Oxidative Free-Radical Cyclization as a Method for Annulating β-Lactams: Syntheses of Functionalized Carbacephams

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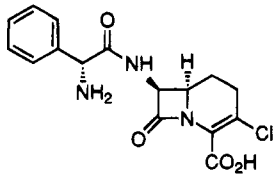
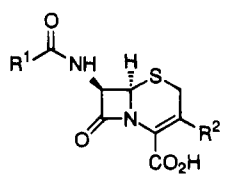


1
loracarbef
(a carbacephem)



2
cephems

One area of interest in our research group is the development of synthetic methodology for the preparation of β-lactam-containing compounds, *e.g.*, antibiotics[1] and β-lactamase inhibitors.[2] We are particularly motivated in this research area due to the recent appearance of strains of pathogens that are no longer susceptible to the antibiotics that have been used against them.[3] This threat to the well-being of mankind necessitates the development of new medicinal agents. In addition to developing β-lactamase inhibitors for coadministration with antibacterial agents,[2,4] and developing siderophore-delivered antimicrobial agents (new "magic bullets"),[5] we are also pursuing the development of structurally-modified antibiotics that may possess enhanced activity against both the new and old strains of pathogens. In the area of antibacterial agents, we chose loracarbef (**1**, LY163892/KT3777)[6] and analogues as general targets. Loracarbef (**1**) is the first example of the new class of antibiotics called the carbacephems to be marketed (Lorabid, Eli Lilly & Co., Inc.). Carbacephems are the carba-dethia analogues of the cephems **2** (commonly called cephalosporins) and are not degraded as rapidly as the cephems.[7]

Our synthetic approach to the carbacephem system is to form the β-lactam ring first, followed by formation of the second ring. Numerous methods for preparing bicyclic β-lactams by annulating monocyclic β-lactams have been reported.[7c,8] Many of the reported methods involve formation of the C-3–C-4 cepham bond (or the corresponding C-2–C-3 penam bond), some examples being reductive free-radical cyclization,[9] aldol cyclization,[10,11] intramolecular Wittig-type reactions,[12] and directed-Dieckmann condensations.[6c,13] (The latter reaction is a particularly attractive method for preparing the 3-hydroxycarbacephem precursor to loracarbef (**1**), as has been reported.[6c,13]) Various annulation methods that form other bonds of the second ring also have been reported,[8] the most notable being Merck's carbene insertion[14] and Wasserman's tricarbonyl[15] methods, both of which form the C-4–N-5 bond.

We noted the oxidative free-radical cyclization chemistry reported recently by Snider[16] and recognized that related reactions could potentially offer an attractive alternative to the above procedures for annulating β-lactams. The advantages of employing free-radical chemistry in organic synthesis have been demonstrated.[17] Besides the difference in ring-size selectivities of radical *vs* ionic cyclizations, the application of radical chemistry to organic synthesis is particularly attractive due to the large variety of functional groups tolerated. We found Snider's *oxidative* free-radical chemistry particularly attractive for our synthetic application as it generates products in higher oxidation states (*i.e.*, more functionalized) from starting materials in lower oxidation states (*i.e.*, less functionalized) than those in the reductive free-radical chemistry. We present here our recent results demonstrating the synthetic utility of applying the manganese(III) acetate-promoted oxidative free-radical cyclization chemistry to the synthesis of bicyclic β-lactams.[18]

This project required the development of a synthetic route to monocyclic *N*-malonyl β-lactams with a C-4 side chain possessing an unsaturated C-3′–C-4′ bond, as such substrates would possess the requisite functionality for

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(4) Clavulanic acid, for example, has found broad use as a β-lactamase inhibitor that is coadministered with antibiotics—for a leading reference, see: Brown, A. G.; Pearson, M. J.; Southgate, R. In *Comprehensive Medicinal Chemistry*; Hansch, C., Sammes, P. G., Taylor, J. B., Eds.; Pergamon Press: Oxford, 1990; Vol. 2, pp 662–671.

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(8) For a recent review of methods of annulating β-lactams, see: Kant, J.; Walker, D. G. In *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; VCH Publishers: New York, 1993; Chapter 3.

