Synthesis of (+)-Darwinolide, a Biofilm-Penetrating Anti-MRSA Agent

*Thomas Siemon, Simon Steinhauer and Mathias Christmann**

Abstract: *Darwinolide, a recently identified marine natural product from the Antarctic sponge Dendrilla membranosa, was shown to exhibit promising activity against the biofilm phase of methicillin-resistant Staphylococcus aureus. Its challenging tetracyclic rearranged spongian diterpenoid structure links a trimethylcyclohexyl subunit to a seven-membered core with two fused tetrahydrofurans. Here we describe the first synthesis of (+)-darwinolide featuring a convergent aldol fragment coupling, an Ireland-Claisen rearrangement and an organocatalytic desymmetrization as the key steps. Our results provide a foundation for the development of novel antibiofilm-specific antibiotics.*

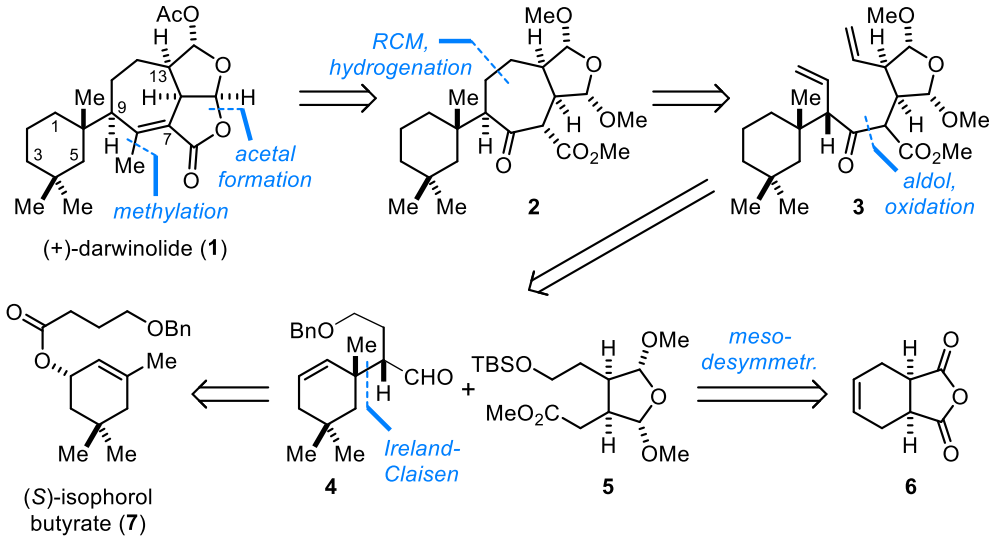
The vast majority of bacterial infections is considered to involve the formation of biofilms,[1] an assemblage of microbial cells embedded within a self-produced extracellular polymeric matrix irreversibly attached to a surface. Chronical and persistent diseases like osteomyelitis, rhinosinusitis, endocarditis, otitis media and especially nosocomial infections are associated with biofilms of *Staphylococcus aureus*.[2][3] Biofilm infections are resistant to conventional antimicrobial treatment[4] and low levels of β-lactam antibiotics may even induce the formation of biofilms in *S. aureus*.[5] Thus, the development of new antibiofilm agents for the treatment of drug resistant bacterial infections remains a priority.

In 2016, Baker *et al.* reported the isolation of the rearranged spongian diterpenoid darwinolide (**1**) from the Antarctic sponge *Dendrilla membranosa*.[6] Darwinolide displays cytotoxic activity against a clinical strain of a highly methicillin-resistant *S. aureus* (MRSA) with a minimal inhibitory concentration (MIC) of 132.9 μM. An *in vitro* established biofilm of the same MRSA strain was inhibited with an IC_{50} value of 33.2 μM. This unique 4-fold selectivity for MRSA biofilms over planktonic cells coupled with a low mammalian cytotoxicity (IC_{50} = 73.4 μM against J774 macrophage cell line) make darwinolide a promising candidate for the development of novel antibiofilm-specific antibiotics.

Darwinolide's structure features a [3.3.0]dioxabicyclooctanone[7] fused to a cycloheptene. This unprecedented tricyclic core is linked to a trimethylcyclohexyl moiety and was suggested to

result from a ring-expansion rearrangement of a common spongian precursor.[6] The structure and absolute configuration of darwinolide were established unambiguously by single crystal X-ray analysis.

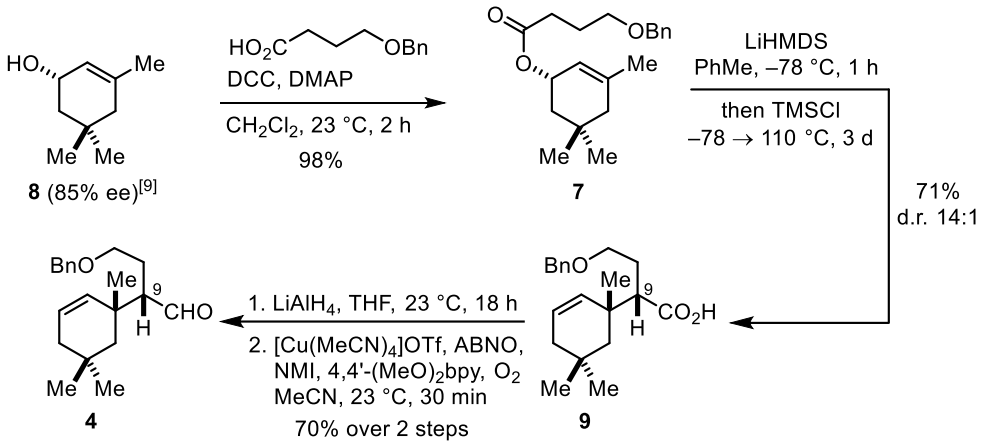
Intrigued by its unique structure and the promising biological profile, we embarked on a total synthesis of **1**. As outlined in our retrosynthetic analysis (Scheme 1), we decided to construct the supposedly labile fused lactone acetal at the final stage of the synthesis while the tetrasubstituted double bond was traced back to a β-keto ester **2**. The two adjacent methylene groups within the seven-membered ring allowed for an olefin metathesis/hydrogenation transform leading to precursor **3**. The terminal alkenes in **3** were envisaged to result from a simultaneous elimination of two primary alcohols. A convergent aldol disconnection of β-keto ester **3** leads to the equally complex aldehyde **4** and ester **5**. The key-step in the synthesis of the 1,3,3-trimethylcyclohexyl fragment **4** is an Ireland-Claisen rearrangement of (*S*)-isophorol 4-(benzyloxy)butyrate (**7**). Finally, the local symmetry of fragment **5** suggested a desymmetrization approach leading back to the commercially available *meso*-anhydride **6**.



Scheme 1. Retrosynthetic analysis.

Our synthesis started with a Steglich esterification[8] of 4-(benzyloxy)butanoic acid and (*S*)-isophorol **8** (Scheme 2), which was available in 85% ee by enzymatic resolution of the commercial available racemic alcohol.[9] An Ireland-Claisen rearrangement[10] of ester **7** proceeded with a yield of 71% to afford isomer **9** in a 14:1 diastereomeric ratio. As the stereogenic center adjacent to

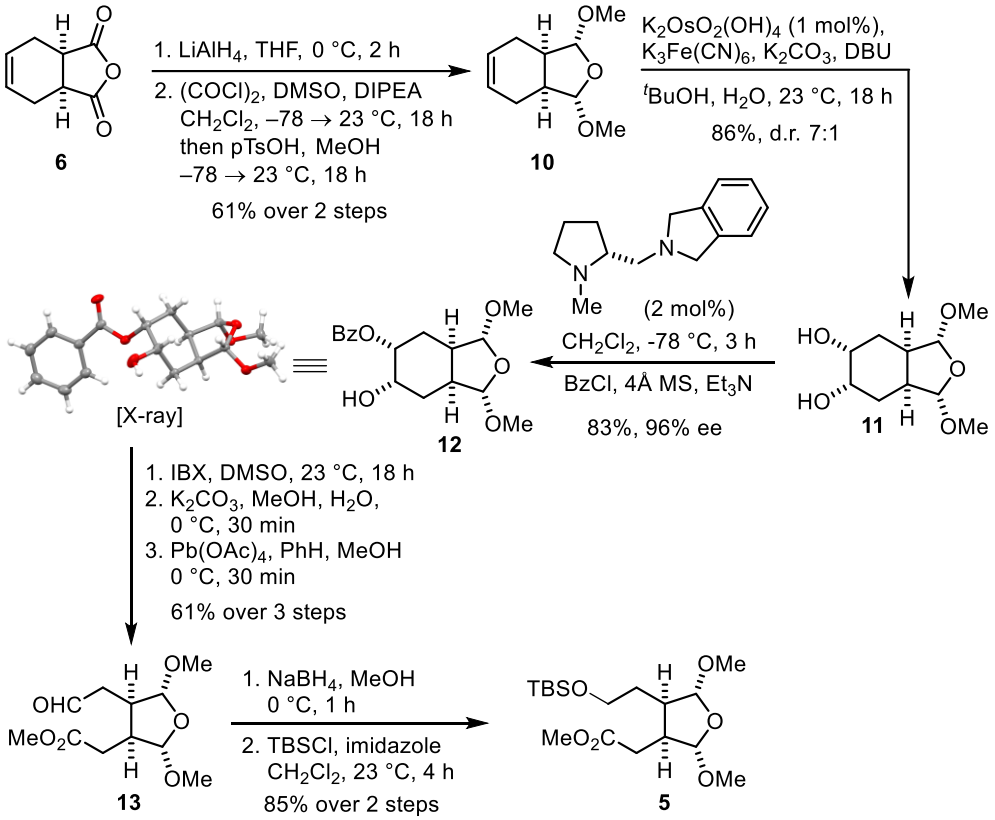
the carboxylic acid possesses the undesired configuration, an epimerization was required at a later stage. Interestingly, having the undesired configuration at C9 came as a blessing in disguise as it turned out to be beneficial in the subsequent aldol step. Reduction of the carboxylic acid **9** and subsequent Cu-catalyzed aerobic oxidation under Stahl conditions[11] gave access to aldehyde **4** in 70% over two steps.



Scheme 2. Construction of the 1,3,3-trimethylcyclohexyl fragment **4**.

The synthesis of the tetrahydrofuran fragment **5** began with the reduction of the commercially available anhydride **6** with $LiAlH_4$ (Scheme 3). A one-pot procedure for the synthesis of the bisacetal **10** involved a Swern oxidation[12] to the dialdehyde followed by an acid-catalyzed bisacetalization. Dihydroxylation under Sharpless conditions[13] proceeded smoothly to give **11** in 86% yield and a diastereomeric ratio of 7:1 in favor of an attack from the convex face. Under Upjohn conditions ($K_2[OsO_2(OH)_4]$, NMO, citric acid)[14] an even better stereoselectivity (17:1 *d.r.*) could be achieved, but the yield was lower (65%) and the isolation troublesome. Desymmetrization of *meso*-diol **11** was accomplished using 2 mol% of Oriyama's proline derived catalyst.[15] Monobenzoate **12** was obtained in 83% yield and with excellent enantioselectivity (96% *ee*). The absolute configuration of **12** was confirmed by single crystal X-ray analysis. A sequence of IBX oxidation, saponification and Criegee oxidation[16] of an α-hydroxy ketone intermediate with $Pb(OAc)_4$ afforded aldehyde **13** in 61% yield over 3 steps. After reduction with $NaBH_4$, protection

of the primary hydroxyl as a benzyl was possible but suffered from unsatisfactory yields. As a viable alternative, we obtained *tert*-butyldimethylsilyl ether **5** in 85% yield over 2 steps.



Scheme 3. Synthesis of methyl ester **5** *via* a desymmetrization approach.

With ester **4** and aldehyde **5** in hand, an aldol reaction was performed (Scheme 4). While the transformation proceeded cleanly, full conversion could not be achieved. Gratifyingly, the starting materials could be recovered, thus β-hydroxy ester **14** was obtained as a single diastereomer in 78% yield after 4 cycles. The configurations of the newly formed stereogenic centers were not determined as they were inconsequential for the final product. After a Dess-Martin oxidation[17] of **14** to ketone **15**, the olefin was reduced and the protecting groups were removed by hydrogenolysis and the subsequent acidic workup, respectively, to give diol **16** in 93% yield. A direct elimination under Sharpless-Grieco conditions[18] was unsuccessful, but a 3-step sequence could be established in which both alcohols were eliminated simultaneously in 72% total yield. The diol **16** was first transformed into the diiodide under Appel conditions and then treated with sodium 2-nitrophenylselenide generated *in situ* from 2-nitrophenylselenocyanate and $NaBH_4$.[19]

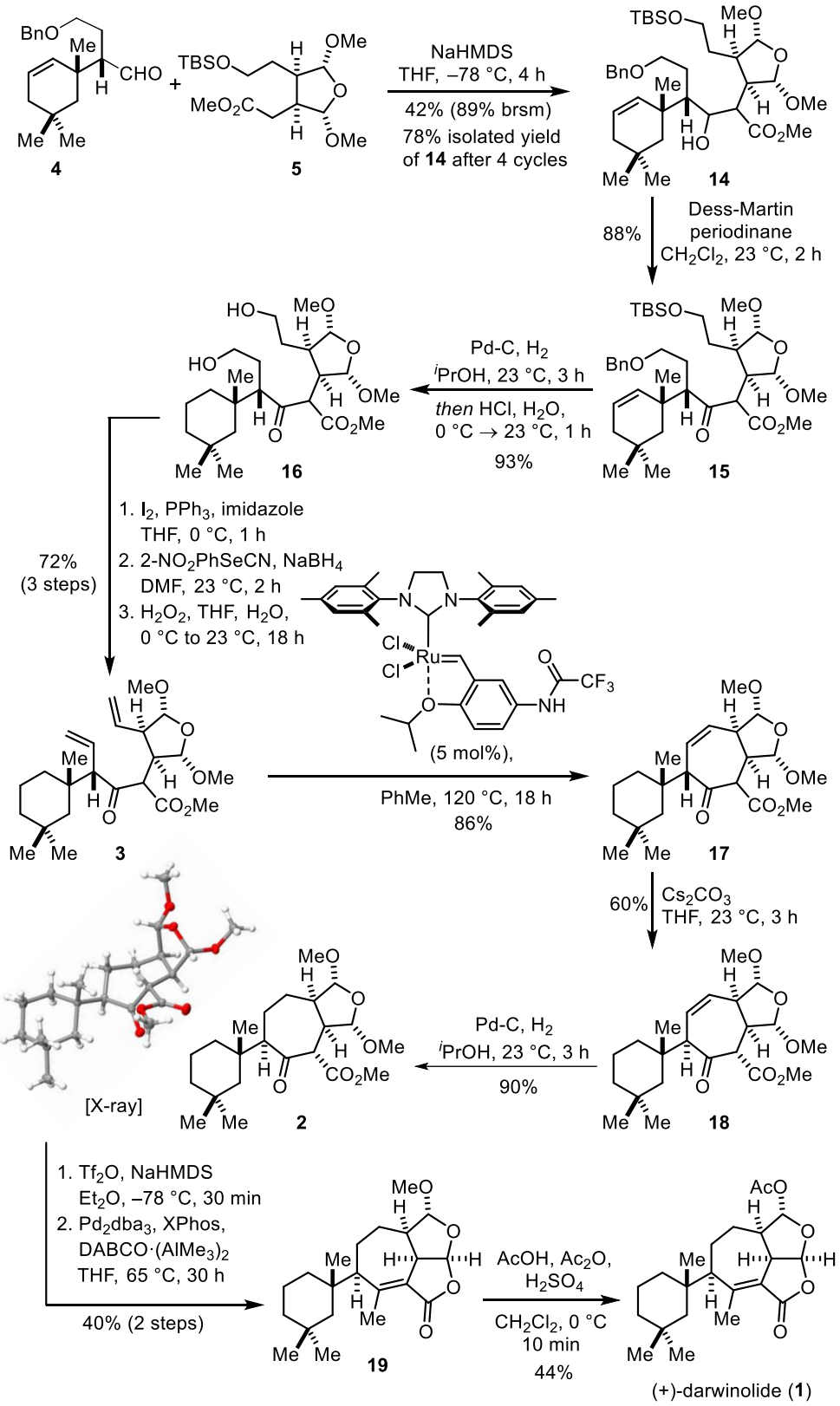
Upon oxidation with H_2O_2 diene **3** was obtained. A ring-closing metathesis[20] was carried out with Umicore's M71SIMes catalyst to generate the central seven-membered core structure **17** in 86% yield. Epimerization at C9 was accomplished under basic conditions to afford the thermodynamically favored β-keto ester **18**. After hydrogenation of the double bond, the correct configuration of the core structure **2** was confirmed by single crystal X-ray analysis. Subsequently, β-keto ester **2** was transformed into the corresponding vinyl triflate. In the subsequent methylation, the best results were obtained with Woodward's cross coupling protocol[21] using Pd_2dba_3 and XPhos as pre-catalysts and a 2:1 adduct of Me_3Al and 1,4-diazabicyclo[2.2.2]octane (DABCO), as the methyl source. Under these conditions, we also observed the formation of the fused lactone acetal moiety, which led to the tricycle **19** in 40% yield over 2 steps. Finally, (+)-darwinolide (**1**) was obtained by transacetalization with AcOH, Ac_2O and H_2SO_4.

In conclusion, we have achieved the first synthesis of darwinolide in 21 steps in the longest linear sequence with an overall yield of 1.4%. Our synthesis offers the possibility to explore the structural basis of darwinolide's unique biological profile with the synthesis of deep-seated analogs and tool compounds.

Acknowledgements

We thank Umicore N.V. for the donation of the metathesis catalyst M71SIMes. We thank Malte Brie (HU Berlin) and Jonas Genz (FU Berlin) for synthetic and Christiane Groneberg (FU Berlin) for analytic support.

Keywords: antibiotics • terpenoids • total synthesis • marine natural products • antibiofilm compounds



Scheme 4. Formation of the central 7-membered ring and conclusion of the total synthesis of darwinolide.

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Synthesis of (+)-Darwinolide, a Biofilm-Penetrating Anti-MRSA Agent

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General Working Methods

The analytical data was obtained with the help of the following equipment.

NMR spectroscopy

^{1}H and ^{13}C NMR spectra were acquired on a JEOL ECX 400 (400 MHz), JEOL ECP 500/ Bruker Avance 500 (500 MHz) and a Bruker Avance 700 (700 MHZ) in $CDCl_3$ or CD_3OD as a solvent. The chemical shifts were reported relative to $CDCl_3$ (δ = ^{1}H: 7.26 ppm, ^{13}C: 77.16 ppm) or CD_3OD (δ = ^{1}H: 3.31 ppm, ^{13}C: 49.00 ppm. The multiplicities of the signals are described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = mulitplet, br = broad and combinations thereof.
The spectra were evaluated with the software MestReNova 10.

Mass spectra were obtained on a ESI-FTICR-MS: Ionspec QFT-7 (Agilent/Varian).

IR: spectra were measured on a JASCO FT/IR-4100 Spectrometer. Characteristic absorption bands are displayed in wavelengths $\tilde{\nu}$ in cm^{-1} and were analyzed with the software Spectral Manager from JASCO.

Melting points were measured on a Thermovar from the company Reichert and are not corrected.

Enantiomeric excess was determined by chiral HPLC using Agilent Technologies 1200 series equipped with Chiralpak® IC or by chiral GC using Agilent 7890B equipped with Lipodex E column.

Optical rotation measurements were performed on a P-2000 polarimeter from Jasco in a 10 cm optical-path length cell with the frequency of the NaD line measured at the temperature and concentration (in g/100 mL) indicated.

Crystal data were collected on a Bruker D8 Venture diffractometer with a Photon 100 CMOS detector with CuK_α radiation.

Chromatography Reaction progress was monitored by thin layer chromatography on aluminum backed silica gel plates (silica gel 60 F 254 from E. Merck), visualizing with UV light (λ = 254 nm). The plates were developed using vanillin dip solution (170 mL methanol, 20.0 ml conc. acetic acid, 10.0 mL conc. sulfuric acid with 1.0 g vanillin), $KMnO_4$ dip solution (3.0 g potassium permanganate, 5.0 mL NaOH-solution (5 w/w), 300 mL dest. water) or an anisaldehyde solution (450 mL ethanol, 25.0 mL anisaldehyde, 25.0 mL conc. sulfuric acid, 8.0 mL acetic acid).
Flash chromatography was performed using silica gel M60 from Macherey & Nagel (particle size: 40 – 63 µm).

Reagents and Solvents Reactions with air or moisture-sensitive substances were, if not otherwise indicated, carried out under an argon atmosphere with the help of the Schlenk technique. All other reagents and solvents were used as purchased from commercial suppliers unless otherwise noted.

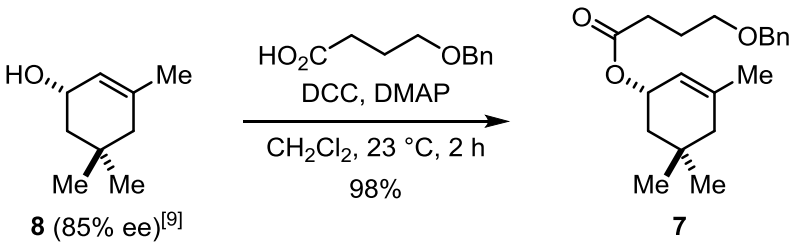
Anhydrous solvents were purified with the solvent purification system MB-SPS-800 (Braun). The solvents (diethyl ether, ethyl acetate, pentane and dichloromethane) used for column chromatography and work up were purified from commercially available technical grade solvents by distillation under reduced pressure with the help of rotatory evaporators (Heidolph or IKA) at 40 °C water bath temperature.

(*S*)-Isophorol was obtained in 85% *ee* by enzymatic resolution of racemic 3,5,5-trimethylcyclohex-2-en-1-ol using *Candida Rugosa* lipase.[1] 4-Benzylbutanoic acid was synthesized from γ-butyrolactone according to the literature.[2] DABAL-Me_3 was obtained by the reaction of 1,4-diazabicyclo[2.2.2]octane and trimethylaluminium.[3]

Compound names are derived from Chemdraw and are not necessarily identical with the IUPAC nomenclature.

Experimental Procedure

(*S*)-3,5,5-Trimethylcyclohex-2-en-1-yl 4-(benzyloxy)butanoate (7)



8 (85% ee)[9] **7**

An oven-dried 500 mL round-bottom-flask equipped with a Teflon-coated magnetic stirring bar was charged with alcohol **8** (7.04 g, 50.2 mmol, 1.0 equiv.) and dry CH_2Cl_2 (250 mL). 4-(benzyloxy)butanoic acid (13.7 g, 70.3 mmol, 1.4 equiv.), *N*,*N*'-dicyclohexyl-carbodiimide (15.5 g, 75.3 mmol, 1.5 equiv.) and 4-(dimethylamino)pyridine (613 mg, 5.02 mmol, 0.1 equiv.) were added at 23 °C. The reaction mixture was stirred under an atmosphere of argon for 18 h and afterwards the solvent was removed under reduced pressure. The residue was taken up in Et_2O (200 mL) and filtered through a sintered glass funnel. The filtrate was concentrated under reduced pressure and purified by column chromatography (SiO_2, pentane/Et_2O 15:1) to afford ester **7** (15.5 g, 98%) as a colorless oil.

$[\alpha]_D^{27}$ = –47.2° (*c* = 0.79, $CHCl_3$).

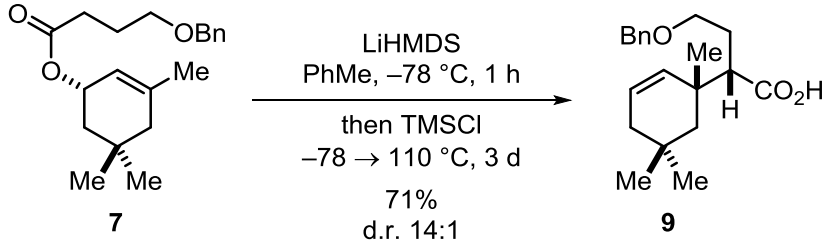
^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 7.36 – 7.31 (m, 4H), 7.31 – 7.25 (m, 1H), 5.38 – 5.36 (m, 1H), 5.36 – 5.32 (m, 1H), 4.50 (s, 2H), 3.51 (t, *J* = 6.2 Hz, 2H), 2.42 (t, *J* = 7.4 Hz, 2H), 1.95 (tt, *J* = 7.5, 6.2 Hz, 2H), 1.87 (d, *J* = 17.3 Hz, 1H), 1.73 (dd, *J* = 12.8, 6.0 Hz, 1H), 1.69 (s, 3H), 1.38 (dd, *J* = 12.9, 7.9 Hz, 1H), 1.67 (d, *J* = 17.3 Hz, 1H), 1.00 (s, 3H), 0.94 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ [ppm] = 172.9, 138.2, 137.9, 128.0, 127.3, 127.2, 119.0, 72.6, 69.6, 68.9, 43.7, 40.4, 31.2, 30.3, 30.1, 26.7, 24.9, 23.4.

HRMS (ESI): m/z calcd for $C_{20}H_{28}O_3Na$ $[M+Na]^+$: 339.1930; found: 339.1939.

IR (ATR): $\tilde{\nu}$ = 2952, 2929, 2869, 2361, 2336, 1728, 1454, 1365, 1256, 1173, 1110, 1077, 1025, 972, 944, 761, 751, 739, 700, 686, 668 cm^{-1}.

(*S*)-4-(Benzyloxy)-2-((*R*)-1,5,5-trimethylcyclohex-2-en-1-yl)butanoic acid (9)



An oven-dried 500 mL three-necked-flask equipped with a reflux condenser, a Schlenk adapter, a dropping funnel and a Teflon-coated magnetic stirring bar was charged with 1,1,1,3,3,3-hexamethyldisilazane (18.0 mL, 86.9 mmol, 2.5 equiv.) and dry PhMe (50 mL) under an atmosphere of argon. *n*-BuLi (2.5 M in hexane, 27.8 mL, 69.5 mmol, 2.0 equiv.) was added at −78 °C and the solution was warmed to 23 °C over 30 min. After re-cooling to −78 °C, a solution of ester **7** (11.0 g, 34.8 mmol, 1.0 equiv.) in dry PhMe (100 mL) was added and the mixture was stirred at −78 °C for 1 h. Chlorotrimethylsilane (8.80 mL, 69.5 mmol, 2.0 equiv.) was added and after another 15 min at −78 °C, the reaction mixture was refluxed for 3 d. HCl (1 M aq. , 200 mL) was added at 0 °C and the aqueous phase was extracted with Et_2O (3 x 200 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Column chromatography (SiO_2, pentane/Et_2O 8:1 + 0.7% HCO_2H) afforded the acid **9** (7.89 g, 71%, 14:1 *d.r.*) as a colorless oil.

$[\alpha]_D^{24}$= +3.00° (*c* = 0.90, $CHCl_3$).

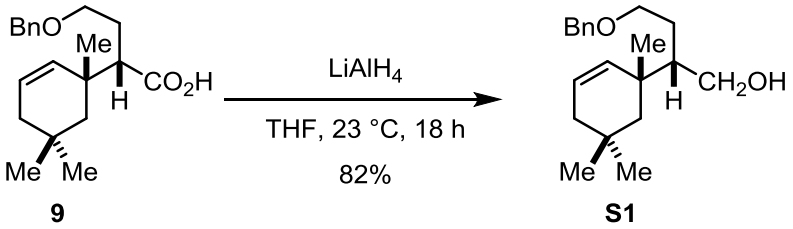
^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 10.72 (br s, 1H), 7.41 – 7.25 (m, 5H), 5.73 (ddd, *J* = 10.1, 5.5, 2.6 Hz, 1H), 5.32 (d, *J* = 10.1 Hz, 1H), 4.52 (d, *J* = 12.1 Hz, 1H), 4.49 (d, *J* = 12.1 Hz, 1H), 3.53 – 3.43 (m, 2H), 2.38 (dd, *J* = 11.3, 2.3 Hz, 1H), 1.98 (ddt, *J* = 13.8, 11.6, 5.9 Hz, 1H), 1.82 (dtd, *J* = 13.9, 7.0, 2.5 Hz, 1H), 1.77 (t, *J* = 2.8 Hz, 1H), 1.75 (dt, *J* = 5.5, 1.6 Hz, 1H), 1.62 (d, *J* = 14.2 Hz, 1H), 1.34 (d, *J* = 14.2 Hz, 1H), 1.19 (s, 3H), 0.99 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$): δ [ppm] = 179.8, 138.3, 133.4, 128.4, 127.6, 127.5, 126.2, 73.0, 69.1, 53.6, 43.9, 38.3, 38.2, 32.6, 30.0, 28.2 (2C), 26.3.

HRMS (ESI): m/z calcd for $C_{20}H_{28}O_3Na$ $[M+Na]^+$: 339.1930; found: 339.1931.

IR (ATR): $\tilde{\nu}$ = 2950, 2923, 2870, 1730, 1701, 1455, 1364, 1254, 1111, 859, 844, 750, 738, 727, 714, 697, 671, 659 cm^{-1}.

(*S*)-4-(benzyloxy)-2-((*R*)-1,5,5-trimethylcyclohex-2-en-1-yl)butan-1-ol (S1)



9 **S1**

An oven-dried 500 mL Schlenk flask equipped with a Teflon-coated magnetic stirring bar was charged with $LiAlH_4$ (2.30 g, 61.5 mmol, 3.0 equiv.) and dry THF (70 mL). A solution of acid **9** (6.50 g, 20.5 mmol, 1.0 equiv) in dry THF (30 mL) was added slowly at 0 °C. After warming to 23 °C the suspension was stirred for 18 h. The reaction mixture was diluted with Et_2O (50 mL) and HCl (1 M aq., 50 mL) was added dropwise at 0 °C. The suspension was filtered through sand and the aqueous phase was extracted with Et_2O (3 x 100 mL). The combined organic phases were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Column chromatography (SiO_2, pentane/Et_2O 4:1) afforded alcohol **S1** (5.07 g, 82%) as a colorless oil.

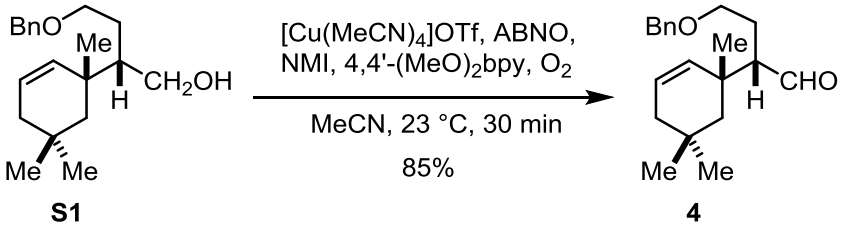
$[\alpha]_D^{24}$= +25.4° (*c* = 0.75, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 7.38 – 7.27 (m, 5H), 5.63 (ddd, *J* = 10.2, 5.6, 2.6 Hz, 1H), 5.32 (d, *J* = 10.1 Hz, 1H), 4.53 (s, 2H), 3.83 (td, *J* = 7.8, 4.0 Hz, 1H), 3.63 (dt, *J* = 9.5, 4.8 Hz, 1H), 3.47 – 3.39 (m, 2H), 3.26 – 3.21 (m, 1H), 1.87 – 1.80 (m, 1H), 1.75 – 1.65 (m, 2H), 1.61 – 1.51 (m, 1H), 1.38 (d, *J* = 13.8 Hz, 1H), 1.36 – 1.30 (m, 1H), 1.15 (d, *J* = 14.3 Hz, 1H), 1.13 (s, 3H), 0.95 (s, 3H), 0.93 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ [ppm] = 137.8, 134.9, 128.6, 128.0 (2C), 125.0, 73.4, 71.1, 63.7, 52.1, 44.2, 38.9, 38.5, 33.1, 30.1, 29.9, 28.2, 26.9.

HRMS (ESI): m/z calcd for $C_{20}H_{30}O_2Na$ $[M+Na]^+$: 325.2138; found: 325.2154.
IR (ATR): $\tilde{\nu}$ = 3440, 3011, 2950, 2867, 1496, 1476, 1455, 1363, 1289, 1263, 1206, 1092, 1029, 994, 731, 697, 680 cm^{-1}.

(*S*)-4-(benzyloxy)-2-((*R*)-1,5,5-trimethylcyclohex-2-en-1-yl)butanal (4)



A 100 mL round-bottom-flask equipped with a Teflon-coated magnetic stirring bar was charged with alcohol **S1** (5.50 g, 18.2 mmol, 1.0 equiv.), $[Cu(MeCN)_4]OTf$ (685 mg, 1.82 mmol, 0.1 equiv.), 9-Aza-bicyclo[3.3.1]nonane *N*-oxyl (25.5 mg, 180 µmol, 0.01 equiv.), *N*-methylimidazole (0.29 mL, 3.64 mmol, 0.2 equiv.), 4,4‘-dimethoxy-2,2‘-bipyridine (394 mg, 1.82 mmol, 0.1 equiv.) and MeCN (50 mL). The atmosphere was exchanged to O_2 by three times evapcuating and flushing with O_2. The reaction mixture was stirred at 23 °C for 30 min und an O_2 atmosphere and HCl (1 M aq., 20 mL) was added. The aqueous phase was extracted with Et_2O (3 x 50 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Column chromatography (SiO_2, pentane/Et_2O 30:1) afforded aldehyde **4** (4.64 g, 85%) as a colorless oil.

$[\alpha]_D^{24}$= +1.00° (*c* = 1.4, $CHCl_3$).

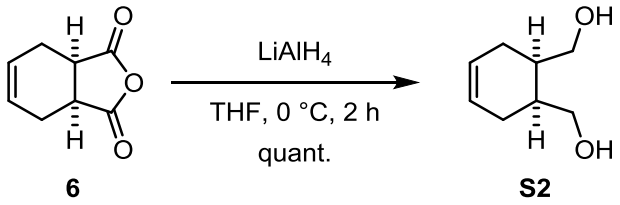
^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] = 9.71 (d, *J* = 4.5 Hz, 1H), 7.36 – 7.25 (m, 5H), 5.72 (ddd, *J* = 10.2, 5.4, 2.9 Hz, 1H), 5.35 (d, *J* = 10.1 Hz, 1H), 4.45 (d, *J* = 12.0 Hz, 1H), 4.41 (d, *J* = 12.0 Hz, 1H), 3.44 – 3.34 (m, 2H), 2.15 (ddd, *J* = 10.8, 4.3, 2.2 Hz, 1H), 2.07 – 1.97 (m, 1H), 1.82 – 1.71 (m, 3H), 1.58 (d, *J* = 13.6 Hz, 1H), 1.27 (d, *J* = 14.0 Hz, 1H), 1.18 (s, 3H), 0.97 (s, 3H), 0.95 (s, 3H).

^{13}C NMR (176 MHz, $CDCl_3$): δ [ppm] = 205.9, 138.3, 132.5, 128.4, 127.7, 127.6, 126.3, 73.0, 68.9, 60.3, 44.7, 38.7, 38.2, 32.7, 29.8, 28.1, 26.7, 25.3.

HRMS (ESI): m/z calcd for $C_{20}H_{28}O_2Na$ $[M+Na]^+$: 323.1981; found: 323.1993.

IR (ATR): $\tilde{\nu}$ = 3013, 2951, 2867, 1717, 1496, 1477, 1455, 1363, 1290, 1265, 1209, 1101, 1028, 993, 935, 906, 731, 698 cm^{-1}.

***cis*-4-Cyclohexene-1,2-dimethanol (S2)**



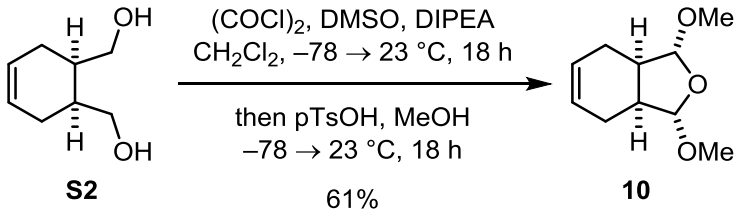
6 **S2**

An oven-dried 1 L Schlenk flask equipped with a Teflon-coated magnetic stirring bar was charged with $LiAlH_4$ (15.2 g, 400 mmol, 2.0 equiv.) and dry THF (500 mL). Anhydride **6** (30.4 g, 200 mmol, 1.0 equiv.) was added in portions at 0 °C and the resulting suspension was stirred at 23 °C for 2 h. The reaction mixture was cooled to 0 °C and diluted with Et_2O (100 mL). H_2O (18 mL), NaOH (10% aq, 30 mL) and again H_2O (45 mL) were added dropwise at 0 °C. The suspension was warmed to 23 °C for 15 min and $MgSO_4$ was added. After 10 min, the precipitation was filtered off and the filtrate was diluted with brine (250 mL). The aqueous phase was extracted with EtOAc (3 x 300 mL) and the combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Diol **S2** (28.1 g, 99%) was obtained as a colorless oil and used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] = 5.60 (s, 2H), 3.71 (dd, *J* = 11.0, 6.8 Hz, 1H), 3.57 (dd, *J* = 11.0, 3.6 Hz, 2H), 3.27 (br. s, 2H), 2.21 – 1.96 (m, 6H).

