nature portfolio

https://doi.org/10.1038/s44160-021-00010-3

Supplementary information

A computer algorithm to discover iterative sequences of organic reactions

In the format provided by the authors and unedited

Supplementary Information for Manuscript titled ***„Computer algorithm discovers iterative sequences of organic reactions"*** by K. Molga, S. Szymkuć, P, Gołębiowska, O. Popik, P. Dittwald, M. Moskal, R. Roszak, J. Mlynarski* & B.A. Grzybowski[1]*

CONTENTS

Section S1. Additional examples of unprecedented iterative sequences discovered by the "basic" algorithm from Figure 2a..... 2

Section S2. Examples of iterative sequences found by the "basic" algorithm from Figure 2a and analogous to – but not identical with – iterations already described in the literature. 6

Section S3. Additional examples of unprecedented iterative sequences found by the "advanced" algorithm from Figure 2b,c..... 7

Section S4. Examples of previously known iterative sequences rediscovered by the algorithm. 18

Section S5. General experimental procedures..... 20

Section S6. Iterative synthesis of 1,5,n polyols 21

Section S7. Iterative synthesis of 1,4,n polyols 29

Section S8. Determination of absolute configuration of newly formed stereogenic centers (Mosher ester analysis)..... 36

Section S9. Iterative synthesis of monhexocin's fragment 44

Section S10. Literature precedents of heterocycle-forming reactions. 54

Section S11. Spectroscopic data..... 55

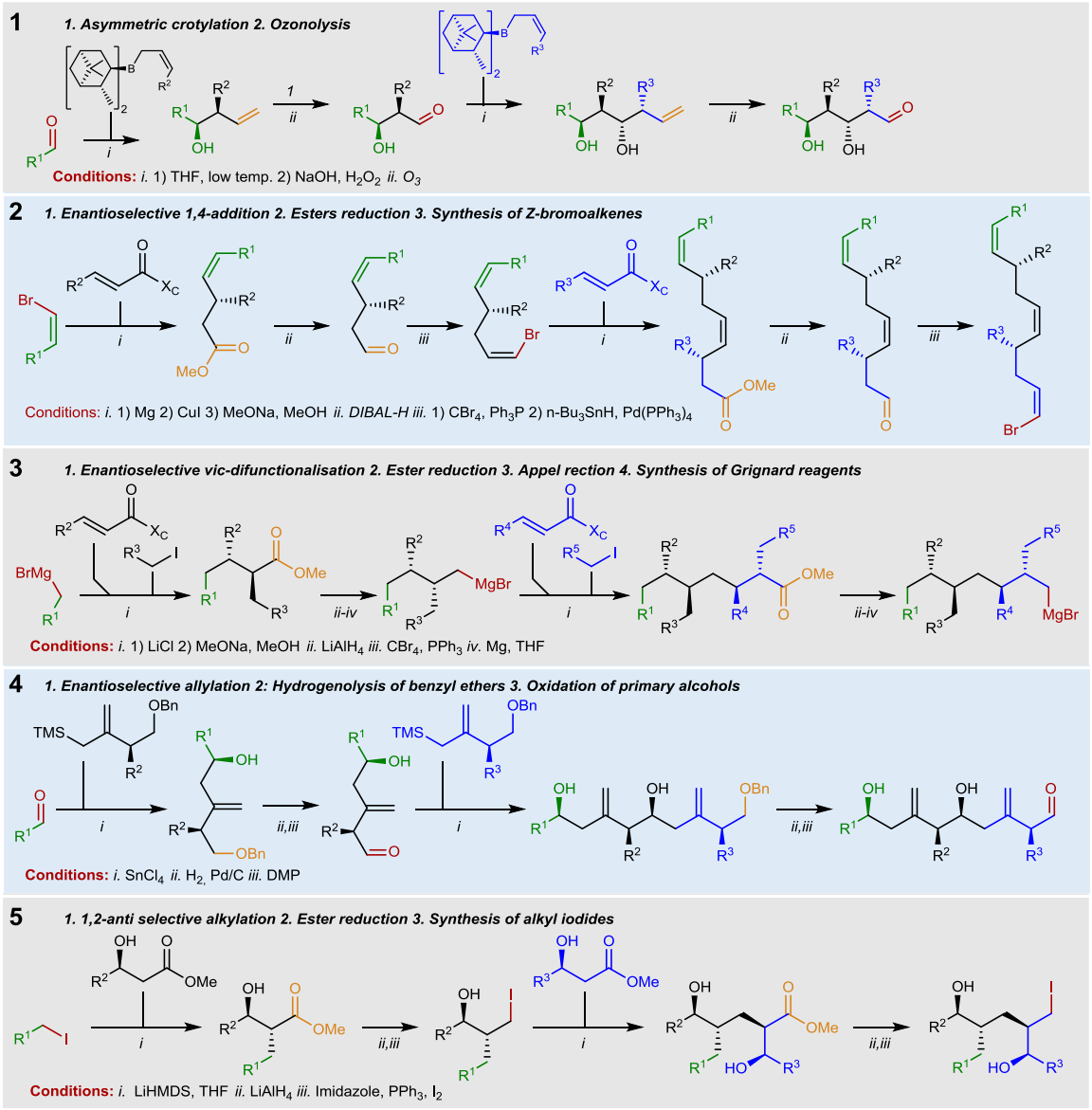
Section S12. User Manual for Allchemy's "Iterator" module..... 87

Section S13. Selection of conditions for iterative sequences. 93

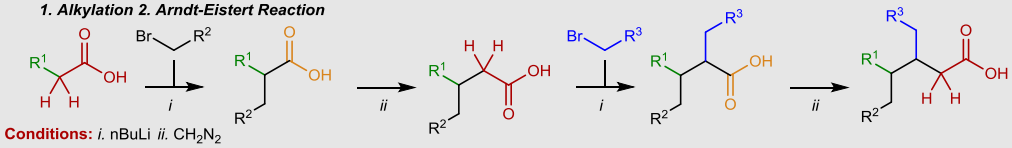
Section S14. Pseudocode for the algorithm to identify iterative sequences. 96

Section S15. References 101

Section S1. Additional examples of unprecedented iterative sequences discovered by the "basic" algorithm from Figure 2a.

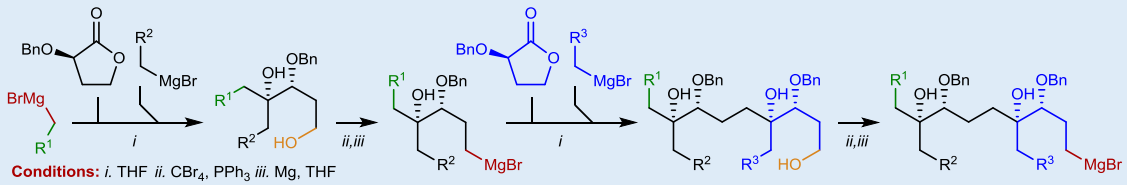


6 ***1. Alkylation 2. Arndt-Eistert Reaction***



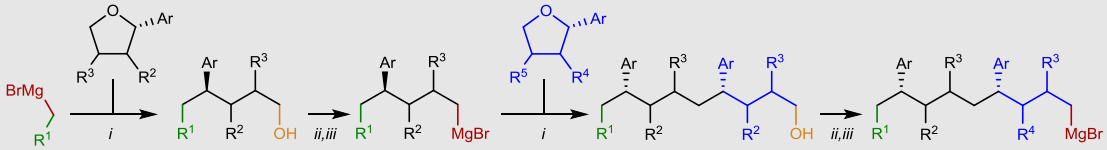
Conditions: *i.* nBuLi *ii.* CH_2N_2

7 ***1. Ring opening of lactones 2. Appel reaction 4. Synthesis of Grignard reagents***



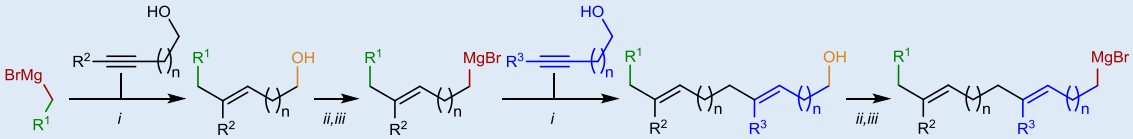
Conditions: *i.* THF *ii.* CBr_4, PPh_3 *iii.* Mg, THF

8 ***1. Opening of tetrahydrofurans 2. Appel reaction 3. Synthesis of Grignard reagents***



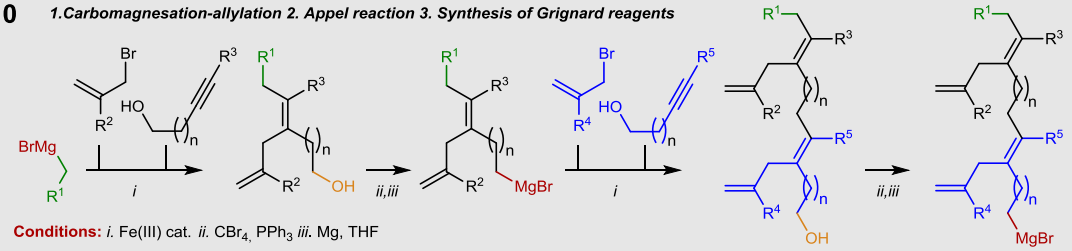
Conditions: *i.* $Ni(cod)_2$, BINAP, toluene *ii.* CBr_4, PPh_3 *iii.* Mg, THF

9 ***1.Carbomagnesation 2. Appel reaction 3. Synthesis of Grignard reagents***



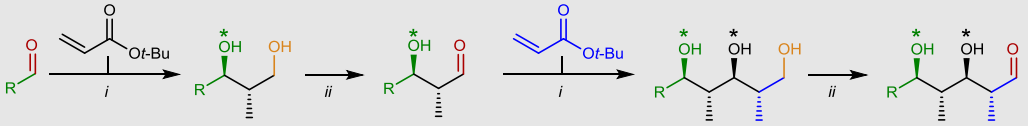
Conditions: *i.* Fe(III) cat. *ii.* CBr_4, PPh_3 *iii.* Mg, THF

10 ***1.Carbomagnesation-allylation 2. Appel reaction 3. Synthesis of Grignard reagents***



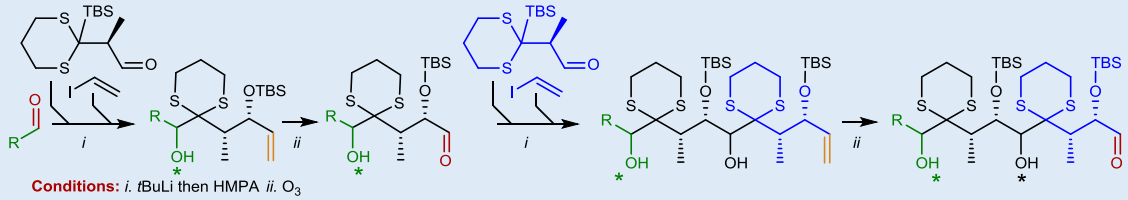
Conditions: *i.* Fe(III) cat. *ii.* CBr_4, PPh_3 *iii.* Mg, THF

11 ***1. Reductive aldol followed by reduction 2. Oxidation***



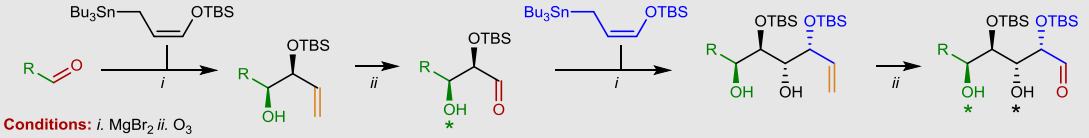
Conditions: *i.* 1) chiral.borane, Et_2O, 0 °C 2) RCHO -78 °C 3) $LiAlH_4$ *ii.* DMP

12 ***1. Tricomponent ARC-II type coupling 2. Ozonolysis***



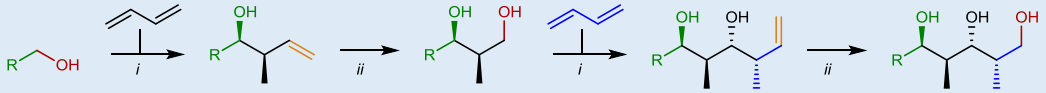
Conditions: *i.* *t*BuLi then HMPA *ii.* O_3

13 ***1. Addition of allylstannanes 2. Ozonolysis***



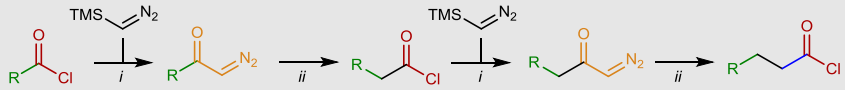
Conditions: *i.* $MgBr_2$ *ii.* O_3

14 ***1. Crotylation 2. Ozonolysis***



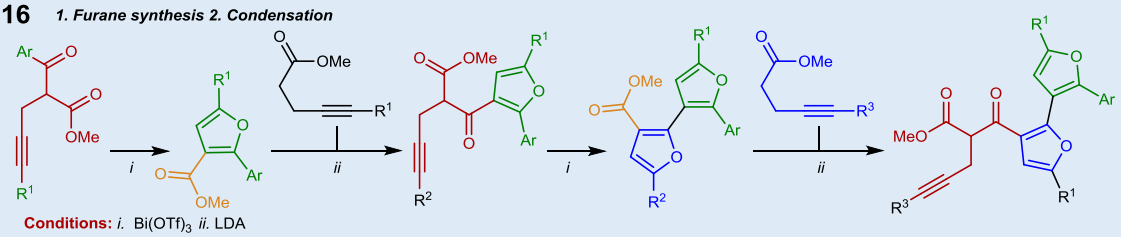
Conditions: *i.* [Ru]-complex, chiral phosphine, chiral acid *ii.* O_3 then $NaBH_4$

15 ***1.Formation of alpha-diazo carbonyls 2. Wolff rearrangement followed by formation of acid halides***



Conditions: *i.* Et_3N, THF, MeCN *ii.* 1) Ag(I) cat., hv 2) oxalyl chloride

16 ***1. Furane synthesis 2. Condensation***



Conditions: *i.* $Bi(OTf)_3$ *ii.* LDA

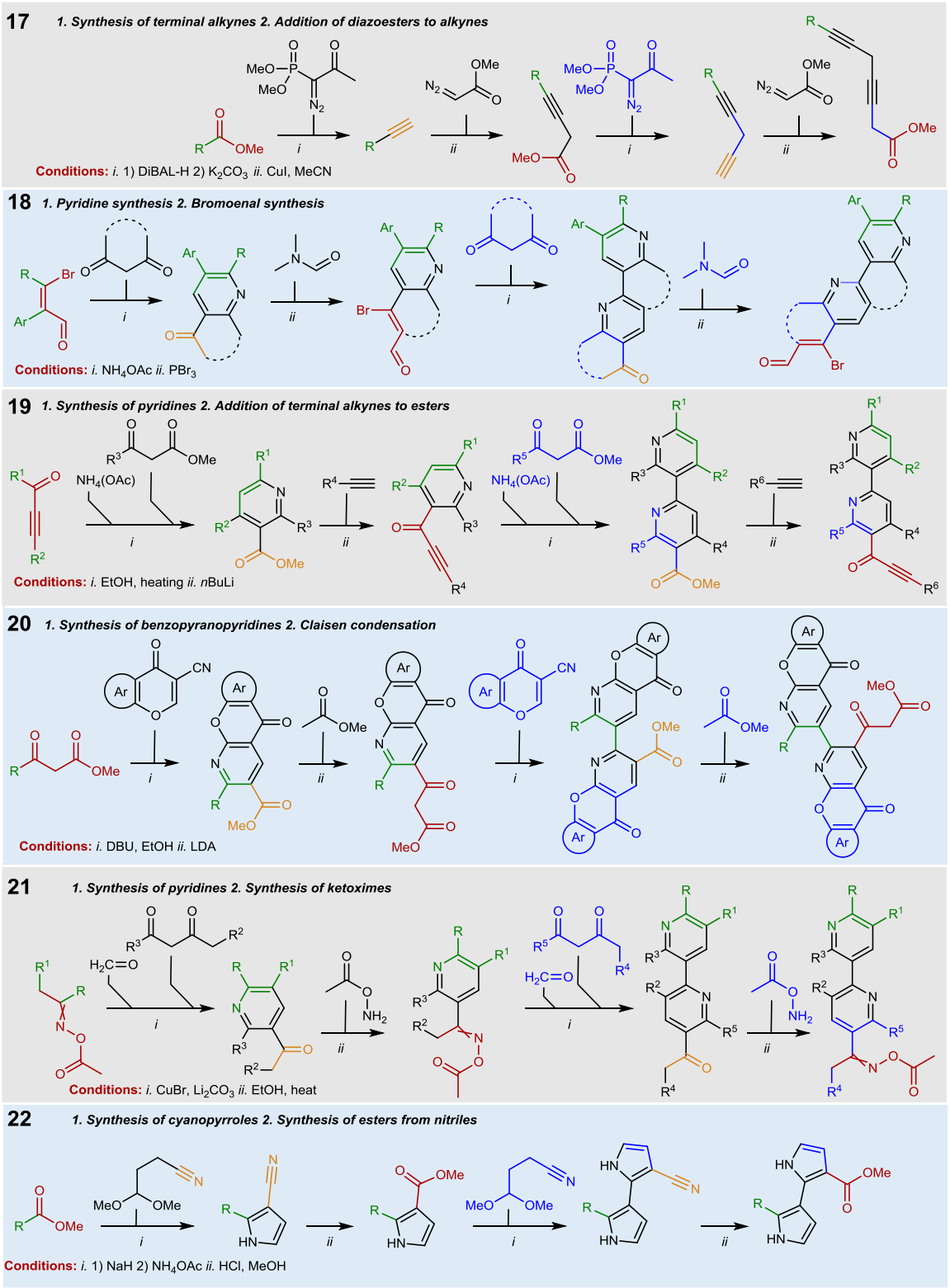


Figure S1. Examples of new iterative sequences discovered by the "basic" algorithm from main-text Figure 2a.

Section S2. Examples of iterative sequences found by the "basic" algorithm from Figure 2a and analogous to – but not identical with – iterations already described in the literature.

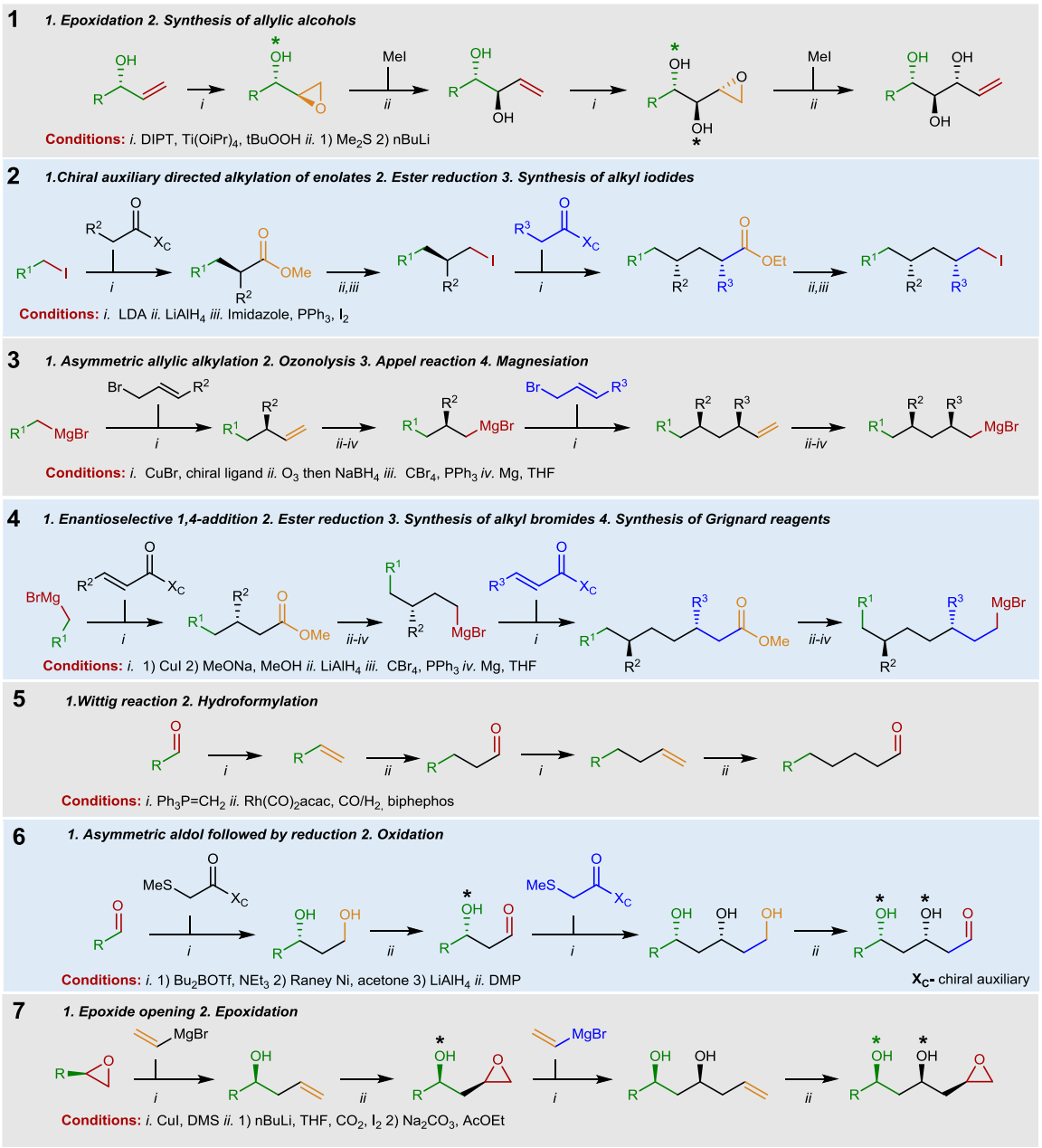
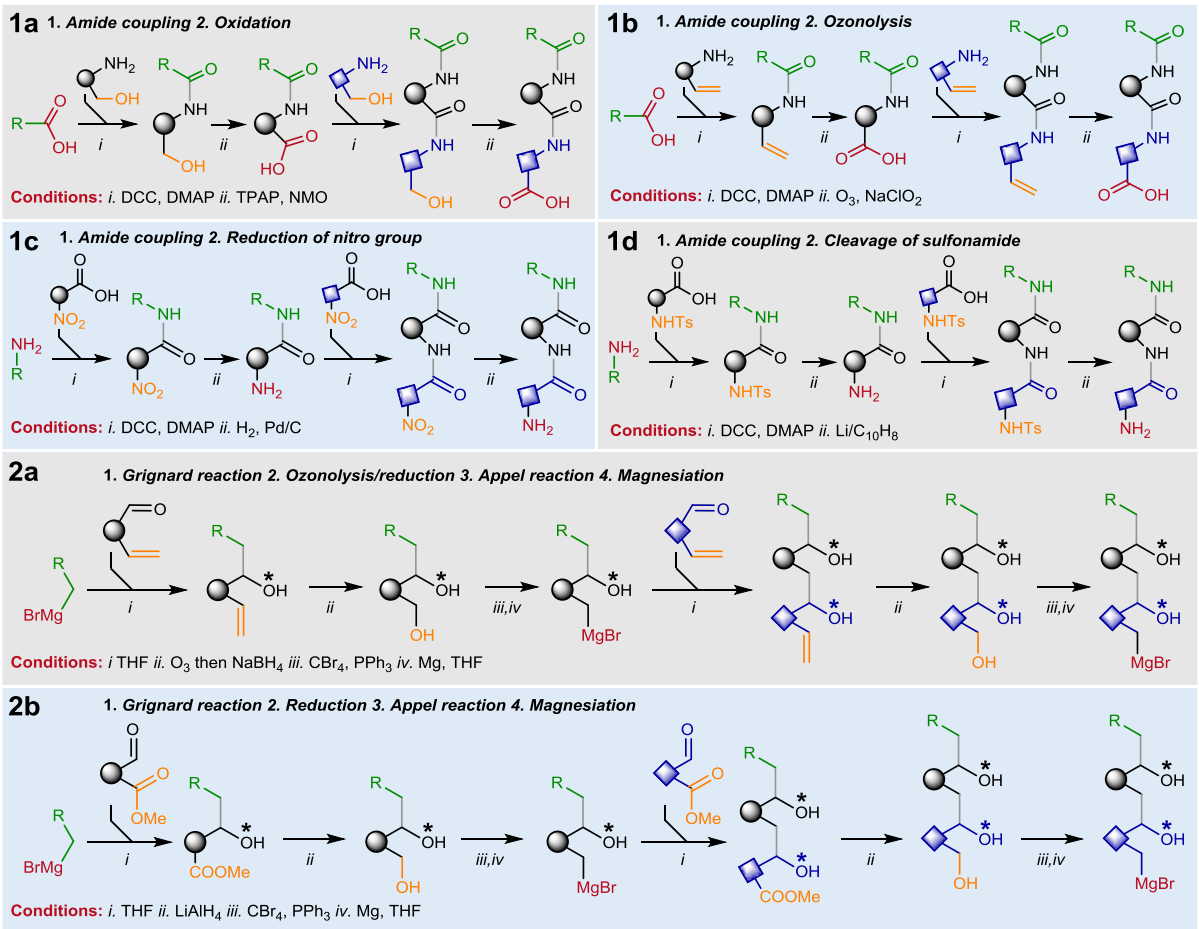
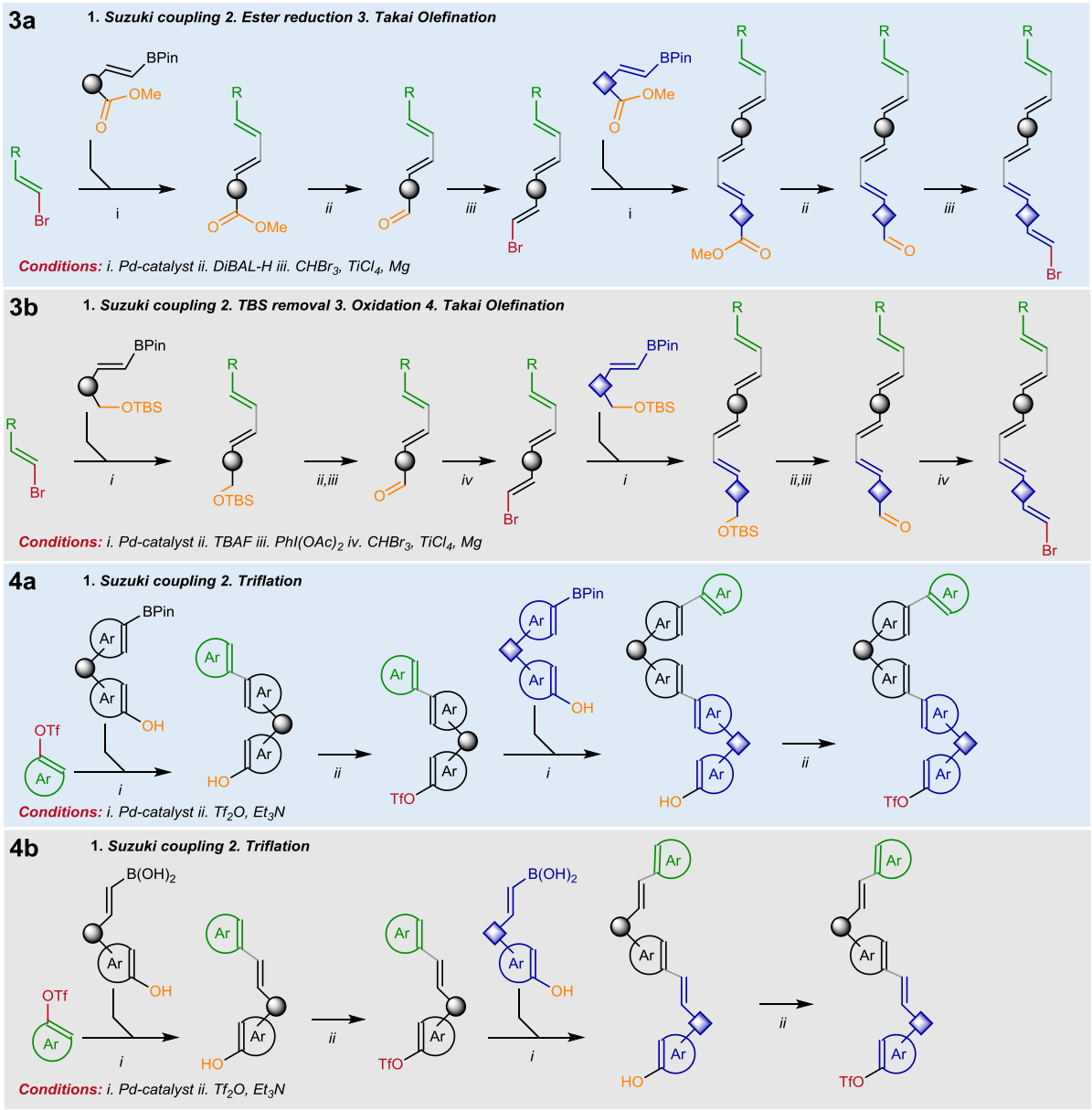


Figure S2. Examples of iterative sequences found by the "basic" algorithm from main-text Figure 2a and analogous to – but not identical with – iterations already described in the literature.

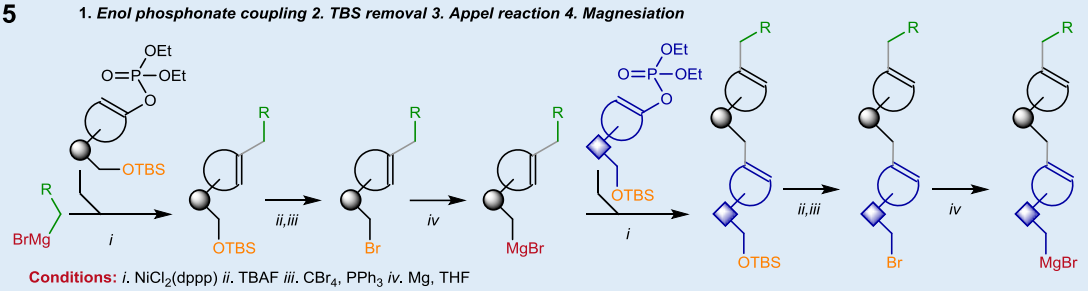
Section S3. Additional examples of unprecedented iterative sequences found by the "advanced" algorithm from Figure 2b,c.

Note: In sequences #1 and #2 below, the final structures (peptides and *1,n*-polyols) can also be prepared by known iterations. The iterations found by the algorithm are shown here because they allow for the use of alternative reagents and/or conditions. For example, amines and carboxylic acids used in known (also rediscovered by our algorithm) iterative amide couplings are commonly regenerated either under acidic (from –NHBoc/–COOtBu groups) or basic (from –NHFmoc/-COOEt groups) conditions. Sequences 1A-D shown below enable regeneration of necessary functional groups under reductive (amine from sulfonamide or nitro groups) or oxidative (carboxylic acid from alcohol or alkene) conditions thus enabling coupling with substrates possessing both acid- and base-labile fragments.



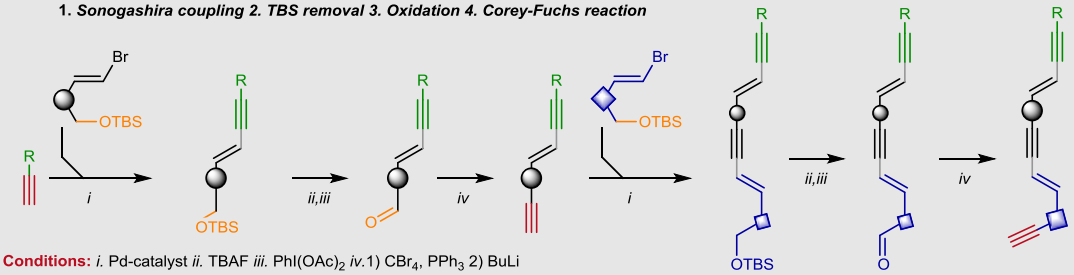

3a
1. Suzuki coupling 2. Ester reduction 3. Takai Olefination
Conditions: i. Pd-catalyst ii. DiBAL-H iii. CHBr3, TiCl4, Mg
3b
1. Suzuki coupling 2. TBS removal 3. Oxidation 4. Takai Olefination
Conditions: i. Pd-catalyst ii. TBAF iii. PhI(OAc)2 iv. CHBr3, TiCl4, Mg
4a
1. Suzuki coupling 2. Triflation
Conditions: i. Pd-catalyst ii. Tf2O, Et3N
4b
1. Suzuki coupling 2. Triflation
Conditions: i. Pd-catalyst ii. Tf2O, Et3N

5 **1. *Enol phosphonate coupling 2. TBS removal 3. Appel reaction 4. Magnesiation***



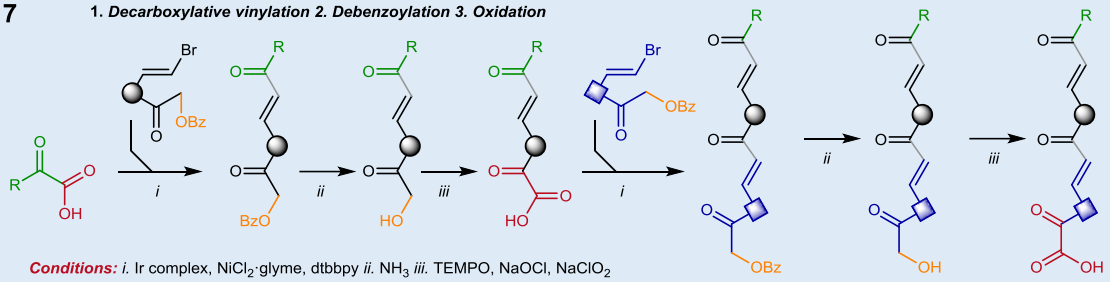
Conditions: *i.* $NiCl_2(dppp)$ *ii.* TBAF *iii.* CBr_4, PPh_3 *iv.* Mg, THF

6 **1. *Sonogashira coupling 2. TBS removal 3. Oxidation 4. Corey-Fuchs reaction***



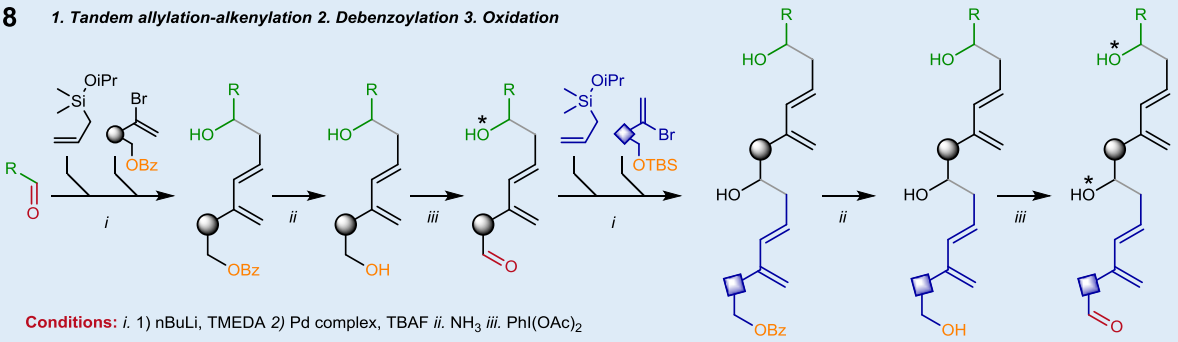
Conditions: *i.* Pd-catalyst *ii.* TBAF *iii.* $PhI(OAc)_2$ *iv.*1) CBr_4, PPh_3 2) BuLi

7 **1. *Decarboxylative vinylation 2. Debenzoylation 3. Oxidation***



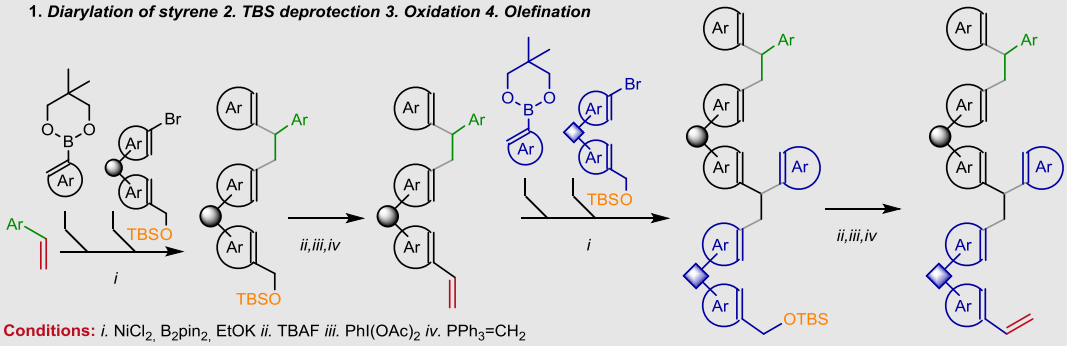
Conditions: *i.* Ir complex, $NiCl_2$·glyme, dtbbpy *ii.* NH_3 *iii.* TEMPO, NaOCl, $NaClO_2$

8 ***1. Tandem allylation-alkenylation 2. Debenzoylation 3. Oxidation***



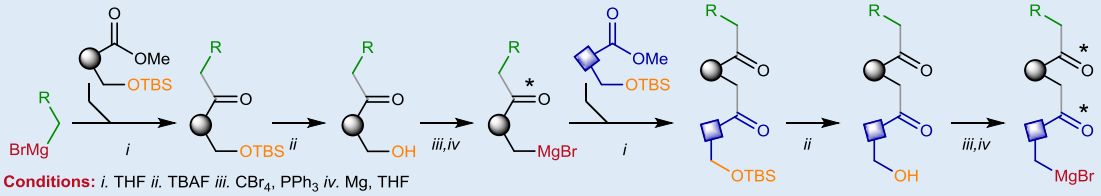
Conditions: *i.* 1) nBuLi, TMEDA *2)* Pd complex, TBAF *ii.* NH_3 *iii.* $PhI(OAc)_2$

9 ***1. Diarylation of styrene 2. TBS deprotection 3. Oxidation 4. Olefination***



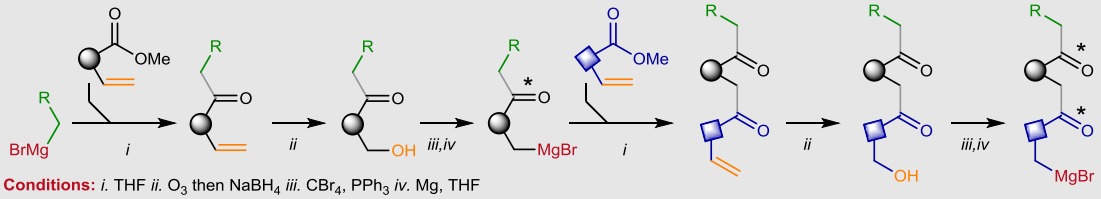
Conditions: *i.* $NiCl_2$, B_2pin_2, EtOK *ii.* TBAF *iii.* $PhI(OAc)_2$ *iv.* $PPh_3{=}CH_2$

10 ***1. Addition of organometallics to esters 2. TBS deprotection 3. Appel reaction 4. Magnesiation***



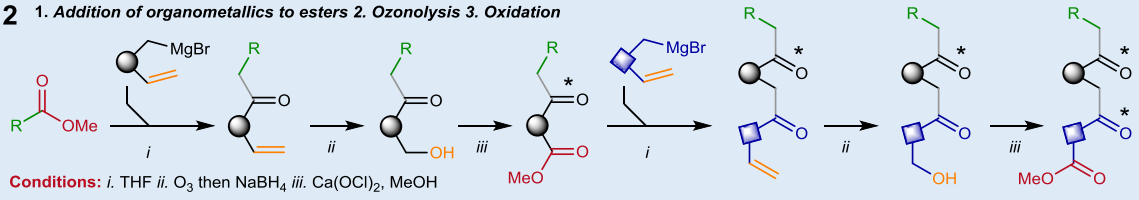
Conditions: *i.* THF *ii.* TBAF *iii.* CBr_4, PPh_3 *iv.* Mg, THF

11 ***1. Addition of organometallics to esters 2. Ozonolysis 3. Appel reaction 4. Magnesiation***



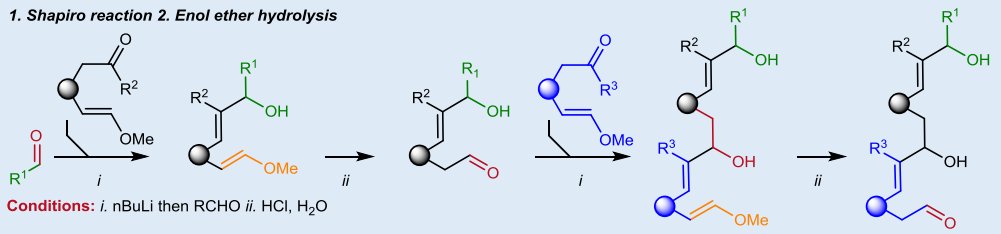
Conditions: *i.* THF *ii.* O_3 then $NaBH_4$ *iii.* CBr_4, PPh_3 *iv.* Mg, THF

12 ***1. Addition of organometallics to esters 2. Ozonolysis 3. Oxidation***



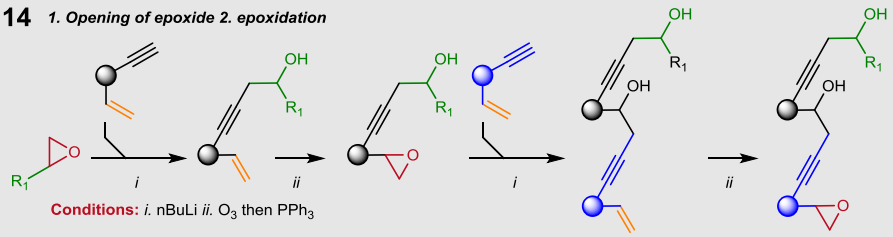
Conditions: *i.* THF *ii.* O_3 then $NaBH_4$ *iii.* $Ca(OCl)_2$, MeOH

13 ***1. Shapiro reaction 2. Enol ether hydrolysis***



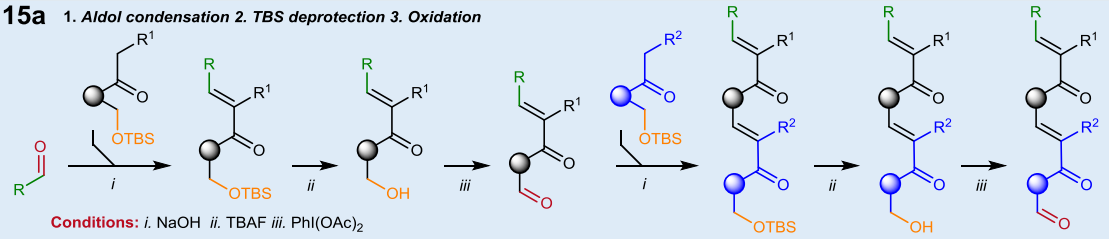
Conditions: *i.* nBuLi then RCHO *ii.* HCl, H_2O

14 ***1. Opening of epoxide 2. epoxidation***



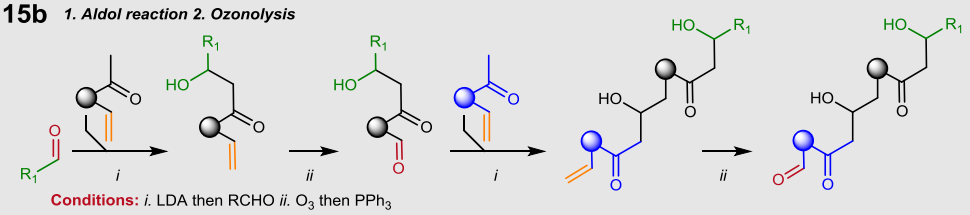
Conditions: *i.* nBuLi *ii.* O_3 then PPh_3

15a ***1. Aldol condensation 2. TBS deprotection 3. Oxidation***



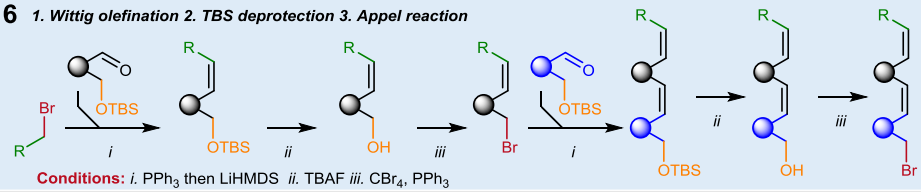
Conditions: *i.* NaOH *ii.* TBAF *iii.* $PhI(OAc)_2$

15b ***1. Aldol reaction 2. Ozonolysis***



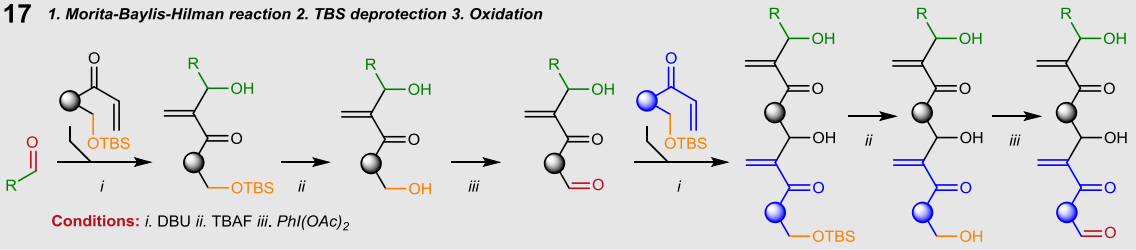
Conditions: *i.* LDA then RCHO *ii.* O_3 then PPh_3