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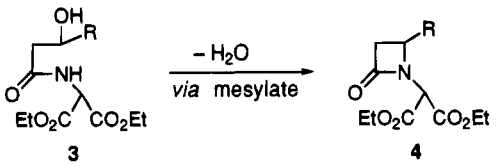
0022-3263/95/1960-6176$09.00/0

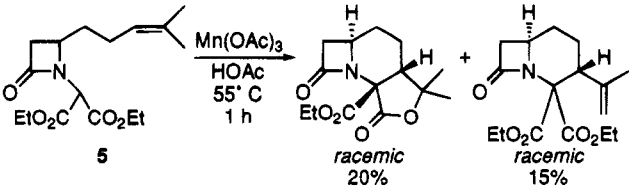
both the manganese(III) acetate-promoted oxidative free-radical cyclization chemistry (both a β-dicarbonyl functionality and an unsaturated carbon–carbon bond) and for the synthesis of appropriately functionalized carbacephems (incorporation of a glycine equivalent). Also, we desired to be able to incorporate a variety of side chains so that we could determine which unsaturated functionalities would afford synthetically useful results. Furthermore, when we began this project, we were unaware of anyone conducting $Mn(OAc)_3$-promoted oxidative free-radical chemistry with substrates possessing an α-acylamino substituent, such as in our proposed cyclization substrates.[19] As we were unsure of the effect that this perturbation would have upon the oxidative free-radical chemistry, we chose to proceed cautiously by employing β-lactams without C-3 amino substituents to avoid potential competing side reactions. Thus, we developed a six-step procedure for the preparation of C-3 desamino substrates **4** which allowed for the incorporation of various C-4 side chains. The key step in the synthesis of our substrates was the formation of the β-lactam ring by dehydrative cyclization of the corresponding β-hydroxy amide **3** *via* the mesylate.[11]



Our initial oxidative cyclization study was conducted with alkene **5**. As reported in detail elsewhere,[11] $Mn(OAc)_3$-promoted cyclization afforded two cyclized products in only 35% combined yield (Scheme 1). We then attempted the cyclization of an analogous alkyne. However, no cyclized products were obtained; instead, we obtained only noncyclized products formed by competitive processes. When compared with the result obtained with alkene **5**, which was also prone to the same competitive processes, this result indicated that the alkyne cyclization was less favored, presumably kinetically. Regardless of the precise controlling mechanism, we decided to redesign our substrate in such a fashion that the cyclization process would be more favorable, by introducing an appropriately-placed phenyl ring to stabilize the cyclized free-radical (**15**) and cationic (**16**) intermediates.[20]

Thus, we prepared styrene **12** in six steps from cinnamyl chloride, methyl acetoacetate (**6**), and diethyl aminomalonate (Scheme 2). $Mn(OAc)_3$-promoted oxidative cyclization of styrene **12** afforded 56–68% (1–7 mmol scale) of tricycle **13**, as a 3:1 mixture of diastereomers, and 13–15% of bicycle **14** (Scheme 3). Fractional recrystallization of tricycle **13** afforded pure samples of the major diastereomer, whose structure was confirmed by X-ray diffraction analysis of a single crystal.[21] Repetition of a 1 mmol scale reaction including 1 equiv of copper(II) acetate as co-oxidant[16] afforded identical yields of the same products, indicating that the intermediate benzylic free radical **15** is oxidized rapidly by Mn(III).

Scheme 1



These results demonstrate that annulation of relatively unfunctionalized β-lactams (*N*-malonyl β-lactams with unsaturated C-4 side chains) by oxidative free-radical cyclization to afford bicyclic β-lactams in an oxidized state is both an efficient process and a synthetically powerful transformation. Further elaboration of our interesting and functionally equivalent multicyclic products is currently under investigation. Our next task in this annulation study is to test this cyclization procedure with C-3 amino-substituted substrates, which would directly afford products possessing the complete antibiotic nucleus.

Experimental Section

Anhydrous THF was obtained by distillation from sodium benzophenone ketyl under a nitrogen atmosphere. Bulk grade EtOAc and Skellysolve B (referred to simply as "hexanes") were distilled before use. The drying of an organic solution over $MgSO_4$ followed by filtration is referred to simply as "dried". Removal of solvents at reduced pressure (*ca.* 20 mmHg) on a rotary evaporator is referred to simply as "concentrated". Flash column chromatography on silica gel is referred to simply as "chromatographed". NMR spectra were obtained in $CDCl_3$ at 300 MHz for ^1H and at 75 MHz for ^{13}C. Elemental analyses were performed by MHW Laboratories, Phoenix, AZ.

