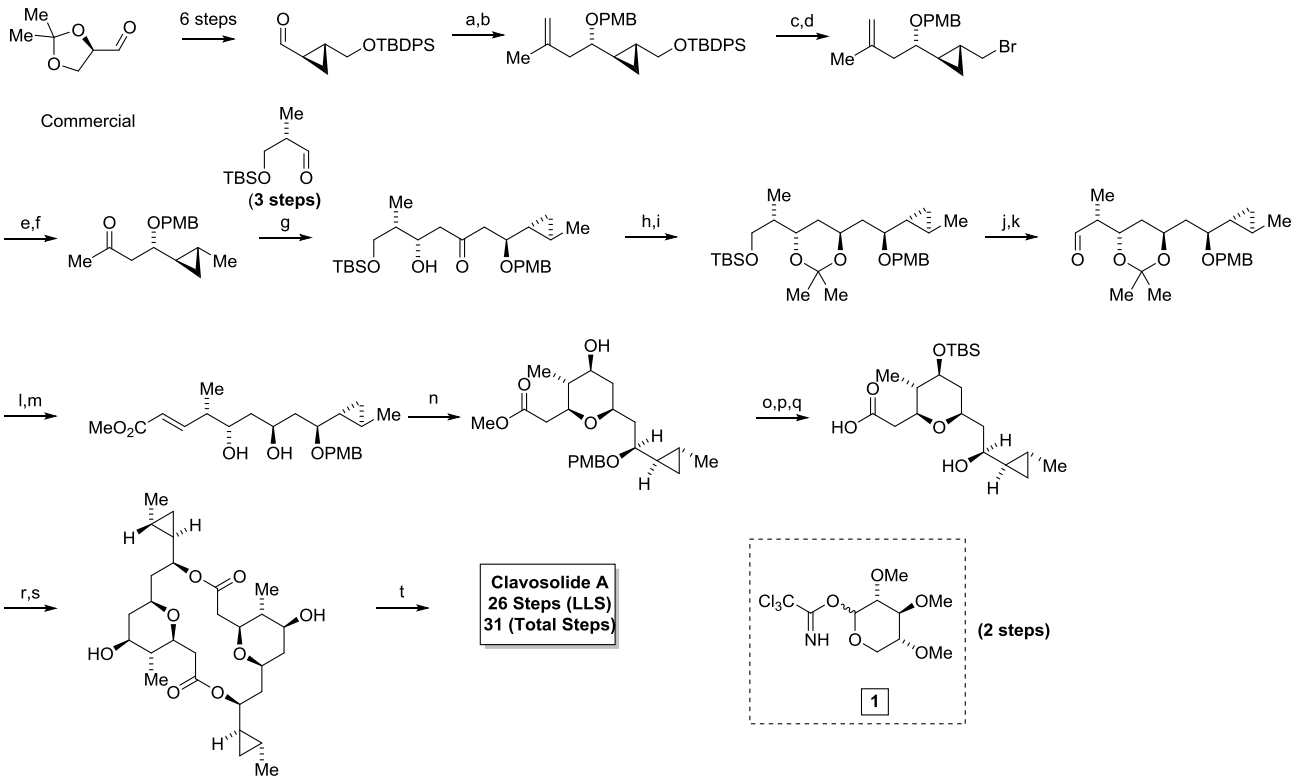
Table of Contents:

I. Summaries of Prior Syntheses

A. Lee, et al., *Org. Lett.*, **2006**, *8*, 661.

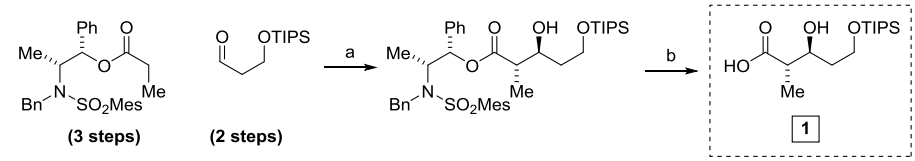
Linear Synthesis



Key: (a) isobutylene, TMEDA, ^{n}BuLi, (-)-(Ipc)$_2$BOMe, Et$_2$O; (b) PMBO(C=NH)CCl$_3$, TsOH; (c) TBAF, THF; (d) CBr$_4$, PPh$_3$, THF; (e) LAH, THF; (f) O$_3$, pyridine, MeOH; (g) ^{i}Pr$_2$NEt, Bu$_2$BOTf, Et$_2$O; (h) Me$_4$NB(OAc)$_3$H, MeCN-AcOH; (i) 2,2-methoxypropane, PPTS, CH$_2$Cl$_2$; (j) TBAF, THF; (k) Dess-Martin periodinane, NaHCO$_3$; (l) MeO$_2$CCH$_2$P(O)(OMe)$_2$, LiCl, ^{i}Pr$_2$NEt, MeCN; (m) CSA, MeOH-H$_2$O; (n) NaH, THF; (o) TBSOTf, Et$_3$N, CH$_2$Cl$_2$; (p) DDQ, CH$_2$Cl$_2$-H$_2$O; (q) LiOH, THF-H$_2$O-MeOH; (r) 2,4,6-Cl$_3$PhCOCl, Et$_3$N, THF, then DMAP, toluene; (s) TBAF, THF; (t) **1**, BF$_3$·OEt$_2$, 4 Å MS, CH$_2$Cl$_2$.

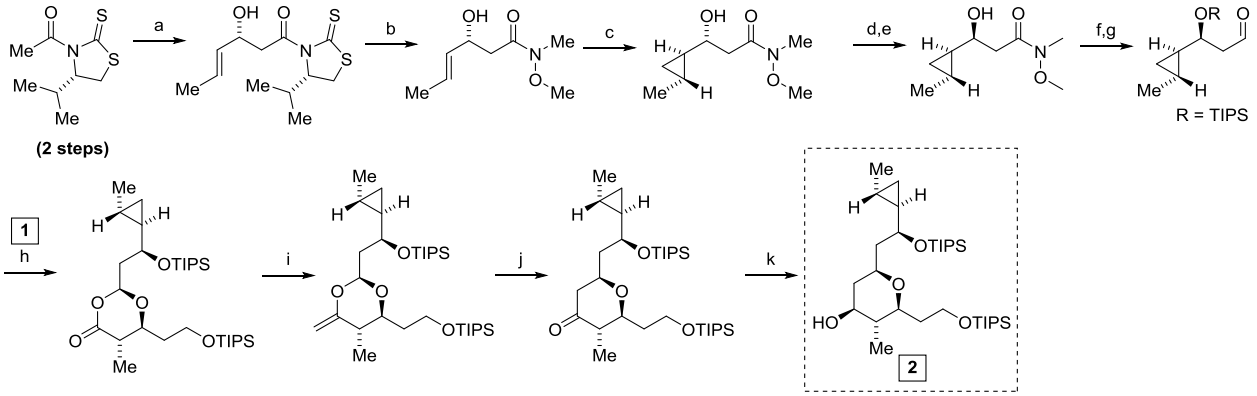
B. Smith, et al., *Org. Lett.* **2006**, *8*, 3315.

Fragment 1



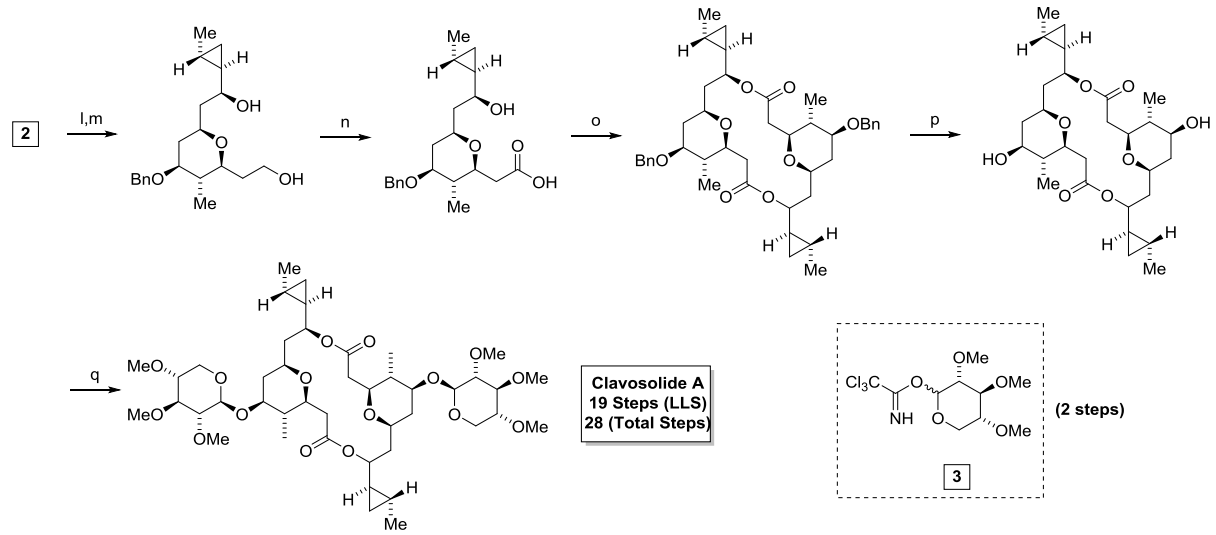
Key: (a) c-Hex_2BOTf, Et_3N, CH_2Cl_2; (b) LiOH, THF/H_2O.

Fragment 2



Key: (a) (*E*)-crotonaldehyde, $TiCl_4$, DIPEA; (b) MeNH(OMe)-HCl, CH_2Cl_2; (c) Et_2Zn, CH_2I_2, CH_2Cl_2; (d) AcOH, PPh_3, DIAD, $PhCH_3$; (e) K_2CO_3, MeOH; (f) TIPSOTf, 2,6-lutidine, CH_2Cl_2; (g) DIBAL, THF; (h) HMDS, **1**, CH_2Cl_2, then lactone, TMSOTf, DtBMP, CH_2Cl_2; (i) Cp_2TiMe_2, $Me_3CCOOEt$, THF, dark; (j) Me_2AlCl, 4 Å MS, CH_2Cl_2; (k) $NaBH_4$, EtOH.

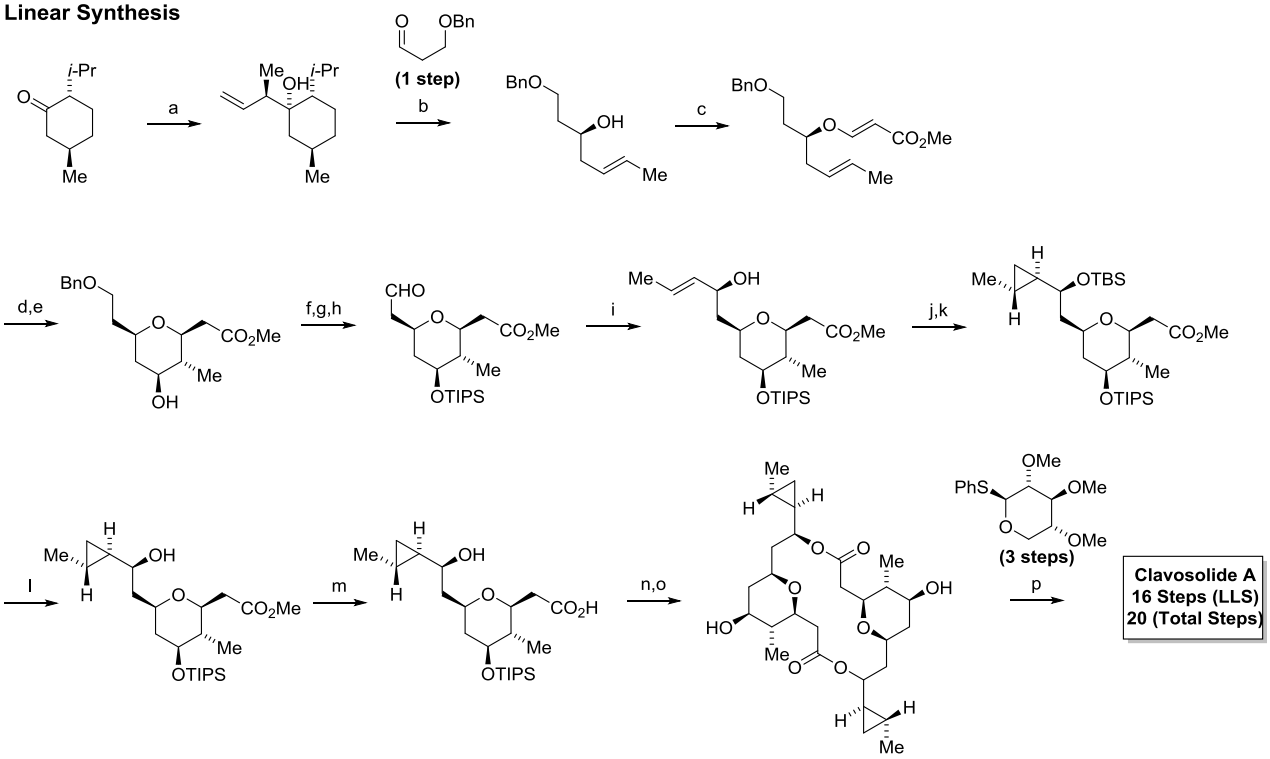
End Game



Reagents: (l) BnBr, NaH, TBAI, DMF; (m) 1% HCl, EtOH; (n) TEMPO, NaOCl, KBr, TBAC, NaCl, $NaHCO_3$, CH_2Cl_2/H_2O; (o) 2,4,6-trichlorobenzoyl chloride, Et_3N, then DMAP, toluene; (p) 10% Pd/C, H_2 (1 atm), EtOH; (q) **3**, TMSOTf, CH_2Cl_2, 4 Å MS.

C. Willis, et al., *Org. Lett.* **2006**, *8*, 3319.

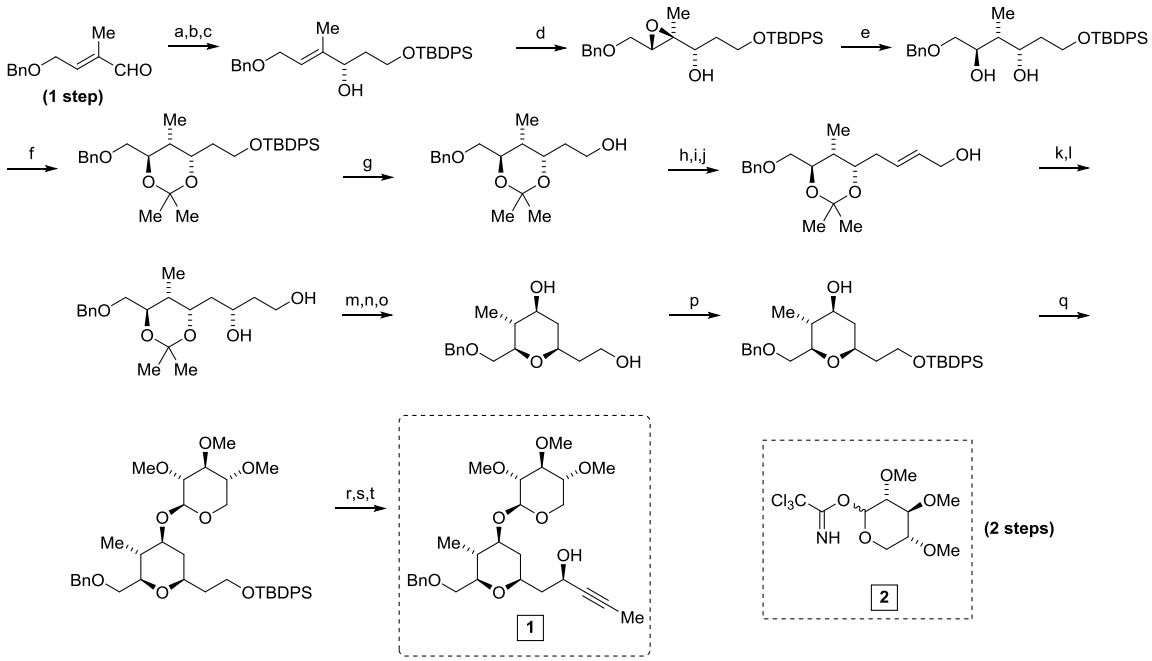
Linear Synthesis



Reagents: (a) But-2-enylmagnesium chloride, THF; (b) $TsOH \cdot H_2O$, CH_2Cl_2; (c) methyl propiolate, quinuclidine; (d) TFA, CH_2Cl_2; (e) K_2CO_3, MeOH; (f) TIPSCl, DMF, imidazole; (g) H_2, Pd/C, EtOH; (h) Dess-Martin periodinane; (i) $CrCl_2$, $NiCl_2$, DMF; (j) TBSOTf, imidazole, DMF; (k) CH_2ICl, Et_2Zn, CH_2Cl_2; (l) 1% v/v HCl, EtOH; (m) TMSONa, CH_2Cl_2; (n) 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, toluene; (o) TBAF, THF; (p) sugar, NBS, CH_3CN

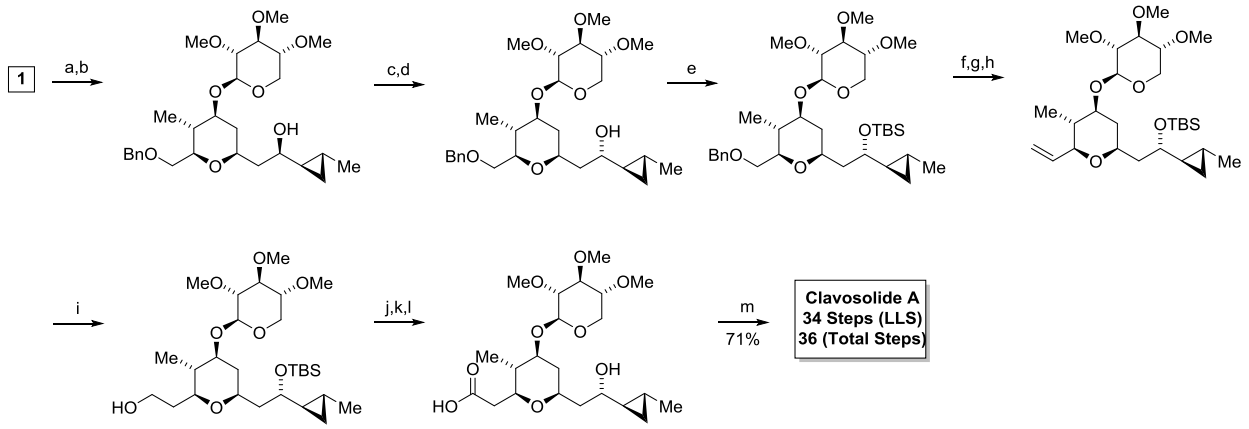
D. Chakraborty, et al. *Tetrahedron*, **2008**, *64*, 5162.

Fragment 1



Key: (a) EtOAc, LDA, THF; (b) LAH, Et_2O; (c) TBDPSCl, Et_3N, DMAP, CH_2Cl_2; (d) (+)-DIPT, TBHP, $Ti(^iPrO)_4$, 4 Å MS, CH_2Cl_2; (e) Cp_2TiCl, cyclohexa-1,4-diene; (f) 2,2-dimethoxypropane, CSA, CH_2Cl_2; (g) TBAF, THF; (h) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; (i) $PH_3P{=}CHCO_2Et$, CH_2Cl_2; (j) DIBAL-H, CH_2Cl_2; (k) (-)-DIPT, $Ti(O^iPr)_4$, TBHP, 4 Å MS, CH_2Cl_2; (l) Red-Al, THF; (m) TBDPSCl, Et_3N, DMAP, DMF; (n) MsCl, Et_3N, DMAP, CH_2Cl_2; (o) CSA, MeOH; (p) TBDPSCl, Et_3N, DMAP, CH_2Cl_2; (q) **2**, TMSOTf, 4 Å MS, CH_2Cl_2; (r) TBAF, THF; (s) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; (t) LDA, propyne, THF, then the aldehyde

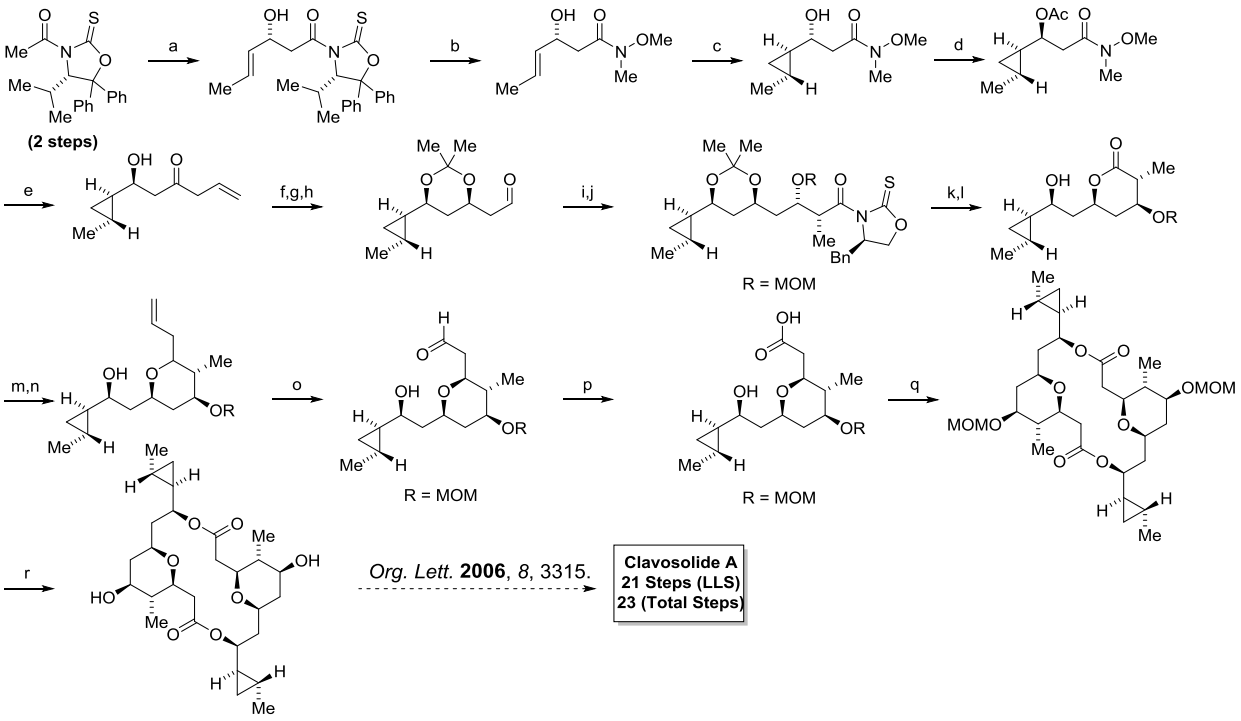
End Game and Dimerization



Key: (a) Red-Al, Et_2O; (b) CH_2I_2, Et_2Zn, CH_2Cl_2; (c) Dess-Martin periodinane, CH_2Cl_2; (d) LAH, THF; (e) TBSOTf, 2,6-lutidine, CH_2Cl_2; (f) H_2, Pd-C, EtOAc; (g) Dess-Martin periodinane, CH_2Cl_2; (h) $Ph_3P{=}CH_2$, Et_2O; (i) $(chex)_2BH$, THF, then 30% H_2O_2, NaOH; (j) Dess-Martin periodinane, CH_2Cl_2; (k) $NaOCl_2$, $NaH_2PO_4{\cdot}2H_2O$, 2-methyl-2-butene, ^tBuOH; (l) CSA, MeOH-CH_2Cl_2 (1:1); (m) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, then DMAP, toluene.

