Supplementary information

Diastereoselective formal total synthesis of (+/-)-triptolide via a novel cationic cyclisation of 2-alkenyl-1,3-dithiolane

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Content:

1. General Methods 2
2. General procedures and Analytical datas 3
3. Cristallographic structure of compound (+/-)-4 9
4. 1H NMR and 13C NMR spectras of new compounds 10
5. References 24
1. General Methods

All reactions were carried out in a flame dried glassware under an argon atmosphere with dry solvents, under anhydrous conditions unless otherwise indicated. Solvents for reactions were dried using a dry solvent station GT S100. All reactions were controlled by analytical thin-layer chromatography using Merck pre-coated silica gel plates with F254 indicator. Visualization was accomplished by UV light (254 nm), cerium sulfate or vanillin stains. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise indicated. Purifications by column chromatography were carried out using Merck silicagel Si 60 (0.040-0.063). Yields determined by liquid chromatography were done using a SPD-20A Shimadzu apparatus equipped with a Zorbax 300SB-C18 column, using a mixture of acetonitrile and water as eluent. $^1$H NMR and $^{13}$C NMR were recorded on a Brucker Advance 400 (400 MHz $^1$HNMR, 100MHz $^{13}$C NMR). Chemical shift values (δ) are reported in ppm (residual chloroform δ = 7.26 ppm for $^1$H; residual chloroform δ = 77.16 ppm for $^{13}$C). The proton spectra are reported as follows δ (multiplicity, coupling constant $J$, number of protons). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), quint. (quintuplet), hept (heptuplet), m (multiplet). Infra-red spectra were recorded with a Nicolet 380 FT-IR apparatus. High resolution mass spectra were recorded with an Agilent Q-Tof 6520 apparatus equipped with a positive ESI source. Melting points were recorded with a Stuart Scientific SMP3 apparatus.

All reagents were purchased from Sigma-Aldrich, ABCR, Alfa-Aesar, and Acros and known compounds were prepared by cited standard literature procedure.
2. General Procedures and Analytical Datas

**Methyl 6-(3-isopropyl-2-methoxyphenyl)-3-oxohexanoate 7**

Methylacetoacetate (1.08 mL, 9.86 mmol, 1.0 eq.) was added, dropwise at 0°C, to a solution of lithium diisopropylamide 1.8 M (20.01 mmol, 2.0 eq.) in tetrahydrofurane (50 mL). After being stirred for 20 minutes, a solution of 1-(2-iodoethyl)-3-isopropyl-2-methoxybenzene 6 (3.00 g, 9.86 mmol, 1.0 eq.) in tetrahydrofurane (2.5 mL) was added at 0°C and then, the reaction mixture stirred overnight at room temperature. After addition of water (50 mL), the aqueous phase was extracted by diethyl ether (3*50 mL). The combined organic extracts were washed with brine, dried over sodium sulfate and evaporated. The residue was purified by flash chromatography on a silica gel column (eluent: 80/20 cyclohexane/ethyl acetate) to give 7 a pale yellow oil (2.19 g, 76 %). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.11 (dd, \(J = 2.0\) Hz, \(J = 7.2\) Hz, 1H), 7.01 (m, 2H), 3.73 (s, 3H), 3.71 (s, 3H), 3.45 (s, 2H), 3.27 (hept., \(J = 6.4\) Hz, 1H), 2.63 (t, \(J = 7.2\) Hz, 2H), 2.54 (t, \(J = 7.2\) Hz, 2H), 1.90 (quint., \(J = 7.2\) Hz, 2H), 1.22 (d, \(J = 7.2\) Hz, 6H) ; \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 202.61, 167.81, 155.76, 142.06, 134.35, 127.66, 124.87, 124.55, 61.75, 52.39, 49.19, 42.33, 29.05, 26.52, 24.44, 24.11 ; IR (neat): \(\nu\) 2960, 1747, 1716, 1461, 1436, 1314, 1250, 1202, 1167, 1050, 1009, 797, 765 ; HRMS (ESI, \(m/z\)): calcd. for C\(_{17}\)H\(_{24}\)O\(_4\) [M+H]\(^+\), 293.1753; found, 293.1757.

