Strains and culture conditions, cloning and homologous recombination

The bacteria *Streptomyces clavuligerus* ATCC 27064, *Streptomyces scabiei* 87.22 and *Streptomyces venezuelae* ATCC 10712 were obtained from the Deutsche Sammlung von Mikroorganismen und Zellkulturen (DSMZ, Braunschweig, Germany). Genomic DNA was isolated from cells grown in Gym 65 liquid culture (glucose: 4.0 g, yeast extract: 4.0 g, malt extract: 4.0 g, water: 1 L, pH 7.2). The genes of the terpene synthases were amplified from genomic DNA using the primers as shown in Table 1. The obtained PCR product was used as a template in a second PCR with elongated primers containing homology arms (Table 1, homology arms are underlined) for homologous recombination with the linearised (HindIII and EcoRI double digest) vector pYE-Express[1] in *S. cerevisiae* FY834. Transformation of *S. cerevisiae* with the PCR product and the linearised vector pYE-Express for homologous recombination was carried out using the LiOAc/SS carrier DNA protocol.[2] The transformed cells were plated on SM-URA[2] agar plates and grown for three days at 28 °C. Plasmid DNA was isolated from the grown yeast using the kit Zymoprep Yeast Plasmid Miniprep II (Zymo Research, Irvine, USA), shuttled into *E. coli* BL 21 cells by electroporation and confirmed by sequencing.

Table 1 Primers for cloning of terpene cyclase genes into pYE-Express by homologous recombination in yeast.

Primer	**Terpene synthase**	**Sequence**
PR016f_ZP06775814	intermedeol	ATGAATCCCCGGATGACACA
PR016r_ZP06775814	intermedeol	CTATCCGGACGCGGTCCGCG
MY021f_ZP06775814	intermedeol	GGCAGCCATATGGCTAGCATGACTGGTGGAATGAATCCCCGGATGACACA
MY021r_ZP06775814	intermedeol	TCTCAGTGGTGGTGGTGGTGGTGCTCGAGTCTATCCGGACGCGGTCCGCG
PR026f_CCA53839	isodaucen-11-ol	ATGACAGTGCGTGCCGTCGA
PR026r_CCA53839	isodaucen-11-ol	TCATGCGCTTCCTGCGGAGG
PR025f_CCA53839	isodaucen-11-ol	GGCAGCCATATGGCTAGCATGACTGGTGGAATGACAGTGCGTGCCGTCGA
PR025r_CCA53839	isodaucen-11-ol	TCTCAGTGGTGGTGGTGGTGGTGCTCGAGTTCATGCGCTTCCTGCGGAGG
PR063f_YP003492893	neomeranol B	GTGGCGGACACCTTCCAGAT
PR063r_YP003492893	neomeranol B	TCAGGCGGCGCACCGGTATC
PR062f_YP003492893	neomeranol B	GGCAGCCATATGGCTAGCATGACTGGTGGAGTGGCGGACACCTTCCAGAT
PR062r_YP003492893	neomeranol B	TCTCAGTGGTGGTGGTGGTGGTGCTCGAGTTCAGGCGGCGCACCGGTATC

Incubation experiments of purified enzyme with FPP and isolation of products

E. coli BL 21 transformants were inoculated in a 2YT liquid preculture (tryptone: 16 g, yeast extract: 10 g, NaCl: 5 g, water: 1 L, pH 7.2) containing kanamycin (50 mg/L) overnight. *E. coli* BL 21 transformants from the preculture were inoculated in large scale 2YT liquid cultures (6-8 x 1 L) containing kanamycin (50 mg/L). Cells were grown to an OD_{600} = 0.4 at 37 °C and 160 rpm, followed by cooling of the cultures to 18 °C for 30 minutes. IPTG (0.4 mM) was added and the culture was incubated at 18 °C and 160 rpm overnight. *E. coli* cells were harvested by centrifugation at 4 °C and 3600 rpm for 60 min. The pellets were resuspended in 2 x 10 mL lysis buffer (20 mM Na_2HPO_4, 0.5 M NaCl, 20 mM imidazole, 1 mM $MgCl_2$, pH 7.0) for each 1 L culture. Cell disruption was done by ultra-sonication on ice for 6 x 60 sec. The soluble enzyme fractions were harvested at 4 °C and 8000 rpm by repeated centrifugation (2 x 10 min). Protein purification was performed by Ni^{2+}-NTA affinity chromatography with Ni^{2+}-NTA superflow (Novagen) using binding buffer (20 mM Na_2HPO_4, 0.5 M NaCl, 20 mM imidazole, 1 mM $MgCl_2$, pH 7.0) and elution buffer (20 mM Na_2HPO_4, 0.5 M NaCl, 500 mM imidazole, 1 mM $MgCl_2$, pH 7.0). All wash and elution fraction were checked by SDS-PAGE. Incubation experiments were performed with the pure protein fractions (80-160 mL) and incubation buffer (100 mL, 50 mM Tris·HCl, 10 mM $MgCl_2$, 20 % glycerin, pH 7.0) containing FPP (50-80 mg, 0.4-0.6 mg/mL) at 28 °C overnight. The reaction mixture was extracted with 3 x 100 mL pentane. The combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. Column chromatography on silica gel of the crude products with pentane/diethyl ether (5:1) yielded the pure sesquiterpene alcohols for structure elucidation by NMR.

Neomeranol B (1). Yield: 4.1 mg. HRMS (TOF): obs. *m*/*z* (calcd., formula) = 222.1970 (222.1978, $C_{15}H_{26}O^+$, $[M]^+$). GC (HP5-MS): *I* = 1607. MS (EI, 70 eV): *m*/*z* (%) = 222 (0.3) $[M]^+$, 204 (2), 189 (3), 161 (4), 137 (5), 123 (4), 109 (24), 97 (35), 85(100), 69 (18), 55 (20), 41 (18). IR (diamond ATR): $\tilde{\nu}$ = 3385 (br m), 2953 (s), 2923 (s), 2891 (m), 2873 (m), 1725 (w), 1453 (m), 1378 (m), 1298 (w), 1261 (w), 1164 (w), 1136 (w), 1019 (s), 1002 (s), 951 (w), 827 (w), 804 (w), 712 (w), 600 (w), 529 (w) cm^{-1}. $[\alpha]_D^{24}$ = -10.2 (CH_2Cl_2, c = 0.082).

Intermedeol (4). Yield: 9.6 mg. HRMS (TOF): obs. *m*/*z* (calcd., formula) = 222.1970 (222.1978, $C_{15}H_{26}O^+$, $[M]^+$). GC (HP5-MS): *I* = 1664. MS (EI, 70 eV): *m*/*z* (%) = 222 (3) $[M]^+$, 204 (100), 189 (95), 175 (17), 161 (94), 147 (34), 133 (38), 122 (46), 107 (46), 107 (45), 93 (45), 81 (65), 71 (30), 55 (26), 43 (34). IR (diamond ATR): $\tilde{\nu}$ = 3438 (br m), 3085 (w), 2969 (m), 2929 (s), 2867 (m), 2850 (m), 1738 (w), 1638 (w), 1452 (m), 1381 (m), 1229 (w), 1168 (w), 1095 (m), 1064 (w), 931 (w), 907 (m), 887 (m), 803 (w), 575 (w), 527 (w) cm^{-1}. $[\alpha]_D^{25}$ = +11.9 (CH_2Cl_2, c = 0.50).

Isodauc-8-en-11-ol (3). Yield: 11.8 mg. HRMS (TOF): obs. *m*/*z* (calcd., formula) = 222.1973 (222.1978, $C_{15}H_{26}O^+$, $[M]^+$). GC (HP5-MS): *I* = 1669. MS (EI, 70 eV): *m*/*z* (%) = 222 (x) $[M]^+$, 204 (35), 189 (14), 163 (18), 161 (16) 149 (41), 135 (16), 121 (27), 107 (41), 95 (77), 81 (44), 67 (29), 59 (100), 55 (20), 42 (32). IR (diamond ATR): $\tilde{\nu}$ = 3364 (br m), 2966 (m), 2923 (m), 2886 (m), 1738 (w), 1454 (w), 1440 (w), 1383 (m), 1364 (m), 1147 (s), 945 (m), 928 (m), 883 (s), 840 (m), 802 (m), 660 (w), 587 (w), 519 (w), 476 (w) cm^{-1}. $[\alpha]_D^{22}$ = +19.4 (CH_2Cl_2, c = 0.505).

NMR data of all natural products are presented in Table 1 of main text.

Incubation experiments of purified enzyme with ^{13}C-labelled FPPs.

For each incubation a 0.5 L 2YT liquid culture (containing kanamycin (50 mg/L)) of *E. coli* BL 21 transformants was inoculated from an overnight preculture. Cells were grown to an OD_{600} = 0.4 at 37 °C and 160 rpm, followed by cooling of the cultures to 18 °C for 30 minutes. IPTG (0.4 mM) was added and the culture was incubated at 18 °C and 160 rpm overnight. *E. coli* cells were harvested by centrifugation at 4 °C and 8000 rpm for 10 min. The pellets were resuspended in 10 mL lysis buffer (20 mM Na_2HPO_4, 0.5 M NaCl, 20 mM imidazole, 1 mM $MgCl_2$, pH 7.0) and lysed by ultra-sonication on ice for 5 x 30 sec. The soluble enzyme fractions were harvested at 4°C and 11000 rpm by centrifugation (1 x 10 min). Protein purification was performed by Ni^{2+}-NTA affinity chromatography with Ni^{2+}-NTA superflow (Novagen) using binding buffer (20 mM Na_2HPO_4, 0.5 M NaCl, 20 mM imidazole, 1 mM $MgCl_2$, pH 7.0) and elution buffer (20 mM Na_2HPO_4, 0.5 M NaCl, 500 mM imidazole, 1 mM $MgCl_2$, pH 7.0). Each pure protein fraction (checked by SDS) was concentrated with a Vivaspin20 concentration tube (MWCO 30000, Sartorius Stedim, Göttingen) for 1.5 h at 6000 rpm to 2 mL enzyme fraction. Incubation experiments were performed with the pure protein (2 mL) and incubation buffer (2 mL, 50 mM Tris·HCl, 10 mM $MgCl_2$, 20 % glycerin, pH 7.0) containing the ^{13}C-labelled FPP (3 mg, 1.5 mg/mL) at 28 °C overnight. The reaction mixture was extracted with 0.6 mL ($^2H_6$)benzene and directly measured by NMR.

The protein purifications of intermedeol synthase and neomeranol B synthase in D_2O were performed by Ni^{2+}-NTA affinity chromatography with Ni^{2+}-NTA superflow (Novagen) using binding buffer (20 mM Na_2HPO_4, 0.5 M NaCl, 20 mM imidazole, 1 mM $MgCl_2$, pH 7.0 in D_2O) and elution buffer (20 mM Na_2HPO_4, 0.5 M NaCl, 500 mM imidazole, 1 mM $MgCl_2$, pH 7.0 in D_2O). Each pure protein fraction (checked by SDS) was concentrated with a Vivaspin20 concentration tube (MWCO 30000, Sartorius Stedim, Göttingen) for 1.5 at 6000 rpm to 2 mL enzyme fraction. Incubation experiments were performed with the pure protein (2 mL) and D_2O (2 mL) containing the (6-^{13}C)FPP (3 mg, 1.5 mg/mL) at 28 °C overnight. The reaction mixture was extracted with 0.6 mL ($^2H_6$)benzene and directly measured by NMR.

Incubation experiments of purified isodaucen-11-ol synthase with (2*Z*,6*E*)FPP

For the incubation experiment of isodaucen-11-ol synthase with the substrate analogue (2*Z*,6*E*)FPP a 0.5 L 2YT liquid culture (containing kanamycin (50 mg/L)) of *E. coli* BL 21 transformants was inoculated. The cultivation and protein isolation conditions are performed as reported above. The pure protein fraction of isodaucen-11-ol synthase was used for an incubation experiment with the pure protein (2 mL) and incubation buffer (2 mL, 50 mM Tris·HCl, 10 mM $MgCl_2$, 20 % glycerin, pH 7.0) containing the (2*Z*,6*E*)FPP[3] (0.6 mg, 0.3 mg/mL) at 28 °C overnight. The reaction mixture was extracted with 0.5 mL *n*hexane and directly injected in GC/MS.

GC-/MS and GC/Q-TOF analysis

GC-MS analyses were carried out with a 7890B gas chromatograph connected to a 5977A inert mass detector (Agilent) fitted with a HP5-MS fused silica capillary column (30 m, 0.25 mm i. d., 0.50 μm film). Instrumental parameters were (1) inlet pressure, 77.1 kPa, He 23.3 mL min^{-1}, (2) injection volume, 1-2 μL, (3) transfer line, 250 °C, and (4) electron energy 70 eV. The GC was programmed as follows: 5 min at 50 °C increasing at 10 °C min^{-1} to 320 °C, and operated in split mode (50:1, 60 s valve time). The carrier gas was He at 1 mL min^{-1}. Retention indices (*I*) were determined from a homologous series of n-alkanes (C8-C40). HRMS analyses were carried out with a 7890B gas chromatograph connected to a 7200 accurate-mass Q-TOF mass detector (Agilent) eqipped with a HP5-MS fused silica capillary

column (30 m, 0.25 mm i. d., 0.50 μm film). Instrumental parameters were (1) inlet pressure, 83.2 kPa, He 24.6 mL min^{-1}, (2) injection volume, 1 μL, (3) transfer line, 250 °C, and (4) electron energy 70 eV. The GC was programmed for HR-MS as follows: 5 min at 50 °C increasing at 10 °C min^{-1} to 320 °C, and operated in split mode (50:1-100:1, 60 s valve time). The carrier gas was He at 1 mL min^{-1}.