E. Jennings, et al., *Org. Lett.* **2009**, *11*, 769.

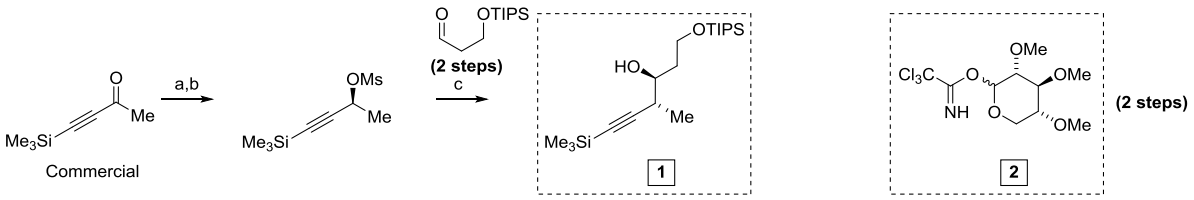
Linear Synthesis



Key: (a) $TiCl_4$, (-)-sparteine, NMP, (*E*)-crotonaldehyde, CH_2Cl_2; (b) imidazole, MeN(H)OMe·HCl, CH_2Cl_2; (c) Et_2Zn, CH_2I_2, CH_2Cl_2; (d) DIAD, PPh_3, HOAc, toluene; (e) allylmagnesium bromide, THF; (f) Et_2BOMe, $NaBH_4$, THF; (g) DMP, PPTS, CH_2Cl_2; (h) O_3, Sudan III, CH_2Cl_2; (i) $^nBu_2BOTf$, Et_3N, (*R*)-4-benzyl-3-propionyloxazolidin-2-one, CH_2Cl_2; (j) MOMCl, DIPEA, CH_2Cl_2; (k) BnOLi, THF; (l) TFA, THF; (m) allylmagnesium bromide, THF; (n) TFA then Et_3SiH; (o) O_3, Sudan III, CH_2Cl_2; (p) $NaOCl_2$, NaH_2PO_4, 2-methyl-2-butene, ^{t}BuOH; (q) 2,4,6-trichlorobenzoyl chloride, DMAP, toluene; (r) 2-bromobenzo[*d*][1,3,2]dioxaborole, CH_2Cl_2.

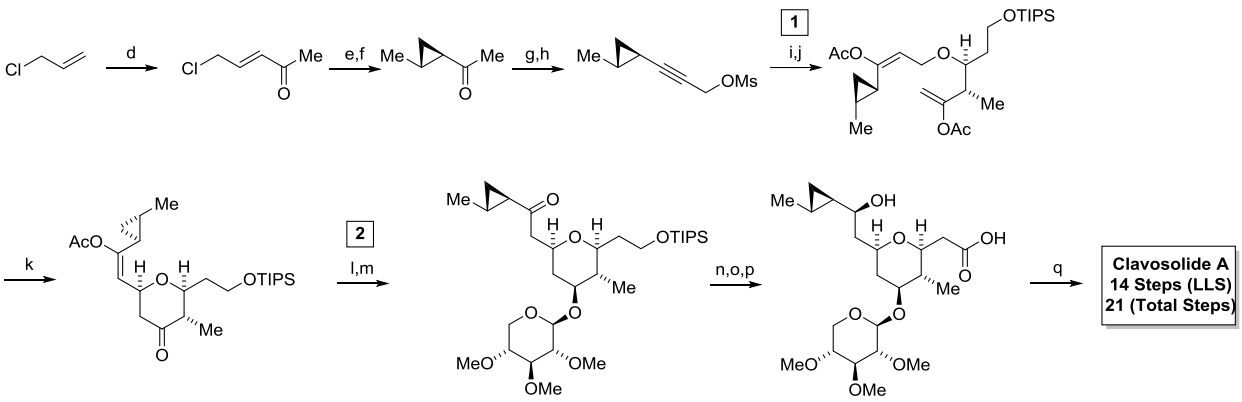
F. Floreancig, et al., *Org. Lett* **2012**, *14*, 5614.

Fragment 1



Key: (a) (*S*,*S*)-Noyori-TsDPEN, CH_2Cl_2, Et_3N, then formic acid; (b) MsCl, Et_3N, CH_2Cl_2; (c) Et_2Zn, $Pd(OAc)_2$, Ph_3P, CH_2Cl_2.

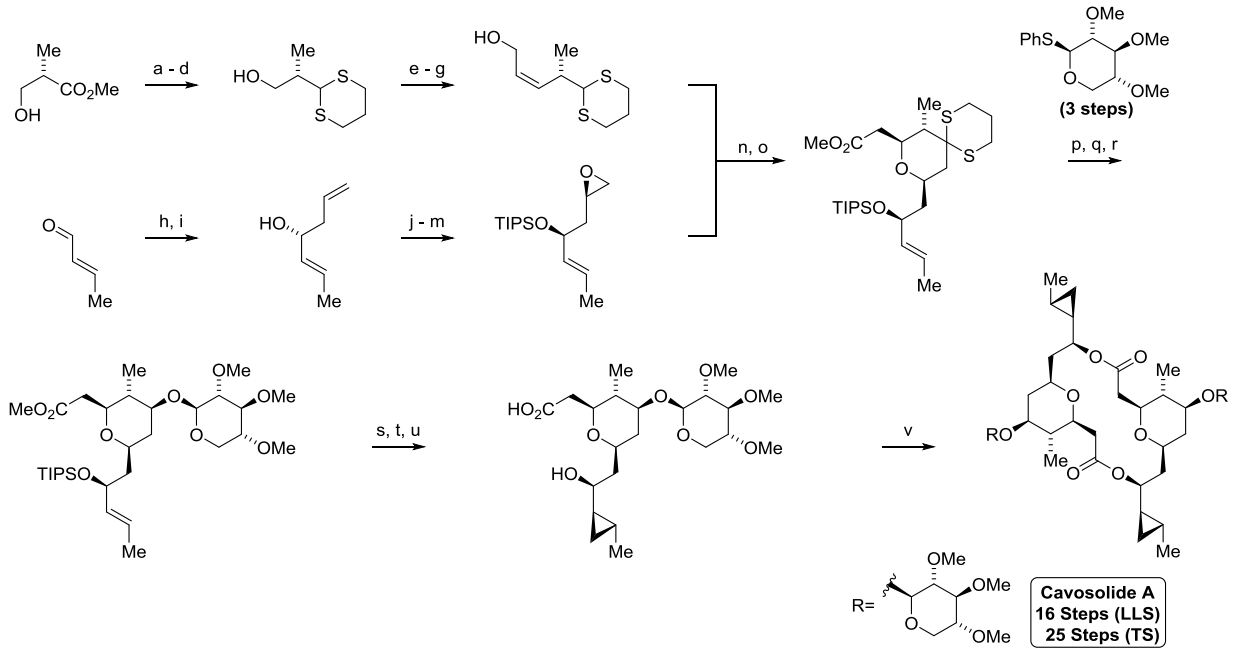
Linear Synthesis



Key: (d) AcCl, $AlCl_3$, CH_2Cl_2, then Et_3N; (e) MeMgBr, CuI, (*R*)-TolBINAP, ^tBuOMe; (f) NaOH, H_2O; (g) LDA, THF, then $(EtO)_2P(O)Cl$, then LDA, then $(CH_2O)_n$; (h) MsCl, Et_3N, CH_2Cl_2; (i) NaH, 15-C-5, THF, then **1;** (j) [(*p*-cymene)$RuCl_2]_2$, HOAc, Na_2CO_3, PhMe; (k) DDQ, $LiClO_4$, 2,6-Cl_2Py, DCE; (l) $NaBH_4$, MeOH, then K_2CO_3, MeOH; (m) **2**, TMSOTf, CH_2Cl_2; (n) $BH_3{\cdot}SMe_2$, (*R*)-1-methyl-3,3-diphenylhexahydropyrrolo[1,2-*c*][1,3,2]oxazaborole, THF; (o) HCl, EtOH; (p) TEMPO, NaOCl, KBr, Bu_4NCl, $NaHCO_3$, CH_2Cl_2, H_2O; (q) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, then DMAP, toluene.

G. Hong, et al. *Tet. Lett.* **2015**, *56*, 3120.

Synthesis



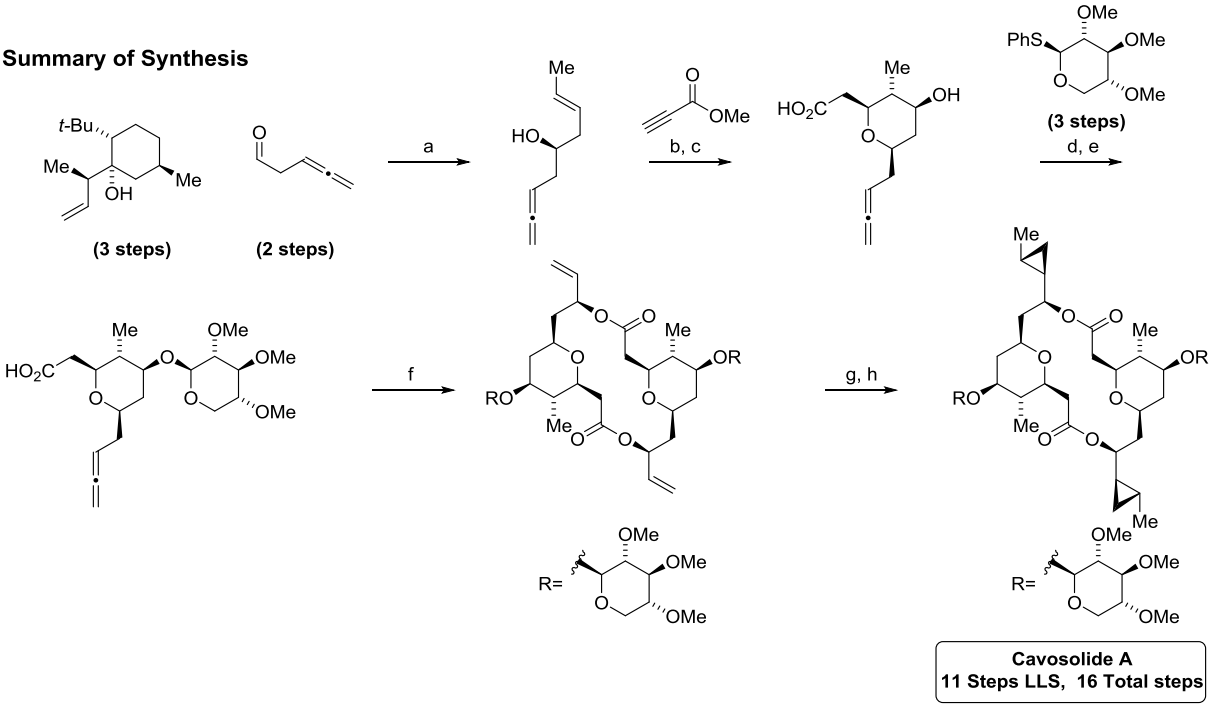
Key: a) TrCl, Et_3N; b) LAH; c) $(COCl)_2$, DMSO, *i*-Pr_2EtN; d) $HS(CH_2)_3SH$, BF_3-OEt_2; e) SO_3-pyridine, DMSO, *i*-Pr_2EtN; f) $(MeO)_2POCH_2CO_2Me$, KHMDS,18-crown-6; g) DIBAL-H; h) allyl bromide, Zn; i) (-)-DIPT, Ti(O*i*-Pr)$_4$, TBHP, 4Å MS (resolution); j) Boc_2O, DMAP; k) NIS; l) K_2CO_3; m) NaH, TIPSOTf; n) *t*-BuLi, HMPA; o) MnO_2, then Me_2-triazolium I, DBU, MnO_2, 4Å MS, MeOH; p) I_2, $NaHCO_3$; q) $NaBH_4$; r) sugar, MeOTf, 4Å MS; s) $ClCH_2I$, Et_2Zn; t) TBAF; u) LiOH, H_2O; v) MNBA, DMAP.

H. Breit, et al., *Angew. Chem. Int. Ed.* **2015**, *54*, 15530.

Synthesis of Starting Materials

Key: a) $AlMe_3$, TMSCl, CuBr (cat.), b) KOH, c) *E*-crotyl chloride, Mg, d) $(EtO_3)COMe$, $MeCH_2CO_2H$, e) DIBAL-H.

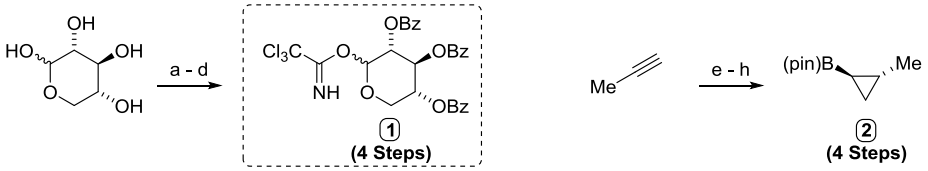
Summary of Synthesis



Key: a) *p*TsOH-H_2O, b) yneone, quinuclidine, TFA, c) K_2CO_3, MeOH, d) MeOTf, 4Å MS, sugar, e) LiOH, H_2O, f) $[Rh(cod)Cl]_2$, (*R*,*R*)-DIOP, Cs_2CO_3, g) Grubbs II, (*Z*)-2-butene, h) ICH_2Cl, Et_2Zn.

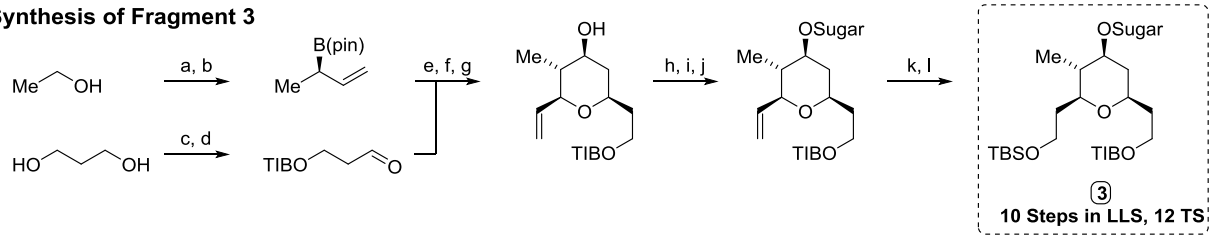
I. Aggarwal, et al., *Angew. Chem. Int. Ed.* **2016**, *55*, 2498.

Sugar and Boronate Synthesis



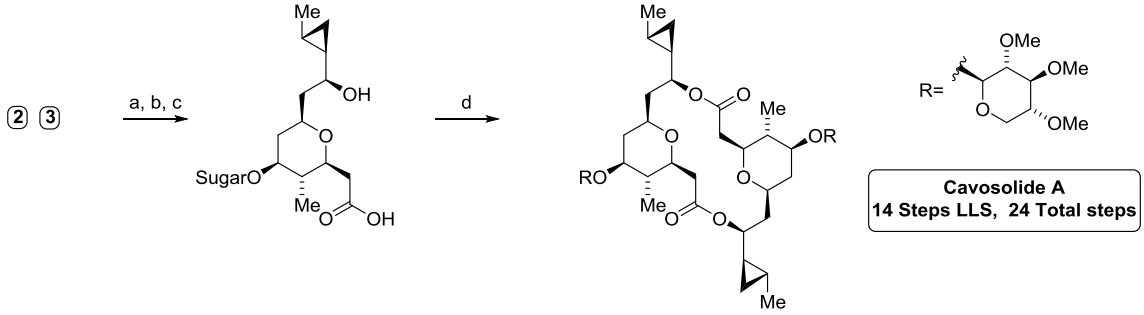
Key: a) BzCl, DMAP, pyr, b) HBr, AcOH, c) Ag_2CO_3, H_2O, acetone, d) DBU,$CNCCl_3$, e) HBBr-SMe_2, then NaOH, then HCl, f) diethanolamine, g) Me_4-L-tartaramide, h) Et_2Zn, CH_2I_2, tartaramide, then pinacol.

Synthesis of Fragment 3



Key: a) Cl(CO)N*i*Pr$_2$, Et_3N, b) *s*-BuLi, (–)-sparteine, then vinyl-B(pin), $MgBr_2$-Et_2O, c) TIB-Cl, NaH, d) TEMPO, KBr, $NaHCO_3$, NaClO, e) *n*-BuLi, TFAA, then aldehyde, f) acrolein, TFA, g) K_2CO_3, h) **1**, TMSOTf, 4Å MS, i) NaOMe, j) MeI, NaH, k) Cy_2BH, then H_2O_2, KOH, l) TBSCl, Et_3N.

Fragment Union and End Game



Key: a) *s*-BuLi, (+)-sparteine, then **2**, then NaOH, H_2O_2, b) HCl, c) TEMPO, KBr, $NaHCO_3$, NaOCl, d) 2,4,6-*i*Pr$_3$BzCl, Et_3N, then DMAP.

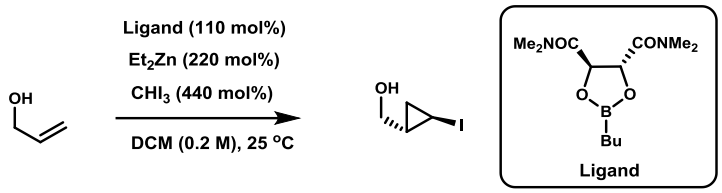
II. General Information

Tetrahydrofuran (THF), diethyl ether (Et_2O), and toluene were distilled from sodium/benzophenone, and dichloromethane (CH_2Cl_2) was distilled from calcium hydride under a nitrogen atmosphere. Reaction control was performed by analytical thin-layer chromatography (TLC) using 0.25 mm commercial silica gel plates (Dynanmic Absorbents F_{254}). Visualization was carried out with UV light followed by staining with potassium permanganate or p-anisaldehyde stain solution and heating. Products were purified by flash chromatography using Silacycle silica gel (40–63 μm) or Fischer Chemical aluminum oxide (basic, Brockman I, 60-325 mesh).

Nuclear magnetic resonance spectra (^1H, ^{13}C) were recorded on a Varian MR-400 or an Avance III 500 spectrometer. The chemical shifts are given as parts per million (ppm) and were referenced to the residual solvent signal ($CDCl_3$: $\delta_H = 7.26$ ppm, $\delta_C = 77.16$ ppm). Infrared spectra were recorded on a Thermo Nicolet 380 spectrometer. High-resolution mass spectra were recorded on an Agilent Technologies 6530 Accurate Mass Q-Tof LC/MS instrument for electrospray ionisation (ESI) or a Micromass Autospec Ultima instrument for chemical ionization (CI) and are reported as a ratio of mass to charge (m/z) in Daltons. Melting points were taken on a Stuart SMP3 melting point apparatus. Specific optical rotations were recorded on an Atago AP-300 automatic polarimeter at the sodium line (589.3 nm) in $CHCl_3$. Solution concentrations are given in the units of 10^{-2} g mL^{-1}.

