ALKYLATION OF AMBIDENT NUCLEOPHILIC HYDROXAMATES WITH 4-SUBSTITUTED 2-AZETIDINONES: FORMATION OF BICYCLIC β-LACTAM INTERMEDIATES

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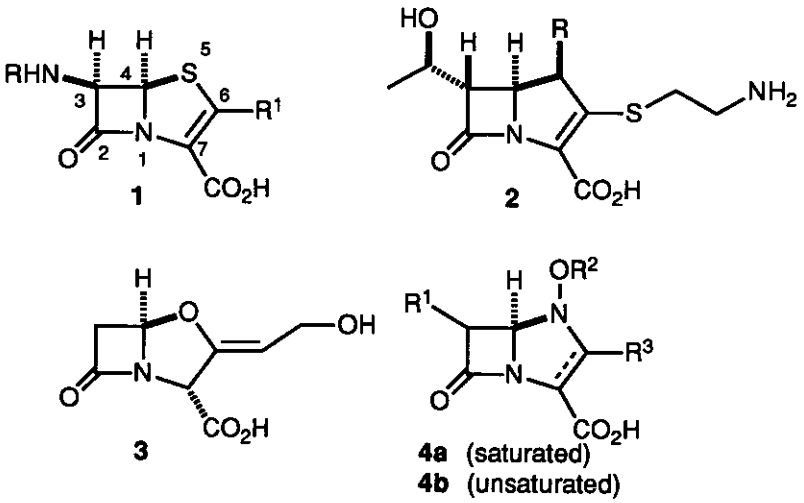
Abstract---Silver salts of various *O*-alkylhydroxamic acids react with 4-substituted 2-azetidinones (**7**) to produce novel substituted β-lactams. *N*- or *O*-alkylation of the hydroxamate silver salts can be controlled by reaction conditions, variation of the leaving group (OAc or SEt) of the 4-substituted 2-azetidinone, and the mode of formation of the silver salt itself. Elaboration of the products to azapenems and oxapenams may produce novel β-lactam derivatives for biological evaluation.

INTRODUCTION

Extensive advances have been made in β-lactam research since the discovery of penicillin. Semisynthetic penicillin-derived β-lactams and totally synthetic analogs have produced a number of important biologically active molecules. One of the key developments in the area of β-lactam antibiotics has been the preparation and study of nuclear analogs of the penicillins and cephalosporins. In the basic [3.2.0] bicyclic system of the penicillins and related penems (**1**), replacement of sulfur with carbon leads to carbapenams and carbapenems, with thienamycin (**2**, R=H), a potent β-lactam antibiotic, being representative. Substitution of the sulfur in **1** with oxygen gives the oxapenems and oxapenams of which clavulanic acid (**3**), a potent β-lactamase inhibitor, is noteworthy. Noticeably absent from this group are nitrogen analogs of these molecules. Only a few examples concerning the synthesis of some azapenams (**4a**) and azapenems (**4b**) have been reported, and most of these molecules have been shown to be unstable or to have only slight antibiotic activity.[1]



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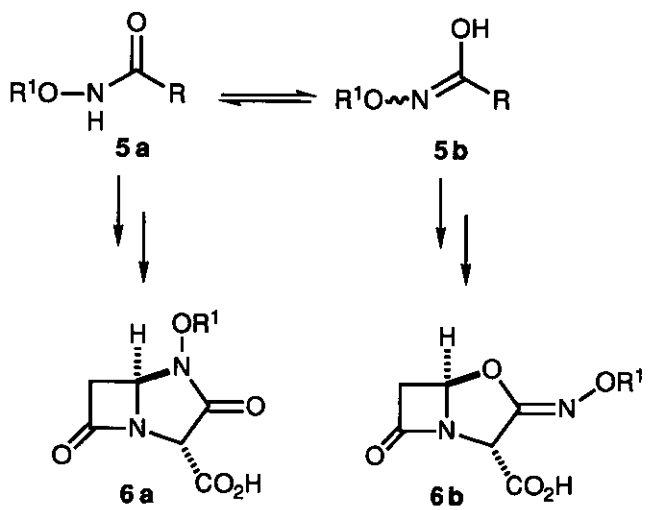
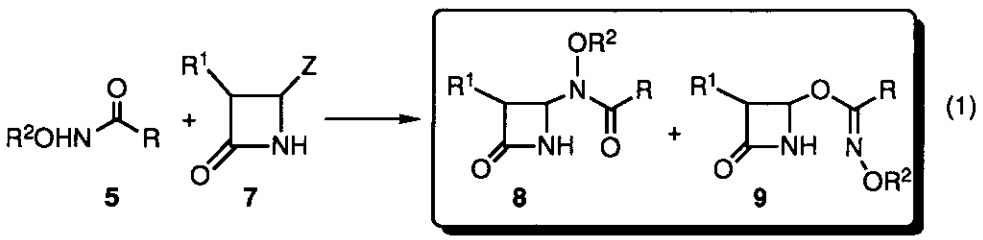
Conceptually, incorporation of hydroxamic acids in bicyclic β-lactam frameworks could produce novel analogs of carbapenems and oxapenams (Scheme 1). Considering the ambident character of hydroxamic acids (**5a** → **5b**) controlled incorporation of hydroxamate nitrogen into a bicyclic β-lactam ring would give an interesting aza analog (**6a**) of the very potent β-methylthienamycin (**2**, R= Me).[2]



Scheme 1

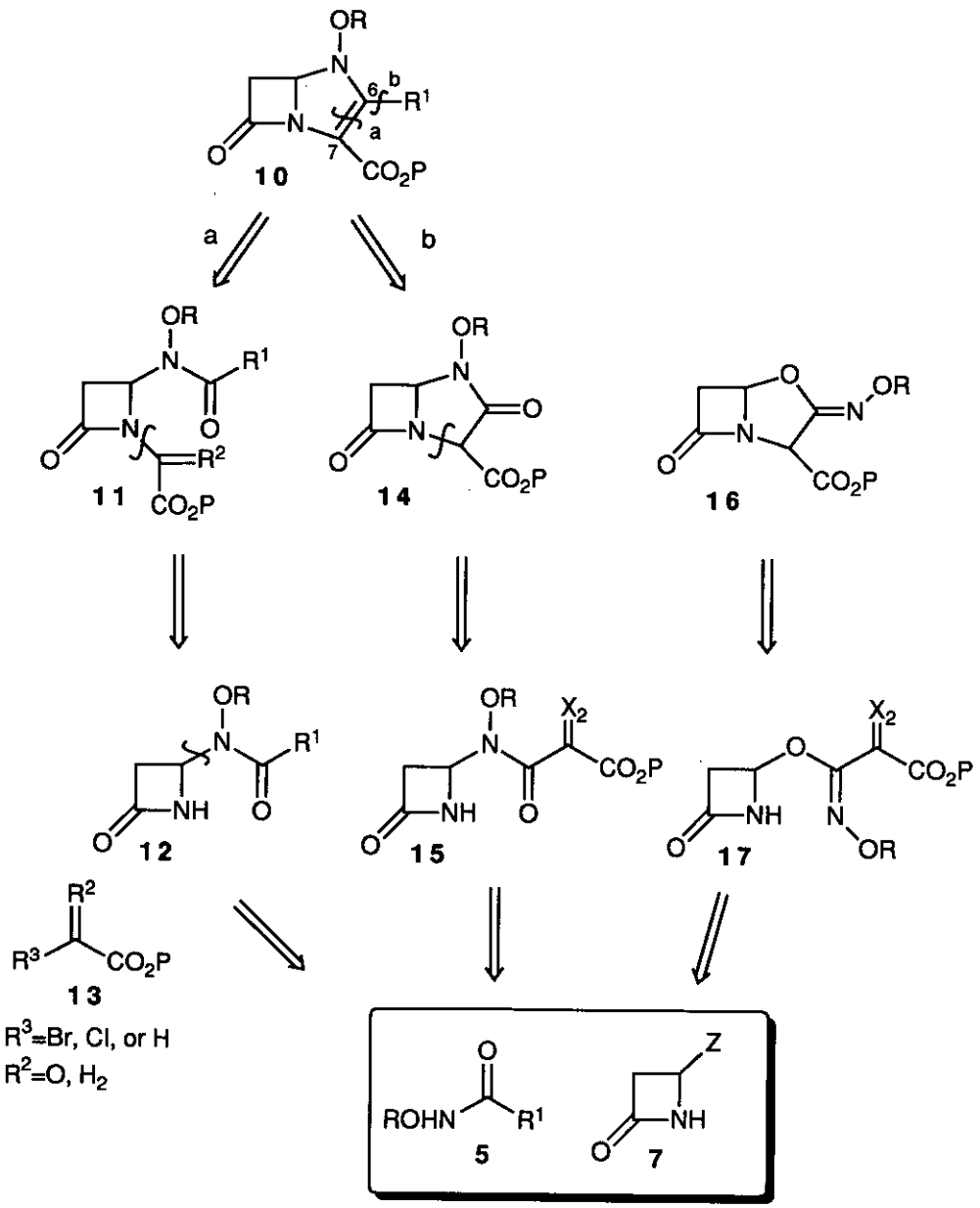
Inclusion of the carbonyl oxygen of a hydroxamic acid into the bicyclic ring would provide novel oxapenam (clavam) analogs (**6b**), which might be especially interesting as potential β-lactamase inhibitors or antifungal agents.[3]

The key transformation in effecting syntheses of these β-lactam analogs was anticipated to be the alkylation (coupling) of a hydroxamate (**5**) with a 4-substituted 2-azetidinone (**7**). Depending upon reaction conditions, the *N*- or *O*-alkylated compounds, (**8**) and (**9**) respectively, might be obtained (Eq. 1). Herein we describe methodology for the selective and controlled preparation of **8** and **9** and the interesting observations of this process.



(1)

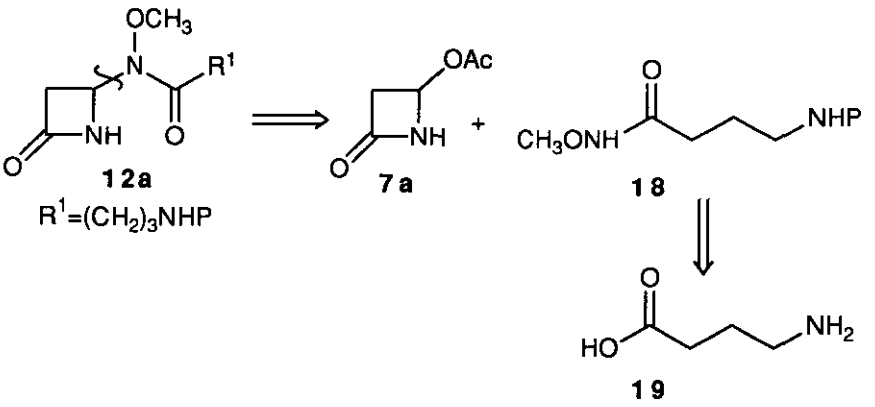
From a retrosynthetic view, two methods could be used for formation of bicyclic *N*-alkylated derivative (**10**). C_6-C_7 bond disconnection (Scheme 2, path a) gives monocyclic compound (**11**) as the penultimate product. This disconnection is precedented in earlier syntheses of penems and carbapenems utilizing Horner-Emmons,[4] Dieckmann,[5] and dicarbonyl condensation[6] chemistry. Conceptually, forms of **11** can be prepared from the corresponding *N*-unsubstituted β-lactams (**12**) by alkylation with a haloacetate, acylation with an oxalyl chloride,[7] or condensation with a glyoxylate. Alternately, by analogy to the Merck carbapenam syntheses,[8] the endo cyclic double bond of **10** might be formed by enolization of the corresponding oxo derivative (**14**) (Scheme 2, path b). By further analogy to carbapenem syntheses, **14** might be accessed from the corresponding α-diazo-β-keto ester (**15**). Similar methods were considered for the preparation of the *O*-alkylated isomers (**16** from **17**).


