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Cascade transformation of 4-hydroxymethyl-2-carene into novel cage methanopyrano[4,3-*b*]thieno[3,2-*g*]benzofuran derivative

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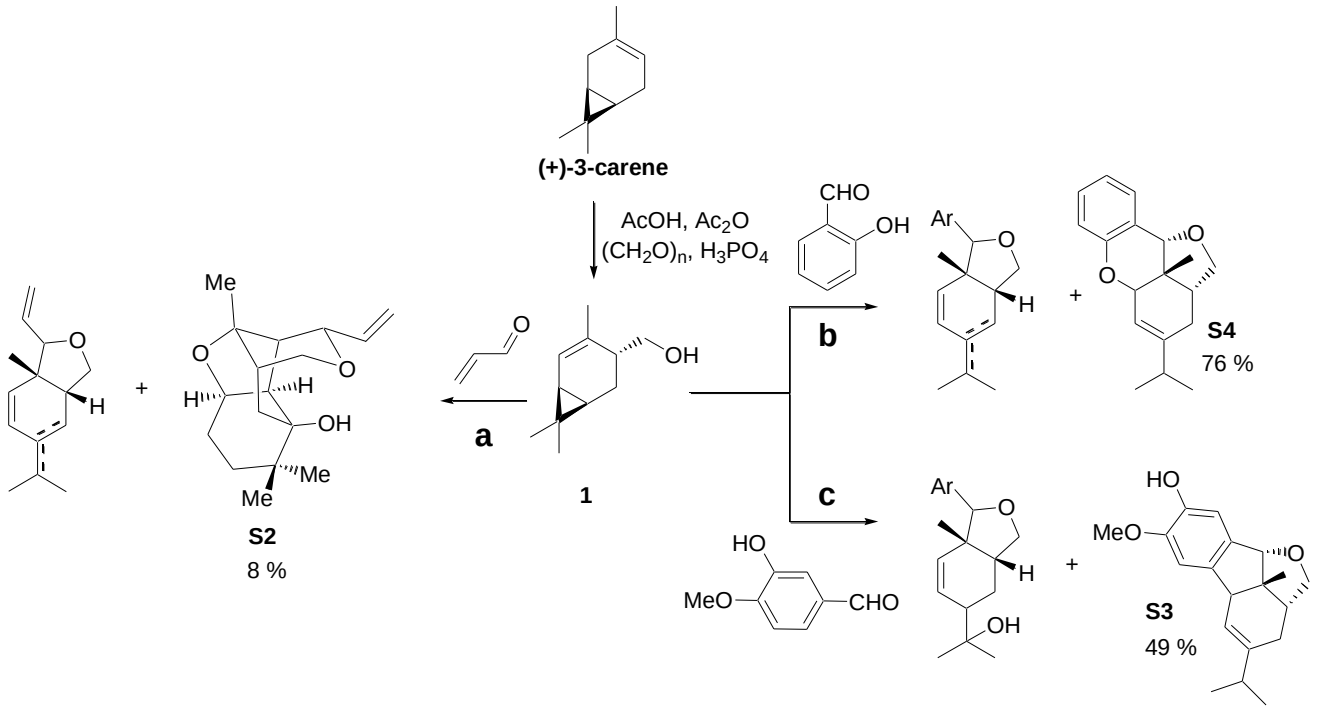


Scheme S1. Literature syntheses of heterocyclic compounds based on (+)-3-carene.

Experimental

General. All commercially available compounds and solvents were reagent grade and were used as purchased unless noted. 3-Carene was purchased from Acros Organics. Column chromatography (CC): silica gel (SiO_2; 60-200 μ; Macherey-Nagel); hexane/EtOAc 100:0 → 0:100. GC/MS (purity control and products analysis): Agilent 7890A with a quadrupole mass spectrometer Agilent 5975C as a detector, HP-5MS quartz column, 30000x0.25 mm, He (1 atm) as carrier gas. Optical rotation: polAAr 3005 spectrometer, EtOH soln. HR-MS: DFS-Thermo-Scientific spectrometer in a full scan mode (15-500 *m/z*, 70 eV electron-impact ionization, direct sample introduction). ^{1}H and ^{13}C NMR: Bruker Avance-III 600 apparatus at 600.30 MHz (^{1}H) and 150.95 MHz (^{13}C) in $CDCl_3$; chemical shifts δ in ppm rel. to residual $CHCl_3$ (δ (H) 7.24, δ (C) 76.90 ppm), *J* in Hz; structure determinations by analyzing the ^{1}H NMR spectra, including ^{1}H – ^{1}H 2D homonuclear correlation (COSY, NOESY); J-modulated ^{13}C NMR spectra (JMOD), and ^{13}C – ^{1}H 2D heteronuclear correlation with one-bond and long-range spin-spin coupling constants

(HSQC, ^{1}J(C,H) = 145 Hz; HMBC, $^{2,3}J$(C,H) = 7 Hz). Numeration of atoms in compound **4** is given for assigning the signals in the NMR spectra and does not coincide with that for systematic name. Spectral and analytical studies were carried out at the Collective Chemical Service Center of the Siberian Branch of the Russian Academy of Sciences.

***trans*-4-Hydroxymethyl-2-carene 1**. Based on [S1],[S2], the following synthetic technique was developed, in which the formation of the desired product proceeded directly from 3-carene. To a mixture of 3-carene (200 g), glacial acetic acid (250 ml), acetic anhydride (50 ml) and paraformaldehyde (45 g), conc. phosphoric acid (55 ml) was added. The mixture was stirred at 13-15°C for 6 h. Then water (200 ml) and ethyl acetate (200 ml) were added. The organic layer was separated and washed with sat. $NaHCO_3$ aq. until there was no further evolution of gas, and then dried over Na_2SO_4. The solvent was distilled off. The residue when distilled to yield 65 g 3-carene and 60 g mixture, containing compound **1** (b.p. 110-115°C/5 Torr, 90 % purity) which was purified by subsequent distillation.

