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SYNTHETIC APPROACH TO BICYCLOMYCIN:

SYNTHESIS OF THE BICYCLIC SYSTEM OF BICYCLOMYCIN

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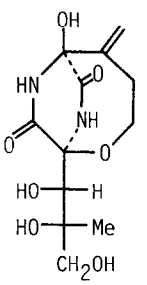
Summary: The bicyclic system of bicyclomycin has been constructed by oxidative cyclization of 6 using phenylselenyl chloride.

Bicyclomycin 1 has been isolated in crystalline form from a culture filtrate of *Streptomyces sapporonensis*[1,2] and has been shown to be active against Gram-negative bacteria.[3] The structure of bicyclomycin was mainly determined by spectroscopic methods and was confirmed by X-ray diffraction analysis.[4] Recently, the absolute configuration of bicyclomycin has been determined.[5] Bicyclomycin is a hitherto unknown piperazinedione with a bicyclo[4.2.2] system. Although these unique structural features of bicyclomycin combined with an interesting profile of antibacterial activities stimulate the curiosity of many synthetic chemists, no total synthesis has yet been reported. Recent synthetic efforts by the other workers[6] have prompted us to report our preliminary results.



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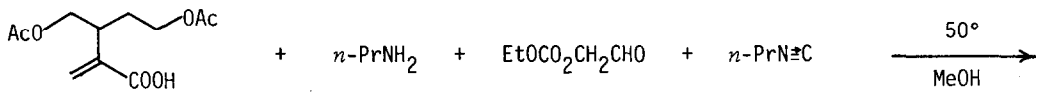
By far the most versatile method for the synthesis of α-N-acylaminocarboxamide is the Ugi's four-component condensation reaction.[7] Using his method the α-N-acylaminocarboxamide 3,[8] a key starting material, was prepared from the α,β-unsaturated carboxylic acid 2[9] (1 eq), *n*-propylamine (1.2 eq), glycolaldehyde ethyl carbonate (1.2 eq), and *n*-propyl isocyanide (1.2 eq) (MeOH, 50°) in 75% yield. The diastereomeric mixture of the α-N-acylaminocarboxamide 3 was subjected to ozonolysis (EtOAc, -78°) followed by Me_2S treatment at room temperature to give the α-keto amide 4.[8] When the α-keto amide 4 was treated with 2 equivalents of DBU in benzene at 50°, three reactions took place in such order as 1) elimination of acetic acid,

2) cyclization to form a piperazinedione ring, and 3) elimination of carbonate to afford the methylidene piperazinedione 5[8,10] in 55% overall yield from 3. Hydrolysis of the acetate 5 (3N NaOH, MeOH, r.t.) furnished the diol 6[8] in 99% yield. The diol 6, as expected, is very sensitive to acid and gave the spiro compound 7[8,11] upon treatment with HCl in CH_2Cl_2 at room temperature. Therefore, construction of the bicyclic system should be performed under either neutral or basic conditions. With this fact in mind, we carried out oxidative cyclization of 6 in the presence of base. Treatment of 6 with pyridinium hydrobromide perbromide (1.1 eq) and pyridine (5 eq) in CH_2Cl_2 at room temperature gave the desired bicyclic bromide 8[8,12] in 65% yield. Unfortunately all attempts to perform S_N2 displacement reaction on the bromide 8 were unsuccessful. In order to elongate the side chain, phenylselenyl chloride was employed for the oxidative cyclization. When 6 was treated with PhSeCl (1.1 eq) and pyridine (5 eq) in CH_2ClCH_2Cl at 70°, the bicyclic selenide 9[8,13] was obtained as colorless crystals (mp 114-115°) in 70% yield. The selenide 9 was oxidized to the selenoxide (1 eq *m*-CPBA, r.t.), which was converted to the α-acetoxy selenide 10[8] by Pummerer rearrangement (NaOAc-Ac_2O, 50°) in 85% overall yield from 9. The α-acetoxy selenide 10, an aldehyde equivalent, yielded the aldehyde 11[8] upon basic hydrolysis (3N NaOH, MeOH, r.t.). The aldehyde 11, however, could not be obtained in a pure form by chromatography presumably due to hydration and/or hemiacetal formation on the aldehyde group. The crude aldehyde 11 was treated with $Ph_3P{=}CMeCO_2Et$ (toluene, reflux) to give the α,β-unsaturated ester 12[8,14] in 44% yield from 10. While addition of alkyllithium or Grignard reagent to the aldehyde 11 was unsuccessful, *in situ* generation of the aldehyde from the α-acetoxy selenide 10 using excess isopropenyllithium at -78° led to the formation of the addition product 13[8,15] (31%).