OR
N
6
b
R1
a
7
CO2P
10
a
b
R2
11
14
16
12
15
17
X2
NH
O
N
R3
13
R3=Br, Cl, or H
R2=O, H2
ROHN
5
Z
7

Scheme 2

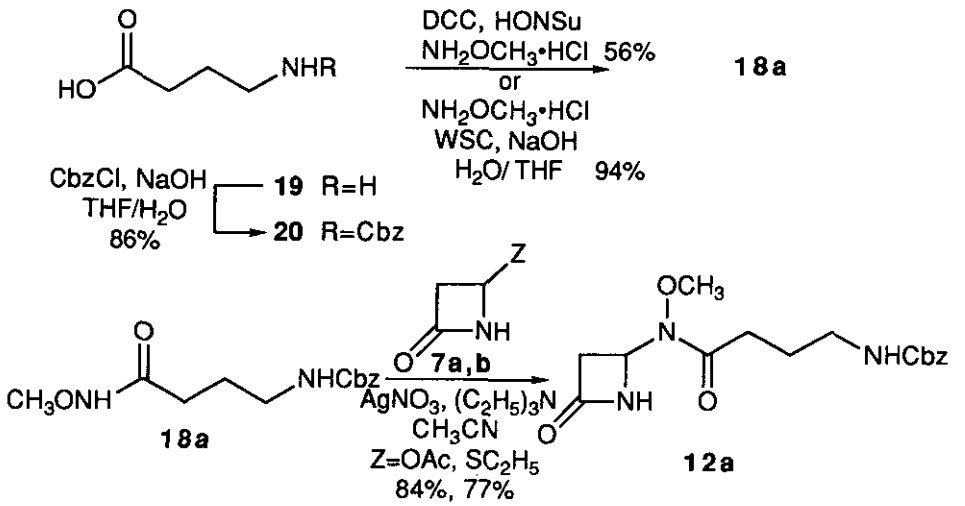
RESULTS AND DISCUSSION

Scheme 3 summarizes the design of a specific example of the *N*-alkylated 4-hydroxamate-2-azetidinone (**12**) from commercially available 4-acetoxy 2-azetidinone (**7a**) and hydroxamate (**18**) derived from γ-aminobutyric acid (GABA, **19**).



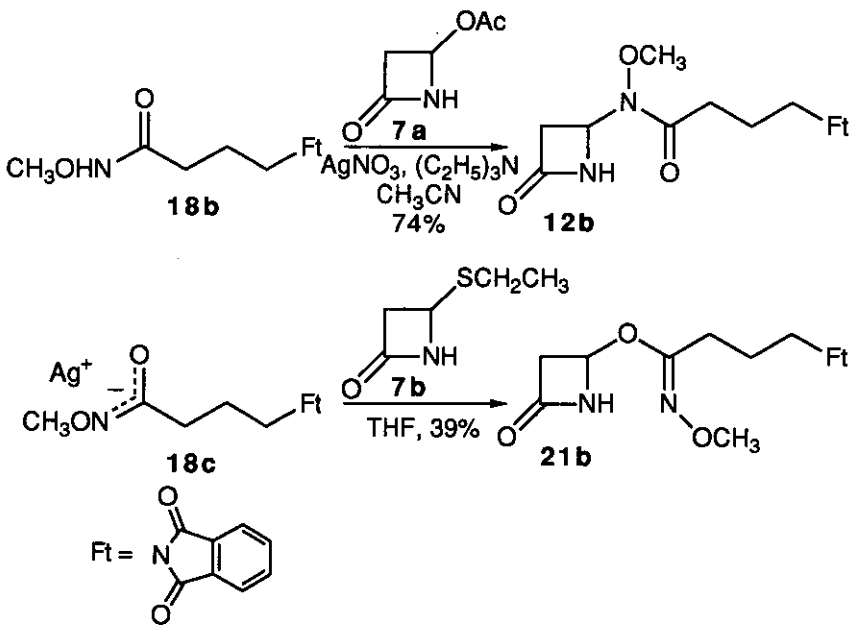
Scheme 3

The actual synthetic sequence is outlined in Scheme 4. Thus, standard reaction of **19** with benzyl chloroformate and sodium hydroxide gave Cbz derivative (**20**) in 86% yield. Conversion to the corresponding hydroxamate (**18a**), was accomplished by use of either dicyclohexylcarbodiimide (DCC) and *N*-hydroxysuccinimide or water soluble carbodiimide (WSC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC), with the latter giving a superior (94%) yield.



Scheme 4

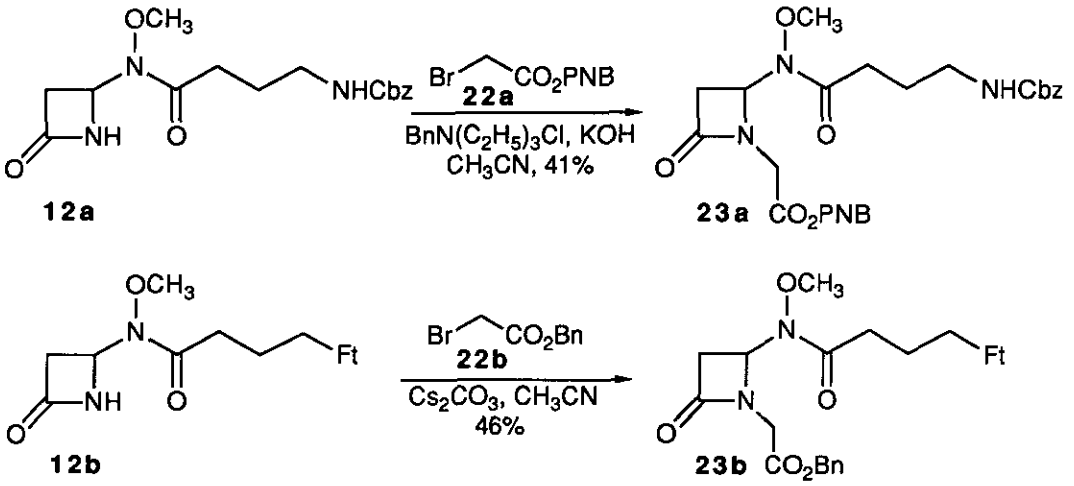
Alkylation of the hydroxamate was done using both the 4-acetoxy[9] and 4-ethylthio 2-azetidinones[10] (**7a,b**) in anticipation of obtaining the *N*- and *O*-alkylated products, respectively. Interestingly, in both cases under the same conditions ($AgNO_3$, $(C_2H_5)_3N$ in CH_3CN) only one product was obtained which was eventually assigned as the *N*-alkylated product (**12a**). The same coupling and alkylation conditions also worked well in the phthalimido[11] case to give **18b** and **12b** respectively (Scheme 5). Variation of conditions (addition of Ag salt of **18b** to a solution of **7b** in THF) led to the corresponding *O*-alkylated product (**21b**).



Scheme 5

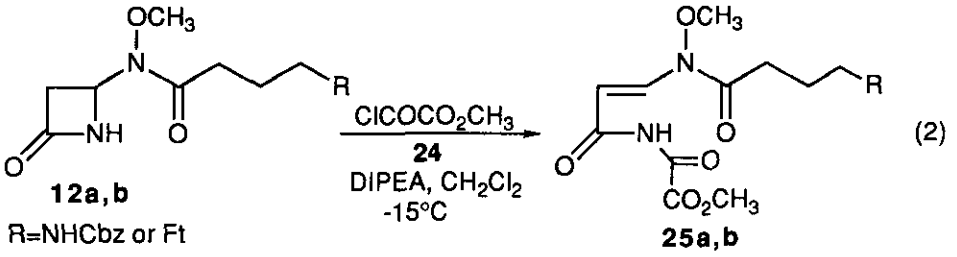
Addition of the remaining carbon framework by reaction of **12a** with methyl 2-bromodiethylphosphonoacetate[12] under several different sets of conditions failed, perhaps because of the acidity of the α proton of the phosphonoacetate. Similarly, treatment of **12a** with sodium hydride followed by addition of *p*-nitrobenzyl 2-bromoacetate (**22a**) was also ineffective. Successful alkylation with *p*-nitrobenzyl 2-bromoacetate (**22a**) or benzyl 2-bromoacetate (**22b**) was accomplished by phase transfer catalysis.[13] Thus, using phase transfer conditions that had been used previously in our group on similar systems,[14] a solution of hydroxamate-substituted β-lactam

(**12a**) and *p*-nitrobenzyl 2-bromoacetate (**22a**) in acetonitrile was added to a solution of a catalytic amount of benzyltriethylammonium chloride and powdered potassium hydroxide (Scheme 6). Subsequent workup and purification gave the alkylated product (**23a**) in 41% yield. Alkylation of the corresponding phthalimido derivative (**12b**), with benzyl bromoacetate using the cesium carbonate procedure reported by Girijavallabhan *et al.*,[15] gave **23b** in 46% yield. All attempts at cyclization of **23a** and **23b** to the corresponding bicyclic β-lactams by aldol/Dieckmann-like condensation conditions failed.



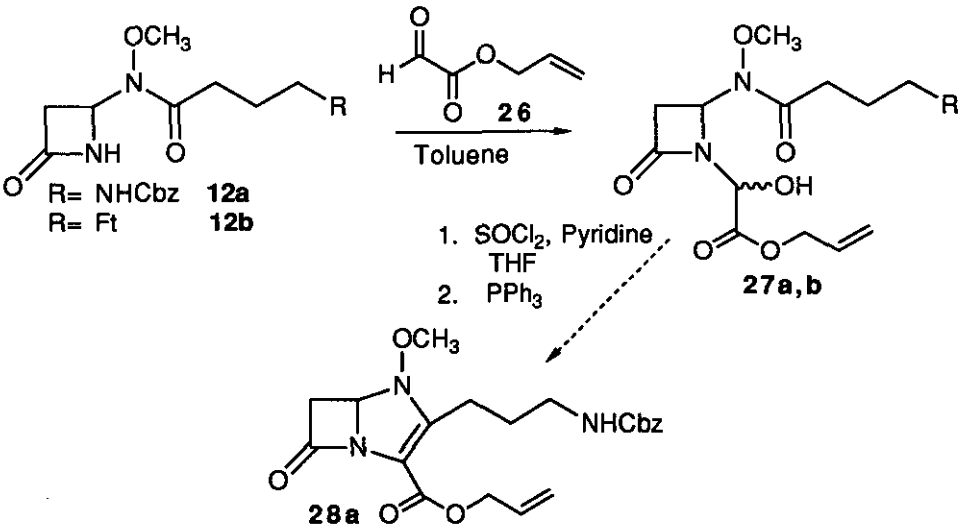
Scheme 6

Attempted formation of the desired bicyclic β-lactams from the corresponding glyoximides also was ineffective. Reactions of **12a** and **12b** with methyl oxalyl chloride (**24**) did not give the desired products but acylated elimination products (**25a,b**; Eq. 2).