CLSA headspace sampling

The volatiles released by *Streptomyces scabiei* 87.22, *Streptomyces venezuelae* ATCC 10712 and *Streptomyces clavuligerus* ATCC 27064 were trapped by use of the CLSA (closed-loop stripping analysis) technique after cultivation of *Streptomyces scabiei* 87.22 on medium Gym 65 (glucose: 4.0 g, yeast extract: 4.0 g, malt extract: 4.0 g, water: 1 L, pH 7.2) and *Streptomyces venezuelae* ATCC 10712 on medium SFM (mannitol: 20.0 g, soya flour: 20.0 g, water: 1 L, pH 7.2) for 3 d at 28°C as reported previously.[4]

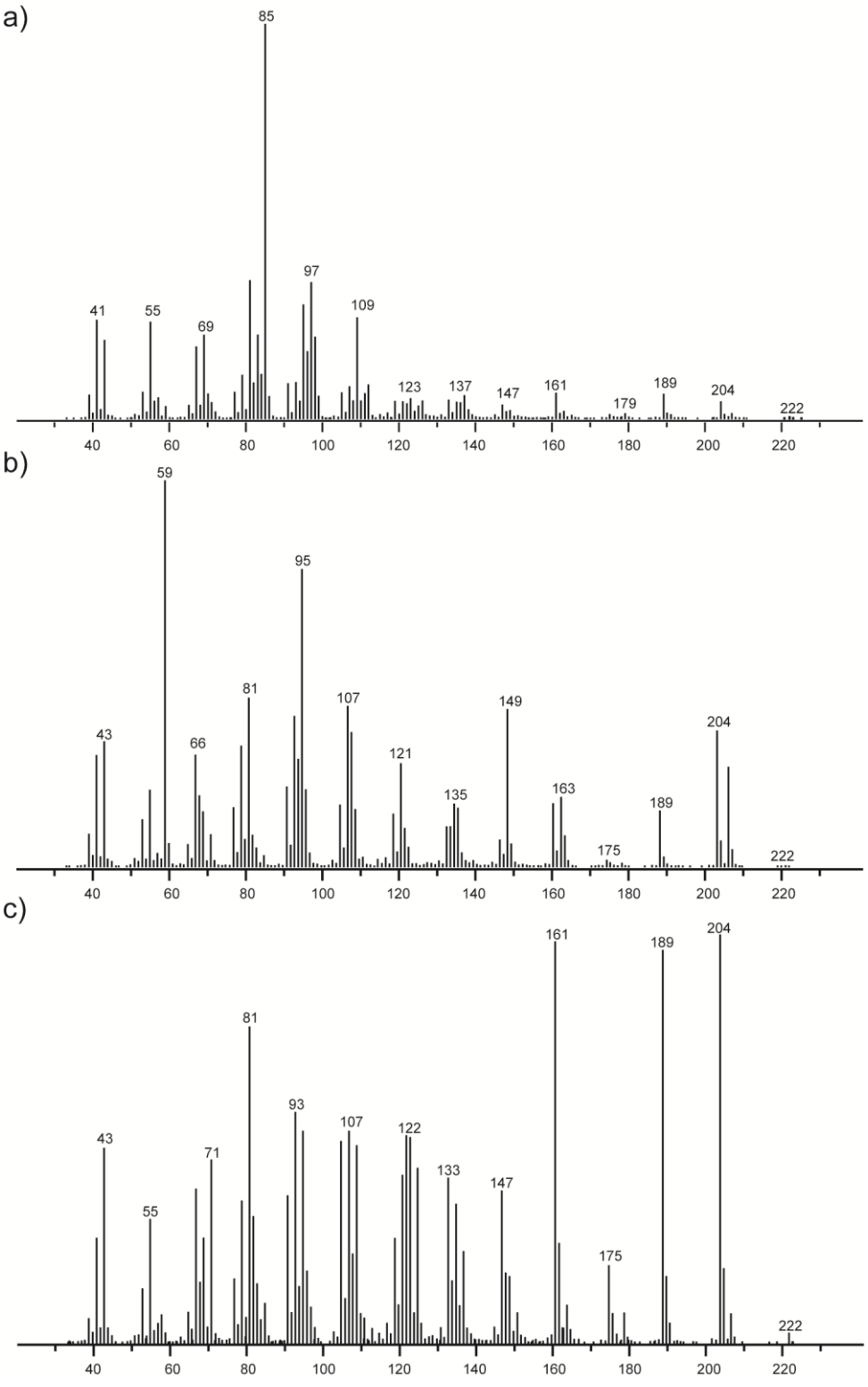


Fig. 1 EI-MS spectra of a) neomeranol B (**1**), b) isodauc-8-en-11-ol (**3**) and c) intermedeol (**4**).

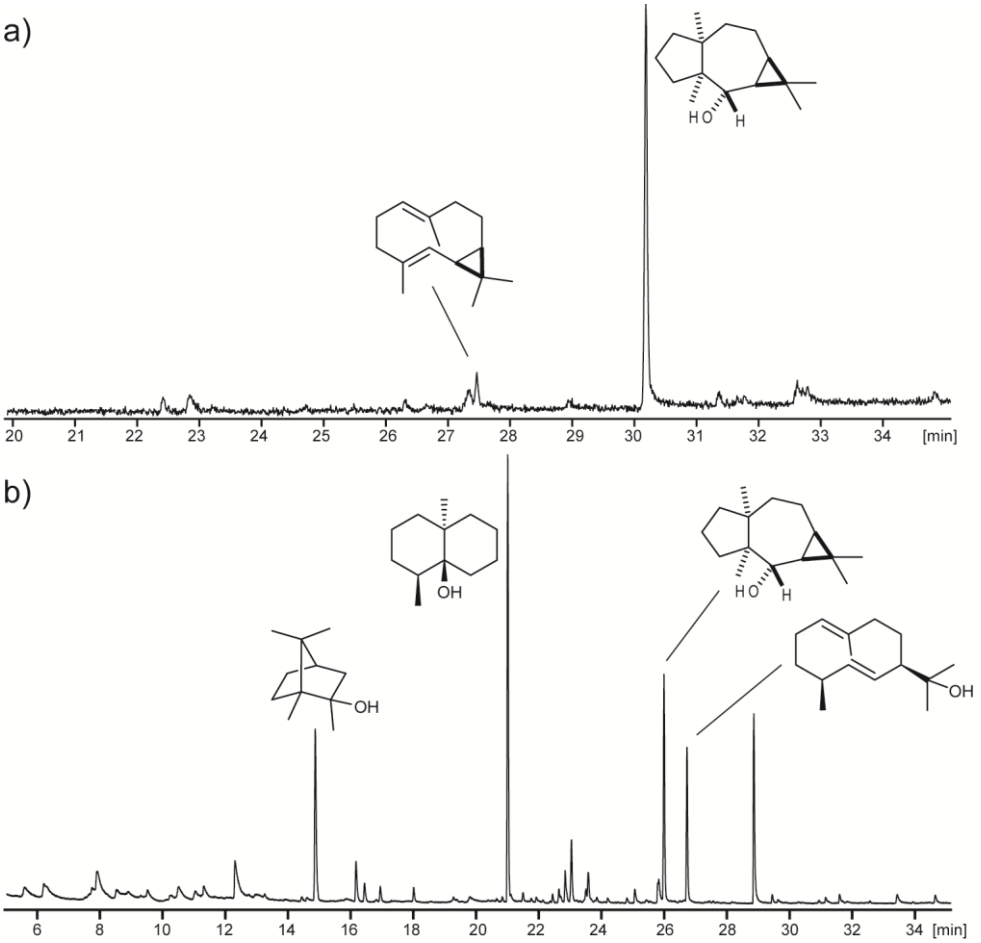


Fig. 2 Total ion chromatograms of a) a hexane extract of an incubation experiment of neomeranol B synthase with FPP at pH 7.0 and b) of a CLSA headspace extract of wildtype *Streptomyces scabiei* 87.22[4] on medium SFM demonstrating the production of **1**. The slighly deviating retention times for one and the same compound in the three samples are due to usage of different GCs, but retention indices matched.

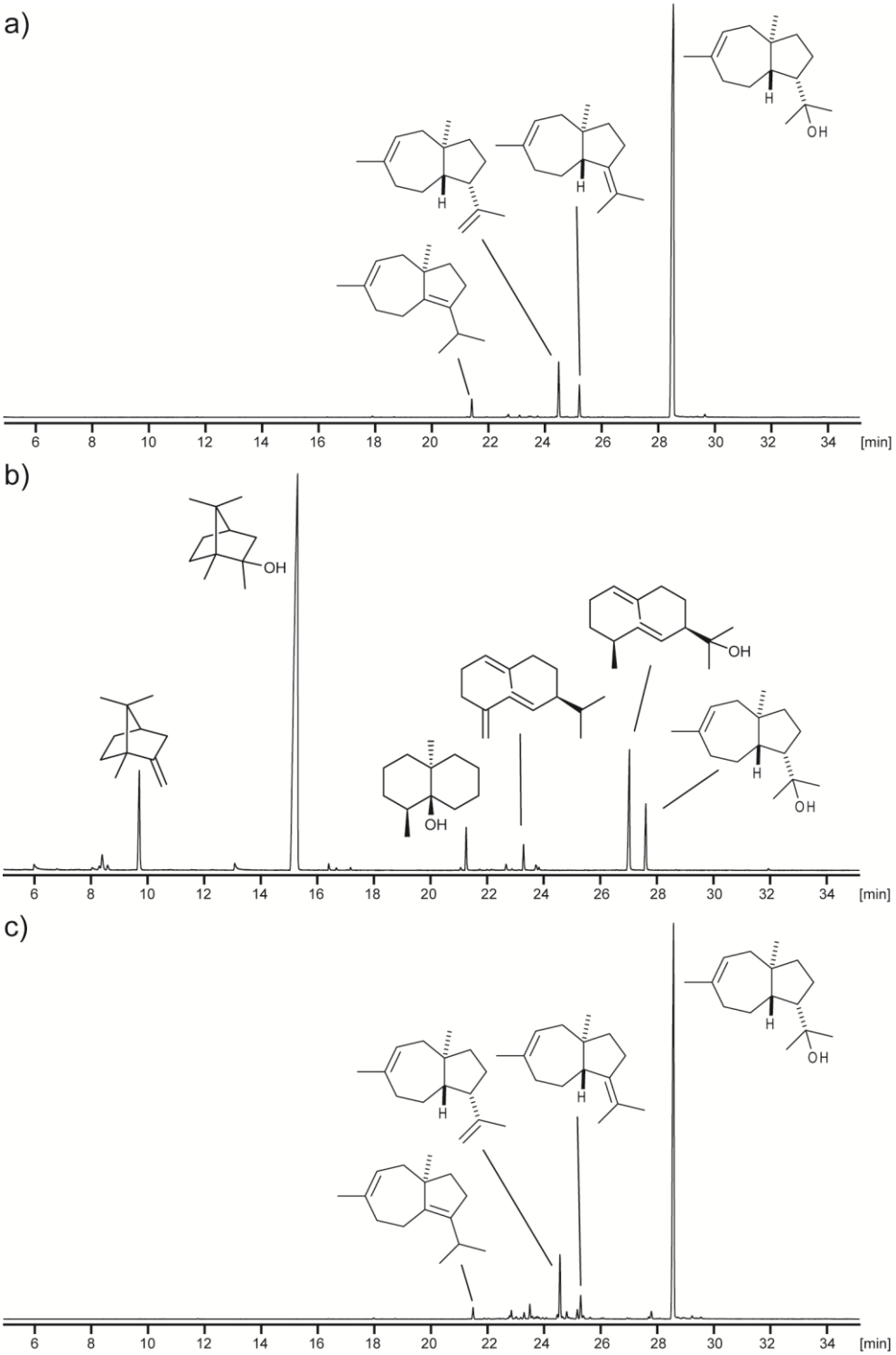


Fig. 3 Total ion chromatograms a) of a hexane extract of an incubation experiment of isodauc-8-en-11-ol synthase with (2*E*,6*E*)-FPP at pH 7.0, b) of a CLSA headspace extract of wildtype *S. venezuelae* ATCC 10712[4] on medium Gym 65 demonstrating the production of **3**, and c) of an hexane extract of an incubation experiment of isodauc-8-en-11-ol synthase with (2*Z*,6*E*)-FPP at pH 7.0. The slighly deviating retention times for one and the same compound in the three samples are due to usage of different GCs, but retention indices matched.

Table 2 Comparison of measured and reported NMR data of intermedeol (**4**) in (^{2}H)chloroform, confirming the identity of isolated **4** and intermedeol.

4 (this study, 100 MHz)[a]	**4** (de Groot et al., 50 MHz)[5]	**4** (San Feliciano et al., 50 MHz)[6]
146.9	146.6	146.8
110.8	110.7	110.7
72.1	72.0	71.9
49.2	49.1	49.1
43.6	43.4	43.5
41.4	41.3	41.4
40.4	40.2	40.4
39.3	39.2	39.4
35.3	35.2	35.2
23.5	23.4	23.5
22.8	22.7	22.7
22.7	22.7	22.7
22.3	22.2	22.3
20.2	20.1	20.1
18.5	18.4	18.4

[a] All signals are given in ppm. Deviations of reported ^{13}C-NMR shifts from data measured in this work are shown in brackets.

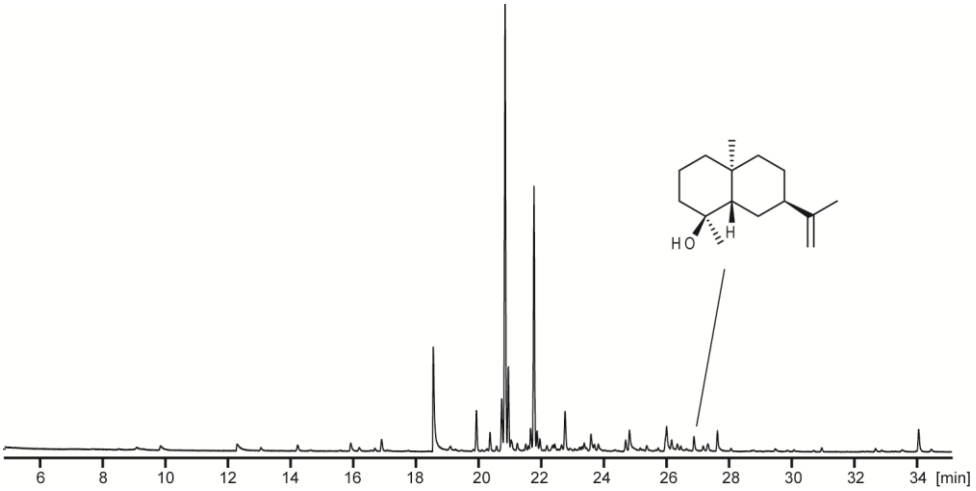
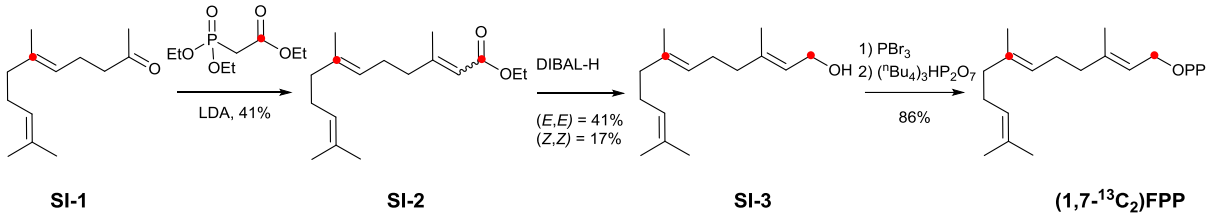


Fig. 4 Total ion chromatogram of a CLSA headspace extract of wildtype *Streptomyces clavuligerus* ATCC 27064[4] on medium SFM demonstrating the production of **4**.

Fig. 5 Synthesis of (1,7-$^{13}C_2$)FPP.



General synthetic methods

Chemicals were purchased from Acros Organics (Geel, Belgium) or Sigma Aldrich Chemie GmbH (Steinheim, Germany) and used without purification. All non-aqueous reactions were performed under an inert atmosphere (N_2 or Ar) in flame-dried flasks. Solvents were purified by distillation and dried according to standard methods. Thin-layer chromatography was performed with 0.2 mm precoated plastic sheets Polygram Sil G/UV254 (Machery-Nagel). Column chromatography was carried out using Merck silica gel 60 (70-200 mesh). NMR spectra of synthetic compounds and isolated natural products were recorded on a Bruker DRX-400 (400 MHz), AV III-400 (400 MHz) or AV Avance DMX-500 (500 MHz) spectrometer, and were referenced against solvent signals (^{1}H NMR: (^{2}H)chloroform δ = 7.26 ppm, ($^2H_6$)benzene δ = 7.16 ppm, ^{13}C NMR: (^{2}H)chloroform δ = 77.16 ppm, ($^2H_6$)benzene δ = 128.06 ppm).

