Supporting Information

for

"Synthetic Studies towards Anisatin: A Formal Synthesis of (±)-8-Deoxyanisatin"

by Teck-Peng Loh and Qi-Ying Hu

(14 pages)

3-*p*-Tolylbutyric acid methyl ester (8). To a suspension of CuI (952 mg, 5 mol%) in ether (50 mL), was added an ethereal solution of *p*-tolylmagnesium bromide (99.9 mmol, 99.9 mL, 1 M in ether) at 0 °C. The mixture was allowed to stir at this temperature for 1 h. At the end of which, a solution of methyl crotonate (2.00 g, 20.0 mmol, 2.12 mL) in ether was added dropwise to the resultant mixture and stirring was continued for another 3 h. The mixture was poured into cold 1 M HCl (150 mL) and extracted with ether (5 × 80 mL). The combined extracts were washed with brine (200 mL), dried (Na_2SO_4) and evaporated *via vacuo*. The residue was distilled under reduced pressure to afford methyl ester **8** (3.09 g, 80% yield) as a colorless liquid: R_f 0.67 (10:1 hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11 (s, 4H), 3.62 (s, 3H), 3.31–3.18 (m, 1H), 2.61 (dd, J = 15.0, 6.62 Hz, 1H), 2.52 (dd, J = 15.0, 8.01 Hz, 1H), 2.32 (s, 3H), 1.28 (d, 3H, J = 6.97, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 173.4, 143.2, 136.4, 129.7, 127.0, 51.9, 43.3, 36.5, 22.3, 21.5; IR (film) 1740, 1515, 1166 cm^{-1}; HRMS Calcd for $C_{12}H_{16}O_2$ [M$^+$]: 192.1150. Found: 192.1141.

3,6-Dimethylindan-1-one (9). A mixture of methyl ester **8** (400 mg, 2.08 mmol) and excess polyphosphoric acid (10 mL) was heated at 90°C for 48 h. The resulting dark brown slurry was poured onto ice and extracted with ether (5 × 20 mL). The combined extracts were washed with brine (70 mL), dried (Na_2SO_4) and evaporated *via vacuo*. The residual oil was purified *via* column chromatography (100:1 hexane/ethyl acetate), yielding 310 mg (1.93 mmol, 93 %) of indanone **9** as a yellow oil: R_f 0.78 (2:1 hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ

7.52 (s, 1H), 7.44–7.41 (m, 1H), 7.38 (d, *J* = 8.01 Hz, 1H), 3.44–3.34 (m, 1H), 2.93 (dd, *J* = 19.1, 7.32 Hz, 1H), 2.40 (s, 3H), 2.27 (dd, *J* = 19.1, 3.48 Hz, 1H), 1.38 (d, *J* = 7.32 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 206.5, 157.4, 137.3, 136.6, 135.9, 124.9, 123.3, 45.7, 32.4, 21.4, 21.0; IR (film) 1712, 1615 cm^{-1}; HRMS Calcd for $C_{11}H_{12}O$ [M$^+$]: 160.0888. Found: 160.0881.

3,6-Dimethylindan-1-ol (10). A suspension of $NaBH_4$ (11.3 mg, 0.30 mmol) in MeOH (3 mL) was stirred at –78 °C for 30 min, followed by the addition of $CeCl_3{\cdot}7H_2O$ (110 mg, 0.30 mmol) and the mixture was stirred for another 30 min. A solution of indanone **9** (32.0 mg, 0.20 mmol) in MeOH (2 mL) was added dropwise to the mixture and stirred at –78 °C for a further 2 h. 1 M HCl was added to the resultant mixture till effervescence ceased. The mixture was extracted with ether (5 × 20 mL) and the combined extracts were washed with brine (30 mL), dried (Na_2SO_4) and evaporated *via vacuo*. The residual oil was purified *via* column chromatography (20:1 hexane/ethyl acetate), yielding 310 mg (1.93 mmol, 96 %) of indanol **10** as a 10:1 *syn*:*anti* diastereomeric mixture: R_f 0.47 (2:1 hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (s, 1H), 7.14 (s, 2H), 5.13 (dd, *J* = 7.31, 7.31 Hz, 1H), 3.07–3.00 (m, 1H), 2.74 (ddd, *J* = 12.5, 6.97, 6.97 Hz, 1H), 2.39 (s, 3H), 1.53–1.43 (m, 1H), 1.37 (d, *J* = 6.62 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 145.1, 144.3, 136.3, 128.8, 124.2, 122.9, 74.8, 45.7, 35.8, 21.2, 20.2; IR (film) 3351, 3258, 1486, 1340, 1053, 814 cm^{-1}; HRMS Calcd for $C_{11}H_{14}O$ [M$^+$]: 162.1045. Found: 162.1038.

