Synthesis of 10-Halogenated Clavulone Derivatives

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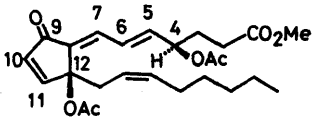
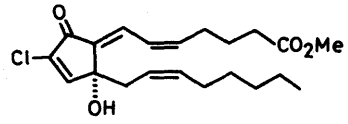
Epoxidation of clavulone II (1) with *tert*-butyl hydroperoxide gave stereoselectively the epoxide 2. Reaction of 2 with lithium chloride gave effectively the 10-chlorinated clavulone derivative 3a. The brominated derivative 3b and iodinated derivative 3c were also synthesized from 2. The 10-fluorinated derivative 3d was synthesized by the reaction of 2 with potassium hydrogen difluoride.

Keywords marine prostanoid; 10-halogenated clavulone derivative; clavulone II; 10,11-epoxyclavulone II; lithium halide; potassium hydrogen difluoride; CD

Coral-derived marine prostanoids, clavulones[1] and their congeners, have recently attracted much interest because of their unique structural features and strong antileukemic activities. The 10-halogenated congeners, chlorovulones,[2] bromovulone I,[3] iodovulone I,[3] and punaglandins,[4] show particularly strong antileukemic activities[2a,3,4a,5] as compared with clavulones.[5] Furthermore these halogenated prostanoids are also of interest owing to the difference in the configuration of the oxygen function at C-12 from that of clavulones. These findings prompted us to synthesize 10-halogenated derivatives of clavulones and to examine the



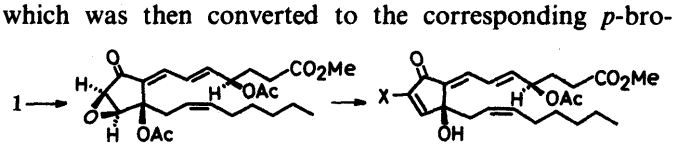
1 clavulone II



chlorovulone I

biological activity of these derivatives. Fortunately clavulones are abundant in the soft coral *Clavularia viridis* (about 0.4% yield based on the freeze-dried organisms) and total syntheses of clavulones have already been accomplished,[6] so we used clavulones as a starting material for the synthesis of 10-halogenated derivatives. This paper describes the synthesis of the 10-halogenated clavulone derivatives **3a**—**d** from clavulone II (**1**).[7]

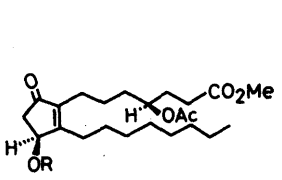
The synthesis of **3a**—**d** from **1** was done *via* the epoxide **2**. Treatment of **1** in benzene with excess *tert*-butyl hydroperoxide[8] (3 M in toluene solution) in the presence of 0.5 eq of Triton B (40% methanol solution) at 0 °C gave stereoselectively the epoxide **2** in 53% yield. The stereochemistry of the epoxide moiety in **2** was established by the circular dichroism (CD) measurement of **5**, which was derived from **2** *via* the following reactions. Hydrogenation of **2** over 10% palladium on carbon in ethyl acetate at room temperature gave the allylic alcohol **4**, which was then converted to the corresponding *p*-bromobenzoate **5** by treatment with *p*-bromobenzoyl chloride in 1,2-dichloroethane in the presence of pyridine and *N*,*N*-dimethylaminopyridine at 50 °C. The CD spectrum (EtOH) of **5** showed a negative Cotton effect at 240 nm ($\Delta\varepsilon -7.0$) caused by the interaction between the conjugated enone and *p*-bromobenzoyloxy groups.[9] A similar negative Cotton effect [245 nm ($\Delta\varepsilon -4.5$)] was also observed in the CD spectrum of **7**, prepared from (*S*)-hydroxycyclopentenone (**6**).[10] These CD data clearly indicated the 11*S* configuration in both **4** and **5**, and thus the stereochemistry of the epoxide moiety in **2** was elucidated as depicted.



