

Supplementary Material

Enantioselective Synthesis of Herbertane Sesquiterpenes

Synthesis of (-)-Herbertene and (-)- α -Herbertenol

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Supplementary Experimental Section

4-Benzyloxy-1-methyl-3-[(1*S*)-1,2,2-trimethylcyclopentyl]-2-cyclohexen-1-ol (16).

A solution of the mixture of epimeric benzylic ethers 11 (99.8 mg, 0.32 mmol) in THF (2 mL) was dropwise treated with a 1.6 M solution of MeLi (0.28 mL, 0.45 mmol) in ether at -78 °C. After stirring at the same temperature for 1 h the reaction mixture was allowed to warm up to -30 °C and then poured into a cold 1 :1 mixture of ether and 5% aqueous NH₄Cl solution. After separation of the phases the aqueous layer was extracted with ether, the combined organic phases were washed with brine, dried over Na₂SO₄ and the solvent evaporated to provide an oily residue. This was purified by column chromatography, using pentane-ether 8:2 as eluent, to afford an equimolecular mixture of chromatographically homogeneous diastereomeric alcohols 16 (70 mg, 67%) as a colorless oil: IR (film) 3590-3154, 2954, 2872, 1457, 1122, 1054, 736, 697 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.4-7.2 (10H, m, Ar), 5.65 and 5.54 (total 1 H, two s, H-2), 4.53 and 4.39 (2H, AB system, J = 11 Hz, OCH₂Ph), 3.92 and 3.89 (total 1 H, two dd, J = 3.9 Hz, H-4), 1.26 and 1.24 (total 3 H, two s, Me-1), 1.11 and 0.73 (total 3 H, two s, Me-1'), 1.04 and 0.75 (total 3 H, two s, Me-2' α), 0.97 and 0.92 (total 3 H, s, Me-2' β); MS (CI) m/z 311 (M⁺-OH), 14), 219 (18), 204 (41), 203 (100), 202 (58), 111 (34), 91 (50); HRMS calcd for C₂₂H₃₁O (M⁺-OH) 311.2375, found 311.2379.

Preparation of (-)-herbertene (3) from benzylic ethers 16. A solution of the above obtained mixture of benzyl ethers 16 (45 mg, 0.13 mmol) in CH₂Cl₂ (1 mL) was treated with camphorsulfonic acid monohydrate (34 mg, 0.13 mmol) and stirred at rt for 2 h. The solvent was evaporated *in vacuo* and the resulting oily residue was filtered through a short column of silica gel using pentane as eluent to afford herbertene (3) (23 mg, 80%) as a colorless oil, identical in all respects to that prepared from 13.

Supplementary Spectroscopic Data

(1a*S*, 5a*S*)-1a-Benzylloxymethyl-2,2,5a-trimethylperhydrobenzo[*b*]oxirene (7).

IR (film) 3068, 3036, 1491, 1469, 1372, 1088, 918, 740, 732, 696 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.4-7.2 (5 H, m, Ar), 4.53 and 4.44 (1 H each, each d, $J = 12.0$ Hz, OCH_2Ph), 3.79 and 3.39 (1 H each, each d, $J = 10.2$ Hz, CH_2O), 1.38 (3 H, s, Me-5' α), 1.15 (3 H, s, Me-2' α), 1.05 (3 H, s, Me-2' β). MS (CI) m/z 261 ($M^+ + 1, 4.5$), 260 (M^+ , 0.5), 153 (13), 135 (9), 127 (14), 109 (14), 91 (100).

2-Benzylloxy-1-[(1*S*)-1,2,2-trimethylcyclopentyl]-1-ethanone (8).

IR (film) 2952, 2873, 1709, 1459, 1375, 1133, 740, 699 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.4-7.2 (5 H, m, Ar), 4.58 (2 H, s, H-2), 4.27 and 4.21 (1 H each, each d, $J = 17.4$ Hz, OCH_2Ph), 2.30 (1H, m, H-5' α), 1.8-1.4 (m, 5H), 1.08 (3 H, s, Me-1'), 1.03 (3 H, s, Me-2' β), 0.85 (3 H, s, Me-2' α). MS (CI) m/z 261 ($M^+ + 6$), 260 (M^+ , 0.5%), 153 (51), 139 (13), 135 (22), 119 (20), 111 (100).

2-Benzylloxy-1-[(1*S*)-1,2,2-trimethylcyclopentyl]hexane-1,5-dione (10).

Less polar diastereoisomer : IR (film) 3032, 2959, 2874, 1709, 1457, 1367, 1165, 1103, 737, 698 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.4-7.2 (5 H, m, Ar), 4.49 and 4.29 (1 H each, each d, $J = 11.2$ Hz, OCH_2Ph), 4.26 (1 H, dd, $J = 7.2$ and 4.1 Hz, H-2), 2.7-2.5 (3H, m), 2.35 (1H, m), 2.09 (3 H, s, H-6), 1.14 (3 H, s, Me-1'), 1.13 (3 H, s, Me-2' β), 0.87 (3 H, s, Me-2' α); MS (CI) m/z 331 ($M^+ + 1$, 9), 330 (M^+ , 1), 224 (70), 223 (100), 205 (32), 191 (97), 177 (18), 147(29), 119 (33).

More polar diastereoisomer : IR (film) 3032, 2959, 2876, 1708, 1454, 1367, 1109, 737, 698 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.4-7.2 (5 H, m, Ar), 4.49 and 4.29 (1 H each, each d, $J = 11.2$ Hz, OCH_2Ph), 4.26 (1 H, dd, $J = 6.8$ and 4.4 Hz, H-2), 2.70-2.30 (3H, m), 2.08 (3 H, s, H-6), 1.12 (3H, s, Me-1'), 1.11 (3 H, s, Me-2' β), 0.91 (3 H, s, Me-2' α); MS (CI) m/z 331 ($M^+ + 1$, 1.2), 224 (68), 223 (100), 205 (40), 192 (42).

4-Benzylloxy-3[(1*S*)-1,2,2-trimethylcyclopentyl]-2-cyclohexen-1-one (11).