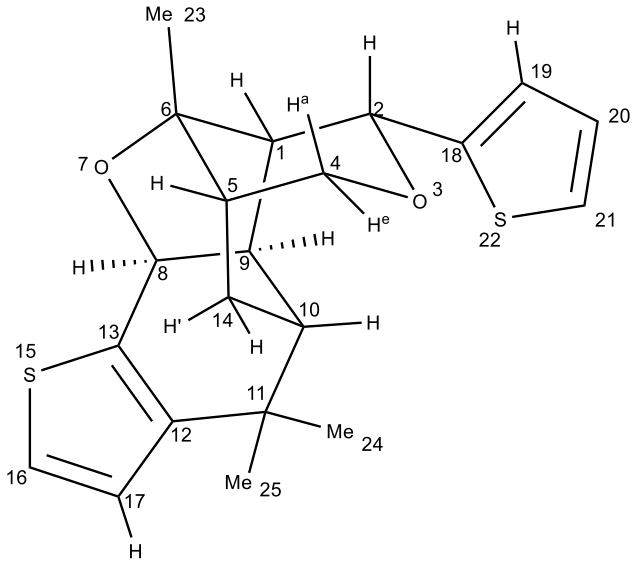
Reaction of *trans*-4-hydroxymethyl-2-carene 1 and thiophene-2-carbaldehyde in the presence of clay. To s suspension of clay K10 or acid-modified halloysite (2.0 g, calcined at 105°C for 3 h) in dichloromethane (10 ml), a solution of *trans*-4-hydroxymethyl-2-carene **1** (0.50 g, 3 mmol) and thiophene-2-carbaldehyde (0.50 g, 4.5 mmol) in dichloromethane (10 ml) were added. The solvent was removed by rotary evaporation from mixture. After 3 hours, ethyl acetate was added, the catalyst was filtered off. The reaction mixture was analyzed by GC-MS. In case of using K10 as a catalyst, product content was as follows: **2a,b**/10%, **3**/65% and **4**/8%. In case of using halloysite, the content was 65%, 24% and 12.5%, respectively.

Reaction of *trans*-4-hydroxymethyl-2-carene 1 and thiophene-2-carbaldehyde in the presence of clay in CH_2Cl_2. A solution of *trans*-4-hydroxymethyl-2-carene **1** (0.50 g, 3 mmol) and thiophene-2-carbaldehyde (0.50 g, 4.5 mmol) in dichloromethane (10 ml) was added to a suspension of clay K10 or acid-modified halloysite (2.0 g, calcined at 105°C for 3 h) in dichloromethane (10 ml). The mixture was stirred at room temperature for 3 h. The catalyst was filtered off, and the filtrate was analyzed by GC-MS. In case of using K10 as a catalyst, product content was as follows: **2a,b**/43%, **3**/24% and **4**/25%. In case of using halloysite, no reaction occurred.

Reaction of *trans*-4-hydroxymethyl-2-carene 1 and thiophene-2-carbaldehyde in the presence of calcined K10 and CH_2Cl_2. To a suspension of K10 clay (2.0 g, calcined at 105°C for 3 h) in dichloromethane (10 ml), a solution of *trans*-4-hydroxymethyl-2-carene **1** (0.50 g, 3 mmol) and thiophene-2-carbaldehyde (0.50 g, 4.5 mmol) in dichloromethane (10 ml) was added. The mixture was stirred at room temoerature for 3 h. The catalyst was removed by filtration and the filtrate was evaporated. Based on GC-MS data, product content in the reaction mixture was as follows: **2a,b**/43%, **3**/24% and **4**/25%. The residue was separated by column chromatography to give mixture of compounds **2a+2b** as a brown oil (0.462 g, 59%), compound **3** as a brown oil (0.120 g, 14%) and compound **4** as a yellow oil (0.052 g, 5%). To obtain

an analytically pure sample of product, **4** two consecutive purifications using column chromatography were used. The first one with 20 g of SiO_2, and the second one with 5 g of SiO_2.

(5*R*,5a*R*,5b*R*,6*R*,9*S*,9a*S*,10a*S*)-4,4,9a-Trimethyl-6-(thiophen-2-yl)-4,5,5a,5b,8,9,9a,10a-octahydro-6*H*-5,9-methanopyrano[4,3-*b*]thieno[3,2-*g*]benzofuran (**4**).



$[\alpha]_D^{23.5} = +60.95$ (c 0.23 in EtOH). ^{1}H NMR (600 MHz, $CDCl_3$, J, Hz) δ: 1.10 (s, 3H, Me-25), 1.27 (s, 3H, Me-24), 1.53 (s, 3H, Me-23), 1.65-1.70 (m, 1H, H-5), 1.72 (dd, 1H, H-14, J 13.3, 7.1), 1.74-1.81 (dddd, 1H, H-14', J 13.3, 10.9, 6.4, 2.0), 2.17-2.20 (m, 1H, H-1), 2.62 (ddd, 1H, H-10, J 10.9, 7.1, 3.3), 2.76-2.79 (m, 1H, H-9), 3.82 (dm, 1H, H-4a, J 11.7), 4.02 (dd, 1H, H-4e, J 11.7, 2.1), 4.84 (d, 1H, H-8, J 3.6), 5.09 (d, 1H, H-2, J 2.8), 6.87 (d, 1H, H-17, J 5.1), 6.99 (dd, 1H, H-20, J 5.0, 3.4), 7.00 (br.d, 1H, H-19, J 3.4), 7.20 (d, 1H, H-16, J 5.1), 7.25 (dd, 1H, H-21, J 5.0, 1.2).

^{13}C NMR (150.94 MHz, $CDCl_3$) δ: 22.41 (Me-23), 26.41 (Me-24), 29.91 (Me-25), 30.31 (C-14), 37.76 (C-11), 40.09 (C-10), 40.33 (C-9), 41.46 (C-5), 51.89 (C-1), 71.42 (C-8), 72.27 (C-4), 74.51 (C-2), 80.45 (C-6), 123.54 (C-19), 124.38 (C-21), 125.00 (C-17), 125.16 (C-16), 126.36 (C-20), 131.70 (C-13), 144.05 (C-18), 144.71 (C-12).

