Design and reactivity of organic functional groups—utility of imidazolylsulfonates in the synthesis of monobactams and 3-amino nocardicinic acid[1]

STEPHEN HANESSIAN,[2] CLAUDE COUTURE, AND HEINZ WYSS
Department of Chemistry, Université de Montréal, Montréal (Qué.), Canada H3C 3V1

Received May 30, 1985

STEPHEN HANESSIAN, CLAUDE COUTURE, and HEINZ WYSS. Can. J. Chem. **63**, 3613 (1985).

The imidazolylsulfonate group has been found to be a versatile leaving group in the intramolecular cyclization of *p*-methoxyphenyl amides and related derivatives of *N*-substituted L-serine to give the corresponding β-lactams.

STEPHEN HANESSIAN, CLAUDE COUTURE et HEINZ WYSS. Can. J. Chem. **63**, 3613 (1985).

Le groupement imidazolylsulfonate est un excellent groupe partant dans des réactions de cyclisation intramoléculaire des *p*-méthoxyphényle amides et d'autres dérivés de la L-sérine. Les produits de cyclisation sont les β-lactames correspondants.

Since the emergence of the monobactam family of monocyclic β-lactam antibiotics (1, 2) much effort has been devoted to their total synthesis (3–5), particularly since they have demonstrated potent antibacterial activity and high stability toward β-lactamases (6). Several reports have also been concerned with the synthesis of 2-oxo-azetidines (7), 4-substituted-2-azetidinones (8), 2-amino-4-substituted-2-azetidinones (9), and related compounds (10). The same monocyclic β-lactam system occurs also in the structure of the nocardicin group of antibiotics (11). Several elegant syntheses of this class of natural products and their components in optically active (12, 13) and racemic forms (14) have been reported. Some relevant structures are shown in Scheme 1. New types of 3-amino-2-azetidinones are continually being discovered from fermentation sources (15). We recently reported the total and stereocontrolled synthesis of 4-substituted 3-amino-2-azetidinones (16), which are known to be immediate precursors to potent antibotics in this series (9).

As already discussed (1, 2), a practical access to the monobactams in general could take advantage of the chiron approach (17) utilizing *N*-substituted L-serine or related amino acid derivatives as templates. A high degree of convergence in functionality and sense of chirality can thus be achieved with the intended target while utilizing the same number of required carbon atoms (Scheme 2). Ring closure by intramolecular attack of the amine nitrogen with a suitable leaving group on the hydroxyl terminus, as previously demonstrated for β-halopropionamides (7) or related derivatives (3–5), would complete the task of assembling the diminutive yet important synthetic intermediate. In spite of the seemingly trivial nature of this exercise, it should be noted that racemization, elimination, and intramolecular reactions could effectively compete with ring closure (5) and loom as major threats to such a strategy.

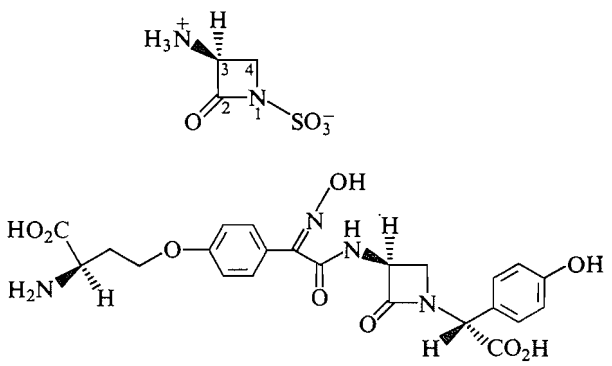
Most of the current syntheses of monobactams rely on using an *N*-alkoxy hydroxamate or *N*-sulfonic acid derivative, in which the NH is significantly acidic, hence more reactive in the internal displacement reaction (4).

