accounts for the preponderance of the Felkin-type of addition, while the second one is close to the transition state H which accounts for the anti-Felkin type of addition.[38] Our experimental results (Table 4, entries 8,9) for the fluoride induced condensations show a 4-5:1 preference for the Felkin-type product derived from transition state G. A 4-5:1 Felkin-type of addition is also tipical of lithium enolates.[40] In the case of the lithium enolates the minor isomer could possibly derive from the chelated transition state F (M=Li), while in the case of the Bu_4NF-catalyzed reaction this explanation is very unlikely.

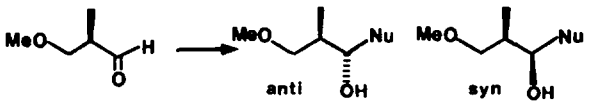
The best selectivity is obtained when a chelating Lewis acid is used ($SnCl_4$ slightly better than $TiCl_4$; Table 4, entries 1-7): in this case the reaction proceeds through the transition state F wich does not resemble any stable conformer.

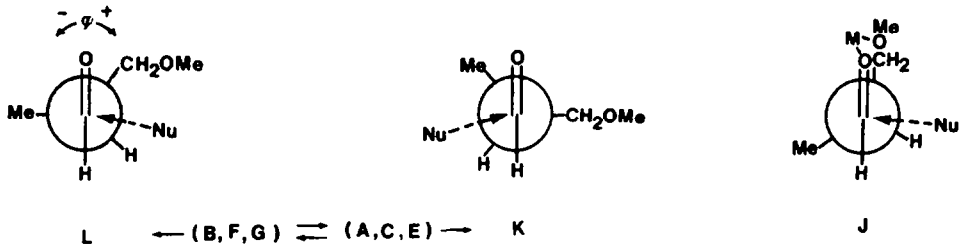
Conformational analysis for the α-methyl-β-alkoxyaldehyde is more complex, due to the presence of three dihedral angles (1728 starting conformations, using a 30° resolution). The results are shown in Table 9.

Table 9. Ground state conformers of 3-methoxy-2-methylpropionaldehyde.

Conformer	Dihedral Angles			Excess MM2-Energy
	O=C-C-Me (φ°)	Csp2-CH-CH_2-O (ω°)	CH-CH_2-O-CH_3 (ψ°)	(Kcal/mol)
A	0	+59	+180	0.0
B	-127	+175	+180	0.5
C	+9	-58	+180	0.6
D	+124	-60	+180	1.0
E	+1	+173	+180	1.1
F	-141	-68	+180	1.2
G	-116	+67	+180	1.3
H	+107	+55	+180	1.3
I	+121	+175	+180	1.9

The methyl-eclipsed conformations (A,C,E) should lead to the syn product through the transition state K, while the CH_2OMe-eclipsed conformations (B,F,G) should lead to the anti product through transition state L.

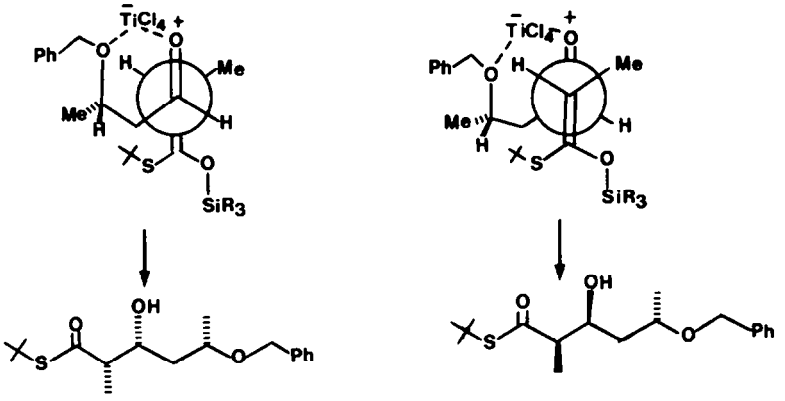




L ⟵ (B,F,G) ⇌ (A,C,E) ⟶ K J

Experimentally there is no precise trend: depending on the particular nucleophile (various lithium enolates) the anti-syn ratios ranged from 2-3:1 to 1:3.[2] This is probably due to the fact that both the transition states have Nu-H interactions and therefore there is no clear preference for one or the other.