The spectral data are in accordance with the literature.[4]

***meso*-(1*R*,3*S*,3a*S*,7a*R*)-1,3-Dimethoxy-1,3,3a,4,7,7a-hexahydroisobenzofuran (10)**



S2 **10**

An oven-dried 2 L three-necked-flask equipped with a mechanical stirrer, a Schlenk adapter and a dropping funnel was charged with oxalyl chloride (50.8 mL, 593 mmol, 3.0 equiv.) and dry CH_2Cl_2 (350 mL) under an atmosphere of argon. Dry DMSO (84.2 mL, 1.19 mol, 6.0 equiv.) was added at –78 °C over a period of 45 min. After stirring for 15 min at –78 °C, a solution of diol **S2** (28.1 g, 198 mmol, 1.0 equiv.) in dry CH_2Cl_2 (500 mL) was added dropwise over 1 h. The solution was further stirred at –78 °C for 1 h and *N*,*N*-diisopropylethylamine (252 mL, 1.48 mol, 7.5 equiv.) was added over a period of 30 min. The reaction mixture was stirred at –78 °C for 2 h and stored at –28 °C for 16 h. After an additional 2 h at –78 °C, a solution of *p*-toluenesulfonic acid monohydrate (140 g, 736 mmol, 3.7 equiv.) in MeOH (300 mL) was added. The solution was stirred at 23 °C for 18 h and NH_4Cl (sat. aq., 300 mL) was added

at 0 °C. The aqueous phase was extracted with CH_2Cl_2 (3 x 250 mL). The combined organic phases were concentrated under reduced pressure. The residue was dissolved in EtOAc (500 mL) and washed with brine (2 x 200 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (SiO_2, pentane/Et_2O 15:1) to afford bisacetal **10** (22.1 g, 61%) as a colorless oil.

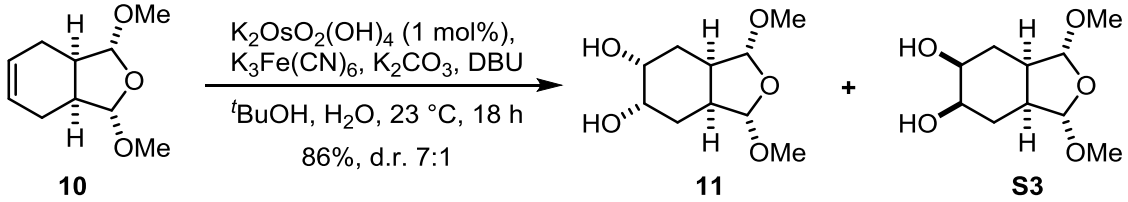
^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 5.68 (t, J = 1.6 Hz, 2H), 4.70 (d, J = 3.0 Hz, 2H), 3.41 (s, 6H), 2.46 – 2.35 (m, 2H), 2.28 – 2.15 (m, 2H), 1.98 – 1.86 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$): δ [ppm] = 125.1, 110.4, 55.7, 39.3, 23.1.

HRMS (ESI): m/z calcd for $C_{10}H_{16}O_3Na$ $[M+Na]^+$: 207.0991; found: 207.0989.

IR (ATR): $\tilde{\nu}$ = 3026, 2952, 2894, 2843, 2362, 1727, 1659, 1440, 1389, 1306, 1252, 1208, 1191, 1123, 1099, 1087, 1040, 999, 968, 921, 884, 846, 803, 758, 738 cm^{-1}.

***meso*-(1*R*,3*S*,3a*S*,5*S*,6*R*,7a*R*)-1,3-Dimethoxyoctahydroisobenzofuran-5,6-diol (11) and *meso*-(1*R*,3*S*,3a*S*,5*R*,6*S*,7a*R*)-1,3-Dimethoxyoctahydroisobenzofuran-5,6-diol (S3)**



A 500 mL round-bottom-flask equipped with a Teflon-coated magnetic stirring bar was charged with bisacetal **10** (22.1 g, 120 mmol, 1 equiv.), *tert*-butanol (150 mL) and H_2O (150 mL). $K_2OsO_2(OH)_4$ (442 mg, 1.20 mmol, 0.01 equiv.), $K_3Fe(CN)_6$ (119 g, 360 mmol, 3.0 equiv.), K_2CO_3 (49.7 g, 360 mmol, 3.0 equiv.) and 1,8-diazabicyclo[5.4.0]undec-7-ene (17.9 mL, 120 mmol, 1.0 equiv.) were added and the reaction mixture was stirred at 23 °C for 18 h. $Na_2S_2O_5$ (ca. 50 g) was added in portions at 0 °C and the mixture was concentrated under reduced pressure. The residue was taken up in EtOAc (500 mL) and the solids were filtered and washed with EtOAc (500 mL) and CH_2Cl_2 (200 mL). The filtrate was concentrated under reduced pressure and column chromatography (SiO_2, CH_2Cl_2/MeOH 30:1) afforded diol **11** (19.7 g, 76%) as a colorless crystalline solid and diols **S3** (2.8 g, 10%) as a colorless oil.

Diol **11**:

m.p.: 138 °C.

^{1}H NMR (700 MHz, MeOH-d_4): δ [ppm] = 4.82 – 4.79 (m, 2H), 3.80 – 3.77 (m, 2H), 3.40 (s, 6H), 2.44 – 2.39 (m, 2H), 1.97 – 1.91 (m, 2H), 1.57 – 1.52 (m, 2H).

^{13}C NMR (176 MHz, MeOH-d_4): δ [ppm] = 109.2, 68.0, 54.4, 40.2, 27.7.

HRMS (ESI): m/z calcd for $C_{10}H_{18}O_5Na$ $[M+Na]^+$: 241,1046; found: 241.1064.

IR (ATR): $\tilde{\nu}$ = 3381, 2956, 2933, 2924, 2883, 2862, 1449, 1395, 1370, 1351, 1338, 1309, 1262, 1225, 1211, 1190, 1135, 1113, 1072, 1047, 1025, 996, 974, 939, 923, 887, 812, 726, 706 cm^{-1}.

Diol **S3**:

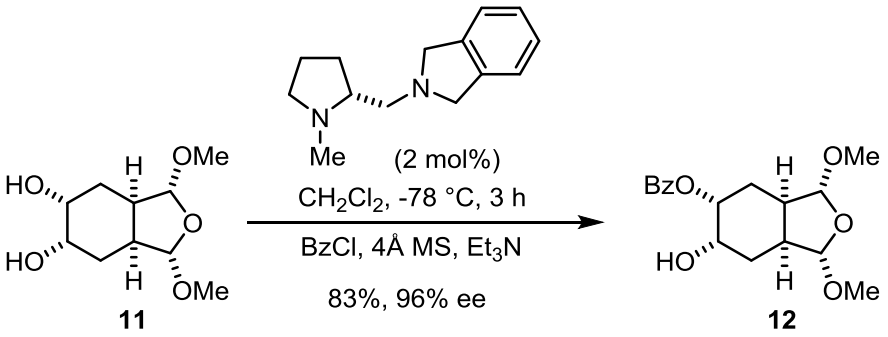
^1H NMR (700 MHz, $CDCl_3$): δ [ppm] = 4.98 (s, 2H), 3.76 – 3.72 (m, 2H), 3.37 (s, 6H), 3.05 – 2.94 (m, 2H), 2.27 – 2.21 (m, 3H), 1.87 – 1.82 (m, 3H), 1.69 – 1.60 (m, 2H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 109.6, 69.4, 55.5, 41.5, 27.6.

HRMS (ESI): m/z calcd for $C_{10}H_{18}O_5Na$ $[M+Na]^+$: 241,1046; found: 241.1058.

IR (ATR): $\tilde{\nu}$ = 3424, 2929, 2834, 1444, 1393, 1328, 1304, 1276, 1233, 1194, 1154, 1096, 1065, 1036, 1006, 990, 966, 933, 882, 852, 784, 734, 703, 679, 657 cm^{-1}.

(1*S*,3*R*,3a*R*,5*R*,6*S*,7a*S*)-6-Hydroxy-1,3-dimethoxyoctahydroisobenzofuran-5-yl benzoate (12)



An oven-dried 1 L Schlenk flask equipped with a Teflon-coated magnetic stirring bar was charged with (*R*)-2-((1-methylpyrrolidin-2-yl)methyl)isoindoline (147 mg, 0.678 mmol, 0.02 equiv.), 4Å molecular sieves (4.40 g) and CH_2Cl_2 (150 mL). Subsequently, triethylamine (4.70 mL, 33.9 mmol, 1.0 equiv.), a solution of *meso*-diol **11** (7.40 g, 33.9 mmol, 1.0 equiv.) in CH_2Cl_2 (200 mL) and a solution benzoyl chloride (5.90 mL, 50.8 mmol, 1.5 equiv.) in CH_2Cl_2 (50 mL) were added dropwise at −78 °C. After stirring at −78 °C for 3 h, NH_4Cl (sat. aq., 100 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 x 150 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (SiO_2, pentane/EtOAc 2:1 → 1:2) afforded ester **12** (9.08 g, 83%, 96% *ee*) as a colorless crystalline solid.

$[\alpha]_D^{28}$= +3.95° (*c* = 1.68, $CHCl_3$).

m.p.: 107 °C.

^1H NMR (400 MHz, $CDCl_3$): δ [ppm] = 8.05 – 8.02 (m, 2H), 7.59 – 7.57 (m, 1H), 7.46 – 7.43 (m, 2H), 5.27 (dt, *J* = 8.1, 3.1 Hz, 1H), 4.84 (t, *J* = 3.0 Hz, 2H), 4.05 (dt, *J* = 8.4, 3.1 Hz, 1H), 3.44 (s, 6H), 2.65 – 2.58 (m,

1H), 2.57 – 2.50 (m, 1H), 2.23 (ddd, *J* = 14.1, 7.9, 6.0 Hz, 1H), 2.04 (ddd, *J* = 14.3, 8.4, 6.1 Hz, 1H), 1.84 – 1.68 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ [ppm] = 166.4, 133.5, 130.1, 129.8, 128.6, 109.2, 109.0, 72.5, 67.5, 55.9, 55.8, 40.7, 40.4, 28.7, 25.9.

HRMS (ESI): m/z calcd for $C_{17}H_{22}O_6Na$ $[M+Na]^+$: 345.1308; found: 345.1316.

IR (ATR): $\tilde{\nu}$ = 3471, 2931, 2833, 1713, 1602, 1584, 1449, 1395, 1379, 1352, 1314, 1273, 1206, 1179, 1098, 1071, 1048, 1025, 994, 974, 942, 923, 897, 854, 806, 713 cm^{-1}.

HPLC: *ee* was determined by HPLC analysis (Chiralpak® IC, 30% *i*PrOH/hexane, 0.9 mL/min, 49 bar, 270.4 nm), retention time: t_{major} = 10.16 min, t_{minor} = 27.46 min, *ee* = 96%.

(1*S*,3*R*,3a*R*,5*R*,7a*S*)-1,3-Dimethoxy-6-oxooctahydroisobenzofuran-5-yl benzoate (S4)

An oven-dried 250 mL round-bottom-flask equipped with a Teflon-coated magnetic stirring bar was charged with alcohol **12** (9.05 g, 28.1 mmol, 1.0 equiv.) and dry DMSO (30 mL) under an atmosphere of argon. 2-Iodoxybenzoic acid (11.8 g, 42.1 mmol, 1.5 equiv.) was added at 23 °C and the reaction mixture was stirred for 18 h. H_2O (50 mL) was added dropwise and the resulting suspension was filtered through sand. The filtrate was extracted with EtOAc (3 x 50 mL) and the combined organic phases were washed with brine (2 x 50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (SiO_2, pentane/EtOAc 2:1) afforded ketone **S4** (8.55 g, 95%) as a colorless crystalline solid.

$[\alpha]_D^{27}$ = +15.3° (*c* = 1.90, $CHCl_3$).

m.p.: 75 °C.

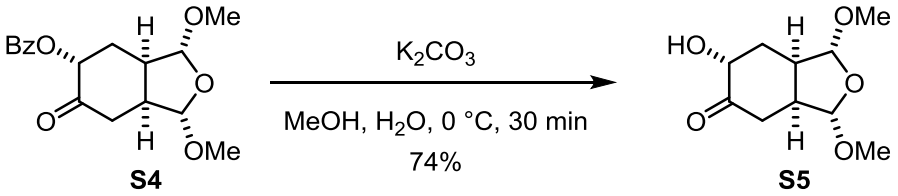
^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 8.09 – 8.04 (m, 2H), 7.60 – 7.55 (m, 1H), 7.45 (t, *J* = 7.9 Hz, 2H), 5.47 (dd, *J* = 11.4, 5.9 Hz, 1H), 5.22 (d, *J* = 4.9 Hz, 1H), 4.75 (s, 1H), 3.51 (s, 3H), 3.41 (s, 3H), 2.84 (dt, *J* = 10.8, 5.9 Hz, 1H), 2.72 (dd, *J* = 27.6, 10.0 Hz, 2H), 2.52 – 2.43 (m, 2H), 2.33 (ddd, *J* = 13.8, 11.2, 5.8 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ [ppm] = 203.5, 165.6, 133.5, 130.0, 129.4, 128.6, 109.3, 109.0, 73.7, 56.5, 55.4, 46.4, 41.5, 39.3, 30.7.

HRMS (ESI): m/z calcd for $C_{17}H_{20}O_6Na$ $[M+Na]^+$: 343,1152; found: 343.1161.

IR (ATR): $\tilde{\nu}$ = 2956, 2925, 2854, 1738, 1452, 1373, 1267, 1240, 1102, 1074, 1047, 1007, 962, 940, 916, 712 cm^{-1}.

(1*R*,3*S*,3a*S*,6*R*,7a*R*)-6-Hydroxy-1,3-dimethoxyhexahydroisobenzofuran-5(3*H*)-one (S5)



A 250 mL round-bottom-flask equipped with a Teflon-coated magnetic stirring bar was charged with ester **S4** (7.89 g, 24.6 mmol, 1.0 equiv.), MeOH (75 mL) and H_2O (10 mL). K_2CO_3 was added at 0 °C and the solution was stirred at 0 °C for 30 min. The reaction mixture was diluted with H_2O (50 mL) and extracted with CH_2Cl_2 (5 x 50 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (SiO_2, pentane/EtOAc 1:1) afforded α-hydroxy ketone **S5** (3.94 g, 74%) as a colorless crystalline solid.

m.p.: 86 °C.

$[\alpha]_D^{29}$= +11.3° (*c* = 0.59, $CHCl_3$).

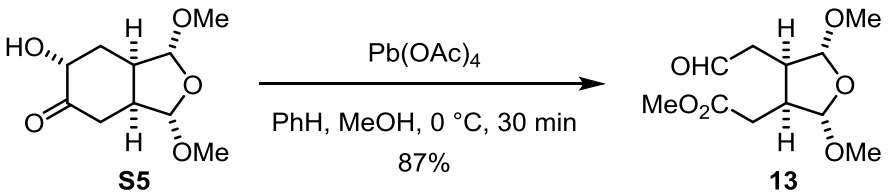
^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 5.20 (d, *J* = 5.5 Hz, 1H), 4.70 (s, 1H), 4.28 (dd, *J* = 11.7, 6.4 Hz, 1H), 3.52 (s, 3H), 3.40 (s, 3H), 2.76 – 2.70 (m, 1H), 2.70 – 2.62 (m, 2H), 2.56 (ddd, *J* = 14.2, 6.9, 2.3 Hz, 1H), 2.42 – 2.32 (m, 1H), 1.85 (ddd, *J* = 14.1, 12.2, 6.0 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ [ppm] = 210.2, 109.4, 109.2, 71.6, 56.7, 55.2, 46.9, 41.7, 38.7, 33.8.

HRMS (ESI): m/z calcd for $C_{10}H_{16}HO_5$ $[M+H]^+$: 217.1073; found: 217.1064.

IR (ATR): $\tilde{\nu}$ = 3439, 2932, 2835, 1721, 1446, 1391, 1239, 1186, 1094, 1075, 1041, 995, 957, 937, 912, 797, 716 cm^{-1}.

Methyl 2-((2*S*,3*S*,4*R*,5*R*)-2,5-dimethoxy-4-(2-oxoethyl)tetrahydrofuran-3-yl)acetate (13)



An oven-dried 250 mL round-bottom-flask equipped with a Teflon-coated magnetic stirring bar was charged with α-hydroxy ketone **S5** (3.29 g, 15.2 mmol, 1.0 equiv.), benzene (75 mL) and MeOH (15 mL). $Pb(OAc)_4$ (6.75 g, 15.2 mmol, 1.0 equiv.) was added at 0 °C and the solution was stirred at 0 °C for 30 min. $Na_2S_2O_5$ (2.90 g) was added and after 10 min the reaction mixture was filtered through sand. The filtrate was concentrated under reduced pressure and purified by column chromatography (SiO_2, pentane/EtOAc 2:1) to afford methyl ester **13** (3.24 g, 87%) as a colorless oil.

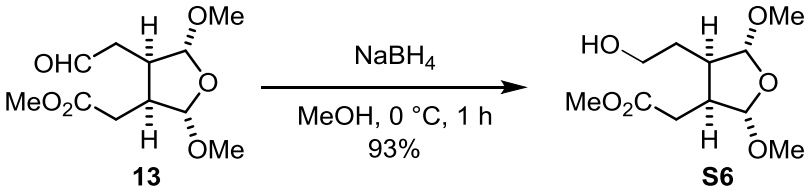
$[\alpha]_D^{23}$= −10.5° (*c* = 0.24, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 9.70 (t, *J* = 1.7 Hz, 1H), 4.75 (d, *J* = 3.1 Hz, 1H), 4.71 (d, *J* = 3.5 Hz, 1H), 3.64 (s, 3H), 3.37 (s, 6H), 2.91 (ddd, *J* = 15.4, 6.9, 3.5 Hz, 1H), 2.82 (ddd, *J* = 15.1, 7.8, 3.0 Hz, 1H), 2.50 (ddd, *J* = 17.0, 6.9, 1.5 Hz, 1H), 2.42 (ddd, *J* = 17.0, 8.5, 1.9 Hz, 1H), 2.29 (d, *J* = 7.8 Hz, 1H), 2.29 (d, *J* = 7.8 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ [ppm] = 200.3, 172.1, 109.2, 109.1, 55.7, 55.6, 52.0, 43.0, 41.2, 40.8, 31.9.

HRMS (ESI): m/z calcd for $C_{11}H_{18}O_6Na$ $[M+Na]^+$: 269.0995; found: 269.0988.
IR (ATR): $\tilde{\nu}$ = 2990, 2953, 2838, 2359, 2322, 1732, 1685, 1541, 1523, 1508, 1472, 1456, 1438, 1418, 1388, 1362, 1339, 1260, 1198, 1171, 1100, 1050, 994, 941, 798 cm^{-1}.

Methyl 2-((2*S*,3*S*,4*R*,5*R*)-4-(2-hydroxyethyl)-2,5-dimethoxytetrahydrofuran-3-yl)acetate (S6)



An oven-dried 250 mL round-bottom-flask equipped with a Teflon-coated magnetic stirring bar was charged with aldehyde **13** (3.93 g, 15.9 mmol, 1.0 equiv.) and MeOH (75 mL). Sodium borohydride (907 mg, 23.9 mmol, 1.5 equiv.) was added at 0 °C. After stirring at 0 °C for 1 h, the reaction mixture was treated with NH_4Cl (sat. aq., 50 mL). The aqueous phase was extracted with CH_2Cl_2 (5 x 50 mL) and the combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (SiO_2, pentane/EtOAc 1:1.5) afforded alcohol **S6** (3.67 g, 93%) as a colorless oil.

$[\alpha]_D^{23}$= −18.5° (*c* = 0.31, $CHCl_3$).

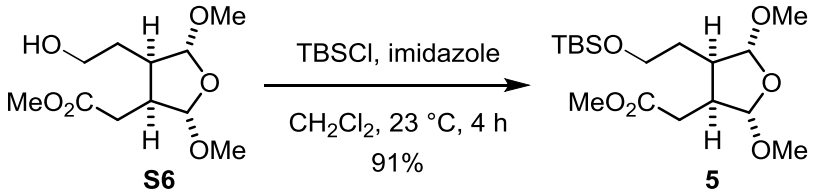
^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] = 4.84 (d, *J* = 5.4 Hz, 1H), 4.79 (s, 1H), 3.73 – 3.66 (m, 2H), 3.69 (s, 3H), 3.46 (s, 3H), 3.39 (s, 3H), 2.75 – 2.67 (m, 1H), 2.63 – 2.50 (m, 1H), 2.42 (dd, *J* = 16.0, 5.6 Hz, 1H), 2.23 (dd, *J* = 16.0, 10.0 Hz, 1H), 2.10 (t, *J* = 6.2 Hz, 1H), 1.74 – 1.65 (m, 1H), 1.62 – 1.52 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ [ppm] = 172.7, 110.2, 108.7, 61.9, 56.1, 55.1, 52.0, 44.7, 43.4, 31.9, 29.8.

HRMS (ESI): m/z calcd for $C_{11}H_{20}O_6Na$ $[M+Na]^+$: 271.1152; found: 271.1140.

IR (ATR): $\tilde{\nu}$ = 3449, 2952, 2915, 2844, 2363, 2322, 1734, 1541, 1508, 1438, 1396, 1261, 1171, 1099, 1052, 986, 942, 771 cm^{-1}.

Methyl-2-((2*S*,3*S*,4*R*,5*R*)-4-(2-((tert-butyldimethylsilyl)oxy)ethyl)-2,5-dimethoxytetrahydrofuran-3-yl)acetate (5)



An oven-dried 250 mL round-bottom-flask equipped with a Teflon-coated magnetic stirring bar was charged with alcohol **S6** (1.05 g, 4.23 mmol, 1.0 equiv.) and CH_2Cl_2 (20 mL). Tert-butylsilyl chloride (1.30 g, 8.46 mmol, 2.0 equiv.) and imidazole (431 mg, 6.34 mmol, 1.5 equiv.) were added and the reaction mixture was stirred for 4 h at 23 °C. The reaction was terminated by the addition of NH_4Cl (sat. aq., 50 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (SiO_2, pentane/Et_2O 4:1) afforded silyl ether **5** (1.40 g, 91%) as a colorless oil.

$[\alpha]_D^{23}$ = −5.90° (*c* = 0.80, $CHCl_3$).

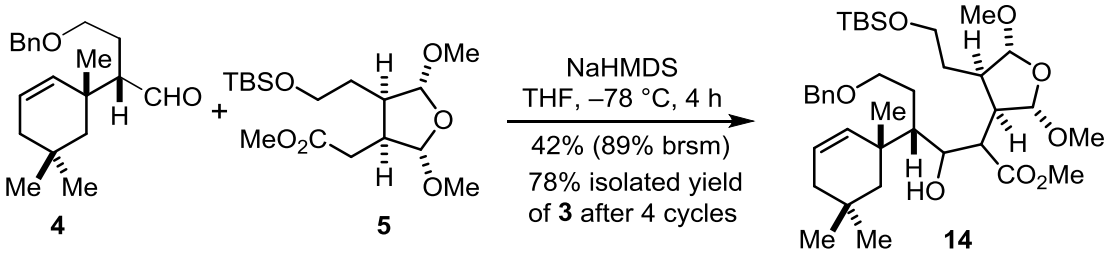
^{1}H NMR (700 MHz, $CDCl_3$): δ [ppm] = 4.77 (s, 1H), 4.77 (d, *J* = 6.6 Hz, 1H), 3.68 (s, 3H), 3.67 – 3.64 (m, 1H), 3.61 (dt, *J* = 10.3, 6.9 Hz, 1H), 3.41 (s, 3H), 3.39 (s, 3H), 2.73 (tdd, *J* = 9.7, 5.9, 2.2 Hz, 1H), 2.48 (dd, *J* = 15.8, 5.9 Hz, 1H), 2.45 (dtd, *J* = 8.6, 6.8, 4.3 Hz, 1H), 2.24 (dd, *J* = 15.8, 10.0 Hz, 1H), 1.61 (dq, *J* = 13.9, 7.0 Hz, 1H), 1.56 – 1.50 (m, 1H), 0.88 (s, 9H), 0.04 (s, 6H).

^{13}C NMR (176 MHz, $CDCl_3$): δ [ppm] = 172.8, 110.2, 109.1, 62.3, 55.9, 55.3, 51.9, 43.8, 43.4, 32.0, 29.9, 26.1, 18.4, –5.3 (2C).

HRMS (ESI): m/z calcd for $C_{17}H_{34}O_6SiNa$ $[M+Na]^+$: 385.2017; found: 385.2021.

IR (ATR): $\tilde{\nu}$ = 2952, 2928, 2857, 1739, 1471, 1438, 1388, 1362, 1254, 1196, 1167, 1099, 1053, 993, 944, 834, 811, 776, 739, 713, 701, 681, 671, 661 cm^{-1}.

Methyl (4*S*)-6-(benzyloxy)-2-((2*S*,3*R*,4*R*,5*R*)-4-(2-((tert-butyldimethylsilyl)oxy)ethyl)-2,5-dimethoxytetrahydrofuran-3-yl)-3-hydroxy-4-((*R*)-1,5,5-trimethylcyclohex-2-en-1-yl)hexanoate (14)



An oven-dried 250 mL Schlenk flask equipped with a Teflon-coated magnetic stirring bar was charged with sodium bis(trimethylsilyl)amide (2 M in THF, 2.60 mL, 5.30 mmol, 1.0 equiv.) and dry THF (20 mL). A solution of methyl ester **5** (1.91 g, 5.26 mmol, 1.0 equiv.) in dry THF (15 mL) was added at –78 °C. After stirring at –78 °C for 1 h, a solution of aldehyde **4** (2.20 g, 7.28 mmol, 1.38 equiv.) in dry THF (15 mL) was added and the reaction mixture was stirred at –78 °C for 3 h. The reaction was terminated by the addition of NH_4Cl (sat. aq., 50 mL) and the aqueous phase was extracted with EtOAc (3 x 50 mL). The combined organic phases were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (SiO_2, pentane/Et_2O 5:1 → 2:1) afforded β-hydroxy ester **14** (1.46 g, 42%) as a colorless oil. The methyl ester **5** (900 mg, 2.48 mmol) and aldehyde **4** (1.40 g, 4.65 mmol) were reisolated and reused. After three repetitions using the same starting materials, a combined yield for β-hydroxy ester **14** of 78% (2.73 g) was isolated.

$[\alpha]_D^{23}$= +0.39° (*c* = 3.07, $CHCl_3$).

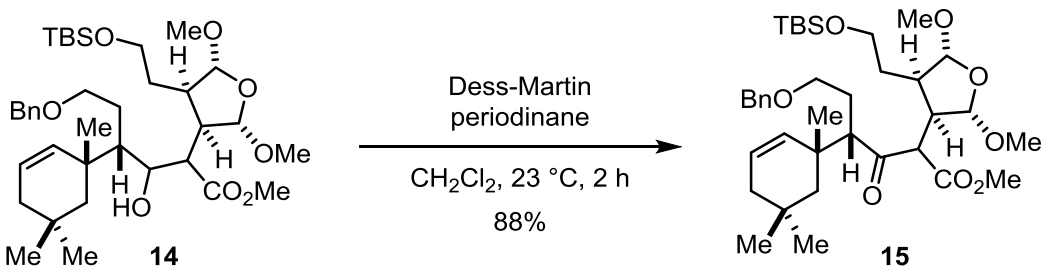
^{1}H NMR (700 MHz, $CDCl_3$): δ [ppm] = 7.34 – 7.30 (m, 5H), 5.63 (ddd, *J* = 10.2, 6.0, 2.2 Hz, 1H), 5.33 (d, *J* = 10.2 Hz, 1H), 4.90 (d, *J* = 6.5 Hz, 1H), 4.83 (s, 1H), 4.49 (d, *J* = 12.1 Hz, 1H), 4.45 (d, *J* = 12.1 Hz, 1H), 4.05 (dt, *J* = 6.7, 3.3 Hz, 1H), 3.59 (s, 3H), 3.59 – 3.55 (m, 2H), 3.48 (s, 3H), 3.46 – 3.43 (m, 1H), 3.36 (s, 3H), 3.36 – 3.34 (m, 1H), 3.07 (dt, *J* = 12.5, 6.5 Hz, 1H), 2.74 (d, *J* = 6.7 Hz, 1H), 2.59 (dd, *J* = 11.9, 3.8 Hz, 1H), 2.26 (ddd, *J* = 12.0, 6.7, 2.7 Hz, 1H), 1.85 – 1.79 (m, 1H), 1.79 – 1.76 (m, 1H), 1.71 – 1.67 (m, 1H), 1.58 (d, *J* = 14.0 Hz, 1H), 1.61 – 1.50 (m, 2H), 1.46 – 1.43 (m, 1H), 1.25 (ddt, *J* = 14.2, 12.0, 5.9 Hz, 1H), 1.19 (d, *J* = 14.0 Hz, 1H), 1.07 (s, 3H), 0.95 (s, 6H), 0.88 (s, 9H), 0.03 (s, 6H).

^{13}C NMR (176 MHz, $CDCl_3$): δ [ppm] = 173.0, 138.6, 134.4, 128.3, 127.6, 127.4, 125.2, 108.1, 107.7, 72.7, 71.5, 69.4, 61.7, 55.8, 54.7, 51.7, 51.0, 49.3, 45.3, 44.8, 44.6, 39.9, 38.4, 33.0, 30.0, 29.1, 28.4, 26.6, 25.9, 25.4, 18.3, -5.4, -5.5.

HRMS (ESI): m/z calcd for $C_{37}H_{62}O_8SiNa$ $[M+Na]^+$: 685.4106; found: 685.4102.

IR (ATR): $\tilde{\nu}$ = 3526, 2951, 2929, 2903, 2858, 1734, 1541, 1507, 1457, 1362, 1253, 1211, 1161, 1096, 1008, 984, 961, 835, 776, 735 cm^{-1}.

Methyl (4*S*)-6-(benzyloxy)-2-((2*S*,3*R*,4*R*,5*R*)-4-(2-((tert-butyldimethylsilyl)oxy)ethyl)-2,5-dimethoxy-tetrahydrofuran-3-yl)-3-oxo-4-((*R*)-1,5,5-trimethylcyclohex-2-en-1-yl)hexanoate (15)



An oven-dried 50 mL round-bottom-flask equipped with a Teflon-coated magnetic stirring bar was charged with alcohol **14** (744 mg, 1.12 mmol, 1.0 equiv.) and CH_2Cl_2 (7 mL). Dess-Martin periodinane (953 mg, 2.24 mmol, 2.0 equiv.) was added at 0 °C The reaction mixture was warmed to 23 °C and stirred for 2 h. Direct purification of the reaction mixture by column chromatography (SiO_2, pentane/Et_2O 6:1) afforded ketone **15** (655 mg, 88%) as a colorless oil.

$[\alpha]_D^{21}$= +64.7° (*c* = 3.66, $CHCl_3$).

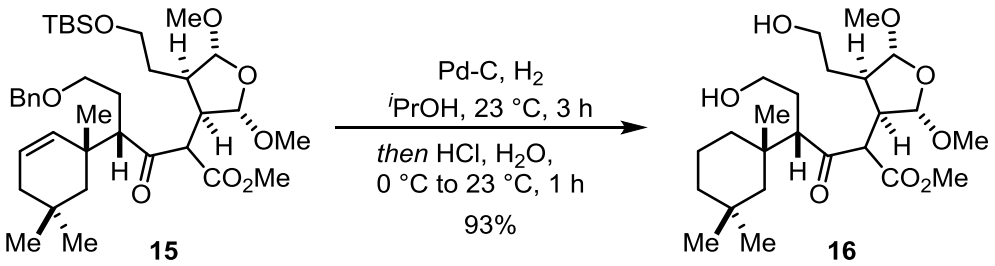
^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 7.37 – 7.20 (m, 5H), 5.69 (ddd, *J* = 10.1, 5.2, 3.1 Hz, 1H), 5.26 (d, *J* = 10.1 Hz, 1H), 4.79 (dd, *J* = 15.6, 3.5 Hz, 2H), 4.40 (d, *J* = 12.2 Hz, 1H), 4.37 (d, *J* = 12.2 Hz, 1H), 3.89 (d, *J* = 11.5 Hz, 1H), 3.62 – 3.51 (m, 2H), 3.53 (s, 3H), 3.39 (s, 3H), 3.37 (s, 3H), 3.35 – 3.24 (m, 1H), 3.19 (ddd, *J* = 9.5, 7.2, 5.7 Hz, 1H), 3.12 (dt, *J* = 9.6, 7.0 Hz, 1H), 2.92 (dd, *J* = 10.3, 2.0 Hz, 1H), 2.43 (ddt, *J* = 10.7, 7.0, 3.7 Hz, 1H), 2.11 – 1.97 (m, 1H), 1.80 (dt, *J* = 17.0, 2.7 Hz, 1H), 1.72 (dd, *J* = 16.9, 5.2 Hz, 1H), 1.65 (dtd, *J* = 14.4, 7.2, 2.0 Hz, 1H), 1.59 (d, *J* = 14.2 Hz, 1H), 1.52 – 1.44 (m, 1H), 1.44 – 1.35 (m, 1H), 1.18 (d, *J* = 14.1 Hz, 1H), 1.08 (s, 3H), 1.00 (s, 3H), 0.94 (s, 3H), 0.87 (s, 9H), 0.02 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$): δ [ppm] = 205.0, 168.2, 138.5, 133.7, 128.4 (2C), 127.7 (2C), 127.6, 126.0, 108.9, 107.7, 72.5, 68.6, 61.9, 61.4, 56.9, 55.4, 54.7, 52.6, 45.3, 45.2, 43.3, 40.1, 38.4, 31.8, 30.1, 29.8, 29.2, 27.5, 26.0 (3C), 25.8, 18.4, –5.3 (2C).

HRMS (ESI): m/z calcd for $C_{37}H_{60}O_8SiNa$ $[M+Na]^+$: 683.3949; found: 683.3969.

IR (ATR): $\tilde{\nu}$ = 2951, 2931, 2859, 1745, 1714, 1455, 1362, 1254, 1194, 1101, 1011, 945, 907, 835, 778, 737, 712, 702, 690, 681, 671, 659 cm^{-1}.

Methyl (4*S*)-6-hydroxy-2-((2*S*,3*R*,4*R*,5*R*)-4-(2-hydroxyethyl)-2,5-dimethoxytetrahydrofuran-3-yl)-3-oxo-4-((*S*)-1,3,3-trimethylcyclohexyl)hexanoate (16)



A 50 mL round-bottom-flask equipped with a Teflon-coated magnetic stirring bar was charged with compound **15** (655 mg, 990 µmol, 1.0 equiv.), Pd/C (5%, 211 mg, 100 µmol, 0.1 equiv.) and ^{i}PrOH (5 mL). The atmosphere was exchange to H_2 by three times evacuating and flushing with H_2 (1 atm). After stirring at 23 °C for 3 h, HCl (1 M aq., 2.50 mL, 2.50 mmol, 2.5 equiv.) was added at 0 °C. The reaction mixture was stirred at 23 °C for 1 h and filtered through Celite®. The filtrate was treated with $NaHCO_3$ (sat. aq., 10 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (SiO_2, pentane/EtOAc 1:4) afforded diol **16** (422 mg, 93%) as a colorless oil.

$[\alpha]_D^{24}$= +89.5° (*c* = 1.86, $CHCl_3$).

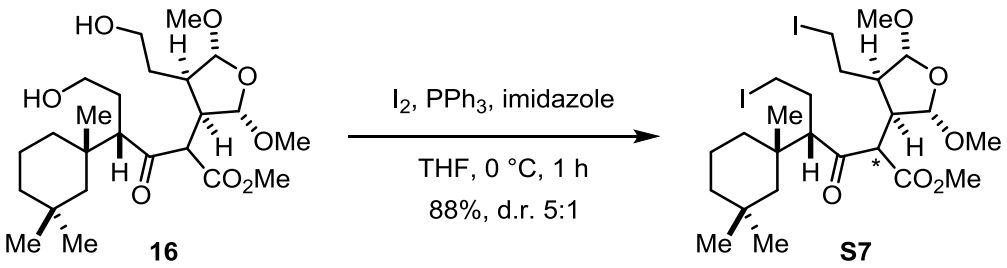
^{1}H NMR (700 MHz, $CDCl_3$): δ [ppm] = 4.82 (d, *J* = 5.3 Hz, 1H), 4.71 (d, *J* = 1.4 Hz, 1H), 3.78 (d, *J* = 11.5 Hz, 1H), 3.75 (s, 3H), 3.67 – 3.58 (m, 2H), 3.44 (s, 3H), 3.41 (dt, *J* = 10.9, 5.3 Hz, 1H), 3.37 (s, 3H), 3.20 (ddd, *J* = 11.5, 6.8, 1.4 Hz, 1H), 3.16 (ddd, *J* = 11.0, 8.8, 5.3 Hz, 1H), 2.96 (d, *J* = 9.9 Hz, 1H), 2.65 – 2.58 (m, 1H), 2.26 (s, 1H), 1.89 (ddt, *J* = 13.9, 11.3, 5.1 Hz, 1H), 1.74 – 1.62 (m, 1H), 1.64 – 1.54 (m, 3H), 1.50 – 1.42 (m, 1H), 1.42 – 1.32 (m, 3H), 1.29 (d, *J* = 14.1 Hz, 1H), 1.27 – 1.24 (m, 1H), 1.21 – 1.14 (m, 1H), 1.18 (d, *J* = 13.6 Hz, 1H), 0.95 (s, 3H), 0.94 (s, 3H), 0.94 (s, 3H).

