Supporting Information

ALTERNATIVE CHIRAL PREPARATIONS OF A SWAMINATHAN KETONE
VIA ASYMMETRIC ALDOL REACTIONS MEDIATED BY CHIRAL AMINES
BEARING A PYRROLIDINE

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**Experimental**

IR spectra were recorded on a Perkin Elmer Spectorum One FT–IR spectrophotometer. $^1$H- and $^{13}$C-NMR spectra were recorded on a JEOL-AX-400 ($^1$H: 400 MHz, $^{13}$C: 100 MHz) or JEOL JNM-ECZ600R ($^1$H: 600 MHz, $^{13}$C: 150 MHz) spectrometer. All $^1$H-NMR spectra were reported in ppm downfield of tetramethylsilane (TMS). All $^{13}$C-NMR spectra were reported in ppm relative to CHCl$_3$ (77 ppm) and were obtained with $^1$H decoupling. MS spectra were recorded on a JEOL-JMS-700V spectrometer. Optical purity was determined using a Hitachi HPLC ELITE LaChrom instrument equipped with a chiral stationary phase column. Optical rotations were measured with a JASCO D-2300 digital polarimeter. All reactions were performed under an argon atmosphere.

**General procedure of the aldol reaction of 7 in Table 1 and 2**

To a stirred solution of (S)-1-(2-pyrrolidinylmethyl)pyrrolidine (10) 73 mg (0.476 mmol) and trifluoroacetic acid (TFA) 55 μL (0.714 mmol) in anhydrous dimethylsulfoxide (DMSO, 0.5 mL) was added the trione (7) 100 mg (0.476 mmol) at room temperature (25 °C). The reaction mixture was stirred at the same temperature for 93 h and was monitored by a reverse phase TLC (RP-18, MeOH/H$_2$O = 1:1, v/v). The mixture was poured into 10 (w/v)% aqueous HCl and was extracted with ethyl acetate (AcOEt). The combined organic layer was washed with saturated aqueous NaHCO$_3$ and brine. After drying (Na$_2$SO$_4$), the solvent was removed under reduced pressure. The residue was chromatographed by a preparative HPLC instrument equipped with a reverse phase column (ODS silica gel, 75 μm, 20 mm φ x 300 mm, eluent: MeOH/H$_2$O = 40:60 (v/v), flow rate: 10 mL/min) to afford (S)-3 43 mg (47%) as a colorless oil and the starting 7 26 mg (26%) as colorless crystals. All spectroscopic data of (S)-3 were identical with those reported. The optical purity was determined to be 64% ee by HPLC with a chiral stationary phase column. HPLC conditions: Chiralpak AS-H, EtOH/hexane = 10/90 (v/v), flow rate 1.0 mL/min, detected at 254 nm, $t_R$ = 37.0 min for (R)-3, 42.5 min for (S)-3.

**Typical procedure of the aldol reaction of 7 on a gram scale**

To a stirred solution of 10 2.20 g (14 mmol) and TFA 1.6 mL (21 mmol) in anhydrous DMSO (15 mL) was added the trione (7) 3.0 g (14 mmol) at room temperature (25 °C). The reaction mixture was stirred at 50 °C for 26 h. The mixture was diluted with ethyl acetate (AcOEt) and was washed with 10 (w/v)% aqueous HCl, saturated aqueous NaHCO$_3$ and brine. After drying (Na$_2$SO$_4$), the solvent was removed.
under reduced pressure. The residue was chromatographed on silica gel (AcOEt/hexane = 10:90, v/v) to afford (S)-3 2.52 g (92%) as a colorless oil. The optical purity was determined to be 55% ee by HPLC described above.
(S)-3: [α]_D^{21} +49.7 (55% ee, c 1.5, CHCl₃), lit.⁴a [α]_D^{24} +7.9 (8% ee, c 1.0, CHCl₃).

Preparation of (R)-3

According to Xu’s method,⁴c (R)-3 was also prepared from trione (7). To a stirred solution of (S)-prolinamide (8) 56 mg (0.476 mmol) and acetic acid (AcOH) 27 μL (0.476 mmol) in anhydrous dichloromethane (DCM, 2.5 mL) was added 7 100 mg (0.476 mmol) at room temperature (25 °C). The reaction mixture was stirred at the same temperature for 48 h. The mixture was poured into 10 (w/v) % aqueous HCl and was extracted with ethyl acetate (AcOEt). The combined organic layer was washed with saturated aqueous NaHCO₃ and brine. After drying (Na₂SO₄), the solvent was removed under reduced pressure. The residue was chromatographed by a preparative HPLC instrument equipped with a reverse phase column (ODS silica gel, 75 μm, 20 mm φ X 300 mm, eluent: MeOH/H₂O = 40:60 (v/v), flow rate: 10 mL/min) to afford (R)-3 45 mg (49%) as a colorless oil and the starting 7 32 mg (32%) as colorless crystals. All spectroscopic data of (R)-3 were identical with those reported.⁴c The optical purity was determined to be 51% ee by HPLC described above.
(R)-3: [α]_D^{24} −47.2 (51% ee, c 1.3, CHCl₃).

