Modified Chiral Triazolium Salts for Enantioselective Benzoin Cyclization of Enolizable Keto-aldehydes: Synthesis of (+)- Sappanone B

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Supporting Information

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General Methods

All reactions utilizing air- or moisture-sensitive reagents were performed in dried glassware under an atmosphere of dry argon and nitrogen. Etheral solvents (anhydrous; Kanto Chemical Co., Inc.) were used as received. Toluene was distilled from CaH_2 prior to use. CH_2Cl_2 was distilled successively from P_2O_5 and CaH_2 , and stored over 4A molecular sieves. DBU was distilled from BaO. Et_3N was distilled from CaH_2 and stored over KOH. Other reagents were used without further purification. Thin layer chromatography (TLC) was performed on Merck precoated plates (silica gel 60 F254, Art 5715, 0.25 mm) and were visualized by fluorescence quenching under UV light or by staining with phosphomolybdic acid. Silica-gel preparative thin-layer chromatography (PTLC) was performed using plates prepared from Merck Kieselgel 60 PF 254 (Art 7747). Silica-gel column chromatography was performed on silica gel 60N (Spherical, neutral, 23–210 μm) from Kanto chemical. Melting point (m.p.) determinations were performed using a Yanaco MP-500 instrument and are uncorrected. ^1H NMR and ^{13}C NMR were measured on a JEOL JMN Lambda-300 or Lambda-400 spectrometer. Chemical shifts are expressed in parts per million (PPM) downfield from internal standard (tetramethylsilane, 0.00 ppm), and coupling constants are reported as hertz (Hz). Splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Infrared (IR) spectra were recorded on a Jasco IRA-202 spectrophotometer or Perkin Elmer Spectrum 100 spectrometer. Attenuated Total Reflectance Fourier Transform Infrared (ATR-FTIR) spectra were recorded on a Perkin Elmer 1600 FTIR. Optical rotations ($[\alpha]_D$) were measured on a JASCO DIP-1000 polarimeter. High performance liquid chromatography (HPLC) analyses were performed using a JASCO CO-2060 plus for column thermostat, UV-2075 plus for UV/VIS detector, CD-2095 plus for chiral detector, PU-2089 plus for HPLC pump. Enantiomeric excesses were assessed by HPLC analysis on a chiral stationary phase, CHIRALPAK[®] AD-H or CHIRALCEL[®] OD-H or CHIRALPAK[®] IA (Daicel Chemical Ind., Ltd., ϕ 0.48 mm x 25 cm). High resolution mass spectra (HRMS) were obtained with a JEOL JMS-700 spectrometer.

Preparation of oxalated silica gel

A mixture of silica gel (200 g) and water solution of oxalic acid (0.25 M, 500 mL) was stirred with mechanical stirrer for 9 h. The resulting slurry was poured into a column equipped with a glass filter. Ion-exchange water was passed through the column until the waste turned into neutral. The resulting gel was dried in an oven at 120 °C for 3 h to give oxalated silica gel.^[1]

[1] For oxalated silica gel, see; Cameron, D. W.; Riches, A. G. *Aust. J. Chem.* **1997**, *50*, 409–424.

Preparation of chiral triazolium salts **3c–3f**

To a solution of iminoether **27**^[2] (173 mg, 0.851 mmol) in MeOH (4.5 mL), 2,6-difluorophenylhydrazine hydrochloride (154 mg, 0.851 mmol) was added at room temperature. The mixture was warmed to 50 °C and stirred for 3 h. After cooling to room temperature, the solvents were evaporated under reduced pressure. The residue was washed with Et₂O and dried *in vacuo* to afford hydrazone hydrochloride **28**. In a flame-dried 20 mL sealed tube was placed hydrazone hydrochloride **28** in trimethyl orthoformate (3.0 mL) and methanol (1.5 mL). The reaction mixture was stirred for 27 h at 80 °C. After the solvents were removed *in vacuo*, precipitation from CH₃CN/Et₂O gave triazolium salt **3c** (237 mg, 77 %, 2 steps) as an off-white solid.

¹H NMR (400 MHz, CDCl₃) δ 3.18 (d, 1 H, *J* = 16.8 Hz), 3.34 (dd, 1 H, *J* = 16.8, 4.8 Hz), 5.08 (s, 2 H), 5.14 (dd, 1 H, *J* = 4.8, 4.0 Hz), 6.69 (d, 1 H, *J* = 4.0 Hz), 7.11–7.15 (m, 2 H), 7.26–7.33 (m, 3 H), 7.55–7.62 (m, 1 H), 7.83–7.86 (m, 1 H), 13.3 (s, 1 H);

¹³C NMR (100 MHz, CDCl₃) δ 37.5, 60.2, 62.7, 77.7, 112.8 (dd, *J* = 18.1, 3.3 Hz), 113.8 (t, *J* = 14.8 Hz), 124.8, 125.1, 127.8, 129.4, 133.5 (t, 10.0 Hz), 134.9, 139.7, 146.9, 149.8, 156.6 (dd, *J* = 258.2, 2.5 Hz);

IR (KBr) 3450, 3047, 2914, 1625, 1591, 1541, 1481, 1428, 1245, 1213, 1101, 1018, 966, 791, 741 cm⁻¹;

Anal. Calc'd for C₁₈H₁₄ClF₂N₃O: C, 59.76; H, 3.90; N, 11.62, Found: C, 59.47; H, 4.16; N, 11.33;

Optical Rotation [α]_D²¹ +207 (CHCl₃, *c* 1.00);

m.p. 237–238 °C (acetone/H₂O).

To a solution of iminoether **27** (165 mg, 0.812 mmol) in MeOH (4.0 mL), 2-fluorophenylhydrazine hydrochloride (132 mg, 0.812 mmol) was added at room temperature. The mixture was warmed to 50 °C and stirred for 4 h. After cooling to room temperature, the solvents were evaporated under reduced pressure. The residue was washed with Et₂O and dried *in vacuo* to afford a corresponding hydrazone hydrochloride. In a flame-dried 20 mL sealed tube was placed the residue in trimethyl orthoformate (3.0 mL) and methanol (1.5 mL). The

[2] Knight, R. L.; Leeper, F. J. *J. Chem. Soc. Perkin Trans. 1* **1998**, 1891–1893.

reaction mixture was stirred for 29 h at 80 °C. After the solvents were removed *in vacuo*, the residue was washed with Et₂O to give triazolium salt **3d** (234 mg, 84 %, 2 steps) as a yellow solid.

¹H NMR (400 MHz, CDCl₃) δ 3.11 (brs, 2 H), 5.03 (brs, 1 H), 5.06 (s, 2 H), 6.62 (brs, 1 H), 7.22–7.34 (m, 5 H), 7.51–7.56 (m, 1 H), 7.93–7.95 (m, 1 H), 8.01–8.05 (m, 1 H), 13.0 (s, 1 H);

¹³C NMR (100 MHz, CDCl₃) δ 37.3, 60.2, 62.4, 77.6, 117.4 (d, *J* = 19.0 Hz), 123.2 (d, *J* = 10.7 Hz), 124.9, 125.1, 125.4 (d, *J* = 3.3 Hz), 125.8, 127.7, 129.4, 132.6 (d, *J* = 7.4 Hz), 135.0, 139.8, 144.7 (d, *J* = 5.0 Hz), 149.3, 154.4 (d, *J* = 254.9 Hz);

IR (KBr) 3440, 3041, 2922, 1627, 1583, 1537, 1498, 1459, 1259, 1223, 1101, 972, 768, 745 cm⁻¹;

Anal. Calc'd for C₁₈H₁₅ClFN₃O: C, 62.89; H, 4.40; N, 12.22, Found: C, 62.60; H, 4.64; N, 11.95;

Optical Rotation [α]_D²³ +226 (CHCl₃, *c* 1.01);

m.p. 163–166 °C (CH₃CN/Et₂O, precipitation).

To a solution of iminoether **27** (465 mg, 2.28 mmol) in MeOH (10 mL), 3,5-difluorophenylhydrazine hydrochloride (413 mg, 2.28 mmol) was added at room temperature. The mixture was warmed to 50 °C and stirred for 3 h. After cooling to room temperature, the solvents were evaporated under reduced pressure. The residue was washed with Et₂O and dried *in vacuo* to afford a corresponding hydrazone hydrochloride. In a flame-dried 20 mL sealed tube was placed the residue in trimethyl orthoformate (4.0 mL) and methanol (2.0 mL). The reaction mixture was stirred for 24 h at 80 °C. The solvents were removed *in vacuo* and the residue was washed with Et₂O to give triazolium salt **3e** (730 mg, 88 %, 2 steps) as an off-white solid.

