Supplementary Material for Organic & Biomolecular Chemistry

Alkylation of natural endoperoxide G3-factor. Synthesis and antimalarial activity studies.

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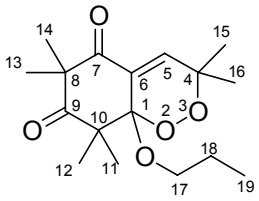
($C_{17}H_{26}O_5$; MM = 310 g.mol^{-1})



3

To a solution of compound **1** (0.57 mmol, 152.5 mg) in DMF (4 mL) is added potassium carbonate K_2CO_3 (2.85 mmol, 394 mg) then 1-iodopropane (1.71 mmol, 167 µL) and tetrabutyl ammonium iodide ($Bu_4N^+I^-$) in catalytic amount (0.06 mmol, 21 mg). After 48 hours, water is added, and extraction with dichloromethane performed, followed by organic phases washing, drying on $MgSO_4$ and evaporation to furnish raw mixture which is purified on silica gel preparative thin layer chromatography (Ethyl acetate/Petroleum ether : 2/8). **3** is obtained as an oil in 30% yield.

^{1}H NMR (250 MHz, $CDCl_3$, δ_{ppm}) : 0.85 (t, 3H, C*H*$_3$ on C_{19}) ; 1.05 ; 1.30 ; 1.31 ; 1.33 ; 1.35; 1.46 (6s, 18H, 6C*H*$_3$ on $C_{11, 12, 13, 14, 15, 16}$) ; 1.48 (m, 2H, C*H*$_2$ on C18) ; 3.63 (m, 2H, C*H*$_2$ on C17 position) ; 7.29 (s, 1H, =C*H* on C5).

^{13}C NMR (75.5 MHz, $CDCl_3$, δ_{ppm}) : 10.5 (C_{19}) ; 15.8 ; 21.8 ; 23.6 ; 24.0 ; 25.3 ; 25.8 ($C_{11, 12, 13, 14, 15, 16}$) ; 23.3 ($C_{18}$) ; 53.3 ($C_{10}$) ; 54.6 ($C_8$) ; 68.3 ($C_{17}$) ; 78.5 ($C_4$) ; 99.7 ($C_1$) ; 129.1 ($C_6$) ; 145.0 ($C_5$) ; 199.4 ($C_7$) ; 210.6 ($C_9$).

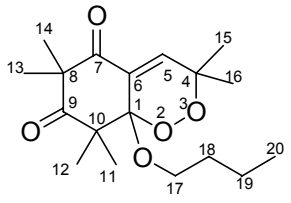
IR (neat) : ν [cm^{-1}] = 1691 (C=O) ; 1640 (C=O) ; 884 (O-O)

MS (DCI /NH_3) : *m/z* (%) = 311$[MH]^+$ (1) ; 328 $[MNH_4]^+$ (100) ; 345 $[MN_2H_7]^+$ (4)

SMHR (CI/NH_3) $C_{17}H_{26}O_5$: $[MH]^+$ Calculated/observed 311.1858/311.18549

Rf (Ethyl acetate / Petroleum ether : 2 / 8) : 0.71

($C_{18}H_{28}O_5$; MM = 324 g.mol^{-1})



4

To a solution of compound **1** (0.19 mmol, 52 mg) in DMF (1.5 mL) is added potassium carbonate K_2CO_3 (0.95 mmol, 132 mg) then 1-iodobutane (0,58 mmol, 66 µL) and tetrabutyl ammonium iodide ($Bu_4N^+I^-$) in catalytic amount (0,02 mmol, 7 mg). After 48 hours, water is

added, and extraction with dichloromethane performed, followed by organic phases washing, drying on $MgSO_4$ and evaporation to furnish raw mixture which is purified on silica gel preparative thin layer chromatography (Ethyl acetate / Petroleum ether : 2/8). **4** is obtained as an oil in 30% yield.

^{1}H NMR (250 MHz, $CDCl_3$, δ_{ppm}) : 0.86 (t, 3H, ^3J = 7,1 Hz, CH_3 on C_{20}) ; 1.06 ; 1.31 ; 1.32 ; 1.34 ; 1.35; 1.46 (6s, 18H, 6CH_3 on $C_{11, 12, 13, 14, 15, 16}$) ; 1.33 (m, 2H, C$H_2$ on C_{19}) ;1.65 (m, 2H, CH_2 on C_{18}) ; 3.68 (m, 2H, CH_2 on C_{17}) ; 7.29 (s, 1H, =CH on C5).

