Synthesis and X-ray Crystal Structure Determination of 1,3-Bridged β -Lactams: Novel, Anti-Bredt β -Lactams

Robert M. Williams,*,[†] Byung H. Lee, Mary M. Miller, and Oren P. Anderson

Contribution from the Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523. Received July 26, 1988

Abstract: The first successful syntheses of several anti-Bredt β -lactams from alkyl acetoacetate in 11–14 steps are described. The key cyclization reaction involves the Rh(II)-catalyzed carbene insertion of the diazo derivatives 12, 23, and 31 into the N-H bond of the β -lactams. These (±)-1,3-bridged β -lactams have IR absorptions of 1780–1795 cm⁻¹ for the β -lactam carbonyls. The structure of 32d has been determined by X-ray crystallography; this derivative exhibits a C-N (amide) bond length of 1.414 (4) Å and a β -lactam pyramid with the nitrogen atom 0.51 Å above the basal plane of three carbon atoms.

The β -lactam antibiotics have figured prominently in chemistry due to their desirable medicinal properties as chemotherapeutic agents, their structural novelty, and their attendant-rich chemistry.¹ In the past few years, a plethora of structurally novel β -lactam antibiotics have been discovered from natural sources as well as the laboratories of academic and industrial scientists. In spite of the voluminous literature on the synthesis, structural parameters, and attendant reactivity of monocyclic and bicyclic β -lactams, there were no reports on the preparation of bicyclic 1,3-bridged β -lactams. In conjunction with an ongoing project in our laboratories, we desired the preparation of bicyclic amides containing the amide nitrogen in a bridgehead position. These strained structures are of interest for several reasons. Geometrical deformation of atoms out of the traditional amide plane provide an experimental test for the theoretical underpinnings of well-accepted doctrines concerning amide resonance. In addition, recent work has attempted to define a working set of structural guidelines that can be utilized to predict and rationalize the intrinsic reactivity of the β -lactam nucleus as this relates to their attendant biological activity (or lack thereof).

Hall² and others³ have employed Bredt's rule, later modified by Wiseman,⁴ Kobrich,⁵ and Schleyer,⁶ as a guide for predicting the stability and attendant isolability of N-bridgehead amides. Maier and Schleyer⁶ have proposed the following empirical rule regarding the relationship between the calculated olefinic strain energy (OS) of bridgehead olefins and the predicted experimental observability: (a) isolable bridgehead olefin, $OS \le 17 \text{ kcal/mol}$; (b) observable bridgehead olefins, 17 kcal/mol \leq OS \leq 21 kcal/mol; and (c) unstable olefins, $OS \ge 21$ kcal/mol.

However, due to the capacity of the amide nitrogen atom to assume a tetrahedral geometry, several "anti-Bredt amides" have been synthesized⁷ such as 1-azabicyclo[2.2.2]octan-2-one (A): the corresponding olefin B is predicted to be an unstable olefin with an olefin strain energy (OS) of >40 kcal/mol (see Chart I). Indeed, amide A displayed unusual properties, such as an anomalously high infrared absorption at $\sim 1750 \text{ cm}^{-1}$ for the carbonyl, high pK_a values, and susceptibility to hydrolysis and polymerization. Synthetically reasonable⁸ target β -lactams, bicyclo[3.1.1] C and bicyclo[4.1.1] E would necessarily have highly pyramidalized nitrogen atoms. The bridgehead disposition of the β -lactam nitrogen atom in such a structure is expected to impart unusual and interesting properties to this system relative to the corresponding traditional monocyclic and bicyclic structures. For comparison purposes, the bicyclo[3.1.1]hept-1(6)-ene (D) and bicyclo[4.1.1]oct-1(7)-ene (F) are predicted to be unstable bridgehead olefins with OS values of 39.1 and 37.8 kcal/mol, respectively. Carbapenam nucleus G would correspond to bicyclo[3.2.0]hept-1(7)-ene (H) and has an OS value of 16.7 kcal/mol. Isomeric amide I corresponds to bicyclo[3.2.0]hept-1-ene (J) and has an OS value of 13.9 kcal/mol. On the basis of this scale of stability, it is expected that the bicyclo[3.1.1]- and bicyclo-

⁺ Fellow of the Alfred P. Sloan Foundation, 1986-1988. NIH Research Career Development Awardee, 1984-1989. Eli Lilly Grantee, 1986-1988. [4.1.1]- β -lactam ring systems should represent highly strained, reactive, and unstable substances relative to the traditional β lactams comprising the penicillin, carbapenem, penem, and cephalosporin classes of antibiotics. Our objectives were to experimentally investigate these interesting structures, evaluate their fundamental structural and physical properties, and assess the OS scale for predicting the reactivity of such compounds.

In this account, we describe the syntheses of several 1,3-bridged β -lactams and the X-ray structural characterization of a member of this new class of structurally unique bicyclic β -lactams.

Results and Discussion

We have recently described, in a preliminary account, synthetic methodology to construct a bicyclo [4.1.1] β -lactam.^{8,9} Synthesis of the 1,3-bridged β -lactam 13 is illustrated in Scheme I. This, along with a newly developed route, is presented herein with complete detail.

Ethyl acetoacetate is alkylated with 4-bromo-1-butene (NaOEt, EtOH, 50%) to afford the β -keto ester 2. Sodium borohydride reduction¹⁰ provided an inseparable mixture of the alcohols 3 and 4 (syn/anti, 1:2), which were directly subjected to a Mitsunobu inversion¹¹ (HCO₂H, Ph₃P, DEAD, THF) to furnish the synformate 5 in 20% overall yield from 2. Hydrolysis to the acid 6 (1 N NaOH, THF) followed by reaction with 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide hydrochloride (1.3 equiv) and

(1) For reviews, see: (a) Philos. Trans. R. Soc. London, B 1980, 289, 165. (b) Chemistry and Biology of β -Lactam Antibiotics; Morin, R. B., Gorman, M., Eds.; Academic: New York, 1982; Vol. 1-3.

- (2) Hall, H. K.; El-Shekeil, A. Chem. Rev. 1983, 83, 549.
- (d) Brouillette, W. J.; Einspahr, H. M. J. Org. Chem. 1984, 49, 5113.
 (d) Wiseman, J. R.; Pletcher, W. A. J. Am. Chem. Soc. 1970, 92, 956.
- (5) Kobrich, G. Angew. Chem., Int. Ed. Engl. 1973, 12, 464.
- (6) Maier, W. F.; Schleyer, P. v. R. J. Am. Chem. Soc. 1981, 103, 1891.

 (7) (a) Pracejus, V. H.; Kehlen, M.; Kehlen, H.; Matschiner, H. Tetra-hedron 1965, 21, 2257.
 (b) Somayaji, V.; Brown, R. S. J. Am. Chem. Soc. 1987, 109, 4738.
 (c) Slebocka-Tilk, H.; Brown, R. S. J. Org. Chem. 1987, 52, 805. (d) Somayaji, V.; Skorey, K. I.; Brown, R. S.; Ball, R. G. J. Org. Chem. 1986, 51, 4866.

(8) Attempts at synthesizing a bicyclo[3.1.1] β -lactam ii from i afforded an unstable product (IR (neat) 1935, 1850, 1795, 1725 cm⁻¹) that rapidly polymerized (IR (neat) 1725, 1630 cm⁻¹).



(9) For a preliminary account of this work, see: Williams, R. M.; Lee, B.

 H. J. Am. Chem. Soc. 1986, 108, 6431.
 (10) Lee, B. H.; Biswas, A.; Miller, M. J. Org. Chem. 1986, 51, 106.
 (11) (a) Mitsunobu, O. Synthesis 1981, 1. (b) Georg, G. I.; Gill, H. S.; Gerhardt, C. Tetrahedron Lett. 1985, 26, 2903.

Chart I

Scheme I



NH₂OCH₃·HCl (1.1 equiv) at pH 4.2 for 1 h at 25 °C furnished the *N*-methoxy amide¹² 7 (94%, mp 64–66.5 °C). Cyclization to the β -lactam 8 according to Miller¹² was accomplished with Ph₃P/DEAD (THF, 25 °C, 75%). Reductive cleavage of the N–O bond¹³ was readily accomplished by dissolving-metal reduction (Na⁰, 2.4 equiv. NH₃(1), THF, -40 °C, 10 min) to furnish the desired β -lactam 9 (80%).

Oxidative cleavage of the olefin 9 to the acid 10 could be accomplished in one step by treatment with NaIO₄ in the presence of a catalytic amount of $RuCl_3$,¹⁴ (MeCN, CCl₄, H₂O) but, was

(13) Floyd, D. M.; Fritz, A. W.; Pluscec, J.; Weaver, E. R.; Cimarusti, C.
 J. Org. Chem. 1982, 47, 5160.

- (14) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. J. Org. Chem. 1981, 46, 3936.
- (15) Kametani, T.; Huang, S. P.; Nagahara, T.; Yokohama, S.; Ihara, M. J. Chem. Soc., Perkin Trans. 1 1981, 964.
- (16) Brooks, D. W.; Lu, L. D.-D.; Masamune, S. Angew. Chem., Int. Ed. Engl. 1979, 18, 72.
- (17) (a) Salzmann, T. N.; Ratcliffe, R. W.; Cristensen, B. G.; Bouffard,
 F. A. J. Am. Chem. Soc. 1980, 102, 6161. (b) Karady, S.; Amato, J. S.;
- Reamer, R. A.; Weinstock, L. M. J. Am. Chem. Soc. 1981, 103, 6765.

not practical for the preparation of multigram quantities of 10. Therefore, a stepwise oxidation proved to be more convenient. Ozonolysis of 9 (MeOH, -78 °C, then Me₂S) followed by Jones oxidation¹⁵ (8 N, acetone, 0 °C) furnished the acid 10 (80%). This material was homologated to the β -keto ester 11 by utilizing the procedure of Brooks, Lu, and Masamune.¹⁶ Reaction of 10 with carbonyldiimidazole (THF, 25 °C, 6 h) followed by condensation with Mg(O₂CCH₂CO₂-*t*-Bu)₂ (0.55 equiv, 12 h, 25 °C) cleanly furnished 11 (20-40%). Diazotization under the standard conditions¹⁷ (TsN₃, MeCN, 25 °C) gave the relatively labile diazo β -keto ester 12 (80%). Reaction of 12 with a catalytic amount of Rh₂(OAc)₄ for 1 h in refluxing benzene followed by filtration and evaporation of the solvent and chromatography on silica gel (PTLC, THF/hexane, 1:1) provided the bicyclic compound 13 in 50% yield.





