

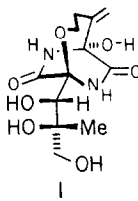
BICYCLOMYCIN SYNTHETIC STUDIES:
UTILIZATION OF BRIDGEHEAD CARBANIONS

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Summary: The synthesis of a bicyclomycin model compound (19) has been achieved utilizing an efficient hydroxylation of a simple bicyclic bridgehead carbanion.

Bicyclomycin 1, an antibiotic recently discovered by two groups,¹ was obtained from cultures of *Streptomyces Sapporonensis*. Bicyclomycin possesses a unique chemical structure and exhibits a unique mechanism of antibacterial action; no relation being noted to any groups of the known antibiotics.²

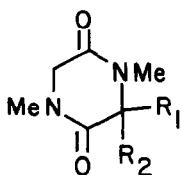
As part of a program directed toward the total synthesis of bicyclomycin, we wish to report a synthetic approach utilizing an efficient bridgehead anion oxidation reaction to construct the bicyclomycin ring system.



Readily available³ 1,4-dimethyl-3-formyl-2,5-piperazinedione (2) was converted into the protected 3-hydroxymethyl-3-methoxy-piperazinedione 6 in four straightforward steps: 1) 1.1 equiv toluenesulfonyl chloride/Et₃N/THF, -78°C (quant. to yield 3⁴); 2) 1.3 equiv LiAl(t-BuO)₃H/THF, -78°C (90% yield of 4⁴); 3) 1.1 equiv Hg(OAc)₂/MeOH, 25°C, 12h (92% yield of 5⁴); 4) t-BuMe₂SiCl/DMF/imidazole, 25°C affords 6⁴ in 81% overall yield from 2.

Reaction of 6 with 1.3 equiv LDA in THF at -78°C followed by quenching the enolate with 2 equiv HMPA and 2.4 equiv t-butyldimethylsiloxy-3-iodopropane furnished a mixture of diastereomers 7⁴ in 64% combined yield (isolated on a silica gel flash column; eluted with 5% MeOH in CH₂Cl₂). Removal of both silyl protecting groups from the diastereomers 7 with 2 equiv tetra-n-butyl ammonium fluoride in THF at 25°C afforded the diastereomeric diols 8⁴ in 83% yield. Refluxing the mixture of diastereomers 8 in acetonitrile in the presence of camphorsulfonic acid⁵ furnished a single bicyclic hydroxymethylpiperazinedione 9^{6, 7} in 75% yield.

We envisioned that the four-carbon poly-oxo side chain of bicyclomycin could be elaborated from the carboxaldehyde⁸ derived from the hydroxymethyl moiety, such as that present in 9.



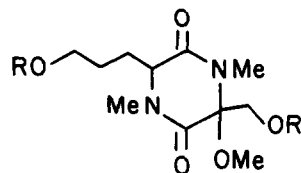
2 $R_1, R_2 = \text{CHOH}$

3 $R_1 = \text{CHO}, R_2 = \text{S}-\text{C}_6\text{H}_4-\text{Me}$

4 $R_1 = \text{CH}_2\text{OH}, R_2 = \text{S}-\text{C}_6\text{H}_4-\text{Me}$

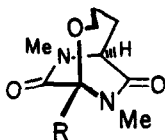
5 $R_1 = \text{CH}_2\text{OH}, R_2 = \text{OMe}$

6 $R_1 = \text{CH}_2\text{OSiMe}_2\text{t-Bu}, R_2 = \text{OMe}$



7 $R = \text{SiMe}_2\text{t-Bu}$

8 $R = \text{H}$

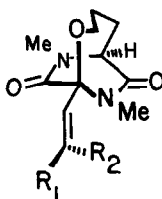


9 $R = \text{CH}_2\text{OH}$

10 $R = \text{CHO}$

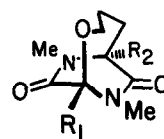
11 $R = \text{H}$

12 $R = \text{CH}_2\text{OSiMe}_2\text{t-Bu}$



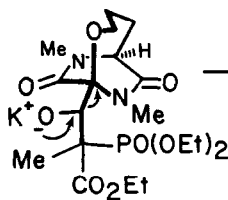
13 $R_1 = \text{CO}_2\text{Et}, R_2 = \text{Me}$