Synthesis of ethyl (1,7-$^{13}C_2$)-(6*E*)-3,7,11-trimethyldodeca-2,6,10-trienoate (SI-2)

A solution of diisopropylamine (95 mg, 0.93 mmol, 1.1 eq.) in abs. THF (5 mL) was cooled to 0 °C and treated with *n*-butyl lithium (59.4 µL, 0.93 mmol, 1.6 M in hexane, 1.1 eq.). It was stirred for 30 min at 0 °C and then the reaction was cooled to -78 °C. Slowly (1-^{13}C)triethyl phoshonoacetate (210 mg, 0.93 mmol, 1.1 eq.) was added and stirring was continued for 2 h at -78 °C. (6-^{13}C)Geranylacetone[7] (**SI-1**) (164 mg, 0.84 mmol, 1.0 eq.) was added dropwise at -78°C and the reaction mixture was stirred over night at room temperature. The reaction was hydrolyzed by addition of distilled water, followed by extraction with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Column chromatography on silica gel with cyclohexane/ethyl acetate (45:1) resulted in a mixture of diastereoisomers **SI-2** (*E*/*Z* : 4/1; 92 mg, 0.35 mmol, 41%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.68-5.62 (m, 1H, CH), 5.12-5.05 (m, 2H, 2xCH), 4.14 (dq, $^3J_{H,H}$ = 7.1 Hz, $^3J_{C,H}$ = 3.0 Hz, 2H, CH_2), 2.19-2.15 (m, 7H, 2xCH_2 + CH_3), 2.09-2.02 (m, 2H, 1xCH_2), 2.01-1.94 (m, 2H, 1xCH_2), 1.27 (t, $^3J_{H,H}$ = 7.1 Hz, 3H, CH_3), 1.68 (s, 3H, CH_3), 1.60 (br, 3H, CH_3), 1.59 (s, 3H, CH_3) ppm.^{13}C-NMR (100 MHz, $CDCl_3$): δ = 167. 0 ($^{13}C_q$), 159.9 (d, $^2J_{C,C}$ = 2.0 Hz, C_q), 136.3 ($^{13}C_q$), 131.5 (C_q), 124.4 (d, $^3J_{C,C}$ = 3.7 Hz, CH), 123.0 (d, $^1J_{C,C}$ = 73.6 Hz, CH), 115.7 (d, $^1J_{C,C}$ = 75.7 Hz, CH), 59.6 (d, $^2J_{C,C}$ = 2.3 Hz, CH_2), 41.1 (dd, $^3J_{C,C}$ = 7.0 Hz, $^3J_{C,C}$ = 3.6 Hz, CH_2), 39.8 (d, $^1J_{C,C}$ = 42.6 Hz, CH_2), 26.8 (d, $^2J_{C,C}$ = 2.3 Hz, CH_2), 26.1 (CH_2), 25.8 (CH_3), 18.9 (d, $^3J_{C,C}$ = 1.5 Hz, CH_3), 17.8 (CH_3), 16.1 (d, $^1J_{C,C}$ = 42.1 Hz, CH_3), 14.5 (d, $^3J_{C,C}$ = 2.2 Hz, CH_3) ppm. MS (EI, 70 eV): *m*/*z* (%) = 266 (11) $[M]^+$, 251 (4), 221 (18), 205 (8), 192 (12), 177 (14), 148 (20), 137 (39), 129 (100), 122 (87), 101 (45), 82 (91), 69 (99), 54 (18), 41 (93).

Synthesis of (1,7-$^{13}C_2$)-(2*E*,6*E*)-farnesol (SI-3)

The mixture of diastereoisomers **SI-2** (92 mg, 0.34 mmol, 1.0 eq.) in abs. THF (3.5 mL) was cooled to -78 °C and a solution of DIBAL-H (0.75 mmol, 0.75 mL 2.2 eq., 1.0 M in hexane) was added dropwise. The reaction mixture was stirred for 2 h at -78 °C. It was hydrolyzed with saturated potassium sodium tartrate solution in water and extracted three times with diethyl ether. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Repeated column chromatography with cyclohexane/ethyl acetate (9:1) yielded in the alcohols (1,7-$^{13}C_2$)-(2*E*,6*E*)-farnesol (30 mg, 0.14 mmol, 41%) and (1,7-$^{13}C_2$)-(2*Z*,6*E*)-farnesol (**SI-3**) (13 mg, 0.06 mmol, 17%) as colorless oils.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.42 (tdq, $^3J_{H,H}$ = 6.9 Hz, $^2J_{C,H}$ = 1.3 Hz, $^4J_{H,H}$ = 1.3 Hz, 1H, CH), 5.14-5.06 (m, 2H, 2xCH), 4.15 (dd, $^1J_{C,H}$ = 142.2 Hz, $^3J_{H,H}$ = 6.9 Hz, 2H, CH_2), 2.16-1.94 (m, 8H, 4xCH_2), 1.68 (s, 6H, 2xCH_3), 1.60 (s, 3H, 1xCH_3), 1.60 (d, $^2J_{C,H}$ = 5.9 Hz, 3H, 1xCH_3) ppm.^{13}C-NMR (100 MHz, $CDCl_3$): δ = 140.0 (d, $^2J_{C,C}$ = 1.3 Hz, C_q), 133.5 ($^{13}C_q$), 131.5 (C_q), 124.4 (d, $^3J_{C,C}$ = 3.4 Hz, CH), 123.9 (d, $^1J_{C,C}$ = 73.5 Hz, CH), 123.5 (d, $^1J_{C,C}$ = 47.1 Hz, CH), 59.6 ($^{13}CH_2$), 39.8 (d, $^1J_{C,C}$ = 42.7 Hz, CH_2), 39.7 (cd, $^3J_{C,C}$ = 4.7 Hz, $^3J_{C,C}$ = 3.6 Hz, CH_2), 26.9 (d, $^2J_{C,C}$ = 2.2 Hz, CH_2), 26.4 (CH_2), 25.8 (CH_3), 17.8 (CH_3), 16.4 (d, $^3J_{C,C}$ = 4.3 Hz, CH_3), 16.2 (d, $^1J_{C,C}$ = 42.4 Hz, CH_3) ppm. MS (EI, 70 eV): *m*/*z* (%) = 224 (5) $[M]^+$, 206 (6), 192 (14), 181 (10), 163 (20), 137 (77), 124 (63), 110 (56), 94 (93), 82 (100), 69 (98), 55 (38), 41 (99).

Synthesis of (1,7-$^{13}C_2$)-(2*E*,6*E*)-farnesyl diphosphate (FPP)

A solution of (1,7-$^{13}C_2$)-(2*E*,6*E*)-farnesol (**SI-3**) (30 mg, 0.14 mmol, 1.0 eq.) in abs. THF (0.4 mL) was treated with PBr_3 (15 mg, 0.056 mmol, 5.3 µL, 0.4 eq.) at 0°C. The reaction was stirred for 30 min at 0°C and quenched by pouring into ice-water. After extraction with pentane the combined organic layers were dried with $MgSO_4$. The solvent was removed under reduced pressure and the pale yellow oil was subsequently added to a solution of (^{n}Bu$_4$)$_3$HP$_2$O$_7$ (190 mg, 0.21 mmol, 1.5 eq.) in abs. CH_3CN (0.8 mL). The reaction mixture was stirred over night at room temperature and then concentrated under reduced pressure. The yellow oil was loaded onto a column containing ion exchange resin (DOWEX 50W-X8, NH4+ form). Elution with two column volumes of ion exchange buffer (0.03 M NH_4HCO_3 in 2% ^{i}PrOH/H_2O) and freeze drying yielded a yellowish solid. This material was dissolved in 0.05 M NH_4HCO_3 and ^{i}PrOH/CH_3CN (1/1) was added. The mixture was shaken until a white solid precipitated. After centrifugation the solution was transferred to a fresh flask and the solid again dissolved in 0.05 M NH_4HCO_3. The procedure was repeated twice. The solvent was pooled and concentrated under reduced pressure and again resolved in 5 mL H_2O. Freeze-drying give (1,7-$^{13}C_2$)FPP (54 mg, 0.12 mmol, 85%) as pale yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.46 (br, 1H, CH), 5.24-5.14 (m, 2H, 2xCH), 4.46 (d, $^1J_{C,H}$=147.9, 2H, CH_2), 2.15-1.95 (m, 8H, 4xCH_2), 1.73 (br, 3H,CH_3), 1.68 (s, 3H,CH_3), 1.62 (d, 3H,CH_3), 1.62 (s, 3H,CH_3).^{13}C-NMR (100 MHz, $CDCl_3$): δ = 145.6 (d, $^2J_{C,C}$ = 1.7 Hz, C_q), 138.4 ($^{13}C_q$), 134.4 (C_q), 127.0 (CH), 126.9 (d, $^3J_{C,C}$ = 3.4 Hz, CH), 122.4 (dd, $^1J_{C,C}$ = 50.7 Hz, $^3J_{C,P}$ = 1.8 Hz, CH), 65.2 (br, $^{13}C_q$), 41.6 (dd, $^3J_{C,C}$ = 4.0 Hz, $^3J_{C,C}$ = 4.2 Hz, CH_2), 41.5 (d, $^1J_{C,C}$ = 42.7 Hz, CH_2), 28.7 (d, $^3J_{C,C}$ = 1.6 Hz, CH_2), 28.4 (CH_2), 27.7 (CH_3), 19.8 (CH_3), 18.5 (d, $^3J_{C,C}$ = 4.2 Hz, CH_3), 18.0 (d, $^1J_{C,C}$ = 42.2 Hz, CH_3) ppm.

References

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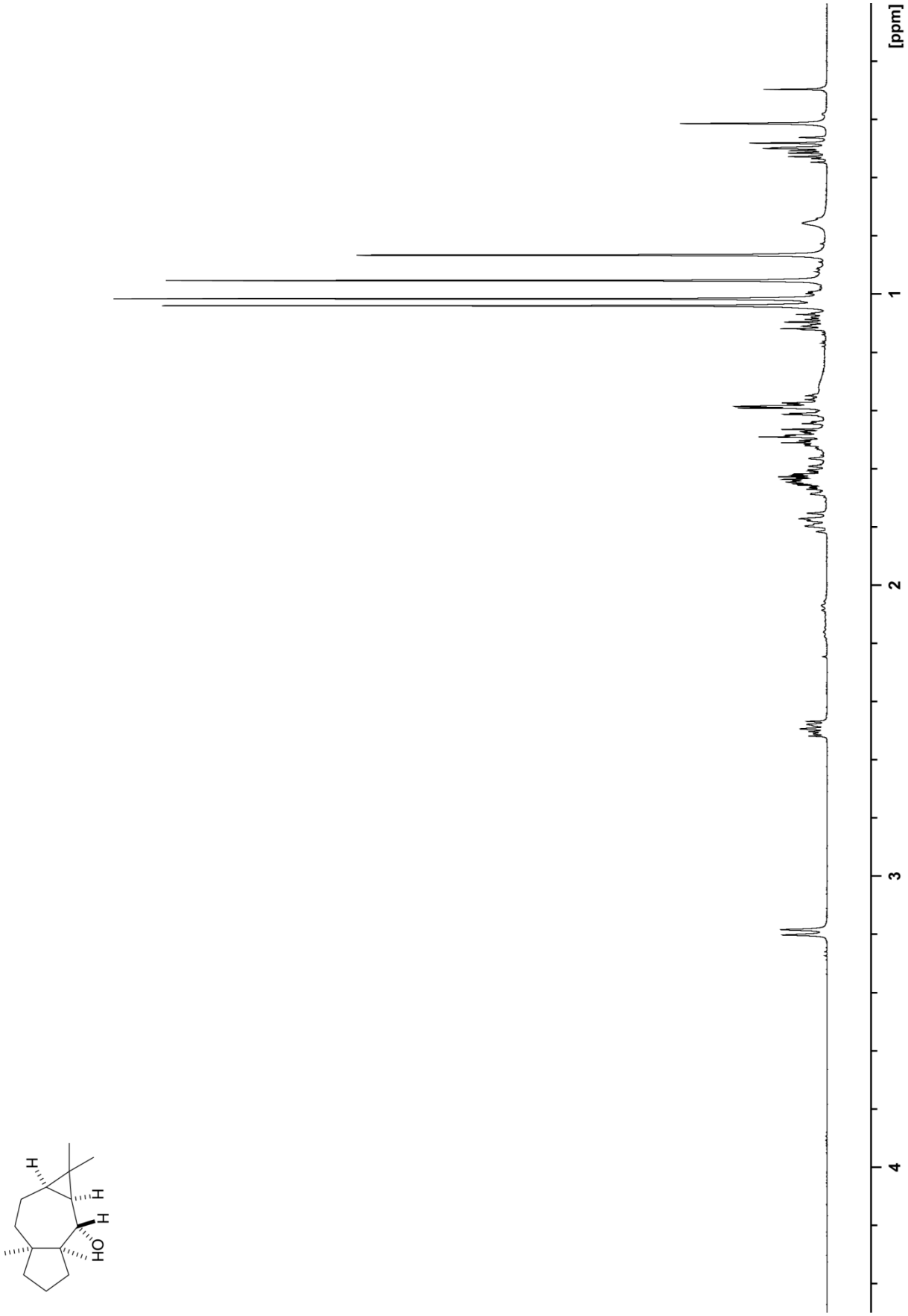

Fig. 6 ^{1}H-NMR-spectrum of neomeranol B (**1**) in ($^{2}H_{6}$)benzene at 298K at 500 MHz.

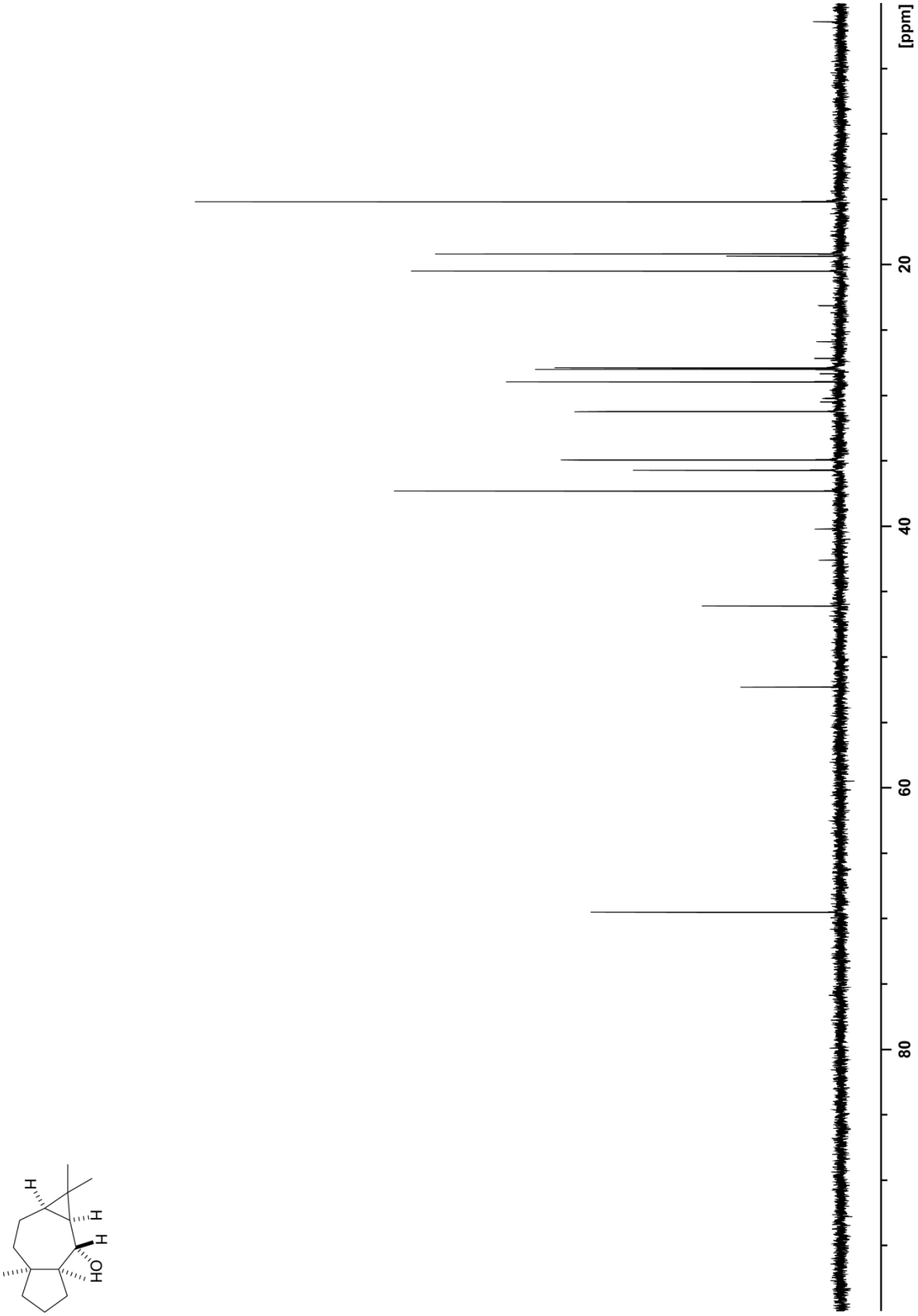

Fig. 7 ^{13}C-NMR-spectrum of neomeranol B (**1**) in ($^{2}H_6$)benzene at 298K at 500 MHz.

