

Microwave-assisted Mild Conversion of Natural Dihydrotagetone into 5-Isobutyl-3-methyl-4,5-dihydro-2(3H)-furanone, an Analogue of Whisky Lactone*

Arun K Sinha,* Bhupendra P. Joshi, Anuj Sharma, Vinod Kumar and Ruchi Acharya

Supporting Information

S 2 - S 5	-----	General Experimental Details
S 6	-----	H ¹ NMR Spectra of 4/Scheme 2
S 7	-----	C ¹³ NMR Spectra of 4/ Scheme 2
S 8	-----	GC of 4/ Scheme 2
S 9	-----	H ¹ NMR Spectra of 3/Scheme 2
S 10	-----	C ¹³ NMR Spectra of 3/Scheme 2
S 11	-----	GC of 3/Scheme 2
S 12	-----	HRMSMS of 3/Scheme 2
S 13	-----	H ¹ NMR Spectra of 1/Scheme 2
S 14	-----	C ¹³ NMR Spectra of 1/Scheme 2
S 15	-----	GC of 1/Scheme 2
S 16	-----	GCMS [Peak 1] of 1/Scheme 2
S 17	-----	GCMS [Peak 2] of 1/Scheme 2
S 18	-----	HMQC of 1/Scheme 2
S 19	-----	HMBC of 1/Scheme 2
S 20	-----	HREIMS of 1/Scheme 2

General

^1H (300 MHz) and ^{13}C (75.4 MHz) NMR spectra were recorded in CDCl_3 on a Bruker Avance-300 spectrometer. CEM Discover[®] focused microwave (2450 MHz, 300 W) was used wherever mentioned. GCMS was determined using a Shimadzu-2010 spectrometer. Optical rotations¹⁶ were measured on a Horiba SEPA 300 polarimeter. Tagetes oil was obtained from hydrodistillation of whole plant of *T. minuta*^{12,13} in Clevenger apparatus.

Method for purification of Dihydrotagetone from *T. minuta* oil

Tagetes oil, upon purification on silica gel column with an increasing polarity of eluent (hexane:ethyl acetate:: 100:0 to 95:5) provided, dihydrotagetone (**4**) (50 to 60% w/w) as a colourless liquid; specific rotation in chloroform $[\alpha]_{\text{D}}^{18} = +7.5$; $R_f = 0.68$ (2.5% ethyl acetate in hexane); IR (film) λ_{max} 2992, 1715, 1463, 1367, 913 cm^{-1} ; ^1H NMR (CDCl_3) δ 5.64-5.58 (m, 1H, 2-CH), 4.91-4.80 (m, 2H, 1- CH_2), 2.64-2.60 (m, 1H, 3-CH), 2.30 (d, $J = 6.46$ Hz, 2H, 4- CH_2), 2.17 (d, $J = 6.86$ Hz, 2H, 6- CH_2), 2.07-2.00 (m, 1H, 7-CH), 0.91 (d, 3H, $J = 6.46$ Hz, 10- CH_3), 0.81 (d, 6H, $J = 6.86$ Hz, 8- CH_3 and 9- CH_3); ^{13}C NMR (CDCl_3) δ 209.8 (C-4), 142.9 (C-2), 112.9 (C-1), 52.4 (C-7), 49.8 (C-3), 33.1 (C-4), 24.4 (C-6), 22.5 (C-8 and C-9) and 19.7 (C-10); EIMS m/z 154 $[\text{M}]^+$ (1.8), 139 (1.7), 112 (1.4), 97 (31.8), 56 (14.7), 42 (12.8), 85 (84.1), 57 (100%), 58 (65.4). The spectral data was found matching with the literature.¹⁷

Method for the synthesis of 2,6-dimethyl-4-oxo-heptanoic acid (3) under Microwave