Synthesis of 12 and 13.

To a stirred solution of (S)-3 (55% ee) 2.49 g (13 mmol) in anhydrous THF (30 mL) was slowly added diisobutylaluminum hydride (DIBALH, 1.02 M in hexane) 32 mL (32 mmol) over 15 min in an ice bath. The reaction mixture was stirred at the same temperature for 1 h. Ammoniac water (28%, w/v) was carefully added and the mixture was stirred at room temperature (25 °C) for 3 h. The mixture was filtered through a Celite pad and the filtrate was extracted with AcOEt. The combined organic layer was washed with brine. After drying (Na₂SO₄), the solvent was removed under reduced pressure. The residue was used
to a next reaction without further purification. The residue 2.40 g was dissolved to anhydrous DCM (50 mL), and MnO$_2$ 10.7 g (122 mmol) was added as one portion to the mixture at room temperature (25 °C). The mixture was stirred at the same temperature for 22 h and was filtered through a Celite pad. The filtrate was concentrated under reduced pressure. The diastereomeric ratio was determined by $^1$H-NMR of crude products to be 12:13 = 82:18. The residue was chromatographed on silica gel (sphere silica gel, AcOEt/hexane = 20:80 to 30:70, v/v) to afford 12 1.37 g (54%), a mixture of 12 and 13 220 mg (9%) and 13 327 mg (13%) as a colorless oil, respectively. All spectroscopic data were identical with those reported.

**General procedure of the acetylation of 12, 16 and 17**

To a stirred solution of 12 50 mg (0.52 mmol) in pyridine (1 mL) was added acetic anhydride (Ac$_2$O) 0.15 mL (1.54 mmol) at room temperature (25 °C). The mixture was stirred at the same temperature for 61 h. The solvent was removed under reduced pressure and the residue was dissolved to AcOEt. The mixture was washed with 10% aqueous HCl, sat. aqueous NaHCO$_3$ and brine, respectively. After drying (Na$_2$SO$_4$), the solvent was removed under reduced pressure. The residue was chromatographed (AcOEt/Hexane = 20/80, v/v) to afford 14 97 mg (80%) as a white solid.

14: $^1$H-NMR (400 MHz, CDCl$_3$), $\delta$ 1.21 (s, 3H), 1.39-1.53 (m, 2H), 1.58-1.78 (m, 2H), 1.74 (dt, $J$ = 5.3 Hz, 13.5 Hz, 1H), 1.89-2.02 (m, 3H), 2.14 (s, 3H), 2.27-2.35 (m, 1H), 2.46-2.56 (m, 3H), 4.83 (d, $J$ = 8.7 Hz, 1H), 5.86 (s, 1H). $^{13}$C-NMR (100 MHz, CDCl$_3$), $\delta$ 20.4, 21.4, 22.1, 28.9, 29.3, 33.6, 33.8, 34.8, 43.1, 76.6, 128.8, 170.4, 171.2, 199.0. EIMS (m/z) 236 (M$^+$), 194 (100%), 208, 176, 137, 124, 109. HRMS calcd for C$_{14}$H$_{20}$O$_3$ 236.1412. Found 236.1405.

18: Yield: 96% as a colorless oil. IR (liquid film) ν (cm$^{-1}$) 1732, 1715, 1602, 1451, 1112, 1924, 963, 712.

