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Syntheses of Novel Bicyclic β-Lactams by Intramolecular Nucleophile Transfer Reactions of *N*-Tosyloxy β-Lactams

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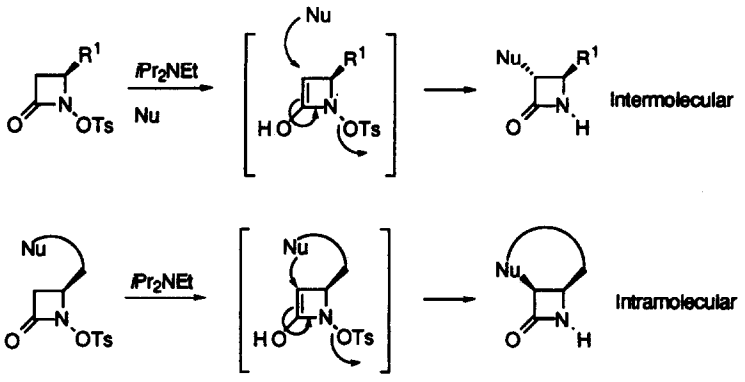
Abstract: Intramolecular nucleophile transfer reaction of several *N*-tosyloxy β-lactams was applied to construct a new six-membered ring in the product bicyclic β-lactams. The bicyclic products generally possessed *cis* stereochemistry on the β-lactam ring. The major competing process appeared to be an intramolecular S_N reaction of the nucleophile at the C4 carbon of the *N*-tosyloxy β-lactam and accounted for the low yield of the desired bicyclic products. Various by-products from the reaction were isolated and characterized which supported the mechanism of the competing process. An efficient intermolecular reaction of *N*-acetyltosylamide **41** with *N*-tosyloxy β-lactam **42** provided β-lactam **43** with *trans* stereochemistry.

INTRODUCTION

For over fifty years, β-lactam antibiotics have enjoyed great success in treating a variety of microbial infections. New and improved antibiotics are constantly being pursued due to the ability of bacteria to develop resistance to the current variety of β-lactam antibiotics, mainly by the action of β-lactamase. New methodology to selectively functionalize the β-lactam ring should aid in the design and syntheses of new antibiotics.

We have recently discovered a remarkable reaction for the addition of nucleophiles to the C3 position of *N*-tosyloxy-β-lactams.[1] Tertiary amine base promoted intermolecular reaction of a variety of nucleophiles with *N*-tosyloxy-β-lactams gave C3 substituted products with predominantly *trans* stereochemistry relative to the C4 substituents and was accompanied by concomitant loss of the tosylate anion (Scheme 1). Presumably, the nucleophile displaces the tosylate in an S_N2' reaction on an enol intermediate. An acyclic version of this same reaction has been independently discovered by Hoffman and was described in an elegant series of recent papers.[2]

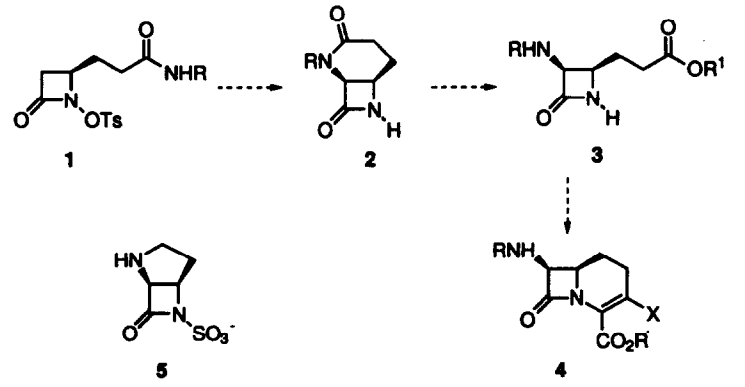
Although the mechanism of the nucleophile transfer reaction with *N*-tosyloxy β-lactams is still in question, the possibility of an intramolecular S_N' version[3] of this reaction was intriguing (Scheme 1). An intramolecular variant of this reaction would complement the intermolecular version and lead to the formation of interesting bicyclic β-lactams. Potentially, *cis* stereochemistry would be incorporated in the bicyclic β-lactams due to a highly constrained transition state leading to the *trans* product.



Scheme 1

We previously developed a catalytic, asymmetric synthesis of the carbacephem framework.[4] Introduction of the nitrogen substituent on the β-lactam ring utilized the efficient intermolecular nucleophile transfer reaction; however, the stereochemistry of the resultant products was *trans*.[4,5] Methods to correct the stereochemistry at the center α to the β-lactam carbonyl are available but most require at least four chemical transformations.[6]

An intramolecular delivery of a nitrogen substituent from **1**, utilizing the nucleophile transfer reaction, potentially would incorporate *cis* stereochemistry on β-lactam **2** (Scheme 2). *Cis* stereochemistry is necessary for antibiotic activity in the carbacephem series and in many other β-lactams as well.[7] Bicyclic β-lactams **2** would not only be interesting novel templates but potentially could be incorporated in a stereoselective synthesis of the important carbacephem antibiotics[8] **4**. For example, selective hydrolysis of bicyclic β-lactam **2** could lead to the precedented monocyclic precursor **3** of the carbacephem framework with the correct absolute stereochemistry required.[9] Furthermore, derivatives of similar bicyclic β-lactam **5** reportedly are potent β-lactamase inhibitors (Scheme 2).[10] This paper provides details of some preliminary results on the scope and limitations of intramolecular nucleophile transfer reactions with *N*-tosyloxy β-lactams.



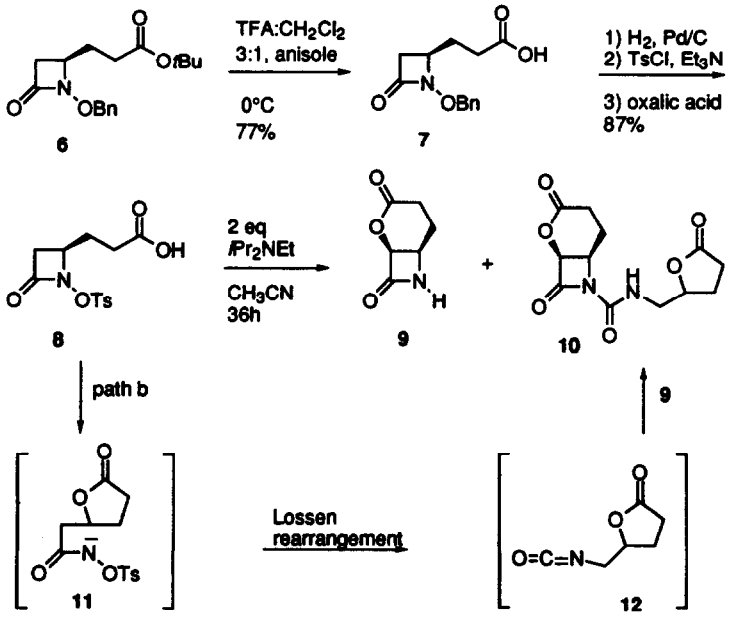
Scheme 2

RESULTS AND DISCUSSION

Both oxygen-based (carboxylate) and nitrogen-based nucleophiles were studied. In order to attempt an intramolecular reaction with the carboxylate ion, a potent nucleophile in the intermolecular nucleophile transfer reaction,[1b] access to *N*-tosyloxy-β-lactam **8** was necessary. The catalytic, asymmetric synthesis of *t*-butyl ester β-lactam **6** has been described.[4] Under carefully controlled conditions, the *t*-butyl ester of **6** was removed with trifluoroacetic acid in the presence of anisole to furnish carboxylic acid **7**. The benzyl group of **7** was removed by hydrogenolysis and the intermediate *N*-hydroxy β-lactam[11] was reacted with tosylchloride and Et_3N to produce **8**. Compound **8** decomposed upon storage and was generally used as soon as possible.

When activated β-lactam **8** was treated with two equivalents of diisopropylethylamine (DIEA) in acetonitrile, typical conditions for intermolecular nucleophile transfer reactions described earlier,[1b] a reaction occurred to provide the desired bicyclic product **9** in 20% yield. The *cis* configuration was readily determined by the coupling constant (5.2 Hz) between the two bridgehead protons on the β-lactam ring.[12] The reaction was fairly clean but surprisingly the mass recovery was low after column chromatography. The product distribution was found to be concentration dependent. For instance, reaction of **8** at 0.01 M with DIEA afforded the desired product **9** while reaction at 0.02 M produced a mixture of **9** and **10** in a ratio of 1:2 in 51% total yield.

Presumably, the formation of **10** occurred by competing pathway (b). Carboxylate anion attack at the C4 position of *N*-tosyloxy β-lactam **8** in an intramolecular S_N reaction gave hydroxamate anion **11** which underwent facile Lossen rearrangement to isocyanate **12**. Subsequent reaction of the isocyanate with the desired product **9** formed the observed by-product **10**. Other decomposing reactions with isocyanate **12** may account for the low mass recovery observed in this reaction.

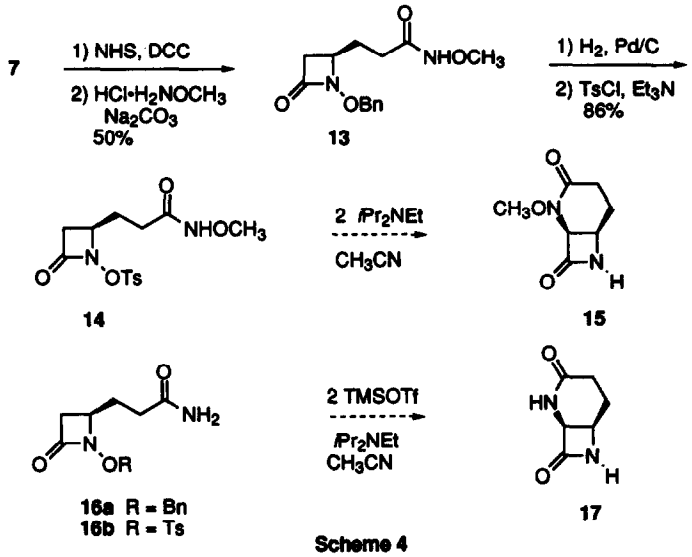


Scheme 3

The demonstration that intramolecular reaction with the carboxylate ion of **8** was possible led to the investigation of some suitably acidified amide substituents to test the feasibility of an intramolecular delivery of a nitrogen nucleophile.

