

HETEROCYCLES, Vol. 73, 2007, pp. 641 - 650. © The Japan Institute of Heterocyclic Chemistry
Received, 29th June, 2007, Accepted, 10th August, 2007, Published online, 17th August, 2007. COM-07-S(U)42

ASYMMETRIC ALKYLATION OF 2-MONOSUBSTITUTED INDOLIN-3-ONES

Kazuhiro Higuchi, Kouhei Masuda, Tamami Koseki, Masahiro Hatori,
Masanori Sakamoto, and Tomomi Kawasaki*

Meiji Pharmaceutical University, 2-522-1 Noshio Kiyose, Tokyo 204-8588,
Japan; E-mail: kawasaki@my-pharm.ac.jp

Abstract – The asymmetric alkylation of 2-monosubstituted indolin-3-ones with optically active phase transfer catalysts (PTCs) has been studied. The prenylation of 2-benzyl indolin-3-one gave 2,2-dialkylated indolin-3-one **9a** in 99% yield and 65% enantioselectivity. The alkylation was investigated with various 2-monosubstituted indolin-3-ones **5a-e** and alkyl halides. The absolute configuration of **5d** was determined by derivatization to the known amino acid.

INTRODUCTION

2,2-Dialkylsubstituted indolin-3-ones **1** are key intermediates in the synthesis of biologically active alkaloids such as brevianamide A (**2**),¹ austamide (**3**)² and hinckdentine A (**4**).³ There are a few examples of the construction of quaternary carbon center for **1**, and it therefore remains a challenging theme.⁴ We previously developed efficient synthetic methodology for 2-monoalkylsubstituted indolin-3-ones **5**, and investigated the chemistry.⁵ In this study, we have described the asymmetric alkylation of **5** with optically active phase transfer catalysts (PTCs).

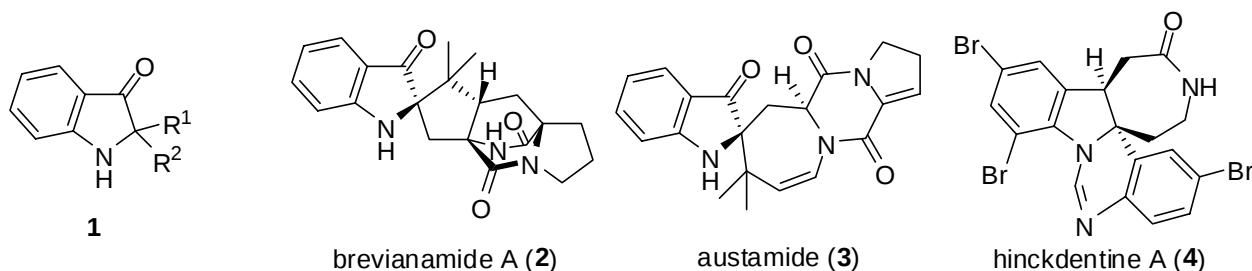
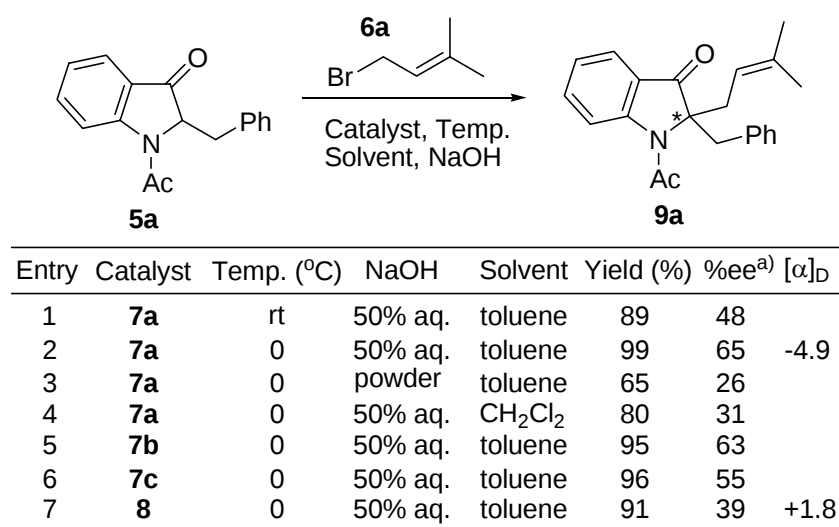


Figure 1

RESULTS AND DISCUSSION

Synthetic application of PTCs has various advantages, for example ease of procedure, large-scale synthesis, easy tuning of the PTC substituent and so on.⁶ Because of these advantages, PTCs have been used for the synthesis of indacrinone⁷ and physostigmine in pharmaceutical laboratories.⁸ We started the asymmetric alkylation of 2-monosubstituted indolin-3-ones **5** with optically active cinchoninium and cinchonidinium salts **7a-c**, **8**.