3-Hydroxy-1,5-dimethylindan-4-carboxylic acid (6). A solution of indanol **10** (80.0 mg, 0.49 mmol), dry hexane (4 mL) and *N*,*N*,*N'*,*N'*-tetramethylethylenediamine (freshly distilled from CaH_2, 229 mg, 0.30 mL, 1.97 mmol) was treated dropwise with *n*-BuLi (1.23 mL, 1.6 M in hexane) at rt. After 20 min, the resulting pink mixture was heated at reflux for 3 h. The resulting deep red mixture was cooled to 0 °C, and gaseous CO_2 was bubbled through the solution overnight, with stirring. The reaction mixture was then diluted with ether (35 mL) and acidified with 1 M HCl to pH 2–3. The layers were separated, and the aqueous layer was extracted with ethyl acetate (5 × 25 mL), and the combined organic layers were washed with brine, dried (Na_2SO_4), and evaporated *via vacuo* to afford 65.9 mg of carboxyindanol **6** (0.32 mmol, 65% yield) as a pale brown oil, which solidified upon standing. The crude carboxyindanol **6** thus obtained is sufficiently pure for the next step. The NMR data were determined for the corresponding methyl ester, prepared by the action of excess ethereal CH_2N_2, followed by purification *via* column chromatography (8:1 hexane/ethyl acetate): R_f 0.48 (2:1 hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, J = 8.01 Hz, 1H), 7.16 (d, J = 8.01 Hz, 1H), 5.27 (dd, J = 7.31, 4.53 Hz, 1H), 3.94 (s, 3H), 3.07 (m, 1H), 2.62 (ddd, J = 13.6, 8.01, 7.31 Hz, 1H), 2.45 (s, 3H), 1.70 (ddd, J = 13.6, 5.58, 4.53 Hz, 1H), 1.35 (d, J = 6.97 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 170.1, 147.0, 145.3, 136.1, 131.5, 127.8, 126.7, 74.6, 52.1, 42.3, 36.9, 22.0, 20.8; IR (KBr) 3384, 1732, 1490, 1268, 1130, 1051 cm^{-1}; HRMS Calcd for $C_{13}H_{16}O_3$ [M$^+$]: 220.1099. Found: 220.1084.

3-Hydroxy-1,5-dimethyl-2,3,4,7-tetrahydro-1*H*-indene-4-carboxylic acid methyl ester (5). Carboxyindanol **6** (400 mg, 1.94 mmol) was dissolved in liquid NH_3 (10 mL) at –78 °C under nitrogen. To the rapidly stirred solution was added sodium metal in small pieces until a blue color persisted (*ca*. 223 mg, 9.70 mmol, over a 15 min period). Towards the end of the addition, a precipitate formed in the reaction mixture. The mixture was then allowed to reflux for 1 h, at the end of which solid ammonium chloride (830 mg, 15.5 mmol) was added to quench the reaction and the ammonia was allowed to evaporate. The solid residue was partitioned between a saturated NaH_2PO_4 solution (10 mL) and ether (5×20 mL). The combined extracts were washed with brine (50 mL), dried (Na_2SO_4) and evaporated *via vacuo*. The crude acid was immediately esterified at 0 °C with ethereal CH_2N_2, and the ether evaporated *via vacuo*. The residual oil was purified *via* column chromatography (6:1 hexane/ethyl acetate), yielding 259 mg (1.16 mmol, 60% over two steps) of 1,4-diene **5** as a pale yellow oil: R_f 0.63 (2:1 hexane/ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.68 (br s, 1H), 4.69 (br s, 1H), 3.71 (s, 3H), 3.72–3.64 (m, 1H), 2.90–2.83 (m, 1H), 2.70 (br s, 2H), 2.04 (ddd, *J* = 13.97, 7.66, 2.79 Hz, 1H), 1.85–1.68 (m, 1H), 1.74 (s, 3H), 1.00 (d, *J* = 6.97 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 174.3, 144.7, 131.4, 129.3, 122.0, 77.8, 52.3, 48.2, 43.1, 38.7, 25.7, 21.4, 19.0; HRMS Calcd for $C_{13}H_{18}O_3$ [M^+]: 222.1256. Found: 222.1260.

