SYNTHESES AND FLASH VACUUM PYROLYSES OF HIGHLY FUNCTIONALIZED α-N-HYDROXY AMINO ACIDS

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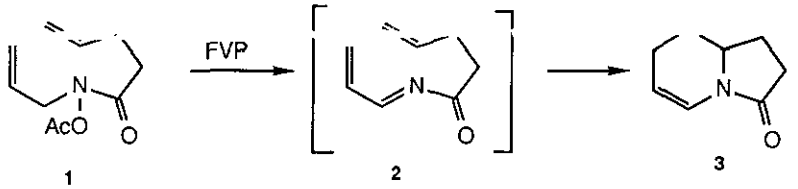
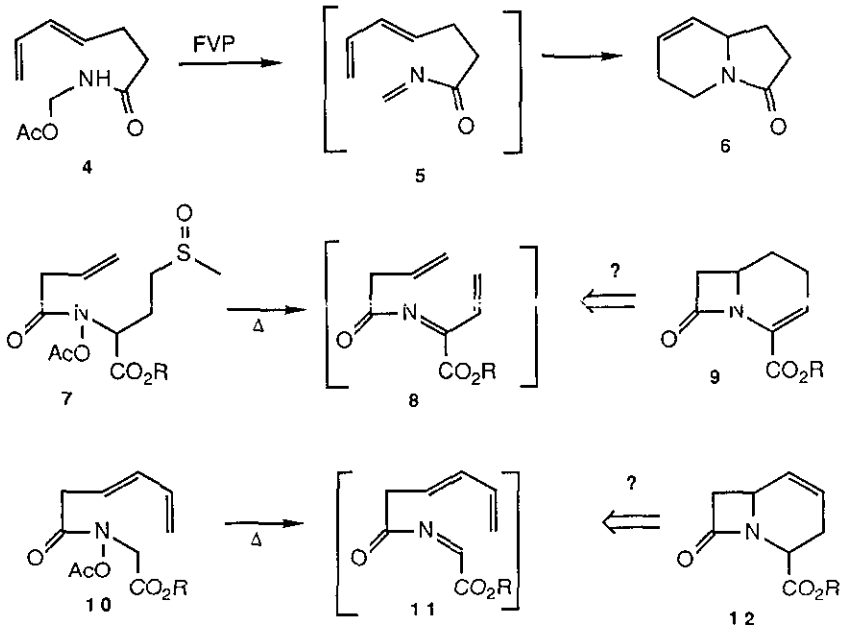
Abstract-Flash vacuum pyrolysis (FVP) of N-acetoxy-N-vinyacetylmethionine sulfoxide and N-acetyl-N-hexadienoylglycine produced dihydropyridones, presumably by cycloaddition reactions of intermediate imines.

Pyrolysis of O-acylhydroxylamine and hydroxamic acid derivatives provides direct access to a number of imines and azadienes which may be used in heterocycloaddition reactions. Fowler and coworkers reported the generation of N-acyl-1-azadienes by the thermal elimination of acetic acid from O-acetylhydroxamic acids.[1] When appropriately substituted, these reactive intermediates underwent intramolecular Diels-Alder reactions to produce bicyclic γ-lactams (**1**→**3**). Weinreb and coworkers have used similar strategy in their development and use of imino Diels-Alder routes for alkaloid syntheses (**4**→**6**).[2] The facile generation of γ-lactams **3** and **6** prompted us to consider the use of related chemistry for the preparation of structurally similar carbacephalosporin nuclei **9** and **12**[3] despite their enhanced reactivity and anticipated strained transition states **8** and **11**. Herein we describe the syntheses two highly functionalized N-hydroxy amino acid derivatives **7** (R=tBu) and **10** (R=Me), which upon pyrolyses were anticipated to form intermediates **8** and **11**. The ultimate isolable products were 2-pyridone derivatives