$^1$H-NMR (400 MHz, CDCl$_3$), $\delta$ 1.22 (s, 3H), 1.38-1.90 (m, 8H), 1.92-2.12 (m, 2H), 2.05 (s, 3H), 2.23 (td, $J$ = 5.3 Hz, 13.5 Hz, 1H), 2.40 (ddd, $J$ = 5.3 Hz, 9.7 Hz, 14.5 Hz, 1H), 4.94 (dd, $J$ = 2.4 Hz, 9.7 Hz, 1H), 5.26 (dt, $J$ = 3.4 Hz, 6.3 Hz, 1H), 5.50 (d, $J$ = 2.9 Hz, 1H), 7.47 (t, $J$ = 7.7 Hz, 2H), 7.58 (tt, $J$ = 1.4 Hz, 7.2 Hz, 1H), 8.07 (dd, $J$ = 1.4 Hz, 7.7 Hz, 2H). $^{13}$C-NMR (100 MHz, CDCl$_3$), $\delta$ 21.2, 21.4, 21.7, 24.4, 28.9, 29.3, 32.3, 32.4, 41.5, 69.1, 77.9, 124.2, 128.4, 129.5, 130.5, 132.9, 148.6, 165.7, 170.8. EIMS (m/z) 282 (M$^+$/AcOH), 220 (M$^+$/BzOH), 178, 160, 105 (100%), 77. HRMS calcd for C$_{14}$H$_{20}$O$_3$ (M$^+$/AcOH) 220.1463. Found 220.1465.
19: Yield: 84% as a colorless oil. [α]D²⁴ = +118.6 (55% ee, c 0.81, CHCl₃). IR (liquid film) ν (cm⁻¹) 1732, 1716, 1451, 1273, 712. ¹H-NMR (400 MHz, CDCl₃), δ 1.15 (s, 3H), 1.40 (ddd, J = 3.4 Hz, 7.7 Hz, 13.5 Hz, 1H), 1.44-1.56 (m, 2H), 1.58-1.59 (m, 6H), 1.91-2.10 (m 2H), 2.06 (s, 3H), 2.21 (td, J = 5.3 Hz, 13.0 Hz, 1H), 2.34-2.44 (m, 1H), 5.06 (dd, J = 2.4 Hz, 9.2 Hz, 1H), 5.22 (dd, J = 4.3 Hz, 9.2 Hz, 1H), 5.52 (d, J = 4.3 Hz, 1H), 7.47 (tt, J = 7.7 Hz, 2H), 7.58 (tt, J = 1.4 Hz, 7.2 Hz, 1H), 8.97 (dd, J = 1.4 Hz, 8.2 Hz, 2H). ¹³C-NMR (100 MHz, CDCl₃), δ 20.9, 21.5, 21.7, 24.2, 28.7, 29.4, 31.7, 32.3, 41.6, 68.2, 78.3, 123.5, 128.5, 129.5, 130.5, 132.9, 149.4, 165.8, 171.0. EIMS (m/z) 342 (M⁺), 282, 220, 178, 160, 105 (100%), 77. HRMS calcd for C₂₁H₂₆O₄ 342.1831. Found 342.1823.

Synthesis of benzoate (15).

To a stirred solution of 12 352 mg (1.8 mmol), triethylamine (TEA) 0.39 mL (2.7 mmol), 4-dimethylaminopyridine (DMAP) 333 mg (2.7 mmol) in anhydrous DCM (5 mL) was added benzoyl chloride (BzCl) 0.32 mL (2.7 mmol) in an ice bath. After stirring at the same temperature for 15 min, the mixture was further stirred at room temperature (25 °C) for 16.5 h. The solvent was removed under reduced pressure and the residue was dissolved to AcOEt. The mixture was washed with 10% aqueous HCl, sat. aqueous NaHCO₃ and brine respectively. After drying (Na₂SO₄), the solvent was removed under reduced pressure. The residue was chromatographed (AcOEt/Hexane = 10/90 to 15/85, v/v) to afford 15 529 mg (98%) as a colorless gummy syrup.

15: [α]D²⁵ =+69.3 (55% ee, c 1.1, CHCl₃). IR (liquid film) ν (cm⁻¹) 1716, 1673, 1450, 1273, 1111, 711. ¹H-NMR (400 MHz, CDCl₃), δ 1.31 (s, 3H), 1.43-1.57 (m, 2H), 1.63-1.86 (m, 3H), 1.9802.19 (m, 3H), 2.42 (td, J = 4.3 Hz, 10.6 Hz, 1H), 2.51 (d, J = 5.3 Hz, 1H), 2.54 (dd, J = 1.9 Hz, 5.3 Hz, 1H), 2.65 (dd, J = 4.3 Hz, 10.1 Hz, 12.6 Hz, 1H), 5.09 (dd, J = 1.4 Hz, 8.7 Hz, 1H), 5.89 (s, 1H), 7.50 (t, J = 7.7 Hz, 2H), 7.61 (tt, J = 1.0 Hz, 8.7 Hz, 1H), 8.08 (dd, J = 1.4 Hz, 8.9 Hz, 2H). ¹³C-NMR (100 MHz, CDCl₃), δ 20.3, 21.8, 28.6, 29.2, 33.2, 33.7, 34.5, 43.2, 77.0, 128.47, 128.54, 129.5, 130.0, 133.2, 165.4, 170.9, 198.7. EIMS (m/z) 298 (M⁺), 176, 105 (100%), 77. HRMS calcd for C₁₉H₂₆O₄ 298.1569. Found 298.1572.
Synthesis of alcohols (16) and (17).

