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Use of chiral enolsilanes and chiral aldehydes in a Mukaiyama-type aldol reaction promoted by titanium(IV)isopropoxide

Christophe Delas, Olivier Blacque and Claude Moïse*

Laboratoire de Synthèse et d'Electrosynthèse Organométalliques (UMR 5632), Faculté des Sciences, 6 bd Gabriel, 21000 Dijon, France

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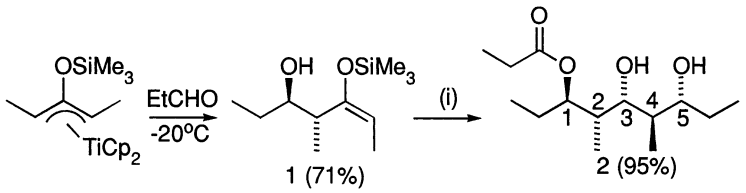
Abstract

In the presence of a catalytic amount of titanium(IV) isopropoxide, an aldol reaction is conducted between chiral enolsilanes formed by an allyltitanation reaction and chiral aldehydes to afford ketones in high yields. These ketones were reduced and esterified by a Tischtschenko reaction to obtain esters bearing six or seven stereocenters.

Keywords: allyltitanation; aldol reaction; Tischtschenko reaction; polypropionate derivatives.

In the course of our work concerning the synthesis of polypropionate-derived natural products, we have recently demonstrated the high level of diastereoselectivity of titanium(IV) isopropoxide-catalyzed tandem aldol–Tischtschenko[1] reactions involving aldehydes and the chiral enolsilane **1**. The silylated derivative was provided by a highly stereoselective allyltitanation reaction.[2,3] Ester **2** resulted from a Tischtschenko reaction that took place on the intermediate ketone arising from the classical Mukaiyama aldol-type reaction (Scheme 1).



Scheme 1. (i) rt, 10 mol% $Ti(O^iPr)_4$, $2CH_3CH_2CHO$, CH_2Cl_2

* Corresponding author. Tel: +33(0)380396081; e-mail: claude.moise@u-bourgogne.fr

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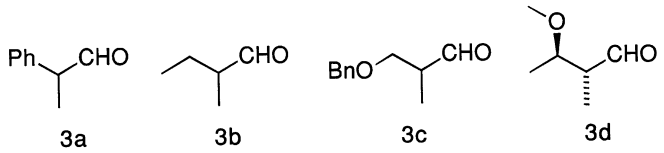
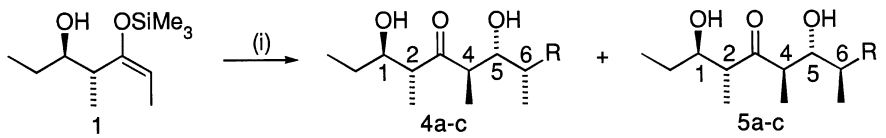
In this letter we wish to report results related to the use of the chiral aldehydes represented below (Scheme 2).[4–6]



Scheme 2.

The reactions involving aldehydes **3a–c** and enolsilane **1** in presence of a catalytic amount (10 mol%) of titanium(IV) isopropoxide are outlined in Scheme 3.

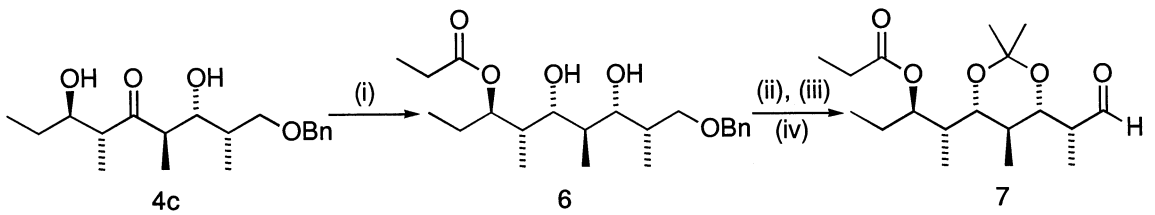


Scheme 3. (i) 0°C, 10 mol% $Ti(O^iPr)_4$, **3a–c**, CH_2Cl_2; **3a** (R = Ph) 12:88; **3b** (R = Et) 71:29; **3c** ($R = CH_2OBn$) 68:32

