Synthesis of (+)-4-Desoxypentenomycin and Analogues

Supakeat Kambutong, Chutima Kuhakarn, Patoomratana Tuchinda, Manat Pohmakotr*

Department of Chemistry and Center for Innovation in Chemistry (PERCH-CIC), Faculty of Science, Mahidol University, Rama VI Road, Bangkok 10400, Thailand
Fax +66(2)6445126; E-mail: scmpk@mahidol.ac.th

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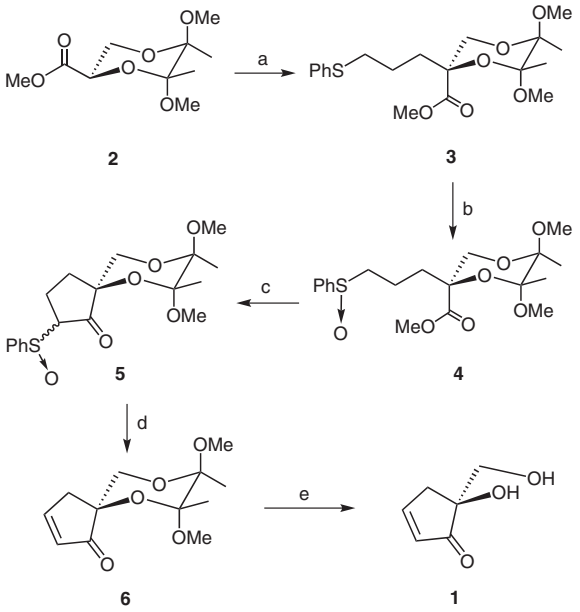
Abstract: A synthesis of (+)-4-desoxypentenomycin is reported here; it involves diastereoselective phenylsulfanylpropylation of an enolate anion derived from methyl (2*R*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl[1,4]dioxane-2-carboxylate, obtained from D-mannitol, and is followed by sulfide oxidation, intramolecular acylation of the α-sulfinyl carbanion, sulfoxide elimination, and hydrolysis. Straightforward access to substituted analogues of (+)-4-desoxypentenomycin was also demonstrated by means of Suzuki–Miyaura, Sonogashira, and Heck coupling reactions.

Key words: oxygenated cyclopentenones, desoxycyclopentenones, α-sulfinyl carbanions, cyclizations, asymmetric synthesis

Highly oxygenated cyclopentanoids have been found in a diverse range of natural products, for example the jasmonates,[1] prostaglandins,[2] and didemnenones,[3] many of which exhibit significant biological activities. As a result, approaches towards general and stereoselective synthesis of this class of compounds have been extensively investigated.[4] Among these, the intramolecular acylation of α-sulfinyl carbanions has proven to be a convenient entry for the construction of functionalized cyclopentenones.[5] Recently, we reported the asymmetric synthesis of pentenomycins and their analogues.[6] We now wish to report the asymmetric synthesis, based on methodology described in our earlier report, of (+)-4-desoxypentenomycin (**1**), prepared by using the diastereoselective phenylsulfanylpropylation of an enolate anion derived from 2*R*,5*R*,6*R*-ester **2** and intramolecular acylation of α-sulfinyl carbanion as the key steps.

The synthetic sequence is summarized in Scheme 1. We started from 2*R*,5*R*,6*R*-ester **2**, which was easily prepared from D-mannitol as previously described by Ley.[7] It was anticipated that diastereoselective phenylsulfanylpropylation of an enolate anion derived from 2*R*,5*R*,6*R*-ester **2** followed by sequential oxidation, intramolecular acylation of the α-sulfinyl carbanion, sulfoxide elimination, and hydrolysis should provide the expected desoxypentenomycin **1**. Furthermore, the adduct **6** was envisioned as being a useful synthetic building block for the synthesis of desoxypentenomycin analogues and some highly oxygenated cyclopentenones.



Scheme 1 *Reagents and conditions*: (a) LDA, THF, –78 °C, then $PhS(CH_2)_3Br$, HMPA, –78 °C to r.t., 66%; (b) $NaIO_4$, MeOH, H_2O, 88%; (c) LDA, THF, –78 to 0 °C, 2 h, 73%; (d) toluene, $CaCO_3$, reflux, 15 h, 80%; (e) 90% TFA, 0 °C, 5 h, 80%.

As previously demonstrated by Ley and co-workers,[7] the enolate anions of 2*R*,5*R*,6*R*-ester **2** and its epimer react with electrophiles at the equatorial position in a highly stereoselective manner (Scheme 1). This advantage was used in the treatment of **2** with lithium diisopropylamide in tetrahydrofuran at –78 °C for two hours, followed by overnight alkylation with 3-bromo-1-(phenylsulfanyl)propane in the presence of hexamethylphosphoramide at –78 °C to room temperature; this afforded the expected sulfide **3** in 66% yield as a single product. Oxidation of sulfide **3** with sodium metaperiodate ($NaIO_4$) in aqueous methanol at 0 °C to room temperature provided the corresponding sulfoxide **4** in 88% yield. Treatment of sulfoxide **4** with lithium diisopropylamide (2.3 equiv) in tetrahydrofuran at –78 °C for two hours and at 0 °C for two hours furnished α-sulfinylcyclopentanone **5** in 73% yield as a mixture of diastereomers. The reaction proceeded via intramolecular acylation of the initially formed α-sulfinyl carbanion of sulfoxide **4**. Subsequent sulfoxide elimination of **5** as a mixture of diastereomers in refluxing toluene in the presence of calcium carbonate under an argon atmosphere for 15 hours yielded the corresponding cyclopentenone derivative **6** in 80% yield. Hydrolysis of the butanediacetal protecting group of **6** was effected by the

