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Concise enantio- and diastereoselective synthesis of α-hydroxy-α-methyl-β-amino acids

Rolf Roers and Gregory L. Verdine*

Department of Chemistry and Chemical Biology, Harvard University, 12 Oxford St., Cambridge, MA 02138, USA

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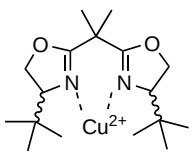
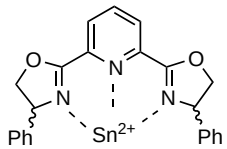
Abstract—Reported here is an efficient procedure for enantio- and diastereoselective synthesis of pure β-amino acids that display a *tert*-hydroxyl functionality in the α-position. Key steps include a catalytic asymmetric aldol reaction and a modified Curtius rearrangement to form oxazolidinone intermediates, which are chemoselectively opened to furnish *N*-protected α-hydroxy-α-methyl-β-amino acids. A modified work-up procedure of the aldol reaction allows for recovery of up to 90% of bisoxazolinyl ligands from the catalysts.

α-Hydroxy-β-amino acids constitute an important class of amino acids because of their occurrence in many biologically relevant compounds.[1] Representative examples are Paclitaxel (Taxol),[2] a clinically significant anticancer agent, and the aminopeptidase inhibitors bestatin[3] and amastatin.[4] Previous synthetic efforts towards α-hydroxy-β-amino acid substructures have used the Sharpless asymmetric aminohydroxylation of α,β-unsaturated amides,[5] Ojima's β-lactam ring-opening procedure,[6a] as well as microbial[7] or asymmetric catalytic reduction of α-keto carboxylic acid derivatives.[8] Some of these approaches are restricted in scope to secondary alcohols at the α-position or by insufficient enantio- or diastereoselectivity.[6b]

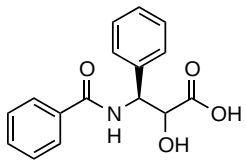
We report here a novel synthesis of β-amino acids **A** that display a tertiary hydroxyl group at the α-position. The present approach allows full control over both stereocenters in **A**. The starting point for the synthesis is a catalytic enantioselective aldol addition of enolsilanes to pyruvate esters (Scheme 1), recently reported by Evans and co-workers.[9]



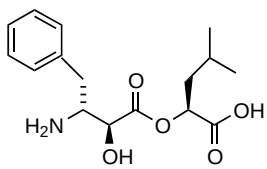
1a (S,S)
1b (R,R)



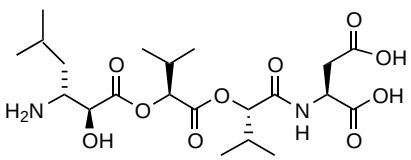
2a (S,S)
2b (R,R)



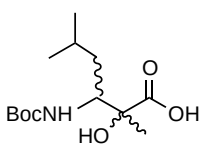
1, Paclitaxel side chain



2, Bestatin



3, Amastatin



A

Keywords: catalytic aldol; Curtius rearrangement; β-amino acid.

* Corresponding author. Tel.: +1 617 495 5323; fax: +1 617 495 8755; e-mail: verdine@chemistry.harvard.edu

