Supporting Information

The Triple Way: Combining Pot, Atom and Step Economy (PASE) for Greener Organic Synthesis. Synthesis of Tetrahydropyran-4-ones

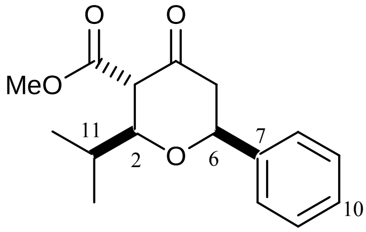
Paul A. Clarke, Soraia Santos and William H. C. Martin

General Method for the PASE Synthesis of THPs 4/5a-i: Method A

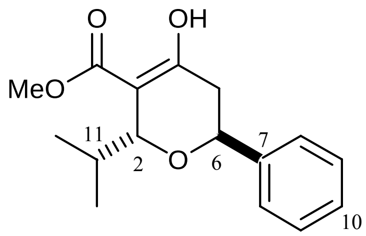
To a stirred solution of diketene (0.1 ml, 1.30 mmol) and aldehyde (0.72 mmol) in CH_2Cl_2 (2 ml) at -78 ^oC, was added $TiCl_4$ (80 µl, 0.72 mmol). After 5 min dry methanol (117 µl, 2.88 mmol) was added to the dark red mixture. The reaction was stirred for 30 min at -30 to -20 ºC before it was again cooled to -78 ºC, when the second aldehyde (0.87 mmol) was added. The reaction mixture was warmed back to -20 ºC and stirred at this temperature for 16 hrs. After dilution with ether, the mixture was washed with a 20 % (w/v) aqueous solution of citric acid (3x 30 ml), brine (2x 40 ml), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (Petrol - EtOAc - Pyridine: 200:1:2 to 100:4:2) gave the products.

General Method for the PASE Synthesis of THPs 4/5a-i: Method B

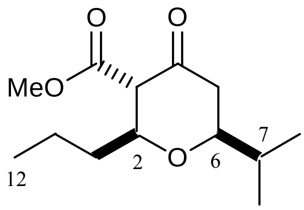
To a solution of diketene (0.1 ml, 1.30 mmol) and the aldehyde (0.72 mmol) in CH_2Cl_2 (2 ml), at -78 ^oC, was added $TiCl_4$ (80 µl, 0.72 mmol). After 5 min dry methanol (117 µl, 2.88 mmol) was added to the dark red mixture. The reaction was stirred for 30 min at -30 to -20 ºC before it was again cooled to -78 ºC, when pyridine (59 µl, 0.72 mmol) was added followed by the second aldehyde (0.87 mmol). The reaction mixture allowed to warm to room temperature and stirred until TLC analysis indicated that it was complete. After dilution with ether, the mixture was extracted with a 20 % (w/v) aqueous solution of citric acid (3x 30 ml), a 5 % (w/v) aqueous solution of $CuSO_4$ (3x 30 ml) and with brine (2x 40 ml), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (Petrol – EtOAc - Pyridine: 200:1:2 to 100:4:2) gave the products.



4a. White solid; m.p. = 106-107 ºC (lit[1]m.p. = 99-101 °C); IR υ_{max} (solution; $CHCl_3$): 3020.0, 2360.4, 1745.3, 1714.4, 1438.6, 1361.5, 1332.6, 1261.2, 1132.0 ; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.30-7.41 (5H, m, Ph), 4.73 (1H, dd, *J* =11.5, 2.5 Hz, CHPh), 4.00 (1H, dd, *J* = 11.0, 2.5 Hz, CH^{i}Pr), 3.79 (3H, s, OMe), 3.53 (1H, dd, *J* = 11.0, 1.0 Hz, CHCO$_2$Me), 2.75 (1H, dd, *J* = 4.5, 2.5 Hz, CHH), 2.52 (1H, ddd, *J* = 14.5, 11.5, 1.0 Hz, CHH), 1.83 (1H, d sept, *J* = 7.0, 2.5 Hz, CHMe$_2$), 1.09 (3H, d, *J* = 7.0 Hz, CHMeMe), 1.05 (3H, d, *J* = 7.0 Hz, CHMeMe); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 202.5, 168.7, 140.6, 128.6, 128.0, 125.3, 82.4, 78.0, 60.6, 52.2, 48.9, 31.6, 19.7, 15.4.



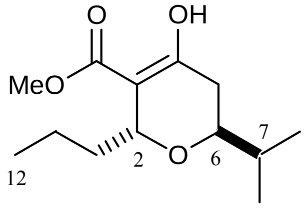
5a. Isomerises to **4a** in solution.



4b. Colourless oil; IR υ_{max} (solution; $CHCl_3$): 3027.7, 2964.1, 2875.3, 1743.3 (C=O), 1712.5 (C=O), 1656.6, 1465.6, 1483.6, 1344.1, 1272.8, 1135.9, 1122.4, 1037.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.82 (1H, ddd, *J* = 10.4, 8.8, 2.4 Hz, CHCHCO$_2$Me), 3.75 (3H, s, OMe), 3.32 (1H, ddd, *J* = 11.6, 6.4, 2.0 Hz, CH^{i}Pr), 3.21 (1H, d, *J* = 10.4 Hz, CHCO$_2$Me), 2.48 (1H, dd, *J* = 14.4, 2.0 Hz, CHHCH^{i}Pr), 2.24 (1H, dd, *J* = 14.4, 11.6 Hz, CHHCH^{i}Pr), 1.77 (1H, d sept, *J* = 6.8, 6.4 Hz, CHMe$_2$), 1.35-1.67 (4H, m, CHCH$_2$CH$_2$CH$_3$), 0.98 (3H, d, *J* = 6.8 Hz, CHMeMe), 0.91 (3H, t, *J* = 8.0 Hz, CH$_2$CH$_2$CH$_3$), 0.90 (3H, d, *J* = 6.8 Hz, CHMeMe); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 203.1, 168.8, 81.8, 78.1, 63.3, 52.04, 44.6, 37.2, 33.4, 18.6, 18.2, 17.9, 13.7.

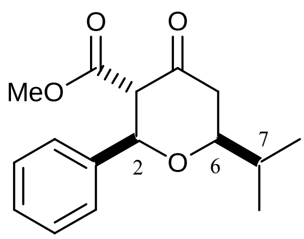
---

[1] Martin, W. H. C. PhD Thesis; "Rapid Construction of Highly Functionalised Pyran Rings"; The University of Nottingham; 2005

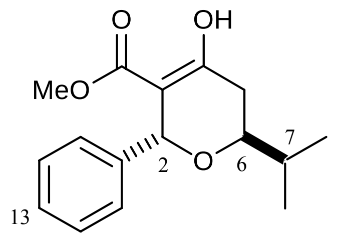


5b. Colourless oil; IR υ_{max} (solution; $CHCl_3$): 2960.2, 2873.4, 1660.4 (C=O), 1621.8, 1444.4, 1365.4, 1272.8, 1228.4, 1064.5; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 12.03 (1H, s, OH), 4.46 (1H, dd, J = 10.5, 2.0 Hz, $C\underline{H}CCO_2Me$), 3.76 (3H, s, OMe), 3.47 (1H, ddd, J = 10.0, 7.5, 5.0 Hz, $C\underline{H}{}^iPr$), 2.24 (1H, dd, J = 18.0, 10.0 Hz, $C\underline{H}HCH^iPr$), 2.19 (1H, dd, J = 18.0, 5.0 Hz, $CH\underline{H}CH^iPr$), 1.33-1.72 (5H, m, $C\underline{H}Me_2$ + $CH_2CH_2CH_3$), 0.99 (3H, d, J = 6.5 Hz, $CH\underline{Me}Me$), 0.94 (3H, t, J = 7.0 Hz, $CH_2CH_2C\underline{H}_3$), 0.92 (3H, d, J = 6.5 Hz, $CHMe\underline{Me}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.1, 169.9, 101.4, 70.9, 51.4, 35.1, 33.2, 32.1, 19.2, 18.7, 18.2, 13.7.

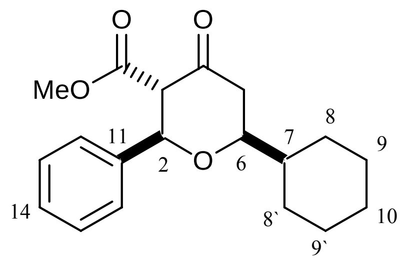
20 % of the sample was the ketone tautomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.40-4.44 (1H, m, $C\underline{H}Pr$), 3.76 (3H, s, OMe), 3.62 (1H, ddd, J = 8.0, 8.0, 4.5 Hz, $C\underline{H}{}^iPr$), 3.19 (1H, dd, J = 5.0, 1.0 Hz, $C\underline{H}CO_2Me$), 2.63 (1H, dd, J = 14.5, 8.0 Hz, $C\underline{H}HCH^iPr$), 2.49 (1H, ddd, J = 14.5, 4.5, 1.0 Hz, $CH\underline{H}CH^iPr$), 1.76-1.84 (1H, d sept, J = 8.0, 6.5 Hz, $C\underline{H}Me_2$), 1.32-1.62 (4H, m, $C\underline{H}_2C\underline{H}_2CH_3$), 0.97 (3H, d, J = 6.5 Hz, $CH\underline{Me}Me$), 0.94 (3H, m, , $CH_2CH_2C\underline{H}_3$), 0.88 (3H, d, J = 6.5 Hz, $CHMe\underline{Me}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 203.4, 168.8, 74.4, 61.7, 52.4, 43.6, 35.1, 31.6, 18.6, 18.4, 13.6.



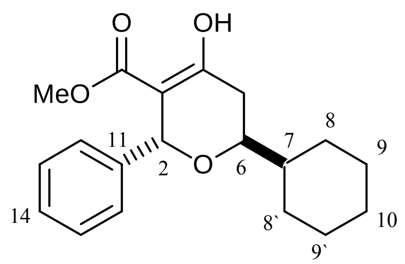
4c. White solid; m.p. = 81-82 ^{o}C (lit[1] m.p. = 59-61 ^{o}C); IR υ_{max} (solution; $CHCl_3$): 2964.1, 1745.3 (C=O), 1714.4 (C=O), 1438.6, 1344.1, 1303.6, 1130.1, 1066.4, 1033.6 ; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.28-7.41 (5H, m, Ph), 4.91 (1H, d, J = 10.8 Hz, $C\underline{H}Ph$), 3.62 (1H, ddd, J = 11.6, 6.0, 2.4 Hz, $C\underline{H}CH_2$), 3.61 (3H, s, OMe), 3.57 (1H, dd, J = 10.8, 0.8, Hz, $C\underline{H}CO_2Me$), 2.57 (1H, dd, J = 14.0, 2.4 Hz, $CH\underline{H}$), 2.44 (1H, ddd, J = 14.0, 11.6, 0.8 Hz, $CH\underline{H}$), 1.92 (1H, d sept, J = 6.8, 6.0 Hz, $C\underline{H}Me_2$), 0.98 (6H, t, J = 6.8 Hz, $CH\underline{Me}_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 202.4, 168.0, 139.1, 128.5, 126.5, 81.9, 80.5, 64.7, 52.0, 43.9, 33.1, 18.0, 17.7.



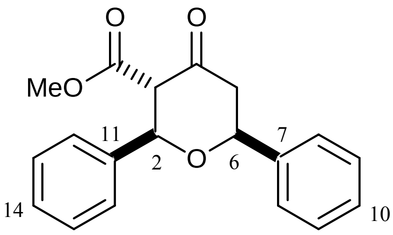
5c. White solid; m.p. = 64-66 °C (lit[1] m.p. = 57-58 °C); IR υ_{max} (solution; $CHCl_3$): 3016.1, 2962.1, 1660.4 (C=O), 1623.8, 1444.4, 1367.3, 1272.8, 1226.5, 1211.1, 1060.6; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 12.29 (1H, s, OH), 7.27-7.37 (5H, m, Ph), 5.62 (1H, br s, C$\underline{H}$Ph), 3.63 (3H, s, OMe), 3.11 (1H, ddd, J = 11.0, 7.0, 4.0 Hz, C$\underline{H}$$CH_2$), 2.36 (1H, ddd, J = 18.0, 11.0, 1.0 Hz, C$\underline{H}$H), 2.23 (1H, dd, J = 18.0, 4.0 Hz, CH$\underline{H}$), 1.60 (1H, d sept , J = 7.0, 6.5 Hz, C$\underline{H}$^{i}Pr), 0.80 (3H, d, J = 6.5 Hz, CH$\underline{Me_2}$), 0.78 (3H, d, J = 6.5 Hz, CH$\underline{Me_2}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.8, 171.1, 140.9, 128.5, 127.9, 127.6, 98.5, 72.5, 71.5, 51.5, 32.7, 32.2 , 18.3, 17.8.



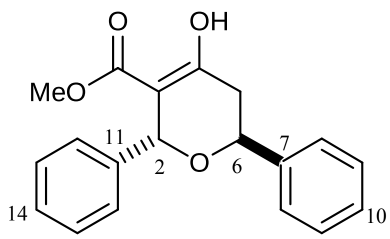
4d. White solid; m.p. = 93-94 °C (lit[1] m.p. = 92-94 ºC); IR υ_{max} (solution; $CHCl_3$): 3825.8, 2929.3, 2856.1, 1743.3 (C=O), 1450.2, 1340.3, 1274.7, 1218.8, 1137.8, 1066.4, 1029.8; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.28-7.41 (5H, m, Ph), 4.89 (1H, d, J = 10.5 Hz, C$\underline{H}$Ph), 3.63 (1H, ddd, J = 11.5, 6.0, 2.5 Hz, H_6), 3.61 (3H, s, OMe), 3.57 (1H, dd, J = 10.5, 1.0 Hz, C$\underline{H}$$CO_2$Me), 2.57 (1H, dd, J = 14.0, 2.5 Hz, C$\underline{H}$HCO), 2.46 (1H, ddd, = 14.0, 11.5, 1.0 Hz, CH$\underline{H}$CO), 1.87-1.93 (1H, m, $H_{9`eq}$ or $H_{9eq}$), 1.70-1.81 (3H, m, $H_8$ + $H_{8`}$ +H_{10}), 1.56-1.64 (1H, m, H_7), 0.95-1.32 (5H, m, $H_{9`ax}$ + $H_{9ax}$ + $H_8$ + $H_{8`}$ + H_{10}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 202.5, 168.0, 139.1, 128.5, 126.6, 81.3, 80.6, 64.8, 51.9, 44.2, 42.8, 28.4, 28.1, 26.3, 25.9, 25.8.



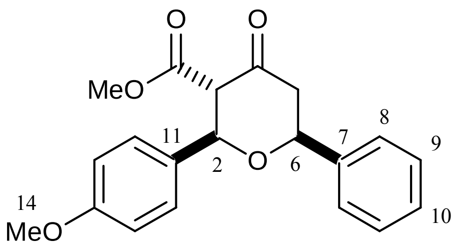
5d. White solid; m.p. = 100-101 °C (lit[1]m.p. = 89-91 °C); IR υ_{max} (solution; $CHCl_3$): 3018.1, 2929.3, 2854.1, 1660.4 (C=O), 1623.8, 1444.4, 1297.8, 1278.6, 1243.9, 1209.1, 1064.5, 1049.1 ; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 12.29 (1H, s, $O\underline{H}$), 7.27-7.36 (5H, m, Ph), 5.61 (1H, s, $C\underline{H}Ph$), 3.63 (3H, s, OMe), 3.15 (1H, ddd, J = 11.0, 7.5, 3.5 Hz, H_6), 2.36 (1H, ddd, J = 18.0, 11.0, 0.5 Hz, $C\underline{H}HCOH$), 2.22 (1H, dd, J = 18.0, 3.5 Hz, $CH\underline{H}COH$), 1.83-1.91 (1H, m, $H_{9`eq}$ or $H_{9eq}$), 1.56-1.70 (3H, m, $H_{9ax}$ + $H_{9`ax}$ +H_{10}), 1.48-1.54 (1H, m, $H_{9`eq}$ or $H_{9eq}$), 1.28-1.36 (1H, m, $H_7$), 0.99-1.23 (3H, m, $H_{8eq}$ + $H_{8`eq}$ + H_{10}), 0.86 (1H, ddd, J = 24.5, 12.5, 3.5 Hz, H_{8ax} or $H_{8`ax}$), 0.66 (1H, m, ddd, $J$ = 24.5, 12.5, 3.5 Hz, $H_{8ax}$ or $H_{8`ax}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.9, 171.1, 140.9, 127.9, 127.6, 127.6, 98.5, 72.5, 70.6, 51.5, 42.3, 32.3, 28.6, 28.0, 26.3, 25.9, 25.6.



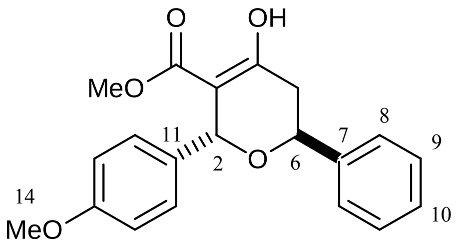
4e. White solid; m.p. = 140-142 °C (lit[1] m.p. = 133-135 °C); IR υ_{max} (solution; $CHCl_3$): 3016.1, 1745.3 (C=O), 1718.3 (C=O), 1496.5, 1446.0, 1438.6, 1348.0, 1130.1, 1066.4, 1027.9; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.30-7.51 (10H, m, Ph), 5.13 (1H, d, J = 10.5 Hz, $PhC\underline{H}CHCO_2Me$), 4.94 (1H, dd, J = 11.5, 2.5 Hz, $PhC\underline{H}CH_2$), 3.76 (1H, d, J = 10.5 Hz, $PhCHC\underline{H}CO_2Me$), 3.65 (3H, s, OMe), 2.85 (1H, dd, J = 14.5, 2.5, Hz, $C\underline{H}H$), 2.77 (1H, dd, J = 14.5, 11.5 Hz, $CH\underline{H}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 201.0, 167.7, 140.0, 138.6, 128.2, 126.8, 125.6, 80.9, 78.8, 64.5, 52.1, 48.8.



