SUPPLEMENTARY MATERIALS

TABLE OF CONTENTS

GENERAL PROCEDURES

All reactions were conducted in oven- or flame-dried glassware under a nitrogen atmosphere unless otherwise noted. Reactions were concentrated under reduced pressure with a rotary evaporator unless otherwise noted. Commercial reagents were used as received or purified using the methods indicated herein. Dichloromethane, diethyl ether, dimethylformamide, pentane, tetrahydrofuran, and toluene were passed through an alumina-drying column (Solv-Tek Inc.) using nitrogen pressure; ethyl acetate, hexanes, and petroleum ether were obtained from Fisher Scientific. Analytical thin-layer chromatography (TLC) was carried out on 250 μm silica gel 60G plates with fluorescent indicator F254 (EMD Millipore). Plates were visualized with UV light and treated with *p*-anisaldehyde, ceric ammonium molybdate, or potassium permanganate stain with gentle heating. Flash column chromatography was performed using silica gel (230-400 mesh, grade 60, particle size 40 to 63 μm) purchased from Fischer Scientific. pH 7 buffered silica gel was prepared by adding 10% weight pH 7 phosphate buffer to silica and rotating for ~12 hrs. NMR spectra were acquired on a Varian INOVA 600, Varian INOVA 500, or Varian 400 magnetic resonance spectrometer. ^{1}H chemical shifts are reported relative to the residual solvent peak ($CHCl_3$ = 7.26 ppm, C_6H_6 = 7.16 ppm) as follows: chemical shift (δ), multiplicity (app = apparent, b = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, or combinations thereof), coupling constant(s) in Hz, integration. ^{13}C chemical shifts are reported relative to the residual solvent peak ($CHCl_3$ = 77.16 ppm, C_6H_6 = 128.06 ppm). Infrared spectra were acquired on a Nicolet iS 5 FT-IR Spectrometer (ThermoFisher). Optical rotations were acquired on a P-2000 Digital Polarimeter (Jasco). High-resolution mass spectra (HRMS) were acquired at the Vincent Coates Foundation Mass Spectrometry Laboratory at Stanford.

Experimental procedures were generally optimized on a small scale, and the results from these optimized procedures are provided below. In addition, for several reactions, gram-to-multigram procedures are also provided. Reaction procedures were performed by multiple investigators to establish the reproducibility of the procedure. While characterization data is provided for all isolable compounds, for several reactions, the reaction product could be used without purification as a way to reduce cost, time, and waste from chromatography. **CAUTION**: Because the hazardous nature of all new compounds is unknown, all procedures were conducted with full personal protective equipment and in a way that avoids exposure.

GRAPHICAL SUMMARY

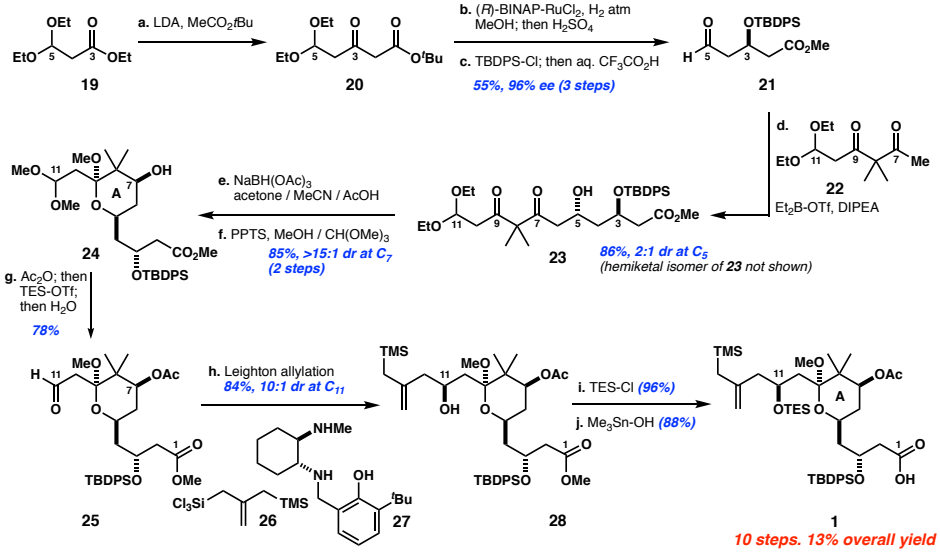


Fig. S1: Synthesis of A-ring subunit, 1

GRAPHICAL SUMMARY

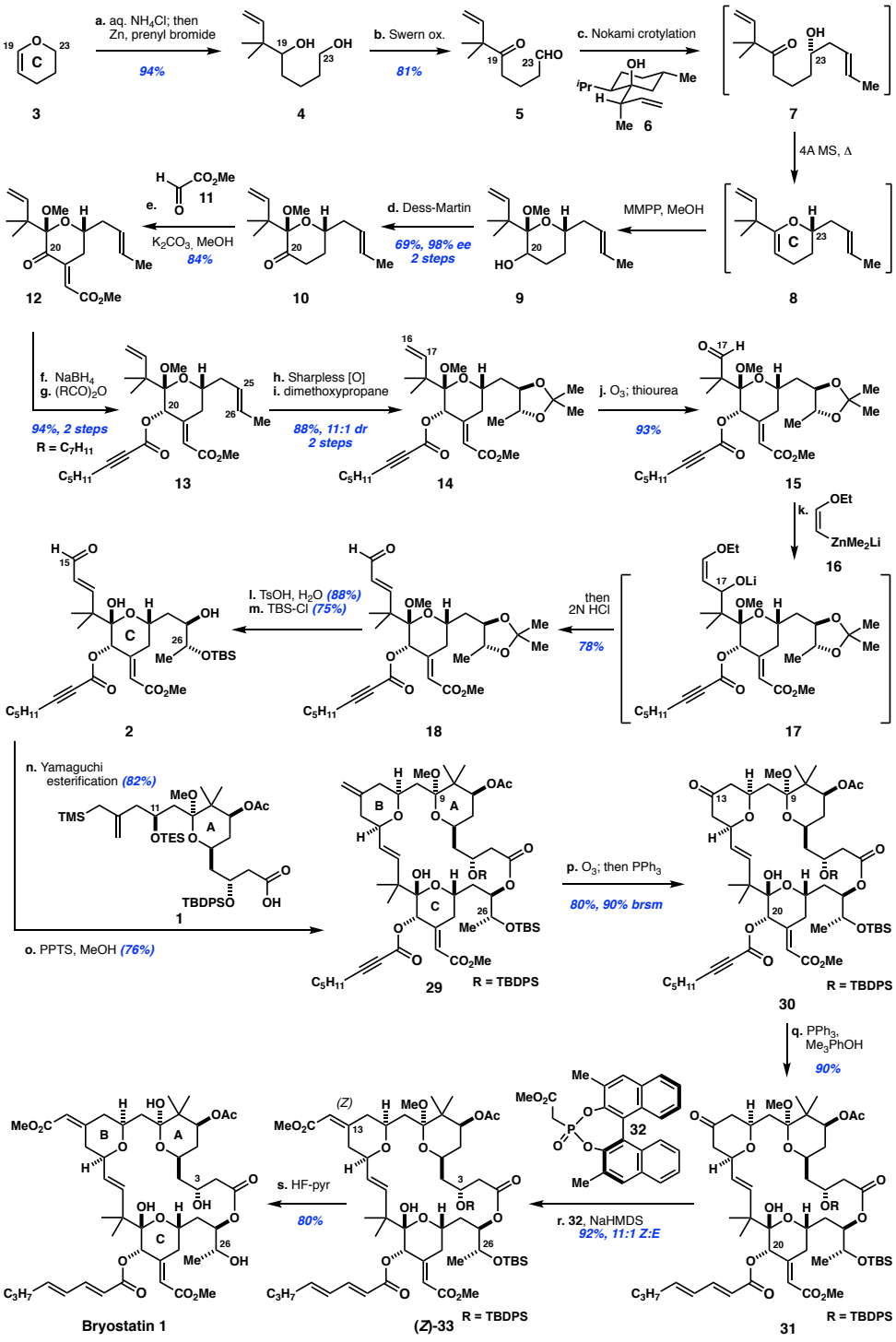
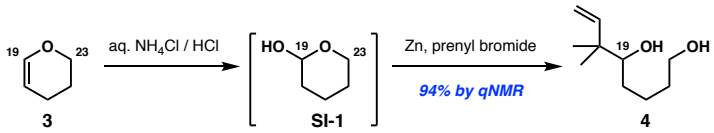


Fig. S2: Longest Linear Sequence to Bryostatin 1

EXPERIMENTAL PROCEDURES

C-ring subunit Step a: conversion of dihydropyran 3 to diol 4



Chemicals:
3,4-dihydro-*2H*-pyran **3** (Sigma-Aldrich): used without purification
Prenyl bromide: purchased from Sigma-Aldrich and distilled prior to use; alternatively, prepared from prenol and phosphorus tribromide (*55*) and stored in the dark at -20 ºC over silver wire
Zinc dust, 325 mesh (Sigma-Aldrich): used without purification

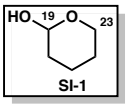
The following procedure was adapted from Cheng, H.S.; *et al.* (*31).*

To a one-neck, 250 mL round-bottom flask equipped with magnetic stir bar was added saturated aqueous NH_4Cl (23 mL) and 0.01 M HCl (1.2 mL) to obtain a pH between 3.5-4. 3,4-Dihydro-2H-pyran **3** (2.35 mL, 25.76 mmol, 1 equiv) was added via syringe over 1 min, during which time the solution became opaque with oily droplets. For the first hour, the pH was monitored and adjusted to maintain a stable pH between 3.5-4 (overall, 0.8 mL of 0.01M HCl were added). The hydrolysis of **3** to **SI-1** was monitored by TLC and determined to be complete after 18h (Note 1). The now-homogeneous reaction mixture was cooled with an ice bath (0 ºC). THF (20 mL) was added, followed by zinc powder (5.73 g, 88.2 mmol, 3.4 equiv) as a single portion, and a solution of prenyl bromide (5.09 mL, 44.1 mmol, 1.7 equiv) in Et_2O (~2 mL) via syringe over ~10 min. After vigorously stirring for 5 min, TLC analysis indicated complete conversion of **SI-**1 and formation of **4**. The reaction mixture was directly concentrated via rotary evaporator to remove THF. The resulting aqueous mixture was diluted with 10% HCl (100 mL) to hydrolyze any tetrahydropyran-protected product, **SI-2** (Note 2). After 1.5h, the reaction mixture was filtered over a plug of cotton (with copious water washings) to remove zinc. The filtrate was then transferred to a separatory funnel. The aqueous layer was extracted with EtOAc (200 mL, then 10x50 mL) until TLC of the aqueous layer no longer showed product. The combined organic layers were washed with a 1:1 mixture of saturated aqueous $NaHCO_3$ and brine (100 mL). This aqueous layer was then extracted with EtOAc (8x50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. This oil was diluted with CH_2Cl_2 (10 mL) and re-concentrated (repeated 5X to facilitate EtOAc removal) to afford crude diol **4** (4.25g, 24.4 mmol, 94% yield based on quantitative ^{1}H-NMR; see spectra below) as a viscous, cloudy, pale yellow oil. Crude diol **4** was between 90-94% pure as determined by quantitative ^{1}H-NMR using dimethyl phthalate as an internal standard. In practice, this material was sufficiently clean to employ for the subsequent Swern oxidation (step **b**); however, crude diol **4** may be purified using one of two procedures: (A) purification by distillation (bp 85-95 °C at ~1 mmHg) to yield clear, colorless material with 96% purity (qNMR); (B) purification by silica gel flash column chromatography to yield material with >99% purity (qNMR). Characterization data matched literature values reported by Cheng, H.S.; *et al.* (*31*).

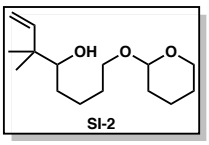
TLC R_f = 0.36 (50% EtOAc/pentane), dark blue spot in *p*-anisaldehyde

^{1}H-NMR (600 MHz, $CDCl_3$) δ 5.81 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.11 – 5.02 (m, 2H), 3.70 – 3.60 (m, 2H), 3.26 (dd, *J* = 10.5, 1.8 Hz, 1H), 1.74 – 1.48 (m, 6H, includes 2xOH), 1.44 – 1.34 (m, 1H), 1.32 – 1.23 (m, 1H), 1.004 (s, 3H), 1.000 (s, 3H)

^{13}C-NMR (125 MHz, $CDCl_3$) δ 145.5, 113.5, 78.3, 62.8, 41.8, 32.6, 31.0, 23.3, 23.2, 22.2



Note 1: Data for 2-hydroxy-tetrahydropyran **SI-1**: **TLC** R_f = 0.36 (50% EtOAc/Hex), green spot in *p*-anisaldehyde; **^{1}H-NMR** (400 MHz, $CDCl_3$) diagnostic peaks δ 4.90 (t, *J* = 5.5, 5.5 Hz, 1H), 4.05 – 3.95 (m, 1H), 3.58 – 3.49 (m, 1H)

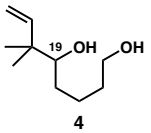


Note 2: On larger-scale (250 mmol) reactions, we have observed small amounts (typically <3%) of the tetrahydropyran-protected diol, **SI-2**. Data for **SI-2**: **TLC** R_f = 0.76 in 50% EtOAc/Hex; **^{1}H-NMR** (400 MHz, $CDCl_3$): diagnostic peaks δ 5.81 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.10 – 5.01 (m, 2H), 4.59 – 4.55 (m, 1H).

On Decagram-Scale: To a one-neck, 1L round-bottom flask equipped with magnetic stir bar was added saturated aqueous NH_4Cl (230 mL) and 0.01M HCl (~12 mL) to obtain a pH between 3.5-4. 3,4-dihydro-2H-pyran **3** (assume 97% pure, 23.5 mL, 250 mmol, 1 equiv) was added via syringe over 5 min, during which time the solution became opaque with oily droplets. For the first hour, the pH was monitored and adjusted (by addition of 0.01M HCl) to maintain a pH between 3.5-4. The hydrolysis of **3** to **SI-1** was monitored by TLC and determined to be complete after 18h. The now-homogeneous reaction mixture was cooled with an ice bath (0 ºC). THF (200 mL) was added, followed by zinc powder (49 g, 750 mmol, 3 equiv) as a single portion, and prenyl bromide (55.9 mL of 80% w/w Et_2O, 375 mmol, 1.5 equiv) via syringe over ~10 min. After 5 min of vigorous stirring, TLC analysis indicated incomplete conversion of **SI-1**. Therefore, additional zinc powder (4g, 61 mmol, 0.25 equiv) and prenyl bromide (8.1 mL, 70 mmol, 0.3 equiv) were sequentially added, each as single portions (Note 1). After 5 additional min, TLC analysis indicated complete conversion of **SI-1** and formation of **4**. The reaction mixture was directly concentrated via rotary evaporator to remove THF. The resulting aqueous mixture was diluted with EtOAc (300 mL) and 5% HCl (500 mL). The layers were shaken and separated, and the aqueous layer was extracted with EtOAc (4x300 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (250 mL), brine (250 mL), dried over $MgSO_4$, and concentrated to afford a viscous, yellow oil. This oil was then re-suspended in CH_2Cl_2 (100 mL) and re-concentrated to afford crude diol **4** (38.5g crude weight, 224 mmol), which was used in the next step without purification.

Note 1: We have observed that additional zinc and prenyl bromide are not always necessary to achieve full conversion of tetrahydro-2H-pyran-2-ol **SI-1** on 250-mmol scale.

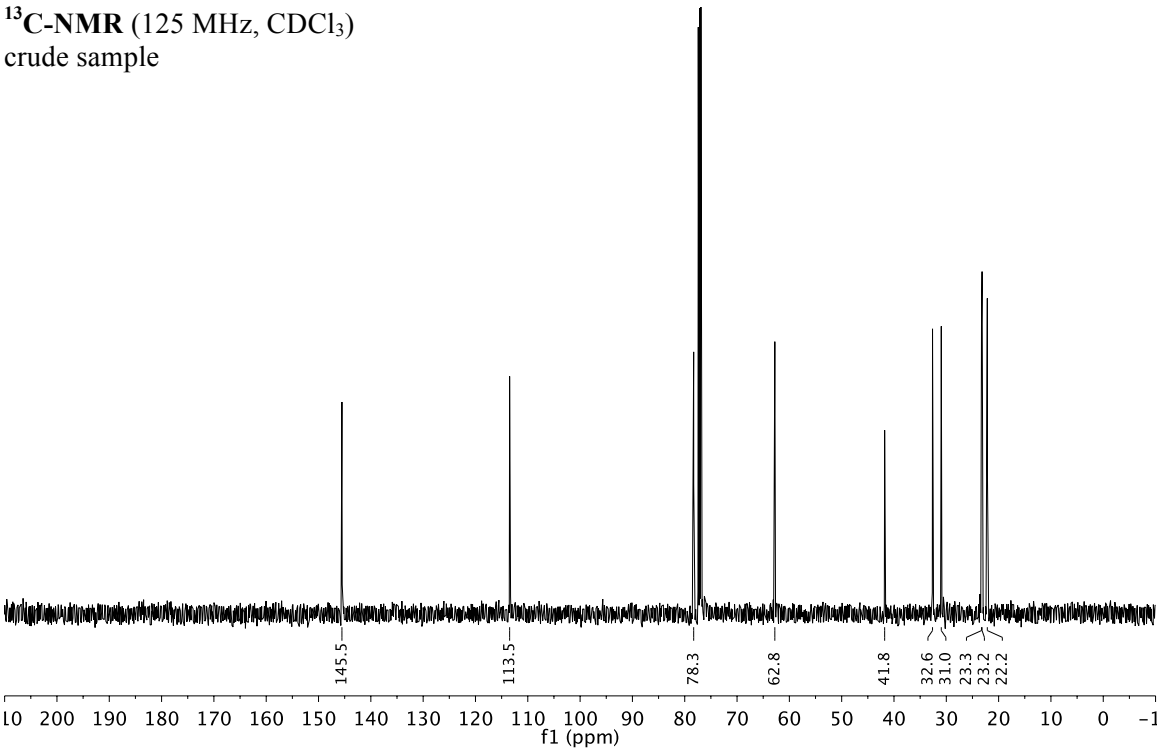
Experimentalists: QLN, MSJ, RVQ, AJS, JLS, MCS, JHT



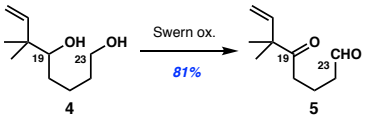
4

^{1}H-NMR (600 MHz, $CDCl_3$)
crude sample

^{13}C-NMR (125 MHz, $CDCl_3$)
crude sample



C-ring subunit Step b: conversion of diol 4 to ketoaldehyde 5



Chemicals:
Oxalyl chloride (98%, Sigma-Aldrich): used without purification
DMSO (99.7+%, ExtraDry, Acros): used without purification
Triethylamine (Sigma-Aldrich): distilled from CaH_2 prior to use

To a flame-dried, three-neck, 2L round-bottom flask equipped with magnetic stir bar, addition funnel, and internal reaction thermometer was added CH_2Cl_2 (~800 mL, 0.2M) and oxalyl chloride (40.5 mL, 463 mmol, 3 equiv). The reaction mixture was cooled with a dry ice/acetone bath (-78 ºC). A solution of DMSO (43.85 mL, 617 mmol, 4 equiv) in CH_2Cl_2 (50 mL) was added dropwise via addition funnel (**CAUTION:** gas evolution), at a rate that maintained the internal temperature below -65 ºC (~35 min). After 25 min at -78º C, a solution of diol **4** (26.6g, 154 mmol, 1 equiv) in CH_2Cl_2 (100 mL) was added dropwise via addition funnel, at a rate that maintained the internal temperature below -65 ºC (~15 min). The solution turned opaque and milky white during the course of this addition. After vigorously stirring for 2h at -78 ºC, triethylamine (172 mL, 1.23 mol, 8 equiv) was added dropwise via addition funnel, at a rate that maintained the internal temperature below -65 ºC (~25 min). Upon completion of addition, the reaction mixture was removed from the ice bath and stirred until the internal temperature reached -30 ºC (~15 min). The reaction mixture was then poured into a separatory funnel containing 1M HCl (1.2L) and pentane (800 mL). The layers were separated, and the aqueous layer was extracted with pentane (2x500 mL). The combined organic layers were washed with water, brine, dried over $MgSO_4$, filtered, and concentrated to afford an orange oil (87% yield by quantitative ^{1}H-NMR using an internal standard, Note 1). Purification was accomplished by silica gel flash column chromatography (25% Et_2O/pentane) affording ketoaldehyde **5** (20.9g, 81% yield) as a straw-colored oil (Note 2). Compound purity was established by TLC (one spot) analysis.

Note 1: Notwithstanding the appearance of the crude ^{1}H-NMR, crude ketoaldehyde **5** should be chromatographically purified to remove ^{1}H-NMR-silent impurities.

Note 2: Ketoaldehyde **5** can also be purified by distillation (bp 73-75 °C at ~3 mmHg), affording ketoaldehyde **5** in 70% yield (10.0 g scale).

TLC R_f = 0.28 (30% Et_2O / petroleum ether, dark purple spot by *p*-anisaldehyde)

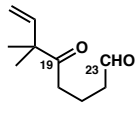
IR (thin film) 3625, 3400, 3088, 2974, 2826, 2724, 1727, 1713, 1634, 1470, 1413, 1366, 1243, 1099, 1057, 998, 923 cm^{-1}

^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.73 (t, *J* = 1.5 Hz, 1H, CHO), 5.92 – 5.83 (m, 1H), 5.16 – 5.09 (m, 2H), 2.51 (t, *J* = 7.0 Hz, 2H), 2.43 (td, *J* = 7.1, 1.5 Hz, 2H), 1.86 (app. p, *J* = 7.1 Hz, 2H), 1.21 (s, 6H)

^{13}C-NMR (100 MHz, $CDCl_3$) δ 212.4, 202.1, 142.5, 114.7, 50.9, 43.1, 36.3, 23.6, 16.5

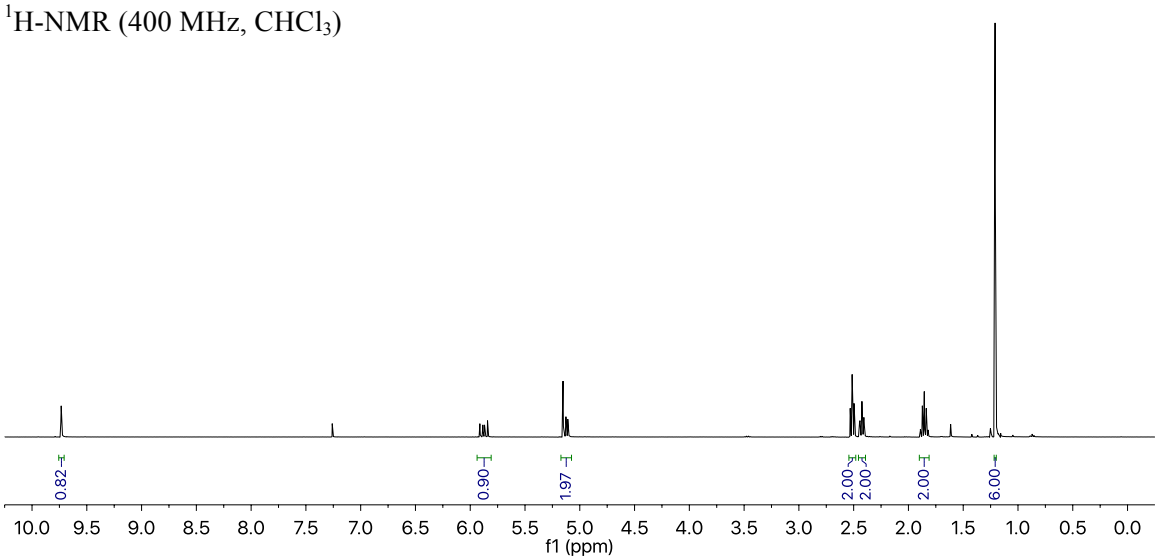
HRMS calculated for $C_{10}H_{17}O_2$ $[M+H]^+$: 169.1229; found 169.1223 (TOF ESI+)

Experimentalists: JLS, MSJ, RVQ, AJS, MCS, JHT

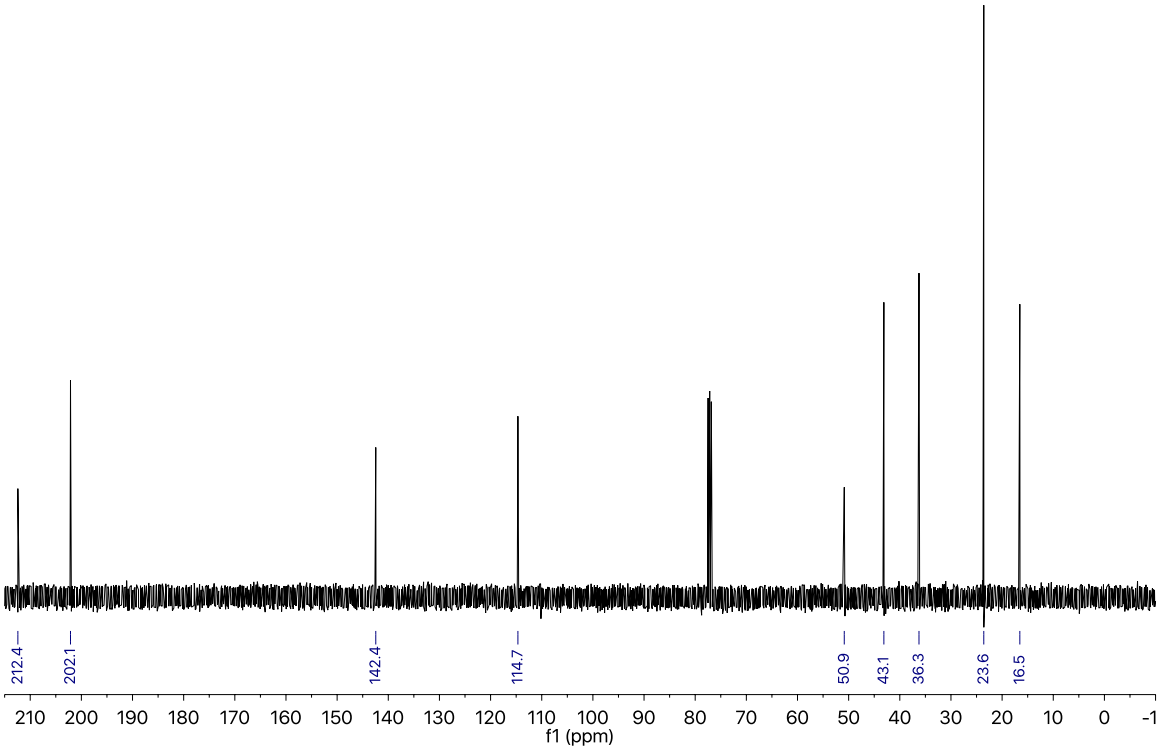


5

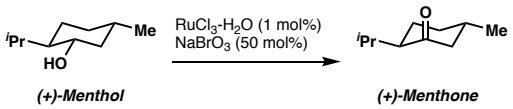
^{1}H-NMR (400 MHz, $CHCl_3$)



^{13}C-NMR (100 MHz, $CHCl_3$)



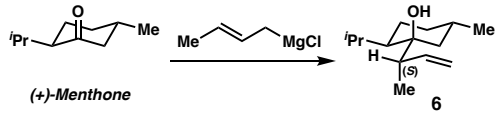
C-ring subunit: preparation of crotyl transfer reagent 6



Chemicals:
(+)-menthol (Alfa Aesar): used without purification
$RuCl_3$-hydrate (35-40% Ruthenium, Acros Organics): used without purification
$NaBrO_3$ (>99%, Sigma-Aldrich): used without purification

The following procedure was adapted from Yamamota, Y.; *et al.*'s seminal report (*56*) and Fleitz, F.J.; *et al.*'s ruthenium oxidation on kilogram-scale (*57*) :

To a flame-dried, three-neck, 2L round-bottom flask equipped with magnetic stir bar, addition funnel, and internal reaction thermometer was sequentially added (+)-menthol (50.0g, 320 mmol, 1 equiv), 1:1 MeCN/H_2O (600 mL, 0.53M), and $RuCl_3$-hydrate (664 mg, 3.2 mmol, 1 mol%). A solution of $NaBrO_3$ (24.1g, 160 mmol, 50 mol%) in H_2O (80 mL) was sonicated to ensure homogeneity and then added dropwise via addition funnel, at a rate that maintained the internal temperature below 31 ºC (addition time of 20 min); additional H_2O (20 mL) was used to rinse the addition funnel. After 2h, the reaction mixture was diluted with pentane (500 mL) and quenched with saturated aqueous $NaHCO_3$ (600 mL). The layers were separated, and the aqueous layer was re-extracted with pentane (500 mL). The combined organic layers were washed with saturated aqueous $NaHSO_3$ (350 mL), H_2O (3x300 mL), dried over $MgSO_4$, filtered, and concentrated to afford crude (+)-menthone (47.3g weight, 96% yield) as a dark green oil, containing trace amounts of ruthenium. This crude material was used in the next step without purification. Characterization data matched literature values.



Chemicals:
Magnesium turnings (99%, Alfa Aesar): pre-activated by sequential washing with 1M HCl and EtOH; dried under vacuum
1,2-Dibromoethane (98%, Sigma-Aldrich): used without purification
Crotyl chloride (~19:1 *E*:*Z*): prepared from crotyl alcohol (Alfa Aesar, ~19:1 *E*:*Z*) and mesyl chloride in DMF. Procedure adapted from Franczyk, T. S.; *et al*. (*58*).

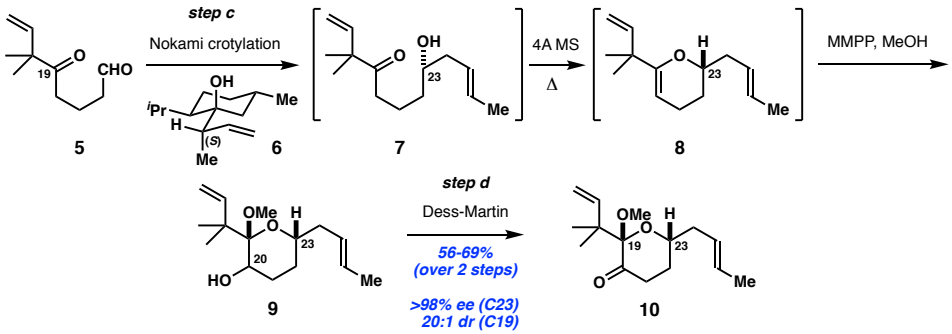
The following procedure was adapted from: Nokami, J.; *et al.* (*32*)

To a flame-dried, three-neck, 2L round-bottom flask equipped with magnetic stir bar, 500 mL addition funnel, and internal reaction thermometer was added magnesium turnings (16.2g, 667 mmol, 3.4 equiv) and 1,2-dibromoethane (0.05 mL). The magnesium turnings were vigorously stirred for 15 min at which point THF (~500 mL) was added. The reaction mixture was cooled with an ice bath (0 ºC). A solution of crotyl chloride (30.2 g, 333 mmol, 1.7 equiv) in THF (~200 mL) was added dropwise via addition funnel, at a rate that maintained the internal temperature below 15 ºC (addition time of 2.5h). Over the course of addition, the solution became gray and turbid. After 45 min, the reaction mixture was cooled with a dry ice/brine bath (-10 ºC). A ~1M solution of menthone (30.3g, 196 mmol, 1 equiv) in THF (~200 mL; final concentration ~0.2M) was added dropwise via addition funnel, at a rate that maintained the internal temperature below -

7 ºC (addition time of 55 min); additional THF (20 mL) was used to rinse the addition funnel. After 25 min, the reaction mixture was quenched by adding brine (700 mL), resulting in the formation of white solids. The solution was decanted from these white solids into a separatory funnel. The reaction flask was washed with Et_2O (2x500 mL). The layers were separated, and the organic layers were dried over $MgSO_4$, filtered, and concentrated to afford a yellow oil (~6:1 dr by ^{1}H-NMR analysis). Purification was accomplished by silica gel flash column chromatography (5% Et_2O/pentane) affording diastereomerically pure transfer reagent **6** (32.2g, 78% yield) as a colorless oil. Compound purity was established by TLC (one spot) analysis. Characterization data matched literature values reported by Nokami, J; *et al.* (*32*).

Experimentalists: AJS, MSJ, RVQ, JLS

C-ring subunit Steps c-d: conversion of ketoaldehyde 5 to ketone 10



<Step c>

Chemicals:

Chloroform (Fisher, HPLC grade, pentene stabilized (~50 ppm)): used without purification

p-TsOH-H_2O (≥98%, Sigma-Aldrich): used without purification

4Å powdered molecular sieves (Sigma-Aldrich): the quality and type of molecular sieves are critical to reaction success; the powdered molecular sieves should be rigorously dried in a vacuum oven (150 °C) for several days to ensure complete activation

$NaHCO_3$ (Sigma-Aldrich): used without purification

Methanol (99.8% Extra Dry, Acros): used without purification

MMPP-$6H_2O$ (80% grade, Sigma-Aldrich): used without purification

The following procedure was adapted from Nokami, J.; *et al.* (*32*).

To a flame-dried, three-neck, 1L round-bottom flask equipped with reflux condenser and magnetic stir bar was sequentially added keto-aldehyde **5** (3.03 g, 18.0 mmol, 1 equiv), chloroform (180 ml, 0.1 M), crotyl transfer reagent **6** (7.58 g, 36.0 mmol, 2 equiv), and *p*-TsOH-H_2O (342 mg, 1.80 mmol, 10 mol%). The crotylation reaction was stirred for 22h, during which time the solution gradually became dark yellow/orange. After 22h, TLC analysis indicated complete conversion of keto-aldehyde **5**. 4Å powdered molecular sieves (27 g) were added in two portions, followed by additional *p*-TsOH-H_2O (342 mg, 1.80 mmol, 10 mol%). The flask was then placed in a 70 °C oil bath. After refluxing for 5h, the cyclodehydration from **7** to **8** was complete as determined by TLC (**8**: TLC R_f = 0.5 in 100% pentane). The reaction mixture was cooled with an ice bath (0 °C), and solid $NaHCO_3$ (3.03 g, 36.0 mmol, 2 equiv) was added in a single portion, followed by methanol (60 mL). MMPP-$6H_2O$ (80% pure, 5.02 g, 8.11 mmol, 0.45 equiv) was added in a single portion. After 40 min at 0 °C, the reaction mixture was poured into a separatory funnel containing Et_2O (1L) and saturated aqueous $NaHCO_3$ (750 mL) (Note: the molecular sieves settle to the bottom, aqueous layer). The layers were separated, and the aqueous layer was extracted with Et_2O (500 mL). The combined organic layers were washed with water (500 mL), brine (500 mL), dried over $MgSO_4$, filtered, and concentrated to afford crude alcohol **9** (~2:1 dr at C20) as a yellow/orange oil. This crude material was used immediately in the next step without purification, as alcohol **9** will decompose upon storage.

<Step d>

Chemicals:

Dess-Martin Periodinane (95%, AK Scientific): used without purification; stored at 4 °C

pyridine (Sigma-Aldrich): distilled from CaH_2 before use

To a flame-dried, three-neck, 500 mL round-bottom flask equipped with magnetic stir bar was added Dess-Martin Periodinane (95% pure, 12.12 g, 27.03 mmol, 1.5 equiv) and CH_2Cl_2 (140

mL). The resulting clear and colorless solution was cooled with an ice bath (0 °C). Pyridine (14.5 mL, 180 mmol, 10 equiv) was added via syringe, followed by a solution of crude alcohol **9** (assume 18.0 mmol, 1 equiv) in CH_2Cl_2 (20 mL with two washes, final concentration ~0.1M). The reaction mixture and ice bath were allowed to warm to room temperature. After 19.5h, TLC analysis indicated complete conversion of alcohol **9** and formation of ketone **10**. The now-orange solution was poured into a separatory funnel containing CH_2Cl_2 (1L), saturated aqueous sodium thiosulfate (400 mL), and brine (200 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (500 mL). The combined organic layers were sequentially washed with saturated aqueous $NaHCO_3$ (500 mL) (**CAUTION**: gas evolution), 1M HCl (500 mL), water (500 mL), and brine (500 mL). The combined organic layers were then dried over $MgSO_4$, filtered, and concentrated. Purification was accomplished by silica gel flash column chromatography (0-10% Et_2O/petroleum ether) affording a 4:1 molar ratio of ketone **10** and isomenthone (Note 1). This mixture was then placed under vacuum (~1 mmHg) for two days to remove isomenthone, affording a pure sample of ketone **10** (3.12 g, 20:1 dr at C19, 69% combined yield over 2 steps) as a yellow oil. Compound purity was established by TLC (one spot) analysis.

Note 1: Crotyl transfer reagent **6** is converted into menthone as a result of the crotylation reaction. Some of this menthone then epimerizes to isomenthone, which partially co-elutes with ketone **10**.

TLC R_f = 0.63 (10% EtOAc/pentane, purple spot in *p*-anisaldehyde)

$[\alpha]^{22.2}_D$ = -21.3° (*c* = 2.6, CH_2Cl_2)

IR (thin film) 3084, 2968, 2934, 2857, 2831, 1727, 1637, 1448, 1414, 1378, 1360, 1114, 1048, 969, 917, 690 cm^{-1}

^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.22 – 6.15 (m, 1H), 5.60 – 5.46 (m, 2H), 5.03 – 4.98 (m, 2H), 3.83 (dq, *J* = 8.3, 6.0 Hz, 1H), 3.28 (s, 3H), 2.52 – 2.39 (m, 2H), 2.39 – 2.32 (m, 1H), 2.30 – 2.22 (m, 1H), 1.94 – 1.86 (m, 2H), 1.70 – 1.67 (m, 3H), 1.15 (s, 3H), 1.08 (s, 3H)

^{13}C-NMR (125 MHz, $CDCl_3$) δ 207.4, 144.3, 128.4, 126.4, 112.6, 104.0, 72.7, 51.7, 44.8, 38.9, 37.2, 28.7, 22.5, 22.2, 18.2

HRMS calculated for $C_{15}H_{24}NaO_3$ $[M+Na]^+$: 275.1618; found 275.1624 (TOF ESI+)

On Decagram-Scale: <Step c> To a flame-dried, 2L round-bottom flask equipped with magnetic stir bar was sequentially added keto-aldehyde **5** (19.2 g, 114.4 mmol, 1 equiv), chloroform (1.14 L, 0.1 M), crotyl transfer reagent **6** (48.1 g, 228.7 mmol, 2 equiv), and *p*-TsOH-H_2O (2.2 g, 11.4 mmol, 10 mol%). The crotylation reaction was stirred for 22h, during which time the solution gradually became dark yellow/orange (Note 1). 4Å powdered molecular sieves (150 g) were then added, followed by additional *p*-TsOH-H_2O (2.2 g, 11.4 mmol, 10 mol%). The 2L round-bottom flask was affixed with a reflux condenser and heated to 65 °C with a heating mantle. After refluxing for 5h, the cyclodehydration from **7** to **8** was complete as determined by TLC (**8**: TLC R_f = 0.5 in 100% pentane). The reaction mixture was cooled with an ice bath (0 ºC), and solid $NaHCO_3$ (19.2 g, 228.7 mmol, 2 equiv) was added in a single portion, followed by methanol (380 mL). MMPP-$6H_2O$ (80% pure, 31.8 g, 51.5 mmol, 0.45 equiv) was then added in several portions over the course of 1 min. After 40 min at 0 ºC, the reaction mixture was poured into a separatory funnel containing Et_2O and saturated aqueous $NaHCO_3$ (Note: the molecular sieves settle to the bottom, aqueous layer). The layers were separated, and the aqueous layer was extracted with

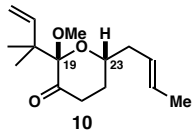
Et_2O. The combined organic layers were washed with water, brine, dried over $MgSO_4$, filtered, and concentrated under vacuum at room temperature to afford crude alcohol **9** (~2:1 dr at C20) as a yellow/orange oil. This crude material was used immediately in the next step without purification, as alcohol **9** will decompose upon storage.

Note 1: A small portion of material from an analogous reaction was quenched and purified to afford alcohol **7**, which was >98% ee as determined by Mosher ester analysis according to: Hoye, T.R.; *et al.* (*59*).

<Step d> To a flame-dried, 2L round-bottom flask equipped with magnetic stir bar was added Dess-Martin Periodinane (95% pure, 77 g, 171.5 mmol, 1.5 equiv) and CH_2Cl_2 (500 mL). The resulting clear and colorless solution was cooled with an ice bath (0 ºC). Pyridine (92 mL, 1.14 mol, 10 equiv) was added, followed by a solution of crude alcohol **9** (assume 114.4 mmol, 1 equiv) in CH_2Cl_2 (500 mL with two washes, final concentration ~0.1M). The reaction mixture and ice bath were allowed to warm to room temperature. After 19.5h, TLC analysis indicated complete conversion of alcohol **9** and formation of ketone **10**. The now-orange solution was poured into a separatory funnel containing saturated aqueous sodium thiosulfate and brine. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were sequentially washed with saturated aqueous $NaHCO_3$ (**CAUTION**: gas evolution), 1M HCl, water, and brine. The combined organic layers were then dried over $MgSO_4$, filtered, and concentrated. Purification was accomplished by silica gel flash column chromatography (0-5-10% Et_2O/petroleum ether) affording unreacted transfer reagent **6** (19.8g, 82% recovered yield) and a mixture of ketone **10** (16.05g, >20:1 dr at C19, >95% pure, 56% combined yield over 2 steps) and isomenthone (~3.9g) (Note 1).

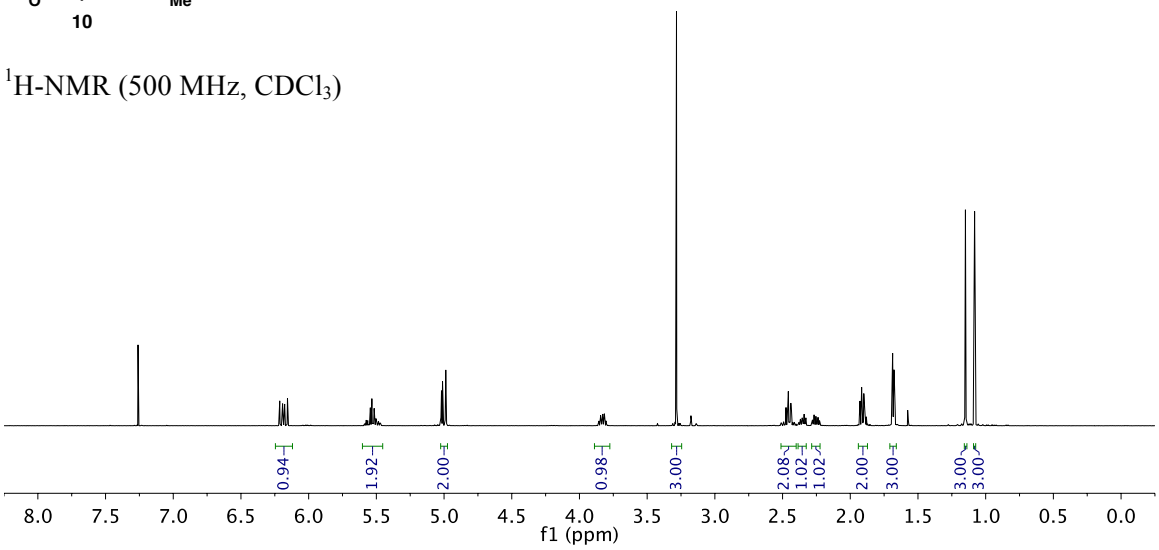
Note 1: Crotyl transfer reagent **6** is converted into menthone as a result of the crotylation reaction. Some of this menthone then epimerizes to isomenthone, which partially co-elutes with ketone **10**. Isomenthone can be removed from ketone **10** by placing the mixture of compounds under vacuum for several days (oil bath 30 ºC, ~1 mmHg). However, in practice, small amounts of isomenthone can be carried into the subsequent aldol reaction without affecting the yield of that reaction.

Experimentalists: CTH, RVQ, MSJ, SMR, AJS, JLS, MCS, JHT

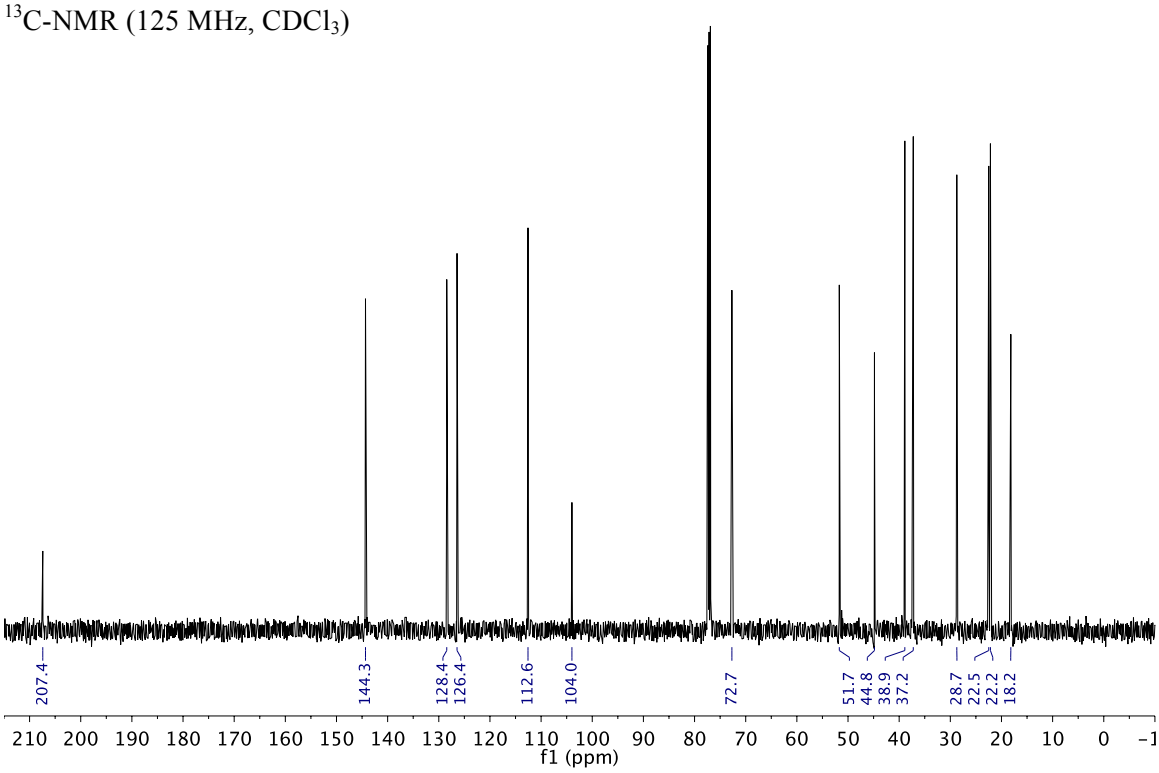


10

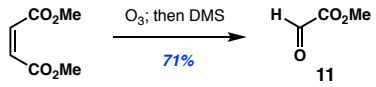
^{1}H-NMR (500 MHz, $CDCl_3$)



^{13}C-NMR (125 MHz, $CDCl_3$)



C-ring subunit: preparation of methyl glyoxylate, 11



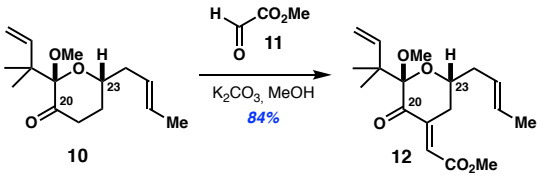
Chemicals:
dimethyl maleate (96%, Sigma-Aldrich): used without purification
dimethyl sulfide (99%, Acros Organics): used without purification

To a 500 mL round-bottom flask equipped with magnetic stir bar was added dimethyl maleate (20g, 138.8 mmol, 1 equiv) and CH_2Cl_2 (200 mL, ~0.7M). The reaction mixture was cooled with a dry ice/acetone bath (-78 °C). Ozone (~4 LPM, prepared with 70 V) was bubbled through the solution until a bright blue color persisted (~1.5h), at which point the ozone generator was turned off, and nitrogen was bubbled through the solution until the blue color disappeared. Dimethyl sulfide (12.2 mL, 166 mmol, 1.2 equiv) was added via syringe (2 min), and the reaction mixture and ice bath were allowed to warm to room temperature. After 18h, analysis by peroxide test strips indicated complete reduction of ozonide. The reaction mixture was directly concentrated via rotary evaporator to remove CH_2Cl_2 and most of the unreacted dimethyl sulfide. Purification was accomplished via distillation. The round-bottom flask was affixed with a Vigreux column coupled to a short-path distillation head and placed in a 100 °C oil bath under reduced pressure (80 mmHg). The first fraction (~1 mL), which contained DMSO, was discarded. Methyl glyoxylate **11** was then collected at 55-65 °C, 80 mmHg (17.3g, 71% yield) as a colorless oil. **11** was found to exothermically polymerize if kept neat; therefore, **11** was immediately dissolved in anhydrous THF for the subsequent aldol reaction (Note 1). Of note, the polymer can be cracked using a heat gun under vacuum to return the monomer. Characterization data matched literature values reported by Donohoe, T.; *et al*. (*60*) and Kelly, R.; *et al.* (*61*).

Experimentalists: AJS, RVQ, MCS

Note 1: Methyl glyoxylate can be temporarily stored (~weeks) as a 2.5 M solution in THF at 0 °C.

C-ring subunit Step e: conversion of ketone 10 to (*E*)-enoate 12



Chemicals:
potassium carbonate (J.T. Baker): used without purification
methyl glyoxylate: distilled prior to use and dissolved to afford a 2-2.5M THF solution
Methanol (99.8% Extra Dry, Acros): used without purification

To a flame-dried, one-neck, 100 mL round-bottom flask equipped with magnetic stir bar was added ketone **10** (1.51g, 5.97 mmol, 1 equiv) and THF (33 mL, 0.18M). Potassium carbonate (4.52 g, 32.7 mmol, 5.5 equiv) was added in a single portion, with vigorous stirring. To the resulting suspension was added methyl glyoxylate **11** (2M THF, 15 mL, 30 mmol, 5 equiv) via syringe (addition time of 1 min), followed by methanol (11 mL) via syringe (addition time of 1 min). The final reaction mixture consisted of a ~0.1M solution of 4.4:1 THF/MeOH. Upon addition of methanol, the suspension turned bright yellow, slowly darkening to orange over the course of the reaction. After 1h, TLC analysis indicated complete conversion of ketone **10**. The reaction mixture was poured into a separatory funnel containing saturated aqueous NH_4Cl (250 mL). The layers were separated, and the aqueous layer was extracted with 1:1 Et_2O/pentane (3x250 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford a crude, yellow oil. Purification was accomplished by silica gel flash column chromatography (5% EtOAc/pentane) affording (*E*)-enoate **12** (1.61g, 84% yield) as a neon yellow oil. Compound purity was established by TLC (one spot) analysis.

TLC R_f = 0.54 (10% EtOAc/pentane, UV active, purple spot in *p*-anisaldehyde)

[α]$^{23.1}_{D}$ = -124.1° (*c* = 0.75, CH_2Cl_2)

IR (thin film) 3085, 2951, 2918, 2833, 1726, 1709, 1634, 1436, 1357, 1238, 1207, 1179, 1124, 1066, 970, 954, 920 cm^{-1}

^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.57 (dd, *J* = 3.4, 1.9 Hz, 1H, $C_{34}H$), 6.04 (dd, *J* = 17.6, 10.9 Hz, 1H, $C_{17}H$), 5.64 – 5.48 (m, 2H, $C_{25}H$, $C_{26}H$), 4.99 – 4.92 (m, 2H, $C_{16}H_2$), 3.89 (dtd, *J* = 12.1, 5.9, 2.3 Hz, 1H, $C_{23}H$), 3.75 (s, 3H, CO_2Me), 3.29 (s, 3H, C19-OMe), 3.26 (dt, *J* = 18.8, 2.2 Hz, 1H, $C_{22}H_a$), 2.86 (ddd, *J* = 18.8, 12.5, 3.4 Hz, 1H, $C_{22}H_b$), 2.43 – 2.31 (m, 2H, $C_{24}H_2$), 1.69 (dd, *J* = 6.0, 1.2 Hz, 3H, $C_{27}H_3$), 1.09 (s, 3H), 1.04 (s, 3H)

^{13}C-NMR (125 MHz, $CDCl_3$) δ 197.6, 166.4, 148.6, 143.2, 129.1, 125.7, 123.2, 113.4, 104.5, 71.8, 52.0, 51.8, 45.6, 38.5, 34.7, 22.3, 21.9, 18.2

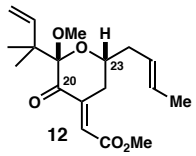
HRMS calculated for $C_{18}H_{26}NaO_5$ $[M+Na]^+$: 345.1678; found 345.1673 (TOF ESI+)

(In practice, we often employed starting material containing isomenthone; this procedure saves time and improves material throughput. It is described below)

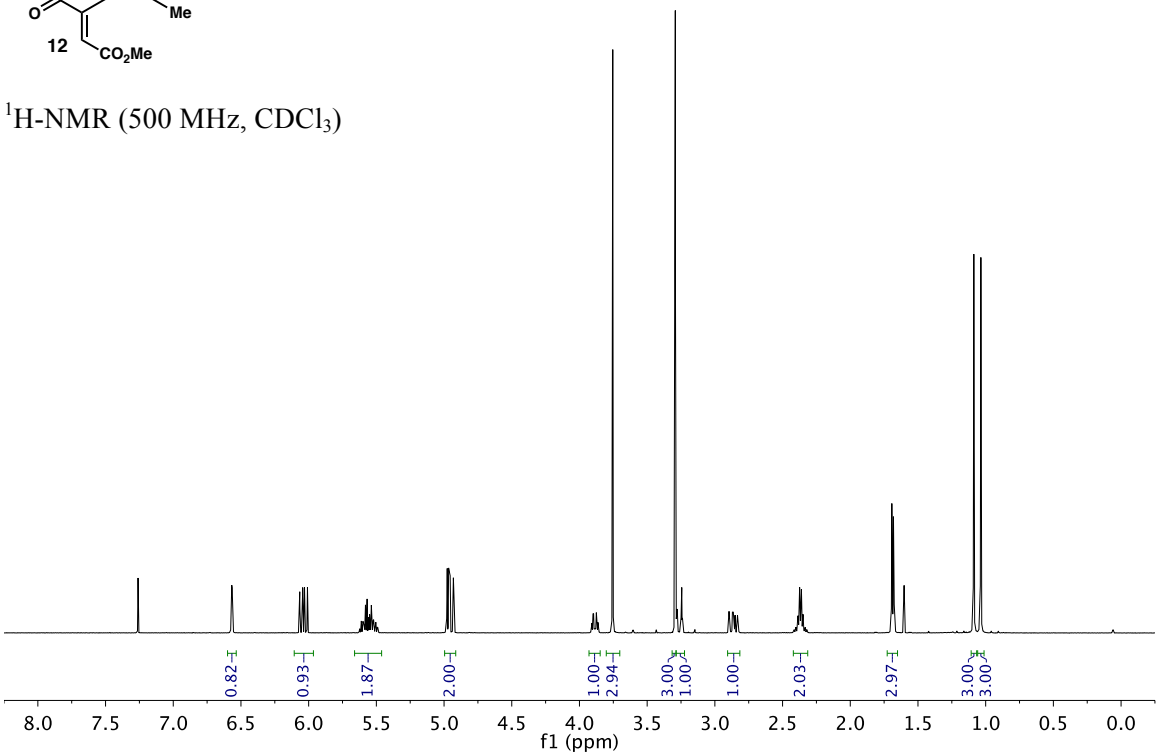
To a flame-dried, one-neck, 1L round-bottom flask equipped with magnetic stir bar was added ketone **12** (16.05 g, 63.59 mmol, 1 equiv, Note 1) and THF (~330 mL, 0.2M). Potassium carbonate (45.5 g, 328.9 mmol, 5.2 equiv) was added in a single portion, with vigorous stirring. To the resulting suspension was added a solution of methyl glyoxylate (28.43 g, 322.9 mmol, 5.1 equiv) in THF (~130 mL, 2.5M), followed by methanol (~110 mL). The final reaction mixture consisted of a ~0.1M solution of 4.2:1 THF/MeOH. Upon addition of methanol, the suspension turned bright yellow, slowly darkening to a burnt orange over the course of the reaction. After 1h, TLC analysis indicated complete conversion of ketone **12**. The reaction mixture was poured into a separatory funnel containing Et_2O (200 mL) and saturated aqueous NH_4Cl (500 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (300 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford a crude, yellow oil. Purification was accomplished by silica gel flash column chromatography (7-10-15% Et_2O/Hex) affording (*E*)-enoate **13** (16.69g, 81% yield), which co-eluted with isomenthone (~1.77g, ~10% of total mass) (Note 2).