The reactions lead to a mixture of two diastereomeric ketones **4** and **5** with good overall yields (90%). No trace of the esters is detected; the bulkiness of the aldehydes **3a–c** may make the Tischtschenko reaction impossible to occur.[7]

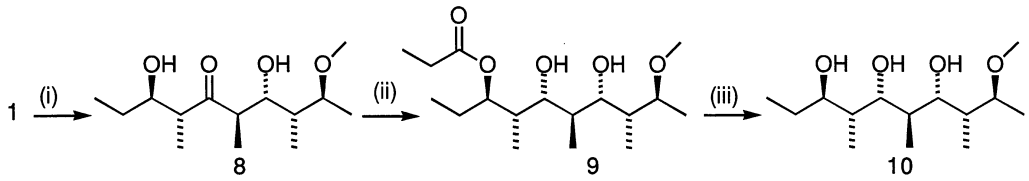
The complete 4,5-*anti* and 2,4-*anti* stereoselectivity as previously observed with simple aliphatic aldehydes is noteworthy.[1] The reversal of the 5,6 relative configuration in ketones **4** and **5** is related to the diastereofacial selectivity of the reaction of the enolsilane over the aldehyde.

In fact, a Tischtschenko reaction catalyzed by titanium(IV) isopropoxide took place when ketone **4c** was opposed to the less sterically-demanding propionaldehyde. The sole ester **6** was provided by this completely regio- and stereoselective reaction (Scheme 4) and its derivatization allows the aldehyde **7**[8] bearing six stereocenters to be obtained (overall yield: 85%).



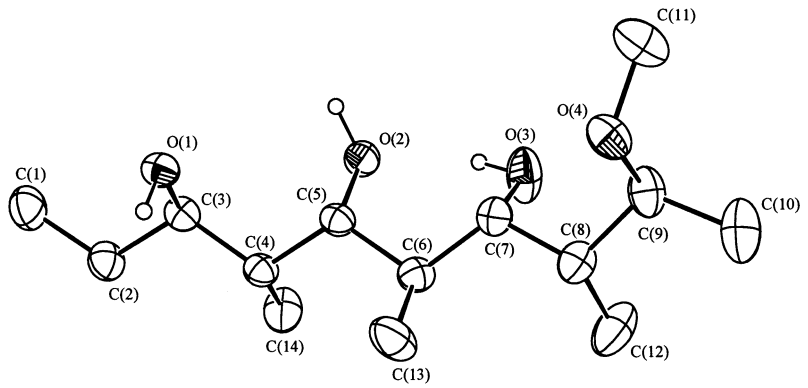
Scheme 4. (i) rt, 10 mol% $Ti(O^iPr)_4$, CH_3CH_2CHO, CH_2Cl_2; (ii) rt, $(MeO)_2CMe_2$, *p*-TsOH; (iii) rt, H_2 Pd/C, MeOH; (iv) rt, PCC, CH_2Cl_2

The *anti*-aldehyde **3d** was also involved in the aldol reaction and yielded a unique ketone (yield: 90%). As for ketone **4c**, a Tischtschenko reaction performed with propionaldehyde led to the ester **9** showing, as expected, the ester functionality on the less hindered hydroxy group. Alkaline hydrolysis of **9** gave rise to the polypropionate derivative **10** carrying seven stereocenters (Scheme 5).



Scheme 5. (i) 0°C, 10 mol% $Ti(O^iPr)_4$, 3d, CH_2Cl_2 (ii) rt, 10 mol% $Ti(O^iPr)_4$, CH_3CH_2CHO, CH_2Cl_2; (iii) rt, NaOH, MeOH

Compound **10** was crystalline and an X-ray structure[9] (Scheme 6) confirmed the relative configuration of the seven stereocenters previously established by NMR studies.



Scheme 6.

