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# Rearrangements of N-Hydroxy β-Lactams

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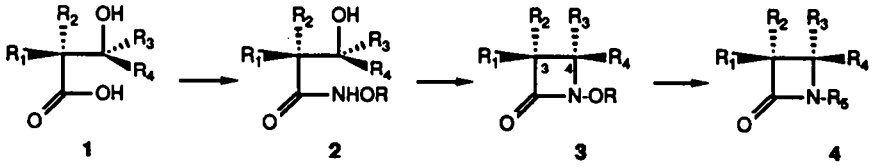
**Abstract** - A number of 4-carboalkoxy-N-hydroxy-2-azetidinones were converted to various derivatives which were shown to undergo novel rearrangements to substituted acryalamides. Under similar conditions, 3,3-dimethyl-4-carboisopropoxy-N-hydroxy-2-azetidinone rearranged to a pyrimidine derivative.

## Introduction

The hydroxamate approach to the synthesis of β-lactams (2-azetidinones, Scheme 1) has provided useful routes to precursors of a number of monocyclic and bicyclic β-lactam antibiotics.[1] An additional attractive feature of this synthetic approach is that retention of the N-O bond, as in structure **3**, provides access to a number of novel heteroatom activated β-lactam antibiotics.[2] Variously substituted N-hydroxy-2-azetidinones (**3**)[3,4] and precursors (**2**)[5] have also been found to be prone to interesting molecular rearrangements. Rearrangements can often lead to reactive intermediates, which, if generated under the proper conditions, may serve as enzyme inhibitors. Thus, we decided to further explore molecular rearrangements of substituted N-hydroxy β-lactams with the anticipation that such studies would not only help further define the chemistry of this important class of compounds, but also possibly lead to the design of novel types of β-lactamase inhibitors. Herein we report the details of rearrangements of a vareity of substituted N-hydroxy β-lactam model compounds under mild conditions.

**Scheme 1**

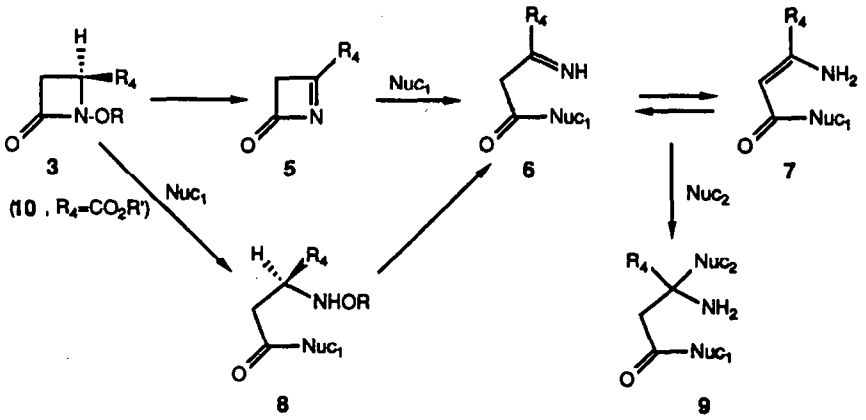



1 2 3 4

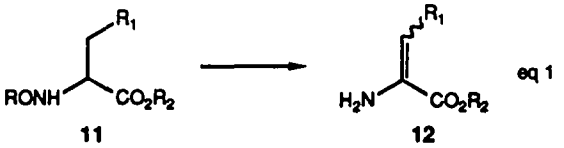
β-Lactamase enzymes are primarily responsible for the development of microbial resistance to currently used β-lactam antibiotics.[6] β-Lactam derived β-lactamase inhibitors are "suicide" or "mechanism based" reagents which are recognized by the enzyme as substrates, but, during or after initial encounter or reaction with the enzyme, react further to generate an electrophilic center for further reaction with the enzyme.[6] This "secondary" reaction usually leads to either transient or irreversible inhibition. Thus, the design of an effective inhibitor not only requires that it be recognized by the enzyme as a potential substrate, but it must also be prone to generation of reactive sites which will facilitate further abnormal reaction with the enzyme.