16 ***1. Wittig olefination 2. TBS deprotection 3. Appel reaction***



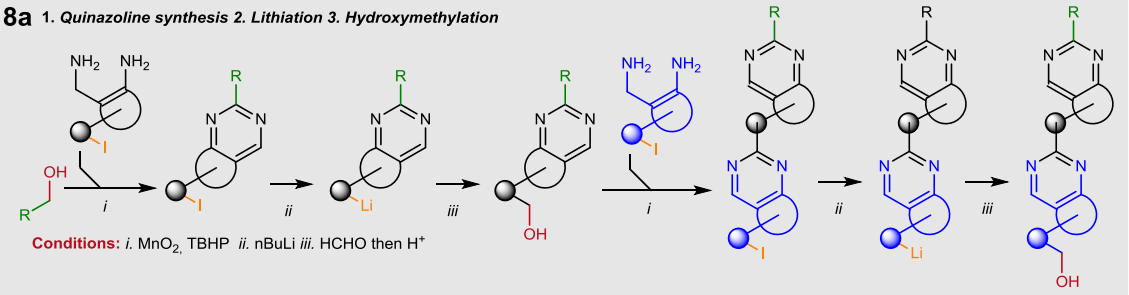
Conditions: *i.* PPh_3 then LiHMDS *ii.* TBAF *iii.* CBr_4, PPh_3

17 ***1. Morita-Baylis-Hilman reaction 2. TBS deprotection 3. Oxidation***

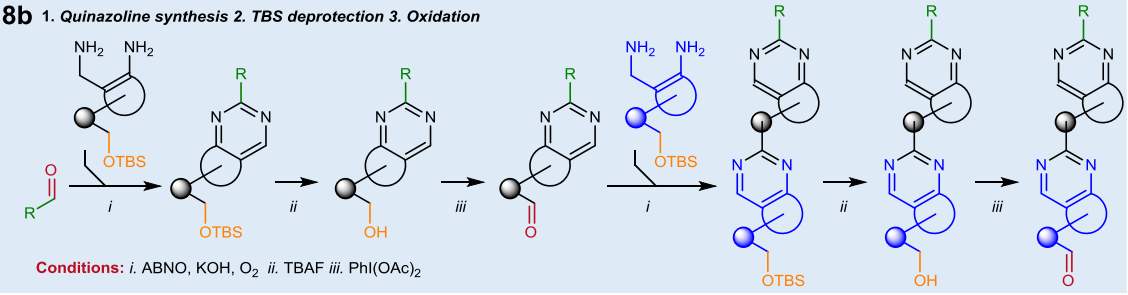


Conditions: *i.* DBU *ii.* TBAF *iii. PhI(OAc)*$_2$

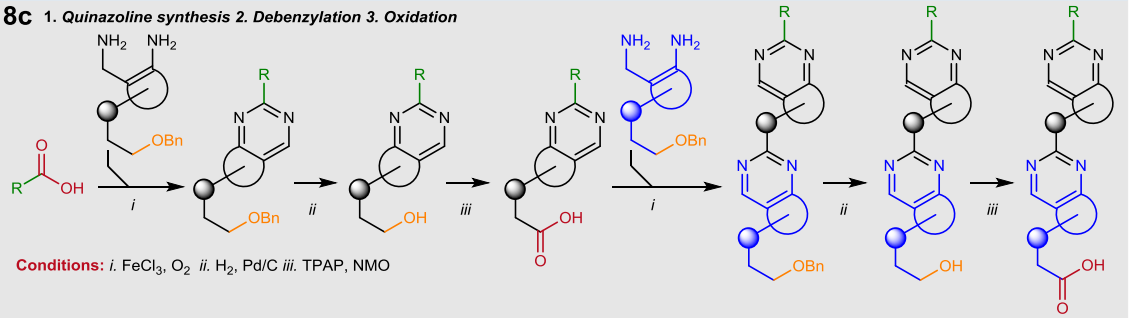
18a 1. *Quinazoline synthesis 2. Lithiation 3. Hydroxymethylation*

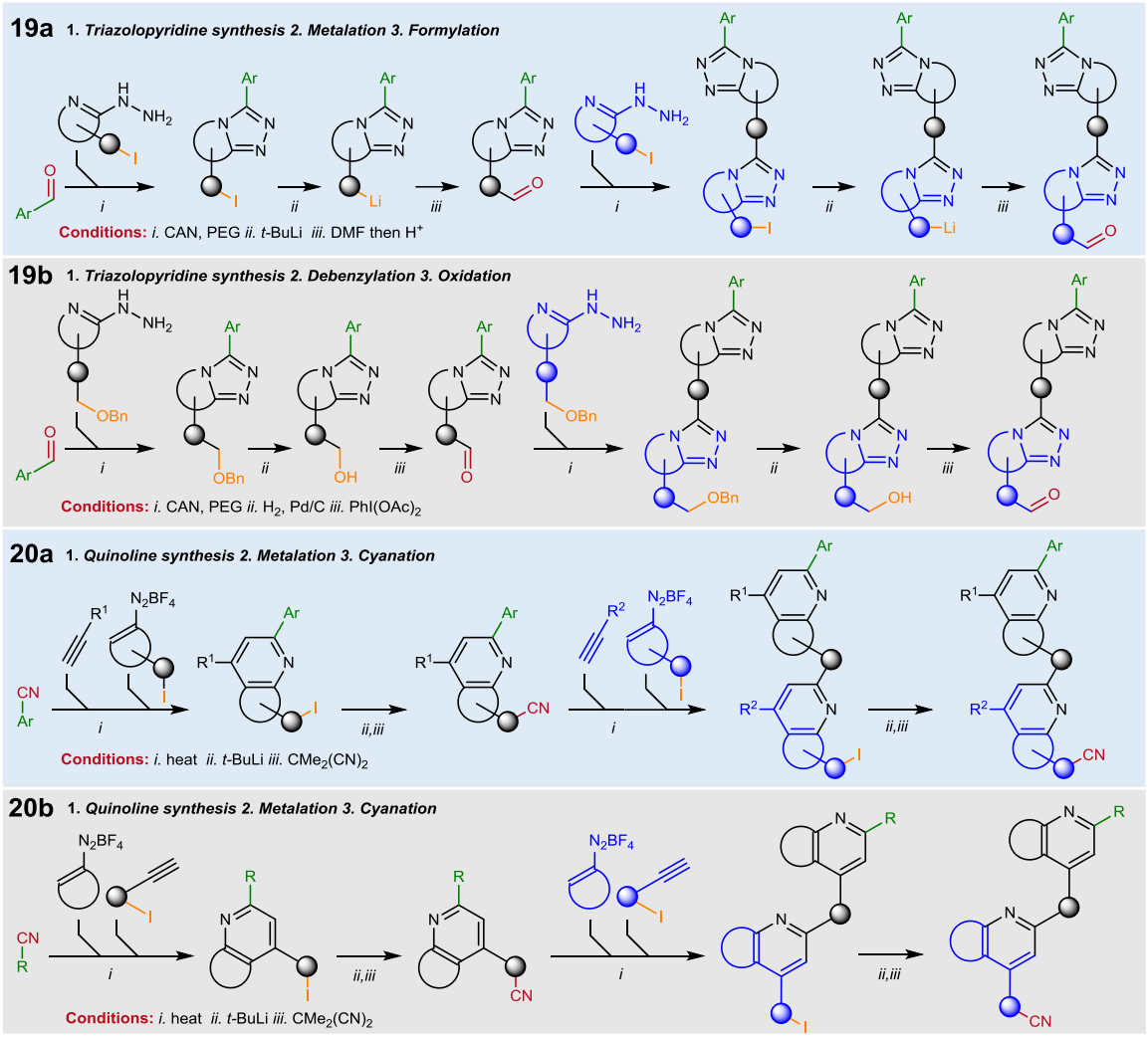


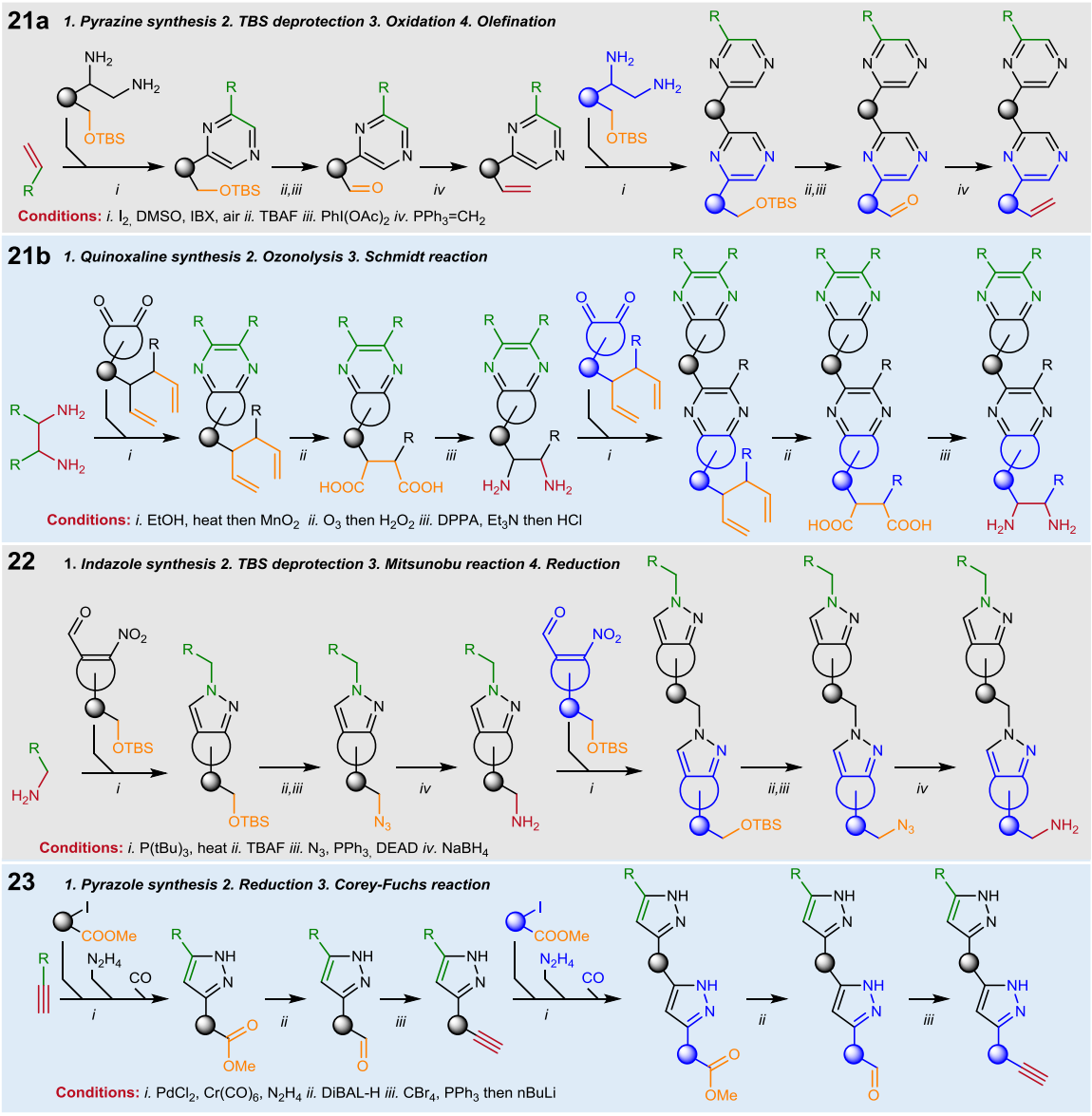
18b 1. *Quinazoline synthesis 2. TBS deprotection 3. Oxidation*



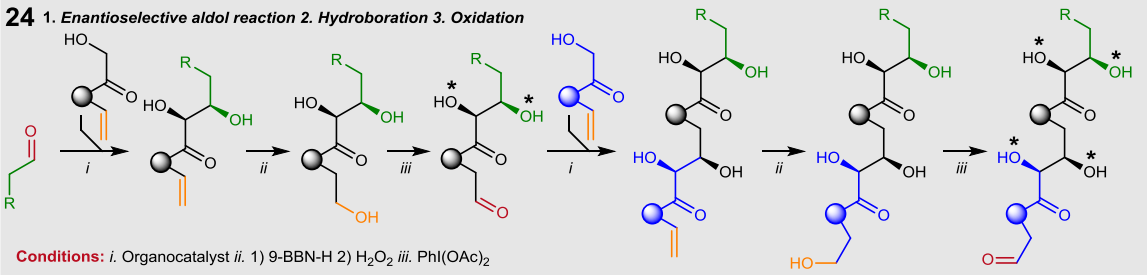
18c 1. *Quinazoline synthesis 2. Debenzylation 3. Oxidation*




19a 1. Triazolopyridine synthesis 2. Metalation 3. Formylation
Conditions: i. CAN, PEG ii. t-BuLi iii. DMF then H+
19b 1. Triazolopyridine synthesis 2. Debenzylation 3. Oxidation
Conditions: i. CAN, PEG ii. H2, Pd/C iii. PhI(OAc)2
20a 1. Quinoline synthesis 2. Metalation 3. Cyanation
Conditions: i. heat ii. t-BuLi iii. CMe2(CN)2
20b 1. Quinoline synthesis 2. Metalation 3. Cyanation
Conditions: i. heat ii. t-BuLi iii. CMe2(CN)2

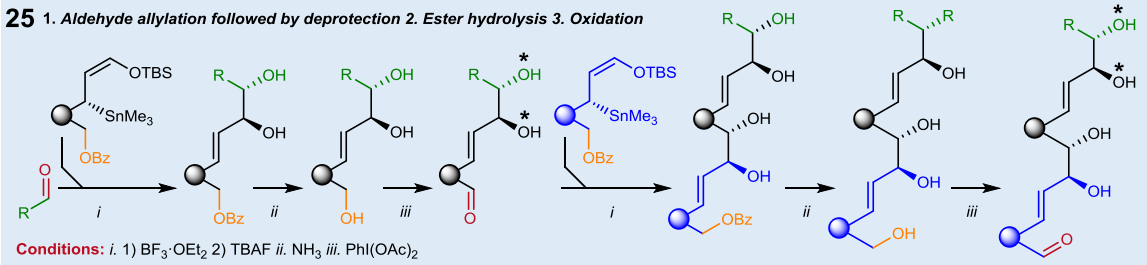

21a 1. Pyrazine synthesis 2. TBS deprotection 3. Oxidation 4. Olefination
Conditions: i. I2, DMSO, IBX, air ii. TBAF iii. PhI(OAc)2 iv. PPh3=CH2
21b 1. Quinoxaline synthesis 2. Ozonolysis 3. Schmidt reaction
Conditions: i. EtOH, heat then MnO2 ii. O3 then H2O2 iii. DPPA, Et3N then HCl
22 1. Indazole synthesis 2. TBS deprotection 3. Mitsunobu reaction 4. Reduction
Conditions: i. P(tBu)3, heat ii. TBAF iii. N3, PPh3, DEAD iv. NaBH4
23 1. Pyrazole synthesis 2. Reduction 3. Corey-Fuchs reaction
Conditions: i. PdCl2, Cr(CO)6, N2H4 ii. DiBAL-H iii. CBr4, PPh3 then nBuLi

24 1. ***Enantioselective aldol reaction 2. Hydroboration 3. Oxidation***



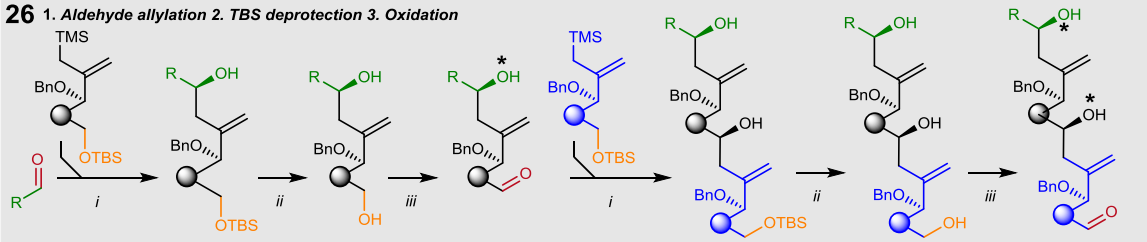
Conditions: *i.* Organocatalyst *ii.* 1) 9-BBN-H 2) H_2O_2 *iii.* $PhI(OAc)_2$

25 1. ***Aldehyde allylation followed by deprotection 2. Ester hydrolysis 3. Oxidation***



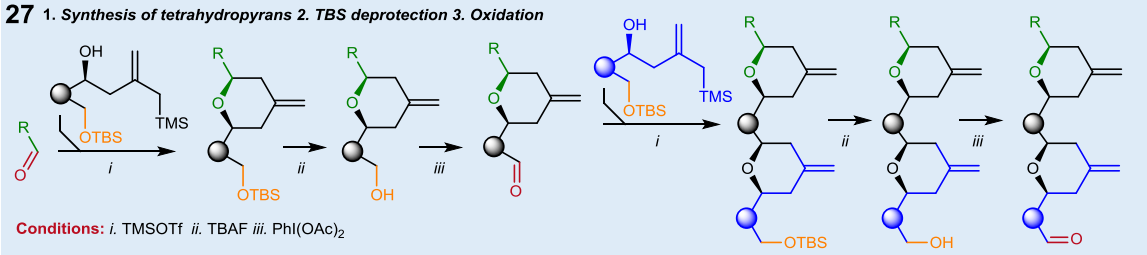
Conditions: *i.* 1) $BF_3{\cdot}OEt_2$ 2) TBAF *ii.* NH_3 *iii.* $PhI(OAc)_2$

26 1. ***Aldehyde allylation 2. TBS deprotection 3. Oxidation***



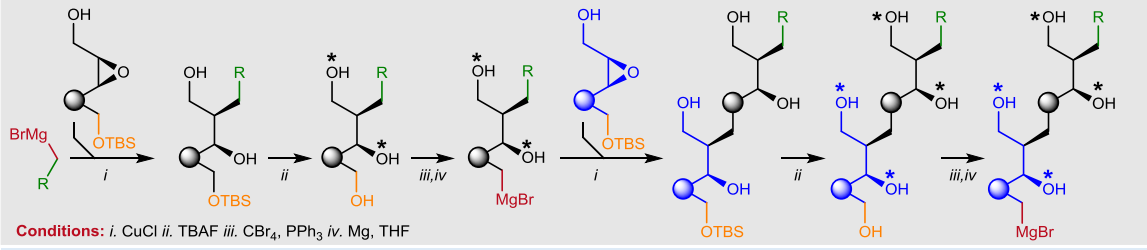
Conditions: *i.* $SnCl_4$ *ii.* TBAF *iii.* $PhI(OAc)_2$

27 1. ***Synthesis of tetrahydropyrans 2. TBS deprotection 3. Oxidation***



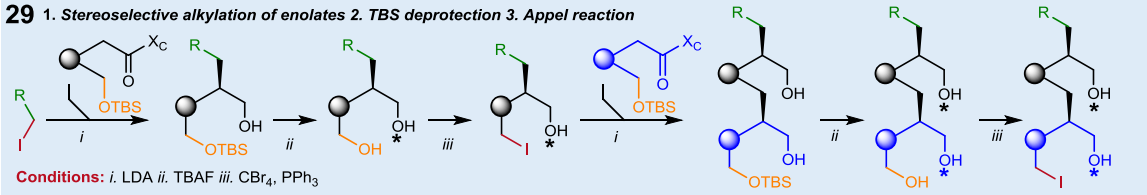
Conditions: *i.* TMSOTf *ii.* TBAF *iii.* $PhI(OAc)_2$

28 1. ***Opening of epoxides 2. TBS deprotection 3. Appel reaction 4. Magnesiation***



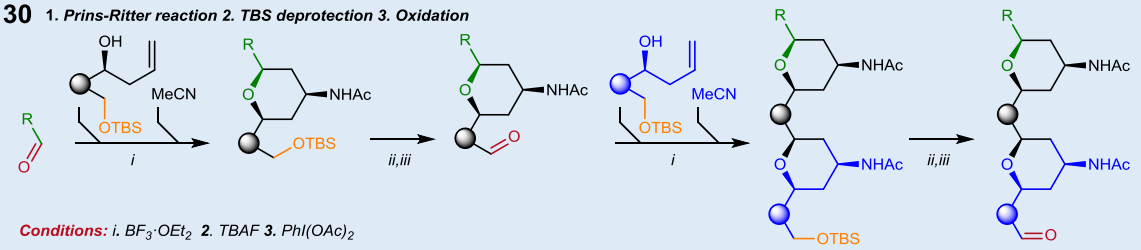
Conditions: *i.* CuCl *ii.* TBAF *iii.* CBr_4, PPh_3 *iv.* Mg, THF

29 1. ***Stereoselective alkylation of enolates 2. TBS deprotection 3. Appel reaction***



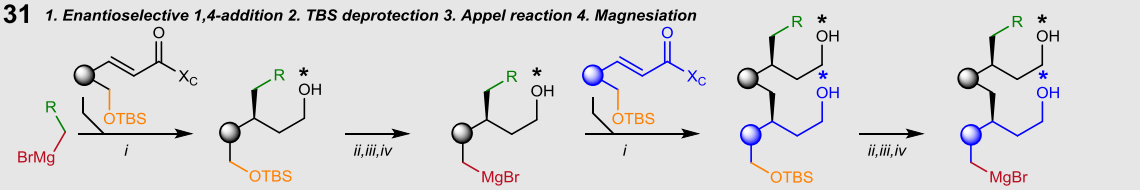
Conditions: *i.* LDA *ii.* TBAF *iii.* CBr_4, PPh_3

30 **1. *Prins-Ritter reaction 2. TBS deprotection 3. Oxidation***



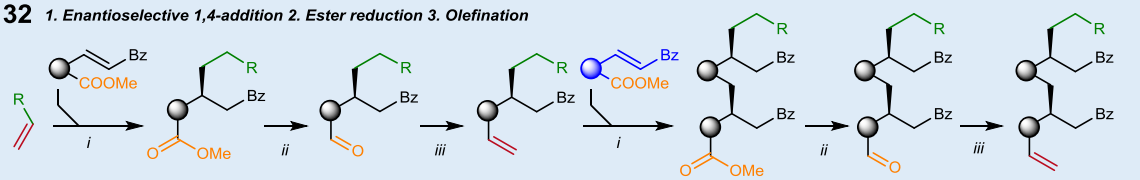
Conditions: *i.* $BF_3{\cdot}OEt_2$ **2.** *TBAF* **3.** $PhI(OAc)_2$

31 ***1. Enantioselective 1,4-addition 2. TBS deprotection 3. Appel reaction 4. Magnesiation***



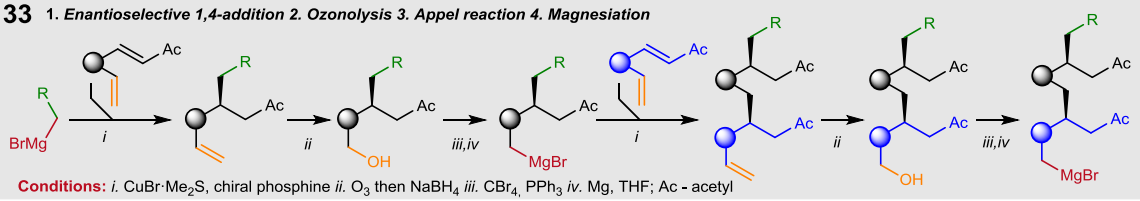
Conditions: *i.* CuI, TMSCl *ii.* TBAF *iii.* CBr_4, PPh_3 *iv.* Mg, THF

32 ***1. Enantioselective 1,4-addition 2. Ester reduction 3. Olefination***



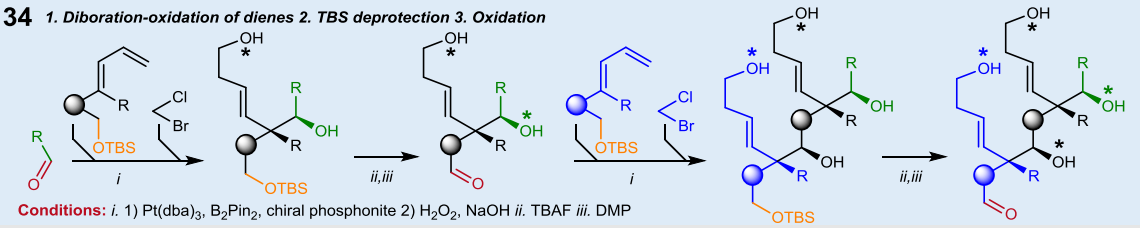
Conditions: *i.* 1) Cp_2ZrHCl 2) CuCl, AgOTf, TMSCl, chiral ligand *ii.* DiBAL-H iii. $Ph_3P{=}CH_2$; Bz - benzoyl

33 ***1. Enantioselective 1,4-addition 2. Ozonolysis 3. Appel reaction 4. Magnesiation***



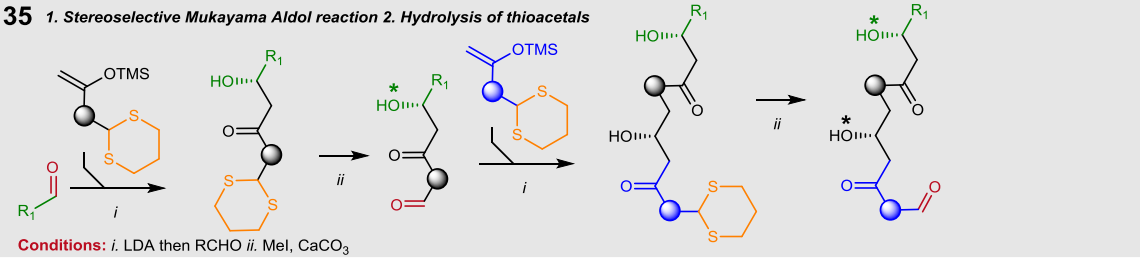
Conditions: *i.* $CuBr{\cdot}Me_2S$, chiral phosphine *ii.* O_3 then $NaBH_4$ *iii.* CBr_4, PPh_3 *iv.* Mg, THF; Ac - acetyl

34 ***1. Diboration-oxidation of dienes 2. TBS deprotection 3. Oxidation***



Conditions: *i.* 1) $Pt(dba)_3$, B_2Pin_2, chiral phosphonite 2) H_2O_2, NaOH *ii.* TBAF *iii.* DMP

35 ***1. Stereoselective Mukayama Aldol reaction 2. Hydrolysis of thioacetals***



Conditions: *i.* LDA then RCHO *ii.* MeI, $CaCO_3$

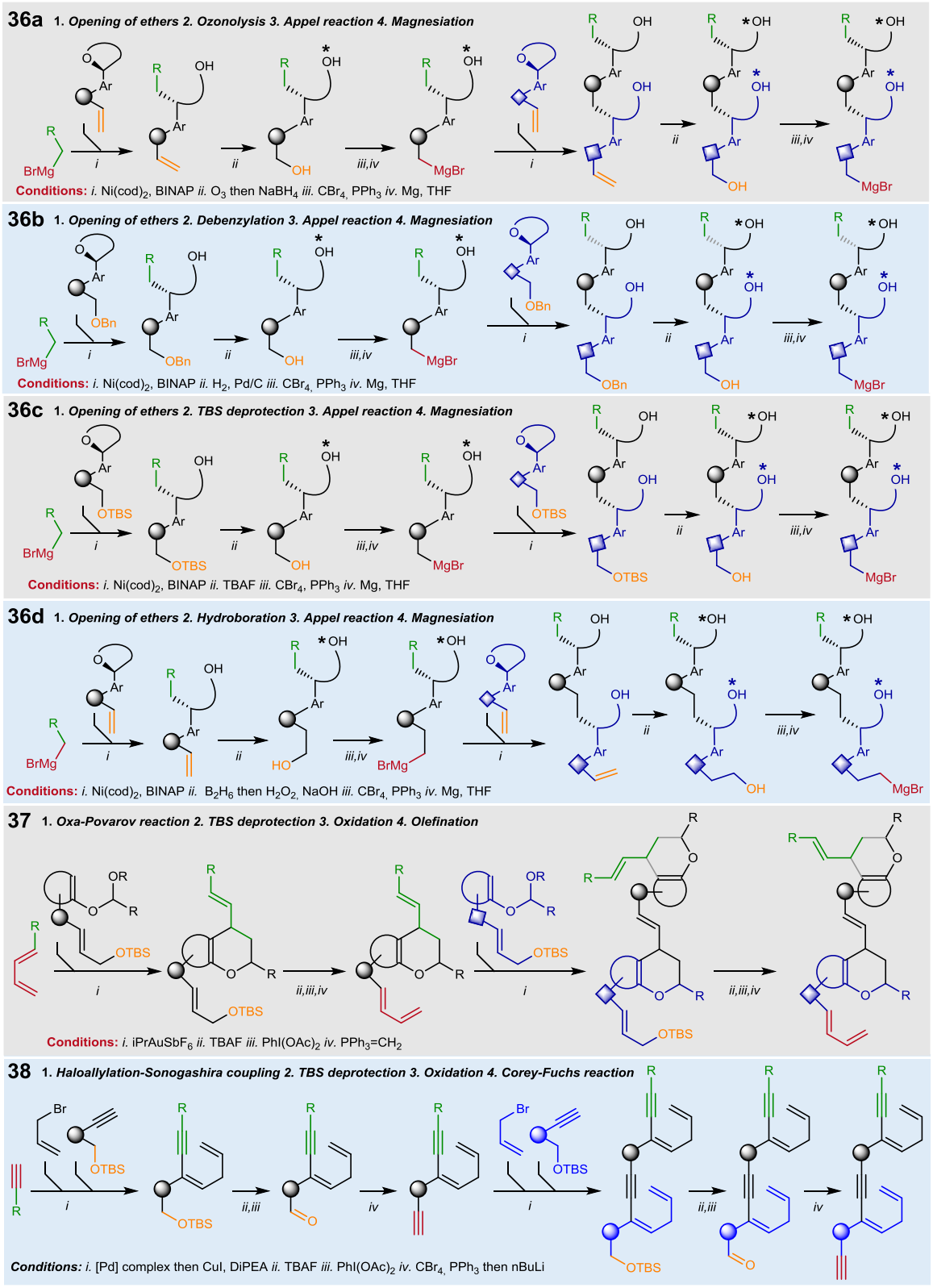
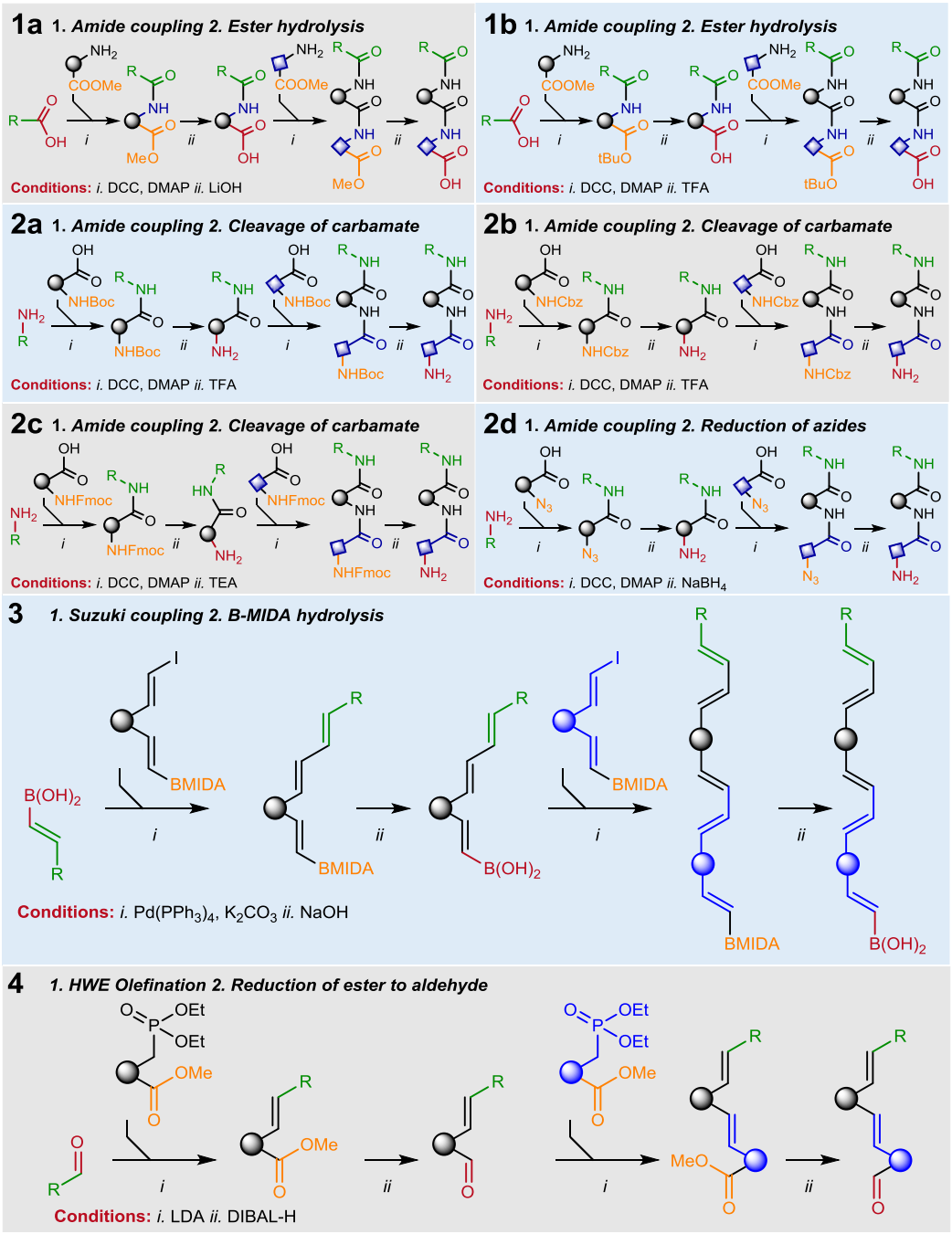


Figure S3. Additional examples of new iterative sequences found by the "advanced" algorithm from main-text Figure 2b,c.

Section S4. Examples of previously known iterative sequences rediscovered by the algorithm.



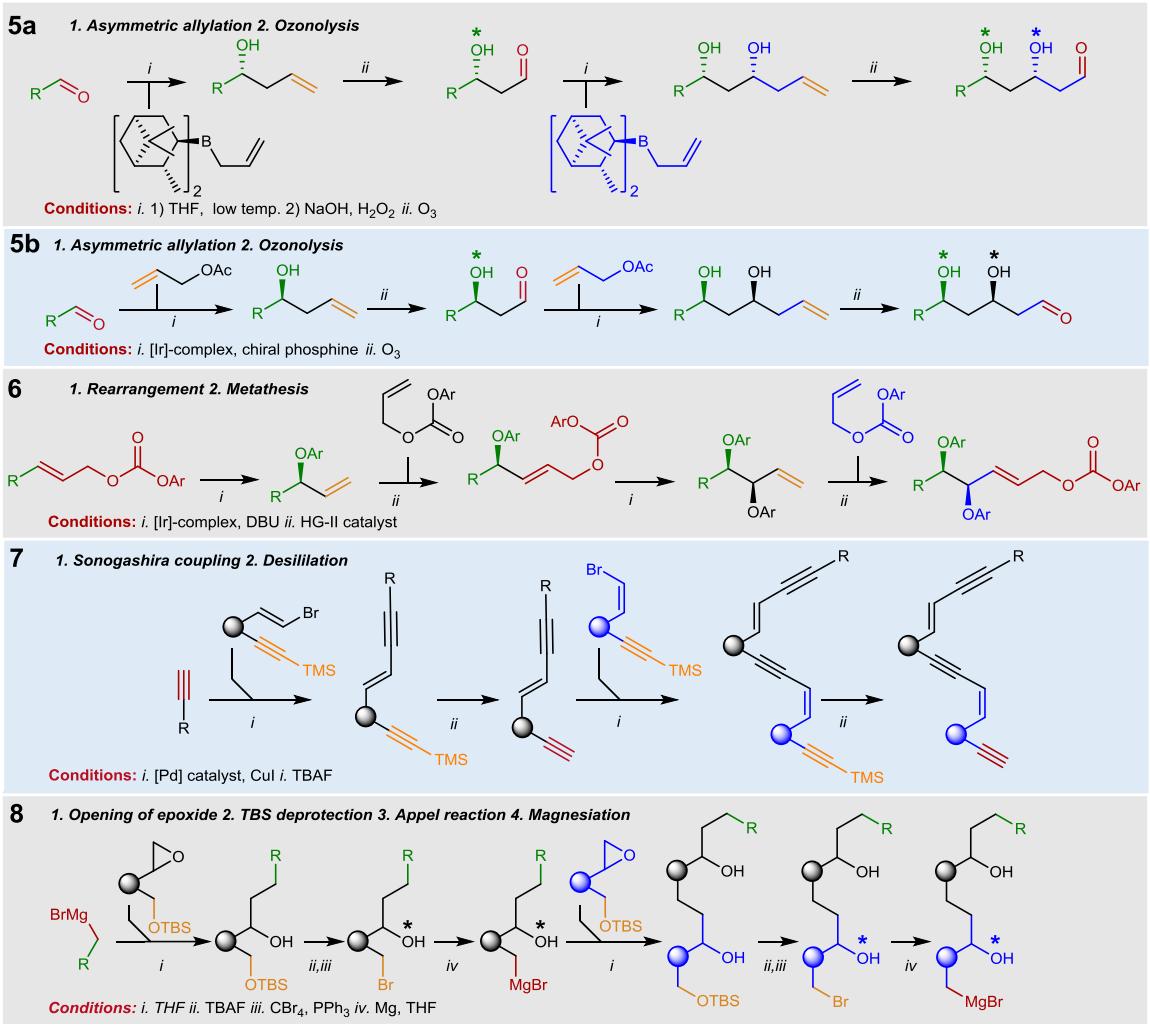
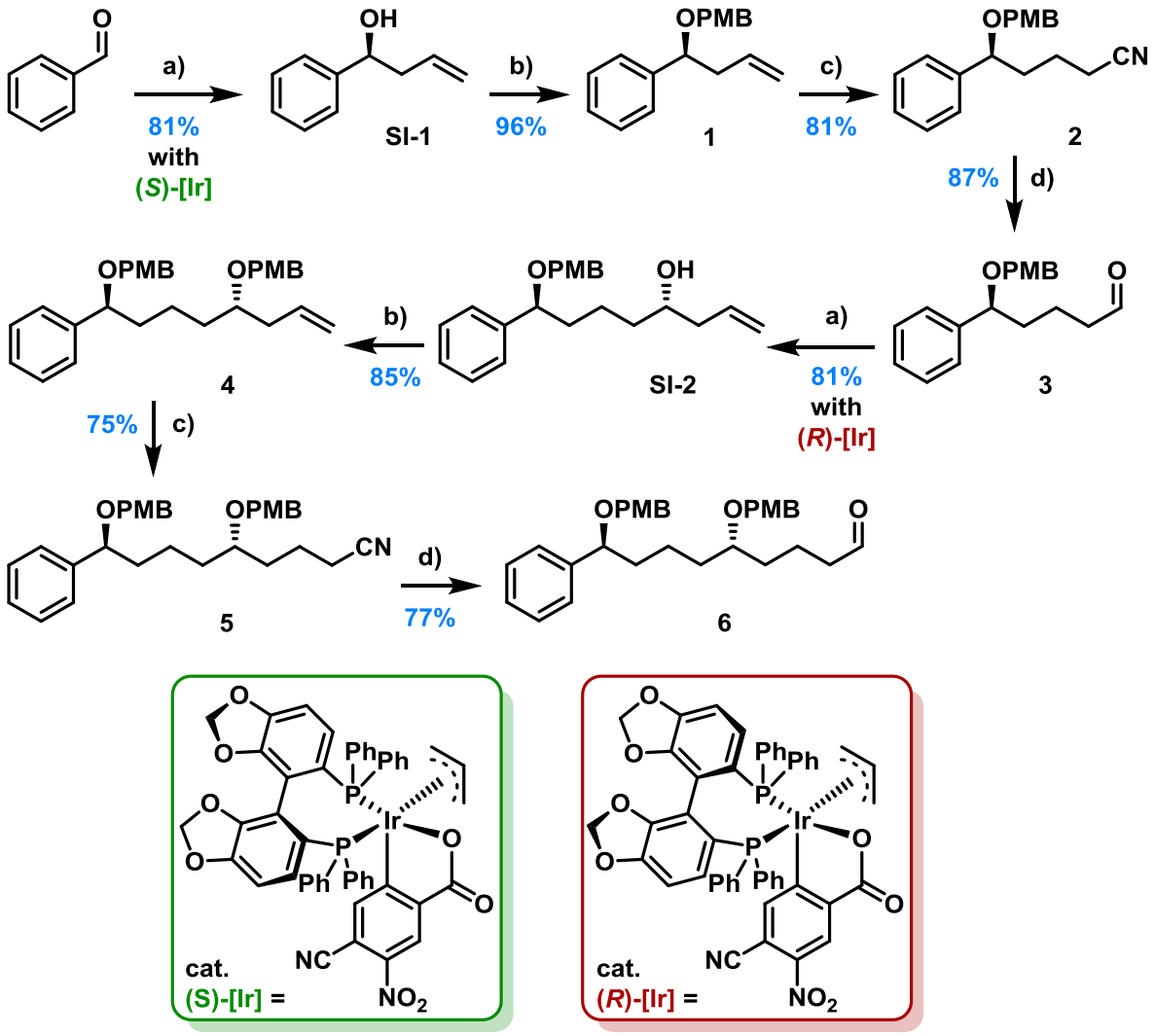


Figure S4. Examples of previously known iterative sequences rediscovered by the algorithm described in the main text.

Section S5. General experimental procedures.

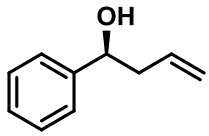
All starting materials and reagents were obtained from commercial sources and, unless otherwise noted, were used as received. All solvents used were freshly distilled prior to use. ^{1}H NMR spectra were recorded at 400, 500 or 600 MHz and ^{13}C NMR spectra were recorded at 100, 125 or 150 MHz with complete proton decoupling. Chemical shifts are given in δ relative to the residual signals of the deuterated solvents. High-resolution mass spectra were acquired using electron ionization (EI) or electrospray ionization (ESI) modes with a time-of-flight detector. Infrared (IR) spectra were recorded on a Fourier transform infrared (FT-IR) spectrometer as a thin film on a NaCl plate (film). HPLC analysis were performed on a HPLC system equipped with chiral stationary phase columns with an UV detector. Optical rotations were measured at room temperature with a polarimeter. TLC was performed with aluminum plates coated with 60 F254 silica gel. Plates were visualized with UV light (254 nm) and by treatment with ethanolic *p*-anisaldehyde with sulfuric and glacial acetic acid followed by heating, aqueous cerium(IV) sulfate solution with molybdic and sulfuric acid followed by heating, or aqueous potassium permanganate with sodium hydroxide and potassium carbonate solution followed by heating. Reaction products were purified by flash chromatography using silica gel 60 (230-400 mesh).

Section S6. Iterative synthesis of 1,5,n polyols



Reagents and conditions: (a) allyl acetate, Krische's Ir Catalyst ((*S*)-Ir or (*R*)-Ir), Cs_2CO_3, *i*-PrOH, THF, 100°C, 16-18 h; (b) PMBCl, NaH, TBAI, DMF, 0°C to rt, 17-20 h; (c) Zn(CN)2, NiCl2·6H2O, dppp, Zn, DMAP, H2O, MeCN, 80°C, 22-24 h; (d) DIBAL-H, DCM, -78°C to rt, 1.5-2 h.

Scheme S1. Iterative synthesis of 1,5,n polyols *via* asymmetric allylation.



(*S*)-1-phenylbut-3-en-1-ol (SI-1). Prepared *via* adaptation of procedure from [R1].

An oven-dried vacuum Schlenk tube equipped with a magnetic stir bar was charged with Cs_2CO_3 (0.078 g, 0.24 mmol, 6 mol%) and Krische Ir Catalyst ((*S*)-SEGPHOS, 4-cyano-3-nitrobenzoate ligated) (0.207 g, 0.20 mmol, 5 mol%). The reaction vessel was placed under an atmosphere of argon, and anhydrous THF (20 mL), benzaldehyde (0.407 mL, 4.00 mmol), allyl acetate (0.863 mL, 8.00 mmol, 2 equiv) and 2-propanol (0.612 mL, 8.00 mmol, 2 equiv) were added by syringe. The reaction vessel was sealed and the reaction mixture was stirred at 100 °C and was monitored by TLC. After 16 h, the mixture was allowed to reach rt and was concentrated *in vacuo*. The residue was purified by flash column chromatography (hexane/ethyl acetate 9:1) to give **SI-1** (0.480 g, 81%, 97% *ee* by HPLC analysis) as a slightly yellow liquid.

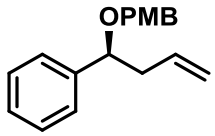
HPLC (Chiralcel OD-H, hexane/*i*-PrOH 95:5, flow rate 0.5 mL/min, λ 220 nm): $t_{R(minor)}$ = 18.2 min (*R*), $t_{R(major)}$ = 19.4 min (*S*); (lit.[R2] t_R = 20.7 min (*R*), t_R =22.1 min (*S*));

$[\alpha]^{27}_D$ -63.0 (c 1.19, $CHCl_3$) (lit.[R3] $[\alpha]^{25}_D$ -63.2 (c 0.95, $CHCl_3$) (for 97% *ee*));

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.31 (m, 4H), 7.29 – 7.25 (m, 1H), 5.80 (dddd, *J* = 17.0, 10.3, 7.6, 6.6 Hz, 1H), 5.20 – 5.10 (m, 2H), 4.73 (dd, *J* = 7.6, 5.2 Hz, 1H), 2.58 – 2.44 (m, 2H), 2.00 (brs, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 144.0, 134.6, 128.5, 127.7, 125.9, 118.5, 73.4, 44.0;

IR (film, DCM) 3541, 3378, 3075, 3030, 2979, 2930, 1641, 1493 cm^{-1}.



(*S*)-1-methoxy-4-(((1-phenylbut-3-en-1-yl)oxy)methyl)benzene (1).

