Supplementary Information for:

The domino intramolecular Diels-Alder approach to 16-oxasteroids

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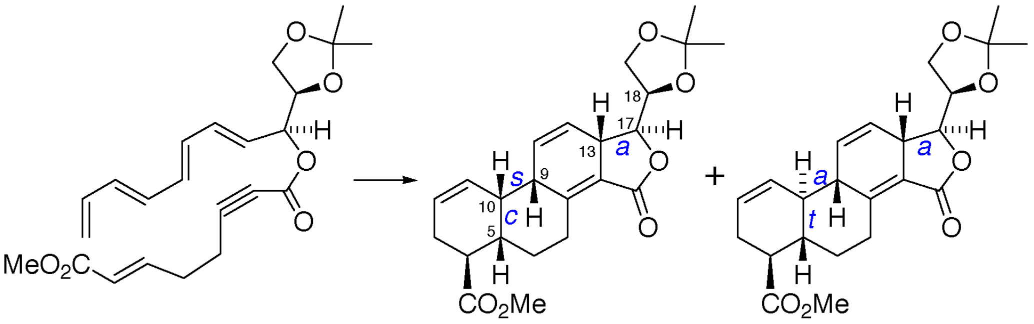
General Experimental Details

NMR spectra were recorded at 300K using a Bruker DPX/DRX 400MHz spectrometer. Residual benzene (δ 7.15) and chloroform (δ 7.26) were used as internal references for ^{1}H NMR spectra measured in these solvents. Residual benzene (δ 128.1) and chloroform (δ 77.1) were used as internal references for ^{13}C NMR spectra. Assignment of proton signals was assisted by ^{1}H–^{1}H COSY, tppi COSY, 1D-nOe and NOESY experiments when necessary; assignment of carbon signals was assisted by DEPT experiments. IR spectra were recorded on a Perkin-Elmer 1600 F.T.I.R. spectrometer as thin films on NaCl plates or as KBr pellets for solid products. Mass spectra were recorded by the Mass Spectrometer Facility of the Research School of Chemistry, Australian National University, Canberra. Optical rotations were measured with an Optical Activity Polaar 2001 optical polarimeter. Microanalyses were performed at the Campbell Microanalytical Laboratory at the Department of Chemistry, University of Otago, New Zealand. Melting points were measured on a Reichert melting point stage and are uncorrected. HPLC was performed using a Waters 510EF chromatograph pump and Waters U6K injector monitored by an ISCO 226 UV spectrophotometer at λ = 254 nm and a Waters R403 refractive index detector. Reactions were conducted under a positive pressure of dry argon or nitrogen in flame-dried glassware, protected from light with aluminium foil. Diethyl ether, toluene and THF were dried over sodium wire and distilled from sodium benzophenone ketyl. Dichloromethane was distilled from calcium hydride. Chlorobenzene was purified by the methods of Perrin and Armarego (D. D. Perrin and W. L. F. Armarego, *Purification of Laboratory Chemicals*, Pergamon Press, Oxford, 1988, 3rd edition). Commercially available chemicals were purified by standard procedures or used as purchased. Analytical TLC was performed with Merck silica gel plates, precoated with silica gel 60 F254 (0.2 mm). Flash chromatography employed Merck Kiesegel 60 (230–400 mesh) silica gel.

Experimental Procedures and Product Characterisation Data

Domino IMDA reaction of 7



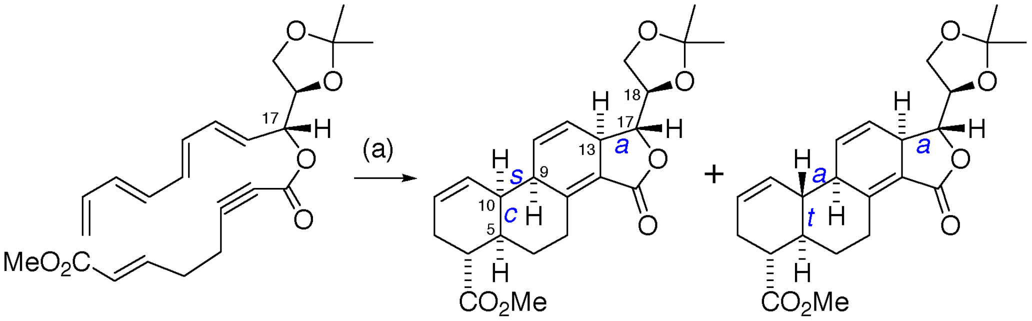
7 **8** **9**

To a stirred solution of **7** (70.0 mg, 0.176 mmol) in chlorobenzene (35 mL) at RT under Ar was added 2,6-di-*tert*-butyl-4-methylphenol (4.6 mg, 20.9 μmol). The solution was warmed to reflux and heating was continued for 45 mins. The solvent was removed under reduced pressure to give the crude product as a yellow oil, found by NMR to contain a mixture of two adducts (**8**:**9** = 61:39). Subjecting the crude material to HPLC gave the two diastereoisomeric adducts **8** and **9** (59.5 mg, 0.150 mmol, 85%).

