Supplementary Information

for

Fast multigram scale microwave-assisted synthesis of vitamin E and C_{10}-, C_{15}-analogues under vacuum

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General procedure

A suspension of TMHQ **1** (33 mmol; MW 152.19) and $Sc(OTf)_3$ (1.0 mol%; MW 492.16) was heated to reflux in toluene (20 mL) under magnetic stirring (20-30 min, 400 rpm) in a four-necked glass reactor equipped with an internal thermometer, a reflux condenser fitted with Dean-Stark trap (filled with toluene) and an argon inlet. Either neat IP **2**, natural pythol **2a** (33.5 mmol, 1.015 mol equiv., MW 296.54, d=0.841 g/mL) or the C_{10}- and C_{15}- analogues (**6, 7**) were dropped via syringe pump over 30 min. The mixture was heated under reflux (110 °C internal temperature; reaction control by GC). The mixture was cooled to room temperature after 3h and poured into deionized water (20 mL). EtOAc (2x30 mL) was used to completely dissolve all organic material from the flask, while the combined organic extracts were washed twice with deionized water (20 mL), dried over sodium sulphate, filtered, evaporated at 20 mbar/50 °C and finally dried for 2 h at 0.02 mbar/23 °C in order to achieved (**3**), (**3a**), (**4**) and (**5**) products.

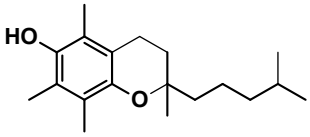
General MW procedure

A suspension of TMHQ **1** (33 mmol; MW 152.19), and $Sc(OTf)_3$ (1.0 mol%; MW 492.16) in toluene (10 mL) was poured into a suitable glass vessel (300 mL) for MW irradiation. Either neat IP **2** (33.5 mmol, 1.015 mol equiv., MW 296.54, d=0.841 g/mL) or the -C10 and -C15 analogues (**6, 7**) were dropped via syringe pump over 5 min inside the MW rotating reaction vessel (200 rpm) and the suspension was heated at 110 °C (400 Watt) for either 1h or 30 min under vacuum (200 mbar). At reaction's end, toluene was evaporated under MW irradiation under more intense vacuum (100 mbar). The mixture was then poured onto deionized water (20 mL) and extracted 3 times with EtOAc (2x30 mL). The combined organic extracts were washed twice with deionized water (20 mL x 2), dried over sodium sulfate, filtered, evaporated at 20 mbar/50°C and finally dried for 2 h at 0.02 mbar/23°C (**3**), (**3a**), (**4**) and (**5**) products.

Experimental section

Commercially available reagents, catalysts and solvents were used without further purification unless otherwise noted (TMHQ: Fluka (96%) and isophytol, natural phytol (*E*: 96.2%; *Z*: 1.2%): Shandong Guangtongbao Pharmaceuticals Co., Ltd.). MW-assisted reactions were carried out in a RotoSYNTH reactor (MLS GmbH, Milestone Srl). GC analyses for reaction control were carried out on a gas chromatograph Agilent 6890A (G1530A) using a capillary column (Restek, BGB Analytik AG) that was 30 m long, while an ID of 0.32 mm and a film thickness of 0.25 mm were used (15°C/min program temperature: from 70°C to 300°C). GC analyses for the quantitative determination of tocopherol and related compound was carried out on a gas chromatograph HP 6890 using a capillary column (Rtx-5SilMS) that was 30 m long, while an ID of 0.28 mm and a film thickness of 0.25 mm were used (5°C/min program temperature: from 150°C to 300°C). Derivatization: squalene (int. standard) in pyridine/BSTFA+1% TMSCl).

