Tetrahedron Letters,Vol.23,No.15,pp 1519-1522,1982 0040-4039/82/151519-04$03.00/0
Printed in Great Britain

NUCLEAR ANALOGS OF β-LACTAM ANTIBIOTICS II.

THE SYNTHESIS OF 6α-(1-HYDROXYLETHYL)-CYCLONOCARDICINS

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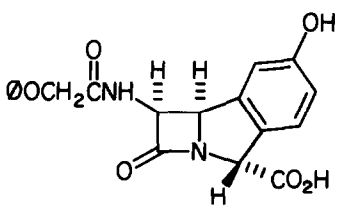
The title compounds were synthesized in ten steps using as key ring-forming reactions an imine-acid chloride cyclization and a rhodium-mediated carbenoid insertion.

In the preceding communication,[1] we described the synthesis of the first cyclonocardicin (**1**), tricyclic analogs of the β-lactam antibiotic nocardicin A. While (**1**) exhibited disappointing low antibacterial activity, its poor stability in aqueous solution left open the possibility that this low activity was not intrinsic to the nucleus but simply a consequence of the failure of (**1**) to reach the target enzymes in the bacterial cell. As the substitution of the 1-hydroxyethyl group for the amide function in bicyclic β-lactam antibiotics is known to confer additional stability to nucleophilic attack,[2] we hoped that such a substitution in our case would result in a substance (**2**) of improved stability and consequently enhanced antimicrobial potency.



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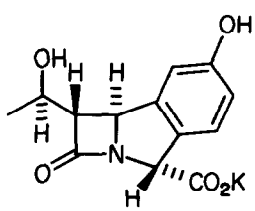

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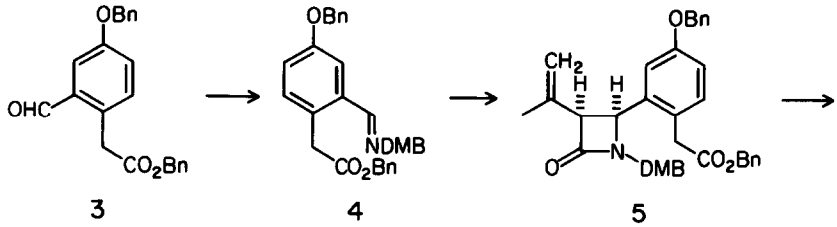
Treatment of the previously described[1] aldehyde (**3**) with 2,4-dimethoxybenzylamine and magnesium sulfate in dichloromethane afforded imine (**4**). Dropwise addition of a solution of 3,3-dimethylacryloyl chloride to a solution of (**4**) and triethylamine in dichloromethane at 25° or 41° (method of Zamboni and Just[3]) produced a mixture containing the desired product (**5**)[4]; the corresponding trans-azetidinone, varying amounts of the conjugated ene-lactam and 3,3-dimethylacryloyl chloride oligomers from which (**5**) could not be readily separated. A study of this reaction revealed a remarkable temperature/solvent effect; substitution of refluxing chloroform for refluxing dichloromethane afforded (**5**) contaminated with only trace amounts of isomers and isolation in 86% yield could be effected by flash chromatography.[5]

Oxidative hydrolysis of the 2,4-dimethoxybenzyl group was effected by exposure to four equivalents of potassium persulfate and two equivalents of dipotassium hydrogen phosphate in refluxing aqueous acetonitrile[6] providing (6) in 46% yield. Oxidative cleavage of the isopropylidene double bond with catalytic osmium tetroxide and pyridine-buffered aqueous sodium periodate under phase-transfer conditions resulted in an 88% yield of the trans-3-acetyl derivative (7), the initially formed cis ketone epimerizing to the thermodynamically favored (7) under the reaction conditions. Reduction of the acetyl group of (7) with 1.5 equivalents of sodium borohydride (6 equivalents hydride) in THF-isopropanol containing 1 equivalent of acetic acid at -60° afforded a 3:4 mixture of isomeric alcohols (8) and (9) in 65% yield.[7] Assignment of the structure (9) to the major isomer is based upon previously established correlations of magnitude of the NMR vicinal coupling constant between the side chain methine proton and the 3-proton of the azetidinone and the chemical shift of the secondary methyl group protons.[8]