III. Experimental Procedures and Characterization of intermediates

((1S,2R)-2-iodocyclopropyl)methanol (7)



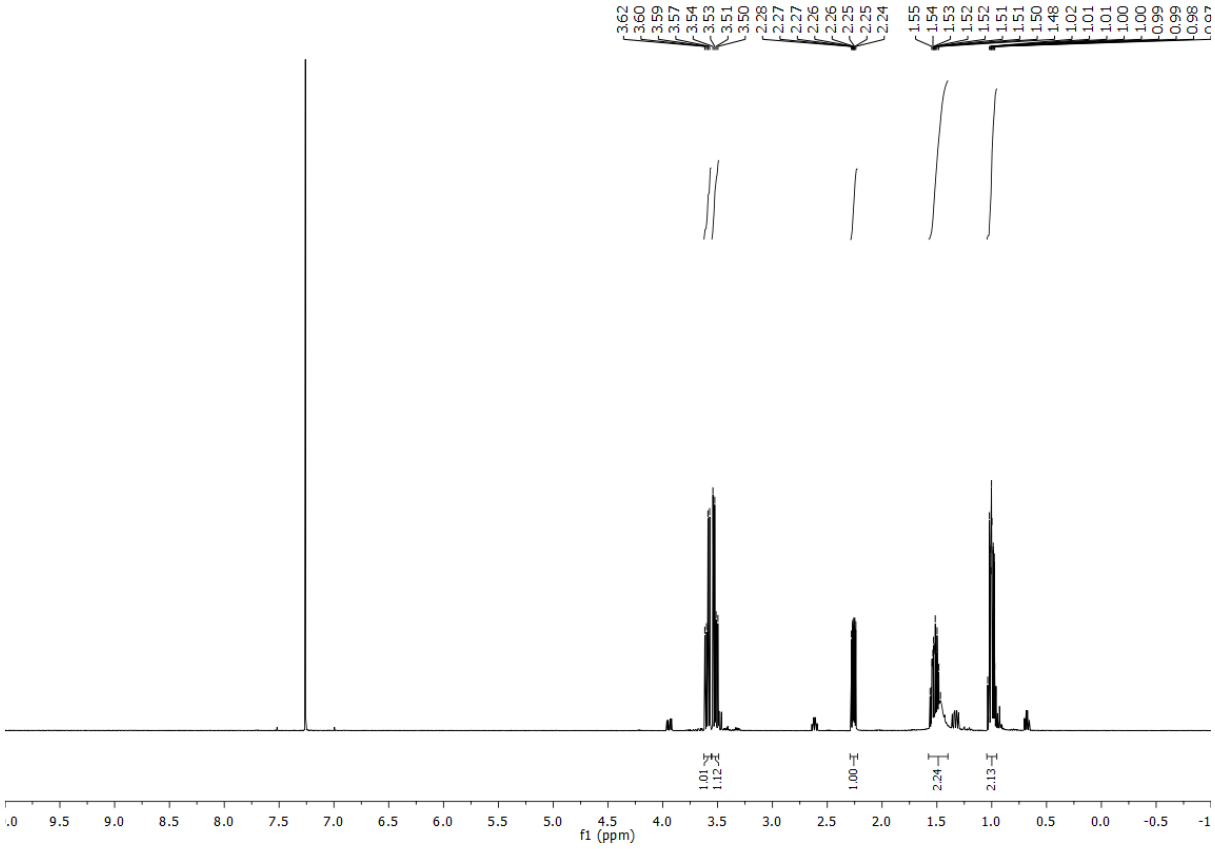
To a stirred suspension of iodoform (61.34 g, 155.8 mmol, 440 mol%) in anhydrous CH_2Cl_2 (130 mL) was added a 1 M solution of diethylzinc in hexanes (77.9 mL, 77.9 mmol, 220 mol%) at room temperature in a water bath. The yellow suspension was stirred at room temperature for 60 min, after which a solution of allyl alcohol **6** (2.05 g, 35.4 mmol, 100 mol%) and ligand (10.5 g, 38.9 mmol, 110 mol%) in anhydrous CH_2Cl_2 (50 mL) was added at room temperature. The reaction flask was removed from the water bath and wrapped in aluminum foil. The yellow suspension was allowed to stir at room temperature for 24 h. The reaction was quenched with saturated aqueous NH_4Cl (200 mL) and diluted with Et_2O (600 mL). The aqueous layer was extracted with Et_2O (2 x 200 mL), and the combined organic layers were transferred into an Erlenmeyer flask, and a solution containing 340 mL of 2 N aqueous NaOH and 60 mL of 30% aqueous H_2O_2 was added in one portion. The resulting mixture was vigorously stirred for 10 min, after which the two layers were separated. The organic phase was washed with 10% aqueous HCl (400 mL), saturated aqueous Na_2SO_3 (400mL), saturated aqueous $NaHCO_3$ (400 mL) and brine (400 mL), dried (Na_2SO_4), filtered and the solvent was removed *in vacuo*. The residue was subjected to flash chromatography on silica (Hex/Et_2O 5:1 → 3:1) to furnish **7** (3.72 g, 18.8 mmol, 8:1 dr) in 53% yield as a yellow oil. The spectral data were identical to those reported.[1]

TLC (SiO_2) R_f = 0.13 (hexanes/diethyl ether = 2:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = δ 3.59 (dd, *J* = 11.4, 6.3 Hz, 1H), 3.52 (dd, *J* = 11.4, 6.7 Hz, 1H), 2.26 (ddd, *J* = 7.7, 4.9, 3.9 Hz, 1H), 1.58 – 1.40 (m, 2H), 1.05 – 0.95 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 64.9, 25.6, 14.6, -18.5.

HPLC: (2x Chiralcel AD-H column, hexanes:*i*-PrOH = 99:1, 0.75 mL/min, 254 nm), *ee* = 86%.


3.62
3.60
3.59
3.57
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3.51
3.50
2.28
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2.27
2.26
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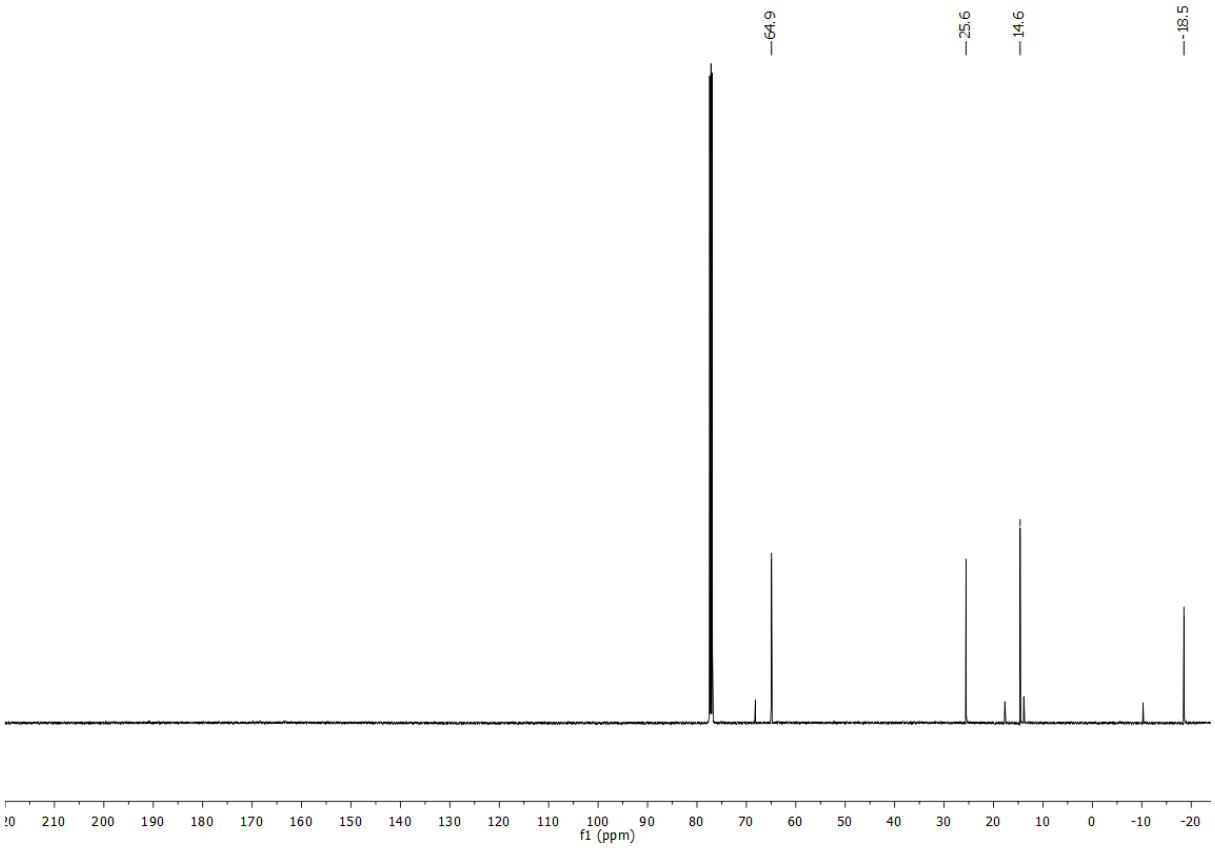
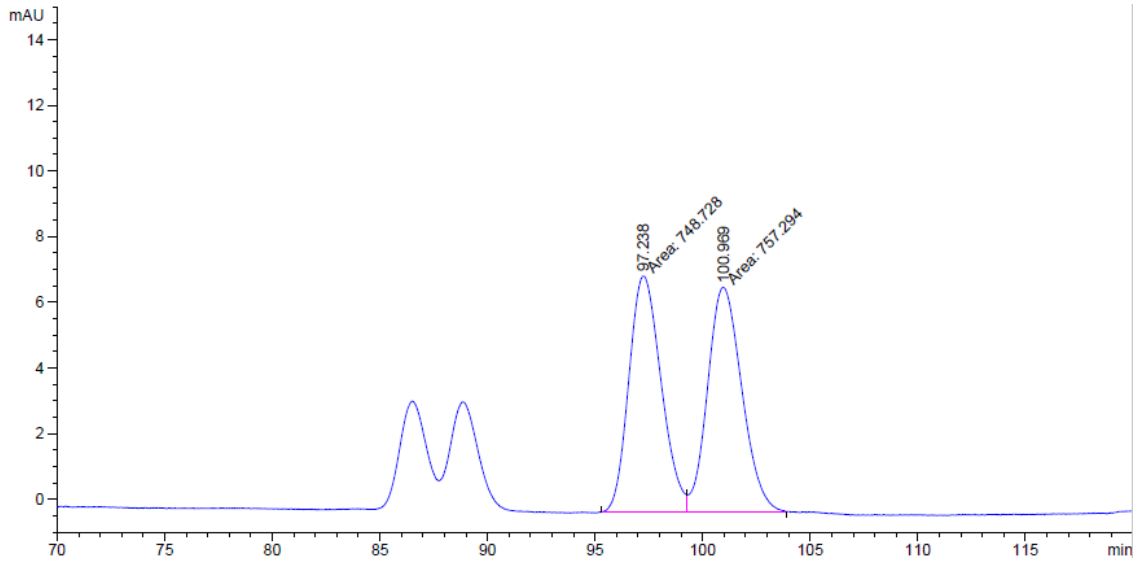
2.25
2.25
2.24
1.55
1.54
1.53
1.52
1.52
1.51
1.51
1.50
1.48
1.02
1.01
1.01
1.00
1.00
0.99
0.99
0.98
1.01
1.12
1.00
2.24
2.13
f1 (ppm)


64.9
25.6
14.6
-18.5
f1 (ppm)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
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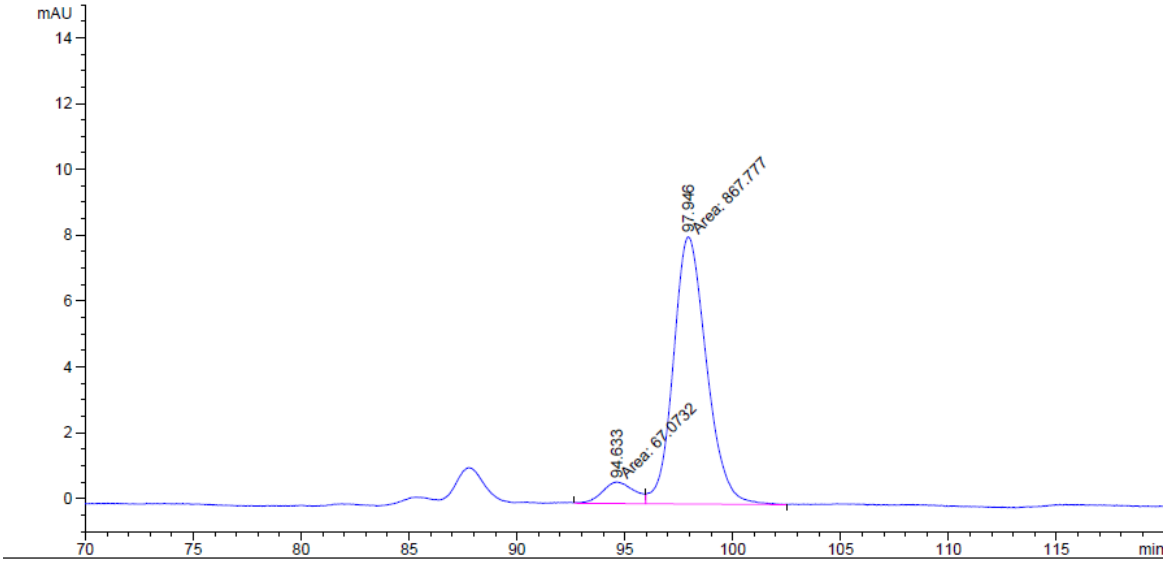
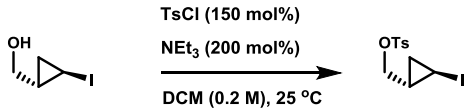
2	100.969	FM	1.8447	757.29419	6.84192	50.2844



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	94.633	MF	1.7161	67.07325	6.51423e-1	7.1748
2	97.946	FM	1.7829	867.77722	8.11182	92.8252

((1S,2R)-2-iodocyclopropyl)methyl 4-methylbenzenesulfonate (S1)



To a solution of alcohol **7** (3.00 g, 15.15 mmol, 100 mol%) in CH_2Cl_2 (50 mL) was added *p*-toluenesulfonyl chloride (3.18 g, 16.67 mmol, 110 mol%) and triethylamine (4.2 mL, 30.30 mmol, 200 mol%). The reaction was allowed to stir at 25 °C for 18 h protected from light. The solvent was removed *in vacuo,* and the residue was subjected to flash chromatography on silica (Hex/EtOAc 10:1 → 5:1) to furnish the title compound **S1** (4.2 g, 11.93 mmol) in 79% yield as a clear oil.

TLC (SiO_2) R_f = 0.36 (hexanes/ethyl acetate = 5:1).

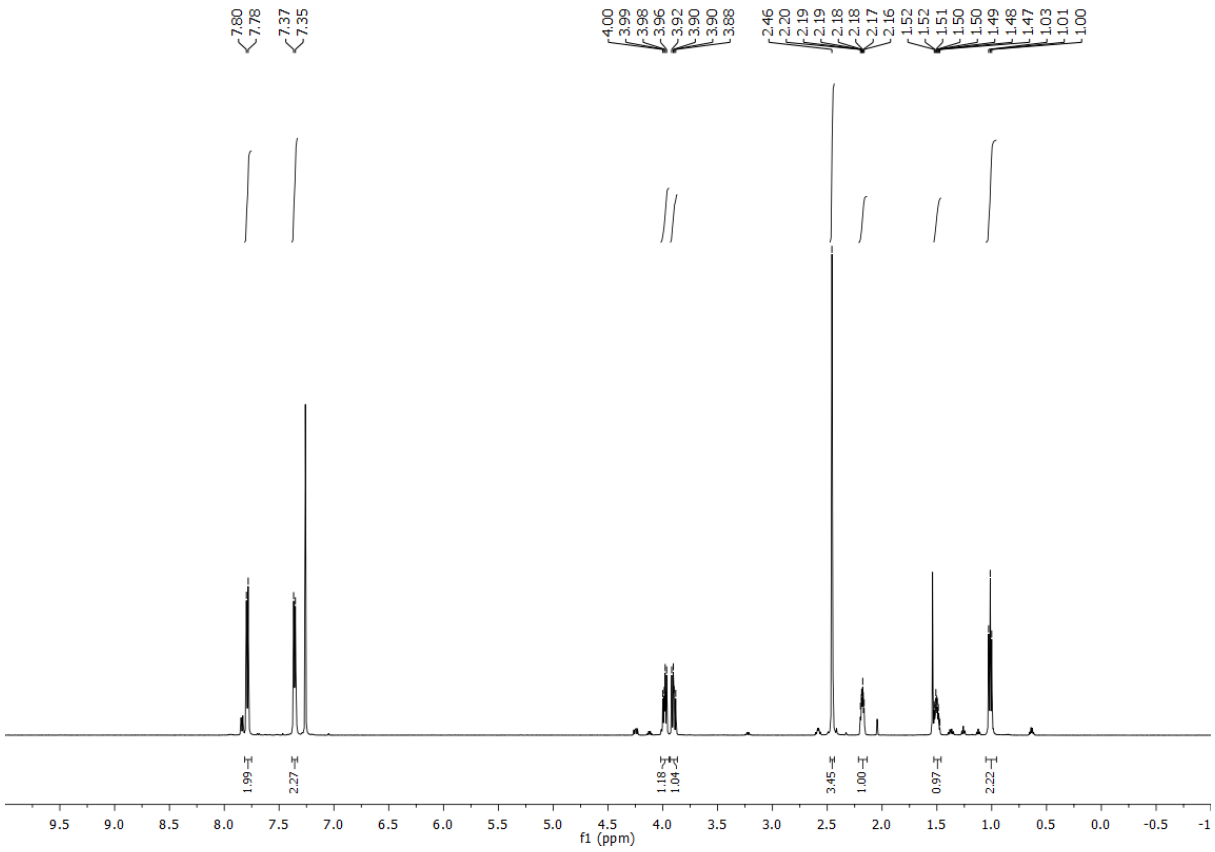
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 8.3 Hz, 2H), 7.36 (d, *J* = 7.9 Hz, 2H), 3.98 (dd, *J* = 10.9, 6.8 Hz, 1H), 3.90 (dd, *J* = 10.9, 7.4 Hz, 1H), 2.46 (s, 3H), 2.21 – 2.14 (m, 1H), 1.53 – 1.47 (m, 1H), 1.04 – 0.99 (m, 2H).

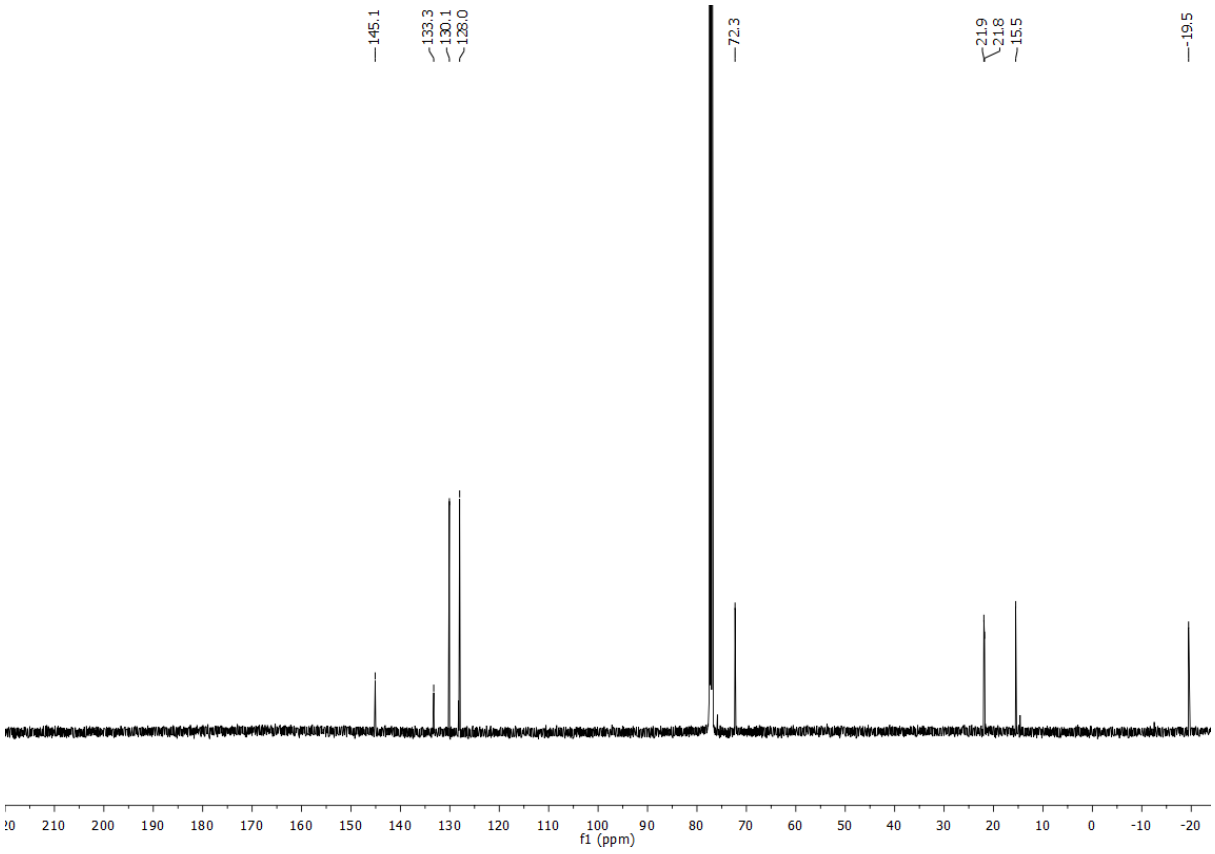
^{13}C NMR (125 MHz, $CDCl_3$): δ = 145.1, 133.3, 130.1, 128.0, 72.3, 21.9, 21.8, 15.5, -19.5.

HRMS (ESI) Calculated for $C_{11}H_{13}IO_3S$ $[M+Na]^+$ = 374.9522, Found 374.9531.

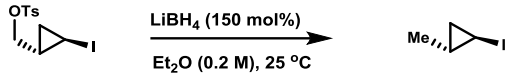
FTIR (neat) 2950, 1598, 1360, 1189, 1175, 1097, 948, 815, 665 cm^{-1}.