^{(12) (}a) Miller, M. J.; Mattingly, P. G.; Morrison, M. A.; Kerwin, J. F., Jr. J. Am. Chem. Soc. **1980**, 102, 7026. (b) Bajwa, J. S.; Peterson, K. P.; Mattingly, P. G.; Miller, M. J. J. Org. Chem. **1982**, 47, 4928. (c) Miller, M. J.; Biswas, A.; Krook, M. A. Tetrahedron **1983**, 39, 2571. (d) Miller, M. J.; Mattingly, P. G.; Copper, R. D. G.; Daugherty, B. W. J. Org. Chem. **1983**, 48, 3556. (e) Morrison, M. A.; Miller, M. J. J. Org. Chem. **1983**, 48, 4221. (12) Eland D. W. Fritz

Scheme II



The structure of 13 was evident by examination of the spectroscopic properties. The infrared spectrum exhibited carbonyl absorptions at 1795, 1750, and 1730 cm⁻¹ (NaCl, neat) for the β -lactam, ester, and ketone moieties, respectively. The mass spectrum (CH₄, CI) gave peaks at m/z 254 and 198 for (M⁺ + 1) and $(M^+ - C_4H_9)$, respectively. The ¹H NMR spectrum exhibited the characteristic one-proton singlet at δ 4.7 for the C-2 methine; a multiplet centered at δ 2.9 for the C-8 methine reflects a 0.6 ppm upfield shift of this resonance from that of the monocyclic precursors 9-12 and probably reflects both increased sp³ character on nitrogen as well as shielding by the C-3 carbonyl.

Although 13 could be isolated by PTLC separation for spectroscopic characterization, it was found to be relatively labile under a variety of conditions (acid, base, or a dilute solution of 13 in chloroform $t_{1/2} \sim 1$ h in CDCl₃). Our first approach to design a 1,3-bridged β -lactam with increased stability over compound 13 was accomplished by placing more sterically encumbering groups at the C-8 position which would more effectively prevent nucleophilic attack at the β -lactam carbonyl from the α -face (Figure 1).

It should be noted that in all 1,3-bridged β -lactams, the kinetically most reactive face of the β -lactam carbonyl moiety should be from the bridged (β) face since the unshared electron pair on the pyramidal nitrogen would favor nucleophilic attack via $n \rightarrow$ σ^* overlap.¹⁸ However, for all of these compounds, the most reactive face is completely shielded from nucleophilic attack by the bridging chain of atoms. It was reasoned that the replacement of the C-8 methyl group with an isopropyl group (14) would more effectively block the preferred Burgi-Dunitz approach vector for

(18) An excellent discussion of this stereoelectronic effect is presented in: Stereoelectronic Effects in Organic Chemistry, Deslongchamps, P., Ed.; Pergamon: Oxford, 1983; Chapter 4.

nucleophilic attack on the β -lactam carbonyl than that possible in 13. The isopropyl residue was also chosen due to synthetic convenience. Synthesis of the 1,3-bridged β -lactam 14 is illustrated in Scheme II.

The β -keto ester 15 was condensed with benzylamine followed by NaBH₃CN reduction¹⁹ to provide the β -amino ester **16** (85%). Hydrolysis (2 M KOH/MeOH, room temperature, 6 h) followed by cyclization with 2-chloro-1-methylpyridinium iodide²⁰ and triethylamine gave the β -lactam 17 (80%). Deprotection of the benzyl group by dissolving-metal reduction²¹ (Na⁰, 2.2 equiv, NH₃(1), THF, -40 °C, 10 min) provided the unprotected β -lactam (93%), which was subsequently treated with tert-butyldimethylsilyl chloride and triethylamine to give 18 (88%). Compound 18 was alkylated²² with 4-bromobutene (n-BuLi or LDA, -78 °C, 10 min and then 4-bromobutene, -78 °C, 30 min) to provide trans- β lactam 19 (90%). The deprotection of the tert-butyldimethylsilyl group was achieved by treatment with tetra-n-butylammonium fluoride in THF to give 20 (90%).

Ozonolysis of 20 (MeOH, -78 °C and then Me₂S) followed by Jones oxidation (8 N, acetone, 0 °C, 15 min) furnished the acid 21 (70%). The acid 21 was homologated to the β -keto ester (35-50%) and diazotized to give 23a (92%). Reaction of 23a with a catalytic amount of $Rh_2(OAc)_4$ for 30 min in refluxing benzene provided the bicyclic compound 14a as an oil in 20% yield. Subsequently, compounds 14b-d were prepared in similar fashions to compare their stabilities and physical properties.

Compounds 14a and 14d in chloroform were stable (IR 1795 cm⁻¹, NC=O), while 14b and 14c in chloroform solution de-

⁽¹⁹⁾ Lane, C. F. Synthesis 1975, 135.

⁽²⁰⁾ Iwasaw, N.; Mukaiyama, T. Chem. Lett. 1986, 637

⁽²¹⁾ Iimori, T.; Shibasaki, M. Tetrahedron Lett. 1986, 27, 2149.

⁽²²⁾ Wasserman, H. H.; Han, W. T. Tetrahedron Letter 1984, 25, 3747.





composed after 24 h at -30 °C (IR 1805, 1780 cm⁻¹ and 1810, 1780 cm⁻¹, respectively). ¹H NMR spectra of **14b** and **14c** showed that substantial amounts of the enol form existed while those of **14a** and **14d** did not show this. These observations prompted us to consider another possible decomposition mechanism of the 1,3-bridged β -lactams shown in eq 1. It was envisaged that enol



tautomers (see eq 1) of these β -keto esters would be acidic enough to protonate the β -lactam nitrogen atom and activate these systems for nucleophilic attack and/or elimination via abstraction of the bridgehead methine proton. While it proved difficult to identify the structures of the products resulting from such an elimination process, it seemed reasonable to preclude α -proton abstraction by substitution of an alkyl residue at this position. In addition, increased steric shielding of the β -lactam carbonyl from nucleophilic opening would be provided by a substituent in this position. For both of these reasons, it was anticipated that a much more stable yet equally strained bicyclic β -lactam would result. The synthesis of C₆-alkylated 1,3-bridged β -lactams is described in Scheme III.

The β -keto ester 1 was condensed with benzylamine (benzene, reflux 2 h with azeotropic water removal) followed by sodium cyanoborohydride reduction (acetic acid, 0 °C \rightarrow room temperature, 2 h) to provide the corresponding β -amino ester, which was

hydrolyzed (2 M KOH/MeOH, room temperature, 16 h) and cyclized (2-chloro-1-methylpyridinium iodide, triethylamine, 0.02 M in CH_2Cl_2 , room temperature, 16 h) to afford **24**.

Deprotection of the benzyl group by dissolving-metal reduction followed by N-silyl protection gave 25 (80%). Compound 25 was alkylated with methyl iodide (LDA, THF, -78 °C, 10 min and then HMPA, -78 °C, 10 min and then CH₃I, -78 °C, 30 min) to provide 26a (90%). When the β -lactam 25 was alkylated with (bromo-*tert*-butyldimethylsilyl)ethanol (LDA, HMPA), the alkylated β -lactam 26b (trans) was obtained as an oil in 90% yield. Compound 26 was again alkylated²³ with 4-bromobutene [lithium diethylamide] (LDEA), HMPA) to provide 27.

After deprotection of 27a with tetra-*n*-butylammonium fluoride trihydrate in THF, compound 28a was ozonized and oxidized to the acid 29a, which was homologated and diazotized in a similar fashion as above to give 31a. The $Rh_2(OAc)_4$ -catalyzed cyclization went smoothly to produce 32a as an oil in 60–70% yield. As expected, compound 32a was significantly more stable than compounds 13 and 14. However, compound 32a when neat decomposed upon standing 1 day at room temperature.

We also prepared the p-bromobenzhydryl ester of 32a (see supplementary material) to compare stabilities. As expected, the p-bromobenzylhydryl ester is less stable than compound 32a. The C-2 hydrogen of the *p*-bromobenzhydryl ester is more acidic than that of 32a so that the decomposition of this substance would be faster than that of 32a. To retard this internal rearrangement, we needed to synthesize either a 1,3-bridged β -lactam with a less acidic proton at the C-2 position or a β -lactam with a crystalline form, which would be more stable. Subsequently, we prepared compounds 32c and 32d in an effort to obtain crystalline materials (Scheme III). After the deprotection of 27b with tetra-n-butylammonium fluoride trihydrate in tetrahydrofuran, compound 28b was then alkylated with p-phenylphenol and 1,6-dibromonaphthol under Mitsunobu conditions (PPh₃/DEAD) to yield 28c and 28d, respectively, in 50-70% yield. Compounds 29c and 29d were each ozonized, oxidized, homologated, diazotized, and cyclized in a similar fashion to give 32c and 32d, respectively. As anticipated, compound 34d was obtained as a low-melting crystalline solid

⁽²³⁾ Thomas, E. J.; Williams, A. C. J. Chem. Soc., Chem. Commun. 1987, 992.