^{13}C NMR (176 MHz, $CDCl_3$): δ [ppm] = 206.1, 168.9, 109.4, 107.4, 62.2, 61.6, 60.8, 57.1, 55.9, 54.8, 53.0, 49.8, 46.7, 43.1, 39.1, 38.4, 37.6, 33.4, 31.1, 30.0, 29.3, 21.4, 19.1.

HRMS (ESI): m/z calcd for $C_{24}H_{42}O_8Na$ $[M+Na]^+$: 481.2772; found: 481.2794.

IR (ATR): $\tilde{\nu}$ = 3456, 2950, 2927, 1743, 1708, 1387, 1267, 1192, 1143, 1102, 1059, 1011, 944, 905, 842, 790, 763, 749, 727 cm^{-1}.

Methyl (4*S*)-6-iodo-2-((2*S*,3*R*,4*R*,5*R*)-4-(2-iodoethyl)-2,5-dimethoxytetrahydrofuran-3-yl)-3-oxo-4-((*S*)-1,3,3-trimethylcyclohexyl)hexanoate (S7)



An oven-dried 50 mL round-bottom-flask equipped with a Teflon-coated magnetic stirring bar was charged with diol **16** (420 mg, 920 µmol, 1.0 equiv.), triphenylphosphine (959 mg, 3.66 mmol, 4.0 equiv.), imidazole (374 mg, 5.49 mmol, 6.0 equiv.) and dry THF (4.5 mL) at 0 °C. After 10 min iodine (930 mg, 3.66 mmol, 4.0 equiv.) was added and the reaction mixture was stirred at 0 °C for 1 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, pentane/Et_2O 6:1) to afford diiodide **S7** (455 mg, 73%) and its C7-epimer (91 mg, 15%) as colorless oils, respectively.

Major epimer:

$[\alpha]_D^{23}$= +41.6° (*c* = 0.90, $CHCl_3$).

^{1}H NMR (700 MHz, $CDCl_3$): δ [ppm] = 4.72 (d, *J* = 4.4 Hz, 1H), 4.69 (d, *J* = 2.5 Hz, 1H), 3.84 (s, 3H), 3.77 (d, *J* = 11.3 Hz, 1H), 3.41 (s, 3H), 3.36 (s, 3H), 3.24 (ddd, *J* = 11.3, 6.7, 2.5 Hz, 1H), 3.16 (ddd, *J* = 9.4, 9.3, 5.8 Hz, 1H), 3.02 (td, *J* = 9.2, 7.4 Hz, 1H), 2.97 (td, *J* = 9.2, 4.6 Hz, 1H), 2.73 (dd, *J* = 10.7, 1.9 Hz, 1H), 2.58 (dt, *J* = 9.6, 8.2 Hz, 1H), 2.50 – 2.45 (m, 1H), 2.34 – 2.27 (m, 1H), 1.94 (dtd, *J* = 14.1, 8.5, 1.9 Hz, 1H), 1.90 – 1.85 (m, 2H), 1.60 – 1.54 (m, 2H), 1.40 – 1.34 (m, 2H), 1.30 (d, *J* = 13.7 Hz, 1H), 1.28 – 1.23 (m, 1H), 1.18 – 1.12 (m, 1H), 1.13 (d, *J* = 13.8 Hz, 1H), 0.96 (s, 3H), 0.94 (s, 3H), 0.94 (s, 3H).

^{13}C NMR (176 MHz, $CDCl_3$): δ [ppm] = 204.5, 168.3, 108.6, 107.6, 62.8, 62.2, 55.9, 55.0, 53.6, 49.8, 47.2, 45.8, 39.1, 38.9, 37.6, 34.3, 31.8, 31.5, 31.2, 28.7, 21.2, 19.1, 3.7, 2.7.

HRMS (ESI): m/z calcd for $C_{24}H_{40}I_2O_6Na$ $[M+Na]^+$: 701.0806; found: 701.0828.

IR (ATR): $\tilde{\nu}$ = 2949, 295, 2844, 1740, 1709, 1435, 1386, 1246, 1196, 1156, 1102, 1034, 1002, 956, 917, 756, 700, 660 cm^{-1}.

Minor epimer:

$[\alpha]_D^{24}$= –36.9° (*c* = 0.79, $CHCl_3$).

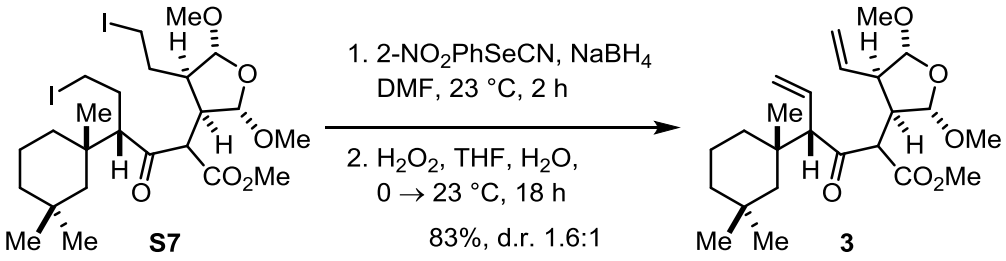
^{1}H NMR (700 MHz $CDCl_3$): δ [ppm] = 5.24 (d, *J* = 2.9 Hz, 1H), 4.71 (d, *J* = 3.7 Hz, 1H), 3.72 (s, 3H), 3.68 (d, *J* = 4.9 Hz, 1H), 3.40 (s, 3H), 3.40 – 3.33 (m, 3H), 3.29 (ddd, *J* = 9.9, 8.1, 4.9 Hz, 1H), 3.24 (ddd, *J* = 9.9, 9.1, 5.1 Hz, 1H), 3.10 (ddd, *J* = 9.9, 8.7, 7.2 Hz, 1H), 2.93 (ddd, *J* = 9.9, 8.7, 7.6 Hz, 1H), 2.79 (ddd, *J* = 7.8, 4.9, 2.8 Hz, 1H), 2.59 – 2.55 (m, 1H), 2.51 (dd, *J* = 8.7, 3.2 Hz, 1H), 2.15 – 2.05 (m, 2H), 2.04 – 1.98 (m, 1H), 1.97 – 1.90 (m, 1H), 1.58 – 1.52 (m, 1H), 1.48 (dt, *J* = 14.0, 3.9 Hz, 1H), 1.40 – 1.33 (m, 3H), 1.25 (td, *J* = 12.4, 4.0 Hz, 1H), 1.12 – 1.06 (m, 2H), 1.03 (s, 3H), 0.96 (s, 3H), 0.91 (s, 3H).

^{13}C NMR (176 MHz, $CDCl_3$): δ [ppm] = 206.7, 168.2, 108.9, 106.4, 64.9, 58.0, 55.6, 55.5, 52.6, 49.4, 47.5, 46.6, 39.0, 38.3, 36.2, 35.0, 31.8, 31.7, 31.0, 28.0, 21.4, 18.9, 5.5, 2.5.

HRMS (ESI): m/z calcd for $C_{24}H_{40}I_2O_6Na$ $[M+Na]^+$: 701.0806; found: 701.0788.

IR (ATR): $\tilde{\nu}$ = 2951, 2924, 2868, 1746, 1714, 1458, 1385, 1246, 1195, 1156, 1103, 1036, 991, 956 cm^{-1}.

Methyl (4*S*)-2-((2*S*,3*R*,4*R*,5*R*)-2,5-dimethoxy-4-vinyltetrahydrofuran-3-yl)-3-oxo-4-((*S*)-1,3,3-trimethylcyclohexyl)hex-5-enoate (3)



An oven-dried 50 mL round-bottom-flask equipped with a Teflon-coated magnetic stirring bar was charged with 2-nitrophenylselenocyanate (450 mg, 1.98 mmol, 3.0 equiv.) and dry DMF (6.0 mL). $NaBH_4$ (94.8 mg, 2.51 mmol, 3.8 equiv.) was added and the mixture was stirred for 1 h at 23 °C under an atmosphere of argon. This solution was added to diiodide **S7** (major epimer, 448 mg, 0.66 mmol, 1.0 equiv.) and the reaction mixture was stirred at 23 °C for 2 h. $NaHCO_3$ (sat. aq., 10 mL) was added at 0 °C and the aqueous phase was extracted with Et_2O (3 x 15 mL). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was dissolved in THF (6.0 mL) and H_2O_2 (30% aq., 0.54 mL, 5.30 mmol, 8.0 equiv.) was added at 0 °C. The reaction was stirred for 18 h at 23 °C and terminated by the addition of $NaHCO_3$ (sat. aq., 10 mL). The aqueous phase was extracted with Et_2O (3 x 10 mL) and the combined organic phases were washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (SiO_2, pentane/Et_2O 10:1) afforded diene **3** (233 mg, 83%, mixture of diastereomers 1.6:1 d.r.) as a colorless oil.

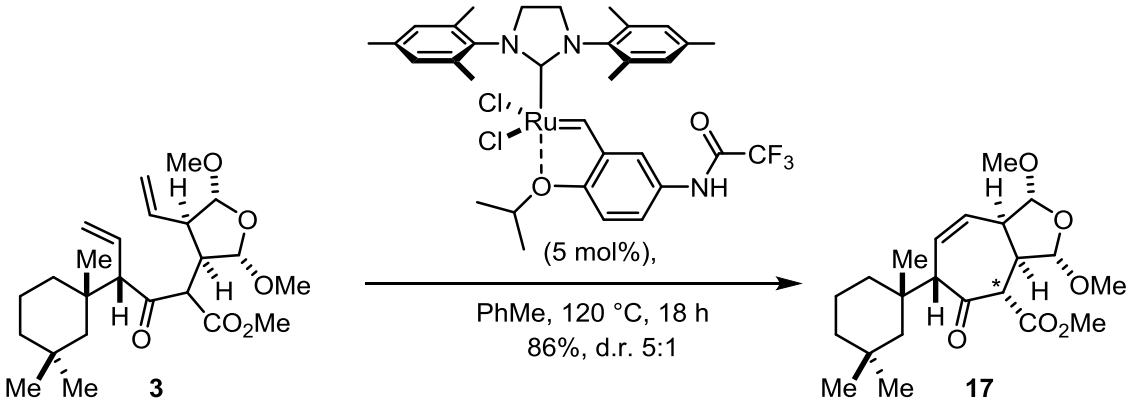
^{1}H NMR (700 MHz, $CDCl_3$): δ [ppm] major epimer = 5.75 (dt, *J* = 17.1, 10.0 Hz, 1H), 5.60 (dt, *J* = 17.0, 10.2 Hz, 1H), 5.15 (dd, *J* = 10.1, 1.7 Hz, 1H), 5.12 (dd, *J* = 10.4, 1.7 Hz, 1H), 5.09 (d, *J* = 16.8 Hz, 1H), 4.99 (dd, *J* = 17.1, 1.7 Hz, 1H), 4.83 (d, *J* = 4.1 Hz, 1H), 4.77 (d, *J* = 2.2 Hz, 1H), 3.62 (d, *J* = 11.5 Hz, 1H), 3.57 (s, 3H), 3.39 (s, 3H), 3.38 (s, 3H), 3.30 – 3.26 (m, 2H), 3.09 (tt, *J* = 7.2, 2.3 Hz, 1H), 1.56 – 1.52 (m, 1H), 1.51 – 1.47 (m, 1H), 1.36 – 1.33 (m, 1H), 1.36 – 1.27 (m, 3H), 1.28 (d, *J* = 14.0 Hz, 1H), 1.08 (s, 3H), 1.04 (d, *J* = 14.0 Hz, 1H), 0.94 (s, 3H), 0.89 (s, 3H); δ [ppm] minor epimer = 5.54 (dt, *J* = 16.9, 10.0 Hz, 1H), 5.43 (dt, *J* = 17.1, 10.2 Hz, 1H), 5.24 (dd, *J* = 10.0, 1.6 Hz, 1H), 5.19 (dd, *J* = 17.0, 1.5 Hz, 1H), 5.04 (dd, *J* = 10.3, 1.7 Hz, 1H), 5.00 (dd, *J* = 17.1, 1.6 Hz, 1H), 4.90 (d, *J* = 6.2 Hz, 1H), 4.68 (s, 1H), 3.68 (s, 3H), 3.59 (d, *J* = 11.1 Hz, 1H), 3.38 (s, 3H), 3.36 (s, 3H), 3.10 – 3.07 (m, 1H), 3.05 (dt, *J* = 11.0, 6.5 Hz, 1H), 2.93 (d, *J* = 10.1 Hz, 1H), 1.60 – 1.46 (m, 2H), 1.39 (dt, *J* = 13.9, 4.1 Hz, 1H), 1.37 – 1.21 (m, 3H), 1.09 (s, 3H), 1.07 – 1.00 (m, 2H), 0.93 (s, 3H), 0.86 (s, 3H).

^{13}C NMR (176 MHz, $CDCl_3$): δ [ppm] major epimer = 203.5, 168.0, 134.4, 133.4, 119.6 (2C), 108.5 (2C), 67.9, 61.5, 55.4, 55.2, 52.3, 52.2, 48.8, 45.7, 39.3, 38.9, 35.7, 34.8, 31.0, 28.3, 22.2, 19.0; δ [ppm] minor epimer = 201.6, 169.0, 133.7, 133.1, 121.9, 120.0, 108.4, 108.2, 68.9, 57.8, 56.3, 54.9, 52.4, 51.7, 48.7, 45.2, 39.4, 37.3, 35.1, 34.7, 30.9, 28.5, 22.8, 19.0.

HRMS (ESI): m/z calcd for $C_{24}H_{38}O_6Na$ $[M+Na]^+$: 445.2560; found: 445.2578.

IR (ATR): $\tilde{\nu}$ = 2950, 2925, 2871, 2851, 2360, 2338, 1747, 1716, 1627, 1509, 1457, 1436, 1386, 1348, 1261, 1237, 1196, 1165, 1038, 995, 952, 924, 741, 718, 698, 682, 670, 652 cm^{-1}.

methyl (1*R*,3*S*,3a*R*,6*S*,8a*R*)-1,3-dimethoxy-5-oxo-6-((*S*)-1,3,3-trimethylcyclohexyl)-3,3a,4,5,6,8a-hexahydro-1H-cyclohepta[*c*]furan-4-carboxylate (17)



An oven-dried 10 mL round-bottom-flask equipped with a Teflon-coated magnetic stirring bar was charged with diene **3** (215 mg, 510 µmol, 1.0 equiv.), Umicore M71SIMes (18.7 mg, 25.4 µmol, 0.05 equiv.) and dry PhMe (2.0 mL) under an atmosphere of argon. The reaction mixture was heated to 120 °C in a sealed flask for 18 h. The solvent was removed under reduced pressure and purification

by column chromatography (SiO_2, pentane/Et_2O 5:1) afforded olefin **17** (172 mg, 86%, mixture of diastereomers 5:1 *d.r.*) as a colorless oil.

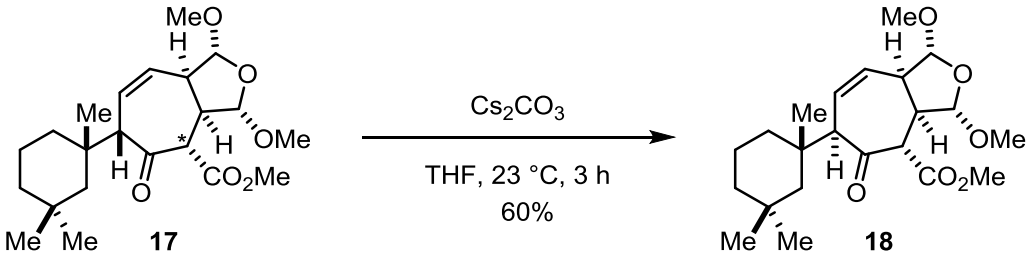
^{1}H NMR (700 MHz, $CDCl_3$): δ [ppm] major epimer = 5.94 (ddd, *J* = 11.4, 6.9, 2.6 Hz, 1H), 5.67 (ddd, *J* = 11.4, 4.8, 1.5 Hz, 1H), 4.91 – 4.87 (m, 1H), 4.88 (s, 1H), 3.84 (d, *J* = 10.5 Hz, 1H), 3.72 (s, 3H), 3.41 (s, 3H), 3.37 (s, 3H), 3.29 (ddd, *J* = 10.6, 7.7, 5.4 Hz, 1H), 3.06 – 3.02 (m, 2H), 1.84 – 1.79 (m, 1H), 1.56 – 1.53 (m, 1H), 1.46 – 1.40 (m, 2H), 1.34 – 1.28 (m, 1H), 1.31 (d, *J* = 13.5 Hz, 1H), 1.16 (d, *J* = 13.7 Hz, 1H), 1.13 – 1.09 (m, 1H), 1.10 (s, 3H), 0.95 (s, 3H), 0.90 (s, 3H); δ [ppm] minor epimer= 6.09 (ddd, *J* = 11.9, 9.0, 2.8 Hz, 1H), 5.98 (dd, *J* = 11.9, 3.0 Hz, 1H), 5.37 (s, 1H), 4.91 – 4.87 (m, 1H), 4.09 (d, *J* = 4.7 Hz, 1H), 3.72 (s, 3H), 3.44 (s, 3H), 3.39 (s, 3H), 3.18 (td, *J* = 9.5, 3.5 Hz, 1H), 3.12 – 3.06 (m, 2H), 1.77 (d, *J* = 14.1 Hz, 1H), 1.59 – 1.51 (m, 2H), 1.46 – 1.40 (m, 1H), 1.36 (d, *J* = 13.9 Hz, 1H), 1.34 – 1.28 (m, 2H), 1.08 (s, 3H), 1.04 – 1.03 (m, 1H), 0.96 (s, 3H), 0.89 (s, 3H).

^{13}C NMR (176 MHz, $CDCl_3$): δ [ppm] major epimer = 202.9, 168.6, 129.5, 128.7, 110.8, 109.4, 66.1, 57.5, 55.7, 54.9, 52.5, 48.4, 48.3, 45.5, 39.5, 38.9, 36.0, 33.9, 31.0, 29.2, 22.2, 19.1. δ [ppm] minor epimer = 206.2, 170.1, 168.6, 129.9, 129.7, 112.5, 108.5, 62.1, 57.3, 56.0, 55.9, 52.4, 50.4, 49.0, 45.6, 39.3, 38.6, 36.3, 33.0, 31.2, 23.5, 19.1.

HRMS (ESI): m/z calcd for $C_{22}H_{34}O_6Na$ $[M+Na]^+$: 417.2247; found: 417.2262.

IR (ATR): $\tilde{\nu}$ = 2948, 2923, 2865, 2844, 2359, 1757, 1715, 1438, 1382, 1250, 1193, 1167, 1102, 1035, 988, 958, 806, 759, 734, 697, 669, 655 cm^{-1}.

Methyl (1*R*,3*S*,3a*R*,4*S*,6*R*,8a*R*)-1,3-dimethoxy-5-oxo-6-((*S*)-1,3,3-trimethylcyclohexyl)-3,3a,4,5,6,8a-hexahydro-1H-cyclohepta[*c*]furan-4-carboxylate (18)



A 10 mL round-bottom-flask equipped with a Teflon-coated magnetic stirring bar was charged with ketone **17** (5:1 *d.r.*, 27.2 mg, 68.9 µmol, 1.0 equiv.), Cs_2CO_3 (46.0 mg, 141 µmol, 2.0 equiv.) and THF (0.5 mL). The mixture was stirred for 3 h at 23 °C and the reaction was terminated by the addition of NH_4Cl (sat. aq., 5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification

by column chromatography (SiO_2, pentane/Et_2O 6:1) afforded ketone **18** (16.3 mg, 60%, single diastereomer) as a colorless oil.

$[\alpha]_D^{25}$= +87.4° (*c* = 0.37, $CHCl_3$).

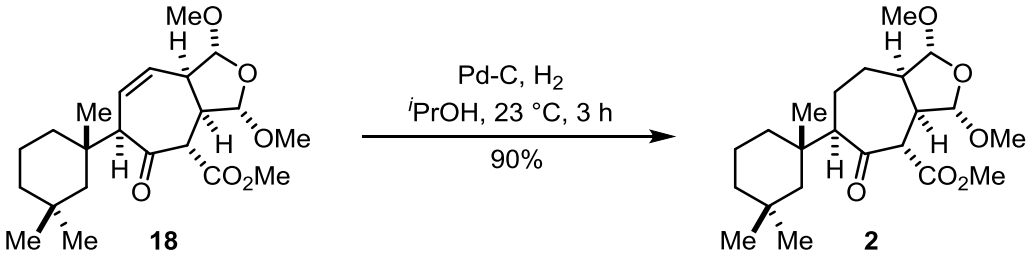
^{1}H NMR (700 MHz, $CDCl_3$): δ [ppm] = 5.74 (dt, *J* = 11.1, 3.1 Hz, 1H), 5.70 (dt, *J* = 11.1, 2.8 Hz, 1H), 4.87 (d, *J* = 3.3 Hz, 1H), 4.77 (d, *J* = 2.6 Hz, 1H), 3.75 (s, 3H), 3.71 (d, *J* = 11.1 Hz, 1H), 3.43 (s, 3H), 3.39 (s, 3H), 3.29 (dt, *J* = 4.4, 2.3 Hz, 1H), 3.26 – 3.19 (m, 2H), 1.54 – 1.50 (m, 2H), 1.46 (dt, *J* = 13.3, 4.3 Hz, 1H), 1.34 (d, *J* = 13.1 Hz, 1H), 1.31 – 1.23 (m, 2H), 1.17 – 1.06 (m, 2H), 1.15 (s, 3H), 0.96 (s, 3H), 0.89 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ [ppm] = 202.5, 169.2, 129.2, 126.3, 110.0, 109.3, 62.4, 58.0, 55.8, 55.3, 52.5, 48.4, 47.1, 46.9, 39.2, 36.4, 36.1, 34.3, 30.8, 28.5, 22.2, 18.6.

HRMS (ESI): m/z calcd for $C_{22}H_{34}O_6Na$ $[M+Na]^+$: 417.2247; found: 417.2255.

IR (ATR): $\tilde{\nu}$ = 2924, 2845, 1751, 1714, 1461, 1437,1384, 1248, 1195, 1104, 1058, 1024, 993, 957, 911, 859, 801, 716 cm^{-1}.

Methyl (1*R*,3*S*,3a*R*,4*S*,6*R*,8a*R*)-1,3-dimethoxy-5-oxo-6-((*S*)-1,3,3-trimethylcyclohexyl)octahydro-1H-cyclohepta[*c*]furan-4-carboxylate (2)



A 10 mL round-bottom-flask equipped with a Teflon-coated magnetic stirring bar was charged with olefin **18** (27.0 mg, 68.0 µmol, 1.0 equiv.), Pd/C (5% Pd, 14.5 mg, 6.80 µmol, 0.1 equiv.) and ^{i}PrOH (0.6 mL). The atmosphere was exchange to H_2 by three times evacuating and flushing with H_2 (1 atm). After stirring at 23 °C for 2 h under an atmosphere of H_2, the mixture was filtered through Celite®. The filtrate was concentrated under reduced pressure and purification by column chromatography (SiO_2, pentane/Et_2O 3:1) afforded ketone **2** (24.2 mg, 90%) as a colorless crystalline solid.

m.p.: 111 °C.

$[\alpha]_D^{25}$= +43.8° (*c* = 0.30, $CHCl_3$).

^{1}H NMR (700 MHz, $CDCl_3$): δ [ppm] = 4.91 (d, *J* = 5.7 Hz, 1H), 4.68 (s, 1H), 3.73 (s, 3H), 3.55 (d, *J* = 12.7 Hz, 1H), 3.47 (s, 3H), 3.37 (s, 3H), 2.85 (dd, *J* = 12.7, 7.7 Hz, 1H), 2.64 (ddd, *J* = 11.4, 5.7, 2.9 Hz, 1H), 2.43 (dd, *J* = 11.1, 5.7 Hz, 1H), 1.80 – 1.74 (m, 2H), 1.71 – 1.60 (m, 2H), 1.55 – 1.52 (m, 1H), 1.47 – 1.42

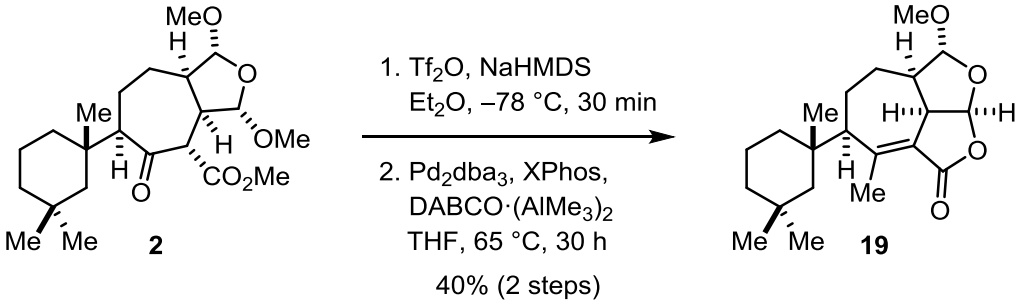
(m, 2H), 1.36 (d, *J* = 13.0 Hz, 1H), 1.26 – 1.19 (m, 3H), 1.14 (s, 3H), 1.09 – 1.02 (m, 2H), 0.96 (s, 3H), 0.87 (s, 3H).

^{13}C NMR (176 MHz, $CDCl_3$): δ [ppm] = 207.5, 169.0, 110.5, 108.5, 64.8, 57.7, 56.6, 54.9, 52.3, 48.7, 48.4, 44.4, 39.2, 36.8, 36.3, 35.0, 30.7, 28.0, 24.4, 21.5, 19.9, 18.6.

HRMS (ESI): m/z calcd for $C_{22}H_{36}O_6Na$ $[M+Na]^+$: 419.2404; found: 419.2418.

IR (ATR): $\tilde{\nu}$ = 2950, 2925, 2868, 2845, 1751, 1713, 1458, 1385, 1293, 1248, 1229, 1202, 1167, 1104, 1029, 995, 954 cm^{-1}.

(2a*S*,2a^1*R*,4*R*,4a*R*,7*R*)-4-methoxy-8-methyl-7-((*S*)-1,3,3-trimethylcyclohexyl)-2a^1,4,4a,5,6,7-hexahydro-2,3-dioxacyclopenta[*cd*]azulen-1(2a*H*)-one (19)



An oven-dried 10 mL round-bottom-flask equipped with a Teflon-coated magnetic stirring bar was charged with ketone **2** (9.8 mg, 25 µmol, 1.0 equiv.) and dry Et_2O (0.7 mL). Sodium bis(trimethylsilyl)amide (2 M in THF, 0.02 mL, 40 µmol, 1.6 equiv.) was added at –78 °C and the solution was stirred at –78 °C for 1 h. After the addition of freshly distilled trifluoromethanesulfonic anhydride (13 µL, 74 µmol, 3.0 equiv.), the reaction was stirred at –78 °C for another 30 min and terminated by the addition of $NaHCO_3$ (sat. aq., 5 mL). The aqueous phase was extracted with Et_2O (3 x 5 mL). The combined organic phases were washed with $NaHCO_3$ (sat. aq., 5 mL) and brine (5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to a volume of 1 mL. Column chromatography (SiO_2, pentane/Et_2O 5:1) afforded the corresponding vinyl triflate, which was directly used for the next reaction step. The solvent was exchange to dry THF (0.5 mL) and tris(dibenzylideneacetone)dipalladium(0) (2.3 mg, 2.5 µmol, 0.1 equiv.), 2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (XPhos, 2.4 mg, 5.0 µmol, 0.2 equiv.) and bis(trimethylaluminum)-1,4-diazabicyclo[2.2.2]octane adduct (19 mg, 74 µmol, 3.0 equiv.) were added under an atmosphere of argon. The reaction was heated in a sealed flask at 65 °C for 30 h and terminated by the addition of HCl (1 M aq., 3 mL). The aqueous phase was extracted with Et_2O (5 x 3 mL) and the combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography

(SiO_2, pentane/Et_2O 8:1) afforded lactone **19** (3.8 mg, containing 10% methyl ester, 40%) as a colorless oil.

$[\alpha]_D^{22}$= –4.60° (*c* = 0.19, $CHCl_3$).

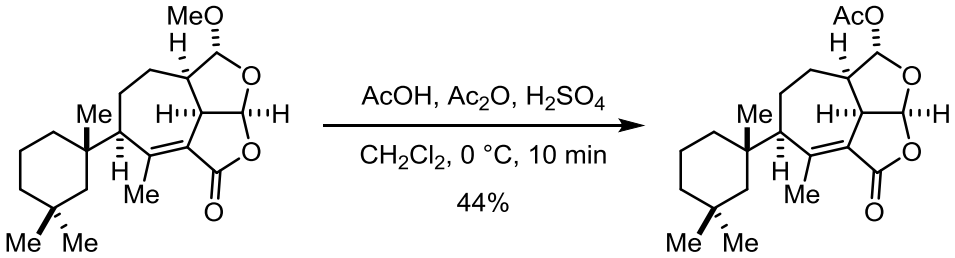
^{1}H NMR (700 MHz, $CDCl_3$): δ [ppm] = 5.95 (d, *J* = 6.5 Hz, 1H), 4.70 (d, *J* = 2.1 Hz, 1H), 3.84 (ddd, *J* = 9.5, 6.5, 2.1 Hz, 1H), 3.39 (s, 3H), 2.37 (d, *J* = 2.4 Hz, 3H), 2.13 – 2.07 (m, 2H), 1.83 – 1.77 (m, 1H), 1.61 – 1.56 (m, 2H), 1.53 – 1.46 (m, 2H), 1.42 – 1.33 (m, 4H), 1.31 – 1.27 (m, 1H), 1.17 – 1.13 (m, 1H), 1.12 (s, 3H), 1.11 – 1.04 (m, 3H), 0.97 (s, 3H), 0.85 (s, 3H).

^{13}C NMR (176 MHz, $CDCl_3$): δ [ppm] = 168.2, 158.7, 120.4, 111.3, 102.9, 57.1, 55.7, 50.5, 45.6, 43.0, 39.3, 38.6, 36.0, 33.9, 30.8, 28.6, 25.7, 22.2, 19.4, 18.7, 15.6.

HRMS (ESI): m/z calcd for $C_{21}H_{32}O_4Na$ $[M+Na]^+$: 371.2193; found: 371.2211.

IR (ATR): $\tilde{\nu}$ = 2924, 2863, 1758, 1636, 1459, 1386, 1243, 1212, 1106, 1043, 1006, 974, 949, 801, 789, 777, 713 cm^{-1}.

Darwinolide (1)



19 (+)-darwinolide (**1**)

A 10 mL round-bottom-flask equipped with a Teflon-coated magnetic stirring bar was charged with acetal **19** (1.7 mg, 4.9 µmol, 1.0 equiv.) and CH_2Cl_2 (0.2 mL). Acetic anhydride (3.4 µL, 33 µmol, 6.8 equiv.), acetic acid (1.9 µL, 33 µmol, 6.8 equiv.) and sulfuric acid (conc., 1.0 µL, 19 µmol, 3.8 equiv.) were added at 0 °C. The reaction was stirred at 0 °C for 10 min and terminated by the addition of $NaHCO_3$ (sat. aq., 2 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 3 mL) and the combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by preparative thin layer chromatography (SiO_2, pentane/Et_2O 1.5:1) afforded darwinolide **1** (0.8 mg, 44%) as a colorless solid.

$[\alpha]_D^{22}$= +20.7° (*c* = 0.07, $CHCl_3$).

^{1}H NMR (700 MHz, $CDCl_3$): δ [ppm] = 6.07 (d, *J* = 6.6 Hz, 1H), 5.94 (s, 1H), 3.93 (ddd, *J* = 9.5, 6.8, 2.4 Hz, 1H), 2.39 (d, *J* = 2.3 Hz, 3H), 2.26 – 2.22 (m, 1H), 2.11 – 2.08 (m, 1H), 2.08 (s, 3H), 1.92 (dd, *J* = 13.3,

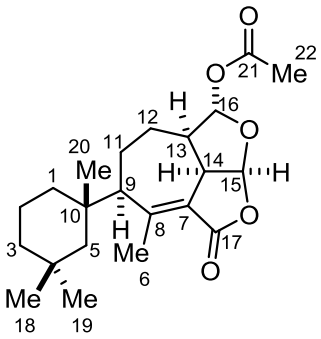
6.7 Hz, 1H), 1.66 – 1.58 (m, 2H), 1.54 – 1.46 (m, 2H), 1.44 – 1.35 (m, 2H), 1.39 (d, *J* = 13.9 Hz, 1H), 1.22 – 1.14 (m, 1H), 1.14(s, 3H), 1.09 (d, *J* = 13.9 Hz, 1H), 1.12 – 1.04 (m, 2H), 0.98 (s, 3H), 0.86 (s, 3H).

^{13}C NMR (176 MHz, $CDCl_3$): δ [ppm] = 169.7, 167.7, 159.4, 119.5, 104.0, 103.8, 57.3, 50.5, 45.1, 43.2, 39.2, 38.6, 36.0, 33.9, 30.8, 28.5, 25.6, 22.2, 21.2, 19.3, 18.7, 15.6.

HRMS (ESI): m/z calcd for $C_{22}H_{32}O_5Na$ $[M+Na]^+$: 399.2142; found: 399.2131.

IR (ATR): $\tilde{\nu}$ = 2923, 2852, 1758, 1636, 1457, 1239, 984, 953, 857, 798, 787, 772 cm^{-1}.

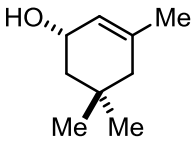
Comparison of NMR data:



No.	^{13}C NMR Isolation 125 MHz [ppm]	^{13}C NMR Synthetic 176 MHz [ppm]	Δ [ppm]
1	38.6	38.6	0
2	18.7	18.7	0
3	39.2	39.2	0
4	30.8	30.8	0
5	50.5	50.5	0
6	15.6	15.6	0
7	119.5	119.5	0
8	159.5	159.4	0.1
9	57.3	57.3	0
10	36.0	36.0	0
11	19.2	19.3	0.1
12	25.6	25.6	0
13	43.2	43.2	0
14	45.1	45.1	0
15	103.9	103.9	0
16	103.8	103.8	0
17	167.7	167.7	0
18	33.9	33.9	0
19	28.5	28.5	0
20	22.1	22.2	0.1
21	169.7	169.7	0
22	21.2	21.2	0

No.	^{1}H NMR Isolation (*J* in Hz) 500 MHz [ppm]	^{1}H NMR Synthetic (*J* in Hz) 700 MHz [ppm]	Δ [ppm]
1	1.08 m; 1.54 m	1.08 m, 1.54 m	0
2	1.50 m; 1.59 m	1.50 m; 1.59 m	0
3	1.11 m; 1.37 m	1.11 m; 1.37 m	0
5	1.08 d (14.1); 1,38 d (14.1)	1.09 d (13.9); 1.39 d (13.9)	0.1
6	2.39 d (2.3)	2.39 d (2.3)	0
9	2.08 m	2.09 m	0.1
11	1.42 m; 1.64 m	1.42 m, 1.64 m	0
12	1.92 m; 1.19 m	1.92 m, 1.19 m	0
13	2.24 m	2.24 m	0
14	3.93 tt (7.0, 2.4)	3.93 ddd (9.5, 6.8, 2.4)	0
15	6.07 d (7.0)	6.07 d (6.6)	0
16	5.93 s	5.94 s	0.1
18	0.86 s	0.86 s	0
19	0.98 s	0.98 s	0
20	1.14 s	1.14 s	0
22	2.08 s	2.08 s	0

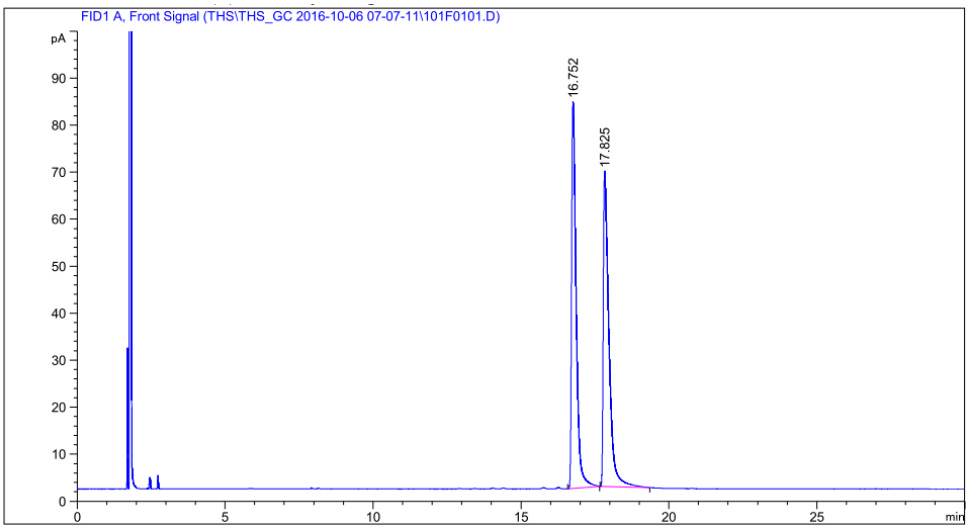
GC Data



8

Lipodex E: isotherm 85 °C, 2 µL/min, split ratio 50:1, FID 200 °C.

