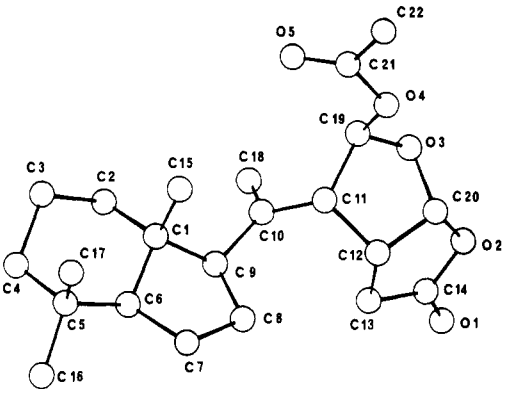


Figure 1. Computer-generated perspective drawing of norrisolide (1). Hydrogens are omitted for clarity, and the enantiomer shown is arbitrary.

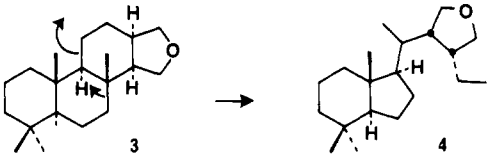


Figure 2. Proposed biosynthesis of the norrisane skeleton.

er-generated perspective drawing less the hydrogens of the final X-ray model of norrisolide (1) is shown in Figure 1. The X-ray experiment did not define the absolute configuration, and the enantiomer shown is an arbitrary choice, the same as that determined for isoagatholactone, a diterpene of known absolute stereochemistry from *Spongia officinalis*.[8,9] There is a perhydroindane bicyclic system with an axial methyl and hydrogen at the bridgeheads. The cyclohexane ring is in the chair conformation, and the conformation of the cyclopentane ring is intermediate between the half-chair and envelope configurations.

After completing this study, we found norrisolide (1) as a very minor constituent of the sponge *Dendrilla* sp. collected at Palau, Western Caroline Islands, but we have been unable to find this or related sponges in the Gulf of California. *Dendrilla* sp. is closely related taxonomically to *Aplysilla rosea* from which Kazlauskas et al.[10] obtained aplysillin (2). We therefore propose that the norrisane skeleton (4) was derived from the spongian[11] skeleton (3) by opening of ring C with concomitant contraction of ring B, a process that results in the observed relative stereochemistry (Figure 2).[12]

(7) All crystallographic calculations were performed on a PRIME 4000 computer operated by the Materials Science Center and the Department of Chemistry, Cornell University. The principal programs used were as follows: REDUCE and UNIQUE, data reduction programs, Leonowicz, M. E., Cornell University, 1978; BLS78A, anisotropic block-diagonal least-squares refinement, Hirotsu K. and Arnold, E., Cornell University, 1980; XRAY76, the X-ray system of crystallographic programs, edited by Stewart, J. M., Technical Report RT-455, University of Maryland, March, 1976; ORTEP, crystallographic illustration program, Johnson, C. K., Report ORNL-3795, Oak Ridge National Laboratory; BOND, molecular metrics program, Hirotsu, K., Cornell University, 1978; "MULTAN-78, A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data", Main, P., principal author, University of York, England. For literature description of MULTAN see: Germain, G.; Main, P.; Woolfson, M. W. *Acta Crystallogr., Sect. B* **1970**, *B26*, 274-285. Woolfson, M. M. *Acta Crystallogr., Sect. A* **1977**, *A33*, 219-225.

(8) Norrisolide (1) is drawn as 1*S**,6*S**,9*R**,11*R**,12*R**,19*R**,20*R**.

(9) Cimino, G.; De Rosa, D.; De Stefano, S.; Minale, L. *Tetrahedron* **1974**, *30*, 645.

(10) Kazlauskas, R.; Murphy, P. T.; Wells, R. J.; Daly, J. M. *Tetrahedron Lett.* **1979**, 903.

(11) Kazlauskas, R.; Murphy, P. T.; Wells, R. J.; Noack, K.; Oberhänsli, W. E.; Schonhölzer, P. *Aust. J. Chem.* **1979**, *32*, 867.

Acknowledgment. Specimens were identified by James R. Lance and Janice E. Thompson. The research was supported by grants from the National Science Foundation (CHE-8121471), National Institutes of Health (CA-24487), and New York Sea Grant Program.

Registry No. 1, 85066-78-0.

Supplementary Material Available: Tables of fractional coordinates, thermal parameters, bond distances, bond angles, and torsion angles (7 pages). Ordering information is given on any current masthead page.