^{13}C NMR (75.5 MHz, $CDCl_3$, δ_{ppm}) : 13.8 (C_{20}) ; 15.8 ; 21.8 ; 23.6 ; 24.0 ; 25.3 ; 25.9 (6 CH$_3$, $C_{11, 12, 13, 14, 15, 16}$) ; 19.2 ($C_{19}$) ; 32.1 ($C_{18}$) ; 53.3 ($C_{10}$) ; 54.6 ($C_8$) ; 66.6 ($C_{17}$) ; 78.5 ($C_4$) ; 99.7 ($C_1$) ; 129.1 ($C_6$) ; 145.0 ($C_5$) ; 199.4 ($C_7$) ; 210.7 ($C_9$).

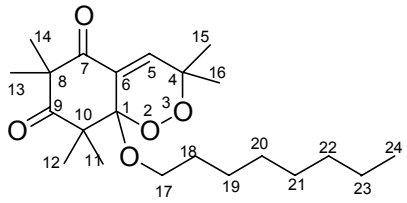
IR (neat) : ν [cm^{-1}] = 1690 (C=O) ; 1639 (C=O) ; 895 (O-O)

MS (DCI /NH_3) : *m/z* (%) = 325 $[MH]^+$ (11) ; 342 $[MNH_4]^+$ (100) ; 359 $[MN_2H_7]^+$ (8)

SMHR (CI/NH_3) $C_{18}H_{28}O_5$: $[MH]^+$ Calculated/observed 325.2015/325.20199

Rf (Ethyl acetate / Petroleum ether : 2/8) : 0.70

($C_{22}H_{36}O_5$; MM = 380 $g.mol^{-1}$)



5

To a solution of compound **1** (0.56 mmol, 150 mg) in DMF (5 mL) is added potassium carbonate K_2CO_3 (2,8 mmol, 387 mg) then 1-iodooctane (1,68 mmol, 303 µL) and tetrabutyl ammonium iodide ($Bu_4N^+I^-$) in catalytic amount (0,06 mmol, 21mg). After 48 hours, water is added, and extraction with dichloromethane performed, followed by organic phases washing, drying on $MgSO_4$ and evaporation to furnish raw mixture which is purified on silica gel preparative thin layer chromatography (Ethyl acetate / Petroleum ether : 2/8). **5** is obtained as an oil in 30% yield.

^{1}H NMR (250 MHz, $CDCl_3$, δ_{ppm}) : 0.86 (t, 3H, CH_3 on C_{24}) ; 1.05 ; 1.22 ; 1.31 ; 1.33 ; 1.35; 1.46 (6s, 18H, 6CH_3 on $C_{11, 12, 13, 14, 15, 16}$) ; 1.25 (m, 10H, C$H_2$ on $C_{19, 20, 21, 22, 23}$) ;1.62 (m, 2H, CH_2 on C_{18}) ; 3.66 (m, 2H, CH_2 on C_{17}) ; 7.29 (s, 1H, =CH on C_5).

^{13}C NMR (75.5 MHz, $CDCl_3$, δ_{ppm}) : 14.1 (C_{24}) ; 15.8 ; 21.8 ; 23.6 ; 24.0 ; 25.2 ; 25.9 ($C_{11, 12, 13, 14, 15, 16}$) ; 22.6 ; 26.0 ; 29.2 ; 29.3 ; 30.0 ; 31.8 ($C_{18, 19, 20, 21, 22, 23}$) ; 53.3 ($C_{10}$) ; 54.7 ($C_8$) ; 66.9 ($C_{17}$) ; 78.5 ($C_4$) ; 99.8 ($C_1$) ; 129.1 ($C_6$) ; 145.0 ($C_5$) ; 199.4 ($C_7$) ; 210.6 ($C_9$).

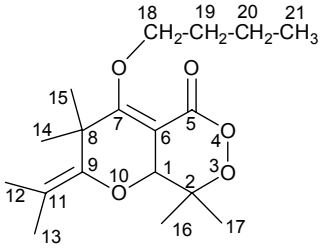
IR (neat) : ν [cm^{-1}] = 1691 (C=O) ; 1638 (C=O) ; 907 (O-O)

MS (DCI /NH_3) : *m/z* (%) = 381 $[MH]^+$ (6) ; 398 $[MNH_4]^+$ (100)

SMHR (CI/NH_3) $C_{22}H_{36}O_5$: $[MH]^+$ Calculated/observed 381.2641/381.26425

Rf (Ethyl acetate / Petroleum ether : 2/8) : 0.68

($C_{18}H_{28}O_5$; MM = 324 $g.mol^{-1}$)



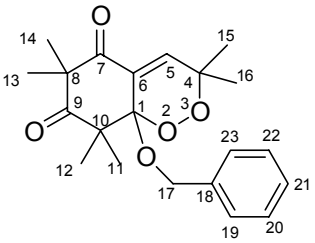
7

^{1}H NMR (400MHz, $CDCl_3$, δ_{ppm}) : 0.97 (t, C*H*$_3$, on C_{21}), 1.39 (s, 6H, 2C*H*$_3$, on C_{14}-C_{15}), 1.41 (m, 2H, C*H*$_2$ on C_{20}), 1.51 (s, 6H, 2C*H*$_3$ on C_{16}-C_{17}), 1.57 (s, 3H, C*H*$_3$ on C_{12} or C_{13}), 1.60 (s, 3H, C*H*$_3$, on C_{12} or C_{13}), 1.67 (m, 2H, C*H*$_2$, on C_{19}), 4.14 (t, 2H,C*H*$_2$, on C_{18}), 6.42 (s, 1H).