Characterization of Products



(all *rac*)-α–tocopherol C_{10} - *analogue* **(4)**

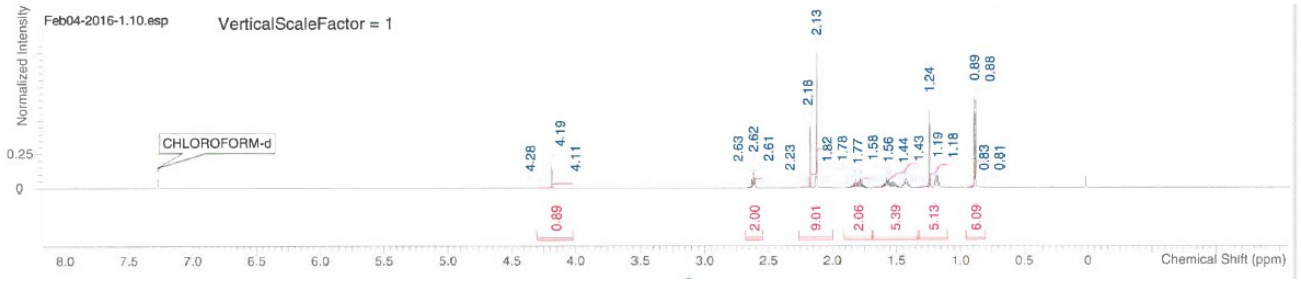
^{1}H NMR (600 MHz, Chloroform-d): δ ppm 4.19 (s, 1 H), 2.62 (t, *J*=6.88 Hz, 2 H), 2.00-2.27 (m, 9 H), 1.69-1.91 (m, 2 H), 1.34.-1.69 (m, 5 H), 1.10-1.32 (m, 5 H), 0.83-0.96 (m, 6 H).

^{13}C NMR (75 MHz, Chloroform-d): δ ppm 145.3, 144.3, 122.4, 120.8, 118.2, 117.1, 74.3, 39.1, 38.1, 31.3, 27.7, 23.6, 22.4, 21.2, 20.5, 12.0, 11.6, 11.1.

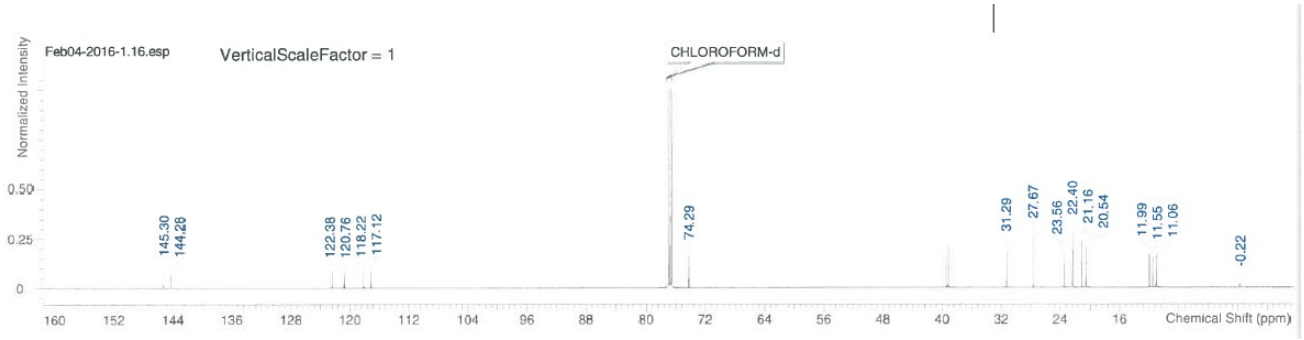
(ESI): calcd. for $[C_{19}H_{30}O_2 + H]^+$: 291.23172; found: 291.23187.

IR (KBr, neat): 3469.17, 2948.74, 2934.35, 2868.49, 2842.19, 1467.44, 1251.90, 1046.11, 863.02, 686.84 cm^{-1}

