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NUCLEAR ANALOGS OF β-LACTAM ANTIBIOTICS I.
THE SYNTHESIS OF 6β-AMIDOCYCLONOCARDICINS

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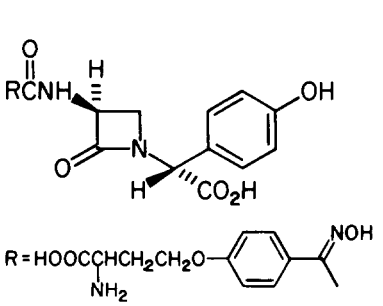
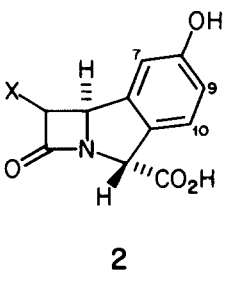
A synthesis of a cyclic analog of the β-lactam antibiotic nocardicin A and a new synthon for N-unsubstituted azetidinones is described.

The discovery of β-lactam fermentation products having novel structures such as thienamycin,[1] the nocardicins,[2] clavulanic acid[3] and sulfazecin[4] has engendered a renewed interest in the synthesis of azetidinone-containing analogs not found in nature. Our attention was attracted in particular to the nocardicins (1) which, until recently,[4] were the only monocyclic azetidinones known to exhibit significant antibacterial activity. The nocardicins are unusual in that they are more active against Gram-negative than Gram-positive microorganisms, and there is considerable evidence that their primary mechanism of action differs from that of the "classical" β-lactam antibiotics.[5] We reasoned that closure of a five-membered ring as in structure (2) would provide the additional ring strain characteristic of penicillin and thienamycin and perhaps afford an antibiotic exhibiting greater potency and a broader spectrum of activity. Some of our efforts toward this objective are described in this communication.[6]