7a-Dimethylcarbamoylmethyl-1,5-dimethyl-2,6,7,7a-tetrahydro-1*H*-indene-4-carboxylic acid methyl ester (13). A solution of 1,4-diene **5** (2.22 g, 9.99 mmol) and *N*,*N*-dimethylacetamide dimethyl acetal (6.65 g, 7.30 mL, 49.9 mmol) in xylene (70 mL) was refluxed for 48 h. After which, xylene was removed *via vacuo* and the residual oil was purified *via* column chromatography (5:1 hexane/ethyl acetate), yielding 1.10 g (4.99 mmol, 50% yield) of amide **13** as a yellow oil: R_f 0.20 (2:1 hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.53 (br s, 1H), 3.80 (s, 3H), 2.97 (s, 3H), 2.87 (s, 3H,), 2.76 (dd, J = 12.5, 5.23 Hz, 1H), 2.57–2.46 (m, 1H), 2.40 (ddd, J = 16.7, 7.67, 3.48 Hz, 1H), 2.27 (d, J = 15.3 Hz), 2.19 (d, J = 15.3 Hz), 2.19–2.10 (m, 2H), 2.03–1.95 (m, 1H), 1.84 (s, 3H), 1.32 (td, J = 12.5, 5.92 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 172.2, 169.2, 143.8, 141.4, 124.7, 123.0, 51.5, 48.9, 46.7, 38.8, 38.1, 35.6, 32.1, 31.3, 31.0, 21.1, 14.0; IR (film) 1726, 1634, 1462, 1278 cm^{-1}; HRMS Calcd for $C_{17}H_{25}NO_3$ [M$^+$]: 291.1834. Found: 291.1834.

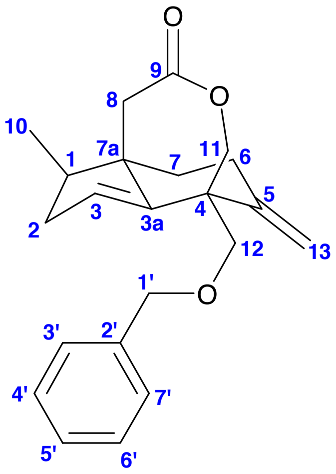
(4-Benzyloxymethyl-7a-dimethylcarbamoylmethyl-1-methyl-5-methylene-2,4,5,6,7,7a-hexahydro-1*H*-inden-4-yl)acetic acid methyl ester (4). LDA (2.75 mL,1.5 M in cyclohexane) was added dropwise to a solution of amide **13** (150 mg, 0.51 mmol) in THF (3 mL) at –78 °C, and the solution was stirred for 1 h. $BnOCH_2Cl$ (161 mg, 0.16 mL, 1.03 mmol, 90% purity) was added, and the mixture was allowed to warm to rt and stirred for a further 2 h. Water (1 mL) was added to quench the reaction and extracted with ethyl acetate (5 × 10 mL). The combined extracts were washed with brine (15 mL), dried (Na_2SO_4) and evaporated *via vacuo*. The residual oil was purified *via* column chromatography (3:1 hexane/ethyl acetate), yielding 87.6 mg (0.21 mmol, 40% yield) of methyl ester **4** as a colourless oil: R_f 0.21 (2:1 hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.25 (m, 5H), 5.57 (t, *J* = 2.44 Hz, 1H), 5.09 (s, 1H), 5.02 (s, 1H), 4.54 (s, 2H), 4.06 (d, *J* = 8.71 Hz, 1H), 3.83 (d, *J* = 8.71 Hz, 1H), 3.61 (s, 3H), 2.98 (s, 3H), 2.89 (s, 3H), 2.71–2.60 (m, 1H), 2.57–2.50 (m, 1H), 2.49 (d, *J* = 17.1 Hz, 1H), 2.21 (d, *J* = 17.1 Hz, 1H), 2.09–1.96 (m, 1H), 1.25 (td, *J* = 12.9, 4.18 Hz), 0.95 (d, *J* = 6.97 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 173.4, 171.2, 147.4, 145.3, 138.0, 128.3, 127.6, 127.5, 126.1, 111.2, 74.1, 73.5, 56.0, 52.0, 51.0, 45.5, 39.4, 39.2, 39.2 (overlap), 37.5, 35.4, 32.6, 31.4, 15.0; IR (film) 1731, 1650, 1450, 1397, 1218, 1099 cm^{-1}; HRMS Calcd for $C_{25}H_{33}NO_4$ [$M^+ - CH_3$]: 410.2331. Found: 410.2313.

