Tetrahedron Letters, Vol.22, No.21, pp 2009 - 2012, 1981
Printed in Great Britain

0040-4039/81/212009-04$02.00/0

SYNTHETIC STUDIES ON BICYCLOMYCIN I

SYNTHESIS OF 1-ALLYL AND BENZOYL-8,10-DIMETHYL-6-METHOXY-5-METHYLENE-8,10-DIAZA-2-OXABICYCLO[4.2.2]DECANE-7,9-DIONE, WHICH HAVE THE BICYCLO RING SYSTEM FOUND IN ANTIBIOTIC BICYCLOMYCIN

Shin-ichi Nakatsuka*, Kumi Yoshida and Toshio Goto

Laboratory of Organic Chemistry, Faculty of Agriculture

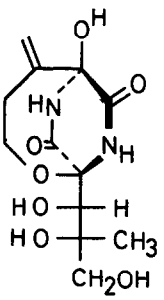
Nagoya University, Chikusa, Nagoya 464, Japan

Summary: Regiospecific cyclization of the alcohol 8 into the bicyclo[4.2.2] compound 12 was achieved via selective activation of the secondary methoxy group and subsequent acid treatment. A side-chain was introduced at the bridge-head position, thus making up the bicyclomycin skeleton.

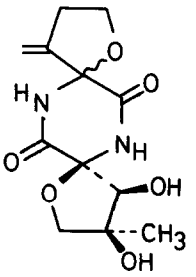
Bicyclomycin, which is produced by Streptomyces sapporonensis[1] and S. aizunensis,[2] possesses unique antibacterial activities.[3] Its structure has been elucidated by chemical[4a] and X-ray diffraction analyses.[4b,c] Its novel bicyclo[4.2.2] system containing oxidized diketopiperazine ring prompted us to initiate its synthetic studies. Although many chemical modifications[5] and synthetic approaches[4c,6] toward bicyclomycin had been studied recently, neither direct synthesis of the bicyclo ring system nor its reconstruction from degradation products of bicyclomycin were reported. Now, we report the first synthesis of the bicyclo ring system represented by formula 3.

Stereocontrolled condensation[7] of 3,6-dimethoxydiketopiperazine derivative 4 [oily isomer][7] with $PhCO_2(CH_2)_2COCH_3$ in the presence of 1.2 eq. of n-BuLi in THF at -78° C gave in 68 % yield the monoalkylated cis compound 5,[7,9] which is a 1:1 mixture of side chain stereoisomers. Treatment of 5 with thionyl chloride and pyridine at room temp gave the endo-olefin 6 [33%, oil, nmr ($CDCl_3$) 1.62 (3H, s), 6.24 (1H, t J=7 Hz)] and the exo-olefin 7 [40%, oil, nmr ($CDCl_3$) 5.33, 5.51 (each 1H, br.s)], which were separated easily by silica gel chromatography. Hydrolysis of the exo-olefin 7 with 1N NaOH in methanol at room temp afforded the alcohol 8 [95%, oil, no aromatic proton in nmr], which was employed for the following cyclization.

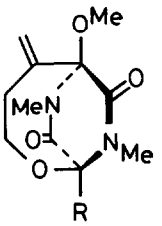
The Hoffmann-La Roche group[4c] showed that natural bicyclomycin is easily isomerized by acid treatment to the bis-spiro compound 2, which is thermodynamically more stable than the former; they stated that synthesis schemes for bicyclomycin should probably contrived in a way that circumvents the energy minimum represented by the bis-spiro compound. As acid catalyzed cyclization of the alcohol 8 was expected to produce the spiro compound 13, and it was indeed realized,[8] selective activation of the methoxy group at 6 position was achieved. Thus, the



