Efficient Solid-Phase Synthesis of Clavulones via Sequential Coupling α- and ω-Chains.

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Supporting Information

General Experimental

NMR spectra were obtained on a JEOL Model EX-270 and JEOL JNM-ECP 400 system instrument with $CDCl_3$ as the solvent unless noted. ^{1}H NMR spectral data are reported as follows: chemical shifts relative to tetramethylsilane (0.00 ppm) or chloroform (7.26 ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling, and integration. ^{13}C signals are reported in ppm relative to $CDCl_3$ (77.0 ppm).

Infrared (IR) spectra were recorded on a JASCO Model IR-700 spectrometer. FT-IR spectra were recorded on a Perkin-Elmer Spectrum One™ spectrometer. Data are given in cm^{-1} with only significant diagnostic bands.

Optical rotations were measured with a JASCO P-1020 polarimeter.

Gas chromatography (GC) was performed on a Simazu Model GC-8A instrument equipped with a silicone DC-550 (3 mm x 3 m) column using He gas as carrier gas.

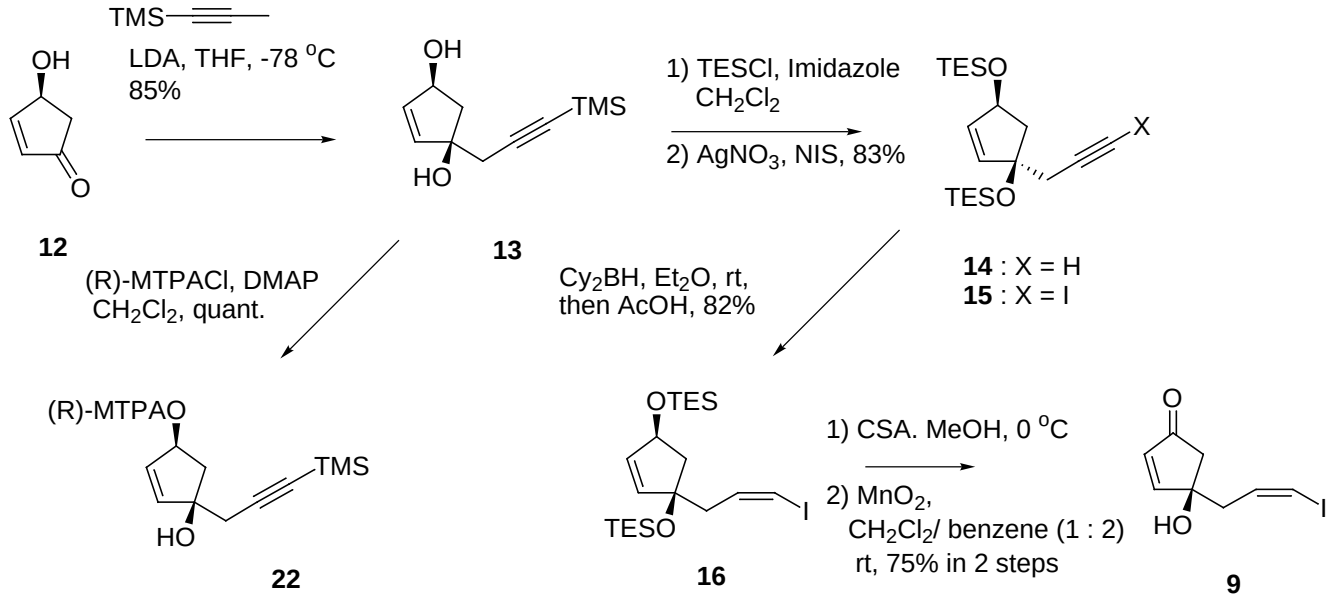
Colum chromatography was performed using silica gel (Merck). Analytical thin layer chromatography were performed on Merk precoated TLC plates 60F 254 (silica gel), visualization was made by black light and anisaldehyde/sulfuric acid/ethanol solution or phosphomolybdic acid/ethanol solution.

High Performance Liqid Chromatography (HPLC) was performed on a Nihon Seimitu Kagaku apparatus using a Senshu Pak Silica-3301-N coloum with a Japan Analytical Industry Model R1-3H refractive detector.

Mass spectra were provided by a Mariner Biospectrometry Workatation from PE science.

Dry tetrahydrofuran, dry ether, dry toluene and dry benzene were distilled from sodium wire contained a catalytic amount of benzophenone. Dry dichloromethane was distilled from P_2O_5. Dry methyl sulfoxide and dry pyridine were distilled from CaH_2. Dry methanol was distilled from Mg.

Preparation of hydroxy-4-(1-iodopropenyl)-2,3-cyclopenten-1-one (9).