Tetracycle 8 Colourless oil: t_R = 9.5 mins hexane–ethyl acetate (4:1); R_f = 0.51 hexane–ethyl acetate (1:1); $[\alpha]_D^{26°}$ = –89.4°, (c = 2.33 CH_2Cl_2); ^{1}H NMR (300 MHz, d_6-benzene) δ 5.95 (1H, ddd, *J* = 9.9, 2.4, 2.4 Hz), 5.70 (1H, ddd, *J* = 10.0, 2.4, 2.4 Hz), 5.58–5.75 (1H, m), 5.50 (1H, dddd, *J* = 10.0, 2.2, 2,0, 2.0 Hz), 4.27 (1H, br. d, *J* = 16.0 Hz), 3.75–3.85 (3H, m), 3.56 (1H, dd, *J* = 9.7, 7.6 Hz), 2.85–2.96 (1H, m), 2.35–2.48 (1H, m [partially obscured]), 2.30 (1H, td, *J* = 10.0, 4.5 Hz), 2.00–2.20 (2H, m), 1.71–1.87 (1H, m), 1.52–1.71 (3H, m), 1.31 (3H, s), 1.20 (3H, s) and 0.86–1.01 (1H, m) ppm; ^{13}C NMR (75 MHz, d_6-benzene) δ 175.5, 167.6, 150.3, 128.2 [2 coincident resonances], 127.4, 125.1, 121.0, 110.2, 81.3, 78.7, 67.9, 51.4, 46.6, 46.4, 43.6, 42.6, 41.3, 29.9, 29.6, 27.5, 27.2 and 25.6 ppm; IR (thin film) ν_{max} 2923, 1750, 1721, 1678, 1258, 1066, 844 cm^{-1}; MS (70 eV, EI): *m/z* (%): 400 (3) $[M]^+$, 398 (34), 385 (45), 286 (22), 101 (100); elemental analysis calc (%) for $C_{23}H_{28}O_6$: C 68.98, H 7.05; found: C 69.28, H 7.32.

Tetracycle 9 White solid: m.p. 160–162 °C (hexane–*tert*butylmethylether); t_R = 8.5 mins hexane–ethyl acetate (4:1); R_f = 0.54 hexane–ethyl acetate (1:1); $[\alpha]_D^{27°}$ = –123.4°, (c = 2.65 CH_2Cl_2); ^{1}H NMR (300 MHz, d_6-benzene) δ 5.95 (1H, ddd, *J* = 10.1, 2.2, 2.2 Hz), 4.7–5.7 (2H, m), 5.15 (1H, ddd, *J* = 10.1, 2.5, 2.5), 4.09 (1H, ddd, *J* = 14.3, 3.7, 3.7 Hz), 3.68–3.84 (3H, m), 3.54 (1H, dd, *J* = 9.8, 7.4 Hz), 3.37 (3H, s), 2.90–3.01 (1H, m), 2.53–2.66 (2H, m), 2.37–2.47 (1H, m), 2.19–2.32 (2H, m), 1.80 (1H, dd, *J* = 7.2, 4.1 Hz), 1.21–1.35 (1H, m [partially obscured]), 1.26 (3H, s), 1.18 (3H, s) and 1.04–1.12 (1H, m) ppm; ^{13}C NMR (75 MHz, d_6-benzene) δ 174.9, 167.3, 148.6, 130.4, 127.0, 125.5, 124.3, 120.6, 110.2, 81.6, 78.6, 67.9, 51.7, 44.0, 43.5, 42.0, 37.6, 36.1, 27.1, 27.0, 26.2, 25.6 and 23.9 ppm; IR (KBr disc) ν_{max} 2923, 1755, 1727, 1633, 1244, 1065, 844 cm^{-1}; MS (70 eV, EI): *m/z* (%): 400 (20) $[M]^+$, 398 (45), 385 (55), 286 (17), 101 (100); elemental analysis calc (%) for $C_{23}H_{28}O_6$: C 68.98, H 7.05; found: C 68.77, H 6.85.