Racemic Mixture:



RetTime [min]	Type	Width [min]	Area [pA*s]	Area %
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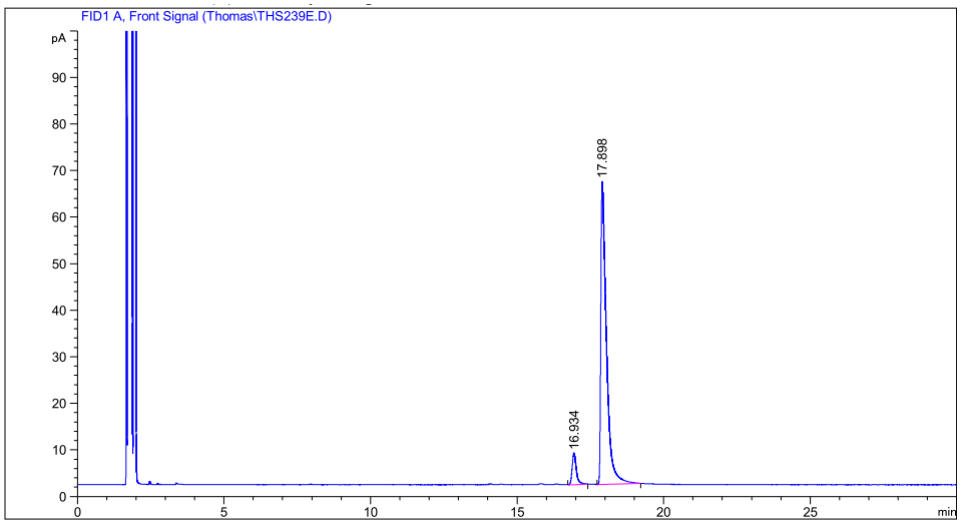
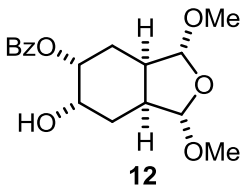
17.825	BB	0.1724	894.54449	50.25229

Enantioenriched:



RetTime [min]	Type	Width [min]	Area [pA*s]	Area %
16.934	BB	0.1370	66.61150	7.14637
17.898	BB	0.1760	865.49060	92.85363

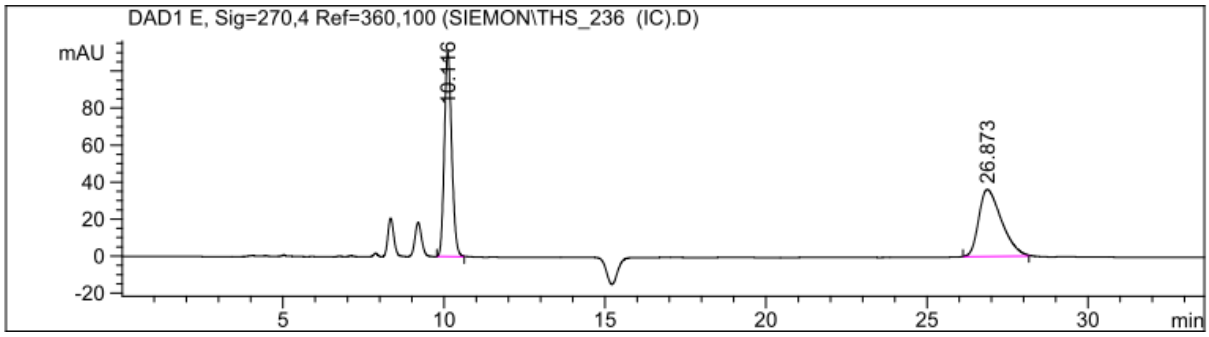
HPLC Data



12

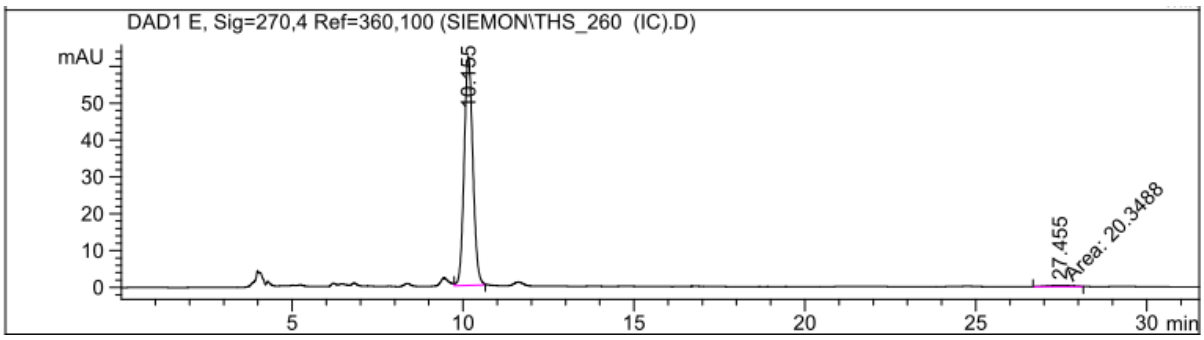
Chiralpak® IC; 20 °C; 30% ^{i}PrOH/hexane; 0.9 mL/min; 49 bar, 270.4 nm.

Racemic Mixture:



RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
10.116	BB	0.2459	1758.69519	110.35031	49.6877
26.873	BB	0.7553	1780.80298	36.23899	50.3123

Enantioenriched:

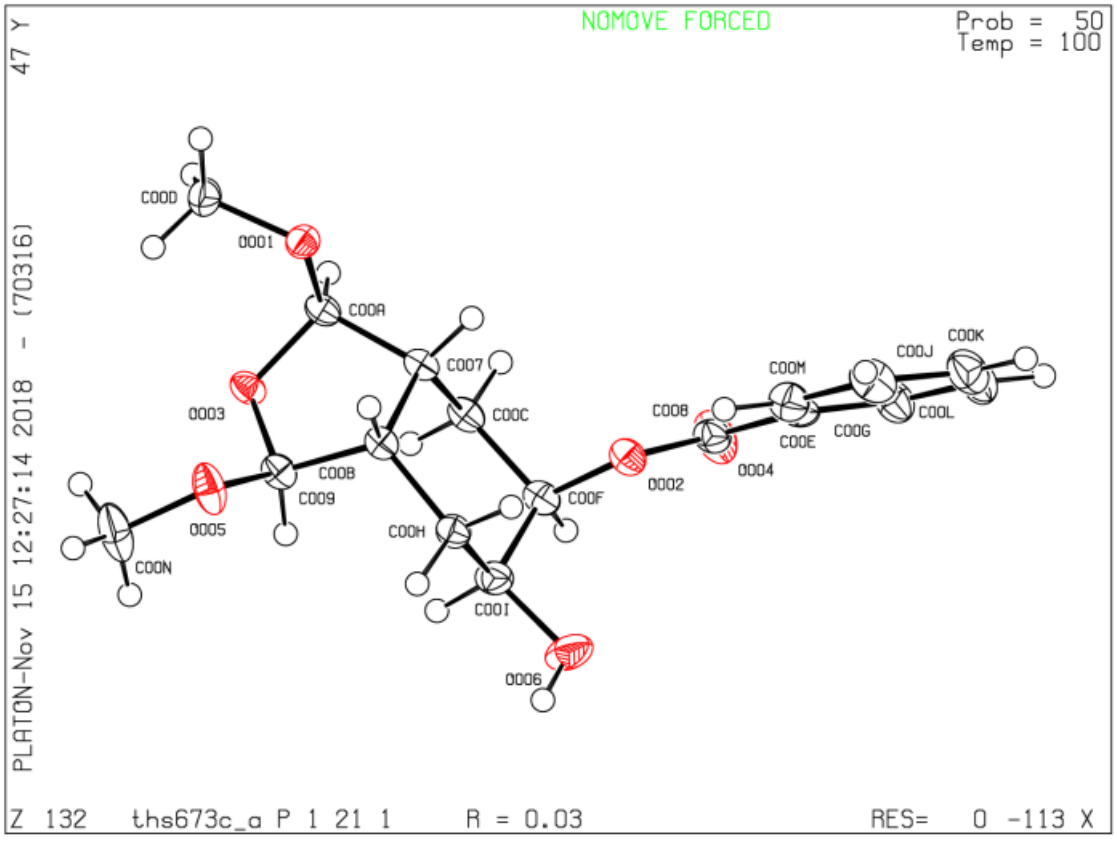


RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
10.155	VB	0.2746	1100.35095	62.12405	98.1843
27.455	MM	0.9373	20.34881	3.61848e-1	1.8157

Crystallographic Data

Crystal data for monobenzoate **12** (M = 322.36 g/mol):

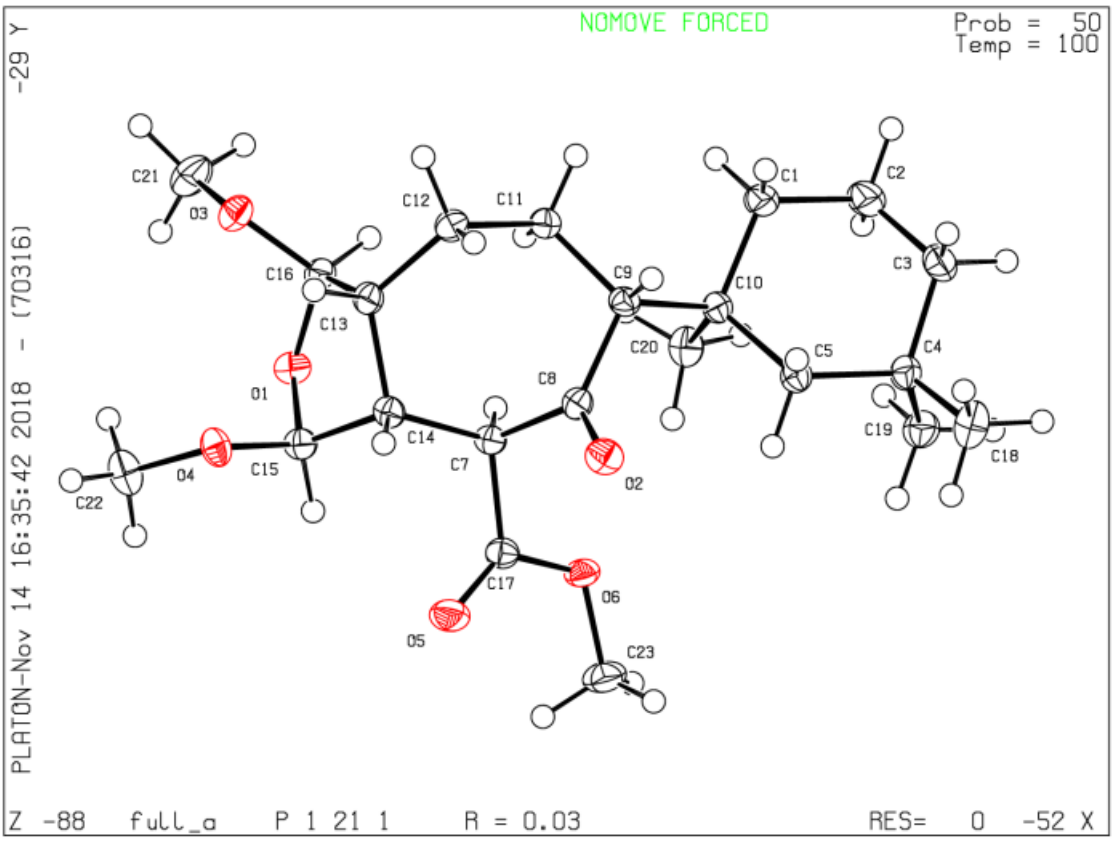
monoclinic; space group: P 1 21 1; a = 12.4774(6) Å, b = 5.4579(3) Å, c = 12.6279(6) Å, α = 90°, β = 111.525(2)°, γ = 90°, V = 799.99(7) Å^3, Z = 2, T = 100 K, μ(CuK$_\alpha$) = 1.54178 mm^{-1}, ρ_{calc} = 1.338 g/cm^3, 13823 reflections measured (3.808° ≤ 2Θ ≤ 68.407°), 2886 unique (R_{int} = 0.0740, R_{sigma} = 0.0371) which were used in all calculations. The final R_1 was 0.0328 ($I > 2\sigma(I)$) and wR_2 was 0.0758.



CCDC 1879212 contains the supplementary crystallographic data for this structure. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/structures.

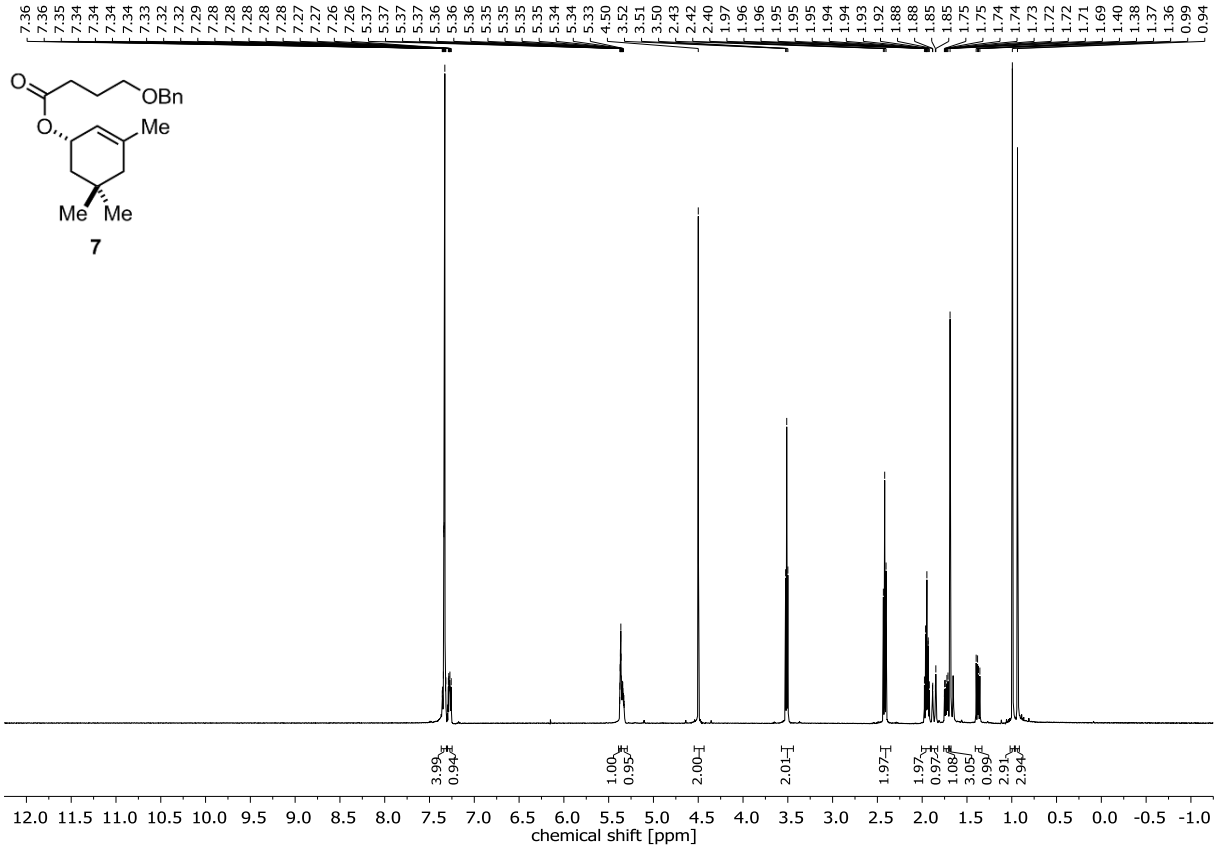
Crystal data for β-keto ester **2** (396.52 g/mol):

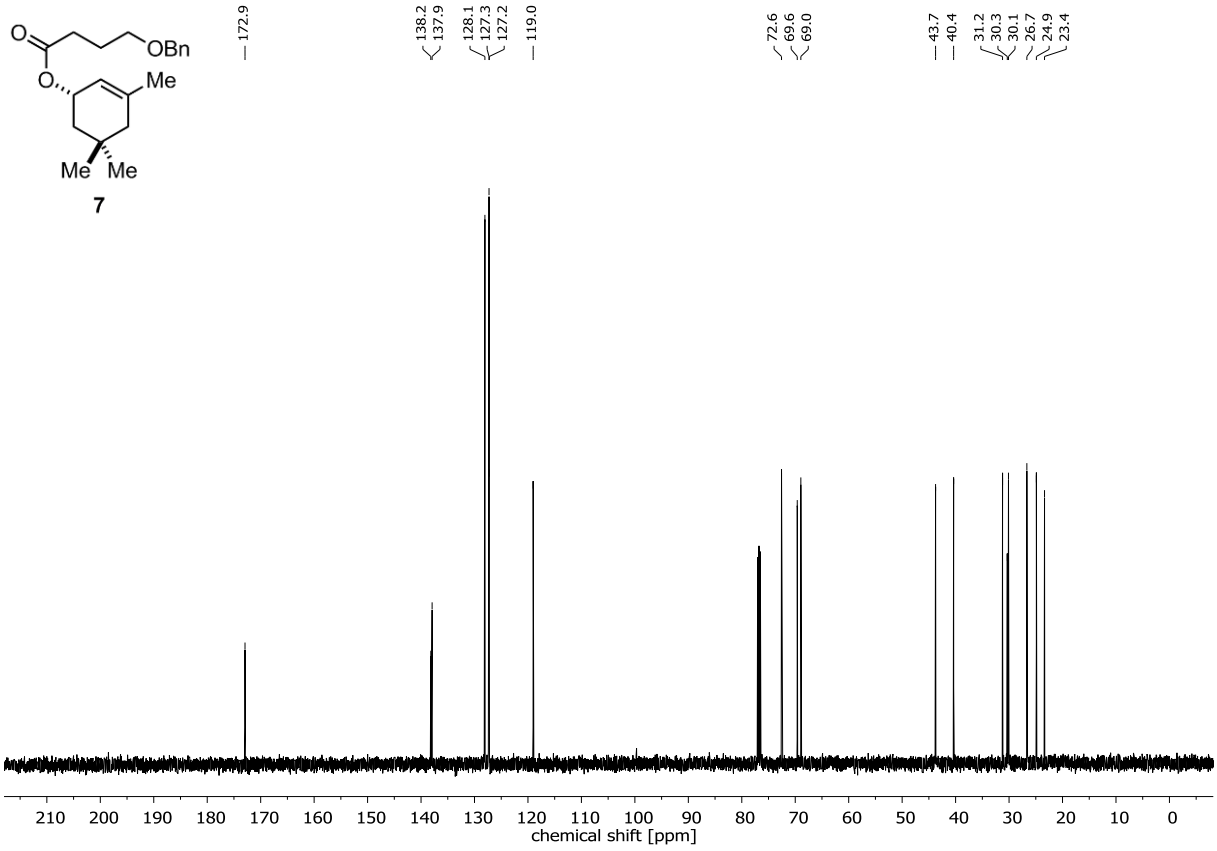
monoclinic, space group P 1 21 1, a = 7.4891(3) Å, b = 17.3135(7) Å, c = 8.4426(4) Å, α = 90°, β = 93.848(2)°, γ = 90°, V = 1092.22(8) Å^3, Z = 2, T = 100 K, μ(CuK$_\alpha$) = 1.54178 mm^{-1}, , ρ_{calc} = 1.206 g/cm^3, 18521 reflections measured (5.109° ≤ 2Θ ≤ 74.355°), 4407 unique (R_{int} = 0.0815, R_{sigma} = 0.0369) which were used in all calculations. The final R_1 was 0.0335 ($I > 2\sigma(I)$) and wR_2 was 0.0836.

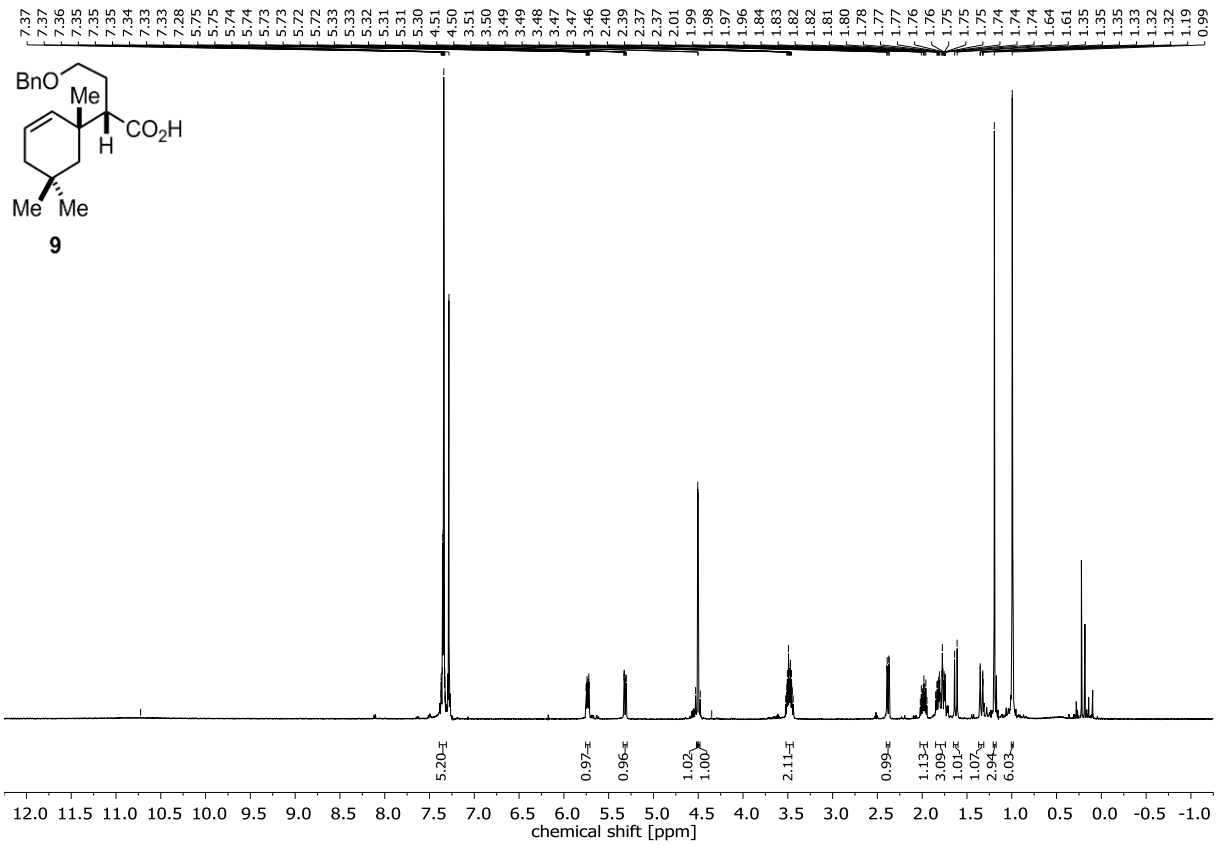


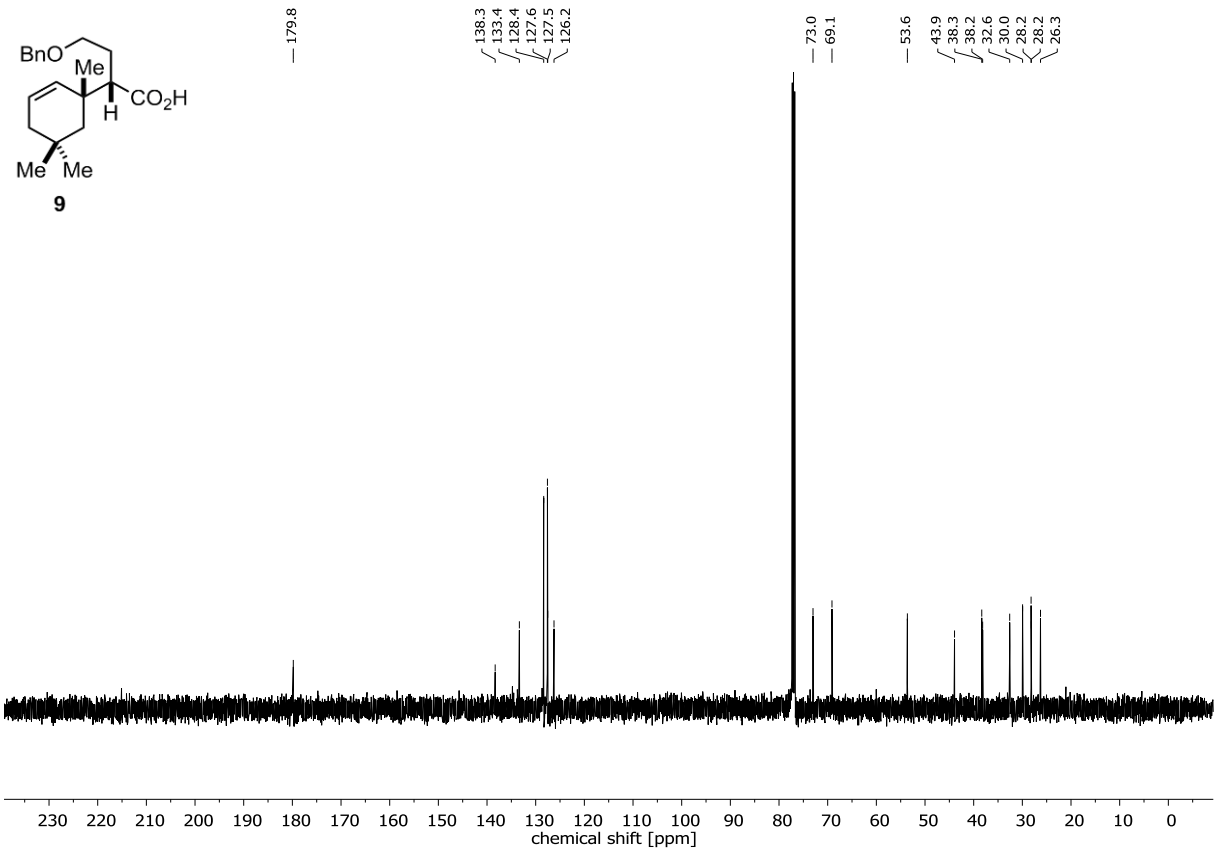
CCDC 1879213 contains the supplementary crystallographic data for this structure. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/structures.

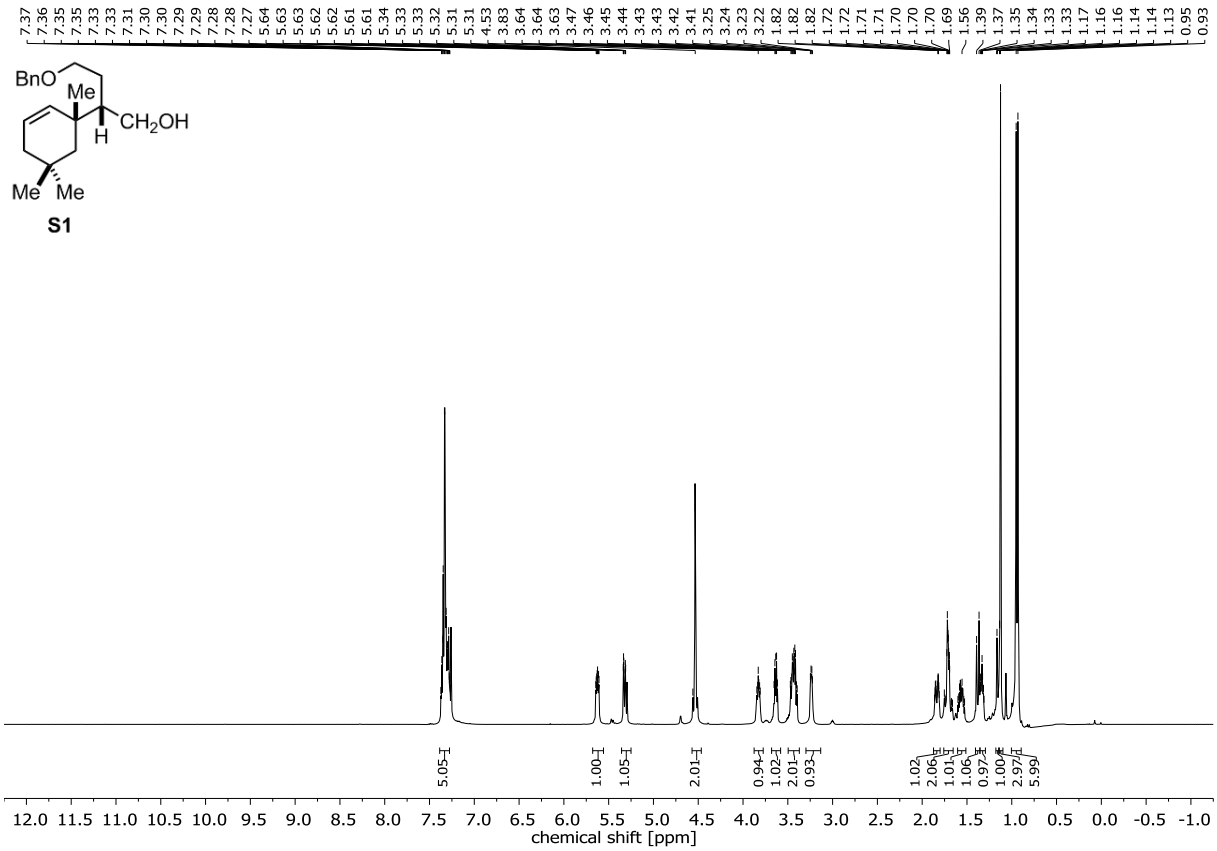
NMR Spectra

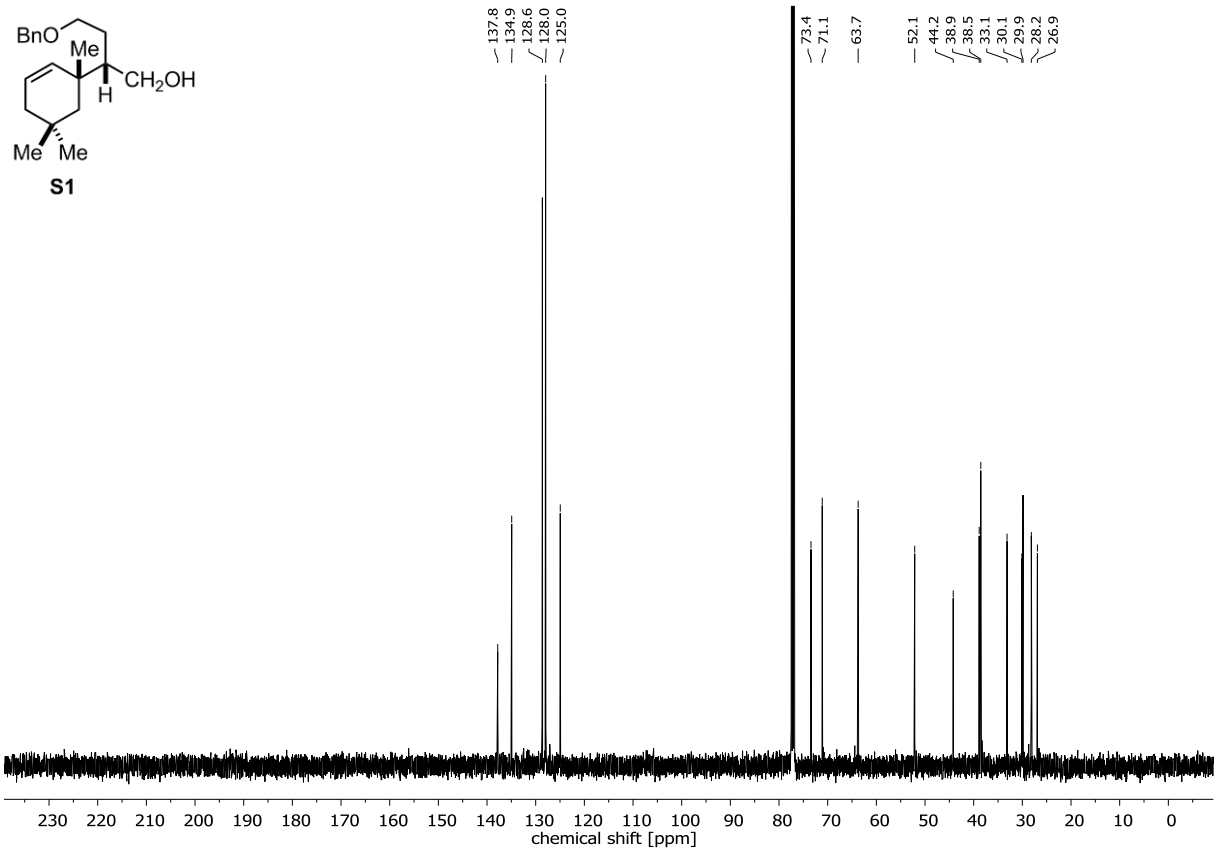

7.36 7.36 7.35 7.34 7.34 7.34 7.34 7.33 7.32 7.32 7.29 7.28 7.28 7.28 7.28 7.28 7.27 7.27 7.26 7.26 5.37 5.37 5.37 5.37 5.36 5.36 5.36 5.35 5.35 5.35 5.35 5.34 5.34 5.33 4.50 3.52 3.51 3.50 2.43 2.42 2.40 1.97 1.96 1.96 1.95 1.95 1.95 1.94 1.94 1.93 1.92 1.88 1.88 1.85 1.85 1.75 1.75 1.74 1.74 1.73 1.72 1.72 1.71 1.69 1.40 1.38 1.37 1.36 0.99 0.94
O
OBn
O
Me
Me Me
7
3.99
0.94
1.00
0.95
2.00
2.01
1.97
1.97
0.97
1.08
3.05
0.99
2.91
2.94
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
chemical shift [ppm]

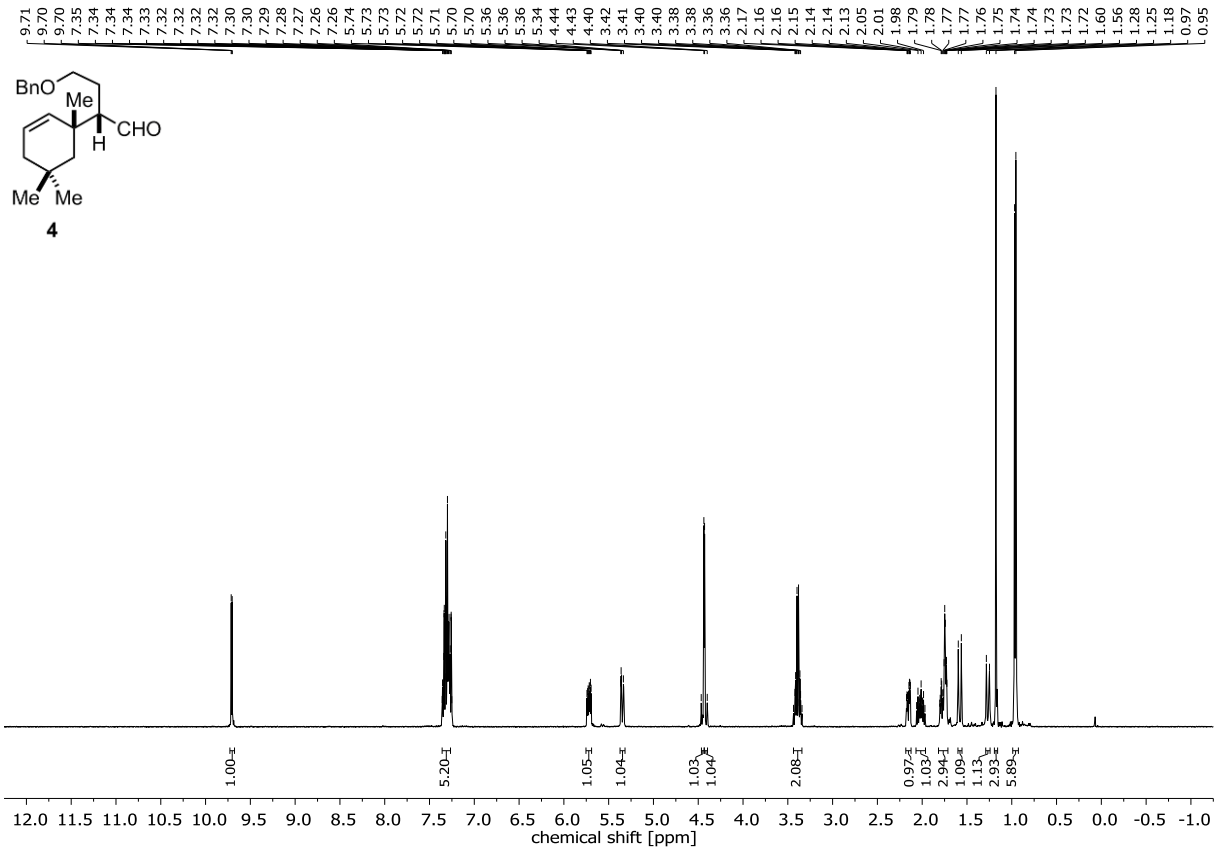

O
OBn
O
Me
Me Me
7
172.9
138.2
137.9
128.1
127.3
127.2
119.0
72.6
69.6
69.0
43.7
40.4
31.2
30.3
30.1
26.7
24.9
23.4
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
chemical shift [ppm]

