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A NOVEL SYNTHESIS OF NOCARDICINS AND THEIR ANALOGUES[1]

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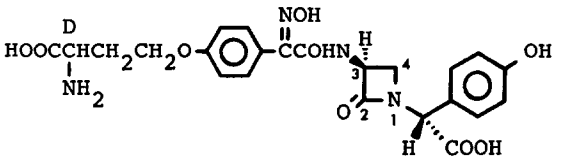
Nocardicins, represented by nocardicin A (1), are a new class of β-lactam antibiotics which show an activity against gram-negative bacteria including Pseudomonas and Proteus[2]. As part of our synthetic program to nocardicins, we have developed an efficient procedure for the preparation of a monocyclic β-lactam ring system and herein report the synthesis of 3-aminonocardicinic acid (3-ANA, 2) which is the basic nucleus of this family of antibiotics. This synthetic method is also of general utility for the preparation of analogous β-lactam compounds.



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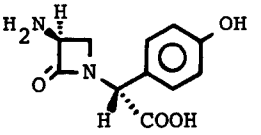

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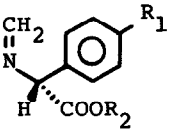

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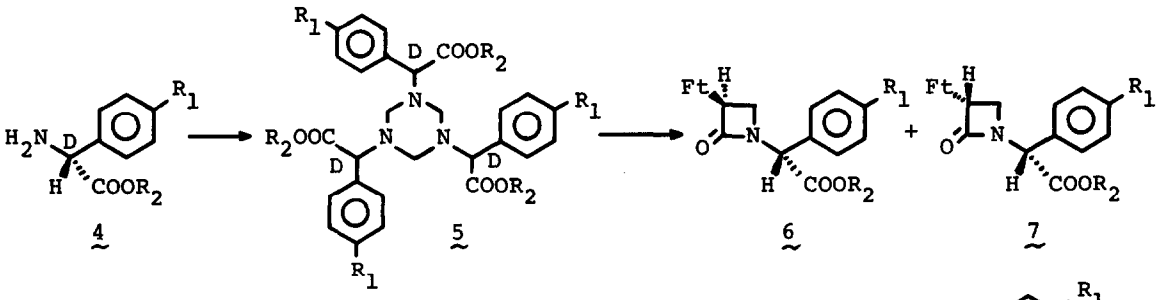
One of the most direct method for the construction of monocyclic β-lactams is the cycloaddition of acid chlorides and imines[3], although this route only provides a group of 4-substituted β-lactams. The synthetic approach to nocardicins, when based on this method, requires formaldimines 3 which usually exist as a trimer, hexahydro-s-triazines 5[4]. We now anticipated that the formers may be revived by treatment of the latter with a Lewis acid, and, when reacted with acid chlorides, can afford azetidinones having no substituents at C-4.

This was realized when hexahydro-s-triazine 5a[5], derived from methyl phenylglycinate (4a) by the usual method[6], was treated with $BF_3 \cdot OEt_2$ in CH_2Cl_2 (room temperature, 10 min), followed by reaction with phthalimidoacetyl chloride-pyri-

dine complex (0°C, 2h). We obtained a 7 : 2 mixture of azetidinones 6a and 7a in 80 % yield (see Table I). Fortunately, the major product 6a was found to be the compound possessing the same configuration at C-3 as that of the natural nocardicins on the basis of the ^1H NMR analysis[7].

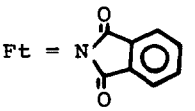
Although the mechanism of β-lactam formation in this reaction is not clear, one reasonable speculation can be made as follows. In the presence of BF_3, the monomer 3 (R_1=H, R_2=CH_3) might exist at least to some extent as a BF_3 complex in equilibrium with the trimer 5a[8], and from the former, the azetidinones could arise via the traditional acid chloride-imine process. The stereochemistry of the products might be governed by the substituents of both reactants. The necessity of BF_3 in this reaction was shown by the fact that the trimer 5a was direc-

