CHEMISTRY LETTERS, pp. 1271-1272, 1983.

A SHORT-STEP SYNTHESIS OF ANTIBIOTIC A26771B UTILIZING THE RING-OPENING REACTION OF β-ETHYNYL-β-PROPIOLACTONE

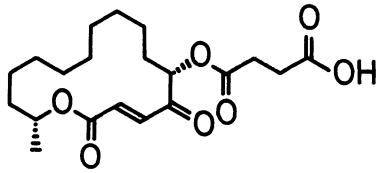
Tamotsu FUJISAWA,* Nobuki OKADA, Masashi TAKEUCHI, and Toshio SATO
Chemistry Department of Resources, Mie University, Tsu, Mie 514

The total synthesis of antibiotic A26771B was completed in short steps from 15-hydroxy-3,4-hexadecadienoic acid which was easily prepared by the ring-opening reaction of β-ethynyl-β-propiolactone with Grignard reagent in the presence of a copper(I) catalyst.

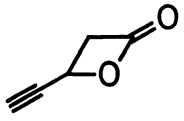
A 16-membered macrocyclic lactone antibiotic A26771B (1), isolated from *Penicillium turbatum*, possesses an interesting antibacterial activity.[1] Total synthesis and antibacterial activities of natural A26771B and all its isomers were recently reported.[2a] We disclose here a short-step synthesis of (±)-1 and its diastereomer utilizing the copper-catalyzed reaction of β-ethynyl-β-propiolactone (2) with Grignard reagent.[3]

The key steps of the present synthesis are five-carbon homologation by regioselective ring-opening of lactone 2 leading to 3,4-alkadienoic acid and selective introduction of oxygen functionalities into the 4 and 5 positions after lactonization. Lactone 2 was treated with the C_{11} chain unit of Grignard reagent 3[4] in THF and Me_2S (20:1) in the presence of 2 mol% copper(I) iodide at -78 °C for 1 h and then with HCl-methanol solution to give 15-hydroxy-3,4-hexadecadienoic acid (4).[5] 3,4-Dienoic acid 4 was converted into 2,4-dienoic acid (5)[5] in 85% overall yield from 2 by heating in 2 mol dm^{-3} KOH aq solution. For lactonization of 5, several reported procedures such as *N*-methylpyridinium salt,[6a] *N*,*N*,*N'*,*N'*-tetramethylchloroformamidinium salt,[6b] and diethyl diazocarboxylate-triphenylphosphine[6c] gave poor results (6-37% yields of the lactone). The mixed anhydride method using trichlorobenzoyl chloride[6d] was most effective to furnish a 96:4 mixture[5] of (2*E*,4*Z*)-lactone (6) and its (4*E*)-isomer in 91% yield.

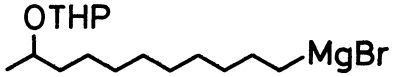
Introduction of oxygen functionalities at the 4 and 5 positions was achieved by treatment of 6 with *m*-chloroperbenzoic acid to give 4,5-epoxylactone (7)[5] in 91% yield. Hydrolysis of lactone 7 in 20% $HClO_4$ aq dioxane at room temperature gave a 1:1 mixture[7] of 4,5-dihydroxylactone (8) and its 15-epimer in 69% yield,



1



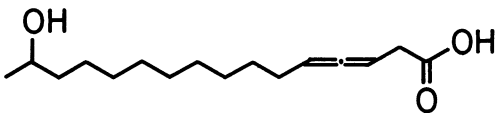
2



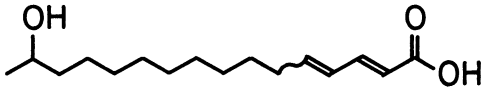
3

which was transformed into (±)-1 and its diastereomer by the reported procedure.[2a)]

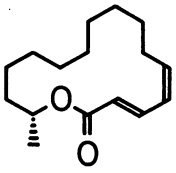
As mentioned above, the present method using 2,4-dienoic acid functionality, prepared easily by the ring-opening of lactone 2, provides an efficient tool for the synthesis of γ,δ-oxygenated α,β-unsaturated macrocyclic lactones without protecting the latter labile functionalities.