¹H NMR (400 MHz, CDCl₃) δ 3.02 (dd, 1 H, *J* = 17.2, 4.1 Hz), 3.10 (d, 1 H, 17.2 Hz), 4.98 (dd, 1 H, 4.1, 4.1 Hz), 5.06 (s, 2 H), 6.41 (d, 1 H, *J* = 4.1 Hz), 6.87–6.91 (m, 1 H), 7.20–7.35 (m, 3 H), 7.97–7.99 (m, 2 H), 8.07–8.09 (m, 1 H), 13.7 (s, 1 H);

¹³C NMR (75 MHz, CDCl₃) δ 37.1, 60.3, 62.4, 77.5, 104.5 (d, *J* = 30.8 Hz), 105.7 (t, *J* = 24.8 Hz), 125.0 (d, *J* = 18.5 Hz), 127.7, 127.8, 129.5, 134.6, 136.6 (t, 13.0 Hz), 139.9, 143.3, 149.6, 164.7 (dd, *J* = 250.4, 13.6 Hz);

IR (KBr) 3440, 3041, 2922, 1627, 1583, 1537, 1498, 1459, 1259, 1223, 1101, 972, 768, 745 cm⁻¹;

Anal. Calc'd for C₁₈H₁₄ClF₂N₃O: C, 59.76; H, 3.90; N, 11.62, Found: C, 59.50; H, 4.16; N, 11.34;

Optical Rotation [α]_D²³ +214 (CHCl₃, *c* 1.02);

m.p. 212–215 °C (CH₃CN/Et₂O, precipitation).

To a solution of iminoether **27** (972 mg, 4.78 mmol) in MeOH (23 mL), 3,5-bis(trifluoromethyl)phenylhydrazine hydrochloride^[3] (1.34 g, 4.78 mmol) was added at room temperature. The mixture was warmed to 50 °C and stirred for 2 h. After cooling to room temperature, the solvents were evaporated under reduced pressure. The residue was washed with Et₂O/hexane (v/v=1:1) and dried *in vacuo* to afford a corresponding hydrazone hydrochloride. In a flame-dried sealed tube was placed the residue in trimethyl orthoformate (8.0 mL) and methanol (4.0 mL). The reaction mixture was stirred for 28 h at 80 °C. After the solvents were removed *in vacuo*, the residue was washed with Et₂O/CH₂Cl₂/hexane (v/v/v=2/1/6) to give triazolium salt **3f** (1.33 g, 60 %, 2 steps) as a off-white solid.

¹H NMR (400 MHz, CDCl₃) δ 2.78 (dd, 1 H, *J* = 16.8, 4.8 Hz), 3.02 (d, 1 H, *J* = 16.8 Hz), 4.95 (dd, 1 H, *J* = 4.8, 4.0 Hz), 5.07 (d, 1 H, *J* = 16.0 Hz), 5.16 (d, 1 H, *J* = 16.0 Hz), 6.41 (d, 1 H, *J* = 4.0 Hz), 7.14–7.16 (m, 1 H), 7.25–7.30 (m, 2 H), 7.91 (s, 1 H), 8.08–8.10 (m, 1 H), 8.96 (s, 2 H), 14.0 (s, 1 H);

¹³C NMR (100 MHz, CDCl₃) δ 37.2, 60.4, 62.6, 77.4, 120.9 (q, *J* = 3.3 Hz), 122.2 (q, *J* = 271 Hz), 123.6 (m), 124.5, 125.2, 127.6, 129.5, 133.5 (q, *J* = 34.7 Hz), 134.4, 136.1, 139.9, 144.2, 149.9;

IR (KBr) 3415, 2929, 1624, 1591, 1535, 1365, 1281, 1184, 1140, 1074, 901, 741, 683 cm⁻¹;

Anal. Calc'd for C₂₀H₁₄ClF₆N₃O: C, 52.02; H, 3.06; N, 9.10, Found: C, 51.77; H, 3.07; N, 8.84;

Optical Rotation [α]_D²² +54.1 (CHCl₃, *c* 1.00);

m.p. 245–248 °C (acetone/H₂O).

[3] 3,5-Bistrifluoromethylphenylhydrazine was prepared from 3,5-bistrifluoromethylaniline by the literature procedure, see: Nagarajan, K; Talwalker, P. K.; Kulkarni, C. L.; Venkateswarlu, A; Prabhu, S. S.; Nayak, G. V. *Ind. J. Chem.* **1984**, 23, 1243–1257.

General Procedure for the preparation of keto-aldehydes **4**, **10**, **11**

To a mixture of acetal **27**^[4] (4.37 g, 24.2 mmol) and *N*-methoxy-*N*-methylchloroacetoamide^[5] (3.50 g, 25.4 mmol) in acetone (81 mL) was added K_2CO_3 (6.69 g, 48.4 mmol). After stirring for 12 h under reflux, the reaction was cooled to room temperature followed by addition of water. The products were extracted with EtOAc (x3). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (EtOAc/hexane = 4/1) to give amide **28** (6.83 g, quant) as a colorless solid.

1H NMR (400 MHz, $CDCl_3$) δ 1.40–1.44 (m, 1 H), 2.17–2.29 (m, 1 H), 3.23 (s, 3 H), 3.72 (s, 3 H), 4.00–4.07 (m, 2 H), 4.21–4.25 (m, 2 H), 4.83 (s, 2 H), 6.01 (s, 1 H), 6.84 (d, 1 H, J = 7.6 Hz), 7.02 (dd, 1 H, J = 8.0, 7.6 Hz), 7.27 (ddd, 1 H, J = 8.0, 7.6, 2.0 Hz), 7.64 (dd, 1 H, J = 7.6, 2.0 Hz);

^{13}C NMR (100 MHz, $CDCl_3$) δ 25.9, 32.3, 61.5, 66.6, 67.5, 96.8, 112.6, 121.7, 127.1, 127.9, 129.7, 155.1, 169.1;

IR (KBr) 2964, 2854, 1685, 1606, 1496, 1458, 1394, 1236, 1178, 1095, 1061, 987, 758 cm^{-1} ;

Anal. Calc'd for $C_{14}H_{19}NO_5$: C, 59.78; H, 6.81; N, 4.98; Found: C, 59.76; H, 6.86; N, 4.68;

m.p. 74.0–77.0 $^{\circ}C$.

The preparation of keto-aldehyde **3** is representative. To a solution of TMEDA (*N,N,N',N'*-tetramethylethylenediamine, 3.11 mL, 20.4 mmol) in toluene (7.0 mL) was added *n*-BuLi (1.6 M in hexane, 12.5 mL, 20.0 mmol) dropwise at room temperature.^[6] The resulting solution was heated to 110 $^{\circ}C$ and stirred for 30 min. The obtained orange solution of benzyl lithium TMEDA complex was used in the following experiment. To a solution of amide **28** (2.82 g, 10.0 mmol) in THF (33 mL) was added benzyl lithium TMEDA complex (2.0 equiv) dropwise at $-40^{\circ}C$. After stirring for 30 min, the reaction was quenched with saturated NH_4Cl . The products were extracted with EtOAc (x3). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. After evaporation, the residue was dissolved in THF (25 mL), to which was added 2 M HCl (5.0 mL, 10 mmol) at 0 $^{\circ}C$. After stirring for 5 h at room temperature, the reaction was quenched with saturated $NaHCO_3$. The products were extracted with EtOAc (x3). The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica-gel

[4] Gopinath, R.; Haque, S. J.; Patel, B. K. *J. Org. Chem.* **2002**, 67, 5842–5845.

[5] Dolling, U. H.; Frey, L. F.; Tillyer, R. D.; Tschaen, D. M. PCT Int. Appl. WO 97/10195, 1997.

[6] Eberhardt, G. G.; Butte, W. A. *J. Org. Chem.* **1964**, 29, 2928–2932.

column chromatography (EtOAc/hexane = 1/4) to give keto-aldehyde **3** (1.20 g, 47%, 2 steps) as a colorless solid.

