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Asymmetric Mukaiyama Aldol Coupling Between *Anti* α-Methyl-β-Hydroxy Enol Silanes and Propanal Catalyzed by Chiral Binaphthol-Titanium Complex

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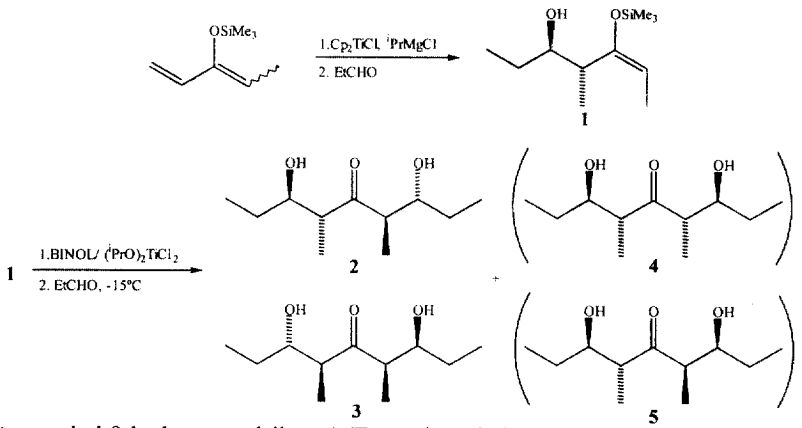
Abstract : In the presence of BINOL-Ti complex as a chiral promoter, the Mukaiyama aldol addition of racemic *anti* α-methyl-β-hydroxy enol silanes to propanal gives dihydroxy ketones bearing four stereocenters with good de and ee up to 50%. The major *anti* diastereoselectivity is in opposite to the *syn* diastereoselectivity obtained using $TiCl_4$ and HO-protected enol silanes.

Recently, we have demonstrated that the combination of allyltitanation and Mukaiyama aldol coupling provide a short entry to the racemic polypropionate five carbon stereosequences[1].
However, polypropionate-derived natural products are optically active molecules[2], and the methods are needed which allow for the preparation of enantiopure products. Our strategy could be applied to the construction of the polypropionate chirons by introducing the asymmetric Mukaiyama aldol step : (i) using the preformed optically active α-methyl-β-hydroxy enolsilanes[3], (ii) starting from racemic functionalized enolsilanes of defined stereogenicity, and employing a chiral Lewis acid as catalyst. Reported herein are attemps to achieve diastereo- and enantioselection in the above reaction, using the catalytic amount of chiral binaphthol-derived titanium dichloride (BINOL-$TiCl_2$)[4].



Racemic *anti* α-methyl β-hydroxy enolsilane **1** (**E**, *anti*/*syn*=95/5) was prepared as previously by allyltitanation reaction[1]. Compound **1** was then used directly, without protection of the hydroxyl group[5], in the further Mukaiyama step. In a representative procedure, to a mixture of 4Å MS powder (1g) and binaphthol (0,11 mmol) in CH_2Cl_2 (7 ml) was added $(^iPrO)_2TiCl_2$ (0,10 mmol) at r.t. under Ar. The mixture was stirred during 2h and cooled to -15°C. Thereafter propanal (1.1 mmol) was successively added followed by a dichloromethane solution (10 ml) of enolsilane **1** (1.0 mmol). The mixture was stirred at -15°C until **1** has disappeared (TLC monitoring). After brine quenching, the aqueous layer was extracted with CH_2Cl_2 (3×100 ml). Separation by

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flash chromatography (hexane/ether=1/2) afforded two diastereomeric dihydroxy ketones **2** and **3**. No traces of diastereomers **4** and **5** were detected by ^1H and GC-MS analyses of crude mixtures. Binaphthol can be easily recovered from column in >80% yield without racemization.

The unique formation of **2** and **3** is noteworthy. Thus, the diastereoselectivity is here opposite (and *complementary*) to that observed for the reactions involving $TiCl_4$, in which only the stereoisomers **4** and **5** were formed with highly favored *syn* stereoselectivity[1]. As depicted in table 1, the **2** (*anti*) / **3** (*syn*) ratio depends on the configuration of BINOL. The highest **2/3** value=75:25 is achieved when the complex prepared from (S)-binaphthol was employed, whereas the intermediate **2/3** value=67:33 was observed using a racemic ligand. Also the ee varies markedly with the configuration of the ligand. As for the diastereoselection, the diastereofacial selectivity achieves the best values (up to 50%) for the (S)-binaphthol as well.