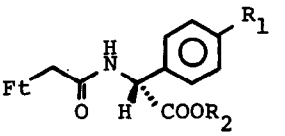


4 5 6 7

a, R_1 = H, R_2 = CH_3

b, R_1 = $OCH_2C_6H_5$, R_2 = $CH_2C_6H_5$

Ft = 



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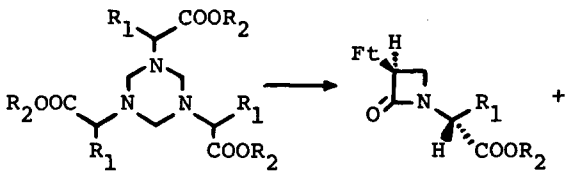
tly reacted with phthalimidoacetyl chloride-pyridine in the absence of $BF_3 \cdot OEt_2$ to give no trace of azetidinones but only the acyl derivative 8a of methyl phenylglycinate, thus corroborating the above mechanistic consideration.

With these results in hand, we turned to the synthesis of 3-ANA (2). Thus, we examined the reaction of hexahydro-s-triazine 5b[5], prepared from benzyl D-p-benzyloxyphenylglycinate (4b)[9], with phthalimidoacetyl chloride. After an exhausive examination, the best yield was obtained under the following conditions. Compound 5b was treated with $BF_3 \cdot OEt_2$ in CH_2Cl_2 (room temperature, 10 min) and added to a mixture of phthalimidoacetyl chloride and pyridine in CH_2Cl_2 at -78°C. After stirring for 2.5 h, the temperature was gradually raised to 0°C, the stirring being continued for an additional 1 h at the same temperature. The usual

workup gave, after a brief silica-gel column chromatography ($CHCl_3$), a 3 : 1 mixture of methyl phthaloylnocardicinate (6b) and its epimer (7b) in 87 % yield[10,11]. This mixture was separated by recrystallization to 40 % yield of 6b ($[\alpha]_D$-178° (c=0.8, $CHCl_3$)) (see Table I) and 12 % yield of 7b (mp 105-8°, $[\alpha]_D$-30° (c=0.8, $CHCl_3$)).

Removal of the protective groups of 6b by debenzylation (10 % Pd-C, EtOH-AcOH) and subsequent dephthaloylation ($H_2N(CH_2)_3N(CH_3)_2$, MeOH) gave 3-ANA (2) (mp 198-200° (dec); $[\alpha]_D$-242°(c=1.1, 0.1N $NaHCO_3$)) in 49 % overall yield. This synthetic sample was identified with the sample derived from the natural nocardicins on comparison of TLC, spectral and optical data.

This new method for the synthesis of monocyclic β-lactams is generally applicable. Apparently, it becomes feasible to replace the p-hydroxyphenyl group of



9 10 11

a, R_1=  (dl), R_2=CH_3
b, R_1=  (D), R_2=CH_3
c, R_1=  (dl), R_2=CH_3
d, R_1= H, R_2=$CH_2C_6H_5$

Table I

Compound	Reaction Temp(°C)	Condition Time(h)	Total Yield of 6(10) and 7(11)(%)	Ratio of 6(10) and 7(11)	Isolation Yield of 6(10)(%) *2
6a and 7a	0	2	80	7 : 2	35*3
6b and 7b	-78~0	3.5	87	3 : 1	40
10a and 11a*1	"	2.5	51	10 : 1	43*4
10b and 11b*1	"	"	65	7 : 2	32*3
10c and 11c*1	"	"	39	3 : 1	17*4
10d and 11d*1	"	"	—	—	35

*1 The corresponding hexahydro-s-triazines 9a-d were prepared, respectively, as in the case of 5a and 5b : 9a, mp 148-51°; 9b, mp 107-9°; 9c, powder, 100 %; 9d, oil, 100 %. *2 Melting points of 6(10) : 6a, mp 133-4°; 6b, 127-8°; 10a, 192-4°; 10b, 167-70°; 10c, 176-8°; 10d, 120-2°. *3 Minor isomers, 7a and 11b, were isolated in low yields by HPLC using μ-Porasil : 7a, mp 96-8°; 11b, mp 134-7°. *4 Minor isomers, 11a and 11c, were not isolated.

nocardicins with other nuclei. Some analogues 10 have thus been prepared without optimization for each compound, as summarized in Table I. Acyl derivatives of these β-lactams and their biological properties will be reported elsewhere.