IR (film) 3060, 2954, 2875, 1673, 1610, 1459, 1343, 1257, 1195, 1063, 1032, 939, 906, 739, 699 cm^{-1} ; ^1H NMR (400 MHz CDCl_3) δ 7.4-7.2 (5 H, m, Ar), 6.02 and 5.94 (total 1 H, two s, H-2), 4.62 and 4.61 (total 1 H, overlapping d, $J = 11$ Hz, OCH_2Ph), 4.482 and 4.478 (total 1 H, overlapping d, $J = 11$ Hz, $\text{OCH}'_2\text{Ph}$), 4.25 and 4.20 (total 1 H, two br s, H-4), 2.72

(1 H, m, H-6), 2.41 (1 H, m, H-5), 2.3 (1 H, m, H'-6), 1.17 and 1.11 (total 3 H, two s, Me-1'), 1.02 and 0.96 (total 3 H, two s, Me-2'β), 0.802 and 0.799 (total 3 H, two s, Me-2'α). MS (CI) *m/z* 313 (M⁺+23), 312 (M⁺, 1), 223 (12), 106 (26), 205 (100), 204 (28), 187 (10), 111 (44).

Benzyl 4-methylene-2-[(1S)-1,2,2-trimethylcyclopentyl]-2-cyclohexeny1-ether (13).

IR (film) 3070, 3032, 2937, 2782, 1628, 1593, 1454, 1375, 1084, 1067, 926, 883, 738, 704 cm⁻¹; ¹H NMR (300 MHz CDCl₃) δ 7.4-7.2 (5H, m, Ar), 6.21 and 6.11 (total 1 H, two s, H-3), 4.83 (2 H, m, =CH₂), 4.58 (1 H, d, *J* = 10.9 Hz, OCH₂Ph), 4.42 and 4.41 (total 1 H, two d, *J* = 10.9 Hz, OCH'₂Ph), 4.08 and 4.04 (total 1 H, two m, H-1), 2.75-2.50 (2H, m), 2.30-2.15 (6H), 1.15 and 1.09 (total 3 H, two s, Me-1'), 0.99 and 0.96 (total 3 H, two s, Me-2'β), 0.77 and 0.76 (total 3 H, two s, Me'-2'α); MS (CI) *m/z* (EI) *m/z* 310 (M⁺, 2), 219 (30), 203 (50), 202 (84), 187 (53), 159 (100), 91 (48).

1-Methyl-3-[(1S)-1,2,2-trimethylcyclopentyl]benzene [(-)-Herbertene (3)].

IR (film) 3030, 2958, 2873, 1604, 1462, 1358, 784, 707 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.16 (3 H, m, H-4, H-5, H-6), 7.0 (1 H, m, H-2), 2.6-2.4 (1 H, m, H-5'), 2.35 (3 H, s, Me-Ar), 1.8-1.6 (4 H, m), 1.6-1.5 (1 H, m), 1.26 (3 H, s, Me-1'), 1.07 (3H, s, Me-2'β), 0.56 (3 H, s, Me-2'α); MS (CI) *m/z* 203 (M⁺+1, 12), 202 (M⁺, 68), 187 (7), 159 (11), 145 (38), 132 (100), 119 (24).

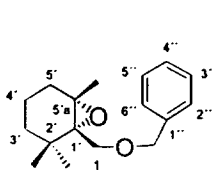
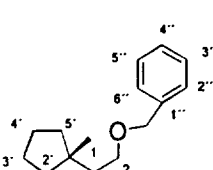
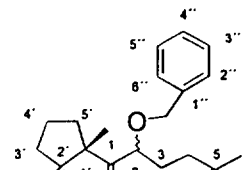
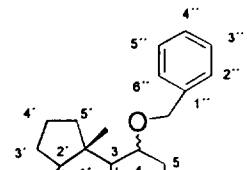
4-Methyl-2-[(1S)-1,2,2-trimethylcyclopentyl]-2-cyclohexen-1-one (15).

IR (film) 3030, 2942, 1680, 1451, 1363, 909 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 6.53 (1 H, br s, H-3), 1.20 and 1.19 (total 3 H, two s, Me-1'), 1.12 (total 3 H, overlapping d, *J* = 7 Hz, Me-4), 1.07 and 1.05 (total 3 H, two s, Me-2'β), 0.69 (3 H, s, Me-2'α); MS (EI) *m/z* 220 (M⁺, 100), 219 (23), 218 (32), 205 (49), 178 (58), 163 (96), 149 (23), 135 (66).

4-Methyl-2-[(1S)-1,2,2-trimethylcyclopentyl]phenol [(-)-α-Herbertenol (4)].

IR (film) 3525, 3400, 3010, 2956, 2873, 1665, 1607, 1507, 1461, 1408, 1370, 1251, 810 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.1 (1 H, s, H-3), 6.86 (1 H, d, *J* = 7.9 Hz, H-5), 6.57 (1 H, d, *J* = 7.9 Hz, H-6), 4.63 (1 H, s, OH), 2.6 (1H, H-5'α), 2.26 (3 H, s, Me-4), 1.41 (3H, s, Me-1'), 1.18 (3H, s, Me-2'β), 0.76 (3 H, s, Me-2'α); MS (CI) *m/z* 219 (M⁺+1, 21), 218 (M⁺, 88), 203 (11), 161 (8), 149 (11), 148 (26), 135 (36), 121 (14), 111 (100).

Table I. ^{13}C Chemical Shifts^a (δ) in ppm from TMS of compounds 7, 8, 10, 11.

