Titanium-Mediated Aldol-Tishchenko Reaction: A Stereoselective Synthesis of Differentiated *anti* 1,3-Diol Monoesters

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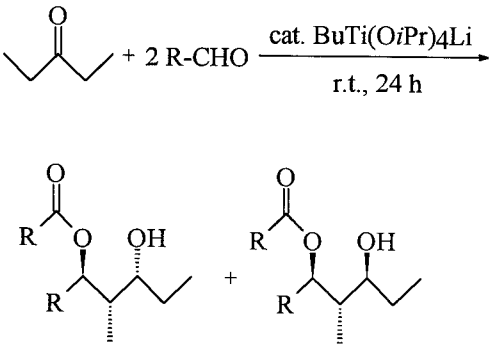
anti 1,3-Diol monoesters were obtained in a high level of stereoselectivity by a one-pot aldol-Tishchenko reaction of ketones with aldehydes using substoichiometric amounts of titanium ate complexes.

The stereoselective synthesis of 1,3-diols is of considerable interest, since this unit is frequently found in a variety of polyketide-derived natural products.[1] There exists several methods for obtaining 1,3-diols, but only a few publications describe the selective synthesis of *anti* 1,3-diols. Most of the authors use the stereoselective reduction of the corresponding β-hydroxy ketones.[2] Reaction of nickel carbon-bound enolates with aldehydes also provide 1,3-dioxygenated products.[3] We report here a simple and efficient synthesis of *anti* 1,3-diol monoesters by a one-pot aldol-Tishchenko reaction mediated by titanium ate complexes.

Titanium ate complexes were used in several areas of organic chemistry although their structure has been unknown until now. Reetz et al. investigated the use of allyltitanium ate complexes in addition reactions.[4] Recently the applicability of titanium ate complexes was shown in the field of 1,4-addition of α,β-unsaturated ketones.[5] Aldol reactions in the presence of titanium ate complexes afforded the *anti* aldol products in a high degree of stereoselectivity.[6]

As we reported recently, carbonyl compounds undergo aldol reaction in the presence of equimolar amounts of titanium ate complexes, to form stereoselective *anti* aldols.[6] In contrast, treatment of pentan-3-one with two equivalents of an aldehyde yields the 1,3-diol monoesters **1** and **2** in the presence of catalytic amounts (20 mol%) of a titanium ate complex [Bu(OPr-*i*)$_4$Li] (Scheme 1). The titanium ate complex was prepared in situ simply by mixing equimolar amounts of titanium(IV) alkoxides and butyllithium. The reactions were carried out at room temperature within 24 hours. Reactions in the presence of an excess of aldehydes lead to byproducts and thus to diminished yields. The use of the described titanium ate complex in these reactions is necessary for obtaining high yields and *anti*-stereoselectivity. Reactions of carbonyl compounds in the presence of catalytic amounts of titanium(IV) alkoxides alone resulted in the formation of the corresponding α,β-unsaturated carbonyl compounds.[7] Products derived from a Tishchenko-type process could not be detected.

The *anti* 1,3-diastereoselectivities, which were observed in all reactions carried out, were greater than 98:2 and were detected by NMR techniques (Scheme 1). The relative configuration of all products was determined by analysis of ^{1}H NMR coupling constants in connection with the data of the ^{13}C NMR spectra.[6] In addition, the confirmation of the relative stereochemistry of these substances was ascertained by hydrolysis of the monoesters **1a** and **3a** to give the *anti* 1,3-diol **5** (Scheme 2). Spectroscopic data for this compound matched with those of authentic **5** prepared by stereoselective reduction.[2a]



1 **2**

1,3-*anti*	1,3-*syn*	R	Ratio of **1** : **2**	Yield (%)
1a	**2a**	Ph	99 : 1	63
1b	**2b**	*t*-Bu	98 : 2	84
1c	**2c**	*i*-Pr	98 : 2	86
1d	**2d**	Pr	97 : 3	79

Scheme 1

During the reaction acyl migration of the 1- and 3-monoesters occurs, as illustrated in Scheme 3. The ratios of the acyl migration depend on the reaction time. The 1-monoesters **1a–d** were observed to be the main products when the reaction was stopped after 6 hours at room temperature. The ratios of the isomerized products after 24 hours at room temperature are shown in Scheme 3. This apparent isomerization was investigated further by adding a substoichiometric amount (20 mol%) of titanium ate complex. As expected, the pure benzoate **3a** was also isomerized to a 5:95 ratio of **1a** and **3a** by catalytic amounts of titanium ate complexes. The degree of this acyl migration depends on the structure of the substrate (Scheme 3), on the solvent used and on the counterion of the titanium ate complexes used. Complexes prepared from lithium alkyls promote this migration whereas titanium ate complexes prepared from magnesium alkyls prevent the acyl migration. Similar results were described by using 2,4,6-trimethylphenoxymagnesium bromide as a catalyst, however, without any stereochemical assignments.[8]

