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TOTAL SYNTHESIS OF BICYCLOMYCIN[1]

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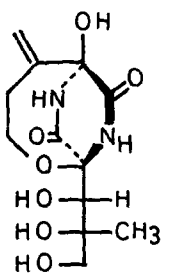
Summary: Total synthesis of (±)-bicyclomycin was achieved in 19 steps starting from diketopyperazine.

Bicyclomycin is an antibiotic found in Japan. It was produced by Streptomyces sapporonensis and S. aizunensis[2] and has a unique spectrum of antibacterial activities. Structure of bicyclomycin (1) has been elucidated by chemical and X-ray analyses.[2] It has a novel bicyclo[4.2.2] system containing oxidized diketopiperazine ring and a side chain at its bridge-head position. Several reports[3] directing to its synthesis have been appeared, but no total synthesis of bicyclomycin has been reported. We have reported synthesis of (±)-N,N',O-trimethylbicyclomycin in the previous papers.[4,5] This paper deals with a total synthesis of (±)-bicyclomycin.



Bicyclomycin (1)

Diketopyperazine (2) was protected by benzyl group[6] (3, 65% yield) and then brominated with bromine in chlorobenzene at 130 °C (4, 92% yield). On heating with benzyl alcohol the dibromide 4 afforded the dibenzyl ether 5 in 85% yield as a 3:1 mixture of cis (mp 60-61 °C) and trans (mp 148 °C) form, which were separated by fractional crystallization. Each isomer or the mixture was used for the next step.

Methyl γ-hydroxycrotonate (6), the component for the side chain, was prepared from methyl crotonate by oxidation with selenium dioxide followed by reduction with $NaBH_4$. Its hydroxy group was protected with t-butyldiphenylsilyl group (TBDPS) by treatment with TBDPS chloride and imidazole to give methyl γ-TBDPS-oxycrotonate (7), mp 77-78 °C[7] (76% yield).

The monoanion prepared from 5 and n-BuLi in THF at -110 °C was treated with 7 at -78 °C. This conjugate addition proceeded stereospecifically and gave only one condensed product 8. Stereochemistry of 8 on the diketopiperazine ring was as shown.[9] It was reduced with $LiAlH_4$ in THF at -78 °C to yield the crude aldehyde 9 [PMR[9] 8.22 (1H, br.t, CHO)], which was further reduced with $NaBH_4$ in methanol followed by silica gel column chromatography to give the alcohol 10, mp 121-122 °C[7] (39% yield from 5). The primary hydroxy group of 10 was protected with t-butyldimethylsilyl group (TBDMS) by treatment with TBDMS chloride and imidazole to 11 almost quantitatively [MS m/z 889; PMR[9] -0.08 (6H, s), 0.86 (9H, s), 1.02 (9H, s)].

In the synthesis of N,N',O-trimethylbicyclomycin the secondary methoxy group corresponding to the secondary benzyl group in 11 was displaced smoothly by acetoxy group by treatment with Ac_2O/CF_3CO_2H,[4] but the secondary benzyl group in 11 could not be displaced by acetoxy group under the similar condition. Therefore, 11 was hydrogenated in ethanol in the presence of 20% Pd-C and pyridine (5 v/v%) at 40 °C. Only one benzyl group (secondary rather than tertiary) was selectively removed and the mono-debenzylated product 12 was crystallized from hexane (88% yield), mp 136 °C[7] [PMR[9] 5.16 (1H, d ⟶ s by addition of D_2O), 5.74 (1H, d ⟶ disappeared by addition of D_2O)]. Acetylation of 12 afforded the acetate 13 (quantitative yield) [MS m/z 841; PMR[9] 1.92 (3H, s)], whose TBDMS group was selectively removed to give the mono-ol 14 (80% yield) [MS m/z 769; no PMR signal around -0.1 ppm]. It was heated in dichloroethane at 80 °C in the presence of pyridinium tosylate, affording the bicyclo compound 15[10] (84% yield), mp 122-123 °C.[7]

Aldol condensation of the bicyclo compound 15 and the aldehyde 16 would give four stereoisomers. We have studied the stereoselectivity of this type of condensation[5] and found that the major isomer was formed in more than 50% of the four stereoisomers and that it had the same relative stereochemistry of that of bicyclomycin (1).