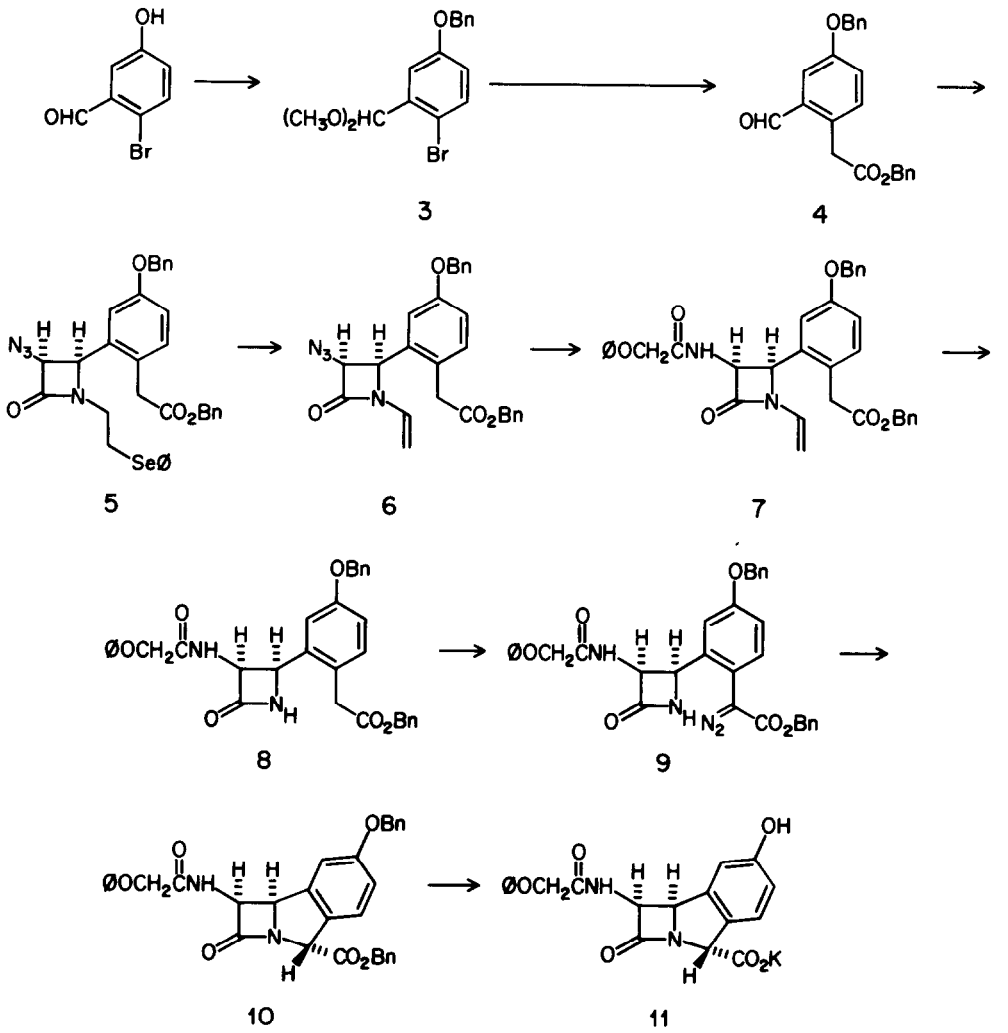


1 Nocardicin A



2 "Cyclonocardicin"

The facile synthesis of 4-arylazetidinones via the imine-acid chloride reaction[7] directed our retrosynthetic analysis of 2 to routes which closed the five-ring through the N4-C3 or C1-C5 bonds. While routes incorporating several different ring-closure reactions were investigated in some detail, only the approach described below, which employs a carbenoid insertion to form the N4-C3 bond,[8] proved compatible with functional group protection suitable for the preparation of the fully elaborated antibiotic.



Treatment of 2-bromo-5-hydroxybenzaldehyde[9] with benzyl bromide and potassium carbonate in acetonitrile (reflux, 4 hrs) followed by trimethylorthoformate and tosic acid in methanol (16 hrs at 25°) afforded bromo acetal (3)[10] in 95% yield. Metal-halogen exchange with n-butyllithium in THF at -78° followed by transmetallation with one equivalent of CuBr-SMe_2 at -60° (1 hr), coupling with benzyl bromo acetate (-60° → -10°, 3 hrs) and acid-catalyzed hydrolysis of the acetal function effected the conversion of **3** to **4** in 63% yield.[11] Condensation of aldehyde (**4**) with 2-(phenylselenenyl)ethylamine[12] in the presence of magnesium sulfate and exposure of the resulting imine to azidoacetyl chloride-triethylamine in dichloromethane (-78° → 0°) afforded azetidinone (**5**) in 93% yield. The stereoselectivity of the cycloaddition was greater than 20:1 cis-trans, in accordance with our expectations based upon previous observations of Bose and Doyle.[13] Oxidative elimination of the phenylselenenyl group in **5** was effected in 99% yield by exposure to m-CPBA in dichloromethane at -20° followed by diisopropylamine (-20°-25°). Reduction of the azide function in **6** with H_2S-triethylamine in dichloromethane[14] followed by acylation of the resulting amine with phenoxyacetyl chloride afforded **7** in 84% yield. Oxidative hydrolysis of the enamide function was effected by exposure of **7** to p-nitroperoxybenzoic acid in 10:10:1 THF-water-formic acid at 25° affording **8** in 80% yield.

Our initial efforts to prepare **9** from **8** by a diazo-transfer reaction[15] were unsuccessful, probably due to the low kinetic acidity of the target methylene-protons and the exceptional acid-lability of the diazo function conferred by the p-alkoxyl group. After considerable experimentation, we found that replacement of the acidic amide protons with trimethylsilyl groups (BSTFA-TMSCl-DMAP-CH_3CN) followed by exposure to p-nitrobenzenesulfonyl azide and $LiOC(C_2H_5)_3$ in THF at -50° afforded diazo compound **9** in low yield.[16] Treatment of **9** with rhodium acetate in toluene at 80° for 30 min afforded the cyclonocardicin derivative (**10**) (5-10% overall yield from **8**). Hydrogenolysis of the benzyl protecting groups ($Pd(OH)_2$, 1 eq. 0.1N $KHCO_3$, 1 atm H_2, THF-water-ethanol) afforded **11** as an amorphous potassium salt. The stability of **11** in neutral aqueous solution was quite poor and microbiological evaluation indicated only low-level activity against a variety of microorganisms.[17]

