the two are not mutually exclusive. Though model chemistry resulting in the metal porphyrin mediated ring hydroxylation of aniline has been reported,[13] no prior biomimetic work has been carried out in which catalytic N-demethylation has been demonstrated. We are currently exploring the reaction of DMANO with P-450 enzymes.

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Asymmetric, Biogenetically Modeled Synthesis of (-)-3-Aminonocardicinic Acid

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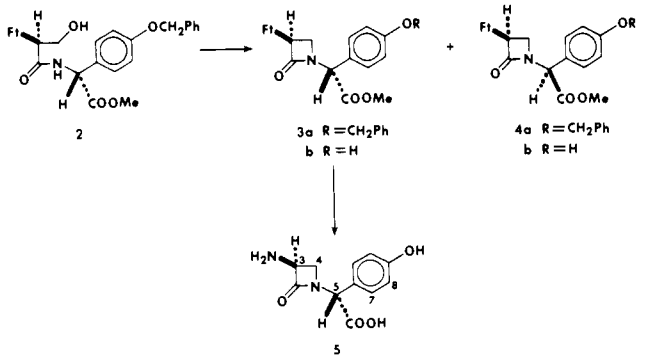
Biosynthetic results obtained in these laboratories support the view that nocardicin A (**1**) is derived from L-methionine, L-serine, and two units of L-(*p*-hydroxyphenyl)glycine (Chart I).[1] Incorporation studies with doubly labeled serine have established that β-lactam formation takes place by cyclization of the seryl residue without alternation of the oxidation state at the β carbon.[1] If generation of a peptide precursor prior to β-lactam formation is presumed, as is now known[2] to be the case in penicillin biosynthesis, a direct mechanistic rationale for β-lactam formation is nucleophilic displacement by amide nitrogen of the presumably activated seryl hydroxyl. This proposal is subject to stereochemical and chemical test. In this communication we demonstrate the latter in a biogenetically modeled cyclization of the appropriately protected, optically active dipeptide **2** (Ft = phthalimido) to a 2:1 mixture of **3** and **4**, the former being a derivative of (-)-3-aminonocardicinic acid (**5**), the structural element common to all the known nocardicins.[3]



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In considering the possible modes of serine activation in vivo, phosphorylation (or the corresponding pyrophosphate) is at once mechanistically attractive and precedented in L-3-phosphoserine, the immediate precursor of L-serine from the intermediates of glycolysis. Similarly, chemical syntheses of β-lactams involving displacements of primary and secondary halides by amide anions generated typically by sodium hydride in dimethylformamide–methylene chloride had been carried out earlier by Kishi,[4] Baldwin,[5] Koppel,[6] and Wasserman.[7] However, to more closely mimic the hypothetical in vivo cyclization to the key four-membered ring, a milder reaction system was sought to generate the desired O-phosphorylated intermediate in situ and the necessary amide anion as well, e.g., **7**. The Mitsunobu reaction[8] held promise to fulfill these two requirements. Recently Miller[9] has reported the conversion of seryl *O*-alkyl hydroxamates to the corresponding N-oxidized β-lactams using the Mitsunobu reaction. While hydroxamates have biochemical relevance in other contexts, presuming the obligate intermediacy of peptide precursors in penicillin[2] and nocardicin[1] formation, their direct involvement in β-lactam biosynthesis is uncertain. In the event, we have found that whatever enhancement in acidity of amide hydrogen afforded by oxidation to the corresponding hydroxamate ($pk_a \sim 6$–10),[9] it is unnecessary for the sake of cyclization as treatment of serine-containing peptides as **2** under Mitsunobu conditions proceeds rapidly and cleanly at room temperature to yield the corresponding β-lactam to the exclusion of acrylamide or γ-lactam products derived from anion formation at C-3 or C-5, respectively.

The biogenetically modeled synthesis was initially attempted by using the racemic dipeptide **6**. *N*-Phthaloyl-DL-serine[10] was condensed with DL-(*p*-benzyloxyphenyl)glycine methyl ester in dry dimethylformamide at room temperature with 1.1 equiv of dicyclohexylcarbodiimide and 2.0 equiv of 1-hydroxybenzotriazole hydrate[11] to afford **6**, after crystallization from ethyl acetate–hexanes (83%, mp 126.5–135 °C), as a 10:1 mixture of diastereomers (favoring **2** and its enantiomer) as judged by ^{1}H NMR spectroscopy at 300 MHz and HPLC analysis. Crystalline **6** was treated under an inert atmosphere with 2.5 equiv each of triphenylphosphine and diethyl diazodicarboxylate in dry tetrahydrofuran at room temperature. After 15 min[12] excess cyclizing reagent was destroyed by addition of water and a mixture of **3a** (and enantiomer) and **4a** (and enantiomer) was isolated as a viscous oil by chromatography on silica gel (ethyl acetate–hexanes 1:1). Coeluting diethyl hydrazodicarboxylate side product **8** was removed by fractional crystallization from chloroform–hexanes. Hydrogenation at atmospheric pressure (sonication) of the oily mixture of isomers (methanol–acetic acid 1:1) with a 50% weight of 5% palladium on carbon gave a 2:1 mixture of racemic **3b** and **4b**, respectively, whose ^{1}H NMR spectra were identical with published data.[13] The change in diastereomeric composition in

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(12) Monitoring the reaction by thin-layer chromatography (silica gel, ethyl acetate–hexanes 2:1) showed clean conversion of **6** to a single less polar spot.