The bicyclo compound 15 in THF was converted to its monoanion with n-BuLi at -110 °C and condensed with (±)-2-methylglyceraldehyde acetonide(16)[11] at -78 °C to give a mixture of four stereoisomers in a 3:1:1:~0 ratio from which the major product 17, mp 186 °C,[7] was isolated in 41% yield by means of preparative tlc. This was treated with 1M n-Bu_4NF in THF to give the primary alcohol 18, mp 177-178 °C,[7] almost quantitatively. All of the benzyl protecting groups of 18 were removed by catalytic hydrogenation in ethanol under H_2 atmosphere in the presence of 20% Pd-C at 80 °C for 12 h to yield the completely debenzylated product 19 (57% yield), mp 216-218 °C (dec).[7] Mesylation of 19 afforded the monomesylate 20 (83% yield) [MS m/z 423; PMR[9] 3.07 (3H, s)], which in abs. ethanol under N_2 atmosphere was treated at room temperature with 0.5M Na[$PhSeBH_3$] solution prepared from $NaBH_4$ and PhSeSePh in ethanol. The selenide 21 was isolated in 40% yield [MS m/z 500, 498; PMR[9] 7.1-7.6 (5H, m)]. Oxidation of 21 with m-chloroperbenzoic acid in dichloromethane gave the selenoxide 22, which, after chromatography on a silica gel column, was dissolved in dichloroethane and the solution was heated at 60 °C for 20 min to give bicyclomycin acetonide (23) (69% yield), mp 164-170 °C (dec).[7,13]

The acetonide 23 was hydrolyzed by careful treatment with 2 equivalents of 0.2N sulfuric acid initially at 0 °C and then at 25 °C for 8 h.[5] Purification using a silica gel column and an ODS RP-18 column, and crystallization from methanol-acetone afforded (±)-bicyclomycin (1) (66% yield), mp 166-170 °C, whose PMR and CMR spectra[14] as well as Rf values on tlc were completely identical with those of natural bicyclomycin.

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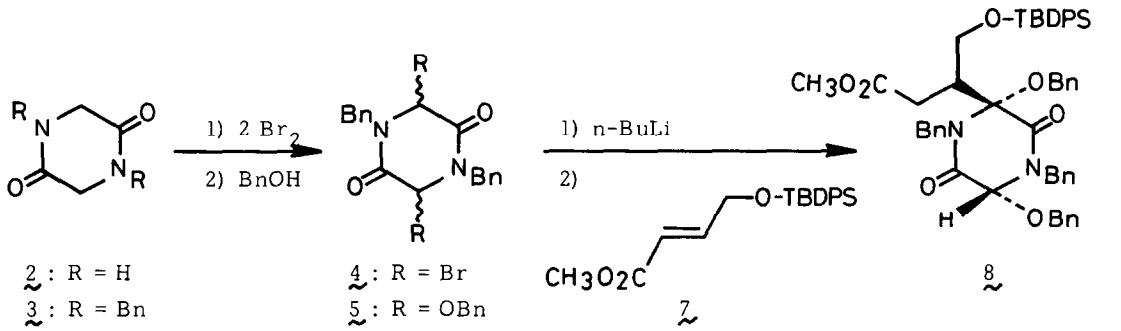
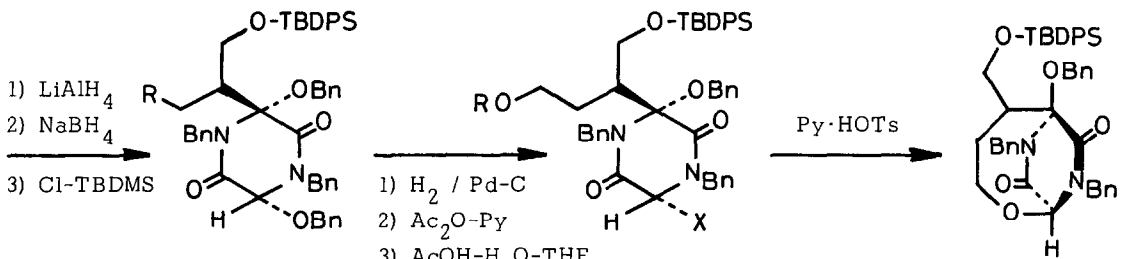