^{13}C NMR (100.6MHz, $CDCl_3$, δ_{ppm}) : 13.98 (C_{21}), 19.10 (C_{12} or C_{13}), 19.38 (C_{12} or C_{13}), 19.40 (C_{20}), 25.29 (C_{14} and C_{15}), 27.09 (C_{16} and C_{17}), 30.85 (C_{19}), 47.03 (C_8), 65.30 (C_{18}), 82.48 (C_2), 121.12 (C_{11}), 126.80 (C_1), 144.18 (C_6), 148.15 (C_9), 167.21 (C_5), 176.91 (C_7).

MS (DCI /NH_3) : *m/z* (%) = 325 $[MH]^+$ (29.7), 342 $[MNH_4]^+$ (100)

($C_{21}H_{26}O_5$; MM = 358 $g.mol^{-1}$)



9

To a solution of compound **1** (0.41 mmol, 109.2 mg) in DMF (5 mL) is added benzyl bromide (1.23 mmol, 145.5 µL) then cesium carbonate Cs_2CO_3 (0.82 mmol, 265.5 mg) and

tetrabutyl ammonium iodide ($Bu_4N^+I^-$) in catalytic amount (0.08 mmol, 30.1 mg). After 48 hours, water is added, and extraction with diethyl ether performed followed by organic phases washing, drying on $MgSO_4$ and evaporation to furnish raw mixture which is purified on silica gel preparative thin layer chromatography (eluant AcEt/EP : 2/8). **9** is obtained as a white powder 40% yield. The separation of the two enantiomers **9a** et **9b** is performed on chiral column OD using Hexane/Isopropanol : 95/5.

^{1}H NMR (250 MHz, $CDCl_3$, δ ppm) : 1.10 ; 1.17 ; 1.33 ; 1.40 ; 1.41 ; 1.51 (6s, 18H, 6CH_3 on $C_{11, 12, 13, 14, 15, 16}$) ; 4.69 (d, 1H, $^2J_{Ha\text{-}Hb}$ = 12 Hz, CH_2 on C_{17}) ; 5.10 (d, 1H, $^2J_{Hb\text{-}Ha}$ = 12 Hz, CH_2 en position 17) ; 7.25 (m, 5H on $C_{19, 20, 21, 22, 23}$) ; 7.38 (s, 1H, =CH on C_5).

^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm) : 15.9 ; 21.8 ; 23.7 ; 23.9 ; 25.2 ; 25.9 ($C_{11, 12, 13, 14, 15, 16}$) ; 53.4 ($C_{10}$) ; 54.8 ($C_8$) ; 68.6 ($C_{17}$) ; 78.8 ($C_4$) ; 100.2 ($C_1$) ; 127.0 ; 127.4 ; 128.3 (C_{19}, C_{20}, C_{21}, C_{22}, C_{23}) ; 128.8 (C_{18} or C_6) ; 137.6 (C_6 or C_{18}) ; 145.4 (C_5) ; 199.2 (C_7) ; 210.4 (C_9).

IR (KBr) : ν [cm^{-1}] = 1686 (C=O) ; 1628 (C=O) ; 895 (O-O)

MS (DCI /NH_3) : *m/z* (%) = 359$[MH]^+$ (2) ; 376 $[MNH_4]^+$ (100)

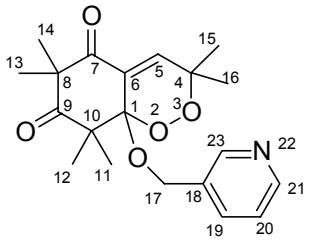
SMHR (CI/NH_3) $C_{21}H_{26}O_5$: $[MH]^+$ Calculated/observed 359.1858/359.18620

FP = 92-94 °C

9a $[\alpha]_D^{25}$ = 3.36 (c 0.5 in $CHCl_3$) **9b** $[\alpha]_D^{25}$ = -3.47 (c 0.5 in $CHCl_3$)

Rf (Ethyl acetate / Petroleum ether : 2 / 8) : 0.65

($C_{20}H_{25}O_5N$; MM = 359 $g.mol^{-1}$)



10

To a solution of compound **1** (0.38 mmol, 101.1 mg) in DMF (3 mL) is added potassium carbonate K_2CO_3 (0.82 mmol, 265.5 mg) then 3-(bromomethyl) pyridine (0.38 mmol, 98.4 mg) and tetrabutyl ammonium iodide ($Bu_4N^+I^-$) in catalytic amount (0.04 mmol, 7.4 mg). After 24 hours, water is added, and extraction with diethyl ether performed followed by organic phases washing, drying on $MgSO_4$ and evaporation to furnish raw mixture which is purified on silica gel preparative thin layer chromatography (eluant AcEt/EP : 2/8). **10** is obtained as an oil in 10% yield.