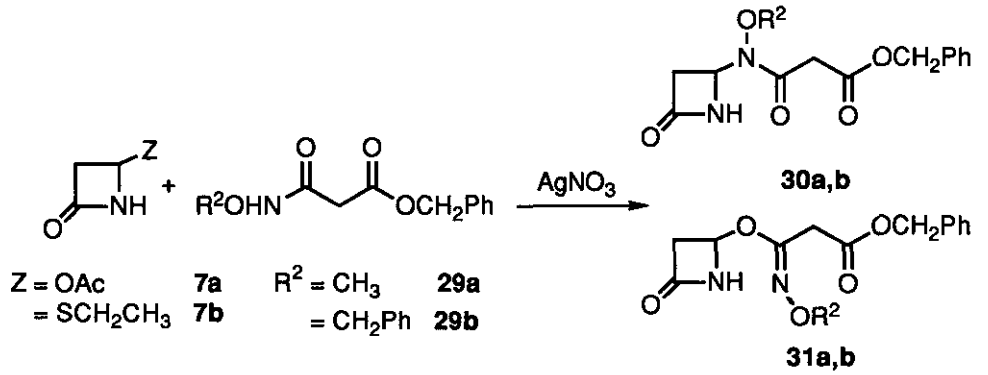
(2)

Allyl glyoxylate (**26**) was prepared by oxidative cleavage of the corresponding tartrate using a method developed at Merck.[4b] This glyoxylate was reacted with **12a** and **12b** to form carbinol (**27a**) and (**27b**) respectively (Scheme 8) in quantitative yields. Carbinol (**27a**) was reacted with thionyl chloride between -20 and -40°C for 30 min followed by the addition of triphenylphosphine at room temperature in an attempt to form the desired cyclized adduct(**28a**), but none could be isolated.



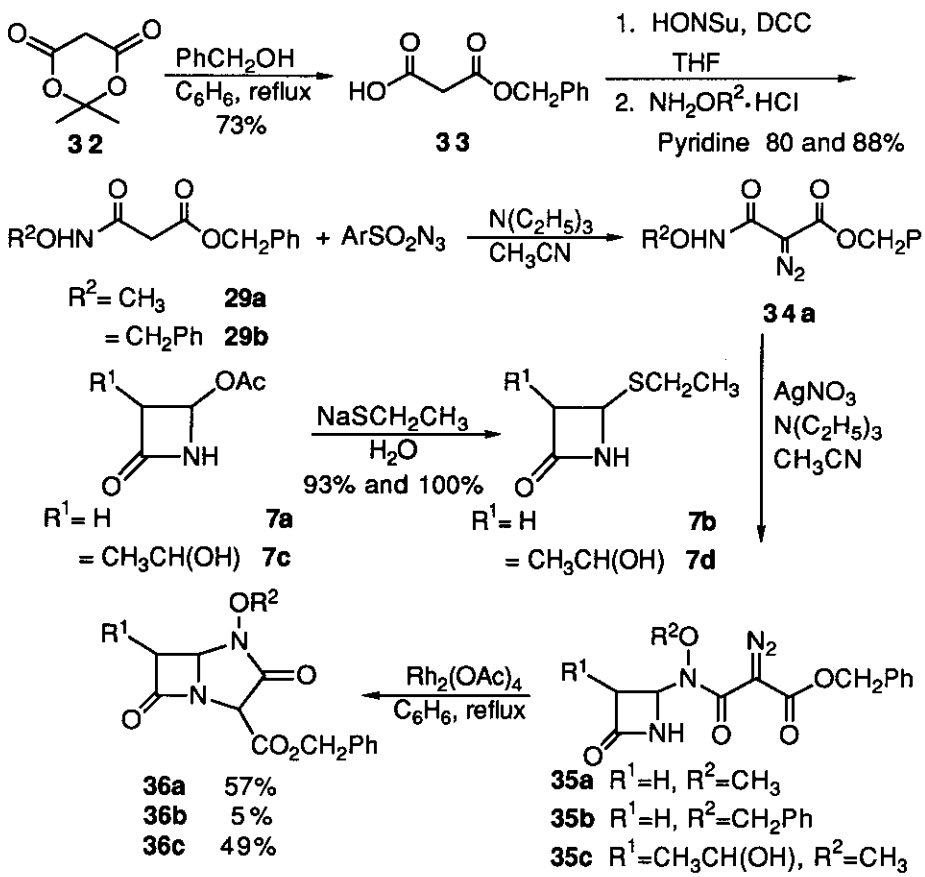
Scheme 8

Second efforts focused on a clavulanic acid derivative where an oxime precursor (**17**) (Scheme 2) could possibly be made from a 4-substituted 2-azetidinone (**7**) and a malonohydroxamate (**29**). Once again the key step in this synthesis was the coupling of 4-substituted 2-azetidinone and an alkylmalonohydroxamate (Eq. 3). Depending upon reaction conditions, the *N*- or the *O*-alkylated compounds could be obtained.



(3)

The malonohydroxamates were prepared by reaction of Meldrum's acid (**32**)[16] with benzyl alcohol in refluxing benzene to give the desired monobenzylmalonate (**33**)[17] (Scheme 9). Coupling the monoacid with *O*-methyl or *O*-benzyl hydroxylamine using dicyclohexylcarbodiimide (DCC) and *N*-hydroxysuccinimide in THF gave the desired hydroxamates (**29a,b**) in 80% and 88% yields respectively. Compounds(**29a**)or(**29b**)were further reacted with a diazo transfer reagent, to give the α-diazo *O*-alkylhydroxamates (**34a,b**) in 85% and 26% yields respectively. Protection of the hydroxamate nitrogen was not necessary when $ArSO_2N_3$ was *p*-carboxybenzenesulfonyl azide,[18] although 2.5 equivalents of base was required for the diazotization.



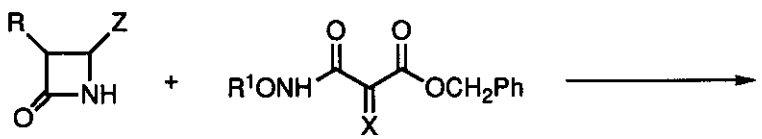
Scheme 9

Reacting the diazo *O*-alkylhydroxamate (**34a** or **34b**) with 4-ethylthio 2-azetidinone (**7b**) instead of 4-acetoxy 2-azetidinone (**7a**), due to its decreased reactivity in the presence of silver nitrate and triethylamine, gave a white crystalline product. This transformation was also effected on [3*R* (1'*R*,

4*R*)]-(+)-4-acetoxy-3-[1-(*tert*-butyldimethylsilyloxy)ethyl-2-azetidinone (**7c**)[19] in 66% yield. X-ray crystallographic analysis revealed that instead of the *O*-alkylated products, expected by literature precedent,[20] the *N*-alkylated products (**35**) were formed. These *N*-alkylated products (**35a,b,c**) were converted to their bicyclic compounds (**36a,b,c**) as single diastereomers using rhodium acetate to initiate a carbenoid *N*-H insertion[21] and in the case of **36a**, it was determined that the newly formed asymmetric center had the β-configuration.

The *N*-selectivity observed in the silver coupling reactions, prompted further investigation of the alkylations of hydroxamates at the C_4 position of the β-lactam using silver salts. Hydroxamate anions are ambident nucleophiles, and their ability to form two or more products has been under investigation for many years. The product formed depends upon a variety of factors such as solvent, counter ion, additives, temperature, catalyst, alkalinity and structure of the alkylating agent.[22] Table 1 summarizes our findings from alkylations of silver salts of hydroxamates with various 4-substituted 2-azetidinones.

Table 1



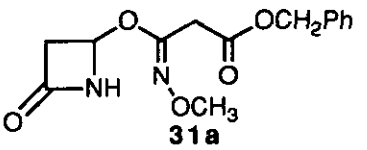
Entry	R	Z	R^1	X	Alkylated products	% Yield
1	H	OAc **7a**	CH_3	H_2 [a,b] **29a**	*N*-alkyl **30a**	25[a] and 37[b]
2	H	SCH_2CH_3 **7b**	CH_3	H_2 [a,c] **29a**	*O*-alkyl **31a**	49[a] and 46[c]
3	H	SCH_2CH_3 **7b**	CH_3	N_2 [b] **34a**	*N*-alkyl **35a**	44
4	3*R* (1'*R*, 4*R*)-$CH_3CH(OH)$	SCH_2CH_3 **7d**	CH_3	N_2 [b] **34a**	*N*-alkyl **35c**	66
5	H	OAc **7a**	CH_2Ph	H_2 [c] **29b**	*N*-alkyl **30b**	45
6	H	SCH_2CH_3 **7b**	CH_2Ph	H_2 [c] **29b**	*N*-and *O*-alkyl **30b** **31b**	38 and 30
7	H	SCH_2CH_3 **7b**	CH_2Ph	N_2 [d] **34b**	*N*-alkyl **35b**	28

a. Formation of the silver salt added to a solution of β-lactam in THF.
b. Addition of $AgNO_3$ and $(C_2H_5)_3N$ to a solution of hydroxamate and β-lactam in CH_3CN.
c. Addition of $AgNO_3$ and $(C_2H_5)_3N$ to a solution of hydroxamate in THF followed by β-lactam.
d. Addition of $AgNO_3$ and $(C_2H_5)_3N$ to a solution of diazohydroxamate in CH_3CN, followed by β-lactam.

Although all of the reactions were heterogeneous, some trends were evident. It was interesting to note that for the benzyl *O*-methylmalonohydroxamate (**29a**), *N*- vs *O*-alkylation selectivity was observed only when the leaving group was changed from acetoxy to ethylthio (entries 1, 2), whereas use of benzyl *O*-benzylmalonohydroxamate (**29b**, entries 5, 6), gave exclusively *N*- or a mixture of *N*- and *O*-alkylated products, respectively. In all cases, conversion of the *O*-alkylated product to the *N*-alkylated product was not observed.

Characterization of the *N*- and *O*-alkylated products was done using a variety of methods. The *N*-alkylated compound (**30a**) was reacted with *p*-carboxybenzenesulfonyl azide and triethylamine to diazotize the active methylene. This was compared with the diazotized product (**35a**) from reacting 4-ethylthio 2-azetidinone (**7b**) and 2-diazo-benzyl-*O*-methylmalonohydroxamate (**32a**) under the usual conditions. Comparing the ^{1}H nmr spectra of both as well as observing no signal doubling in the ^{1}H nmr spectrum of an equal mixture of **35a** and diazotized **30a** suggested that they were indeed the same compound. Diazotization of the *O*-alkylated product (**31a**) has proved to be unsuccessful to date.

O-Alkylated azetidinone (**31a**) was a white crystalline solid and X-ray analysis confirmed its structure (Figure 1).



31a

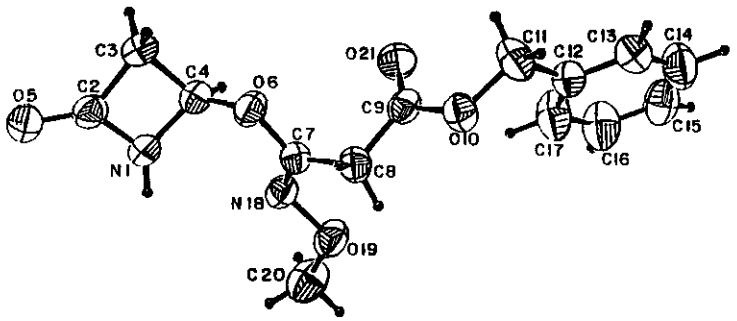
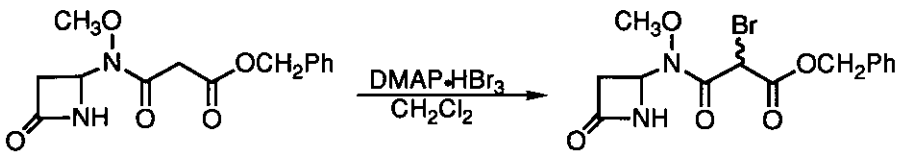


Figure 1

A crystalline racemic brominated *N*-alkylated azetidinone (**37**, Eq. 4) product was formed using 4-dimethylaminopyridinium bromide perbromide.[23] X-ray crystallographic analysis verified that the *N*-alkylated product (**30a**) was obtained (Figure 2).