A mixture of dihydrotagetone (**4**) (3.53 g, 22.92 mmole), sodium bicarbonate (1.8 g, 21.43 mmole), sodium metaperiodate (22.84 g, 106.78 mmole), potassium permanganate (0.65 g, 4.11 mmole), alumina (0.8-1.2 g) and tert-butanol-water (20 mL, 1:3) was taken in a 100 ml round bottom flask. The flask was shaken well for a while and

then placed inside a microwave oven (CEM[®] Organic Synthesizer) and irradiated for 30 minutes at 180° C, 200W. After completion of the reaction (monitored by TLC), the contents of the flask were poured into saturated solution of sodium bisulphite so as to destroy excess permanganate, the resulting mixture was filtered and residue washed with aqueous acetone (40 mL x 3, 3:1). The filtrate and washings were combined and the solution concentrated under reduced pressure to remove organic solvent. The mixture was cooled to 5 °C and acidified with dilute acid and then extracted with ethyl acetate (3 x 25 mL). The ethyl acetate layers were then combined, washed with saturated sodium chloride (3 x 15 mL), dried over anhydrous sodium sulphate and then filtered. Ethyl acetate layer was removed under vacuum to obtain a crude product which was purified on silica column (hexane:ethyl acetate:: 100:0 to 95:5 as an eluent) to afford 2,6-dimethyl-4-oxo-heptanoic acid (**3**) in 81% as a viscous liquid. Specific rotation of (**3**) in chloroform $[\alpha]_D^{18} = -10.5$; $R_f = 0.69$ (toluene:ethylacetate:methanol:: 6.5:3.4:0.1 mL); IR (film) λ_{\max} 2958, 1709, 1465, 1376, 937 cm^{-1} ; $^1\text{H NMR}$ δ 8.37 (br, 1H, COOH), 2.86-2.82 (m, 1H, 2-CH), 2.39 (d, 2H, $J=6.46$ Hz, 3-CH₂), 2.19 (d, 2H, $J=6.06$ Hz, 5-CH₂), 2.07-2.00 (m, 1H, 6-CH), 1.11 (d, 3H, $J=7.27$ Hz, 9-CH₃), 0.81 (d, 6H, $J=6.86$ Hz, 7-CH₃ and 8-CH₃); $^{13}\text{C NMR}$ 208.9 (C=O, C-4), 181.6 (COOH, C-1), 51.8 (C-2), 46.0 (C-6), 34.4 (C-3), 24.6 (C-5), 22.4 (C-7 and C-8), 16.8 (C-9). Methylation of acid **3** provided corresponding volatile methyl 2,6-dimethyl-4-oxo-heptanoate;^{6a} EIMS of methyl ester of **3** m/z 186 $[\text{M}]^+$ (1.8), 171 (1.1), 155 (19.1), 144 (31.4), 129 (43.5), 112 (25.0), 101 (23.4), 85 (77.4), 58 (74.4), 57 (100%), 41 (80.0).

Method for the synthesis of 2,6-dimethyl-4-oxo-heptanoic acid (3)(conventional)

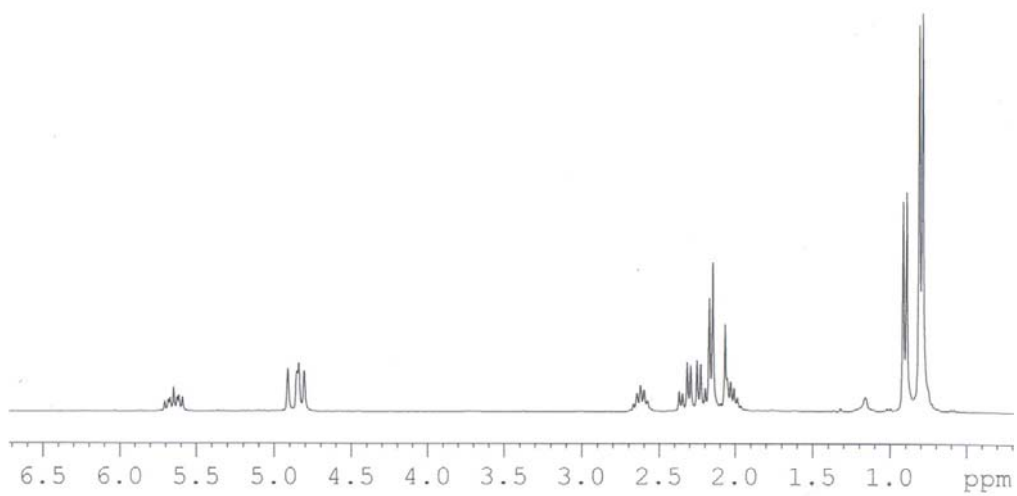
A mixture of dihydrotagetone (**4**) (3.53 g, 22.92 mmole), sodium bicarbonate (1.8 g, 21.43 mmole), sodium metaperiodate (22.84 g, 106.78 mmole), potassium permanganate (0.65 g, 4.11 mmole), alumina (0.8-1.2 g) and tert-butanol-water (50 mL, 1:3) were taken in a 100 ml round bottom flask. The flask was shaken well for a while and then refluxed on heating mantle for 16 h (conventional heating). After completion of the reaction (monitored by TLC), the reaction mixture was worked up and purified by the above mentioned procedure and the product 2,6-dimethyl-4-oxo-heptanoic acid (**3**) was obtained in 68% yield as a viscous liquid.

