MHz) δ 4.18 (2 H, q, J = 7.0 Hz), 3.28 (2 H, t, J = 4.4 Hz), 2.85 (2 H, t, J = 4.4 Hz), 1.55 (6 H, s), 1.26 (3 H, t, J = 7.0 Hz); high-resolution mass spectrum, calcd for $C_9H_{15}NO_3$ m/e 185.1047, found m/e 185.1049.

Ethyl α-Isopropyl-2-oxo-1-azetidineacetate (21b). By the above procedure, 285 mg of *N*-(2,2-dimethyl-1-carbethoxyethyl)-2-(carbo-*tert*-butoxy)azetidine (**3t**) was converted to 121 mg (61%) of ethyl α-isopropyl-2-oxo-1-azetidineacetate (**21b**) identical with an authentic sample.[35]

Ethyl α-(*p*-Methoxyphenyl)-2-oxo-1-azetidineacetate (21c). By the above procedure, 700 mg of *N*-(α-carbethoxy-*p*-methoxybenzyl)-2-(carbo-*tert*-butoxy)azetidine (**3u**) was converted to 320 mg (61%) of ethyl α-(*p*-methoxyphenyl)-2-oxo-1-azetidineacetate (**21c**): IR (neat) 1740 (split) cm^{-1}; NMR (CCl_4) δ 7.15 (2 H, d, J = 8.1 Hz), 6.82 (2 H, d, J = 8.1 Hz), 5.38 (1 H, s), 4.16 (2 H, s), 3.78 (3 H, s), 3.56 (1 H, m), 2.98 (1 H, m), 2.90 (1 H, m), 2.73 (1 H, m), 1.25 (3 H, t, J = 7.3 Hz).

Molecular distillation [80 °C (0.1 mmHg), 7 days] gave the analytical sample as a colorless oil.

Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.66; H, 6.39; N, 5.29.

Ethyl α-[*p*-(Benzyloxy)phenyl]-2-oxo-1-azetidineacetate (21d). By the above procedure 425 mg of *N*-[*p*-(benzyloxy)-α-carbethoxyphenyl]-2-(carbo-*tert*-butoxy)azetidine (**3y**) was converted to 180 mg (53%) of ethyl α-[(*p*-benzyloxy)phenyl]-2-oxo-1-azetidineacetate (**21d**): mp 57-59 °C; IR ($CHCl_3$) 1740 (split) cm^{-1}; NMR ($CDCl_3$, 270 MHz) δ 7.33 (5 H, m), 7.14 (2 H, d, J = 8.8 Hz), 6.91 (2 H, d, J = 8.8 Hz), 5.46 (1 H, s), 4.99 (2 H, s), 4.14 (2 H, q (split), J = 6.6 Hz), 3.54 (1 H, m), 2.99 (1 H, m), 2.92 (1 H, m), 2.76 (1 H, m), 1.18 (3 H, t, J = 6.6 Hz).

The analytical sample was prepared by two recrystallizations from ether-heptane, mp 61-62 °C.

(35) Wasserman, H. H.; Glazer, E. *J. Org. Chem.* **1975**, *40*, 1505.

Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.50; H, 6.14; N, 4.02.

Acknowledgment. This work was supported by Grants GM-07874 and GM-13854 from the National Institutes of Health.

Registry No. 1, 96-48-0; **2a**, 29547-04-4; **2b**, 36847-51-5; **2c**, 71725-02-5; **3a**, 18085-35-3; **3b**, 77647-92-2; **3c**, 18085-36-4; **3d**, 72089-77-1; **3e**, 62664-93-1; **3f**, 71556-69-9; **3g**, 72089-76-0; **3h**, 62664-90-8; **3i**, 62664-92-0; **3j**, 77647-97-3; **3k**, 71556-64-4; **3l**, 72081-67-5; **3m**, 62664-91-9; **3n**, 65219-09-2; **3o**, 18085-37-5; **3p**, 77647-98-4; **3q**, 77647-99-5; **3r**, 77648-00-1; **3s**, 77648-01-2; **3t** (isomer 1), 77648-02-3; **3t** (isomer 2), 77648-03-4; **3u** (isomer 1), 77648-04-5; **3u** (isomer 2), 77648-05-6; **3v** (isomer 1), 77648-06-7; **3v** (isomer 2), 77648-07-8; **5a**, 18085-38-6; **5a**·$HClO_4$, 77648-08-9; **5b**, 18085-39-7; **5c**, 62664-97-5; **5d**, 62664-94-2; **5e**, 62664-96-4; **5f**, 77648-09-0; **5g**, 64264-57-9; **5h**, 62664-95-3; **9a**, 34094-42-3; **9b**, 34094-39-8; **9c**, 62665-01-4; **9d**, 62664-98-6; **9e**, 62665-00-3; **9f**, 77648-10-3; **9g**, 64218-77-5; **9h**, 62664-99-7; **9i**, 4458-64-4; **9j**, 65219-06-9; **9k**, 65219-07-0; **9l**, 65219-08-1; **9m**, 70875-47-7; **10a**, 18085-40-0; **12a**, 77648-11-4; **12b**, 77648-12-5; **12c**, 70339-93-4; **12d**, 77648-13-6; **17** (R = *c*-C_6H_{11}; R′ = CH_3), 77648-15-8; **17** (R = $CH_2CH_2C_6H_4$-*p*-OCH_3; R′ = $C(CH_3)_3$), 77648-16-9; **17** (R = CH_2-2,4,-trimethoxyphenyl; R′ = $C(CH_3)_3$), 65219-12-7; **17** (R = CH_2CH = CH_2; R′ = $C(CH_3)_3$), 77648-17-0; **17** (R = $CH(C_6H_5)_2$; R′ = CH_2CH_3), 77648-18-1; **21a**, 70875-38-6; **21b**, 54643-15-1; **21c**, 77648-19-2; **21d**, 70875-48-8; cyclohexylamine, 108-91-8; *p*-methoxyphenethylamine, 55-81-2; 1,1-dimethylglycine ethyl ester, 1113-49-1; *tert*-butylamine, 75-64-9; 2,2-dimethoxyethylamine, 22483-09-6; allylamine, 107-11-9; *n*-pentylamine, 110-58-7; cyclooctylamine, 5452-37-9; *N,N*-dimethyl-1,3-propanediamine, 109-55-7; 1,1-diphenylmethylamine, 91-00-9; phenethylamine, 64-04-0; 2,4,6-trimethoxybenzylamine, 77648-20-5; benzylamine, 100-46-9; *p*-methoxybenzylamine, 2393-23-9; ethyl 2-amino-3-methylbutyrate, 13893-45-3; ethyl α-amino-*p*-methoxyphenylacetate, 77648-21-6; ethyl α-amino-*p*-(benzyloxy)phenylacetate, 70875-50-2.

Application of New β-Lactam Syntheses to the Preparation of (±)-3-Aminonocardicinic Acid[1,2]

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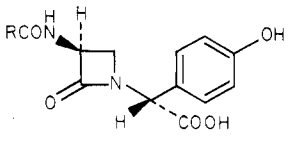
Department of Chemistry, Yale University, New Haven, Connecticut 06511

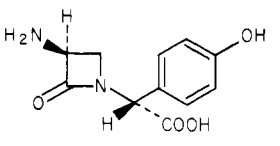
Received March 6, 1981

Three novel β-lactam-forming reactions have been applied to the synthesis of (±)-3-aminonocardicinic acid (3-ANA). These procedures include (a) ring expansion of a cyclopropanolamine, (b) azetidine carboxylate oxidative decarbonylation, and (c) β-halopropionamide ring closure.

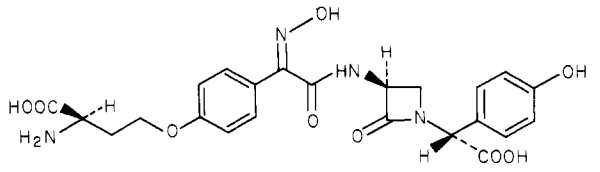
The nocardicins (1), isolated from a strain of *Nocardia*,[3,4] are the first monocyclic β-lactams to exhibit high antibacterial activity.[5] One of the major constituents of these cultures, nocardicin A (2), shows relatively high activity against gram-negative bacteria. Other less abundant



1



3



2

members of this group consist of varied acyl derivatives of 3-aminonocardicinic acid (3, 3-ANA), the nucleus of this family of antibiotics.

(1) For preliminary reports on this work see: (a) Wasserman, H. H.; Hlasta, D. J. *J. Am. Chem. Soc.* **1978**, *100*, 6780; (b) Wasserman, H. H.; Tremper, A. W.; Wu, J. S. *Tetrahedron Lett.* **1979**, 1089.

(2) Taken in part from Ph.D. dissertations of D.J.H., Yale University, 1979, and J.S.W., Yale University, 1978.

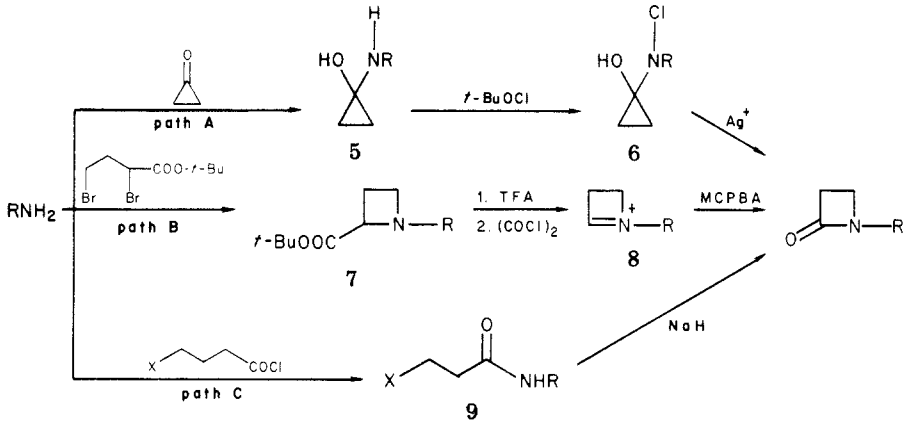
(3) Aoki, H.; Sakai, H.; Kohsaka, M.; Konomi, T.; Hosoda, J.; Kubochi, T.; Iguchi, E.; Imanaka, H. *J. Antibiot.* **1976**, *29*, 492.

(4) (a) Hashimoto, M.; Komori, T.; Kamiya, T. *J. Antibiot.* **1976**, *29*, 890. (b) Kamiya, T. "Recent Advances in the Chemistry of β-Lactam Antibiotics"; Cambridge University Press: London, 1976; p 281. (c) Hashimoto, M.; Komori, T.; Kamiya, T. *J. Am. Chem. Soc.* **1976**, *98*, 3023.

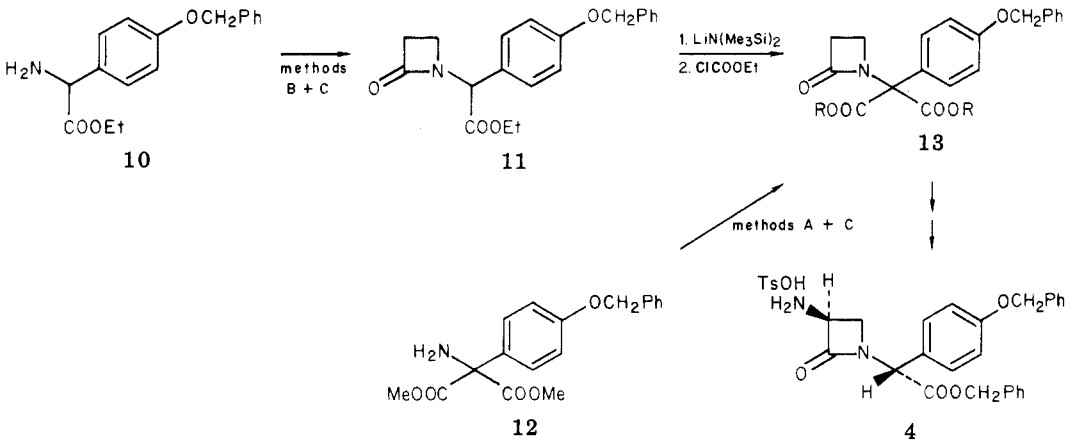
(5) For early studies on monocyclic β-lactams showing antibacterial activity see: Bose, A. K.; Manhas, M. S.; Kapur, J. C.; Sharma, S. D.; Amin, S. G. *J. Med. Chem.* **1974**, *17*, 541.

0022-3263/81/1946-2999$01.25/0

Scheme I



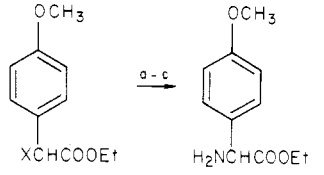
Scheme II



Recent syntheses[4b,6] of nocardicin A (2) have involved the preparation of 3-ANA (3) followed by the introduction of a protected side chain by acylation. Deprotection and oxime formation yielded 2.

In the course of our studies on the chemistry of β-lactams, we have developed new methods for the formation of the azetidinone ring. As outlined in Scheme I, we have now applied three of these procedures (A–C) to the synthesis of 3-ANA (3). Method A[1a,7] involves the addition of a primary amine to cyclopropanone to form the carbinol amine 5. Reaction with hypochlorite gives the *N*-chloro derivative 6 which undergoes ring expansion upon treatment with silver nitrate. In method B,[1b,8,23] azetidine-2-carboxylates 7 are prepared by the condensation of a primary amine with *tert*-butyl 2,4-dibromobutyrate. Cleavage of the *tert*-butyl ester with acid followed by treatment of the resulting amino acid with oxalyl chloride provides the iminium salt 8. Oxidation with *m*-chloroperbenzoic acid in the presence of pyridine yields the β-lactam. In extension of Knunyants' work,[9] method C[1a,10] involves initial acylation of the primary amine to give a β-halopropionamide (9). Treatment of 9 with sodium hydride in dilute solution gives the β-lactam. These methods have all been applied to the synthesis of the tosyl salt of (±)-benzyl *O*-benzyl-3-aminonocardicinate (4) which is the immediate precursor of 3-ANA (3). As has recently been reported,[6a] debenzylation of 4 by catalytic hydrogenation of the free base completes the synthesis of 3-ANA (3).

Scheme III[a]



[a] a, NBS, benzoyl peroxide, CCl_4, reflux, 3 h; b, KN_3, 18-crown-6 ether, benzene, 25 °C; c, H_2, Pd/C, TsOH, EtOH.

In each of the above routes, the malonic ester derivative 13 is the key intermediate in the synthetic sequence. It can be obtained by the following methods (see Scheme II): the β-lactam 11, prepared from amine 10 by either path B or C, is selectively acylated to give 13 (R = Et). Alternatively, β-lactam 13 can be prepared directly from the amine malonate 12 by methods A and C. It is then converted to 3-ANA (4) as described below.

