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Stereochemical control of tertiary alcohol: aldol condensation of lactate derivatives

Tomoyuki Kamino, Yoshihisa Murata, Nobuyuki Kawai, Seijiro Hosokawa and Susumu Kobayashi*

Faculty of Pharmaceutical Sciences, Science University of Tokyo, Ichigaya-Funagawara-machi, Shinjuku-ku, Tokyo 162-0826, Japan

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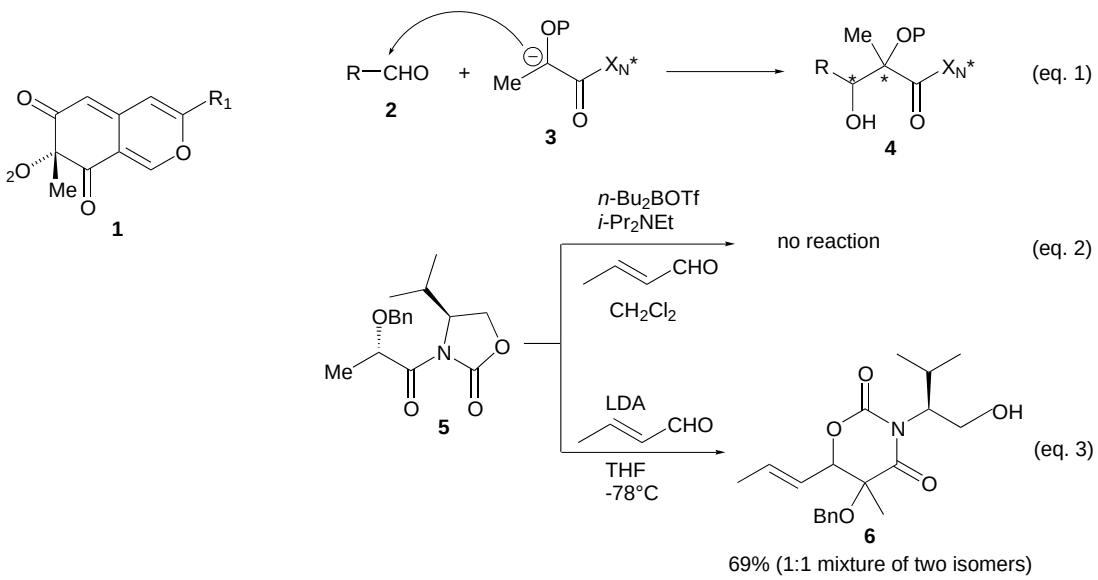
Abstract—Stereoselective construction of aldol adducts having tertiary alcohol at the α position was achieved via a titanium(IV) enolate derived from a lactate derivative with an Evans chiral auxiliary. The stereochemistry at α-tertiary alcohol could be controlled by selecting the protective group of the starting lactate.

The azaphilone skeleton **1** is seen in many biologically active natural products such as mitorubinic acid[1] and diazaphilonic acid.[2] Although the azaphilone family exhibits significant biological activities, only a few synthetic studies which start from aromatic compounds have been reported and there is no precedent for asymmetric synthesis.[3] One of characteristic features seen in the azaphilone skeleton is a tertiary alcohol surrounded by two carbonyls. Coupled with our continuing interest in chiral quaternary carbons,[4] we embarked on an enantioselective construction of a chiral tertiary alcohol toward the azaphilone skeleton. We first examined the aldol-type reaction of lactic acid-derived chiral enolate with an aldehyde, and we observed some interesting findings.

Although our strategy (Scheme 1, eq. 1) is very simple, the aldol reaction of lactate derivatives having an Evans chiral auxiliary was not known. Actually, a stereoselective aldol addition of **3** under conventional conditions



Scheme 1.

* Corresponding author.