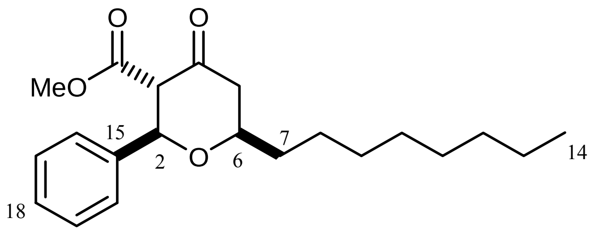
5e. White solid; m.p. = 123-125 °C (lit[1] m.p. = 118-120 °C); IR υ_{max} (solution; $CHCl_3$): 2956.3, 1662 (C=O), 1623.8, 1444.4, 1365.4, 1270, 1187.9, 1062.6, 1024.0 ; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 12.34 (1H, s, $O\underline{H}$), 7.20-7.39 (10H, m, Ph), 5.76 (1H, s, $C\underline{H}CCO_2Me$), 4.54 (1H, dd, J = 10.5, 4.0 Hz, $C\underline{H}CH_2$), 3.60 (3H, s, OMe), 2.70 (1H, dd, J =, 18.0, 10.5 Hz, CH̲H), 2.56 (1H, dd, *J* = 18.0, 4.0 Hz, CHH̲); [13]C NMR (125 MHz, $CDCl_3$) *δ*: 171.0, 170.9, 140.8, 140.6, 128.4, 128.4, 128.4, 128.1, 127.9, 127.7, 125.8, 98.5, 73.1, 68.2, 51.5, 35.4.



4f. White solid; m.p. = 127-128 °C; IR υ_{max} (solution; $CHCl_3$): 3029.6, 1745.3 (C=O), 1718.3 (C=O), 1614.1, 1517.8, 1348.0, 1305.6, 1251.6, 1211.1, 1176.4, 1130.1, 1072.2, 1035.6; [1]H NMR (500 MHz, $CDCl_3$) *δ*: 7.29-7.42 (7H, m, Ph + CH̲CHCOMe), 6.87-6.91 (2H, m, CHCH̲COMe), 5.06 (1H, d, *J* = 10.5 Hz, CH̲CHCO_2Me), 4.91 (1H, dd, *J* = 11.5, 3.0 Hz, CH̲CH_2), 3.80 (3H, s, OMe), 3.74 (1H, d, *J* = 10.5 Hz, CHCH̲CO_2Me), 3.64 (3H, s, CO_2M̲e̲), 2.83 (1H, dd, J = 14.5, 3.0 Hz, CH̲H), 2.74 (1H, dd, J = 14.5, 11.5, Hz, CHH̲); [13]C NMR (125 MHz, $CDCl_3$) *δ*: 201.2, 167.9, 159.8, 140.1, 130.8, 128.7, 128.3, 128.2, 125.6, 114.0, 80.7, 78.8, 64.6, 55.2, 52.1, 48.9.

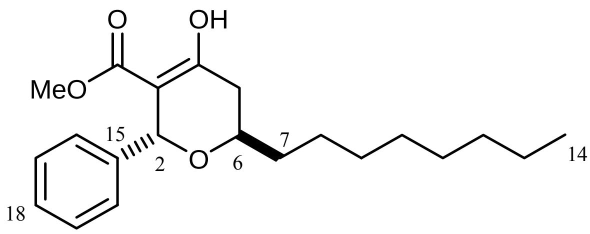


5f. White solid; m.p. = 112-114 °C ; IR υ_{max} (solution; $CHCl_3$): 2931.3, 1660.4 (C=O), 1623.8, 1510.0, 1444.4, 1270.8, 1249.6, 12211.6, 1174.4, 1062.6, 1031.7; [1]H NMR (500 MHz, $CDCl_3$) *δ*: 12.32 (1H, s, OH), 7.22-7.32 (7H, m, Ph + CH̲CHCOMe), 6.85-6.89 (2H, m, CHCH̲COMe), 5.73 (1H, s, CH̲CCO_2Me), 4.56 (1H, dd, *J* = 11.0, 4.0 Hz, CH̲CH_2), 3.80 (3H, s, OM̲e̲), 3.64 (3H, s, CO_2M̲e̲), 2.70 (1H, dd, *J* = 18.0, 11.0 Hz, CHH̲), 2.57 (1H, dd, J = 18.0, 4.0 Hz, CHH̲); [13]C NMR (100 MHz, $CDCl_3$) *δ*: 171.0, 159.2, 140.9, 132.8, 129.7, 128.4, 127.8, 125.9, 113.5, 98.8, 72.7, 67.9, 55.2, 51.6, 35.4.

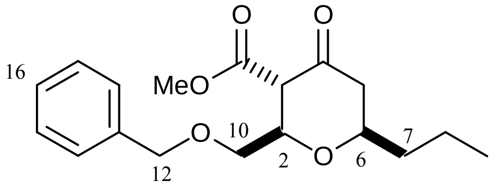


4g. Colourless oil; IR υ_{max} (NaCl, film): 3021.1, 2927.0, 2855.3, 1745.2 (C=O), 1716.6 (C=O), 1658.7, 1618.4, 1438.3, 1343.3, 1273.8, 1216.0, 1123.4, 1062.6; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.28-7.41 (5H, m, Ph), 4.91 (1H, d, J = 10.4 Hz, $C\underline{H}Ph$), 3.85 (1H, dddd, J = 11.2, 6.8, 5.2, 2.4 Hz, $C\underline{H}C_8H_{17}$), 3.61 (3H, s, OMe), 2.78 (1H, dd, J = 14.4, 2.4 Hz, $C\underline{H}HC{=}O$), 2.43 (1H, ddd, J = 14.4, 11.2, 0.8 Hz, $CH\underline{H}C{=}O$), 1.68-1.79 (1H, m, $CHC\underline{H}H(CH_2)_6CH_3$), 1.52-1.68 (1H, m, $CHCH\underline{H}(CH_2)_6CH_3$), 1.51-1.20 (12H, m, $CHCHH(C\underline{H}_2)_6CH_3$), 0.88 (3H, t, J = 7.0 Hz, $CHCHH(CH_2)_6C\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 202.1, 168.1, 139.1, 128.7, 128.2, 126.8, 77.5, 73.4, 64.7, 52.1, 36.3, 31.9, 31.9, 29.6, 29.3, 29.3, 25.1, 22.7, 14.2.

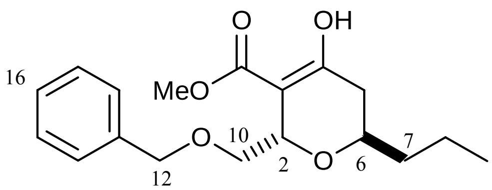
39 % of the sample was the enol tautomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 12.04 (1H, s, OH), 7.28-7.41 (5H, m, Ph), 5.36 (1H, dd, J = 2.4, 1.6 Hz, $C\underline{H}Ph$), 3.64-3.70 (1H, m, $C\underline{H}C_8H_{17}$), 3.46 (3H, s, OMe), 2.45 (1H, ddd, J = 17.2, 10.4, 2.4 Hz, $C\underline{H}HCOH$), 2.32 (1H, ddd, J = 17.2, 2.8, 1.6 Hz, $CH\underline{H}OH$), 1.52-1.68 (2H, m, $CHC\underline{H}_2(CH_2)_6CH_3$), 1.51-1.20 (12H, m, $CHCH_2(C\underline{H}_2)_6CH_3$), 0.88 (3H, t, J = 6.4 Hz, $CHCH_2(C\underline{H}_2)_6C\underline{H}_3$).



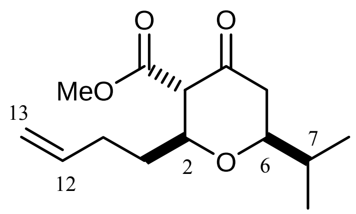
5g. White solid; m.p. = 62.5-62.9 ºC; IR υ_{max} (NaCl, film): 3027.6, 2926.6, 2855.1, 1661.1 (C=O), 1622.7, 1443.4, 1269.0, 1218.2, 1039.4, 846.6; ^{1}H NMR (270 MHz, $CDCl_3$) δ: 12.30 (1H, s, OH), 7.27-7.37 (5H, m, Ph), 5.61 (1H, s, $C\underline{H}Ph$), 3.63 (3H, s, OMe), 3.44 (1H, ddd, J = 12.7, 10.0, 4.9 Hz, $C\underline{H}CH_2COH$), 2.32 (1H, dd, J = 18.1, 10.0 Hz, $C\underline{H}HCOH$), 2.23 (1H, dd, J = 18.1, 14.9 Hz, $CH\underline{H}COH$), 1.01-1.56 (17H, m, $CH(CH_2)_7CH_3$), 0.86 (3H, t, J = 6.8 Hz, $CH(CH_2)_7C\underline{H}_3$); ^{13}C NMR (68 MHz, $CDCl_3$) δ: 171.7, 171.2, 141.1, 128.5, 128.0, 127.8, 98.6, 72.7, 66.4, 51.6, 35.6, 34.9, 31.9, 29.5, 29.3, 25.0, 22.7, 14.2.



4h. Colourless oil; IR υ_{max} (NaCl, film): 3027.1, 2957.7, 2032.8, 2871.8, 1744.4 (C=O), 1715.4 (C=O), 1453.3, 1350.3, 1263.0, 1215.8, 1126.4, 1028.8, 752.5; ^{1}H NMR (270 MHz, $CDCl_3$) δ: 7.27-7.37 (5H, m, Ph), 4.65 (1H, d, J = 12.4 Hz, $C\underline{H}HPh$), 4.50 (1H, d, J = 12.4 Hz, $CH\underline{H}Ph$), 4.11 (1H, ddd, J = 10.5, 4.1, 3.2 Hz, $C\underline{H}CH_2OBn$), 3.62-3.72 (3H, m, $C\underline{H}HOBn$ + $C\underline{H}CO_2Me$ + $C\underline{H}Pr$), 3.66 (3H, s, OMe), 3.58 (1H, dd, J = 10.2, 3.8 Hz, $CH\underline{H}OBn$), 2.48 (1H, dd, J = 14.3, 2.7 Hz, $C\underline{H}HC{=}O$), 2.30 (1H, ddd, J = 14.3, 11.3, 0.8 Hz, $CH\underline{H}C{=}O$), 1.32-1.58 (4H, m, $CHC\underline{H_2}C\underline{H_2}CH_3$), 0.93 (3H, t, J = 7.2 Hz, $CHCH_2CH_2C\underline{H_3}$); ^{13}C NMR (68 MHz, $CDCl_3$) δ: 202.6, 168.4, 137.7, 128.3, 127.8, 127.7, 77.7, 77.1, 73.5, 70.6, 59.1, 52.1, 47.0, 38.1, 18.4, 13.8.



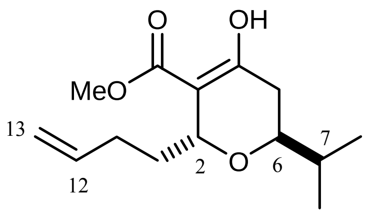
5h. Colourless oil; IR υ_{max} (NaCl, film): 2955.7, 2870.2, 1661.3 (C=O), 1622.1, 1442.7, 1360.6, 1289.9, 1217.5, 1073.4, 836.1; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 12.15 (1H, s, OH), 7.26-7.34 (5H, m, Ph), 4.73 (1H, dd, J = 8.0, 2.0 Hz, $C\underline{H}CH_2OBn$), 4.62 (1H, d, J = 12.4 Hz, $C\underline{H}HPh$), 4.55 (1H, d, J = 12.4 Hz, , $CH\underline{H}Ph$), 3.86-3.93 (1H, m, $C\underline{H}Pr$), 3.69 (3H, s, OMe), 3.63 (1H, dd, J = 10.8, 8.0 Hz, $C\underline{H}HOBn$), 3.53 (1H, dd, J = 10.8, 2.0 Hz, $CH\underline{H}OBn$), 2.18-2.22 (2H, m, $C\underline{H_2}CHPr$), 1.20-1.62 (4H, m, $CHC\underline{H_2}C\underline{H_2}CH_3$), 0.93 (3H, t, J = 7.2 Hz, $CHCH_2CH_2C\underline{H_3}$); ^{13}C NMR (68 MHz, $CDCl_3$) δ: 171.5, 170.7, 138.4, 128.3, 127.7, 127.6, 96.9, 72.9, 71.0, 69.7, 66.8, 51.4, 37.8, 34.2, 18.5, 14.0.



4i. Colourless oil; IR υ_{max} (NaCl, film): 2960.0, 1746.9 (C=O), 1716.7 (C=O), 1641.4, 1437.5, 1343.3, 1268.4, 1129.8, 757.9; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.34-5.89 (1H, m, $H_2C{=}C\underline{H}$), 4.97-5.07 (2H, m, $\underline{H_2}C{=}CH$), 3.85 (1H, ddd, J = 10.4, 9.2, 2.6 Hz, $C\underline{H}CH_2CH_2CH{=}CH_2$), 3.77

(3H, s, OMe), 3.33 (1H, ddd, *J* = 11.8, 6.8, 2.4 Hz, $C\underline{H}^{i}Pr$), 3.24 (1H, d, *J* = 10.4 Hz, $C\underline{H}CO_2Me$), 2.51 (1H, dd, *J* = 14.0, 2.4 Hz, $C\underline{H}HCH^{i}Pr$), 2.26 (1H, dd, *J* = 14.0, 11.8 Hz, $C\underline{H}HCH^{i}Pr$), 2.12-2.28 (2H, m, $H_2C{=}CHC\underline{H_2}CH_2CH$), 1.79 (1H, oct, *J* = 6.8 Hz, $C\underline{H}Me_2$), 1.73 (2H, m, $H_2C{=}CHCH_2C\underline{H_2}CH$), 1.01 (3H, d, *J* = 6.8 Hz, $CH\underline{Me}Me$), 0.92 (3H, d, *J* = 6.8 Hz, $CHMe\underline{Me}$); ^{13}C NMR (68 MHz, $CDCl_3$) δ: 202.7, 168.5, 137.5, 115.1, 81.7, 77.4, 63.1, 52.0, 44.5, 34.1, 33.3, 29.4, 18.1, 18.0.

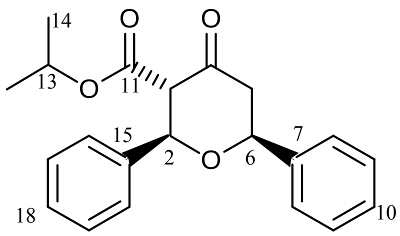
30 % of the sample was the enol tautomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 12.06 (1H, s, OH), 5.34-5.89 (1H, m, $H_2C{=}C\underline{H}$), 4.92-5.04 (2H, m, $\underline{H_2}C{=}CH$), 4.37 (1H, dq, *J* = 7.6, 2.0 Hz, $CHCH_2CH_2CH{=}CH_2$), 3.77 (3H, s, OMe), 3.13 (1H ddd, *J* = 9.6, 6.8, 4.0 Hz, $C\underline{H}^{i}Pr$), 2.45-2.29 (2H, m, $C\underline{H_2}CH^{i}Pr$), 2.12-2.28 (1H, m, $H_2C{=}CHC\underline{H}HCH_2CH$), 1.98 (1H, dddd, *J* = 14.0, 9.6, 6.8, 2.4 Hz, $H_2C{=}CHCH\underline{H}CH_2CH$), 1.54-1.77 (3H, m, $H_2C{=}CHCHHC\underline{H_2}CH$ + $C\underline{H}Me_2$), 0.98 (3H, d, *J* = 6.8 Hz, $CH\underline{Me}Me$), 0.91 (3H, d, *J* = 6.8 Hz, $CHMe\underline{Me}$); ^{13}C NMR (68 MHz, $CDCl_3$) δ: 171.2, 171.1, 138.9, 114.1, 100.4, 76.9, 72.1, 51.2, 34.2, 32.6, 32.5, 29.1, 18.4, 17.9.



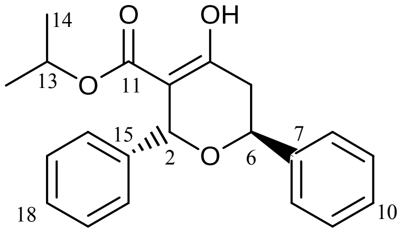
5i. Colourless oil; IR υ_{max} (NaCl, film): 2956.3, 1661.7 (C=O), 1623.1, 1443.2, 1364.2, 1270.2, 1220.6, 1066.5, 913.7, 819.4; ^{1}H NMR (270 MHz, $CDCl_3$) δ: 12.07 (1H, s, OH), 5.87 (1H, qt, *J* = 17.0, 10.4, 6.6 Hz, $H_2C{=}C\underline{H}$), 4.95-5.10 (2H, m, $\underline{H_2}C{=}CH$), 4.48 (1H, dd, *J* = 7.0, 6.5 Hz, $C\underline{H}CCO_2Me$), 3.77 (3H, s, OMe), 3.43-3.51 (1H, m, $CH^{i}Pr$), 2.09-2.34 (5H, m, $H_2C{=}CHC\underline{H_2}C\underline{H_2}CH$ + $C\underline{H}Me_2$), 1.73 (1H, dd, *J* = 8.4, 6.8 Hz, $C\underline{H}HCH^{i}Pr$), 1.68 (1H, dd, *J* = 6.8, 4.6 Hz, $CH\underline{H}CH^{i}Pr$), 1.02 (3H, d, *J* = 6.8 Hz, $CH\underline{Me}Me$), 0.93 (3H, d, *J* = 6.8 Hz, $CHMe\underline{Me}$); ^{13}C NMR (68 MHz, $CDCl_3$) δ: 170.1, 168.2, 138.3, 114.6, 70.9, 70.5, 51.5, 33.2, 32.3, 31.8, 30.2, 18.8, 18.2.