(±)-Nocardicinic Acid. In initial work leading to the synthesis of 3-ANA, we undertook to develop methods for the preparation of the unsubstituted system (±)-nocardicinic acid (14). The starting point for this model study was (*p*-methoxyphenyl)glycine ethyl ester (15) which was

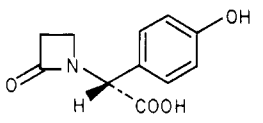
(6) (a) Koppel, G. A.; McShane, L.; Jose, F.; Cooper, R. D. G. *J. Am. Chem. Soc.* **1978**, *100*, 3933. (b) Kamiya, T.; Hashimoto, M.; Nakaguchi, O.; Oku, T. *Tetrahedron* **1979**, *35*, 323. (c) Kamiya, T.; Oku, T.; Nakaguchi, O.; Takeno, H.; Hashimoto, M. *Tetrahedron Lett.* **1978**, 5119.

(7) (a) Wasserman, H. H.; Adickes, H. W.; de Ochoa, O. E. *J. Am. Chem. Soc.* **1971**, *93*, 5586. (b) Wasserman, H. H.; Glazer, E. *J. Org. Chem.* **1975**, *40*, 1505.

(8) Wasserman, H. H.; Tremper, A. W. *Tetrahedron Lett.* **1977**, 1449.

(9) Knunyants, I. L.; Gambaryan, N. P. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1955**, 1037.

(10) Wasserman, H. H.; Hlasta, D. J.; Tremper, A. W.; Wu, J. S. *Tetrahedron Lett.* **1979**, 549.



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conveniently prepared as shown in Scheme III. Bromination of ethyl (*p*-methoxyphenyl)acetate (**16**)[11] with NBS gave bromide **17**. Reaction of the bromide with potassium azide in the presence of 18-crown-6 ether provided the azide **18**. Hydrogenation of **18** over palladium catalyst in the presence of *p*-toluenesulfonic acid gave (*p*-methoxyphenyl)glycine ethyl ester (**15**) as the hydrotosylate salt.

The β-lactam **20** was formed either by the cyclopropanone route (method A) or by the 3-halopropionamide route (method C). Thus, addition of **15** as the free amine to a standard solution of cyclopropanone in methylene chloride at −78 °C gave the intermediate carbonol amine **19** (not isolated) which was N-chlorinated in situ ($ClOC(CH_3)_3$) and rearranged by addition of silver nitrate to give the ring-expanded product **20** in 52% yield (Scheme IV). Alternatively, the amine **15** was acylated with 3-bromopropionyl chloride to give **21**. Addition of a 0.1 M solution of **21** in DMF/CH_2Cl_2 to a 0.1 M suspension of sodium hydride in DMF/CH_2Cl_2 gave the cyclized product **20** in 54% overall yield from **15**.

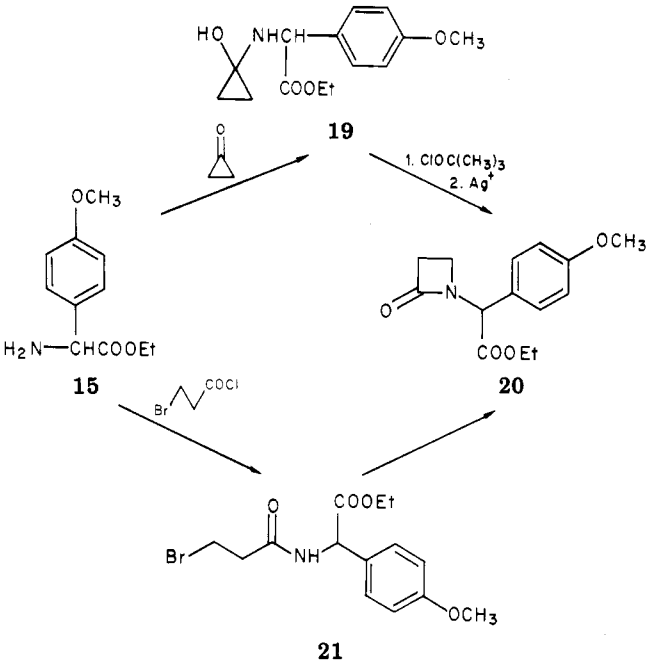
Treatment of the β-lactam **20** in methanol at 0 °C with 1 equiv of lithium hydroxide resulted in selective ester hydrolysis to give (±)-*O*-methylnocardicinic acid (**22**, 60%). The methyl ether **20** was cleaved with boron tribromide in methylene chloride to give (±)-ethyl nocardicinate (**23**, 83%; Scheme V). Attempts to hydrolyze the ethyl ester of **23** with base to yield nocardicinic acid (**14**) were not successful, however, most probably due to opening of the β-lactam ring under the conditions of hydrolysis. It was clear that a more easily removed protecting group was needed for both the carboxylate and phenolic functions. Accordingly, we chose the known amine **24** containing benzyl protecting groups as the substrate for the conversions to **14**.

The dibenzyl derivative **24** was easily prepared in three steps from (*p*-hydroxyphenyl)glycine (**25**) as previously reported[6a] (Scheme VI). It was converted to the β-lactam **26** both by the cyclopropane method (method A, 59%) and by the 3-halopropionamide cyclization route (method C, 46%) via intermediate **27**. Hydrogenolysis of **26** at 50 psi of hydrogen over palladium on charcoal in 95% ethanol gave (±)-nocardicinic acid (**14**, 98%).

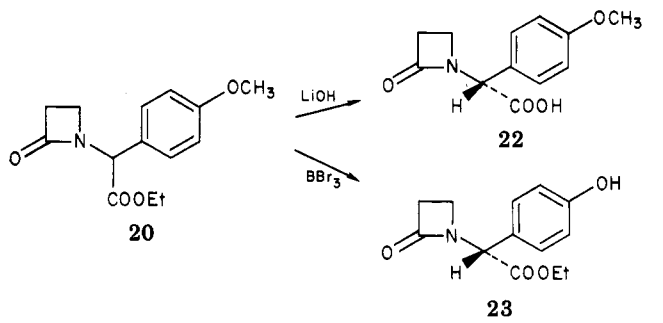
The sequences described above thus constitute useful procedures for the preparation of nocardicin-like compunds from convenient starting materials.

3-Aminonocardicinic Acid. With procedures available for the preparation of compounds having the general structure **28**, we sought methods for the introduction of the amine functionality to give the 3-ANA derivative **28a**. Our first objective was to introduce an azide function at C-3 in the manner reported by Kühlein and Jensen.[15] This procedure involved formation of an anion at C-3 followed

Scheme IV



Scheme V



by azide transfer with *p*-toluenesulfonyl azide and trimethylsilyl chloride. In the case of **28**, dianion formation would be required for substitution at C-3, since the proton at C-5 is more acidic than the proton at C-3. We found that reaction of the dianion of **28** with *p*-toluenesulfonyl azide, however, yielded none of the desired azide **28a**, and we therefore chose to mask the C-5 proton with a protecting group. Accordingly, the ester **28** was converted by selective C-5 acylation with ethyl chloroformate and hexamethyl disilazide to the malonate **29** (R = Et; Scheme VII). The malonate **29** was then treated with lithium diisopropylamide at −78 °C followed by *p*-toluenesulfonyl azide and Me_3SiCl to yield the 3-azidolactam **30**. Hydrolysis and decarboxylation gave the azide acid **31**. The malonate **29** (R = Me) could also be obtained directly by the amine malonate–cyclopropanone procedure discussed below.

Amine Malonate–Cyclopropanone Procedure. Method A. A suitably protected amine was prepared from methyl [*p*-(benzyloxy)phenyl]acetate (**32**).[12] Claisen condensation of **32** with dimethyl carbonate in ether at room temperature gave the dimethyl malonate **33**. Treatment of **33** with sodium hydride followed by *p*-toluenesulfonyl azide[13,14] and Me_3SiCl gave the azide **34** (76%) which could be reduced with either aluminum amalgam or zinc dust/aqueous acetic acid to the amine **12** in 53% yield. Addition of the amine **12** to a ketene-free solution of cyclopropanone in methylene chloride at −78 °C afforded the carbinol amine **35** in quantitative yield (Scheme VIII). In situ treatment of **35** with *tert*-butyl

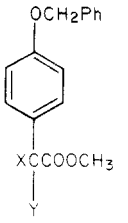
(11) (a) Cain, J. C.; Simonsen, J. L.; Smith, C. *J. Chem. Soc.* **1913**, 1035. (b) Kindler, K. *Justus Liebigs Ann. Chem.* **1927**, *452*, 107.

(12) (a) Weiss, P. *J. Am. Chem. Soc.* **1948**, *70*, 4263. (b) Collins, D. J.; Hobbs, J. J. *Aust. J. Chem.* **1967**, *20*, 1413.

(13) Regitz, M.; Hocker, J.; Liedhegener, A. "Organic Syntheses"; Wiley: New York, 1973; Collect Vol. V, p 179. Prior to use, tosyl azide was dried by passing it through a column of neutral alumina with ether. Concentration in vacuo at room temperature gave a colorless oil which crystallized on being dried under vacuum overnight.

(14) Weininger, S. J.; Kohen, S.; Mataka, S.; Koga, G.; Anselme, J.-P. *J. Org. Chem.* **1974**, *39*, 1591.

(15) Kühlein, K.; Jensen, J. *Justus Liebigs Ann. Chem.* **1974**, 369.

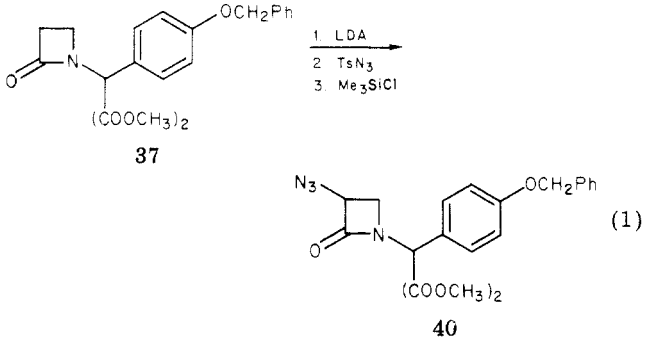


32, X = H; Y = H
33, X = H; Y = $COOCH_3$
34, X = N_3; Y = $COOCH_3$
12, X = NH_2; Y = $COOCH_3$
12a, X = NH_2; Y = H

hypochlorite gave **36** (not isolated) which, upon reaction with silver nitrate, rearranged to give β-lactam **37** (38% from **12**). The chloropropionamide **38** was formed in 29% yield as a byproduct of this reaction sequence.

β-Halopropionamide Cyclization Procedure. Method C. A more convenient route to β-lactam **37** involved the initial acylation of the amine hydrochloride of **12** with 3-chloropropionyl chloride to give chloropropionamide **38** (86%; Scheme IX). Subsequent addition of a dilute solution of **38** in DMF–CH_2Cl_2 to a suspension of sodium hydride in DMF–CH_2Cl_2 at 25 °C gave the β-lactam in 76% yield. Along with **37**, a small quantity (<5%) of the acrylamide **39** was formed. A substantially greater amount of this byproduct was formed in more concentrated solutions.

The β-lactam **37** was converted to the 3-azido derivative[15] as follows: formation of the anion at the 3-position of the β-lactam with lithium diisopropylamide in THF was followed by treatment with *p*-toluenesulfonyl azide[13] and then trimethylsilyl chloride to give the 3-azido lactam **40** (76%, eq 1). This lactam malonate (**40**) was saponified

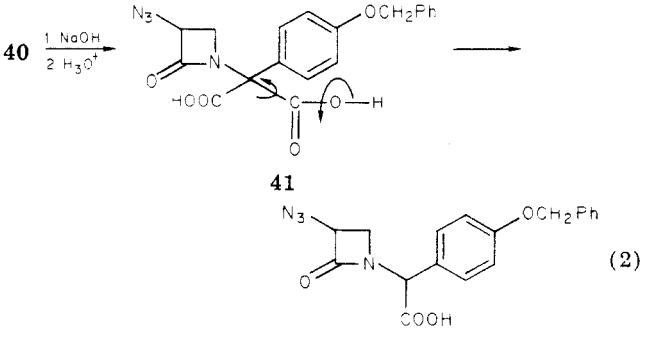


(1)

37

40

with 1 N methanolic sodium hydroxide and then acidified with 1 N hydrochloric acid, resulting in decarboxylation to give the azide acids **42** (eq 2) as a 1:1 mixture of diastereomers (71%).



(2)

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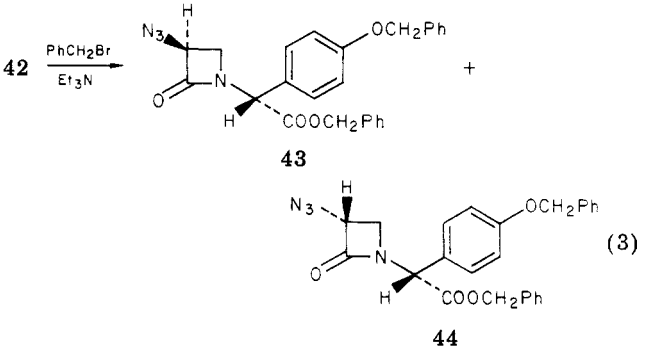
42

Since the complete separation of the azide acids by chromatography proved to be difficult, we utilized HPLC to separate the benzyl esters. The latter (**43** and **44**) were prepared by refluxing a solution of the acid **42**, benzyl bromide, and triethylamine in acetonitrile (eq 3). This 1:1 mixture (by NMR) of the diastereomeric benzyl esters was obtained in 77% yield.



(3)

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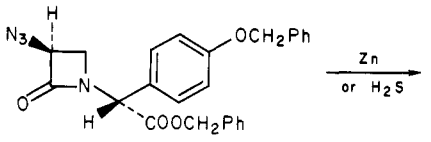
44

The diastereomers were separated on a Waters Prep LC/System 500 liquid chromatograph[16] using two silica gel cartridges with two recycles and elution with toluene–ethyl acetate (95:5). Alternatively, the diastereomers were separated with difficulty by preparative layer chromatography on silica gel with 22 elutions (hexane–ether, 3:2). The diastereomers **43** and **44** had nearly identical IR spectra with bands at 2120 (azide), 1760 (β-lactam), and 1740 (ester) cm^{-1}. However, the NMR spectra revealed their diastereomeric nature. The ring protons of **43** appeared at δ 2.95 (dd, J = 3 Hz (trans), J = 6 Hz (gem), 1 H), 3.86 (apparent t, J = 6 Hz, 1 H), and 4.66 (dd, J = 3 Hz (trans), J = 5 Hz (cis), 1 H). The ring protons of **44** appeared at δ 3.36 (apparent t, J = 6 Hz, 1 H), 3.57 (dd, J = 3 Hz (trans, J = 6 Hz (gem, 1 H), and 4.47 (dd, J = 3 Hz (trans), J = 5 Hz (cis), 1 H).

