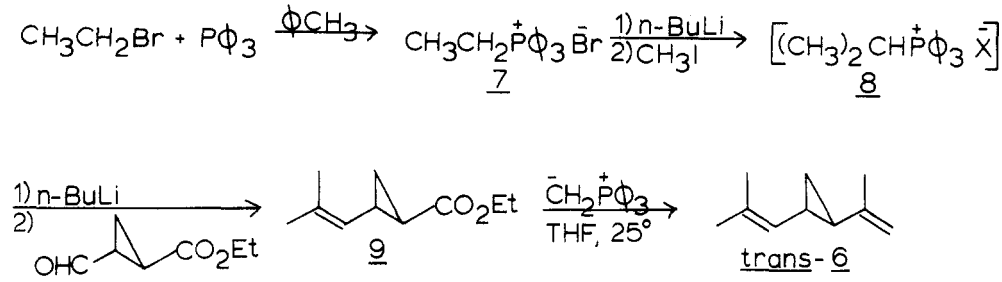
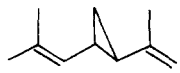
Scheme I



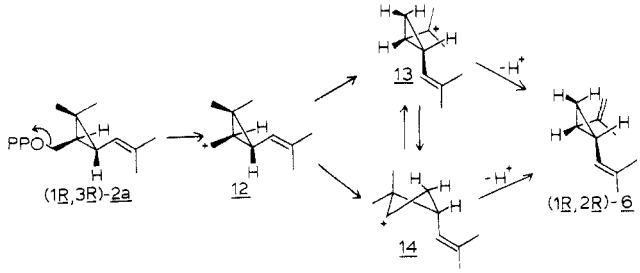
bility of *cis*-dialkenylcyclopropanes[10] argues against this possibility, leaving structure **6** for rothrockene.



**6**

Structure **6** was unambiguously confirmed by the synthetic sequence shown in Scheme I. A "one-pot" conversion of ethyltriphenylphosphonium bromide **7** into cyclopropyl ester **9** was effected by using the procedure of Bertel and Schudel[11] followed by purification by silica gel chromatography (100% $CH_2Cl_2$).[12,13] Transformation of **9** into **6** was achieved by use of a fourfold excess of "salt-free" methylenetriphenylphosphorane.[14-16] The product was purified by silica gel chromatography (5:95, ethyl acetate–hexanes) and preparative gas chromatography (Tween-80) to yield a colorless oil with IR, MS, and NMR spectral properties identical in every respect except optical activity with those of **6** isolated from *A. tridentata rothrockii*. The possibility that epimerization of **9** had occurred during the Wittig reaction was ruled out when strong base equilibration experiments failed to induce such a transformation, establishing the relative stereochemistry as trans.

Experiments to determine the absolute configuration of **6** are now in progress; however, a consideration of the proposed biosynthetic route suggests the stereochemical outcome. Ionization of **2a** to **12** followed by rearrangement can lead to **6** directly via **13** or indirectly via the cyclobutyl intermediate **14**. In either case, loss of a proton would be expected to yield rothrockene with the 1*R*,2*R* absolute configuration. The assumption that **2a** is the precursor to the non-head-to-tail monoterpenes in *A. tridentata rothrockii* rather than the 1*R*,3*S* cis isomer[7] is in agreement with the chiroptical properties of other non-head-to-tail components isolated from these oils.[17]



Although the "rothrockyl" skeleton represents a new structural class of naturally occurring organic molecules, its biological existence was predicted in 1973.[2] The isolation of **6** provides support for the unified approach to irregular monoterpene biosynthesis and for the proposal that plant enzyme systems might act as simple models for the study of squalene biosynthesis in mammals.

**Registry No.** (−)-*trans*-**6**, 80082-35-5; (±)-*trans*-**6**, 80082-36-6; **7**, 1530-32-1; (±)-*trans*-**9**, 53166-50-0; ethyl (±)-*trans*-2-formylcyclopropanecarboxylate, 77183-91-6.

(17) Gaudioso, L. A. Ph.D. Dissertation, University of Utah, Salt Lake City, UT, 1980.

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## Monobactams. Stereospecific Synthesis of (*S*)-3-Amino-2-oxoazetidine-1-sulfonic Acids

*Summary:* A facile, stereospecific synthesis of 3-amino-2-oxoazetidine-1-sulfonic acids (monobactams) by the cyclization of acyl sulfamates derived from β-hydroxy amino acids is described.

