PREPARATION OF BETA-LACTAMS FROM BETA-HYDROXY AMIDES, AND ANNULATION OF N-MALONYL BETA-LACTAMS BY MANGANESE(III) ACETATE-PROMOTED FREE RADICAL CYCLIZATION AND BY ALDOL CYCLIZATION

Peter J. Crocker, Ulrika Karlsson–Andreasson, Bruce T. Lotz, and Marvin J. Miller*

Department of Chemistry and Biochemistry, College of Science, University of Notre Dame, Notre Dame, IN 46556, USA

Abstract—β-Lactams are formed from β-hydroxy amides by base-promoted cyclization of the β-methylsulfonoxyamide. In the system studied, this amide-based mesylate cyclization proceeded in high yields, whereas the analogous β-chloroamide afforded only the α,β-unsaturated amide. Also, two new methods of synthesizing carbacephams by annulation of malonate-substituted β-lactams were demonstrated. The first was a manganese(III) acetate-promoted oxidative free radical cyclization. The second was a spontaneous aldol cyclization of an intermediate aldehyde generated by ozonolysis of an alkene.

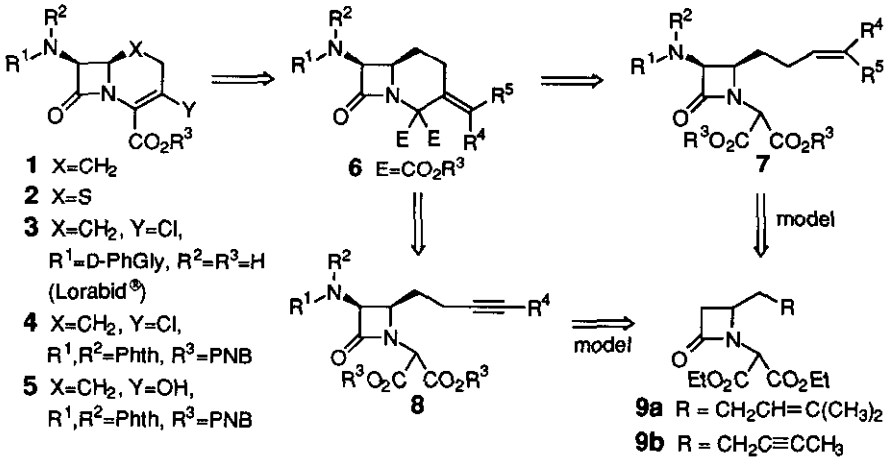
INTRODUCTION

One of the interests of our research group is the study of the application of new synthetic methods to the synthesis of β-lactam antibiotics and their analogues. Recently we have directed our synthetic efforts to the carbacephem class of bicyclic β-lactam antibiotics. The carbacephems (**1**) are the carba-dethia analogues of the cephems (**2**) (Figure 1). The cephem class of antibiotics is represented by the naturally occurring cephalosporins, isolated originally from the fungus Cephalosporium acremonium.[1] Structurally, the cephalosporins are the ring-expanded analogues of the penicillins, isolated originally from the fungus

Dedicated to Professor Rolf Huisgen on the occasion of his 75th birthday.

Penicillium notatum.[1a] The cephalosporins have been widely used to treat infections by bacteria that are resistant to the penicillins.[2] Likewise, the carbacephems have proven to be more effective per dose than the cephems as they are not degraded as readily.[3] Our eventual target is the carbacephalosporin Lorabid® (**3**, Eli Lilly & Co., Inc., LY163892/KT3777), a new commercially available, orally active antibiotic that is prepared by total synthesis.[4]

Figure 1



Our retrosynthetic analysis of Lorabid® targets the six membered ring initially, as we are already familiar with methods to form the four membered ring.[5] Recently Snider has published a series of papers regarding ring formation by oxidative free radical cyclization of 1,3-dicarbonyl-ω-alkenes upon treatment with manganese(III) acetate to afford, among other things, exocyclic olefins.[6] Or alternatively, Snider also has shown that he can generate such exocyclic olefins by a $Mn(OAc)_3$-promoted free radical cyclization of 1,3-dicarbonyl-ω-alkynes in an oxidatively neutral process by a net hydrogen transfer cyclization.[6b,c] We decided to apply this chemistry to our synthesis of carbacephalosporins as a potentially useful alternative to known methods of annulation of β-lactams.[7] There is precedent for reductive free radical annulations of β-lactams,[8] thus demonstrating the feasibility of free radical annulations of β-lactams to form the 4,6-fused bicyclic ring system. However, such procedures are not as synthetically attractive as the $Mn(OAc)_3$-promoted procedure as they typically require more complex (i.e., more functionalized) substrates, afford products in a

lower oxidation state (i.e., less functionalized[9]), and employ toxic[10] Bu_3SnH as the reducing reagent which frequently gives rise to purification difficulties.[11]

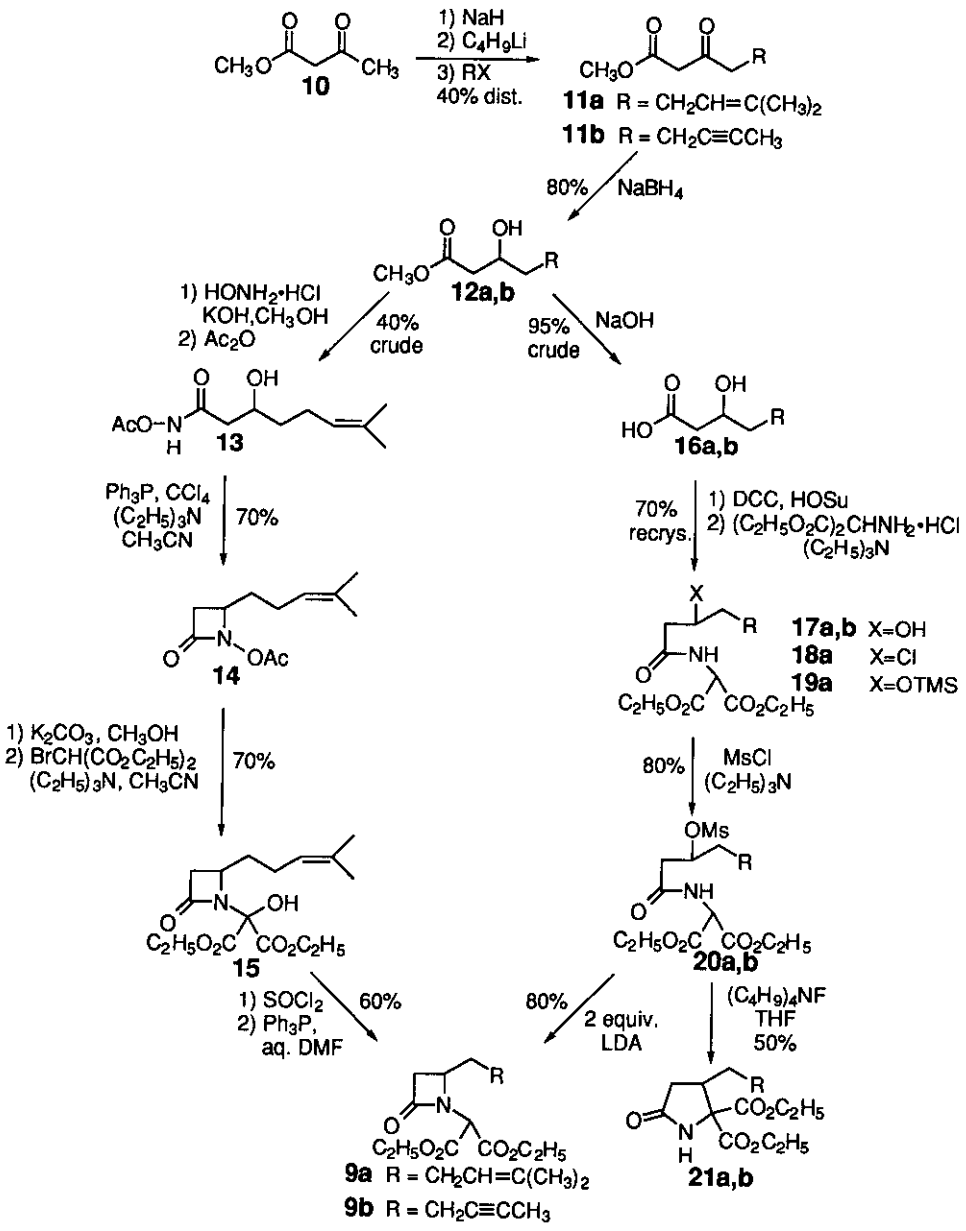
To arrive at our proposed cyclization product, it is necessary to proceed a couple of steps retrosynthetically from Lorabid (**3**). Lorabid (**3**) has been prepared from vinyl chloride (**4**), which has been prepared from the corresponding alcohol (**5**), the enol tautomer of a ketone.[4c] Next we envisioned the decarboxylation of a malonate species and oxidative cleavage of an olefin to afford, retrosynthetically, bicyclic β-lactam (**6**) which possesses an exocyclic olefin bond adjacent to a malonate system. This was our target for the $Mn(OAc)_3$-promoted free radical cyclization chemistry. Application of Snider's procedures to alkene (**6**) afforded, retrosynthetically, alkene (**7**) and alkyne (**8**). To test our hypothesis, we first needed to design and prepare the substrates for the cyclization studies. For the purposes of our initial cyclization studies, we chose to prepare racemic, desamino model substrates as this would facilitate the substrate syntheses and would avoid any potential functional group incompatibilities. As Snider[6a,b] and Bachi[8] reported that the undesired 7-endo cyclization mode could be inhibited by including terminal substituents on the unsaturated bonds, we designed two substrates (**9a**) and (**9b**), both incorporating terminal methyl substituents to direct the cyclization of our substrates to the desired 6-exo mode. (Bachi has observed that free radical annulations of β-lactams occur preferentially by the [6- and 7-] endo mode "in the absence of otherwise directing groups."[8d])

RESULTS AND DISCUSSION

Substrate syntheses

We prepared alkene substrate (**9a**) initially via a route utilizing the facile cyclization of β-hydroxy hydroxamates to β-lactams as reported from our labs previously.[12] This synthesis began with the γ-alkylation[13] of methyl acetoacetate (**10**) with prenyl bromide to afford β-keto ester (**11a**)[14] (*Figure 2*). Selective reduction of the ketone was performed with $NaBH_4$ to give racemic β-hydroxy ester (**12a**).[15] (β-Keto esters can be reduced asymmetrically,[16] e.g., by catalytic hydrogenation with single enantiomers of Ru-BINAP.[17]) Hydroxaminolysis of ester (**12a**) followed by quenching with Ac_2O afforded β-hydroxy hydroxamate (**13**), which was cyclized to *N*-acetoxy-β-lactam (**14**) upon treatment with $Ph_3P/CCl_4/Et_3N$ in MeCN.[12b] Deprotection of *N*-acetoxy-β-lactam (**14**) with K_2CO_3/MeOH[12b] followed by alkylation with diethyl bromomalonate and in situ base-catalyzed rearrangement gave carbinolamine (**15**).[18]

Figure 2


1) NaH
2) C4H9Li
3) RX
40% dist.
10
11a R = CH2CH=C(CH3)2
11b R = CH2C≡CCH3
80% NaBH4
12a,b
1) HONH2•HCl
KOH,CH3OH
2) Ac2O
40% crude
95% crude
NaOH
13
16a,b
Ph3P, CCl4
(C2H5)3N
CH3CN
70%
14
70% recrys.
1) DCC, HOSu
2) (C2H5O2C)2CHNH2•HCl
(C2H5)3N
17a,b X=OH
18a X=Cl
19a X=OTMS
1) K2CO3, CH3OH
2) BrCH(CO2C2H5)2
(C2H5)3N, CH3CN
70%
15
80% MsCl
(C2H5)3N
20a,b
1) SOCl2
2) Ph3P,
aq. DMF
60%
80%
2 equiv.
LDA
(C4H9)4NF
THF
50%
9a R = CH2CH=C(CH3)2
9b R = CH2C≡CCH3
21a,b

Dehydroxylation of carbinolamine (**15**) was accomplished by conversion to the corresponding chloride with $SOCl_2$,[19] followed by reduction with Ph_3P in buffered aqueous DMF[20] to afford alkene (**9a**) for the planned cyclization studies.