2-(7-Benzyloxymethyl-7-hydroxymethyl-3-methyl-6-methylene-2,3,4,5,6,7-hexahydroinden-3a-yl)-*N,N*-dimethylacetamide (14). To a solution of methyl ester **4** (85.0 mg, 0.20 mmol) in THF (3 mL) was added excess $LiBH_4$ (1 mL, 2 M in THF) and the mixture was allowed to stir at rt for 48 h. 1 M HCl was added dropwise till a clear solution was obtained. The resulting solution was extracted with ethyl acetate (5 × 10 mL), and the combined extracts were washed with brine (15 mL), dried (Na_2SO_4) and evaporated *via vacuo*. The residual oil was purified *via* column chromatography (3:1 hexane/ethyl acetate), yielding 38.3 mg (0.10 mmol, 50% yield) of amide **14** as a colourless oil: R_f 0.08 (2:1 hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.27 (m, 5H), 5.73 (d, *J* = 2.09 Hz, 1H), 4.97 (s, 1H), 4.96 (s, 1H), 4.59 (d, *J* = 12.5 Hz, 1H), 4.53 (d, *J* = 12.5 Hz, 1H), 3.74 (s, 2H), 3.70 (d, *J* = 11.5 Hz, 1H), 3.56 (d, *J* = 11.5 Hz, 1H), 3.09 (s, 3H), 2.91 (s, 3H), 2.49 (d, *J* = 15.7 Hz, 1H), 2.37 (d, *J* = 15.7 Hz, 1H), 2.31–2.20 (m, 3H), 2.08–2.00 (m, 1H), 1.96–1.87 (m, 1H), 1.75–1.66 (m, 1H), 1.56–1.47 (m, 1H), 0.99 (d, *J* = 6.96 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 172.9, 148.3, 144.9, 138.7, 129.5, 128.2, 127.6, 127.3, 110.5, 73.6, 73.5, 65.7, 51.4, 50.9, 47.3, 40.1, 39.4, 38.0, 36.0, 35.5, 30.7, 14.1; IR (film) 1624, 1400, 1260 cm^{-1}; HRMS Calcd for $C_{24}H_{33}NO_3$ [M$^+$]: 383.2460. Found: 383.2463.