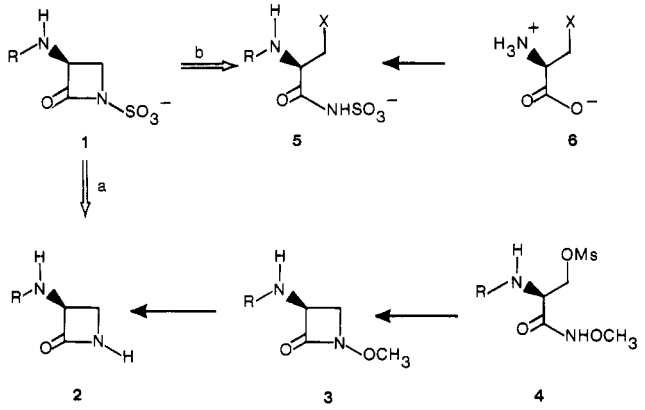
*Sir:* In the preceding communication we described initial synthetic work on monobactams in which the characteristic 2-oxoazetidine-1-sulfonic acid functionality **1** was prepared by the sulfonation of penicillin-derived azetidinone **2** (retrosynthetic path a).[2] In this communication we describe a novel, stereospecific synthesis of monobactams (**1**) based on retrosynthetic path b in which an acylic acylsulfamate (**5**) is cyclized to afford **1** directly. Impetus for this investigation was provided by the finding of increased β-lactamase stability and antimicrobial activity for certain 4-methylmonobactams not readily available from penicillin and the inefficiency of the sequence **6** → **4** → **3** → **2** → **1** utilized to convert β-hydroxy amino acids to **1**. This latter sequence incorporates our modifications[3] of the initial Miller methodology.[4] For the conversion of **6** (X = OH) to **1**, the *N*-methoxyl group, used to facilitate cyclization,[5] is replaced by reductive removal followed by sulfonation.

(10) Baldwin, J. E.; Ullenius, C. *J. Am. Chem. Soc.* **1974**, *96*, 1542.
(11) Bertele, E.; Schudel, P. *Helv. Chim. Acta* **1967**, *50*, 2445.
(12) Coates, R. M.; Robinson, W. *J. Am. Chem. Soc.* **1971**, *93*, 1785.
(13) Poulter, C. D.; Muscio, O. J.; Goodfellow, R. J. *J. Org. Chem.* **1975**, *40*, 139.
(14) Uijttewaal, A. P.; Jonkers, F. L.; van de Gen, A. *J. Org. Chem.* **1978**, *43*, 3306.
(15) Uijttewaal, A. P.; Jonkers, F. L.; van de Gen, A. *J. Org. Chem.* **1979**, *44*, 3157.
(16) Koster, R.; Simic, D.; Grassberger, M. A. *Justus Liebigs Ann. Chem.* **1970**, *739*, 211.

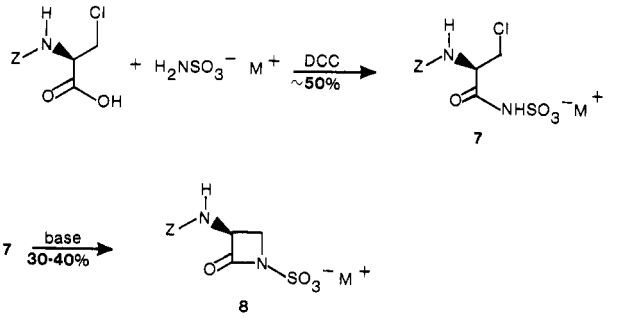
(1) Present address: FMC Corporation, Agricultural Chemicals Group, Princeton, NJ 08540.
(2) Cimarusti, C. M.; Applegate, H. E.; Chang, H. W.; Floyd, D. M.; Koster, W. H.; Slusarchyk, W. A. Young, M. G. *J. Org. Chem.* **1982**, *47*, 179.
(3) Floyd, D. M.; et al., manuscript in preparation.
(4) Miller, M. J.; Mattingly, P. G.; Morrison, M. A.; Kerwin, T. F., Jr. *J. Am. Chem. Soc.* **1980**, *102*, 7026–7032 and references therein.
(5) Miller has discussed the effect of the alkoxyl group on lowering the amide $pK_a$ and the ramifications of this effect.[4] See also Bose, A. K.; Sahu, D. P.; Manhas, M. S *J. Org. Chem.* **1981**, *46*, 1229–1230.

0022-3263/82/1947-0176$01.25/0 

Scheme I



Scheme II [$M^+ = (n\text{-}Bu)_4N^+$]

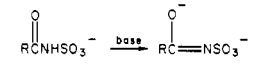


We therefore decided to use the *N*-sulfonyl group to facilitate selective deprotonation of **5** and cyclization to give **1** directly (Scheme I).