To a stirred solution of 15 529 mg (1.8 mmol) in anhydrous MeOH (5 mL) was added NaBH₄ 170 mg (4.5 mmol) as a small portion over 15 min at −10 °C. After stirring at the same temperature for 2 h, acetone was added to the mixture to quench the reaction. The solvent was removed under reduced pressure and the residue was dissolved in AcOEt. The mixture was washed with sat. aqueous NaHCO₃ and brine respectively. After drying (Na₂SO₄), the solvent was removed under reduced pressure. The diastereomeric ratio was determined by ¹H-NMR of crude products to be 16:17 = 75:25. The residue was chromatographed (AcOEt/toluene = 5/95, v/v) to afford 16 315 mg (59%), a mixture of 16 and 17 42 mg (8%) and 17 53 mg (10%) as a colorless gummy syrup, respectively.

16: [α]D²² +17.3 (55% ee, c 1.2, CHCl₃). IR (liquid film) ν (cm⁻¹) 3369, 1714, 1601, 1450, 1314, 711. ¹H-NMR (400 MHz, CDCl₃), δ 1.21 (s, 3H), 1.39-1.88 (m, 9H, 1H: D₂O exchangeable), 1.93-2.08 (m, 2H), 2.21 (td, J = 5.3 Hz, 11.1 Hz, 1H), 2.38 (ddd, J = 5.3 Hz, 9.2 Hz, 14.0 Hz, 1H), 4.16-4.23 (brm, 1H), 4.93 (dd, J = 1.9 Hz, 9.2 Hz, 1H), 5.55 (d, J = 2.9 Hz, 1H), 7.47 (t, J = 7.7 Hz, 2H), 7.58 (tt, J = 1.4 Hz, 7.7 Hz, 1H), 8.07 (dd, J = 1.4 Hz, 8.2 Hz, 2H). ¹³C-NMR (100 MHz, CDCl₃), δ 21.3, 21.7, 28.0, 28.9, 29.4, 32.3, 41.5, 66.1, 78.1, 128.4, 129.5, 130.4, 132.9, 146.3, 165.7. EIMS (m/z) 298 (M⁺-2), 178, 160, 105 (100%), 77. HRMS calcd for C₁₉H₂₀O₃ (M⁺-2) 298.1569. Found 298.1566.

17: [α]D²⁵ +66.6 (55% ee, c 1.1, CHCl₃). IR (liquid film) ν (cm⁻¹) 3391, 1715, 1699, 1601, 1451, 1274, 1116, 711. ¹H-NMR (400 MHz, CDCl₃), δ 1.14 (s, 3H), 1.31-1.56 (m, 3H), 1.57-2.06 (m, 8H, 1H: D₂O exchangeable), 2.18 (td, J = 5.3 Hz, 13.0 Hz, 1H), 2.34-2.44 (m, 1H), 4.17 (brs, 1H), 5.06 (dd, J = 1.9 Hz, 9.2 Hz, 1H), 5.58 (d, J = 3.9 Hz, 1H), 7.47 (t, J = 7.7 Hz, 2H), 7.58 (td, J = 1.4 Hz, 7.2 Hz, 1H), 8.07 (dd, J = 1.0 Hz, 8.2 Hz, 2H). ¹³C-NMR (100 MHz, CDCl₃), δ 21.0, 21.6, 27.6 28.7, 29.4, 31.5, 32.1, 41.6, 65.2, 78.4, 127.8, 128.4, 129.5, 130.5, 132.8, 147.0, 165.7. EIMS (m/z) 298 (M⁺-2), 178, 160, 105 (100%), 77. HRMS calcd for C₁₉H₂₀O₃ (M⁺-2) 298.1569. Found 298.1566.