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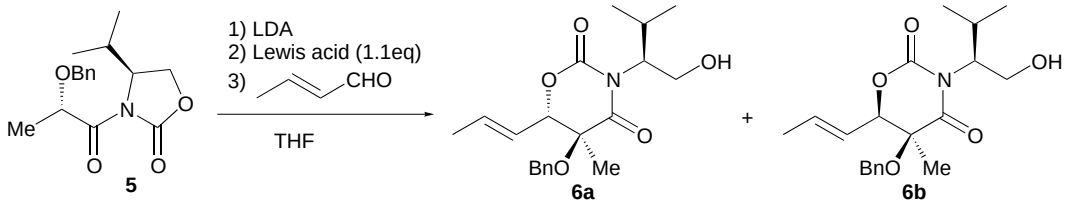
was found difficult. For example, the Evans aldol reaction[5] did not work for **5** (eq. 2) and a lithium enolate derived from **5** gave an almost 1:1 mixture of two isomers as cyclic carbamates **6** (eq. 3). Therefore, we examined the addition of Lewis acid to the lithium enolate (Table 1). Most of the Lewis acids exerted no influence on the stereoselectivity, but $TiCl(Oi\text{-}Pr)_3$[6] changed the diastereo ratio significantly (entry 8). Further, addition of 3.3 equivalents of $TiCl(Oi\text{-}Pr)_3$[6] improved the diastereoselectivity (20:1) affording *anti*-adduct **6a**[7] in good yield (entry 9).

The relative stereochemistry of **6a** was determined by the NOE spectrum of **7**, which was derived from **6a** in five steps,[9] and the absolute stereochemistry was established as shown by optical rotation of **8**,[8] which was derived from **6a** in seven steps.[10] The stereochemistry of the other adduct was proven to be **6b** by conversion of both stereoisomers into the β-ketoester **9**, which show the same sign of optical rotation (Scheme 2).[11]

Similar results (yield and stereoselectivity) were obtained when D-lactate derived **10** and a mixture (**5** and **10**/1:1) were reacted with crotonaldehyde under the same conditions (Scheme 3). Accordingly, the present aldol reaction is independent of the stereochemistry of the starting lactate, and it seems that the same enolate was generated stereoselectively from **5** and **10**. Although the lithium enolate derived from **5** gave the corresponding silyl enol ether as a single isomer, the determination of the stereochemistry of the resulting silyl ether was difficult by ^1H NMR analysis because the signals of the silyl ether lay one upon another (eq. 4). On the other hand, clean NOE was observed with silyl enol ether **13** obtained stereoselectively by treatment of **12** with LDA and TESCl. In analogy to **13**, we tentatively assume the stereochemistry of **11** as *E*-**11** (eq. 5).

We next examined TBS-ether **14** as a substrate. In this case, no oxazolidone-opening products were detected and *syn*-adduct **15**[12] was obtained in good yield with 7:1 selectivity (Scheme 4). The relative stereochemistry