Domino IMDA reaction of 10



10 **11** **12**

To a stirred solution of **10** (82.0 mg, 0.206 mmol) in chlorobenzene (40 mL) at RT under Ar was added 2,6-di-*tert*-butyl-4-methylphenol (5.0 mg, 22.7 μmol). The solution was warmed to reflux and heating was continued for 45 mins. The solvent was removed under reduced pressure to give the crude product as a pale yellow oil, found by NMR to contain a mixture of two adducts (**11**:**12** 57:43). Subjecting the crude material to HPLC gave the two diastereoisomeric adducts **11** and **12** (71.3 mg, 0.179 mmol, 87%).

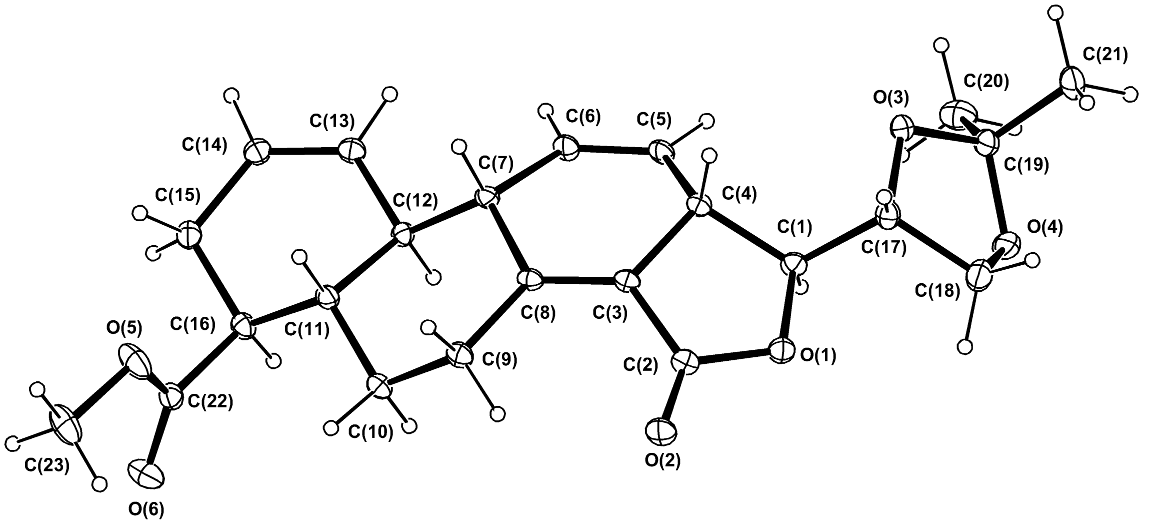
Tetracycle 11 White solid: m.p. 163–165 °C; t_R = 11.5 mins hexane–ethyl acetate (4:1); R_f = 0.49 hexane–ethyl acetate (1:1); $[\alpha]_D^{24°} = -69.6$ (c = 1.25 CH_2Cl_2); ^{1}H NMR (300 MHz, d_6-benzene) δ 5.66 (1H, ddd, J = 10.0, 2.4, 2.4 Hz), 5.8–5.63 (1H, m [partially obscured]), 5.48–5.55 (2H, m), 4.28 (1H, br. d, J = 16.5 Hz), 3.95 (1H, ddd, J = 6.7, 3.3 Hz), 3.80 (1H, dd, J = 8.5, 6.5 Hz), 3.66 (1H, dd, J = 8.5, 6.9 Hz), 3.60 (1H, dd, J = 9.9, 3.3 Hz), 3.34 (3H, s), 3.14–3.25 (1H, m), 2.35–2.50 (1H, m), 2.29 (1H, ddd, J = 10.2, 10.2, 4.8 Hz), 2.20–2.13 (2H, m), 1.70–1.86 (1H, m), 1.53–1.70 (3H, m), 1.42 (3H, s), 1.27 (3H, s) and 0.83–0.98 (1H, m) ppm; ^{13}C NMR (75 MHz, d_6-benzene) δ 174.5, 166.9, 147.4, 130.4, 126.6, 125.2, 122.5, 120.6, 110.0, 79.7, 74.5, 65.2, 51.3, 43.1, 41.6, 39.8, 37.2, 35.7, 26.6, 26.2, 25.8, 25.6 and 23.5 ppm; IR (KBr disc) ν_{max} 2964, 2663, 1752, 1714, 1201, 1049, 860, 666 cm^{-1}; MS (70 eV, EI): *m/z* (%): 400 (5) $[M]^+$, 398 (21), 385 (74), 286 (32), 101 (100); elemental analysis calc (%) for $C_{23}H_{28}O_6$: C 68.98, H 7.05; found: C 68.72, H 7.09.

