Screening of a Selection of Commercially Available Homogeneous Ru-Catalysts in Valuable Olefin Metathesis Transformations

Frédéric Caijo,*[a] Fabien Tripoteau,[a] Aurélien Bellec,[a] Christophe Crévisy,[b] Olivier Baslé,[b] Marc Mauduit*[a,b] and Oliver Briel*

[a] *OMEGA CAT SYSTEM SARL, ENSCR, avenue du Général Leclerc - CS 50837 - 35708 Rennes Cedex 7, France. Fax: 33 (0) 299 388 516; Tel: 33 (0) 299 388 516; E-mail: f.caijo@omcat-system.com*
[b] *Ecole Nationale Supérieure de Chimie de Rennes, CNRS, UMR 6226, avenue du Général Leclerc, CS 50837, 35708 Rennes Cedex 7, France. Fax: 33 (0) 223 238 108; Tel: 33 (0) 223 238 112; E-mail: marc.mauduit@ensc-rennes.fr*
[c] *Precious Metals Chemistry Research & Development, UMICORE AG&Co. KG Rodenbacher Chaussee 4, 63457 Hanau-Wolfgang, Germany. Fax: 49 6181 592970; Tel: 49 6181 593894; E-mail: oliver.briel@eu-umicore.com*

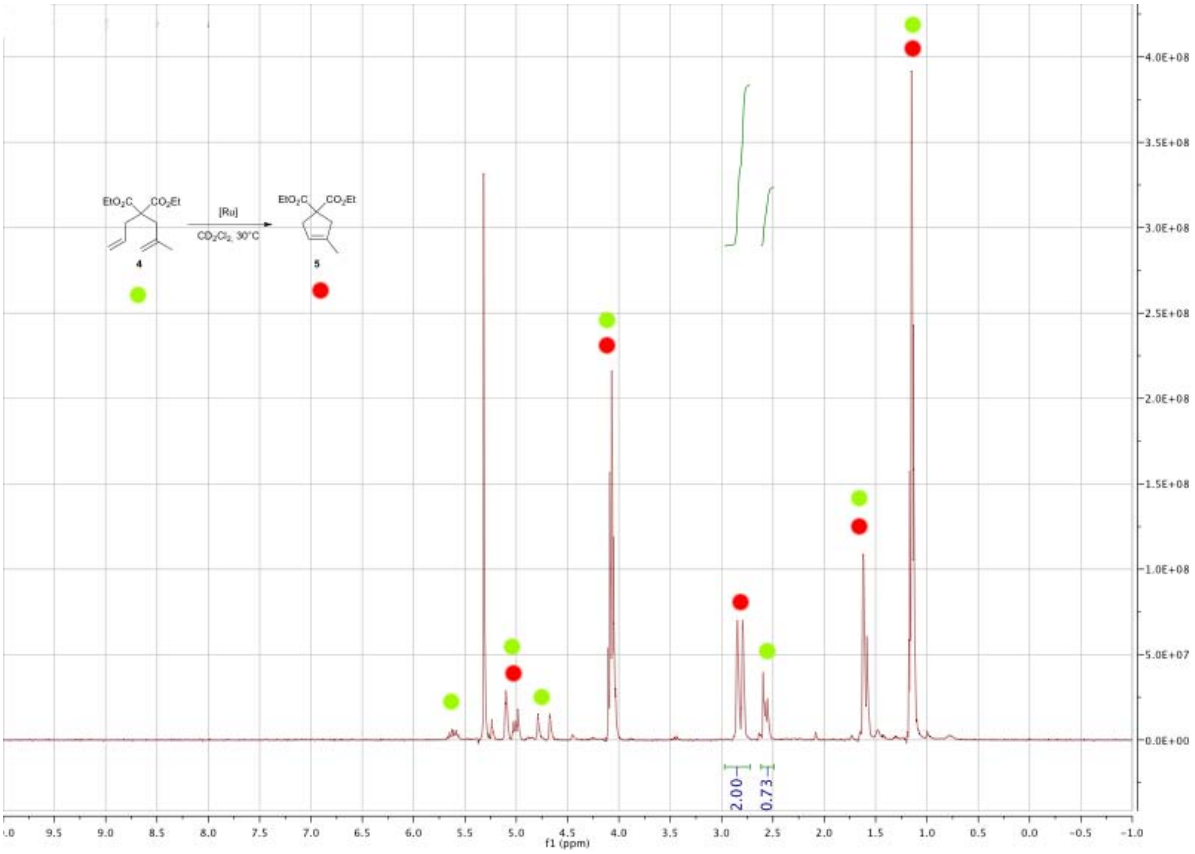
SUPPORTING INFORMATION

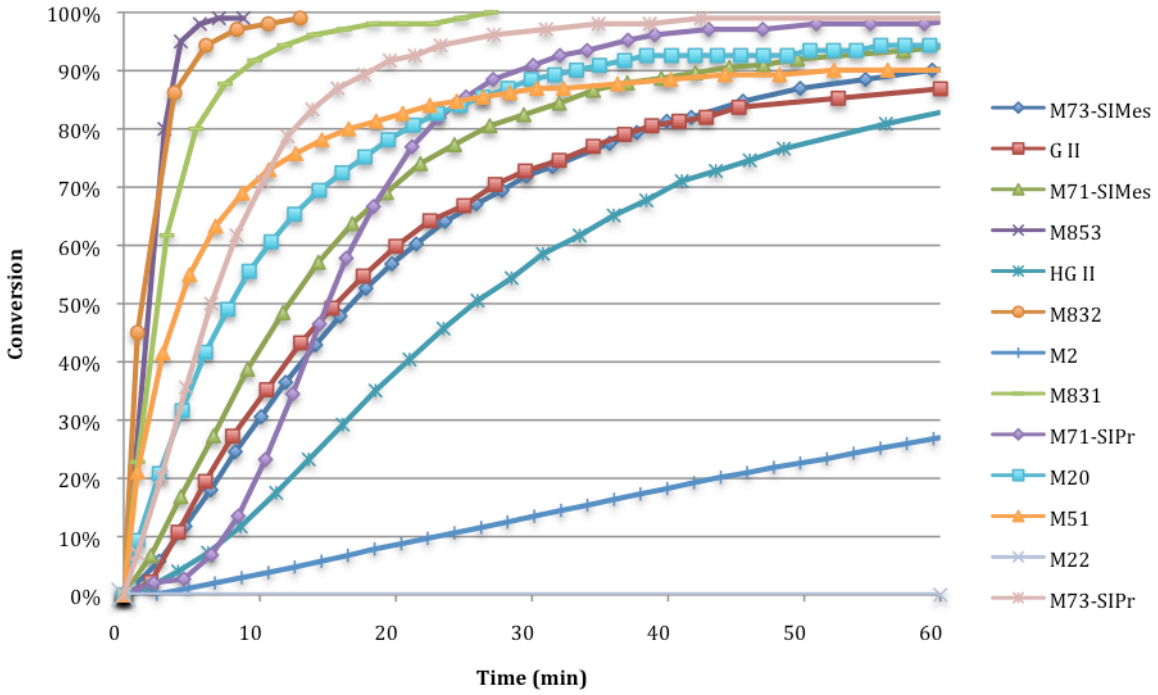
General information. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a Bruker ARX400 spectrometer with complete proton decoupling for nucleus other than ^{1}H. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: ^{1}H δ 7.26 ppm, ^{13}C δ 77.0 ppm, MeOD: ^{1}H δ 3.31 ppm, ^{13}C δ 49.0 ppm, DMSO-d6: ^{1}H δ 2.5 ppm, ^{13}C δ 39.5 ppm). Data are reported as follows: chemical shift δ in ppm, multiplicity (s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet), coupling constants (Hz) and integration. High resolution mass spectroscopy analyses were performed on a Waters Q-Tof 2 at the Centre Régional de Mesures Physiques de l'Ouest (CRMPO), Université de Rennes 1. Toluene and THF were dried by passing through purification columns containing activated alumina. DCM was distilled over CaH_2. All commercial chemicals were used as received unless otherwise noted.

1. Evaluation of the kinetic profile of Ru-catalyst during the RCM reaction of diethyl 2-allyl-2-(2-methylallyl)malonate 4

In a NMR tube, Ru-catalyst (1 mol%) was added to a solution of metallylallyl diethylmalonate **4** (25.4 mg, 0.1 mmol) in CD_2Cl_2 (500 µL). The reaction mixture was warmed up to 30 °C and conversion was determined by ^{1}H NMR spectroscopy analysis.

Example of NMR kinetic calculation for $M5_1$ at 10 min (73% conversion):