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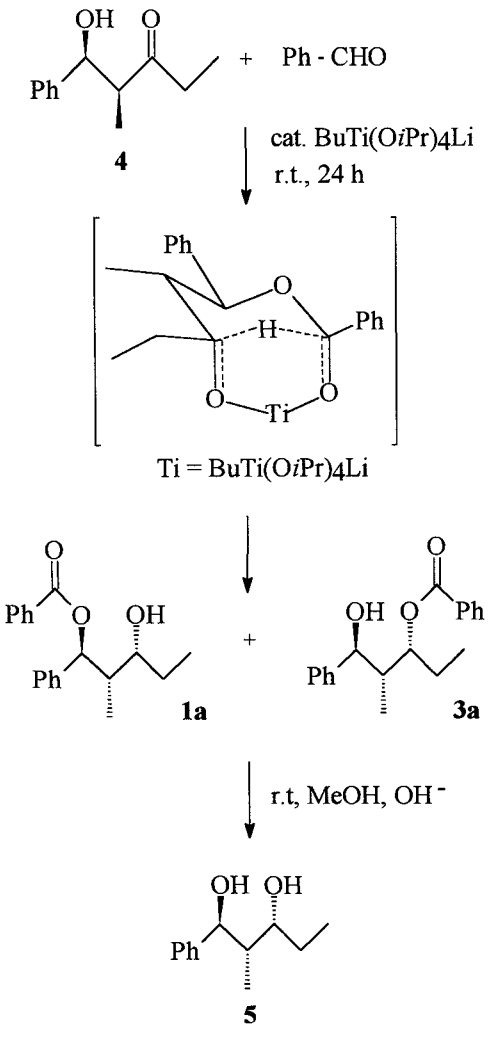
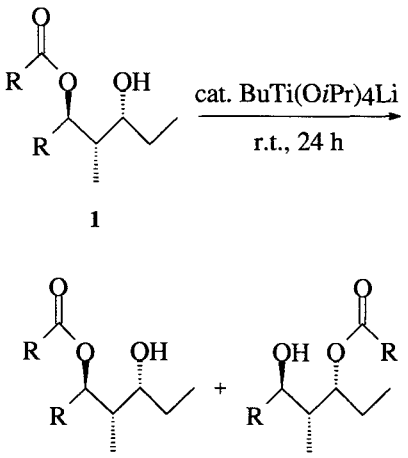


1-Monoester	3-Monoester	R	Ratio of 1 : 3
1a	**3a**	Ph	5 : 95
1b	**3b**	*t*-Bu	34 : 66
1c	**3c**	*i*-Pr	48 : 52
1d	**3d**	Pr	56 : 44

Scheme 2



Scheme 3

To investigate the mechanism of this reaction, the *syn* β-hydroxy ketone **4** was treated with benzaldehyde in the presence of catalytic amounts of a titanium ate complex (Scheme 2). After 24 hours at room temperature the two monoesters **1a** and **3a** were isolated in a ratio of about 10:90. This result indicates the thermodynamically driven equilibration during the Tishchenko reaction. The *syn* aldol **4** was equilibrated to the more stable *anti* 1,2-/*anti* 1,3-diol monoesters **1a** and **3a**.

Though the structure of the titanium ate complexes used is still unknown, there exist some concepts about the mechanism of this reaction. A mechanism for this titanium-catalyzed aldol-Tishchenko reaction should involve simultaneous coordination of the aldehyde and the hydroxy ketone to the catalyst. These conditions correspond at best with the transition structure shown in Scheme 2. Such a "bicyclic" transition structure is a requirement for a rigid, stereoselective hydride transfer from benzaldehyde to the carbonyl C-atom. This strict 1,3-relative asymmetric induction was also found in samarium promoted intramolecular Reformatsky-type reactions.[9] The observed high 1,3-asymmetric induction was explained by an analogous transition state model.

Similar explanations were given by Evans for the samarium-catalyzed intramolecular Tishchenko reduction of β-hydroxy ketones with high *anti* 1,3-selectivities.[10]

^{1}H NMR spectra were recorded on a Bruker WP 200 SY and Varian UNITY 500; the ^{13}C NMR spectra were obtained at 75 MHz on a Varian GEMINI 300 instrument in $CDCl_3$ (unless otherwise stated); chemical shifts are related to TMS. Low-resolution impact mass spectra: GC/MS Datensystem HP 5985 B. Microanalyses: Carlo Erba autoanalyzer 1106.