$[\alpha]_D^{26}$: –105.8 (*c* = 1.0, $CHCl_3$)


7.80
7.78
7.37
7.35
4.00
3.99
3.98
3.96
3.92
3.90
3.90
3.88
2.46
2.20
2.19
2.19
2.18
2.18
2.17
2.16
1.52
1.52
1.51
1.50
1.50
1.49
1.48
1.47
1.03
1.01
1.00
1.99
2.27
1.18
1.04
3.45
1.00
0.97
2.22
f1 (ppm)


145.1
133.3
130.1
128.0
72.3
21.9
21.8
15.5
-19.5
f1 (ppm)

(1R,2R)-1-iodo-2-methylcyclopropane (8)

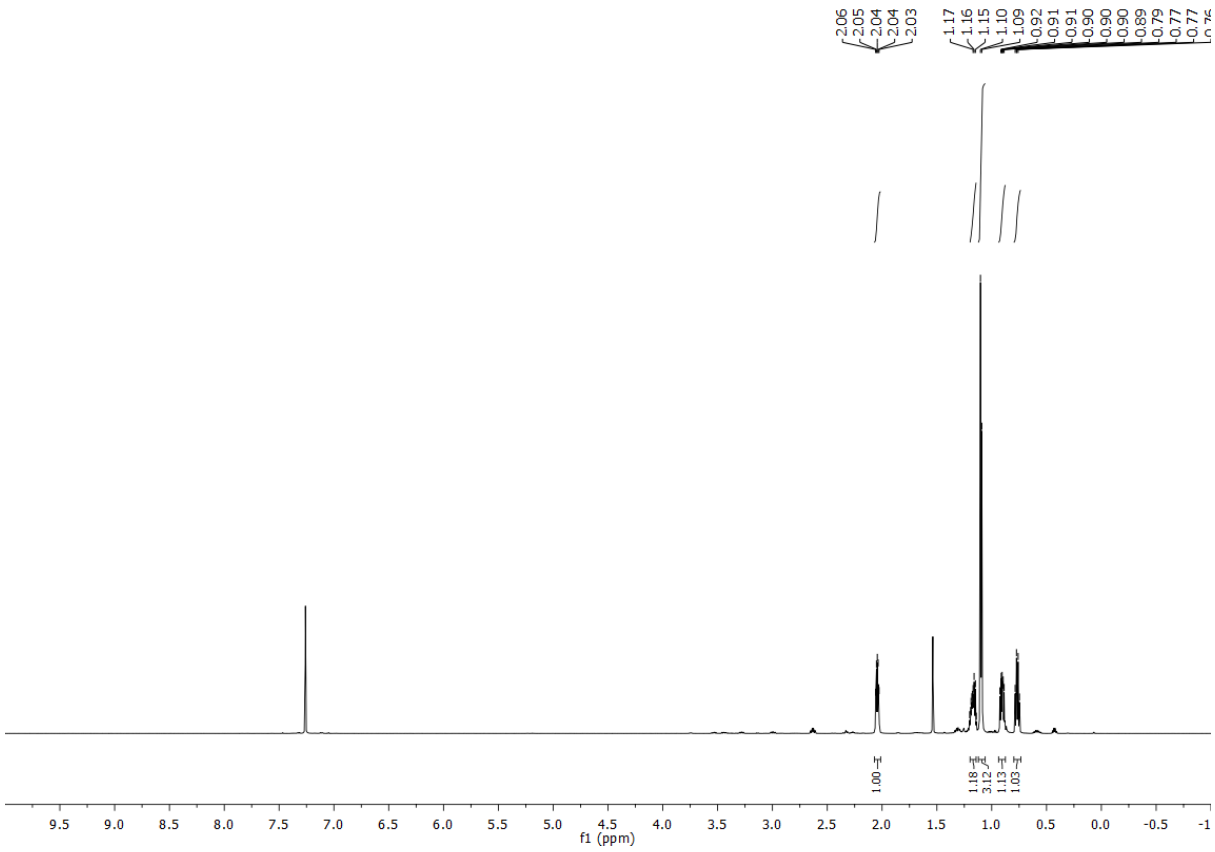


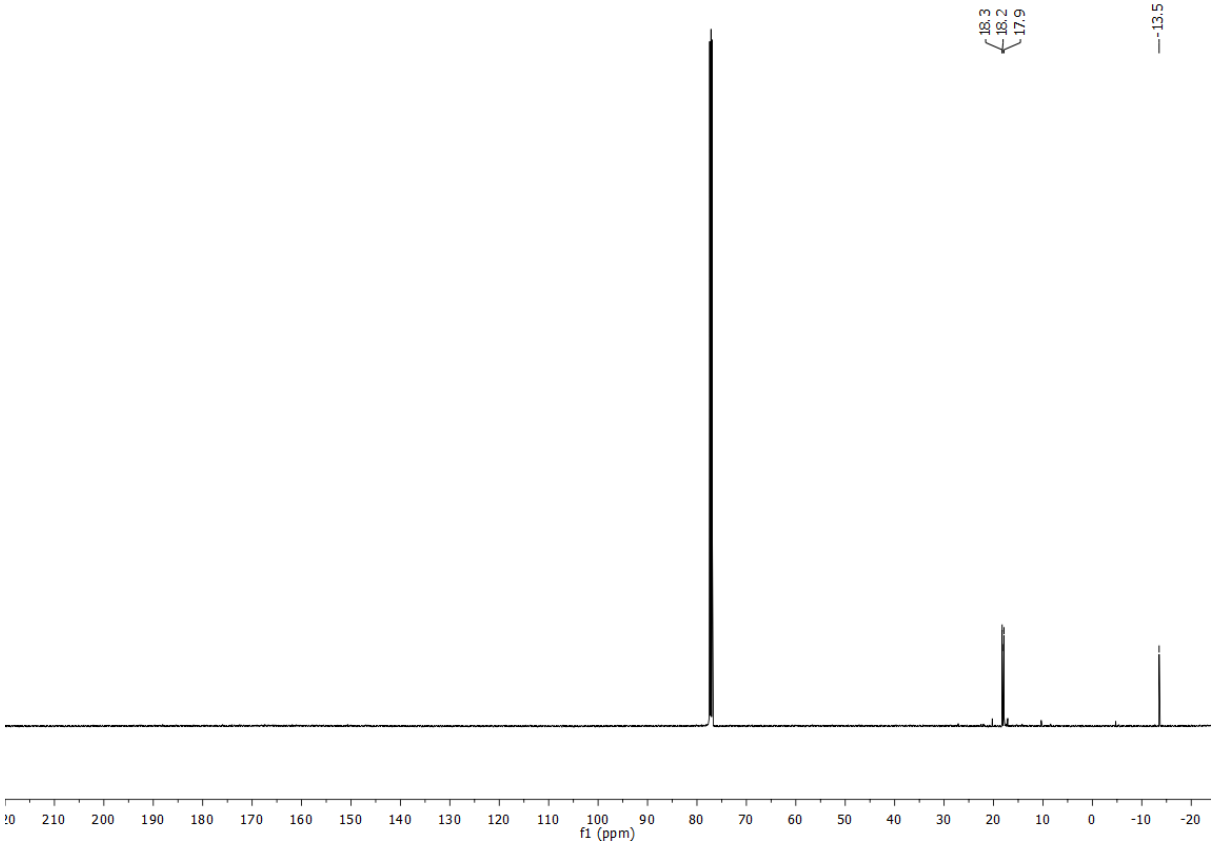
To a solution of tosylate **S1** (3.0 g, 8.52 mmol, 100 mol%) in Et_2O (42 mL) was added a 4 M solution of $LiBH_4$ in tetrahydrofuran (3.2 mL, 12.78 mmol, 150 mol%). The reaction was allowed to stir at 25 °C for 24 h protected from light. The mixture was quenched by careful addition of water (10 mL). The aqueous layer was extracted with Et_2O (20 mL), and the combined organic phases were dried (Na_2SO_4), filtered and the solvent was removed *in vacuo*. The residue was subjected to flash chromatography on silica (pentane) to furnish iodide **8** (702.0 mg, 3.86 mmol) in 45% yield as a clear liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.04 (dt, *J* = 7.8, 4.0 Hz, 1H), 1.20 – 1.14 (m, 1H), 1.10 (d, *J* = 6.1 Hz, 3H), 0.91 (ddd, *J* = 8.9, 6.1, 4.3 Hz, 1H), 0.77 (dt, *J* = 7.6, 5.9 Hz, 1H).

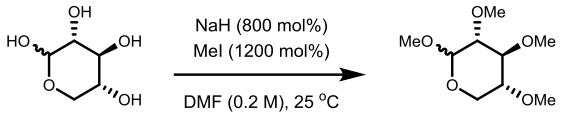
^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.3, 18.2, 17.9, -13.5.

HRMS (EI) Calculated for C_4H_7I $[M]^+$ = 181.9593, Found 181.9585.


2.06
2.05
2.04
2.04
2.03
1.17
1.16
1.15
1.10
1.09
0.92
0.91
0.91
0.90
0.90
0.90
0.89
0.79
0.77
0.77
1.00
1.18
3.12
1.13
1.03
f1 (ppm)


18.3
18.2
17.9
-13.5
f1 (ppm)

(3R,4S,5R)-2,3,4,5-tetramethoxytetrahydro-2H-pyran (S2)



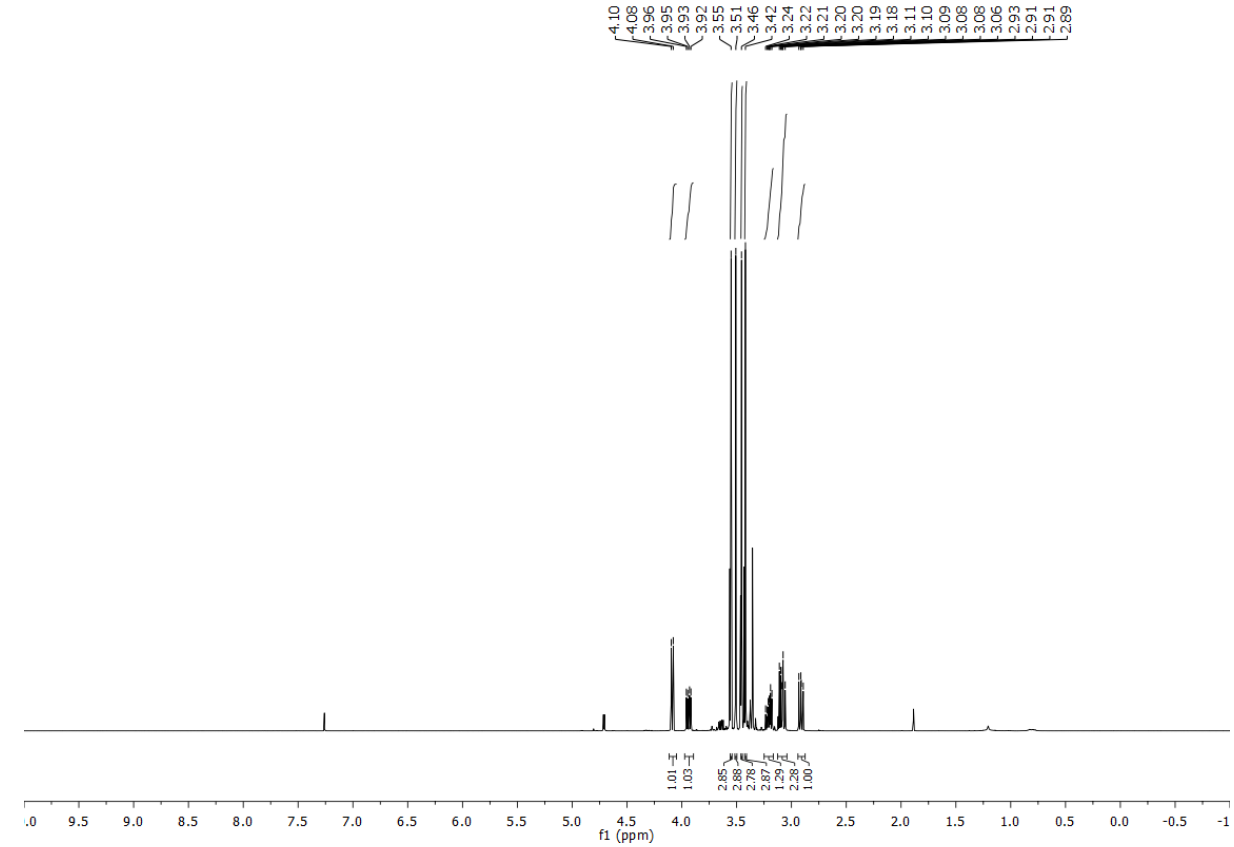
D-xylose (6.0 g, 40.0 mmol) was dissolved in DMF (200 ml) and cooled down to 0 °C. This solution was treated with NaH (60%, 12.8 g, 320.0 mmol, 8.0 equiv.), followed by dropwise addition of MeI (30.0 ml, 68.1 g, 480.0 mmol, 12.0 equiv.). The reaction was allowed to stir at 25 °C for 24 h. A saturated aqueous solution of NH_4Cl (200 mL), water (100 mL), and Et_2O (200 mL) were added to the reaction and the mixture was transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with Et_2O (200 mL × 3). The combined organic layers were dried (Na_2SO_4), filtered and the solvent was removed *in vacuo*. The residue was subjected to flash chromatography (SiO_2, hexanes: ethyl acetate = 1:1) to furnish **S2** as a clear oil (8.1 g, 39.3 mmol, dr = 4:1) in 98% yield, which solidified upon standing. The spectral data were identical to those reported.[2]

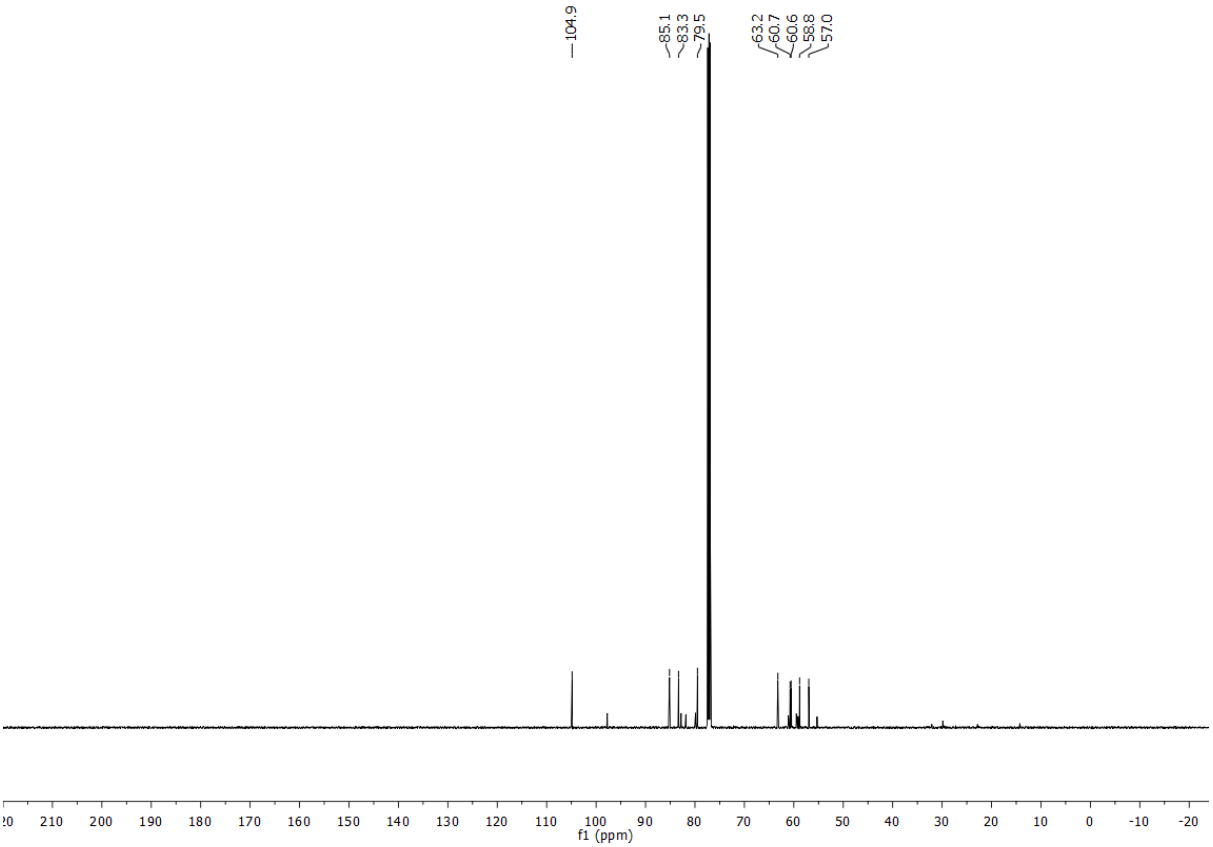
Data of the major isomer are reported.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.09 (d, *J* = 7.3 Hz, 1H), 3.94 (dd, *J* = 11.6, 5.0 Hz, 1H), 3.55 (s, 3H), 3.51 (s, 3H), 3.46 (s, 3H), 3.42 (s, 3H), 3.24 – 3.16 (m, 1H), 3.11 – 3.05 (m, 2H), 2.91 (dd, *J* = 8.8, 7.3 Hz, 1H).

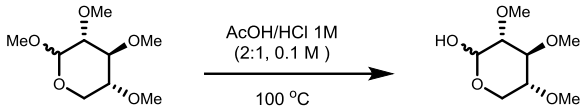
^{13}C NMR (125 MHz, $CDCl_3$): δ = 104.9, 85.1, 83.3, 79.5, 63.2, 60.7, 60.6, 58.8, 57.0.

HRMS (CI) Calculated for $C_9H_{18}O_5$ $[M+H]^+$ = 207.1232, Found: 207.1229.


4.10
4.08
3.96
3.95
3.93
3.92
3.55
3.51
3.46
3.42
3.24
3.22
3.21
3.20
3.20
3.19
3.18
3.11
3.10
3.09
3.08
3.08
3.06
2.93
2.91
2.91
2.89
1.01
1.03
2.85
2.88
2.78
2.87
1.29
2.28
1.00
f1 (ppm)


104.9
85.1
83.3
79.5
63.2
60.7
60.6
58.8
57.0
f1 (ppm)

(3R,4S,5R)-3,4,5-trimethoxytetrahydro-2H-pyran-2-ol (S3)



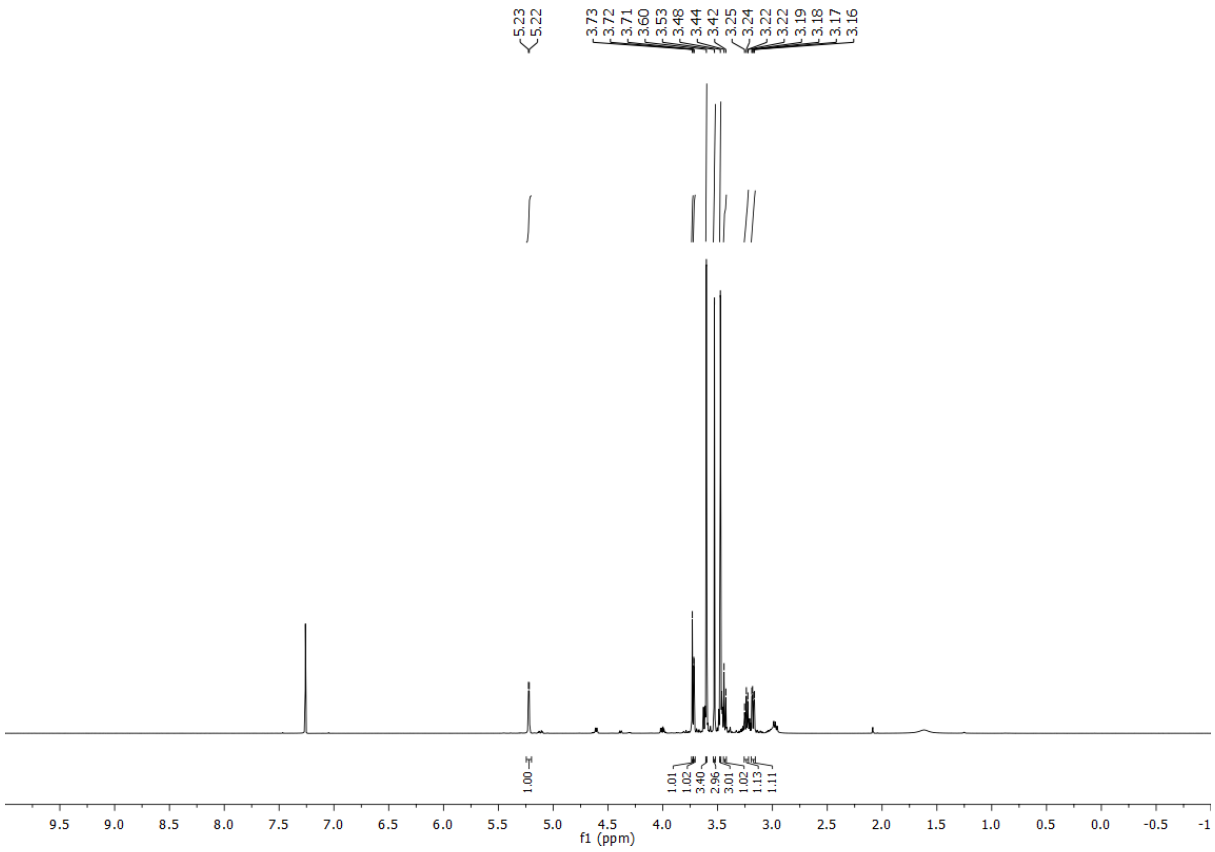
Compound **S2** (2.00 g, 9.70 mmol, 100 mol%) was dissolved in AcOH (60 mL) and 1 M HCl (30 mL). and the mixture was stirred at 100 °C for 4 h. The reaction was allowed to cool down to room temperature and the solvent was removed *in vacuo*. The residue was subjected to flash chromatography on silica (Hex/EtOAc 1:3) to furnish **S3** (1.21 g, 6.30 mmol, dr = 4:1) in 65% yield as a solid. The spectral data were identical to those reported.[2]

Data of the major isomer are reported.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.22 (d, *J* = 3.4 Hz, 1H), 3.73 (s, 1H), 3.72 (d, *J* = 1.5 Hz, 1H), 3.60 (s, 3H), 3.53 (s, 3H), 3.47 (s, 3H), 3.43 (d, *J* = 8.3 Hz, 1H), 3.26 – 3.22 (m, 1H), 3.18 (dd, *J* = 8.6, 3.4 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 91.1, 81.6, 81.5, 79.1, 60.8, 60.1, 59.1, 58.8.

HRMS (CI) Calculated for $C_8H_{16}O_5$ $[M-H]^+$ = 191.0919, Found: 191.0920.