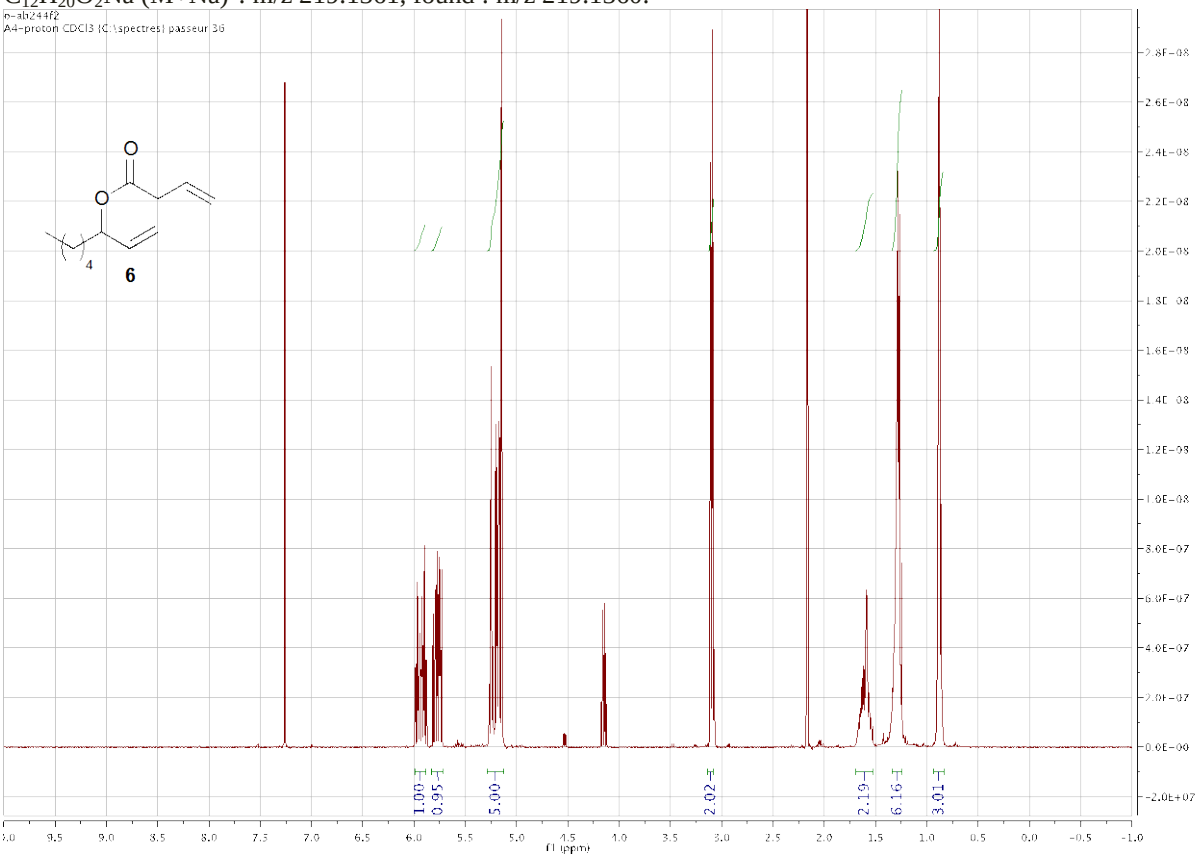


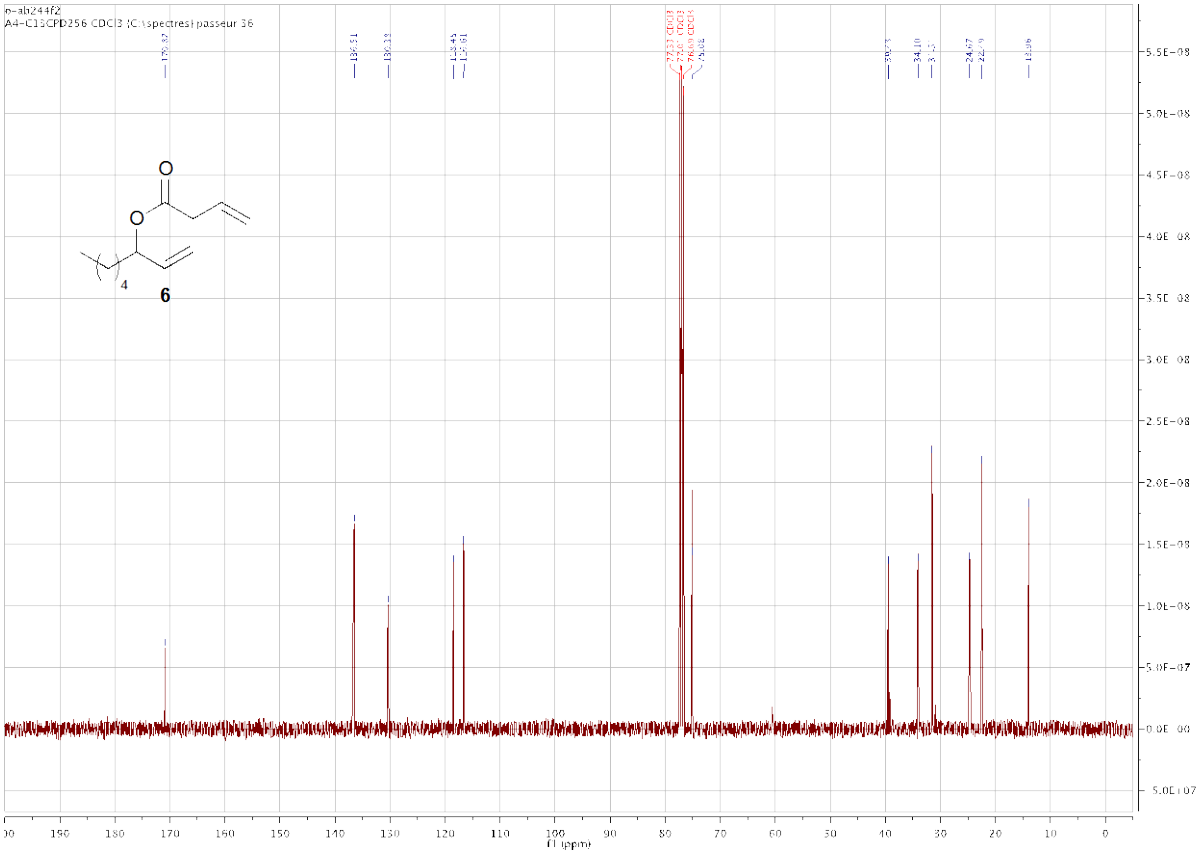


2. Syntheses and data of compounds 1, 2, 6, 7, 10b, 10c, 11, 14, 16, 18, 19.

oct-1-en-3-yl but-3-enoate **6**

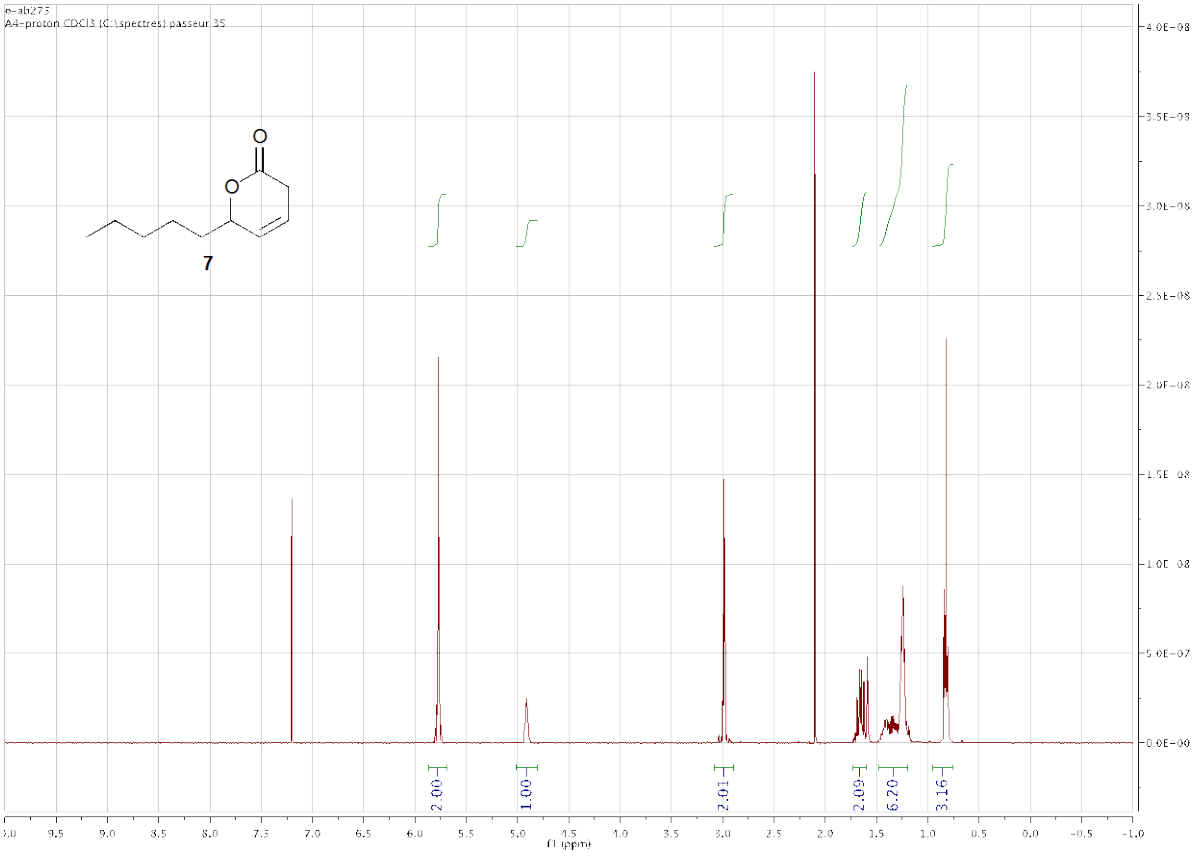
To a solution of butenoic acid **9** (5 g, 58 mmol) in $CHCl_3$ (87 mL) was added 1-octen-3-ol **8** (7.45 g, 58 mmol) and *p*-toluenesulfonic acid (110 mg, 0.58 mmol). The reaction mixture was stirred at reflux for 24h using a Dean-Stark trap filled with 4Å molecular sieves. After cooling down to room temperature, the solvent was evaporated and the residue was purified by silica gel chromatography (pentane/Et_2O 98/2) to afford **6** as a yellow oil (8.65 g, 76%). ^1H NMR (400 MHz, $CDCl_3$): δ = 6.01-5.88 (m, 1H), 5.76-5.65 (m, 1H), 5.29-5.14 (m, 5H), 3.11 (dt, *J* = 7.0, 1.5 Hz, 2H), 1.74-1.49 (m, 2H), 1.40-1.24 (m, 6H), 0.89 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.8, 136.5, 130.4, 118.4, 116.6, 75.1, 39.4, 34.1, 31.5, 24.7, 22.5, 14.0.; HRMS calcd for $C_{12}H_{20}O_2Na$ $(M+Na)^+$: m/z 219.1361, found : m/z 219.1360.