(2*R*,4*S*)-2-(1-Trimethylsilylpropynyl)-1,5-cyclopenten-2,3-diol (13).

To a stirred solution of diisopropylamine (3.4 mL, 24.5 mmol) in dry tetrahydrofuran (40 mL) was added *n*-butyllithium (14.2 mL, 1.59 M in hexane, 22.5 mmol) at 0 °C under Ar. After being stirred for 20 min, the mixture was cooled to -20 °C and 1-trimethylsilylpropyne (3.3 mL, 22.5 mmol) in dry tetrahydrofuran (5 mL) was added. After 20 min, to the mixture was added a solution of (4*R*)-4-hydroxy-2-cyclopentenone (**12**) (950 mg, 9.79 mmol) in dry tetrahydrofuran (10 mL) at -78 °C. After being stirred at the same temperature for 10 min, the reaction mixture was diluted with ether and poured into saturated aqueous NH_4Cl (50 mL) at 0 °C. The aqueous layer was extracted with ether (3 x 50 mL) and the combined extracts were washed with brine (50 mL), dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo*. The residue was subjected to flash chromatography, eluting with 60:40 hexane-ethyl acetate to afford **13** (1.74 g, 8.29 mmol, 85%) as a white solid

(TLC R_f 0.26, 1:1 hexane-ethyl acetate); m.p. 98-100 °C; $[\alpha]^{30.3}_{D}$ = -93.1° (*c* 1.0, $CHCl_3$); IR (KBr) 3724, 2180, 1353, 1306, 1248, 1082 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 6.00 (1H, dd, *J* = 2.0, 5.6 Hz), 5.93 (1H, d, *J* = 5.6 Hz), 4.72 (1H, m), 2.56 (1H, dd, *J* = 6.9, 14.2 Hz), 2.54 (2H, s), 1.81 (1H, dd, *J* = 3.6, 14.2 Hz), 0.17 (9H, s, Me_3Si); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 138.4, 136.2, 102.3, 82.5, 81.4, 75.5, 48.0, 32.4, 0.002.

(2*R*,4*S*)-4-[(*R*)-2-Methoxy-2-(trifluoromethyl)phenylactoxy]-2-(1-trimethylsilylpropynyl)-1,5-cyclopenten-2-ol (22).

To a stirred solution of diol **13** (4.1 mg, 0.0195 mmol) in dry dichloromethane (0.4 mL) was added dry pyridine (8 µL, 0.0585 mmol), a catalytic amount of 4-dimethylaminopyridine (1 mg), and (*R*)-(-)-α-methoxy-α-(trifluoromethyl)phenylacetic acid chloride (6 µL, 0.0293 mmol) at 0 °C under Ar. After being stirred for 1.5 h at the same temperature, the reaction mixture was partitioned between ether (20 mL) and saturated aqueous $NaHCO_3$ (20 mL) at 0 °C. The aqueous layer was extracted with ether (3 x 20 mL) and the combined extracts were washed with 3 N HCl (20 mL), saturated aqueous $NaHCO_3$ (2 x 20 mL), and brine (20 mL), dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo*. The residue was subjected to flash chromatography, eluting with 75:25 hexane-ethyl acetate to afford **22** (9.5 mg, 0.0195 mmol, quant) as a colorless syrup.

(TLC R_f 0.69, 1:2 hexane-ethyl acetate); IR (neat) 3436, 2959, 2170, 1746 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.50-7.39 (5H, m, aromatic), 6.06 (1H, d, J = 5.3 Hz), 5.96 (1H, dd, J = 2.0, 5.3 Hz), 5.80-5.75 (1H, m), 3.55 (3H, d, J = 1.3 Hz, OMe), 2.76 (1H, dd, J = 7.3, 14.5 Hz), 2.58 (2H, s), 2.00 (1H, dd, J = 4.0, 14.5 Hz), 0.16 (9H, s, Me_3Si); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 166.2, 141.5, 132.1, 131.0, 129.7, 128.5, 127.3, 116.9, 102.6, 82.5, 79.6, 66.9, 56.0, 44.1, 33.2, 29.7, -0.03.

(2*R*,4*S*)-2-(1-Iodopropynyl)-2,4-ditriethylsilyloxy-1,5-cyclopentene (15).

To a stirred solution of diol **12** (2.06 g, 9.79 mmol) in dry dichloromethane (50 mL) was added imidazole (2.90 g, 43.1 mmol) and triethyllsilyl chloride (3.20 g, 21.5 mmol) at 0 °C under Ar. After being stirred for 20 min at the same temperature, the reaction mixture was partitioned between ether (30 mL) and saturated aqueous NH_4Cl (50 mL) at 0 °C. The aqueous layer was extracted with ether (3 x 50 mL) and the combined extracts were washed with brine (50 mL), dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo* to give crude terminal acetylene **14**. The residue was used for the next reaction without further purification.