Note 1: The starting material used in this procedure contained ~20% isomenthone (by weight).
Note 2: Isomenthone can co-elute with the product; however, further purification via column chromatography affords pure material.

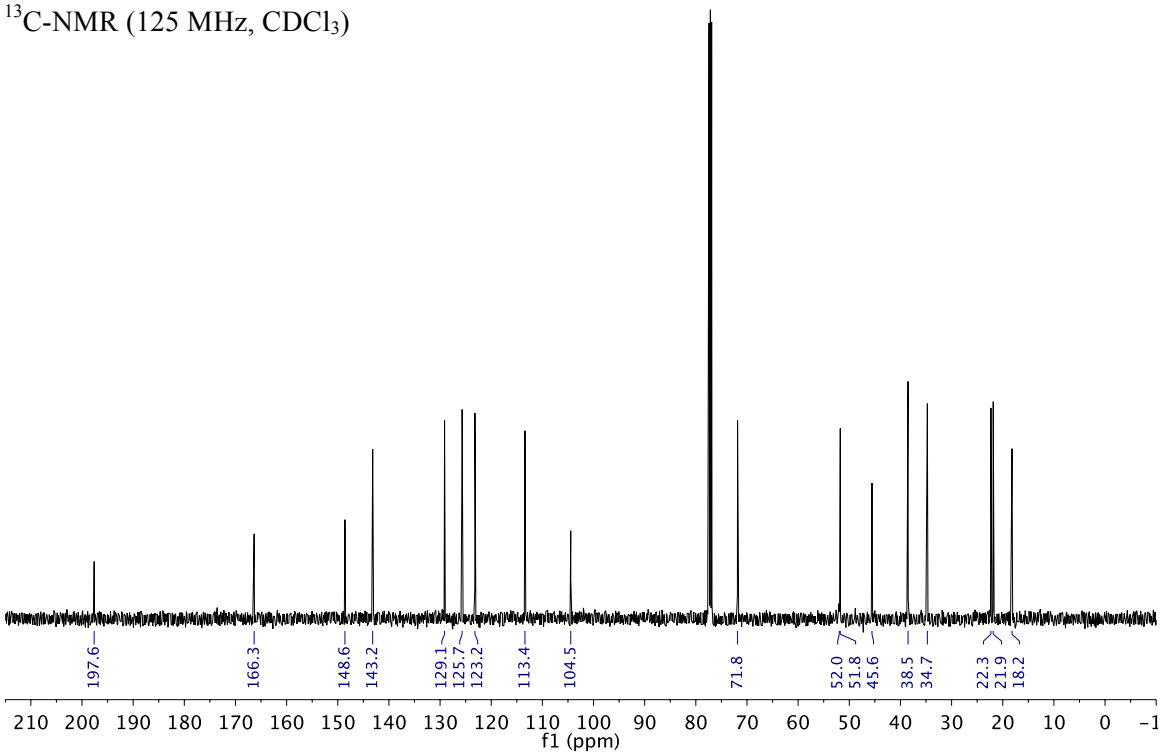
Experimentalists: AJS, RVQ, MCS



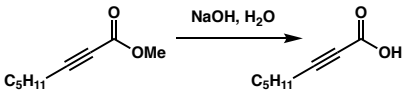
^{1}H-NMR (500 MHz, $CDCl_3$)



^{13}C-NMR (125 MHz, $CDCl_3$)

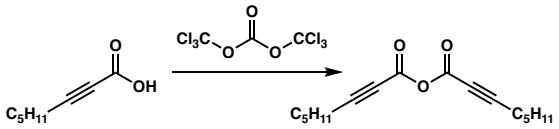


C-ring subunit: preparation of 2-octynoic anhydride



Chemicals:
Methyl 2-octynoate (Kosher grade, Sigma-Aldrich): used without purification

To a 1L round-bottom flask equipped with magnetic stir bar was added water (550 mL) and NaOH (48 g, 1.2 mol, 4 equiv). After equilibration to room temperature, methyl 2-octynoate (50 mL, 298 mmol, 1 equiv) was added. The resulting biphasic mixture was vigorously stirred and monitored for completion by TLC. After 3h, the reaction mixture was slowly acidified with 3M HCl (~400 mL) until the resulting solution read pH ~1. The reaction mixture was extracted with Et_2O (2x250 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford 2-octynoic acid (quantitative yield), which was used in the next step without purification.



Chemicals:
2-octynoic acid: commercially available from Aldrich or prepared as above; stored at -20 °C
Triphosgene (AK Scientific): used without purification; stored at -20 °C
Triethylamine (Sigma-Aldrich): distilled from CaH_2 prior to use

To a flame-dried, one-neck, 2L round-bottom flask equipped with magnetic stir bar was added EtOAc (1L, 0.2M) and 2-octynoic acid (28.0 g, 200 mmol, 1 equiv). The reaction mixture was cooled with an ice bath (0 °C). Triethylamine (27.9 mL, 200 mmol, 1 equiv) was added via syringe and after equilibration at 0 °C, triphosgene (9.89 g, 33.33 mmol, 0.167 equiv) was added as a single portion. Solids immediately precipitated out of the solution. After vigorously stirring for 10 min, the reaction mixture was warmed to room temperature by removing the ice bath. After an additional 30 min, the reaction mixture was filtered over celite and concentrated (Note 1). Purification was accomplished by silica gel flash column chromatography (2-5% EtOAc/Hex) affording 2-octynoic anhydride with >98% purity as determined by quantitative ^{1}H-NMR using an internal standard. Isolated yields are typically >80% but can vary because the anhydride decomposes on silica gel.

Note 1: Notwithstanding the appearance of the crude ^{1}H-NMR, the crude anhydride should be chromatographically purified to remove ^{1}H-NMR-silent impurities. We have observed a significant decrease in yield for the subsequent C19 esterification (step **g**) using crude anhydride.

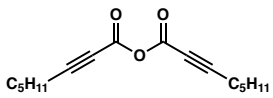
IR (thin film) 2958, 2933, 2231, 1783, 1157, 1004 cm^{-1}

^{1}H-NMR (500 MHz, $CDCl_3$) δ 2.37 (t, *J* = 7.1, 7.1 Hz, 4H), 1.64 – 1.54 (m, 4H), 1.42 – 1.25 (m, 8H), 0.89 (t, *J* = 7.2, 7.2 Hz, 7H)

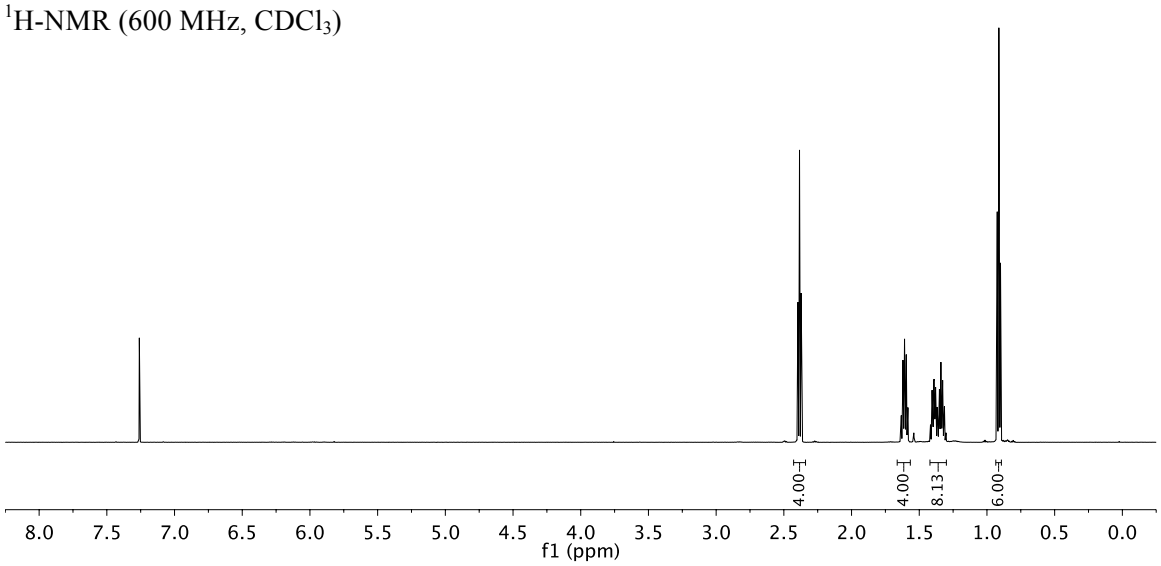
^{13}C-NMR (125 MHz, $CDCl_3$) δ 147.0, 95.4, 72.1, 31.0, 27.0, 22.2, 19.0, 13.9

HRMS calculated for $C_{16}H_{22}NaO_3$ $[M+Na]^+$: 285.1494; found 285.1461 (TOF ESI+)

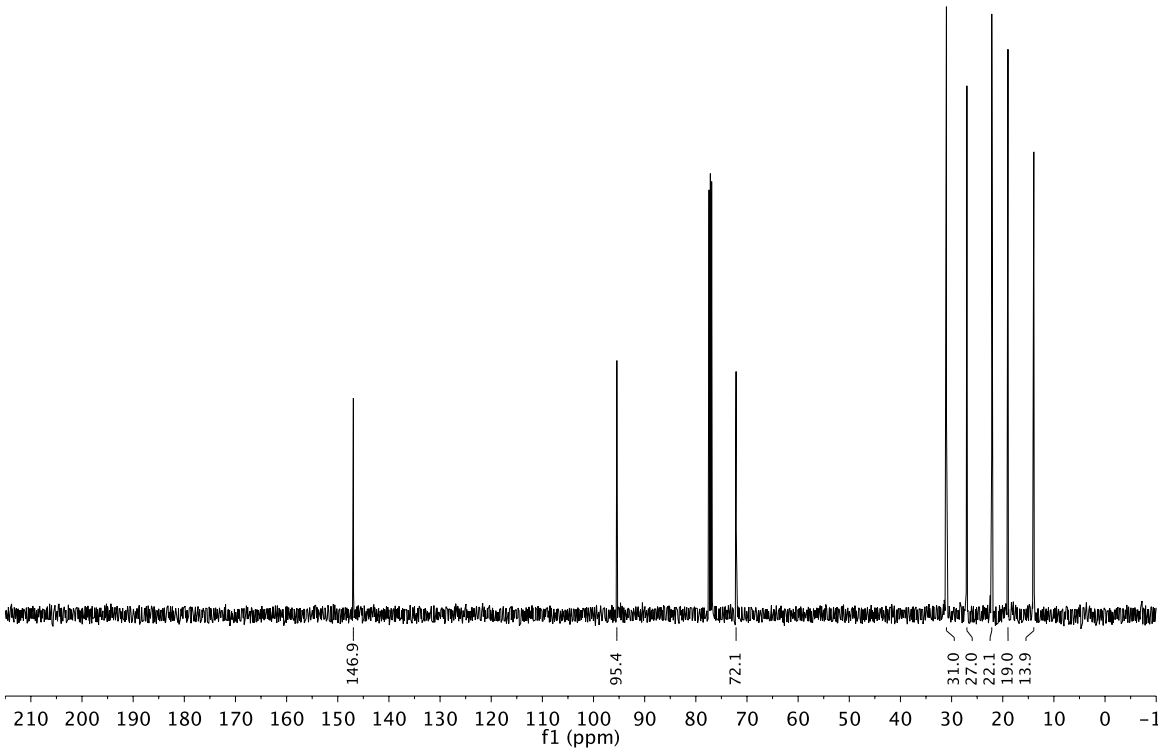
Experimentalists: MSJ, RVQ



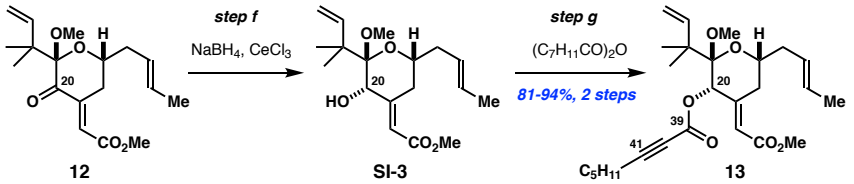
^{1}H-NMR (600 MHz, $CDCl_3$)



^{13}C-NMR (125 MHz, $CDCl_3$)



C-ring subunit Steps f-g: conversion of C20-ketone 12 to C20-ester 13



<Step f>
Chemicals:
Methanol (99.8% Extra Dry, Acros): used without purification
$CeCl_3$-$7H_2O$ (≥98%, Sigma-Aldrich): used without purification
$NaBH_4$ (99%, Sigma-Aldrich): used without purification

To a flame-dried, one-neck, 50 mL round-bottom flask equipped with magnetic stir bar was added ketone **12** (400 mg, 1.24 mmol, 1 equiv) and methanol (15 mL, 0.08M). The reaction mixture was cooled with an acetonitrile/dry ice bath (-50 °C). $CeCl_3$-$7H_2O$ (231 mg, 0.62 mmol, 0.5 equiv) was added in a single portion. After 10 min, $NaBH_4$ (94 mg, 2.48 mmol, 2 equiv) was added in a single portion. After an additional 20 min at -50 °C, the initially yellow solution turned colorless, and TLC showed complete conversion of ketone **12**. The reaction mixture was warmed to room temperature by removing the ice bath and poured into a separatory funnel containing Et_2O (30 mL) and a 3:2:1 mixture of saturated aqueous NH_4Cl / brine / water (40 mL) (caution: vigorous bubbling). The layers were separated, and the aqueous layer was extracted with Et_2O (3x30 mL). The combined organic layers were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$, filtered, and concentrated to afford crude alcohol **SI-3** (400 mg) as a colorless oil. This crude material was divided into two portions for immediate processing in the next step, as alcohol **SI-3** will decompose upon storage.

<Step g>
Chemicals:
DMAP (>99%, Sigma-Aldrich): used without purification
C20-alcohol **SI-3**: azeotroped with benzene prior to use

To a flame-dried, 8-dram vial equipped with magnetic stir bar was added crude alcohol **SI-3** (302 mg, 0.93 mmol, 1 equiv), CH_2Cl_2 (2.3 mL, 0.4M), and 2-octynoic anhydride (732 mg, 2.79 mmol, 3 equiv). The reaction mixture was cooled to -20 °C. A solution of DMAP (113 mg, 0.93 mmol, 1 equiv) in CH_2Cl_2 (~500 µL) was added dropwise via syringe over ~3 min, resulting in a dark orange solution. After 1.5h, the cooling bath had naturally warmed to 0 °C, and TLC showed complete conversion of **SI-3** and formation of octynoate **13**. The reaction mixture was quenched at 0 °C by adding saturated aqueous NH_4Cl (5 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3x5 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL), dried over $MgSO_4$, filtered, and concentrated to afford an orange oil. Purification was accomplished by silica gel flash column chromatography (10-20% Et_2O/pentane) affording octynoate **13** (391 mg, >20:1 dr at C20, 94% yield over 2 steps) as a viscous yellow oil (Note 1). Compound purity was established by TLC (one spot) analysis.

TLC R_f = 0.40 (10% Et_2O/pentane, purple spot in *p*-anisaldehyde)

$[\alpha]^{24.1}_D$ = -63.1° (*c* = 1.99, CH_2Cl_2)

IR (thin film) 3083, 2955, 2874, 2861, 2234, 1720, 1667, 1638, 1460, 1436, 1379, 1361, 1328, 1243, 1172, 1158, 1082, 1059, 1040, 969, 906, 745 cm^{-1}

^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.20 (dd, *J* = 17.7, 10.8 Hz, 1H), 5.92 – 5.91 (m, 1H), 5.62 – 5.50 (m, 2H), 5.31 (s, 1H), 4.94 – 4.85 (m, 2H), 3.69 (s, 3H), 3.73 – 3.64 (m, 1H), 3.53 (dd, *J* = 15.1, 2.7 Hz, 1H), 3.29 (s, 3H), 2.32 (t, *J* = 7.2 Hz, 2H), 2.41 – 2.22 (m, 3H), 1.69 (d, *J* = 4.8 Hz, 3H), 1.62 – 1.53 (m, 2H), 1.43 – 1.27 (m, 4H), 1.14 (s, 3H), 1.11 (s, 3H), 0.91 (t, *J* = 7.1 Hz, 3H)

^{13}C-NMR (125 MHz, $CDCl_3$) δ 166.8, 152.4, 152.0, 145.5, 128.4, 126.4, 118.3, 109.9, 102.7, 91.3, 73.7, 73.1, 72.0, 51.8, 51.3, 46.8, 39.1, 31.14, 31.06, 27.3, 23.8, 23.3, 22.2, 18.9, 18.2, 14.1

HRMS calculated for $C_{26}H_{38}NaO_6$ $[M+Na]^+$: 469.2561; found 469.2551 (TOF ESI+)

Note 1: We have observed that when using non-neutralized $CDCl_3$ for NMR analysis, the C20-ester **13** can decompose. Thus, NMRs were taken in either neutralized $CDCl_3$ or C_6D_6.

On Gram-Scale: <Step f> To a flame-dried, one-neck, 500 mL round-bottom flask equipped with magnetic stir bar was added ketone **12** (4.15 g, 12.87 mmol, 1 equiv) and methanol (257 mL, 0.05M). The reaction mixture was cooled with an acetonitrile/dry ice bath (-50 ºC, Note 1). $CeCl_3$-$7H_2O$ (2.4 g, 6.44 mmol, 0.5 equiv) was added in a single portion. After 15 min, $NaBH_4$ (974 mg, 25.74 mmol, 2 equiv) was added in a single portion. After an additional 25 min at ~-60 ºC (Note 1), the reaction mixture was warmed to room temperature over ~30 min by removing the cold bath. During the course of the reaction, the initially yellow solution turned colorless, and TLC showed complete conversion of ketone **12**. The reaction mixture was poured into a separatory funnel containing Et_2O (300 mL) and a 3:2:1 mixture of saturated aqueous NH_4Cl / brine / water (400 mL) (caution: vigorous bubbling). The layers were separated, and the aqueous layer was extracted with Et_2O (200 mL). The combined organic layers were washed with water (400 mL), brine (2x300 mL), dried over $MgSO_4$, filtered, and concentrated to afford crude alcohol **SI-3** as a light, straw yellow oil. This crude material was used immediately in the next step without purification, as alcohol **SI-3** will decompose upon storage.

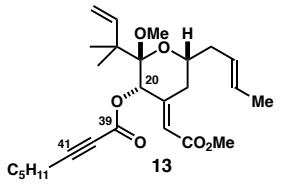
<Step g> To a flame-dried, one-neck, 200 mL round-bottom flask equipped with magnetic stir bar was added crude alcohol **SI-3** (assume 12.87 mmol, 1 equiv), CH_2Cl_2 (32 mL, 0.4M), and 2-octynoic anhydride (10.13 g, 38.62 mmol, 3 equiv). The reaction mixture was cooled to -20 ºC. A solution of DMAP (1.57 g, 12.87 mmol, 1 equiv) in CH_2Cl_2 (4 mL) was added dropwise via syringe over 6 min. After 55 min, the cooling bath had naturally warmed to -7 ºC, and TLC showed complete conversion of **SI-3** and formation of octynoate **13**. The reaction mixture was poured into a separatory funnel containing Et_2O (400 mL) and saturated aqueous NH_4Cl (250 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (150 mL). The combined organic layers were washed with water (300 mL), brine (200 mL), dried over $MgSO_4$, filtered and concentrated. Purification was accomplished by silica gel flash column chromatography (7% Et_2O/petroleum ether) affording octynoate **13** (4.67g, >20:1 dr at C20, 81% over 2 steps) as a viscous orange oil (Notes 2, 3). Compound purity was established by TLC (one spot) analysis and quantitative ^{1}H-NMR with an internal standard.

Note 1: Temperatures were read from a thermometer placed directly in the dry ice/acetonitrile bath, which had partially frozen over 25 minutes after the addition of $NaBH_4$.

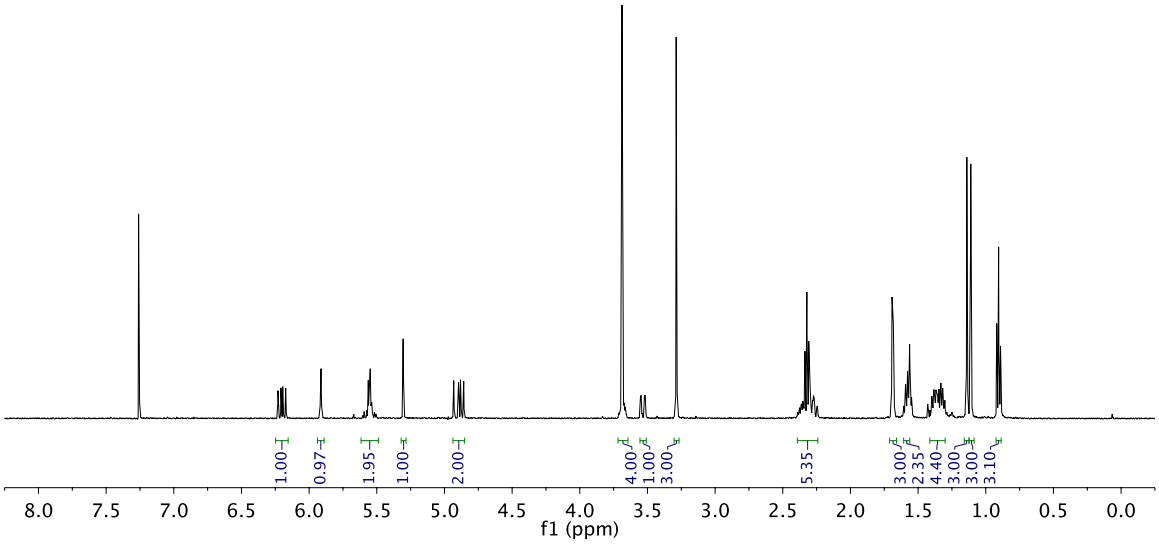
Note 2: We have observed that when using non-neutralized $CDCl_3$ for NMR analysis, the C20-ester **13** can decompose. Thus, NMRs were taken in either neutralized $CDCl_3$ or C_6D_6.

Note 3: The orange color of octynoate **13** can be removed by stirring the substrate with activated charcoal in hexanes. However, the subsequent Sharpless dihydroxylation reaction does not appear to have negatively affected by the color of **13**.

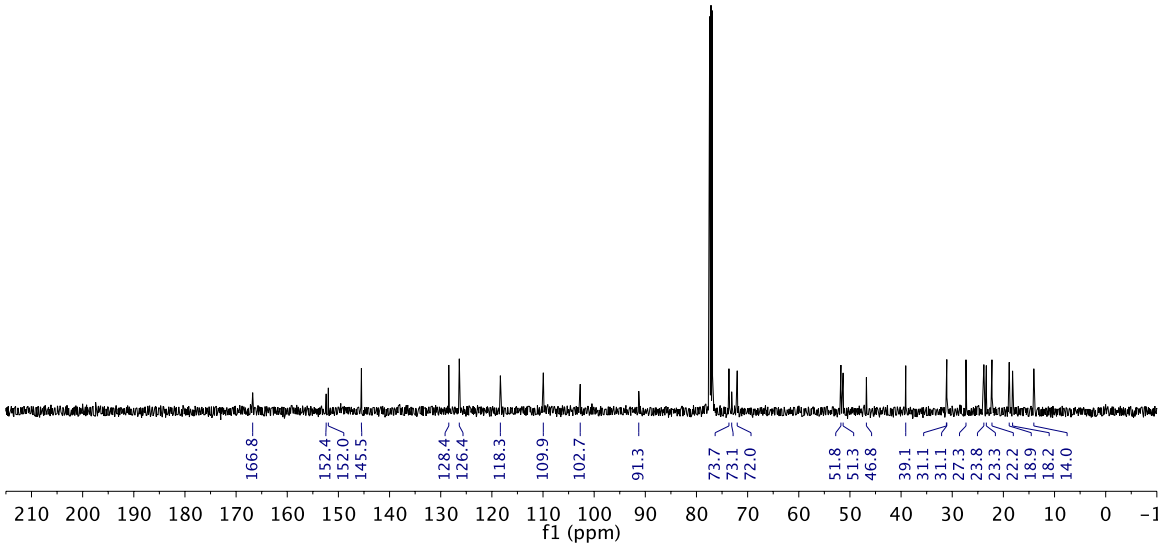
Experimentalists: SH, RVQ, AJS, MCS, MSJ



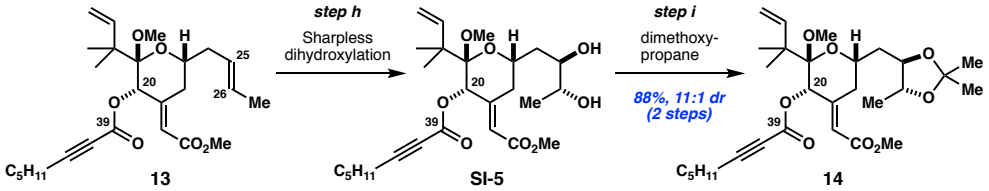
^{1}H-NMR (500 MHz, $CDCl_3$)



^{13}C-NMR (125 MHz, $CDCl_3$)



C-ring subunit Steps h-i: conversion of 13 to acetonide 14



<Step h>
Chemicals:
$K_2OsO_2(OH)_4$ (Sigma-Aldrich): used without purification
$K_3Fe(CN)_6$ (≥99%, Sigma-Aldrich): used without purification
K_2CO_3 (J.T. Baker): used without purification
$MeSO_2NH_2$ (97%, Sigma-Aldrich): used without purification
$(DHQD)_2PHAL$ (≥95%, Sigma-Aldrich): used without purification

A 500 mL round-bottom flask equipped with magnetic stir bar was sequentially charged with $K_2OsO_2(OH)_4$ (20 mg, 0.054 mmol, 1 mol%), $K_3Fe(CN)_6$ (5.37 g, 16.32 mmol, 3 equiv), K_2CO_3 (2.26 g, 16.32 mmol, 3 equiv), $MeSO_2NH_2$ (518 mg, 5.44 mmol, 1 equiv), $(DHQD)_2PHAL$ (212 mg, 0.27 mmol, 5 mol%), and 1:1 $^tBuOH/H_2O$ (110 mL, 0.05M). The reaction mixture was vigorously stirred under nitrogen for 30 min, after which stirring was stopped. Separately, a 500 mL round-bottom flask equipped with magnetic stir bar was charged with compound **13** (2.43 g, 5.44 mmol, 1 equiv) and cooled with an ice bath (0º C). Into the flask containing **13** was poured the pre-mixed osmium solution. The resulting biphasic mixture was vigorously stirred at 0 ºC and monitored for completion by TLC. After 100 min, the reaction mixture was poured into a separatory funnel containing water (150 mL) and EtOAc (150 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (150 mL). The combined organic layers were washed with a solution of 3% sulfuric acid (w/v) saturated with potassium sulfate (100 mL) (see Note 1), brine (200 mL), dried briefly over $MgSO_4$, filtered, and concentrated to afford crude diol **SI-5** as a purple/brown oil containing residual osmium. This crude material was used immediately in the next step without purification, as diol **SI-5** will decompose upon storage.

Note 1: We found that residual $(DHQD)_2PHAL$ inhibits the subsequent acid-catalyzed ketalization step. Therefore, we employed a brief sulfuric acid / potassium sulfate wash as outlined by Kolb, H.C.; *et al.* (*62*). However, we note that prolonged exposure to acid will result in diol decomposition.

<Step i>
Chemicals:
2,2-dimethoxypropane (98%, Sigma-Aldrich): used without purification
PPTS (98%, Sigma-Aldrich): used without purification

To a flame-dried, 100 mL round-bottom flask equipped with magnetic stir bar was added crude diol **SI-5** (assume 5.44 mmol, 1 equiv) and CH_2Cl_2 (55 mL, 0.1M). To the resulting solution was added 2,2-dimethoxypropane (2.7 mL, 21.764 mmol, 4 equiv) followed by PPTS (137 mg, 0.54 mmol, 10 mol%). After 40 min, TLC analysis indicated complete conversion of **SI-5** and formation of **14**. The reaction mixture was poured into a separatory funnel containing saturated aqueous $NaHCO_3$ (100 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2x100 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification was accomplished by silica gel flash column chromatography (15-20%

Et_2O/pentane) affording 2.03g (72% yield) of diasteromerically pure acetonide **14** and 464 mg of mixed isomers (1.21:1 dr), overall providing 2.49 g of acetonide **14** (10.9:1 dr, 88% combined yield over 2 steps). Further chromatography provided diastereomerically pure product. Compound purity of **14** was established by TLC (one spot) analysis.

TLC R_f = 0.3 (20% Et_2O/pentane, UV active, dark purple spot in *p*-anisaldehyde)

$[\alpha]^{23.5}_D$ = -45.1° (*c* = 1.23, CH_2Cl_2)

IR (thin film) 2982, 2935, 2234, 1720, 1668, 1459, 1436, 1415, 1242, 1168, 1095 cm^{-1}

^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.19 (dd, *J* = 17.7, 10.8 Hz, 1H, $C_{17}H$), 5.92 (s, 1H, $C_{34}H$), 5.31 (s, 1H, $C_{20}H$), 4.94 – 4.85 (m, 2H, $C_{16}H_2$), 4.01 – 3.95 (m, 1H), 3.92 – 3.86 (m, 1H), 3.74 – 3.65 (m, 1H), 3.69 (s, 3H, CO_2Me), 3.59 (dd, *J* = 14.8, 2.6 Hz, 1H, $C_{22}H_a$), 3.34 (s, 3H, C19-OMe), 2.32 (t, *J* = 7.2 Hz, 2H, $C_{42}H_2$), 2.30 – 2.23 (m, 1H, $C_{22}H_b$), 1.88 – 1.81 (m, 1H, $C_{24}H_a$), 1.72 – 1.65 (m, 1H, $C_{24}H_b$), 1.57 (app. p, *J* = 7.3 Hz, 2H), 1.45 – 1.29 (m, 4H), 1.37 (s, 3H, acetonide), 1.35 (s, 3H, acetonide), 1.29 (d, *J* = 6.0 Hz, 3H, $C_{27}H_3$), 1.14 (s, 3H), 1.12 (s, 3H), 0.90 (t, *J* = 7.1 Hz, 3H, $C_{46}H_3$)

^{13}C-NMR (125 MHz, $CDCl_3$) δ 166.7, 152.3, 151.2, 145.4, 118.7, 109.9, 107.9, 102.6, 91.3, 78.3, 77.1, 73.7, 73.1, 68.7, 51.8, 51.4, 46.7, 38.4, 31.9, 31.1, 27.5, 27.3, 27.3, 23.9, 23.2, 22.2, 18.9, 17.1, 14.0

HRMS calculated for $C_{29}H_{44}NaO_8$ $[M+Na]^+$: 543.2928; found 543.2931 (TOF ESI+)

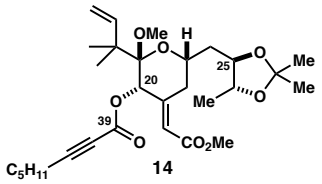
On Decagram-Scale: <Step h> A 1L round-bottom flask equipped with magnetic stir bar was sequentially charged with $K_2OsO_2(OH)_4$ (122 mg, 0.332 mmol, 1 mol%), $K_3Fe(CN)_6$ (32.7 g, 99.5 mmol, 3 equiv), K_2CO_3 (13.8 g, 99.5 mmol, 3 equiv), $MeSO_2NH_2$ (3.15 g, 33.2 mmol, 1 equiv), $(DHQD)_2PHAL$ (1.29 g, 1.66 mmol, 5 mol%), and 1:1 ^{t}BuOH/H_2O (660 mL, 0.05M). The reaction mixture was vigorously stirred under nitrogen for 30 min, after which stirring was stopped. Separately, a 1L round-bottom flask equipped with magnetic stir bar was charged with compound **13** (14.8g, 33.15 mmol, 1 equiv) and cooled with an ice bath (0 ºC). Into the flask containing **13** was poured the pre-mixed osmium solution. The resulting biphasic mixture was vigorously stirred at 0 ºC and monitored for completion by TLC. After 2h, the reaction mixture was poured into a separatory funnel containing water (250 mL) and EtOAc (250 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3x250 mL). The combined organic layers were washed with a cooled (0º) solution of 3% sulfuric acid (w/v) saturated with potassium sulfate (see Note 1), brine, dried briefly over $MgSO_4$ filtered, and concentrated to afford crude diol **SI-5** as a purple/brown oil containing residual osmium. This crude material was used immediately in the next step without purification, as diol **SI-5** will decompose upon storage.

Note 1: We found that residual $(DHQD)_2PHAL$ inhibits the subsequent acid-catalyzed ketalization step. Therefore, we employed a brief sulfuric acid / potassium sulfate wash as outlined by Kolb, H.C.; *et al.* (*62*). However, we note that prolonged exposure to acid will result in diol decomposition.

<Step i> To a flame-dried, 1L round-bottom flask equipped with magnetic stir bar was added crude diol **SI-5** (assume 33.15 mmol, 1 equiv) and CH_2Cl_2 (330 mL, 0.1M). To the resulting solution was added 2,2-dimethoxypropane (16.2 mL, 132.6 mmol, 4.0 equiv) followed by PPTS

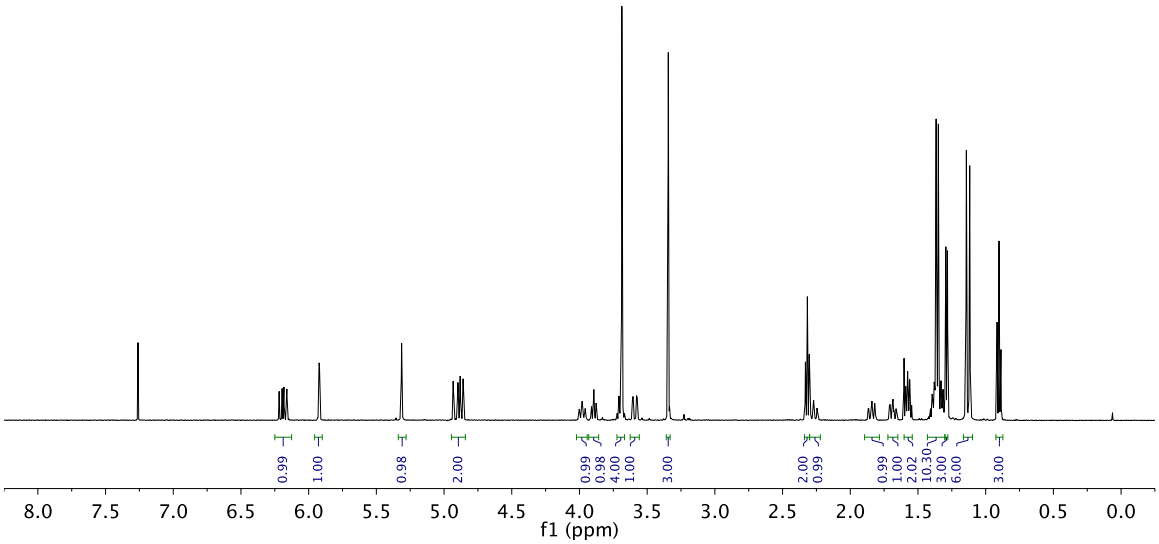
(833 mg, 3.31 mmol, 10 mol%). After 15 min, TLC analysis indicated complete conversion of **SI-5** and formation of **14**. The reaction mixture was poured into a separatory funnel containing saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (4x250 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification was accomplished by silica gel flash column chromatography (4L of 10-20% Et_2O/pentane) affording acetonide **14** (13.46g, 14:1 dr, 78% combined yield) as a pale yellow oil. Further chromatography provided diastereomerically pure product.

Experimentalists: RVQ, MCS

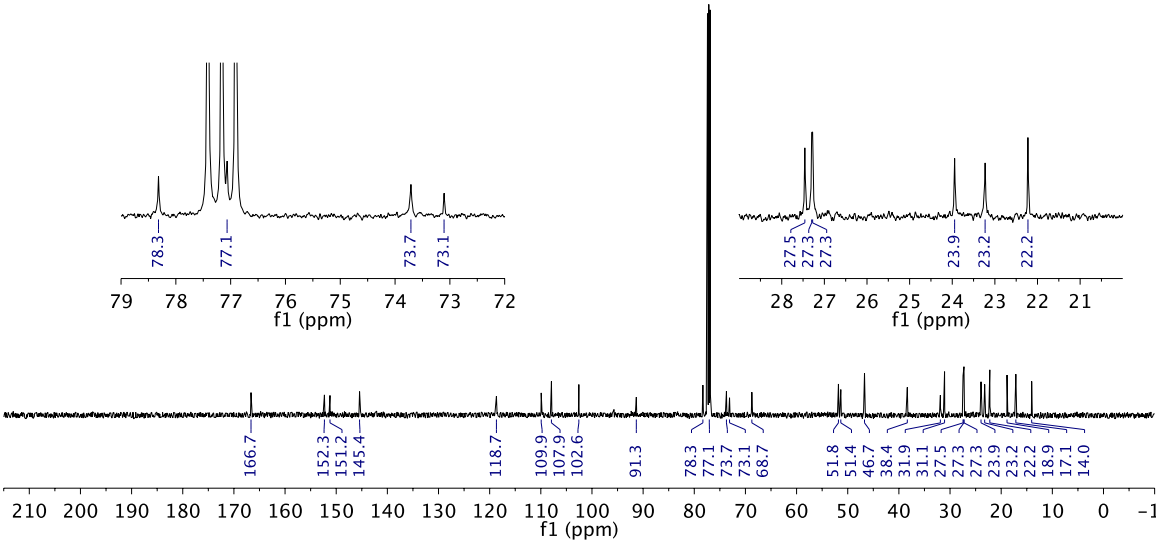


14

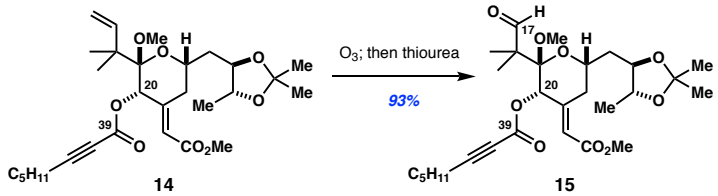
^{1}H-NMR (500 MHz, $CDCl_3$)



^{13}C-NMR (125 MHz, $CDCl_3$)



C-ring subunit Step j: conversion of 14 to aldehyde 15



Chemicals:
Thiourea (>99%, Sigma-Aldrich): used without purification
Isopropanol (certified ACS, Fisher): used without purification

To a flame-dried, three-neck, 2L round-bottom flask equipped with 500 mL jacketed addition funnel and magnetic stir bar was added olefin **14** (3.65 g, 7.01 mmol, 1 equiv) and CH_2Cl_2 (70 mL, 0.1 M). The reaction mixture was cooled with a dry ice/acetone bath (-78 °C). CH_2Cl_2 (500 mL) was added to the jacketed addition funnel, which was also cooled with dry ice/acetone. A saturated ozone solution (~0.025M CH_2Cl_2) was prepared by bubbling ozone (~4 LPM, prepared with 70 V) through the CH_2Cl_2 in the addition funnel until a bright blue color persisted (~10 min), at which point the headspace of the solution was purged with oxygen, and the addition funnel sealed with a septum and kept under a nitrogen atmosphere for the remainder of the reaction (Note 1). The freshly-prepared ozone solution was then added dropwise to the reaction mixture over ~2h: the reaction was monitored by TLC upon addition of 0.9 equiv. of ozone and determined to be incomplete; additional ozone was then added in 0.1 equiv portions until all of **14** was consumed (~1.8 equiv, 500 mL). Subsequently, the reaction mixture was diluted with isopropanol (500 mL) and quenched by adding thiourea (3.34 g, 70.1 mmol, 10 equiv) as a single portion. The reaction mixture was warmed to room temperature by removing the dry ice bath. After 16h, analysis by peroxide test strips indicated complete reduction of ozonide. The reaction mixture was poured into a separatory funnel containing Et_2O (800 mL) and H_2O (1.1L). The layers were separated, and the aqueous layer was extracted with Et_2O (2x600 mL). The combined organic layers were washed with brine (1L), and the combined aqueous layers back-extracted with Et_2O (500 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification was accomplished by silica gel flash column chromatography (10-40% Et_2O/pentane) affording aldehyde **15** (3.42 g, 93% yield) as a clear, colorless oil. Compound purity was established by TLC (one spot) analysis.

TLC R_f = 0.5 (40% EtOAc/Hex, UV active, dark purple spot in *p*-anisaldehyde)

$[\alpha]^{23.9}_{D}$ = -30.7° (*c* = 0.7, CH_2Cl_2)

IR (thin film) 2981, 2933, 2873, 2233, 1719, 1668, 1458, 1436, 1379, 1369, 1232, 1168, 1094 cm^{-1}

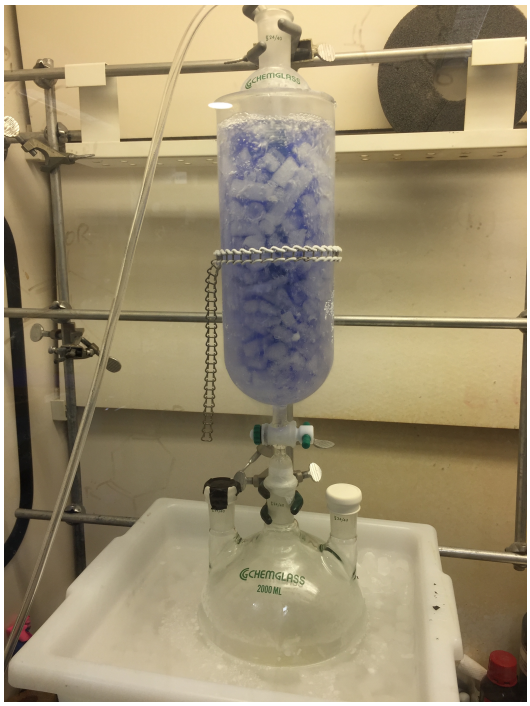
^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.75 (s, 1H, CHO), 5.96 (s, 1H, $C_{34}H$), 5.25 (s, 1H, $C_{20}H$), 4.07 (app. t, *J* = 10.8 Hz, 1H), 3.88 (app t, *J* = 9.5, 1H), 3.75-3.67 (m, 1H), 3.70 (s, 3H, CO_2Me), 3.65 (dd, *J* = 15.1, 2.5 Hz, 1H, $C_{22}H_a$), 3.43 (s, 3H, C19-OMe), 2.33 (t, *J* = 7.2 Hz, 2H, $C_{42}H_2$), 2.26 (app. t, *J* = 13.5 Hz, 1H, $C_{22}H_b$), 1.91-1.81 (m, 1H, $C_{24}H_a$), 1.76-1.68 (m, 1H, $C_{24}H_b$), 1.64 – 1.53 (m, 2H), 1.44-1.19 (m, 4H), 1.37 (s, 3H, acetonide), 1.35 (s, 3H, acetonide), 1.29 (d, *J* = 6.0 Hz, 3H, $C_{27}H_3$), 1.17 (s, 3H), 1.05 (s, 3H), 0.90 (t, *J* = 7.0 Hz, 3H, $C_{46}H_3$)

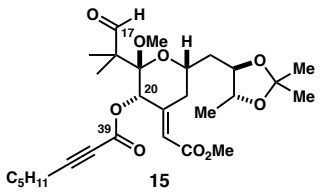
^{13}C-NMR (125 MHz, $CDCl_3$) δ 202.0, 166.4, 151.6, 149.4, 120.1, 108.0, 101.9, 92.7, 78.2, 77.1, 72.8, 72.3, 69.2, 54.2, 51.5, 51.4, 38.2, 31.7, 31.1, 27.4, 27.3, 27.2, 22.2, 19.2, 18.9, 17.1, 16.9, 14.0

HRMS calculated for $C_{28}H_{42}NaO_9$ $[M+Na]^+$: 545.2721; found 545.2714 (TOF ESI+)

Experimentalists: CTH, RVQ, AJS, JLS

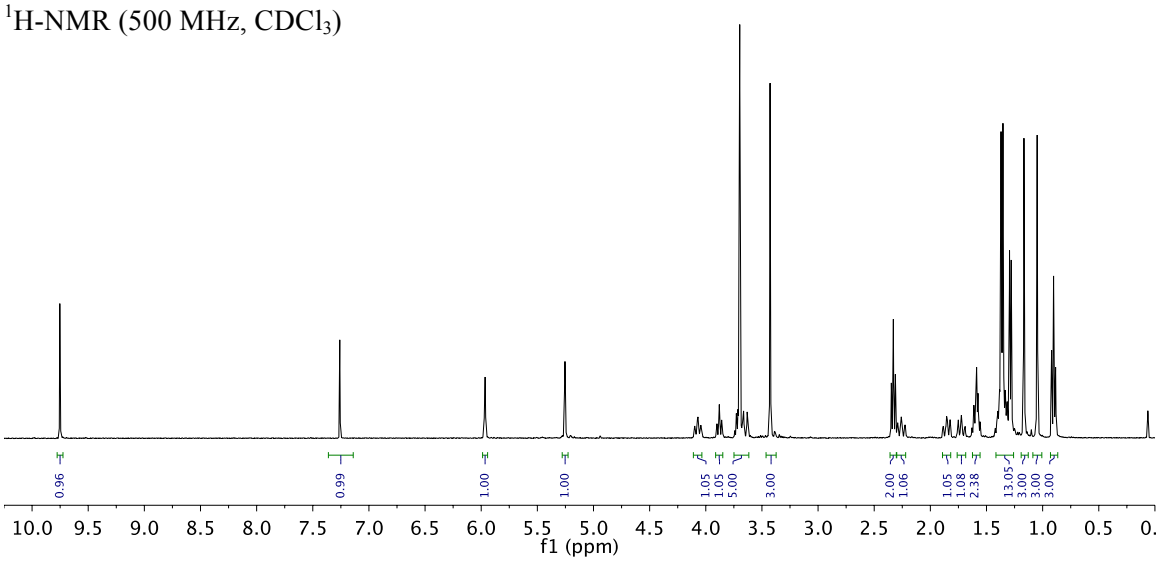
Note 1: See picture for reaction setup. The dry ice/acetone coolant for the ozone solution surrounds the addition funnel. The blue color in the addition funnel is characteristic of a saturated ozone solution.



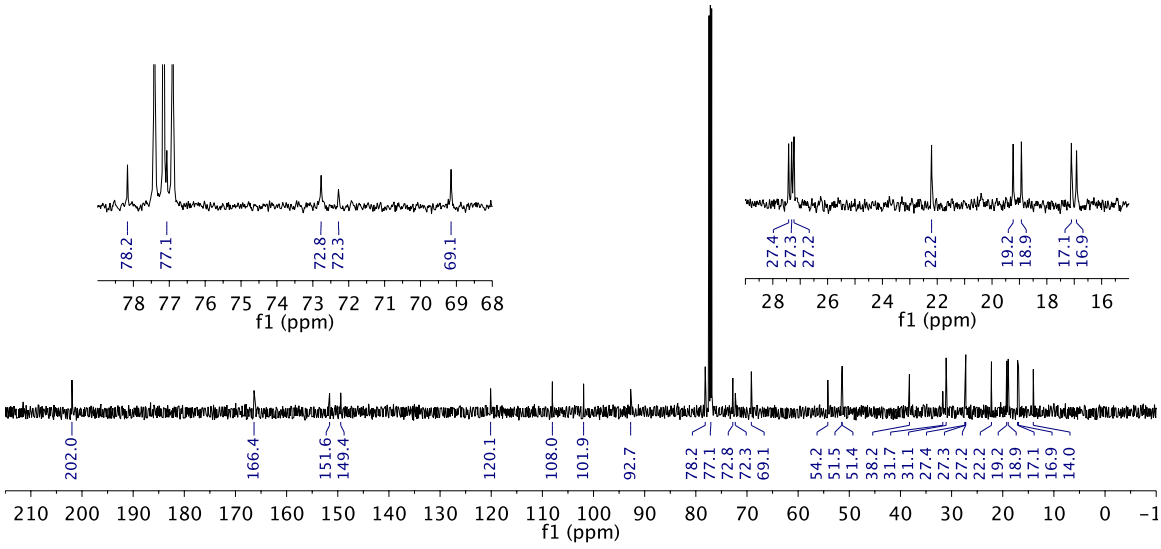


15

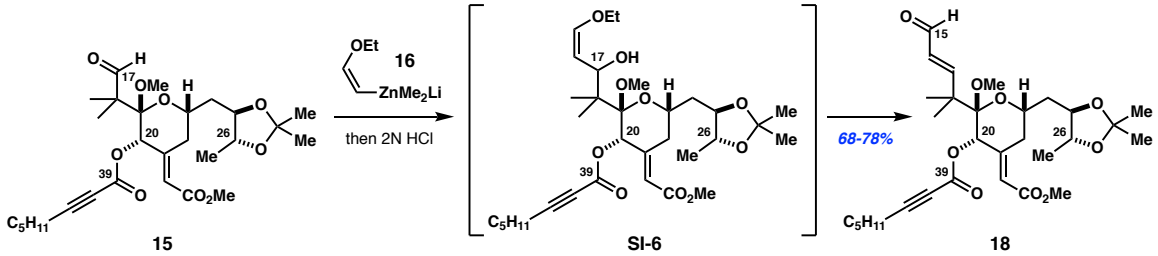
^{1}H-NMR (500 MHz, $CDCl_3$)



^{13}C-NMR (125 MHz, $CDCl_3$)



C-ring subunit Step k: conversion of aldehyde 15 to enal 18



Chemicals:
cis-1-bromo-2-ethoxyethylene (95% pure by ^{1}H-NMR, Sigma-Aldrich): used without purification
tert-butyllithium (Sigma-Aldrich): freshly-titrated; **CAUTION**: pyrophoric material
dimethylzinc (Sigma-Aldrich): freshly-titrated according to Krasovskiy, A; *et al.* (*63*)

To a flame-dried, 8-dram vial equipped with magnetic stir bar was added *cis*-1-bromo-2-ethoxyethylene (95% pure, 257 µL, 2.30 mmol, 8 equiv) and Et_2O (957 µL, 0.3M) under Argon. The reaction mixture was cooled with a dry ice/acetone bath (-78 °C). *t*-BuLi (1.55M pentane, 2.96 mL, 4.59 mmol, 16 equiv) was added dropwise via syringe down the side of the vial over 1 min. The clear, colorless solution gradually turned into a cloudy, white suspension. After 30 min at -78 °C, Me_2Zn (0.75M toluene, 3.37 mL, 2.53 mmol, 8.8 equiv) was added via syringe down the side of the vial (3 min). The suspended solids gradually began to aggregate. After 1h at -78 °C, a solution of aldehyde **15** (150 mg, 0.29 mmol, 1 equiv) in Et_2O (2.9 mL, 0.1M) was added via syringe down the side of the vial (3 min). The solution turned pale yellow, and the white solids gradually went into solution. After 1.5h at -78 °C, the reaction mixture was quenched by adding 1M HCl (18 mL, 8 equiv with respect to zincate **16**) via syringe over 5 min. The reaction mixture was warmed to room temperature over ~30 min by removing the dry ice bath and vigorously stirred for 18h, at which point TLC analysis indicated full conversion of 1,2-addition adduct **SI-6** (TLC R_f = 0.25, 20% EtOAc/Hex, purple spot in *p*-anisaldehyde). The layers were separated, and the aqueous layer was extracted with Et_2O (3x50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification was accomplished via pH 7 buffered silica gel flash column chromatography (30% Et_2O/Hex) affording enal **18** (122 mg, 78% yield) as an off-white foam. Compound purity was established by TLC (one spot) analysis.

- **TLC** R_f = 0.50 (20% EtOAc/Hex, purple spot in *p*-anisaldehyde)
- **[α]$^{23.2}_D$** = -39.8° (*c* = 0.46, CH_2Cl_2)
- **IR** (thin film) 2982, 2934, 2874, 2232, 1717, 1689, 1628, 1458, 1436, 1380, 1369, 1240, 1168, 1095, 1064, 1043, 933, 888, 744 cm^{-1}
- **HRMS** calculated for $C_{30}H_{44}NaO_9$ $[M+Na]^+$: 571.2878; found 571.2882 (TOF ESI+)

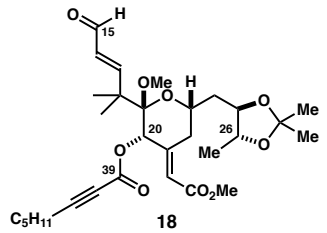
^{1}H-NMR (500 MHz, $CDCl_3$) δ 9.54 (d, *J* = 7.8 Hz, 1H, CHO), 7.28 (d, *J* = 16.0 Hz, 1H, $C_{17}H$), 5.92 (s, 1H, $C_{34}H$), 5.92 (dd, *J*= 16.0, 7.8 Hz, 1H, $C_{16}H$), 5.40 (s, 1H, $C_{20}H$), 4.17 – 4.04 (m, 1H), 3.92 – 3.84 (m, 1H), 3.75 – 3.70 (m, 1H), 3.69 (s, 3H, CO_2Me), 3.59 – 3.54 (m, 1H, $C_{22}H_a$), 3.41 (s, 3H, C19-OMe), 2.39 – 2.31 (m, 1H, $C_{22}H_b$), 2.25 (td, J = 7.2, 2.6 Hz, 2H, $C_{40}H_2$), 1.91 – 1.84 (m, 1H, $C_{24}H_a$), 1.75 – 1.68 (m, 1H, $C_{24}H_b$), 1.53 (app. p, *J* = 7.3 Hz, 2H), 1.37 (s, 3H), 1.35 (s, 3H), 1.38 – 1.27 (m, 4H), 1.30 (d, *J* = 6.0 Hz, 3H, $C_{27}H_3$), 1.19 (s, 3H), 1.15 (s, 3H), 0.89 (t, *J* = 7.1 Hz, 3H, $C_{46}H_3$)

^{13}C-NMR (125 MHz, $CDCl_3$) δ 195.1, 166.44, 166.42, 151.8, 150.5, 126.7, 118.7, 108.0, 102.4, 92.9, 78.1, 77.1, 72.7, 72.3, 69.2, 51.48, 51.45, 47.3, 38.3, 32.4, 31.1, 27.4, 27.3, 27.1, 24.0, 22.2, 21.5, 18.8, 17.2, 14.0

On Gram-Scale:
Chemicals:
cis-1-bromo-2-ethoxyethylene (92% pure by ^{1}H-NMR, Synthonix): used without purification
tert-butyllithium (Sigma-Aldrich): freshly-titrated; **CAUTION**: pyrophoric material
dimethylzinc (Sigma-Aldrich): freshly-titrated according to Krasovskiy, A; *et al.* (*63*).

