Total Synthesis of (±)-Clavulones

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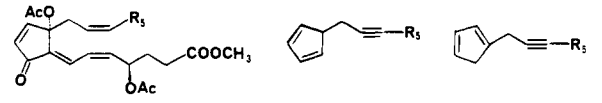
Recently a family of novel marine eicosanoids isolated from *Clavularia viridis* (Quoy and Gaimard), clavulones I, II, and III, has been reported by a Japanese group.[1] Clavulone I is represented by formula **1**, clavulone II is the 5,6-*E* isomer of **1** and, clavulone III is the 5,6-*E*, 7,8-*Z* isomer of **1**. These substances bear a superficial structural resemblance to prostaglandins and would appear also to be derived from arachidonic acid. We have proposed elsewhere[2] that the clavulones may be formed biosynthetically by an unusual nonstop pathway involving an unbroken series of 10 free radical intermediates. Our concern with the biogenetic questions has led us to study the synthesis of these interesting new substances, which are reported to have antiinflammatory and antitumor activity.[1,3] We report herein the first synthesis of the clavulones (racemic form). Clavulone I was chosen as the primary synthetic target since it can be isomerized to clavulones II and III by acid catalysis.[1] The synthetic plan called for the attachment of the ω- and α-carbon appendages (in that order) to a preformed five-membered ring originating from cyclopentadiene. It was designed to allow for the synthesis of chiral clavulones in a straightforward way.

Lithium cyclopentadienide was generated from cyclopentadiene and *n*-butyllithium in pentane–tetrahydrofuran (THF) (−78 to 0 °C over 1 h) and alkylated with 1.1 equiv of 1-iodo-2-octyne (−78 to −30 °C, 3 h), and the product was isolated by addition of saturated salt solution at −30 °C followed by drying and concentration of the organic layer at 0 °C. Proton magnetic resonance ^{1}H (NMR) analysis indicated the product (95% yield) to be > 90% of the cyclopentadiene **2**.[4] At 23 °C **2** underwent



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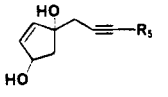

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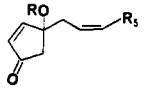
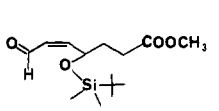


5 R = H
6 R = TBDMS



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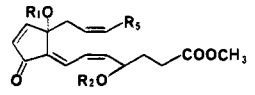

R_5 = n-C_5H_{11}

8 R_1 = R_2 = TBDMS

9 R_1 = Ac, R_2 = TBDMS

essentially complete 1,5-prototropic shift in 4 h to form the desired isomer **3** (purity >90% by ^{1}H NMR analysis). Photooxidation of **3** was carried out by bubbling oxygen through a methanolic solution containing Rose Bengal as sensitizer at −40 °C with irradiation by an external sunlamp. After 2 h the reaction mixture was treated with methanolic sodium borohydride to reduce endoperoxide, and the expected diol **4** was isolated (60% yield) by concentration of solvent and column chromatography. Oxidation of **4** (pyridinium dichromate[5] –methylene chloride, 4-Å molecular sieves, 23 °C, 2 h) afforded 96% yield of the γ-hydroxycyclopentenone, which was transformed by selective hydrogenation (1 atm H_2, 23 °C, 3 wt % Lindlar Pd–$CaCO_3$ catalyst, 9:1 ethyl acetate–pyridine) into the hydroxy dienone **5** (94%). Silylation of **5** gave the *tert*-butyldimethylsilyl (TBDMS) ether **6** (96% yield, 2 equiv of TBDMS triflate[6] –3.5 equiv 2,6-lutidine, methylene chloride, 0–23 °C, 2.5 h).