^{1}H NMR (250 MHz, $CDCl_3$, δ ppm) : 1.11 ; 1.17 ; 1.34 ; 1.39 ; 1.42 ; 1.51 (6s, 18H, 6C*H*$_3$ on $C_{11, 12, 13, 14, 15, 16}$) ; 4.5 (d, 1H, $^{2}J_{Ha\text{-}Hb}$ = 12.2 Hz, C*H*$_2$ on C_{17}) ; 5.10 (d, 1H, $^{2}J_{Hb\text{-}Ha}$ = 12,2 Hz, C*H*$_2$ on C_{17}) ; 7.25 (m, 1H, *H* on C_{20}) ; 7.41 (s, 1H, =C*H* on C_5) ; 7.60 (d, 1H, *H* on C_{19}) ; 8.44 (s, 1H, *H* on C_{23}) ; 8.47 (d, 1H, *H* on C_{21}).

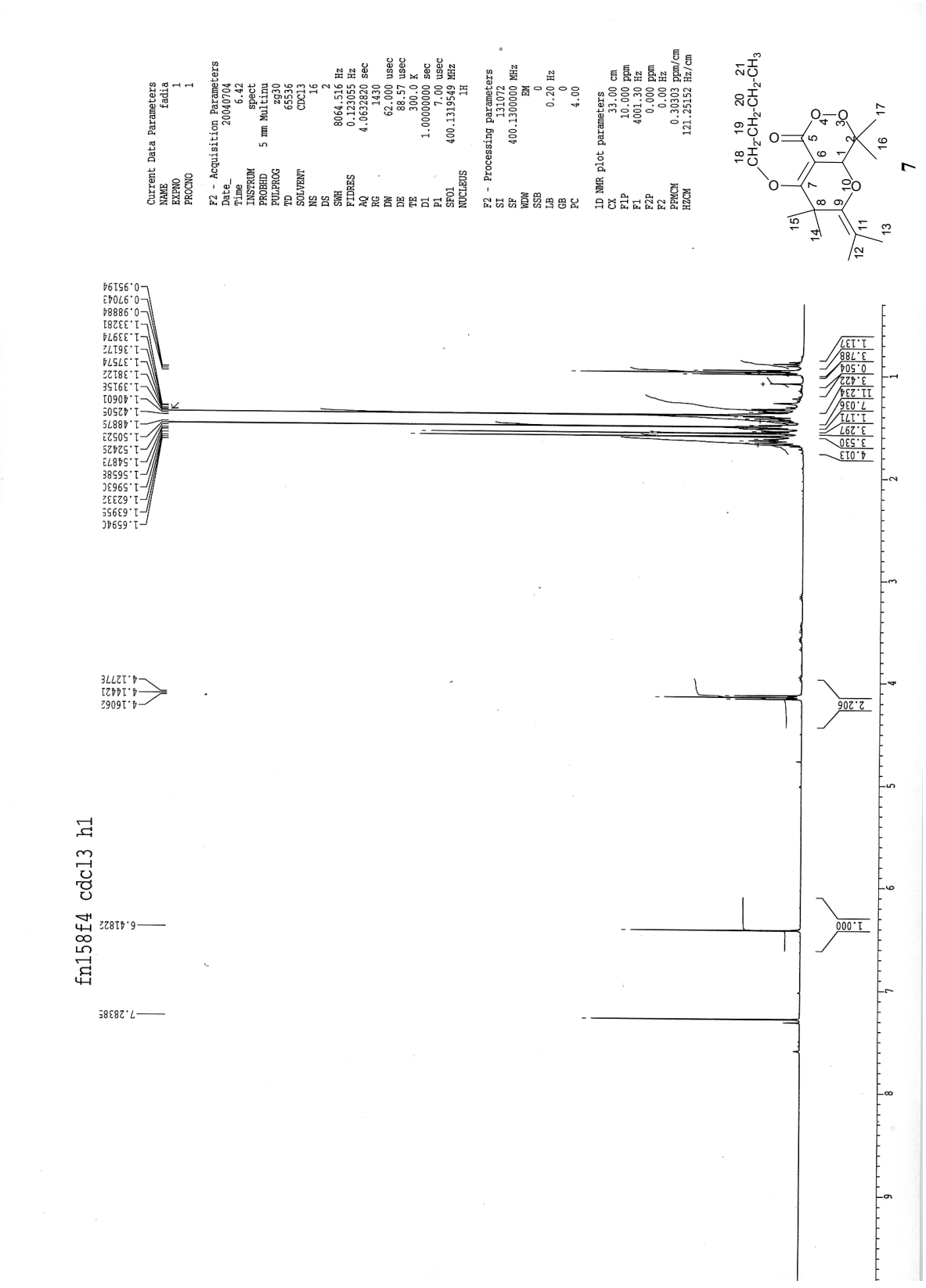
^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm) : 15.9 ; 21.8 ; 23.7 ; 23.9 ; 25.2 ; 25.9 ($C_{11, 12, 13, 14, 15, 16}$) ; 53.3 ($C_{10}$) ; 54.7 ($C_8$) ; 66.1 ($C_{17}$) ; 78.9 ($C_4$) ; 100.3 ($C_1$) ; 128.4 ($C_{18}$ or C_6) ; 133.2 (C_6 or C_{18}) ; 145.9 (C_5) ; 123.5 ; 134.9 ; 148.4 ; 149.0 (C_{19}, C_{20}, C_{21}, C_{23}) ; 199.0 (C_7) ; 210.3 (C_9).