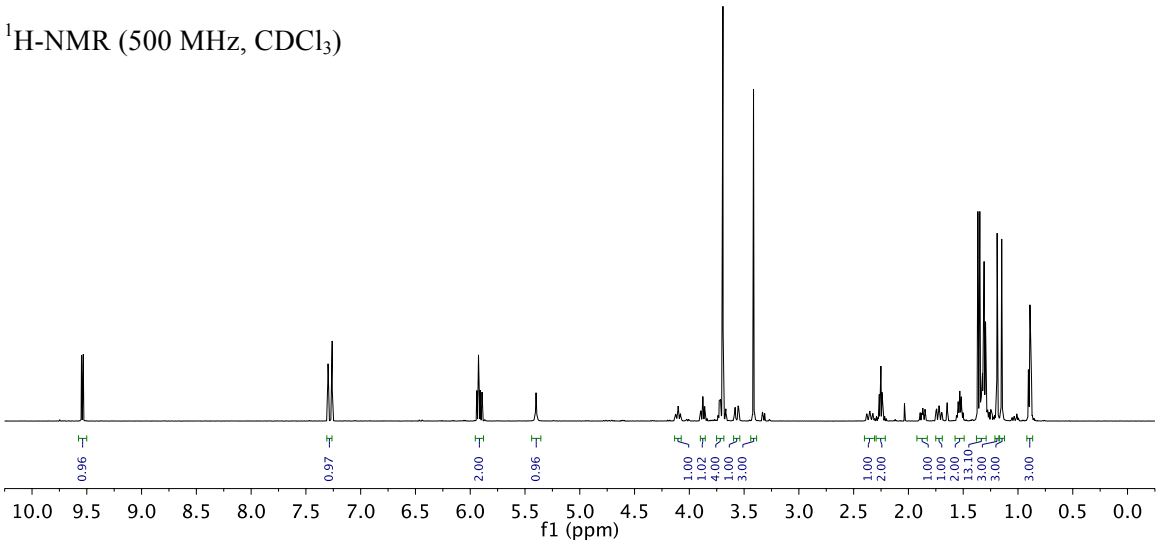
To a flame-dried, two-neck, 500 mL round-bottom flask equipped with magnetic stir bar was added *cis*-1-bromo-2-ethoxyethylene (92% pure, 2.8 mL, 24.5 mmol, 8 equiv) and Et_2O (10 mL, 0.3M) under Argon. The reaction mixture was cooled with a dry ice/acetone bath (-78 °C). *t*-BuLi (1.55M pentane, 31.6 mL, 49.0 mmol, 16 equiv) was added dropwise via three 24 mL plastic Luer Lock syringes over 8 min (each syringe containing ~10.5 mL t-BuLi). The clear, colorless solution gradually turned into a cloudy, white suspension. After 30 min at -78 °C, Me_2Zn (1.03M toluene, 26.2 mL, 26.9 mmol, 8.8 equiv) was added dropwise via syringe over 6 min. The suspended solids gradually began to aggregate. After 1h at -78 °C, a solution of aldehyde **15** (1.6 g, 3.06 mmol, 1 equiv) in Et_2O (16 mL followed by two 7.5 mL washes, 0.1M) was added dropwise via syringe over 10 min. The solution turned pale yellow, and the white solids gradually went into solution. After 1.5h at -78 °C, the reaction mixture was quenched by adding 2M HCl (98 mL, 8 equiv with respect to zincate **16**) over 10 min, followed by additional Et_2O (100 mL). The reaction mixture was warmed to room temperature over ~1h by removing the dry ice bath and vigorously stirred for 18h, at which point TLC analysis indicated full conversion of 1,2-addition adduct **SI-6** (TLC R_f = 0.25, 20% EtOAc/Hex, purple spot in *p*-anisaldehyde). The layers were separated, and the aqueous layer was extracted with Et_2O (4x100 mL). The combined organic layers were washed with a phosphate buffer solution (pH 7.4, 50 mL), and the resulting aqueous layer back-extracted with Et_2O (2x100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification was accomplished via pH 7 buffered silica gel flash column chromatography (20-60% Et_2O/pentane) affording affording enal **18** (1.14 g, 68% yield) as an off-white foam. Compound purity was established by TLC (one spot) analysis.

Experimentalists: SH, AJS, RVQ

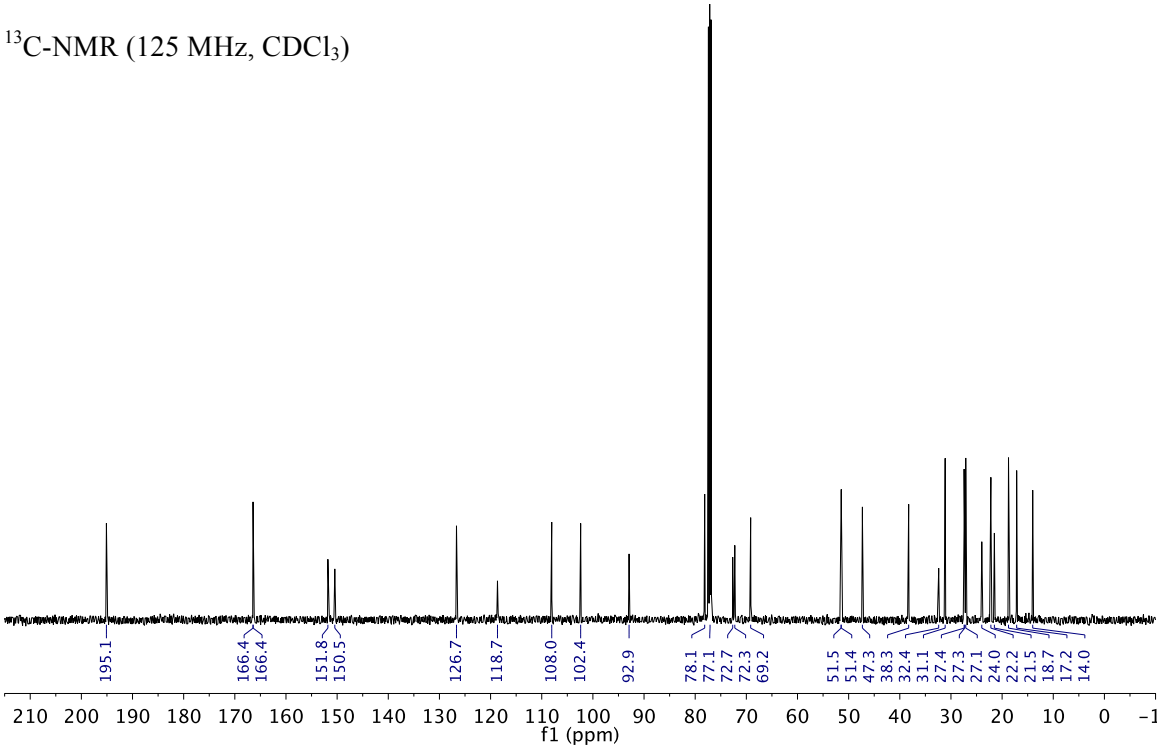


18

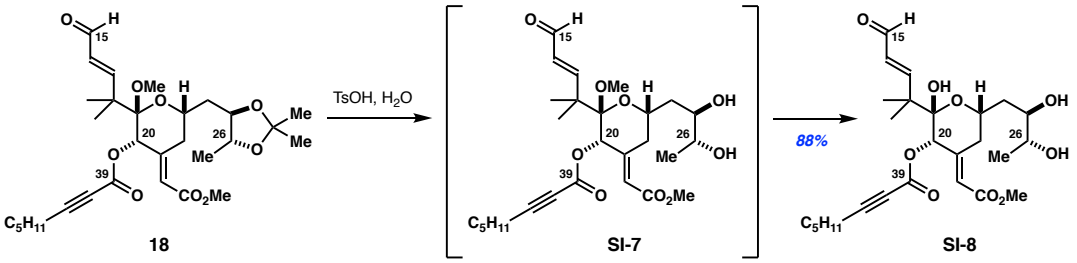
^{1}H-NMR (500 MHz, $CDCl_3$)



^{13}C-NMR (125 MHz, $CDCl_3$)



C-ring subunit Step l: conversion of 18 to triol SI-8



Chemicals:
p-TsOH-H_2O (≥98%, Sigma-Aldrich): used without purification

To an 8-dram vial equipped with magnetic stir bar was sequentially added acetonide **18** (54 mg, 0.10 mmol, 1 equiv), 4:1 MeCN/H_2O (5 mL, 0.02M), and *p*-TsOH-H_2O (186 mg, 1.0 mmol, 10 equiv) in a single portion. The colorless reaction mixture was stirred at room temperature for 28h, in a 45 °C oil bath for 45 min, and then at room temperature for an additional 18h, at which point the reaction mixture was one spot by TLC (Note 1). The reaction mixture was quenched at 0 °C by adding saturated aqueous $NaHCO_3$ (5 mL) via pipette and extracted with EtOAc (4x15 mL) until TLC of the aqueous layer no longer showed product. The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. Purification was accomplished by pH 7 buffered silica gel chromatography (80-100% EtOAc/Hex), affording triol **SI-8** (42 mg, 88% yield) as a white amorphous solid (Notes 2, 3). Compound purity was established by TLC (one spot) analysis.

Note 1: By TLC, the C25/C26 acetonide is hydrolyzed within a few hours at room temperature while the C19-OMe requires extended reaction times: **SI-7 TLC** R_f = 0.38 (80% EtOAc/Hex, UV active, purple spot in *p*-anisaldehyde); **SI-**8 **TLC** R_f = 0.24 (80% EtOAc/Hex, UV active, purple spot in *p*-anisaldehyde).
Note 2: Buffered silica gel was prepared by adding 10% weight pH 7 phosphate buffer to silica and rotating for ~12 hrs. Triol **SI-8** will decompose if exposed to a long column of silica gel.
Note 3: Triol **SI-8** will slowly polymerize over the course of weeks-to-months, even when stored in benzene at -20 °C. Therefore, its C26 alcohol should be silyl protected as soon as possible.
Note 4: The alcohol protons in the ^{1}H-NMR spectra have variable chemical shifts.

TLC R_f = 0.24 (80% EtOAc/Hex, UV active, purple spot in *p*-anisaldehyde)

[α]$^{23.4}_{D}$ = -44.5° (*c* = 0.55, CH_2Cl_2)

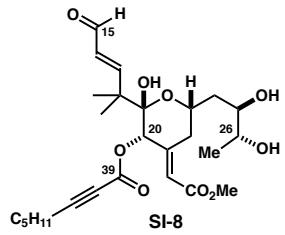
IR (thin film) 3418 (br), 2954, 2873, 2233, 1716, 1688, 1628, 1436, 1383, 1241, 1159, 1055, 981, 890, 745 cm^{-1}

^{1}H-NMR (600 MHz, C_6D_6, see Note 4) δ 9.70 (d, *J* = 7.6 Hz, 1H, CHO), 7.39 (d, *J* = 16.1 Hz, 1H, $C_{17}H$), 6.29 (d, *J* = 1.9 Hz, 1H, $C_{34}H$), 6.12 (dd, *J* = 16.1, 7.6 Hz, 1H, $C_{16}H$), 5.50 (s, 1H, $C_{20}H$), 4.48 (bs, 1H, OH), 4.31 (app. t, *J* = 11.0 Hz, 1H, $C_{23}H$), 3.98 (dd, *J* = 14.0, 2.3 Hz, 1H, $C_{22}H_a$), 3.62 – 3.55 (m, 1H, $C_{24}H$), 3.30 (s, 3H, CO_2Me), 3.24 – 3.17 (m, 1H, $C_{25}H$), 3.15 (bs, 1H, OH), 2.30 – 2.23 (m, 2H, $C_{22}H_b$, OH), 1.94 – 1.81 (m, 2H), 1.45 – 1.37 (m, 1H, $C_{24}H_a$), 1.29 – 1.22 (m, 1H, $C_{24}H_b$), 1.19 (app. p, *J* = 7.3 Hz, 2H), 1.10 (s, 3H), 1.07 (s, 3H), 1.06 – 1.00 (m, 4H), 0.94 (d, *J* = 6.3 Hz, 3H, $C_{27}H_3$), 0.74 (t, *J* = 6.9 Hz, 3H, $C_{46}H_3$)

^{13}C-NMR (125 MHz, C_6D_6, 25 total peaks, 1 peak is obscured by the benzene solvent peak) δ 193.9, 166.5, 164.6, 152.1, 150.6, 121.5, 100.3, 92.6, 74.1, 73.6, 72.5, 71.3, 67.4, 51.0, 45.9, 39.3, 31.5, 31.2, 27.2, 23.1, 22.3, 20.2, 19.7, 18.7, 14.0

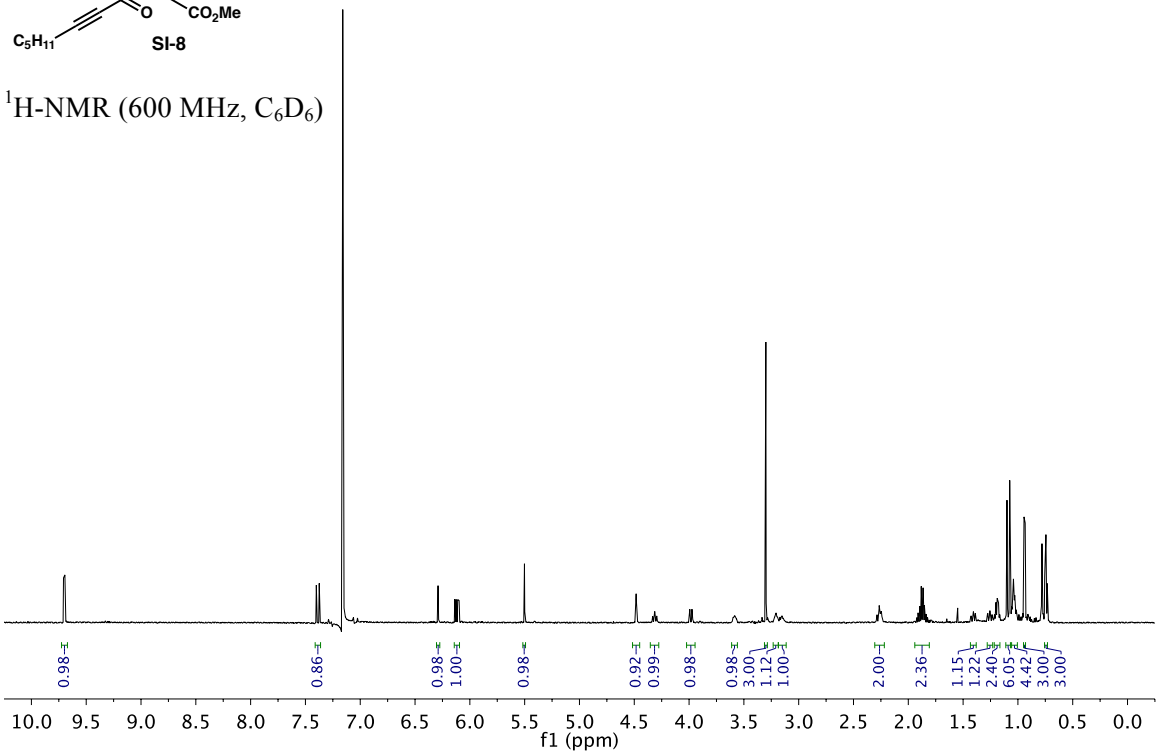
HRMS calculated for $C_{26}H_{38}NaO_9$ $[M+Na]^+$: 517.2408; found 517.2402 (TOF ESI+)

Experimentalists: SH, AJS, CTH, RVQ

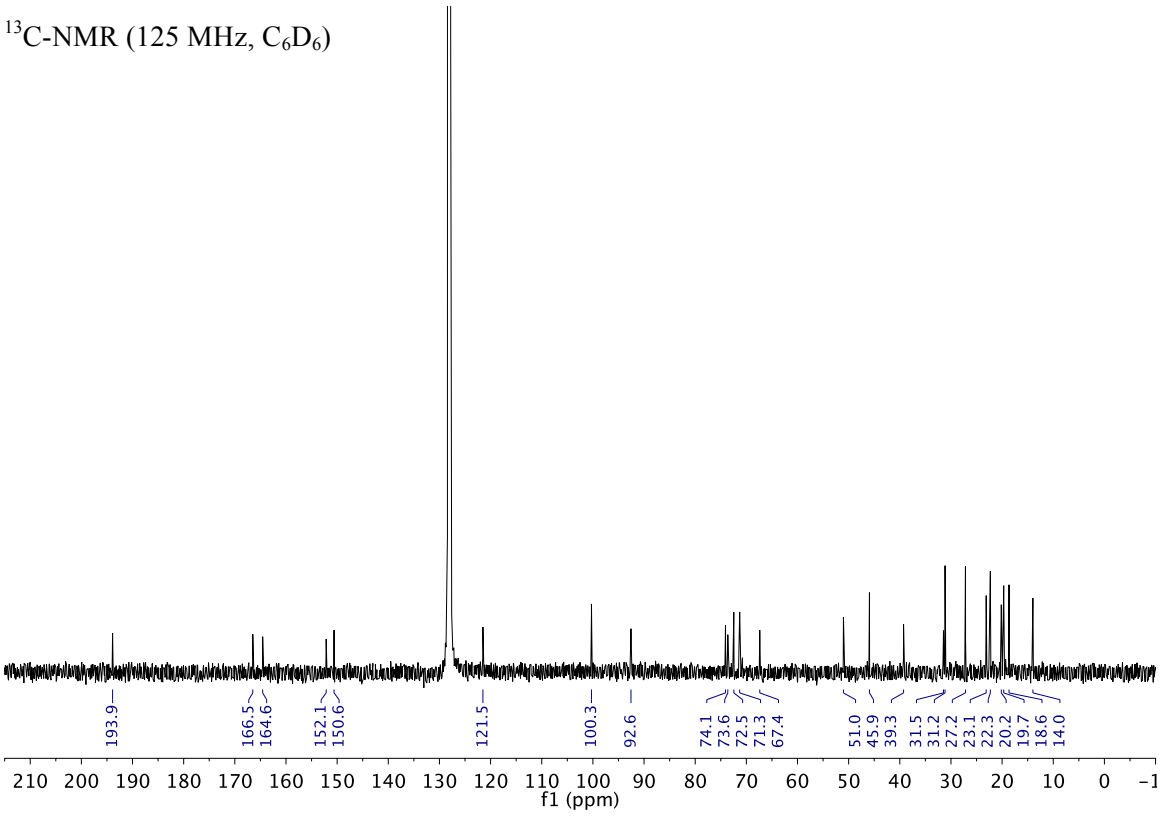


SI-8

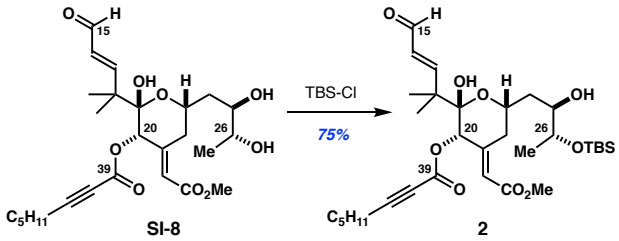
^{1}H-NMR (600 MHz, C_6D_6)



^{13}C-NMR (125 MHz, C_6D_6)



C-ring subunit Step m: conversion of C26-alcohol SI-8 to C26-TBS ether 2



Chemicals:
imidazole (99%, Acros): used without purification
TBS-Cl (98%, AK Scientific): used without purification

To a flame-dried, 1-dram vial equipped with magnetic stir bar was added triol **SI-8** (61 mg, 0.12 mmol, 1 equiv) and DMF (650 μL, 0.2 M). Imidazole (22 mg, 0.33 mmol, 2.5 equiv) was added in a single portion, followed by TBS-Cl (29 mg, 0.19 mmol, 1.5 equiv). The reaction mixture was stirred for 1.5h, at which point TLC analysis indicated complete conversion of **SI-8**. The reaction mixture was poured into a separatory funnel containing saturated aqueous NH_4Cl (10 mL) and EtOAc (15 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (10 mL). The combined organic layers were washed with water (2x10 mL) and brine (10 mL). The combined aqueous layers were then back-extracted with EtOAc (2x15 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification was accomplished by pH 7 buffered silica gel chromatography (100% pentane to elute TBS silanol, then 40% EtOAc/pentane to elute product), affording TBS ether **2** (56 mg, 75% yield) as an off-white foam. Compound purity was established by TLC (one spot) analysis.

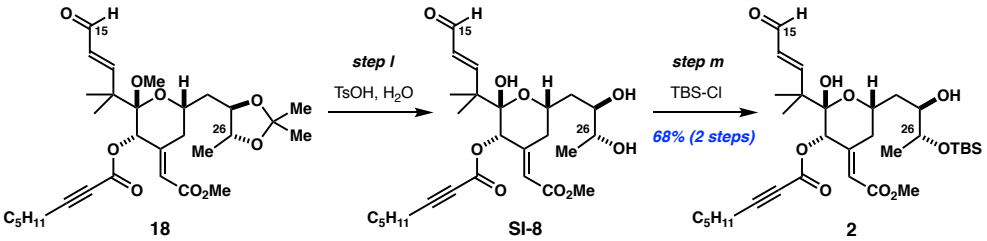
- **TLC** R_f = 0.47 (35% EtOAc/Hex, UV active, purple spot in *p*-anisaldehyde)
- **[α]$^{24.1}_{D}$** = -45.2° (*c* = 0.11, CH_2Cl_2)
- **IR** (thin film) 3422 (br), 2954, 2931, 2858, 2234, 1718, 1690, 1629, 1471, 1436, 1382, 1241, 1158, 1055, 982, 945, 888, 837, 777, 746 cm^{-1}

^{1}H-NMR (600 MHz, C_6D_6) δ 9.77 (d, *J* = 7.6 Hz, 1H, CHO), 7.43 (d, *J* = 16.1 Hz, 1H, $C_{17}H$), 6.27 (d, *J* = 1.9 Hz, 1H, $C_{34}H$), 6.10 (dd, *J* = 16.1, 7.6 Hz, 1H, $C_{16}H$), 5.48 (s, 1H, $C_{20}H$), 4.46 – 4.38 (m, 1H, $C_{23}H$), 4.07 (dd, *J* = 14.1, 2.5 Hz, 1H, $C_{22}H_a$), 3.77 – 3.70 (m, 1H, $C_{25}H$), 3.55 (bs, 1H, OH), 3.47 – 3.41 (m, 1H, $C_{26}H$), 3.29 (s, 3H, CO_2Me), 2.62 (bs, 1H, OH), 2.35 – 2.27 (m, 1H, $C_{22}H_b$), 1.94 – 1.83 (m, 2H, $C_{42}H_2$), 1.59 – 1.51 (m, 1H, $C_{24}H_a$), 1.43 – 1.37 (m, 1H, $C_{24}H_b$), 1.20 (app. p, *J* = 7.3 Hz, 2H), 1.10 – 1.02 (m, 4H), 1.04 (s, 3H), 1.02 (d, *J* = 6.1 Hz, 3H, $C_{27}H_3$), 0.98 (s, 3H), 0.91 (s, 9H, TBS), 0.75 (t, *J* = 6.9 Hz, 3H, $C_{46}H_3$), 0.02 (s, 3H, TBS), 0.00 (s, 3H, TBS); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 9.57 (d, *J* = 7.7 Hz, 1H, CHO), 7.33 (d, *J* = 16.1 Hz, 1H, $C_{17}H$), 6.04 (s, 1H, $C_{34}H$), 5.98 (dd, *J* = 16.1, 7.7 Hz, 1H, $C_{16}H$), 5.16 (s, 1H, $C_{20}H$), 4.28 – 4.20 (m, 1H), 3.70 (s, 3H, CO_2Me), 3.74 – 3.66 (m, 2H), 3.65 – 3.58 (m, 1H), 2.78 (bs, 1H, OH), 2.37 (d, *J* = 6.2 Hz, 1H, OH), 2.25 (app. td, *J* = 7.3, 3.7 Hz, 2H, $C_{42}H_2$), 2.22 – 2.14 (m, 1H), 1.80 – 1.72 (m, 1H, $C_{24}H_a$), 1.69 – 1.61 (m, 1H, $C_{24}H_b$), 1.53 (app. p, *J* = 7.2 Hz, 2H), 1.38 – 1.27 (m, 4H), 1.21 (d, *J* = 6.1 Hz, 3H), 1.16 (s, 3H), 1.15 (s, 3H), 0.91 (s, 9H, TBS), 0.90 (t, *J* = 6.9 Hz, 3H, $C_{46}H_3$), 0.11 (s, 3H, TBS), 0.10 (s, 3H, TBS)

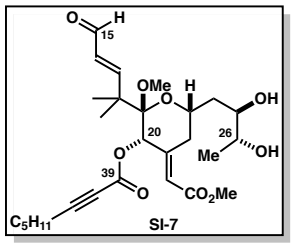
^{13}C-NMR (125 MHz, $CDCl_3$) δ 195.0, 166.4, 165.9, 151.9, 149.7, 127.6, 121.1, 99.7, 92.5, 73.5, 72.8, 71.5, 71.4, 67.2, 51.5, 45.8, 39.6, 31.3, 31.1, 27.1, 26.0, 23.2, 22.2, 20.1, 19.9, 18.7, 18.2, 14.0, -4.1, -4.7

HRMS calculated for $C_{32}H_{52}NaO_9Si$ $[M+Na]^+$: 631.3273; found 631.3267 (TOF ESI+)

C-ring subunit Steps l-m
(in practice, we employed this 2-step / 1 purification procedure for increased material throughput)



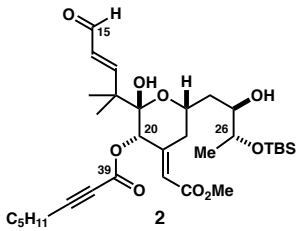
<Step l> To a one-neck, 250 mL round-bottom flask equipped with magnetic stir bar was added acetonide **18** (1.40 g, 2.08 mmol, 1 equiv) and 4:1 MeCN/H_2O (104 mL, 0.02M). *p*-TsOH-H_2O (3.95 g, 20.8 mmol, 10 equiv) was added in a single portion. The colorless reaction mixture was stirred at room temperature for 20.5h and in a 45 °C oil bath for 3.5h, at which point the reaction mixture was one spot by TLC (Note 1). The reaction mixture was cooled to 0 °C and poured into a 1L separatory funnel containing cooled (0 °C) saturated aqueous $NaHCO_3$ (125 mL) and CH_2Cl_2 (150 mL). The layers were separated, and the aqueous layer was sequentially extracted with CH_2Cl_2 (3x125 mL) and EtOAc (3x150 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to afford crude triol **SI-8** (1.00 g crude weight, ~97% yield), which was used immediately in the next step without purification, as triol **SI-8** will decompose upon storage.



Note 1: By TLC, the C25/C26 acetonide is hydrolyzed within a few hours at room temperature while the C19-OMe requires extended reaction times: **SI-7 TLC** R_f = 0.38 (80% EtOAc/Hex, UV active, purple spot in *p*-anisaldehyde); **SI-8 TLC** R_f = 0.24 (80% EtOAc/Hex, UV active, purple spot in *p*-anisaldehyde).

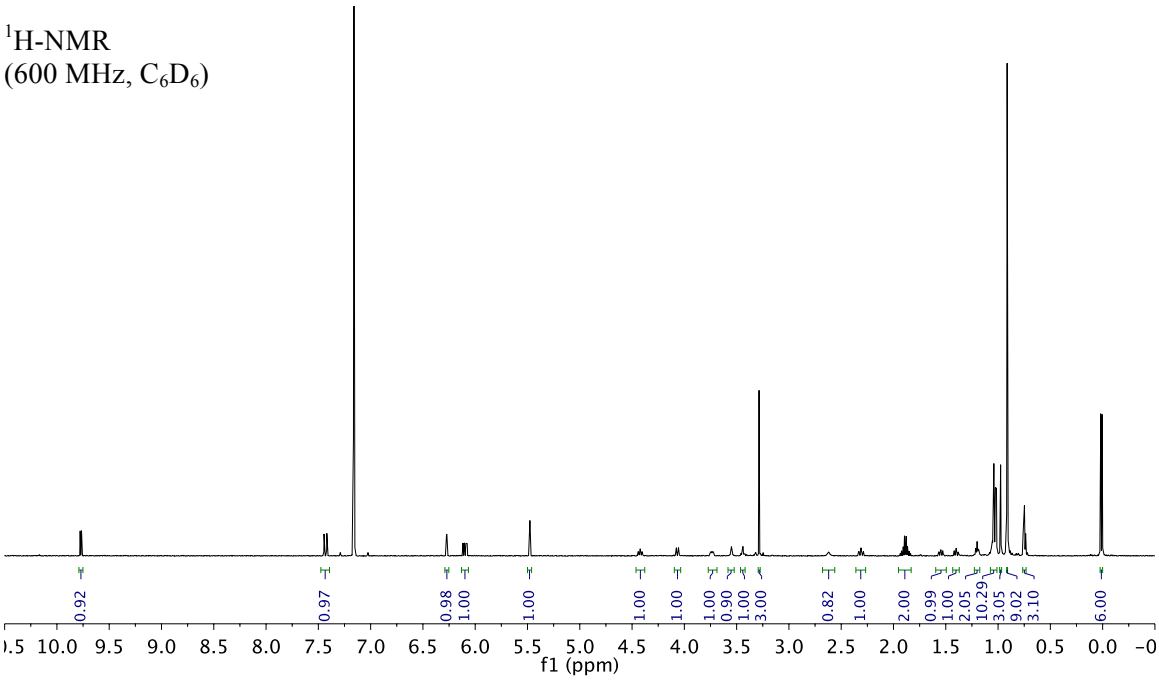
<Step m> To a flame-dried, one-neck, 50 mL round-bottom flask equipped with magnetic stir bar was added crude triol **SI-8** (assume 2.02 mmol, 1 equiv), DMF (10.1 mL, 0.2 M), and imidazole (481 mg, 7.07 mmol, 3.5 equiv). The reaction mixture was cooled with an ice bath (0 °C). TBS-Cl (456 mg, 3.03 mmol, 1.5 equiv) was added in a single portion and after 30 min at 0 °C, the reaction mixture was warmed to room temperature by removing the ice bath. After 1h at room temperature, an additional portion of TBS-Cl (152 mg, 0.5 equiv) was added. After an additional 30 min, TLC analysis indicated complete conversion of **SI-8**. The reaction mixture was poured into a separatory funnel containing an aqueous solution of phosphate buffer (pH 7.4, 100 mL) and EtOAc (150 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2x150 mL). The combined organic layers were washed with H_2O (2x100 ml) and brine (100 mL). The combined aqueous layers were then back-extracted with EtOAc (150 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification was accomplished by pH 7 buffered silica gel flash column chromatography (4.5x7 cm; 20% Et_2O/pentane to elute TBS silanol, then 70% Et_2O/pentane to elute product), affording TBS ether **2** (856 mg, 68% over 2 steps) as an off-white foam. Compound purity was established by TLC (one spot) analysis.

Experimentalists: SH, AJS, CTH, RVQ

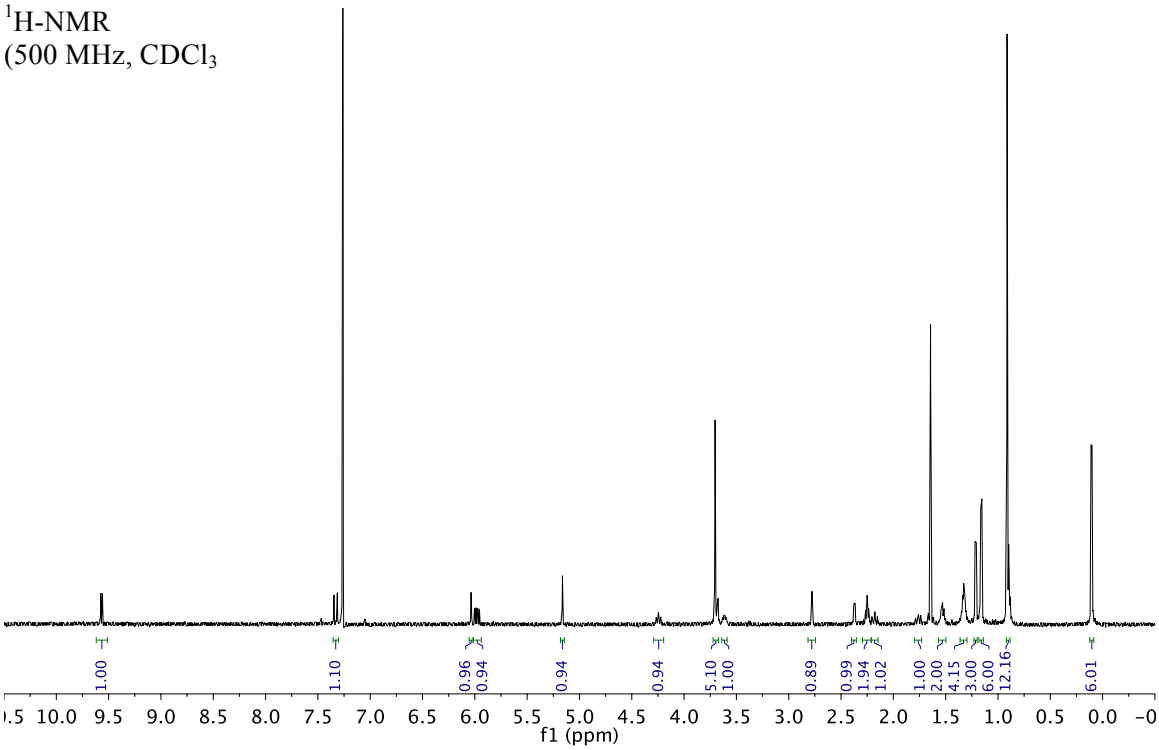


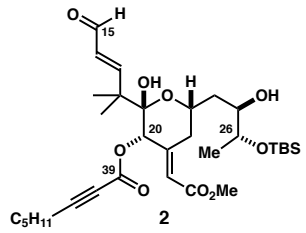
2

^{1}H-NMR
(600 MHz, C_6D_6)



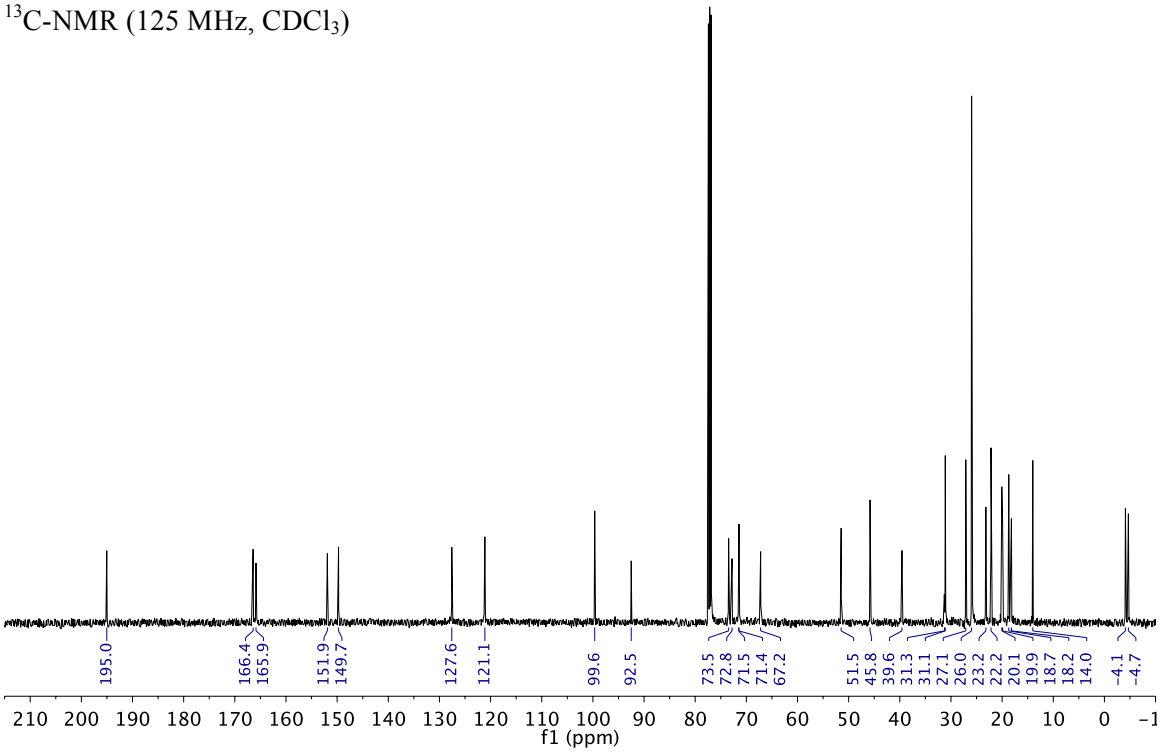
^{1}H-NMR
(500 MHz, $CDCl_3$)



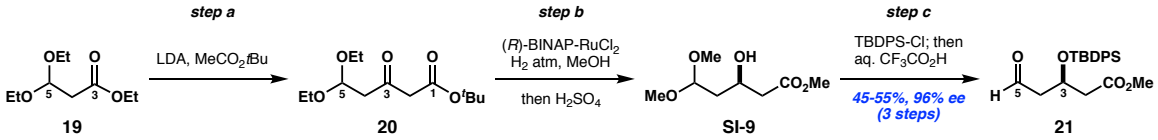


2

^{13}C-NMR (125 MHz, $CDCl_3$)

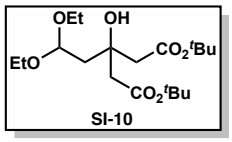


A-ring Subunit Steps a-c: conversion of 19 to aldehyde 21



<Step a>
Chemicals:
diisopropylamine: distilled from CaH_2 before use
ethyl 3,3-diethoxypropionate **19** (>95%, TCI): used without purification
n-BuLi (Sigma-Aldrich, 2.5 M solution in hexanes): used without purification
t-butyl acetate (>99%, Sigma-Aldrich): used without purification

To a flame-dried, one-neck, 250 mL round-bottom flask equipped with magnetic stir bar was added diisopropylamine (17.3 mL, 123 mmol, 4.1 equiv) and THF (60 mL, 0.5 M). The reaction mixture was cooled with a dry ice/acetone bath (-78 °C). n-BuLi (2.5M Hex, 48 mL, 121.5 mmol, 4 equiv) was added dropwise via syringe over 10 min. After an additional 15 min at -78 °C, t-butyl acetate (17.2 mL, 121.5 mmol, 4.05 equiv) was added via syringe down the side of the flask (10 min). After an additional 45 min at -78 °C, propionate **19** (5.8 mL, 30 mmol, 1 equiv) was added via syringe down the side of the flask (10 min). The reaction mixture was warmed to room temperature by removing the dry ice bath. After 90 min, the reaction mixture was quenched at 0 °C by adding saturated aqueous NH_4Cl (60 mL) and extracted with CH_2Cl_2 (3x60 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude material was placed under vacuum (~1 mmHg) in a 50 °C oil bath for 12h to remove t-butyl acetoacetate. The resulting material (8.6 g crude weight; 8:1 molar ratio of β-ketoester **20** and 3° alcohol **SI-10**) was divided into two equal portions (4.3g) for the next step (Noyori).



Characterization of β-ketoester **20**: To separate **20** from 3° alcohol **SI-10**, we acylated **SI-10** as follows: to a flame-dried, 10 mL round-bottom flask was added a mixture of **20** and **SI-10** (~80% wt. **20**, 100 mg combined weight, 0.05 mmol **20**, 1 equiv) in THF (4 mL), followed by freshly distilled pyridine (~10 µL, 0.10 mmol, 2 equiv). The reaction mixture was cooled with an ice bath (0 °C). Freshly distilled trifluoroacetic anhydride (~10 µL, 0.08 mmol, 1.5 equiv) was added and after 15 min, a new spot appeared by TLC. After an additional hour, the reaction mixture was quenched with triethylamine (1 mL), followed by saturated aqueous $NaHCO_3$ (1 mL). The reaction mixture was extracted with CH_2Cl_2 (3x5mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification was accomplished by silica gel flash column chromatography (5-30% EtOAc/Hex) affording a pure sample of β-ketoester **20** (~40 mg) for characterization. Compound purity was established by TLC (one spot) analysis.

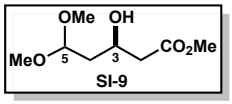
- **TLC** R_f = 0.56 (40% EtOAc/Hex)
- **IR** (thin film) 2978, 2931, 1742, 1717, 1648, 1370, 1326, 1254, 1152, 1062, 956, 840 cm^{-1}

^{1}H-NMR (500 MHz, $CDCl_3$): Ketone tautomer δ 4.88 (t, *J* = 5.6 Hz, 1H, C_5H), 3.66 (m, 2H), 3.53 (m, 2H), 3.40 (s, 2H, C_2H_2), 2.84 (d, *J* = 5.6 Hz, 2H, C_4H), 1.46 (s, 9H), 1.19 (t, *J* = 7.0 Hz, 6H); Enol tautomer δ 4.95 (s, 1H, C_2H), 4.83 (t, *J* = 5.8 Hz, 2H, C_5H), 2.49 (d, *J* = 5.8 Hz, 2H, C_4H), 1.48 (s, 9H); **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 200.9, 166.5, 100.0, 82.2, 62.8, 51.9, 47.8, 28.2, 15.5

HRMS calculated for $C_{13}H_{24}NaO_5$ $[M+Na]^+$: 283.1521; found 283.1512

<Step b>
Chemicals:
Methanol (99.8% Extra Dry, Acros): used without purification
Sulfuric acid (certified ACS plus, Fisher): used without purification
(*R*)-BINAP-$RuCl_2$: prepared according to Kitamura, M.; *et al.* (*64*).

To a flame-dried, one-neck, 50 mL round-bottom flask was added crude β-ketoester **20** (4.3 g, 16.4 mmol, assume 1 equiv) and methanol (16.4 mL, 1.0 M). The solution was degassed by sparging with Argon for 10 min and then transferred via syringe directly to the metal cylinder of a Parr apparatus equipped with magnetic stir bar. (*R*)-BINAP-$RuCl_2$ (55 mg, 0.06 mmol, 0.4 mol%) was added in one portion. With vigorous stirring, the Parr apparatus was charged to 200 psi with H_2 and vented (repeated 5X). The apparatus was then pressurized to 650 psi and placed in a 45 °C oil bath. After 48h, the apparatus was allowed to cool to room temperature and depressurized. Aliquot ^{1}H-NMR indicated full conversion of β-ketoester **20**. The solution was transferred via syringe to a flame-dried, one-neck, 50 mL round-bottom flask equipped with magnetic stir bar. Concentrated sulfuric acid (66 μL, 1.2 mmol, 7.5 mol%) was added dropwise, and the reaction mixture was placed in a 60 °C oil bath. After 10h, the trans-esterification to the methyl ester was complete as determined by aliquot ^{1}H-NMR. The reaction mixture was quenched at 0 °C by adding saturated aqueous $NaHCO_3$ (60 mL) and extracted with CH_2Cl_2 (4x60 mL) until TLC of the aqueous layer no longer showed product. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford crude alcohol **SI-9**. This crude material (3.3 g crude weight) was then divided into two portions for the next step (TBDPS protection).



Characterization of alcohol **SI-9**: A small portion of the crude material was purified by silica gel chromatography. The data matched literature values reported by Poupardin, O.; *et al.* (*65*). The enantiomeric excess of **SI-9** was 96% ee according to ^{1}H-NMR analysis of the derived 3(S)-MTPA Mosher ester performed according to Hoye, T.R.; *et al.* (*59*). **^{1}H-NMR** (600 MHz, $CDCl_3$): diagnostic peaks 3(S)-MTPA ester: 3.23 ppm (s, 3H), 3.27 ppm (s, 3H); 3(R)-MTPA ester: 3.30 ppm (s, 3H), 3.32 ppm (s, 3H).

Characterization data for **SI-9**:

TLC R_f 0.29 (60% EtOAc/Hex)

$[\alpha]^{24.0}_D$ = -11.4° (*c* = 0.3, CH_2Cl_2)

IR (thin film): 3446, 2953, 2931, 1737, 1439, 1127, 1064, 1049, 852, 817 cm^{-1}

^{1}H-NMR (600 MHz, $CDCl_3$) δ 4.60 (t, *J* = 5.6 Hz, 1H, C_5H), 4.25 – 4.16 (m, 1H, C_3H), 3.70 (s, 3H, CO_2Me), 3.36 (s, 3H), 3.36 (s, 3H), 3.32 (d, *J* = 3.2 Hz, 1H, OH), 2.55 – 2.44 (m, 2H), 1.85 – 1.74 (m, 2H)

^{13}C-NMR (125 MHz, $CDCl_3$) δ 172.8, 103.2, 65.1, 53.8, 53.5, 51.9, 41.5, 39.1

HRMS calculated for $C_8H_{16}NaO_5$ $[M+Na]^+$: 215.0895; found 215.0889

<Step c>
Chemicals:
imidazole (99%, Acros): used without purification
TBDPS-Cl (98%, AK Scientific): used without purification
trifluoroacetic acid (99%, Sigma-Aldrich): used without purification

To a flame-dried, two-neck, 50 mL round-bottom flask equipped with internal reaction thermometer and magnetic stir bar was added crude alcohol **SI-9** (1.0 g, 5.3 mmol, assume 1 equiv) and CH_2Cl_2 (10.6 mL, 0.5M). Imidazole (541 mg, 8.0 mmol, 1.5 equiv) was added in one portion, followed by TBDPS-Cl (1.38 mL, 5.3 mmol, 1 equiv) dropwise via syringe. After 4h, TLC analysis indicated complete conversion of alcohol **SI-9**. The reaction mixture was cooled with an ice bath (0 °C) and quenched by adding water (5.8 mL) followed by trifluoroacetic acid (5.8 mL), at a rate that maintained the internal temperature below 5 °C (~1 min). After 3h at 0 °C, aliquot ^{1}H-NMR indicated complete hydrolysis of the C5 acetal. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3x10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (20 mL), dried over $MgSO_4$, filtered, and concentrated. Purification was accomplished by silica gel flash column chromatography (5-10% EtOAc/Hex to elute silanol, then 10-20% EtOAc/Hex to elute product) affording aldehyde **21** (1.2 g) as a viscous, colorless oil. The remainder of crude alcohol **SI-9** (2.3 g) was processed identically to afford an additional 2.3g of aldehyde **21** (3.5g combined weight, 55% yield over 3 steps) (Note 1). Compound purity was established by TLC (one spot) analysis. Characterization data matched literature values reported by Moslin, R.; *et al.* (*66*) and Chikashita, H.; *et al.* (*67*).

Note 1: We have observed that aldehyde **21** slowly decomposes, even when stored in a benzene matrix at -20 °C. Therefore, aldehyde **21** was used in the next step (aldol) as soon as possible.

On Decagram-Scale: <Step a> To a flame-dried, three-neck, 1L round-bottom flask equipped with 125 mL addition funnel and magnetic stir bar was added diisopropylamine (45.3 mL, 320.3 mmol, 4.1 equiv) and THF (156 mL, 0.5 M). The reaction mixture was cooled with a dry ice/acetone bath (-78 °C). n-BuLi (2.5M Hex, 125 mL, 312.5 mmol, 4 equiv) was transferred to the addition funnel via positive pressure cannula, and added to the reaction mixture dropwise over 30 min. After an additional 20 min at -78 °C, t-butyl acetate (45.0 mL, 336.0 mmol, 4.3 equiv) was added via syringe down the side of the flask (addition time of 20 min). After an additional 45 min at -78 °C, propionate **19** (15.1 mL, 74 mmol, 1 equiv) was added via syringe down the side of the flask (10 min). The reaction mixture was warmed to room temperature by removing the dry ice bath. After 3.5h, the reaction mixture was quenched at 0 °C by adding saturated aqueous NH_4Cl (320 mL) and extracted with CH_2Cl_2 (3x125 mL). The combined organic layers were washed with 1M HCl (250 mL) to remove any residual amine that will inhibit the subsequent Noyori reduction. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude material was placed under vacuum (~1 mmHg) in a 35 °C oil bath for ~3 days to remove t-butyl acetoacetate. The resulting material (23.2 g crude weight; 16.8g of β-ketoester **20**, ~87% yield by ^{1}H-NMR; 7.1:1 molar ratio of β-ketoester **20** and 3° alcohol **SI-10**) was used directly in the next step.

<Step b> To a flame-dried, one-neck, 100 mL round-bottom flask equipped with magnetic stir bar was added crude β-ketoester **20** (23.2g crude weight, 16.8g of β-ketoester **20**, 64.3 mmol, 1 equiv) and methanol (64.3 mL, 1.0 M). The solution was degassed by sparging with Argon for 10 min, after which (*R*)-BINAP-$RuCl_2$ (102 mg, 0.13 mmol, 0.2 mol%) was added in one portion. The flask was placed in the metal cylinder of a Parr apparatus under Argon. With vigorous

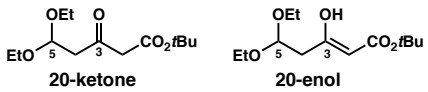
stirring, the Parr apparatus was charged to 400 psi with H_2 and vented (repeated 3X). The apparatus was then pressurized to 650 psi and placed in a 45 °C oil bath. After 3h, the apparatus was allowed to cool to room temperature and depressurized. Aliquot ^{1}H-NMR indicated incomplete conversion of β-ketoester **20**; therefore, additional (R)-BINAP-$RuCl_2$ (102 mg, 0.13 mmol, 0.2 mol%) was added (Note 1). The Parr apparatus was again charged to 650 psi with H_2. After 10h at 45 °C, aliquot ^{1}H-NMR indicated full conversion of β-ketoester **20**. Concentrated sulfuric acid (265 µL, 4.82 mmol, 7.5 mol%) was added dropwise, and the reaction mixture was placed in a 60 °C oil bath. After 10h, the trans-esterification to the methyl ester was complete as determined by aliquot ^{1}H-NMR. The reaction mixture was quenched at 0 °C by adding saturated aqueous $NaHCO_3$ (250 mL) and extracted with CH_2Cl_2 (4x250 mL) until TLC of the aqueous layer no longer showed product. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford crude alcohol **SI-9**. This crude material was used directly in the next step. The enantiomeric excess of **SI-9** was determined to be 96% ee by ^{1}H-NMR analysis of the derived 3(*S*)-MTPA Mosher ester according to Hoye, T.R. *et al.* (*59*).

Note 1: Typically, this Noyori hydrogenation is complete after 3-4h. However, depending on the amount of residual amines remaining from the Claisen condensation, additional Noyori catalyst may be necessary.

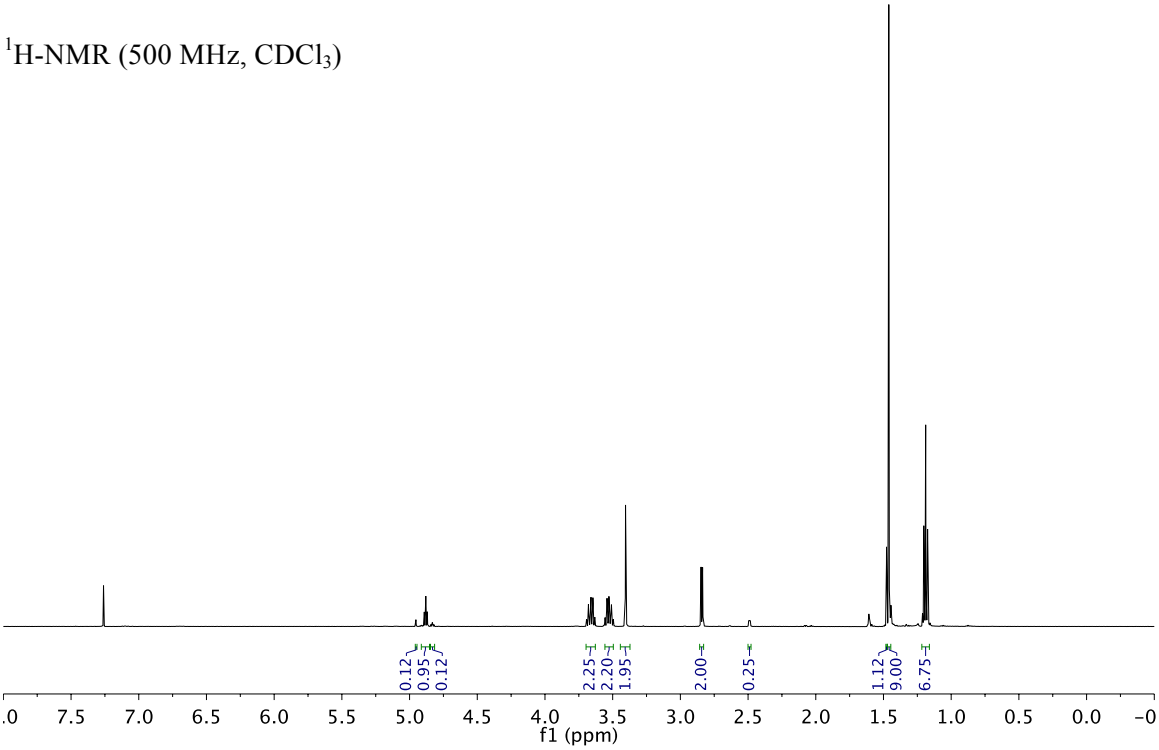
<Step c> To a flame-dried, one-neck, 1L round-bottom flask equipped with magnetic stir bar was added crude alcohol **SI-9** (assume 64.3 mmol, 1 equiv) and CH_2Cl_2 (128 mL, 0.5M). Imidazole (6.80 g, 99.8 mmol, 1.5 equiv) was added in one portion, followed by TBDPS-Cl (17.3 ml, 66.5 mmol, 1.05 equiv) dropwise via syringe. After 4h, TLC analysis indicated complete conversion of alcohol **SI-9**. The reaction mixture was cooled with an ice bath (0 °C) and quenched by adding water (73 mL) followed by trifluoroacetic acid (73 ml), at a rate that maintained the internal temperature below 5 °C (~25 min). After 3h at 0 °C, aliquot ^{1}H-NMR indicated complete hydrolysis of the C5 acetal. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3x150 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (275 mL), dried over $MgSO_4$, filtered, and concentrated. Purification was accomplished by silica gel flash column chromatography (5-10% EtOAc/Hex to elute silanol, then 10-20% EtOAc/Hex to elute product) affording aldehyde **21** (12.7 g, 45% yield over 3 steps) as a viscous, colorless oil (Note 1). Compound purity was established by TLC (one spot) analysis.