Table I. Structural and Physical Parameters of Various β -Lactams

	h	N-C=0	IR	sum of angles at N	
1.456 A N 1.414 A H 1.495 A h .506 1.201 A O N C) — R 0.50 0₂H	1.419 A	1785 cm ⁻¹	324.1°	
	≻— R 0.42 A D₂H	1.419 A	1798 cm ⁻¹	331.5°	
		1.37 A	1775 cm ⁻¹	337°	
Br Br CO ₂ H	~0.24 / `R	A 1.38 A	1770 cm ⁻¹	350.7°	
O NR			1740 cm ⁻¹	360°	
Me ₃ N	0.56			324°	
32d	0.50	6 1.414	1785 cm ⁻¹	326.8°	



Figure 2. A thermal ellipsoid plot (50% probability) of 32d. The hydrogen atoms have been drawn as spheres of arbitrary radius for clarity.

(mp 68-70 °C) and was stable at room temperature in CDCl₃ solution for several days.

Slow, careful, multiple recrystallizations of 32d provided crystals suitable for a single-crystal X-ray structure determination. The molecular structure of 32d is depicted in Figure 2. Table I lists the most salient structural parameters of the bicyclo[4.1.1] β lactam system and also tabulates comparison data²⁴ for the carbapenem, penem, penicillin, cephalosporin, and unfused β lactam systems. The nitrogen atom (N1) of 32d is highly pyramidal with a height (h) of 0.51 Å from the plane through the three adjacent carbon atoms. This value is very similar to the corresponding value from the carbapenem system ($h \sim 0.50$ Å), but is slightly smaller than that for the Δ^1, Δ^2 double bond isomer $(\sim 0.56 \text{ Å})$. In addition, the C–N (amide) bond length (C7–N1 = 1.414 (4) Å) and infrared stretching frequency of the β -lactam carbonyl (1785 cm⁻¹) for 32d are virtually identical with those for the carbapenem system (1.419 Å and 1785 cm⁻¹, respectively). The sum of the bond angles about N1 in 32d is 326.8°, which may be compared to 324.1° for the carbapenem system, 324° for trimethylamine, and 328.5° for a perfectly tetrahedral atom.

From these observations, it can be concluded that the geometry and strain of the bicyclo[4.1.1] β -lactam nucleus closely ap-

Table II. Atomic Coordinates (Fractional, $\times 10^4$) and Equivalent Isotropic Thermal Parameters ($Å^2 \times 10^3$) for Compound **32d**^{*a*}

		()	,	
atom	<i>x</i>	у	Z	U _{iso} ^b
Br 1	16139 (1)	7884 (1)	5190 (1)	28 (1)
Br2	21108 (1)	8268 (1)	10960 (1)	38 (1)
N1	8919 (3)	6509 (3)	3539 (3)	22 (1)
O 1	10289 (2)	6830 (3)	5599 (2)	29 (1)
O2	13728 (2)	6202 (2)	5184 (2)	31 (1)
O3	9690 (3)	9594 (3)	3233 (3)	38 (1)
O4	6952 (3)	6718 (3)	1579 (2)	34 (1)
O5	6789 (2)	8484 (2)	2971 (2)	27 (1)
C2	8660 (3)	7767 (3)	3658 (3)	22 (1)
C3	9878 (4)	8771 (3)	3663 (3)	25 (1)
C4	11309 (3)	8776 (3)	4351 (4)	29 (2)
C5	11789 (3)	7566 (3)	3917 (4)	26 (1)
C6	10814 (3)	6197 (3)	3649 (3)	21(1)
C7	10052 (3)	6528 (3)	4508 (3)	23 (1)
C8	9461 (3)	5944 (3)	2582 (3)	24 (1)
C9	8610 (4)	4522 (4)	1730 (4)	39 (2)
C10	7352 (3)	7568 (3)	2595 (3)	26 (2)
C11	5586 (4)	8599 (4)	2062 (4)	41 (2)
C12	4415 (4)	7323 (5)	1518 (5)	65 (2)
C13	5283 (5)	9726 (5)	2882 (4)	56 (2)
C14	6000 (6)	8968 (6)	1110 (4)	67 (3)
C15	11490 (3)	5108 (3)	3610 (3)	25 (1)
C16	12444 (3)	5247 (3)	4875 (3)	25 (1)
C17	14794 (3)	6418 (3)	6243 (3)	24 (1)
C18	14679 (4)	5885 (4)	7135 (4)	28 (2)
C19	15807 (4)	6155 (4)	8166 (3)	28 (2)
C20	17109 (4)	6959 (4)	8369 (3)	26 (2)
C21	18282 (4)	7208 (4)	9428 (3)	28 (2)
C22	19515 (4)	7953 (4)	9557 (3)	28 (1)
C23	19666 (4)	8484 (4)	8691 (3)	30 (2)
C24	18553 (3)	8268 (3)	7669 (3)	27 (2)
C25	17237 (3)	7491 (3)	7477 (3)	22 (1)
C26	16044 (3)	7208 (3)	6426 (3)	23 (1)
a 12 - 1			1	

^aEstimated standard deviations in the least significant digits are given in parentheses. ^bThe equivalent isotropic U is equal to 1/3 of the trace of the U_{ij} tensor.

proximates that of the Δ^2 , Δ^3 -carbapenem ring system, and that the bicyclo[4.1.1] β -lactam system is highly pyramidalized at N to accommodate the bicyclo[4.1.1] geometry. This distortion does

^{(24) (}a) Sweet, R. M.; Dahl, L. F. J. Am. Chem. Soc. 1970, 92, 5289. (b) Pfaendler, H. R.; Gosteli, J.; Woodward, R. B.; Rihs, G. J. Am. Chem. Soc. 1981, 103, 4526. (c) Ahmed, F. R. Acta Crystallogr. 1983, C39, 735.

not have a profound effect on the conventional amide resonance interaction of the N atom with the β -lactam carbonyl, as evidenced by the normal C-N and C=O bond lengths. Wiberg²⁵ has recently pointed out that rotation about the N-C (amide) bond has little effect on the C=O bond length and that charge transfer occurs between carbon and nitrogen. The structure of **32d** provides an example of an interesting "frozen" nonplanar amide, the metric parameters of which closely parallel the calculated values around N. The large difference in the calculated OS values for hydrocarbons F and H does not correlate well to the similarity in properties between the corresponding bicyclo[4.1.1] and bicyclo[3.2.0] β -lactams. The OS scale then would seem to be of limited value for use in predicting the properties of the corresponding β -lactams.

Biological Activity. The primary difficulty that has been encountered in preparing derivatives of the bicyclo[4.1.1] β -lactam system for antimicrobial evaluation has been the problems associated with deprotecting the esters to the corresponding water-soluble carboxylates. This problem has not been solved as of this writing. However, compound **32d** (as the *tert*-butyl ester) was submitted for antimicrobial assay against a standard 20-microorganism screen. Activity against *Bacillus subtilis* (only) was observed with an MIC of 64 μ g/mL. This preliminary result provides considerable impetus to more thoroughly examine this new class of structures for biological activity.

In summary, the first successful preparations and structural characterizations of several 1,3-bridged β -lactams were achieved from alkyl acetoacetates in 11–14 steps. The key cyclization reaction involved the rhodium(II)-catalyzed carbene insertion of the diazo keto esters to the N-H bond of the β -lactams. These successful efforts to synthesize stable 1,3-bridged β -lactams open the possibility for a new class of structurally unique β -lactams of possible antibiotic importance. Investigation along these lines is in progress and shall be reported on in due course.

Experimental Section

General Procedures. ¹³C NMR spectra were obtained on an IBM WP-270 (68 MHz) instrument and are reported in δ valves relative to CDCl₃ (77.06 ppm).

 1H NMR spectra were obtained on an IBM WP-270 instrument (270 MHz) and are reported in δ values downfield from (CH₃)₄Si.

Thin-layer chromatography (TLC) was carried out on 0.25-mm E. Merck precoated silica gel glass plates (60F-254) by using 5% phosphomolybdic acid in ethanol and heat and/or UV light as developing agent. Preparative layer chromatography was carried out on a Harrison Research Chromatotron with 1.0, 2.0, or 4.0 mm layer thickness silica gel adsorbents. The following abbreviations are used throughout this section; ether = diethyl ether, THF = tetrahydrofuran, WSC = 1ethyl-3-[3-(dimethylamino)propyl]carbodiimide, HMPA = hexamethylphosphoramide, DEAD = diethyl azodicarboxylate.

Ethyl 2-Acetyl-5-hexenoate (2). Ethyl acetoacetate (1) (13 g, 0.1 mmol) was dissolved in ethanol (50 mL) and treated with sodium ethoxide [freshly generated with sodium (2.53 g, 0.11 mmol, 1.1 equiv)]. After 10 min, 4-bromo-1-butene (13.5 g, 0.1 mmol, 1.0 equiv) was added to the mixture. The resulting solution was heated to reflux for 3 h, taken up in ethyl acetate (200 mL), and washed twice with 0.5 N HCl (2 × 100 mL) and brine. After the solvent was dried (MgSO₄) and evaporated, the residue was distilled in vacuo. Compound 2 was obtained as an oil in 60% yield; bp 97–99 °C (17 mmHg); ¹H NMR (CDCl₃) δ 1.20 (t, 3 H), 1.8–2.1 (m, 4 H), 2.15 (s, 3 H), 3.37 (t, 1 H), 4.11 (q, 2 H), 4.85–5.05 (m, 2 H), 5.65 (m, 1 H); IR (NaCl, neat) 1750, 1720, 1655 cm⁻¹; ¹³C NMR (CDCl₃) δ 202.58, 169.55, 136.94, 115.68, 61.09, 58.80, 31.18, 28.69, 27.05, 13.91; mass spectrum (EI), *m/e* 184 (M). Anal. Calcd for C₁₀H₁₆O₃: C, 65.19; H, 8.75. Found: C, 65.11; H, 8.82. Ethyl 2-(1'-Hydroxyethyl)-5-hexenoate (3 and 4). The β -keto ester

(25) Wiberg, K. B.; Laidig, K. E. J. Am. Chem. Soc. **1987**, 109, 5935. (26) Software used for diffractometer operations and data collection was provided with the Nicolet R3m diffractometer. Crystallographic computations were carried out with the SHELXTL program library, written by G. M. Sheldrick and supplied by Nicolet Corp., XRD Division.

drick and supplied by Nicolet Corp., XRD Division. (27) International Tables for X-Ray Crystallography; Kynoch: Birmingham, England, 1974; Vol. IV, pp 99, 149.