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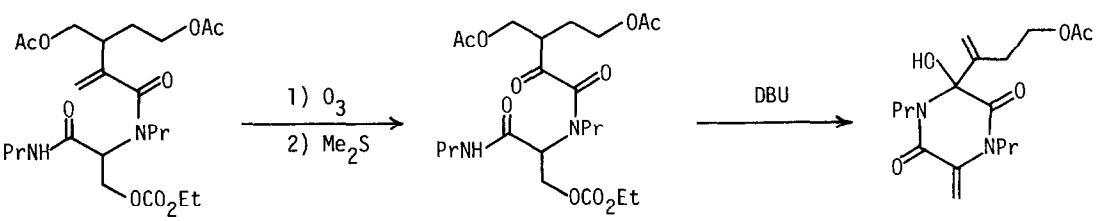
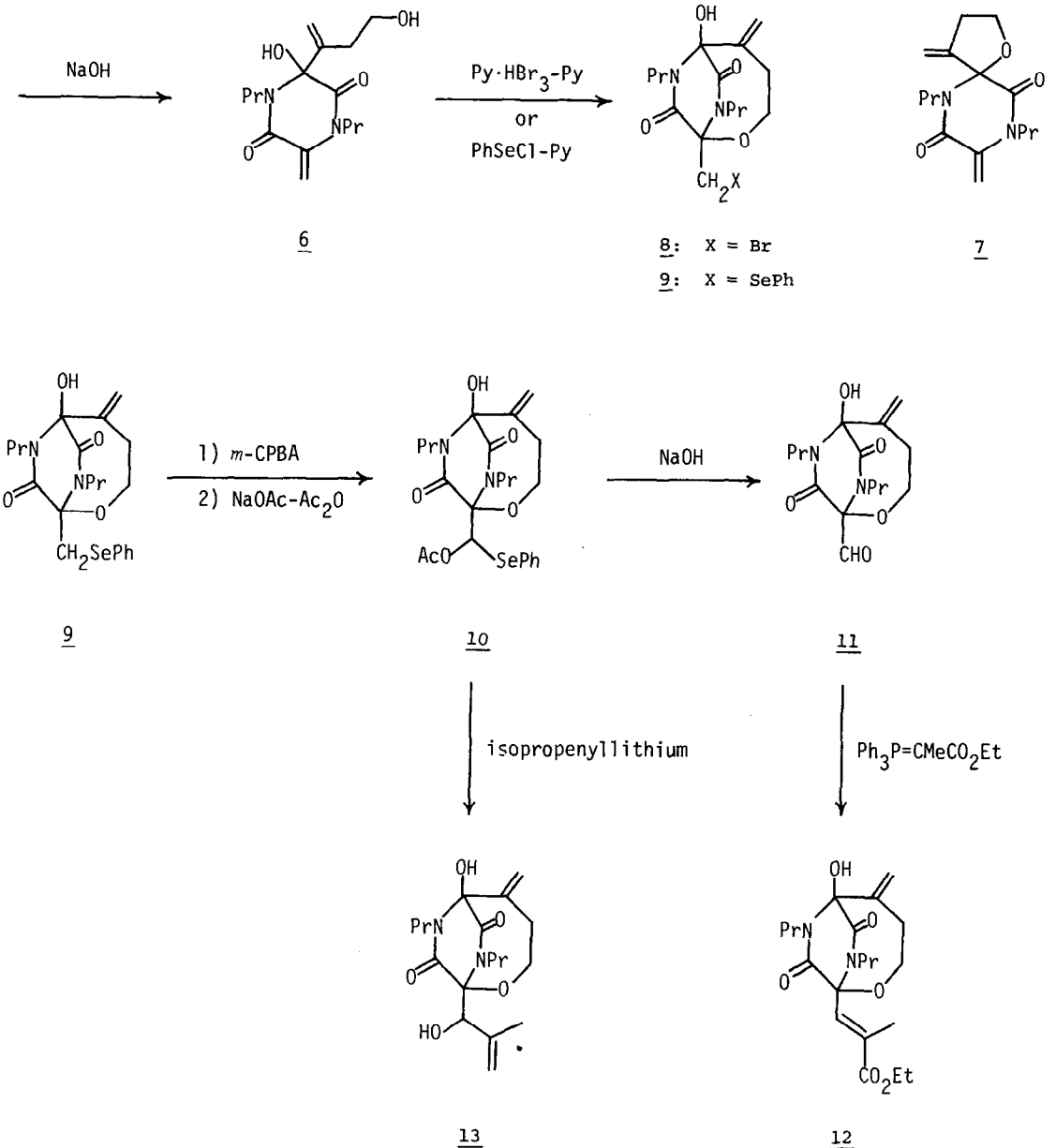


3 4 5



6

8: X = Br

9: X = SePh

7

9

10

11

13

12

The present method will provide a wide variety of bicyclomycin analogues by choosing an appropriate combination of carboxylic acid, amine, aldehyde, and isocyanide for the four-component condensation reaction. Application of these model studies to a total synthesis of bicyclomycin is now in progress.