¹H NMR (300 MHz, CDCl₃) δ 3.92 (s, 2 H), 4.75 (s, 2 H), 6.70 (d, 1 H, *J* = 8.4 Hz), 7.08 (t, 1 H, *J* = 7.5 Hz), 7.22–7.37 (m, 5 H), 7.46–7.51 (m, 1 H), 7.87 (dd, 1 H, *J* = 7.5, 1.8 Hz), 10.5 (s, 1 H);

¹³C NMR (75 MHz, CDCl₃) δ 46.5, 72.1, 112.3, 121.8, 125.2, 127.5, 128.9, 129.1, 129.4, 132.6, 135.8, 159.7, 189.2, 203.3;

IR (KBr) 3028, 2898, 2863, 2767, 1722, 1685, 1599, 1483, 1284, 1246, 1061, 769, 704 cm⁻¹;

Anal. Calc'd for C₁₆H₁₄O₃: C, 75.57; H, 5.55; Found: C, 75.57; H, 5.57;

m.p. 109–110 °C.

10 (Table 3, entry 1)

Prepared according to the general procedure from **28** (1.03 g, 3.64 mmol) with MeLi (1.14 M in Et₂O, 3.84 mL, 4.37 mmol) followed by hydrolysis with 2 M HCl. The crude product was purified by column chromatography (hexane/EtOAc = 2/1) to afford keto-aldehyde **10** (569 mg, 88%, 2 steps) as a colorless oil.

¹H NMR (300 MHz, CDCl₃) δ 2.33 (s, 3 H), 4.69 (s, 2 H), 6.82 (d, 1 H, *J* = 8.5 Hz), 7.10 (dd, 1 H, *J* = 7.3, 7.3 Hz), 7.55 (ddd, 1 H, *J* = 8.5, 7.3, 1.7 Hz), 7.87 (dd, 1 H, *J* = 7.3, 1.7 Hz), 10.6 (s, 1 H);

¹³C NMR (75 MHz, CDCl₃) δ 26.6, 73.0, 112.3, 121.8, 125.1, 129.0, 135.9, 159.8, 189.1, 204.1;

IR (neat) 3419, 3342, 3017, 2904, 2769, 1732, 1685, 1599, 1487, 1394, 1361, 1290, 1241, 1059, 768 cm⁻¹;

11 (Table 3, entry 2)

Prepared according to the general procedure from **28** (1.18 g, 4.18 mmol) with PhLi (0.98 M in cyclohexane/Et₂O, 4.69 mL, 4.60 mmol) followed by hydrolysis with 2 M HCl. The crude product was purified by column chromatography (hexane/EtOAc = 3/1) to afford keto-aldehyde **11** (721 mg, 72%, 2 steps) as a colorless solid.

¹H NMR (400 MHz, CDCl₃) δ 5.43 (s, 2 H), 6.87 (d, 1 H, *J* = 8.4 Hz), 7.07 (dd, 1 H, *J* = 7.2, 7.2 Hz), 7.48–7.54 (m, 3 H), 7.65 (tt, 1 H, *J* = 7.6, 1.2 Hz), 7.87 (dd, 1 H, *J* = 8.0, 1.6 Hz), 7.97–8.00 (m, 2 H), 10.6 (s, 1 H);

¹³C NMR (100 MHz, *d*₆-acetone) δ 71.5, 114.6, 122.0, 126.1, 128.3, 128.7, 129.7, 134.6, 135.5, 136.6, 161.7, 189.6, 194.3;

IR (KBr) 3066, 2902, 2875, 2777, 1705, 1685, 1597, 1485, 1288, 1232, 980, 756 cm⁻¹;

Anal. Calc'd for C₁₅H₁₂O₃: C, 74.99; H, 5.03; Found: C, 74.96; H, 5.27;

mp 114–116 °C (EtOAc/hexane).

General Procedure for Benzoin Cyclization of Keto-aldehyde

The reaction of keto-aldehyde **4** is representative (Table 2, entry 5). A mixture of **4** (83.5 mg, 0.330 mmol) and triazolium salt **3f** (22.8 mg, 0.049 mmol) in toluene (1.1 mL) was degassed by two cycles of freeze-pump-thaw. To the mixture was added Et₃N (4.6 μL, 0.033 mmol) at room temperature under nitrogen atmosphere. After stirring at this temperature for 5 h, the reaction was cooled to 0 °C, and water was added. The products were extracted with EtOAc (x3). The combined organic extracts were dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (EtOAc/CH₂Cl₂/hexane = 1/1/3) to give benzoin product (R)-**5**^[7] (72.6 mg, 87%, 94% ee) as colorless oil. The enantiomeric excess was assessed by HPLC analysis on a chiral stationary phase: CHIRALPAK® AD-H. (eluent: 2-propanol:hexane = 2:98, flow rate: 1.0 mL/min, 25 °C: (S)-**5**: t₁ = 23.8 min; (R)-**5**: t₂ = 28.8 min). The corresponding byproducts **6–9** were also obtained in 11% combined yield. Since β-hydroxyketones **6** and **7** were inseparable on silica-gel chromatography (R_f 0.2, silica-gel TLC, EtOAc/hexane = 1:3), the extent of these side reactions was assessed after treatment with DBU (ca. 1 equiv., THF, room temperature) that converted the aldols into the corresponding enones **8**^[8] and **9**^[9] (R_f 0.6).

¹H NMR (300 MHz, CDCl₃) δ 2.97 (d, 1 H, *J* = 13.8 Hz), 3.04 (d, 1 H, *J* = 13.8 Hz), 3.58 (brs, 1 H), 4.11 (d, 1 H, *J* = 11.3 Hz), 4.30 (d, 1 H, *J* = 11.3 Hz), 7.04–7.33 (m, 7 H), 7.54–7.60 (m, 1 H), 7.89 (dd, 1 H, *J* = 7.8, 2.1 Hz);

¹³C NMR (75 MHz, CDCl₃) δ 40.9, 72.2, 73.0, 118.0, 118.4, 122.0, 127.1, 127.6, 128.2, 130.6, 134.3, 136.7, 161.4, 196.0;

IR (neat) 3475, 3062, 3029, 2920, 2871, 1695, 1608, 1477, 1306, 1217, 1093, 1036, 1018, 764, 700 cm⁻¹;

Anal. Calc'd for C₁₆H₁₄O₃: C, 75.57; H, 5.55; Found: C, 75.50; H, 5.59;

Optical Rotation [α]_D³⁰ –11.1 (CHCl₃, *c* 3.04) for 94% ee; Lit.^[7b] [α]_D²⁰ –10.0 (CHCl₃, *c* 3.00) for 91% ee.

- [7] (a) Takikawa, H.; Hachisu, Y.; Bode, J. W.; Suzuki, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 3492–3494; (b) Davis, F. A.; Weismiller, M. C. *J. Org. Chem.* **1990**, *55*, 3715–3717; (c) Jew, S.-S.; Kim, H.-A.; Kim, J.-H.; Park, H. -G. *Heterocycles* **1997**, *46*, 65–70; (d) Kirkiacharian, B. S.; Gomis, M. H.; Tongo, G.; Mahuteau, J.; Brion, J. D. *Org. Magn. Reson.* **1984**, *22*, 106–108.
- [8] Gill, M. *Tetrahedron* **1984**, *40*, 621–626.
- [9] Hofmann, H.; Hofmann, P. *Justus Liebigs Ann. Chem.* **1974**, 1301–1314.

Prepared according to the general procedure from keto-aldehyde **10** (247 mg, 1.38 mmol) under the conditions indicated in Table 3. The crude product was purified by column chromatography (hexane/EtOAc = 2/3) to afford α -ketol **15** (222 mg, 90%, 94% ee) as colorless oil. The enantiomeric excess was assessed by HPLC analysis on a chiral stationary phase (CHIRALPAK® AD-H, eluent: 2-propanol:hexane = 2:98, flow rate: 1.0 mL/min, 25 °C: (*R*)-**15**: t_1 = 17.3 min; (*S*)-**15**: t_2 = 21.5 min).

¹H NMR (400 MHz, CDCl₃) δ 1.47 (s, 3 H), 3.61 (brs, 1 H), 4.21 (d, 1 H, J = 11.2 Hz), 4.31 (d, 1 H, J = 11.2 Hz), 6.99 (d, 1 H, J = 8.0 Hz), 7.07 (dd, 1 H, J = 7.8, 7.8 Hz), 7.53 (ddd, 1 H, J = 8.0, 7.8, 1.7 Hz), 7.89 (dd, 1 H, J = 7.8, 1.7 Hz);

¹³C NMR (100 MHz, CDCl₃) δ 22.4, 70.6, 74.6, 117.9, 118.1, 121.8, 127.6, 136.5, 161.3, 196.5;

IR (neat) 3471, 3070, 2979, 2929, 2873, 1697, 1608, 1477, 1308, 1215, 1149, 1038, 966, 760 cm⁻¹;

Anal. Calc'd for C₁₀H₁₀O₃: C, 67.41; H, 5.66; Found: C, 67.13; H, 5.90;

Optical Rotation $[\alpha]_D^{23}$ +15.1 (CHCl₃, c 1.10) for 94% ee; Lit.^[7b] $[\alpha]_D^{20}$ -9.4 (CHCl₃, c 1.8) for $\geq 96\%$ ee.^[10]

Prepared according to the procedure in our previous report (see reference 7a) from α -ketol **15** [(*S*)-camphanic chloride, DMAP, CH₂Cl₂].