Stereochemical assignments of all products were determined by analysis of ^{1}H NMR coupling constants, via homodecoupling techniques.

(1*SR*,2*SR*,3*RS*)-3-Hydroxy-2-methyl-1-phenylpentyl Benzoate (1a) and (1*SR*,2*RS*,3*SR*)-1-Ethyl-3-hydroxy-2-methyl-3-phenylpropyl Benzoate (3a); Typical Procedure:

To a solution of titanium(IV) isopropoxide (0.32 mL, 1.0 mmol) in 1-*tert*-butoxy-2-methoxyethane (1.5 mL) was carefully added BuLi (0.64 mL, 1.0 mmol in hexane) under inert conditions. After stirring for 30 min at r.t. pentan-3-one (0.5 mL, 5 mmol) and then benzaldehyde (1.0 mL, 10 mmol) were added. The solution was stirred for further 24 h at r.t., Et_2O (50 mL) was added and the organic phase was extracted with water until neutral. The organic layer was separated, dried (Na_2SO_4), filtered and evaporated in vacuo. The pure products **1a** and **3a** were separated by flash chromatography using hexane/*i*-PrOH (95:5) as eluent (Table).

(1*SR*,2*SR*,3*RS*)-2-Methyl-1-phenylpentane-1,3-diol (5):[2a]

A solution of monoesters **1a** and **1b** (1.00 g, 3.4 mmol) in anhyd MeOH (20 mL) was stirred with anionic ion exchanger SBW at r.t. The suspension was filtered after 2 h. The filtrate was evaporated in vacuo and the residue was purified by flash chromatography (hexane/EtOAc, 9:1) to give the diol **5** as a colorless oil; yield: 570 mg (88%).

^{1}H NMR (300 MHz): δ = 0.85 (d, *J* = 7.3 Hz, 3H), 0.90 (*t*, *J* = 7.5 Hz, 3H), 1.4–1.6 (m, 2H), 1.92 (ddq, *J* = 2.0, 6.9, 7.5 Hz, 1H), 3.70 (m, 1H), 4.69 (d, *J* = 6.9 Hz, 1H), 7.33 (m, 5H).

^{13}C NMR (76 MHz): δ = 10.63, 11.42, 26.64, 43.27, 73.99, 78.21, 126.23, 127.35, 128.30, 143.82.

$C_{12}H_{18}O_2$ (194.27): calc. C 74.19 H 9.34
found 74.32 9.25

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Table. Spectral Data of Compounds **1** and **3**