While the above "hydroxamate" route did provide alkene substrate (**9a**), thus allowing initiation of preliminary cyclization studies, this route proceeded in only moderate overall yield (4%, unoptimized) and via several intermediates of limited hydrolytic and thermal stability. Thus, an alternate route to β-lactam (**9a**) via the corresponding β-hydroxy amide (**17a**) was attempted. Conversion of a β-hydroxy amide to a β-lactam is "simply" a dehydration, yet it is in competition with other dehydrative processes—namely, elimination to an α,β-unsaturated amide and, in the present malonate-bearing substrate, cyclization to a γ-lactam. Previously both we[21] and others[22] have shown that such a dehydrative cyclization of β-hydroxy amides to β-lactams could be performed in certain cases using the Mitsunobu reagent as the dehydrating agent. Preparation of the requisite β-hydroxy amide (**17a**) was straightforward. After preparing β-hydroxy ester (**12a**) by the method described above, simple hydrolysis to carboxylic acid (**16a**)[15a,23] followed by activation[24] and then coupling with diethyl aminomalonate afforded β-hydroxy amide (**17a**).

With large quantities of β-hydroxy amide (**17a**) readily available, several procedures to dehydratively cyclize it to β-lactam (**9a**) were tested. Treatment of β-hydroxy amide (**17a**) to Mitsunobu conditions,[25] using DIAD/Ph_3P rather than DEAD/Ph_3P,[21a] afforded only ~15% of β-lactam (**9a**). The major product (~60%) from this procedure was the corresponding α,β-unsaturated amide. We also tried this procedure with triethyl phosphite rather than with triphenylphosphine, but no improvement in yield or product ratio was obtained.[22b] Treatment of β-hydroxy amide (**17a**) with $Ph_3P/CCl_4/Et_3N$ in MeCN (a procedure used to cyclize β-hydroxy hydroxamates to β-lactams,[12] as demonstrated by the conversion of **13** to **14**) afforded only β-chloroamide (**18a**), indicating that chloride ion substitution[26] is faster than the desired cyclization to the β-lactam, and also faster than the cyclization to the γ-lactam (vide infra). An attempt to cyclize β-chloroamide (**18a**) to the β-lactam by treatment with two equivalents of LDA gave only the α,β-unsaturated amide.[27]

Treatment of β-hydroxy amide (**17a**) with excess sulfuryl diimidazole (SO_2Im_2) and Bu_4NF in THF for one week afforded 18% of β-lactam (**9a**), 8% of α,β-unsaturated amide, and 74% of recovered starting material.[28]

This was an interesting result as the ratio of cyclization to the β-lactam versus simple elimination to the α,β-unsaturated amide was 2:1, respectively, whereas the ratio was unfavorably 1:4 with the Mitsunobu reagent. Comparable yields of β-lactam and α,β-unsaturated amide were obtained overnight when the substrate was pretreated with one equivalent of NaH to generate the more reactive alkoxide ion, but much less of the unreacted starting material was recovered, presumably due to polyesterification. When silyl ether (**19a**) was treated with SO_2Im_2/Bu_4NF, only deprotected β-hydroxy amide (**17a**) was obtained. Despite the reasonable yields of β-lactams obtained by Hanessian when certain serine amides were treated with SO_2Im_2 and bases, we were unable to improve our yields with this reagent. Perhaps this was due to the fact that our substrate was a less reactive secondary alcohol, as opposed to the primary alcohol of serine.

As we were obtaining a favorable product ratio with SO_2Im_2 and an unfavorable product ratio with the Mitsunobu reagent, it appeared that we should try the cyclization reaction via sulfonate intermediates as opposed to phosphonium ion intermediates. The reactions with SO_2Im_2 appeared to suffer low conversion yields due to slow formation of the sulfonate intermediate. Consequently we prepared mesylate (**20a**) instead, as mesylates are readily formed from secondary alcohols.[29] Treatment of mesylate (**20a**) with excess Bu_4NF in THF, as in the SO_2Im_2 procedure, afforded not β-lactam (**9a**), but instead gave γ-lactam (**21a**) (56%). Actually this is not a truly unexpected result, but just further emphasizes the unusual formation of the β-lactam when using the Mitsunobu reagent or SO_2Im_2/Bu_4NF. Finally, as the formation of the γ-lactam could occur via the malonate anion, we decided to try to form the β-lactam by the selective cyclization of the dianion of the mesylate. Gratifyingly, treatment of mesylate (**20a**) with two equivalents of LDA afforded the desired β-lactam (**9a**) in 80% post-chromatographic yields on gram scale. This was especially noteworthy since the dianion of chloride (**18a**) eliminated to the α,β-unsaturated amide. An attempt to substitute NaH for LDA afforded only γ-lactam (**21a**) from mesylate (**20a**). Thus, by choice of reagent, either the γ- or β-lactam could be selectively formed from the mesylate. This amide-based[30] mesylate cyclization constitutes a synthetically useful procedure for preparing β-lactams from β-hydroxy amides when the hydroxyl group is attached to a secondary carbon, a class of cyclization that has only limited precedent.[21b,22a,31] We are aware of only two such amide-based sulfonate cyclizations being reported previously.[31] And while in both cases the sulfonate was secondary, E2 anti-elimination to the α,β-unsaturated amide was not possible as it was with our substrate. Thus, our result indicates that this procedure may be of more general utility than would be

suspected initially. This "amide" route is an attractive alternative to the "hydroxamate" route for preparing β-lactam substrate (**9a**) as it proceeds in higher overall yield, is simpler to perform, and proceeds via intermediates that are considerably more stable.

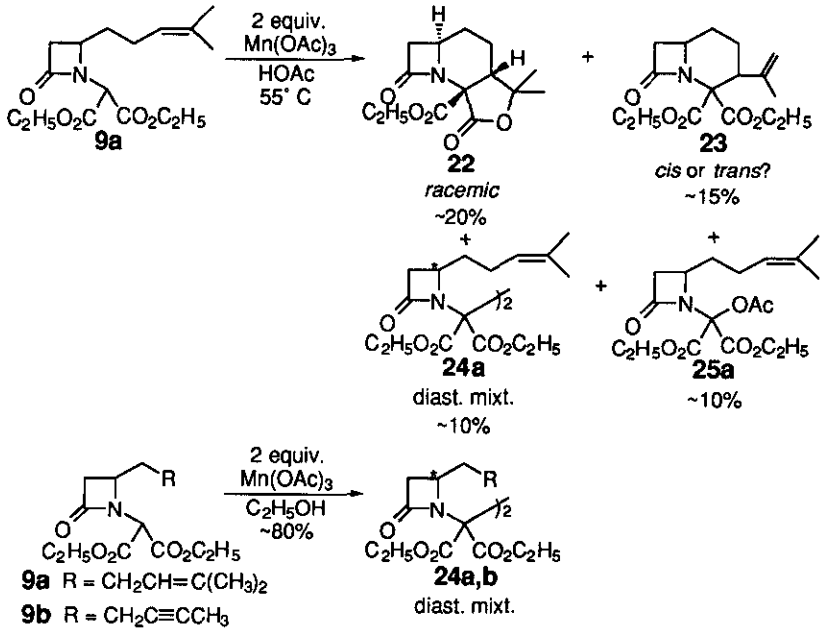
Manganese(III) acetate-promoted reactions

Treatment of alkene β-lactam (**9a**) with two equivalents of $Mn(OAc)_3$ in HOAc afforded a complex mixture of products, most of which were chromatographically separated (Figure 3). This reaction was conducted several times under various conditions, including 1) 55°C, 1 h; 2) 25°C, 20 h; 3) reflux (117°C), 10 min (all Mn^{3+} consumed—as indicated by the initial brown suspension changing to a clear solution); 4) 55°C, 1 h, with one equivalent of $Cu(OAc)_2$ included, but only minor variations in the product mixture composition were obtained. Apparently for substrate (**9a**) which cyclizes via a tertiary free radical intermediate, Mn^{3+} is a sufficient oxidizing agent such that the inclusion of Cu^{2+} as a co-oxidant has no observable effect. Snider showed that the inclusion of Cu^{2+} was necessary in his cyclization studies that proceeded via primary and secondary free radical intermediates, as Mn^{3+} does not oxidize these species rapidly enough to avoid free radical quenching by hydrogen atom abstraction from the medium.[6a] When the reaction was conducted in EtOH[6c] (25°C, 19 h), the only product obtained was malonyl dimer (**24a**) (85%). The two products obtained in greatest yields from the reactions conducted in HOAc were cyclized products (~35% combined yield), while the other two isolated products were not cyclized (~20% combined yield).

The major product from these reactions was tricyclic lactone (**22**) (~20%), which afforded crystals of sufficient quality for structural determination by X-ray diffraction measurements. Snider[6c] and Bertrand[32] also observed the formation of analogous lactones in several cases. These lactones are presumably formed by the intramolecular trapping of the nearby ester carbonyl oxygen by an intermediate cation, which is formed by oxidation of the corresponding free radical, with concommitant loss of an ethyl cation equivalent (presumably trapped by the solvent HOAc to form EtOAc). Recently, analogous bicyclic lactone forming reactions have been reported using titanium(IV) enolate-mediated cyclizations of ε-unsaturated malonate systems in the presence of molecular iodine to form cyclopentane-fused γ-lactones.[33] However, our attempts to apply this procedure to our alkene β-lactam substrate (**9a**) proved fruitless. Taguchi did report that his attempts to extend his procedure to the formation of cyclohexane-fused γ-lactones, such as ours, was unsuccessful.

The other cyclized product from these reactions was bicyclic alkene (**23**) (~15%), the olefinic isomer of our desired exocyclic alkene. Its formation is understandable (Hofmann vs. Zaitsev elimination), and analogous olefins were also obtained by Snider[6a] and Bertrand.[32] The formation of tricyclic lactone (**22**) and bicyclic alkene (**23**) demonstrated that preparation of carbacepham ring systems by $Mn(OAc)_3$-promoted oxidative free radical cyclizations is possible.

Figure 3



The two non-cyclized products obtained from the $Mn(OAc)_3$-promoted reactions of alkene β-lactam (**9a**) in HOAc were malonyl dimer (**24a**) (~10%, mixture of two racemic diastereomers, partially separable by chromatography) and malonyl acetate (**25a**) (~10%). Malonyl dimer (**24a**) is probably formed simply by free radical coupling. Cossy has recently reported a similar dimerization of a β-keto amide upon treatment with $Mn(OAc)_3$.[34] As mentioned previously, malonyl dimer (**24a**) was the only product obtained (85%) when this reaction was conducted in EtOH using either anhydrous $Mn(OAc)_3$[35] or the commercially available dihydrate. Malonyl acetate (**25a**) was readily identified as we had prepared a sample of this compound previously as a derivative of carbinolamine (**15**). It is presumably formed by solvent-trapping of an intermediate malonyl

cation (acyliminium ion) formed by oxidation of the malonyl free radical. Recently, Citterio also reported obtaining small amounts of malonyl acetates from his $Mn(OAc)_3$-promoted intermolecular reactions of *N*-acylaminomalonate derivatives with olefins; although with one particular substrate, diethyl *N*-cinnamoyl-aminomalonate, the malonyl acetate was the sole product (81%).[36]

A potential solution to the lack of product selectivity encountered with the alkene substrate above, but a solution that still employs the mild $Mn(OAc)_3$-promoted free radical cyclization chemistry, would be to change the substrate to the analogous alkyne (**9b**) similar to one of the alkyne-based, oxidatively neutral, free radical cyclizations demonstrated by Snider.[6b,c] By such a process, there would be no doubt as to the location of the resulting alkene's C-C double bond—it would be located where the alkyne's C-C triple bond had been. We prepared alkyne β-lactam (**9b**) by our "amide" route, merely by substituting 1-chloro-2-butyne[37] for the prenyl bromide employed in the alkene substrate synthesis. One noteworthy point is that the LDA-promoted, amide-based mesylate cyclization reaction to form the β-lactam ring performed well with this substrate also, affording 87% post-chromatographic yield on gram scale. However, attempted $Mn(OAc)_3$-promoted cyclization of alkyne β-lactam (**9b**) in EtOH, the solvent preferred by Snider for alkyne substrates,[6b,c] produced only malonyl dimer (**24b**) (76%, mixture of two racemic diastereomers, partially separable by chromatography), a result analogous to that obtained with alkene substrate (**9a**) when the same solvent was used. Substitution of AcOH as solvent, since this had afforded better results with alkene substrate (**9a**), afforded only malonyl dimer (**24b**) and malonyl acetate (**25b**). The lack of any cyclized products indicated that the radical cyclization of the alkyne substrate (6-exo-dig, with a fused β-lactam ring) was not as fast as that of the alkene substrate (6-exo-trig, with a fused β–lactam ring), which resulted in the malonyl radicals undergoing competing reactions only.