HR-MS: 372.1207 (M^+, $C_{21}H_{24}O_2S_2$; Calc. 372.1212).

References

[S1] G. Ohloff, H. Farnow, W. Philipp, Homologous alcohols of the terpene and sesquiterpene series. X. Synthesis of (+)-3-hydroxymethyl-4-carene, *Liebigs Ann. Chem.*, 1958, **613**, 43−55.

[S2] Yu. Watanabe, Reaction of α-Pinene with Formaldehyde, *Nippon Kagaku Kaishi*, 1960, **81**, 931 [*Chem. Abstr.*, 1962, p. 7357].

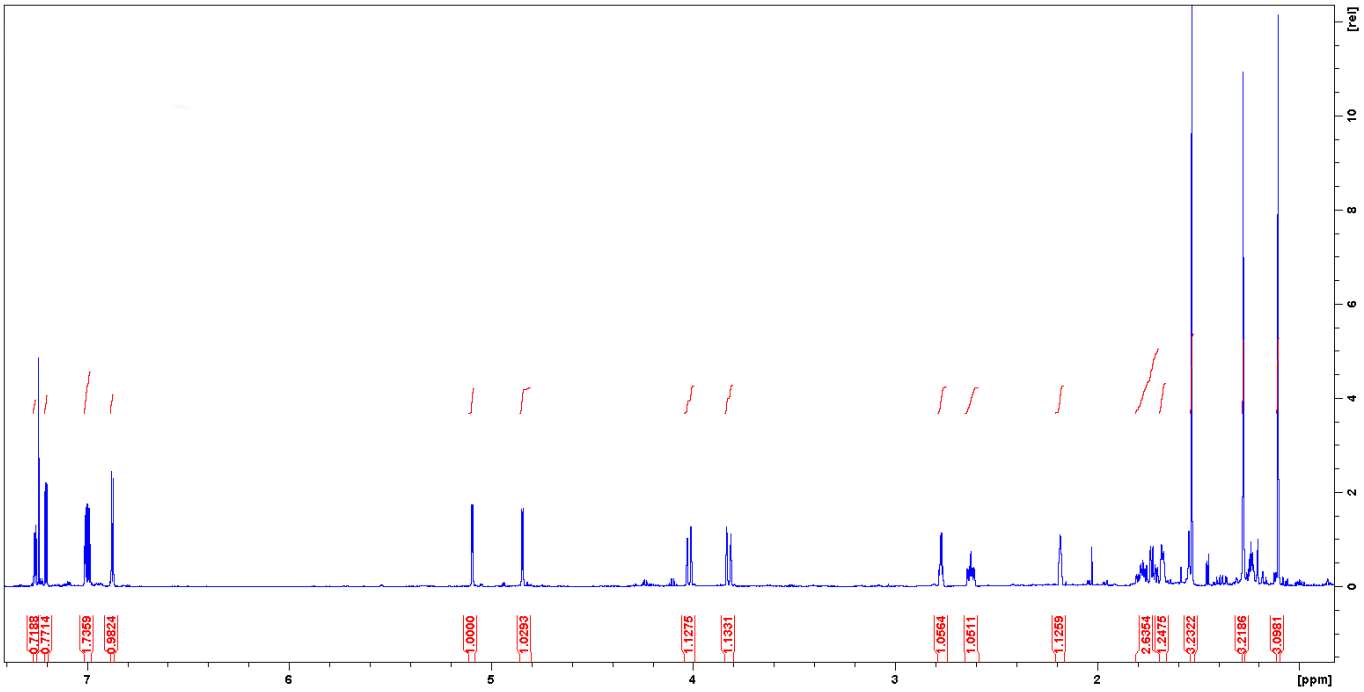


Figure S1 ^{1}H NMR spectrum of **4**.

