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Synthesis of a Bicyclic Oxamazin. A Novel Heteroatom Activated β-Lactam

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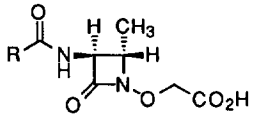
Abstract: The synthesis of the bicyclic oxamazin **23** was accomplished by an intramolecular cyclization process. Allyl protected *N*-hydroxy β-lactam **22** served as the key intermediate during a simultaneous deprotection and cyclization in the presence of Pd(0).

INTRODUCTION

The discovery of oxamazins **1**[1], a potent class of monocyclic β-lactam antibiotics, has attracted further attention not only due to their unique structural features, but also for their inherent antibacterial activity against a wide spectrum of Gram-negative bacteria. Though the carboxylate functionality is located one bond further than what is normally observed for β-lactam antibiotics, the biological activity of oxamazins has been attributed to the electronic activation of the azetidinone ring by the directly attached oxygen atom and appropriate enzyme active site fit.[2] Indeed, among all members of the unnatural heteroatom activated β-lactams (e.g., oxamazins, monosulfactams, thiamazins, and azamazins), oxamazins and monosulfactams were found to have activity comparable to the corresponding monobactams.



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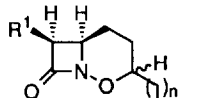

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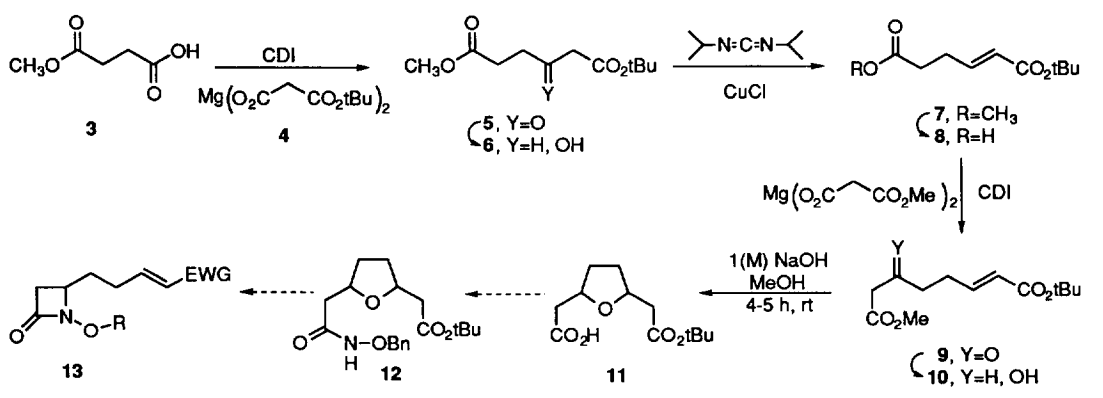
Bicyclic oxamazins (**2**) which would combine a [4.2.0] ring system, a common feature of many bicyclic β-lactam antibiotics (e.g., cephalosporins, carbacephalosporins), and the heteroatom activation effect are especially attractive targets in the search for new antibiotics. Attempted syntheses of bicyclic oxamazins have been reported by our laboratory[3] and others.[4] Interestingly, the only bicyclic oxamazins reported [**2a** (n=0, R^2=H, R^1=variable acyl amino groups)] were described in an abstract,[4] and, interestingly, both diastereomers at the point of attachment of the carboxyl group reportedly displayed good antibacterial

activity, though no details were given. Herein, we describe methodology that allows direct access to a protected bicyclic oxamazin (**2b**, n=1, R^1=H, R^2=tBu) through an intramolecular Michael addition of an *N*-hydroxy β-lactam onto an appropriately appended acceptor.

RESULTS AND DISCUSSIONS

Design and Syntheses: The design of the monocyclic *N*-hydroxy β-lactam precursor of the targeted bicyclic oxamazin employed the hydroxamate mediated β-lactam synthesis developed in our laboratory.[5] Initial efforts to construct the required carbon framework are described in Scheme 1. Monomethyl succinate **3** was transformed to the corresponding acylimidazole and treated with the magnesium salt of mono-*tert*-butyl malonate (**4**), to provide β-keto ester **5** in 75% yield using the procedure of Masamune.[6] Careful reduction of the β-keto ester with $NaBH_4$ gave racemic secondary alcohol **6** in 92% yield without lactonization. Dehydration of **6** under our established conditions (CuCl/*N,N'*-diisopropylcarbodiimide)[7] provided α,β-unsaturated ester **7** in 72% yield. Saponification of **7** to acid **8**, followed by another reaction of its acylimidazole derivative with the magnesium salt of monomethyl malonate provided the entire required carbon framework **9** of the β-lactam precursor. However, a direct hydroxaminolysis of the derived β-hydroxy ester **10**, obtained from the reduction of keto ester **9**, led only to a mixture of products. Interestingly, attempted saponification of methyl ester **10** using methanolic NaOH resulted in the formation of substituted tetrahydrofuran **11**. Indeed, such an easy entry to the 2,5-disubstituted tetrahydrofuran rings merits further attention as many biologically active compounds[8] (e.g., polyether antibiotics[9]) contain this ring system. Moreover, acid **11** itself might serve as an immediate precursor to the desired *N*-hydroxy β-lactam framework. In order to avoid formation of the furan ring, an alternative approach was initiated which generated the desired α,β-unsaturated ester at a later stage of the synthetic sequence (Scheme 2).

