A SIMPLE SYNTHESIS OF BICYCLOMYCIN SKELETON

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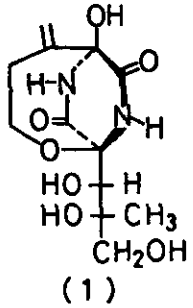
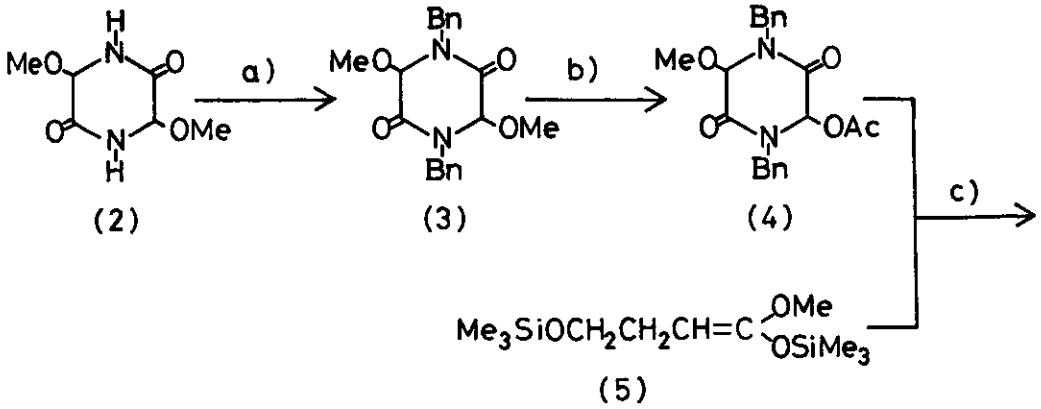
Abstract — The bicyclomycin skeleton(7,9-dibenzyl-5-methylene-7,9-diaza-2-oxabicyclo[4.2.2]decane-8,10-dione) was synthesized from 3,6-dimethoxy-2,5-piperazinedione by 6 steps in a 32% yield.

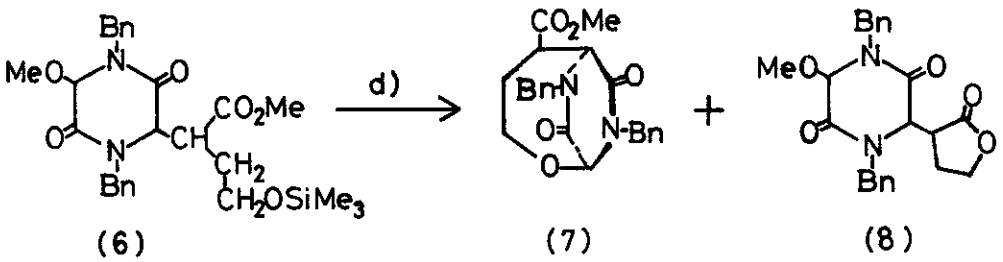
Since the discovery of bicyclomycin(1)[1], an antibiotic substance having unusual antibacterial activity and a unique heterobicyclo[4.2.2] skeleton many attempts have been made to synthesize this new type compound.[2] Commonly employed synthetic strategy has started from a base catalyzed condensation of 2,5-piperazinedione derivative with an appropriate electrophile, or a cyclization of a suitably functionalyzed dipeptide derivative. Both synthetic routes, however, have involved rather tedious manipulation. Recently, an elegant total synthesis of bicyclomycin was achieved by Nakatsuka, Goto, and their coworkers starting from a 2,5-piperazinedione derivative.[3] We report here a short synthesis of the bicyclomycin skeleton(12) from 3,6-dimethoxy-2,5-piperazinedione (2), which can be prepared easily from 2,5-piperazinedione.[4]

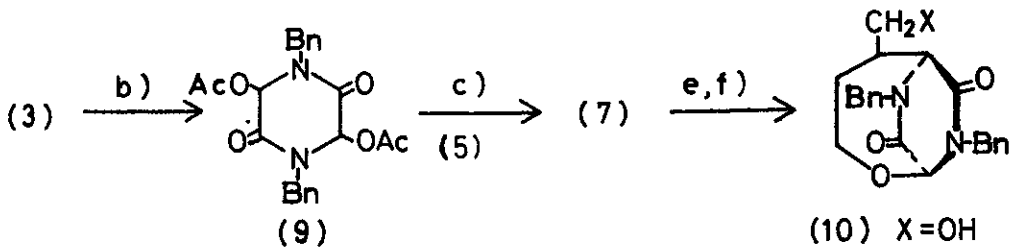


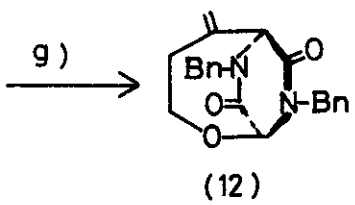
(1)