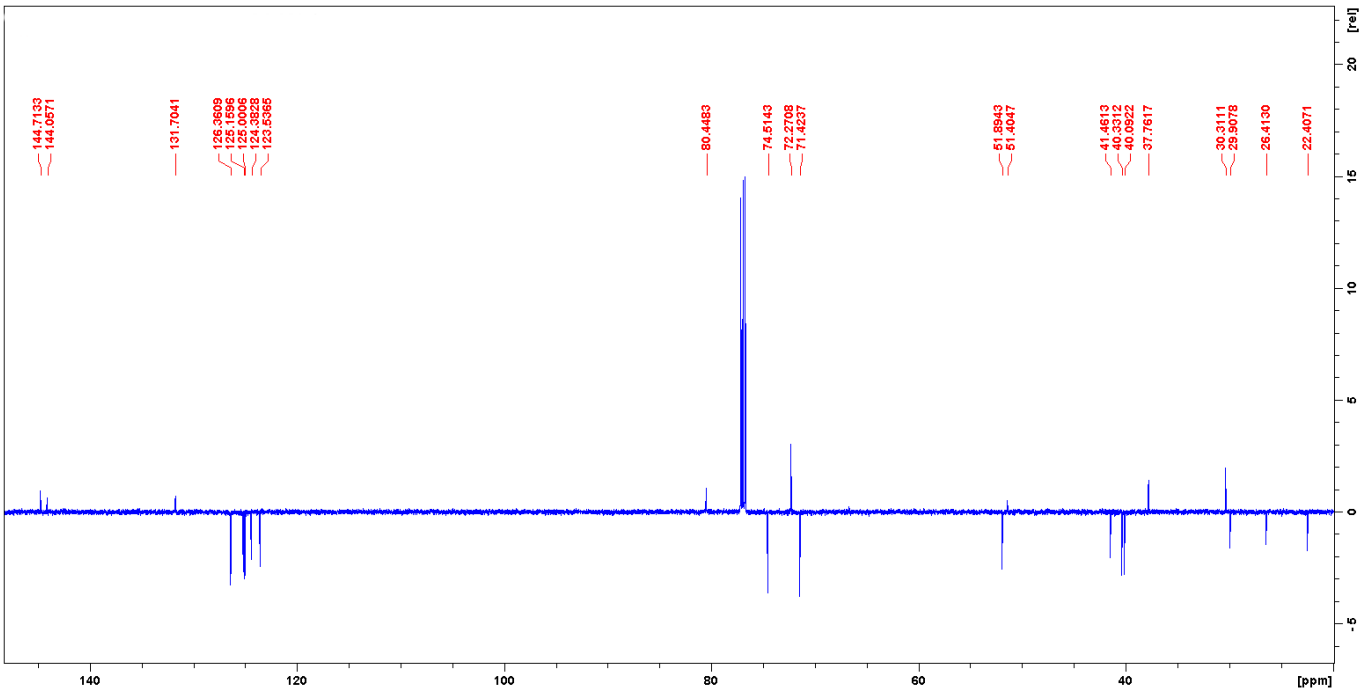


Figure S2 ^{13}C NMR spectrum of **4**.

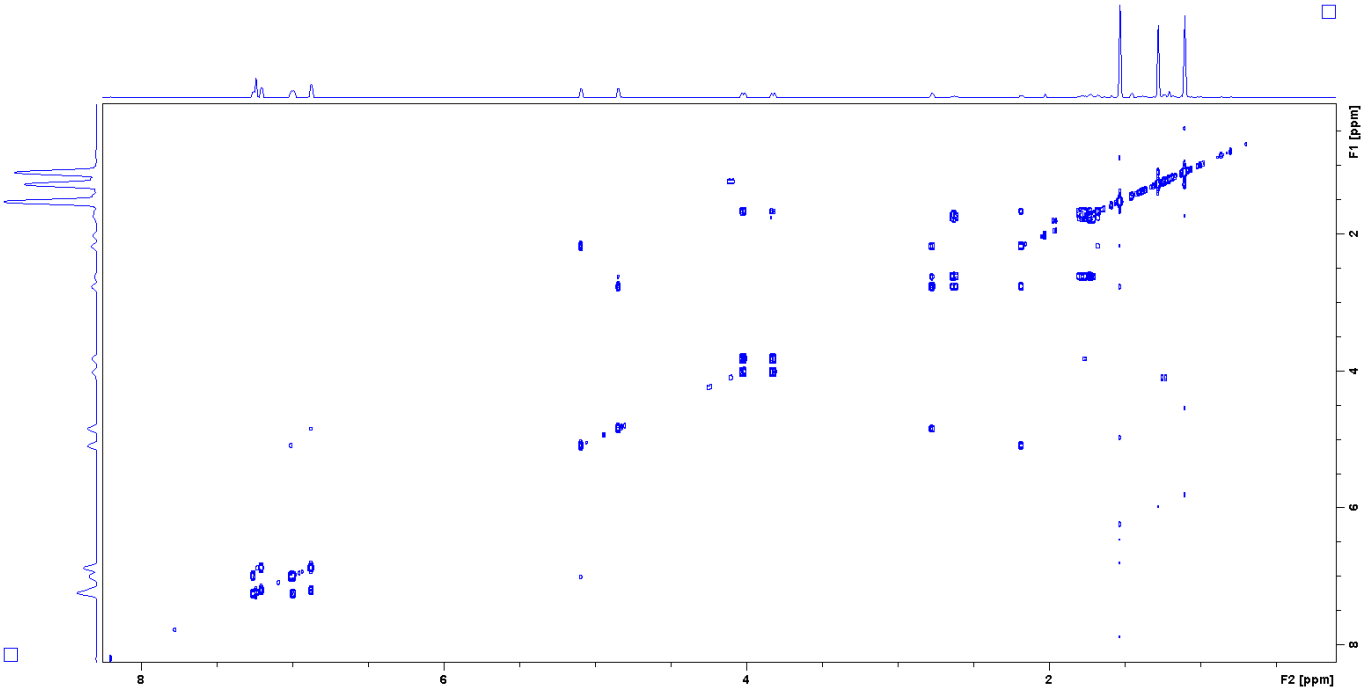


Figure S3 2D ^{1}H-^{1}H COSY NMR spectrum of **4**.