We wish to report an exceptionally mild and efficient ring closure reaction of *N*-substituted serine amides, based on a novel activation of the hydroxyl group as the imidazolylsulfonate (imidazylate) (18; for a preliminary announcement of a portion of this work, see also ref. 19). This method leads to the efficient syntheses of (*S*)-3-amino-2-azetidinone and 3-amino nocardicinic acid. Thus, treatment of *N*-[(benzyloxy)carbonyl]-L-serine *p*-(methoxyphenyl) amide **2***a* or the corresponding N-Boc derivative **2***b* with *N,N*-sulfuryl diimidazole (20) in DMF, and adding sodium hydride at −40°C, resulted in sequential *O*-imidazolysulfonylation and ring closure to give the crystalline azetidinones **3***a* and **3***b* in 70 and 85% yields, respectively, isolated by direct crystallization (Scheme 3). Bose and co-workers (5) have reported the successful application of the Mitsunobu reaction (21) to the toluidide derived from *N*-benzyloxycarbonyl L-serine, and the isolation of a β-lactam in 53% yield. Cleavage of the *p*-anisyl group with ceric ammonium nitrate (22) led to the known crystalline azetidinone derivatives **4***a* and **4***b*, respectively, in 70% yield. The isolation of these compounds in good yields indicates that the internal cyclization via the imidazolylsulfonates (Scheme 3) proceeded without racemization, elimination, or aziridine formation (5). The transformation of **4***a* and **4***b* into biologically active monobactams has been described elsewhere (3). Application of the same reaction conditions to the L-threonine series (Scheme 4) gave a poor yield of the expected cyclization product, with aziridine formation being prevalent. Since the imidazolylsulfonate is known to be an excellent leaving group in displacement reactions of secondary alcohols (18), it is likely that aziridine formation in the L-threonine derivatives is the result of the prevalence of a particular conformation in solution that favors attack by the carbamate nitrogen. Related examples can also be encountered in other work (5).

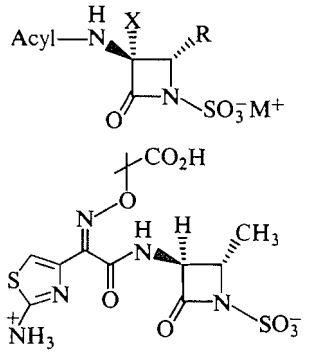
We then turned our attention to the prospects of utilizing the *O*-imidazolylsulfonyl group in the intramolecular cyclization of a precursor to 3-amino nocardicinic acid (Scheme 5). Thus, *N*-phthalimido L-serine **5** (23) was converted into the corresponding dipeptide derivative **6** (24) and the latter was subjected to ring closure via the imidazylate procedure. Under conditions that led to smooth cyclization, in the case of **2***a* or **2***b*, little if any reaction took place. However, gradual warming of the reaction mixture to 0°C led to the expected cyclization to give the diastereomeric β-lactams **8** and **9** (1:1) in 46% yield. It was found that simple treatment of **6** with fluoride ion in the presence of *N,N*-sulfuryl diimidazole resulted in the desired ring closure to give **8** and **9** in 63% yield as a 1:1 mixture of diastereomers. Thus, even though the conditions for cyclization were extremely mild and essentially neutral, considerable epimerization had occurred at the highly susceptible benzylic carbon, which is not unexpected in this series (13*b*). Again, little if any β-elimination was observed, in contrast to the results of the Mitsunobu reaction under some conditions

[1] Presented in part at the Xth European Symposium on Heterocyclic Chemistry, Kaiserslautern, Germany, Oct. 2–4, 1984. See also ref. 19.

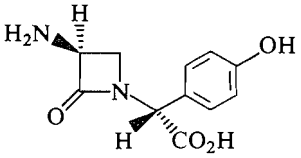
[2] Author to whom correspondence may be addressed.



Nocardicin A

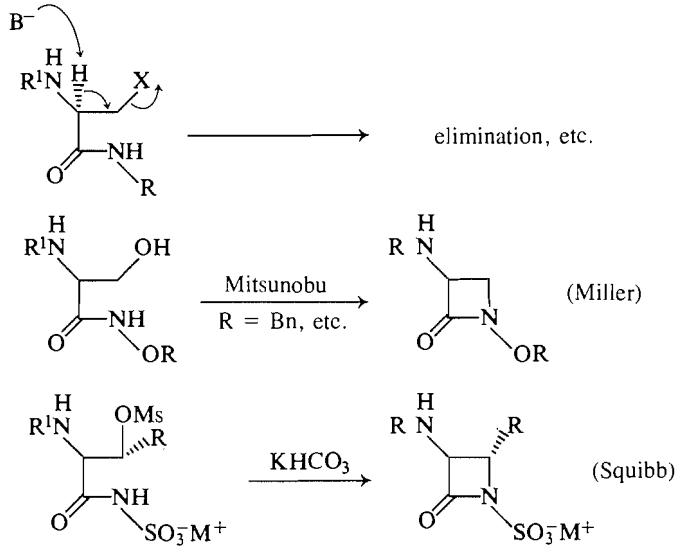


Azthreonam
(SQ 26,776)



Amino nocardicinic acid

SCHEME 1



SCHEME 2

(13*b*). It should be noted, however, that Townsend and Nguyen had succeeded in considerably improving the ratio of **8** and **9** by utilizing tri-n-butylphosphine in the Mitsunobu reaction (13*b*). Catalytic debenzylation of the mixture of **8** and **9** led to **10** and **11**, from which the desired natural isomer **10** could be separated by direct fractional crystallization. The mother liquors were subjected to repeated equilibration in the presence of triethylamine to give **10** in 67% yield. The final mother liquors consisted of a 1:2 mixture of **10** and **11**, respectively. The overall yield of **10** from *N*-phthalimido L-serine **5** was ~33%. The conversion of **10** into (−)-3-amino nocardicinic acid by sequential deprotection has been previously described (13*a*).