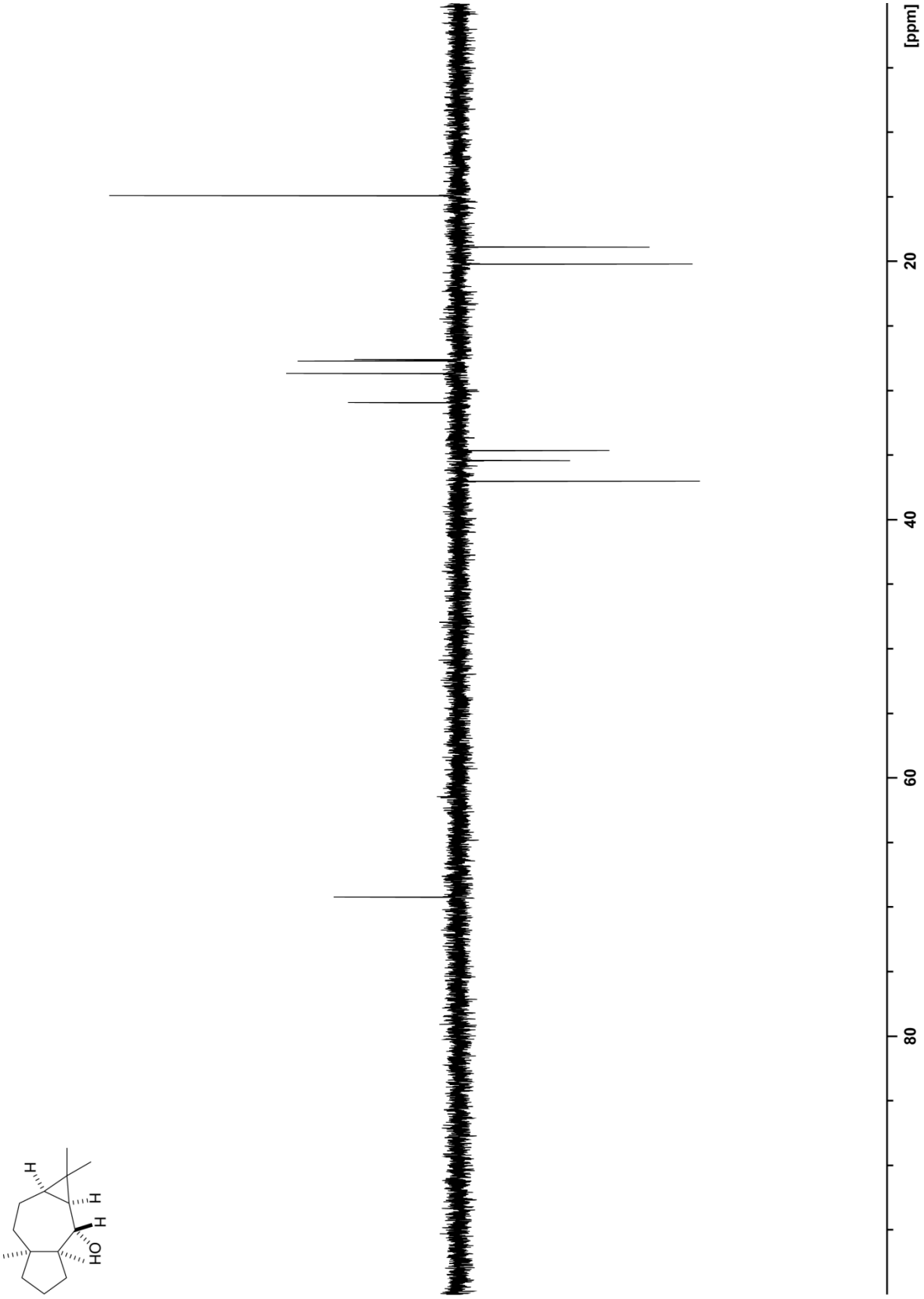

Fig. 8 ^{13}C-DEPT135-NMR-spectrum of neomeranol B (**1**) in ($^{2}H_6$)benzene at 298K at 500 MHz.

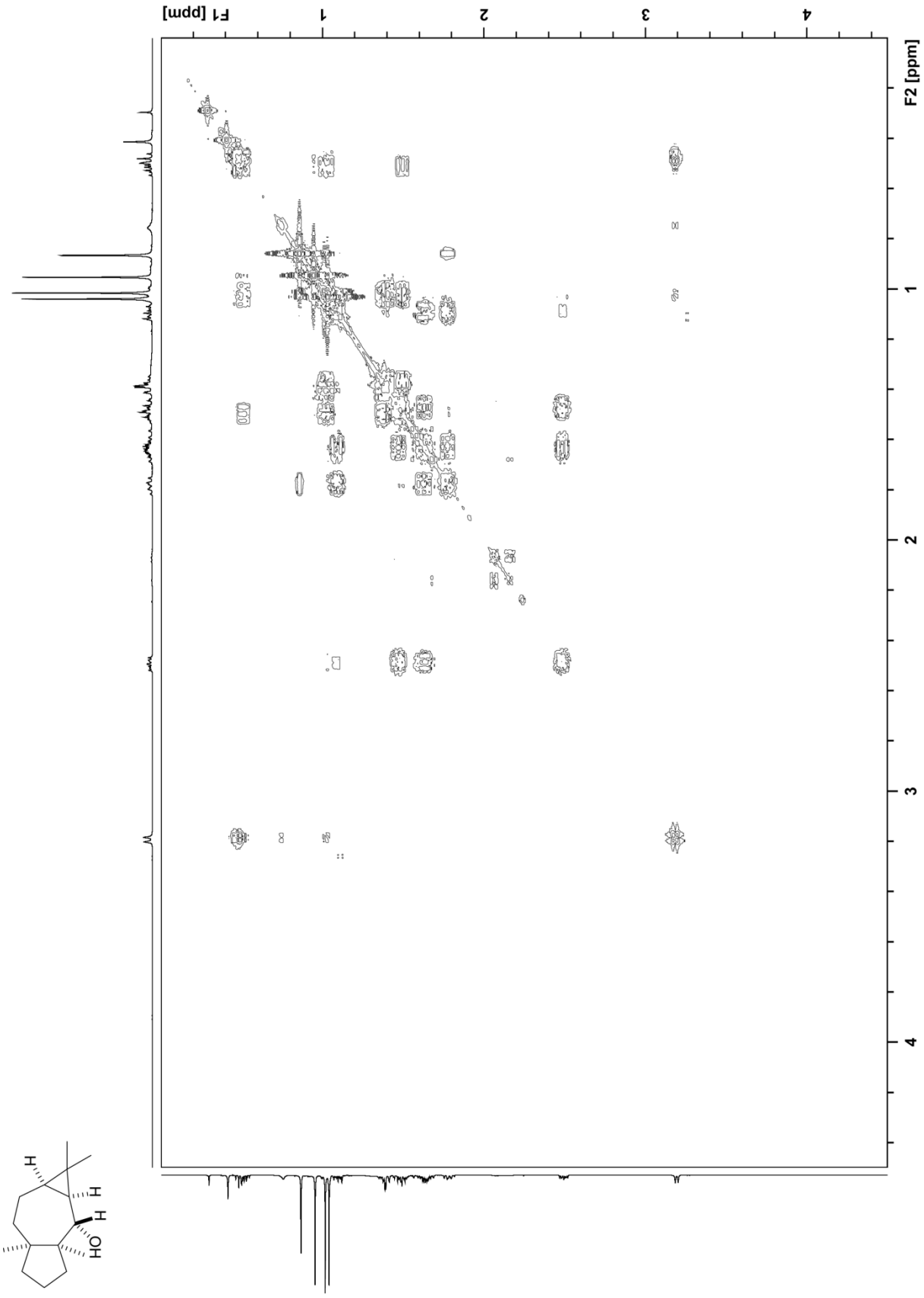

Fig. 9 $^{1}H,^{1}H$-COSY spectrum of neomeranol B (**1**) in ($^{2}H_{6}$)benzene at 298K at 500 MHz.

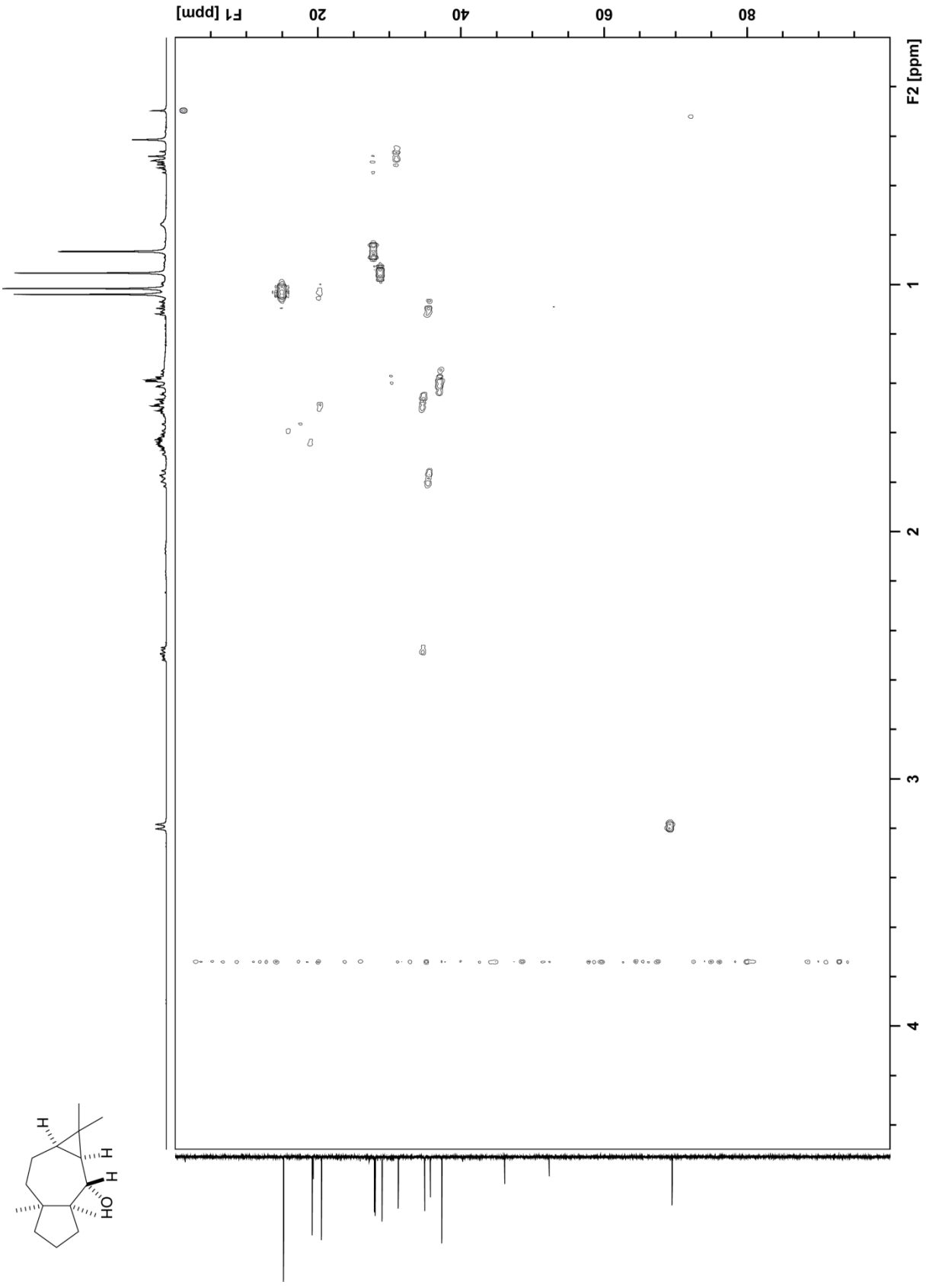

Fig. 10 HSQC spectrum of neomeranol B (**1**) in ($^2H_6$)benzene at 298K at 500 MHz.