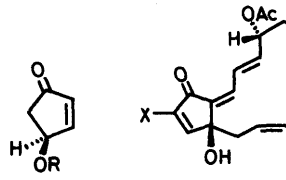
2

3a : X=Cl
3b : X=Br
3c : X=I
3d : X=F

Chart 1



4 : R=H
5 : R=C(=O)-C6H4-Br



6 : R=H
7 : R=C(=O)-C6H4-Br

8a : X=Cl
8b : X=Br

The epoxide **2** was then converted to the 10-halogenated derivatives **3a**—**c** by the reaction of **2** with hydrohalogenic acids or lithium halides. Treatment of **2** in methanol with concentrated hydrochloric acid at room temperature gave the 10-chlorinated derivative **3a** and its 7*Z* isomer **8a** in 21% yield in a ratio of 2:1. The 7*Z* isomer **8a** may be formed by acid-catalyzed isomerization[1] of **3a**. The presence of the chlorine atom at C-10 in **3a** was shown by the similarity of the proton chemical shifts of the protons at C-7 and -11 in the proton nuclear magnetic resonance (^{1}H-NMR) spectrum [δ_{ppm} 7.00 (1H, d, J=11.9 Hz, H-7), 7.23 (1H, s, H-11)] to those of chlorovulone II.[2a] Similar reaction of **2** with concentrated hydrobromic acid gave the 10-brominated derivative **3b** [δ_{ppm} 7.00 (1H, dd, J=0.6, 11.8 Hz, H-7), 7.43 (1H, d, J=0.6 Hz, H-11)] and its 7*Z* isomer **8b** in 32% yield in a ratio of 1:1. However, in the case of the reaction of **2** with hydriodic acid and hydrofluoric acid, a good result was not obtained. In the former case a complex mixture containing a trace amount of the 10-iodinated derivative **3c** was formed, while in the latter case the reaction did not proceed.

The improved synthesis of **3a**—**c** from **2** was effected by using lithium halides instead of hydrohalogenic acids. Treatment of **2** in *N*,*N*-dimethylformamide (DMF) with excess anhydrous lithium chloride at room temperature gave **3a** in 60% yield. The formation of the 7*Z* isomer **8a**

was decreased in this reaction (5% yield). Similar reaction of **2** with anhydrous lithium bromide gave **3b** in 47% yield, and the reaction of **2** with anhydrous lithium iodide gave **3c** [δ_{ppm} 6.99 (1H, br d, J=11.7 Hz, H-7), 7.70 (1H, d, J=0.5 Hz, H-11)] in 51% yield. The fluorinated derivative **3d**, however, was not obtained under these conditions using lithium fluoride, but the epoxide **2** was recovered.

The 10-fluorinated derivative **3d** was successfully synthesized by reacting **2** with potassium hydrogen difluoride.[11] Treatment of **2** in ethylene glycol with excess potassium hydrogen difluoride at 100 °C gave **3d** in 51% yield. The 7*Z* isomer of **3d** was not detected in this reaction. The following NMR data of **3d** indicated the presence of the fluorine atom at C-10 in **3d**: fluorine-19 nuclear magnetic resonance (^{19}F-NMR) spectrum (benzotrifluoride as an internal standard) δ_{ppm} −72.3 (br s), ^{1}H-NMR δ_{ppm} 6.62 (1H, br s, H-11), carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectrum δ_{ppm} 160.5 (d, J=293 Hz, C-10), 185.5 (d, J=21 Hz, C-9).

The formation of the 10-halogenated derivatives **3a**—**d** having a hydroxy group at C-12 in the reaction of **2** with lithium halide or potassium hydrogen difluoride can be explained by the reaction pathway shown in Chart 2, which involves a neighboring participation of the acetoxyl group at C-12. The attack of the halide ion on the epoxide, which is activated by lithium ion or proton, and the subsequent acetyl migration from the C-12 oxygen to the C-11 oxygen gives the intermediate B *via* A. Then the *β*-elimination of the acetoxyl group in B takes place *via* the corresponding enolate anion C to give rise to the 10-halogenated cyclopentenone **3** with the hydroxy group at C-12.