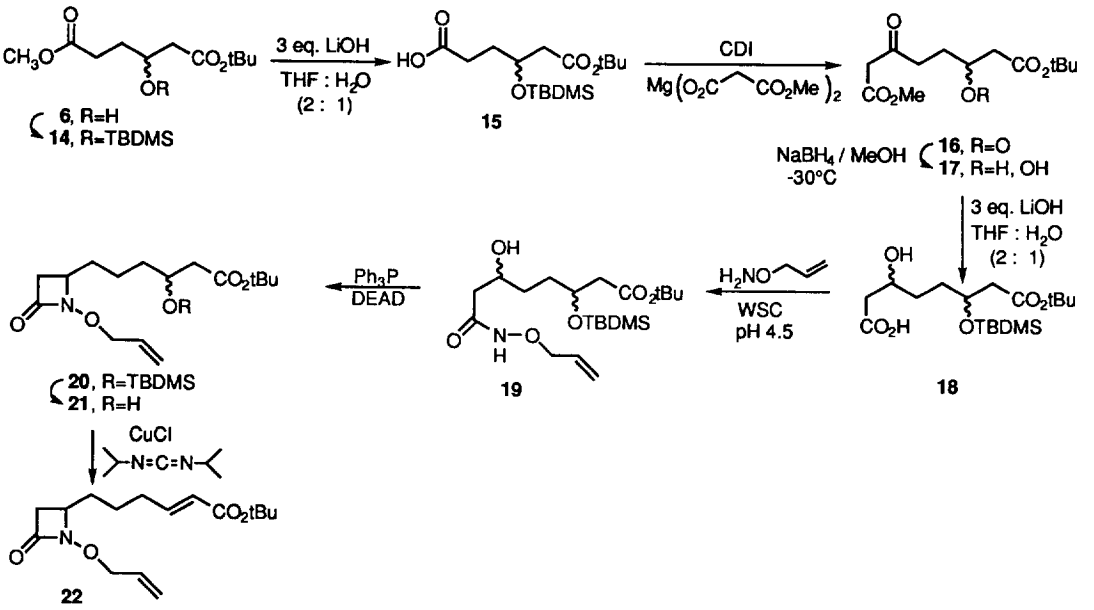
Scheme 1



Protection of the hydroxyl group of **6** was anticipated to avoid the complications noted in Scheme 1. Thus, silyl protection of **6** gave **14**. Subsequent saponification using LiOH gave acid **15**. Masamune's magnesium malonate procedure provided β-keto-ester **16** in 70% yield. Reduction of ketone **16** to alcohol **17** using $NaBH_4$, and hydrolysis of the ester afforded β-hydroxy-acid **18** cleanly. Water soluble carbodiimide

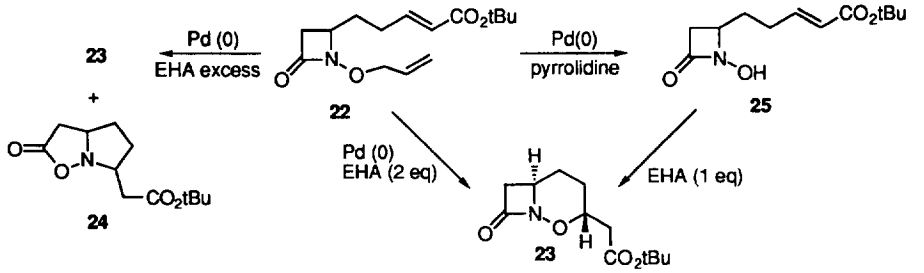
(EDC)-mediated coupling of this acid **18** with *O*-allylhydroxylamine furnished the desired β-hydroxy hydroxamate **19**. Cyclization of **19** under Mitsunobu conditions (diethylazodicarboxylate, triphenylphosphine)[10] gave β-lactam **20** (76%) as a mixture of diastereoisomers. Deprotection of the silyl ether with tetrabutylammonium fluoride[11] provided alcohol **21** in 86% yield. Dehydration of the alcohol, using our previously employed procedure, [7] provided α, β-unsaturated ester **22** in 75% isolated yield.

Scheme 2



Having obtained the desired protected monocyclic β-lactam, a simultaneous removal of the allyl group and cyclization of the resulting free *N*-hydroxy β-lactam was attempted (Scheme 3). Displacements of allyl esters by nucleophiles (allyl scavengers) when activated with Pd(0) are well documented in the literature.[12] Indeed, when 2-ethylhexanoic acid (EHA, 150 mol%) was used as the allyl scavenger in this Pd(0) catalyzed deprotection step, a simultaneous deprotection followed by intramolecular cyclization was observed to furnish bicyclic oxamazin **23** in 45% yield as a single racemic diastereomer after 30 h at room temperature along with a 10% recovery of the starting material. Use of 200 mole% of EHA for 30 h slightly improved the yield to 50%. However, a further increase in the amount of EHA to 250 mole% produced **23** plus a new ring expanded compound (**24**). In order to test further the scope of the formation of the bicyclic oxamazin system, allyl ester **22** was smoothly deprotected with pyrrolidine as the allyl scavenger in the presence of catalytic $Pd(Ph_3)_4$ at room temperature to provide *N*-hydroxy β-lactam **25** in 85% yield. Upon treatment of **25** with EHA (100 mol%), but in the absence of Pd(0), the desired bicyclic oxamazin **23** was obtained in only 10% yield.[13] Reaction of **25** under more basic conditions (Et_3N), again in the absence of Pd(0), produced rearranged compound **24**, rather than bicyclic form **23**. The tendency of *N*-hydroxy-β-lactams to this type of rearrangement has been described earlier.[14]

Scheme 3



At this stage, removal of the *t*-butyl group from **23** was attempted. Use of TFA/CH_2Cl_2 (1:2) at 0 °C for 1 h induced a partial deprotection of the product (75%) by NMR analysis. Increasing the reaction time or temperature to promote complete deprotection of the *tert* butyl ester gave complete decomposition of the starting material. An attempt to isolate the potassium salt by employing an aqueous K_2CO_3 work-up or by ion exchange chromatography after partial (75%) deprotection, led to complete destruction of the β-lactam ring system. Thus, the lability of the bicyclic β-lactam and the monocyclic *N*-hydroxy-β-lactam precursor suggests that extreme care must be employed in the selection of appropriate protecting groups for the preparation of an α-amido derivative (**2b**, n=1, R^1=acylamino, R^2=H) of bicyclic oxamazins by the methodology described in this model study. Related and appropriate extensions are under consideration.

Structural Considerations of Bicyclic Oxamazin 23 and Rearranged Product 24.

^{1}H Chemical Shifts and ^{1}H-^{1}H Coupling Constants. for 23. As depicted in the structure of **23**, its C_4 and C_7 methine protons (numbering based on the monocyclic azetidinone precursors) have similar electronic environments, each being adjacent to a hetero atom, and located β to a carbonyl functionality. Both of the C_3 and C_8 methylene groups are α-to carbonyl groups, but protons on C_3, being part of an azetidinone ring system, should show a different coupling pattern for the *cis* and *trans* protons with respect to the C_4 hydrogen. Indeed, the ^{1}H spectrum of **23** showed four distinct doublet of doublets (dd) for the C_3 and C_8 protons. Two relatively downfield multiplets at 4.13 and 3.88 ppm are due to the hetero atom substituted C_4 and C_7 protons. Three distinct coupling patterns of the 4.13 ppm resonance (ddd, J = 15.5, 8.0, 4.5 Hz) allowed its direct assignment as the C_4 proton. The resonances at 3.88 ppm were assigned to the C_7 proton. The C_3 protons were then identified as the 3.05 ppm and 2.63 ppm resonances as *cis* (J = 8.5 Hz) and *trans* (J = 4.5 Hz) protons relative to the C_4 proton. Each proton of the methylene groups at C_5 and C_6 had distinct chemical shifts positions indicating a different disposition (equatorial or axial) for each proton in the six membered ring system. Typically axial hydrogens exhibit upfield hydrogen resonances and this has been used for assignment of anomeric configuration of sugars[15] even when the sugar is in a half chair conformation. With two hetero atoms and a fused β-lactam on the six-membered ring of **23**, the substituents are only pseudoequatorially or pseudoaxially disposed. Indeed, model building suggests that the six membered ring favors a boat-like conformation. A Chem3D Plus minimization also resulted in a boat conformation (Figure1).