References and Notes

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4) A. Imada, K. Katano, K. Kintaka, M. Muroi and M. Asai, Nature, **289**, 590 (1981); R. B. Sykes, C. M. Cimarusti, D. P. Bonner, K. Bush, D. M. Floyd, N. H. Georgopapadakou, N. H. Koster, W. C. Liu, W. L. Parker, P. A. Principe, M. L. Rathnum, W. A. Slusarchyk, W. H. Trejo and J. Swells, Nature, **291**, 489 (1981).

5) H. Kojo, Y. Mine, M. Nishida and T. Yokota, J. Antibiot., **30**, 926 (1977).

6) When this work was nearly complete, a paper appeared describing the synthesis of a "homocyclonocardicin" in which a methylene bridge is inserted between the azetidinone C4 and the aromatic ring (G. H. Hakimelahi and G. Just, Can. J. Chem., **57**, 1939 (1979)). The lack of antibacterial activity displayed by this molecule was not entirely discouraging as the 5α-membered ring imposes very little additional ring strain on the nocardicin azetidinone.

7) For leading references see A. K. Mukerjee and A. K. Singh, Tetrahedron, **34**, 1731 (1978).

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10) This and all subsequently described compounds were characterized by spectroscopic means. A selection of significant data is collected in reference **17**.

11) While this transformation appears to be without literature precedent, ethyl phenylacetate has been prepared in modest yield from excess lithium diphenylcuprate and ethyl bromoacetate (O. P. Vig, S. D. Sharma and J. C. Kapur, J. Indian Chem. Soc., **46**, 167 (1969)).

12) Prepared from ØSeNa and 2-bromoethylamine in ethanol. Further exploitation of this versatile new synthon for N-unsubstituted azetidinones and enamides will be described in a forthcoming communication.

13) A. K. Bose, Y. H. Chiang and M. S. Manhas, Tetrahedron Letters, 4091 (1972); A. K. Bose, G. Spiegelman and M. S. Manhas, Tetrahedron Letters, 3167 (1971); T. W. Doyle, B. Belleau, B.-Y. Luh, C. F. Ferrari and M. P. Cunningham, Can. J. Chem., **55**, 468 (1977). The last cited paper contains a good discussion of the mechanism and stereoselectivity of the imine-acid chloride reaction.

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16) Assay of the crude product by IR and NMR indicated a 40-50% yield, but the low-temperature Florisil chromatography used to remove by-product sulfonamide and the amide trimethylsilyl groups caused significant decomposition.

17) The N-phenylacetyl analog of **10** was prepared from **6** by a similar series of transformations but proved too sensitive to deblock. This result is in accord with the relative stability of penicillins V and G.