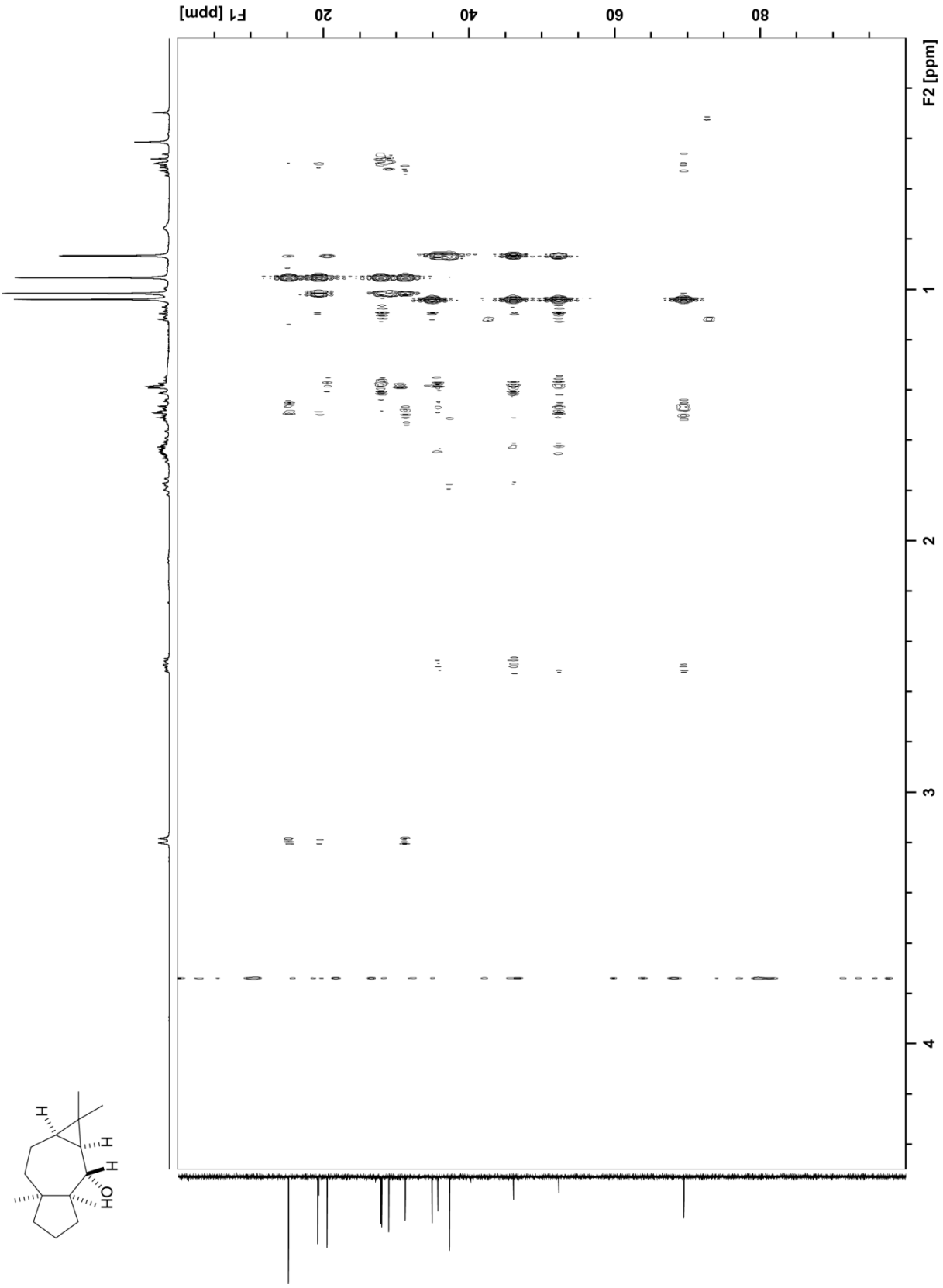

Fig. 11 HMBC spectrum of neomeranol B (**1**) in ($^2H_6$)benzene at 298K at 500 MHz.

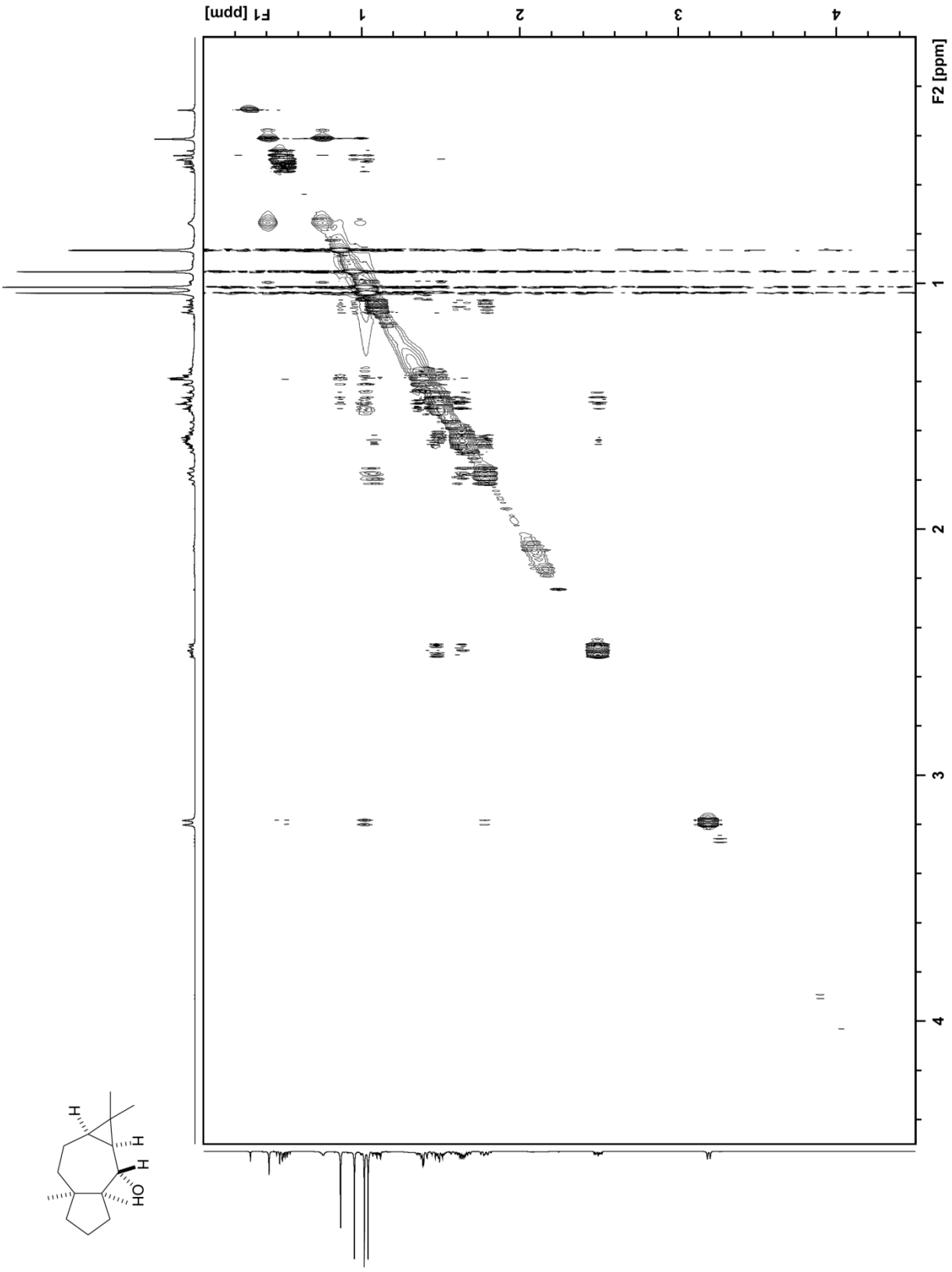

Fig. 12 NOESY spectrum of neomeranol B (**1**) in ($^2H_6$)benzene at 298K at 500 MHz.

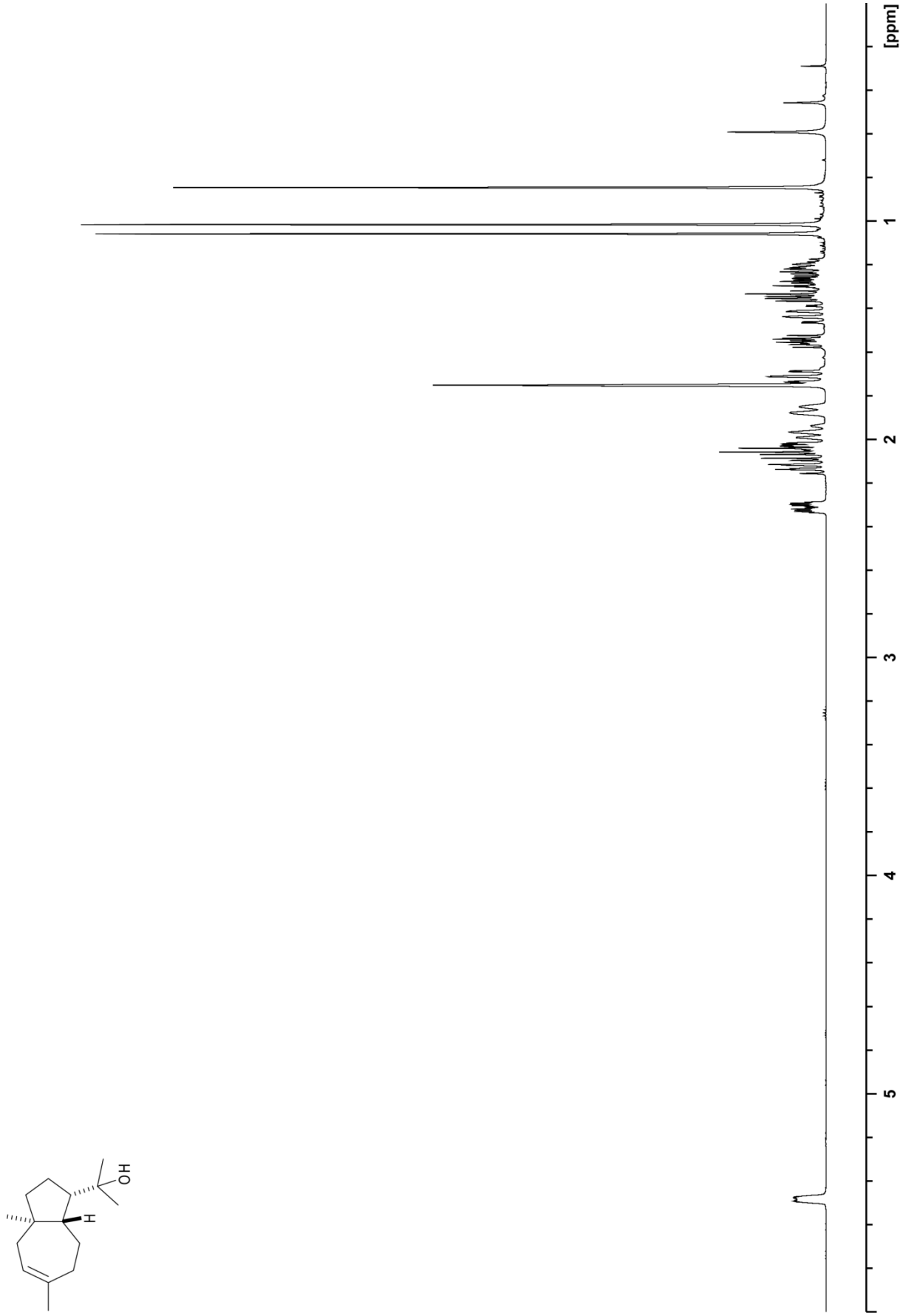

Fig. 13 ^{1}H-NMR spectrum of isodauc-8-en-11-ol (**3**) in ($^{2}H_6$)benzene at 298K at 500 MHz.

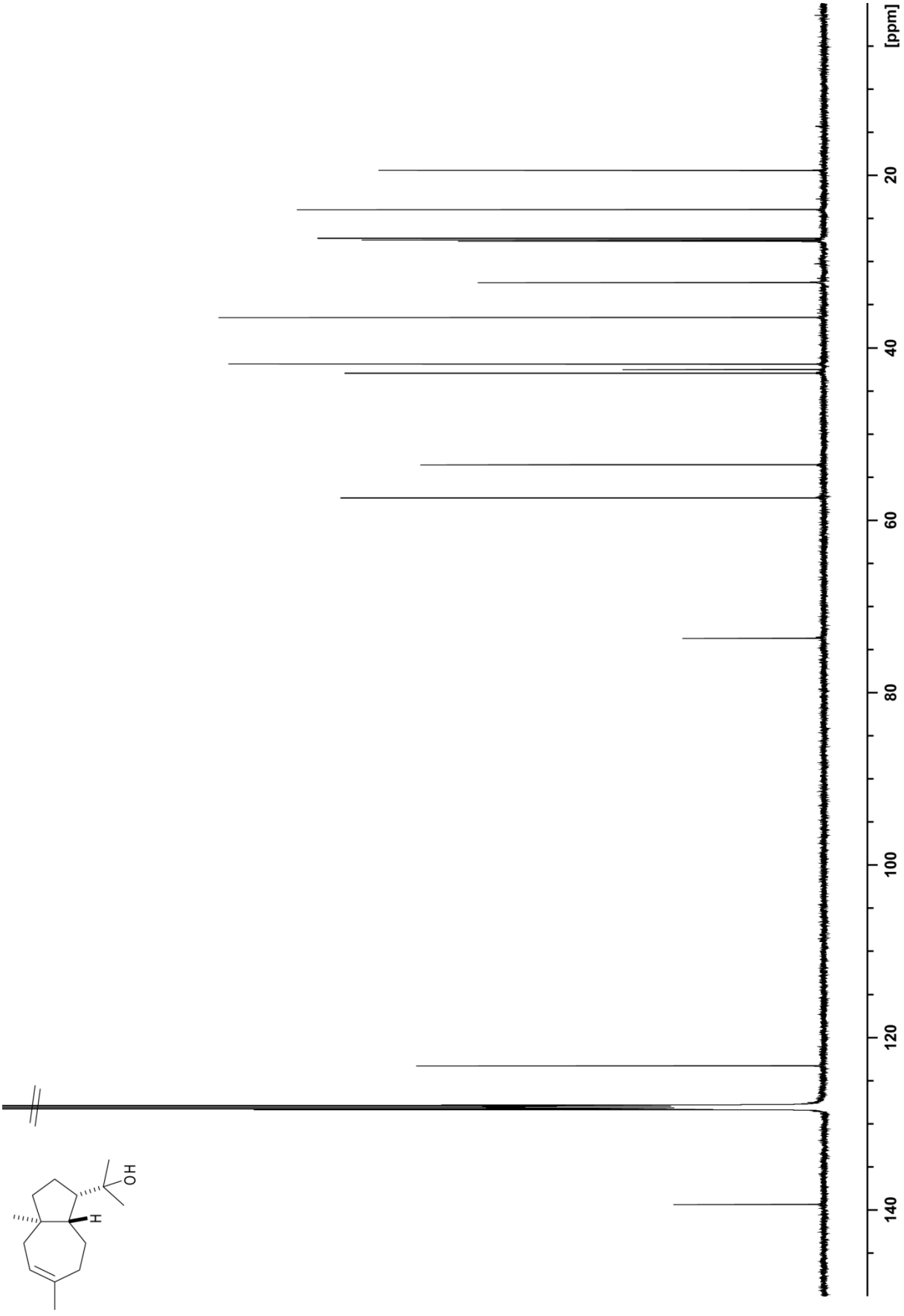

Fig. 14 ^{13}C-NMR spectrum of isodauc-8-en-11-ol (**3**) in ($^{2}H_6$)benzene at 298K at 500 MHz.

