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THE APPLICATION OF HIGHLY STEREOSELECTIVE ALDOL CONDENSATIONS TO THE SYNTHESIS OF β-LACTAM ANTIBIOTICS.

by

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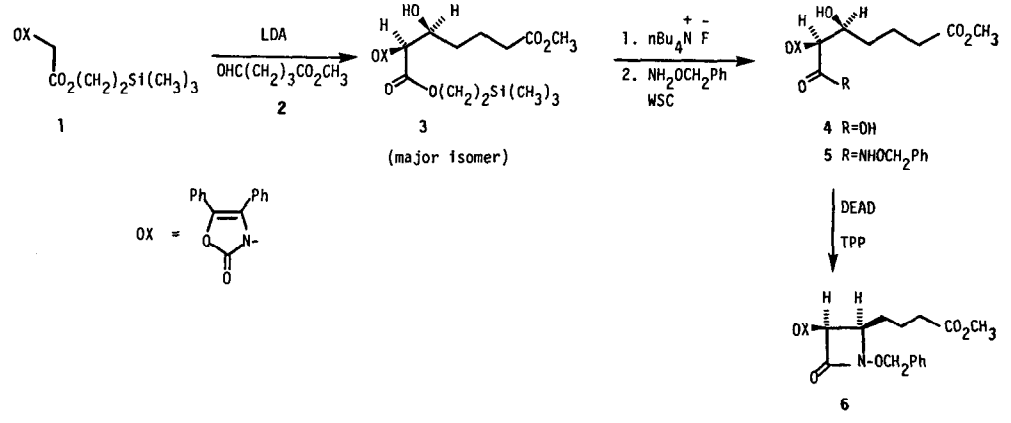
Stereoselective aldol condensations of fully protected glycine and 3-butyryl thiazolidine-2-thiones with achiral aldehydes afforded β-hydroxyesters suitable for elaboration to key intermediates for the synthesis of β-lactam antibiotics.

Recent discoveries of novel biologically active monocyclic and bicyclic β-lactam antibiotics has stimulated considerable interest in the development of efficient syntheses of appropriately substituted 2-azetidinones. Because of their inherent relative complexity, syntheses of the bicyclic β-lactams, like the carbapenems, from monocyclic precursors usually requires several steps.[1,2] We wish to report here a short and stereoselective route which provides the entire carbon framework of the carbapenems or carbacephams in a single aldol condensation. Using our previously described hydroxamic acid based β-lactam synthesis,[3] the key to the preparation of many monocyclic β-lactams is the availability of the corresponding β-hydroxy carboxylic acid. Extensions to the synthesis of bicyclic β-lactams conceptually required only formation of β-hydroxy carboxylic acids with more elaborate carbon frameworks. Our first attempt to test the feasibility of this approach is shown in Scheme 1.

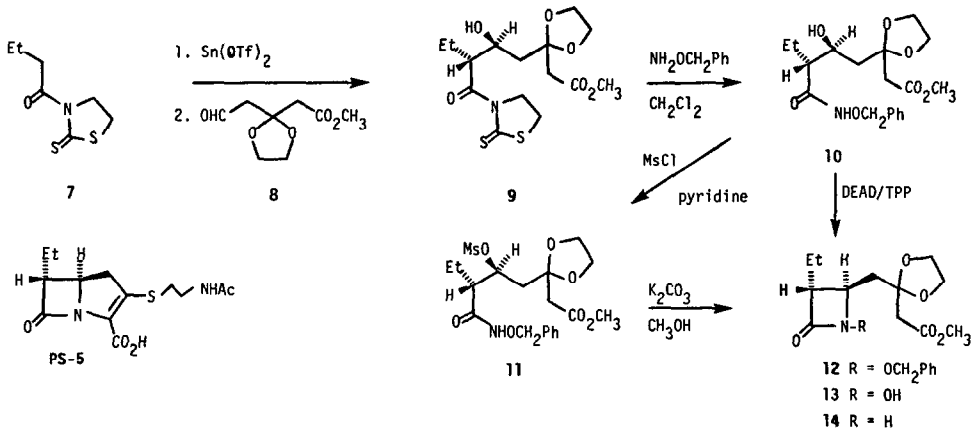
Scheme 1



The fully protected glycine **1**,[4] was condensed with the aldehyde ester **2**[5] to afford the desired aldol product **3**[6,7] in low (25%) yield [LDA, THF, 1h, -78°C, followed by a quench with NH_4Cl, aqueous workup and chromatography on silica gel with ethyl acetate - hexanes (1:3)] as a mixture of S*,S* (threo, if drawn in the chain extended form) and S*,R* (erythro) isomers (4:1, as determined by 300 MHz NMR).[7] Treatment of **3** with $nBu_4N^+F^-$ in THF for two min at room temperature provided the free acid **4** in quantitive yield. Coupling of **4** with O-benzylhydroxylamine in the usual fashion (water soluble carbodiimide in H_2O/THF at pH 4-5)[3] provided the hydroxamate **5** which was cyclized to the azetidinone **6** in 69% yield with Ph_3P/DEAD.[3] Thus, although the initial aldol condensation proceeded with modest stereoselectivity, the major isomer leads to the desired **cis** stereochemistry in the final β-lactam. Essentially all biologically active bicyclic β-lactams with substituted amino groups at C_3 are of the **cis** form.