NaH (60 % dispersion in mineral oil) (0.132 g, 3.31 mmol, 2 equiv) was added to a flask containing **SI-1** (0.245 g, 1.65 mmol) and TBAI (0.061 g, 0.17 mmol, 10 mol%) in anhydrous DMF (3.30 mL) cooled to 0 ºC. Reaction mixture was flushed with argon and stirred for 30 min at 0 ºC. Then, 4-methoxybenzyl chloride (0.448 mL, 3.31 mmol, 2 equiv) was added dropwise

and the mixture was stirred at rt. The reaction was monitored by TLC and after 18 h the mixture was quenched by addition of sat. NH_4Cl solution. The mixture was extracted with ethyl acetate. Combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Crude product was purified by flash column chromatography (hexane/ethyl acetate 98:2) to give **1** (0.425 g, 96%) as a slightly yellow liquid.

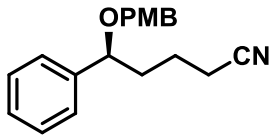
[α]$^{28}_{D}$ -70.7 (c 1.09, C_6H_6) (lit.[R4] $[\alpha]^{20}_{D}$ = +67.3 (c 0.95, C_6H_6) (for (*R*)-enantiomer);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.28 (m, 5H), 7.25 – 7.21 (m, 2H), 6.90 – 6.85 (m, 2H), 5.78 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1H), 5.09 – 4.96 (m, 2H), 4.41 (d, *J* = 11.5 Hz, 1H), 4.35 (dd, *J* = 7.6, 5.9 Hz, 1H), 4.22 (d, *J* = 11.4 Hz, 1H), 3.81 (s, 3H), 2.68 – 2.57 (m, 1H), 2.43 (dddt, *J* = 14.2, 7.2, 5.9, 1.3 Hz, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 142.2, 135.1, 130.8, 129.5, 128.5, 127.8, 127.1, 116.9, 113.9, 81.0, 70.2, 55.4, 42.8;

HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{18}H_{20}O_2Na$ 291.1361; Found 291.1356;

IR (film) 3067, 3030, 3003, 2934, 2906, 2861, 2837, 1612, 1513, 1455 cm^{-1}.



(*S*)-5-((4-methoxybenzyl)oxy)-5-phenylpentanenitrile (2). Prepared *via* adaptation of procedure from [R5].

An oven-dried vacuum Schlenk tube equipped with a magnetic stir bar was placed under an atmosphere of argon and charged with $NiCl_2 \cdot 6H_2O$ (0.018 g, 0.08 mmol, 5 mol%), dppp (0.037 g, 0.09 mmol, 6 mol%), zinc powder (0.098 g, 1.50 mmol, 1 equiv), $Zn(CN)_2$ (0.106 g, 0.90 mmol, 0.6 equiv), DMAP (0.183 g, 1.50 mmol, 1 equiv), anhydrous CH_3CN (7.50 mL), compound **1** (0.403 g, 1.50 mmol) and water (0.054 mL, 3.00 mmol, 2 equiv). The reaction vessel was sealed and the reaction mixture was stirred at 80 °C and was monitored by TLC. After 24 h, the mixture was allowed to reach rt. Next, it was filtered through a short pad of silica gel and washed with ethyl acetate. The solvent was concentrated *in vacuo* and the residue was purified by flash column chromatography (hexane/ethyl acetate 85:15) to give **2** (0.357 g, 81%) as a colorless oil.

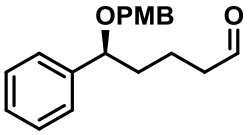
[α]$^{19}_{D}$ -91.0 (c 1.29, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.36 (m, 2H), 7.35 – 7.30 (m, 3H), 7.24 – 7.19 (m, 2H), 6.92 – 6.86 (m, 2H), 4.42 (d, *J* = 11.4 Hz, 1H), 4.32 (dd, *J* = 8.1, 4.3 Hz, 1H), 4.18 (d, *J* = 11.4 Hz, 1H), 3.82 (s, 3H), 2.37 – 2.22 (m, 2H), 1.99 – 1.88 (m, 1H), 1.87 – 1.75 (m, 2H), 1.73 – 1.61 (m, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 141.9, 130.4, 129.5, 128.7, 128.0, 126.7, 119.7, 114.0, 79.9, 70.2, 55.4, 37.2, 22.1, 17.1;

HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{19}H_{21}NO_2Na$ 318.1470; Found 318.1475;

IR (film, DCM) 3061, 3030, 3003, 2935, 2865, 2838, 2245, 1612, 1585, 1513, 1454 cm^{-1}.



(*S*)-5-((4-methoxybenzyl)oxy)-5-phenylpentanal (3).

To a stirred solution of **2** (0.325 g, 1.10 mmol) in anhydrous DCM (11.0 mL) cooled to -78 °C was added DIBAL-H solution (1.0 M in DCM) (1.320 mL, 1.32 mmol, 1.2 equiv) in a drop-wise manner. The mixture was stirred at -78 °C and was monitored by TLC. After 1.5 h, the reaction was quenched by addition of sat. Na_2SO_4 solution (0.143 mL) and the mixture was allowed to slowly reach rt. The mixture was diluted with DCM and sat. potassium sodium tartrate solution was added. After the layers were separated, the aqueous phase was extracted with DCM. Combined organic phases were washed with 50% potassium sodium tartrate solution and then brine, dried over Na_2SO_4 and concentrated *in vacuo*. Crude product was purified by flash column chromatography (hexane/ethyl acetate 85:15) to give **3** (0.284 g, 87%) as a colorless oil.

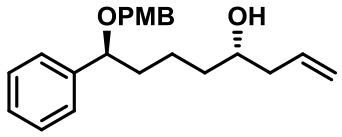
[α]$^{19}_{D}$ -79.9 (c 1.42, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (t, *J* = 1.7 Hz, 1H), 7.41 – 7.28 (m, 5H), 7.24 – 7.18 (m, 2H), 6.92 – 6.85 (m, 2H), 4.40 (d, *J* = 11.3 Hz, 1H), 4.30 (dd, *J* = 7.8, 5.0 Hz, 1H), 4.18 (d, *J* = 11.3 Hz, 1H), 3.81 (s, 3H), 2.48 – 2.31 (m, 2H), 1.92 – 1.75 (m, 2H), 1.74 – 1.50 (m, 2H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 202.5, 159.3, 142.4, 130.7, 129.5, 128.6, 127.8, 126.9, 113.9, 80.7, 70.2, 55.4, 43.8, 37.8, 18.8;

HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{19}H_{22}O_3Na$ 321.1467; Found 321.1461;

IR (film, DCM) 3061, 3029, 3002, 2935, 2863, 2837, 2721, 1722, 1612, 1585, 1513 cm^{-1}.



(4*S*,8*S*)-8-((4-methoxybenzyl)oxy)-8-phenyloct-1-en-4-ol (SI-2). Prepared *via* adaptation of procedure from [R1].

An oven-dried vacuum Schlenk tube equipped with a magnetic stir bar was charged with Cs_2CO_3 (0.030 g, 0.09 mmol, 12 mol%) and Krische Ir Catalyst ((*R*)-SEGPHOS, 4-cyano-3-nitrobenzoate ligated) (0.081 g, 0.08 mmol, 10 mol%). The reaction vessel was placed under an atmosphere of argon, and anhydrous THF (3.90 mL), **3** (0.233 g, 0.78 mmol), allyl acetate (0.168 mL, 1.56 mmol, 2 equiv) and 2-propanol (0.119 mL, 1.56 mmol, 2 equiv) were added by syringe. The reaction vessel was sealed and the reaction mixture was stirred at 100 °C and was monitored by TLC. After 18 h, the mixture was allowed to reach rt and was concentrated *in vacuo*. The residue was purified by flash column chromatography (hexane/ethyl acetate 4:1) to give **SI-2** (0.215 g, 81%) as a colorless oil.

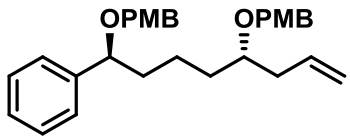
$[\alpha]^{19}_D$ -68.4 (c 1.08, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 5H), 7.24 – 7.20 (m, 2H), 6.89 – 6.84 (m, 2H), 5.85 – 5.73 (m, 1H), 5.15 – 5.05 (m, 2H), 4.39 (d, *J* = 11.4 Hz, 1H), 4.28 (dd, *J* = 7.9, 5.4 Hz, 1H), 4.17 (d, *J* = 11.4 Hz, 1H), 3.80 (s, 3H), 3.64 – 3.58 (m, 1H), 2.28 – 2.21 (m, 1H), 2.14 – 2.04 (m, 1H), 1.93 – 1.82 (m, 1H), 1.69 – 1.58 (m, 2H), 1.53 – 1.37 (m, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 159.3, 142.8, 135.0, 130.8, 129.6, 128.6, 127.7, 126.9, 118.2, 113.9, 81.2, 70.6, 70.2, 55.4, 42.0, 38.4, 36.7, 22.3;

HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{22}H_{28}O_3Na$ 363.1936; Found 363.1944;

IR (film, DCM) 3436, 3066, 3029, 3001, 2933, 2862, 1640, 1612, 1586, 1513 cm^{-1}.



4,4'-((((1*S*,5*S*)-1-phenyloct-7-ene-1,5-diyl)bis(oxy))bis(methylene))bis(methoxybenzene) (4).

NaH (60 % dispersion in mineral oil) (0.040 g, 1.00 mmol, 2 equiv) was added to a flask containing **SI-2** (0.170 g, 0.50 mmol) and TBAI (0.018 g, 0.05 mmol, 10 mol%) in anhydrous DMF (1.00 mL) cooled to 0 ºC. Reaction mixture was flushed with argon and stirred for 30 min at 0 ºC. Then, 4-methoxybenzyl chloride (0.136 mL, 1.00 mmol, 2 equiv) was added dropwise and the mixture was stirred at rt. The reaction was monitored by TLC and after 17 h the mixture was quenched by addition of sat. NH_4Cl solution. The mixture was extracted with ethyl acetate. Combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Crude product was purified by flash column chromatography (hexane/ethyl acetate 95:5) to give **4** (0.195 g, 85%) as a colorless oil.

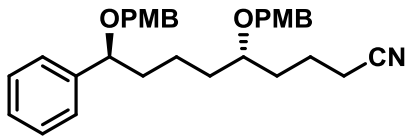
$[\alpha]^{19}_D$ -54.0 (c 1.17, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.27 (m, 5H), 7.24 – 7.19 (m, 4H), 6.90 – 6.82 (m, 4H), 5.81 (ddt, *J* = 17.3, 10.3, 7.1 Hz, 1H), 5.09 – 5.04 (m, 1H), 5.04 – 5.01 (m, 1H), 4.47 (d, *J* = 11.2 Hz, 1H), 4.40 (d, *J* = 4.2 Hz, 1H), 4.37 (d, *J* = 4.2 Hz, 1H), 4.27 (dd, *J* = 7.8, 5.5 Hz, 1H), 4.18 (d, *J* = 11.2 Hz, 1H), 3.80 (s, 6H), 3.42 – 3.33 (m, 1H), 2.34 – 2.19 (m, 2H), 1.90 – 1.79 (m, 1H), 1.68 – 1.55 (m, 1H), 1.54 – 1.35 (m, 4H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 159.2, 142.9, 135.2, 131.2, 131.0, 129.5, 129.4, 128.5, 127.6, 127.0, 116.9, 113.9, 113.9, 81.3, 78.2, 70.7, 70.2, 55.4, 38.5, 38.5, 33.9, 22.0;

HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{30}H_{36}O_4Na$ 483.2511; Found 483.2495;

IR (film, DCM) 3064, 3030, 3001, 2935, 2861, 2837, 1639, 1612, 1586, 1513 cm^{-1}.



(5*R*,9*S*)-5,9-bis((4-methoxybenzyl)oxy)-9-phenylnonanenitrile (5). Prepared *via* adaptation of procedure from [R5].

An oven-dried vacuum Schlenk tube equipped with a magnetic stir bar was placed under an atmosphere of argon and charged with $NiCl_2 \cdot 6H_2O$ (0.004 g, 0.02 mmol, 5 mol%), dppp (0.009 g, 0.02 mmol, 6 mol%), zinc powder (0.023 g, 0.35 mmol, 1 equiv), $Zn(CN)_2$ (0.025 g, 0.21 mmol, 0.6 equiv), DMAP (0.043 g, 0.35 mmol, 1 equiv), anhydrous CH_3CN (1.75 mL), compound **4** (0.161 g, 0.35 mmol) and water (0.013 mL, 0.70 mmol, 2 equiv). The reaction vessel was sealed and the reaction mixture was stirred at 80 °C and was monitored by TLC. After 22 h, the mixture was allowed to reach rt. Next, it was filtered through a short pad of silica gel and washed with ethyl acetate. The solvent was concentrated *in vacuo* and the residue was purified by flash column chromatography (hexane/ethyl acetate 85:15) to give **5** (0.128 g, 75%) as a colorless oil.

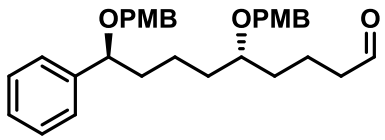
$[\alpha]^{20}_D$ -26.4 (c 0.98, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.29 (m, 5H), 7.24 – 7.18 (m, 4H), 6.89 – 6.84 (m, 4H), 4.44 – 4.37 (m, 2H), 4.34 (d, *J* = 11.2 Hz, 1H), 4.28 (dd, *J* = 7.7, 5.5 Hz, 1H), 4.18 (d, *J* = 11.2 Hz, 1H), 3.80 (s, 3H), 3.80 (s, 3H), 3.38 – 3.31 (m, 1H), 2.33 – 2.22 (m, 2H), 1.86 (dddd, *J* = 13.4, 9.6, 7.7, 4.7 Hz, 1H), 1.73 – 1.40 (m, 8H), 1.39 – 1.30 (m, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 159.3, 142.8, 130.8, 130.8, 129.5, 129.5, 128.6, 127.7, 126.9, 119.8, 114.0, 113.9, 81.1, 77.4, 70.7, 70.2, 55.4, 38.5, 33.6, 32.8, 21.8, 21.5, 17.3;

HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{31}H_{37}NO_4Na$ 510.2620; Found 510.2613;

IR (film, DCM) 3060, 3030, 3001, 2936, 2863, 2837, 2244, 1612, 1585, 1513, 1455 cm^{-1}.



(5*S*,9*S*)-5,9-bis((4-methoxybenzyl)oxy)-9-phenylnonanal (6)

To a stirred solution of **5** (0.029 g, 0.06 mmol) in anhydrous DCM (0.60 mL) cooled to -78 °C was added DIBAL-H solution (1.0 M in DCM) (0.072 mL, 0.07 mmol, 1.2 equiv) in a drop-wise manner. The mixture was stirred at -78 °C and was monitored by TLC. After 2 h, the reaction was quenched by addition of sat. Na_2SO_4 solution (0.008 mL) and the mixture was allowed to slowly reach rt. The mixture was diluted with DCM and sat. potassium sodium tartrate solution was added. After the layers were separated, the aqueous phase was extracted with DCM. Combined organic phases were washed with 50% potassium sodium tartrate solution and then brine, dried over Na_2SO_4 and concentrated *in vacuo*. Crude product was purified by flash column chromatography (hexane/ethyl acetate 4:1) to give **6** (0.023 g, 77%) as a slightly yellow oil.

$[\alpha]^{20}_D$ -33.9 (c 1.59, $CHCl_3$);

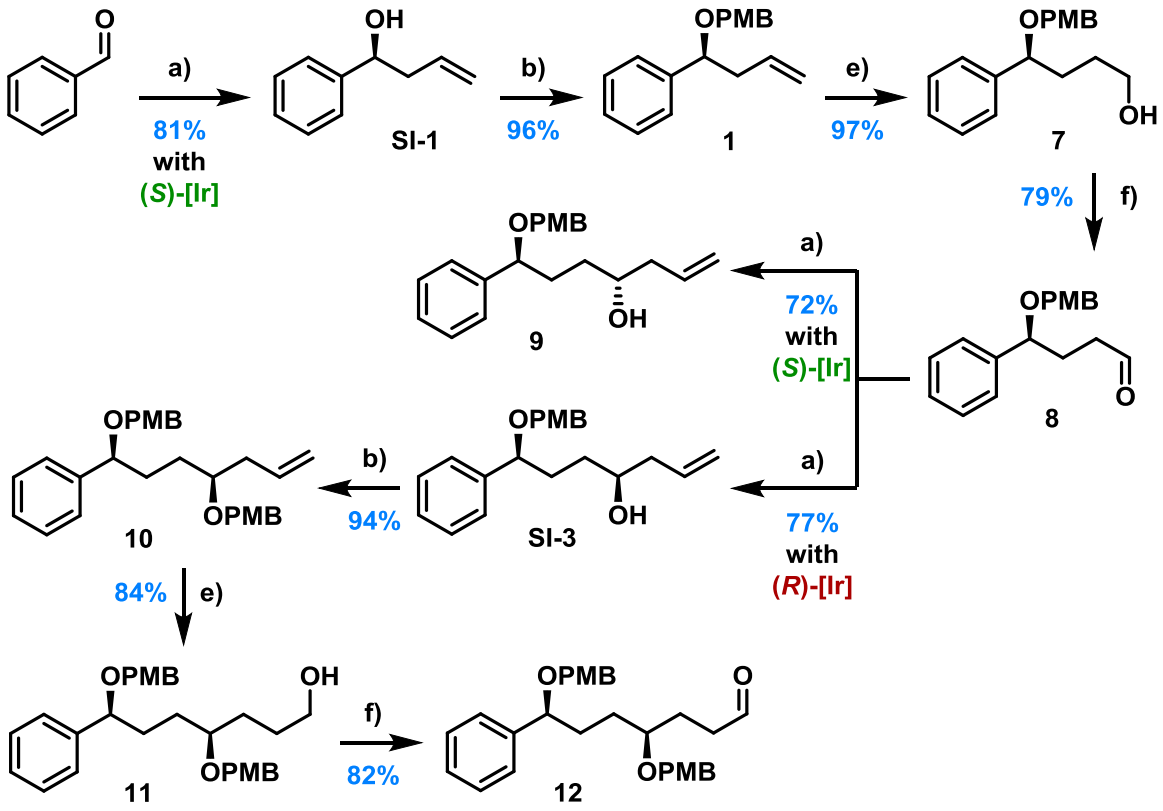
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.72 (t, *J* = 1.8 Hz, 1H), 7.40 – 7.29 (m, 5H), 7.24 – 7.17 (m, 4H), 6.89 – 6.79 (m, 4H), 4.42 – 4.34 (m, 3H), 4.27 (dd, *J* = 7.7, 5.6 Hz, 1H), 4.17 (d, *J* = 11.4 Hz, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.32 (p, *J* = 5.6 Hz, 1H), 2.42 – 2.35 (m, 2H), 1.91 – 1.80 (m, 1H), 1.75 – 1.58 (m, 4H), 1.53 – 1.41 (m, 4H), 1.38 – 1.30 (m, 1H);

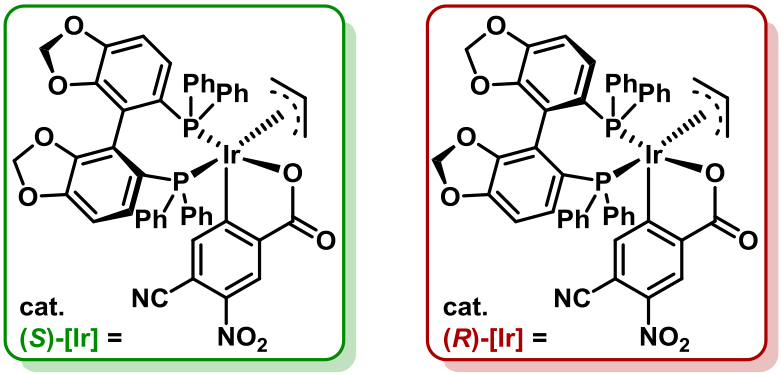
^{13}C NMR (100 MHz, $CDCl_3$) δ 202.6, 159.3, 142.9, 131.1, 130.9, 129.5, 129.5, 128.6, 127.6, 127.0, 113.9, 81.2, 78.2, 70.7, 70.2, 55.4, 55.4, 44.0, 38.6, 33.7, 33.4, 21.9, 18.2;

HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{31}H_{38}O_5Na$ 513.2617; Found 513.2627;

IR (film, DCM) 3061, 3030, 3000, 2935, 2862, 2720, 1723, 1612, 1586, 1513 cm^{-1}.

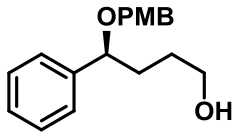
Section S7. Iterative synthesis of 1,4,n polyols





Reagents and conditions: (a) allyl acetate, Krische's Ir Catalyst ((*S*)-Ir or (*R*)-Ir), Cs_2CO_3, *i*-PrOH, THF, 100°C, 16-18 h; (b) PMBCl, NaH, TBAI, DMF, 0°C to rt, 17-20 h; (e) 1) 9-BBN, THF, reflux, 1-2 h, 2) NaOH (aq) (0.5 M), H_2O_2 (30%), EtOH, 50°C, 1 h; (f) PCC, MS 4 Å, DCM, rt, 1.5 h.

Scheme S2. Iterative synthesis of 1,4,n polyols *via* asymmetric allylation.



(*S*)-4-((4-methoxybenzyl)oxy)-4-phenylbutan-1-ol (7).

To a solution of **1** (0.309 g, 1.15 mmol) in anhydrous THF (4.60 mL) was added drop-wise 9-borabicyclo[3.3.1]nonane solution (0.5 M in THF) (6.90 mL, 3.45 mmol, 3 equiv) over 10 min and the mixture was heated under reflux for 2 h. After cooling, the reaction mixture was treated with ethanol (3.00 mL), 2 M NaOH solution (1.50 mL) and H_2O_2 solution (30% (w/w) in H_2O) (1.50 mL) and the mixture was stirred at 50 °C for 1 h. The reaction was monitored by TLC and upon completion sat. K_2CO_3 solution and Et_2O were added. The aqueous phase was extracted with Et_2O, combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Crude product was purified by flash column chromatography (hexane/ethyl acetate 7:3) to give **7** (0.319 g, 97%) as a slightly yellow oil.

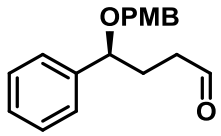
$[\alpha]^{23}_D$ -82.2 (c 1.08, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.28 (m, 5H), 7.24 – 7.19 (m, 2H), 6.90 – 6.85 (m, 2H), 4.40 (d, *J* = 11.3 Hz, 1H), 4.33 (dd, *J* = 8.1, 4.7 Hz, 1H), 4.20 (d, *J* = 11.3 Hz, 1H), 3.80 (s, 3H), 3.61 (t, *J* = 6.2 Hz, 2H), 2.03 – 1.82 (m, 2H), 1.80 – 1.66 (m, 2H), 1.64 – 1.55 (m, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 142.5, 130.4, 129.7, 128.6, 127.7, 126.9, 114.0, 81.2, 70.3, 62.9, 55.4, 35.2, 29.5;

HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{18}H_{22}O_3Na$ 309.1467; Found 309.1471;

IR (film, DCM) 3399, 3061, 3030, 3001, 2935, 2865, 1612, 1585, 1513 cm^{-1}.



(*S*)-4-((4-methoxybenzyl)oxy)-4-phenylbutanal (8).

To a solution of **7** (0.315 g, 1.10 mmol) in anhydrous DCM (5.50 mL) were added molecular sieves 4 Å (beads) (0.550 g) and pyridinium chlorochromate (0.474 g, 2.20 mmol, 2 equiv) and the mixture was stirred at rt. The reaction was monitored by TLC and after 1.5 h Et_2O (5.50 mL) was added. After 30 min of intensive stirring, the mixture was filtered through a Celite

plug, which was thoroughly washed with Et_2O. The filtrate was washed with water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. Crude product was purified by flash column chromatography (hexane/ethyl acetate 9:1) to give **8** (0.246 g, 79%) as a colorless oil.

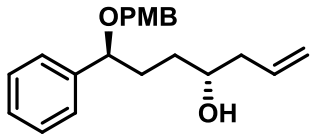
$[\alpha]^{20}_D$ -91.1 (c 1.31, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.73 (t, *J* = 1.7 Hz, 1H), 7.42 – 7.29 (m, 5H), 7.23 – 7.18 (m, 2H), 6.92 – 6.81 (m, 2H), 4.40 (d, *J* = 11.3 Hz, 1H), 4.35 (dd, *J* = 8.3, 4.8 Hz, 1H), 4.18 (d, *J* = 11.3 Hz, 1H), 3.81 (s, 3H), 2.58 – 2.42 (m, 2H), 2.13 (ddt, *J* = 14.2, 8.3, 7.1 Hz, 1H), 2.01 (dddd, *J* = 14.2, 7.5, 6.8, 4.8 Hz, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 202.2, 159.3, 141.8, 130.4, 129.5, 128.7, 127.9, 126.8, 113.9, 80.0, 70.3, 55.4, 40.6, 31.1;

HRMS (ESI) *m/z*: $[M-H]^-$ Calcd for $C_{18}H_{19}O_3$ 283.1334; Found 283.1329;

IR (film, DCM) 3061, 3030, 3003, 2934, 2836, 2725, 1721, 1611, 1585, 1512 cm^{-1}.



(4*R*,7*S*)-7-((4-methoxybenzyl)oxy)-7-phenylhept-1-en-4-ol (9). Prepared *via* adaptation of procedure from [R1].

An oven-dried vacuum Schlenk tube equipped with a magnetic stir bar was charged with Cs_2CO_3 (0.007 g, 0.020 mmol, 12 mol%) and Krische Ir Catalyst ((*S*)-SEGPHOS, 4-cyano-3-nitrobenzoate ligated) (0.019 g, 0.018 mmol, 10 mol%). The reaction vessel was placed under an atmosphere of argon, and anhydrous THF (0.90 mL), **8** (0.051 g, 0.180 mmol), allyl acetate (0.039 mL, 0.360 mmol, 2 equiv) and 2-propanol (0.028 mL, 0.360 mmol, 2 equiv) were added by syringe. The reaction vessel was sealed and the reaction mixture was stirred at 100 °C and was monitored by TLC. After 16 h, the mixture was allowed to reach rt and was concentrated *in vacuo*. The residue was purified by flash column chromatography (hexane/ethyl acetate 4:1) to give **9** (0.042 g, 72%) as a slightly yellow oil.

$[\alpha]^{24}_D$ -64.4 (c 1.28, $CHCl_3$);

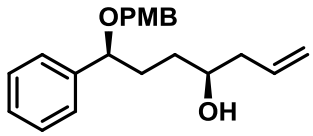
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.28 (m, 5H), 7.24 – 7.19 (m, 2H), 6.91 – 6.82 (m, 2H), 5.80 (dddd, *J* = 20.3, 9.7, 7.8, 6.7 Hz, 1H), 5.12 – 5.10 (m, 1H), 5.10 – 5.08 (m, 1H), 4.40 (d, *J*

= 11.3 Hz, 1H), 4.33 (dd, *J* = 7.8, 5.0 Hz, 1H), 4.20 (d, *J* = 11.3 Hz, 1H), 3.81 (s, 3H), 3.68 – 3.61 (m, 1H), 2.29 – 2.22 (m, 1H), 2.19 – 2.11 (m, 1H), 2.03 (s, 1H), 1.93 – 1.79 (m, 2H), 1.73 – 1.62 (m, 1H), 1.47 – 1.36 (m, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 159.3, 142.6, 135.1, 130.6, 129.6, 129.6, 128.6, 127.7, 126.9, 117.9, 113.9, 81.4, 70.7, 70.3, 55.4, 42.0, 34.6, 33.4;

HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{21}H_{26}O_3Na$ 349.1780; Found 349.1781;

IR (film, DCM) 3442, 3079, 2932, 2862, 1641, 1613, 1512 cm^{-1}.



(4*S*,7*S*)-7-((4-methoxybenzyl)oxy)-7-phenylhept-1-en-4-ol (SI-3). Prepared *via* adaptation of procedure from [R1].

An oven-dried vacuum Schlenk tube equipped with a magnetic stir bar was charged with Cs_2CO_3 (0.033 g, 0.10 mmol, 12 mol%) and Krische Ir Catalyst ((*R*)-SEGPHOS, 4-cyano-3-nitrobenzoate ligated) (0.088 g, 0.09 mmol, 10 mol%). The reaction vessel was placed under an atmosphere of argon, and anhydrous THF (4.25 mL), **8** (0.242 g, 0.85 mmol), allyl acetate (0.183 mL, 1.70 mmol, 2 equiv) and 2-propanol (0.130 mL, 1.70 mmol, 2 equiv) were added by syringe. The reaction vessel was sealed and the reaction mixture was stirred at 100 °C and was monitored by TLC. After 16 h, the mixture was allowed to reach rt and was concentrated *in vacuo*. The residue was purified by flash column chromatography (hexane/ethyl acetate 4:1) to give **SI-3** (0.214 g, 77%) as a slightly yellow oil.

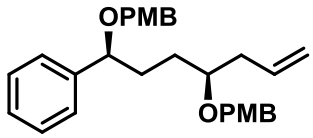
$[\alpha]^{23}_D$ -79.7 (c 1.31, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.28 (m, 5H), 7.23 – 7.19 (m, 2H), 6.91 – 6.83 (m, 2H), 5.86 – 5.73 (m, 1H), 5.12 – 5.10 (m, 1H), 5.09 – 5.06 (m, 1H), 4.41 (d, *J* = 11.4 Hz, 1H), 4.31 (dd, *J* = 8.3, 4.9 Hz, 1H), 4.19 (d, *J* = 11.4 Hz, 1H), 3.81 (s, 3H), 3.65 – 3.55 (m, 1H), 2.27 – 2.09 (m, 3H), 2.01 – 1.89 (m, 1H), 1.85 – 1.72 (m, 1H), 1.60 – 1.48 (m, 2H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 142.6, 135.1, 130.5, 129.6, 128.6, 127.7, 126.9, 117.9, 113.9, 81.1, 70.8, 70.2, 55.4, 42.1, 34.9, 33.4;

HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{21}H_{26}O_3Na$ 349.1780; Found 349.1782;

IR (film, DCM) 3423, 3072, 3030, 3003, 2932, 2863, 1640, 1612, 1586, 1513 cm^{-1}.



4,4'-((((1*S*,4*S*)-1-phenylhept-6-ene-1,4-diyl)bis(oxy))bis(methylene))bis(methoxybenzene) (10).

NaH (60 % dispersion in mineral oil) (0.052 g, 1.30 mmol, 2 equiv) was added to a flask containing **SI-3** (0.212 g, 0.65 mmol) and TBAI (0.024 g, 0.07 mmol, 10 mol%) in anhydrous DMF (1.30 mL) cooled to 0 ºC. Reaction mixture was flushed with argon and stirred for 30 min at 0 ºC. Then, 4-methoxybenzyl chloride (0.176 mL, 1.30 mmol, 2 equiv) was added dropwise and the mixture was stirred at rt. The reaction was monitored by TLC and after 20 h the mixture was quenched by addition of sat. NH_4Cl solution. The mixture was extracted with ethyl acetate. Combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Crude product was purified by flash column chromatography (hexane/ethyl acetate 95:5) to give **10** (0.272 g, 94%) as a colorless oil.

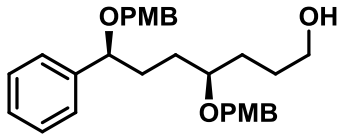
$[\alpha]^{23}_D$ -58.1 (c 1.05, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 5H), 7.25 – 7.19 (m, 4H), 6.89 – 6.83 (m, 4H), 5.79 (ddt, *J* = 17.2, 10.2, 7.1 Hz, 1H), 5.09 – 5.05 (m, 1H), 5.05 – 4.98 (m, 1H), 4.45 – 4.33 (m, 3H), 4.24 (dd, *J* = 7.6, 5.4 Hz, 1H), 4.16 (d, *J* = 11.5 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.44 – 3.32 (m, 1H), 2.31 – 2.21 (m, 2H), 2.01 – 1.89 (m, 1H), 1.78 – 1.61 (m, 2H), 1.52 – 1.39 (m, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 159.2, 142.8, 135.1, 131.2, 130.9, 129.5, 129.4, 128.5, 127.6, 127.0, 116.9, 113.9, 80.9, 77.8, 70.6, 70.1, 55.4, 38.3, 33.9, 29.9;

HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{29}H_{34}O_4Na$ 469.2355; Found 469.2357;

IR (film, DCM) 3063, 3030, 3001, 2934, 2861, 2836, 1612, 1585, 1513 cm^{-1}.



(4*R*,7*S*)-4,7-bis((4-methoxybenzyl)oxy)-7-phenylheptan-1-ol (11)

To a solution of **10** (0.277 g, 0.62 mmol) in anhydrous THF (2.86 mL) was added drop-wise 9-borabicyclo[3.3.1]nonane solution (0.5 M in THF) (3.72 mL, 1.86 mmol, 3 equiv) over 10 min and the mixture was heated under reflux for 1 h. After cooling the reaction mixture was treated with ethanol (1.90 mL), 2 M NaOH solution (0.95 mL) and H_2O_2 solution (30% (w/w) in H_2O) (0.95 mL) and the mixture was stirred at 50 °C for 1 h. The reaction was monitored by TLC and upon completion sat. K_2CO_3 solution and Et_2O were added. The aqueous phase was extracted with Et_2O, combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Crude product was purified by flash column chromatography (hexane/ethyl acetate 7:3) to give **11** (0.243 g, 84%) as a colorless oil.

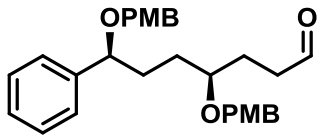
$[\alpha]^{19}_D$ -36.7 (c 1.21, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.35 (m, 2H), 7.33 – 7.28 (m, 3H), 7.23 – 7.19 (m, 4H), 6.90 – 6.83 (m, 4H), 4.42 – 4.33 (m, 3H), 4.26 (dd, *J* = 7.7, 5.1 Hz, 1H), 4.17 (d, *J* = 11.4 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.60 – 3.54 (m, 2H), 3.42 – 3.34 (m, 1H), 1.98 – 1.85 (m, 2H), 1.76 – 1.67 (m, 2H), 1.61 – 1.42 (m, 5H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 159.3, 142.7, 130.9, 130.8, 129.5, 128.6, 127.7, 127.0, 113.9, 113.9, 81.1, 78.2, 70.5, 70.1, 63.1, 55.4, 55.4, 33.8, 30.3, 29.6, 28.7;

HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{29}H_{36}O_5Na$ 487.2460; Found 487.2455;

IR (film, DCM) 3413, 3060, 3030, 3000, 2936, 2863, 1612, 1586, 1513 cm^{-1}.



(4*S*,7*S*)-4,7-bis((4-methoxybenzyl)oxy)-7-phenylheptanal (12)

To a solution of **11** (0.107 g, 0.23 mmol) in anhydrous DCM (1.15 mL) were added molecular sieves 4 Å (beads) (0.115 g) and pyridinium chlorochromate (0.099 g, 0.46 mmol, 2 equiv) and the mixture was stirred at rt. The reaction was monitored by TLC and after 1.5 h Et_2O (1.15

mL) was added. After 30 min of intensive stirring the mixture was filtered through a Celite plug, which was thoroughly washed with Et_2O. The filtrate was washed with water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. Crude product was purified by flash column chromatography (hexane/ethyl acetate 85:15) to give **12** (0.087 g, 82%) as a colorless oil.

$[\alpha]^{19}_D$ -31.2 (c 1.12, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (t, *J* = 1.7 Hz, 1H), 7.41 – 7.28 (m, 5H), 7.24 – 7.16 (m, 4H), 6.91 – 6.82 (m, 4H), 4.42 – 4.34 (m, 2H), 4.30 (d, *J* = 11.3 Hz, 1H), 4.26 (dd, *J* = 7.8, 5.1 Hz, 1H), 4.17 (d, *J* = 11.3 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.41 – 3.30 (m, 1H), 2.42 (td, *J* = 7.2, 1.7 Hz, 2H), 1.95 – 1.80 (m, 2H), 1.78 – 1.64 (m, 3H), 1.49 – 1.37 (m, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 202.5, 159.3, 159.3, 142.6, 130.8, 129.5, 128.6, 127.7, 127.0, 113.9, 113.9, 80.9, 77.2, 70.5, 70.1, 55.4, 55.4, 40.0, 33.7, 29.7, 26.3;

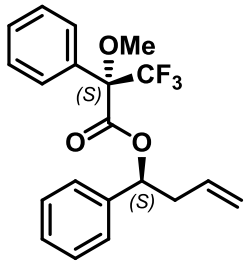
HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{29}H_{34}O_5Na$ 485.2304; Found 485.2295;

IR (film, DCM) 3030, 3001, 2935, 2862, 2837, 1722, 1612, 1585, 1513 cm^{-1}.

Section S8. Determination of absolute configuration of newly formed stereogenic centers (Mosher ester analysis)

General procedure GP-1. Procedure adapted from [R6].

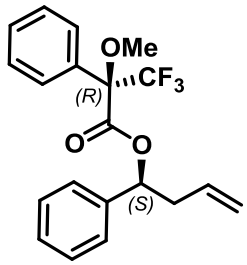
Alcohol (1 equiv) was transferred to a screw-capped 4 mL glass vial and anhydrous DCM (*c* = 0.07 M) was added followed by addition of anhydrous pyridine (3.1 equiv) and (*R*)- or (*S*)-MTPA-Cl (1.9 equiv). The vial was sealed and the mixture was stirred at rt for 12 h. Upon completion, the reaction mixture was diluted with Et_2O and water was added. The aqueous phase was extracted with Et_2O. Combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Crude product was purified by flash column chromatography.



(*S*)-1-phenylbut-3-en-1-yl (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (SI-4).

According to general procedure **GP-1**, the reaction was performed with compound **SI-1** (10 mg, 0.07 mmol). After purification by flash column chromatography (hexane/ethyl acetate 20:1) Mosher ester **SI-4** was obtained (21 mg, 85%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 – 7.40 (m, 3H), 7.38 – 7.30 (m, 7H), 6.03 (dd, *J* = 8.1, 5.6 Hz, 1H), 5.61 (ddt, *J* = 17.2, 10.3, 7.0 Hz, 1H), 5.05 – 4.99 (m, 2H), 3.45 (q, *J* = 1.2 Hz, 3H), 2.70 (dddt, *J* = 14.4, 8.3, 7.2, 1.2 Hz, 1H), 2.58 (dddt, *J* = 14.4, 6.9, 5.6, 1.2 Hz, 1H).



(*S*)-1-phenylbut-3-en-1-yl (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (SI-5).

According to general procedure **GP-1**, the reaction was performed with compound **SI-1** (10 mg, 0.07 mmol). After purification by flash column chromatography (hexane/ethyl acetate 20:1) Mosher ester **SI-5** was obtained (23 mg, 94%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.34 (m, 3H), 7.33 – 7.28 (m, 5H), 7.24 – 7.21 (m, 2H), 5.97 (dd, *J* = 8.4, 5.4 Hz, 1H), 5.74 (ddt, *J* = 17.1, 10.3, 6.9 Hz, 1H), 5.16 – 5.08 (m, 2H), 3.54 (q, *J* = 1.3 Hz, 3H), 2.74 (dddt, *J* = 14.6, 8.4, 7.4, 1.3 Hz, 1H), 2.61 (dddt, *J* = 14.6, 6.7, 5.4, 1.3 Hz, 1H).

Table S1. Δδ (=δ_S - δ_R) data for the (*S*)-MTPA Mosher ester **SI-4** and (*R*)-MTPA Mosher ester **SI-5**

	δ (*S*)-ester SI-4 (ppm)	δ (*R*)-ester SI-5 (ppm)	$\Delta\delta^{SR}$ (=δ_S - δ_R)	
			ppm	Hz (500 MHz)
H-1	6.03	5.97	0.06	30
H-2_b	2.58	2.61	-0.03	-15
H-2_a	2.70	2.74	-0.04	-20
H-4_a & H-4_b	5.01	5.12	-0.11	-55
H-3	5.61	5.74	-0.13	-65

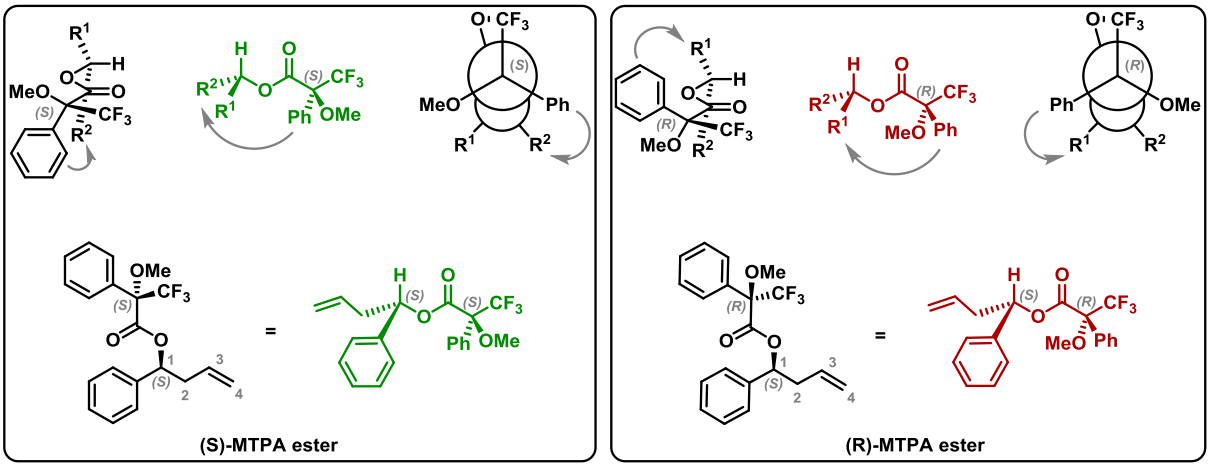
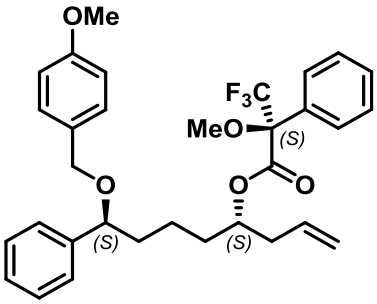


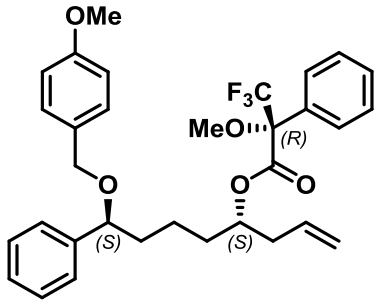
Figure S5. Conformational analysis of each of the diastereoisomeric MTPA esters of **SI-4** and **SI-5**. Gray arrow indicates the phenyl group shielding effect.



(4*S*,8*S*)-8-((4-methoxybenzyl)oxy)-8-phenyloct-1-en-4-yl (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (SI-6).

According to general procedure **GP-1**, the reaction was performed with compound **SI-2** (14 mg, 0.04 mmol). After purification by flash column chromatography (hexane/ethyl acetate 95:5) Mosher ester **SI-6** was obtained (20 mg, 87%) as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.55 – 7.48 (m, 2H), 7.40 – 7.32 (m, 5H), 7.31 – 7.26 (m, 3H), 7.22 – 7.17 (m, 2H), 6.90 – 6.84 (m, 2H), 5.72 (ddt, *J* = 19.3, 9.6, 7.0 Hz, 1H), 5.12 (p, *J* = 6.4 Hz, 1H), 5.10 – 5.06 (m, 2H), 4.36 (d, *J* = 11.4 Hz, 1H), 4.17 (dd, *J* = 7.9, 5.6 Hz, 1H), 4.14 (d, *J* = 11.4 Hz, 1H), 3.80 (s, 3H), 3.54 – 3.46 (m, 3H), 2.37 (td, *J* = 6.4, 5.9, 1.5 Hz, 2H), 1.80 (dddd, *J* = 13.2, 10.2, 7.8, 5.0 Hz, 1H), 1.57 – 1.51 (m, 3H), 1.38 – 1.29 (m, 1H), 1.23 – 1.16 (m, 1H).



(4*S*,8*S*)-8-((4-methoxybenzyl)oxy)-8-phenyloct-1-en-4-yl (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (SI-7).

According to general procedure **GP-1**, the reaction was performed with compound **SI-2** (14 mg, 0.04 mmol). After purification by flash column chromatography (hexane/ethyl acetate 95:5) Mosher ester **SI-7** was obtained (19 mg, 83%) as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.54 – 7.48 (m, 2H), 7.39 – 7.33 (m, 5H), 7.32 – 7.28 (m, 3H), 7.23 – 7.16 (m, 2H), 6.89 – 6.83 (m, 2H), 5.58 (ddt, *J* = 17.3, 10.5, 7.1 Hz, 1H), 5.09 (p, *J* = 5.9 Hz, 1H), 5.01 – 4.94 (m, 2H), 4.38 (d, *J* = 11.4 Hz, 1H), 4.24 (dd, *J* = 7.7, 5.7 Hz, 1H), 4.16 (d, *J* = 11.4 Hz, 1H), 3.80 (s, 3H), 3.47 – 3.43 (m, 3H), 2.29 (td, *J* = 6.5, 5.7, 1.3 Hz, 2H), 1.86 (dddd, *J* = 13.0, 10.2, 7.7, 5.0 Hz, 1H), 1.65 – 1.54 (m, 3H), 1.50 – 1.39 (m, 1H), 1.32 (dddd, *J* = 16.0, 12.3, 10.2, 5.9 Hz, 1H).