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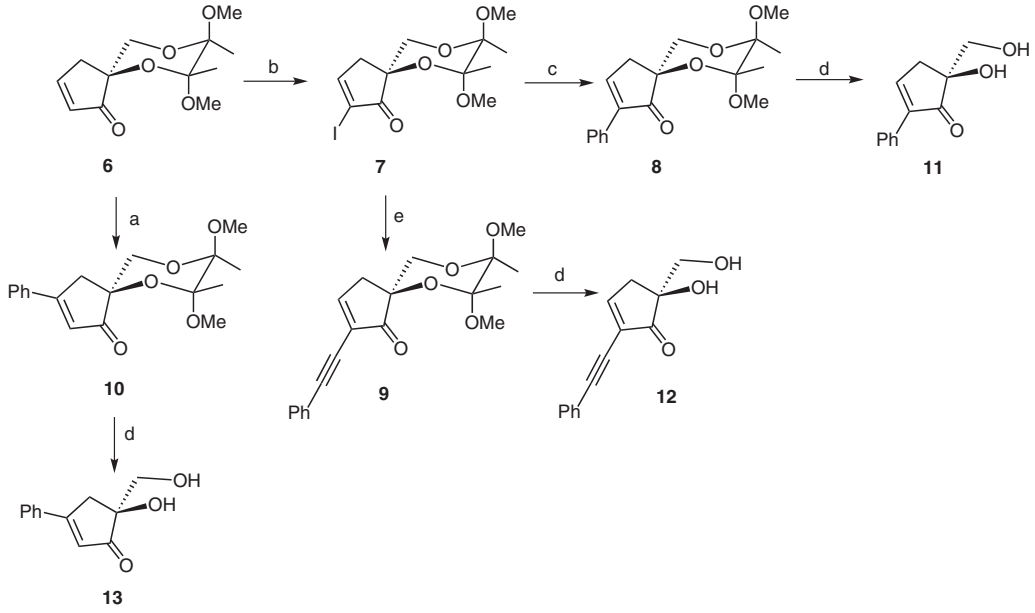

Scheme 2 *Reagents and conditions*: (a) $Pd(OAc)_2$, TBAB, PhI, K_2CO_3, DMF, 80 °C, 12 h, 72%; (b) I_2, py, CCl_4, 95%; (c) $[PdCl_2(PPh_3)_2]$, $PhB(OH)_2$, Na_2CO_3, THF, 40 °C, 10 h, 95%; (d) 90% TFA, 0 °C, 5 h; (e) $[PdCl_2(PPh_3)_2]$, phenylacetylene, *i*-Pr_2NH, CuI, THF, 0 °C, 66%.

use of 90% trifluoroacetic acid at 0 °C for five hours, leading to (+)-4-desoxypentenomycin (**1**) in 80% yield.

Having succeeded in synthesizing (+)-4-desoxypentenomycin (**1**), we next demonstrated the synthetic use of the oxygenated cyclopentenone intermediate **6** isolated during our synthetic access to **1** in the synthesis of 4-desoxypentenomycin analogues (Scheme 2). This allowed the preparation of α-iodo derivative **7** in 95% yield by treatment of compound **6** with iodine in the presence of pyridine.[8]

The Suzuki–Miyaura coupling reaction of **7** with phenylboronic acid in tetrahydrofuran in the presence of $[PdCl_2(PPh_3)_2]$ and sodium carbonate at 40 °C for 10 hours under an argon atmosphere afforded compound **8** in 95% yield (Scheme 2).[9] Similarly, phenylethynyl-substituted cyclopentenone **9** was obtained in 68% yield by the Sonogashira coupling reaction of **1** with phenylacetylene in the presence of $[PdCl_2(PPh_3)_2]$, copper(I) iodide, and diisopropylamine in tetrahydrofuran at 0 °C for one hour.[10]

Our success with the Suzuki–Miyaura and Sonogashira coupling reactions encouraged us to carry out the Heck coupling reaction.[11] The reaction of **6** with iodobenzene in the presence of palladium(II) acetate, tetrabutylammonium bromide, and potassium carbonate in *N*,*N*-dimethylformamide at 60 °C under an argon atmosphere for 12 hours provided the expected β-phenylcyclopentenone **10** in 72% yield (Scheme 2). Standard acid-catalyzed hydrolysis of the butanediacetal protecting group (90% TFA, 0 °C, 5 h) of compounds **8**, **9**, and **10** gave the corresponding 4-desoxypentenomycin analogues **11**, **12**, and **13** in 82, 74, and 95% yield, respectively.

In conclusion, the synthetic utility of the intramolecular acylation of α-sulfinyl carbanions was demonstrated to be an efficient and general synthetic approach for the preparation of highly oxygenated cyclopentenones such as (+)-4-desoxypentenomycin **1**, starting from readily available 2*R*,5*R*,6*R*-ester **2**. Compound **6** was employed as a precursor for the synthesis of substituted analogues of compound **1** by means of Suzuki–Miyaura, Sonogashira, and Heck coupling reactions followed by hydrolysis.

^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker DPX-300 and Bruker Avance 500 spectrometers. IR spectroscopy was carried out on a Jasco A-302 and a Perkin-Elmer 683 infrared spectrometer. MS was performed on a Thermo Finnigan Polaris Q mass spectrometer. HRMS was carried out on either an HR-TOF-MS Micromass model VQ-TOF2 or a Finnigan MAT 95 mass spectrometer. Microanalyses were determined with a Perkin-Elmer Elemental Analyzer 2400 CHN.