Experimental

Melting points are uncorrected. Optical rotations were measured on a Perkin–Elmer automatic spectropolarimeter model 141. The ^{1}H nmr spectra were recorded on Bruker WH 900 and 400 MHz instruments with tetramethylsilane as internal standard in deuteriochloroform as solvent. Mass spectra were recorded on a VG 1212 low resolution mass spectrometer by the direct chemical ionization technique (DCI). Column chromatography was done by the flash technique. EDAC.HCl is the abbreviation for 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride.

N-*Benzyloxycarbonyl* L-*serine* (N-p-*methoxyphenyl*)*amide* (**2**a)

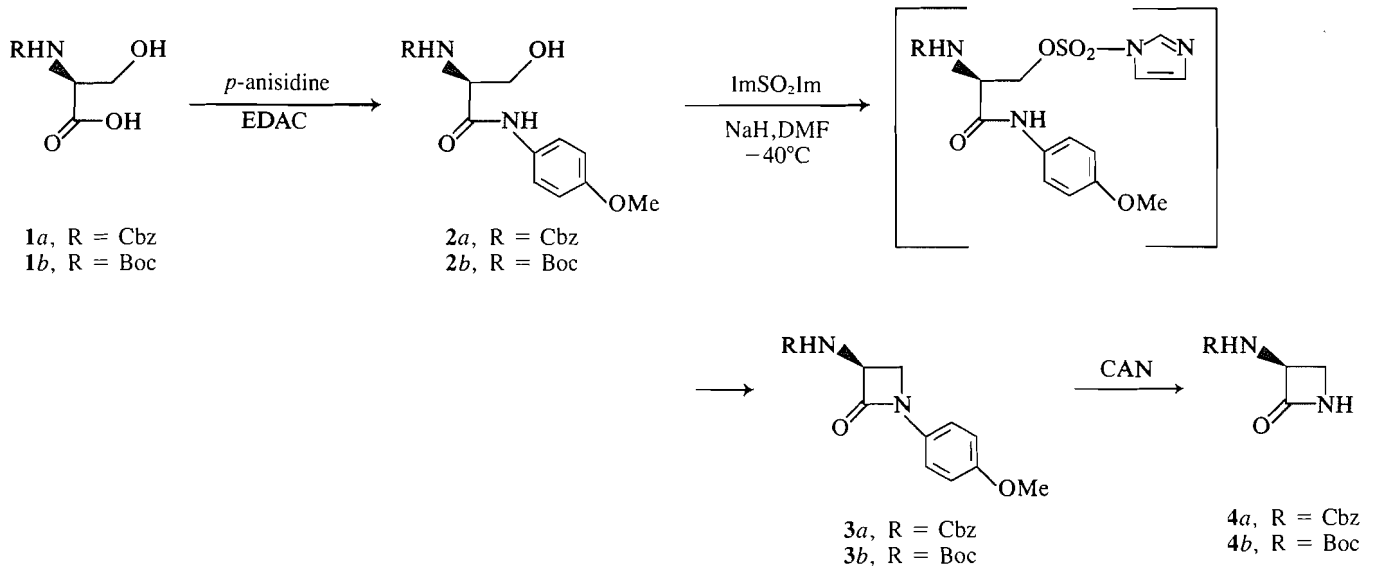
To a solution of **1***a* (1.5 g, 6.28 mmol) in 8 mL of THF were added, in succession, 960 mg (1.1 equiv.) of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDAC.HCl) (25) in 8 mL of dichloromethane. The solution was stirred for 1 h, the solvents were evaporated, and the residue was suspended in ethyl acetate. Washing with dilute aqueous hydrochloric acid, aqueous sodium bicarbonate, then water, and processing the organic phase in the usual manner gave a colorless solid. Trituration with a mixture of ethyl acetate and hexanes (1:1) gave 1.79 g (83%) of the title compound, which was used as such in the next step. Recrystallization of a portion from ethyl acetate gave an analytical sample, mp 146–147°C; $[\alpha]_D$ −16° (*c* 1, THF); λ_{max}: 1660 (amide) cm^{-1}; ms: 345 (M + 1), etc. *Anal.* calcd. for $C_{18}H_{19}N_2O_5$: C 62.79, H 5.81, N 8.14; found: C 62.86, H 5.79, N 8.17.