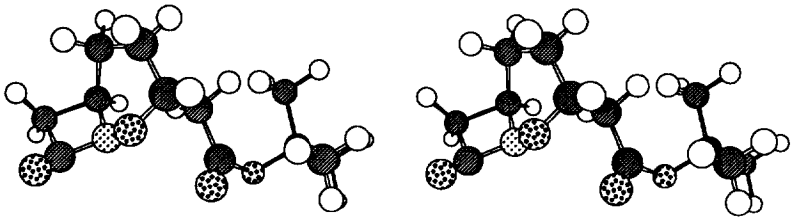


Figure 1. Computer-Generated (Chem3D Plus) Stereoview of Compound 23

^1H Decoupling and 2D COSY Experiment for 23. The connectivity of all protons was definitively assigned with 1D homonuclear decoupling and 2D COSY experiments. Thus, irradiation of the C_4 proton (4.13 ppm) resonance showed a pronounced affect on the C_3 (2.63 and 3.05 ppm) and C_5 (1.78 and 2.19 ppm) proton resonances. Decoupling of the C_7 proton (3.88 ppm) resonances simplified the coupling of

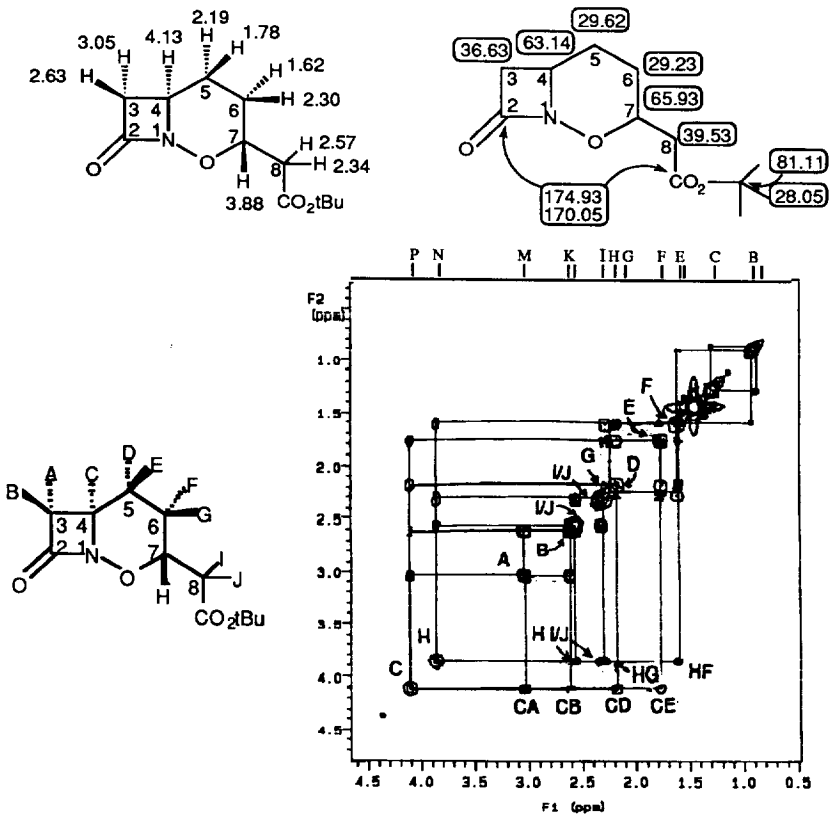


Fig. 2. 500 MHz COSY Spectrum of Compound 23 in $CDCl_3$.

C_8 (2.57 and 2.34 ppm) and C_6 (2.30 and 1.62 ppm) proton resonances. The 2D COSY experiment (Figure 2) also showed the same connectivity through pronounced coupling between adjacent protons except a smaller

contour between 4.13 and 2.63 ppm resonances due to weaker coupling between C_4 and $C_{3\text{-}trans}$. Thus, the mutually coupled resonances at 4.13, 3.05, 2.63, 2.19 and 1.78 are the protons on C_4, $C_{3\text{-}cis}$, $C_{3\text{-}trans}$, $C_{5(eq)}$, $C_{5(ax)}$ respectively, and the five other mutually coupled resonances at 3.88, 2.57, 2.34, 2.30 and 1.62 ppm are the protons on C_7, C_8, C_8, $C_{6\,eq}$, $C_{6\,ax}$ respectively (Table 1).

Table 1. ^1H NMR and ^{13}C NMR Signals for **23**.

Position	^1H δ (ppm), mult, J(Hz)	^{13}C, δ (ppm)
3α	3.05, dd, 17.5, 8.5	36.63
3β	2.63, dd, 18.0, 4.5	
4	4.13, ddd, 15.5, 8.0, 4.5	63.14
5α	2.19, m	29.62
5β	1.78, m	
6α	1.62, m.	29.23
6β	2.30, m	
7	3.88	65.93
8	2.57, dd, 15.0, 6.0	39.53
8	2.34, dd, 16.0, 7.5	

2D HETCOR Studies of 23. The 2D proton-carbon correlation NMR (HETCOR) of **23** further established the atomic connectivity, and was helpful in making peak assignments for every carbon (Figure 3). Again the two downfield resonances at 63.14 ppm and 65.93 ppm were clearly due to the two hetero atom substituted C_4 and C_7 carbons. As expected, C_7 being attached to the more electronegative oxygen atom appeared at 65.93 ppm, and C_4 at 63.14 ppm. Similarly, C_8 being α-to the ester functionality was downfield (39.53 ppm) relative to the C_3 carbon (36.63 ppm). The C_5 and C_6 carbons were also distinguished and were identified as the 29.62 and 29.23 ppm resonances, respectively.

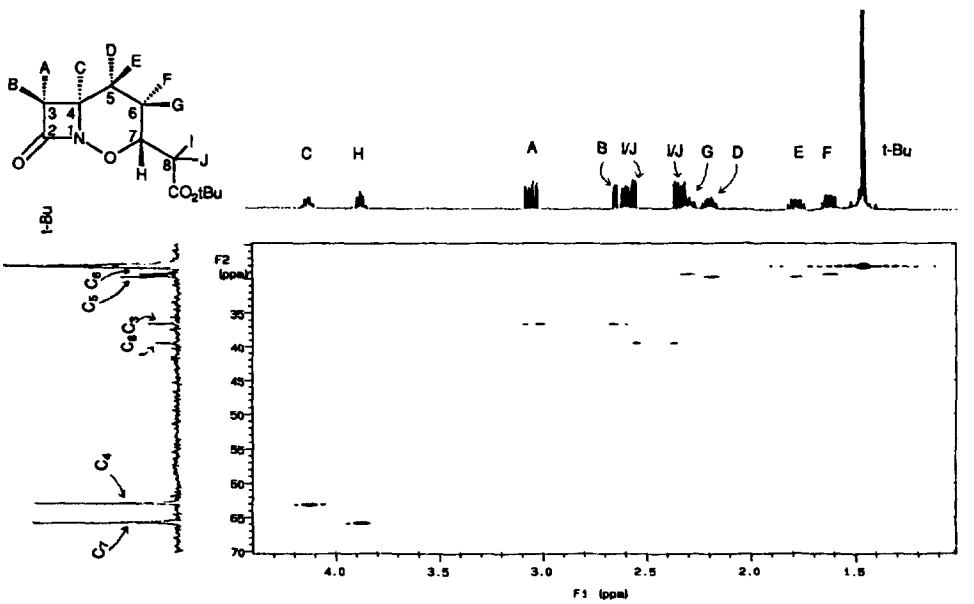


Fig. 3. 500 MHz HETCOR Spectrum of Compound 23 in $CDCl_3$.