18) **3:** IR (CH_2Cl_2) 1735 cm^{-1}; δ ($CDCl_3$) 3.40 (s) CH_3O-, 5.05 (S) ϕCH_2O, 5.42 (S) -$CH(OCH_3)_2$, 6.80 (dd, $J_{7,9}$ = 2, $J_{9,10}$ = 7) H_9, 7.20 (d) H_7, 7.25 (s) C_6H_5, 7.30 (d) H_{10}. **4:** IR (CH_2Cl_2) 1735, 1700 cm^{-1}; δ ($CDCl_3$) 4.00 (s) $ArCH_2CO_2$-, 5.16 (s) $2\phi CH_2$, 7.2-7.5 (m) 2φ, $H_{7,9,10}$, 10.20 (s) CHO. **5:** IR (CH_2Cl_2) 2110, 1765, 1735 cm^{-1}; δ ($CDCl_3$) 2.90 (m) -CH_2Se-, 3.05 and 3.65 (m) -NCH_2-, 3.62 (AB, J = 15, Δδ = 15) $ArCH_2CO_2$-, 4.58 (d, $J_{5,6}$ = 6) H_5, 5.06 (d) H_6, 5.10 (AB, J = 13, Δδ = 13) ϕCH_2OAr, 5.14 (s) ϕCH_2OCO-, 6.86 (d, $J_{7,9}$ = 2) H_7, 7.00 (dd, $J_{9,10}$ = 7) H_9, 7.2-7.5 (m) H_{10}, 3φ. **6:** IR (CH_2Cl_2) 2110, 1775, 1735, 1635 cm^{-1}; δ ($CDCl_2$) 3.68 (AB, J = 15, Δδ = 13) $ArCH_2CO_2$-, 4.30 (d, J_{cis} = 16) vinyl CH, 4.46 (d, J_{trans} = 9) vinyl CH, 4.84 (d, $J_{5,6}$ = 6) H_6, 5.08 (s) ϕCH_2OAr, 5.16 (s) ϕCH_2OCO-, 5.32 (d) H_5, 6.72 (dd) N-vinyl CH, 6.90 (d, $J_{7,9}$ - 2) H_7, 7.00 (dd, $J_{9,10}$ = 7) H_9, 7.2-7.5 (m) H_{10}, 2φ. **7:** IR (CH_2Cl_2) 3400, 1770, 1735, 1690, 1630 cm^{-1}; δ ($CDCl_3$) 3.62 (AB, J = 16, Δδ = 22) $ArCH_2CO_2$-, 4.26 (AB, J = 16, Δδ = 23) ϕOCH_2-, 4.40 (d, J_{cis} = 16) vinyl CH, 4.48 (d, J_{trans} = 9) vinyl CH, 5.00 (s) ϕCH_2OAr, 5.16 (s) ϕCH_2OCO, 5.42 (d, $J_{5,6}$ = 6) H_5, 5.66 (dd, J = 8) H_6, 6.6-7.5 (m) 3φ, NH, N-vinyl CH, H_7, H_9, H_{10}. **8:** IR (CH_2Cl_2) 3400, 1780, 1735, 1690 cm^{-1}; δ ($CDCl_3$) 3.56 (AB, J = 16, Δδ = 18) $ArCH_2CO_2$-, 4.26 (AB, J = 15, Δδ = 20) ϕOCH_2-, 5.06 (s) ϕCH_2OAr, 5.16 (s) ϕCH_2OCO-, 5.26 (d, $J_{5,6}$ = 5) H_5, 5.70 (ddd, J_{6NH} = 9, $J_{4,6}$ = 1.5) H_6, 6.18 (d) H_4, 6.6-7.5 (m) 3φ, H_7, H_9, H_{10}, NH. **10:** IR (CH_2Cl_2) 3400, 1775, 1745, 1690 cm^{-1}; δ ($CDCl_3$) 4.44 (AB, J = 14, Δδ = 15) ϕOCH_2-, 5.00 (AB, J = 13, Δδ = 11) ϕCH_2OAr, 5.2 (s) ϕCH_2OCO-, 5.36 (d, $J_{5,6}$ = 5) H_5, 5.66 (s) H_3, 5.80 (dd, J_{6NH} = 8) H_6, 6.80 (bt, J = 7), 6.90 (d, $J_{7,9}$ = 1.5), 7.02 (dd, $J_{9,10}$ = 7) H_9, 7.2-7.5 (m) 3φ, H_{10}. ms 548 (M^+), 357 (M-$\phi OCH_2CONHCH{=}C{=}O$), Calc. for $C_{23}H_{19}NO_3$: 357.1364; Found: 357.1357. **11:** δ (D_2O) 4.66 (s) ϕOCH_2, 5.32 (d, J = 5) H_5, 5.46 (s) H_3, 5.62 (d) H_6, 6.8-7.5 (m) φO.

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