We have examined two possible approaches for the conversion of amino acid **6** to acylsulfamate **5**. As an example of the first, we attempted to couple L-Z-β-chloroalanine (Z = carbobenzyloxy) and tetra-*n*-butylammonium sulfamate (Scheme II). However, the sulfamate anion was an extremely poor nucleophile and only moderate yields of **7** were realized when dicyclohexylcarbodiimide (DCC) was used as the coupling agent. Employing DCC and *N*-hydroxybenzotriazole gave essentially none of the desired product, as did other standard coupling procedures. The transformation of sulfamate **7** to azetidinone **8**[7] under basic conditions, albeit in low yield, supplied the impetus for a detailed study of retrosynthetic path b. The second, and better, route to acylsulfamate **5** involved initial conversion of amino acid **6** to a protected α-amino amide and subsequent sulfonation of the primary amide. Based on our successful modification of the hydroxamate synthesis we employed a mesylate as the β leaving group.[3] Scheme III depicts the application of this approach for the conversion of L-threonine to sulfamates **17–19** which were cyclized to azetidinones **20–22** and finally deprotected to afford zwitterion **23**. The scheme also shows that, in addition to commonly employed urethane protecting groups, the route is amenable to simple amide protection of the α-amino function.

L-Threonine was converted to methyl ester **9** in 93% yield after recrystallization from 2-propanol–ethyl acetate mixtures.[8,9] Ammonolysis of **9** at 5 °C in aqueous ammonia (saturated at 0 °C) gave a crude product that contained less than 5% of the hydrolysis product (L-threonine). Although the pure amide **10**[10] could be isolated in greater than 90% yields after recrystallization from aqueous ethanol, it was generally acylated under aqueous conditions without purification. Thus, 1 M aqueous solutions of crude **10** were treated with the appropriate reagents to give **11–13**[11] in 75–85% yields (based on **9**) after recrystallization from ethyl acetate–hexane. Mesylation of the hydroxyamides **11–13** under standard conditions[12] afforded mesylates **14–16**[13] in 80–90% yields following recrystallization from ethyl acetate–hexane. Although the literature indicates that secondary amides were easily sulfonated under a variety of conditions, no general methods for the sulfonation of primary amides were apparent prior to this work.[14] Attempted sulfonation of **14** with freshly prepared pyridine sulfur trioxide complex[15] under a variety of conditions gave incomplete conversion to **17**.[16] An involved study employing several amine sulfur trioxide complexes finally lead to the observation that treatment of **14** with 2.5–3 equiv of 2-picoline–sulfur trioxide complex[15,17] (Pic·$SO_3$) in methylene chloride (room temperature, 4–5 h) followed by ion-pair extraction[18] gave the desired acylsulfamate **17** in greater than 90% yield. Attempting to avoid the isolation of Pic·$SO_3$, we prepared the complex by the addition of chlorosulfonic acid to a cold methylene chloride solution of 2-picoline. The addition of **14** to this solution, which contains an equivalent of 2-picolinium hydrochloride, afforded a very sluggish conversion to **17** at ambient temperature. However, refluxing the reaction for 18–20 h again gave **17** in 90–95% crude yields. Analysis of the crude tetra-*n*-butylammonium salt by TLC[19] demonstrated it to be essentially homogeneous as did $^1H$ and $^{13}C$ NMR analysis.[20] Under identical conditions the Z-amide **16** was converted to sulfamate **18** in 85–90% crude yields. The

(6) Graf, R. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 172–182. This work clearly demonstrates the relative acidity of the amide proton. However, questions concerning the reactivity of dianion i were, at the onset, unanswered.



i

(7) **8**: mp 114–116 °C, $[\alpha]_D$ −9.5° (*c* 1, MeOH). All crystalline compounds gave satisfactory microanalysis.

(8) Guttmann, St.; Boissonnas, R. A. *Helv. Chim. Acta* **1958** *41*, 1852–1867.

(9) **9**: mp. 75–78 °C, $[\alpha]_D$ −10.2° (*c* 5, MeOH). To our knowledge L-threonine methyl ester hydrochloride has not been previously reported as a crystalline solid. Weinstein, B.; Crews, O. P., Jr.; Leaffer, M. A.; Baker, B. R.; Goodman, L. *J. Org. Chem.* **1962**, *27*, 1389–1395; Weinstein et al. report $[\alpha]_D$ −7.8° (EtOH) for the crude oil.