O-Methyl hydroxamate **14** was prepared to attempt an intramolecular cyclization (Scheme 4). Activation of carboxylic acid **7** with DCC and subsequent reaction with *O*-methylhydroxylamine provided hydroxamate **13**. Hydrogenolytic removal of the benzyl group of **13** followed by tosylation of the intermediate *N*-hydroxy β-lactam provided **14**.

Interestingly, treatment of **14** with two equivalents of DIEA in CH_3CN did not produce any of the desired bicyclic product **15**. Only decomposition of the starting material occurred. Likewise, attempted cyclization of the *in situ* prepared bis trimethylsilyl derivative of amide **16**,[13] prepared in a similar manner as **14** (see experimental section), did not produce any of the desired bicyclic product **17**. Possibly these substrates have insufficient nucleophilicity for successful reaction under the conditions employed. In fact, bis(trimethylsilyl)acetamide had proven ineffective as a nucleophile in the intermolecular reaction previously.[1b] The pKa of hydroxamate **14** is approximately 9, while that of Et_3NH^+ is 10.35. Perhaps the concentration of the nitrogen anion of **14** is not sufficient to trap the proposed *in situ* generated enol and other decomposing pathways predominate.

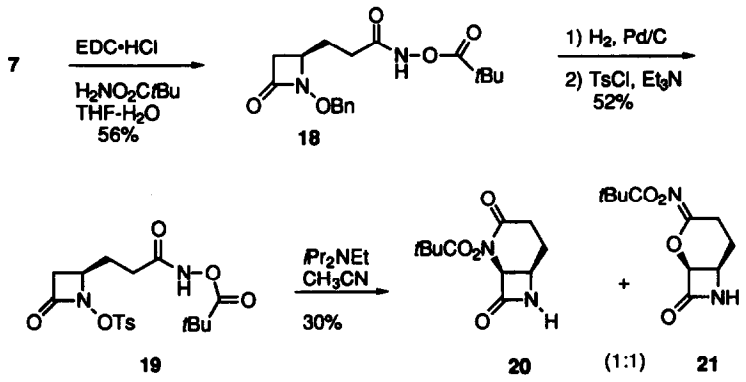


Scheme 4

In order to circumvent these apparent problems, the more acidic *O*-pivaloyl hydroxamate (pKa ~ 6.5-7) **19** was prepared (Scheme 5). The *O*-pivaloyl hydroxamate functionality was chosen simply because of its relatively high stability compared to other *O*-acyl hydroxamates.[14] Water soluble carbodiimide[15] promoted coupling of *O*-pivaloyl hydroxylamine to carboxylic acid **7** provided **18**. The preparation of *N*-tosyloxy β-lactam **19** followed typical conditions.

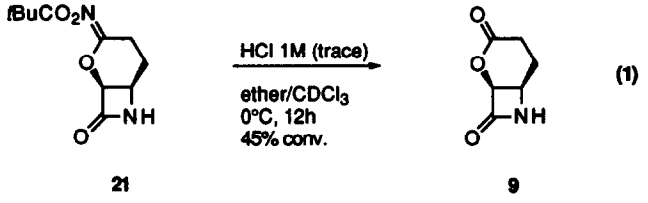
Indeed, treatment of **19** with two equivalents of DIEA in CH_3CN gave a 30% yield of two intramolecular cyclized products **20** and **21** in a 1:1 ratio derived from *N*- and *O*-alkylation respectively. Both products **20** and **21** contained *cis* stereochemistry. Using CH_2Cl_2 as solvent, the ratio of *N*- and *O*-alkylated products was improved to 3:1. The *N*-alkylated product was increased to a 6:1 ratio using DBU as

base; however, the reaction mixture was more complex and the yield of the desired product **20** was not significantly improved.



Scheme 5

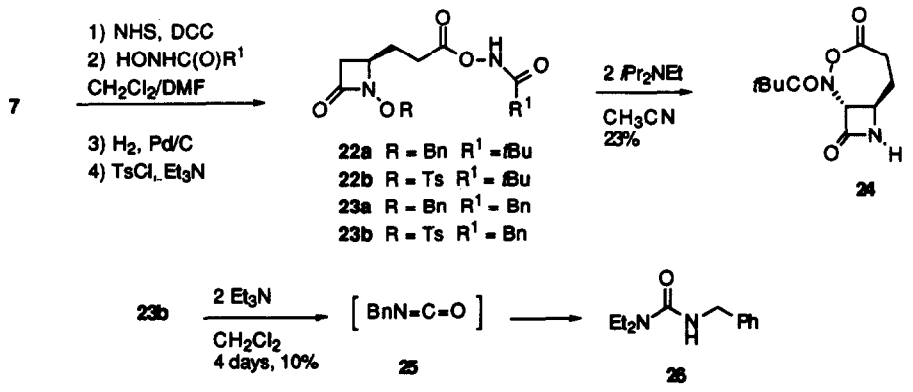
Close examination of the ^1H NMR spectra of both *N*- and *O*-alkylated products **20** and **21** revealed that the chemical shifts and splitting patterns of *O*-alkylated product **21** resembled those of bicyclic compound **9**. The infrared spectra of both the *N*- and *O*-alkylated products also provided clues to their structural identities. The C=O absorption band of the hydroxamate in **20** was at 1675 cm^{-1} while that of the C=N bond in **21** was found at 1625 cm^{-1}. Finally, the assignments for the *N*- and *O*-alkylated products were unambiguously determined by hydrolysis of **21** to **9** with a trace amount of dilute acid (Equation 1).



With the goal of obtaining only the *N*-alkylated bicyclic product, hydroxamates **22b** and **23b**, where the *N-O* linkage is reversed compared with **19**, were prepared by a routine procedure (Scheme 6). Cyclization of hydroxamates **22b** and **23b** was anticipated to favor formation of a seven-membered ring derived from *N*-alkylation compared to a nine-membered ring derived from carbonyl *O*-alkylation.

Treatment of **22b** with two equivalents of DIEA in CH_3CN provided some of the desired bicyclic product **24**. Interestingly, the cyclized material contained *trans* stereochemistry. Whether the longer side chain on C4 of **22b** accommodates a *trans* transition state or the product was originally introduced as *cis* and epimerized to the more thermodynamically stable *trans* product is not known.

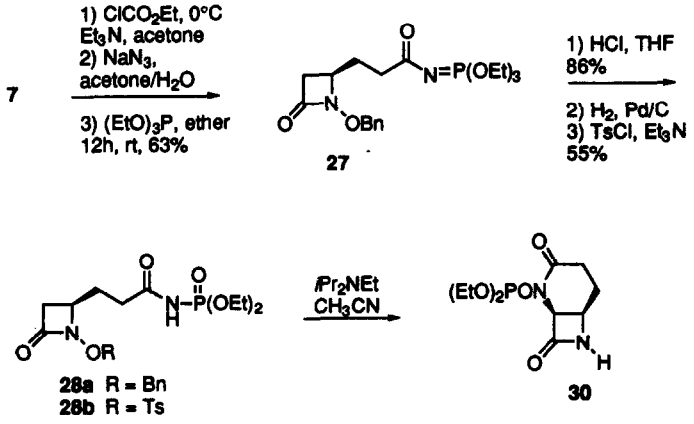
Interestingly, treatment of hydroxamate **23b** with two equivalents of Et_3N did not provide any of the desired bicyclic β-lactam, but only urea **26** was isolated. Presumably, urea **26** originated from isocyanate **25** derived from a more competitive Lossen rearrangement from the side chain of **23b**.[16] Subsequent reaction of isocyanate **25** with Et_3N followed by loss of ethene would account for the observed product.



Scheme 6

N-Acyl phosphoramides have been reported to be quite nucleophilic at nitrogen in the Mitsunobu reaction.[17] In an attempt to exploit this concept in an intramolecular nucleophile transfer reaction, *N*-acyl phosphoramide **28b** was prepared. Preliminary investigation of coupling diethyl phosphoramide to an activated ester of **7** in refluxing acetonitrile did not result in an effective reaction. However, **28a** could be synthesized by another route (Scheme 7). Formation of the mixed anhydride of **7** followed by the addition of NaN_3 afforded an acyl azide. Reaction with triethylphosphite gave acyl phosphinimine **27**. Quick reaction of **27** with dry HCl in THF provided *N*-acylphosphoramide **28a**. *N*-Tosyloxy β-lactam **28b** was formed by hydrogenolytic removal of the benzyl group and subsequent tosylation of the *N*-hydroxy β-lactam in 55% overall yield from **28a**.

Attempted intramolecular nucleophile transfer reaction with **28b** by treatment with two equivalents of DIEA in CH_3CN resulted in only a small amount (5%) of desired product **30** as observed in the crude ^1H NMR. Chromatographic purification of **30** was difficult due to the highly polar nature of the product.