a) determined by ¹H-NMR with Eu(hfc)₃

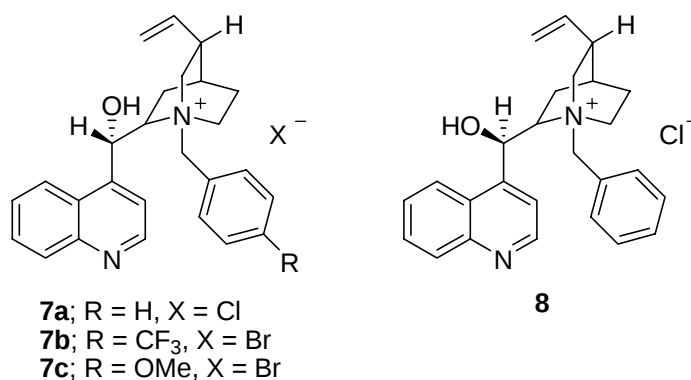


Table 1 Prenylation of **5a** with optically active PTCs

To find out the optimized reaction conditions, prenylation of 2-benzyl indolin-3-one **5a**^{5e} was carried out (Table 1). Higher enantioselectivity was observed by using cinchoninium salt **7a** and 50% NaOH at lower temperature (entry 1 vs. 2). Powder-NaOH applied to the PTC reaction at low temperature gave unsatisfactory results (entry 3). As a solvent, toluene gave better selectivity than dichloromethane (entry 2 vs. 4). These results support the tight ion pair hypothesis that enantioselectivity between the catalysts and enolates is important in the alkylation of indolin-3-one **5a**.⁹ We also investigated the electrostatic effect of benzyl groups in PTCs **7a-c**, **8**, but there were no remarkable differences in enantioselectivity (entry 2 vs. 5, 6). The use of cinchonidinium salt **8** gave rise to (+)-**9a** (entry 7).

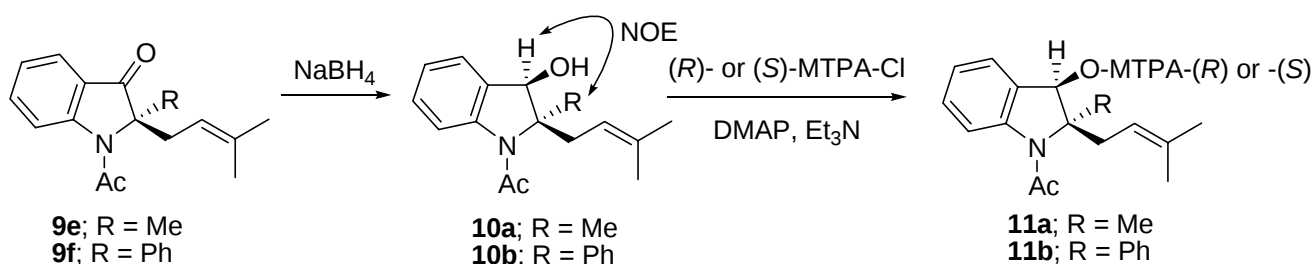
$\text{5a-e} \xrightarrow[\text{50\% aq. NaOH, toluene, 0 } ^\circ\text{C}]{\text{R}^2\text{-Br (6), Catalyst (7a)}} \text{9}$

Entry	5	R ¹	R ²	9	Yield (%)	%ee
1	5a	CH ₂ Ph	CH ₂ CH=CH ₂	9b	86	33
2	5a	CH ₂ Ph	Me ^{a)}	9c	39	—
3	5b	CH ₂ -C ₆ H ₄ -NO ₂ - <i>p</i>	CH ₂ CH=CMe ₂	9d	94	50
4	5c	CH ₂ CH=CMe ₂	CH ₂ Ph	9a	68	13
5	5d	Me	CH ₂ CH=CMe ₂	9e	77	12 ^{b)}
6	5e	Ph	CH ₂ CH=CMe ₂	9f	88	37 ^{b)}

a) MeI b) determined by MTPA esters

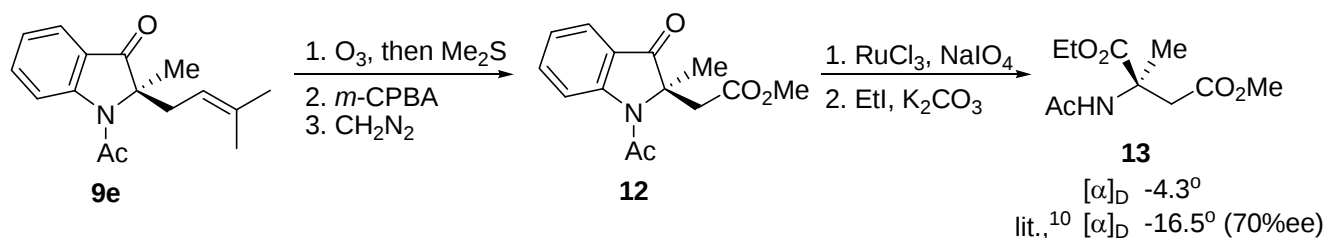
Table 2 PTC-Alkylation of **5a-e** with alkylhalides **6**