Acknowledgment: We thank the Robert A. Welch Foundation for support of this work.

References and Notes

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2. Bicyclomycin was also isolated from cultures of *Streptomyces aizunensis*: 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 H. Hoshino, J. Antibiot., 25, 610 (1972); S. Miyamura N. Ogasawara, H. Otsuka, S. Niwayama, H. Tanaka, T. Take, T. Uchiyama, and H. Ochiai, *ibid.*, 26, 479 (1973).
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6. a) R. M. Williams, Tetrahedron Lett., 2341 (1981); b) C.-G. Shin, Y. Sato, and J. Yoshimura, *ibid.*, 2401 (1981); c) S. Nakatsuka, K. Yoshida, and T. Goto, *ibid.*, 2009 (1981); d) H. Maag, J. F. Blount, and T. V. Steppe, presented at the Second Chemical Congress of North American Continent, Las Vegas, Nevada, August, 1980, Abstracts, Org. 347; e) L. V. Dunkerton and R. M. Ahmed, Tetrahedron Lett., 1803 (1980).
7. For a monograph, see I. Ugi, "Isonitrile Chemistry," Academic Press, Inc., New York, 1971.
8. Satisfactory spectroscopic data were obtained for this substance.
9. Prepared from γ-phenylallylsuccinic anhydride [Org. Syn. Coll. Vol., 4, 766 (1963)] in five steps [(1) $LiAlH_4$, THF, reflux; (2) Ac_2O-Py, r.t.; (3) O_3, 20% MeOH-CH_2Cl_2, -78°, then treated with Me_2S at r.t.; (4) Me_2NH·HCl, 38% HCHO, Et_3N, EtOH-H_2O (2:1), 60°; (5) 30% H_2O_2, SeO_2, *t*-AmOH, 60°] in 59% overall yield.
10. ^1H NMR ($CDCl_3$) δ 0.89 (3H, t, J = 7 Hz), 0.92 (3H, t, J = 7 Hz), 1.4-1.9 (4H, m), 2.03 (3H, s), 2.33 (2H, t, J = 7 Hz), 2.88-3.20 (1H, m), 3.37-3.98 (3H, m), 4.17 (2H, t, J = 7 Hz), 4.82 (1H, s), 5.02 (1H, d, J = 1 Hz), 5.15 (1H, s), 5.24 (1H, s), 5.94 (1H, d, J = 1 Hz).
11. ^1H NMR ($CDCl_3$) δ 0.89 (3H, t, J = 7 Hz), 0.93 (3H, t, J = 7 Hz), 1.4-1.9 (4H, m), 2.64-3.08 (3H, m), 3.32-3.88 (3H, m), 4.08-4.56 (2H, m), 4.95 (1H, d, J = 1 Hz), 5.03 (1H, m), 5.28 (1H, m), 5.92 (1H, d, J = 1 Hz).
12. ^1H NMR ($CDCl_3$) δ 0.91 (3H, t, J = 7 Hz), 0.97 (3H, t, J = 7 Hz), 1.4-2.0 (4H, m), 2.12-2.72 (2H, m), 2.88-4.10 (6H, m), 3.48 (1H, d, J = 11 Hz), 4.36 (1H, d, J = 11 Hz), 4.88 (1H, br s), 5.17 (1H, s), 5.62 (1H, s).
13. ^1H NMR ($CDCl_3$) δ 0.91 (3H, t, J = 7 Hz), 0.97 (3H, t, J = 7 Hz), 1.4-1.9 (4H, m), 2.10-2.70 (2H, m), 2.82-4.08 (6H, m), 3.40 (1H, d, J = 13 Hz), 3.99 (1H, d, J = 13 Hz), 4.87 (1H, s), 5.16 (1H, s), 5.61 (1H, s), 7.12-7.68 (5H, m).
14. ^1H NMR ($CDCl_3$) δ 0.87 (3H, t, J = 7 Hz), 0.90 (3H, t, J = 7 Hz), 1.31 (3H, t, J = 7 Hz), 1.4-1.9 (4H, m), 1.80 (3H, d, J= 1 Hz), 2.16-2.72 (2H, m), 2.84-4.08 (6H, m), 4.24 (2H, q, J = 7 Hz), 4.80 (1H, s), 5.19 (1H, s), 5.63 (1H, s), 6.81 (1H, q, J = 1 Hz).
15. Judging from NMR and TLC behavior, 13 appears to be a single compound. However, stereochemistry of the resulting chiral center has not been determined: ^1H NMR ($CDCl_3$) δ 0.88 (6H, t, J = 7 Hz), 1.4-1.9 (4H, m), 1.76 (3H, s), 2.12-2.73 (2H, m), 2.80-4.16 (6H, m), 5.00 (1H, m), 5.10 (1H, s), 5.17 (1H, s), 5.44 (1H, br s), 5.61 (1H, s).

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