IR (neat) : ν [cm^{-1}] = 1686 (C=O) ; 1628 (C=O) ; 895 (O-O)

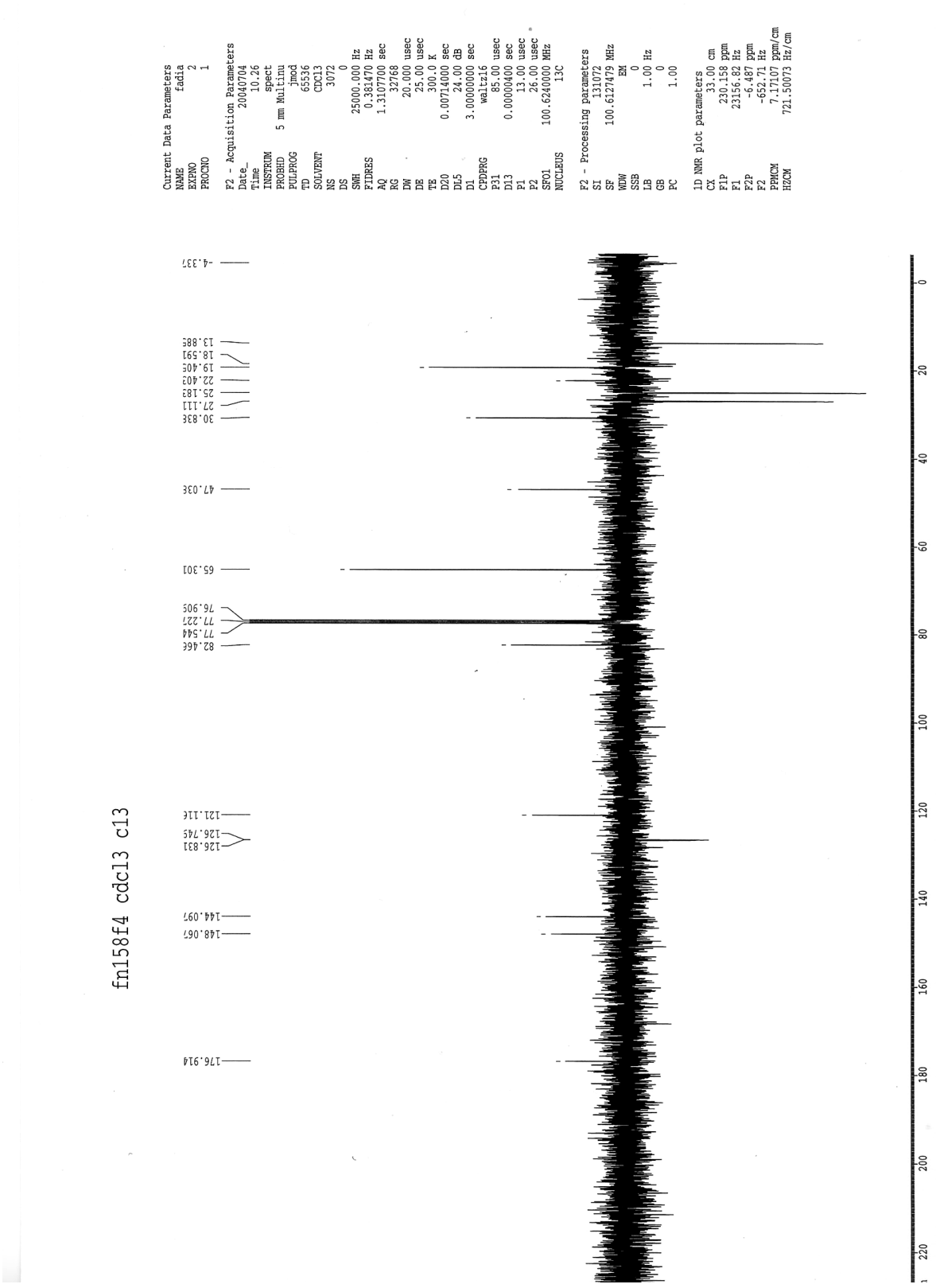
MS (IS, positif) : *m/z* (%) = 360.15 $[MH]^+$