Tetracycle 12 Colourless oil: t_R = 10.0 mins hexane–ethyl acetate (4:1); R_f = 0.51 hexane–ethyl acetate (1:1); $[\alpha]_D^{24°} = -98.2$ (c = 0.95 CH_2Cl_2); ^{1}H NMR (300 MHz, d_6-benzene) δ 5.51–5.59 (1H, m), 5.45–5.50 (1H, m [partially obscured]), 5.44 (1H, ddd, J = 10.0, 2.6 Hz), 5.12 (1H, ddd, J = 10.0, 10.0, 2.6 Hz), 4.08 (1H, ddd, J = 15.1, 3.9, 2.9 Hz), 3.88 (1H, ddd, J = 6.8, 6.8, 3.2 Hz, 3.77 (1H, dd, J = 8.3, 6.8 Hz), 3.66 (1H, dd, J = 8.3, 6.9 Hz), 3.49 (1H, dd, J = 10.3, 3.1 Hz), 3.38 (3H, s), 3.18–3.30 (1H, m), 2.38–2.65 (3H, m), 2.20–2.31 (2H, m), 1.65–1.85 (2H, m), 1.37 (3H, s), 1.20–1.35 (1H, m), 1.21 (3H, s) and 1.02–1.12 (1H, m) ppm; ^{13}C NMR (75 MHz, d_6-benzene) δ 174.9, 167.3, 147.8, 130.8, 127.0, 125.6, 122.9, 121.0, 110.4, 80.1, 74.9, 65.6, 51.7, 43.5, 42.0, 40.2, 37.6, 36.1, 26.9, 26.6, 26.2, 26.0 and 23.9 ppm; IR (thin film) ν_{max} 2985, 2923, 1752, 1710, 1202, 1072, 860, 655 cm^{-1}; MS (70 eV, EI): *m/z* (%): 400 (12) $[M]^+$, 398 (29), 385 (66), 286 (25), 101 (100); elemental analysis calc (%) for $C_{23}H_{28}O_6$: C 68.98, H 7.05; found: C 69.33, H 7.21.

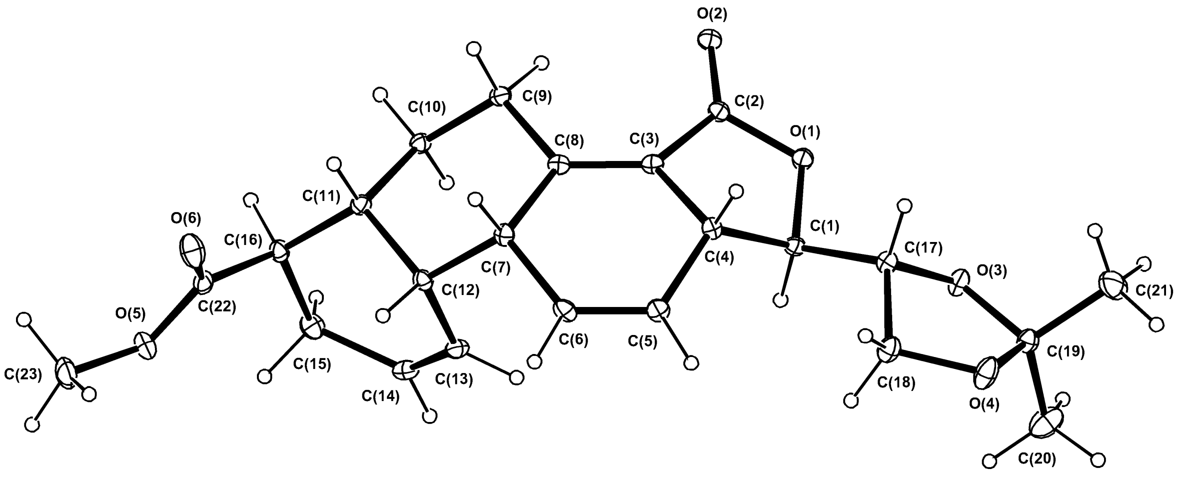
Proof of Stereochemistry of the Four Domino IMDA Products

Single crystal X-ray analyses were carried out on adducts **9** (minor isomer from glucose series) and **11** (major isomer from galactose series). ORTEP diagrams are provided below – full details will be published elsewhere. Remarkably close similarities can be seen between the ^{1}H NMR spectra of the major and minor cycloadducts from the two series, allowing the stereochemistries of the two non-crystalline adducts to be assigned with some certainty. The regions containing resonances due to aliphatic protons of the AB-ring system (δ 0.8–2.7 ppm) are expanded on the following two pages.