The stereochemistry of the diastereomers **43** and **44** was determined by transformation to an authentic sample of known stereochemistry. This was accomplished by convergence with the Lilly synthesis of 3-ANA and nocardicin A[6a] through reduction of the separated azide benzyl esters **43** and **44** to the amine hydrotosylates **4** and **45**. The azides **43** and **44** were reduced by two methods. A solution of the azide in 90% aqueous acetic acid at room temperature was treated with zinc dust to give the amine hydrotosylates **4** and **45** in 46% and 30% yield, respectively (eq 4 and 5). Alternatively, in a milder procedure, hydrogen sulfide[17] was bubbled through a solution of the azide in methylene chloride in the presence of 3 equiv of triethylamine, yielding the amine hydrotosylates **4** and **45** in 67% and 70% yield, respectively. Comparison of **4** and **45** showed **4** to be identical in all respects (IR, NMR, and TLC behavior) with an authentic sample of dibenzyl 3-aminonocardicinic acid.[18] Additional quantities of the desired azide benzyl ester **43** could be obtained by equilibration of azide benzyl ester **44** with a catalytic amount of potassium *tert*-butoxide in *tert*-butyl alcohol/tetrahydrofuran at 0 °C. The 1:1 mixture of **43** and **44** was formed in quantitative yield.

The final conversion of the amine hydrotosylate **4** to 3-aminonocardicinic acid (3-ANA, **3**) by hydrogenation over palladium on charcoal has already been reported,[5a] as has the introduction of the side chain at the 3-amino position of 3-ANA to give nocardicin A (**2**). Thus, our

(16) We thank Mr. Kenneth Conroe of Waters Associates for help in the separation of the diastereomers.
(17) (a) Adachi, T.; Yamada, Y.; Inoue, I.; Saneyoshi, M. *Synthesis* 1977, 45. (b) Kovacic, A., Stanovnik, B.; Tisler, M. *J. Heterocyl. Chem.* 1968, *5*, 351.
(18) Provided by Dr. G. A. Koppel, The Lilly Research Laboratories, Ili Lilly and Co.



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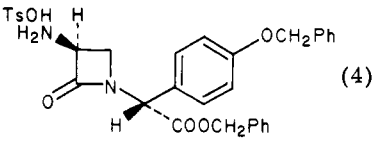

(4)

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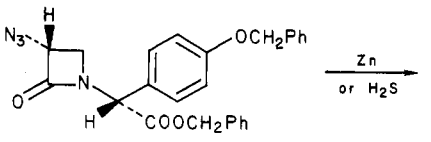

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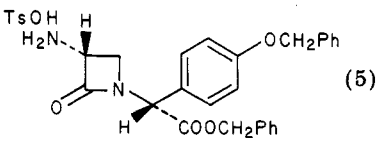


(5)

45

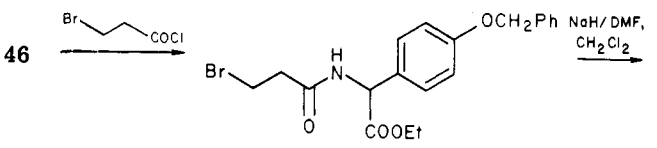
preparation of (±)-benzyl *O*-benzyl-3-aminonocardicinate hydrotosylate (4) constitutes a formal total synthesis of (±)-nocardicin A (2).

Azetidine-2-carboxylate Procedure. Method B. A suitably protected amino acid ester (46)[19] was prepared from 2-(*p*-hydroxyphenyl)glycine (47, Scheme X). Esterification of 2-(*p*-hydroxyphenyl)glycine (47) with ethanol–sulfuric acid gave 48 in 42% yield. Treatment of 48 with 1 equiv of benzaldehyde in DMF over 4-Å sieves gave the benzylidine derivative 49 which was not isolated but treated directly with excess potassium carbonate followed by 1 equiv of benzyl bromide. Following hydrolysis with 10% hydrochloric acid, the crude amino ester was isolated as the hydrotosylate salt 46 (37% yield from ester 48).

The β-lactam was prepared by two methods. In the first method (B), the azetidine 50 was obtained in 63% yield as a 1:1 mixture of diastereomers following reaction of the amine 46 and *tert*-butyl 2,4-dibromo butyrate (51, Scheme XI). Use of the ethyl ester 46 rather than the corresponding methyl ester 12a was necessary for the formation of the azetidine 50. Under the reaction conditions the methyl ester 12a underwent self-condensation and gave little or none of the four-membered product.[19]

Azetidine 50 was deprotected at the *tert*-butyl ester site with anhydrous TFA in methylene chloride, and the reaction mixture treated with oxalyl chloride followed by 70% perchloric acid to form the iminium salt 52. Oxidation with 1 equiv of *m*-chloroperbenzoic acid and 2 equiv of pyridine in methylene chloride then afforded the β-lactam 11 in 53% overall yield from azetidine 50.

Alternatively, the β-lactam 11 could be prepared by the 3-halopropionamide route (method C). Acylation of the amine 46 with 3-bromopropionyl chloride gave the bromopropionamide (53, 87%; eq 6). Slow addition of the amide 53 to a suspension of sodium hydride in DMF/CH_2Cl_2 resulted in cyclization to give β-lactam 11 in 80% yield. Treatment of β-lactam ester 11 with 1 equiv of lithium hexamethyl disilazide in tetrahydrofuran at −78 °C followed by 1 equiv of ethyl chloroformate resulted in selective carbethoxylation to yield to β-lactam malonate 54 (64, eq 7).



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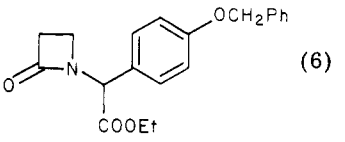

(6)

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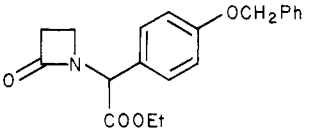

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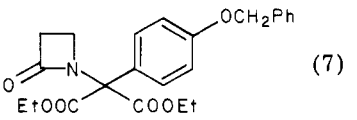

(7)

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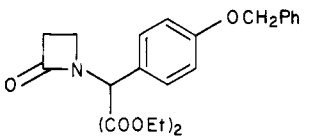
In a sequence which parallels the previous procedure for preparing dibenzyl 3-aminonocardicinic acid (4) through the dimethyl analogue 37, the β-lactam 54 was converted to the diastereomeric azide benzyl esters 43 and 44 in three steps. The nitrogen functionality was introduced at the 3-position of the lactam ring by azide transfer according to the method of Kühlein and Jensen.[15] Thus, treatment of β-lactam malonate 54 with 2 equiv of LDA in tetrahydrofuran at −78 °C followed by 1 equiv of *p*-toluenesulfonyl azide[12] and finally by excess trimethyl chlorosilane gave 3-azido β-lactam malonate 55 in 48% yield (eq 8).



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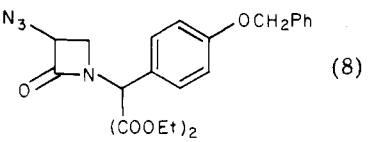

(8)

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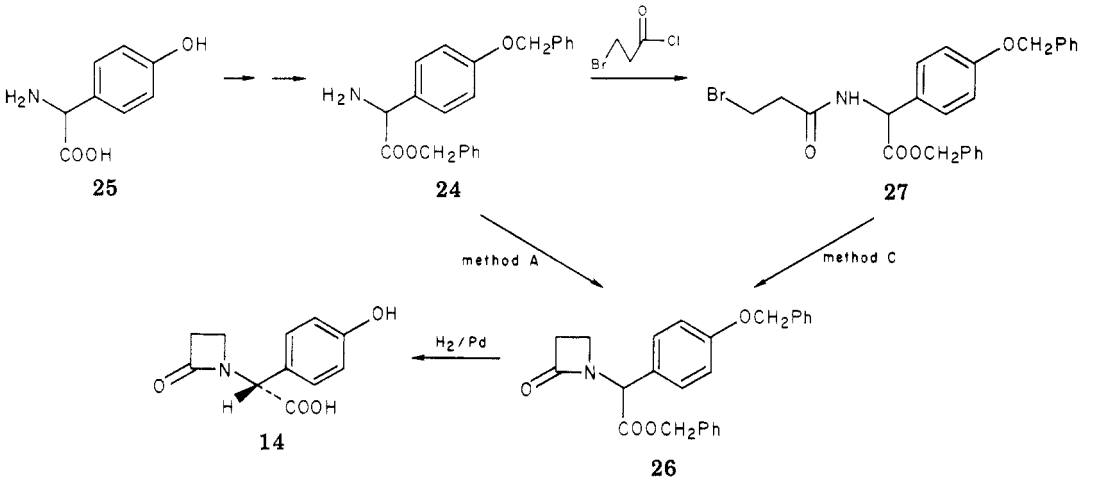
Treatment of 55 with 2 equiv of 1 N sodium hydroxide in methanol followed by decarboxylation of the intermediate diacid 41 with 1 N hydrochloric acid gave azide acid 42 (Scheme XII) as a 1:1 mixture of diastereomers which showed identical TLC behavior with diastereomeric 42 obtained by decarboxylation of the corresponding dimethyl analogue 40. The crude acids were then esterified by treatment with 1 equiv of benzyl bromide in the presence of 1 equiv of triethylamine in refluxing acetonitrile to give dibenzyl 3-azidonocardicinic acids 43 and 44 as a 1:1 mixture of diastereomers. The overall yield of the reaction was 23% from azide malonate 55.

Experimental Section

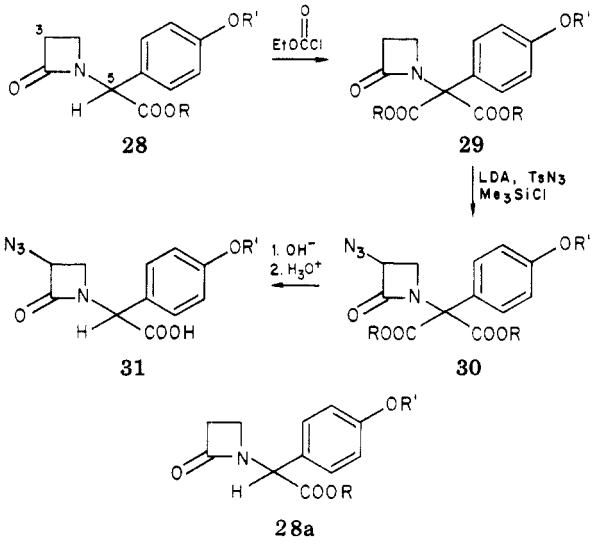
General Methods. Melting points were determined on a Mel-Temp melting point apparatus. All melting points and boiling points are uncorrected. Infrared (IR) spectra were recorded on

(19) The ethyl ester 47 was used since [*p*-(benzyloxy)phenyl]glycine methyl ester appears to form a dioxopiperazine under the reaction conditions.

Scheme VI



Scheme VII



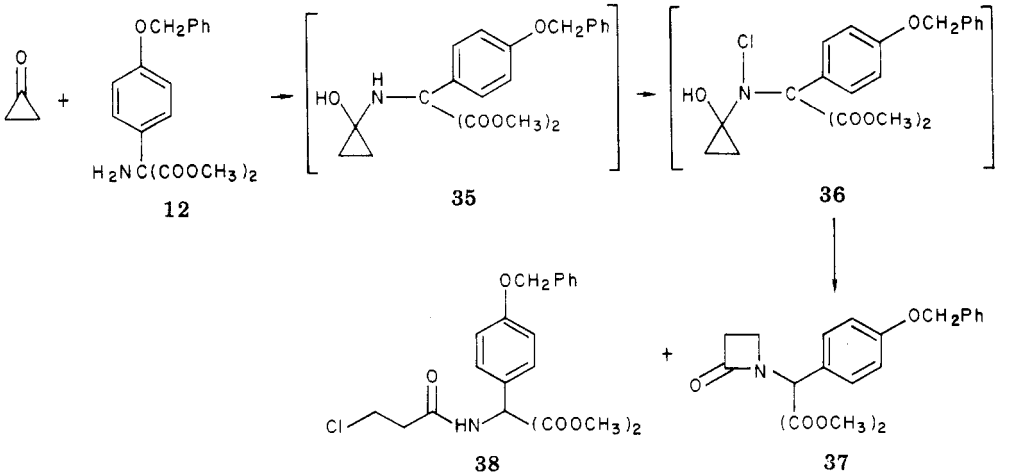
a Perkin-Elmer 700A spectrophotometer by using neat liquid films, chloroform solutions, Nujol mulls, or KBr pellets as noted. Proton nuclear magnetic resonance (NMR) spectra were determined in the indicated solvent on a Perkin-Elmer R-32 at 90 MHz or if noted on a Bruker XH-270 at 270 MHz. Chemical shifts are reported in δ units from an internal standard of tetramethylsilane. Mass spectra were recorded on a Hitachi Perkin-Elmer RMU-6 instrument at 70 eV. High-resolution mass spectra were recorded on an AEI Model MS-9 instrument courtesy of Dr. W. McMurray, Yale Medical School. Elemental analyses were performed by Dr. Robert Rittner, Olin Laboratories. Column chromatography was performed on silica gel (Woelm, activity I, 70–150 mesh) obtained from ICN Laboratories. Dry-column chromatography was performed on silica gel (ICN Laboratories, activity III, 30 μm) according to a reported procedure.[19] Thin-layer and preparative layer chromatography were performed on glass plates precoated with silica gel 60 F-254 (0.25- and 2-mm thickness, EM Laboratories). Reagent grade solvents and reagents were dried and/or distilled prior to use as follows. Tetrahydrofuran and benzene were distilled from sodium benzophenone ketyl. Anhydrous ether was used as obtained from Mallinckrodt. Methylene chloride, methanol, hexamethylphosphoramide, diisopropylamine, *N,N*-dimethylaniline, dimethyl carbonate, and diethyl carbonate were distilled from calcium hydride. *N,N*-Dimethylformamide and acetonitrile were stored over 4-Å molecular sieves for a minimum of 2 weeks prior to use. A Büchi Kugelrohr apparatus was used for bulb-to-bulb distillations, and the recorded temperatures refer to the oven temperature. Reactions requiring the slow addition of solutions were performed with the aid of a Sage Syringe pump.