Table S2. Δδ (=δ_S - δ_R) data for the (*S*)-MTPA Mosher ester **SI-6** and (*R*)-MTPA Mosher ester **SI-7**

	δ (*S*)-ester SI-6 (ppm)	δ (*R*)-ester SI-7 (ppm)	$\Delta\delta^{SR}$ (=δ_S - δ_R)	
			ppm	Hz (600 MHz)
H-2	5.72	5.58	0.14	84
H-1_a&H-1_b	5.08	4.98	0.10	60
H-3_a&H-3_b	2.37	2.29	0.08	48
OMe	3.50	3.45	0.05	30
H-4	5.12	5.09	0.03	18
OMe (PMB)	3.80	3.80	0.00	0
CH_2Ar (PMB)	4.36	4.38	-0.02	-12
CH_2Ar (PMB)	4.14	4.16	-0.02	-12
H-7	1.80	1.86	-0.06	-36
H-8	4.17	4.24	-0.07	-42

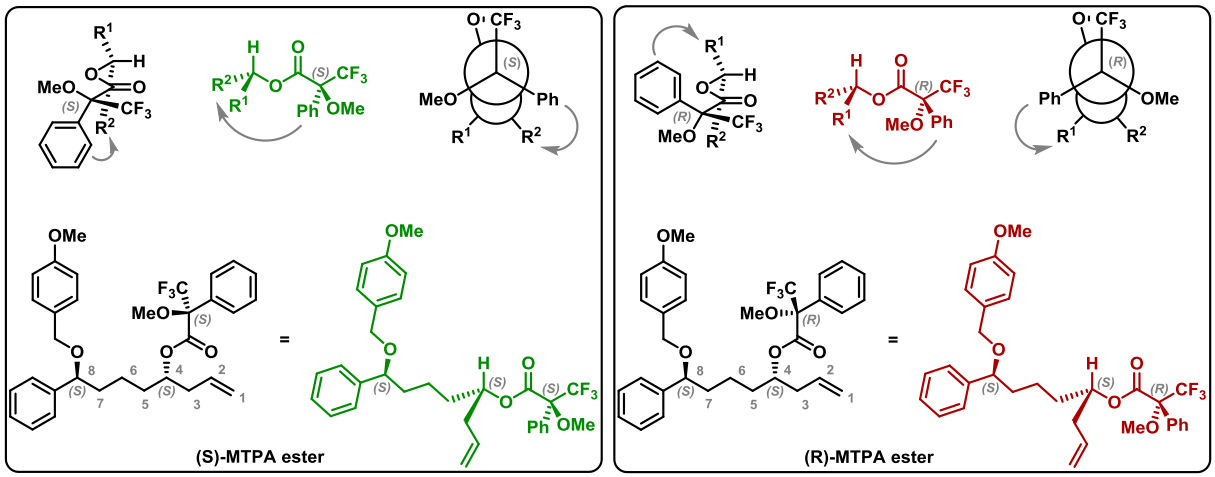
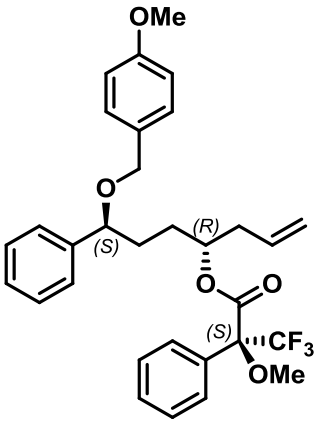


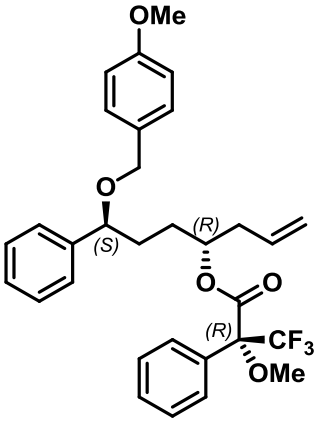
Figure S6. Conformational analysis of each of the diastereoisomeric MTPA esters of **SI-6** and **SI-7**. Gray arrow indicates the phenyl group shielding effect.



(4R,7S)-7-((4-methoxybenzyl)oxy)-7-phenylhept-1-en-4-yl (S)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (SI-8).

According to general procedure **GP-1**, the reaction was performed with compound **9** (13 mg, 0.04 mmol). After purification by flash column chromatography (hexane/ethyl acetate 95:5) Mosher ester **SI-8** was obtained (18 mg, 83%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.47 (m, 2H), 7.37 – 7.27 (m, 8H), 7.23 – 7.16 (m, 2H), 6.89 – 6.82 (m, 2H), 5.65 – 5.52 (m, 1H), 5.19 – 5.09 (m, 1H), 5.01 – 4.94 (m, 2H), 4.38 (d, *J* = 11.4 Hz, 1H), 4.24 (dd, *J* = 7.7, 4.9 Hz, 1H), 4.16 (d, *J* = 11.4 Hz, 1H), 3.80 (s, 3H), 3.49 (q, *J* = 1.3 Hz, 3H), 2.34 – 2.28 (m, 2H), 1.91 – 1.77 (m, 2H), 1.72 – 1.65 (m, 1H), 1.61 – 1.53 (m, 1H).



(4*R*,7*S*)-7-((4-methoxybenzyl)oxy)-7-phenylhept-1-en-4-yl (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (SI-9).

According to general procedure **GP-1**, the reaction was performed with compound **9** (10 mg, 0.03 mmol). After purification by flash column chromatography (hexane/ethyl acetate 95:5) Mosher ester **SI-9** was obtained (14 mg, 86%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.46 (m, 2H), 7.39 – 7.27 (m, 6H), 7.23 – 7.16 (m, 4H), 6.88 – 6.79 (m, 2H), 5.77 – 5.66 (m, 1H), 5.20 – 5.11 (m, 1H), 5.11 – 5.02 (m, 2H), 4.34 (d, *J* = 11.4 Hz, 1H), 4.15 (dd, *J* = 8.3, 4.9 Hz, 1H), 4.12 (d, *J* = 11.4 Hz, 1H), 3.80 (s, 3H), 3.52 (q, *J* = 1.3 Hz, 3H), 2.44 – 2.30 (m, 2H), 1.87 – 1.77 (m, 1H), 1.72 – 1.62 (m, 1H), 1.56 – 1.43 (m, 2H).

Table S3. Δδ (=δ_S - δ_R) data for the (*S*)-MTPA Mosher ester **SI-8** and (*R*)-MTPA Mosher ester **SI-9**

	δ (*S*)-ester SI-8 (ppm)	δ (*R*)-ester SI-9 (ppm)	$\Delta\delta^{SR}$ (=δ_S - δ_R)	
			ppm	Hz (400 MHz)
H-7	4.24	4.15	0.09	36
CH_2Ar (PMB)	4.38	4.34	0.04	16
CH_2Ar (PMB)	4.16	4.12	0.04	16
OMe (PMB)	3.80	3.80	0.00	0
H-4	5.13	5.15	-0.02	-8
OMe	3.49	3.52	-0.03	-12
H-3_a&H-3_b	2.31	2.38	-0.07	-28
H-1_a&H-1_b	4.98	5.07	-0.09	-36
H-2	5.59	5.71	-0.12	-48

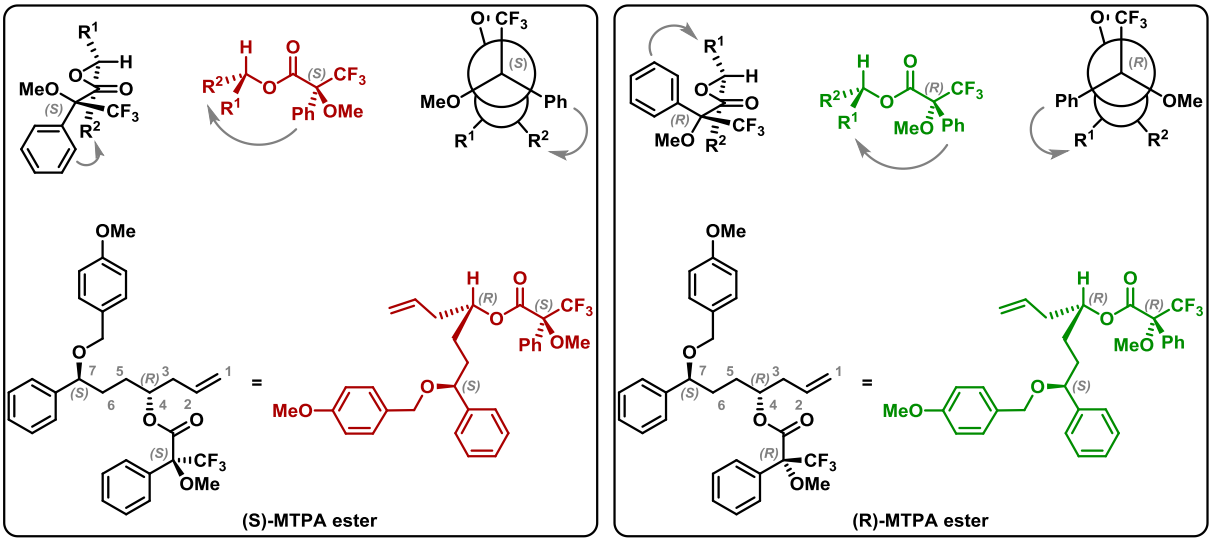
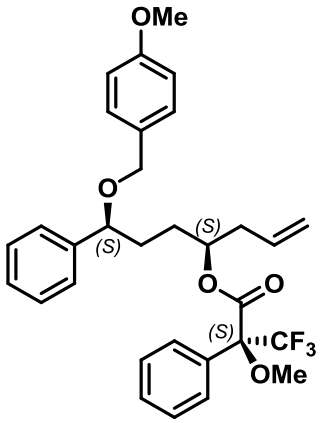


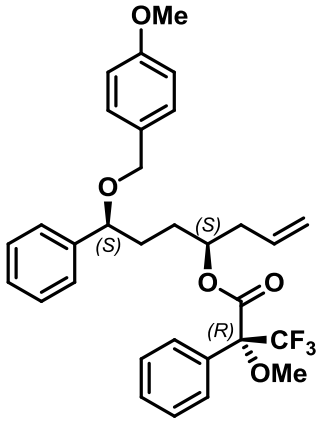
Figure S7. Conformational analysis of each of the diastereoisomeric MTPA esters of **SI-8** and **SI-9**. Gray arrow indicates the phenyl group shielding effect.



(4*S*,7*S*)-7-((4-methoxybenzyl)oxy)-7-phenylhept-1-en-4-yl (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (SI-10).

According to general procedure **GP-1**, the reaction was performed with compound **SI-3** (36 mg, 0.11 mmol). After purification by flash column chromatography (hexane/ethyl acetate 95:5) Mosher ester **SI-10** was obtained (54 mg, 90%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.48 (m, 2H), 7.39 – 7.27 (m, 6H), 7.26 – 7.22 (m, 2H), 7.21 – 7.17 (m, 2H), 6.89 – 6.84 (m, 2H), 5.77 – 5.64 (m, 1H), 5.21 – 5.12 (m, 1H), 5.11 – 5.04 (m, 2H), 4.37 (d, *J* = 11.5 Hz, 1H), 4.22 (dd, *J* = 8.0, 4.8 Hz, 1H), 4.13 (d, *J* = 11.4 Hz, 1H), 3.81 (s, 3H), 3.53 (q, *J* = 1.3 Hz, 3H), 2.44 – 2.29 (m, 2H), 1.80 – 1.67 (m, 2H), 1.64 – 1.45 (m, 2H).



(4*S*,7*S*)-7-((4-methoxybenzyl)oxy)-7-phenylhept-1-en-4-yl (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (SI-11).

According to general procedure **GP-1**, the reaction was performed with compound **SI-3** (29 mg, 0.09 mmol). After purification by flash column chromatography (hexane/ethyl acetate 95:5) Mosher ester **SI-11** was obtained (45 mg, 92%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.48 (m, 2H), 7.39 – 7.27 (m, 8H), 7.23 – 7.19 (m, 2H), 6.90 – 6.84 (m, 2H), 5.64 – 5.52 (m, 1H), 5.18 – 5.10 (m, 1H), 5.02 – 4.92 (m, 2H), 4.39 (d, *J* = 11.4 Hz, 1H), 4.29 (dd, *J* = 8.1, 4.5 Hz, 1H), 4.16 (d, *J* = 11.4 Hz, 1H), 3.81 (s, 3H), 3.49 (q, *J* = 1.3 Hz, 3H), 2.38 – 2.24 (m, 2H), 1.92 – 1.75 (m, 2H), 1.71 – 1.56 (m, 2H).

Table S4. Δδ (=δ_S - δ_R) data for the (*S*)-MTPA Mosher ester **SI-10** and (*R*)-MTPA Mosher ester **SI-11.**

	δ (*S*)-ester SI-10 (ppm)	δ (*R*)-ester SI-11 (ppm)	$\Delta\delta^{SR}$ (=δ_S - δ_R)	
			ppm	Hz (400 MHz)
H-2	5.70	5.58	0.12	48
H-1_a&H-1_b	5.07	4.97	0.10	40
H-3_a&H-3_b	2.37	2.30	0.07	28
OMe	3.53	3.49	0.04	16
H-4	5.16	5.15	0.01	4
OMe (PMB)	3.81	3.81	0.00	0
CH_2Ar (PMB)	4.37	4.39	-0.02	-8
CH_2Ar (PMB)	4.13	4.16	-0.03	-12
H-7	4.22	4.29	-0.07	-28

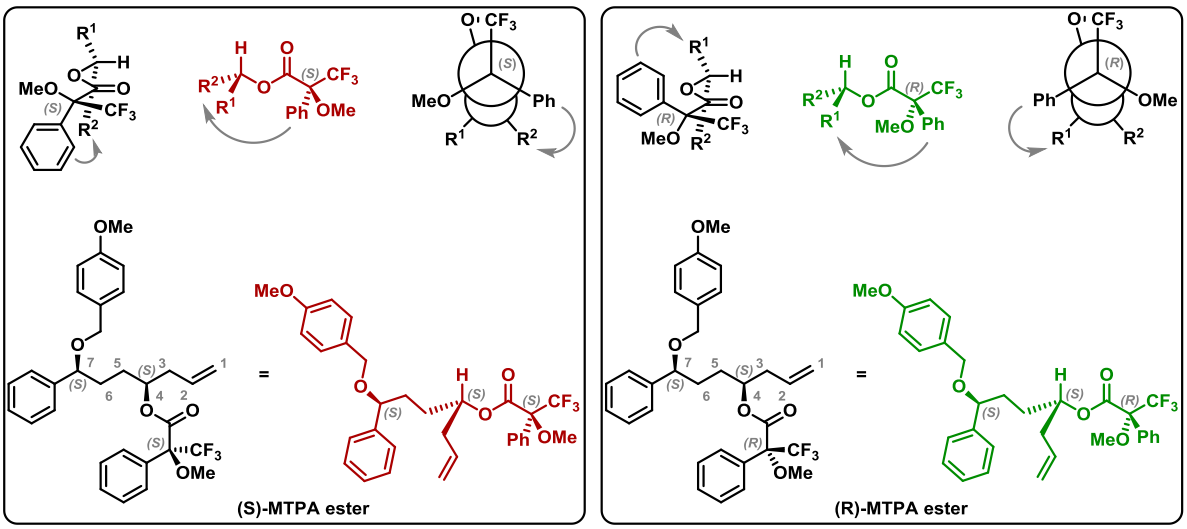
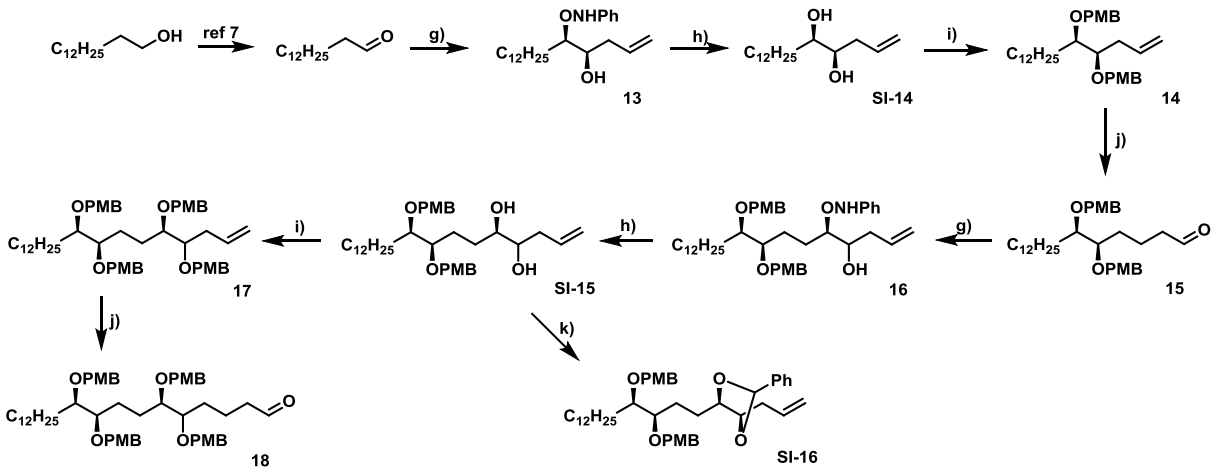
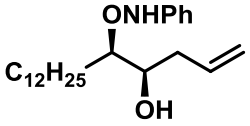


Figure S8. Conformational analysis of each of the diastereoisomeric MTPA esters of **SI-10** and **SI-11**. Gray arrow indicates the phenyl group shielding effect.

Section S9. Iterative synthesis of monhexocin's fragment



Scheme S3. Iterative synthesis towards monhexocin.
Reagents and conditions: (g) L-proline, PhNO, allyl bromide, NaI, TBAI, DMF, 0 °C, 3 h, 59-62%, (h) Zn, AcOH, THF, H_2O, 60 °C, 1 h, 91-99%, (i) PMBCl, NaH, TBAI, DMF, 0 °C to rt, 17 h, 88%, (j) $Rh(CO)_2acac$, 6-DPPon, TBAI, Ac_2O, HCOOH, MS 4 Å, DMF, 80 °C, 20 h, 39-61%, (k) PhCHO, CSA, MS 4 Å, PhH, 0 °C, 1 h, 37%.



(4*R*,5*R*)-5-((phenylamino)oxy)heptadec-1-en-4-ol (13). Prepared *via* adaptation of procedure from[R7].

To a solution of 1-tetradecanal (1.7 g, 8 mmol, 3 equiv) in anhydrous DMF (30 mL), L-proline (921 mg, 8 mmol) was added and stirred at rt for 1 h. Then, nitrosobenzene (285 mg, 2.67 mmol, 1 equiv) was added. The endpoint of the reaction was monitored by its color change from green to orange. After 45 min, the solution was cooled to 0 °C and allylindium iodide solution (prepared by heating for 1 h at 70 °C: granular indium (916 mg, 8 mmol), NaI (1.2 g, 8 mmol), allyl bromide (1.38 mL, 16 mmol) and anhydrous DMF (10 mL)) was slowly added. The stirring was kept at 0 °C for 2 h. It was then diluted with Et_2O and washed with water. The aqueous layer was extracted with Et_2O. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Crude product was purified by column chromatography (hexane/ethyl acetate 9:1) to give two diastereoisomeric products as yellow oils with 59% yield for *syn*-configured product **13** (faster-eluting diastereoisomer) and 40% yield for *anti*-

configured product (slower-eluting diastereoisomer). The diastereomeric ratio of the products were determined by preparing Mosher esters of slower-eluting diastereoisomer (analysis below).

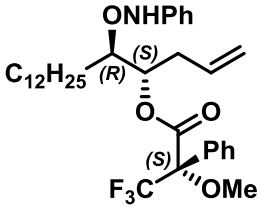
$[\alpha]^{21}_{D}$ 19.17 (c 0.9, C_6H_6);

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.91 – 5.81 (m, 1H), 5.19 – 5.13 (m, 2H), 3.53 – 3.42 (m, 2H), 2.39 – 2.33 (m, 1H), 2.27 – 2.20 (m, 1H), 2.09 – 2.03 (m, 2H), 1.54 – 1.42 (m, 3H), 1.26 (s, 19H), 0.88 (t, *J* = 6.8 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 148.3, 134.7, 129.0, 122.5, 117.8, 115.1, 85.5, 72.7, 38.2, 31.9, 29.8, 29.7, 29.6, 29.6, 29.5, 29.5, 29.3, 25.6, 22.7, 14.1;

IR (film, CH_2Cl_2); 3270, 3075, 2925, 2853, 1643, 1603, 1522, 1495, 1466, 1360, 1280, 1183, 1166, 1145, 1111, 1051, 1026, 997, 913, 822, 769, 741, 694 cm^{-1};

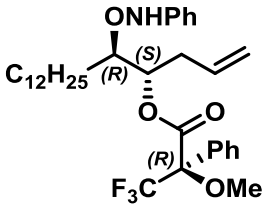
HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{23}H_{50}NO_2$ 362.3059; Found 362.3057.



(4*S*,5*R*)-5-((phenylamino)oxy)heptadec-1-en-4-yl (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (SI-12).

According to general procedure **GP-1**, the reaction was performed with diastereoisomer of compound **13** (20 mg, 0.055 mmol). After purification by flash column chromatography (hexane/ethyl acetate 95:5) Mosher ester **SI-12** was obtained (27 mg, 84%) as a white solid.

^{1}H NMR (400 MHz, C_6D_6) δ 7.26 (d, *J* = 7.7 Hz, 2H), 6.87 – 6.71 (m, 4H), 6.68 – 6.57 (m, 4H), 6.03 – 5.89 (m, 1H), 5.10 (d, *J* = 17.1 Hz, 1H), 5.03 (d, *J* = 10.1 Hz, 1H), 4.62 (brs, 1H), 4.18 (brs, 1H), 3.70 (d, *J* = 9.4 Hz, 1H), 3.45 (s, 3H), 2.62 – 2.46 (m, 1H), 2.16 – 2.05 (m, 1H), 1.87 – 1.82 (m, 1H), 1.30 – 1.13 (m, 16H), 1.11 – 1.03 (m, 3H), 0.93 – 0.89 (m, 2H), 0.89 – 0.86 (m, 3H).



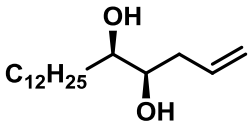
(4*S*,5*R*)-5-((phenylamino)oxy)heptadec-1-en-4-yl (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (SI-13).

According to general procedure **GP-1**, the reaction was performed with diastereoisomer of compound **13** (20 mg, 0.055 mmol). After purification by flash column chromatography (hexane/ethyl acetate 95:5). Mosher ester **SI-13** was obtained (23 mg, 72%) as a colorless oil.

^{1}H NMR (400 MHz, C_6D_6) δ 7.58 (dd, *J* = 6.9, 2.8 Hz, 1H), 7.02 (dd, *J* = 5.3, 2.0 Hz, 1H), 6.79 (d, *J* = 7.2 Hz, 1H), 6.72 (brs, 2H), 6.44 (brs, 1H), 5.98 – 5.84 (m, 1H), 5.02 (d, *J* = 17.1 Hz, 1H), 4.97 (d, *J* = 10.2 Hz, 1H), 4.90 (brs, 1H), 4.15 (brs, 1H), 3.44 (d, *J* = 10.1 Hz, 1H), 3.08 (brs, 3H), 2.46 (brs, 1H), 2.02 – 1.87 (m, 2H), 1.32 – 1.20 (m, 16H), 1.15 (brs, 3H), 0.96 (brs, 2H), 0.91 – 0.85 (m, 3H).

Table S5. Δδ (=δ_S - δ_R) data for the (*S*)-MTPA Mosher ester **SI-12** and (*R*)-MTPA Mosher ester **SI-13**

	δ (*S*)-ester SI-12 (ppm)	**δ (*R*)-ester SI-13 (ppm)**	**$\Delta\delta^{SR}$ (=δ_S - δ_R)**	
			ppm	**Hz (400 MHz)**
H-5	3.70	3.49	0.21	84
H-3_a	2.10	1.98	0.12	48
H-1	5.06	5.04	0.02	8
H-3_b	2.53	2.51	0.02	8
H-2	5.96	5.96	0	0
H-4	4.18	4.19	-0.01	-4
H-6_b	1.35	1.36	-0.01	-4
H-17	0.87	0.93	-0.06	-24
Alkyl chain	1.24	1.30	-0.06	-24
H-6_a	1.87	1.98	-0.11	-44
-NH**Ph**	6.79	7.06	-0.27	-108
-N**H**Ph	4.63	4.94	-0.31	-124
-NH**Ph**	7.25	7.62	-0.37	-148



(4*R*,5*R*)-heptadec-1-ene-4,5-diol (SI-14). Prepared under conditions from[R8].

Diastereoisomer **13** (550 mg, 1.52 mmol) was dissolved in a 1:1 THF/H_2O mixture (22 mL). Acetic acid (33.5 mL) and Zn dust (3.78 g, 57 mmol) was added. The mixture was stirred at 60 °C for 1 h. After cooling to rt, the mixture was diluted with Et_2O and filtered through a plug of silica gel, which was washed by Et_2O. After evaporation of the solvents, the resulting crude mixture was redissolved in EtOAc, preadsorbed on silica gel and purified by column chromatography (hexane/ethyl acetate 4:1) to give **SI-14** (374 mg, 91%) as a white solid.

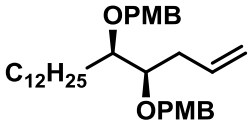
$[\alpha]^{21}_D$ 7.28 (c 2.4, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.91 – 5.81 (m, 1H), 5.19 – 5.13 (m, 2H), 3.53 – 3.42 (m, 2H), 2.39 – 2.33 (m, 1H), 2.28 – 2.20 (m, 1H), 2.09 – 2.03 (m, 2H), 1.54 – 1.43 (m, 3H), 1.26 (s, 19H), 0.88 (t, *J* = 6.8 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 134.5, 118.2, 73.9, 73.2, 38.3, 33.6, 31.9, 29.7, 29.6, 29.6, 29.6, 29.6, 29.3, 25.6, 22.7, 14.1;

IR (film, CH_2Cl_2); 3193, 2916, 2848, 1643, 1469, 1436, 1281, 1065, 989, 915, 872, 718 cm^{-1};

HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{17}H_{54}O_2Na$ 293.2408; Found 293.2416.



4,4'-((((4*R*,5*R*)-heptadec-1-ene-4,5-diyl)bis(oxy))bis(methylene))bis(methoxybenzene) (14).

NaH (60% dispersion in mineral oil, 213 mg, 5.32 mmol, 4 equiv) was added to a flask containing **SI-14** (360 mg, 1.33 mmol) and TBAI (25 mg, 0.067 mmol, 5 mol%) in anhydrous DMF (15 mL) cooled to 0 ºC. Reaction mixture was stirred at 0 ºC for 30 min. Then, PMBCl (0.72 mL, 5.32 mmol, 4 equiv) was added dropwise and the mixture was stirred at rt for 17 h. Saturated NH_4Cl was added to quench the reaction followed by the extraction with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Crude

product was purified by column chromatography (hexane/ethyl acetate 95:5) to give **14** (598 mg, 88%, >99% *ee* by HPLC analysis) as a colorless oil.

HPLC (Chiralcel OD-H, hexane/*i*-PrOH 99.5:0.5, flow rate 1 mL/min, λ 220 nm): t_R = 8.1 min (*S*,*S*), t_R = 8.4 min (*S*,*R*), t_R = 9.0 min (*R*,*R*), t_R = 13.7 min (*R*,*S*);

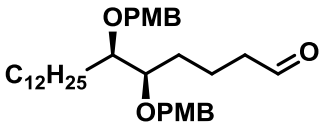
$[\alpha]^{20}_D$ -1.36 (c 2.1, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.22 (m, 4H), 6.89 – 6.84 (m, 4H), 5.90 – 5.78 (m, 1H), 5.12 – 5.01 (m, 2H), 4.58 – 4.43 (m, 4H), 3.80 (s, 6H), 3.50 (dt, *J* = 7.7, 4.6 Hz, 1H), 3.41 (dt, *J* = 8.7, 4.3 Hz, 1H), 2.44 – 2.36 (m, 1H), 2.30 – 2.19 (m, 1H), 1.63 – 1.53 (m, 1H), 1.49 – 1.34 (m, 2H), 1.26 (m, 20H), 0.92 – 0.86 (m, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 135.8, 131.1, 131.0, 129.5, 129.5, 116.5, 113.7, 79.7, 79.6, 72.3, 72.1, 55.3, 34.7, 31.9, 29.9, 29.8, 29.7, 29.7, 29.7, 29.6, 29.4, 25.9, 22.7, 14.1;

IR (film, CH_2Cl_2); 3072, 2999, 2925, 2853, 2063, 1739, 1640, 1612, 1586, 1513, 1464, 1357, 1302, 1248, 1174, 1089, 1038, 912, 822 cm^{-1};

HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{33}H_{50}O_4Na$ 533.3607; Found 533.3588.



(5*R*,6*R*)-5,6-bis((4-methoxybenzyl)oxy)octadecanal (15).

Mixture of catalyst $Rh(CO)_2acac$ (30 mg, 0.115 mmol, 10 mol%), ligand 6-DPPon (64 mg, 0.23 mmol, 20 mol%), additive TBAI (10.6 mg, 0.029 mmol, 2.5 mol%), 4 Å molecular sieves and anhydrous DMF (8 mL) was stirred in an ampule flushed with argon. Then **14** (585 mg, 1.15 mmol) dissolved in anhydrous DMF (8 mL) was added, stirred at rt for 5 min and Ac_2O (653 µL, 6.9 mmol, 6 equiv) and HCOOH (340 µL, 8.97 mmol, 7.8 equiv) were successively added. The reaction mixture was stirred at 80 ºC for 20 h. It was then cooled to rt and poured directly on silica gel. Column chromatography (hexane/ethyl acetate 9:1) afforded aldehyde **15** (378 mg, 61%) as a brownish oil.

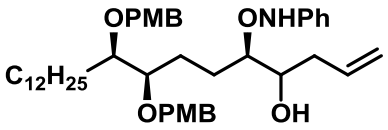
$[\alpha]^{20}_D$ 13.15 (c 1.57, $CHCl_3$);

^{1}H NMR (400 MHz, C_6D_6) δ 9.29 (t, *J* = 1.6 Hz, 1H), 7.24 (dd, *J* = 13.1, 8.6 Hz, 4H), 6.79 (dd, *J* = 8.6, 5.3 Hz, 4H), 4.51 (dd, *J* = 11.4, 3.9 Hz, 2H), 4.41 (dd, *J* = 26.3, 11.4 Hz, 2H), 3.53 – 3.47 (m, 1H), 3.46 – 3.40 (m, 1H), 3.30 (s, 6H), 1.85 – 1.78 (m, 2H), 1.75 – 1.38 (m, 7H), 1.34 – 1.20 (m, 20H), 0.90 – 0.85 (m, 3H);

^{13}C NMR (100 MHz, C_6D_6) δ 200.3, 159.4, 131.4, 131.2, 129.3, 129.3, 113.7, 79.5, 79.3, 72.1, 72.0, 54.4, 43.6, 32.0, 30.0, 29.9, 29.8, 29.8, 29.4, 29.3, 26.3, 22.7, 18.7, 14.0;

IR (film, $CHCl_3$); 2999, 2925, 2853, 2717, 2062, 1724, 1612, 1586, 1513, 1463, 1359, 1302, 1248, 1174, 1070, 1037, 821cm^{-1};

HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{34}H_{52}O_5Na$ 563.3712; Found 563.3706.



(5*R*,8*R*,9*R*)-8,9-bis((4-methoxybenzyl)oxy)-5-((phenylamino)oxy)henicos-1-en-4-ol (16). Prepared *via* adaptation of procedure from[R7].

To a solution of aldehyde **15** (362 mg, 0.67 mmol, 3 equiv) in anhydrous DMF (2.5 mL), L-proline (77 mg, 0.67 mmol) was added and stirred at rt for 17 h. Then, nitrosobenzene (24 mg, 0.223 mmol, 1 equiv) was added. The endpoint of the reaction was monitored by its color change from green to orange. After 1.5 h, the solution was cooled to 0 °C and allylindium iodide solution (prepared by heating for 1 h at 70 °C: granular indium (73 mg, 0.67 mmol), NaI (95 mg, 0.67 mmol), allyl bromide (110 μL, 1.27 mmol) and anhydrous DMF (1 mL)) was slowly added. The stirring was kept at 0 °C for 2 h then at rt for 15 h. It was then diluted with Et_2O and washed with water. The aqueous layer was extracted with Et_2O. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Crude product was purified by column chromatography (hexane/acetone 85:15) to give inseparable 1:1 mixture of diastereoisomers **16** (95 mg, 62%) as yellow oil.

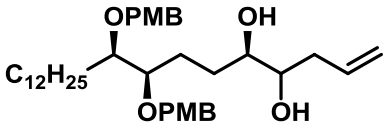
^{1}H NMR (400 MHz, C_6D_6) δ 7.30 – 7.20 (m, 4H), 7.11 – 7.06 (m, 2H), 6.93 – 6.86 (m, 2H), 6.84 – 6.73 (m, 6H), 5.97 – 5.74 (m, 1H), 5.10 – 4.96 (m, 2H), 4.59 – 4.53 (m, 2H), 4.45 (ddd, *J* = 19.7, 11.4, 5.4 Hz, 2H), 3.99 – 3.93 (m, 1H), 3.81 – 3.73 (m, 1H), 3.62 – 3.53 (m, 2H), 3.32

– 3.25 (m, 6H), 2.59 – 2.49 (m, 1H), 2.40 – 2.30 (m, 1H), 2.29 – 2.14 (m, 2H), 2.10 – 1.91 (m, 2H), 1.86 – 1.70 (m, 2H), 1.49 – 1.37 (m, 1H), 1.35 – 1.17 (m, 20H), 0.91 – 0.82 (m, 3H);

^{13}C NMR (100 MHz, C_6D_6) δ 159.4, 159.4, 149.1, 149.0, 135.5, 135.3, 131.4, 131.2, 129.4, 129.4, 129.3, 128.8, 121.8, 121.8, 116.9, 114.8, 114.7, 113.8, 113.8, 113.7, 85.8, 85.4, 79.7, 72.4, 72.2, 72.1, 71.6, 59.7, 54.4, 37.6, 32.0, 30.0, 29.8, 29.8, 29.4, 26.3, 24.4, 22.7, 14.0;

IR (film, CH_2Cl_2); 3446, 3267, 2999, 2925, 2853, 2062, 1688, 1640, 1611, 1513, 1494, 1464, 1358, 1302, 1248, 1174, 1037, 914, 821, 762 cm^{-1};

HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{43}H_{63}NO_6Na$ 712.4553; Found 712.4542.



(5*R*,8*R*,9*R*)-8,9-bis((4-methoxybenzyl)oxy)henicos-1-ene-4,5-diol (SI-15). Prepared under conditions from[R8].

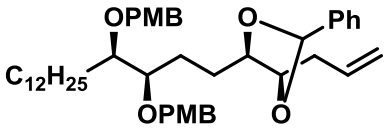
Diastereoisomers **16** (90 mg, 0.13 mmol) were dissolved in a 1:1 THF/H_2O mixture (2 mL). Acetic acid (3 mL) and Zn dust (296 mg, 4.48 mmol) was added. The mixture was stirred at 60 °C for 1 h. After cooling to rt, the mixture was diluted with Et_2O and filtered through a plug of silica gel, which was washed by Et_2O. After evaporation of the solvents, the resulting crude mixture was redissolved in EtOAc, preadsorbed on silica gel and purified by column chromatography (hexane/ethyl acetate 3:2) to give **SI-15** (77 mg, 99%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.19 (m, 4H), 6.89 – 6.83 (m, 4H), 5.89 – 5.77 (m, 1H), 5.17 – 5.08 (m, 2H), 4.58 – 4.40 (m, 4H), 3.79 (s, 6H), 3.59 – 3.32 (m, 4H), 2.36 (s, 2H), 2.31 – 2.10 (m, 2H), 1.80 – 1.66 (m, 1H), 1.63 – 1.48 (m, 3H), 1.48 – 1.36 (m, 3H), 1.26 (s, 23H), 0.91 – 0.85 (m, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 159.2, 135.1, 134.7, 130.9, 130.5, 129.7, 129.7, 129.5, 118.0, 117.8, 113.8, 113.8, 79.7, 79.4, 79.4, 74.0, 73.4, 73.2, 72.3, 72.2, 55.3, 38.3, 36.2, 31.9, 29.8, 29.7, 29.7, 29.7, 29.6, 29.4, 27.9, 26.0, 22.7, 14.1;

IR (film, CH_2Cl_2); 3425, 3073, 2998, 2925, 2853, 2063, 1881, 1708, 1640, 1612, 1586, 1514, 1465, 1358, 1302, 1249, 1210, 1173, 1065, 1038, 914, 822, 755 cm^{-1};

HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{37}H_{58}O_6Na$ 621.4131; Found 621.4144.



(2*S*,4*R*,5*R*)-4-allyl-5-((3*R*,4*R*)-3,4-bis((4-methoxybenzyl)oxy)hexadecyl)-2-phenyl-1,3-dioxolane (SI-16). Prepared under conditions from[R9].

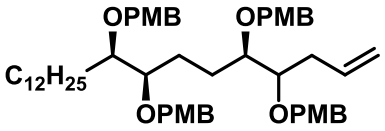
Mixture of diastereoisomers **SI-15** (20 mg, 0.033 mmol) was dissolved in PhH (0.35 mL) with camphorsulfonic acid (10 mg, 0.033 mmol) and 4 Å molecular sieves. Solution was cooled to 0 ºC and PhCHO (85 μL, 0.825 mmol) was added. The mixture was stirred at 0 °C for 1 h. It was then warmed to rt and poured directly on silica gel. Column chromatography (hexane/ethyl acetate 95:5) afforded *threo/threo* diastereoisomer **SI-16** (8.5 mg, 37%) as a colorless oil. Structure was confirmed by NOE experiment.

^{1}H NMR (600 MHz, C_6D_6) δ 7.35 – 7.32 (m, 2H), 7.02 (d, *J* = 8.6 Hz, 2H), 6.97 (d, *J* = 8.6 Hz, 2H), 6.90 – 6.88 (m, 2H), 6.84 – 6.80 (m, 1H), 6.53 (dd, *J* = 8.6, 7.8 Hz, 4H), 5.67 – 5.58 (m, 1H), 5.50 (s, 1H), 4.83 – 4.78 (m, 1H), 4.77 – 4.74 (m, 1H), 4.32 (dd, *J* = 11.4, 4.4 Hz, 2H), 4.21 (dd, *J* = 39.4, 11.4 Hz, 2H), 3.69 – 3.64 (m, 1H), 3.63 – 3.59 (m, 1H), 3.33 (m, 2H), 3.03 (s, 6H), 2.10 – 2.04 (m, 1H), 1.82 – 1.77 (m, 1H), 1.73 – 1.64 (m, 1H), 1.63 – 1.47 (m, 4H), 1.41 – 1.30 (m, 3H), 1.21 – 1.11 (m, 3H), 1.06 – 0.98 (m, 20H), 0.62 (m, 3H);

^{13}C NMR (150 MHz, C_6D_6) δ 159.4, 159.4, 138.7, 135.1, 131.4, 131.3, 129.5, 129.3, 128.8, 128.1, 127.9, 127.7, 127.6, 126.9, 116.5, 113.7, 103.1, 79.9, 78.8, 78.7, 78.4, 72.1, 71.8, 54.4, 54.4, 34.7, 32.0, 30.0, 29.8, 29.8, 29.8, 29.4, 26.7, 26.3, 26.2, 22.7, 14.0;

IR (film, CH_2Cl_2); 3464, 3070, 2925, 2853, 1745, 1641, 1612, 1586, 1513, 1462, 1376, 1301, 1248, 1173, 1090, 1066, 1037, 916, 821, 758 cm^{-1};

HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{44}H_{62}O_6Na$ 709.4443; Found 709.4444.



4,4',4'',4'''-((((5*R*,8*R*,9*R*)-henicos-1-ene-4,5,8,9-tetrayl)tetrakis(oxy))tetrakis(methylene))tetrakis(methoxybenzene) (17).

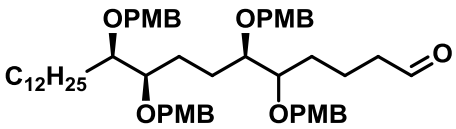
NaH (60% dispersion in mineral oil, 15 mg, 0.368 mmol, 4 equiv) was added to a flask containing **SI-14** (55 mg, 0.092 mmol) and TBAI (1.7 mg, 4.6 μmol, 5 mol%) in anhydrous DMF (1 mL) cooled to 0 ºC. Reaction mixture was stirred at 0 ºC for 30 min. Then, PMBCl (50 μL, 0.368 mmol, 4 equiv) was added dropwise and the mixture was stirred at rt for 17 h. Saturated NH_4Cl was added to quench the reaction followed by the extraction with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Crude product was purified by column chromatography (hexane/ethyl acetate 95:5) to give **17** (68 mg, 88%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.18 (m, 8H), 6.87 – 6.79 (m, 8H), 5.95 – 5.76 (m, 1H), 5.14 – 4.99 (m, 2H), 4.63 – 4.39 (m, 8H), 3.78 (s, 12H), 3.53 – 3.36 (m, 4H), 2.45 – 2.17 (m, 2H), 1.88 – 1.53 (m, 5H), 1.48 – 1.38 (m, 2H), 1.33 – 1.23 (m, 19H), 0.92 – 0.85 (m, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 129.5, 129.4, 129.3, 113.7, 71.9, 55.2, 31.9, 30.7, 29.8, 29.7, 29.7, 29.4, 22.7, 14.1;

IR (film, CH_2Cl_2); 3070, 2999, 2925, 2853, 2062, 1881, 1612, 1586, 1513, 1464, 1356, 1301, 1248, 1173, 1087, 1037, 913, 821, 756 cm^{-1};

HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{53}H_{74}O_8Na$ 861.5281; Found 861.5273.



(6*R*,9*R*,10*R*)-5,6,9,10-tetrakis((4-methoxybenzyl)oxy)docosanal (18).

Mixture of catalyst $Rh(CO)_2acac$ (1.8 mg, 7.2 μmol, 10 mol%), ligand 6-DPPon (4 mg, 14.4 μmol, 20 mol%), additive TBAI (0.6 mg, 1.8 μmol, 2.5 mol%), 4 Å molecular sieves and anhydrous DMF (0.6 mL) was stirred in an ampule flushed with argon. Then **17** (60 mg, 0.072 mmol) dissolved in anhydrous DMF (0.6 mL) was added, stirred at rt for 5 min and Ac_2O (38.4

μL, 0.432 mmol, 6 equiv) and HCOOH (20 μL, 0.562 mmol, 7.8 equiv) were successively added. The reaction mixture was stirred at 80 ºC for 20 h. It was then cooled to rt and poured directly on silica gel. Column chromatography (hexane/ethyl acetate 4:1) afforded aldehyde **18** (24 mg, 39%) as a brownish oil.

^{1}H NMR (600 MHz, C_6D_6) δ 9.28 – 9.25 (m, 1H), 7.32 – 7.19 (m, 8H), 6.81 – 6.74 (m, 8H), 4.68 – 4.55 (m, 3H), 4.53 – 4.42 (m, 4H), 4.38 – 4.32 (m, 1H), 3.63 – 3.49 (m, 3H), 3.45 – 3.38 (m, 1H), 3.30 – 3.25 (m, 12H), 2.14 – 2.02 (m, 1H), 1.99 – 1.82 (m, 4H), 1.82 – 1.77 (m, 2H), 1.67 – 1.56 (m, 4H), 1.51 – 1.41 (m, 2H), 1.34 – 1.20 (m, 19H), 0.89 – 0.83 (m, 3H);

^{13}C NMR (150 MHz, C_6D_6) δ 200.4, 200.4, 159.3, 131.5, 131.4, 131.4, 131.2, 129.3, 129.3, 129.3, 129.2, 129.2, 127.9, 113.7, 113.7, 113.7, 81.1, 80.9, 80.6, 80.5, 80.2, 80.1, 79.3, 72.2, 72.0, 71.8, 71.8, 71.7, 71.6, 54.4, 43.6, 43.5, 32.0, 31.0, 30.1, 30.0, 29.9, 29.8, 29.8, 29.8, 29.5, 29.3, 27.5, 27.3, 27.2, 26.5, 26.2, 26.1, 22.7, 18.7, 18.5, 14.0;

IR (film, CH_2Cl_2); 2999, 2925, 2853, 2061, 1882, 1724, 1612, 1586, 1513, 1463, 1356, 1301, 1248, 1174, 1087, 1037, 821, 756 cm^{-1};

HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{54}H_{76}O_9Na$ 891.5387; Found 891.5389.

Section S10. Literature precedents of heterocycle-forming reactions.

