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A practical diastereoselective synthesis of β-amino-α-hydroxy carboxylates

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Abstract—Practical synthetic routes to β-amino-α-hydroxy carboxylates (AHC) have been developed from amino acids. Reduction of β-amino-α-keto esters **6** with $NaBH_4$ was found to give *anti*-AHCs **7** in high de, which were efficiently converted to the corresponding *syn*-AHCs **8** via oxazolidine ring **10** formation.

β-Amino-α-hydroxy carboxylic acids (AHC) have received much attention because they are essential structural components in a variety of biologically important compounds such as taxol,[1] a potent anticancer agent, bestatin,[2] an aminopeptidase inhibitor, amastatin,[3] a protease inhibitor, KNI-227 and KNI-272,[4] highly potent HIV protease inhibitors, and kanamicin A,[5] an antibacterial agent (Fig. 1). Much effort has been devoted to the development of efficient stereoselective synthetic routes to enantiomerically pure AHC.[6] Recently, we developed a highly practical route to diastereoselective syntheses of all four sphingosine stereoisomers via non-chelation controlled and chelation controlled reduction of *N*-trityl protected amino enones and free amino enones using $NaBH_4$ and $Zn(BH_4)_2$, respectively.[7] We describe herein an extension of this method to the preparation of optically active *syn*/*anti* AHC derivatives.

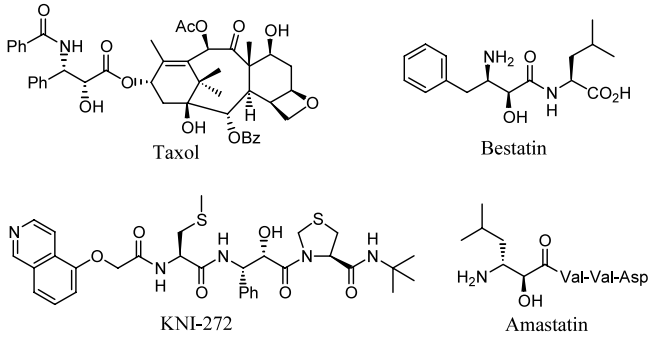
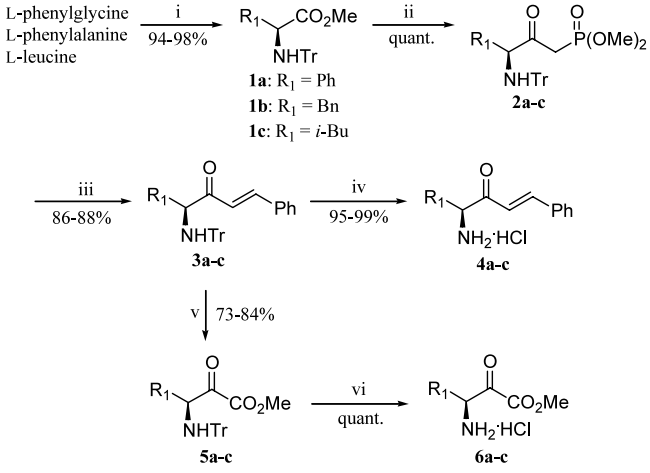


Figure 1.

Our synthesis procedures are based on commercially available amino acids and are illustrated with three representative amino acids; L-phenylglycine, L-phenylalanine and L-leucine (Scheme 1). Esterification of the



Scheme 1. *Reagents and conditions*: (i) (a) AcCl, MeOH, reflux, (b) TrCl, Et_3N, CH_2Cl_2, rt; (ii) $LiCH_2PO(OMe)_2$, THF, −78°C; (iii) PhCHO, NaH, THF, rt; (iv) conc. HCl, THF, reflux; (v) O_3, NaOH, MeOH–CH_2Cl_2, −78°C; (vi) conc. HCl, MeOH, rt.

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amino acids with methanolic hydrogen chloride, followed by protection of the amino functionality with trityl chloride gave the protected amino esters **1a**–**c** in high yields. The esters **1a**–**c** were quantitatively converted to the β-keto phosphonates **2a**–**c** by treatment with excess lithium dimethyl methylphosphonate. The Horner–Wadsworth–Emmons olefination of the β-keto phosphonates **2a**–**c** with benzaldehyde under the NaH/THF conditions provided the corresponding enones **3a**–**c** in good yields as previously reported.[8] The enones **3a**–**c** were treated with conc. HCl in THF at reflux to give the deprotected amino enones **4a**–**c**. We first examined possible diastereoselective reduction of these types of enones (**3** and **4**) using the methodology previously developed in our laboratory,[7] on the premise that the amino alcohol products could be converted to AHCs by an oxidative cleavage reaction in the next stage. As expected, reduction of the *N*-trityl protected enones **3a**–**c** and the unprotected amino enones **4a**–**c** with $NaBH_4$ and $Zn(BH_4)_2$ provided the *syn*- and *anti*-amino alcohols as the major products, respectively.[9] However, the observed ratios of the *syn*/*anti*-diastereoselectivity (in the range of 52–85% de) were not satisfactory for our practical synthetic goal.