Next, we examined the reactivity and enantioselectivity between various indolin-3-ones **5a-e** and alkylhalides **6** with the above optimized conditions (Table 2). The methylation of **5a** was slower than both the allylation and benzylation (entry 2). Enantioselectivity was better with benzyl substituted indolin-3-one **5a** than with the *p*-nitrobenzyl substituted compound **5b** (Table 1, entry 2 vs. Table 2, entry 3). Interestingly, better enantioselectivity of **9a** was observed in the prenylation of 2-benzyl indolin-3-one **5a** than in the benzylation of 2-prenyl indolin-3-one **5c** (Table 1, entry 2 vs. Table 2, entry 4). This indicates that the interaction between PTC **7a** and the enolate of **5a** was much better than that of **5c**.



Scheme 1 Determination of enantioselectivity for **9e** and **9f**

The determination of enantioselectivity for **9e** and **9f** was not available by ¹H-NMR experiments with the chiral shift reagents. So, these compounds were introduced to MTPA esters **11** and the ratio of diastereomers was determined by ¹H-NMR. The reduction of **9e** with NaBH₄ gave **10a** as a single diastereomer and the stereochemistries were determined by NOE measurement (Scheme 1). Then **10a** was acylated with MTPA-Cl to afford **11a**.



Scheme 2 Transformation of **9e** to amino acid ester **13**

The absolute stereochemistry of **9e** was confirmed by introduction to the known amino acid ester *R*-(-)-**13** (Scheme 2).¹⁰ The ozonolysis of **9e** followed by oxidation and methylation afforded ester **12**. RuO₄-oxidation and esterification of **12** provided the desired compound (-)-**13**. The *R* configuration of **13** indicates that the transition state in the alkylation of indolin-3-one is similar to that of indanone, as suggested by Dolling.¹¹

In this study, we have developed the asymmetric alkylation of indolin-3-ones by optically active phase transfer catalyst. Further applications of this methodology to the synthesis of biologically active alkaloids are in progress.

EXPERIMENTAL

All melting points are uncorrected, and were measured on a Yanagimoto micromelting point apparatus. Optical rotations were obtained on a JASCO DIP-140 digital polarimeter. IR spectra were recorded on a Shimadzu FTIR-8400s spectrophotometer. ¹H and ¹³C NMR spectra were measured on a JEOL JMN-PMX270 (270 MHz) or JEOL JMN-GSX 400 (400 MHz) spectrometer with tetramethylsilane as an internal standard. J-Values are given in Hertz. Mass spectra were recorded on a JEOL JMS-DX 302 or JEOL JMS 700 instrument with a direct inlet system. Elemental analyses were obtained using a Perkin-Elmer Model 240B elemental analyzer. [α]_D were measured on a JEOL DIP-140. Column chromatography was carried out on a silica gel (Kanto Chemical Co. Inc., 230-400 mesh and Merck, 230-400 mesh).

1-Acetyl-2-(*p*-nitrobenzyl)indolin-3-one (**5b**)

To a solution of 1-acetyl-2-methoxyindolin-3-one^{5e} (1.2 g, 6.0 mmol) in benzene (60 mL) was added *p*-nitrobenzyl bromide (6.5 g, 30 mmol), triethylbenzylammonium bromide (30 mg) and 33% aqueous NaOH (15 mL) and then stirred at rt for 4 h. The mixture was added AcOEt (60 mL) and washed with H₂O (10 mL $\times$ 3). The organic layer was dried over MgSO₄ and concentrated. The residue was purified by column chromatography (CH₂Cl₂) gave 1-acetyl-2-methoxy-2-(*p*-nitrobenzyl)indolin-3-one (1.2 g, 60%) as a yellow oil.

Mp 133-134 °C. ^1H NMR (CDCl_3 , 270 MHz): δ 2.63 (3H, s), 3.21 (3H, s), 3.54 (2H, d, J = 3.6 Hz), 7.05-7.58 (6H, m), 7.93 (2H, d, J = 8.6 Hz). MS (EI) m/z (%): 251 (M^+ , 4), 204 (55), 162 (100). HRMS (EI): m/z calcd for $\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}_5$: 340.1065. Found: 340.1059.