Using strongly chelating metals the preference for the anti isomer becomes very clear, due to the metal coordination to the carbonyl- and to the ether-oxygen (transition state J). $TiCl_4$ proved better than $SnCl_4$ to determine high stereoselectivities (Table 6, entries 1-4). It is interesting to observe that using 3-benzyloxy-3-methylpropionaldehyde[41] the $TiCl_4$-mediated additions of thioester silylketene acetals (1-4) were stereorandom. Although chelation should still effectively control internal stereoselection (syn) the chiral center is too remote here to control relative stereoselectivity (see below).



EXPERIMENTAL.

Synthesis of Z-silylketene acetals (1) and (2).- To a solution of LDA (1.1 mmol) in dry THF (5 ml) at -78°C tButyl thiopropionate (1 mmol) was added dropwise under nitrogen with stirring. After 30 min Me_2tBuSiOTf or Me_3SiCl (1.1 mmol) was added, then the mixture was warmed to room temperature, diluted with pentane and quenched with pH-7 phosphate buffer. The phases were separated and the organic layer washed twice with pH-7 phosphate buffer and dried with Na_2SO_4. The solvent was evaporated under reduced pressure to give (1) and (2) respectively as a 95:5 or a 90:10 Z-E mixture.

^{1}H NMR (80MHz, $CDCl_3$) δ

(1): 0.15 (6H, s, Me_2Si), 0.95 (9H, s, tBuSi), 1.30 (9H, s, tBuS), 1.65 (3H, d, J=6.7 Hz, MeC=), 5.22 (1H, q, J=6.7 Hz, HC=).

(2): 0.20 (9H, s, Me_3Si), 1.35 (9H, s, tBuS), 1.72 (3H, d, J=6.8 Hz, MeC=), 5.25 (1H, q, J= 6.8 Hz, HC=).

Synthesis of E-silylketene acetals (3) and (4).- To a solution of LDA (1.1 mmol) in 75:25 THF:HMPA mixture (5 ml) at -78°C tButyl thiopropionate (1 mmol) was added dropwise under nitrogen with stirring. After 30 min Me_2tBuSiCl or Me_3SiCl (1.1 mmol) was added. The mixture was warmed to room temperature, diluted with pentane, quenched and worked-up as described for the synthesis of (1) and (2). Silylketene acetals (3) and (4) were obtained respectively as a 95:5 or a 93:7 E-Z mixture.

^{1}H NMR (80 MHz, $CDCl_3$) δ

(3): 0.18 (6H, s, Me_2Si), 0.95 (9H, s, tBuSi), 1.30 (9H, s, tBuS), 1.60 (3H, d, J=6.8 Hz, MeC=), 5.22 (1H, q, J=6.8 Hz, HC=).

(4): 0.20 (9H, s, Me_3Si), 1.30 (9H, s, tBuS), 1.58 (3H, d, J=6.9 Hz, MeC=), 5.25 (1H, q, J= 6.9 Hz, HC=).

General procedure for the aldol condensations with achiral aldehydes.- To a mixture of 1.0 mol.equiv. of aldehyde and 1.5 mol.equiv. of silylketene acetal in CH_2Cl_2 at -78°C, BF_3OEt_2 (1.0 mol.equiv.) was added dropwise. After 30 min at -78°C the reaction was quenched with

pH-7 phosphate buffer and worked-up as usual. The crude product was analyzed by ^{1}H and ^{13}C NMR spectroscopy and by HPLC (silica gel 10 μm, 4.6X250 mm column) or capillary VPC (OV1 column) for determining ratios. The compounds were then isolated by flash chromatography for determining yields.

Reaction with Benzaldehyde.- The ratios were determined by ^{1}H NMR and by HPLC. δ ($CDCl_3$): 4.75 (CHO, anti, d, J=8 Hz); 5.05 (CHO, syn, d, J=3.4 Hz). HPLC eluant 96:4 n-hexane:AcOEt, 2 ml/min: syn 5.9 min, anti 7.9 min.

Reaction with $n\text{-}C_5H_{11}CHO$. The ratios were determined by ^{1}H NMR and by capillary VPC (80-130°C). δ ($CDCl_3$): 3.60 (CHO, anti, m); 3.85 (CHO, syn, m).

Reaction with iPrCHO.- The ratios were determined by ^{1}H NMR and by capillary VPC (60 - 140°C). δ ($CDCl_3$): 3.30 (CHO, anti, t, J=7 Hz); 3.50 (CHO, syn, dd, J=3.7 Hz, J=7.5 Hz).

Reaction with Cyclohexylcarboxyaldehyde.- Ratios were determined by ^{1}H NMR and capillary VPC (80-140°C). δ ($CDCl_3$): 3.30 (CHO, anti, m); 3.60 (CHO, syn, m).