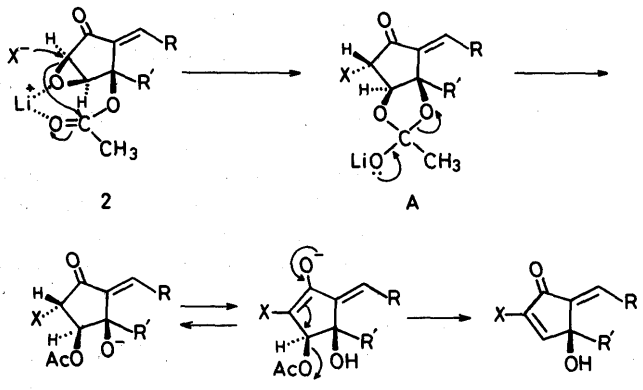


Chart 2

The antiproliferative and cytotoxic activities of the 10-halogenated derivatives thus obtained against HL-60 leukemia cells have been measured. The fluorinated derivative **3d** and chlorinated derivative **3a** showed stronger activities than those of clavulones and other synthetic halogenated derivatives. The details have been presented in a separate paper.[12]

Experimental

Melting points were measured on a Kofler block and are uncorrected. Optical rotations were measured with a JASCO DIP-360 automatic polarimeter. Infrared (IR) spectra were recorded with a Hitachi 215 spectrometer, and ultraviolet (UV) spectra with a Hitachi 124 spectrometer. ^{1}H- and ^{13}C-NMR spectra were recorded with a Bruker AM-400 (400 MHz for ^{1}H and 100 MHz for ^{13}C) spectrometer. Chemical shifts are given on a δ (ppm) scale with tetramethylsilane (TMS) as an internal standard (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad). The ^{19}F-NMR spectrum was obtained with a Varian EM-360 (54.6 MHz) spectrometer. Chemical shifts are given on a δ (ppm) scale with benzotrifluoride (BTF) as an internal standard. Mass spectra (MS) were taken with a Hitachi M-80 spectrometer. CD spectra were taken with a JASCO J-500 spectropolarimeter. Column chromatography was carried out on Merck Silica gel 60 (70—230 mesh), and preparative thin layer chromatography (PTLC) was carried out on Silica gel F_{254} TLC plates. High-pressure liquid chromatography (HPLC) was conducted with an HPLC-8502 (YMC) apparatus using a YMC-Pack A-043 S-5 column (silica gel).

Epoxidation of Clavulone II (1) with *tert*-Butyl Hydroperoxide A solution (0.83 ml) of *tert*-butyl hydroperoxide in toluene (3 M) was added to a solution of **1** (74 mg) in benzene (5 ml) at 0 °C, and then Triton B (benzyltrimethylammonium hydroxide) in methanol (40%, 0.0144 ml) was added. The reaction mixture was stirred at 0 °C for 90 min, and then diluted with ether. The solution was washed successively with water and saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on a silica gel column to give **2** (40 mg) together with the starting material (14 mg).

(10*R*,11*S*)-10,11-Epoxyclavulone II (**2**): Pale yellow oil. $[\alpha]_D$ +13.4° (c=6.0, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1730, 1720, 1705. UV λ_{max}^{EtOH} nm (ε): 285 (15000). ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=7.2 Hz), 2.06 (3H, s), 2.18 (3H, s), 2.37 (2H, t, J=7.5 Hz), 2.82 (1H, br dd, J=8.0, 14.0 Hz), 3.14 (1H, br dd, J=8.0, 14.0 Hz), 3.59 (1H, d, J=2.5 Hz), 3.68 (3H, s), 4.56 (1H, d, J=2.5 Hz), 5.19 (1H, m), 5.43 (1H, br q, J=6.6 Hz), 5.51 (1H, m), 6.07 (1H, dd, J=6.6, 15.2 Hz), 6.83 (1H, dd, J=11.9, 15.2 Hz), 7.10 (1H, d, J=11.9 Hz). EIMS m/z: 402 (M^+ − AcOH). High-resolution MS Calcd for $C_{23}H_{30}O_6$ (M^+ − AcOH): 402.2034. Found: 402.2031.