(28) The compound was stable to isolation and determination of ¹H NMR, IR, and low-resolution manuscript data. High-resolution manuscript and elemental analyses were not obtained due to the instability of these materials to shipment to out-of-state analytical facilities.

2 (6.8 g, 37 mmol) was dissolved in methanol (75 mL) and treated with sodium borohydride (0.7 g, 18.7 mmol, 2.02 equiv) at -40 °C. The mixture was stirred for 30 min at -40 °C and taken up in ethyl acetate (350 mL). This solution was washed with 1 N HCl (2×100 mL) and brine. After the solvent was dried (MgSO₄) and evaporated, the desired alcohol 3 and 4 was obtained as an oil (6.4 g, 95% yield): ¹H NMR (CDCl₃) δ 1.1-1.4 (m, 6 H), 1.6-1.85 (m, 2 H), 2.05 (m, 2 H), 2.42 (m, 1 H), 2.85 (br s, 1 H, OH), 3.85-4.0 (m, 1 H), 4.20 (dq, 2 H), 4.95-5.10 (m, 2 H), 5.76 (m, 1 H); IR (NaCl, neat) 3480, 1740, 1650 cm⁻¹; ¹³C NMR (CDCl₃) δ 174.84, 137.68, 115.16, 68.23, 60.37, 51.84, 31.67, 26.73, 20.39, 14.16; mass spectrum (EI), m/e 140 (M - H₂O).

Ethyl 2-[1'-(Formyloxy)ethyl]-5-hexenoate (5). The alcohol 3 and 4 (3:4 = 1:2, 150 mg, 0.806 mmol), PPh₃ (317 mg, 1.209 mmol, 1.5 equiv), and formic acid (36 μ L, 0.967 mmol, 1.2 equiv) were dissolved in THF (6 mL) and treated dropwise with diethyl azodicarboxylate (DEAD) (0.190 mL, 1.209 mmol, 1.5 equiv) at room temperature over 10 min. The mixture was stirred for 2 h at room temperature. After the solvent was evaporated, the residue was triturated with ether and filtered. The filtrate was evaporated and the residue was chromatographed on a silica plate (2 mm, Chromatotron) with ethyl acetate/hexane (1:6) as eluant. The desired *syn-5* was obtained as an oil in 40% yield: ¹H NMR (CD-Cl₃) δ 1.2-1.35 (m, 6 H), 1.55-1.8 (m, 2 H), 1.9-2.2 (m, 2 H), 2.62 (m, 1 H), 8.04 (s, 1 H); IR (NaCl, neat) 1750, 1660 cm⁻¹; ¹³C NMR (CDCl₃) δ 172.25, 159.83, 137.10, 115.16, 70.34, 60.24, 49.67, 31.10, 27.31, 17.43, 13.89; mass spectrum (EI), *m/e* 169 (M - OCOH).

2-(1'-Hydroxyethyl)-5-hexenoic Acid (6). Compound **5** (6.1 g, 33.89 mmol) was dissolved in THF (40 mL) and treated with 1 N NaOH (40 mL, 40 mmol, 1.2 equiv). The mixture was heated to reflux for 6 h and then extracted with ether (2 × 30 mL). The aqueous layer was acidified with 3 N HCl to pH 2 and reextracted several times with ether (4 × 30 mL). After the solvent was dried (MgSO₄) and evaporated, the desired **6** was obtained as an oil (3.4 g, 66% yield): ¹H NMR (CDCl₃) δ 1.25 (d, 3 H), 2.5–2.9 (m, 2 H), 3.0–3.3 (m, 2 H), 2.48 (quintet, 1 H), 4.06 (quintet, 1 H), 4.9–5.1 (m, 2 H), 5.76 (m, 1 H), 7.5 (br s, 2 H, CO₂H and OH); IR (neat) 3400, 1715, 1650 cm⁻¹; mass spectrum (EI), m/e 140(M⁺ – H₂O).

Methyl 2-(1'-Hydroxyethyl)-5-hexenohydroxamate (7). Compound 6 (2.7 g, 17.09 mmol) was dissolved in 1 N NaOH (30 mL) and the mixture was treated with methoxyamine hydrochloride (1.57 g, 18.8 mmol, 1.1 equiv). The pH of the solution was adjusted to 4.2 with 1 N HCl. This solution was treated with WSC (4.3 g, 22.2 mmol, 1.3 equiv). The mixture was stirred for 1 h at room temperature while its pH was maintained at 4.2. Sodium chloride (solid) was added and themixture was extracted several times with ethyl acetate. After the solvent was dried (MgSO₄) and evaporated, the desired hydroxamate 7 was obtained as an oil (3.0 g, 94% yield), which slowly solidified. mp (recrystallized with ethyl acetate) 64-66.5 °C; ¹H NMR (CDCl₃) δ 1.25 (d, 3 H), 1.70 (m, 1 H), 1.85 (m, 1 H), 2.12 (m, 3 H), 3.62 (br s, 1 H, OH), 3.80 (s, 3 H), 3.95 (quintet, 1 H), 4.95-5.10 (m, 2 H), 5.78 (m, 1 H), 9.55 (s, 1 H); IR (NaCl, CDCl₃) 3420, 3230, 1660 cm⁻¹; mass spectrum [CI (NH₃)], m/e 188 (M⁺ + H⁺). Anal. Calcd for C₉H₁₇NO₃: C, 57.73; H, 9.15; N, 7.48. Found: C, 57.88; H, 9.33; N, 7.66.

(3R, 4RS)-3-(3-Butenyl)-4-methyl-1-methoxyazetidin-2-one (8). Compound 7 (2.22 g, 11.76 mmol) and PPh₃ (3.7 g, 14.12 mmol, 1.2 equiv) were dissolved in THF (80 mL) and treated with DEAD (2.03 mL, 12.94 mmol, 1.1 equiv) in THF (10 mL) over 20 min. After the addition was complete, the mixture was stirred at room temperature for 1 h. Volatile components were removed in vacuo, and the residue was chromatographed on a silica plate (4 mm, Chromatotron) with ethyl acetate/hexanes (1:2) as eluant. The desired 8 was obtained as an oil (75% yield): ¹H NMR (CDCl₃) δ 1.40 (d, 3 H), 1.68 (m, 1 H), 1.90 (m, 1 H), 2.19 (q, 2 H), 2.49 (m, 1 H), 3.62 (dq, 1 H, J = 1.6 Hz), 3.80 (s, 3 H), 4.98-5.10 (m, 2 H), 5.75 (m, 1 H); IR (NaCl, CDCl₃) 1775, 1650 cm⁻¹; mass spectrum [Cl (NH₃)], m/e 170 (M⁺ + H⁺); ¹³C NMR (CDCl₃) δ 165.59, 137.05, 115.40, 63.50, 59.14, 51.84, 31.24, 27.16, 17.50.

(3RS,4RS)-3-(3-Butenyl)-4-methylazetidin-2-one (9). After condensation of the anhydrous ammonia (20 mL) at -40 °C, sodium (60 mg, 2.6 mmol, 2.2 equiv) was added in several small pieces. The resulting blue solution was stirred for 10 min, and compound 8 (200 mg, 1.18 mmol) was added as a solution in THF (2 mL) over a 2-min period. The mixture was stirred for 10 min, whereupon NH₄Cl (391 mg) was added. The ammonia was then allowed to distill off and THF (15 mL) was added to the white slurry. After filtration and washing of the solid with additional THF (5 mL), the combined organics were concentrated. The residue was chromatographed on a silica plate (2 mm, Chromatotron) with ethyl acetate/hexanes (2:1) as eluant. The desired N-H β -lactam 9 was obtained as an oil (137 mg, 84% yield): ¹H NMR (CDCl₃) δ 1.36 (d, 3 H), 1.6-2.0 (m, 2 H), 2.18 (q, 2 H), 2.71 (t, 1 H), 3.45 (dq, 1 H,

J = 2.1 Hz), 4.9-5.1 (m, 2 H), 5.8 (m, 1 H), 6.66 (br s, 1 H, NH); IR (NaCl, neat) 3270, 1755, 1655 cm⁻¹; mass spectrum [Cl (NH₃)], m/e140 (M⁺ + H⁺); ¹³C NMR (CDCl₃) δ 170.92, 137.53, 115.27, 57.71, 50.89, 31.28, 27.69, 20.50. Anal. Calcd for C₈H₁₃NO: C, 69.03; H, 9.41; N, 10.06. Found: C, 69.18; H, 9.32; N, 9.85.

(3'RS,4'RS)-3-(4'-Methyl-2'-oxoazetidin-3'-yl)propionic Acid (10). Method A. A flask is charged with a magnetic stirrer, CCl₄/CH₃CN/H₂O (1:1:2, total 4 mL), compound 9 (50 mg, 0.36 mmol), and NaIO₄ (316 mg, 1.48 mmol, 4.1 equiv). To this biphasic solution, a catalytic amount of RuCl₃-3H₂O was added. The mixture was stirred for 1 h at room temperature and taken up in ethyl acetate (20 mL) and H₂O (10 mL). The organic layer was separated and the aqueous layer was saturated with sodium chloride (solid) and extracted with ethyl acetate (2 × 20 mL). The combined organic solutions were dried (MgSO₄) and concentrated to give **10** as an oil in 40–50% yield.