Reaction with tBuCHO.- Ratios were determined by ^{1}H NMR and capillary VPC (60-130°C). δ ($CDCl_3$): 3.14 (CHO, anti, d, J=2.0 Hz); 3.58 (CHO, syn, d, J=3.6 Hz).

Reaction with cinnamic aldehyde.- Ratios were determined by ^{1}H NMR and by HPLC. δ ($CDCl_3$): 4.40 (CHO, anti, m); 4.55 (CHO, syn, m). HPLC eluant 98:2 n-hexane:AcOEt, 3.5 ml/min: syn 10.9 min, anti 12.9 min.

Reactions with 2-Phenyl-propionaldehyde. (Table 2).

Entry 1.- The BF_3OEt_2 mediated enolsilane addition was conducted as described above. Diastereoisomeric ratios were determined by HPLC and ^{13}C NMR. HPLC eluant 98:2 n-hexane: AcOEt, 5 ml/min: (6) 3.7 min; (8) 2.7 min; (9) 2.5 min.

Entry 2.- To a stirred solution of ECB (see Ref. 19g) (1.5 mmol) and DPEA (1.6 mmol) in CH_2Cl_2 (3 ml), at 0°C, under nitrogen, the thioester (1.5 mmol) was added dropwise. The mixture was stirred at +5°C for 30 min, then cooled to -78°C and the aldehyde (1 mmol) was added at-78°C. The reaction was stirred at that temperature for 30 min, slowly warmed up to 0°C, and then quenched by adding pH-7 phosphate buffer. The product was extracted into CH_2Cl_2, the extracts were dried (Na_2SO_4) and evaporated. Ratios were determined on the crude reaction mixture by HPLC and ^{13}C NMR. HPLC eluant 98:2 n-hexane:AcOEt, 5 ml/min: (6) 3.7 min, (7) 4.8 min, (8) 2.7 min.

Entry 3.- A solution of trimethylsilylketene acetal (2) or (4) (1 mmol) in dry CH_2Cl_2 (2 ml) at -78°C under nitrogen was treated with a 1M solution of $SnCl_4$ in CH_2Cl_2 (1 ml). The mixture was stirred for 1 hr, then 2-phenyl propionaldehyde (0.8 mmol) was added. After 2 hr at -78°C the reaction was quenched with 1M KOH solution and worked-up as usual. Ratios were determined on the crude reaction mixture by HPLC and ^{13}C NMR. HPLC eluant 98:2 n-hexane:AcOEt, 5 ml/min: (6) 3.7 min, (7) 4.8 min, (8) 2.7 min.

Aldols (6), (7) and (8) were isolated by flash chromatography (9:1 n-hexane:AcOEt) and their configuration was assigned by reduction ($LiAlH_4$, Et_2O) to the corresponding diols (see Ref. 42).

^{13}C NMR ($CDCl_3$) selected values δ

(6): 10.9, 18.0, 29.7, 42.9, 47.9, 50.4, 76.1.

(7): 11.4, 18.5, 29.7, 43.1, 51.2, 75.7.

(8): 16.5, 29.7, 44.1, 48.2, 50.3, 79.1.

Reactions with (S)-(+)-O-Benzyl-lacticaldehyde. (Table 4).

Entries 1-6.- To a solution of the aldehyde (1 mmol) in CH_2Cl_2 (2 ml) a 1M solution of Lewis acid in CH_2Cl_2 (1 mmol) was added at -78°C under nitrogen. After 5 min the appropriate silylketene acetal was added dropwise and the resulting solution was stirred for 20 min at -78°C. The reaction was quenched with 0.5M KOH solution and worked-up as usual.

Entry 7.- The α-trichlorostannyl-thioester (11) (1.5 mmol) was generated as described above (Table 2, Entry 3) and the aldehyde (1 mmol) was added at -78°C. The temperature was allowed to raise to -20°C, then the reaction was quenched with a 0.5M KOH solution and worked-up as usual.

Entries 8 and 9.- To a solution of the aldehyde (1 mmol) and silylketene acetal (1.5 mmol) in dry THF (2 ml) at -78°C, Bu_4NF (0.06 mmol) was added. After 20 min at -78°C the mixture was quenched with 10% HCl solution and worked-up as usual.

Entry 10.- The BF_3OEt_2 mediated enolsilane addition was carried out as described for the achiral aldehydes.

Diastereomeric ratios were determined on the crude reaction mixtures by capillary VPC (145-165°C) and ^{13}C NMR. Configurational assignments were made using ^{13}C NMR data as delineated by Reetz.[9]

^{13}C NMR ($CDCl_3$) selected values δ

(12): 14.1, 16.1, 29.7, 47.6, 51.7, 71.0, 75.1, 76.1, 202.7.