To our chagrin, the transformation of (9) to the diazo ester (10) proved no less an obstacle in this case than it was in the amido series,[1] but application of the previously optimized conditions (silylation of (9) with bis(trimethylsilyl)trifluoroacetamide-chlorotrimethylsilane and 4-dimethylaminopyridine followed by treatment with p-nitrobenzenesulfonyl azide and $LiOC(C_2H_5)_3$ in THF at -60°) afforded the unstable diazoester (10) in low yield. The low-temperature flash chromatography employed in the isolation of (10) effected selective N-desilylation. Exposure of (10) to a catalytic amount of rhodium acetate in toluene at 80° yielded a 2:1 mixture of cyclonocardicins (11) and (12), which could not be readily separated by chromatography. The assignment of structure (11) to the major diastereomer rests upon the relative chemical shifts of H-3 in the two compounds.[9] Hydrogenolysis of this mixture (palladium hydroxide, hydrogen at one atmosphere, one equivalent of potassium bicarbonate in THF-ethanol-water) provided the corresponding potassium salts (2) and (13) which were readily separated by reversed-phase TLC (Analtech RP plates, 20% aqueous methanol as eluant). While these compounds exhibited the anticipated increase in stability over (1) (no significant hydrolysis was observed after several days at 25° in D_2O), only low level activity was observed against two sensitive strains of Micrococcus upon bioassay.[10]

The decreased antimicrobial potency of 1 and 2 relative to nocardicin A is quite surprising and requires some explanation. While the elaborate side chain of the natural antibiotic probably has some influence on its biological properties, the lack of antimicrobial activity of the "homocyclonocardicin" 14,[11] which differs from nocardicin A only in the addition of a methylene bridge, suggests that another factor is the critical determinant of bioactivity. We believe that these results are best rationalized by the hypothesis that the binding of nocardicin to its target enzyme entails a rotation of the phenol ring to a plane perpendicular to that defined by the azetidinone ring. This geometry preserves the spatial relationship of the azetidinone and carboxyl groups common to the "classical" β-lactam antibiotics but is inaccessible to 1, 2, and 14. Further results of our investigation of nocardicin analogs will be reported in due course.



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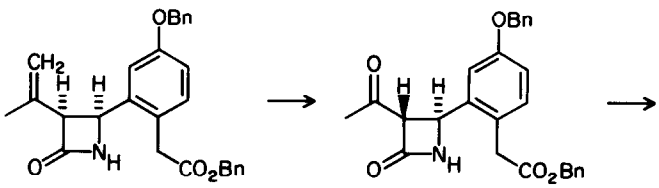

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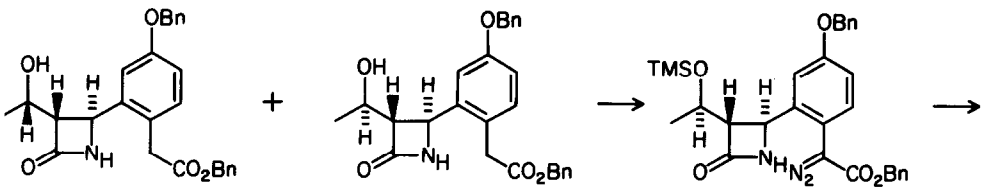

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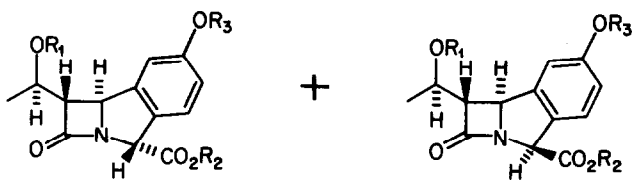
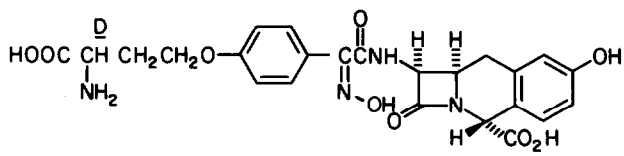


11 R_1 = TMS, R_2 = R_3 = Bn
2 R_1 = R_3 = H, R_2 = K

12 R_1 = TMS, R_2 = R_3 = Bn
13 R_1 = R_3 = H, R_2 = K



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References and Notes

1) J. V. Heck and B. G. Christensen, Tetrahedron Letters, **22**, 5027 (1981).