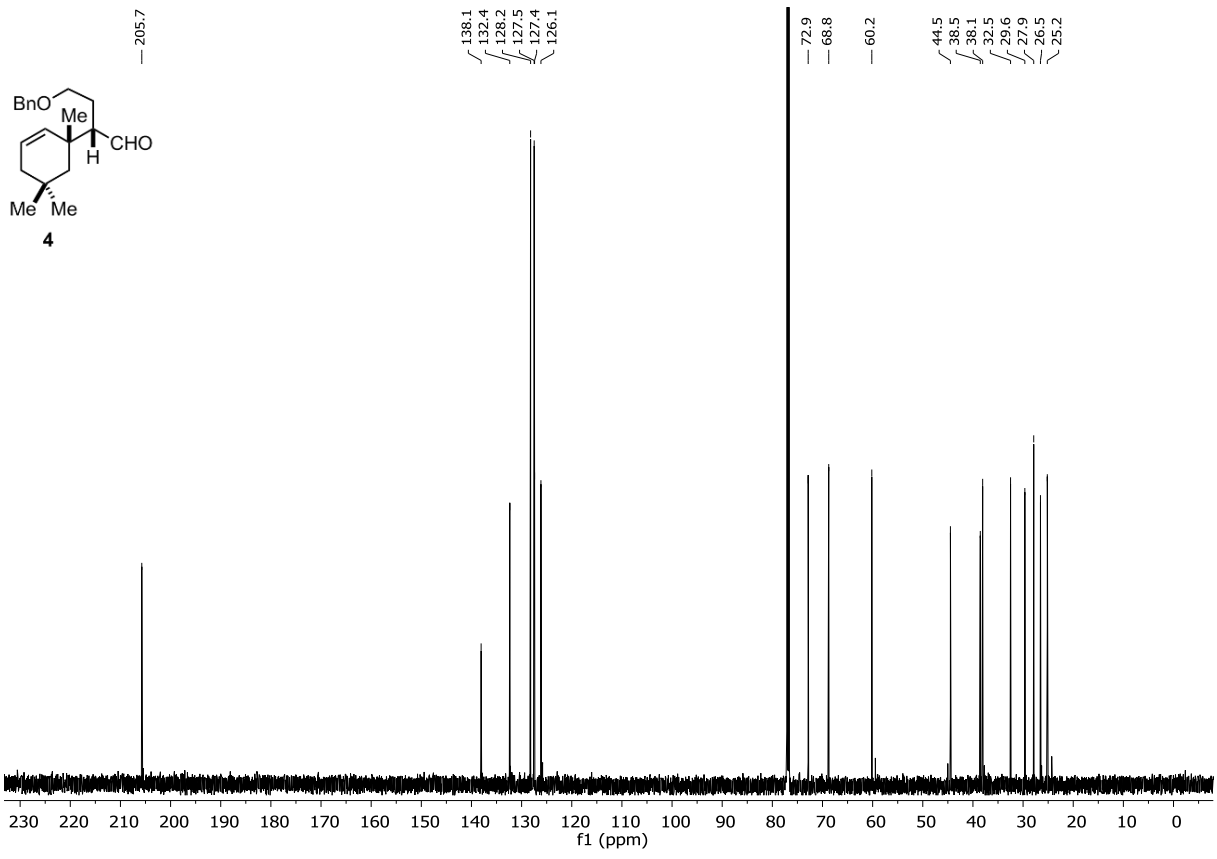

BnO
Me
CO2H
H
Me Me
9
chemical shift [ppm]

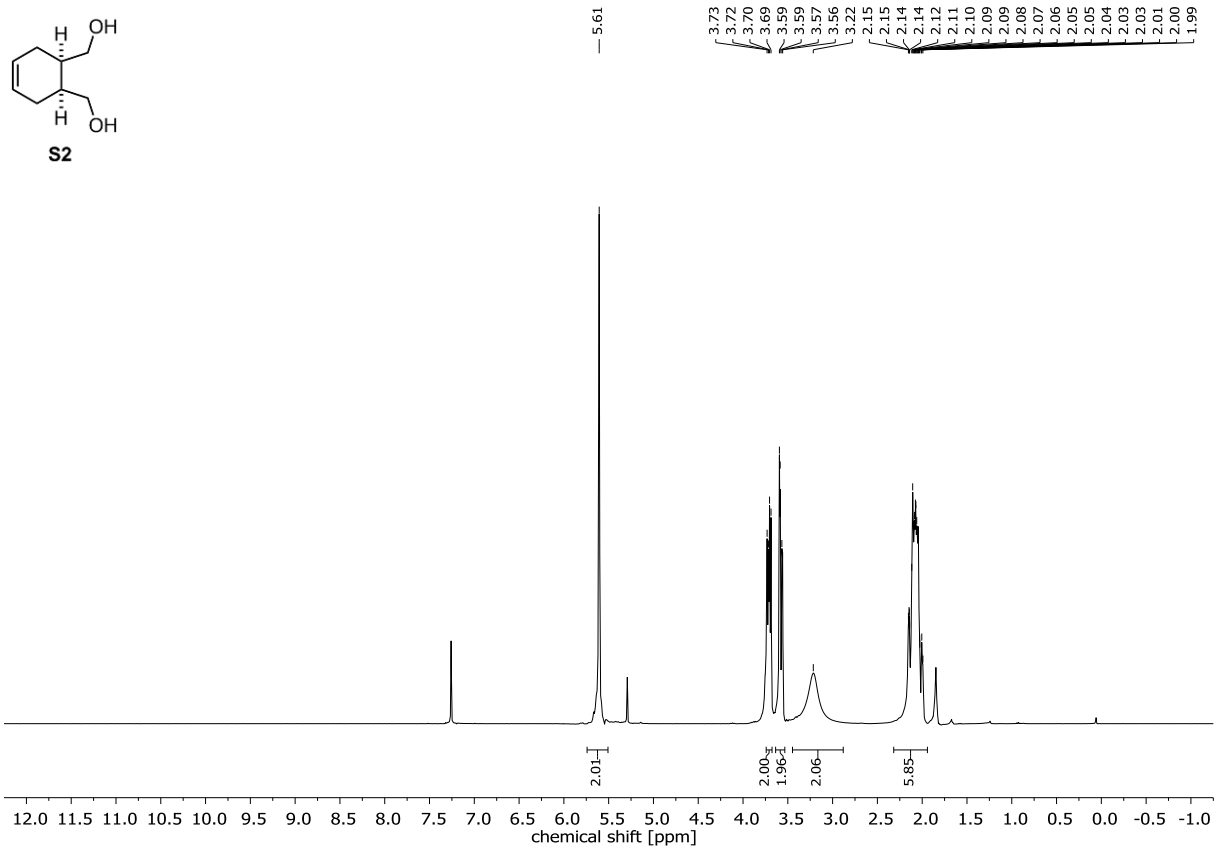

BnO
Me
CO2H
H
Me Me
9
chemical shift [ppm]

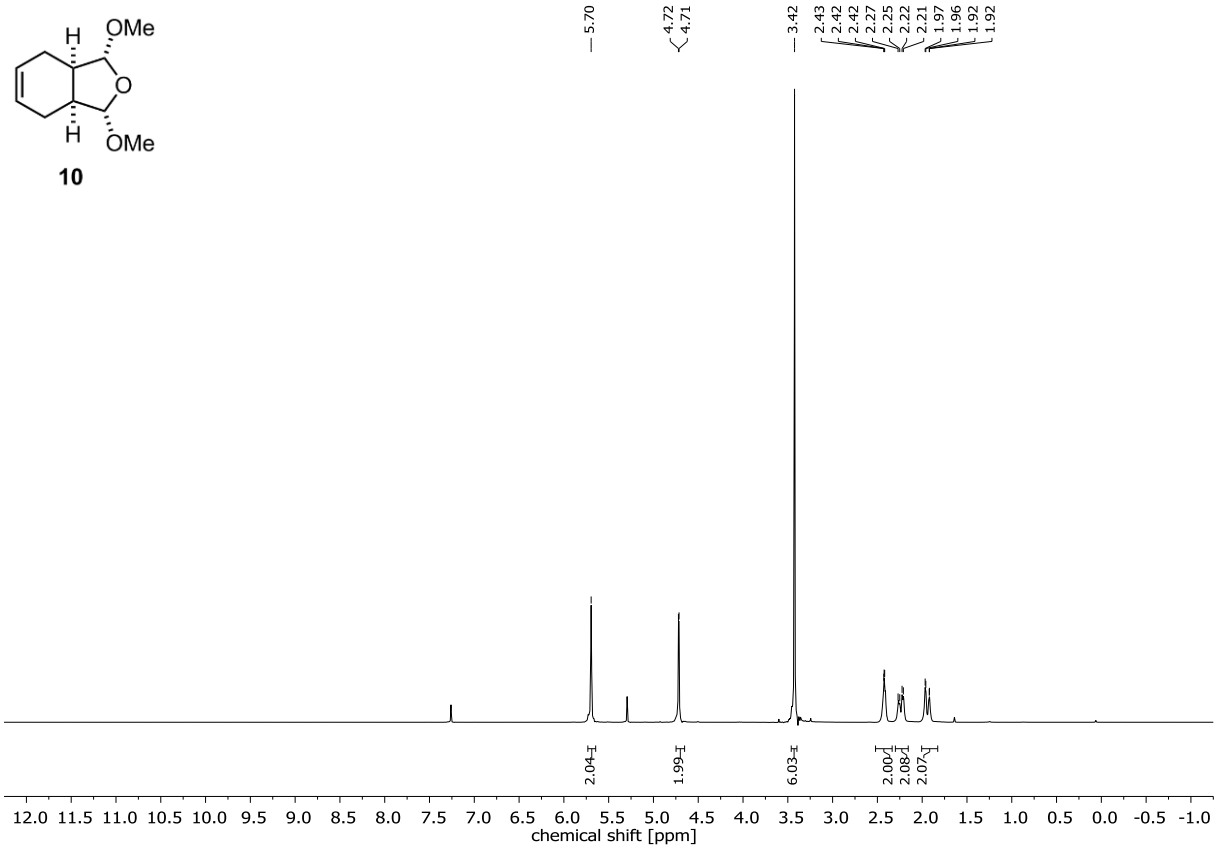

BnO
Me
CH2OH
H
Me Me
S1
chemical shift [ppm]

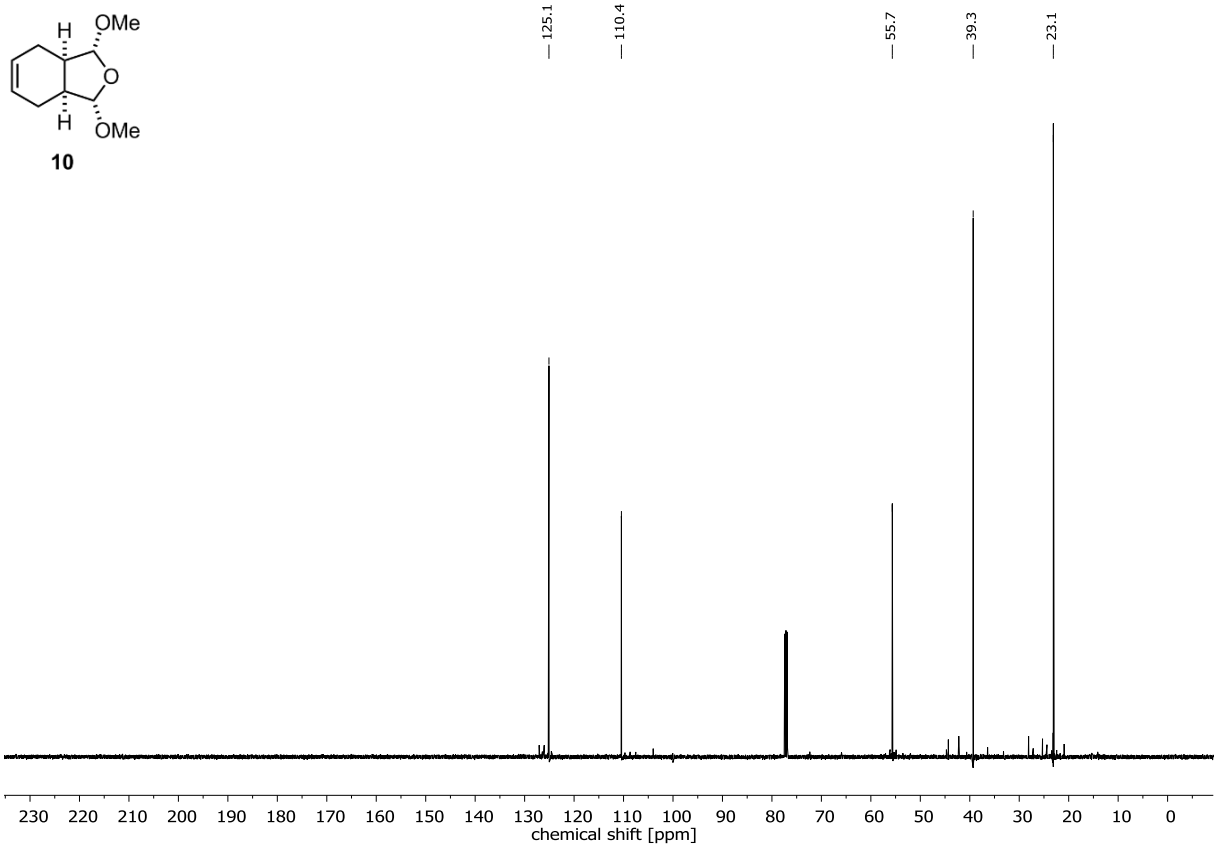

BnO
Me
CH2OH
H
Me Me
S1
chemical shift [ppm]

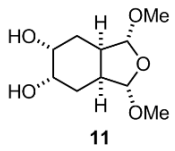

9.71 9.70 9.70 7.35 7.34 7.34 7.33 7.32 7.32 7.32 7.30 7.30 7.29 7.28 7.27 7.26 7.26 5.74 5.73 5.73 5.72 5.72 5.71 5.70 5.70 5.36 5.36 5.34 4.44 4.43 4.40 3.42 3.41 3.40 3.40 3.38 3.38 3.36 3.36 2.17 2.16 2.16 2.15 2.14 2.14 2.13 2.05 2.01 1.98 1.79 1.78 1.77 1.77 1.76 1.75 1.74 1.74 1.73 1.73 1.72 1.60 1.56 1.28 1.25 1.18 0.97 0.95
BnO
Me
CHO
H
Me Me
4
1.00 5.20 1.05 1.04 1.03 1.04 2.08 0.97 1.03 2.94 1.09 1.13 2.93 5.89
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
chemical shift [ppm]


205.7
138.1 132.4 128.2 127.5 127.4 126.1
72.9 68.8 60.2
44.5 38.5 38.1 32.5 29.6 27.9 26.5 25.2
BnO
Me
CHO
H
Me Me
4
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


OH
H
H
OH
S2
5.61
3.73
3.72
3.70
3.69
3.59
3.59
3.57
3.56
3.22
2.15
2.15
2.14
2.14
2.12
2.11
2.10
2.09
2.09
2.08
2.07
2.06
2.05
2.05
2.04
2.03
2.03
2.01
2.00
1.99
2.01
2.00
1.96
2.06
5.85
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
chemical shift [ppm]

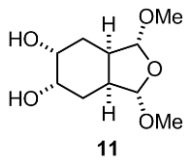

OMe
H
O
H
OMe
10
5.70
4.72
4.71
3.42
2.43
2.42
2.42
2.27
2.25
2.22
2.21
1.97
1.96
1.92
1.92
2.04
1.99
6.03
2.00
2.08
2.07
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
chemical shift [ppm]


OMe
H
O
H
OMe
10
125.1
110.4
55.7
39.3
23.1
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
chemical shift [ppm]


HO
H
OMe
O
HO
H
OMe

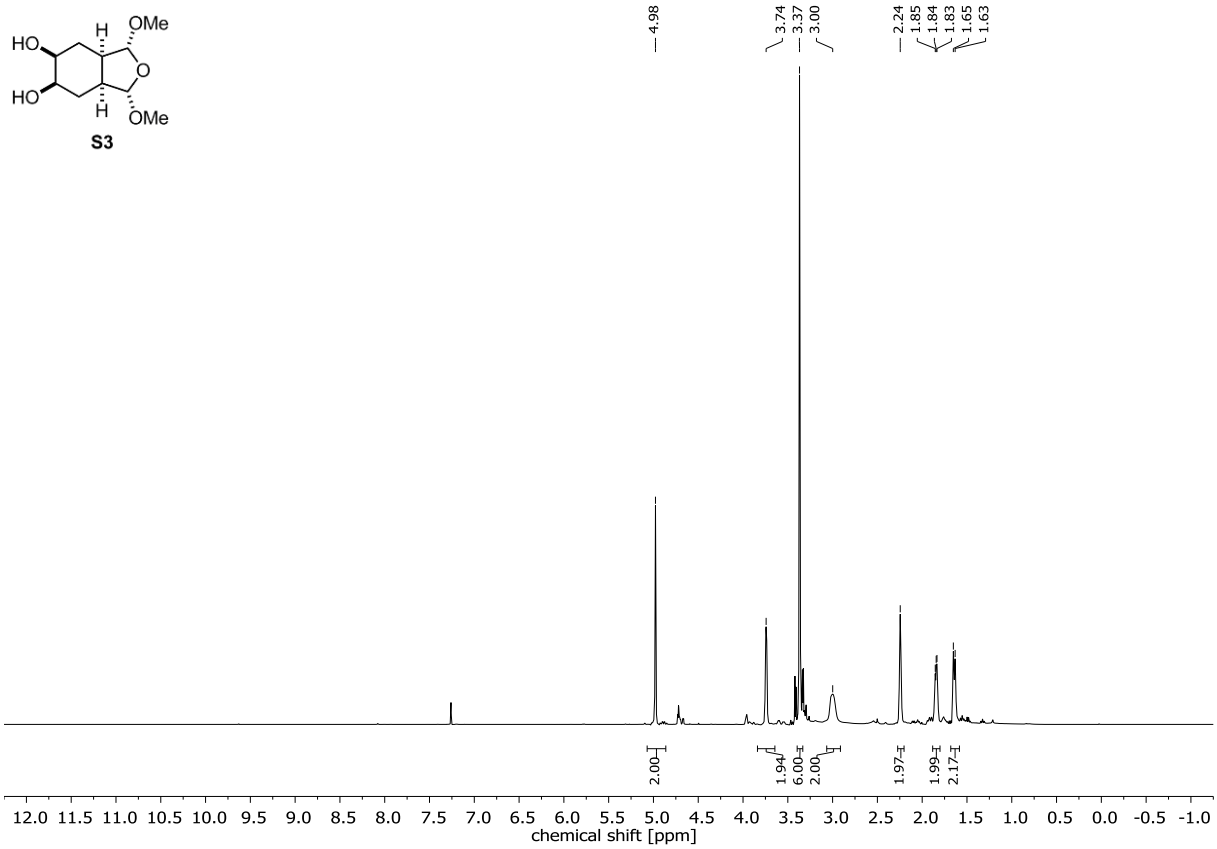
11

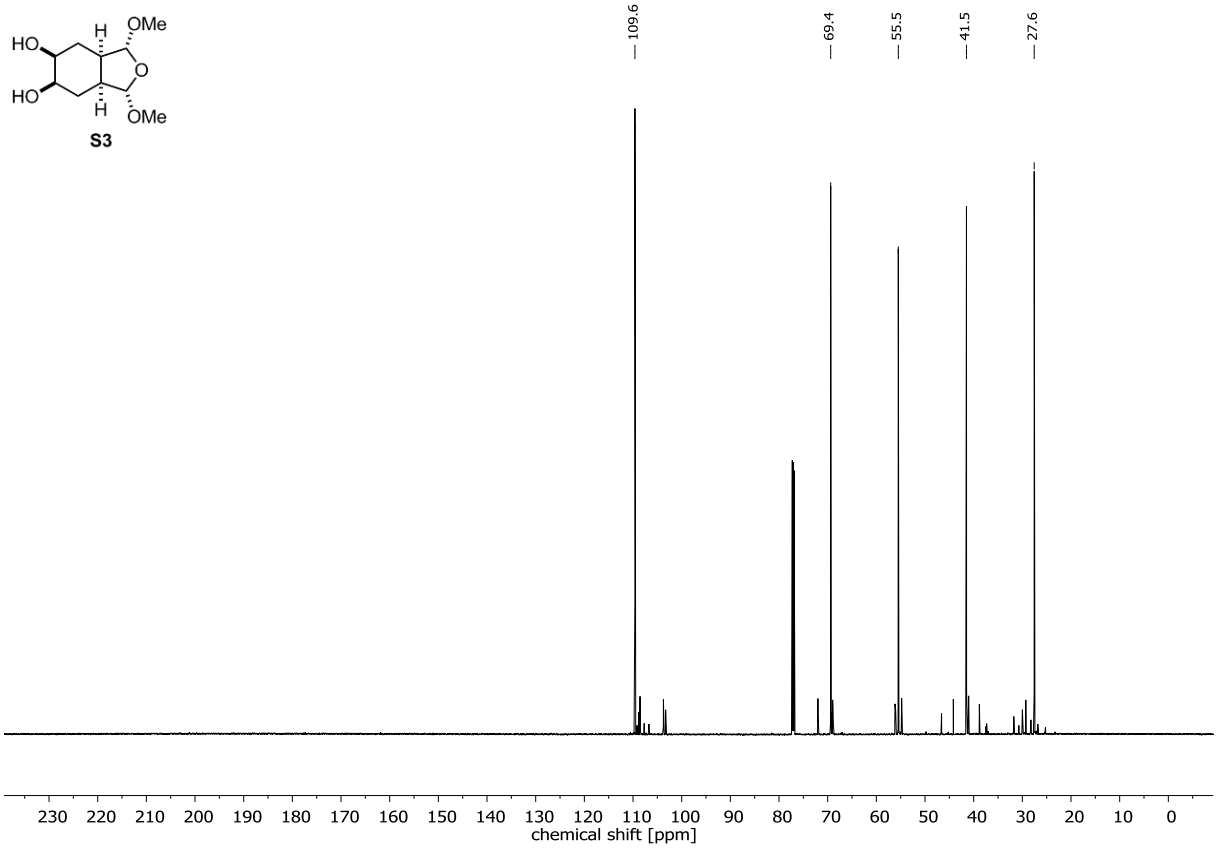
4.81
4.80
4.80
3.79
3.79
3.79
3.78
3.78
3.78
3.40
2.42
2.42
2.42
2.42
2.41
1.95
1.95
1.95
1.95
1.94
1.93
1.93
1.93
1.93
1.92
1.56
1.56
1.55
1.55
1.54
1.54
1.53
1.99
2.00
6.04
2.03
2.03
2.01
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
chemical shift [ppm]

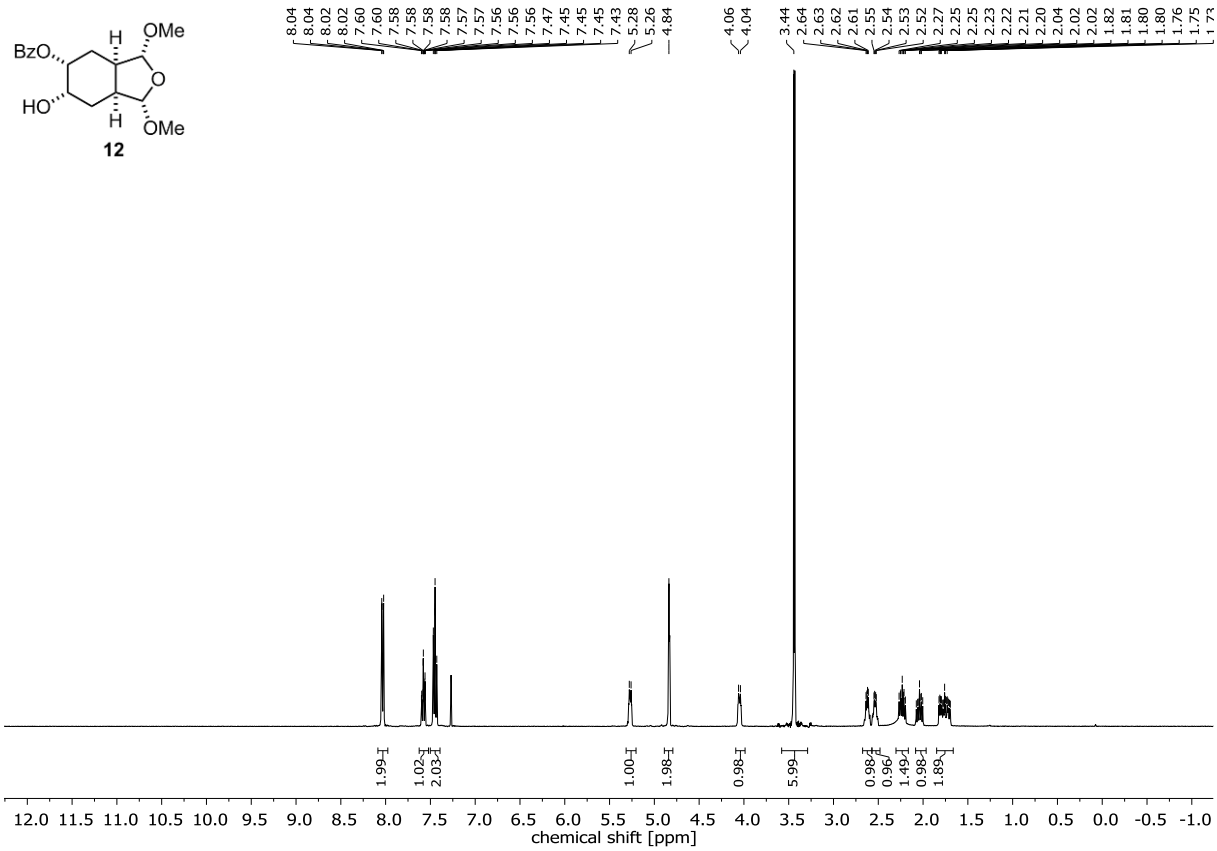

HO
H
OMe
O
HO
H
OMe

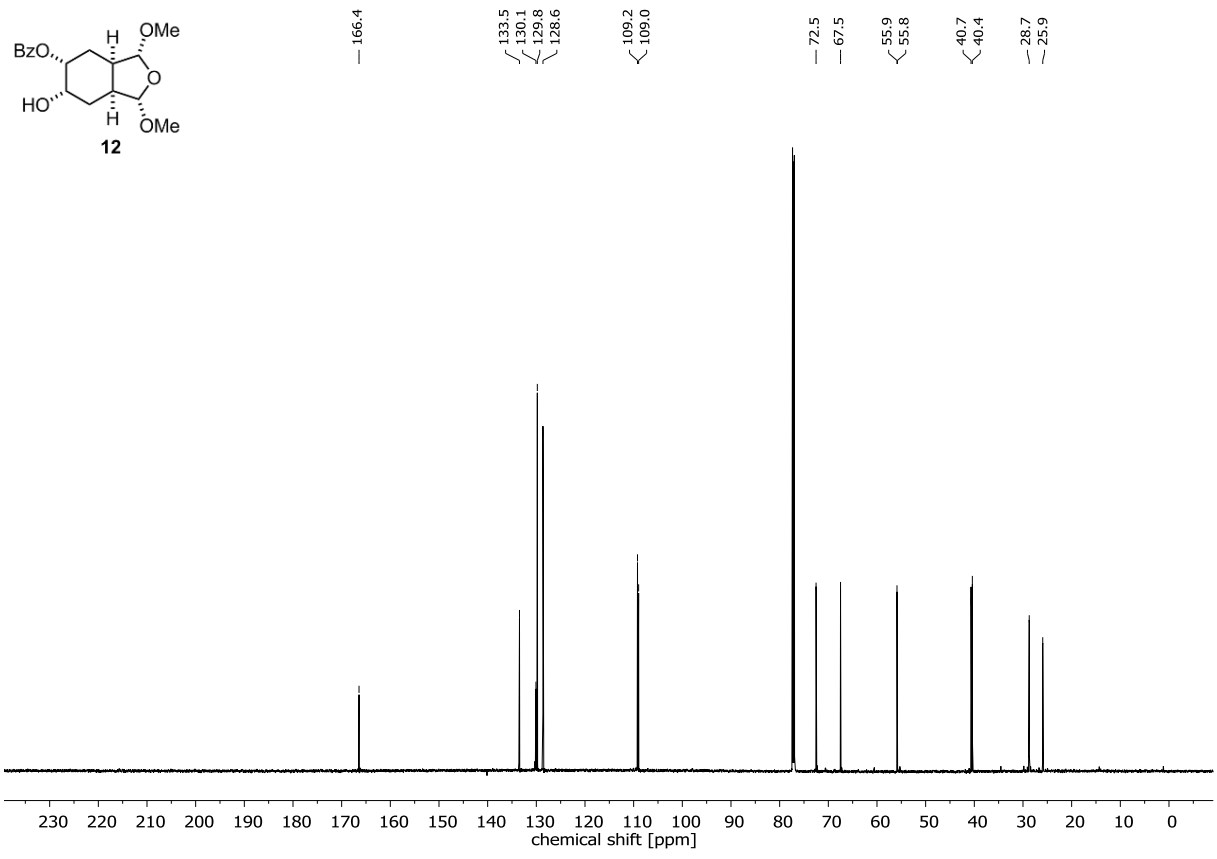
11

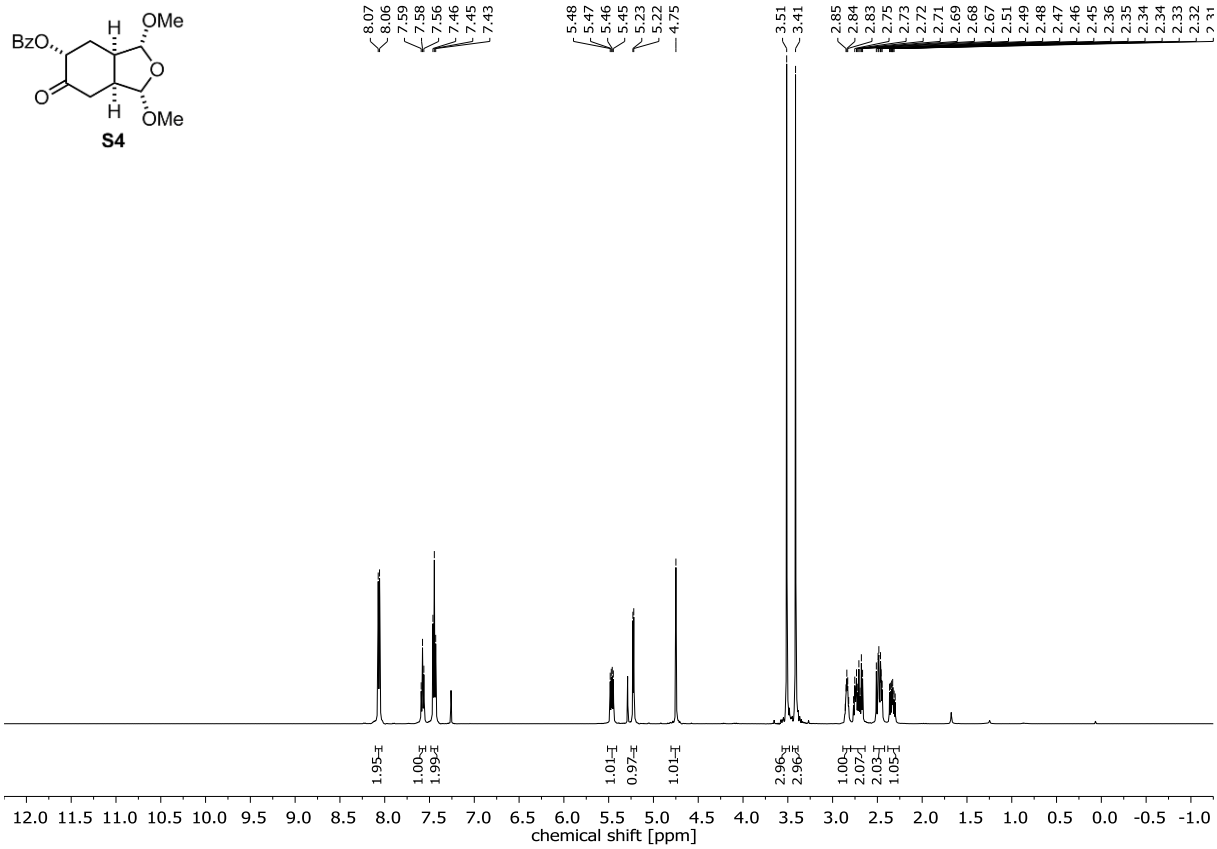
109.2
68.0
54.4
40.2
27.7
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
chemical shift [ppm]

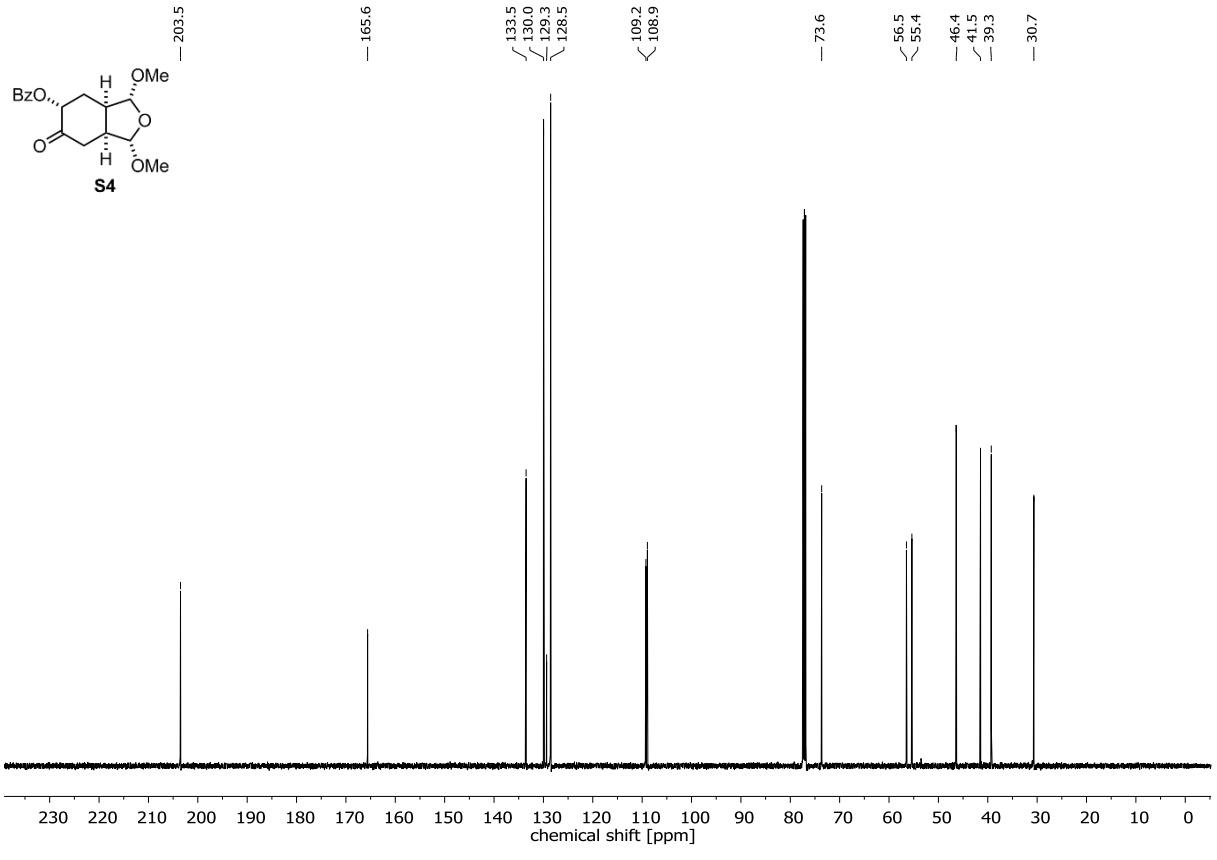

HO
HO
H
OMe
O
H
OMe
S3
4.98
3.74
3.37
3.00
2.24
1.85
1.84
1.83
1.65
1.63
2.00
1.94
6.00
2.00
1.97
1.99
2.17
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
chemical shift [ppm]