30a **37** (4)

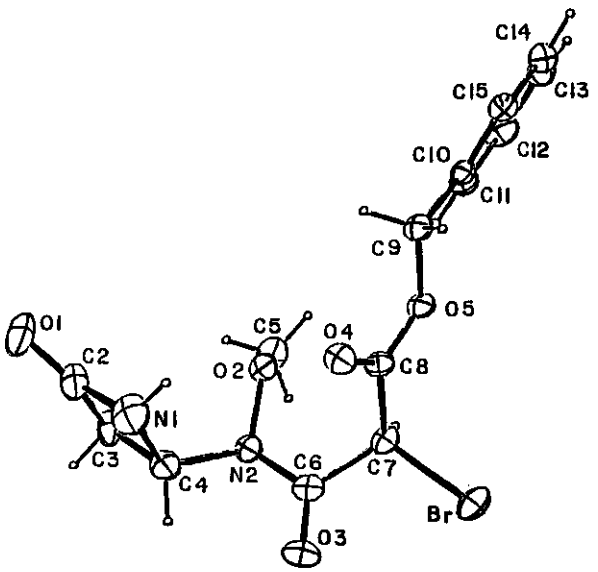


Figure 2

Having this data, some additional diagnostic features of both *N*- and *O*-alkylated products (**30a,b** and **31a,b**) were noted. First, in the ^{1}H nmr spectra, the methylene alpha to the hydroxamate and benzyl ester in the *O*-alkylated products (**31a,b**) appear as doublets of doublets, whereas in the *N*-alkylated products (**30a,b**), they are singlets. Second, in the carbonyl region of the ^{13}C nmr, the *N*-alkylated compounds all show two strong signals and one weak, broad signal. This weak signal may correspond to a quadrupolar effect of nitrogen on the hydroxamate carbonyl.[24]

In conclusion, selective formation of *N*- or *O*-alkylated products can be obtained from the alkylation of various silver hydroxamates with β-lactams which contain specific leaving groups at C_4. Intermediates of the azapenam analog (**36a,b,c**) have been formed through the use of the silver chemistry of a diazo hydroxamate followed by rhodium catalyzed carbene insertion. The results

provide potentially useful intermediates for the synthesis of analogs of known active antibiotics and β-lactamase inhibitors.

EXPERIMENTAL

General Methods. Melting points were taken on a Thomas-Hoover Capillary Melting Point Apparatus and are uncorrected. ^{1}H Nmr and ^{13}C nmr spectra were obtained at 300 MHz and 75 MHz respectively on a General Electric GN-300 spectrometer in chloroform-d. ^{1}H Nmr spectra are referenced to internal tetramethylsilane at 0.00 ppm. Coupling constants (*J*) for ^{1}H nmr spectra are given in hertz. ^{13}C Nmr spectra are referenced to the center line of the chloroform-d triplet at 77.00 ppm unless indicated otherwise. Mass spectra (ms) were recorded on a Finnagan MAT Model 8430 spectrometer using electron impact ionization (70 eV) or, if indicated, chemical ionization (Clms) with isobutane and NH_3. Ir spectra were taken as a thin film on NaCl plates (tf) or by potassium bromide pellet (KBr) on a Perkin-Elmer Model 1420 spectrophotometer and referenced to polystyrene at 1601 cm^{-1}. X-Ray crystallographic studies were carried out with Mo-K α radiation (λ = 0.71073Å) on an automated Enraf-Nonius CAD4 diffractometer. High-pressure liquid chromatography (hplc) was conducted on a Beckmann Model 332 Liquid Chromatograph System equipped with Alltech Econosil columns (25 x 4.6 mm, 5μ silica) using optical peak detection at 254 nm. Flash chromatography[25] was performed with silica gel 60, 230-400 mesh (EM Science). Radial chromatography was performed using a Harrison Research Chromatotron Model 7924 on plates prepared with Kieselgel 60 PF_{254} (EM Science). Tlc analysis was performed on aluminum-backed silica gel 60 F_{254}, 0.2 mm plates (MCB Reagents) and visualized with uv light or ethanolic phosphomolybdic acid followed by heating. Anhydrous THF was distilled from sodium/benzophenone, while methylene chloride, acetonitrile and pyridine were distilled from calcium hydride and other solvents were distilled before use.

N-Cbz-4-Aminobutyric Acid (20)

To a solution of 4-aminobutyric acid (**19**, 3.01 g, 29.2 mmol) in water (30 ml) was added sodium hydroxide (2.35 g, 58.8 mmol) and the mixture was cooled to 0°C in an ice bath. Carbobenzoxy chloride (4.2 ml, 29.6 mmol) was added to the colorless solution and the resulting mixture was stirred vigorously. The reaction was monitored by tlc (1:1 ethyl acetate:hexanes) from quenched

aliquots (1N HCl/ethyl acetate) and subsequent staining with ninhydrin. The reaction was stirred for 30 min at 0°C then allowed to warm up to room temperature and stirred an additional 1.5 h when it appeared that most of the chloride had gone into solution. Methylene chloride was added to the flask and the reaction was quenched by adding 1N HCl to pH 2. The layers were separated and the aqueous layer was extracted with three more poritons of methylene chloride. The organic layers were combined, washed with brine, dried over magnesium sulfate, and filtered. The solvent was removed under reduced pressure to give a white solid that was pure enough to use in the next reaction (5.97 g, 86%). mp 59-61°C; ^{1}H nmr (300 MHz) $CDCl_3$ δ 1.83 (apparent quint, 2H), 2.39 (t, *J*=7.2 Hz, 2H), 3.23 (q, *J*=6.6 Hz, 2H), 5.09 (s, 2H), 7.34 (s, 5H); ^{13}C nmr (75 MHz) $CDCl_3$ δ 24.88, 31.09, 40.21, 66.76, 127.91, 127.95, 128.05, 128.09, 128.47, 136.37, 165.57, 178.36.

Methyl *N*-Cbz-4-Aminobutyrohydroxamate (18a)

N-Cbz-4-aminobutyric acid (**20**, 3.01 g, 12.7 mmol) was dissolved in a water (65 ml)/ THF (60 ml) mixture. The pH was adjusted to 4.5. Methoxyamine hydrochloride (1.6 g, 19.1 mmol) was dissolved in 1N sodium hydroxide (13 ml) and the pH of this solution was also adjusted to 4.5 with acid. The two solutions were mixed, allowed to equilibrate, and the slightly cloudy solution was readjusted to pH 4.5. Water soluble carbodiimide (1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide, 4.9 g, 25.5 mmol) was added portionwise over a 15 min period maintaining the pH of the solution at 4.5. The solution became homogeneous during the WSC addition. Once the addition was complete, the reaction was stirred for 40 min. The reaction was saturated with sodium chloride to form two layers. The layers were separated and the aqueous phase was extracted with three 40 ml portions of ethyl acetate. The combined organic layers were washed with 5% citric acid, water, 5% sodium bicarbonate, and brine (50 ml each), dried over magnesium sulfate, and filtered. The solvent was removed to provide a light yellow oil. The yellow oil was purified by column chromatography (2:1 ethyl acetate:hexanes) to give the product **18a** as white crystals (3.18 g, 94%) which were used without further purification. mp 62-64.5°C; ^{1}H nmr (300 MHz) $CDCl_3$ δ 1.82 (apparent quint, 2H), 2.12 (m, 2H), 3.22 (m, 2H), 3.74 (s, 3H), 5.09 (s, 2H), 5.29 (br s, 1H), 7.34 (s, 5H), 9.62 (br s, 1H); ^{13}C nmr (75 MHz) $CDCl_3$ δ 25.89, 30.05, 39.93, 63.95, 66.61, 127.86, 128.00, 128.38, 136.38, 157.02, 170.60; Exact mass (EI) for $C_{13}H_{18}N_2O_4$ Calcd 266.12666. Found 266.1262.

4-Aza-β-lactam (12a) from 4-Ethylthio 2-azetidinone (7b)

4-Ethylthio 2-azetidinone (**7b**, 70.2 mg, 0.54 mmol) was dissolved in acetonitrile (5 ml) and cooled to 0°C in an ice bath. To this was added methyl *N*-Cbz-4-aminobutyrohydroxamate (**18a**, 118.2 mg, 0.45 mmol) and after it dissolved, silver nitrate (151.7 mg, 0.89 mmol) and triethylamine (80 μl, 0.58 mmol) were added. A precipitate was observed 15 min after the base addition. The reaction was allowed to stir at 0°C for 1 h then slowly allowed to warm up to room temperature and stirred overnight. The reaction was filtered through Celite and the filtrate was added to ethyl acetate (10 ml). This was washed with water, 5% citric acid, 5% sodium carbonate, and brine (10 ml each). The organic layer was dried with magnesium sulfate and filtered. The solvent was removed under reduced pressure to provide a yellow oil. This oil was purified by radial chromatography (2: 1 ethyl acetate:hexanes to 100% ethyl acetate) to give two compounds. The first (2.3 mg) was a yellow semisolid byproduct and the second (114.4 mg, 77% yield) was the desired alkylated product (**12a**) *as a colorless oil. Ir (tf) 3280-3340, 1765, 1655-1705cm*$^{-1}$; ^{1}H *nmr (300 MHz)* $CDCl_3$ δ 1.84 (m, 2H), 2.52 (m, 2H), 3.10 (ddd, *J*=15.0, 4.7, 2.9 Hz, 1H), 3.23 (m, 3H), 3.80 (s, 3H), 5.08 (s, 2H), 5.36 (br s, 1H), 5.96 (br s, 1H), 6.61 (br s, 1H), 7.34 (s, 5H); ^{13}C nmr (75 MHz) $CDCl_3$ δ 24.23, 29.77, 40.27, 41.47, 58.82, 66.18, 66.54, 127.93, 128.01, 128.41, 136.48, 156.53, 166.45, 176.06; ms (CI) MH^+ 336.

From 4-Acetoxy 2-azetidinone (7a)

Methyl *N*-Cbz-4-aminobutyrohydroxamate (**18a**, 102.3 mg, 0.38 mmol) and 4-acetoxy 2-azetidinone (**7a**, 62.5 mg, 0.48 mmol) were dissolved in acetonitrile (5 ml) and cooled to 0°C in an ice bath. To this was added silver nitrate (111.7 mg, 0.66 mmol) and triethylamine (64 μl, 0.46 mmol). A precipitate began to appear after the base addition. The reaction was stirred at 0°C for 1 h then allowed to warm up to room temperature and stirred overnight wrapped in foil. Workup as before gave a light yellow oil. The oil was purified by radial chromatography using 2:1 ethyl acetate:hexanes as eluent to give the alkylated product (**12a**)(107.2 mg, 84%) which was identical to that obtained earlier.