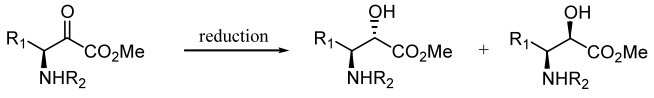
In an attempt to improve diastereoselectivity, we wished to subject the β-amino-α-keto esters **5** and **6** to the reduction conditions. Ozonolysis of the enones **3a-c** in MeOH and CH_2Cl_2 afforded *N*-trityl-α-keto esters **5a**–**c** in acceptable yields.[10] The *N*-trityl-α-keto esters **5a**–**c** in THF were treated with conc. HCl to give deprotected amino-α-keto esters **6a**–**c** as the HCl salt form. We have then examined diastereoselective reduction of these α-keto esters and the results are shown in Table 1.

Initially, for direct comparison we examined the *syn*/*anti* selectivity in the reduction of **5a** and **6a**. It was hoped that reduction of *N*-trityl protected α-keto ester **5a** would give as the major product the *syn*-product via an open Felkin–Anh transition state, whereas the free amino α-keto ester **6a** would yield the *anti*-product via a chelation controlled transition state. To our dismay, however, we obtained the *anti*-product as the major product in both cases. With trityl protected compounds **5a**–**c** the observed diastereoselectivities were rather low with either $NaBH_4$ or $Zn(BH_4)_2$ (entries 1–7). The reduction of compound **5** is supposed to proceed via the Felkin–Anh transition state model since the R_1 group is bulkier than the *N*-trityl protected amino group, unlike our previous cases in which the *N*-trityl protected amino group is the largest group. The low selectivities observed with compound **5** are perhaps due to small differences of bulkiness between the R_1 group and the *N*-trityl protected amino group.

On the other hand, reduction of the free amino α-keto esters **6a** gave the *anti*-product in excellent diastereoselectivity in accord with the expected cyclic Felkin–Anh transition state model (entries 8 and 9). Under the same conditions **6b** and **c** could also be converted to the corresponding *anti*-products in good yields and with equally excellent diastereoselectivities (entries 10–13).[11] The stereochemical assignment of **7a** were made by comparison with the literature values,[6d] and also after its conversion to the benzoyl derivative **9a**.[12,13]

In order to secure a ready access to the desired *syn*-AHC, we had to resort to the inversion of the alcohol configuration of the *anti*-products **7a**–**c** (Scheme 2). Thus, the amino groups of **7** were benzoylated to give **9**, and compounds **9** were converted to oxazolidine derivatives **10** in excellent yields by reaction with $SOCl_2$ in CH_2Cl_2. Successive treatment of **10a**–**c** with HCl in methanol, and then aqueous $NaHCO_3$ provided in better than 70% overall yields the *syn*-AHCs **8a**–**c**.[14] The

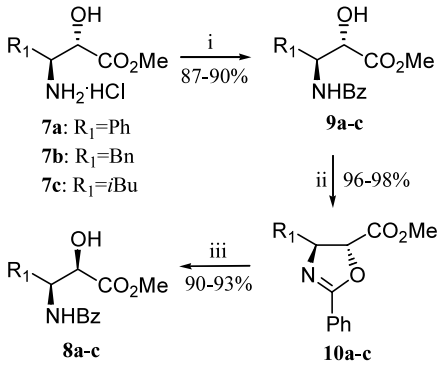
Table 1. Reduction of α-keto esters



5, **6** **7** (*anti*) **8** (*syn*)

Entry	Substrate	R_1	R_2	Conditions	Yield (%)[a]	Ratio *anti*:*syn*[b]	De (%)
1	**5a**	Phenyl	Trityl	$NaBH_4$/MeOH/–20°C	77	5.9:1	71
2	**5a**	Phenyl	Trityl	$NaBH_4/CeCl_3{\cdot}7H_2O$/MeOH/0°C	63	2.4:1	41
3	**5a**	Phenyl	Trityl	$Zn(BH_4)_2$/THF/–78°C	79	8.5:1	79
4	**5b**	Benzyl	Trityl	$NaBH_4$/MeOH/–20°C	55	1.9:1	31
5	**5b**	Benzyl	Trityl	$Zn(BH_4)_2$/THF/–78°C	78	2.6:1	44
6	**5c**	*i*-Butyl	Trityl	$NaBH_4$/MeOH/–20°C	63	2.7:1	46
7	**5c**	*i*-Butyl	Trityl	$Zn(BH_4)_2$/THF/–78°C	72	5.7:1	70
8	**6a**	Phenyl	H·HCl	$NaBH_4$/MeOH/–20°C	73	99:1	**98**
9	**6a**	Phenyl	H·HCl	$Zn(BH_4)_2$/THF/–78°C	75	49:1	96
10	**6b**	Benzyl	H·HCl	$NaBH_4$/MeOH/–20°C	77	99:1	**98**
11	**6b**	Benzyl	H·HCl	$Zn(BH_4)_2$/THF/–78°C	74	15.3:1	88
12	**6c**	*i*-Butyl	H·HCl	$NaBH_4$/MeOH/–20°C	86	15.7:1	88
13	**6c**	*i*-Butyl	H·HCl	$Zn(BH_4)_2$/THF/–78°C	75	18.6:1	**90**

[a] Yields of isolated *anti* products.
[b] The *anti*/*syn* ratio was determined by NMR analysis of the crude mixture.



