Thermal Reactions of Clavulones Leading to a Novel Prostanoid with a 10-Acetoxy-11-ene Structure

Kazuo IGUCHI,* Soichiro KANETA and Yasuji YAMADA*

Tokyo College of Pharmacy, Horinouchi, Hachioji, Tokyo 192–03, Japan. *Received October 22, 1991*

Thermal reactions of clavulones, I, II, and III gave a novel prostanoid with a 10-acetoxy-11-ene system through a [3,3]-sigmatropic rearrangement of allylic acetate.

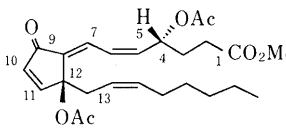
Keywords marine prostanoid; clavulone; thermal reaction; [3,3]-sigmatropic rearrangement; exciton chirality rule; CD

Clavulones are members of a new class of antitumor marine prostanoids abundant in the Okinawan soft coral *Clavularia viridis*.[1] Their structures are characterized by the presence of a unique cross-conjugated system and oxygen functions at the C-4 and -12 positions. These structural features prompted us to investigate thermal reactions of clavulones. Here we wish to describe the thermal reactions of clavulones leading to the formation of a novel prostanoid with a 10-acetoxy-11-ene system.

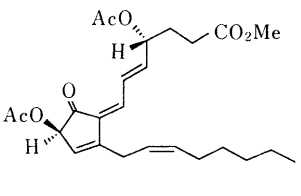
Clavulone I (**1**) was heated at 190 °C in *o*-dichlorobenzene to give compound **4** in 40% yield as the only isolable product.[2] A similar reaction of clavulone II (**2**) (5*E*-isomer of **1**) and clavulone III (**3**) (5*E*,7*Z*-isomer of **1**) also gave the same compound **4** in 40% and 45% yields, respectively.[3] The structure of **4** having the molecular formula $C_{25}H_{34}O_7$, the same as those of **1**, **2** and **3**, was determined based on the results of spectroscopic analysis. The proton nuclear magnetic resonance (^{1}H-NMR) signals due to protons on the α- and ω-side chains of **4**, except the C-13 proton signal, were similar to those of clavulone III (**3**). However, the signals due to protons at C-10 [δ 6.09 (1H, br s)], C-11 [δ 5.50 (1H, quintet, J=2.3 Hz)], and C-13 [δ 3.02 (2H, br d, J=6.9 Hz)] were different from those of **3**, demonstrating an acetoxyl group at C-10 and a bis-allylic methylene group at C-13 in **4**. A conjugated triene system was demonstrated by characteristic ultraviolet (UV) absorptions (265, 275, 285 nm) in **5**[4] obtained by the sodium borohydride reduction of **4** (methanol, 0 °C, 94% yield). The stereochemistry of the acetoxyl group at C-10 in **4** was determined by circular dichroism (CD) measurement of the *p*-bromobenzoate **7** obtained from **5** by a three-step procedure; 1) protection of the hydroxy group at C-9 as a methoxymethyl group (85% yield), 2) treatment with potassium carbonate in methanol to give **6** (28% yield), and 3) *p*-bromobenzoylation with *p*-boromobenzoyl chloride (55% yield). The CD spectrum (EtOH) of **7** indicated a negative Cotton effect at 270 nm ($\Delta\varepsilon$ −3.5) and a positive Cotton effect at 240 nm ($\Delta\varepsilon$ +3.0). There is thus negative chirality between two chromophores (*p*-bromobenzoyloxy group at C-10 and conjugated triene group)[5] and this is consistent with the β-configuration of the *p*-bromobenzoyl group in **7**.

