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ASYMMETRIC SYNTHESIS OF *ANTI*-β-HYDROXY-α-AMINO ACIDS

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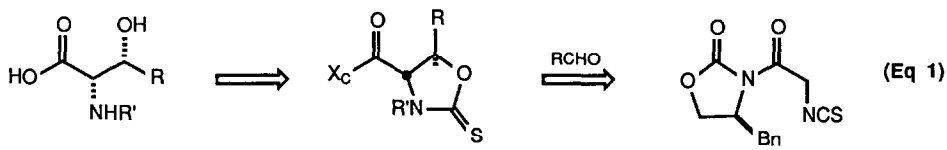
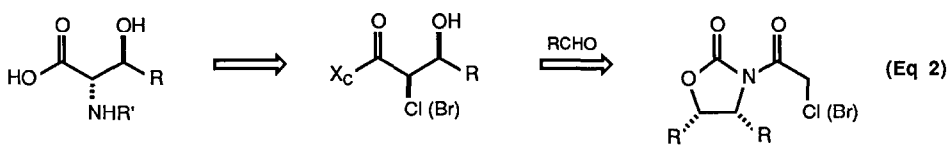
Abstract: The stereoselective aldol addition reactions of chiral haloacetate enolates is reported. The conversion of these adducts to enantiomerically pure *anti*-β-hydroxy-α-amino acids is demonstrated (Eq 2).

β-Hydroxy-α-amino acids are important both as constituents of biologically active peptides[1] and as precursors to β-lactam antibiotics.[2] We recently disclosed a method for synthesizing enantiomerically pure *syn*-β-hydroxy-α-amino acids via diastereoselective aldol reaction of 3-isothiocyanoacetyl-2-oxazolidinone[3] (Eq 1). The purpose of this Letter is to report a complementary approach to the synthesis of enantiomerically pure *anti*-β-hydroxy-α-amino acids[4] from 3-halo-acetyl-2-oxazolidinones[5] (Eq 2).

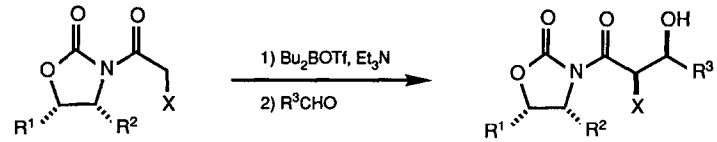


(Eq 1)



(Eq 2)

Initially, we examined the reaction of imide **1** with benzaldehyde under conditions known to be effective for the aldol reaction of 3-propionyl-2-oxazolidinones[6] (Eq 3). Enolization of **1** with di-*n*-butylboryl triflate and diisopropylethylamine in methylene chloride (-78 °C to 0 °C) followed by treatment with benzaldehyde (0 °C, 1h) afforded the α-chloro aldol adduct **3c** along with significant quantities of recovered starting material. Subsequent reaction optimization studies revealed that enolization with triethylamine in diethyl ether at room temperature resulted in an increase in yield. Under these reaction conditions both the chloro and bromoacetyl-2-oxazolidinones **1** and **2** undergo diastereoselective aldol addition with a variety of aldehydes. These results are summarized in the Table.

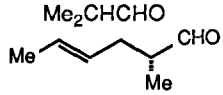


1, R^1 = Ph, R^2 = Me, X = Cl
2, R^1 = H, R^2 = Bn, X = Br

3 (a,b,c)
4 (a,b)

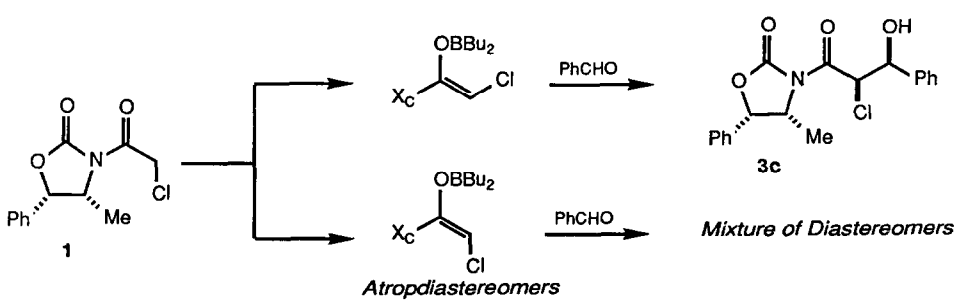
(Eq 3)

Table. Diastereoselective Aldol Reactions of Imides 1 and 2.[13]

Entry	Imide	R^3CHO	Ratio[a]	Yield[b]	Adduct
1	1	MeCHO	95:5	67%	**3a**
2	1	Me_2CHCHO	96:4	75%	**3b**
3	1	PhCHO	97:3	79%	**3c**
4	1	PhCHO	95:5	94%[c]	**3c**
5	2	Me_2CHCHO	98:2	63%	**4a**
6	2		94:6	63%[d]	**4b**

[a]The ratio of product diastereomers is defined as the fraction of desired isomer divided by the sum of all others. [b]Yields reported are for isolated major diastereomer of diastereomeric purity >99% as determined by HPLC or GC. [c]1.5 equiv of imide were used; yield based on aldehyde. [d]Two equiv of imide were used; yield based on aldehyde.