Table 1:

BINOL	*2(%)*	*3(%)*
S	75 (ee : 50%)[a,b]	25 (ee : 30%)[a,c]
R	58 (ee : 20%)[a,b]	42 (ee : 6%)[a,c]
S+R	67	33

[a] Determined by analysis of NMR spectra of the (S)-(-)-and (R)-(+)-MTPA ester derivatives.
[b] Configuration of the major enantiomer : 3R,4R,6R,7R.
[c] Configuration of the major enantiomer : 3S,4S,6R,7S.

The stereochemical outcome of the reaction reported here is not entirely clear at present. The changeover of the diastereoselection, relatively to the $TiCl_4$-promoted Mukaiyama coupling of the hydroxy-protected enolsilanes, can be rationalized, however by an « open transition state », that could involve the chelation-controlled (synclinal) geometry[6][2]. Further studies are in progress in the hope of clarifying and improving simple and diastereofacial stereoselectivities.

References :

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[3] Lefranc, H. ; Szymoniak, J. ; Tréma, R. ;Moïse, C., Synth. Commun. 1997 ; 27: 1689-1695.

[4] This derivative has been succesfully used to catalyze [4+2] cycloadditions, ene reactions, additions of allylmetals to the carbonyl compounds, and some Mukaiyama reactions ; Mikami, K.; Motoyama, Y.;Terada, M., J. Am. Chem. Soc. 1994; 116: 2812-2820; Mikami, K; Terada, M.; Nakai, T., J. Am. Chem. Soc. 1990; 112 : 3949-3954; Mukaiyama, T.; Uchiro, H. ; Shiina, I.; Kobayashi, S., Chem. Lett. 1990 ; 1019-1022.

[5] The protection of the OH group is essential, using $TiCl_4$ as catalyst ; see [1].

[6] An open transition structure with antiperiplanar geometry was generally postulated for the Lewis acid-mediated Mukaiyama aldol reaction : see [1], Danda , H. ; Hansen, M.M. ; Heathcock,C.H. J. Org. Chem. 1990; 55: 173.

[1] Spectral data of **2** and **3** : **2** : ^1H NMR ($CDCl_3$) δ 0.96 (t, J=7.3 Hz, 3H), 1.08 (d, J=7.1 Hz, 3H), 1.4-1.6 (m, 2H), 2.71 (pseudoquintet, J=7.3 Hz, 1H), 2.85 (br.s., D_2O exchangeable), 3.66 (ddd, J=3.1, 7.1, 7.1 Hz) : ^{13}C NMR ($CDCl_3$) δ 9.7, 13.9, 27.2, 50.9, 74.5, 219.6; MS m/z 202 (M^+, 10), 173 (14), 144 (25), 126 (8), 115 (100), 99 (23), 86 (53), 70 (70), 57 (100). Anal. Calcd for $C_{11}H_{22}O_3$: C, 65.30 ; H, 10.97. Found C, 65.37 ; H, 10.83. **3** : ^1H NMR ($CDCl_3$) δ 0.94 (t, J=7.3 Hz, 3H), 0.97 (t, J=7.3 Hz, 3H), 1.10 (d, J=7.1 Hz, 3H), 1.12 (d, J=7.3 Hz, 3H), 1.3-1.6 (m, 4H), 2.66 (dq, J=3.0, 7.4 Hz, 1H), 2.80 (pseudoquintet, J=7.1 Hz, 1H), 3.64 (ddd, J=3.6, 7.5, 7.5 Hz,1H), 3.80 (m, 1H) : ^{13}C NMR ($CDCl_3$) δ 9.2, 9.8, 10.5, 14.3, 27.0, 27.4, 49.4, 49.8, 72.7, 74.9, 221.3 ; MS m/z 203(M+1, 50), 173 (6), 144 (40), 126 (6), 115 (100), 97 (23), 86 (53), 70 (50), 57 (68). Anal. Calcd for $C_{11}H_{22}O_3$: C, 65.30 ; H, 10.97. Found C, 65.79 ; H, 11.06.The stereochemical asignement of **2** and **3** was based on the ^1H and ^{13}C NMR data of the corresponding triols (DIBALH reduction). The absolute configurations and ee of **2** and **3** (Table 1) were determined by Mosher's method, using ^1H and ^{19}F NMR resonances of the (S)- and (R)-MTPA esters derivatives.

[2] Also the diastereofacial selectivity for the major *anti* isomer is consistent with the chelation-controlled transition structure.