To a stirred solution of the residue in dry acetone (40 mL) was added *N*-iodosuccinimide (2.37 g, 10.6 mmol) and $AgNO_3$ (0.97 g, 8.80 mmol) at 0 °C under Ar. After being stirred for 3.5 h at the same temperature, the reaction mixture was partitioned between ether (20 mL), saturated aqueous $Na_2S_2O_3$ (30 mL) and saturated aqueous $NaHCO_3$ (30 mL) at 0 °C. The aqueous layer was extracted with ether (3 x 50 mL) and the combined extracts were washed with brine (50 mL), dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo*. The residue was subjected to flash chromatography, eluting with 90:10 hexane-ether to afford **15** (4.00 g, 8.12 mmol, 2 steps 83% yield based on **12**) as a yellow oil.

(TLC R_f 0.57, 5:1 hexane-ethyl acetate): $[\alpha]^{29.7}_D$ = -56.8° (*c* 1.0, $CHCl_3$); IR (neat) 3314, 2912, 1459, 1425, 1367 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.82 (1H, dd, *J* = 5.3, 7.6 Hz), 5.80 (1H, d, *J* = 7.6 Hz), 4.69 (1H, dt, *J* = 5.3 , 7.6 Hz), 2.59 (2H, s), 2.57 (1H, dd, *J* = 9.6, 16.5 Hz), 1.84 (1H, ddt, *J* = 2.6, 7.6, 16.5 Hz), 0.97, 0.94 (18H, 2t, *J* = 7.9, 8.2 Hz, $MeCH_2Si$), 0.61, 0.60 (12H, 2q, *J* = 7.9, 8.2 Hz, CH_2Si); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 137.1, 136.4, 91.6, 84.6, 74.9, 69.1, 49.8, 35.3, 6.9, 6.8, 4.8.

(2*R*,4*S*)-2-(1-Iodopropenyl)-2,4-ditriethylsilyloxy)-1,5-cyclopentene (16).

To a stirred solution of cyclohexene (3.5 mL, 34.8 mmol) in dry ether (20 mL) was added $BH_3 \cdot SMe_2$ (1.8 mL, 17.4 mmol) at 0 °C under Ar. The reaction mixture was then warmed to room temperature. After 1 h, to the mixture was added a solution of alkynyl iodide **15** (2.86 g, 5.80 mmol) in ether (10 mL) at 0 °C. After 1 h, glacial acetic acid (4 mL) was added at 0 °C. After additional 30 min, the reaction mixture was partitioned between ether (20 mL) and saturated aqueous $NaHCO_3$ (40 mL) at 0 °C. The aqueous layer was extracted with ether (3 x 40 mL) and the combined extracts were washed with brine (40 mL), dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo*. The residue was subjected to flash chromatography, eluting with 98:2 hexane-ether to afford **16** (2.36 g, 4.76 mmol, 82%) as a yellow oil.

(TLC R_f 0.51, 5:1 hexane-ethyl acetate): $[\alpha]^{30.5}_D$ = -37.0° (*c* 1.0, $CHCl_3$); IR (neat) 2912, 1459, 1415, 1367 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 6.26 (1H, dt, *J* = 6.3, 12.9 Hz), 6.24 (1H, d, *J* = 12.9 Hz), 5.77 (1H, dt, *J* = 5.6, 7.3 Hz), 5.77 (1H, d, *J* = 7.3 Hz), 4.63 (1H, ddd, *J* = 1.3, 5.3, 5.6 Hz), 2.45 (1H, dd, *J* = 6.9, 13.2 Hz), 2.36 (1H, d, *J* = 6.3 Hz), 2.26 (1H, dd, *J* = 6.3, 14.5 Hz), 1.75 (1H, dd, *J* = 5.3, 13.2 Hz), 0.96, 0.94 (18H, 2t, *J* = 7.9, 8.3 Hz, Me), 0.60 (12H, q, *J* = 8.3 Hz, CH_2Si); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 138.3, 137.8, 135.5, 84.4, 84.2, 74.6, 49.2, 47.9, 7.0, 6.8, 6.5, 4.8.

(4*R*)-4-Hydroxy-4-(1-iodopropenyl)-2,3-cyclopenten-1-one (9).

To a stirred solution of iodide **16** (2.36 g, 4.77 mmol) in methanol (30 mL) was added (1*S*)-(+)-10-camphorsulfonic acid (30.0 mg, 0.13 mmol) at 0 °C. After being stirred for 2 h at the same temperature, the reaction mixture was neutralized with triethylamine (20 µL). The solvent was removed *in vacuo*. The residue was used for the next reaction without further purification.