¹H NMR (400 MHz, CDCl₃) δ 1.03 (s, 3 H), 1.08 (s, 3H), 1.12 (s, 3 H), 1.68 (s, 3 H), 1.70–1.73 (m, 1 H), 1.90–1.97 (m, 1 H), 2.05–2.11 (m, 1 H), 2.41–2.48 (m, 1 H), 4.20 (d, 1 H, J = 11.0 Hz), 5.09 (d, 1 H, J = 11.0 Hz), 6.99 (dd, 1 H, J = 8.3, 0.7 Hz), 7.09 (ddd, 1 H, J = 8.0, 8.0, 0.7 Hz), 7.53 (ddd, 1 H, J = 8.3, 8.0, 1.6 Hz), 7.93 (dd, 1 H, J = 8.0, 1.6 Hz);

¹³C NMR (100 MHz, CDCl₃) δ 9.7, 16.4, 16.5, 19.8, 29.0, 30.6, 54.6, 54.8, 71.4, 79.2, 90.6, 117.8, 119.3, 122.2, 128.0, 136.3, 160.4, 165.7, 177.8, 188.8;

IR (KBr) 2976, 2939, 2898, 1788, 1736, 1699, 1606, 1479, 1350, 1313, 1267, 1173, 1088, 760 cm⁻¹;

Anal. Calc'd for C₂₀H₂₂O₆: C, 67.03; H, 6.19; Found: C, 66.91; H, 6.46;

Optical Rotation $[\alpha]_D^{29}$ +9.0 (CHCl₃, c 1.0);

mp 188–189 °C (acetone/hexane).

CCDC 290473 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

[10] Although the value of optical rotation indicated the opposite absolute configuration to the reported one, we ensured it by X-ray analysis of the corresponding (*S*)-camphanyl derivative.

16 (Table 3, entry 2)

Prepared according to the general procedure from keto-aldehyde **11** (151 mg, 0.630 mmol) under the conditions indicated in Table 3. The crude product was purified by PTLC (hexane/EtOAc = 1/3) to afford α -ketol **16** (92.6 mg, 61%, 90% ee) as a colorless solid. The enantiomeric excess was assessed by HPLC analysis on a chiral stationary phase (CHIRALPAK[®] AD-H, eluent: 2-propanol:hexane = 2:98, flow rate: 1.0 mL/min, 25 °C: (*S*)-**16**: t_1 = 31.5 min; (*R*)-**16**: t_2 = 39.5 min). The corresponding benzofuran^[11] and aldol were also obtained in 27% combined yield.

¹H NMR (400 MHz, CDCl₃) δ 4.25 (brs, 1 H), 4.46 (d, 1 H, J = 11.5 Hz), 4.84 (d, 1 H, J = 11.5 Hz), 6.95 (d, 1 H, J = 8.4 Hz), 7.05 (dd, 1 H, J = 7.8, 7.8 Hz), 7.27–7.34 (m, 3 H), 7.43–7.51 (m, 3 H), 7.93 (dd, 1 H, J = 7.6, 1.6 Hz);

¹³C NMR (100 MHz, CDCl₃) δ 73.4, 73.7, 118.0, 119.1, 121.9, 125.9, 127.5, 128.6, 128.7, 136.7, 138.4, 161.4, 194.4;

IR (KBr) 3386, 3059, 3024, 2891, 1689, 1608, 1481, 1460, 1257, 1097, 949, 760 cm⁻¹;

Anal. Calc'd for C₁₅H₁₂O₃: C, 74.99; H, 5.03; Found: C, 74.92; H, 5.28;

Optical Rotation [α]_D²³ +76.5 (CHCl₃, c 1.00) for 90% ee;

m.p. 83.0–84.0 °C (EtOAc/hexane).

Prepared according to the procedure in our previous report (see reference 7a) from α -ketol **16** [(*S*)-champhanic chloride, DMAP, CH₂Cl₂].

¹H NMR (400 MHz, CDCl₃) δ 1.08 (s, 3 H), 1.11 (s, 3 H), 1.12 (s, 3 H), 1.66–1.73 (m, 1 H), 1.89–1.96 (m, 1 H), 2.07–2.14 (m, 1 H), 2.43–2.50 (m, 1 H), 4.88 (d, 1 H, J = 11.0 Hz), 5.35 (d, 1 H, J = 11.0 Hz), 6.97 (d, 1 H, J = 8.0 Hz), 7.07 (dd, 1 H, J = 8.0, 8.0 Hz), 7.36–7.41 (m, 3 H), 7.50 (ddd, 1 H, J = 8.0, 8.0, 1.6 Hz), 7.57–7.61 (m, 2 H), 7.95 (dd, 1 H, J = 8.0, 1.6 Hz);

¹³C NMR (100 MHz, CDCl₃) δ 9.8, 16.6, 16.7, 29.0, 30.7, 54.7, 54.9, 70.2, 81.4, 90.8, 117.9, 119.8, 122.3, 126.6, 128.1, 128.8, 129.5, 134.1, 136.5, 160.3, 165.8, 177.8, 187.1;

IR (KBr) 3074, 2966, 2873, 1792, 1759, 1701, 1604, 1463, 1265, 1101, 1063, 760 cm⁻¹;

Anal. Calc'd for C₂₅H₂₄O₆: C, 71.41; H, 5.75; Found: C, 71.22; H, 6.03;

Optical Rotation [α]_D²⁸ +16.8 (CHCl₃, c 0.70);

m.p. 212–214 °C (acetone/hexane).

CCDC 290475 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

[11] Wahab Khan, M.; Jahangir Alam, M.; Rashidb, M. A.; Chowdhuryb, R. *Bioorg. Med. Chem.* **2005**, *13*, 4796–4805.

19 (Table 3, entry 5)

Prepared according to the general procedure from keto-aldehyde **14**^[12] (134 mg, 0.763 mmol) under the conditions indicated in Table 3. The crude product was purified by PTLC (hexane/CHCl₃/Et₂O = 5/3/2) to afford α -ketol **19**^[7b] (121 mg, 90%, 60% ee) as colorless oil. The enantiomeric excess was assessed by HPLC analysis on a chiral stationary phase (CHIRALPAK[®] AD-H, eluent: 2-propanol:hexane = 0.5:99.5, flow rate: 1.0 mL/min, 25 °C: (*S*)-**19**: *t*₁ = 13.7 min; (*R*)-**19**: *t*₂ = 17.3 min).

¹H NMR (400 MHz, CDCl₃) δ 1.56 (s, 3 H), 2.61–2.69 (m, 1 H), 2.92–2.99 (m, 1 H), 3.04–3.11 (m, 1 H), 3.27–3.35 (m, 1 H), 3.93 (s, 1 H), 7.17 (brd, 1 H, *J* = 7.6 Hz), 7.23–7.28 (m, 1 H), 7.33 (dd, 1 H, *J* = 7.6, 7.6 Hz), 7.66 (brd, 1 H, *J* = 7.6 Hz);

¹³C NMR (100 MHz, CDCl₃) δ 27.8, 27.9, 33.5, 76.1, 125.2, 127.4, 127.55, 127.60, 133.6, 140.7, 212.8;

IR (neat) 3483, 3066, 3023, 2975, 2927, 1718, 1458, 1130, 1080, 762 cm⁻¹;

Anal. Calc'd for C₁₁H₁₂O₂: C, 74.98; H, 6.86; Found: C, 74.82; H, 6.59;

Optical Rotation [α]_D²⁹ -75.7 (CHCl₃, *c* 1.14) for 60% ee; Lit.^[7b] [α]_D²⁰ +77.0 (CHCl₃, *c* 4.2) for 76% ee (*S*).

Prepared according to the procedure in our previous report (see reference 7a) from α -ketol **16** [(*S*)-champhanic chloride, DMAP, CH₂Cl₂].