**Methyl 6-(3-isopropyl-2-methoxyphenyl)-3-oxo-2-(3-oxobutyl)hexanoate 8**

Potassium carbonate (554 mg, 4.00 mmol, 1.0 eq.) followed by a solution of methylvinylketone (340 \(\mu\)L, 4.00 mmol, 1.0 eq.) in dichloromethane (2 mL) were added to a solution of 7 (1.17 g, 4.00 mmol, 1.0 eq.) in dichloromethane (11 mL). The reaction mixture was stirred 16 hours. After addition of water (25 mL), the aqueous phase was extracted by diethyl ether (3*20 mL). The combined organic extracts were washed with brine, dried over
sodium sulfate and evaporated. The residue was purified by flash chromatography on a silica gel column (eluent: chloroform) to give 8 as a pale yellow oil (1.42 g, 96 %). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.10 (dd, $J = 2.0$ Hz, $J = 7.2$ Hz, 1H), 6.98 (m, 2H), 3.71 (s, 3H), 3.70 (s, 3H), 3.51 (t, $J = 6.8$ Hz, 1H), 3.26 (hept., $J = 6.8$ Hz, 1H), 2.53 (m, 4H), 2.46 (t, $J = 7.2$ Hz, 1H), 2.12 (s, 3H), 2.07 (m, 2H), 1.87 (m, 2H), 1.21 (d, $J = 6.8$ Hz, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 207.55, 204.87, 170.16, 155.75, 142.04, 134.40, 127.57, 124.82, 124.50, 61.78, 57.41, 52.49, 41.56, 40.66, 30.03, 29.10, 26.52, 24.43, 24.13, 24.08, 21.95; IR (neat): $\nu$ 2960, 1743, 1712, 1461, 1430, 1362, 1250, 1202, 1163, 1009, 797, 766; HRMS (ESI, m/z): calcd. for C$_{21}$H$_{30}$O$_5$ [M+K]$^+$, 401.1730; found, 401.1725.

2-[2-(3-isopropyl-2-methoxyphenyl)ethyl]-3-methylcyclohex-2-en-1-one 5

1,5-Diazabicyclo[5.4.0]undec-5-ene (660 μL, 4.39 mmol, 1.1 eq.) was added to a solution of 8 (1.42 g, 3.92 mmol, 1.0 eq.) in acetonitrile (60 mL) and the reaction mixture stirred for 3.5 hours at 80°C. Then, after cooling and addition of water (40 mL), the aqueous phase was extracted by diethyl ether (3*30 mL). The combined organic extracts were washed with brine, dried over sodium sulfate and evaporated. The residue was purified by flash chromatography on a silica gel column (eluent: 80/20 cyclohexane/ethyl acetate) to give 5 as a yellow oil (1.02 g, 90 %). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.09 (t, $J = 4.8$ Hz, 1H), 7.01 (d, $J = 4.8$ Hz, 1H), 3.74 (s, 3H), 3.27 (sept., $J = 7.2$ Hz, 1H), 2.56 (m, 4H), 2.38 (t, $J = 7.2$ Hz, 2H), 2.25 (t, $J = 6.0$ Hz, 2H), 1.89 (quint., $J = 6.8$ Hz, 2H), 1.69 (s, 3H), 1.21 (d, $J = 7.2$ Hz, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 198.87, 155.92, 155.86, 141.83, 135.08, 134.88, 128.26, 124.60, 124.30, 61.80, 38.08, 33.02, 29.62, 26.87, 26.49, 24.13, 22.40, 20.94; IR (neat): $\nu$ 2961, 2934, 2868, 1664, 1629, 1462, 1428, 1380, 1252, 1202, 1169, 1050, 1012, 797, 767; HRMS (ESI, m/z): calcd. for C$_{19}$H$_{26}$O$_2$ [M+K]$^+$, 325.1569; found, 325.1564.
2-isopropyl-6-[2-(7-methyl-1,4-dithiaspiro[4.5]dec-6-en-6-yl)ethyl]phenylmethyl ether 10

1,2-ethanedithiol (490 µL, 5.73 mmol, 1.1 eq.) and indium (III) trifluoromethanesulfonate (295 mg, 0.524 mmol, 0.1 eq.) were added successively to a solution of 5 (1.50 g, 5.25 mmol, 1.0 eq.) in dichloromethane (25 mL) and the reaction mixture was stirred for 24 hours. Then, additional 1,2-ethanedithiol (490 µL, 5.73 mmol, 1.1 eq.) and In(OTf)₃ (295 mg, 0.524 mmol, 0.1 eq.) were added. After 6 hours of stirring, dilution with dichloromethane (20 mL) and water (40 mL), the aqueous phase was extracted by dichloromethane (2*20 mL). The combined organic extracts were washed with brine, dried over sodium sulfate and evaporated. The residue was purified by flash chromatography on a silica gel column (elucent: 95/5 cyclohexane/ethyl acetate) to give 10 as a colorless solid (1.86 g, 98%). Mp: 55-56°C. ¹H NMR (400 MHz, CDCl₃): δ 7.11 (m, 2H), 7.03 (m, 1H), 3.78 (s, 3H), 3.31 (m, 5H), 2.91 (m, 2H), 2.53 (m, 2H), 2.00 (m, 2H), 1.80 (m, 5H), 1.23 (d, J = 8.0 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃): δ 155.71, 141.94, 136.11, 134.51, 131.22, 127.50, 124.47, 124.46, 61.94, 44.55, 40.38, 32.65, 31.91, 31.52, 26.45, 24.23, 22.68, 20.80; IR (neat): ν 2961, 2930, 2864, 1487, 1450, 1413, 1327, 1277, 1238, 1163, 1032, 913, 746, 669; HRMS (ESI, m/z): calcd. for C₂₁H₃₀O₂S₂ [M+Na]⁺, 385.1636, found, 385.1638.