Methyl (2*S*,5*R*,6*R*)-5,6-Dimethoxy-5,6-dimethyl-2-[3-(phenylsulfanyl)propyl][1,4]dioxane-2-carboxylate (3)

A soln of (2*R*,5*R*,6*R*)-**2** (1.340 g, 5.72 mmol) in THF (30 mL) was added slowly to a THF (10 mL) soln of LDA (7.15 mmol) at –78 °C. The mixture was stirred at –78 °C for 2 h. To this soln was added a soln of 1-bromo-3-(phenylsulfanyl)propane (6.61 g, 28.62 mmol) and HMPA (4 mL) in THF (15 mL). The resulting soln was stirred at –78 °C for 2 h and quenched with sat. aq NH_4Cl (30 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with H_2O (20 mL) and brine (20 mL) and dried (Na_2SO_4). The organic phase was concentrated to give a crude pale yellow liquid. Column chromatography (silica gel, EtOAc–hexanes, 13:87) gave the title compound.

Yield: 1.451 g (66%); pale yellow liquid; single diastereomer; $[\alpha]_D^{29}$ –167.7 (*c* 0.7, $CHCl_3$).

IR (neat): 1715 (s), 1585 (m), 1481 (m), 1298 (s), 1196 (s), 987 (s), 747 (s), 692 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.28–7.02 (m, 5 H, Ar*H*), 4.03 (d, *J* = 11.5 Hz, 1 H, OCH*H*), 3.61 (s, 3 H, CO_2CH_3), 3.5 (d, *J* = 11.5 Hz, 1 H, OC*H*H), 3.18 (s, 3 H, OCH_3), 3.14 (s, 3 H, OCH_3), 2.90–

2.85 (m, 2 H, SCH_2), 1.82–1.72 (m, 2 H, CCH_2), 1.63–1.44 (m, 2 H, CH_2CH$_2$), 1.22 (s, 3 H, CH_3), 1.19 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.2 (C=O), 136.0 (C), 129.3 (2 × CH), 128.8 (2 × CH), 125.9 (CH), 99.5 (C), 98.0 (C), 73.4 (C), 61.8 (CH_2), 51.9 (CH_3), 50.3 (CH_3), 48.0 (CH_3), 36.3 (CH_2), 33.7 (CH_2), 22.4 (CH_2), 17.75 (CH_3), 17.71 (CH_3).

MS (EI): *m*/*z* (%) = 384 (16), 353 (100), 149 (25), 127 (19).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{28}O_6SNa$: 407.1503; found: 407.1483.

Methyl (2*S*,5*R*,6*R*)-5,6-Dimethoxy-5,6-dimethyl-2-[3-(phenylsulfinyl)propyl][1,4]dioxane-2-carboxylate (4)

Powdered $NaIO_4$ (0.35 g, 3.3 mmol) and H_2O (5 mL) were mixed in a round-bottomed flask and the mixture was brought to 0 °C by cooling in an ice bath. To this mixture was added dropwise a soln of (2*S*,5*R*,6*R*)-**3** (1.153 g, 3.00 mmol) in MeOH (12 mL). The resulting mixture was stirred at 0 °C to r.t. overnight. The precipitate of $NaIO_3$ was filtered and washed several times with EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with H_2O (20 mL) and brine (20 mL), and dried (Na_2SO_4). Filtration followed by evaporation gave a crude product as yellow liquid. Column chromatography (silica gel, EtOAc–hexanes, 80:20) gave the title compound.

Yield: 1.056 g (88%); pale yellow liquid; a mixture of two diastereomers.

IR (neat): 1732 (s), 1444 (s), 1246 (s), 1148 (s), 1093 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.60–7.45 (m, 2 × 5 H, Ar*H*), 4.03 (d, *J* = 11.5 Hz, 1 H, OCH*H*), 4.02 (d, *J* = 11.5 Hz, 1 H, OCH*H*), 3.68 (s, 3 H, CO_2CH_3), 3.63 (s, 3 H, CO_2CH_3), 3.56 (d, *J* = 11.5 Hz, 1 H, OC*H*H), 3.51 (d, *J* = 11.5 Hz, 1 H, OC*H*H), 3.17 (s, 3 H, OCH_3), 3.15 (s, 3 H, OCH_3), 3.12 (s, 3 H, OCH_3), 3.12 (s, 3 H, OCH_3), 2.74–2.69 (m, 2 × 2 H, SOCH_2), 1.85–1.66 (m, 2 × 4 H, CH_2CH_2), 1.21 (s, 3 H, CH_3), 1.19 (s, 2 × 3 H, CH_3), 1.18 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.98 (C=O), 172.90 (C=O), 143.59 (C), 143.52 (C), 130.9 (2 × CH), 129.1 (4 × CH), 123.9 (4 × CH), 99.5 (C), 99.47 (C), 98.0 (C), 97.9 (C), 73.25 (C), 73.21 (C), 61.5 (CH_2), 61.4 (CH_2), 57.0 (CH_2), 56.9 (CH_2), 52.0 (CH_3), 51.9 (CH_3), 50.3 (2 × CH_3), 48.01 (CH_3), 48.02 (CH_3), 35.9 (CH_2), 35.8 (CH_2), 17.65 (2 × CH_3), 17.62 (2 × CH_3), 16.3 (CH_2), 16.2 (CH_2).

MS (EI): *m*/*z* (%) = 400 [M$^+$] (7), 368 (25), 336 (100), 251 (17), 127 (26), 115 (25), 67 (37).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{28}O_7SNa$: 423.1452; found: 423.1424.

