Synthesis of Optically Pure 2-Azetidinones Having *N*-Dehydroamino Acid Side-Chains

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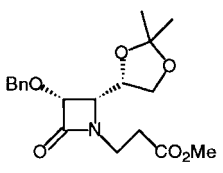
Abstract. An efficient, three step synthesis of optically pure *N*-vinyl-2-azetidinones **1** starting from α- or β-amino ester imines has been developed. Staüdinger reaction between amino ester derived imines and ketene precursors gave 2-azetidinones **2**. Enolate formation on the amino ester moiety of the optically pure 2-azetidinones **2**, selenylation and, finally, MCPBA treatment afforded *N*-vinyl-2-azetidinones **1** in good to excellent yields, with total retention of the stereochemistry of the starting material. Compounds **2** bear the functionality needed to place a carboxy group contiguous to the lactam nitrogen, a structural feature common to all the active β-lactam antibiotics.

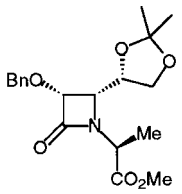
2-Azetidinones having a vinyl moiety attached to the lactam nitrogen have been used several times as intermediates in the preparation of different types of β-lactam antibiotics.[1] The main approach to these compounds rests mainly in penicillin derivatives to produce, by ring fission and basic isomerization of the double bond, the *N*-vinyl moiety.[2,3] Alternatively, this structural feature can be incorporated by the Staüdinger reaction of 2-aza-1,3-diene derivatives and a ketene precursor.[4] The reported routes to prepare *N*-vinyl-2-azetidinone derivatives are, either, designed to accomplish the synthesis of a particular product, or lack the necessary versatility, specially in the introduction of the carboxy group contiguous to the lactam nitrogen, which is always present on active β-lactam antibiotics.[5] We report herein a three step synthesis of *N*-vinyl-2-azetidinones **1** in optically pure form, starting from α- or β-amino ester-derived imines. Our approach is based on the sequential Staüdinger reaction between a ketene and a β-amino ester derived imine to yield 2-azetidinones **2**, followed by α-selenylation of the amino ester moiety, and, finally, oxidative selenoxide elimination to produce the desired compounds **1**.[6] It should be noted that compounds **2** bear the functionality needed to place a carboxy group contiguous to the lactam nitrogen, a structural feature common to all the active β-lactam antibiotics. Compounds **2** are, in turn, α,β-dehydroaminoacids having a 2-azetidinone-1-yl substituent. The role of α,β-dehydroaminoacids as key intermediates in amino acid and peptide synthesis, and as constituents of naturally occurring antibiotics and phytotoxic peptide is well documented.[7]

A series of imines derived from β-alanine, *L*-alanine, and *L*-aspartic acid methyl esters, prepared in quantitative yield by condensation of different aldehydes and the corresponding amino ester in CH_2Cl_2 / $MgSO_4$,[8] were reacted, without further purification, with the corresponding acid chloride in the presence of Et_3N,[9] except for compound **2d** where the acid/ $Cl_2P(O)OPh/Et_3N$ modification[10] of the Staüdinger reaction was used (Figure 1). 2-Azetidinones **2** were always obtained as *cis*-diastereomers. A single *cis*-diastereomer was obtained, except for compound **2b**, when either a chiral ketene precursor or an imine derived from D-glyceraldehyde acetonide, were used. The assignment of a 3*S*,4*R* stereochemistry for 2-azetidinones derived from Evans' ketene (**2c** and **2d**), and 3*R*,4*S* to those derived from D-glyceraldehyde acetonide (**2a**, and **2b** major isomer) is based on the current model for the asymmetric induction in the Staüdinger reaction.[11] When diastereomeric mixtures were obtained, both diastereoisomers were easily obtained, as optically pure compounds, by flash chromatography.