SMHR (CI/NH_3) $C_{20}H_{25}O_5N$: $[MH]^+$ Calculated/observed 360.1811/360.18154

Rf (Ethyl acetate / Petroleum ether : 2 / 8) : 0.05



^{1}H NMR 400MHz, $CDCl_3$ for 7



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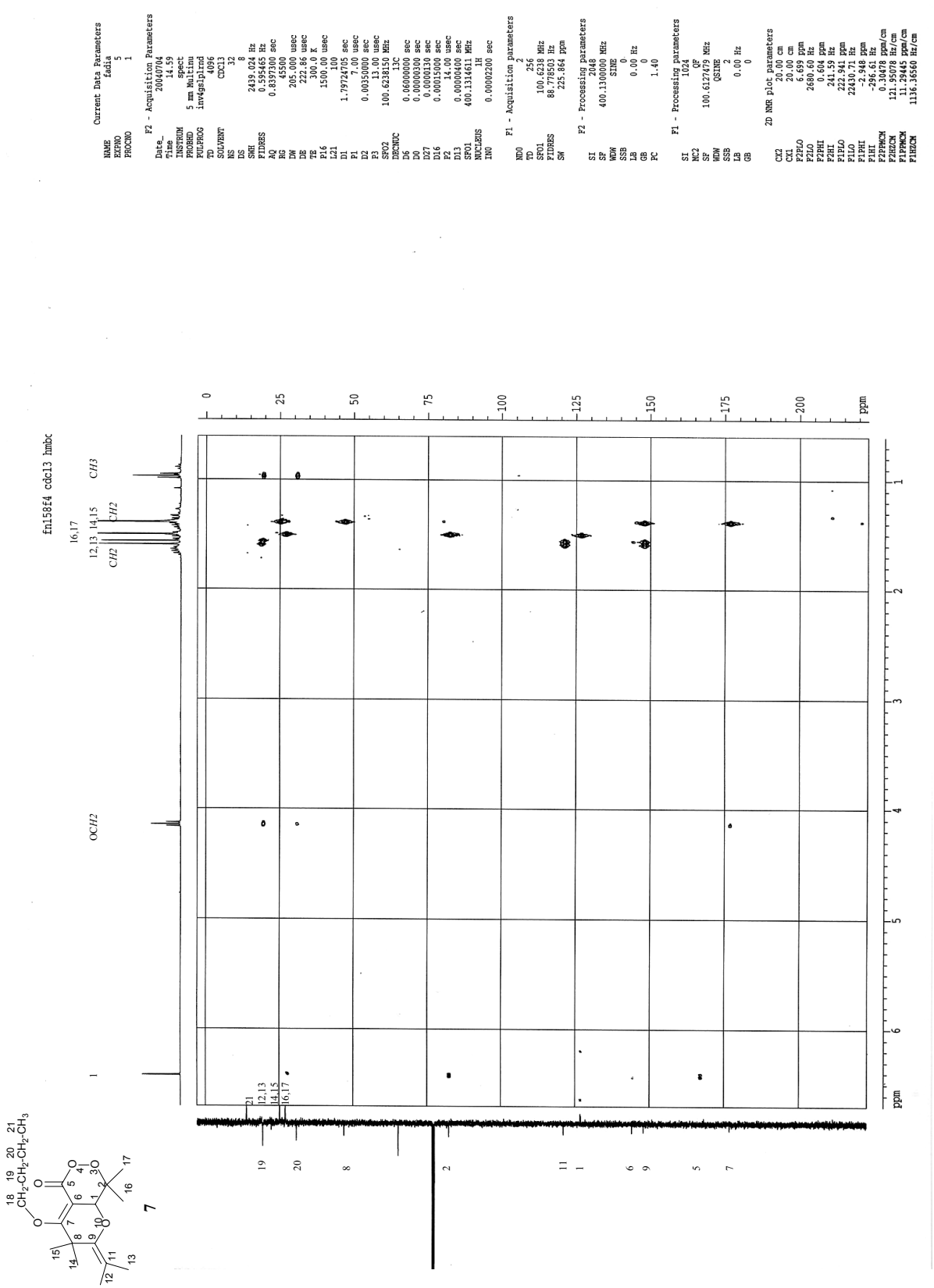