To a solution of 1-acetyl-2-methoxy-2-(*p*-nitrobenzyl)indolin-3-one (1.5 g, 4.4 mmol) in MeOH (35 mL) was added NaBH_4 (1.7 g, 44 mmol) at 0 °C and stirred for 20 min. The reaction mixture was concentrated and added H_2O (30 mL). The mixture was extracted by AcOEt (20 mLx3) and the extract was dried over MgSO_4 . The organic layer was concentrated to give crude alcohol (1.5 g, 4.4 mmol). To a solution of above crude alcohol in CH_2Cl_2 (80 mL) was added SnCl_4 (2.0 g, 5.7 mmol) and stirred at 0 °C for 20 min. The reaction mixture was washed by H_2O (10 mLx3) and dried over MgSO_4 . The concentrated residue was purified by column chromatography (AcOEt:hexane=1:1) gave **5b** (0.73 g, 54%) as white crystals.

Mp 151-152 °C. ^1H NMR (CDCl_3 , 270 MHz): δ 2.50 (3H, s), 3.54 (2H, d, J = 2.6 Hz), 4.68 (1H, brs), 7.11 (2H, t, J = 7.9 Hz), 7.20 (2H, d, J = 8.6 Hz), 7.54 (1H, m), 7.62 (1H, brd, J = 7.6 Hz), 7.96 (2H, d, J = 8.6 Hz). IR (CHCl_3); 1723, 1670 cm^{-1} . Anal. Calcd for $\text{C}_{17}\text{H}_{14}\text{N}_2\text{O}_4$: C, 65.80; H, 4.55; N, 9.03. Found: C, 65.72; H, 4.61; N, 8.80. MS (EI) m/z (%): 310 (M^+ , 41), 268 (13), 174 (12), 137 (13), 132 (100), 43 (24).

1-Acetyl-2-phenylindolin-3-one (5e)

To a solution of 1-acetyl-2-methoxy-2-phenylindolin-3-one^{5f} (0.57g, 2.0 mmol) in MeOH (20 mL) was added NaBH_4 (0.76 g, 20 mmol) at 0 °C and stirred for 50 min. The reaction mixture was concentrated and added H_2O (10 mL). The mixture was extracted by AcOEt (10 mLx3) and the extract was dried over MgSO_4 . The organic layer was concentrated to give a crude alcohol (0.52 g). To a solution of alcohol in CH_2Cl_2 (40 mL) was added SnCl_4 (0.62 g, 2.4 mmol) and stirred at 0 °C for 30 min. The reaction mixture was washed by H_2O (10 mLx3) and dried over MgSO_4 . The concentrated residue was purified by column chromatography (CH_2Cl_2 :hexane=1:1) gave **5b** (0.28 g, 61%) as white crystals.

Mp 128-129 °C. ^1H NMR (CDCl_3 , 270 MHz): δ 2.07 (3H, s), 5.20 (1H, s), 7.20-7.30 (4H, m), 7.34-7.41 (2H, m), 7.71-7.76 (2H, m), 8.69 (1H, d, J = 7.6 Hz). IR (CHCl_3); 1727, 1682 cm^{-1} . Anal. Calcd for $\text{C}_{16}\text{H}_{13}\text{NO}_2$: C, 76.47; H, 5.22; N, 5.57. Found: C, 76.19; H, 5.29; N, 5.61. MS (EI) m/z (%): 251 (M^+ , 80), 209 (56), 208 (44), 181 (57), 180 (100), 152 (21), 104 (12), 77 (17).

Representative procedure for alkylation of 5a with PTC

1-Acetyl-2-benzyl-2-(3-methylbut-2-enyl)indolin-3-one (9a)

To a solution of **5a** (53 mg, 0.20 mmol), 50% NaOH (1.0 mL) and **7a** (4.5 mg, 0.01 mmol) in toluene (5.0 mL) was added 1-bromo-3-methyl-2-butene (0.12 mL, 1.0 mmol) and the reaction mixture was stirred at

0 °C under Ar atmosphere for 3 h. The mixture was added AcOEt (5.0 mL) and washed by H₂O (2.0 mL x 4). The organic layer was dried over MgSO₄ and concentrated. The residue was purified by column chromatography (AcOEt:hexane=1:4) gave **9a** (66 mg, 99%) as a pale yellow oil.

$[\alpha]_D^{25}$ -4.9° (c 1.62, CHCl₃). ¹H NMR (CDCl₃, 270 MHz): δ 1.45 (3H, s), 1.59 (3H, s), 2.45 (3H, s), 2.82 (1H, brs), 3.27 (2H, br), 3.77 (1H, br), 4.63 (1H, t, *J* = 7.3 Hz), 6.95-7.14 (6H, m), 7.14 (1H, br), 7.42 (1H, t, *J* = 7.3 Hz), 7.62 (1H, d, *J* = 7.3 Hz). IR (CHCl₃); 1716, 1668 cm⁻¹. Anal. Calcd for C₂₂H₂₃NO₂: C, 79.25; H, 6.95; N, 4.20. Found: C, 78.85; H, 6.93; N, 4.08. HRMS (EI): *m/z* calcd for C₂₂H₂₃NO₂: 333.1729. Found: 333.1754.