¹H NMR (400 MHz, CDCl₃) δ 0.95 (s, 3 H), 1.107 (s, 3H), 1.111 (s, 3 H), 1.68 (s, 3 H), 1.70–1.73 (m, 1 H), 1.90–1.97 (m, 1 H), 2.06–2.13 (m, 1 H), 2.43–2.50 (m, 1 H), 2.82–2.86 (m, 2 H), 3.06–3.13 (m, 1 H), 3.25–3.33 (m, 1 H), 7.19–7.31 (m, 4 H);

¹³C NMR (100 MHz, CDCl₃) δ 9.7, 16.3, 16.7, 27.1, 28.1, 29.1, 30.6, 37.1, 54.6, 54.8, 80.9, 90.4, 124.5, 127.2, 127.9, 128.0, 135.2, 138.4, 165.6, 177.8, 206.1;

IR (KBr) 2975, 2939, 2873, 1785, 1751, 1738, 1491, 1446, 1315, 1275 1107, 1068, 1022, 769 cm⁻¹;

Anal. Calc'd for C₂₁H₂₄O₅: C, 70.77; H, 6.79, Found: C, 70.53; H, 6.84;

Optical Rotation [α]_D³⁰ +13.6 (CHCl₃, *c* 0.93);

m.p. 212–214 °C (acetone/hexane).

CCDC 290478 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

[12] Enders, D.; Niemeier, O. *Synlett* **2004**, 2111–2114.

Preparation of keto-aldehydes **2** (Scheme 2)

To a solution of aldehyde **20** (3.81 g, 25.0 mmol) in pyridine (5 mL) was added Ac_2O (5 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 4 h. After dilution with water at 0 °C, the products were extracted with Et_2O (x3). The combined organic layer was washed with 1 M HCl (x2), H_2O and brine followed by drying over Na_2SO_4 . After the solvents were evaporated under reduced pressure, the residue was dissolved in 1,3-propanediol (7.3 mL) and triethylorthoformate (8.3 mL). To the mixture was added tetrabutylammonium tribromide (241 mg, 0.500 mmol) at 10 °C. After stirring for 1 h at room temperature, MeOH (5 mL) and K_2CO_3 (3.46 g, 25.0 mmol) were added to the mixture at 0 °C. The resulting suspension was allowed to warm to room temperature and stirred for 1 h. Extraction with EtOAc (x3) followed by washing with brine, drying over Na_2SO_4 and purification with column chromatography (hexane/EtOAc = 3/1) gave acetal **21** [5.00 g, 95% (2 steps)] as colorless oil.

^1H NMR (400 MHz, CDCl_3) δ 1.45–1.50 (m, 1 H), 2.17–2.29 (m, 1 H), 3.75 (s, 3 H), 3.94–4.01 (m, 2 H), 4.24–4.29 (m, 2 H), 5.58 (s, 1 H), 6.41 (dd, 1 H, $J = 8.4, 2.4$ Hz), 6.44 (d, 1 H, $J = 2.4$ Hz), 7.05 (d, 1 H, $J = 8.4$ Hz), 7.93 (s, 1 H);

^{13}C NMR (100 MHz, CDCl_3) δ 25.7, 55.2, 67.3, 102.1, 103.0, 105.8, 114.9, 128.5, 156.4, 161.2;

IR (neat) 3369, 2962, 2861, 1631, 1588, 1513, 1395, 1274, 1204, 1156, 1107, 1093, 984 cm^{-1} ;

Anal. Calc'd for $\text{C}_{11}\text{H}_{14}\text{O}_4$: C, 62.85; H, 6.71; Found: C, 63.06; H, 6.50.

To a mixture of acetal **21** (4.10 g, 19.5 mmol) and *N*-methoxy-*N*-methylchloroacetoamide^[13] (2.82 g, 20.5 mmol) in acetone (65 mL) was added K_2CO_3 (5.39 g, 20.5 mmol). After stirring for 14 h under reflux, the reaction was cooled to room temperature followed by addition of water. The aqueous layer was extracted with EtOAc (x3). The combined organic layer was washed with brine, dried over Na_2SO_4 , and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (EtOAc/ hexane = 3/2 to 1/0) to give amide **22** (6.08 g, quant) as a colorless amorphous solid.

^1H NMR (400 MHz, CDCl_3) δ 1.38–1.43 (m, 1 H), 2.15–2.28 (m, 1 H), 3.23 (s, 3 H), 3.73 (s, 3 H), 3.78 (s, 3 H), 3.98–4.05 (m, 2 H), 4.20–4.24 (m, 2 H), 4.80 (s, 2 H), 5.93 (s, 1 H), 6.41 (d, 1 H, $J = 2.0$ Hz), 6.55 (dd, 1 H, $J = 8.4, 2.0$ Hz), 7.55 (d, 1 H, $J = 8.4$);

^{13}C NMR (100 MHz, CDCl_3) δ 25.9, 32.4, 55.4, 61.6, 66.6, 67.5, 96.8, 100.1, 105.7, 120.9, 128.0, 156.2, 160.8, 169.0;

IR (ATR) 2959, 2885, 2838, 1673, 1617, 1590, 1513, 1451, 1396, 1258, 1092, 1051, 983, 829,

[13] Dolling, U. H.; Frey L. F.; Tillyer, R. D.; Tschaen, D. M. PCT Int. Appl. WO 97/10195, 1997.

794 cm⁻¹;

Anal. Calc'd for C₁₅H₂₁NO₆: C, 57.87; H, 6.80; N, 4.77; Found: C, 57.64; H, 6.94; N, 4.77;

2

To a solution of amide (7.82 g, 25.0 mmol) in THF (50 mL) was added 3,4-dimethoxyphenylmethylmagnesium chloride^[14] [generated from 3,4-dimethoxybenzyl chloride (9.78 g, 37.6 mmol), Mg (6.09 g, 250 mmol) and 1,2-dibromoethane (2 drops) in THF (100 mL) at -10 °C] dropwise at -20 °C by steel cannula. After 15 min at this temperature, the reaction was quenched with saturated NH₄Cl. The products were extracted with EtOAc (x3). The combined organic layer was concentrated under reduced pressure. After evaporation, the residue was purified by silica-gel column chromatography (EtOAc/ hexane = 1/2 to 1/1) to give the corresponding keto-acetal (10.8 g, containing some impurities). Keto-acetal was dissolved in THF (25 mL), to which was added 2 M HCl (5.0 mL) at 0 °C. After stirring for 2 h at this temperature, the reaction was quenched with saturated NaHCO₃. The products were extracted with EtOAc (x3). The combined organic layer was washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. The residue was washed with Et₂O to give keto-aldehyde **2** (7.53 g, 87%) as a colorless solid.

¹H NMR (400 MHz, CDCl₃) δ 3.79 (s, 3 H), 3.84 (s, 3 H), 3.855 (s, 2 H), 3.863 (s, 3 H), 4.71 (s, 2 H), 6.15 (d, 1 H, *J* = 2.2 Hz), 6.58 (dd, 1 H, *J* = 8.8, 2.2 Hz), 6.74 (d, 1 H, *J* = 1.6 Hz), 6.78 (dd, 1 H, *J* = 8.4, 1.6 Hz), 6.83 (d, 1 H, *J* = 8.4 Hz), 7.83 (d, 1 H, *J* = 8.8 Hz), 10.4 (s, 1 H);

¹³C NMR (100 MHz, CDCl₃) δ 46.1, 55.6, 55.8, 55.9, 71.8, 98.7, 106.6, 111.4, 112.2, 119.0, 121.5, 124.8, 131.2, 148.3, 149.1, 161.2, 165.8, 187.6, 203.4;

IR (KBr) 3023, 2940, 2904, 2880, 2838, 1727, 1678, 1599, 1514, 1261, 1138, 1023, 962, 750, 725 cm⁻¹;

Anal. Calc'd for C₁₉H₂₀O₆: C, 66.27; H, 5.85; Found: C, 66.03; H, 5.87;

m.p. 117–118 °C (acetone/hexane).

[14] Hashigaki, K.; Kan, K.; Qais, N.; Takeuchi, Y.; Yamato, M. *Chem. Pharm. Bull.* **1991**, 39, 1126–1131.

Synthesis of (+)-sappanone B (Scheme 3)

A mixture of **2** (6.22 g, 18.1 mmol) and triazolium salt **3f** (626 mg, 1.36 mmol) in toluene (90 mL) was degassed by two cycles of freeze-pump-thaw. To the mixture was added Et₃N (189 μ L, 1.36 mmol) at room temperature under nitrogen atmosphere. After stirring at this temperature for 12 h, the reaction was cooled to 0 °C followed by the addition of water. The products were extracted with EtOAc (x3). The combined organic extracts were dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (EtOAc/hexane = 1/2) to give benzoin product (*R*)-**23** (5.73 g, 92%, 95% ee) as light-yellow oil. The enantiomeric excess was assessed by HPLC analysis on a chiral stationary phase: CHIRALPAK® IA (eluent: 2-propanol:hexane = 40:60, flow rate: 1.0 mL/min, 25 °C: (*S*)-**23**: *t*₁ = 9.0 min; (*R*)-**23**: *t*₂ = 16.2 min).