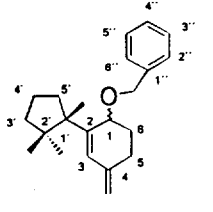
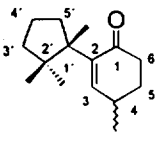
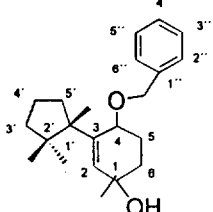
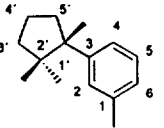
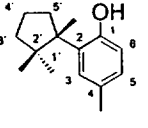
					
	7	8	10 ^b		11 ^c
C-1	71.44*	211.16	214.09	214.4	200.25 / 201.13
C-2	-	73.12*	78.94	78.74	127.90 / 128.62*
C-3	-	-	24.71	24.99	166.72 / 166.23
C-4	-	-	38.36	38.86	71.57 / 71.79
C-5	-	-	208.24	208.24	25.20 / 24.75
C-6	-	-	29.98	30.05	31.52 / 31.40
C-1'	67.80	58.13	58.51	57.82	52.12 / 51.60
C-2'	32.80	44.57	44.56	46.12	44.71 / 46.08
C-3'	37.32	39.70	39.52	39.21	40.19 / 39.45
C-4'	17.14	19.76	19.15	19.69	19.41 / 19.50
C-5'	31.53	33.91	33.54	33.70	36.85 / 34.81
CH ₃ -1' β	-	20.29	21.46	21.89	21.19 / 23.79
CH ₃ -2' α	25.32	25.47	25.57	25.82	26.36
CH ₃ -2' β	25.73	24.27	24.28	24.04	25.20 / 22.29
OCH ₂ Ph	73.38*	73.07*	71.07	71.30	71.35 / 71.35
C-1''	138.0	137.54	137.75	137.90	137.92 / 137.96
C-2'' / C-6''	128.28**	128.41**	128.36*	128.38*	128.39 / 128.43*
C-3'' / C-5''	127.81**	127.90**	127.81*	127.90*	127.90 / 127.71*
C-4''	127.60	127.81	127.75*	127.77*	127.75 / 127.82*
Others	63.80 (C-5'a) 21.19 (Me-5'a)	- -	- -	- -	- -

^a At 75.4 MHz in CDCl₃. The signals with the same superscript may be interchanged within the same column.

^b A set of resonance signals, obtained from the spectra of separated isomers, is given for each of the epimers at C-2.

^c Each set of resonance signals were obtained from the spectra of the 1 : 1 mixture of diastereomers. Assignment of the resonance signals are based on a combination of HMQC and NOE experiments performed on the mixture.

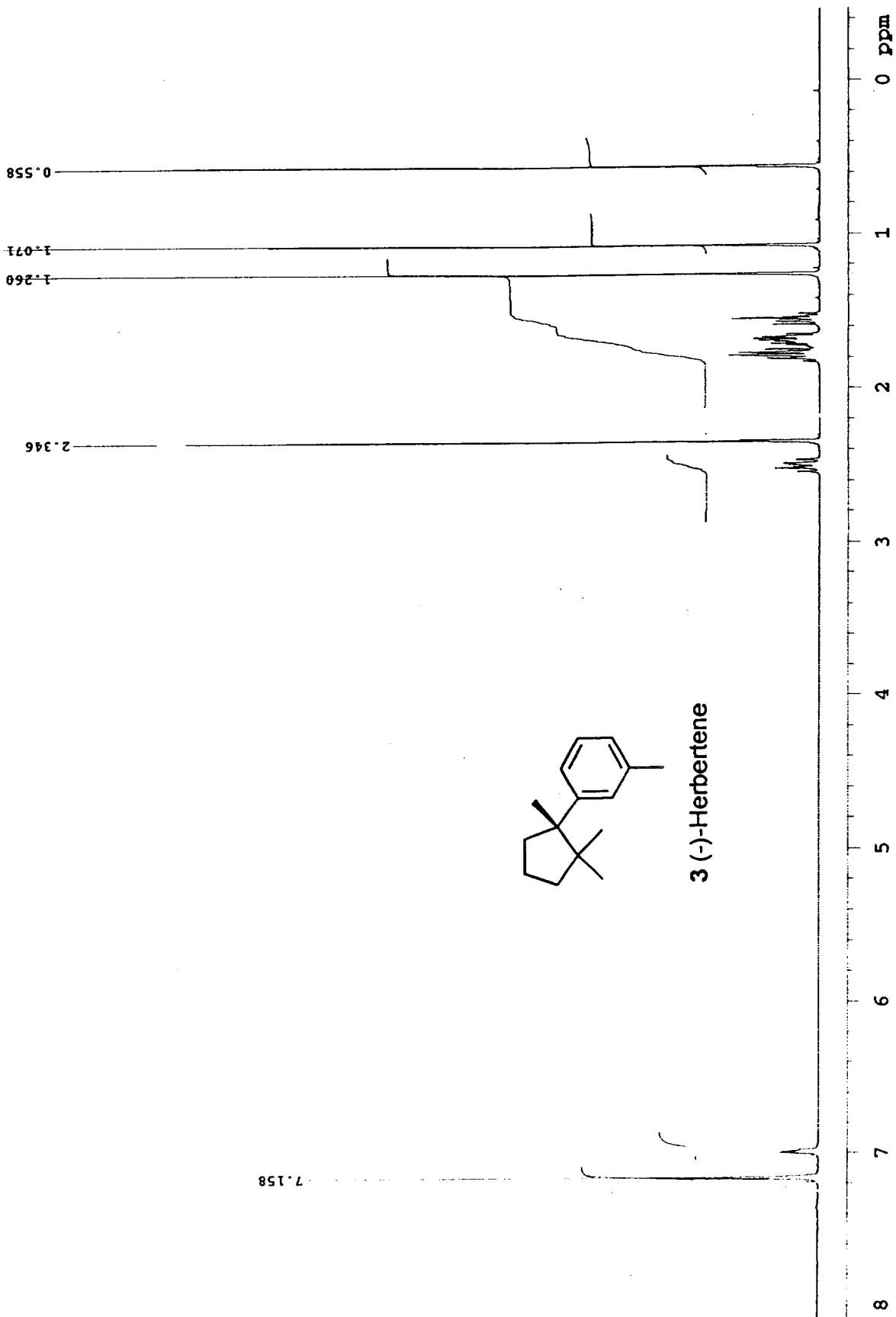
Table II. ^{13}C Chemical Shifts^a (δ) in ppm from TMS of compounds 13, 15, 16, 3 and 4.