Alkylation of 12a to 22a using Phase Transfer Conditions

Azetidinone(**12a**, 101.2 mg, 0.30 mmol) and *p*-nitrobenzyl 2-bromoacetate (**21a**, 247 mg, 0.90 mmol) were dissolved in acetonitrile (6 ml) and added to a stirred solution of benzyltriethylammonium chloride (6.8 mg, 10 mol%) and powdered potassium hydroxide (19.1 mg, 0.34 mmol) at 0°C. The addition *via* cannula was done over a 15 min period. Once the addition was complete, the reaction was allowed to warm up to room temperature and stirred overnight. The reaction was filtered and the filtrate was taken up by ethyl acetate and washed with water and brine. The organic layer was dried with magnesium sulfate, filtered, and the solvent was removed under reduced pressure to give a light yellow oil. The oil was purified by radial chromatography first eluting with 2:1 methylene chloride:hexanes, then 100% ethyl acetate to remove the excess PNB bromoacetate and continued elution with 100% ethyl acetate gave product **22a** (60.8 mg, 41%). Ir (tf) 3350-3420, 1755-1775, 1685-1715cm^{-1}; ^{1}H nmr (300 MHz) $CDCl_3$ δ 1.82 (apparent quint, 2H), 2.54 (t, *J*=7.0 Hz, 2H), 3.20 (dd, *J*=15.0, 4.9 Hz, 1H), 3.23 (quint, *J*=6.5 Hz, 2H), 3.33 (dd, *J*=15.0, 2.2 Hz, 1H), 3.76 (s, 3H), 3.82 (d, *J*=18.1 Hz, 1H), 4.21 (d, *J*=18.1 Hz, 1H), 5.03 (br s, 1H), 5.06 (s, 2H), 5.23 (s, 2H), 6.04 (dd, *J*=4.9, 2.2 Hz, 1H), 7.32 (s, 5H), 7.48 (d, *J*=8.8 Hz, 2H), 8.20 (d, *J*=8.8 Hz, 2H); ^{13}C nmr (75 MHz) $CDCl_3$ δ 24.17, 29.67, 40.78, 42.15, 61.70, 63.93, 64.61, 65.67, 65.73, 122.72, 124.90, 127.00, 127.42, 129.08, 129.53, 136.44, 142.10, 156.43, 166.20, 167.57, 176.84; Exact mass (FAB) for $C_{25}H_{29}N_4O_9$ (MH^+) Calcd 529.19345. Found 529.1923.

Methyl 4-*N*-Phthalimido-butyrohydroxamate (18b)

Using the same procedure as for the formation of **18a**, a solution of *O*-methyl hydroxylamine (1.66 g, 19.9 mmol) in 1N sodium hydroxide (13 ml) and another solution containing *N*-phthalimido-4-aminobutyric acid[11] (**20b**, 3.09 g, 13.2 mmol), saturated sodium bicarbonate (30 ml) and THF (30 ml) were added together. Once the pH was adjusted to 4.5, the WSC was added over a 20 min period keeping the pH at 4.5. The reaction was allowed to stir at room temperature for 1 h, while maintaining the pH at 4.5. Sodium chloride was added to saturate the reaction mixture and the layers were separated. The aqueous layer was extracted with ethyl acetate (3x40 ml). The organic layers were combined and washed with water, 5% citric acid, 5% sodium bicarbonate, brine (50 ml each), dried with magnesium sulfate, and filtered. The solvent was removed under reduced pressure to provide a colorless oil which crystallized upon standing (2.39 g, 69%) and was used

without further purification. mp 124-126°C. Ir (tf) 3220, 1770, 1710, 1660cm^{-1}; ^{1}H nmr (300 MHz) $CDCl_3$ δ 1.97-2.15 (m, 4H), 3.69-3.73 (m and s overlap, 5H), 7.68-7.82 (m, 4H), 9.5 (br s, 1H); ^{13}C nmr (75 MHz) $CDCl_3$ δ 24.67, 30.35, 37.03, 64.18, 123.18, 131.83, 133.88, 134.00, 168.51, 169.91; Exact mass (EI) for $C_{13}H_{14}N_2O_4$ Calcd 262.09536. Found 262.0953.

4-Aza-β-lactam (12b)

4-Acetoxy 2-azetidinone (**7a**, 970 mg, 7.5 mmol) and methyl 4-*N*-phthalimido-butyrohydroxamate (**18b**, 1.55 g, 5.9 mmol) were dissolved in acetonitrile (80 ml) and cooled to 0°C in an ice bath. To this was added silver nitrate (1.63 g, 9.56 mmol) and triethylamine (1.25 ml, 9.0 mmol). After the addition, the reaction was allowed to slowly warm up to room temperature and stirred overnight while protected from light with foil. The reaction was filtered through Celite and was rinsed with ethyl acetate. The filtrate was taken up in more ethyl acetate, then washed with water, 5% citric acid, 5% sodium bicarbonate, and brine (50 ml each), dried with magnesium sulfate, and filtered. The solvent was removed under reduced pressure to give a yellow oil. The oil was purified by radial chromotography (2:1 ethyl acetate:hexanes then 100% ethyl acetate) to isolate three compounds. The first and the second were unidentifiable byproducts and the third was the desired compound (**12b**, 1.45 g, 74%). Ir (tf) 3240-3340, 1670-1790cm^{-1}; ^{1}H nmr (300 MHz) $CDCl_3$ δ 2.0-2.1 (m, 2H), 2.46-2.67 (m, 2H), 3.14 (ddd, *J*=15.0, 4.7, 2.8 Hz, 1H), 3.28 (dd, *J*=15.0, 2.0 Hz, 1H), 3.74-3.8 (m, 2H), 3.86 (s, 3H), 6.00 (d, *J*=2.3 Hz, 1H), 6.76 (br s, 1H), 7.7-7.86 (m, 4H); ^{13}C nmr (75 MHz) $CDCl_3$ δ 22.76, 29.71, 36.96, 41.45, 58.87, 66.11, 123.08, 131.83, 133.90, 166.48, 168.31, 175.51; Exact mass (EI) for $C_{16}H_{17}N_3O_5$ (M^+) Calcd 331.11682. Found 331.1173.

4-Oxa-β-lactam (21b)

Methyl 4-*N*-phthalimidobutyrohydroxamate (**18b**, 204.6 mg, 0.78 mmol) was dissolved in methanol (4 ml) and to this was added silver nitrate (226 mg, 1.3 mmol). After 5 min, several drops of ammonium hydroxide were added to give an immediate white precipitate. The solid was filtered off and dried under vacuum overnight. The resulting hydroxamate silver salt(**18c**, 244.2 mg, 0.66 mmol, 85%) was added to a stirred solution of 4-ethylthio 2-azetidinone (**7b**, 120 mg, 0.92 mmol) in THF (8 ml). The reaction was stirred overnight wrapped in foil to protect it from the light. The resulting yellow solid was filtered off through a plug of Celite and rinsed with methylene chloride.

The filtrate was washed twice with brine and the organic layer was dried with magnesium sulfate and filtered. The solvent was removed under reduced pressure to give a yellow oil which crystallized upon standing. The solid was then purified by radial chromatography to give the desired product as a white crystalline product. Attempts to recrystallize using various solvents failed (86 mg, 39%). Ir (tf) 3300, 1765, 1705, 1690cm^{-1}; ^{1}H nmr (300 MHz) $CDCl_3$ δ 1.96 (apparent quint, 2H), 2.46 (t, *J*=7.5 Hz, 2H), 2.96 (ddd, *J*=15.2, 1.3, 0.7 Hz, 1H), 3.18 (ddd, *J*=15.2, 3.9, 2.5 Hz, 1H), 3.66 (s, 3H), 3.71 (t, *J*=7.2 Hz, 2H), 5.65 (dd, *J*=3.9, 1.4 Hz, 1H), 6.70 (br s, 1H), 7.86-7.72 (m, 4H); ^{13}C nmr (75 MHz) $CDCl_3$ δ 23.66, 23.94, 37.30, 44.94, 61.86, 74.32, 123.16, 131.97, 133.95, 161.94, 165.77, 168.21; Clms (MH^+) 332; Exact mass (FAB) for $C_{16}H_{17}N_3O_5$ (M^+-OCH_3) Calcd 300.09843. Found 300.0987.

Azetidinone Hydroxamate (23b)

Azetidinone (**12b**, 117 mg, 0.35 mmol) and benzyl 2-bromoacetate (**22b**, 900 μl, 5.7 mmol) were dissolved in acetonitrile (10 ml) and cesium carbonate (126 mg, 0.39 mmol) was added at room temperature. The reaction started to become cloudy after 5 min as a precipatate began to form. The mixture was allowed to stir overnight at room temperature. Most of the solid was filtered off and the filtrate was evaporated to a light yellow oil. The oil was partitioned between ethyl acetate and water. The water layer was extracted once more with ethyl acetate. The organic layers were combined, washed with brine, dried with magnesium sulfate, and filtered. The solvent was removed under reduced pressure to give a yellow oil. The oil was purified by radial chromatography (1:1 ethyl acetate:hexanes then 100% ethyl acetate) to isolate two compounds as oils. The first was recovered benzyl 2-bromoacetate (82.4 mg). The other was the alkylated product(**23b**, 78 mg, 46%). Ir (tf) 1775, 1750, 1710, 1688cm^{-1}; ^{1}H nmr (300 MHz) $CDCl_3$ δ 2.01 (apparent quint, 2H), 2.53-2.57 (m, 2H), 3.21 (dd, *J*=14.9, 5.0 Hz, 1H), 3.34 (dd, *J*=14.9, 2.2 Hz, 1H), 3.76 (s, 3H), 3.82 (d, *J*=18.1 Hz, 1H), 5.15 (s, 2H), 6.06 (d, *J*=2.6 Hz, 1H) 7.34 (s, 5H), 7.69-7.84 (m, 4H); ^{13}C nmr (75 MHz) $CDCl_3$ δ 22.90, 29.86, 37.00, 40.85, 42.05, 62.87, 65.44, 67.34, 123.14, 128.32, 128.46, 128.55, 131.97, 133.92, 134.90, 166.37, 167.65, 168.34, 169.69; Exact mass (EI) for $C_{25}H_{25}N_3O_7$ (M^+) Calcd 479.16925. Found 479.1698.

Acylated Elimination Product (25a)

Azetidinone (**12a**, 151 mg, 0.45 mmol) was dissolved in methylene chloride (5 ml) and cooled to -15°C in an ethylene glycol/dry ice bath. Methyl oxalylchloride (**24**, 80 µl, 0.87 mmol) and diisopropylethylamine (155 µl, 0.89 mmol) were then added. Immediately after the addition of the amine, the reaction turned yellow. After 10 min, the reaction was partitioned between methylene chloride and water. The organic layer was washed with 5% citric acid and brine (8 ml of each), dried with magnesium sulfate, and filtered. The solvent was removed under reduced pressure to give a yellow oil. The oil was purified by radial chromatography using a step gradient of 2:1 ethyl acetate:hexanes to 100% ethyl acetate as eluent to give **25a** as a white foam (86.3mg, 45.6%). Ir (tf) 3350, 1775, 1755, 1700, 1685cm^{-1}; ^{1}H nmr (300 MHz) $CDCl_3$ δ 1.90 (quint, J=6.8 Hz, 2H), 2.64 (t, J=7.0 Hz, 2H), 3.28 (q, J=6.5 Hz, 2H), 3.81 (s, 3H), 3.96 (s, 3H), 5.08 (s, 2H), 5.20 (br s, 1H), 6.61 (d, J=12.97 Hz, 1H), 7.33 (s, 5H), 8.39 (d, J=10.62 Hz, 1H), 9.38 (s, 1H); ^{13}C nmr (75 MHz) $CDCl_3$ δ 24.08, 29.60, 40.09, 54.22, 64.45, 66.55, 98.80, 127.94, 128.01, 128.41, 136.41, 137.35, 150.25, 156.53, 160.00, 165.46, 171.41; Clms (MH^+) 422.