¹H NMR (400 MHz, CDCl₃) δ 2.90 (d, 1 H, *J* = 14.4 Hz), 2.95 (d, 1 H, *J* = 14.4 Hz), 3.65 (brs, 1 H), 3.85 (s, 3 H), 3.86 (s, 3 H), 3.88 (s, 3 H), 4.09 (d, 1 H, *J* = 10.8 Hz), 4.29 (d, 1 H, *J* = 10.8 Hz), 6.48 (d, 1 H, *J* = 2.4 Hz), 6.66 (dd, 1 H, *J* = 8.8, 2.4 Hz), 6.71–6.74 (m, 2 H), 6.79 (brd, 1 H, *J* = 8.4 Hz), 7.81 (d, 1 H, *J* = 8.8 Hz);

¹³C NMR (100 MHz, CDCl₃) δ 40.8, 55.7, 55.8 (2 C), 72.4, 72.7, 100.8, 110.7, 110.8, 112.0, 113.7, 122.5, 126.9, 129.0, 148.0, 148.4, 163.4, 166.5, 194.4;

IR (neat) 3475, 3062, 3029, 2920, 2871, 1695, 1608, 1477, 1306, 1217, 1093, 1036, 1018, 764, 700 cm⁻¹;

Anal. Calc'd for C₁₉H₂₀O₆: C, 66.27; H, 5.85; Found: C, 66.49; H, 5.61;

Optical Rotation [α]_D³³ –29.7 (CHCl₃, *c* 1.01) for 95% ee; Lit. (1)^[15] [α]_D²⁰ –30.2 (CHCl₃, *c* 1.68) for 94% ee; (2) [α]_D²⁰ –32.1 (CHCl₃, *c* 1.00).

NaSC₁₂H₂₅ was prepared by the following method. To a solution of dodecanethiol in MeOH was added sodium methoxide (28 wt% in MeOH, 1 equiv). After the solvents were removed by evaporation, the residue was dried at 50 °C overnight to give NaSC₁₂H₂₅ as a white solid, which was used in the following experiment.

To a solution of α -ketol **23** (141 mg, 0.410 mmol) in DMF (2.0 mL) was added NaSC₁₂H₂₅ (552 mg, 2.46 mmol) at room temperature. The reaction was heated to 80 °C and stirred for 5 h at this temperature. The reaction was quenched with saturated NH₄Cl at room temperature, and products were extracted with EtOAc (x3). The combined organic extracts were washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (EtOAc/hexane = 1/2 to 3/2) to give phenol **24** (124 mg, 92%) as a colorless solid.

[15] (a) Davis, F. A.; Chen, B.-C. *J. Org. Chem.* **1993**, 58, 1751–1753; (b) Namikoshi, M.; Saitoh, T. *Chem. Pharm. Bull.* **1987**, 35, 3597–3602.

¹H NMR (400 MHz, CDCl₃) δ 2.92 (d, 1 H, *J* = 14.4 Hz), 2.97 (d, 1 H, *J* = 14.4 Hz), 3.74 (brs, 1 H), 3.836 (s, 3 H), 3.842 (s, 3 H), 4.10 (d, 1 H, *J* = 11.2 Hz), 4.28 (d, 1 H, *J* = 11.2 Hz), 6.45 (d, 1 H, *J* = 2.0 Hz), 6.58 (dd, 1 H, *J* = 8.8, 2.0 Hz), 6.72–6.75 (m, 2 H), 6.80 (brd, 1 H, *J* = 8.4 Hz), 7.40 (brs, 1 H), 7.77 (d, 1 H, *J* = 8.8 Hz);

¹³C NMR (100 MHz, CDCl₃) δ 40.8, 55.8 (2 C), 72.2, 72.8, 103.3, 111.0, 111.3, 111.9, 113.7, 122.7, 126.9, 129.6, 147.9, 148.3, 163.4, 164.0, 194.6;

IR (ATR) 3371, 3266, 2940, 2833, 1672, 1611, 1584, 1514, 1475, 1455, 1264, 1160, 1029, 952 cm⁻¹;

Anal. Calc'd for C₁₈H₁₈O₆: C, 65.45; H, 5.49; Found: C, 65.69; H, 5.74;

Optical Rotation [α]_D²³ –28.2 (CHCl₃, *c* 1.01) for 95% ee.

m.p. 116–117 °C.

¹H NMR (400 MHz, CDCl₃) δ 2.95 (d, 1 H, *J* = 14.4 Hz), 3.00 (d, 1 H, *J* = 14.4 Hz), 3.58 (brs, 1 H), 3.86 (s, 3 H), 3.87 (s, 3 H), 4.16 (d, 1 H, *J* = 11.5 Hz), 4.34 (d, 1 H, *J* = 11.5 Hz), 6.72–6.74 (m, 2 H), 6.81 (brd, 1 H, *J* = 8.8 Hz), 6.97–7.00 (m, 2 H), 7.68 (brd, 2 H, *J* = 8.8 Hz), 7.96 (brd, 1 H, *J* = 8.8 Hz), 8.05 (brd, 2 H, *J* = 8.8 Hz);

¹³C NMR (100 MHz, CDCl₃) δ 40.6, 55.8 (2 C), 72.6, 73.1, 111.0, 111.2, 113.7, 116.2, 116.5, 122.7, 126.6, 127.7, 129.0, 129.5, 131.7, 132.2, 148.2, 148.6, 157.1, 162.5, 1636, 195.0;

IR (ATR) 3448, 3098, 2999, 2957, 2832, 1734, 1682, 1609, 1588, 1514, 1431, 1260, 1221, 1139, 1024, 1009, 748 cm⁻¹;

Anal. Calc'd for C₂₅H₂₁BrO₇: C, 58.49; H, 4.12; Found: C, 58.53; H, 4.24;

Optical Rotation [α]_D²⁶ –5.2 (CHCl₃, *c* 1.0).

m.p. 145–146.5 °C (acetone/hexane).

CCDC 627134 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

To a solution of phenol **24** (1.02 g, 3.07 mmol) in CH₂Cl₂ (70 mL) was added BBr₃ (2.38 g, 9.50 mmol) in CH₂Cl₂ (30 mL) dropwise at –10 °C. The reaction was allowed to warm to 0 °C and stirred for 30 min at this temperature. After the reaction was quenched with H₂O, the products were extracted with EtOAc (x3). The combined organic extracts were concentrated under reduced pressure. The residue was purified by column chromatography on oxalated silica-

gel^[16] [under an argon atmosphere, eluent: Et₂O/pentane = 1/1 (degassed)] followed by drying *in vacuo* overnight to give (+)-sappanone B (**1**, ca. 790 mg, ca. 88%, containing Et₂O) as an off-white solid. Although an irremovable Et₂O was contained in the final product,^[17] it was replaceable with other solvents (acetone, MeOH) by co-evaporation. The ¹H NMR and optical rotation was measured after co-evaporation with *d*₆-acetone and MeOH, respectively.