General procedure for the synthesis of 6-pentyl-3,6-dihydro-2*H*-pyran-2-one **7**

Ru-catalyst (0.1 mol%) was added to a solution of **6** (200 mg, 1.01 mmol) in toluene (51 mL). The reaction mixture was stirred for 2h at 80 °C. After cooling down to room temperature, the solvent was evaporated and the residue was purified by silica gel chromatography (cyclohexane/EtOAc 100/0 to 90/10) to produce **7** as a yellow oil (see Table 1 for yields). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.78-5.77 (m, 2H), 4.99-4.83 (m, 1H), 3.01-2.96 (m, 2H), 1.71-1.60 (m, 2H), 1.34-1.18 (m, 6H), 0.82 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.2, 126.7, 121.4, 79.7, 35.7, 31.5, 29.9, 24.0, 22.5, 14.0. HRMS calcd for $C_{10}H_{16}O_2Na$ $(M+Na)^+$: m/z 191.1048, found : m/z 191.1050.



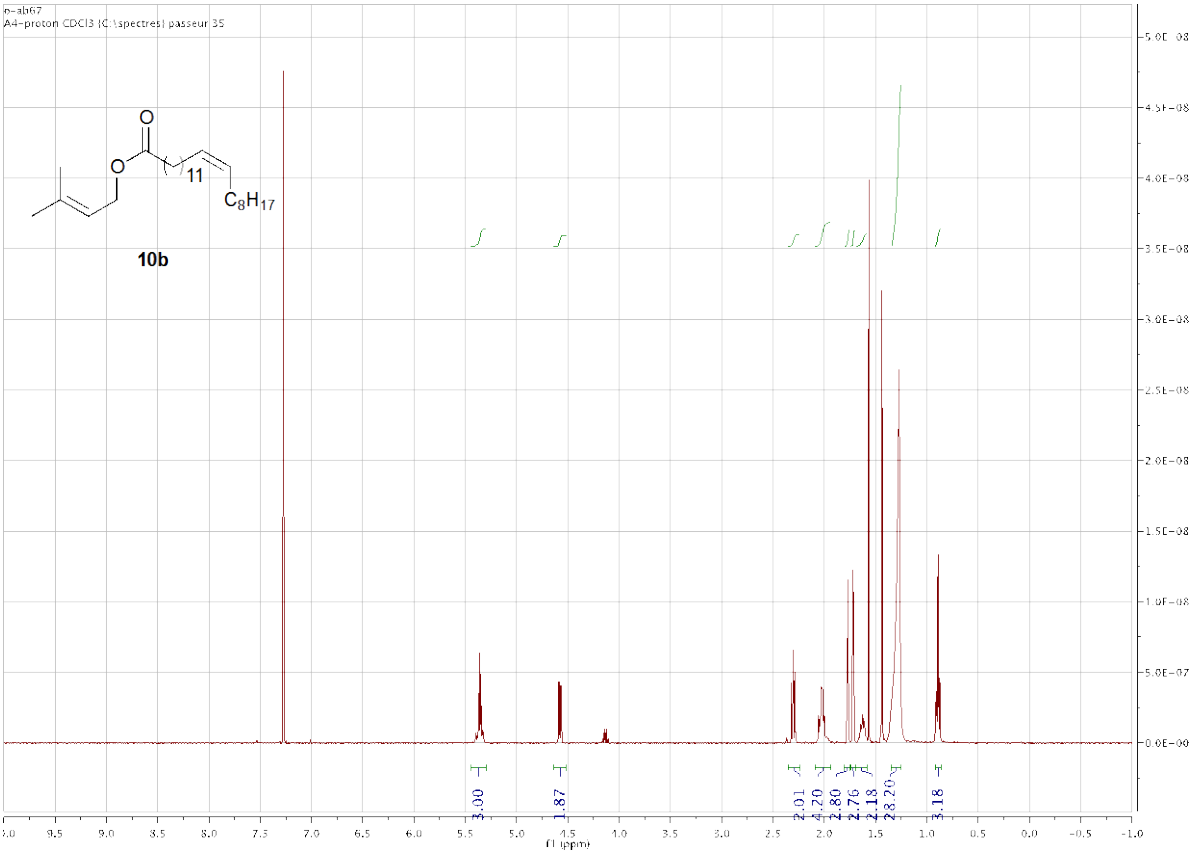
δ-decalactone **1**[1]

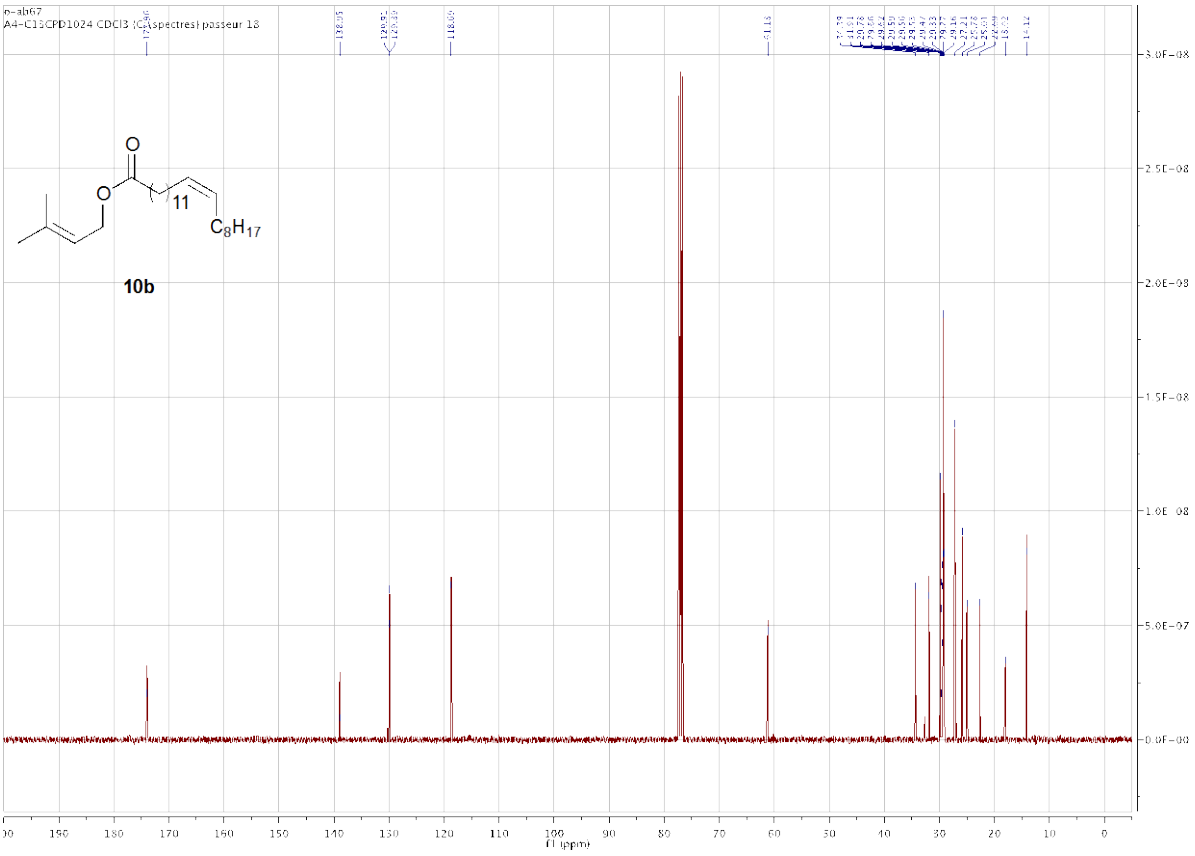
To a solution of **7** (170 mg, 1 mmol) in MeOH (5 mL), Pd/C (15 mg) was added and the reaction flask was pressured with hydrogen (1 atm). After stirring overnight at room temperature, the reaction mixture was filtrated over a celite pad and the solvent was removed under vacuum to afford **1** as a colourless oil (151 mg, 89%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.28 (dddd, *J* = 10.7, 8.0, 5.0, 2.9 Hz, 1H), 2.64-2.53 (m, 1H), 2.49-2.40 (m, 1H), 1.99-1.77 (m, 3H), 1.76-1.66 (m, 1H), 1.63-1.44 (m, 3H), 1.47-1.23 (m, 5H), 0.90 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.0, 80.6, 35.8, 31.6, 29.4, 27.8, 24.6, 22.5, 18.5, 14.0.

For synthesis of **10a** see D. Villemin, *Tetrahedron Lett.*, 1980, **21**(18), 1715.