Synthesis of 5-isobutyl-3-methyl-4,5-dihydro-2(3H)-furanone (1).

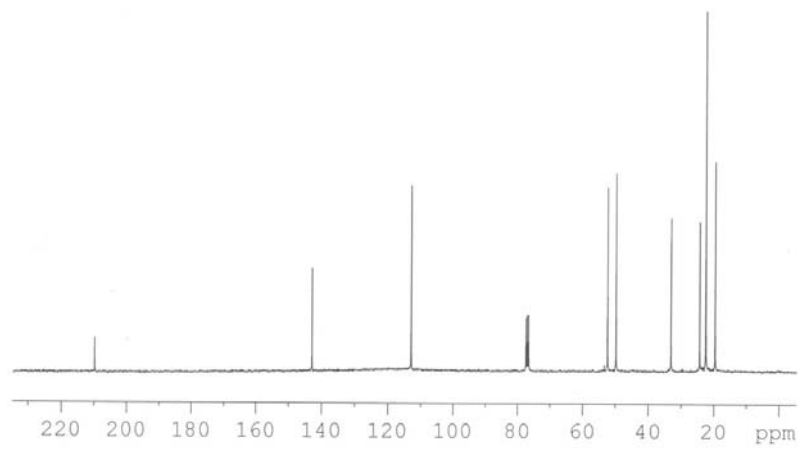
Sodium borohydride (0.6 g) was added drop wise to a ice cold solution of 2,6-dimethyl-4-oxo-heptanoic acid (**3**) (1.0 g) in 2N-sodium hydroxide (1.5 mL) and methanol (20 mL). The reaction mixture was stirred at room temperature for 2 hr and after completion of reaction the mixture was cooled to 5 °C, acidified with dilute hydrochloric acid (0.5N) followed by stirring for 5 min and then extracted with ether (3 x 50 mL). The combined extracts were washed with brine, dried (anhydrous Na₂SO₄) and then concentrated to obtain a crude liquid which was purified on silica column (hexane:ethyl acetate:: 100:0 to 95:5 as an eluent) to afford a diastereomeric mixture of 5-Isobutyl-3-methyl-4,5-dihydro-2(3H)-furanone (**1**) as a colourless oil with coconut flavour in 76% yield. Specific rotation in chloroform $[\alpha]_D^{18} = -1.5$; $R_f = 0.80$ (10% ethylacetate in hexane); IR (film) λ_{max} 2962, 1772, 1558, 1457, 1362, 1173, 1135, 1004, 1024, 926 cm⁻¹; ¹H NMR δ 4.47-4.43 (m, 0.43H, cis-5-CH), 4.32-4.29 (m, 0.57H, trans-5-CH), 2.58-2.52 and 2.41-2.37 (2m, 1H, 3-CH), 1.97-1.91 (m, 1H, 7-CH), 1.70-1.68 and 1.56-1.49 (2m, 2H, 4-CH₂),

1.38-1.32 and 1.29-1.25 (2m, 2H, 6-CH₂), 1.16 and 1.12 (2d, $J=6.86$ Hz, 3H, 10-CH₃), 0.83 (d, 6H, $J=6.46$ Hz, 8-CH₃ & 9-CH₃); ¹³C NMR δ 180.1 and 179.4 (C-2), 76.8 and 76.6 (C-5), 44.6 and 44.4 (C-3), 37.8 (C-4), 35.8 (C-6), 22.8 (C-7), 22.8 and 22.1 (C-8 and C-9), 15.7 and 15.0 (C-10); EIMS m/z 156 [M]⁺ (1.3), 99 (100%), 84 (5.4), 71 (28.5), 56 (14.7), 42 (12.8). On the basis of above spectral data and comparing it with reported literature,⁶ the liquid was identified as **1**.