14 $R_1 = \text{Me}, R_2 = \text{CO}_2\text{Et}$

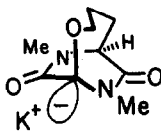


17 $R_1 = \text{H}, R_2 = \text{Me}$

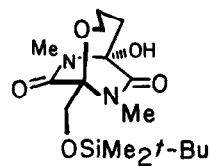
18 $R_1 = \text{Me}, R_2 = \text{H}$



15



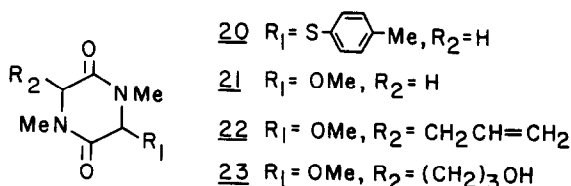
16



19

Thus, Swern⁹ oxidation of 9 (DMSO, oxalyl chloride, CH₂Cl₂, Et₃N) cleanly afforded the labile aldehyde 10⁴ in virtually quantitative yield (IR: 1745, 1665 cm⁻¹; NMR (CDCl₃) δ 9.67, 1H, s, RCHO). Reaction of 10 with (EtO)₂POCH(CH₃)CO₂Et and t-BuOK in THF provided a 1:1.3/E:Z mixture of olefins 13⁴ and 14⁴ (33% combined yield) and quite surprisingly, deformylated derivative 11¹⁰ (34%). This unexpected deformylation must result from the collapse of the intermediate oxy-anion addition product (15) of the Horner-Emmons reagent and aldehyde 10, expelling bridgehead carbanion 16, which is then protonated upon work-up to furnish 11.

The structure of 11¹⁰ was confirmed by comparison to an authentic sample prepared from 3 in five steps: 1) 0.1 N NaOH/THF provides 20; 2) 1.1 equiv Hg(OAc)₂/MeOH provides 21; 3) 1.2 equiv LDA/THF, -78°C followed by addition of 3 equiv allyl bromide provides 22; 4) B₂H₆/THF, then 1 N NaOH/30% H₂O₂ provides 23; 5) camphorsulfonic acid/ acetonitrile, reflux affords 11 in 13% overall yield from 3.



This unexpected deformylation reaction prompted us to investigate the bridgehead carbanion chemistry¹¹ of 11 and 12. Treatment of 11 with 1.3 equiv t-butyllithium in THF at -78°C, followed by quenching with 5 equiv CH₃I afforded 17⁴ as the major product plus a small amount of 18⁴ (3:1, respectively, 54% combined based on recovered 11). The preponderance of 17 formed indicates that for 11 the methine proton adjacent to the methylene is slightly more acidic than the methine adjacent to the ether-oxygen; neither proton exchanges (3 days) in CD₃OD containing 1 equiv NaOMe.

Thus, conversion of 9 into the corresponding silyl ether 12⁴ was accomplished in the standard manner (t-BuMe₂SiCl/DMF/imidazole, quant.). Treatment of 12 with 1.5 equiv t-butyllithium in THF at -78°C, followed by addition of MoOPH¹² afforded bicyclomycin model 19¹³ in 62% yield (48% conversion).

Synthesis of 19 constitutes the first successful approach to a piperazinedione nucleus bearing the substitution pattern present in the bicyclomycin ring system. Application of these strategies to a total synthesis of bicyclomycin is currently under investigation in these laboratories.