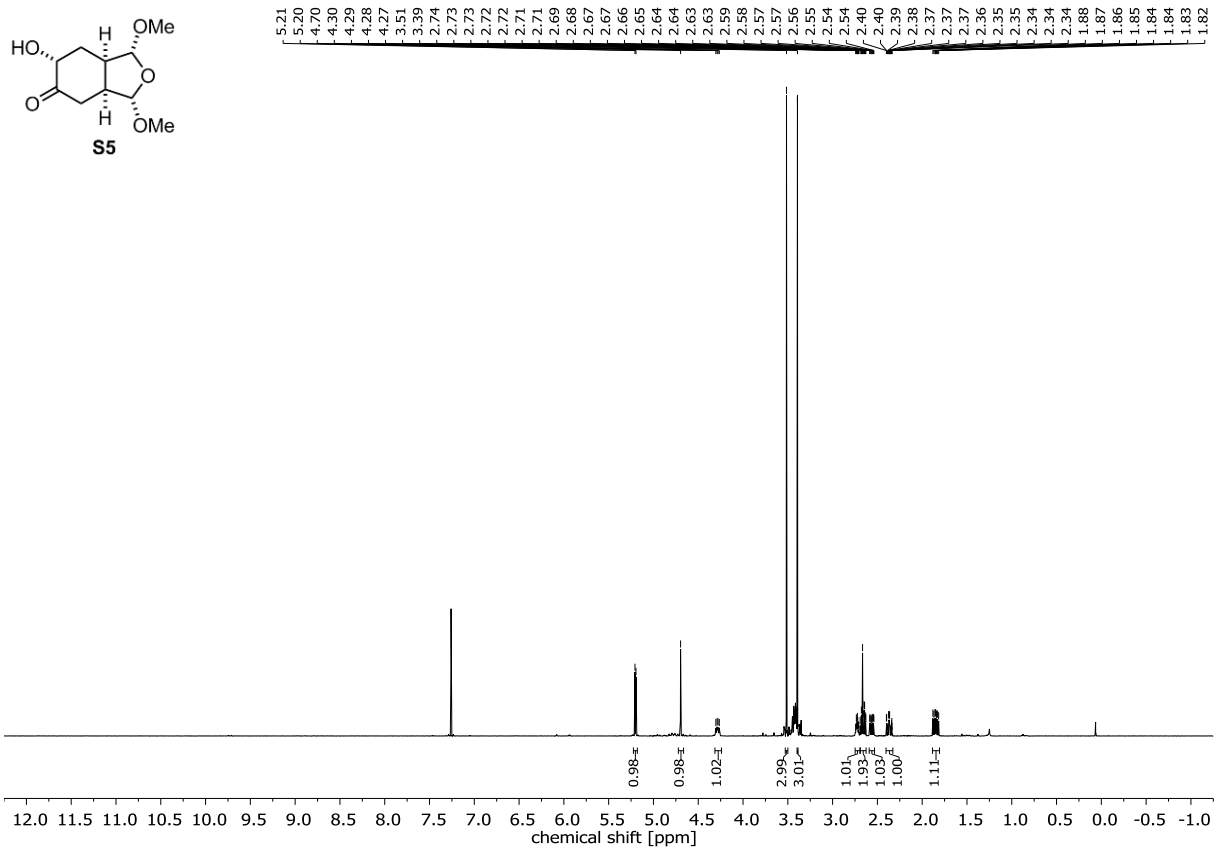

HO
HO
H
OMe
O
H
OMe
S3
109.6
69.4
55.5
41.5
27.6
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
chemical shift [ppm]

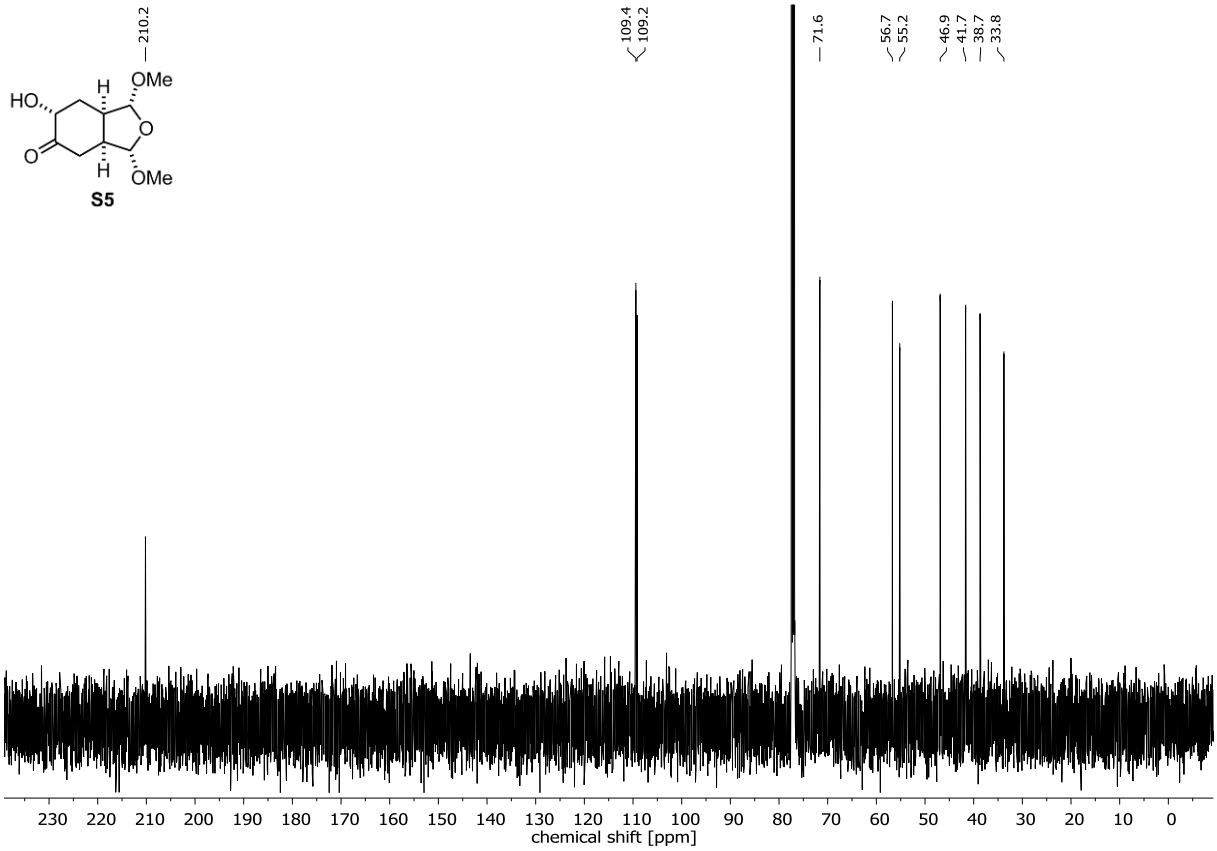

BzO
HO
H
OMe
O
H
OMe
12
chemical shift [ppm]

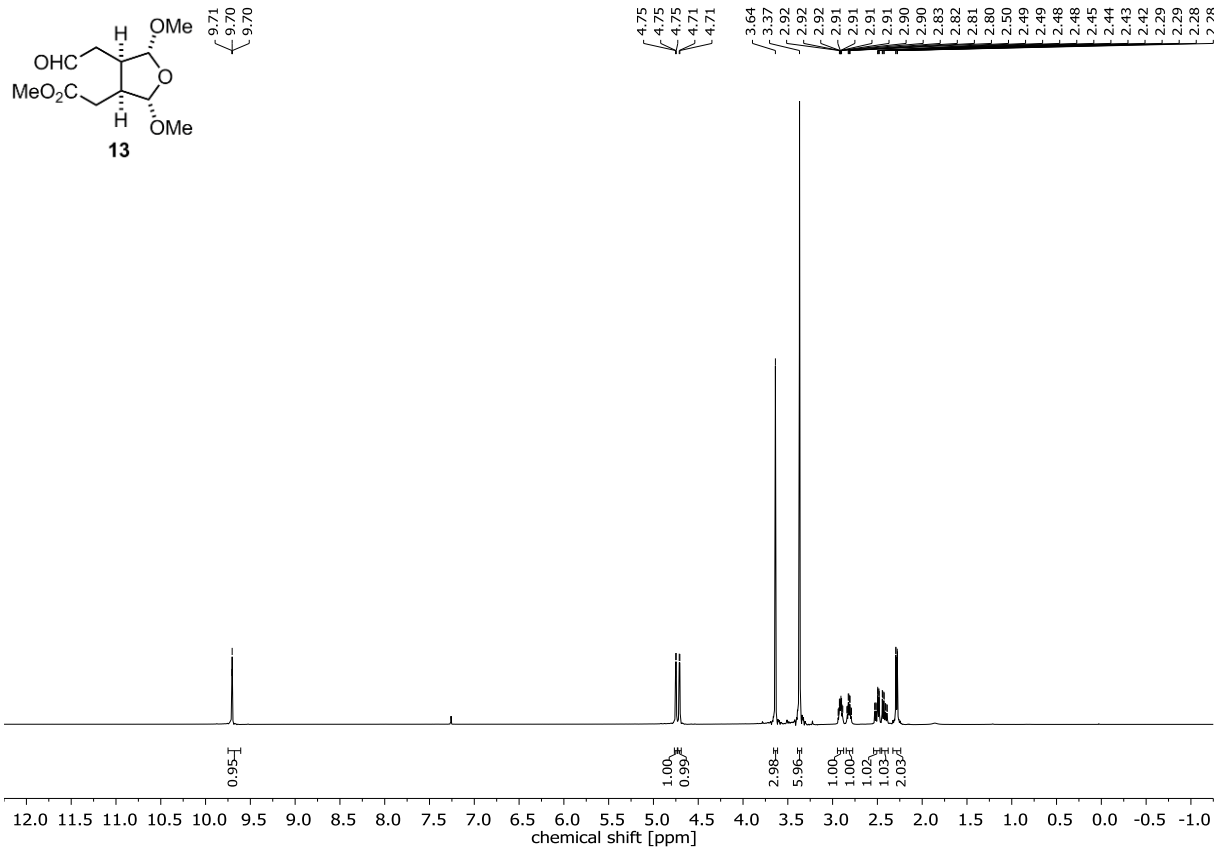

BzO
HO
H
OMe
O
H
OMe
12
chemical shift [ppm]

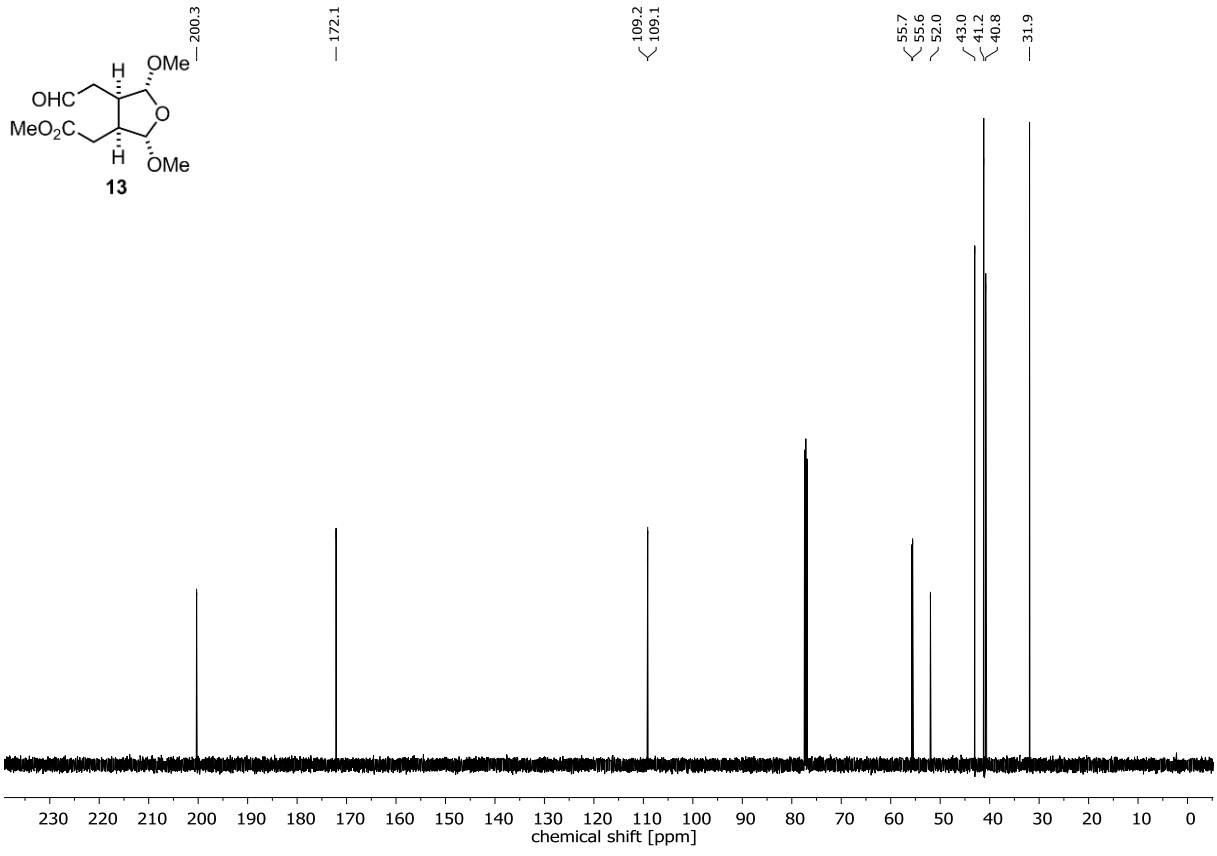

BzO
OMe
H
O
H
OMe
O
S4
8.07
8.06
7.59
7.58
7.56
7.46
7.45
7.43
5.48
5.47
5.46
5.45
5.23
5.22
4.75
3.51
3.41
2.85
2.84
2.83
2.75
2.73
2.72
2.71
2.69
2.68
2.67
2.51
2.49
2.48
2.47
2.46
2.45
2.36
2.35
2.34
2.33
2.32
1.95
1.00
1.99
1.01
0.97
1.01
2.96
2.96
1.00
2.07
2.03
1.05
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
chemical shift [ppm]

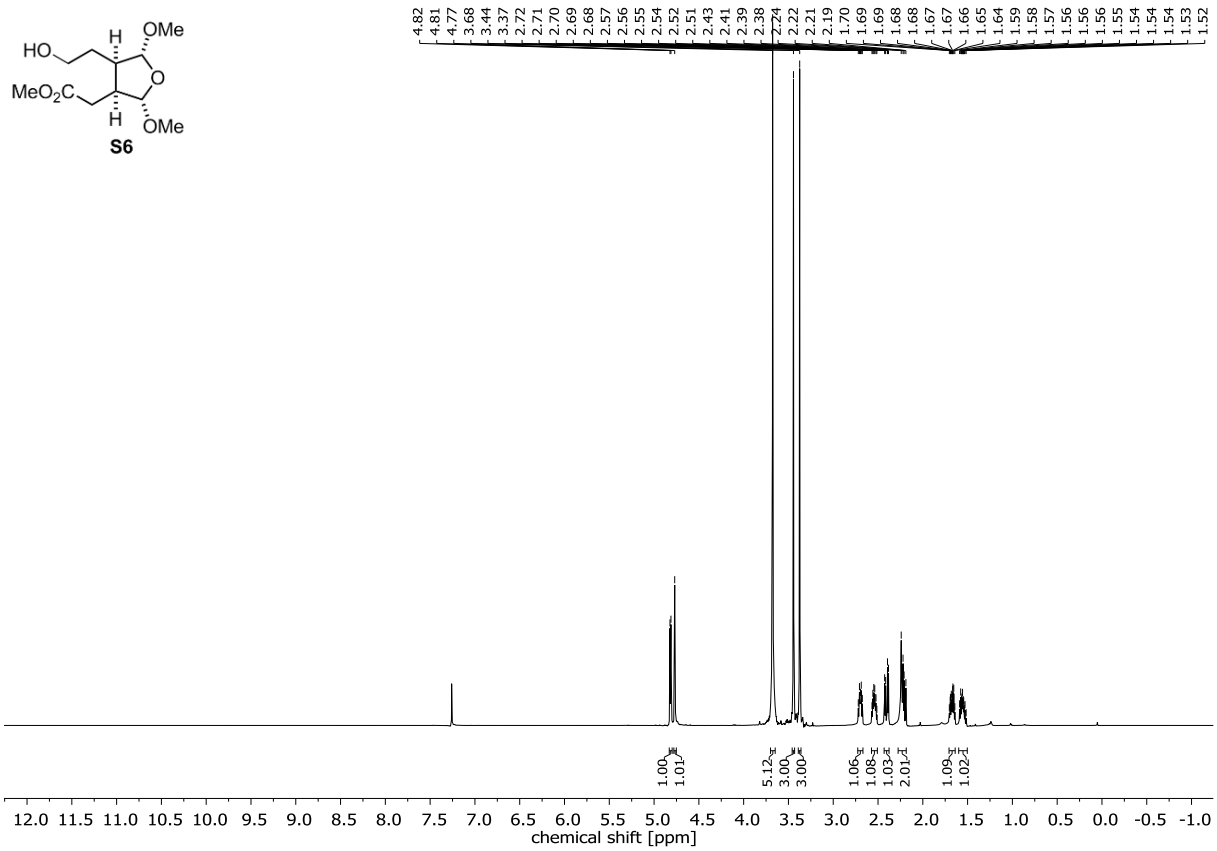

BzO
OMe
H
O
H
OMe
O
S4
203.5
165.6
133.5
130.0
129.3
128.5
109.2
108.9
73.6
56.5
55.4
46.4
41.5
39.3
30.7
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
chemical shift [ppm]

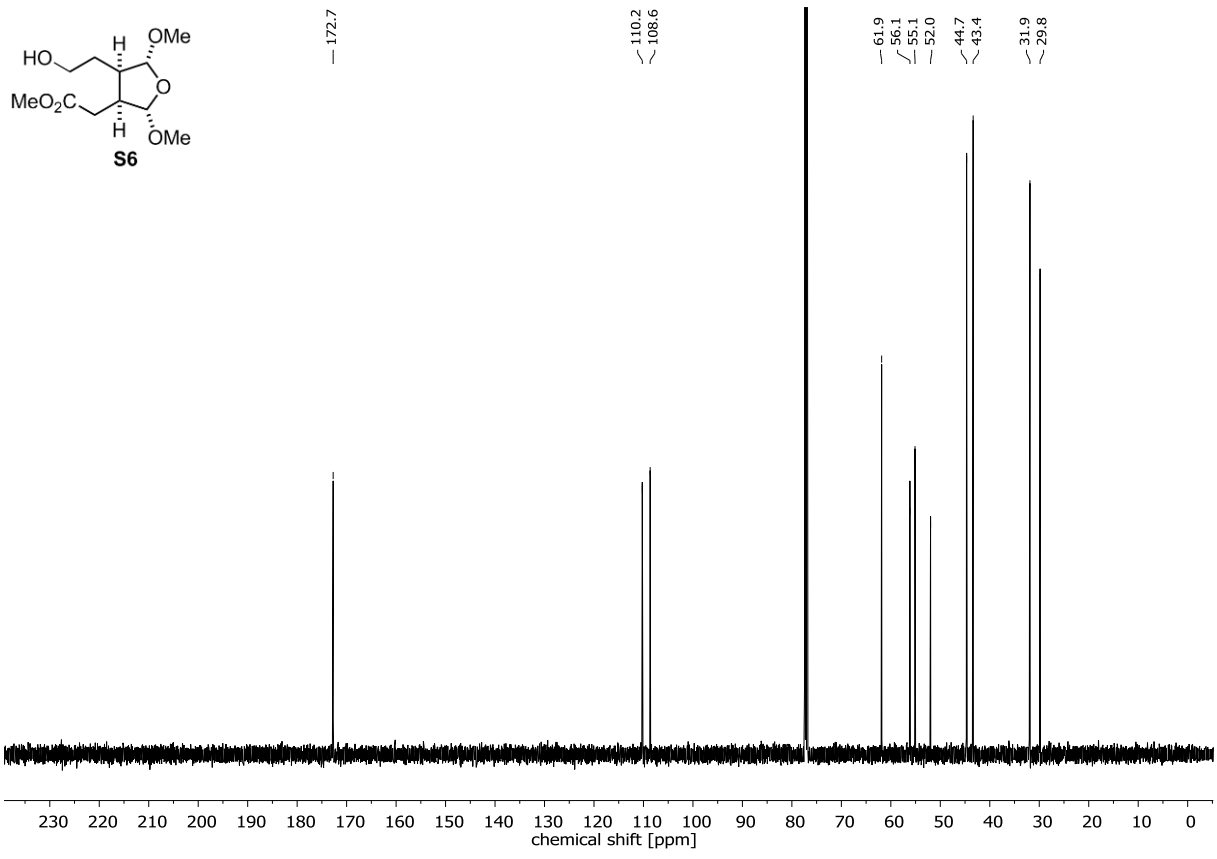

HO
H
OMe
O
O
H
OMe
S5
5.21 5.20 4.70 4.30 4.29 4.28 4.27 3.51 3.39 2.74 2.73 2.73 2.72 2.72 2.71 2.71 2.69 2.68 2.67 2.67 2.66 2.65 2.64 2.64 2.63 2.63 2.59 2.58 2.57 2.57 2.56 2.55 2.54 2.54 2.40 2.40 2.39 2.38 2.37 2.37 2.36 2.35 2.35 2.34 2.34 2.34 1.88 1.87 1.86 1.85 1.84 1.84 1.84 1.83 1.82
0.98 0.98 1.02 2.99 3.01 1.01 1.93 1.03 1.00 1.11
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
chemical shift [ppm]

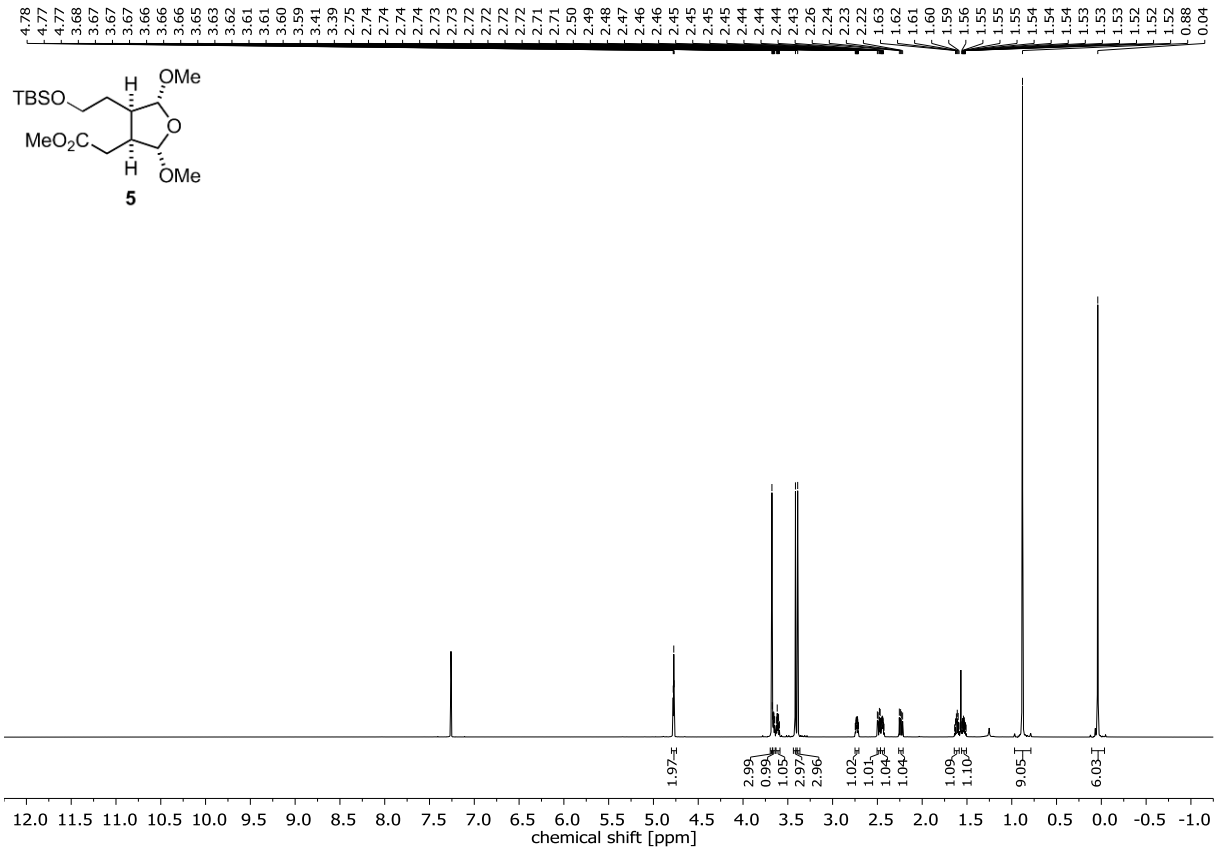

210.2
HO
H
OMe
O
O
H
OMe
S5
109.4
109.2
71.6
56.7
55.2
46.9
41.7
38.7
33.8
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
chemical shift [ppm]

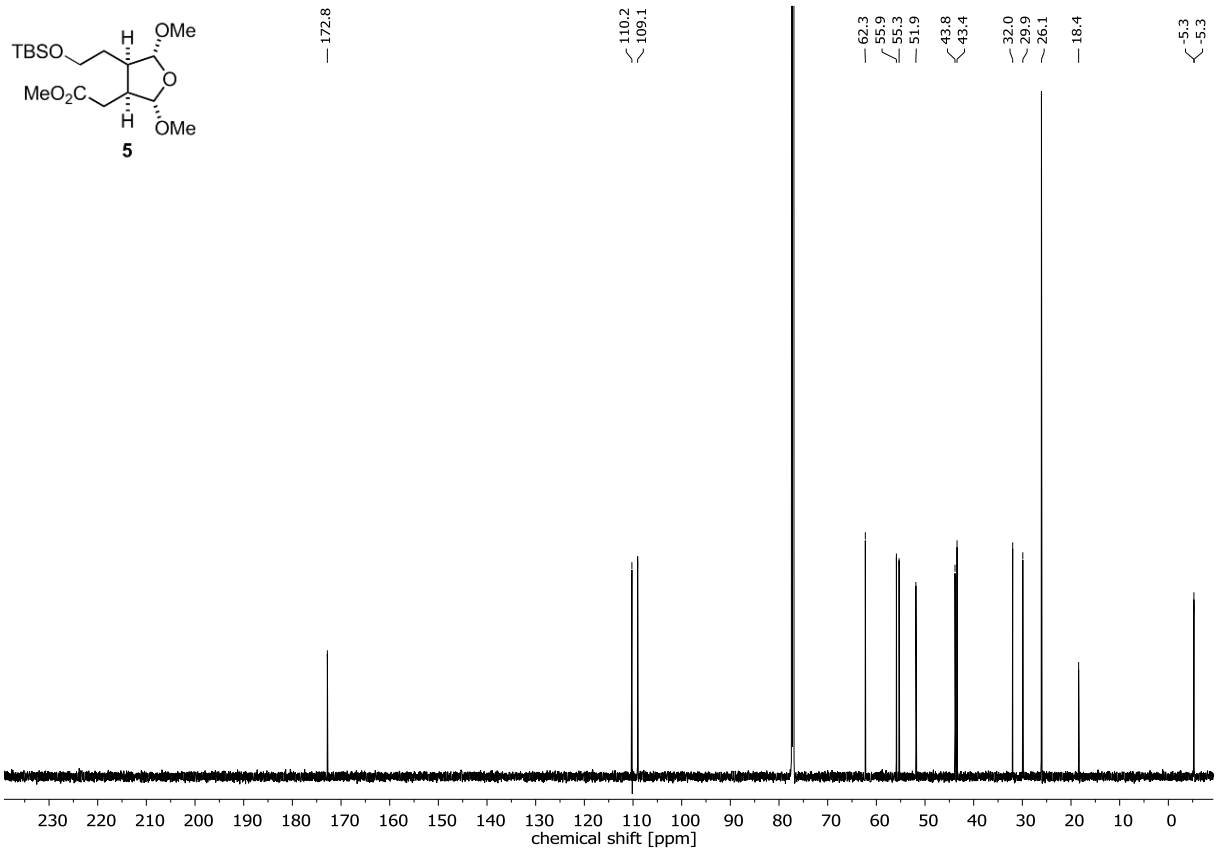

OMe
H
OHC
MeO2C
O
H
OMe
13
chemical shift [ppm]

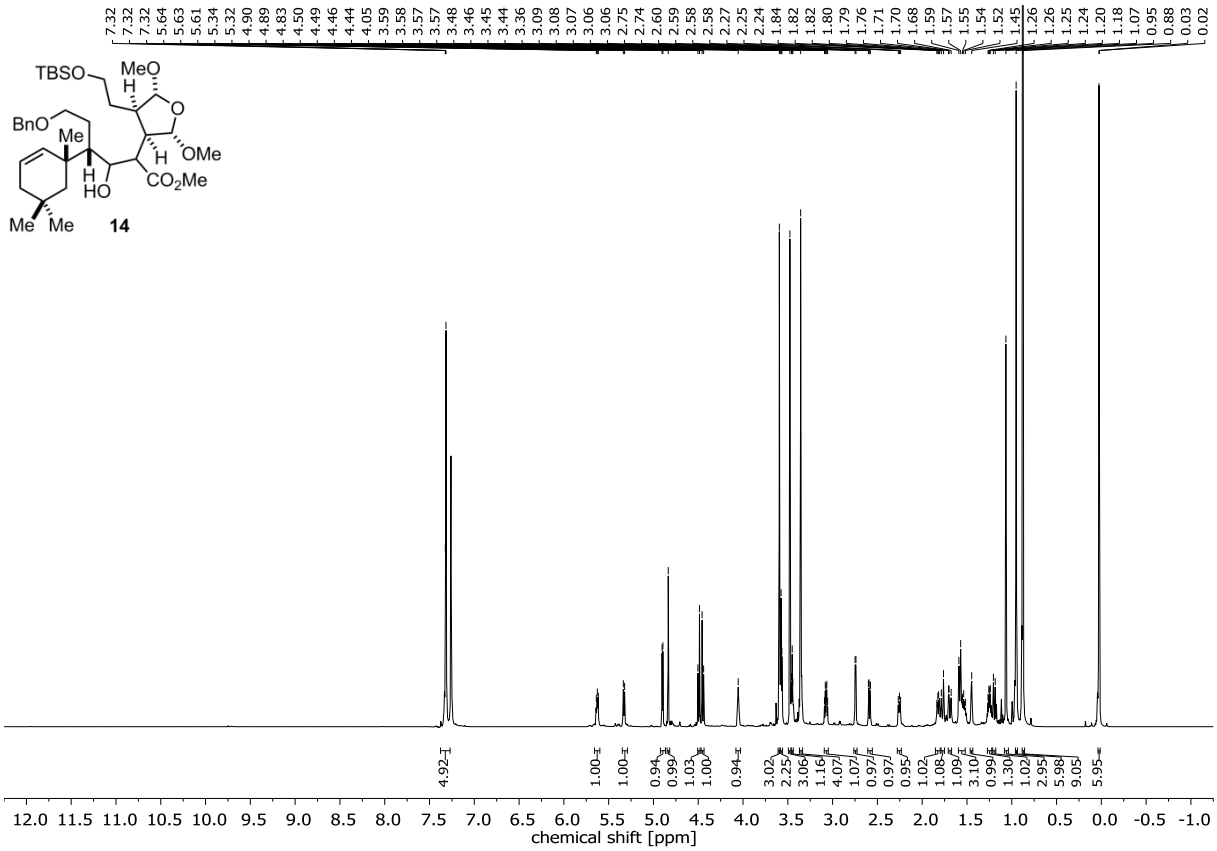

OMe
H
OHC
MeO2C
O
H
OMe
13
chemical shift [ppm]

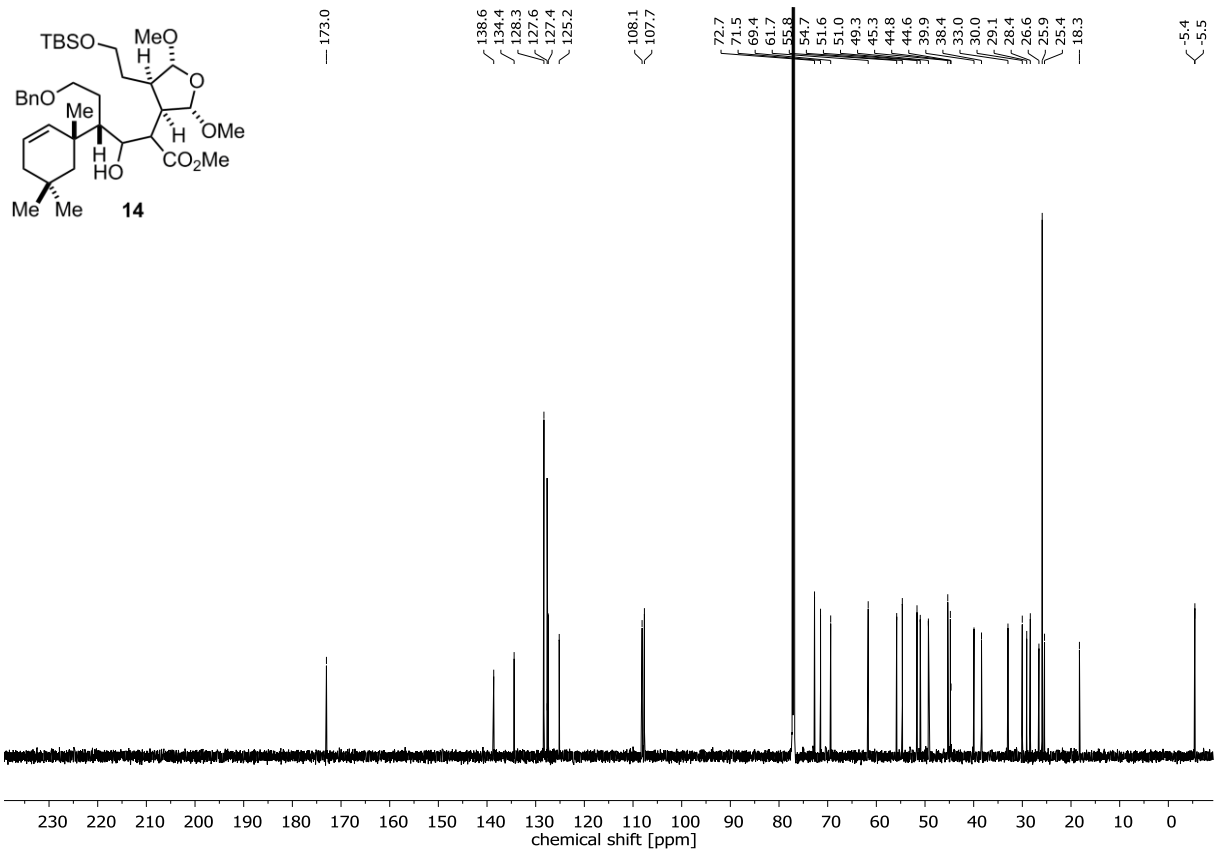

HO
OMe
H
MeO2C
O
H
OMe
S6
4.82 4.81 4.77 3.68 3.44 3.37 2.72 2.71 2.70 2.69 2.68 2.57 2.56 2.55 2.54 2.52 2.51 2.43 2.41 2.39 2.38 2.24 2.22 2.21 2.19 1.70 1.69 1.69 1.68 1.68 1.67 1.67 1.66 1.65 1.64 1.59 1.58 1.57 1.56 1.56 1.56 1.55 1.54 1.54 1.54 1.53 1.52
1.00 1.01 5.12 3.00 3.00 1.06 1.08 1.03 2.01 1.09 1.02
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
chemical shift [ppm]