Method B. Compound 9 (140 mg, 1 mmol) was dissolved in methanol (10 mL). The solution was ozonized at -78 °C until H was saturated with ozone. The mixture was treated with dimethyl sulfide (2 mL) at -78 °C and warmed to room temperature for 1.5 h. After the solvent was evaporated, the crude aldehyde was dissolved in acetone (10 mL) and treated dropwise with Jones reagent (8 N) at 0 °C until the color persisted. 2-Propanol (1 mL) was added to destroy the excess reagent. The mixture was evaporated and the residue was partitioned between brine (20 mL) and ethyl acetate (40 mL). The organic layer was dried (Mg-SO₄) and evaporated to give 10 (80% yield): ¹H NMR (CDCl₃) δ 1.3 (d, 3 H), 2.0 (br m, 2 H), 2.5 (br m, 2 H), 2.8 (br, 1 H), 3.5 (br, 1 H), 6.5 (br, 2 H, CO₂H and NH); IR (NaCl, neat) 3260, 1725 (br) cm⁻¹; mass spectrum [Cl (NH₃)], m/e 172 (M⁺ + NH₄⁺), 158 (M⁺ + H⁺).

tert-Butyl (3'RS,4'RS)-3-Oxo-5-(4'-methyl-2'-oxoazetidin-3'-yl)pentanoate (11). To a solution of the acid 10 (205 mg, 1.306 mmol) in dry THF (10 mL) was added N,N'-carbonyldiimidazole (222 mg, 1.371 mmol, 1.05 equiv). The mixture was stirred at room temperature for 6 h. The magnesium salt of tert-butyl hydrogen malonate (246 mg, 0.718 mmol, 0.55 equiv) was added, and the mixture was stirred for 12-16 h and evaporated to dryness at reduced pressure. The residue was chromatographed on a silica plate (2 mm, Chromatotron) eluting with tetrahydrofuran/hexane (3:2) as eluant. The desired 11 was isolated as an oil (25–40% yield): ¹H NMR (CDCl₃) δ 1.35 (d, 3 H, J = 6.5 Hz), 1.47 (s, 9 H), 1.9-2.05 (m, 2 H), 2.7-2.95 (m, 3 H), 3.35 (s, 2 H), 3.45 (dq, 1 H, J = 2.5, 6.5 Hz), 5.9 (br s, 1 H, NH); ¹³C NMR (CDCl₃) 202.08 (s), 170.15 (s), 166.08 (s), 81.71 (s), 56.79 (d), 50.57 (d), 50.25 (t), 39.79 (t), 27.74 (q), 21.91 (t), 20.23 (t); IR (NaCl, neat) 3280, 1740 (br) cm⁻¹; mass speectrum [Cl (NH₃)], m/e 256 (M⁺ + H⁺), 200 [(M⁺ + H⁺) - $(Bu - H^+)$], 156(M⁺ + 2 - CO₂'Bu). Anal. Calcd for C₁₃H₂₁NO₄: C, 61.16; H, 8.29; N, 5.49. Found: C, 60.93; H, 8.34; N, 5.41.

tert-Butyl (3'RS,4'RS)-2-Diazo-3-oxo-5-(4'-methyl-2'-oxoazetidin-3'-yl)pentanoate (12). Compound 11 (25.5 mg, 0.1 mmol) and tosyl azide (39.5 mg, 0.2 mmol, 2 equiv) were dissolved in acetonitrile (5 mL) and treated with triethylamine (27.8 μ L, 0.2 mmol, 2.0 equiv). The resulting mixture was stirred at room temperature for 3 h. After the solvent was evaporated, the residue was separated by PTLC silica gel [with tetrahydrofuran/hexanes (1:1) as eluant] to afford 12 as an oil in 80% yield: ¹H NMR (CDCl₃) δ 1.36 (d, 3 H, J = 6.5 Hz), 1.52 (s, 9 H), 1.95-2.1 (m, 2 H), 2.78 (m, 1 H), 2.98 (m, 2 H), 3.52 (dq, 1 H, J= 2.2, 6.5 Hz), 5.75 (br s, 1 H, NH); IR (NaCl, neat) 3300, 2140, 1755, 1720 cm⁻¹; mass spectrum [Cl (NH₃)], m/e 282 (M⁺ + H⁺), 254 (M⁺ + 1 - N₂), 226 (M⁺ + 2 - 'Bu).

3,7-Dioxo-2-(tert-butylcarboxy)-8-methyl-1-azabicyclo[4.1.1]octane (13). Compound 12 (28 mg, 0.1 mmol) was dissolved in benzene (10 mL) and heated to reflux. The mixture was treated with rhodium acetate dimer (catalytic amount). After 30 min, the mixture was cooled down, and the volatile components were removed. The residue was separated by PTLC silica gel [with tetrahydrofuran/hexanes (1:1) as eluant] to afford 13 as an oil in 50% yield: ¹H NMR (CDCl₃) δ 1.50 (s, 9 H), 1.53 (d, 3 H, J = 6 Hz), 2.3–2.5 (m, 2 H), 2.51–2.80 (m, 2 H), 2.93 (dq, 1 H, $J = \sim 1, 6$ Hz), 3.13 (dd, 1 H, J = 5, 1.3 Hz), 4.68 (s, 1 H); IR (NaCl, neat) 1795, 1750, 1730 cm⁻¹; exact mass calcd for C₁₃H₂₀NO₄ 254.1393, found 254.1379.

Ethyl 3-(Benzylamino)-4-methylpentanoate (16). The β -keto ester 15 (10 g, 63.2 mmol) was dissolved in benzene (80 mL) and treated with benzylamine (6.9 mL, 63.2 mmol, 1.0 equiv). The mixture was heated to reflux under nitrogen with azeotropic water removal for 2–3 h. After the solvent was evaporated, the residue was dissolved in acetic acid (100 mL) and treated with sodium cyanoborohydride (9.38 g, 94.2 mmol, 4.5 equiv). The mixture was stirred at room temperature for 2 h. After the solvent was evaporated, the residue was taken up in ether (300 mL) and washed with 1 N NaOH (2 × 50 mL) and brine. The ethereal solution was dried (MgSO₄) and evaporated to give 16 as an oil in 85% yield: 'H NMR (CDCl₃) δ 0.9 (d, 3 H), 0.93 (d, 3 H), 1.25 (t, 3 H), 1.5 (br s, 1 H, NH) 1.87 (m, 1 H), 2.40 (m, 2 H), 2.90 (m, 1 H), 3.80 (s, 2 H), 4.15

(q, 2 H), 7.1-7.4 (m, 5 H); IR (NaCl, neat) 3350, 1740 cm⁻¹; mass spectrum [Cl (NH₃)], m/e 250 (M⁺ + H⁺), 160 (M⁺ + 2 - CH₂Ph).

4-Isopropyl-1-benzylazetidin-2-one (17). Compound 16 (4.98 g, 20 mmol) was dissolved in 2 M KOH/methanol (15 mL, 30 mmol, 1.5 equiv) and the mixture was stirred for 5 h at room temperature. The resulting mixture was acidified to pH 5 with HCl/MeOH. Diethyl ether (50 mL) was added and the precipitate was filtered. The filtrate was evaporated to afford the amino acid as a hygroscopic solid. The crude amino acid was then suspended in methylene chloride (1 L) and treated with triethylamine (8.34 mL, 60 mmol, 3.0 equiv) and 1-methyl-2chloropyridinium iodide (5.36 g, 21 mmol, 1.05 equiv). The mixture was stirred at room temperature for 16 h. After the volatile components were removed in vacuo, the residue was distilled in vacuo to afford 17 as an oil in 80% yield: bp 120 \pm 2 °C (0.6 mmHg); ¹H NMR (CDCl₃) δ 0.82 (d, 3 H), 0.90 (d, 3 H), 1.85 (m, 1 H), 2.63 (dd, 1 H), 2.85 (dd, 1 H), 3.3 (dt, 1 H), 4.05 and 4.72 (ABq, 2 H), 7.2-7.4 (m, 5 H); IR (NaCl, neat) 1765, 1610 cm⁻¹; mass spectrum [Cl (NH₃)], m/e 204 (M⁺ + H⁺). Anal. Calcd for C₁₃H₁₇NO: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.65: H. 8.47: N. 6.83.

4-Isopropyl-1-(*tert***-butyldimethylsilyl)azetidin-2-one (18).** After the condensation of 200 mL of anhydrous ammonia at -40 °C, Na (1.37 g, 59.6 mmol, 2.2 equiv) was added in several small pieces. The resulting blue solution was stirred for 10 min and compound **17** (5.5 g, 27.09 mmol) as a solution in THF (20 mL) was added over a 10-min period. The mixture was stirred for 10 min, whereupon NH₄Cl (11 g) was added. The ammonia was then allowed to distill off and THF (200 mL) was added to the white slurry. After filtration and washing of the solids with an additional 50 mL of THF, the combined organics were concentrated. The residue was distilled in vacuo to afford 4-isopropylazetidin-2-one in 93% yield: bp 72-76 °C (0.6 mmHg); ¹H NMR (CDCl₃) δ 0.09 (d, 3 H), 0.96 (d, 3 H), 1.70 (m, 1 H), 2.60 (dd, 1 H), 2.97 (dd, 1 H), 3.33 (m, 1 H), 6.57 (br s, 1 H, NH); IR (NaCl, neat) 3270, 1760 cm⁻¹; mass spectrum [Cl (NH₃)], *m/e* 131 (M⁺ + NH₄⁺), 114 (M⁺ + H⁺).