(*Z*)-3-methylbut-2-en-1-yl erucate **10b**

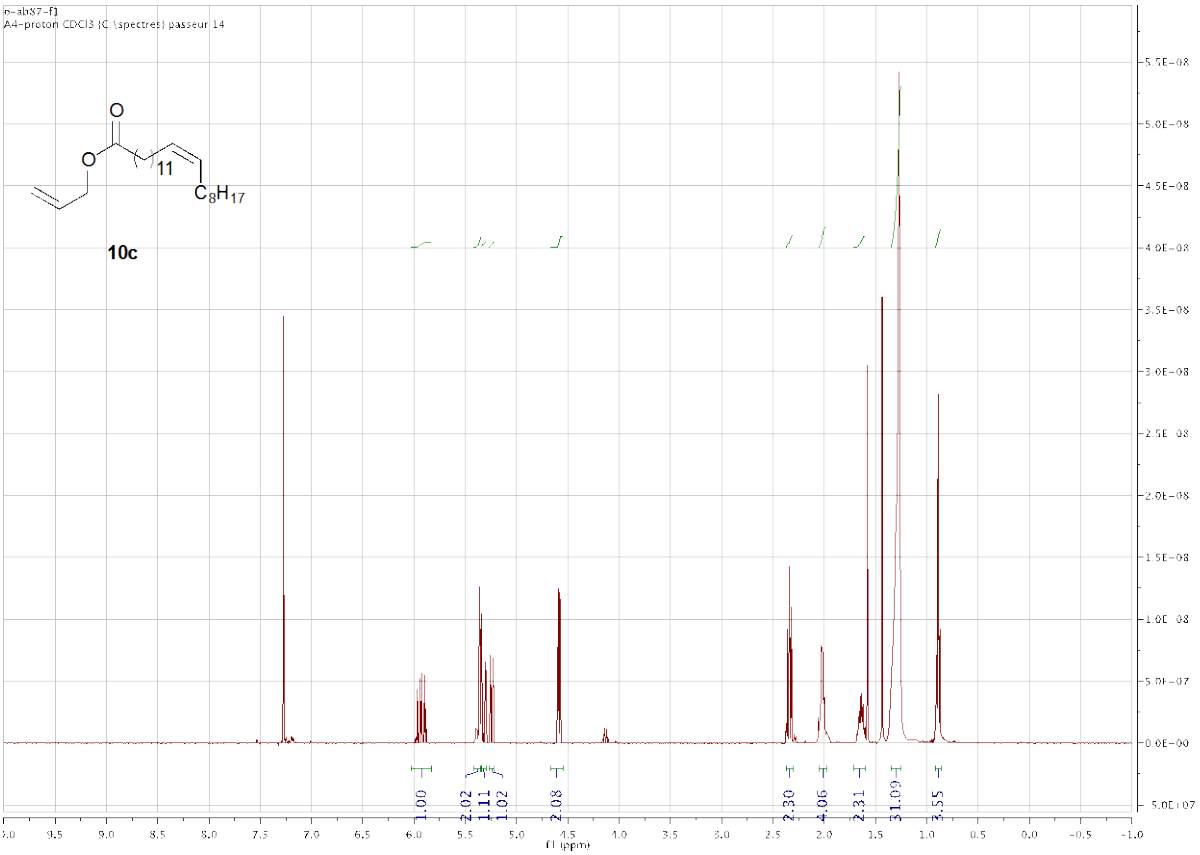
To a solution of erucic acid **12b** (10 g, 26 mmol) in toluene (50 mL), $SOCl_2$ (3.9 mL, 53 mmol) was added dropwise at 0°C. The reaction mixture was stirred for 2h at 80 °C. After cooling down to room temperature, the solvent was evaporated. The residue was solubilised in CH_2Cl_2 (50 mL), pyridine (4.3 mL, 53 mmol) and 3-methyl-2-buten-1-ol (3.24 mL, 32 mmol) were added dropwise at 0°C. The reaction mixture was stirred 2h at room temperature, quenched with water (100 mL) and extracted with CH_2Cl_2 (2 x 100 mL). The combined organic layers were washed with a saturated aqueous solution of NH_4Cl (200 mL), dried over $MgSO_4$ and solvent was removed under vacuum. The residue was purified by silica gel chromatography (cyclohexane/CH_2Cl_2 70/30) to afford **10b** as a pale yellow oil (10.5 g, 97%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.46-5.33 (m, 3H), 4.50 (d, *J* = 7.2 Hz, 2H), 2.22 (t, *J* = 7.6 Hz, 2H), 2.00-1.90 (m, 4H), 1.69 (s, 3H), 1.64 (s, 3H), 1.59-1.50 (m, 2H), 1.30-1.15 (m, 28H), 0.81 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.0, 138.9, 129.9, 129.8, 118.7, 61.2, 34.4, 32.6, 31.9, 29.8, 29.7, 29.7, 29.6, 29.6, 29.6, 29.5, 29.5, 29.3 (2C), 29.3, 29.2, 27.2, 25.8, 25.0, 22.7, 18.0, 14.1. HRMS calcd for $C_{27}H_{50}O_2Na$ $(M+Na)^+$: m/z 429.3708, found : m/z 429.3709.

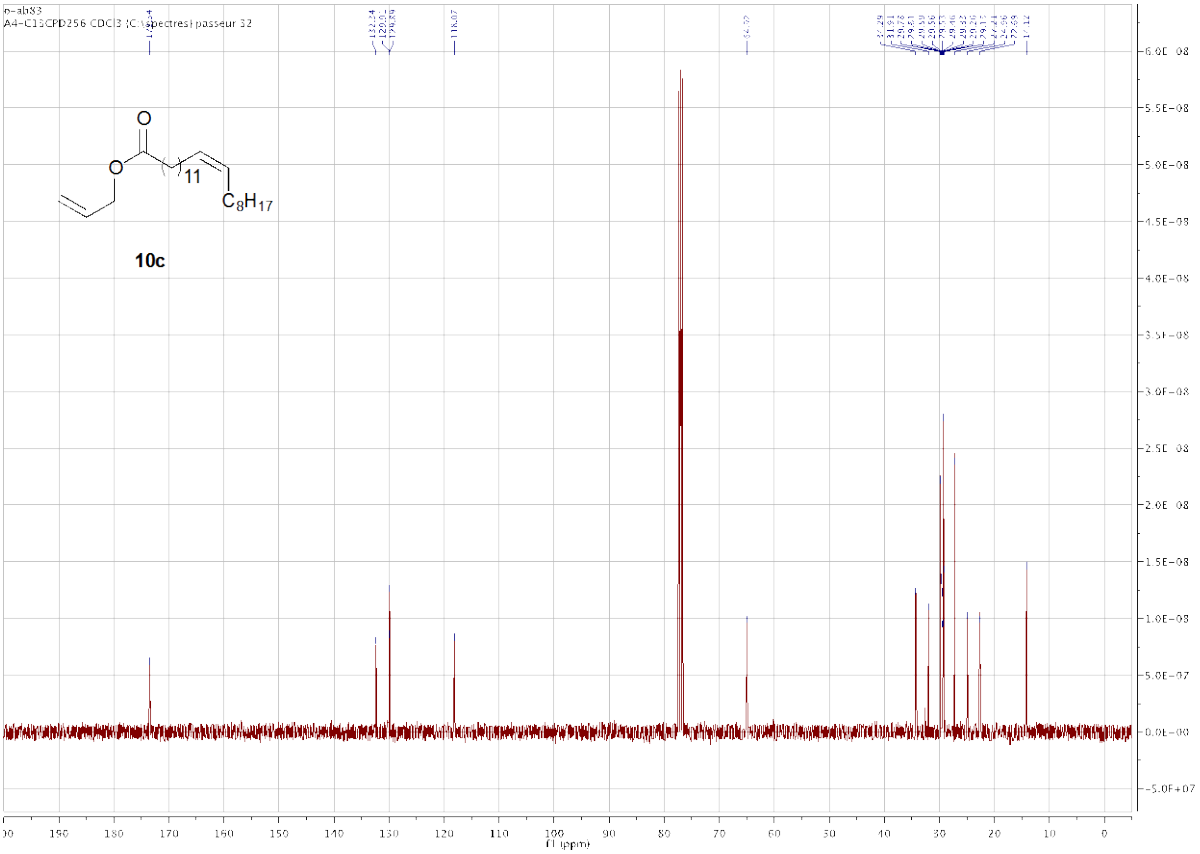




(*Z*)-allyl erucate **10c**

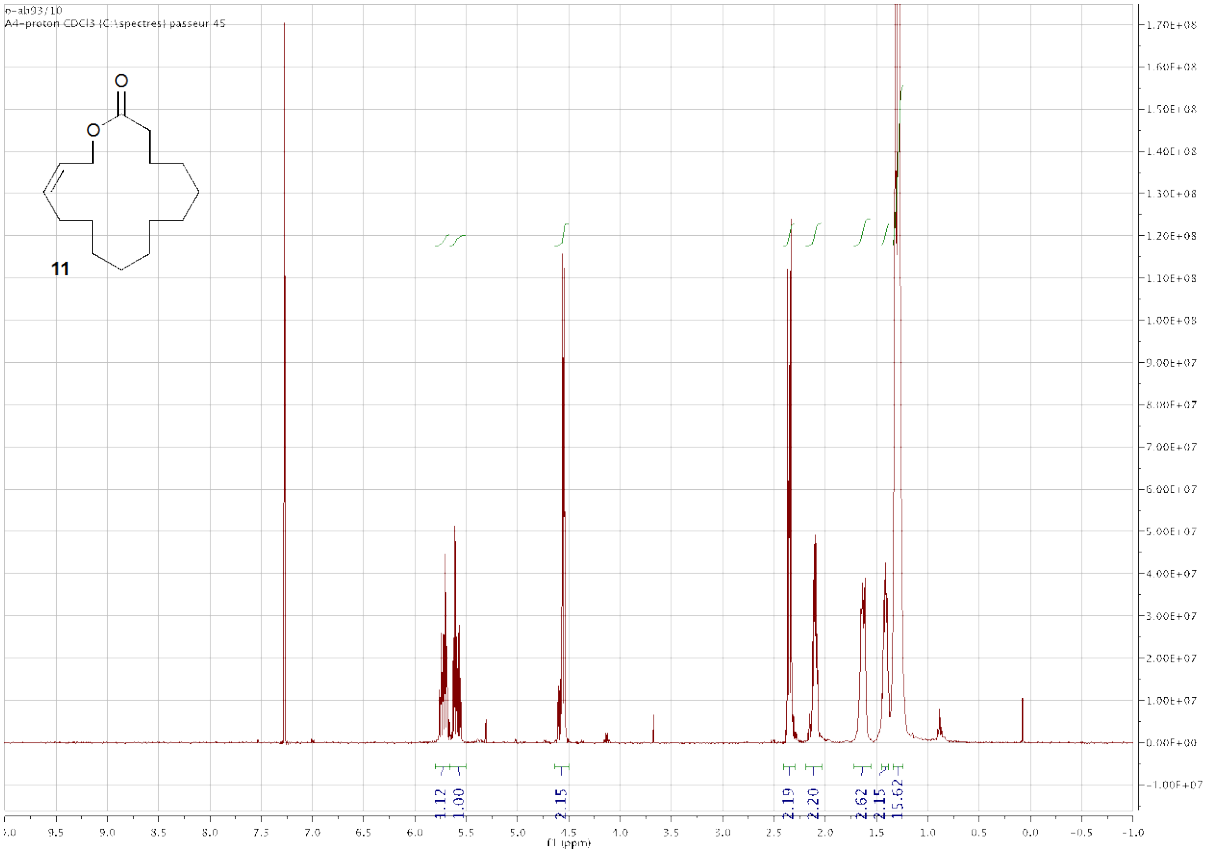
To a solution of erucic acid **12b** (10 g, 26 mmol) in toluene (50 mL), $SOCl_2$ (3.9 mL, 53 mmol) was added dropwise at 0°C. The reaction mixture was stirred for 2h at 80 °C. After cooling down to room temperature, the solvent was evaporated. The residue was solubilised in CH_2Cl_2 (50 mL), pyridine (4.3 mL, 53 mmol) and allyl alcohol (2.2 mL, 32 mmol) were added dropwise at 0 °C. The reaction mixture was stirred 2h at room temperature, quenched with water (200 mL) and extracted with CH_2Cl_2 (2 x 200 mL). The combined organic layers were washed with 1N HCl (100 mL) and a saturated aqueous solution of NH_4Cl (200 mL), dried over $MgSO_4$ and solvent was removed under vacuum. The residue was purified by silica gel chromatography (cyclohexane/CH_2Cl_2 70/30) to afford **10c** as a pale yellow oil (9.06 g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.85 (ddt, *J* = 17.2, 10.5, 5.7 Hz, 1H), 5.30-5.26 (m, 2H), 5.24 (qd, *J* = 17.2, 1.6 Hz, 1H), 5.16 (qd, *J* = 10.4, 1.3 Hz, 1H), 4.51 (dt, *J* = 5.7, 1.4 Hz, 2H), 2.26 (dd, *J* = 7.8, 7.3 Hz, 2H), 2.07-1.95 (m, 4H), 1.63-1.49 (m, 2H), 1.32-1.14 (m, 28H), 0.81 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.5, 132.3, 129.9, 129.8, 118.1, 64.9, 34.3, 32.6, 31.9, 29.8, 29.7, 29.7, 29.6, 29.6, 29.6, 29.5, 29.5, 29.3 (2C), 29.3, 29.2, 27.2, 25.0, 22.7, 14.1; HRMS calcd for $C_{25}H_{46}O_2Na$ $(M+Na)^+$: m/z 401.3395, found : m/z 401.3395.