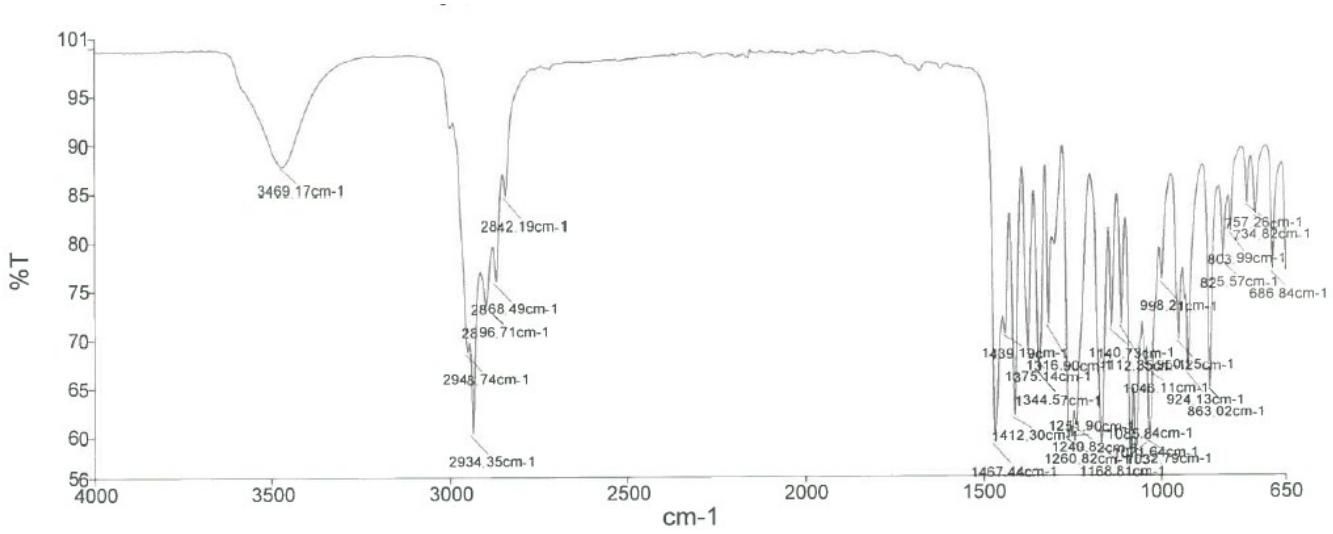
^{1}H NMR (600 MHz, Chloroform-d): (all *rac*)-α-tocopherol C10 - analogue **(4)**



^{13}C NMR (75 MHz, Chloroform-d): (all *rac*)–α-tocopherol C10 - analogue **(4)**



