The Enantioselective Synthesis of *anti*-β-Hydroxy-α-Amino Acids *via* the Reaction of Lithium Enolates of Glycine Bearing an Oxazolidine Chiral Auxiliary with Aldehydes

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Abstract:A new anti-selective aldol reaction utilizing 2,4-disubstituted oxazolidine functionalized-glycine ester **1** is described. The corresponding lithium enolate of **1**, has been demonstrated to undergo a highly anti-diastereoselective aldol reation with a variety of aldehydes. Facile removal of the chiral auxiliary allows for the efficient preparation of chiral β-hydroxy-α-amino acids of erythro stereochemistry.

As part of an effort to construct analogs and develop new molecular frameworks for thrombin active site inhibitors we examined the behavior of the lithium enolate derived from **1** in an aldol process. Based upon the crystallographic structure of **BMS 183,507** complexed with human α-thrombin we observed the methyl group of the *allo*-threonine residue was positioned over the specificity pocket proximal to the guanidine moiety.[1] This spatial relationship would allow for the direct attachment of a guanidine residue to the *allo*-threonine moiety *via* the insertion of an alkyl chain. Preparation of inhibitors based upon this structural motif required an efficient method for the preparation of derivatives of *allo*-threonine.

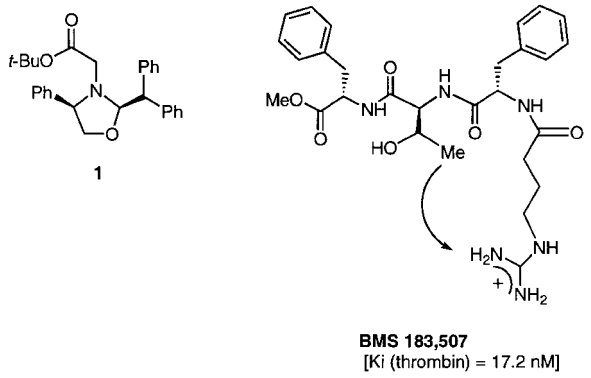
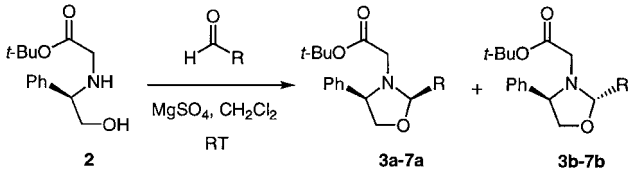


Figure 1. Application of **1** to the Synthesis of Retro-Binding Analogs of **BMS 183,507**

The development of methods for the preparation of nonproteinogenic α-amino acids continues to be an active area of research.[2] Although many methods for the construction of a variety of α-amino acids have been described, a chiral glycine equivalent that efficiently undergoes a highly *anti*-selective aldol reaction in high yield has remained an elusive target.[3,4] Reported here is the development of a novel oxazolidine-based chiral glycine equivalent of high isomeric purity which addresses this issue.

Oxazolidines derived from optically active phenylglycinol have been utilized as chiral auxiliaries or reactants for the formation of chiral products.[5] We have prepared several 2,4-disubstituted oxazolidine-functionalized glycine *tert*-butyl esters in an attempt to find an appropriate combination of high diastereomeric purity and required steric bulk necessary for good diastereofacial selectivity in subsequent aldol reactions.[6]



Scheme 1. Preparation of Oxazolidine-Functionalized Glycine *tert*-Butyl Esters

Table 1. Isomer ratios derived from the formation of the oxazolidine moiety

Compd	RCHO	a/b[a]	Yield [b]
3	CH_3CHO	16/1	96
4	*n*-BuCHO	16/1	91
5	*i*-PrCHO	34/1	98
6	*t*-BuCHO	54/1	88[c]
7	$(Ph)_2CHCHO$	37/1 (>99/1[d,e])	95 (83[d])

a) Based on ^{1}H NMR of crude reaction mixtures. b) Percent yield of crude products. c) Reaction temperature of 50 °C. d) Recrystallized from hexanes. e) Based on ^{1}H NMR of the recrystallized material

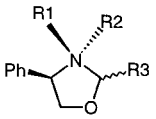
Various aldehydes were condensed with **2** and the results are summarized in Table 1. The crude reaction products **3-7** contained varying amounts of the minor isomers. Recrystallization of the crude mixture of **7a** and **7b** from hexanes provided pure **7a**, $[\alpha]_D$ +51.7° (c 2.0, acetone) in 83 % yield, the only crystalline analog of this series.