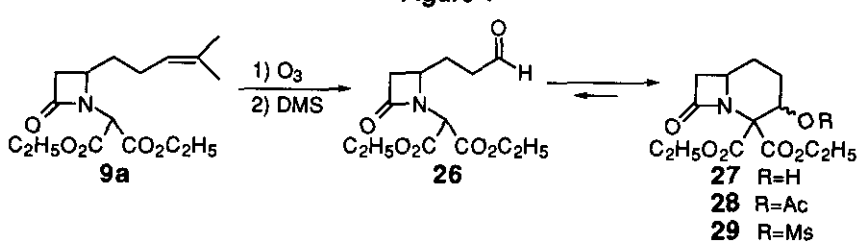
The results presented here suggest that further modifications of alkene (**9a**) may provide substrates capable of producing enhanced yields of important carbacephams related to compounds (**22**) and (**23**).

Aldol annulation

We also recognized that these same substrates might be converted to carbacephems by alternative reactions. Based on Hirata's work that demonstrated the spontaneous aldol cyclization of a malonate-substituted

β-lactam similar to alkene (**9a**), but with an aldehyde at the terminus of the C-4 side chain,[38] we reasoned that we could generate the same reactive situation by merely ozonolyzing alkene (**9a**), followed by a standard reductive workup to generate aldehyde (**26**) which would then cyclize spontaneously. This is indeed what occurred, affording a nearly quantitative crude yield of a mixture of epimeric alcohols (**27**) in equilibrium with a small amount of the uncyclized aldehyde (**26**) (Figure 4). Rather than attempting to characterize this dynamic system, we decided merely to prepare derivatives of the bicyclic isomers. Thus, we prepared the acetate (**28**, 40%) and the mesylate (**29**, 28%). Only one diastereomer was isolated in each case, although we did obtain a small amount of what we tentatively identified as the epimeric mesylate. However, as we were unsure of the conformation of the six membered rings, we could not assign the relative stereochemistry of their substituents. As Hirata converted his mesylate to the carbacephalosporin structure,[4b,38] the synthesis of our mesylate constitutes a formal synthesis of the desamino carbacephalosporin nucleus. And as α-amino substituents can be introduced into β-lactams,[39] or as we could incorporate the amino substituent into our acyclic substrates now that our desamino model studies have proven effective, this methodology can potentially be used for the total synthesis of carbacephalosporin antibiotics.

Figure 4



In summary, malonate-substituted β-lactams are readily prepared by a base-promoted, amide-based mesylate cyclization. These malonate-substituted β-lactams are versatile intermediates for the preparation of bicyclic β-lactams by oxidative cyclization or condensation reactions.

EXPERIMENTAL

Equipment and materials. Reagents were obtained from commercial sources and were used without further purification unless stated otherwise. Solutions of *n*BuLi in hexanes were titrated with diphenylacetic acid.[40] Anhydrous tetrahydrofuran (THF) was obtained by freshly distilling from sodium benzophenone ketyl under

nitrogen. Anhydrous acetonitrile (MeCN) and dichloromethane (CH_2Cl_2) were obtained by fresh distillation from calcium hydride under nitrogen. Triethylamine (Et_3N) and diisopropylamine (iPr_2NH) were distilled from calcium hydride under nitrogen and then stored under argon. Bulk grade ethyl acetate (EtOAc), Skellysolve B (referred to simply as "hexanes"), and dichloromethane (CH_2Cl_2) were distilled before use. The drying of an organic solution over anhydrous magnesium sulfate followed by filtration to remove the drying agent is referred to simply as "dried". Evaporation of a solvent first at reduced pressure (*ca.* 20 mm Hg) on a rotary evaporator and then at high vacuum (*ca.* 1 mm Hg) is referred to simply as "concentrated". Thin-layer chromatography (tlc) was conducted on silica gel 60 F_{254} (EM Science, 0.2 mm thickness, aluminum support) and was visualized with ultraviolet light (254 nm) and by dipping in 10% phosphomolybdic acid in ethanol and then heating. Flash column chromatography on silica gel 60 (EM Science, 230-400 mesh ASTM) is referred to simply as "chromatographed". Melting points (mp) were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared (ir) spectra were obtained on a Perkin Elmer 1420 ir spectrometer and were calibrated with the 1601 cm^{-1} band of polystyrene. Nuclear magnetic resonance (nmr) spectra were obtained in $CDCl_3$, unless stated otherwise, at 300 MHz for ^1H, with tetramethylsilane as an internal reference, and at 75 MHz for ^{13}C, referenced to solvent, on a General Electric GN-300 nmr spectrometer. Coupling constants (*J*) are reported in Hertz. Mass spectra (ms) using electron impact (EI) or chemical ionization (CI) were obtained on a Finnigan MAT-8400 mass spectrometer. Fast atom bombardment (FAB, xenon, 1:1 glycerol-(3-nitrobenzyl alcohol) matrix) mass spectra were obtained on a Jeol JMS-AX505HA mass spectrometer. Elemental analyses were performed by MHW Laboratories, Phoenix, AZ.

Methyl 7-methyl-3-oxo-6-octenoate (11a)[14] was prepared from methyl acetoacetate (**10**) by the procedure of Huckin and Weiler[13] using prenyl bromide to afford 12.6 g (43%) of β-keto ester (**11a**), as a clear, colorless liquid.

Methyl 3-oxo-6-octynoate (11b)[41] was prepared from methyl acetoacetate (**10**) by the procedure of Huckin and Weiler[13] using 1-chloro-2-butyne[37] to afford 8.20 g (40%) of β-keto ester (**11b**), as a clear, colorless liquid: bp 83°C (0.5 mm Hg); ir (neat) 1750, 1719 cm^{-1}; ^1H nmr δ 1.76 (t, *J*=2.6, 3H, CH_3), 2.42 (tq, *J*=7.2 and 2.6, 2H, $COCH_2C\underline{H}_2$), 2.75 (t, *J*=7.2, 2H, $COC\underline{H}_2CH_2$), 3.49 (s, 2H, $COCH_2CO$), 3.75 (s, 3H, CO_2CH_3); ^{13}C nmr δ 2.8, 12.6, 41.6, 48.3, 51.7, 75.7, 76.8, 167.0, 200.7; EIms *m/z* (rel. int.) 168 (M^+, 2), 153 (36), 95 (100); HREIms calcd for $C_8H_9O_3$ (M^+ - CH_3) 153.0552, found 153.0568.

Methyl 3-hydroxy-7-methyl-6-octenoate (12a).[15] To a stirred solution of 10.9 g (59 mmol) of β-keto ester (**11a**) in 130 ml of MeOH at -65°C in a flask capped with a drying tube ($CaSO_4$) was added 0.74 g (20 mmol) of $NaBH_4$. The temperature was allowed to rise to and maintained at -20° to -30°C for 1 h, after which time tlc analysis indicated that all the starting material had been reduced. The reaction was quenched while still at -25°C by the addition of 20 ml of 1 *M* HCl. The resulting solution was extracted with EtOAc. The extract was washed with H_2O and satd. NaCl, dried, concentrated, and then chromatographed eluting with 1:4 EtOAc-hexanes to afford 9.61 g (87%) of β-hydroxy ester (**12a**), as a clear, colorless liquid; ir (neat) 1739 cm^{-1}; ^1H nmr δ 1.40-1.63 (m, 2H, CHOHC$\underline{H}_2CH_2$), 1.62 (s, 3H, CH_3), 1.69 (d, *J*=1.0, 3H, CH_3), 2.11 (br q, *J*=7.5, 2H, C$\underline{H}_2$CH=), 2.42 (dd, *J*=16.4 and 8.7, 1H, $COCH_2$), 2.52 (dd, *J*=16.4 and 3.5, 1H, $COCH_2$), 2.87 (br s, 1H, OH), 3.72 (s, 3H, CO_2CH_3), 3.97-4.06 (m, 1H, C$\underline{H}$OH), 5.11 (tm, J_t=7.2, 1H, CH=); ^{13}C nmr δ 17.5, 23.9, 25.5, 36.4, 41.1, 51.5, 67.5, 123.5, 132.1, 173.2; HREIms calcd for $C_{10}H_{18}O_3$ (M^+) 186.1256, found 186.1253.

Methyl 3-hydroxy-6-octynoate (12b) was prepared from β-keto ester (**11b**) by the procedure used to prepare β-hydroxy ester (**12a**). The product was distilled to afford 6.41 g (77%) of β-hydroxy ester (**12b**), as a clear, colorless liquid: bp 81°C (0.15 mm Hg); ir (neat) 3470 br, 1736 cm^{-1}; ^1H nmr δ 1.54-1.75 (m, 2H, C$\underline{H}_2CH_2C\equiv$), 1.78 (t, *J*=2.6, 3H, CH_3), 2.26-2.35 (m, 2H, $CH_2C\equiv$), 2.45 (dd, *J*=16.5 and 8.6, 1H, $COCH_2$), 2.54 (dd, *J*=16.5 and 3.6, 1H, $COCH_2$), 2.66 (br, 1H, OH), 3.72 (s, 3H, OCH_3), 4.12-4.22 (m, 1H, C$\underline{H}$OH); ^{13}C nmr δ 3.0, 14.7, 35.3, 40.9, 51.4, 66.6, 75.7, 78.0, 172.7; EIms *m/z* (rel. int.) 170 (M^+, 3), 152 ($M^+ - H_2O$, 43), 97 (100); HREIms calcd for $C_9H_{12}O_2$ ($M^+ - H_2O$) 152.0837, found 152.0838.

***N*-Acetoxy-3-hydroxy-7-methyl-6-octenamide (13)** was prepared from β-hydroxy ester (**12a**) by the procedure of Miller *et al.*[12b] to afford 2.91 g (44% crude) of hydroxamate (**13**), as clear, light yellow crystals: mp 91-93°C (decomp., EtOAc-CH_2Cl_2-$CHCl_3$); ir (KBr) 1801, 1692, 1193 cm^{-1}; ^1H nmr δ 1.47-1.68 (m, 2H, C$\underline{H}_2CH_2CH$=), 1.63 (s, 3H, CH_3), 1.69 (d, *J*=1.1, 3H, CH_3), 2.12 (br q, *J*=7.3, 2H, C$\underline{H}_2$CH=), 2.24 (s, 3H, $COCH_3$), 2.38 (dd, *J*=14.9 and 8.7, 1H, $COCH_2$), 2.49 (dd, *J*=14.9 and 3.0, 1H, $COCH_2$), 2.91 (br s, 1H, OH), 4.00-4.12 (m, 1H, C$\underline{H}$OH), 5.12 (tm, J_t=7.2, 1H, CH=), 9.46 (br s, 1H, NH); ^{13}C nmr δ 17.6, 18.2, 24.1, 25.7, 36.7, 40.7, 68.2, 123.3, 132.6, 169.0, 169.9; FABms gave MH^+ 230; Anal. Calcd for $C_{11}H_{19}NO_4$: C, 57.63; H, 8.35; N, 6.11. Found: C, 57.59; H, 8.36; N, 6.11.