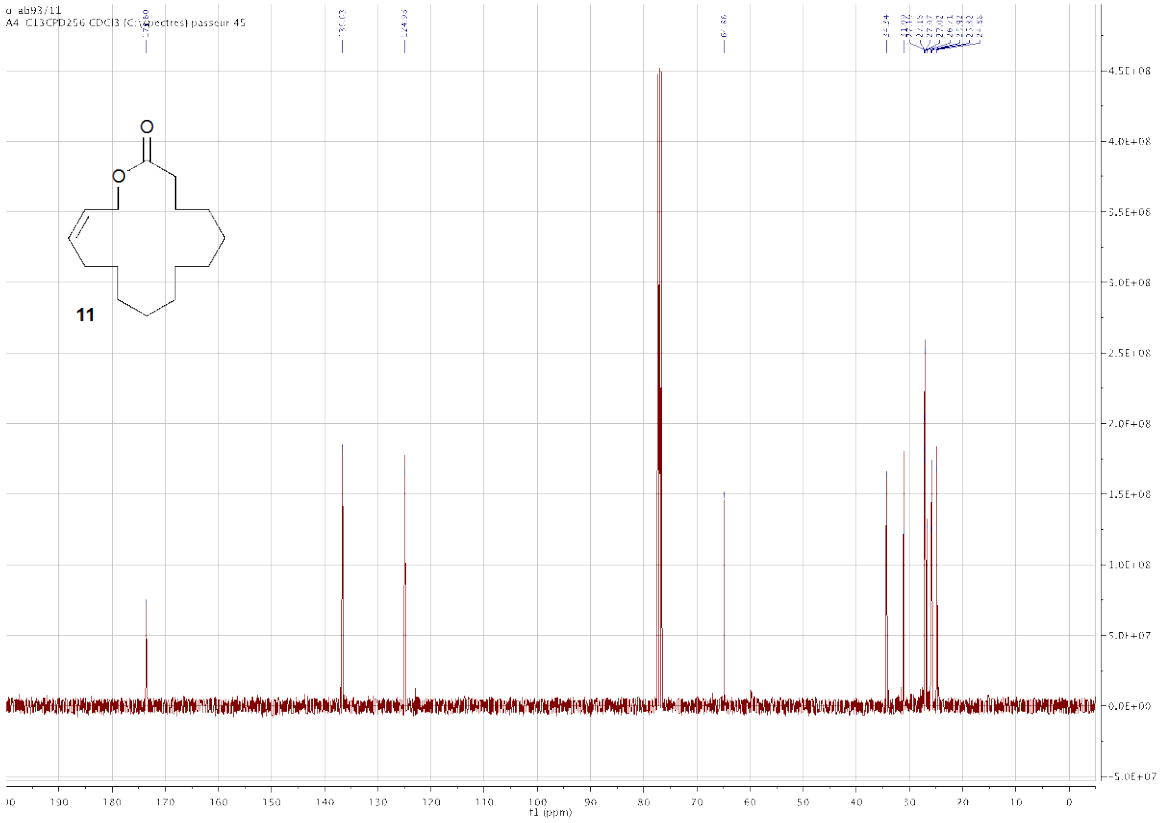




(*Z*)-oxacyclohexadec-14-en-2-one **11**[2]

To a solution of ester **10c** (200 mg, 0.53 mmol) in toluene (0.001M to neat conditions) was added **M7$_1$SIPr** (1 mol% to 5 mol%). The reaction mixture was stirred for 2h at 80 °C. After cooling down to room temperature, solvent was evaporated and the residue was purified by silica gel chromatography (cyclohexane/CH_2Cl_2 70/30) to afford **11** as a colourless oil (see Table 2 for yields). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.79-5.66 (m, 1H), 5.65-5.52 (m, 1H), 4.55 (dd, *J* = 6.5, 1.0 Hz, 2H), 2.39-2.31 (m, 2H), 2.16-2.05 (m, 2H), 1.68-1.59 (m, 2H), 1.45-1.38 (m, 2H), 1.29 (m, 14H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.6, 136.6, 125.0, 64.9, 34.3, 31.1, 27.2, 27.2 (2C), 27.1, 27.0, 26.7, 25.9, 25.8, 24.9.

