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Stereoselective synthesis of (2*R*,3*R*) and (2*R*,3*S*)-3-hydroxyleucines ☆

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Abstract—A stereoselective synthesis of (2*R*,3*R*) and (2*R*,3*S*)-3-hydroxyleucine is disclosed. The key step of the reaction sequence involves, stereo- and regioselective bromohydration of **7**, using a brominating agent derived in situ from *N*-bromosuccinimide and 2,6-lutidine, via intramolecular sulfinyl group participation.

β-Hydroxy α-amino acids are constituents of many bioactive natural products. (2*S*,3*S*)-3-Hydroxyleucine is a key constituent of a range of naturally occurring cyclic depsipeptides that include telomycin,[1] A-83586C,[2] azinothricin,[3] citropeptin,[4] varicapeptin,[4] L-156602,[5] verucopeptin,[6] and sanjoinine.[7] Lysobactin[8] contains the the (2*S*,3*R*) diastereoisomer while lactacystin[9] incorporates the (2*R*,3*S*) isomer. As a consequence of the essential role played by this amino acid in biological systems and its utility as a synthon, a number of useful strategies have been disclosed for its preparation.[10] The majority of the reported methods utilize, Sharpless asymmetric epoxidation/dihydroxylation reaction or chiral pool starting materials for the introduction of the desired stereocenters. In continuation of our interest in utilizing the sulfinyl group as an intramolecular nucleophile to heterofunctionalize olefins,[11] we disclose herein a stereoselective approach to (2*R*,3*R*) and (2*R*,3*S*)-3-hydroxyleucine (Fig. 1).

The bromohydrin **2**, elaborated stereoselectively from the unsaturated ester **1**,[11e] was subjected to treatment with tetramethylguanidinium azide (TMGA)[12] in dichloromethane to yield stereoselectively the azidoester **3**.[10k] Treatment of **3** with di *tert*-butyldicarbonate and Raney-Nickel under an atmosphere of hydrogen in ethanol as the solvent yielded cleanly the urethane **4** (Scheme 1), whose physical characteristics[13] were in good agreement with the data reported in the literature.[14]

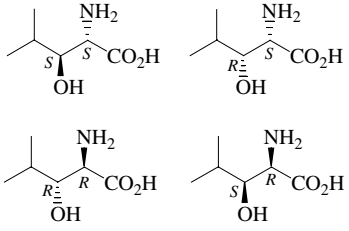

Figure 1.

Aldehyde **5**[11e] on treatment with methyl(triphenylphosphoranylidene)acetate in benzene as the solvent afforded the *trans* α,β-unsaturated ester **6** exclusively.[15] Oxidation of the sulfide with $NaIO_4$[16] yielded an epimeric mixture of sulfoxides **7** in equimolar proportions as an inseparable mixture. Bromohydration of **7** with NBS yielded a product mixture of **8** and **9**, stereoisomeric at C3 and C4 in a 3:1 ratio, respectively.[17] After much experimentation varying the solvents, temperature, and the halogenating agent bromohydration, when carried out with NBS in the presence of an equivalent of 2,6-lutidine (relative to NBS), yielded cleanly the bromohydrin **8** (Scheme 2). Probably a new sterically bulkier brominating agent is formed (as an indication of which the reaction proceeds slower) in situ by the reaction of NBS with 2,6-lutidine, which reacts with **7** in a stereoselective fashion.

Keywords: 3-Hydroxyleucine; Intramolecular participation; Bromohydration.
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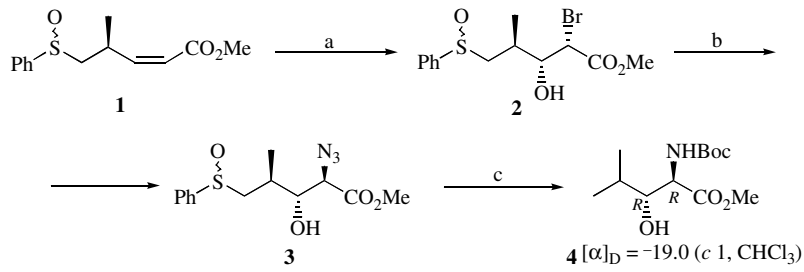
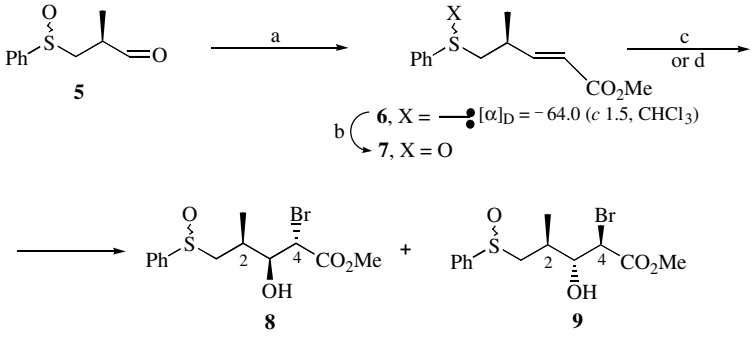


Scheme 1. Reagents and conditions: (a) NBS, H_2O, toluene, rt, 3 h, 80%; (b) TMGA, CH_2Cl_2, 0 °C to rt, 1 h, 80%; (c) H_2, $(Boc)_2O$, Raney-Ni, EtOH, 60 °C, 2 h, 70%.