1-Acetoxy-4-(4-methyl-3-pentenyl)-2-azetidinone (14) was prepared from hydroxamate (**13**) by the procedure of Miller *et al.*[12b] using Ph_3P, CCl_4, and Et_3N in MeCN. After stirring for 11 h at 25°C, the

reaction solution was directly chromatographed eluting with 1:3 EtOAc-hexanes to afford 266 mg (77%) of *N*-acetoxy-β-lactam **14**, as a clear, colorless liquid; ir (neat) 1810, 1775, 1175, 1040 cm^{-1}; ^1H nmr δ 1.58-1.72 (m, 1H, $C\underline{H}_2CH_2$=), 1.60 (s, 3H, CH_3), 1.69 (s, 3H, CH_3), 1.81-1.93 (m, 1H, $C\underline{H}_2CH_2$=), 2.07 (br q, *J*=7.3, 2H, $C\underline{H}_2CH$=), 2.17 (s, 3H, $COCH_3$), 2.54 (dd, *J*=13.8 and 2.7, 1H, $COCH_2$-*cis*), 3.00 (dd, *J*=13.8 and 5.5, 1H, $COCH_2$-*trans*), 4.00-4.09 (m, 1H, NCH), 5.08 (tm, J_t=7.2, 1H, CH=); ^{13}C nmr δ 17.3, 17.7, 24.0, 25.3, 32.5, 37.9, 58.7, 122.4, 132.5, 164.1, 167.6; HREIms calcd for $C_{11}H_{17}NO_3$ (M^+) 211.1208, found 211.1219.

1-(Diethyl 2-hydroxymalonate-2-yl)-4-(4-methyl-3-pentenyl)-2-azetidinone (15). *N*-Acetoxy-β-lactam (**14**) (1.68 g, 7.95 mmol) was deprotected by the procedure of Miller *et al.*[12b] using Na_2CO_3 in aq. MeOH to afford the crude *N*-hydroxy-β-lactam, as a clear, yellow oil, which was used immediately in the next step. (Procedure[18] modified.) To a stirred solution of the crude *N*-hydroxy-β-lactam in 80 ml of anhyd. MeCN under argon was added activated 3Å molecular sieves, 1.4 ml (8.4 mmol) of diethyl bromomalonate, and 1.2 ml (8.6 mmol) of Et_3N. After stirring for 2 days at 25°C, the reaction mixture was filtered through Celite, washing with EtOAc, to remove a white precipitate (Et_3N•HBr) and the filtrate was concentrated, dissolved in 1:1 EtOAc-hexanes to afford a suspension (presumably more Et_3N•HBr), filtered through Celite, and the filtrate was concentrated and then chromatographed eluting with 1:1 EtOAc-hexanes to afford 1.93 g (74%, for 2 steps) of carbinolamine (**15**), as clear, yellow crystals: mp 62-65°C (EtOAc-hexanes); ir (KBr) 3270 br, 1777 (CON), 1759, 1733, 1224, 1205, 1129 cm^{-1}; ^1H nmr δ 1.316 (t, *J*=7.1, 3H, $CH_2C\underline{H}_3$), 1.320 (t, *J*=7.1, 3H, $CH_2C\underline{H}_3$), 1.53-1.65 (m, 1H, $C\underline{H}_2CH_2CH$=), 1.59 (br s, 3H, CH_3), 1.68 (br s, 3H, CH_3), 1.93-2.07 (m, 3H, $C\underline{H}_2CH_2CH$= and $C\underline{H}_2CH$=), 2.60 (dd, *J*=15.0 and 2.6, 1H, $COCH_2$-*cis*), 3.07 (dd, *J*=15.0 and 5.4, 1H, $COCH_2$-*trans*), 4.13-4.21 (m, 1H, NCH), 4.23-4.45 (m, 4H, 2 × $C\underline{H}_2CH_3$), 4.70 (s, 1H, OH), 5.09 (tm, J_t=6.9, 1H, CH=); ^{13}C nmr δ 13.71, 13.76, 17.5, 24.2, 25.5, 33.8, 42.3, 53.4, 63.0, 63.8, 80.4, 122.9, 132.3, 165.6, 166.5, 166.7; FABms gave MH^+ 328; Anal. Calcd (Eli Lilly & Co.) for $C_{16}H_{25}NO_6$: C, 58.70; H, 7.70; N, 4.28. Found: C, 58.78; H, 7.48; N, 4.20.

3-Hydroxy-7-methyl-6-octenoic acid (16a).[15a,23] To a stirred solution of 4.02 g (21.6 mmol) of β-hydroxy ester (**12a**) in 15 ml of THF was added 30 ml of 1 *M* NaOH. After stirring for 30 min at 25°C, the reaction solution was extracted with EtOAc, the extract was washed with 0.1 *M* NaOH. The aqueous wash was combined with the original aqueous phase. The mixture was acidified to pH 3 with 6 *M* HCl and extracted with EtOAc. The extract was washed with satd. NaCl, dried, and concentrated to afford 3.53 g (95%) of crude

β-hydroxy acid (**16a**), as a clear, pale yellow liquid that was used in the following reaction without further purification; ir (neat) 3300 br (OH), 3000 br (CO_2H), 1715 cm^{-1}; ^1H nmr δ 1.41-1.67 (m, 2H, $C\underline{H}_2CH_2C$=), 1.63 (s, 3H, CH_3), 1.69 (d, *J*=1.0, 3H, CH_3), 2.11 (s, 1H, OH), 2.12 (br q, *J*=7.5, 2H, $C\underline{H}_2CH$=), 2.48 (dd, *J*=16.6 and 8.6, 1H, $COCH_2$), 2.58 (dd, *J*=16.6 and 3.6, 1H, $COCH_2$), 4.00-4.10 (m, 1H, C<u>H</u>OH), 5.11 (tm, J_t=7.2, 1H, CH=), 7.2 (br "baseline" peak, CO_2H); ^{13}C nmr δ 17.5, 23.9, 25.6, 36.2, 41.1, 67.8, 123.3, 132.3, 177.2.

3-Hydroxy-6-octynoic acid (16b) was prepared from β-hydroxy ester (**12b**) by the procedure used to prepare β-hydroxy acid (**16a**) to afford 163 mg (107% crude—repetition on 40× scale afforded 97%) of crude β-hydroxy acid (**16b**), as a clear, colorless oil; ir (neat) 1709 cm^{-1}; ^1H nmr δ 1.58-1.77 (m, 2H, $C\underline{H}_2CH_2C\equiv$), 1.78 (t, *J*=2.6, 3H, CH_3), 2.11 (s, 1H, CHO<u>H</u>), 2.27-2.36 (m, 2H, $CH_2C\equiv$), 2.52 (dd, *J*=16.7 and 8.4, 1H, $COCH_2$), 2.61 (dd, *J*=16.6 and 3.8, 1H, $COCH_2$), 4.16-4.26 (m, 1H, C<u>H</u>OH); ^{13}C nmr δ 3.3, 14.9, 35.1, 40.9, 67.0, 76.3, 78.0, 177.0; EIms *m/z* (rel. int.) 138 (M^+ - H_2O, 21), 43 (100); CIms (isobutane) gave MH^+ 157; HREIms calcd for $C_8H_{10}O_2$ (M^+ - H_2O) 138.0681, found 138.0675.

***N*-(Diethyl malonate-2-yl)-3-hydroxy-7-methyl-6-octenamide (17a).** (General procedure.[24]) To a flask containing 972 mg (8.45 mmol) of *N*-hydroxysuccinimide (HOSu) and 1.75 g (8.48 mmol) of *N,N'*-dicyclohexylcarbodiimide (DCC) was transferred 1.21 g (7.04 mmol) of β-hydroxy acid (**16a**) with a total of 35 ml anhyd. THF. The flask was capped with a drying tube ($CaSO_4$) and the solution was stirred overnight. After stirring for 15 h at 25°C, the reaction suspension was filtered through Celite to remove the bulk of the precipitated *N,N'*-dicyclohexylurea by-product. The filtrate was concentrated, the residue was dissolved in EtOAc, washed with aq. 5% $NaHCO_3$ and satd. NaCl, dried, and concentrated to afford 1.81 g (95%) of crude succinimidyl ester, as a cloudy, yellow oil. This crude product was used directly in the next step.

To a stirred suspension of 1.78 g (6.61 mmol) of crude succinimidyl ester and 1.68 g (7.94 mmol) of diethyl aminomalonate hydrochloride in 25 ml of DMSO at 25°C was added 1.8 ml (13 mmol) of Et_3N. The flask was capped with a drying tube ($CaSO_4$) and the solution was stirred overnight. After stirring for 19 h at 25°C, the reaction solution was diluted with EtOAc, washed with H_2O, 0.5 *M* citric acid, H_2O, and satd. NaCl, dried, concentrated, chromatographed eluting with 2:3 EtOAc-hexanes, and then recrystallized from EtOAc-hexanes to afford in three crops 1.49 g (69%) of β-hydroxy amide (**17a**), as colorless crystals: mp 60-62°C (EtOAc-hexanes); ir (KBr) 3490, 3320, 1745, 1650 cm^{-1}; ^1H nmr δ 1.31 (t, *J*=7.2, 6H, 2 × $CH_2C\underline{H}_3$), 1.42-1.67 (m, 2H, $CHOHC\underline{H}_2CH_2$), 1.62 (s, 3H, CH_3), 1.69 (s, 3H, CH_3), 2.11 (br q, *J*=7.6, 2H, $C\underline{H}_2CH$=),

2.38 (dd, *J*=15.1 and 8.7, 1H, $COCH_2$), 2.49 (dd, *J*=15.2 and 3.0, 1H, $COCH_2$), 3.97-4.08 (m, 1H, CHOH), 4.19-4.37 (m, 4H, 2 × CH_2CH_3), 5.12 (tm, J_t=7.2, 1H, CH=), 5.17 (d, *J*=7.0, 1H, CHNH), 6.9 (br d, *J*=7, 1H, NH); ^{13}C nmr δ 13.8, 17.5, 23.9, 25.5, 36.6, 42.4, 56.3, 62.47, 62.51, 68.1, 123.5, 132.1, 166.1, 166.2, 172.1; HREIms calcd for $C_{16}H_{27}NO_6$ (M^+) 329.1838, found 329.1834; Anal. Calcd for $C_{16}H_{27}NO_6$: C, 58.34; H, 8.26; N, 4.25. Found: C, 58.20; H, 8.20; N, 4.31.

***N*-(Diethyl malonate-2-yl)-3-hydroxy-6-octynamide (17b)** was prepared from β-hydroxy acid (**16b**) by the procedure used to prepare β-hydroxy amide (**17a**), to afford the crude product as an off-white amorphous solid. Recrystallization from EtOAc afforded 761 mg of a by-product that was discarded. Then recystallization from EtOAc-hexanes afforded in two crops 7.98 g (69%) of β-hydroxy amide (**17b**), as a white amorphous solid: mp 75-77°C (EtOAc-hexanes); ir (KBr) 3300 br, 1752, 1734, 1654, 1542, 1180 cm^{-1}; ^{1}H nmr δ 1.308 (t, *J*=7.1, 3H, CH_2CH_3), 1.310 (t, *J*=7.1, 3H, CH_2CH_3), 1.56-1.80 (m, 2H, $CHOHCH_2CH_2$), 1.77 (t, *J*=2.6, 3H, $\equiv CCH_3$), 2.25-2.34 (m, 2H, $CH_2C\equiv$), 2.42 (app. dd, *J*=15.2 and 8.5, 1H, $COCH_2$), 2.51 (app. dd, *J*=15.2 and 3.2, 1H, $COCH_2$), 2.95 (br s, 1H, OH), 4.12-4.22 (m, 1H, CHOH), 4.20-4.37 (m, 4H, 2 × CH_2CH_3), 5.17 (d, *J*=7.0, 1H, CH), 6.95 (d, *J*=6.9, 1H, NH); ^{13}C nmr δ 3.2, 13.7, 14.8, 35.4, 42.1, 56.2, 62.41, 62.46, 67.3, 75.9, 78.1, 166.07, 166.15, 171.9; HREIms calcd for $C_{15}H_{23}NO_6$ (M^+) 313.1525, found 313.1513; Anal. Calcd for $C_{15}H_{23}NO_6$: C, 57.50; H, 7.40; N, 4.47. Found: C, 57.50; H, 7.21; N, 4.51.