To a stirred solution of the residue in dry dichloromethane (60 mL) was added MnO_2 (4.10 g, 47.7 mmol) at room temperature under Ar. After being stirred for 14 h at the same temperature, the reaction mixture was filtered through Celite. After the removal of the solvent, the residue was subjected to flash chromatography, eluting with 70:30 hexane-ethyl acetate to afford **9** (948.4 mg, 3.59 mmol, 2 steps 75% yield based on **16**) as a yellow syrup.

(TLC R_f 0.34, 1:1 hexane-ethyl acetate): $[\alpha]^{31.3}_D$ = -74.4° (*c* 0.50, $CHCl_3$); IR (neat) 3356, 2926, 1716, 1609, 1590 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.45 (1H, d, *J* = 5.6 Hz), 6.53 (1H, dt, *J* = 1.3, 7.3 Hz), 6.28 (1H, dt, *J* = 6.9, 7.3 Hz), 6.17 (1H, d, *J* = 5.6 Hz), 2.65 (2H, dd, *J* = 1.3, 6.9 Hz), 2.54 (2H, dd AB syst, *J* = 18.5 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 164.5, 134.9, 134.1, 87.3, 78.6, 48.6, 45.1; HRMS (ESI-TOF) *m/z* calcd for $[C_8H_9IO_2]^+Na$, 264.9726; found, 264.9726.

Solid-phase synthesis of clavulones 21.

Loading of (4*R*)-hydroxy-4-(1-iodopropenyl)-2,3-cyclopenten-1-one (9)

The Quest 210 was fit with 2 mL reaction vessel which was then charged with approximately 3,4-dihydro-2*H*-pyran-2-ylmethoxymethyl polystyrene (150 mg, 0.980 mmol/g, 0.147 mmol). To the reaction vessel was added a solution of (4*R*)-hydroxy-4-(1-iodopropenyl)-2,3-cyclopeten-1-one (**9**) (240 mg, 0.975 mmol, azeotropically dried with toluene) in dry dichloromethane (2.0 mL) via cannula and pyridinium *p*-toluenesulfornate (20 mg) at room temperature under Ar. The mixture was heated to 42 °C. After being agitated (1.8 s stroke, 45% upward) for 20 h while shielded from light, the reaction mixture was drained. The beads were washed with dichloromethane (3 x 2 mL), 1:1 tetrahydrofuran/water (3 x 2 mL), methanol (3 x 2 mL), tetrahydrofuran (3 x 2 mL), dichloromethane (3 x 2 mL), and dried *in vacuo* to afford solid-supported cyclopentenone **8** (181.4 mg). The resin was monitored by IR analysis: 1724 cm^{-1} (enone).

The resin was treated with a solution of trifluoroacetic acid (0.1 mL) in dichloromethane (2 mL) for 30 min at room temperature. The reaction mixture was filtered and rinsed with dry dichloromethane (3 x 3 mL). The filtrate was concentrated and azeotroped three times with toluene to give (4*R*)-hydroxy-4-(1-iodopropenyl)-2,3-cyclopenten-1-one (**9**) as a colorless syrup (27.9 mg, 0.106 mmol, 2 steps 72% yield based on 3,4-dihydro-2*H*-pyran-2-ylmethoxymethyl polystyrene).

Suzuki-Miyaura coupling to provide (4*R*)-4-hydroxy-4-(2-octenyl)-2,3-cyclopenten-1-one (18).

To a stirred solution of 1-pentene (0.13 mL, 1.21 mmol) in dry tetrahydrofuran (2.5 mL) was added 9-BBN dimmer (147.6 mg, 1.21 mmol) at 0 °C under Ar. The reaction mixture was stirred for 6 h at room temperature. The Quest 210 was fit with 2 mL reaction vessel which was then charged with vinyl iodide resin **6** (165.1 mg) and $Pd(PPh_3)_4$ (30.6 mg, 0.0265 mmol) and purged with Ar for 30 min. Then to the reaction vessel was added the boron solution via cannula, and a degassed sodium carbonate solution (0.50 mL, 2.0 M in water) at room temperature and the mixture was heated to 45 °C. The reaction mixture turned red. After being agitated (1.8 s stroke, 45% upward) for 16 h while shielded from light, the reaction mixture was drained. The beads were washed with DMF (3 x 2 mL), 1:1 DMF/water (3 x 2 mL), DMF (3 x 2 mL), tetrahydrofuran (3 x 2 mL), 5% glacial acetic

acid/tetrahydrofuran (3 x 2 mL), tetrahydrofuran (3 x 2 mL) and dried *in vacuo* to afford resin **17** (172.1 mg).