(5*S*,7*R*,8*R*)-7,8-Dimethoxy-7,8-dimethyl-2-(phenylsulfinyl)-6,9-dioxaspiro[4.5]decan-1-one (5)

A soln of (2*S*,5*R*,6*R*)-**4** (1.07 g, 2.67 mmol) in THF (5 mL) was added slowly to a THF (8 mL) soln of LDA (6.14 mmol), prepared by reaction of *N*,*N*-diisopropylamine (0.86 mL, 6.14 mmol) with 1.35 M *n*-BuLi in hexane (4.6 mL, 6.2 mmol)] at –78 °C. The reaction mixture was stirred at –78 °C for 2 h and at 0 °C for 2 h before it was quenched with sat. aq NH_4Cl (30 mL). The aqueous phase was extracted with EtOAc (3 × 30 mL). The combined organic phase was washed with H_2O (30 mL) and brine (20 mL), and then dried (Na_2SO_4) to provide a crude product. Column chromatography (silica gel, EtOAc–hexanes, 20:80 to 35:65) gave the title compound.

Yield: 0.715 g (73%); pale yellow viscous liquid; a mixture of diastereomers.

IR (neat): 1745 (m), 1456 (m), 1446 (m), 1142 (m), 1043 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.70–7.61 (m, 2 × 2 H, Ar*H*), 7.59–7.48 (m, 2 × 3 H, Ar*H*), 4.33 (br d, *J* = 9.5 Hz, 1 H), 3.81 (d, *J* = 11.9 Hz, 2 H), 3.74 (d, *J* = 11.9 Hz, 1 H), 3.59 (br d, *J* = 9.5 Hz, 1 H), 3.38 (d, *J* = 12.0 Hz, 1 H), 3.28 (s, 3 H, OCH_3), 3.19 (s, 3 H, OCH_3), 3.17 (s, 3 H, OCH_3), 3.16 (s, 3 H, OCH$_3$), 2.50–2.25 (m, 1 H), 2.00–1.92 (m, 1 H), 1.85–1.50 (m, 3 H), 1.28 (s, 3 H, CH_3), 1.27 (s, 3 H, CH_3), 1.26 (s, 3 H, CH_3), 1.25 (s, 3 H, CH_3), 0.21 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 206.2 (C=O), 206.1 (C=O), 142.4 (C), 139.5 (C), 131.8 (CH), 131.0 (CH), 129.2 (2 × CH), 128.9 (2 × CH), 125.4 (2 × CH), 124.1 (2 × CH), 99.5 (C), 99.4 (C), 98.2 (2 × C), 76.3 (C), 75.9 (C), 68.0 (CH), 68.8 (CH), 58.6 (CH_2), 58.3 (CH_2), 49.1 (CH_3), 48.9 (CH_3), 48.2 (CH_3), 48.1 (CH_3), 32.4 (CH_2), 32.0 (CH_2), 18.4 (CH_3), 18.3 (CH_3), 17.8 (CH_3), 17.7 (CH_3), 16.0 (CH_2), 14.8 (CH_2).

MS (EI): *m*/*z* (%) = 368 [M$^+$] (1), 202 (43), 173 (50), 149 (91), 115 (99), 97 (100), 73 (99).

HRMS (ESI-TOF): *m*/*z* [M]$^+$ calcd for $C_{18}H_{23}O_6S$: 367.1215; found: 367.1219.

(5*S*,7*R*,8*R*)-7,8-Dimethoxy-7,8-dimethyl-6,9-dioxaspiro[4.5]dec-2-en-1-one (6)

A mixture of (5*S*,7*R*,8*R*)-**5** (0.541 g, 1.47 mmol) and anhyd $CaCO_3$ (0.25 g, 2.5 mmol) in anhyd toluene (20 mL) was refluxed at 110 °C for 15 h under an argon atmosphere. Filtration followed by evaporation gave a residue, which was purified by preparatory TLC (silica gel, EtOAc–hexanes, 20:80).

Yield: 0.2845 g (80%); colorless liquid; a single diastereomer; $[\alpha]_D^{29}$ –78.37 (*c* 0.3, $CHCl_3$).

IR (Nujol): 1722 (s), 1588 (m), 1456 (s), 1114 (s), 1076 (m), 1058 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.57 (dt, *J* = 6.0, 2.9 Hz, 1 H, =CH_β), 6.08 (dt, *J* = 6.0, 2.1 Hz, 1 H, =CH_α), 4.12 (d, *J* = 10.8 Hz, 1 H, OC*H*H), 3.38 (s, 3 H, OCH_3), 3.37 (d, *J* = 10.8 Hz, 1 H, CH*H*), 3.25 (s, 3 H, OCH_3), 2.84 (m, 2 H, CCH_2), 1.30 (s, 3 H, CH_3), 1.25 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.5 (C=O), 162.5 (CH), 131.6 (CH), 100.6 (C), 99.4 (C), 76.7 (C), 64.8 (CH_2), 48.2 (CH_2), 47.8 (CH_2), 43.5 (CH_2), 18.9 (CH_3), 18.7 (CH_3).

MS (EI): *m*/*z* (%) = 243 [M$^+$ + 1] (1), 211 (100), 179 (17), 94 (20), 73 (31).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{18}O_5Na$: 265.1052; found: 265.1054.

(+)-4-Desoxypentenomycin (1)

(5*S*,7*R*,8*R*)-**6** (0.114 g, 0.43 mmol) was treated with 90% TFA (5 mL) at 0 °C. The mixture was slowly warmed to r.t. and was further stirred for an additional 5 h. The mixture was freeze-dried overnight to give a crude product, which was purified by preparatory TLC (silica gel, MeOH–EtOAc, 5:95).

Yield: 48 mg (80%); colorless viscous liquid; $[\alpha]_D^{29}$ +214.54 (*c* 0.2, $CHCl_3$).