IR analysis: (all *rac*)-α-tocopherol C10 - analogue **(4)**



GC-MS analysis: (all *rac*)-a-tocopherol C10 - analogue **(4)**

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Vial Number: 36
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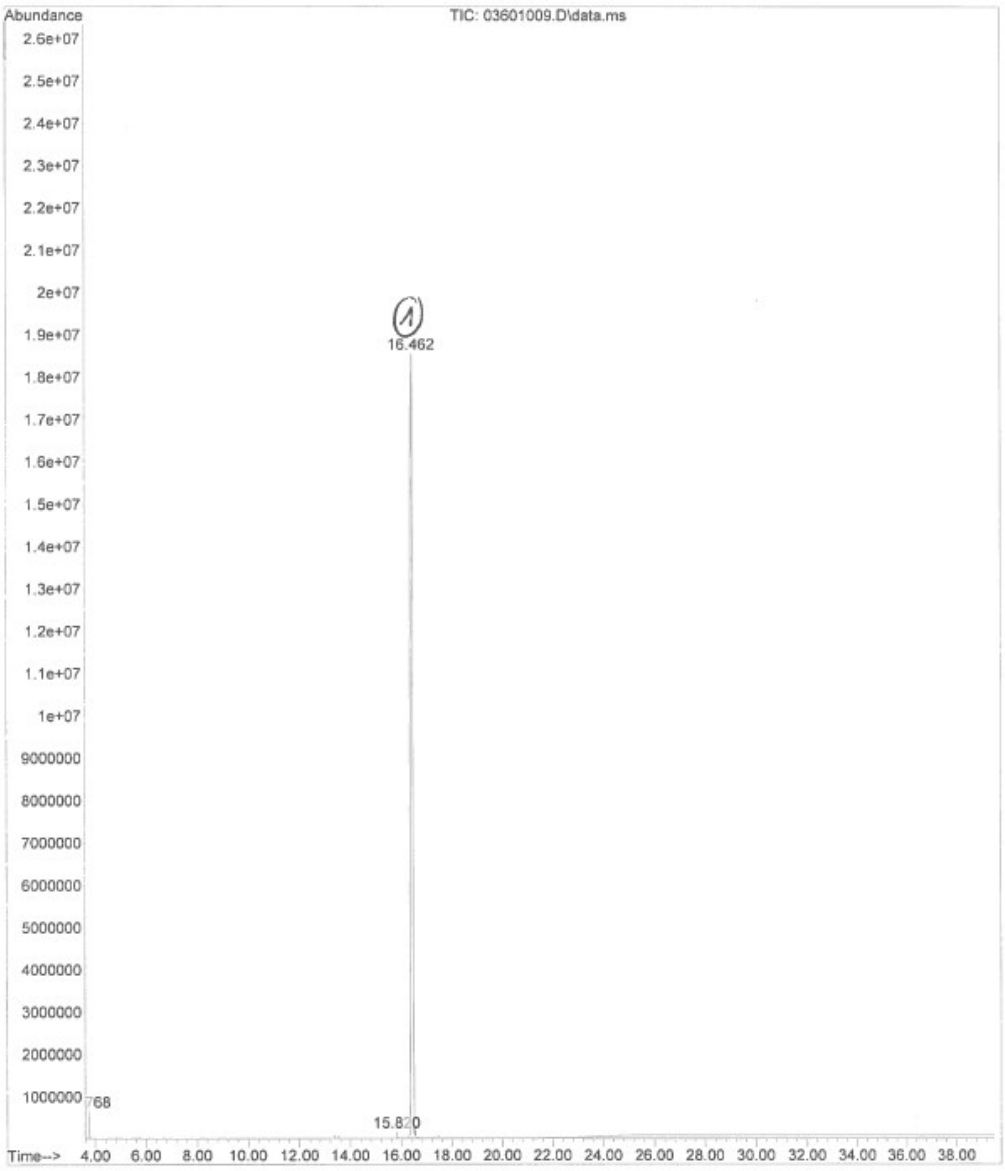