N-tert-*Butoxycarbonyl* L-*serine* (N-p-*methoxyphenyl*)*amide* (**2**b)

A solution containing **1***b* (8.85 g, 43 mmol), 5.83 g (1.1 equiv.) of *p*-anisidine, and 9.07 g (1.1 equiv.) of EDAC.HCl in a total of 75 mL of THF and 25 mL of dichloromethane was stirred and processed as described for **2***a*. The title compound was obtained as a colorless solid in 68.6% yield (9.18 g). Recrystallization from ethyl acetate gave pure product, mp 105–106°C; $[\alpha]_D$ −76° (*c* 1, $CHCl_3$); λ_{max}: 1660 (amide) cm^{-1}; ms: 311 (M + 1), etc. *Anal.* calcd. for $C_{15}H_{21}N_2O_5$: C 58.06, H 7.10, N 9.03; found: C 58.14, H 7.12, N 8.92.

(S)-3-N-[(*Benzyloxycarbonyl*)*amino*]-1-p-*methoxyphenyl*-2-*azetidinone* (**3**a)

A solution containing **2***a* (2 g, 5.81 mmol) in 30 mL of DMF was added dropwise at 0°C to 5 mL of DMF containing 348 mg (1.5 equiv.) of sodium hydride (60% suspension in mineral oil) that was previously washed with hexanes. The mixture was cooled to −40°C and 1.72 g (1.5 equiv.) of *N*,*N*-sulfuryl diimidazole in 7 mL