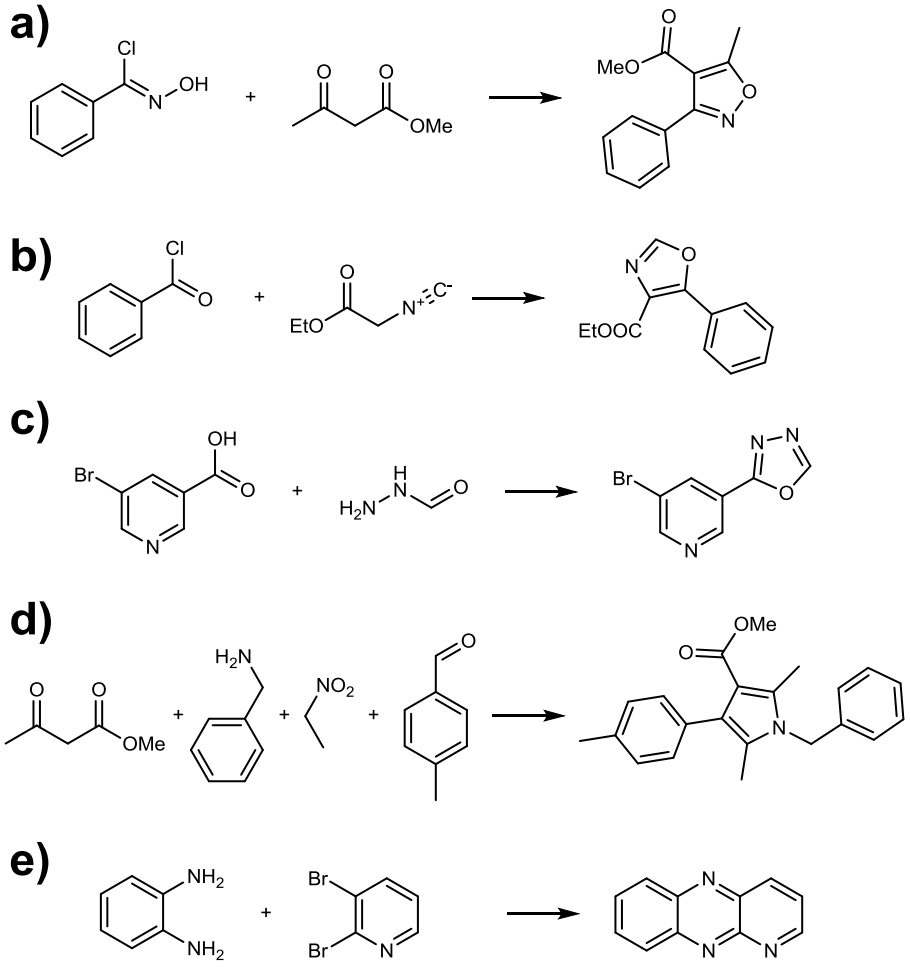
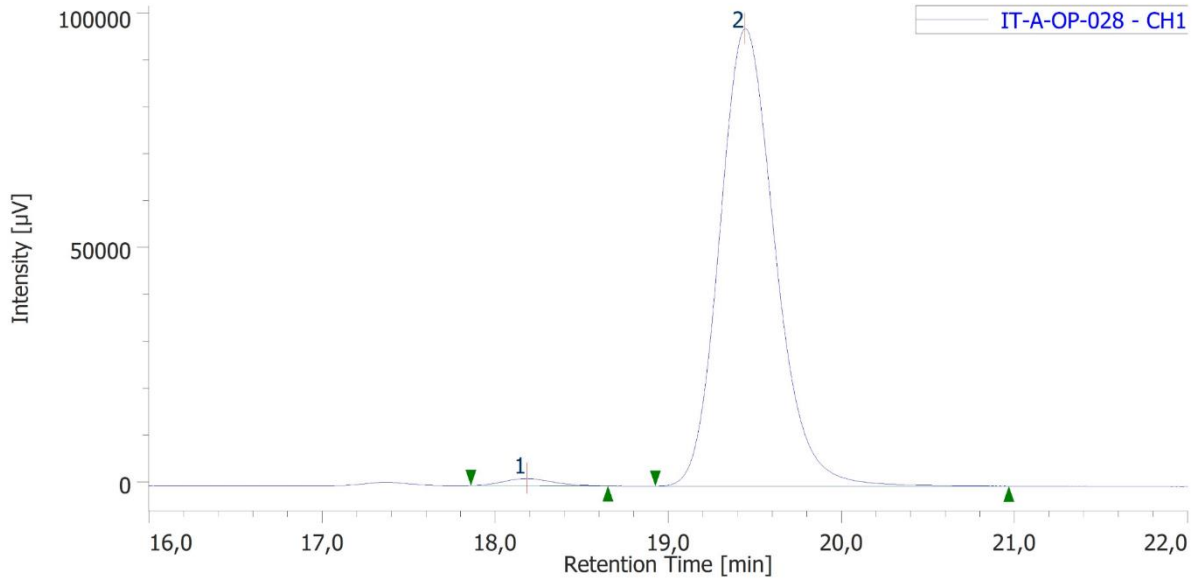
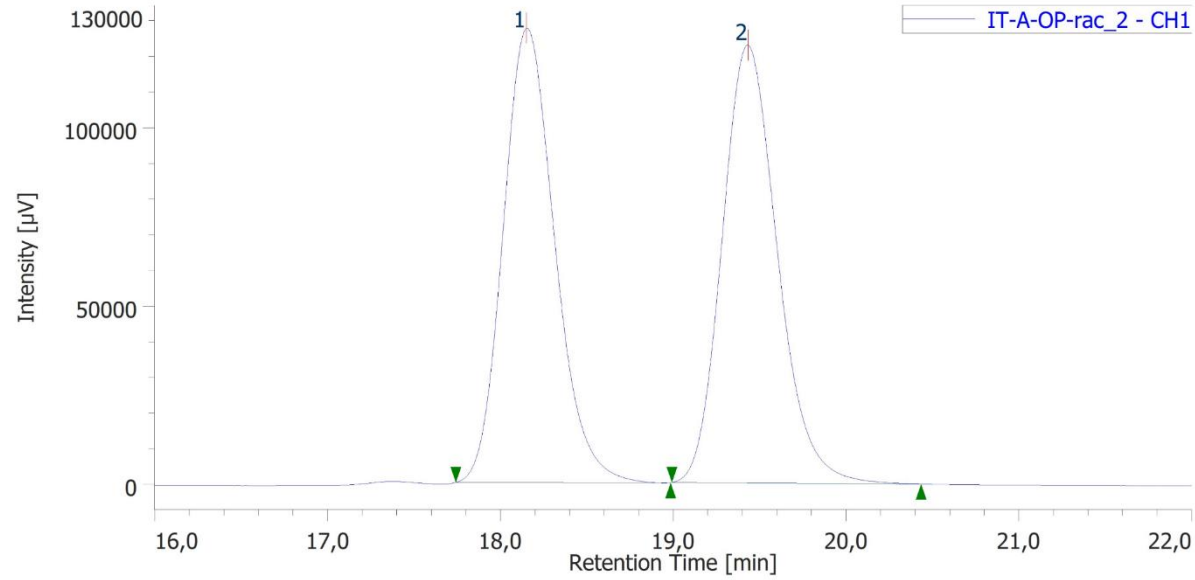


Figure S9. Literature precedents of heterocycle-forming reactions that are part of iterative sequences from main-text Figure 3. a) Synthesis of isoxazoles via condensation of imidoyl chlorides with active methylene compounds[R10]; **b)** Synthesis of oxazoles from isocyanides[R11]; **c)** Synthesis of 1,3,4-oxadiazoles from *N*-formyl hydrazine[R12]**; d)** Four-component synthesis of pyrroles[R13]; **e)** Synthesis of phenazines from dibromoaarenes[R14].

Section S11. Spectroscopic data



#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	1	18,183	29473	1519	1,343	1,534	N/A	19798	2,312	1,148	
2	Unknown	1	19,442	2165495	97501	98,657	98,466	N/A	18334	N/A	1,188	



#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	1	18,150	2643690	127332	49,211	50,931	N/A	17984	2,297	1,194	
2	Unknown	1	19,433	2728429	122679	50,789	49,069	N/A	18026	N/A	1,174	

Figure S10. HPLC chromatogram of compound **SI-1** (top) and racemate of **SI-1** (bottom).

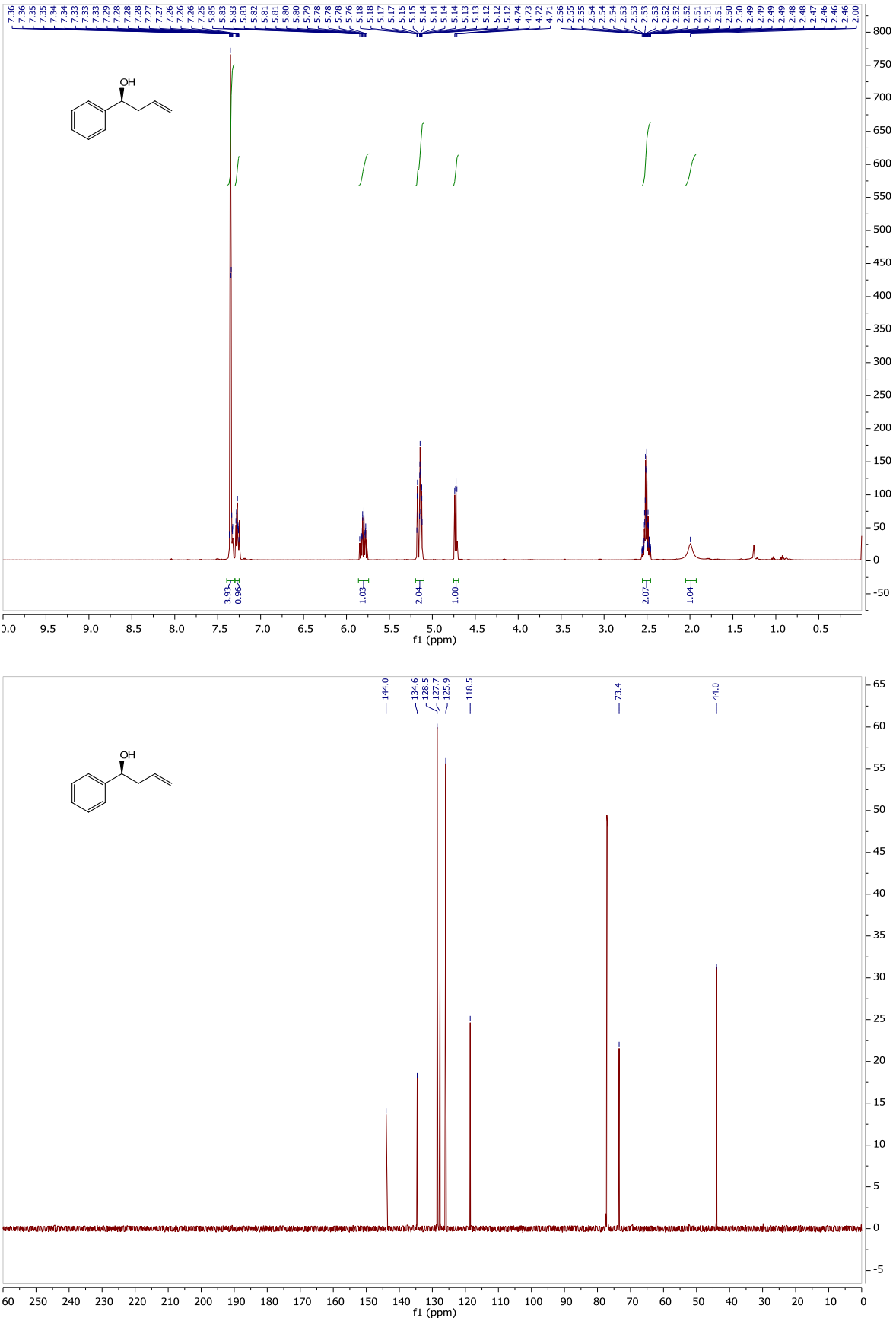


Figure S11. ^{1}H NMR (top) and ^{13}C NMR (bottom) spectra of compound **SI-1**.

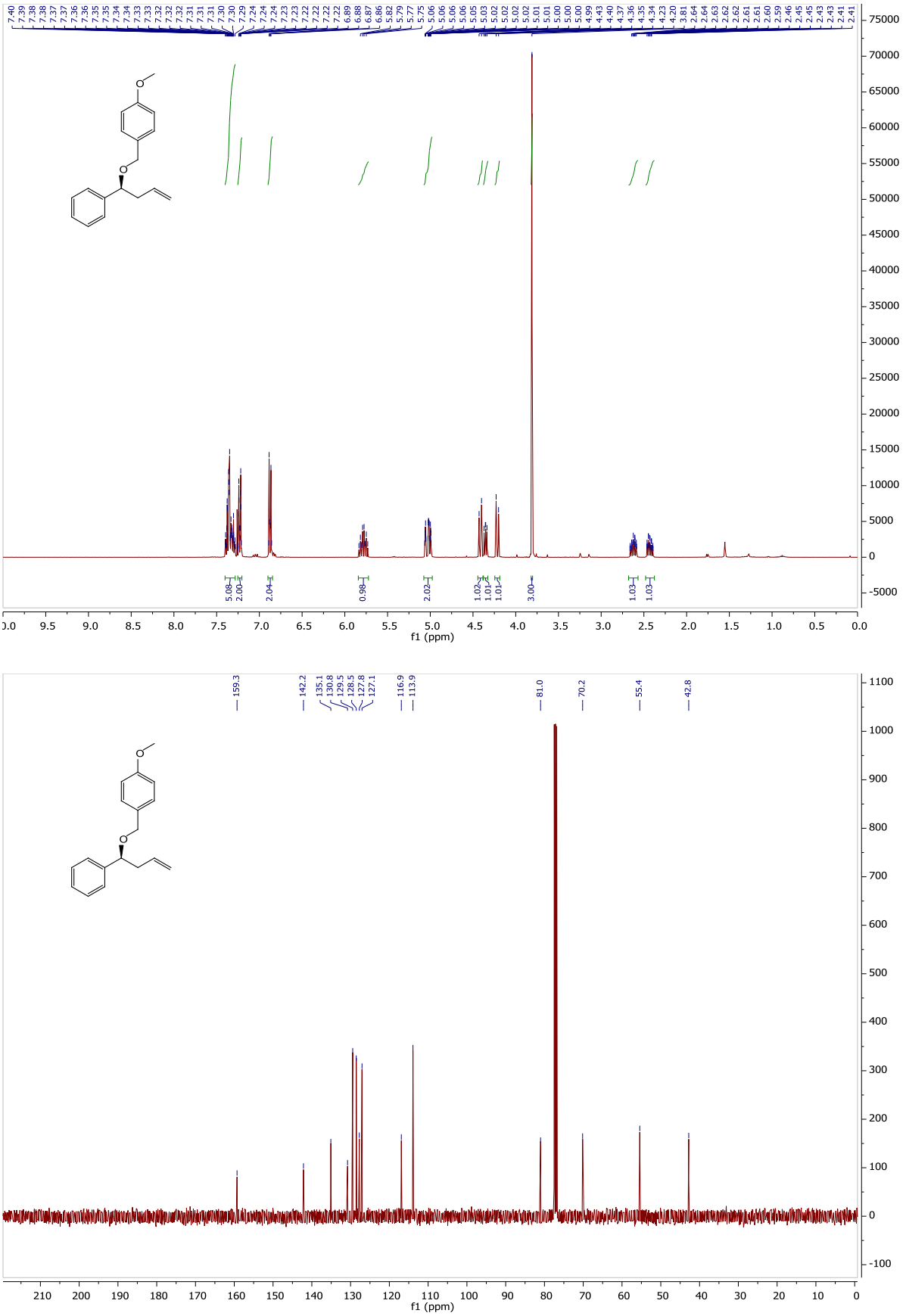


Figure S12. ^{1}H NMR (top) and ^{13}C NMR (bottom) spectra of compound **1**.

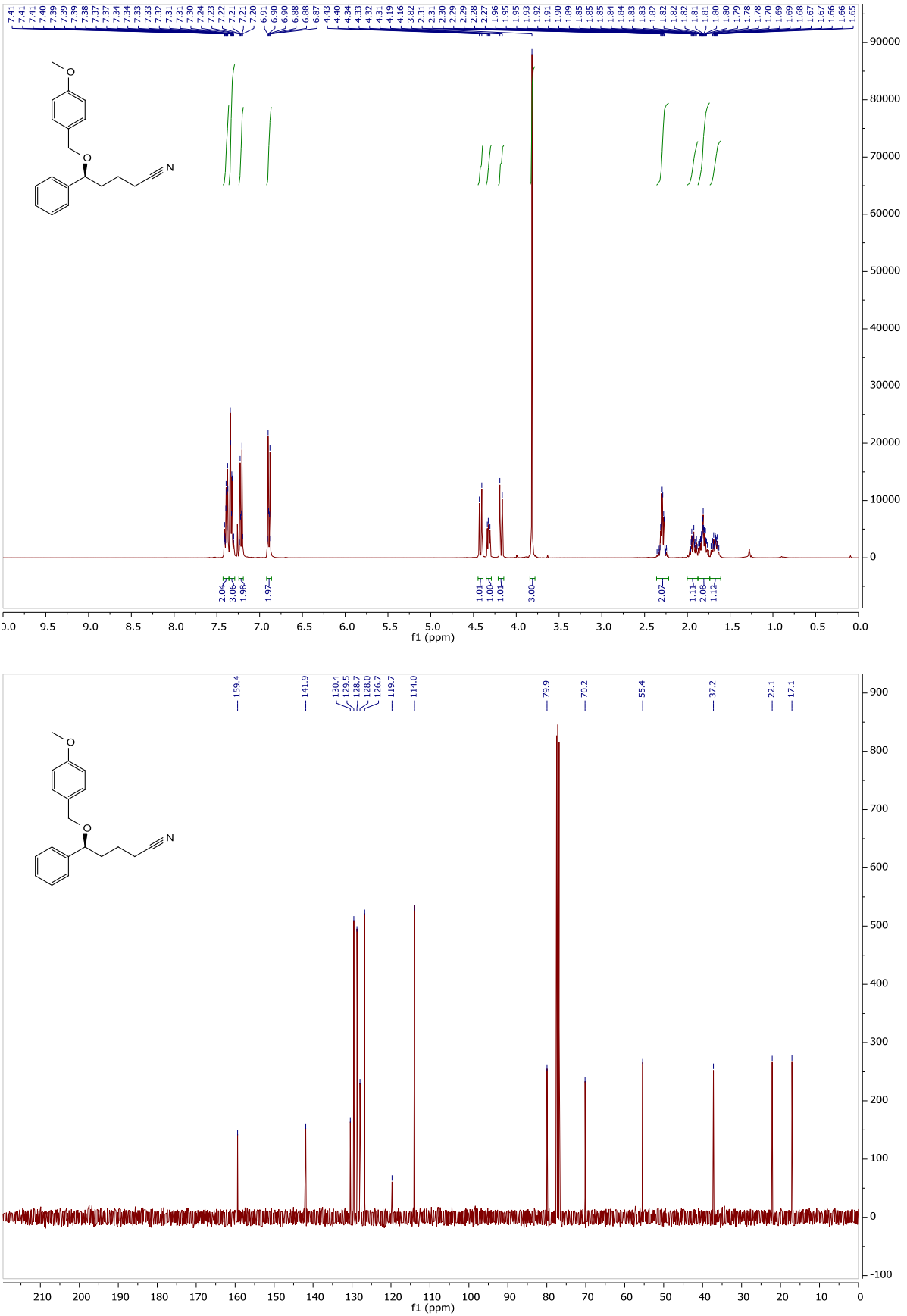


Figure S13. ^{1}H NMR (top) and ^{13}C NMR (bottom) spectra of compound **2**.

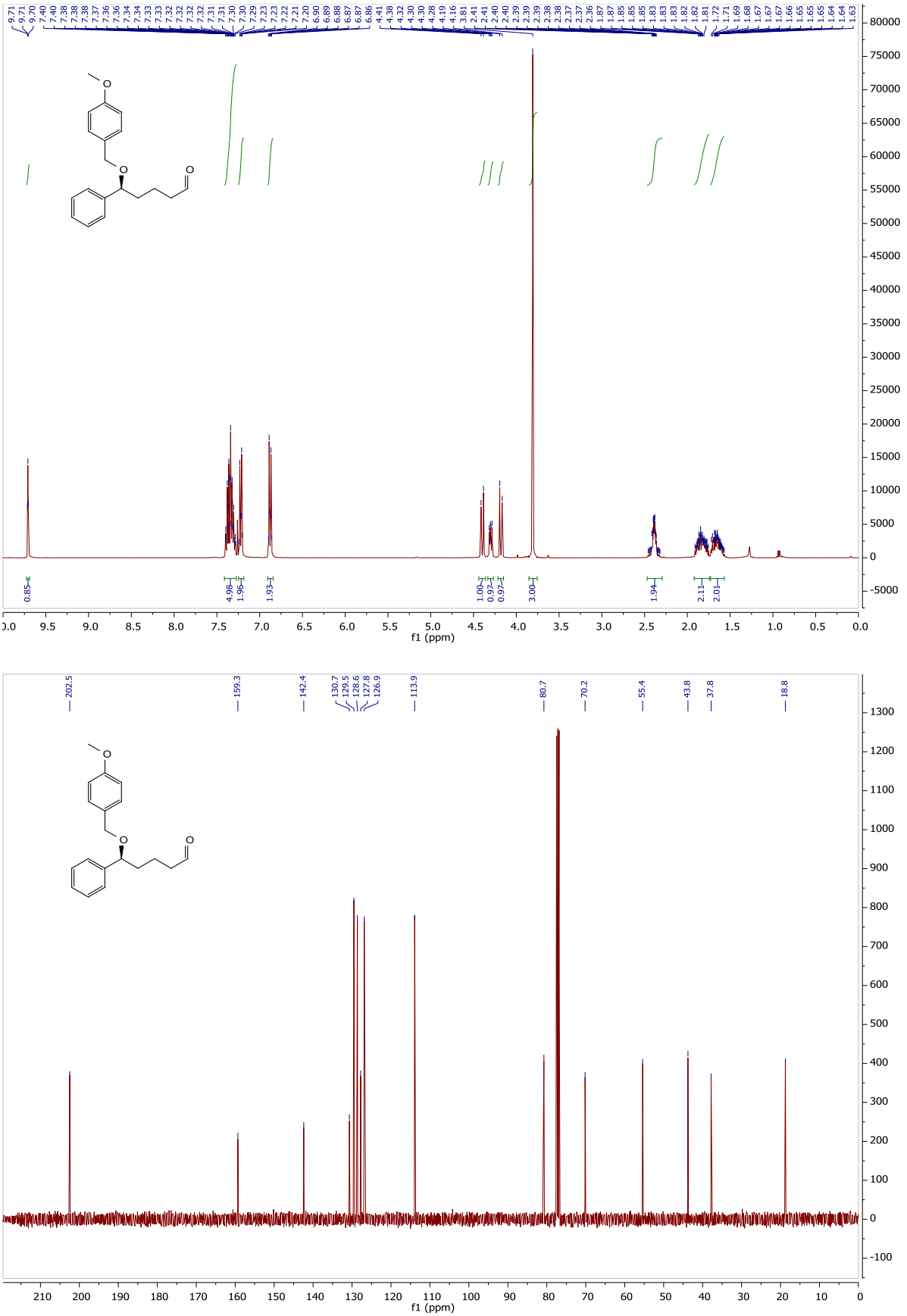


Figure S14. ^{1}H NMR (top) and ^{13}C NMR (bottom) spectra of compound **3**.

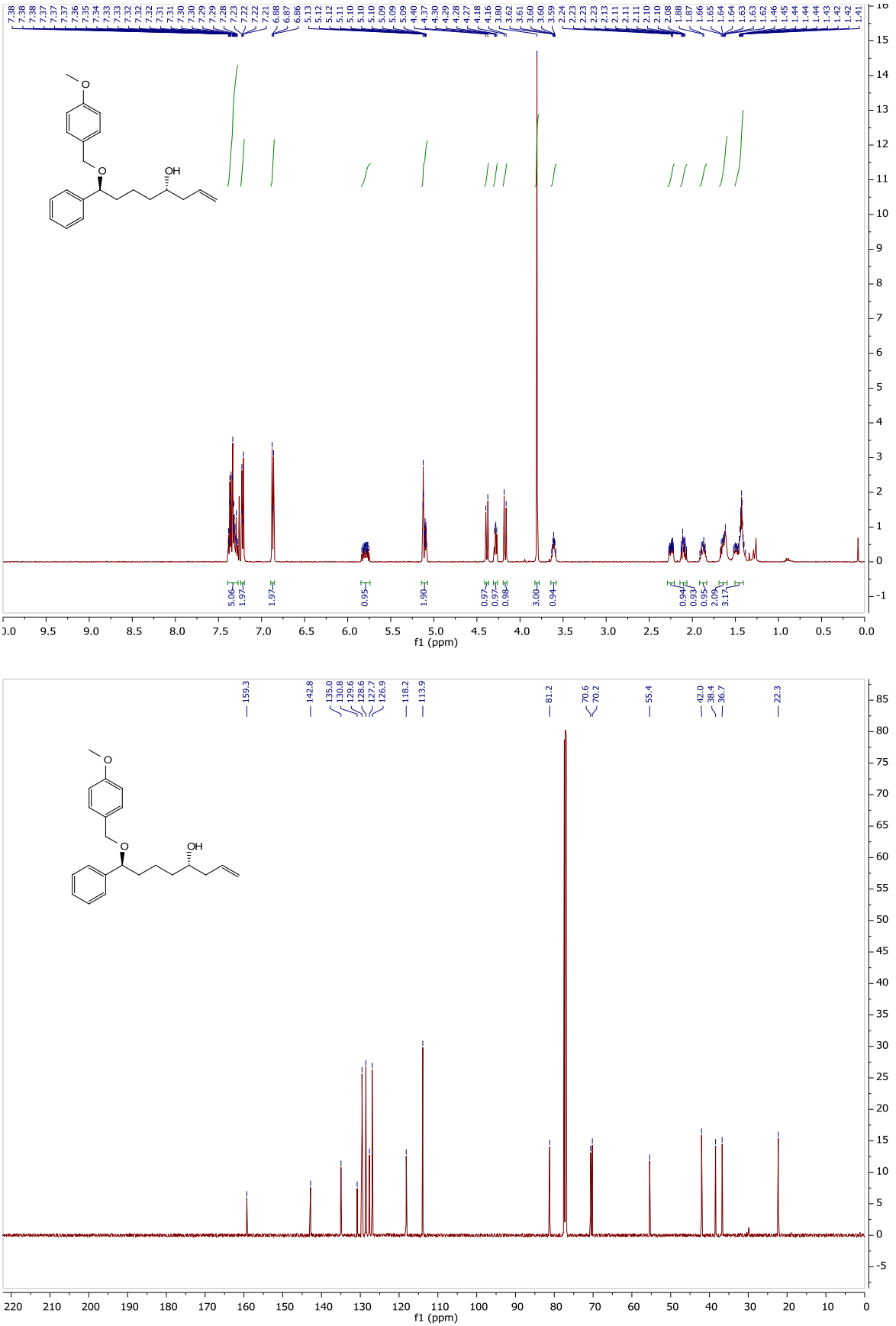


Figure S15. ^{1}H NMR (top) and ^{13}C NMR (bottom) spectra of compound **SI-2**.

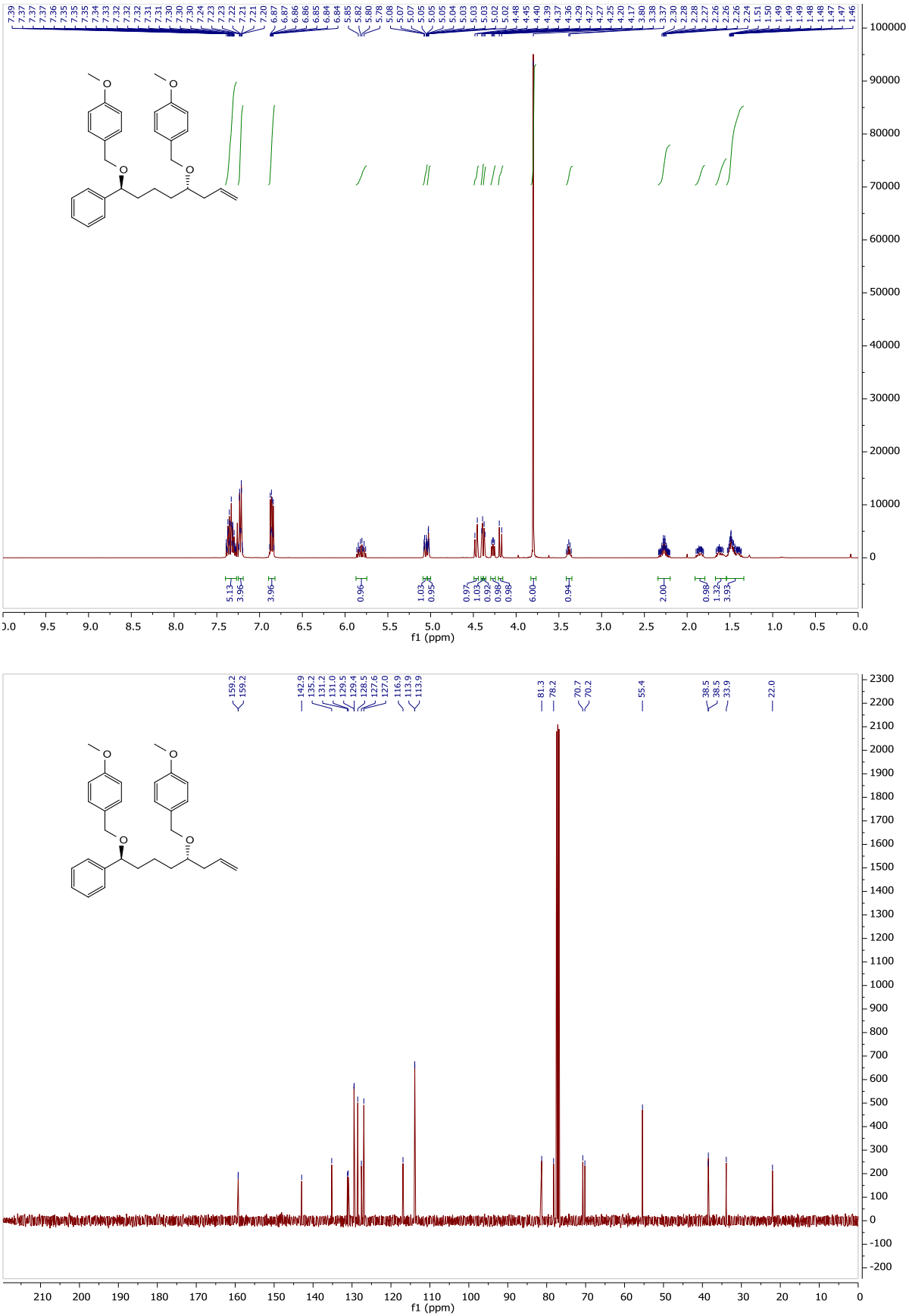


Figure S16. ^{1}H NMR (top) and ^{13}C NMR (bottom) spectra of compound **4**.

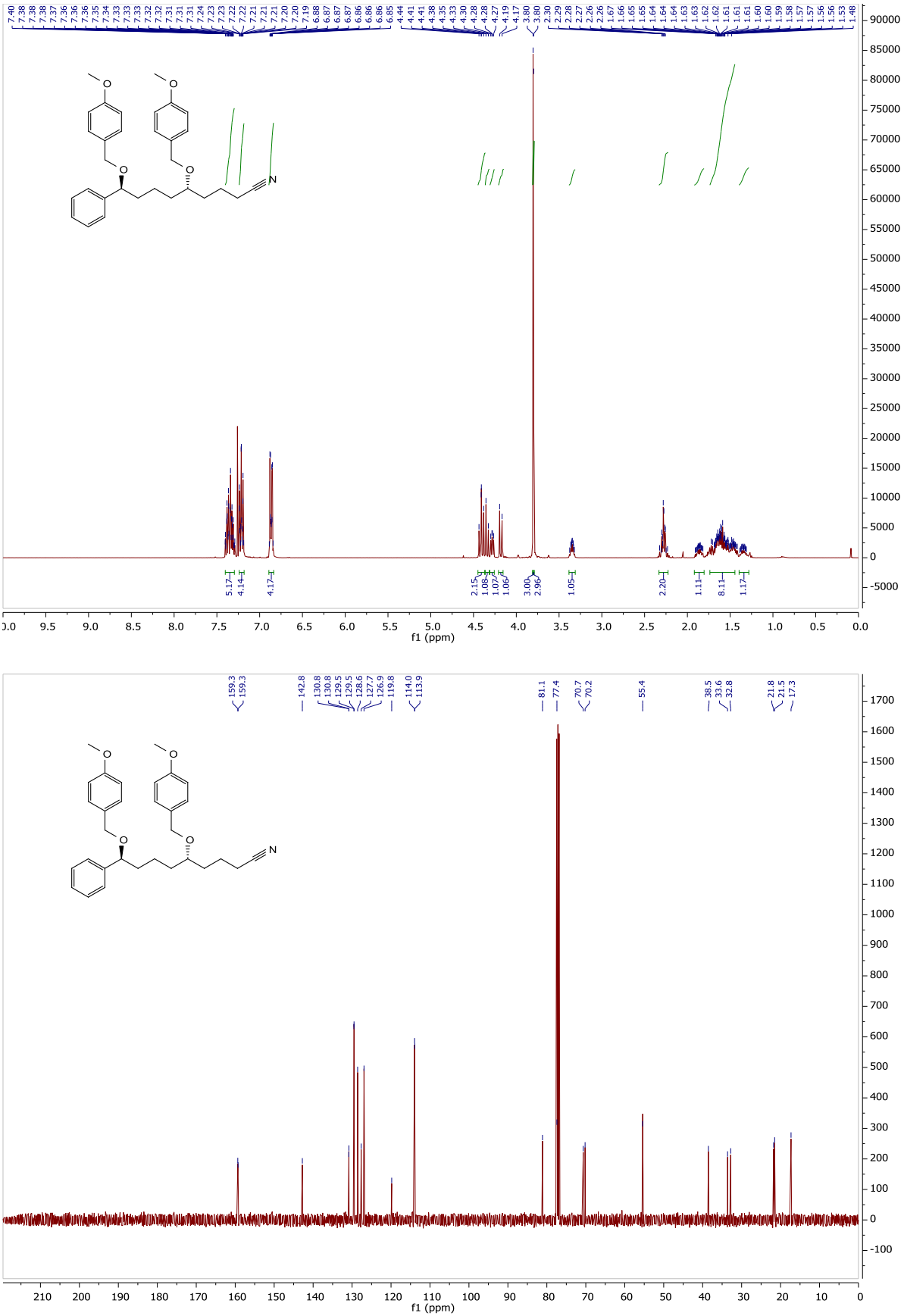


Figure S17. ^{1}H NMR (top) and ^{13}C NMR (bottom) spectra of compound **5**.

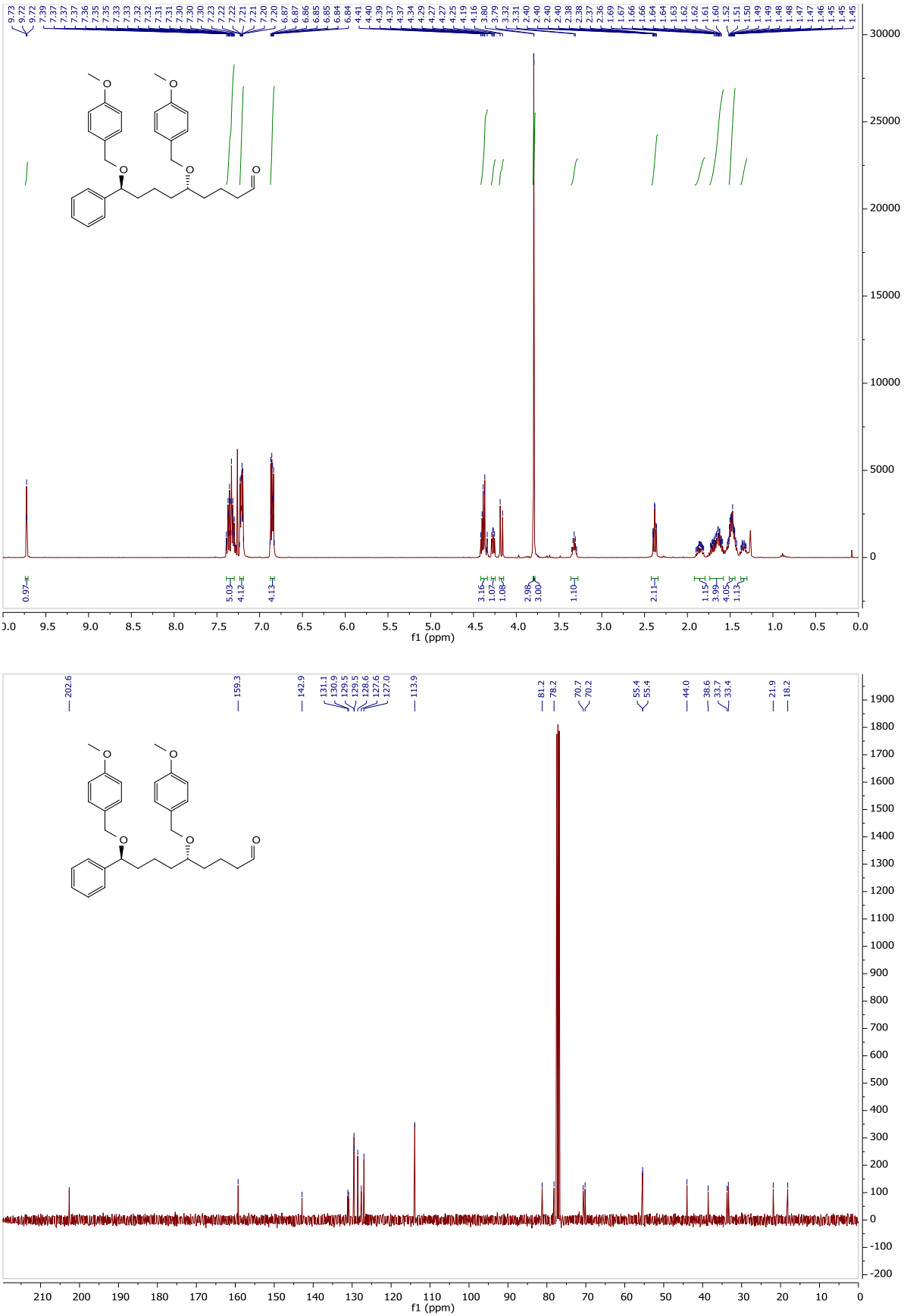


Figure S18. ^{1}H NMR (top) and ^{13}C NMR (bottom) spectra of compound **6**.

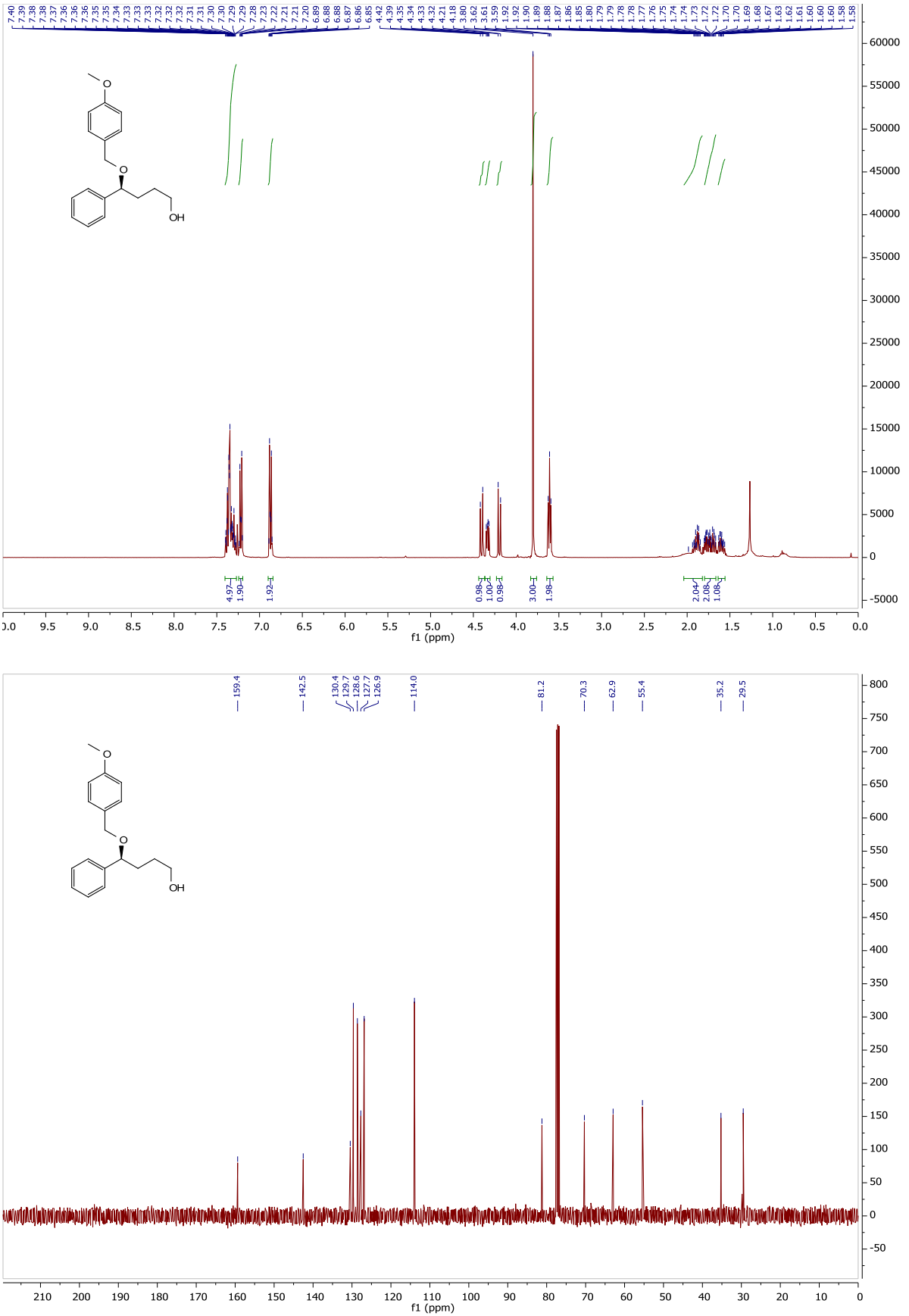


Figure S19. ^{1}H NMR (top) and ^{13}C NMR (bottom) spectra of compound **7**.

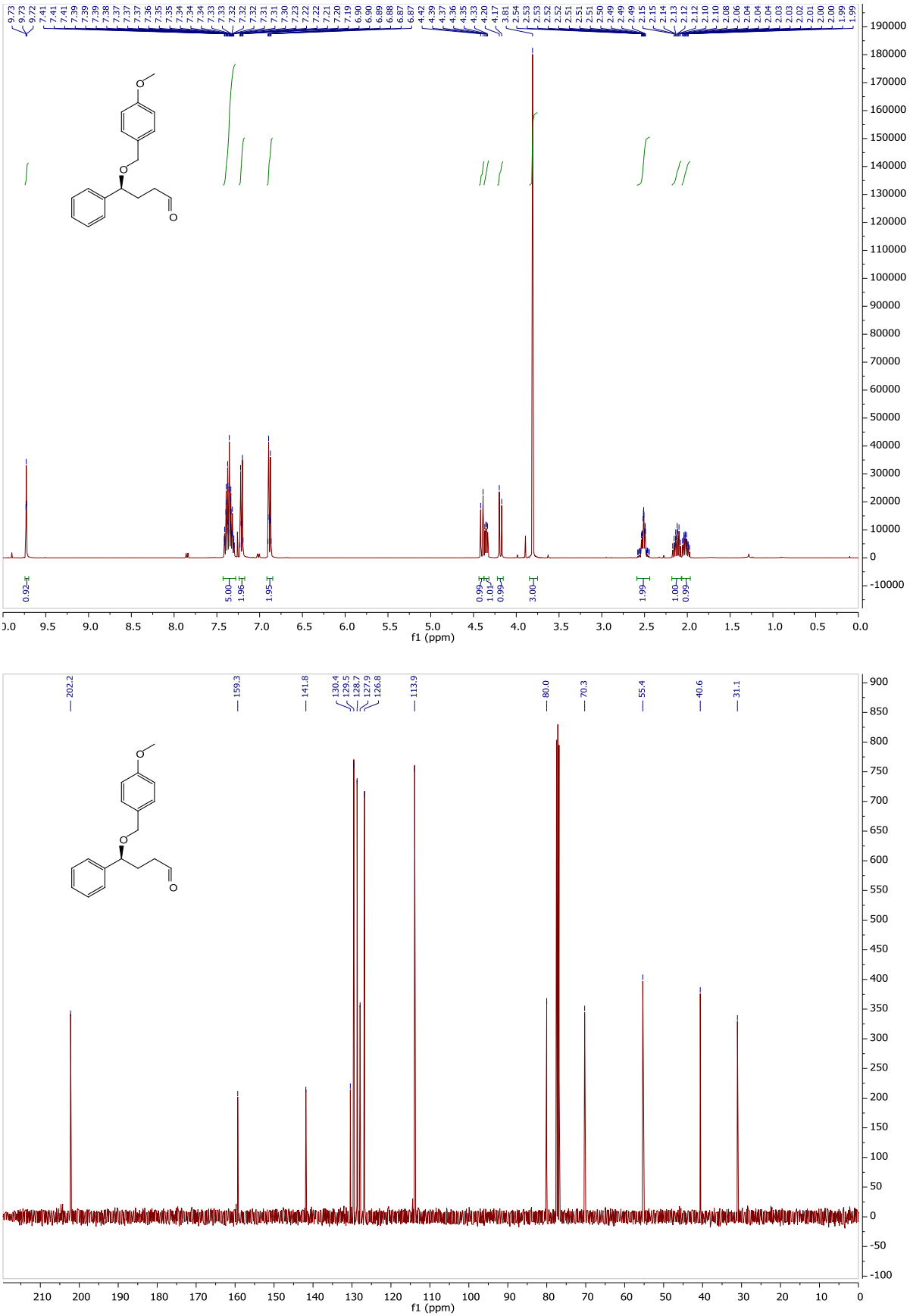


Figure S20. ^{1}H NMR (top) and ^{13}C NMR (bottom) spectra of compound **8**.