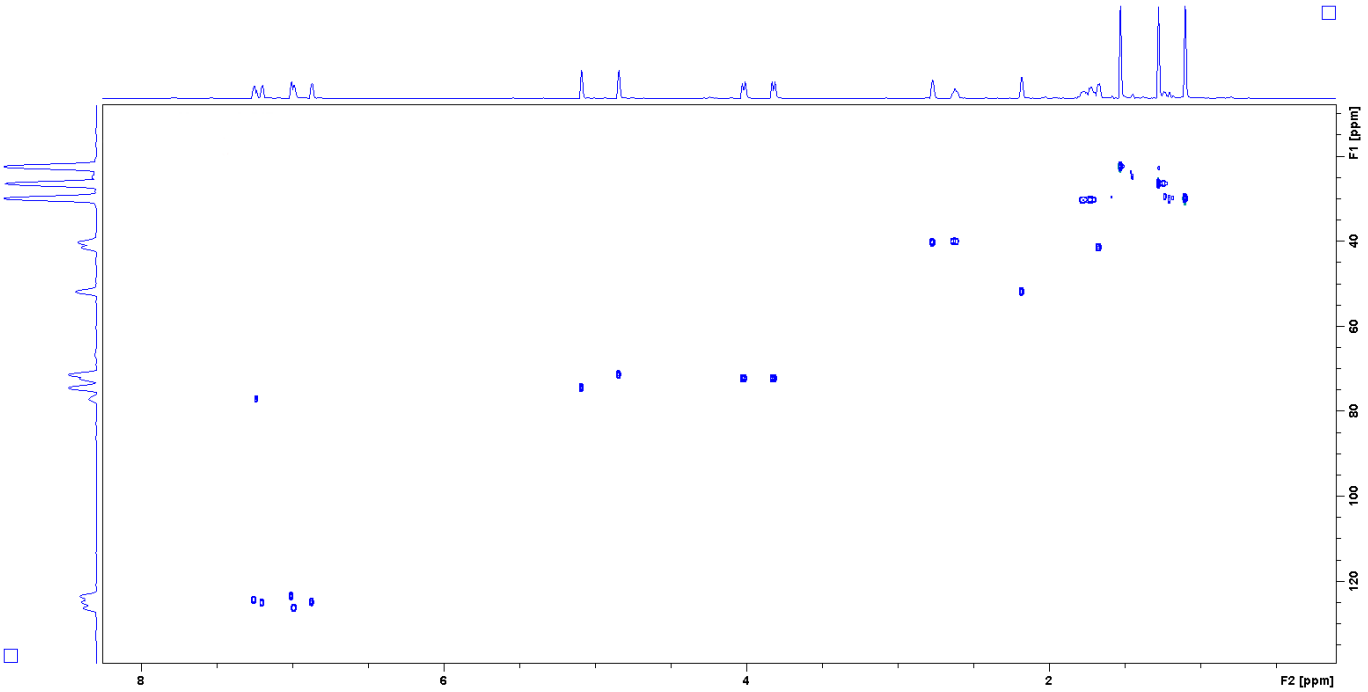


Figure S4 2D ^{1}H-^{13}C HSQC NMR spectrum of **4**.

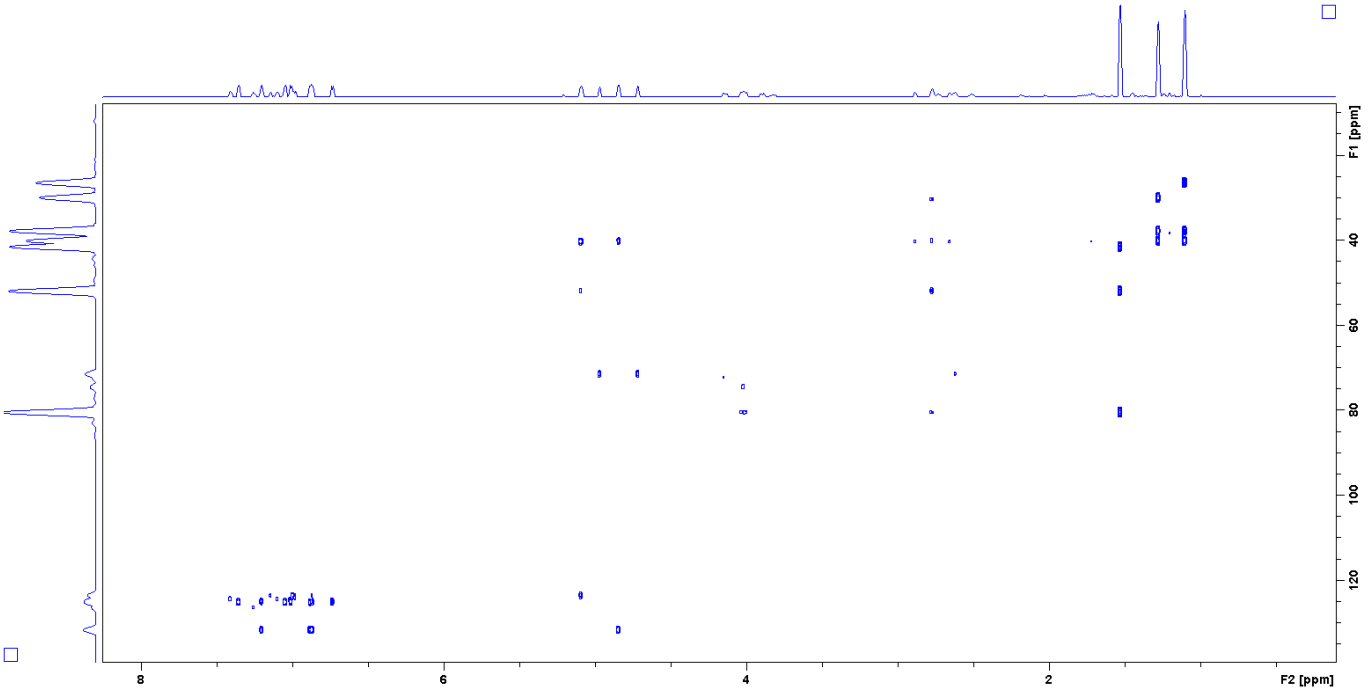


Figure S5 2D ^{1}H-^{13}C HMBC spectrum of **4**.