(12) The proposed biosynthetic scheme was a key factor in the elucidation of new structural types from *Dendrilla* sp. Sullivan, B., research in progress.

Jill E. Hochlowski, D. John Faulkner*
Scripps Institution of Oceanography
La Jolla, California 92093

Gayle K. Matsumoto, Jon Clardy*
Department of Chemistry
Baker Laboratory
Cornell University
Ithaca, New York 14853
Received January 25, 1983

Synthesis of Optically Active β-Lactams from Serinylphenylserine. A Convenient Route to Nocardicins and Monobactams[1]

Summary: Chiral synthesis of 3-amido-2-azetidinones has been achieved in good yield by the reaction of L-serinylphenylserine with triphenylphosphine and diethyl azodicarboxylate. These β-lactams can be easily converted to N-unsubstituted β-lactams which are convenient intermediates for nocardicins and monobactams.

Sir: Monocyclic β-lactams[2] have become subjects of renewed attention from synthetic and medicinal chemists since the discovery in nature of nocardicins[3] and monobactams.[4,5]

The absolute configuration of at least one of the β-lactam carbons is of critical importance for antibacterial activity.[6] The value of a synthetic approach to a β-lactam is therefore enhanced if the synthesis leads to an optically active compound with control of the relative configuration of the various asymmetric centers in the molecule. We describe here a convenient synthesis of optically active 3-amino-2-azetidinones starting with readily available derivatives of serinylphenylalanine.

(1) Part 66 in the series "Studies on Lactams". For part 65 see: Bose, A. K.; Manhas, M. S.; Vincent, J. E.; Gala, K.; Fernandez, I. F. *J. Org. Chem.* **1982**, *47*, 4075.

(2) For reviews see: Manhas, M. S.; Bose, A. K. "Beta-Lactams—Natural and Synthetic"; Wiley-Interscience: New York, 1971. Christensen, B. G.; Ratcliffe, R. W. *Annu. Rep. Med. Chem.* **1976**, *11*, 271.

(3) Kamiya, D. In "Recent Advances in the Chemistry of beta-Lactam Antibiotics"; Elks, J., Ed.; The Chemical Society: London, 1977; p 281.

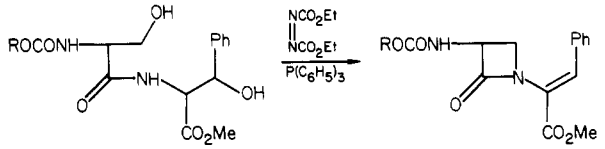
(4) Imada, A.; Kitano, K.; Kintaka, K.; Muroi, M.; Asai, M. *Nature (London)* **1981**, *289*, 590.

(5) Sykes, R. B.; Cimarusti, C. M.; Bonner, D. P.; Bush, K.; Floyd, D. M.; Georgopapadakou, N. H.; Koster, W. H.; Liu, W. C. Parker, W. L.; Principe, P. A.; Rathnum, M. L.; Slusarchyk, W. A.; Trejo, W. H.; Wells, J. S. *Nature (London)* **1981**, *291*, 489.

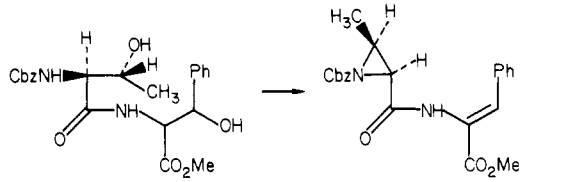
(6) Pfaendler, H. R.; Gosteli, J.; Woodward, R. B. *J. Am. Chem. Soc.* **1980**, *102*, 2039 and references cited therein.

0022-3263/83/1948-1142$01.50/0

The key step in our synthesis involves a two-fold Mitsunobu-type reaction.[7] Our starting material is the easily prepared N-protected serinylphenylserine ester **1**, and the product is the β-lactam **2** obtained in 40–70% yield.

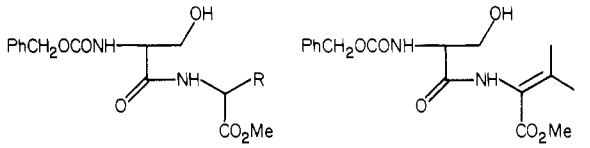


1 **2**



3 **4**

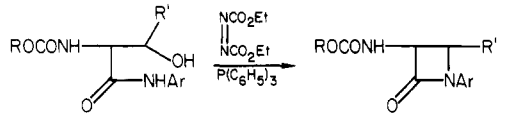
There are several interesting aspects of this β-lactam synthesis. Under similar conditions no β-lactam was formed from serinyl peptides **5–8**; the reaction products