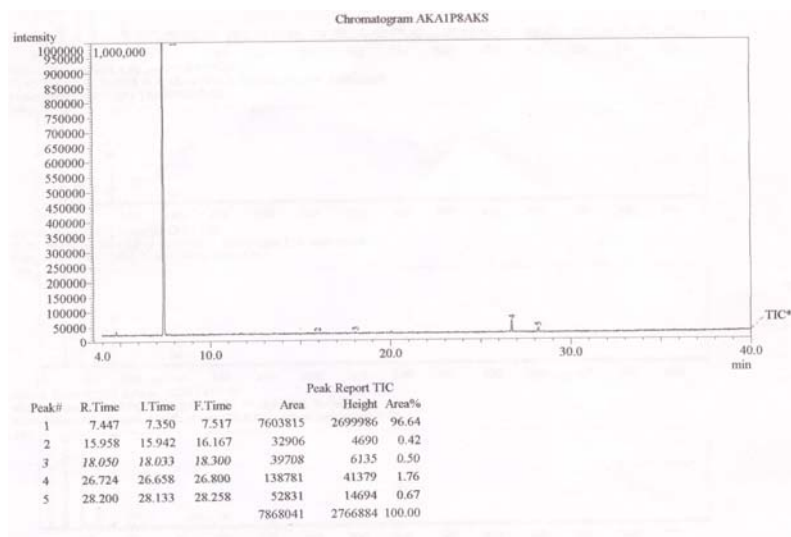
H^1 NMR Spectra of 4/Scheme 2



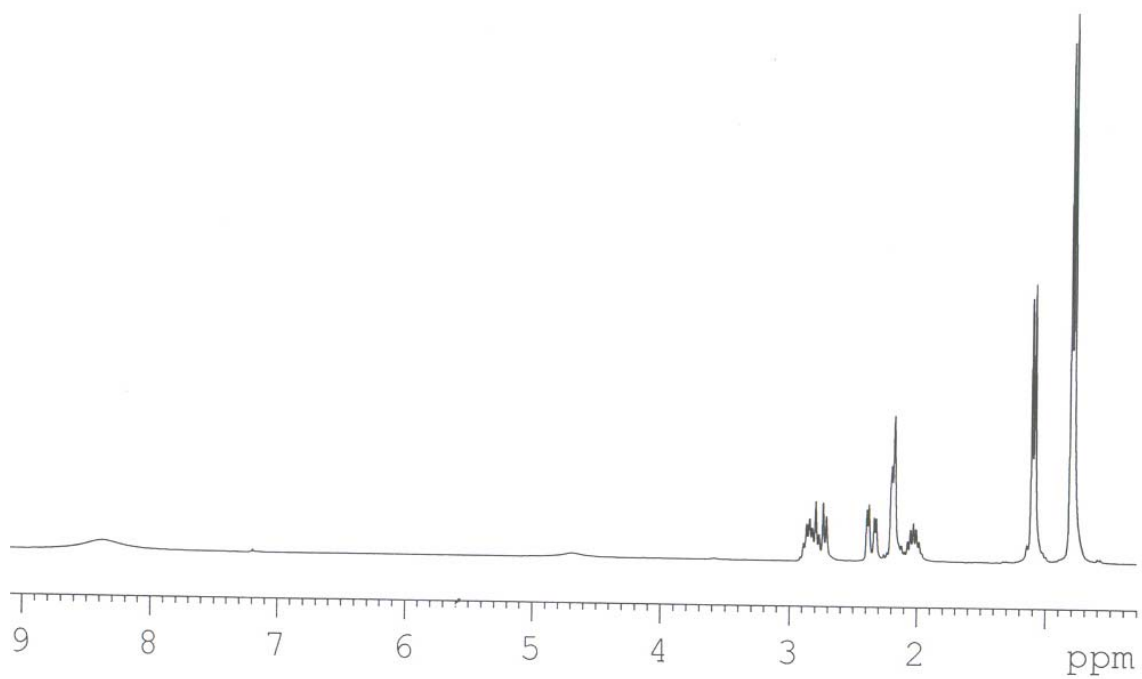
C^{13} NMR Spectra of 4/Scheme 2



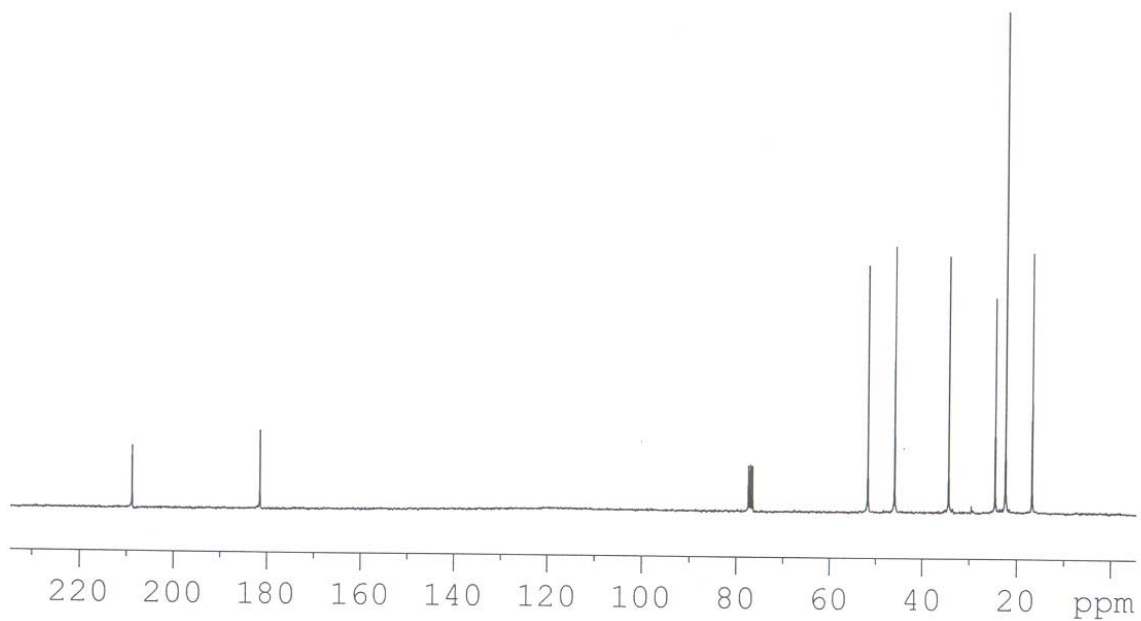
GC of 4/ Scheme 2