Methyl 3-oxo-7-phenyl-6-heptenoate (7)[22] was prepared by the method of Huckin and Weiler[23] using cinnamyl chloride to afford, after chromatography eluting with 5% → 15% EtOAc in hexanes, 27 g of a mixture whose major component was the desired ester **7**. A small portion was rechromatographed to afford a sample for characterization: IR (neat) 1745 (CO_2), 1715 (CO) cm^{-1}; ^1H NMR δ 2.51 (q, J = 7.0 Hz, 2 H), 2.74 (t, J = 7.2 Hz, 2 H), 3.48 (s, 2 H), 3.74 (s, 3 H), 6.18 (dt, J = 15.8, 6.8 Hz, 1 H), 6.42 (dt, J = 15.8, 1.3 Hz, 1 H), 7.17–7.23 (m, 1 H), 7.25–7.37 (m, 4 H); ^{13}C NMR δ 26.5, 42.2, 48.8, 52.1, 125.8, 127.0, 128.1, 128.3, 130.8, 137.1, 167.4, 201.7; HRMS (EI) calcd for $C_{14}H_{16}O_3$ (M^+) 232.1099, found 232.1097.

Methyl 3-Hydroxy-7-phenyl-6-heptenoate (8). To a stirred solution of ~27 g (~116 mmol) of impure β-keto ester **7** in 300 mL of MeOH at −60 °C in a flask capped with a drying tube ($CaSO_4$) was added 1.36 g (36 mmol) of $NaBH_4$. The reaction temperature was allowed to rise to 10 °C over 1.5 h, at which time no remaining starting material was detected by TLC analysis. The reaction was quenched by the addition of 100 mL of saturated NaCl, and then most of the MeOH was removed at reduced pressure on a rotary evaporator. The resulting aqueous mixture was diluted with H_2O and then extracted twice with EtOAc, washing each extract with H_2O and saturated NaCl. The extracts were combined, dried, concentrated, and then chromatographed, eluting with 20% → 30% EtOAc in hexanes to afford 13.7 g (32% two-step) of slightly impure β-hydroxy ester **8** as a clear, yellow liquid. A small portion was rechromatographed to afford a pure sample for characterization: IR (neat) 3450 br (OH), 1730 (CO), 1438 cm^{-1}; ^1H NMR δ 1.54–1.79 (m, 2 H), 2.25–2.42 (m, 2 H), 2.46 (dd, J = 16.6, 8.7 Hz, 1 H), 2.55 (dd, J = 16.5, 3.5 Hz, 1 H), 2.97 (d, J = 4.1 Hz, 1 H), 3.72 (s, 3 H), 4.08 (m, 1 H), 6.22 (dt, J = 15.8, 6.9 Hz, 1 H), 6.43 (d, J = 15.9 Hz, 1 H), 7.17–7.23 (m, 1 H), 7.25–7.38 (m, 4 H); ^{13}C NMR

(19) Later, Citterio *et al.* reported their study of $Mn(OAc)_3$-promoted intermolecular reactions of *N*-acylaminomalonate derivatives with olefins: Citterio, A.; Marion, A.; Maronati, A.; Nicolini, M. *Tetrahedron Lett.* **1993**, *34*, 7981.

(20) For an example of enhanced (reductive) free-radical cyclization yields in the annulation of monocyclic β-lactams by stabilization of the cyclized free-radical intermediate by a phenyl group, see ref 9a.

(21) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.