Subsequent to obtaining these initial results, our goal was to utilize an even more stereoselective aldol condensation to provide β-hydroxy acids with the carbon skeleton and functionality needed for elaboration to carbapenems, most of which are **trans** substituted (like thienamycin, PS-5, and others). For this preliminary demonstration, we chose to synthesize a precursor of the carbapenem PS-5.[1,8] Thus, (Scheme 2), condensation of 3-butyryl thiazolidine-2-thione **7** with aldehyde **8**[9] by the methods developed by Mukaiyama[10] (**7** + N-ethylpiperidine and $Sn(OTf)_2$ in CH_2Cl_2 for 30 min at room temperature followed by cooling to -20°, adding **8** and stirring for 2h) afforded the expected R*,S* (erythro)[10] aldol product **9** in 72% yield (None of the R*,R* (threo) product was detected by 300 MHz NMR). Direct reaction of **9** with NH_2OBz in CH_2Cl_2 for 11h at room temperature provided the hydroxamate **10** in low (33%) yield. Subsequent cyclization (DEAD/Ph_3P, THF, room temperature , 1.5h) afforded the **trans** substituted monocyclic β-lactam **12** in 73% yield. Since complete chromatographic removal of the reduced DEAD from the product **12** was difficult, an alternative cyclization was attempted. Mesylation of **10** provided **11** in 65% yield (CH_3SO_2Cl, pyridine, room temperature, 2h). Treatment of **11** with K_2CO_3 in CH_3OH at room temperature for 7h gave **12** in 82% yield.[11] Hydrogenolyis[3] of **12** with 10% Pd/C in CH_3OH generated the N-hydroxy β-lactam **13** cleanly in 91% yield.

Scheme 2



Ample literature precedent exists for the reductive cleavage of N-hydroxy β-lactams[3] (like **13**) and the deketalization of substituted β-lactams similar to **14**.[12] Efficient conversion of the resulting β-keto esters to carbapenems has been well established by the reports from the Merck group and others.[1,12,13] Thus the route shown in Scheme 2 should provide a versatile and stereoselective approach to the carbapenems. Asymmetric aldol-type reactions[14] of analogues of **1** or **7** with achiral aldehydes should also afford chiral aldol products which can be transformed into chiral β-lactam antibiotics by the procedures shown in Schemes 1 and 2. Such extensions are currently being studied in our laboratory.

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Notes and References

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7. All compounds prepared were racemic. Thus, all indicated stereochemistry is relative. Representative characterization data includes: **3**,oil, ^{1}HNMR (300 MHz, $CDCl_3$) δ 1.1 (m, 2H), 1.45-1.85 (m, 4H), 2.37 (m, 2H), 3.69 (s, 3H), 3.94 (d, 1H, J = 4.8 Hz), 4.34 (dd, 1H, J = 4.8 Hz), 4.45 (m, 2H), 7.21-7.68 (m, 10H); MS (EI) m/e 525 (M^+). **5**, oil, ^{1}HNMR δ 1.5 - 1.78 (m, 4H), 2.37 (m, 2H), 3.17 (br s, OH), 3.66 (s, 3H), 3.81 (m, 1H), 4.28 (m, 1H), 4.98 (s, 2H), 7.2 - 7.6 (m, 15H). **6**, oil, ^{1}H NMR δ 1.5 - 1.68 (m, 4H), 2.21 (m, 2H), 3.68 (s, 3H), 4.45 (dt, 1H, J = 3.9Hz), 5.04 (br d, 2H, OCH_2), 5.10 (d, 1H, J = 3.9 Hz),

7.2 - 7.55 (m, 15H); IR ($CHCl_3$) 1770, 1750, 1740 cm^{-1}; MS (EI) m/e 512 (M^+). **9**, oil ^1H NMR δ 1.93 (t, 3H), 1.5 - 1.95 (m, 2H), 2.10 (m, 2H), 2.73 (s, 2H), 2.95 (s, OH), 3.30 (m, 2H), 3.67 (s, 3H), 4.02 (m, 4H), 4.25 (m, 1H), 4.57 (dt, 2H), 4.8(m, 1H); IR ($CHCl_3$) 3550 (OH), 1730, 1690, 1270 (C=S) cm^{-1}; MS (EI) m/e 377 (M^+). **10**, glass, ^1HNMR δ 0.91 (t, 3H), 1.40 - 2.25 (m, 4H), 2.67 (s, 2H), 3.68 (s, 3H), 3.98 (m, 4H), 4.10 (m, 1H), 4.90 (s, 2H), 5.04(m, 1H), 7.40 (m, 5H), 8.95 (br, NH); IR ($CHCl_3$) 3500, 1730, 1680 cm^{-1}. **12**, oil, ^1HNMR δ 0.97 (t, 3H), 1.58 - 1.80 (m, 2H), 2.05 (dd, 1H, one proton of $-CH_2CHN$), 2.38 (dd, 1H, one proton of $-CH_2CHN$), 2.60 (s, 2H), 2.64 (dt, C_3-H, irradiation at δ 1.65 collapsed this peak to a doublet J = 2Hz), 3.38 (dt, C_4-H; collapsed to dd upon irradiation at δ 2.05), 3.74 (s, 3H), 3.85 - 4.05 (m, 4H), 4.97 (s, 2H), 7.30 - 7.45 (m, 5H); IR($CHCl_3$) 3750, 3050, 1770, 1750 cm^{-1}; MS (EI) m/e 363 (M^+). **13** ^1HNMR δ 1.05 (t, 3H), 1.70 (m, 2H), 2.2 (dd 1H of $-CH_2CHN-$), 2.4 (dd, 1H of CH_2CHN), 2.64 (dt, J = ~2 and 6.3 Hz, C_3-H, collapsed to a doublet with J = 2Hz upon irradiation at δ 1.7), 2.76 (dd, J = 14 Hz, 2H,$-CH_2CO_2-$), 3.72 (m, 1H, C_4-H), 3.74 (s, 3H), 4.08 (br, 4H), 7.38 - 7.82 (br, OH); IR ($CHCl_3$) 3600, 3050, 1770, 1750 cm^{-1}.

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