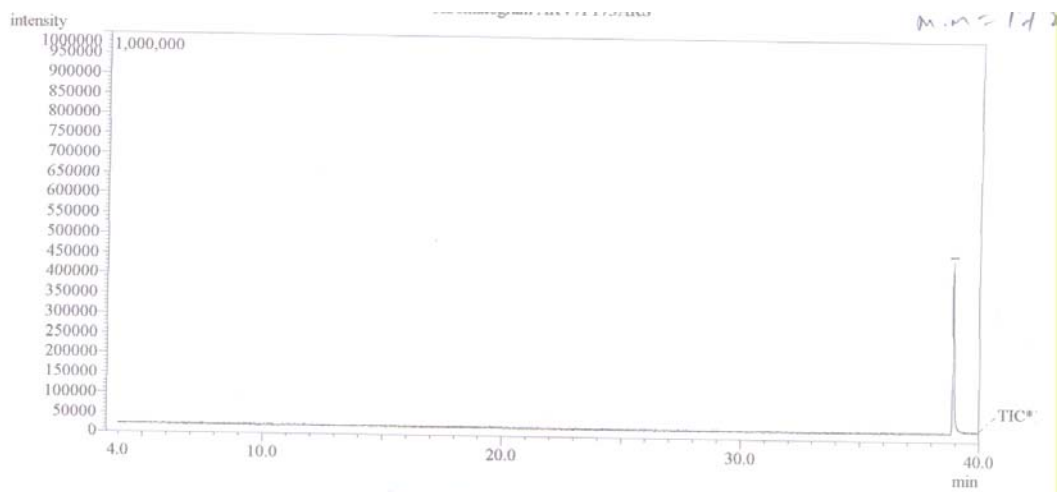
H^1 NMR Spectra of 3/Scheme 2



**C¹³ NMR Spectra
3/Scheme 2**



GC of 3/Scheme 2



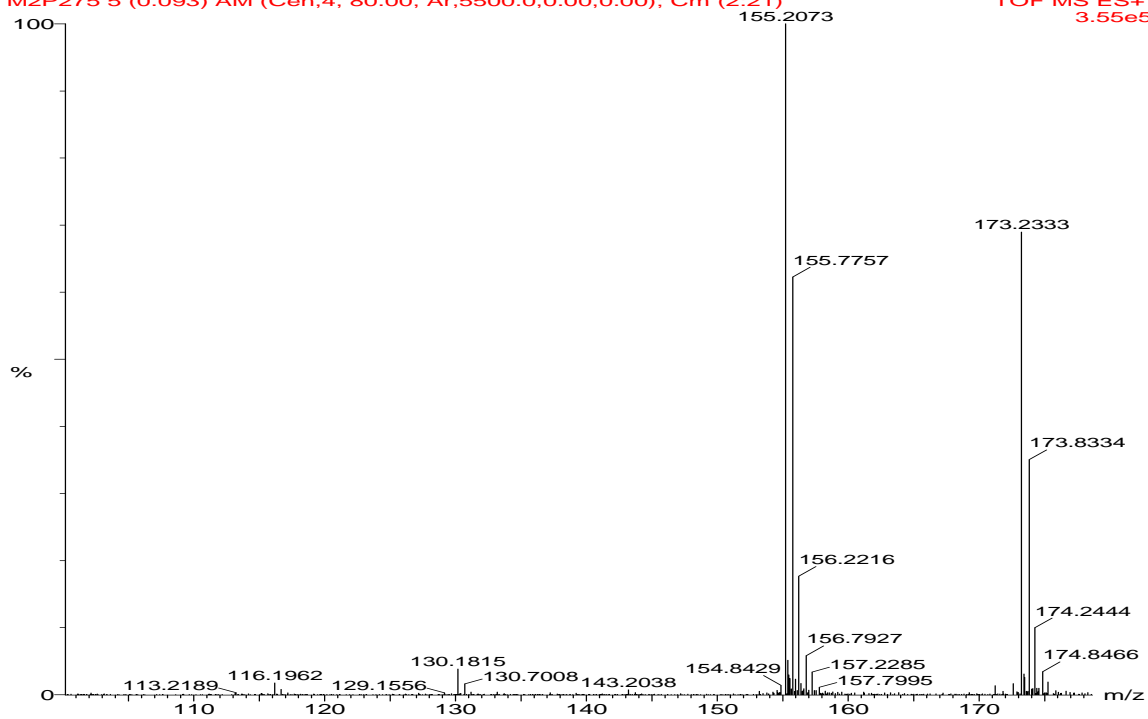
Peak Report TIC						
Peak#	R.Time	I.Time	F.Time	Area	Height	Area%