¹H NMR (400 MHz, *d*₆-acetone) δ 2.77 (d, 1 H, *J* = 13.9 Hz), 2.85 (d, 1 H, *J* = 13.9 Hz), 4.03 (d, 1 H, *J* = 11.5 Hz), 4.17 (d, 1 H, *J* = 11.5 Hz), 4.44 (s, 1 H), 6.44 (d, 1 H, *J* = 2.2 Hz), 6.58 (dd, 1 H, *J* = 8.1, 2.0 Hz), 6.63 (dd, 1 H, *J* = 8.6, 2.2 Hz), 6.73 (d, 1 H, *J* = 8.1 Hz), 6.78 (d, 1 H, *J* = 2.0 Hz), 7.72 (d, 1 H, *J* = 8.6 Hz), 7.72 (brs, 2 H), 9.53 (brs, 1 H);

¹³C NMR (100 MHz, *d*₆-DMSO) δ 15.2 (Et₂O), 38.9 (concealed by *d*₆-DMSO), 64.9 (Et₂O), 72.0, 72.2, 102.3, 111.0, 111.8, 115.0, 118.1, 121.5, 126.1, 129.2, 143.9, 144.6, 162.7, 164.6, 193.0;

IR (ATR) 3314, 2976, 2926, 2873, 1668, 1600, 1580, 1519, 1473, 1418, 1366, 1276, 1237, 1083, 1031, 954 cm⁻¹;

HRMS (EI-MS) calc'd for C₁₆H₁₄O₆: [M⁺] 302.0788; Found: 302.0782;

Optical Rotation [α]_D²⁵ +51 (MeOH, *c* 1.0) for 95% ee; Lit. (1) ^[18a] [α]_D²⁴ +51.6 (MeOH, *c* 1.00); (2) [α]_D²⁵ +53.7 (MeOH, *c* 0.41).^[18b]

To a solution of **1** (127 mg, 0.420 mmol) in pyridine (0.8 mL) was added dropwise Ac₂O (0.4 mL) at 0 °C. The reaction mixture was stirred for 1 h at this temperature. After dilution with water, the products were extracted with Et₂O (x3). The combined organic extracts were washed with 1 M HCl (x2), H₂O and brine followed by drying over MgSO₄. After concentration under reduced pressure, the residue was purified by PTLC (hexane/EtOAc = 2/3) to give *O*-triacetylsappanone B (**25**) (166 mg, 92%, 95% ee) as a colorless amorphous solid. The enantiomeric excess was assessed by HPLC analysis on a chiral stationary phase: CHIRALPAK[®] IA (eluent: 2-propanol:hexane = 50:50, flow rate: 1.0 mL/min, 25 °C: (*S*)-**25**: *t*₁ = 9.4 min; (*R*)-**25**: *t*₂ = 12.5 min).

¹H NMR (400 MHz, CDCl₃) δ 2.29 (s, 6 H), 2.34 (s, 3 H), 2.89 (d, 1 H, *J* = 14.2 Hz), 3.02 (d, 1 H, *J* = 14.2 Hz), 3.61 (brs, 1 H), 4.10 (d, 1 H, *J* = 11.5 Hz), 4.30 (d, 1 H, *J* = 11.5 Hz), 6.85–6.88 (m, 2 H), 7.08–7.14 (m, 3 H), 7.92 (d, 1 H, *J* = 8.6 Hz);

¹³C NMR (100 MHz, CDCl₃) δ 20.6 (2 C), 21.1, 40.1, 72.1, 72.7, 111.1, 116.0, 116.3, 123.0, 125.5, 128.7, 129.0, 133.0, 141.2, 141.6, 157.1, 162.4, 168.16, 168.19, 168.4, 194.7;

IR (ATR) 3478, 2935, 1762, 1692, 1609, 1505, 1434, 1369, 1182, 1142, 1111, 1029, 1012, 896 cm⁻¹;

Anal. Calc'd for C₂₂H₂₀O₉: C, 61.68; H, 4.71; Found: C, 61.46; H, 4.82;

Optical Rotation [α]_D²⁴ +21.6 (CHCl₃, *c* 1.00) for 95% ee.

[16] See general methods.

[17] Recrystallization, precipitation (Et₂O/pentane) and freeze-drying (MeOH/H₂O) were ineffective, causing partial decomposition of the product.

[18] (a) Saitoh, T.; Sakashita, S.; Nakata, H.; Shimokawa, T.; Kinjo, J.-E.; Yamahara, J.; Yamasaki, M.; Nohara, T. *Chem. Pharm. Bull.* **1986**, *34*, 2506–2511; (b) Namikoshi, M.; Nakata, H.; Yamada, H.; Nagai, M.; Saitoh, T. *Chem. Pharm. Bull.* **1987**, *35*, 2761–2773.

S17

DATIM Fri Jan 07 18:17:22 2005
DFILE C:\ALICE\3f_13C.als
OBNUC 13C
EXMOD BCM
OFR 100.40 MHz
OBSET 125.00 KHz
OBFIN 10500.0 Hz
POINT 32768
FREQU 27173.9 Hz
SCANS 465
ACQTM 1.206 sec
PD 2.000 sec
PW1 5.9 us
IRN
CTEMP 23.6 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 0.12 Hz
RGAIN 24

3f
13C NMR

DATIM Wed Sep 29 15:45:17 2004
DFILE C:\ALICE\10_1H.als
OBNUC 1H
EXMOD non
OFR 300.40 MHz
OBSET 130.00 KHz
OBFIN 1156.7 Hz
POINT 16384
FREQU 4000.0 Hz
SCANS 16
ACQTM 4.096 sec
PD 2.000 sec
PW1 4.8 us
IRN
CTEMP 24.0 c
SLVNT CDCL3
EXREF 0.00 ppm
BF 1.00 Hz
RGAIN 21

DATIM
DFILE C:\ALICE\10_13C.als
OBNUC 13C
EXMOD bcm
OFR 75.45 MHz
OBSET 120.00 KHz
OBFIN 6173.0 Hz
POINT 32768
FREQU 20366.6 Hz
SCANS 169
ACQTM 1.609 sec
PD 2.195 sec
PW1 4.2 us
IRN
CTEMP 25.4 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 1.00 Hz
RGAIN 30

DATIM Tue Feb 15 15:24:39 2005
DFILE C:\ALICE\11_1H.als
OBNUC 1H
EXMOD NON
OFR 399.65 MHz
OBSET 124.00 KHz
OBFIN 10500.0 Hz
POINT 32768
FREQU 8000.0 Hz
SCANS 8
ACQTM 4.096 sec
PD 2.000 sec
PW1 6.2 us
IRN
CTEMP 22.9 c
SLVNT CDCL3
EXREF 0.00 ppm
BF 0.12 Hz
RGAIN 15

11
1H NMR

DATIM Wed Nov 29 10:09:26 2006
DFILE C:\ALICE\11_13C-2.als
OBNUC 13C
EXMOD bcm
OFR 99.45 MHz
OBSET 100.00 KHz
OBFIN 4750.0 Hz
POINT 65536
FREQU 26881.7 Hz
SCANS 1733
ACQTM 2.438 sec
PD 1.000 sec
PW1 4.9 us
IRN
CTEMP 25.0 c
SLVNT ACETN
EXREF 29.80 ppm
BF 1.00 Hz
RGAIN 23

11
13C NMR

DATIM Mon Oct 2 10:24:51 2006
DFILE C:\ALICE\15_1H.als
OBNUC 1H
EXMOD non
OFR 395.75 MHz
OBSET 130.00 KHz
OBFIN 4498.0 Hz
POINT 32768
FREQU 7917.7 Hz
SCANS 16
ACQTM 4.139 sec
PD 1.500 sec
PW1 7.0 us
IRN
CTEMP 27.1 c
SLVNT CDCL3
EXREF 0.00 ppm
BF 1.00 Hz
RGAIN 27

15
1H NMR

DATIM Wed Feb 28 12:16:24 2007
DFILE C:\ALICE\15_13C.als
OBNUC 13C
EXMOD bcm
OFR 99.45 MHz
OBSET 100.00 KHz
OBFIN 4750.0 Hz
POINT 65536
FREQU 26881.7 Hz
SCANS 2319
ACQTM 2.438 sec
PD 1.000 sec
PW1 4.9 us
IRN
CTEMP 25.2 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 1.00 Hz
RGAIN 35

15
13C NMR

DATIM Wed Feb 16 18:03:30 2005
DFILE C:\ALICE\16_1H.als
OBNUC 1H
EXMOD NON
OFR 399.65 MHz
OBSET 124.00 KHz
OBFIN 10500.0 Hz
POINT 32768
FREQU 8000.0 Hz
SCANS 16
ACQTM 4.096 sec
PD 1.500 sec
PW1 6.2 us
IRN
CTEMP 23.3 c
SLVNT CDCL3
EXREF 0.00 ppm
BF 0.12 Hz
RGAIN 13

16
1H NMR

DATIM Wed Feb 16 18:12:02 2005
DFILE C:\ALICE\16_13C.als
OBNUC 13C
EXMOD BCM
OFR 100.40 MHz
OBSET 125.00 KHz
OBFIN 10500.0 Hz
POINT 32768
FREQU 27173.9 Hz
SCANS 119
ACQTM 1.206 sec
PD 2.500 sec
PW1 5.9 us
IRN
CTEMP 23.9 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 0.12 Hz
RGAIN 24