2D NOESY Studies of 23. To determine the configuration and conformation adopted by the fused bicyclic system, an estimate of the through space interaction between protons was obtained from a 2D NOESY experiment (Figure 4). The results are summarized in Figure 5. One of the protons on C_5, corresponding to multiplets at either 2.19 or 1.78 ppm, must be on the same side of the ring system as the C_4 proton, and the NOE the observed between $C_{4\text{-}H}$ and the 2.19 resonance confirmed their proximity. Again from chemical shift correlation, this 2.19 ppm resonance $C_{5\text{-}H}$ must have a pseudoequtaorial orientation. Similar NOE was observed between the proton on C_7 and the 2.30 ppm (psuedoequatorial $C_{6\text{-}H}$) resonance. The NOE between 2.30 ($C_{6\text{-eq}}$) and 1.78 ($C_{5\text{-axial}}$) then establishes that C_4 and C_7 protons are anti.

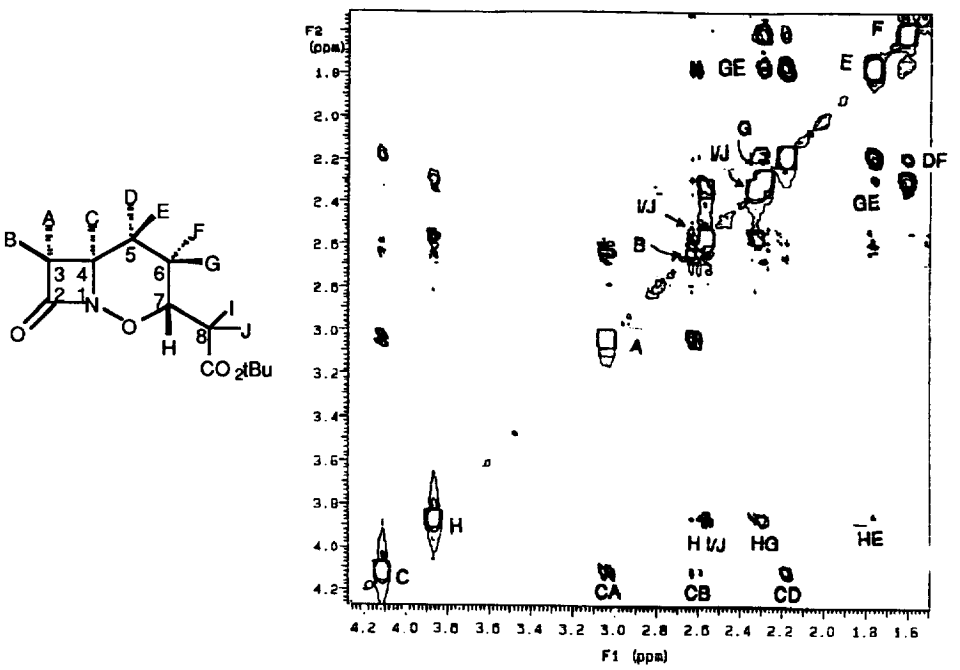


Fig. 4. 500 MHz NOESY Spectrum of Compound 23 in $CDCl_3$.

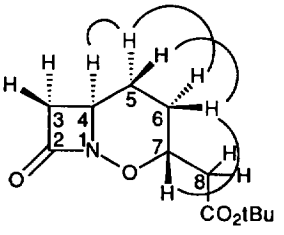


Fig. 5 . The NOE connectivity of compound 23 as obtained from a 2D NOESY Experiment.

The disposition of the carboxylate residue in β-lactam antibiotics usually has a significant affect on biological activity [2,16] However, in compound **23** the conformational restriction imposed on the carboxylic functionality by the fused ring system was reduced by the introduction of the C_8 methylene spacer. The increased flexibility of the carboxyl group thus may allow favorable proximity to the β-lactam carbonyl.

NMR Spectroscopic Studies of 24. As expected for the rearranged product, assigned structure **24**, the chemical shifts of the C_4 and C_7 methine protons also are similar as they each are adjacent to a hetero atom and located β to a carbonyl group. However, relative to β-lactam **23**, the C_7 methine is now attached to the less electronegative nitrogen atom, and is shifted upfield (from δ 3.88 for **23** to δ 3.61 for **24**, Fig 6). Also, the C_4 proton did not show a distinct coupling pattern characteristic for an azetidinone ring system as noted for compound **23** (ddd). The difference in vicinal coupling ($J_{3,4cis}$ and $J_{3,4trans}$), typical of an azetidinone ring system, also was not seen. The ^1H-^1H connectivity of **24** was determined by ^1H decoupling and a 2D COSY experiment. Irradiation of the C_4 proton (4.20 ppm) resonance affected proton resonances at C_3 (2.37 and 2.59 ppm) and C_5 (1.92 and 1.59 ppm). Similarly, decoupling the C_7 proton (3.61 ppm) affected proton resonances at C_8 (2.95 and 2.40 ppm) and C_6 (2.29 and 1.55 ppm). The ^{13}C NMR also was diagonistic, and further supported structure **24**. As expected C_7 being attached to the less electronegative nitrogen atom appeared upfield (49.3). The ring carbonyl carbon also showed a significant upfield shift (from 174.9 in compound **23** to 164.0). An estimate of the through space interaction between protons, obtained from a 2D NOESY experiment, also suggested a rather flat environment for the 5-membered ring containing bicyclic system. The observed NOE (major) between $C_{4\text{-}H}$ and one of the $C_{3\text{-}H}$ (2.59) protons as well as one of the $C_{5\text{-}H}$ (1.59) protons indicated that they were on the same side of the molecule. Similarly, pronounced NOE was observed between the other $C_{5\text{-}H}$ (1.92) and the $C_{6\text{-}H}$ (2.29). The NOE between the resonance at 2.29 ppm and the $C_{7\text{-}H}$ (3.61) then indicated that the $C_{7\text{-}H}$ and $C_{4\text{-}H}$ are anti to each other. Thus, the comparative spectral data and considerable precedent for related rearrangements of *N*-hydroxy-2-azetidinones,[13] allowed assignment of structures **23** and **24**.