(10) **10**: mp 227–229 °C, $[\alpha]_D$ +4.1° (*c* 1.5, MeOH).

(11) **11**: $Boc_2O$, 2 equiv of KOH, mp 121–122 °C, $[\alpha]_D$ +12.4° (*c* 5, MeOH). **12**: Z-Cl, 2 equiv of $NaHCO_3$, mp 103–105 °C, $[\alpha]_D$ +5.2° (*c* 5, MeOH). **13**: Phenylacetyl chloride, pH 6, mp 163–164 °C, $[\alpha]_D$ +3.0° (*c* 5, MeOH).

(12) Crossland, R. K.; Servis, K. L. *J. Org. Chem.* **1970**, *35*, 3195–3196. Mesylation could also be performed in pyridine at 0 °C with equal success.

(13) **14**: mp 129–131 °C, $[\alpha]_D$ +18.9° (*c* 10, MeOH). **15**: mp 162–164 °C, $[\alpha]_D$ +8.2° (*c* 1, MeOH). **16**: mp 132–133 °C, $[\alpha]_D$ +19.3° (*c* 2, MeOH).

(14) Gilbert, E. E. "Sulfonations and Related Reactions"; Interscience: New York, 1965; p 413 and references.

(15) Hofmann, K.; Simchen, G. *Synthesis* **1979**, 699–700.

(16) Baumgarten, P; Marggraff, I. *Chem. Ber.* **1931**, *64*, 1582–1588.

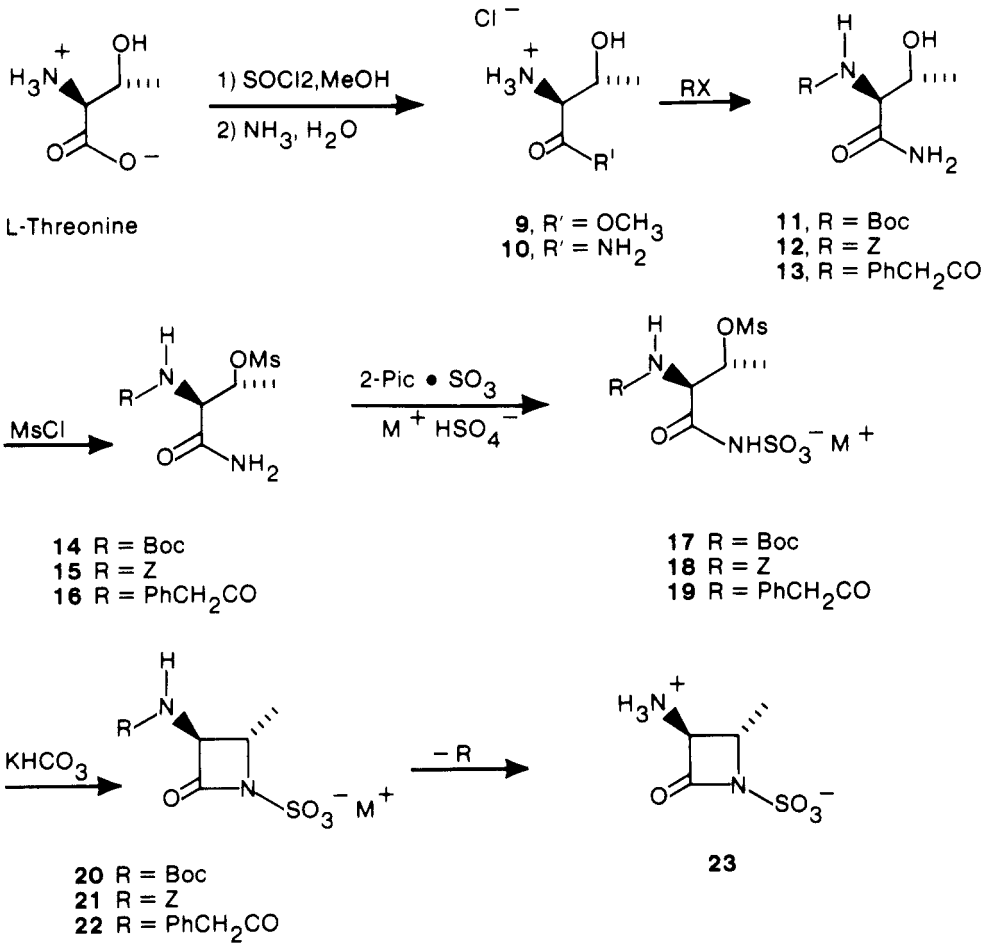
(17) Pic·$SO_3$ was chosen as a more reactive sulfonating agent by consideration of Brown's front strain theory.