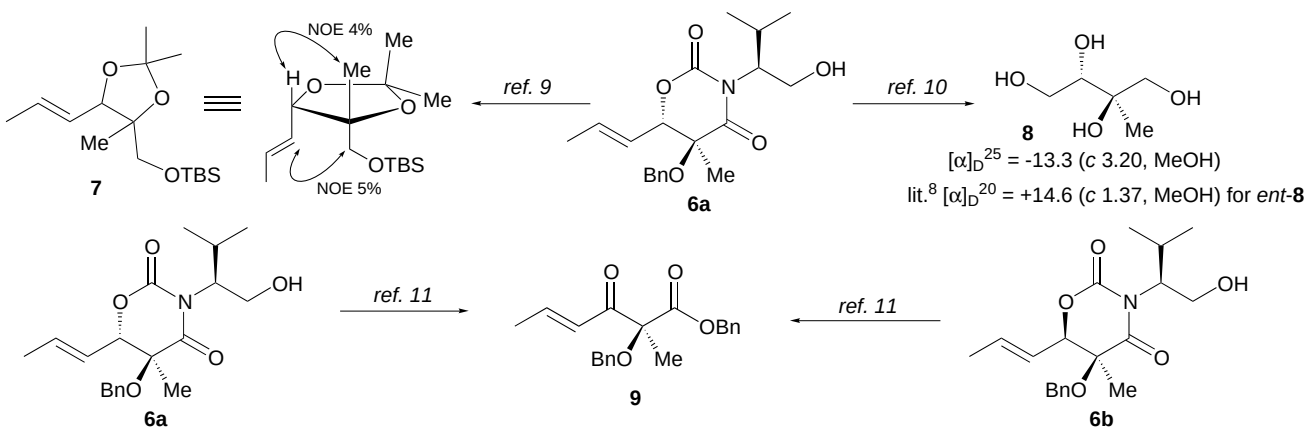
Table 1. The effect of Lewis acid



5 6a 6b

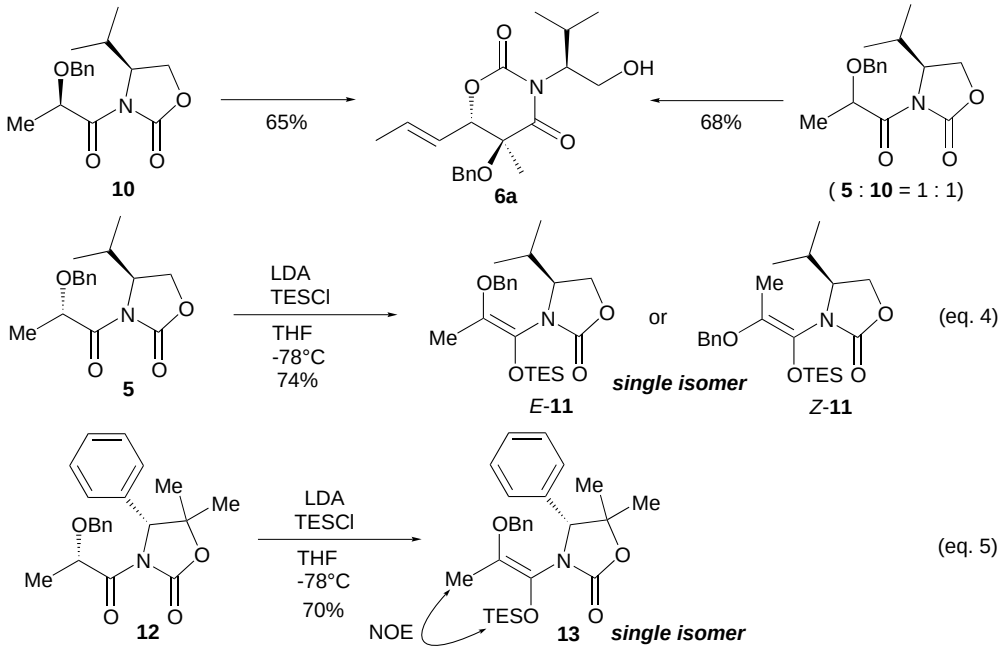
Entry	Lewis acid	Temperature (°C)	Yield (%)	a:b
1	–	−78	69	1:1
2	$n\text{-}Bu_2BOTf$	−78 to 0	41	1:1
3	$SnCl_2$	−78	9	–
4	$TiCl_4$	−78	No reaction	–
5	Et_2AlCl	−78	33	1:1
6	$n\text{-}Bu_3SnCl$	−78	57	1:1
7	$Ti(Oi\text{-}Pr)_4$	−78 to −40	13[a]	–
8	$Ti(Oi\text{-}Pr)_3Cl$	−78 to −40	52	8:1
9	$Ti(Oi\text{-}Pr)_3Cl$ (3.3 equiv.)	−78 to −40	63	20:1

[a] 1,4-Adducts were obtained as major products (70%).