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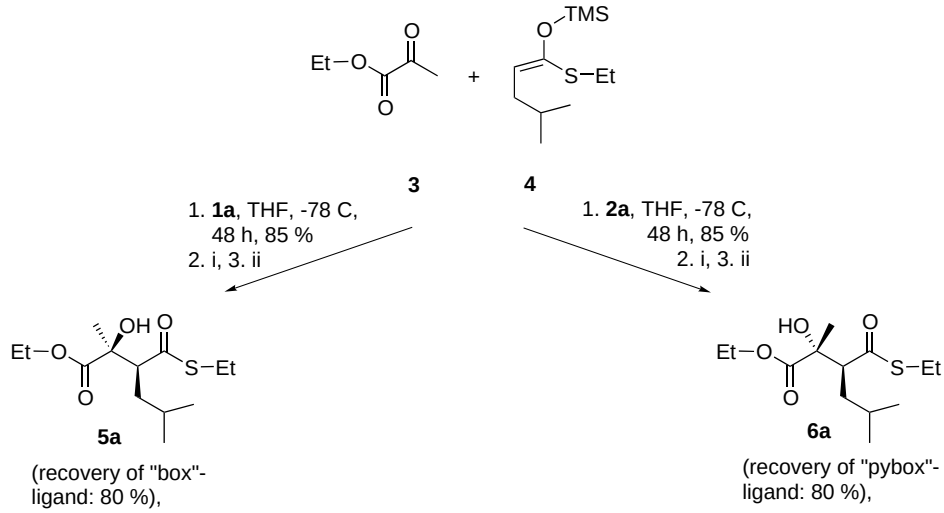
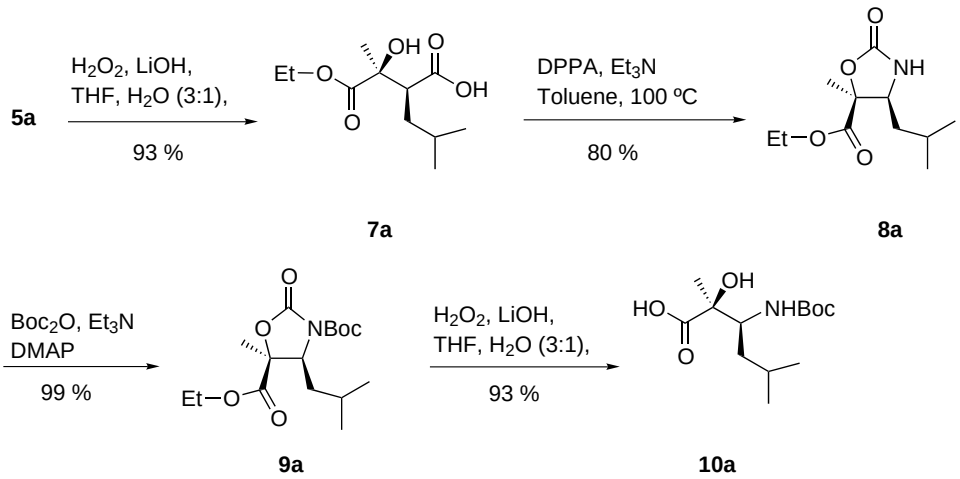


Scheme 1. Synthesis of the hydroxythioesters **5a** and **6a**. (i) aq. EDTA (0.5 M); (ii) HCl, THF.

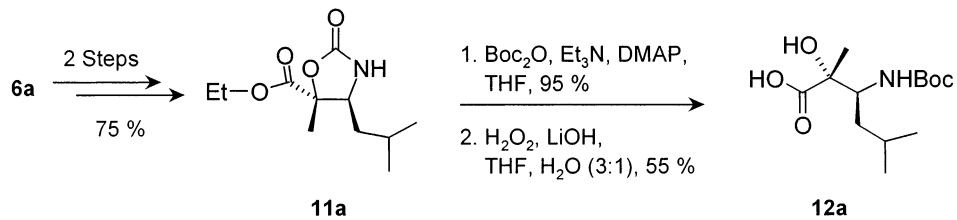
The C_2-symmetric bis(*tert*-butyl-oxazolinyl)Cu(OTf)$_2$ ('box') complexes **1a**,**b**[10] catalyze the addition of **4**[11] to **3** to give the *syn*-aldol product. The corresponding *anti*-aldol product **6a** is synthesized via a {bis(phenyl-oxazolinyl)pyridine}Sn(OTf)$_2$ ('pybox', **2a**) catalyzed reaction.[12]

Exclusive usage of Schlenck technique leads to diastereomeric ratios of 10:1–15:1, and the enantiopurity of the major diastereomer over 91% ee. In order to recover the ligands[13] we modified the typical work-up procedure: extraction of the reaction mixture with 0.5 M aq. EDTA (pH 8) allows complete sequestration of Sn(II) and Cu(II). The aldol products (before deprotection of the TMS unit) and ligands easily can then be separated by column filtration. This simple procedure typically leads to 80% ligand recovery for 'box' and 'pybox', respectively.