In spite of extensive efforts at yield optimization, these reactions consistently proceed to no more than 80% conversion with the attendant recovery of *ca.* 20% carboximide **1** or **2.** A series of ^1H NMR experiments provided a concise explanation for this observation. Treatment of **1** in deuterochloroform with di-*n*-butylboryl triflate and either triethylamine or 2,6-lutidine resulted in a mixture of *E* and *Z* enolates exhibiting three singlets (δ 5.2, 4.0, 3.8 ppm) in the NMR spectrum. NOE experiments revealed that the low-field singlet is associated with the vinyl proton in the *Z* enolate while *both* of the high-field singlets are associated with the vinyl proton in the *E* enolate! At elevated temperatures these two resonances partially coalesced. The integration of these three resonances indicated a 75:25 ratio of *Z* and *E* enolates, respectively. The presence of two diastereomeric vinyl protons in the *E* isomer suggests considerable steric hindrance to rotation about the C-N single bond. Apparently, allylic strain prevents the π system and the oxazolidinone ring from adopting a coplanar arrangement, and two bisected conformations result (Eq 4).



(Eq 4)

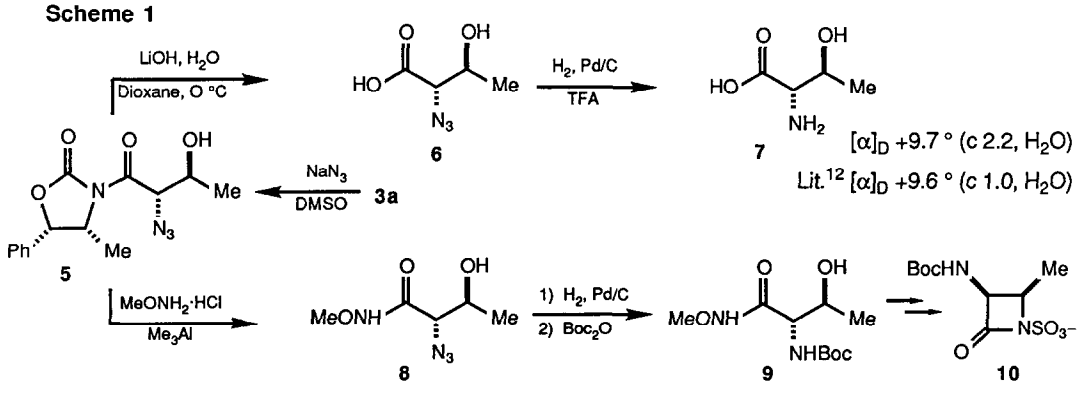
When benzaldehyde was added to this *E:Z* enolate mixture, we observed by NMR a large difference in the aldol reaction rates for the two isomers. While the *Z* enolate was rapidly consumed at room temperature, the *E* enolate required 15 h for complete reaction. Furthermore, while the reaction of the *Z* enolate exhibited high levels of reaction diastereoselection, the reaction of the *E* enolate was stereorandom (Eq 4). The low reactivity of the *E* enolate allows one to use a slight excess of the enolate mixture to give both high diastereoselectivity and high yield based on aldehyde (Table, Entry 4).

In a typical procedure, 1 equiv of imide **1** or **2**, 0.2 M in diethyl ether,[7] is cooled to -78 °C. To the resultant suspension is added 1.4 equiv of triethylamine, followed by 1.1 equiv of di-*n*-butylboryl triflate. The cooling bath is removed and the reaction mixture is stirred at room temperature for 1.5 h. The resultant two-phase mixture is cooled to -78 °C with vigorous stirring. After 1 equiv of aldehyde is added, the reaction is stirred at -78 °C for 0.5 h, and 0 °C for 1 to 2 h. The solution is diluted with ether, washed with 1 N aqueous sodium bisulfate, and concentrated. Following oxidation with 30 % aqueous hydrogen peroxide (10 equiv, 1:1 methanol/water, 0 °C, 1 h), extractive workup, and chromatographic purification, the aldol adduct is obtained with >99% diastereomeric purity.