***N*-(Diethyl malonate-2-yl)-3-chloro-7-methyl-6-octenamide (18a)** was prepared from β-hydroxy amide (**17a**) by the procedure of Slagle *et al.*,[26] then chromatographed eluting with 1:19 EtOAc-CH_2Cl_2 to afford 143 mg (68%) of β-chloroamide (**18a**), as a white, amorphous solid. (A parallel experiment that included one equivalent of Et_3N gave approximately the same result, based on tlc analysis.): mp 71-74°C (decomp.); ir (KBr) 3275, 1762, 1730, 1654, 1187 cm^{-1}; ^{1}H nmr δ 1.30 (t, *J*=7.1, 6H, 2 × CH_2CH_3), 1.62 (s, 3H, CH_3), 1.68 (br s, 3H, CH_3), 1.72-1.84 (m, 2H, CH_2CH_2CH=), 2.19 (br q, *J*=7.3, 2H, CH_2CH=), 2.74 (d, *J*=6.8, 2H, $COCH_2$), 4.19-4.39 (m, 5H, CHCl and 2 × CH_2CH_3), 5.07 (tm, J_t=7.2, 1H, CH=), 5.19 (d, *J*=6.9, 1H, CHN), 6.90 (br d, *J*=6.8, 1H, NH); ^{13}C nmr δ 13.8, 17.6, 24.7, 25.6, 37.9, 45.0, 56.4, 57.9, 62.50, 62.55, 122.3, 132.9, 166.0, 166.1 169.1; EIms *m/z* (rel. int.) 347 ($M^+(^{35}Cl)$, 20), 349 ($M^+(^{37}Cl)$, 7); HREIms calcd for $C_{16}H_{26}ClNO_5$ ($M^+(^{35}Cl)$) 347.1500, found 347.1499.

***N*-(Diethyl malonate-2-yl)-7-methyl-3-trimethylsilyloxy-6-octenamide (19a).** To a stirred solution of 305 mg (926 μmol) of alcohol (**17a**) in 10 ml of anhyd. THF was added 155 μl (1.12 mmol) of Et_3N and 140 μl (1.10 mmol) of TMSCl. After stirring for 22 h at 25°C, the reaction suspension was filtered through Celite,

the filtrate was concentrated, and then chromatographed eluting with 1:4 EtOAc-hexanes to afford 355 mg (95%) of silyl ether (**19a**), as a clear, colorless oil; ir (neat) 1761, 1744, 1677, 1253, 845 cm^{-1}; ^1H nmr δ 0.15 (s, 9H, $Si(CH_3)_3$), 1.29 (t, *J*=7.1, 3H, $CH_2C\underline{H}_3$), 1.30 (t, *J*=7.1, 3H, $CH_2C\underline{H}_3$), 1.54-1.67 (m, 2H, $C\underline{H}_2CH_2CH$=), 1.59 (s, 3H, CH_3), 1.68 (d, *J*=1.1, 3H, CH_3), 1.94-2.07 (br m, 2H, $C\underline{H}_2CH$=), 2.39 (dd, *J*=14.9 and 5.8, 1H, $COCH_2$), 2.52 (dd, *J*=14.9 and 4.3, 1H, $COCH_2$), 4.01-4.10 (m, 1H, CHOSi), 4.18-4.35 (m, 4H, 2 × $C\underline{H}_2CH_3$), 5.08 (tm, J_t=7.0, 1H, CH=), 5.16 (d, *J*=6.9, 1H, CHN), 7.39 (br d, *J*=6.8, 1H, NH); ^{13}C nmr δ 0.03, 13.9, 17.6, 24.1, 25.5, 36.6, 43.3, 56.3, 62.26, 62.32, 69.1, 123.5, 131.9, 166.21, 166.23, 170.8; HREIms calcd for $C_{19}H_{35}NO_6Si$ (M^+) 401.2234, found 401.2219.

***N*-(Diethyl malonate-2-yl)-3-methanesulfonoxy-7-methyl-6-octenamide (20a)** was prepared from β-hydroxy amide (**17a**) in anhyd. THF by the procedure of Crossland and Servis,[29] then chromatographed eluting with 2:3 EtOAc-hexanes to afford 347 mg (94%) of mesylate (**20a**), as a clear, colorless oil. (Repetition on a 15 g scale afforded 85% of mesylate (**20a**), as a pale yellow wax-like solid.); ir (neat) 1759, 1744, 1173 cm^{-1}; ^1H nmr δ 1.30 (t, *J*=7.1, 6H, 2 × $CH_2C\underline{H}_3$), 1.61 (s, 3H, CH_3), 1.68 (s, 3H, CH_3), 1.73-1.95 (m, 2H, $C\underline{H}_2CH_2CH$=), 2.10 (br q, *J*=7.6, 2H, $C\underline{H}_2CH$=), 2.70 (dd, *J*=15.1 and 4.8, 1H, $COCH_2$), 2.77 (dd, *J*=15.1 and 7.0, 1H, $COCH_2$), 3.03 (s, 3H, SO_2CH_3), 4.18-4.37 (m, 4H, 2 × $C\underline{H}_2CH_3$), 5.02-5.13 (m, 2H, CH= and CHOS), 5.15 (d, *J*=6.9, 1H, CHN), 7.06 (br d, *J*=6.9, 1H, NH); ^{13}C nmr δ 13.7, 17.5, 23.2, 25.4, 34.7, 37.9, 40.4, 56.3, 62.5, 79.4, 122.3, 132.7, 165.9, 168.7; HRFABms calcd for $C_{17}H_{29}NO_8S$ (MH^+) 408.1692, found 408.1697.

***N*-(Diethyl malonate-2-yl)-3-methanesulfonoxy-6-octynamide (20b)** was prepared from β-hydroxy amide (**17b**) in anhyd. THF by the procedure of Crossland and Servis[29] to afford the crude product as a light yellow crystalline solid. Recrystallization from EtOAc-hexanes afforded in two crops 7.18 g (79%) of mesylate (**20b**), as a colorless crystalline solid: mp 103-105°C (EtOAc-hexanes); ir (KBr) 1750, 1733, 1653, 1351, 1180 cm^{-1}; ^1H nmr δ 1.31 (t, *J*=7.2, 6H, 2 × $CH_2C\underline{H}_3$), 1.78 (t, *J*=2.5, 3H, ≡CCH_3), 1.88-2.11 (m, 2H, $C\underline{H}_2CH_2C$≡), 2.26-2.35 (m, 2H, CH_2C≡), 2.74 (dd, *J*=15.2 and 6.6, 1H, $COCH_2$), 2.82 (dd, *J*=15.2 and 5.1, 1H, $COCH_2$), 3.07 (s, 3H, SO_2CH_3), 4.19-4.38 (m, 4H, 2 × $C\underline{H}_2CH_3$), 5.13 (d, *J*=6.8, 1H, C<u>H</u>NH), 5.11-5.21 (m, 1H, CHOS), 6.75 (br d, *J*=6.7, 1H, NH); ^{13}C nmr δ 3.1, 13.7, 14.3, 33.4, 37.7, 40.2, 56.2, 62.4, 76.7, 76.9, 78.5, 165.8, 168.5; HRFABms calcd for $C_{16}H_{26}NO_8S$ (MH^+) 392.1379, found 392.1389.

Diethyl 4-(4-methyl-3-pentenyl)pyrrolidin-2-one-5,5-dicarboxylate (21a). To a stirred solution of 134 mg (329 μmol) of mesylate (**20a**) and 140 μl (1.0 mmol) of Et_3N in 1.0 ml of anhyd. THF under argon was added

1.0 ml (1.0 mmol) of 1.0 *M* Bu_4NF in THF. After stirring for 19 h at 25°C, the solution was diluted with H_2O, extracted with EtOAc, the organic phase was washed with satd. NaCl, dried, concentrated, and chromatographed eluting with 1:1 EtOAc-hexanes to afford 57 mg (56%) of γ-lactam (**21a**), as clear, colorless crystals. (A parallel reaction without Et_3N afforded approximately the same result, based on tlc analysis.): mp 95-97°C (EtOAc-hexanes); ir (KBr) 1754, 1737, 1708, 1298, 1288, 1218 cm^{-1}; ^1H nmr δ 1.16-1.29 (m, 1H, C$\underline{H}_2$CH$_2$CH=), 1.295 (t, *J*=7.1, 3H, CH$_2$C$\underline{H}_3$), 1.302 (t, *J*=7.1, 3H, CH$_2$C$\underline{H}_3$), 1.60 (s, 3H, CH_3), 1.69 (d, *J*=0.9, 3H, CH_3), 1.75-1.88 (m, 1H, C$\underline{H}_2$CH$_2$CH=), 1.93-2.14 (m, 2H, C$\underline{H}_2$CH=), 2.22 (dd, *J*=16.7 and 9.3, 1H, $COCH_2$), 2.54 (dd, *J*=16.7 and 8.4, 1H, $COCH_2$), 2.87-2.99 (m, 1H, CH), 4.18-4.36 (m, 4H, 2 × C$\underline{H}_2$CH$_3$), 5.06 (tm, J_t=7.1, 1H, CH=), 6.64 (br s, 1H, NH); ^{13}C nmr δ 13.9, 14.1, 17.6, 25.6, 26.0, 30.5, 35.5, 40.6, 62.28, 62.34, 71.4, 122.9, 132.7, 168.0, 168.4, 176.2; HREIms calcd for $C_{16}H_{25}NO_5$ (M^+) 311.1733, found 311.1730; Anal. Calcd for $C_{16}H_{25}NO_5$: C, 61.72; H, 8.09; N, 4.50. Found: C, 61.70; H, 8.06; N, 4.50.

Diethyl 4-(3-pentynyl)pyrrolidin-2-one-5,5-dicarboxylate (21b). To a flask containing 316 mg (0.81 mmol) of mesylate (**20b**) was added 3.0 ml (3.0 mmol) of 1 *M* Bu_4NF in THF. After stirring for 10 min at 25°C, tlc showed no starting material remaining. After stirring for a total of 20 min the reaction solution was diluted with EtOAc, washed with H_2O, satd. $NaHCO_3$, and satd. NaCl, dried, concentrated, and then chromatographed eluting with 2:3 → 3:2 EtOAc-hexanes to afford 61 mg (26%) of α,β-unsaturated amide and 109 mg (46%) of γ-lactam (**21b**), as a clear, faint yellow oil; ir (neat) 1725 br, 1270, 1203 cm^{-1}; ^1H nmr δ 1.302 (t, *J*=7.1, 3H, CH$_2$C$\underline{H}_3$), 1.309 (t, *J*=7.1, 3H, CH$_2$C$\underline{H}_3$), 1.31-1.45 (m, 1H, C$\underline{H}_2$CH$_2$C≡), 1.77 (t, *J*=2.5, 3H, ≡CCH_3), 1.92-2.07 (m, 1H, C$\underline{H}_2$CH$_2$C≡), 2.09-2.34 (m, 2H, CH_2C≡), 2.24 (dd, *J*=16.7 and 9.6, 1H, $COCH_2$), 2.60 (dd, *J*=16.7 and 8.4, 1H, $COCH_2$), 3.02-3.14 (m, 1H, CH), 4.18-4.38 (m, 4H, 2 × C$\underline{H}_2$CH$_3$), 6.48 (br s, 1H, NH); ^{13}C nmr δ 3.3, 13.7, 13.9, 17.1, 29.7, 35.2, 40.2, 62.2, 62.3, 71.2, 76.5, 77.1, 167.8, 168.3, 176.2; HREIms calcd for $C_{15}H_{21}NO_5$ (M^+) 295.1420, found 295.1434.