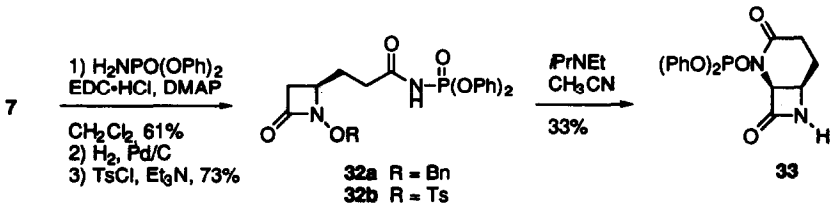


Scheme 7

Concurrent studies with *N*-acylphosphoramide **32b** were more fruitful (Scheme 8). Diphenylphosphoramide was effectively coupled to carboxylic acid **7** using a water soluble carbodiimide, and 4-dimethylaminopyridine (DMAP) in CH_2Cl_2 to provide **32a**. Subsequent removal of the benzyl group and tosylation provided **32b** for cyclization studies.

Remarkably, *N*-acylphosphoramide **32b** produced *N*-alkylated bicyclic β-lactam **33** with the desired *cis* stereochemistry in 33% yield upon treatment with DIEA in CH_3CN. Apparently, the more electron withdrawing phenyl groups on **32b** compared with the ethyl groups of **28b** acidify the *N-H* bond of the *N*-acylphosphoramide and allowed for a more effective nucleophile transfer reaction. This is consistent with the results obtained with hydroxamates **14** and **19**. Chromatographic separation of phenyl derivative **33** also was more convenient than ethyl derivative **30**.

The coupling constant between the proton α to the β-lactam carbonyl and the phosphorous was 10 Hz and was indicative of *N*-alkylated product **33**.[18] None of the corresponding *O*-alkylated product was detected in this reaction. This was the best intramolecular reaction for a nitrogen nucleophile tested in this study. The remainder of the material had low solubility in both organic solvents and water. Analysis by mass spectroscopy indicated fragments over 1000 which suggested a polymeric composition.



Scheme 8

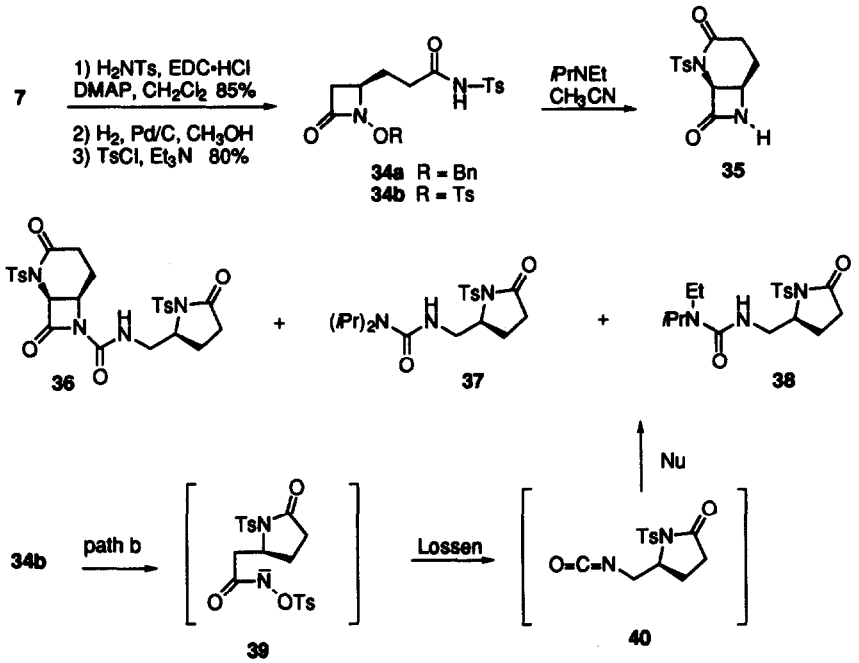
N-Acyl sulfonamides reportedly also gave selective nitrogen alkylations in the Mitsunobu process.[19] For preparing this functionality to test in the intramolecular nucleophile transfer reaction, several coupling conditions with acid **7** and tosylamide were tried. However, only the use of a water soluble carbodiimide and a full equivalent of DMAP in CH_2Cl_2 provided *N*-acyl sulfonamide **34a** in good yields (Scheme 9).[20] The benzyl group of **34a** was removed by hydrogenation and the intermediate *N*-hydroxy β-lactam was immediately allowed to react with tosylchloride to give activated β-lactam **34b** in 80% yield after chromatography. The pK_a of the *NH* bond of *N*-acyl sulfonamide **34b** was estimated to be between 8-9 based on literature precedent[21] and appeared to be within the range of pK_a's useful for nucleophile transfer ($pK_a < 9$).

Surprisingly, attempted intramolecular cyclization with two equivalents of DIEA in CH_3CN did not give any of desired product **35**. After aqueous workup and column chromatography, products **36** (10%), **37** (12%), and **38** (9%) were isolated instead. The mass recovery was generally low (35-45%) as it was in all of the attempted intramolecular cyclizations. Changing the reaction concentration from 0.035 M to 0.2 M did not appear to have any effect on the product ratio. The use of 15 equivalents of DIEA in the reaction, however, led to the isolation of the desired *cis* product **35** in 12% yield along with by-products **36** (4%), **37** (12%) and **38** (3%).

By-products **36-38** are believed to be formed from a common competing pathway (b). Presumably, *N*-acylsulfonamide **34b** competitively reacted at the C4 position of the β-lactam in an intramolecular S_N reaction and displaced hydroxamate **39** which underwent fast Lossen rearrangement to provide isocyanate

40. Subsequent reaction of isocyanate **40** with the amide of desired product **35** gave dimer **36**. Even the hindered DIEA apparently reacted with the isocyanate **40**, and following the loss of ethene and propene, respectively, **37** and **38** were formed. Starting with optically active **34** led to the isolation of optically active **37**, which gave support for the initial competing intramolecular S_N reaction and likewise the stereochemistry assigned for products **36-38**.

Simple evaporation and then analysis of the crude reaction mixture before purification by mass spectrometry (FAB) gave evidence for cationic DIEA adducts with isocyanate **40** as well as dimers. These compounds were not able to be purified most likely due to the highly polar nature of the cation and their reactivity.

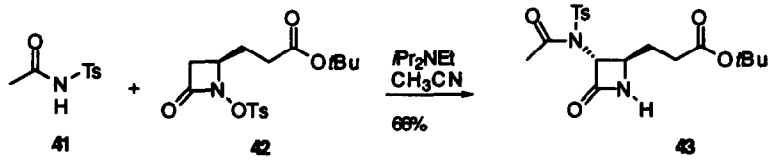


Scheme 9

The effect of changing the cation on the *N*-acylsulfonamide **34b** was studied to see if the ratio of products from cyclization could be changed. Treatment of **34b** with one equivalent of BuLi at -78°C followed by the addition of two equivalents of DIEA in THF resulted in a very low mass recovery (25%) after aqueous workup which contained mostly starting material among other unidentified products. The use of cesium carbonate[22] as base led to a complex mixture which did not contain the desired product **35**. Interestingly, with trimethylaluminum as base, only recovered starting material **34b** (97%) was recovered after an acidic aqueous quench. However, the use of Me_3Al in THF while in the presence of five equivalents of DIEA resulted in a reaction that gave, after chromatography, 16% of desired product **35** and 15% recovered starting material after three days reaction time. Surprisingly, the reaction was slower in the presence of added Me_3Al than when only DIEA was used as base.

In order to test the effectiveness of the previously unexplored *N*-acylsulfonamide functionality in the intermolecular nucleophile transfer reaction, **41** was prepared from acetyl chloride and tosylamide (Scheme 10).[23] Interestingly, *N*-acyl sulfonamide **41** was found to react with *N*-tosyloxy β-lactam **42**,[24] under conditions typical for intermolecular reaction,[1b] and gave exclusively *trans* addition product **43** derived only from *N*-alkylation in good yield (66%). This result was remarkable because **41** was the largest nucleophile transferred to date and also one of the best yielding. It also suggests that the addition of biologically important side chains to the α-position of β-lactams may be possible.

After observing the successful *intermolecular* addition of *N*-acylsulfonamide **41**, it appeared that the complications observed in the intramolecular reaction of **34**, and potentially the low yields observed in all of the intramolecular substrates tested, may be due to a competing intramolecular S_N reaction at the C4 carbon of the β-lactam. Competitive S_N2 reactions at the C4 carbon of *N*-tosyloxy β-lactams have not been observed in intermolecular nucleophile transfer reactions and may be particular to intramolecular reactions where there is a competition between forming a five membered ring from an S_N reaction or a six membered ring from intramolecular nucleophile transfer reaction. The fact that **34** gave the desired product **35** only with use of a large excess of DIEA provides support that the previously postulated enolization[1] is the rate determining step for addition of nucleophiles to the α-carbon of the β-lactam.



Scheme 10

In summary, intramolecular nucleophile transfer reaction to *N*-tosyloxy β-lactams with concomitant loss of tosylate anion, to form a new six-membered ring is feasible but low yielding with the substrates tested. The intramolecular process generally gave expected *cis* addition products and complements the intermolecular addition of nucleophiles to *N*-tosyloxy β-lactams which gave predominantly *trans* addition. Apparently, the pK_a of the nucleophile must be 9 or less for successful tertiary amine promoted reaction. The major competing reaction appears to be an intramolecular S_N reaction of the nucleophile at the C4 carbon of the *N*-tosyloxy β-lactam. A reactive *O*-tosyloxyhydroxamate was generated from this side reaction which underwent facile Lossen rearrangement to give an isocyanate intermediate. A variety of reactions are possible with this isocyanate intermediate, some of which have been noted and characterized. Optimization of the intramolecular nucleophile transfer reaction will depend upon limiting this prevailing decomposing pathway and could lead to a synthetically useful process. Studies to determine if a new five membered ring can be formed with this new intramolecular process and the effectiveness of different nucleophiles are currently under investigation.