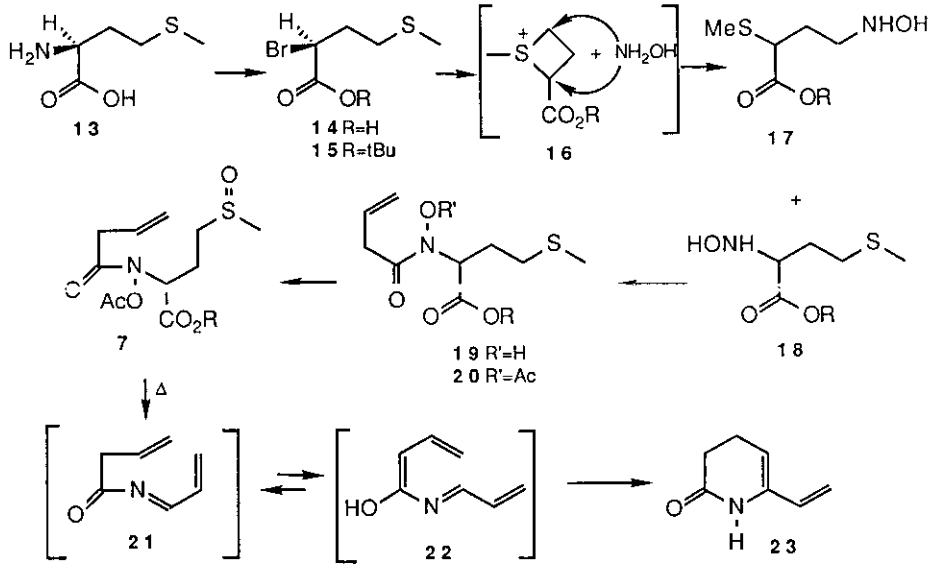
1 **2** **3**



The choice of **7** *as a precursor of* **8** *was based on* Fowler's precedent for pyrolytic generation of imines from O-acylhydroxamates,[1] and Rapoport's thermal conversion of methionine sulfoxides to vinylglycine derivatives.[4] Thus, the first requirement was the conversion of L-methionine to N-hydroxy-L-methionine. Towards this end, L-methionine was treated with sodium nitrate and 3N H_2SO_4, the usual amino acid diazotization conditions,[5] in the presence of excess KBr to afford the α-bromo carboxylic acid **14** in 62% yield. Conversion of **14** to the t-butyl ester **15** was accomplished in 63% yield by treatment with t-butyl acetate (solvent) and catalytic perchloric acid in a sealed flask at room temperature for 60h.[6] The reaction of hydroxylamine with bromide **15**[7] required the use of a large excess of hydroxylamine (800 mole %) in refluxing methanol.

The desired N-hydroxy amino acid **18** was then isolated in 50% yield along with 11% of its isomer **17**. While the details related to the formation of isomer **17** have yet to be elucidated, formation of an intermediate sulfonium ion (**16**) would be consistent. In fact, both of the isomers could be obtained from the same intermediate. If so, the desired product may have been formed with net retention of configuration. These and other details of this interesting reaction are being considered. Careful reaction of hydroxylamine **18** with vinyl acetyl chloride in pyridine gave the hydroxamate **19** in 84% yield without conjugation of the double bond.[8] Subsequent acylation with acetyl chloride in pyridine gave the O-acetyl hydroxamate **20** in 82% yield. Oxidation of **20** with $NaIO_4$[4] gave the desired substrate, sulfoxide **7**, in quantitative yield.