Catalytic Hydrogenation of 2 A mixture of **2** (39 mg) in ethyl acetate (0.5 ml) and 10% palladium–carbon (3 mg) was stirred under a hydrogen atmosphere at room temperature for 1 h. The reaction mixture was diluted with ethyl acetate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by PTLC to give **4** (6.2 mg).

(4*S*)-2-[(4*S*)-4-Acetoxy-6-carbomethoxyhexyl]-4-hydroxy-3-octyl-2-cyclopenten-1-one (**4**): Colorless oil. $[\alpha]_D$ +6.0° (c=0.1, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 3459, 1739, 1706, 1642. UV λ_{max}^{EtOH} nm (ε): 234 (9300). ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, J=6.8 Hz), 2.07 (3H, s), 2.77 (2H, dd, J=6.3, 18.5 Hz), 3.69 (3H, s), 4.84 (2H, m). EIMS m/z: 410 (M^+). High-resolution MS Calcd for $C_{23}H_{38}O_6$ (M^+): 410.2666. Found: 410.2676.

***p*-Bromobenzoylation of 4** *p*-Bromobenzoyl chloride (18 mg) was added to a solution of **4** (3.4 mg) in 1,2-dichloroethane (0.6 ml) and pyridine (0.15 ml), and the mixture was stirred at 50 °C for 9 h. The reaction mixture was diluted with ether, washed with water and then saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by PTLC to give **5** (4.3 mg).

(4*S*)-2-[(4*S*)-4-Acetoxy-6-carbomethoxyhexyl]-4-(*p*-bromobenzoyloxy)-3-octyl-2-cyclopenten-1-one (**5**): Colorless crystals. mp 115 °C. $[\alpha]_D$ −15.4° (c=0.13, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1728, 1718. UV λ_{max}^{EtOH} nm (ε): 242 (13200). CD λ_{max}^{EtOH} nm ($\Delta\varepsilon$): 240 (−7.0). ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, J=6.8 Hz), 2.09 (3H, s), 2.93 (1H, d, J=6.4 Hz), 2.96 (1H, d, J=6.4 Hz), 3.69 (3H, s), 4.93 (1H, tt, J=4.2, 8.4 Hz), 6.02 (1H, br d, J=4.8 Hz), 7.61 (2H, br d, J=8.5 Hz), 7.90 (2H, br d, J=8.5 Hz). EIMS m/z: 592, 594 (M^+, 1:1).

***p*-Bromobenzoylation of 6** *p*-Bromobenzoyl chloride (11 mg) was added to a solution of **6** (1 mg) in 1,2-dichloroethane (0.2 ml) and pyridine (0.2 ml), and the mixture was stirred at 50 °C for 2 h. The reaction mixture was diluted with ether, washed with water and then saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by PTLC to give **7** (2.5 mg).

(4*S*)-4-(*p*-Bromobenzoyloxy)-2-cyclopenten-1-one (**7**): Colorless crystals. mp 89 °C. $[\alpha]_D$ −167.7° (c=0.43, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730, 1720. UV λ_{max}^{EtOH} nm (ε): 245 (9700). CD λ_{max}^{EtOH} nm ($\Delta\varepsilon$): 245 (−4.5). ^{1}H-NMR ($CDCl_3$) δ: 2.48 (1H, dd, J=0.2, 18.7 Hz), 2.94 (1H, dd, J=6.4, 18.7 Hz), 6.10 (1H, m), 6.41 (1H, dd, J=1.0, 5.7 Hz), 7.60 (2H, m), 7.68 (1H, dd, J=2.4, 5.7 Hz), 7.89 (2H, m). EIMS m/z: 280, 282 (M^+, 1:1). High-resolution MS Calcd for $C_{12}H_9{}^{81}BrO_3$ (M^+): 281.9716. Found: 281.9720.

Reaction of 2 with Hydrochloric Acid Concentrated hydrochloric acid (35%, 0.1 ml) was added to a solution of **2** (17 mg) in methanol (0.5 ml), and the mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with ether, washed successively with saturated $NaHCO_3$ solution, water and saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to HPLC (hexane–ether, 2:1) to give **3a** (2.4 mg) and **8a** (1.2 mg)

in order of increasing polarity.