(7-Benzyloxymethyl-7-hydroxymethyl-3-methyl-6-methylene-2,3,4,5,6,7-hexahydroinden-3a-yl)acetic acid (15). A mixture of amide **14** (20.0 mg, 52.1 μmol) and excess KOH (1 pellet, 250 mg) in ethylene glycol (1 mL) was heated to 200 °C in a sealed tube for 12 h. Water (10 mL) was added to the resultant mixture followed by extraction with ether (3 × 10 mL). The aqueous layer was acidified to pH 2 with 1 M HCl and extracted with ether (5 × 15 mL). The combined extracts were washed with brine (20 mL), dried (Na_2SO_4) and evaporated *via vacuo* to afford 17.0 mg of crude carboxylic acid **15**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23–7.31 (m, 5H), 6.05 (d, *J* = 2.79 Hz, 1H), 4.97 (s, 1H), 4.78 (s, 1H), 4.58, (s, 2H), 3.89 (d, *J* = 11.9 Hz, 1H), 3.80 (d, *J* = 15.7 Hz, 1H), 3.78 (d, *J* = 11.9 Hz, 1H), 3.77 (d, *J* = 15.7 Hz, 1H), 2.49 (d, *J* = 13.6 Hz, 1H), 2.34 (d, *J* = 13.6 Hz, 1H), 2.26–2.10 (m, 5H), 1.66–1.58 (m, 1H), 1.47–1.39 (m, 1H), 1.24 (d, *J* = 5.93 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 173.9, 148.3, 145.5, 137.2, 132.8, 128.7, 128.1, 127.9, 110.7, 78.3, 74.0, 68.5, 50.6, 49.7, 46.9, 42.5, 37.8, 37.2, 30.7, 12.2; IR (film) 1701, 1555, 1261 cm^{-1}; HRMS Calcd for $C_{22}H_{28}O_4$ [M$^+$]:

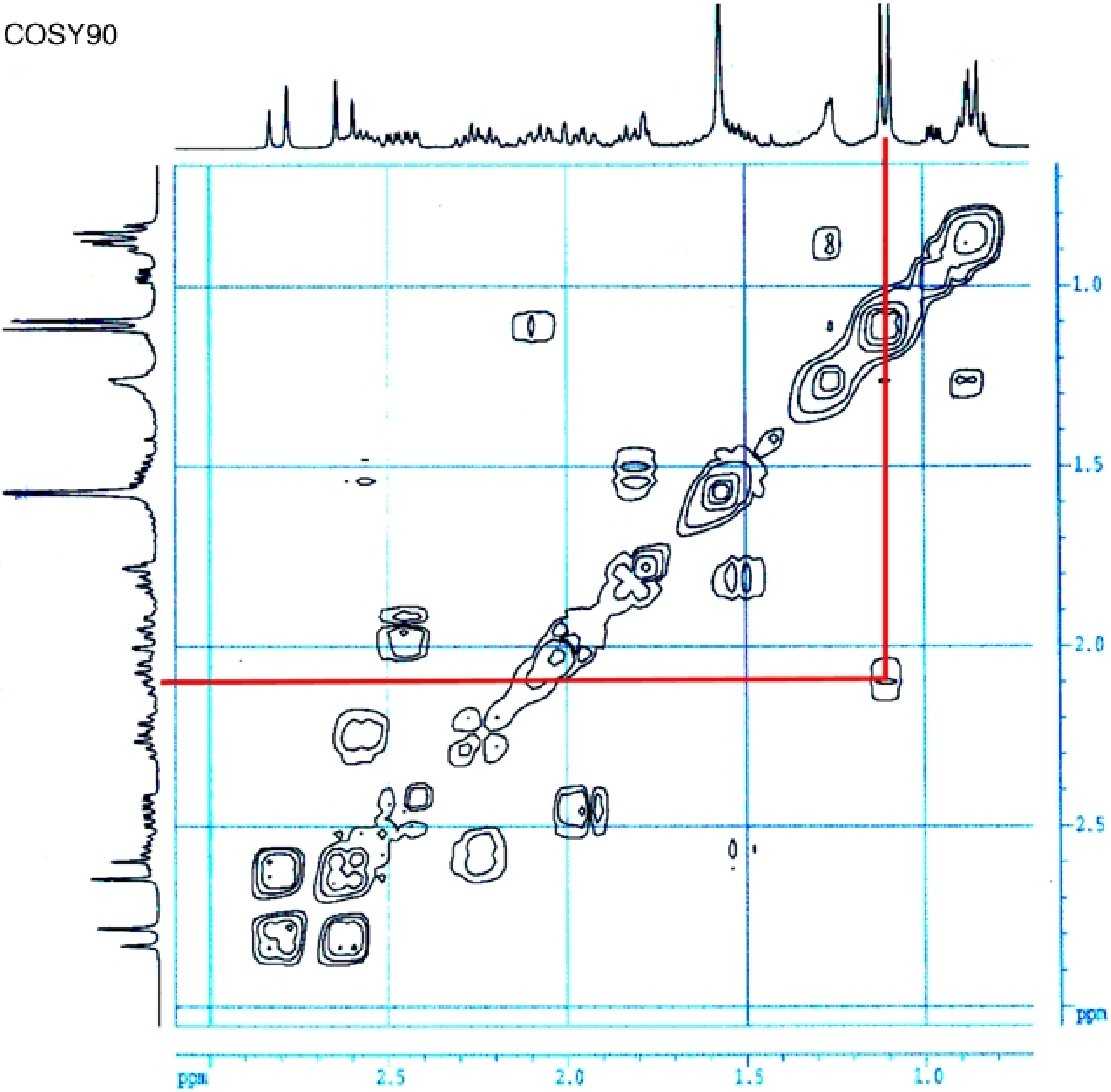
356.1988. Found: 356.2001. The crude acid thus obtained was used directly for lactonization.