EXPERIMENTAL

General Methods. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^1H NMR and ^{13}C NMR spectra were obtained on a General Electric GN-300 spectrometer and were performed in chloroform-*d*. ^1H NMR chemical shifts are reported in parts per million relative to tetramethylsilane. *J* values are given in hertz. For ^{13}C NMR, reference was the center peak of chloroform-*d* (77.0 ppm). Infrared spectra were recorded on a Perkin-Elmer 1420 spectrophotometer. TF

refers to thin film, and KBr refers to potassium bromide disk. Electron impact (EI) mass spectra, Chemical ionization (CI) mass spectra, and fast atom bombardment (FAB) were recorded on an AEI Scientific Apparatus MS 902 and Finnigan MAT Model 8430 spectrometers. Analytical TLC was carried out using commercially available aluminum-backed 0.2-mm silica gel 60 F-254 plates. Flash silica gel column chromatography was conducted using Merck silica gel 60 (230-400 mesh).

All reactions were periodically monitored by TLC and worked up after the complete consumption of starting material unless specified otherwise. Solvents for flash column chromatography were distilled. Anhydrous methylene chloride, acetonitrile, triethylamine, and diisopropylethylamine (DIEA) were freshly distilled from CaH_2 and stored under nitrogen. All purchased reagents were of reagent grade quality and were used without further purification.

2-Azetidinepropanoic acid, 1-(phenylmethoxy)-4-oxo (7):[25] β-Lactam *t*-butyl ester **6** [4] (1g, 3.28 mmol) was dissolved in 1 mL of CH_2Cl_2 and cooled in an ice bath. Anisole (355 μL, 3.28 mmol), followed by trifluoroacetic acid (3 mL), was added and stirred for 2.5 h at 0°C. Toluene (15 mL) was added and the solvents were evaporated *in vacuo*. The residue was dissolved in 15 mL of ethyl acetate and extracted with three 10 mL portions of saturated $NaHCO_3$ solution. The combined aqueous layer was acidified to pH = 2 by slow addition of 3 M HCl. The aqueous layer was extracted with four 20 mL portions of CH_2Cl_2. The pooled organic extracts were dried over Na_2SO_4, filtered, and evaporated to give 619 mg (77%) of **7** as an oil. If the reaction was left for longer reaction times or higher temperatures, a by-product was formed which was not fully characterized but was carried throughout all of the extraction process and thus appeared to be a carboxylic acid. An analytical sample of acid **7** was obtained by recrystallization from ether-hexanes to yield colorless prisms: mp 62-64°C; TLC (ethyl acetate with 3 drops of acetic acid) $R_f = 0.35$ (UV, PMA). ^1H NMR δ 7.39 (m, 5H), 4.96 (dd, 2H, AB system), 3.55 (m, 1H), 2.75 (dd, 1H, J = 5.2, 13.8), 2.32 (dd, 1H, J = 2.4, 13.8), 1.87-1.99 (m, 1H), 1.72-1.84 (m, 1H); ^{13}C NMR δ 177.5, 164.1, 135.0, 129.4, 129.1, 128.7, 78.3, 57.0, 37.6, 29.9, 27.4; $[\alpha]^{23} = 29.5°$ ($CHCl_3$, c = 0.95); IR (CCl_4) 3700-2500 (br), 1775, 1750, 1710 cm^{-1}; HRMS (EI) Calcd for $C_{13}H_{15}NO_4$ 249.1001, Found: 249.1011.

2-Azetidinepropanoic acid, 1-[[(4-methylphenyl)sulfonyl]oxy]-4-oxo (8): To a solution of **7** (57 mg, 0.23 mmol) in methanol (2.0 mL) was added 10% Pd on C and the solution was placed under a hydrogen balloon for 4 h. After filtration and concentration, the resultant *N*-hydroxy-β-lactam was used in the next reaction without further purification. To a solution of this *N*-hydroxy-β-lactam in CH_3CN was added TsCl (43.6 mg, 0.23 mmol) and Et_3N (0.064 mL, 0.46 mmol). After 10 min, $HO_2CCO_2H{\cdot}2H_2O$ (28.8 mg, 0.23 mmol) was added to the reaction mixture. After 1 min, the reaction was concentrated under reduced pressure and the residue was purified by column chromatography with pure ethyl acetate as the eluent to yield **8** as an oily product (52 mg, 72.6%). ^1H NMR δ 1.96-2.05 (m, 1H), 2.11-2.26 (m, 1H), 2.47 (s, 3H), 2.48-2.53 (m, 3H), 2.90 (dd, J_1 = 6.0, J_2 = 14.5, 1H), 4.08-4.12 (m, 1H), 7.39 (d, J = 8.0, 2H), 7.88 (d, J = 8.4, 2H), 8.75 (b, 1H); ^{13}C NMR δ 21.8, 27.0, 29.6, 37.9, 58.8, 129.2, 130.0, 130.5, 146.6, 165.0, 177.7; IR (TF) 3650-2500 (br), 1800, 1710 cm^{-1}; MS (FAB) 314 (MH^+); MS (EI) 313 (M^+), 172, 155, 141, 97, 91; HRMS (FAB) MH^+ Calcd for $C_{13}H_{25}NO_6S$ 314.0698, Found 314.0698.

2-Oxa-7-azabicyclo [4.2.0] octane, 3,8-dioxo (9): To a solution of **8** (213 mg, 0.68 mmol) in CH_3CN (22 mL) was added DIEA (0.24 mL, 1.36 mmol). The reaction mixture was left for 60 h at room temperature (monitored by TLC) and then passed through a plug of silica gel to remove salts and any polar impurities. The clear oil contained mainly desired product **9** and by-product **10** in a ratio of 1:2 (by ^1H NMR analysis). These products were further purified by column chromatography with pure ethyl acetate to a yield colorless oil (49 mg, 51% combined yield. Note that these two products were isographic on TLC. This made the complete separation of the two products by column chromatography difficult). ^1H NMR δ 2.02-2.10 (m, 1H), 2.23-2.30 (m, 1H), 2.64-2.70 (m, 2H), 4.19 (t, J = 4.3, 1H), 5.39 (dd, J_1 = 2.2, J_2 = 5.2, 1H),

6.05 (b, 1H); IR (TF) 3300, 2985, 2940, 1760-1790 cm^{-1}; MS (CI with isobutane), MH^+ 142; HRMS (FAB) MH^+ Calcd for $C_6H_7NO_3$ 142.0504, Found 142.0507. **By-product 10**: ^1H NMR δ 1.90-2.71 (m, 8H), 3.35-3.52 (m, 1H), 3.65-3.79 (m, 1H), 4.58 (t, J = 3.1, 1H), 4.63-4.69 (m, 1H), 5.47 (d, J = 5.7, 1H), 6.81 (b, 1H); IR (TF) 3360, 2980, 1760-1785, 1695, 1530 cm^{-1}; MS (FAB) MH^+ 283 , 243, 229.

2-Azetidinepropanamide, N-methoxy-1-[[(4-methylphenyl)sulfonyl]oxy]-4-oxo (14). To a solution of **7** (306 mg, 1.23 mmol) and *N*-hydroxysuccinimide (141 mg, 1.23 mmol) in CH_2Cl_2 (5 mL) was added a solution of dicyclohexylcarbodiimide (255 mg, 1.23 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was stirred for 12 h. The solvent was evaporated and the residue was purified by column chromatography with ethyl acetate/hexanes (1:1) to yield the corresponding *N*-hydroxysuccinimide active ester. To a solution of the *N*-hydroxysuccinimide ester and $NaHCO_3$ in THF (3 mL) and H_2O (3 mL) was added NH_2OCH_3·HCl (15 mg, 1.50 mmol). The reaction mixture was stirred for 12 h and concentrated to remove most of the THF. The aqueous layer was extracted with ethyl acetate four times. The combined organic layers were dried, concentrated and purified by column chromatography with ethyl acetate as the eluting solvent to provide **13** as a white solid (188 mg, 50%). Mp 93.5-95 °C; ^1H NMR δ 1.76-2.09 (m, 4H), 2.27 (d, J = 13.6, 1H), 2.65 (dd, J_1 = 5.1, J_2 = 13.6, 1H), 3.58-3.59 (m, 1H), 3.67 (s, 3H), 4.88 (dd, J = 10.9, 13.4, 2H), 7.37 (s, 5H), 9.94 (b, 1H); ^{13}C NMR δ 27.5, 28.3, 37.1, 56.9, 63.9, 78.0, 128.5, 128.9, 129.1, 134.7, 163.9, 169.3; IR (KBr) 3220, 3000, 1760, 1650 cm^{-1}; MS (CI) MH^+ 279, 261, 232, 186, 174, 146; HRMS Calcd for $C_{14}H_{17}N_2O_3$ (M^+-OH) 261.1239, Found 261.1244.

Compound **13** (39 mg, 0.14 mmol) in CH_3OH (3 mL) was subjected to hydrogenolysis as described for compound **8** for 1 h. The resulting *N*-hydroxy β-lactam without further purification, was reacted with tosyl chloride (24.5 mg, 0.13 mmol) and Et_3N (0.018 mL, 0.13 mmol) in CH_2Cl_2 (2 mL) for 10 min. The solvent was evaporated and residue was purified by column chromatography with ethyl acetate as eluting solvent to provide **14** as a white solid (43 mg, 86%). Mp 95-96.5 °C; ^1H NMR δ 2.08-2.28 (m, 4H), 2.46 (s, 3H), 2.52 (dd, J_1 = 2.9, J_2 = 14.6), 2.90 (dd, J_1 = 5.9, J_2 = 14.5, 1H), 3.76 (s, 3H), 4.08-4.09 (m, 1H), 7.39 (d, J = 8.0, 2H), 7.85-7.88 (d, J = 8.0, 2H), 9.53 (b, 1H); IR 3060, 1805, 1650, 1380, 1195, 1180 cm^{-1}.