IR (neat): 3420 (s), 3242 (s), 1704 (s), 1633 (m), 1583 (m), 1052 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.68 (dt, *J* = 5.9, 2.9 Hz, 1 H, =CH_β), 6.15–6.12 (m, 1 H, =CH_α), 3.56 (s, 2 H, CH_2OH), 2.70 (br s, 2 H, CCH_2), 2.1 (br s, 2 H, O*H*).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 210.1 (C=O), 163.0 (CH), 131.1 (CH), 76.0 (C), 66.9 (CH_2), 39.7 (CH_2).

MS (EI): *m*/*z* (%) = 128 [M$^+$] (27), 115 (38), 97 (64), 81 (73), 67 (93), 57 (100).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_6H_8O_3Na$: 151.0371; found: 151.0366.

(5*S*,7*R*,8*R*)-2-Iodo-7,8-dimethoxy-7,8-dimethyl-6,9-dioxaspiro[4.5]dec-2-en-1-one (7)

A soln of (5*S*,7*R*,8*R*)-**6** (0.741 g, 3.06 mmol) in pyridine (14 mL) and CCl_4 (7 mL) was treated with a soln of I_2 (3.084 g, 12.23 mmol) in CCl_4 (7 mL). After stirring for 1 h at r.t. in the dark, the mixture was diluted with Et_2O (70 mL) and washed successively with H_2O (3 × 15 mL), 1 M aq HCl (5 mL), sat. aq $Na_2S_2O_3$ (20 mL), and brine (15 mL). The organic layer was dried (Na_2SO_4). Filtration followed by evaporation gave a residue, which was purified by column chromatography (silica gel, EtOAc–hexanes, 17:83).

Yield: 1.07 g (95%); pale yellow viscous oil which was unstable upon standing at r.t.; $[\alpha]_D^{29}$ –75.13 (*c* 0.25, $CHCl_3$).

IR (Nujol): 1715 (s), 1574 (s), 1462 (m), 1008 (m) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.96 (app t, *J* = 2.9 Hz, 1 H, =C*H*), 4.21 (d, *J* = 10.8 Hz, 1 H, OCH*H*), 3.44 (d, *J* = 10.8 Hz, 1 H, OC*H*H), 3.42 (s, 3 H, OCH_3), 3.30 (s, 3 H, OCH_3), 2.99 (dd, *J* = 19.5, 2.8 Hz, 1 H, CHCHH_A), 2.89 (dd, *J* = 19.5, 2.8 Hz, 1 H, CHCHH_B), 1.35 (s, 3 H, CH_3), 1.29 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.2 (C=O), 167.6 (CH), 100.9 (C), 99.5 (C), 99.3 (C), 74.2 (C), 64.6 (CH_2), 48.3 (CH_2), 47.9 (CH_2), 45.9 (CH_2), 18.8 (CH_3), 18.6 (CH_3).

MS (EI): *m*/*z* (%) = 368 [M^+] (0.13), 337 (26), 220 (100), 101 (40), 93 (40), 73 (68).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{17}IO_5Na$: 391.0017; found: 391.0015.

(5*S*,7*R*,8*R*)-7,8-Dimethoxy-7,8-dimethyl-2-phenyl-6,9-dioxaspiro[4.5]dec-2-en-1-one (8)

Under an argon atmosphere, a round-bottomed flask was charged with phenylboronic acid (49 mg, 0.406 mmol), (5*S*,7*R*,8*R*)-**7** (100 mg, 0.271 mmol), and [$PdCl_2(PPh_3)_2$] (11 mg, 5 mol%). THF (2 mL) was added followed by 2 M aq Na_2CO_3 (0.7 mL, 1.4 mmol). The resulting mixture was heated overnight at 40 °C under an argon atmosphere. The mixture was cooled to r.t. and EtOAc (10 mL) was added followed by sat. aq $NaHCO_3$ (20 mL) and H_2O (15 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with 0.5 N NaOH (2 × 10 mL) and brine (2 × 10 mL) and dried (Na_2SO_4). Filtration followed by evaporation gave a crude product, which was purified by column chromatography (silica gel, EtOAc–hexanes, 20:80).

Yield: 82 mg (95%); white solid; mp 148–150 °C; $[\alpha]_D^{29}$ –58.28 (*c* 0.2, $CHCl_3$).

IR (Nujol): 1704 (s), 1607 (m), 1462 (s), 1118 (s), 1052 (m) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.67 (app t, *J* = 2.9 Hz, 1 H, =C*H*), 7.62 (d, *J* = 6.5 Hz, 2 H, Ar*H*), 7.30–7.21 (m, 3 H, Ar*H*), 4.19 (d, *J* = 10.7 Hz, 1 H, OCH*H*), 3.43 (d, *J* = 10.7 Hz, 1 H, OC*H*H), 3.42 (s, 3 H, OCH_3), 3.28 (s, 3 H, OCH_3), 2.91 (dd, *J* = 9.5, 3.1 Hz, 1 H, CHCHH_A), 2.84 (dd, *J* = 9.5, 3.1 Hz, 1H, CHCHH_B), 1.32 (s, 3 H, CH_3), 1.28 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.4 (C=O), 156.1 (CH), 140.4 (C), 131.1 (C), 128.5 (CH), 128.3 (2 × CH), 126.7 (2 × CH), 100.8 (C), 99.5 (C), 78.5 (C), 65.2 (CH_2), 48.3 (CH_3), 47.8 (CH_3), 41.4 (CH_2), 19.0 (CH_3), 18.7 (CH_3).

MS (EI): *m*/*z* (%) = 319 [M^+ + 1] (0.05), 142 (76), 141 (100), 115 (77).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{22}O_5Na$: 341.1364; found: 341.1347.