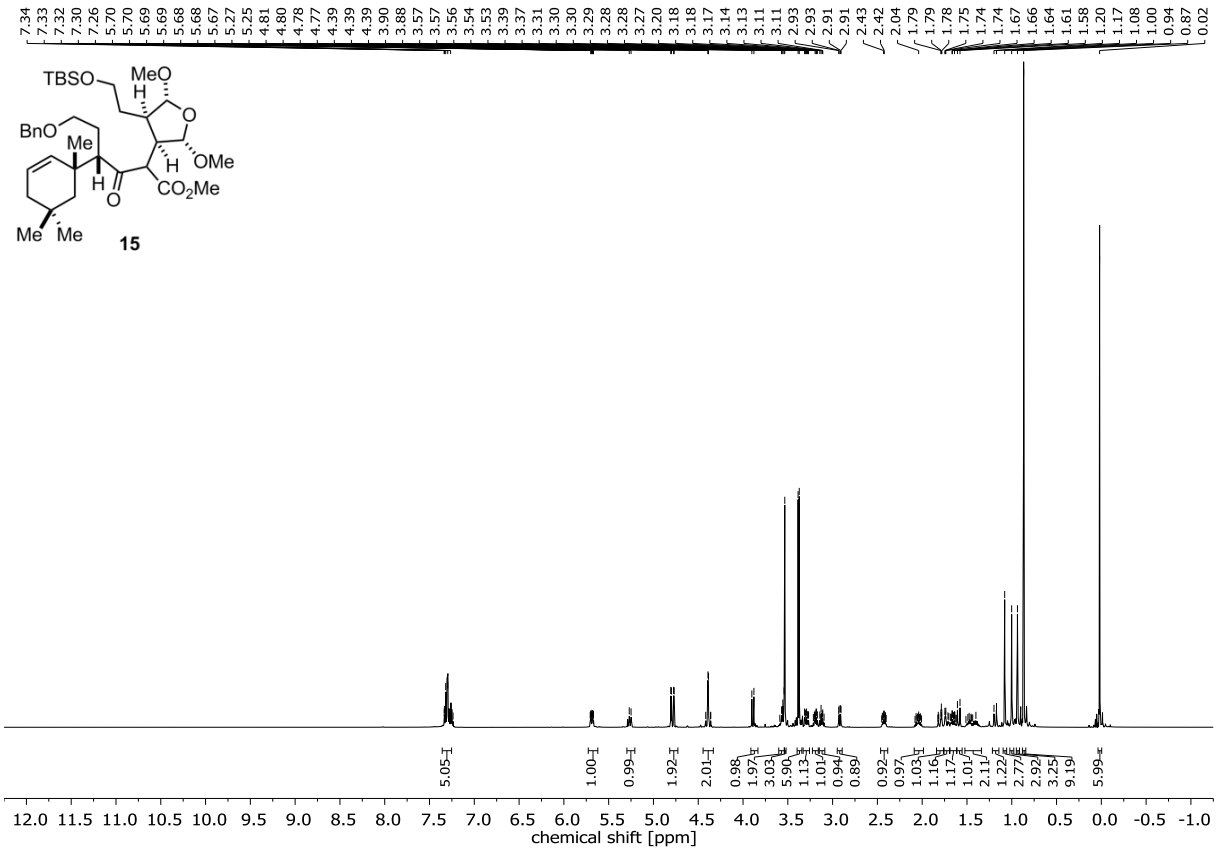

HO
OMe
H
MeO2C
O
H
OMe
S6
172.7
110.2
108.6
61.9
56.1
55.1
52.0
44.7
43.4
31.9
29.8
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
chemical shift [ppm]

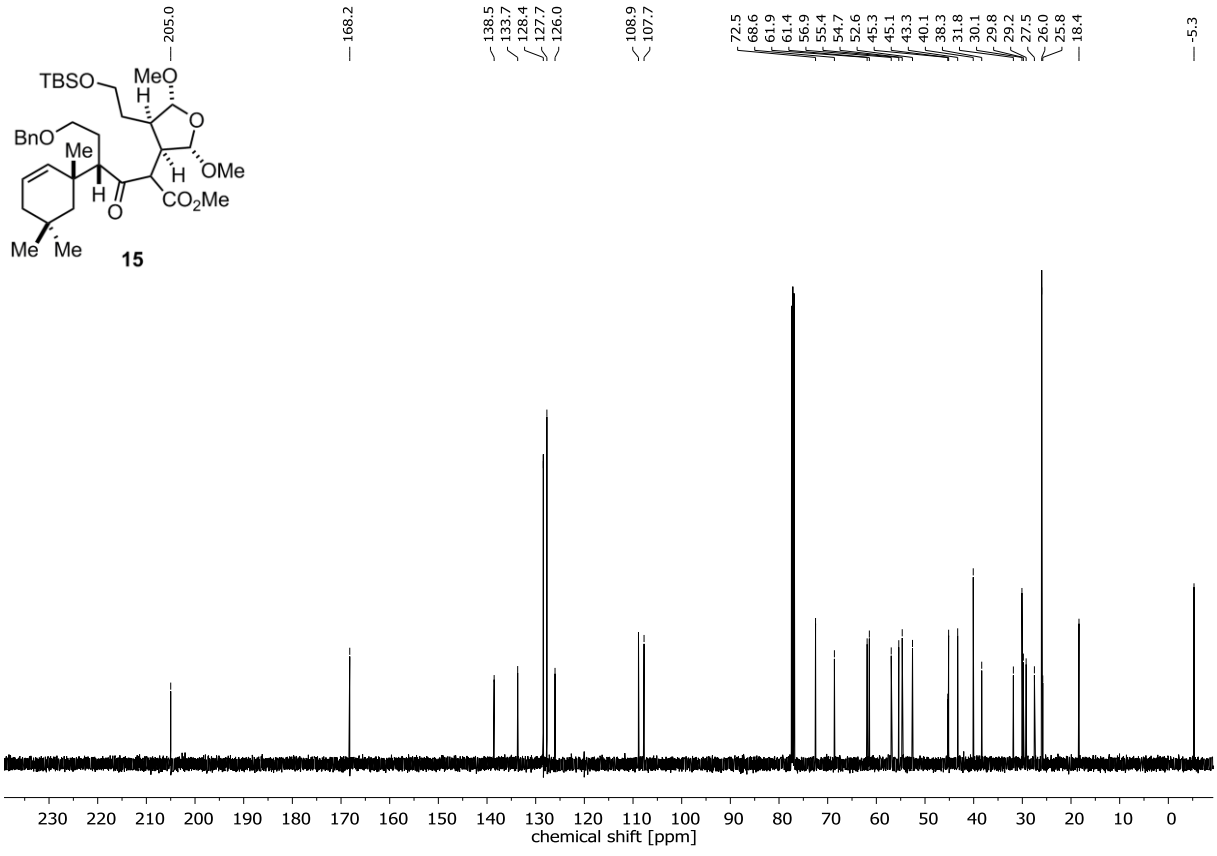

TBSO
MeO2C
H
OMe
O
H
OMe
5
chemical shift [ppm]

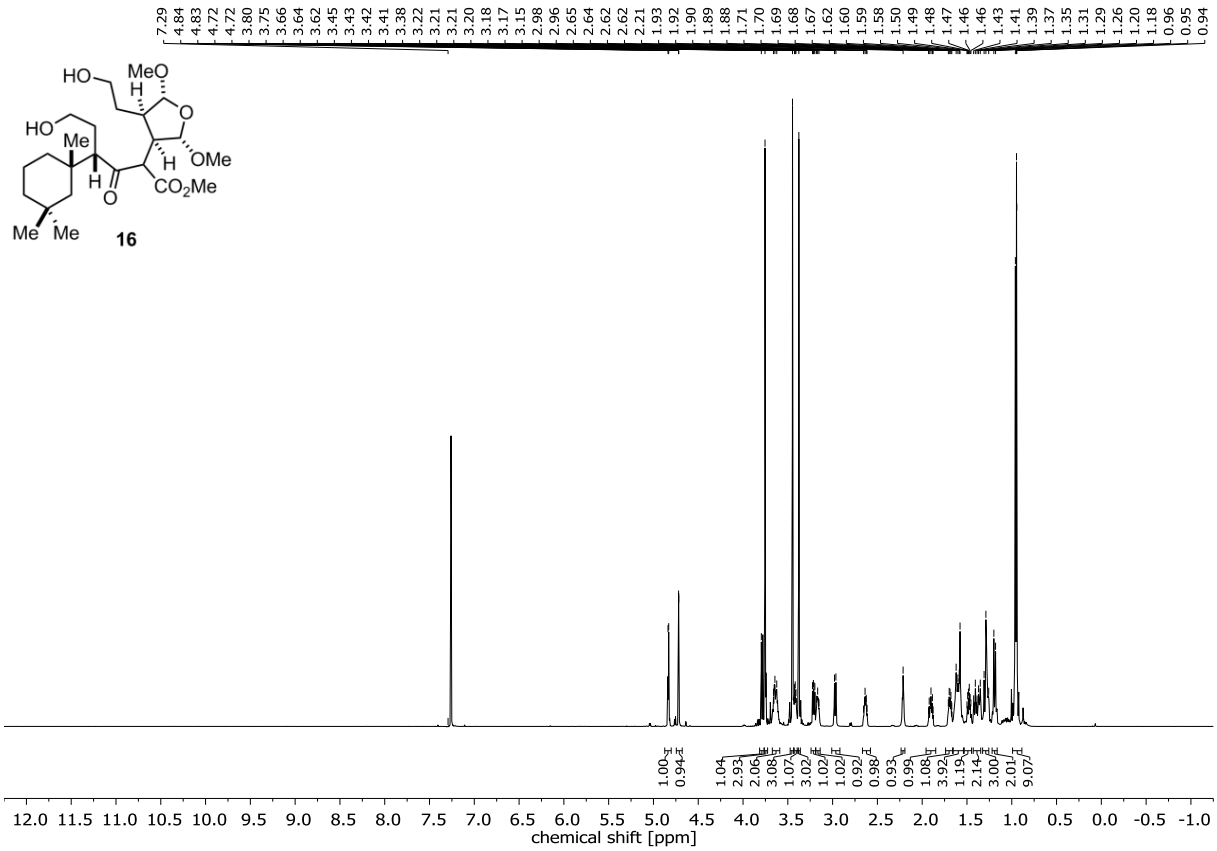

TBSO
MeO2C
H
OMe
O
H
OMe
5
chemical shift [ppm]

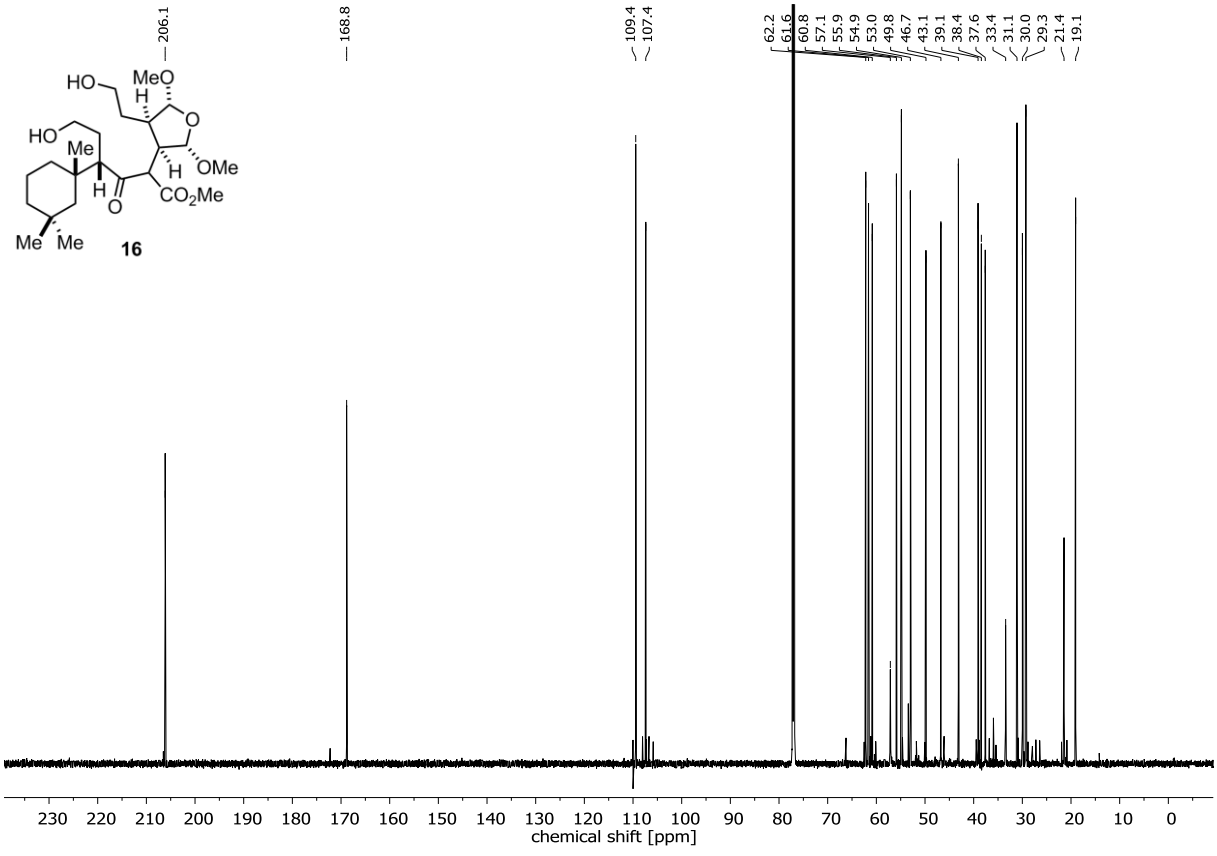

TBSO
MeO
BnO
Me
OMe
HO
CO2Me
Me Me
14
chemical shift [ppm]

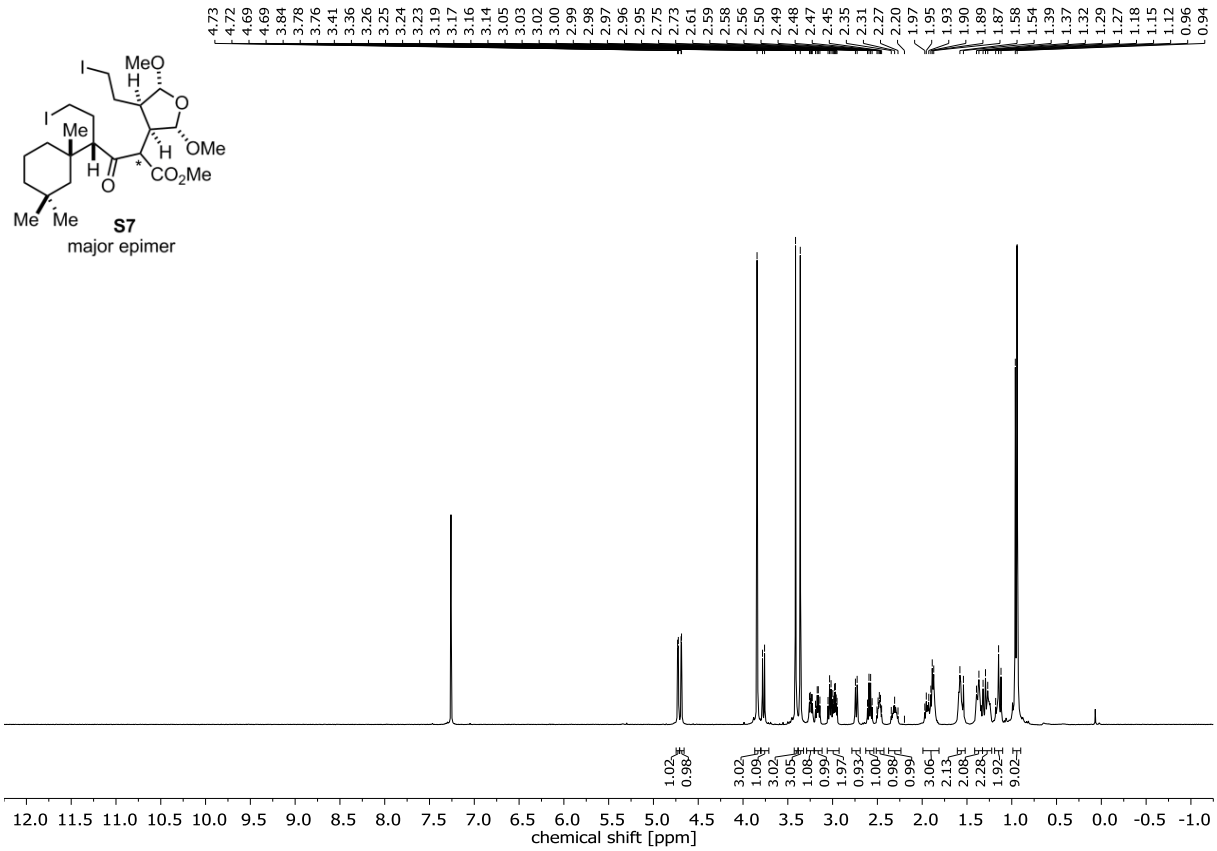

TBSO
MeO
BnO
Me
OMe
HO
CO2Me
Me Me
14
chemical shift [ppm]

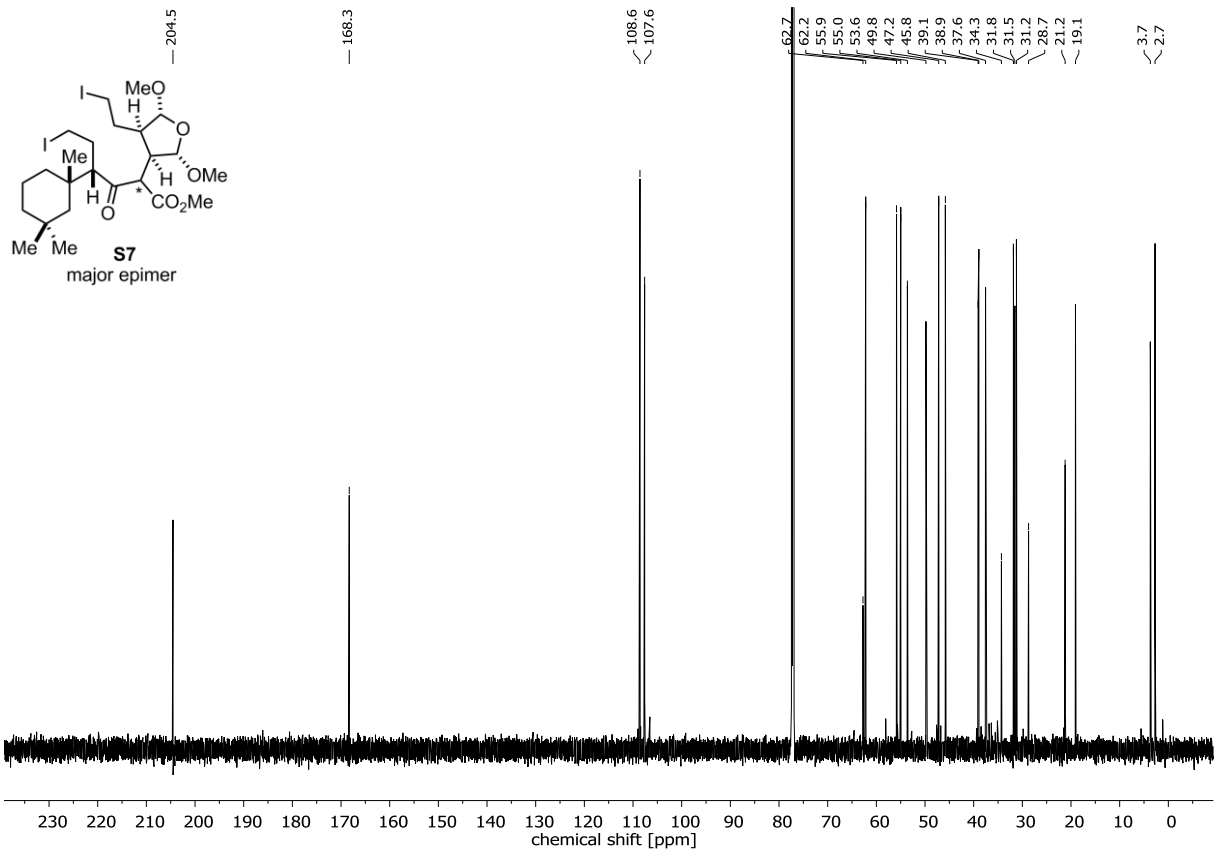

TBSO
MeO
BnO
Me
OMe
CO2Me
Me
Me
15
chemical shift [ppm]

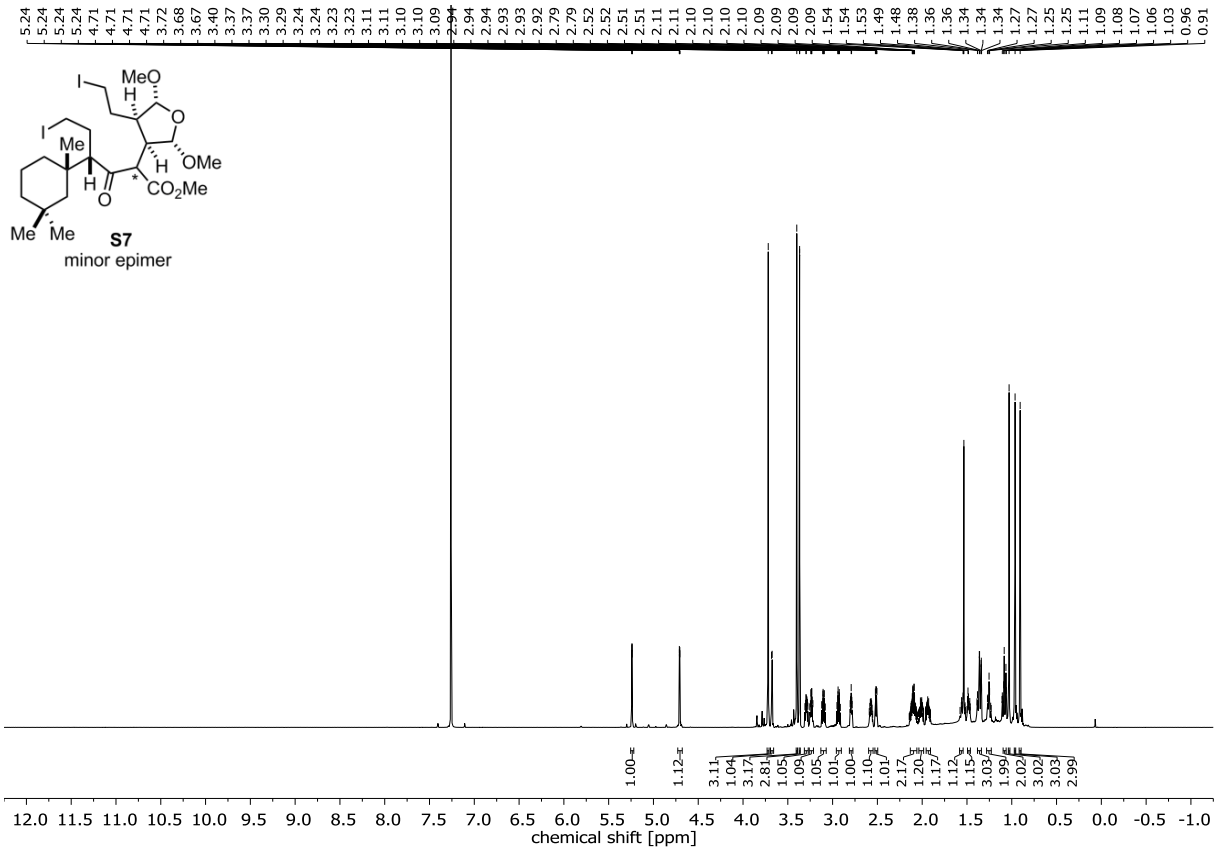

TBSO
MeO
BnO
Me
OMe
CO2Me
Me
Me
15
chemical shift [ppm]

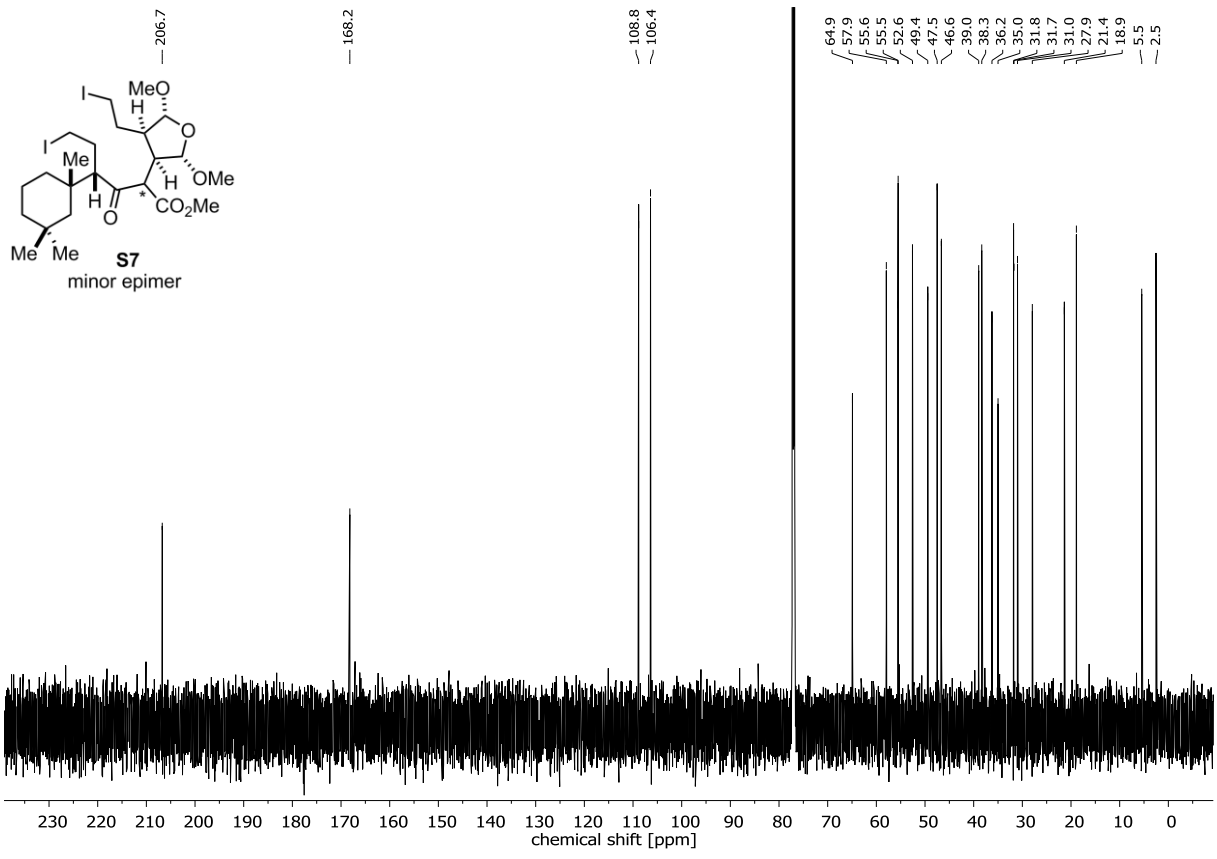

7.29 4.84 4.83 4.72 4.72 3.80 3.75 3.66 3.64 3.62 3.45 3.43 3.42 3.41 3.38 3.22 3.21 3.21 3.20 3.18 3.17 3.15 2.98 2.96 2.65 2.64 2.62 2.62 2.21 1.93 1.92 1.90 1.89 1.88 1.71 1.70 1.69 1.68 1.67 1.62 1.60 1.59 1.58 1.50 1.49 1.48 1.47 1.46 1.46 1.43 1.41 1.39 1.37 1.35 1.31 1.29 1.26 1.20 1.18 0.96 0.95 0.94
HO
MeO
H
O
HO
Me
H
OMe
H
O
CO2Me
Me Me
16
1.00 0.94 1.04 2.93 2.06 3.08 1.07 3.02 1.02 1.02 0.92 0.98 0.93 0.99 1.08 3.92 1.19 2.14 3.00 2.01 9.07
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
chemical shift [ppm]

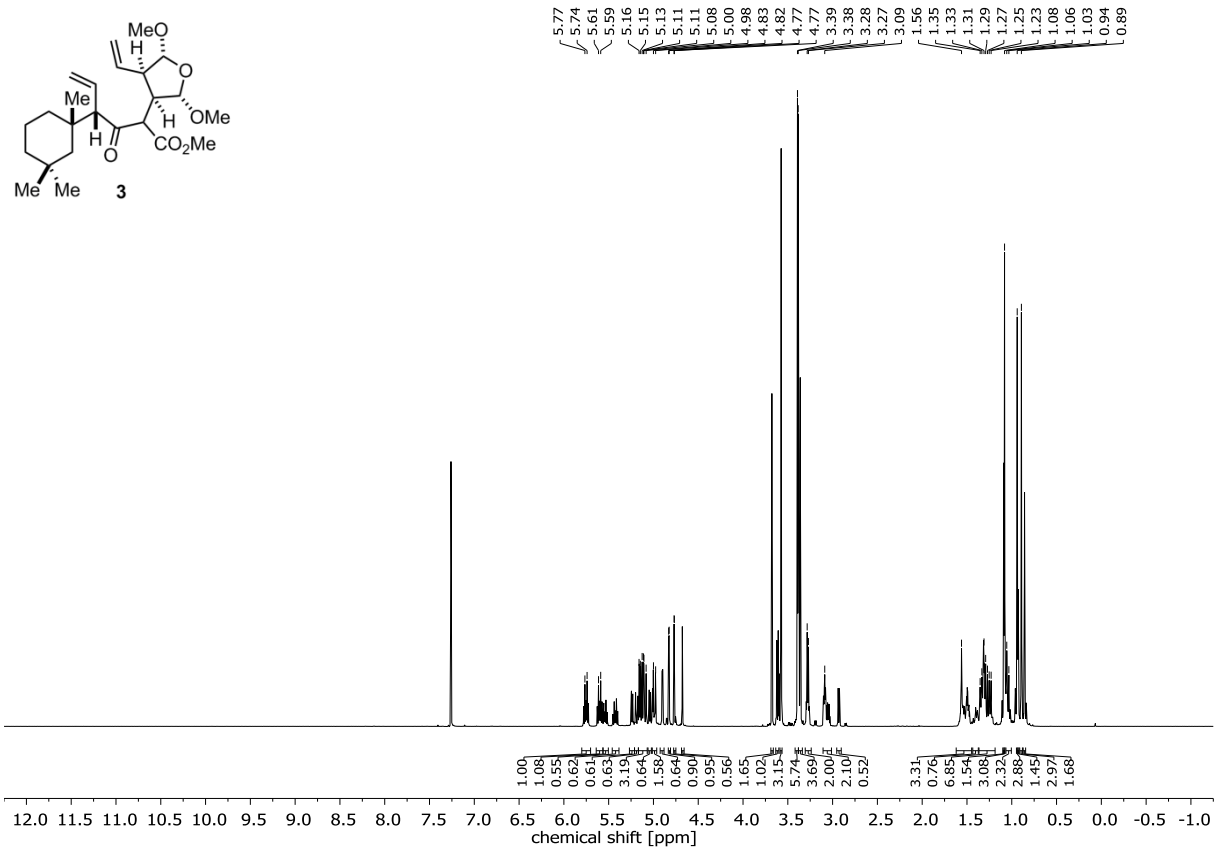

206.1
168.8
109.4
107.4
62.2
61.6
60.8
57.1
55.9
54.9
53.0
49.8
46.7
43.1
39.1
38.4
37.6
33.4
31.1
30.0
29.3
21.4
19.1
HO
MeO
H
O
HO
Me
H
OMe
H
O
CO2Me
Me Me
16
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
chemical shift [ppm]

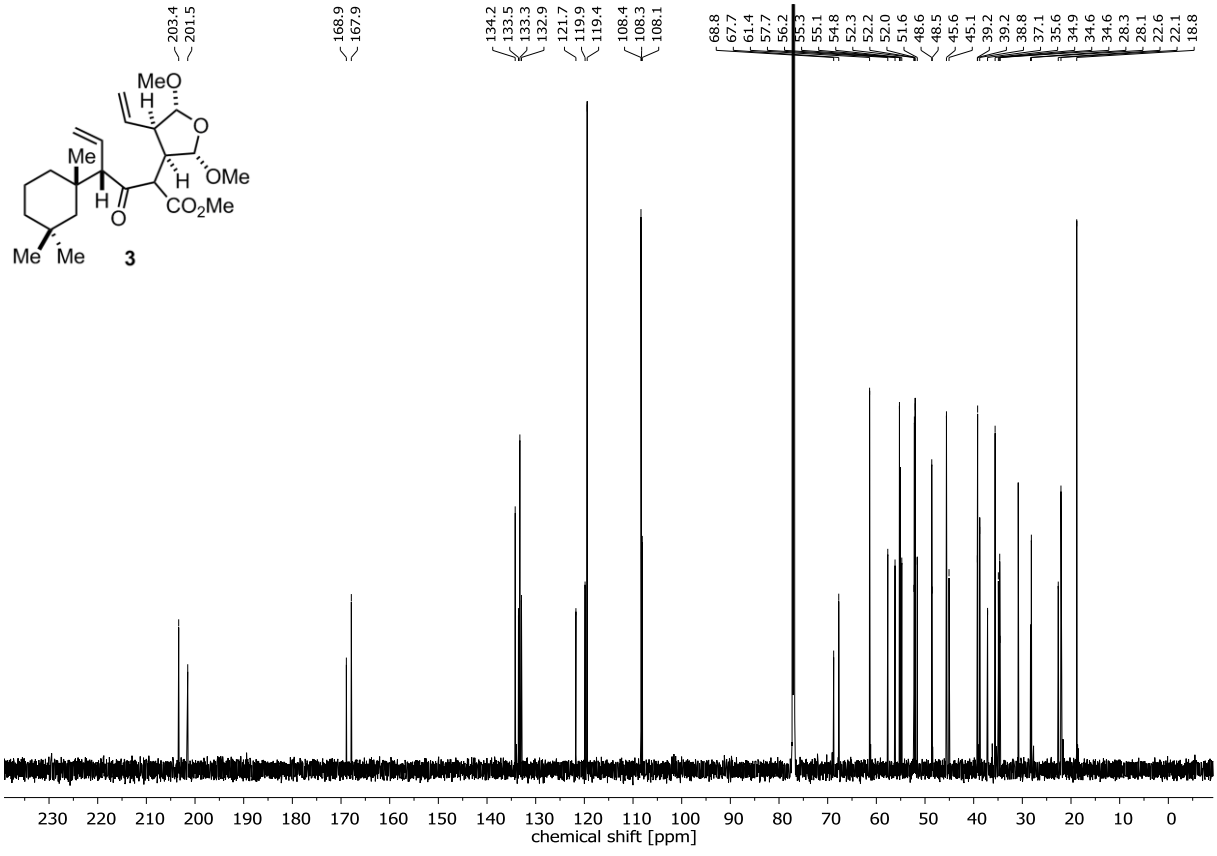

S7
major epimer
chemical shift [ppm]

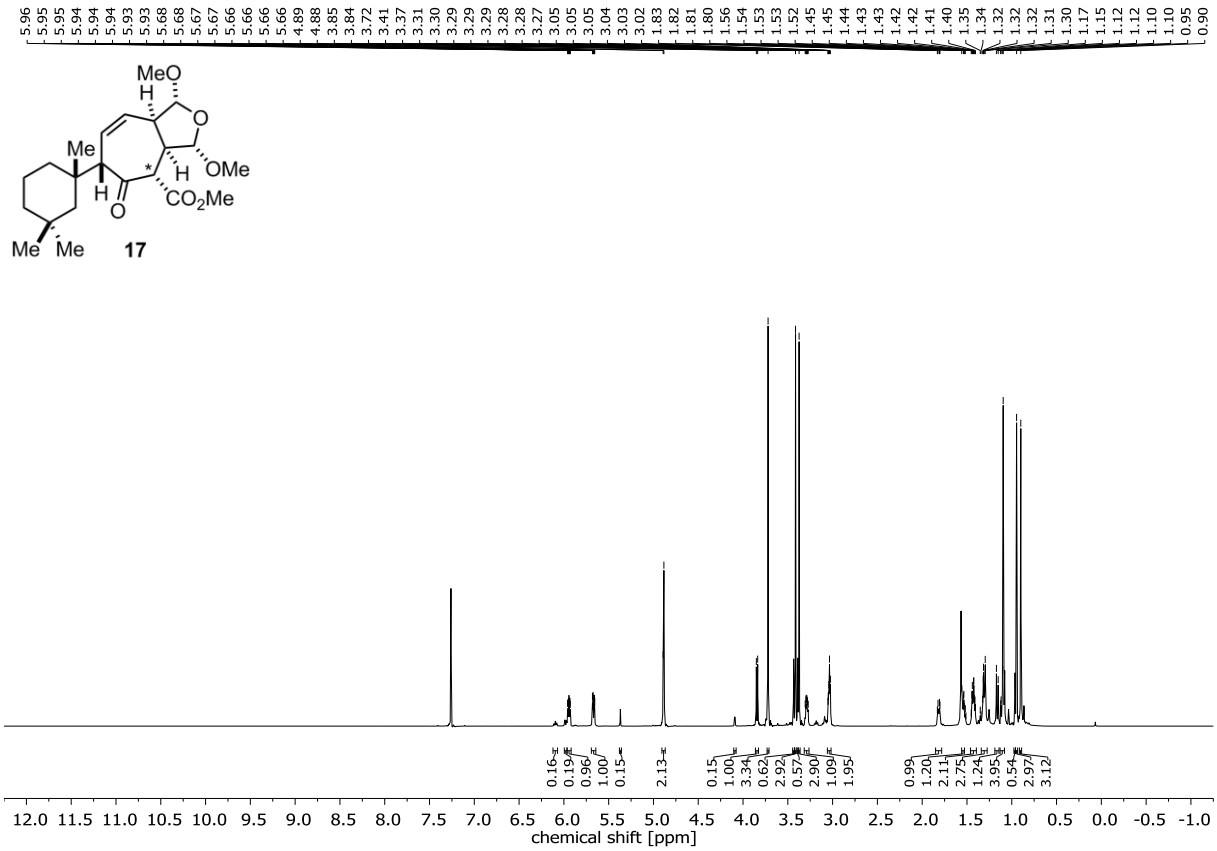

S7
major epimer
chemical shift [ppm]