2-Azetidinepropanamide, 1-[[(4-methylphenyl)sulfonyl]oxy]-4-oxo (16b): β-Lactam carboxylic acid **7** (780 mg, 3.13 mmol) was dissolved in CH_2Cl_2 (16 mL) and *N*-hydroxysuccinimide (378 mg, 3.29 mmol) followed by 1-ethyl-3-(dimethylaminopropyl) carbodiimide (EDC•HCl) (645 mg, 3.75 mmol) were added. After stirring for 1.5 h, NH_4Cl (335 mg, 6.26 mmol) and triethylamine (875 μL, 6.26 mmol) were added. After 18 h, the organic layer was washed with two portions of 2M NH_4OH, once with 10% citric acid, filtered and evaporated. Column chromatography was done with 5% methanol in ethyl acetate to give 275 mg (35%) of **16a** as an oil after evaporation. Note, the oil contained ~5-10% of an unidentified by-product which was inseparable by column chromatography at this point. The oil did was not able to be recrystallized. ^1H NMR δ 7.38 (m, 5H), 6.08-6.12 (br d, J = 11.4, NH_2), 4.92 (d, 2H, 1.5), 3.61 (m, 1H), 2.69 (dd, 1H, J = 5.1, 13.8), 2.31 (dd, 1H, J = 2.1, 13.8), 2.1-2.25 (m, 2H), 1.75-2.01 (m, 2H); ^{13}C NMR δ 174.3, 163.9, 134.8, 129.1, 128.9, 128.5, 78.0, 56.9, 37.2, 30.9, 27.6; IR neat oil 3320 s br, 1760, 1665 cm^{-1}; HRMS (FAB) MH^+ Calcd for $C_{13}H_{16}N_2O_3$ 249.1239, Found 249.1247.

O-Benzyl β-lactam amide **16a** (200 mg, 0.806 mmol) was dissolved in methanol (2 mL) and 10% Pd on C (50 mg) was added. The stirred solution was placed under a hydrogen balloon. After 1.5h, the catalyst was removed by filtration through celite and rinsed with ethyl acetate. The pooled organic layer was evaporated and the residue was dissolved in CH_2Cl_2 (2 mL). Tosyl chloride (155 mg, 0.806 mmol) and triethylamine (115 μL, 0.806 mmol) were added and stirred for 20 min. The solvent was evaporated and the residue was dissolved in a minimal amount of $CHCl_3$ and placed on a silica gel column containing 5% methanol in ethyl acetate. The product fractions were collected (R_f = 0.1, ethyl acetate, UV detection) and

evaporated to give 160 mg (64%) of **16b** as an oil. ^{1}H NMR δ 7.86 (d, 2H, *J* = 8.4), 7.38 (d, 2H, *J* = 8.4), 6.25 (br d, 2H, *J* = 22.3 Hz), 4.05 (m, 1H), 2.88 (dd, 1H, *J* = 6.0, 14.4), 2.50 (dd, 1H, *J* = 3.3, 14.4), 2.45 (s, 3H), 2.33 (t, 2H, *J* = 7.5), 2.05-2.2 (m, 1H), 1.9-2.05 (m, 1H); ^{13}C NMR δ 174.4, 165.5, 146.6, 130.1, 130.0, 129.0, 59.1, 37.6, 30.9, 27.5, 21.7; IR neat oil 3415, 1795, 1650-1680 cm^{-1}; HRMS (FAB) MH$^+$ Calcd for $C_{13}H_{16}N_2O_5S$ 313.0858, Found 313.0858.

2-Azetidinepropanamide, N-(2,2-dimethyl-1-oxopropoxy)-1-(phenylmethoxy)-4-oxo (18): A solution of **7** (86 mg, 0.345 mmol) and *O*-pivaloylhydroxylamine hydrochloride (64 mg, 0.414 mmol) in a mixture of THF and H_2O (25 mL, 1:1) was adjusted with 0.5 N NaOH to pH = 4.5. To the above solution was added EDC•HCl (240 mg, 1.24 mmol) divided into 6 portions (5 min for each portion). The reaction mixture was stirred at room temperature for 30 min over which time the pH of the solution was maintained at 4.5-5.0 with addition of either 0.5N NaOH or 1.5 N HCl as needed. The solution was extracted with three 10 mL portions of ethyl acetate. The combined organic layers were washed with brine and dried over $MgSO_4$ and filtered. The dried solution was concentrated and the residue was purified by column chromatography with ethyl acetate / hexanes (1:1) to afford **18** as an oil (67 mg, 56%). ^{1}H NMR δ 1.31 (s, 9H), 1.86-1.99 (m, 2H), 2.22-2.27 (m, 2H), 2.31 (dd, J_1 = 2.2, J_2 = 13.8), 2.72 (dd, J_1 = 5.2, J_2 = 13.8, 1H), 3.64-3.68 (m, 1H), 4.95 (s, 2H), 7.38-7.39 (m, 5H), 9.64 (b, 1H); ^{13}C NMR δ 26.9, 27.4, 28.1, 37.2, 38.1, 56.7, 78.0, 128.5, 129.0, 129.2, 134.7, 164.0, 169.4, 176.2; IR (TF) 3200, 2980, 1775, 1710, 1085 cm^{-1}; MS (CI with isobutane) 349 (MH$^+$), 247, 141, 107, 103.

2-Azetidinepropanamide, N-(2,2-dimethyl-3-oxopropoxy)-1-[[(4-methylphenyl)sulfonyl]oxy]-4-oxo (19): A solution of **18** (60 mg, 0.172 mmol) in methanol (3 mL) was hydrogenolyzed by Pd/C for 1 h as described for the conversion of **16a** to **16b**. After filtration and concentration, the resultant *N*-hydroxy β-lactam was used for the next reaction without further purification. To a solution of this *N*-hydroxy β-lactam in CH_2Cl_2 (2 mL) was added TsCl (32.9 mg, 0.172 mmol) and Et_3N (0.024 mL, 0.172 mmol). The reaction mixture was stirred at room temperature for 30 min. After concentration, the residue was purified by column chromatography with ethyl acetate / hexanes (1:1) to afford **19** as an oily product (37 mg, 52%). ^{1}H NMR δ 1.33 (s, 9H), 2.15-2.22 (m, 2H), 2.45-2.54 (m, 3H), 2.47 (s, 3H), 2.90 (dd, J_1 = 6.0, J_2 = 14.6), 4.14-4.20 (m, 1H), 7.39 (d, *J* = 8.4, 2H), 7.89 (d, *J* = 8.3, 2H); IR (TF) 3240, 2980, 1790, 1780, 1700, 1680 cm^{-1}; MS 413 (M$^+$H), 329, 296, 241, 184, 155, 137, 91; HRMS (FAB) MH$^+$ Calcd for $C_{18}H_{24}N_2O_7S$ 413.1382, Found 413.1386.

2,7-Diazabicyclo [4.2.0] octane, 3,8-dioxo-2-(2,2-dimethyl-1-oxopropoxy) (20) and 2-Oxa-7-azabicyclo [4.2.0] octane, 3-[imino(2,2-dimethyl-1-oxo-propoxy)]-8-oxo (21): To a solution of **19** (64 mg, 0.15 mmol) in CH_3CN (10 mL) was added DIEA (0.054 mL, 0.3 mmol). The reaction mixture was left at room temperature for 60 h and turned brown. After concentration under reduced pressure, the residue was purified by column chromatography with ethyl acetate to yield a mixture of **20** and **21** as white solids (11 mg, 30%). ^{1}H NMR spectrum indicated the ratio of **20** to **21** was 1:1. These two products could only be enriched from each other through column chromatography. **Compound 20:** ^{1}H NMR δ 1.33 (s, 9H), 2.05-2.16 (m, 2H), 2.57-2.62 (m, 2H), 4.38-4.41 (m, 1H), 4.74 (dd, J_1 = 1.7, J_2 = 5.7, 1H), 5.86 (b, 1H); IR (TF) 3280, 2980, 1775, 1765, 1685; MS 197 (M$^+$-43), 156, 113, 57; HRMS (FAB) MH$^+$ Calcd for $C_{11}H_{16}N_2O_4$ 241.1188, Found 241.1200. **Compound 21:** Mp 163-167 °C (dec.). ^{1}H NMR δ 1.27 (s, 3H), 1.96-2.06 (m, 1H), 2.22-2.30 (dtd, J_1 = 14.8, J_2 = 3.6, J_3 = 1.2, 1H), 2.68-2.71 (m, 2H), 4.21-4.25 (m, 1H), 5.29 (dd, J_1 = 2.0, J_2 = 5.3, 1H), 5.92 (b, 1H); IR (TF) 3240, 2980, 2880, 1755-1780, 1645 cm^{-1}; MS 241, 157, 57; HRMS FAB MH$^+$ Calcd for $C_{11}H_{16}N_2O_4$ 241.1188, Found 241.1191.

The conversion of (21) to (9). To a solution of **21** (5 mg) in a mixture of ether (1.0 mL), ethyl acetate (1.0 mL) and chloroform (0.5 mL) was added 3 drops of HCl (1M in H_2O). This reaction mixture

was stored at 0 °C overnight and then dried over $MgSO_4$. ^1H NMR spectrum of the concentrated reaction revealed a clean mixture of **21** and **9** in a ratio of 1:1.

