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Addition of Chiral β-Hydroxy (Protected) Enol Silanes to Benzaldehyde Dimethyl Acetal : Access to Polypropionate Five-Carbon Stereosequences

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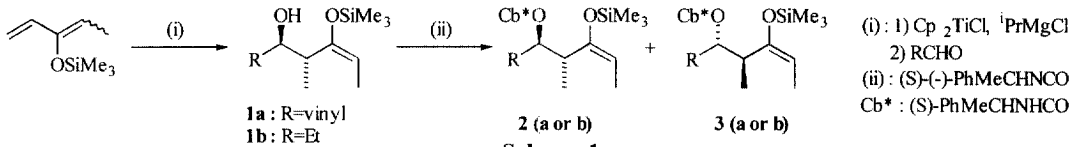
Abstract : The title enol silanes react with benzaldehyde dimethyl acetal to give dihydroxy (protected) ketones with good to excellent de and enantiocontrol. Further DIBALH reduction affords stereoselectively (de=95%) polypropionate chirons.

In the preceding letter in this issue we reported on our attempts to synthesize polypropionate chirons by the allyltitanation-Mukaiyama aldol sequence. Thus, the racemic α-methyl-β-hydroxy enol silanes obtained in the allyltitanation reaction [1,2], undergo BINOL-$TiCl_2$ catalyzed Mukaiyama aldol coupling to give chiral dihydroxy ketones bearing four stereocenters. In the complementary approach reported in this letter, the asymmetric aldol-type reaction was performed using enantiopure α-methyl-β-hydroxy (carbamate protected) enol silanes and an acetal as substrates, and TMSOTf as catalyst.

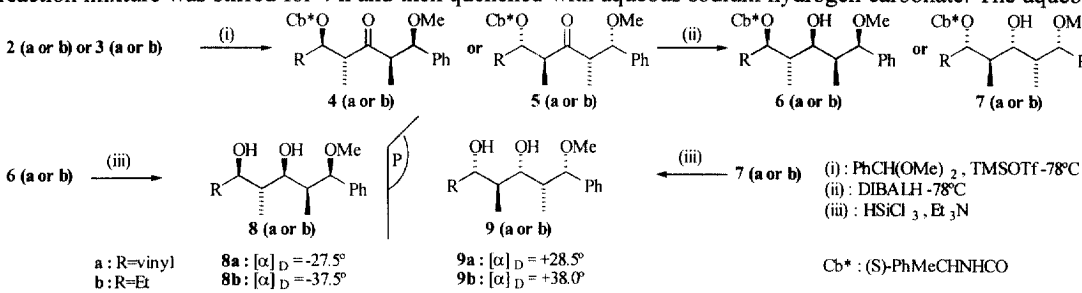


1a : R=vinyl
1b : R=Et

2 (a or b) **3 (a or b)**

Scheme 1

The starting chiral hydroxy (carbamate protected) enol silanes **2** and **3** were obtained by resolving the racemic allyltitanation products (**1**) with the aim of an chiral isocyanate (Scheme 1) [3]. The absolute configuration of each protected chiral enol silanes has been well established in comparison with the (4R,5S) sitophilure and its stereoisomers [4]. The diastereomers **2** and **3** were then reacted with benzaldehyde dimethyl acetal to afford the OH-double protected dihydroxy ketones **4** and **5** (Scheme 2). In a typical experiment to a stirred solution of **2a** (0.3 mmol) in 5 ml of anhydrous CH_2Cl_2 was added benzaldehyde dimethyl acetal (1.0 mmol, about 0.15 ml). After the mixture was cooled to -78°C, a catalytic amount of TMSOTf (0.03 mmol, 10%) was added. The reaction mixture was stirred for 4 h and then quenched with aqueous sodium hydrogen carbonate. The aqueous



4 (a or b) **5 (a or b)** **6 (a or b)** **7 (a or b)**

8 (a or b) **9 (a or b)**

a : R=vinyl
b : R=Et

8a : $[\alpha]_D$ = -27.5°
8b : $[\alpha]_D$ = -37.5°

9a : $[\alpha]_D$ = +28.5°
9b : $[\alpha]_D$ = +38.0°

Scheme 2

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layer was extracted with CH_2Cl_2. After removal of the solvent, the crude products were separated by flash chromatography to afford the major **4a** (52%) and three other stereomers **4a**$_{1,2,3}$ (overall yield 81%). Similarly, the diastereomeric enol silane **3a** afforded **5a** as a major coumpound[1].
Further DIBALH reduction of **4** and **5** produced stereoselectively (de=95%) bis-protected sterepentads **6** and **7**[2]. The absolute configurations of C-4 and C-5 in **6** and **7** (and thus in **4** and **5**) were determined by NMR selective decoupling experiments. The stereochemical assignement was confirmed by deprotection of carbamates **6** and **7** ($HSiCl_3$, Et_3N) [5], affording the enantiomeric pentads **8** and **9** (Scheme 2).
The predominant *syn* relationship at the two new stereogenic centers (C-4 and C-5) is in account with the simple diastereoselectivity usually observed in the Mukaiyama reactions of enol silanes with acetals [6,7]. Noteworthy is a good level of asymmetric induction controlled by enol silane face selectivity. The favoured 1,3-*anti*-dimethyl arrangement contrasts with the *syn* arrangement for the reactions using similarly functionalized chiral (E)-enolsilanes and aldehydes as electrophiles [8]. Moreover, the degree of diastereofacial selectivity markedly depends upon the subtle changes in the enol silane structure. Thus, compounds **2b** and **3b** which are saturated analogues of **2a** and **2b**, undergo the Mukaiyama reaction to give dihydroxy ketones **4b** and **5b** which a total enantiocontrol combined with a high level of simple diastereoselectivity (de=90%)[3].
Nevertheless, other factors influencing the selectivity in the above reactions must also be considered and the work is in progress. The efficient construction of the polyketide chirons, using the title enol silanes, could be then envisaged.