(+/-)-7'-isopropyl-4a'-methyl-3',4',4a',9',10',10a'-hexahydro-2'H-spiro[1,3-dithiolane-2,1'-phenanthren]-8'-yl methyl ether 12

Fresh trimethylsilyl trifluoromethanesulfonate (50 µL, 0.243 mmol, 1.1 eq.) was added to a solution of 1,3-dithiolane (80 mg, 0.221 mmol, 1.0 eq.) in 1,2-dichloroethane (7 mL) and the reaction mixture was stirred 16 hours at room temperature. Then, after addition of water (20 mL), the aqueous phase was extracted by dichloromethane (3*10 mL). The combined organic extracts were washed with brine, dried over sodium sulfate and evaporated. The residue was
purified by flash chromatography on a silica gel column (eluent: 95/5 cyclohexane/ethyl acetate) to give 12 as a colorless solid (72 mg, 90%). Mp: 129-131°C. 1H NMR (400 MHz, CDCl₃): δ 7.00 (q, J = 8.4 Hz, 2H), 3.72 (s, 3H), 3.22 (m, 4H), 3.03 (m, 2H), 2.73 (m, 1H), 2.37 (m, 1H), 2.24 (m, 2H), 2.05 (d, J = 11.6 Hz, 1H), 1.83 (m, 3H), 1.71 (m, 1H), 1.43 (m, 1H), 1.25 (s, 3H), 1.20 (d, J = 7.2 Hz, 6H); 13C NMR (100 MHz, CDCl₃): δ 155.11, 147.51, 136.38, 128.90, 123.95, 120.67, 73.01, 60.61, 51.30, 46.82, 40.77, 39.67, 38.50, 38.19, 26.25, 24.97, 24.92, 24.08, 24.04, 22.06, 21.13; IR (neat): ν 2959, 2930, 2866, 1484, 1451, 1410, 1327, 1277, 1032, 913, 817, 734, 669; HRMS (ESI, m/z): calcd. for C₂₁H₂₉O₂ [M+Na]⁺, 385.1636, found, 385.1638.

(+/-)-7-isopropyl-8-methoxy-4a-methyl-3,4,4a,9,10,10a-hexahydrophenanthren-1(2H)-one 4

Trifluoroacetic acid (70 µL, 0.790 mmol, 10.0 eq) and bis-trifluoroacetoxyiodobenzene (39 mg, 0.079 mmol, 1.0 eq.) was added to a solution of 12 (29 mg, 0.079 mmol, 1.0 eq.) in a mixture of acetonitrile (400 µL) and water (400 µL). After being stirred 30 minutes, additional bis-trifluoroacetoxyiodobenzene (79 mg, 0.158 mmol, 2.0 eq.) was added and the mixture stirred 2.5 hours. Then, after addition of water (10 mL), the aqueous phase was extracted by diethyl ether (3*10 mL). The combined organic extracts were washed with brine, dried over sodium sulfate and evaporated. The residue was purified by flash chromatography on a silica gel column (eluent: 80/20 cyclohexane/ethyl acetate) to give (+/-)-4 as a colorless solid (19 mg, 85%). Mp: 130-132°C; 1H NMR (400 MHz, CDCl₃): δ 7.06 (dd, J = 4.0 Hz, J = 8.4 Hz, 2H), 3.25 (sept., J = 6.8 Hz, 1H), 3.03 (qd, J = 1.2 Hz, J = 17.6 Hz, 1H), 2.56 (m, 2H), 2.38 (m, 3H), 1.97 (m, 3H), 1.84 (td, J = 4.4 Hz, J = 12.8 Hz, 1H), 1.69 (m, 1H), 1.20 (dd, J = 3.6 Hz, J = 7.2 Hz, 6H), 1.05 (s, 3H); 13C NMR (100 MHz, CDCl₃): δ 212.57, 155.28, 144.79, 139.03, 128.65, 124.16, 121.15, 60.66, 55.24, 42.55, 41.01, 37.35, 26.29, 24.05, 24.00, 23.79, 23.24, 22.72, 17.20; IR (neat): ν 2959, 1712, 1484, 1455, 1410, 1377, 1327, 1261, 1139, 1071, 1058, 1031, 948, 818; HRMS (ESI, m/z): calcd. for C₁₉H₂₆O₂ [M+H]⁺, 287.2011, found, 287.2013.