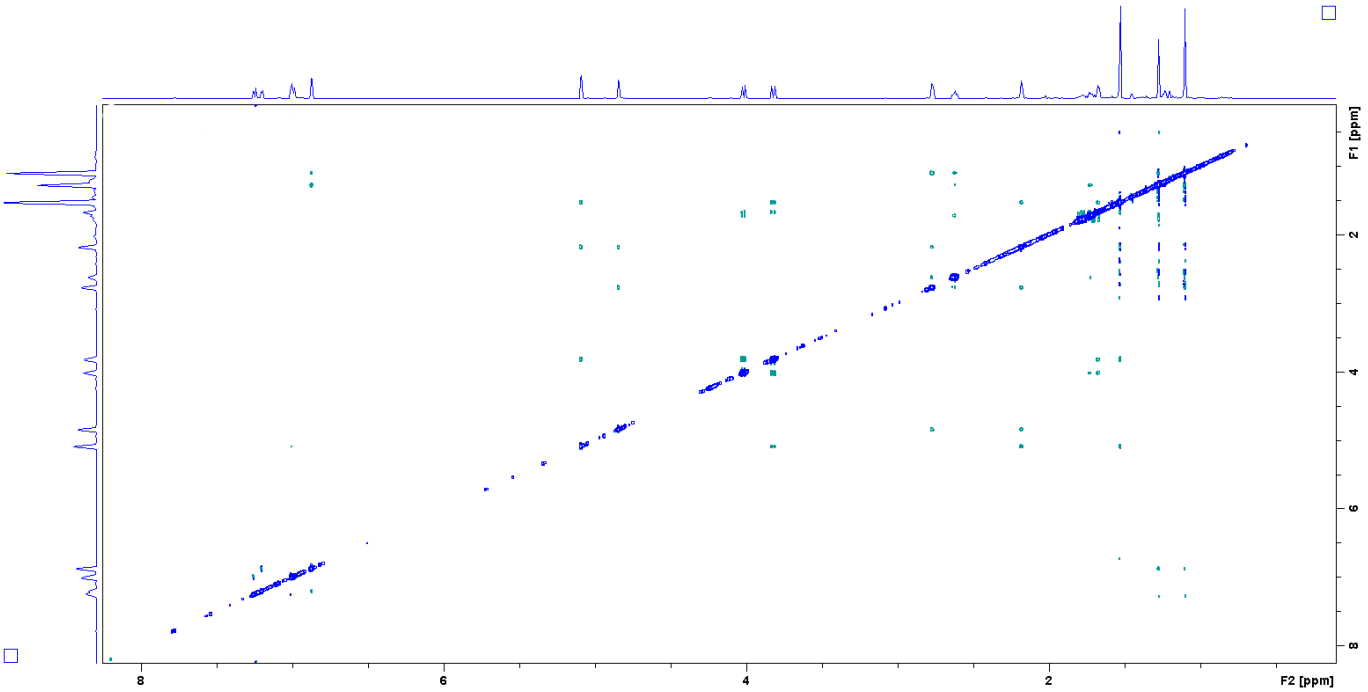


Figure S6 2D ^{1}H-^{1}H NOESY NMR spectrum of the compound **4**.

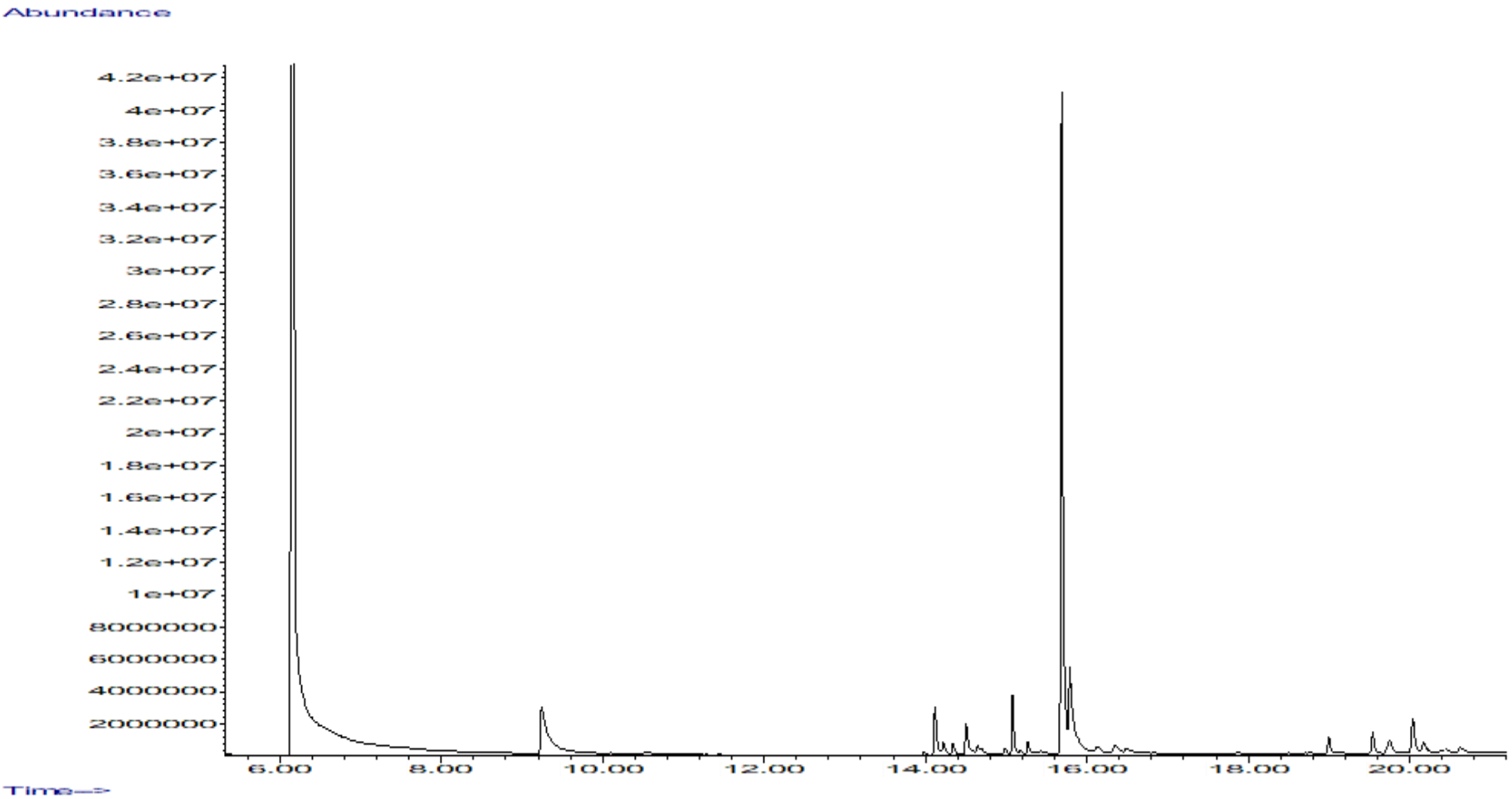


Figure S7 GC chromatogram for reaction *trans*-4-hydroxymethyl-2-carene with thiophene-2-carbaldehyde on K10 without solvent.