General Procedure for the Asymmetric Preparation of Tetrahydropyrans 4j-m and 5j-m

Titanium tetra-*iso*propoxide (432 μl, 1.45 mmol) was added to a stirred solution of the Schiff base **6** (631 mg, 1.59 mmol) in CH_2Cl_2 (3 ml) at room temperature. The resulting solution was stirred for 1h then cooled to -20 ºC. Freshly distilled aldehyde (1.45 mmol), diketene (0.2 ml, 2.61 mmol) and dry *iso*propyl alcohol (333 μl, 4.35 mmol) were added to the reaction and the resulting mixture kept at -20 °C for 5 days. (A sample of the reaction was taken and submitted to the same work up described below in order to determinated % e.e. values by ^{1}H NMR of the aldol intermediate **7**). The reaction was cooled to -78 °C and the second aldehyde (1.74 mmol) was added followed by a 3M solution of $TiCl_4$ in CH_2Cl_2 (1.59 mmol, 0.53 ml). The resulting dark mixture was stirred at the same temperature for 30 minutes and then at -20 °C for 16 hr. The reaction mixture was poured into a 20 ml EtOAc/10 ml H_20 and stirred vigorously for 2 h. This mixture was dried with Na_2SO_4, filtered and concentrated *in vacuo* to yield an orange oil. Purification by flash chromatography (Petrol – EtOAc - Pyridine: 200:1:2 to 100:4:2) gave tetrahydropyrans **4j** and **5j**.

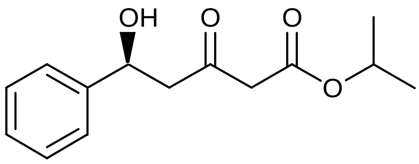


40 % ; white solid; m.p. = 127-129 ºC; IR (NaCl, film) υ_{max} 3031.4, 2982.2, 1738.0, 1715.4, 1456.4, 1363.6, 1322.8, 1216.4, 1132.1, 1104.3, 1066.6, 981.3, 755.9 cm^{-1}; ^{1}H NMR (500 MHz; $CDCl_3$) δ: 7.49 (2H, br d, J = 7.5 Hz, Ar), 7.42 (2H, br d, J = 7.5 Hz, Ar), 7.30-7.40 (6H, m, Ar), 5.10 (1H, d, J = 10.5 Hz, H_2), 5.00 (1H, sept, J = 6.0 Hz, H_{13}), 4.95 (1H, dd, J = 3.0, 11.5 Hz, H_6), 3.70 (1H, d, J = 1.0, 10.5 Hz, H_3), 2.83 (1H, dd, J = 3.0, 14.5 Hz, H_{5eq}), 2.76 (1H, ddd, J = 1.0, 11.5, 14.5 Hz, H_{5ax}), 1.19 (3H, d, J = 6.0 Hz, H_{14}), 1.04 (3H, d, J = 6.0 Hz, H_{14}) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 201.2 (C_4), 166.8 (C_{11}), 140.0 (C_7), 138.5 (C_{15}), 128.7 (CH, Ar), 128.6 (CH, Ar), 128.5 (CH, Ar), 128.2 (CH, Ar), 127.0 (CH, Ar), 125.6 (CH, Ar), 81.1 (C_2), 78.9 (C_6), 68.8 (C_{13}), 64.6 (C_3), 48.9 (C_5), 21.5 (C_{14}), 21.5 (C_{14}); m/z (CI+) 233 (100 % M^+), 356 (85 %, M^+ + $NH4^+$); HRMS: found (M^+ + NH_4^+), 356.1859 $C_{21}H_{26}NO_4$ requires (M^+ + NH_4^+) 356.1862; Anal. Calc. for $C_{21}H_{22}O_4$: C, 74.54; H 6.55 %. Found C, 74.29; H, 6.52 %. $[\alpha]_D^{25}$ = -29.45 ° (c 0.51, $CHCl_3$); e.e. = 92 % as determined by ^{1}H NMR chiral shift experiments with tris [3-(heptafluoropropylhydroxy-methylene)-*d*-camphorato] europium (III) 17 mol %, 7.0 mg, C_6D_6).



3 %, white solid; m.p. = 102-103 ºC; IR (NaCl, film) υ_{max} 3090.1, 2981.9, 1656.5, 1396.7, 1268.1, 1218.2, 1104.6, 1057.5, 1024.9, 755.2 cm^{-1}; ^{1}H NMR (500 MHz; $CDCl_3$) δ: 12.41 (1H, s, OH), 7.38 (2H, br d, J = 7.5 Hz, Ph), 7.25-7.34 (8H, m, Ph), 5.72 (1H, s, H_2), 5.02 (1H, sept, J = 6.5 Hz, H_{13}), 4.62 (1H, dd, J = 4.0, 11.0 Hz, H_6), 2.71 (1H, dd, J = 1.8, 11.0 Hz, H_{5a}), 2.58 (1H, dd, J = 4.0, 18.0 Hz, H_{5eq}), 1.15 (3H, d, J = 6.5 Hz, H_{14}), 0.89 (3H, d, J = 6.5 Hz, H_{14}) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.5 (C_4), 170.1 (C_{11}), 140.9 (C_{15}), 140.8 (C_7), 128.4 (CH, Ar), 128.4 (CH, Ar), 128.0 (CH, Ar), 127.7 (CH, Ar), 127.7 (CH, Ar), 125.9 (CH, Ar), 99.0 (C_3), 73.3 (C_2), 68.3 (C_6), 68.1 (C_{13}), 35.4 (C_5), 21.7 (C_{14}), 21.2 (C_{14}); m/z (CI+) 321 (100 % M^+- OH), 356 (40 %, M^+ + $NH4^+$); HRMS: found (M^+ + NH_4^+), 356.1857 $C_{21}H_{26}NO_4$ requires (M^+ + NH_4^+) 356.1862; Anal. Calc. for $C_{21}H_{22}O_4$: C, 74.54; H 6.55 %. Found C, 74.63; H, 6.66 %. $[\alpha]_D^{25}$ = -63.57 ° (c 0.07, $CHCl_3$); e.e. = >95 % as determined by HPLC: CHIRACEL OD-H, Hexane/Isopropanol 99:1, flow rate = 0.1 ml/min, T = 10 °C, t_r(minor) = 53.8 min., t_r (major) = 50.0 min.

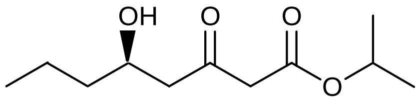
Asymmetric Hayashi aldol Adducts 7j, k, m



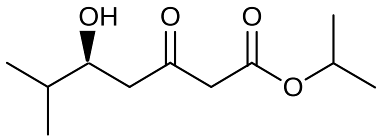
7j. oil; $[\alpha]_D^{25}$ = -38.32 ° (c 1.15, $CHCl_3$) literature[2]: $[\alpha]^{24}_D$ -40.8º (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ :7.39-7.28 (5H, m, Ar), 5.21 (1H, dt, J = 9.2, 3.3 Hz, C<u>H</u>OH), 5.07 (1H, sept, J = 6.4 Hz, C<u>H</u>Me_2), 3.46 (2H, br s, C<u>H</u>$_2$$CO_2$^{i}Pr), 3.04 (1H, d, J = 3.2 Hz, O<u>H</u>), 3.01 (1H, dd, J = 8.8, 17.4 Hz, C<u>H</u>$_2$CHOH), 2.93 (1H, dd, J = 3.4, 17.4 Hz, C<u>H</u>$_2$CHOH), 1.27 (6H, d, J = 6.4 Hz, ^{i}Pr). The e.e. of the product was 82 % and was determinated by ^{1}H NMR (500 MHz, C_6H_6, 11 mg of compound) shift reagent experiments with Tris [3-(heptafluoropropylhydroxy-methylene)-d-camphorato] europium (III) (26 mol %).

---

[2] Hayashi M.; Inoue T.; Miyamoto Y; Oguni N., *Tetrahedron*, **1994**, *50*, 4385-98.



7k. oil; $[\alpha]_D^{25}$ = -37.62 ° (c 0.67, $CHCl_3$), (lit.[2] $[\alpha]^{24}_D$ – 18.4º (c 1.1, $CHCl_3$); ^{1}H NMR (400 MHz; $CDCl_3$) δ : 5.08 (1H, sept, *J* = 6.0 Hz, C<u>H</u>Me$_2$), 4.08 (1H, m, C<u>H</u>OH), 3.40-3.48 (2H, t, J = 16.0 Hz, C<u>H</u>$_2$CO$_2{}^i$Pr), 4.17 (1H, dd, *J* = 17.6, 3.2 Hz, C<u>H</u>HCHOH), 2.64 (1H, dd, J = 17.6, 9.2 Hz, CH<u>H</u>CHOH), 1.58-1.31 (4H, m, C<u>H</u>$_2$C<u>H</u>$_2$CH$_3$), 1.27 (6H, d, *J* = 6.0 Hz, OCH<u>Me</u>$_2$), 0.92 (3H, t, *J* = 8.8. Hz, CH$_2$CH$_2$C<u>H</u>$_3$) ppm; The e.e. of the product - 62 %, was determinated by ^{1}H NMR (500 MHz, C_6D_6, 24 mg of compound) shift reagent experiments with Tris [3-(heptafluoropropylhydroxy-methylene)-d-camphorato] europium (III) (12 mol %).

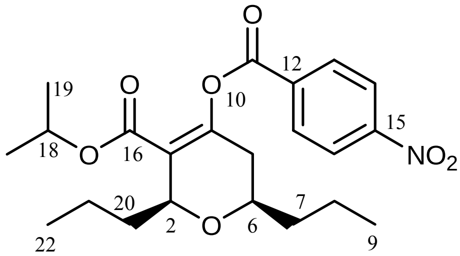


7m. oil; $[\alpha]_D^{24}$ = -29.21 ° (c 0.67, $CHCl_3$); IR ($CHCl_3$) υ_{max} 2964, 2934, 2877, 1733 (O-C=O), 1709 (C=O), 1388, 1374, 1315, 1104 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ : 5.07 (1H, sept, *J* = 6.4 Hz, OC<u>H</u>Me$_2$), 3.86 (1H, m, C<u>H</u>OH), 3.50-3.43 (2H, m, C<u>H</u>$_2$CO$_2{}^i$Pr), 2.73 (1H, dd, *J* = 17.6, 2.8 Hz, C<u>H</u>HCHOH), 2.69 (1H, d, *J* = 3.6 Hz, O<u>H</u>), 2.64 (1H, dd, *J* = 17.2, 9.2 Hz, CH<u>H</u>CHOH), 1.70 (1H, oct, *J* = 6.0 Hz, HOHCC<u>H</u>Me$_2$), 1,27 (6H, d, *J* = 6.4 Hz, HOHCCHMe$_2$), 0.96 (3H, d, *J* = 6.0 Hz, OCHMe$_2$), 0.92 (3H, d, *J* = 6.0 Hz, OCH<u>Me</u>$_2$) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ : 204.2 (C=O), 166.5 (O-C=O), 72.2, 69.2, 50.4 (CH_2), 46.6 (CH_2), 33.1, 21.7, 18.3, 17.7 ppm; m/z (ES+) 280 (25 % M^+ + Na + CH_3CN), 239 (100 % M^+ + Na), 199 (10 % M^+ - OH); HRMS: found (M^+ + Na), 239.1241 $C_{11}H_{20}O_4$ requires (M^+ + Na) 239.1259; the e.e. of the product - 59 % and was determinated by ^{1}H NMR (500 MHz, C_6D_6, 13 mg of compound) shift reagent experiments with Tris [3-(heptafluoropropylhydroxy-methylene)-d-camphorato] europium (III) (14 mol %).

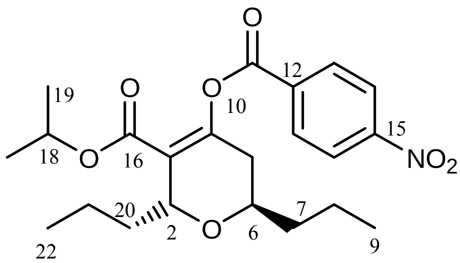
General Procedure for the Preparation of Tetrahydropyran enol *para*-nitrobenzoates 8k-m and 9k-m

The crude mixtures of the tetrahydropyrans **4k-m**/**5k-m** were dissolved dry CH_2Cl_2 (15 ml) and 4-nitrobenzoyl chloride (1.08 g, 5.80 mmol), triethylamine (1.21 ml, 8.70 mmol) and DMAP (1 crystal) were added at room temperature. The resulting mixture was stirred for 16 hr and then extracted with aqueous NH_4Cl (2x 20 ml), aqueous $NaHCO_3$ (4x 20 ml), brine (2x

30 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The resulting dark solids were submitted to flash column chromatography (Benzene – CH_2Cl_2 95:5 to 85:5) to give the tetrahydropyran enol *para*-nitrobenzoates **8k-m** and **9k-m**.

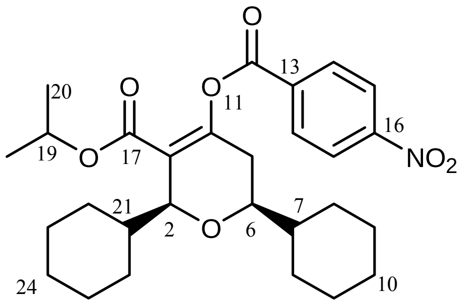


8k. 31 %; oil; IR (NaCl, film) υ_{max} 3010.5; 2961.8, 2873.1, 1743.2, 1711.9, 1530.7, 1350.0, 1271.0, 1216.0, 1106.4, 1058.8, 841.4, 714.8 cm^{-1}; ^{1}H NMR (500 MHz; $CDCl_3$) δ: 8.34 (2H, br d, J = 9.0 Hz, Ar), 8.26 (2H, br d, J = 9.0 Hz, Ar), 5.00 (1H, sept, J = 6.0 Hz, H_{18}), 4.58 (1H, m, H_2), 3.64 (1H, dddd, J = 10.0, 7.5, 4.5, 2.5 Hz, H_6), 3.46 (1H, ddd, J = 17.0, 10.5, 4.0 Hz, H_{5ax}), 2.16 (1H, dt, J = 17.0, 2.5 Hz, H_{5eq}), 1.57-1.72 (3H, m, H_7, H_{20}), 1.54-1.25 (5H, m, H_7, H_{20}, H_{21}, H_8), 1.12 (3H, d, J = 6.0 Hz, H_{19}), 1.03 (3H, d, J = 6.0 Hz, H_{19}), 0.94 (3H, t, J = 7.5 Hz, H_{22} or H_9), 0.92 (3H, t, J = 7.5 Hz, H_{22} or H_9); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 164.0 (C_{16}), 162.1 (C_{11}), 150.8 (C_{15}), 150.5 (C_4), 134.7 (C_{12}), 131.2 (Ar, CH), 123.6 (Ar, CH), 122.6 (C_3), 74.2 (C_2), 72.7 (C_6), 68.1 (C_{18}), 37.3 (CH_2), 35.8 (CH_2), 34.6 (C_5), 21.7, 21.6 (C_{19}, C_{22}, C_9), 18.5 (CH_2), 18.1 (CH_2), 13.9 (C_{19});); m/z (CI+) 288 (100 %), 437 (30 % M^++NH_4^+); HRMS: found (M^+ + NH_4^+), 437.2281 $C_{22}H_{33}N_2O_7$ requires (M^+ + NH_4^+) 437.2282. $[\alpha]_D^{26}$ = -40.20 ° (c 0.85, $CHCl_3$)

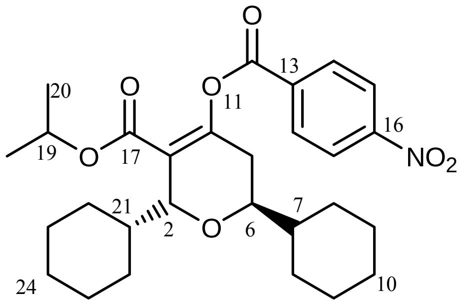


9k. 10 %; oil; IR (NaCl, film) υ_{max} 3013.2; 2960.6, 1743.9, 1709.0, 1530.5, 1349.0, 1270.7, 1216.1, 1106.5, 1060.8, 714.4 cm^{-1}; ^{1}H NMR (500 MHz; $CDCl_3$) δ: 8.33 (2H, br d, J = 9.0 Hz, Ar), 8.27 (2H, br d, J = 9.0 Hz, Ar), 4.98 (1H, sept, J = 6.5 Hz, H_{18}), 4.71 (1H, br d, J = 10.5 Hz, H_2), 3.93 (1H, tdd, J = 12.0, 7.5, 4.5 Hz, H_6), 2.43 (1H, ddd, J = 18.5, 7.5, 1.5 Hz, H_{5ax}), 2.27 (1H, dd, J = 18.5, 4.5 Hz, H_{5eq}), 1.77 (1H, dddd, J = 20.0, 10.5, 9.5, 3.5 Hz, H_{20}), 1.64-1.34 (7H, m, H_7, H_{20}, H_{21}, H_8), 1.07 (3H, d, J = 6.5 Hz, H_{19}), 1.03 (3H, d, J = 6.5 Hz, H_{19}), 0.97 (3H, t, J = 7.0 Hz, H_{22} or H_9), 0.95 (3H, t, J = 7.0 Hz, H_{22} or H_9); ^{13}C NMR (125 MHz,

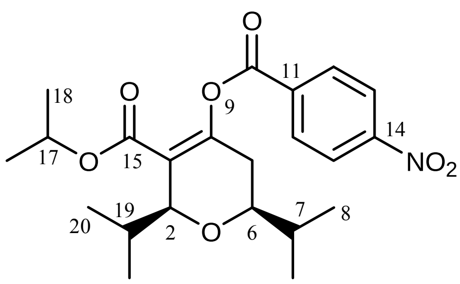
$CDCl_3$) δ: 163.0 (C_{16}), 162.2 (C_{11}), 152.1 (C_4), 150.1 (C_{15}), 134.8 (C_{12}), 131.2 (Ar, CH), 123.7 (Ar, CH), 122.4 (C_3), 72.3 (C_2), 68.1 (C_{18}), 66.4 (C_6), 37.6 (CH_2), 34.7 (C_5), 34.3 (C_{20}), 21.7, 21.6 (C_{19}), 19.2 (CH_2), 18.7 (CH_2), 14.0 (C_{22} or C_{19}), 13.7 (C_{22} or C_{19}); m/z (CI+) 437 (50 % M^++NH_4^+), 288 (50 %); HRMS: found (M^+ + NH_4^+), 437.2280 $C_{22}H_{33}N_2O_7$ requires (M^+ + NH_4^+) 437.2282. $[\alpha]_D^{25}$ = -14.80 ° (c 1.03, $CHCl_3$); e.e. = 59 % as determined by HPLC: CHIRACEL OD-H, Hexane/Isopropanol 98:2, flow rate = 0.2 ml/min, T = 20 °C, t_r(minor) = 38.5 min., t_r (major) = 46.2 min.