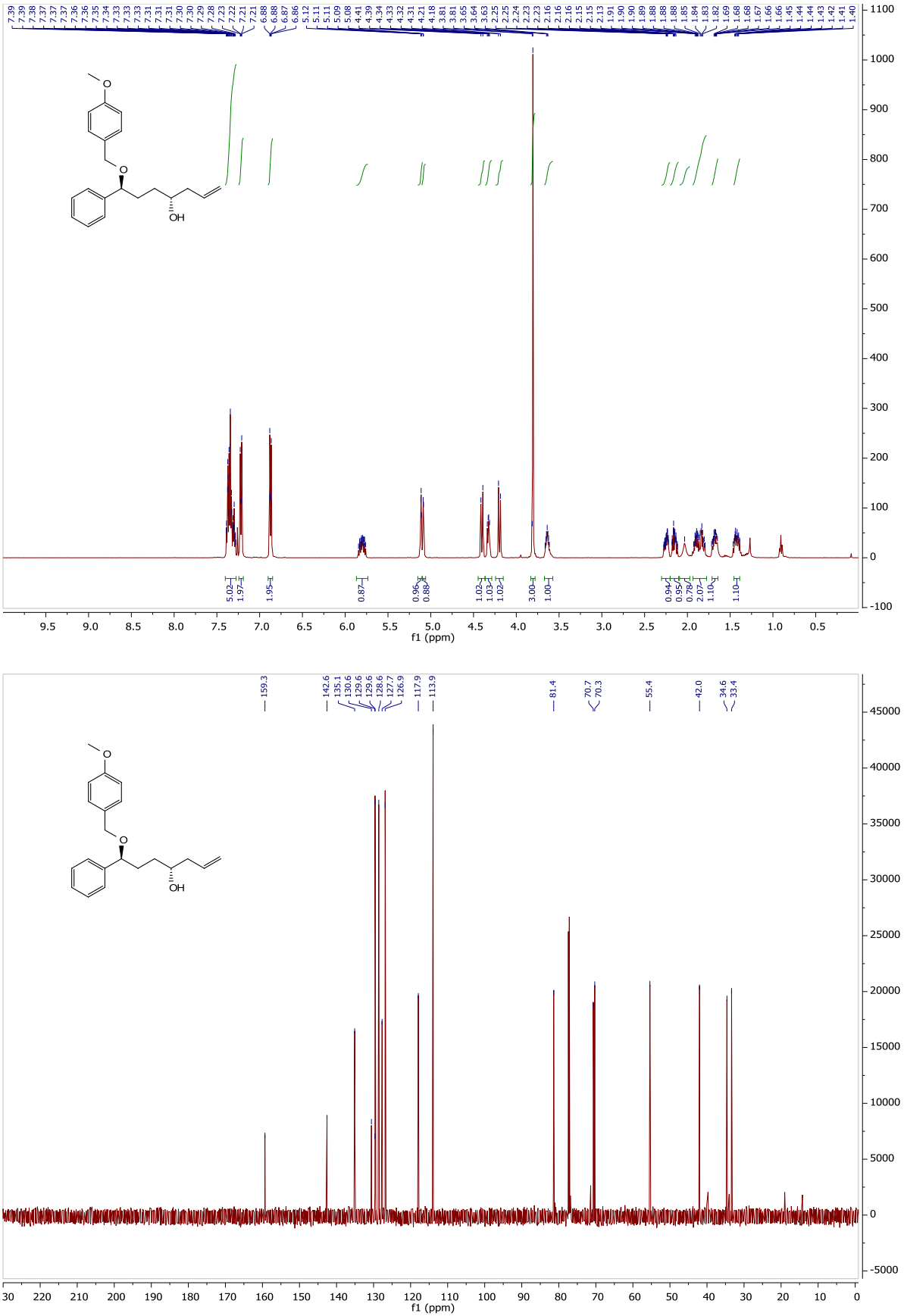


Figure S21. ^{1}H NMR (top) and ^{13}C NMR (bottom) spectra of compound **9**.

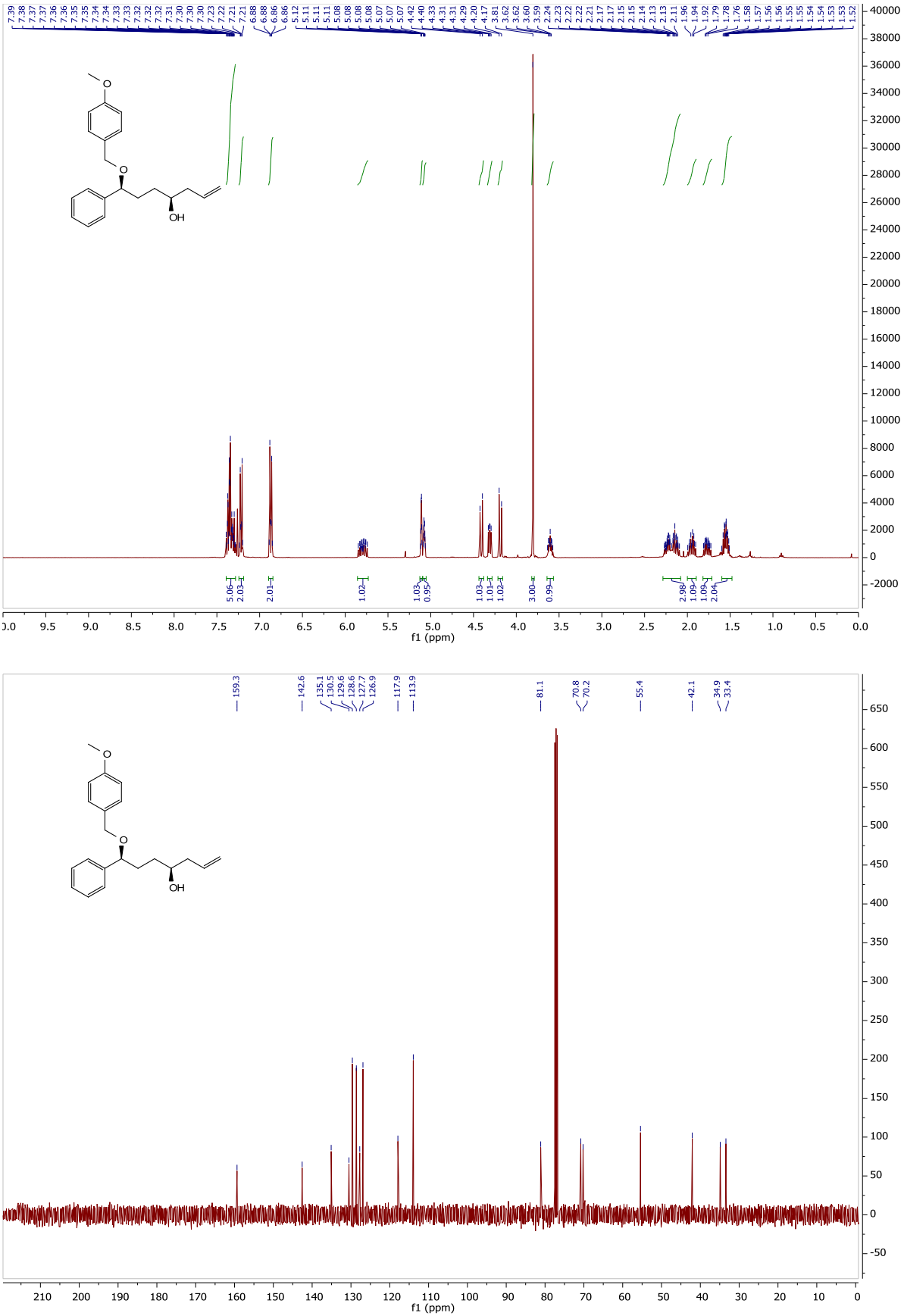


Figure S22. ^{1}H NMR (top) and ^{13}C NMR (bottom) spectra of compound **SI-3**.

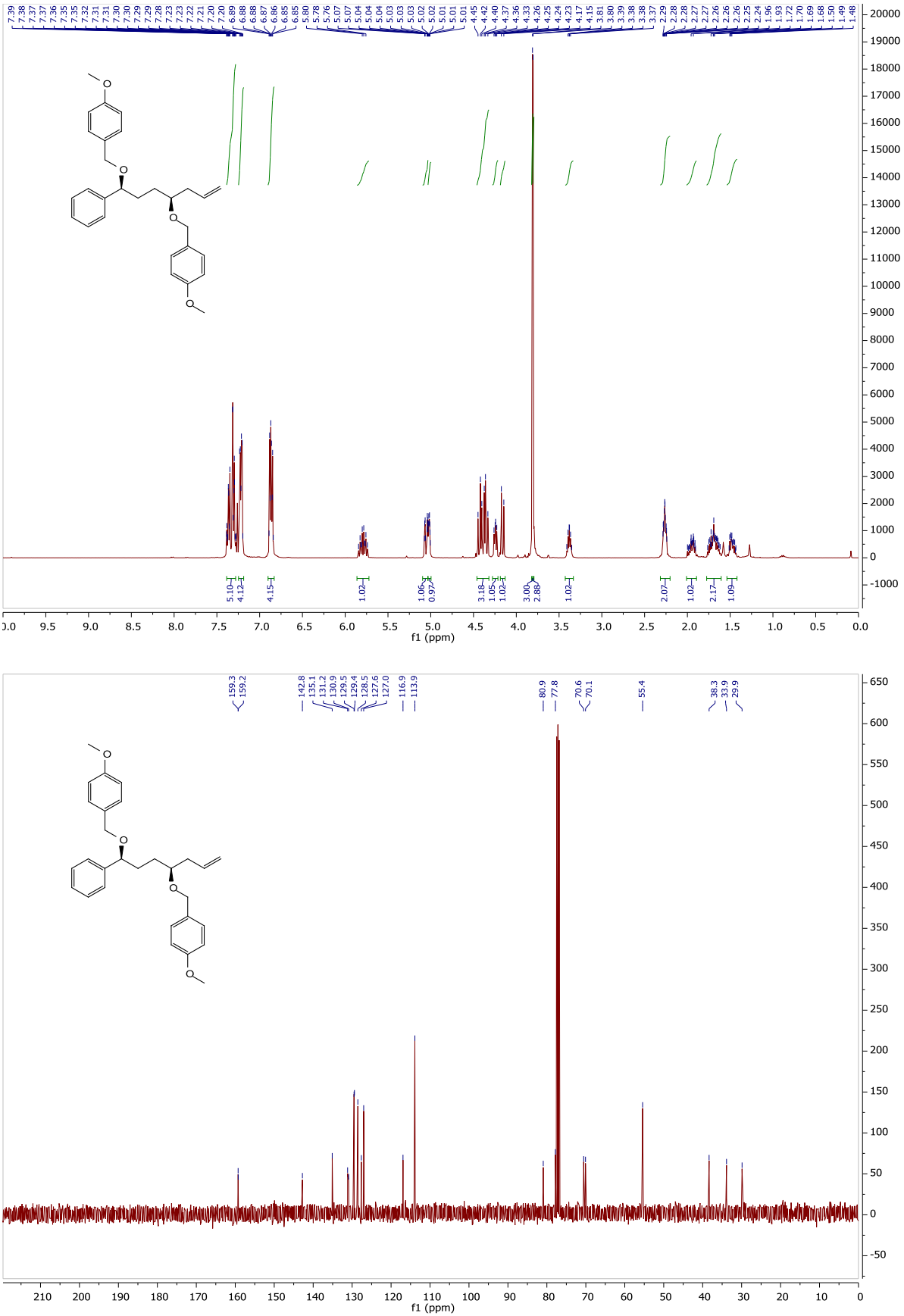


Figure S23. ^{1}H NMR (top) and ^{13}C NMR (bottom) spectra of compound **10**.

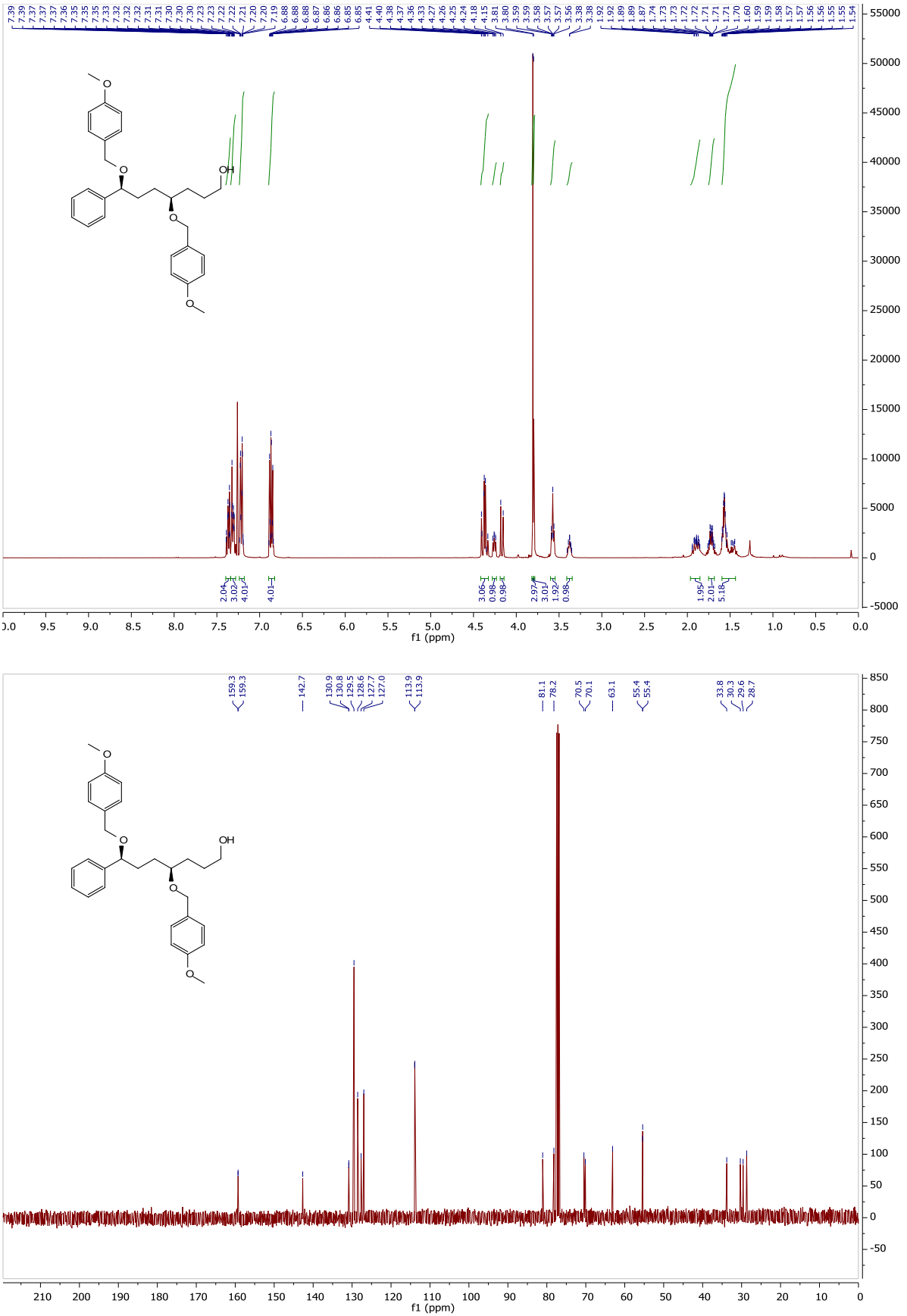


Figure S24. ^{1}H NMR (top) and ^{13}C NMR (bottom) spectra of compound **11**.

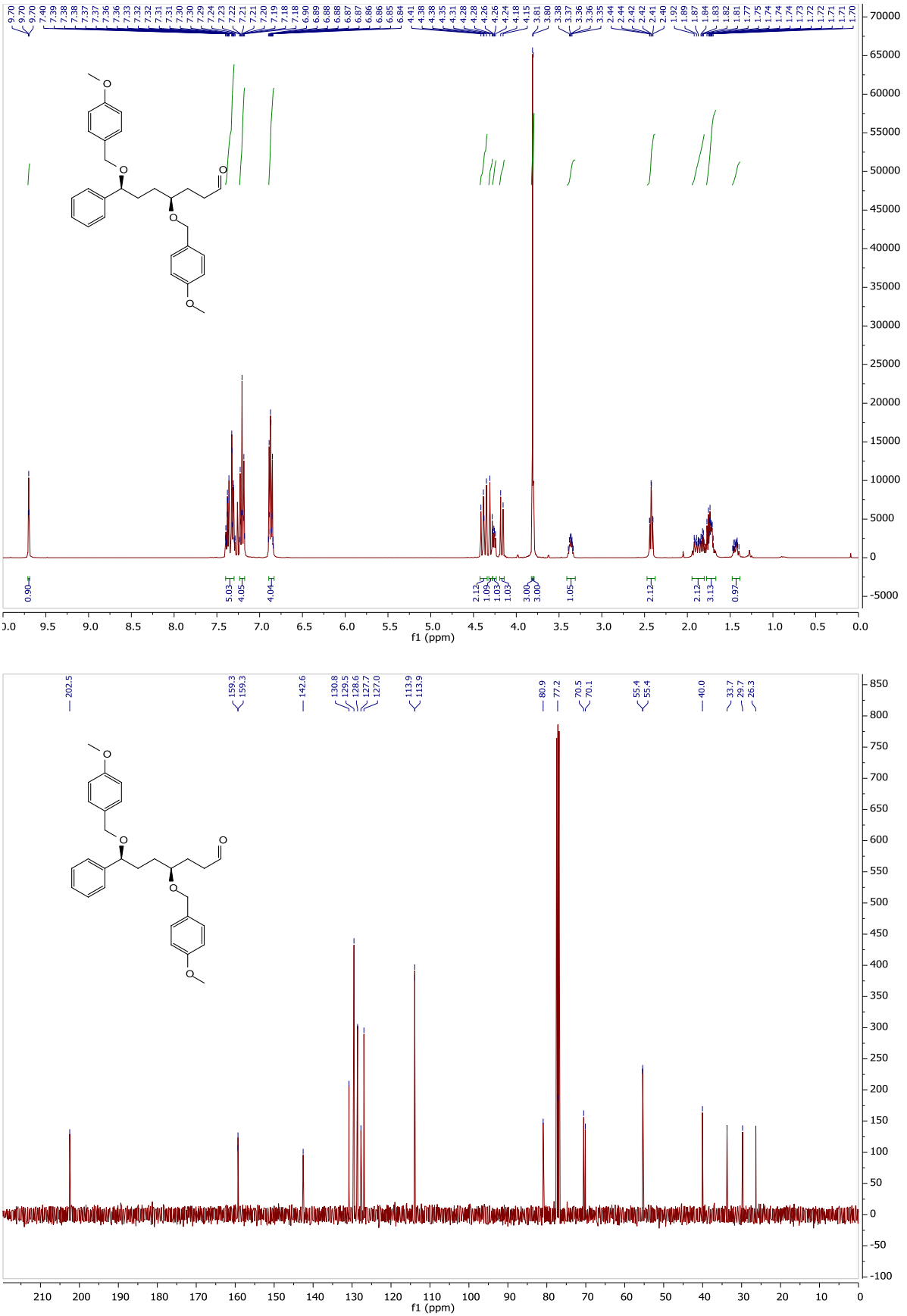


Figure S25. ^{1}H NMR (top) and ^{13}C NMR (bottom) spectra of compound **12**.

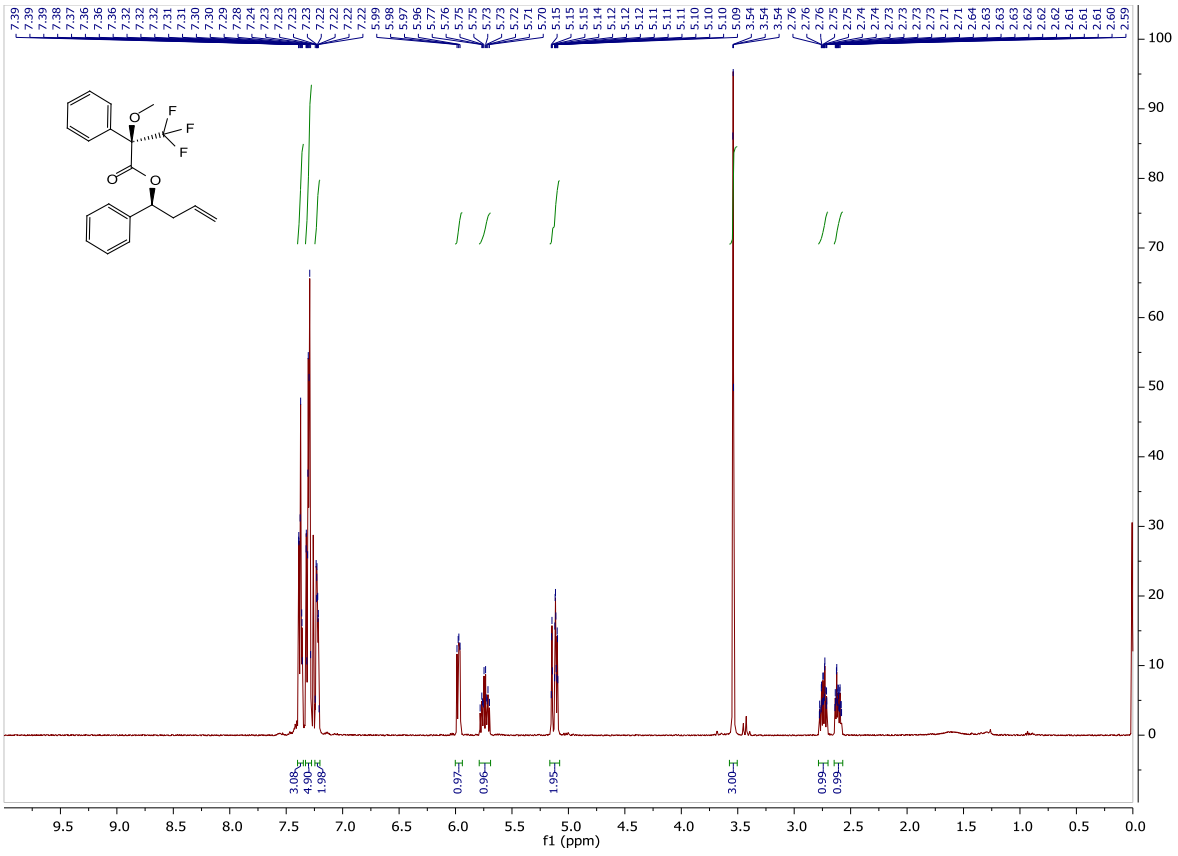


Figure S26. ^{1}H NMR spectrum of compound **SI-4**.

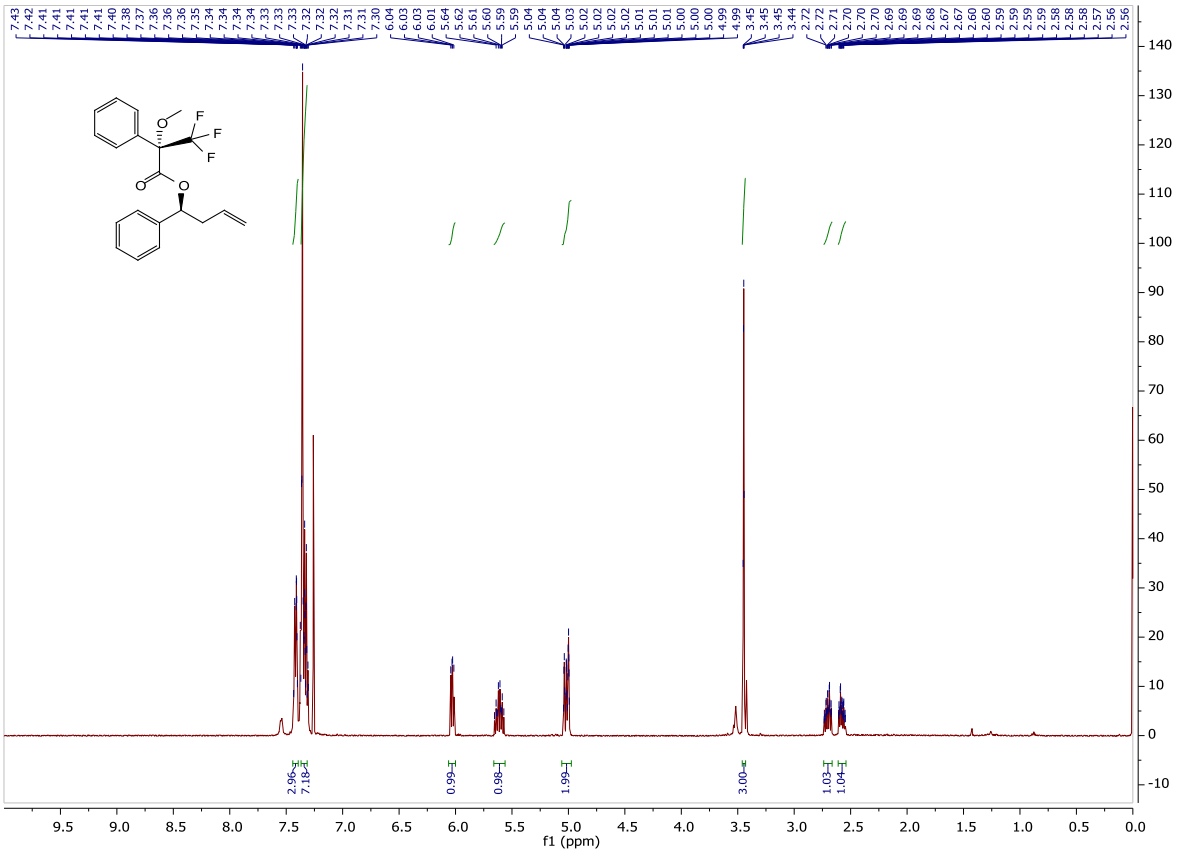


Figure S27. ^{1}H NMR spectrum of compound **SI-5**.

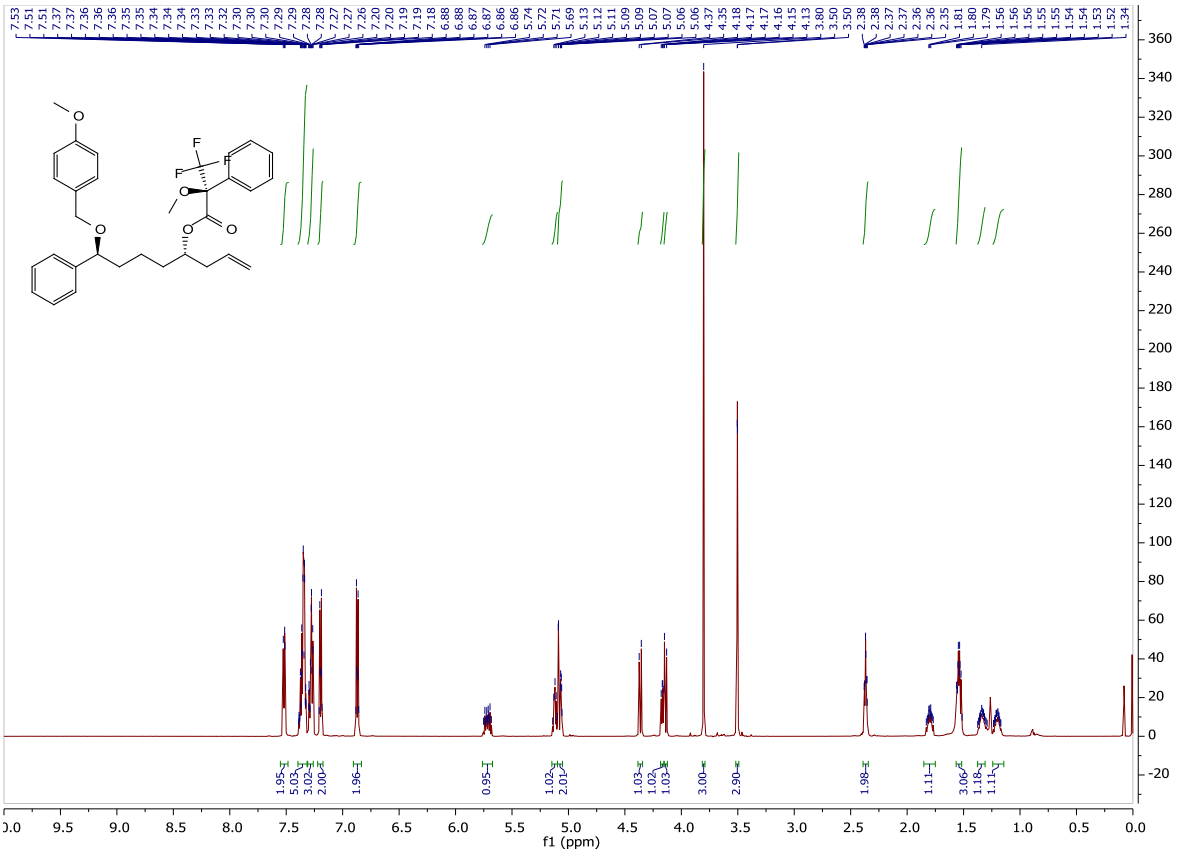


Figure S28. ^{1}H NMR spectrum of compound **SI-6**.

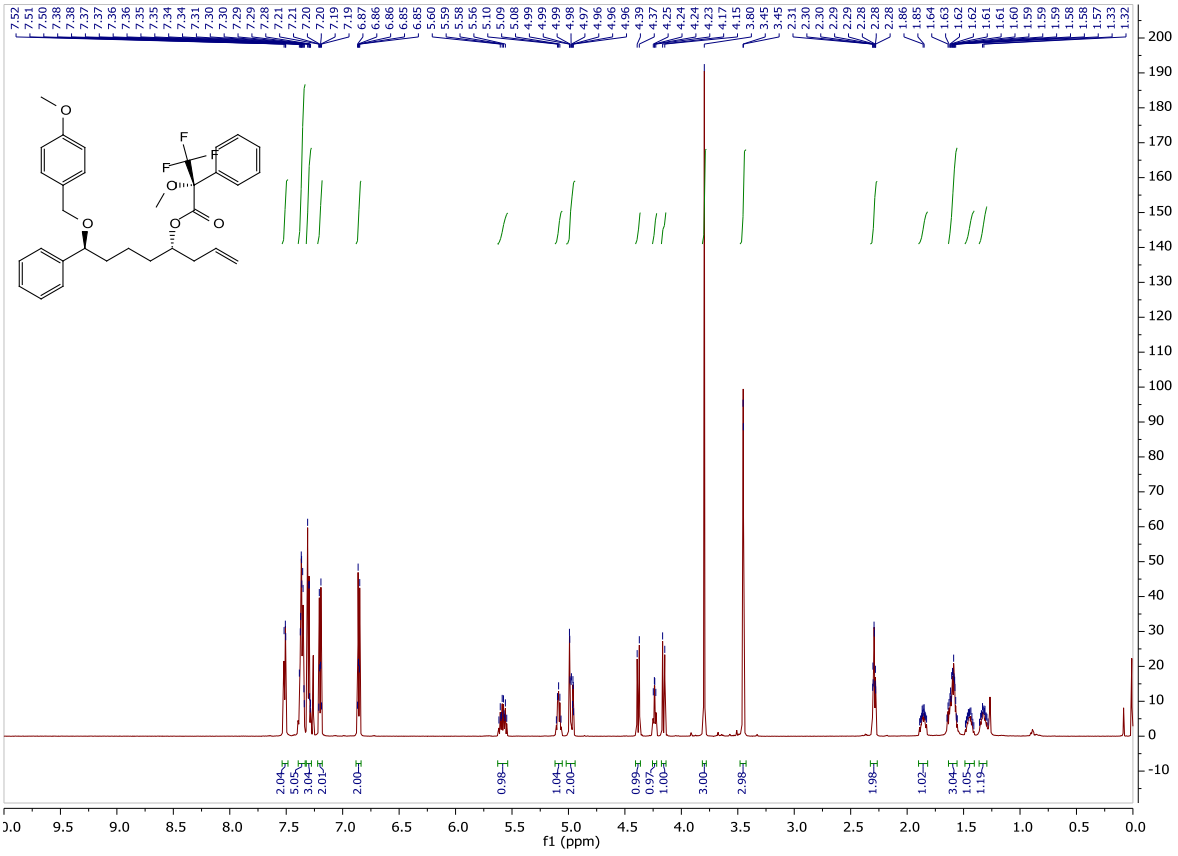


Figure S29. ^{1}H NMR spectrum of compound **SI-7**.

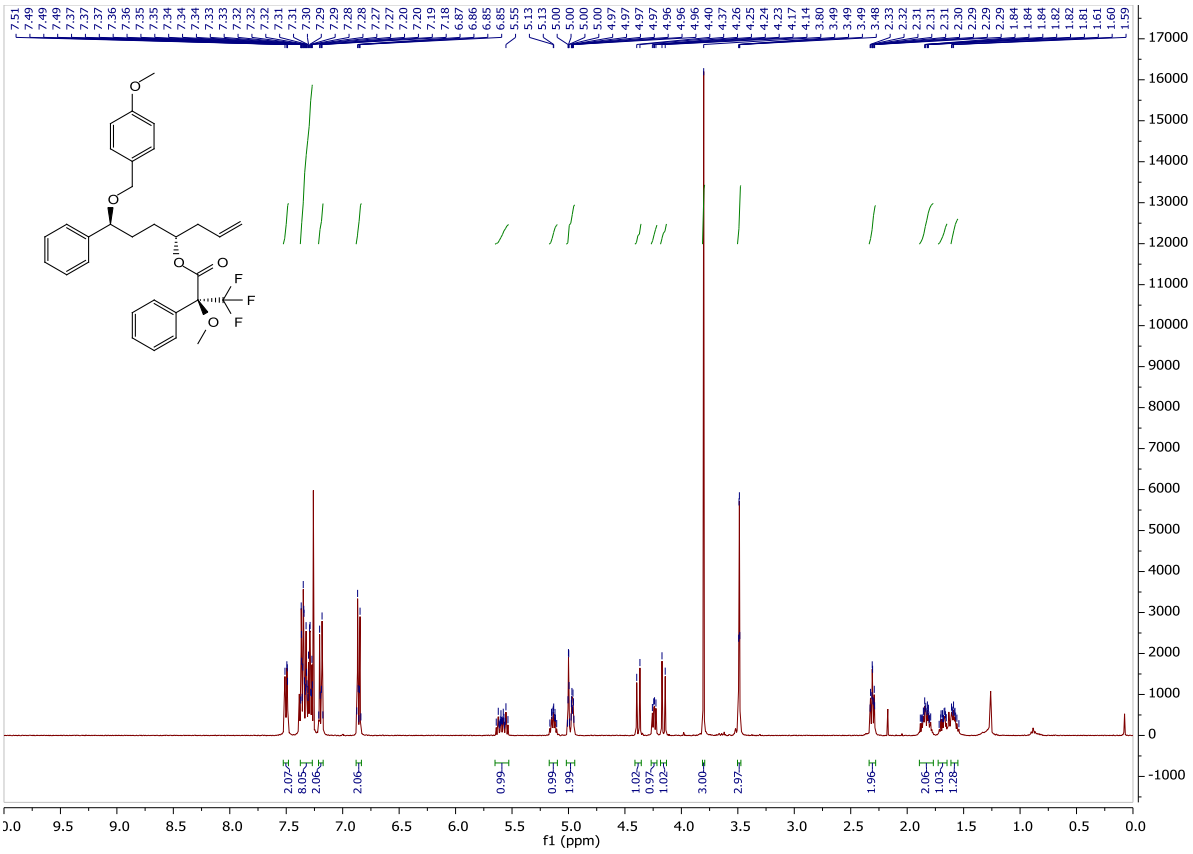


Figure S30. ^{1}H NMR spectrum of compound **SI-8**.

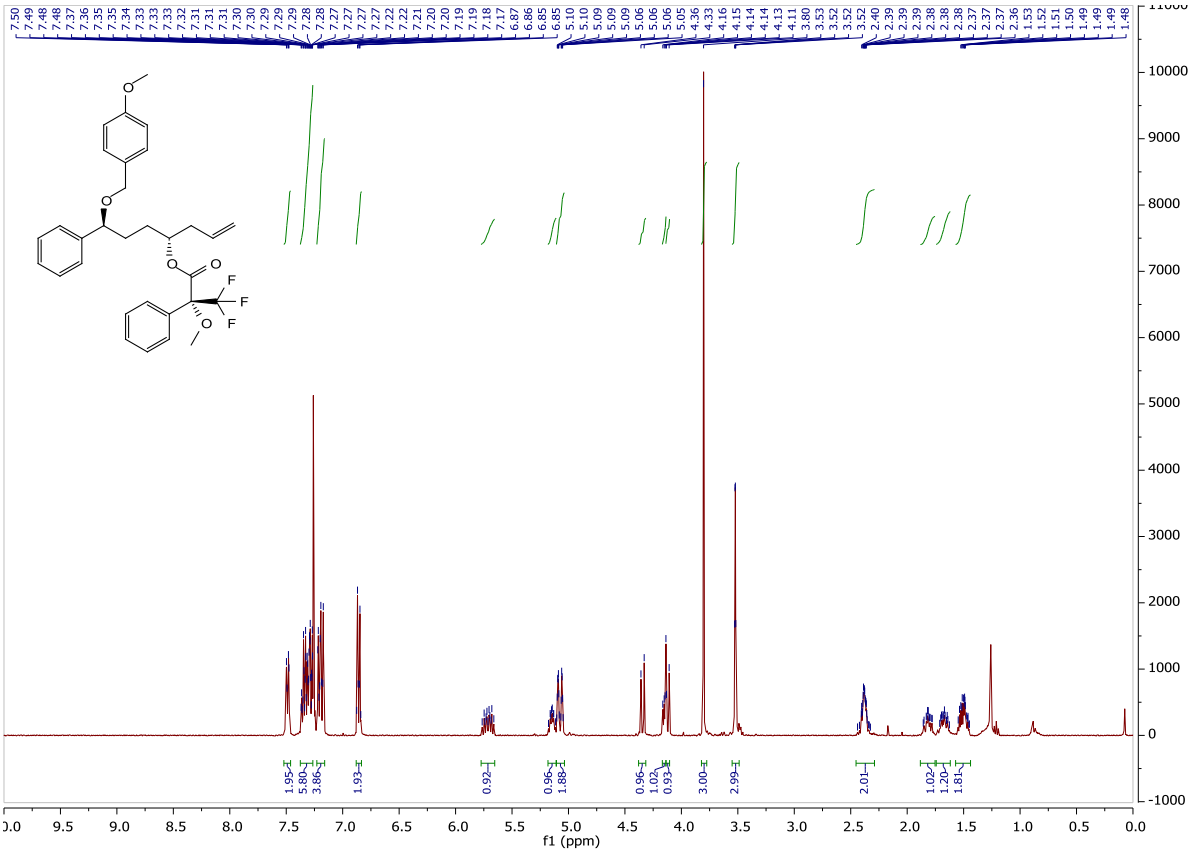


Figure S31. ^{1}H NMR spectrum of compound **SI-9**.

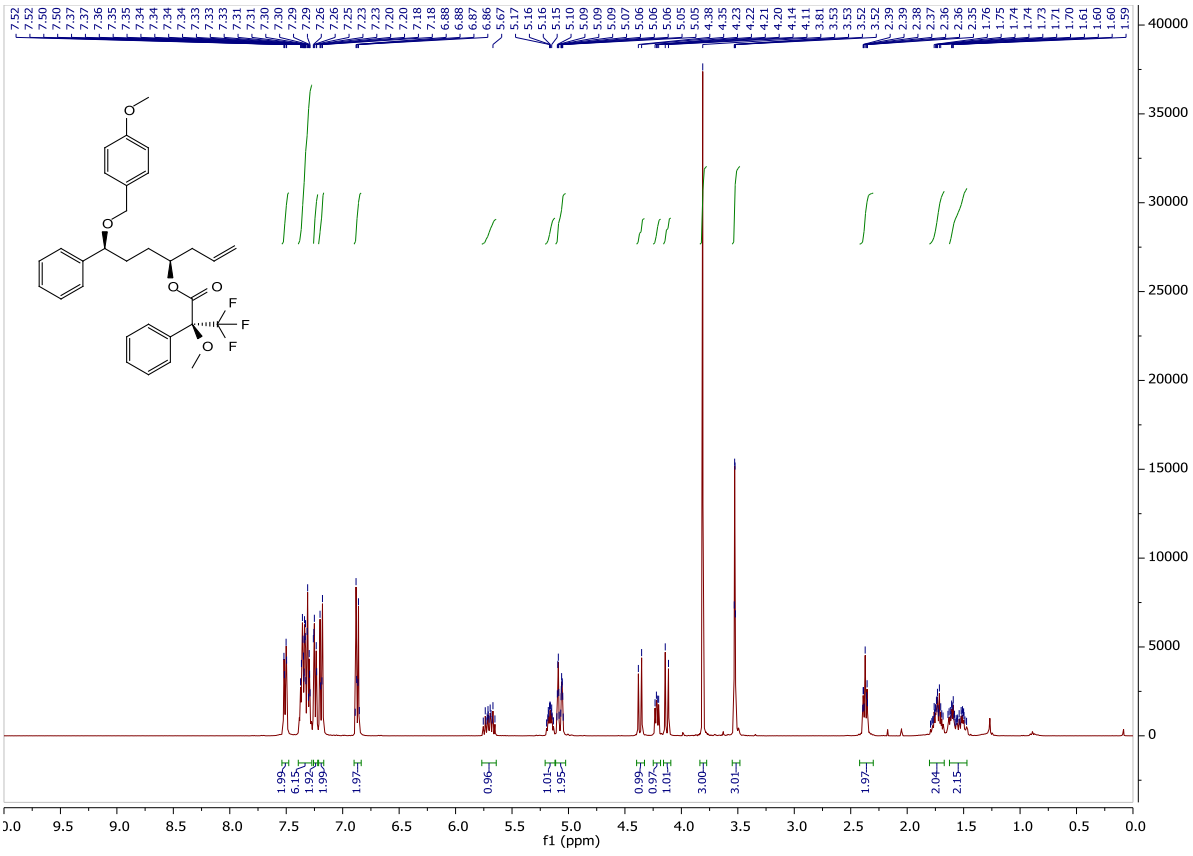


Figure S32. ^{1}H NMR spectrum of compound **SI-10**.

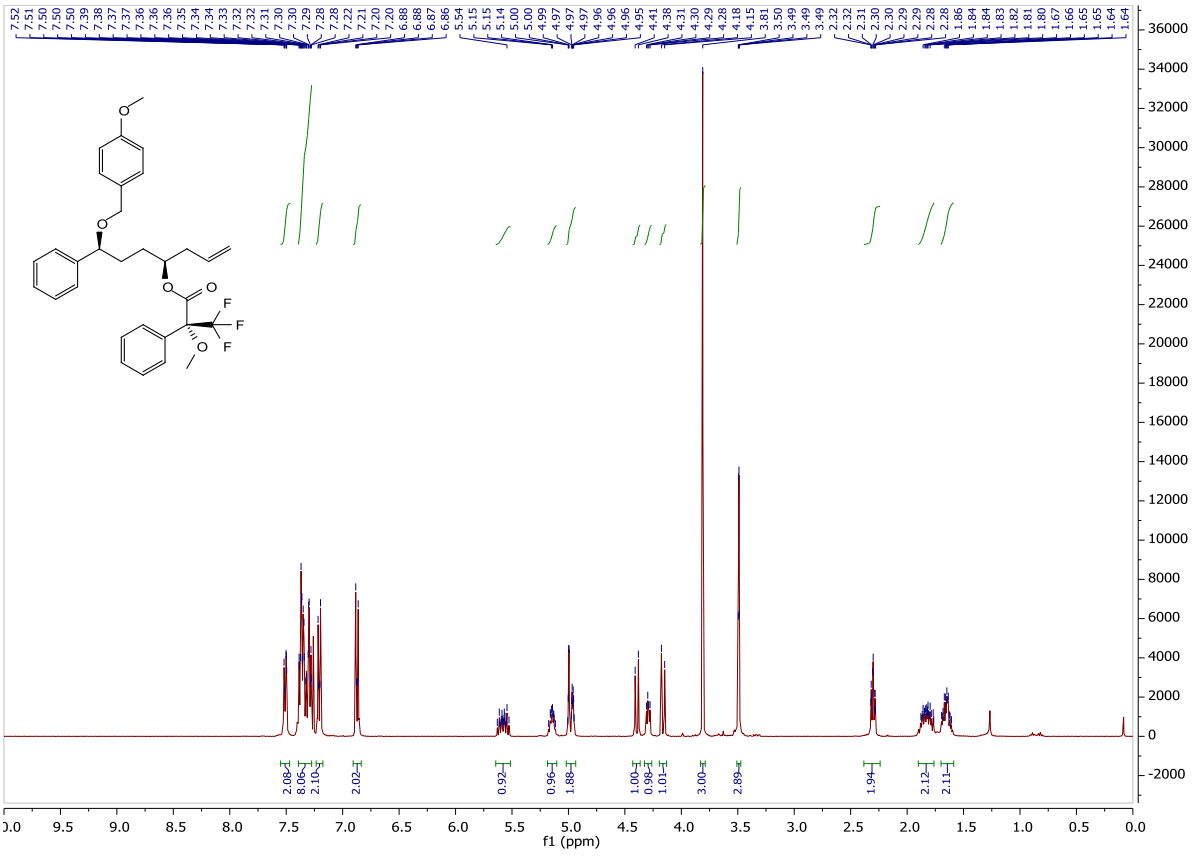


Figure S33. ^{1}H NMR spectrum of compound **SI-11**.

