Tetrahedron Letters, Vol. 34, No. 28, pp. 4447-4448, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

AN EFFICIENT ASYMMETRIC SYNTHESIS OF THE FOUR STEREOISOMERS OF 3-HYDROXYLEUCINE

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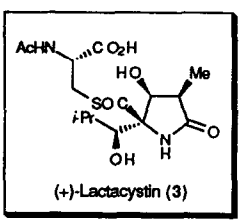
Abstract: The four stereoisomers of 3-hydroxyleucine have been prepared in high overall yield and enantiomeric purity. Key steps include Sharpless asymmetric epoxidation, benzyl isocyanate-induced epoxide opening, and epimerization of an intermediate oxazolidinone ester.

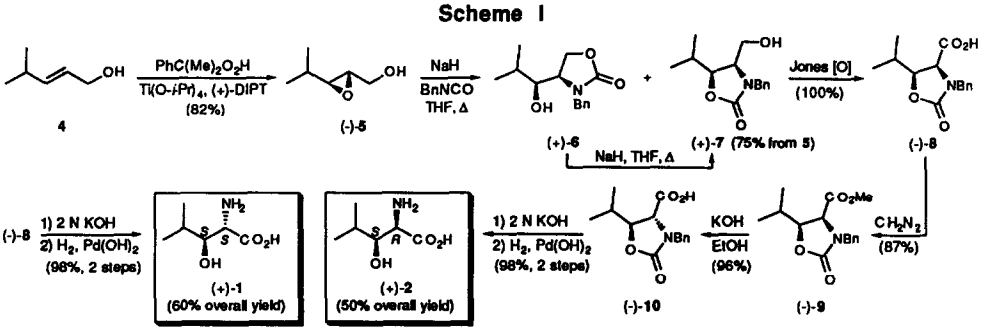
3-Hydroxyleucine initially attracted considerable interest as an amino-acid constituent of naturally occurring peptide antibiotics; the (2*S*,3*S*) diastereomer [(+)-**1**] is found in azinothricin,[1] telomycin,[2] and A83586C,[3] whereas lysobactin[4] contains the (2*S*,3*R*) diastereomer [(-)-**2**]. More recently we isolated and characterized the first non-protein neurotrophic agent, (+)-lactacystin (**3**), which incorporates the (2*R*,3*S*) isomer [(+)-**2**].[5] For the synthesis of lactacystin and analogues thereof, we required multigram amounts of all four stereoisomers of 3-hydroxyleucine. Several meritorious synthetic approaches have been reported previously.[6] Herein we describe a simple, concise strategy which significantly extends the earlier work of Caldwell and Bondy.[6b] Exploiting an efficient epimerization tactic, we have prepared (+)- and (-)-**1** as well as (+)- and (-)-**2**, in high enantiomeric purity and overall yield, from the two antipodes of a new carbomethoxy oxazolidinone intermediate.



(+)-Lactacystin (3)

The synthesis of (+)-**1** and (+)-**2** is outlined in Scheme I. As our point of departure, (*E*)-4-methyl-2-penten-1-ol (**4**) was prepared in quantity via condensation of isobutyraldehyde with triethyl phosphonoacetate followed by DIBAL reduction and distillation.[6b] Sharpless epoxidation[7] with cumene hydroperoxide, diisopropyl L-tartrate [(+)-DIPT], and titanium(IV) isopropoxide smoothly afforded epoxide

Scheme I



(-)-5[8] in 82% yield and greater than 95% enantiomeric excess, as determined by ^{1}H NMR analysis of the derived (+)-MPTA ester.[9] Treatment of epoxy alcohol **5** with benzyl isocyanate and sodium hydride in THF at reflux initially furnished a mixture of regioisomeric oxazolidinones (+)-**6** and (+)-**7**; reexposure of the mixture to NaH in THF at reflux then produced the rearranged heterocycle (+)-**7** in 75% yield.[10] Jones oxidation gave the corresponding carboxylic acid (-)-**8** (quantitative). Finally, hydrolysis of the urethane (2N KOH, reflux) and debenzylation [H_2, $Pd(OH)_2$, MeOH] generated (2*S*,3*S*)-3-hydroxyleucine [(+)-**1**][11] in 98% yield (60% overall from **4**).

For the synthesis of the (2*R*,3*S*) epimer [(+)-**2**], the cis carbomethoxy oxazolidinone (-)-**9** was prepared via diazomethane esterification of (-)-**8** (87%). Exposure of **9** to ethanolic KOH at reflux effected both epimerization and saponification, affording the trans acid (-)-**10** in 96% yield.[12] Urethane cleavage and hydrogenolysis as before then gave (+)-**2**[11] (98% yield, 50% from **4**). The enantiomers (-)-**1**[11] and (-)-**2**[11] were generated via an analogous sequence, simply by employing (-)-DIPT in the asymmetric epoxidation of **4**.

In summary, multigram quantities of the four stereoisomers of 3-hydroxyleucine can be readily prepared in high overall yield and enantiomeric purity. Whereas **5** and **7** require chromatographic isolation, all of the other intermediates are carried forward without purification, greatly enhancing the practicality of the approach. Applications of these amino acids to the synthesis of lactacystin and its analogues will be reported in due course.[13]

Acknowledgment. Financial support by the National Institutes of Health (Institute of Neurology, Communicative Disorders and Stroke) through grant 18254 is gratefully acknowledged.

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6. See for example: (a) Corey, E. J.; Lee, D.-H.; Choi, S. *Tetrahedron Lett.* **1992**, *33*, 6735. (b) Caldwell, C. G.; Bondy, S. S. *Synthesis* **1990**, 34. (c) Jung, M. E.; Jung, Y. H. *Tetrahedron Lett.* **1989**, *48*, 6637. These authors proposed a sequence embodying elements of our approach. (d) Evans, D. A.; Sjogren, E. B.; Weber, A. E.; Conn, R. E. *Tetrahedron Lett.* **1987**, *28*, 39. (e) Seebach, D.; Juaristi, E.; Miller, D. D.; Schickli, C.; Weber, T. *Helv. Chim. Acta* **1987**, *70*, 237.
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8. Caldwell and Bondy prepared (-)-**5** via an alternative Sharpless protocol. Our optical rotation {$[\alpha]_D^{23}$ -32.5° (*c* 1.0, $CHCl_3$)} is identical with the literature values (ref 6b).
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11. (+)-**1**: $[\alpha]_D^{23}$ +37.0° (*c* 1.0, H_2O) {lit.[6b] $[\alpha]_D$ +37° (*c* 0.99, 1N aq HCl)}, mp 219-222 °C (dec) [lit.[6b] 220-3 °C (dec)]; (+)-**2**: $[\alpha]_D^{23}$ +3.5° (*c* 1.0, H_2O), mp 213-4 °C (dec; (-)-**1**: $[\alpha]_D^{23}$ -36.8° (*c* 1.0, H_2O), mp 218-220 °C (dec); (-)-**2**: $[\alpha]_D^{23}$ -3.5° (*c* 1.0, H_2O) {lit.[6e] $[\alpha]_D$ -3.5° (*c* 2.2, H_2O)}, mp 213-6 °C (dec) [lit.[6e] 213-7 °C (dec)]..
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(Received in USA 20 April 1993)