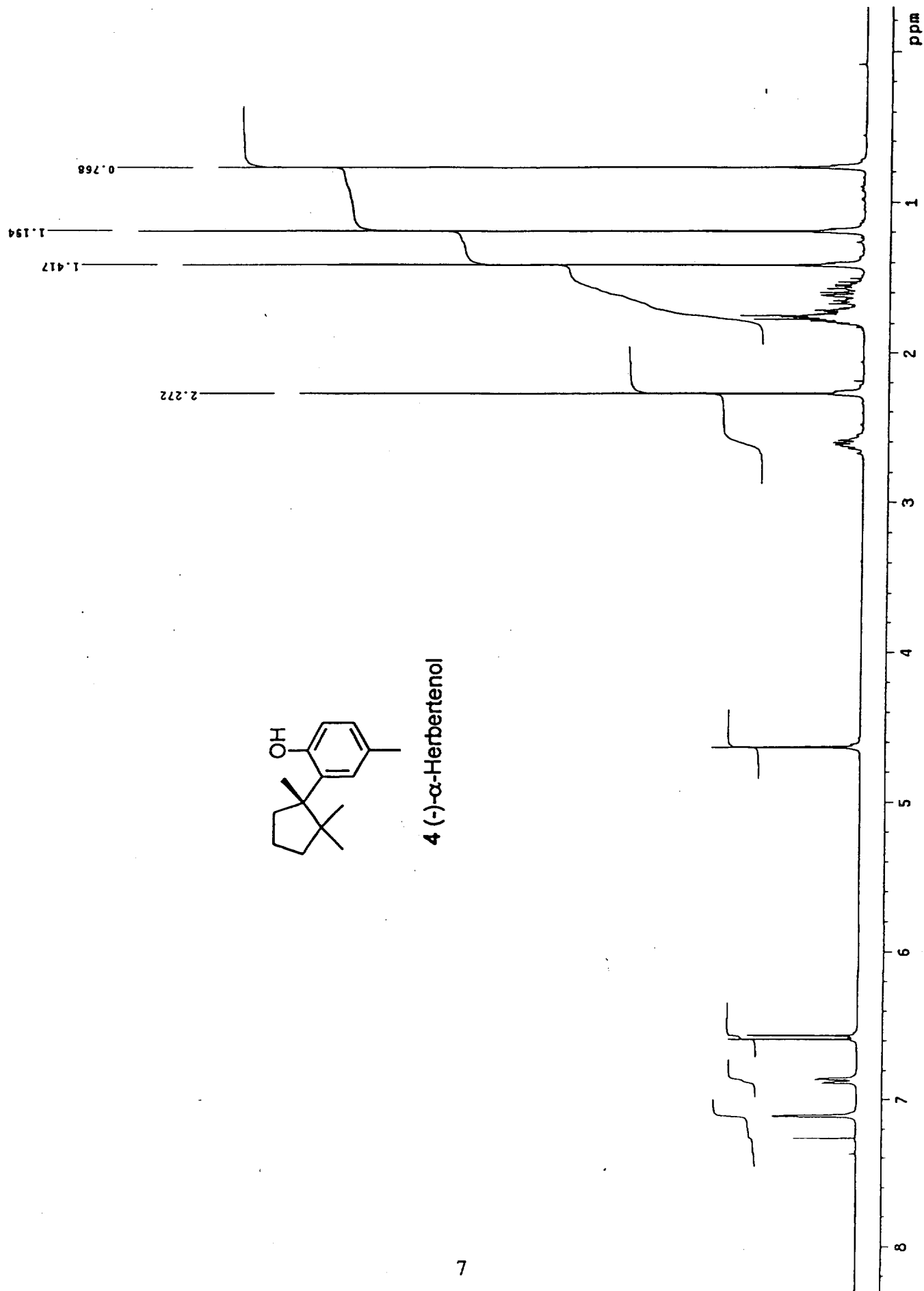
					
	13 ^b	15 ^b	16a / 16b ^{b,c}	3	4
C-1	72.59 / 72.34	199.61 / 200.15	70.42 / 70.08	136.72	152.24
C-2	143.31 / 143.04	143.84 / 143.71	133.98 / 134.30	126.04	138.01
C-3	129.29 / 128.48*	150.65 / 150.41	143.18 / 142.42	147.57	127.20
C-4	145.24	27.60 / 27.50	72.59 / 72.21	124.09	133.01
C-5	25.51 / 24.75	30.96 / 30.53	25.06 / 24.59	127.82	129.99
C-6	23.99 / 23.82	41.52 / 41.43	32.73 / 32.63	127.32	116.68
C-1'	51.09 / 50.53	50.29 / 50.43	50.54 / 49.62	50.47	50.92
C-2'	44.62 / 45.81	43.25 / 43.42	44.32 / 45.42	44.21	44.64
C-3'	40.31 / 39.35	39.60 / 39.37	40.19 / 38.98	39.79	41.23
C-4'	19.67 / 19.54	19.79 / 19.92	19.71 / 19.36	19.71	20.31
C-5'	34.98 / 27.15	38.83 / 38.63	37.28 / 34.78	36.78	39.40
CH ₃ -1' β	21.71 / 24.16	21.09 / 21.04	21.59 / 24.26	24.43	26.95
CH ₃ -2' α	26.45	25.41 / 25.51	26.32	26.49	25.51
CH ₃ -2' β	25.32 / 23.12	23.04 / 22.39	25.27 / 22.87	24.31	23.89
OCH ₂ Ph	70.55 / 70.45	-	70.90 / 70.85	-	-
C-1''	138.78 / 138.71	-	138.52	-	-
C2''/C6''	128.19*	-	128.13 / 127.90*	-	-
C3''/C5''	128.10 / 127.81*	-	128.29 / 128.25*	-	-
C-4''	127.40 / 127.34*	-	127.54 / 127.45*	-	-
CH ₂ -4	111.69 / 111.32	-	-	-	-
CH ₃ -4	-	31.89 / 31.97	-	-	-
Others	-	-	27.62 / 27.24 (CH ₃ -1)	21.73 (CH ₃ -Ar)	20.84 (CH ₃ -Ar)