The eventual deactivating reaction of most β-lactamase inhibitors involves generation of an electrophilic center at the β-carbon of the original β-lactam or the acyl-enzyme derivative of the β-lactam. Consequently, our first goal in these model studies was to initiate reactions on substituted N-hydroxy β-lactams which would be centered about the β-position ($C_4$ of a mono-substituted β-lactam such as **3**). Conceptually, this could be accomplished by converting the hydroxyl group of N-hydroxy substituted β-lactams to a good leaving group (OR of **3**) to promote an elimination to produce a reactive imine intermediate before, after, or during ring opening of the β-lactam (Scheme 2). Since, under eventual physiological conditions the leaving group (OR of **3**) most likely could not be one such as a triflate or mesylate used commonly in organic chemistry, we decided to explore the utility of more modest, but easily generated leaving groups. We also considered that initiation of the desired elimination reaction would be facilitated by incorporation of an ester group at $C_4$ which would increase the acidity of the $C_4$ proton. Such compounds (**10**) were considered especially attractive since the portion of these molecules containing the ester group, the original $C_4$ carbon of the β-lactam, and the N-hydroxy group constitute the backbone of a N-hydroxy amino acid. A number of N-hydroxy amino acids have been converted to dehydro amino acids (eq 1)[7,8] With these considerations in mind, we prepared a number of specific examples of **10** and studied the induction of rearrangements under mild conditions.

**Scheme 2**




For an enzymatic reaction, $Nuc_1$ or $Nuc_2$ might be nucleophilic components of the enzyme



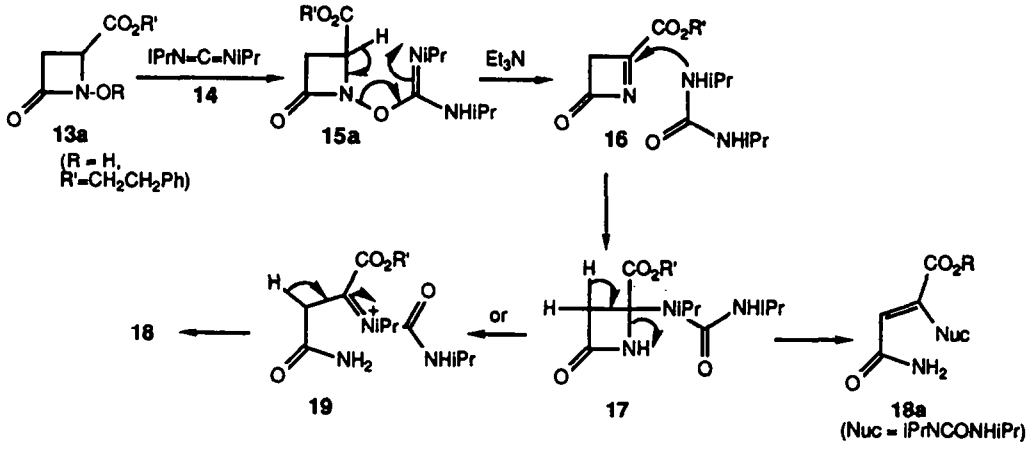

eq 1

## Results

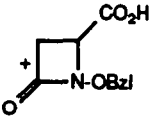
As a first example, 4-carbophenethoxy N-hydroxy-2-azetidinone **13a** (Scheme 3) was prepared from malic acid using our previously reported process.[9,10] The phenethoxy ester was chosen for convenience since it is compatible with the synthetic conditions, it provides a chromophore to assist chromotography and the final N-hydroxy compound (**13a**) is soluble in common organic solvents for our model studies. Since isoureas are effective leaving groups under mild conditions,[11,12] **13a** was treated with diisopropyl carbodiimide, **14**, to provide the isolable isourea **15a** in 80% yield (Scheme 3). Reaction of **15a** with triethylamine promoted a smooth

