

## TOTAL SYNTHESIS OF CLAVULONES<sup>1</sup>

Masakatsu Shibasaki\* and Yuji Ogawa

Sagami Chemical Research Center, Nishi-Onnuma, Sagamihara, Kanagawa 229, Japan

*Summary:* Total synthesis of clavulones in naturally occurring form has been accomplished by the aldol coupling of the hydroxy-cyclopentenone **2** efficiently obtainable from 1,2-bis-trimethylsilyloxycyclopentene (**4**) by using 1,3-hydroxy transposition via the allylic methanesulfonate **11** and the  $\alpha,\beta$ -unsaturated aldehyde **3**.

Clavulones, novel marine prostanoids from *Clavularia viridis* (Quoy and Gaimard)<sup>2</sup>, have attracted interest of synthetic chemists because of their unique structures and their strong antitumor and antiinflammatory activities. Recently Corey has reported the first synthesis of clavulones in racemic form<sup>3</sup> and Yamada in optically active form.<sup>4</sup> We herein wish to report an efficient total synthesis of clavulones in naturally occurring form, which involves the completely different tactics for the construction of the hydroxy-cyclopentenone **2** from those already reported.<sup>3,4</sup>

As shown in Scheme I we planned to construct the clavulone skeleton by aldol condensation of the hydroxy-cyclopentenone **2** and the  $\alpha,\beta$ -unsaturated aldehyde **3**, which was expected to proceed smoothly for the relative slowness of cyclopentadienone-forming eliminations.

The requisite hydroxy-cyclopentenone **2** was efficiently synthesized in the reaction sequence described in Scheme II. The dilithium 1,2-enediolate **5** derived from 1,2-bis-trimethylsilyloxycyclopentene (**4**) was coupled with 1-bromo-2-octyne<sup>5</sup> according to Wakamatsu's method<sup>6</sup> with minor modification (solvent; DME/ether/HMPA = ca. 5/5/1, -25 °C), giving the hydroxy-ketone **6** contaminated with the chromatographically inseparable dialkylated by-product. Subsequently the mixture of the products underwent hydrogenation (Lindlar catalyst, 1 atm of H<sub>2</sub>, hexane, 25 °C, 3 hr) followed by silica gel column chromatography to afford pure **7** in 66% overall yield from **4**. Compound **7** was then converted to the silyl enol ether **8** with 3 equiv of TMS-triflate in the presence of 2,6-lutidine or triethylamine,<sup>8</sup> which was immediately treated with Pd(OAc)<sub>2</sub> in CH<sub>3</sub>CN<sup>9</sup> to give the enone **9** in 60~63% yield from **7**. Transformation of **9** into the allylic alcohol **12** including 1,3-transposition of oxygen



functionality is the most important part of this synthesis.<sup>10</sup> We anticipated that in the hydrolysis of the allylic methanesulfonate 11 the attack of water molecule would occur predominantly at the  $\gamma$ -position of the allylic methanesulfonate functionality because of steric influence of two substituents. This anticipation turned out to be true. Reduction of 9 with  $\text{NaBH}_4$  in the presence of  $\text{CeCl}_3$ <sup>11</sup> in MeOH (0 °C) afforded the allylic alcohols 10<sup>7</sup> as a diastereomeric mixture (ca. 9 : 1),<sup>12,13</sup> which was subjected to mesylation with 2 equiv of methanesulfonic anhydride,<sup>14</sup> 10 equiv of pyridine and a catalytic amount of 4-dimethylaminopyridine in  $\text{CH}_2\text{Cl}_2$  (0 °C, 0.5 hr). The reaction mixture was filtered through a column packed with  $\text{MgSO}_4$  to remove the insoluble salts. To this filtered solution was added aqueous acetone (acetone/water = 3/1), and the resulting solution was stirred at room temperature for 0.5 hr. Under these conditions the allylic methanesulfonate 11 was completely hydrolyzed. In order to hydrolyze excess methanesulfonic anhydride, after addition of sat.  $\text{NaHCO}_3$  aq., the solution was stirred vigorously at room temperature for an additional 4 hr. The product was isolated by extractive workup and silica gel column chromatography to afford a diastereomeric mixture of the allylic alcohols 12<sup>7,12</sup> in a ratio of ca. 1 : 1 (79% yield from 10) with a small amount of 10 (<10%). Collins oxidation of 12 (r.t., 5-10 min) followed by deprotection of the TMS ether ( $\text{AcOH}/\text{THF}/\text{H}_2\text{O} = 8/8/1$ , r.t., 12 hr) provided the enone 2<sup>7</sup> in quantitative yield.