Ethyl Bromo(*p*-methoxyphenyl)acetate (17). A mixture of 20.0 g (103 mmol) of ethyl ester **16**,[10] 20.2 g (113 mmol) of *N*-bromosuccinimide (recrystallized from water), and 100 mg of benzoyl peroxide in 10 mL of carbon tetrachloride was refluxed for 3 h and then allowed to stand overnight to precipitate any dissolved succinimide. After the mixture was filtered and the filtrate concentrated and dried under vacuum overnight, 32.0 g (quantitative yield) of a yellow oil was obtained: IR (neat) 1740, 1610 cm^{-1}; NMR ($CDCl_3$) δ 1.31 (t, J = 7 Hz, 3 H), 3.83 (s, 3 H), 4.28 (q, J = 7 Hz, 2 H), 5.38 (s, 1 H), 6.92 (d, J = 9 Hz, 2 H), 7.55 (d, J = 9 Hz, 2 H).

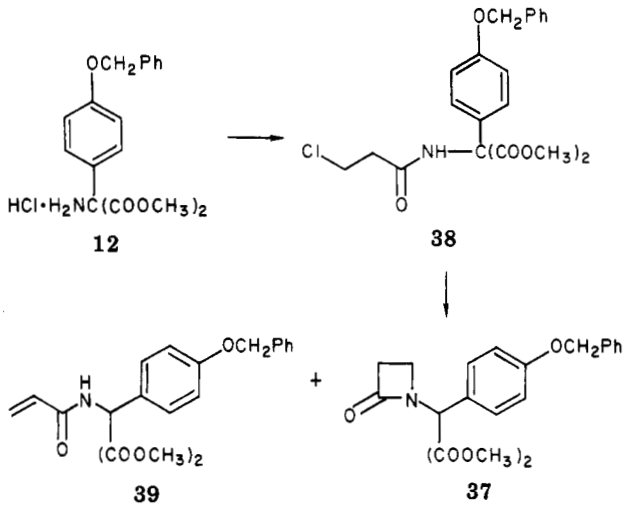
The analytical sample was prepared by bulb-to-bulb distillation [110 °C (0.05 mmHg)] to give a colorless oil.

Anal. Calcd for $C_{11}H_{13}BrO_3$: C, 48.37; H, 4.80. Found: C, 48.71; H, 5.03.

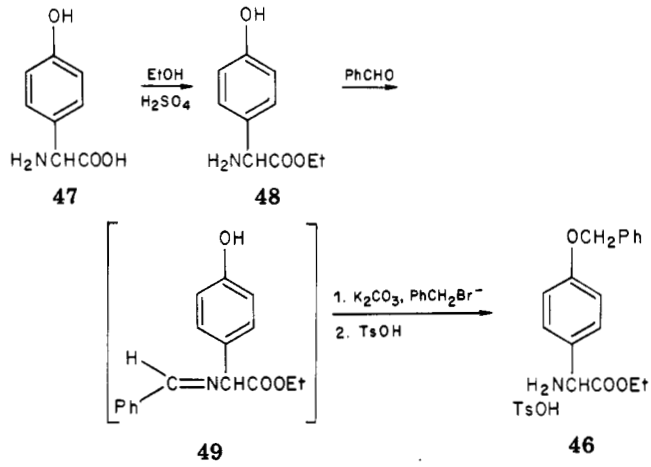
Scheme VIII



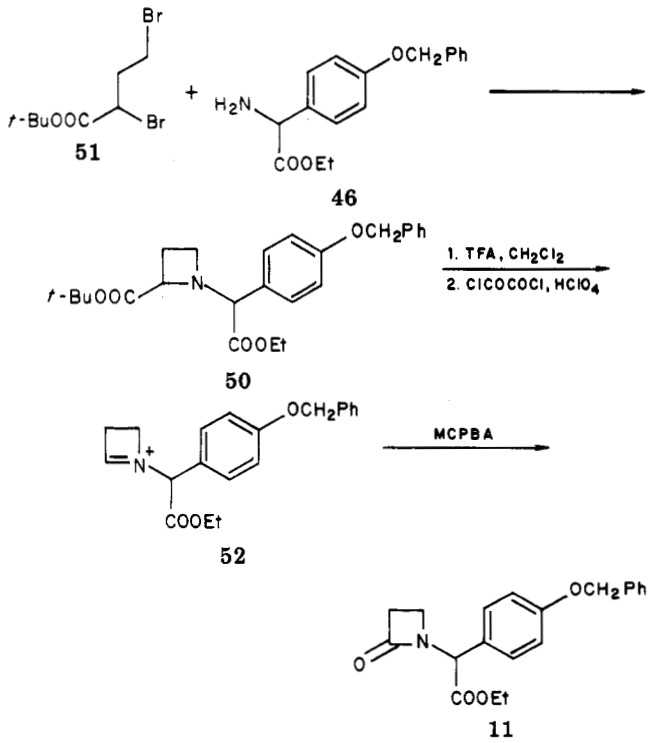
Scheme IX



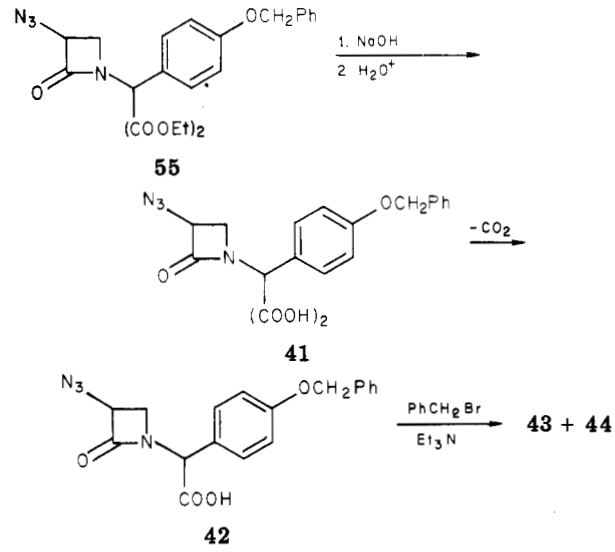
Scheme X



Scheme XI



Scheme XII



Ethyl Azido(*p*-methoxyphenyl)acetate (18). A solution of 0.5 g (2 mmol) of 18-crown-6 in 60 mL of benzene was refluxed for 2 h with azeotropic removal of water. On cooling, 7.5 g (28 mmol) of bromo ethyl ester **17** and 2.3 g (28 mmol) of potassium azide were added. The mixture was stirred at room temperature for 6 h and then passed through a column (30 × 2) of silica gel, washing with benzene. The filtrate was concentrated and dried under vacuum to give 6.1 g (94%) of a light oil: IR (neat) 2130, 1750, 1610 cm^{-1}; NMR ($CDCl_3$) δ 1.21 (t, J = 7 Hz, 3 H), 3.74 (s, 3 H), 4.19 (q, J = 7 Hz, 2 H), 4.86 (s, 1 H), 6.88 (d, J = 9 Hz, 2 H), 7.28 (d, J = 9 Hz, 2 H).

The analytical sample was prepared by molecular distillation [40 °C (0.01 mmHg)] to give a light yellow oil.

Anal. Calcd for $C_{11}H_{13}N_3O_3$: C, 56.16; H, 5.57; N, 17.86. Found: C, 56.48; H, 5.81; N, 17.73.

2-(*p*-Methoxyphenyl)glycine Ethyl Ester (15). A mixture of 3.1 g (13 mmol) of azide ester **18**, 3.0 g (16 mmol) of *p*-toluenesulfonic acid monohydrate, and 0.5 g of 10% palladium on charcoal in 100 mL of 95% ethanol was hydrogenated at room temperature at 50 psi of H_2 for 24 h. The mixture was filtered through a pad of Celite and concentrated to give yellow crystals. One recrystallization from ethyl acetate gave 3.5 g (71%) of white crystals: mp 157–161 °C; IR (KBr) 3400, 2840, 1740, 1610 cm^{-1}; NMR ($CDCl_3$) δ 1.02 (t, J = 7 Hz, 3 H), 2.31 (s, 3 H), 3.68 (s, 3 H), 3.99 (q, J = 7 Hz, 2 H), 5.02 (br d, J = 5 Hz, 1 H), 6.62 (d, J = 9 Hz, 2 H), 7.00 (d, J = 8 Hz, 2 H), 7.21 (d, J = 9 Hz, 2 H), 7.50 (d, J = 8 Hz, 2 H), 8.42 (br s, 3 H).

The amine could be freed quantitatively from its hydrotosylate salt by extraction from saturated aqueous sodium bicarbonate with ether.

The analytical sample was prepared by vacuum distillation to give a light yellow oil, bp 106–110 °C (0.1 mmHg).

Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 62.95; H, 7.15; N, 6.72.

***N*-(3-Bromopropionyl)-2-(*p*-methoxyphenyl)glycine Ethyl Ester (21).** To a stirred solution of 1.9 g (5.0 mmol) of the hydrotosylate of **15** and 1.9 mL (15 mmol) of *N,N*-dimethylaniline in 20 mL of methylene chloride at 0 °C was added over 15 min 1.0 mL (10 mmol) of 3-bromopropionyl chloride in 2 mL of methylene chloride. After completion of the addition, the reaction was allowed to come to room temperature and stirred for 4 h. The solution was diluted with methylene chloride and washed successively with 1 N hydrochloric acid, water, saturated aqueous sodium bicarbonate, and water. The organic layer was dried over anhydrous magnesium sulfate, concentrated, and recrystallized from ethyl acetate–hexanes to give 1.2 g (70%) of light yellow needles: mp 84–86 °C; IR ($CHCl_3$) 3430, 1730, 1675, 1610, 1500 cm^{-1}; NMR ($CDCl_3$) δ 1.22 (t, J = 7 Hz, 3 H), 2.80 (t, J = 6 Hz, 2 H), 3.60 (t, J = 6 Hz, 2 H), 3.78 (s, 3 H), 4.20 (q, J = 7 Hz, 2 H), 5.51 (d, J = 7 Hz, 1 H), 6.64 (br d, J = 7 Hz, 1 H), 6.86 (d, J = 9 Hz, 2 H), 7.30 (d, J = 9 Hz, 2 H).

The analytical sample was prepared by four recrystallizations from benzene–hexanes to give white needles, mp 88.5–89.0 °C.

Anal. Calcd for $C_{14}H_{18}BrNO_4$: C, 48.85; H, 5.27; N, 4.07. Found: C, 48.75; H, 5.28; N, 4.06.

Table I. Data on the Calibration of Distilled Ketene

time (X), min	run	mmol of *tert*-butylamine (Y)	ratio (amide/amine)	mmol of ketene	average mmol
7.0	1	90.0	12.5:27	28.5	
	2	89.9	42:74	32.5	30
9.5	1	120	25.7:21.1	65.9	
	2	120	27.0:20.0	68.9	67

Generation of Ketene. Caution: Ketene is a strong irritant, and this procedure should be carried out in an efficient fume hood.

Ketene generated (ketene generator from Ace Glass Inc.) by pyrolysis of acetone was passed through a trap at −78 °C (dry ice–acetone) to remove higher molecular weight impurities and then condensed in a second trap at −125 °C (liquid nitrogen–petroleum ether slurry) for 3 h. The trap containing the liquid ketene was closed off from the ketene generator and was removed from the cooling bath. After 480 s (8.0 min) to allow the rate of ketene distillation to stabilize, ketene was bubbled (Pyrex 12C glass-fritted bubbler) for 420 s (7.0 min, 30 mmol; see Table I for calibration) through 200 mL of dry methylene chloride in a 500-mL, fire-polished, three-necked flask cooled to −78 °C and under a nitrogen atmosphere.

Calibration of Distilled Ketene. The ketene solution prepared above was stirred for 5 min at −78 °C and then Y millimoles (Table I) of *tert*-butylamine (excess) was added dropwise. After the mixture was stirred 5 min, an aliquot was removed, and the ratio of *N*-*tert*-butylacetamide to *tert*-butylamine was determined by integration of the *tert*-butyl singlets (δ 1.33 and 1.12, respectively) in their NMR spectra. Thus, knowing the ratio and the millimoles of *tert*-butylamine added, the number of millimoles of ketene in solution was determined. The trap containing the liquid ketene was recooled to −125 °C, and a second run was obtained.

Two runs were taken for two time intervals, 7.0 and 9.5 min. The results are shown in Table I.

Standardized Ethereal Diazomethane. Caution: Whenever, diazomethane is used or generated, it should be done in a fume hood behind a safety shield. Diazomethane is a mild carcinogen and is explosive. *N*-methyl-*N*-nitrosourea is also a known carcinogen and should be handled with due caution.

To a two-phase mixture of 67 mL of 40% aqueous potassium hydroxide and 80 mL of ether at 0 °C was added 12.8 g (124 mmol) of *N*-methyl-*N*-nitrosourea in several portions over 30 min with stirring. After 30 min the mixture was cooled to −78 °C to freeze the aqueous phase, and the yellow ether layer was decanted off and stored over potassium hydroxide pellets.

To standardize the diazomethane solution, 5.0 mL of the solution was added to 733 mg (6.01 mmol) of benzoic acid (excess) in 10 mL of ether. The solution was titrated to the phenolphthalein end point with 20.2 mL of 0.100 N sodium hydroxide; thus the concentration of diazomethane was 0.80 M.

Preparation of Ketene-Free Cyclopropane Solutions. A 30-mmol ketene solution (prepared as described above) was stirred for 5 min at −78 °C, and then 29 mL (925 mmol) of a precooled (−78 °C) 0.87 M ethereal diazomethane solution was added rapidly dropwise from a vacuum-jacketed addition funnel. After the mixture was stirred for 5 min at −78 °C, the flask was evacuated at 8 mmHg for 2 h under a stream of nitrogen from a capillary tube beneath the solution's surface. The vacuum line was closed, the pressure was allowed to come to atmospheric pressure, and the ketene-free cyclopropanone solution (25 mmol) was used immediately.

Following the above procedure, 52 mmol of diazomethane was reacted with 67 mmol of ketene (see Table I) to give a 52-mmol ketene-free cyclopropanone solution.