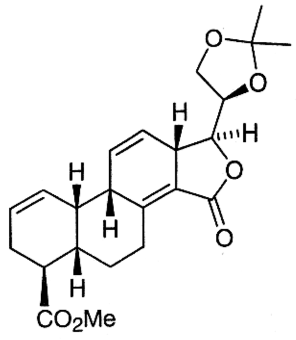
ORTEP diagram of ***9:***



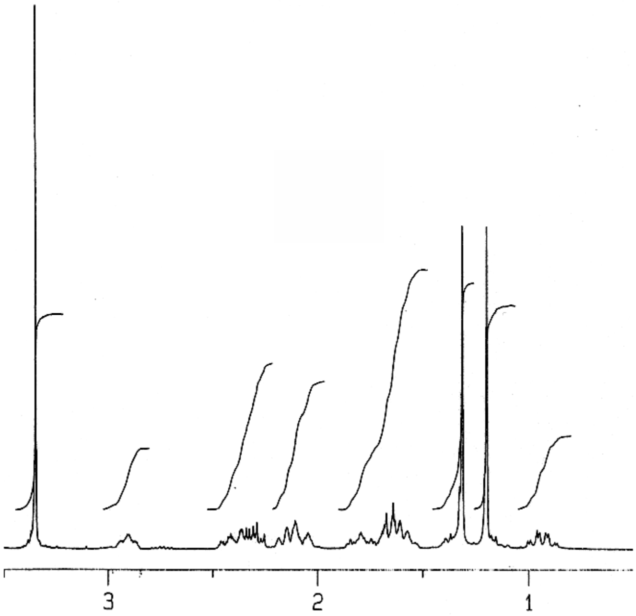
ORTEP diagram of ***11:***

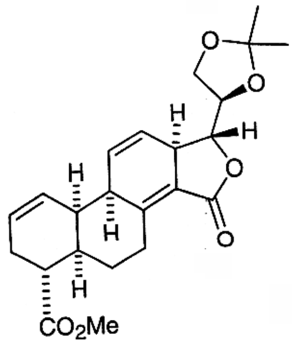


Major Adducts

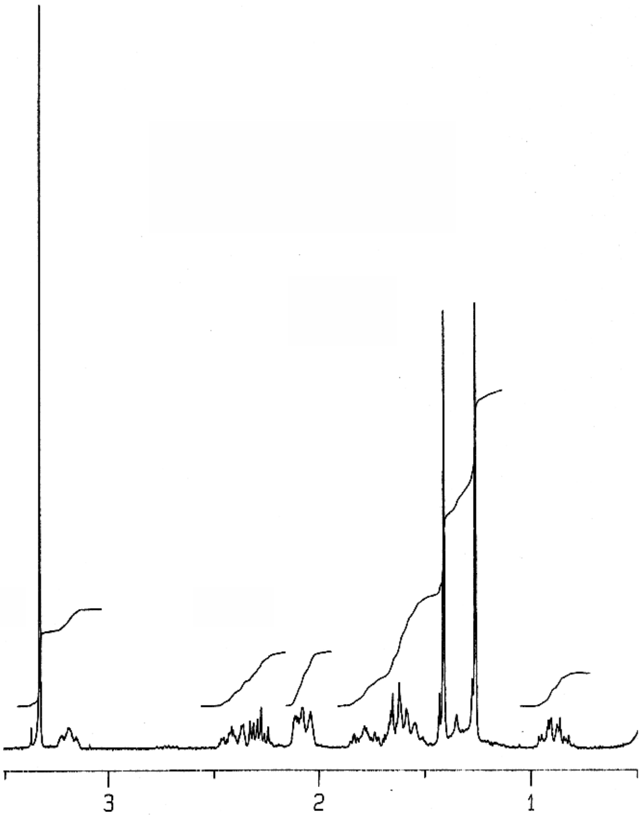


(8)
300 MHz, d_6-benzene