Acylated Elimination Product (25b)

The same addition procedure was used as in the preparation of **25a** with the following amounts of materials: β-lactam (**12b**, 150.2 mg, 0.45 mmol) in methylene chloride (5 ml); methyl oxalylchloride (**24**, 83 µl, 0.90 mmol) and diisopropylethylamine (157 µl, 0.90 mmol)). However, the reaction was stirred for 45 min instead of 10 min. The reaction was removed from the cooling bath and partitioned between methylene chloride and water. The water layer was extracted once more with methylene chloride. The organic layers were combined, washed with 5% citric acid, 5% sodium bicarbonate, brine, dried with magnesium sulfate, and filtered. The solvent was removed under reduced pressure to give a yellow oil. The oil was purified by radial chromatography (1:1 ethyl acetate:hexanes) to isolate one compound (99.6 mg, 53%) as a white solid. This product did not have a β-lactam as determined by spectral interpretation. Instead, it was determined to be elimination product (**25b**). Ir (tf) 3220, 1730, 1705-1655cm^{-1}; ^{1}H nmr (300 MHz) $CDCl_3$ δ 2.08 (quint, J=6.75 Hz, 2H), 2.69 (t, J=7.0 Hz, 2H), 3.81 (t, J=6.5 Hz, 2H), 3.87 (s, 3H), 3.98 (s, 3H), 6.68 (d, J=13.6 Hz, 1H), 6.62 (d, 1H), 7.71-7.88 (m, 4H), 8.40 (d, J=12.3 Hz, 1H), 9.15 (s, 1H); ^{13}C nmr (75 MHz) $CDCl_3$ δ 22.86, 29.97, 36.94, 54.26, 62.45, 98.69, 123.21, 131.88, 133.99, 137.45,

154.71, 159.99, 165.38, 168.36, 170.80; Exact mass (EI) for $C_{19}H_{19}N_3O_8$ (M^+) Calcd 417.11721. Found 417.1178

Carbinolamide (27a)

β-Lactam (**12a**, 300 mg, 0.90 mmol) and allyl glyoxylate (**26**, 156 mg, 1.18 mmol) were dissolved in toluene (4.5 ml) and heated to reflux for 21 h using a Dean-Stark trap containing calcium hydride to remove the water from the reaction mixture. The reaction was cooled and the solvent was removed under reduced pressure to give a yellow oil. Some of the oil (35 mg) was purified by column chromatography (2:1 ethyl acetate:hexanes) to isolate a light yellow foam (14.2 mg, 3.5%). Ir (tf) 3350, 1775, 1755, 1700, 1685cm $^{-1}$; ^{1}H nmr (300 MHz) $CDCl_3$ δ 1.87 (m, *J*=7.2 Hz, 2H), 2.54 (t, *J*=6.8 Hz, 2H), 3.17 (dd, *J*=15.1, 5.3 Hz, 1H), 3.26-3.31 (m, 2H), 3.36 (dd, *J*=15.1, 2.3 Hz, 1H), 3.85 (s, 3H), 4.62-4.66 (m, 1H), 4.76 (dquint, *J*=6.0, 1.3 Hz, 1H), 4.98 (br s, 1H), 5.08 (s, 2H), 5.29-5.41 (m, 2H), 5.89-6.00 (m, 1H), 6.02 (br s, 1H), 7.35 (s, 5H); ^{13}C nmr (75 MHz) $CDCl_3$ δ 14.17, 24.15, 29.56, 40.16, 40.70, 61.19, 65.75, 66.72, 67.57, 72.06, 119.95, 128.11, 128.50, 130.88, 136.44, 156.64, 165.34, 167.87; Elms (M^+) 449.

Carbinolamide (27b)

The same procedure was used as above, using β-lactam (**12b**, 268.1 mg, 0.81 mmol) and allyl glyoxylate (**26**, 166 mg, 1.3 mmol) in toluene (4 ml) and refluxing for 22 h. The solvent was removed under reduced pressure to give an oil. The oil was purified by column chomatography (2:1 ethyl acetate:hexanes) to give carbinol (**27b**) as a light yellow oil (127.8 mg, 35.4%). Ir (tf) 3410, 1786-1755, 1710cm $^{-1}$; ^{1}H nmr (300 MHz) $CDCl_3$ δ 2.02-2.08 (m, 2H), 2.52-2.58 (m, 2H), 3.16 (dt, *J*=10.0, 5.0 Hz, 1H), 3.36 (td, *J*=15.0, 2.4 Hz, 1H), 3.77-3.84 (m, 2H), 3.88 (s, 1H), 4.64 (m *J*=5.2, 5.2, 1.3 Hz, 1H), 4.76 (d, *J*=5.3 Hz, 1H), 5.25-5.38 (m, 2H), 5.40-5.41 (m, 1H), 5.81-6.0 (m, 1H), 6.02-6.04 (m 1H), 7.71-7.86 (m, 4H); Clms (MH^+) 416.

Monobenzylmalonate (33)

Meldrum's acid (**32**, 21.08 g, 0.146 mol), made using the procedure of Davidson,[16] was dissolved in benzene (113 ml) to which was added benzyl alcohol (22.7 ml, 0.22 mol). This colorless solution was refluxed overnight. The reaction was allowed to cool to room temperature and then made

basic with saturated sodium bicarbonate. The resulting two phase solution was washed with ethyl acetate (3x75 ml). The aqueous layer was then made acidic with 6N HCl. This solution was extracted with ethyl acetate (3x100 ml). The organic layers were combined, washed with brine (100 ml), dried with magnesium sulfate, filtered, and evaporated under reduced pressure to give a solid, which was recrystallized from carbon tetrachloride and dried under vacuum to give white crystals (20.65 g, 73%). mp 48-49.5°C (lit.,[17] 46-48°C); ^{1}H nmr (300 MHz) $CDCl_3$ δ 3.48 (s, 2H); 5.20 (s, 2H); 7.36 (s, 5H); ^{13}C (75 MHz) $CDCl_3$ δ 40.71, 67.63, 128.36, 128.58, 128.63, 134.90, 166.61, 171.13.

Benzyl *O*-Methylmalonohydroxamate (29a)

Monobenzylmalonate (**33**, 2.00 g, 10.3 mmol) was dissolved in THF (40 ml) and was cooled to 0°C with an ice bath. After 15 min, *N*-hydroxysuccinimide (1.19 g, 10.3 mmol) and dicyclohexylcarbodiimide (2.34 g, 11.4 mmol) were added. Solid started to appear after 5 min and the reaction was allowed to warm slowly to room temperature. After 5 h, recrystallized methoxyamine hydrochloride (1.29 g, 15.5 mmol) and pyridine (1.25 ml, 15.5 mmol) were added and the reaction was stirred for 11 h. The reaction was cooled to 0°C and dicyclohexylurea (DCU) was removed by filtration. The solvent was evaporated. The residue was dissolved in ethyl acetate (80 ml) and was washed with water, 5% citric acid, 5% sodium bicarbonate, brine (60 ml each), dried with magnesium sulfate, and filtered. The solvent was evaporated and a dark pink oil was obtained. The oil was dissolved in a water/methanol (1:2) solution and ascorbic acid (1 g) was added. The solution was extracted with ethyl acetate (2x25 ml). The organic layers were combined, dried with magnesium sulfate, and filtered. The solvent was evaporated under reduced pressure and a light yellow oil (**29a**, 1.84 g, 80%) was obtained. Ir (tf) 3200, 1745, 1670cm^{-1}; ^{1}H nmr (300 MHz) $CDCl_3$ δ 3.32 (s, 2H, $COC\underline{H}_2CO$), 3.71 (s, 3H, $C\underline{H}_3$), 5.14 (s, 2H, $C\underline{H}_2$), 7.34 (s, 5H, Ph), 9.95 (br s, 1H, N<u>H</u>); ^{13}C nmr (75 MHz) $CDCl_3$ δ 39.61, 64.00, 67.19, 128.13, 128.33, 128.43, 134.88, 163.06, 167.72; Exact mass (EI) for $C_{11}H_{13}NO_4$ (M+) Calcd 223.084459. Found 223.0846.

2-Diazobenzyl-*O*-methylmalonohydroxamate (34a)

Benzyl *O*-methylmalonohydroxamate (**29a**, 538.6 mg, 2.42 mmol) was dissolved in acetonitrile (3.45 ml). The solution was cooled to 0°C by an ice bath after which *p*–carboxybenzenesulfonyl azide[18] (603.6 mg, 2.66 mmol) and triethylamine (0.84 ml, 6.04 mmol) were added. A white precipitate was observed after 20 min. The reaction was stirred at 0°C for 1 h after the addition then allowed to warm to room temperature and stirred overnight since analysis by tlc (2:1 ethyl acetate:hexanes) taken after 2.5 h still indicated the presence of starting material. The reaction was filtered and methylene chloride (25 ml) was added to the filtrate. The filtrate was washed with 5% citric acid (3x25 ml), brine (2x25 ml), dried with magnesium sulfate, and filtered. The solvent was evaporated under reduced pressure to give a yellow solid (**34a**, 510 mg, 85%) which was recrystallized from ether. mp 84-86°C. Ir (tf) 3322, 2140, 1686, 1654 cm^{-1}; ^1H nmr (300 MHz) $CDCl_3$ δ 3.81 (s, 3H, CH_3), 5.26 (s, 2H, CH_2), 7.38 (s, 5H, Ph), 9.95 (br s, 1H, NH); ^{13}C nmr (75 MHz) $CDCl_3$ δ 65.05, 67.49,128.38, 128.66, 128.76, 128.84, 134.65, 159.79 163.40; Exact mass (EI) for $C_{11}H_{11}N_3O_4$ (M^+) Calcd 249.0749. Found 249.0766.

Monocyclic β-Lactam (35a)

4-Ethylthio 2-azetidinone (**7b**, 119.6 mg, 0.91 mmol) was dissolved in acetonitrile (40 ml) and to this solution was added **34a** (249.2 mg, 1.0 mmol). The mixture was cooled to 0°C by an ice bath. Once this was achieved, silver nitrate (0.270 g, 1.6 mmol) and triethylamine (0.15 ml, 1.1 mmol) were added. The reaction was stirred at 0°C for 1 h during which a solid appeared. The reaction was allowed to slowly warm up to room temperature and stirred overnight. The reaction was filtered and the filtrate was dissolved in ethyl acetate (40 ml), washed with brine (3 x 40 ml), and dried with magnesium sulfate. The solution was filtered and the solvent was removed under reduced pressure. By nmr and tlc, the oil (159.5 mg) was impure, therefore it was purified by column chromatrography using 6:1 ethyl acetate:hexanes as eluent. Two compounds were isolated. The faster moving spot was azetidinone(**7b**). The slower moving spot was recrystallized using methylene chloride and hexanes to give white crystals of **35a** (127 mg, 44%). mp 101-103°C. Ir (KBr) 2130, 1775, 1725, 1655cm^{-1}; ^1H nmr (300 MHz) $CDCl_3$ δ 3.01 (ddd, *J*=15.0, 4.7, 3.1 Hz, 1H, cis CH_2), 3.27 (dd, *J*=15.0, 2.0 Hz, 1H, trans CH_2), 3.78 (s, 3H, CH_3), 5.17 (s, 2H, CH_2Ph), 5.6 (dd, *J*=4.7, 2.0 Hz, 1H, CH), 6.48 (br s, 1H, NH), 7.27 (s, 5H, Ph); ^{13}C nmr (75 MHz)

$CDCl_3$ δ 41.51, 61.27, 65.05, 66.26, 67.34, 128.26, 128.65, 128.65, 128.62, 134.92, 160.66, 161.53, 166.02; CIms (MH^+) 319.