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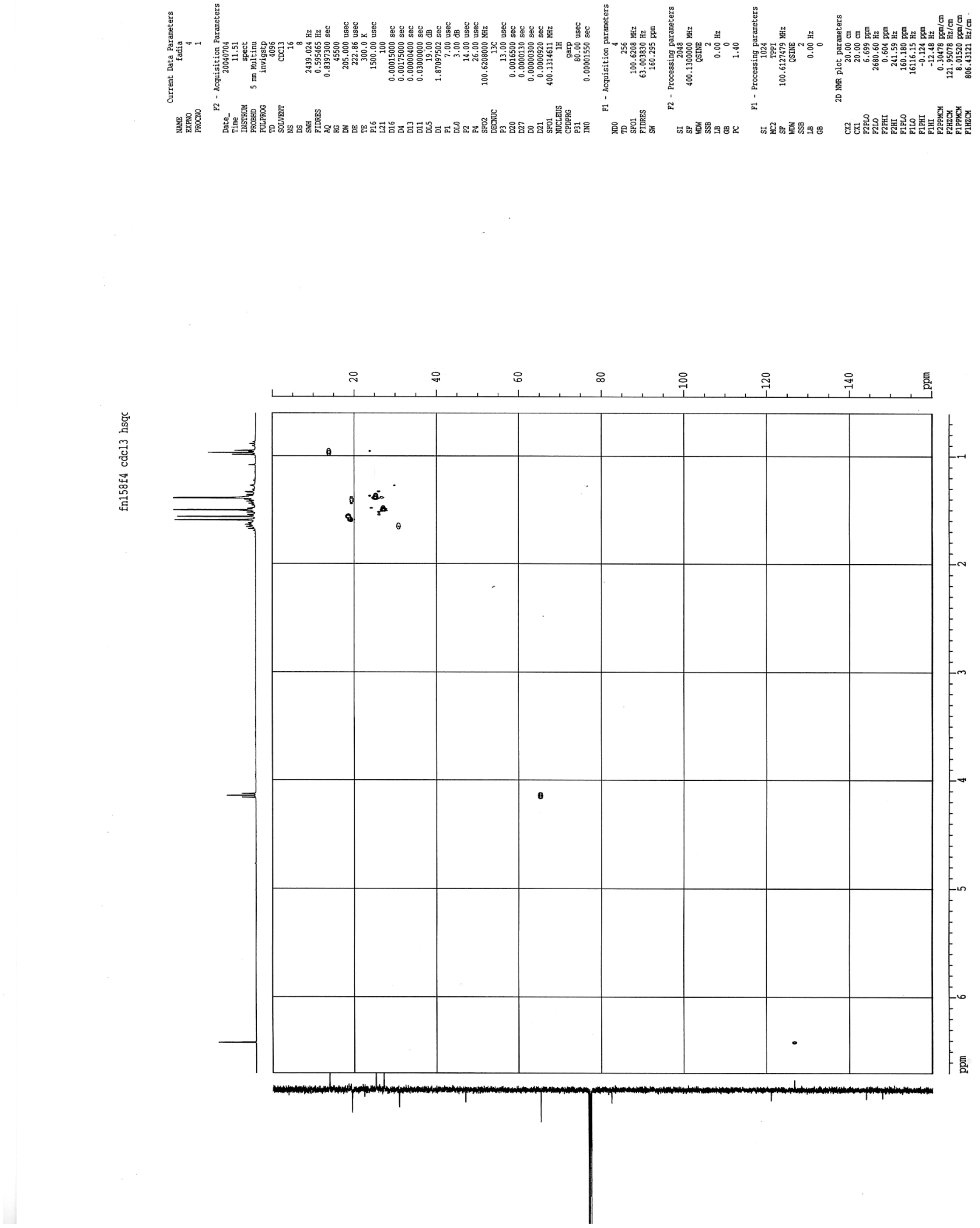
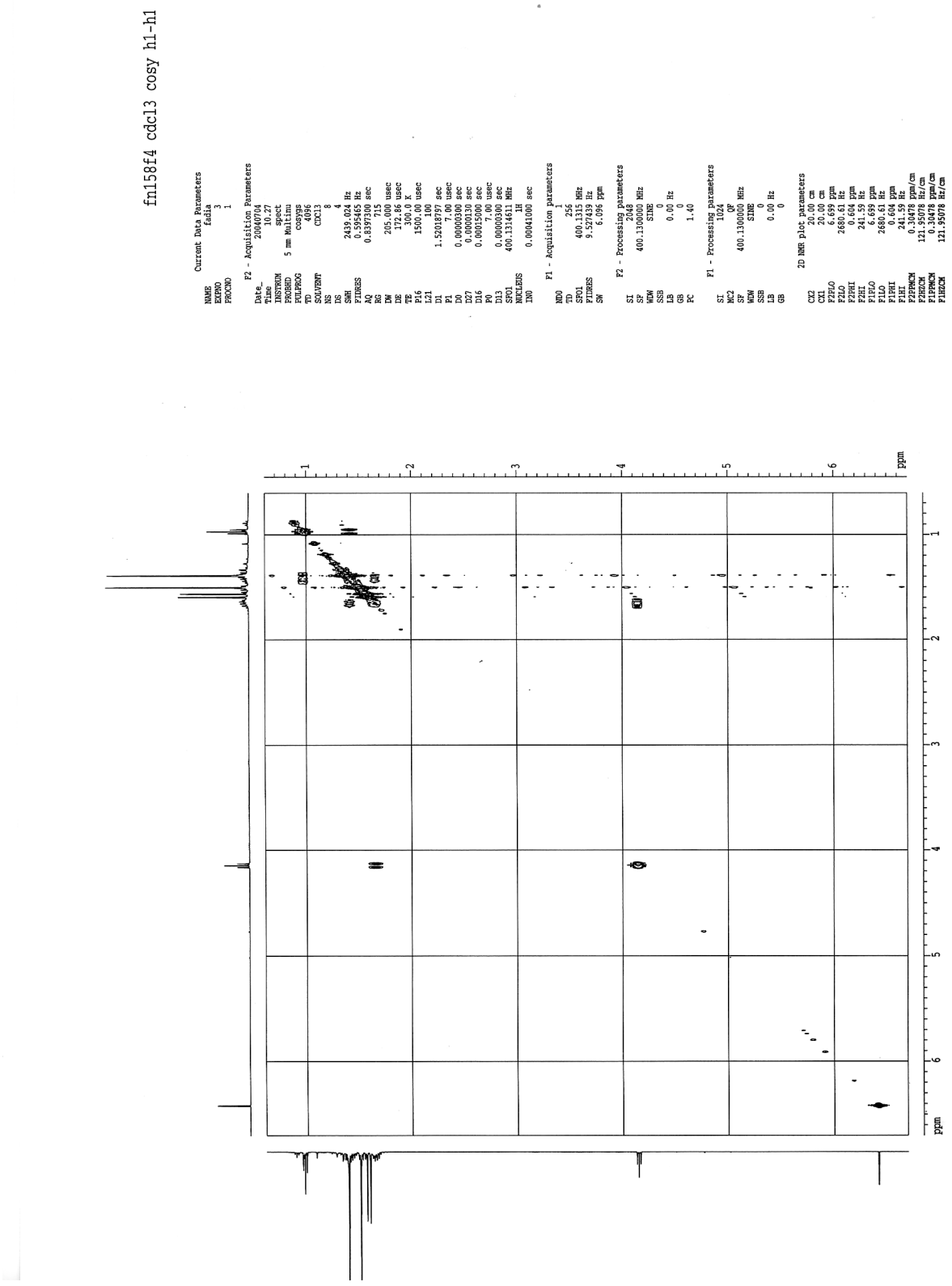