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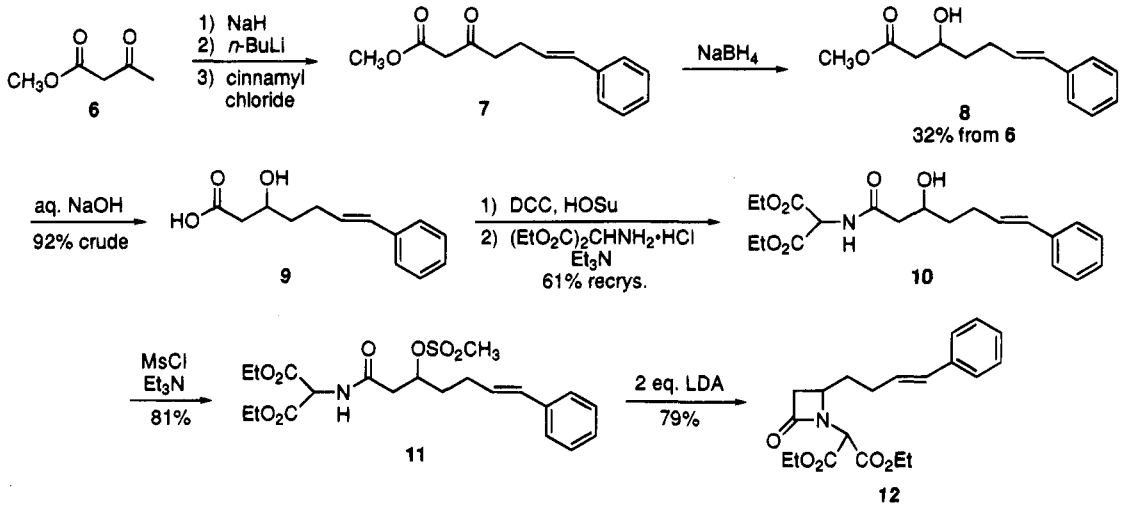
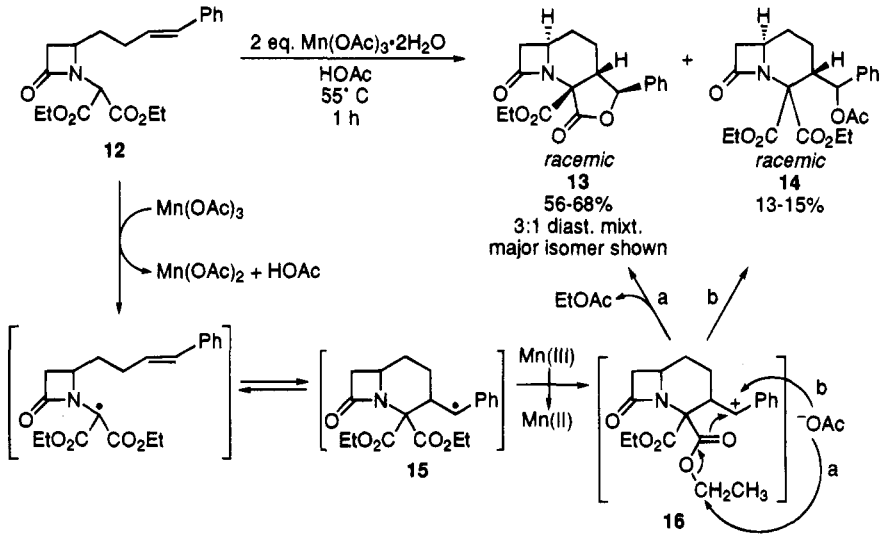
Scheme 2



Scheme 3



δ 28.8, 35.9, 41.1, 51.5, 67.2, 125.7, 126.7, 128.3, 129.6, 130.2, 137.4, 173.0; HRMS (EI) calcd for $C_{14}H_{18}O_3$ (M^+) 234.1256, found 234.1252.

3-Hydroxy-7-phenyl-6-heptenoic Acid (9). To a stirred solution of 13.3 g (57 mmol) of methyl ester **8** in 70 mL of THF was added 70 mL of 1 M NaOH. After being stirred for 1 h at 25 °C, the mixture was extracted with Et_2O to remove any neutral or basic contaminants. The aqueous phase was acidified by the addition of 6 M HCl and then extracted with EtOAc. The organic phase was dried and then concentrated to afford 11.5 g (92%) of crude acid **9**, as a pale yellow waxlike solid. A small portion was recrystallized from EtOAc–hexanes to afford colorless needles for characterization: mp 71–73 °C; IR (KBr) 3280 m, br (OH), 2900 w, br (CO_2H), 1685 (CO) cm^{-1}; ^1H NMR δ 1.57–1.81 (m, 2 H), 2.25–2.47 (m, 2 H), 2.52 (dd, J = 16.7, 8.5 Hz, 1 H), 2.61 (dd, J = 16.6, 3.6 Hz, 1 H), 4.05–4.15 (m, 1 H), 4.4 (br, CO_2H), 6.21 (dt, J = 15.8, 6.9 Hz, 1 H), 6.43 (d, J = 15.9 Hz, 1 H), 7.17–7.23 (m, 1 H), 7.25–7.37 (m, 4 H); ^{13}C NMR δ 28.9, 35.8, 41.1, 67.5, 125.9, 126.9, 128.4, 129.5, 130.5, 137.4, 177.4. Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.73; H, 7.12.