Benzyl 3,7-Dioxo-4-methoxy-1,4-diazabicyclo[3.2.0]heptane-2-carboxylate (36a)

Compound(**35a**, 180.9 mg, 0.57 mmol) was dissolved in benzene (25.5 ml) to which was added rhodium (II) acetate dimer (11.5 mg, 0.026 mmol). The heterogeneous mixture was heated (oil bath temperature 85°C; reaction temperature 80°C) and the reaction was completed after 25 min as determined by tlc analysis (6:1 ethyl acetate:hexanes). Nitrogen bubbles were also observed during the reaction. The reaction was then allowed to cool, the catalyst was filtered off using Celite and the solvent was removed under reduced pressure. A dark brown oil was obtained (185.8 mg). The oil was purified by flash column chromatography using 4:1 ethyl acetate:hexanes as the eluent. A light brown oil was obtained of **36a** (94.2 mg, 57%). Ir (tf) 1800, 1745, 1685 cm^{-1}; ^1H nmr (300 MHz) $CDCl_3$ δ 3.19 (dd, *J*=16.5, 1.1 Hz, 1H, *trans* C$\underline{H}_2$), 3.53 (dd, *J*=16.5, 3.2 Hz, 1H, *cis* C$\underline{H}_2$), 3.87 (s, 3H, C$\underline{H}_3$), 4.83 (d, *J*=1.2 Hz, 1H, COC$\underline{H}$), 5.11 (dt, *J*=3.2, 1.1 Hz, 1H, C$\underline{H}$), 5.22 (s, 2H, C$\underline{H}_2$Ph), 7.36 (s, 5H, Ph); ^{13}C nmr (75 MHz) $CDCl_3$ δ 46.34, 58.61, 63.82, 65.01, 68.07, 128.10, 128.52, 134.42, 164.74, 166.03, 173.02; CIms (MH^+) 291.

[3*R* (1'*R*, 4*R*)]-4-Ethylthio-3-[1-(*tert*-butyldimethylsilyloxy)ethyl]-2-azetidinone (7d)

To a solution of sodium hydroxide (117.4 mg, 2.94 mmol) in water (10 ml) was added ethanethiol (85 μl, 1.15 mmol) and this light yellow solution was stirred for 35 min. [3*R* (1'*R*, 4*R*)]-4-acetoxy-3-[1-(*tert*-butyldimethylsilyloxy)ethyl-2-azetidinone[19] (**7c**, 99.6 mg, 0.35 mmol) was added with THF (8 ml) *via* a pressure equalizing addition funnel. The reaction was followed by tlc (3:1 hexanes:ethyl acetate, 2 elutions) while stirring for 5 h. The yellow solution was extracted with ethyl acetate (3 x 15 ml). The organic layers were combined and washed with brine (20 ml), dried with magnesium sulfate, and filtered. The solvent was removed under reduced pressure to give a white crystalline product which was recrystallized from methylene chloride/hexanes (100.8 mg, 100%). mp 112.5-114.5°C; Ir (tf) 3100, 1765, 1715 cm^{-1}; ^1H nmr (300 MHz) $CDCl_3$ δ 0.07 (s, 3H), 0.08 (s, 3H), 0.88 (s, 9H), 1.24 (d, *J*=6.3 Hz, 3H), 1.31 (t, *J*=7.4 Hz, 3H), 2.65 (q, *J*=7.4 Hz, 2H), 3.12 (ddd, *J*=3.6, 2.2, 0.82 Hz, 1H), 4.25 (dd, *J*=6.3, 3.6 Hz, 1H), 4.85 (d, *J*=2.2 Hz, 1H), 6.11 (br s, 1H); ^{13}C nmr (75 MHz)

$CDCl_3$ δ -5.09, -4.39, 15.03, 17.89, 22.24, 24.15, 25.67, 54.19, 64.66, 66.16, 167.65; Exact mass (EI) for $C_9H_{18}NO_2SSi$ (M–*t*-Bu) Calc'd 232.082756. Found 232.0826.

Monocyclic β-lactam (35c)

To a solution of **7d** (169 mg, 0.58 mmol) and **34a** (155.5 mg, 0.63 mmol) in acetonitrile (40 ml) at 0°C was added silver nitrate (204.5 mg, 1.2 mmol) and triethylamine (81 μl, 0.58 mmol). The reaction was stirred overnight. The reaction was quenched with the addition of 1N HCl (2 ml) to the mixture and was then immediately filtered through Celite. The filtrate was added to ethyl acetate (50 ml) and was washed with brine (2x), dried with magnesium sulfate, and filtered. The solvent was evaporated under reduced pressure to give a yellow residue. The oil was purified by radial chromatography (9:1 hexanes/ ethyl acetate) to give two compounds. The first was recovered hydroxamate(**34a**, 41.6 mg) and the second was coupled product (**35c**, 183.5 mg, 66%). Ir (tf) 2150, 1780cm^{-1}; ^1H nmr (300 MHz) $CDCl_3$ δ –0.09 (s, 3H), -0.77 (s, 3H), 0.71 (s, 9H), 1.03 (d, *J*=6.3 Hz, 3H), 3.44(dd, *J*=5.7, 2.1 Hz, 1H), 3.72 (s, 3H), 4.07 (m, 1H), 5.11 (dd, *J*=12.3 Hz, 2H), 5.56 (d, *J*=1.5 Hz, 1H), 6.23 (br s, 1H), 7.23 (s, 5H); Exact mass (EI) for $C_{22}H_{32}N_4O_6Si$ (M^+) Calc d 476.20913. Found 476.208; Anal. Calcd. C, 55.44; H,6.77; N, 11.75. Found: C, 55.26; H, 6.53; N, 11.50.

Benzyl [*3R* (*1'R*, *4R*]-3-(*tert*-butyldimethylsilyloxy)ethyl)- 3,7-dioxo-4-methoxy -1,4-diazabicyclo[3.2.0]heptane-2-carboxylate (36c)

Compound(**35c**, 270.6 mg, 0.57 mmol) was dissolved in benzene (20 ml). Rhodium (II) acetate dimer (3 mg, 0.007 mmol) was added and the solution was heated to reflux. After 2 h, the solution was cooled to room temperature and the solvent was evaporated under reduced pressure. The residue was purified by radial chromatography (4:1 hexanes:ethyl acetate) and the desired bicyclic product was obtained (127.3 mg, 49%). Ir (tf) 1800cm^{-1}; ^1H nmr (300 MHz) $CDCl_3$ δ -0.15 (s, 6H), 0.70 (s, 9H), 1.10-1.15 (d, 3H), 3.20-3.25 (d, 1H), 3.80 (s, 3H), 4.05-4.35 (m, 1H), 4.75 (d, 1H), 5.00 (s, 1H), 5.20 (s, 2H), 7.45 (s, 5H); Exact mass (EI) for $C_{22}H_{32}N_2O_6Si$ (M^+) Calcd 448.20299. Found 448.203.

4-Oxa-β-lactam (31a)

Benzyl *O*-methylmalonohydroxamate (**29a**, 509.5 mg, 2.28 mmol) was dissolved in methanol (10 ml) to which was added silver nitrate (391.1 mg, 2.35 mmol). Water was added to this stirred mixture until all the silver nitrate had dissolved. After 3 min of stirring, ammonium hydroxide (0.31 ml, 7.97 mmol) was added immediately producing a white precipitate. The reaction was stirred for an additional 15 min, then the solvent was evaporated. Methanol was added again to the solid and removed under reduced pressure. A white solid was obtained (929.2 mg).

4-Ethylthio 2-azetidinone (**7b**, 301.6 mg, 2.3 mmol) was dissolved in THF (10 ml) to which was added the hydroxamate silver salt (506.4 mg, 1.5 mmol). The light yellow reaction mixture was stirred overnight. The dark yellow reaction mixture was analyzed by tlc (1:1 ethyl acetate:hexanes) and comparing this to the starting materials a new spot was seen (R_f=0.38). The reaction was filtered through Celite. Ethyl acetate (60 ml) was added to the filtrate, washed with brine (3x20 ml), dried with magnesium sulfate, and filtered. The solvent was removed under reduced pressure to give a light yellow oil. This oil was purified by column chromatography using 1:1 ethyl acetate:hexanes as eluent to isolate three compounds. The first was a white solid (**31a**) which was recrystallized from methylene chloride/hexanes to give white crystals (214.6 mg, 49%). Ir (tf) 3310,1784, 1740, 1643cm^{-1}; ^{1}H nmr (300 MHz) $CDCl_3$ δ 2.93 (d, *J*=15.0 Hz, 1H, *trans* C$\underline{H}_2$), 3.16 (dd, *J*=2.95, 15.0 Hz, 1H, *cis* C$\underline{H}_2$), 3.46 (dd, *J*=15.6 Hz, 2H, C$\underline{H}_2$), 3.69 (s, 3H, C$\underline{H}_3$), 5.16 (s, 2H, C$\underline{H}_2$), 5.71 (d, *J*=2.95 Hz, 1H, C$\underline{H}$), 6.74 (br s, 1H, N$\underline{H}$), 7.35 (s, 5H, Ph); ^{13}C nmr (75 MHz) $CDCl_3$ δ 33.7, 45.13, 62.1, 67.02, 74.92, 128.17, 128.54, 128.38, 135.32, 156.76, 165.57, 166.86; Exact mass (EI) for $C_{14}H_{16}N_2O_4$ (M^+) Calcd 292.105923. Found 292.1065. The second component (186.3 mg) was a mixture of the azetidinone (**7b**) and the product (**31a**) which were separated by radial chromatography to give an additional 24.7 mg of **31a**. The third (109.4 mg) was the starting hydroxamate (**29a**).

Formation of **31a** was also accomplished by *in situ* formation of the silver salt followed by the addition of 4-ethylthio 2-azetidinone (**7b**). Following workup and purification by radial chromatography (1:1 ethyl acetate:hexanes), *O*-alkylated product(**31a**)was isolated in 46% yield.

4-Aza-β-lactam (30a)

The silver salt was made using the same procedure as for **31a**, except that additional methanol was added and the solid was isolated by filtration. The white solid was dried under vacuum (308.6 mg, 50%). The solid was added to a solution of 4-acetoxy 2-azetidinone (**7a**, 181.1 mg, 1.4 mmol) in THF (5 ml). The reaction was followed by tlc (2:1 ethyl acetate:hexanes) and was stirred overnight wrapped in foil to protect it from light. The gray reaction mixture was filtered through Celite and ethyl acetate (20 ml) was added to the filtrate. The filtrate was washed with brine (3x10 ml), dried with magnesium sulfate, and filtered. The solvent was removed under reduced pressure to give a light yellow oil. The oil was purified by column chromatography using 2:1 ethyl acetate:hexanes as the eluent. Two compounds were isolated. The faster eluted compound was a yellow oil (1.1 mg) which was a byproduct. The other was a colorless oil (248.4 mg) which by ^{1}H nmr was found to be a mixture of starting material and possible product. The product was compared by tlc with starting hydroxamate and the product obtained from the ethylthio reaction. It ran different than both. The colorless oil was purified again by column chromatography using 2:1 ethyl acetate:hexanes as eluent to give another colorless oil (67 mg) plus a fraction of a mixture of β–lactam (**7a**) and product (**30a**). The nmr of the product showed differences in the β–lactam protons (H_3 and H_4) and methylene protons (a singlet vs doublet of doublets in ethylthio reaction). The ^{13}C nmr spectra of this product was dramatically different from the ethylthio reaction suggesting another product (**30a**) was formed (79.2 mg, 25%). Ir (tf) 3300, 1776, 1740, 1675cm^{-1}; ^{1}H nmr (300 MHz) $CDCl_3$ δ 3.07 (ddd, J=15.1, 4.7, 2.9 Hz, 1H, cis C$\underline{H}_2$), 3.19 (dd, J=15.1, 2.1 Hz, 1H, trans C$\underline{H}_2$), 3.56 (s, 2H, C$\underline{H}_2$), 3.84 (s, 3H, C$\underline{H}_3$), 5.17 (s, 2H, C$\underline{H}_2$), 5.96 (s, 1H, C$\underline{H}$), 6.46 (br s, 1H, N$\underline{H}$), 7.35 (s, 5H, Ph); ^{13}C nmr (75 MHz) $CDCl_3$ δ 41.0, 41.6, 59.2,66.56, 67.28, 128.4, 128.51, 128.55, 135.01, 166.2, 166.4, 169.6; Exact mass (EI) for $C_{14}H_{16}N_2O_5$ (M^+) Calcd 292.105923. Found 292.1068.