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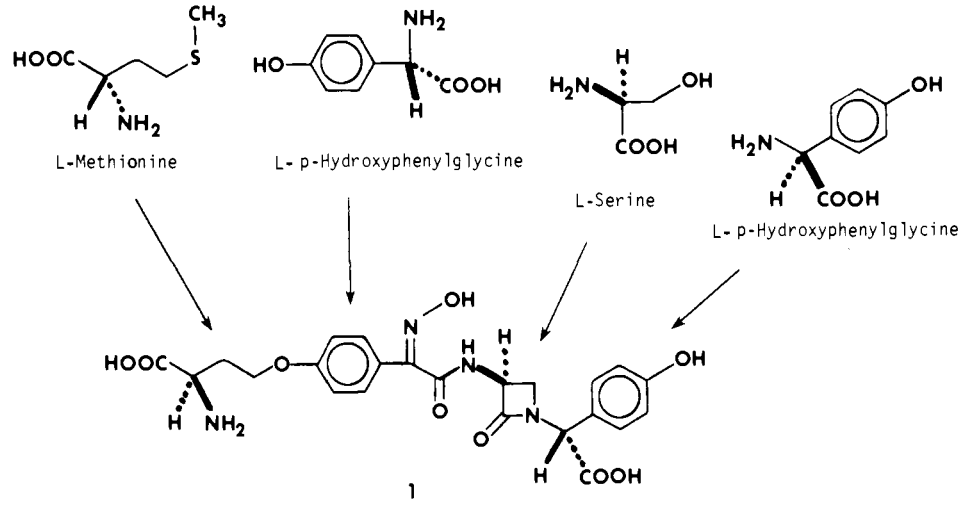
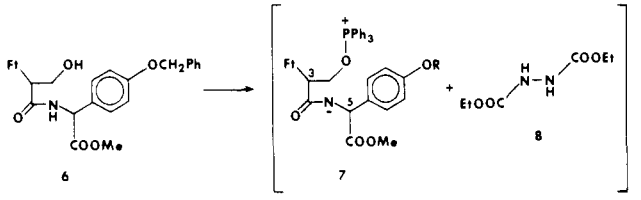
Chart I



the course of the cyclization indicated epimerization at one or more of the asymmetric centers. However, the absence of any detectable acrylamide product implied anion formation had not occurred at C-3.



Heartened by the success of the model reaction, we immediately sought to test this approach in an efficient, completely asymmetric synthesis of (−)-3-aminonocardicinic acid (**5**).[6,7,13,14] To that end *N*-phthaloyl-L-serine[15] was condensed with methyl D-(*p*-benzyloxyphenyl)glycinate[13] as above to afford **2** as a highly crystalline solid,[16] mp 189–191 °C, $[\alpha]_D = -118°$ (*c* 1.0, $CHCl_3$). The optically active peptide was treated under the dehydrating and workup conditions used previously. ^1H NMR analysis of the oily product again showed a 2:1 mixture of diastereomers **3a** and **4a**. Hydrogenation of this mixture gave **3b** and **4b** which upon crystallization from absolute ethanol gave pure **3b** [43%, mp 169–170 °C, $[\alpha]_D$ −239° (*c* 0.030, MeOH); lit.[13] mp 203–204°, $[\alpha]_D$ −236° (*c* 0.025, MeOH)],[17] establishing, as expected, that the stereochemical integrity of the serine α position remained intact throughout the reaction.[18] The optically pure β-lactam **3b** has been sequentially deprotected to (−)-3-aminonocardicinic acid (**5**) previously,[13] and hence its obtention constitutes formal completion of the synthesis.

Recognizing the similar acidities of the C-3, C-5, and amide hydrogens, the rapid and highly selective formation of β-lactam in the cyclization reaction is remarkable. Nonetheless, this observation linked with biosynthetic results[1] which show retention of both hydrogens in vivo at the serine β carbon through the course of four-membered-ring formation supports nucleophilic displacement of activated seryl hydroxyl[19] as the key step for β-lactam formation in nocardicin A.

Acknowledgment. We gratefully acknowledge financial support of the National Institutes of Health for the present work (5 R01 AI14937 and 5 S07 RR07041) and providing partial funding to acquire the Bruker WH-300 used (1P41 GM27512).

(19) Triethyl phosphite may be substituted for triphenylphosphine in the in vitro cyclization step with equal success.

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(16) Partial NMR (300 MHz, $CDCl_3$) δ 3.70 (s, 3 H, OMe), 4.05–4.13 (4 lines, 1 H, *A*BX H-4), 4.35–4.41 (4 lines, 1 H, A*B*X H-4), 4.98–5.02 (4 lines, 1 H, AB*X* H-3), 5.04 (s, 2 H, OCH_2Ph), 5.51 (d, J = 7 Hz 1 H, H-5), 6.96 (d, J = 8.5 Hz, 2 H, H-8), 7.30 (d, J = 8.5 Hz, 2 H, H-7); IR ($CHCl_3$) 1780, 1760 (sh), 1720, 1685, 1610, 1510, 1390, 1180 cm^{-1}.

(17) The overall yield of **3b**, after drying under high vacuum, is based on the *total* amount of peptide **2** used. The melting point observed in the present work for **3b** does not agree with that cited in the literature[13] and may represent an isomorph. However, with respect to all spectral data and specific rotation, agreement is exact.

(18) Facile base-catalyzed epimerization at C-5 has been observed in **3b**[13] and related esters.[6]

Excited-State Energetics and Dynamics of Magnesium Tetraphenylporphyrin Cooled in Supersonic Expansions

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The merger between laser technology and supersonic beams[1] led to remarkable progress in spectroscopy of large molecules. Supersonic expansions[2] provide a source of ultracold "isolated" molecules, characterized by extreme rotational and vibrational cooling.[1,3,4] Laser spectroscopy of large molecules[3-14] seeded in

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