The relative stereochemical assignment of the C-2 asymmetric center of phenylglycinol-derived oxazolidines formed by condensation with an aldehyde has been controversial.[7] Recent ^{1}H NMR studies suggest that a *cis* relationship between the C-2 and C-4 residues predominates.[8] Compound **7a** was subjected to single crystal X-ray analysis. Substituents at the C-2 and the C-4 asymmetric centers (both in the R configuration) of the oxazolidine ring are on the same face. The nitrogen has pyramidal geometry (S configuration) with the lone electron pair *cis* to the phenyl and benzhydryl substituents.[9]

To determine the relative stability of the various isomers and related conformers of **6**, molecular mechanics calculations were performed on the model structures **8** -**11** using the MM2 molecular mechanics force field as implemented in the MACROMODEL software package.[10] For each molecule, Monte Carlo searching (MACROMODEL) of conformational space was used to calculate all possible low energy conformers within 10 kcal/mol.[11] The bond between O-1 and C-5 in the oxazolidine ring was defined as the ring closure bond for the purpose of MC torsion angle searching. The torsion angles that defined the atoms in the ring, the *tert*-butyl group and the phenyl group were varied. The relative energies of the respective lowest energy conformers are given in Table 2. The relative energy difference between the *cis* **8** and *trans* **10** conformers is 2.7 kcal/mol, which predicts a theoretical ratio of 67/1 respectively, at 50 °C.[12] In addition, the residues at C-2 and C-4 and the

lone pair of electrons of structure **8**, are on the same face, which is consistent with the solid state structure of **7a**.

Table 2. Molecular Mechanics Relative Energies of Minimized Structures



Compd	R1	R2	R3	Energy(kcal/mol)
8	LP[a]	CH_3	—*t*-Bu	0.0
9	CH_3	LP	—*t*-Bu	5.5
10	CH_3	LP	·····*t*-Bu	2.7
11	LP	CH_3	·····*t*-Bu	4.4

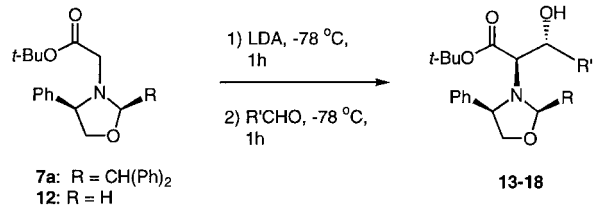
[a] LP signifies the lone pair of electrons

Compound **7a** readily epimerizes *via* an acid catalyzed process to give the thermodynamic ratio of products. Exposure to either $CDCl_3$ with trace DCl or $MgSO_4/CH_2Cl_2$ gave a 38/1 mixture of **7a** and **7b,** respectively.[13] However, the stereochemical integrity of **7a** was easily preserved by avoiding exposure to acids.

Treatment of **7a** or **12** with lithium diisopropylamide (LDA) in THF (1h at -78 °C), followed by the reaction of the resultant lithium enolate with various aldehydes gave aldol products **13-18**.[14] The crude reaction products were examined by ^{1}H NMR under neutral conditions (acetone-d_6 at 55 °C) to ascertain the ratios of diastereomers. The diastereomeric product ratios and the purified yields are given in Table 3. The reaction of the lithium enolate of **12** with isobutyraldehyde (1.0 M, THF) gave a mixture of all four possible diastereomers. Contrary to this result, the reaction of the lithium enolate derived from **7a** when reacted with various aldehydes led predominantly to a single diastereomeric product. Reactions involving sterically hindered aldehydes, entries **15** and **16**, displayed the highest selectivity (99/1) whereas a decrease in steric bulk about the carbonyl group led to a reduction in diastero- and enantioselectivity. The reactions gave the isolated aldol product in good to excellent yields; in many cases **7a** was not observed by ^{1}H NMR in the crude reaction mixtures.

In addition to the acid-catalyzed isomerization of the oxazolidine moiety described earlier, a second isomerization gave a trisubstituted oxazolidine. The aldol product **15** was found to equilibrate through an acid catalyzed reaction to give a 55/45 mixture of the two oxazolidines **15** and **19** respectively, as shown in Figure 2. This equilibration process provided additional complexity for the direct determination of the ratio of diastereomeric aldol products by methods other than NMR in neutral solvents. Irradiation of H_3 with subsequent observation of a nuclear Overhauser effect (NOE) at H_1 and H_4 establishes that the substituents at C-2, C-4 and C-5 are on the same face of the oxazolidine ring confirming the relative *anti*-stereochemistry for the aldol process. However this study provided no details as to the absolute stereochemistry of these asymetric centers.

The aldol product **18** was converted to the corresponding amino diol which was examined by single crystal X-ray analysis.[9,15] The two contiguous asymmetric centers were found to be R in configuration, relative to the known asymmetric center (R) contained in the phenyl glycinol residue, thus confirming the anti-stereochemistry for the aldol reaction.