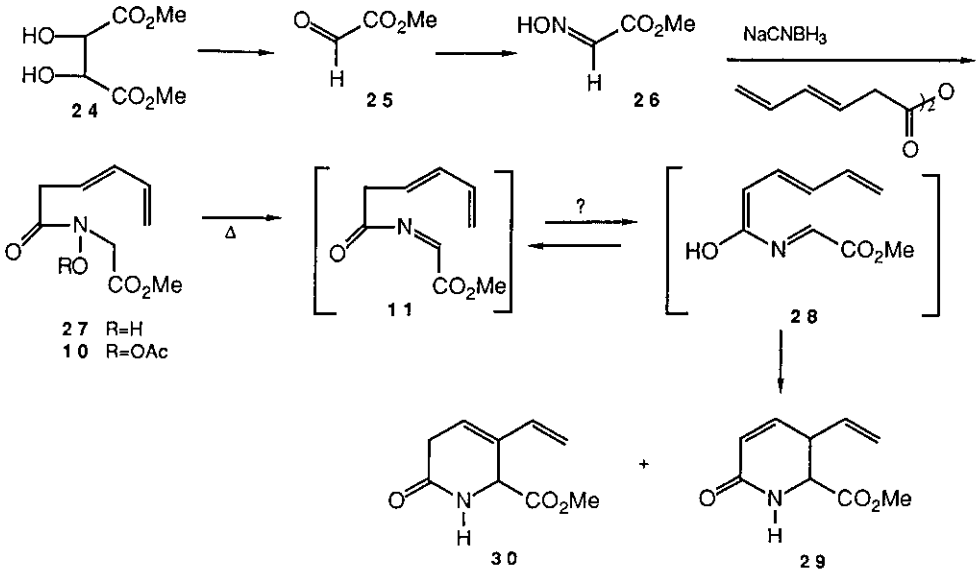
Scheme 1



Flash vacuum pyrolysis of **7** was performed in Professor Fowler's laboratory at Stony Brook Below 300°C no reaction occurred. Nmr, ir and chromatographic analysis of crude pyrolysis products during a progression from 300°C to 450°C indicated that elimination of sulfenic acid and acetic acid proceeded as desired, but an additional loss of the t-butyl ester was competitive [9]. Of the several products formed, no carbacephalosporin was detected. Only a low yield (11%) of the dihydropyridone **23** was obtained. Formation of **23** may proceed through diene **21** produced from the desired eliminations and concommitant decarboalkoxylation. Thermal cyclization of the enol form **22** would produce the observed product **23**. These results prompted the study of a less highly functionalized substrate.

Preparation of the alternate substrate **10** was accomplished as shown in Scheme 2. Dimethyl tartarate was oxidatively cleaved with periodic acid[10] to give methyl glyoxylate (**25**) in 80% yield. Oxime **26** was obtained in 83% yield by reaction of **25** with 100 mole% each of $NH_2OH{\cdot}HCl$ and $NaHCO_3$ in water, followed by extraction. The reduction of **26** with sodium cyanoborohydride in the presence of 3,5-hexadienoic anhydride[11] gave the N-acylated N-hydroxyglycine methyl ester (**27**) in low (16%) yield because of apparent competitive polymerization of the hexadienoic anhydride. O-Acetylation with acetyl chloride in pyridine produced the desired substrate **10** in 86% yield. Submission of **10** to flash vacuum pyrolysis also did not produce **12**, but a mixture of two dihydropyridones **29** and **30** in 10% yield as the only isolable products. Presumably **29** and **30** formed from alternate reactions of the desired intermediate **11** (Scheme 2).

Scheme 2



Although the intramolecular aza Diels-Alder cyclization provides an efficient strategy for the preparation of the carbacephalosporin nucleus, the reduction of this strategy to practice will have to solve the problems encountered in this communication. However, further optimization may result in useful methodology for the preparation of substituted dihydropyridones and other heterocycles.[12]