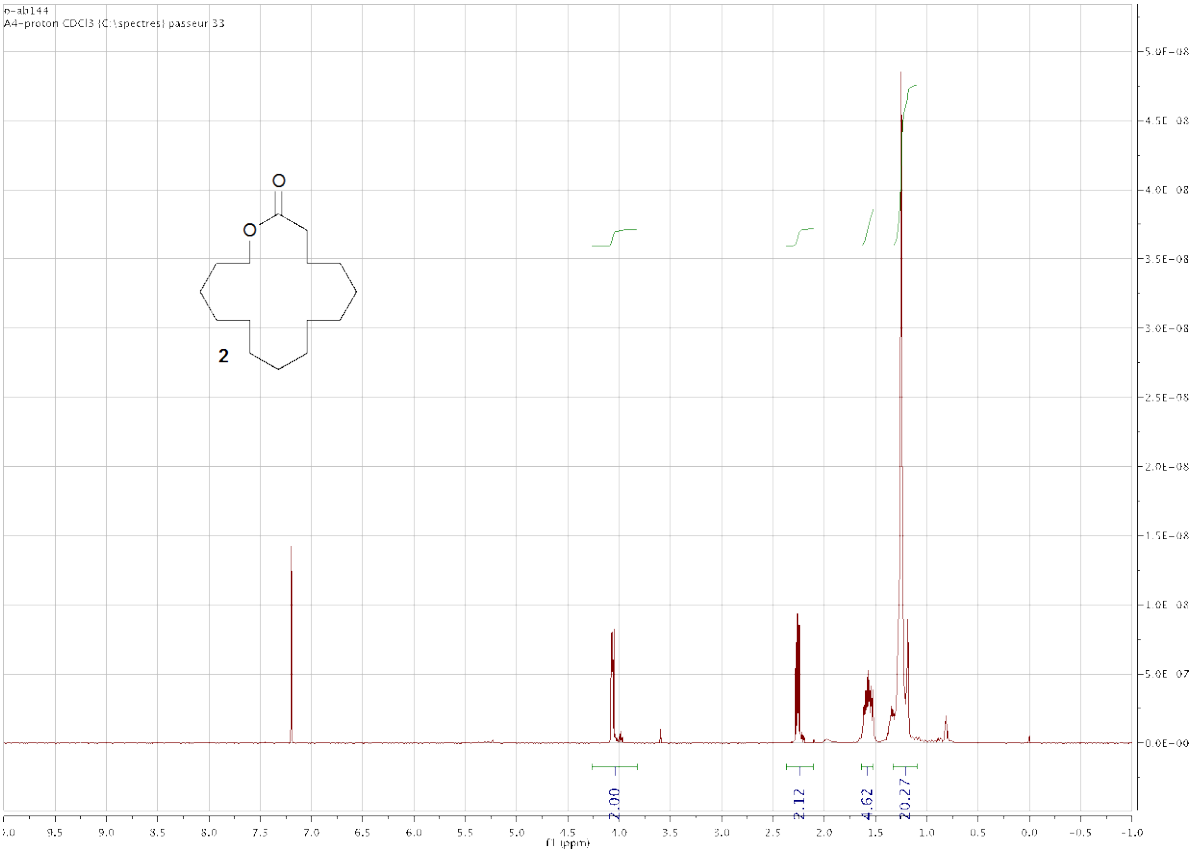


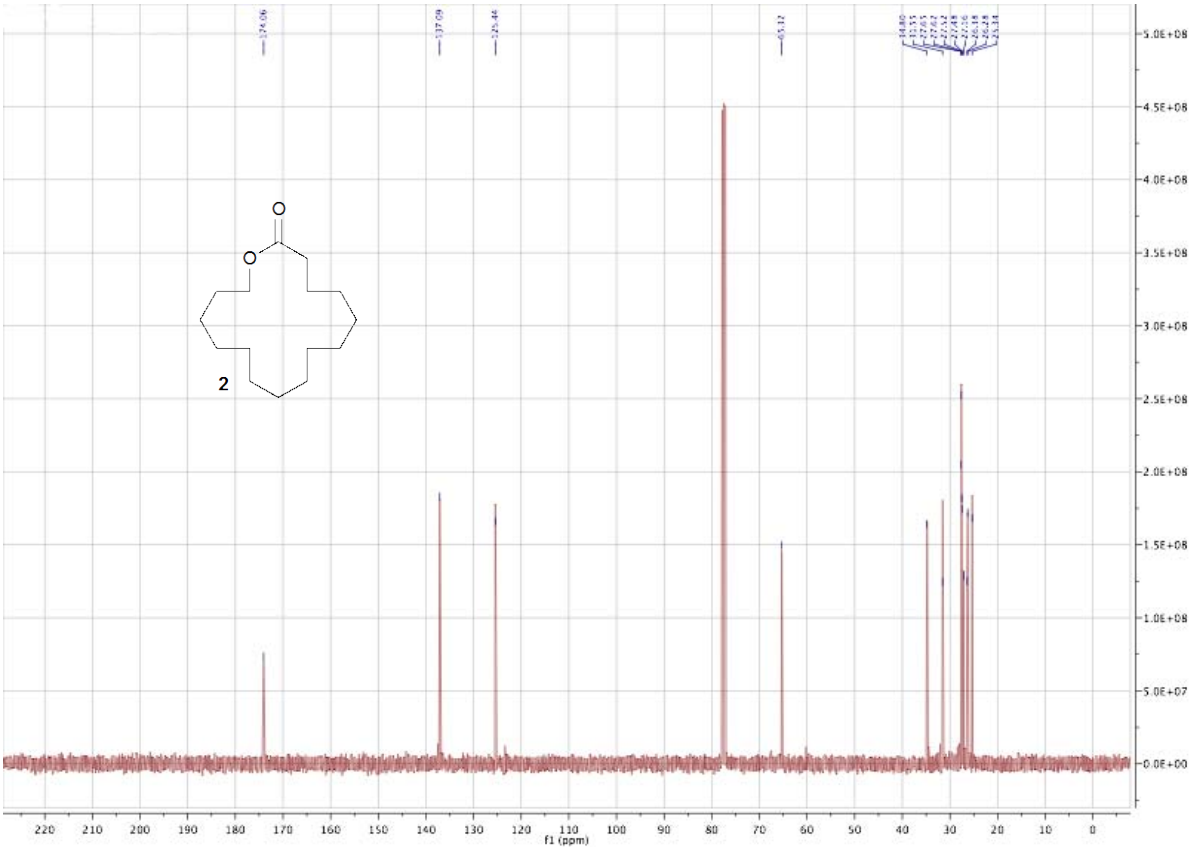


General procedure for the synthesis of Exaltolide **2**[3]

Ru-catalyst (1 mol%) was added to a solution of ester **10c** (200 mg, 0.53 mmol) in toluene (53 mL). The reaction mixture was stirred for 4h at 80°C. After cooling down to room temperature, Pd/C (15 mg) was added and the

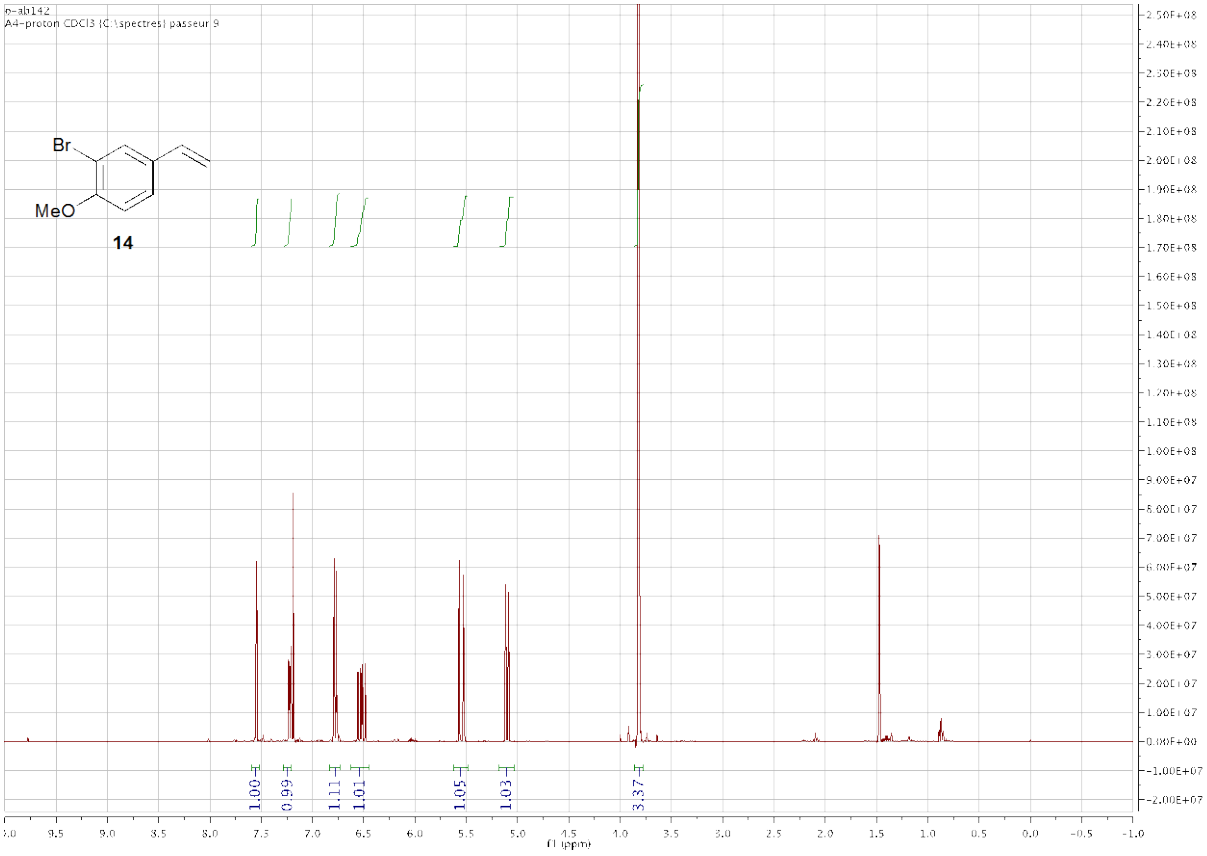
reaction flask pressured with 1 atm hydrogen. After stirring overnight at room temperature, the reaction mixture was filtrated over a celite pad and the solvent was evaporated. The residue was purified by silica gel chromatography (cyclohexane/CH_2Cl_2 70/30) to produce **2** as a colourless oil (see Table 3 for yields). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.13 (m, 2H), 2.32 (t, *J* = 6.6 Hz, 2H), 1.68-1.59 (m, 4H), 1.42-1.25 (m, 20H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.0, 64.0, 34.4, 28.4, 27.8, 27.1, 27.1, 26.9, 26.7, 26.3, 26.0, 25.9, 25.8, 25.1, 24.9.