The resin was treated with a solution of trifluoroacetic acid (0.1 mL) in dichloromethane (2 mL) for 30 min at room temperature. The reaction mixture was filtered and rinsed with dry dichloromethane (3 x 3 mL). The filtrate was concentrated and azeotroped three times with toluene to give a crude enone as a yellow oil. The crude enone was subjected to flash chromatography, eluting with 90:10 hexane-ethyl acetate to afford **18** (17.2 mg, 0.0827 mmol, 2 steps 78% yield based on resin **8**) as a yellow oil:

(TLC R_f 0.47, 1:1 hexane-ethyl acetate); $[\alpha]^{28.9}_{D}$ -84.6° (*c* 0.68, $CHCl_3$); IR (neat) 3440, 2928, 1714 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.42 (1H, d, *J* = 5.6 Hz), 6.15 (1H, d, *J* = 5.6 Hz), 5.69 (1H, dt, *J* = 7.3, 10.9 Hz), 5.39 (1H, dt, *J* = 7.6, 10.9 Hz), 2.57 (2H, d, *J* = 7.6 Hz), 2.51 (2H, dd AB syst, *J* = 11.3 Hz), 2.07 (2H, dt , *J* = 6.9, 7.3 Hz), 1.39-1.26 (6H, m), 0.89 (3H, t , *J* = 6.9 Hz); ^{13}C NMR (67.8 MHz, CDCl3) δ 206.5, 165.2, 135.9, 133.7, 121.9, 78.8, 48.6, 38.0, 31.5, 29.1, 27.4, 22.5, 14.0; HRMS (ESI-TOF) *m/z* calcd for $[C_{13}H_{20}O_2]^+Na$, 231.1361; found, 231.1359.

Typical procedure of solid-phase synthesis of clavulones 21 from 17.

4-Deacetoxyclavulone II (21a).

To a suspension of the resin **17** (100.5 mg) in dry tetrahydrofuran (1.5 mL) in a 5 mL of syringe-shaped vessel (Varian Reservoirs) was added potassium bis(trimethylsilyl)amide (0.30 mL, 0.50 M in toluene, 0.149 mmol) at -78 °C under Ar and the reaction mixture turned orange. After 40 min, to the mixture was added a solution of aldehyde **11a** (80 mg, 0.512 mmol) in dry tetrahydrofuran (0.5 mL) via cannula at -78 °C. After being shakened for 1.5 h, the reaction mixture was drained and the beads were washed with 1:1 tetrahydrofuran/cool saturated aqueous NH_4Cl (3 x 2 mL), methanol (3 x 2 mL), tetrahydrofuran (3 x 2 mL), dichloromethane (3 x 2 mL), ether (3 x 2 mL) and dried *in vacuo* to afford resin (113.5 mg).

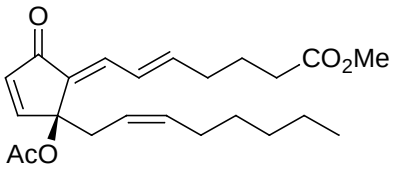
The resin was treated with a solution of trifluoroacetic acid (0.1 mL) in dichloromethane (2 mL) for 30 min at room temperature. The reaction mixture was filtered and rinsed with dry dichloromethane (3 x 3 mL). The filtrate was concentrated and azeotroped three times with toluene to give a crude 12-hydroxyl clavulones as a yellow oil. The crude 12-hydroxyl clavulones was used for the next reaction without further purification.

To a stirred solution of the crude 12-hydroxyl clavulones in dry pyridine (1.3 mL) was added acetic anhydride (8 µL, 0.0808 mmol) and a catalytic amount of 4-dimethylaminopyridine (1 mg) at 0 °C under Ar. After being stirred for 2 h at room temperature, the reaction mixture was partitioned between ether (10 mL) and saturated aqueous NH_4Cl (20 mL) at 0 °C. The aqueous layer was extracted with ether (3 x 20 mL) and the combined extracts were washed with 1 N HCl (20 mL), saturated aqueous $NaHCO_3$ (20 mL), and brine (20 mL), dried over anhydrous Na_2SO_4, filtered and

evaporated *in vacuo*. The residue was subjected to flash chromatography, eluting with 70:30 hexane-ethyl acetate to afford *5E*-4-deacetoxyclavulone (**21a**) (9.5 mg, 0.0246 mmol, 3 steps 52% yield based on resin **17**) as a pale yellow oil.