7a: R = $CH(Ph)_2$
12: R = H

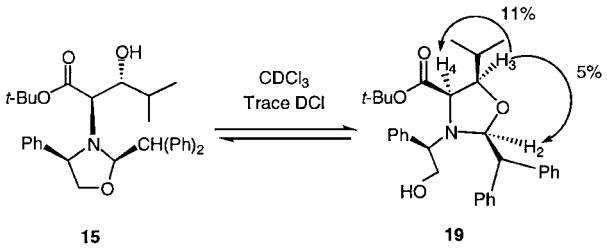
13-18

Scheme 2. Deprotonation and Reaction of Gylcine Ester Enolates with Various Aldehydes

Table 3. Yield and ratios of the diastereomeric products derived from the aldol reactions

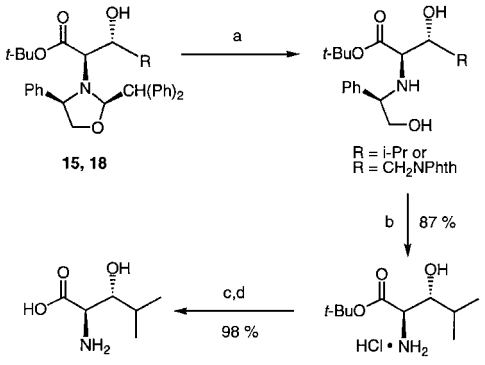
Compd	R	R'CHO	M/m[a,b]	Yield (%)[c]
13	H	*i*-PrCHO	31(69)[d]	84
14	$CH(Ph)_2$	*n*-PrCHO	92/8	87
15	" "	*i*-PrCHO	99/1	94
16	" "	*t*-BuCHO	99/1	91
17	" "	PhCHO	>90/1[e]	85
18	" "	PhthNCH$_2$CHO	94/6	73

a) Based on ^{1}HNMR of the crude reaction mixture. b) M denotes major isomer and m denotes the sum of the minor isomers. c) Yield of chromatographed aldol products. d) A mixture of all four diastereomers was obtained. e) A minor isomer was observed; however, a more accurate determination was not possible



15 **19**

Figure 2. Acid catalyzed isomerization and NOE enhancements



15, 18

R = i-Pr or
R = CH_2NPhth

Exp.:[α]D -21.8° (c 1, H_2O)
Lit. :[α]D -22.0° (c 1, H_2O)[4d]

a) THF/H_2O/HCO_2H (6/1/1) at rt., 24h. b) Pd/C (10 %), 1atm H_2, MeOH. c) anhydrous HF at 0°C, 15min. d) Dowex-1

Scheme 3

The aldol product **15** was converted to the corresponding amino acid *via* a three step procedure.[15] The optical rotation determined for this acid compared favorably with the data reported by Kanemasa *et al* for the enantiomerically pure amino acid.[4d,15]

A re (enolate)/si (aldehyde) combination yields the observed aldol products **14-18.** We believe the enolate/aldehyde complex adopts a configuration that would minimize the non-bonded interactions between the large bulky residues and this would result in the pre-aldol complex given in Figure 3.[16,17,18] Studies are now ongoing to determine the steric requirements of the chiral auxiliary with regard to stereochemical control of the aldol process.

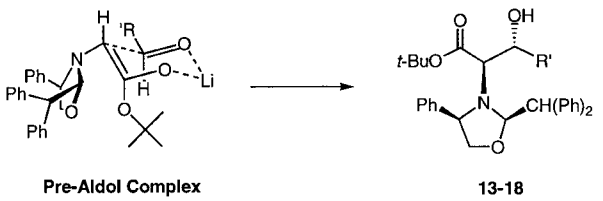


Figure 3. Pre-Aldol Complex, shown as a monomer

In conclusion, as part of our effort to prepare potent novel inhibitors of thrombin catalytic activity, we have developed an easily prepared chiral glycine equivalent. The lithium enolate derived from this ester reacts with a variety of aldehydes in an enantio- and diastereoselective manner to afford aldol products of *erythro* stereochemistry. In addition, we have demonstrated that these adducts are easily converted to the corresponding amino acids under mild conditions.

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12. Value calculated from Æ G = -RTlnK at 298 K.
13. Determined by ^{1}H NMR in CD_3COCD_3 at 50 ^{o}C.
14. A 1.0 M solution of LDA in THF was used that contains 0.4 M hexanes. The aldol reactions were quenched with saturated $NaHCO_3$, extracted with ethyl acetate and dried over $NaSO_4$.
15) Degradation sequences for **15** and **18**.
a) THF/H_2O/HCO_2H (6/1/1) at rt., 24h. b) Pd/C (10 %), 1atm H_2, MeOH. c) anhydrous HF at 0^{o}C, 15min. d) Dowex-1.
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