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BIOGENETICALLY-MODELLED TOTAL SYNTHESES (-)-NOCARDICIN A AND (-)-NOCARDICIN G

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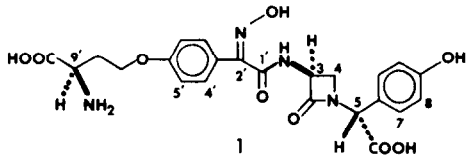
Abstract: *A protected form of L-seryl-D-(p-hydroxyphenyl)glycine was cyclized in a biogenetic sense and partially deprotected to give (-)-t-butyl 3-amino nocardicinate (5) from which (-)-nocardicin A (1) and (-)-nocardicin G (11) were prepared.*



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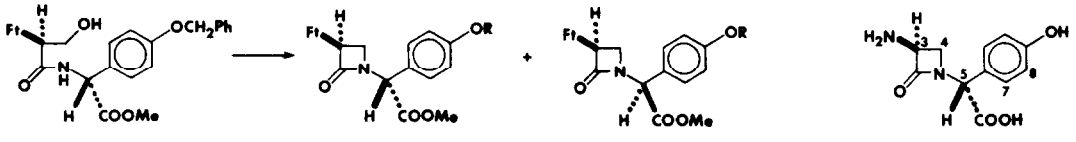
Biosynthetic studies have established the origin of nocardicin A (**1**) from the L-enantiomers of methionine, serine and (*p*-hydroxyphenyl)glycine.[2] Detailed examination of monocyclic β-lactam formation *in vivo* has revealed no change in oxidation state at the seryl β-carbon and clean stereochemical inversion at this center.[3,4] These observations were interpreted[4] most simply by a mechanism involving cyclization of a hypothetical serine-containing peptide to a β-lactam-containing product by an overall process that renders the amide nitrogen nucleophilic and the primary hydroxyl group displaceable in an S_N2 sense. A model of such a net conversion was found in the reaction of protected dipeptide **2** (Ft= phthalimide) under Mitsunobu conditions (EtOOC-N=N-COOEt, PPh_3, THF, r.t., 15 min)[5] to afford an equilibrium 2:1 mixture of **3a** and **4a**.[4,6] Debenzylation of this mixture and fractional crystallization gave the biochemically correct diastereomer **3b** (43% yield) in optically pure form. Maintenance of stereochemical control at the difficult C-5 position has plagued all published syntheses of nocardicin A.[7] However, subsequent mechanistic examination of this four-membered ring-forming transformation led to the discovery that reaction of **2** with 1.0 equivalent of EtOOC-N=N-COOEt/$P(OEt)_3$ (r.t., 4 hr) gave **3a**:**4a** in a ratio of >50:1.[4,8] Unfortunately, in our hands deprotection of optically pure **3b** to (-)-3-aminonocardicinic acid (**5**, 3-ANA) by published[7c] and other routes either failed to proceed to a synthetically useful extent or gave material where the hard-won optical integrity of the starting material was substantially lost.

