

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 C₂₅H₃₄O₇, the same as those of **1**, **2** and **3**, was determined based on the results of spectroscopic analysis. The proton nuclear magnetic resonance (¹H-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, brs)], C-11 [δ 5.50 (1H, quintet, *J* = 2.3 Hz)], and C-13 [δ 3.02 (2H, brd, *J* = 6.9 Hz)] were different from those of **3**, demonstrating an acetoxy 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 acetoxy 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*-bromobenzylation with *p*-bromobenzoyl chloride (55% yield). The CD spectrum (EtOH) of **7** indicated a negative Cotton effect at 270 nm ($\Delta\epsilon$ -3.5) and a positive Cotton effect at 240 nm ($\Delta\epsilon$ +3.0). There is thus negative chirality between two chromophores (*p*-bromobenzyloxy 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 acetoxy group at C-10 in **4** indicated that the acetoxy 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 acetoxy 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.

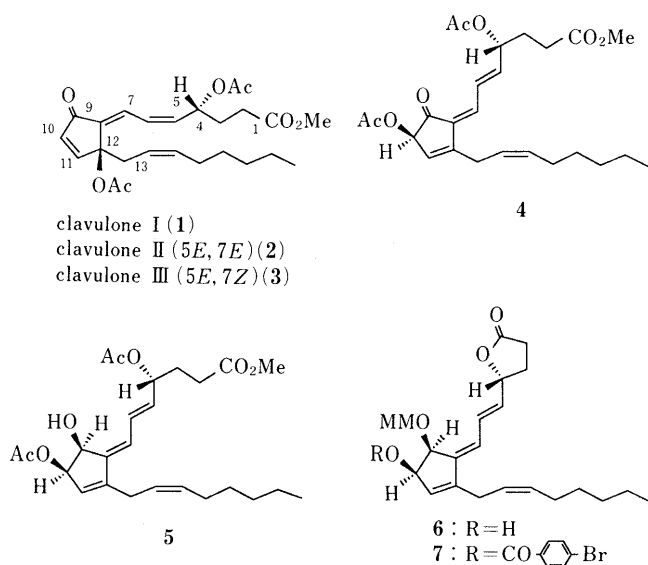
Experimental

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. ¹H-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). ¹H-NMR (CDCl₃) 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, OCH₃), 5.45 (2H, m, H-4, -14), 5.62 (1H, m, H-15), 6.01 (1H, m, H-5), 6.35 (1H, brd, *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 C₂₅H₃₄O₇ (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



(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). $^1\text{H-NMR}$ (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).