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SYNTHETIC STUDIES ON BICYCLOMYCIN II[1]
SYNTHESIS OF (±)-N,N',O-TRIMETHYLBICYCLOMYCIN

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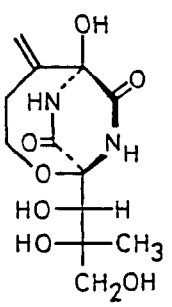
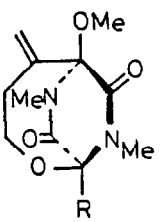
Summary: Stereospecific aldol condensation of 2 at the bridge-head position with i-butyraldehyde gave 6a and 6b in a ratio of 4:1. Using the aldehyde 8 the chiral centers were controlled to produce 9a-d in a ratio of 9:3:3:1. Deprotection of the major isomer 9a afforded (±)-N,N',O-trimethylbicyclomycin 5.

Although many synthetic approaches[2-5] toward antibiotic bicyclomycin 1[6,7], which possesses a unique structure containing the novel bicyclo[4.2.2] system involving diketopiperazine nucleus, total synthesis of neither 1 nor its derivative has been achieved. We have reported stereospecific alkylation[8] of 3,6-dimethoxy-1,4-dimethylpiperazine-2,5-dione and the synthesis[1] of bicyclo[4.2.2] compounds 2, 3 and 4 via selective cyclization and subsequent alkylation or acylation at the newly formed bridge-head position. We report herewith the first synthesis of (±)-N,N',O-trimethylbicyclomycin 5 starting from 2.



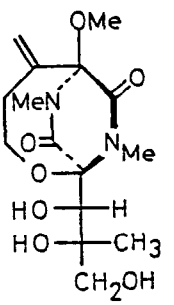
1 Bicyclomycin



2 R = H

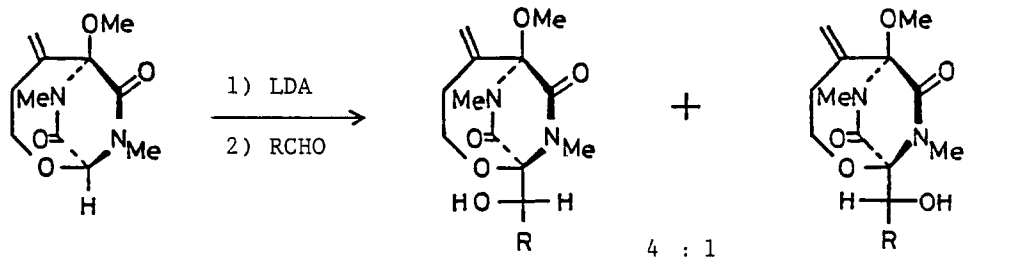
3 R = $CH_2CH{=}CH_2$

4 R = COC_6H_5



5 N,N',O-Trimethyl-bicyclomycin

Aldol condensation of bicyclo[4.2.2] compound 2[1] with i-butyraldehyde was achieved as follows: To the lithium enolate of 2, which was prepared by treating 2 with 1.2 eq lithium diisopropylamide at -78°C, i-butyraldehyde was added at -78°C. After 10 min. at -78°C, the reaction mixture was quenched with acetic acid. In this reaction, stereochemistry concerning with the newly formed secondary alcohol was highly controlled (74%; ratio of 6a[9] and 6b[10] is 4:1; separable by silica gel TLC). The inspection through the CPK model clearly indicates that the major product has the desired configuration as shown in 6a because of the steric hindrance between the i-butyl group and the N-methyl group (Figure I). The allyl alcohol 7a[11] and 7b[10] were also obtained in 60% yield using methacrolein instead of i-butyraldehyde. The ratio of the products 7a and 7b was also 4:1. These highly stereocontrolled aldol condensations prompted us to try to condence 2 with the protected aldehyde 8.