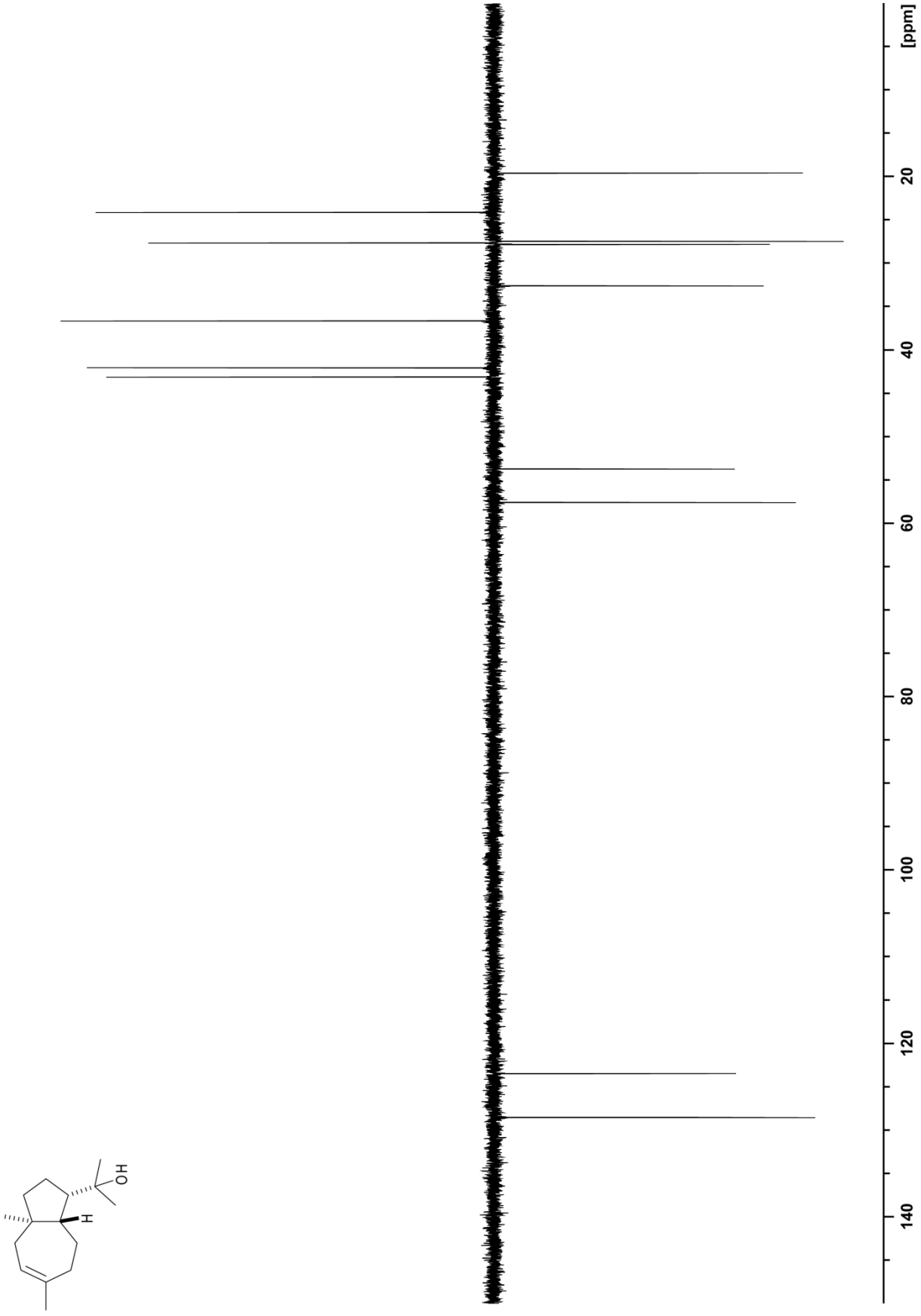

Fig. 15 ^{13}C-DEPT135-NMR spectrum of isodauc-8-en-11-ol (**3**) in ($^{2}H_6$)benzene at 298K at 500 MHz.

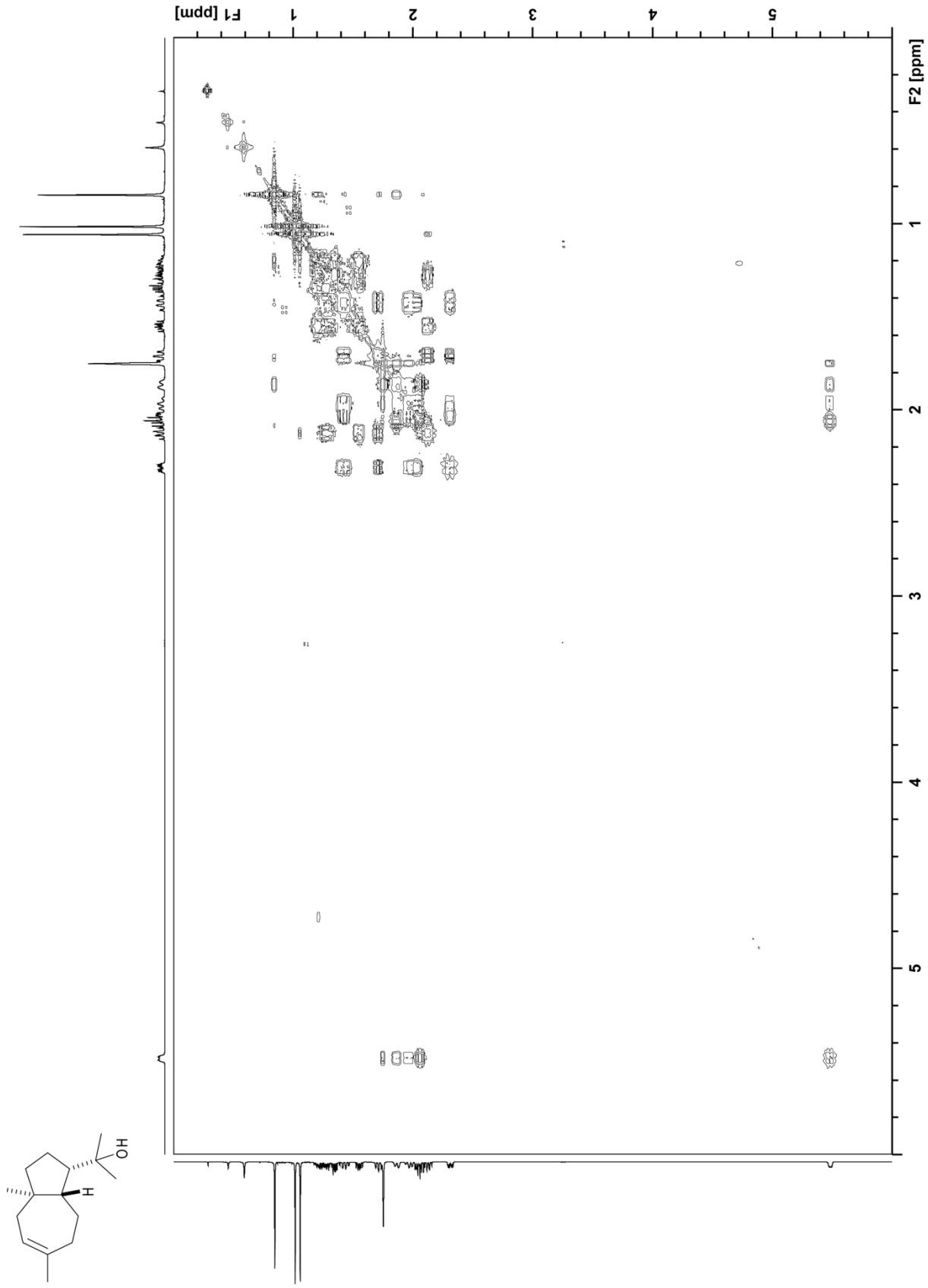

Fig. 16 $^{1}H,^{1}H$-COSY spectrum of isodauc-8-en-11-ol (**3**) in ($^{2}H_{6}$)benzene at 298K at 500 MHz.

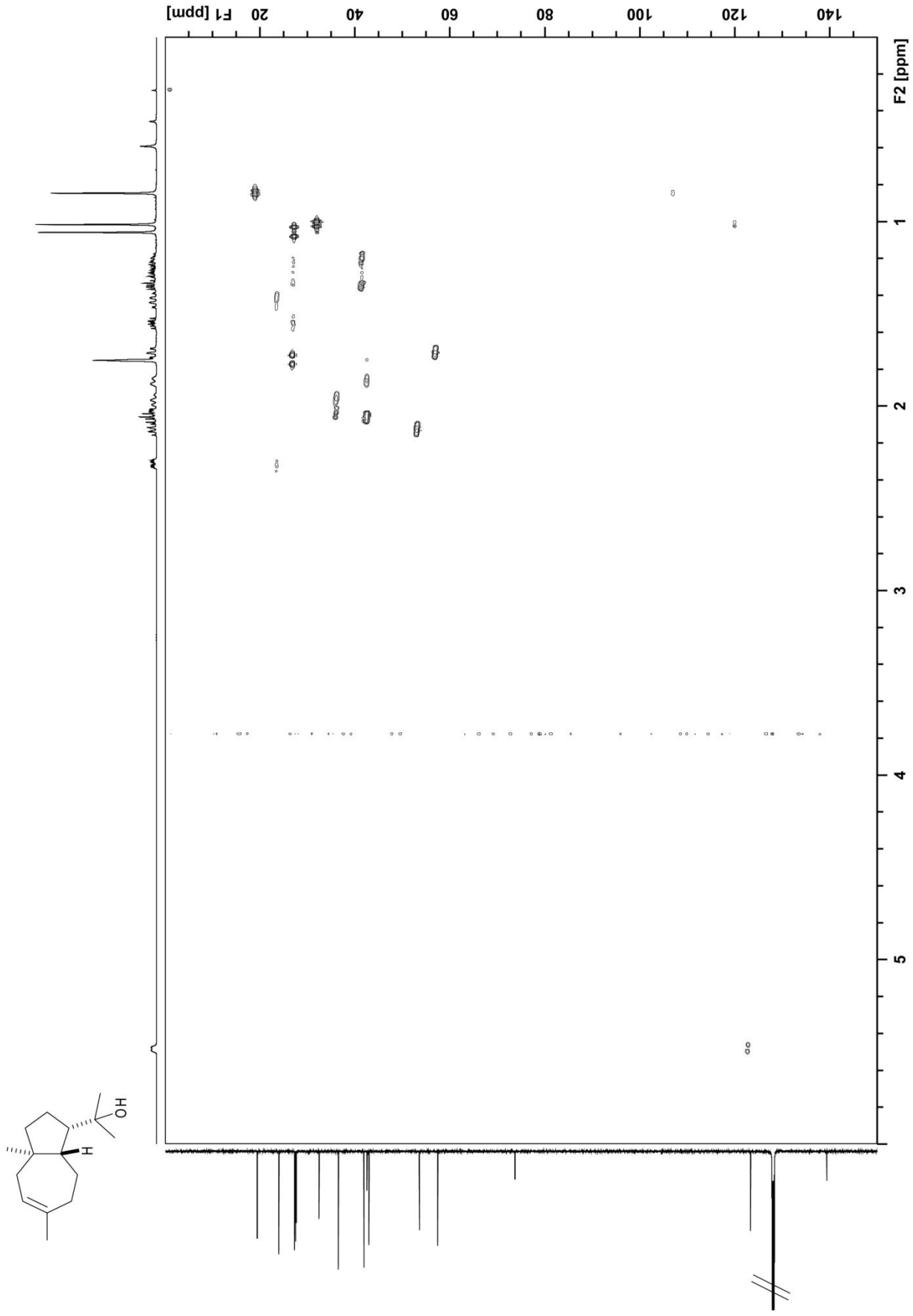

Fig. 17 HSQC spectrum of isodauc-8-en-11-ol (**3**) in ($^2H_6$)benzene at 298K at 500 MHz.

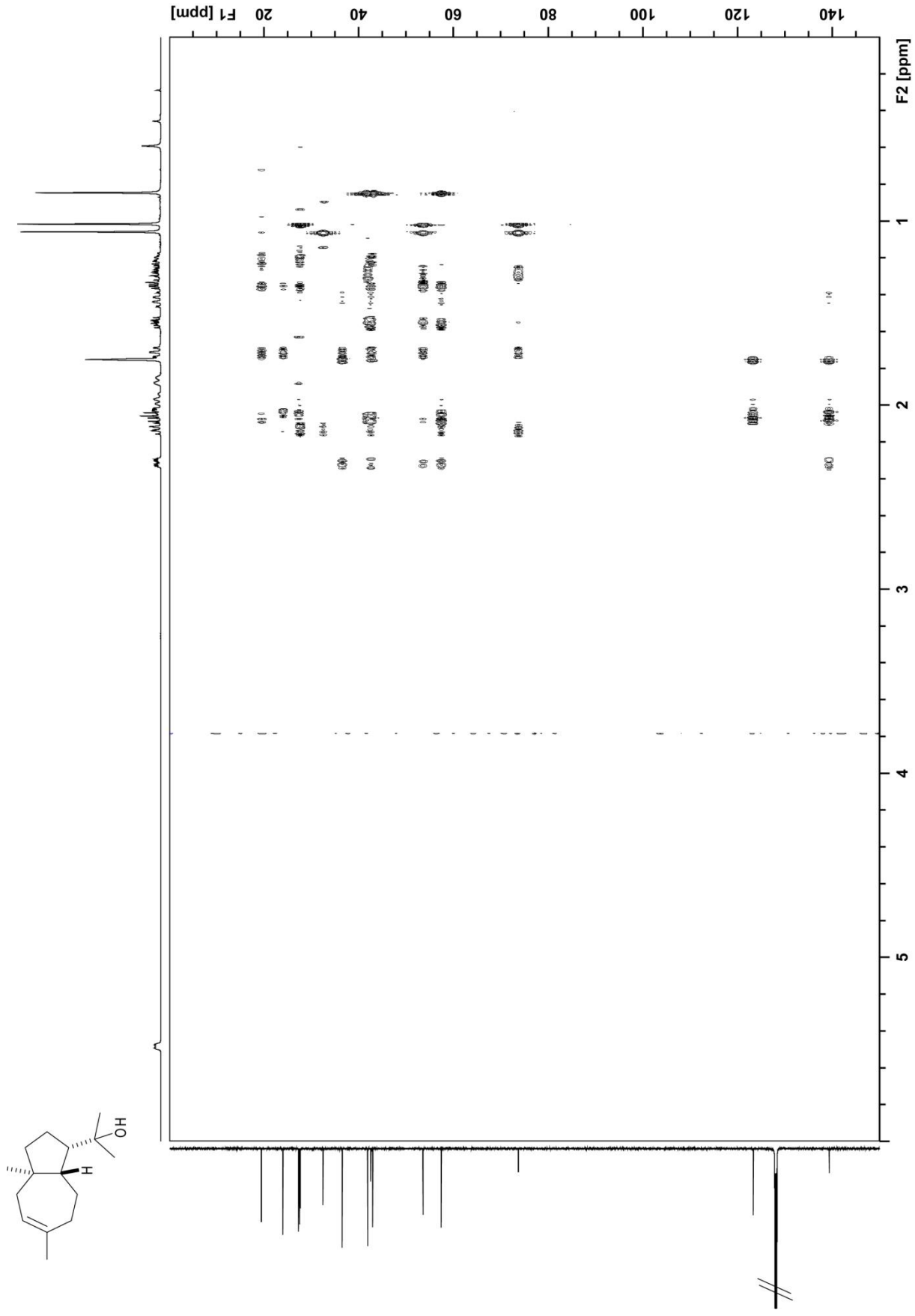

Fig. 18 HMBC spectrum of isodauc-8-en-11-ol (**3**) in ($^2H_6$)benzene at 298K at 500 MHz.