6-Benzyloxymethyl-2-methyl-13-methylene-8-oxa-tricyclo[4.4.3.0^{1,5}]tridec-4-en-9-one (3).

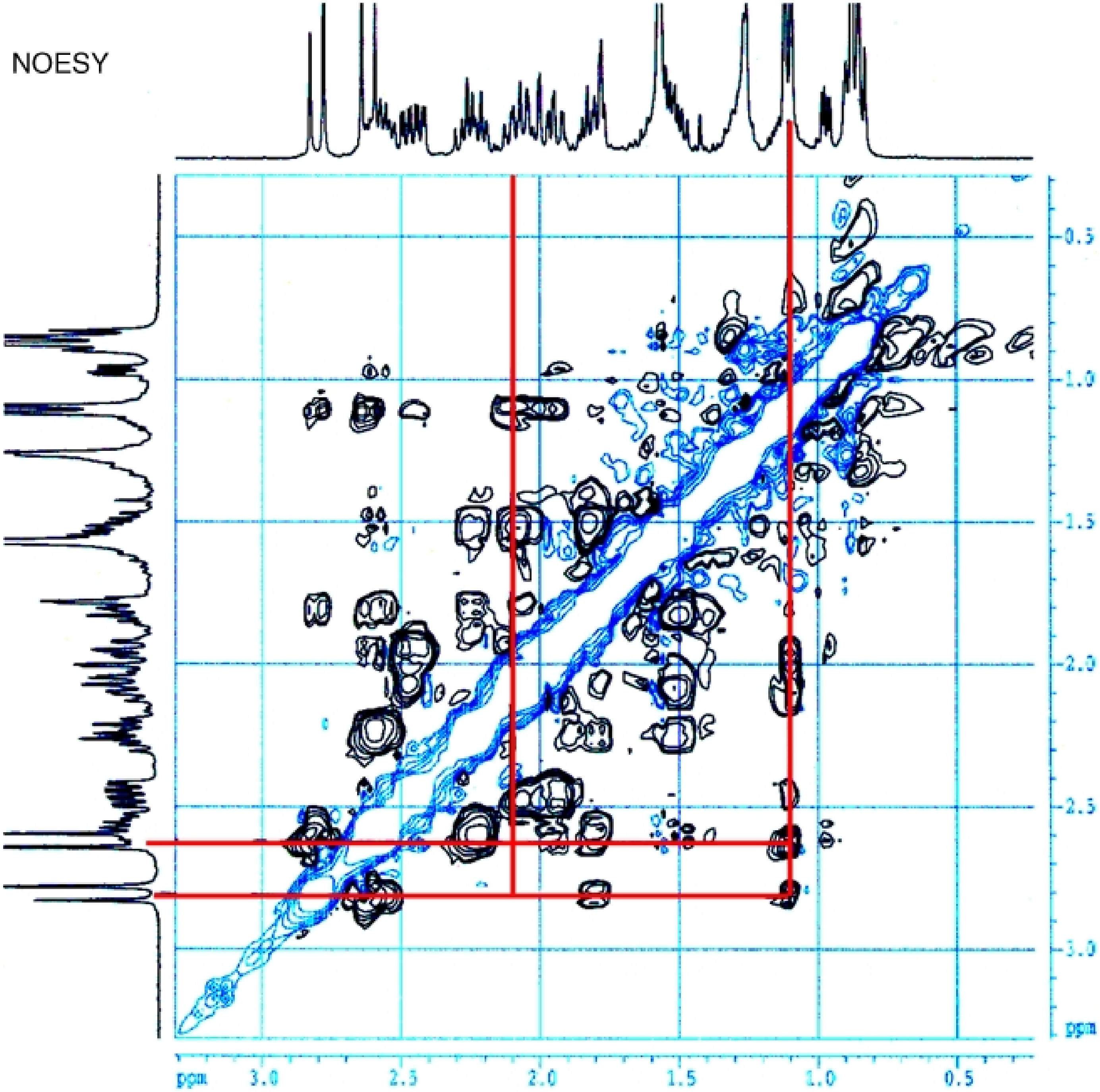


To a solution of crude carboxylic acid **15** (17.0 mg) in toluene was added catalytic amount of *p*-TsOH, and the solution was heated at 70 °C for 30 min. Water (10 mL) was added and extracted with ethyl acetate (5 × 15 mL). The combined extracts were washed with brine (20 mL), dried over Na_2SO_4 and evaporated *via vacuo*. The residual oil was purified *via* column chromatography (10:1 hexane:ethyl acetate), yielding 12.4 mg (36.5 μmol, 70% over two steps) of ε-lactone **3** as a colourless oil: R_f 0.36 (4:1 hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (m, 5H, Ph—**H**), 5.53 (br s, 1H, 3-**H**), 5.04 (s, 1H, 13-**H**), 5.02 (s, 1H, 13-**H**), 4.57 (s, 2H, 1'-**H**), 4.30 (d, *J* = 12.5 Hz, 1H, 11-**H**), 4.21 (d, *J* = 12.5 Hz, 1H, 