1-(Diethyl malonate-2-yl)-4-(4-methyl-3-pentenyl)azetidin-2-one (9a). To a stirred solution of 1.2 ml (8.6 mmol) of *i*Pr_2NH in 5.0 ml of anhyd. THF at 0° under argon was added 2.5 ml (6.5 mmol) of 2.6 *M* *n*BuLi to afford a clear, faint yellow solution. After stirring for 5 min at 0°C, this LDA solution was transferred dropwise over 5 min to a stirred solution of 1.04 g (2.56 mmol) of mesylate (**20a**) in 18 ml of anhyd. THF at 0°C under argon. After stirring for 15 min, the reaction was quenched with 1 *M* HCl and extracted with EtOAc. The extract was washed with H_2O, satd. $NaHCO_3$, and satd. NaCl, dried, concentrated, and then chromatographed eluting with 1:4 EtOAc-hexanes to afford 623 mg (78%) of β-lactam (**9a**), as a clear, light

yellow liquid; ir (neat) 1755 br cm^{-1}; ^1H nmr δ 1.30 (t, *J*=7.1, 3H, $CH_2C\underline{H}_3$), 1.31 (t, *J*=7.1, 3H, $CH_2C\underline{H}_3$), 1.47-1.55 (m, 1H, $C\underline{H}_2CH_2CH$=), 1.59 (d, *J*=0.5, 3H, CH_3), 1.68 (d, *J*=0.6, 3H, CH_3), 1.90-2.04 (m, 3H, $C\underline{H}_2CH_2CH$=), 2.68 (dd, *J*=14.8 and 2.7, 1H, $COCH_2$-*cis*), 3.10 (dd, *J*=14.8 and 5.2, 1H, $COCH_2$-*trans*), 3.98-4.06 (m, 1H, $C\underline{H}CH_2$), 4.20-4.33 (m, 4H, 2 × $C\underline{H}_2CH_3$), 5.07 (tm, J_t=7.0, 1H, CH=), 5.15 (s, 1H, $CHCO_2$); ^{13}C nmr δ 13.7, 13.8, 17.5, 24.1, 25.5, 33.0, 42.7, 53.5, 56.8, 62.2, 62.4, 122.8, 132.4, 165.0, 165.5, 167.5; HREIms calcd for $C_{16}H_{25}NO_5$ (M^+) 311.1733, found 311.1736.

1-(Diethyl malonate-2-yl)-4-(3-pentynyl)azetidin-2-one (9b) was prepared from mesylate (**20b**) by the procedure used to prepare β-lactam (**9a**). The crude product was chromatographed eluting with 2:3 EtOAc-hexanes to afford 657 mg (87%) of β-lactam (**9b**), as a clear, light yellow liquid; ir (neat) 1773 (CON), 1750 (CO_2) cm^{-1}; ^1H nmr δ 1.312 (t, *J*=7.1, 3H, $CH_2C\underline{H}_3$), 1.319 (t, *J*=7.1, 3H, $CH_2C\underline{H}_3$), 1.66-1.75 (m, 1H, $C\underline{H}_2CH_2C\equiv$), 1.76 (t, *J*=2.4, 3H, CH_3), 2.07-2.23 (m, 3H, $C\underline{H}_2C\underline{H}_2C\equiv$), 2.79 (dd, *J*=14.9 and 2.7, 1H, $COCH_2$-*cis*), 3.15 (dd, *J*=14.9 and 5.2, 1H, $COCH_2$-*trans*), 4.08-4.18 (m, 1H, $C\underline{H}CH_2$), 4.22-4.34 (m, 4H, 2 × $C\underline{H}_2CH_3$), 5.17 (s, 1H, $CHCO_2$); ^{13}C nmr δ 2.8, 13.43, 13.47, 14.7, 31.8, 42.2, 52.7, 56.6, 61.9, 62.0, 76.0, 77.0, 164.4, 165.1, 166.8; EIms *m/z* (rel. int.) 295 (M^+, 2), 253 (M^+ - C_2H_2O, 100); CIms (isobutane) gave 296 (MH^+); HREIms calcd for $C_{13}H_{19}NO_4$ (M^+ - C_2H_2O) 253.1314, found 253.1320.

A representative $Mn(OAc)_3$-promoted experiment: The reaction of β-lactam (9a) with $Mn(OAc)_3$ in HOAc.[6a,b,c] A degassed solution of 306 mg (0.98 mmol) of β-lactam (**9a**) in 3.0 ml of degassed HOAc was added to a degassed suspension of 579 mg (2.2 mmol) of $Mn(OAc)_3 \cdot 2H_2O$ in 7.0 ml of degassed HOAc. The resulting stirred suspension was heated at 55°C under N_2 for 1 h, then diluted with H_2O, extracted with CH_2Cl_2, the extract was washed with H_2O and satd. $NaHCO_3$, dried, concentrated, and then chromatographed eluting with a solvent gradient of 3:7 EtOAc-hexanes → EtOAc to afford the following products:

(1*S, 5*R**, 8*S**)-1-ethoxycarbonyl-9,9-dimethyl-2-aza-10-oxatricyclo[6,3,0,$0^{2,5}$]undecane-3,11-dione (22).** 56 mg (20%), as colorless crystals: R_f 0.57 (EtOAc); mp 114-116°C; ir (KBr) 1785, 1750, 1730, 1270, 1220, 1170 cm^{-1}; ^1H nmr δ 1.30-1.62 (m, 2H, one each of $C\underline{H}_2C\underline{H}_2$), 1.367 (t, *J*=7.2, 3H, $CH_2C\underline{H}_3$), 1.370 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 2.01-2.19 (m, 2H, one each of $C\underline{H}_2C\underline{H}_2$), 2.70-2.76 (m, 1H, CH), 2.71 (dd, *J*=15.0 and 2.3, 1H, $COCH_2$-*cis*), 3.13 (dd, J=15.0 and 4.8, 1H, $COCH_2$-*trans*), 3.34-3.43 (m, 1H, NCH), 4.29-4.48 (m, 2H, $C\underline{H}_2CH_3$); ^{13}C nmr δ (multiplicity of off-resonance decoupled ^{13}C nmr) 13.6 (q), 22.5 (t), 24.2 (q), 27.1 (t), 28.2 (q), 43.6 (t), 45.3 (d), 47.9 (d), 63.8 (t), 66.8 (s), 83.5 (s), 165.3 (s), 166.0 (s), 169.3 (s);

HREIms calcd for $C_{14}H_{19}NO_5$ (M^+) 281.1263, found 281.1243; Anal. Calcd for $C_{14}H_{19}NO_5$: C, 59.78; H, 6.81; N, 4.98. Found: C, 59.80; H, 6.72; N, 5.03.

1-Aza-2,2-bis(ethoxycarbonyl)-3-(1-methylethenyl)bicyclo[4,2,0]octan-8-one (23). 20 mg (7%) as a clear, colorless oil: R_f 0.34 (1:19 EtOAc-CH_2Cl_2); ir (neat) 1750 br, 1270, 1225, 1210, 1200 cm^{-1}; ^1H nmr δ 1.27 (t, *J*=7.2, 3H, $CH_2C\underline{H}_3$), 1.31 (t, *J*=7.2, 3H, $CH_2C\underline{H}_3$), 1.42 (qd, *J*=11.3 and 3.7, 1H, $NCHC\underline{H}_2$-*cis*(axial)), 1.73 (br s, 3H, CH_3), 1.75 (qd, *J*=12.4 and 2.9, 1H, $NCHCH_2C\underline{H}_2$-*trans*(axial)), 1.86 (dq, *J*=14.1 and 3.8, 1H, $NCHCH_2C\underline{H}_2$-*cis*(equatorial)), 2.14 (dq, *J*=12.8 and 3.3, 1H, $NCHC\underline{H}_2$-*trans*(equatorial)), 2.58 (dd, *J*=14.6 and 2.1, 1H, $COCH_2$-*cis*), 3.08 (dd, *J*=12.2 and 3.6, 1H, CH), 3.10 (dd, *J*=14.6 and 4.8, 1H, $COCH_2$-*trans*), 3.89 (dtd, *J*=11.3, 4.5, and 2.1, 1H, NCH), 3.99-4.12 and 4.21-4.45 (two m, 4H, 2 × $C\underline{H}_2CH_3$), 4.86 (br s, 1H, $=CH_E$), 4.89 (pentet, *J*=1.4, 1H, $=CH_Z$); ^{13}C nmr δ (multiplicity of off-resonance decoupled ^{13}C nmr) 13.7 (q), 13.9 (q), 23.1 (q), 25.0 (t), 30.5 (t), 43.8 (t), 46.5 (d), 48.4 (d), 61.4 (t), 62.6 (t), 68.5 (s), 114.5 (t), 144.1 (s), 164.1 (s), 165.6 (s), 167.3 (s); HREIms calcd for $C_{16}H_{23}NO_5$ (M^+) 309.1576, found 309.1566.

Diastereomeric malonyl dimers (24a):

One diastereomer: 21 mg (4 mass%), as a colorless oil: R_f 0.47 (1:1 EtOAc-hexanes); ^1H nmr δ 1.308 (t, *J*=7.2, 2 × 3H, $CH_2C\underline{H}_3$), 1.314 (t, *J*=7.2, 2 × 3H, $CH_2C\underline{H}_3$), 1.45-1.57 (m, 2 × 1H, $C\underline{H}_2CH_2CH$=), 1.58 (br s, 2 × 3H, CH_3), 1.67 (br s, 2 × 3H, CH_3), 1.78-2.06 (m, 2 × 3H, $C\underline{H}_2CH$= and one of $C\underline{H}_2CH_2CH$=), 2.44 (dd, *J*=14.4 and 1.9, 2 × 1H, $COCH_2$-*cis*), 3.06 (dd, *J*=14.5 and 5.5, 2 × 1H, $COCH_2$-*trans*), 3.87-3.98 (m, 2 × 1H, NCH), 4.23-4.38 (m, 8H, 4 × $C\underline{H}_2CH_3$), 5.05 (tm, J_t=6.9, 2 × 1H, CH=); CIms (isobutane) *m/z* (rel. int.) 621 (MH^+, 100), 579 (MH^+ - C_2H_2O, 72), 310 ($(M + 2)^+$, 13); FABms *m/z* 579 (MH^+ - C_2H_2O).

One diastereomer: 30 mg (5 mass%), as a colorless oil: R_f 0.42 (1:1 EtOAc-hexanes); ^1H nmr δ 1.30 (t, *J*=7.1, 2 × 3H, $CH_2C\underline{H}_3$), 1.31 (t, *J*=7.2, 2 × 3H, $CH_2C\underline{H}_3$), ~1.5 – ~1.7 (m, 2 × 1H, $C\underline{H}_2CH_2CH$=), 1.57 (br s, 2 × 3H, CH_3), 1.67 (br s, 2 × 3H, CH_3), 1.79-2.05 (m, 2 × 3H, $C\underline{H}_2CH$= and one of $C\underline{H}_2CH_2CH$=), 2.46 (dd, *J*=14.6 and 2.1, 2 × 1H, $COCH_2$-*cis*), 3.07 (dd, *J*=14.5 and 5.5, 2 × 1H, $COCH_2$-*trans*), 3.74-3.86 (m, 2 × 1H, NCH), 4.29 (app. pentet, *J*=7.0, 8H, 4 × $C\underline{H}_2CH_3$), 5.02 (tm, J_t=7.0, 2 × 1H, CH=); EIms *m/z* 620 (M^+, small), 310 ($(M + 2)^+$, large); CIms (isobutane) *m/z* 621 (MH^+, small), 310 ($(M + 2)^+$, large); FABms *m/z* 579 (MH^+ - C_2H_2O).