5, R = Ph
6, R = CH_2Ph
7, R = $CH(OH)CH_3$

8

appeared mostly to be dehydroamino acid containing material. The threonine analogue **3** of **1** led to an aziridine, **4**, instead of a 2-azetidinone. In our earlier work,[9] also involving the cyclization of *N*-aryl amides of β-hydroxy-α-amino acids (**9**) to *N*-aryl β-lactams (**10**), we had ob-

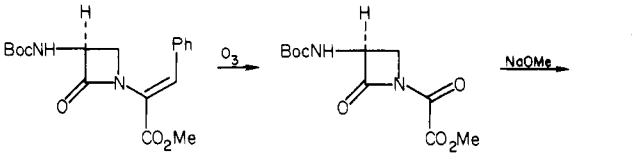


9 **10**

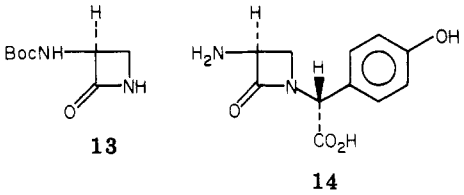
served aziridine formation when threonine (**9**, $R^1 = CH_3$) or phenylserine (**9**, R^1 = Ph) derivatives were the starting material.

Since the chirality of the phenylserine moiety is destroyed in the course of β-lactam formation, it is not necessary to employ optically active phenylserine as the starting material. Formation of a dipeptide (**1**) from an amino-protected L-serine and the methyl ester of DL-phenylserine proceeds readily in good yield under the influence of dicyclohexylcarbodiimide; the β-hydroxy groups need no protection. The nature of the protective group for the amino function of serine does not affect the yield of the β-lactam formed.[11]

The functional groups in β-lactams of type **2** can be manipulated in different ways for preparing diversely substituted β-lactams. Thus, a well-known sequence[12] of ozonation and mild base treatment of **11** leads to a keto



11 **12**

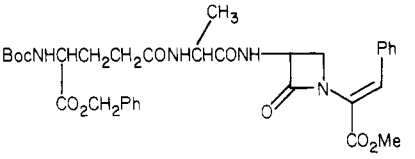


13 **14**

carboxylate, **12**, and then to an N-unsubstituted β-lactam such as **13**. A sample of **12** prepared this way[13] by starting with the dipeptide derivative **11** from L-serine had properties identical with those reported by Miller et al.[14] Compound **13** had the same optical rotation as Miller's compound, showing thereby that no racemization had occurred at C-3 of the β-lactam **11**. Miller et al. have converted **13** to 3-ANA (**14**) which has been converted to nocardicin and analogues.[15] Our synthesis therefore provides convenient access to nocardicin type of antibiotics.

The unsaturated substituent on the β-lactam nitrogen in **2** serves as a protective group for that nitrogen for a variety of reactions aimed at modifying other functional groups in the molecule.

The urethane (or an imido group) at C-3 of the β-lactam **2** can be modified in various ways: for example, the Boc protective group can be removed by treatment with formic or trifluoracetic acid and the amino group acylated. By use of an appropriate group for acylation a β-lactam (**15**) related to sulfazecin[4] (**16**) was prepared.[16]



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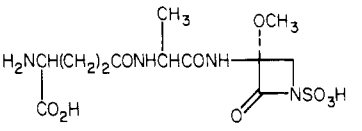


16

(7) For a recent review on the Mitsunobu reaction, see: Mitsunobu, O. *Synthesis* **1981**, 1. For the application of Mitsunobu-type reactions to the synthesis of β-lactams, see ref 8–10.

(8) Miller et al. assumed that a fairly acidic N–H would be required for the internal Mitsunobu reaction to proceed and used hydroxamic acid amides for cyclization to β-lactams and titanium(III) chloride for preparing an N-unsubstituted β-lactam; Mattingly, P. G.; Kerwin, J. F.; Miller, M. J. *J. Am. Chem. Soc.* **1979**, *101*, 3982.

(9) Bose, A. K.; Sahu, D. P.; Manhas, M. S. *J. Org. Chem.* **1981**, *46*, 1229.

(10) Townsend, C. A.; Nguyen, L. T. *J. Am. Chem. Soc.* **1981**, *103*, 4582.