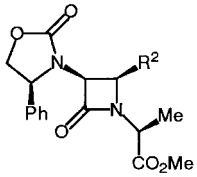
With a variety of compounds **2** in hand, their transformation to the desired *N*-vinyl-2-azetidinones was studied. Treatment of diastereomerically pure β-lactams **2** with LHMDS at -78 °C, generated the corresponding ester enolates, which were quenched with BrSePh to produce the α-seleno derivatives **3**, as diastereomeric mixtures. Although compounds **3** can be isolated, purified, and characterized, they were submitted to oxidation as obtained. Thus, reaction of compounds **3** with MCPBA at -78 °C gave *N*-vinyl-2-azetidinones **1** in nearly quantitative yields. The overall yields for the synthesis of compounds **1**, range from good to excellent (Table 1). 2-Azetidinone **1a** derived from β-alanine was obtained as a single *E*-isomer at the newly formed double bond, while L-aspartic acid derivative **1e** was obtained as an *E/Z* mixture without selectivity. In this case, the stereochemistry of the double bond was determined by n.O.e. experiments, and by comparison with related compounds.[12] The stereochemical integrity of the stereogenic centers at the four membered ring remains unaltered during the transformation of compounds **2** to products **1**.[13]



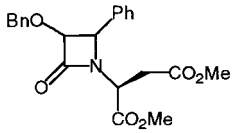
2a 88%, dr 100:0



2b 72 %, dr 84:16



2c R^2 = Ph, 91 %, dr 100:0
2d R^2 = *o*-BrC_6H_4, 70 %, dr 100:0

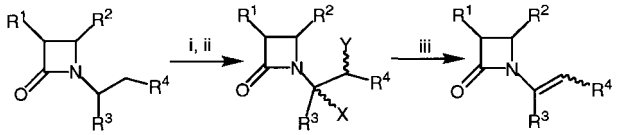


2e 87 %, dr 57:43

In conclusion, a three step synthesis of optically pure α,β-dehydroaminoacid esters having an *N*-2-azetidinone-1-yl substituent has been developed. Efforts to develop efficient synthesis of diverse polycyclic β-lactam systems, using the methodology reported here, are now in progress.

Experimental Procedures.[14] *General Method for the Synthesis of 2-Azetidinones, **2a-e**. Method A* (Compounds **2a-b,2e**): The acid chloride (7.5 mmol) in anhydrous benzene (25 mL) was added dropwise *via* syringe to a solution of the imine (5 mmol) and Et_3N (10 mmol) in benzene (25 mL). The resulting mixture was stirred until complete disappearance of the imine (TLC). The crude mixture was diluted with CH_2Cl_2 (25 mL) and successively washed with aqueous $NaHCO_3$ (2 x 40 mL, saturated solution) and brine (20 mL). The organic layer was dried ($MgSO_4$) and the solvent removed under vacuum. Residues were purified by crystallization from the indicated solvent, or by flash chromatography (EtOAc/hexanes mixtures). *Method B* (Compound **2c**): A solution of Et_3N (6 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a solution of (*S*)-(4-phenyl-2-oxooxazolidinyl)acetyl chloride (0.71 g, 3 mmol) in CH_2Cl_2 (10 mL) at -78 °C under argon. The mixture was stirred for 30 min, and a solution of the imine (2 mmol) in CH_2Cl_2 (5 mL) was added. The reaction was allowed to reach room temperature and stirred for 12 h. Then, MeOH (2 mL) and CH_2Cl_2 (20 mL) were

Table 1. Synthesis of *N*-Vinyl-2-azetidinones, 1



2 **3** X = SePh; Y = H
X = H, Y = SePh **1**

i. LHMDS, THF/- 78°C. ii. PhSeBr. iii. MCPBA, CH_2Cl_2, - 78°C

	R^1	R^2	R^3	R^4	Yield[a]
1a	BnO	Diox[b]	H	CO_2Me	91
1b	BnO	Diox[b]	CO_2Me	H	—[d]
1c	Ox[c]	Ph	CO_2Me	H	55
1d	Ox[c]	*o*-BrC_6H_4	CO_2Me	H	85
1e	BnO	Ph	CO_2Me	CO_2Me	83[e]

[a] Yields are for pure, isolated, material. [b] Diox = (*S*)-2,2-dimethyl-1,3-dioxolan-4-yl. [c] Ox = (*S*)-4-phenyl-2-oxooxazolidin-3-yl. [d] Compound **1b** was obtained in quantitative yield. However, extensive decomposition was observed during purification, [e] Obtained as an *E*/*Z* (50:50) mixture

successively added. The mixture was washed with water and brine. The organic layer was dried ($MgSO_4$) and the solvent eliminated under reduced pressure. The crude product was purified by column chromatography (EtOAc/hexane 1/2)