2) Unpublished observations in these laboratories.

3) R. Zamboni and G. Just, Can. J. Chem., 57, 1945 (1979).

4) This and all subsequently described compounds were characterized by spectroscopic means. Significant data are collected in reference 12.

5) W. C. Still, M. Kahn and A. Mitra, J. Org. Chem., **43**, 2923 (1978).

6) W. F. Huffman, K. G. Holden, T. F. Buckley III, J. G. Gleason and L. Wu, J. Am. Chem. Soc., **99**, 2352 (1977).

7) The use of more hindered hydride-reducing agents ($KBH(s\text{-}Bu)_3$ or $LiBH(s\text{-}Bu)_3$)[8] resulted in a lower overall yield with no improvement in the isomer ratio.

8) F. A. Bouffard and B. G. Christensen, J. Org. Chem., **46**, 2208 (1981).

9) For previous correlations of this type, see D. O. Spry, Tetrahedron Letters, 165 (1973) and T. Kamiya, T. Teraji, M. Hashimoto, O. Nakaguchi and T. Oku, J. Am. Chem. Soc., **98**, 2342 (1976).

10) The 8S* diastereomers corresponding to (**2**) and (**13**) were prepared from (**8**) by an analogous series of transformations and were also devoid of antibacterial activity.

11) G. H. Hakimelahi and G. Just, Can. J. Chem., **57**, 1939 (1979).