(11) To a stirred solution of 0.416 g of **4** (R = CH_2Ph) in 30 mL of anhydrous THF containing 0.7 g of triphenylphosphine was added dropwise a solution of diethyl azodicarboxylate (0.52 g) in 15 mL of THF over a period of about 20 min under an N_2 atmosphere. The reactants were stirred for additional 4 h. Evaporation of the solvent and chromatography (silica gel) of the residue led to **5** (R = CH_2Ph): mp 171–173 °C; 39% yield. In a similar fashion **15** was prepared: mp 165–166 °C; $[\alpha]^{25}_D$ −48° (*c* 1, $CHCl_3$); 53% yield. The corresponding α-phthalimido β-lactam (mp 140–142 °C) was obtained in 54% yield. Reaction conditions have not been optimized.

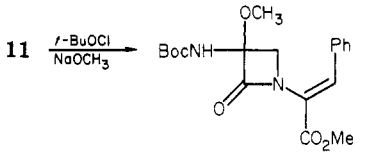
(12) Brain, E. G.; Eglington, A. J.; Nayler, J. H. C.; Pearson, M. J.; Southgate, R. *J. Chem. Soc., Chem. Commun.* **1972**, 299.

(13) Ozonolysis of **15** in methylene chloride solution at −78 °C for a few minutes, warming to room temperature, and subsequent treatment with methanolic sodium methoxide led in 60% yield to **17**: mp 171–172 °C; $[\alpha]^{25}_D$ −25.5° (*c* 2, $CHCl_3$) [lit.[14] $[\alpha]^{25}_D$ −23.5° (*c* 1.27, CH_3OH)].

(14) Mattingly, P. G.; Miller, M. J. *J. Am. Chem. Soc.* **1980**, *102*, 410.

(15) Kamiya, T.; Hashimoto; M.; Makagochi, O.; Oku, T. *Tetrahedron* **1979**, *35*, 323.

Most naturally occurring monobactams are characterized by the cephamycin-type chain. Adaptation of methods[17] developed for the preparation of cephamycin has led to a procedure for converting 11 to racemic 17 in high yield. The reagents used are *tert*-butyl hypochlorite and sodium methoxide.



17

In summary, chiral synthesis of 2-azetidinones[18] variously substituted at C-3 can be achieved in good yield by starting with easily available L-serinylphenylserine. These compounds can be converted readily to N-unsubstituted β-lactams; upon sulfonation of the β-lactam nitrogen,[19] these compounds can become members of the monobactam family with the correct absolute configuration (3*S*) for antibacterial activity.

Experimental details and the applications of this synthetic method to the preparation of various types of β-lactams will be described in a future publication.

Acknowledgment. We are grateful to Provost R. Cotellessa for his interest in this work and to the Stevens Institute of Technology for the support of this research. We thank Dr. Om Prakash for chemical-ionization mass spectra.

Registry No. 1 (R = $PhCH_2$), 85097-39-8; 2 (R = $PhCH_2$), 85097-40-1; 3, 85097-41-2; 4, 85097-42-3; 11, 85097-43-4; 12, 85097-44-5; 13, 80582-10-1; 15, 67509-41-5; 17, 85097-45-6.

Supplementary Material Available: Physical properties, spectral data, and analyses for compounds 3, 4, 8, 11, 13, 15, 17 (2 pages). Ordering information is given on any current masthead page.

(16) Cleavage of the urethane protective group of 15 with formic acid followed by acylation with *tert*-butoxycarbonyl-D-alanine under the influence of dicyclohexylcarbodiimide and 1-hydroxybenzotriazole led to a Boc compound, mp 125–126 °C.[1] Removal of the N-protective group from this intermediate and reaction with *tert*-butoxycarbonyl-D-glutamic acid benzyl ester, dicyclohexylcarbodiimide, and 1-hydroxybenzotriazole produced 19, mp 160.5–161 °C.

(17) Koppel, G. A.; Koehler, R. E. *J. Am. Chem. Soc.* **1973**, *95*, 2403. Firesone, R. A.; Christensen, B. G. *J. Org. Chem.* **1973**, *38*, 1436. Poisel, H.; Schmidt, U. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 295.

(18) The new β-lactams gave satisfactory elemental and spectral analyses.

(19) Floyd, D. M.; Fritz, A. W.; Cimarusti, C. M. *J. Org. Chem.* **1982**, *47*, 176.