***N*-(Bis(ethoxycarbonyl)methyl)-3-hydroxy-7-phenyl-6-heptenamide (10).** To a flask containing 9.94 g (45 mmol) of β-hydroxy acid **9**, 6.23 g (54 mmol) of *N*-hydroxysuccinimide (HOSu), and 11.2 g (54 mmol) of DCC under N_2 was added 150 mL of anhyd THF. After stirring for 16 h at 25 °C, the mixture was filtered through a pad of diatomaceous earth to remove the bulk of the DCU byproduct, the filtrate was concentrated, and the resulting residue was dissolved in 150 mL of DMSO. To this solution were added 11.45 g (54 mmol) of diethyl aminomalonate hydrochloride and 12.6 mL (90 mmol) of Et_3N, and then the flask was capped with a drying tube ($CaSO_4$). After stirring for 16 h at 25 °C, the mixture was diluted with EtOAc, washed with H_2O, 0.5 M HCl, H_2O, saturated $NaHCO_3$, and saturated NaCl, then dried, concentrated, and recrystallized from EtOAc-hexanes to afford in two batches 10.3 g (61%) of slightly contaminated β-hydroxy amide **10** as a white, amorphous (granular) solid. Some of the contaminant was removed by dissolving the product in CH_2Cl_2, filtering the solution through diatomaceous earth, and then concentrating the filtrate to afford a white, amorphous (not granular) solid which was used for characterization. Numerous attempts to recrystallize this product proved futile, producing only floculous suspensions: mp 68–71 °C; IR (KBr) 3495 (OH), 3315 (NH), 1746 (CO_2), 1648 (CON) cm^{-1}; ^1H NMR δ 1.30 (t, J = 7.1 Hz, 6 H), 1.57–1.81 (m, 2 H), 2.25–2.45 (m, 2 H), 2.42 (dd, J = 15.1, 8.6 Hz, 1 H), 2.52 (dd, J = 15.1, 3.1 Hz, 1 H), 3.43 (d, J = 3.8 Hz, 1 H), 4.02–4.14 (m, 1 H), 4.20–4.38 (m, 4 H), 5.16 (d, J = 7.0 Hz, 1 H), 6.22 (dt, J = 15.8, 6.9 Hz, 1 H), 6.43 (d, J = 15.9 Hz, 1 H), 6.86 (br d, J = 6.9 Hz, 1 H), 7.16–7.22 (m, 1 H), 7.26–7.36 (m, 4 H); ^{13}C NMR δ 13.8, 28.9, 36.2, 42.4, 56.3, 62.54, 62.58, 67.9, 125.8, 126.8, 128.3, 129.8, 130.3, 137.5, 166.1, 166.3, 172.0; HRMS (EI) calcd for $C_{20}H_{27}NO_6$ (M^+) 377.1838, found 377.1845.

***N*-(Bis(ethoxycarbonyl)methyl)-3-(methylsulfonoxy)-7-phenyl-6-heptenamide (11).** To a stirred suspension of 1.00 g (2.7 mmol) of β-hydroxyamide **10** in 10 mL of anhyd THF at 0 °C under N_2 was added 250 μL (3.2 mmol) of MsCl, followed by 560 μL (4.0 mmol) of Et_3N. After the mixture was stirred for 2 h at 0 °C, most of the THF was removed at reduced pressure on a rotary evaporator and the residue was diluted with EtOAc, washed with H_2O, 0.5 M HCl, H_2O, saturated $NaHCO_3$, and saturated NaCl, then dried, concentrated, and chromatographed,