With the construction of **6**, the cyclopentenolone and ω-chain appendage were in place and only the attachment of the α-appendage was required to reach the clavulone system. This could be accomplished by use of a remarkable alkylation whose success evidently derives from the relative slowness of cyclopentadienone-forming eliminations. The enone **6** was added dropwise to 1 equiv of lithium diisopropylamide in THF at −78 °C, and after 5 min the resulting enolate was treated with 1 equiv of hexamethylphosphoramide and immediately thereafter with 1 equiv of ester aldehyde **7**.[7] The reaction mixture was allowed to warm from −78 to 10 °C over 6 h, and the product was isolated by extractive workup and silica gel column chromatography to afford **8** (84% yield) as a 1:1 mixture of two diastereomers, which were most readily separated after the next step. No 7,8-*Z* product could be detected by ^{1}H NMR analysis. Treatment of the mixture with 5 equiv of anhydrous tetra-*n*-butylammonium fluoride, 20 equiv of acetic anhydride, and 3 equiv of 4-dimethylaminopyridine at 0–23 °C for 30 min resulted in selective replacement of TBDMS by acetyl at the tertiary oxygen to give a mixture of two diastereomeric mono TBDMS ether–mono acetates **9**.[8] The diastereomers **9** were easily separated by column chromatography on silica gel (R_f values on silica gel TLC plates 0.48 and 0.37, using 6:4 ether–hexane). The less polar diastereomer (R_f 0.48) upon treatment with 5 equiv of tetra-*n*-butylammonium fluoride, 20 equiv of acetic anhydride, and 3 equiv of 4-dimethylaminopyridine at 45 °C for 6 h provided after extractive isolation and chromatography 60% yield of clavulone I (**1**) and 15% yield of clavulone II.[9,10] ^{1}H NMR, IR, UV, and mass spectra of synthetic and natural clavulones were identical, as were TLC and HPLC elution times.[11]

The three-component synthesis described herein is direct and efficient and illustrates useful methodology for the manipulation of cyclopentadiene and cyclopentenone intermediates. The synthesis of optically active clavulones using this approach is currently under study.[12]

Supplementary Material Available: Proton magnetic resonance, infrared, and mass spectral data for compounds **1–9** (2 pages). Ordering information is given on any current masthead page.

(1) (a) Kikuchi, H.; Tsukitani, Y.; Iguchi, K.; Yamada, Y. *Tetrahedron Lett.* **1982**, *23*, 5171; (b) *Ibid.* **1983**, *24*, 1549.

(2) (a) Corey, E. J. *Experientia* **1983**, *39*, 1084. (b) Corey, E. J.; Schmidt, G.; Shimoji, K. *Tetrahedron Lett* **1983**, *24*, 3169.

(3) Kobayashi, M.; Yasuzawa, T.; Yoshihara, M.; Son, B. W.; Lee, N. K.; Kitagawa, I.; Kido, M.; Kyogoku, Y. *Symp. Pap.-Symp. Chem. Nat. Prod., 26th* **1983**, 228–235.

(4) All reactions involving air-sensitive reactants or reagents were carried out under nitrogen or argon. Satisfactory spectroscopic data were obtained for each synthetic intermediate.

(5) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.

(6) Corey, E. J.; Cho, H.; Rücker, Ch.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455.

(7) The (±)-ester aldehyde **7** was prepared by the sequence (1) methyl 3-chloroformylpropionate → methyl 3-formylpropionate (H_2, 1 atm, 5% Pd–C, THF–2,6-lutidine, 25 °C, 2 h), (2) methyl 3-formylpropionate → methyl 4,7-dihydroxy-5-heptynoate 4-(*tert*-butyldimethylsilyl) ether (addition of (3-(trimethylsilyloxy)-1-propynyl)lithium in THF at 78 → −40 °C for 1 h followed by reaction with 2 equiv of *tert*-butyldimethylsilyl triflate at −78 to −40 °C for 2 h and trimethylsilyl cleavage with citric acid–methanol at 20 °C for 15 min, (3) reduction of C≡C to *Z* HC=CH (H_2, 1 atm, 5% Pd–$CaCO_3$, 95:5 ethyl acetate–pyridine at 23 °C for 2 h), and (4) oxidation of primary alcohol to aldehyde by 5 equiv of activated manganese dioxide in methylene chloride at 23 °C for 9 h. The average yield per step was 94%.

(8) The selectivity of this reaction for acetylation at tertiary oxygen in the presence of secondary oxygen is of considerable interest and is under further study. For earlier examples of silyl ether → acetate interconversion, see: Beaucage, S. L.; Ogilvie, K. K. *Tetrahedron Lett.* **1977**, 1691.

(9) The more polar diastereomer **9** upon more forcing desilylation–acetylation was converted to a diastereomer of clavulone I. At 45 °C fluoride ion promotes 5,6-*Z* → 5,6-*E* interconversion.

(10) The conversion of **9** to clavulone I (**1**) occurs without γ-lactone formation, a critical danger that was successfully avoided.

(11) We are indebted to Dr. Y. Yamada, University of Tokyo, for generously providing authentic samples of clavulones I, II, and III.

(12) This work was assisted financially by a grant from the National Institutes of Health.

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