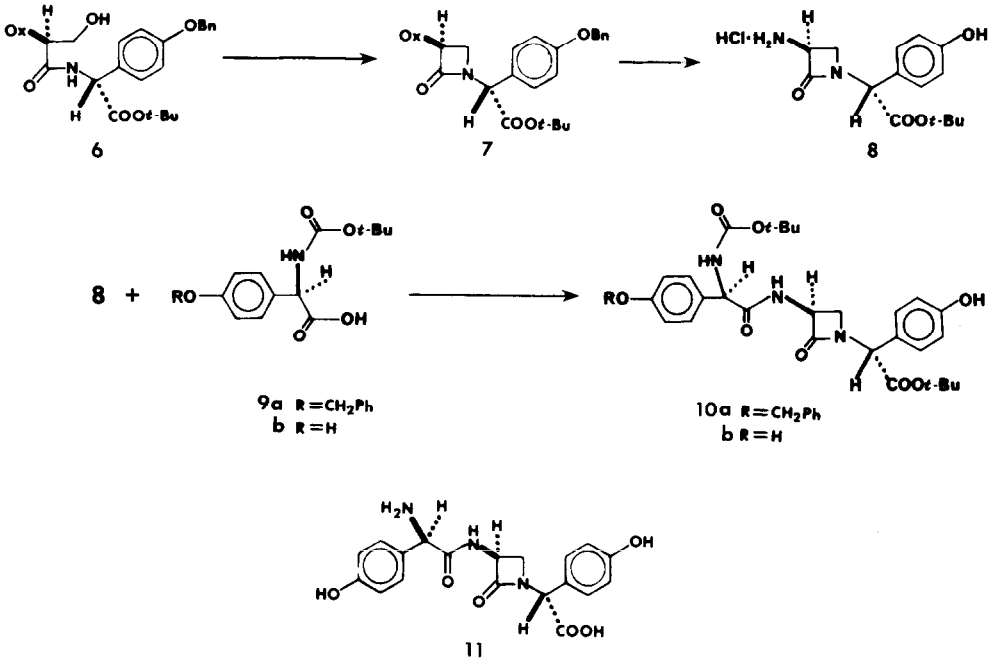


2 **3a** R=CH_2Ph **4a** R=CH_2Ph **5**
b R=H **b** R=H

However, guided by biogenetic considerations and applying alternate protection schemes, efficient total syntheses of all seven of the known nocardicins A-G have been achieved with effectively complete control at each stereogenic center.[9] In this Letter we illustrate the development of this approach in the preparation of (-)-nocardicin G (**11**), the simplest of the nocardicins, and of nocardicin A (**1**), the most fully elaborated.

The first task was to generate a protected form of 3-ANA (5) more tractable to modification at the C-3 amine. The problems associated with deprotection of **3b** were solved by replacing the phthalimide with 4,5-diphenyl-4-oxazolin-2-one (Ox)[10] and substituting a t-butyl ester to mask the carboxylate. Cyclization of **6**, prepared in 93% yield by DCC/1-HBT coupling[11] of the appropriately blocked amino acids,[9,10] under the modified Mitsunobu conditions developed earlier[8] gave **7** as a single diastereomer in 83% yield. Hydrogenolysis (50 psi, 10% Pd/C, 2 days) of **7** in the presence of an equivalent of HCl afforded t-butyl 3-aminonocardicinate (**8**) in 94% yield, mp 128°C (dec), $[\alpha]_D^{21}$ = -148.5° (c=0.12, MeOH). Attempted deprotection at higher pressure (500 psi) led to epimerization at C-5 while catalytic transfer hydrogenation[12] failed to remove the Ox group.

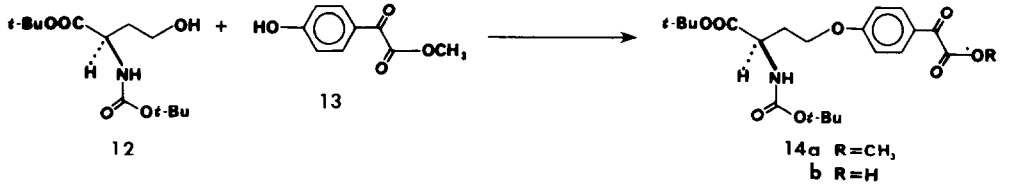
With a suitably protected derivative of 3-ANA now in hand, attempts to couple it to N-t-Boc-D-(*p*-benzyloxyphenyl)glycine (**9a**) and N-t-Boc-D-(*p*-hydroxyphenyl)glycine (**9b**), with and without silyl protection of the phenolic hydroxyl (of **8**), gave only poor yields according to several standard peptide coupling procedures. Finally, reaction of **9b** through a mixed anhydride (i-BuOCOCl, 2,6-lutidine, acetone/DMF, -5°→20°C, 1.5 hr) with **8** gave **10b** in 34% yield with no epimerization detectable at C-5 by 400 MHz ^{1}H-NMR spectroscopy. The use of 1.5 equivalents of **9b** increased the yield of **10b** to an acceptable 59%. Treatment of **10b** with trifluoroacetic acid (TFA)/anisole (0°→20°C, 1 hr) smoothly afforded nocardicin G (**11**) in 90% yield after crystallization from water at pH 5, mp 225-227°C (dec) lit.[13] 200-230°C (dec), $[\alpha]_D^{21}$ = -198° (c=1, 1% aq. $NaHCO_3$), lit.[13] $[\alpha]_D^{24}$ = -205° (c=1, 1% aq. $NaHCO_3$). Spectral characterizations of **11** were in complete accord with those published for the natural product and confirm the absolute configuration of the N-acyl side chain as D.[13]