rearrangement to the acrylamide **18a**. It was subsequently noted that the isourea **15a** was not very stable since upon storage at room temperature for 2 days it also began to rearrange to produce **18**. While the rearrangement might have proceeded through the interesting acylimine intermediate **16**,[14-16] the imine could not be isolated. Similar results were obtained upon reaction of the N-hydroxy compound **13** with 1,1'-carbonyl dimidazole (CDI).[17] In this case, acrylamide **18b** was obtained as a white solid in almost quantitative yield. Acrylamide **18c** was also obtained quantitatively when **13** was treated with trichloroacetonitrile and triethylamine. Use of weaker bases such as N-methylmorpholine and pyridine also promoted these rearrangements, but the reactions were slower. Separate attempts to trap the potential intermediate acylimine **16** with methanol to form the corresponding 4-methoxy β-lactam failed. Instead, the same acrylamides, **18**, were isolated. In related cases (compounds **13d** and **13e**) in which pivalic acid or benzyl alcohol served as the leaving group during reactions with base in methanol, the methyl enol ethers **18d** and **18e** were obtained as minor products indicating that trapping reactive intermediates with external nucleophiles may be possible. While the conversion of intermediates similar to **17** to acrylamides like **18** has precedent,[18] regardless of which mechanism is operative in these rearrangements, apparently functionalization at the $C_4$ position of the original β-lactam had occurred, as planned, along with opening of the β-lactam ring. Again it should be noted that the acrylamides (**18**) are similar to intermediates postulated to be involved in the inhibition of β-lactamase enzymes,[6] and design of appropriately substituted N-hydroxy β-lactams should be of interest. However, for this initial model study we decided to continue to test the susceptibility of other more simply modified substrates to rearrangements.