8l. 30 %; white solid; m.p. = 133-134 ºC; IR (NaCl, film) υ_{max} 2928.5, 2852.8, 1744.1, 1715.2, 1530.2, 1348.6, 1264.3, 1107.1, 1062.6, 757.0, 714.7 cm^{-1}; ^1H NMR (500 MHz; $CDCl_3$) δ: 8.31 (2H, br d, J = 9.0 Hz, Ar), 8.25 (2H, br d, J = 9.0 Hz, Ar), 5.00 (1H, sept, J = 6.5 Hz, H_{19}), 4.43 (1H, br s, H_2), 3.32 (1H, ddd, J = 10.5, 7.0, 2.5 Hz, H_6), 2.46 (1H, ddd, J = 17.0, 10.5, 4.0 Hz, H_{5ax}), 2.10 (1H, dt, J = 7.0, 2.5 Hz, H_{5eq}), 1.97 (1H, br d, H_{22} or H_{23} or H_{24}), 1.44-1.76 (12H, m, Cy), 1.26-0.98 (11H, m, Cy), 1.12 (3H, d, J = 6.5 Hz, H_{20}), 1.00 (3H, d, J = 6.5 Hz, H_{20}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.3 (C17), 162.1 (C_{12}), 150.8 (C_{16}), 150.5 (C_4), 134.8 (C_{13}), 131.2 (Ar, CH), 123.6 (Ar, CH), 122.1 (C_3), 78.1 (C_2), 76.9 (C_6), 68.0 (C_{19}), 42.3 (C_7), 41.2 (C_{21}), 31.9 (C_5), 29.9 (CH_2), 28.7 (CH_2), 28.4 (CH_2), 26.8 (CH_2), 26.5 (CH_2), 26.4 (CH_2), 26.3 (CH_2), 26.0 (CH_2), 25.9 (CH_2), 25.4 (CH_2), 21.6 (C_{20}), 21.5 (C_{20}); m/z (CI+) 517 (85 % M^++NH_4^+), 94 (100 %); HRMS: found (M^+ + NH_4^+), 517.2910 $C_{28}H_{41}N_2O_7$ requires (M^+ + NH_4^+) 517.2910; Anal. Calc. for $C_{28}H_{37}NO_7$: C, 67.31; H 7.46; N, 2.80 %. Found C, 67.42; H, 7.30; N, 2.95 %. $[\alpha]_D^{26}$ = -25.40 ° (c 0.80, $CHCl_3$).

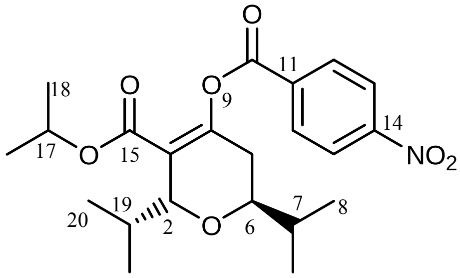


9l. 5 %; white solid; m.p. = 153-155 ºC; IR (NaCl, film) υ_{max} 3020.6; 2929.1, 2854.2, 1742.3, 1713.4, 1530.8, 1450.2, 1350.1, 1263.0, 1216.3, 1105.6, 757.2, 716.1 cm^{-1}; ^{1}H NMR (500 MHz; $CDCl_3$) δ: 8.32 (2H, br d, J = 9.0 Hz, Ar), 8.26 (2H, br d, J = 9.0 Hz, Ar), 4.96 (1H, sept, J = 6.0 Hz, H_{19}), 4.50 (1H, br d, J = 7.5 Hz, H_2), 3.74 (1H, ddd, J = 9.0, 8.0, 4.5 Hz, H_6), 2.39 (1H, dd, J = 18.0, 4.5 Hz, H_{5eq}), 2.28 (1H, dd, J = 18.0, 9.0 Hz, H_{5ax}), 2.00 (1H, d, J = 12.5 Hz, Cy), 1.82-1.60 (8H, m, Cy), 1.51 (1H, d, J = 12.0, Cy), 1.46-1.43 (1H, m, Cy), 0.97-1.29 (10H, m, Cy), 1.11 (3H, d, J = 6.0 Hz, H_{20}), 0.99 (3H, d, J = 6.0 Hz, H_{20}); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 164.1 (C17), 162.4 (C_{12}), 150.9 (C_{16}), 150.6 (C_4), 134.8 (C_{13}), 131.2 (Ar, CH), 123.7 (Ar, CH), 122.5 (C_3), 76.6 (C_2), 72.1 (C_6), 68.3 (C_{19}), 42.6 (C_7), 42.0 (C_{21}), 31.8 (CH_2), 29.8 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 28.5 (CH_2), 26.5 (2×CH_2), 26.3 (CH_2), 26.2 (CH_2), 26.0 (CH_2), 25.8 (CH_2), 21.6 (2×C_{20}); m/z (CI+) 517 (40 % M^{+}+NH_4^{+}), 94 (100 %); HRMS: found (M^{+} + NH_4^{+}), 517.2905 $C_{28}H_{41}N_2O_7$ requires (M^{+} + NH_4^{+}) 517.2908. $[\alpha]_D^{26}$ = -14.67 ° (c 0.70, $CHCl_3$); e.e. = 47 % as determined by HPLC: CHIRACEL OD-H, Hexane/Isopropanol 99:1, flow rate = 0.08 ml/min, T = 10 °C, t_r(minor) = 116.4 min., t_r (major) = 124.9 min.

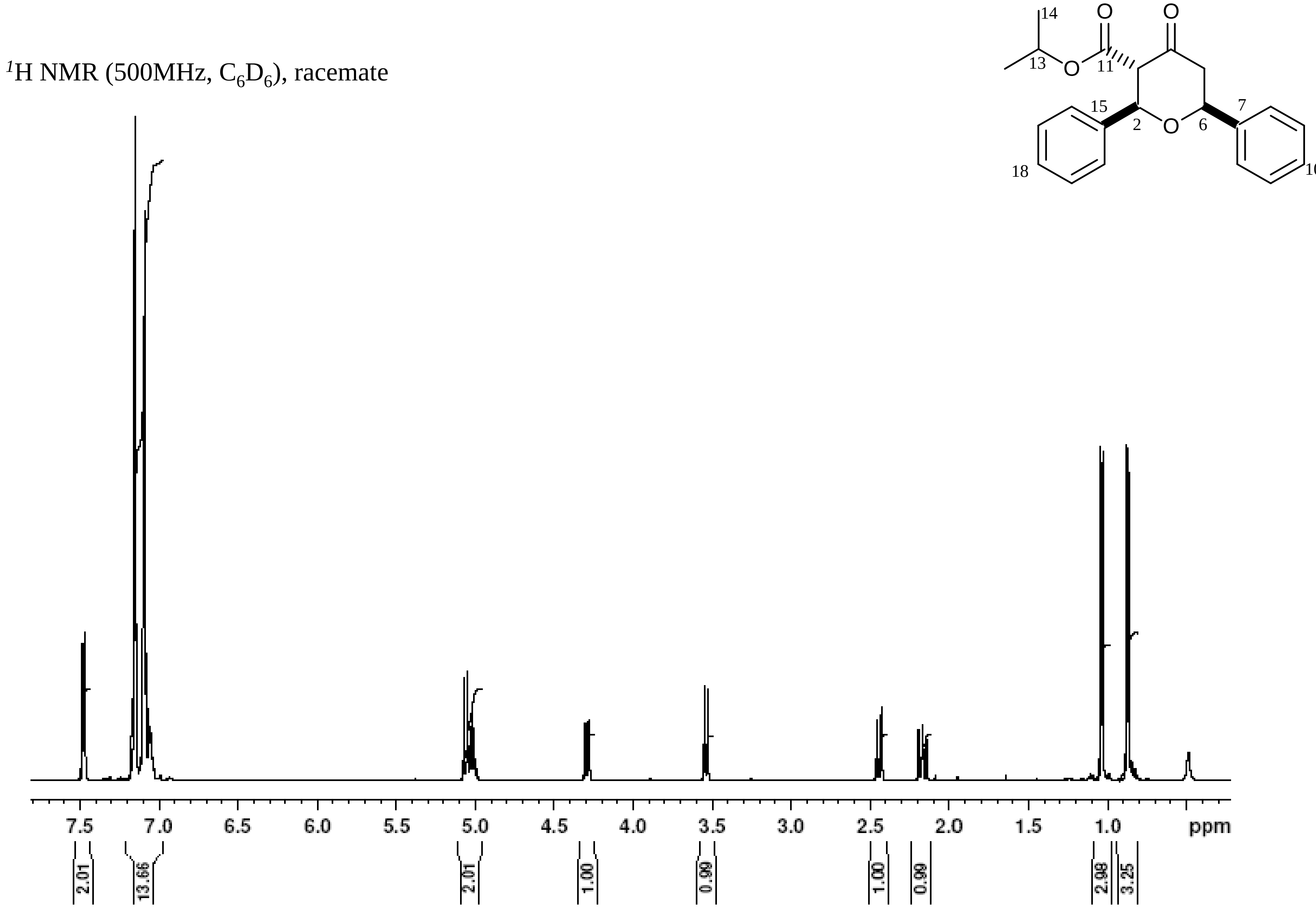


8m. 37 %; white solid; m.p. = 94-95 ºC; IR (NaCl, film) υ_{max} 2964.2, 1744.4, 1714.6, 1530.3, 1349.0, 1270.4, 1106.4, 1056.2, 1014.4, 910.4, 841.6, 733.5, 714.8 cm^{-1}; ^{1}H NMR (500 MHz; $CDCl_3$) δ: 8.32 (2H, br d, J = 9.0 Hz, Ar), 8.26 (2H, br d, J = 9.0Hz, Ar), 4.98 (1H, sept, J = 6.0 Hz, H_{17}), 4.48 (1H, ddd, J = 4.0, 2.5, 2.0 Hz, H_2), 3.31 (1H, ddd, J = 10.0, 7.0, 2.5 Hz, H_6), 2.47 (1H, ddd, J = 16.5, 10.0, 4.0 Hz, H_{5a}), 2.12 (1H, ddd, J = 16.5, 2.5, 2.0 Hz, H_{5e}), 2.01 (1H, d sept, J = 7.0, 2.5 Hz, H_{19}), 1.78 (1H, oct, J = 7.0 Hz, H_7), 1.11 (3H, d, J = 6.0 Hz, H_{18}), 1.09 (3H, d, J = 7.0 Hz, H_{20}), 1.01 (3H, d, J = 6.0 Hz, H_{18}), 0.99 (3H, d, J = 7.0 Hz, H_8), 0.92 (3H, d, J = 7.0 Hz, H_8), 0.86 (3H, d, J = 7.0 Hz, H_{20}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.2 (C_{15}), 162.1 (C_{10}), 150.8 (C_4 or C_{14}), 150.8 (C_4 or C_{14}), 134.8 (C_{11}), 131.2 (Ar, CH), 123.6 (Ar, CH), 122.3 (C_3), 78.1 (C_2), 77.4 (C_6), 68.1 (C_{17}), 32.6 (C_7), 31.8 (C_5), 31.0 (C_{19}), 21.6 (C_{18}), 21.6 (C_{18}), 19.6 (C_{20}), 18.2 (C_8), 18.0 (C_8), 15.0 (C_{20}); m/z (CI+) 437 (100 % M^{+}+NH_4^{+}), 360 (30 %, M^{+} - $O^{i}Pr$); HRMS: found (M^{+} + NH_4^{+}), 437.2277 $C_{22}H_{33}N_2O_7$

requires ($M^+ + NH_4^+$) 437.2288; Anal. Calc. for $C_{22}H_{29}NO_7$: C, 62.99; H 6.97; N, 3.34 %. Found C, 62.98; H, 7.09; N, 3.44 %. $[\alpha]_D^{26}$ = -45.25 ° (c 0.80, $CHCl_3$)

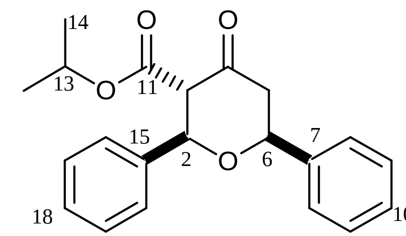


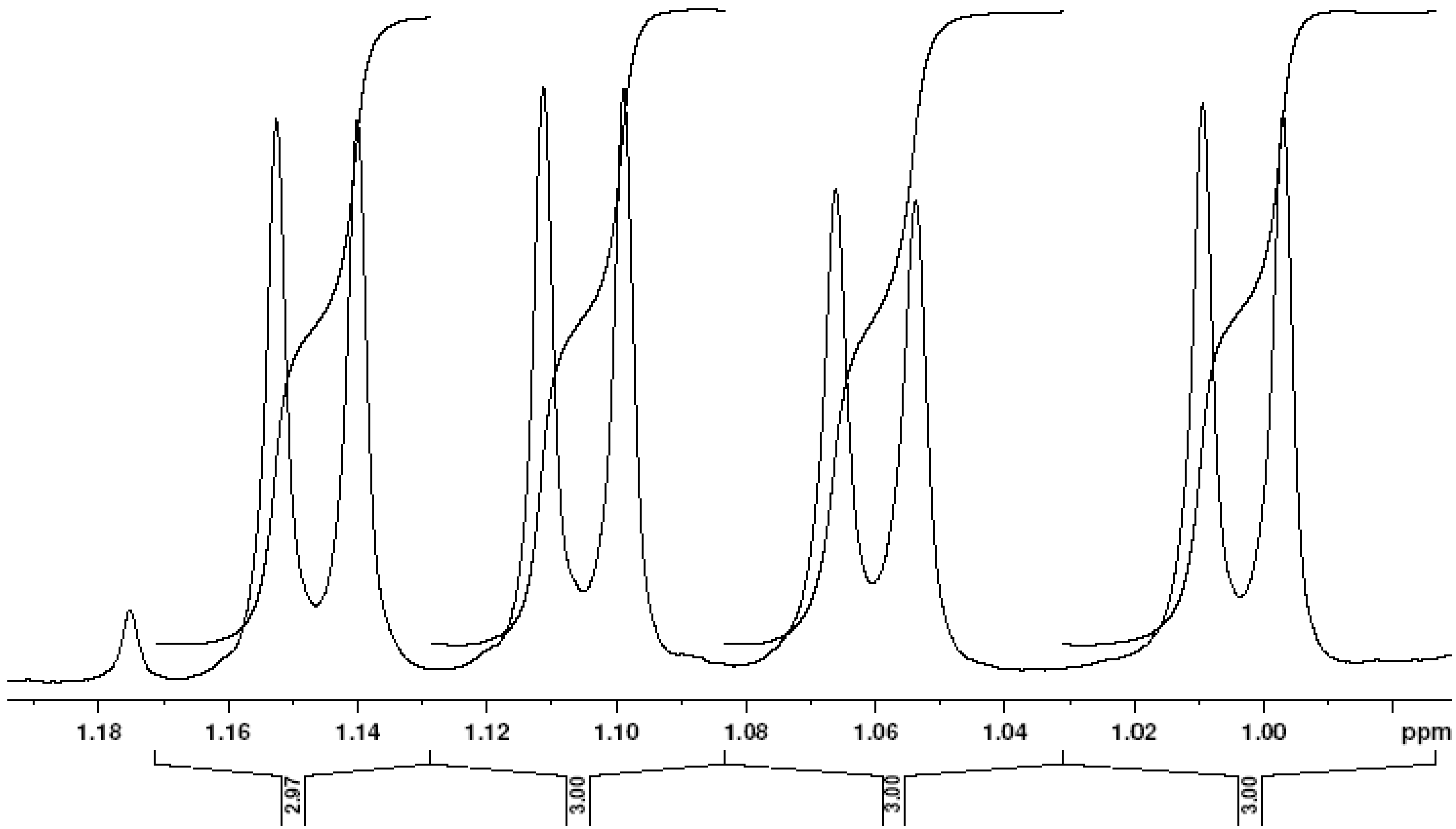
9m. 8 %; white solid; m.p. = 101-103 ºC; IR (NaCl, film) υ_{max} 2964.2, 1743.2, 1710.1, 1530.1, 1349.4, 1272.6, 1143.5, 1105.8, 1052.0, 1015.0 cm^{-1}; ^{1}H NMR (500 MHz; $CDCl_3$) δ: 8.32 (2H, br d, J = 9.0 Hz, Ar), 8.27 (2H, br d, J = 9.0Hz, Ar), 4.96 (1H, sept, J = 6.5 Hz, H_{17}), 4.46 (1H, d, J = 7.5 Hz, H_2), 3.70 (1H, ddd, J = 9.0, 7.0, 4.5 Hz, H_6), 2.42 (1H, ddd, J = 18.0, 4.5, 1.0 Hz, H_{5eq}), 2.27 (1H, ddd, J = 18.0, 9.0, 2.0 Hz, H_{5ax}), 2.09 (1H, oct, J = 7.0 Hz, H_{19}), 1.76 (1H, oct, J = 7.0 Hz, H_7), 1.10 (3H, d, J = 6.5 Hz, H_{18}), 1.05 (3H, d, J = 7.0 Hz, H_{20}), 1.04 (3H, d, J = 7.0 Hz, H_8), 0.99 (3H, d, J = 6.5 Hz, H_{18}), 0.95 (3H, d, J = 7.0 Hz, H_{20}), 0.93 (3H, d, J = 7.0 Hz, H_8); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.1 (C_{15}), 162.4 (C_{10}), 150.8 (C_4 or C_{14}), 150.6 (C_4 or C_{14}), 134.7 (C_{11}), 131.2 (Ar, CH), 123.7 (Ar, CH), 122.6 (C_3), 77.2 (C_2), 73.1 (C_6), 68.4 (C_{17}), 32.8 (C_7), 32.2 (C_{19}), 31.7 (C_5), 21.6 (C_{18}), 21.6 (C_{18}), 19.4 (C_{20}), 19.2 (C_{20}), 18.8 (C_8), 18.3 (C_8); m/z (CI+) 437 (100 % M^++NH_4^+); HRMS: found (M^+ + NH_4^+), 437.2277 $C_{22}H_{33}N_2O_7$ requires (M^+ + NH_4^+) 437.2282. $[\alpha]_D^{26}$ = -11.48 ° (c 0.99, $CHCl_3$); e.e. = 59 % as determined by ^{1}H NMR chiral shift experiments on the aldol intermediate