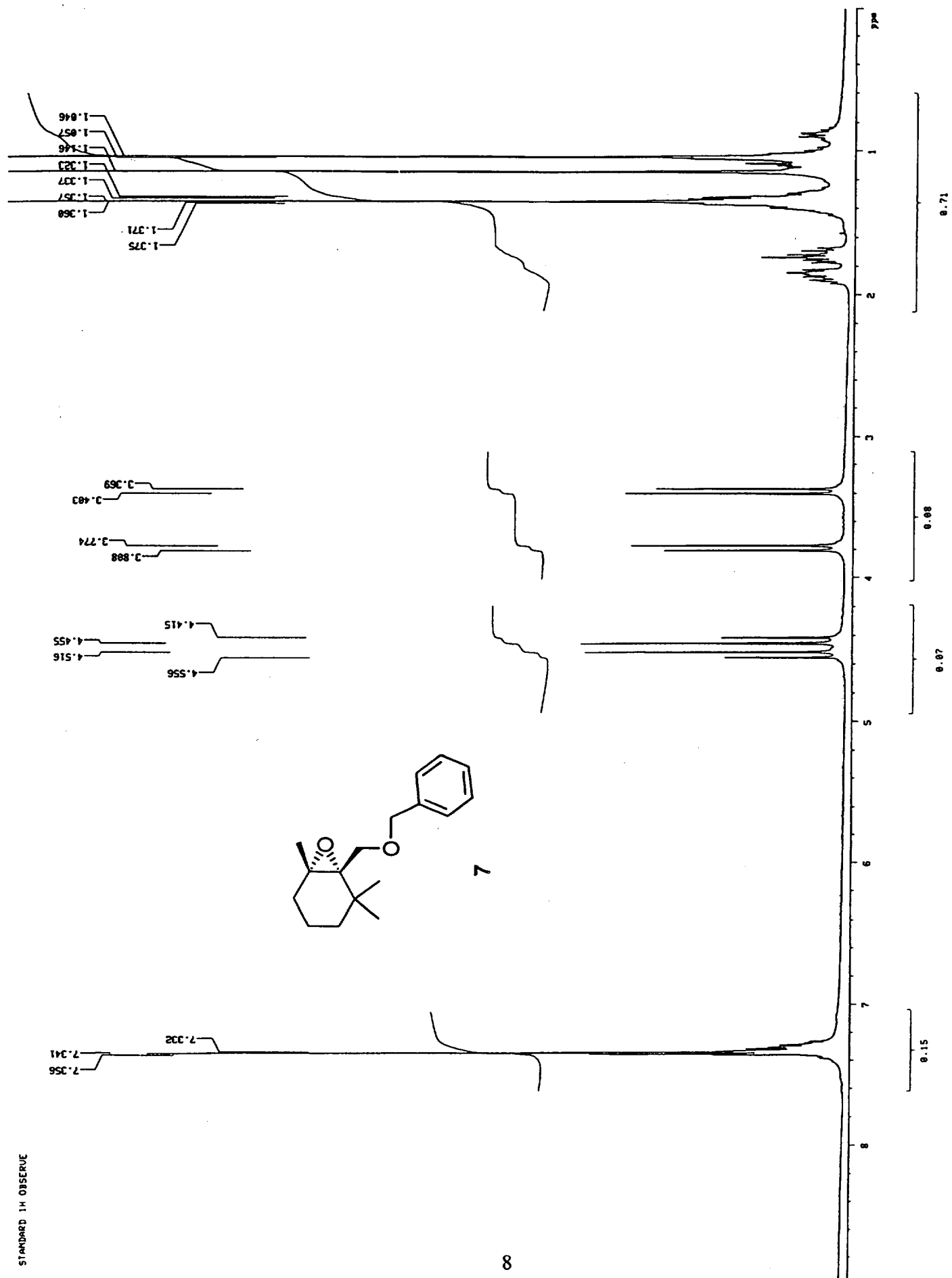
^a At 75.4 MHz in CDCl₃. The signals with the same superscript may be interchanged within the same column.