**Scheme 3**

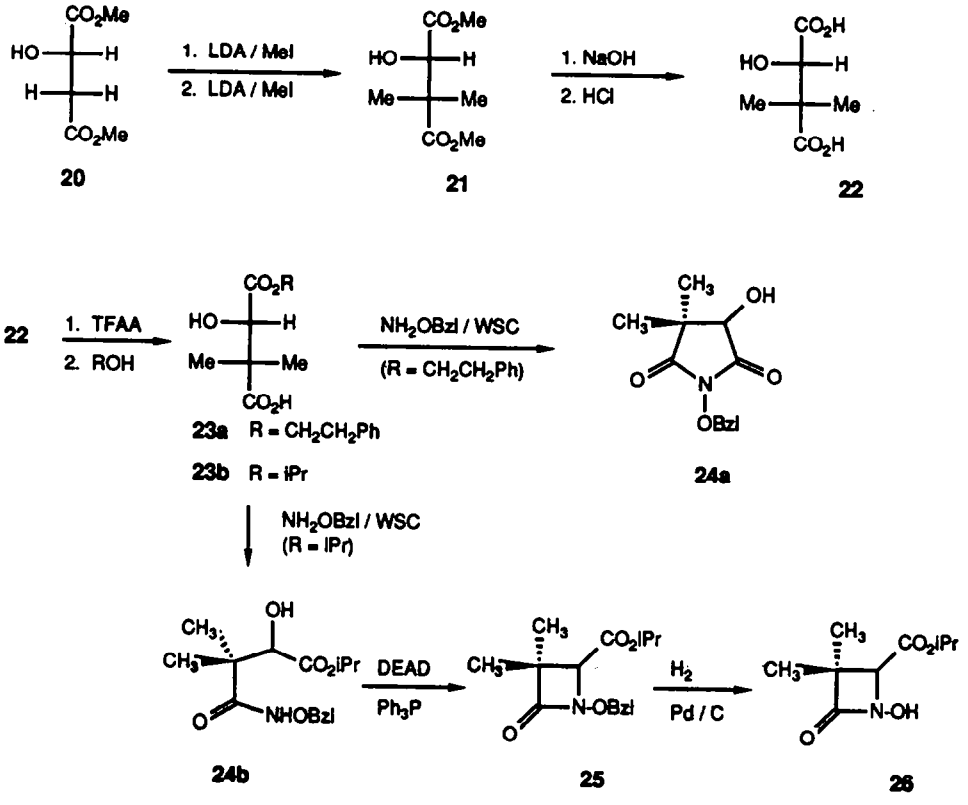



13 → 18

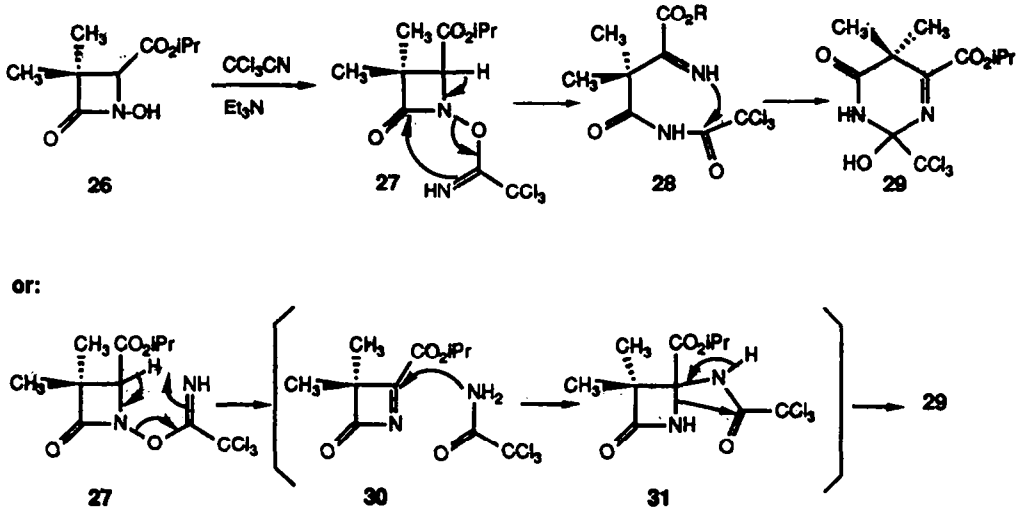
| | R' | R | reagents | products |
|---|---|---|---|---|
| b | $-CH_2CH_2Ph$ | -H | CDI | Nuc = imidazole |
| c | $-CH_2CH_2Ph$ | -H | $Cl_3CN$ / $Et_3N$ | Nuc = $NHCOCl_3$ |
| d | $-CH_2CH_2Ph$ | $-COC(CH_3)_3$ | $Et_3N$ / $CH_3OH$ | Nuc = $OCH_3$ |
| e | $-CH_3$ | $-CH_2Ph$ | KOH / $CH_3OH$ | Nuc = $OCH_3$ (20%) +  |

Formation of the unsaturated products **18** obviously required deprotonation at the $C_3$ position at some point in the reaction. Therefore, we decided to determine whether substrates which lacked a $C_3$ proton would be susceptible to rearrangement under similar sets of conditions. A representative 3,3-dimethyl-N-Hydroxy β-lactam **26** was prepared by the process illustrated in Scheme 4. Dimethyl malate **20** was α-methylated twice[19] and then hydrolyzed to the diacid **22** which was converted to the desired N-hydroxy-3,3-dimethyl-2-azetidinone **26** by the previously described route.[9,10] Interestingly, treatment of **26** with $Cl_3CCN$ / $Et_3N$ resulted in rapid formation of a product isomeric with the initially expected adduct **27**. While the proton NMR spectrum of this product was relatively simple, and consistent with **27** or a rearranged β-lactam such as **31**, the highest carbonyl frequency in the infrared spectrum was at 1750 $cm^{-1}$. Related substituted 4-amino-2-azetidinones[5] have β-lactam carbonyl peaks at 1770 - 1780 $cm^{-1}$. The unusually low IR frequency for the carbonyl group of the observed product suggested that it was either a larger ring or acyclic. Subsequent determination of the structure by X-ray crystallography revealed that the product was the unusual pyrimidine **29** (Fig 1), which may have formed by one of the processes shown in Scheme 5.

**Scheme 4**



**Scheme 5**



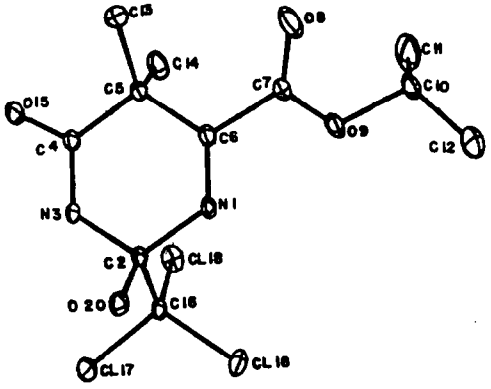




**Figure 1.** X-ray structure of pyrimidine 29

In summary, we have demonstrated that N-hydroxy-2-azetidinones with relatively acidic $C_4$ protons can be induced to undergo novel molecular rearrangements. Further studies related to the peripheral substitutional requirements for these rearrangements and the potential to induce similar rearrangements on substituted N-hydroxy-β-lactam antibiotics under physiological conditions are under consideration.