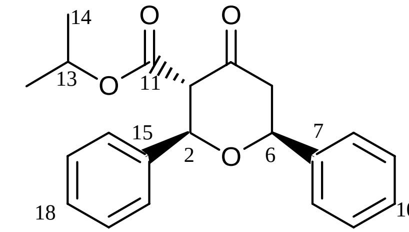
1H NMR (500MHz, C6D6), racemate
14
13
11
15
2
6
7
18
10
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
2.01
13.66
2.01
1.00
0.99
1.00
0.99
2.98
3.25

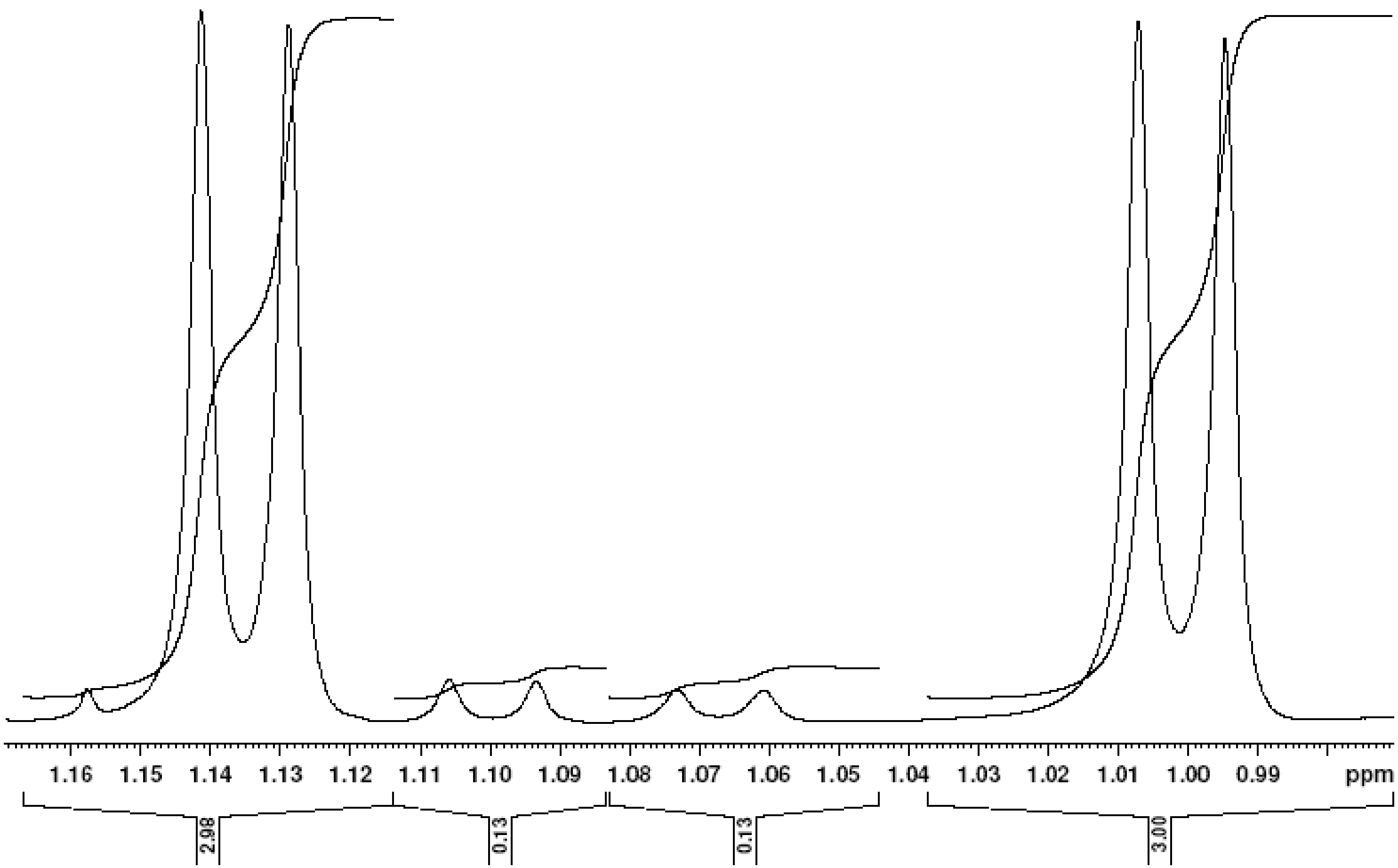
Detail ^{1}H NMR (500MHz, C_6D_6), racemate + chiral shiff reagent, tris [3-(heptafluoropropylhydroxy-methylene)-*d*-camphorato] europium (III)



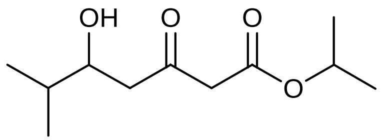


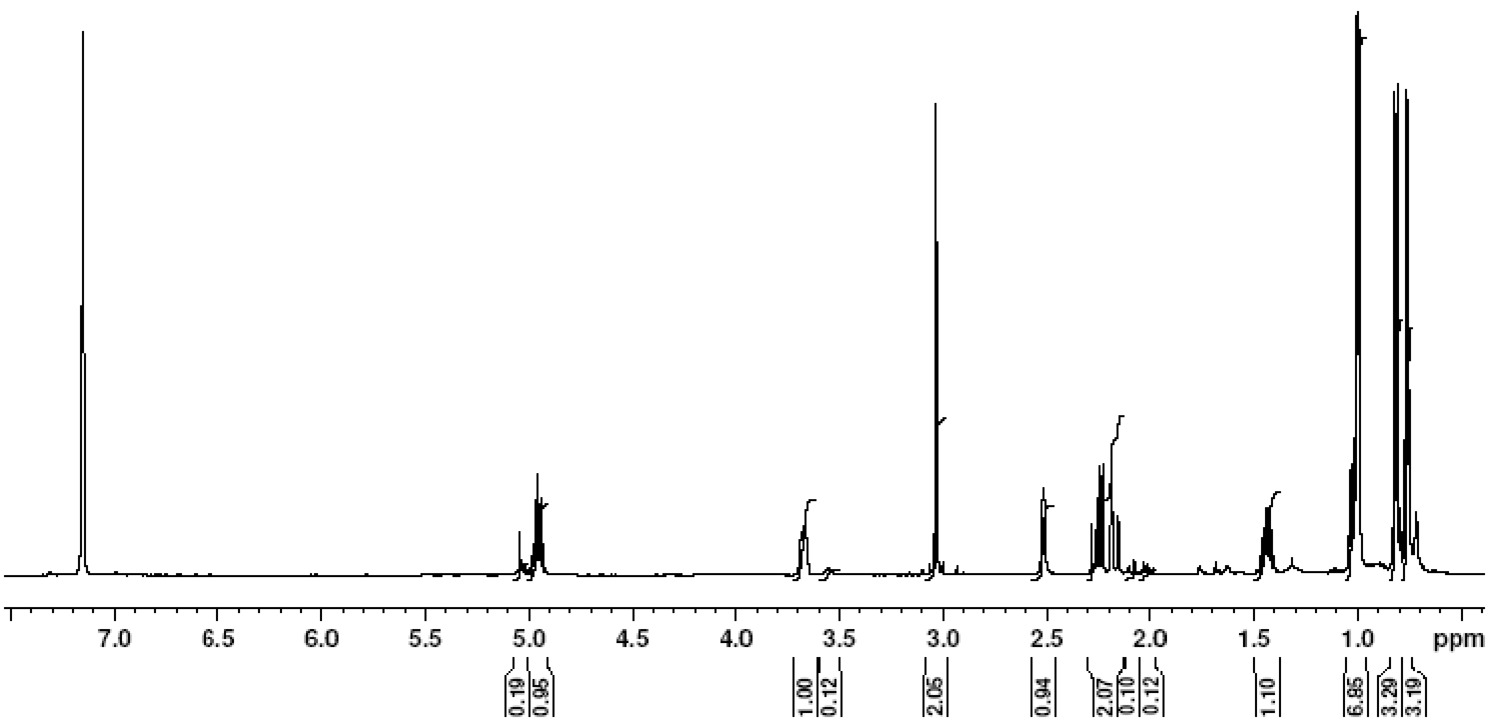
Detail ^{1}H NMR (500MHz, C_6D_6) of enantiomerically enriched **4j** (7.0 mg) + chiral shiff reagent, tris [3-(heptafluoropropylhydroxy-methylene)-*d*-camphorato] europium (III) 17 mol %.



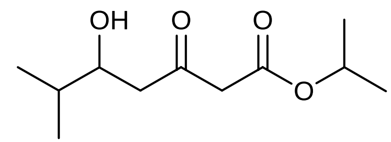


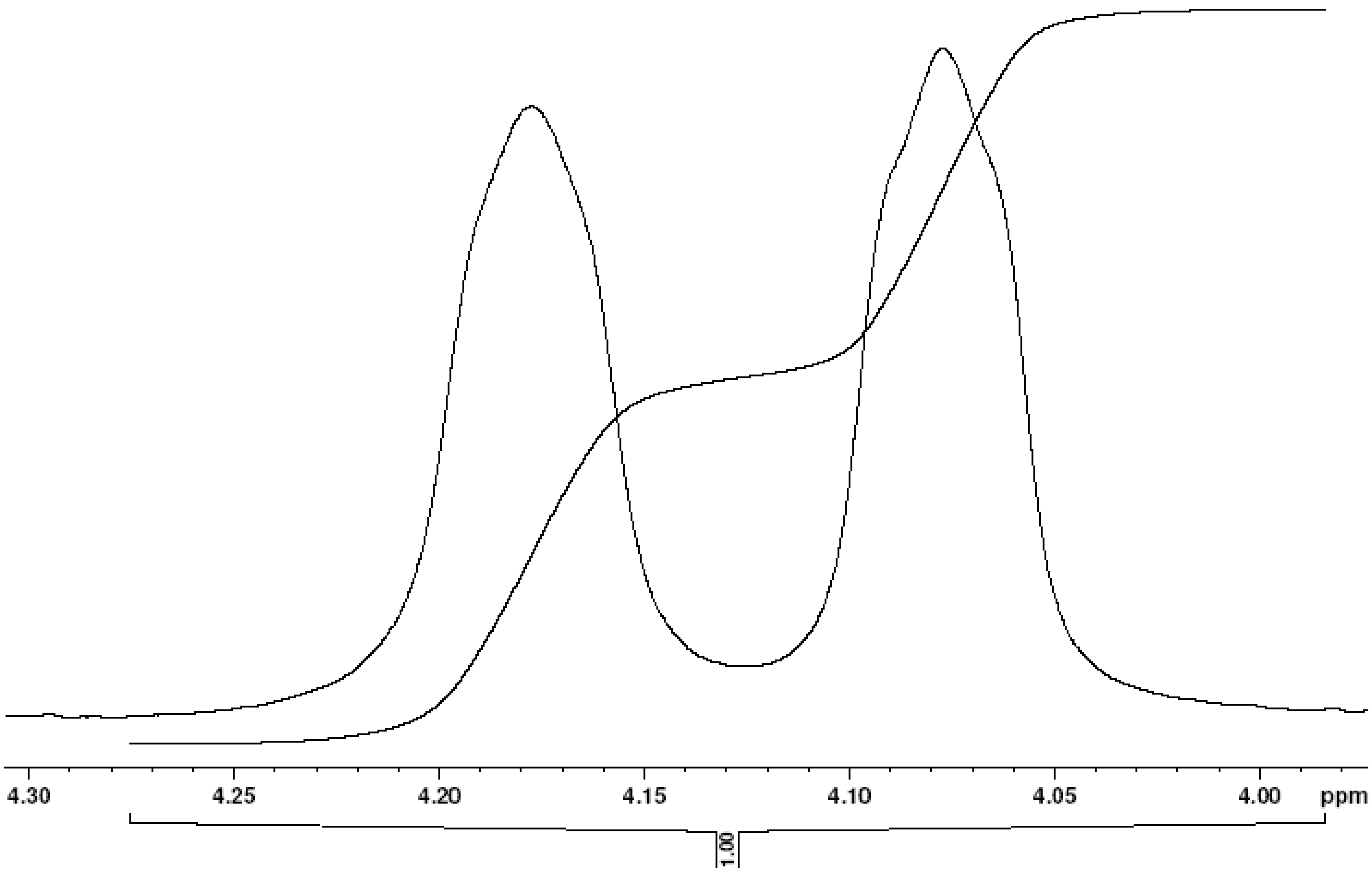
[1]H NMR (500MHz, C_6D_6), racemate



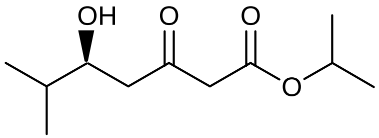


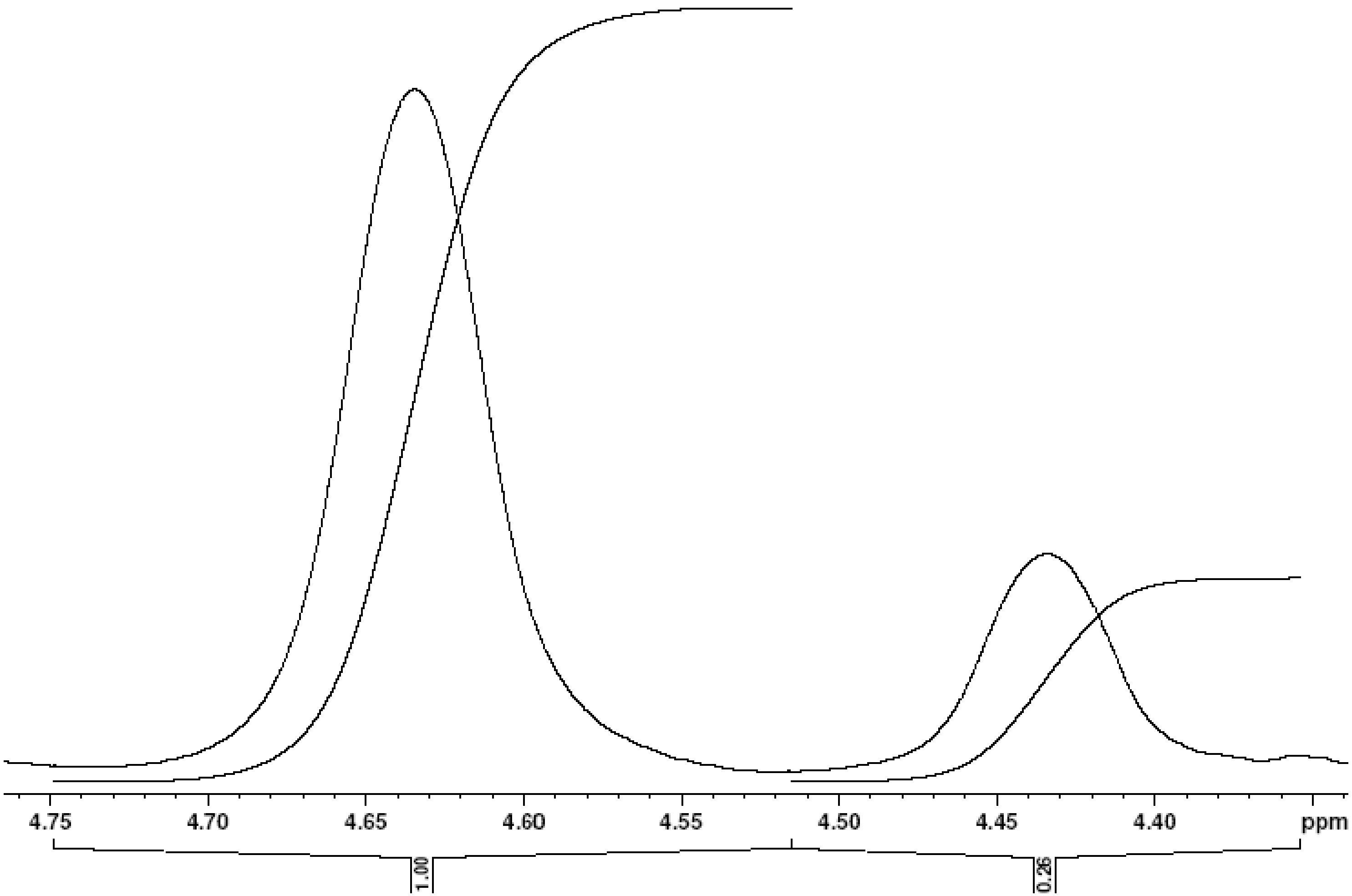
Detail ^{1}H NMR (500MHz, C_6D_6), racemate + chiral shiff reagent, tris [3-(heptafluoropropylhydroxy-methylene)-*d*-camphorato] europium (III)