Instrument : GCMSD
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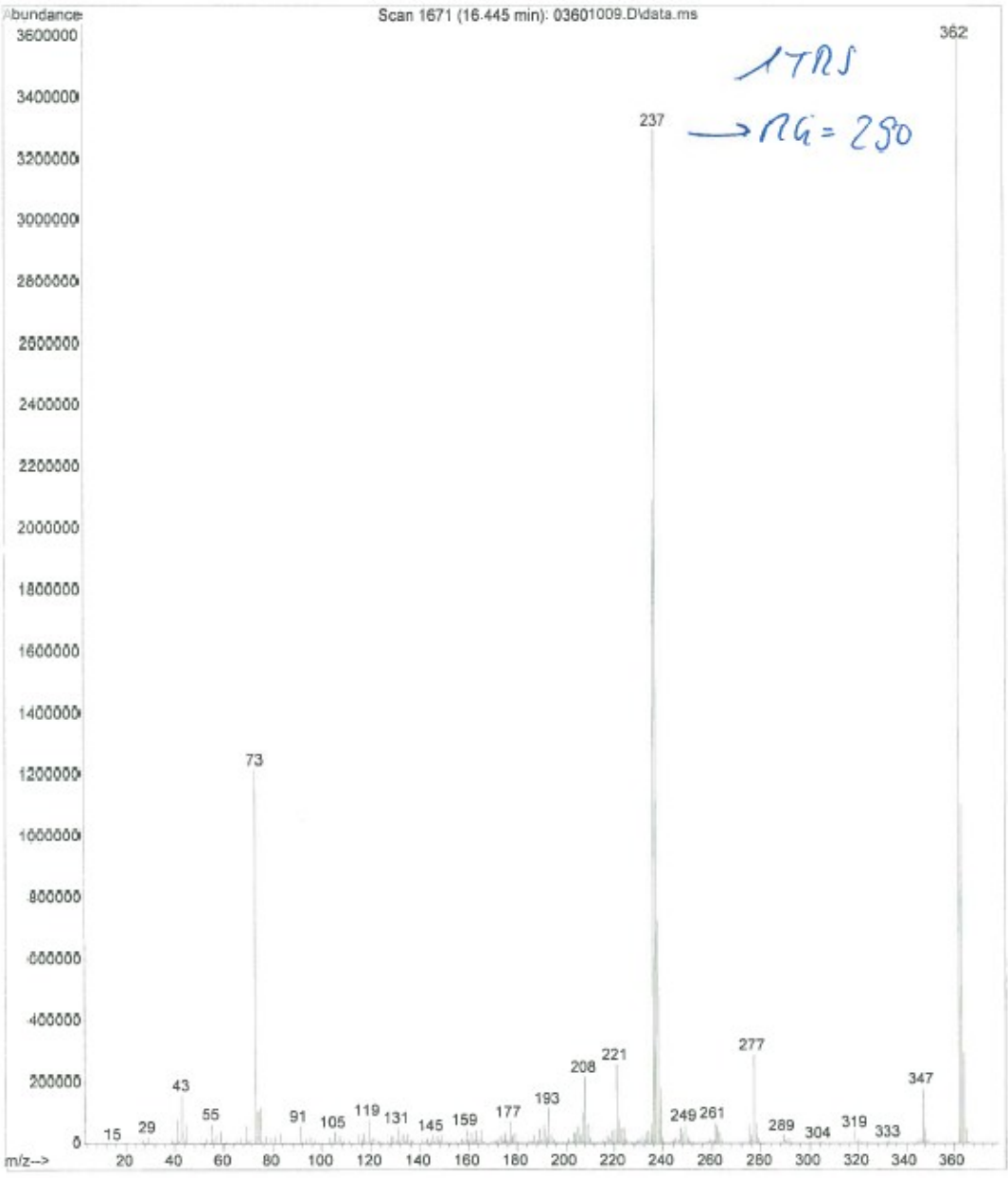
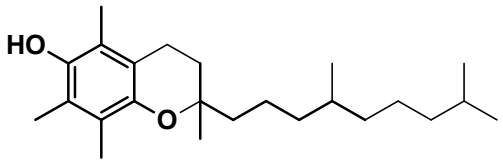
Vial Number: 36





(all *rac*)-α–tocopherol C_{15} - *analogue* **(5)**

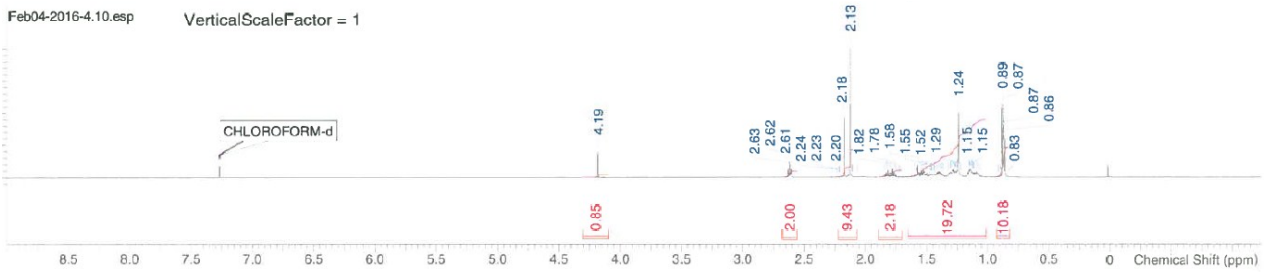
^{1}H NMR (600 MHz, Chloroform-d): δ ppm 4.19 (s, 1 H), 2.62 (t, *J*=6.88 Hz, 2 H), 2.06-2.31 (m, 10 H), 1.71-1.90 (m, 2 H), 1.01.-1.65 (m, 20 H), 0.80-0.94 (m, 10 H).