Malonyl acetate (25a): 42 mg (12%)—an authentic sample of this compound was prepared previously by an independent route:

1-(Diethyl 2-acetoxymalonate-2-yl)-4-(4-methyl-3-pentenyl)-2-azetidinone (25a). To a stirred solution of

103 mg (315 μmol) carbinolamine (**15**) in 1.5 ml pyridine was added 0.4 ml (4.2 mmol) Ac_2O. After stirring for 17 h at 25°C, the solution was diluted with EtOAc, washed with several portions of 1 *M* HCl until the aqueous wash remained strongly acidic, then washed with satd. $NaHCO_3$ and satd. NaCl, dried, concentrated, and then chromatographed eluting with 3:7 EtOAc-hexanes to afford 78 mg (67%) of acetate (**25a**), as a clear, colorless oil; ir (neat) 1770 br, 1230 cm^{-1}; ^1H nmr δ 1.31 (t, *J*=7.1, 6H, 2 × $CH_2\underline{CH_3}$), 1.45-1.57 (m, 1H, $C\underline{H_2}CH_2CH$=), 1.60 (s, 3H, CH_3), 1.69 (d, *J*=1.0, 3H, CH_3), 1.99 (br q, *J*=7.2, 2H, $C\underline{H_2}CH$=), 2.04-2.18 (m, 1H, $C\underline{H_2}CH_2CH$=), 2.19 (s, 3H, $COCH_3$), 2.63 (dd, *J*=15.2 and 2.9, 1H, $COCH_2$-*cis*), 3.06 (dd, *J*=15.2 and 5.6, 1H, $COCH_2$-*trans*), 4.05-4.15 (m, 1H, NCH), 4.32 (q, *J*=7.1, 4H, 2 × $C\underline{H_2}CH_3$), 5.08 (tm, J_t=7.0, 1H, CH=); ^{13}C nmr δ 13.7, 17.58, 17.63, 23.8, 25.6, 33.4, 42.4, 54.6, 63.2, 63.3, 82.8, 122.8, 132.5, 162.35, 162.40, 166.7, 169.2; HREIms calcd for $C_{16}H_{23}NO_5$ $(M - CH_3CO_2H)^+$ 309.1576, found 309.1574; FABms gave MH^+ 370.

A representative $Mn(OAc)_3$-promoted reaction: The reaction of β-lactam (9b) with $Mn(OAc)_3$ in EtOH.[6a,b,c] To a degassed solution of 682 mg (2.5 mmol) of $Mn(OAc)_3 \cdot 2H_2O$ in 5 ml of EtOH under N_2 was added a degassed solution of 302 mg (1.0 mmol) of β-lactam (**9b**) in 5 ml of EtOH. After stirring for 20 h at 25°C, the suspension was diluted with H_2O and extracted with EtOAc. The organic phase was washed with satd. $NaHCO_3$ and satd. NaCl, dried, concentrated, and chromatographed eluting with 1:1 EtOAc-hexanes to afford 228 mg (76%) of diastereomeric malonyl dimers (**24b**), which were partially separated by chromatography to obtain samples of the individual racemic diastereomers for characterization:

One diastereomer: R_f 0.35 (1:1 EtOAc-hexanes); ir (neat) 1760 br, 1240 cm^{-1}; ^1H nmr δ 1.32 (t, *J*=7.2, 2 × 3H, $CH_2C\underline{H_3}$), 1.33 (t, *J*=7.2, 2 × 3H, $CH_2C\underline{H_3}$), 1.61-1.73 (m, 2 × 1H), 1.75 (t, *J*=2.3, 2 × 3H, ≡CCH_3), 1.95-2.12 (m, 2 × 2H), 2.14-2.28 (m, 2 × 1H), 2.52 (dd, *J*=14.6 and 2.0, 2 × 1H, $COCH_2$-*cis*), 3.17 (dd, *J*=14.6 and 5.4, 2 × 1H, $COCH_2$-*trans*), 4.04-4.14 (m, 2 × 1H, NCH), 4.31 (q, *J*=7.2, 8H, 4 × $C\underline{H_2}CH_3$); ^{13}C nmr δ 3.3, 13.6, 15.3, 32.1, 41.9, 55.2, 63.1, 76.5, 77.5, 164.2, 164.6, 167.5; FABms *m/z* (rel. int.) 589 (MH^+, 13), 547 ($MH^+ - C_2H_2O$, 100); CIms (isobutane) *m/z* (rel. int.) 589 (MH^+, 64), 547 ($MH^+ - C_2H_2O$, 19), 296 (100).

One diastereomer: R_f 0.29 (1:1 EtOAc-hexanes); ir (neat) 1760 br, 1240, 1030 cm^{-1}; ^1H nmr δ 1.31 (t, *J*=7.2, 2 × 3H, $CH_2C\underline{H_3}$), 1.34 (t, *J*=7.2, 2 × 3H, $CH_2C\underline{H_3}$), 1.61-1.79 (m, 2 × 1H), 1.75 (t, *J*=2.4, 2 × 3H, ≡CCH_3), 1.88-2.12 (m, 2 × 2H), 2.14-2.27 (m, 2 × 1H), 2.54 (dd, *J*=14.8 and 1.9, 2 × 1H, $COCH_2$-*cis*), 3.13 (dd, *J*=14.7 and 5.6, 2 × 1H, $COCH_2$-*trans*), 3.91-4.02 (m, 2 × 1H, NCH), 4.31 (q, *J*=7.2, 2 × 2H, $C\underline{H_2}CH_3$),

4.32 (q, *J*=7.2, 2 × 2H, $C\underline{H}_2CH_3$); ^{13}C nmr δ 3.4, 13.60, 13.62, 15.1, 32.2, 41.5, 54.5, 63.0, 63.1, 76.5, 77.4, 164.2, 164.4, 167.8; FABms *m/z* (rel. int.) 589 (MH^+, 10), 547 ($MH^+ - C_2H_2O$, 100); CIms (isobutane) *m/z* (rel. int.) 589 (MH^+, 48), 547 ($MH^+ - C_2H_2O$, 12), 296 (100).

1-(Diethyl 2-acetoxymalonate-2-yl)-4-(3-pentynyl)-2-azetidinone (25b). Ir (neat) 2220w (C≡C), 1760 br, 1230, 1050 cm^{-1}; ^1H nmr δ 1.310 (t, *J*=7.1, 3H, $CH_2C\underline{H}_3$), 1.314 (t, *J*=7.1, 3H, $CH_2C\underline{H}_3$), 1.61-1.73 (m, 1H, $CHC\underline{H}_2CH_2$), 1.76 (t, *J*=2.5, 3H, ≡CCH_3), 2.13-2.33 (m, 3H, $CHC\underline{H}_2C\underline{H}_2$), 2.20 (s, 3H, $COCH_3$), 2.76 (dd, *J*=15.3 and 2.9, 1H, $COCH_2$-*cis*), 3.12 (dd, *J*=15.3 and 5.6, 1H, $COCH_2$-*trans*), 4.17-4.25 (m, 1H, NCH), 4.32 (q, *J*=7.1, 4H, 2 × $C\underline{H}_2CH_3$); ^{13}C nmr δ 3.4, 13.8, 15.0, 20.7, 32.5, 42.4, 54.5, 63.3, 63.4, 82.9, 162.4, 166.7, 169.2; HRFABms calcd for $C_{17}H_{24}NO_7$ (MH^+) 354.1553, found 354. 1540.

Bicyclic alcohol (27). Ozone-enriched oxygen was bubbled through a stirred suspension of 113 mg (363 μmol) of β-lactam (**9a**) in 2.0 ml of anhyd. CH_2Cl_2 at -78°C until a blue color persisted in the mixture. Then nitrogen was bubbled through the mixture until the blue color was gone, and then for a few minutes extra. Then 80 μl (1.1 mmol) of dimethyl sulfide (DMS) was added, and the cooling bath was removed and the reaction allowed to rise to room temperature while stirring overnight under N_2. After stirring for 16 h at 25°C, the solution was diluted with EtOAc, washed with H_2O and satd. NaCl, dried, and concentrated to afford 110 mg of a dark yellow oil. ^1H nmr showed a mixture of β-lactams, presumably the epimeric alcohols (**27**), and a trace of the monocyclic aldehyde (**26**). Rather than characterizing this dynamic mixture, the acetate and mesylate derivatives were prepared.

1-Aza-2,2-bis(ethoxycarbonyl)-3-acetoxybicyclo[4.2.0]octan-8-one (28). To a stirred solution of 59 mg (0.21 mmol) of crude epimeric alcohol (**27**) in 1.0 ml of pyridine was added 0.20 ml (2.1 mmol) of Ac_2O. After stirring for 18 h at 25°C, the solution was diluted with EtOAc, washed with several small portions of 1 *M* HCl until the aqueous phase remained strongly acidic, then washed with H_2O, satd. $NaHCO_3$, and satd. NaCl, dried, concentrated, and then chromatographed eluting with 2:3 EtOAc-hexanes to afford 27 mg (40%) of acetate (**28**), as a clear, colorless oil; ir (neat) 1750 br, 1230 cm^{-1}; ^1H nmr δ 1.30 (t, *J*=7.2, 3H, $CH_2C\underline{H}_3$), 1.32 (t, *J*=7.1, 3H, $CH_2C\underline{H}_3$), 1.54-1.79 (m, 2H, one each of $C\underline{H}_2C\underline{H}_2$), 2.04 (s, 3H, CH_3), 2.05 (dq, *J*=12.9 and 4.0, 1H, $C\underline{H}_2CHO$), 2.16 (dq, *J*=12.9 and 4.1, 1H, $NHCC\underline{H}_2$), 2.54 (dd, *J*=14.8 and 1.9, 1H, $COCH_2$-*cis*), 3.18 (dd, *J*=14.8 and 4.9, 1H, $COCH_2$-*trans*), 3.99 (dtd, *J*=10.5, 4.8, and 1.9, 1H, NCH), 4.22-4.43 (m, 4H, 2

× $C\underline{H}_2CH_3$), 5.41 (dd, *J*=10.5 and 3.9, 1H, CHOAc); ^{13}C nmr δ 13.7, 14.1, 20.9, 24.9, 28.8, 44.2, 47.2, 62.1, 62.7, 67.2, 70.1, 164.1, 165.0, 166.2, 169.1; HREIms calcd for $C_{15}H_{21}NO_7$ (M^+) 327.1318, found 327.1332.

1-Aza-2,2-bis(ethoxycarbonyl)-3-methanesulfonoxybicyclo[4.2.0]octan-8-one (29). (Procedure[38]) To a stirred solution of 122 mg (428 μmol) of crude epimeric alcohol (**27**) in 1.0 ml of pyridine under N_2 was added 100 μl (1.3 mmol) of methanesulfonyl chloride. After stirring for 1.5 h at 25°C, the solution was diluted with EtOAc, washed repeatedly with 0.5 *M* HCl until the aqueous phase remained strongly acidic, then washed with H_2O, satd. $NaHCO_3$, and satd. NaCl, dried, concentrated, and then chromatographed eluting with 2:3 → 1:1 EtOAc-hexanes to afford 43 mg (28%) of mesylate (**29**), as a clear, colorless oil; ir (neat) 1769 (CON), 1753, 1738, 1364, 1179 cm^{-1}; ^1H nmr δ 1.32 (t, *J*=7.1, 6H, 2 × $CH_2C\underline{H}_3$), 1.60 (qm, J_q=13.3, 1H, NCHC$\underline{H}_2$), 1.96 (qm, J_q=13.4, 1H, C$\underline{H}_2$CHO), 2.23 (dq, *J*=13.6 and 4.2, 1H, NCHC$\underline{H}_2$), 2.34 (dd, *J*=13.4 and 4.0, 1H, C$\underline{H}_2$CHO), 2.53 (dd, *J*=14.9 and 1.9, 1H, $COCH_2$-*cis*), 3.13 (s, 3H, CH_3), 3.20 (dd, *J*=14.9 and 5.0, 1H, $COCH_2$-*trans*), 4.02 (dtd, *J*=10.8, 4.7, and 1.8, 1H, NCH), 4.23-4.46 (m, 4H, 2 × $C\underline{H}_2CH_3$), 5.08 (dd, *J*=11.6 and 4.1, 1H, CHOMs); ^{13}C nmr δ 13.6, 14.0, 27.3, 29.5, 38.6, 44.1, 47.3, 62.6, 63.1, 66.7, 77.4, 164.4, 165.1, 165.4; HREIms calcd for $C_{14}H_{21}NO_8S$ (M^+) 363.0988, found 363.0981.