eluting with 40% EtOAc in hexanes to afford 987 mg (81%) of mesylate **11** as a white amorphous solid. A portion was recrystallized from CH_2Cl_2–hexanes to afford a white, cotton-like crystalline solid for characterization: mp 90–92 °C; IR (KBr) 3330 (NH), 1748 (CO_2), 1736, 1640 (CON), 1364, 1177 cm^{-1}; ^1H NMR δ 1.30 (t, J = 7.2 Hz, 6 H), 1.90–2.12 (m, 2 H), 2.36 (q, J = 7.2 Hz, 2 H), 2.74 (d, J = 5.9 Hz, 2 H), 3.05 (s, 3 H), 4.19–4.38 (m, 4 H), 5.08–5.17 (m, 1 H), 5.13 (d, J = 6.8 Hz, 1 H), 6.18 (dt, J = 15.9, 6.8 Hz, 1 H), 6.44 (d, J = 15.9 Hz, 1 H), 6.71 (br d, J = 6.6 Hz, 1 H), 7.17–7.24 (m, 1 H), 7.25–7.37 (m, 4 H); ^{13}C NMR δ 13.9, 28.2, 34.3, 38.1, 40.6, 56.4, 62.6, 78.9, 125.9, 127.0, 128.4, 130.9, 137.2, 166.0, 168.5. Anal. Calcd for $C_{21}H_{29}NO_8S$: C, 55.37; H, 6.42; N, 3.07. Found: C, 55.29; H, 6.47; N, 3.14.

1-(Bis(ethoxycarbonyl)methyl)-4-(4-phenylbut-3-en-1-yl)azetidin-2-one (12). To a stirred solution of 385 μL (2.8 mmol) of i-Pr_2NH in 3 mL of anhyd THF at 0 °C under argon was added 1.30 mL (2.5 mmol) of 1.9 M n-BuLi in hexanes. After stirring for 5 min, this LDA solution was transferred by cannula to another flask containing a stirred solution of 500 mg (1.1 mmol) of mesylate **11** in 6 mL of anhyd THF at 0 °C under argon. The LDA flask was rinsed with an additional 1 mL of anhyd THF, and this was also transferred to the reaction flask. After stirring for 15 min at 0 °C, the reaction was quenched by the addition of 5 mL of 1 M HCl and the solution was diluted with H_2O and then extracted with EtOAc. The extract was washed with 0.5 M HCl until the aqueous phase remained strongly acidic (pH < 3), then washed with H_2O, saturated $NaHCO_3$, and saturated NaCl, dried, concentrated, and chromatographed, eluting with 30% EtOAc in hexanes to afford 314 mg (79%) of β-lactam **12**, as a clear, light yellow oil: IR (neat) 1769 (CON), 1750 (CO_2) cm^{-1}; ^1H NMR δ 1.301 (t, J = 7.1 Hz, 3 H), 1.306 (t, J = 7.1 Hz, 3 H), 1.64–1.78 (m, 1 H), 2.07–2.30 (m, 3 H), 2.72 (dd, J = 14.8, 2.7 Hz, 1 H), 3.14 (dd, J = 14.8, 5.2 Hz, 1 H), 4.05–4.16 (m, 1 H), 4.18–4.37 (m, 4 H), 5.18 (s, 1 H), 6.17 (dt, J = 15.8, 6.7 Hz, 1 H), 6.40 (d, J = 15.8 Hz, 1 H), 7.17–7.24 (m, 1 H), 7.26–7.35 (m, 4 H); ^{13}C NMR δ 13.8, 28.9, 32.6, 42.7, 53.3, 56.7, 62.2, 62.3, 125.8, 126.9, 128.3, 128.7, 130.6, 137.1, 164.9, 165.5, 167.2; HRMS (EI) calcd for $C_{20}H_{25}NO_5$ (M^+) 359.1733, found 359.1723.

$Mn(OAc)_3$-Promoted Oxidative Cyclization of β-Lactam 12. (Solutions were degassed (*i.e.*, deoxygenated) by bubbling N_2 through them for 20 min.) A degassed solution of 360 mg (1.0 mmol) of β-lactam **12** in 1.5 mL of HOAc was added by cannula to a degassed suspension of 594 mg (2.2 mmol) of $Mn(OAc)_3 \cdot 2H_2O$ in 7.0 mL of HOAc. Then a preheated oil bath was applied to heat the reaction mixture to approximately 55 °C. The starting material flask was rinsed with an additional 1.5 mL of HOAc, and after degassing the rinse was also added to the reaction mixture. After stirring at 55 °C for 1 h, the mixture was cooled briefly, diluted with H_2O, and then extracted twice with EtOAc. The extracts were washed several times each with H_2O, saturated $NaHCO_3$ (*CAUTION*! evolution of large amounts of CO_2 gas), and saturated NaCl, then combined, dried, concentrated, and chromatographed, eluting with 30% → 70% EtOAc in hexanes to afford 225 mg (68%) of tricycle **13** as a 3:1 mixture of diastereomers and 62 mg (15%) of bicycle **14**. Fractional recrystallization of tricycle **13** from EtOAc–hexanes afforded a pure sample of the major diastereomer, as colorless crystals, which was used for characterization, including structural determination by X-ray diffraction analysis of a single crystal.[21] Recrystallization of bicycle **14** from EtOAc–hexanes afforded colorless crystals for characterization.