5.23
5.22
3.73
3.72
3.71
3.60
3.53
3.48
3.44
3.42
3.25
3.24
3.22
3.22
3.19
3.18
3.17
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1.02
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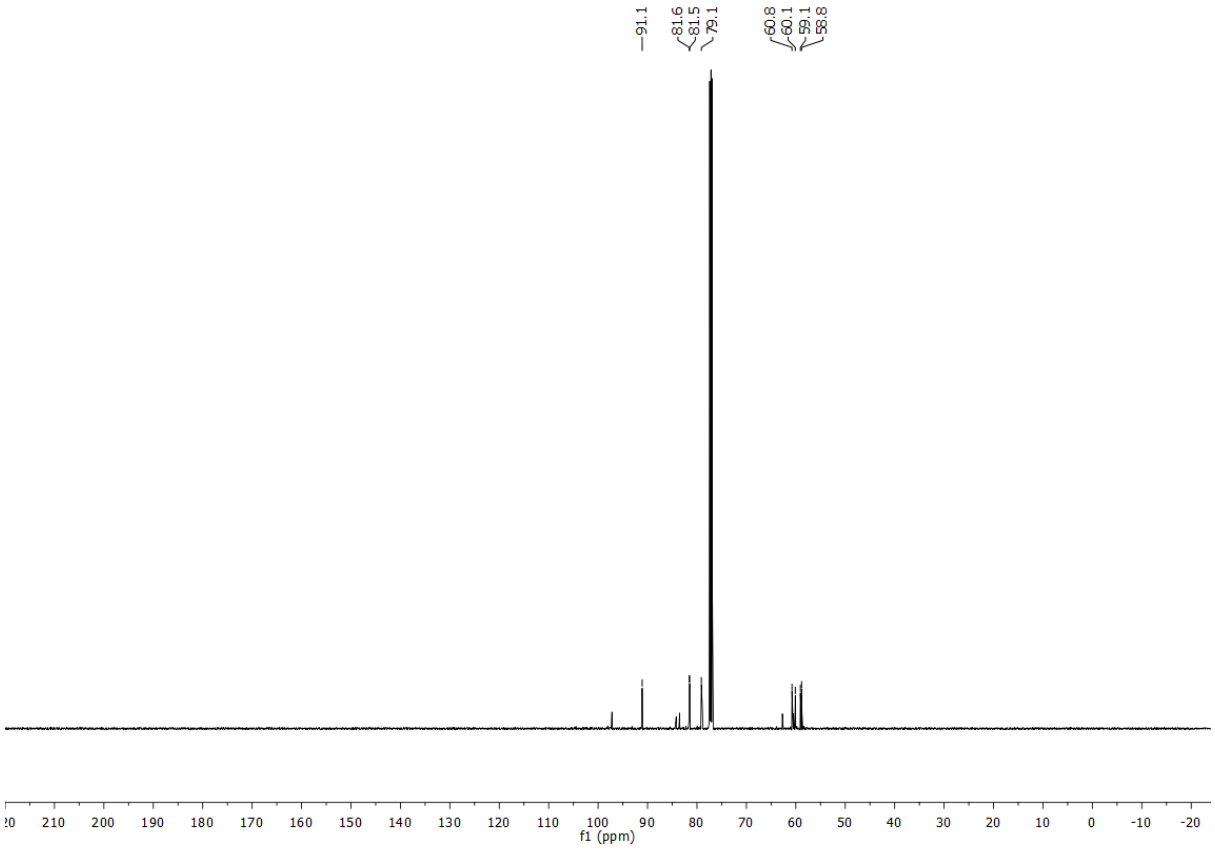
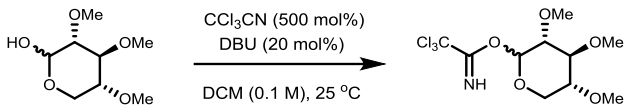
2.96
3.01
1.02
1.13
1.11
f1 (ppm)


91.1
81.6
81.5
79.1
60.8
60.1
59.1
58.8
f1 (ppm)

(3R,4S,5R)-3,4,5-trimethoxytetrahydro-2H-pyran-2-yl 2,2,2-trichloroacetimidate (4)



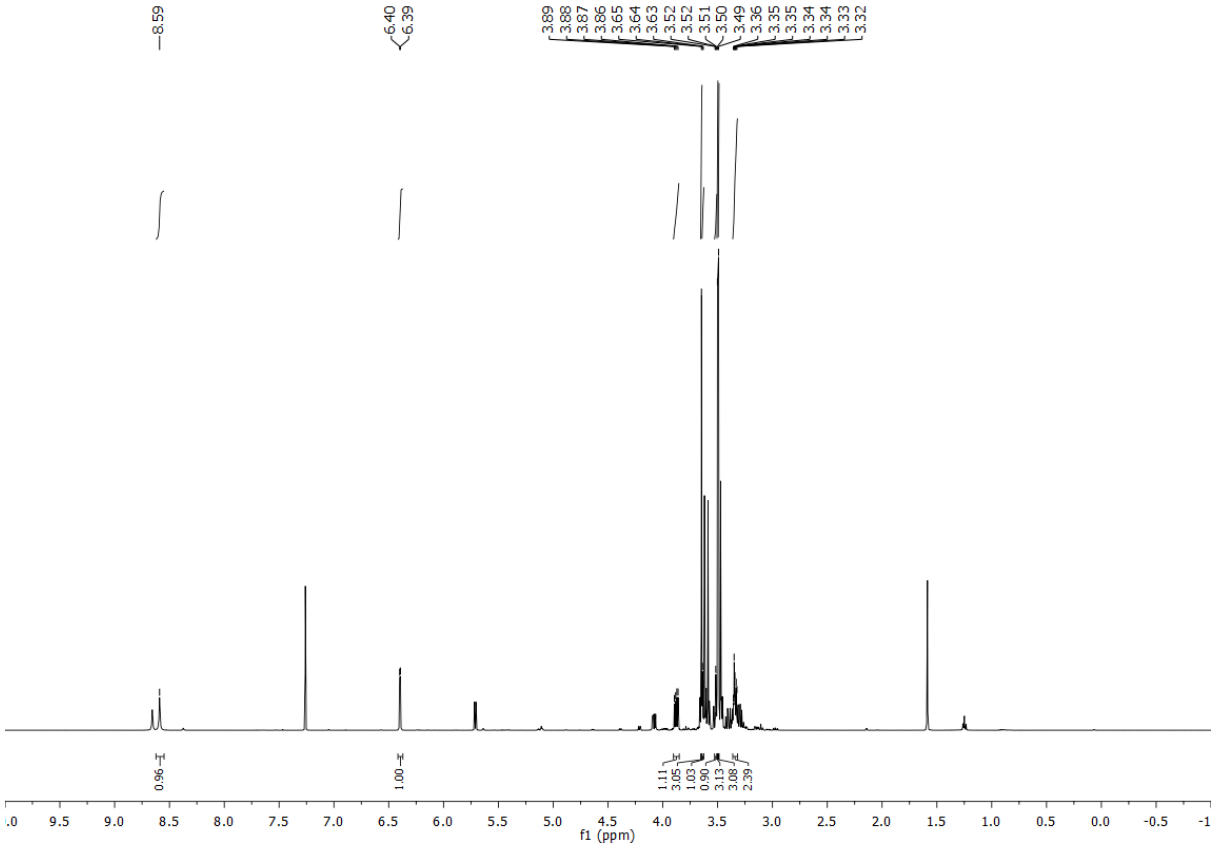
To a solution of hemiacetal **S3** (500.0 mg, 2.60 mmol, 100 mol%) in CH_2Cl_2 (13 mL) was added trichloroacetonitrile (1.3 mL, 1.88 g, 13.0 mmol, 500 mol%) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (78 µL, 0.52 mmol, 20 mol%). The reaction was allowed to stir at 25 °C for 24 h. The solvent was removed *in vacuo,* and the residue was subjected to flash chromatography on basic alumina (Hex/EtOAc 4:1) to furnish trichloroacetimidate **4** (646.2 mg, 1.92 mmol, dr = 2:1) in 74% yield as a pale yellow oil. The spectral data were identical to those reported.[2]

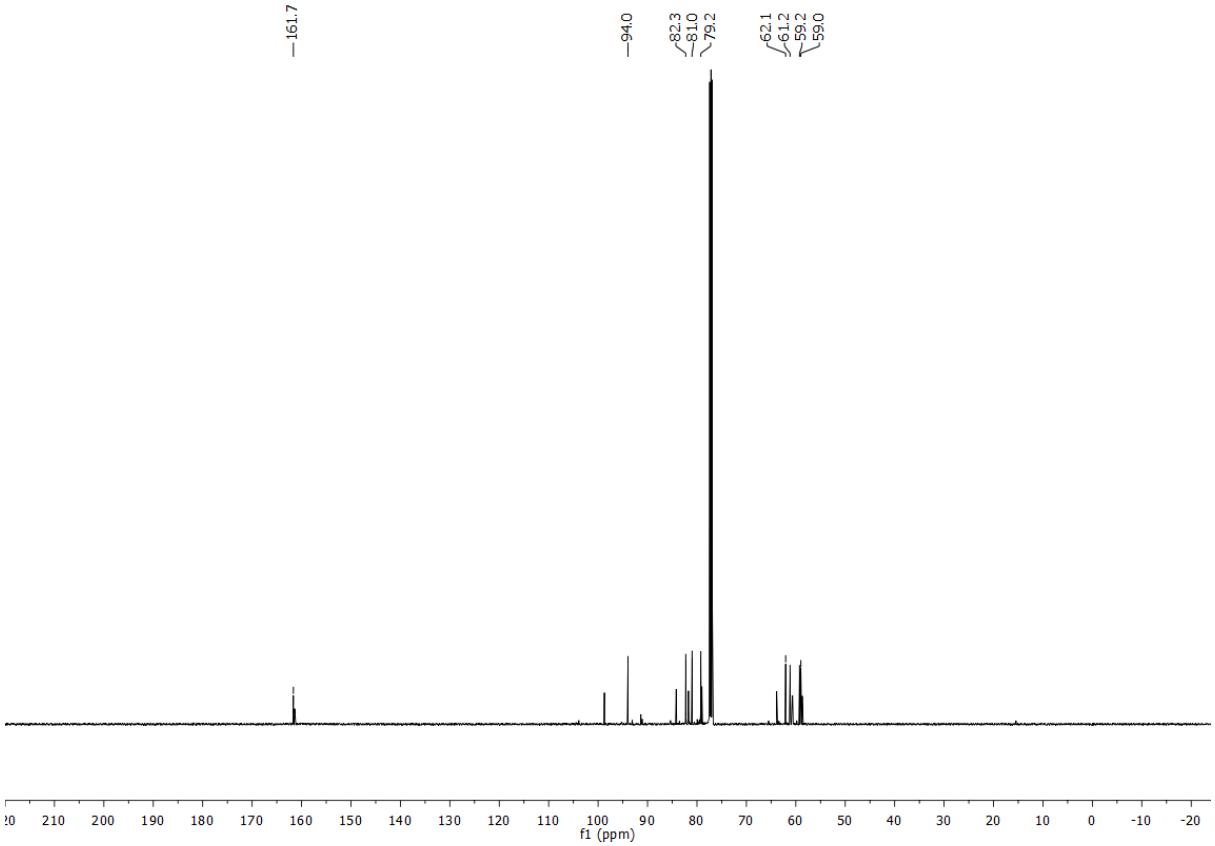
Data of the major isomer are reported.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.59 (s, 1H), 6.40 (d, *J* = 3.5 Hz, 1H), 3.88 (dd, *J* = 11.3, 5.8 Hz, 1H), 3.65 (s, 3H), 3.64 – 3.63 (m, 1H), 3.53 – 3.51 (m, 1H), 3.50 (s, 3H), 3.49 (s, 3H), 3.36 – 3.32 (m, 2H).

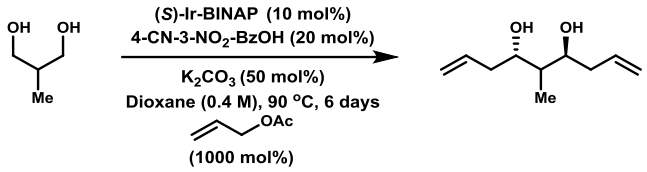
^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.7, 94.0, 82.3, 81.0, 79.2, 62.1, 61.2, 59.2, 59.0.

HRMS (ESI) Calculated for $C_{10}H_{16}Cl_3NO_5$ $[M+Na]^+$ = 357.9986, Found: 357.9991.


8.59
6.40
6.39
3.89
3.88
3.87
3.86
3.65
3.64
3.63
3.52
3.52
3.51
3.50
3.49
3.36
3.35
3.35
3.34
3.34
3.33
3.32
0.96
1.00
1.11
3.05
1.03
0.90
3.13
3.08
2.39
f1 (ppm)


161.7
94.0
82.3
81.0
79.2
62.1
61.2
59.2
59.0
f1 (ppm)

(4*S*,6*S*)-5-Methylnona-1,8-diene-4,6-diol (2)



To an oven-dried sealed tube under one atmosphere of argon gas charged with (*S*)-Ir-BINAP catalyst (1.05 g, 1.00 mmol, 10 mol%), 4-cyano-3-nitrobenzoic acid (384 mg, 2.00 mmol, 20 mol%), K_2CO_3 (691 mg, 5.00 mmol, 50 mol%) and diol **1** (901 mg, 10.0 mmol) was added 1,4-dioxane (25 mL) followed by allyl acetate (10 g, 10.0 mmol, 1000 mol%). The reaction mixture was sealed and allowed to stir at 90 °C for 6 days. The mixture was cooled to room temperature, filtered through celite, and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, Hex/EtOAc 5:1 → 4:1 → 3:1) afforded diol **2** (895 mg, 5.26 mmol, dr ≥ 20:1, ee >99%) as a pale-yellow oil in 53% yield.

TLC (SiO_2): Rf = 0.28 (ethyl acetate:hexanes, 1:3).

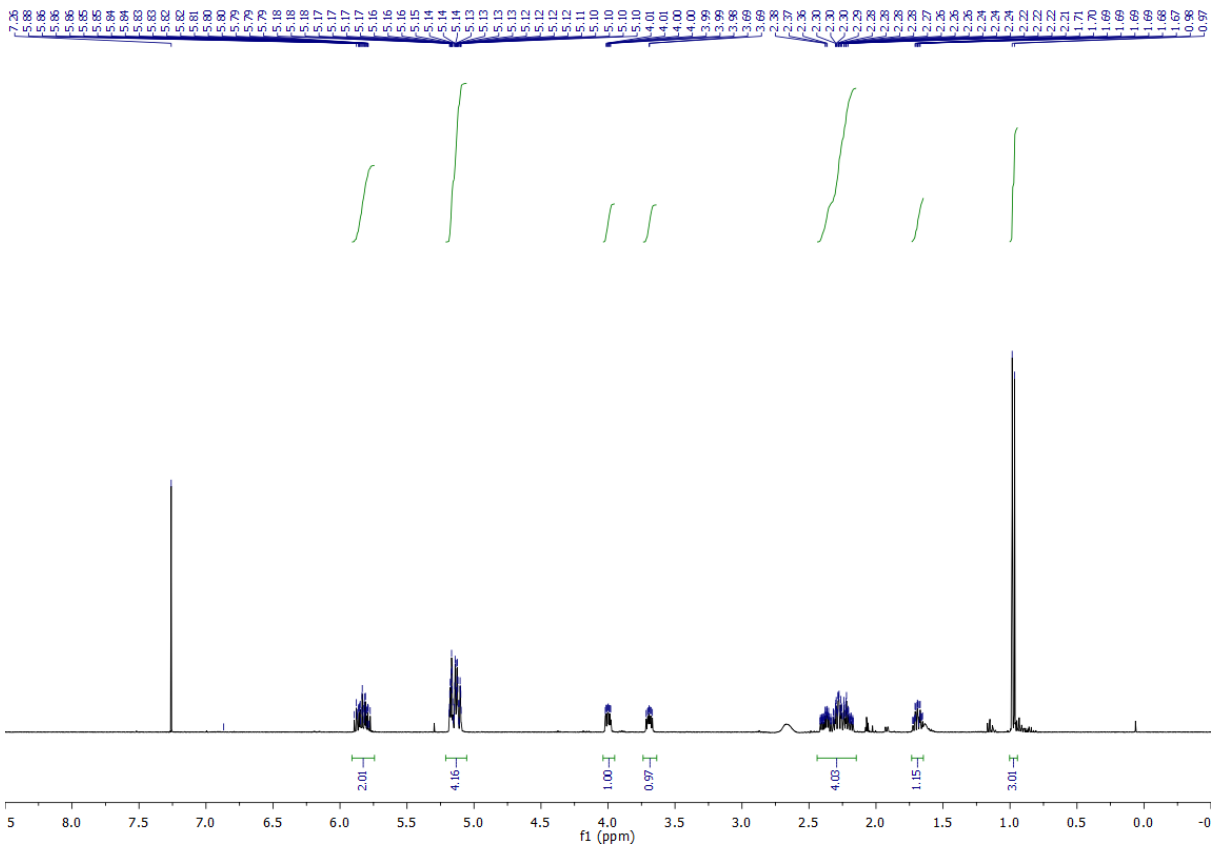
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.89-5.76 (m, 2H), 5.17-5.08 (m, 4H), 4.02-3.97 (m, 1H), 3.69-3.66 (m, 1H), 3.99 (br s, 1H), 3.67 (br s, 1H), 2.84-2.15 (m, 4H), 1.71-1.63 (m, 1H), 0.96 (d, J = 7.2 Hz, 3H).

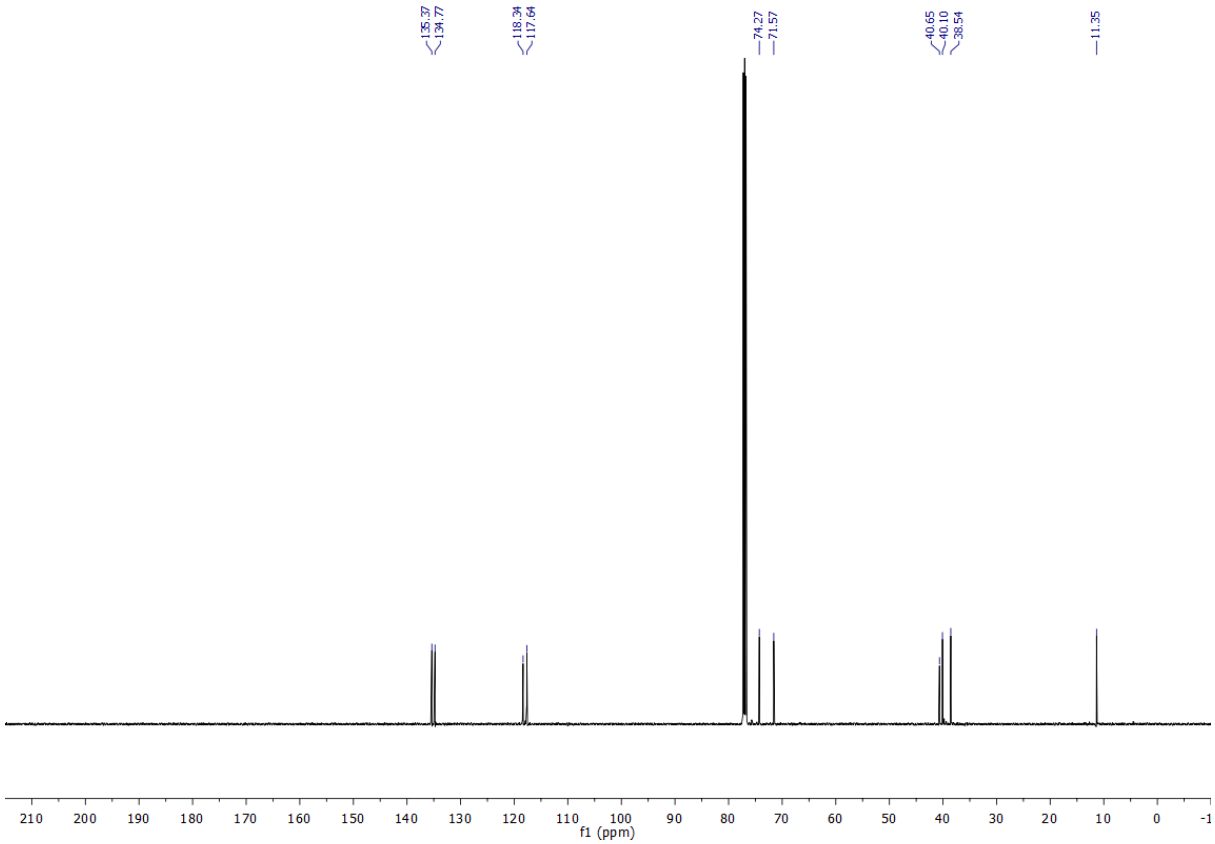
^{13}C NMR (125 MHz, $CDCl_3$): δ 135.4, 134.8, 118.3, 117.6, 74.3, 71.6, 40.7, 40.1, 38.5, 11.4.

FTIR (neat): υ 3341, 3074, 2976, 2936, 2905, 1632, 1427, 1321, 1080, 1018, 991, 965, 907, 858 cm^{-1}.

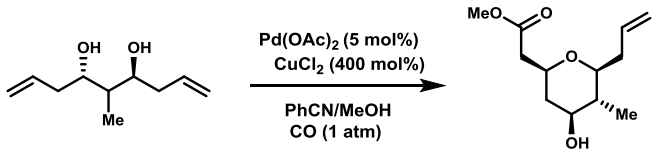
HRMS (CI) Calcd. for $C_{10}H_{18}O_2$ $[M+H]^+$: 171.1385, Found: 171.1387.

HPLC: The enantiomeric excess was determined by chiral HPLC as described by Krische and coworkers.[3]


2.01
4.16
1.00
0.97
4.03
1.15
3.01
f1 (ppm)


135.37
134.77
118.34
117.64
74.27
71.57
40.65
40.10
38.54
11.35
f1 (ppm)

Methyl 2-((2*S*,4*S*,5*R*,6*S*)-6-allyl-4-hydroxy-5-methyltetrahydro-2H-pyran-2-yl)acetate (3)



To a round bottom flask containing a magnetic stir bar was added palladium (II) acetate (39.5 mg, 0.176 mmol, 5 mol%) and copper (II) chloride (1.895 g, 14.10 mmol, 400 mol%). The flask was purged with carbon monoxide for 5 minutes. Benzonitrile (9 mL) was added and the heterogeneous mixture was stirred vigorously for 1 hour. A solution of diol **2** (600 mg, 3.524 mmol, 100 mol%) in methanol (9 mL) was added over 10 minutes. The resulting mixture was stirred at ambient temperature for 2 h. A saturated aqueous solution of NH_4Cl (50 mL) and water (20 mL) were added to the reaction mixture and the mixture was transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with EtOAc (50 mL × 3). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting oily residue was subjected to flash column chromatography (SiO_2, hexanes: ethyl acetate = 2:1) to furnish **3** as a yellow oil (562.0 mg, 2.46 mmol, dr = 6:1, inseparable) in 72% yield.