General Method for the Synthesis of Compounds, **1a-e**. *Method A* (Compounds **1a** and **1e**). BuLi (1.3 mmol, 1.6 M in hexanes) was added dropwise *via* syringe to a cooled (-78°C) solution of hexamethyldisilazane (1.35 mmol) in anhydrous THF (5 mL) under argon. After 30 minutes, the resulting solution was transferred *via* cannula to a cooled solution (-78°C) of the corresponding β-lactam (1 mmol) in anhydrous THF (5 mL) by using argon pressure. After stirring 1 h from -78°C to -60 °C, PhSeBr (1.3 mmol) in THF (5 mL) was added rapidly to the enolate solution, which causes an instantaneous decolourization of the solution. After stirring for 1 h, the reaction mixture was quenched with saturated aqueous NH_4Cl solution (7 mL) and extracted with ethyl acetate (10 x 3 mL). The organic layer was washed with saturated $NaHCO_3$ solution (15 mL), brine (15 mL), and dried ($MgSO_4$). The solvent was removed under reduced pressure and the obtained compound **3** was used in the next step without further purification. *Method B* (Compounds **1b-d**). This method was identical to method A except for that the corresponding β-lactam was added dropwise over the solution of LHMDS .

To a solution of the corresponding seleno-β-lactam **3** (1 mmol) in CH_2Cl_2 (5 mL), cooled to -78 °C, was added dropwise a solution of *m*-chloroperbenzoic acid (1.1 mmol, 55%) in 5 mL of CH_2Cl_2. Immediately after the end of the addition, TLC analysis showed the complete transformation of the starting material. The cold reaction mixture was poured into a separatory funnel containing 30 mL of Et_2O and 30 mL of 10% aqueous Na_2SO_3. The organic layer was separated, washed twice with saturated aqueous $NaHCO_3$ solution, dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by crystallization or flash chromatography.

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13. ^1H NMR analysis of the reaction mixtures showed a single diastereoisomer in all cases.

14. All new compounds were fully characterized by ^{1}H NMR, ^{13}C NMR, and IR and gave correct elemental analyses. Representative data are given for compound **1a**.
(+)-(3R,4S)-cis-3-Benzyloxy-4-[(S)-2,2-dimethyl-1,3-dioxolan-4-yl]-1-[E-(2-methoxycarbonylethenyl)]-2-azetidinone, **1a.** Method A. From 0.18 (0.5 mmol) of β-lactam **2a**, was obtained 0.17 g (91%) of compound **1a** as a pale green oil, after purification by flash chromatography (EtOAc/hexane 1/6). $[\alpha]_D$ = +116.3 (c = 1.16, $CHCl_3$). ^{1}H NMR: δ 1.35 (s, 3 H), 1.50 (s, 3 H), 3.62-3.73 (m, 1 H), 3.73 (s, 3 H), 3.97 (dd, J_1 = 9.0 Hz, J_2 = 5.7 Hz, 1 H), 4.21 (dd, J_1 = 9.0 Hz, J_2 = 6.9 Hz, 1 H), 4.31-4.42 (m, 1 H), 4.66 (d, J = 11.5 Hz, 1 H), 4.75 (d, J = 5.7 Hz, 1 H), 4.90 (d, J = 11.5 Hz, 1 H), 6.05 (d, J = 14.1 Hz, 1 H), 7.22-7.40 (m, 5 H), 7.48 (d, J = 14.1 Hz, 1 H). ^{13}C NMR: δ 167.6, 165.7, 136.8, 134.4, 128.7, 128.3, 128.4, 128.0, 110.1, 104.3, 80.5, 73.3, 66.7, 62.3, 51.5, 26.7, 25.0. IR ($CHCl_3$): ν 1780, 1710, 1640. Anal. Calcd for $C_{19}H_{23}NO_6$: C, 63.15; H, 6.41; N, 3.88. Found: C, 63.36; H, 6.67; N, 4.04.