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Facile Syntheses and Rearrangements of Peptide Derived β-Lactams

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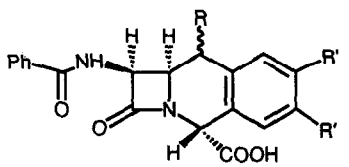
Summary: Stereoselective aldol condensation of a 4, 5-diphenyl-oxazolin-2-one (Ox) glycine provided α-amino-β-hydroxy acid **4**, which, after coupling with phenylglycine derivatives, was directly cyclized to β-lactams. Ozonolysis cleaved both the Ox and isopropylidene groups and initiated a Chapman rearrangement to the corresponding α-benzamido-β-acyl-2-azetidinone **8**. Subsequent reduction induced a diastereoselective rearrangement to the corresponding γ-lactone **13**.

Considerable interest has been generated in the synthesis of phenol- and catechol-containing carbacephalosporin and cephalosporin derivatives.[1] Reportedly, the catechol constituents chelate physiologically available ferric ion and facilitate active transport of the antibiotics into cells of pathogenic organisms by microbial iron assimilation processes. In this Letter, we report a series of model reactions related to planned syntheses of catechol-containing β-lactams **1**, tricyclic analogs of 3-aminonocardicinic acid[2] and carbacephalosporins.[3] Noteworthy features include an *erythro* (anti) selective aldol condensation of a 4,5-diphenyl-oxazolidin-2-one (Ox) protected glycine derivative, conversion of the useful Ox protecting group to a benzoyl group by ozonolysis followed by an apparent Chapman rearrangement (**10** → **11**), and the diastereoselective rearrangement of 4-α-hydroxyethyl-2-azetidinone derivative **12** to the corresponding γ-lactone **13**.

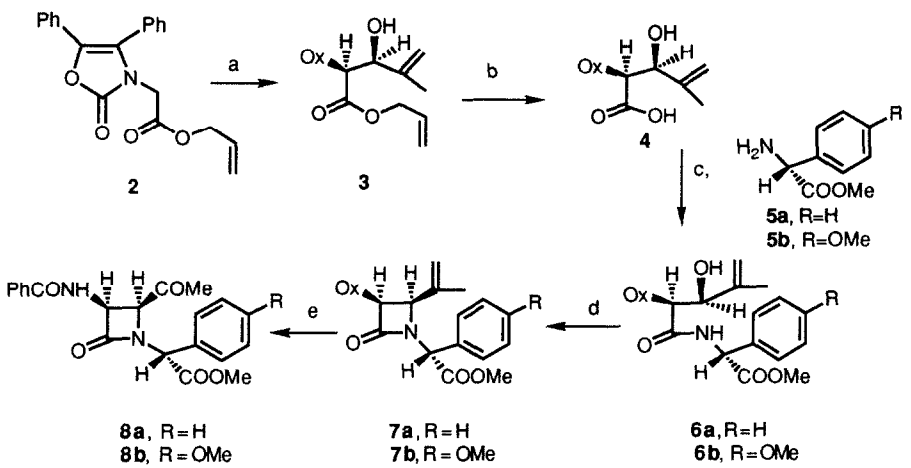


R = Me, CH_2OH
R' = H, OH

1

Initiation of the planned synthesis (Scheme 1) relied on the preparation of appropriate β-hydroxy amino acids and the subsequent precedented direct cyclization of β-hydroxy amino acid derived peptides to monocyclic β-lactams[4] and elaboration. Syntheses of β-lactams similar to **1** (R=H) have been reported by Just,[5] however, construction of the β-lactam ring was accomplished by a [2+2] annelation ring closure.