## Experimental Section

General Comments. Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 727B spectrometer. $^1$H NMR spectra were obtained in chloroform-d with tetramethylsilane as a reference, unless otherwise stated, on a Varian EM 390, XL-100 or Nicolet NB 300 spectrometer. Mass spectra were obtained by Mr. John Occolowitz at Eli Lilly and Co. or on an AEI Scientific Apparatus MS 902. Elemental Analyses were performed by Midwest Micro Labs, Indianapolis, IN or M-H-W Laboratories, Phoenix, AZ. X-ray crystallographic studies were performed by Dr. Charles Eigenbrot at the Molecular Structure Facility, Department of Chemistry, University of Notre Dame. Radial Chromotography was performed on a Chromatotron Model 7924 purchased from Harrison Research Inc., Palo Alto, CA. Optical rotation was obtained using a Rudolf Autopol III polarimeter. TLC was performed using EM, aluminum backed silica gel 60 F-254, 0.2 mm plates. Solvents used were dried and purified by standard methods.

**Preparation of N-hydroxy-4-carbophenethoxy-2-azetidinone (13a).** This compound was prepared from malic acid by the method described earlier.[10a] This particular derivative, **13a** was chosen because the phenethyl group facilitated monitoring by TLC [ethyl acetate - hexanes (3:2), Rf=0.40]; moreover, it was UV active, and was thus readily detected during purification on the chromatotron: oil; $^1$H NMR ($CDCl_3$) δ 8.1 (br s, 1H), 7.3 (m, 5H), 4.4 (m, 3H), 2.9 (m, 4H); IR($CHCl_3$) 3100, 1790, 1740 $cm^{-1}$.

**Preparation of the Isourea 15a from compound 13a.** Compound **13a** (235 mg, 1 mmol) was dissolved at room temperature in 5 mL of acetonitrile. To this solution was added N,N'-diisopropyl carbodiimide (156 µl, 1 mmol, Aldrich). This mixture was stirred under a nitrogen atmosphere and the reaction was followed by TLC. After 1 h, when all of **13a** was consumed, the acetonitrile was evaporated under vacuum and the mixture was chromatographed using ethyl acetate-hexanes (1:3) as the eluent. The isourea **15a** was obtained as a colorless oil (275 mg, 80% yield). Attempts to crystallize it from various solvents were not successful. $^1$H NMR ($CDCl_3$) δ 7.33 (m, 5H), 4.7 (m, 1H), 4.5 (t, 2H) 4.0 (m, 2H), 3.0 (m, 4H), 1.33 (m, 6H), 1.10 (m, 6H); IR($CHCl_3$) 3500, 1800-1600 $cm^{-1}$ (br); mass spectrum (EI), m/e 361 (M+1).

**Formation of acrylamide derivative 18a.** Isourea **15a** (200 mg, 10.58 mmol) was dissolved in 5 mL of dry ether and $Et_3N$ (28 µL, 35 mole %) was added at room temperature. The reaction was followed by TLC. After 15 minutes at room temperature all of compound **15a** was consumed. The ether was evaporated under vacuum and the residue was chromatographed using ethyl acetate - hexanes (1:3) as the eluting solvent to provide **18a** as a colorless oil (192 mg, 96% yield). All attempts to crystallize **18a** were unsuccessful. $^1$H NMR ($CDCl_3$) δ 7.75 (d, 1H), 7.33 (s, 5H), 6.8 (br s, 2H), 5.70 (s, 1H), 4.5 (br t, 3H), 4.0 (m, 4H), 3.0 (t, 2H), 1.4 (d, 6H), 1.16 (d. 6H); IR ($CHCl_3$), 3500, 3350, 1730, 1680, 1630 $cm^{-1}$; mass spectrum (EI), m/e 361 (M+1).