Note 1: We have observed that aldehyde **21** slowly decomposes, even when stored in a benzene matrix at -20 °C. Therefore, aldehyde **21** was used in the next step (aldol) as soon as possible.

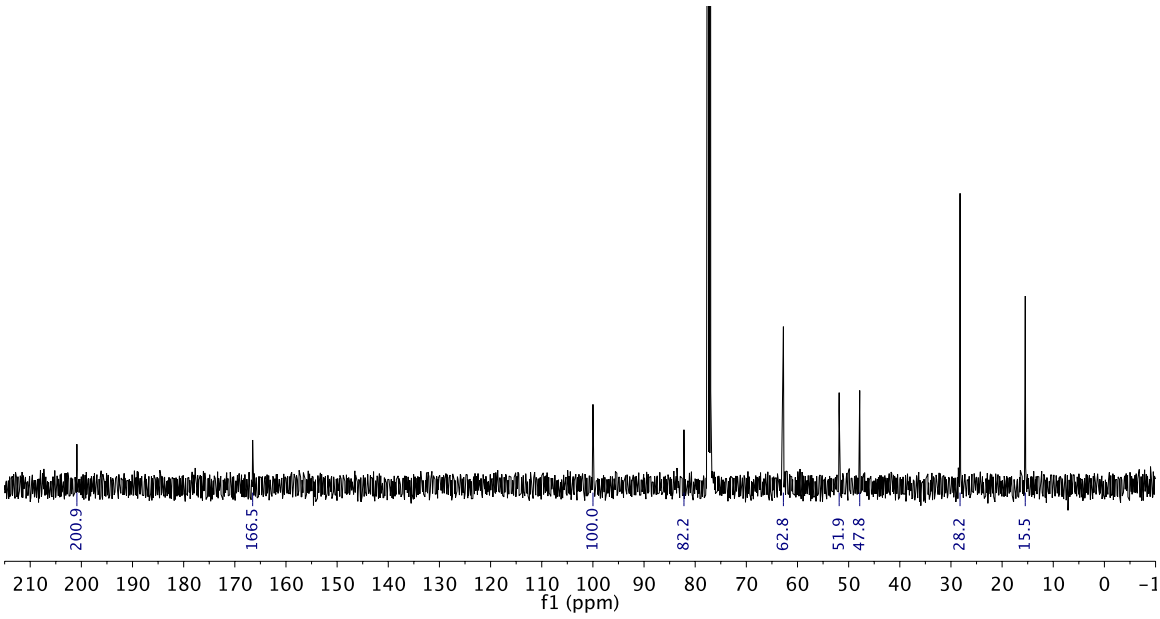
Experimentalists: CTH, SH, MSJ

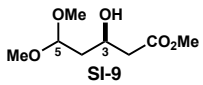


^{1}H-NMR (500 MHz, $CDCl_3$)



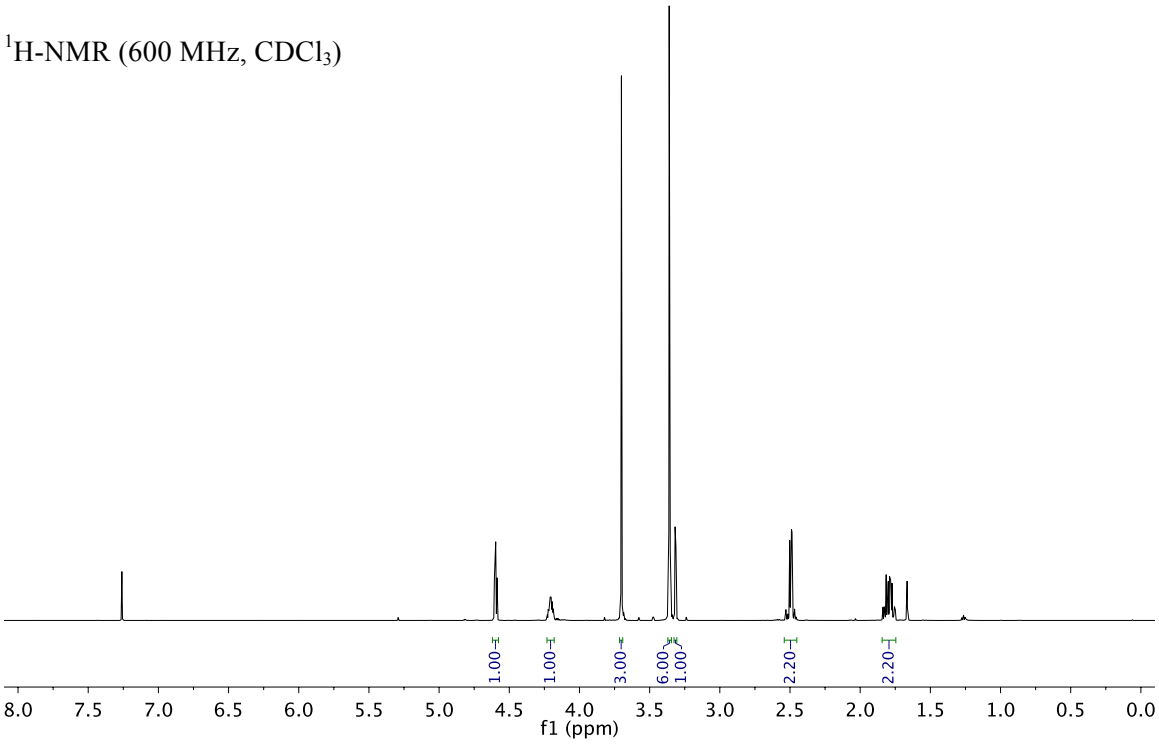
^{13}C-NMR (125 MHz, $CDCl_3$)



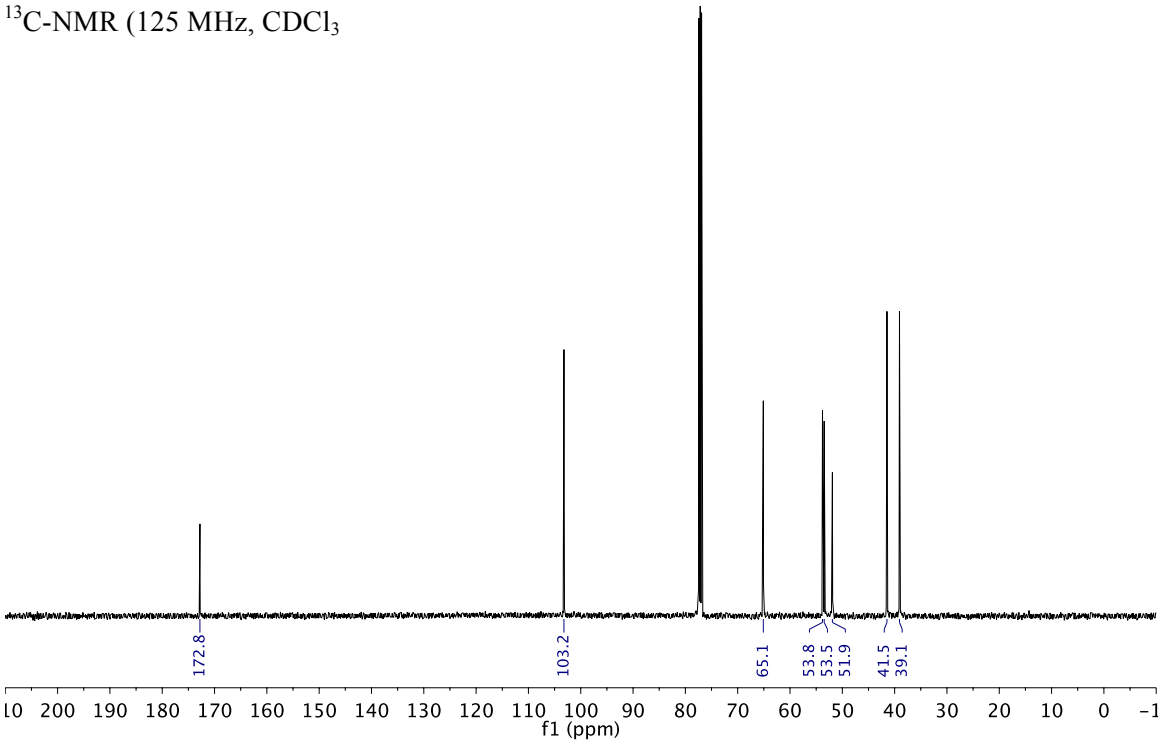


SI-9

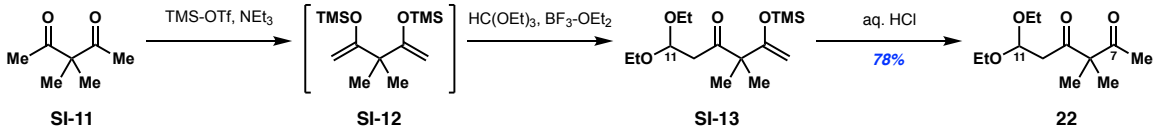
^{1}H-NMR (600 MHz, $CDCl_3$)



^{13}C-NMR (125 MHz, $CDCl_3$



A-ring Subunit: Preparation of β-diketone 22



Chemicals:
3,3-dimethyl-2,4-pentanedione **SI-11**: Sigma-Aldrich or according to Beck, K.; *et al.* (*68*).
Triethylamine (Sigma-Aldrich): distilled from CaH_2 before use
TMS-OTf (Oakwood): distilled from CaH_2 and stored under nitrogen
Triethylorthoformate (Sigma-Aldrich): distilled to remove ethanol and stored under nitrogen
BF_3-OEt_2 (Sigma-Aldrich): used without purification
Absolute EtOH (99.5%, Acros): used without purification
Concentrated HCl (Fisher): used without purification

To a flame-dried, three-necked, 1L round-bottom flask equipped with addition funnel and magnetic stir bar was added pentanedione **SI-11** (10 g, 78 mmol, 1 equiv) and CH_2Cl_2 (195 mL, 0.4M). The reaction mixture was cooled with an ice/acetone bath (-10 °C). Triethylamine (25 mL, 179 mmol, 2.3 equiv) was added via syringe over 1 min, followed by TMS-OTf (31.1 mL, 172 mmol, 2.2 equiv) dropwise via addition funnel over 15 min. The reaction mixture and ice bath were allowed to warm to room temperature over 2h. The solution gradually turned dark orange. After an additional 15h, aliquot ^{1}H-NMR indicated complete conversion of **SI-11**. **^{1}H-NMR** (300 MHz, $CDCl_3$): diagnostic peaks, mono-enolsilane of **SI-11** δ 4.27 (d, J = 2.1 Hz, 1H), 4.15 (d, J = 2.1 Hz, 1H); bis-enolsilane of **SI-11** δ 4.17 (d, J = 1.5 Hz, 1H), 4.02 (d, J = 1.5 Hz, 1H). The reaction mixture was cooled with a dry ice/acetone bath (-78 °C). Triethylorthoformate (15.5 mL, 93.6 mmol, 1.2 equiv) was added via syringe over 1 min, followed by BF_3-OEt_2 (11.6 mL, 1.2 equiv) dropwise via syringe over 5 min; at this point, the solution turned a brighter yellow/orange. After 1.5h at -78 °C, TLC analysis indicated complete conversion of bis-enolsilane **SI-12** and formation of **SI-13**. Absolute ethanol (50 mL) was added via syringe over 5 min, followed by concentrated HCl (~12M, 600 µL). The reaction mixture was stirred at -78 °C for 10 min and then warmed to 0 °C with an ice/water bath. After 10 min at 0 °C, TLC analysis indicated complete conversion of **SI-13** and formation of β-diketone **22**. The reaction mixture was quenched by adding saturated aqueous $NaHCO_3$ (300 mL) and extracted with CH_2Cl_2 (2x400 mL). The combined organic layers were washed with brine (300 mL), dried over $MgSO_4$, filtered, and concentrated to afford a dark orange oil. Purification was accomplished by silica gel flash column chromatography (1.5L of 10-20% EtOAc/Hex) affording β-diketone **22** (14.03 g, 78% yield) as a pale yellow oil. Compound purity of **22** was established by TLC (one spot) analysis.

Characterization data for **SI-13**:
TLC R_f = 0.56 (10% EtOAc/Hex, bright yellow spot in *p*-anisaldehyde)

IR (thin film): 2976, 2931, 1721, 1630, 1377, 1286, 1254, 1163, 1061, 1011, 847, 756 cm^{-1}

^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.94 (ddt, J = 5.6, 4.0, 1.8 Hz, 1H), 4.30 – 4.24 (m, 1H), 4.16 (dd, J = 2.2, 1.2 Hz, 1H), 3.66 (p, J = 7.0 Hz, 2H), 3.52 (p, J = 7.1 Hz, 2H), 2.84 (d, J = 5.5 Hz, 2H), 1.16 (m, 12H), 0.19 (s, 9H)

^{13}C-NMR (125 MHz, $CDCl_3$) δ 209.4, 161.8, 100.7, 89.1, 62.8, 54.1, 42.2, 22.5, 15.4, 0.1

HRMS calculated for $C_{15}H_{30}NaO_4Si$ $[M+Na]^+$: 325.1811; found 325.1796 (TOF ESI+)

Characterization data for β-diketone **22**:
TLC R_f = 0.48 (20% EtOAc/Hex, UV active, yellow spot in *p*-anisaldehyde)

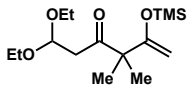
IR (thin film): 2978, 2932, 1720, 1701, 1566, 1373, 1357, 1126, 1060 cm^{-1}

^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.96 (t, *J* = 5.6 Hz, 1H, $C_{11}H$), 3.71 – 3.61 (m, 2H), 3.57 – 3.46 (m, 2H), 2.73 (d, *J* = 5.6 Hz, 2H, $C_{10}H$), 2.11 (s, 3H), 1.32 (s, 6H), 1.17 (t, *J* = 7.0 Hz, 6H)

^{13}C-NMR (125 MHz, $CDCl_3$) δ 207.5, 206.9, 100.3, 63.0 (2C), 43.5, 26.5, 21.0, 15.4

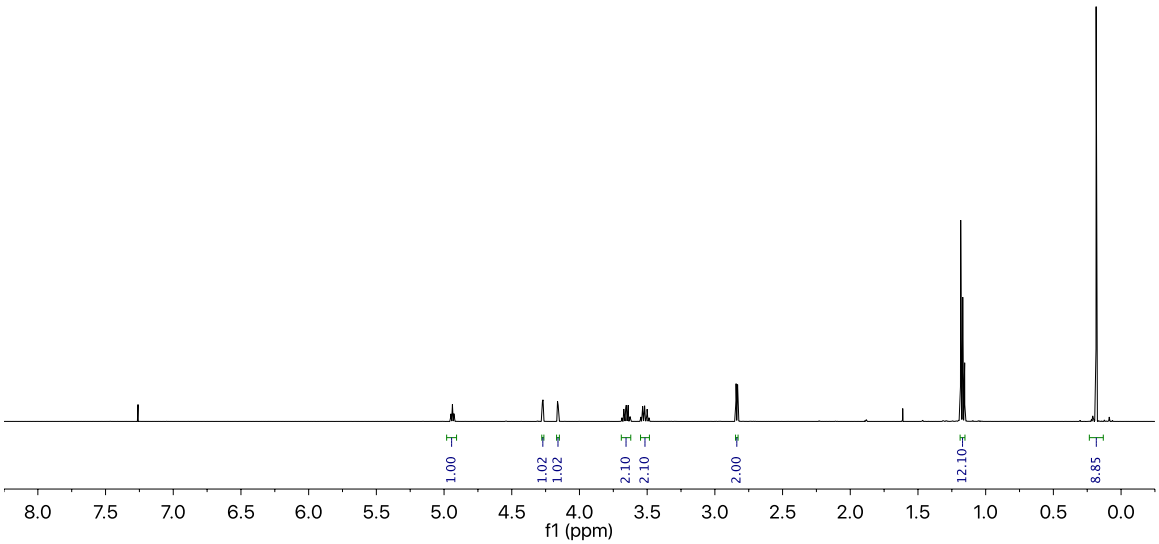
HRMS calculated for $C_{12}H_{22}NaO_4$ $[M+Na]^+$: 253.1410; found 253.1415 (TOF ESI+)

Experimentalists: JLS, SH, CTH

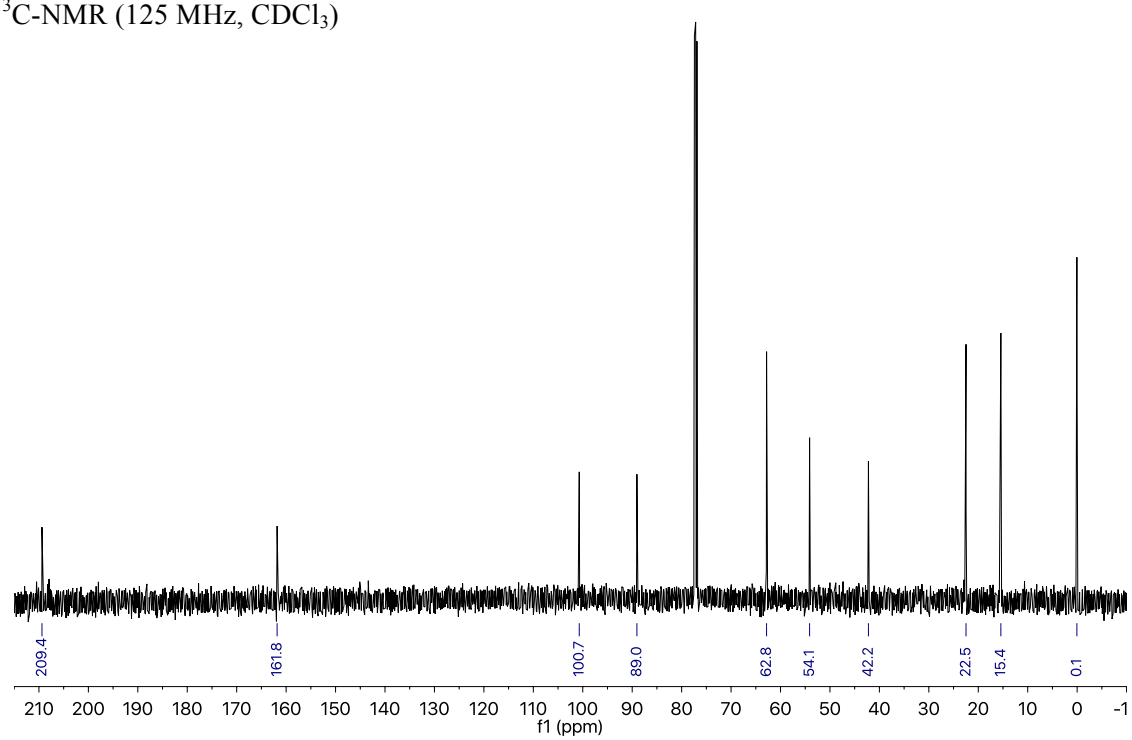


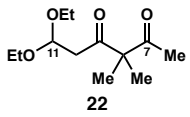
SI-13

^{1}H-NMR (500 MHz, $CDCl_3$)



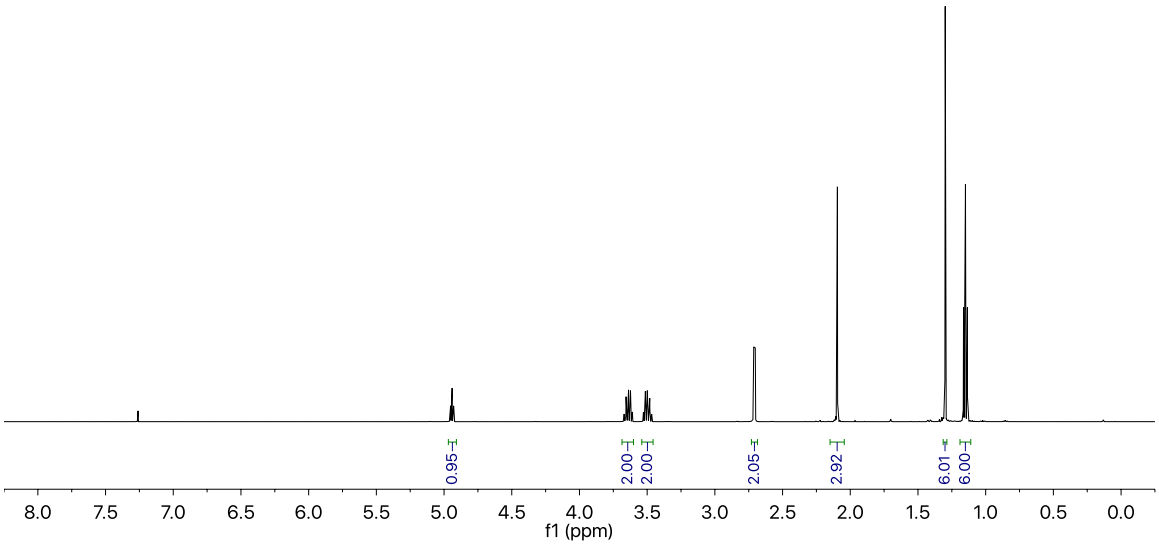
^{13}C-NMR (125 MHz, $CDCl_3$)



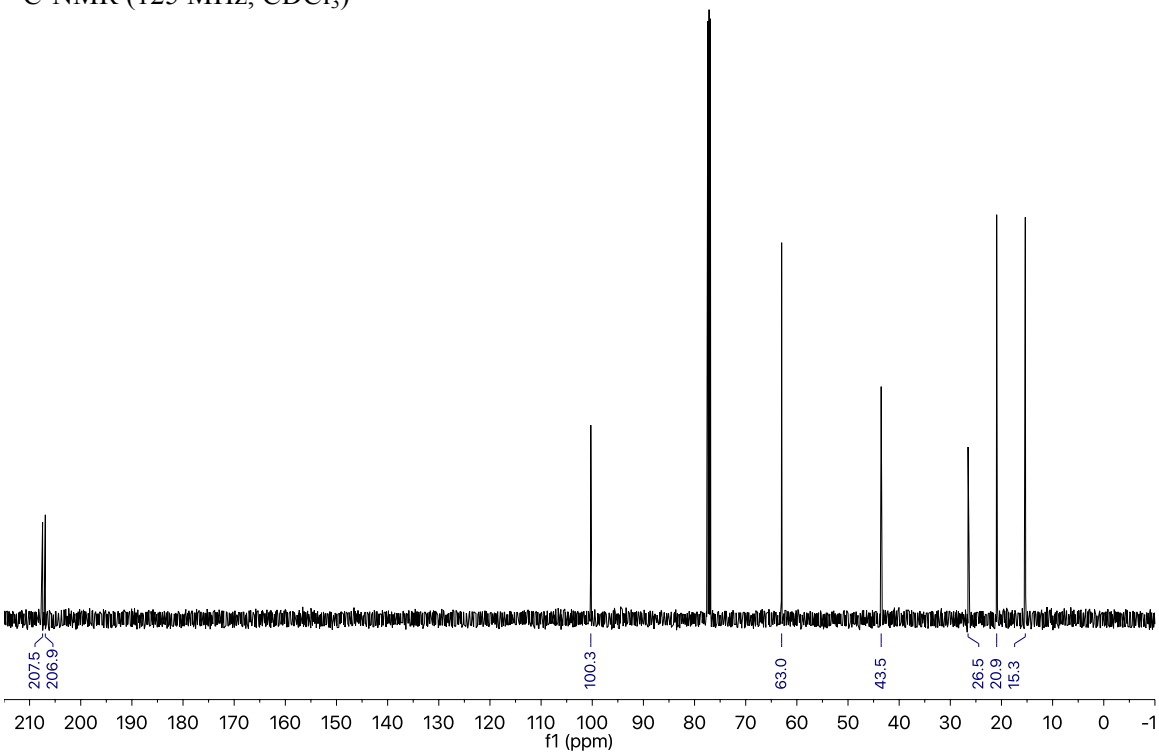


22

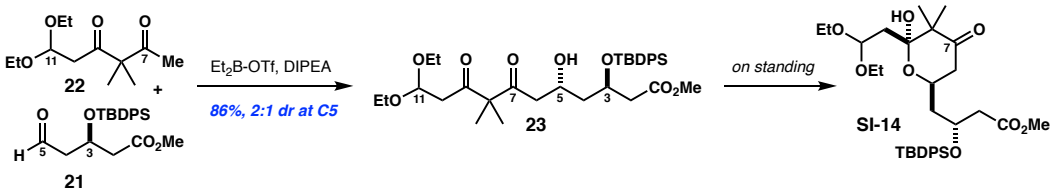
^{1}H-NMR (500 MHz, $CDCl_3$)



^{13}C-NMR (125 MHz, $CDCl_3$)



A-ring Subunit Step d: conversion of ketone 21 and aldehyde 22 to hemiketal SI-14



Chemicals:
Triethylborane (1M Hexanes, Sigma-Aldrich): used without purification
Triflic acid (Oakwood): distilled before use (bp 70 °C at 15 mmHg); forerun was discarded
Hunig's base (Sigma-Aldrich): distilled from CaH_2 before use
21 and **22**: azeotroped with benzene (3x5 mL) and placed under vacuum for 15 min before use

Preparation of diethyl boron triflate (hexanes solution): To a flame-dried, one-neck, 200 mL round-bottom flask equipped with magnetic stir bar was added triethylborane (1M Hexanes, 29 mL, 29 mmol, 1 equiv) via syringe over 1 min. Triflic acid (2.55 mL, 29 mmol, 1 equiv) was added dropwise via *glass* syringe over 1 min. The reaction mixture was stirred for 60 min and immediately used without purification.

Note 1: Triflic acid is insoluble in hexanes but over the course of several minutes, gas evolution is observed from the formation of ethane, and the solution becomes homogeneous and pale yellow.
Note 2: The aldol crucially depends on the quality of triflic acid and diethyl boron triflate.

Aldol: To a flame-dried, two-neck, 500 mL round-bottom flask equipped with magnetic stir bar was added β-diketone **22** (6.8 g, 29.6 mmol, 2 equiv) and Et_2O (59 mL, 0.25M). The reaction mixture was cooled with a dry ice/acetone bath (-78 °C). After 10 min, diethyl boron triflate (freshly-prepared hexanes solution, 29 mmol, 1.95 equiv) was added dropwise via syringe over 10 min. The reaction mixture turned pale yellow (Note 1). After 10 min, Hunig's base (5.16 mL, 29.6 mmol, 2 equiv) was added dropwise via syringe over 10 min. The reaction mixture gradually turned orange-red. After 40 min at -78 °C, ^{1}H-NMR analysis from a MeOD quenching experiment indicated quantitative enolization (Note 2). n-Pentane (120 mL) was added via syringe down the side of the flask over 30 min, and the reaction mixture was cooled with a liquid N_2/MeOH bath (-95 °C, Note 3). After 10 min, a solution of aldehyde **21** (5.7 g, 14.8 mmol, 1 equiv) in n-pentane (20 mL) was added dropwise over 5 min. After 4h at -95 °C, aliquot ^{1}H-NMR indicated complete conversion of aldehyde **21**. The reaction mixture was quenched by adding methanol (74 mL; 5 mL MeOH / 1 mmol aldehyde) via pipette (~15 min), at a rate that maintained the internal temperature below -60 °C (at this point, the internal reaction temperature was monitored by placing a thermometer directly into the solution). The reaction mixture was warmed to -20 °C over ~15 min by removing the cooling bath, and then poured into a cooled (0 °C) Erlenmeyer flask containing Et_2O (100 mL) and pH 7.4 buffer (100 mL). After stirring for 10 min, the layers were separated, and the aqueous layer was extracted with Et_2O (5x200 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification was accomplished by pH 7 buffered silica gel flash column chromatography (7x13 cm), collecting 30 mL fractions and eluting with CH_2Cl_2 (1L) followed by 33-50% Et_2O/Hex (1.5L), affording a mixture of hydroxy-ketone **23** and its hemiketal isomer **SI-14** (7.8g, 2:1 dr at C5, 86% combined yield) (Notes 4, 5). This mixture of open and closed isomers was used in the next step without separation, as **23** and **SI-14** are in equilibrium. The C5 diastereomers were separated at a later stage in the sequence (after C11 silylation). However, a small portion of the material was purified by silica gel chromatography to afford a sample of hemiketal **SI-14** for characterization; diagnostic ^{1}H-NMR peaks are also provided for the undesired isomers.

Note 1: The following pictures depict typical solution colors (from a smaller-scale reaction).


10 min after addition of Et_2B-OTf


30 min after addition of DIPEA


10 min after addition of aldehyde


2h after addition of aldehyde

Note 2: A 100 µL aliquot of the reaction mixture was rapidly quenched at -78 °C with MeOD. The resulting mixture was concentrated and analyzed by ^{1}H-NMR in $CDCl_3$.
Note 3: The diastereoselectivity of the reaction at -78 °C is ~1.6-1.8:1 dr (at C5).
Note 4: Hydroxy-ketone **23** slowly cyclizes to its hemiketal isomer, **SI-14**, even when stored in a benzene matrix at -20 °C. Therefore, the product of this aldol reaction was generally isolated as a mixture of equilibrating isomers and used in the next step without separation.
Note 5: Unreacted β-diketone **22** and hemiketal **SI-14** have similar retention factors on silica gel and are difficult to separate by chromatography. However, the mixture may be used together in steps **e**/**f**, as β-diketone **22** is inert under the reaction conditions; afterwards, the compounds are readily separable.

Experimentalists: SH, MSJ, SMR

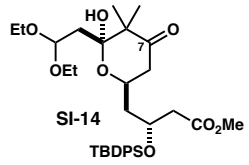
1. Characterization data for hemiketal **SI-14** (desired diastereomer):
- **TLC** R_f = 0.5 (20% EtOAc/Hex)
- $[\alpha]^{23.0}_D$ = -16.7° (*c* = 2.0, CH_2Cl_2)
- **IR** (thin film) 3419, 2974, 2932, 1740, 1719, 1473, 1428, 1375, 1112, 1072 cm^{-1}
- **HRMS** calculated for $C_{34}H_{50}NaO_8Si$ $[M+Na]^+$: 637.3167; found 637.3167 (TOF ESI+)

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.73 – 7.61 (m, 4H), 7.46 – 7.34 (m, 6H), 5.14 (s, 1H, C_9-OH), 4.91 (dd, *J* = 9.1, 2.8 Hz, 1H, $C_{11}H$), 4.27 – 4.19 (m, 1H, C_5H), 4.01 – 3.92 (m, 1H, C_3H), 3.81 – 3.71 (m, 1H, OEt), 3.58 (s, 3H, CO_2Me), 3.64 – 3.51 (m, 2H, OEt), 3.51 – 3.42 (m, 1H, OEt), 2.61 – 2.51 (m, 2H, C_6H_2), 2.06 (dd, *J* = 14.6, 11.2 Hz, 1H, C_2H_a), 1.98 – 1.81 (m, 4H, C_2H_b, $C_{10}H_2$, C_4H_a), 1.58 (app. dt, *J* = 14.0, 4.3 Hz, 1H, C_4H_b), 1.20 (t, *J* = 7.0 Hz, 3H, OEt), 1.16 (t, *J* = 7.1 Hz, 3H, OEt), 1.06 (s, 3H), 1.03 (s, 3H), 1.01 (s, 9H, TBDPS); **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 210.2, 171.8, 135.9, 135.9, 134.0, 133.6, 130.0, 129.9, 127.7 (2C), 101.9, 100.7, 69.1, 66.4, 62.5, 61.9, 53.2, 51.6, 44.0, 43.3, 43.0, 35.8, 27.0, 23.0, 19.4, 17.9, 15.5, 15.3

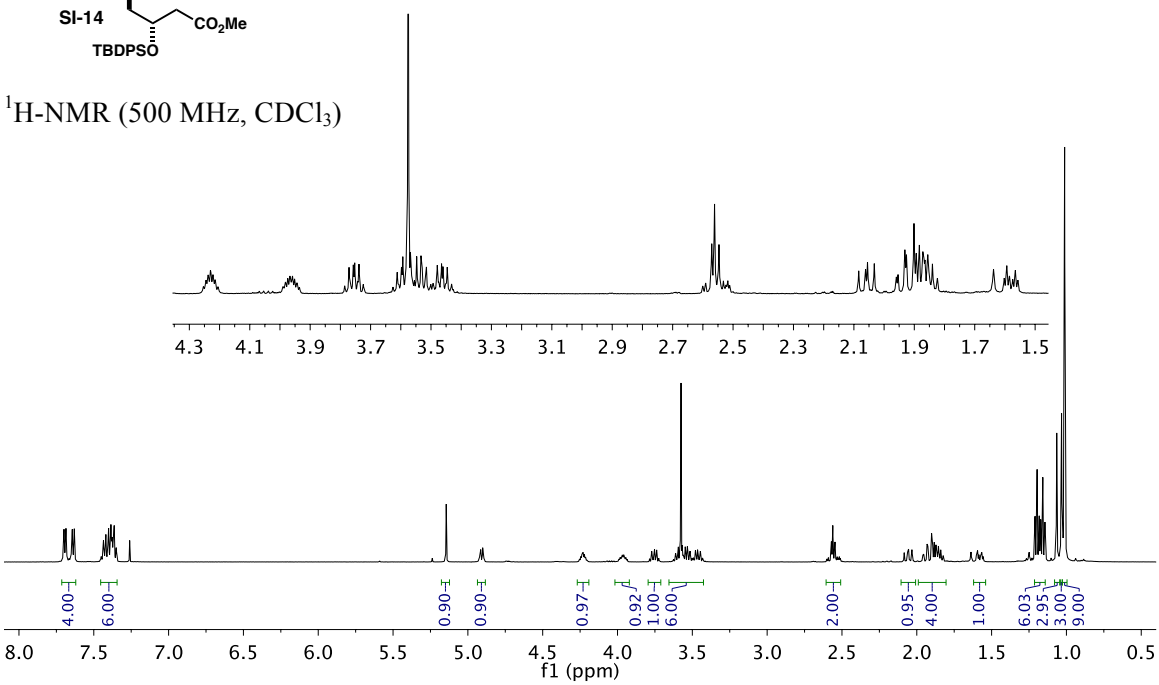
2. Diagnostic data for hemiketal **SI-14** (undesired diastereomer):
^{1}H-NMR (400 MHz, $CDCl_3$) diagnostic peaks δ 5.24 (s, 1H, C_9-OH), 4.74 (dd, *J* = 7.8, 4.1 Hz, 1H, $C_{11}H$), 3.57 (s, 3H, CO_2Me)

3. Diagnostic data for hydroxy-ketone **23** (as a mixture of C5 diastereomers):
TLC R_f = 0.23 (30% EtOAc/Hex)

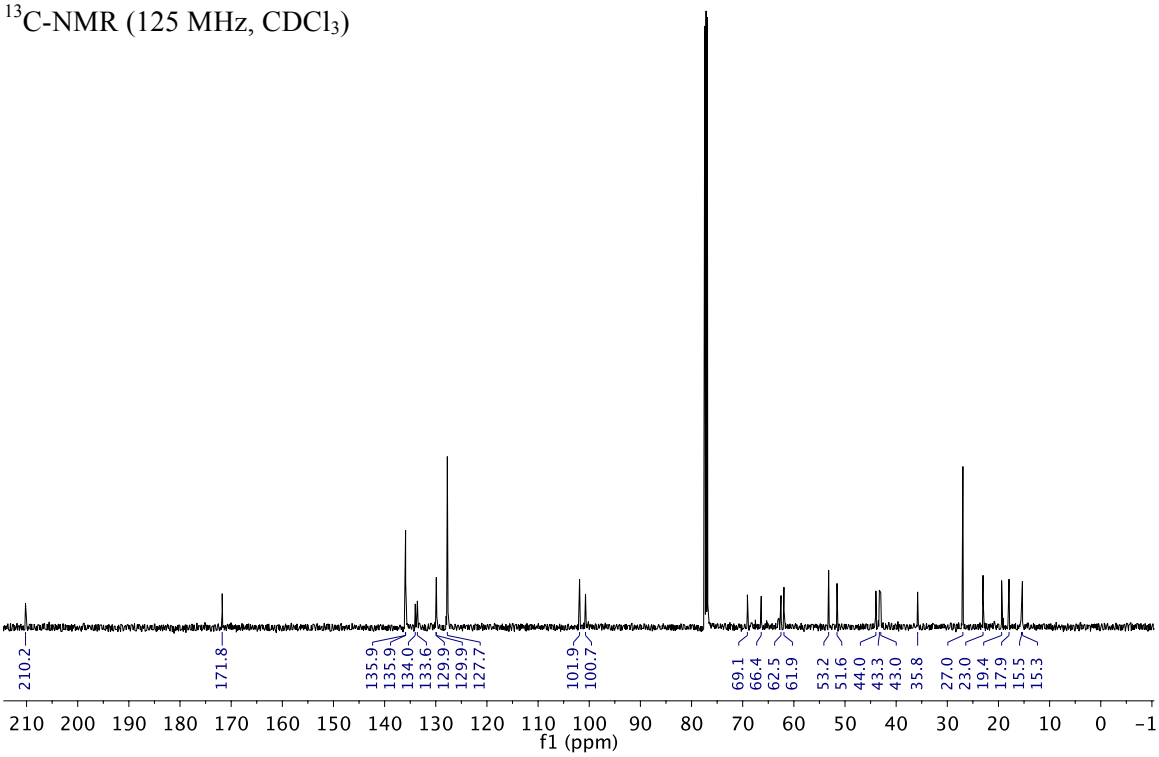
^{1}H-NMR (500 MHz, $CDCl_3$): diagnostic peaks δ 4.94 (t, *J* = 5.6 Hz, 1H, $C_{11}H$), 4.41 – 4.32 (m, 1H), 4.22 – 4.08 (m, 1H), 3.67 – 3.59 (m, 2H, OEt), 3.58 – 3.46 (m, 5H, OEt, CO_2Me), 2.76 – 2.64 (m, 2H), 2.62 – 2.48 (m, 2H), 2.47 – 2.23 (m, 2H)



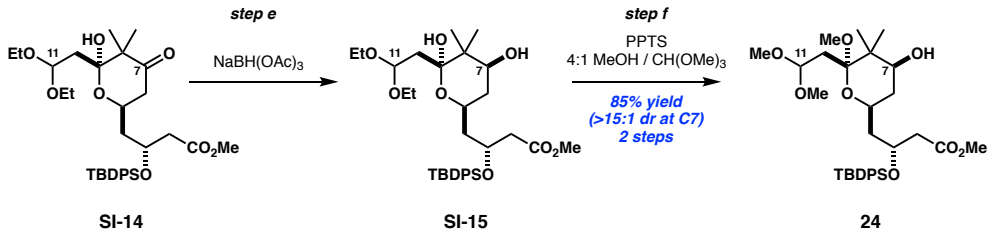
^{1}H-NMR (500 MHz, $CDCl_3$)



^{13}C-NMR (125 MHz, $CDCl_3$)



A-ring Subunit Steps e-f: conversion of SI-14 to 24



SI-14 SI-15 24

<Step e>

Chemicals:
Acetic acid (>99%, Sigma-Aldrich): used without purification
Acetone (99.8%, Extra Dry, Acros): used without purification
Acetonitrile (99.9%, Extra Dry, Acros): used without purification
Sodium triacetoxyborohydride (97%, Sigma-Aldrich): used without purification
SI-14: azeotroped with benzene (3x15 mL) and placed under vacuum for 10 min before use

The following procedure was adapted from Evans, D.A.; *et al.* (*40)*.

Preparation of $NaBH(OAc)_3$ solution: To a flame-dried, one-neck, 250 mL round-bottom flask equipped with magnetic stir bar was added acetone (75 mL) via syringe, followed by acetic acid (75 mL) via syringe. The reaction mixture was cooled with an ice bath (0 °C). Sodium triacetoxyborohydride (23.8 g, 112 mmol, 5 equiv) was added in four portions over 10 min. The reaction mixture was vigorously stirred for 20 min, during which time the solution became homogeneous, and immediately used without purification.

Reduction: To a flame-dried, one-neck, 1L round-bottom flask equipped with magnetic stir bar was added hemiketal **SI-14** (13.8 g, 22.4 mmol, 1 equiv, Note 1). The flask was cooled with an ice bath (0 °C). Acetonitrile (37 mL) was added via syringe, followed by acetic acid (37 mL) via syringe. After 20 min, $NaBH(OAc)_3$ (150 mL of freshly-prepared solution) was added via nitrogen positive pressure cannula down the side of the flask (20 min). The final reaction mixture consisted of a 0.1M solution of 1:2:3 MeCN / acetone / AcOH. The reaction mixture and ice bath were allowed to warm to 15 °C over 2h. After an additional 6h, the reaction mixture was cooled with an ice bath and additional $NaBH(OAc)_3$ (9.5 g, 2 equiv) was added, this time as two solid portions over 5 min. The reaction mixture was again allowed to warm to 15 °C over 2h. After an additional 10h (total reaction time of 20h), aliquot ^{1}H-NMR indicated complete conversion of hemiketal **SI-14**. The reaction mixture was cooled with an ice bath (0 °C) and then poured into a cooled (0 °C) 2L Erlenmeyer flask containing 50% Et_2O / petroleum ether (400 mL). The reaction mixture was quenched at 0 °C by adding saturated aqueous Rochelle's salt (250 mL) over 15 min. After vigorously stirring for 10 min, saturated aqueous $NaHCO_3$ (500 mL) was added over 30 min until bubbling ceased (**CAUTION**: significant amounts of carbon dioxide are generated). The layers were separated, and the aqueous layer was extracted with 80% Et_2O / petroleum ether (4x250 mL) until TLC of the aqueous layer showed no remaining product. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford crude alcohol **SI-15**, which was used in the next step without purification (the equilibrium between open and closed isomers complicated purification and ^{1}H-NMR analysis).

<Step f>
Chemicals:
Methanol (99.8% Extra Dry, Acros): used without purification
PPTS (98%, Sigma-Aldrich): used without purification
Trimethylorthoformate (Sigma-Aldrich): distilled prior to use and stored under nitrogen

To a flame-dried, one-neck, 1L round-bottom flask equipped with magnetic stir bar was added crude alcohol **SI-15** (assume 22.4 mmol, 1 equiv) and 4:1 MeOH / $CH(OMe)_3$ (125 mL, 0.18M). The flask was cooled with an ice bath (0 °C), and PPTS (5.6 g, 6.2 mmol, 1 equiv) was added in one portion. The reaction mixture and ice bath were allowed to warm to 15 °C over 2h. After an additional 22h, aliquot ^{1}H-NMR indicated complete conversion of alcohol **SI-15**. The reaction mixture was cooled with an ice bath, diluted with cooled (0 °C) 50% Et_2O/petroleum ether (500 mL), and then quenched by adding saturated aqueous $NaHCO_3$ (250 mL) over 15 min. The layers were separated, and the aqueous layer was extracted with 80% Et_2O/petroleum ether (4x250 mL) until TLC of the aqueous layer showed no remaining product. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification was accomplished by silica gel flash column chromatography (7x15 cm), collecting 30 mL fractions, and eluting with 10% EtOAc/petroleum ether (500 mL), 15% EtOAc/PE (500 mL), 20% EtOAc/PE (500 mL), 30% EtOAc/PE (500 mL), 40% EtOAc/PE (1L), affording product **24** (11.5g, >15:1 dr at C7, 85% combined yield) as a viscous, colorless oil (Note 1).

Note 1: This reaction sequence (steps **e/f**) was conducted with the 2:1 mixture of diastereomers obtained from the aldol step; the complete separation of diastereomers was performed following C11 silylation (step **i**). However, the front fractions collected from the silica gel column are enriched in the desired aldol adduct. Therefore, this material was re-purified to afford a sample of **24** for characterization.

TLC R_f = 0.26 (20% EtOAc/Hex, CAM)

$[\alpha]^{23.3}_{D}$ = +3.8° (*c* = 0.9, CH_2Cl_2)

IR (thin film) 3479 (bs), 2951, 1740, 1473, 1428, 1384, 1112, 704 cm^{-1}

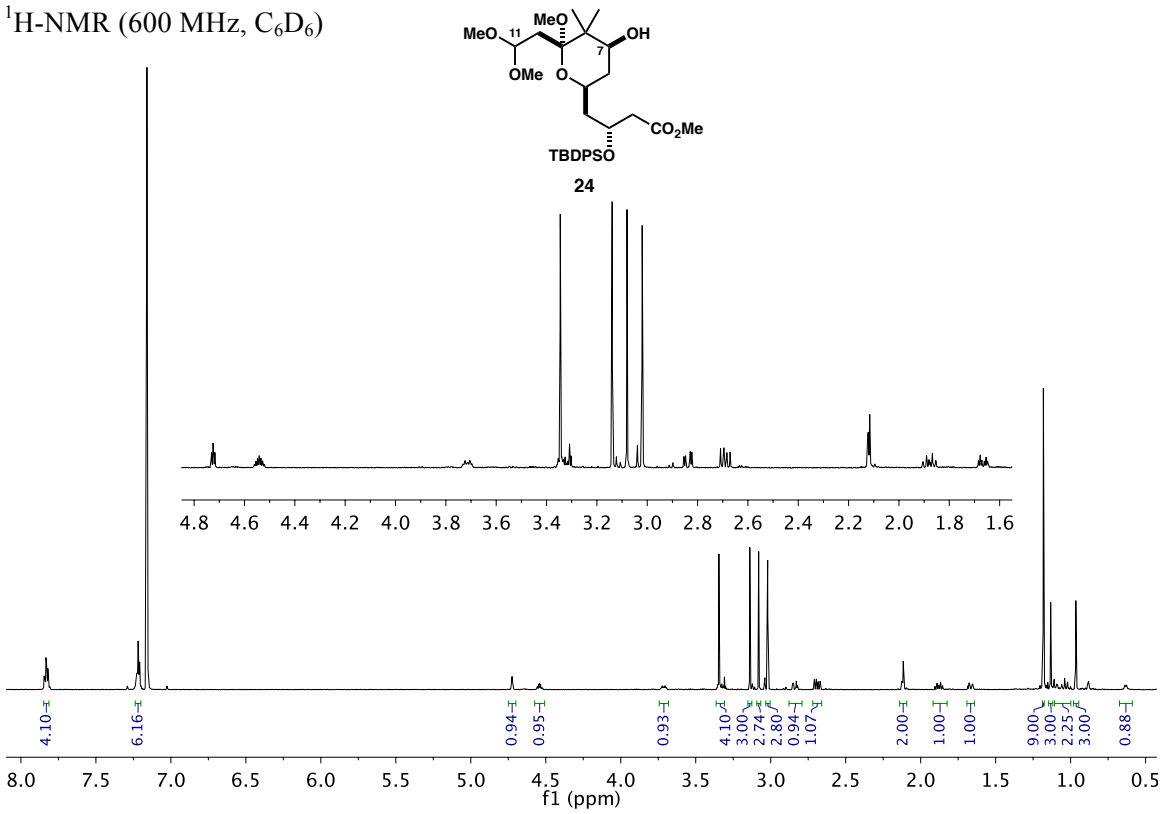
^{1}H-NMR (600 MHz, C_6D_6) δ 7.85 – 7.81 (m, 4H), 7.24 – 7.20 (m, 6H), 4.72 (dd, *J* = 4.5, 3.6 Hz, 1H, $C_{11}H$), 4.54 (app. tt, *J* = 8.0, 3.9 Hz, 1H, C_3H), 3.75 – 3.68 (m, 1H, C_7H), 3.35 (s, 3H, CO_2Me), 3.37 – 3.31 (m, 1H, C_5H), 3.14 (s, 3H), 3.08 (s, 3H), 3.02 (s, 3H), 2.84 (dd, *J* = 15.0, 4.0 Hz, 1H, C_2H_a), 2.69 (dd, *J* = 15.0, 7.9 Hz, 1H, C_2H_b), 2.13 – 2.11 (m, 2H, $C_{10}H_2$), 1.88 (dt, *J* = 14.0, 8.2 Hz, 1H, C_4H_a), 1.67 (dt, *J* = 14.0, 4.1 Hz, 1H, C_4H_b), 1.18 (s, 9H, TBDPS), 1.13 (s, 3H), 1.12 – 1.08 (m, 1H, C_6H_a), 1.08 – 1.00 (m, 1H, C_6H_b), 0.97 (s, 3H), 0.65 (bs, 1H, C7-OH)

^{13}C-NMR (125 MHz, $CDCl_3$) δ 172.2, 136.1 (2C), 134.3, 133.9, 130.0, 129.9, 127.8 (2C), 103.9, 101.5, 71.0, 69.7, 66.5, 53.4, 51.9, 51.7, 48.4, 44.0, 43.4, 43.1, 37.5, 36.1, 27.1, 20.0, 19.5, 15.9

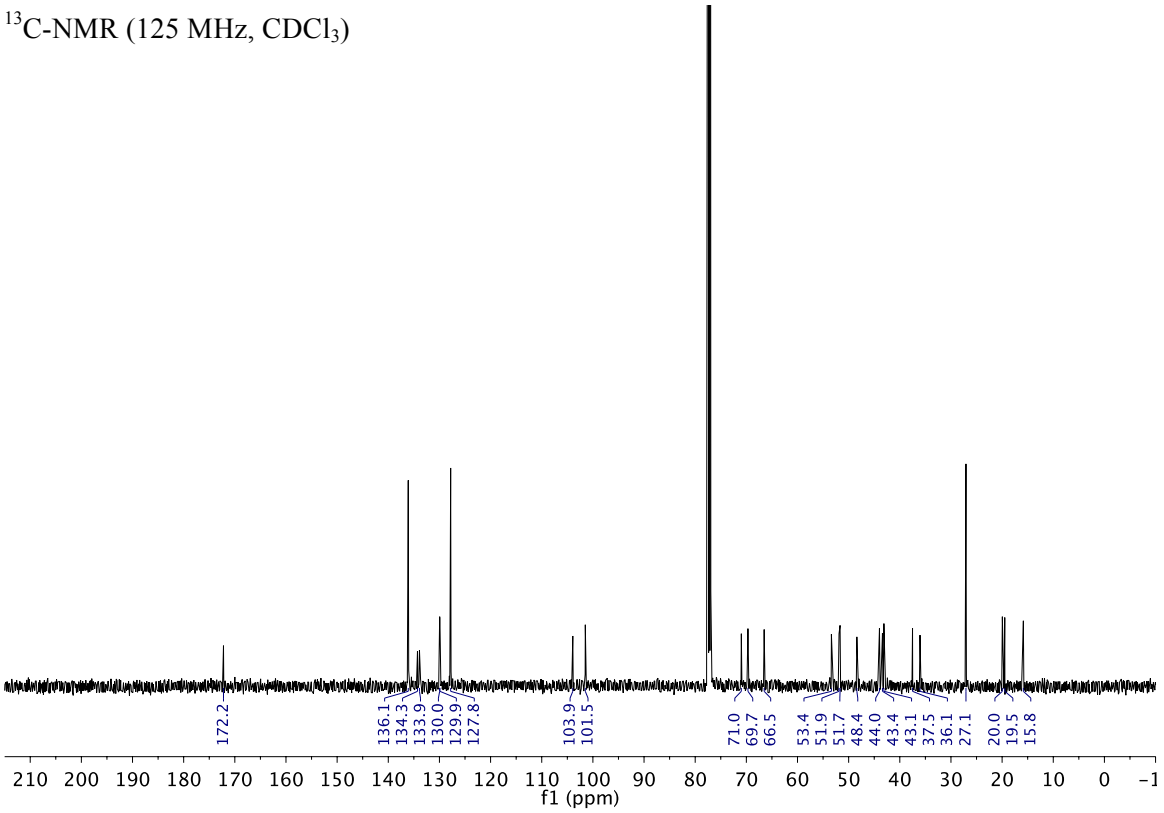
HRMS calculated for $C_{33}H_{50}NaO_8Si$ $[M+Na]^+$: 625.3167; found 625.3166 (TOF ESI+)

Experimentalists: SH, CTH, SMR

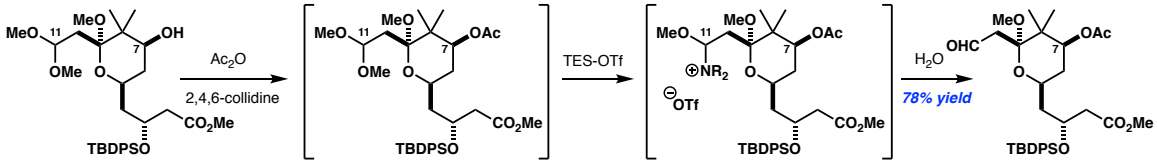
^{1}H-NMR (600 MHz, C_6D_6)



^{13}C-NMR (125 MHz, $CDCl_3$)



A-ring Subunit Step g: conversion of 24 to aldehyde 25



Chemicals:
DMAP (>99%, Sigma-Aldrich): used without purification
Acetic anhydride (>99%, Sigma-Aldrich): distilled before use
2,4,6-collidine (Sigma-Aldrich): distilled from CaH_2 and stored under nitrogen
TES-OTf (Oakwood): distilled from CaH_2 and stored under nitrogen
24: azeotroped with benzene (3x15 mL) and placed under vacuum for 15 min before use

The following procedure was adapted from Fujioka, H.; *et al.* (41).

To a flame-dried, one-neck, 500 mL round-bottom flask equipped with magnetic stir bar was sequentially added C7-alcohol **24** (10.0g, 16.6 mmol, 1 equiv, Note 1), CH_2Cl_2 (166 mL, 0.1M), and DMAP (203 mg, 1.66 mmol, 10 mol%). The reaction mixture was cooled with an acetonitrile/dry ice bath (-40 °C). 2,4,6-collidine (19.7 mL, 149 mmol, 9 equiv) was added via syringe over 5 min, followed by acetic anhydride (1.7 mL, 18.2 mmol, 1.1 equiv) via syringe (addition time of 2 min). After 4h at -40 °C, aliquot ^{1}H-NMR indicated complete conversion of C7-alcohol **24** (diagnostic peak C_9-OMe). TES-OTf (20.6 mL, 91.2 mmol, 5.5 equiv) was added dropwise via syringe down the side of the flask (addition time of 5 min). The solution gradually turned pink/brown. After 2h at -40 °C, a small reaction aliquot was quenched with H_2O and analyzed by ^{1}H-NMR, which indicated complete conversion of **SI-16** (diagnostic peak C_{11}H). Therefore, the remainder of the reaction mixture was quenched by adding H_2O (166 mL) over 10 min. The now-frozen solution was placed in an ice bath (0 °C). After vigorously stirring for 2h at 0 °C, aliquot ^{1}H-NMR indicated complete hydrolysis of the C11 acetal. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3x250 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to ~100 mL. At this point, 5% EtOAc/Hex (250 mL) was added to precipitate collidine-triflate salts. The resulting suspension was concentrated to ~30 mL. The supernatant was transferred via pipette to the top of a slurry-packed silica gel column (7x18 cm), using several thorough washings (Note 2), which was eluted with 5-40% EtOAc/Hex (2.5L) to afford aldehyde **25** (7.7 g, 78% yield) as a viscous, colorless oil (Note 1).

Note 1: This reaction (step **g**) was conducted with the 2:1 mixture of diastereomers obtained from the aldol step; the complete separation of diastereomers was performed following C11 silylation (step **i**). However, a small portion was diastereomerically enriched to afford a sample of aldehyde **25** for characterization.
Note 2: The remaining collidine-triflate salts were dissolved in CH_2Cl_2 and analyzed by TLC to confirm that all of the crude material was transferred to the silica gel column.