2-Azetidinepropanoic acid, *O*-[(2,2-dimethyl-1-oxo-propyl)amino]-1-(phenylmethoxy)-4-oxo (22a). To a solution of **7** (324 mg, 1.30 mmol) in CH_2Cl_2 in an ice bath (10 mL) was added *N*-hydroxysuccinimde (179.5 mg, 1.56 mmol). To this solution was added a solution of dicyclohexylcarbodiimide (268 mg, 1.31 mmol) in CH_2Cl_2 (2.0 mL). The reaction mixture was stirred for 12 h. The white precipitate of dicyclohexylurea was removed by filtration through celite and the solution was concentrated under reduced pressure to yield an *N*-hydroxysuccinimidyl ester as an oily product. Without further purification, the residue was dissolved in a mixture of CH_2Cl_2 and DMF (8:3). To this solution was added *N*-2,2-dimethylpropionyl hydroxylamine (152.0 mg, 1.30 mmol) at room temperature. The coupling reaction was stirred for 15 h. The reaction mixture was poured into cold brine (5.0 mL) and separated. The organic layer was further washed with brine (5.0 mL) to remove most of the DMF and the hydroxylamine derivative. The combined organic layers were dried over $MgSO_4$. After filtration and concentration, the product was purified by column chromatography (ethyl acetate/hexanes 1:1) to yield desired product **22a** as a colorless oil (274 mg, 61%). ^1H NMR δ 1.27 (s, 9H), 1.83-2.26 (m, 2H), 2.32 (dd, J_1 = 2.4, J_2 = 13.8, 1H), 2.49 (t, J = 7.2, 2H), 2.76 (dd, J_1 = 5.2, J_2 = 13.8, 1H), 3.61-3.66 (m, 1H), 4.93 (d, J = 11.0, 1H), 4.98 (d, J = 11.0, 1H), 7.27-7.41 (m, 5H), 9.15 (b, 1H); ^{13}C NMR δ 25.5, 27.1, 27.5, 27.9, 37.6, 55.4, 78.1, 128.7, 129.1, 129.4, 135.0, 163.7, 170.9, 176.9; IR (TF) 3250, 2970, 1745-1785 (b), 1685 cm^{-1}; MS (CI with isobutane) MH^+ 349, 335, 250, 232, 225, 215, 156 (base peak), 144.

2-Azetidinepropanoic acid, *O*-[(2,2-dimethyl-1-oxo-propyl)amino]-1-[[(4-methylphenyl)sulfonyl]oxy]-4-oxo (22b) Compound **22a** (137 mg, 0.39 mmol) in methanol (10 mL) was subjected to hydrogenolysis catalyzed by Pd/C for 1 h according to the procedure used to convert **16a** to **16b**. The resultant product, without further purification, was dissolved in CH_2Cl_2 (3.0 mL). To the above solution was added TsCl (75.0 mg, 0.39 mmol) and TEA (0.05 mL, 0.39 mmol). After 40 min, the reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography (ethyl acetate/hexanes 3:1) to yield the desired product **22b** as an oil (83 mg, 51%). ^1H NMR δ 1.27 (s, 9H), 2.03-2.36 (m, 2H), 2.47 (s, 3H), 2.51 (dd, J_1 = 3.3, J_2 = 14.6, 1H), 2.63 (t, J = 7.3, 2H), 2.92 (dd, J_1 = 6.1, J_2 = 14.6, 1H), 4.11-4.14 (m, 1H), 7.39 (d, J = 8.2, 2H), 7.87 (d, J = 8.3, 2H), 9.17 (b, 1H); IR (TF) 3250, 2970, 1795, 1680 cm^{-1}; MS 412 (M^+), 296, 172, 155, 141, 124, 107, 91; HRMS (FAB) MH^+ Calcd for $C_{18}H_{24}N_2O_7S$ 413.1383, Found 413.13787.

3-Oxa-2,8-diazabicyclo [5.2.0] nonane, 2-(2,2-dimethyl-1-oxo-propyl)-4,9-dioxo (24). To a solution of **22b** (12 mg, 0.03 mmol) in CH_3CN (1.0 mL) was added DIEA (0.01 mL, 0.06 mmol). The above reaction mixture was left at room temperature for 5 days. The solvent was evaporated and the residue was purified by column chromatography with ethyl acetate to afford the cyclized product as a brownish solid (1.6 mg, 23%). ^1H NMR δ 1.29 (s, 9H), 1.70-1.90 (m, 1H), 2.20-2.40 (m, 1H), 2.63-2.69 (m, 2H), 4.03 (dt, J_1 = 2.5, J_2 = 11.6, 1H), 4.29 (t, J = 1.7, 1H), 6.13 (b, 1H); IR (TF) 3260, 2970, 2940, 1760-1775 (b), 1670-1680 (b) cm^{-1}; MS (CI with isobutane) 241 (MH^+), 200, 156, 142, 102; HRMS Calcd on M^+-43 for $C_{10}H_{15}NO_4$ 197.1052, Found 197.1038.

2-Azetidinepropanoic acid, *O*-[(2-phenyl-1-oxo-ethyl)amino]-1-[[(4-methylphenyl)sulfonyl]oxy]-4-oxo (23b) Compound **23a** was prepared by a similar procedure as **22a**. ^1H NMR δ 1.81-2.00 (m, 2H), 2.29 (dd, J = 2.4, 13.8, 1H), 2.46 (t, J = 7.4, 2H), 2.74 (dd, J = 5.2, 13.8, 1H), 3.58-3.61 (m, 1H), 4.92 (d, J = 11.1, 1H), 4.97 (d, J = 11.1, 1H), 7.33-7.39 (m, 5H), 8.63 (br s, 1H); IR (KBr) 3140br, 1790, 1650 cm^{-1}. The hydrogenolysis reaction in the preparation of **23b** was quite sensitive. Reductive cleavage of the *N-O* bond of hydroxamate **23a** to give acid **7** was observed when 10% Pd/C and methanol were employed. This problem was minimized when methanol was replaced by CH_3CN and 5% Pd/C was used. The reaction was

also closely monitored by TLC for reaction completion to stop overreduction. Subsequent treatment of **23b** with Et_3N in CH_3CN did not give any bicyclic product but instead urea **26**. **Compound 23b:** IR (TF) 3200 br, 1800, 1680 cm^{-1}; MS (FAB) $MH^+ = 447$.

Urea, N,N-diethyl-N'-phenylmethyl (26). ^1H NMR δ 1.15 (t, 6H), 3.28 (q, 4H), 4.41 (br d, 2H), 4.55 (br s, 1H), 7.3 (m, 5H); MS (IBCI) $MH^+ = 207$.

2-Azetidinepropanamide, *N*-(triethoxyphosphorimidic)-1-(phenylmethoxy)-4-oxo (27): To a solution of **7** (80 mg, 0.32 mmol) in acetone (4.0 mL) was added Et_3N (0.05 mL, 0.35 mmol) and ethyl chloroformate (0.032 mL, 0.34 mmol) at 0 °C. The reaction was finished within 30 min and formed the desired activated ester (monitored by TLC). To this reaction mixture was then added a solution of NaN_3 (31.4 mg, 0.48 mmol) in water (0.25 mL) at 0 °C. The resulting suspension was left at 0 °C for 1 h. Then brine (0.5 mL) was added to this reaction mixture which was further extracted with three 0.5 mL portions of ethyl acetate. The combined organic layers were dried over $MgSO_4$ and concentrated to give the desired acyl azide as a colorless oil. Due to the instability of this compound, it was only partially characterized. ^1H NMR δ 1.74-1.93 (m, 2H), 2.27-2.36 (m, 3H), 2.74 (dd, $J_1 = 5.2$, $J_2 = 13.7$, 1H), 3.48-3.55 (m, 1H), 4.95-4.96 (d, 2H), 7.40 (s, 5H); IR (TF) 2940, 2140, 1770, 1710, 1360, 1180, 1150.

To a solution of acyl azide in diethyl ether (2.0 mL) was added EtO_3P (0.082 mL, 0.48 mmol) at room temperature. This reaction mixture was warmed to reflux. Evolution of nitrogen was observed. After 30 min, the reaction was cooled down and was left at room temperature overnight. After concentration, the residue was purified by column chromatography, eluting with pure ethyl acetate, to afford **27** as an oil (83 mg, 63% from **7**). ^1H NMR δ 1.32-1.37 (t, $J = 7.07$, 9H), 1.73-1.85 (m, 1H), 2.03-2.12 (m, 1H), 2.29-2.38 (m, 3H), 2.70 (dd, $J_1 = 5.2$, $J_2 = 13.6$, 1H), 3.63-3.69 (m, 1H), 4.13-4.23 (q, $J = 7.1$, 6H), 4.93 (d, $J = 10.9$, 1H), 4.99 (d, $J = 10.9$, 1H), 7.35-7.43 (m, 5H); IR (TF) 2980, 1770, 1615 cm^{-1}; MS 412 (M^+), 354, 305, 263, 208, 183, 180, 152, 124, 91.

2-Azetidinepropanamide, *N*-(diethoxyphosphoramidic)-1-(phenylmethoxy)-4-oxo (28a). *N*-Acyl phosphinimine **27** (50 mg) was dissolved in dry THF (10 mL). Through this solution was passed dry HCl (generated from dehydration of an HCl solution by concentrated H_2SO_4). The reaction took only a few seconds (quickly monitored by TLC). Then the solvent was evaporated and the residue was added to a saturated solution of $KHCO_3$. This solution was then extracted with three portions of ethyl acetate and the combined organic solution was washed with brine once. The organic solution was dried and then concentrated to yield **28a** as a colorless oil (40 mg, 86%). ^1H NMR δ 1.32-1.37 (t, $J = 7.0$, 6H), 1.73-1.85 (m, 1H), 2.01-2.12 (m, 1H), 2.29-2.38 (m, 2H), 2.67-2.74 (dd, $J_1 = 5.2$, $J_2 = 13.6$, 1H), 3.62-3.69 (m, 1H), 4.13-4.23 (m, 4H), 4.92-4.95 (d, $J = 10.9$, 1H), 4.97-5.01 (d, $J = 11.0$, 1H), 7.35-7.43 (m, 5H), 9.00 (b, 1H); ^{13}C NMR δ 16.0 (d, $J_{C-P} = 6.7$), 27.2, 32.3 (d, $J_{C-P} = 9.5$), 37.5, 56.8, 64.1 (d, $J_{C-P} = 6.7$), 78.1, 128.5, 128.6, 128.9, 129.2, 135.0, 163.9, 173.4 (d, $J_{C-P} = 4.0$); IR (TF) 3120, 2980, 1770, 1710 cm^{-1}; MS 384 (M^+), 262, 234, 220, 195, 180, 155 (base peak), 146, 127; HRMS Calcd for $C_{17}H_{25}N_2O_6P$ 384.1450, Found 384.1468.