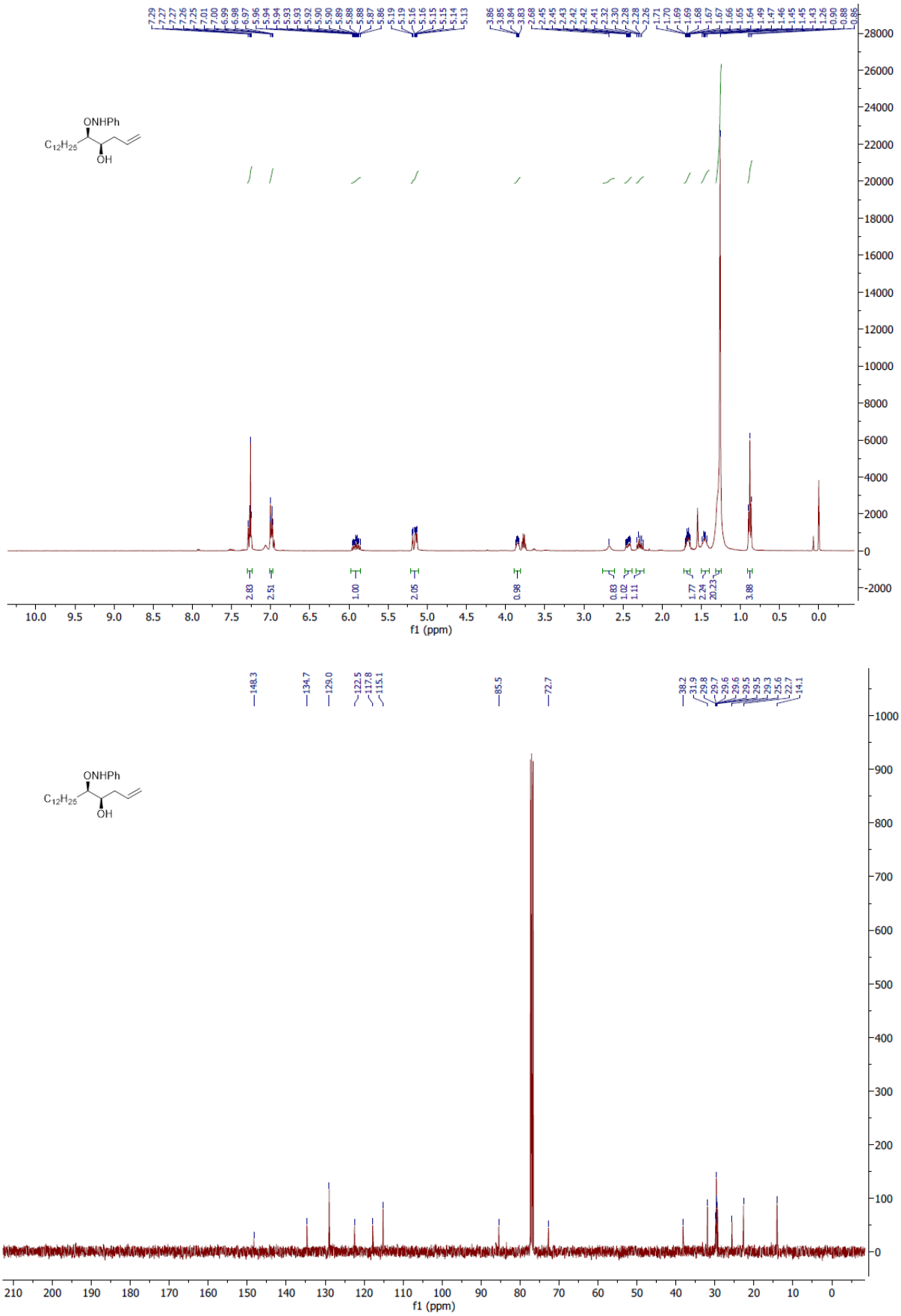


Figure S34. ^{1}H NMR (top) and ^{13}C NMR (bottom) spectra of compound **13**.

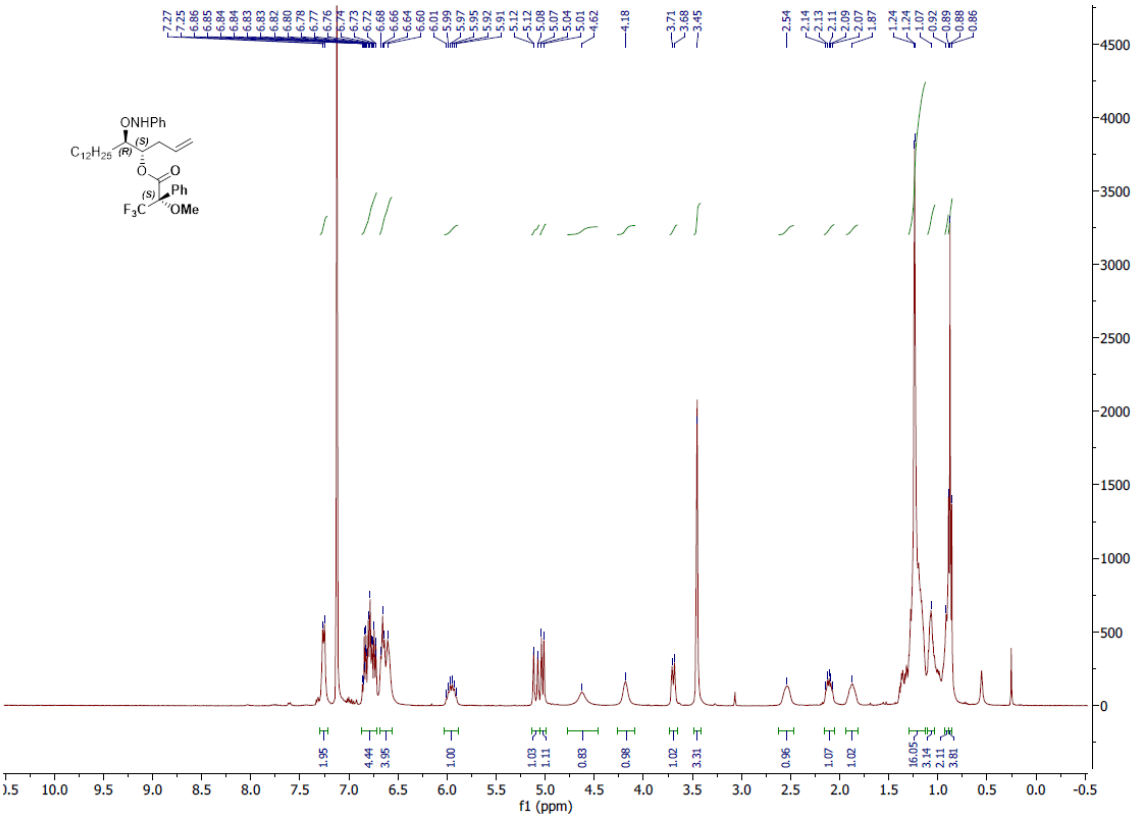


Figure S35. ^{1}H NMR spectra of compound **SI-12**.

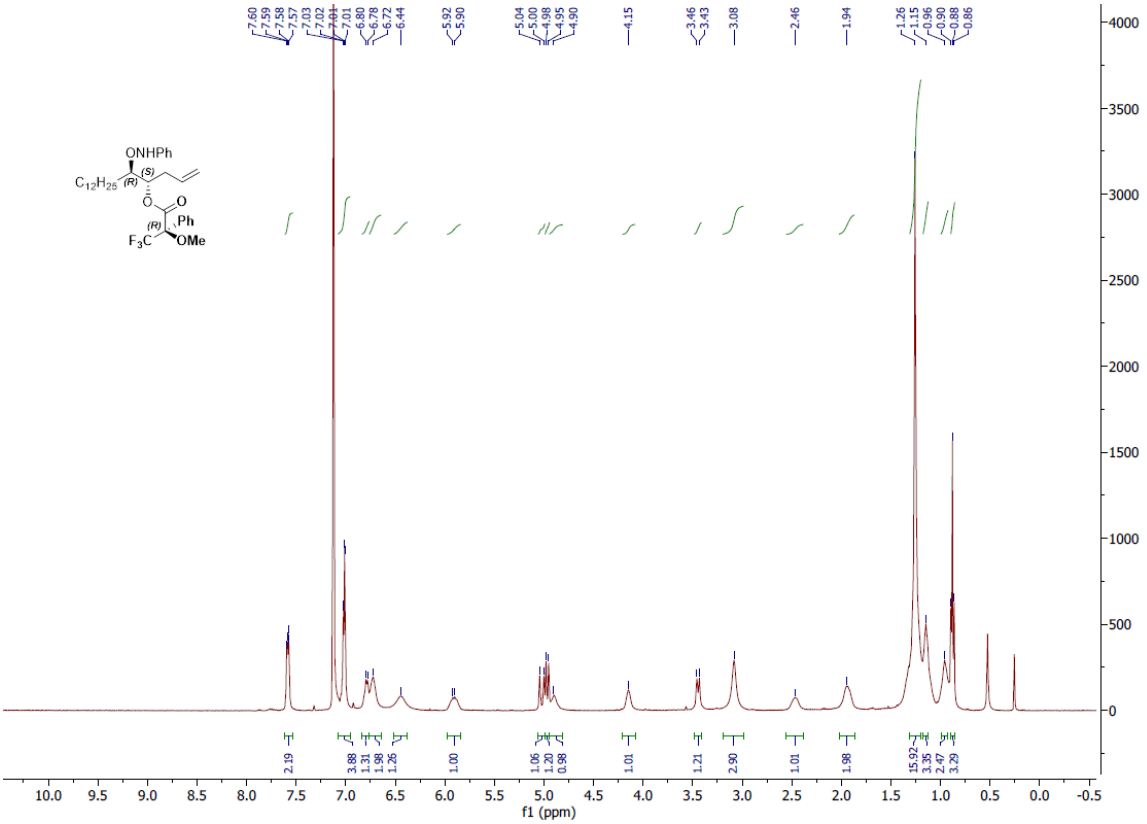


Figure S36. ^{1}H NMR spectra of compound **SI-13**.

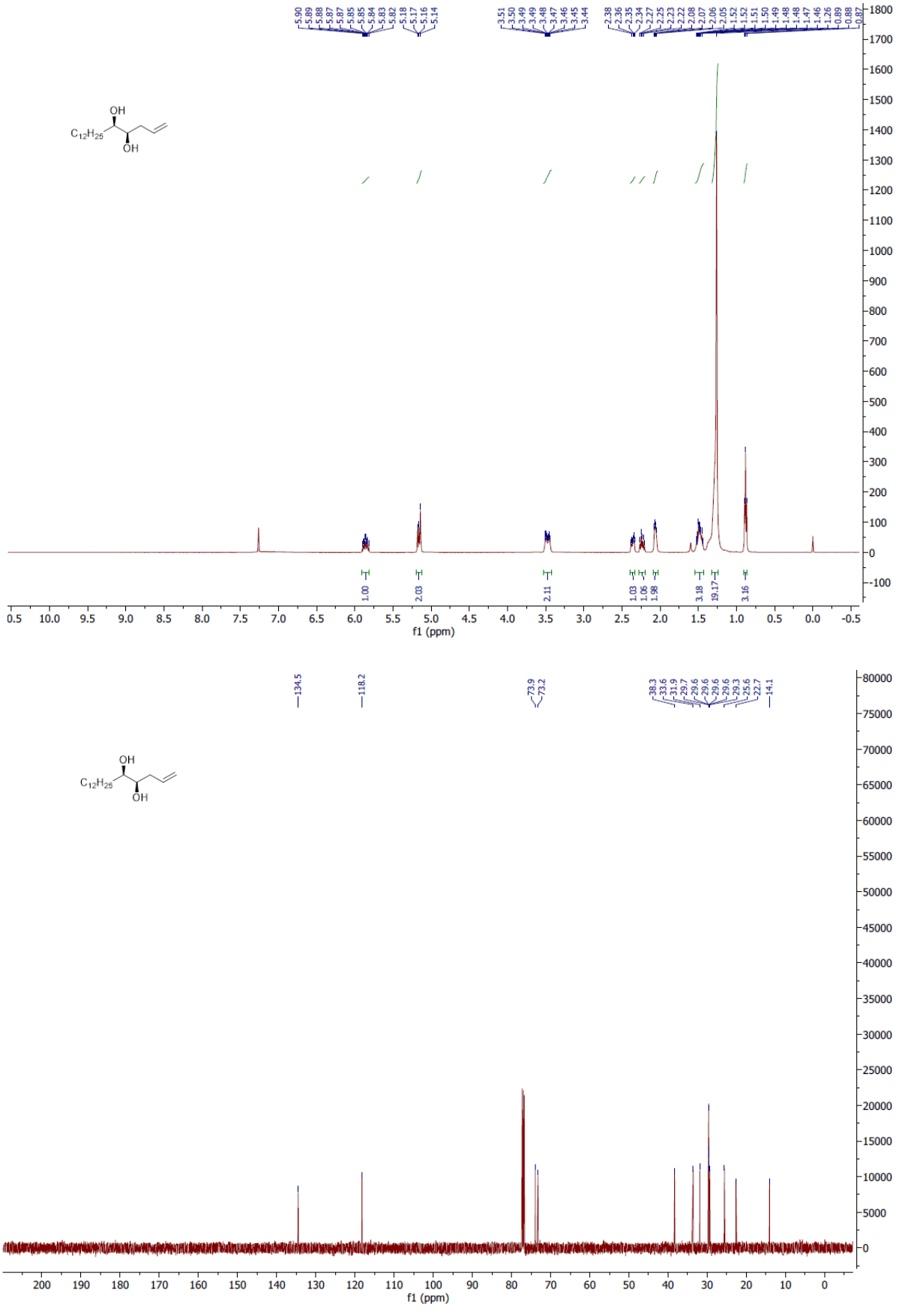


Figure S37. ^{1}H NMR (top) and ^{13}C NMR (bottom) spectra of compound **SI-14**.

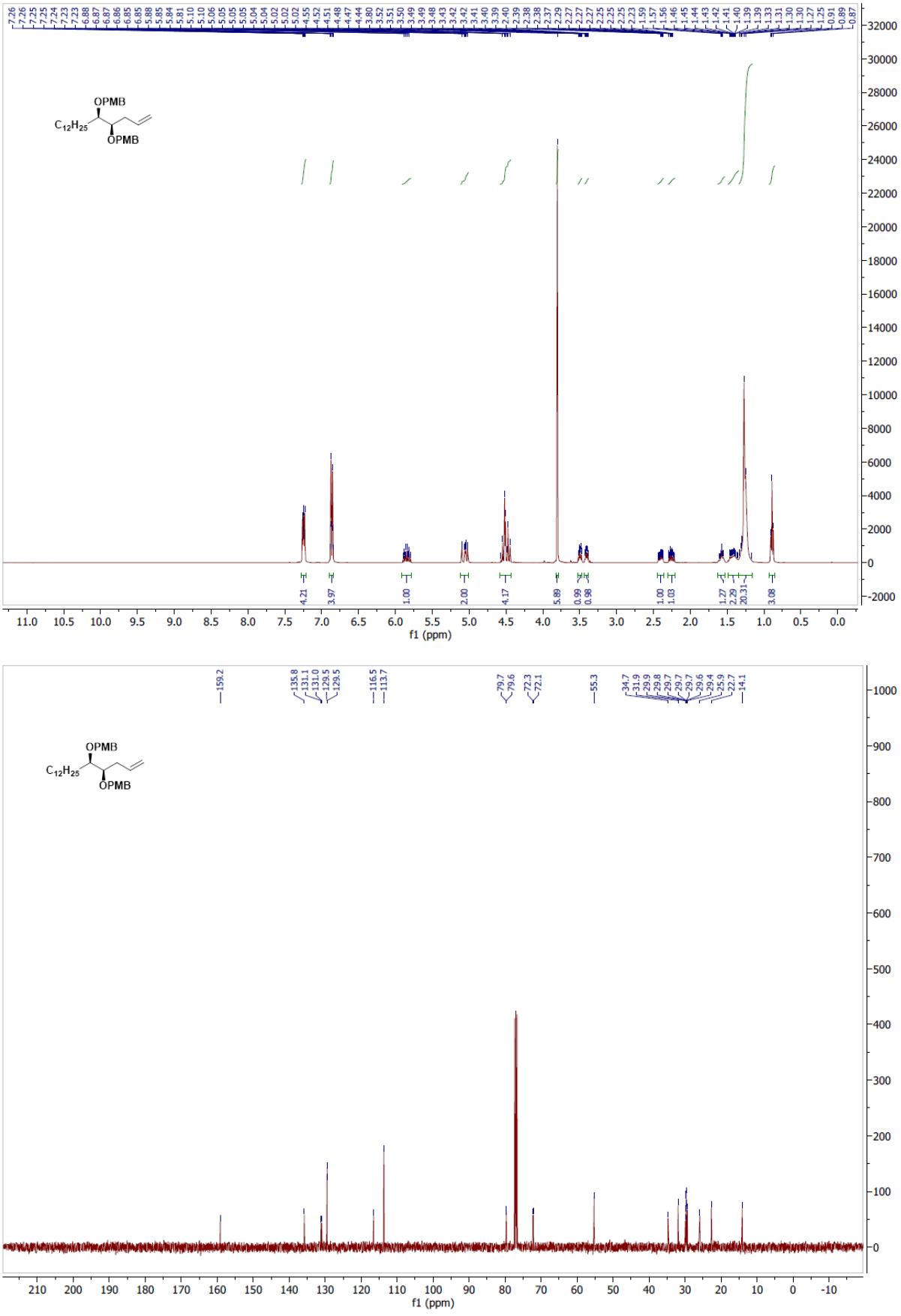
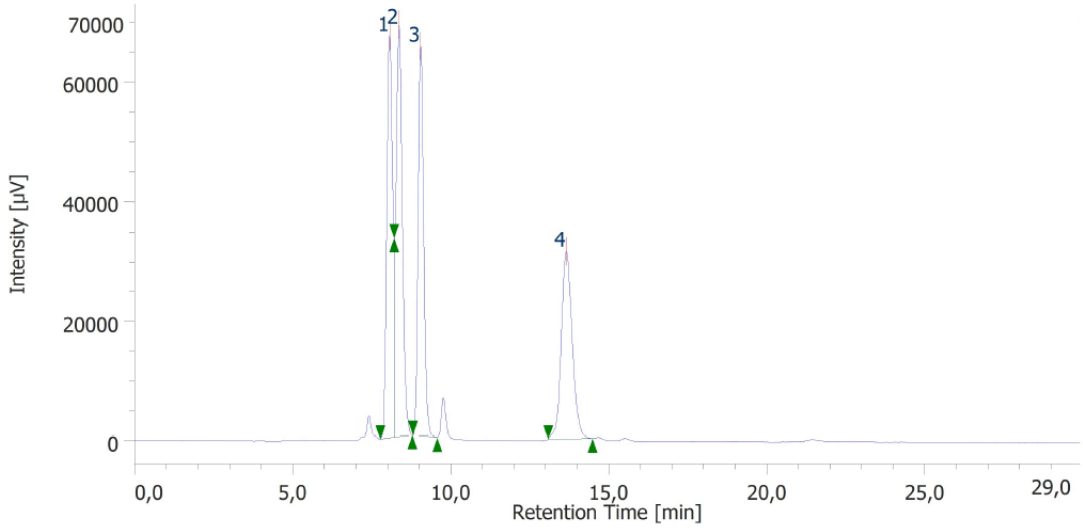
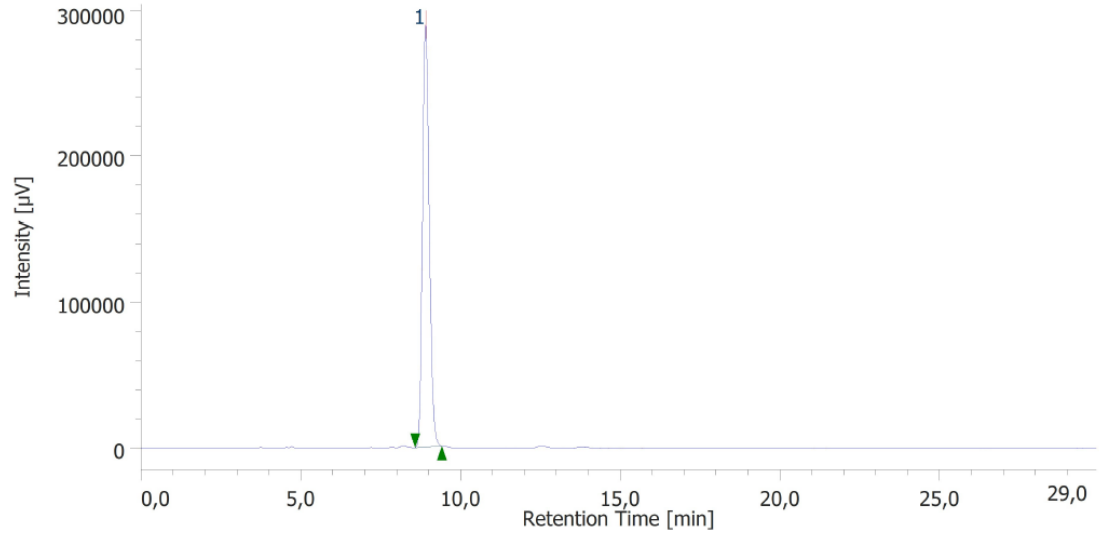


Figure S38. ^{1}H NMR (top) and ^{13}C NMR (bottom) spectra of compound **14**.



#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	1	8,067	859766	67212	25,409	28,899	N/A	6226	0,709	N/A	
2	Unknown	1	8,358	976141	68870	28,848	29,612	N/A	6467	1,874	N/A	
3	Unknown	1	9,042	790407	65053	23,359	27,971	N/A	13152	9,907	1,202	
4	Unknown	1	13,650	757437	31438	22,385	13,517	N/A	7819	N/A	1,127	

Figure S39. HPLC spectra of compound **14** racemate.



#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	1	8,908	4255104	289141	100,000	100,000	N/A	8560	N/A	1,159	

Figure S40. HPLC spectra of compound **14**.

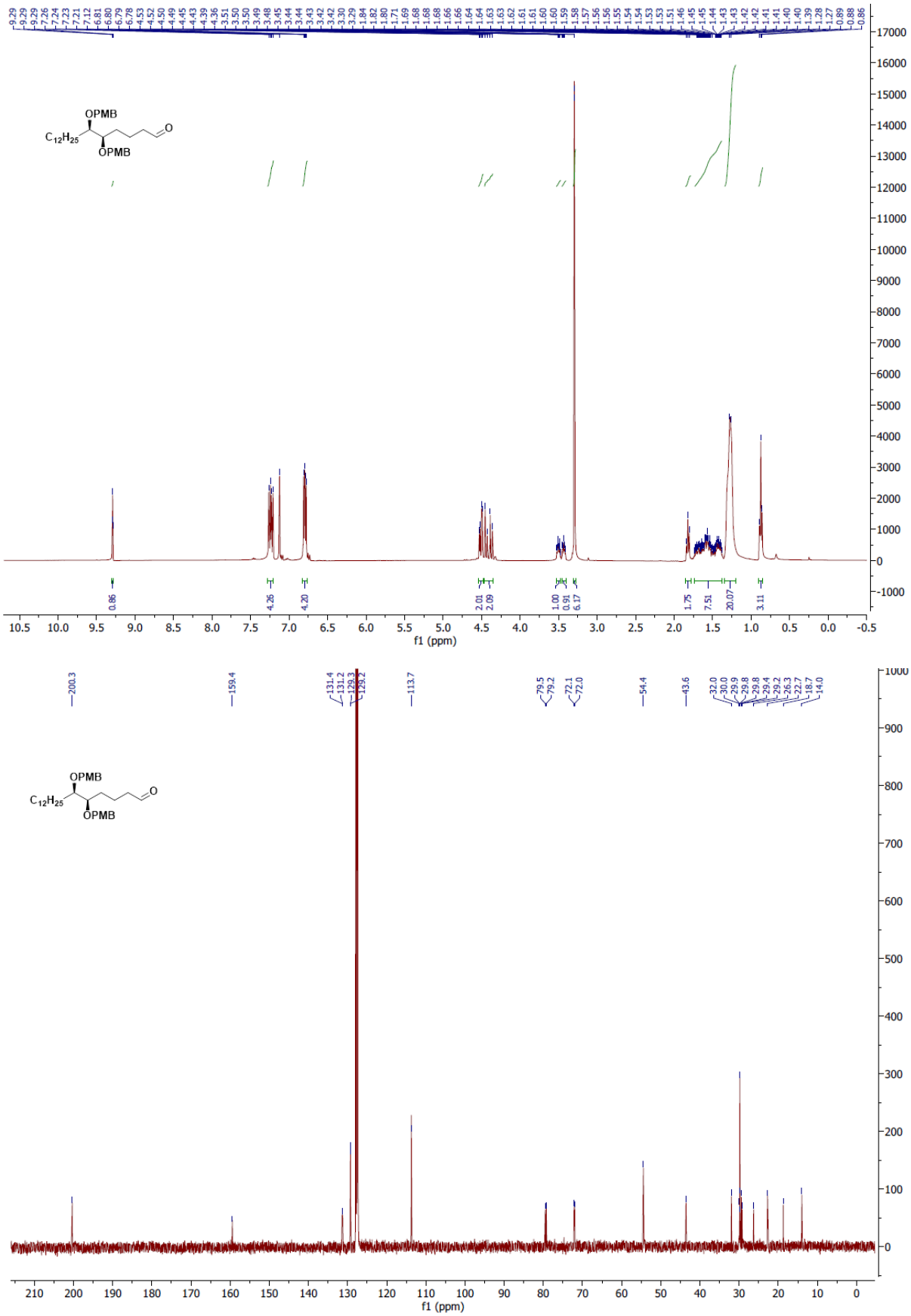


Figure S41. ^{1}H NMR (top) and ^{13}C NMR (bottom) spectra of compound **15**.

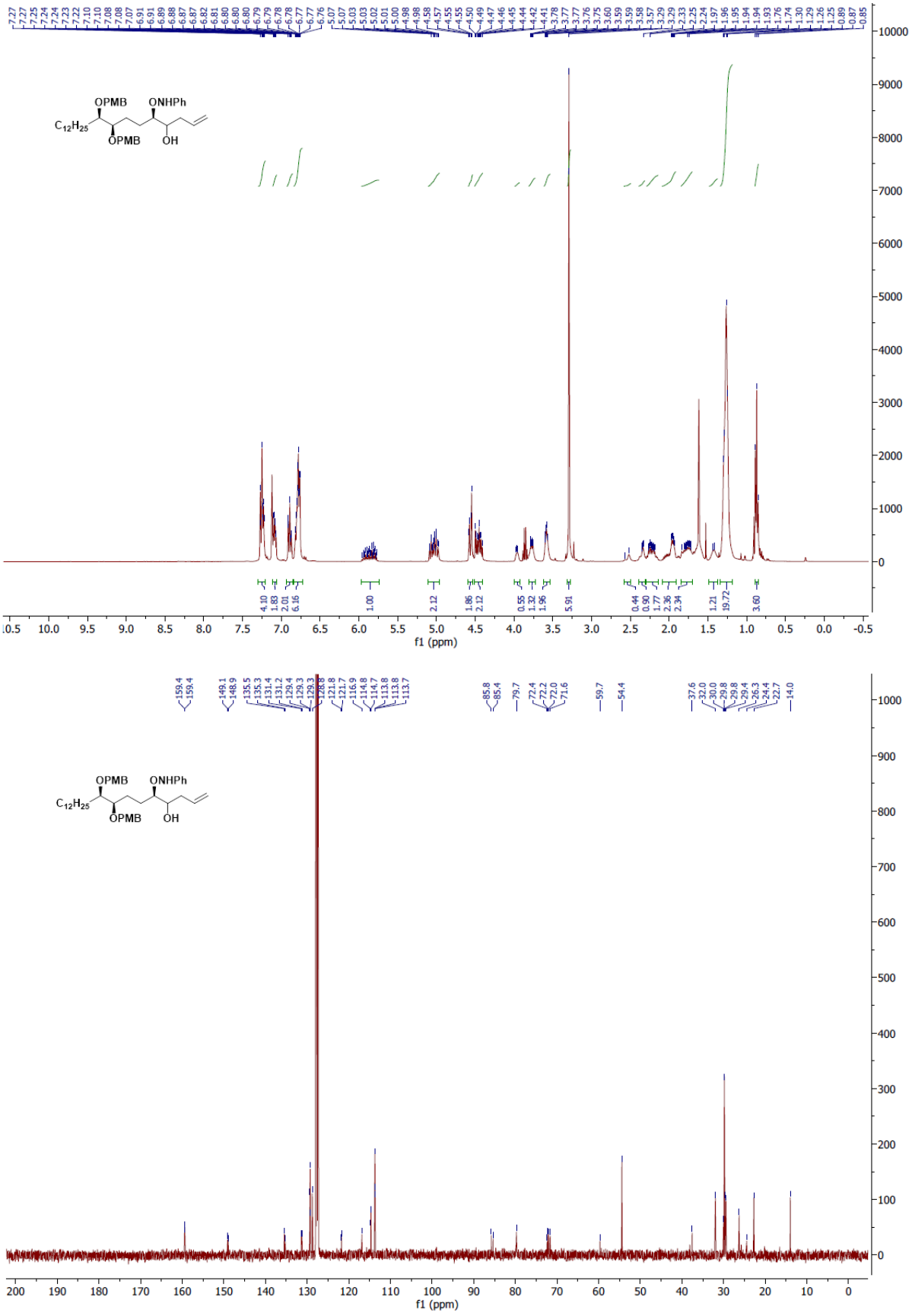


Figure S42. ^{1}H NMR (top) and ^{13}C NMR (bottom) spectra of compound **16**.

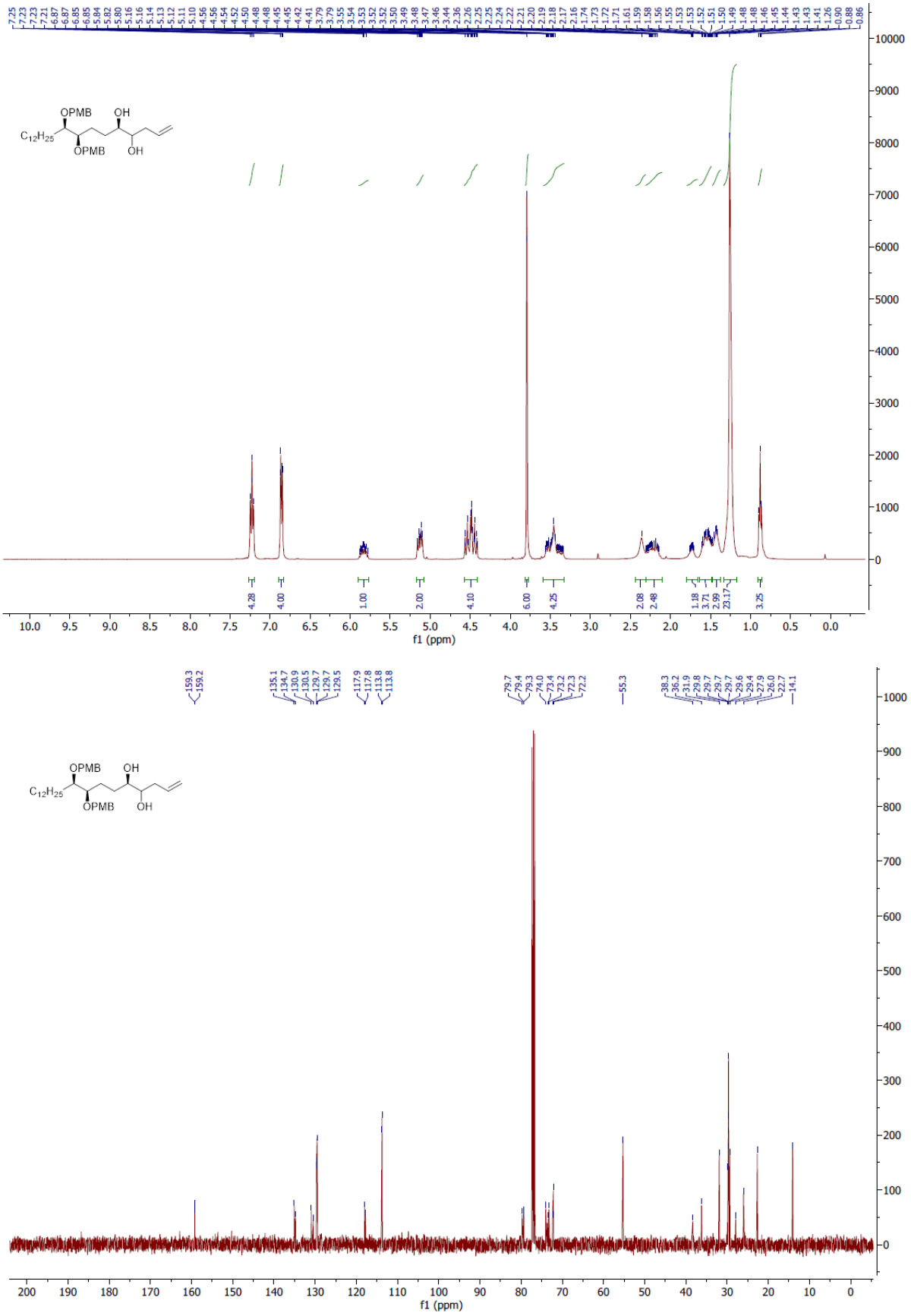


Figure S43. ^{1}H NMR (top) and ^{13}C NMR (bottom) spectra of compound **SI-15**.

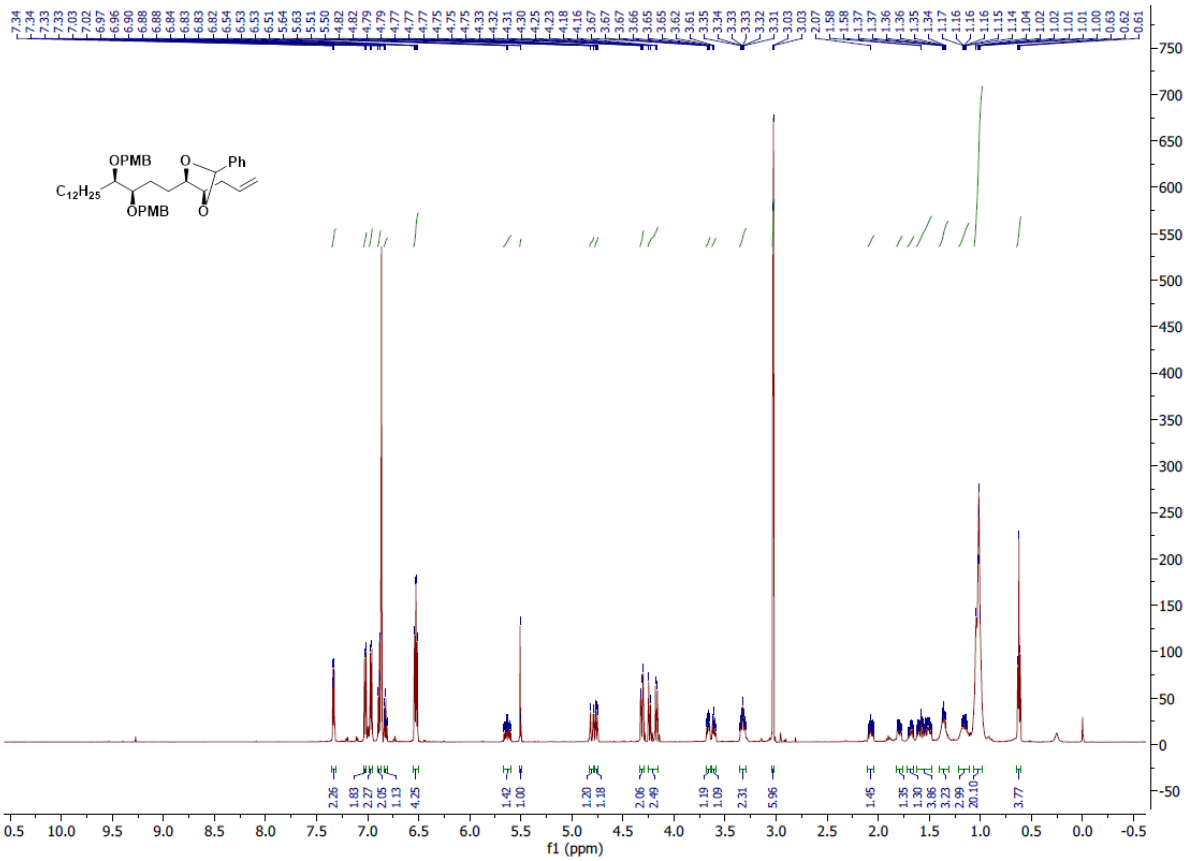


Figure S44. ^{1}H NMR spectra of compound **SI-16**.

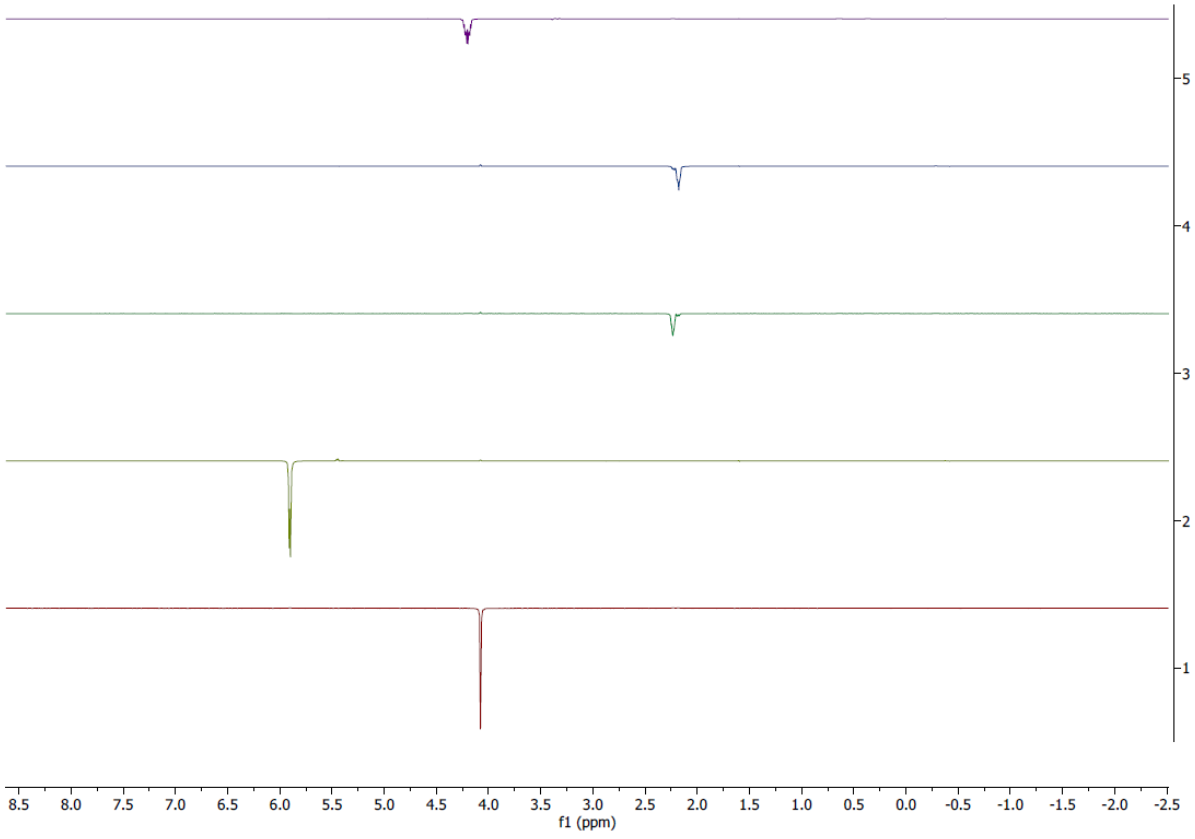


Figure S45. ^{1}H NMR NOE spectra of compound **SI-16**.

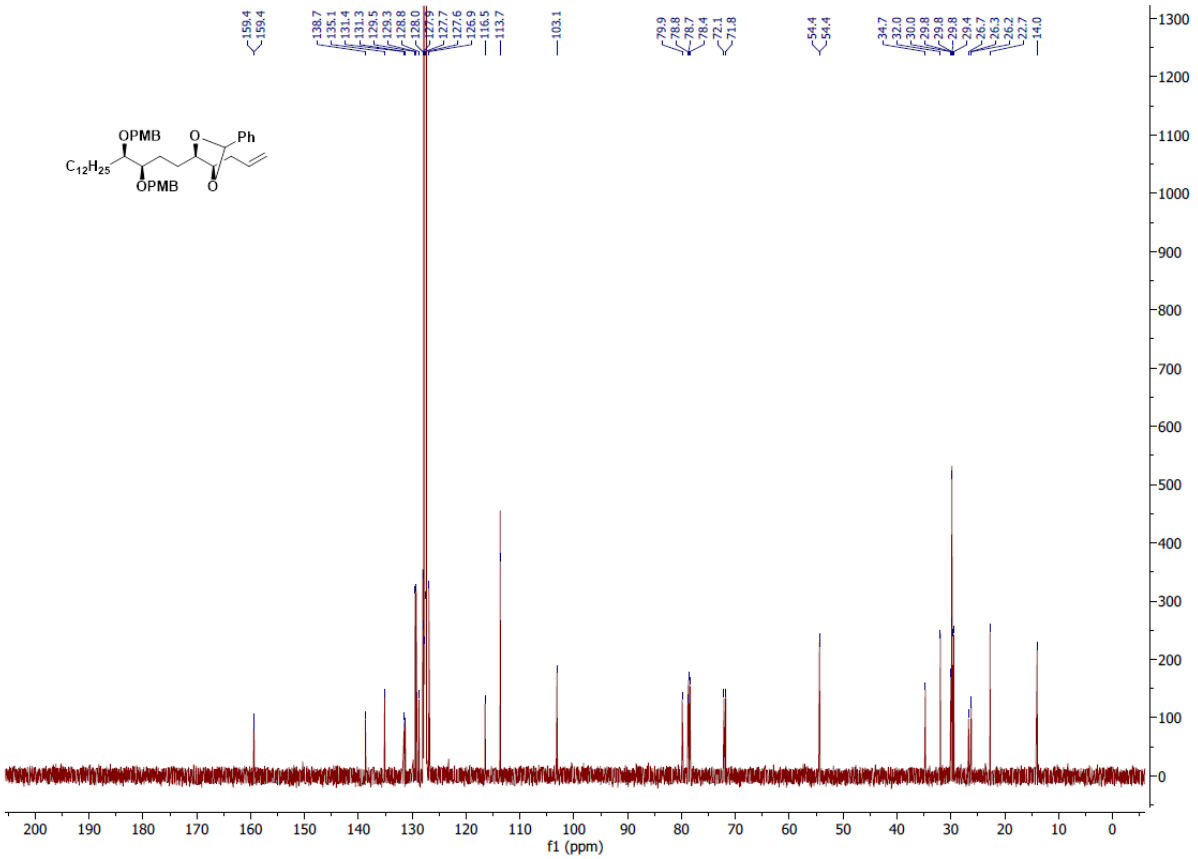


Figure S46. ^{13}C NMR spectra of compound **SI-16**.

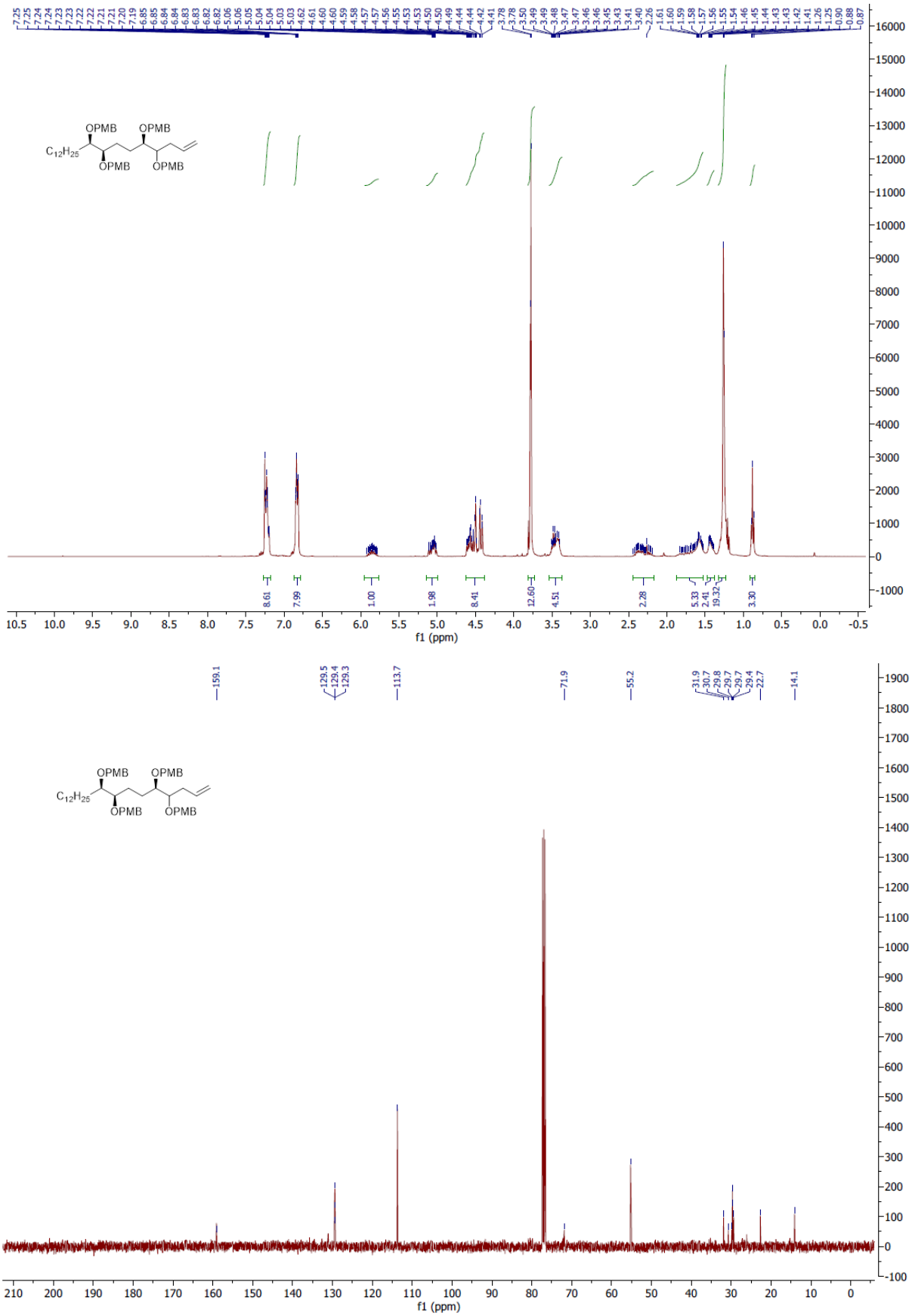


Figure S47. ^{1}H NMR (top) and ^{13}C NMR (bottom) spectra of compound **17**.