2 : R = H
3 : R = Bn

4 : R = Br
5 : R = OBn

7

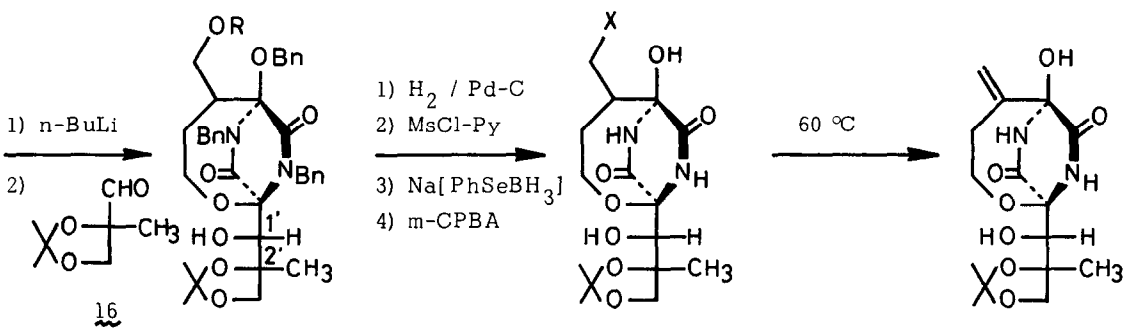
8



9 : R = CHO
10 : R = CH_2OH
11 : R = CH_2O-TBDMS

12 : R = TBDMS, X = OH
13 : R = TBDMS, X = $OCOCH_3$
14 : R = H, X = $OCOCH_3$

15



16

17 : R = TBDPS
18 : R = H

19 : X = OH
20 : X = OMs
21 : X = SePh
22 : X = Se(O)Ph

23

0.2 N H_2SO_4

Bicyclomycin (1)

REFERENCES AND NOTES

1. Synthetic Studies on Bicyclomycin III. The preceding paper, see Ref. 5.
2. See references cited in Ref. 5.
3. (a) H. Maag, J. F. Blount, D. L. Coffen, T. V. Steppe, and F. Wong, J Am. Chem. Soc., 100, 6786 (1978); (b) L. V. Dunkerton and R. W. Ahmed, Tetrahedron Lett., 21, 1803 (1980); (c) C. Shin, Y. Sato, and J. Yoshimura, Tetrahedron Lett., 22, 2401 (1981); (d) T. Fukuyama, B. D. Robins, and R. A. Sachleben, Tetrahedron Lett., 22, 4155 (1981); (e) J. H. Hoare and P. Yates, J. Chem. Soc., Chem. Commun., 1126 (1981); P. Yates and J. H. Hoare, Can. J. Chem, 61, 519 (1983); (f) R. M. Williams, O. P. Anderson, R. Armstrong, J. Josey, H. Meyers and C. Eriksson, J. Am. Chem. Soc., 104, 6092 (1982); (g) R. M. Williams, J. S. Dung, J. Jesey, R. W. Armstrong and H. Meyers, J. Am. Chem. Soc. 105, 3214 (1983).
4. S. Nakatsuka, K. Yoshida and T. Goto, Tetrahedron Lett., 22, 2009 (1981).
5. S. Nakatsuka, K. Yoshida and T. Goto, Tetrahedron Lett., 22, 4973 (1981).
6. p-Methoxybenzyl group may be a better protecting group than benzyl group for easy removal, but in this case it cannot be used, for it is susceptible toward bromination.
7. Satisfactory elemental analyses were obtained.
8. S. Nakatsuka, K. Sasaki, K. Yamaguchi and T. Goto, Chemistry Lett., 695 (1981).
9. PMR spectra were taken in $CDCl_3$ at 100 MHz and the chemical shifts are in δ(ppm).
10. PMR[9] of 15: 0.98 (9H, s), 1.62 (2H,m), 1.7-2.4 (1H,m), 3.20-3.64 (2H,m), 3.90 (1H,d,J=10 Hz), 4.06 (1H,d,J=14 Hz), 4.3 (1H,m), 4.46 (1H,d,J=15 Hz), 4.60 (1H,d,J=10 Hz), 4.74 (1H, d,J=15 Hz), 5.12 (1H,d,J=14 Hz), 5.16 (1H,s), 6.9-7.7 (25H,m).
11. Ref. 3(a).
12. Compound 17 could not be debenzylated completely by catalytic hydrogenation owing to the steric bulkiness of t-butyldiphenylsilyl group.
13. PMR of 23 (CD_3OD) ppm : 1.38 (3H, s), 1.43 (3H, s), 1.45 (3H, s), 2.64 (2H, m), 3.74 1H, d, J = 8 Hz), 3.89 (2H, m), 4.15 (1H, s), 4.45 (1H, d, J = 8 Hz), 5.14 (1H, d, J = 1.5 Hz), 5.58 (1H, d, J = 1.5 Hz); CMR (CD_3OD) ppm: 25.0, 26.8, 28.2, 36.5, 66.5, 73.1, 82.8, 86.4, 88.9, 111.5, 116.7, 149.1, 168.3, 172.0.
14. PMR of 1 (CD_3OD) ppm: 1.34 (3H, s), 2.60 (2H, m), 3.52 (1H, d, J = 11 Hz), 3.65 (1H, d, J = 11 Hz), 3.86 (2H, m), 4.08 (1H, s), 5.13 (1H, d, J = 1 Hz), 5.56 (1H, d, J = 1 Hz), CMR (CD_3OD) ppm: 24.2, 36.7, 65.5, 68.4, 72.0, 78.2, 82.9, 89.4, 119.8, 149.4, 168.6, 172.4.

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