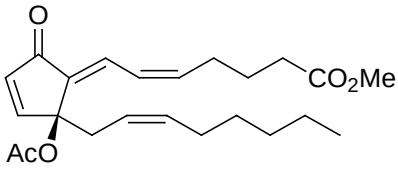
4-Deacetoxyclavulone II (21a)

(TLC R_f 0.33, 2:1 hexane-ethyl acetate); IR (neat) 2927, 2856, 1739, 1704, 1636, 1368, 1230 cm-1; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.47 (1H, d, *J* = 5.9 Hz, H-11), 6.92 (1H, d, *J* = 11.9 Hz, H-7), 6.54 (1H, dd, *J* = 11.9, 15.2 Hz, H-6), 6.40 (1H, d, *J* = 5.9 Hz, H-10), 6.21 (1H, dt, *J* = 6.9, 15.2 Hz, H-5), 5.51 (1H, dt, *J* = 8.7, 10.4 Hz, H-15), 5.17 (1H, dt, *J* = 7.7, 10.4 Hz, H-14), 3.67 (3H, s, MeO_2C), 2.96 (1H, dd, *J* = 7.7, 14.3 Hz, H-13), 2.69 (1H, dd, *J* = 7.8, 14.3 Hz, H-13), 2.39-2.26 (2H, m, H-4), 2.04 (3H, s, Ac), 1.95 (2H, dt, *J* = 6.9, 8.7 Hz, H-16), 1.80 (2H, tt, *J* = 7.1, 7.8 Hz, H-3), 1.40-1.15 (6H, m, H-17,18,19), 0.88 (3H, t , *J* = 7.2 Hz, H-20); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 193.8, 173.5, 169.5, 157.4, 146.4, 135.3, 134.8, 133.9, 125.3, 121.3, 85.5, 51.8, 35.6, 33.2, 32.7, 31.5, 23.8, 22.5, 15.3; HRMS (ESI-TOF) m/z calcd for $[C_{25}H_{34}O_7]$+Na, 411.2142; found, 411.2143.



4-Deacetoxyclavulone I (21b).

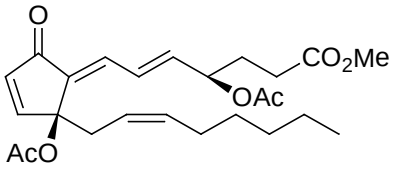
(TLC R_f 0.33, 2:1 hexane-ethyl acetate); IR (neat) 2927, 2856, 1739, 1698, 1635, 1232 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.49 (1H, d, *J* = 6.3 Hz, H-11), 6.53 (1H, d, *J* = 11.2 Hz, H-7), 6.51 (1H, dd, *J* = 10.9, 11.2 Hz, H-6), 6.35 (1H, d, *J* = 6.3 Hz, H-10), 6.10 (1H, dt, *J* = 7.3, 10.9 Hz, H-5), 5.52 (1H, dt, *J* = 8.7, 10.4 Hz, H-15), 5.20 (1H, dt, *J* = 7.7, 10.4 Hz, H-14), 3.67 (3H, s, MeO2C), 2.91 (1H, dd, *J* = 7.7, 14.2 Hz, H-13), 2.69 (1H, dd, *J* = 7.8, 14.2 Hz, H-13), 2.44-2.22 (2H, m, H-4), 2.35 (2H, t , *J* = 7.9 Hz, H-2), 2.02 (3H, s, Ac), 1.94 (2H, dt, *J* = 6.9, 8.7 Hz, H-16), 1.79 (2H, tt, *J* = 7.3, 7.9 Hz, H-3), 1.34-1.20 (6H, m, H-17,18,19), 0.88 (3H, t , *J* = 7.2 Hz, H-20); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 194.4, 173.9, 169.9, 155.8, 145.1, 137.0, 135.4, 134.7, 133.3, 121.6, 85.7, 51.6, 35.7, 33.5, 32.5, 31.6, 30.4, 29.2, 24.2, 22.6, 21.8, 14.1; ; HRMS (ESI-TOF) m/z calcd for $[C_{25}H_{34}O_7]$+Na, 411.2142; found, 411.2143



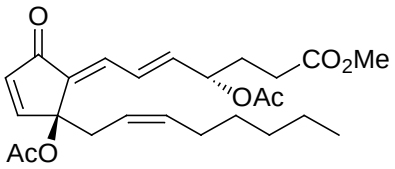
***5E*-Clavulones 21c : clavulone II (3) and 4-epi-clavulone II**