16
13C NMR

DATIM Thu May 26 16:04:24 2005
DFILE C:\ALICE\19_1H.als
OBNUC 1H
EXMOD NON
OFR 399.65 MHz
OBSET 124.00 KHz
OBFIN 10500.0 Hz
POINT 32768
FREQU 8000.0 Hz
SCANS 8
ACQTM 4.096 sec
PD 1.500 sec
PW1 6.2 us
IRN
CTEMP 25.2 c
SLVNT CDCL3
EXREF 0.00 ppm
BF 0.12 Hz
RGAIN 21

DATIM Thu May 26 22:13:54 2005
DFILE C:\ALICE\19_13C.als
OBNUC 13C
EXMOD BCM
OFR 100.40 MHz
OBSET 125.00 KHz
OBFIN 10500.0 Hz
POINT 32768
FREQU 27173.9 Hz
SCANS 500
ACQTM 1.206 sec
PD 2.000 sec
PW1 5.9 us
IRN
CTEMP 23.9 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 0.12 Hz
RGAIN 23

19
13C NMR

DATIM Thu Oct 26 02:19:01 2006
DFILE C:\ALICE\21_1H.als
OBNUC 1H
EXMOD NON
OFR 399.65 MHz
OBSET 124.00 KHz
OBFIN 10500.0 Hz
POINT 32768
FREQU 8000.0 Hz
SCANS 8
ACQTM 4.096 sec
PD 1.500 sec
PW1 6.2 us
IRN
CTEMP 25.9 c
SLVNT CDCL3
EXREF 7.26 ppm
BF 0.12 Hz
RGAIN 12

21
1H NMR

DATIM Thu Oct 26 02:37:50 2006
DFILE C:\ALICE\21_13C.als
OBNUC 13C
EXMOD BCM
OFR 100.40 MHz
OBSET 125.00 KHz
OBFIN 10500.0 Hz
POINT 32768
FREQU 27173.9 Hz
SCANS 202
ACQTM 1.206 sec
PD 1.000 sec
PW1 5.9 us
IRN
CTEMP 27.0 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 0.12 Hz
RGAIN 24

21
13C NMR

DATIM Wed Apr 05 22:15:40 2006
DFILE C:\ALICE\22_1H.als
OBNUC 1H
EXMOD NON
OFR 399.65 MHz
OBSET 124.00 KHz
OBFIN 10500.0 Hz
POINT 32768
FREQU 8000.0 Hz
SCANS 32
ACQTM 4.096 sec
PD 2.000 sec
PW1 5.8 us
IRN
CTEMP 22.9 c
SLVNT CDCL3
EXREF 0.00 ppm
BF 0.12 Hz
RGAIN 15

22
1H NMR

DATIM Thu Apr 06 09:52:16 2006
DFILE C:\ALICE\22_13C.als
OBNUC 13C
EXMOD BCM
OFR 100.40 MHz
OBSET 125.00 KHz
OBFIN 10500.0 Hz
POINT 32768
FREQU 27173.9 Hz
SCANS 4992
ACQTM 1.206 sec
PD 5.000 sec
PW1 5.0 us
IRN
CTEMP 24.0 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 0.12 Hz
RGAIN 25

22
13C NMR

DATIM Wed Apr 05 23:24:29 2006
DFILE C:\ALICE\2_1H.als
OBNUC 1H
EXMOD NON
OFR 399.65 MHz
OBSET 124.00 KHz
OBFIN 10500.0 Hz
POINT 32768
FREQU 8000.0 Hz
SCANS 16
ACQTM 4.096 sec
PD 2.000 sec
PW1 5.8 us
IRN
CTEMP 23.5 c
SLVNT CDCL3
EXREF 0.00 ppm
BF 0.12 Hz
RGAIN 12

2

1H NMR

DATIM Wed Apr 05 23:44:17 2006
DFILE C:\ALICE\2_13C.als
OBNUC 13C
EXMOD BCM
OFR 100.40 MHz
OBSET 125.00 KHz
OBFIN 10500.0 Hz
POINT 32768
FREQU 27173.9 Hz
SCANS 207
ACQTM 1.206 sec
PD 2.000 sec
PW1 5.0 us
IRN
CTEMP 23.3 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 0.12 Hz
RGAIN 24

2
13C NMR

DATIM Tue Apr 18 19:20:01 2006
DFILE C:\ALICE\23_1H.als
OBNUC 1H
EXMOD NON
OFR 399.65 MHz
OBSET 124.00 KHz
OBFIN 10500.0 Hz
POINT 32768
FREQU 8000.0 Hz
SCANS 16
ACQTM 4.096 sec
PD 2.000 sec
PW1 5.8 us
IRN
CTEMP 23.4 c
SLVNT CDCL3
EXREF 0.00 ppm
BF 0.12 Hz
RGAIN 15

23
1H NMR

DATIM Thu Apr 13 13:15:32 2006
DFILE C:\ALICE\23_13C.als
OBNUC 13C
EXMOD BCM
OFR 100.40 MHz
OBSET 125.00 KHz
OBFIN 10500.0 Hz
POINT 32768
FREQU 27173.9 Hz
SCANS 747
ACQTM 1.206 sec
PD 2.000 sec
PW1 5.0 us
IRN
CTEMP 23.3 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 0.12 Hz
RGAIN 24

23
13C NMR

S37

DATIM Wed Apr 05 18:15:46 2006
DFILE C:\ALICE\24_13C.als
OBNUC 13C
EXMOD BCM
OFR 100.40 MHz
OBSET 125.00 KHz
OBFIN 10500.0 Hz
POINT 32768
FREQU 27173.9 Hz
SCANS 585
ACQTM 1.206 sec
PD 2.000 sec
PW1 5.0 us
IRN
CTEMP 23.2 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 0.12 Hz
RGAIN 25

24
13C NMR

DATIM Tue Nov 21 12:07:16 2006
DFILE C:\ALICE\1_1H.als
OBNUC 1H
EXMOD non
OFR 395.75 MHz
OBSET 130.00 KHz
OBFIN 4498.0 Hz
POINT 32768
FREQU 7917.7 Hz
SCANS 16
ACQTM 4.139 sec
PD 1.500 sec
PW1 17.0 us
IRN
CTEMP 25.4 c
SLVNT ACETN
EXREF 0.00 ppm
BF 0.12 Hz
RGAIN 21

1
1H NMR

DATIM Wed May 31 16:15:53 2006
DFILE C:\ALICE\1_13C_acetone.als
OBNUC 13C
EXMOD bcm
OFR 99.45 MHz
OBSET 100.00 KHz
OBFIN 4750.0 Hz
POINT 65536
FREQU 26881.7 Hz
SCANS 8103
ACQTM 2.438 sec
PD 1.000 sec
PWL 4.9 us
IRN
CTEMP 25.3 c
SLVNT ACETN
EXREF 29.80 ppm
BF 1.00 Hz
RGAIN 23

1
13C NMR in *d*₆-acetone

DFILE C:\ALICE\1_13C_DMSO.als
 COMNT 13C_sappanoneB_DMSO
 DATIM Sat_Dec 2 09:23:04 2006
 OBNUC 13C
 EXMOD bcm
 OBPRQ 99.45 MHz
 OBSET 100.00 KHz
 OBFIN 4750.0 Hz
 POINT 65536
 FREQU 26881.7 Hz
 SCANS 8000
 ACQTM 2.438 sec
 PD 1.000 sec
 PWL 4.9 us
 IRNUC 1H
 CTEMP 25.5 c
 SLVNT DMSO
 EXREF 39.50 ppm
 BF 1.00 Hz
 RGAIN 35

S41

1
 13C NMR in d₆-DMSO

DATIM Thu Feb 1 21:52:45 2007
DFILE C:\ALICE\25_1H.als
OBNUC 1H
EXMOD non
OFR 395.75 MHz
OBSET 130.00 KHz
OBFIN 4498.0 Hz
POINT 32768
FREQU 7917.7 Hz
SCANS 16
ACQTM 4.139 sec
PD 1.500 sec
PW1 7.2 us
IRN
CTEMP 24.2 c
SLVNT CDCL3
EXREF 0.00 ppm
BF 0.12 Hz
RGAIN 24

25
1H NMR

DATIM Sat Feb 3 09:09:55 2007
DFILE C:\ALICE\25_13C.als
OBNUC 13C
EXMOD bcm
OFR 99.45 MHz
OBSET 100.00 KHz
OBFIN 4750.0 Hz
POINT 65536
FREQU 26881.7 Hz
SCANS 9000
ACQTM 2.438 sec
PD 1.000 sec
PW1 4.9 us
IRN
CTEMP 25.0 c
SLVNT CDCL3
EXREF 0.00 ppm
BF 0.12 Hz
RGAIN 35

25
13C NMR