**Reaction of 1,1'carbonyldiimidazole (CDI) with 13a to form 3-carbophenethoxy-3-imidazoyl-acrylamide (18b).** Compound **13a** (235 mg, 1 mmol) was dissolved in 20 mL of freshly distilled THF and the solution was stirred at 0°C under a nitrogen atmosphere for 2 h. $Et_3N$ (140 µl, 1 mmol) was then added. After 15 minutes at 0°C the reaction mixture was poured into 50 mL of ethyl acetate. This mixture was washed with 25 mL of 0.5 M citric acid solution, 5% $NaHCO_3$ solution, brine, dried over $MgSO_4$ and evaporated to yield a white solid residue. Chromatography of this solid using ethyl acetate - hexanes (1:3) as the eluting solvent provided **18b** as a white solid (243 mg, 85% yield), which was crystallized from ethyl acetate - hexanes. Mp 109-111°C; $^1$H NMR (90 MHz, $CDCl_3$) δ 8.6 (br s, 1H), 8.15 (s, 1H), 7.5 (s 1H), 7.3 (s, 5H), 7.1 (s 1H), 6.3 (br s, 1H), 6.0 (s, 1H), 4.5 (t, 2H), 3.0 (t, 2H); IR ($CHCl_3$) 3400, 1740, 1650, 1600 $cm^{-1}$; mass spectrum (EI), m/e 285 ($M^+$). Anal. Calcd. for $C_{15}H_{15}N_3O_3$: C, 63.15; H, 5.29; N, 14.73; Found: C, 62.97; H, 5.44; N, 14.77.

**Reaction of 13a with Trichloroacetonitrile to form 3-carbophenethoxy-3-trichloroacetamido-acrylamide (18c).** Compound **13a** (235 mg, 1 mmol) was dissolved in 20 mL of anhydrous ether at 0°C under a nitrogen atmosphere. $Cl_3CCN$ (100 µL, 1 mmol) was added and the reaction mixture was stirred at 0°C. After 5 minutes the ice bath was removed and, as the reaction temperature approached room temperature, white solid began to precipitate from the solution. After stirring the reaction mixture for 15 more minutes at room temperature, the ether was evaporated and the white residue was subjected to chromatographic separation using ethyl acetate - hexanes (2:3) as the eluting solvent. Compound **18c** was obtained as a white solid (370 mg, quantitative yield). Recrystallization from ethyl acetate - hexanes provided white crystals. Mp 145-147°C. $^1$H NMR($CDCl_3$) δ 8.85 (br s, 2H), 7.33 (s, 5H), 6.7 (s, 1H), 4.5 (t, 3H), 3.00 (br t, 2H); IR ($CH_2Cl_2$) 3450, 1740, (ester), 1650 (amide), 1600 $cm^{-1}$ (double bond). Anal. Calcd. for $C_{14}H_{13}O_4N_2Cl_3$: C, 44.29; H, 3.45; N, 7.38. Found: C, 44.54; H, 3.59; N, 7.50.

**Reaction of 4-carbomethoxy-N-benzyloxy-2-azetidinone (13e) with methanol/KOH to form 3-carbomethoxy-3-methoxy-acrylamide 18e** (same as **18d**). Compound **13e** (221 mg, 1 mmol) was dissolved in 20 mL of methanol at 0°C. Powdered 85% KOH (66 mg, 1 mmol) was added to the solution and the reaction mixture was stirred at 0°C. After 1/2 h when all of compound **13e** was consumed (by TLC analysis) the reaction mixture was poured into 50 mL of ethyl acetate which was then washed with 25 mL of 5% $NaHCO_3$ solution. The bicarbonate extract was saved. The ethyl acetate layer was dried (brine, $MgSO_4$) and evaporated to provide a colorless oil. Further purification by chromatography using ethyl acetate-hexanes (2:3) as the eluting solvent gave compound **18e** (32 mg, 20% yield): $^1$H NMR ($CDCl_3$) δ 6.5 (br s, 2H), 5.5 (s, 1H), 3.85 (s, 3H), 3.7 (s, 3H); IR (neat) 1740, 1680, 1615 $cm^{-1}$; mass spectrum (EI), m/e 159 ($M^+$).