TLC (SiO_2): Rf = 0.37 (ethyl acetate:hexanes, 1:1).

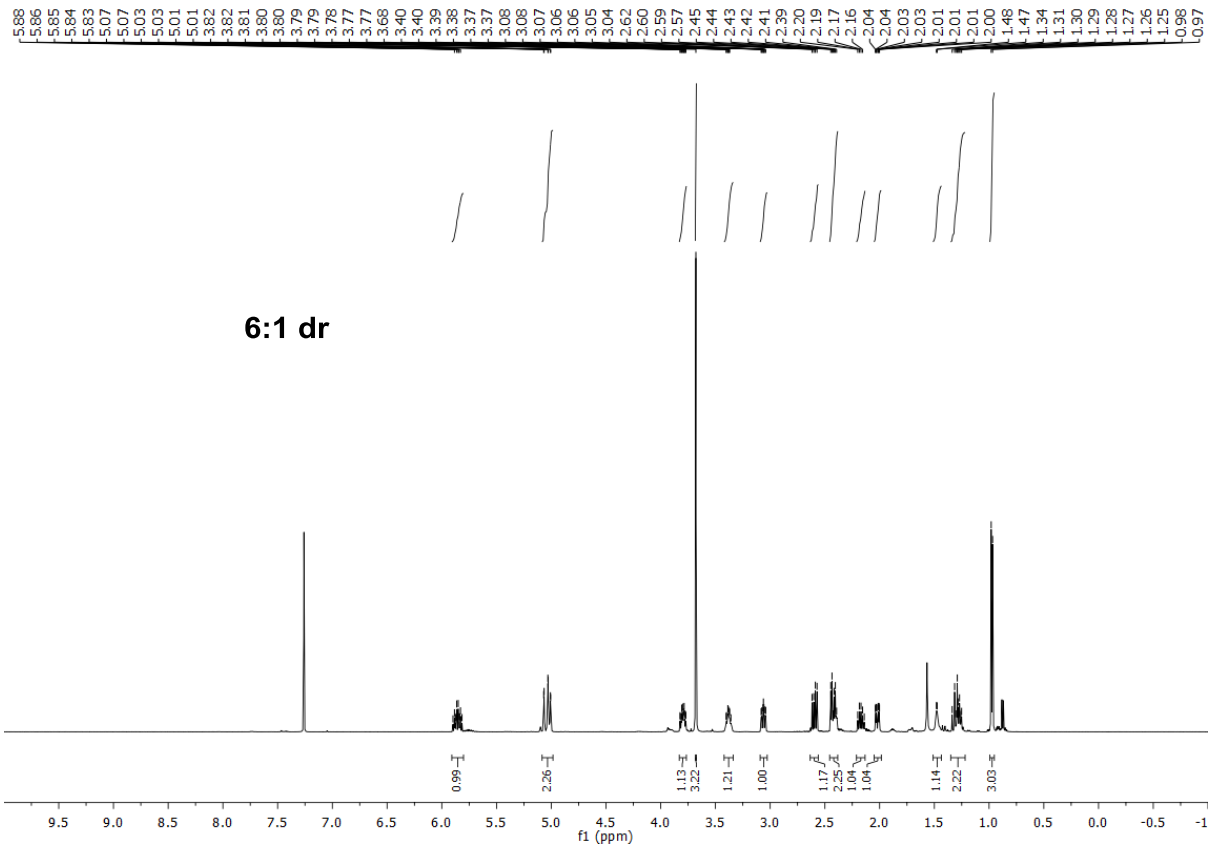
^{1}H NMR (500 MHz, $CDCl_3$): δ 5.86 (ddt, *J* = 17.1, 10.2, 6.8 Hz, 1H), 5.09 – 4.98 (m, 2H), 3.80 (dddd, *J* = 11.4, 7.7, 5.5, 1.9 Hz, 1H), 3.68 (s, 3H), 3.42 – 3.34 (m, 1H), 3.06 (ddd, *J* = 9.8, 7.9, 3.1 Hz, 1H), 2.59 (dd, *J* = 15.1, 7.9 Hz, 1H), 2.46 – 2.38 (m, 2H), 2.17 (dtd, *J* = 13.6, 7.6, 7.0, 1.3 Hz, 1H), 2.02 (ddd, *J* = 12.3, 4.8, 2.0 Hz, 1H), 1.48 (d, *J* = 5.2 Hz, 1H), 1.35 – 1.23 (m, 2H), 0.97 (d, *J* = 6.5 Hz, 3H).

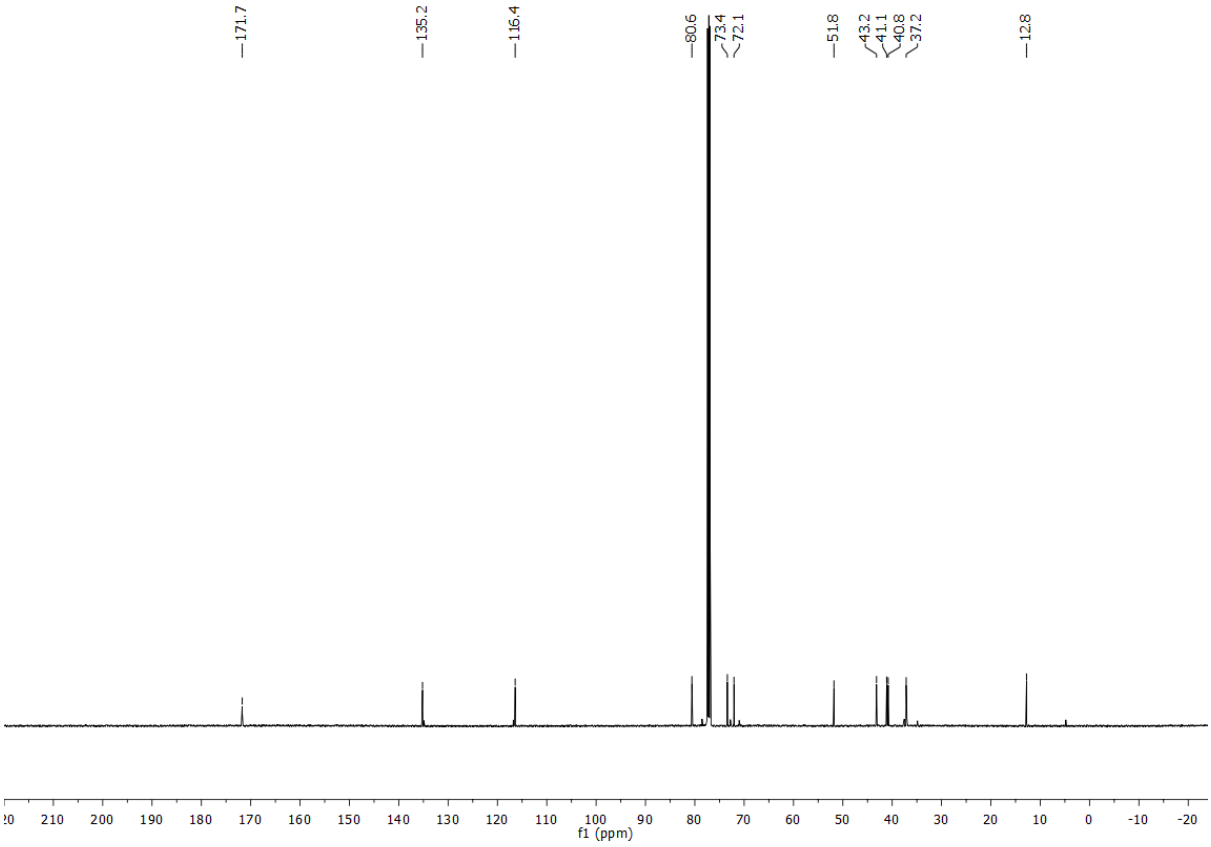
^{13}C NMR (125 MHz, $CDCl_3$): δ 171.7, 135.2, 116.4, 80.6, 73.4, 72.1, 51.8, 43.2, 41.1, 40.8, 37.2, 12.8.

HRMS (ESI) Calculated for $C_{12}H_{20}O_4$ $[M+Na]^+$ = 251.1254, Found 251.1256.

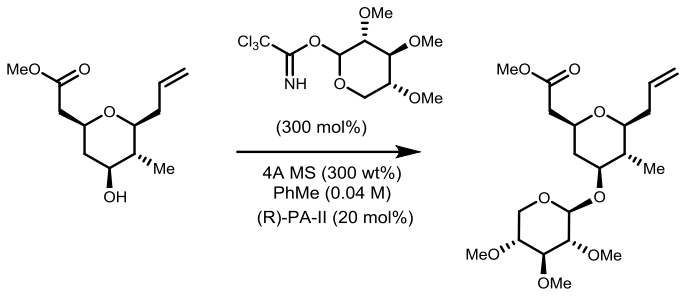
FTIR (neat): υ 3431, 2947, 1738, 1438, 1374, 1207, 1147, 1084, 1008, 914 cm^{-1}.

$[\alpha]^{28}_D$: -3.75° (c = 1.0, $CHCl_3$).


6:1 dr
f1 (ppm)


f1 (ppm)

Methyl 2-((2*S*,4*S*,5*S*,6*S*)-6-allyl-5-methyl-4-(((2*S*,3*R*,4*S*,5*R*)-3,4,5-trimethoxytetrahydro-2H-pyran-2-yl)oxy)tetrahydro-2H-pyran-2-yl)acetate (5)



To a stirred solution of **3** (100.0 mg, 0.438 mmol, 100 mol%) and (3R,4S,5R)-3,4,5-trimethoxytetrahydro-2H-pyran-2-yl 2,2,2-trichloroacetimidate **4** (442.3 mg, 1.314 mmol, 300 mol%) in toluene (10.0 mL, 0.044 M) was added 4 Å MS (300 mg, 300 wt. %) and stirred for 45 minutes. The reaction was cooled down to 0 ^{o}C and (R)-PA-II (68.0 mg, 0.088 mmol, 20 mol%) was added in one portion. The resulting mixture was warmed up to room temperature and stirred for 48 h. The reaction was quenched with NEt_3 (500 μL) and stirred for 10 minutes. The mixture was filtered through celite, and the solvent removed *in vacuo.* Hexanes was added to the residue, the mixture was filtered, and the solvent removed *in vacuo*. The crude material was purified via column chromatography (SiO_2: DCM: Et_2O, 19:1 → 8:1) to afford **5** (114.4 mg, 0.284 mmol, dr = 6:1, separable) in 65% yield as a clear oil.

Data of the major isomer are reported.

TLC (SiO_2): R_f = 0.53 (ethyl acetate:hexanes, 1:1).

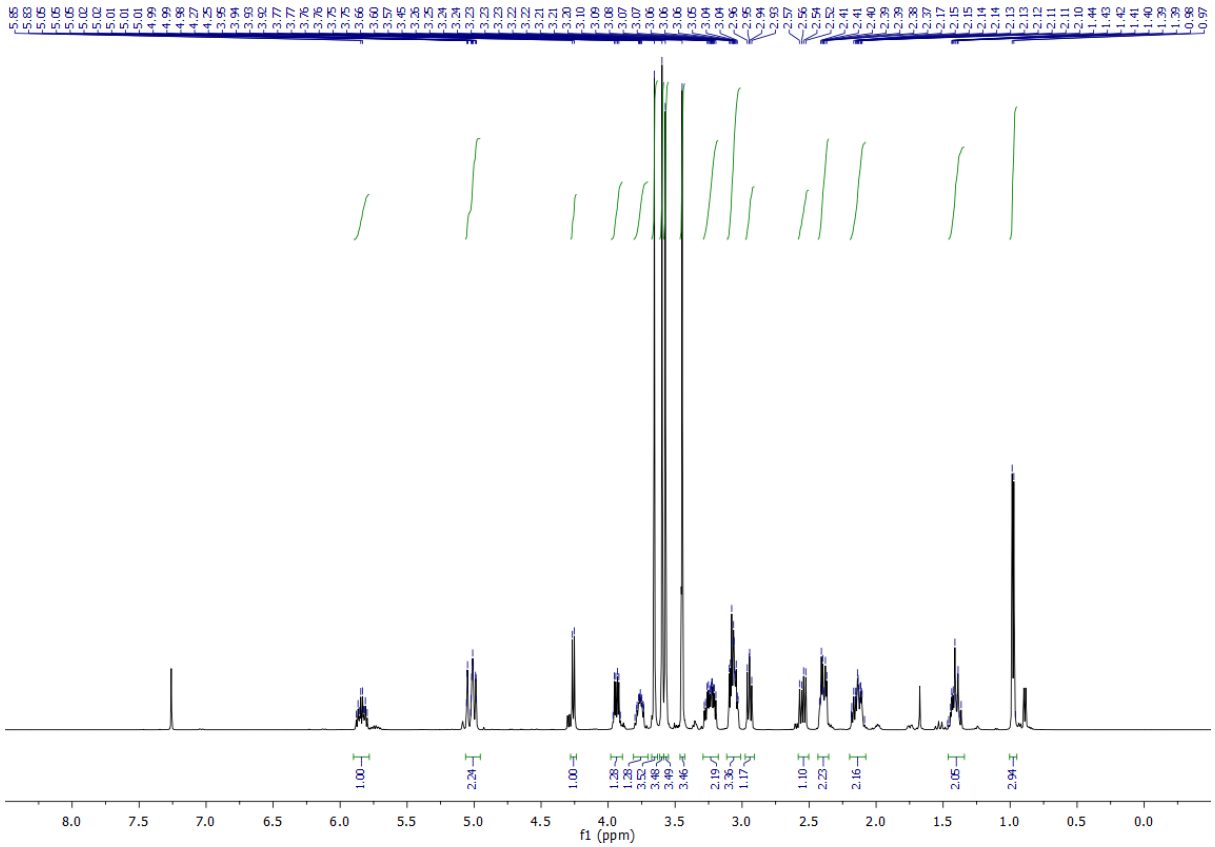
^{1}H NMR (500 MHz, $CDCl_3$): δ 5.84 (ddt, *J* = 17.1, 10.3, 6.8 Hz, 1H), 5.06–4.98 (m, 2H), 4.26 (d, *J* = 7.6 Hz, 1H), 3.94 (dd, *J* = 11.6, 5.2 Hz, 1H), 3.80–3.73 (m, 1H), 3.66 (s, 3H), 3.60 (s, 3H), 3.57 (s, 3H), 3.45 (s, 3H), 3.28–3.20 (m, 2H), 3.10–3.03 (m, 3H), 2.95 (dd, *J* = 9.0, 7.6 Hz, 1H), 2.55 (dd, *J* = 15.2, 8.1 Hz, 1H), 2.44–2.35 (m, 2H), 2.20–2.09 (m, 2H), 1.47–1.34 (m, 2H), 0.98 (d, *J* = 6.5 Hz, 3H).

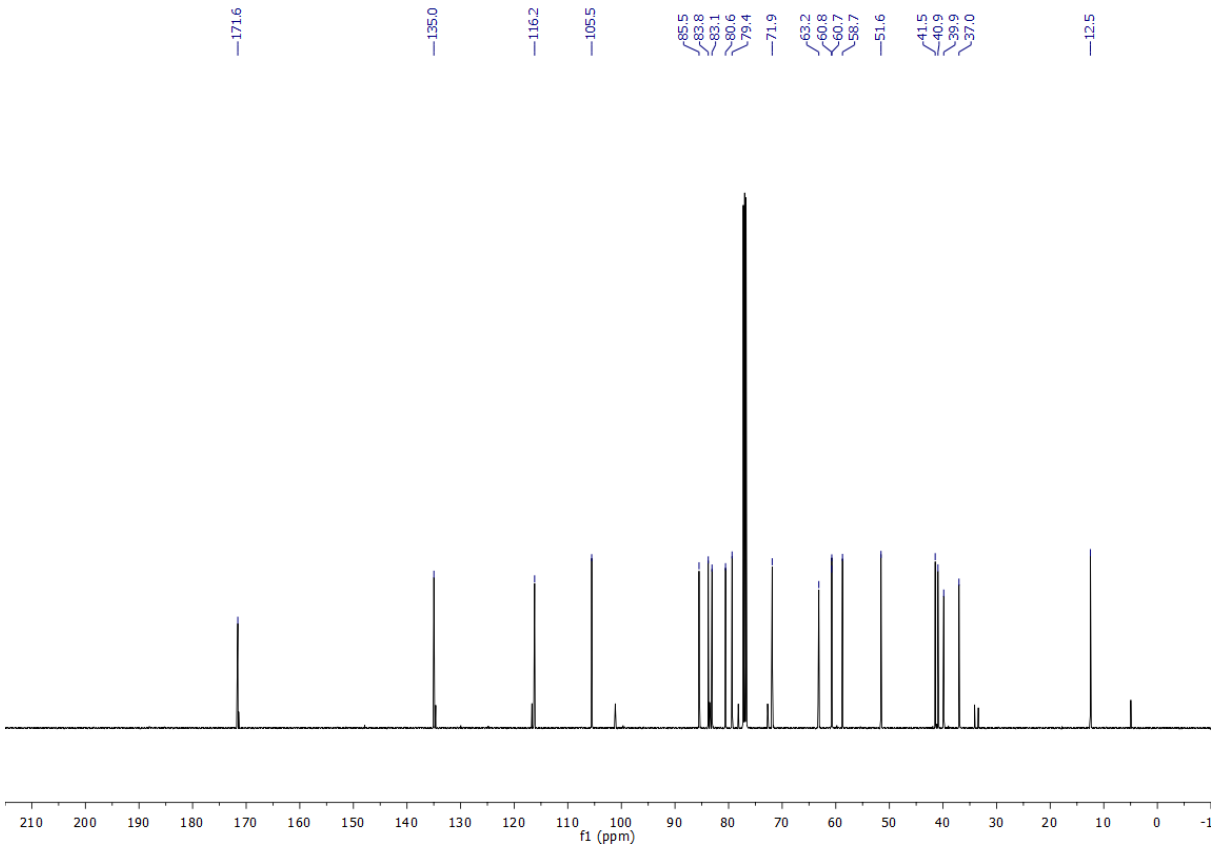
^{13}C NMR (125 MHz, $CDCl_3$): δ 171.6, 135.0, 116.2, 105.5, 85.5, 83.8, 83.1, 80.6, 79.4, 71.9, 63.2, 60.8, 60.7, 58.7, 51.6, 41.5, 40.9, 39.9, 37.0, 12.5.

HRMS (ESI) Calculated for $C_{20}H_{34}O_8$ $[M+Na]^+$ = 425.2146, Found 425.2152.

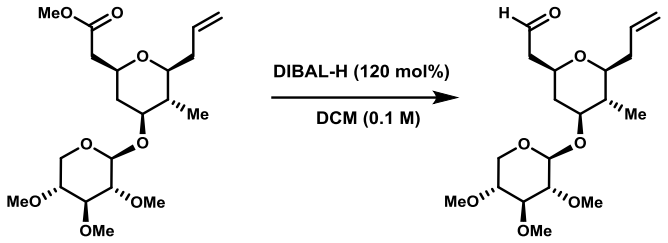
FTIR (neat): υ 2930, 1742, 1439, 1371, 1261, 1163, 1093, 988, 911 cm^{-1}.

$[\alpha]^{28}_D$: -17.50° (c = 0.5, $CHCl_3$).


f1 (ppm)


f1 (ppm)

2-((2*S*,4*S*,5*S*,6*S*)-6-allyl-5-methyl-4-(((2*S*,3*R*,4*S*,5*R*)-3,4,5-trimethoxytetrahydro-2H-pyran-2-yl)oxy)tetrahydro-2H-pyran-2-yl)acetaldehyde (9)



To a stirred solution of **5** (130 mg, 0.323 mmol, 100 mol%) in CH_2Cl_2 (3.2 mL, 0.1 M) was added DIBAL-H (1 M in hexanes, 388 µL, 0.388 mmol, 120 mol%) dropwise at -78 °C and the resultant solution was stirred at this temperature for 30 min. The reaction was quenched with Rochelle's salt (saturated solution). After stirring for 2 h at ambient temperature, the mixture was extracted with CH_2Cl_2 (3 x 3 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified via column chromatography (SiO_2: ethyl acetate:hexanes, 1:2) to afford **9** (97.0 mg, 81%) as a clear oil.

TLC (SiO_2): R_f = 0.47 (ethyl acetate: hexanes, 1:1).