^{13}C NMR (75 MHz, Chloroform-d): δ ppm 145.5, 144.5, 122.6, 120.9, 118.4, 117.3, 74.5, 39.9, 39.8, 39.4, 37.5, 37.3, 32.7, 28.0, 24.8, 22.6, 21.1, 20.8, 19.6, 12.2, 11.8, 11.3.

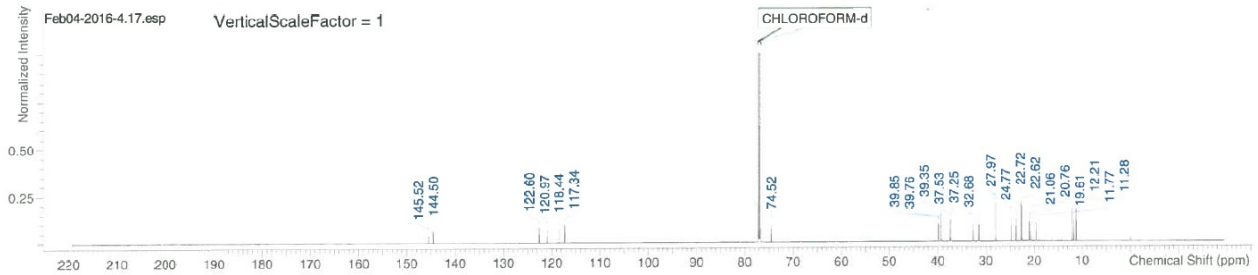
(ESI): calcd. for $[C_{24}H_{40}O_2 + H]^+$: 361.30337; found: 361.31010.

IR (KBr, neat): 3465.93, 2925.81, 2867.94, 1458.77, 1377.58, 1261.93, 917.76, 811.34 cm^{-1}

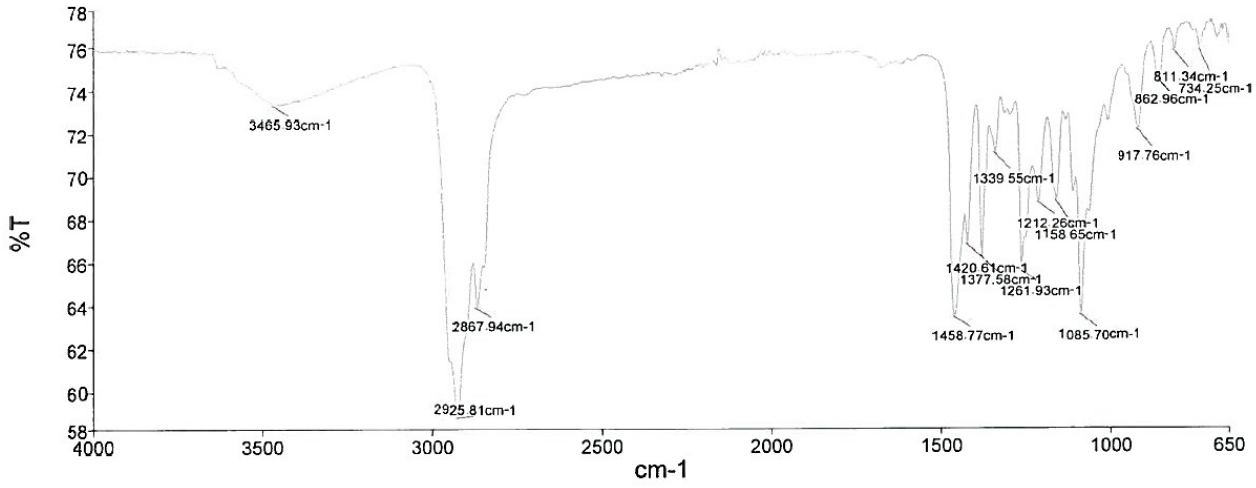
^{1}H NMR (600 MHz, Chloroform-d): (all *rac*)-α-tocopherol C15 - analogue **(5)**



^{13}C NMR (75 MHz, Chloroform-d): (all *rac*)-α-tocopherol C15 - analogue **(5)**