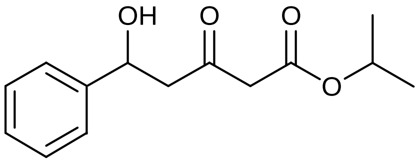


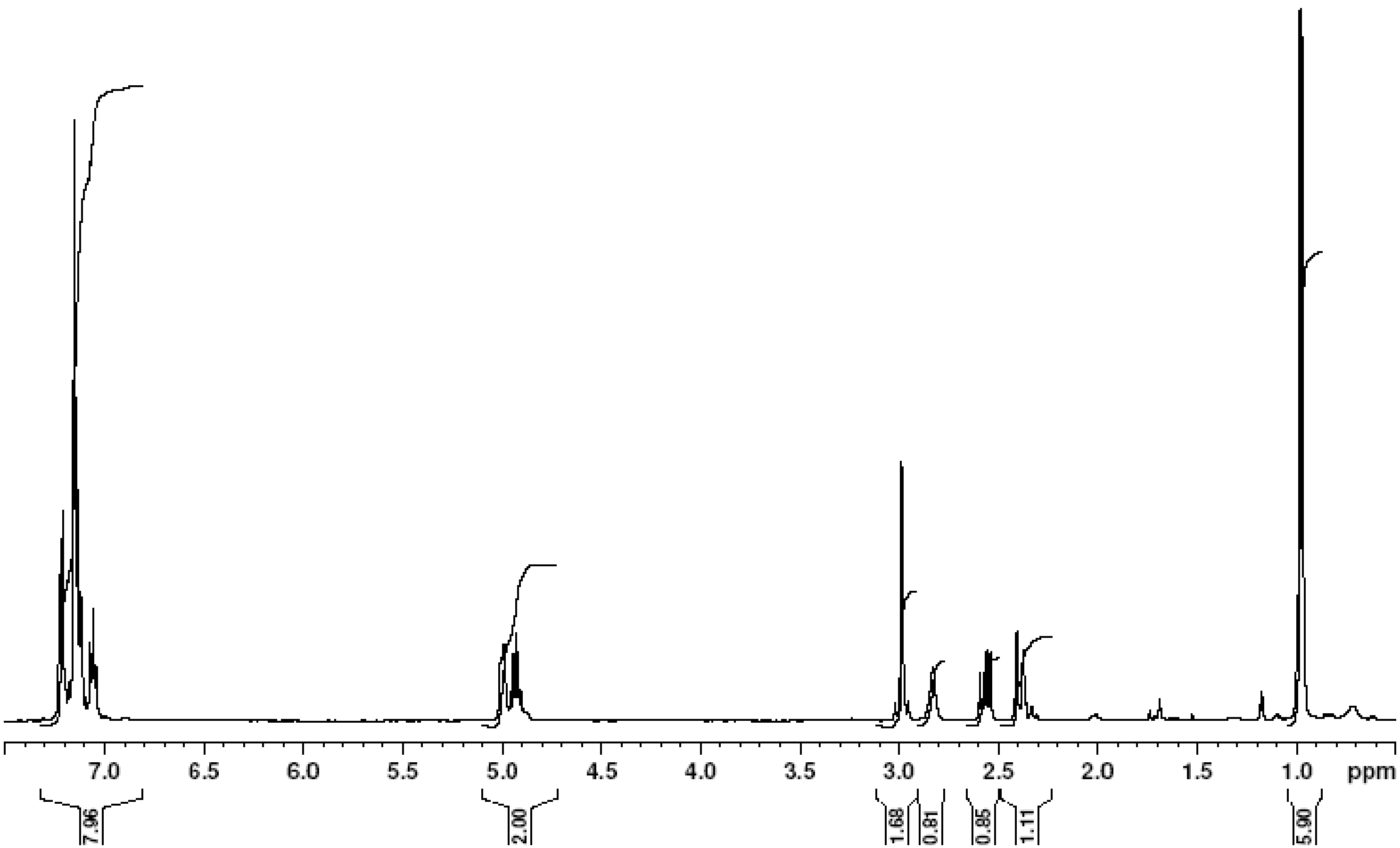
Detail [1]H NMR (500MHz, C_6D_6) of enantiomerically enriched **7m** (13.0 mg) + chiral shiff reagent, tris [3-(heptafluoropropylhydroxy-methylene)-*d*-camphorato] europium (III) 14 mol %.



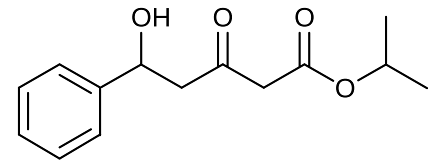


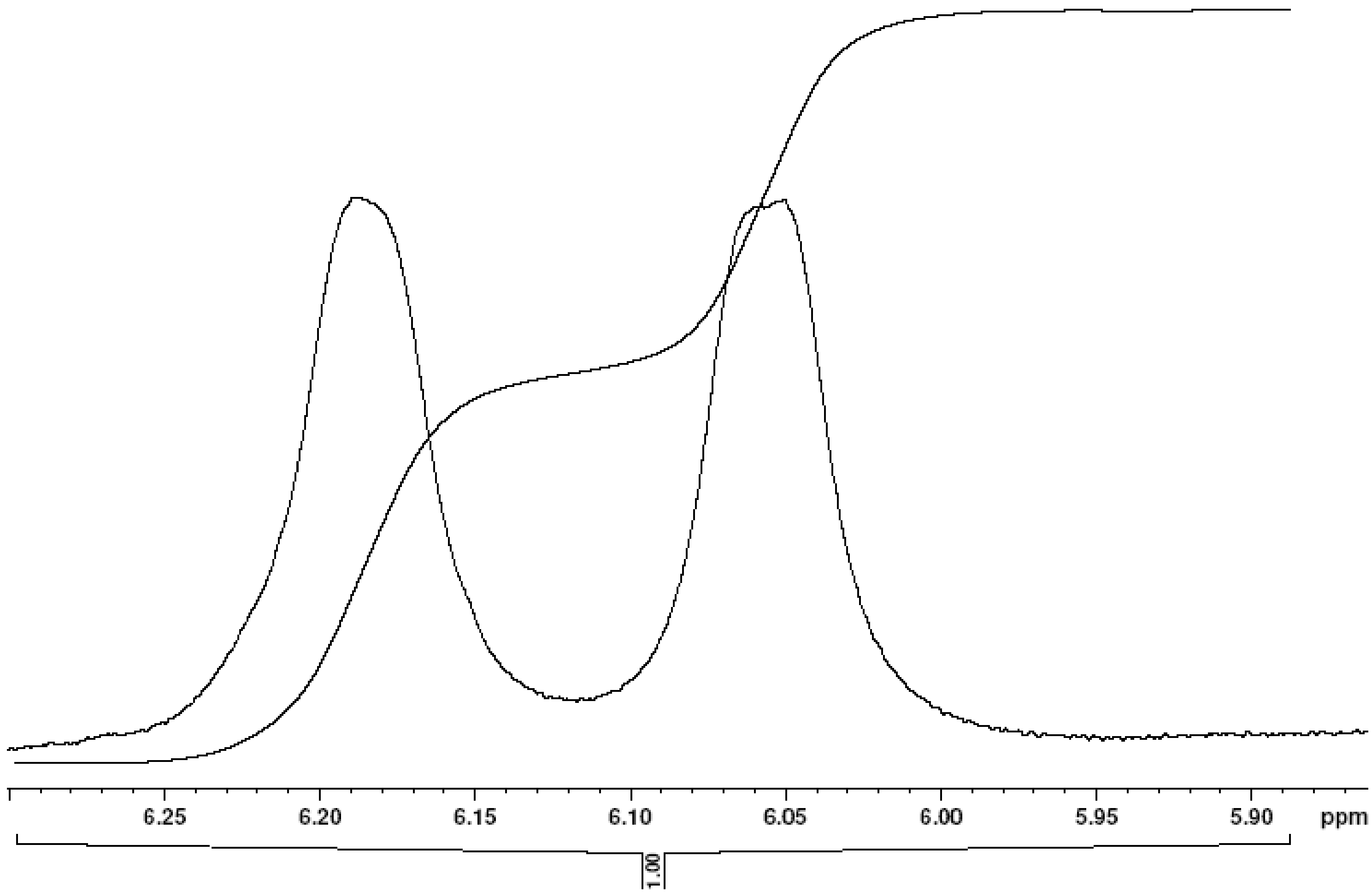
[1]H NMR (500MHz, C_6D_6), racemate



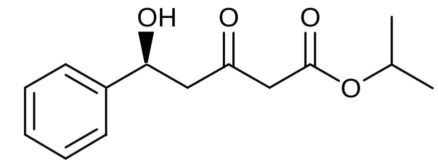


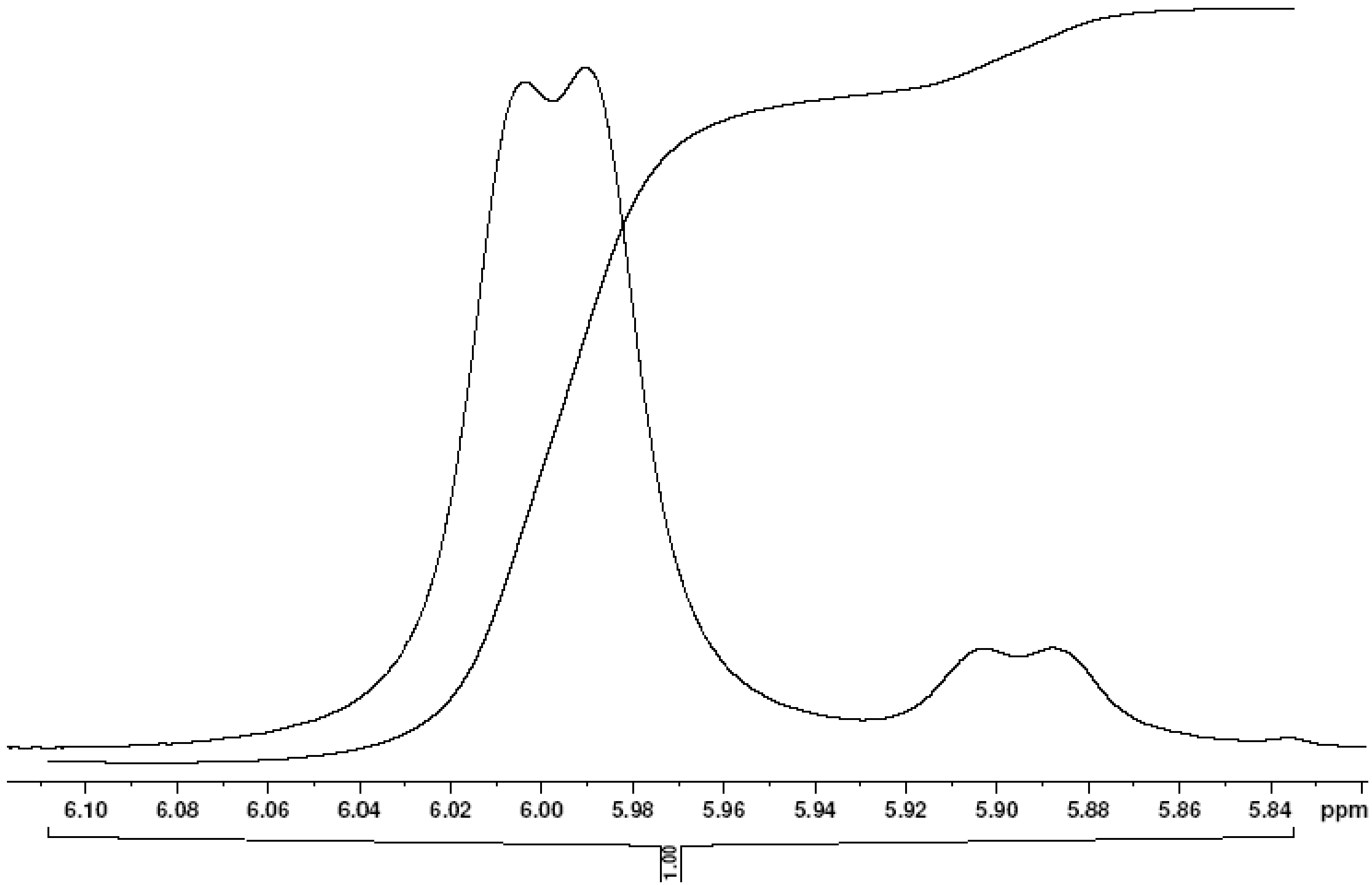
Detail [1]H NMR (500MHz, C_6D_6), racemate + chiral shiff reagent, tris [3-(heptafluoropropylhydroxy-methylene)-*d*-camphorato] europium (III)



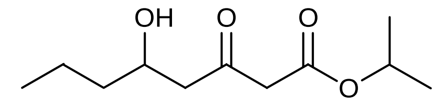


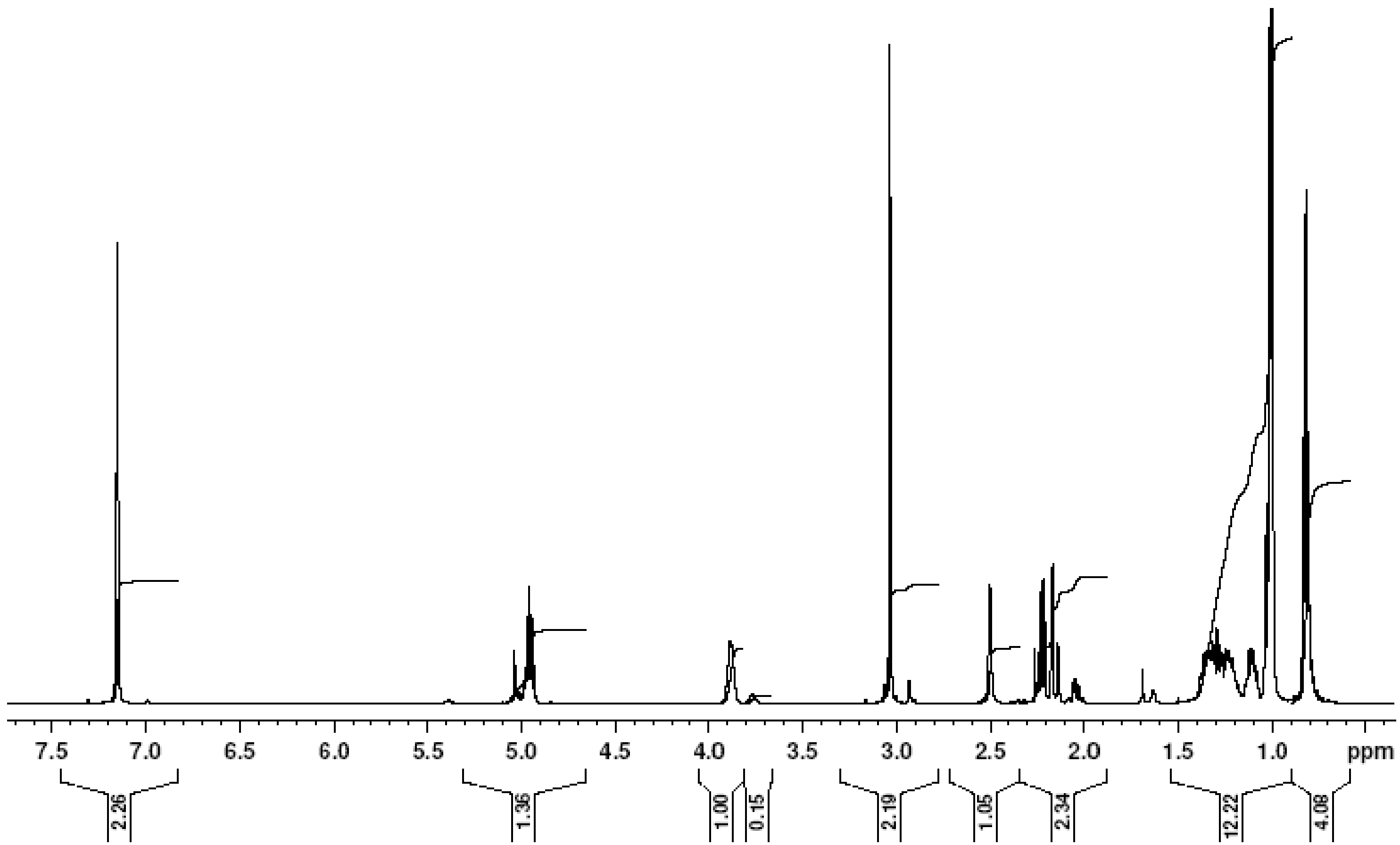
Detail [1]H NMR (500MHz, C_6D_6) of enantiomerically enriched **7j** (11.0 mg) + chiral shiff reagent, tris [3-(heptafluoropropylhydroxy-methylene)-*d*-camphorato] europium (III) 26 mol %.