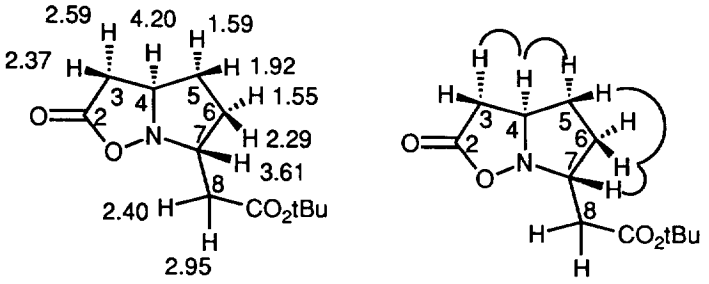


Fig 6. ^1H NMR Spectral Assignments and NOE connectivity relationships for 24

EXPERIMENTAL SECTION

General. Instruments and general methods used have been described earlier.[17] The 2D NMR experiments were performed on a Varian VXR-500 instrument. Mass spectra were recorded on an AEI Scientific Apparatus MS 902, Du Pont DP 102 spectrometer or JEOL AX505 HA either by FAB or with an Analytica Electrospray Source. Solvents used were dried and purified by standard methods.[18] The term "dried" refers to the drying of an organic layer over anhydrous magnesium or sodium sulfate. All reactions were performed under a nitrogen atmosphere.

1-*tert*-Butyl, 6-methyl 3-Oxo-1,6-hexanedicarboxylate (5). Monomethyl succinate (**3**, 10.0 g, 75.7 mmol) in THF (80 mL) was treated with CDI (12.18 g, 75.7 mmol) in portions at 0 °C (ice bath). After 15 min at 0

°C the ice bath was removed, and the reaction mixture was allowed to stir for 1h at room temperature. In a separate flask, mono-*tert*-butyl malonate (**4**, 12.12 g, 75.7 mmol) was dissolved in THF (120 mL) and cooled to -78°C, and to this was added dibutylmagnesium (75 mL of a 0.5 M solution in heptane (Aldrich), 75.7 mmol) via syringe over a 10 min period. This mixture was stirred for 15 min at -78 °C and then for 1 h at room temperature. The solvent was evaporated, and the acyl imidazole was added via cannula to the magnesium salt. The resulting heterogeneous mixture was stirred overnight at room temperature. The THF was evaporated from the reaction mixture, and the crude residue was taken up in Et_2O (500 mL) and washed with 10% citric acid, saturated $NaHCO_3$, water, brine, dried, filtered and concentrated. The crude compound was purified by chromatography on silica-gel (30% ethyl acetate/hexanes) to provide β-keto ester **5** (13.18 g, 75%) as a colorless oil. IR (neat) 1735, 1710, 1360, 1310 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.68 (s, 3H), 3.41 (s, 2H), 2.87 (t, J = 6.6 Hz, 2H), 2.61 (t, J = 6.6 Hz, 2H), 1.47 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.2, 172.6, 166.0, 81.7, 51.5, 50.3, 37.0, 27.7, 27.4; HRMS (EIMS) calcd for M-56 fragment $C_7H_{10}O_5$ 174.0582, found 174.0526. Anal. Calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 57.15; H, 7.71.

1-*tert*-Butyl, 6-methyl 3-hydroxy-1,6-hexanedicarboxylate (6). To β-keto ester **5** (5.0 g, 21.7 mmol) in methanol (60 mL) at -30 °C was added $NaBH_4$ (246 mg, 6.52 mmol) all at once. The temperature of the reaction mixture was strictly maintained at -30 °C, and the reduction was complete within 40 min (TLC monitoring). The reaction mixture was quenched with cold brine (40 mL) and extracted with ethylacetate. The organic layers were combined, washed with brine, dried, filtered and concentrated to provide β-hydroxy ester **6** (4.6 g, 92%) sufficiently pure for the next step. IR (neat) 1770, 1730, 1360 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.81-4.91 (m, 1H), 3.92-4.05 (m, 1H). 3.68 (s, 3H), 2.3-2.62 (m, 4H), 1.75-1.82 (m, 2H), 1.46 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.5, 173.9, 171.8, 168.5, 81.3, 81.0, 76.4, 67.0, 51.4, 42.2, 41.0, 31.1, 29.9, 28.3, 27.8; HRMS (EIMS) calcd for M - 56 fragment $C_7H_{12}O_5$ 176.0684, found 176.0679. Anal. Calcd for $C_{11}H_{20}O_5$: C, 56.88; H, 8.58. Found: C, 57.07; H, 8.58;

1-*tert*-Butyl, 6-methyl 2-hexene-1,6-dicarboxylate (7). To a solution of alcohol **6** (4.0 g, 17.2 mmol) in dry acetonitrile (20 mL) was added *N,N'*-diisopropylcarbodiimide (2.82 g, 22.3 mmol), CuCl (510 mg, 5.16 mmol), and the resulting solution was stirred at room temperature for 21 h. The solid urea byproduct was removed by filtration, and the residual oil was chromatographed on silica-gel (30% ethyl acetate/hexanes) to afford **7** (2.65 g, 72%). ^1H NMR (300 MHz, $CDCl_3$) δ 6.84 (m, 1H), 5.80 (m, 1H), 3.71 (s, 3H), 2.5 (m, 4H), 1.45 (s, 9H); Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.56; H, 8.43.

1-*tert*-Butyl 2-hexene-1,6-dicarboxylate (8). Unsaturated ester **7** (2.0 g, 9.34 mmol) was dissolved in THF:H_2O (2:1, 30 mL) and treated with NaOH (411 mg, 10.27 mmol). The reaction mixture was stirred at room temperature for 5 h for complete consumption of starting material (TLC). The THF was removed at reduced pressure, and the aqueous portion was extracted with EtOAc once. The pH of the aqueous layer was adjusted to 4.5 using cold 0.5 N HCl, extracted repeatedly with EtOAc, and the combined organic extracts were washed with brine, dried, filtered and concentrated to afford unsaturated acid **8** (1.58 g, 85%). IR (neat) 1740-1680 (br), 1660, 1370 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.85 (m, 1H), 5.79 (d, J =15.6 Hz, 1H), 2.5 (m, 4H), 1.48 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.2, 165.8, 145.1, 123.9, 80.4, 32.2, 28.0, 26.6; HRMS (FAB) calcd for $C_{10}H_{16}O_4$ (MH^+) 201.1127, found 201.1135.

1-*tert*-Butyl, 8 methyl 6-oxo-2-octene-1,8-dicarboxylate (9). As for **5**, the acyl imidazole, obtained from reaction of acid **8** (3 g, 0.015 mmol) with CDI (2.67 g, 0.015 mmol), was added to the preformed magnesium salt of monomethyl malonate [prepared from monomethyl malonate (1.94, 0.165 mmol) and dibutyl

magnesium (16.5 mL, 0.5 M in heptane, 0.165 mmol)]. The reaction mixture was stirred overnight. Workup followed by chromatography afforded β-keto ester **9** (3.2 g, 83%). IR (neat) 1745, 1730-1690 (br), 1650 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) δ 6.80 (dt, *J* = 15.6, 6.7 Hz, 1H) , 5.75 (dt, *J* = 15.6, 1.6 Hz, 1H), 3.74 (s, 3H), 3.47 (s, 2H), 2.73 (t, *J* = 7.5 Hz, 2H), 2.47 (m, 2H), 1.48 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.8, 167.3, 165.6, 145.1, 124.0, 80.2, 52.4, 48.9, 40.9, 28.0, 25.4; HRMS (FAB) calcd for $C_{13}H_{20}O_5$ (MH^+) 257.1389, found 257.1396.