(5*S*,7*R*,8*R*)-7,8-Dimethoxy-7,8-dimethyl-2-(phenylethynyl)-6,9-dioxaspiro[4.5]dec-2-en-1-one (9)

Under an argon atmosphere, a mixture of (5*S*,7*R*,8*R*)-**7** (238 mg, 0.646 mmol), phenylacetylene (0.328 mL, 3.232 mmol), [$PdCl_2(PPh_3)_2$] (23 mg, 0.032 mmol), and CuI (12.8 mg, 0.064 mmol) in THF (1 mL) was treated with *N*,*N*-diisopropylamine (0.49 mL, 3.5 mmol) at 0 °C. The resulting yellow to dark brown soln was stirred at 0 °C for 1 h. The mixture was partitioned between Et_2O (10 mL) and 1 M aq HCl (10 mL) and extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (2 × 10 mL) and dried (Na_2SO_4). Filtration followed by concentration gave a crude reaction mixture, which was purified by column chromatography (silica gel, EtOAc–hexanes, 18:82).

Yield: 145.7 mg (66%); pale yellow viscous liquid; $[\alpha]_D^{29}$ –24.5 (*c* 0.34, $CHCl_3$).

IR (neat): 2992 (s), 2834 (s), 1731 (s), 1574 (s), 1463 (m), 1372 (s), 1110 (s), 972 (m) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.68 (t, *J* = 3.1 Hz, 1 H, =C*H*), 7.44–7.38 (m, 2 H, Ar*H*), 7.28–7.22 (m, 3 H, Ar*H*), 4.18 (d, *J* = 9.3 Hz, 1 H, OCH*H*), 3.42 (s, 3 H, OCH_3), 3.40 (d, *J* = 9.3 Hz, 1 H, OCH*H*), 3.27 (s, 3 H, OCH_3), 2.92 (dd, *J* = 15.0, 3.0 Hz, 2 H, CH_2), 1.31 (s, 3 H, CH_3), 1.27 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.6 (C=O), 162.4 (CH), 131.8 (2 × CH), 128.8 (CH), 128.3 (2 × CH), 127.3 (C), 122.2 (C), 100.9 (C), 99.6 (C), 95.7 (C), 79.6 (C), 77.2 (C), 64.9 (CH_2), 48.3 (CH_3), 47.9 (CH_3), 42.3 (CH_2), 18.9 (CH_3), 18.7 (CH_3).

MS (EI): *m*/*z* (%) = 241 [M^+ – phenylacetylene] (1), 166 (20), 165 (100), 153 (28), 139 (34), 115 (39).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{22}O_5Na$: 365.1364; found: 365.1356.

(5*S*,7*R*,8*R*)-7,8-Dimethoxy-7,8-dimethyl-3-phenyl-6,9-dioxaspiro[4.5]dec-2-en-1-one (10)

DMF (5 mL) was added to a mixture of (5*S*,7*R*,8*R*)-**6** (106 mg, 0.438 mmol), PhI (0.96 mL, 0.48 mmol), $Pd(OAc)_2$ (26.6 mg, 0.116 mmol), K_2CO_3 (181.5 mg, 2.409 mmol), and TBAB (253.8 mg, 0.88 mmol), and the resulting mixture was heated at 80 °C under an argon atmosphere for 12 h. After cooling to r.t., the mixture was diluted with H_2O (20 mL) and extracted with EtOAc (3 × 25 mL). The combined organic extracts were washed with H_2O (15 mL) and brine (15 mL) and dried (Na_2SO_4). Filtration followed by evaporation gave a crude product, which was purified by preparatory TLC (silica gel, EtOAc–hexanes, 20:80).

Yield: 99.8 mg (72%); pale yellow viscous liquid; $[\alpha]_D^{29}$ –43.04 (*c* 0.1, $CHCl_3$).

IR (neat): 3061 (m), 1710 (s), 1597 (s), 1571 (s), 1494 (s), 1037 (m) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.60–7.52 (m, 2 H, Ar*H*), 7.42–7.30 (m, 3 H, Ar*H*), 6.40 (s, 1 H, =C*H*), 4.21 (d, *J* = 10.9 Hz, 1 H, OCH*H*), 3.46 (d, *J* = 10.9 Hz, 1 H, OC*H*H), 3.43 (s, 3 H, OCH_3), 3.35 (s, 3 H, OCH_3), 3.18 (br, 2 H, CCH_2), 1.36 (s, 3 H, CH_3), 1.28 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 204.5 (C=O), 170.9 (C), 133.6 (C), 131.6 (CH), 128.9 (2 × CH), 126.9 (2 × CH), 124.3 (CH), 100.7 (C), 99.5 (C), 78.2 (C), 65.0 (CH_2), 48.3 (CH_3), 47.9 (CH_3), 43.4 (CH_2), 19.0 (CH_3), 18.7 (CH_3).

MS (EI): *m*/*z* (%) = 319 [M^+ + 1] (6), 265 (55), 251 (100), 215 (33), 239 (36).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{22}O_5Na$: 341.1364; found: 341.1352.

(+)-5-Hydroxy-5-(hydroxymethyl)-2-phenylcyclopent-2-enone (11)

Compound (5*S*,7*R*,8*R*)-**8** (71 mg, 0.223 mmol) was treated with 90% TFA (2 mL) at 0 °C. The mixture was slowly warmed to r.t. and further stirred for an additional 5 h. The mixture was freeze-dried overnight to give a crude product, which was purified by preparatory TLC (silica gel, EtOAc–hexanes, 1:1).

Yield: 37.4 mg (82%); white solid; mp 130–134 °C; $[\alpha]_D^{29}$ +48.28 (*c* 2.0, EtOH).

IR (Nujol): 3401 (m), 2924 (s), 1693 (s), 1571 (m), 1089 (m), 1051 (s), 998 (m) cm^{-1}.