bicyclomycin 1



2



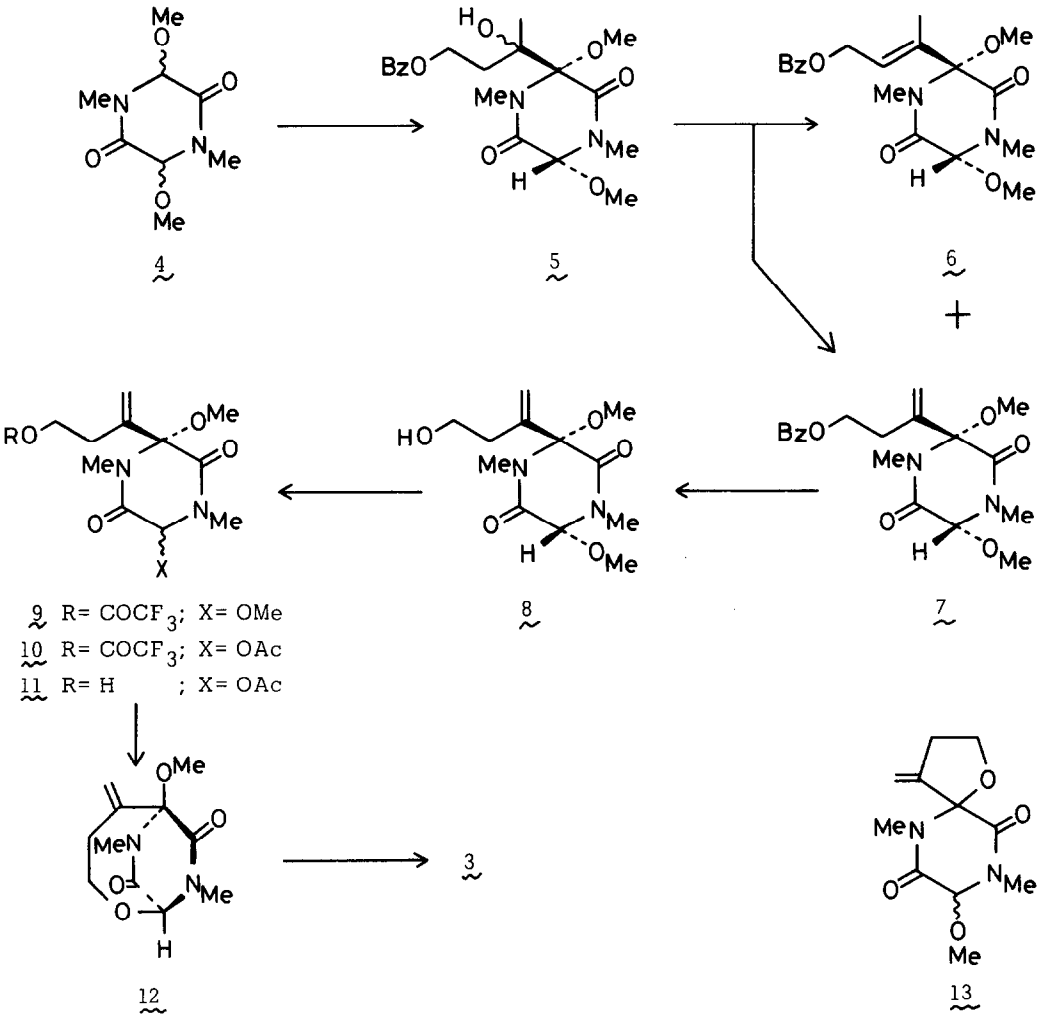
3a R = $CH_2CH{=}CH_2$

3b R = COC_6H_5

alcohol 8 was treated with trifluoroacetic anhydride at room temp for 1 hr and then the reaction mixture was dried in vacuo to give crude trifluoroacetate 9.[9,10] The residue was dissolved in acetic anhydride and trifluoroacetic acid (1:1) and the mixture heated at 40° C for 2 hr to give the 6-monoacetoxy compound 10.[9,10] Introduction of the acetoxy group at 6 position was confirmed by ca 1.6 ppm down-field shift of the nmr signal of the proton at 6 position of 10 in comparison with that of 9 [9: nmr 4.76 (H-6); 10 (a mixture of two stereoisomers): nmr 6.46 (major product) and 6.42 (minor product) (H-6)]. removal of trifluoroacetyl group was carried out by treatment of 10 with 20% aqueous Na_2HPO_4-dioxane (1:1) at room temp. Column chromatography on silica gel gave a mixture of stereoisomers 11[9] [55% from 7, ratio of the isomers 3:2].

Cyclization of 11 in dichloroethane in the presence of pyridinium tosylate at 80° C for 2 hr afforded solely the desired compound 12[9,11] containing the bicyclo ring system [50%, mp 182-183° C, nmr ($CDCl_3$) 2.20-2.60 (2H, m), 2.80, 3.07, and 3.19 (each 3H, s), 3.20-3.92 (2H, m), 5.16 (1H, s), 5.17 and 5.60 (each 1H, br.s)]. In this reaction, the spiro derivative 13 was not detected on tlc. Like bicyclomycin, the bicyclo compound 12 was isomerized by treatment with camphorsulfonic acid in methanol under reflux to the spiro compound 13[9] [yield over 80%], which was a 1:1 mixture of two stereoisomers. The reverse reaction from 13 to 12 did not proceed at all, indicating that the spiro compound 13 is energetically favored over the bicyclo compound 12 as suggested by the Hoffmann-La Roche group.[4c]