The diastereoisomers of the products **21c** were separated by HPLC (Lichrosorb Si60-5, 7.5x300 mm, eluted with 22% ethyl acetate in hexane, 3.00 mL/min). The first eluent (Rt = 13-14 min) was clavulone II and the second (Rt = 14-15 min) was 4-*epi*-clavulone II

clavulone II (**3**) (colorless oil; TLC R_f 0.55, 1:1 hexane-ethyl acetate); $[\alpha]^{23.5}_{D}$ +16.4° (*c* 0.05, $CHCl_3$); IR (neat) 2924, 2853, 1740, 1705, 1645, 1234 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47 (1H, d, *J* = 5.8 Hz, H-11), 6.87 (1H, d, *J* = 12.1 Hz, H-7), 6.75 (1H, dd, *J* = 12.1, 15.0 Hz, H-6), 6.41 (1H, d, *J* = 5.8 Hz, H-10), 6.02 (1H, dd, *J* = 7.2, 15.0 Hz, H-5), 5.52 (1H, dt, *J* = 7.2, 10.6 Hz, H-15), 5.41 (1H, dt, *J* = 6.3, 7.2 Hz, H-4), 5.19 (1H, dt, *J* = 8.2, 10.6 Hz, H-14), 3.68 (3H, s, MeO_2C), 2.88 (1H, dd, *J* = 7.2, 14.0 Hz, H-13), 2.68 (1H, dd, *J* = 8.2, 14.0 Hz, H-13), 2.38 (2H, t , *J* = 7.2 Hz, H-2), 2.07, 2.06 (6H, 2s, Ac), 2.02 (2H, dt , *J* = 6.3, 7.2 Hz, H-3), 1.94 (2H, dt , *J* = 6.8, 7.2 Hz, H-16), 1.34-1.20 (6H, m, H-17,18,19), 0.88 (3H, t , *J* = 6.8 Hz, H-20); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.4, 172.9, 169.9, 169.5, 158.1, 141.2, 136.9, 135.0x2, 129.3, 126.9, 121.0, 85.1, 76.1, 51.8, 36.0, 31.5, 29.7, 29.5, 29.0, 27.4, 22.5, 21.2, 21.0, 14.1; HRMS (ESI-TOF) *m/z* calcd for $[C_{25}H_{34}O_7]^+Na$, 469.2222; found, 469.2223.

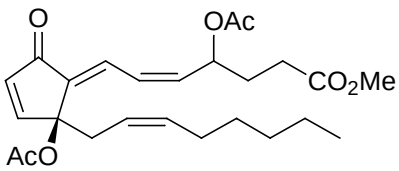


4-*epi*-clavulone II (4-*epi*-**3**) (colorless oil; TLC R_f 0.55, 1:1 hexane-ethyl acetate); IR (neat) 2924, 2852, 1740, 1703, 1642, 1230 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.48 (1H, d, *J* = 6.3 Hz, H-11), 6.88 (1H, d, *J* = 11.9 Hz, H-7), 6.72 (1H, ddd, *J* = 0.7, 11.9, 15.2 Hz, H-6), 6.41 (1H, d, *J* = 6.3 Hz, H-10), 6.07 (1H, dd, *J* = 6.6, 15.2 Hz, H-5), 5.52 (1H, dt, *J* = 7.6, 10.9 Hz, H-15), 5.43 (1H, dt, *J* = 5.9, 6.6 Hz, H-4), 5.18 (1H, dt, *J* = 7.6, 10.9 Hz, H-14), 3.67 (3H, s, MeO2C), 2.98 (1H, dd, *J* = 7.6, 14.2 Hz, H-13), 2.70 (1H, dd, *J* = 7.3, 14.2 Hz, H-13), 2.37 (2H, t , *J* = 7.6 Hz, H-2), 2.06-2.03 (2H, m, H-3), 2.09, 2.03 (6H, 2s, Ac), 1.94 (2H, dt , *J* = 6.9, 7.6 Hz, H-16), 1.34-1.20 (6H, m, H-17,18,19), 0.88 (3H, t , *J* = 6.8 Hz, H-20); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 193.4, 172.9, 169.9, 169.2, 157.9, 141.3, 136.6, 135.0 x 2, 130.0, 126.5, 121.0, 85.3, 76.2, 51.8, 36.0, 31.5, 29.7, 29.5, 29.0, 27.4, 22.5, 21.2, 21.0, 14.1; HRMS (ESI-TOF) *m/z* calcd for $[C_{25}H_{34}O_7]^+Na$, 469.22022; found, 469.22021.