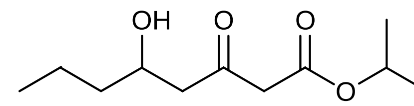




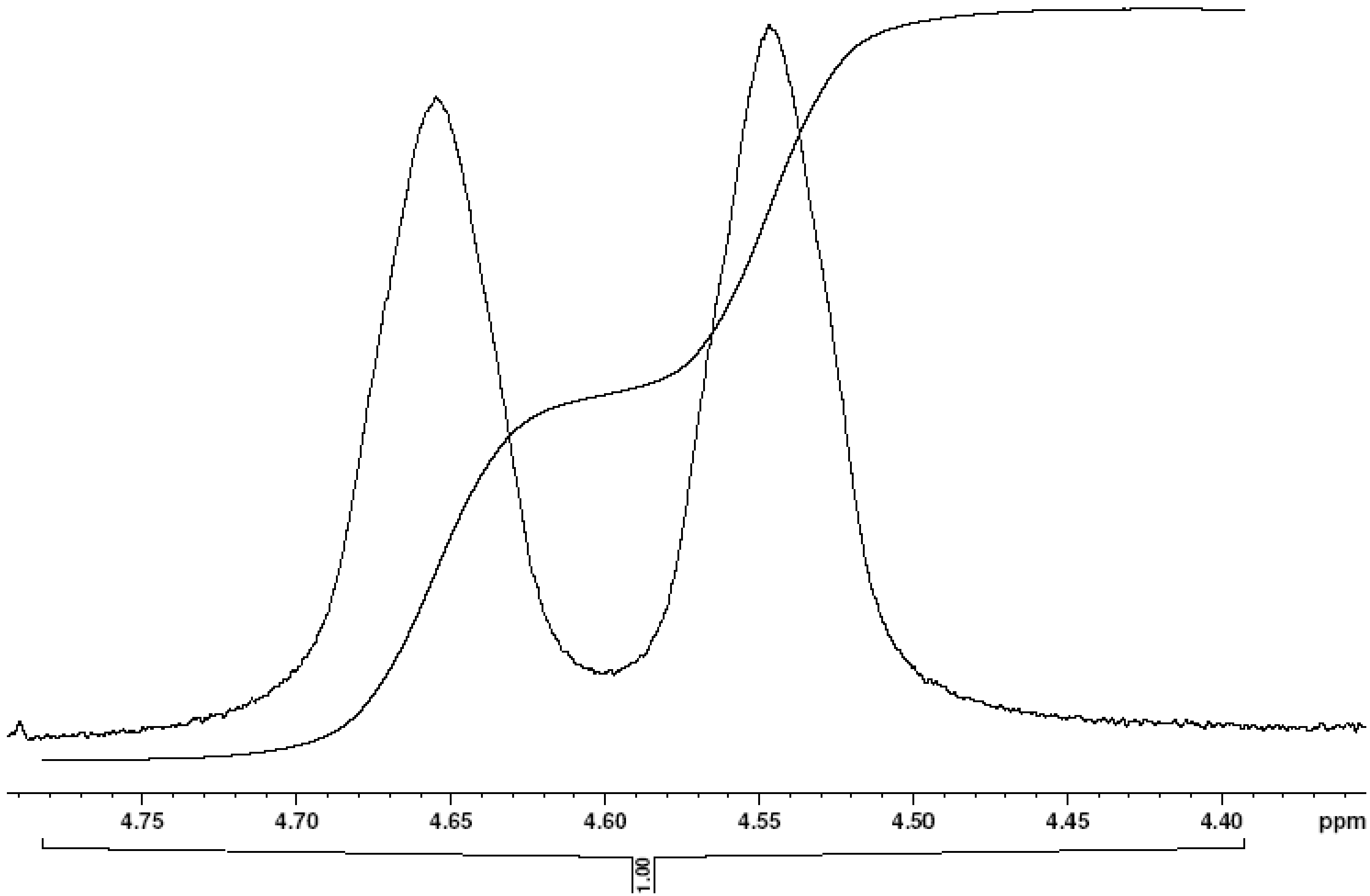
^{1}H NMR (500MHz, C_6D_6), racemate



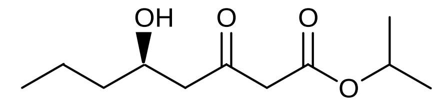


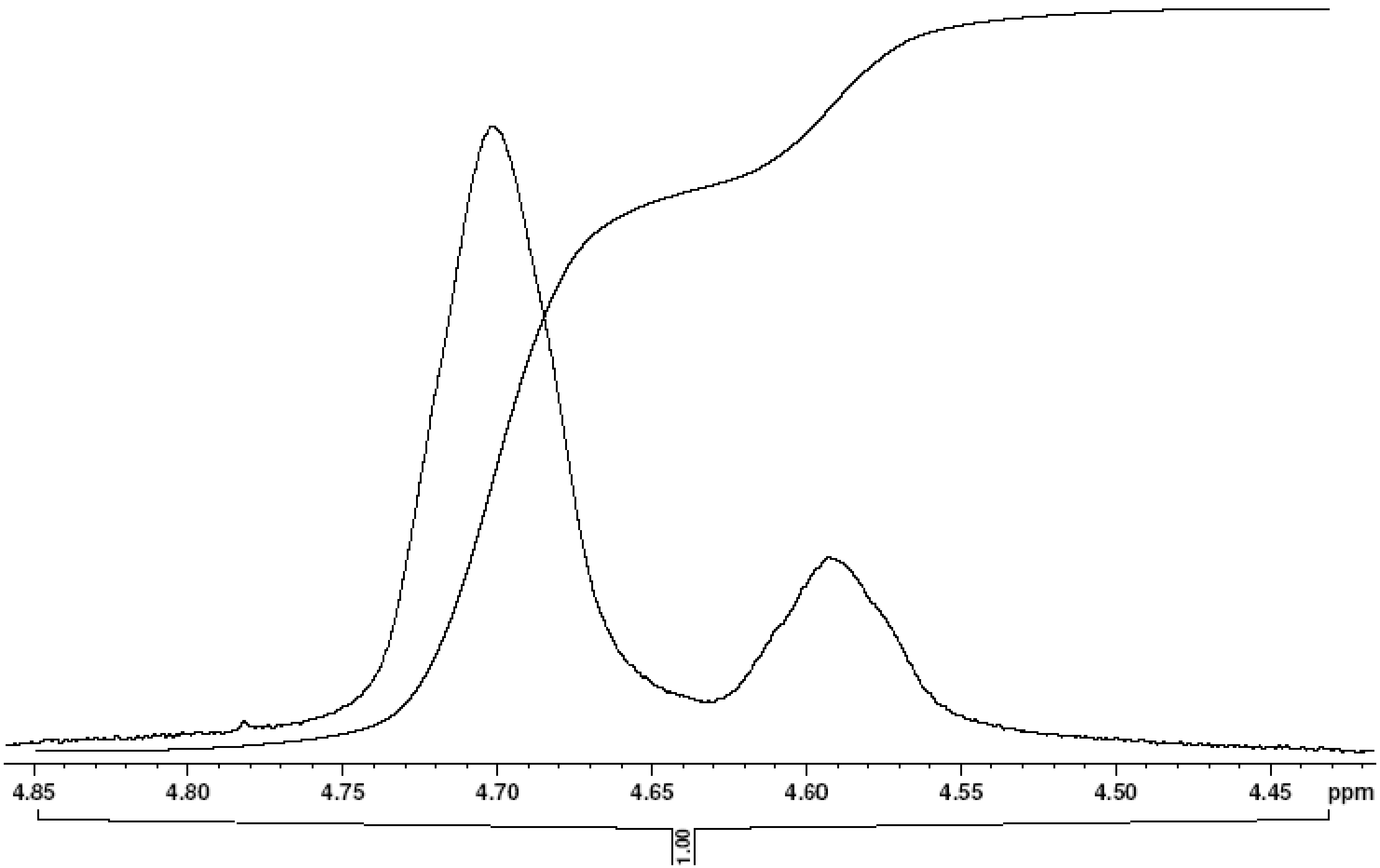


Detail ^{1}H NMR (500MHz, C_6D_6), racemate + chiral shiff reagent, tris [3-(heptafluoropropylhydroxy-methylene)-*d*-camphorato] europium (III)



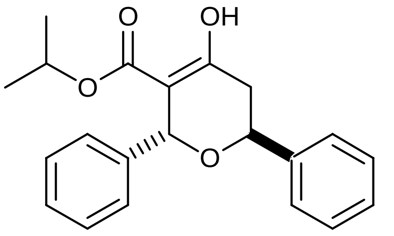
Detail [1]H NMR (500MHz, C_6D_6) of enantiomerically enriched **7j** (24.0 mg) + chiral shiff reagent, tris [3-(heptafluoropropylhydroxy-methylene)-*d*-camphorato] europium (III) 12 mol %.



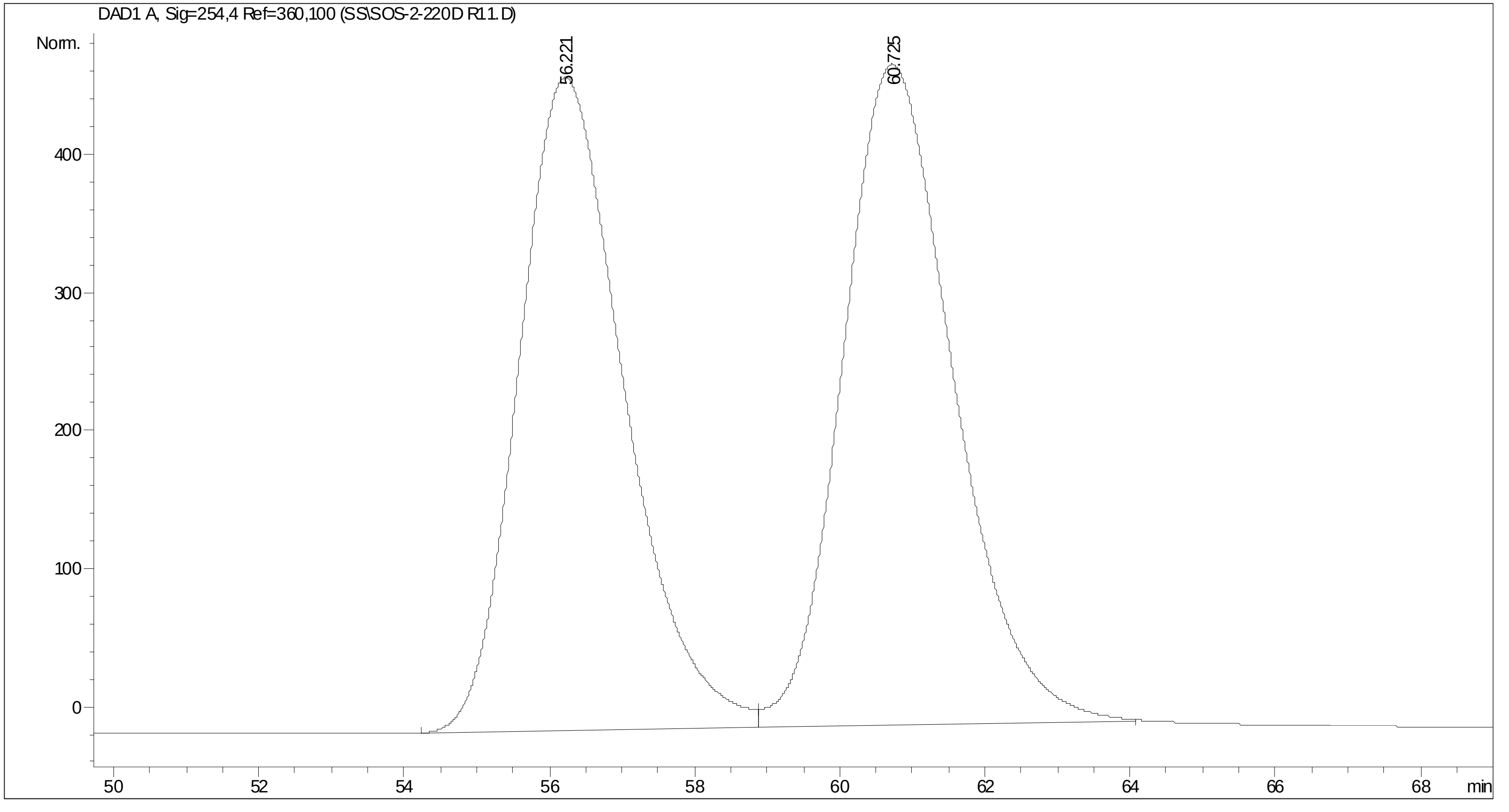


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	56.221	BB	1.5502	4.78318e4	472.82602	48.5613
2	60.725	BB	1.6238	5.06660e4	478.33328	51.4387
Totals :				9.84978e4	951.15930	

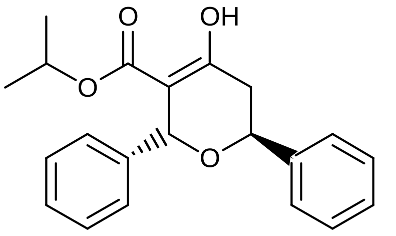


Racemate

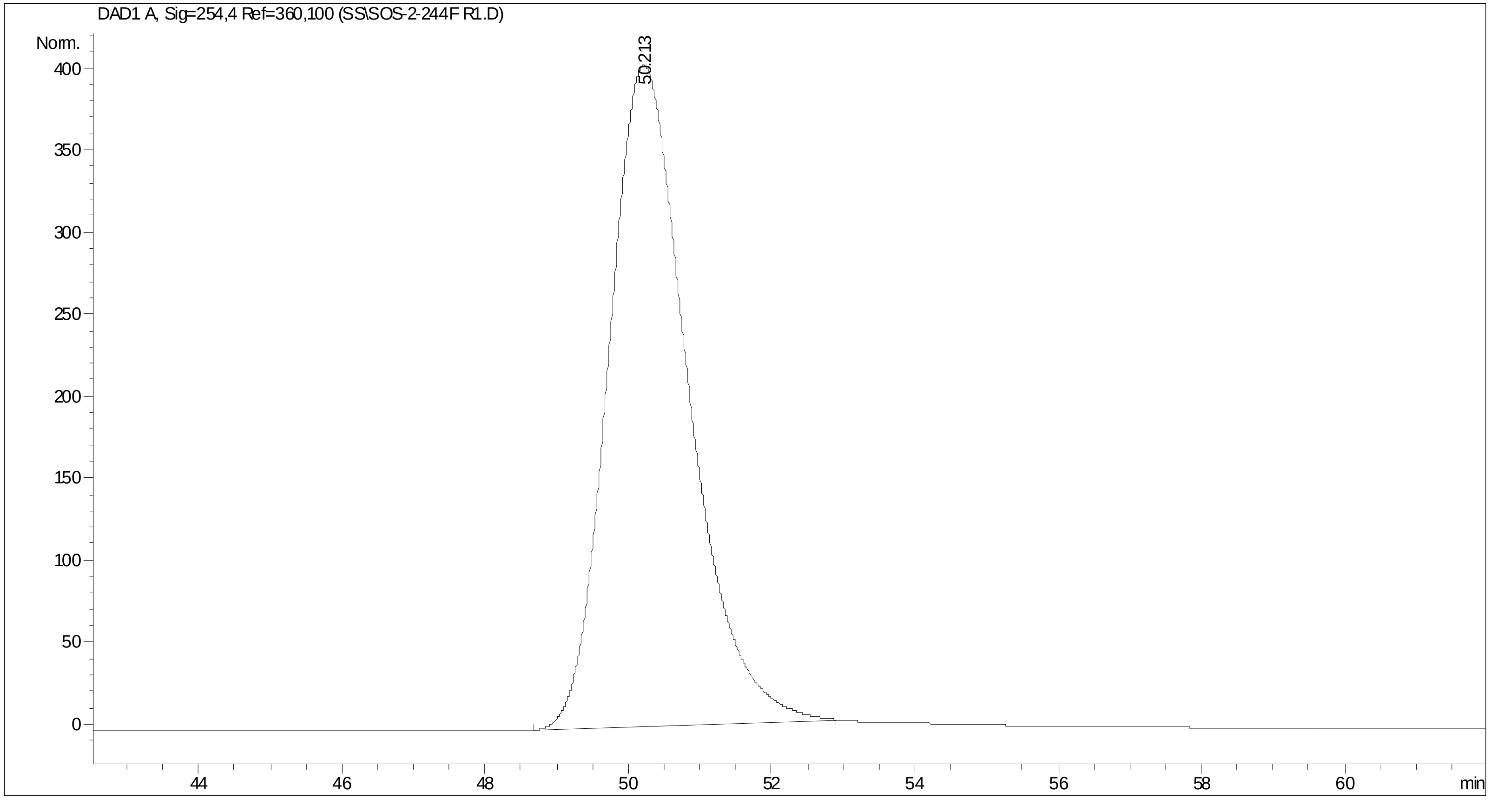


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	50.213	BB	1.1905	3.13303e4	403.20007	100.0000
Totals :				3.13303e4	403.20007	