General procedure of the lipase-mediated asymmetric esterification of 16

General procedure of the lipase-mediated asymmetric esterification of 16
To a stirred solution of 16 50 mg (55% ee, 0.17 mmol) and lipase AS 120 mg (2.4 times the weight of 16) in ’BuOMe (1 mL) was added vinyl acetate 31 μL (0.33 mmol) at room temperature. The mixture was stirred at the same temperature (25 °C) for 68 h. The mixture was filtered through a Celite pad and the filtrate was concentrated under reduced pressure. The residue was chromatographed (AcOEt/hexane = 4/96 to 20/80, v/v) to afford 18 13 mg (23%) and 16 38 mg (76%) as a colorless oil, respectively. All spectroscopic data were identical with those described above. The optical purity of 18 was determined to be 88% ee by HPLC with a chiral stationary phase column. HPLC conditions: Chiralpak AD-H, 2-propanol/hexane = 2/98 (v/v), flow rate 1.0 mL/min, detected at 254 nm, tR = 9.1 min for (7S)-18, 13.2 min for (7R)-18. The optical purity of 16 was determined to be 45% ee by HPLC with a chiral stationary phase column. HPLC conditions: Chiralpak AY-H, 2-propanol/hexane = 10/90 (v/v), flow rate 1.0 mL/min, detected at 254 nm, tR = 7.1 min for (7R)-16, 8.1 min for (7S)-16. 18: [α]D22 −16.6 (88% ee, c 1.3, CHCl3).

**General procedure for synthesis of Mosher’s esters (20a) and (20b)**

![Mosher’s esters (20a) and (20b)](image)

To a stirred solution of 16 12 mg (55% ee, 40.7 μmol), TEA 17 μL (122 μmol) and DMAP 15 mg (122 μmol) in anhydrous DCM (0.2 mL) was added a solution of (R)-MTPACl 31 mg (122 μmol) in DCM (0.3 mL) at room temperature (25 °C). The mixture was stirred at the same temperature for 1 h. The solvent was removed under reduced pressure and the residue was dissolved to AcOEt. The mixture was washed with 10% (w/v) aqueous HCl, sat. aqueous NaHCO3 and brine respectively. After drying (Na2SO4), the solvent was removed under reduced pressure. The residue was chromatographed (AcOEt/hexane = 2/98, v/v) to afford a diastereomeric mixture of 20a and ent-20b 19.4 mg (92%) as a colorless oil. 1H-NMR of 20a was measured without further purifications. (R)-MTPA ester (20b) was also obtained in 82% yield by using (S)-MTPACl.
Spectra of compound (S)-3

(S)-3
Spectra of compound (R)-3

(R)-3

(S)-3

(R)-3
Spectra of compound 14
Spectra of compound 15
Spectra of compound 16
Spectra of compound 17
Spectra of compound 18
Spectra of compound 19
Spectra of compound 20a and 20b
Compound (S)-3
HPLC conditions: Chiralpak AS-H, EtOH/hexane = 10/90 (v/v), flow rate 1.0 mL/min, detected at 254 nm, $t_R = 37.0$ min for (R)-3, 42.5 min for (S)-3.

Compound (R)-3
HPLC conditions: Chiralpak AS-H, EtOH/hexane = 10/90 (v/v), flow rate 1.0 mL/min, detected at 254 nm, $t_R = 36.7$ min for (R)-3, 44.2 min for (S)-3.
Compound (S)-3
HPLC conditions: Chiralpak OB-H, 2-propanol/hexane = 4/96 (v/v), flow rate 1.0 mL/min, detected at 254 nm, \( t_R = 27.8 \text{ min} \) for (S)-3, 40.7 min for (R)-3.

![HPLC chromatogram of (S)-3](image)

Compound (S)-3
HPLC conditions: Chiralpak OJ-H, 2-propanol/hexane = 10/90 (v/v), flow rate 1.0 mL/min, detected at 254 nm, \( t_R = 15.2 \text{ min} \) for (R)-3, 17.3 min for (S)-3.

![HPLC chromatogram of (S)-3](image)
Compound (7S)-18
HPLC conditions: Chiralpak AD-H, 2-propanol/hexane = 2/98 (v/v), flow rate 1.0 mL/min, detected at 254 nm, \( t_R = 9.1 \) min for (7S)-18, 13.2 min for (7R)-18.

Compound (7S)-16
HPLC conditions: Chiralpak AY-H, 2-propanol/hexane = 10/90 (v/v), flow rate 1.0 mL/min, detected at 254 nm, \( t_R = 7.1 \) min for (7R)-16, 8.1 min for (7S)-18.
References and note

1. The trione (7) was prepared from 2-methylcycloheptan-1,3-dione\(^6\) by using a following method previously reported. X. Wang, S. C. Butler, J. C. Gallucci, and L. A. Paquette, *J. Org. Chem.*, 2009, 74, 6825.

2. The reaction could not be monitored by a normal phase TLC, because retardation factors (\(R_f\)) of 3 and 7 were very close each other.

3. A preparative HPLC instrument was used to separate 3 and 7, when the reaction did not complete.