1	38.921	38.842	39.092	1790098	425042	100.00
				1790098	425042	100.00

HREIMS of 3/Scheme 2

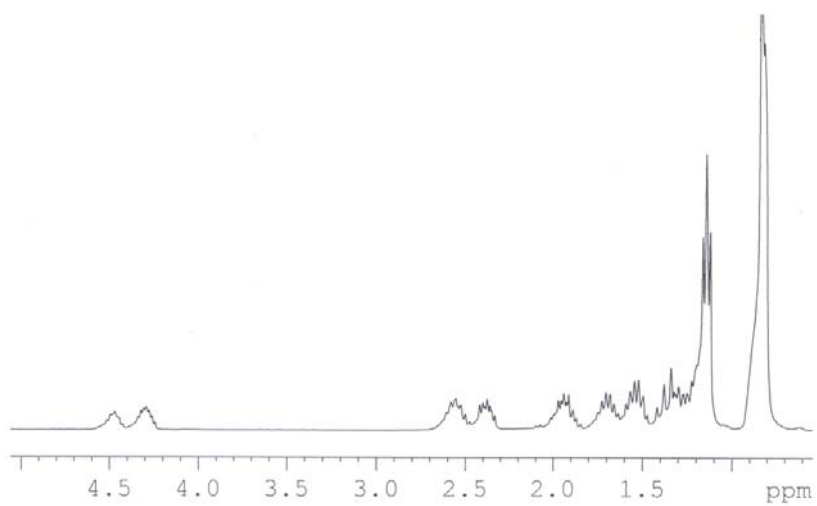
22-Nov-200604:15:12

M2P275 5 (0.093) AM (Cen,4, 80.00, Ar,5500.0,0.00,0.00); Cm (2:21)