1-Acethyl-2-allyl-2-benzylindolin-3-one (9b)

The mixture of **5a** (53 mg, 0.20 mmol), allyl bromide (87 μL, 1.0 mmol), **7a** (4.5 mg), 50% aqueous NaOH (1.0 mL) and toluene (5.0 mL) stirring at 0 °C for 20 h gave **9b** (53 mg, 86%) as a white solid.

Mp 86-87 °C. $[\alpha]_D^{25}$ -1.25° (c 0.8, CHCl₃). ¹H NMR (CDCl₃, 270 MHz): δ 2.47 (3H, s), 2.86 (1H, br), 3.25 (1H, d, *J* = 13.2 Hz), 3.38 (1H, br), 3.77 (3H, d, *J* = 12.9 Hz), 4.87 (1H, d, *J* = 10.2 Hz), 5.07 (1H, d, *J* = 16.7 Hz), 5.26-5.41 (1H, m), 6.93-7.05 (6H, m), 7.16 (1H, br), 7.40-7.47 (1H, m), 7.63 (1H, d, *J* = 7.5 Hz). IR (CHCl₃); 1719, 1667 cm⁻¹. MS (EI) *m/z* (%): 305 (M⁺, 42), 264 (12), 222 (47), 214 (17), 172 (100), 91 (12), 43 (16). HRMS (EI): *m/z* Calcd for C₂₀H₁₉NO₂: 305.1416. Found: 305.1416.

1-Acethyl-2-benzyl-2-methylindolin-3-one (9c)

The mixture of **5a** (53 mg, 0.20 mmol), methyl iodide (67 μL, 1.0 mmol), **7a** (4.5 mg), 50% aqueous NaOH (1.0 mL) and toluene (5.0 mL) stirring at rt for 3 days gave **9c** (22 mg, 39%) as a viscous oil.

¹H NMR (CDCl₃, 270 MHz): δ 1.74 (3H, s), 2.49 (3H, s), 3.28 (1H, d, *J* = 13.2 Hz), 3.73 (1H, brs), 6.92-7.08 (5H, m), 7.47 (2H, t, *J* = 8.0 Hz), 7.67 (2H, d, *J* = 7.6 Hz). IR (CHCl₃); 1718, 1670 cm⁻¹. MS (EI) *m/z* (%): 279 (M⁺, 32), 188 (19), 147 (12), 146 (100), 43 (10). HRMS (EI): *m/z* Calcd for C₁₈H₁₇NO₂: 279.1259. Found: 279.1267.

1-Acethyl-2-(3-methylbut-2-enyl)-2-*p*-nitrobenzylindolin-3-one (9d)

The mixture of **5b** (62 mg, 0.20 mmol), 1-bromo-3-methyl-2-butene (0.12 mL, 1.0 mmol), **7a** (4.5 mg), 50% aqueous NaOH (1.0 mL), and toluene (5.0 mL) stirring at 0 °C for 2.5 h gave **9d** (71 mg, 94%) as a yellow oil.

$[\alpha]_D^{25}$ -23° (c 1.31, CHCl₃). ¹H NMR (CDCl₃, 270 MHz): δ 1.45 (3H, s), 1.59 (3H, s), 2.47 (3H, s), 2.82 (1H, brs), 3.34 (1H, brs), 3.37 (1H, d, *J* = 12.9 Hz), 3.90 (1H, d, *J* = 13.2 Hz), 4.62 (1H, t, *J* = 6.9 Hz), 7.04-7.15 (2H, m), 7.13, (2H, d, *J* = 8.9 Hz), 7.47 (1H, t, *J* = 7.3 Hz), 7.65 (1H, t, *J* = 7.3 Hz), 7.87 (2H, d, *J* = 8.9 Hz). IR (CHCl₃); 1722, 1675 cm⁻¹. MS (EI) *m/z* (%): 378 (M⁺, 13), 311 (20), 310 (98),

268 (100), 242 (12), 221 (14), 200 (26), 149 (15), 69 (21), 43 (23). HRMS (EI): m/z Calcd for $C_{22}H_{22}N_2O_4$: 378.1579. Found: 378.1575.

1-Acetyl-2-benzyl-2-(3-methylbut-2-enyl)indolin-3-one (9a): benzylation of 5c

The mixture of **5c**^{5e} (50 mg, 0.20 mmol), benzyl bromide (0.12 mL, 1.0 mmol), **7a** (4.5 mg), 50% NaOH (1.0 mL) and toluene (5.0 mL) stirring at 0 °C for 20 h gave **9a** (46 mg, 68%) as a pale yellow oil. $[\alpha]_D^{25}$ -4.9° (c 1.22, $CHCl_3$).

