by full-matrix least-squares techniques.[64] The final R value was 0.051. The same details for the NRC data are $2\theta_{max} = 45°$ with 1851 unique data which, when treated with profile analysis,[65] yielded 1116 reflections with $I_{net} \geq 2.5\sigma(I_{net})$. The data were processed with the NRC VAX system,[66] and the final R value was 0.036. The final Fourier map showed densities ranging from +0.35 to −0.35 with no indication of missing or incorrectly placed atoms. Computer-generated figures were drawn on an Apple computer by typing the X-ray coordinates into the program "Molecular Animator".[67]

Acknowledgment. P. J. W. thanks the National Science Foundation for continuing support, the John Simon Guggenheim Foundation for a Fellowship, Felowship, the NRC for its hospitality, and Dr. Joseph McGrath and Lee Sprinkle for preparing OTBBP. S. E. Sugamori provided invaluable technical assistance.

Registry No. 2, 97337-16-1; OTBBP, 22679-53-4; 3,3-dimethyl-1-phenyl-1-indanol, 24387-75-5.

Supplementary Material Available: Five tables of positional parameters, bond lengths, bond angles, and thermal parameters (5 pages). Ordering information is given on any current masthead page.

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Possible Biomimetic Synthesis of β-Lactams

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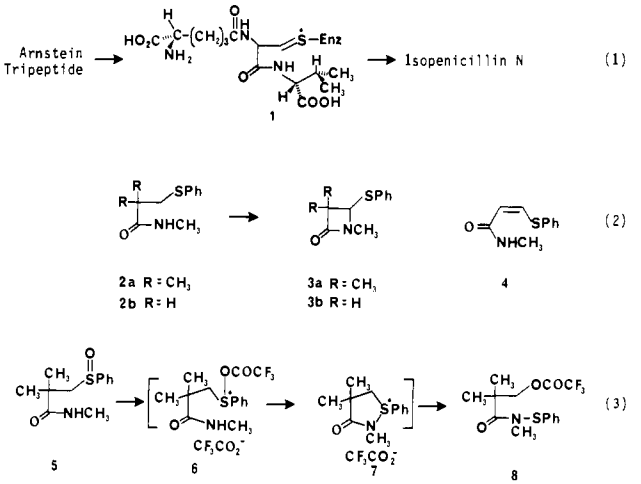
Contribution from Bristol-Myers Company, Pharmaceutical Research and Development Division, Syracuse, New York 13221-4755. *Received February 5, 1985*

Abstract: The first successful syntheses of β-lactams via a Pummerer rearrangement of the corresponding sulfoxides are described. Thus, variously substituted 3-(phenylsulfinyl)propionamides were converted to 4-(phenylthio)-2-azetidinones in 14–50% yields with trimethylsilyl trifluoromethanesulfonate and triethylamine. The sulfonium ion intermediate in the Pummerer rearrangement may be considered as a chemical equivalent of the proposed intermediate involved in the biosynthesis of β-lactam antibiotics.

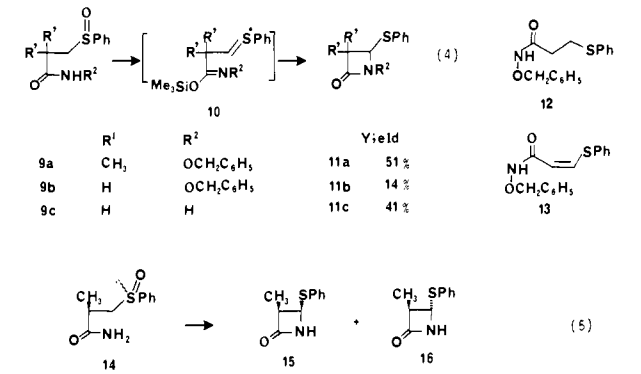
Ever since the structures of penicillins and cephalosporins were elucidated, the biosynthesis of these compounds has been the center of intense research.[1] Although the exact mechanism of conversion of the Arnstein tripeptide, δ-(L-α-aminoadipyl)-L-cysteinyl-D-valine (ACV), to penams and cephems is unknown, Baldwin and co-workers[2] have shown recently that the β-lactam ring is formed first during the enzymatic conversion of ACV into isopenicillin N. Many elegant works have been carried out to probe the biosynthesis of β-lactam antibiotics. Presently, there are three general mechanisms which are consistent with the results of these studies.[3] One of them might be represented by eq 1 in Scheme I.