Ethyl α-(*p*-Methoxyphenyl)-2-oxo-1-azetidineacetate (20). Method A. To 25 mmol of ketene-free cyclopropanone solution at −78 °C under nitrogen was added dropwise a solution of 5.7 g (27 mmol) of 2-(*p*-methoxyphenyl)glycine ethyl ester (*15*) in 5 mL of anhydrous ether. After 45 min at −78 °C and 30 min at −10 °C (stirring), 0.5 g of sodium bicarbonate was added. Then, in the dark, 3.0 g (27 mmol) of *tert*-butyl hypochlorite was added dropwise. After 40 min at −10 °C (stirring) the solution was diluted with 200 mL of dry acetonitrile, and 13.8 g (81 mmol) of silver nitrate was added in one portion. The mixture was allowed to come to room temperature, and after 1.5 h it was filtered and concentrated. The residue was diluted with 7 N ammonium hydroxide and extracted three times with ether. The combined extracts were washed once with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated to give 6.2 g of a yellow oil. Dry-column chromatography on a 24 × 1.5 in. column of silica gel eluted with 20% methylene chloride in ether gave a yellow oil: 3.6 g (52%); IR ($CHCl_3$) 1740, 1610 cm^{-1}; NMR ($CHCl_3$) δ 1.28 (t, J = 7 Hz, 3 H), 2.82–3.19 (m, 3 H), 3.64 (m, 1 H), 3.84 (s, 3 H), 4.26 (q, J = 7 Hz, 2 H), 5.56 (s, 1 H), 6.95 (d, J = 9 Hz, 2 H), .727 (d, J = 9 Hz, 2 H); mass spectrum, m/e 263 (M^+).

The analytical sample was prepared by molecular distillation [80 °C (0.1 mmHg)] to give a colorless oil.

Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.66; H, 6.39; N, 5.29.

Method C. To a suspension of 60 mg (1.2 mmol) of a 50% mineral oil dispersion of sodium hydride (prewashed with pentane) in 10 mL of *N*,*N*-dimethylformamide–methylene chloride (1:4) at room temperature and under nitrogen was added, over 2.5 h, a solution of 344 mg (1.0 mmol) of the bromoamide **21** in 10 mL of *N*,*N*-dimethylformamide–methylene chloride (1:4). After the addition was completed, the reaction was stirred at room temperature for 1 h, poured onto saturated aqueous ammonium chloride, and diluted with ether. The organic layer was washed five times with water then with brine, dried over anhydrous magnesium sulfate, and concentrated to give 231 mg of a yellow oil. Bulb-to-bulb distillation gave 203 mg (77%) of a colorless oil. The IR and NMR spectra of this compound were identical with those obtained for β-lactam **20** prepared from cyclopropanone.

α-(*p*-Methoxyphenyl)-2-oxo-1-azetidineacetic Acid (22). To a stirred solution of 528 mg (2.0 mmol) of β-lactam **20** in 20 mL of methanol at 0 °C was added dropwise 2.3 mL (2.0 mmol) of a 0.87 M solution of lithium hydroxide in methanol. After 2 h at 0 °C (stirring) the mixture was concentrated, the residue was dissolved in water, and the solution was acidified with 1 N hydrochloric acid and then extracted four times with methylene chloride. The combined extracts were dried over anhydrous magnesium sulfate and concentrated to give 0.4 g of a yellow solid. Recrystallization from ethyl acetate–hexanes gave 280 mg (60%) of white crystals: mp 113–114 °C; IR ($CHCl_3$) 1740 (br), 1610, 1510 cm^{-1}; NMR ($CDCl_3$) δ 2.89 (m, 2 H), 3.05 (m, 1 H), 3.58 (m, 1 H), 3.76 (s, 3 H), 5.53 (s, 1 H), 6.86 (d, J = 9 Hz, 2 H), 7.23 (d, J = 9 Hz, 2 H), 10.45 (s, 1 H).

The analytical sample was prepared by three recrystallizations from ethyl acetate to give white crystals, mp 113–114 °C.

Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.43; H, 5.78; N, 5.97.

Ethyl α-(*p*-Hydroxyphenyl)-2-oxo-1-azetidineacetate (23). To a solution of 267 mg (1.0 mmol) of β-lactam **21** in 10 mL of dry methylene chloride at −78 °C under nitrogen was added dropwise 13 mL (13 mmol) of a 1 M solution of boron tribromide in methylene chloride. The cloudy orange solution was stirred at −78 °C for 45 min and then at −25 °C (dry ice–CCl_4 slurry) for 2 h. The reaction was quenched by dropwise addition of 20 mL of anhydrous ether, and stirring was continued for 20 min. After it was poured onto 40 mL of saturated aqueous sodium bicarbonate and gas evolution ceased, the mixture was brought to pH ~5 with 1 N hydrochloric acid and extracted three times with ethyl acetate. The combined extracts were washed with brine, dried over anhydrous magnesium sulfate, and concentrated to give 266 mg of a yellow oil. Preparative layer chromatography of the oil on silica gel eluted three times with ether gave 208 mg (83%) of a colorless oil which crystallized on standing: IR ($CHCl_3$) 3580, 3300 (b), 1740 (br) cm^{-1}; NMR ($CDCl_3$) δ 1.22 (t, J = 7 Hz, 3 H), 2.93 (m, 2 H), 3.10 (m, 1 H), 3.61 (m, 1 H), 4.19 (q, J = 7 Hz, 2 H), 5.48 (s, 1 H), 6.87 (d, J = 9 Hz, 2 H), 7.12 (d, J = 9 Hz, 2 H), 7.80 (br s, 1 H).

The analytical sample was prepared by two recrystallizations from ethyl acetate–hexanes to give white crystals, mp 87–88 °C.

Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.84; H, 5.98; N, 5.47.

2-[*p*-(Benzyloxy)phenyl]-*N*-(3-bromopropionyl)glycine Benzyl Ester (27). To 343 mg (2.0 mmol) of 3-bromopropionyl chloride in 5 mL of methylene chloride at 0 °C was added dropwise a solution of 695 mg (2.0 mmol) of amine **25** and 237 mg (3.0 mmol) of pyridine in 5 mL of methylene chloride. After it was stirred for 12 h at room temperature, the reaction mixture was diluted with ether and was washed usccessively with 1 N hydrochloric acid, 1 N sodium hydroxide, and brine. The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated. Recrystallization of the residue from ethyl acetate–ether–hexanes gave 772 mg (80%) of white needles: mp 114–116 °C; IR ($CHCl_3$) 3320, 1730, 1675, 1610 cm^{-1}; NMR ($CDCl_3$) δ 7.38–7.23 (m, 12 H), 6.92 (d, J = 9 Hz, 2 H), 6.80 (d, J = 6 Hz, 1 H), 5.61 (d, J = 6 Hz, 1 H), 5.15 (s, 2 H), 5.03 (s, 2 H), 3.57 (t, J = 6 Hz, 2 H), 2.76 (t, J = 6 Hz, 2 H).

The analytical sample was prepared by recrystallization from methyl acetate–ether–heptane to give needles, mp 115–116 °C.

Anal. Calcd for $C_{25}H_{24}NO_4Br$: C, 62.25; H, 5.02; N, 2.90. Found: C, 62.37; H, 5.12; N, 3.03.

Benzyl α-[*p*-(Benzyloxy)phenyl]-2-oxo-1-azetidineacetate (26). Method A. By use of the procedures described earlier, 30 mL (27 mmol) of a 0.90 M ethereal diazomethane solution was reacted with 30 mmol of ketene to give a 27 mmol ketene-free cyclopropanone solution.

To the cyclopropanone solution at −78 °C and under nitrogen was added 8.8 g (25 mmol) of amine **25**[5a] in 10 mL of dry methylene chloride, and after 1 h (stirred), 0.5 g of solid sodium bicarbonate was added. Then 2.7 g (25 mmol) of *tert*-butyl hypochlorite was added dropwise at −78 °C in the dark and stirring continued at −10 °C for 40 min. On dilution with 200 mL of dry acetonitrile, 11.9 g (70 mmol) of solid silver nitrate was added. The mixture was stirred at room temperature for 1.5 h, filtered, and concentrated. The residue was diluted with 7 N ammonium hydroxide and extracted three times with ether. The combined extracts were washed successively with 1 N hydrochloric acid, water, and brine. The organic layer was dried over anhydrous magnesium sulfate and concentrated to give 8.7 g of a yellow oil. Chromatography on 260 g of silica gel with gradient elution (10% ether in petroleum ether to 50% ether in petroleum ether) gave 5.9 g (59%) of a colorless oil, which crystallized on being allowed to stand: mp 76–79 °C; IR (neat) 1740, 1610, 1515 cm^{-1}; NMR ($CDCl_3$, 270 MHz) δ 2.77 (m, 1 H), 2.93 (m, 1 H), 3.02 (, 1 H), 3.56 (m, 1 H), 5.02 (s, 2 H), 5.15 (s, 2 H), 5.58 (s, 1 H), 6.92 (d, J = 8.8 Hz, 2 H), 7.15 (d, J = 8.8 Hz, 2 H), 7.19–7.44 (m, 10 H); high-resolution mass spectrum, calcd for $C_{25}H_{23}NO_4$ m/e 401.1620, found m/e 401.16.

Method C. To a suspension of 100 mg (2.1 mmol) of a 50% mineral oil dispersion of sodium hydride in 20 mL of dimethylformamide–methylene chloride (1:4) was added over 1 h a solution containing 0.90 g (1.9 mmol) of bromoamide **27** in 20 mL of dimethylformamide–methylene chloride (1:4). After completion of the addition, the reaction was stirred for 1 h at room temperature, diluted with 40 mL of ether, and washed with saturated sodium chloride solution (6 × 50 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 700 mg of yellow oil. Gradient chromatography over silica gel (hexane–ether) provided 352 mg (46%) of β-lactam **26** as a colorless oil.

α-(*p*-Hydroxyphenyl)-2-oxo-1-azetidineacetic Acid (14). A mixture of 380 mg (0.95 mmol) of β-lactam **26** and 30 mg of 10% palladium on charcoal in 30 mL of 95% ethanol was hydrogenated at 50 psi of hydrogen for 14 h. The mixture was filtered through a pad of Celite, concentrated, and dried under vacuum to give 206 mg (98%) of a white foam: IR (KBr) 2300–3600 (vbr), 1720 (br, 1615, 1610, 1515 cm^{-1}; NMR ($CDCl_3$–pyridine-d_5) δ 2.90 (m, 2 H), 3.13 (m, 1 H), 3.74 (m, 1 H), 5.72 (s, 1 H), 7.05 (d, J = 9 Hz, 2 H), 7.41 (d, J = 9 Hz, 2 H), 10.48 (br s, 2 H).

Repeated attempts to crystallize foam **14** for analysis were unsuccessful due to its instability. It was converted to the known ethyl ester **24** as follows. To a mixture of 90 mg (0.41 mmol) of the foam **14** and 100 mL of absolute ethanol in methylene chloride at room temperature were added 85 mg (0.41 mmol) of dicyclohexylcarbodiimide and then 3 drops of pyridine. After being stirred at room temperature for 26 h, the mixture was poured onto saturated aqueous sodium bicarbonate and extracted three times with methylene chloride. The combined extracts were dried over magnesium sulfate and concentrated. The residue was diluted with a minimal amount of methylene chloride and filtered, and the filtrate was concentrated to give 125 mg of a yellow oil. Preparative layer chromatography on silica gel eluted three times with ether gave a yellow solid, the IR and NMR spectra of which were identical with those obtained for the ethyl ester prepared earlier.

Dimethyl *p*-(Benzyloxy)phenylmalonate (33). To a suspension of 68.2 g (1.42 mol) of a 50% dispersion of sodium hydride in mineral oil (prewashed with pentane) in 800 mL of dimethyl carbonate (distilled from calcium hydride) and 660 mL of anhydrous ether was added in one portion a solution of 166.3 g (0.649 mol) of methyl ester **32** in 470 mL of anhydrous ether with mechanical stirring under nitrogen. After 19 mL of absolute methanol was added dropwise, the mixture was stirred at room temperature for 24 h, at which time the mixture became viscous with a white precipitate. The reaction was quenched by the cautious addition of 100 mL of glacial acetic acid and then 300 mL of water. The organic phase was washed twice with water and then brine, dried over anhydrous magnesium sulfate, filtered, and evaporated. The yellow solid was recrystallized once from methanol to give 153.5 g (75%) of pale yellow crystals: mp 85–88 °C; IR ($CHCl_3$) 1740, 1610, 1585 cm^{-1}; NMR ($CDCl_3$) δ 3.67 (s, 6 H), 4.54 (s, 1 H), 4.96 (s, 2 H), 6.90 (d, J = 8 Hz, 2 H), 7.25–7.40 (m, 7 H); mass spectrum, m/e 314 (M^+).

The analytical sample was prepared by four recrystallizations from methanol to give white glistening plates, mp 91–92 °C.

Anal. Calcd for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77. Found: C, 68.50; H, 5.69.

Dimethyl Azido[*p*-(benzyloxy)phenyl]malonate (34). To a suspension of 2.5 g (52 mmol) of a 50% dispersion of sodium hydride in mineral oil (prewashed with pentane) in 25 mL of dry hexamethylphosphoramide and 250 mL of dry tetrahydrofuran at room temperature under nitrogen was added in one portion 15.7 g (50 mmol) of malonate **33**. After the mixture was stirred for 2 h at room temperature 10.8 g (55 mmol) of *p*-toluenesulfonyl azide[12] was added in one portion, and the solution was refluxed for 2 h. On cooling, the heterogeneous mixture was concentrated, and the residue was diluted with saturated aqueous sodium bicarbonate and extracted twice with benzene. The extracts were washed three times with water and finally with brine. Drying over anhydrous magnesium sulfate and concentration gave a yellow solid which was recrystallized once from ether to give 13.5 g (76%) of light yellow crystals: mp 78–81 °C; IR ($CHCl_3$) 2120, 1740, 1610, 1590 cm^{-1}; NMR ($CDCl_3$) δ 3.80 (s, 6 H), 5.02 (s, 2 H), 6.96 (d, J = 9 Hz, 2 H), 7.3–7.5 (m, 7 H); mass spectrum, m/e 327 (M^+ − 28).

The analytical sample was prepared by five recrystallizations from ether to give pale yellow crystals, mp 82–83 °C.

Anal. Calcd for $C_{18}H_{17}N_3O_5$: C, 60.84; H, 4.82; N, 11.82. Found: C, 60.84; H, 4.90; N, 11.73.

Dimethyl Amino[*p*-(benzyloxy)phenyl]malonate (12). Reduction with Zinc Dust. To a suspension of 13.5 g (38 mmol) of azide **34** in 70 mL of 90% aqueous acetic acid at room temperature was added in several portions 5.0 g (76 mmol) of zinc dust over 20 min. On completion of the addition, the mixture was stirred at room temperature for 2 h and then filtered. The filtrate was concentrated, diluted with water, and neutralized with saturated aqueous sodium bicarbonate. The heterogeneous solution was diluted with ether and filtered, and the filter cake was washed with ether. The organic layer was separated, and the aqueous layer was extracted twice with ether. The combined ether extracts were saturated with dry hydrogen chloride and then filtered to give 11.7 g (84%) of light yellow lustrous crystals. The amine was freed from its hydrochloride by extraction with methylene chloride from saturated aqueous sodium bicarbonate to give 10.6 g (100%) of light yellow crystals: mp 62–66 °C; IR ($CHCl_3$) 3400, 3330, 1740, 1610, 1585 cm^{-1}; NMR ($CDCl_3$) δ 2.33 (br s, 2 H), 3.77 (s, 6 H), 5.04 (s 2 H), 6.96 (d, J = 9 Hz, 2 H), 7.4–7.5 (m, 7 H); mass spectrum, m/e 270 (M^+ − 59).