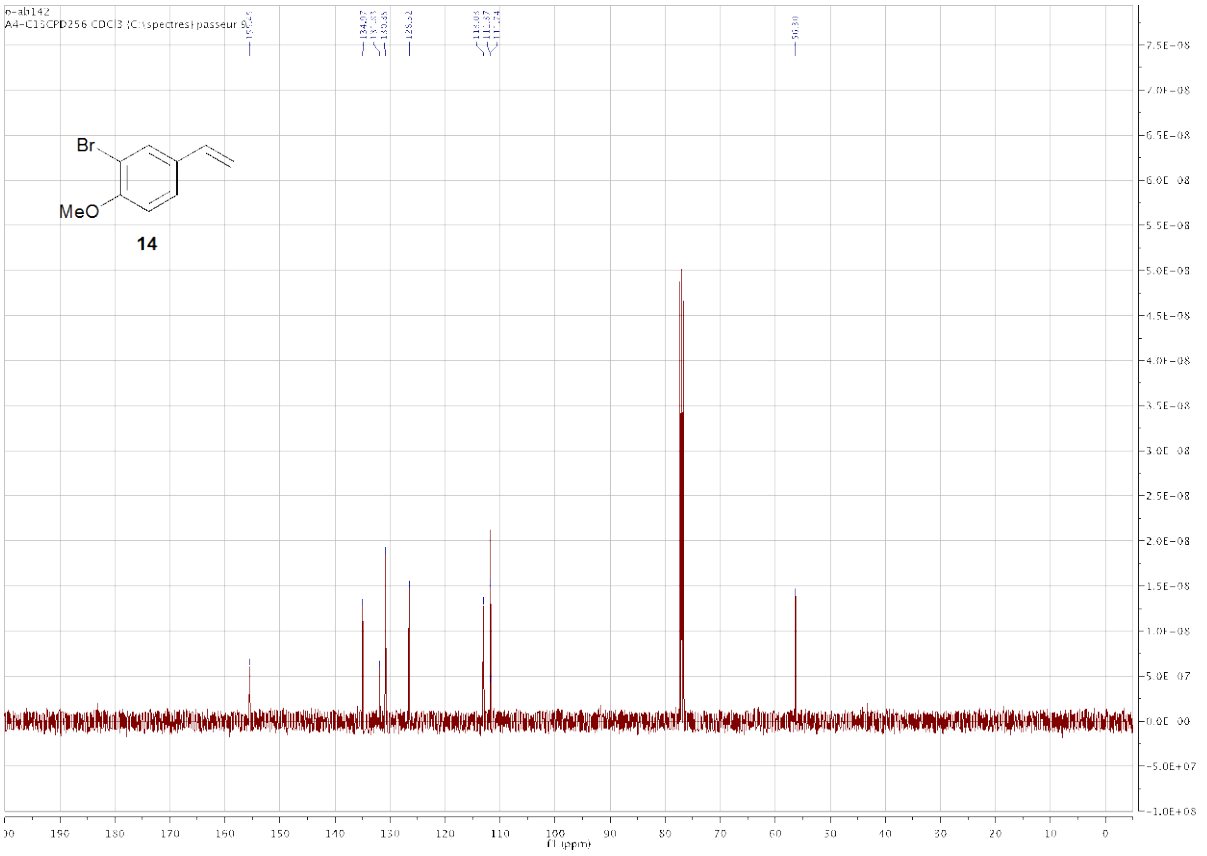




2-bromo-1-methoxy-4-vinylbenzene **14**

To a solution of methyltriphenylphosphonium bromide (5.48 g, 15.3 mmol) in THF (30 mL), 1.6M *n*-BuLi (9.6 mL, 15.3 mmol) was added at 0 °C over a 10 min period. After stirring 30 min at 0 °C, a solution of 4-methoxy-3-bromobenzaldehyde **13** (3 g, 13.9 mmol) in THF (20 mL) was added dropwise and the reaction mixture was stirred at room temperature. After 2h, the solution was quenched with water (150 mL) and extracted with CH_2Cl_2 (3 x 200 mL). The combined organic layers were washed with brine (200 mL), dried over $MgSO_4$ and solvent was evaporated. The residue was diluted with Et_2O (200 mL) and kept 2h at 5 °C to complete the precipitation. The solid was filtrated off over Büchner and the filtrate was concentrated. Purification by silica gel chromatography (cyclohexane/EtOAc 95/5) afforded **14** as a yellow oil (2.71 g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63 (d, *J* = 2.2 Hz, 1H), 7.31 (dd, *J* = 8.4, 2.3 Hz, 1H), 6.86 (d, *J* = 8.5 Hz, 1H), 6.61 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.63 (dd, *J* = 17.5, 0.7 Hz, 1H), 5.19 (dd, *J* = 10.9, 0.7 Hz, 1H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.5, 135.0, 131.8, 130.9, 126.5, 113.0, 111.9, 111.7, 56.3; HRMS calcd for $C_9H_{10}O^{79}Br$ $(M+H)^+$: m/z 2012.9915, found : m/z 212.9912.



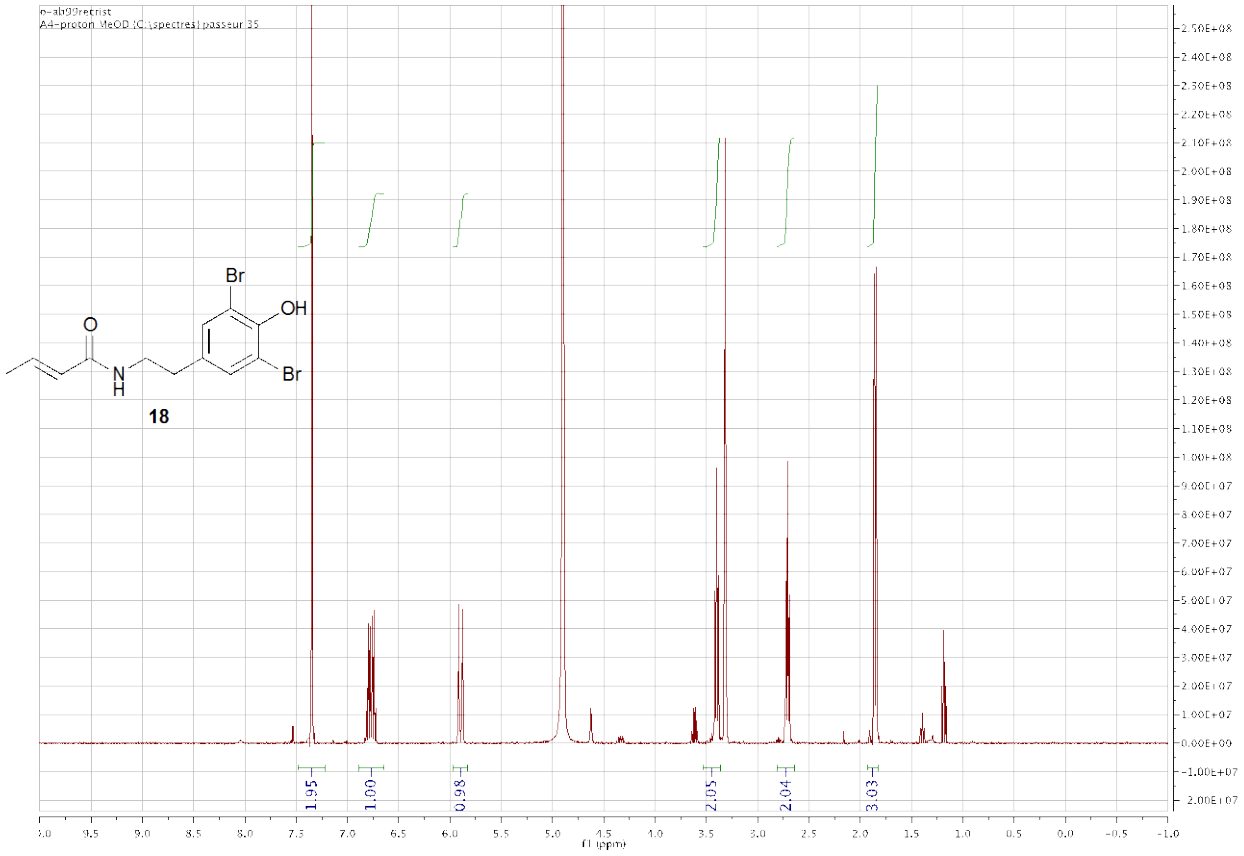


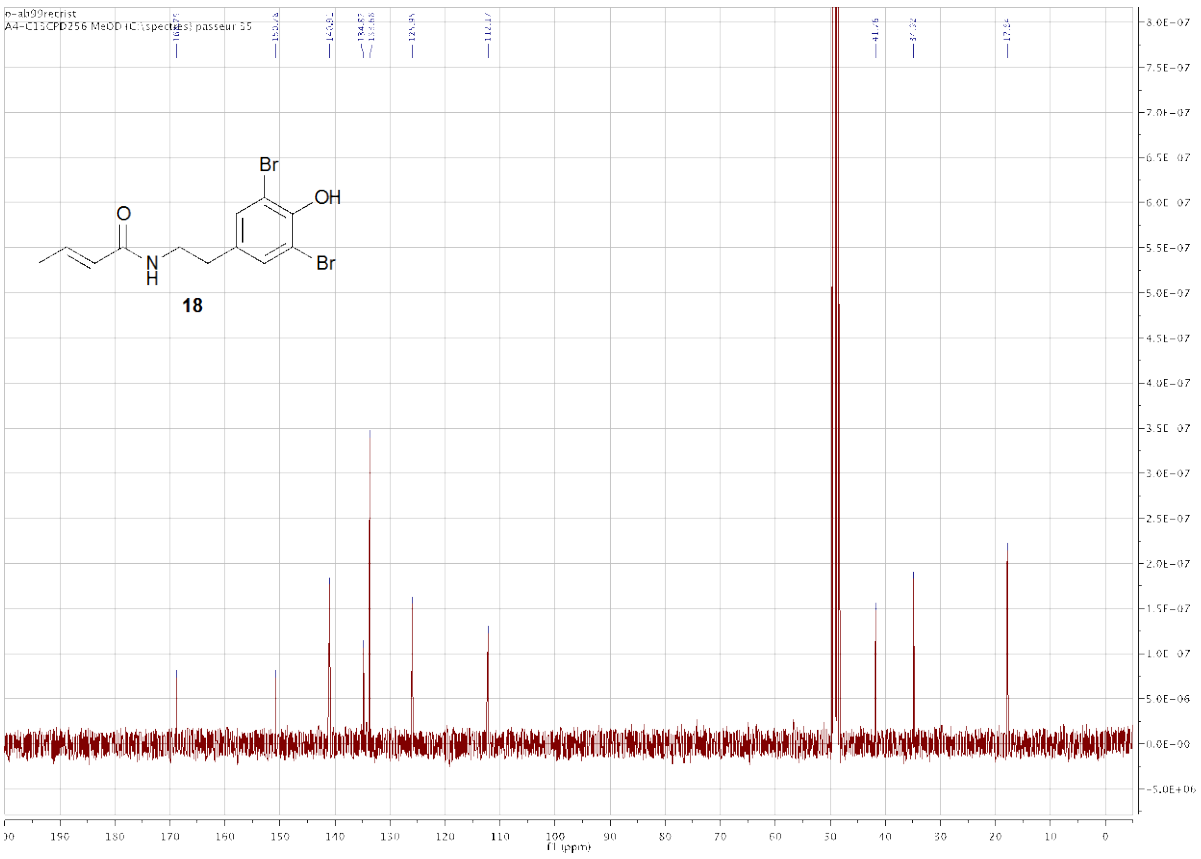
4-(2-aminoethyl)-2,6-dibromophenol hydrobromide **16**[4]

A solution of tyramine **15** (6 g, 34.5 mmol) in acetic acid (70 mL) was warmed up at 50 °C and a solution of bromine (6.72 mL, 103.6 mmol) in acetic acid (40 mL) was added dropwise. After completion of the addition, the reaction mixture was stirred for 1h at 50 °C. After cooling down to room temperature, the solid formed was filtrated off and washed with a large amount of Et_2O to afford the expected dibromophenol **16** as a yellow solid (10.4 g, 80%). ^{1}H NMR (400 MHz, DMSO-d6): δ = 9.80 (broad s, 1H), 7.85 (broad s, 3H), 7.46 (s, 2H), 3.13-2.92 (m, 2H), 2.80 (t, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d6): δ = 149.4, 132.5 (2C), 131.6, 111.9 (2C), 39.6, 31.1; HRMS calcd for $C_8H_{10}NO^{79}Br_2$ $(M+H)^+$: m/z 293.9129, found : m/z 293.9131.