Benzylation of (2) with benzyl chloride and sodium hydride gave 1,4-dibenzyl-3,6-dimethoxy-2,5-piperazinedione(3) in a 90% yield. We had observed that alkoxy or acetoxy groups of 3,6-dialkoxy- or diacetoxy-2,5-piperazinedione easily undergo a carbon-oxygen fission to give rise to carbocation centers at C-3 and/or C-6 positions of the ring.[4] Accordingly, (3) was converted into 1,4-dibenzyl-3-acetoxy-6-methoxy-2,5-piperazinedione(4). To introduce a C_4 fragment into the C-3 position









Bn: $PhCH_2$-

a) NaH/DMF, $PhCH_2Cl$ b) p-TsOH/Ac_2O c) $ZnCl_2/CH_2Cl_2$ d) p-TsOH/PhH

e) LAH/THF f) MsCl/pyridine g) t-BuOK/DMSO

of (4), zinc chloride catalyzed reaction with 1,4-bis(trimethylsilyloxy)-1-methoxy-1-butene(5)[5] was attempted. The expected alkylation was achieved to give (6). However, a following acid treatment of (6) yielded a lactonic product(8) exclusively; the desired (7) was obtained only in a trace amount. This suggested that the leaving ability of the C-6 methoxy group was not good enough to afford a carbocation under the present reaction conditions.

Accordingly, 3,6-diacetoxy derivatives(9)[6] was prepared from (3) in a nearly quantitative yield. A dichloromethane solution of (9) and (5) was treated with a catalytic amount of anhydrous zinc chloride at room temperature for 25 h. Usual work up and following SiO_2 chromatography gave the desired bicyclic derivative(7) in a 50% yield.[7] That is, alkylation of the C-3 position with the silyl enol ether(5) and consequent cyclization to the bicyclic skeleton proceeded fortunately in one pot. Lithium aluminum hydride reduction of the methoxycarbonyl group of (7), followed by mesylation of the hydroxyl group yielded the mesylate(11) in an 88% yield. Treatment of (11) with potassium *t*-butoxide in DMSO at room temperature for 2.5 h afforded the bicyclomycin skeleton(12)[8] in an 89% yield. Total yield of (12) was fairly good; 32% from the starting compound(2).[9]

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3. S. Nakatsuka, K. Yamada, K. Yoshida, O. Asano, Y. Murakami, and T. Goto, Tetrahedron Lett., 24, 5627 (1983). We thank Professor T. Goto and S. Nakatsuka for letting us see a copy of their paper in advance of publication.
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5. Compound (5) was prepared by silylation of methyl 4-trimethylsilyloxybutanoate with chlorotrimethylsilane and lithium diisopropylamide.
6. A syrup containing trans/cis[1/4] isomers. Both isomers could react with (6) to give (7). Cis isomer: MS (m/z); 410(M^+). IR; 1750(acetoxy carbonyl), 1690 cm^{-1}(amide carbonyl). NMR(δ in $CDCl_3$); 2.0(CH_3CO, s), 4.3 and 4.8($PhCH_2$, AB quartet, J=14 Hz), 6.3(H-3 and H-6, s), 7.1(C_6H_5, s). Trans isomer: NMR(δ in $CDCl_3$); 1.9(CH_3CO, s), 4.4 and 4.8($PhCH_2$, AB quartet, J=14 Hz), 5.9 (H-3 and H-6, s), 7.1(C_6H_5, s).
7. Yield was given based on the consumed amount of(9); 40% of (9) was recovered unchanged.
8. An oil: MS (m/z); 362(M^+). IR; 1680 cm^{-1}(amide carbonyl). NMR(δ in $CDCl_3$); 2.25 (2H, H-4, broad t, J=4.5 Hz), 3.3 and 3.7(2H, H-3 and H-3', tripleted AB quartet, J=4.5 and 15 Hz), 3.9 and 4.8; and 4.1 and 4.9(4H, $PhCH_2$, two AB quartets, J=14 and 15 Hz), 4.35(1H, H-6, s), 4.9 and 5.0(1H each, exo $=CH_2$, s), 5.2(1H, H-1, s), 7.1(10H, two C_6H_5, m).
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