The analytical sample was prepared by five recrystallizations from ether to give white needles, mp 68–69 °C.

Anal. Calcd for $C_{18}H_{19}NO_5$: C, 65.64; H, 5.81; N, 4.25. Found: C, 65.63; H, 5.76; N, 4.30.

Reduction with Aluminum Amalgam. To a solution of 15.7 g (50 mmol) of malonate **33** in 25 mL of dry hexamethylphosphoramide and 250 mL of dry tetrahydrofuran was added 1.2 g (50 mmol) of 99% sodium hydride. The cloudy mixture was stirred at room temperature under nitrogen for 30 min until it became clear and hydrogen evolution ceased, and 9.9 g (50 mmol) of *p*-toluenesulfonyl azide[12] was added. After the solution was heated at 50 °C for 2 h and a precipitate had formed, 16 mL (126 mmol) of trimethylsilyl chloride was added and heating continued for 15 min. On cooling, the mixture was filtered and the filtrate concentrated. The residue was diluted with saturated aqueous sodium bicarbonate and extracted twice with benzene. The combined extracts were washed three times with water and then brine, dried over anhydrous magnesium sulfate, filtered, and concentrated to give 19.8 g of a yellow-brown solid azide (**34**).

To aluminum amalgam,[20] prepared from 5.4 g (200 mmol) of aluminum foil, in 250 mL of ether at 0 °C was added one-fourth of a solution of the above crude azide in 100 mL of ether and then 15 mL of a 10% aqueous tetrahydrofuran solution. Gas evolution was noted, and the remainder of the azide solution was added dropwise over 20 min, during which time 15-mL portions of 10% aqueous tetrahydrofuran were added for a total of 100 mL. After 2.5 h at 0 °C the gray solids which formed were filtered off and washed with ether. The filtrate was washed three times with 1 N hydrochloric acid, and the acid washings were neutralized with saturated aqueous sodium bicarbonate and extracted three times with ether. The combined extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated to give 9.9 g of a pale yellow solid. Recrystallization from ether gave 8.8 g (53%) of pale yellow crystals, mp 64–67 °C. The IR and NMR spectra of this compound were identical with those obtained for amine **12** in the preceding experiment.

Reaction of Dimethyl Amino[*p*-(benzyloxy)phenyl]malonate (12) with Cyclopropanone. To 25 mmol of a ketene-free cyclopropanone solution at −78 °C under nitrogen was added dropwise a solution of 8.2 g (25 mmol) of amine **12** in 15 mL of methylene chloride. After the mixture was stirred for 1 h at −78 °C, 0.5 g of sodium bicarbonate was added. Then 2.9 g (27 mmol) of *tert*-butyl hypochlorite was added dropwise in the dark and stirring continued for 1 h at −78 °C and then for 30 min at −10 °C. On dilution with 200 mL of dry acetonitrile, 11.9 g (70 mmol) of silver nitrate was added. The heterogeneous solution was stirred for 1.5 h at room temperature, filtered, and concentrated. The residue was diluted with 7 N ammonium hydroxide and extracted three times with ether. The combined extracts were washed successively with 1 N hydrochloric acid, water, and then brine. The organic layer was dried over anhydrous magnesium sulfate and concentrated to give 8.7 g of yellow solid. Trituration with ether gave 3.0 g (29%) of white crystals of dimethyl [*p*-(benzyloxy)phenyl](3-chloropropionamido)malonate (**38**): IR ($CHCl_3$) 3400, 1740, 1680, 1610, 1500 cm^{-1}; NMR ($CDCl_3$) δ 2.73 (t, J = 6 Hz, 2 H), 3.68–3.87 (m, 8 H), 5.04 (s, 2 H), 6.94 (d, J = 9 Hz, 2 H), 7.25–7.60 (m, 8 H); mass spectrum, m/e 419 (M^+).

The analytical sample was prepared by three recrystallizations from ethyl acetate to give white crystals, mp 151–153 °C. The melting point was undepressed on mixture with the compound prepared from amine hydrochloride **12** and 3-chloropropionyl chloride.

Anal. Calcd for $C_{21}H_{22}ClNO_6$: C, 60.07; H, 5.28; N, 3.34. Found: C, 60.14; H, 5.54; N, 3.28.

From the mother liquor was crystallized with ether 1.3 g (14%) of pale yellow crystals. The mother liquor (4.0 g) was dry-column chromatographed on silica gel (24 × 0.5 in. column) eluted with ether to give 2.3 g (24%) of pale yellow crystals. Thus the total yield was 3.6 g (38%) of dimethyl α-[*p*-(benzyloxy)phenyl]-2-oxo-1-azetidinemalonate (**37**): IR ($CHCl_3$) 1750 (br), 1610 cm^{-1}; NMR ($CDCl_3$) δ 2.93 (t, J = 4 Hz, 2 H), 3.43 (t, J = 4 Hz, 2 H), 3.85 (s, 6 H), 5.07 (s, 2 H), 6.98 (d, J = 9 Hz, 2 H), 7.25–7.50 (, 7 H); mass spectrum, m/e 383 (M^+).

The analytical sample was prepared by four recrystallizations from ether–chloroform to give white crystals, mp 103–104 °C.

Anal. Calcd for $C_{21}H_{21}NO_6$: C, 65.79; H, 5.52; N, 3.65. Found: C, 65.38; H, 5.59; N, 3.81.

Dimethyl [*p*-(Benzyloxy)phenyl](3-chloropropionamido)malonate (38). To a stirred solution of 1.8 g (5 mmol) of amine hydrochloride **12** and 1.9 mL (15 mmol) of *N,N*-dimethylaniline in 20 mL of dry methylene chloride at 0 °C was added over 15 min 0.53 mL (5.5 mmol) of 3-chloropropionyl chloride in 2 mL of dry methylene chloride. After completion of the addition, the reaction mixture was stirred at room temperature for 4 h. The solution was diluted with methylene chloride and washed successively with 1 N hydrochloric acid, water, saturated aqueous sodium bicarbonate, and then water. The organic layer was dried over anhydrous magnesium sulfate and concentrated to give 2.1 g of a white solid. Recrystallization from ethyl acetate gave 1.8 g (86%) of white crystals, mp 154–157 °C. The IR and NMR spectra of this compound were identical with those obtained for chloropropionamide **38** prepared from cyclopropanone.

Dimethyl α-[*p*-(Benzyloxy)phenyl]-2-oxo-1-azetidinemalonate (37). To a suspension of 576 mg (12 mmol) of a 50% mineral oil dispersion of sodium hydride (prewashed with pentane) in 100 mL of *N,N*-dimethylformamide–methylene chloride (1:4) at room temperature and under nitrogen was added over 5.5 h a solution of 4.2 g (10 mmol) of chloropropionamide **38** in 100 mL of *N,N*-dimethylformamide–methylene chloride (1:4). After completion of the addition, the reaction mixture was stirred at room temperature for 1 h, poured onto saturated aqueous ammonium chloride and diluted with ether. The organic layer was washed five times with water and then with brine, dried over anhydrous magnesium sulfate, and concentrated to give 4.0 g of a yellow solid. Recrystallization from acetone gave 2.9 g (76%) of white crystals, mp 98–101 °C. The IR and NMR spectra of this compound were identical with those obtained for β-lactam **37** prepared from cyclopropanone.

By use of the above reaction conditions, with faster addition (0.5 h or 2 h) of chloropropionamide **38** to sodium hydride, a second product was isolated, dimethyl (acrylamido)[*p*-(benzyloxy)phenyl]malonate (**39**): IR ($CHCl_3$) 3400, 1740, 1680, 1610, 1500 cm^{-1}; NMR ($CDCl_3$) δ 3.77 (s, 6 H), 5.00 (s, 2 H), 5.67 (m, 1 H), 6.25 (m, 2 H), 6.98 (d, J = 9 Hz, 2 H), 7.20 (br s), 7.31 (br s), 7.44 (d, J = 9 Hz, 8 H); mass spectrum, m/e 383 (M^+).

The analytical sample was prepared by four recrystallizations from ethyl acetate to give white crystals, mp 132–133 °C.

Anal. Calcd for $C_{21}H_{21}NO_6$: C, 65.79; H, 5.52; N, 3.65. Found: C, 65.78; H, 5.46; N, 3.76.

Dimethyl 3-Azido-α-[*p*-(benzyloxy)phenyl]-2-oxo-1-azetidinemalonate (40). Three reactions with the following quantities were run at the same time and then combined for workup.

To 0.64 mL (4.6 mmol) of diisopropylamine in 40 mL of tetrahydrofuran at −78 °C and under nitrogen was added dropwise 1.65 mL (4.0 mmol) of a 2.45 M solution in *n*-butyllithium in hexanes and stirring continued for 45 min. A solution of 767 mg (2.0 mmol) of β-lactam **37** in 5 mL of tetrahydrofuran was added dropwise. After 2 h at −78 °C, 945 mg (4.8 mmol) of *p*-toluenesulfonyl azide[12] in 3 mL of tetrahydrofuran was added and the mixture stirred for 1 h. A solution of 1.1 g (10 mmol) of trimethylsilyl chloride in 3 mL of tetrahydrofuran was added, and the mixture was stirred for 1 h at room temperature. The three reaction mixtures were combined and evaporated, and the residue was diluted with saturated aqueous sodium bicarbonate and extracted twice with methylene chloride. The combined extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated to give 4.5 g of an orange oil. Column chromatography on 70 g of silica gel eluted with 40% hexanes in ether gave light yellow crystals which were recrystallized once from ethyl acetate–hexanes to give 1.94 g (76%) of white crystals: mp 105–106 °C; IR ($CHCl_3$) 2120, 1775, 1750, 1610 cm^{-1}; NMR ($CDCl_3$) δ 3.3 (dd, J = 2, 6 Hz, 1 H), 3.74 (apparent t, J = 6 Hz, 1 H), 3.85 (s, 6 H), 4.56 (dd, J = 2, 5 Hz, 1 H), 5.06 (s, 2 H), 6.97 (d, J = 9 Hz, 2 H), 7.20–7.45 (m, 7 H); mass spectrum, m/e 396 (M^+ − 28).

The analytical sample was prepared by three recrystallizations from ethyl acetate–hexanes to give white crystals, mp 105–106 °C.

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Anal. Calcd for $C_{21}H_{20}N_4O_6$: C, 59.43; H, 4.75; N, 13.20. Found: C, 59.10; H, 4.76; N, 13.18.

3-Azido-α-[p-(benzyloxy)phenyl]-2-oxo-1-azetidineacetic Acid (42). To 1.12 g (2.6 mmol) of azide β-lactam **40** in 50 mL of methanol at 0 °C was added over 20 min 5.7 mL (5.7 mmol) of 1 N sodium hydroxide. Stirring was continued for 4 h at 0 °C, and the solution was acidified with 1 N hydrochloric acid (gas evolution noted). After the mixture was diluted with 100 mL of water and stirred for 30 min at 0 °C, a white amorphous solid (427 mg, 47%) was obtained on filtration. The filtrate was extracted twice with ethyl acetate, and the combined extracts were washed with brine. The organic layer was dried over anhydrous magnesium sulfate and concentrated to give 445 mg of a yellow foam. Chromatography on 15 g of silica gel eluted with ethyl acetate–hexanes (1:1) gave 221 mg (24%) of a light yellow amorphous solid. The total yield was 648 mg (71%): IR (KBr) 3200–2500, 2120, 1730 (br) cm^{-1}; NMR ($CDCl_3$) δ 2.98 (m, 0.5 H), 3.38 (m, 0.5 H), 3.55 (m, 0.5 H), 3.86 (m, 0.5 H), 4.52 (m, 0.5 H), 4.69 (m, 0.5 H), 5.07 (s, 2 H), 5.61 (s, 1 H), 7.00 (d, J = 9 Hz, 2 H), 7.20–7.50 (m, 7 H), 8.10 (br s, 1 H).

The analytical sample was prepared by five recrystallizations from ethyl acetate–hexanes to give a white powder, mp 140–142 °C dec.

Anal. Calcd for $C_{18}H_{16}H_4O_4$: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.38; H, 4.65; N, 15.78.

Benzyl 3-Azido-α-[p-(benzyloxy)phenyl]-2-oxo-1-azetidineacetate (43 and 44). A solution of 378 mg (1.1 mmol) of azide acids **42**, 0.22 mL (1.6 mmol) of triethylamine, and 0.15 mL (1.3 mmol) of benzyl bromide in 10 mL of dry acetonitrile was refluxed for 6 h. On cooling, the mixture was concentrated. The residue was diluted with ether and washed successively with saturated aqueous sodium bicarbonate, water, and brine. The organic layer was dried over anhydrous magnesium sulfate and concentrated to give 375 mg (77%) of a yellow oil: IR ($CHCl_3$) 2120, 1760, 1740 cm^{-1}; NMR ($CDCl_3$) δ 2.92 (m, 0.5 H), 3.29 (m, 0.5 H), 3.51 (m, 0.5 H), 3.80 (m, 0.5 H), 4.38 (m, 0.5 H), 4.56 (m, 0.5 H), 5.00 (s, 2 H), 5.15 (s, 2 H), 5.56 (overlapping s, 1 H), 6.90 (d, J = 9 Hz, 2 H), 7.10 (d, J = 9 Hz, 2 H), 7.20–7.45 (m, 10 H).

The analytical sample was prepared by five recrystallizations at low temperature from benzene–hexanes to give a white powder which at room temperature was a colorless oil.

Anal. Calcd for $C_{25}H_{22}N_4O_4$: C, 67.86; H, 5.01; N, 12.66. Found: C, 67.85; H, 5.07; N, 12.62.