10-Chloro-12-*O*-desacetylclavulone II (**3a**): Pale yellow oil. $[\alpha]_D$ −15.2° (c=0.33, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 1740, 1710. UV λ_{max}^{EtOH} nm (ε): 230 (11700), 300 (11700). ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=7.2 Hz), 1.26 (6H, m), 1.96 (2H, m), 2.06 (2H, m), 2.17 (3H, s), 2.39 (2H, t, J=7.5 Hz), 2.66 (1H, ddd, J=0.5, 7.4, 14.0 Hz), 3.68 (3H, s), 5.23 (1H, ttd, J=0.5, 7.8, 11.0 Hz), 5.45 (1H, br q, J=7.1 Hz), 5.55 (1H, ttd, J=0.5, 7.5, 11.0 Hz), 6.14 (1H, dd, J=6.4, 14.3 Hz), 6.93 (1H, dd, J=0.9, 14.1 Hz), 7.00 (1H, d, J=11.9 Hz), 7.23 (1H, s). EIMS m/z: 438, 440 (M^+, 3:1), 378, 380 (M^+−AcOH, 3:1). High-resolution MS Calcd for $C_{21}H_{27}{}^{35}ClO_4$ (M^+−AcOH): 378.1595. Found: 378.1555.

10-Chloro-12-*O*-desacetylclavulone III (**8a**): Pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, J=6.7 Hz), 2.12 (3H, s), 2.39 (2H, t, J=7.5 Hz), 2.54 (1H, br dd, J=7.3, 14.6 Hz), 2.67 (1H, dd, J=8.1, 14.6 Hz), 3.68 (3H, s), 5.31 (1H, m), 5.46 (1H, br q, J=5.7 Hz), 5.60 (1H, m), 6.11 (1H, dd, J=5.7, 15.3 Hz), 6.67 (1H, d, J=11.4 Hz), 7.31 (1H, s), 7.68 (1H, ddd, J=1.3, 11.4, 15.3 Hz).

Reaction of 2 with Lithium Chloride Anhydrous lithium chloride (10 mg) was added to a solution of **2** (5 mg) in dry DMF (0.4 ml), and the mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with ether, washed with water and then saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to HPLC (hexane–ether, 2:1) to give **3a** (2.9 mg) and **8a** (0.2 mg).

Reaction of 2 with Hydrobromic Acid Concentrated hydrobromic acid (48%, 0.03 ml) was added to a solution of **2** (9 mg) in methanol (0.5 ml), and the mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with ether, washed successively with saturated $NaHCO_3$ solution, water, and saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by PTLC (benzene–AcOEt, 5:1) to give **3b** (1.6 mg) and **8b** (1.6 mg).

10-Bromo-12-*O*-desacetylclavulone II (**3b**): Pale yellow oil. IR ν_{max}^{film} cm^{-1}: 3468, 1740, 1641. UV λ_{max}^{EtOH} nm (ε): 235 (12100), 304 (10800). ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=7.5 Hz), 1.30 (6H, m), 1.96 (2H, m), 2.03 (2H, m), 2.09 (3H, s), 2.38 (2H, t, J=8.4 Hz), 2.67 (1H, ddd, J=0.5, 8.0, 14.4 Hz), 3.68 (3H, s), 5.23 (1H, ttd, J=0.5, 7.6, 11.0 Hz), 6.14 (1H, dd, J=6.3, 14.5 Hz), 6.93 (1H, m), 7.00 (1H, dd, J=0.6, 11.8 Hz), 7.43 (1H, d, J=0.6 Hz). EIMS m/z: 482, 484 (M^+, 1:1), 422, 424 (M^+−AcOH, 1:1). High-resolution MS Calcd for $C_{21}H_{27}{}^{79}BrO_4$ (M^+−AcOH): 422.1092. Found: 422.1102.