(*E*)-*N*-(3,5-dibromo-4-hydroxyphenethyl)but-2-enamide **18**[4]

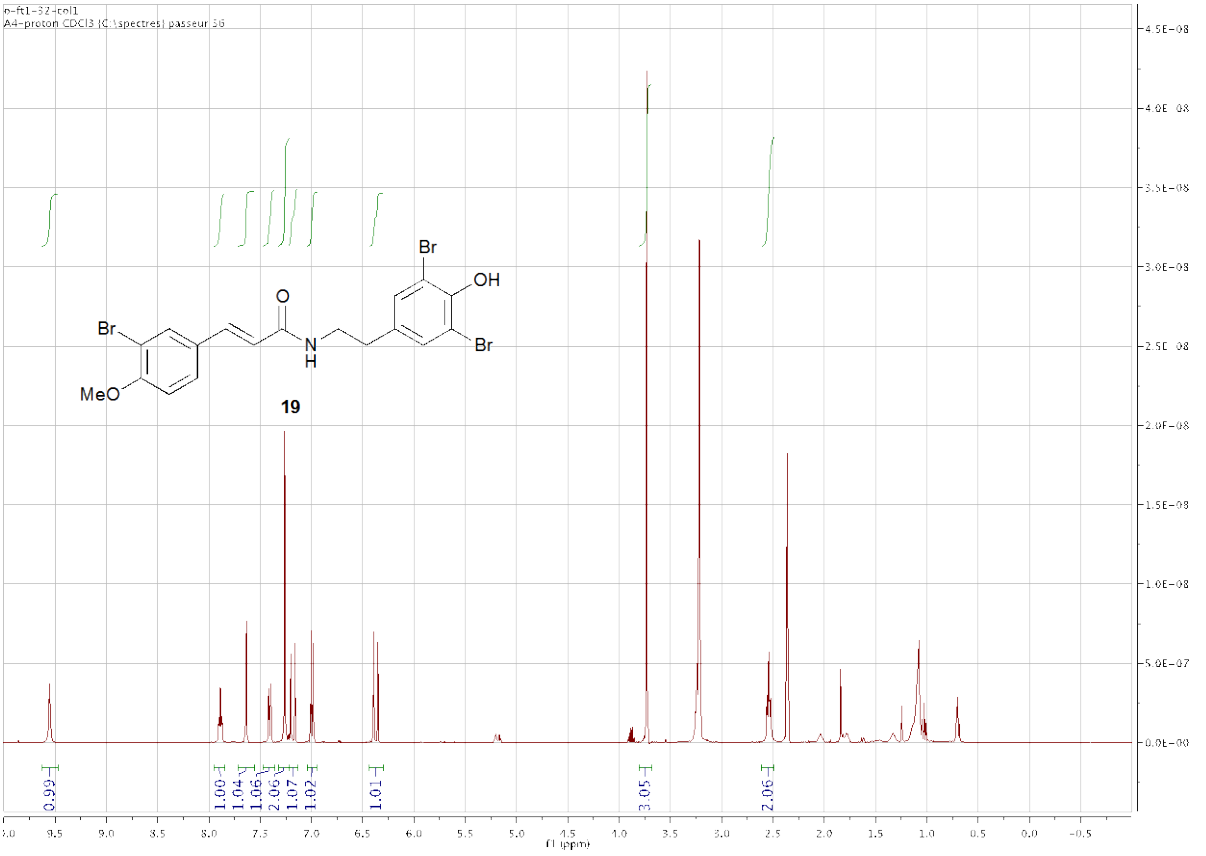
To a solution of crotonic acid **17** (916 mg, 10.6 mmol) in THF (100 mL), triethylamine (4.4 mL, 26.6 mmol) was added and the reaction mixture was stirred at room temperature for 2 min. A solution of DEPC (2.15 mL, 6.4 mmol) in THF (40 mL) was added dropwise followed by the dibromo tyramine compound **16** (4 g, 10.6 mmol). The reaction mixture was stirred 2h at room temperature. The solvent was evaporated, the residue diluted in Et_2O (100 mL) and kept 1h à -18 °C to complete precipitation. The solid was filtrated off over Büchner and the filtrate concentrated. The residue was purified by silica gel chromatography (CH_2Cl_2/MeOH 95/5) and recrystallized in CH_2Cl_2 to afford **18** as a white solid (2.7 g, 70%). ^{1}H NMR (400 MHz, MeOD): δ = 7.34 (s, 2H), 6.77 (dq, *J* = 15.3, 6.9 Hz, 1H), 5.89 (dq, *J* = 15.3, 1.7 Hz, 1H), 3.40 (t, *J* = 7.1 Hz, 2H), 2.71 (t, *J* = 7.1 Hz, 2H), 1.85 (dd, *J* = 6.8, 1.7 Hz, 3H); ^{13}C NMR (100 MHz, MeOD): δ = 168.8, 150.8, 140.9, 134.8, 133.7 (2C), 126.0, 112.2 (2C), 41.8, 34.9, 17.8; HRMS calcd for $C_{12}H_{13}NO_2{}^{79}Br_2Na$ $(M+Na)^+$: m/z 383.9211, found : m/z 383.9213.

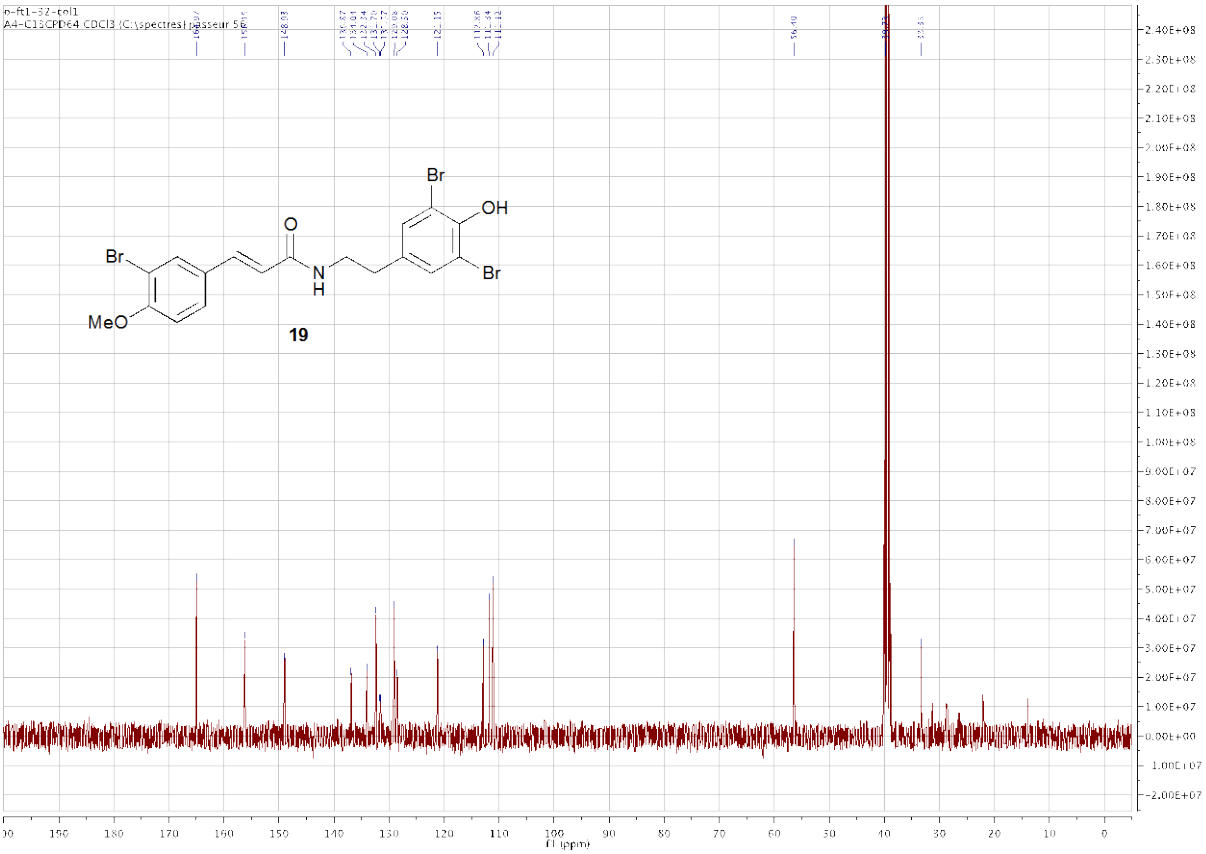




General procedure for the synthesis of (*E*)-3-(3-bromo-4-methoxyphenyl)-*N*-(3,5-dibromo-4-hydroxyphenethyl)acrylamide **19**

Ru-catalyst (1 mol%) was added to a solution of **14** (200 mg, 0.93 mmol) and **18** (170 mg, 0.47 mmol) in CH_2Cl_2 (2.3 mL). The reaction mixture was stirred for 2h at 40 °C. The crude mixture was analysed by ^{1}H NMR to determine the conversion (see Table 4). After cooling down to room temperature, Et_2O (5 mL) was added and the solution was kept for 1h at 5 °C to complete the precipitation. The solid was filtrated over Büchner filter to remove amide by-products. When **M71SIPr** catalyst was used, the desired product **19** was purified by silica gel chromatography (cyclohexane/EtOAc 60/40) and isolated in 74% (185 mg) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.69 (s, 1H), 8.03 (dd, *J* = 5.7, 5.6 Hz, 1H), 7.78 (d, *J* = 2.1 Hz, 1H), 7.54 (dd, *J* = 8.6, 2.1 Hz, 1H), 7.40 (s, 2H), 7.32 (d, *J* = 15.8 Hz, 1H), 7.13 (d, *J* = 8.7 Hz, 1H), 6.51 (d, *J* = 15.8 Hz, 1H), 3.87 (s, 3H), 3.38 (t, *J* = 6.8 Hz, 2H), 2.68 (t, *J* = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.9, 156.1, 148.8, 136.8, 133.9, 132.3, 131.6, 131.5, 129.0, 128.4, 121.1, 112.8, 111.7 (2C), 111.0, 56.3, 39.8, 33.2.





[1] M. Alchihab, J. Destain, M. Aguedo, P. Thonart, *Biotechnol. Agron. Soc. Environ.* 2010, **14**, 681.

[2] (a) A. Fürstner, K. Langemann, *Synthesis* 1997, 792; (b) H. Hagiwara, T. Nakamura, N. Okunaka, T. Hoshi, T. Suzuki, *Helvetica Chimica Acta* 2010, **93**, 175.

[3] A. S. Williams, *Synthesis* 1999, 1707.

[4] W. Erb, E. Payet, *l'actualité chimique* 2010, **345**, 33.