2

6a R = $CH(CH_3)_2$ 6b R = $CH(CH_3)_2$

7a R = $C(CH_3)=CH_2$ 7b R = $C(CH_3)=CH_2$

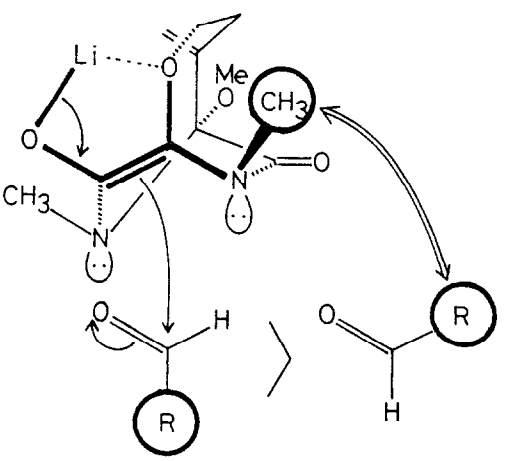
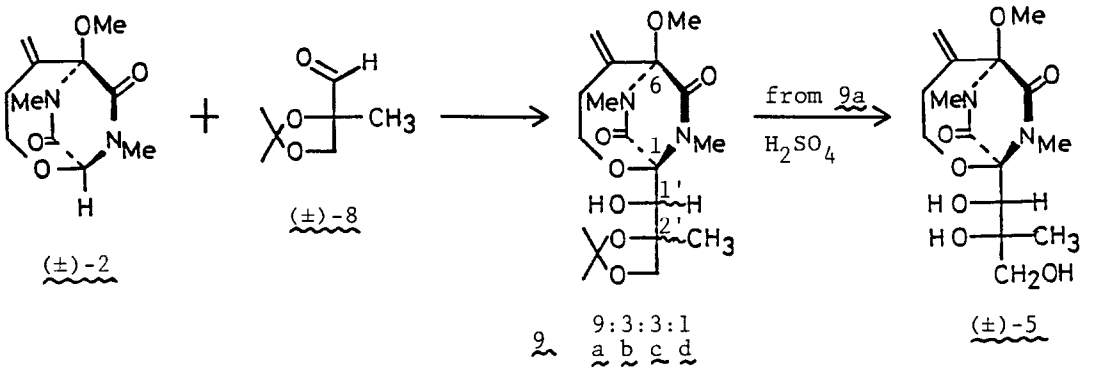


Figure I



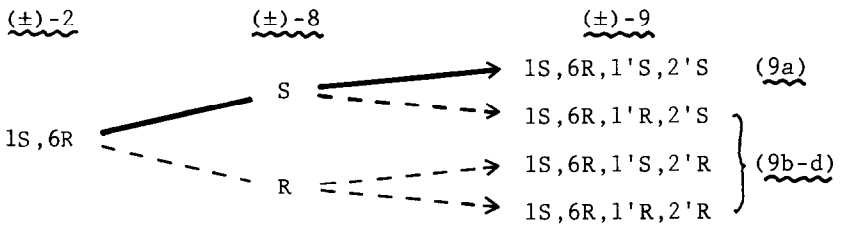


Figure II

Aldol condensation of (±)-2 with the protected aldehyde (±)-8 was smoothly proceeded to give a mixture of four kinds of stereoisomers 9a-d[10,12] (46%), which were separable by silica gel TLC. If the stereoselectivity is assumed to be controlled only by the chirality of the diketopiperazine nucleus, the ratio of the isomers is estimated to be 4:4:1:1. But, the ratio of the four products were 9:3:3:1. Surprisingly, in this reaction not only the chiral center of the newly formed secondary alcohol but also the combination of the chiral centers of 2 and 8 was controlled by each other[13] (Figure II). Pmr, cmr and mass spectra as well as the Rf value on TLC of the major product 9a were completely identical with those of 9[14] derived from natural bicyclomycin 1. Hydrolysis of the acetonide group of 9a gave (±)-N,N',O-trimethylbicyclomycin 5 as reported in the literature[14]. Spectral data of 5 were also identical with those reported. Further synthetic studies toward bicyclomycin 1 are now in progress.

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9. 6a[pmr ($CDCl_3$) 0.88, 1.04 (each 3H, d, J=8Hz), 1.60-2.00 (1H, m), 2.35 (2H, br, t, J=7Hz), 2.80, 2.98, 3.22 (each 3H, s), 3.20-4.08 (3H, m), 5.16 (1H, br. s), 5.33 (1H, br. d, J=10Hz), 5.58 (1H, br. s)].
10. Satisfactory spectroscopic data (ms,pmr,ir) were obtained for all new compounds.
11. 7a[pmr ($CDCl_3$) 1.83 (3H, s), 2.39 (2H, br. t, J=8Hz), 2.85, 3.05, 3.35 (each 3H, s), 2.20-4.10 (2H, m), 4.43 (1H, br. d, J=10Hz), 4.93 (2H, br. s), 5.22, 5.65 (each 1H, br. s), 5.86 (1H, d, J=10Hz)].
12. 9a[pmr ($CDCl_3$) 1.19, 1.34, 1.39 (each 3H, br. s), 2.34 (2H, br. t, J=8Hz), 2.80, 3.08, 3.38 (each 3H, s), 3.20-4.20 (2H, m), 3.97, 4.13 (each 1H, d, J=10Hz), 5.20, 5.64(1H, br. s), 6.40 (1H, d, J=9Hz)].
13. cf. double stereodifferentiation with mutual kinetic resolution; (a) C. H. Heathcock, M. C. Pirrung, C. T. Buse, J. P. Hagen, S. D. Young, and J. E. Sohn, J. Am. Chem. Soc., 101, 7077 (1979). (b) C. H. Heathcock, M. C. Pirrung, J. Lampe, C. T. Buse, and S. D. Young, J. Org. Chem., 46, 2290(1981).
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