As shown in Scheme 2, the thioester in the aldol products can be selectively hydrolyzed using lithium hydroxide and hydrogen peroxide in aq. THF. In order to obtain complete conversion, it is important to use 3 equiv. of LiOH together with an 15-fold excess of



Scheme 2. Transformation of the *syn*-aldol adduct **5a** into the α-hydroxy β-amino acid **10a**.



Scheme 3. Transformation of the *anti*-aldol adduct **6a** into **12a**.

H_2O_2. Reaction of **7a** with DPPA leads to the oxazolidinone **8a** in 80% yield. The formation of the azide intermediate can be monitored by TLC at rt. Heating to 100°C completes the ring closure to form the carbamate. After Boc-protection of **8a** with di-*tert*-butyl dicarbonate the resultant oxazolidinone **9a** was hydrolyzed using LiOH in aq. THF to furnish the acid **10a** in 63% yield.[14]

Scheme 3 shows the analogous transformation of the *anti*-diastereomer **6a** into the corresponding α-hydroxy β-amino acid **12a**. The constitution and relative configuration of the two stereocenters of the oxazolidinone **11a** was confirmed by single-crystal X-ray analysis.[15] The final hydrolysis step leading to **12a** was observed to proceed more slowly than that of **9a** to **10a**.

The synthetic scheme presented here can be adopted for a general synthesis of substituted β-amino acids with diverse variations of the alkyl side chains.