REFERENCES AND NOTES

1. (a) For total syntheses of nocardicin A, see (i) T. Kamiya, "Recent Advances in the Chemistry of β-Lactam Antibiotics", The Chemistry Society, special publication no.28, p.281, 1977: T. Kamiya, M. Hashimoto, O. Nakaguchi, and T. Oku, Tetrahedron, in press; (ii) G.A. Koppel, L. McShane, F. Jose, and R.D.G. Cooper, J.Am.Chem.Soc., 100, 3933 (1978). (b) A synthesis of 3-ANA has been accomplished by H.H. Wasserman and D.J. Hlasta: private communication.
2. (a) M. Hashimoto, T. Komori, and T. Kamiya, J.Am.Chem.Soc., 98, 3023 (1976); J.Antibiot., 29, 890 (1976); (b) H. Aoki, H. Sakai, M. Kohsaka, T. Konomi, J. Hosoda, T. Kubochi, E. Iguchi, and H. Imanaka, J.Antibiot., 29, 492 (1976); (c) M. Kurita, K. Jomon, T. Komori, N. Miyairi, H. Aoki, S. Kuge, T. Kamiya, and H. Imanaka, J.Antibiot., 29, 1243 (1976); (d) J. Hosoda, T. Konomi, N. Tani, H. Aoki, and H. Imanaka, Agric.Biol.Chem., 41 2013 (1977).
3. (a) H. Staudinger, Justus Liebigs Ann.Chem., 356, 51, (1907); (b) A.K. Bose, G. Spiegelman, and M.S. Manhas, J.Am.Chem.Soc., 90, 4506 (1968).
4. E.M. Smolin and L. Rapoport, "The Chemistry of Heterocyclic Compound", Vol. 13, A. Weissberger, Ed., Interscience Publishers Inc., New York, N.Y., 1959.
5. Prepared by treatment of 4a or 4b with 40 % formaline in AcOEt/H_2O at 0°C: 5a, mp 148-155°, 86 %; 5b, mp 108-110°, 86 %.
6. D.D. Reynolds and B.C. Sossar, J.Heterocycl.Chem., 8, 597 (1971).
7. Major product 6a: ^{1}H NMR ($CDCl_3$) δ 3.46 (dd, 1H, J=3, 5Hz, 4β-H), 3.94 (t, 1H, J=5Hz, 4α-H), 5.48 (dd, 1H, J=3, 5Hz, 3α-H). Minor product 7a: ^{1}H NMR ($CDCl_3$) δ 3.60 (t, 1H, J=5Hz, 4β-H), 4.10 (dd, 1H, J=3, 5Hz, 4α-H), 5.34 (dd, 1H, J=3, 5Hz, 3β-H). In 6a, the 4β proton is trans coupled (J=3Hz) to the 3α proton in agreement with the data of nocardicins[2a].
8. For other examples of reaction which seemed to proceed through formaldimine intermediates, see e.g. (a) ref 6; (b) R. Menten and G. Muller, Angew.Chem., 74, 866 (1962).
9. Prepared from D-p-hydroxyphenylglycine by the standard methods (1. $C_6H_5CH_2Cl$-$CuSO_4$-NaOH, 2. $C_6H_5CH_2OH$-HCl).
10. Major isomer 6b: ^{1}H NMR ($CDCl_3$) δ 3.40 (dd, 1H, J=2.5, 4.5Hz, 4β-H), 3.89 (t, 1H, J=4.5Hz, 4α-H), 5.47 (dd, 1H, J=2.5, 4.5Hz, 3α-H). Minor isomer 7b: ^{1}H-NMR ($CDCl_3$) δ 3.55 (t, 1H, J=4.5Hz, 4β-H), 4.05 (dd, 1H, J=2.5, 4.5Hz, 4α-H), 5.31 (dd, 1H, J=2.5, 4.5Hz, 3β-H).
11. It is interesting to note that this reaction, when carried out at -55°C, gave a higher stereoselectivity (10 : 1 ratio of 6b and 7b, 30 %), although the reaction was not completed even after 96 h.

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