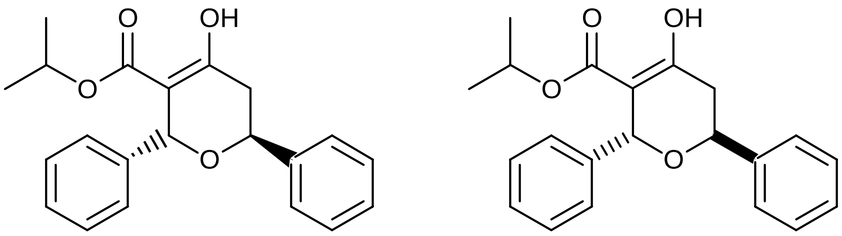


Enantiomerically enriched **5j**

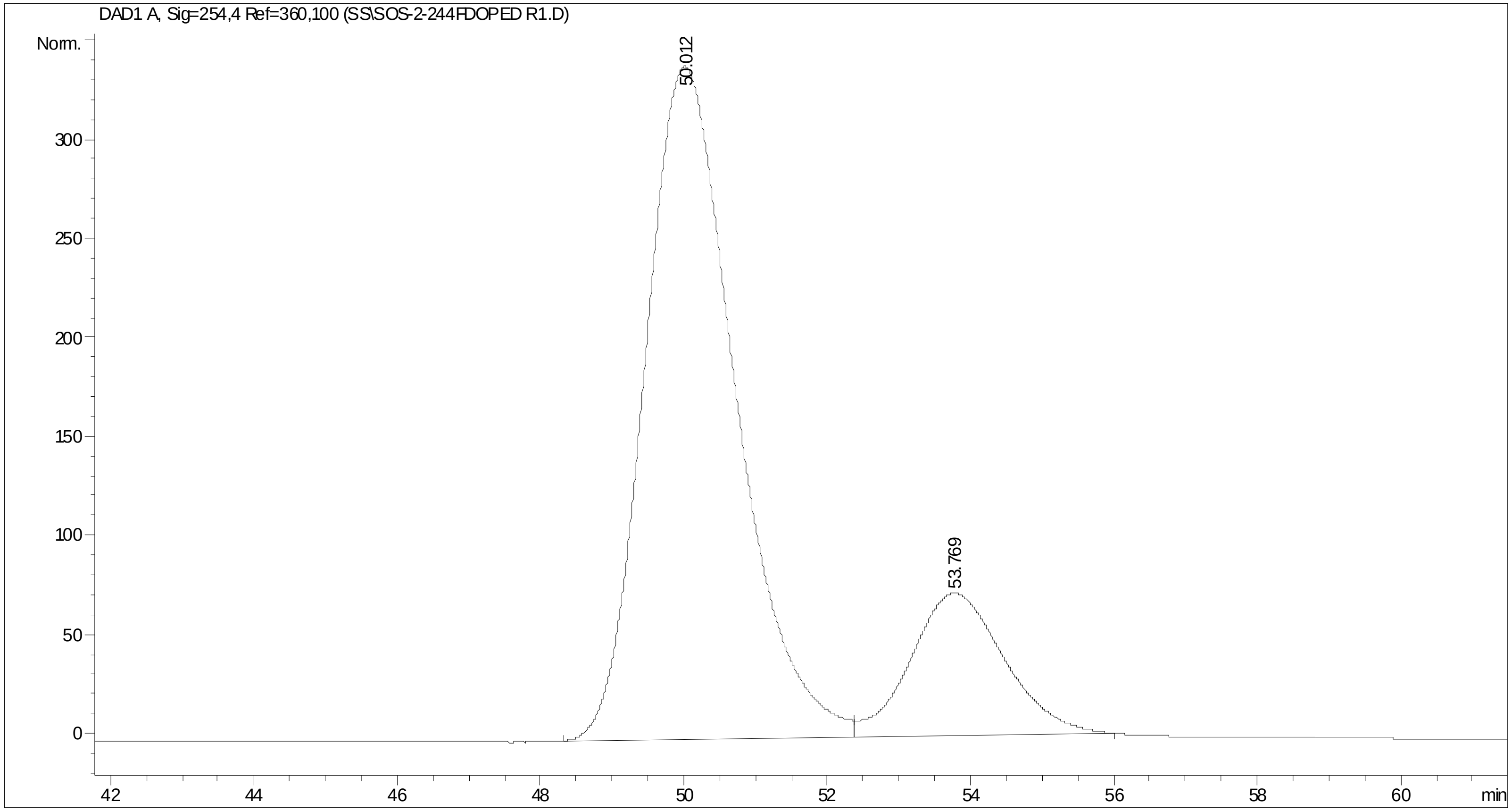


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	50.012	BB	1.3538	2.98949e4	339.99969	81.9074
2	53.769	BB	1.3558	6603.52002	72.15257	18.0926
Totals :				3.64984e4	412.15226	

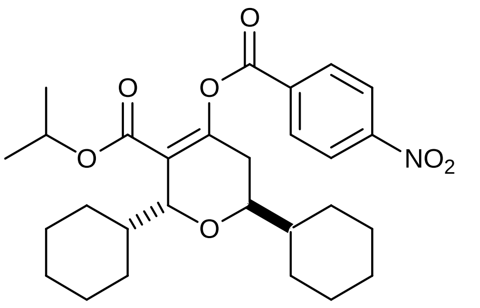


Chiral THP **5j** doped with racemate

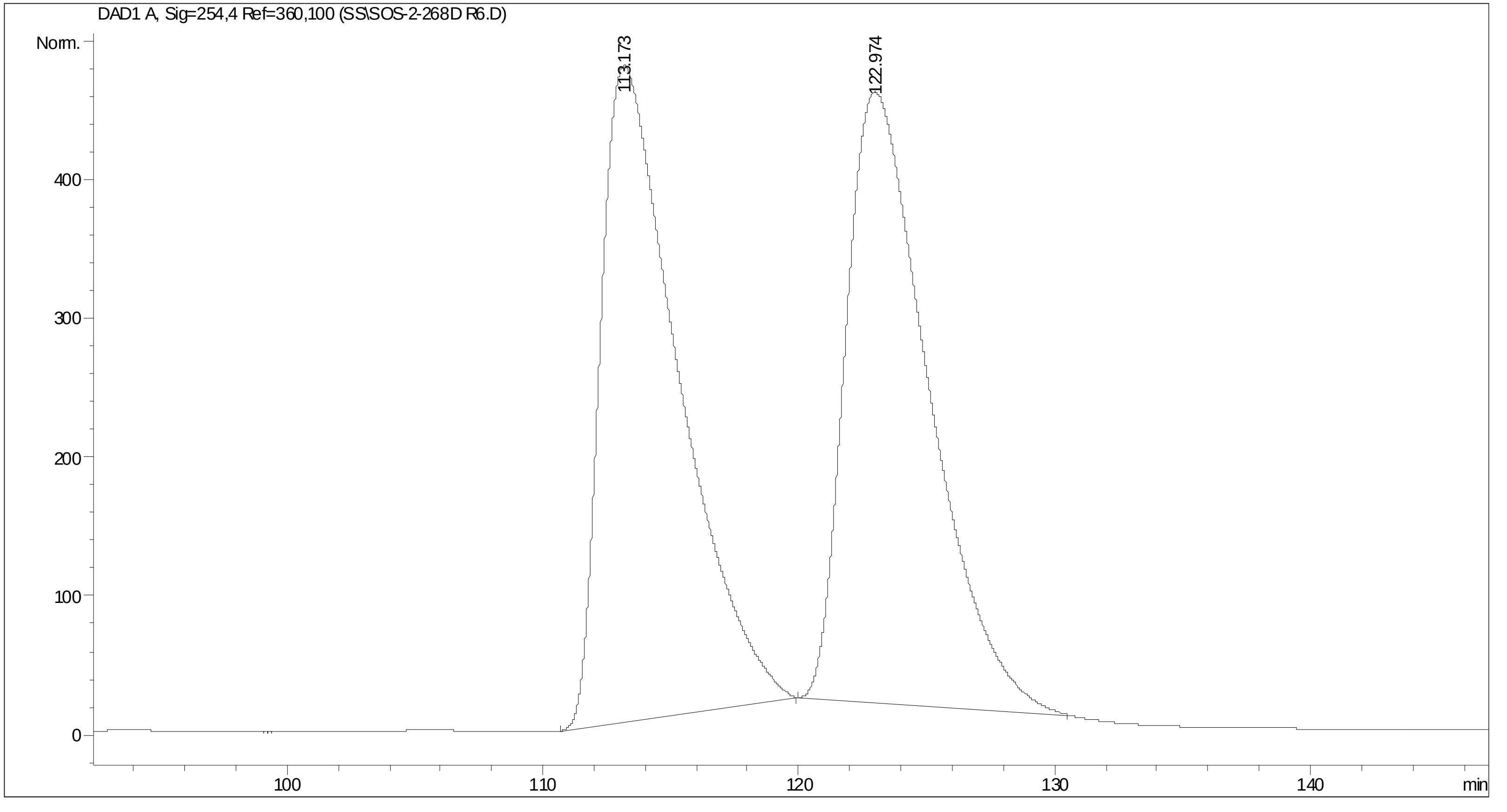


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	113.173	BB	2.9718	1.00539e5	473.39105	50.1383
2	122.974	BB	3.3146	9.99840e4	440.75446	49.8617
Totals :				2.00523e5	914.14551	

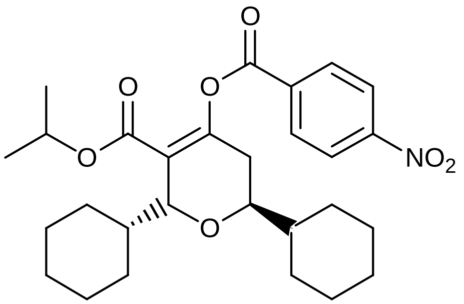


racemate

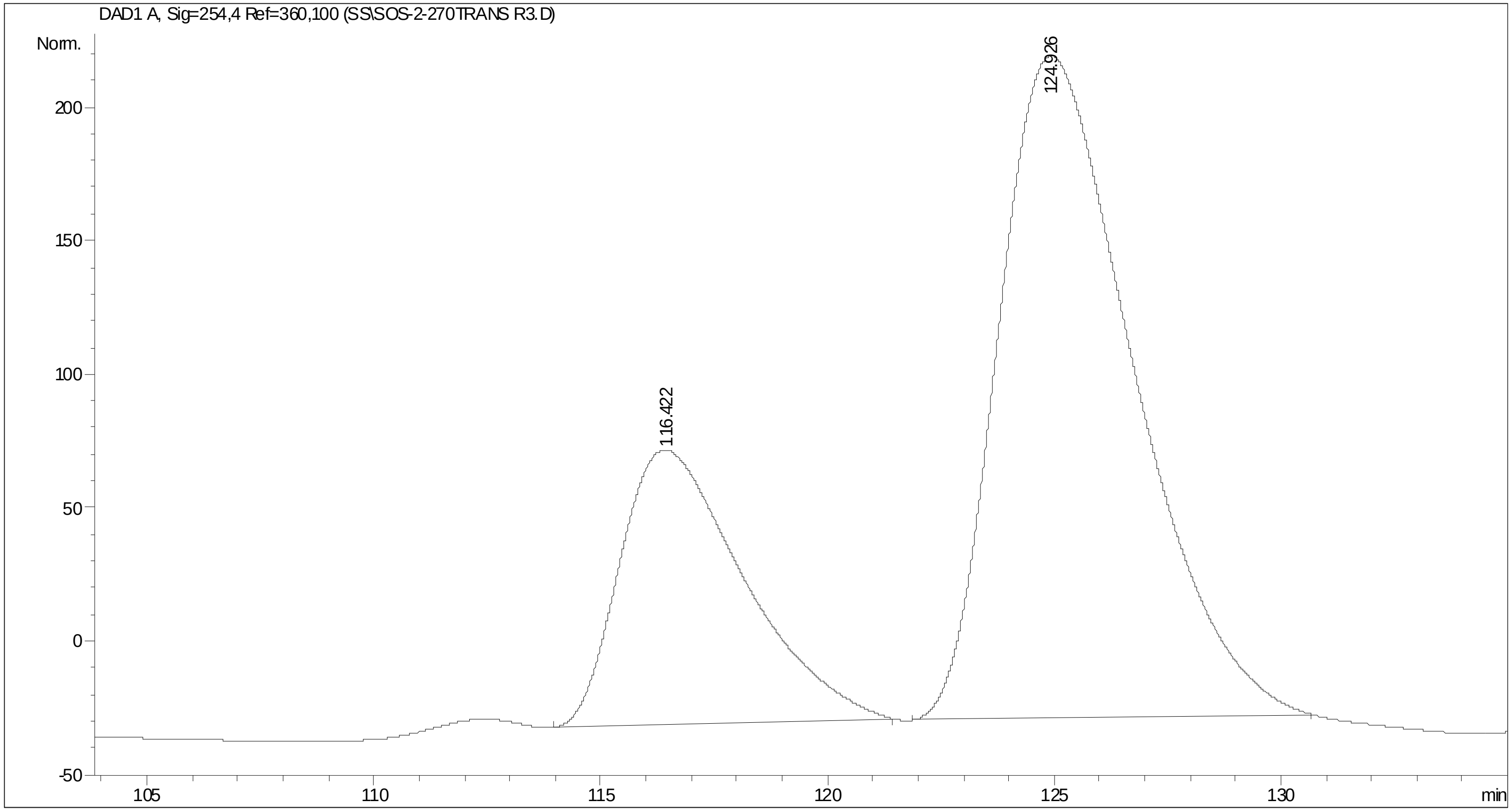


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	43.798	BB	1.4776	1.51737e4	142.58403	16.0175
2	62.169	BB	1.2737	1583.12085	15.34446	1.6712
3	79.142	BB	1.3385	1036.61853	9.20063	1.0943
4	98.849	BB	2.0062	6057.99316	35.54767	6.3949
5	116.422	BB	2.6041	1.95826e4	102.99774	20.6716
6	124.926	BB	2.9323	5.12980e4	248.09840	54.1506
Totals :				9.47321e4	553.77293	

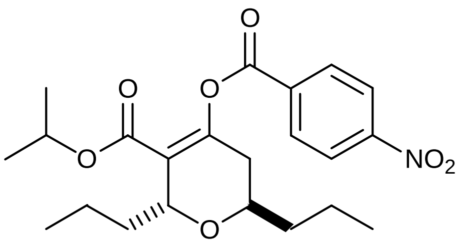


Enantiomerically enriched **9l**

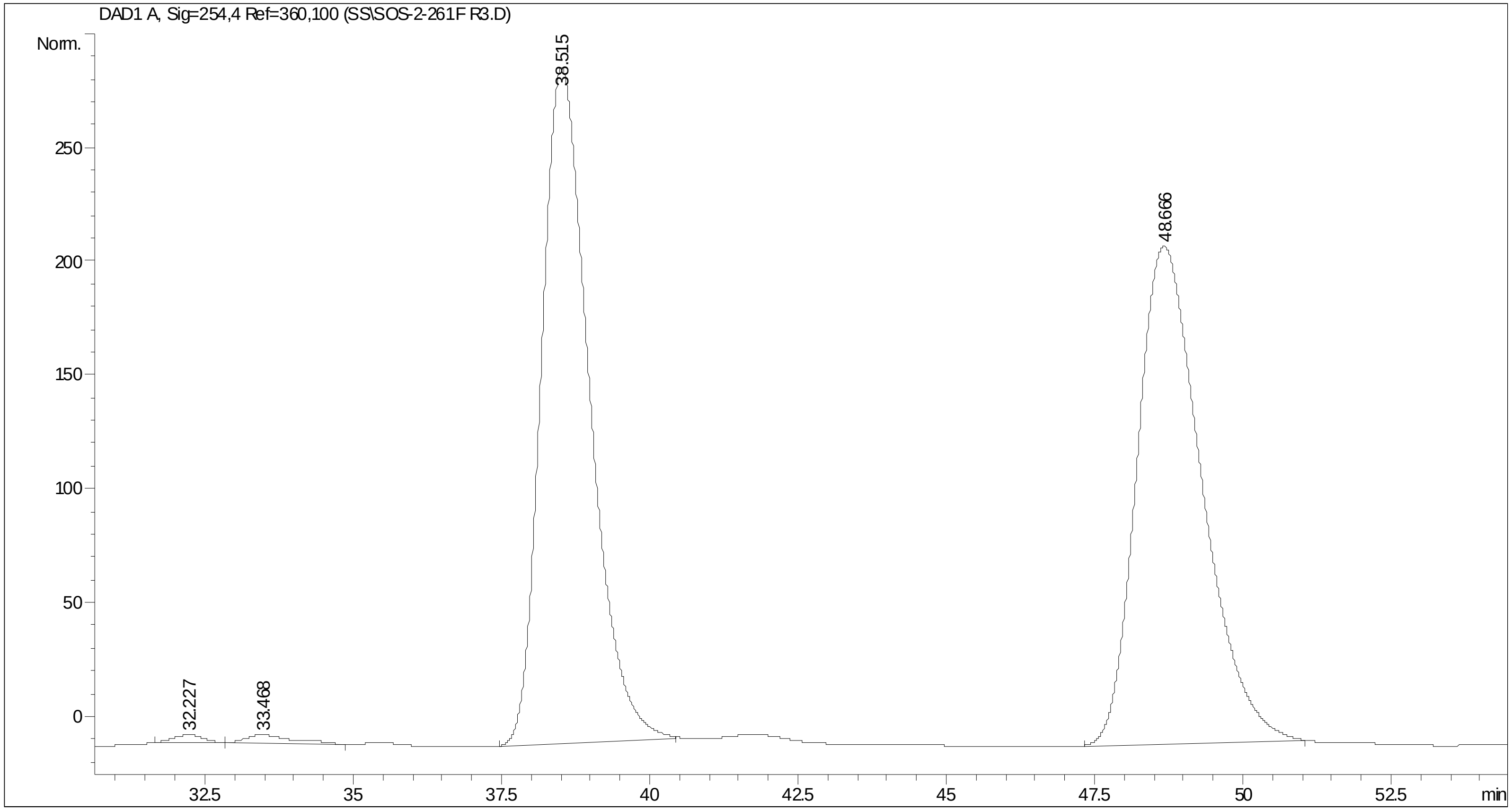


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.223	BB	0.2262	35.38881	2.04229	0.1019
2	17.538	BB	0.4237	59.33599	2.01398	0.1709
3	22.500	BB	0.4302	129.93774	4.56395	0.3742
4	23.727	BB	0.4974	190.95885	5.72161	0.5499
5	27.386	BV	0.4880	240.57144	7.34786	0.6928
6	28.123	VB	0.5549	280.68863	7.52936	0.8084
7	32.227	BV	0.5398	138.00352	3.64463	0.3974
8	33.468	VB	0.7795	226.88466	3.95390	0.6534
9	38.515	BB	0.8671	1.67457e4	297.30847	48.2260
10	48.666	BB	1.1526	1.66759e4	218.93280	48.0250
Totals :				3.47233e4	553.05886	

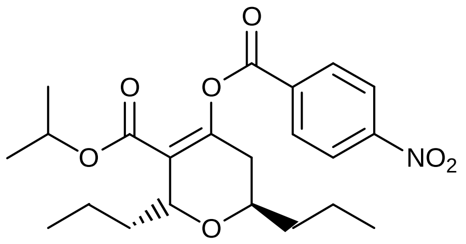


Racemate



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.869	BV	0.4035	6365.55273	236.87651	2.0864
2	17.583	VB	0.4702	1.23025e4	381.56369	4.0323
3	25.434	BV	0.7026	286.28516	5.13361	0.0938
4	27.489	VV	0.5969	1919.25720	46.75898	0.6291
5	28.211	VB	0.5655	1732.41736	45.77631	0.5678
6	30.224	BB	0.5918	136.41519	3.02666	0.0447
7	32.410	BB	0.6419	1667.07544	40.69660	0.5464
8	38.495	BB	0.8786	5.58618e4	957.59467	18.3094
9	42.680	BV	1.1575	8579.64648	114.59092	2.8121
10	46.250	VB	1.2810	2.15210e5	2344.32251	70.5377
11	54.607	BB	1.1047	1037.96143	13.53510	0.3402
Totals :				3.05099e5	4189.87555	



Enantiomerically enriched **9k**