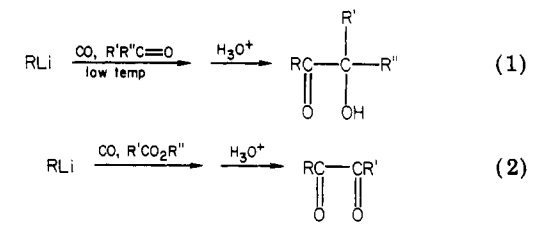
D. P. Sahu, P. Mashava
Maghar S. Manhas, Ajay K. Bose*
Department of Chemistry and Chemical Engineering
Stevens Institute of Technology
Hoboken, New Jersey 07030
Received October 26, 1982

High-Yield Acyl Anion Trapping Reactions: Syntheses of α-Hydroxy Ketones and 1,2-Diketones

Summary: The in situ generation of *n*-$C_4H_9C(O)Li$ by the reaction of *n*-C_4H_9Li with CO at −110 °C in the presence of ketones gives good (50–90%) yields of α-hydroxy ketones. When the *n*-$C_4H_9C(O)Li$ reaction is carried out in the presence of esters, good (65–80%) yields of α-diketones are obtained, thus demonstrating that RC(O)Li can be reagents of practical utility. Similar reactions were observed with *sec*-C_4H_9Li and *tert*-C_4H_9Li.

Sir: Much effort has been expended on the development of reagents and procedures for nucleophilic acylation. In the absence of a *stable* alkali metal or magnesium acyl reagent, which would provide an acyl anion *directly* on reaction with a suitable electrophile, numerous acyl anion synthons have been developed.[2] Attempts to adapt the reaction of organolithium reagents with carbon monoxide, which gives an acyl- or aroyllithium as the initial product,[3,4] have met with only limited success. The synthesis of dialkyl and diaryl ketones by the introduction of CO into an ethereal RLi[5] or R_2CuLi[6] solution at low temperature and the preparation of diarylalkylcarbinols by the atmospheric-pressure carbonylation of solutions of aryllithium reagents at −78 °C in THF in the presence of bromoalkanes[7] represent useful preparative applications.

In experiments designed to extend the synthetic applicability of the RLi + CO reaction, we examined the possibility of preparing acyltrimethylsilanes, $RC(O)SiMe_3$, by the slow, controlled addition of the alkyllithium solution to a solution of Me_3SiCl that was being kept saturated at −110 °C with gaseous carbon monoxide. As reported,[8] such syntheses were successful, and in the case of primary alkyllithiums, they provided acyltrimethylsilanes in good yield. The success of this procedure was due to a combination of favorable relative rates under these reaction conditions: first, the RLi + CO reaction was faster than the alkylation of Me_3SiCl by RLi; second, the reaction of the RC(O)Li thus formed with Me_3SiCl was faster than any other irreversible reaction (such as dimerization[3,4]) that RC(O)Li might undergo. This $RC(O)SiMe_3$ synthesis represents a rather narrow and limited application of the RLi + CO reaction, but our success encouraged us to seek more generally useful organic applications, i.e., applications in which the "acyl anion synthon" alternative has been used in the belief that the unstable RC(O)Li species cannot be usefully applied. We report here the successful nucleophilic acylation of two classes of organic compounds: ketones, which react to give, after hydrolysis, α-hydroxy ketones (eq 1), and esters, which react to give 1,2-diketones (eq 2). Our results are summarized in Table I.



The experimental procedure that was used in these reactions is very similar to that used in our acylsilane synthesis.[8] In one experiment, a 500-mL Morton (creased) three-necked flask was equipped with an overhead mechanical stirrer, a Claisen adapter fitted with a gas outlet

(1) (a) Rhône-Poulenc Co. Graduate Research Fellow. (b) Visiting Scientist; on leave from the Chenguang Chemical Industry Research Institute, Sichuan Province, PRC.

(2) Reviews: (a) Hase, T. A.; Koskimies, J. K. *Aldrichim. Acta* **1981**, *14*, 73; **1982**, *15*, 35. (b) Martin, S. F. *Synthesis* **1979**, 633. (c) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239. (d) Lever, O., Jr. *Tetrahedron* **1976**, *32*, 1943. (e) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 639. (f) Seebach, D. *Synthesis* **1969**, 13.

(3) Jutzi, P.; Schröder, F.-W. *J. Organomet. Chem.* **1970**, *24*, 1.

(4) Trzupek, L. S.; Newirth, T. L.; Kelly, E. G.; Sbarbati, N. E.; Whitesides, G. M. *J. Am. Chem. Soc.* **1973**, *95*, 8118.

(5) Ryang, M.; Tsutsumi, S. *Bull. Chem. Soc. Jpn.* **1967**, *35*, 1121.

(6) Schwartz, J. *Tetrahedron Lett.* **1972**, 2803.

(7) Nudelman, N. S.; Vitale, A. A. *J. Org. Chem.* **1981**, *46*, 4626.

(8) Seyferth, D.; Weinstein, R. M. *J. Am. Chem. Soc.* **1982**, *104*, 5534.

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