Acknowledgements

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References

1. For a recent review: Juaristi, E. *Enantioselective Synthesis of β-Amino acids*, Wiley-VCH: New York, 1997.
2. Nicolau, K. C.; Dai, W.-M.; Guy, R. K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 15.
3. Suda, H.; Takita, T.; Aoyagi, T.; Umezawa, H. *J. Antibiot.* **1976**, *29*, 100.
4. Aoyagi, T.; Tobe, H.; Kojima, F.; Hamada, F.; Takeuchi, T.; Umezawa, H. *J. Antibiot.* **1978**, *31*, 636.
5. Rubin, A. E.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2637.
6. (a) Ojima, I.; Delaloge, F. *Chem. Soc. Rev.* **1997**, *26*, 377; (b) An efficient synthesis of α-hydroxy-β-amino acids via highly efficient alkylation at the C-3 position of a β-lactam is reported by Ojima et al. (*Tetrahedron Lett.* **1998**, *39*, 3663). A highly efficient methylation of a 3-oxo-β-lactam is reported by Kant et al. (*Tetrahedron Lett.* **1996**, *37*, 6495).
7. Kearns, J.; Kayser, M. M. *Tetrahedron Lett.* **1994**, *35*, 2845.
8. Nozaki, K.; Sato, N.; Takaya, H. *Tetrahedron: Asymmetry* **1993**, *4*, 2179.
9. Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325.
10. Evans, D. A.; Burgey, C. S.; Kozlowski, M. C.; Tregay, S. W. *J. Am. Chem. Soc.* **1999**, *121*, 686.
11. For the synthesis of silyl ketene acetals of thioesters, see: Gennari, C.; Beretta, M. G.; Bernardi, A.; Moro, G.; Solastico, C.; Todeschini, R. *Tetrahedron* **1986**, *42*, 893.
12. Evans, D. A.; MacMillan, D. W. C.; Campos, K. R. *J. Am. Chem. Soc.* **1997**, *119*, 10859.
13. For the ligands' synthesis: 1. ('pybox') Davies, I. W.; Gerena, L.; Lu, N.; Larsen, R. D.; Reider, P. J. *J. Org. Chem.* **1996**, *61*, 9629; 2. ('box') Evans, D. A.; Peterson, G. S.; Johnson, J. S.; Barnes, D. M.; Campos, K. R.; Woerpel, K. A. *J. Org. Chem.* **1998**, *63*, 4541.
14. The new α-hydroxy β-amino acids were fully characterized as methyl esters:
Analytical data of *syn*-(2*S*,3*S*)-methyl-2,5-dimethyl-2-hydroxy-3-*tert*-butoxycarbonylamino-hexanoate prepared from (2*S*,3*S*)-2,5-dimethyl-2-hydroxy-3-*tert*-butoxycarbonylamino-hexanoic acid **10a**: IR 3391.0, 2956.7, 1715.0, 1504.1, 1366.9, 1255.5, 1166.3, 1045.9, 772.0 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.61 (d, 1H, $J=$ 10.4 Hz, NH), 3.92 (dd, 1H, $J=7.4$, 2 Hz, C**H**$CH_2CH(CH_3)_2$), 3.76 (s, 3H, $COOCH_3$), 3.48 (s, 1H, $C(CH_3)$**OH**, 1.60 (m, 1H, CH_2C**H**$(CH_3)_2$), 1.40 (s, 9H, C(**CH_3**$)_3$), 1.39 (m, 2H, **CH_2**$CH(CH_3)_2$), 1.36 (s, 3H, C(OH)**CH_3**), 0.92 (d, 6H, $J=6.8$ Hz, CH(**CH_3**$)_2$); ^{13}C NMR (100 MHz) δ 176.8, 157.2, 79.2, 78.2, 55.1, 53.0, 39.8, 28.5, 25.5, 23.9, 23.4, 21.4; LRMS (ES+) m/z 289 $(MH)^+$, 312 $(MNa)^+$, 353 (MNa+acetonitrile)$^+$; HRMS (ES+) exact mass calcd for $(C_{14}H_{27}NO_5+Na)^+$ requires m/z 312.1787; found m/z 312.1766.
(2*R*,3*S*)-Methyl-2,5-dimethyl-2-hydroxy-3-*tert*-butoxycarbonylamino-hexanoate from (2*S*,3*S*)-2,5-dimethyl-2-hydroxy-3-*tert*-butoxycarbonylamino-hexanoic acid **12a**: IR 3356.2, 2955.7, 1731.6, 1514.0, 1366.5, 1252.1, 1173.2, 1107.8 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.63 (d, 1H, $J=10.4$ Hz, NH), 3.97 (ddd, 1H, $J=16.4$, 7, 2.4 Hz, C**H**$CH_2CH(CH_3)_2$), 3.79 (s, 3H, $COOCH_3$), 3.23 (s, 1H, $C(CH_3)$**OH**, 1.63 (m, 2H, CH_2C**H**$(CH_3)_2$, **CH_2**CH-$(CH_3)_2$), 1.43 (s, 9H, C(**CH_3**$)_3$), 1.38 (s, 3H, C(OH)**CH_3**), 0.89 (d, 3H, $J=2$ Hz, CH(**CH_3**$)_2$), 0.87 (d, 3H, $J=2.4$ Hz, CH(**CH_3**$)_2$), 0.78 (ddd, 1H, $J=18$, 10.4, 2.4 Hz, **CH_2**$CH(CH_3)_2$), ^{13}C NMR (100 MHz) δ 176.9, 156.6, 79.2, 78.0, 55.7, 52.9, 38.2, 28.4, 25.4, 24.0, 22.9, 21.5; LRMS (ES+) m/z 289 $(MH)^+$, 312 $(MNa)^+$, 353 (MNa+acetonitrile)$^+$; HRMS (ES+) exact mass calcd for $(C_{14}H_{27}NO_5+Na)^+$ requires m/z 312.1787; found m/z 312.1797.
15. Roers, R.; Verdine, G. L., unpublished results.