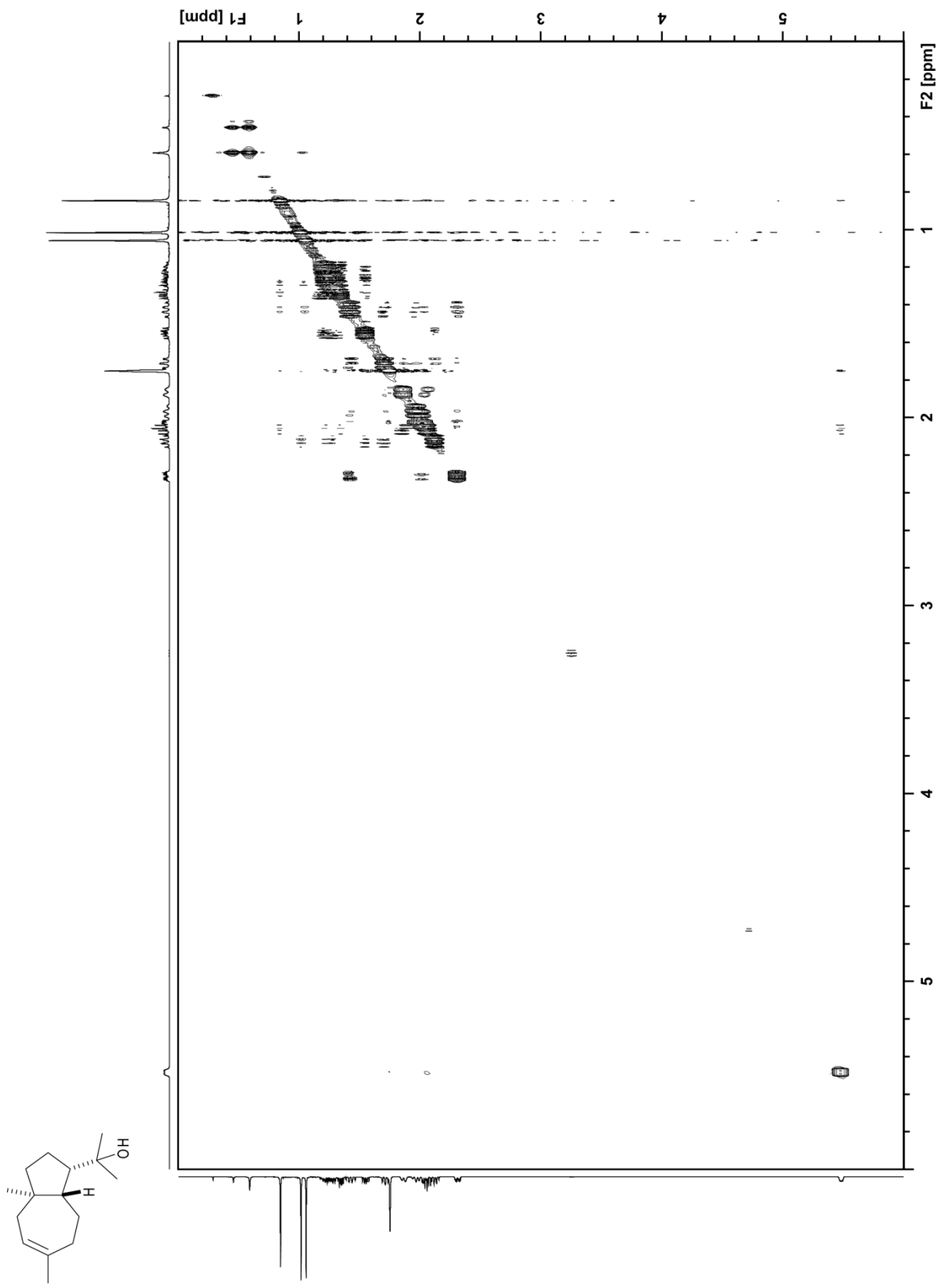

Fig. 19 NOESY spectrum of isodauc-8-en-11-ol (**3**) in ($^2H_6$)benzene at 298K at 500 MHz.

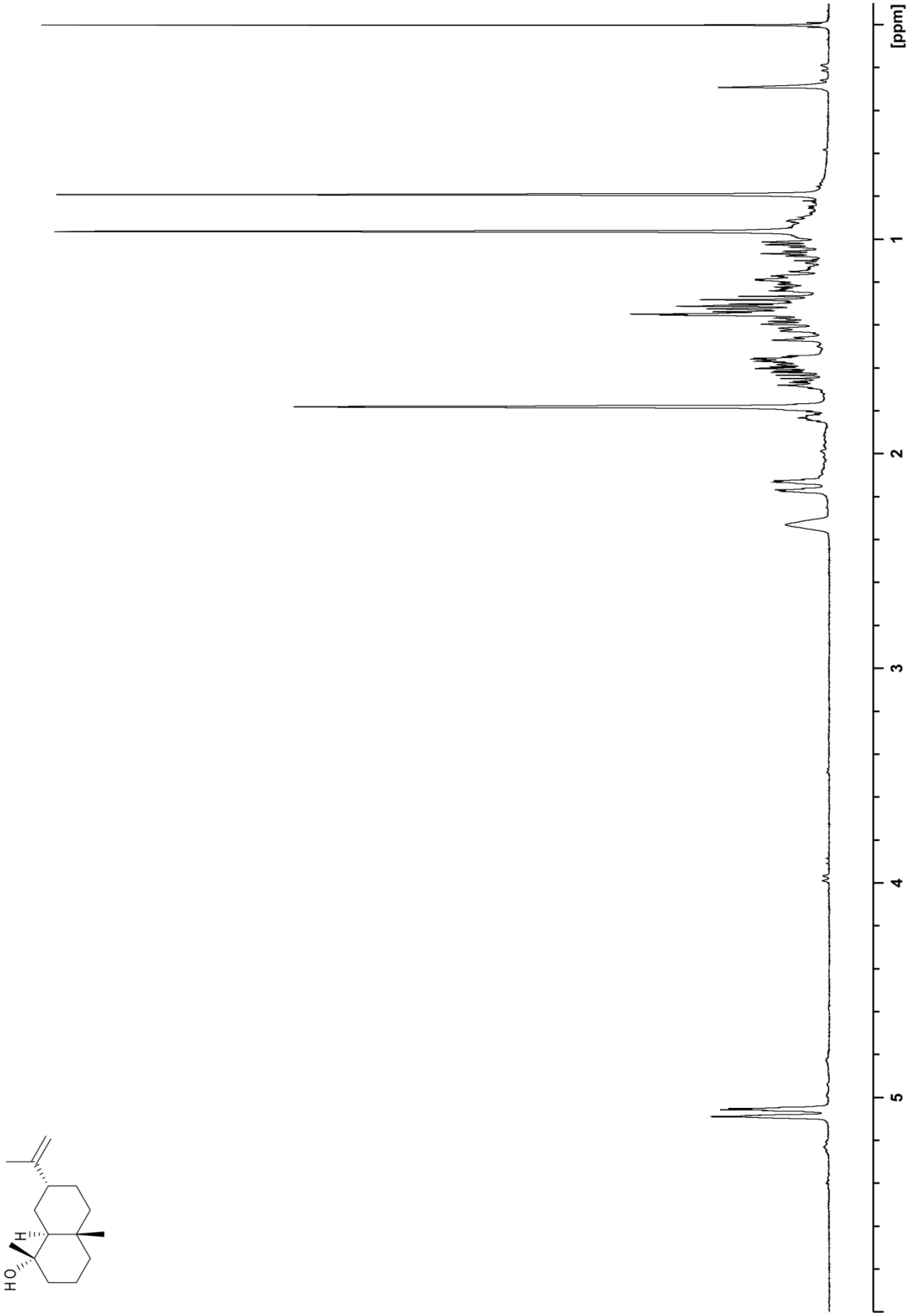

Fig. 20 ^{1}H-NMR spectrum of intermedeol (**4**) in ($^{2}H_6$)benzene at 298K at 300 MHz.

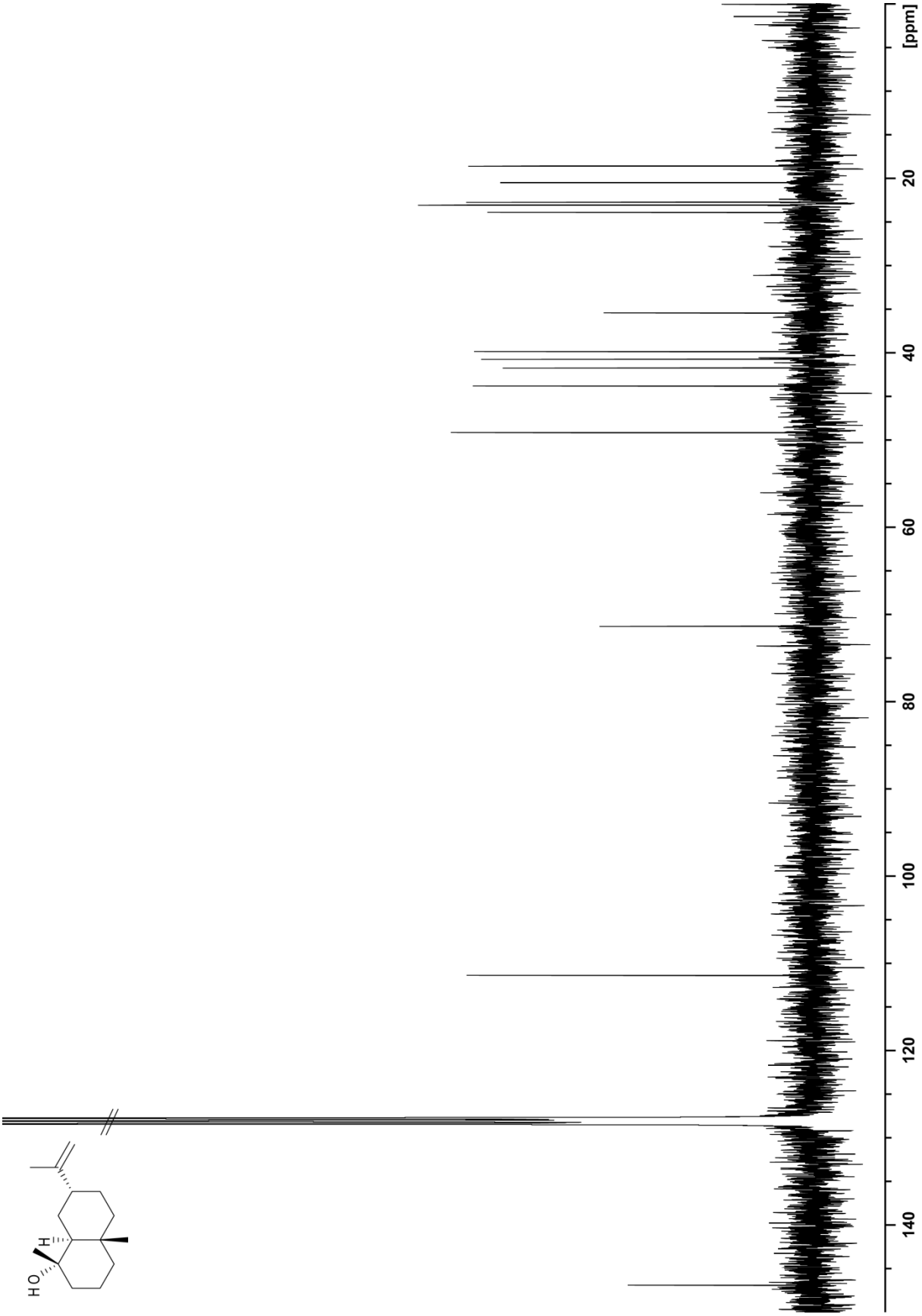

Fig. 21 ^{13}C-NMR spectrum of intermedeol (**4**) in ($^{2}H_6$)benzene at 298K at 300 MHz.

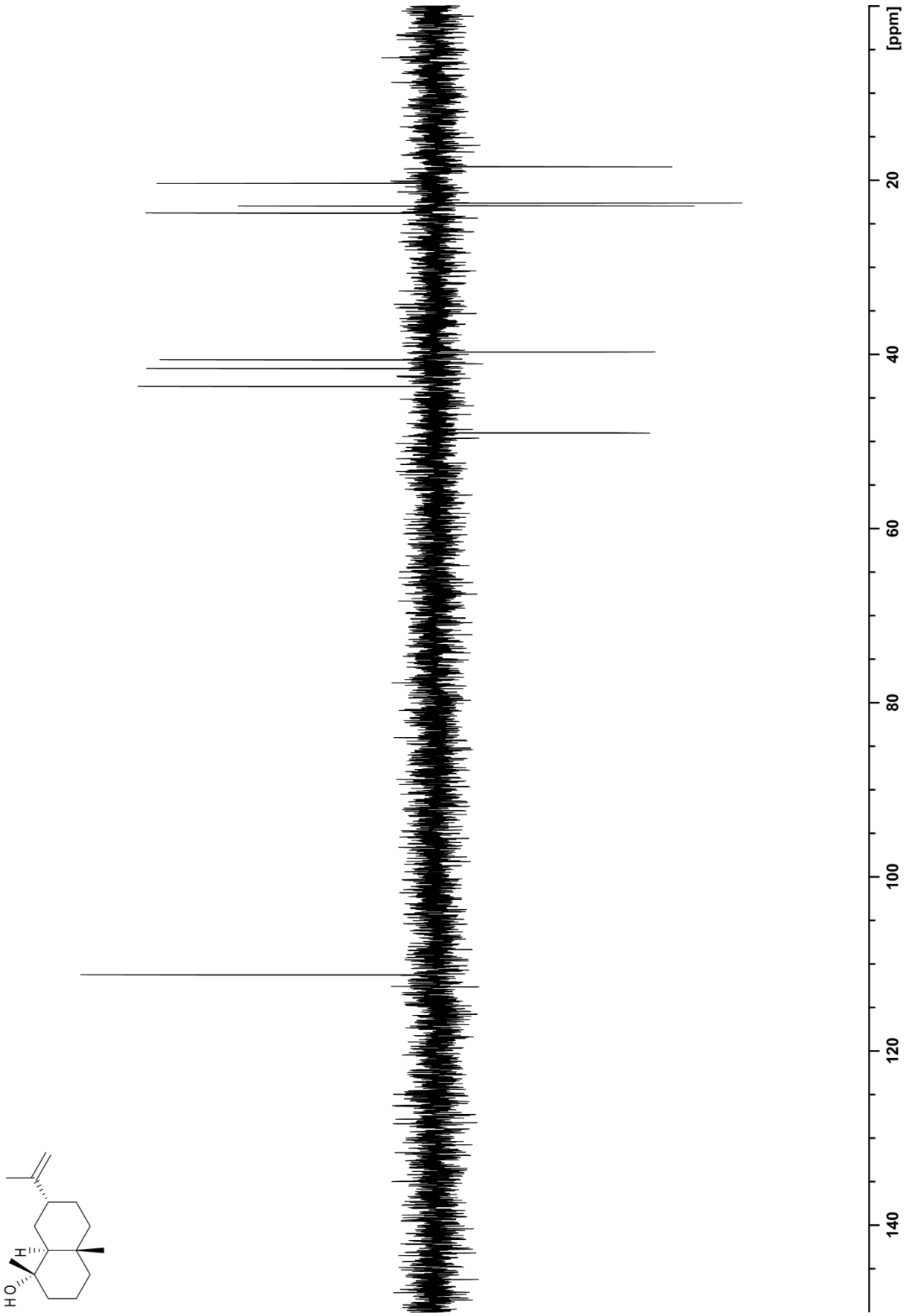

Fig. 22 ^{13}C-DEPT135-NMR spectrum of intermedeol (**4**) in ($^{2}H_6$)benzene at 298K at 300 MHz.