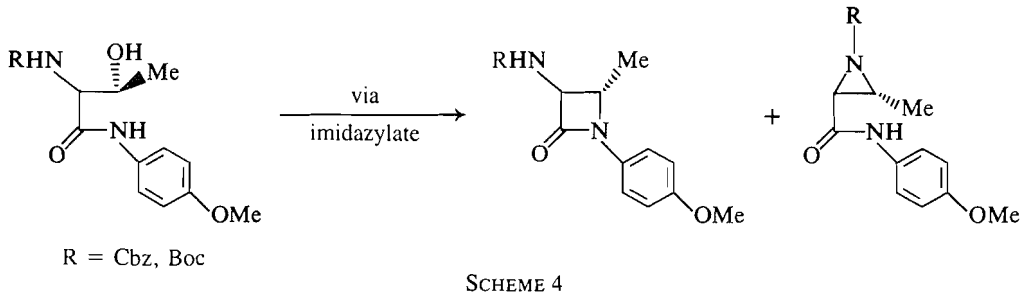
1*a*, R = Cbz
1*b*, R = Boc

2*a*, R = Cbz
2*b*, R = Boc

3*a*, R = Cbz
3*b*, R = Boc

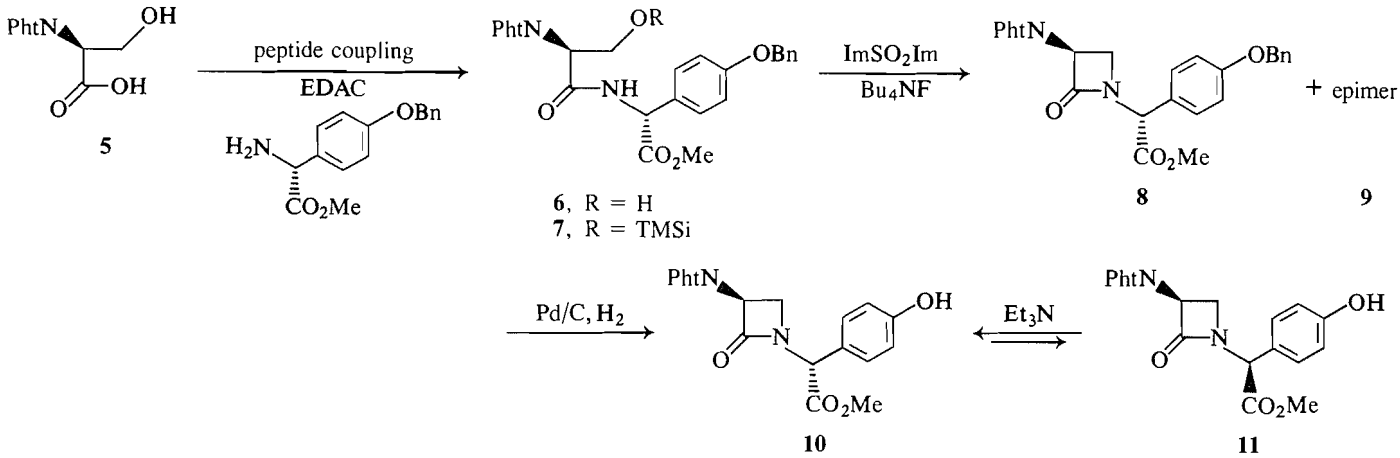
4*a*, R = Cbz
4*b*, R = Boc

SCHEME 3



R = Cbz, Boc

SCHEME 4



SCHEME 5

of DMF was added with efficient stirring under argon over a period of 25 min. After stirring for a further 30 min, the solution was allowed to warm up to room temperature, methanol (0.5 mL) and chloroform (100 mL) were added, and the solution was washed with saturated brine, then with water. Processing the organic phase gave a colorless solid, which when triturated with ethyl acetate gave 1.42 g (75%) of the desired product **3***a*. Recrystallization from a mixture of ethyl acetate and dichloromethane gave an analytical sample, mp 178°C; $[\alpha]_D$ +35.8° (*c* 1, $CHCl_3$); λ_{max}: 1740 (β-lactam C=O), 1700 (urethane C=O) cm^{-1}; ^1H nmr (90 MHz) ppm: 3.50 (dd, H4β, *J* = 2.3, 5.3 Hz), 3.73 (s, 3H, OCH_3), 3.88 (t, H4α, *J* = 5.3 Hz), 4.90 (dd, H3), 5.09 (s, 2H, OCH_2Ph), 5.8 (bd, N*H*, *J* ~ 8 Hz), 7, 7.3 (arom); ms: 327 (M + 1), etc. *Anal.* calcd. for $C_{18}H_{17}N_2O_4$: C 66.26, H 5.52, N 8.59; found: C 66.16, H 5.53, N 8.42.

*(S)-3-[(*tert*-Butoxycarbonyl)amino]-1-*p*-methoxyphenyl-2-azetidinone (3b)*

A solution containing 0.5 g (1.61 mmol) of **2***b*, 96.8 mg (1.5 equiv.) of sodium hydride, and 480 mg (1.5 equiv.) of *N,N*-sulfuryl diimidazole in a total of 13 mL of DMF was stirred at −20°C (addition done at −20°C) under argon for 1 h. Work-up as described above gave a solid, which was recrystallized from ethyl acetate to give 406 mg (85%) of the title compound, mp 180–180.5°C; $[\alpha]_D$ +48.5° (*c* 1.30, $CHCl_3$); λ_{max}: 1750 (β-lactam C=O), 1680 (urethane C=O) cm^{-1}; ^1H nmr (90 MHz) ppm: 1.46 (s, 9H, *tert*-butyoxycarbonyl), 3.51 (dd, H4β, *J* = 2.3, 5.3 Hz), 3.79 (s, 3H, OCH_3), 3.86 (t, H4α, *J* = 5.3 Hz), 4.90 (m, H3), 5.54 (dd, NH, *J* ~ 7 Hz), 7.6 (arom); ms: 293 (M + 1), etc. *Anal.* calcd. for $C_{15}H_{19}N_2O_4$: C 61.64, H 6.85, N 9.59; found: C 61.72, H 6.81, N 9.60.

(S)-3-[Benzyloxycarbonyl)amino]-2-azetidinone (4a)

To a cooled solution of **3***a* (760 mg, 2.33 mmol) in 60 mL of acetonitrile was added a solution of ceric ammonium nitrate (3.8 g, 3 equiv.) in 15 mL of water, dropwise and with stirring. After 30 min at 0°C, the solution was allowed to warm up to room temperature, diluted with water, and extracted with ethyl acetate (100 mL × 3). Processing the organic phase in the usual manner and decolorization with 10% aqueous sodium sulfite gave the title compound as a colorless solid. Trituration with ethyl acetate and hexanes (1:1) gave 360 mg (70%) of **4***a*, mp 164–165°C; $[\alpha]_D$ −17.6° (*c* 1.4, MeOH) (lit. (3) mp 163–164°C; $[\alpha]_D$ −17.8°). The overall yield from L-serine was ~40%; ^{1}H nmr (90 MHz) ppm: 3.33 (dd, H4β, J = 2.3, 5.3 Hz), 3.60 (t, H4α, J = 5.3 Hz), 4.83 (m, H3), 5.1 (s, 3H, OCH_3), 5.43 (m, NH β-lactam C=O); ms: 221 (M + 1), etc. *Anal.* calcd. for $C_{11}H_{11}N_2O_3$: C 60.00, H 5.45, N 12.73; found: C 59.95, H 5.39, N 12.52.