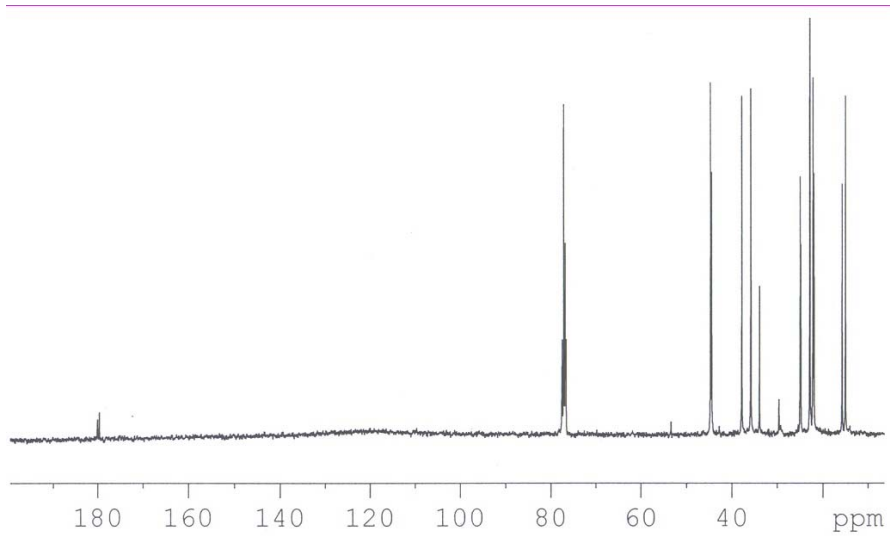
TOF MS ES+
3.55e5



H^1 NMR Spectra of 1/Scheme 2



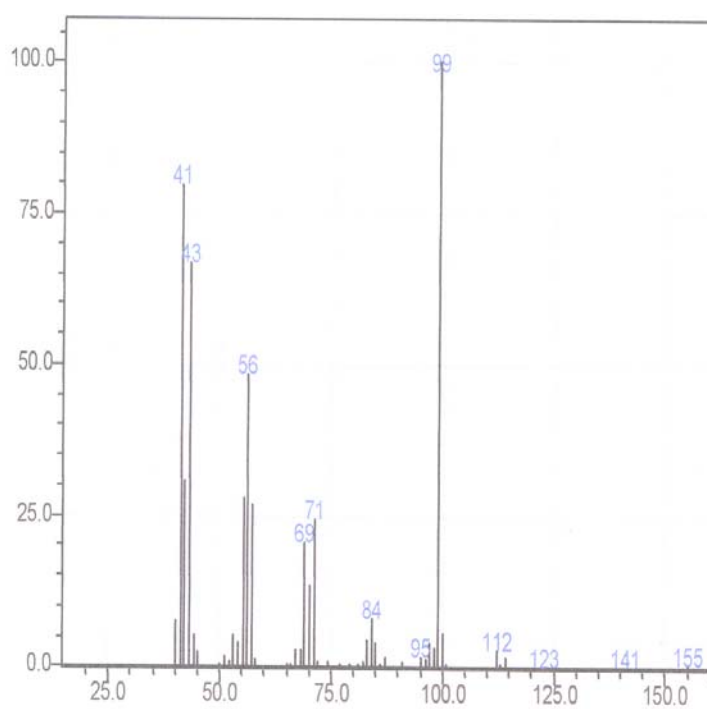
C^{13} NMR Spectra of 1/Scheme 2



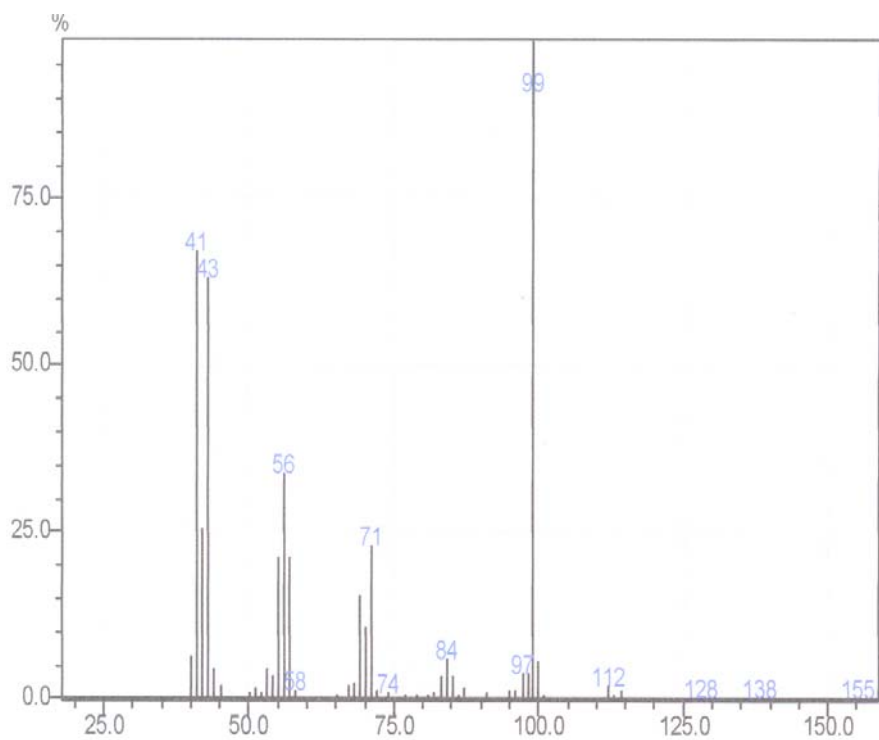