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Crystallographic Data could be obtained via the Cambridge Crystallographic Data Center, e-mail: www.cdc.cam.ac.uk/data_request/cif, n° of deposite: CCDC 753095.

(+/-)-2-[bis(methylthio)methylene]-7-isopropyl-8-methoxy-4a-methyl-3,4,4a,9,10,10a-hexahydrophenanthren-1(2H)-one 17

Lithium diisopropylamide 1.8 M (100 µL, 0.179 mmol, 1.0 eq.) was slowly added at -78°C to a solution of (+/-)-4 (50 mg, 0.175 mmol, 1.0 eq.) in tetrahydrofurane (250 µL) and the reaction mixture stirred 30 minutes. Then, carbon disulfide (20 µL, 0.193 mmol, 1.1 eq.) was added rapidly and the reaction mixture stirred again 2 hours at -78°C before the addition of methyl iodide (30 µL, 0.385 mmol, 2.2 eq.). The reaction mixture was stirred at room temperature and water (10 mL) was added. The aqueous phase was extracted by diethyl ether (3*10 mL). The combined organic extracts were washed with brine, dried over sodium sulfate and evaporated. The residue was purified by flash chromatography on a silica gel column (eluent: 90/10 cyclohexane/ethyl acetate) to give (+/-)-15 as a yellow solid (57 mg, 84 %). Mp: 104-106°C ; ^1H NMR (400 MHz, CDCl3): δ 7.06 (m, 2H), 3.72 (s, 3H), 3.36 (m, 1H), 3.27 (quint., J = 6.8 Hz, 1H), 3.07 (m, 1H), 2.82-2.57 (m, 4H), 2.45 (m, 1H), 2.39 (s, 3H), 2.37 (s, 3H), 1.90 (dt, 1H), 1.69 (dq, 1H), 1.21 (dd, J = 6.8 Hz, J = 3.2 Hz, 6H), 1.11 (s, 3H) ; ^13C NMR (100 MHz, CDCl3): δ 201.19, 155.18, 144.55, 144.05, 139.56, 139.02, 128.86, 124.21, 121.33, 60.69, 56.09, 40.22, 37.25, 29.83, 26.29, 24.04, 24.02, 23.89, 23.60, 18.31, 17.98, 17.62 ; IR (neat): ν 2959, 2867, 1684, 1485, 1456, 1410, 1327, 1263, 1200, 1107, 1059, 1032, 972, 819 ; HRMS (ESI, m/z): calcd. for C_{22}H_{30}O_{2}S_{2} [M+H]^+, 391.1765, found, 391.1766.
(+/−)-Triptophenolide Methyl Ether 3

Butyllithium 1.6 M (530 µL, 0.791 mmol, 1.1 eq.) was slowly added at 0°C, over a period of several minutes, to a solution of trimethylsulphonium iodide (178 mg, 0.863 mmol, 1.2 eq.) in tetrahydrofurane (2.3 mL) and the reaction mixture stirred 5 minutes at 0°C. Then, a solution of (+/−)-24 (281 mg, 0.719 mmol, 1.0 eq) in tetrahydrofuran (150 µL) was added and the reaction mixture stirred 30 minutes at 0°C followed by 2 hours at room temperature. The reaction mixture was concentrated, taken up into methanol (9 mL) and HCl 6N (1.5 mL) and stirred overnight. After addition of water (300mL) was added, the aqueous phase was extracted by diethyl ether (3*20 mL). The combined organic extracts were washed with brine, dried over sodium sulfate and evaporated. The residue was purified by flash chromatography on a silica gel column (eluent: 80/20 cyclohexane/ethyl acetate) to give (+/−)-3 as a colorless solid (124 mg, 53 %). Analytical datas were identical to the ones reported in the literature.²

(+/−)-Triptophenolide 2

(+/−)-2 was obtained from (+/−)-3 via a described procedure in 92% of yield. Analytical datas were identical to the ones reported in the literature.²
3. Crystallographic structure of the *trans*-decaline (+/-)-4
4. $^1$H NMR and $^{13}$C NMR spectra of new compounds
5. References