*(S)-3-[(*tert*-Butoxycarbonyl)amino]-2-azetidinone, (4b)*

A solution of **3***b* (800 mg, 2.74 mmol) in 70 mL of acetonitrile was treated with ceric ammonium nitrate (1.65 g, 3 equiv.) in 5 mL of water as described for **4***a*. Processing of the reaction mixture gave the title compound **4***b* (350 mg) in 70% yield after recrystallization from ethyl acetate and hexanes (5:1), mp 172–173°C; $[\alpha]_D$ −18.9° (*c* 1, MeOH) (lit. (3) mp 173–175°C; $[\alpha]_D$ −23.5°; lit. (13*c*) mp 171.5–172.5°C; $[\alpha]_D$ −19.8°); λ_{max}: 1760 (β-lactam C=O) cm^{-1}; ^{1}H nmr (90 MHz) ppm: 1.43 (s, 9H, *tert*-butoxycarbonyl), 3.26 (dd, H4β, J = 2.3, 5.3 Hz), 3.54 (t, H4α, J = 5.3 Hz), 4.76 (m, H3), 5.43 (dd, J ~ 8 Hz, NH β-lactam), 6.9 (m, urethane NH); ms: 189 (M+), etc.

Preparation of dipeptide 6

To a solution of *N*-phthalimido L-serine (86 mg, 0.37 mmol) in 0.5 mL of THF were added successively 109 mg (1.1 equiv.) of 4-*O*-benzyl-*p*-hydroxyphenyl L-glycine methyl ester (13*d*) in 0.5 mL of THF and 77 mg (1.1 equiv.) of EDAC.HCl suspended in 5 mL of dichloromethane. After stirring for 2.5 h at room temperature the solution was evaporated to dryness, the residue was dissolved in dichloromethane, and the solution was washed with aqueous acid, then aqueous bicarbonate, and finally with water. Processing of the organic phase gave 140 mg (78.5%) of the desired dipeptide **6** as a colorless solid. Recrystallization from a mixture of ethyl acetate and hexanes gave pure material (103 mg, 58%); compare 48% with a DCC coupling (24); mp 185–186°C; $[\alpha]_D$ −115.5° (*c* 1, $CHCl_3$) (lit. (24) mp 189–191°C; $[\alpha]_D$ −188°); ^{1}H nmr (90 MHz) ppm: 3.39 (bs, OH), 3.65 (s, 3H, CO_2CH_3), 3.7–4.9 (m, 3H, H3, H 4.4′), 5.00 (s, 2H, OCH_2Ph), 5.47 (d, 1H, J = 6 Hz, CH—CO_2CH_3), 7.34 (NH), 7.38–7.78 (arom). A single isomer was detected when the spectrum was recorded in the presence of a shift reagent [Eu(hfc)$_3$]; ms: 489 (M + 1).

Intramolecular cyclization of 6 to a mixture of 8 and 9

A solution of **6** (370 mg, 0.76 mmol) in 15 mL of THF was treated with 1.14 mL (1.5 equiv.) of a 1 *M* solution of tetra-n-butylammonium fluoride in THF, then with 225 mg (1.5 equiv.) of *N*,*N*-sulfuryl diimidazole. After stirring overnight, a few drops of aqueous acetic acid were added, the solvent was evaporated, and the residue was dissolved in dichloromethane. Washing with aqueous hydrochloric acid, then water, and usual processing gave a syrup that was chromatographed (ethyl acetate – hexanes 1:1) to give a mixture of **8** and **9** (224 mg, 63%) as a colorless solid, mp 55–65°C; $[\alpha]_D$ −110.5° (*c* 1, $CHCl_3$); λ_{max}: 1745 (β-lactam C=O), 1760 (phthalimido), 1720 (CO_2CH_3) cm^{-1}; ^{1}H nmr (90 MHz) ppm: 2.10–3.60 (dd, H4β), 3.8, 3.82 (s, H, CO_2CH_3), 3.70–4.08 (t, H4α), 5.07 (s, 2H, OCH_2Ph), 5.32–5.55 (dd, H3), 5.69, 5.76 (s, $CHCO_2CH_3$), etc; ms: 471 (M + 1), etc.