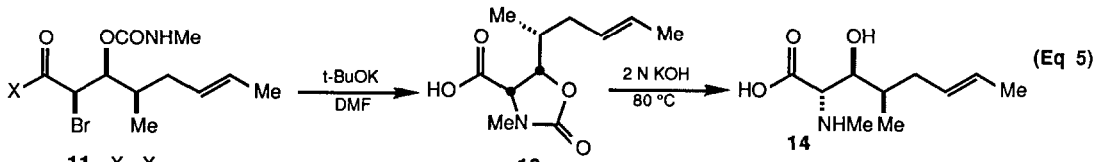
Aldol adducts **3** and **4** are versatile sythons for the synthesis of β-hydroxy-α-amino acids. Treatment of **3a** with sodium azide in DMF at 45 °C affords the corresponding azide **5** in 70% yield, along with 10% of the C-2 diastereomer (Scheme 1). In contrast, the bromo aldol adducts undergo azide displacement at room temperature to give the corresponding azides in 90 to 95% yield with no apparent loss of stereochemistry.

The azide **5** can be converted directly to L-*allo*-threonine **7** in 82% overall yield by hydrolysis with lithium hydroxide (dioxane/water, 0 °C) and hydrogenation of the resultant acid **6** over 5% palladium on carbon in the presence of trifluoroacetic acid (Scheme 1). In addition, the β-lactam synthon **9** is readily available as follows: transamination of **5** with the aluminum amide reagent[8] prepared from methoxyamine hydrochloride and trimethylaluminum affords **8** in 94% yield with no epimerization. Hydrogenation of **8** as above, followed by *in situ* protection of the amine with di-*tert*-butyl dicarbonate affords **9** in 93% yield (Scheme 1). In as much as Floyd and coworkers[2a] have converted this compound to the corresponding monobactam **10**, the methodology presented herein provides access to a range of 3,4-disubstituted monobactam analogs.

Scheme 1



N-alkyl-β-hydroxy-α-amino acids are also readily available from the α-halo aldol adducts. This is demonstated in the context of a synthesis of 3-epiMeBmt **14**, the hydroxyl epimer of MeBmt,[9] the unusual amino acid found in the immunosuppressive peptide cyclosporine[10] (Eq 5). Acylation of **4b** with methyl isocyanate[11] (5 equiv, 1.1 equiv $BF_3{\cdot}OEt_2$, toluene, 25 °C, 1h) affords **11** in 94% yield. After hydrolysis of **11** with lithium hydroxide (THF/H_2O, 0 °C, 10 min) and cyclization of the resultant acid **12** (5 equiv t-BuOK, DMF, RT, 5 min), oxazolidinone **13** is isolated in 76% yield from **11**. Treatment of **13** with 2 N aqueous potassium hydroxide at 80 °C affords the desired amino acid in 94% yield as a 93:7 mixture of C-2 diastereomers. The minor isomer is readily removed by recrystallization from ethanol-water. It is interesting to note that when aldol adduct **4a** is carried through this sequence of reactions, no epimerization is detected in the final hydrolysis.



11, X = X_c
12, X = OH

13

14

mp 265-267 °C

[α] +28.7 ° (c 0.83, 0.4 N aq HCl)

(Eq 5)

In conclusion, α-halo aldol adducts **1** and **2** have proven to be useful and versatile synthons for the synthesis of *anti*-β-hydroxy-α-amino acids and derivatives.

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References and Notes

1. "Amino Acids, Peptides and Proteins." Specialist Periodical Reports, Chem. Soc., London, 1968-1983; Vol. 1-16.
2. a) Floyd, D. M.; Fritz, A. W.; Pluscec, J.; Weaver, E. R.; Cimarusti, C. M. *J.Org.Chem.* **1982**, *47*, 5160. b) Labia, R.; Morin, C. *J. Antibiotics* **1984**, *37*, 1103. c) Miller, M. J. *Acc. Chem. Res.* **1986**, *19*, 49. d) Holden, K. G. in "Cephalosporins and Penicillins: Chemistry and Biology," Flynn, E. H., ed.; Academic Press: New York, 1972, Vol. 2, pp133-136.
3. Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1986**, *108*, 0000.
4. For other syntheses of *anti*-β-hydroxy-α-amino acids see: Saito, S.; Bunya, N.; Inaba, M.; Moriwake, T.; Torii, S. *Tetrahedron Lett.* **1985**, *26*, 5309 and references therein.
5. For the use of these compounds in the synthesis of epoxides see: Abdel-Magid, A.; Pridgen, L. N.; Eggleston, D. S.; Lantos, I. *J. Am. Chem. Soc.* **1986**, *108*, 4595.
6. Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.
7. The *Z*:*E* ratio is presumably higher than 75:25 in this solvent, since a 79% yield of **3c** was obtained (Table, Entry 3).
8. Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989.
9. (4*R*)-4-((*E*)-2-Butenyl)-4,*N*-dimethyl-L-threonine (IUPAC/IUB three-letter amino acid notation).
10. Wenger, R. M. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 77.
11. Ibuka, T.; Chu, G.-N.; Aoyagi, T.; Kitada, K.; Tsukida, T.; Yoneda, F. *Chem. Pharm. Bull.* **1985**, *33*, 451.
12. West, H. D.; Carter, H. E. *J. Biol.Chem.* **1938**, *122*, 611.
13. Satisfactory spectral data and elementary analyses were obtained for all compounds.

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