(13): 14.9, 15.8, 29.7, 48.0, 51.3, 70.6, 74.0, 77.1, 203.5.

(14): 12.9, 14.8, 29.7, 47.9, 49.9, 70.4, 74.1, 74.6, 202.8.

(15): 15.0, 15.6, 29.7, 48.1, 48.7, 70.9, 76.4, 76.7, 202.8.

Reaction with (R)-2,3-O,O-dibenzyl Glyceraldehide. (Table 5).

Entry 1.- To a solution of the aldehyde (1 mmol) in CH_2Cl_2 (2 ml) a 1M solution of $SnCl_4$ was added at -78°C under nitrogen. After 2 min silylketene acetal (3) (1.8 mmol) was added and the solution stirred at -78°C for 45 min. The reaction was quenched with 0.5M KOH solution and worked-up as usual.

Entry 2.- The α-trichlorostannyl-thioester (11) (1.5 mmol) was generated as described above (Table 2. Entry 3) and the aldehyde (1 mmol) was added at -78°C. The reaction was warmed to -20°C and, after 1 hr, quenched with a 0.5M KOH solution and worked-up as usual.

Diastereoisomeric ratios were determined on the crude reaction mixtures by ^1H and ^{13}C NMR. The isomers were isolated by flash chromatography (80·20 n-hexane:AcOEt) and characterized by ^1H and ^{13}C NMR.

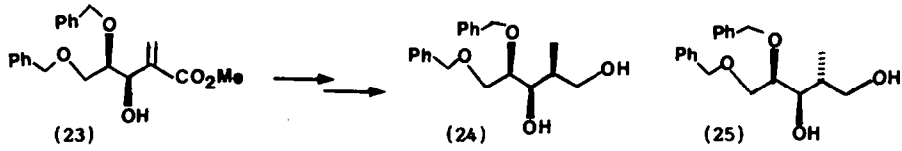
(16) ^1H NMR ($CDCl_3$): 1.3 (3H, d, J=6.7 Hz), 1.48 (9H, s), 2.90 (1H, dq, J=6.7 Hz, J=6.7 Hz), 3.0 (1H, bs), 3.80-4.10 (4H, m), 4.55 (2H, s), 4.60-4.85 (2H, AB system), 7.30 (10H, s).

^{13}C NMR ($CDCl_3$), selected values: 14.6, 29.7, 47.9, 51.8, 70.8, 73.0, 73.3, 77.8.

(17) ^1H NMR ($CDCl_3$): δ 1.05 (3H, d, J=6.7 Hz), 1.45 (9H, s), 2.85 (1H, dq, J=6.7 Hz), 3.50-4.00 (4H, m), 4.55 (2H, s), 4.50-4.90 (2H, AB system), 7.35 (10H, s).

^{13}C NMR ($CDCl_3$), selected values: 14.8, 29.7, 47.9, 51.4, 70.5, 72.4, 73.4, 74.0, 76.7.

Configurational assignments were made as follows: α-methylene ester (23) was synthesized and its 3,4-syn configuration was assigned on the basis of its ^{13}C NMR spectrum (see Ref. 43).



(23) was then converted into the diols (24) and (25) whose 2,3 relative configuration was established by ^{13}C NMR (see Ref. 44).

Reduction (Raney-Ni / H_2) of (16) and (17) gave respectively diol (24) and (25).

(23) ^1H NMR ($CDCl_3$): δ 3.14 (1H, d, J=7.0 Hz, exchangeable), 3.67 (3H, s), 3.60-3.90 (3H, m) 4.53-4.67 (5H, m), 5.96 (1H, t, J=1.3 Hz), 6.33 (1H, m), 7.30 (10H, s).

^{13}C NMR ($CDCl_3$), selected values: 51.5, 70.6, 70.8, 73.2, 73.3, 78.5, 126.0, 137.9, 140.2.

(24) ^1H NMR ($CDCl_3/D_2O$): δ 0.95 (3H, d, J=6.7 Hz), 1.60-2.00 (1H, m), 3.55-3.90 (6H, m), 4.55 (2H, s), 4.50-4.90 (2H, AB system), 7.30 (10H, s).

^{13}C NMR ($CDCl_3$), selected values: 10.4, 37.0, 66.5, 70.0, 72.7, 73.36, 73.44, 79.3.