*(S)-3-(Phthalimido)-1-(*p*-hydroxyphenyl-L-glycinyl methyl ester)-2-azetidinone **10** and its epimer **11***

A solution containing 231 mg (0.6 mmol) of a mixture of **8** and **9** in a mixture of methanol and acetic acid (1:1, 15 mL) was hydrogenated in the presence of 150 mg of 10% palladium-on-charcoal. After an overnight treatment, the catalyst was filtered, washed with methanol, and the filtrate was coevaporated with benzene several times to remove all the residual acetic acid. The residue thus obtained (quant.) showed a 2:1 mixture (nmr) of **10** and **11**, respectively. Fractional recrystallization from ethyl acetate – hexanes (4:1) gave 68 mg of **10** as colorless crystals, mp 169–171°C; $[\alpha]_D$ −238.5° (*c* 0.58, MeOH) (lit. (24) mp 169–170°C; $[\alpha]_D$ −239°; lit. (13*d*) mp 203–204°C; $[\alpha]_D$ −236°; λ_{max}: 1770 (β-lactam C=O), 1750 (phthalimido), 1730 (CO_2CH_3) cm^{-1}; ^{1}H nmr (90 MHz), ppm: 3.46 (dd, H4β, J = 2.9, 5.5 Hz), 3.79 (s, 3H, CO_2CH_3), 3.95 (t, H4α, J = 5.5 Hz), 5.51 (dd, J = 2.9, 5.5 Hz), 7.1–7.76 (arom.); ms: 381 (M + 1), etc.

Treatment of the mother liquors of recrystallization overnight with dichloromethane containing ~10% triethylamine, evaporation to dryness, and chromatography (ethyl acetate – hexanes 2:1) gave a mixture of **10** and **11** in a ratio of 2:1. After recrystallization, a further 75 mg of **10** was obtained, for a total of 142 mg (67%). The final mother liquors gave 28 mg of a 1:2 mixture of **10** and **11**, respectively.

Acknowledgements

We wish to acknowledge the generous financial assistance of the Natural Sciences and Engineering Research Council of Canada, Sandoz (Vienna), and Le Ministère de l'éducation du Québec. We thank Mr. M. Evans for recording the mass spectra.

1. C. M. CIMARUSTI and R. B. SYKES. Med. Res. Rev. **4**, 1 (1984); Chem. Br. 302 (1983).
2. R. B. SYKES, C. M. CIMARUSTI, D. P. BONNER, K. BUSH, D. M. FLOYD, N. H. GEOROGOPAPADAKOU, W. KOSTER, W. C. LIU, W. L. PARKER, P. A. PRINCIPE, M. L. RATHUM, W. A. SLUSARCHYK, W. H. TREJO, and J. S. WELL. Nature, **291**, 489 (1981); A. IMADA, K. KITANO, K. KINTAKA, M. MUROI, and M. ASAI. Nature, **289**, 590 (1981); C. M. CIMARUSTI and R. B. SYKES. Chem. Br. 302 (1983).
3. W. L. PARKER, W. H. KOSTER, C. M. CIMARUSTI, D. M. FLOYD, W. LIU, and L. RATHUM. J. Antibiot. **35**, 189 (1982); W. L. PARKER and M. L. RATHUM. J. Antibiot. **35**, 300 (1982); C. M. CIMARUSTI, H. E. APPLEGATE, H. W. CHANG, D. M. FLOYD, W. H. KOSTER, W. A. SLUSARCHYK, and M. G. YOUNG. J. Org. Chem. **47**, 179 (1982); D. M. FLOYD, A. W. FRITZ, and C. M. CIMARUSTI. J. Org. Chem. **47**, 176 (1982); E. M. GORDON, M. A. ONDETTI, J. PLUSCEC, C. M. CIMARUSTI, D. P. BONNER, and R. B. SYKES. J. Am. Chem. Soc. **104**, 6053 (1982); D. M. FLOYD, A. W. FRITZ, J. PLUSCEC, E. R. WEAVER, and C. M. CIMARUSTI. J. Org. Chem. **47**, 5160 (1982).
4. M. J. MILLER, P. G. MATTINGLY, M. A. MORRISON, and J. F. KERWIN, JR. J. Am. Chem. Soc. **102**, 7026 (1980).
5. (*a*) A. K. BOSE, M. S. MANHAS, D. P. SAHU, and V. R. HEGDE. Can. J. Chem. **62**, 2498 (1984); (*b*) D. P. SAHU, P. MASHAVA, M. S. MANHAS, and A. K. BOSE. J. Org. Chem. **48**, 1142 (1983); (*c*) A. K. BOSE, D. O. SAHU, and M. S. MANHAS. J. Org. Chem. **46**, 1229 (1981).
6. C. M. CIMARUSTI. J. Med. Chem. **27**, 247 (1984).
7. H. H. WASSERMAN, D. J. HLASTA, A.-W. TREMPER, and J. S. WU. Tetrahedron Lett. 549 (1979).
8. G. GEORG and T. DURST. J. Org. Chem. **48**, 2092 (1983); H. MATSUNAGA, T. SAKAMAKI, H. NAGUAKA, and Y. YAMADA. Tetrahedron Lett. **24**, 3009 (1983); M. J. MILLER, J. S. BAJNA, P. G. MATTINGLY, and K. PETERSON. J. Org. Chem. **47**, 4928 (1982); M. A. MORRISON and M. J. MILLER. J. Org. Chem. **48**, 4421 (1983).
9. A. MISHIDA, M. SHIBASAKI, and S. IKEGAMI. Tetrahedron Lett. **25**, 765 (1984); S. R. WOULFE and M. J. MILLER. Tetrahedron Lett. **25**, 3293 (1984).
10. H. P. ISENRING and W. HOFHEINZ. Synthesis, 385 (1981).
11. H. AOKI, H. SAKAI, M. KOHSAKA, T. KONOMI, J. HOSADA, J. KUBOCHI, and E. IGUSHI. J. Antibiot. **29**, 492 (1976); M. HASHIMOTO, T. KOMORI, and T. KAMIYA. J. Antibiot. **29**, 890 (1976).