Experimentalists: SH, CTH, SMR

TLC R_f = 0.45 (30% EtOAc/Hex, UV active, purple spot in *p*-anisaldehyde)

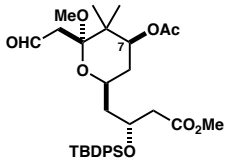
IR (thin film) 2951, 2934, 2857, 1736, 1428, 1388, 1366, 1238, 1110, 1070, 1023, 737, 701 cm^{-1}

^{1}H-NMR (500 MHz, C_6D_6) δ 9.62 (t, *J* = 3.1 Hz, 1H, CHO), 7.84 – 7.75 (m, 4H), 7.33 – 7.19 (m, 6H), 5.27 (dd, *J* = 11.8, 4.8 Hz, 1H, C_7H), 4.48 – 4.39 (m, 1H, C_3H), 3.36 (s, 3H, CO_2Me), 3.37 – 3.28 (m, 1H, C_5H), 2.74 (s, 3H, C_9-OMe), 2.65 – 2.54 (m, 2H, C_2H_2), 2.27 (d, *J* = 3.1 Hz, 2H, $C_{10}H_2$), 1.85 – 1.76 (m, 1H), 1.61 (s, 3H, C7-OAc), 1.63 – 1.57 (m, 1H), 1.47 – 1.38 (m, 1H), 1.16 (s, 9H, TBDPS), 1.06 (app. q, *J* = 11.9 Hz, 1H), 0.85 (s, 3H), 0.83 (s, 3H)

^{13}C-NMR (125 MHz, $CDCl_3$) δ 201.3, 171.7, 170.6, 135.99, 135.97, 133.9, 133.7, 130.0 (2C), 127.80, 127.77, 104.0, 72.8, 69.1, 66.5, 51.6, 48.7, 45.8, 43.6, 43.3, 41.9, 32.9, 27.0, 21.3, 20.8, 19.4, 17.5

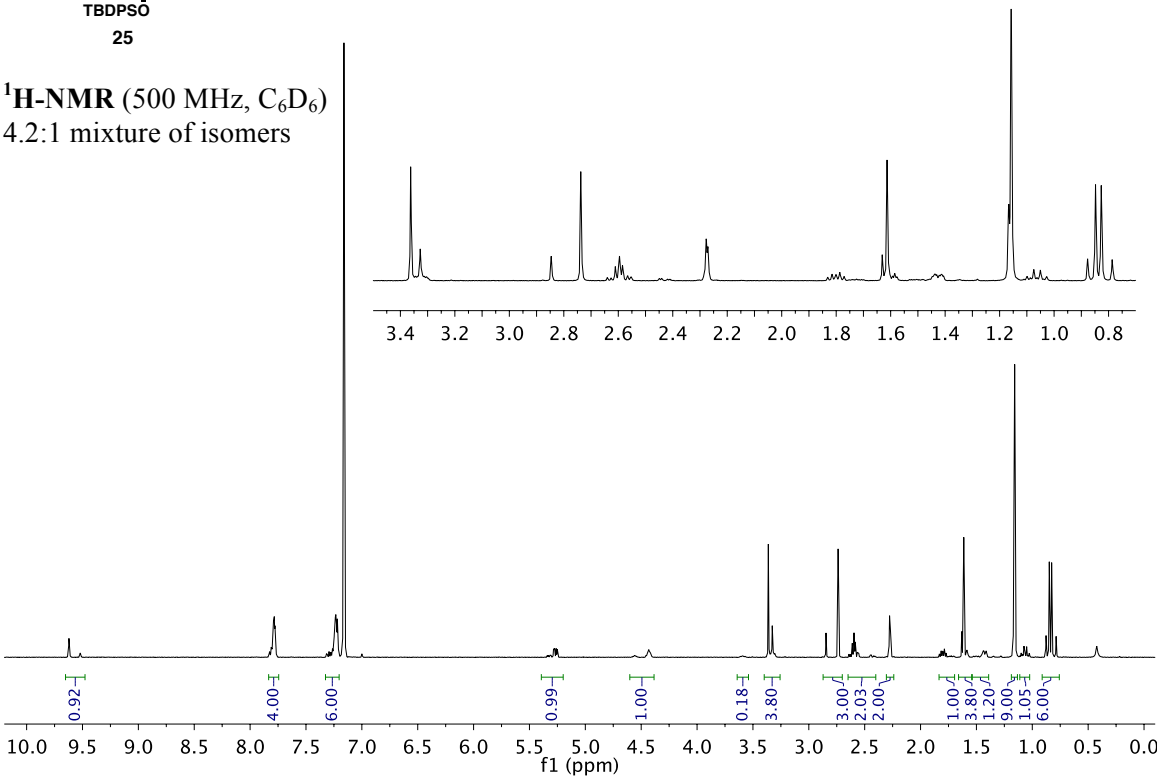
HRMS calculated for $C_{33}H_{46}NaO_8Si$ $[M+Na]^+$: 621.2860; found 621.2864 (TOF ESI+)

Experimentalists: SH, CTH, SMR

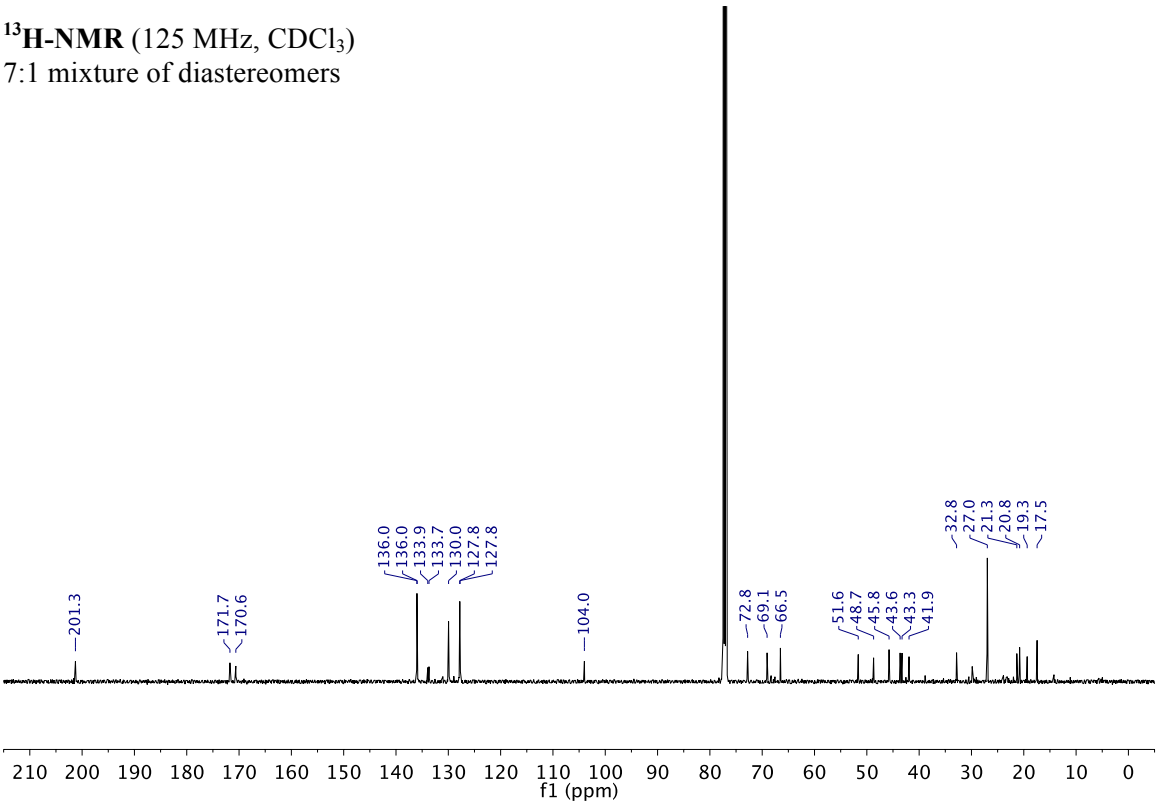


25

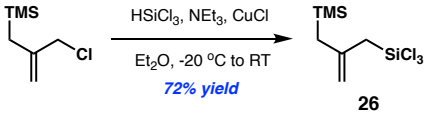
^{1}H-NMR (500 MHz, C_6D_6)
4.2:1 mixture of isomers



^{13}H-NMR (125 MHz, $CDCl_3$)
7:1 mixture of diastereomers



A-ring Subunit: preparation of silane 26



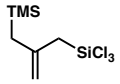
Chemicals:
2-(chloromethyl)allyl-trimethylsilane: commercially avilable from Sigma-Aldrich (97%); alternatively, prepared according to Trost, B.M.; *et al.* (*69*)
Copper(I) chloride (97%, Sigma-Aldrich): used without purification
4Å powdered molecular sieves: dried in vacuum oven (150 °C) for several days prior to use
Trichlorosilane (99%, Sigma-Aldrich): used without purification
Triethylamine (Sigma-Aldrich): distilled from CaH_2 before use

To a flame-dried, one-neck, 250 mL round-bottom flask equipped with magnetic stir bar was added 4Å powdered molecular sieves (4 g), Et_2O (155 mL, 0.25 M) and copper (I) chloride (4.6 g, 46.5 mmol, 1.2 equiv). The reaction mixture was vigorously stirred for 1h and then cooled to -20 °C. Triethylamine (18.9 mL, 136 mmol, 3.5 equiv) was added dropwise via syringe (addition time of 5 min), followed by 2-(chloromethyl)allyl-trimethylsilane (6.3 g, 38.7 mmol, 1 equiv) dropwise via syringe (5 min), and finally tricholorosilane (8.2 mL, 81.3 mmol, 2.1 equiv) dropwise via syringe (15 min). The reaction mixture and cooling bath were allowed to warm to 20 °C over 3h. After an additional 13h, aliquot ^{1}H-NMR indicated complete conversion of starting material. The supernatant was carefully transferred (air-free) via syringe to a flame-dried, one-neck, 250 mL round-bottom flask equipped with magnetic stir bar. Et_2O washes (3x30mL) were performed to facilitate quantitative transfer. The round-bottom flask was affixed with a short-path distillation head and placed in a 50 °C oil bath to remove solvent (Et_2O) and residual tricholorosilane. Subsequently, the short-path distillation head was exchanged for a clean one (free from HCl salts), which was used to collect silane **26** at 65-70 °C, ~1 mmHg (7.3 g, 72% yield) as a colorless oil (measured density, 1.1). Silane **26** was found to be hydrolytically unstable and prone to decomposition if stored in a -20 °C freezer. Therefore, **26** was immediately dissolved in CH_2Cl_2 for the subsequent allylation reaction (step **h**). A small sample of this CH_2Cl_2 solution was analyzed for characterization purposes.

^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.74 (s, 1H), 4.71 (s, 1H), 2.30 (s, 2H), 1.65 (s, 2H), 0.04 (s, 9H)

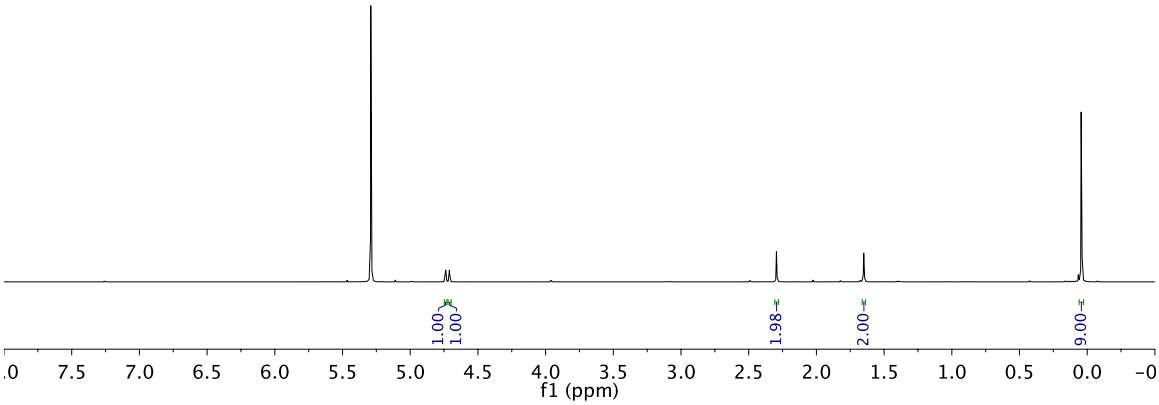
^{13}C-NMR (125 MHz, $CDCl_3$) δ 137.9, 111.7, 35.3, 28.8, -1.4.

Experimentalists: SH, SMR

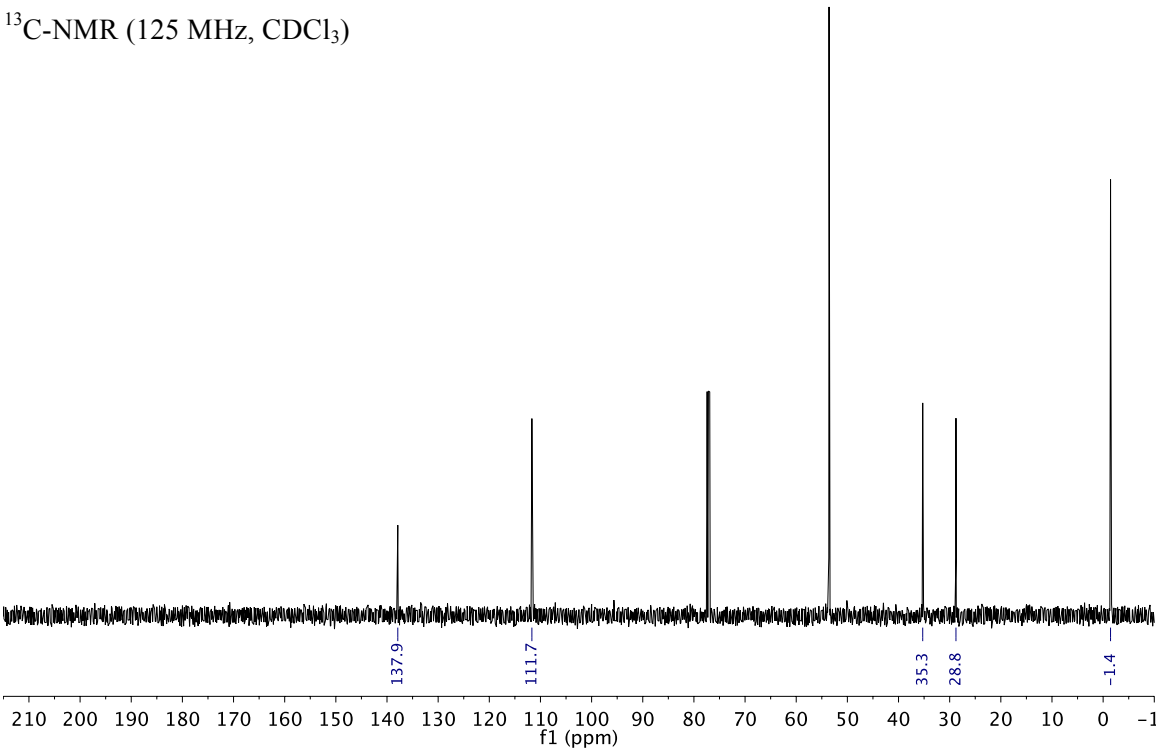


26

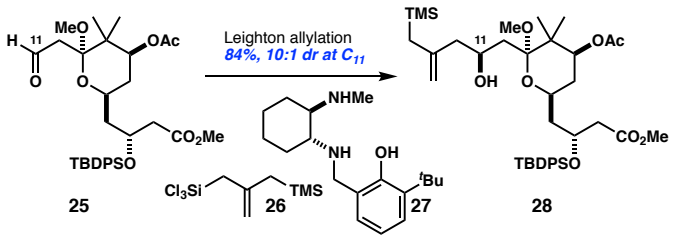
Trichlorosilane **26** in a CH_2Cl_2 solution
^{1}H-NMR (500 MHz, $CDCl_3$)



^{13}C-NMR (125 MHz, $CDCl_3$)



A-ring Subunit Step h: conversion of aldehyde 25 to allylsilane 28



Chemicals:
DBU (Sigma-Aldrich): distilled from CaH_2 and stored under nitrogen
TBAF (1M THF, Sigma-Aldrich): used without purification
25: azeotroped with benzene (3x15 mL) and placed under vacuum for 10 min before use
Diaminophenol **27**: prepared according to Suen, L.M.; *et al.* (*42*).

The following procedure was adapted from Suen, L.M.; *et al*. (*42*).

Preparation of diaminophenol **27** and DBU solution: To a flame-dried, one-neck, 100 mL round-bottom flask equipped with magnetic stir bar was added diaminophenol **27** (6.17 g, 21.2 mmol, 1.2 equiv) and CH_2Cl_2 (30 mL, 0.6 M). The reaction mixture was cooled with an ice bath (0 °C), and DBU (9.53 mL, 63.7 mmol, 3.6 equiv) was added dropwise via syringe over 5 min. The reaction mixture was stirred for 5 min and used immediately.

Allylation: To a flame-dried, one-neck, 250 mL round-bottom flask equipped with magnetic stir bar was added a solution of silane **26** (7.4g in 40 mL CH_2Cl_2, 28.3 mmol, 1.6 equiv). The reaction mixture was cooled with an ice bath (0 °C), and the freshly prepared solution of diaminophenol **27** / DBU was added dropwise via syringe (addition time of 5 min). The reaction mixture was allowed to warm to room temperature by removing the ice bath. After 30 min, the reaction mixture was cooled with a liquid N_2/MeOH bath (-95 °C, Note 1). A solution of aldehyde **25** (10.6g, 17.7 mmol, 1 equiv, Note 2) in CH_2Cl_2 (20 mL; final volume 89 mL CH_2Cl_2, 0.2M) was added via syringe down the side of the flask (5 min). After 2h, TLC analysis indicated complete conversion of aldehyde **25**. The reaction mixture was diluted with hexanes (20 mL) and quenched with TBAF (1M THF, 17.7 mL, 1 equiv) dropwise via syringe (5 min), followed by pH 7.4 buffer (100 mL) over 5 min. The reaction mixture was allowed to warm to 0 °C by removing the cooling bath. After 15 min, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (5x200mL) until TLC of the aqueous layer no longer showed product. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to ~30 mL (the residual solvent enables easy transfer of an otherwise viscous crude reaction mixture). Purification was accomplished by silica gel flash column chromatography (7x15 cm), collecting 30 mL fractions, and eluting with 10% Et_2O/petroleum ether (1L), 20% Et_2O/PE (1L), 30% Et_2O/PE (1L), 40% Et_2O/PE (1L), affording product **28** (10.8g, 10:1 dr at C11, 84% combined yield) as a colorless oil (Note 2). For recovery of diaminophenol **27**, see Note 3.

Note 1: The diastereoselectivity of the reaction at -78 °C is approximately 8:1 dr (at C11).
Note 2: This reaction (step **h**) was conducted with the 2:1 mixture of diastereomers obtained from the aldol step; the complete separation of diastereomers was performed following C11 silylation (step **i**). However, a small portion was purified to afford a sample of **28** for characterization.
Note 3: ~50% of diaminophenol **27** was recovered by (a) flushing the silica gel column with 80-100% EtOAc/Hex and (b) treating the aqueous layer from the reaction workup with 1 M NaOH at 0 °C, followed by exhaustive extraction with CH_2Cl_2. The combined solids were recrystallized from hot hexanes (*42*).

TLC R_f = 0.47 (20% EtOAc/Hex, UV active, purple spot in *p*-anisaldehyde)

[α]$^{23.4}_{D}$ = +22.9° (*c* = 0.3, CH_2Cl_2)

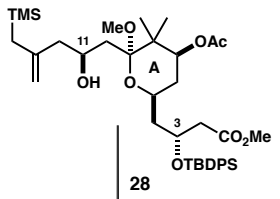
IR (thin film) 3563 (bs), 3072, 2953, 2858, 1740, 1632, 1428, 1367, 1246, 1111, 1074, 1026, 848, 703 cm^{-1}

^{1}H-NMR (600 MHz, C_6D_6) δ 7.81 – 7.73 (m, 4H), 7.27 – 7.22 (m, 6H), 5.43 (dd, *J* = 11.7, 4.9 Hz, 1H, C_7H), 4.82 (bs, 1H), 4.72 (bs, 1H), 4.49 (app. p, *J* = 6.2 Hz, 1H, C_3H), 4.31 – 4.24 (m, 1H, $C_{11}H$), 3.59 – 3.49 (m, 1H, C_5H), 3.38 (s, 3H, CO_2Me), 3.15 (bs, 1H, C_{11}-OH), 2.94 (s, 3H, C_9-OMe), 2.66 (dd, *J* = 14.8, 6.6 Hz, 1H, C_2H_a), 2.60 (dd, *J* = 14.8, 5.6 Hz, 1H, C_2H_b), 2.43 (dd, *J* = 13.6, 6.0 Hz, 1H, $C_{12}H_a$), 2.14 (dd, *J* = 13.6, 6.8 Hz, 1H, $C_{12}H_b$), 1.98 (dd, *J* = 15.7, 9.9 Hz, 1H, $C_{10}H_a$), 1.90 (dd, *J* = 15.7, 1.3 Hz, 1H, $C_{10}H_b$), 1.80 (ddd, *J* = 14.7, 8.4, 6.5 Hz, 1H, C_4H_a), 1.71 – 1.62 (m, 2H, $C_{30}H_2$), 1.67 (s, 3H, C7-OAc), 1.61 – 1.56 (m, 1H, C_4H_b), 1.53 (ddd, *J* = 12.4, 4.9, 3.0 Hz, 1H, C_6H_a), 1.20 – 1.10 (m, 1H, C_6H_b), 1.15 (s, 9H, TBDPS), 1.04 (s, 3H), 1.00 (s, 3H), 0.08 (s, 9H, TMS)

^{13}C-NMR (125 MHz, C_6D_6, 30 total peaks, 2 peaks from the TBDPS group are obscured by the benzene solvent peak) δ 171.3, 169.7, 145.1, 136.31, 136.27, 134.3, 134.1, 130.27, 130.23, 110.4, 105.1, 73.1, 69.7, 67.3, 66.9, 51.3, 48.9, 46.6, 44.2, 43.2, 42.3, 40.1, 33.3, 27.2, 27.1 (3C, TBDPS), 20.8, 20.6, 19.5, 17.7, -1.2 (3C, TMS)

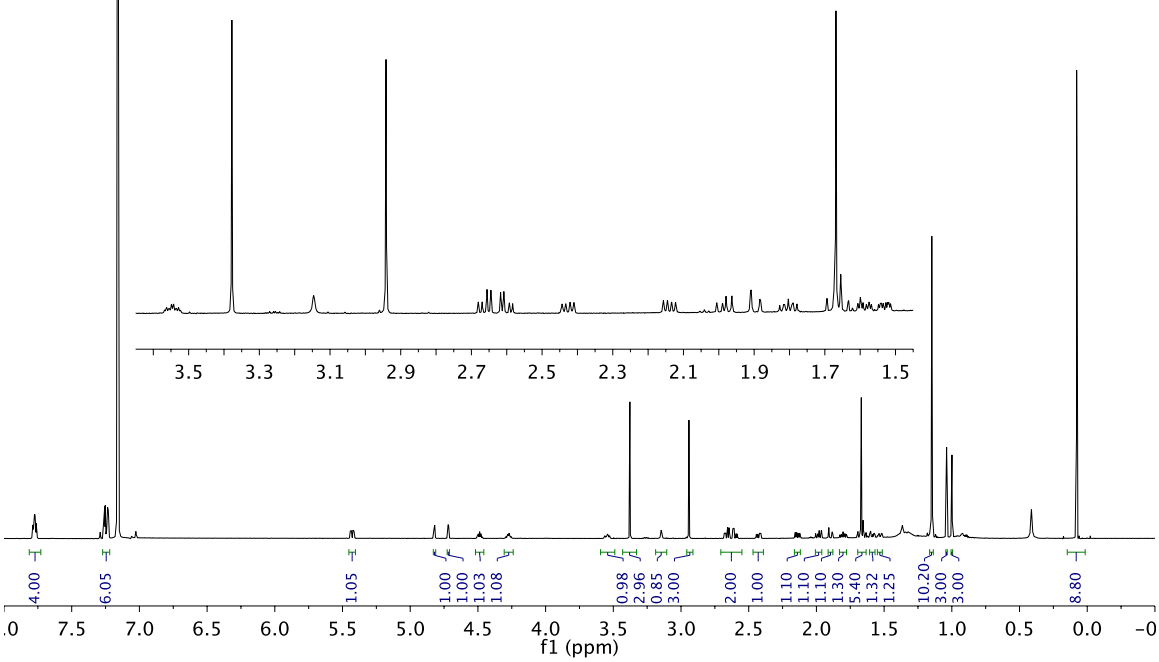
HRMS calculated for $C_{40}H_{62}NaO_8Si_2$ $[M+Na]^+$: 749.3875; found 749.3881 (TOF ESI+)

Experimentalists: SH

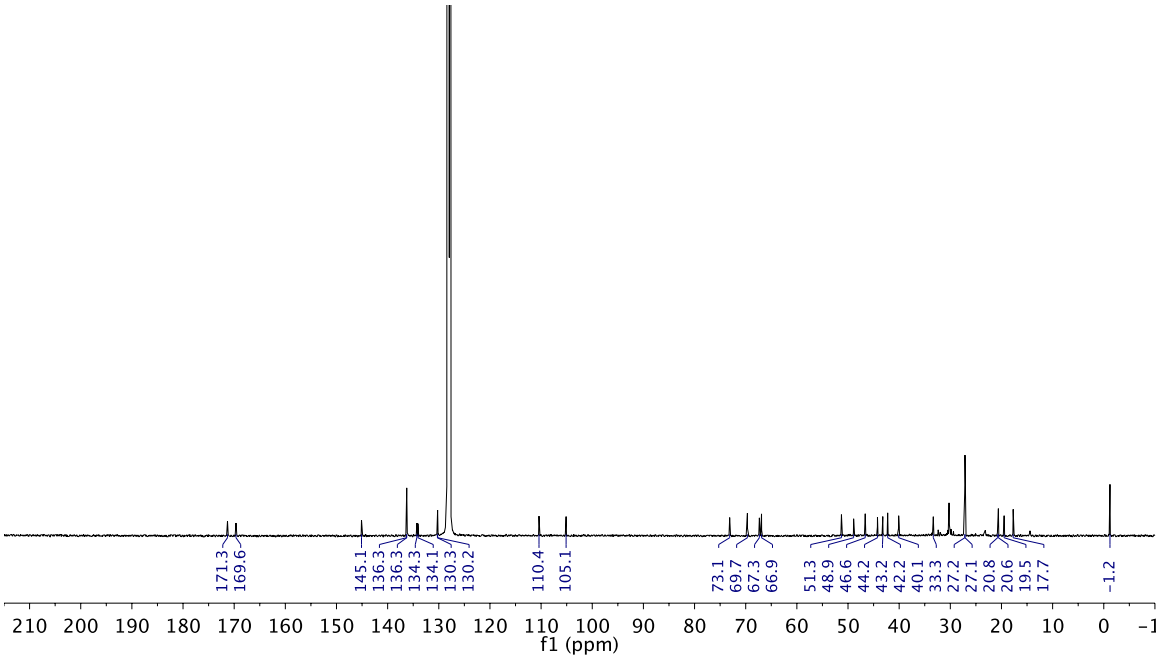


28

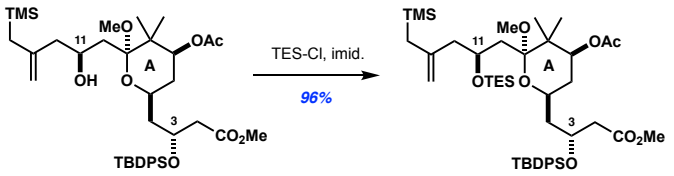
^{1}H-NMR (600 MHz, C_6D_6)



^{13}C-NMR (125 MHz, C_6D_6)



A-ring Subunit Step i: conversion of C11-alcohol 28 to C11-TES ether SI-18



28 **SI-18**

Chemicals:
imidazole (99%, Acros): used without purification
TES-Cl (99%, Sigma-Aldrich): distilled from CaH_2 and stored under nitrogen
28: azeotroped with benzene (3x15 mL) and placed under vacuum for 10 min before use

To a flame-dried, one-neck, 250 mL round-bottom flask equipped with magnetic stir bar was added C11-alcohol **28** (10g, 13.8 mmol, 1 equiv, Note 1) and CH_2Cl_2 (92 mL, 0.15M). The reaction mixture was cooled with an ice bath (0 °C). Imidazole (5.6g, 82.5 mmol, 6 equiv) was added in one portion, followed by TES-Cl (3.46 mL, 20.6 mmol, 1.5 equiv) dropwise via syringe over 3 min. After 3h, TLC analysis indicated full conversion of C11-alcohol **28**. The reaction mixture was quenched by adding pH 7.4 buffer (100 mL) dropwise over 10 min. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (5x150 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification was accomplished by silica gel flash column chromatography (7.5x15 cm), eluting with 10-20% Et_2O/petroleum ether (3L), affording TES ether **SI-18** (11.1 g, 96% yield) as a colorless oil (Note 1). Compound purity was established by TLC (one spot) analysis.

Note 1: This reaction (step **i**), as well as all previous reactions following step **d**, were conducted with the 2:1 mixture of diastereomers obtained from the aldol step (step **d**). The complete separation of diastereomers was performed following C11 silylation, as the diastereomers were found to be the most readily separable at this stage. Purification of the desired diastereomer was accomplished via silica gel flash column chromatography using a gradient elution (5-10-15-20% Et_2O in petroleum ether). Purification was typically carried out on ~5 grams of material using a 9x40 cm column, affording ~33% of the desired diastereomer, ~50% as a mixture of diastereomers, and ~17% of the undesired diastereomer. Mass recoveries >95% were obtained, and the mixed material was iteratively re-subjected to purification.

TLC R_f = 0.46 (10% EtOAc/Hex, UV active, dark purple spot in *p*-anisaldehyde)

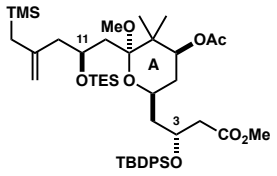
IR (thin film) 3071, 2953, 1743, 1631, 1473, 1428, 1366, 1247, 1112, 1020, 854 cm^{-1}

^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.70 – 7.62 (m, 4H), 7.45 – 7.34 (m, 6H), 4.97 (dd, *J* = 11.8, 5.0 Hz, 1H, C_7H), 4.62 (bs, 1H), 4.57 (bs, 1H), 4.19 – 4.08 (m, 2H, C_3, C_{11}), 3.57 (s, 3H, CO_2Me), 3.26 (app. dtd, *J* = 12.3, 6.4, 2.8 Hz, 1H, C_5H), 2.94 (s, 3H, C_9-OMe), 2.61 (dd, *J* = 14.8, 4.0 Hz, 1H, C_2H_a), 2.51 (dd, *J* = 14.8, 7.7 Hz, 1H, C_2H_b), 2.14 – 2.04 (m, 2H, $C_{12}H_2$), 2.01 (s, 3H, C7-Oac), 1.84 (dd, *J* = 15.9, 3.8 Hz, 1H, $C_{10}H_a$), 1.82 – 1.78 (m, 1H, C_4H_a), 1.72 (dd, *J* = 15.9, 7.2 Hz, 1H, $C_{10}H_b$), 1.56 – 1.52 (m, 1H, C_4H_b), 1.53 – 1.44 (m, 2H), 1.31 (ddd, *J* = 12.4, 5.0, 2.9 Hz, 1H, C_6H_a), 1.01 (s, 9H, TBDPS), 0.94 (t, *J* = 8.0 Hz, 9H, TES), 0.97 – 0.90 (m, 1H, C_6H_b), 0.88 (s, 3H), 0.87 (s, 3H), 0.58 (q, *J* = 8.0 Hz, 6H, TES), 0.03 (s, 9H, TMS)

^{13}C-NMR (125 MHz, C_6D_6, 31 total peaks, 2 peaks from the TBDPS group are obscured by the benzene solvent peak) δ 171.3, 169.6, 144.8, 136.37, 136.35, 134.4, 134.0, 130.2 (2C, TBDPS), 110.9, 104.6, 73.9, 69.7, 68.7, 66.3, 51.2, 48.9, 48.3, 44.3, 43.1, 42.4, 40.2, 33.2, 27.5, 27.2 (3C, TBDPS), 21.2, 20.8, 19.5, 17.6, 7.5 (3C, TES), 6.1 (3C, TES), -1.3 (3C, TMS)

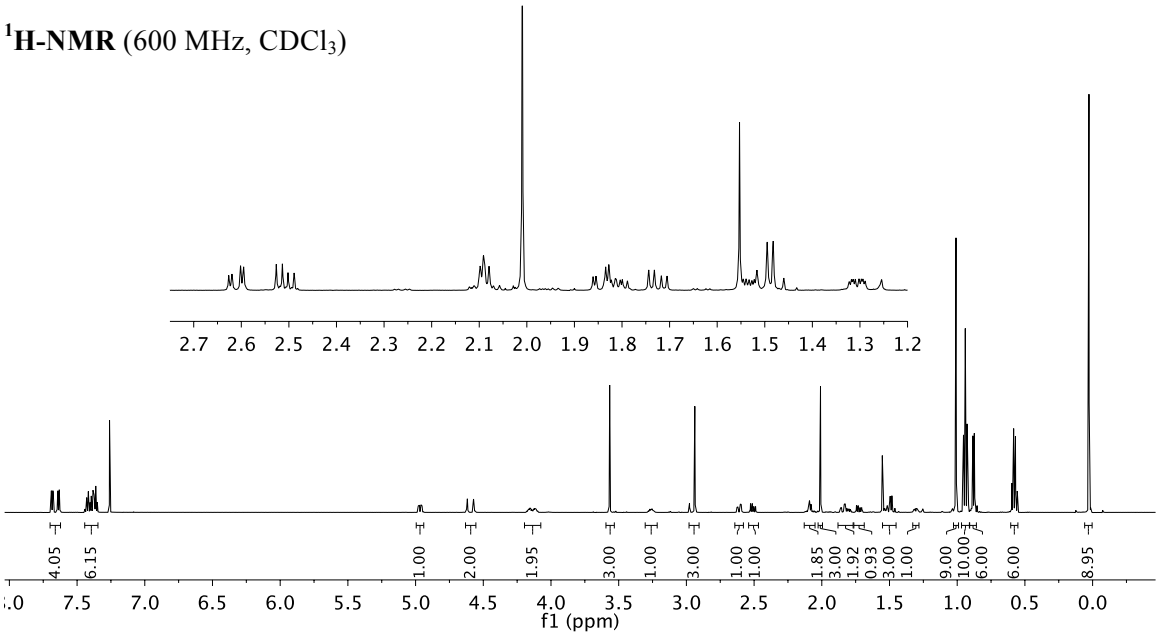
HRMS calculated for $C_{46}H_{76}NaO_8Si_3$ $[M+Na]^+$: 863.4740; found 863.4739 (TOF ESI+)

Experimentalists: SH

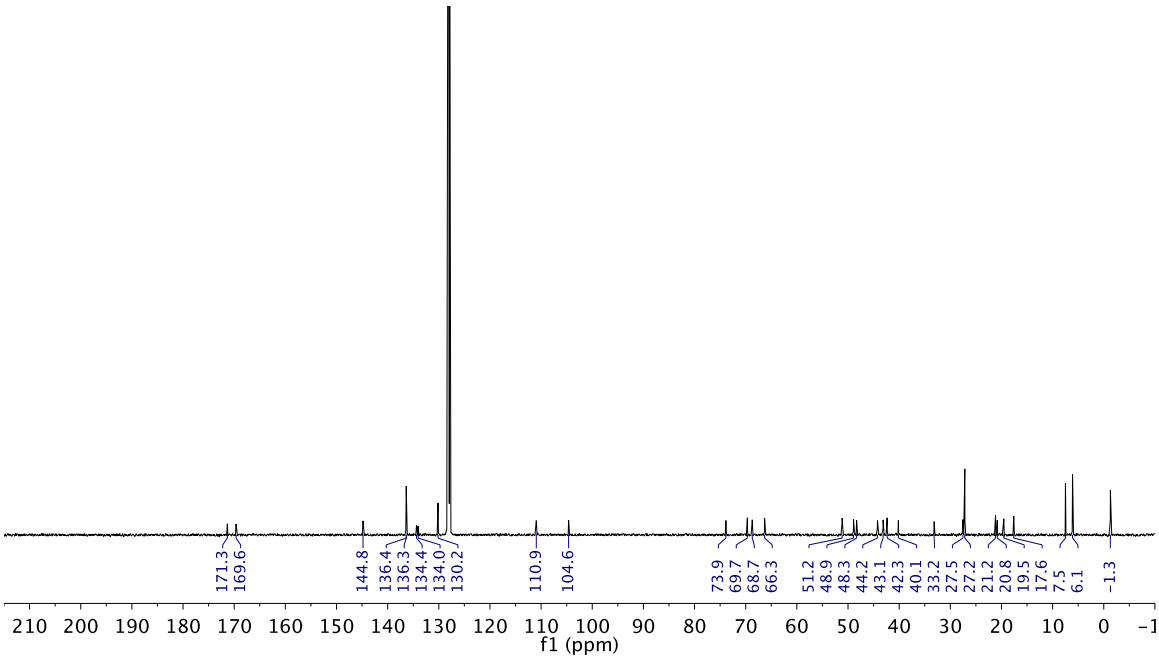


SI-18

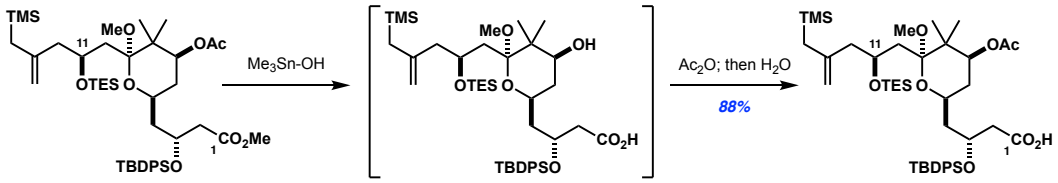
^{1}H-NMR (600 MHz, $CDCl_3$)



^{13}C-NMR (125 MHz, C_6D_6)



A-ring Subunit Step j: conversion of ester SI-18 to acid 1



SI-18 **1**

Chemicals:
Me_3Sn-OH (98%, Acros): used without purification from a nitrogen-atmosphere glove box
Acetic anhydride (>99%, Sigma-Aldrich): distilled before use
DMAP (>99%, Sigma-Aldrich): used without purification

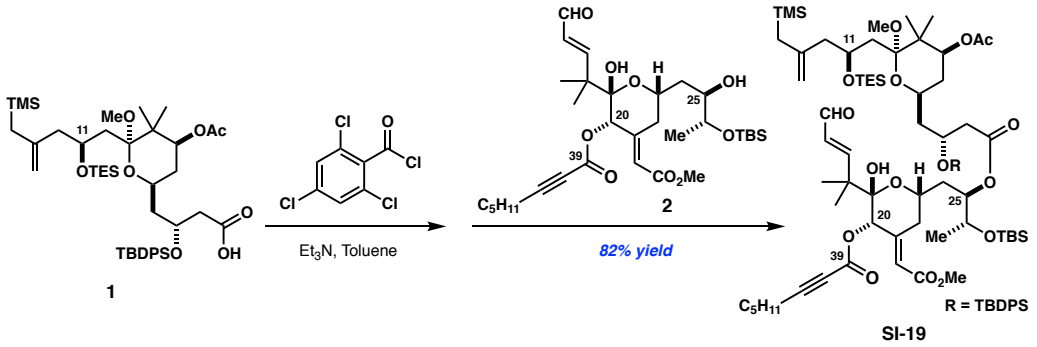
The following procedure was adapted from Nicolaou, K.C.; *et al*. (*46*).

In a nitrogen-atmosphere glove box, a flame-dried, one-neck, 100 mL round-bottom flask equipped with magnetic stir bar was charged with Me_3Sn-OH (2.15 g, 11.90 mmol, 3.5 equiv). The flask was removed from the glove box and placed under an atmosphere of Argon (balloon). A solution of ester **SI-18** (2.86 g, 3.40 mmol, 1 equiv) in toluene (30 mL, 0.11M) was added via syringe, and the resulting mixture was placed in an 85 °C oil bath, affording a cloudy solution. After 14h at 85 °C, TLC and aliquot ^{1}H-NMR indicated complete conversion of ester **SI-18** and formation of acid **1** (along with ~30% of the corresponding C7-*des*-OAc compound). To re-esterify C7, the reaction mixture was allowed to cool to room temperature. DMAP (2.49 g, 20.4 mmol, 6 equiv) was added in one portion, and the resulting suspension was cooled with an ice bath (0 °C). Acetic anhydride (1.60 mL, 17.0 mmol, 5 equiv) was added dropwise via syringe. After 15 min at 0 °C, saturated aqueous $NaHCO_3$ (30 mL) was added, and the resulting biphasic mixture was allowed to warm to room temperature by removing the ice bath. After 4h of vigorous stirring, the reaction mixture was poured into a separatory funnel containing saturated aqueous NH_4Cl (200 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3x100 mL) until TLC of the aqueous layer no longer showed product. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification was accomplished by silica gel flash column chromatography (2L of 10-50% Et_2O/pentane) affording acid **1** (2.48 g, 88% yield) as a white foam (Note 1). Compound purity was established by TLC (one spot) analysis. **TLC** R_f = 0.68 (30% EtOAc/Hex, UV active, purple streak in *p*-anisaldehyde). Characterization data matched literature values reported by Wender, P.A.; *et al.* (*25*).

Note 1: Acid **1** was found to be prone to C9-OMe hydrolysis. Therefore, **1** was either frozen in benzene at -20 °C or used immediately in the next step (Yamaguchi esterification). NMRs were taken in either neutralized $CDCl_3$ or C_6D_6.

Experimentalists: MCS, JLS, SH, CTH, SMR

Endgame Step n: conversion of acid 1 and alcohol 2 to ester SI-19



Chemicals:
Triethylamine (Sigma-Aldrich): distilled from CaH_2 before use
2,4,6-trichlorobenzoyl chloride (97%, Sigma-Aldrich): distilled prior to use and stored under N_2
DMAP (>99%, Sigma-Aldrich): used without purification

To a flame-dried, one-neck, 500 mL round-bottom flask equipped with magnetic stir bar was added acid **1** (2.72 g, 3.28 mmol, 1 equiv) and toluene (131 mL, 0.025M). The reaction mixture was cooled with an ice bath (0 °C). Triethylamine (2.75 mL, 19.7 mmol, 6 equiv) was added dropwise via syringe over 30 sec, followed by 2,4,6-trichlorobenzoyl chloride (924 µL, 5.91 mmol, 1.8 equiv) dropwise via syringe over 15 sec. The reaction mixture was warmed to room temperature by removing the ice bath. The solution gradually turned cloudy with salts. After 2h, the reaction mixture was re-cooled to 0 °C. Separately, a flame-dried, 250 mL round-bottom flask was charged with C25-alcohol **2** (2.00 g, 3.28 mmol, 1 equiv), DMAP (1.20 g, 9.85 mmol, 3 equiv), and toluene (131 mL, 0.025M). This solution was sonicated to ensure homogeneity and then transferred to the flask containing acid **1** via syringe over 10 min. The resulting reaction mixture was warmed to room temperature by removing the ice bath. The solution turned yellow-orange and even cloudier. After 45 min, TLC analysis indicated complete conversion of **2** and formation of ester **SI-19**. The reaction mixture was cooled to 0 °C and quenched by adding H_2O (200 mL) slowly over 5 min. The layers were separated, and the aqueous layer was extracted with 20% EtOAc/Hex (5x100mL). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated. Purification was accomplished by pH 7.0 buffered silica gel flash column chromatography (5.5x10 cm), collecting 20 mL fractions, and eluting with 5% EtOAc/Hex (500 mL), 10% EtOAc/Hex (500 mL), and 20% EtOAc/Hex (500 mL), affording ester **SI-19** (3.82 g, 82% yield) as an off-white foam (Note 1). Compound purity was established by TLC (one spot) analysis.

Note 1: All endgame intermediates (i.e. post-Yamaguchi esterification) were found to be prone to C9-OMe hydrolysis. Therefore, NMRs were taken in either neutralized $CDCl_3$ or C_6D_6.

TLC R_f = 0.559 (30% EtOAc/Hex, UV active, dark purple spot in *p*-anisaldehyde)

$[\alpha]^{22.2}_{D}$ = -18.6 ± 0.5° (*c* = 0.18, CH_2Cl_2)

IR (thin film) 3583, 3474, 2955, 2927, 2856, 2233, 1721, 1690, 1578, 1466, 1428, 1381, 1243, 1156, 1112 cm^{-1}

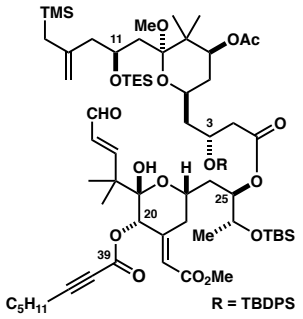
^{1}H-NMR (600 MHz, C_6D_6) δ 9.95 (d, *J* = 7.7 Hz, 1H, CHO), 7.84 – 7.77 (m, 4H, TBDPS), 7.64 (d, *J* = 16.1 Hz, 1H, $C_{17}H$), 7.31 – 7.23 (m, 6H, TBDPS), 6.28 (d, *J* = 1.9 Hz, 1H, $C_{34}H$), 6.17 (dd, *J* = 16.1, 7.7 Hz, 1H, $C_{16}H$), 5.55 (s, 1H, $C_{20}H$), 5.43 (dd, *J* = 10.9, 4.5 Hz, 1H, $C_{25}H$), 5.34

(dd, J = 11.8, 4.8 Hz, 1H, C_7H), 4.81 (bs, 1H), 4.71 (bs, 1H), 4.43 – 4.32 (m, 2H, $C_{11}H$, C_3H), 4.13 – 4.03 (m, 2H, $C_{23}H$, $C_{22}H$), 3.92 – 3.85 (m, 1H, $C_{26}H$), 3.52 – 3.44 (m, 1H, C_5H), 3.44 (s, 1H, C19-OH), 3.28 (s, 3H, CO_2Me), 3.07 (s, 3H, C9-OMe), 2.60 (dd, J = 15.7, 4.6 Hz, 1H, C_2H_a), 2.53 (dd, J = 15.7, 6.1 Hz, 1H, C_2H_b), 2.36 (dd, J = 13.1, 5.1 Hz, 1H, $C_{12}H_a$), 2.34 – 2.29 (m, 1H, $C_{22}H_a$), 2.26 (dd, J = 13.1, 8.1 Hz, 1H, $C_{12}H_b$), 2.11 (dd, J = 16.0, 3.2 Hz, 1H, $C_{10}H_a$), 2.10 – 2.03 (m, 1H, C_4H_a), 2.04 – 1.97 (m, 2H, $C_{24}H_a$, $C_{10}H_b$), 1.97 – 1.87 (m, 2H, $C_{42}H_2$), 1.75 – 1.69 (m, 1H, C_4H_b), 1.69 (s, 3H, C7-Oac), 1.66 – 1.57 (m, 3H, CH_2-TMS, $C_{24}H_b$), 1.54 (ddd, J = 12.3, 4.9, 2.8 Hz, 1H, C_6H_a), 1.27 (s, 3H), 1.26 – 1.20 (m, 2H, $C_{43}H_2$), 1.19 – 1.15 (m, 18H), 1.14 (d, J = 6.3 Hz, 3H, $C_{27}H_3$), 1.10 (t, J = 7.9 Hz, 9H, TES), 1.14 – 1.05 (m, 5H, C_6H_b, $C_{44}H_2$, $C_{45}H_2$), 0.99 (s, 9H), 0.77 (d, J = 6.9 Hz, 3H, $C_{46}H_3$), 0.75 (d, J = 7.9 Hz, 6H, TES), 0.11 (s, 3H, TBS), 0.102 (s, 9H, TMS), 0.098 (s, 3H, TBS)

^{13}C-NMR (125 MHz, $CDCl_3$, 63 total peaks) δ 195.1 (CHO), 172.4, 170.8, 166.4, 166.2, 151.9, 149.9, 144.3, 136.1, 135.9, 134.0, 133.4, 130.0, 129.8, 127.8, 127.7, 127.4, 121.4, 110.7, 104.3 (C9), 99.5, 92.5, 74.1, 73.5, 73.4, 72.9, 68.5, 68.3, 68.1, 66.3, 65.2, 51.4, 48.6, 48.3, 45.8, 43.2, 42.5, 41.9, 39.7, 34.6, 32.4, 31.1, 31.0, 27.4, 27.1, 27.0 (3C, TBDPS), 25.9 (3C, TBS), 23.0, 22.2, 21.4, 20.8, 19.9, 19.4, 18.7, 18.22, 18.17, 17.1, 14.0 (C46), 7.2 (3C, TES), 5.6 (3C, TES), -1.3 (3C, TMS), -4.4 (TBS), -4.8 (TBS)

HRMS calculated for $C_{77}H_{124}NaO_{16}Si_4$ $[M+Na]^+$: 1439.7859; found 1440.7896 (TOF ESI+)

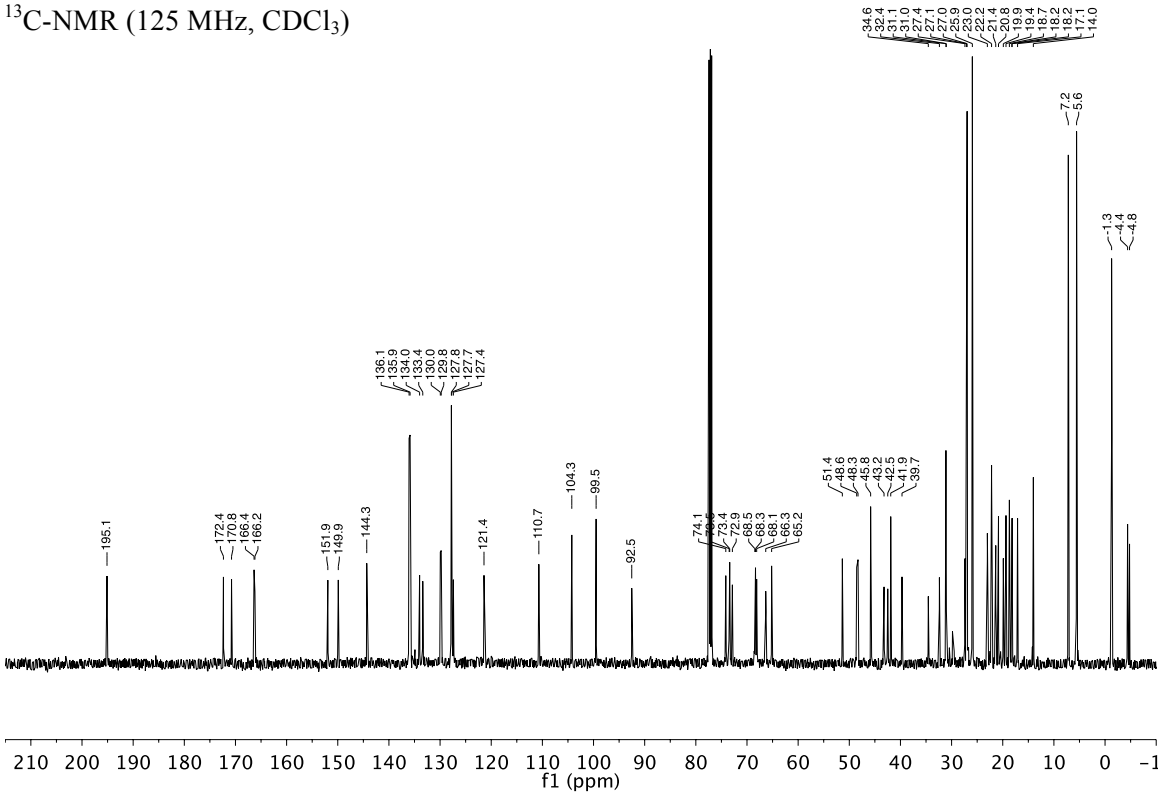
Experimentalists: SH, JLS, MSJ, RVQ



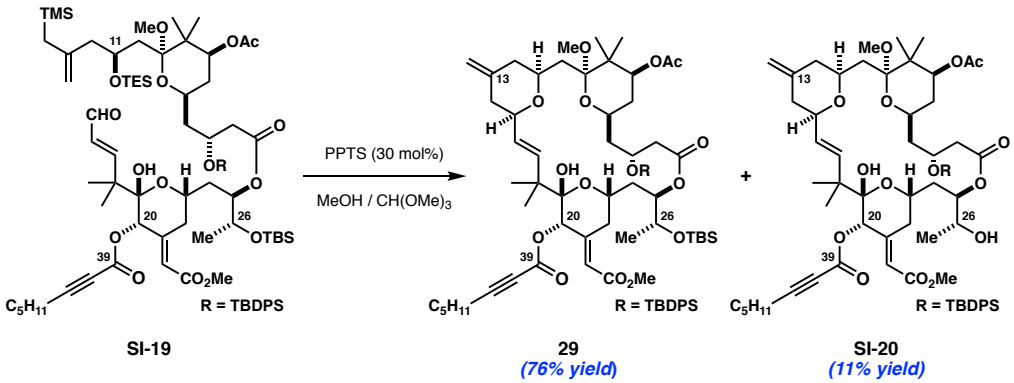
SI-19

^{1}H-NMR (600 MHz, C_6D_6)

^{13}C-NMR (125 MHz, $CDCl_3$)



Endgame Step o: conversion of SI-19 to macrolactone 29



SI-19 | **29** *(76% yield)* | **SI-20** *(11% yield)*

Chemicals:
Methanol (99.8% Extra Dry, Acros): used without purification
Trimethylorthoformate (Sigma-Aldrich): distilled prior to use and stored under nitrogen
PPTS (98%, Sigma-Aldrich): used without purification

To a flame-dried, one-neck, 500 mL round-bottom flask equipped with magnetic stir bar was added allylsilane **SI-19** (3.82 g, 2.69 mmol, 1 equiv), followed by methanol (135 mL, 0.02 M) and trimethylorthoformate (2.69 mL, 2% of MeOH volume). The reaction mixture was cooled with an ice bath (0 °C). PPTS (203 mg, 0.81 mmol, 30 mol%) was added in one portion. The reaction mixture and ice bath were allowed to warm to room temperature over 1.5h. After an additional 20h, the reaction mixture was cooled with an ice bath (0 °C), diluted with hexanes (100 mL), and quenched with saturated aqueous $NaHCO_3$ (50 mL) followed by water (100 mL). The layers were separated, and the aqueous layer was extracted with 25% EtOAc/Hex (5x100 mL) until TLC of the aqueous layer no longer showed product. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification was accomplished by silica gel flash column chromatography (5.5x9 cm, 2L of 10-35% EtOAc/Hex) affording macrocycle **29** (2.49 g, 76% yield) as an off-white foam and the C26-des-TBS macrocycle, **SI-20** (320 mg, 11% yield) (Note 1). Compound purity of **29** was established by TLC (one spot) analysis.