GC of 1/Scheme 2



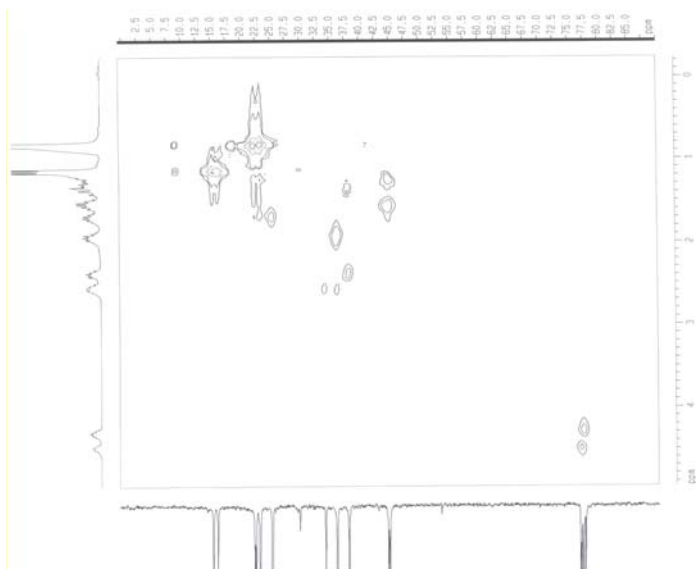
GCMS [Peak 1] of 1/Scheme 2



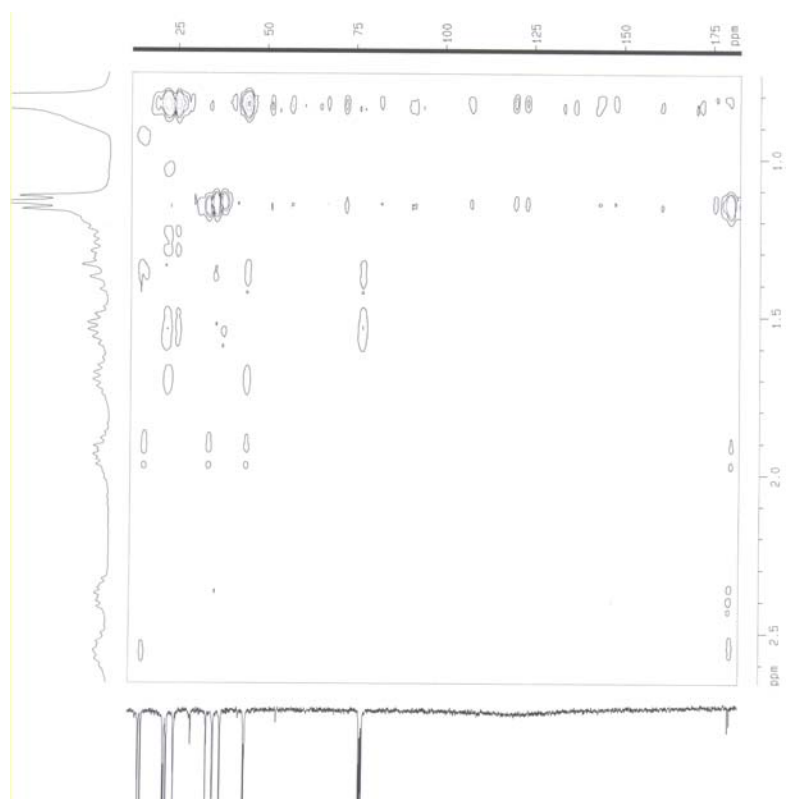
GCMS [Peak 2] of 1/Scheme 2



HMQC of 1/Scheme 2



HMBC of 1/Scheme 2



HREIMS of 1/Scheme 2