ACKNOWLEDGMENTS

We thank Dr. Maoyu Shang of the X-ray Crystallographic Facility of our department for determining the structure of compound (**22**). We are grateful to Eli Lilly & Co., Inc. for generous financial support.

REFERENCES

1. a) R. P. Elander and H. Aoki in 'Chemistry and Biology of β-Lactam Antibiotics,' ed. by R. B. Morin and M. Gorman, Academic Press, 1982, Vol. 3, pp. 83-153.
   b) E. P. Abraham in 'β-Lactam Antibiotics: Mode of Action, New Developments, and Future Prospects,' ed. by M. Salton and G. Shockman, Academic Press, New York, 1981, pp. 311-325.
2. a) R. B. Kammer in ref. 1a, Vol. 3, pp. 287-301.
   b) H. C. Neu in ref. 1b, pp. 545-566.
3. R. D. G. Cooper in 'The Chemistry of Beta-Lactams,' ed. by M. I. Page, Chapman and Hall, London, 1992, pp. 272-305.

4. a) Bioactivity: K. Sato, R. Okachi, I. Matsukuma, K. Mochida, and T. Hirata, *J. Antibiot.*, 1989, **42**, 1844.

b) Partial synthesis from a 3-H-carbacephem; bioactivity and stability data: I. Matsukuma, S. Yoshiiye, K. Mochida, Y. Hashimoto, K. Sato, R. Okachi, and T. Hirata, *Chem. Pharm. Bull.*, 1989, **37**, 1239.

c) Total syntheses, for a lead reference, see: J. W. Frazier, M. A. Staszak, and L. O. Weigel, *Tetrahedron Lett.*, 1992, **33**, 857.

5. R. J. Ternansky and J. M. Morin, Jr., 'The Organic Chemistry of β-Lactams,' ed. by G. I. Georg, VCH Publishers, New York, 1993, pp. 257-293.

6. a) S. A. Kates, M. A. Dombroski, and B. B. Snider, *J. Org. Chem.*, 1990, **55**, 2427.

b) B. B. Snider and J. E. Merritt, *Tetrahedron*, 1991, **47**, 8663.

c) B. B. Snider, J. E. Merritt, M. A. Dombroski, and B. O. Buckman, *J. Org. Chem.*, 1991, **56**, 5544.

d) D. P. Curran, T. M. Morgan, C. E. Schwartz, B. B. Snider, and M. A. Dombroski, *J. Am. Chem. Soc.*, 1991, **113**, 6607.

e) For a recent review of the reactions, both inter- and intramolecular, of alkenes and alkynes with α-oxo- and α,α-dioxoalkyl radicals generated with manganese(III), see: G. G. Melikyan, *Synthesis*, 1993, 833.

7. a) For a recent review, see: J. Kant and D. G. Walker in ref. 5, pp. 129-190.

b) For additional examples applied specifically to the syntheses of carbacephalosporins, see—rhodium-catalyzed carbene insertion:

i) C. C. Bodurow, B. D. Boyer, J. Brennan, C. A. Bunnell, J. E. Burks, M. A. Carr, C. W. Doecke, T. M. Eckrich, J. W. Fisher, J. P. Gardner, B. J. Graves, P. Hines, R. C. Hoying, B. G. Jackson, M. D. Kinnick, C. D. Kochert, J. S. Lewis, W. D. Luke, L. L. Moore, J. M. Morin, R. L. Nist, D. E. Prather, D. L. Sparks, and W. C. Vladuchick, *Tetrahedron Lett.*, 1989, **30**, 2321.

ii) D. A. Evans and E. B. Sjogren, *Tetrahedron Lett.*, 1985, **26**, 3787.

Dieckmann:

iii) Ref. 4c.

8. a) J. Kant and D. G. Walker in ref. 5, pp. 159-167.

b) M. D. Bachi, 'Recent Advances in the Chemistry of β-Lactam Antibiotics,' ed. by P. H. Bentley and R. Southgate, Royal Society of Chemistry, London, 1989, pp. 91-105.

c) M. D. Bachi, F. Frolow, and C. Hoornaert, *J. Org. Chem.*, 1983, **48**, 1841.

d) E. Bosch and M. D. Bachi, *J. Org. Chem.*, 1993, **58**, 5581.

9. An exception to this is Curran's atom transfer cyclization procedure which is oxidatively neutral—but this still requires a more functionalized substrate than the $Mn(OAc)_3$-promoted procedures: D. P. Curran and C.-T. Chang, *J. Org. Chem.*, 1989, **54**, 3140.

10. a) C. Chatgilialoglu, D. Griller, and M. Lesage, *J. Org. Chem.*, 1988, **53**, 3641.

b) M. Ballestri, C. Chatgilialoglu, K. B. Clark, D. Griller, B. Giese, and B. Kopping, *J. Org. Chem.*, 1991, **56**, 678.

11. As evidenced by the various procedures that have been developed to remove tin contaminants from reaction products—

a) aq. KF: J. E. Leibner and J. Jacobus, *J. Org. Chem.*, 1979, **44**, 449.

b) CrO_3, py: P. E. Bauer, N. K. Dunlap, S. Arseniyadis, D. S. Watt, W. K. Seifert, and J. M. Moldowan, *J. Org. Chem.*, 1983, **48**, 4493 (see prep. of cmpd. 2).

c) DBU, I_2: Ref. 9.

And by substitution of TTMS (see ref. 10) for Bu_3SnH—

d) For example: S. Knapp and F. S. Gibson, *J. Org. Chem.*, 1992, **57**, 4802 (in the reaction of cmpd. 33).

12. a) M. J. Miller, P. G. Mattingly, M. A. Morrison, and J. F. Kerwin, Jr., *J. Am. Chem. Soc.*, 1980, **102**, 7026.

b) M. J. Miller, A. Biswas, and M. A. Krook, *Tetrahedron*, 1983, **39**, 2571.

c) M. J. Miller, *Acc. Chem. Res.*, 1986, **19**, 49.

13. S. N. Huckin and L. Weiler, *J. Am. Chem. Soc.*, 1974, **96**, 1082.

14. a) R. T. LaLonde, N. Muhammad, and C. F. Wong, *J. Org. Chem.*, 1977, **42**, 2113.

b) D. F. Taber, P. B. Deker, and M. D. Gaul, *J. Am. Chem. Soc.*, 1987, **109**, 7488.

15. a) M. Hirama, M. Shimizu, and M. Iwashita, *J. Chem. Soc., Chem. Comm.*, 1983, 599.

b) JP patent 59 175 893 (*Chem. Abstr.*, 1985, **102**, 165 269g).

16. For chemical, enzymatic, and microbial asymmetric reductions of β-keto esters, see pertinent references cited in: R. C. Larock, 'Comprehensive Organic Transformations: A Guide to Functional Group Preparation,' VCH Publishers, New York, 1989, pp. 540-547.

17. a) For a reference that reports the Ru-BINAP-mediated asymmetric reduction of β-keto ester (**11a**), see: D. F. Taber and L. J. Silverberg, *Tetrahedron Lett.*, 1991, **32**, 4227.

b) For a lead reference for asymmetric reductions using the Ru-BINAP methodology, see: M. Kitamura, M. Tokunaga, T. Ohkuma, and R. Noyori, *Org. Synth.*, 1993, **71**, 1.

18. B. H. Lee, A. Biswas, and M. J. Miller, *J. Org. Chem.*, 1986, **51**, 106.

19. R. Scartazzini, H. Peter, H. Bickel, K. Heusler, and R. B. Woodward, *Helv. Chim. Acta*, 1972, **55**, 408.

20. D. B. R. Johnston, S. M. Schmitt, F. A. Bouffard, and B. G. Christensen, *J. Am. Chem. Soc.*, 1978, **100**, 313.

21. a) M. J. Miller and P. G. Mattingly, *Tetrahedron*, 1983, **39**, 2563.

b) B. T. Lotz and M. J. Miller, *J. Org. Chem.*, 1993, **58**, 618.

22. a) A. K. Bose, M. S. Manhas, D. P. Sahu, and V. R. Hegde, *Can. J. Chem.*, 1984, **62**, 2498.

b) C. A. Townsend, A. M. Brown, and L. T. Nguyen, *J. Am. Chem. Soc.*, 1983, **105**, 919.

c) M. J. Genin, W. B. Gleason, and R. L. Johnson, *J. Org. Chem.*, 1993, **58**, 860.

23. M. Hirama, T. Noda, and S. Ito, *J. Org. Chem.*, 1985, **50**, 127.

24. G. W. Anderson, J. E. Zimmerman, and F. M. Callahan, *J. Am. Chem. Soc.*, 1964, **86**, 1839.

25. D. L. Hughes, *Org. React.*, 1992, **42**, 335.

26. J. D. Slagle, T. T.-S. Huang, and B. Franzus, *J. Org. Chem.*, 1981, **46**, 3526.

27. For examples of base-promoted cyclizations of β-haloamides to β-lactams, see pertinent references cited in ref. 5 or ref. 22b.

28. S. Hanessian, C. Couture, and H. Wyss, *Can. J. Chem.*, 1985, **63**, 3613.

29. R. K. Crossland and K. L. Servis, *J. Org. Chem.*, 1970, **35**, 3195.

30. Mesylates have also been used to form β-lactams by cyclizing hydroxamates and acyl sulfamates, as originally reported by Floyd:

a) D. M. Floyd, A. W. Fritz, J. Pluscec, E. R. Weaver, and C. M. Cimarusti, *J. Org. Chem.*, 1982, **47**, 5160.

b) D. M. Floyd, A. W. Fritz, and C. M. Cimarusti, *J. Org. Chem.*, 1982, **47**, 176.

31. a) Tosylate: R. M. Adlington, A. G. M. Barrett, P. Quayle, A. Walker, and M. J. Betts, *J. Chem. Soc., Chem. Commun.*, 1981, 404.

b) Mesylate: A. Knierzinger and A. Vasella, *J. Chem. Soc., Chem. Commun.*, 1984, 9.

32. M. P. Bertrand, J.-M. Surzur, H. Oumar-Mahamat, and C. Moustrou, *J. Org. Chem.*, 1991, **56**, 3089.

33. O. Kitagawa, T. Inoue, K. Hirano, and T. Taguchi, *J. Org. Chem.*, 1993, **58**, 3106.

34. J. Cossy and A. Bouzide, *Tetrahedron Lett.*, 1993, **34**, 5583.

35. E. I. Heiba, R. M. Dessau, and W. J. Koehl, Jr. *J. Am. Chem. Soc.*, 1969, **91**, 138.

36. A. Citterio, A. Marion, A. Maronati, and M. Nicolini, *Tetrahedron Lett.*, 1993, **34**, 7981.

37. L. Crombie, S. H. Harper, R. E. Stedman, and D. Thompson, *J. Chem. Soc.*, 1951, 2445.

38. K. Mochida and T. Hirata, *Chem. Pharm. Bull.*, 1988, **36**, 3642.

39. a) cis-selective: Y. Takahashi, H. Yamashita, S. Kobayashi, and M. Ohno, *Chem. Pharm. Bull.*, 1986, **34**, 2732.

b) trans-selective: M. Shibuya, Y. Jinbo, and S. Kubota, *Chem. Pharm. Bull.*, 1984, **32**, 1303.

c) trans-selective: H. Yamashita, N. Minami, K. Sakakibara, S. Kobayashi, and M. Ohno, *Chem. Pharm. Bull.*, 1988, **36**, 469.

40. W. G. Kofron and L. M. Baclawski, *J. Org. Chem.*, 1976, **41**, 1879.

41. D. F. Taber, K. R. Krewson, K. Raman, and A. L. Rheingold, *Tetrahedron Lett.*, 1984, **25**, 5283.

Received, 9th May, 1994