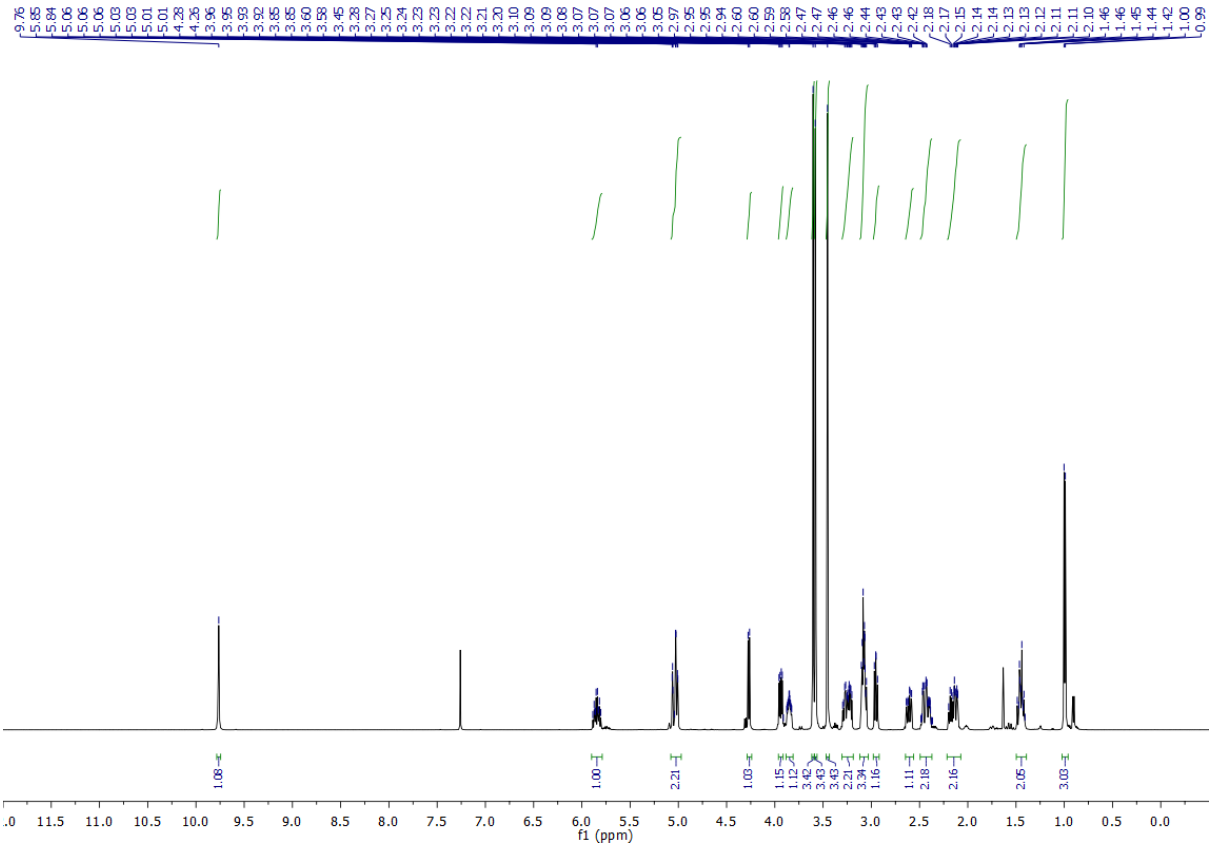
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.76 (s, 1H), 5.85 (ddt, *J* = 17.1, 10.3, 6.8 Hz, 1H), 5.08–4.97 (m, 2H), 4.27 (d, *J* = 7.5 Hz, 1H), 3.94 (dd, *J* = 11.6, 5.3 Hz, 1H), 3.85 (dddd, *J* = 11.6, 7.9, 4.2, 1.8 Hz, 1H), 3.60 (s, 3H), 3.58 (s, 3H), 3.45 (s, 3H), 3.32–3.17 (m, 2H), 3.12–3.02 (m, 3H), 2.95 (dd, *J* = 9.1, 7.6 Hz, 1H), 2.61 (ddd, *J* = 16.4, 8.2, 2.5 Hz, 1H), 2.49–2.36 (m, 2H), 2.21–2.08 (m, 2H), 1.50–1.39 (m, 2H), 1.00 (d, *J* = 6.5 Hz, 3H).

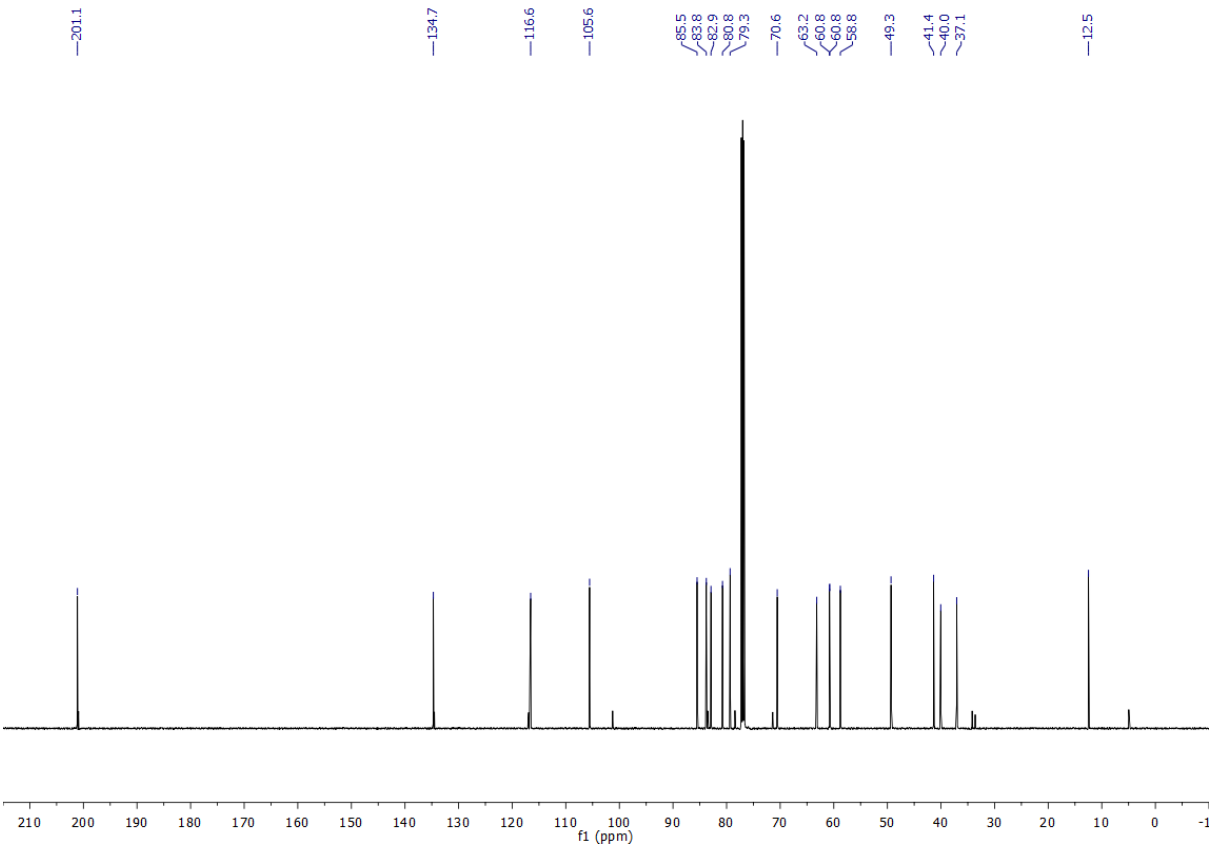
^{13}C NMR (125 MHz, $CDCl_3$): δ 201.1, 134.7, 116.6, 105.6, 85.5, 83.8, 82.9, 80.8, 79.3, 70.6, 63.2, 60.8, 60.8, 58.8, 49.3, 41.4, 40.0, 37.1, 12.5.

HRMS (ESI) Calculated for $C_{19}H_{32}O_7$ $[M+Na]^+$ = 395.2040, Found 395.2046.

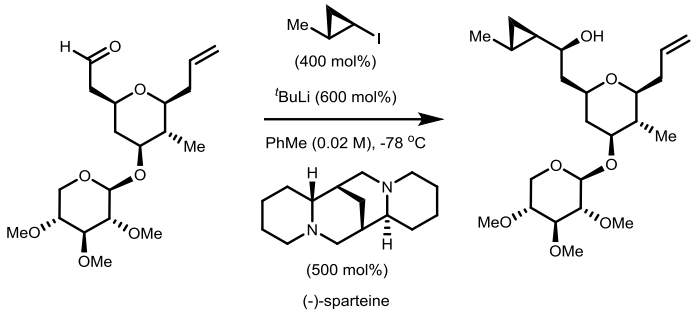
FTIR (neat): υ 2922, 2854, 1726, 1465, 1373, 1162, 1092, 989, 916 cm^{-1}.

$[\alpha]^{25}_D$: -213.00° (c = 0.5, $CHCl_3$).


f1 (ppm)


f1 (ppm)

(S)-2-((2R,4S,5S,6S)-6-allyl-5-methyl-4-(((2S,3R,4S,5R)-3,4,5-trimethoxytetrahydro-2H-pyran-2-yl)oxy)tetrahydro-2H-pyran-2-yl)-1-((1R,2R)-2-methylcyclopropyl)ethan-1-ol (10)



To an oven-dried round bottomed flask equipped with a stir bar was added toluene (6.0 mL), (-)-sparteine (188.7 mg, 0.805 mmol, 500 mol%), and iodide **8** (117.2 mg, 0.644 mmol, 400 mol%). The solution was cooled to -78 °C and tert-butyl lithium (1.7 M in pentane, 570 µL, 0.966 mmol, 600 mol%) was added dropwise. The solution was allowed to stir for 120 minutes at -78 °C before aldehyde **9** (60.0 mg, 0.161 mmol, 100 mol%) was added in toluene (2.0 ml) dropwise over 5 minutes. The reaction was allowed to stir at -78 °C for 120 minutes. A saturated aqueous solution of NH_4Cl (2 mL) and water (2 mL) were added to the reaction mixture. The aqueous layer was extracted with Et_2O (3 × 4 mL). The combined organic layers were dried (Na_2SO_4), filtered and the solvent was removed *in vacuo.* The residue was dissolved in EtOAc and passed through a short silica plug. The solvent was removed *in vacuo* and the residue was subjected to flash column chromatography (basic alumina, hexanes/ethyl acetate 2:1 → 1:1) to afford alcohol **10** (49.0 mg, 0.114 mmol, dr = 4:1, separable) as a clear oil in 71 % yield.

Data of the major isomer are reported.

TLC (SiO_2): R_f = 0.40 (ethyl acetate: hexanes, 1:1).

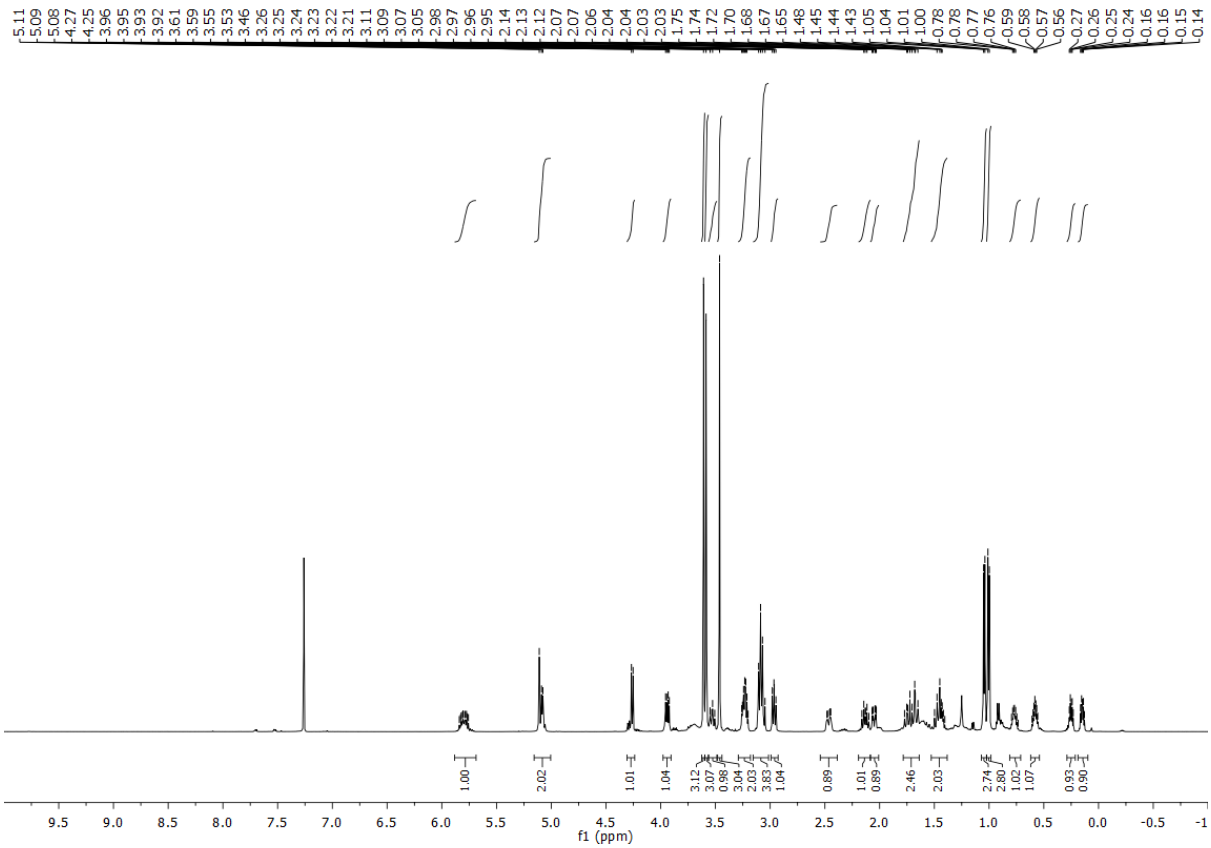
^{1}H NMR (500 MHz, $CDCl_3$): δ 5.80 (dddd, *J* = 17.1, 11.5, 8.6, 5.6 Hz, 1H), 5.14 – 5.03 (m, 2H), 4.26 (d, *J* = 7.6 Hz, 1H), 3.94 (dd, *J* = 11.6, 5.2 Hz, 1H), 3.61 (s, 3H), 3.59 (s, 3H), 3.56 – 3.49 (m, 1H), 3.46 (s, 3H), 3.28 – 3.18 (m, 2H), 3.12 – 3.03 (m, 4H), 2.97 (dd, *J* = 9.0, 7.6 Hz, 1H), 2.53 – 2.40 (m, 1H), 2.13 (dt, *J* = 14.5, 8.6 Hz, 1H), 2.05 (ddd, *J* = 12.8, 4.8, 1.9 Hz, 1H), 1.79 – 1.63 (m, 2H), 1.51 – 1.38 (m, 2H), 1.04 (d, *J* = 6.0 Hz, 3H), 1.00 (d, *J* = 6.5 Hz, 3H), 0.81 – 0.73 (m, 1H), 0.62 – 0.54 (m, *J* = 8.6, 4.6 Hz, 1H), 0.25 (dt, *J* = 8.8, 4.6 Hz, 1H), 0.15 (dt, *J* = 8.4, 4.8 Hz, 1H).

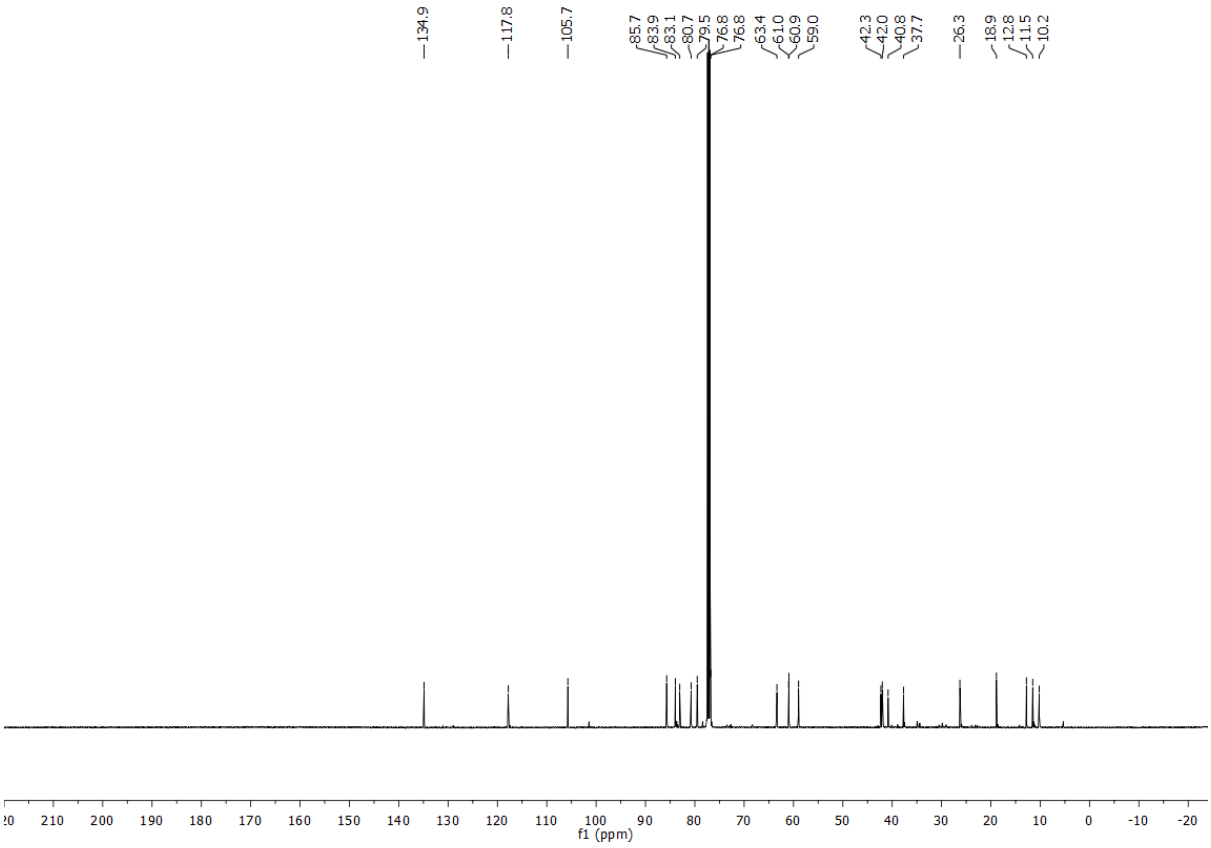
^{13}C NMR (125 MHz, $CDCl_3$): δ 134.9, 117.8, 105.7, 85.7, 83.9, 83.1, 80.7, 79.5, 76.8, 76.8, 63.4, 61.0, 60.9, 59.0, 42.3, 42.0, 40.8, 37.7, 26.3, 18.9, 12.8, 11.5, 10.2.

HRMS (ESI) Calculated for $C_{23}H_{40}O_7$ $[M+Na]^+$ = 451.2666, Found 451.2669.

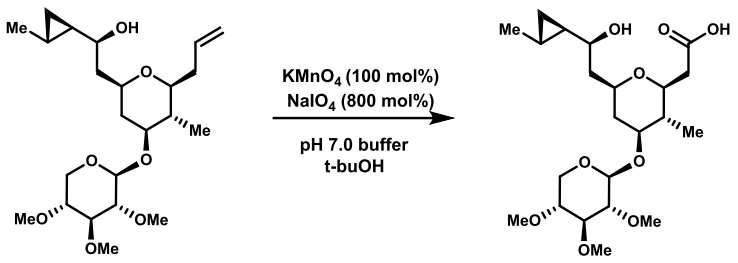
FTIR (neat): υ 3510, 2928, 1456, 1372, 1162, 1092, 988 cm^{-1}.

$[\alpha]^{26}_D$: -111.25° (c = 1.0, $CHCl_3$).


5.11 5.09 5.08 4.27 4.25 3.96 3.95 3.93 3.92 3.61 3.59 3.55 3.53 3.46 3.26 3.25 3.24 3.23 3.22 3.21 3.11 3.09 3.07 3.05 2.98 2.97 2.96 2.95 2.14 2.13 2.12 2.07 2.07 2.06 2.04 2.04 2.03 2.03 1.75 1.74 1.72 1.70 1.68 1.67 1.65 1.48 1.45 1.44 1.43 1.05 1.04 1.01 1.00 0.78 0.78 0.77 0.76 0.59 0.58 0.57 0.56 0.27 0.26 0.25 0.24 0.16 0.15 0.14
1.00 2.02 1.01 1.04 3.12 3.07 0.98 3.04 2.03 3.83 1.04 0.89 1.01 0.89 2.46 2.03 2.74 2.80 1.02 1.07 0.93 0.90
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)


134.9 117.8 105.7 85.7 83.9 83.1 80.7 79.5 76.8 76.8 63.4 61.0 60.9 59.0 42.3 42.0 40.8 37.7 26.3 18.9 12.8 11.5 10.2
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

2-((2S,3S,4S,6R)-6-((S)-2-hydroxy-2-((1R,2R)-2-methylcyclopropyl)ethyl)-3-methyl-4-(((2S,3R,4S,5R)-3,4,5-trimethoxytetrahydro-2H-pyran-2-yl)oxy)tetrahydro-2H-pyran-2-yl)acetic acid (11)



To a suspension of $NaIO_4$ (92.4 mg, 0.432 mmol, 800 mol%) in pH 7.0 buffer (3.5 mL) was added $KMnO_4$ (8.5 mg, 0.054 mmol, 100 mol%). After 20 minutes of stirring at room temperature, the mixture was added to a solution of alcohol **10** (23.0 mg, 0.054 mmol, 100 mol%) in *t*-BuOH (3.5 mL), and the resulting mixture was stirred at room temperature for 6 hours. The reaction was quenched with $Na_2S_2O_3.5H_2O$ (40.2 mg, 0.162 mmol, 300 mol%) and stirred for a further 30 minutes. H_2O (10 mL), EtOAc (10 mL) and 10% aqueous citric acid (3 mL) were added and the reaction mixture was transferred to a separatory funnel. The aqueous phase was extracted with EtOAc (10 mL). The combined organic phases were washed with brine (5 mL), dried ($MgSO_4$), filtered and the solvent was removed *in vacuo*. Compound **11** (20.5 mg, 0.046 mmol) was obtained in 85% yield as a colorless oil and was used without further purification in the next step.