(1S*,5R*,8S*,9S*)-1-(Ethoxycarbonyl)-9-phenyl-2-aza-10-oxatricyclo[6.3.0.0^{2,5}]undecane-3,11-dione (13): R_f 0.41 (7:3 EtOAc–hexanes); mp 157–159 °C (EtOAc–hexanes); IR (KBr) 1795 (CON), 1750 br (CO_2) cm^{-1}; ^1H NMR δ 1.04 (t, J = 7.2 Hz, 3 H), 1.46 (qm, J_q = ~12 Hz, 1 H), 1.65 (qm, J_q = ~13 Hz, 1 H), 2.15 (dq, J = 13.0, 2.8 Hz, 1 H), 2.44 (dm, J_d = 13.9 Hz, 1 H), 2.72 (dd, J = 15.0, 2.3 Hz, 1 H), 3.08 (dd, J = 12.3, 6.0 Hz, 1 H), 3.15 (dd, J = 15.0, 4.8 Hz, 1 H), 3.46 (dm, J_d = 11.3 Hz, 1 H), 3.79 (dq, J = 10.7, 7.2 Hz, 1 H), 3.93 (dq, J = 10.7, 7.2 Hz, 1 H), 5.30 (s, 1 H), 7.24–7.40 (m, 5 H); ^{13}C NMR δ (multiplicity of off-resonance decoupled ^{13}C NMR) 13.2 (q), 25.9 (t), 27.1 (t), 44.0 (t), 44.2 (d), 47.5 (d), 63.1 (t), 64.5, 82.2 (d), 124.4 (d), 128.2 (d), 128.4 (d), 136.9 (s), 163.7, 165.0, 169.5; HRMS (FAB) calcd for $C_{18}H_{20}NO_5$ (MH^+) 330.1341, found 330.1365; structure also determined by X-ray diffraction analysis of a single crystal.[21]

(3S*,6R*,9*)-1-Aza-2,2-bis(ethoxycarbonyl)-3-(1-(1-oxoethoxy)-1-phenyl)methyl-8-oxobicyclo[4.2.0]octane (14). (The stereochemistry at C-9 (the benzylic carbon) has not been determined.) **14**: R_f 0.51 (1:1 EtOAc–hexanes); mp 159–160 °C (EtOAc–hexanes); IR (KBr) 1767 (CON), 1750 (CO_2), 1734 (CO_2), 1228 cm^{-1}; ^1H NMR δ 1.15 (qd, J = 12.6, 4.3 Hz, 1 H), 1.31 (t, J = 7.2 Hz, 3 H), 1.34 (t, J = 7.2 Hz, 3 H), 1.80 (qd, J = 12.5, 2.9 Hz, 1 H), 1.88 (dq, J = 14.2, 3.6 Hz, 1 H), 2.08 (s, 3 H), 2.07–2.16 (m, 1 H), 2.44 (dd, J = 14.6, 1.7 Hz, 1 H), 2.53 (dd, J = 11.9, 3.7 Hz, 1 H), 3.15 (dd, J = 14.6, 4.9 Hz, 1 H), 3.95 (dq, J = 10.7, 7.2 Hz, 1 H), 3.93–4.02 (m, 1 H), 4.30 (dq, J = 10.7, 7.2 Hz, 1 H), 4.39–4.53 (m, 2 H), 6.12 (s, 1 H), 7.22–7.40 (m, 5 H); ^{13}C NMR δ 13.7, 13.8, 17.9, 21.0, 30.9, 44.4, 47.8, 48.3, 62.0, 62.8, 67.1, 73.4, 125.2, 127.5, 128.4, 140.3, 164.7, 165.8, 167.5, 169.0; HRMS (FAB) calcd for $C_{22}H_{28}NO_7$ (MH^+) 418.1866, found 418.1915.

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Supporting Information Available: ^1H and ^{13}C NMR spectra for compounds **8–14** (14 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from ACS; see any current masthead page for ordering information.

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