IR analysis: (all *rac*)-α-tocopherol C15 - analogue **(5)**



GC-MS analysis: (all *rac*)-α-tocopherol C15 - analogue **(5)**

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Vial Number: 37
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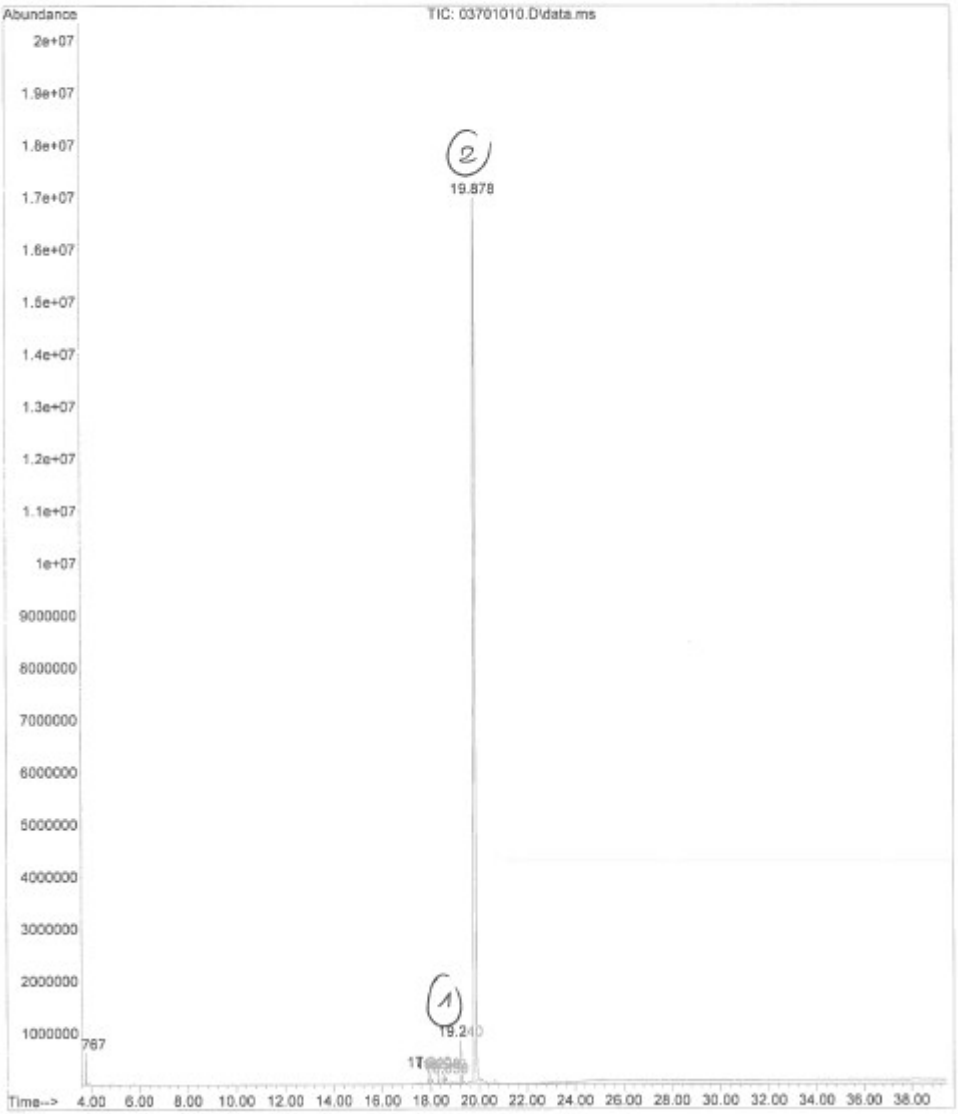

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File       :H:\data\160202\03701010.D
Operator   : lb
Acquired   :  3 Feb 2016  00:39      using AcqMethod HP5_70_liquid.M
Instrument :   GCMSD
Sample Name: Toco C15, 32808B-53; 4.2 mg/ml Sil
Misc Info  : HP-5MS,30mx0.25mm,0.25um;70°(0)10°/m 315°(15)
Vial Number: 37
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