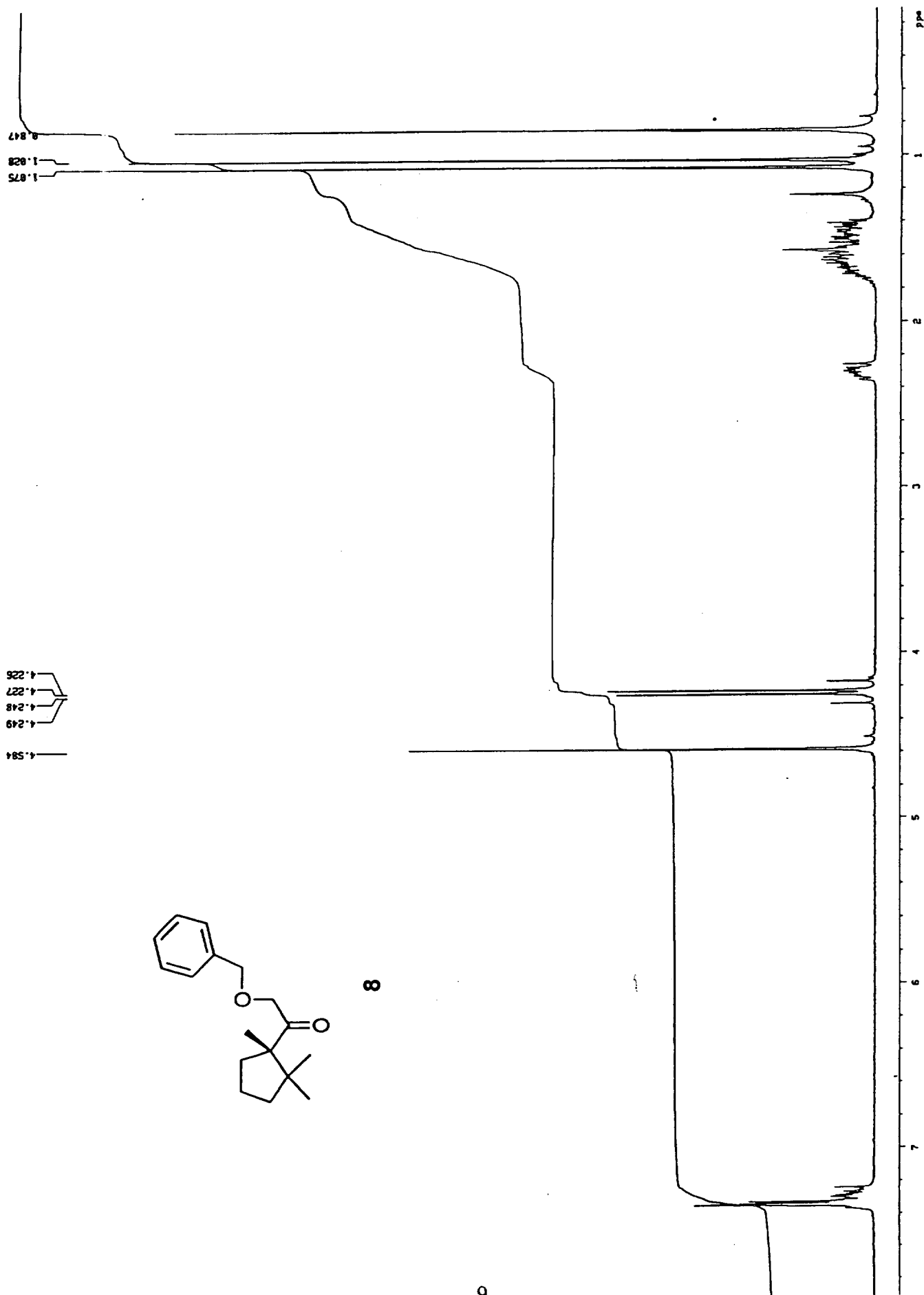
^b Each set of resonance signals were obtained from the spectra of the 1 : 1 mixture of diastereomers.

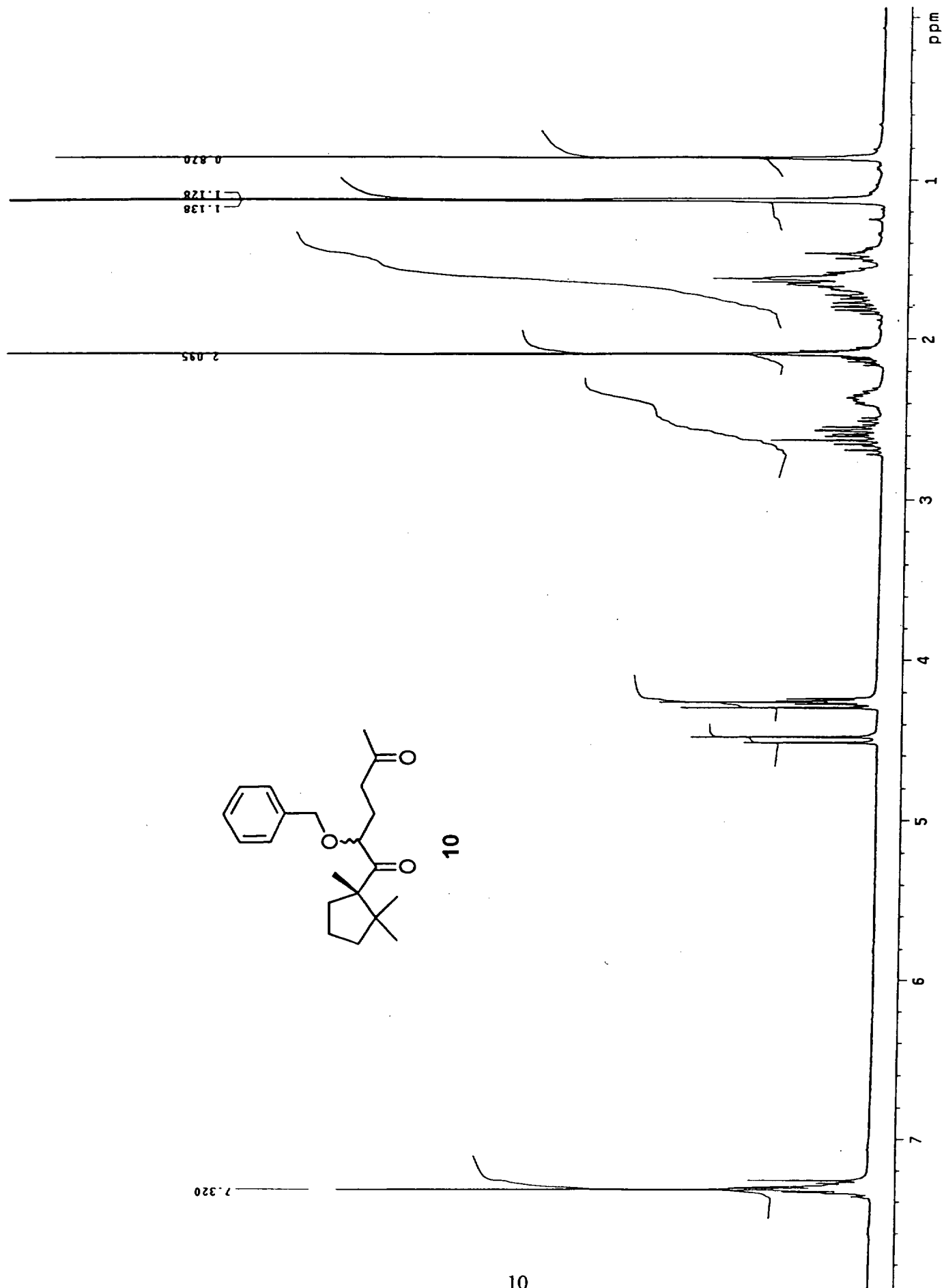
^c Assignment of the resonance signals are based on a combination of HMQC and NOE experiments performed on the mixture.