11-**H**), 3.74 (s, 2H, 12-**H**), 2.81 (d, *J* = 14.3 Hz, 1H, 8-**H**), 2.62 (d, *J* = 14.3 Hz, 1H, 8-**H**), 2.63–2.53 (m, 1H, 6-**H**), 2.46 (ddd, *J* = 15.3, 7.7, 2.8 Hz, 1H, 2-**H**), 2.31–2.19 (m, 1H, 6-**H**), 2.17–2.05 (m, 1H, 1-**H**), 2.07–1.92 (m, 1H, 2-**H**), 1.86–1.77 (m, 1H, 7-**H**), 1.60–1.47 (m, 1H, 7-**H**), 1.11 (d, *J* = 7.0 Hz, 3H, 10-**H**); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 174.3 (9-**C**), 147.2 (3a-C), 146.2 (5-C), 137.8 (2’-**C**), 128.5 (4’-**C** and 6’-**C**), 127.9 (3’-**C** and 7’-**C**), 127.8 (5’-**C**), 123.8 (3-**C**), 112.1 (13-**C**), 73.8 (1’-**C**), 72.5 (12-**C**), 71.8 (11-**C**), 48.8 (4-**C**), 48.2 (7a-**C**), 45.6 (1-**C**), 39.4 (2-**C**), 38.7 (7-**C**), 38.5 (8-**C**), 30.6 (6-**C**), 15.2 (10-**C**); IR(film) 1734, 1638, 1452, 1185, 1095 cm^{-1}; HRMS Calcd for $C_{22}H_{26}O_3$ [M$^+$]: 338.1882. Found: 338.1909.