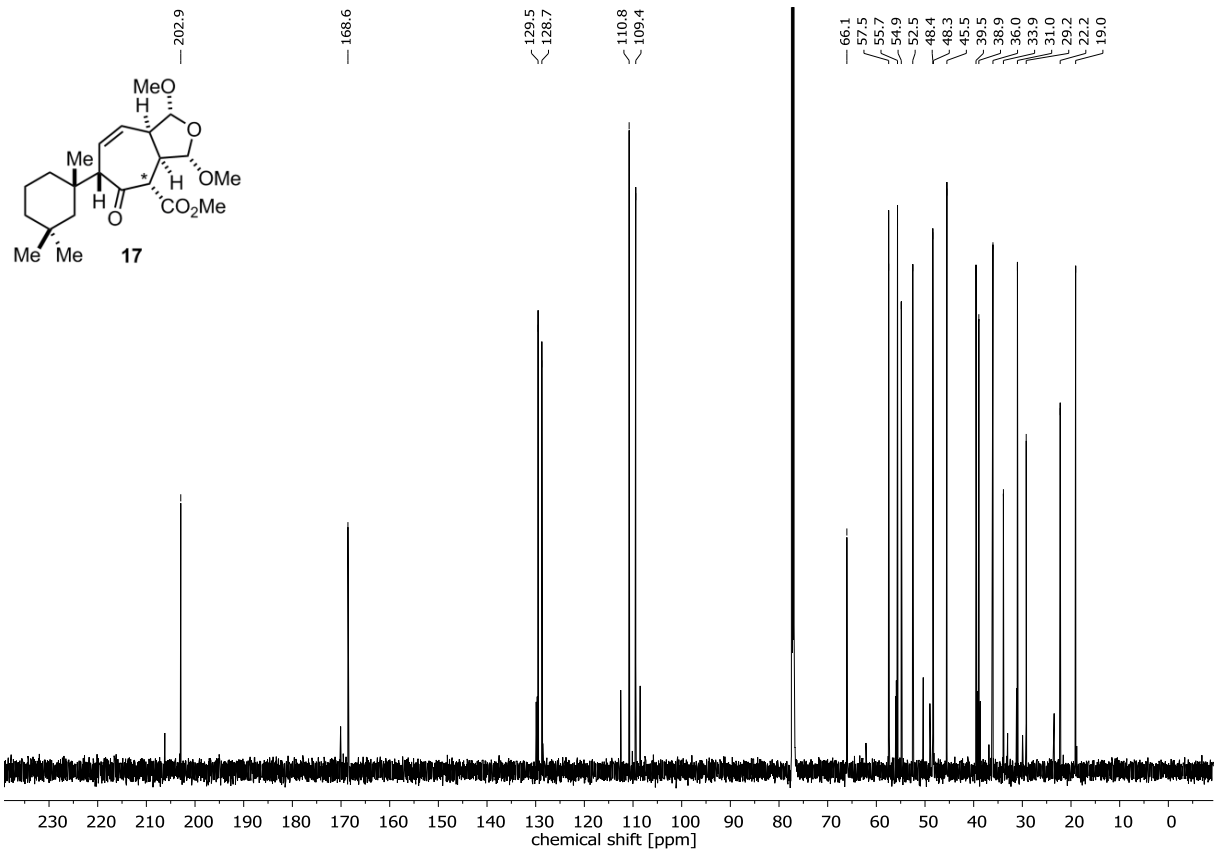

S7
minor epimer
chemical shift [ppm]

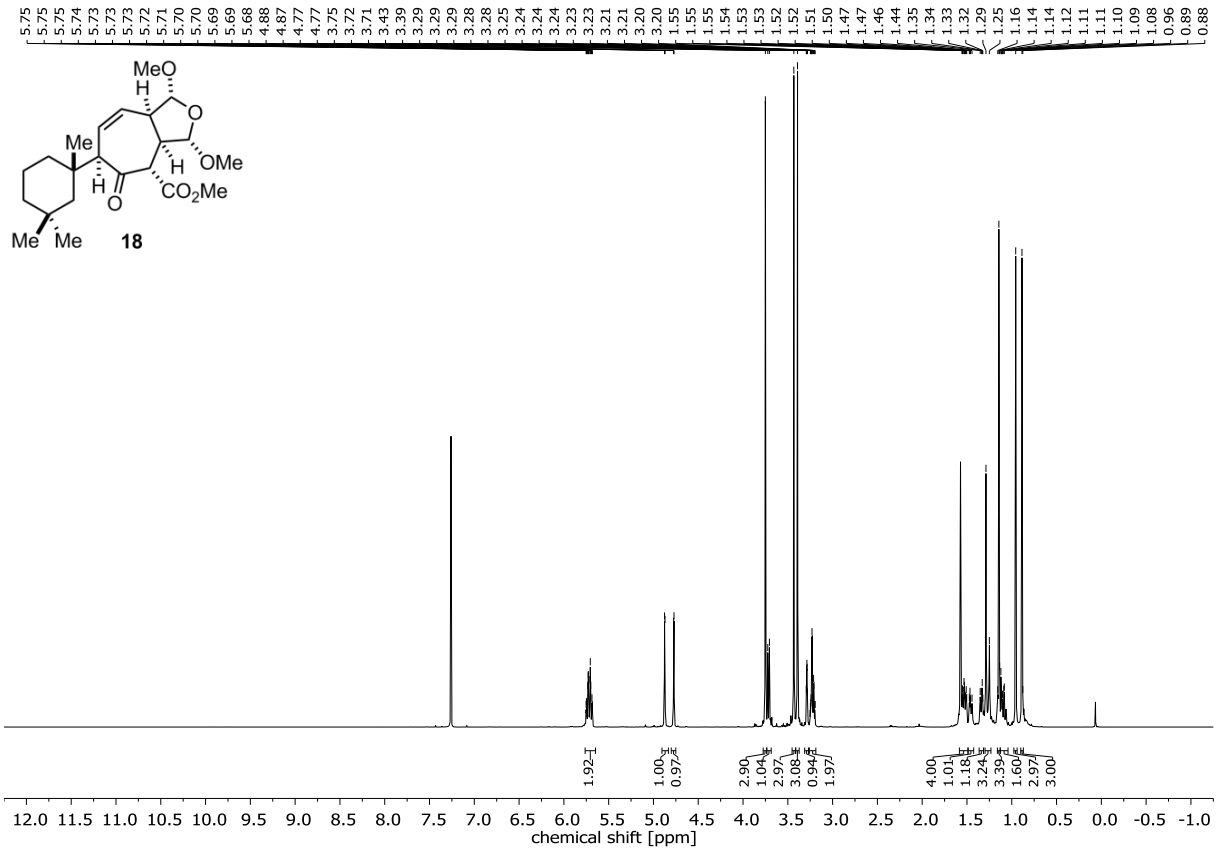

S7
minor epimer
chemical shift [ppm]

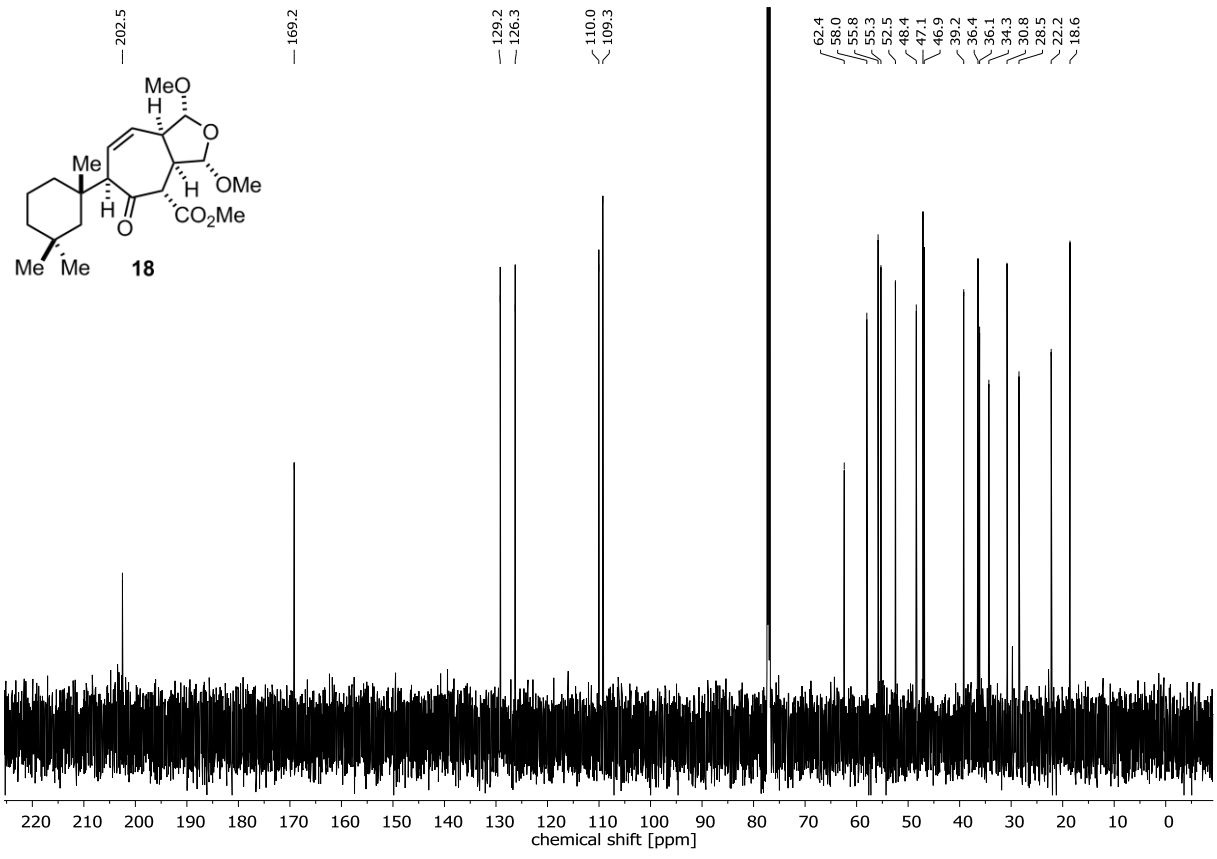

MeO
H
O
Me
H
OMe
O
CO2Me
Me Me
3
5.77
5.74
5.61
5.59
5.16
5.15
5.13
5.11
5.11
5.08
5.00
4.98
4.83
4.82
4.77
4.77
3.39
3.38
3.28
3.27
3.09
1.56
1.35
1.33
1.31
1.29
1.27
1.25
1.23
1.08
1.06
1.03
0.94
0.89
1.00
1.08
0.55
0.62
0.61
0.63
3.19
0.64
1.58
0.64
0.90
0.95
0.56
1.65
1.02
3.15
5.74
3.69
2.00
2.10
0.52
3.31
0.76
6.85
1.54
3.08
2.32
2.88
1.45
2.97
1.68
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
chemical shift [ppm]

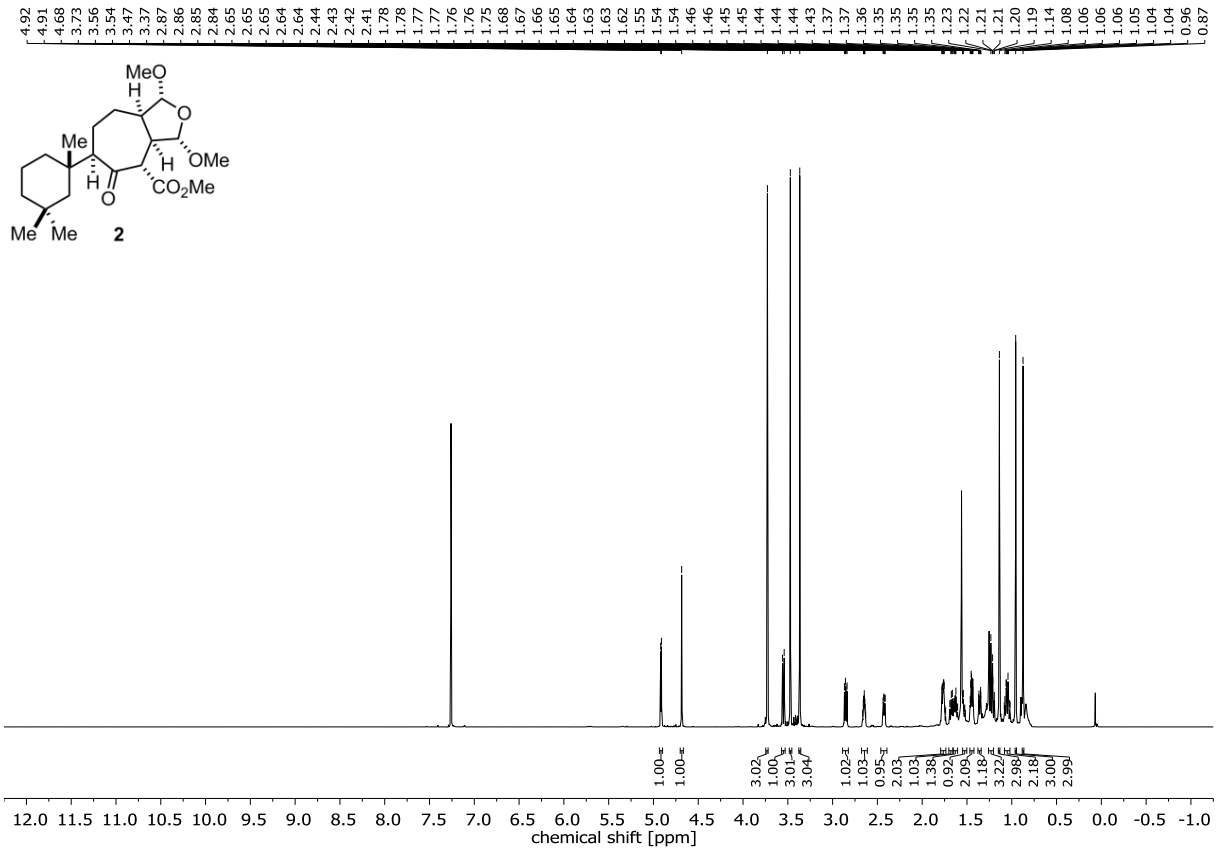

MeO
H
O
Me
H
OMe
O
CO2Me
Me Me
3
203.4
201.5
168.9
167.9
134.2
133.5
133.3
132.9
121.7
119.9
119.4
108.4
108.3
108.1
68.8
67.7
61.4
57.7
56.2
55.3
55.1
54.8
52.3
52.2
52.0
51.6
48.6
48.5
45.6
45.1
39.2
39.2
38.8
37.1
35.6
34.9
34.6
34.6
28.3
28.1
22.6
22.1
18.8
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
chemical shift [ppm]

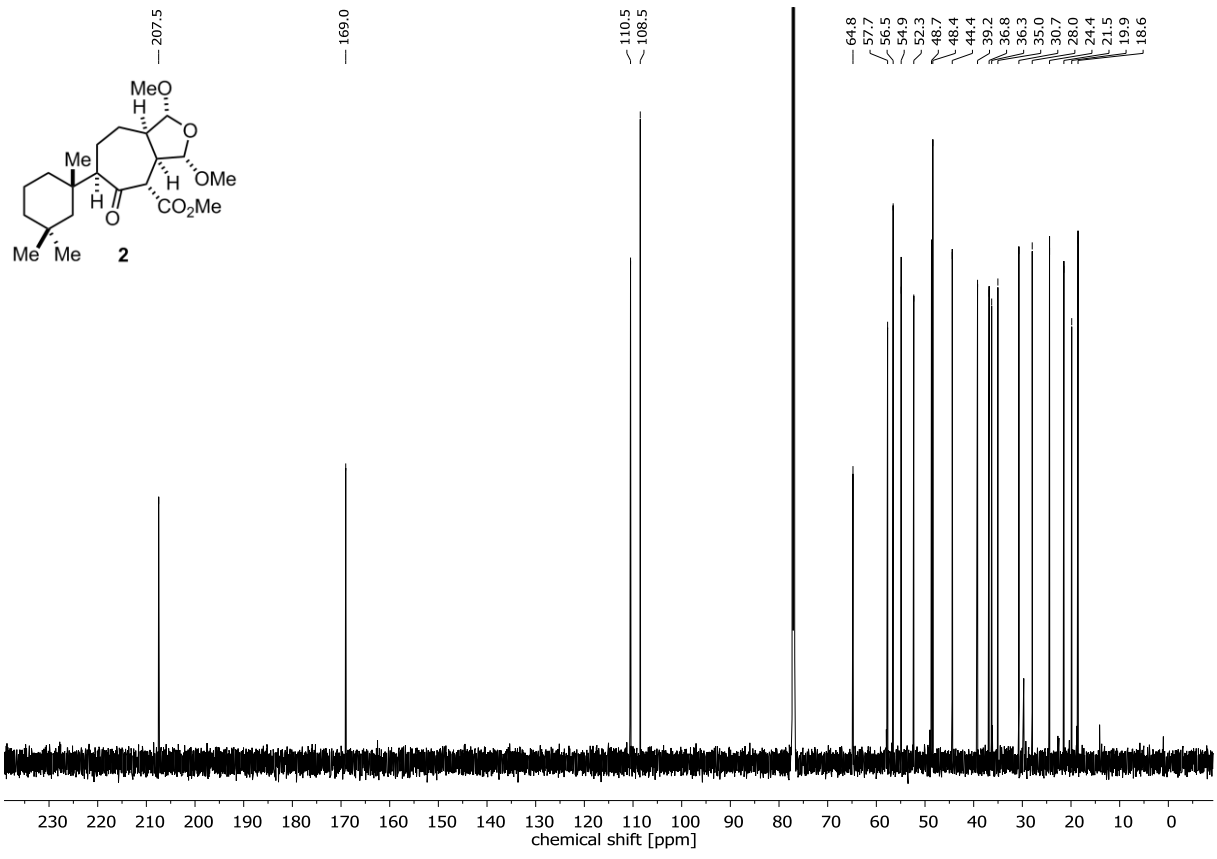

MeO
H
O
Me
H
OMe
*
H
O
CO2Me
Me Me
17
chemical shift [ppm]

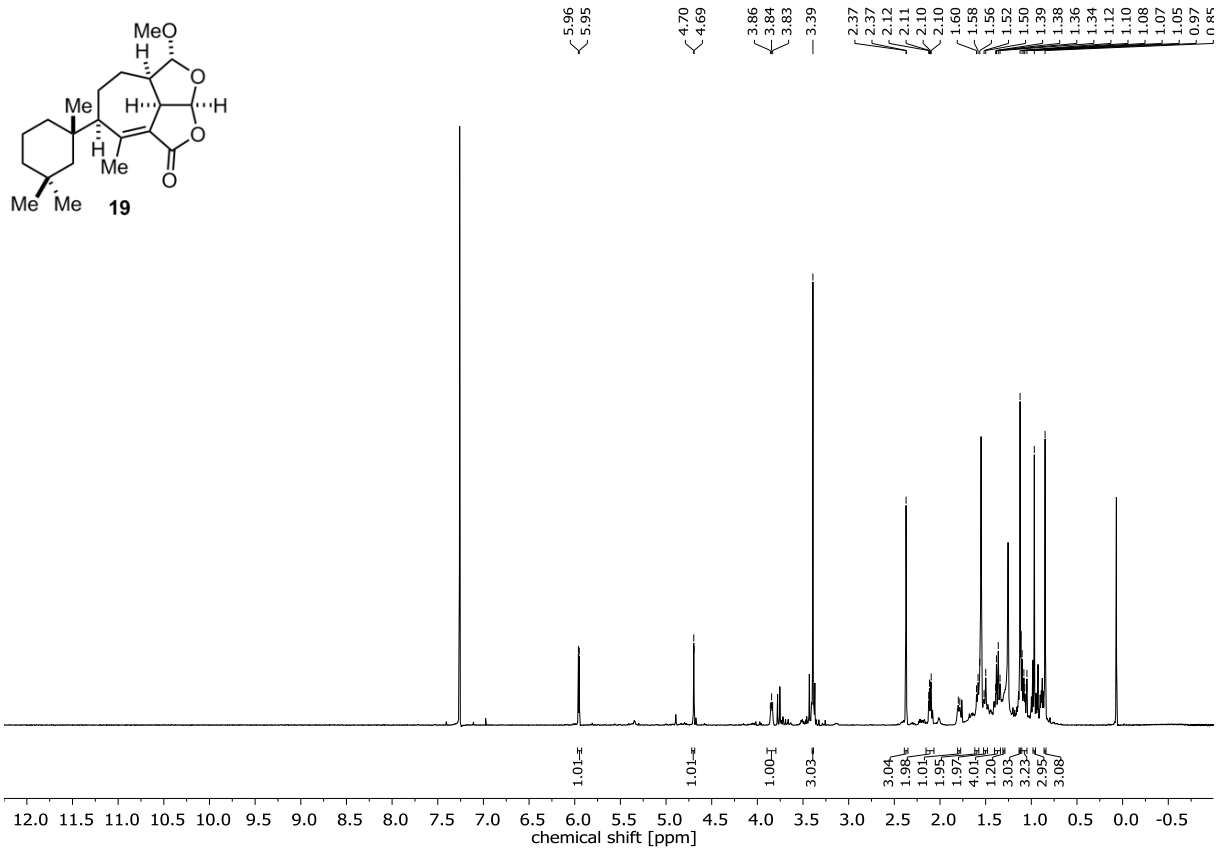

MeO
H
O
Me
H
OMe
*
H
O
CO2Me
Me Me
17
chemical shift [ppm]

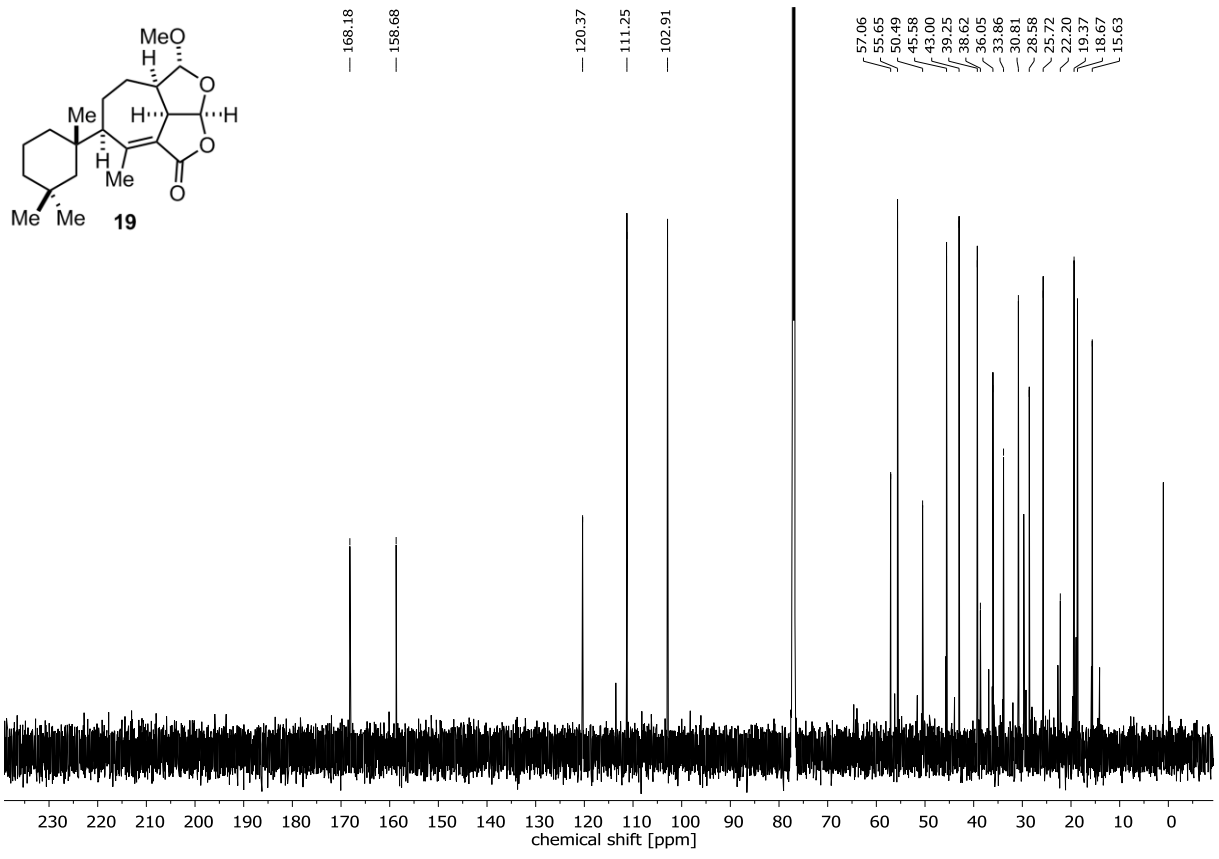

MeO
H
O
Me
H
OMe
H
O
CO2Me
Me Me
18
chemical shift [ppm]

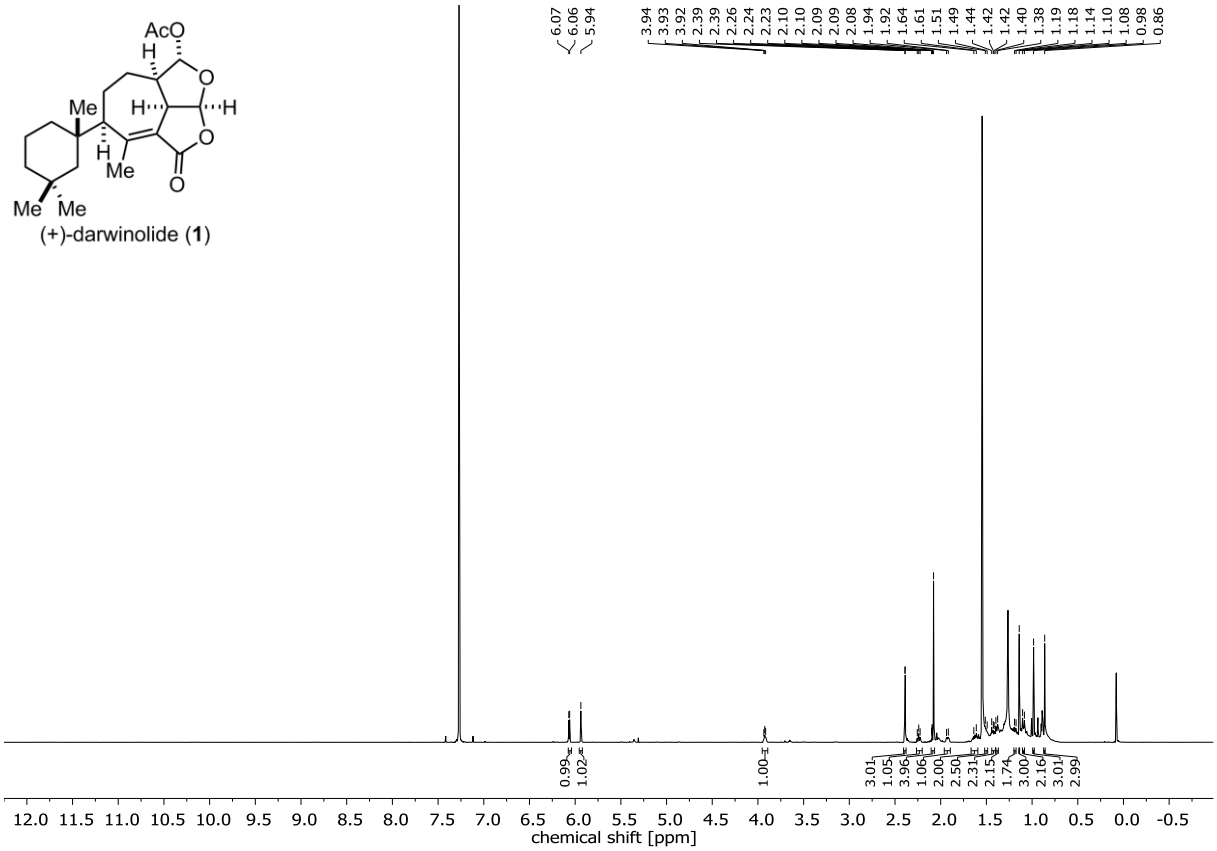

MeO
H
O
Me
H
OMe
H
O
CO2Me
Me Me
18
chemical shift [ppm]

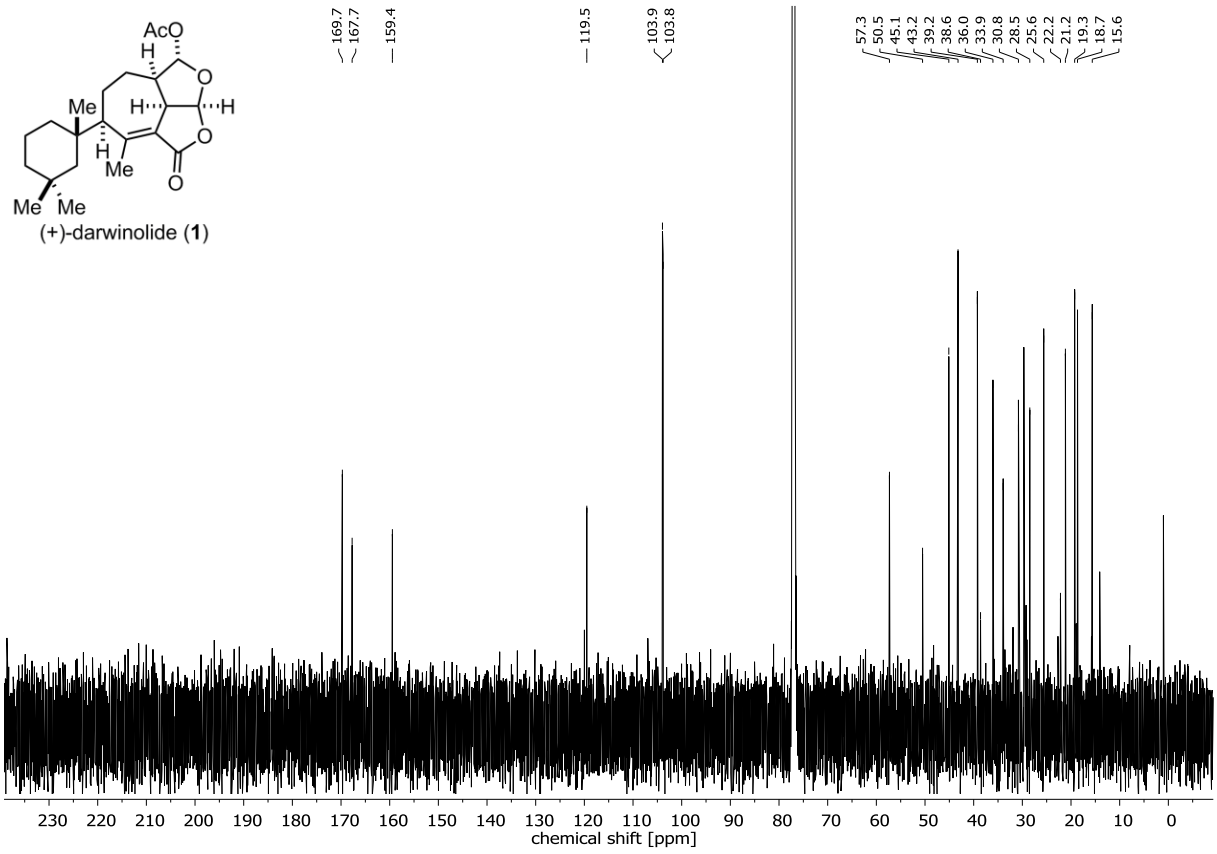

MeO
H
O
Me
H
OMe
H
O
CO2Me
Me Me
2
4.92 4.91 4.68 3.73 3.56 3.54 3.47 3.37 2.87 2.86 2.85 2.84 2.65 2.65 2.64 2.64 2.44 2.43 2.42 2.41 1.78 1.78 1.77 1.76 1.76 1.75 1.68 1.67 1.66 1.65 1.64 1.63 1.63 1.62 1.55 1.54 1.54 1.46 1.46 1.45 1.45 1.44 1.44 1.44 1.43 1.37 1.37 1.36 1.35 1.35 1.35 1.23 1.22 1.21 1.21 1.20 1.19 1.14 1.08 1.06 1.06 1.06 1.05 1.04 1.04 0.96 0.87
1.00 1.00 3.02 1.00 3.01 3.04 1.02 1.03 0.95 2.03 1.03 1.38 0.92 2.09 1.18 3.22 2.98 2.18 3.00 2.99
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
chemical shift [ppm]


207.5
169.0
110.5
108.5
64.8
57.7
56.5
54.9
52.3
48.7
48.4
44.4
39.2
36.8
36.3
35.0
30.7
28.0
24.4
21.5
19.9
18.6
MeO
H
O
Me
H
OMe
H
O
CO2Me
Me Me
2
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
chemical shift [ppm]


MeO
H
O
H
H
Me
O
H
Me
O
Me
Me
19
5.96
5.95
4.70
4.69
3.86
3.84
3.83
3.39
2.37
2.37
2.12
2.11
2.10
2.10
1.60
1.58
1.56
1.52
1.50
1.39
1.38
1.36
1.34
1.12
1.10
1.08
1.07
1.05
0.97
1.01
1.01
1.00
3.03
3.04
1.98
1.01
1.95
1.97
4.01
1.20
3.03
3.23
2.95
3.08
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
chemical shift [ppm]


MeO
H
O
H
H
Me
O
H
Me
O
Me
Me
19
168.18
158.68
120.37
111.25
102.91
57.06
55.65
50.49
45.58
43.00
39.25
38.62
36.05
33.86
30.81
28.58
25.72
22.20
19.37
18.67
15.63
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
chemical shift [ppm]


AcO
H
O
Me
H
H
O
H
Me
O
Me Me
(+)-darwinolide (1)
6.07
6.06
5.94
3.94
3.93
3.92
2.39
2.26
2.24
2.23
2.10
2.09
2.09
2.08
1.94
1.92
1.64
1.61
1.51
1.49
1.44
1.42
1.42
1.40
1.38
1.19
1.18
1.14
1.10
1.08
0.98
0.86
0.99
1.02
1.00
3.01
1.05
3.96
1.06
2.00
2.50
2.31
2.15
1.74
3.00
2.16
3.01
2.99
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
chemical shift [ppm]


AcO
H
O
Me
H
H
O
H
Me
O
Me Me
(+)-darwinolide (1)
169.7
167.7
159.4
119.5
103.9
103.8
57.3
50.5
45.1
43.2
39.2
38.6
36.0
33.9
30.8
28.5
25.6
22.2
21.2
19.3
18.7
15.6
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
chemical shift [ppm]

Literature

[1] a) K. Winska, C. Wawrzenczyk, *Pol. J. Chem.* **2007**, *81*, 1887; b) K. Winska, C. Wawrzenczyk, J. Kula, PL209581 (B1).

[2] J. A. Lafontaine, D. P. Provencal, C. Gardelli, J. W. Leahy, *J. Org. Chem.* **2003**, *68*, 4215.

[3] K. Biswas, O. Prieto, P. J. Goldsmith, S. Woodward, *Angew. Chem. Int. Ed.* **2005**, *44*, 2232.

[4] M. Ito, A. Osaku, A. Shiibashi, T. Ikariya, *Org. Lett.* **2007**, *9*, 1821.