12) **5**: IR (CH_2Cl_2) 1745 (br) cm^{-1}; δ ($CDCl_3$) 1.20 (s) $C\underline{H}_3C{=}CH_2$, 3.46 (AB, J = 16, $\Delta\delta$ = 0.046) $ArC\underline{H}_2CO_2$-, 3.52 and 3.73 (s) $OC\underline{H}_3$, 4.30 (AB, J = 16, $\Delta\delta$ = 0.6) $ArC\underline{H}_2N$-, 4.08 (d, $J_{5,6}$ = 6) H_6, 4.80 and 5.10 (s) $={C\underline{H}_2}$, 4.82 (d) H_5, 4.94 (s) $\phi C\underline{H}_2OAr$, 5.06 (AB, J = 12, $\Delta\delta$ = 0.06), 6.4 (m) 6.8-7.5 (m) Ar. **6**: IR (CH_2Cl_2) 3400, 1765, 1735 cm^{-1}; δ ($CDCl_3$) 1.20 (s) $C\underline{H}_3C{=}CH_2$, 3.62 (AB, J = 15, $\Delta\delta$ = 0.06), 4.22 (dd, $J_{5,6}$ = 6, $J_{4,6}$ = 1) H_6, 4.84 and 5.02 (s) $={C\underline{H}_2}$, 5.08 (AB, J = 12, $\Delta\delta$ = 0.04) $\phi C\underline{H}_2OAr$, 5.14 (s) $\phi C\underline{H}_2OCO$-, 5.16 (d) H_5, 5.94 (s) H_4, 6.92 (dd, $J_{10,11}$ = 1.5, $J_{11,12}$ = 7) H_{11}, 7.08 (d) H_{10}, 7.18 (d) H_{12}, 7.3-7.5 (m) 2ϕ. **7**: IR (CCl_4) 1785, 1740, 1720 cm^{-1}; δ ($CDCl_3$) 2.28 (s) $C\underline{H}_3CO$-, 3.74 (s) $ArC\underline{H}_2CO_2$-, 4.10 (d, $J_{5,6}$ = 2) H_6, 5.08 (AB, J = 15, $\Delta\delta$ = 0.06) $\phi C\underline{H}_2OAr$, 5.10 (s) $\phi C\underline{H}_2OCO$-, 5.34 (d) H_5, 6.04 (s) H_4, 6.92 (dd, $J_{10,11}$ = 1.5, $J_{11,12}$ = 7) H_{11}, 7.16 (d) H_{10}, 7.20 (d) H_{12}, 7.3-7.5 (m) 2ϕ. **8**: IR (CH_2Cl_2) 3400, 1765, 1735 cm^{-1}; δ($CDCl_3$) 1.32 (d, $J_{8,9}$ = 7) H_9, 3.12 (dd, $J_{5,6}$ = 2.5, $J_{6,8}$ = 5) H_6, 3.72 (AB, J = 16, $\Delta\delta$ = 0.11 $ArC\underline{H}_2CO_2$-, 4.12 (dq) H_8, 4.84 (d) H_5, 5.08 (s) $\phi C\underline{H}_2OAr$, 5.14 (s) $\phi C\underline{H}_2OCO$-, 6.14 (s) H_4, 6.90 (dd, $J_{10,11}$ = 1.5, $J_{11,12}$ = 7) H_{11}, 7.16 (d) H_{10}, 7.16 (d) H_{12}, 7.3-7.5 (m) 2ϕ. **9**: IR (CH_2Cl_2) 340 cm^{-1}, 1765, 1735 cm^{-1}; δ ($CDCl_3$) 1.26 (d, $J_{8,9}$ = 7) H_9, 3.03 (dd, $J_{5,6}$ = 2, $J_{6,8}$ = 7) H_6, 3.82 (AB, J = 16, $\Delta\delta$ = 0.265) $ArCH_2$, 4.14 (dq) H_6, 4.83 (d) H_5, 5.04 (s) $\phi C\underline{H}_2OAr$, 5.12 (s) $\phi C\underline{H}_2OCO$-, 6.6 (s) H_4, 6.86 (dd, $J_{10,11}$ = 2, $J_{11,12}$ = 7) H_{11}, 7.12 (d) H_{12}, 7.16 (d) H_{11}, 7.3-7.5 (m) 2ϕ. **11**: δ ($CDCl_3$) 0.20 (s) $Si(C\underline{H}_3)_3$, 1.34 (d, $J_{8,9}$ = 7) H_9, 3.12 (dd, $J_{5,6}$ = 2, $J_{6,8}$ = 7) H_6, 4.32 (dq) H_8, 4.92 (bd) H_5, 5.08 (s) $\phi C\underline{H}_2OAr$, 5.16 (s) $\phi C\underline{H}_2OCO$-, 5.60 (d, $J_{3,5}$ = 1) H_3, 6.9 (d, $J_{10,12}$ = 2) H_{10}, 6.96 (dd, $J_{12,13}$ = 7) H_{12}, 7.3-7.5 (m) 2ϕ, H_{13}. **12**: δ ($CDCl_3$) 0.20 (s) $Si(C\underline{H}_3)_3$, 1.34 (d, $J_{8,9}$ = 7) H_9, 3.32 (dd, $J_{5,6}$ = 2.5, $J_{6,8}$ = 6) H_6, 4.32 (dq) H_8, 4.80 (d) H_5, 5.08 (s) $\phi C\underline{H}_2OAr$, 5.16 (s) $\phi C\underline{H}_2OCO$-, 5.27 (bs) H_3, 6.92 (d, $J_{10,12}$ = 2) H_{10}, 6.96 (dd, $J_{12,13}$ = 7) H_{12}, 7.12 (d) H_{13}, 7.3-7.5 (m) 2ϕ. **12**: δ ($CDCl_3$) 1.40 (d, $J_{8,9}$ = 7) H_9, 3.36 (dd, $J_{5,6}$ = 2, $J_{6,8}$ = 6) H_6, 4.40 (dq) H_8, 5.02 (d) H_5, 5.40 (s) H_3, 6.92 (dd, $J_{10,12}$ = 2, $J_{12,13}$ = 7) H_{12}, 6.98 (d) H_{12}, 7.38 (d) H_{13}. **13**: δ ($CDCl_3$) 1.40 (d, $J_{8,9}$ = 7) H_9, 3.52 (dd, $J_{5,6}$ = 2, $J_{6,8}$ = 5) H_6, 4.40 (dq) H_8, 5.16 (s) H_3, 5.94 (d, $J_{10,12}$ = 2) H_{10}, 5.96 (dd, $J_{12,13}$ = 7) H_{12}, 7.20 (d) H_{13}.

(Received in USA 21 December 1981)