1-Acetyl-2-methyl-2-(3-methylbut-2-enyl)indolin-3-one (9e)

The mixture of **5d**^{5e} (38 mg, 0.20 mmol), 1-bromo-3-methyl-2-butene (0.12 mL, 1.0 mmol), **7a** (4.5 mg), 50% aqueous NaOH (1.0 mL) and toluene (5.0 mL) stirring at 0 °C for 3.5 h gave **9e** (40 mg, 77%) as an yellow oil.

$[\alpha]_D^{25}$ -4.3° (c 0.70, $CHCl_3$). 1H NMR ($CDCl_3$, 270 MHz): δ 1.45 (3H, s), 1.56 (3H, s), 1.61 (3H, s), 2.49 (3H, s), 2.76 (1H, brs), 3.00 (1H, brs), 4.60 (1H, t, J = 7.3 Hz), 7.20 (1H, t, J = 7.9 Hz), 7.62-7.70 (1H, m), 7.77 (1H, d, J = 7.6 Hz). IR ($CHCl_3$); 1726, 1670 cm^{-1} . MS (EI) m/z (%): 257 (M^+ , 10), 189 (50), 147 (49), 146 (100), 43 (13). HRMS (EI): m/z Calcd for $C_{16}H_{19}NO_2$: 257.1416. Found: 257.1413.

1-Acetyl-2-(3-methylbut-2-enyl)-2-phenylindolin-3-one (9f)

The mixture of **5e** (50 mg, 0.20 mmol), 1-bromo-3-methyl-2-butene (0.12 mL, 1.0 mmol), **7a** (4.5 mg), 50% aqueous NaOH (1.0 mL) and toluene (5.0 mL) stirring at 0 °C for 4.5 h gave **9f** (57 mg, 88%) as an yellow oil.

$[\alpha]_D^{25}$ -150° (c = 1.02, $CHCl_3$). 1H NMR ($CDCl_3$, 270 MHz): δ 1.50 (3H, s), 1.64 (3H, s), 1.97 (3H, s), 3.10 (1H, brs), 3.64 (1H, brs), 4.73 (1H, t, J = 6.9 Hz), 7.21-7.38 (6H, m), 7.74 (2H, m), 8.82 (1H, br). IR ($CHCl_3$); 1722, 1666 cm^{-1} . MS (EI) m/z (%): 319 (M^+ , 5), 251 (39), 250 (11), 209 (41), 208 (100). HRMS (EI): m/z Calcd for $C_{21}H_{21}NO_2$: 319.1572. Found: 319.1573.

1-Acetyl-3-hydroxy-2-methyl-2-(3-methylbut-2-enyl)indoline (10a)

To a solution of **9e** (30 mg, 0.12 mmol) in MeOH (3.0 mL) was added $NaBH_4$ (44 mg, 1.2 mmol) at 0 °C and the reaction mixture was stirred for 15 min. The mixture was concentrated and added H_2O (5.0 mL). The mixture was extracted with AcOEt (5.0 mLx3) and the extract was dried over $MgSO_4$. The residue was purified by column chromatography (AcOEt:hexane=1:2) gave **10a** (24 mg, 79%) as a colorless oil.

1H NMR ($CDCl_3$, 270 MHz): δ 1.52 (3H, s), 1.60 (3H, s), 1.65 (3H, s), 2.33 (1H, d, J = 6.1 Hz), 2.43 (3H, s), 2.82 (1H, br), 2.97 (1H, br), 4.77 (1H, d, J = 7.6 Hz), 5.09 (1H, t, J = 6.4 Hz), 7.08 (1H, t, J = 7.5 Hz), 7.29 (1H, t, J = 7.5 Hz), 7.41 (1H, d, J = 7.2 Hz). IR ($CHCl_3$); 3504, 1645 cm^{-1} . MS (EI) m/z (%): 259

(M^+ , 11), 241 (16), 190 (50), 184 (23), 149 (13), 148 (100), 131 (15), 130 (10). HRMS (EI): m/z Calcd for $C_{16}H_{21}NO_2$: 259.1572. Found: 259.1570.

1-Acetyl-3-[(2-methoxy-2-phenyl-3,3,3-trifluoro)propioxy]-2-methyl-2-(3-methylbut-2-enyl)indoline (11a)

To a solution of **10a** (13 mg, 0.050 mmol) in CH_2Cl_2 (1.0 mL) was added dry Et_3N (14 μ L, 1.0 mmol), DMAP (12 mg, 1.0 mmol) and (S)-MTPA chloride (56 μ L, 0.30 mmol) at 0 °C and then stirred for 1.5 h. The reaction mixture was concentrated and the residue was purified by preparative TLC (AcOEt:hexane=1:3) gave (S)-MTPA ester **11a** (15 mg, 61%) as an yellow oil. (R)-MTPA ester was obtained by similar procedure as above.