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[1] The diastereomeric ratio was determined by GC and ^1H NMR on the crude reaction mixtures. The relative *syn* or *anti* stereochemistry was assigned to isolated products on the basis of the ^1H NMR vicinal coupling constants, ^{13}C NMR shifts and by comparison with similar data, see refs 1,2. Stereomers ratio **4a**(*syn*):**4a**$_1$ (*anti*):**4a**$_2$(*syn*):**4a**$_3$(*anti*)= 52:28:12:8 ; **5a**(*syn*):**5a**$_1$(*anti*):**5a**$_2$(*syn*):**5a**$_3$(*anti*) = 57:19:14:10.

[2] Selected spectral data for **6a** and **7a** :

6a : $[\alpha]_D$ = -78° (c = 8.5 g.l^{-1} in $CHCl_3$) ; ^1H NMR (CD_3COCD_3, 200 MHz) d 7.40-7.15 (m, 10H) ; 6.73-6.62 (m, 1H) ; 5.76-5.52 (m, 2H) ; 5.14-4.95 (m, 2H) ; 4.79 (quintet, *J* = 7.3 Hz, 1H) ; 4.33 (d, *J* = 6.2 Hz; 1H) ; 3.58 (d, *J* = 4.0 Hz, 1H, D_2O exchangeable) ; 3.32-3.20 (m,1H) ; 3.18 (s, 3H) ; 2.02-1.75 (m, 2H) ; 1.44 (d, *J* = 6.9 Hz, 3H) ; 0.95 (d, *J* = 6.9 Hz, 3H) ; 0.68 (d, *J* = 6.6 Hz, 3H) ; ^{13}C NMR {^1H} (CD_3COCD_3) 155.9 ; 146.1 ; 142.0 ; 135.0 ; 129.2 ; 129.0 ; 128.3 ; 128.1 ; 127.6 ; 126.8 ; 116.5 ; 88.5 ; 75.2 ; 74.7 ; 57.2 ; 51.4 ; 42.7 ; 41.1 ; 23.2 ; 10.8 ; 7.7 ; MS m/z : 411 (M^+, 1) ; 291 (2) ; 273 (15) ; 166 (62) ; 121 (100) ; 105 (98) ; 91 (6) ; Anal. Calcd for $C_{25}H_{33}O_4N$: C : 72,96 % H : 8,08 % ; found : C : 72,12 % H : 8,09 %
7a : $[\alpha]_D$ = +31° (c = 3.2 g.l^{-1} in $CHCl_3$) ; ^1H NMR (CD_3COCD_3, 200 MHz) δ 7.40-7.18 (m, 10H) ; 6.75-6.67 (m, 1H) ; 5.70-5.59 (m, 1H) ; 5.56-5.49 (m, 1H) ; 5.22-5.00 (m, 3H) ; 4.29 (d, *J* = 6.6 Hz; 1H) ; 3.54 (d, *J* = 5.1 Hz, 1H, D_2O exchangeable) ; 3.24 (ddd, *J* = 2.2 ; 5.1 ; 9.9 Hz, 1H) ; 3.17 (s, 3H) ; 1.96-1.86 (m, 1H) ; 1.81 (dquintet, *J* = 2.2 ; 6.6 Hz, 1H) ; 1.43 (d, *J* = 6.9 Hz, 3H) ; 0.91 (d, *J* = 6.9 Hz, 3H) ; 0.66 (d, *J* = 6.9 Hz, 3H) ; ^{13}C NMR {^1H} (CD_3COCD_3) δ 155.8 ; 146.1 ; 142.0 ; 135.0 ; 129.2 ; 129.0 ; 128.2 ; 128.1 ; 127.6 ; 126.9 ; 116.7 ; 88.5 ; 75.2 ; 74.7 ; 57.2 ; 51.4 ; 42.7 ; 41.1 ; 23.2 ; 10.9 ; 7.7 ; MS m/z: 411 (M^+, 1) ; 291 (3) ; 273 (1) ; 166 (78) ; 121 (16) ; 105 (100) ; 91 (3) ; Anal. Calcd $C_{25}H_{33}O_4N$: C : 72,96 % ; H : 8,08 % ; Found : C : 72,61 % ; H : 8,34 %.

[3] Stereomers ratio **4b**(*syn*):**4b**$_1$(*anti*)= 90:10 ; **5b**(*syn*):**5b**$_1$(*anti*)= 95:5.