Product[a]	^{1}H NMR ($CDCl_3$/TMS) δ, J (Hz)	^{13}C NMR ($CDCl_3$/TMS) δ	MS (70 eV) m/z (%)
1a	0.68 (d, 3H, J = 7.0), 0.88 (t, 3H, J = 6.6), 1.43 (m, 2H, CH_2), 2.05 (ddq, 1H, J = 1.6, 7.0, 7.9, 9.8, H-2), 2.38 (br s, 1H, OH), 3.68 (ddd, 1H, J = 1.6, 2.0, 5.2, H-3), 5.85 (d, 1H, J = 9.9, H-1), 7.05–8.01 (10H$_{arom}$)	8.9, 10.9, 27.3, 43.1, 71.2, 78.9, 127.4, 128.2, 128.4, 128.5, 129.7, 129.9, 133.2, 139.5, 166.6	298 (3), 280 (4), 269 (2), 241 (3), 193 (15), 118 (60), 105 (100)
1b	0.81 (d, 3H, J = 6.7, CH_3), 0.89 (t, 3H, J = 6.7, CH_3), 0.98 (s, 9H, t-C_4H_9), 1.26 (s, 9H, t-C_4H_9), 1.35, 1.52 (m, 2H, CH_2), 1.88 (ddq, 1H, J = 1.7, 5.5, 6.7, H-2), 3.75 (ddd, 1H, J = 1.6, 5.7, 7.5, H-3), 4.70 (d, 1H, J = 5.5, H-1)	10.6, 11.7, 26.4, 27.0, 27.5, 35.3, 37.5, 38.8, 71.8, 82.7, 177.9	229 (5), 201 (2), 183 (5), 171 (12), 141 (15), 103 (40), 98 (55), 85 (42), 83 (85), 57 (100)
1c	0.81–0.92 (m, 9H, 3 × CH_3), 1.17, 1.21 [2d, 6H, J = 2.5, $CH(CH_3)_2$], 1.30–1.80 [m, 3H, $CH(CH_3)_2$ + CH_2], 2.00 (m, 1H, H-2), 2.61 [m, 1H, $CH(CH_3)_2$], 2.92 (m, 1H, H-3), 4.77 (dd, 1H, J = 3.3, 6.3, H-1)	9.1, 10.3, 18.5, 18.6, 18.7, 18.8, 26.7, 28.6, 34.0, 39.9, 70.8, 78.8, 177.9	187 (5), 169 (7), 143 (8), 99 (30), 89 (70), 71 (100)
1d	0.83 (t, 3H, J = 6.9, CH_3), 0.87 (t, 3H, J = 6.7, CH_3), 0.91 (t, 3H, J = 6.7, CH_3), 0.92 (d, 3H, J = 6.8, CH_3), 1.3–1.7 (m, 9H), 2.33 (t, 2H, J = 7.6, $COCH_2$), 3.13 (d, 1H, J = 2.1, 8.9, H-6), 4.90 (d, 1H, J = 3.7, 8.5, H-4)	9.9, 11.3, 13.3, 13.7, 18.4, 18.9, 26.9, 35.9, 36.6, 45.7, 71.2, 73.4, 174.5	212 (2), 201 (5), 169 (15), 113 (20), 89 (81), 84 (69), 70 (100)
3a	0.77 (d, 3H, J = 6.7, CH_3), 0.99 (t, 3H, J = 6.6, CH_3), 1.68, 1.93 (m, 2H, CH_2), 2.07 (ddq, 1H, J = 1.5, 6.7, 9.6, H-2), 3.79 (d, 1H, J = 3.9, OH), 4.22 (dd, 1H, J = 3.7, 9.7, H-3), 5.65 (ddd, 1H, J = 1.8, 5.2, 6.7, H-1), 7.2–8.1 (10H$_{arom}$)	9.9, 10.5, 25.6, 44.3, 75.7, 75.8, 126.9, 127.5, 128.2, 128.4, 129.7, 130.0, 133.1, 142.8, 167.5	–
3b	0.82 (d, 3H, J = 6.7, CH_3), 0.87 (t, 3H, J = 6.6, CH_3), 0.96 (s, 9H, t-C_4H_9), 1.25 (s, 9H, t-C_4H_9), 1.3–1.6 (m, 2H, CH_2), 1.85 (m, 1H, H-2), 3.07 (dd, 1H, J = 2.7, 6.8, H-3), 3.23 (d, H, J = 2.5, OH), 5.14 (ddd, 1H, J = 0.9, 4.8, 6.9, H-1)	10.1, 11.9, 26.8, 27.5, 28.4, 33.4, 38.7, 38.9, 75.2, 78.0, 178.6	229 (1), 201 (2), 183 (2), 171 (1.5), 141 (1), 103 (20), 98 (12), 85 (15), 83 (20), 57 (100)
3c	0.73 (m, 3H, CH_3), 0.86 [m, 3H, $CH(CH_3)_2$], 0.88 [m, 3H, $CH(CH_3)_2$], 0.93 (m, 3H, CH_3), 1.17, 1.20 [2d, 6H, J = 2.5, $CH(CH_3)_2$], 1.30–1.70 [m, 2H, CH_2 + $CH(CH_3)_2$], 2.00 (m, 1H, H-2), 2.60 [m, 1H, $CH(CH_3)_2$], 2.93 (m, 1H, H-3), 3.17 (d, 1H, J = 4.4, OH), 5.17 (ddd, 1H, J = 1.5, 4.4, 6.1, H-1)	9.3, 10.8, 18.8, 18.9, 19.0, 19.7, 25.3, 28.3, 34.2, 38.5, 75.3, 75.5, 178.5	169 (3), 143 (4), 129 (7), 113 (12), 99 (18), 89 (42), 84 (71), 71 (100)
3d	0.84 (d, 3H, J = 7.0, CH_3), 0.89 (t, 3H, J = 7.0, CH_3), 0.92 (t, 3H, J = 6.9, CH_3), 0.98 (t, 3H, J = 6.7, CH_3), 1.3–1.7 (m, 9H), 2.33 (t, 2H, J = 7.7, $COCH_2$), 3.49 (ddd, 1H, J = 2.2, 5.2, 7.7, H-5), 5.16 (ddd, 1H, J = 1.9, 4.6, 6.4, H-3)	9.5, 10.9, 13.3, 13.5, 18.2, 18.3, 25.2, 29.9, 33.8, 40.8, 71.2, 71.5, 174.0	201 (1), 169 (1.5), 159 (2), 129 (10), 113 (18), 89 (72), 84 (65), 71 (100)

[a] Products **1** and **3** were separated by flash chromatography on silica gel (see experimental). For yields and ratio of **1 : 3**, see Schemes 2 and 3. All products are oils and gave satisfactory microanalyses: C ± 0.49, H ± 0.35 (exceptions: **3b**, C − 0.51; **1c**, C + 0.53).

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