Scheme 2. Reagents and conditions: (a) Ph_3PCHCO_2Me, PhH, rt, 3 h, 85%; (b) $NaIO_4$, MeOH/H_2O (2:1), 0 °C to rt, 5 h, 85%; (c) NBS, H_2O, toluene, rt, 3 h, 75% 3:1 of **8**:**9**; (d) NBS, H_2O, 2,6-lutidine, toluene, rt, 6 h, 65% of **8** only.

The bromohydrin **8** on treatment with NaN_3 in DMF at rt afforded a mixture of products[18] epimeric at C4. Corey et al.[10h] in their study aimed at the preparation of (2*S*,3*S*)-3-hydroxyleucine made a similar observation, when attempted displacement of the bromide α to the ester by the azido group, yielded the epimeric azides and the epoxide. The side reaction could be averted by silyl protection. Attempted protection of the hydroxy group in **8** as its silyl ether by treatment with *tert*-butyldimethylsilyl triflate and 2,6-lutidine yielded a mixture of products resulting from the activation of the sulfinyl group by the reagent. Therefore the sulfinyl group was reduced[19] to yield the sulfide **10**, which on treatment with *tert*-butyldimethylsilyl triflate cleanly afforded the silyl ether **11**. Displacement of the bromide in **11** proceeded without incident to yield the azide **12** on warming the DMF solution with excess of sodium azide. Treatment of **12** with excess of Raney-Nickel in the presence of $(Boc)_2O$ under an atmosphere of hydrogen in ethanol as the solvent yielded the silyl ether **13**. Deprotection of the silyl group with TBAF afforded urethane **14**[20] (Scheme 3).

In conclusion we have devised a very stereoselective route to (2*R*,3*R*) and (2*R*,3*S*)-3-hydroxyleucine diastereomers from the *cis* and *trans* α,β-unsaturated esters **1** and **7**, respectively. The brominating agent generated in situ from NBS and 2,6-lutidine proved to more stereoselective in the reaction with ester **7**.

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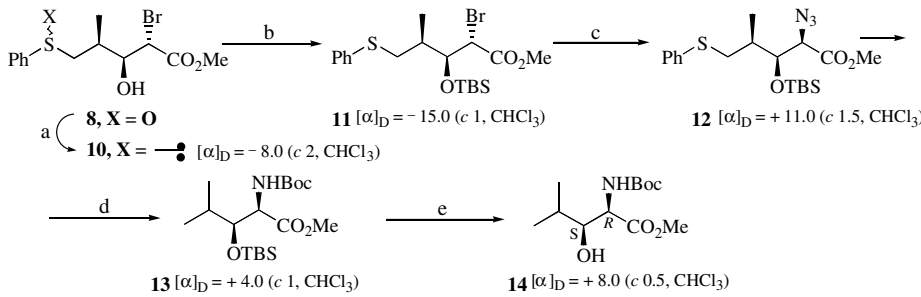

Scheme 3. Reagents and conditions: (a) $TiCl_3$, EtOH, rt, 30 min 65%; (b) TBS-OTf, 2,6-lutidine, CH_2Cl_2, 0 °C to rt, 1 h, 70%; (c) NaN_3, DMF, 50 °C, 3 h, 65%; (d) H_2, $(Boc)_2O$, Raney-Ni, EtOH, 60 °C, 2 h, 70%; (e) *n*-Bu_4NF, THF, rt, 2 h, 85%.

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13. ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.4 (d, $J = 6.8$ Hz, 1H), 4.40 (dd, $J = 7.9$, 3.4 Hz, 1H), 3.75 (s, 3H), 3.42 (br s, 1H), 1.7 (m, 1H), 1.45 (s, 9H), 1.02 (d, $J = 6.4$ Hz, 3H), 0.96 (d, $J = 6.8$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) 19.0, 19.2, 28.1, 30.6, 52.2, 78.6, 80.1, 153.4, 171.7.
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18. The product distribution was not any different using TMGA in dichloromethane.
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20. ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.20 (d, $J = 9.5$ Hz, 1H), 4.40 (d, $J = 8.8$ Hz, 1H), 3.75 (s, 3H), 3.65 (d, $J = 9.5$ Hz, 1H), 1.70 (m, 1H), 1.45 (s, 9H), 1.0 (d, $J = 6.6$ Hz, 3H), 0.90 (d, $J = 6.6$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.9, 28.3, 30.8, 52.4, 55.6, 80.0, 156.0, 172.7.