A Pummerer reaction[4] of the appropriate sulfoxide may be considered to generate a chemical equivalent of the enzymatic system such as **1**. In this paper the first β-lactam synthesis via a sulfonium ion similar to **1** is reported. Historically, there are some previous attempts to effect such a transformation. For example, Wolfe and co-workers have reported that cyclization of

Scheme I



Scheme II



	R¹	R²	Yield
9a	CH_3	$OCH_2C_6H_5$	11a 51%
9b	H	$OCH_2C_6H_5$	11b 14%
9c	H	H	11c 41%

S-phenylcysteinamide sulfoxides to β-lactams could not be achieved under Pummerer rearrangement conditions.[5] Beckwith

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(3) Reference 1a, pp 19.
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and Easton obtained β-lactam **3a** in 4% yield from **2a** under free radical cyclization conditions.[6] When the β-positions to the sulfur atom were not blocked, however, a facile elimination took place to give vinylsulfide **4**, and no β-lactam **3b** was obtained.

Treatment of 2,2,*N*-trimethyl-3-(phenylsulfinyl)propionamide (**5**) under typical Pummerer rearrangement conditions[7] produced compound **8** in 55% yield. This suggested the use of a base to abstract a hydrogen α to the sulfur atom for converting the initial adduct (**6**) to a Pummerer intermediate (i.e., **10**). However, the conditions had to be mild enough for **10** not to undergo a further β-elimination in case the β-positions were not blocked.

For this purpose, use of trimethylsilyl trifluoromethanesulfonate (TMSOTf) appeared ideal although its use in Pummerer rearrangements had not been reported.[8] In the presence of a hindered base, TMSOTf should convert sulfoxide **9** to a Pummerer reaction intermediate **10** and, at the same time, derivatize the carboxamide moiety to a silyl imidate[9] which should decrease the acidity of the β-protons and increase the nucleophilicity of this moiety.

Thus when *N*-(phenylmethoxy)-2,2-dimethyl-3-(phenylsulfinyl)propionamide (**9a**) was treated with 2.2 equiv of TMSOTf and triethylamine in CH_2Cl_2 at −20 °C for 30 min, β-lactam **11a** was obtained after an aqueous workup in a 51% unoptimized yield. Similarly, sulfoxides **9b,c** were transformed to β-lactams **11b,c**[10] in modest yields. The byproducts, for example, in the case of **9b**, are the reduced product[11] **12** (13%), the β-elimination product **13** (7%), and recovered starting material (30%). The ease of cyclization depends on the amide substituent. Thus the sulfoxide derived from **2b** gave only **4** (16%) and its trans isomer (4%) along with the recovered starting material (33%). Sulfoxide **5** yielded only recovered starting material under the conditions described above for **9a**.[12]

Except for some thienamycin-related compounds,[13] most of the naturally occurring β-lactams have cis substituents at C5 and C6 (in the penicillin numbering system). It was, therefore, of interest to investigate the stereochemical outcome of the present method. When 2-methyl-3-(phenylthio)propionamide was oxidized with *m*-chloroperoxybenzoic acid, an approximate 1:1 mixture of diastereomers (**14**) was obtained.[14] When this mixture was treated with 5 equiv of TMSOTf and triethylamine at 20 °C, a mixture of cis (**15**) and trans (**16**) β-lactams was obtained in 41% yield and the starting material was recovered in 23% yield. The ratio of **15** and **16** was 2.7:1. Thus, the fact the major product of this reaction being the cis isomer also appears analogous to the biosyntheses of β-lactams.[15]

Compound **11c** has been utilized for the synthesis of carbapenems,[16,17] penems,[18] oxapenams,[19] monobactams,[20] and the corresponding S-methyl compound in the clavulanic acid synthesis.[21] A model reaction for the cyclization of the thiazolidine ring of penicillins has been carried out by Baldwin.[22] The present work, therefore, not only provides a new method for a β-lactam synthesis but also offers a possible lead in the completely biomimetic syntheses of penicillins and cephalosporins.

Experimental Section

General. NMR spectra were recorded on a JEOL FX90Q or Bruker 360 spectrometer. Chemical shifts are reported in δ values relative to tetramethylsilane as internal standard. Infrared spectra were determined on a Nicolet 5DX FT-IR spectrophotometer. Mass spectra were recorded on a DuPont DP-102, Kratos MS-30, or Kratos MS-50 mass spectrometer. Melting points were taken on a Kofler hot stage melting point apparatus and are uncorrected. Preparative TLC was normally carried out with use of 0.5 mm thick E. Merck F-254 silica gel plates.