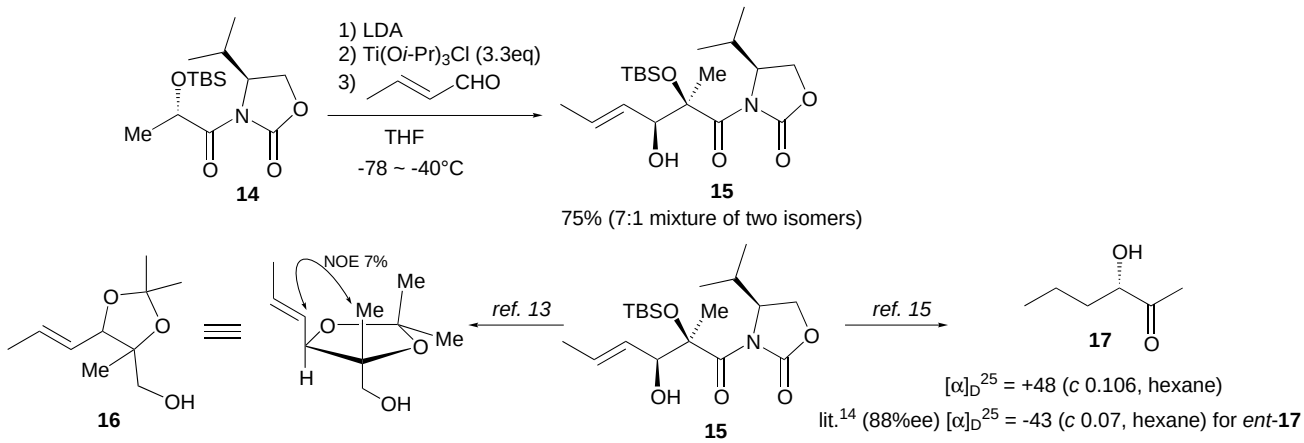


7 6a 9 6b

Scheme 2.



Scheme 3.



Scheme 4.

of **15** was determined by the NOE spectrum of **16**, which was derived from **15** in five steps,[13] and the absolute stereochemistry was determined by optical rotation of **17**,[14] which was derived from **15** in six steps.[15] Thus, the aldol adduct **15** has the opposite stereochemistry of a tertiary alcohol and the same stereochemistry as a secondary alcohol as compared to **6a**.

In conclusion, we have found a stereoselective aldol reaction with a lactic acid-derived chiral enolate. It should be noted that the stereochemistry of the quaternary chiral center (tertiary alcohol) could be controlled by proper choice of the protecting group of the starting lactate. Work on the scope and limitation, as well as a precise mechanism of the reaction is now in progress.