1-*tert*-Butyl, 8-methyl 6-hydroxy-2-octene-1, 8-dicarboxylate (10). β-Keto ester **9** (2.06 g, 8.04 mmol) was reduced using $NaBH_4$ (100 mg, 2.4 mmol) in MeOH (50 mL) at –30 °C. Workup as before afforded alcohol **10** (1.8 g, 90%). ^1H NMR (300 MHz, $CDCl_3$) δ 6.86 (dt, *J* = 15.6, 6.9 Hz, 1H), 5.77 (dt, *J* = 15.6 Hz, 1.6 Hz, 1H), 4.02 (m, 1H), 3.72 (s, 3H), 2.6-2.2 (m, 5H), 1.75-1.5 (m, 2H), 1.48 (s, 9H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 165.8, 146.8, 123.3, 79.9, 66.9, 51, 6, 41.1, 34.6, 18.0, 27.9.

Substituted tetrahydrofuran 11. A solution of hydroxy ester **10** (0.633 g, 2.45 mmol) in THF (15 mL) was treated with aqueous NaOH (1.0 M, 2.6 mL). After the starting material was consumed (5 h, TLC monitoring), the THF was evaporated, and the aqueous layer was extracted once with EtOAc. After acidification, the combined organic extracts were washed with brine, dried, filtered and concentrated to provide substituted furan **11** (510 mg, 85%) as an isomeric mixture. IR (neat) 1740-1710 (br), 1370, 1160 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.5-4.2 (m, 2H), 2.7-2.45 (m, 3H), 2.42-2.3 (m, 1H), 2.24-2.04 (m, 2H), 1.7-1.58 (m, 2H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.3, 170.4, 80.7, 76.0, 75.4, 75.1, 74.7, 42.1, 41.7, 40.7, 40.3, 31.5, 31.3, 30.7, 30.5, 27.9; HRMS (FAB) calcd for $C_{12}H_{21}O_5$ (MH^+) 245.1389, found 245.1394. Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 58.83; H, 8.05

1-*tert*-Butyl, 6-methyl 3-((*tert*-butyldimethylsilyl)oxy)-1,6-hexanedicarboxylate (14). β-Hydroxy diester **6** (5.8 g, 25 mmol) was dissolved in dry DMF (8 mL). Imidazole (4.25 g, 62.5 mmol) and TBDMSCl (4.52 g, 30.0 mmol) were added. The reaction mixture was stirred overnight, diluted with water, and extracted with EtOAc. The organic layers were combined, washed with 0.5 M HCl, water, brine, dried, filtered and concentrated. The crude compound was purified by silica-gel chromatography eluting with 50% EtOAc-hexanes to provide **14** (7.8 g, 90%) as a clear oil. IR (neat) 1735, 1360, 1295 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.19-4.09 (m, 1H), 3.67 (s, 3H), 2.46-2.26 (m, 4H), 1.95-1.7 (m, 2H), 1.45 (s, 9H), 0.87 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 170.4, 80.4, 68.0, 51.4, 43.4, 31.9, 29.4, 28.0, 25.7, 17.9, -4.8; HRMS (EIMS) calcd for M–56 fragment $C_{13}H_{26}O_5Si$ 315.19916, found 315.1982. Anal. Calcd for $C_{17}H_{34}O_5Si$: C, 58.92; H, 9.89. Found: C, 58.75; H, 9.77.

1-*tert*-Butyl 3-((*tert*-butyldimethylsilyl)oxy)-1,6-hexanedicarboxylate (15). Silyl protected β-hydroxy diester **14** (7.5 g, 21.6 mmol) was dissolved in a mixed solvent [THF:H_2O (2:1), 60 mL], and to this solution lithium hydroxide (2.0 g, 87.6 mmol) was added. The reaction was stirred for overnight. The THF was removed, and the aqueous solution was extracted once with EtOAc to remove any unreacted compound. After acidification to pH 4.5 with cold 1N HCl, the aqueous layer was extracted repeatedly with EtOAc. The organic layers were combined, washed with brine, dried, filtered and concentrated to afford **15** (6.47 g, 90%). IR (neat) 1735-1700, 1310, 1240; ^1H NMR (300 MHz, $CDCl_3$) δ 4.21-4.11 (m, 1H), 2.48-2.28 (m, 4H), 1.98-1.73 (m, 2H), 1.45 (s, 9H), 0.87 (s, 9H), 0.076 (s, 3H), 0.071 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.7, 170.5, 80.5, 67.90, 43.3, 31.5, 29.3, 27.9, 25.7, 17.8, -4.9; HRMS (EIMS) for M-73 calcd for $C_{12}H_{29}O_5Si$ 259.13656, found 259.1368.

1-*tert*-Butyl, 8-methyl 3-((*tert*-butyldimethylsilyl)oxy)-6-oxo-1,8-octanedicarboxylate (16). Compound **16** was prepared in 70% yield following the Masamune conditions as described earlier. IR (neat): 1750-1710, 1365, 1315 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.2-4.1 (m, 1H), 3.74 (s, 3H), 3.46 (s, 2H), 2.68-2.58 (m, 2H), 2.41 (dd, J = 14.9, 6.0 Hz, 1H), 2.29 (dd, J = 14.9, 6.6 Hz, 1H), 1.93-1.68 (m, 2H), 1.44 (s, 9H), 0.87 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.2, 170.4, 167.5, 80.5, 67.9, 52.3, 49.0, 43.4, 38.2, 30.3, 28.0, 25.7, 17.9, -4.8; MS (IBCI) gave M+1 at 389; HRMS (EIMS) for M-73 calcd for $C_{15}H_{27}O_5Si$315.16278, found 315.1627. Anal. Calcd for $C_{19}H_{36}O_6Si$: C, 58.73; H, 9.36. Found: C, 58.54, H, 9.18

1-*tert*-Butyl, 8-methyl 3-((*tert*-butyldimethylsilyl)oxy)-6-hydroxy-1,8-octanedicarboxylate (17). Compound **17** was prepared in 93% yield by reduction of **16** using $NaBH_4$ following the procedure described above. IR (neat) 1740-1710 (br), 1425, 1360 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.2-4.1 (m, 1H), 4.06-3.92 (m, 1H), 3.71 (s, 3H), 3.22-2.98 (2 brs, 1H, exchangeable with D_2O), 2.56-2.28 (m, 4H), 1.78-1.48 (m, 4H), 1.44 (2s, 9H), 0.87 (2s, 9H), 0.08, 0.07, 0.06 (3s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 173.0, 170.8, 170.7, 80.3, 69.0, 68.7, 68.1, 67.8, 51.6, 43.4, 43.3, 41.23, 41.17, 33.1, 32.8, 31.9. 31.5, 28.01, 25.7, 17.9, -4.8, -4.7; HRMS (EIMS) for M -73 calcd for $C_{15}H_{29}O_5Si$ 317.17843, found 317.1770. Anal. Calcd for $C_{19}H_{38}O_6Si$: C, 58.43, H, 9.81. Found: C, 58.20; H, 9.73.