General Procedure for the Preparation of Sulfoxides. Phenylsulfinyl amides **5**, **9a–c**, and **14** and the sulfoxide of **2b** were prepared by a *m*-chloroperoxybenzoic acid oxidation of the corresponding phenylthio amides which were in turn prepared by a Schotten–Baumann reaction of the acid chloride with an appropriate amine.[6] As an example, the preparation of 3-(phenylsulfinyl)propionamide (**9c**) is cited.

m-Chloroperoxybenzoic acid (1.72 g, 10 mmol) was added at 3 °C to a solution of 3-(phenylthio)propionamide (1.81 g, 10 mmol) in 150 mL of CH_2Cl_2. After the mixture was stirred for 3 °C for 1 h, 15 mL of 2-propanol was added and the mixture was washed successively with 10% sodium bisulfite solution, saturated $NaHCO_3$ solution, and brine. Drying over Na_2SO_4 and removal of the solvent gave a white crystalline solid which was collected by filteration with ether to give 1.69 g (86%) of **9c**: mp 129–130.5 °C; NMR ($CDCl_3$ + Me_2SO-d_6) δ 2.29–3.49 (m, 4 H), 5.26 (br s, 1 H), 6.80 (br s, 1 H), 7.63 (m, 5 H); IR (film) 1686, 1040 cm^{-1}; MS *m/e* 197 (M^+).

***N*-Methyl-2,2-dimethyl-3-(phenylsulfinyl)propionamide (5)**: yield 85%; mp 71–73 °C; NMR ($CDCl_3$) δ 1.44 (s, 3 H), 1.54 (s, 3 H), 2.91 (d, 1 H, *J* = 14 Hz), 2.94 (d, 3 H, *J* = 5 Hz), 3.14 (d, 1 H, *J* = 14 Hz), 6.51 (br s, 1 H), 7.51–7.86 (m, 5 H); IR (film) 1656, 1038 cm^{-1}; MS *m/e* 239 (M^+).

***N*-Methyl-3-(phenylsulfinyl)propionamide (Sulfoxide of 2b)**: yield 73%; mp 54–55 °C; NMR ($CDCl_3$) δ 2.29–3.36 (m, 4 H), 2.84 (d, 3 H, *J* = 5 Hz), 6.20 (br s, 1 H), 7.67 (m, 5 H); IR (film) 1653, 1040 cm^{-1}; MS *m/e* 211 (M^+).

***N*-(Phenylmethoxy)-2,2-dimethyl-3-(phenylsulfinyl)propionamide (9a)**: yield 98%; mp 78–80 °C; NMR ($CDCl_3$) δ 1.46 (s, 3 H), 1.50 (s, 3 H), 2.91 (d, 1 H, *J* = 5 Hz), 2.97 (d, 1 H, *J* = 5 Hz), 5.03 (s, 2 H), 7.51 (m, 5 H), 7.66 (m, 5 H), 9.94 (s, 1 H); IR (film) 1663, 1038 cm^{-1}; MS *m/e* 331 (M^+).

***N*-(Phenylmethoxy)-3-(phenylsulfinyl)propanamide (9b)**: yield 98%; a colorless viscous oil; NMR ($CDCl_3$) δ 2.34–3.47 (m, 4 H), 4.93 (s, 2 H), 747 (s, 5 H), 7.67 (s, 5 H), 9.40 (br s, 1 H); IR (film) 1669, 1031 cm^{-1}; MS *m/e* 303 (M^+).

2-Methyl-3-(phenylsulfinyl)propionamide (14): obtained as a 9:8 mixture of diastereomers in 85% yield; mp 108–110 °C; NMR ($CDCl_3$) δ [1.25 (d, *J* = 6.8 Hz) + 1.46 (d, *J* = 6.8 Hz), 3 H], [2.75 (dd, *J* = 13.2, 2.9 Hz) + 2.80 (dd, *J* = 13.2, 8.8 Hz), 1 H], 3.06 (m, 1 H), [3.19 (dd, *J* = 13.2, 4.9 Hz) + 3.26 (dd, *J* = 13.2, 10.3 Hz), 1 H], [5.76 (br s) + 5.90 (br s), 1 H], [6.50 (br s) + 6.79 (br s), 1 H], [7.52 (m) + 7.63 (m), 5 H]; IR (film) 1684, 1674, 1034, 1019 cm^{-1}; MS *m/e* 211 (M^+).