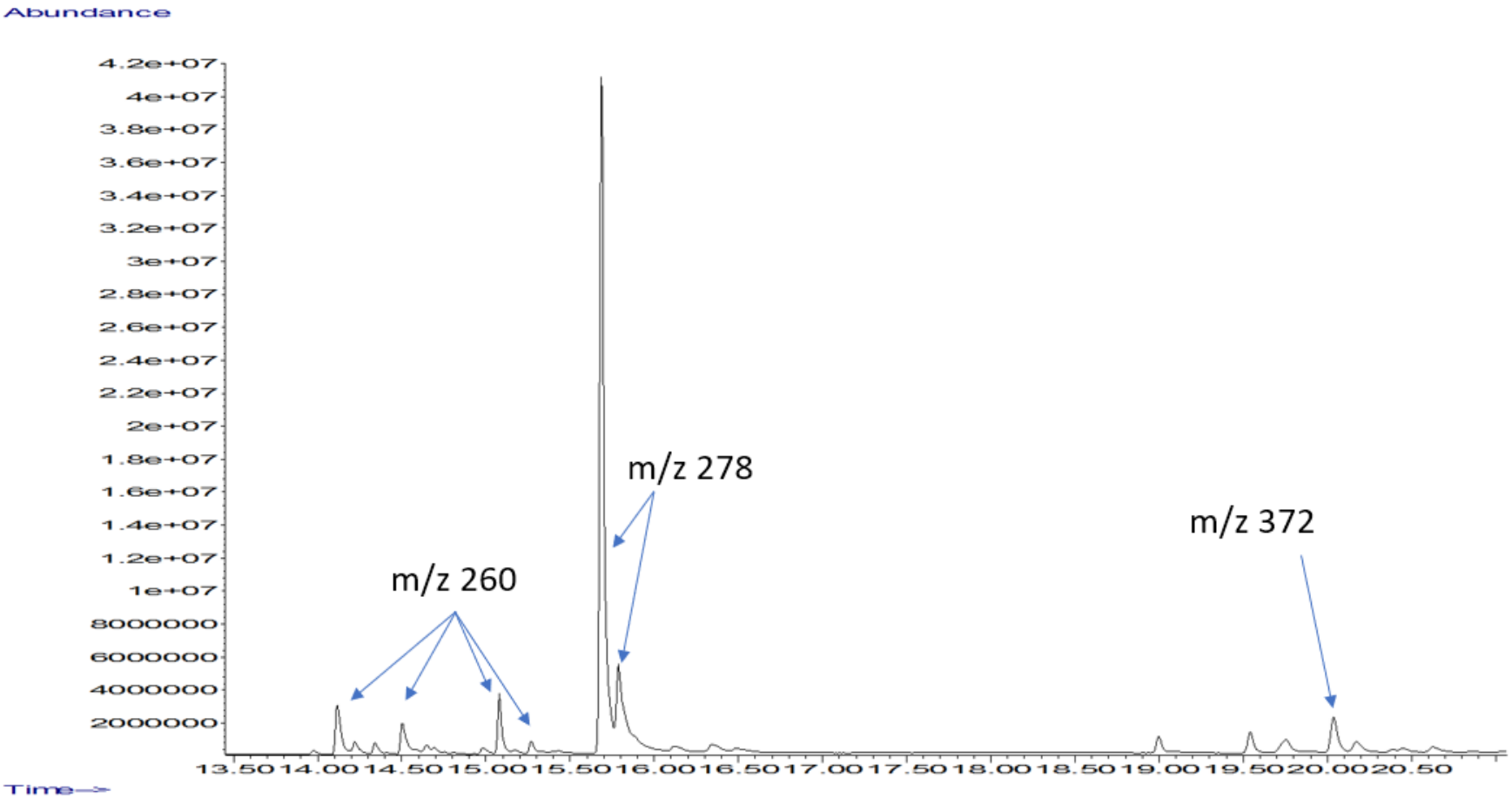


Figure S8 GC chromatogram of region 13.50-21.00 for reaction *trans*-4-hydroxymethyl-2-carene with thiophene-2-carbaldehyde on K10 without solvent.