Aldehydes **3b–d** exhibit high or very high (**3d**) levels of Felkin selectivity.[10,11] Indeed ketones **4b–d** show a *syn* configuration between carbon 5 and carbon 6. In contrast, aldehyde **3a** reveals a very high *anti*-Felkin selectivity, providing a 5,6-*anti* ketone as the major product.

The simple *anti* diastereoselectivity of the aldol reaction is not affected by the use of bulky and/or alkoxy aldehydes, and furthermore all reactions lead to a 1,5-*anti* configuration between the hydroxy group afforded by the enolsilane and the one created during the aldol step.

Formation of aldehyde **7** shows the efficiency of the method described here to build functionalized polypropionate derivatives. All the steps are stereoselective and proceed in high yields; allyltitanation and aldol reactions are *anti* selective. Furthermore, the Tischtschenko reaction that operates regioselectively on the less hindered site exhibits a very high 1,3-*anti* diastereoselectivity.

References

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2. Szymoniak, J.; Lefranc, H.; Moïse, C. *J. Org. Chem.* **1996**, *61*, 3926–3928.
3. Szymoniak, J.; Lefranc, H.; Besançon, J.; Moïse, C. *Synthesis* **1995**, 815–819.
4. Aldehydes **3a** and **3b** were provided by oxidation of the corresponding primary alcohols using PCC.

5. **3c** was prepared according to the method described in Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*; VCH: New York, 1996; p. 198.
6. Synthesis of **3d** was reported in Hoffmann, R. W.; Weidmann, U. *Chem. Ber.* **1985**, *118*, 3966–3979.
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8. **7**: colorless oil; MS: m/z 329 $[M+1]^+$ (69%); ^1H NMR ($CDCl_3$, 200 MHz, rt): δ 9.60 (s, 1H, C*H*O); 4.88 (dt, $J=3.2$ Hz, $J=8.5$ Hz, 1H, $CH_3CH_2CHOCOEt$); 4.06 (dd, $J=2.7$ Hz, $J=10.3$ Hz, 1H, C*H*–O); 3.61 (dd, $J=2.1$ Hz, $J=10.0$ Hz, 1H, C*H*–O); 2.46 (dq, $J=2.7$ Hz, $J=6.8$ Hz, 1H, $CH(CH_3)$); 2.31 (q, $J=7.3$ Hz, 2H, CH_2); 1.90–1.40 (m, 4H); 1.27 (s, 3H, CH_3 acetonide); 1.22 (s, 3H, CH_3 acetonide); 1.13 (t, $J=7.3$ Hz, 3H, CH_3); 1.09 (d, $J=7.0$ Hz, 3H, CH_3); 0.84 (d, $J=7.0$ Hz, 3H, CH_3); 0.82 (t, $J=7.3$ Hz, 3H, CH_3); 0.73 (d, $J=6.8$ Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz, rt): δ 204.7 (CHO); 173.7 (*C*=O); 98.0 (acetonide); 75.2 (*C*H–O); 73.7 (*C*H–O); 72.6 (*C*H–O); 47.2 ($CH(CH_3)$); 36.3 ($CH(CH_3)$); 31.4 ($CH(CH_3)$); 29.5 (CH_3 acetonide); 27.8 (CH_2); 24.5 (CH_2); 19.0 CH_3 acetonide); 11.1 (CH_3); 9.4 (CH_3); 8.8 (CH_3); 8.6 (CH_3); 6.3 (CH_3).
9. Crystal data of **10**: $C_{14}H_{30}O_4$; Mr = 262.38, colorless needles, space group $P2_1/c$ (#14), $a=7.948(1)$, $b=11.921(1)$, $c=16.992(1)$ Å, $\beta=100.114(9)°$, $V=1585.0(3)$ Å^3, $Z=4$, $D_{calc}=1.100$ g cm^{-3}, μ(Mo–K$_\alpha$) = 0.078 mm^{-1}. The R (R_w) value of **10** was 0.049 (0.116). The data were collected on an Enraf–Nonius CAD4 diffractometer at 296(1) K using graphic monochromated Mo–K$_\alpha$ ($\lambda=0.71073$ Å) radiation.
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