HSQC for 7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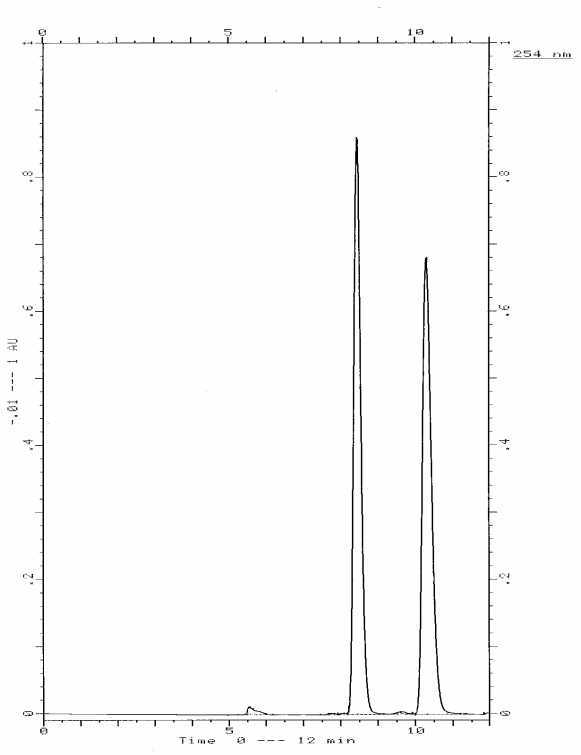
ppm

COSY for 7



Chiral separation chromatogram for compounds 9a, 9b.