The diastereomeric azid esters **43** and **44** were separated on a Waters Prep LC/System 500 liquid chromatograph using two silica gel cartridges with two recycles and elution with toluene–ethyl acetate (95:5). Eluted first was azide ester **44**: oil; IR ($CHCl_3$) 2120, 1760, 1740 cm^{-1}; NMR ($CDCl_3$, 270 MHz) δ 3.36 (apparent t, J = 6 Hz, 1 H), 3.57 (dd, J = 3, 6 Hz, 1 H), 4.47 (dd, J = 3, 5 Hz, 1 H), 5.05 (s, 2 H), 2.21 (s, 2 H), 5.58 (s, 1 H), 6.94 (d, J = 9 Hz, 2 H), 7.12 (d, J = 9 Hz, 2 H), 7.26–7.42 (m, 10 H); mass spectrum, m/e 414 (M^+ – 28). Eluted second was azide ester **43**: oil; IR ($CHCl_3$) 2120, 1760, 1740 cm^{-1}; NMR ($CDCl_3$, 270 MHz) δ 2.95 (dd, J = 3 Hz, 1 H), 3.86 (apparent t, J = 6 Hz, 1 H), 4.66 (dd, J = 3, 5 Hz, 1 H), 5.05 (s, 2 H), 5.18 (s, 2 H), 5.61 (s, 1 H), 6.95 (d, J = 9 Hz, 2 H), 7.13 (d, J = 9 Hz, 2 H), 7.26–7.42 (m, 10 H); mass spectrum, m/e 414 (M^+ – 28).

The diastereomeric azide esters **43** and **44** also could be separated by preparative layer chromatography on E. Merck silica gel plates eluted 22 times with hexanes–ether (3:2) to give two major bands. The more mobile band was isolated as a light yellow oil which had spectroscopic properties identical with those of azide ester **43**. The less mobile band was isolated as a light yellow oil which had spectroscopic properties identical with those of azide ester **44**.

Equilibration of Benzyl 3-Azido-α-[p-(benzyloxy)-phenyl]-2-oxo-1-azetidineacetate (44). To a stirred solution of 19 mg (0.043 mmol) of azide benzyl ester **44** in 5 mL of dry tetrahydrofuran at 0 °C under nitrogen was added dropwise a solution of 2 mg (0.005 mmol) of potassium *tert*-butoxide and 0.25 mL of *tert*-butyl alcohol in 2 mL of dry tetrahydrofuran. After being stirred for 2 h at 0 °C, the reaction mixture was poured onto saturated aqueous ammonium chloride and extracted twice with ether. The combined extracts were dried over anhydrous magnesium sulfate and concentrated to give 19 mg (100%) of a yellow oil shown to be a 1:1 mixture of **43** and **44** by NMR. The NMR spectrum was identical with that obtained previously for the mixture of diastereomers **43** and **44**.

Properties of Authentic Benzyl (αR,3S)-3-Amino-α-[p-(benzyloxy)phenyl]-2-oxo-1-azetidineacetate Hydrotosylate (4). This sample was provided by Dr. G. A. Koppel of the Lilly Research Laboratories and was an intermediate in their synthesis of nocardicin A.[5a] The compound had the following properties: mp 167–171 °C dec; TLC (silica gel, ninhydrin indicated) R_f 0.62 (*n*-BuOH–HOAc–H_2O, 4:1:1), 0.78 (1% NH_3 in CH_3OH–$CHCl_3$, 1:5), 0.45 (1% NH_3 in CH_3H–EtOAc, 1:9); IR (KBr) 2950 (vbr), 1750 (split), 1610, 1510 cm^{-1}; NMR δ (Me_2SO-d_6, 270 MHz), 2.29 (s, 3 H), 3.08 (dd, J = 2, 6 Hz, 1 H), 3.35 (br s, H_2O), 3.77 (apparent t, J = 6 Hz, 1 H), 4.60 (dd, J = 2, 5 Hz, 1 H), 5.12 (s, 2 H), 5.19 (s, 2 H), 5.69 (s, 1 H), 7.03–7.49 (m, 18 H), 8.62 (br s, 3 H).

Benzyl (±)-(αR*,3S*)-3-Amino-α-[p-(benzyloxy)-phenyl]-2-oxo-1-azetidineacetate Hydrotosylate (4). Reduction with Zinc Dust. To a solution of 34 mg (0.077 mmol) of azide benzyl ester **43** in 3 mL of 90% aqueous acetic acid at room temperature was added 29 mg (0.44 mmol) of zinc dust, and stirring was continued for 1 h. The mixture was neutralized with 10 mL of saturated aqueous sodium bicarbonate and then with solid sodium bicarbonate and was extracted three times with ether. The combined extracts were washed once with brine, dried over anhydrous magnesium sulfate, and concentrated to give 26 mg of a yellow oil. The oil was dissolved in a small amount of ethyl acetate, and 15 mg of *p*-toluenesulfonic acid monohydrate was added. A white solid formed, the supernatant was discarded, and the solids were washed twice with ethyl acetate–ether to give 21 mg (46%) of a white amorphous solid: mp 169–173 °C dec; TLC (silica gel, ninhydrin indicated) R_f 0.62 (*n*-BuOH–HOAc–H_2O, 4:1:1), 0.78 (1% NH_3 in CH_3OH–$CHCl_3$, 1:5), 0.45 (1% NH_3 in CH_3OH–EtOAc, 1:9); IR (KBr) 2950 (vbr), 1750 (split), 1610, 1510 cm^{-1}; NMR (Me_2SO-d_6, 270 MHz) δ 2.29 (s, 3 H), 3.08 (dd, J = 2, 6 Hz, 1 H), 3.36 (br s, H_2O), 3.76 (apparent t, J = 6 Hz, 1 H), 4.61 (dd, J = 2, 5 Hz, 1 H), 5.12 (s, 2 H), 5.19 (s, 2 H), 5.70 (s, 1 H), 7.03–7.49 (m, 18 H), 8.63 (br s, 3 H). This compound had properties identical (IR, NMR, TLC behavior) with those of an authentic sample of amine hydrotosylate **5**.[5a,16] (See the preceding list of the authentic sample's properties.)

Reduction with Hydrogen Sulfide. To a stirred solution of 87 mg (0.20 mmol) of azide benzyl ester **43** in 8 mL of dry methylene chloride at 0 °C was added 82 mL (0.59 mmol) of triethylamine. Hydrogen sulfide was bubbled through the solution for 5 min, the ice–water bath was removed, and bubbling was continued for 30 min. The mixture was concentrated, diluted with ethyl acetate–ether, the yellow solid (sulfur) which formed was filtered off, and the filtrate was concentrated. The yellow oil was then diluted with ethyl acetate, 57 mg (0.30 mmol) of *p*-toluenesulfonic acid monohydrate was added, and hexanes were added to the saturation point. Cooling gave a light yellow solid which was washed twice with ethyl acetate–ether to give 79 mg (67%) of a light yellow amorphous solid, mp 162–169 °C dec. The spectroscopic properties of this compound were identical with those of the compound prepared in the preceding experiment.

Benzyl (±)-(αR*,3R*)-3-Amino-α-[p-(benzyloxy)-phenyl]-2-oxo-1-azetidineacetate Hydrotosylate (45). Reduction with Zinc Dust. To a solution of 36 mg (0.080 mmol) of azide benzyl ester **44** in 3 mL of 90% aqueous acetic acid at room temperature was added 30 mg (0.46 mmol) of zinc dust, and stirring was continued for 1 h. The mixture was neutralized with 10 mL of saturated aqueous sodium bicarbonate and then with solid sodium bicarbonate. The white solid which formed was filtered off and washed with water and ether. The combined organic layers were washed once with brine, dried over anhydrous magnesium sulfate, and concentrated to give 23 mg of a white foam. The foam was dissolved in a small amount of ethyl acetate, and 18 mg of *p*-toluenesulfonic acid monohydrate was added. A white solid formed, the supernatant was discarded, and the solids were washed twice with ethyl acetate–ether to give 14 mg (30%) of a white amorphous solid: mp 178–181 °C dec; TLC (silica gel, ninhydrin indicated) R_f 0.62 (*n*-BuOH–HOAc–H_2O, 4:1:1), 0.78 (1% NH_3 in CH_3OH–$CHCl_3$, 1:5), 0.45 (1% of NH_3 in CH_3OH–EtOAc, 1:9); IR (KBr) 2950 (vbr), 1750 (split, 1600, 1510 cm^{-1}; NMR (Me_2SO-d_6, 270 MHz) δ 2.29 (s, 3 H), 3.49 (br s, H_2O), 4.53 (m, 1 H), 5.11 (s, 2 H), 5.20 (s, 2 H), 5.64 (s, 1 H), 7.02–7.49 (m, 18 H), 8.72 (br s, 3 H).

Reduction with Hydrogen Sulfide. To a solution of 100 mg (0.23 mmol) of azide benzyl ester **44** in 5 mL of dry methylene chloride at 0 °C was added 95 mL (0.68 mmol) of triethylamine. Hydrogen sulfide was bubbled through the solution for 5 min, the ice–water bath was removed, and bubbling was continued for 30 min. The mixture was concentrated, diluted with ethyl acetate–ether, the yellow solid (sulfur) which formed was filtered off, and the filtrate was concentrated. The yellow oil was then diluted with ethyl acetate, 64 mg (0.34 mmol) of *p*-toluenesulfonic acid monohydrate was added, and hexanes were added to the saturation point. Cooling gave a light yellow solid which was washed twice with ethyl acetate–ether to give 93 mg (70%) of a light yellow amorphous solid, mp 164–170 °C dec. The spectroscopic properties of this compound were identical with those obtained for the compound prepared in the preceding experiment.

2-(*p*-Hydroxyphenyl)glycine Ethyl Ester (48). To a suspension of 10.0 g (59.8 mmol) of 2-(*p*-hydroxyphenyl)glycine (**47**) in 40 mL of absolute ethanol was added 8 mL of concentrated sulfuric acid. The resulting yellow solution was heated at reflux for 2 h, cooled to 0 °C, and neutralized with concentrated ammonium hydroxide. The precipitated product was then collected by filtration, washed with cold water, and recrystallized from aqueous ethanol to give 4.9 g (42%) of pure amino acid ester **48**: mp 160–162 °C; IR (KBr) 3250, 2800–2100 (scalloped), 1700, 1575 cm^{-1}; NMR (Me_2SO-d_6/$CDCl_3$) δ 7.12 (d, J = 9 Hz, 2 H), 6.68 (d, J = 9 Hz, 2 H), 4.05 (q, J = 7 Hz, 2 H), 1.14 (t, J = 7 Hz, 3 H).

2-[*p*-(Benzyloxy)phenyl]glycine Ethyl Ester Hydrotosylate (46). A mixture of 2.7 g (14.6 mmol) of 2-(*p*-hydroxyphenyl)glycine ethyl ester (**48**), 1.6 g (15.1 mmol) of benzaldehyde, and a catalytic amount of *p*-toluenesulfonic acid monohydrate was added to 25 mL of dimethylformamide containing 5 g of 4-Å molecular sieves. The mixture was stirred at 40 °C under nitrogen for 12 h, decanted to remove the sieves, and treated with 2.8 g (20.3 mmol) of anhydrous potassium carbonate followed after 15 min by 1.9 g (15.0 mmol) of dry benzyl chloride. After being heated at 60 °C for 16 h, the reaction mixture was poured onto 50 mL of 10% hydrochloric acid, stirred for 15 min, and then extracted with ether (2 × 50 mL). Following neutralization with solid sodium carbonate, the aqueous layer was reextracted with fresh ether (3 × 75 mL), and the combined ethereal portions were washed with water (5 × 100 mL), dried over anhydrous magnesium sulfate, and concentrated to a yellow oil, 1.3 g. The oily residue was then dissolved in 10 mL of ethyl acetate and treated with 0.9 g (4.8 mmol) of *p*-toluenesulfonic acid monohydrate in 20 mL of ethyl acetate. The resulting precipitate was collected by filtration and dried under vacuum to give 2.5 g (37%) of amino acid ester **46**; mp 174–175 °C; IR (KBr) 3400, 1740, 1600, 1500, 1380 cm^{-1}; NMR (Me_2SO-d_6) δ 8.75 (br s, 3 H), 7.55–7.02 (m, 13 H), 5.11 (s, 3 H), 4.17 (q, J = 7 Hz, 2 H), 2.29 (s, 3 H), 1.16 (t, J = 7 Hz, 3 H).

The analytical sample was prepared by two recrystallizations from ethanol–ether–heptane.

Anal. Calcd for $C_{24}H_{27}HO_6S$: C, 63.00; H, 5.95; N, 3.06. Found: C, 62.77; H, 5.98; N, 2.97.

***tert*-Butyl-2,4-dibromobutyrate (51).** A mixture of 25 g (0.290 mol) of γ-butyrolactone and 1 mL of phosphorus tribromide was heated to 110 °C, and then 46.4 g (0.291 mol) of brimine was added dropwise over 1 h. The yellow solution was then transferred to a pressure bottle containing 60 mL of anhydrous tetrahydrofuran, cooled to −78 °C, and treated with 50 mL of liquid isobutylene and 5 mL of sulfuric acid. After the bottle was sealed and the mixture stirred at 25 °C for 16 h, the mixture was cooled to 0 °C, poured onto 300 mL ice-cold saturated sodium carbonate, and extracted with ether (5 × 100 mL). The ethereal extracts were washed with saturated ammonium chloride solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to a light yellow oil which was purified by chromatography over 200 g of neutral I alumina (5% ethyl acetate–hexanes) to give 58.6 g (70%) of *tert*-butyl-2,4-dibromobutyrate (**51**) as a colorless liquid: IR (neat) 1735 cm^{-1}; NMR (CCl_4) δ 4.24 (t, J = 7 Hz, 1 H), 3.47 (t, J = 7 Hz, 2 H), 2.44 (q, J = 7 Hz, 2 H), 1.47 (s, 9 H).

Anal. Calcd for $C_8H_{14}Br_2O_2$: C, 31.82; H, 4.67. Found: C, 32.12; H, 4.85.