12. T. KAMIYA. *In* Recent advances in the chemistry of β-lactam antibiotics. *Edited by* J. Elks. Spec. Publ. No. 28, Chem. Soc. London. 1977. pp. 281–294. T. KAMIYA, H. AOKI, and Y. MINE. *In* Chemistry and biology of β-lactam antibiotics. Vol. 2. *Edited by* R. B. Morin and M. Gorman. Academic Press, New York. 1982. pp. 165–226.
13. (*a*) H. P. ISENRING and W. HOFHEINZ. Tetrahedron, **39**, 2591 (1983); (*b*) C. A. TOWNSEND and L. T. NGUYEN. Tetrahedron Lett. **23**, 4859 (1982); (*c*) P. G. MATTINGLY and M. J. MILLER. J. Org. Chem. **46**, 1557 (1981); **45**, 410 (1979); (*d*) T. KAMIYA, M. HASHIMOTO, O. NAKAGUCHI, and T. OKU. Tetrahedron, **35**, 323 (1979); (*e*) T. KAMIYA, T. OKU, O. NAKAGUCHI, H. TAKENO, and M. HASHIMOTO. Tetrahedron Lett. 5119 (1978); (*f*) G. A. KOPPEL, L. MCSHANE, F. JOSE, and R. D. G. COOPER. J. Am. Chem. Soc. **100**, 3933 (1978).
14. H. H. WASSERMAN, D. J. HLASTA, A. W. TREMPER, and J. S. WU. J. Org. Chem. **46**, 2999 (1981); K. CHIBA, M. MORI, and Y. BAN. J. Chem. Soc. Chem. Commun. 770 (1980).
15. W. L. PARKER, W. H. KOSTER, C. M. CIMARUSTI, D. M. FLOYD, W. C. LIU, and M. L. RATHNUM. J. Antibiot. **35**, 189 (1982).
16. S. HANESSIAN and S. P. SAHOO. Can. J. Chem. **62**, 1400 (1984).
17. S. HANESSIAN. Total synthesis of natural products: the 'chiron' approach. *Edited by* J. E. Baldwin. Pergamon Press, Oxford, England. 1983.
18. S. HANESSIAN and J.-M. VATELE. Tetrahedron Lett. **22**, 3579 (1981).
19. S. HANESSIAN, S. SAHOO, C. COUTURE, and H. WYSS. Bull. Soc. Chim. Belg. **7**, 571 (1984).
20. H. STAAB. Angew. Chem. Int. Ed. Engl. **1**, 351 (1962).
21. O. MITSUNOBU. Synthesis, 1 (1981).
22. D. R. KRONENTHAL, C. T. HAN, and M. F. TAYLOR. J. Org. Chem. **47**, 2765 (1982).
23. G. H. L. NEFKENS, G. I. TESSER, and R. I. F. NIVARD. Recl. Trav. Chim. Pays-Bas, **79**, 688 (1960); R. S. HODGES and R. B. MERRIFIELD. J. Org. Chem. **39**, 1870 (1974).
24. C. A. TOWNSEND, A. M. BROWN, and L. T. NGUYEN. J. Am. Chem. Soc. **105**, 919 (1983).
25. J. C. SHEEHAN, J. PRESTON, and P. A. CRUICKSHANK. J. Am. Chem. Soc. **87**, 2491 (1965).