4-Isopropylazetidin-2-one, obtained above (3.4 g, 30.1 mmol), was dissovled in DMF (100 mmL) and treated with *tert*-butyldimethylsilyl chloride (4.97 g, 33 mmol, 1.1 equiv) and triethylamine (4.59 mL, 33 mmol, 1.1 equiv). The mixture was stirred at room temperature for 16 h and taken up in ether (300 mL). The ethereal solution was washed with 1 N HCl (2×50 mL), H₂O (2×50 mL), and brine (1×50 mL). After the solution was dried (MgSO₄) and evaporated, the residue was distilled in vacuo to afford **18** as an oil in 88% yield: bp 78 °C (0.6 mmHg); ¹H NMR (CDCl₃) δ 0.12 (s, 3 H), 0.23 (s, 3 H), 0.85 (d, 3 H), 0.87 (d, 3 H), 0.92 (s, 9 H), 2.0 (m, 1 H), 2.55 (dd, 1 H), 2.83 (dd, 1 H), 3.52 (m, 1 H); IR (NaCl, neat) 1755 cm⁻¹; mass spectrum [Cl (NH₃)], m/e 228 (M⁺ + H⁺). Anal. Calcd for C₁₂H₂₅NOSi: C, 63.38; H, 11.08; N, 6.16. Found: C, 63.59; H, 11.34; N, 6.32.

(3'RS,4RS)-3-(3'-Butenyl)-4-isopropyl-1-(tert-butyldimethylsilyl)azetidin-2-one (19). Method A. To a solution of 18 (2.27 g, 10 mmol) in THF (30 mL) at -20 °C was added *n*-BuLi (1.54 M, 6.49 mL, 10 mmol, 1.0 equiv). After 10 min, 4-bromobutene (2.7 g, 20 mmol, 2 equiv) was added to the mixture at -20 °C. The resulting mixture was stirred for 10 min at -20 °C and NH₄Cl (saturated aqueous solution) was added. After the mixture was taken up in ethyl acetate (100 mL), it was washed with saturated NaCl (aqueous solution). After the solution was dried (MgSO₄) and evaporated, the residue was chromatographed on a silica plate (4 mm) with ethyl acetate/hexanes as eluant, (1:6) to afford 19 as an oil in 90% yield: ¹H NMR (CDCl₃) δ 0.18 (s, 3 H), 0.29 (s, 3 H), 0.90 (d, 3 H), 0.92 (d, 3 H), 0.95 (s, 9 H), 1.5-1.8 (m, 1 H), 1.82 (m, 1 H), 2.0 (m, 1 H), 2.18 (q, 2 H), 2.85 (apparent t, 1 H), 3.25 (m, 1 H), 4.9-5.1 (m, 2 H), 5.8 (m, 1 H); IR (NaCl, neat) 1750, 1645 cm⁻¹; mass spectrum [Cl (NH₃)], *m/e* 282 (M⁺ + H⁺).

Method B. To a solution of diisopropylamine (0.678 mL, 4.84 mmol, 1.1 equiv) in THF (30 mL) was added *n*-BuLi (1.6 M in hexane, 2.89 mL, 4.4 mmol, 1.0 equiv) at -78 °C with stirring. After 10 min, the β -lactam 18 (1.0 g, 4.4 mmol) was added and the solution was stirred for 20 min at -78 °C. HMPA (0.8 mL, 4.4 mmol, 1.0 equiv) was added at -78 °C. After 20 min, 4-bromobutene (0.8 mL, ~ 2 eq) was added at -78 °C. The resulting mixture was stirred at -78 °C for 30 min and then allowed to warm to room temperature, and saturated NH₄Cl (10 mL) and ethyl acetate (30 mL) were added. After the layers were shaken and separated, and the organic phase was washed with brine, dried (MgSO₄), and concentrated to give 19 in 95% yield.

(3RS,4RS)-3-(3-Butenyl)-4-isopropylazetidin-2-one (20). Compound 19 (281 mg, 1 mmol) was dissolved in THF (5 mL) and treated with tetra-*n*-butylammonium fluoride trihydrate (347 mg, 1.1 mmol, 1.1 equiv). The mixture was stirred at room temperature for 0.5 h. After the solvent was evaporated, the residue was chromatographed on a silica plate (2 mm) with ethyl acetate hexanes (1:1) as eluant, to afford 20 as an oil in 90% yield: ¹H NMR (CDCl₃) δ 0.97 (m, 6 H), 1.65-1.97 (m, 3 H), 2.20 (q, 2 H), 2.80 (m, 1 H), 3.03 (dd, 1 H, J = 2.1 Hz), 4.95-5.10 (m, 2 H), 5.8 (m, 1 H), 6.33 (br s, 1 H, NH); IR (NaCl, neat) 3250, 1750, 1640 cm⁻¹; mass spectrum [Cl (NH₃)], m/e, 185 (M⁺ + NH₄⁺), 168 (M⁺ + H⁺).

(3'RS,4'RS)-3-(4'-Isopropyl-2'-oxoazetidin-3'-yl)propionic Acid (21). Compound 21 was obtained as a crystalline solid (70%, mp 169–171 °C), as described in the preparation of 10 by method A, except that the starting material was compound 20: ¹H NMR (CDCl₃) δ 1.0 (br, 6 H), 1.75 (m, 1 H), 2.0 (m, 2 H), 2.5 (m, 2 H), 2.85 (m, 1 H), 3.0 (m, 1 H), 6.5 (br, 1 H, NH), 8.2 (br, 1 H, OH); IR (NaCl, neat) 3280, 1735, 1630 cm⁻¹; mass spectrum [Cl (NH₃)], m/e 186 (M⁺ + H⁺), 140 (M + 2 – CO₂H). Anal. Calcd for C₉H₁₅NO₃: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.17; H, 8.43; N, 7.36.

tert-Butyl (3'*R*S,4'*R*S)-3-Oxo-5-(4'-isopropyl-2'-oxoazetidin-3'-yl)pentanoate (22a). Compound 22a was prepared as described in the preparation of 11, except that the starting material was compound 21. The desired 22a was obtained as an oil in 20–35% yield after separation by PTLC silica gel [with ethyl acetate/hexanes (1:1) as eluan1]: ¹H NMR (CDCl₃) δ 0.94 (d, 3 H), 0.98 (d, 3 H), 1.48 (s, 9 H), 1.70 (m, 1 H), 2.02 (q, 2 H), 2.7–2.9 (m, 3 H), 3.00 (dd, 1 H), 3.37 (s, 2 H), 6.4 (br s, 1 H, NH); 1R (NaCl, neat) 3360, 1750, 1725 (sh) cm⁻¹; mass spectrum [Cl (NH₃)], *m/e* 284 (M⁺ + H⁺), 245 [(M⁺ + NH₄⁺) – ('Bu - H)], 228 [(M⁺ + H⁺)] – ('Bu – H)], 200 [(M⁺ + H⁺) – (CO/Bu – H)], 184 [(M⁺ + H⁺) – (CO₂'Bu – H⁺)]; ¹³C NMR (CDCl₃) δ 201.93 (s), 170.51 (s), 166.12 (s), 81.76 (s), 61.14 (d), 53.43 (d), 50.47 (t), 39.83 (t), 32.39 (d), 27.84 (q), 22.61 (t), 18.69 (q), 18.04 (q).

(3'RS, 4'RS)-tert-Butyl 2-Diazo-3-oxo-5-(4'-isopropyl-2'-oxoazetidin-3'-yl)pentanoate (23a). Compound 23a was similarly prepared as described in the preparation of 12, except that the starting material was 22a. The desired 23a was obtained as a solid in 85% yield after separation by PTLC silica gel [with ethyl acetate/hexanes (1:1) as eluant]: mp 88-89 °C (recrystallized with ethyl acetate/hexanes); ¹H NMR (CDCl₃) δ 0.97 (d, 6 He, 1.53 (s, 9 H), 1.72 (m, 1 H), 2.05 (m, 2 H), 2.85 (m, 1 H), 2.95-3.1 (m, 3 H), 6.12 (br s, 1 H, NH); IR (NaCl, neat) 3300, 2130, 1750, 1720 cm⁻¹; mass spectrum [Cl (NH₃)], m/e 310 (M⁺ + H⁺), 282 [(M + H⁺) - N₂], 228 [(M⁺ + H⁺) - N₂ - ('Bu - H)], 184 [(M⁺ + H⁺) - N₂ - (CO₂'Bu - H)]. Anal. Calcd for C₁₅H₂₃N₃O₄: C, 58.24; H, 7.49; N, 13.58. Found: C, 58.18; H, 7.53; N, 13.49.

(3RS,4RS)-(Trimethylsilyl)ethyl 2-Diazo-3-oxo-5-(4'-isopropyl-2'-oxoazetidin-3'-yl)pentanoate (23d). Compound 23d was similarly prepared as described in the preparation of 12 except that the starting material was 22c. The desired 23d was obtained as an oil in 80% yield after separation by PTLC silica gel [with ethyl acetate/hexanes (3:2) as eluant]: ¹H NMR (CDCl₃) δ 0.02 (s, 9 H), 0.87 (d, 6 H), 0.85–1.0 (m, 2 H), 1.5–1.8 (m, 1 H), 1.8–2.1 (m, 2 H), 2.80 (m, 1 H), 2.9–3.1 (m, 3 H), 4.28 (t, 2 H), 5.95 (s, 1 H, NH); IR (NaCl, neat) 3250, 2120, 1755, 1720 cm⁻¹.

3,7-Dioxo-2-(*tert*-butylcarboxy)-8-isopropyl-1-azabicyclo[4.1.1]octane (14a). Compound 14a was similarly prepared as described in the preparation of 13, except that the starting material was 23a. The desired 14a was obtained as an oil in 20-35% yield after separation by PTLC silica gel [with ethyl acetate/hexanes (1:1) as eluant]: ¹H NMR (CDCl₃) δ 0.98 (2 d, 6 H, J = 9.1 Hz), 1.52 (s, 9 H), 2.13–2.32 (m, 1 H), 2.33–2.47 (m, 2 H), 2.6–2.8 (m, 3 H), 3.27 (m, 1 H), 4.75 (s, 1 H); IR (NaCl, neat) 1795, 1750, 1725 (sh) cm⁻¹; exact mass calcd for C₁₅H₂₄NO₄ 282.1706, found 282.1658.