The original aqueous bicarbonate extract was acidified to pH 3.5 with 6 N HCl and extracted with ethyl acetate, dried and evaporated to give **4-carboxy-N-benzyloxy-β-lactam** (103 mg, 5% yield) as a oily solid. $^1$H NMR($CDCl_3$) δ 10.4 (s, 1H), 7.4 (s, 5H), 5.0 (s, 2H), 4.1 (m, 1H), 2.9 (m, 2H); IR ($CHCl_3$) 1800, 1740 $cm^{-1}$.

**Preparation of N-hydroxy-3,3-dimethyl-4-carboisopropoxy-2-azetidinone (26).** As described earlier,[19] the dimethyl ester of malic acid **20** was alkylated twice with LDA/MeI to give compound **21**. Subsequent hydrolysis gave diacid **22**. Dimethyl malic acid **22** was converted to the mono esters **23** (a,b). When phenethyl ester **23a** was coupled with O-Benzyl-hydroxylamine, succinimide derivative **24a** was the major product. To circumvent this problem, the mono isopropyl ester **23b** was coupled to give **24b** as the major product, which was eventually converted to compound **25** as described.[10a] Compound **25** on hydrogenation gave N-hydroxy-β-lactam **26**. Mp 87-89°C; $[\alpha]_D$ = +

46.2 (c=0.45, $CHCl_3$); $^1H$ NMR ($CDCl_3$) δ 5.2 (m, 1H), 4.55 (s, 1H), 1.3-1.2 (m, 12H); IR ($CHCl_3$) 3500, 1760, 1740 $cm^{-1}$; mass spectrum (FD), m/e 201 ($M^+$).

**Reaction of 26 with trichloroacetonitrile to form pyrimidine derivative 29.** Compound 26 (100 mg, 0.5 mmol) was dissolved in 15 mL of freshly distilled ether and $Et_3N$ (70 μL, 0.25 mmol) was added to the solution followed by the addition of $Cl_3CCN$ (100 μL, 1 mmol). The reaction mixture was allowed to stir at room temperature under a nitrogen atmosphere. After 1 h the reaction mixture was poured into 30 mL of ether, washed with water and brine, dried over $MgSO_4$ and evaporated to yield a colorless oil. After overnight dessication under vacuum, the oil turned into white solid, which was crystallized from chloroform-hexane to provide compound 29 as a white solid (120 mg, 70% yield). Mp 140-142°C; $^1H$ NMR ($CDCl_3$) δ 8.18 (br s, 1H), 7.52 (s, 1H), 5.25-5.10 (m, 1H), 1.49-1.47, 1.36-1.33 (dd, 12H); IR (KBr) 1750, 1640 $cm^{-1}$; mass spectrum (FD), m/e 345, 347, 349 ($M^+$). Anal. Calcd. for $C_{11}Cl_3H_{15}N_2O_4$: C 38.23, H 4.37, N 8.10. Found: C 37.96, H 4.53, N 7.91.

The crystal structure of 29 was determined by x-ray diffraction. It has the molecular formula = $C_{11}H_{15}N_2Cl_3O_4$, molecular weight = 345.61 amu. It crystallized in space group $P\bar{1}$ (no. 2) with a = 6.6703 (33)Å, b = 10.5444 (43)Å, c = 12.1108 (69)Å, α = 68.8107 (401), β = 83.3578 (441), γ = 72.898 (373) and λ = 0.71073Å. Calculated density was 1.512 g/cc (Z = 2). A total of 3000 data were collected. The structure was solved by direct methods. Least-squares refinement of 2173 data [$I > 3\sigma(I)$] and 181 parameters led to final agreement factors of R = 4.5% and $R_w$ = 4.9%. In the final difference Fourier map, the largest residual peak was 0.4 electron/cubic Angstrom, less than one Angstrom from $O_8$, which exhibited particularly high thermal motion. A localized double bond between $N_1$ and $C_6$ is indicated by the bond distance of 1.260 (5)Å (Figure 1). The 6-membered ring is planer. The $C_4$-bound carbonyl oxygen atom as well as the atoms of the isopropyl ester group, except for $C_{11}$ are within an Angstrom of this plane. The remaining atoms bound to tetrahedral carbon atom are appropriate distances above or below this plane. The atomic co-ordinates for this work are available on request from the director of the Cambridge Crystallographic Data Center, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this paper.

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§Molecular Structure Facility, University of Notre Dame.

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