(18) Workup of the sulfonation reactions involved pouring of the reaction mixture into a large excess of 0.5 M $KH_2PO_4$, separation of the organic phase which contained neutral organic byproducts and, finally, addition of 1 equiv of tetra-*n*-butylammonium hydrogen sulfate to the aqueous solution. Extraction with methylene chloride removed the desired product as the tetra-*n*-butylammonium salt. Concentration afforded the crude product as a colorless to amber glass. These materials were frequently hygroscopic.

(19) Analysis on Merck silica gel 60 with either EtOAc–MeOH (4:1) or EtOAc–MeOH–HOAc (19:2:2).

(20) The most definitive evidence for sulfonation was obtained from $^{13}C$ NMR in which a 3.4–4.7-ppm upfield shift of the amide carbonyl was observed upon sulfonation.

Scheme III




addition of **17** to a refluxing mixture of 1,2-dichloroethane and water containing 4 equiv of potassium carbonate resulted in a rapid reaction yielding azetidinone **20** as the major product. A cleaner reaction was observed when potassium bicarbonate was employed as the base. Under these conditions (reflux, 15 min), sulfamates **17** and **18** were converted to azetidinones **20** and **21**[21] in 90–99% yields of materials that were virtually homogenous by TLC and spectral analysis. Initial attempts to effect these cyclizations with potassium carbonate in refluxing acetone or acetonitrile, conditions which were successful for the cyclization of β-mesyloxy hydroxamates (**3** → **4**),[3] gave highly variable results.

In view of the extremely mild conditions employed for the ring closure, it seemed possible that the route would be applicable to simple amide protection of the α-amino function if selective sulfonation of a primary amide in the presence of a secondary amide could be achieved. Sulfonation of the phenylacetyl amide **16** under the conditions described above gave an 83% yield of a homogeneous product. Analysis of this material by IR and[13] C NMR indicated, but did not prove, it to be the desired sulfamate **19**. In light of literature precedent[14] we were unable to explain this result, but given the proverbial gift horse, we subjected this product to the cyclization conditions and obtained a 92% yield of monobactam **22**.[22] It is apparent that a significant latitude exists for the protection of the α-amino function.

Deprotection of the amino function of azetidinones **20–22** was performed on the crude isolated products under standard conditions. Simply dissolving the Boc-azetidinone **20** in 97% formic acid[23] (0.3 M) and stirring for 5 h resulted in the precipitation of analytically pure **23**[24] in 65–70% yield. Hydrogenolysis of the Z-azetidinone **21** (EtOH, 5% Pd–C) followed by the addition of formic acid precipitated **23** in 50% yield. Finally, treatment of a methylene chloride solution of **22** with excess phosgene (pyridine, 0 °C) and then addition of methanol again resulted in the precipitation of **23** in 41% yield. The yields in the last two examples have not been optimized.

The conversion of L-threonine to zwitterion **23** proceeds in approximately 50% overall yield in seven steps with Boc protection of the amino function. Due to the remarkable selectivity of the sulfonation reaction and the extremely mild cyclization conditions, a variety of amino protecting groups can be tolerated. The full details of this work, further modifications, and its application to serine and *allo*-threonine will be reported in due course.

**Registry No.** **8**, 80082-47-9; **9**, 39994-75-7; **10**, 33209-01-7; **11**, 80082-48-0; **12**, 49705-98-8; **13**, 80082-49-1; **14**, 80082-50-4; **15**, 80082-51-5; **16**, 80082-52-6; **17**, 80082-54-8; **18**, 80082-56-0; **19**, 80082-58-2; **20**, 80082-60-6; **21**, 80082-62-8; **22**, 80082-64-0; **23**, 80082-65-1; L-threonine, 72-19-5; phenylacetyl chloride, 103-80-0; Z-Cl, 501-53-1; $Boc_2O$, 24424-99-5.

(21) **20**: mp 144–146 °C, $[\alpha]_D$ −14.6° (*c* 2, MeOH). **21**: mp 119–121 °C, $[\alpha]_D$ −12.8° (*c* 2, MeOH).
(22) **22**: mp 141–143 °C, $[\alpha]_D$ −8.7° (*c* 2, MeOH).
(23) Halpern, B.; Nitecki, D. E. *Tetrahedron Lett.* **1967**, 3031–3033.
(24) **23**: mp >200 °C dec, $[\alpha]_D$ −41.0° (*c* 1, $H_2O$).

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