10-Bromo-12-*O*-desacetylclavulone III (**8b**): Pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, J=7.5 Hz), 2.12 (3H, s), 2.39 (2H, t, J=7.6 Hz), 2.53 (1H, ddd, J=0.5, 8.0, 14.2 Hz), 2.66 (1H, ddd, J=0.5, 8.5, 14.2 Hz), 3.68 (3H, s), 5.31 (1H, ttd, J=0.5, 7.7, 10.9 Hz), 5.45 (1H, m), 5.60 (1H, ttd, J=0.5, 7.4, 10.9 Hz), 6.11 (1H, ddd, J=0.5, 5.5, 15.5 Hz), 6.66 (1H, d, J=11.4 Hz), 7.39 (1H, s), 7.69 (1H, ddd, J=1.4, 7.5, 11.4 Hz).

Reaction of 2 with Lithium Bromide Anhydrous lithium bromide (19 mg) was added to a solution of **2** (5 mg) in dry DMF (0.5 ml), and the mixture was stirred at room temperature for 6 h. The reaction mixture was diluted with ether, washed with water and then saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by PTLC to give **3b** (2.5 mg) and **8b** (0.5 mg).

Reaction of 2 with Lithium Iodide Anhydrous lithium iodide (29 mg) was added to a solution of **2** (5 mg) in dry DMF (0.5 mg), and the mixture was stirred at room temperature for 10 h. The reaction mixture was diluted with ether, washed with water and then saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by PTLC (benzene–AcOEt, 5:1) to give **3c** (3.0 mg) and its 7*Z* isomer (0.5 mg, not characterized).

12-*O*-Desacetyl-10-iodoclavulone II (**3c**): Pale yellow oil. $[\alpha]_D$ −17.4° (c=0.09, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3456, 1740, 1707. UV λ_{max}^{EtOH} (ε): 235 (12100), 300 (11800). ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.9 Hz), 2.08 (3H, s), 2.38 (2H, t, J=7.5 Hz), 2.61 (1H, dd, J=8.4, 15.1 Hz), 2.73 (1H, dd, J=8.1, 15.1 Hz), 3.67 (3H, s), 5.21 (1H, m), 5.44 (1H, br q, J=6.1 Hz), 5.54 (1H, m), 6.13 (1H, dd, J=6.4, 14.3 Hz), 6.93 (1H, ddd, J=1.2, 11.7, 14.3 Hz), 6.99 (1H, br d, J=11.7 Hz), 7.70 (1H, d, J=0.5 Hz). EIMS m/z: 530 (M^+), 470 (M^+−AcOH). High-resolution MS Calcd for $C_{21}H_{27}IO_4$ (M^+−AcOH): 470.0953. Found: 470.0937.

Reaction of 2 with Potassium Hydrogen Difluoride Potassium hydrogen difluoride (164 mg) was added to a solution of **2** (96 mg) in ethylene glycol (6 ml), and the mixture was stirred at 100 °C for 2 h. The reaction mixture was diluted with ether, washed successively with water, saturated $NaHCO_3$ solution, and saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane–AcOEt, 2:1) to give **3d** (45 mg).

12-*O*-Desacetyl-10-fluoroclavulone II (**3d**): Colorless oil. $[\alpha]_D$ −35.4° (c=1.56, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3300, 1730, 1710. UV λ_{max}^{EtOH} nm (ε): 225 (20000), 303 (25300). ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=7.5 Hz), 2.04 (2H, m), 2.08 (3H, s), 2.38 (2H, t, J=7.5 Hz), 2.64 (1H, dd, J=7.8, 14.3 Hz), 2.76 (1H, dd, J=7.5, 14.3 Hz), 3.69 (3H, s), 5.24 (1H, m), 5.43 (1H, br q, J=6.4 Hz), 5.55 (1H, m), 6.12 (1H, dd, J=6.4, 14.5 Hz), 6.62 (1H, br s), 6.93 (2H, m). ^{19}F-NMR ($CDCl_3$) δ: −72.3 (br s). ^{13}C-NMR ($CDCl_3$) δ: 160.5 (d, J=293 Hz, C-10), 185.5 (d, J=21 Hz, C-7). CIMS (NH_3) m/z: 440 (M^++H+NH_3), 363 (M^++H−AcOH). High-resolution MS Calcd for $C_{21}H_{27}FO_4$ (M^+−AcOH): 362.1891. Found: 362.1903.

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