Diazotization of 4-Aza-β-lactam (30a)

The same diazotization procedure for the preparation of **34a** was used with the following starting materials and amounts: Alkylated product (**30a**, 30.4 mg, 0.10 mmol) in acetonitrile (0.5 ml); *p*-carboxybenzenesulfonyl azide (26.1mg, 0.12mmol) and triethylamine (17 μl, 0.12 mmol) to give a light yellow oil (21.7 mg) following workup. The oil was purified by column chromatography (6:1

ethyl acetate:hexanes) to isolate three compounds. Only the middle fraction was of interest which was a mixture of compounds—starting material and diazotized product. Purification by hplc (3:1 hexanes:isopropyl alcohol) failed, therefore fractional recrystallization on the oil (6.9 mg) was attempted using a Craig tube and methylene chloride:hexanes as the solvent system. The white solid (2.5 mg) obtained from this reaction, by ^{1}H nmr, still contained some of the starting material (**30a**), but also contained product(**35a**). Further proof was achieved by the addition of authentic **35a** (0.5 mg) to some of the solid (0.5 mg). From the ^{1}H nmr taken of this mixture, no doubling of peaks was observed and the peaks corresponding to the starting material became smaller. Ir (tf) 3300, 2130, 1774, 1735, 1676cm^{-1}; ^{1}H nmr (300 MHz) $CDCl_3$ δ 3.11 (ddd, *J*=15.0, 4.5, 3.6 Hz, 1H, cis C$\underline{H}_2$), 3.22 (dd, *J*=15.2, 1.7 Hz, 1H), 3.44 (dd, *J*=15.0, 1.5 Hz, 1H, trans C$\underline{H}_2$), 3.89 (s, 3H, CH_3), 5.27 (s, 2H, C$\underline{H}_2$), 5.66 (dd, *J*=4.5, 1.5 Hz, 1H, CH), 6.13 (br s, 1H, N$\underline{H}$), 7.38 (s, 5H, Ph).

Benzyl *O*-Benzylmalonohydroxamate (29b)

Monobenzylmalonate(**33**, 505.5 g, 2.6 mmol) was dissolved in THF (10 ml) and cooled to 0°C by an ice bath. To this was added *N*-hydroxysuccinimide (302.0 mg, 2.6 mmol) and dicyclohexycarbodiimide (590.4 mg. 2.87 mmol). Dicyclohexylurea (DCU) began to precipitate out after 4 min and the reaction was stirred at 0°C for 1 h then allowed to warm up to room temperature and stirred overnight. The reaction was again cooled to 0°C and benzylamine (483 mg, 2.39 mmol) was added *via* syringe. Additional THF (2 ml) was used to rinse the flask that had contained the benzylamine solution and then transfered to the reaction flask. This was stirred at 0°C for 1 h then allowed to warm to room temperature and stirred for 19 h, after which the reaction was cooled to 0°C again and the DCU was filtered off. The filtrate was reduced down to an oil to which ethyl acetate (25 ml) was added. The solution was washed with water, 5% citric acid, 5% sodium bicarbonate, brine (20 ml each) and dried with magnesium sulfate. By tlc analysis, only one spot was observed. The solvent was removed under reduced pressure to give a colorless oil of **29b** which crystallized upon standing and was used without further purification (690.5 mg, 88%). mp 55-57°C. Ir (KBr) 1730, 1650cm^{-1}; ^{1}H nmr (300 MHz) $CDCl_3$ δ 3.33 (s, 2H), 4.91 (s, 2H), 5.14 (s, 2H), 7.35 (s, 5H), 7.36 (s 5H), 9.65 (br s, 1H); ^{13}C nmr (75 MHz) $CDCl_3$ δ 39.92, 67.40, 78.20, 128.30, 128.40, 128.52, 128.57, 129.12, 135.01, 135.07, 162.77, 168.00.

4-Oxa-β-lactam (31b) and 4-Aza-β-lactam (30b)

To a solution of benzyl *O*-benzylmalonohydroxamate (**29b**, 253.3 mg, 0.85 mmol) in THF (6.5 ml) cooled to 0°C by an ice bath was added silver nitrate (244.4 mg, 1.4 mmol) and triethylamine (130 µl, 0.93 mmol). After 10 min, only some of the silver nitrate had dissolved. A solution of 4-ethylthio 2-azetidinone (**7b**, 145 mg, 1.1 mmol) in THF (2 ml) was added dropwise over a 10 min period along with additional THF (2 ml) as a rinse. During the azetidinone addition, a precipitate began to appear. The reaction was stirred for 1 h at 0°C then allowed to warm up to room temperature and stirred overnight. The dark yellow reaction mixture was filtered through Celite and ethyl acetate was added to the filtrate. The filtrate was washed with 5% citric acid, brine (2x), dried with magnesium sulfate, and filtered. The solvent was removed under reduced pressure to give a light yellow oil, which by tlc (2:1 ethyl acetate:hexanes) was two compounds. The oil was purified by radial chromatography (1:1 ethyl acetate:hexanes) to isolate two fractions. The first was a mixture of two components, benzyl *O*-benzylmalonohydroxamate (**7b**) and an alkylated product that by spectral analysis was determined to be *O*-alkylated product (**31b**, 92.2 mg, 30%). ^{1}HNmr (300 MHz) $CDCl_3$ δ 2.84 (ddd, *J*=15.2, 1.2, 0.64 Hz, 1H), 3.08 (ddd, *J*=15.2, 3.9, 2.45 Hz, 1H), 3.27 (s, 2H), 3.46 (dd, *J*=30.8, 16.1 Hz, 2H) 4.88 (s, 2H), 4.91 (d, *J*=2.34 Hz, 2H), 5.11 (s, 4H), 5.61 (dd, *J*=3.9, 1.3 Hz, 1H), 6.5 (br s, 1H), 7.33 (m, 20H), 9.49 (br s, 1H); ^{13}C nmr (75 MHz) $CDCl_3$ δ 24.45, 33.82, 39.88, 44.87, 66.98, 67.34, 74.87, 76.08, 78.11, 127.92, 128.06, 128.25, 128.47, 128.52, 128.60, 129.09, 134.85, 135.02, 135.21, 127.26, 156.81, 162.74, 165.56, 166.71, 167.89; Clms (MH^+) 300 and 369.

The second compound was another coupled product determined by spectral analysis to be *N*-alkylated compound (**30b**, 120.6 mg, 38%). ^{1}HNmr (300 MHz) $CDCl_3$ δ 3.05 (ddd, 1H, *J*=15.2, 4.6, 3.1 Hz), 3.2 (dd, *J*=15.2, 2.1 Hz, 1H), 3.53 (s, 2H), 4.96 (dd, *J*=32.8, 10.0 Hz, 2H), 5.11 (dd, *J*=29.1, 12.1 Hz, 2H), 5.99 (br s, 1H), 6.35 (br s, 1H), 7.32 (m, 10H); ^{13}C nmr (75 MHz) $CDCl_3$ δ 41.21, 41.76, 59.75, 67.25, 81.16, 128.42, 128.48, 128.52, 128.79, 129.32, 133.39, 134.95, 166.28, 166.41; Elms (M^+) 368.

4-Aza-β-lactam (30b)

Benzyl *O*-benzylmalonohydroxamate (**29b**, 142 mg, 0.47 mmol) was dissolved in THF (4 ml) and to this solution was added silver nitrate (138.2 mg, 0.81 mmol). This was cooled to 0°C by an ice bath. Triethylamine (73 µl, 0.52 mmol) was added and stirred at 0°C for 15 min then 4-acetoxy 2-azetidinone (**7a**, 73.5 mg, 0.57 mmol) in THF (1 ml) was added *via* cannula followed by more THF (1 ml) as a rinse. The reaction was stirred for 1 h at 0°C then allowed at warm to room temperature and stirred overnight. The reaction was filtered through Celite and ethyl acetate was added to the filtrate. This was washed with 5% citric acid and brine (3x). The organic layer was dried with magnesium sulfate and filtered. The solvent was removed under reduced pressure to give a light yellow oil. The oil was purified by radial chromatography (1:1 ethyl acetate:hexanes) to isolate the major compound which was the *N*-alkylated product (**30b**, 81.1 mg, 45%). Ir (tf) 3300, 1770, 1740, 1670 cm^{-1}; ^1H nmr (300 MHz) $CDCl_3$ δ 3.04 (ddd, *J*=15.2, 4.7, 3.0 Hz, 1H), 3.19 (dd, *J*=15.2, 2.1 Hz, 1H), 3.52 (d, *J*=1.1 Hz, 2H), 4.96 (dd, *J*=23.5, 10.0 Hz, 2H), 5.11 (dd, *J*=17.6, 12.1 Hz, 2H), 5.98 (br s, 1H), 6.46 (br s, 1H), 7.33 (m, 10H).

Brominated 4-Aza-β-lactam (37)

4-(Benzyl-*O*-methylmalonohydroxamate)-2-azetidinone (**30a**, 101.6 mg, 0.35 mmol) was dissolved in methylene chloride (8 ml) and cooled to 0°C by an ice bath. To this was added 4-(dimethylamino)pyridinium bromide perbromide[23] (140.2 mg, 0.39 mmol). The orange heterogeneous mixture was stirred at 0°C for 15 min, monitoring the reaction by tlc (1:1 ethyl acetate:hexanes). The reaction was then diluted with methylene chloride (20 ml) and washed with water (15 ml) and brine (2x15 ml). The organic layer was dried with magnesium sulfate, filtered, and the solvent was removed under reduced pressure to give a light yellow oil (125.6 mg). The oil was purified by radial chromatography (1:1 ethyl acetate:hexanes) to isolate the starting *N*-alkylated compound (**30a**, 24.2 mg) and the desired mono brominated product (**37**). The white solid was fractionally recrystallized using methylene chloride/hexanes (42 mg, 27%). mp 88-90°C. Ir (tf) 1790, 1740, 1580cm^{-1}; ^1H nmr (300 MHz) $CDCl_3$ δ 3.02 (ddd, *J*=15.3, 4.5,2.9 Hz, 1H), 2.13 (dd, *J*=15.3, 2.3 Hz, 1H), 3.87 (s, 3H), 5.22 (s 1H), 5.22 (dd, *J*=11.8, 6.3 Hz, 2H), 5.94 (dd, *J*=4.3, 2.1 Hz, 1H), 6.45 (br s, 1H), 7.36 (m, 5H); ^{13}C nmr (75 MHz) $CDCl_3$ δ 41.65, 44.20, 60.55, 67.03, 68.59, 128.53, 128.60, 128.65, 128.69, 128.84, 134.44, 164.24, 165.93, 166.38.

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