1H NMR ($CDCl_3$, 270 MHz): δ 1.41 (1.68H, s), 1.47 (1.32H, s), 1.52 (3H, s), 1.55 (1.32H, s), 1.58 (1.68H, s), 2.37 (1.32H, s), 2.40 (1.68H, s), 2.51 (0.56H, dd, J = 6.6, 14.8 Hz), 2.68 (0.44H, dd, J = 7.3, 15.5 Hz), 2.96 (0.56H, d, J = 14.5 Hz), 2.98 (0.44H, d, J = 14.5 Hz), 3.41 (1.68H, s), 3.43 (1.32 H, s), 4.75 (0.56H, t, J = 6.6 Hz), 4.87 (0.44H, t, J = 6.9 Hz), 6.03 (0.56H, s), 6.06 (0.44H, s), 6.98-7.09 (1H, m), 7.10-7.50 (8H, m). IR ($CHCl_3$); 1747, 1655 cm^{-1} . MS (EI) m/z (%): 475 (M^+ , 2), 406 (18), 364 (14), 241 (35), 199 (16), 198 (13), 190 (19), 189 (100), 184 (47), 175 (11), 148 (47), 146 (13), 144 (15), 131 (34), 130 (16), 105 (17), 91 (17), 77 (13), 43 (11). HRMS (EI): m/z Calcd for $C_{26}H_{28}NO_4F_3$: 475.1970. Found: 475.1971.

1-Acetyl-3-hydroxy -2-(3-methylbut-2-enyl) -2-phenylindoline (10b)

As a similar procedure of the preparation of **10a**, to a solution of **9f** (56 mg, 0.18 mmol) in MeOH (1.4 mL) was added $NaBH_4$ (166 mg, 4.4 mmol) at 0 °C and the reaction mixture was stirred for 25 h to afford **10b** (32 mg, 57%).

1H NMR ($CDCl_3$, 270 MHz): δ 1.56 (3H, s), 1.71 (3H, s), 1.86 (3H, br), 2.33 (1H, d, J = 10.2 Hz), 2.96 (1H, br), 3.56 (1H, br), 5.05 (1H, t, J = 5.9 Hz), 5.12 (1H, d, J = 10.6 Hz), 7.13 (1H, t, J = 7.6 Hz), 7.26-7.40 (7H, m), 8.47 (1H, br).

1-Acetyl-3-[(2-methoxy-2-phenyl-3,3,3-trifluoro)propioxy]-2-(3-methylbut-2-enyl)-2-phenylindoline (11b)

As a similar procedure of the preparation of **11a**, to a solution of major alcohol **10b** (8.0 mg, 0.025mmol) in dry CH_2Cl_2 (0.3 mL) was added dry Et_3N (21 μ L, 0.15 mmol), DMAP (24 mg, 0.20 mmol) and (R)-MTPA chloride (21 μ L, 0.15 mmol) at rt and stirred for 23 h to give (R)-MTPA ester **11b** (5.8 mg, 43%) as an yellow oil. (S)-MTPA ester was prepared by similar procedure as above.

^1H NMR (CDCl_3 , 270 MHz): δ 1.26 (2.04H, s), 1.37 (0.96H, s), 1.46 (3H, s), 1.91 (3H, brs), 2.75-3.25 (2H, m), 3.46 (2.04H, s), 3.49 (0.96H, s), 4.90 (1H, s), 6.39 (0.32H, s), 6.42 (0.68H, s), 7.00-7.49 (13H, m), 8.30 (1H, brs). IR (CHCl_3); 1750, 1662 cm^{-1} .

1-Acethyl-2-methyl-2-(2-methoxy-2-oxoethyl)indolin-3-one (12)

A solution of **9e** (200 mg, 0.78 mmol) in CH_2Cl_2 -MeOH (25 mL, 10:1) was bubbled with O_3 at -78°C . After the starting material consumption on TLC, Me_2S (53 mg) was added and stirred at rt for 1 day. The reaction mixture was concentrated and dissolved in CH_2Cl_2 (20 mL). *m*-CPBA (380 mg, 80%, 1.8 mmol) was added to the solution at rt and stirred for 2 h. The reaction mixture was concentrated and dissolved in Et_2O (20 mL). CH_2N_2 in Et_2O was added to the solution and stirred at rt for 1 day. The reaction mixture was concentrated and the residue was purified by column chromatography (AcOEt:hexane=1:2) gave **12** (185 mg, 91%) as a white solid.

^1H NMR (CDCl_3 , 270 MHz): δ 1.56 (3H, s), 2.54 (3H, s), 3.15 (1H, d, $J = 16.8$ Hz), 3.47 (3H, s), 3.74 (1H, brs), 7.24 (2H, t, $J = 7.9$ Hz), 7.67 (1H, t, $J = 7.3$ Hz), 7.86 (1H, d, $J = 7.6$ Hz). IR (CHCl_3); 1714, 1609 cm^{-1} . MS (EI) m/z (%): 261 (M^+ , 33), 230 (12), 220 (13), 219 (100), 191 (42), 190 (39), 188 (18), 176 (17), 160 (11), 159 (16), 146 (42), 144 (13), 132 (11), 130 (19), 118 (27), 117 (14), 43 (21).