^1H NMR (300 MHz, acetone-d_6): δ = 7.88 (t, *J* = 2.9 Hz, 1 H, =C*H*), 7.64 (d, *J* = 7.4 Hz, 2 H, Ar*H*), 7.22–7.12 (m, 3 H, Ar*H*), 4.40 (s, 1 H, O*H*), 3.95 (t, *J* = 5.6 Hz, 1 H, CH_2O*H*), 3.59 (dd, *J* = 10.5, 5.1 Hz, 1 H, CHCH*H*), 3.46 (dd, *J* = 10.5, 5.1 Hz, 1 H, CHC*H*H), 2.91 (dd, *J* = 19.2, 2.8 Hz, 1 H, CH*H*OH), 2.46 (dd, *J* = 19.2, 2.8 Hz, 1 H, C*H*HOH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 208.0 (C=O), 158.0 (CH), 141.0 (C), 132.8 (C), 129.05 (2 × CH), 129.01 (CH), 127.5 (2 × CH), 78.6 (C), 66.9 (CH_2), 31.2 (CH_2).

MS (EI): *m*/*z* (%) = 205 [M^+ + 1] (1), 128 (31), 115 (100), 89 (24).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{12}O_3Na$: 227.0683; found: 227.0678.

(+)-5-Hydroxy-5-(hydroxymethyl)-2-(phenylethynyl)cyclopent-2-enone (12)

Compound (5*S*,7*R*,8*R*)-**9** (107 mg, 0.313 mmol) was treated with 90% TFA (1 mL) at 0 °C. The mixture was slowly warmed to r.t. and further stirred for an additional 5 h. The mixture was freeze-dried overnight to give a crude product, which was purified by preparatory TLC (silica gel, EtOAc–hexanes, 7:3).

Yield: 52.9 mg (74%); colorless viscous liquid; $[\alpha]_D^{29}$ +25.23 (*c* 0.5, EtOH).

IR (neat): 3417 (s), 2229 (m), 1713 (s), 1571 (m), 1140 (m), 1051 (m) cm^{-1}.

^1H NMR (300 MHz, acetone-d_6 + D_2O): δ = 7.94 (t, *J* = 3.0 Hz, 1 H, =C*H*), 7.48–7.32 (m, 5 H, Ar*H*), 3.63 (d, *J* = 10.6 Hz, 1 H, CH*H*OH), 3.50 (d, *J* = 10.6 Hz, 1 H, CH*H*OH), 3.08 (dd, *J* = 20.2, 3.2 Hz, 1 H, CHCH*H*), 2.63 (dd, *J* = 20.2, 3.2 Hz, 1 H, CHC*H*H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 206.6 (C=O), 165.7 (CH), 132.1 (2 × CH), 129.6 (CH), 129.3 (CH), 127.5 (2 × C), 122.9 (C), 95.0 (C), 81.0 (C), 77.2 (C), 65.8 (CH_2), 40.1 (CH_2).

MS (EI): *m*/*z* (%) = 252 [M^+ + 1] (2), 141 (74), 115 (100).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{12}O_3Na$: 251.0683; found: 251.0666.

(+)-5-Hydroxy-5-(hydroxymethyl)-3-phenylcyclopent-2-enone (13)

Compound (5*S*,7*R*,8*R*)-**10** (111 mg, 0.348 mmol) was treated with 90% TFA (9 mL) at 0 °C. The mixture was slowly warmed to r.t. and further stirred for an additional 5 h. The mixture was freeze-dried overnight to give a crude product, which was purified by preparatory TLC (silica gel, EtOAc–hexanes, 8:2).

Yield: 67.6 mg (95%); white solid; mp 112–115 °C; $[\alpha]_D^{29}$ +219.8 (*c* 0.2, EtOH).

IR (Nujol): 3315 (s), 1695 (s), 1463 (m), 1057 (m), 1039 (m), 727 (m), 698 (m) cm^{-1}.

^1H NMR (300 MHz, acetone-d_6 + D_2O): δ = 7.81 (m, 2 H, Ar*H*), 7.56–7.48 (m, 3 H, Ar*H*), 6.64 (s, 1 H, =C*H*), 3.75 (d, *J* = 11.0 Hz, 1 H, C*H*HOH), 3.62 (d, *J* = 11.0 Hz, 1 H, CH*H*OH), 3.48 (d, *J* = 18.0 Hz, 1 H, CH*H*), 3.04 (d, *J* = 18.0 Hz, 1 H, C*H*H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 211.4 (C=O), 175.1 (C), 134.7 (C), 133.1 (CH), 130.1 (2 × CH), 128.4 (2 × CH), 125.2 (CH), 79.0 (C), 66.4 (CH_2), 41.4 (CH_2).

MS (EI): *m*/*z* (%) = 206 [M^+ + 2] (1), 145 (24), 128 (26), 115 (100).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{12}O_3Na$: 227.0683; found: 227.0670.

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References

(1) For a review, see: Beale, M. H.; Ward, J. L. *Nat. Prod. Rep.* **1998**, 533.

(2) (a) Mitra, A. *The Synthesis of Prostaglandins*; Wiley-Interscience: New York, **1977**. (b) Bindra, J. S.; Bindra, R. *Prostaglandin Synthesis*; Academic Press: London, **1977**.

(3) (a) Beil, W.; Goeres, M.; Nerenz, F.; Winterfeldt, E. *Adv. Synth. Catal.* **1999**, *341*, 384. (b) Bauermeister, H.; Riechers, H.; Schomburg, D.; Washausen, P.; Winterfeldt, E. *Angew. Chem. Int. Ed.* **1991**, *30*, 191. (c) Forsyth, C. J.; Clardy, J. *J. Am. Chem. Soc.* **1988**, *110*, 5911. (d) Lindquist, N.; Fenical, W.; Sesin, D. F.; Ireland, C. M.; Van Duyne, G. D.; Forsyth, C. J.; Clardy, J. *J. Am. Chem. Soc.* **1988**, *110*, 1308.