Scheme 2. *Reagents and conditions*: (i) BzCl, $NaHCO_3$, MeOH, 0°C; (ii) $SOCl_2$, CH_2Cl_2, reflux; (iii) 1N HCl, MeOH, reflux, followed by satd $NaHCO_3$, 50°C.

spectroscopic and physical properties of **8a** were satisfactorily compared with the literature data.[15]

In summary, we have developed practical synthetic routes to *syn*/*anti* β-amino-α-hydroxy carboxylates from amino acids using highly efficient diastereoselective reduction of β-amino-α-keto ester derivatives **6** via a chelation control. This method is expected to be useful in preparing a variety of biologically important compounds containing the *syn*/*anti* AHC moiety.

Acknowledgements

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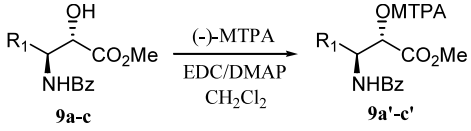
9. Compounds **3** and **4** were reduced by a variety of conditions employing $NaBH_4$, $LiBH_4$, $Zn(BH_4)_2$, L-Selectride, $LiAlH_4$, $NaBH_3CN$, and DIBAL to give *syn*/*anti* products in good chemical yields (68–99%) but moderate diastereoselectivities (52–85% de).
10. (a) The paucity of examples of the direct preparation of α-keto esters from enones via oxidative cleavages such as ozonolysis in the literature may suggest that a further detailed study of this reaction might be warranted; (b) Marshall, J. A.; Garofalo, A. W. *J. Org. Chem.* **1993**, *58*, 3675.
11. It is also conceivable that the reduction of α-keto esters **5** and **6** takes place in the H-bonded cyclic structure between the amino group and the ester group.
12. No racemization during the reduction was confirmed by converting benzoylated *anti*-AHC compounds **9a**–**c** to the corresponding *O*-(−)-MTPA esters **9a′**–**9c′**.[17] ^1H and ^{19}F NMR data indicated their homogeneity. Compound **9a′**: ^1H NMR ($CDCl_3$) δ 3.62 (s, 3H), 3.69 (s, 3H), 5.80 (m, 2H), 6.42 (d, $J=7.8$ Hz, 1H), 7.26–7.60 (m, 15H), ^{19}F NMR ($CDCl_3$) δ 5.00. Compound **9b′**: ^1H NMR ($CDCl_3$) δ 2.87 (m, 2H), 3.66 (s, 3H), 3.68 (d, $J=1.1$ Hz, 3H), 5.09 (m, 1H), 5.55 (d, $J=3.6$ Hz, 1H), 5.85 (d, $J=8.5$ Hz, 1H), 7.12–7.48 (m, 15H), ^{19}F NMR ($CDCl_3$) δ 5.05. Compound **9c′**: ^1H NMR ($CDCl_3$) δ 0.89 (d, $J=6.4$ Hz, 6H), 0.97 (m, 1H), 1.26 (m, 1H), 1.56 (m, 1H), 3.66 (d, $J=1.1$ Hz, 3H), 3.86 (s, 1H), 4.86 (m, 1H), 5.50 (d, $J=1.9$ Hz, 1H), 5.76 (d, $J=3.4$ Hz, 1H), 7.26–7.62 (m, 10H), ^{19}F NMR ($CDCl_3$) δ 4.92.



13. Compound **9a**: $[\alpha]_D^{20}$ −25.6 (*c* 0.68, $CHCl_3$), mp 155–157°C {lit.[6d] $[\alpha]_D^{21}$ −23.7 (*c* 1.1, $CHCl_3$), mp 158–159°C}. To the best of our knowledge, compounds **9b** and **9c** were not previously synthesized. Compound **9b**: $[\alpha]_D^{20}$ −14.6 (*c* 0.56, $CHCl_3$), mp 183–184°C. Compound **9c**: $[\alpha]_D^{20}$ −9.8 (*c* 0.46, $CHCl_3$), mp 141–142°C.
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15. Compound **8a**: $[\alpha]_D^{25}$ −48.6 (*c* 0.42, MeOH), mp 182–183°C {lit.[16] $[\alpha]_D^{20}$ −47.5 (*c* 0.99, MeOH), mp 180–181°C}. To the best of our knowledge, compounds **8b** and **8c** were not previously synthesized. **8b**: $[\alpha]_D^{25}$ −89.5 (*c* 0.35, $CHCl_3$), mp 129–130°C. **8c**: $[\alpha]_D^{25}$ −53.1 (*c* 0.40, $CHCl_3$), mp 122–123.5°C.
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