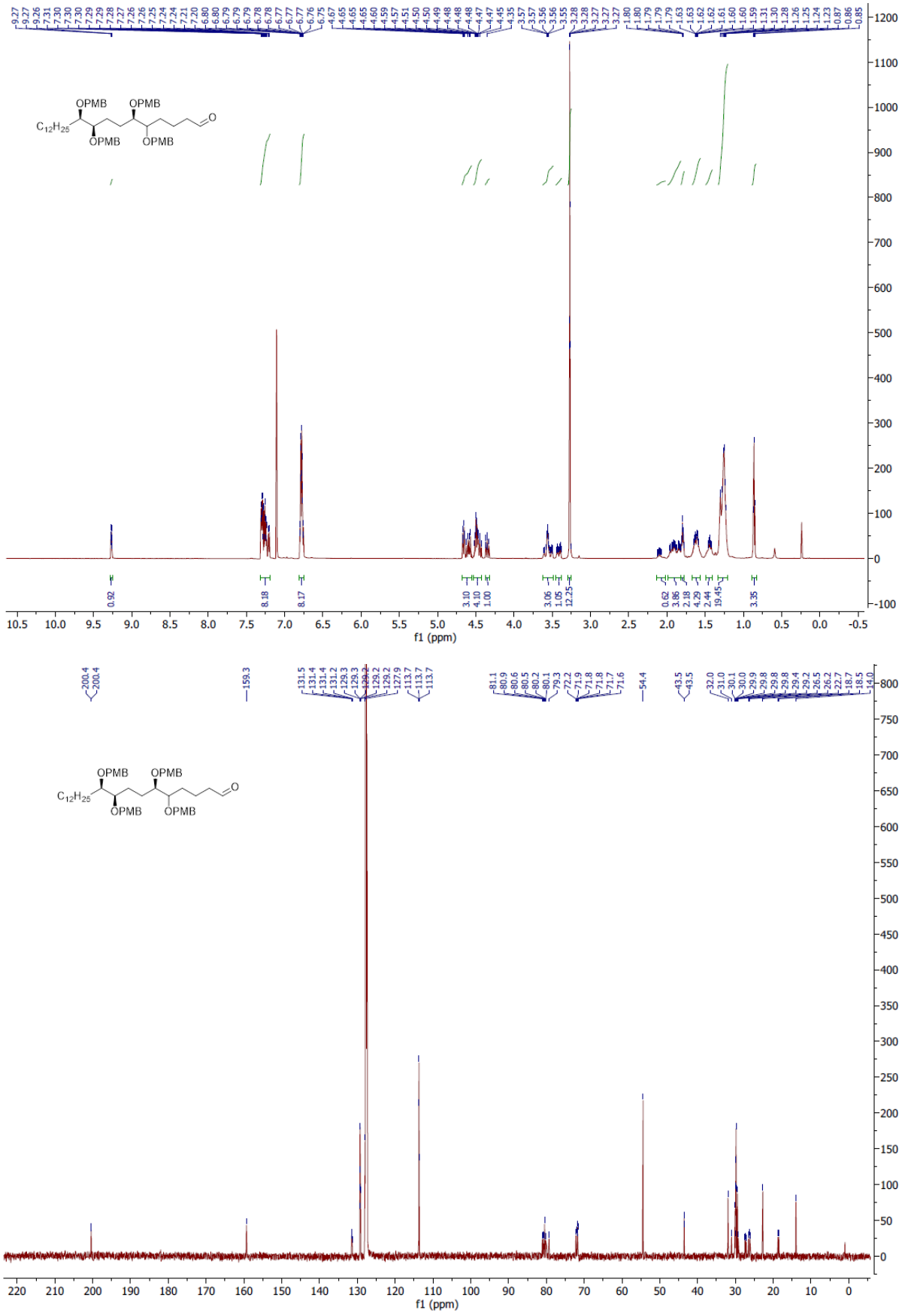


Figure S48. ^{1}H NMR (top) and ^{13}C NMR (bottom) spectra of compound **18**.

Section S12. User Manual for Allchemy's "Iterator" module

S12.1. Basic Information

Allchemy's "Iterator" module is freely available to academic users at https://iterator.allchemy.net. For optimal performance, we recommend using Google Chrome or other web-browsers supporting SVG2. To register a new account, send an e-mail to admin@allchemy.net from your academic address. Each user should create individual account. To start using the software, please log in using a valid username and password. After logging in you will see a window providing some technical information. Due to limited capacity of our servers and the fact that iterative searches can easily explode for large number of products (especially when larger numbers of substrates are used) the searches are limited to three iterative loops and three additional, user defined starting materials.

The main control panel visible after logging in is divided into three sections: the first one enables starting new searches (**A** in **Figure S49**; described in detail in **Section S12.2**), the second tab allows for displaying recent results and currently performed operations (**B** in **Figure S49**; described further in **Section S12.3**), while the third one provides access to the previously stored results (**C** in **Figure S49**; described further in **Section S12.4**).

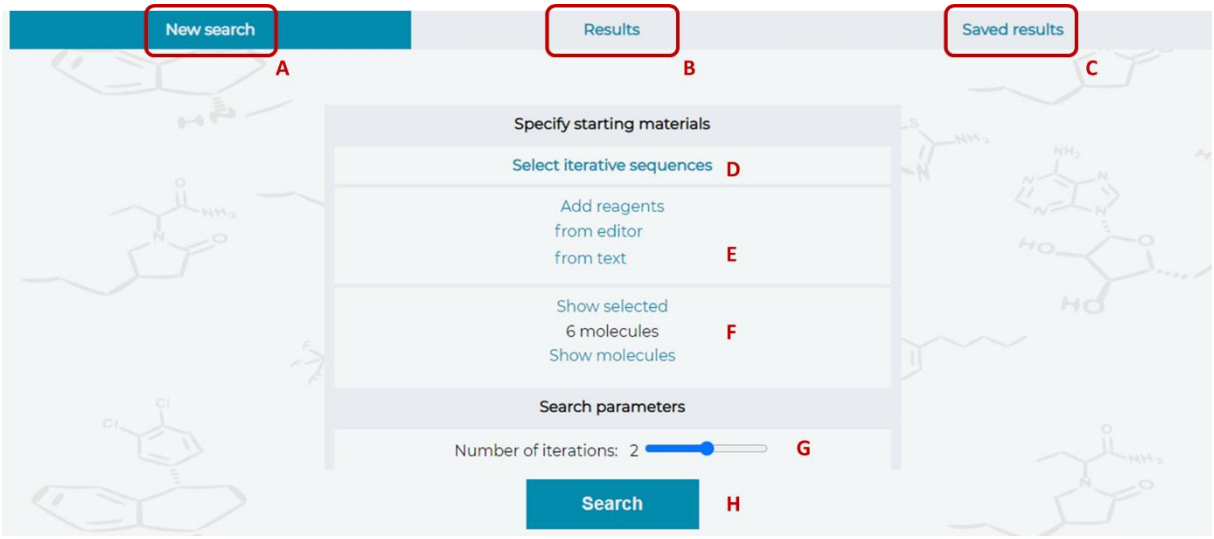


Figure S49. Main control panel of Allchemy's "Iterator" module. a, Setting up a new search is available under "*New search*" (**A**) tab**; b,** Preview of currently performed operations (including checking the position in server's calculation queue and termination of searches) is available under "*Results*" (**B**) tab. When no calculations are currently performed, the last calculation's results are displayed; **c,** Results of the previously performed searches can be retrieved under "*Saved results*" (**C**) tab; **d,** Selection of iterative sequences; **e,** Panel for adding user-specified building blocks. Adding up to three additional substrates to the calculation is allowed; **f,** Preview of currently selected substrates; **g,)** Number of iterations to be performed**; h,** Launch "*Search*" button

S12.2 Starting a new search

Starting a new calculation requires:

i) Choosing types of iterative sequences to be used during network generation (button **D** in **Figure S49**). The user may select up to three sequences from the displayed list (**Figure S50a**). Once these sequences are selected, their background will change color to light blue. After selecting desired sequences, push "*Apply*" button to confirm selection.

ii) Selecting proper building blocks/reagents for selected iterative sequence(s)

Note 1: For user's convenience, basic set of appropriate reagents will be proposed automatically for each iterative sequence selected (**Figure S50b**).

- The user can remove some of the simple starting materials proposed by the software (or replace them with more complicated ones) using "*Keep selected*" and "*Remove selected*" controls (**I** in **Figure S50b**)
- The user will be asked to confirm the removal operation (**Figure S50c**).

The calculation will not work properly if indispensable substrates are removed (e.g., allylating reagents necessary for Krische's/Brown allylation or carbon monoxide necessary for the hydroformylation step).

Note 2: Optionally, the user can add up to three of his/her own starting materials (**E** in **Figure S49**). The molecules can be added using structure-drawing editor (**recommended,** one can draw multiple molecules at once) or from SMILES string (separated by full stops). The software checks if the added molecule(s) match any of the selected iterative sequences (non-matching ones will not be added to the list). We recommend previewing the selected molecules (**F**) before launching the calculation, especially if the list of reagents was modified.

iii) specifying the number of iterations to be performed (**G**). User can select up to three iterations to be performed during a single search.

iv) Pushing the "*Search*" (**H**) button.

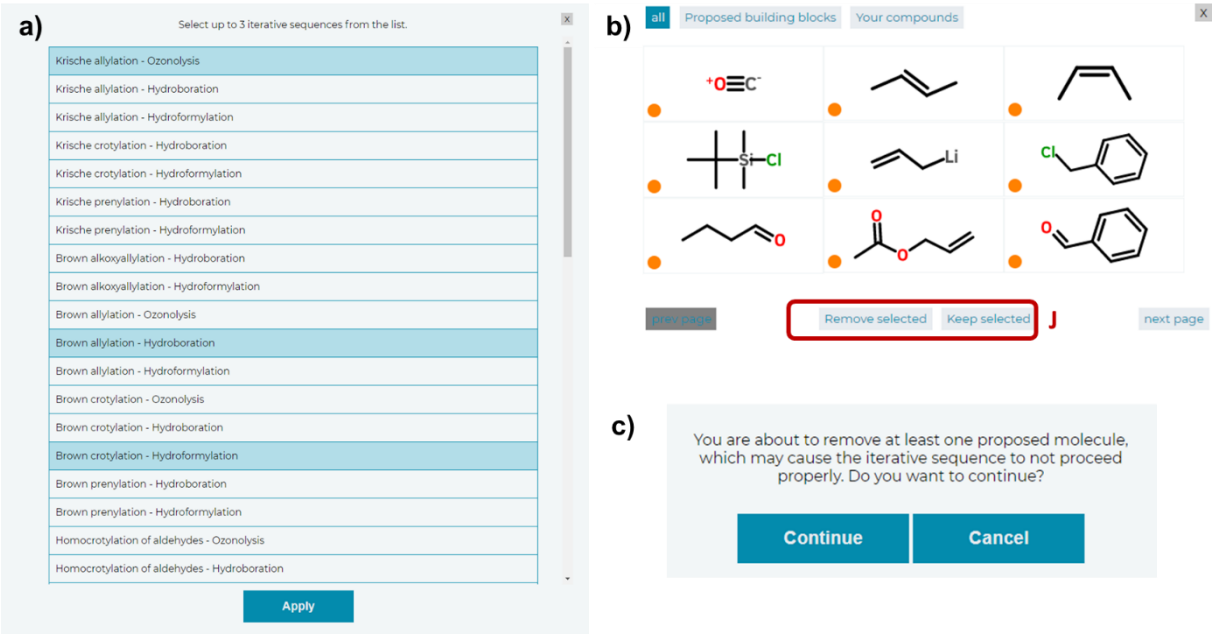


Figure S50. Starting a new search. a, The user is allowed to select up to three types of iterative sequences from the displayed list. The selected sequences are highlighted in light-blue. **b,** After confirming the choice with "*Apply*" button, a basic set of matching substrates and reagents is suggested and displayed. User can remove any of the proposed molecules (e.g., to replace them

with more complicated ones) using **J** controls. **c,** Removal of a key reagent will return empty result as the sequence will not be calculated properly. To avoid such outcomes, the user will be asked to confirm the removal operation.

S12.3 Analysis of results

After launching calculations, the user is transferred to the Results (**B**) tab. The calculation may take from few seconds up to several minutes and the results will be displayed automatically. The search is limited to 30 minutes due to server capacity. Longer calculations will be stopped automatically and already generated results will be returned.

In the default view, results are displayed as a panel of molecular structures (**Figure S51**). As the number of generated products may be in the thousands, we implemented filtering and sorting functionalities (**Figure S51 J** and **K**, respectively) to facilitate their analysis. In particular, the user can sort generated products according to their mass, number of rings, number of stereocenters, etc. using the **K** drop-down menu confirming the new choice with "*Sort again*" button. By default, the molecules are sorted according to their molecular mass. Panel **J** allows for filtering out products that do not meet user-specified structural criteria (molecular mass, number of rings, number of stereocenters, number of H-bond donor/acceptors, number of basic/acidic groups, number of halogens, Polar Surface Area (PSA), etc.). Additionally, the user can filter out molecules according to the number of substrates used to make them or by substructure. The latter filtering option can be used both for retaining or excluding products containing a specific structural motif. The structural motifs should be input in the SMARTS notation.

Filters are activated by clicking "*Apply filters*" button (**N** in **Figure S51**). To remove any applied filters, the user should use "*Clean all filters*" button (**M**). Left-clicking on any structure, will display details of the iterative synthetic pathway leading to this molecule. Each reaction in this plan is accompanied by reaction name, typical conditions, typical solvents and literature references (with DOIs as hyperlinks).

The generated results can be saved under user-specified name using "*Save*" button (**O** in **Figure S51**). These saved results will appear in the "*Saved results*" tab (**C**).

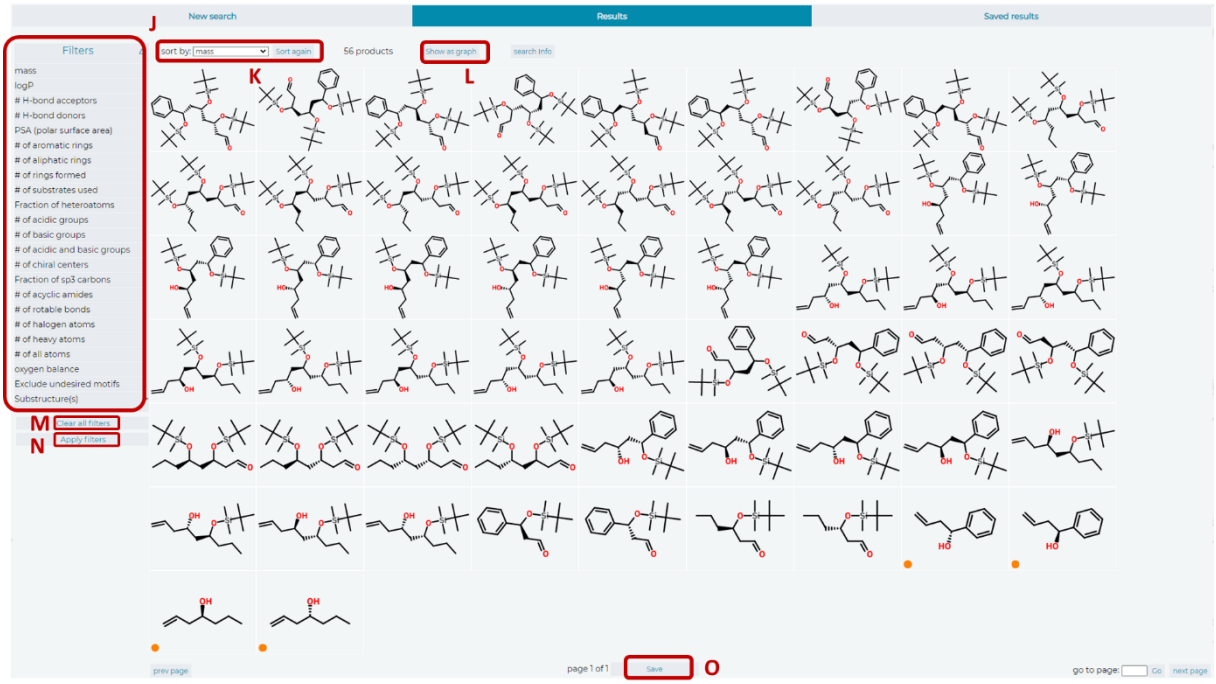


Figure S51. Analysis of results. In the default mode, the results are displayed as a panel of molecular structures sorted by molecular mass in descending order. The user may change sorting criteria using drop-down menu **K**. After changing these sorting criteria, the choice is confirmed by clicking "*Sort again*" button. Additionally, the user may apply filtering of products according to their masses, numbers of rings, numbers of stereocenters, etc. using list of filters in panel **J**. The filters are applied by using "*Apply filters*" **N** button whereas removing any applied filters is possible with "*Clear all filters*" **M** button. The results are saved under a user-given name by using "*Save*" (**O**) button. To change the view mode to network, the user should use "*View as graph*" (**L**) button.

Finally, the results can be displayed in network format (using **L** button **in Figure S52**). In this mode (**Figure S52**) molecules are represented as nodes. The nodes are layered according to the synthetic generation in which they are produced, with substrates in the first row at the very bottom. Hovering over any node displays a structure of a molecule while left-clicking on any node displays the synthetic pathway leading to this molecule. Right-clicking on the node selects the pathway leading to given molecule or from a given molecule, depending on the chosen selection mode **Q.**

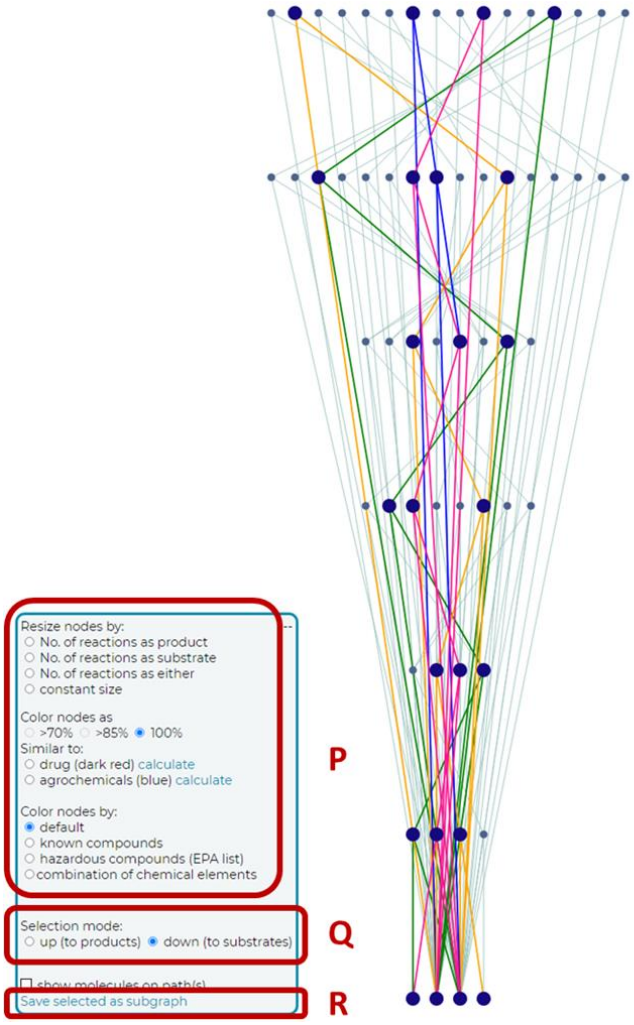


Figure S52. Network view of results with molecules represented as nodes. In this view, the substrates are located at the bottom. The user can select the synthetic pathway(s) leading to or from a given compound(s) (mode chosen with **Q** control) using right-mouse-button click on any molecule. The selected pathways can be saved as a subgraph using **R** control – the saved search appears in the "*Saved results*" tab (**C**). Left-mouse button click displays the synthetic pathway leading to a given molecule. Additionally, the **P** panel allows for coloring the nodes according to their status (known/present in EPA list/combination of chemical elements), for resizing nodes according to their popularity in the network, or for calculating their similarity to drugs or agrochemicals.

S12.4 Managing results

The results of searches are displayed automatically after being calculated in the Results (**B**) tab. Any unsaved results calculated during current session are available under "Temporarily stored calculation" in "*Saved results*" tab (**C**). These unsaved calculations are permanently lost after logging out. Calculations saved using "*Save*" button (**O**) and sub-networksaved using "*Save selected as subgraph*" (**R**) are stored unless deleted by the user.

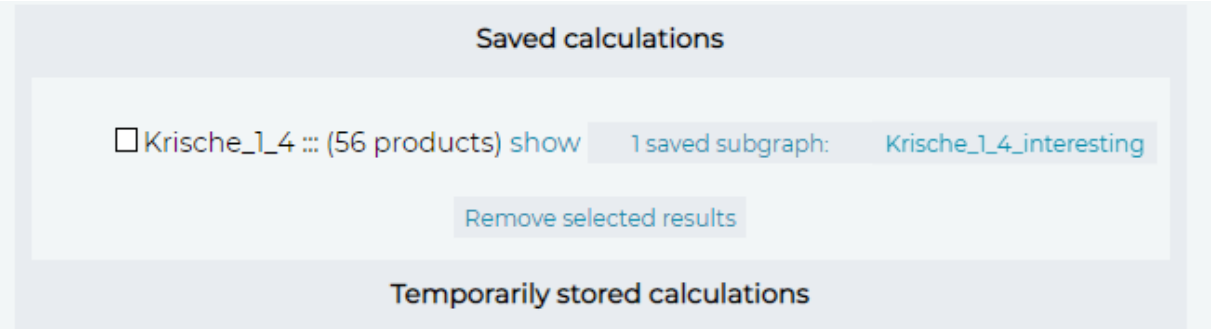


Figure S53. Saved results tab. Calculations are saved in "*Saved calculations*" section of "*Saved results*" (**C**) tab (saving is performed with **O** button) under user-given names and are not removed after logging out. The saved subgraphs (saved with **R** button) are available close to parent searches. The results stored in "*Temporarily stored calculations*" section are available only during current session and will be lost after logging out.

Section S13. Selection of conditions for iterative sequences.

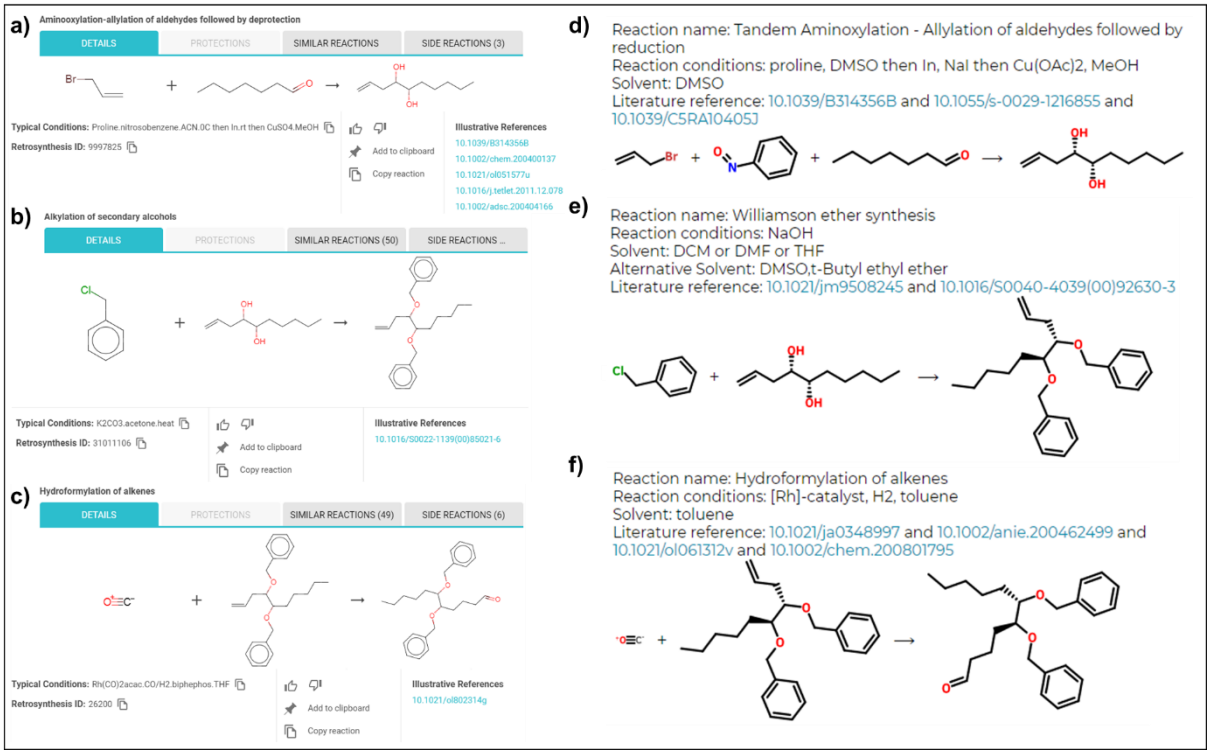


Figure S54. Conditions for iterative sequences are sourced from individual reaction rules taught to the computer. This example shows screenshots from **a-c,** Chematica and **d-f,** Allchemy programs for individual steps of the iterative synthesis of *1,2,5,6*-polyols via aminoxylation-allylation. Each step lists suggested conditions and provides hyperlinks to illustrative references (please note that Chematica and Allchemy are coded independently of one another and so illustrative literature links are generally not identical). As to the most noticeable adjustments in the computer-proposed conditions, for the cleavage of N-O bond step corresponding to panels (**a**-Chematica, **d**-Allchemy), we used the Zn/AcOH system to achieve 91% yield while the Cu^{2+} salts (as suggested by Chematica/Allchemy based on, e.g., [R7]) produced the desired product in 45% yield. Additionally, the Breit's[R15] catalytic system (Rh/6-DPPon) was used rather than the proposed Rh/Xantphos system, because it allowed us to replace the highly flammable and toxic H_2/CO mixture with HCOOH as the formylating agent[R16] during hydroformylation of alkenes. Finally, in this and other examples from Figure 5, we used the NaH in DMF as a base for protection of secondary alcohols with PMBCl rather than K_2CO_3 in acetone proposed by Chematica.

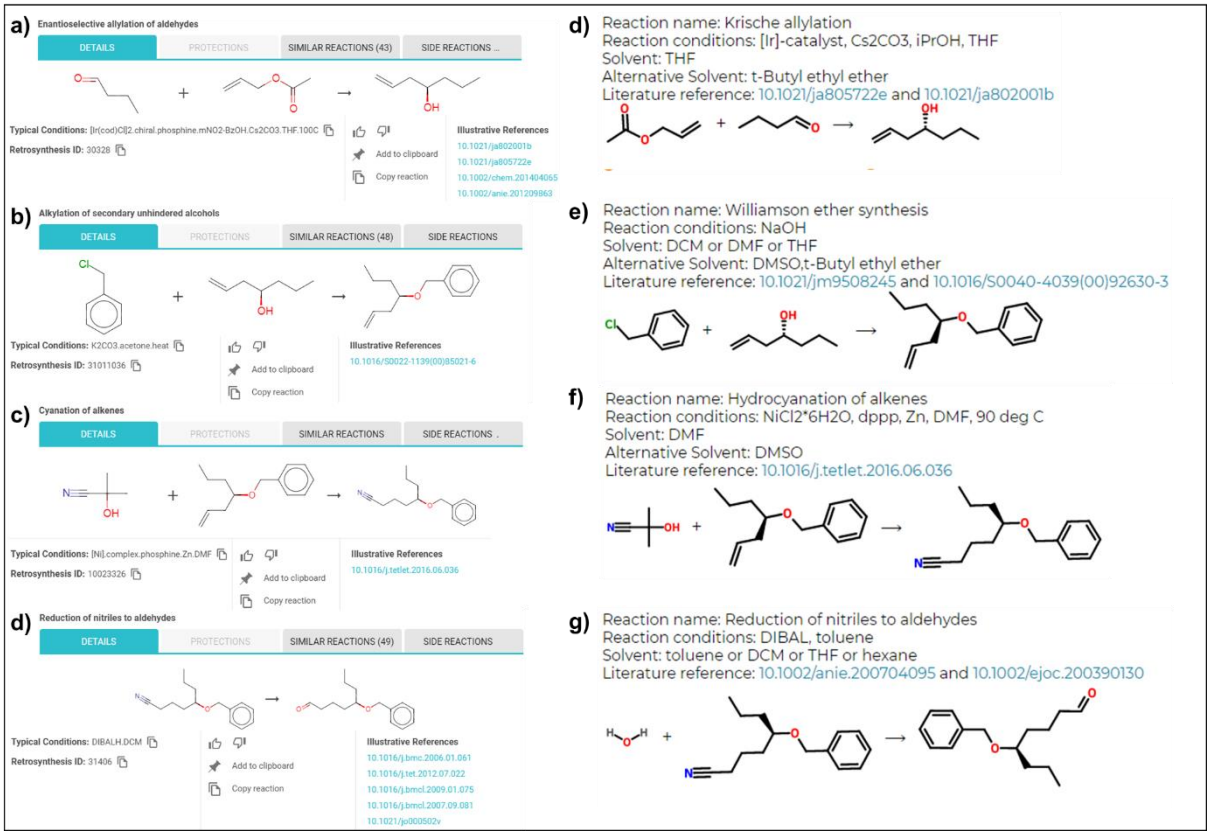


Figure S55. Conditions for iterative sequences are sourced from individual reaction rules taught to the computer. This example shows screenshots from **a-d,** Chematica and **e-g,** Allchemy programs for individual steps of the iterative synthesis of *1,5*-polyols via Krische's allylation (cf. main-text **Figure 5a**). Each step lists suggested conditions and provides hyperlinks to illustrative references (please note that Chematica and Allchemy are coded independently of one another and so illustrative literature links are generally not identical). As to the differences between computer-suggested and experimental conditions, in allylation step corresponding to panels (**a**-Chematica, **d**-Allchemy), we used the improved Krische's catalyst that we happened to have on the shelve – with 4-CN-3-NO_2-BzOH instead of 3-NO_2-BzOH ligand proposed by Chematica. In the same spirit of shelve-availability, the hydrocyanation step (**c**-Chematica, **f**-Allchemy) was performed with simple $Zn(CN)_2$ salt rather than proposed acetone cyanohydrin.

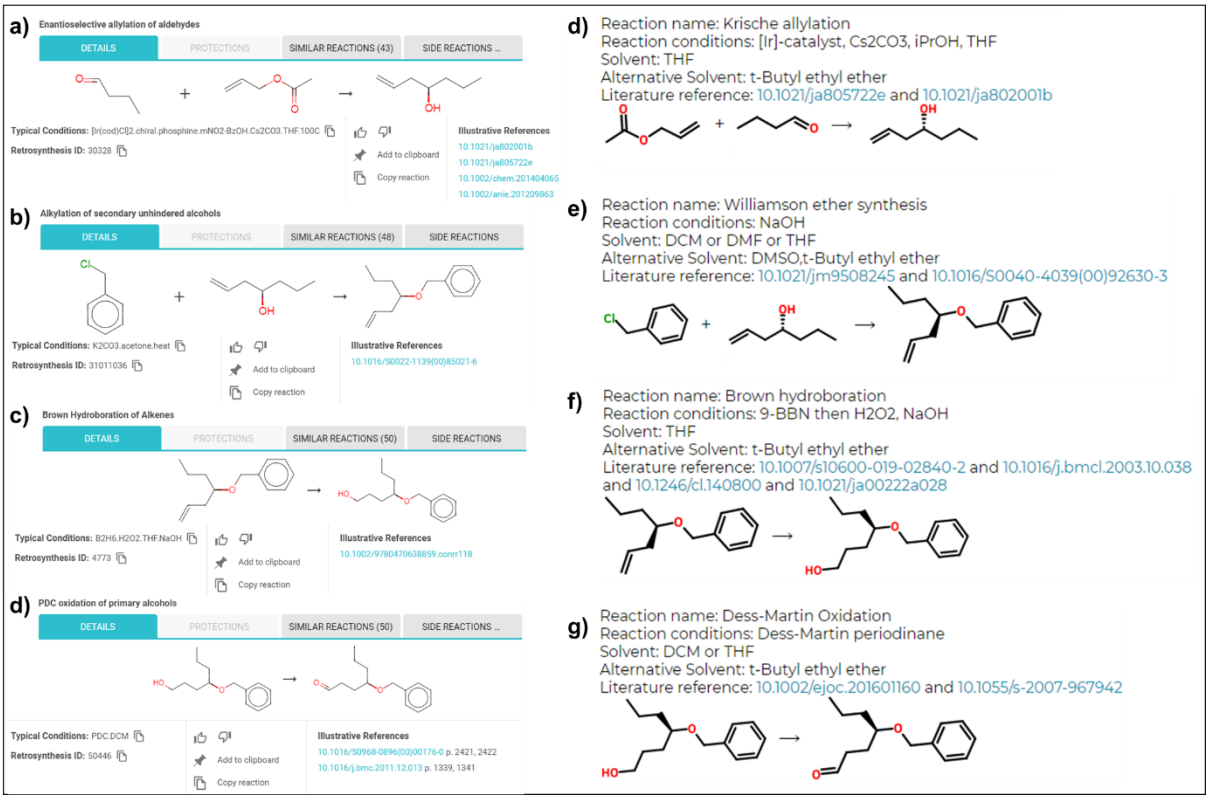


Figure S56. Conditions for iterative sequences are sourced from individual reaction rules taught to the computer. This example shows screenshots from **a-d,** Chematica and **e-g,** Allchemy programs for individual steps of the iterative synthesis of *1,4*-polyols via Krische's allylation (**Figure 5b**). Each step lists suggested conditions and provides hyperlinks to illustrative references (please note that Chematica and Allchemy are coded independently of one another and so illustrative literature links are generally not identical). Regarding the differences between computer-suggested and experimental conditions, in the allylation step corresponding to panels (**a**-Chematica, **d**-Allchemy), we used the improved Krische's catalyst that we happened to have on the shelve – with 4-CN-3-NO_2-BzOH instead of 3-NO_2-BzOH ligand proposed by Chematica.

Section S14. Pseudocode for the algorithm to identify iterative sequences.

```
1: function generalFiltering(seq)
   ▷ seq - considered reaction sequence
   ▷ returns False if basic conditions for considered reaction sequence are not satisfied

2:     if seq.m_t = seq.m_s then return False
3:     if seq.m_s.isTrivial() then return False
                                   ▷ removes substrates like water etc.
4:     if commonAtoms(seq.m_t, seq.m_i) = ∅ then return False
5:     if commonAtoms(seq.m_i, seq.m_s) = ∅ then return False
       return True

6: function getFragments(m)
   ▷ returns set of substructures (fragments) within radius R = 2 for atoms of molecule m

7: function findIteratives(seq)
   ▷ seq - considered reaction sequence, has the following fields:
   ▷ seq.r_1 - reaction closer to target
   ▷ seq.r_2 - reaction further from target
   ▷ seq.m_t, seq.m_i, seq.m_s, - target, intermediate, considered substrate
   ▷ seq.m_inters - all intermediates (ie. intermediate and its 'siblings' from r_1)
   ▷ seq.m_subs - all substrates (ie. considered substrate and its 'siblings' from r_2)
8:     if not generalFiltering(seq) then return False
9:     fr_t ← getFragments(seq.m_t)
10:    fr_i ← getFragments(seq.m_i)
11:    fr_subs ← getFragments(seq.m_subs)
12:    F_i ← (fr_i − fr_t) ∩ (fr_i − fr_subs)
13:    if (F_i = ∅) then return False
14:    fr_s ← getFragments(seq.m_s)
15:    F_ts ← (fr_t − fr_i) ∩ (fr_s − fr_i)
16:    if findCoreLoop(seq, F_ts) then return True
17:    if findABLoop(seq) then return True
18:    return False
```

Figure S57: A general scheme of detecting iterative sequences (function findIteratives; lines 7-18). As input, the algorithm takes sequence *seq* of individual reaction steps (and/or sequences of steps, like FGI, see main text). Reactions entailing any incompatibilities – as determined

based on the list of groups incompatible with a given reaction rule – are excluded. In the 'general filtering' phase (generalFiltering; lines 1-5) the algorithm removes trivially useless pairs of reactions sequences such as simple loops (*substrate* = *target*, e.g., reduction and then oxidation of the same group), or sequences in which *target* or *substrate* have no atoms common with the sequence's *intermediates*. In the 'structural fragment A regeneration filtering' phase (lines 9-13) the algorithm retains sequences if there exists any fragment (functional substructure within radius R=2 of the molecule's atom; getFragments; line 6) present exclusively in the *intermediate*. Furthermore, iterative sequences are to be identified by the following two functions: findCoreLoop (cf. also Figure 53) and findABLoop; cf. also **Figure S54**).

```
1: function acceptedFts(r_1, m_t, m_inters, F_ts)
   ▷ at least one member of F_ts has only one matching to target and overlaps with core of r_1 applied on m_t producing m_inters
2:     for f_ts in F_ts do
3:         if (m_t.countSubstructures(f_ts) ≠ 1) then continue
4:         if (m_t.substructure(f_ts) ∩ core(r_1, m_t, m_inters) ≠ ∅)) then return True
5:     return False

6: function getSynthon(r, m_1, m_2, m_lst)
   ▷ returns synthon of reaction r that, when applied to product m returning substrates m_lst, corresponds to substrate m_2

7: function getSynthonForReactionCluster(r_1, r, m_1, m_2, m_lst)
   ▷ returns synthon of reaction r_1 analogous to getSynthon(r, m_1, m_2, m_lst)
   ▷ assumption: r and r_1 are from the same reaction cluster (have the same name, number of products and number of synthons)

8: function closeLoopCondition(seq)
   ▷ seq - considered reaction sequence
   ▷ condition checking the possiblity of iterating more times with seq
9:     synt_2 ← getSynthon(seq.r_2, seq.m_i, seq.m_s, seq.m_subs)
10:    if not seq.m_t.hasSubstructure(synt_2) then return False
11:    m_fi ← applyReaction(reverted(seq.r_2), seq.m_t)    ▷ generating forward intermediate
12:    if m_fi.atomCount() ≤ m_i.atomCount() then return False
13:    for r in getClass(seq.r_1) do
14:        synt_1 ← getSynthonForReactionCluster(r, seq.r_1, seq.m_t, seq.m_i, seq.m_inters)
15:        if m_fi.hasSubstructure(synt_1) then return True
16:    return False

17: function findCoreLoop(seq, F_ts)
   ▷ seq - considered reaction sequence
   ▷ F_ts - structural fragments present both in the target and the substrate, but is absent in the intermediate of considered sequence
18:    if not acceptedFts(seq.r_1, seq.m_t, seq.m_inters, F_ts) then return False
19:    if not closeLoopCondition(seq) then return False
20:    return True
```

Figure S58: Pseudocode of CoreLoops (for example see main-text **Figure 2a**) identification (findCoreLoop; lines 17-20). The algorithm selects sequences of reactions having a substructure (structural motif) present both in the *target* and the *substrate*, but absent in the

intermediate. This structural motif overlaps with the "core" of reaction r_1 ('structural fragment B regeneration'). More precisely, we define collection of substructures F_{ts} = $(fr_{target} - fr_{intermediate}) \cap (fr_{substrate} - fr_{intermediate})$ (cf. **Figure S52** lines 9-10 and 14-15), and retain sequences in which at least one member of F_{ts} has only one matching to *target* and overlaps with the r_1 core (acceptedFts; lines 1-5). In addition, in order to assign a sequence of transformations to this category, the following close-the loop conditions have to be satisfied (closeLoopCondition; lines 8-16): *target* contains r_2 core synthon, *forward intermediate*, i.e., product of r_2 applied to the *target* in the forward direction ("reverted r_2") contains core of the synthon from the r_1 class (i.e., expert-coded reaction rule from the same chemical category having the same name, number of products and number of synthons as transformation r_1); *forward intermediate* must have more non-hydrogen atoms than *intermediate* to avoid, e.g., unproductive iterations (line 12).

```
1: function countNonTrivial(m_lst)
   ▷ counts members of m_lst without trivial molecules (eg. water, iodine mono-
   bromide, carbon dioxide)

2: function crossIncompatible(seq)
   ▷ seq - considered reaction sequence

3:     for g in seq.r1.incompatibilities ∪ seq.r1.protections do
4:         if seq.m_s.hasSubstructure(g) then return True
                                   ▷ substrate not compatible with seq.r1
5:     for g in seq.r2.incompatibilities do
6:         if seq.m_t.hasSubstructure(g) then return True
                                   ▷ target not compatible with seq.r1

7: function additionalChemicalFilter(seq)
   ▷ seq - considered reaction sequence
   ▷ returns True for sequences with Grignard reagent as an intermediatea-
   mong intermediates, where a functional group incompatible with the syn-
   thesis of organomagnesium compounds was found among substrates (apart
   from cases, where this group overlapped with core of r2 creating considered
   Grignard reagent)

8: function findABLoop(seq)
   ▷ seq - considered reaction sequence
9:     if countNonTrivial(seq.m_inters) < 2 then
10:        if countNonTrivial(seq.m_subs) < 2 then return False
11:    if hasProtection(seq.r1, seq.m_t, seq.m_inters then return False
           ▷ reactions with incompatibilities already removed while generating
   candidates for reaction sequences
12:    if crossIncompatible(seq) then return False
13:    if additionalChemicalFilter(seq) then return False
```

Figure S59: Pseudocode of ABLoops (for example see main-text **Figure 2b**) identification (findABLoop; lines 8-13). The algorithms filters out the following groups of sequences: (a) one-molecule sequences, i.e., only one non-trivial (countNonTrivial; line 1) synthon resulting from r_1 and r_2 (lines 9-10), (b) having protection on r_1 (line 11; note sequences with incompatibilities at this step are removed earlier), (c) satisfying cross-incompatibility condition, i.e., *target* with incompatibility from r_2, or *substrate* with either protection or incompatibility from r_1 (crossIncompatible; lines 2-6) (d) returning True when applying additionalChemicalFilter (line 7) .

Section S15. References

R1) I. S. Kim, M.-Y. Ngai, M. J. Krische, Enantioselective iridium-catalyzed carbonyl allylation from the alcohol or aldehyde oxidation level using allyl acetate as an allyl metal surrogate. *J. Am. Chem. Soc.* **130**, 6340–6341 (2008).

R2) D. Ghosh *et al.*, Synthetically amenable amide derivatives of tosylated-amino acids as organocatalysts for enantioselective allylation of aldehydes: computational rationale for enantioselectivity. *Org. Biomol. Chem.* **11**, 3451–3460 (2013).

R3) F. Hessler, A. Korotvička, D. Nečas, I. Valterová, M. Kotora, Syntheses of a Flobufen metabolite and Dapoxetine based on enantioselective allylation of aromatic aldehydes. *Eur. J. Org. Chem.* **2014**, 2543–2548 (2014).

R4) J. Cossy, C. Willis, V. Bellosta, S. BouzBouz, Enantioselective allyltitanations and metathesis reactions. Application to the synthesis of piperidine alkaloids (+)-Sedamine and (−)-Prosophylline. *J. Org. Chem.* **67**, 1982–1992 (2002).

R5) G. Wang, X. Xie, W. Xu, Y. Liu, Nickel-catalyzed highly regioselective hydrocyanation of alkenes with $Zn(CN)_2$. *Org. Chem. Front.* **6**, 2037–2042 (2019).

R6) T. R. Hoye, C. S. Jeffrey, F. Shao, Mosher ester analysis for the determination of absolute configuration of stereogenic (chiral) carbinol carbons. *Nat. Protoc.* **2**, 2451–2458 (2007).

R7) G. Zhong, Tandem aminoxylation–allylation reactions: a rapid, asymmetric conversion of aldehydes to mono-substituted 1,2-diols. *Chem. Commun.* 606-607 (2004).

R8) M. Simek, K. Bartova, R. Pohl, I. Cisarova, U. Jahn, Tandem anionic oxy-Cope rearrangement/oxygenation reactions as a versatile method for approaching diverse scaffolds. *Angew. Chem. Int. Ed.* **59**, 6160-6165 (2020).

R9) A. G. M. Barrett, W. W. Doubleday, K. Kasdorf, G. J. Tustin, Stereochemical elucidation of the pentacyclopropane antifungal agent FR-900848. *J. Org. Chem.* **61**, 3280-3288 (1996).

R10) Huang, H. *et al.* Design, synthesis, and biological evaluation of novel nonsteroidal farnesoid X receptor (FXR) antagonists: Molecular basis of FXR antagonism. *ChemMedChem* **10**, 1184–1199 (2015).

R11) Schöllkopf, U. & Schröder, R. 2-Unsubstituted oxazoles from α-metalated isocyanides and acylating Agents. *Angew. Chem. Int. Ed.* **10**, 333–333 (1971).

R12) J.K. Augustine, V. Vairaperumal, S. Narasimhan, P. Alagarsamy & A. Radhakrishnan, Propylphosphonic anhydride (T3P®): an efficient reagent for the one-pot synthesis of 1,2,4-oxadiazoles, 1,3,4-oxadiazoles, and 1,3,4-thiadiazoles. *Tetrahedron* **65**, 9989–9996 (2009).

R13) Khan, A. T. *et al.* Synthesis of tetra-substituted pyrroles, a potential phosphodiesterase 4B inhibitor, through nickel(II) chloride hexahydrate catalyzed one-pot four-component reaction. *Tetrahedron Lett.* **53**, 4145–4150 (2012).

R14) Laha, J. K., Tummalapalli, K. S. S. & Gupta, A. Palladium-catalyzed domino double *N* –arylations (inter- and intramolecular) of 1,2-diamino(hetero)arenes with *o,o′*-dihalo(hetero)-arenes for the synthesis of phenazines and pyridoquinoxalines. *European J. Org. Chem.* **2013**, 8330–8335 (2013).

R15) Kemme, S. T., Šmejkal, T. & Breit, B. Combined Transition-Metal- and Organocatalysis: An Atom Economic C3 Homologation of Alkenes to Carbonyl and Carboxylic Compounds. *Chem. - A Eur. J.* **16**, 3423–3433 (2010).

R16) Ren, W. *et al.* An Effective Pd-Catalyzed Regioselective Hydroformylation of Olefins with Formic Acid. *J. Am. Chem. Soc.* **138**, 14864–14867 (2016).