2-Azetidinepropanamide, *N*-(triethoxyphosphoramidic)-1-[[(4-methylphenyl)sulfonyl]oxy]-4-oxo (28b). A solution of compound **28a** (40 mg, 0.1 mmoL) was subjected to hydrogenolysis for 3 h according to the general procedure (see **16a - 16b**). The resultant *N*-hydroxy β-lactam was dissolved CH_2Cl_2. To the above solution was in turn added TsCl (14 mg, 0.07 mmoL) and triethylamine (0.01 mL, 0.07 mmoL). The reaction mixture was stirred for 10 min. After concentration, the residue was purified by column chromatography with pure ethyl acetate as the eluent to afford **28b** as an oil (24 mg, 55%). ^1H NMR δ 1.35-1.39 (t, $J = 7.1$, 6H), 2.01-2.18 (m, 1H), 2.20-2.25 (m, 1H), 2.47 (s, 3H), 2.48-2.55 (m, 2H), 2.87 (dd, $J_1 = 6.0$, $J_2 = 14.5$, 1H), 4.08-4.17 (m, 1H), 4.18-4.29 (m, 4H), 7.38 (d, $J = 8.2$, 2H), 7.88 (d, $J = 8.3$, 2H),

8.86 (b, 1H); ^{13}C NMR δ 16.0, 16.1, 21.8, 27.0, 32.2, 32.3, 37.9, 59.0, 64.2, 64.3, 129.1, 130.0, 130.3, 146.5, 165.0, 173.4; IR (TF) 3230, 2985, 2920, 1800, 1710 cm^{-1}.

2-Azetidinepropanamide, *N*-(diphenoxyphosphoramidic)-1-(phenylmethoxy)-4-oxo (32a). A mixture of compound **7** (269 mg, 1.08 mmol), diphenylphosphoramide (207 mg, 0.83 mmol), 4-dimethylaminopyridine (158 mg, 1.30 mmol), EDC•HCl (248 mg, 1.30 mmol) were dissolved CH_2Cl_2 (7.0 mL). After stirring for 15 min, another portion of diphenylphosphoramide (104 mg, 0.42 mmol) was added to the solution. The color of the reaction changed from colorless to yellow within 40 min and at the same time became homogeneous. After 1 h and 20 min, more EDC•HCl (200 mg, 1.0 mmol) was added to the yellow solution. The reaction mixture was left at room temperature for a total of 40 h. The solvent was evaporated and the residue was purified by column chromatography with ethyl acetate/hexanes (3:1) to afford **32a** as a colorless oil (314 mg, 61%) ^{1}H NMR δ 1.64-1.73 (m, 1H), 1.79-1.90 (m, 1H), 2.14-2.24 (m, 3H), 2.58 (dd, J_1 = 5.2, J_2 = 13.7, 1H), 3.39-3.46 (m, 1H), 4.86 (d, J = 11.1, 1H), 4.92 (d, J = 11.1, 1H), 7.16-7.40 (m, 15H), 9.20 (b, 1H); ^{13}C NMR δ 27.1, 32.5 (d, $J_{C\text{-}P}$ = 9.69), 37.4, 56.6, 78.0, 120.2, 120.3, 120.3, 125.1, 125.7, 128.6, 129.0, 129.3, 129.7, 129.8, 135.0, 149.8 (d, $J_{C\text{-}P}$ = 6.5), 163.9, 172.9 (d, J = 3.36); IR (TF) 3120, 3070, 3040, 2930, 1770, 1720 cm^{-1}; MS 480 (M+), 436, 341, 281, 251 (base peak), 173, 146; HRMS FAB MH$^+$ Calcd for $C_{25}H_{25}N_2O_6P$ 481.1529, Found 481.1528.

2-Azetidinepropanamide, *N*-(diphenoxyphosphoramidic)-1-[[(4-methylphenyl)sulfonyl]oxy]-4-oxo (32b). Compound **32a** (304 mg, 0.63 mmol) in methanol (10 mL) was subjected to hydrogenolysis for 2 h according to the general procedure used for the conversion of **16a** to **16b**. The resultant oil was dissolved in CH_2Cl_2 (5.0 mL). To this solution was added TsCl (120.7 mg, 0.63 mmol) and TEA (0.088 mL, 0.63 mmol). After 40 min, the solvent was removed and the residue was purified by column chromatography (ethyl acetate/hexanes 3:1) to yield the desired product as a colorless oil (302 mg, 87%). ^{1}H NMR δ 1.83-1.95 (m, 1H), 2.09-2.16 (m, 1H), 2.31-2.37 (m, 3H), 2.43 (s, 3H), 2.70 (dd, J_1 = 6.0, J_2 = 14.5, 1H), 3.88-3.92 (m, 1H), 7.19-7.35 (m, 12H), 7.85 (d, J = 8.4, 2H), 9.20 (b, 1H); ^{13}C NMR δ 21.4, 26.4, 32.0 (d, $J_{C\text{-}P}$ = 10.3 Hz), 37.3, 58.5, 120.0 (d, $J_{C\text{-}P}$ = 4.7), 125.5, 128.8, 129.4, 129.6, 129.8, 130.0, 146.3, 149.6 (d, $J_{C\text{-}P}$ = 6.5), 165.1, 172.8 (d, $J_{C\text{-}P}$ = 5.2); IR (TF) 3100, 2910, 1800, 1725, 1590 cm^{-1}; MS 482, 404, 389 (base peak), 340, 249, 216, 172, 155; HRMS (FAB) MH$^+$ Calcd for $C_{25}H_{25}N_2O_8PS$ 545.1148, Found 545.1147.

2,7-Diazabicyclo [4.2.0] octane, 3,8-dioxo-2-(diphenoxyphosphoramide) (33). Compound **32b** (297 mg, 0.546 mmol) was dissolved in CH_3CN (20.0 mL). To this solution was added DIEA (0.19 mL, 1.09 mmol). The reaction mixture was stirred at room temperature for 46 h. The solvent was evaporated under vacuum and the residue was purified by column chromatography (ethyl acetate/hexanes 3:1) to yield the desired product as a colorless oil (67 mg, 33%). From the above reaction mixture were also isolated diphenylphosphoramide (13.0 mg) and *N*-(4-oxo-pentanoyl) diphenylphosphoramide (8 mg). Data for **33**: ^{1}H NMR δ 1.41-1.53 (m, 1H), 2.05-2.13 (m, 1H), 2.50-2.63 (m, 2H), 4.06-4.09 (m, 1H), 5.55 (ddd, J_1 = 0.6, J_2 = 5.8, J_3 = 10.2, 1H), 5.76 (b, 1H), 7.20-7.38 (m, 10H); ^{13}C NMR δ 23.9, 28.4-28.5 (J = 5.9), 47.3-47.4 (J = 4.3), 62.6 (J = 1.3), 120.3, 120.4, 120.4, 120.5, 120.5, 125.6, 125.9, 129.7, 129.8, 149.7, 149.8, 149.8, 15.0, 166.5, 172.7; IR (TF) 3250, 1770, 1710 cm^{-1}; MS 372 (M+), 329 (base peak), 316, 277, 236, 173, 91; HRMS Calcd for $C_{18}H_{17}N_2O_5P$ 372.08751, Found 372.0872. Data for ***N*-(4-oxo-pentanoyl) diphenylphosphoramide.** ^{1}H NMR δ 2.18 (s, 3H), 2.53-2.57 (t, 1H, J = 5.9), 2.71-2.75 (t, J = 6.5), 7.21-7.37 (m, 10H), 7.87 (b, 1H); IR (TF) 3140, 2920, 1720, 1590 cm^{-1}; MS 347 (M+), 333, 332, 276, 254, 251, 240, 175, 121, 94, 77.

2-Azetidinepropanamide, *N*-[(4-methylphenyl)sulfonyl]-1-(phenylmethoxy)-4-oxo (34a): β-Lactam carboxylic acid **7** (135 mg, 0.542 mmol) was dissolved in CH_2Cl_2 (4 mL) and then tosylamide (96 mg, 0.558 mmol), dimethylaminopyridine (70 mg, 0.369 mmol), and EDC•HCl (125 mg, 0.651 mmol) were added. The reaction was stirred for 2 days at room temperature and the color of the solution turned yellow.

Ethyl acetate (15 mL) was added and the organic layer was washed three times with 5 mL of 0.5 M HCl and once with 5 mL of brine. The organic layer was dried over $MgSO_4$, filtered and evaporated to give 223 mg of an oil. Column chromatography, eluting with ethyl acetate, gave 185 mg (85%) of an analytical sample as a sticky glass. $R_f = 0.46$ (UV, PMA, ethyl acetate); ^1H NMR δ 9.04 (br s, 1H), 7.93 (d, 2H, $J = 8.1$ Hz), 7.34 (7H, benzyl and sulfonate doublet overlapped), 4.91 (d, 1H, $J = 11.1$ Hz), 4.86 (d, 1H, $J = 11.1$ Hz), 3.53 (m, 1H), 2.65 (dd, 1H, $J = 13.8$, 5.1Hz), 2.42 (s, 3H), 2.18-2.38 (m, 3H), 1.79 (m, 2H); ^{13}C δ 170.2, 164.3, 145.0, 135.7, 134.8, 129.6, 129.4, 129.1, 128.7, 128.3, 78.2, 56.8, 37.1, 31.4, 26.3, 21.7; IR (TF) 3200 br, 1770 s, 1750 s, 1715 s cm^{-1}; $[\alpha]_D = 15°$ ($CHCl_3$, c = 1); HRMS: (ammonia CI) Calcd $M^+NH_4^+$ 420.15932, Found 420.1613.