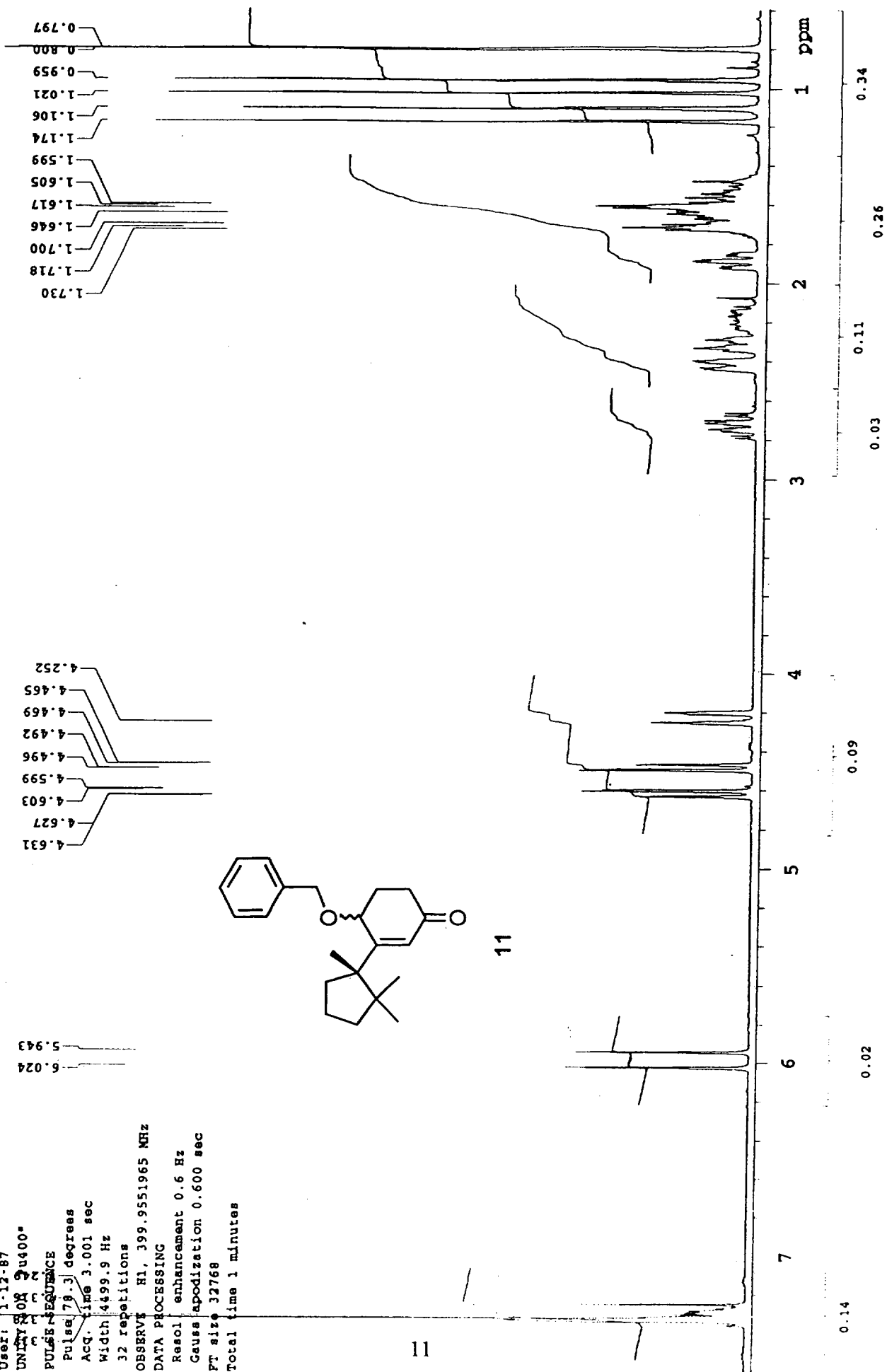


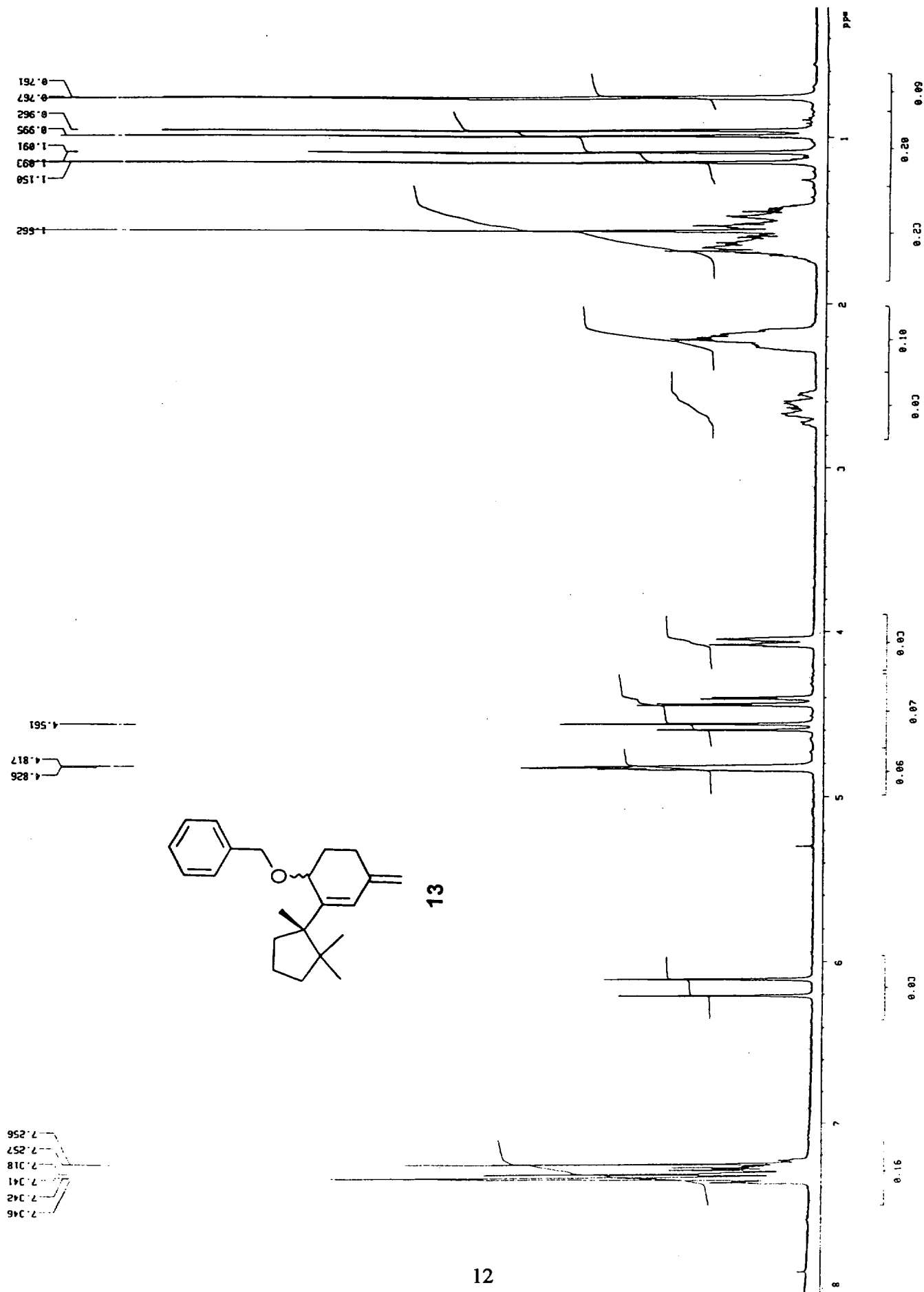


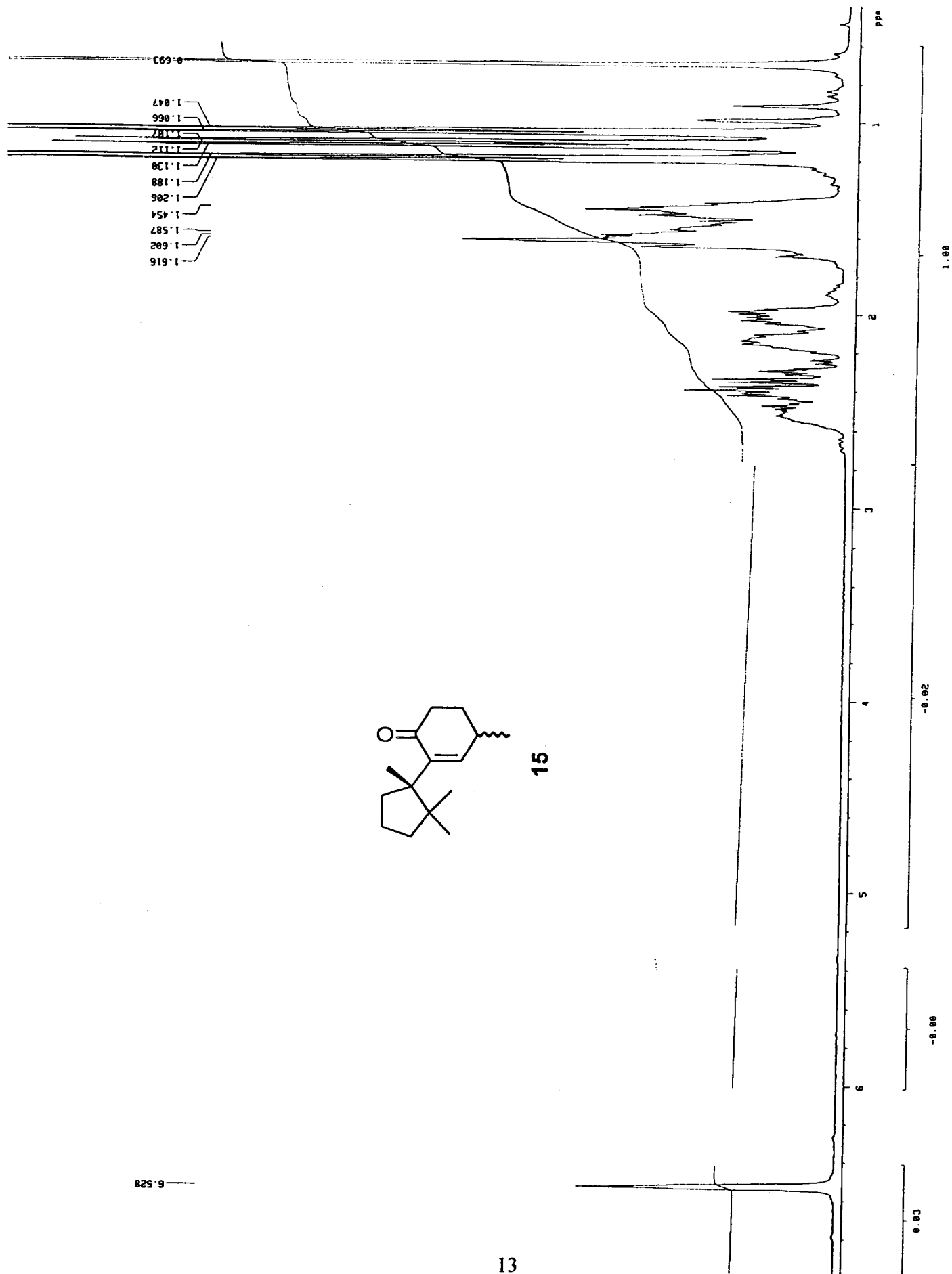




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 32 repetitions
 OBSERVE H1, 399.9551965 MHz
 DATA PROCESSING
 Resol. enhancement 0.6 Hz
 Gauss apodization 0.600 sec
 FT size 32768
 Total time 1 minutes







6.528