Ethyl α-[*p*-(Benzyloxy)phenyl]-2-(carbo-*tert*-butoxy)-1-azetidineacetate (50). A mixture of 1.7 g (5.6 mmol) of *tert*-butyl 2,4-dibromobutyrate, 2.6 g (5.6 mmol) of 2-[*p*-(benzyloxy)-phenyl]glycine ethyl ester hydrotosylate (**46**), and 2.3 g (21.7 mmol) of anhydrous sodium carbonate in 50 mL of acetonitrile was heated at 50 °C for 3 days. At the end of this time, an additional 0.5 g (1.7 mmol) of *tert*-butyl 2,4-dibromobutyrate was added, and heating was continued for an additional 24 h. The mixture was then filtered and and concentrated in vacuo to a yellow oil. Gradient column chromatography over silica gel with hexane–ethyl acetate elution gave 1.5 g (63%) of azetidine **50** as a 1:1 mixture of diastereomers (R_f 0.76 and 0.65; hexane–ethyl acetate, 1:1): IR ($CDCl_3$) 1735, 1610, 1510, 1450, 1375, 1220 cm^{-1}; NMR ($CDCl_3$) δ 7.30 (m, 7 H), 6.90 (d, J = 9 Hz, 2 H), 5.01 (s, 2 H), 4.21 (s, 1 H), 4.12 (q, J = 7 Hz, 2 H), 3.79 (t, J = 8 Hz, 1 H), 3.56–2.90 (m, 2 H), 2.34–2.05 (m, 2 H), 1.28 (s, 9 H), 1.17 (t, J = 7 Hz, 3 H), and δ 7.30 (m, 7 H), 6.88 (d, J = 9 Hz, 2 H), 5.01 (s, 2 H), 4.32 (s, 1 H), 4.10 (q, J = 7 Hz, 2 H), 5.01 (s, 2 H), 4.32 (s, 1 H), 4.10 (q, J = 7 Hz, 2 H), 3.79 (t, J = 8 Hz, 1 H), 3.56–2.90 (m, 2 H), 2.34–2.05 (m, 2 H), 1.40 (s, 9 H), 1.17 (t, J = 7 Hz, 3 H).

When the mixture was allowed to stand under dry heptane for a prolonged time, one of the diastereomers (R_f 0.76) crystallized as a white solid. An analytical sample was prepared from this material following three recrystallizations from ether–methyl acetate–heptane, mp 108–109 °C.

Anal. Calcd for $C_{25}H_{31}NO_5$: C, 70.57; H, 7.34; N, 3.29. Found: C, 70.44; H, 7.21; N, 3.24.

2-[*p*-(Benzyloxy)phenyl]-*N*-(3-bromopropionyl)glycine Ethyl Ester (53). To a stirred solution of 2.5 g (5.5 mmol) of 2-[*p*-(benzyloxy)phenyl]glycine ethyl ester hydrotosylate (**46**) and 2.4 g (19.9 mmol) of *N*,*N*-dimethylaniline in 65 mL of dry methylene chloride at −20 °C (ice–methanol bath) was added over 20 min 1.2 g (6.3 mmol) of 3-bromopropionyl chloride in 5 mL of dry methylene chloride. After completion of the addition, the reaction mixture was allowed to come to room temperature and stirred for 1.5 h. The clear solution was diluted with methylene chloride–ether (2:1) and washed successively with 1 N hydrochloric acid, 5% sodium bicarbonate solution, and saturated sodium chloride solution. The organic layer was dried over anhydrous sodium sulfate and concentrated to give 2.5 g of light blue solid. Following column chromatography over silica gel with ether elution, the product was recrystallized from aqueous ethanol to provide 2.0 g (87%) of white crystals: mp 98–99 °C; IR $CHCl_3$) 3330, 1730, 1660, 1500, 1220 cm^{-1}; NMR ($CDCl_3$) δ 7.32 (s, 5 H), 7.26 (d, J = 9 Hz, 2 H), 6.88 (d, J = 9 Hz, 2 H), 6.58 (d, J = 7 Hz, 1 H), 5.46 (d, J = 7 Hz, 2 H), 5.00 (s, 2 H), 4.16 (q (split), J = 7 Hz, 2 H), 3.55 (t, J = 6 Hz, 2 H), 2.75 (t, J = 6 Hz, 2 H), 1.18 (t, J = 7 Hz, 3 H).

The analytical sample was prepared by two recrystallizations from methyl acetate–heptane–ether.

Anal. Calcd for $C_{20}H_{22}NO_4Br$: C, 57.15; H, 5.28; N, 3.33. Found: C, 57.29; H, 5.35; N, 3.22.

Ethyl α-[(*p*-Benzyloxy)phenyl]-2-oxo-1-azetidineacetate (11). Method B. To a stirred solution of 425 mg (1.0 mmol) of azetidine *tert*-butyl ester **50** at 0 °C was added dropwise 0.5 mL of cold anhydrous trifluoroacetic acid. After completion of the addition, the reaction mixture was stirred at room temperature for 1 h, cooled to 0 °C, and treated dropwise with 1 mL of cold oxalyl chloride. After cessation of gas evolution (2 h), the mixture was poured onto 100 mL of cold anhydrous ether, acidified with 2 drops of 70% perchloric acid, and refrigerated overnight. The solvent was decanted off to give an oily residue which was washed with fresh ether, dissolved in 15 mL of methylene chloride, and treated at 0 °C with 190 mg (1.1 mmol) of 100% *m*-chloroperbenzoic acid[21] followed by 174 mg (2.2 mmol) of dry pyridine. After 40 min, the reaction was diluted with 15 mL of methylene chloride–ether (1:4) and washed successively with water, cold 1 N hydrochloric acid, 5% sodium bicarbonate solution, and saturated sodium chloride solution. Removal of the solvent in vacuo after drying over anhydrous sodium sulfate gave 230 mg of yellow oil. Preparative layer chromatography over silica gel with ether–hexane (1:1) elution gave 180 mg (53%) of β-lactam 11 as a colorless oil which solidified upon standing under vacuum: mp 57–59 °C; IR ($CHCl_3$) 1740 (split), 1610, 1510 cm^{-1}; NMR ($CDCl_3$, 270 MHz) δ 7.33 (m, 5 H), 7.14 (d, J = 8.8 Hz, 2 H), 6.91 (d, J = 8.8 Hz, 2 H), 5.46 (s, 1 H), 4.99 (s, 2 H), 4.14 (q (split), J = 6.6 Hz, 2 H), 3.54 (m, 1 H), 2.99 (m, 1 H), 2.92 (m, 1 H), 2.76 (m, 1 H), 1.18 (t, J = 6.6 Hz, 3 H).

The analytical sample was prepared by two recrystallizations from ether–heptane; mp 61–62 °C.

Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.50; H, 6.14; N, 4.02.

Method C. To a suspension of 0.375 g (7.8 mmol) of a 50% mineral oil dispersion of NaH (prewashed with pentane) and 15 mL of dry *N,N*-dimethylformamide in 55 mL of CH_2Cl_2 was added over 3.5 h a solution containing 2.98 g (7.1 mmol) of **53** and 15 mL of dry *N,N*-dimethylformamide in 55 mL of CH_2Cl_2. After completion of the addition, the reaction mixture was stirred for 3 h at room temperature and then quenched with 10 mL of a saturated ammonium chloride solution. The resulting mixture was diluted with ether and CH_2Cl_2. The organic phase was separated, washed with water and with saturated aqueous sodium chloride, and then dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure gave an orange oil which was crystallized from ether–hexane to give 1.9 g (80%) of white solid, mp 52–54 °C.

Diethyl α-[p-(Benzyloxy)phenyl]-2-oxo-1-azetidinemalonate (54). To a stirred solution of 0.33 g (2.0 mmol) of hexamethyldisilazane in 20 mL of dry tetrahydrofuran was added dropwise at −78 °C under nitrogen atmosphere 0.92 mL (2.0 mmol) of 2.2 M *n*-butyllithium in hexane. The solution was warmed to 0 °C for 15 min, cooled to −78 °C, and treated dropwise with 574 mg (1.7 mmol) of β-lactam **11** in 5 mL of tetrahydrofuran. After 2 h, the reaction mixture was treated dropwise with 0.22 g (2.0 mmol) of ethyl chloroformate, stirred for 2 h at room temperature, and quenched with 1 mL of saturated sodium chloride solution. Removal of the solvent under reduced pressure gave an oily residue which was dissolved in 100 mL of methylene chloride–ether (2:1) and washed successively with 1 N hydrochloric acid, 5% sodium bicarbonate solution, and saturated sodium chloride solution. The organic layer was dried over anhydrous magnesium sulfate and concentrated to give 710 mg of yellow oil. Preparative layer chromatography over silica gel (hexane–ether, 1:1) gave 443 mg (64%) of malonate **54** as a colorless oil: IR (neat) 1740 (split), 1610, 1510 cm^{-1}; NMR ($CDCl_3$, 270 MHz) δ 7.40 (m, 5 H), 7.33 (d, J = 8.8 Hz, 2 H), 6.97 (d, J = 8.8 Hz, 2 H), 5.06 (s, 2 H), 4.33 (q, J = 7.0 Hz, 4 H), 3.47 (t, J = 4.4 Hz, 2 H), 2.95 (t, J = 4.4 Hz, 2 H), 1.30 (t, J = 7.0 Hz, 6 H); high-resolution mass spectrum, calcd for $C_{23}H_{25}NO_6$ m/e 411.1674, found m/e 411.1687.

Diethyl 3-Azido-α-[p-(benzyloxy)phenyl]-2-oxo-1-azetidinemalonate (55). To a stirred solution of 107 mg (1.1 mmol) of diisopropylamine in 20 mL of dry tetrahydrofuran at −78 °C under nitrogen atmosphere was added dropwise 0.5 mL of a 2.2 M solution of *n*-butyllithium in hexane. The solution was warmed to 0 °C for 15 min, cooled to −78 °C, and treated dropwise with 196 mg (0.48 mmol) of malonate **54** in 3 mL of tetrahydrofuran. After 2 h, 114 mg (0.58 mmol) of *p*-toluenesulfonylazide[12] was added in 2 mL of tetrahydrofuran, and stirring was continued for 2 h. The reaction was then treated dropwise with 265 mg (2.4 mmol) of trimethylchlorosilane and warmed to room temperature for 1 h. Removal of the solvent under reduced pressure gave an oily residue which was dissolved in 50 mL of methylene chloride–ether (2:1) and washed successively with 5% sodium bicarbonate solution and saturated sodium chloride solution. The organic layer was dried over anhydrous magnesium sulfate and concentrated to give 126 mg of yellow oil. Preparative layer chromatography with 5% ethyl acetate–benzene gave 105 mg (48%) of azide **55**: IR (neat 2130, 1775, 1750, 1610, 1510, 1450, 1375, 1275 cm^{-1}; NMR ($CDCl_3$, 270 MHz) δ 7.37 (m, 5 H), 7.30 (d, J = 8.0 Hz, 2 H), 6.97 (d, J = 8.9 Hz, 2 H), 5.05 (s, 2 H), 4.57 (dd, J = 5.2, 2.6 Hz, 1 H), 4.32 (q, J = 7.0 Hz, 4 H), 3.78 (dd, J = 6.4, 5.2 Hz, 1 H), 3.36 (dd, J = 6.4, 2.6 Hz, 1 H), 1.29 (t, J = 7.0 Hz, 6 H).

Benzyl 3-Azido-α-[p-(benzyloxy)phenyl]-2-oxo-1-azetidineacetate (43 and 44). To a stirred solution of 31.0 mg (0.07 mmol) of azide malonate **55** in 0.5 mL of absolute methanol at 0 °C was added dropwise 0.14 mL (0.14 mmol) of 1 N sodium hydroxide solution. After completion of the addition, the reaction mixture was stirred at room temperature for 1 h and then neutralized with 0.14 mL (0.14 mmol) of 1 N hydrochloric acid. The solvent was then removed under reduced pressure, and the residue was chromatographed over silica gel with ethyl acetate elution to give 20.0 mg of yellow oil. Thin-layer chromatographic analysis of this material showed a 1:1 mixture of two products (R_f 0.63 and 0.41, 2% acetic acid–ethyl acetate) which compared identically with an athentic sample of a diastereomeric mixture of 3-azido-α-[*p*-(benzyloxy)phenyl]-2-oxo-azetidineacetic acid (**42**). To a suspension of azide acids **42** in 2.5 mL of dry acetonitrile was added 9.1 mg (0.09 mmol) of triethylamine followed by 15 mg (0.09 mmol) of benzyl bromide. After the mixture was heated at reflux for 6 h, the solvent was removed under reduced pressure, and the residue was chromatographed over silica gel (PLC, 0.25-mm layer) with 25% ethyl acetate–benzene. Recovery of the major band (R_f 0.56) gave 6.0 mg of azide benzyl esters **43** and **44** as a 1:1 mixture of diastereomers in 23% overall yield from **55**.

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Registry No. (±)-**4**, 68682-19-9; (±)-**11**, 77629-81-3; (±)-**12**, 68641-19-0; (±)-**14**, 77698-53-4; (±)-**15**, 43189-27-1; (±)-**15** hydrotosylate salt, 77629-82-4; **16**, 14062-18-1; (±)-**17**, 77629-83-5; (±)-**18**, 77629-84-6; (±)-**20**, 77629-85-7; (±)-**21**, 77629-86-8; (±)-**22**, 77629-87-9; (±)-**23**, 77629-88-0; (±)-**24**, 72028-75-2; (±)-**25**, 6324-01-2; (±)-**26**, 77629-89-1; (±)-**27**, 77629-90-4; **32**, 68641-16-7; **33**, 68641-17-8; **34**, 68641-18-9; **35**, 68641-20-3; **37**, 68641-21-4; **38**, 68641-22-5; **39**, 68641-23-6; **40**, 68641-24-7; (±)-**42** (isomer 1), 68641-25-8; (±)-**42** (isomer 2), 68641-26-9; (±)-**43**, 68682-16-6; (±)-**44**, 68682-17-7; (±)-**45**, 68682-21-3; (±)-**46**, 77629-92-6; (±)-**47**, 6324-01-2; (±)-**48**, 43189-09-9; (±)-**49**, 77629-93-7; (±)-**50** (isomer 1), 77629-94-8; (±)-**50** (isomer 2), 77629-95-9; (±)-**51**, 77629-96-0; (±)-**53**, 77629-97-1; **54**, 71725-07-0; **55**, 77629-98-2; 3-bromopropionyl chloride, 15486-96-1; cyclopropanone, 5009-27-8; ethyl chloroformate, 541-41-3.

2,4-Bis(arylimino)-1,3,5-triarylhexahydro-*s*-triazinones

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2,4-Bis(arylimino)-1,3,5-triarylhexahydro-*s*-triazinones (**7**) have been synthesized by several routes: (A) addition of phosgene to 2,4-bis(arylimino)-1,3-diaryl-1,3-diazetidines (**2**) leads to ring opening, giving *N*-(chloroimidoyl)-*N'*-(chlorocarbonyl)guanidines (**9**), which are readily cyclized to **7** with arylamine; (B) heating of N^1,N^2,N^3,N^4,N^5-pentaarylbiguanides (**10**) or N^1,N^2,N^3-triarylguanidines with diphenyl carbonate to 200–210 °C or reacting **10** with phosgene in the presence of triethylamine produces the diimino-*s*-triazinones **7** in good yield.

Aryl isocyanates and *N,N'*-diarylcarbodiimides are each known to cyclodimerize or trimerize in a head to tail fashion under certain conditions to afford either the 1,3-diazetidine derivatives **1** and **2** or the hexahydro-*s*-triazines

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