Aldol condensation of 2 with the optically active  $\alpha,\beta$ -unsaturated aldehyde 3 and subsequent acetylation according to Yamada's procedure<sup>4</sup> completed the synthesis. Clavulone II (less polar, silica gel,  $\text{AcOEt}/n$ -hexane = 1/3) and 12-epi-clavulone II (more polar) thus obtained could be separated chromatographically. Synthetic clavulone II is indistinguishable spectroscopically from naturally obtained clavulone II.<sup>2,15</sup>

On the basis of the arguments presented above, it is concluded that 1,2-bis-trimethylsilyloxycyclopentene (4) is a reasonable starting material for the synthesis of a family of novel marine prostanoids (eicosanoids).

#### References and Notes

- 1) This paper is dedicated to Professor Shun-ichi Yamada on the occasion of his 70th birthday.
- 2) a. H. Kikuchi, Y. Tsukitani, K. Iguchi, and Y. Yamada, *Tetrahedron Lett.*, 23, 5171 (1982); b. H. Kikuchi, Y. Tsukitani, K. Iguchi, and Y. Yamada, *Tetrahedron Lett.*, 24, 1549 (1983); c. K. Iguchi, Y. Yamada, H. Kikuchi, and Y. Tsukitani, *Tetrahedron Lett.*, 24, 4433 (1983); d. M. Kobayashi, T. Yasuzawa, M. Yoshihara, H. Akutsu, Y. Kyogoku, and I. Kitagawa, *Tetrahedron Lett.*, 23, 5331 (1982); e. M. Kobayashi, T. Yasuzawa, B.W. Son, Y. Kyogoku, and I. Kitagawa, *Chem. Pharm. Bull.*, 31, 1440 (1983).

- 3) E.J. Corey and M.M. Mehrotra, J. Am. Chem. Soc., 106, 3384 (1984).
- 4) H. Nagaoka, T. Miyakoshi, and Y. Yamada, Tetrahedron Lett., 25, 3621 (1984).
- 5) Hydrogenation of 1-hydroxy-2-octyne using Lindlar catalyst provided a mixture of 1-hydroxy-2-Z-octene and 1-hydroxy-2-E-octene in a ratio of ca. 93 : 7. However, in contrast to this result, hydrogenation of 6 using Lindlar catalyst resulted in the stereospecific formation of the Z-olefin 7 (purity >99.5% by 400MHz <sup>1</sup>NMR analysis). Accordingly 1-bromo-2-octyne instead of 1-bromo-2-Z-octene was utilized for this coupling reaction.
- 6) T. Wakamatsu, K. Hashimoto, M. Ogura, and Y. Ban, Synthetic Commun., 8, 319 (1978).
- 7) Satisfactory spectroscopic data were obtained for each synthetic intermediate.
- 8) a. G. Simchen and W. Kober, Synthesis, 259 (1976); b. G. Simchen, Synthesis, 867 (1977).
- 9) Y. Ito, H. Hirao, and T. Saegusa, J. Org. Chem., 43, 1011 (1978).
- 10) Wharton reaction of the corresponding  $\alpha,\beta$ -epoxy ketone gave the unsatisfactory result.
- 11) A.L. Gemal and J.-L. Luche, J. Am. Chem. Soc., 103, 5454 (1981).
- 12) Stereochemistry of the both diastereomers has not been determined.
- 13) Reduction of 9 with DIBAL in toluene gave a large amount of the 1,4-reduction product.
- 14) Use of methanesulfonyl chloride instead of methanesulfonic anhydride provided a large amount of the allylic chlorides.
- 15) Since isomerization of clavulone II (1) to clavulone I, III and IV is already known,<sup>2</sup> the present synthesis of 1 means the formal total synthesis of clavulone I, III and IV.

(Received in Japan 14 May 1985)