The β-configuration of the acetoxyl group at C-10 in **4** indicated that the acetoxyl group at C-12 in clavulones rearranged stereospecifically to C-10 in the thermal reaction. This stereospecific rearrangement can be interpreted in terms of [3,3]-sigmatropic rearrangement[6,7] of the allylic acetoxyl group from C-12 to C-10 in clavulones. The exclusive formation of **4** with a 5*E*,7*Z*-diene system from both clavulone I (**1**) with a 5*Z*,7*E*-diene and clavulone II (**2**) with a 5*E*,7*E*-diene is explicable by thermal isomerization of the diene of the initially formed rearranged compound with the 5*Z*,7*E*-diene and 5*E*,7*E*-diene, respectively. This isomerization could release a steric repulsion between the α- and ω-side chains in initially formed compounds.

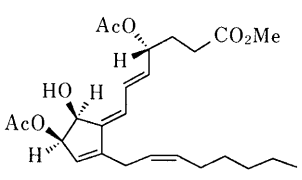
Biological activity of **4** and related compounds obtained in this study is currently being investigated.



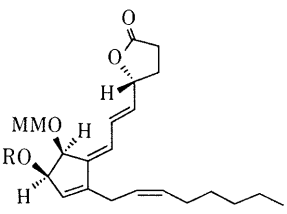
clavulone I (**1**)
clavulone II (5*E*, 7*E*) (**2**)
clavulone III (5*E*, 7*Z*) (**3**)



4



5



6 : R=H
7 : R=CO-(C$_6$H$_4$)-Br

Experimental

Melting points were measured on a Kofler block and are uncorrected. Infrared (IR) spectra were recorded with a Perkin-Elmer FT-IR 1710 spectrophotometer and UV spectra with a Hitachi 124 spectrophotometer. ^{1}H-NMR spectra were recorded with a Bruker AM-400 spectrometer (400 MHz). Chemical shifts are given on a δ (ppm) scale with tetramethylsilane as an internal standard (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad). Electron-impact mass spectra (EIMS) were taken with a Hitachi M-80 spectrometer. Column chromatography was carried out on Fuji Davison Silica gel BW-820MH (70—200 mesh).

Thermal Reaction of Clavulones A solution of clavulone I (**1**) (120 mg) in *o*-dichlorobenzene (30 ml) in a sealed tube was stirred at 190 °C for 6 h. The reaction mixture was concentrated under reduced pressure. The residue was chromatographed on a silica gel column (hexane : ethyl acetate = 2 : 1 as an eluent) to give **4** (48 mg) as a pale yellow oil. IR (film) cm^{-1}: 1741, 1602, 1230. UV (EtOH) nm (ε): 260 (9800), 315 (11600). ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, J=7.0 Hz, H-20), 2.05 (2H, m, H-16), 2.10 (3H, s, OAc), 2.12 (3H, s, OAc), 3.68 (3H, s, OCH_3), 5.45 (2H, m, H-4, -14), 5.62 (1H, m, H-15), 6.01 (1H, m, H-5), 6.35 (1H, br d, J=11.5 Hz, H-7), 7.65 (1H, tdd, J=1.5, 11.5, 15.3 Hz, H-6). EIMS m/z: 446 (M^+), 386 (M^+ − AcOH). High-resolution MS calculated for $C_{25}H_{34}O_7$ (M^+): 446.2302. Found: 446.2276.

Similar reactions of clavulone II (**2**) and clavulone III (**3**) also gave **4** in 40% and 45% yields, respectively.

Conversion of 4 into the *p*-Bromobenzoate 7 Sodium borohydride

© 1992 Pharmaceutical Society of Japan

NII-Electronic Library Service

(4 mg) was added to a solution of **4** (50 mg) in methanol (2 ml) and the mixture was stirred at 0 °C for 10 min. Saturated NH_4Cl solution (1 ml) was added to the solution, and the mixture was stirred for 5 min and concentrated under reduced pressure. The residue was extracted with ether and the ethereal solution was washed with water and saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated to give **5** (47 mg).