(4) (a) For general approaches to cyclopentanoids, see: Hudlicky, T.; Price, J. D. *Chem. Rev.* **1989**, *89*, 1467. (b) Tius, M. A. *Eur. J. Org. Chem.* **2005**, 2193. (c) Tius, M. A. *Acc. Chem. Res.* **2003**, *36*, 284. (d) Cowen, B. J.; Miller, S. J. *J. Am. Chem. Soc.* **2007**, *129*, 10988. (e) Bunell, J.; Gao, F. *J. Org. Chem.* **2006**, *71*, 356. (f) Johnson, T. A.; Curtis, M. D.; Beak, P. *Org. Lett.* **2002**, *4*, 2747. (g) Trost, B. M.; Pinkerton, A. B. *J. Org. Chem.* **2001**, *66*, 7714. (h) La, D. S.; Sattely, E. S.; Ford, J. G.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 7767. (i) Denmark, S. E.; Dixon, J. A. *J. Org. Chem.* **1998**, *63*, 6178.

(5) (a) Pohmakotr, M.; Phinyocheep, P. *Tetrahedron Lett.* **1984**, *25*, 2249. (b) Pohmakotr, M.; Popuang, S.; Chancharunee, S. *Tetrahedron Lett.* **1989**, *30*, 1715. (c) Pohmakotr, M.; Popuang, S. *Tetrahedron Lett.* **1990**, 3783. (d) Pohmakotr, M.; Bunlaksananusorn, T.; Tuchinda, P. *Tetrahedron Lett.* **2000**, *41*, 377. (e) Pohmakotr, M.; Popuang, S. *Tetrahedron Lett.* **1991**, *32*, 275. (f) Pohmakotr, M.; Junpirom, T.; Popuang, S.; Tuchinda, P.; Reutrakul, V. *Tetrahedron Lett.* **2002**, *43*, 7385.

(6) For syntheses of pentenomycins, see: (a) Shono, T.; Matsumura, Y.; Yamane, S.; Suzuki, M. *Chem. Lett.* **1980**, 1619. (b) Branca, S. J.; Smith, A. B. III *J. Am. Chem. Soc.* **1978**, *100*, 7767. (c) Smith, A. B. III; Pilla, N. N. *Tetrahedron Lett.* **1980**, *21*, 4691. (d) Smith, A. B. III; Branca, S. J.; Pilla, N. N.; Guaciara, M. A. *J. Org. Chem.* **1982**, *47*, 1855. (e) Elliott, J. D.; Hetmanski, M.; Palfreyman, M. N.; Purcell, N.; Stoodley, R. J. *Tetrahedron Lett.* **1983**, *24*, 965. (f) Hetmanski, M.; Purcell, N.; Stoodley, R. J.; Palfreyman, M. N. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2089. (g) Verlaak, J. M. J.; Klunder, A. J. H.; Zwanenburg, B. *Tetrahedron Lett.* **1982**, *23*, 5463. (h) Phutdhawong, W.; Pyne, S. G.; Baramee, A.; Buddhasukh, D.; Skelton, B. W.; White, A. H. *Tetrahedron Lett.* **2002**, *43*, 6047. (i) Khan, F. A.; Rout, B. *Tetrahedron Lett.* **2006**, *47*, 5251. (j) Verheyden, J. P. H.; Richardson, A. C.; Bhatt, R. S.; Grant, B. D.; Fitch, W. L.; Moffatt, J. G. *Pure Appl. Chem.* **1978**, *50*, 1363. (k) Achab, S.; Cosson, J.-P.; Das, B. C. *J. Chem. Soc., Chem. Commun.* **1984**, 1040. (l) Seepersaud, M.; Al-Abed, Y. *Tetrahedron Lett.* **2000**, *41*, 4291. (m) Gallos, J. K.; Damianou, K. C.; Dellios, C. C. *Tetrahedron Lett.* **2001**, *42*, 5769. (n) Ramana, G. V.; Rao, B. V. *Tetrahedron Lett.* **2003**, *44*, 5103. (o) Klomklao, T.; Pyne, S. G.; Baramee, A.; Skelton, B. W.; White, A. H. *Tetrahedron: Asymmetry* **2003**, *14*, 3885. (p) Khan, F. A.;

Dash, J.; Rout, B. *Tetrahedron Lett.* **2004**, *45*, 9285.
(q) Gallos, J. K.; Stathakis, C. I.; Kotoulas, S. S.; Koumbis, A. E. *J. Org. Chem.* **2005**, *70*, 6884.
(7) (a) Ley, S. V.; Michel, P.; Trapella, C. *Org. Lett.* **2003**, *5*, 4553. (b) Ley, S. V.; Dixon, D. J.; Guy, R. T.; Palomelo, M. A.; Polara, A.; Rodríguez, F.; Sheppard, T. D. *Org. Biomol. Chem.* **2004**, *2*, 3618. (c) Ley, S. V.; Diez, E.; Dixon, D. J.; Guy, R. T.; Michel, P.; Nattrass, G. L.; Sheppard, T. D. *Org. Biomol. Chem.* **2004**, *2*, 3608.
(8) Krafft, M. E.; Cran, J. W. *Synlett* **2005**, 1263.
(9) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
(10) (a) Chinchilla, R.; Najera, C. *Chem. Rev.* **2007**, *107*, 872. (b) Doucet, H.; Hierso, J.-C. *Angew. Chem. Int. Ed.* **2007**, *46*, 834.
(11) Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: London, **1985**.