2-Azetidinepropanamide, *N*-[(4-methylphenyl)sulfonyl]-1-[[(4-methylphenyl)sulfonyl]oxy]-4-oxo (34b): *N*-Acylsulfonamide **34a** (527 mg, 1.31 mmol) was dissolved in methanol (12 mL) and 10% Pd on carbon (180 mg) was added and the solution was placed under a hydrogen balloon. After 30 minutes TLC analysis (ethyl acetate) showed reaction completion. The starting material had an $R_f = 0.48$ (UV, PMA), and the product *N*-hydroxy β-lactam an $R_f = 0.15$ (UV, PMA). The Pd catalyst was removed by filtration through celite which was subsequently rinsed several times with ethyl acetate. The combined solvent was removed by rotary evaporation to leave a white foam which was dissolved in 15 mL of CH_2Cl_2. Tosyl chloride (247 mg, 1.3 mmol) and triethylamine (181 μL, 1.3 mmol) were added sequentially to this solution. A small amount of gas evolved. After 20 min, TLC analysis (ethyl acetate) showed the product ($R_f = 0.50$ UV, PMA) and tosyl chloride $R_f = 0.64$ (UV). The solvent was evaporated and the residue was dissolved in a minimal amount of $CHCl_3$ and placed on a silica gel column and eluted with 3:1 ethyl acetate : hexanes. After evaporation of the pooled fractions 465 mg (78%) of **34a** as a foam was obtained. ^1H NMR δ 9.23 (br s, 1H), 7.94 (d, 2H, $J = 8.4$), 7.85 (d, 2H, $J = 8.4$), 7.3-7.41 (m, 4H), 3.98 (m, 1H), 2.81 (dd, 1H, $J = 6$, 14.4), 2.35-2.45 (m, 9H), 1.9-2.1 (m, 2H); IR 3220 br, 1795 s, 1725 s, 1595 m, 1370, 1190, 1170 cm^{-1}; MS (FAB) $MH^+ = 467$.

Intramolecular Cyclization of (34b): *N*-Tosyloxy-β-lactam **34b** (500 mg, 1.07 mmol) was dissolved in acetonitrile (50 mL) and DIEA (2.8 mL, 16.05 mmol, 15 eq.) was added. After two days, the solvent was evaporated and the residue was dissolved in ethyl acetate (75 mL) and washed with two 10 mL portions of 0.5 M HCl, once with 15 mL of saturated $NaHCO_3$ solution, dried over $MgSO_4$, filtered, and evaporated to give 180 mg of residue. Column chromatography with 3:1 ethyl acetate in hexanes gave 37 mg (12%) of **35**, 10 mg (4 %) of **36**, 49 mg (12%) of **37**, and 11 mg (3%) of **38** after evaporation of the pooled fractions.

2,7-Diazabicyclo [4.2.0] octane, 3,8-dioxo-2-[(4-methylphenyl)sulfonyl] (35): Recrystallized from CH_2Cl_2/hexanes Mp 192-194°C dec. $R_f = 0.33$ ethyl acetate (UV, PMA slight blue). ^1H NMR δ 8.07 (d, 2H, $J = 8.4$), 7.34 (d, 2H, $J = 8.4$), 5.93 (br s NH, 1H), 5.89 (dd, 1H, $J = 5.4$, 0.6), 4.38 (t, 1H, $J = 3.9$), 2.43 (s, 3H), 2.4-2.5 (m, 1H), 2.15-2.22 (m, 1H), 1.9-2.05 (m, 2H); ^{13}C NMR δ 169.2, 165.4, 145.3, 135.1, 129.3, 128.3, 61.8, 48.4, 28.7, 24.0, 21.7; IR (TF) 3450 br, 1770 s, 1700, 1350, 1170 s cm^{-1}; $[\alpha]_D = -132°$ ($CHCl_3$, c = 0.28); MS (EI) gave $M^+ = 294$, CI (isobutane) gave $MH^+ = 295$, HRMS MNH_4^+ (ammonia CI) Calcd for $C_{13}H_{14}N_2O_4S$ 312.1018, Found 312.1032.

Characterization data for (36): $R_f = 0.43$ (ethyl acetate). ^1H NMR δ 8.03 (d, 2H, $J = 8.4$), 7.90 (d, 2H, $J = 8.4$), 7.3-7.4 (t, 4H), 6.78 (t, 1H, $J = 6.3$), 5.96 (d, 1H, $J = 6.6$), 4.78 (m, 1H), 4.51 (m, 1H), 3.63 (dt, 1H, $J = 1.8$, 6), 2.5-2.7 (m, 2H), 2.44 (s, 3H), 2.43 (s, 3H), 2.1-2.4 (m, 4H), 1.9-2.0 (m, 2H); IR 3360 br, 1775, 1710, 1355, 1165 cm^{-1}; HRMS (FAB) MH^+ Calcd for $C_{26}H_{28}N_4O_8S_2$ 589.1428, Found 589.1426.

Characterization data for (37): $R_f = 0.37$ (ethyl acetate). ^1H NMR δ 7.98 (d, 2H, $J = 8.4$), 7.35 (d, 2H, $J = 8.4$), 4.45 (m, 2H), 3.55-3.89 (m, 4H), 2.44 (s, 3H), 2.10-2.35 (m, 2H), 1.12 (dd, 12H, $J = 2.7$, 6.9); ^{13}C NMR δ 174.2, 157.0, 145.3, 135.5, 129.7, 128.4, 61.0, 45.3, 43.6, 31.1, 23.4, 23.1, 21.7, 21.3, 21.2

(Note that both ^1H and ^{13}C NMR spectra contain diastereotopic isopropyl groups); IR 3450 br, 3350 br, 1735 s, 1625, 1510, 1350, 1160, 665 cm^{-1}; $[\alpha]_D$ = -50.7° ($CHCl_3$, c=0.6); HRMS (FAB) MH^+ Calcd for $C_{19}H_{29}N_3O_4S$ 396.1957, Found 396.1950.

Characterization for (38): Compound **38** was not isolated pure but the ^1H NMR resembled that of compound **36**. R_f = 0.25 (ethyl acetate). IR neat oil 3450, 1745-1730, 1625, 1165 cm^{-1}; MS (FAB) MH^+ Calcd for $C_{18}H_{27}N_3O_4S$ 382, Found 382.

(4-methylphenyl)sulfonamide, *N*-1-oxoethyl (41): *p*-Toluenesulfonamide (1g, 5.84 mmol) was dissolved in THF (10 mL) and acetyl chloride (425 mL, 6 mmol) followed by triethylamine (820 μL, 5.9 mmol) were added and a white precipitate formed immediately. After 1h, 10 mL of 10% Na_2CO_3 was added and stirred for 1h. Ether (10 mL) was added and the layers were separated. The organic layer was washed once with 5% Na_2CO_3 and the pooled aqueous layers were acidified to pH 6 with 6 M HCl. The aqueous layer was extracted three times with CH_2Cl_2. The estracts were combined, dried over Na_2SO_4, filtered and evaporated to give 600 mg (50%) of an oil that crystallized upon standing. The solid was recrystallized from CH_2Cl_2:hexanes (Mp = 136-137°C). ^1H NMR δ 7.93 (d, 2H, *J* = 8.4), 7.33 (d, 2H, *J* = 8.4), 2.44 (s, 3H), 2.05 (s, 3H); IR ($CHCl_3$) 3300, 1720, 1330, 815, 665 cm^{-1}; MS (FAB) MH^+ for $C_9H_{11}NO_3S$ 214.

2-Azetidinepropanoic acid, 3-[N-1-oxoethyl-(4-methylphenyl)sulfonamide)]-4-oxo-(1,1-dimethylethyl) ester, trans (43): *N*-Tosyloxy β-lactam **42** (153 mg, 0.415 mmol) was dissolved in CH_3CN (8 mL, c = 0.052 M) and **41** (132 mg, 0.622 mmol, 1.5 eq) was added followed by DIEA (360 μL, 2.075 mmol, 5 eq). The reaction was judged complete by loss of **42** (R_f = 0.43 1:1 ethyl acetate : hexanes) after 2 days. The solvent was evaporated and the residue was dissolved in ethyl acetate. The organic layer was washed twice with 10% citric acid solution, three times with saturated $NaHCO_3$ solution, dried over $MgSO_4$, filtered and evaporated to give 112 mg (66%) of **43** as an oil that resisted attempts at crystallization. ^1H NMR δ 7.92 (d, 2H, *J* = 8.4), 7.40 (d, 2H, *J* = 8.4), 6.55 (br s, 1H) NH, 5.04 (d, 1H, *J* = 2.7), 4.02 (dt, 1H, *J* = 2.7, 7.2), 2.45 (s, 3H), 2.3-2.42 (m, 2H), 2.31 (s, 3H), 1.9-2.1 (m, 2H), 1.45 (s, 9H); ^{13}C NMR δ 172.0, 170.1, 165.4, 145.5, 135.8, 130.2, 127.4, 80.8, 65.9, 55.1, 31.7, 28.6, 28.0, 24.9, 21.6; IR (TF) 3320 br, 1775, 1720, 1365, 1250, 1170 cm^{-1}; HRMS (FAB) MH^+ Calcd for $C_{19}H_{26}N_2O_6S$ 411.1590, Found 411.1603.

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