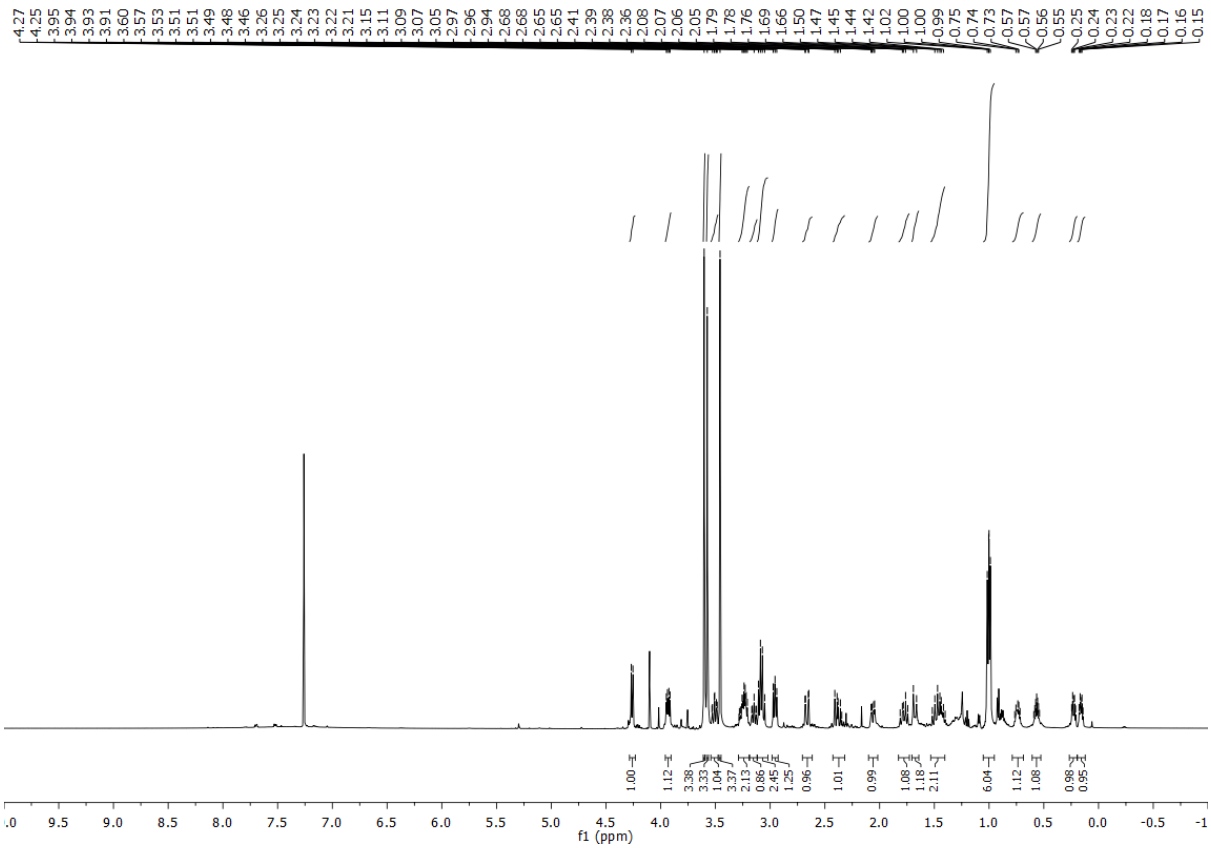
^{1}H NMR (500 MHz, $CDCl_3$): δ 4.26 (d, *J* = 7.6 Hz, 1H), 3.93 (dd, *J* = 11.6, 5.1 Hz, 1H), 3.60 (s, 3H), 3.57 (s, 3H), 3.51 (td, *J* = 10.3, 2.7 Hz, 1H), 3.46 (s, 3H), 3.29 – 3.20 (m, 2H), 3.15 (td, *J* = 9.5, 2.2 Hz, 1H), 3.11 – 3.04 (m, 3H), 2.96 (dd, *J* = 9.1, 7.6 Hz, 1H), 2.66 (dd, *J* = 15.0, 2.5 Hz, 1H), 2.38 (dd, *J* = 15.0, 10.6 Hz, 1H), 2.06 (ddd, *J* = 12.9, 4.9, 1.8 Hz, 1H), 1.83 – 1.73 (m, 1H), 1.70 – 1.64 (m, 1H), 1.53 – 1.38 (m, 2H), 1.03 (app t, *J* = 6.4 Hz, 6H), 0.74 (tt, *J* = 10.2, 5.0 Hz, 1H), 0.57 (tt, *J* = 8.8, 4.6 Hz, 1H), 0.23 (dt, *J* = 8.8, 4.7 Hz, 1H), 0.16 (dt, *J* = 8.4, 4.9 Hz, 1H).

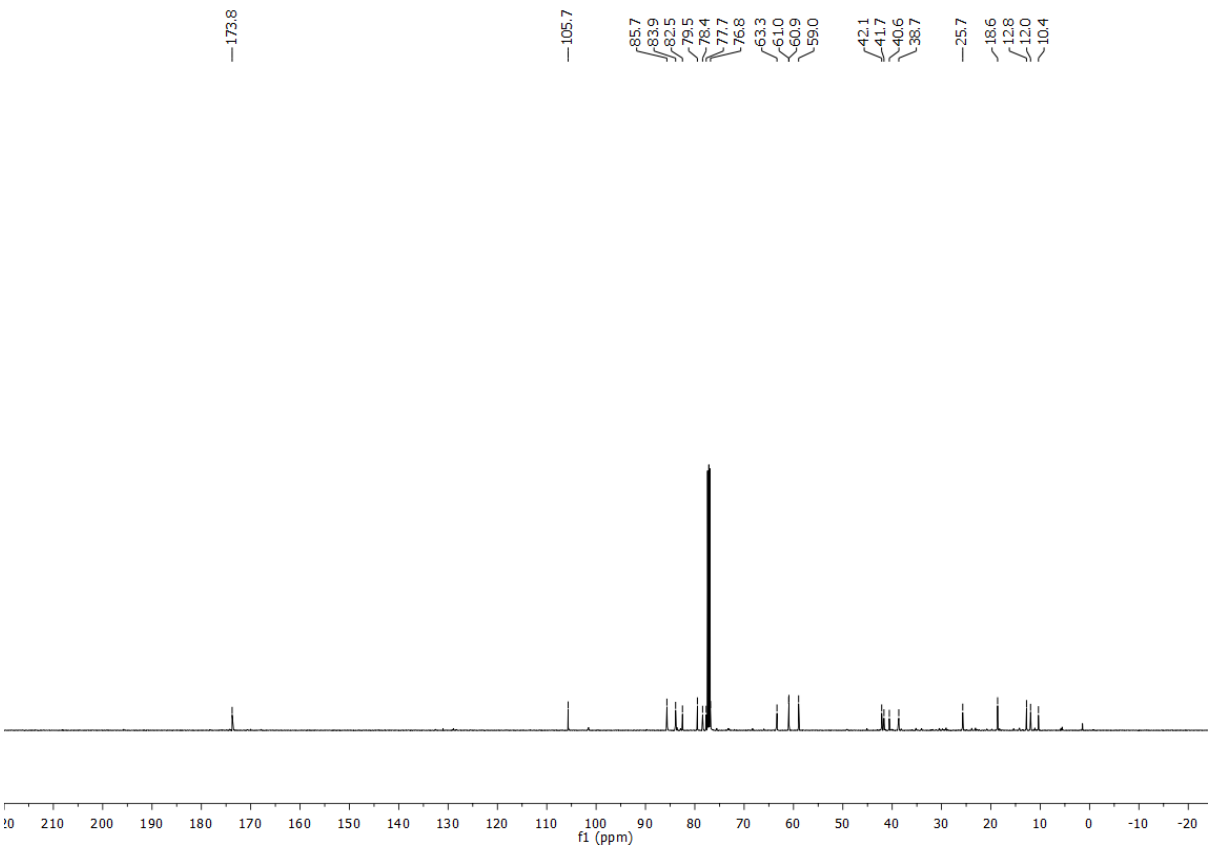
^{13}C NMR (125 MHz, $CDCl_3$): δ 173.8, 105.7, 85.7, 83.9, 82.5, 79.5, 78.4, 77.7, 76.8, 63.3, 61.0, 60.9, 59.0, 42.1, 41.7, 40.6, 38.7, 25.7, 18.6, 12.8, 12.0, 10.4.

HRMS (ESI) Calculated for $C_{22}H_{38}O_9$ $[M+Na]^+$ = 469.2408, Found 469.2413.

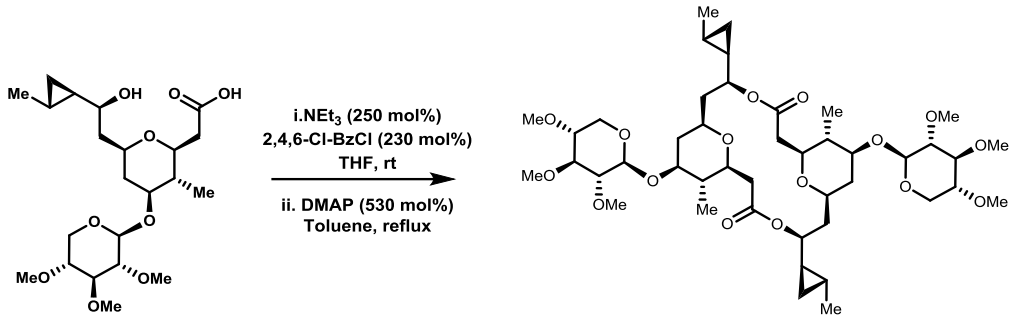
FTIR (neat): υ 3450, 2929, 1732, 1163, 1089, 986 cm^{-1}.

$[\alpha]^{29}_D$: -33.00° (c = 1.0, $CHCl_3$).


f1 (ppm)


f1 (ppm)

Clavosolide A



To a stirred solution of **11** (10.0 mg, 0.0224 mmol, 100 mol%) in THF (200 mL) was added Et_3N (7.8 µL, 0.0560 mmol, 250 mol%) and 2,4,6-trichlorobenzoyl chloride (8.0 µL, 0.0515 mmol, 230 mol%). The solution was stirred at room temperature for 2.5 h. The reaction mixture was diluted with toluene (900 µL) and added dropwise over 5 h to a solution of DMAP (14.5 mg, 0.119 mmol, 530 mol%) in toluene (4.2 mL) at 110 ºC. The reaction mixture continued to stir at 110 ºC for an additional 15 hours. The solution was cooled to room temperature and diluted with H_2O (3 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 4 mL). The combined organic phases were washed with brine (3 mL), dried (Na_2SO_4), filtered and the solvent was removed *in vacuo*. The crude material was purified via column chromatography (SiO_2, hexanes: ethyl acetate, 2:1 → 1:1) to afford clavosolide A (5.0 mg, 0.0058 mmol) as a white solid in 52% yield.

TLC (SiO_2): R_f = 0.52 (ethyl acetate: hexanes, 7:3).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.41 (td, *J* = 8.9, 1.9 Hz, 2H), 4.26 (d, *J* = 7.6 Hz, 2H), 3.95 (dd, *J* = 11.6, 5.2 Hz, 2H), 3.61 (s, 6H), 3.58 (s, 6H), 3.46 (s, 6H), 3.46 – 3.42 (m, 4H), 3.28 – 3.21 (m, 4H), 3.12 – 3.07 (m, 4H), 2.96 (dd, *J* = 9.1, 7.6 Hz, 2H), 2.54 (dd, *J* = 17.4, 3.7 Hz, 2H), 2.41 (dd, *J* = 17.3, 6.6 Hz, 2H), 2.04 (dd, *J* = 11.3, 4.8 Hz, 2H), 1.89 (dt, *J* = 15.0, 8.9 Hz, 2H), 1.68 (dt, *J* = 15.0, 2.8 Hz, 2H), 1.42 – 1.33 (m, 4H), 0.97 (d, *J* = 6.2 Hz, 12H), 0.90-0.77 (m, 2H), 0.71 (tt, *J* = 8.9, 4.7 Hz, 2H), 0.34 (dt, *J* = 8.9, 4.7 Hz, 2H), 0.22 (dt, *J* = 8.4, 4.9 Hz, 2H).

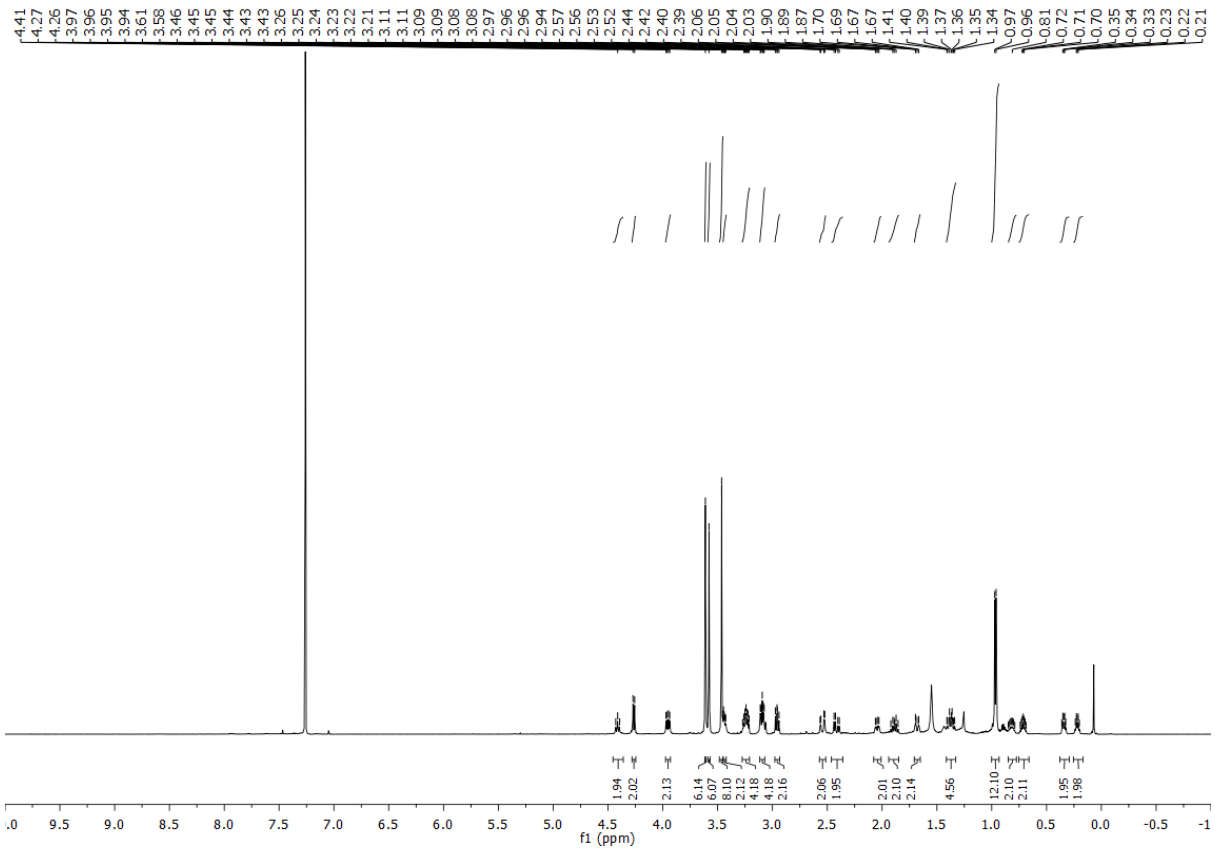
^{13}C NMR (125 MHz, $CDCl_3$): δ 171.0, 105.5, 85.6, 83.8, 83.2, 79.4, 77.1, 77.0, 74.8, 63.2, 60.8, 60.8, 58.8, 42.5, 41.3, 40.7, 39.2, 24.7, 18.5, 12.6, 11.9, 10.9.

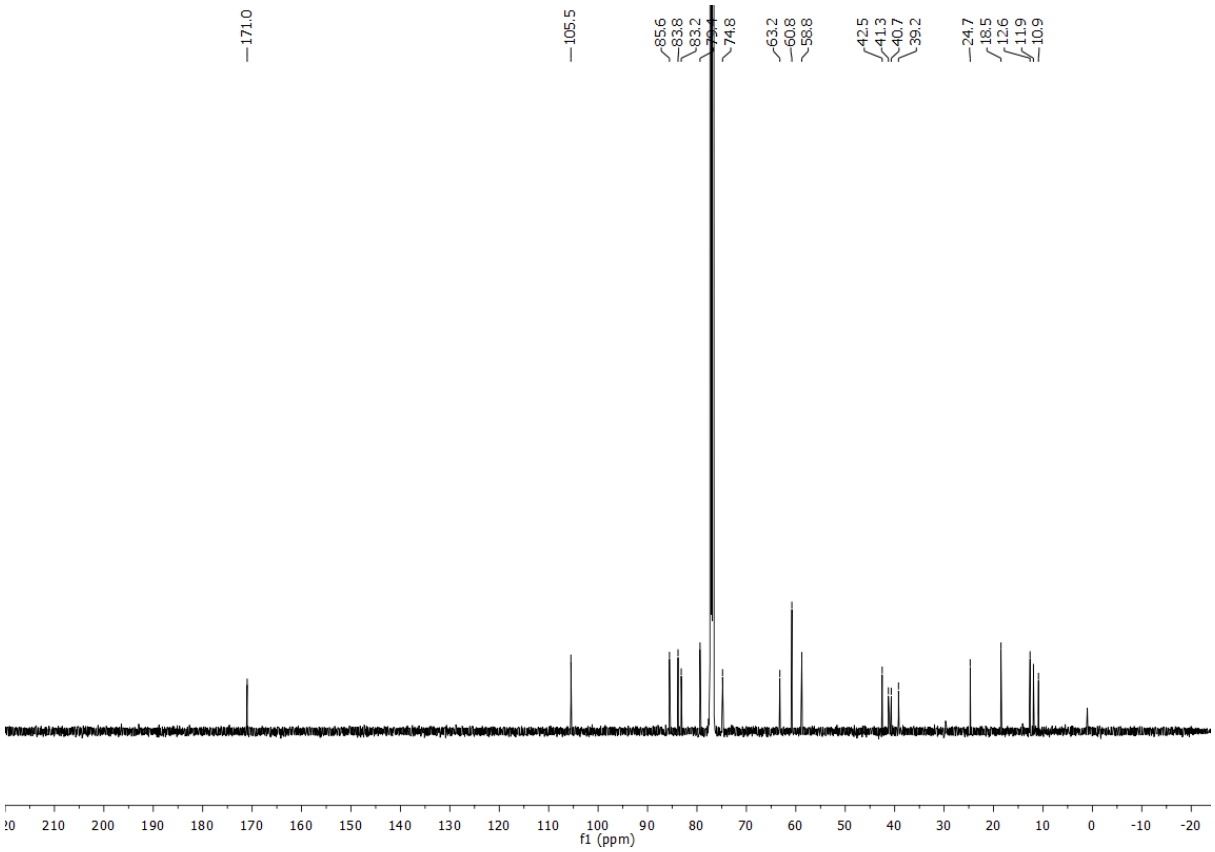
HRMS (ESI) Calculated for $C_{44}H_{72}O_{16}$ $[M+Na]^+$ = 879.4713, Found 879.4722.

FTIR (neat): υ 2935, 1733, 1163, 1090 cm^{-1}.

$[\alpha]^{26}_D$: -45.00° (c = 0.1, $CHCl_3$).

MP: 241-245 ˚C


f1 (ppm)


f1 (ppm)

^{13}C NMR of Synthetic Clavosolide A (by Krische)

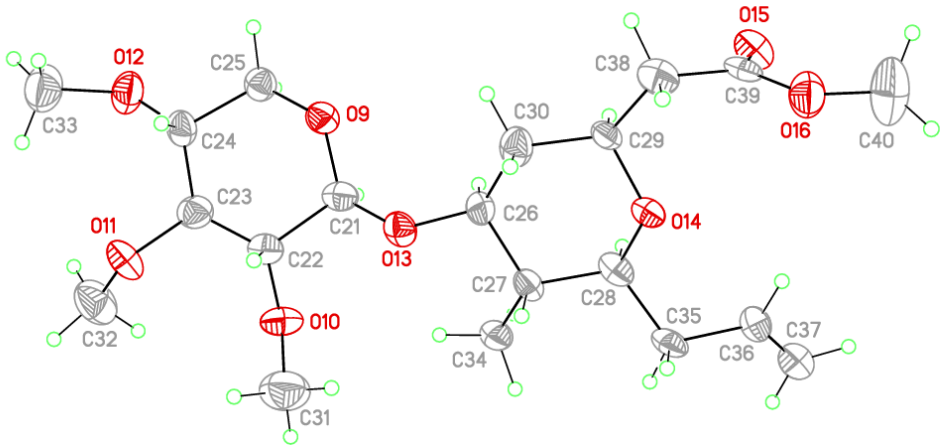
Comparison with Natural Compound (by Faulkner)[4] and Synthetic Clavosolide A (by Aggarwal)[5]

Carbon #	Faulkner	Aggarwal	Krische
1	170.7	171.0	171.0
2	39.3	39.2	39.2
3	77.0	77.0	77.0
4	42.6	42.5	42.5
5	83.1	83.2	83.2
6	40.8	40.7	40.7
7	74.8	74.8	74.8
8	41.1	41.3	41.3
9	77.1	77.1	77.1
10	24.8	24.7	24.7
11	12.0	11.9	11.9
12	18.6	18.5	18.5
13	11.0	10.9	10.9
14	12.7	12.6	12.6
15	105.4	105.5	105.5
16	83.8	83.8	83.8
17	85.6	85.6	85.6
18	79.4	79.4	79.4
19	63.2	63.2	63.2
20	60.7	60.8	60.8
21	60.8	60.8	60.8
22	58.5	58.8	58.8

Single Crystal Diffraction Data for Compound 5

Empirical formula	C20 H34 O8	
Formula weight	402.47	
Temperature	123(2) K	
Wavelength	0.71073 Å	
Crystal system	triclinic	
Space group	P 1	
Unit cell dimensions	a = 8.377(6) Å	α= 99.117(9)°.
	b = 9.361(6) Å	β= 90.212(9)°.
	c = 30.655(20) Å	γ = 112.893(7)°.
Volume	2181(2) $Å^3$	
Z	4	
Density (calculated)	1.226 Mg/m^3	
Absorption coefficient	0.094 mm^{-1}	
F(000)	872	
Crystal size	0.360 x 0.210 x 0.160 mm^3	
Theta range for data collection	0.674 to 25.247°.	
Index ranges	-10<=h<=10, -11<=k<=11, 0<=l<=36	
Reflections collected	7632	
Independent reflections	7632 [R(int) = ?]	
Completeness to theta = 25.242°	97.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00 and 0.671	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7632 / 675 / 1030	
Goodness-of-fit on F^2	0.897	
Final R indices [I>2sigma(I)]	R1 = 0.0586, wR2 = 0.1157	
R indices (all data)	R1 = 0.1485, wR2 = 0.1380	
Absolute structure parameter	1.3(8)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.337 and -0.409 $e.Å^{-3}$	

View of **5** showing the atom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level.



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