Acknowledgements

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7. General procedure: To a solution of LDA (prepared from DIPA (27.1 μl, 206 μmol), and *n*-BuLi (1.6 M in hexane, 118 μl, 189 μmol) at −15°C for 15 min) was added a solution of **5** (50.0 mg, 172 μmol) at −78°C. After stirring for 30 min at −78°C, $TiCl(O\textit{i}\text{-}Pr)_3$ (1.0 M in hexane, 568 μl, 568 μmol) was added and the resulting mixture was stirred for 1 h at −40°C. After cooling to −78°C, crotonaldehyde (15.2 μl, 189 μmol) was added to the mixture which was additionally stirred at −40°C for 2 h. The reaction mixture was quenched with sat. NH_4Cl and stirred with Celite for 1 h at rt. Filtration, extraction with AcOEt, washing the organic layer with brine followed by drying with Na_2SO_4 and evaporation gave a crude oil, which was purified by preparative TLC (hexane:AcOEt = 2:1) to yield **6a** (39.1 mg, 63%). **6a**: $R_f = 0.50$ (hexane:AcOEt = 2:1); $[\alpha]_D^{23} = -35.3$ (*c* 4.94, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 0.86 (3H, d, $J = 6.59$ Hz), 1.03 (3H, d, $J = 6.6$ Hz), 1.45 (3H, s), 1.77 (3H, d, $J = 6.3$ Hz), 2.38–2.47 (1H, m), 2.69 (1H, bs), 3.73 (1H, dd, $J = 11.6$, 9.3 Hz), 4.06 (1H, dd, $J = 11.5$, 8.5 Hz), 4.41 (1H, bs), 4.49 (1H, d, $J = 10.0$ Hz), 4.61 (1H, d, $J = 10.9$ Hz), 4.88 (1H, d, $J = 7.8$ Hz), 5.45 (1H, dd, $J = 14.8$, 7.8 Hz), 6.01 (1H, dq, $J = 14.8$, 6.3 Hz), 7.26–7.39 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 15.7, 18.0, 19.9, 20.1, 26.0, 62.0, 75.5, 81.7, 121.9, 127.3, 127.8, 135.8, 137.1, 170.5; IR (neat) 3491, 2968, 2455, 1755, 1697, 1454, 1372, 1213, 1124, 1027, 760 cm^{-1}.
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9. (i) $NaBH_4$, THF–H_2O (3:1); (ii) LiOOH, THF–H_2O (3:1), 63% in two steps; (iii) TBSCl, *i*-Pr_2NEt, DMAP, DMF, 0°C, 3.5 h, 75%; (iv) Li, NH_3, THF, −78°C, 2 h, 64%; (v) 2,2-dimethoxypropane, CSA, CH_2Cl_2, rt, 2 h, 82%.
10. (i) $NaBH_4$, THF–H_2O (3:1); (ii) LiOOH, THF–H_2O (3:1), 63% in two steps; (iii) BnCl, NaH, TBAI, THF, 91%; (iv) OsO_4, NMO, acetone–H_2O (5:1), 99%; (v) $Pb(OAc)_4$, benzene; (vi) $NaBH_4$, MeOH, 80% in two steps; (vii) H_2, Pd–C, MeOH, quant.
11. (i) BnOLi, BnOH, THF, −78 to 0°C, 32% for **6a**, 34% for **6b**; (ii) MnO_2, CH_2Cl_2, rt, 46% for **6a**, 59% for **6b**. **9** (from **6a**) $[\alpha]_D^{25} = +7.02$ (*c* 0.340, $CHCl_3$); **9** (from **6b**) $[\alpha]_D^{25} = +7.81$ (*c* 0.573, $CHCl_3$).
12. **15**: $R_f = 0.39$ (hexane:AcOEt = 5:1); $[\alpha]_D^{22} = +26.8$ (*c* 0.774, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 0.11 (3H, s), 0.24 (3H, s) 0.91–0.93 (15H, m), 1.57 (3H, s), 1.74 (3H, dd, $J = 6.3$, 1.2 Hz), 2.29–2.37 (1H, m), 2.52 (1H, bs), 4.23 (1H, dd, $J = 8.4$, 3.4 Hz), 4.32 (1H, t, $J = 8.7$ Hz), 4.57 (1H, dt, $J = 8.7$, 3.4 Hz), 4.97 (1H, dd, $J = 11.1$, 7.7 Hz), 5.53 (1H, ddq, $J = 15.3$, 7.7, 1.2), 5.80 (1H, dq, $J = 15.3$, 6.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) −2.5, 14.5, 17.9, 17.9, 18.8, 21.3, 26.1, 28.1, 60.4, 63.3, 75.1, 83.8, 128.6, 130.1, 152.9, 174.6; IR (neat) 3555, 2956, 2856, 1780, 1702, 1471, 1388, 1252, 1190, 1130, 996, 837, 758 cm^{-1}; HR-EIMS: calcd for $C_{18}H_{32}NO_5Si$ ($[M-Me]^+$) 370.2050, found 370.2032.
13. (i) TESCl, DMAP, imidazole, DMF, rt, overnight; (ii) BnSLi, BnSH, THF, 0°C, 1.5 h; (iii) TBAF, THF, 0°C, 1 h, 70% in three steps; (iv) 2,2-dimethoxypropane, CSA, CH_2Cl_2, rt, overnight, 92%; (v) $NaBH_4$, *i*-PrOH, rt, overnight, 55%.
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15. (i) BOMCl, DMAP, *i*-Pr_2NEt, CH_2Cl_2, rt, 2 days, 89%; (ii) DIBAL, CH_2Cl_2, rt, 2 h; (iii) TBAF, THF, 0°C, 2 h, 69% in two steps; (iv) H_2, Pd–C, AcOEt, rt, 1.5 h; (v) $Pb(OAc)_4$, benzene, 1 h, 88% in two steps; (vi) H_2, $Pd(OH)_2$, MeOH, 5 h, 53%.