Note 1: All endgame intermediates (i.e. post-Yamaguchi esterification) were found to be prone to C9-OMe hydrolysis. Therefore, NMRs were taken in either neutralized $CDCl_3$ or C_6D_6.

TLC R_f = 0.529 (30% EtOAc/Hex, UV active, dark purple spot in *p*-anisaldehyde)

$[\alpha]^{22.2}_{D}$ = -2.4° (*c* = 0.9, CH_2Cl_2)

IR (thin film) 3509, 3072, 2933, 2235, 1720, 1665, 1472, 1429, 1387, 1366, 1245, 1105, 1049, 910, 835, 737, 704 cm^{-1}

^{1}H-NMR (600 MHz, C_6D_6) δ 7.75 – 7.67 (m, 4H), 7.31 – 7.20 (m, 6H), 6.36 (d, *J* = 16.1 Hz, 1H, $C_{17}H$), 6.32 (d, *J* = 1.9 Hz, 1H, $C_{34}H$), 5.82 (dd, *J* = 16.1, 6.9 Hz, 1H, $C_{16}H$), 5.65 (s, 1H, $C_{20}H$), 5.61 (dd, *J* = 11.7, 4.9 Hz, 1H, C_7H), 5.37 (dd, *J* = 11.3, 4.8 Hz, 1H, $C_{25}H$), 4.83 – 4.75 (m, 3H, $C_{13}CH_2$, C_3H), 4.30 – 4.25 (m, 1H, $C_{15}H$), 4.19 (dd, *J* = 13.8, 1.9 Hz, 1H, $C_{22}H_a$), 4.13 (t, *J* = 11.4 Hz, 1H, $C_{23}H$), 4.02 (app. t, *J* = 10.6 Hz, 1H, C_5H), 3.67 (app. t, *J* = 10.5 Hz, 1H, $C_{11}H$), 3.57 (app. p, *J* = 6.1 Hz, 1H, $C_{26}H$), 3.15 (s, 3H, CO_2Me), 2.96 (bs, 1H, C19-OH), 2.80 (dd, *J* = 17.1, 3.8 Hz, 1H, C_2H_a), 2.70 (s, 3H, C9-OMe), 2.39 (ddd, *J* = 13.8, 11.4, 1.9 Hz, 1H, $C_{22}H_b$), 2.31 (dd, *J* = 17.1, 9.6 Hz, 1H, C_2H_b), 2.19 (d, *J* = 12.4 Hz, 1H, $C_{14}H_a$), 2.12 (dd, *J* = 16.1, 8.9 Hz, 1H, $C_{10}H_a$), 2.05 (t, *J* = 12.4 Hz, 1H, $C_{14}H_b$), 1.99 (d, *J* = 12.3 Hz, 1H, $C_{12}H_a$), 1.88 (t, *J* = 12.3 Hz,

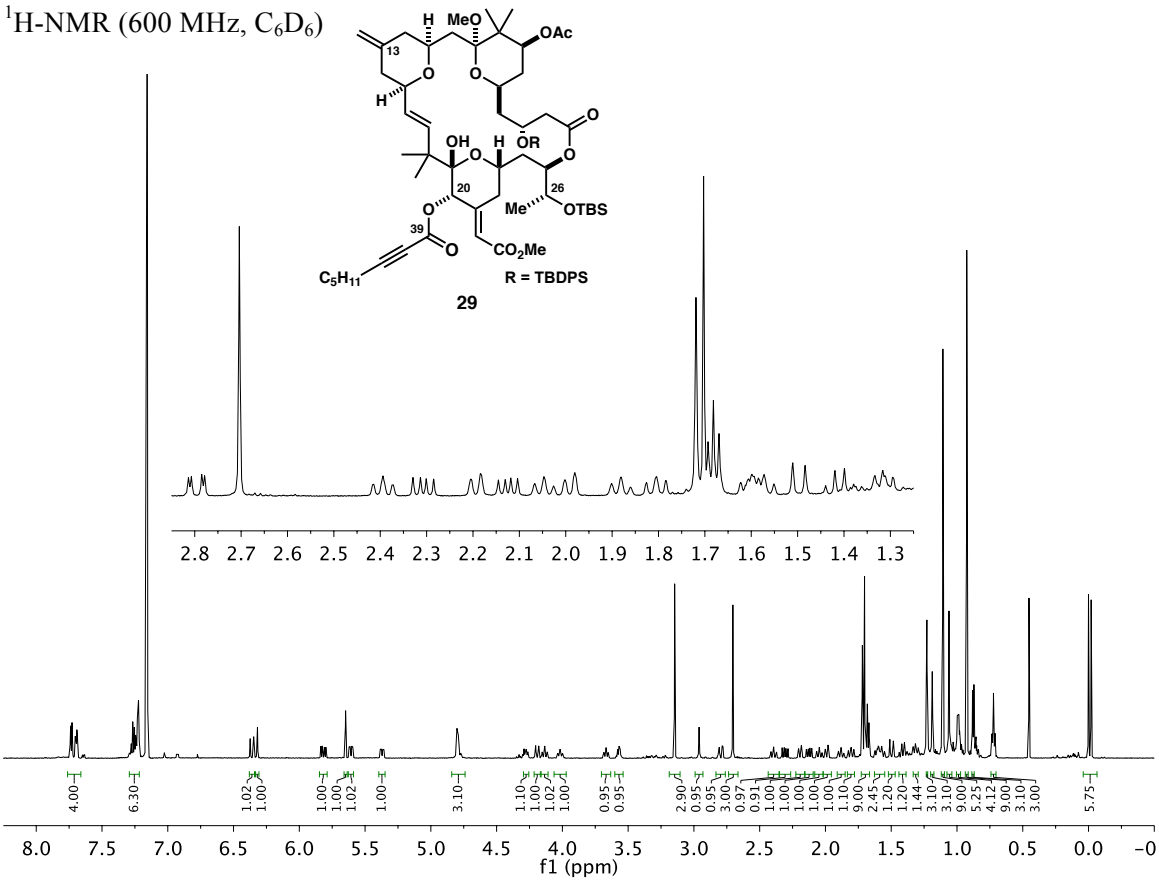
1H, $C_{12}H_b$), 1.81 (app. t, J = 12.7 Hz, 1H, $C_{24}H_a$), 1.72 (s, 3H), 1.70 (s, 3H), 1.68 (t, J = 7.1 Hz, 2H, $C_{42}H_2$), 1.70 – 1.65 (m, 1H, C_6H_a), 1.64 – 1.54 (m, 2H, C_4H_a, $C_{24}H_b$), 1.50 (d, J = 16.1 Hz, 1H, $C_{10}H_b$), 1.44 – 1.38 (m, 1H, C_6H_b), 1.35 – 1.28 (m, 1H, C_4H_b), 1.23 (s, 3H), 1.19 (s, 3H), 1.11 (s, 9H), 1.06 (s, 3H), 1.09 – 1.01 (m, 2H, $C_{43}H_2$), 1.02 – 0.96 (m, 4H, $C_{44}H_2$, $C_{45}H_2$), 0.93 (s, 9H), 0.88 (d, J = 6.3 Hz, 3H, $C_{27}H_3$), 0.72 (t, J = 6.8 Hz, 3H, $C_{46}H_3$), 0.00 (s, 3H, TBS), -0.02 (s, 3H, TBS)

^{13}C-NMR (100 MHz, $CDCl_3$, 60 total peaks) δ 170.9, 170.2, 166.8, 152.4, 150.9, 145.1 (C13), 135.9, 135.8, 135.1, 134.9, 134.2, 134.0, 129.8, 129.78, 127.81, 127.77, 120.5, 108.6 (C30), 103.0, 97.9, 91.4 (C41), 78.4, 75.2, 74.2, 73.3, 73.0, 72.1, 68.6, 67.4, 65.2, 64.7, 51.4, 48.1, 45.4, 45.0, 42.7, 41.7, 41.6, 40.8, 39.8, 34.6, 33.6, 31.2, 31.0 (C44), 27.2 (C43), 27.1 (3C, TBDPS), 26.0 (3C, TBS), 23.9, 22.2 (C45), 21.5, 20.4, 20.2, 19.4, 18.9 (C42), 18.5, 18.3, 17.5, 14.0 (C46), -4.6 (TBS), -4.7 (TBS)

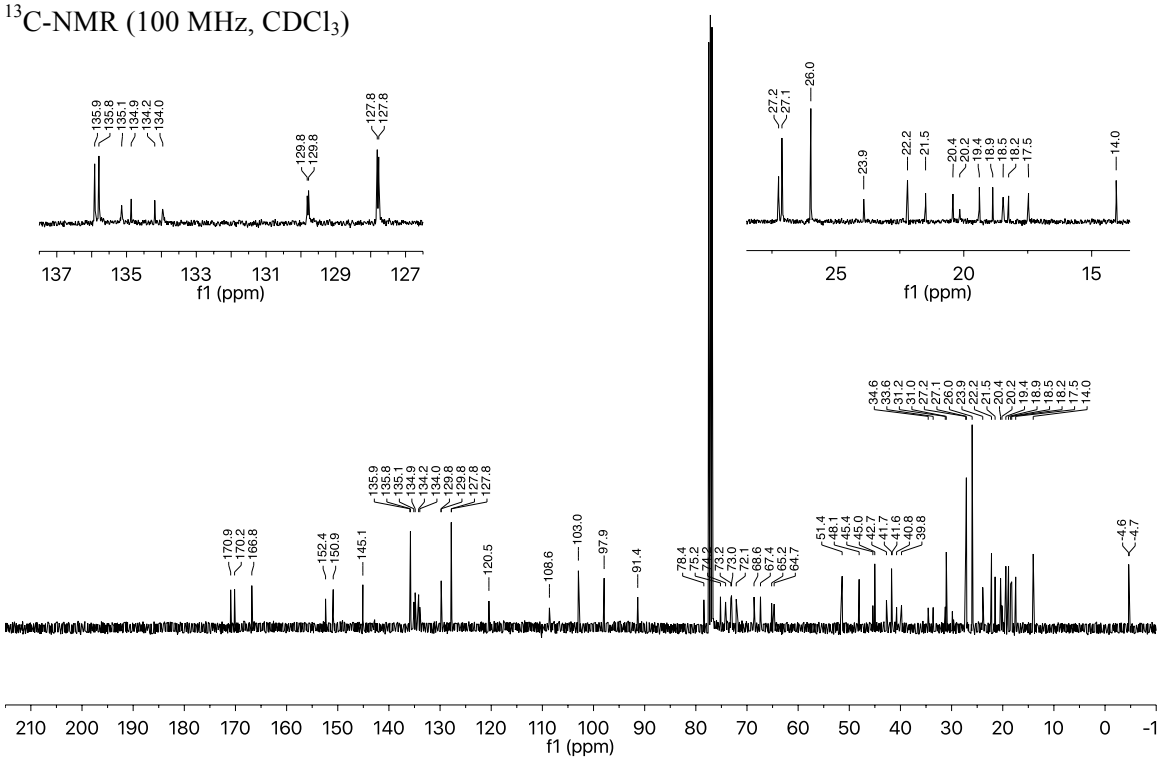
HRMS calculated for $C_{68}H_{100}NaO_{15}Si_2$ $[M+Na]^+$: 1235.6499; found 1235.6493 (TOF ESI+)

Experimentalists: SH, JLS, MSJ, RVQ

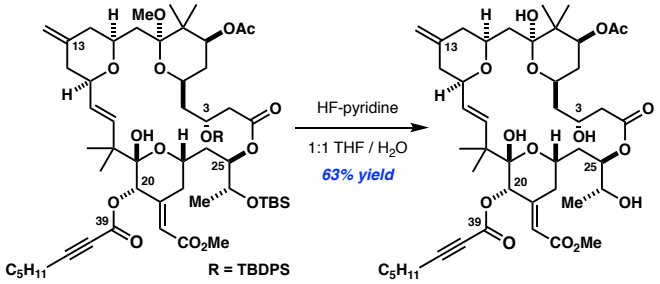
^{1}H-NMR (600 MHz, C_6D_6)



^{13}C-NMR (100 MHz, $CDCl_3$)



Synthesis of Analog 34



Chemicals:
70% HF-pyridine (Sigma-Aldrich): used without purification

To a 15mL polypropylene falcon tube equipped with magnetic stir bar was added compound **29** (15 mg, 0.0124 mmol, 1 equiv) and 3:1 THF / H_2O (1 mL). The falcon tube was transferred to a 4 °C cold room. HF-pyridine (0.32 mL) was added (final concentration ~0.01M). After 96h, the reaction mixture was warmed to room temperature. After an additional 64h (~6.5 days in total), the reaction mixture was quenched by slowly syringing the solution into a separatory funnel containing saturated aqueous $NaHCO_3$ (20mL) and EtOAc (20 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (4x20mL). The combined organic layers were washed with 0.5M HCl (10 mL) to remove pyridine, and aqueous layer back-extracted with EtOAc (2x20mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification was accomplished by silica gel flash column chromatography (25-65% EtOAc/Hex) affording analog **34** (6.6 mg, 63% yield) as a white solid. Compound purity was established by TLC (one spot) analysis.

- **TLC** R_f = 0.56 (60% EtOAc/Hex, UV active, dark purple spot in *p*-anisaldehyde)
- **[α]$^{22.3}_{D}$** = -1.8° (*c* = 0.18, CH_2Cl_2)
- **IR** (thin film): 3460, 3331, 2929, 2855, 2234, 1738, 1716, 1666, 1435, 1408, 1366, 1244, 1157, 1098, 1055, 982 cm^{-1}

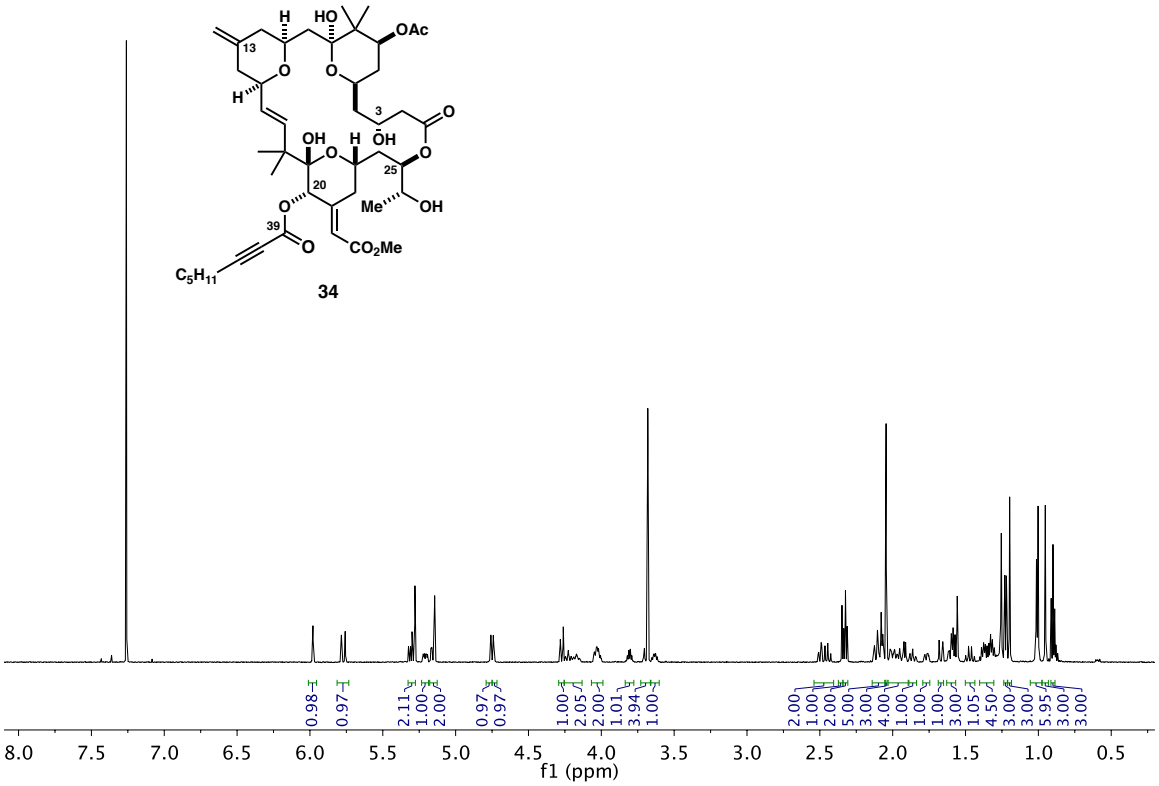
^{1}H-NMR (600 MHz, $CDCl_3$) δ 5.98 (d, *J* = 2.0 Hz, 1H, $C_{34}H$), 5.77 (d, *J* = 15.8 Hz, 1H, $C_{17}H$), 5.30 (dd, *J* = 15.8, 8.6 Hz, 1H, $C_{16}H$), 5.28 (s, 1H, C_{19}-OH), 5.21 (ddd, *J* = 12.0, 5.5, 3.0 Hz, 1H, $C_{25}H$), 5.16 (dd, *J* = 11.9, 4.8 Hz, 1H, C_7H), 5.14 (s, 1H, $C_{20}H$), 4.76 (bs, 1H, $C_{30}H_a$), 4.74 (bs, 1H, $C_{30}H_b$), 4.27 (d, *J* = 12.1 Hz, 1H, C_3-OH), 4.27 – 4.19 (m, 1H), 4.20 – 4.13 (m, 1H), 4.07 – 3.99 (m, 2H), 3.85 – 3.76 (m, 1H), 3.72 – 3.67 (m, 1H, $C_{22}H_a$), 3.68 (s, 3H, CO_2Me), 3.66 – 3.61 (m, 1H), 2.50 (dd, *J* = 12.5, 2.4 Hz, 1H, C_2H_a), 2.45 (app. t, *J* = 12.0 Hz, 1H, C_2H_b), 2.35 (s, 1H, C9-OH), 2.32 (t, *J* = 7.2 Hz, 2H, $C_{42}H_2$), 2.14 – 2.05 (m, 5H), 2.05 (s, 3H, C7-OAc), 2.03 – 1.90 (m, 4H), 1.86 (ddd, *J* = 14.0, 11.6, 3.0 Hz, 1H, $C_{24}H_b$), 1.77 (ddd, *J* = 12.2, 4.6, 2.7 Hz, 1H, C_6H_{eq}), 1.67 (d, *J* = 15.1 Hz, 1H, $C_{10}H_b$), 1.64 – 1.55 (m, 3H, C_4H_b, $C_{43}H_2$), 1.47 (app. q, *J* = 12.0 Hz, 1H, C_6H_b), 1.41 – 1.28 (m, 4H, $C_{44}H_2$, $C_{45}H_2$), 1.22 (d, *J* = 6.5 Hz, 3H, $C_{27}H_3$), 1.20 (s, 3H), 1.01 (s, 3H), 1.00 (s, 3H), 0.95 (s, 3H), 0.90 (t, *J* = 7.2 Hz, 3H, $C_{46}H_3$)

^{13}C-NMR (125 MHz, $CDCl_3$) δ 172.3, 170.9, 167.0, 152.4, 151.1, 143.5 (C13), 138.8, 130.0, 120.4, 109.2 (C30), 102.0, 98.9, 91.3 (C41), 80.2, 75.4, 73.8, 73.1, 72.9, 72.1, 70.3, 68.7, 65.9, 64.8, 51.3, 45.0, 42.8, 42.6, 42.1, 41.3, 41.1, 40.1, 35.8, 33.5, 31.3, 31.1 (C44), 29.9, 27.3 (C43), 24.6, 22.2(C45), 21.3, 21.2, 19.9, 18.9 (C42), 17.0, 14.1 (C46)

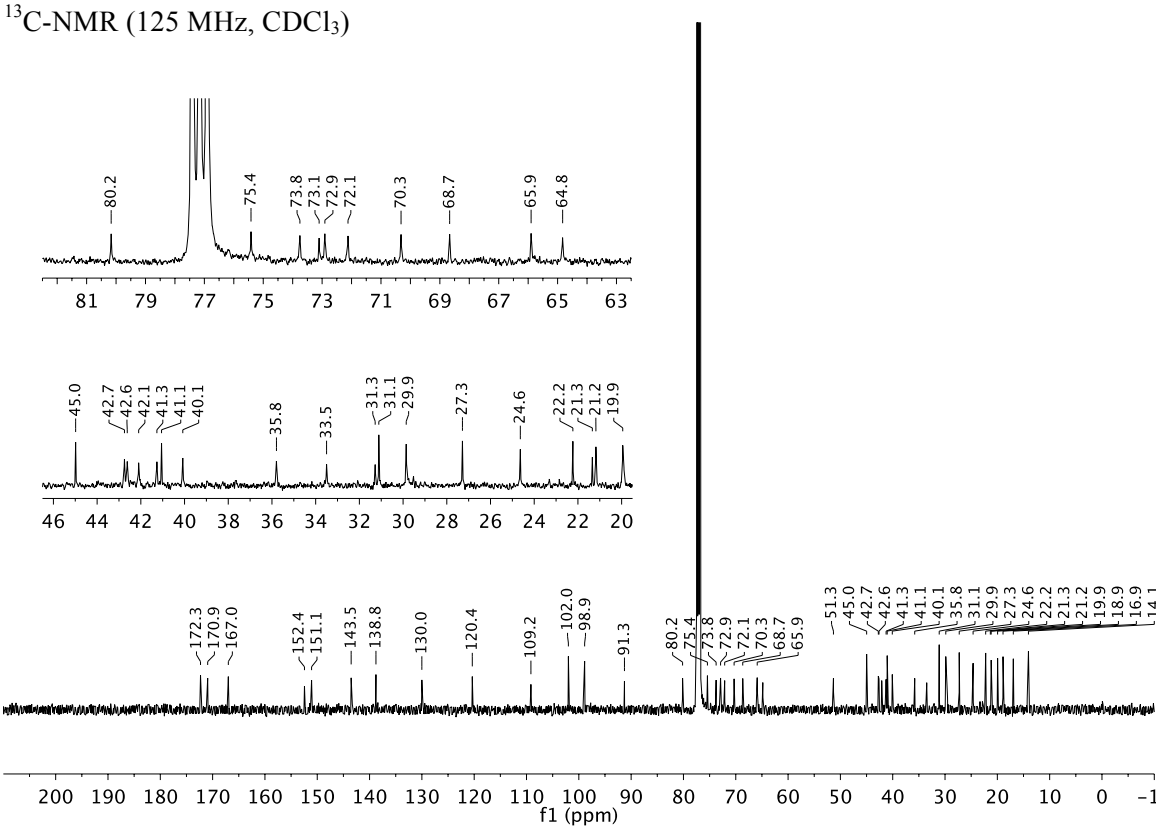
HRMS calculated for $C_{45}H_{66}NaO_{15}$ $[M+Na]^+$: 869.4294; found 869.4290 (TOF ESI+)

Experimentalist: AJS

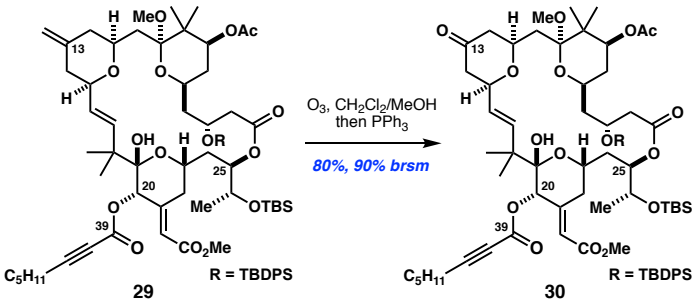
^{1}H-NMR (600 MHz, $CDCl_3$)



^{13}C-NMR (125 MHz, $CDCl_3$)



Endgame Step p: conversion of 29 to C13-ketone 30



Chemicals:
Methanol (99.8% Extra Dry, Acros): used without purification
Triphenylphosphine (99%, Oakwood): used without purification

Preparation of saturated ozone solution (~0.03 M CH_2Cl_2): A one-neck, 500 mL round-bottom flask equipped with magnetic stir bar was charged with CH_2Cl_2 (~250 mL) and cooled with a dry ice/acetone bath (-78 °C). Ozone (~4 LPM, prepared with 70 V) was bubbled through the solution until a bright blue color persisted (~15 min), at which point the headspace of the solution was purged with O_2 and sealed with a septum.

Ozonolysis: To a flame-dried, one-neck, 500 mL round-bottom flask equipped with magnetic stir bar was added alkene **29** (1.26 g, 1.04 mmol, 1 equiv) and methanol (83 mL, 0.0125M). After stirring for 5 min, the homogeneous reaction mixture was cooled with a dry ice/acetone bath (-78 °C). The solution turned slightly cloudy. Ozone (~0.03M CH_2Cl_2, 3 mL, 0.09 equiv) was added slowly via syringe down the side of the flask (addition time of ~1 min). After 5 min, the reaction was monitored by TLC and determined to be incomplete (Note 1). Additional ozone was then added in 3 mL (0.09 equiv) portions until **29** could no longer visualized by UV (Note 2). The total amount of ozone solution added was 66 mL (~1.9 equiv); the total time required to add this solution was ~3h. The reaction mixture was quenched by adding triphenylphosphine (545 mg, 2.08 mmol, 2 equiv) as a single portion. After 5 min, the reaction mixture was warmed to room temperature by removing the dry ice bath. After 80 min, both TLC and peroxide test strips indicated complete conversion of the intermediate peroxide (Note 1). The reaction mixture was concentrated to ~10 mL (Note 3) and directly purified by pH 7.0 buffered silica gel flash column chromatography (5.5x11.5 cm, 2L of 5-40% EtOAc/Hex) affording unreacted alkene **29** (141 mg) and C13-ketone **30** (1.01g, 80% yield, 90% brsm) as a white foam (Note 4). Compound purity of **30** was established by TLC (one spot) analysis.

Note 1: TLC eluent of 25% EtOAc/Hex with residual MeOH/CH_2Cl_2 from TLC capillary tube
- alkene **29**: R_f = 0.74 (UV active, dark purple spot in *p*-anisaldehyde)
- intermediate peroxide: R_f = 0.52 (UV active, yellow spot in *p*-anisaldehyde)
- C13-ketone **30**: R_f = 0.63 (UV active, yellow spot in *p*-anisaldehyde)

Note 2: To minimize over-oxidation products, this reaction was only run to partial conversion. Specifically, ozone was only added if alkene **29** could be visualized by UV (TLC); however, **29** was still present when the TLC plate was treated with *p*-anisaldehyde stain and heated.

Note 3: The crude reaction mixture should not be fully concentrated as this action may promote byproduct formation arising from conjugate addition of triphenylphosphine. Similarly, the crude mixture should be purified as soon as possible to remove triphenylphosphine.

Note 4: All endgame intermediates (i.e. post-Yamaguchi esterification) were found to be prone to C9-OMe hydrolysis. Therefore, NMRs were taken in either neutralized $CDCl_3$ or C_6D_6.

TLC R_f = 0.32 (25% EtOAc/Hex, UV active, yellow spot in *p*-anisaldehyde)

$[\alpha]^{23.0}_D$ = +0.9° (*c* = 0.15, CH_2Cl_2)

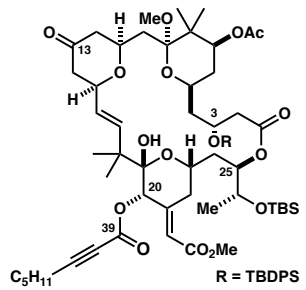
IR (thin film): 3516, 2956, 2933, 2234, 1721, 1665, 1472, 1429, 1387, 1366, 1245, 1105, 1049, 835, 704 cm^{-1}

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.68 – 7.56 (m, 4H, TBDPS), 7.47 – 7.31 (m, 6H, TBDPS), 6.00 (d, *J* = 2.0 Hz, 1H, $C_{34}H$), 5.96 (d, *J* = 16.1 Hz, 1H, $C_{17}H$), 5.56 (dd, *J* = 16.1, 6.7 Hz, 1H, $C_{16}H$), 5.21 (dd, *J* = 11.7, 4.9 Hz, 1H, C_7H), 5.14 (s, 1H, $C_{20}H$), 5.05 (ddd, *J* = 11.5, 4.1, 1.2 Hz, 1H, $C_{25}H$), 4.52 – 4.43 (m, 1H, C_3H), 4.33 – 4.27 (m, 1H, $C_{15}H$), 3.94 – 3.85 (m, 1H, C_5H), 3.80 – 3.72 (m, 1H, $C_{11}H$), 3.70 (s, 3H, CO_2Me), 3.66 – 3.52 (m, 3H, $C_{23}H$, $C_{22}H_a$, $C_{26}H$), 2.67 (s, 3H, C9-OMe), 2.63 (dd, *J* = 17.5, 3.4 Hz, 1H, C_2H_a), 2.37 (s, 1H, C19-OH), 2.32 (t, *J* = 7.1 Hz, 2H, $C_{42}H_2$), 2.29 – 2.05 (m, 7H, $C_{14}H_2$, C_2H_b, $C_{10}H_a$, $C_{12}H_2$, $C_{22}H_b$), 2.05 (s, 3H, C7-Oac), 1.79 – 1.71 (m, 1H, $C_{24}H_a$), 1.69 – 1.61 (m, 2H, C_6H_a, $C_{24}H_b$), 1.61 – 1.52 (m, 2H, $C_{43}H_2$), 1.51 (d, *J* = 16.2 Hz, 1H, $C_{10}H_b$), 1.51 – 1.45 (m, 2H, C_4H_2), 1.40 – 1.26 (m, 5H, C_6H_b, $C_{44}H_2$, $C_{45}H_2$), 1.20 (s, 3H), 1.02 (bs, 12H), 0.95 (s, 3H), 0.90 (d, *J* = 6.3 Hz, 3H, $C_{27}H_3$), 0.89 (t, *J* = 7.3 Hz, 3H, $C_{46}H_3$), 0.85 (s, 9H), 0.82 (s, 3H), 0.00 (s, 3H, TBS), -0.03 (s, 3H, TBS)

^{13}C-NMR (125 MHz, $CDCl_3$, 59 total peaks) δ 207.5 (C13), 170.9, 170.3, 166.8, 152.3, 150.6, 136.0, 135.9, 135.8, 134.8, 133.8, 132.3, 130.1, 129.9, 127.8, 127.7, 120.6, 102.6, 97.9, 91.5 (C41), 76.7, 75.0, 74.0, 72.9, 72.1, 71.9, 68.7, 67.1, 65.2, 64.6, 51.4, 48.7, 48.0, 47.8, 45.5, 45.1, 42.4, 41.7, 39.6, 34.8, 33.6, 31.1, 31.0 (C44), 27.2 (C43), 27.1 (3C, TBDPS), 25.9 (3C, TBS), 23.8, 22.2 (C45), 21.5, 20.4, 20.1, 19.4, 18.8 (C42), 18.6, 18.2, 17.4, 14.0 (C46), -4.6 (TBS), -4.7 (TBS)

HRMS calculated for $C_{67}H_{98}NaO_{16}Si_2$ $[M+Na]^+$: 1237.6291; found 1237.6286 (TOF ESI+)

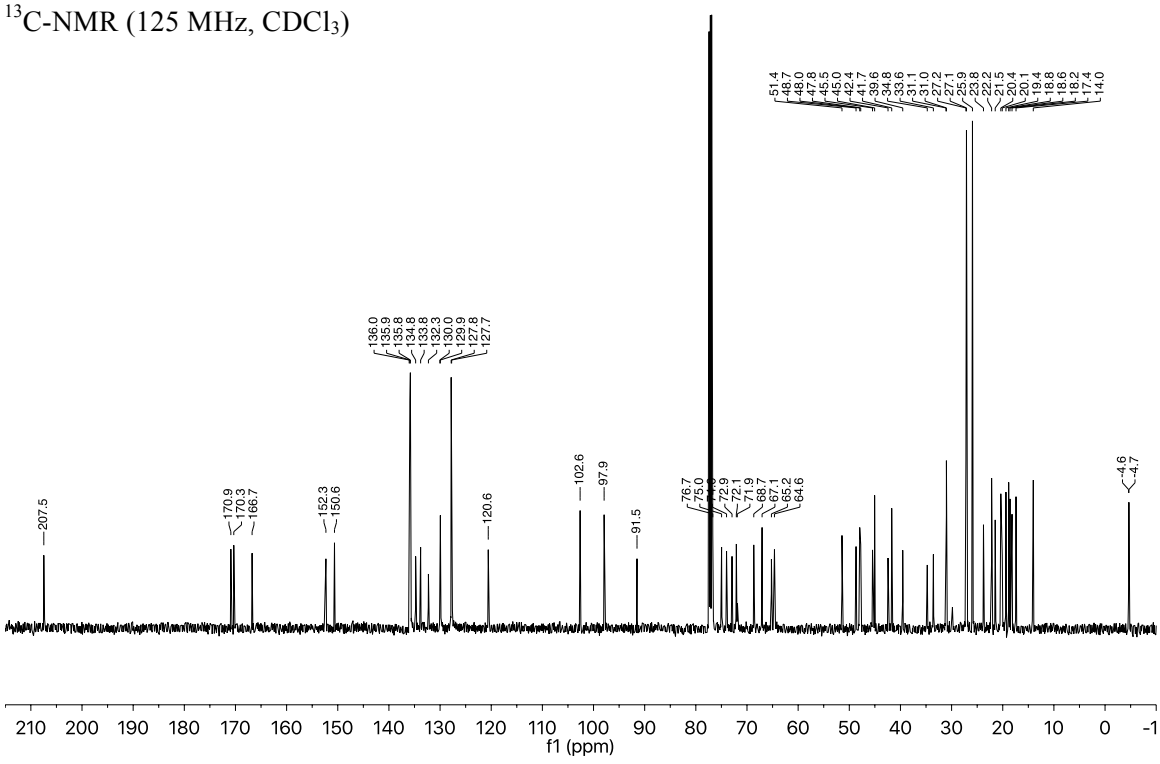
Experimentalists: SH, JLS, RVQ, SMR



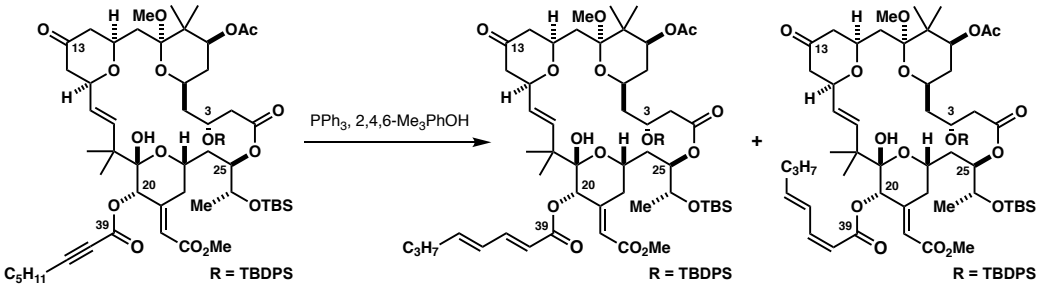
30

^{1}H-NMR (500 MHz, $CDCl_3$)

^{13}C-NMR (125 MHz, $CDCl_3$)



Endgame Step q: conversion of ynoate 30 to dienoate 31



30 | **31** (90% yield) | **SI-21** (6% yield)

Chemicals:
30: azeotroped with benzene (3x5 mL) and placed under vacuum for 15 min before use
Triphenylphosphine (99%, Oakwood): used without purification
2,4,6-Trimethylphenol (97%, Sigma-Aldrich): used without purification

The following procedure was adapted from Rychnovsky, S.D.; *et al.* (*48*)

To a flame-dried, one-neck, 100 mL round-bottom flask equipped with magnetic stir bar was added octynoate **30** (2.0 g, 1.65 mmol, 1 equiv) and benzene (16.5 mL, 0.1M). The flask was cooled with an ice bath (0 °C). Triphenylphosphine (2.16 g, 8.23 mmol, 5 equiv) and 2,4,6-trimethylphenol (1.12 g, 8.23 mmol, 5 equiv) were sequentially added as single portions. The reaction mixture and ice bath were allowed to warm to room temperature over 1h. After an additional 18h, TLC analysis indicated complete conversion of octynoate **30** and formation of dienoates **31**/**SI-21** (Note 1). The reaction mixture was directly purified by pH 7.0 buffered silica gel flash column chromatography (5x8cm, 500 mL of 5% EtOAc/Hex to elute triphenylphosphine and 2,4,6-trimethylphenol, then 1.5 L of 10-35% EtOAc/Hex) affording a mixture of *cis-trans*-dienoate **SI-21** (114 mg, 6%) and *trans-trans*-dienoate **31** (1.8 g, 90%) as white foams (Note 2). Further chromatography provided isomerically pure product. Compound purity was established by TLC (one spot) analysis.

Note 1: Retention factors; TLC eluent of 25% EtOAc/Hex
- octynoate **30**: R_f = 0.32 (UV active, yellow spot in *p*-anisaldehyde)
- *cis-trans*-dienoate **SI-21**: R_f = 0.35 (UV active, yellow/brown spot in *p*-anisaldehyde)
- *trans-trans*-dienoate **31**: R_f = 0.29 (UV active, yellow/brown spot in *p*-anisaldehyde)

Note 2: All endgame intermediates (i.e. post-Yamaguchi esterification) were found to be prone to C9-OMe hydrolysis. Therefore, NMRs were taken in either neutralized $CDCl_3$ or C_6D_6.

TLC R_f = 0.29 (25% EtOAc/Hex, UV active, yellow/brown spot in *p*-anisaldehyde)

$[\alpha]^{23.2}_{D}$ = +1.1° (*c* = 0.38, CH_2Cl_2)

IR (thin film) 3517, 2956, 2932, 1721, 1665, 1642, 1472, 1386, 1248, 1105, 912, 835, 735, 704 cm^{-1}

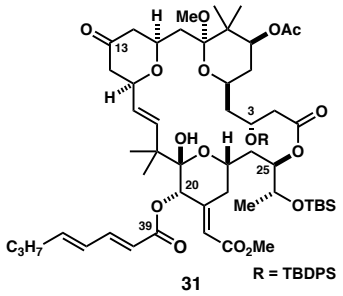
^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.69 – 7.57 (m, 4H, TBDPS), 7.48 – 7.32 (m, 6H, TBDPS), 7.22 (dd, *J* = 15.4, 9.8 Hz, 1H, $C_{41}H$), 6.21 – 6.09 (m, 2H, $C_{42}H$, $C_{43}H$), 6.02 (d, *J* = 1.9 Hz, 1H, $C_{34}H$), 5.97 (d, *J* = 16.1 Hz, 1H, $C_{17}H$), 5.76 (d, *J* = 15.4 Hz, 1H, $C_{40}H$), 5.55 (dd, *J* = 16.1, 6.7 Hz, 1H, $C_{16}H$), 5.21 (dd, *J* = 11.9, 4.8 Hz, 1H, C_7H), 5.20 (s, 1H, $C_{20}H$), 5.08 (app. dd, *J* = 11.1, 4.1 Hz,

1H, $C_{25}H$), 4.54 – 4.44 (m, 1H, C_3H), 4.34 – 4.26 (m, 1H, $C_{15}H$), 3.93 – 3.85 (m, 1H, C_5H), 3.81 – 3.73 (m, 1H, $C_{11}H$), 3.69 (s, 3H, CO_2Me), 3.67 – 3.53 (m, 3H, $C_{23}H$, $C_{22}H_a$, $C_{26}H$), 2.68 (s, 3H, C_9-OMe), 2.63 (dd, *J* = 17.5, 3.6 Hz, 1H, C_2H_a), 2.36 (s, 1H, C_{19}-OH), 2.32 – 2.18 (m, 4H, $C_{14}H_2$, C_2H_b, $C_{10}H_a$), 2.19 – 2.02 (m, 5H, $C_{12}H_2$, $C_{44}H_2$, $C_{22}H_b$), 2.05 (s, 3H, C7-Oac), 1.75 (dd, *J* = 13.8, 11.2 Hz, 1H, $C_{24}H_a$), 1.70 – 1.58 (m, 2H, C_6H_a, $C_{24}H_b$), 1.54 – 1.41 (m, 5H, $C_{10}H_b$, C_4H_2, $C_{45}H_2$), 1.36 (app. q, *J* = 12.2 Hz, 1H, C_6H_b), 1.16 (s, 3H), 1.02 (bs, 12H), 0.95 (s, 3H), 0.911 (t, *J* = 7.4 Hz, 3H, $C_{46}H_3$), 0.908 (d, *J* = 6.3 Hz, 3H, $C_{27}H_3$), 0.86 (s, 9H), 0.83 (s, 3H), 0.01 (s, 3H, TBS), 0.00 (s, 3H, TBS)

^{13}C-NMR (125 MHz, $CDCl_3$, 58 total peaks) δ 207.5 (C13), 170.9, 170.3, 166.9, 165.5, 151.6, 146.7 (C41), 145.9 (C43), 136.2, 135.9, 135.8, 134.8, 133.8, 132.2, 130.1, 129.9, 128.5 (C42), 127.83, 127.75, 119.9, 118.5, 102.6, 98.2, 76.7, 74.0, 73.7, 71.9 (2C, as confirmed by HMBC), 68.4, 67.1, 65.2, 64.7, 51.4, 48.7, 48.0, 47.8, 45.5, 45.1, 42.5, 41.7, 39.6, 35.2 (C44), 34.5, 33.6, 31.3, 27.1 (3C, TBDPS), 25.9 (3C, TBS), 24.0, 22.0 (C45), 21.5, 20.4, 20.1, 19.4, 18.3, 18.2, 17.4, 13.8 (C46), -4.6 (TBS), -4.7 (TBS)

HRMS calculated for $C_{67}H_{98}NaO_{16}Si_2$ $[M+Na]^+$: 1237.6291; found 1237.6286 (TOF ESI+)

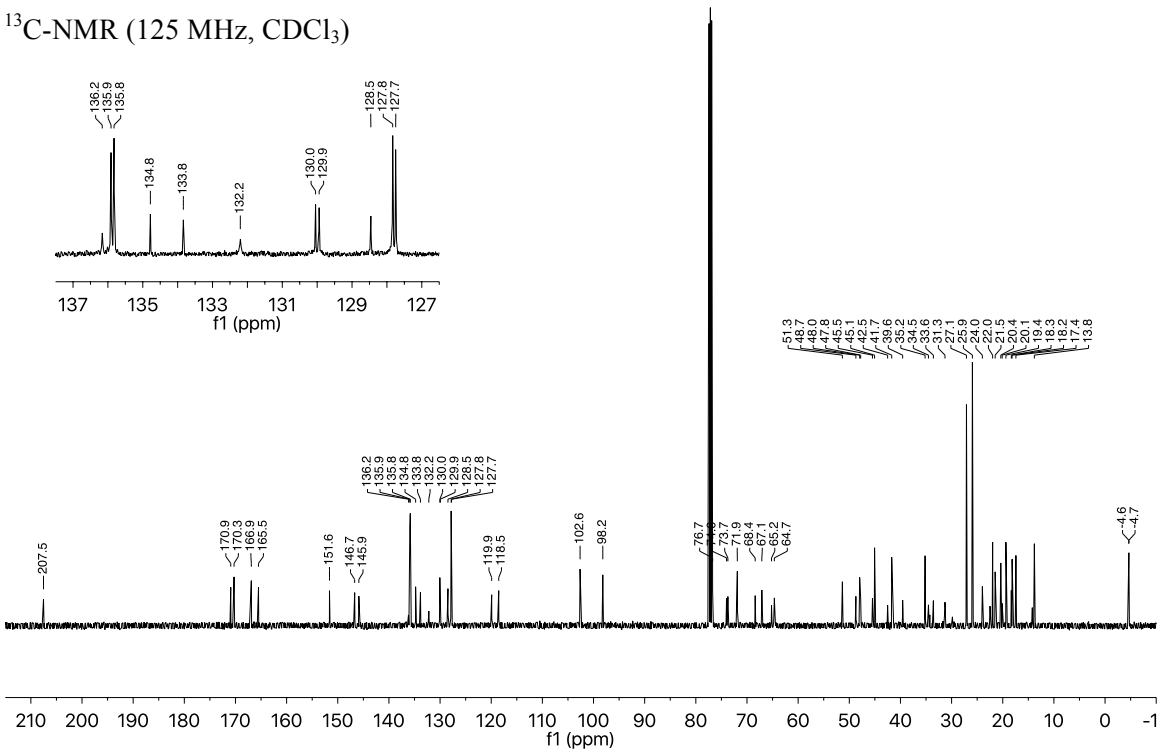
Experimentalists: JLS, SH, CTH, RVQ



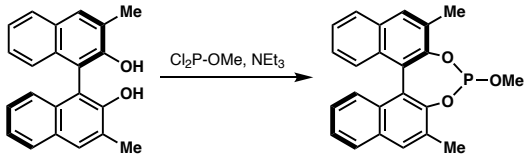
31

^{1}H-NMR (500 MHz, $CDCl_3$)

^{13}C-NMR (125 MHz, $CDCl_3$)



Endgame: preparation of phosphonate 32

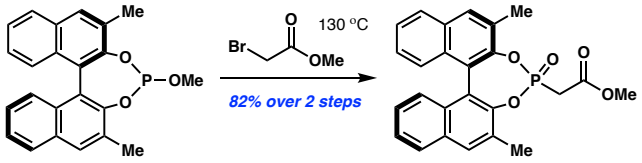


SI-22

Chemicals:
(*R*)-3,3'-dimethyl-[1,1'-binaphthalene]-2,2'-diol: prepared according to Wu, R.; *et al.* (*70*).
Triethylamine (Sigma-Aldrich): distilled from CaH_2 before use
Methyl dichlorophosphite (technical grade, Sigma-Aldrich): used without purification

To a flame-dried, one-neck, 1L round-bottom flask equipped with magnetic stir bar was added (*R*)-3,3'-dimethyl-[1,1'-binaphthalene]-2,2'-diol (10.07 g, 32.02 mmol, 1 equiv) in CH_2Cl_2 (213 mL, 0.15M). The reaction mixture was cooled with an ice bath (0 °C). Triethylamine (11.7 mL, 73.6 mmol, 2.6 equiv) was added via syringe over 30 sec, followed by methyl dichlorophosphite (3.7 mL, 36.86 mmol, 1.15 equiv) dropwise via syringe over 30 sec. After 30 min at 0 °C, the reaction mixture was warmed to room temperature by removing the ice bath. After 2h at room temperature, aliquot ^{1}H-NMR indicated full conversion of starting material and formation of phosphite **SI-22** (Note 1). Et_2O (300 mL) was added to precipitate triethylamine salts, and the resulting suspension was filtered over celite using Et_2O washings. The filtrate was concentrated to afford crude phosphite **SI-22** as a white foam, which was used immediately in the next step.

Note 1: diagnostic NMR peaks:
- 3,3'-dimethyl-[1,1'-binaphthalene]-2,2'-diol: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.52 (s, 6H)
- methyl dichlorophosphite
  - ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.90 (d, $^3J_{H,P}$ = 10.0 Hz, 2H)
  - ^{31}P-NMR (162 MHz, $CDCl_3$) δ 180.8
- phosphite **SI-22**
  - ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.48 (d, $^3J_{H,P}$ = 9.6 Hz, 2H), 2.59 (s, 3H), 2.57 (s, 3H).
  - ^{31}P-NMR (162 MHz, $CDCl_3$) δ 137.9



SI-22 **32**

Chemicals:
Methyl bromoacetate (>98%, Alfa Aesar): used without purification

To a flame-dried, one-neck, 250 mL round-bottom flask equipped with magnetic stir bar was added crude phosphite **SI-22** (assume 32.02 mmol, 1 equiv) and methyl bromoacetate (~60 mL, 0.5M). The round-bottom flask was affixed with a short-path distillation head and placed in a 130 °C oil bath. After 2h at 130 °C, aliquot ^{1}H-NMR indicated full conversion of **SI-22** and formation of phosphonate **32**. Methyl bromide and methyl bromoacetate were distilled off (oil bath 90 °C, ~2 mmHg), and the remaining oil was purified by silica gel flash column chromatography (40-90% EtOAc/Hex) affording phosphonate **32** (11.35 g, 82% yield over two steps) as a white foam. Compound purity was established by TLC (one spot) analysis.

TLC R_f = 0.54 (80% EtOAc/Hex, yellow spot in $KMnO_4$)

[α]$^{22.0}_{D}$ = -517.5° (*c* = 0.44, CH_2Cl_2)

IR (thin film): 3054, 1743, 1503, 1437, 1418, 1290, 1264, 1236, 929, 732, 702 cm^{-1}

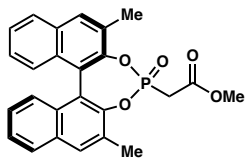
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 8.4, 3.0 Hz, 4H), 7.40-7.48 (m, 2H), 7.25 – 7.11 (m, 4H), 3.67 (s, 3H), 3.32 – 3.04 (m, 2H), 2.67 (s, 3H), 2.62 (s, 3H)

^{13}C-NMR (125 MHz, $CDCl_3$) δ 164.9 (d, $^{2}J_{C,P}$ = 5.6 Hz), 146.6 (d, $^{2}J_{C,P}$ = 10.8 Hz), 145.2 (d, $^{2}J_{C,P}$ = 9.9 Hz), 132.1, 131.58, 131.55, 131.3, 131.0 (2C), 130.0 (d, $^{3}J_{C,P}$ = 1.8 Hz), 128.6 (d, $^{3}J_{C,P}$ = 3.5 Hz), 127.9, 127.6, 127.3, 126.8, 126.1 (2C), 125.89, 125.87, 121.9 (2C), 53.1, 32.5 (d, $^{1}J_{C,P}$ = 130.7 Hz), 17.5, 17.3

^{31}P-NMR (162 MHz, $CDCl_3$) δ 28.4

HRMS calculated for $C_{25}H_{21}NaO_5P$ $[M+Na]^+$: 455.1024; found 455.1010 (TOF ESI+)

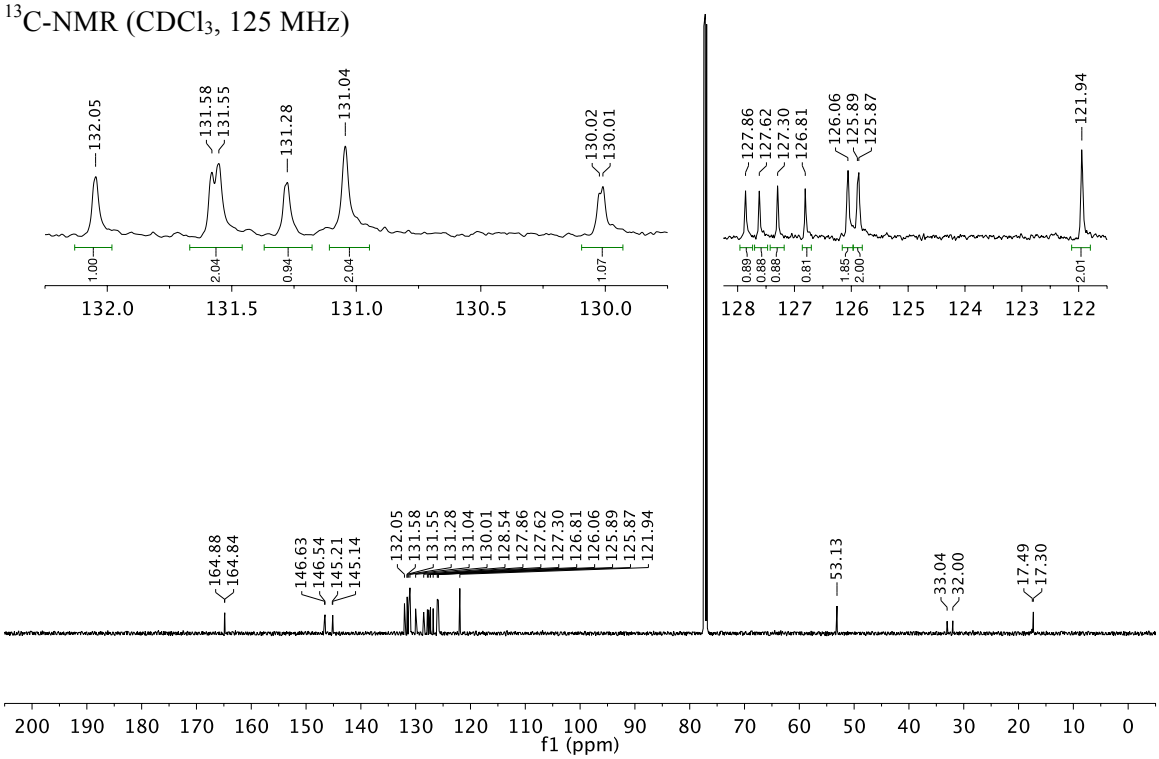
Experimentalists: CTH, SH



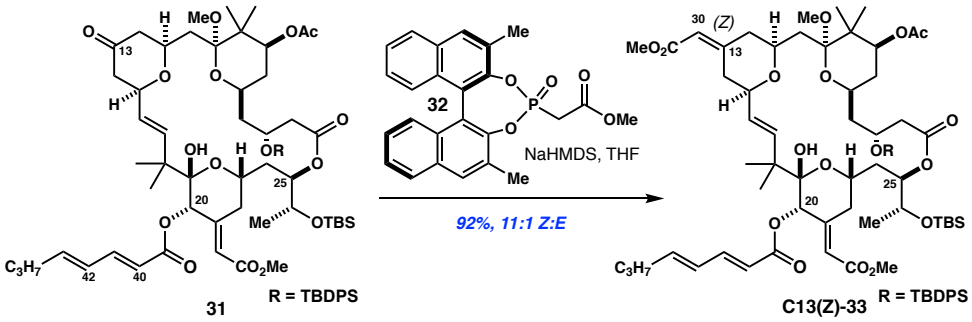
32

^{1}H-NMR ($CDCl_3$, 400 MHz)

^{13}C-NMR ($CDCl_3$, 125 MHz)



Endgame Step r: conversion of C13-ketone 31 to (*Z*)-enoate 33



31 C13(Z)-33

Chemicals:
NaHMDS (1M THF, Sigma-Aldrich): used without purification
Phosphonate **32**: azeotroped with benzene (3x15 mL) and placed under vacuum 1h before use

To a flame-dried, one-neck, 250 mL round-bottom flask equipped with magnetic stir bar was added phosphonate **32** (6.05g, 14 mmol, 14 equiv) and THF (25 mL, 0.04M). The reaction mixture was cooled with a dry ice/acetone bath (-78 °C). NaHMDS (1M THF, 13 mL, 13 mmol, 13 equiv) was added dropwise via syringe over 1 min. After 30 min at -78 °C, a solution of C13-ketone **31** (1.22g, 1 mmol, 1 equiv) in THF (12 mL; final volume 50 mL THF, 0.02M) was added dropwise via syringe over 1 min. After 5 min at -78 °C, the flask was transferred to a 4 °C cold room. The solution gradually turned yellow/orange. After 70h at 4 °C (Note 1), the reaction mixture was quenched at 4 °C by adding saturated aqueous NH_4Cl (10 mL) and diluted with Et_2O (100 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (5x50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to ~15 mL (Note 2). Purification was accomplished by silica gel flash column chromatography (2L of 25-35% Et_2O/Hex to elute product, then 750 mL of EtOAc to elute unreacted phosphonate **32**) affording enoate **33** (1.17 g, 11.6:1 Z:E, 92% combined yield) as a white foam (Notes 3-4) and unreacted phosphonate **32** (3.72 g, 66% recovered yield). Further chromatography provided **33** in >30:1 *Z*:*E* (the front fractions from the column are enriched in the desired 13(*Z*)-enoate).