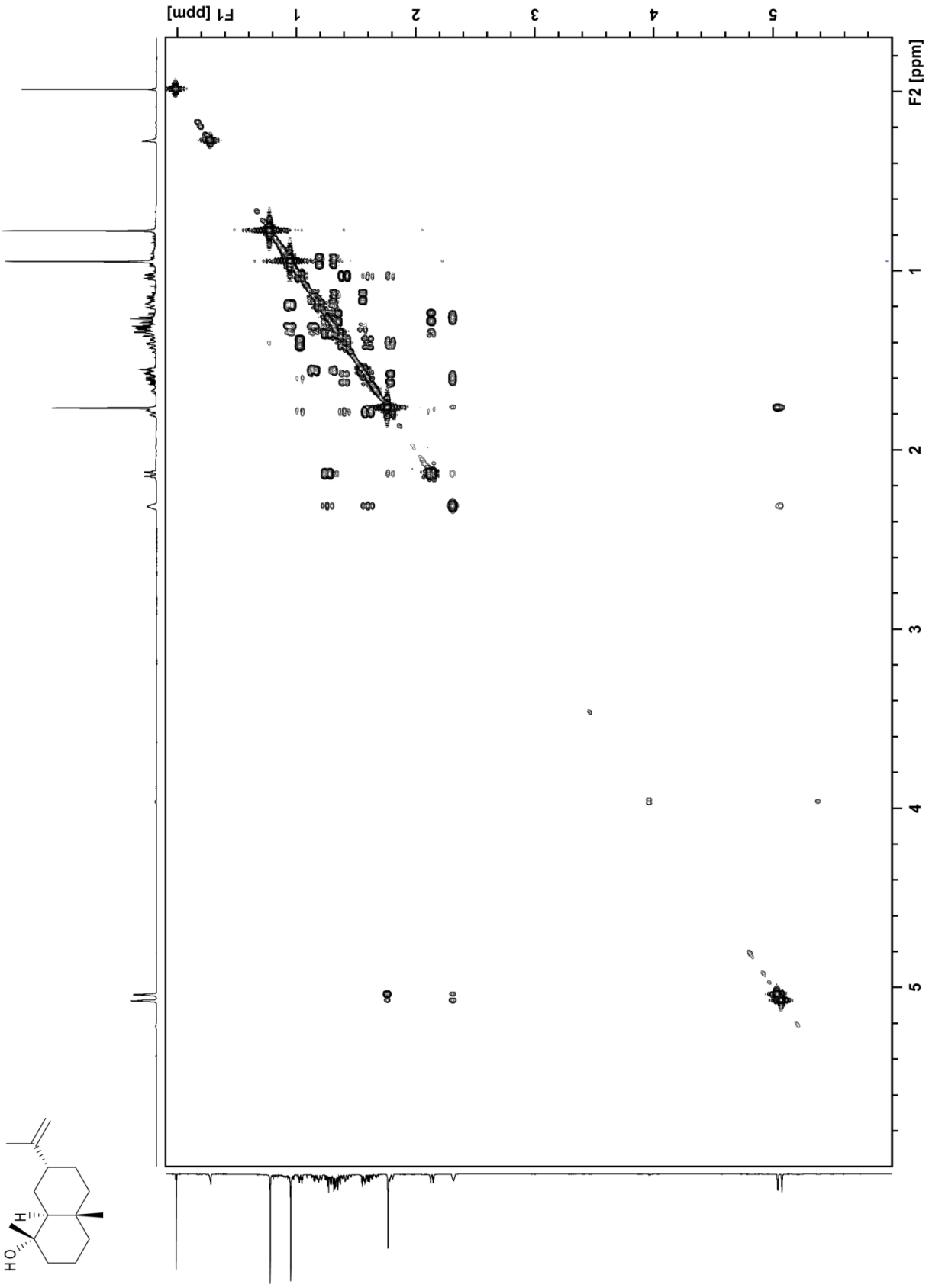

Fig. 23 $^{1}H,^{1}H$-COSY spectrum of intermedeol (**4**) in ($^{2}H_{6}$)benzene at 298K at 600 MHz.

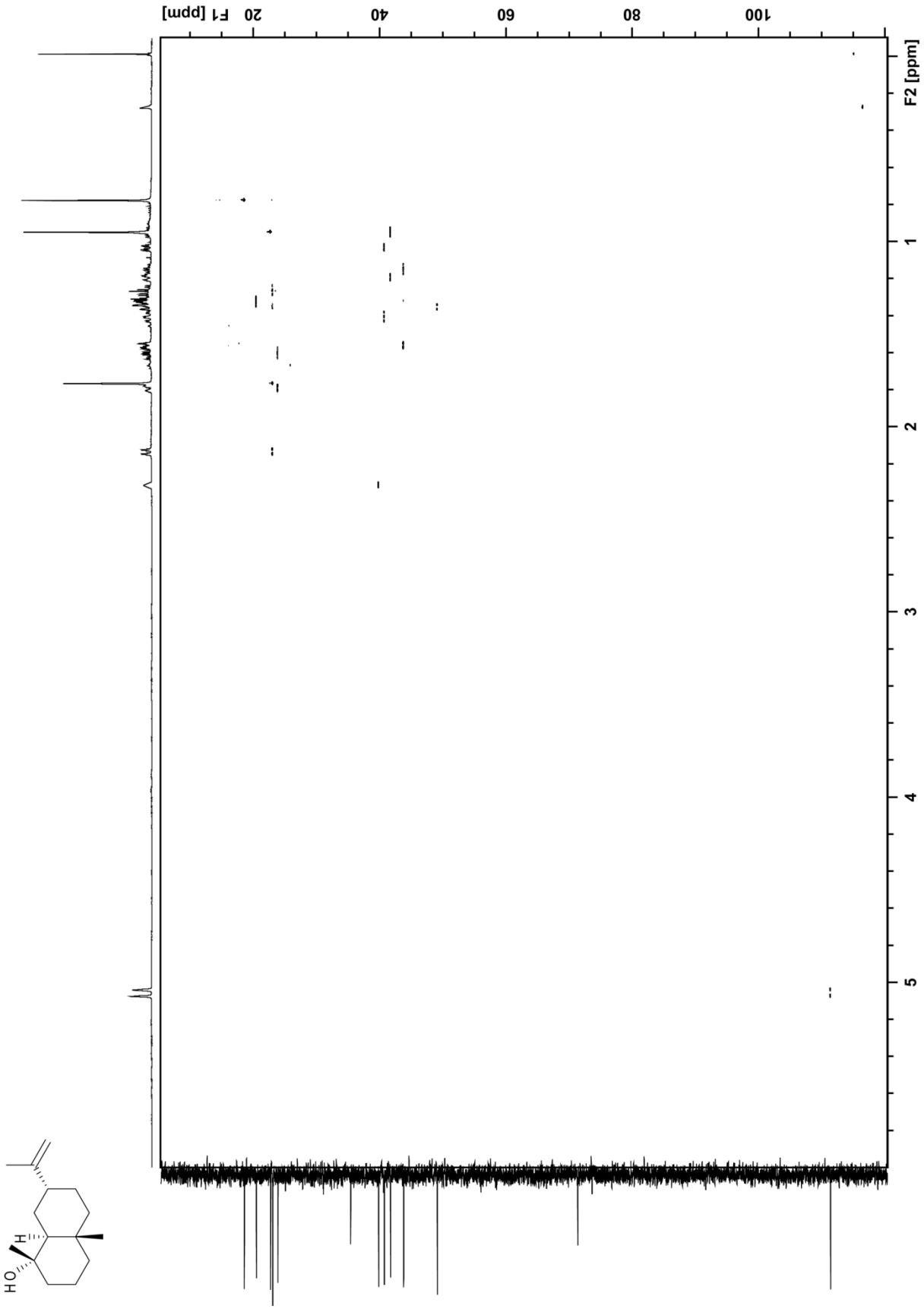

Fig. 24 HSQC spectrum of intermedeol (**4**) in ($^2H_6$)benzene at 298K at 600 MHz.

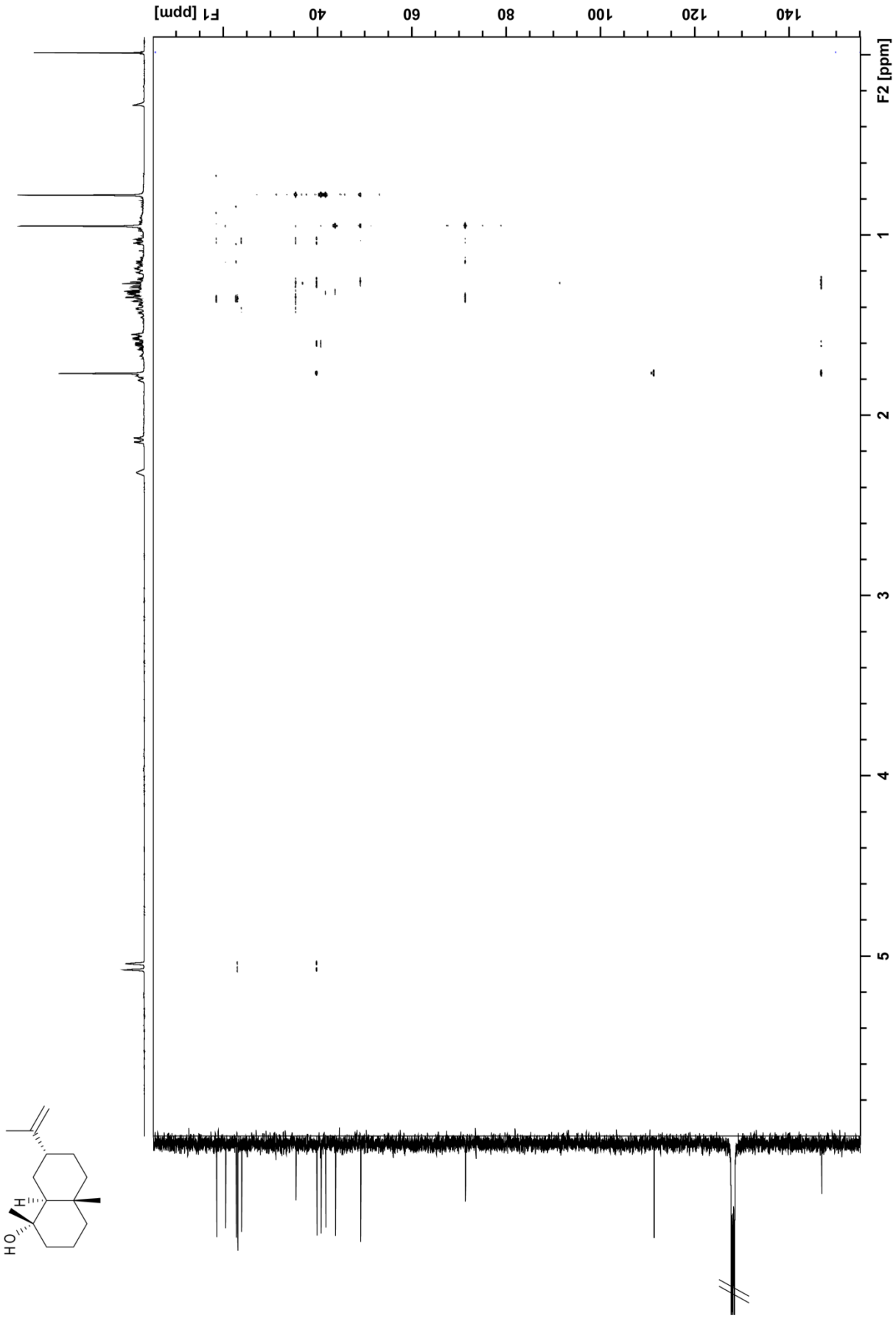

Fig. 25 HMBC spectrum of intermedeol (**4**) in ($^2H_6$)benzene at 298K at 600 MHz.

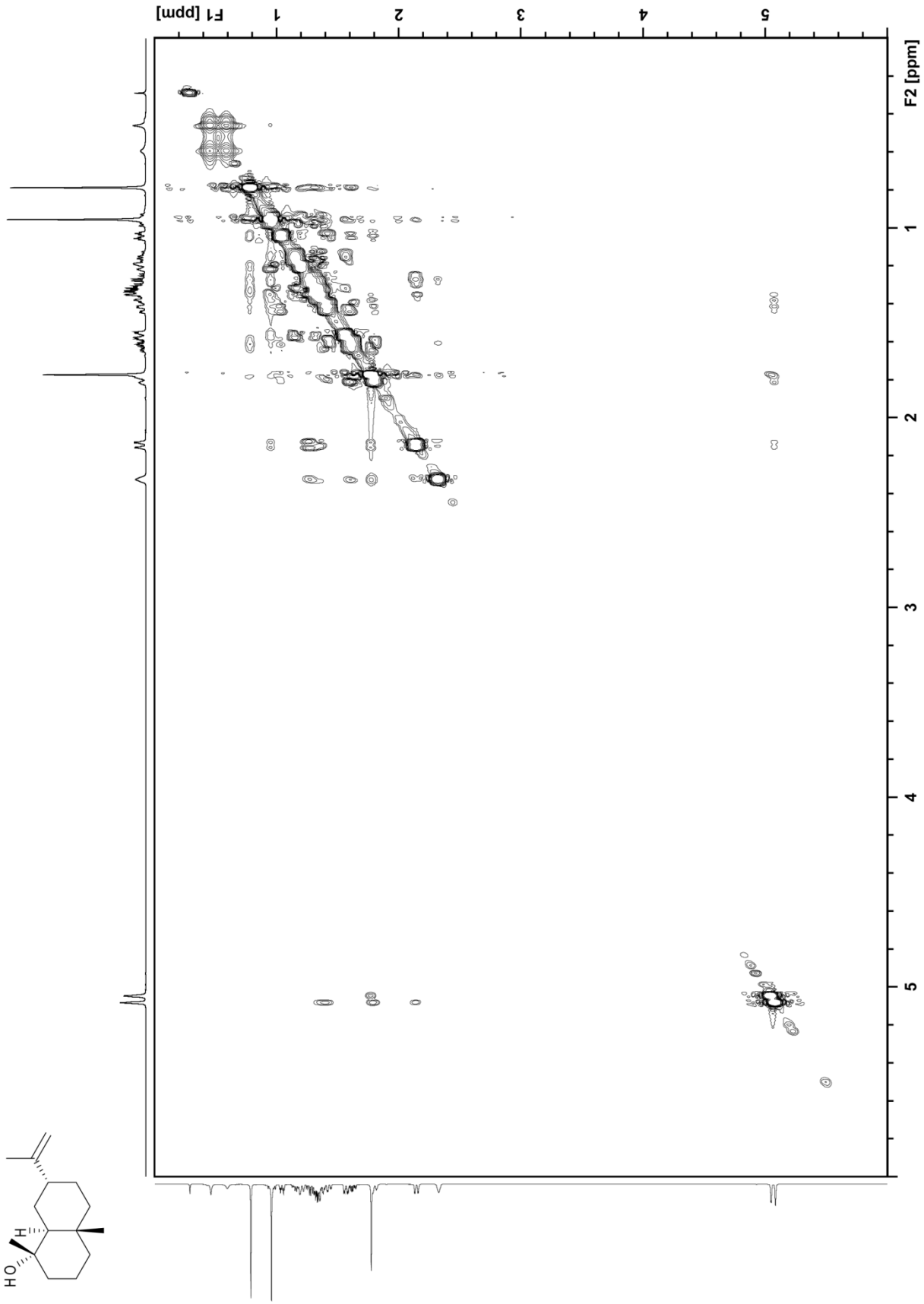

Fig. 26 NOESY spectrum of intermedeol (**4**) in ($^2H_6$)benzene at 298K at 500 MHz.