Scheme 1



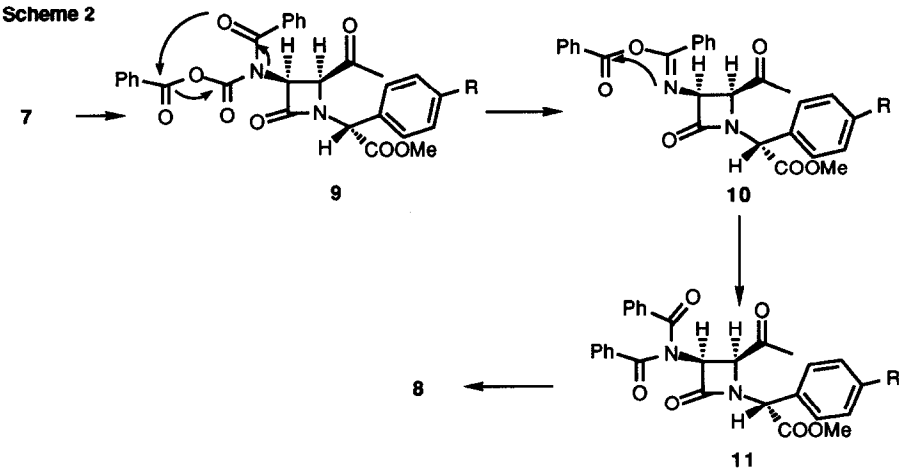
Reagents and Conditions: a) LDA, methacrolein, THF, b) $Pd(P(Ph)_3)_4$, H_2NOBn, CH_2Cl_2 , c) DCC/ HOBT CH_2Cl_2 , d) PPh_3, DBAD, THF, e) O_3, Me_2S, CH_2Cl_2

Ox glycine allyl ester **2**[6] was condensed with methacrolein (2.0 eq) to afford the desired aldol product **3** in 75% yield [LDA (1.1 eq), THF, 2 hours, -78°C, followed by a quench at this temperature with a phosphate buffer solution (pH 7.2), aqueous work-up and column chromatography on silica with ethyl acetate-hexanes 1 : 7].[7] As expected with use of an Ox protected glycine enolate,[8] the *anti* (S*, S*) aldol product was obtained. In fact, no trace of the *syn* aldol could be detected by 300 MHz proton and 75 MHz carbon NMR. Removal of the allyl moiety was accomplished with a catalytic amount of $Pd(PPh_3)_4$ and O-benzylhydroxylamine (1.0 eq) as the allyl cation scavenger,[9] to provide the desired carboxylic acid **4** as a fluffy solid in 65% yield. Separate coupling of **4** with D-phenylglycine methyl ester **5a** and D-(*p*-methoxyphenyl)glycine methyl ester **5b** under standard procedures (dicyclohexylcarbodiimide, N-hydroxybenzotriazole) in dichloromethane provided the corresponding peptides **6a** and **6b**, respectively, in 60-70% yield. Ring closure was achieved under Mitsunobu conditions,[10] (2.5 eq $P(Ph)_3$/ di-*tert*-butylazodicarboxylate[11]) as applied for β-lactam syntheses in this laboratory and others.[12] The *cis* β-lactams **7a**, **7b** were isolated in 50% yield as 1 : 1 mixtures of diastereomers from epimerization at the phenylgycine methine position. Exclusive production of the *cis* β-lactam was consistent with initial formation of the *anti* aldol **3**. Also noteworthy was the obtention of only the β-lactam by a direct S_N2 Mitsunobu-mediated reaction rather than the corresponding δ-lactam from a potentially competitive S_N2' process.

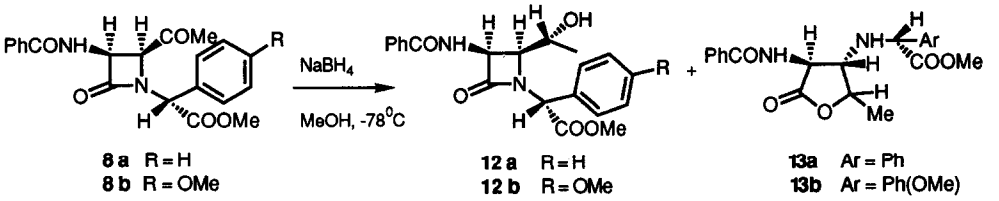
Interestingly, ozonolysis of **7a** and **7b** in dichloromethane at -78°C, followed by reductive work-up in the presence of dimethylsulfide (5.0 eq) gave **8a** and **8b**, directly. Thus, not only was the methylene group oxidized, as expected, but the Ox group also was oxidatively modified by a procedure which eventually produced the monobenzoyl derivative. A sequence of reactions consistent with this result is shown in Scheme 2. Initial ozonolysis would be expected to produce mixed anhydride / imide **9**. Intramolecular transacylation with loss of carbon dioxide may give imidate **10**. Chapman rearrangement of **10** would provide imide **11**.[13] We have found in related systems[14] that the same ozonolytic degradation stops at the imide stage if the β-lactam contains no

functional substituents at the β-carbon. In the case described here, the imide is very labile, presumably because of anchimeric assistance of the methyl ketone at C_4, and readily hydrolysed to the observed monobenzylated product **8**.