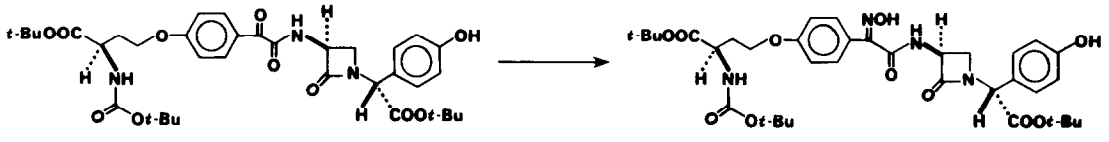
Paralleling the general approach taken in earlier syntheses of nocardicin A (**1**),[7] we planned to couple t-butyl 3-aminonocardicinate (**8**) with an appropriately functionalized and protected side chain, the α-ketoacid **14b**. The route devised, however, embodied several

strategic and practical improvements over the earlier syntheses that, moreover, conserved all of the chiral centers to provide nocardicin A (1) directly in optically pure form.

N-t-Boc-D-Homoserine t-butyl ester (**12**), available in five steps from D-aspartic acid,[14] and methyl (*p*-hydroxyphenyl)glyoxylate (**13**), readily prepared from the commercially-available sodium salt [$(CH_3O)_2SO_2$/DMSO], under standard Mitsunobu reaction conditions[5] gave complex product mixtures. The desired arylalkyl ether **14a** was present in less than 40% yield while *inter alia* the symmetrical alkylalkyl ether from **12** accounted for 30-35% of the mass balance. We have frequently encountered problems of low yields and multiple product mixtures in ether-forming reactions of this type. The observation in this instance of the symmetrical ether formed by the mutual condensation of two molecules of **12** suggested a simple experimental solution that has proved universally successful in our experience. To maintain the concentration of **12** and the Mitsunobu reagent low during the coupling reaction (all are second, or possibly higher, order), THF solutions of **12** and diethyl azodicarboxylate were added *via* syringe pump over 2 hr to the other reagents (**13**, PPh_3, THF, r.t.). A much cleaner reaction was observed from which **14a** could be isolated by flash chromatography (silica gel, hexanes:EtOAc 3:1) in 84% yield. Saponification of the methyl ester was selectively achieved (1.1 equiv. 1*N* NaOH, MeOH, 0°C, 15 min) to provide the desired keto acid **14b** in 86% yield as a white foam.



12 13 14a R=CH3 b R=H



15 16

Formation of the peptide linkage between **14b** and **8** was again accomplished using the anhydride method (i-BuOCOCl, 2,6-lutidine, CH_2Cl_2/DMF, -20°→ r.t., 2 hr) to give **15**, a protected form of nocardicin D, 78%, mp 188-191°C, $[\alpha]_D^{21}$ = -101.6° (c=1.05, MeOH). Oximination of **15** (NH_2OH·HCl, 2,6-lutidine, EtOH, r.t., 9 hr) afforded the nocardicin A derivative **16**, mp 138.5-141°C, $[\alpha]_D^{23}$ = -90.1° (c=0.635, MeOH) in 79% yield together with a 17% yield (separated by preparative tlc, CH_2Cl_2:MeOH 10:1), of the oxime geometric isomer, the corresponding derivative of nocardicin B. These could be individually deprotected or the mixture of oxime isomers could be treated with TFA/$HSCH_2CH_2OH$[15] (r.t., 7 min) to give nocardicin A in 67% yield after crystallization from water at pH 3, mp 211-214°C (dec), lit.[16] 214-216°C (dec), $[\alpha]_D^{21}$ = -148° (c=1, 1% aq. $NaHCO_3$), lit.[7c] $[\alpha]_D$ = -146° (c=1.0, 1% aq. $NaHCO_3$); and spectroscopically indistinguishable from the natural material isolated from *Nocardia uniformis* (ATCC 21806).

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