1-*tert*-Butyl 3-((*tert*-butyldimethylsilyl)oxy)-6-hydroxy-1,8-octanedicarboxylate (18). Compound **18** was isolated in 95% yield by saponification of **17** using LiOH following the procedure described earlier. IR (neat) 3000-2900 (br), 1730-1680 (br), 1360 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.2-6.8, (br, 1H), 4.22-4.11 (m, 1H), 4.1-3.95 (m, 1H), 2.6-2.3 (m, 4H), 1.78-1.54 (m, 4H), 1.44 (s, 9H), 0.88 (2s, 9H), 0.09, 0.08, 0.07 (3s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 167.8, 162.5, 162.4, 80.3, 69.7, 69.5, 69.0, 68.7, 46.5, 46.2, 44.4, 37.1, 36.7, 35.9, 35.6, 32.5, 30.4, 23.3, 2.7, 2.8; HRMS (EIMS) for M -73 calcd for $C_{14}H_{27}O_5Si$ 303.16278, found 303.1626. Anal. Calcd for $C_{18}H_{36}O_6Si$: C, 57.41; H, 9.64. Found: C, 57.63; H, 9.43.

1-*tert*-Butyl 3-((*tert*-butyldimethylsilyl)oxy)-6-hydroxy-1,8-octanedicarboxylate 8-*N*-(allyloxy)amide (19). Hydroxy acid **18** (5.45 g, 14.49 mmol) was dissolved in THF:H_2O (1:1, 40 mL) under a nitrogen atmosphere. *O*-Allylhydroxylamine hydrochloride (1.74 g, 15.94 mmol) was dissolved in THF:H_2O (1:1, 10 mL) in a separate flask and neutralized with Et_3N (2.2 mL, 15.94 mmol). The *O*-allyl hydroxylamine solution was added to the solution of **18**, and the pH of the resulting solution was adjusted to 4.5. EDC (5.54 g, 28.98 mmol) was added to the solution in four portions at 15 min intervals, and the reaction mixture was stirred for 45 min. The THF was removed from the reaction mixture under reduced pressure, and the remaining aqueous portion was extracted with EtOAc. The organic extracts were combined, washed with 10% aqueous citric acid, H_2O, brine, dried, filtered and concentrated. The crude residue was purified by column chromatography eluting with 70% EtOAc/hexanes to afford **19** (5.24 g, 84%) as a low melting solid; mp 42-45 °C. IR (KBr) ; ^1H NMR (300 MHz, $CDCl_3$) δ 9.1, 9.4 (2s, 1H), 6.05-5.85 (m, 1H), 5.4-5.2 (m, 2H), 4.37 (d, 2H, J = 6.3 Hz), 4.25-3.5 (m, 3H), 2.5-2.2 (m, 4H), 1.7-1.5 (m, 4H), 1.42 (s, 9H), 0.86, 0.85 (2s, 9H), 0.08, 0.07, 0.05 (3s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 170.8, 169.9, 169.8, 132.09, 120.3, 80.5, 77.1, 68.9, 68.4, 68.1, 43.31, 42.9, 40.5, 40.2, 33.2, 32.6, 32.2, 32.0, 28.0, 25.7, 17.9, -4.6, -4.7, -4.9.; HRMS (EIMS) for M–73 calcd for $C_{17}H_{33}NO_6Si$ 375.20772 found 375.2090. Anal. Calcd for $C_{21}H_{41}NO_6Si$: C, 58.43; H, 9.57; N, 3.24. Found: C, 58.53; H, 9.61; N, 3.29.

***tert*-Butyl 6-[1-(allyloxy)-2-oxo-4-azetidinyl]-3-[(*tert*-butyldimethylsilyl)oxy]-hexanoate (20).** Hydroxamate **19** (4.52 g, 10.50 mmol) was dissolved in dry acetonitrile (135 mL). Solid Ph_3P (2.89 g, 11.02

mmol) was added, and the solution was cooled to 0 °C. Diisopropyl azodicarboxylate (2.27 mL, 11.55 mmol) was added dropwise over 10 min. The reaction flask was covered with aluminum foil to avoid light. The reaction was stirred at 0 °C for 45 min, and then stirred overnight at room temperature. The solvent was evaporated and the crude residue was purified by column chromatography eluting with 50% ethyl acetate/hexanes to afford **20** (3.37 g, 76%) as a clear oil. IR (Neat): 1775, 1735, 1460, 1365 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.05-5.92 (m, 1H), 5.4-5.28 (m, 2H), 4.47-4.34 (m, 2H), 4.15-4.05 (m, 1H), 3.86-3.76 (m, 1H), 2.77 (ddd, J = 13.6, 5.2, 1.0 Hz, 1H), 2.43 (ddd, J = 15.0, 5.8, 2.5 Hz, 1H), 2.36-2.26 (m, 2H), 2.0-1.85 (m, 1H), 1.7-1.45 (m, 3H), 0.87 (s, 9H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 170.5, 164.07, 132.2, 120.6, 80.5, 77.0, 68.5, 68.4, 57.6, 57.56, 43.5, 43.4, 37.5, 37.4, 32.7, 32.66, 28.0, 25.7, 17.9, -4.7; HRMS (EIMS) calcd for $C_{21}H_{39}NO_5Si$ 413.2598, found 413.2579. Anal. Calcd for $C_{21}H_{39}NO_5Si$: C, 60.98; H, 9.5; N, 3.39. Found: C, 60.73; H, 9.41; N, 3.41.

***tert*-Butyl 6-[1-(allyloxy)-2-oxo-4-azetidinyl]-3-hydroxy-hexanoate (21).** To a stirred solution of the diasteroisomeric mixture of **20** (2 g, 7.64 mmol) in THF (10 mL) was added nBu$_4$NF (6.6 mL of a 1M solution in THF, 22.9 mmol) at 0 °C. The resulting solution was stirred at 0 °C for 15 min, and then 1h at room temperature. After evaporation of the THF under reduced pressure, the crude residue was extracted with ethyl acetate, and the combined organic layers were washed with 0.5N HCl solution, water, brine, dried, filtered and concentrated. The residue was purified by flash chromatography on silica gel (3:1 ethyl acetate/hexanes) to provide diasteromeric alcohols **21** (1.2 g, 86%) as a pale yellow oil. IR (neat): 2980-2930 (br), 1765, 1725, 1370 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.07-5.92 (m, 1H), 5.42-5.3 (m, 2H), 4.48-4.37 (m, 2H), 3.93-2.50 (m, 1H), 3.92-3.85 (m, 1H), 3.36 (t, J = 4.21 Hz, 1H), 2.78 (dd, J = 13.6, 5.2 Hz, 1H), 2.47-2.30 (m, 3H), 2.2-1.5 (m, 4H), 1.47 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 172.1, 172.0, 164.1, 164.1, 132.2, 120.6, 81.4, 77.0, 67.5, 67.4, 57.5, 57.4, 42.2, 37.5, 37.4, 32.1, 31.9, 28.7, 28.5, 28.0; Anal. Calcd for $C_{15}H_{25}NO_5$: C, 60.18; H, 8.42; N, 4.68. Found: C, 59.91; H, 8.19; N, 4.56.