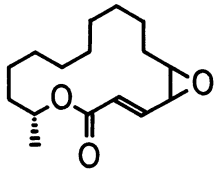
4



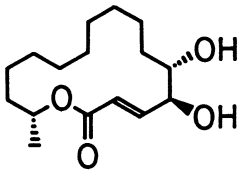
5



6



7



8

References

1) K. H. Michel, P. V. Demarco, and R. Nagarajan, *J. Antibiot.*, 30, 571 (1977).

2) a) K. Tatsuta, Y. Amemiya, Y. Kanemura, and M. Kinoshita, *Bull. Chem. Soc. Jpn.*, 55, 3248 (1982). For recent synthesis of (±)-A26771B see, b) B. M. Trost and S. J. Brickner, *J. Am. Chem. Soc.*, 105, 568 (1983) and c) M. Asaoka, M. Abe, T. Mukuta, and H. Takei, *Chem. Lett.*, 1982, 215.

3) T. Sato, M. Kawashima, and T. Fujisawa, *Tetrahedron Lett.*, 22, 2375 (1981).

4) T. A. Hase and E.-L. Nylund, *Tetrahedron Lett.*, 1979, 2633.

5) NMR data of intermediates are as follows. 4: δ 1.17 (3H, d, J = 6 Hz), 1.1-1.7 (16H, m), 1.75-2.21 (2H, m), 3.00 (2H, dd, J = 4 and 6 Hz), 3.52-4.14 (1H, m), 4.95-5.43 (2H, m), and 6.77 (s, 2H). 5: (mp 210 °C, 2*E*,4*Z*:2*E*,4*E* = 41:59), δ 1.18 (3H, d, J = 6 Hz), 1.1-1.8 (16H, m), 1.9-2.5 (2H, m), 3.50-4.05 (1H, m), 5.54-6.50 (3H, m), 6.87 (2H, s), and 7.10-7.93 (1H, m). 6 and its isomer: (2*E*, 4*Z*:2*E*,4*E* = 96:4),[8)] δ 1.10-2.00 (19H, m), 2.0-2.7 (2H, m), 4.6-5.1 (1H, m), 5.70 -6.40 (3H, m), and 7.60 (1H, dd, J = 10 and 16 Hz). 7: (mp 60 °C), δ 1.1-2.1 (21H, m), 3.0-3.4 (m, 1H), 3.55 (1H, dd, J = 4 and 7 Hz), 4.93-5.30 (1H, m), 6.10 (1H, d, J = 16 Hz), and 6.78 (1H, dd, J = 7 and 16 Hz). 8 and its epimer: δ 1.1-2.0 (21H, m), 3.17-3.83 (3H, m), 3.83-4.33 (1H, m), 4.77-5.23 (1H, m), 6.02 (0.5H, d, J = 16 Hz), 6.80 (0.5H, dd, J = 8 and 16 Hz), 6.09 (0.5H, d, J = 16 Hz), and 6.90 (0.5H, dd, J = 6 and 16 Hz).

6) a) T. Mukaiyama, M. Usui, and K. Saigo, *Chem. Lett.*, 1976, 49; b) T. Fujisawa, T. Mori, K. Fukumoto, and T. Sato, *ibid.*, 1982, 1891; c) T. Kurihara, Y. Nakajima, and O. Mitsunobu, *Tetrahedron Lett.*, 1976, 2455; d) J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, M. Yamaguchi, *Bull. Chem. Soc. Jpn.*, 52, 1989 (1979).

7) Isopropylidene derivatives of 8 and its 15-epimer were separated by silica-gel TLC and confirmed by NMR spectra.[2a)]

8) S. Tsuboi, T. Masuda, H. Makino, and A. Takeda, *Tetrahedron Lett.*, 23, 209 (1982).

(Received June 15, 1983)