Note 1: Shorter reaction times (36-48h) can be obtained by increasing the equiv. of phosphonate **32**; however, a slight drop in selectivity accompanies this change. For example, using NaHMDS (15.5 eq.) and **32** (17 eq.) affords enoate **33** in 8.5:1 Z:E (90% combined yield, 500 mg scale).

Note 2: Residual THF enables easy transfer of unreacted phosphonate **32**; additionally, a small amount of CH_2Cl_2 may be required to fully transfer the crude mixture onto the silica gel column. Alternatively, the reaction mixture may be "dry loaded" by (a) dissolving the crude mixture in EtOAc and adding ~10X its weight in silica gel; (b) concentrating the resulting solution via rotary evaporator, with a cotton plug in the bump trap to minimize silica gel loss; and (c) transferring the compound-adsorbed silica onto the top of a slurry-packed column with 25% Et_2O/Hex.

Note 3: On some larger scale reactions, full conversion of **31** is not achieved (typically, 2-3% of unreacted starting material remains). In these cases, the back fractions collected from the column contain both starting material and product. Rather than separate this mixture via chromatography, we have found it to be more convenient to pool samples from several reactions together and re-subject the combined mixture to a second HWE reaction.
- Retention factors; TLC eluent of 25% EtOAc/Hex
  - C13-ketone **31**: R_f = 0.29 (UV active, yellow/brown spot in *p*-anisaldehyde)
  - (*Z*)-enoate **33**: R*f* = 0.35 (UV active, dark purple spot in *p*-anisaldehyde)

Note 4: All endgame intermediates (i.e. post-Yamaguchi esterification) were found to be prone to C9-OMe hydrolysis. Therefore, NMRs were taken in either neutralized $CDCl_3$ or C_6D_6.

TLC R_f = 0.35 (25% EtOAc/Hex, UV active, dark purple spot in *p*-anisaldehyde)

$[\alpha]^{23.5}_D$ = +8.83° (*c* = 1.33, CH_2Cl_2)

IR (thin film) 3510, 2954, 2933, 2858, 1721, 1644, 1616, 1472, 1435, 1365, 1248, 1162, 1105, 1025, 1004, 879, 835, 778, 740, 705 cm^{-1}

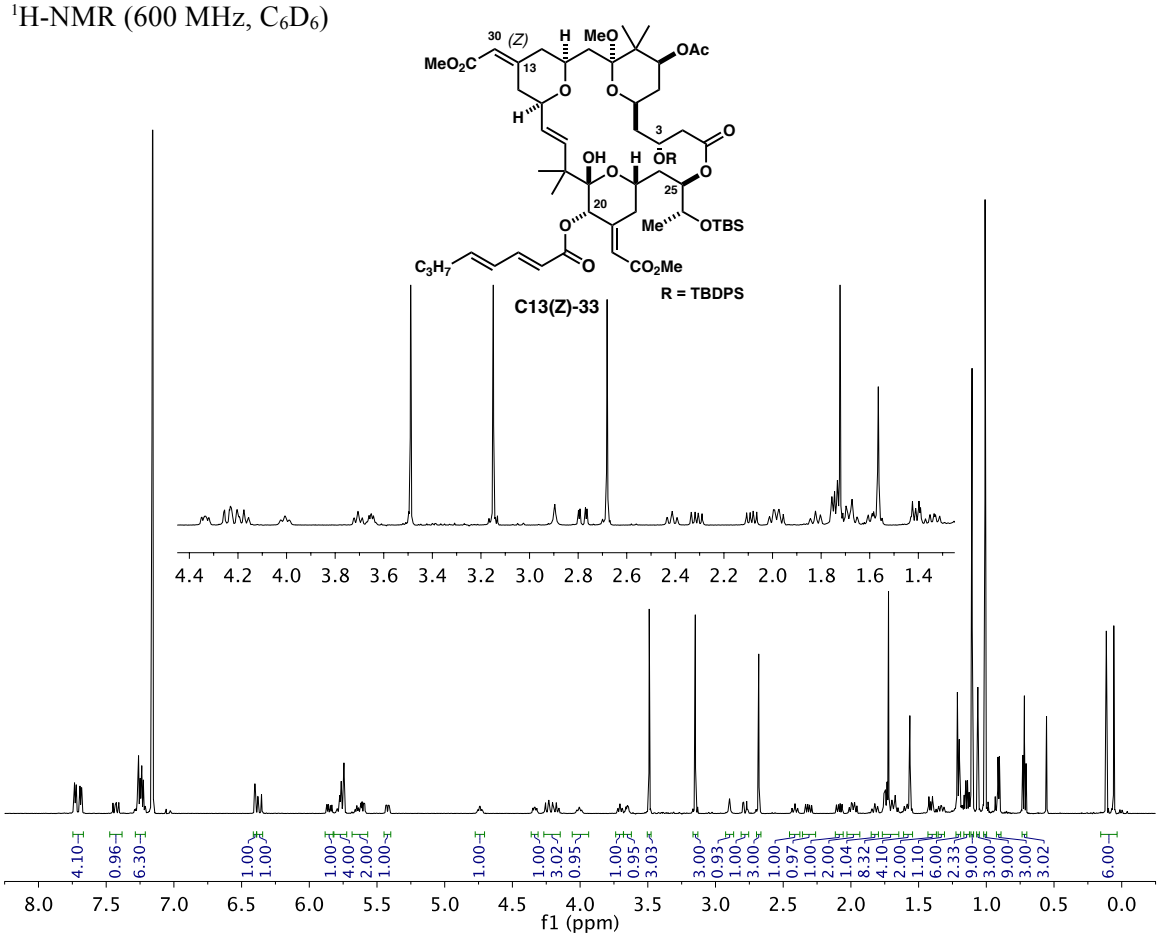
^{1}H-NMR (600 MHz, C_6D_6) δ 7.75 – 7.66 (m, 4H, TBDPS), 7.43 (dd, *J* = 15.3, 10.9 Hz, 1H, $C_{41}H$), 7.30 – 7.20 (m, 6H, TBDPS), 6.40 (d, *J* = 1.9 Hz, 1H, $C_{34}H$), 6.37 (d, *J* = 16.1 Hz, 1H, $C_{17}H$), 5.85 (dd, *J* = 16.1, 6.5 Hz, 1H, $C_{16}H$), 5.80 – 5.75 (m, 1H, $C_{42}H$), 5.77 (t, *J* = 1.9 Hz, 1H, $C_{30}H$), 5.76 (d, *J* = 15.3 Hz, 2H, $C_{40}H$), 5.74 (s, 1H, $C_{20}H$), 5.67 – 5.61 (m, 1H, $C_{43}H$), 5.42 (ddd, *J* = 11.6, 4.6, 1.2 Hz, 1H, C_7H), 4.78 – 4.70 (m, 1H, C_3H), 4.37 – 4.30 (m, 1H, $C_{15}H$), 4.27 – 4.15 (m, 3H, $C_{22}H_{eq}$, $C_{14}H_{eq}$, $C_{23}H$), 4.01 (app. t, *J* = 10.9 Hz, 1H, C_5H), 3.74 – 3.68 (m, 1H, $C_{11}H$), 3.68 – 3.62 (m, 1H, $C_{26}H$), 3.49 (s, 3H, B-ring CO_2Me), 3.15 (s, 3H, C-ring CO_2Me), 2.90 (bs, 1H, C_{19}-OH), 2.78 (dd, *J* = 17.1, 3.8 Hz, 1H, C_2H_a), 2.68 (s, 3H, C9-OMe), 2.41 (ddd, *J* = 13.8, 11.4, 2.1 Hz, 1H, $C_{22}H_{aq}$), 2.31 (dd, *J* = 17.1, 9.4 Hz, 1H, C_2H_b), 2.09 (dd, *J* = 16.2, 8.7 Hz, 1H, $C_{10}H_a$), 2.03 – 1.94 (m, 2H, $C_{14}H_{aq}$, $C_{24}H_a$), 1.86 – 1.79 (m, 1H, $C_{12}H_a$), 1.72 (s, 3H, C7-OAc), 1.78 – 1.64 (m, 5H, $C_{12}H_b$, $C_{44}H_2$, C_6H_a, $C_{24}H_b$), 1.63 – 1.53 (m, 1H, C_4H_a), 1.56 (s, 3H), 1.41 (d, *J* = 16.2 Hz, 1H, $C_{10}H_b$), 1.40 (app. q, *J* = 12.0 Hz, 1H, C_6H_b), 1.36 – 1.29 (m, 1H, C_4H_b), 1.21 (s, 3H), 1.20 (s, 3H), 1.18 – 1.11 (m, 2H, $C_{45}H_2$), 1.11 (s, 9H), 1.06 (s, 3H), 1.01 (s, 9H), 0.91 (d, *J* = 6.3 Hz, 3H, $C_{27}H_3$), 0.72 (t, *J* = 7.3 Hz, 3H, $C_{46}H_3$), 0.11 (s, 3H), 0.06 (s, 3H)

^{13}C-NMR (125 MHz, $CDCl_3$) δ 170.9, 170.2, 167.0, 166.9, 165.6, 158.1 (C13), 151.8, 146.6 (C41), 145.8 (C43), 135.9, 135.8 (2C), 134.8, 134.1, 133.3, 129.83, 129.79, 128.5, 127.8, 127.7, 119.8, 118.6, 114.6 (C30), 102.8, 98.2, 77.7, 74.0, 73.9, 72.7, 72.0, 68.5, 67.3, 65.2, 64.8, 51.3, 51.1, 48.1, 45.4, 45.1, 42.8, 42.6, 41.7, 39.8, 36.7, 35.2 (C44), 34.8, 33.6, 31.4, 27.1 (3C, TBDPS), 25.9 (3C, TBS), 24.1, 22.0 (C45), 21.5, 20.4, 20.2, 19.4, 18.4, 18.2, 17.5, 13.8 (C46), -4.6 (TBS), -4.7 (TBS)

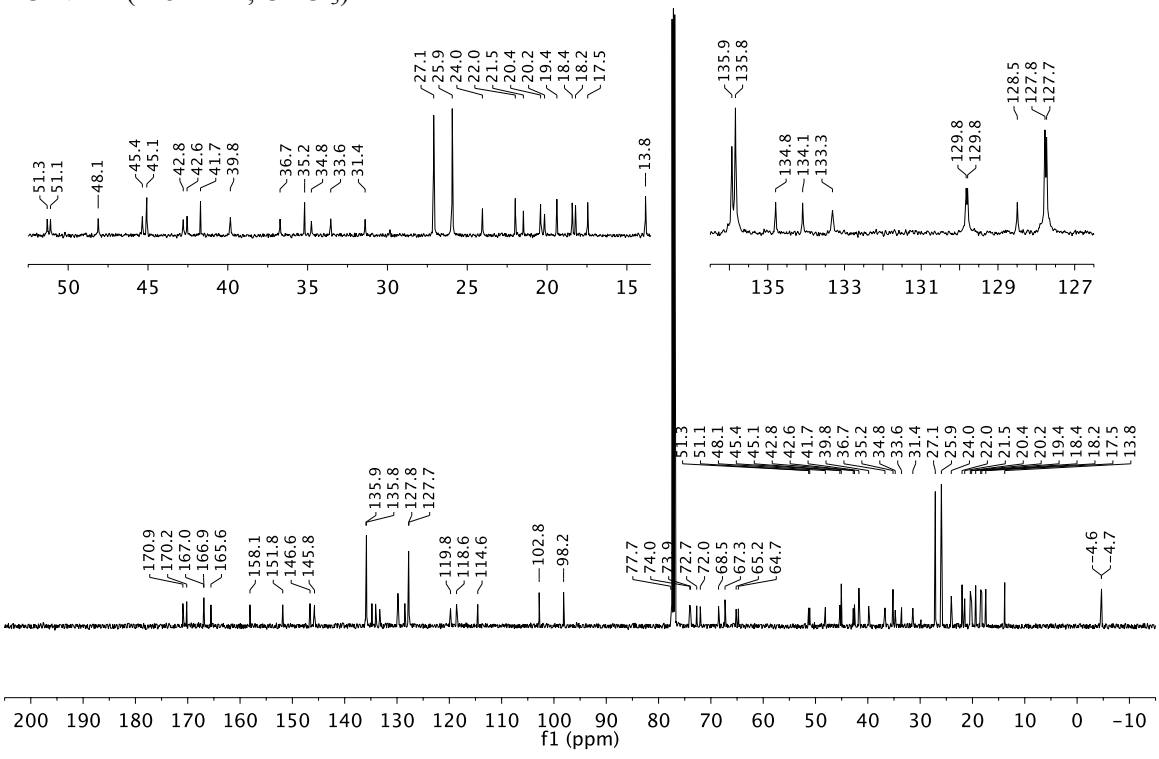
HRMS calculated for $C_{70}H_{102}NaO_{17}Si_2$ $[M+Na]^+$: 1293.6554; found 1293.6550 (TOF ESI+)

Experimentalists: SH, AJS, RVQ

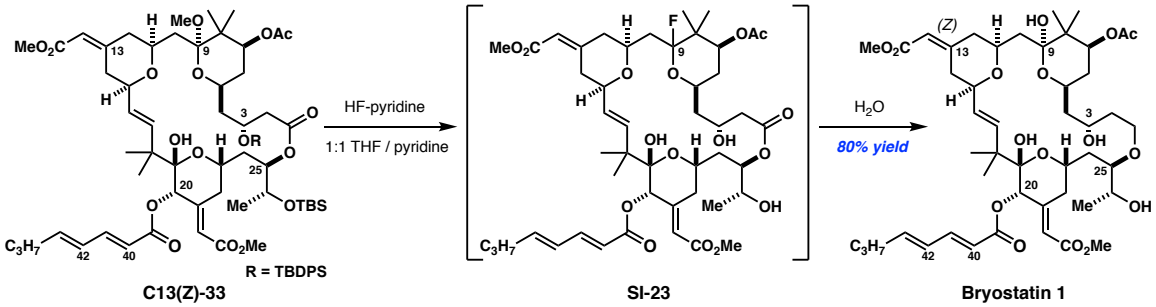
^{1}H-NMR (600 MHz, C_6D_6)



^{13}C-NMR (125 MHz, $CDCl_3$)



Endgame Step s: conversion of 33 to bryostatin 1



Chemicals:
70% HF-pyridine (Sigma-Aldrich): used without purification
pyridine (Sigma-Aldrich): distilled from CaH_2 before use

CAUTION: Bryostatin 1 is a biologically potent agent; proper personal protective gear should be used and contact avoided.

To a 50 mL polypropylene falcon tube equipped with magnetic stir bar was added compound **33** (170 mg, 30:1 Z:E at C13, 0.134 mmol, 1 equiv), THF (7.1 mL), and pyridine (7.1 mL). The reaction mixture was cooled with an ice bath (0 °C). HF-pyridine (3.55 mL) (**CAUTION**: corrosive agent) was added via a plastic Luer Lock syringe down the side of the tube (addition time of ~1.5 min), affording a ~0.0075M solution of 1:2:2 HF-pyr / THF / pyridine. The reaction mixture was placed in a 40 °C oil bath. After 19.5h at 40 °C, TLC analysis indicated full conversion of compound **33**. To hydrolyze the C9-F-intermediate, **SI-23**, water (3.55 mL) was added via syringe down the side of the tube (~1 min). After an additional 2.5h at 40 °C, the reaction mixture was allowed to cool to room temperature and quenched by slowly syringing the solution directly into the aqueous layer in a separatory funnel containing saturated aqueous $NaHCO_3$ (130 mL, chilled on ice before use) and EtOAc (50 mL) (**CAUTION**: significant amounts of carbon dioxide are generated). The falcon tube was washed with additional saturated aqueous $NaHCO_3$ (10 mL) and EtOAc (3x10 mL). After bubbling ceased, the layers were separated, and the aqueous layer was extracted with EtOAc (2x50 mL). The combined organic layers were washed with 1M HCl (110 mL, chilled on ice before use) to remove pyridine, brine (50 mL), dried over Na_2SO_4, filtered, and concentrated. Purification was accomplished by silica gel flash column chromatography (loaded with CH_2Cl_2, then 10-35-45% EtOAc/pentane) affording bryostatin 1 (96.2 mg, 18:1 *Z*:*E* at C13, 80% combined yield) as a white solid. ^{19}F-NMR showed no peaks corresponding to intermediate **SI-23**: **^{19}F-NMR** (377 MHz, $CDCl_3$) δ -128.0. See below for HPLC purification procedure.

Procedure in PFA round-bottom flask: A 100 mL PFA round-bottom flask (Chemglass Life Sciences) equipped with magnetic stir bar was charged with compound **33** (552 mg, 9.2:1 Z:E at C13, 0.434 mmol, 1 equiv), THF (23 mL), and pyridine (23 mL). The reaction mixture was cooled with an ice bath (0 °C). HF-pyridine (11.5 mL) was added via a plastic Luer Lock syringe down the side of the flask (addition time of ~1.5 min), affording a ~0.0075M solution of 1:2:2 HF-pyr / THF / pyridine. The reaction mixture was placed in a 40 °C oil bath. After 20h at 40 °C, TLC analysis indicated full conversion of compound **33**. To hydrolyze the C9-F-intermediate, **SI-23**, water (11.5 mL) was added via syringe down the side of the flask (~1 min). After an additional 2.5h at 40 °C, the reaction mixture was allowed to cool to room temperature and quenched by slowly syringing the solution directly into the aqueous layer in a separatory funnel containing saturated aqueous $NaHCO_3$ (410 mL, chilled on ice before use) and EtOAc (150 mL) (**CAUTION**: significant amounts of carbon dioxide are generated). The flask was washed with

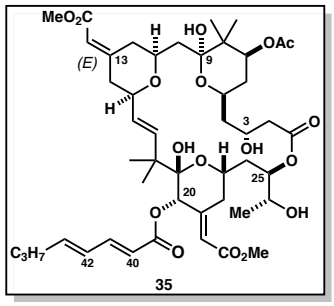
additional saturated aqueous $NaHCO_3$ (30 mL) and EtOAc (3x20 mL). After bubbling ceased, the layers were separated, and the aqueous layer was extracted with EtOAc (2x150 mL). The combined organic layers were washed with 1M HCl (340 mL, chilled on ice before use) to remove pyridine, additional saturated aqueous $NaHCO_3$ (50 mL), and brine (100 mL). The combined organic layers were then dried over Na_2SO_4, filtered, and concentrated. Purification was accomplished by silica gel flash column chromatography (10-35-45% EtOAc/pentane) affording bryostatin 1 (304 mg, 8.7:1 *Z*:*E* at C13, 77% combined yield) as a white solid. ^{19}F-NMR showed no peaks corresponding to intermediate **SI-23**: **^{19}F-NMR** (377 MHz, $CDCl_3$) δ -128.0. See below for HPLC purification procedure.

Preparative HPLC: Bryostatin 1 (as a ~10:1 *Z*:*E* mixture of C13 enoate isomers) was further purified by preparative HPLC using a Varian ProStar 210 Solvent Delivery System with an Agilent ProStar 325 detector set to detect at 256 nm and 214 nm. Separations were performed using a Grace Alltima C18 reverse-phase column (10 μm particle size, 280 mm x 22 mm). The mobile phase was a gradient elution from 75% MeCN/H_2O to 95% MeCN/H_2O over 30 min, followed by 100% MeCN for 10 min (flow rate of 12 mL/min). The sample was dissolved in 2:1 MeCN/MeOH (final concentration 50 mg/mL). ~50 mg (1 mL) of material were loaded on the column per run, each run producing ~40 mg of bryostatin 1, with the C13 enoate isomers separated. The fractions were concentrated, first by rotary evaporation then by lyophilization, to yield bryostatin 1 as a white, airy powder in >99.5% purity. A representative HPLC chromatogram is shown on SI-107.

Crystallization: HPLC purified bryostatin 1 was crystallized from a slowly evaporating mixture of 1:1 CH_2Cl_2 / MeOH. A detailed procedure is provided on SI-112.

Experimentalists: RVQ, AJS, JLS

Characterization data for C13(*E*)-enoate of bryostatin 1, **35**



TLC: R_f = 0.32 (60% EtOAc/Hex, UV active, purple spot in *p*-anisaldehyde)

$[\alpha]^{23.2}_{D}$ = -35.5° (*c* = 0.26, CH_2Cl_2)

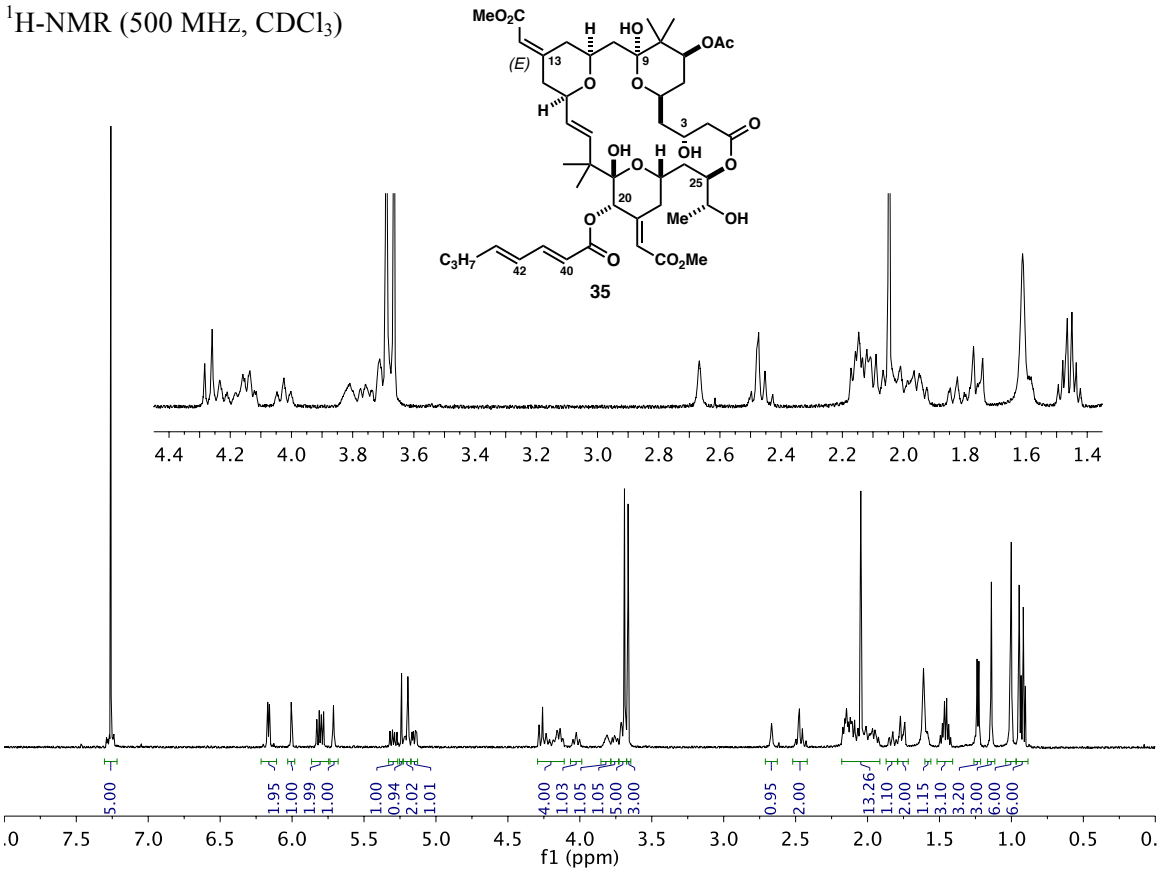
IR (thin film): 3464, 3336, 2951, 2928, 1716, 1657, 1643, 1615, 1435, 1408, 1366, 1284, 1242, 1156, 1098, 1078, 1057, 1002, 859 cm^{-1}

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.23 (dd obscured by chloroform peak, 1H, $C_{41}H$), 6.21 – 6.11 (m, 2H, $C_{42}H$, $C_{43}H$), 6.00 (d, *J* = 1.9 Hz, 1H, $C_{34}H$), 5.81 (d, *J* = 15.8 Hz, 1H), 5.80 (d, *J* = 15.3 Hz, 1H), 5.71 (s, 1H, $C_{30}H$), 5.30 (dd, *J* = 15.9, 8.4 Hz, 1H, $C_{16}H$), 5.24 (s, 1H, C_{19}-OH), 5.24 – 5.18 (m, 1H, $C_{25}H$), 5.20 (s, 1H, $C_{20}H$), 5.15 (dd, *J* = 11.8, 4.7 Hz, 1H, C_7H), 4.27 (d, *J* = 12.1 Hz, 1H, C_3-OH), 4.28 – 4.20 (m, 1H, C_5H), 4.21 – 4.09 (m, 2H, C_3H, $C_{15}H$), 4.02 (app. t, *J* = 11.4 Hz, 1H, $C_{23}H$), 3.86 – 3.78 (m, 1H, $C_{11}H$), 3.79 – 3.73 (m, 1H, $C_{26}H$), 3.74 – 3.67 (m, 2H, $C_{22}H_{eq}$, $C_{14}H_{eq}$), 3.69 (s, 3H, CO_2Me), 3.66 (s, 3H, CO_2Me), 2.67 (bs, 1H, C_9-OH), 2.53 – 2.38 (m, 2H, C_2H_2), 2.19 – 1.90 (m, 10H), 2.05 (s, 3H, C7-OAc), 1.86 – 1.79 (m, 1H, $C_{24}H_b$), 1.79 – 1.72 (m, 2H, C_6H_{eq}, $C_{10}H_b$), 1.63 – 1.56 (m, 1H, C_4H_b), 1.54 – 1.41 (m, 3H, C_6H_{ax}, $C_{45}H_2$), 1.23 (d, *J* = 6.5 Hz, 3H, $C_{27}H_3$), 1.14 (s, 3H), 1.004 (s, 3H), 1.001 (s, 3H), 0.95 (s, 3H), 0.92 (t, *J* = 7.4 Hz, 3H, $C_{46}H_3$)

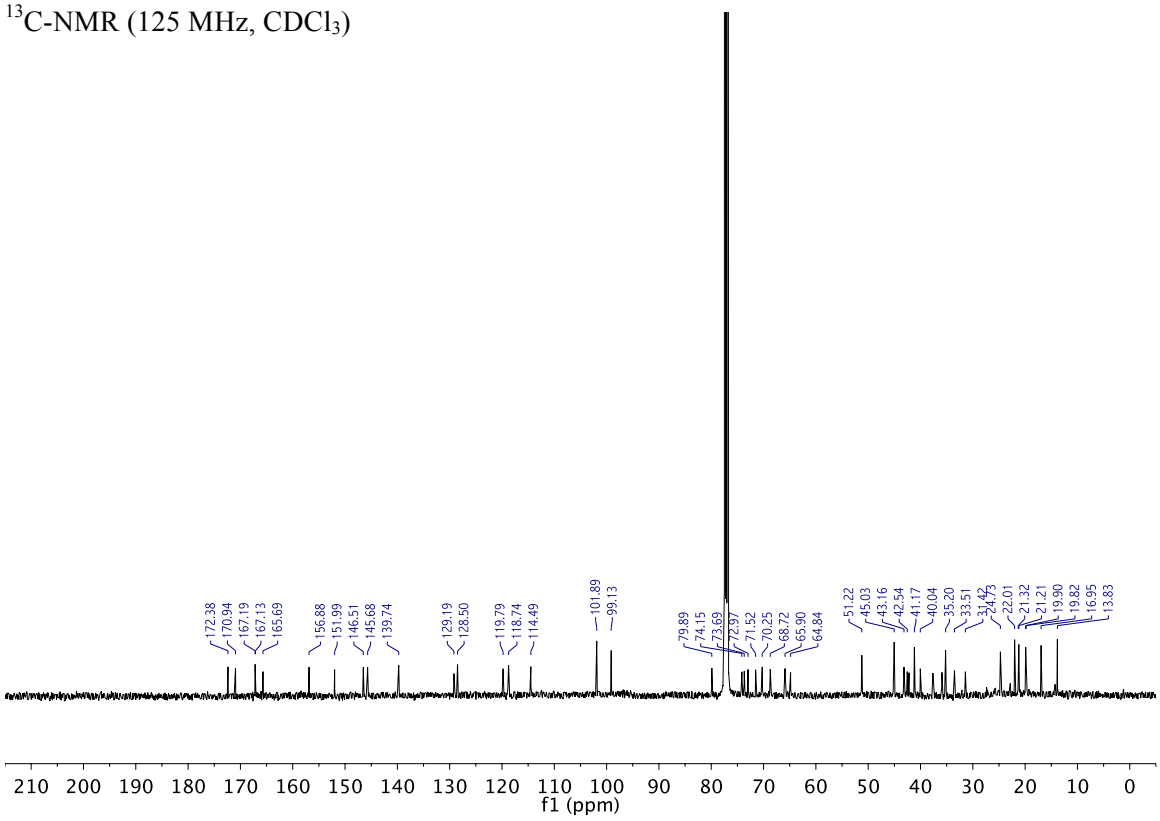
^{13}C-NMR (125 MHz, $CDCl_3$) δ 172.4, 171.0, 167.2, 167.1, 165.7, 156.9, 152.0, 146.5, 145.7, 139.7, 129.2, 128.5, 119.8, 118.7, 114.5, 101.9, 99.1, 79.9, 74.2, 73.7, 73.0, 71.5, 70.3, 68.7, 65.9, 64.8, 51.2 (2C), 45.0, 43.2, 42.5, 42.2, 41.2, 40.0, 37.6, 35.9, 35.2, 33.5, 31.4, 24.7, 22.0, 21.3, 21.2, 19.9, 19.8, 17.0, 13.8

HRMS calculated for $C_{47}H_{68}NaO_{17}$ $[M+Na]^+$: 927.4349; found 927.4338 (TOF ESI+)

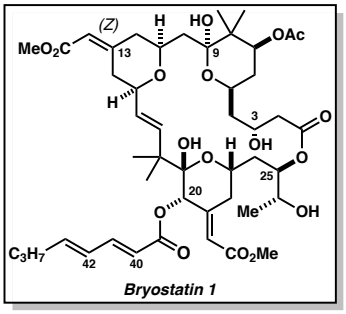
^{1}H-NMR (500 MHz, $CDCl_3$)



^{13}C-NMR (125 MHz, $CDCl_3$)



Characterization data for synthetic bryostatin 1



Bryostatin 1

- **TLC**: R_f = 0.32 (60% EtOAc/Hex, UV active, purple spot in *p*-anisaldehyde)
- **melting point**: 213-214 °C (melts with decomposition, Note 3)
- **$[\alpha]^{23.0}_D$** = +39.2° std 0.252 (*c* = 0.225, MeOH)
- **HRMS** calculated for $C_{47}H_{68}NaO_{17}$ $[M+Na]^+$: 927.4349; found 927.4348 (TOF ESI+)

IR (thin film) 3470, 3277, 3018, 2974, 2945, 2926, 1733, 1715, 1697, 1657, 1640, 1460, 1453, 1435, 1409, 1384, 1366, 1349, 1323, 1289, 1247, 1197, 1186, 1165, 1129, 1101, 1080, 1063, 1028, 1009, 987, 968, 939, 926, 876, 860, 711 cm^{-1}

^{1}H-NMR (600 MHz, $CDCl_3$, 11.4 mg in 0.75 mL $CDCl_3$) δ 7.27 (dd, *J* = 15.3, 10.1 Hz, 1H), 6.21 – 6.12 (m, 2H, $C_{42}H$, $C_{43}H$), 6.00 (d, *J* = 1.9 Hz, 1H, $C_{34}H$), 5.80 (d, *J* = 15.3 Hz, 1H, $C_{40}H$), 5.78 (d, *J* = 15.7 Hz, 1H, $C_{17}H$), 5.68 (t, *J* = 1.8 Hz, 1H, $C_{30}H$), 5.31 (dd, *J* = 15.7, 8.4 Hz, 1H, $C_{16}H$), 5.18 (s, 1H), 5.21 – 5.14 (m, 2H, C_7H, $C_{25}H$), 5.17 (s, 1H), 4.23 (d, *J* = 12.0 Hz, 1H, C_3-OH), 4.20 (tt, *J* = 11.7, 2.7 Hz, 1H, C_5H), 4.17 – 4.10 (m, 1H, C_3H), 4.08 (ddd, *J* = 11.1, 8.4, 2.5 Hz, 1H, $C_{15}H$), 4.01 (tt, *J* = 11.4, 2.5 Hz, 1H, $C_{23}H$), 3.89 (ddd, *J* = 10.5, 7.1, 2.3 Hz, 1H, $C_{11}H$), 3.77 (app. hextet, *J* = 6.4 Hz, 1H, $C_{26}H$), 3.70 (s, 3H), 3.70 – 3.63 (m, 2H, $C_{22}H_{eq}$, $C_{14}H_{eq}$), 3.66 (s, 3H), 3.19 (s, 1H, C_9-OH), 2.59 (d, *J* = 7.9 Hz, 1H, C_{26}-OH), 2.49 (t, *J* = 11.9 Hz, 1H, C_2H_a), 2.44 (dd, *J* = 12.4, 2.6 Hz, 1H, C_2H_b), 2.20 (t, *J* = 12.4 Hz, 1H, $C_{12}H_{ax}$), 2.19 – 2.12 (m, 2H, $C_{44}H_2$), 2.06 (s, 3H, C_7-OAc), 2.11 – 1.93 (m, 5H, $C_{12}H_{eq}$, $C_{22}H_{ax}$, $C_{10}H_b$, C_4H_b, $C_{24}H_b$), 1.90 (dd, *J* = 14.0, 11.5 Hz, 1H, $C_{14}H_{ax}$), 1.82 (ddd, *J* = 14.1, 11.4, 3.0 Hz, 1H, $C_{24}H_a$), 1.73 (ddd, *J* = 12.0, 4.3, 2.3 Hz, 1H, C_6H_{eq}), 1.66 (d, *J* = 15.0 Hz, 1H, $C_{10}H_a$), 1.56 (dt, *J* = 14.8, 3.4 Hz, 1H, C_4H_a), 1.48 (q, *J* = 12.0 Hz, 1H, C_6H_{ax}), 1.46 (app. hextet, *J* = 7.4 Hz, 2H, $C_{45}H_2$), 1.24 (d, *J* = 6.5 Hz, 3H, $C_{27}H_3$), 1.15 (s, 3H), 1.00 (bs, 6H), 0.94 (s, 3H), 0.92 (t, *J* = 7.3 Hz, 3H, $C_{46}H_3$)

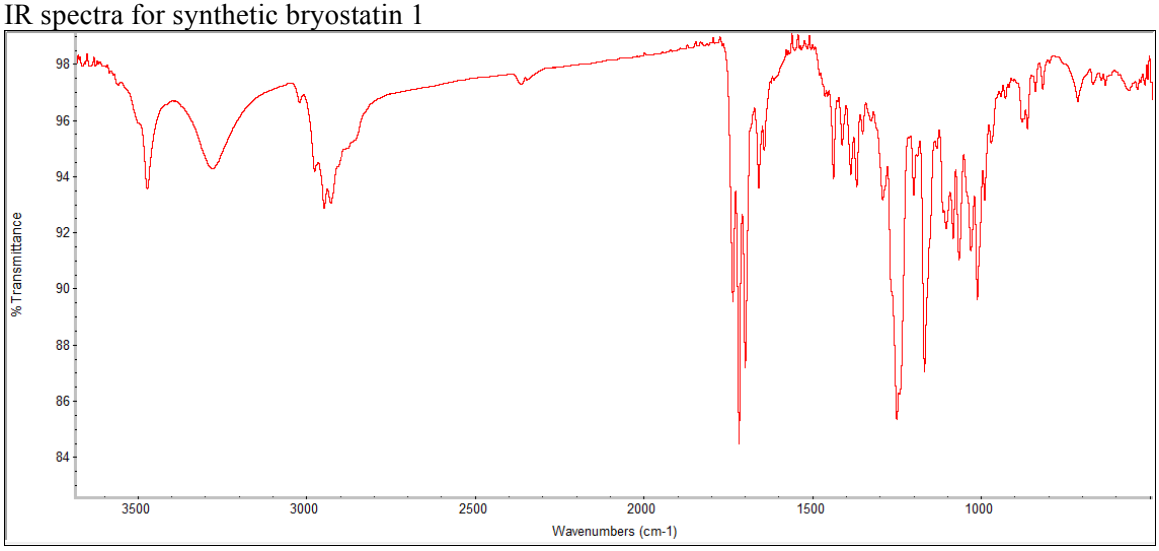
Note 1: At this concentration, we observe a water molecule with chemical shift δ 1.66.
Note 2: Several ^{1}H-NMR chemical shifts are concentration-dependent (page SI-99 for overlays).
Note 3: A pure sample of racemic BINOL was found to melt at 214-215 °C (reported value 214-217 °C) in a separate capillary tube during the same experiment.

^{13}C-NMR (125 MHz, $CDCl_3$, 11.4 mg in 0.75 mL $CDCl_3$) δ 172.3, 171.1, 167.2, 166.9, 165.7, 156.9, 152.1, 146.5, 145.7, 139.4, 129.6, 128.5, 119.7, 118.8, 114.5, 102.0, 99.1, 79.3, 74.2, 73.8, 73.0, 71.7, 70.3, 68.6, 65.9, 64.9, 51.2 (2C), 45.1, 44.3, 42.5, 42.1, 41.1, 40.0, 36.5, 36.1, 35.2, 33.5, 31.4, 24.8, 22.0, 21.3, 21.2, 20.0, 19.9, 17.0, 13.9

Characterization data for natural bryostatin 1 (NCI sample)
- **melting point**: 212-214 °C (melts with decomposition)
- **$[\alpha]^{23.3}_D$** = +33.3° std 0.577 (*c* = 0.10, MeOH)
- **IR** (thin film): 3465, 3302, 2922, 2851, 1733, 1716, 1699, 1653, 1636, 1436, 1382, 1366, 1348, 1287, 1247, 1165, 1100, 1063, 1028, 1007, 987, 968, 860 cm^{-1}

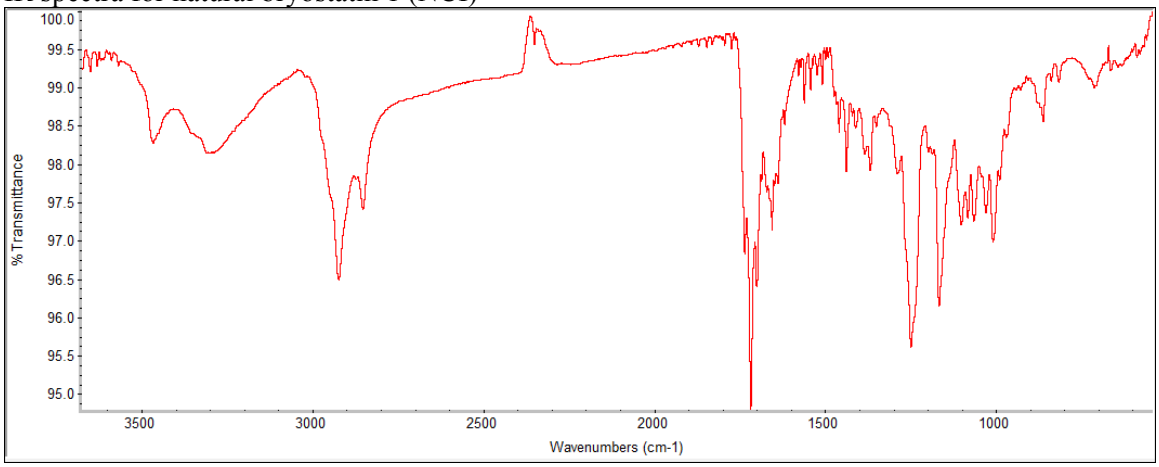
Data reported by Pettit, G.R.; *et al.* (*12*).
- **melting point**: 230-235 °C
- **$[\alpha]^{25}_D$** = +34.1° (*c* = 0.044, MeOH)
- **TLC** R_f = 0.7 (9:1 CH_2Cl_2/MeOH)
- **IR** (KBr) 3470, 3400, 2970, 2950, 1735, 1716, 1700, 1640, 1600, 1433, 1385, 1365, 1245, 1160, 1100, 1080, 1000 cm^{-1}

IR spectra for synthetic bryostatin 1

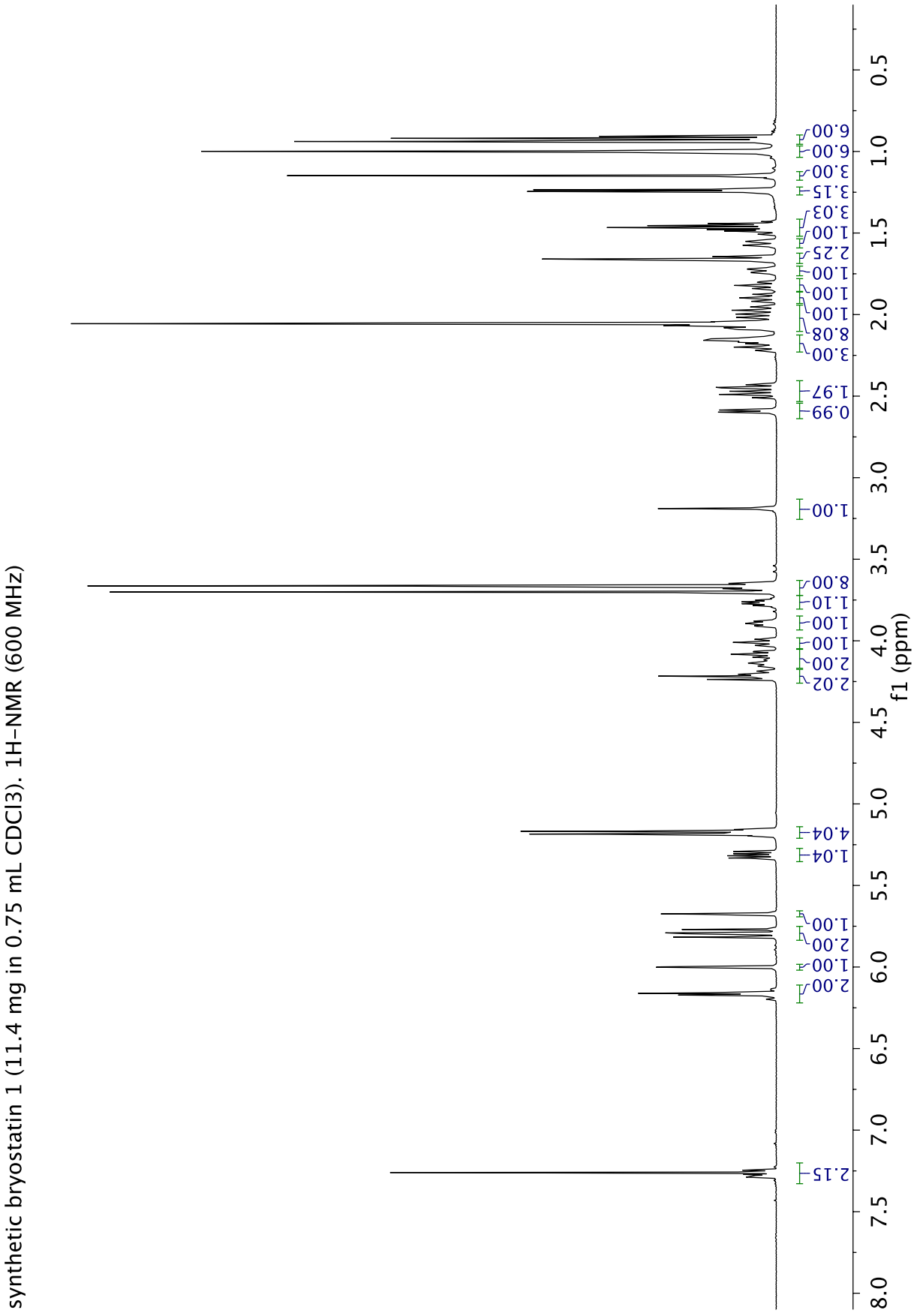


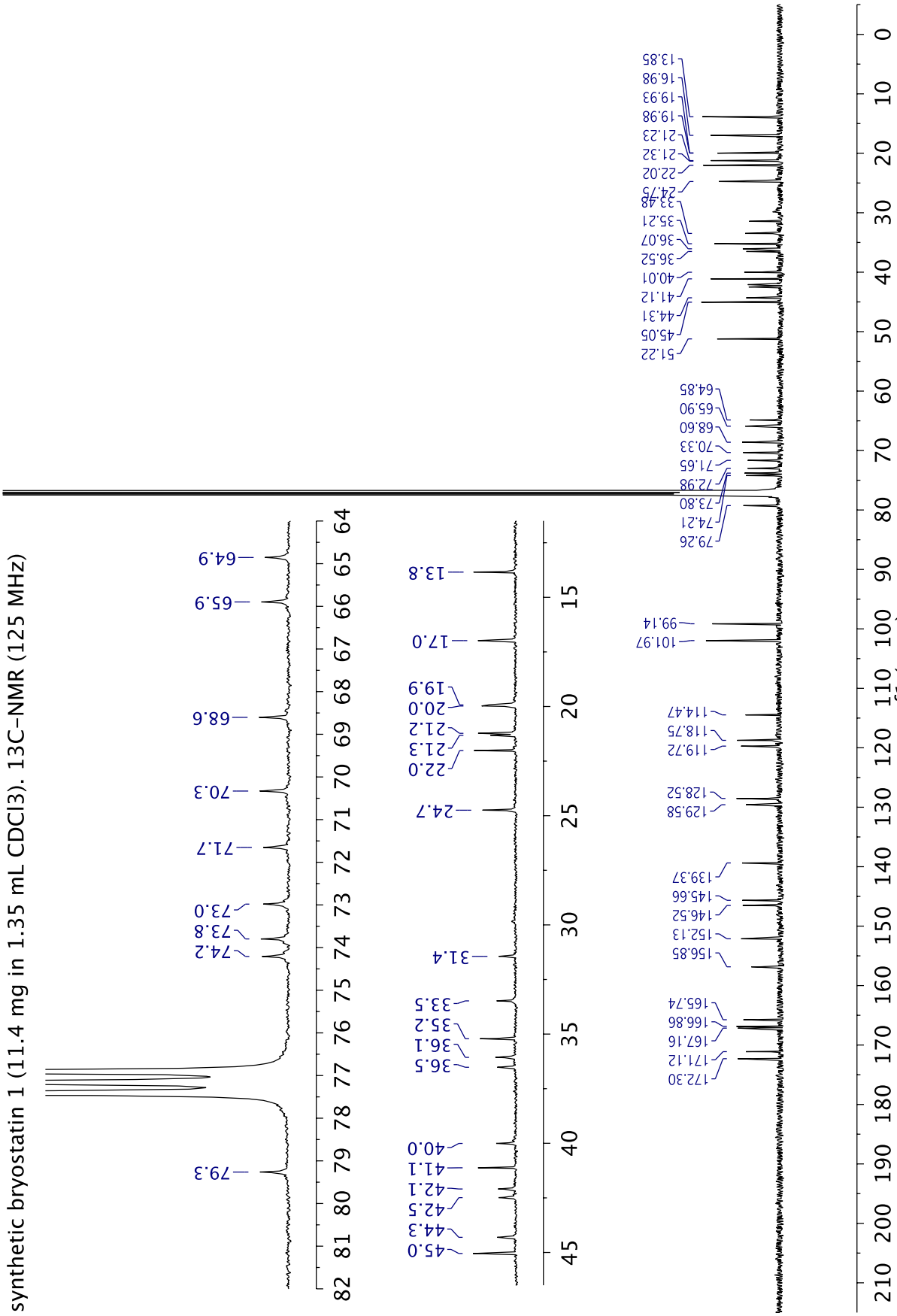
IR (thin film) 3470, 3277, 3018, 2974, 2945, 2926, 1733, 1715, 1697, 1657, 1640, 1460, 1453, 1435, 1409, 1384, 1366, 1349, 1323, 1289, 1247, 1197, 1186, 1165, 1129, 1101, 1080, 1063, 1028, 1009, 987, 968, 939, 926, 876, 860, 711 cm^{-1}

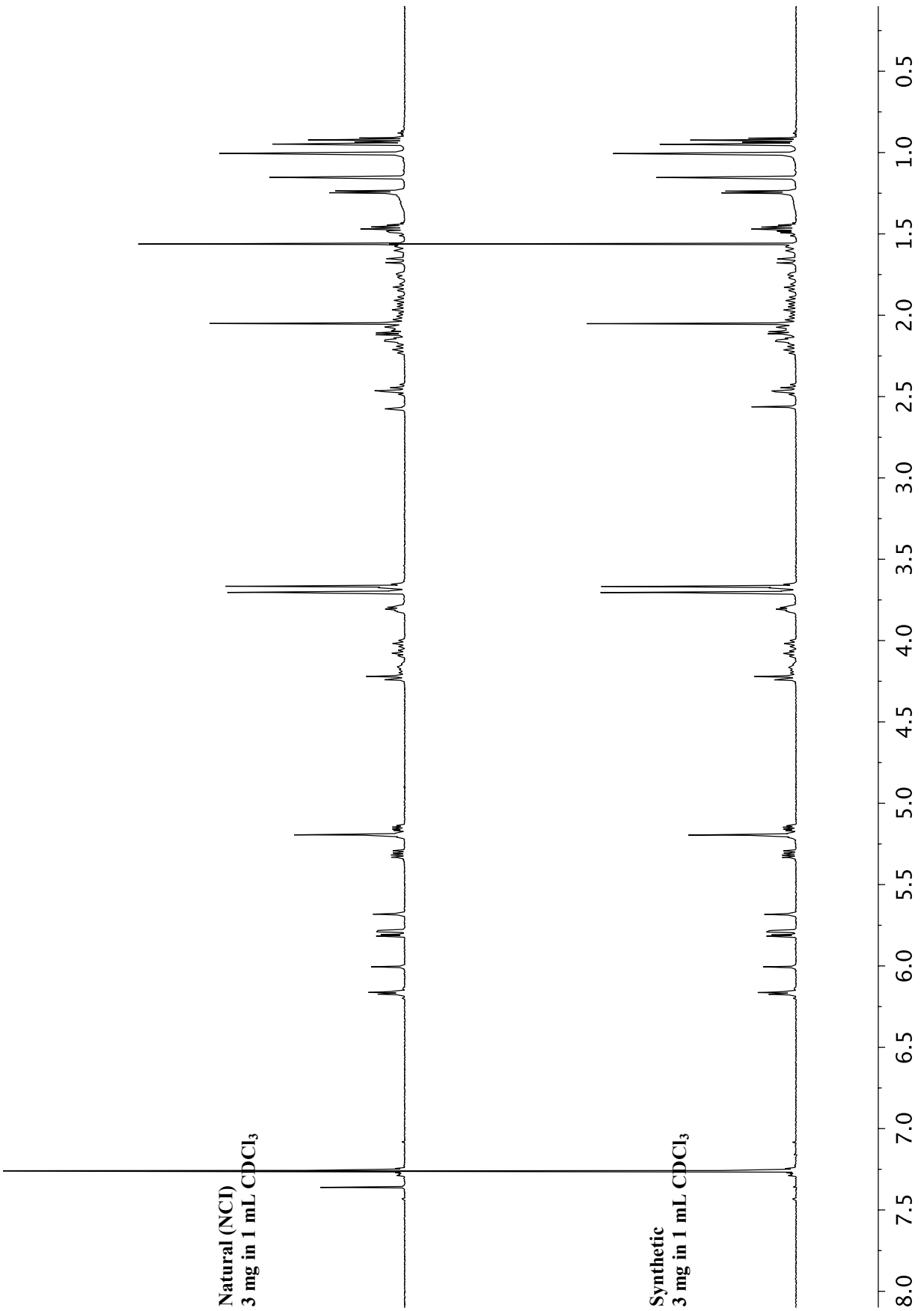
IR spectra for natural bryostatin 1 (NCI)