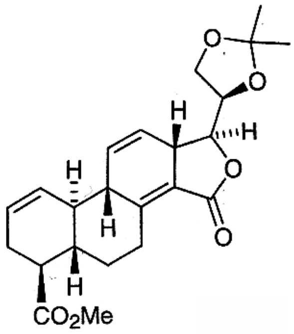




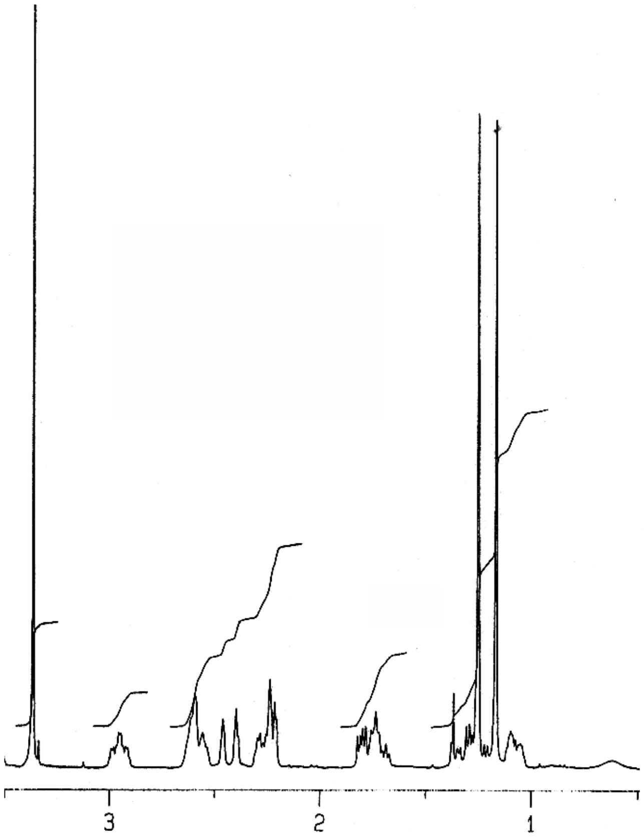
(11)
300 MHz, d_6-benzene



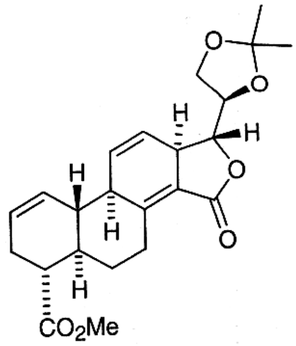
Minor Adducts



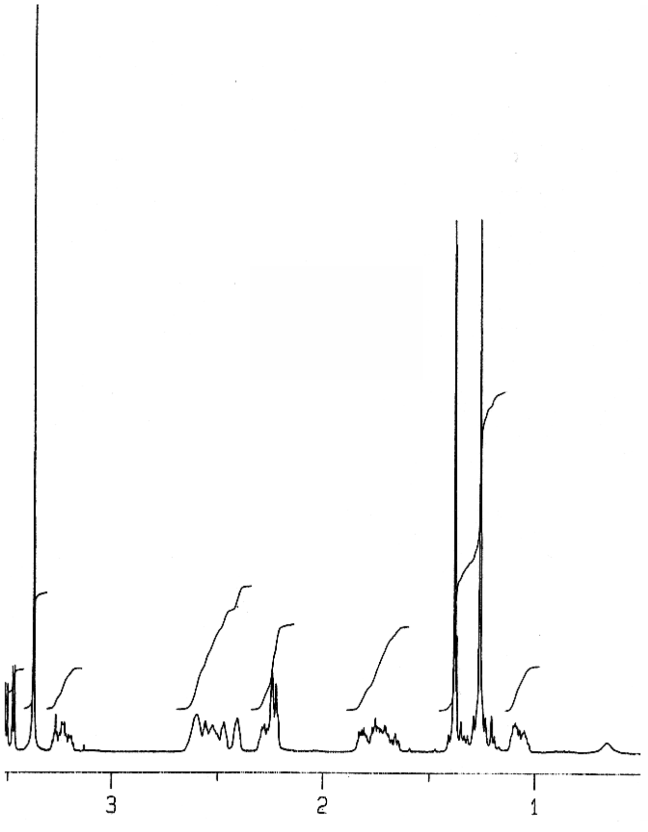
(9)



300 MHz, d_6-benzene



(12)



300 MHz, d_6-benzene