***tert*-Butyl 6-[1-(allyloxy)-2-oxo-4-azetidinyl]-2-hexenoate (22).** Compound **21** (1.0 g, 3.33 mmol) was dissolved in dry acetonitrile (30 mL). Freshly prepared CuCl (98 mg, 0.99 mmol) and *N,N'*-diisopropylcarbodiimide (1.5 mL, 9.99 mol) were added. The resulting solution was stirred for 21 h at room temperature. The reaction mixture was filtered to remove the urea byproduct, and the solvent was evaporated. The crude residue was diluted with EtOAc, and washed with H_2O and brine. After concentration, compound **22** (700 mg, 74.5%) was obtained as an oil by column chromatography eluting with 50% EtOAc/hexanes. IR (neat): 1775, 1710, 1365, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.83 (dt, J = 15.6, 6.9 Hz, 1H), 6.06-5.93 (m, 1H), 4.5-4.33 (m, 2H), 3.89-3.82 (m, 1H), 2.80 (dd, J = 13.7, 5.2 Hz, 1H), 2.35 (dd, J = 13.7, 2.4 Hz, 1H), 2.31-2.25 (m, 2H), 2.08-1.97 (m, 1H), 1.79-1.67 (m, 1H), 1.48 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 165.6, 164, 0 145.5, 132.2, 124.1, 120.9, 80.4, 77.2, 56.9, 37.6, 31.2, 28.1, 28.0; HRMS (EIMS) calcd for M-73 fragment $C_{11}H_{30}NO_3$ 208.09737, found 208.0965. Anal. calcd for $C_{15}H_{23}NO_4$: C, 64.04; H, 8.24; N, 4.98. Found: C, 64.18, H, 8.4; N, 4.64.

***tert*-Butyl 6-[1-hydroxy-2-oxo-4-azetidinyl]-2-hexenoate (25).** Protected monocyclic β-lactam **22** (200 mg, 0.709 mmol) was dissolved in 2 mL of acetonitrile. To the solution, pyrolidine (65 μl, 0.78 mmol), PPh_3 (15 mg) and $Pd(PPh_3)_4$ (55 mg) were added. The resulting reaction mixture was stirred for 15 h at room temperature. The solvent was evaporated, and the crude residue was diluted with ethyl acetate (20 mL). The *N*-hydroxy β-lactam was extracted with Na_2CO_3 solution (5%, 10 mL). The combined basic extracts were acidified to pH 4.5 with cold 0.5 N HCl, and then reextracted with ethyl acetate. After evaporation of the

organic extracts, compound **25** (144 mg, 85%) was obtained as a pale yellow liquid. IR (neat): 2980-2930 (br), 1780-1730 (br), 1710, 1150 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.84 (dt, *J* = 15.6, 6.6 Hz, 1H), 5.79 (dt, *J* = 15.6, 1.2 Hz, 1H), 3.89 (m, 1H), 2.82 (dd, *J* = 13.5, 4.5 Hz, 1H), 2.35 (m, 3H), 2.02 (m, 1H), 1.76 (m, 1H), 1.48 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 165.9, 164.4, 145.8, 123.9, 80.4, 58.0, 37.0, 30.6, 28.0, 27.9; HRMS (FAB) calcd for $C_{12}H_{20}NO_4$ (MH^+) 242.1392; found 242.1396.

Protected bicyclic oxamazin 23. Compound **22** (150 mg, 0.531mmol) was dissolved in dry methylene chloride (3 mL). PPh_3 (8.2 mg, 0.053 mmol), $Pd(PPh_3)_4$ (25 mg, 0.021 mmol) and 2-ethylhexanoic acid (114 mg, 0.796 mmol) were added to the solution. The reaction mixture was stirred at room temperature for 30 h while being monitored periodically by TLC. After concentration of the reaction mixture, the crude compound was purified by column chromatography (silica-gel) eluting with 40% ethylacetate/hexanes to afford **23** (57 mg, 45%); IR (neat): 1780, 1730, 1315, 1150 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.13(ddd, *J* = 15.5, 8.0, 4.5 Hz, 1H), 3.88 (m, 1H), 3.05 (dd, *J* = 17.5, 8.5 Hz, 1H), 2.63 (dd, *J* = 18.0, 4.5 Hz, 1H), 2.57 (dd, *J* = 15.0, 6.0 Hz, 1H), 2.34 (dd, J =16.0, 7.5 Hz, 1H), 2.30 (m, 1H), 2.19 (m, 1H), 1.78 (m, 1H), 1.62 (m, 1H), 1.48 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 174.9, 170.1, 81.1, 65.9, 63.1, 39.5, 36.6, 29.6, 29.2, 28.1; MS (Electrospray) with added Ag^+ gave MAg^+ at 349; IBCI gave MH^+ at 242, HRMS (EIMS) calcd for M-73 fragment for $C_{12}H_{19}NO_4$ 168.0661, found 168.0664.

Ring expanded product 24. To a solution of *N*-hydroxy β-lactam **25** (74 mg, 0.307 mmol) in acetonitrile (1 mL), was added Et_3N (47 μl, 0.337 mmol) and tBuOH (100 μl). The resulting reaction mixture was stirred at room temperature for 3h. TLC analysis indicated no reaction. The reaction was then stirred overnight at 50°C. The solvent was evaporated and the crude residue was purified by preparative layer chromatography (silica-gel) eluting with 40% ethylacetate/hexanes to afford **24** (15 mg, 20%); IR (Neat): 1780, 1730, 1315, 1150 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.20 (m, 1H), 3.61 (m, 1H), 2.95 (dd, *J* = 13.5, 4.5 Hz, 1H), 2.59 (dd, *J* = 16.0, 5.5 Hz, 1H), 2.40 (dd, *J* = 14.0, 1.5 Hz, 1H), 2.37 (dd, *J* = 16.0, 7.5 Hz, 1H), 2.29 (m, 1H), 1.92 (m, 1H), 1.59 (m, 1H), 1.55 (m, 1H), 1.46 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 168.7, 164.0, 81.4, 79.3, 49.3, 41.1, 40.1, 28.6, 28.0, 27.4; HRMS found for $C_{12}H_{19}NO_4$ 241.1314.

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