***N*-Methyl-*N*-(phenylthio)-2,2-dimethyl-3-(trifluoroacetoxy)propionamide (8).** Trifluoroacetic anhydride (71 μL, 0.5 mmol) was added at 3 °C to a solution of **5** (60 mg, 0.25 mmol) in 5 mL of CH_2Cl_2. After 30 min of stirring at 3 °C, chlorobenzene (5 mL) was added and the solution was warmed in an oil bath. CH_2Cl_2 was evaporated under a stream of N_2 and the resulting solution was heated to 132 °C for 30 min. After the solution was cooled, saturated $NaHCO_3$ solution was added and the organic layer diluted with CH_2Cl_2. The CH_2Cl_2 layer was dried over Na_2SO_4 and evaporated. Flash chromatography (silica gel, CH_2Cl_2) of the residue gave 46 mg (55%) of **8** as a colorless oil: NMR ($CDCl_3$) δ

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(12) A reaction of **5** at room temperature produced only a small amount of the reduced product **2a**. The lack of cyclization of these sulfoxides is most likely due to the steric factors associated with a β-lactam ring since *N*-methyl-5-(phenylsulfinyl)valeramide was found to cyclize to 1-methyl-6-(phenylthio)-2-piperidone.
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(14) The diastereomers were not easily separable by TLC nor HPLC, and the mixture was used as such.
(15) The recovered starting material was an approximately 2:3 mixture of diastereomers. The only identified byproduct (9%) was a sulfimide, 4,5-dihydro-4-methyl-1-phenyl-1*H*,3*H*-isothiazol-3-one. The origin of the stereoselectivity is still under study.
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1.48 (s, 6 H), 3.32 (s, 3 H), 4.58 (s, 2 H), 7.02-7.55 (m, 5 H); IR (film) 1789, 1663 cm^{-1}; MS exact mass, *m/e* 335.0812 (calcd for $C_{14}H_{16}F_3NO_3S$ 335.0803).

General Procedure for the Conversion of Sulfoxides to β-Lactams. As an example, preparation of 4-(phenylthio)-2-azetidinone (**11c**) is cited. To a solution of **9c** (99 mg, 0.5 mmol) in 20 mL of CH_2Cl_2 were added at -20 °C triethylamine (251 μL, 1.8 mmol) and TMSOTf (348 μL, 1.8 mmol). The solution was stirred at -20 °C for 15 min and then quenched by addition of 5% $NaHCO_3$ solution. The organic layer was washed with 0.5% HCl solution and brine. Drying over Na_2SO_4 and removal of the solvent gave a colorless oil. A preparative silica gel TLC (5% CH_3OH-CH_2Cl_2) of this material yielded, besides the starting material (18%) and *trans*-3-(phenylthio)acrylamide (8%), 37 mg (41%) of **11c** which was recrystallized from diethyl ether: mp 72-73 °C (lit.[23] mp 72 °C); NMR ($CDCl_3$) δ 2.90 (ddd, 1 H, *J* = 15.0, 2.26, 1.3 Hz), 3.33 (ddd, 1 H, *J* = 15.0, 5.0, 2.1 Hz), 5.06 (dd, 1 H, *J* = 5.0, 2.6 Hz), 6.49 (br s, 1 H), 7.47 (m, 5 H); IR (film) 1740 cm^{-1}; MS exact mass, *m/e* 179.0411 (calcd for C_9H_9NOS 179.0405).

***N*-(Phenylmethoxy)-3,3-dimethyl-4-(phenylthio)-2-azetidinone (11a)**: yield 51%; a colorless oil; NMR ($CDCl_3$) δ 1.28 (s, 3 H), 1.32 (s, 3 H), 4.73 (s, 1 H), 5.00 (d, 1 H, *J* = 10 Hz), 5.14 (d, 1 H, *J* = 10 Hz), 7.39 (m, 5 H); IR (film) 1780 cm^{-1}; MS exact mass, *m/e* 313.1133 (calcd for $C_{18}H_{19}NO_2S$ 313.1137).

***N*-(Phenylmethoxy)-4-(phenylthio)-2-azetidinone (11b)**: yield 14%; mp 50.5-51 °C; NMR ($CDCl_3$) δ 2.51 (dd, H, *J* = 2.6 Hz), 3.01 (dd, 1 H, *J* = 14, 5 Hz), 4.81 (dd, 1 H, *J* = 5, 2.6 Hz), 5.05 (s, 2 H), 7.41 (m, 5 H); IR (film) 1780 cm^{-1}; MS exact mass, *m/e* 285.0815 (calcd for $C_{16}H_{15}NO_2S$ 285.0824).