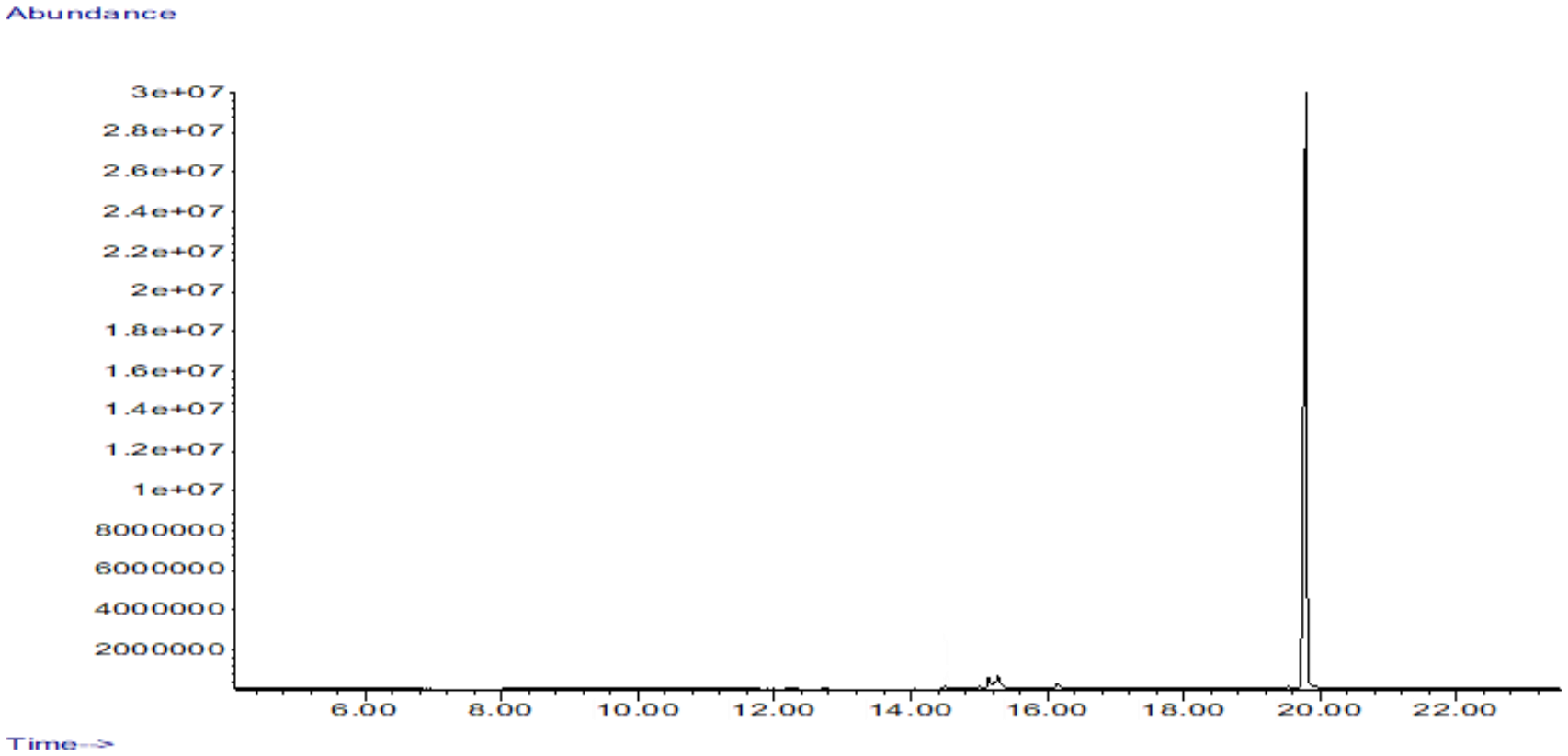


Figure S9 GC chromatogram of product **4**.

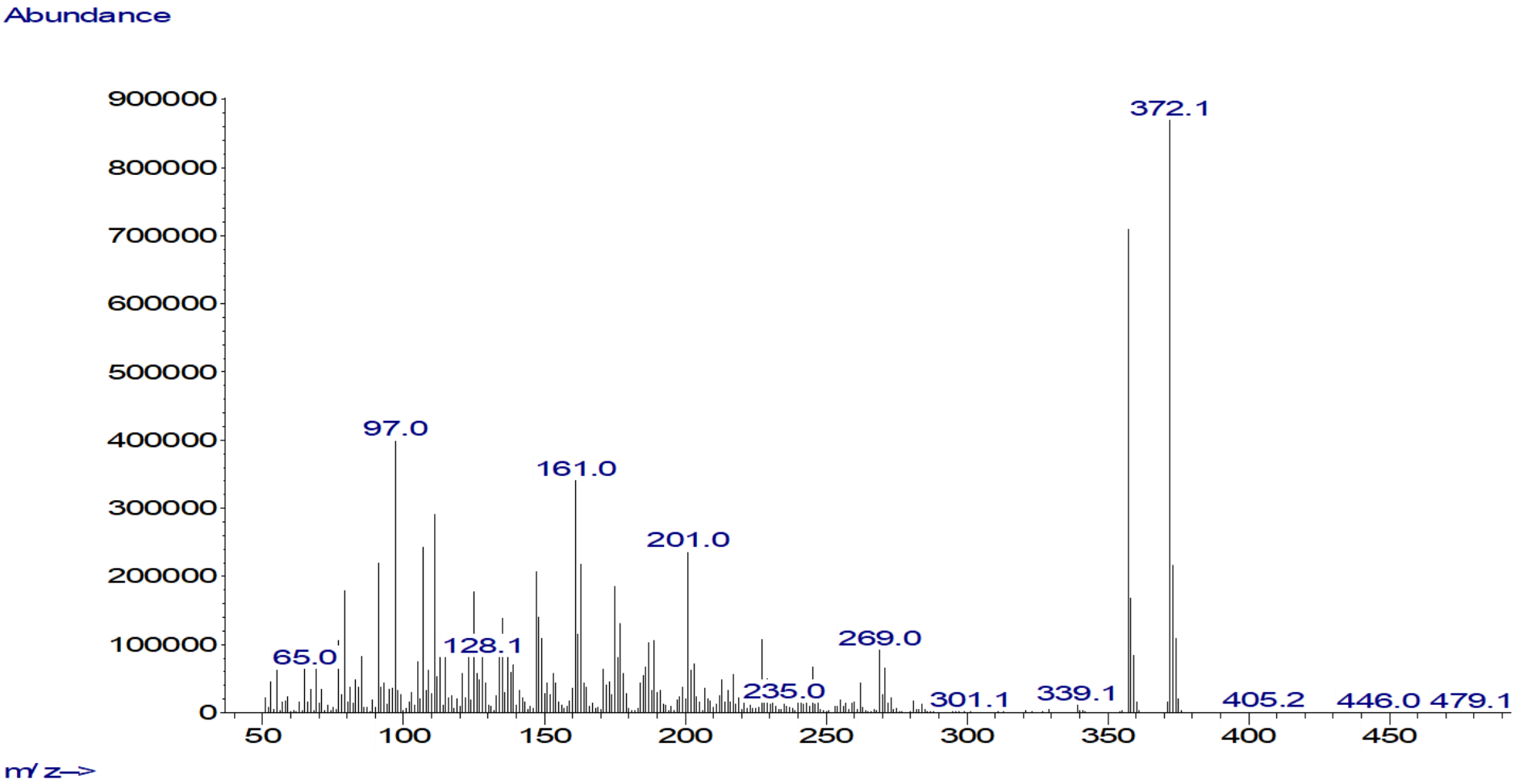


Figure S10 Mass spectrum of product **4**.