4-Methyl-1-benzylazetidin-2-one (24). Compound 1 (30 g, 0.231 mol) was dissolved in benzene (80 mL) and treated with benzylamine (26.5 mL, 0.243 mol, 1.05 equiv). The mixture was heated to reflux with azeotropic water removal. After the solvent was evaporated, the residue was dissolved in acetic acid (150 mL) and treated with sodium cyanoborohydride (14.5 g, 0.231 mol, 3 equiv) at 0 °C. The mixture was stirred at room temperature for 2 h. The acetic acid was removed and 2 N NaOH was added to the mixture until the pH of the solution reached 10. The resulting solution was extracted with ether $(3 \times 500 \text{ mL})$. The ethereal solution was dried over MgSO4 and evaporated to give the amino ester as an oil. The crude amino ester (46.2 g, 0.2 mol) was treated with KOH/MeOH (2 M, 102 mL, 0.24 mol, 1.2 equiv). The resulting mixture was stirred for 16 h at room temperature. HCl/MeOH (4.2 M) was added to the mixture until the pH of the solution reached 6.0. Ether $(\sim 200 \text{ mL})$ was added to the mixture and the precipitate was collected (KCl). After filtration, ether (400 mL) was added to the filtrate and the precipitate was collected and dried to afford the amino acid (mp 180-182 °C). The amino acid (35 g, 0.181 mol) was suspended in methylene chloride (9 L, 0.02 M solution) and treated with triethylamine (75.6 mL, 0.543 mol, 3.0 equiv) and 1-methyl-2-chloropyridinium iodide (50.9 g, 0.199 mol, 1.1 equiv). After stirring 16 h at room temperature, the solvent was evaporated and the residue was triturated with ethyl acetate (70 mL). After the filtration, the filtrate was evaporated and the residue was distilled in vacuo to afford 24 as an oil in 50% yield from 1: bp 105 °C (1.0 mmHg); ¹H NMR (CDCl₃) δ 1.21 (d, 3 H, J = 6.0 Hz), 2.53 (dd, 1 H, J = 15.4, 1.4 Hz), 3.07 (dd, 1 H, J = 15.4, 4.9 Hz), 3.55 (m, 1 H), 4.10 ($^{1}_{2}$ AB q, 1 H, J = 15.2 Hz), 4.58 ($^{1}_{2}$ AB q, 1 H, J = 15.2 Hz), 7.2–7.4 (m, 5 H); IR (NaCl, neat) 1750 cm⁻¹; mass spectrum [C (NH₃)], m/e 176 (M⁺ + H⁺). Anal. Calcd for C₁₁H₁₃NO: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.66; H, 7.39; N, 7.81.

4-Methyl-1-(*tert*-butyldimethylsilyl)azetidin-2-one (25). Compound 25 was similarly prepared as described in the preparation of 18, except that the starting material was 24. The desired 24 was isolated as an oil by vacuum distillation in 80% yield: bp 113-115 °C (17 mmHg); ¹H NMR (CDCl₃) δ 0.22 (2 s, 6 H), 0.85 (s, 9 H), 1.32 (d, 3 H), 2.55 (dd, 1 H), 3.17 (dd, 1 H), 3.55 (m, 1 H); IR (NaCl, neat) 1745 cm⁻¹; mass spectrum [Cl (NH₃)], *m/e* 200 (M⁺ + H⁺). Anal. Calcd for C₁₀H₂₁NOSi: C, 60.25; H, 10.62; N, 7.03. Found: C, 60.09; H, 10.81; N, 6.99.

(3RS,4RS)-3,4-Dimethyl-1-(*tert*-butyldimethylsilyl)azetidin-2-one (26a). Compound 26a was similarly prepared as described in the preparation of 19 by method B, except that the starting material was 25 and the electrophile was CH₃I. The desired 26a was obtained as an oil in 95% yield after separation by chromatography on a silica plate [with ethyl acetate/hexanes (1:6) as eluant]: ¹H NMR (CDCl₃) δ 0.21 (s, 3 H), 0.25 (s, 3 H), 0.96 (s, 9 H), 1.27 (d, 3 H, J = 7.5 Hz), 1.34 (d, 3 H, J = 6.1 Hz), 2.70 (dq, 1 H, J = 7.5, 2.4 Hz), 3.28 (dq, 1 H, J = 6.1, 2.4 Hz); IR (NaCl, neat) 1745 cm⁻¹; mass spectrum [Cl (NH₃)], *m/e* 214 (M⁺ + H⁺). Anal. Calcd for Cl₁₁H₂₃NOSi: C, 61.91; H, 10.86; N, 6.56. Found: C, 61.83; H, 10.91; N, 6.53.

(3RS, 4RS)-3-[2'-[(tert -Butyldimethylsilyl)oxy]ethyl]-4-methyl-1-(tert -butyldimethylsilyl)azetidin-2-one (26b). Compound 26b was similarly prepared as described in the preparation of 19 by method B except that the starting material was 25 and the electrophile was 1-[(tert-butyldimethylsilyl)oxy]-2-bromoethane (BrCH₂CH₂OSi'BuMe₂). Compound 26b was obtained as an oil in 75% yield after separation by chromatography on a silica plate [with ethyl acetate/hexane (1:6) as eluan1]: ¹H NMR (CDCl₃) δ 0.01 (s, 6 H), 0.15 (s, 3 H), 0.18 (s, 3 H), 0.83 (s, 9 H), 0.90 (s, 9 H), 1.29 (d, 3 H, J = 6.1 Hz), 1.7-2.0 (m, 2 H), 2.75 (m, 1 H), 3.39 (dq, 1 H, J = 2.3, 6.1 Hz), 3.6-3.8 (m, 2 H); IR (NaCl, neat) 1745 cm⁻¹; mass spectrum [Cl (NH₃)], m/e 358 (M⁺ + H⁺).

3,4-Dimethyl-3-(3'-butenyl)-1-(tert-butyldimethylsilyl)azetidin-2-one (27a). To a solution of diethylamine (distilled from NaOH, 0.38 mL, 3.04 mmol, 1.3 equiv) in THF (20 mL) was added n-butyllithium (1.6 M in hexane, 2.1 mL, 3.36 mmol, 1.2 equiv) at -78 °C with stirring. After 10 min, the β -lactam **26a** (596 mg, 2.8 mmol) in THF (4 mL) was added to the cold solution at -78 °C. After 15 min, HMPA (0.59 mL, 3.36 mmol, 1.2 equiv) was added to the mixture, which was stirred for 15 min at -78 °C. 4-Bromobutene (0.57 mL, 5.6 mmol, 2.0 equiv) in THF (4 mL) was added to the mixture and the mixture was stirred for 30 min at -78 °C. Saturated NH₄Cl (10 mL) and ethyl acetate (30 mL) were added, and the layers were shaken and separated. The organic phase was washed with brine, dried (MgSO₄), and concentrated. The residue was chromatographed on a silica plate (2 mm) with ethyl acetate/hexanes (1:6) as eluant to afford 27a as an oil in 95% yield: ¹H NMR (CDCl₃) δ 0.21 (s, 3 H), 0.23 (s, 3 H), 0.96 (s, 9 H), 1.12 (s, 3 H), 1.22 (d, 3 H, J = 6.4 Hz), 1.6–2.2 (m, 4 H), 3.46 (q, 1 H, J = 6.4Hz), 4.8-5.1 (m, 2 H), 5.7-5.9 (m, 1 H); IR (NaCl, neat) 1745, 1640 cm⁻¹; mass spectrum [Cl (NH₃)], m/e 268 (M⁺ + H⁺).

3-[2-[(tert-Butyldimethylsilyl)oxy]ethyl]-3-(3'-butenyl)-4-methylazetidin-2-one (27b). Compound 27b was similarly prepared as described in the preparation of 27a except that the starting material was 26b. The desired 27b was obtained as an oil in 75% yield after separation by chromatography on a silica plate [with ether/hexanes (1:4) as eluant]: ¹H NMR (CDCl₃) δ 0.05 (s, 6 H), 0.20 (s, 3 H), 0.22 (s, 3 H), 0.89 (s, 9 H), 0.95 (s, 9 H), 1.25 (d, 3 H, J = 6.4 Hz), 1.6-2.3 (m, 6 H), 3.42 (q, 1 H, J = 6.4 Hz), 3.7-4.0 (m, 2 H), 4.9-5.1 (m, 2 H), 5.8 (m, 1 H); mass spectrum [Cl (NH₃)], m/e 412 (M⁺ + H⁺).

3,4-Dimethyl-3-(3'-butenyl)azetidin-2-one (28a). Compound 28a was similarly prepared as described in the preparation of 20 except that the starting material was 27a. The desired 28a was obtained as an oil in 90% yield after separation by chromatography on a silica plate [with ethyl acetate/hexanes (1:1) as eluant]: ¹H NMR (CDCl₃) δ 1.16 (is, 3 H), 1.22 (d, 3 H, J = 6.3 Hz), 1.5–2.3 (m, 4 H), 3.51 (q, 1 H, J = 6.3 Hz), 4.8–5.1 (m, 2 H), 5.7–5.9 (m, 1 H), 6.8 (br s, 1 H, NH); IR (NaCl, neat) 3250, 1750, 1640 cm⁻¹; mass spectrum [Cl (NH₃)], *m/e* 154 (M⁺ + H⁺).