Scheme 2



Finally, treatment of ketone **8** with 100 mole % of $NaBH_4$ in methanol at -78°C for 5-10 minutes followed by quenching with two drops of a 5% citric acid solution in water provided **12**[15] and **13**[16] in a 1 : 1 ratio (equation below).



8a R = H
8b R = OMe

12a R = H
12b R = OMe

13a Ar = Ph
13b Ar = Ph(OMe)

Thus, while the reduction step did not proceed stereoselectively, and an epimeric mixture of alcohols was formed, the S alcohol apparently rearranged spontaneously to *trans* γ-lactone **13**. Construction of a model of the intermediate S alcohol revealed that the alkoxide generated was perfectly oriented to attack the carbonyl bond of the β-lactam. All attempts to trap the intermediate alcohol or attempted modifications of the experimental conditions ($NaCNBH_3$ in 10% glacial acetic acid / methanol at 0°C) to facilitate isolation of the S alcohol rather than γ-lactone **10** were ineffective.[17,18] Separate hydrolyses of **12** and **13** are expected to provide diastereoselective approaches to novel diamino acid derivatives. Further studies related to the conversion of **12** to derivatives of **1** are in progress.

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15 Selected characterization data for **12b** isolated as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.8- 6.9 (9H, m, aromatic), 7.62 (1H, d, CONH, J = 10.50 Hz), 5.84 (1H, dd, CONHCH, J = 5.50, 10.50 Hz), 5.42 (1H, s, CHCOOMe), 4.10 (1H, dd, CHN, J = 1.50, 5.50 Hz), 3.787 (3H, s, PhOMe), 3.783 (3H, s, COOMe), 1.10 (3H, d, CHMe, J = 6.60 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.95, 167.93, 167.15, 160.12, 133.49, 131.92, 130.18, 128.58, 127.19, 126.29, 114.67, 65.82, 63.63, 60.7, 57.86, 55.32, 53.22, 21.31; MS (EI) 412 (M^+) exact mass calcd 412.1634, found 412.1624.

16 Selected data for **13b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.8-7.4 (5H, m, aromatic), 7.15 (2H, d, aromatic, J = 7.50 Hz), 6.8 (2H, d, aromatic, J = 7.50 Hz), 5.76 (1H, s, CHCOOMe), 5.71 (1H, dd, CHNHCO, J = 5.33, 10.29 Hz), 4.14 (1H, qd, OCHMe, J = 1.47, 7.00 Hz), 3.81 (3H, s, PhOMe), 3.75 (3H, s, COOMe), 3.36 (1H, dd, CHCHNHCO, J = 1.50, 5.30 Hz), 1.11 (3H, d, CHMe, J = 6.90 Hz); irradiation of the double doublet at 5.71 ppm led to a doublet at 3.36 ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.18, 172.71, 167.81, 160.89, 160.04, 131.83, 129.54, 128.61, 128.55, 127.14, 114.9, 65.75, 60.71, 57.34, 56.88, 55.4, 53.4, 17.08; MS (EI) 412 (M^+) exact mass calcd 412.1634, found 412.1628; IR (neat) 3400, 1750, 1720, 1660 cm^{-1}.

17 These experimental conditions were tested on a system where D-(*p*-methoxyphenyl)glycine methyl ester was replaced with 1-amino 1-cyclopropane carboxylic acid. In this case, only the lactone rearrangement product was isolated.

18 While this work was in progress, Palomo reported similar reductions with stereoselectivity not in agreement with that which we observed. This might be explained by the difference of the substituents at the C_3 position. Palomo, C.; Arrieta, A.; Cossio, F. P.; Aizpurua, J. M.; Mielgo, A.; Aurrekoetxea, N. *Tetrahedron Lett.* **1990**, *44*, 6429.

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