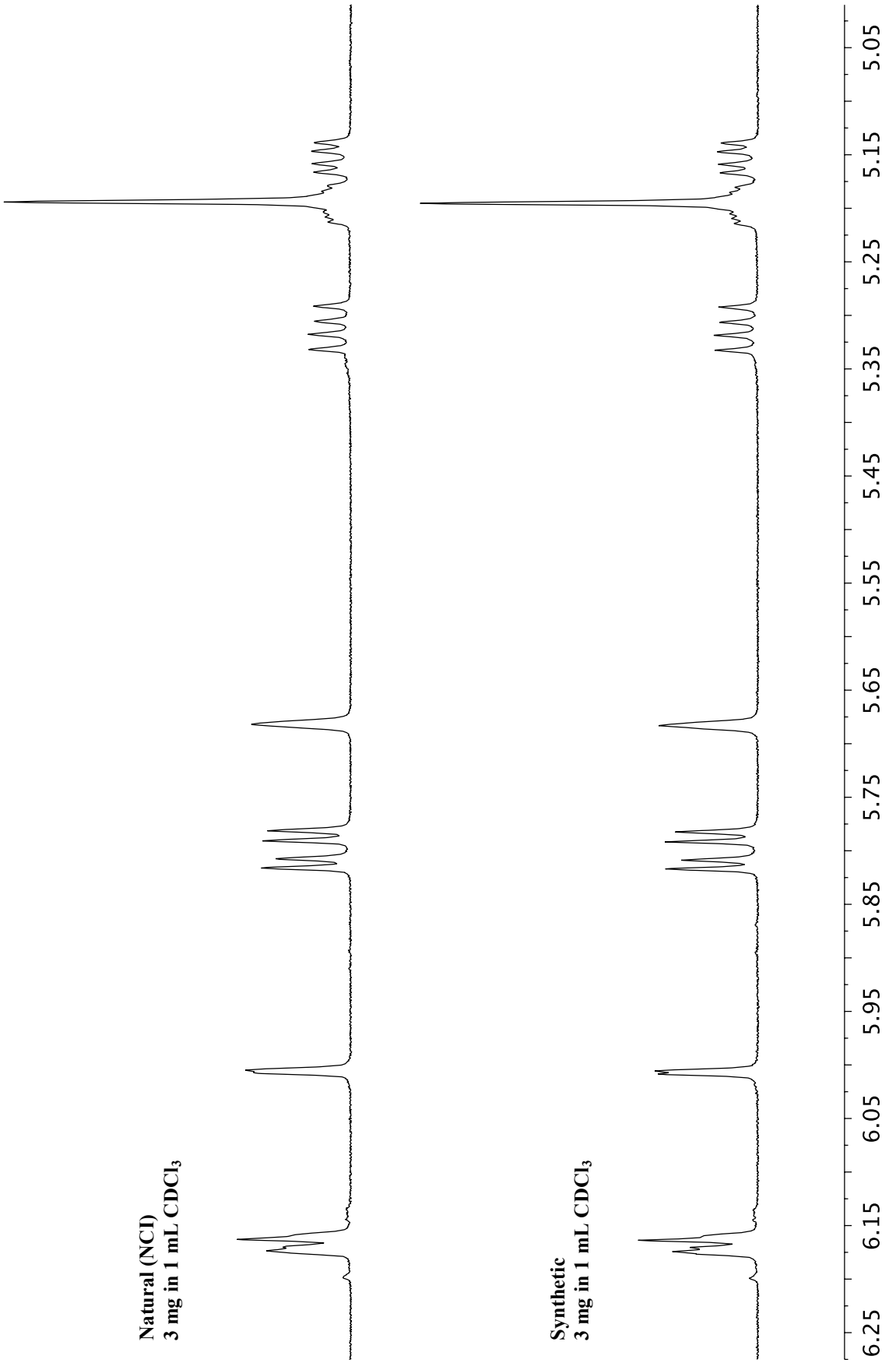


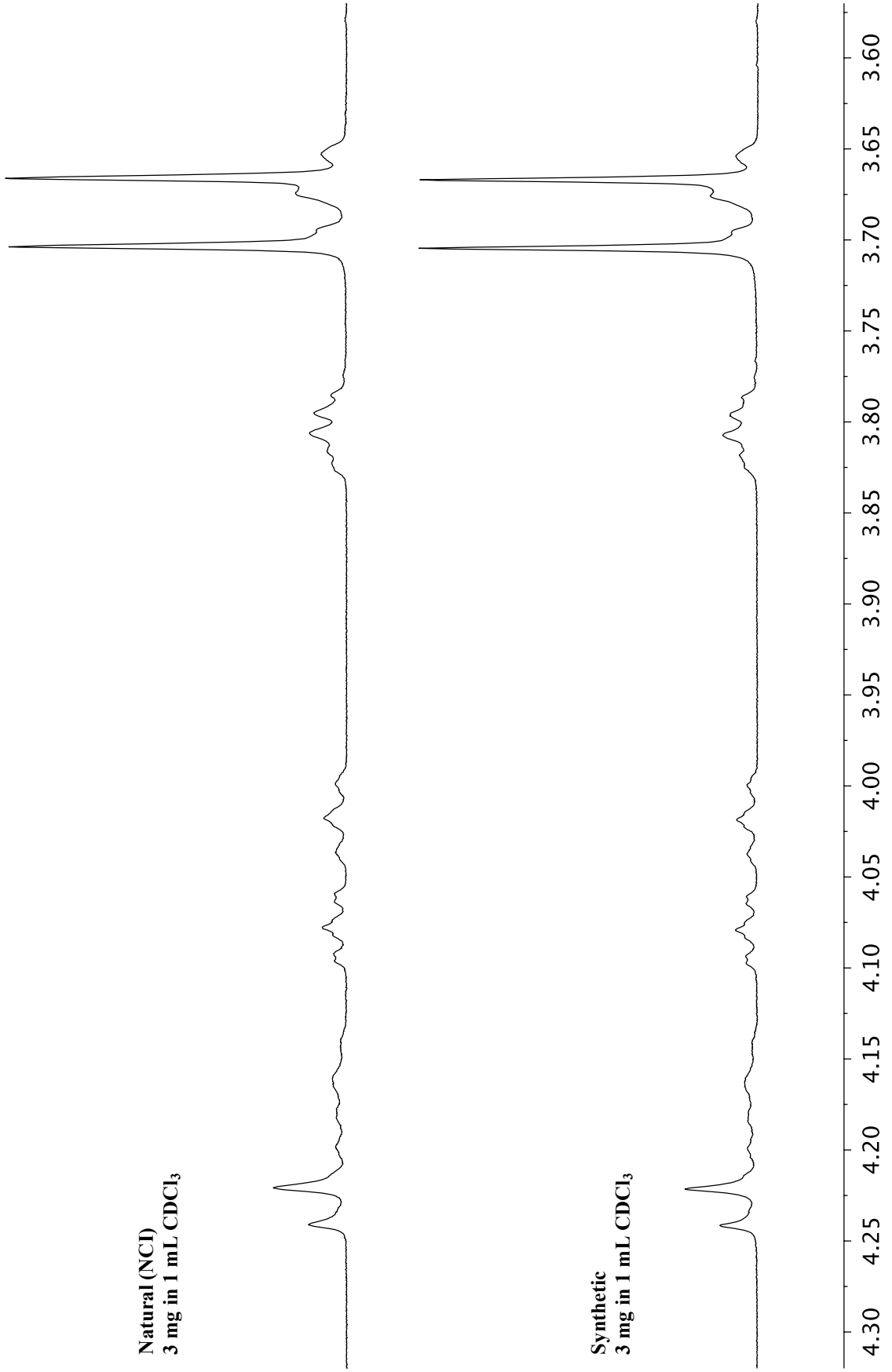
IR (thin film): 3465, 3302, 2922, 2851, 1733, 1716, 1699, 1653, 1636, 1436, 1382, 1366, 1348, 1287, 1247, 1165, 1100, 1063, 1028, 1007, 987, 968, 860 cm^{-1}

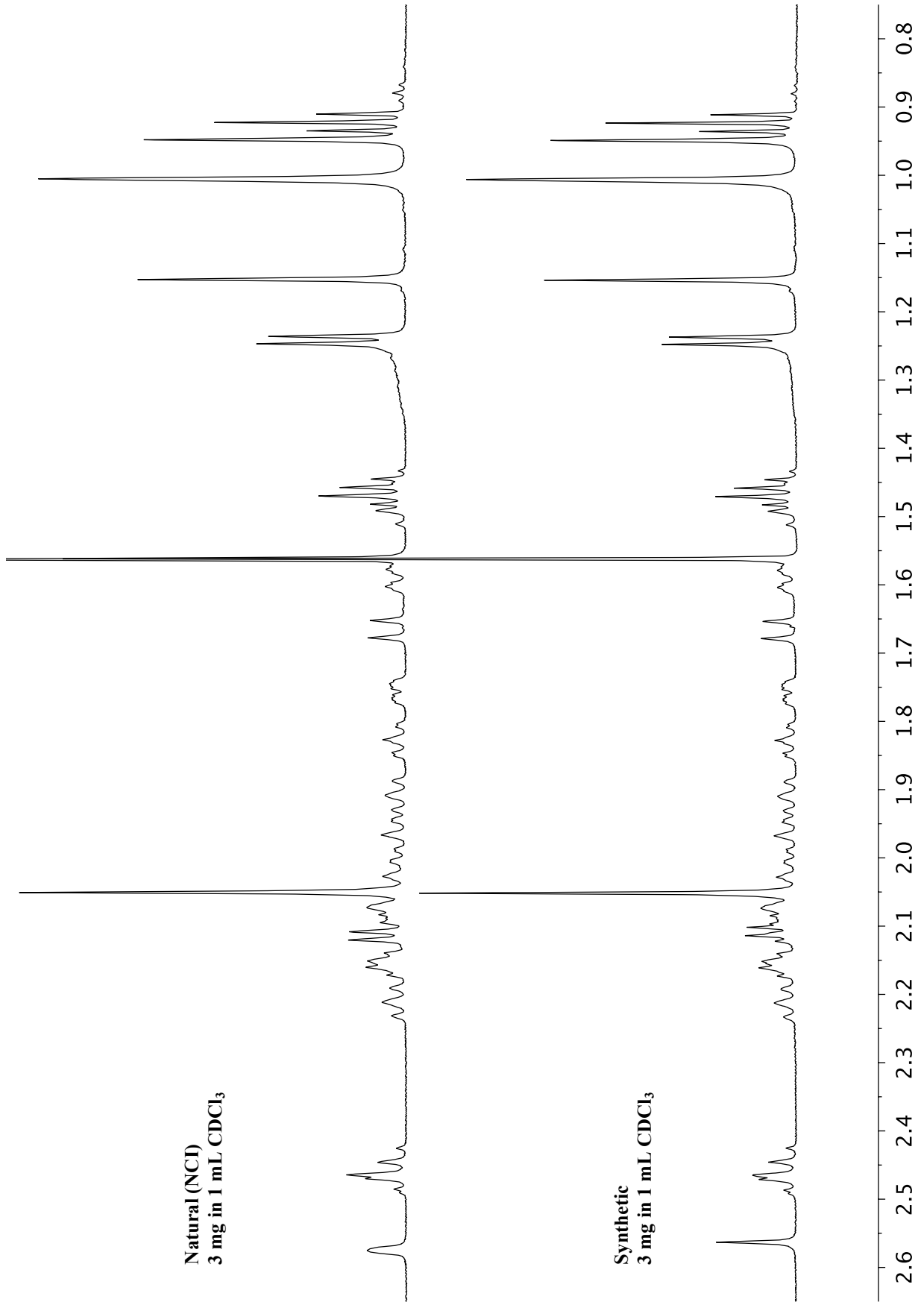

synthetic bryostatin 1 (11.4 mg in 0.75 mL CDCl3). 1H–NMR (600 MHz)
f1 (ppm)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
2.15
2.00
1.00
2.00
1.00
1.04
4.04
1.00
2.00
2.02
1.00
1.00
1.10
8.00
1.00
0.99
1.97
3.00
8.08
1.00
1.00
1.00
2.25
1.00
3.03
3.15
3.00
6.00
6.00

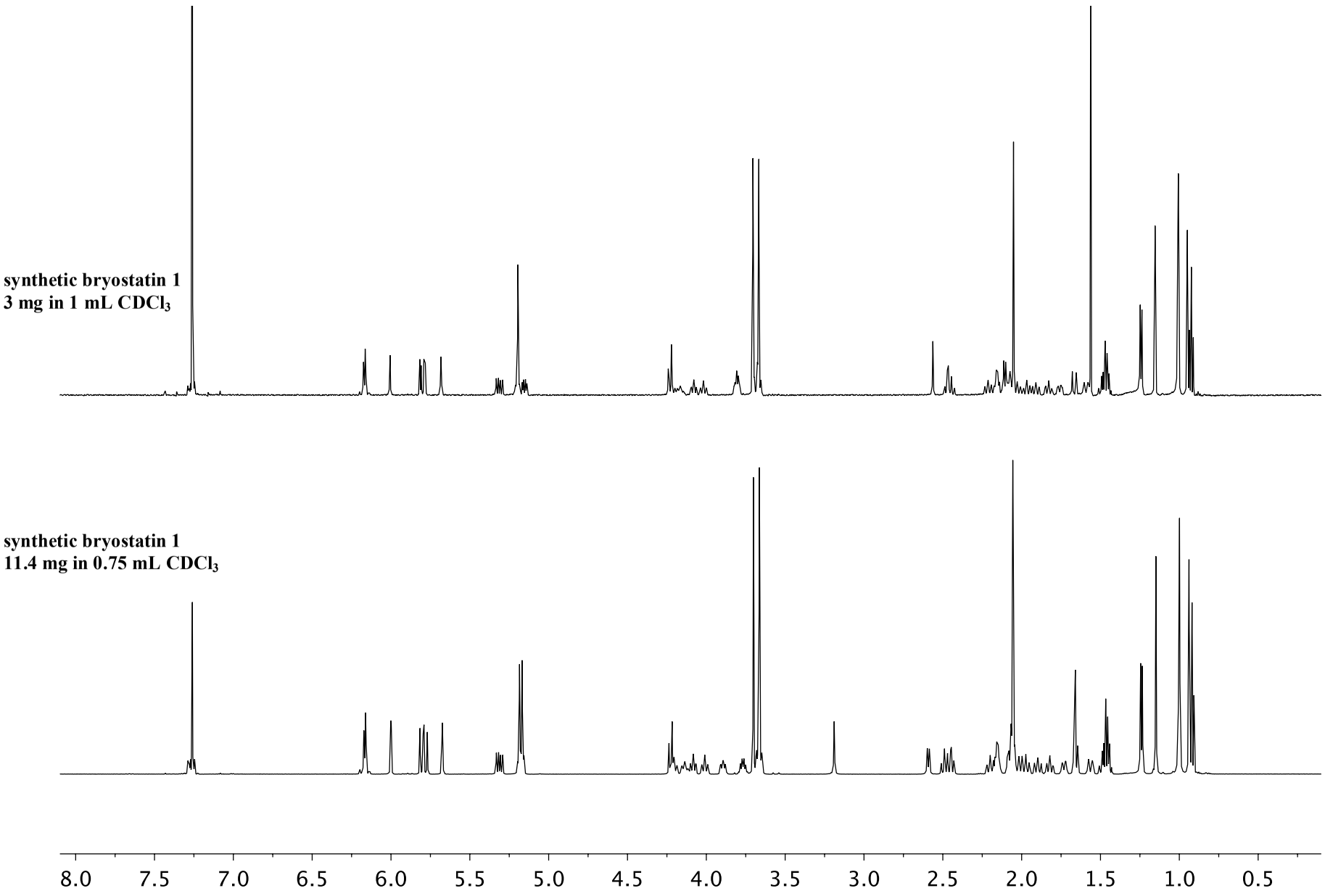

synthetic bryostatin 1 (11.4 mg in 1.35 mL CDCl3). 13C–NMR (125 MHz)
f1 (ppm)


Natural (NCI)
3 mg in 1 mL CDCl3
Synthetic
3 mg in 1 mL CDCl3
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


Natural (NCI)
3 mg in 1 mL CDCl3
Synthetic
3 mg in 1 mL CDCl3
6.25
6.15
6.05
5.95
5.85
5.75
5.65
5.55
5.45
5.35
5.25
5.15
5.05


Natural (NCI)
3 mg in 1 mL CDCl3
Synthetic
3 mg in 1 mL CDCl3
4.30
4.25
4.20
4.15
4.10
4.05
4.00
3.95
3.90
3.85
3.80
3.75
3.70
3.65
3.60


Natural (NCI)
3 mg in 1 mL CDCl3
Synthetic
3 mg in 1 mL CDCl3
2.6
2.5
2.4
2.3
2.2
2.1
2.0
1.9
1.8
1.7
1.6
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0.8


synthetic bryostatin 1
3 mg in 1 mL CDCl3
synthetic bryostatin 1
11.4 mg in 0.75 mL CDCl3
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

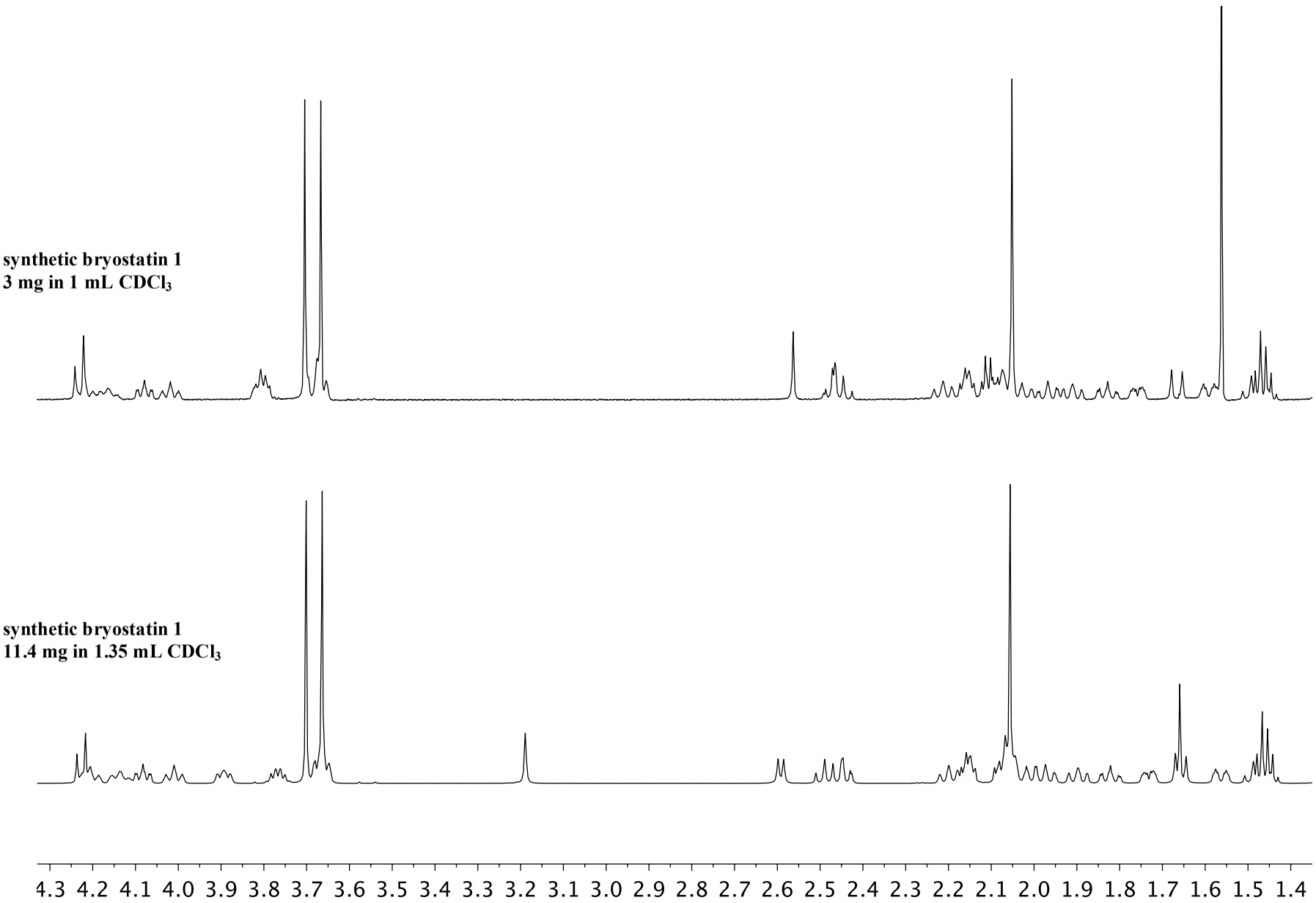

synthetic bryostatin 1
3 mg in 1 mL CDCl3
synthetic bryostatin 1
11.4 mg in 1.35 mL CDCl3
4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4

Table S1: ^{1}H-NMR comparison for bryostatin 1

Proton No.	Natural Bryostatin 1 500 MHz, CDCl3 (Note 1)	Synthetic Bryostatin 1 600 MHz, CDCl3 (Note 2)
2a (Note 3)	2.42 (dd, *J* = 12.2, 2.1)	2.49 (t, *J* = 11.9)
2b	2.53 (dd, *J* = 12.2, 12.0)	2.53 (dd, *J* = 12.4, 2.6)
3	4.12 (m)	4.14 (m)
3-OH	4.24 (d, *J* = 12.0)	4.23 (d, *J* = 12.0)
4a	1.55 (ddd, *J* = 14.8, 3.6, 3.1)	1.56 (dt, *J* = 14.8, 3.4)
4b	2.02 (m)	2.02 (m)
5	4.21 (tt, *J* = 11.6, 2.3)	4.20 (tt, *J* = 11.7, 2.7)
6ax	1.48 (q, *J* = 11.7)	1.48 (q, *J* = 12.0)
6eq	1.72 (ddd, *J* = 12.3, 4.6, 2.6)	1.73 (ddd, *J* = 12.0, 4.3, 2.3)
7	5.19 (m)	5.18 (m)
9-OH	3.25 (br s)	3.19 (s)
10a	1.66 (d, *J* = 14.9)	1.66 (d, *J* = 15.0)
10b	2.06 (m)	2.02 (m)
11	3.96 (ddd, *J* = 11.2, 7.5, 2.2)	3.89 (ddd, *J* = 10.5, 7.1, 2.3)
12ax	2.22 (t, *J* = ~12)	2.20 (t, *J* = 12.4)
12eq	2.10 (m)	2.02 (m)
14ax	1.87 (br dd, *J* = 14, 11)	1.90 (dd, *J* = 14.0, 11.5)
14eq	3.66 (m)	3.66 (m)
15	4.09 (ddd, *J* = 11.0, 8.5, 2.5)	4.08 (ddd, *J* = 11.1, 8.4, 2.5)
16	5.32 (dd, *J* = 15.7, 8.5)	5.31 (dd, *J* = 15.7, 8.4)
17	5.78 (d, *J* = 15.6)	5.78 (d, *J* = 15.7)
19-OH	5.15 (br s)	5.17 (s)
20	5.18 (s)	5.18 (s)
22ax	2.06 (m)	2.02 (m)
22eq	3.69 (m)	3.67 (m)
23	4.02 (tt, *J* = 11.3, 2.4)	4.01 (tt, *J* = 11.4, 2.5)
24a	1.83 (ddd, *J* = 13.8, 11.6, 2.9)	1.82 (ddd, *J* = 14.1, 11.4, 3.0)
24b	1.99 (m)	2.02 (m)
25	5.17 (m)	5.17 (m)
26	3.78 (m)	3.77 (app. hext, *J* = 6.4)
26-OH	3.75 (n.d.)	2.59 (d, *J* = 7.9)
27 (3H)	1.24 (d, *J* = 6.4)	1.24 (d, *J* = 6.5)
28 (3H)	1.00 (s)	1.00 (br s)
29 (3H)	0.96 (s)	0.94 (s)
30	5.68 (t, *J* = 1.7)	5.68 (t, *J* = 1.8)
32 (3H)	1.15 (s)	1.15 (s)
33 (3H)	1.01 (s)	1.00 (br s)
34	6.00 (d, *J* = 2.0)	6.00 (d, *J* = 1.9)
37 (3H, C7-OAc)	2.08 (s)	2.06 (s)
38 (3H, C13-enoate)	3.73 (s)	3.70 (s)
40	5.81 (d, *J* = 15.2)	5.80 (d, *J* = 15.3)
41	7.28 (dd, *J* = 15.4, 10.2)	7.27 (dd, *J* = 15.3, 10.1)
42	6.18 (m)	6.17 (m)
43	6.17 (m)	6.17 (m)
44 (2H)	2.16 (m)	2.15 (m)
45 (2H)	1.47 (hext, *J* = 7.4)	1.46 (hext, *J* = 7.4)
46 (3H)	0.92 (t, *J* = 7.4)	0.92 (t, *J* = 7.3)
47 (3H, C21-enoate)	3.66 (Note 4)	3.66 (s)

Note 1: Reference: Mag. Res. Chem. 1991, 29, 366-374. ca. 30 mg of bryostatin 1 in 0.5 mL CDCl3

Note 2: ppm assigned relative to CDCl3 at 7.26. 11.4 mg of bryostatin 1 in 1.35 mL CDCl3

Note 3: The concentration-dependent splitting pattern of the C2 protons has been well-documented by Pettit et. al. (see J. Org. Chem. 1987, 52, 2854-2860)

Note 4: see J. Org. Chem. 1987, 52, 2854-2860 for peak assignment

Table S2: ^{13}C-NMR comparison for bryostatin 1

Carbon No.	**Natural Bryostatin 1** 125 MHz, CDCl3 (Note 1)	**Synthetic Bryostatin 1** 125 MHz, CDCl3 (Note 2)	**difference** (Note 3)
1	172.21	172.30	0.07
2	42.28	42.49	-0.05
3	68.44	68.60	0.00
4	39.87	40.01	0.02
5	65.71	65.90	-0.03
6	33.35	33.48	0.03
7	72.92	72.98	0.10
8	41.00	41.12	0.04
9	101.85	101.97	0.04
10	41.95	42.09	0.02
11	71.52	71.65	0.03
12	44.19	44.31	0.04
13	156.82	156.85	0.13
14	36.42	36.52	0.06
15	79.10	79.26	0.00
16	129.50	129.58	0.08
17	139.19	139.37	-0.02
18	44.89	45.05	0.00
19	99.02	99.14	0.04
20	74.09	74.21	0.04
21	151.97	152.13	0.00
22	31.32	31.44	0.04
23	64.71	64.85	0.02
24	35.93	36.07	0.02
25	73.68	73.80	0.04
26	70.15	70.33	-0.02
27	19.77	19.98	-0.05
28	16.86	16.98	0.04
29	21.07	21.23	0.00
30	114.24	114.47	-0.07
31	166.72	166.86	0.02
32	24.64	24.75	0.05
33	19.77	19.93	0.00
34	119.57	119.72	0.01
35	167.00	167.16	0.00
36	171.00	171.12	0.04
37	21.15	21.32	-0.01
38	51.04	51.22	-0.02
39	165.58	165.74	0.00
40	118.63	118.75	0.04
41	146.35	146.52	-0.01
42	128.39	128.52	0.03
43	145.44	145.66	-0.06
44	35.04	35.21	-0.01
45	21.86	22.02	0.00
46	13.65	13.85	-0.04
47	51.04	51.22	-0.02

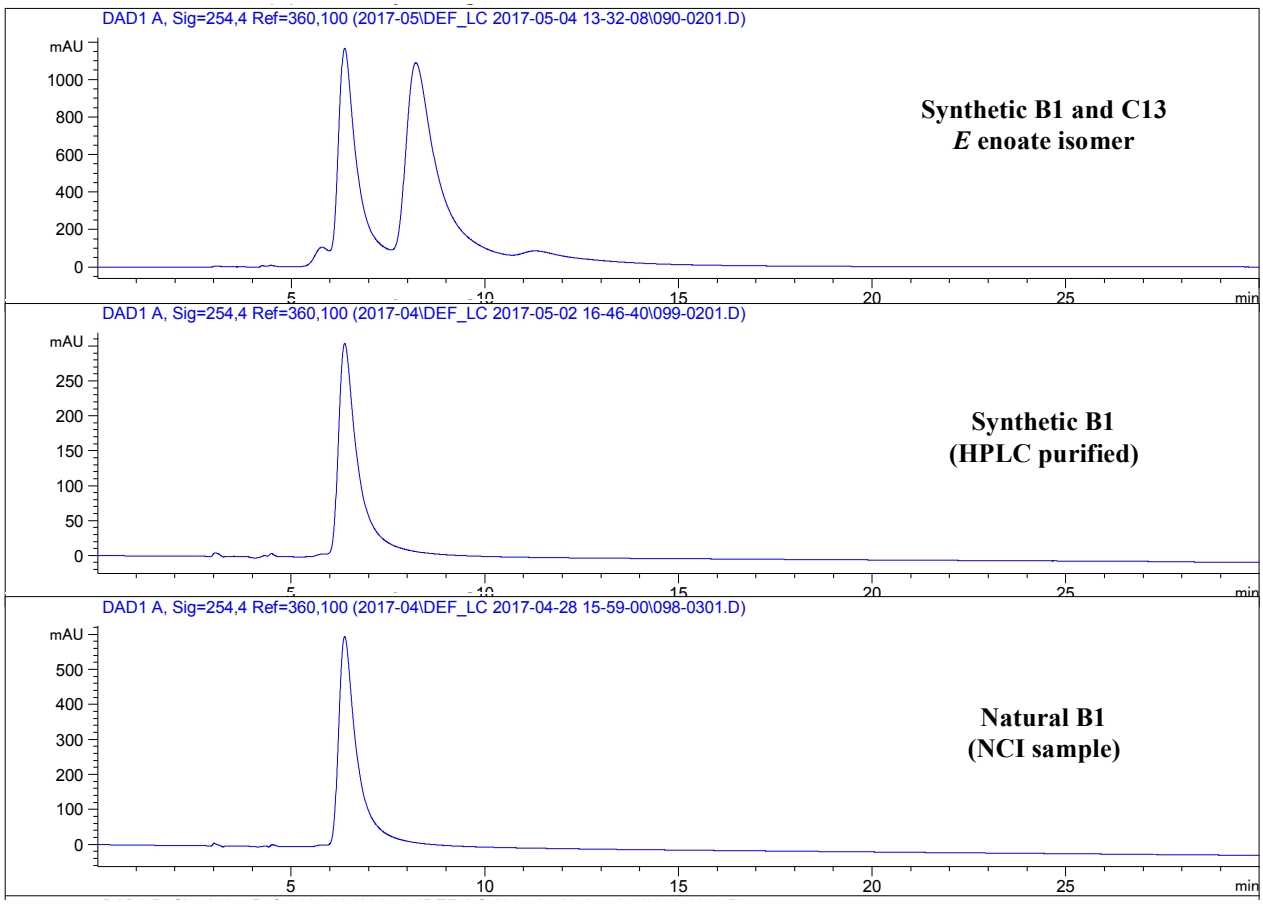
Note 1: Reference: Mag. Res. Chem. 1991, 29, 366-374 (ppm assigned relative to CDCl3 at 77.0) ca. 30 mg of bryostatin 1 in 0.5 mL CDCl3

Note 2: ppm assigned relative to CDCl3 at 77.16. 11.4 mg of bryostatin 1 in 1.35 mL CDCl3

Note 3: adjusted for differences in chloroform referencing (77.0 vs. 77.16)

HPLC traces of synthetic and natural bryostatin 1

Acquisition parameters:
Flow rate: 1 mL/min
Gradient: isocratic 10% EtOH/hexane
Chiralpak AD-H Column
254 nm detection



PKC binding assay protocol

The protein kinase C (PKC) affinity of bryostatin 1 and compounds **34** and **35** was performed via competition with ^{3}H-phorbol-12,13-dibutyrate (^{3}H-PDBu) as described below. This procedure entails a glass-fiber filtration method to determine bound radioligand. PKC-beta-I and PKC-delta were selected for preliminary evaluation. The former is a member of the conventional PKC sub-family while the latter is a member of the novel PKC sub-family (*71*). More extensive biological evaluations of these and other analogs will be published separately.

Preparation of PKC binding assay buffer

To a 50 mL polypropylene tube was added Tris-HCl (pH 7.4, 1 M, 1 mL), KCl (1 M, 2 mL), $CaCl_2$ (0.1 M, 30 μL), and bovine serum albumin (40 mg, Sigma-Aldrich). This mixture was diluted to 20 mL with deionized H_2O and mixed gently. The buffer was stored on ice until use. The final concentration of these constituents is shown in the following table:

PKC binding assay buffer composition

Constituent	Stock concentration	Quantity	Final Concentration
pH 7.4 Tris-HCl	1.0 M	1.0 mL	50 mM
KCl	1.0 M	2.0 mL	100 mM
$CaCl_2$	0.10 M	30 μL	0.15 mM
Bovine Serum Albumin	-	40 mg	2 mg/mL
Deionized H_2O	-	Final vol of 20 mL	-

Preparation of phosphatidylserine (PS) vesicles solution

For every two assays, 3.5 mg phosphatidylserine (Avanti Polar Lipids, porcine, 25 mg/mL $CHCl_3$ solution) was concentrated by removing chloroform under a stream of nitrogen followed by reduced pressure. The solid PS was suspended as vesicles in freshly prepared PKC binding assay buffer (3.5 mL) by sonicating six times for 30 sec, with a 30 sec rest between sonications (Branson Sonifier 250, power = 2, 50% duty cycle). The resulting milky cloudy mixture (1 mg/mL) was stored on ice until use.

Preparation of PKC isoform solution

Assay PKC was prepared by dissolving a 4 μg aliquot of the indicated recombinant human PKC isoform (Invitrogen) into 11.6 mL of PKC binding assay buffer (this amount is sufficient for two assays). The diluted PKC was stored on ice for immediate use.

Preparation of ^{3}H-PDBu solution

^{3}H-PDBu (American Radiolabeled Chemicals, Inc.; 1 mCi/mL acetone solution; specific activity: 20 μCi/mmol) was diluted 10-fold with DMSO. The resulting 500 nM stock solution was further diluted with DMSO to 30 nM.

Preparation of analog compound dilutions

Compound dilutions were prepared by serially diluting from a chosen "high" concentration by factors of 3 or 4. For each analog compound, seven concentrations were used to define the inhibition curve (i.e. for exocyclic alkene **34**, the analog concentrations used were 3000 nM, 750 nM, 188 nM, 46.9 nM, 11.7 nM, 2.93 nM, and 0.73 nM).

"Master Mix" Solution
To a polypropylene tube was added 3.3 mL of 1 mg/mL PS vesicles solution, 11 mL of PKC isoform solution, and 1.1 mL of 30 nM ^{3}H-PDBu solution were added. The resulting solution was vortexed to mix and stored on ice.

PKC binding assay protocol
Materials:

- Glass-fiber filters (Whatman GF/B) were prepared by soaking them in a solution of aqueous polyethyleneimine (10% by vol, 18 mL) in deionized water (600 mL) for ≥1h.
- 500 mL "rinsing buffer" of 20 mM Tris, pH 7.4 was cooled on ice for the duration of the incubation period and for the remainder of the assay.

Triplicate data points were obtained for each analog concentration. For each data point, 280 µL of "Master Mix" Solution and 20 µL of analog compound at a specified concentration were added to a polypropylene tube. Non-specific ^{3}H-PDBu binding was assessed in triplicate by substitution of the analog compound with unlabeled PDBu (20 µL of a 75 µM stock, assay concentration: 5 µM). Maximal ^{3}H-PDBu binding was assessed in triplicate by substitution of the analog compound with 20 µL DMSO. The solutions were vortexed to mix, incubated at 37 °C for 10 min, and incubated on ice for at least 30 min prior to filtration. Using a Brandel Harvester, the assay contents from each polypropylene tube were vacuum-filtered through polyethylenimine-soaked filters, washing with rinsing buffer (3X) and drying first under vacuum for 5 min and then under ambient conditions for ≥ 2h. The resulting filters had circular perforations for each data point, which were removed with forceps and placed in a scintillation vial. Scintillation vials were filled with Bio-Safe II scintillation fluid (5 mL) and measured for radioactivity using a Beckman LS 6000SC scintillation counter. Counts per minute (cpm) were averaged for each triplicate dilution. The data were plotted – cpm vs. log(concentration) – using Prism® by GraphPad Software and an IC_{50} was determined using that program's built-in one-site competition least squares regression function. K_i values were calculated using the equation: $K_i = IC_{50} / (1 + ([^3H\text{-}PDBu] / K_d))$. The K_d of ^{3}H-PDBu was measured via saturation binding under identical conditions and found to be 8.8 nM for PKC beta-I and 4.5 nM for PKC delta.

Using this method, **34** was found to bind PKC beta-1 with a K_i of 3.9 (2.7-5.9) nM and PKC delta with a K_i of 0.76 (0.53-1.1) nM (Note 1). Similarly, **35** was found to bind PKC beta-1 with a K_i of 12 (8.4-17) nM and PKC delta with a K_i of 1.4 (1.0-2.0) nM. As a control, bryostatin 1 was found to bind PKC beta-1 with a K_i of 1.6 (1.1-2.3) nM and PKC delta with a K_i of 2.4 (1.5-3.6) nM.

Table S3. PKC binding data for bryostatin 1 and analogs.

	PKC K_i (nM)	
compound	**beta-I**	**delta**
bryostatin 1	1.6 (1.1-2.3)	2.4 (1.5-3.6)
alkene **34**	3.9 (2.7-5.9)	0.76 (0.53-1.1)
(E)-enoate **35**	12 (8.4-17)	1.4 (1.0-2.0)

Note 1: Error ranges presented in parentheses indicate 95% confidence intervals from nonlinear regression analysis.

Experimentalists: AJS, SH

Crystallographic Data

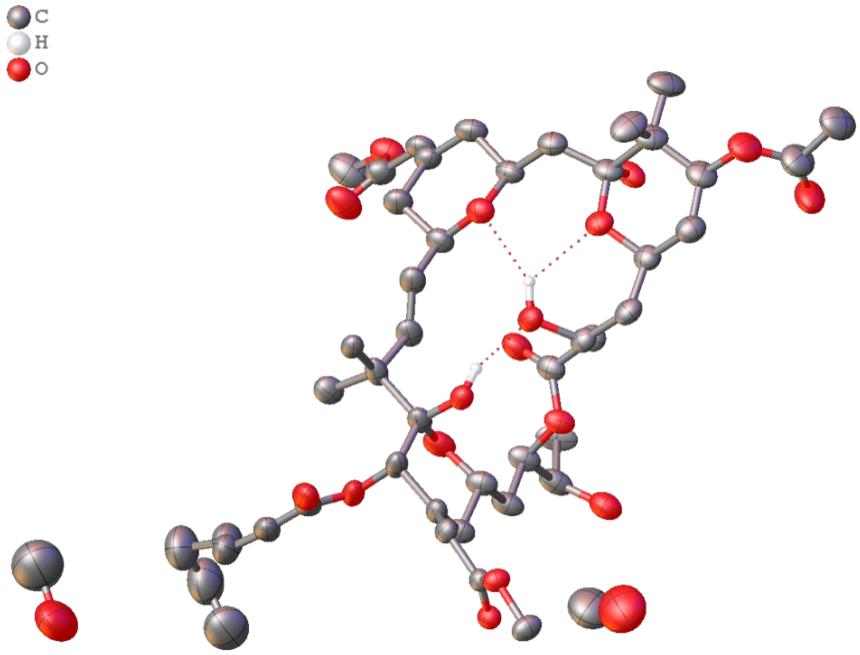


Fig. S3: Crystal structure of synthetic bryostatin 1 determined by x-ray diffraction (ellipsoid contour percent probability level of 40%). For clarity, proton atoms are omitted and disorder is not displayed. Structural parameters for **bryostatin 1** are available free of charge from the Cambridge Crystallographic Data Centre under CCDC 1564674.

Table S4. Crystal Data and Structure Refinement for bryostatin 1•$MeOH_{1.55}$

Identification Code	Bryostatin 1
Empirical Formula	$C_{48.55}H_{74.2}O_{18.55}$
Moiety formula	$C_{47}H_{68}O_{17}$, 1.551(CH_4O)
Formula weight	954.68
Temperature/K	100.0
Crystal system	orthorhombic
Space group	$P2_12_12$
a/Å	20.5411(11)
b/Å	21.7772(11)
c/Å	12.0392(6)
α/°	90
β/°	90
γ/°	90
Volume/Å3	5385.5(5)
Z	4
$\rho_{calc}g/cm^3$	1.177
μ/mm^{-1}	0.747
F(000)	2056.0
Crystal size/mm^3	1.0 × 0.09 × 0.05
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	5.914 to 145.334
Index ranges	$-25 \leq h \leq 25$, $-25 \leq k \leq 26$, $-14 \leq l \leq 14$
Reflections collected	100153
Independent reflections	10324 [R_{int} = 0.0544, R_{sigma} = 0.0258]
Data/restraints/parameters	10324/904/922
Goodness-of-fit on F^2	1.023
Final R indexes [I>=2σ (I)]	R_1 = 0.0769, wR_2 = 0.2167
Final R indexes [all data]	R_1 = 0.0862, wR_2 = 0.2285
Largest diff. peak/hole / e $Å^{-3}$	0.37/-0.39
Flack parameter	0.11(4)
Hooft parameter	0.09(5)

X-ray Experimental.

Single crystals of $C_{47}H_{68}O_{17}\cdot MeOH_{1.55}$ (**bryostatin 1 methanol solvate**) were prepared by dissolving a sample in dichloromethane (~23 mg/ml), carefully layering an equal volume of methanol on top of the solution, and allowing the solvent to slowly evaporate over the course of multiple days. Crystals were very fragile and sensitive to mechanical stress. Rapid solvent loss was observed upon removal from mother liquor. A suitable needle-shaped crystal was selected without further cutting and mounted in ParatoneN on a D8Venture diffractometer. The X-ray beam was focused on the tip of the needle. The crystal was kept at 100.0 K during data collection. Upon removal of the crystal, severe radiation damage was visible. SADABS-2016/2 (*72*) was used for absorption correction. The ratio of minimum to maximum transmission was 0.7333, wR2(int) was 0.1645 before and 0.0906 after correction, and the B-value was refined with linear dependence on frame number to allow for crystal decomposition. Using the Apex3 suite (*72*), the structure was solved with the ShelXT (*73*) structure solution program using 'Intrinsic Phasing.' Using Olex2 (*74*), the structure was refined with the XL (*75*) refinement package using least squares minimization. Flack parameter x = 0.11(4) was determined using 3386 quotients [(I+)-(I-)]/[(I+)+(I-)] (*76*). Hooft parameter (*77*) y = 0.09(5) was determined using Platon (*78*) Bijvoet-Pair analysis.

References

1. C. Gutiérrez *et al.*, Bryostatin-1 for latent virus reactivation in HIV-infected patients on antiretroviral therapy. *AIDS*. **30**, 1385–1392 (2016).
2. C. K. Bullen, G. M. Laird, C. M. Durand, J. D. Siliciano, R. F. Siliciano, New *ex vivo* approaches distinguish effective and ineffective single agents for reversing HIV-1 latency *in vivo*. *Nat. Med.* **20**, 425–429 (2014).
3. G. M. Laird *et al.*, Ex vivo analysis identifies effective HIV-1 latency–reversing drug combinations. *J. Clin. Invest.* **125**, 1901–1912 (2015).
4. A Study Assessing Bryostatin in the Treatment of Moderately Severe to Severe Alzheimer's Disease, (available at https://clinicaltrials.gov/ct2/show/NCT02431468).
5. T. J. Nelson *et al.*, Bryostatin Effects on Cognitive Function and PKCε in Alzheimer's Disease Phase IIa and Expanded Access Trials. *J. Alzheimers Dis.* **58**, 521–535 (2017).
6. S. I. Alfonso *et al.*, Gain-of-function mutations in protein kinase Cα (PKCα) may promote synaptic defects in Alzheimer's disease. *Sci. Signal.* **9**, 47ra (2016).
7. C. Hammond *et al.*, Effect of serum and antioxidants on the immunogenicity of protein kinase C-activated chronic lymphocytic leukemia cells. *J. Immunother.* **28**, 28–39 (2005).
8. S. P. Shaha *et al.*, Prolonging microtubule dysruption enhances the immunogenicity of chronic lymphocytic leukaemia cells. *Clin. Exp. Immunol.* **158**, 186–198 (2009).
9. J. Kortmansky, G. K. Schwartz, Bryostatin-1: A Novel PKC Inhibitor in Clinical Development. *Cancer Invest.* **21**, 924–936 (2003).
10. D. Mochly-Rosen, K. Das, K. V. Grimes, Protein kinase C, an elusive therapeutic target? *Nat. Rev. Drug. Discov.* **11**, 937–957 (2012).
11. P. M. Barr *et al.*, Phase II study of bryostatin 1 and vincristine for aggressive non-Hodgkin lymphoma relapsing after an autologous stem cell transplant. *Am. J. Hematol.* **84**, 484–487 (2009).
12. G. R. Pettit *et al.*, Isolation and structure of bryostatin 1. *J. Am. Chem. Soc.* **104**, 6846–6848 (1982).
13. G. R. Pettit, J. F. Day, J. L. Hartwell, H. B. Wood, Antineoplastic Components of Marine Animals. *Nature*. **227**, 962–963 (1970).
14. D. E. Schaufelberger *et al.*, The Large-Scale Isolation of Bryostatin 1 from Bugula neritina Following Current Good Manufacturing Practices. *J. Nat. Prod.* **54**, 1265–1270 (1991).
15. T. P. Castor, Method and apparatus for isolating therapeutic compositions from source materials. US Patent 5750709 A (1998).
16. M. J. Keough, Variation in Growth Rate and Reproduction of the Bryozoan Bugula neritina. *Biol. Bull.* **177**, 277–286 (1989).
17. D. Mendola, Aquaculture of three phyla of marine invertebrates to yield bioactive metabolites: process developments and economics. *Biomol. Eng.* **20**, 441–458 (2003).
18. A. E. Trindade-Silva, G. E. Lim-Fong, K. H. Sharp, M. G. Haygood, Bryostatins: biological context and biotechnological prospects. *Curr. Opin. Biotech.* **21**, 834–842 (2010).
19. I. J. Miller, N. Vanee, S. S. Fong, G. E. Lim-Fong, J. C. Kwan, Lack of overt genome reduction in the bryostatin-producing bryozoan symbiont "Candidatus Endobugula sertula." *Appl. Environ. Microbiol.* **82**, 6573–6583 (2016).
20. M. Kageyama *et al.*, Synthesis of bryostatin 7. *J. Am. Chem. Soc.* **112**, 7407–7408 (1990).
21. D. A. Evans *et al.*, Total Synthesis of Bryostatin 2. *J. Am. Chem. Soc.* **121**, 7540–7552 (1999).
22. K. Ohmori *et al.*, Total Synthesis of Bryostatin 3. *Angew. Chem., Int. Ed.* **39**, 2290–2294 (2000).
23. B. M. Trost, G. Dong, Total synthesis of bryostatin 16 using atom-economical and

chemoselective approaches. *Nature*. **456**, 485–488 (2008).
24. G. E. Keck, Y. B. Poudel, T. J. Cummins, A. Rudra, J. A. Covel, Total Synthesis of Bryostatin 1. *J. Am. Chem. Soc.* **133**, 744–747 (2011).
25. P. A. Wender, A. J. Schrier, Total Synthesis of Bryostatin 9. *J. Am. Chem. Soc.* **133**, 9228–9231 (2011).
26. Y. Lu, S. K. Woo, M. J. Krische, Total Synthesis of Bryostatin 7 *via* C–C Bond-Forming Hydrogenation. *J. Am. Chem. Soc.* **133**, 13876–13879 (2011).
27. P. A. Wender *et al.*, The Practical Synthesis of a Novel and Highly Potent Analogue of Bryostatin. *J. Am. Chem. Soc.* **124**, 13648–13649 (2002).
28. P. A. Wender, B. A. DeChristopher, A. J. Schrier, Efficient Synthetic Access to a New Family of Highly Potent Bryostatin Analogues via a Prins-Driven Macrocyclization Strategy. *J. Am. Chem. Soc.* **130**, 6658–6659 (2008).
29. B. A. DeChristopher *et al.*, Designed, synthetically accessible bryostatin analogues potently induce activation of latent HIV reservoirs *in vitro*. *Nat. Chem.* **4**, 705–710 (2012).
30. P. A. Wender *et al.*, Modeling of the bryostatins to the phorbol ester pharmacophore on protein kinase C. *Proc. Natl. Acad. Sci. USA*. **85**, 7197–7201 (1988).
31. H.-S. Cheng, T.-P. Loh, A Novel and General α-Regioselective and Highly Enantioselective Prenylation of Aldehydes. *J. Am. Chem. Soc.* **125**, 4990–4991 (2003).
32. J. Nokami *et al.*, The First and Highly Enantioselective Crotylation of Aldehydes via an Allyl-Transfer Reaction from a Chiral Crotyl-Donor. *J. Am. Chem. Soc.* **123**, 9168–9169 (2001).
33. K. J. Hale, M. Frigerio, S. Manaviazar, New, Abridged Pathway to Masamune's "Southern Hemisphere" Intermediate for the Total Synthesis of Bryostatin 7. *Org. Lett.* **5**, 503–505 (2003).
34. G. E. Keck, A. P. Truong, Synthetic Studies on the Bryostatins: Preparation of a Truncated BC-Ring Intermediate by Pyran Annulation. *Org. Lett.* **7**, 2149–2152 (2005).
35. B. M. Trost, H. Yang, G. Dong, Total Syntheses of Bryostatins: Synthesis of Two Ring-Expanded Bryostatin Analogues and the Development of a New-Generation Strategy to Access the C7–C27 Fragment. *Chemistry.* **17**, 9789–9805 (2011).
36. P. Valenta, N. A. Drucker, J. W. Bode, P. J. Walsh, Simple One-pot Conversion of Aldehydes and Ketones to Enals. *Org. Lett.* **11**, 2117–2119 (2009).
37. T. Imamoto *et al.*, Carbon-carbon bond-forming reactions using cerium metal or organocerium(III) reagents. *J. Org. Chem.* **49**, 3904–3912 (1984).
38. I. Paterson *et al.*, Enantio- and diastereoselective aldol reactions of achiral ethyl and methyl ketones with aldehydes: the use of enol diisopinocampheylborinates. *Tetrahedron*. **46**, 4663–4684 (1990).
39. H. C. Brown, J. Chandrasekharan, P. V Ramachandran, Chiral synthesis via organoboranes. 14. Selective reductions. 41. Diisopinocampheylchloroborane, an exceptionally efficient chiral reducing agent. *J. Am. Chem. Soc.* **110**, 1539–1546 (1988).
40. D. A. Evans, K. T. Chapman, E. M. Carreira, Directed reduction of β-hydroxy ketones employing tetramethylammonium triacetoxyborohydride. *J. Am. Chem. Soc.* **110**, 3560–3578 (1988).
41. H. Fujioka *et al.*, Reaction of the Acetals with TESOTf−Base Combination; Speculation of the Intermediates and Efficient Mixed Acetal Formation. *J. Am. Chem. Soc.* **128**, 5930–5938 (2006).
42. L. M. Suen, M. L. Steigerwald, J. L. Leighton, A new and more powerfully activating diamine for practical and scalable enantioselective aldehyde crotylsilylation reactions. *Chem. Sci.* **4**, 2413–2417 (2013).
43. M. Srebnik, P. V. Ramachandran, The Utility of Chiral Organoboranes in the Preparation of Optically Active Compounds. *Aldrichim. Acta1*. **20**, 9 (1987).
44. G. E. Keck, J. A. Covel, T. Schiff, T. Yu, Pyran Annulation: Asymmetric Synthesis of

2,6-Disubstituted-4-methylene Tetrahydropyrans. *Org. Lett.* **4**, 1189–1192 (2002).
45. C.-M. Yu, J.-Y. Lee, B. So, J. Hong, Sequential Catalytic Asymmetric Allylic Transfer Reaction: Enantioselective and Diastereoselective Construction of Tetrahydropyran Units. *Angew. Chem., Int. Ed.* **41**, 161–163 (2002).
46. K. C. Nicolaou, A. A. Estrada, M. Zak, S. H. Lee, B. S. Safina, A Mild and Selective Method for the Hydrolysis of Esters with Trimethyltin Hydroxide. *Angew. Chem., Int. Ed.* **44**, 1378–1382 (2005).
47. X. Han, G. Peh, P. E. Floreancig, Prins-Type Cyclization Reactions in Natural Product Synthesis. *Eur. J. Org. Chem.* **2013**, 1193–1208 (2013).
48. S. D. Rychnovsky, J. Kim, Triphenylphosphine-Catalyzed Isomerizations of Enynes to (E,E,E)-Trienes: Phenol as a Cocatalyst. *J. Org. Chem.* **59**, 2659–2660 (1994).
49. C. K.-W. Kwong, M. Y. Fu, C. S.-L. La, P. H. Toy, The Phosphine-Catalyzed Alkyne to 1,3-Diene Isomerization Reaction. *Synthesis (Stuttg).* **15**, 2307–2317 (2008).
50. K. Tanaka, Y. Ohta, K. Fuji, T. Taga, Differentiation of enantiotopic carbonyl groups by the Horner-Wadsworth-Emmons reaction. *Tetrahedron Lett.* **34**, 4071–4074 (1993).
51. S. M. Ryckbosch, P. A. Wender, V. S. Pande, Molecular dynamics simulations reveal ligand-controlled positioning of a peripheral protein complex in membranes. *Nat. Commun.* **8**, 6 (2017).
52. Trushin, S. A. *et al.* Human Immunodeficiency Virus Reactivation by Phorbol Esters or T-Cell Receptor Ligation Requires both PKCα and PKCθ. *J. Virol.* **79,** 9821–9830 (2005).
53. McKernan, L. N., Momjian, D. & Kulkosky, J. Protein Kinase C: One Pathway towards the Eradication of Latent HIV-1 Reservoirs. *Advances in Virology.* **2012,** 1-8 (2012).
54. P. A. Wender, A. C. Donnelly, B. A. Loy, K. E. Near, D. Staveness, in *Natural Products in Medicinal Chemistry* (Wiley-VCH, 2014), pp. 473–544.
55. J. K. Stille, Y. Becker, Isomerization of N-allylamides and -imides to aliphatic enamides by iron, rhodium, and ruthenium complexes. *J. Org. Chem.* **45**, 2139–2145 (1980).
56. Y. Yamamoto, H. Suzuki, Y. Moro-oka, Ruthenium-catalyzed oxidation of alcohols with sodium bromate. *Tetrahedron Lett.* **26**, 2107–2108 (1985).
57. F. J. Fleitz, T. A. Lyle, N. Zheng, J. D. Armstrong, R. P. Volante, Kilogram Scale Synthesis of the Pyrazinone Acetic Acid Core of an Orally Efficacious Thrombin Inhibitor. *Synth. Commun.* **30**, 3171–3180 (2000).
58. Franczyk, T. S. *et al*. Preparation of optically pure beta-amino acids having affinity for the alpha-2-delta protein. WO 2006100568 A1
59. 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).
60. T. J. Donohoe, L. P. Fishlock, P. A. Procopiou, A Metathesis-Based Approach to the Synthesis of 2-Pyridones and Pyridines. *Org. Lett.* **10**, 285–288 (2008).
61. T. R. Kelly, T. E. Schmidt, J. G. Haggerty, A Convenient Preparation of Methyl and Ethyl Glyoxylate. *Synthesis (Stuttg).* **10**, 544–545 (1972).
62. H. C. Kolb, M. S. VanNieuwenhze, K. B. Sharpless, Catalytic Asymmetric Dihydroxylation. *Chem. Rev.* **94**, 2483–2547 (1994).
63. A. Krasovskiy, P. Knochel, Convenient Titration Method for Organometallic Zinc, Magnesium, and Lanthanide Reagents. *Synthesis (Stuttg).* **5**, 890–891 (2006).
64. M. Kitamura, M. Tokunaga, T. Ohkuma, R. Noyori, Asymmetric Hydrogenation of 3-Oxo Carboxylates Using BINAP-Ruthenium Complexes: (R)-(−)-Methyl 3-Hydroxybutanoate. *Org. Synth.* **71**, 1 (1993).
65. Poupardin, O.; Greck, C.; Genet, J.P. Rapid Asymmetric Synthesis of Highly Functionalized C5 Chiral Synthons. Practical Preparation of *trans*-3-Hydroxy-*D*-Proline. *Synlett*. **11**, 1279-1281 (1998).
66. R. M. Moslin, T. F. Jamison, Total Synthesis of (+)-Acutiphycin. *J. Org. Chem.* **72**, 9736–9745 (2007).

67. H. Chikashita, K. Ohkawa, K. Itoh, Synthesis of 1,5-Bifunctionalized Optically Active 3-Pentanol as a Reversible Chiral Building Block. Asymmetric Reduction of 4-(1,3-Dithian-2-yl)-3-oxobutanoates with Fermenting Bakers' Yeast. *Bull. Chem. Soc. Jpn.* **62**, 3513–3517 (1989).
68. K. Beck, S. Hünig, Azobrücken aus Azinen, VI Substituierte Isopyrazole als elektronenarme Diene zur Synthese von 2,3-Diazabicyclo[2.2.1]heptenen und deren Photoreaktionen. *Chem. Ber.* **120**, 477–483 (1987).
69. B. M. Trost, M. Buch, M. L. Miller, Convenient alternative approach to 2-(acetoxymethyl)-3-(trimethylsilyl)propene. *J. Org. Chem.* **53**, 4887–4888 (1988).
70. T. R. Wu, L. Shen, J. M. Chong, Asymmetric Allylboration of Aldehydes and Ketones Using 3,3'-Disubstitutedbinaphthol-Modified Boronates. *Org. Lett.* **6**, 2701–2704 (2004).
71. A.C. Newton. Protein Kinase C: Structure, Function, and Regulation. *J. Biol. Chem.* **270**, 28495-28498 (1995).
72. Bruker-AXS (2016). APEX3. Version 2016.9-0. Madison, Wisconsin
73. G. Sheldrick, SHELXT - Integrated space-group and crystal-structure determination. *Acta Cryst.* **A71**, 3–8 (2015).
74. O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard, H. Puschmann, OLEX2: a complete structure solution, refinement and analysis program. *J. Appl. Cryst.* **42**, 339–341 (2009).
75. G. Sheldrick, A short history of SHELX. *Acta Cryst.* **A64**, 112–122 (2008).
76. S. Parsons, H. D. Flack, T. Wagner, Use of intensity quotients and differences in absolute structure refinement. *Acta Cryst.* **B69**, 249–259 (2013).
77. R. W. W. Hooft, L. H. Straver, A. L. Spek, Determination of absolute structure using Bayesian statistics on Bijvoet differences. *J. Appl. Cryst.* **41**, 96–103 (2008).
78. A. Spek, Structure validation in chemical crystallography. *Acta Cryst.* **D65**, 148–155 (2009).