3-(2'-Hydroxyethyl)-3-(3'-Butenyl)-4-methylazetidin-2-one (28b). Compound 28b was similarly prepared as described in the preparation of 20 except that the starting material was 27b. The desired 28b was obtained as an oil in 50% yield after separation by chromatography on a silica plate [with ethyl acetate as eluant]: ¹H NMR (CDCl₃) δ 1.26 (d, 3 H, J = 6.5 Hz), 1.6-2.3 (m, 6 H), 3.5-3.9 (m, 3 H, including OH), 3.61 (q, 1 H, J = 6.5 Hz), 4.9-5.1 (m, 2 H), 5.8 (m, 1 H), 6.18 (br s, 1 H, NH). 3-[2'-(1'',6''-Dibromonaphthoxy)ethyl]-3-(3'-butenyl)-4-methylazetidin-2-one (28d). Compound 28d was similarly prepared as described in the preparation of 28c except that 1,6-dibromonaphthol was substituted for *p*-phenylphenol. The desired 28d was obtained as a solid in 70% yield after separation by chromatography on a silica plate [with ethyl acetate/hexanes (1:2) as eluant]: mp 128-130 °C (recrystallized with methylene chloride/hexanes); ¹H NMR (CDCl₃) δ 1.34 (d, 3 H, J = 6.3 Hz), 1.8-2.5 (m, 6 H), 3.64 (q, 1 H, J = 6.3 Hz), 4.3-4.5 (m, 2 H), 4.95-5.1 (m, 2 H), 5.7-5.9 (m, 1 H), 5.95 (s, 1 H, NH), 7.2-8.1 (m, 5 H); mass spectrum [Cl (NH₃)], *m/e* 468 (M⁺ + H⁺). Anal. Calcd for C₁₀H₂₁NO₂Br₂: C, 51.41; H, 4.53; N, 3.00. Found: C, 51.34; H, 4.42; N, 2.91.

3-(3',4'-Dimethyl-2'-oxoazetidin-3'-yl)propionic Acid (29a). Compound 29a was similarly prepared as described in the preparation of 10 by method B, except that the starting material was 28a. The desired 29a was obtained as an oil in 60% yield: ¹H NMR (CDCl₃) δ 1.17 (s, 3 H), 1.24 (d, 3 H, J = 6.1 Hz), 1.8-2.6 (m, 4 H), 3.56 (q, 1 H, J = 6.1 Hz), 6.7 (br s, 1 H, NH), 10.37 (br s, 1 H, CO₂H).

3-[3-[2'-(1",6"-Dibromonaphthoxy)ethyl]-4-methyl-2-oxoazetidin-3yl]propionic Acid (29d). Compound 29d was similarly prepared as described in the preparation of 10 by method B except that the starting material was 28d. The desired 29d was obtained as a foam in 80% yield: ¹H NMR (CDCl₃) δ 1.35 (d, 3 H), 2.1–2.8 (m, 6 H), 3.6 (m, 1 H), 4.4 apparent t, 2 H), 5.9 (br, 1 H, NH), 7.3–8.1 (m, 5 H), 9.4 (br, 1 H, CO₂H).

tert-Butyl 5-(3',4'-Dimethyl-2'-oxoazetidin-3'-yl)-3-oxopentanoate (30a). Compound 30a was similarly prepared as described in the preparation of 11 except that the starting material was 24a. The desired 30a was obtained as an oil in 30% yield after separation by PTLC silica gel [with ethyl acetate/hexane (3:2) as eluant]: ¹H NMR (CDCl₃) δ 1.16 (s, 3 H), 1.24 (d, 3 H, J = 6.3 Hz), 1.47 (s, 9 H), 1.9-2.05 (m, 2 H), 2.65-2.9 (m, 2 H), 3.37 (s, 2 H), 3.51 (q, 1 H, J = 6.3 Hz), 5.8 (br s, 1 H, NH); IR (NaCl, neat) 3250, 1760-1720 cm⁻¹.

tert-Butyl 5-[3'-[2-(1",6"-Dibromonaphthoxy)ethyl]-4'-methyl-2'-oxoazetidin-3'-yl]-3-oxopentanoate (30d). Compound 30d was similarly prepared as described in the preparation of 11 except that the starting material was 29d. The desired 30d was obtained as a foam in 20% yield after separation by PTLC silica gel [with ethyl acetate/hexanes (3:1) as eluant]: ¹H NMR (CDCl₃) δ 1.36 (d, 3 H, J = 6.3 Hz), 1.45 (s, 9 H), 2.1-2.3 (m, 4 H), 2.5-3.0 (m, 2 H), 3.38 (s, 2 H), 3.61 (q, 1 H, J = 6.3Hz), 4.38 (apparent t, 2 H), 5.85 (br s, 1 H, NH), 7.25-8.1 (m, 5 H); mass spectrum [Cl (NH₃)], m/e 484 [(M⁺ + H⁺) - (CO₂'Bu - H⁺)]; IR (NaCl, neat) 3280, 1720-1750 cm⁻¹.

tert-Butyl 2-Diazo-5-(3',4'-dimethyl-2'-oxoazetidin-3'-yl)-3-oxopentanoate (31a). Compound 31a was similarly prepared as described in the preparation of 12, except that the starting material was 30a. The desired 31a was obtained as an oil in 80% yield after separation by PTLC silica gel [with THF/hexanes (1:1) as eluant]: ¹H NMR (CDCl₃) δ 1.18 (s, 3 H), 1.24 (d, 3 H, J = 6.3 Hz), 1.53 (s, 9 H), 1.9–2.1 (m, 2 H)e, 2.7–3.1 (m, 2 H), 3.58 (q, 1 H, J = 6.3 Hz), 5.94 (br s, 1 H, NH); IR (NaCl, neat) 3250, 2120, 1755, 1715 cm⁻¹.

tert-Butyl 2-Diazo-5-[3'-[(1",6"-dibromonaphthoxy)ethyl]-4'-methyl-2'-oxoazetidin-3-yl]-3-oxopentanoate (31d). Compound 31d was similarly prepared as described in the preparation of 12, except that the starting material was 30d. The desired 31d was obtained as a foam in 80% yield after separation by PTLC silica gel [with ethyl acetate/hexane (3:1) as eluant]: ¹H NMR (CDCl₃) δ 1.35 (d, 3 H), 1.49 (s, 9 H), 2.0–2.4 (m, 4 H), 2.7–3.3 (m, 2 H), 3.68 (q, 1 H), 4.45 (t, 2 H), 5.82 (br s, 1 H, NH), 7.3–8.1 (m, 5 H); IR (NaCl, neat) 3280, 2140, 1755, 1715 cm⁻¹.

2-[(*tert*-Butyloxy)carbonyl]-6,8-dimethyl-3,7-dioxo-1-azabicyclo-[4.1.]octane (32a). Compound 32a was similarly prepared as described in the preparation of 13, except that the starting materials was 31a. The desired 32a was obtained as an oil in 70% yield after separation by PTLC silica gel [with ethyl acetate/hexanes (1:2) as eluant]: ¹H NMR (CD-Cl₃) δ 1.15 (s, 3 H), 1.45 (d, 3 H, J = 6.2 Hz), 1.51 (s, 9 H), 2.1-2.8 (m, 4 H), 2.99 (q, 1 H, J = 6.2 Hz), 4.71 (s, 1 H); IR (NaCl, neat) 1780, 1745, 1720 cm⁻¹; mass spectrum [Cl (NH₃)], *m/e* 268 (M⁺ + H⁺), 229 [(M⁺ + NH⁺₄) - ('Bu - H⁺)], 212 [(M⁺ + H⁺) - ('Bu - H)], 168 [(M⁺ + H⁺) - (CO₂/Bu - H⁺)].

2-[(tert-Butyloxy)carbonyl]-6-[2-(p-phenylphenoxy)ethyl]-8-methyl-3,7-dioxo-1-azabicyclo[4.1.1]octane (32c). Compound 32c was similarly prepared as described in the preparation of 13, except that the starting material was 31c. The desired 32c was obtained as a foam in 50% yield after separation by PTLC silica gel [with ethyl acetate/hexanes (1:2) as eluant]: ¹H NMR (CDCl₃) δ 1.51 (s, 9 H), 1.60 (d, 3 H, J = 6.2 Hz), 2.1-2.8 (m, 6 H), 3.11 (q, 1 H, J = 6.2 Hz), 4.0-4.2 (m, 2 H), 4.75 (s, 1 H), 6.9-7.6 (m, 9 H); IR (NaCl, neat) 1785, 1750, 1725 cm⁻¹; mass spectrum [Cl (NH₃)], m/e 394 [(M⁺ + H⁺) - ('Bu - H⁺)].

3,7-Dioxo-2-[(*tert*-butyloxy)carboxy]-6-[2'-(1'',6''-dibromonaphthoxy)ethyl]-8-methyl-1-azabicyclo[4.1.1]octane (32d). Compound 32d was similarly prepared as described in the preparation of 13, except that the starting material was 31d. The desired 32d was obtained as a solid in 70% yield after separation by PTLC silica gel [with ethyl acetate/hexanes (1:1) as eluant]. Multiple, slow recrystallizations from cyclohexane/hexanes provided a white, crystalline solid: mp 68-70 °C; ¹H NMR (CDCl₃) δ 1.52 (s, 9 H), 1.63 (d, 3 H, J = 6.1 Hz), 2.2-2.8 (m, 6 H), 3.21 (q, 1 H, J = 6.1 Hz), 4.2-4.4 (m, 2 H), 4.74 (s, 1 H), 7.2-8.1 (m, 5 H); IR (NaCl, neat) 1785, 1750, 1730 cm⁻¹; mass spectrum [Cl (NH₃)], m/e 583 (M⁺ + H⁺), 483 [(M⁺ + H⁺) - (CO₂/Bu - H)]. Anal. Calcd for C₂₅H₂₇NO₅Br₂: C, 51.66; H, 4.68; N, 2.41. Found: C, 51.83; H, 4.80; N, 2.34. Crystal data: space group PI; a = 10.858 (2) Å, b == 11.128 (3) Å, c = 12.211 (3) Å, $\alpha = 107.50$ (2)°, $\beta = 107.80$ (2)°, $\gamma = 101.44$ (2)°; R = 0.040, $R_w = 0.044$.

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Supplementary Material Available: Detailed experimental section for compounds 22b-d, 23b-d, 14b-d, 28c, 29c, 30c, and 31c; experimental details of the X-ray structure determination, crystallographic computations, and a table of bond lengths and angles for 32d (12 pages). Ordering information is given on any current masthead page.