***5Z*-Clavulones 21d.**

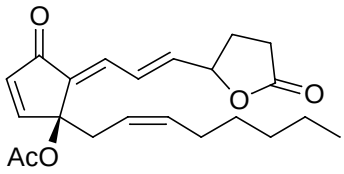
(TLC R_f 0.57, 1:1 hexane-ethyl acetate); diasteromixture; IR (neat) 2956, 1732, 1701, 1633, 1232 cm^{-1}; ^1H H NMR (270 MHz, $CDCl_3$) δ 7.47 (1H, d, *J* = 6.3 Hz, H-11), 7.25 (1H, d, *J* = 12.5 Hz, H-7), 6.62 (1H, dd, *J* = 10.0, 12.5 Hz, H-6), 6.59 (1H, dd, *J* = 10.0, 12.5 Hz, H-6), 6.43 (1H, d, *J* = 6.3 Hz, H-10), 6.42 (1H, d, *J* = 6.3 Hz, H-10), 5.88-5.77 (1H, m, H-5), 5.53-5.12 (3H, m, H-4,14,15), 3.69 (3H, s, MeO_2C), 2.97 (1H, dd, *J* = 7.1, 14.5 Hz, H-13), 2.96 (1H, dd, *J* = 7.1, 14.5 Hz, H-13), 2.66 (1H, dd, *J* = 7.1, 14.5 Hz, H-13), 2.65 (1H, dd, *J* = 7.1, 14.5 Hz, H-13), 2.38 (2H, t , *J* = 7.7 Hz, H-2), 2.09-1.94 (4H, m, H-3,16), 2.06, 2.05, 2.03 (9H, 3s, Ac), 1.39-1.18 (6H, m, H-17,18,19), 0.88 (3H, t , *J* = 6.7 Hz, H-20); HRMS



(ESI-TOF) *m/z* calcd for $[C_{25}H_{34}O_7]^+Na$, 469.22022; found, 469.22025.

***5E*-Clavulolactones 21e.**

(TLC R_f 0.59, 1:1 hexane-ethyl acetate); IR (neat) 2927, 2856, 1779, 1745, 1704, 1645, 1461, 1370, 1230, 759 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.50 (1H, d, *J* = 5.9 Hz, H-11),7.49 (1H, d, *J* = 6.3 Hz, H-11), 6.96 (1H, d, *J* = 13.5 Hz, H-7), 6.92 (1H, d, *J* = 13.5 Hz, H-7), 6.84 (1H, dd, *J* = 13.5, 14.5 Hz, H-6), 6.83 (1H, dd, *J* = 13.5, 14.5 Hz, H-6) 6.59 (1H, dd, *J* = 10.0, 12.5 Hz, H-6), 6.42 (1H, d, *J* = 5.9 Hz, H-10), 6.42 (1H, d, *J* = 6.3 Hz, H-10), 6.18 (1H, dd, *J* = 5.3, 14.5, Hz, H-5), 6.17 (1H, dd, *J* = 5.2, 14.5, Hz, H-5), 5.56-5.47 (1H, m, H-15), 5.22-5.00 (2H, m, H-4, 14), 2.95-2.87 (1H, m, H-13), 2.78-2.66 (1H, m, H-13), 2.59-2.46 (2H, m, H-2), 2.05 (3H, s, Ac), 2.03 (3H, s, Ac), 2.00-1.90 (4H, m, H-3,16), 1.39-1.18 (6H, m, H-17,18,19), 0.88 (3H, t , *J* = 6.7 Hz, H-20); HRMS (ESI-TOF) *m/z* calcd for $[C_{25}H_{34}O_7]^+Na$, 395.1829; found, 395.1830.



5Z-**Clavulolactones 21f**

(TLC R_f 0.59, 1:1 hexane-ethyl acetate); diasteromixture; IR (neat) 2926, 2856, 1778, 1742, 1699, 1644, 1621, 1461, 1369, 848 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.52 (1H, d, *J* = 6.3 Hz, H-11), 7.49 (1H, d, *J* = 5.9 Hz, H-11), 7.25 (1H, d, *J* = 12.5 Hz, H-7), 6.84 (1H, dd, *J* = 11.2, 15.5 Hz, H-6), 6.83 (1H, dd, *J* = 11.2, 15.5 Hz, H-6), 6.55 (1H, d, *J* = 15.5 Hz, H-7), 6.54 (1H, d, *J* = 15.5 Hz, H-7), 6.38 (1H, d, *J* = 6.3 Hz, H-10), 6.09 (1H, dd, *J* = 8.3, 11.2 Hz, H-5), 6.10 (1H, dd, *J* = 8.3, 11.2 Hz, H-5), 5.59-5.49 (1H, m, H-15), 5.26-5.06 (2H, m, H-4, 14), 2.88-2.80 (1H, m, H-13), 2.69-2.61 (1H, m, H-13), 2.59-2.41 (2H, m, H-2), 2.04 (3H, s, Ac), 2.03 (3H, s, Ac), 2.00-1.90 (4H, m, H-3,16), 1.42-1.20 (6H, m, H-17,18,19), 0.88 (3H, t , *J* = 6.7 Hz, H-20); HRMS (ESI-TOF) *m/z* calcd for $[C_{25}H_{34}O_7]^+Na$, 395.1829; found, 395.1830.