3-Methyl-4-(phenylthio)-2-azetidinone (15 and 16). This was obtained in 41% yield as a 2.7:1 mixture of cis (**15**) and trans (**16**) isomers. The NMR spectra was assignable to each isomer, but IR and MS were taken as a mixture.[24] **15**: NMR ($CDCl_3$) δ 1.36 (d, 3 H, *J* = 7.6 Hz), 3.59 (qdd, 1 H, *J* = 7.6, 4.9, 1.5 Hz), 7.31 (m, 5 H). **16**: NMR ($CDCl_3$) δ 1.32 (d, 3 H, *J* = 7.5 Hz), 3.06 (qdd, 1 H, *J* = 7.5, 2.5, 1.0 Hz), 4.59 (d, 1 H, *J* = 2.5 Hz), 7.31 (m, 5 H); IR (film) 1762 cm^{-1}; MS exact mass, *m/e* 193.0566 (calcd for $C_{10}H_{11}NOS$ 193.0562).

Acknowledgment. I thank Drs. C. U. Kim, D. N. McGregor, and Y. Ueda for helpful discussions and the Analytical Department for recording spectra.

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Metabolites of the Marine Prosobranch Mollusc *Lamellaria* sp.

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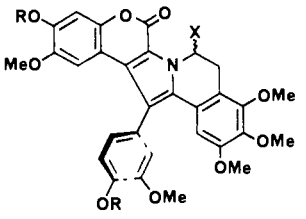
Abstract: The marine prosobranch mollusc, *Lamellaria* sp. contains four aromatic metabolites, lamellarins A-D (**1-4**). The structure of lamellarin A (**1**) was determined by an X-ray crystallographic study and the structures of lamellarins B-D (**2-4**) were assigned by interpretation of spectral data. Lamellarian A (**1**) exists in solution as a 1:1 mixture of two geometrical isomers due to restricted rotation about the C1-C11 bond. Molecular mechanics calculations revealed that the barrier to rotation was large (>600 kcal/mol).

Chemical studies of prosobranch molluscs are rare,[1] particularly when compared with the frequent investigations of opisthobranch molluscs.[2] Six specimens of a species of *Lamellaria*[3] were collected by hand during a night dive (-5 m) near Koror, Palau. Although they are prosobranchs, the *Lamellaria* sp. resembles an opisthobranch since the shell is completely concealed by dark brown, almost black, fleshy tissue. In this paper we report the structural elucidation of four aromatic metabolites, lamellarins A-D (**1-4**) (Chart I).

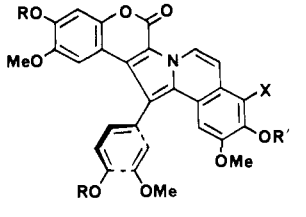
The specimens of *Lamellaria* were stored in methanol (1 L) at 4 °C for 3 years. Dichloromethane and ethyl acetate soluble materials from the methanol extract were combined and subjected to preparative thick-layer chromatography to obtain four UV-active bands. Each band was further purified by reverse-phase LC to obtain lamellarin A (**1**, 13 mg/animal), lamellarin B (**2**, 4 mg/animal), lamellarin C (**3**, 3 mg/animal), and lamellarin D (**4**, 6 mg/animal).

Lamellarin A (**1**) was obtained as pale yellow prisms, mp 168-172 °C dec, from methanol. A parent ion at *m/z* 561.1669 in the mass spectrum was appropriate for a molecular formula of $C_{30}H_{27}NO_{10}$. The highly aromatic character of lamellarin A (**1**) was apparent from the UV spectrum [326 (ε 25 000), 309 (ε 28 000), 275 (ε 33 000), 215 nm (ε 41 000)] and from the number

Chart I



1 R = H X = OH
3 R = H X = H
5 R = Ac X = OAc
7 R = Ac X = H



2 R = H R' = Me X = OMe
4 R = H R' = H X = H
6 R = Ac R' = Me X = OMe
8 R = Ac R' = Ac X = H

of signals in the aromatic region of the ^1H NMR spectrum. A simple analysis of the ^1H NMR specrum (360 MHz, acetone-d_6)

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[‡] Cornell University.
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[⊥] Visiting scholar from the Biophysics Institute, Chinese Academy of Medical Sciences, Beijing, PRC.

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