Diisopropylamine (52 μl) and chloromethyl methyl ether (15 μl) were added to a solution of **5** (47 mg) in 1,2-dichloroethane (1.5 ml). The mixture was stirred at 50 °C for 2 h. Saturated $NaHCO_3$ solution was added and then the mixture was stirred for 5 min. The reaction mixture was extracted with ether and the ethereal solution was washed with water and saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give the methoxymethyl ether (42 mg).

K_2CO_3 (20 mg) was added to a solution of methoxymethyl ether (42 mg) in methanol (2 ml), and the mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with ether, and then washed successively with saturated NH_4Cl, water and saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on a silica gel column (hexane : ethyl acetate = 1 : 1 as an eluent) to give the lactone **6** (10 mg).

A mixture of **6** (10 mg), 1,2-dichloroethane (0.4 ml), pyridine (0.1 ml) and *p*-bromobenzoyl chloride (15.7 mg) was stirred at 50 °C for 4 h. The reaction mixture was concentrated under reduced pressure, and then the residue was chromatographed on a silica gel column (hexane : ethyl acetate = 5 : 2 as an eluent) to give **7** (8 mg) as colorless crystals (mp 136 °C). UV (EtOH) nm (ε): 250 (14000), 263 (11600), 275 (11200), 286 (8300). ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, t, J = 7.1 Hz, H-20), 3.29 (3H, s, OCH_3), 4.48 (1H, d, J = 6.7 Hz, OCH_2OCH_3), 4.65 (1H, d, J = 6.7 Hz, OCH_2OCH_3), 4.79 (1H, m, H-9), 4.91 (1H, br q, J = 7.2 Hz, H-4), 5.48 (1H, m, H-14), 5.58 (1H, m, H-15), 5.78 (1H, dd, J = 7.2, 15.4 Hz, H-5), 5.98 (1H, br s, H-11), 6.11 (1H, dd, J = 0.7, 5.8 Hz, H-10), 6.20 (1H, br d, J = 11.4 Hz, H-7), 6.54 (1H, dd, J = 11.4, 15.4 Hz, H-6), 7.68 (2H, d, J = 8.6 Hz, aromatic H), 7.99 (2H, d, J = 8.6 Hz, aromatic H).

References and Notes

1) Isolation and structures; H. Kikuchi, Y. Tsukitani, K. Iguchi and Y. Yamada, *Tetrahedron Lett.*, **23**, 5171 (1982); *idem*, *ibid.*, **24**, 1549 (1983). Total synthesis; H. Nagaoka, T. Miyakoshi and Y. Yamada, *ibid.*, **25**, 3621 (1984). Biological activity; A. Honda, Y. Yamamoto, Y. Mori, Y. Yamada and H. Kikuchi, *Biochem. Biophys. Res. Commun.*, **130**, 515 (1985). See also the reports on claviridenones: M. Kobayashi, T. Yasuzawa, M. Yoshihara, H. Akutsu, Y. Kyogoku and I. Kitagawa, *Tetrahedron Lett.*, **23**, 5331 (1982); I. Kitagawa, M. Kobayashi, T. Yasuzawa, B. W. Son, M. Yoshihara and Y. Kyogoku, *Tetrahedron*, **41**, 995 (1985).
2) The formation of highly polar products was observed in this reaction, but none of these products was isolable.
3) The reaction of clavulone III proceeded about three times faster than those of clavulones I and II.
4) The hydroxy group at C-9 in **5** is suggested to have a β-configuration, since hydride anion is expected to attack the carbonyl group at C-9 from the less-hindered side.
5) N. Harada, J. Iwabuchi, Y. Yokota, H. Uda and K. Nakanishi, *J. Am. Chem. Soc.*, **103**, 5590 (1981).
6) R. P. Lutz, *Chem. Rev.*, **84**, 205 (1984).
7) E. S. Lewis and J. T. Hill, *J. Am. Chem. Soc.*, **91**, 7458 (1969).

NII-Electronic Library Service