Amino acid (13)

To a solution of **12** (90 mg, 0.35 mmol) in MeCN (1.4 mL) was added NaIO_4 (1.3g 6.2 mmol) and a solution of RuCl_3 (1.6 mg, 0.076 mmol) in CCl_4 - H_2O (4.2 mL, 1:2). The reaction mixture was stirred at rt for 3 days. The mixture was filtrated and extracted by AcOEt (10 mLx3) and dried over MgSO_4 . After the extract was concentrated, the residue was dissolved in acetone (3.0 mL), K_2CO_3 (0.20 g) and EtI (1.3 mL) were added to the solution and stirred at rt for 3 h. The reaction mixture was concentrated and the residue was purified by column chromatography (AcOEt:hexane=1:1) gave **13** (6.0 mg, 8%) as a white solid.

Mp $72-73^\circ\text{C}$. $[\alpha]_{\text{D}}^{25} -4.3^\circ$ (c 0.6, CHCl_3). [lit.,¹⁰ $[\alpha]_{\text{D}} = -16.5^\circ$ (c 1, CHCl_3), 70%ee]. ^1H NMR (CDCl_3 , 270 MHz): δ 1.28 (3H, t, $J = 6.9$ Hz), 1.64 (3H, s), 1.98 (3H, s), 2.93 (1H, d, $J = 16.8$ Hz), 3.56 (1H, d, $J = 16.5$ Hz), 3.65 (3H, s), 4.18-4.30 (2H, m), 6.65 (1H, brs). IR (CHCl_3); 1719, 1667 cm^{-1} . MS (EI) m/z (%): 231 (M^+ , 1.2), 158 (69), 116 (100), 84 (25), 43 (38), 42 (29). HRMS (EI): m/z Calcd for $\text{C}_{10}\text{H}_{17}\text{NO}_5$: 231.1107. Found: 231.1109.

ACKNOWLEDGEMENTS

We thank N. Eguchi, T. Koseki, and S. Kubota of the Analytical Center at our University for microanalysis and mass spectral measurements.

REFERENCES

1. L. A. Adams, M. W. N. Valente, and R. M. Williams, *Tetrahedron*, 2006, **62**, 5195, and references were cited therein.
2. P. S. Baran and E. J. Corey, *J. Am. Chem. Soc.*, 2002, **124**, 7904.
3. Y. Liu and W. W. McWhorter Jr., *J. Am. Chem. Soc.*, 2003, **125**, 4240.
4. X. Zhang and C. S. Foote, *J. Am. Chem. Soc.*, 1993, **115**, 8867.
5. a) T. Kawasaki, Y. Nonaka, K. Watanabe, A. Ogawa, K. Higuchi, R. Terashima, K. Masuda, and M. Sakamoto, *J. Org. Chem.*, 2001, **66**, 1200. b) T. Kawasaki, K. Masuda, Y. Baba, R. Terashima, K. Takada, and M. Sakamoto, *J. Chem. Soc., Perkin Trans. 1*, 1996, 729. c) T. Kawasaki, K. Watanabe, K. Masuda, and M. Sakamoto, *J. Chem. Soc., Chem. Commun.*, 1995, 381. d) T. Kawasaki, K. Masuda, Y. Baba, R. Terashima, K. Takada, and M. Sakamoto, *Chem. Pharm. Bull.*, 1994, **42**, 1974. e) T. Kawasaki, Y. Nonaka, M. Kobayashi, and M. Sakamoto, *J. Chem. Soc., Perkin Trans. 1*, 1991, 2445. f) C.-S. Chien, T. Takanami, T. Kawasaki, and M. Sakamoto, *Chem. Pharm. Bull.*, 1985, **33**, 1843.
6. Reviews: a) B. Lygo and B. I. Andrews, *Acc. Chem. Res.*, 2004, **37**, 518. b) K. Maruoka and T. Ooi, *Chem. Rev.*, 2003, **103**, 3013.
7. U.-H. Dolling, P. Davis, and E. J. J. Grabowski, *J. Am. Chem. Soc.*, 1984, **106**, 446.
8. B. K. Thomas and G. S. K. Wong, *J. Org. Chem.*, 1991, **56**, 872.
9. D. L. Hughes, U.-H. Dolling, K. M. Ryan, E. F. Schoenewaldt, and E. J. J. Grabowski, *J. Org. Chem.*, 1987, **52**, 4545.
10. G. I. Georg, X. Guand, and J. Kant, *Tetrahedron Lett.*, 1988, **29**, 403.
11. A. Bhattacharya, U.-H. Dolling, E. J. J. Grabowski, S. Karady, K. M. Ryan, and L. M. Weinstock, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 476.