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REFERENCES AND NOTES

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12. Selected characterization data includes: **14**, nmr ($CDCl_3$) δ 2.1 (s, 3H), 2.3 (m, 2H), 2.6 (t, J = 6 2 Hz, 2H), and 4.5 (t, J = 6.5 Hz, 1H) ; ir (neat) 1700 cm^{-1}; ms, m/z 215 (M^+ + 2), 213 (M^+). **15**, nmr ($CDCl_3$) δ 1.5 (s, 9H), 2.2 (s, 3H), 2.2 - 2.4 (m, 2H), 2.7 (m, 2H), 4.5 (t, J = 6.1 Hz, 1H); ir (neat) 1720 cm^{-1}. **18**, nmr ($CDCl_3$) δ 1 44 (s, 9H), 1.84 (m, 2H), 2.04 (s, 3H), 2.52 (t, J=7.5 Hz, 2H) and 3.60 (dd, J=7.4 and 7.4 Hz, 1H); ir ($CDCl_3$) 1725 cm^{-1} (C=O); ms, exact mass calcd for $C_9H_{19}NO_3$, 221.108, found 221.108 **19**, nmr ($CDCl_3$) δ 1.50 (s, 9H), 2.11 (s, 3H), 2.14 (m, 2H), 2.52 (t, J=7.1 Hz, 2H), 3.34 (d, J=6.4 Hz, 2H), 5.20 (m, 3H) and 5.98 (m, 1H); ir 1730, 1640 cm^{-1} (C=O); ms, exact mass calcd for $C_{13}H_{23}NO_4S$, 289.134, found 289.135. **20**, nmr ($CDCl_3$) δ 1.5 (s, 9H), 2.0 (s, 3H), 2.1 (m, 2H), 2.2 (s, 3H), 2.6 (t, J=6.2 Hz, 2H), 3.2 (d, J=6.4 Hz, 2H), 5.2 (m, 3H) and 6.0 (m, 1H); ir ($CDCl_3$) 1790, 1730 cm^{-1} (C=O); ms, exact mass calcd for $C_{15}H_{25}NO_5S$, 331.145, found 331.145. **7**, nmr ($CDCl_3$) δ 1.41 (s, 9H), 2.18 (s, 3H), 2.45 (m, 2H), 2.55 (double singlets, 3H), 2.85 (m, 2H), 3.10 (m, 2H), 4.96 (dd, J=11.2 and 4.2 Hz, 1H), 5.12 (d, J=17.5 Hz, 1H), 5.17 (d, J=11.2 Hz, 1H) and 5.88 (m, 1H); ir ($CDCl_3$) 1790, 1730 cm^{-1} (C=O); ms, exact mass calcd for $C_{15}H_{25}NO_6S$, 347.140 found 347.140. **27**, nmr ($CDCl_3$) δ 3.4 (d, J=6.5 Hz, 2H), 3.8 (s, 3H), 4.4 (s, 2H), 5.1 (dd, J=16.4 and 9.5 Hz, 2H), 5.8 (m, 1H) and 6.2-6.4 (m, 2H); ir ($CDCl_3$) 1745, 1640 cm-1 (C=O); ms, exact mass calcd for $C_9H_{13}NO_4$ 199.084 found 199.085. **10**, nmr ($CDCl_3$) δ 2.20 (s, 3H), 3.20 (d, J=6.5 Hz, 2H), 3.72 (s, 3H), 4.42 (s, 2H), 5.12 (dd, J=17.2 and 10.3 Hz, 2H) 5.97 (m, 1H) and 6.1-6.5 (m, 2 H); ir ($CDCl_3$) 1795, 1750, 1683 cm^{-1} (C=O); ms, exact mass calcd for $C_{11}H_{15}NO_5$ 241.095 found 241.096. **23**, nmr ($CDCl_3$) δ 2.26 (m, 4H), 5.06 (m, 2H), 5.70 (dd, J=17.6 and 10.6 Hz, 1H) and 6.00 (t, J=7.7 Hz, 1H). Irradiation at δ 2.26 resulted in the collapse of δ 6.0 from triplet to singlet; ir ($CDCl_3$) 3520, 3400 cm^{-1} (NH), 1700 cm^{-1} (C=O); ms, m/z 123 (M^+); mixture of **29** and **30**, ir ($CDCl_3$) 3425 cm^{-1} (NH) 1740, 1670 cm^{-1} (C=O); ms, m/z 181 (M^+). **29**, nmr ($CDCl_3$) δ 3.15 (ddd, J=7.3 Hz, 1H), 3.67 (s, 3H), 4 63 (dd, J=7.6 and 5.8 Hz, 1H), 5.10 (dd, J=16 0 and 9.3 Hz, 2H), 5.7 (m, 2H) and 6.3 (ddd, J=16.0, 9.7 and 7.3 Hz, 1H) Irradiation at δ 4.7 region resulted in the collapse of δ 3.15 from double double doublet to double doublet. Irradiation at δ 3.2 resulted in the collapse of δ 4.7 from double doublet to doublet. **30**, nmr ($CDCl_3$) δ 3.0 (d, J=7.2 Hz, 2H), 3.7 (s, 3H), 5.1 (m, 2H), 5.7 (m, 1H), 6.0 (d, J=7.0 Hz, 1H) and 6.1 (dd, J=15 and 10.9 Hz, 1H) Irradiation at δ 5 7 resulted in the collapse of δ 3 0 from a doublet to a singlet.

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