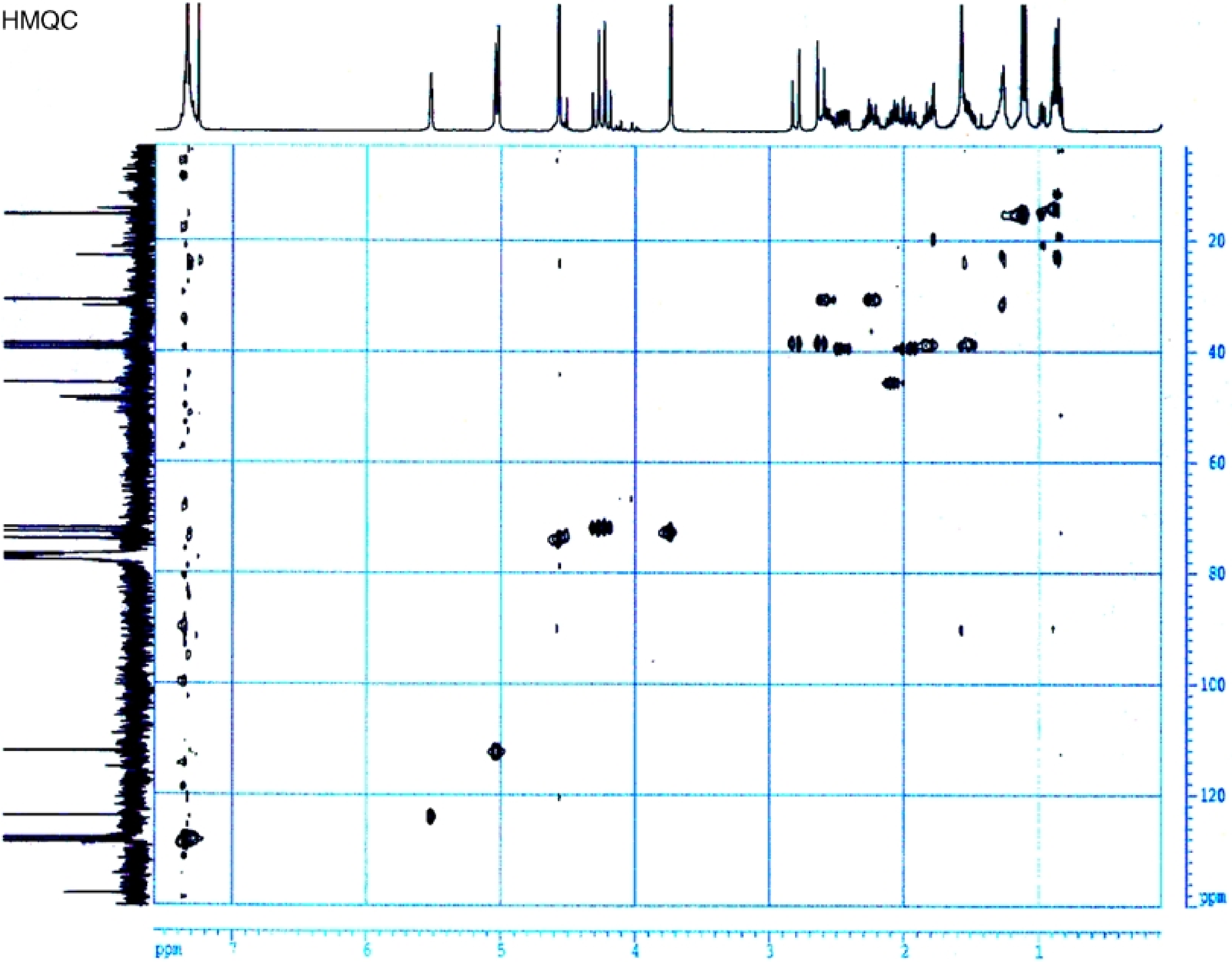
COSY90



NOESY



HMQC



HMBC