The last step was the alkylation at the bridge-head position of the bicyclo[4.2.2] 12 through its bridge-head carbanion, whose formation had not been reported, although in the course of the total synthesis of gliotoxin and sporidesmin, Kishi et al.[12] carried out the alkylation on the bridge-head position of bicyclo[3.2.2] compounds containing diketopiperazine ring, but in this case the carbanion might be stabilized with a sulfur atom. Our case gave the expected carbanion with lithium diisopropylamide (LDA). Thus, the addition of 1.2 eq of LDA at -78° C to a tetrahydrofuran solution of 12, followed by addition of allyl bromide, afforded, after chromatography on silica gel, the allyl derivative 3a [54%, mp 117-119° C, nmr ($CDCl_3$) 2.10-2.80 (4H, m), 2.80, 3.05, and 3.18 (each 3H, s), 3.20-4.00 (2H, m), 5.00-5.60 (3H, m), 5.15 and 5.68 (each 1H, br.s)].[11] Similarly the benzoyl derivative 3b [75%, mp 164-165° C, nmr



($CDCl_3$) 2.46 (2H, m), 2.80, 2.85, and 3.47 (each 3H, s), 3.95-4.30 (2H, m), 5.22 and 5.65 (each 1H, br.s), 7.20-8.10 (5H, m)}[11] was obtained using benzoyl chloride instead of allyl bromide. These compounds have the same ring system with bicyclomycin 1. Further synthetic approach toward bicyclomycin is now in progress.

Acknowledgement —— This research was supported in part by the grant from the Foundation for the Promotion of Research on Medicinal Resources.

REFERENCES AND FOOTNOTES

1. T. Miyoshi, N. Miyairi, H. Aoki, M. Kohsaka, H. Sakai, and H. Imanaka, J. Antibiotics, 25 569 (1972).
2. S. Miyamura, N. Ogasawara, H. Otsuka, S. Niwayama, H. Tanaka, T. Take, T. Uchiyama, H. Ochiai, K. Abe, K. Koizumi, K. Asao, K. Mitsuki, and T. Hoshino, J. Antibiotics, 25, 610 (1972); S. Miyamura, N. Ogasawara, H. Otsuka, S. Niwayama, H. Tanaka, T. Take, T. Uchiyama, and H. Ochiai, J. Antibiotics, 26, 479 (1973).
3. M. Nishida, Y. Mine, T. Matsubara, S. Goto, and S. Kuwahara, J. Antibiotics, 25, 582 (1972).
4. (a) T. Kamiya, S. Maeno, M. Hashimoto, and Y. Mine, J. Antibiotics, 25, 576 (1972); (b) Y. Tokuma, S. Koda, T. Miyoshi, and Y. Morimoto, Bull. Chem. Soc. Jpn., 47, 18 (1974); (c) H. Maag, J. F. Blount, D. L. Coffen, T. V. Steppe, and F. Wong, J. am. Chem. Soc., 100, 6786 (1978).
5. (a) Fujisawa Pharmaceutical Co. Ltd.; Germany, Offenlegungschrift 2,150, 593; (b) B. W. Muller, O. Zak, K. Kump, W. Tosch, and O. Wacker, J. Antibiotics, 32, 689 (1979).
6. L. V. Dunkerton and R. M. Ahmed, Tetrahedron Lett., 21, 1807 (1980).
7. 4 [nmr ($CDCl_3$ 3.02 and 3.52 (s, each 6H), 4.68 (2H, s H-6)] was obtained from 3,6-dibromo-1,4-dimethyl-2,5-piperazinedione in 65 % yield by treatment with methanol in the presence of triethylamine at 0° C and then chromatographycally separated from its crystalline diastereomer (20 %; mp 118-119° C; nmr 4.84 (H-3 and 6)].[9] A general procedure of this condensation and determination of stereochemistry of the condensation products are reported in Chemistry Letters (submitted for publication).
8. When being heated with catalytic amounts of CSA in dichloroethane at 80° C, 8 gave a 1:1 stereomixture of the spiro compounds 13 (40%) accompanied with a small amount of the desired bicyclo compound 12 (20%). These compounds, however, were difficult to be separated.
9. Satisfactory spectroscopic data (ms, nmr, ir) were obtained for all new compounds.
10. Further purification of these compounds on silica gel tlc gave pure products, but the yields were low.
11. Satisfactory elemental analyses were obtained for all crystalline compounds.
12. Y. Kishi, T. Fukuyama, and S. Nakatsuka, J. Am. Chem. Soc., 95, 6490 (1973).

(Received in Japan 14 February 1981)