(25) ^1H NMR ($CDCl_3/D_2O$): δ 0.78 (3H, d, J=6.7 Hz), 1.65-2.15 (1H, m), 3.50-3.75 (6H, m), 4.55 (2H, s), 4.48-4.88 (2H, AB system), 7.30 (10H, s).

^{13}C NMR ($CDCl_3$), selected values: 13.9, 37.0, 67.0, 70.0, 70.5, 72.5, 73.5.

Reactions with (R)-(-)-3-Benzyloxy-2-Methyl propionaldehyde. (Table 6).

Entries 1-4.- The reactions were carried out as described for lactic aldehyde (Table 4. Entries 1-6).

Entries 5-6.- BF_3OEt_2 (2.0 mmol) was added dropwise to a mixture of aldehyde (18) (1 mmol) and silylketene acetal (1.5 mmol) at -78°C in CH_2Cl_2. After 2 hr at -78°C the mixture was quenched with pH-7 phosphate buffer and worked-up as usual.

Diastereomeric ratios were determined by capillary VPC (155-175°C) and by ^{13}C NMR on the crude reaction mixtures. The isomers were separated by flash chromatography (95:5 benzene: Et_2O) and characterized by ^1H and ^{13}C NMR.

(19) ^1H NMR ($CDCl_3$): δ 0.95 (3H, d, J=7 Hz), 1.20 (3H, d, J=7 Hz), 1.45 (9H, s), 1.65-2.00 (1H, m), 2.65 (1H, dq, J=7 Hz, J=4 Hz), 3.30-3.95 (4H, m), 4.50 (2H, s), 7.30 (5H,s).

^{13}C NMR ($CDCl_3$), selected values: 11.6, 14.5, 29.7, 36.0, 47.7, 51.6, 73.3, 73.5, 75.5.

(20) ^1H NMR ($CDCl_3$): δ 0.95 (3H, d, J=6.7 Hz), 1.20 (3H, d, J=7.5 Hz), 1.45 (9H, s), 1.65-2.10 (1H, m), 2.68 (1H, dq, J=7.5 Hz, J=8.5 Hz), 2.75 (1H, bs), 3.40-3.60 (2H, m), 3.95 (1H, dd,J=8.5 Hz, J=2.7 Hz), 4.50 (2H, s), 7.30 (5H, s).

^{13}C NMR ($CDCl_3$) selected values: 10.1, 15.2, 29.8, 35.6, 48.0, 52.0, 73.4, 74.5, 74.9.

(21) ^{13}C NMR ($CDCl_3$), selected values: 11.3, 14.2, 29.7, 35.9, 47.9, 51.9, 73.3, 74.8, 74.9.

(22) ^{13}C NMR ($CDCl_3$), selected values: 15.6, 36.8, 48.2, 51.4, 72.8, 73.2, 73.7.

Aldols (19), (20) and (21) were separately reduced (Raney-Ni / H_2) and the resulting diols were characterized by ^1H NMR (see Ref. 45).

Diol (26) was obtained from (19).

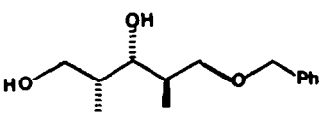
(26) ^1H NMR (C_6D_6/D_2O): δ 0.58 (3H, d, J=6.9 Hz), 1.0 (3H, d, J=6.9 Hz), 1.30-2.10 (2H, m), 3.25-3.40 (2H, m), 3.62-3.75 (3H, m), 4.20 (2H, s), 7.20 (5H, s).

Diol (27) was obtained from (20).

(27) ^1H NMR (C_6D_6/D_2O): δ 0.75 (3H, d, J=6.9 Hz), 0.98 (3H, d, J=7.5 Hz), 1.55-2.15 (2H, m), 3.35-3.78 (5H, m), 4.50 (2H, s), 7.30 (5H, s).

Diol (28) was obtained from (21)

(28) ^{1}*H NMR* (C_6D_6/D_2O): *δ 1.00 (3H, d. J=6.6 Hz), 1.09 (3H, d, J=6.6 Hz), 1.60-2.10 (2H, m), 3.28 (2H, d, J=5.3 Hz), 3.43 (2H, d, J=5.3 Hz), 3.73 (1H, t, J= 5.3 Hz), 4.27 (2H, s), 7.30 (5H, s).*



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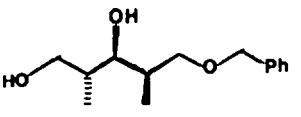

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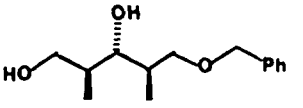

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