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1. T. Miyoshi, N. Miyairi, H. Aoki, M. Kohsaka, H. Sakai, and H. Imanaka, *J. Antibiotics*, **25**, 569 (1972); T. Kamiya, S. Maeno, M. Hashimoto, Y. Mine, *ibid.*, **25**, 576 (1972); M. Nishida, Y. Mine, and T. Matsubara, *ibid.*, **25**, 582 (1972); M. Nishida, Y. Mine, T. Matsubara, S. Goto, and S. Kuwahara, *ibid.*, **25**, 594 (1972); S. Miyamura, N. Ogasawara, H. Otsuka, S. Niwayama, H. Tanaka, T. Take, T. Uchiyama, H. Ochiai, K. Abe, K. Koizumi, K. Asao, K. Matsuki, and T. Hoshino, *ibid.*, **25**, 620 (1972); S. Miyamura, N. Ogasawara, H. Otsuka, S. Niwayama, H. Tanaka, T. Take, T. Uchiyama, and H. Ochiai, *ibid.*, **26**, 479 (1973).
2. A. Someya, M. Iseki, and N. Tanaka, *J. Antibiotics*, **31**, 712 (1978); N. Tanaka, M. Iseki, T. Miyoshi, H. Aoki, and H. Imanaka, *ibid.*, **29**, 155 (1976).
3. R. M. Williams and W. H. Rastetter, *J. Org. Chem.*, **45**, 2625 (1980).
4. Satisfactory spectroscopic data (nmr, ir, ms) were obtained for all compounds.
5. This cyclisation procedure is similar to that reported by H. Maag, Abstract #347 2nd Chemical Congress of the North American Continent, Division of Organic Chemistry Las Vegas, Nevada, August 1980; see also H. Maag, J. F. Blount, D. L. Coffen, T. J. Steppe, and F. Wong, *J. Am. Chem. Soc.*, **100**, 6786 (1978).
6. Both diastereomers (8) are capable of furnishing the same product 9, since when they are subjected to the cyclisation conditions separately (separated on PTLC silica gel using 89 parts CH_2Cl_2 /9 parts MeOH/1 part NH_4OH), 9 is obtained from each in good yield.
7. Data for 9: NMR (CDCl_3) δ TMS: 1.6-1.85(2H,m); 2.08-2.8(2H,m); 2.42(1H,dd, $J_{ax} = 9.0$ Hz, $J_{bx} = 6.0$ Hz, D_2O exch.); 3.00(3H,s); 3.10(3H,s); 3.27-3.85(2H,m); 3.78(1H,dd, $J_{ax} = 9.0$ Hz, $J_{ab} = 12.5$ Hz); 4.10(1H,t, $J = 4.5$ Hz); 4.37(1H,dd, $J_{bx} = 6.0$ Hz, $J_{ab} = 12.5$ Hz); MS:m/e = 228(M^+ , 37.9%), 198(29.8), 170(26.7), 113(100); IR (NaCl, neat): 3400(broad) 1660, 1455, 1385 cm^{-1} .
8. Synthesis and chain elongation of a corresponding carboxaldehyde derived from bicyclomycin has been described: B. W. Müller, O. Zak, W. Kump, W. Tosch, and O. Wacker, *J. Antibiotics*, **32**, 689 (1979).
9. A. J. Mancuso, S-L. Huang, and D. Swern, *J. Org. Chem.*, **43**, 2480 (1978).
10. Data for 11: NMR(CDCl_3) δ TMS: 1.73(2H,m); 2.14(2H,m); 2.97(3H,s); 3.03(3H,s); 3.3-3.9 (2H,m); 4.04(1H,t, $J = 3$ Hz); 5.12(1H,s); MS:m/e = 198(M^+ , 57%); 140(19.5); 32(100); IR(NaCl, neat): 1660, 1480, 1405, 1390, 1300, 1258, 1245 cm^{-1} .
11. For related bicyclic piperazinedione dithioacetal stabilized (sulfur-stabilized) bridgehead carbanions, see Y. Kishi, T. Fukuyama, and S. Nakatsuka, *J. Am. Chem. Soc.*, **95**, 6490 (1973).
12. MoOPH = Oxodiperoxymolybdenum (hexamethylphosphorictriamide) (pyridine); E. Vedejs and J. E. Telschow, *J. Org. Chem.*, **41**, 740 (1976).
13. Data for 19: NMR (CDCl_3) δ TMS: 0.02(6H,s); 0.83(9H,s); 1.4-1.8(2H,m); 1.8-2.5(2H,m); 3.03 (3H,s); 3.16(3H,s); 3.4-4.1(2H,m); 3.72(1H, $\frac{1}{2}$ ABq, $J = 11$ Hz); 4.56(1H, $\frac{1}{2}$ ABq, $J = 11$ Hz); 4.70 (1H, broad s, D_2O exch.); MS m/e = 358(M^+ , 0.83%), 343(2.66), 301(71.87), 84(100); IR(NaCl, neat): 3380 (broad), 1668, 1380, 1110 cm^{-1} .

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