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A Practical Stereoselective Synthesis of (2*S*, 3*S*)-3-Hydroxyleucine

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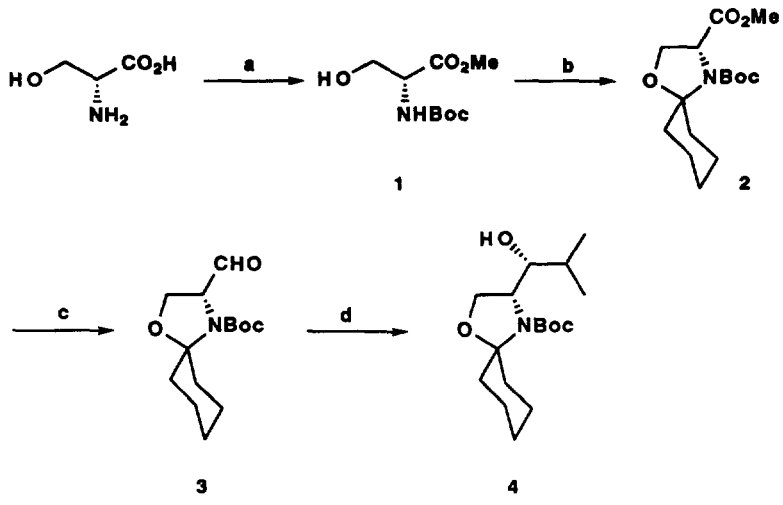
Abstract: A practical and convenient procedure is described for the preparation of gram quantities of (2*S*, 3*S*)-3-hydroxyleucine. The key step involves the triflate-mediated cyclization of spirooxazolidine **4** to the spirobicyclic compound **5**, which is easily converted to the title compound in high yield.

3-Hydroxyleucine is a constituent of many natural peptide antibiotics.[1] A number of accomplished syntheses of this β-hydroxyamino acid are already documented within the literature,[1, 2] the majority of which utilize Sharpless asymmetric dihydroxylation/epoxidation methodology for the introduction of the desired stereocenters. We required a convenient synthesis of the (2*S*, 3*S*) diastereomer on a multigram scale for the synthesis of cyclopeptide alkaloids of the Rhamnaceae family,[3] for which we chose an alternative pathway.

D-Serine was used as the chiral source for the synthesis of the 3-hydroxyleucine precursor **4**, using a Garner type aldehyde **3**[4] (Scheme 1). Methylation of the carboxyl group of D-serine and subsequent derivatization of the free amino group afforded D-*tert*-butoxycarbonylserine methyl ester **1** in high yield. Conversion to the spirooxazolidine **2**[5] was effected by treatment with cyclohexanone in the presence of a catalytic amount of 4-toluenesulfonic acid at reflux. Reduction of the methyl ester followed by oxidation of the corresponding alcohol gave aldehyde **3**.[6] Non-chelation controlled addition of isopropylmagnesium chloride to the resultant aldehyde, proceeded at -78 °C to yield alcohol **4**[7] as a diastereomeric mixture in a ratio of 8:1 in favor of the desired isomer. These diastereomers could easily be separated by flash column chromatography or crystallization, and confirmation of the requisite stereogenic centers was achieved by X-ray analysis.[8]

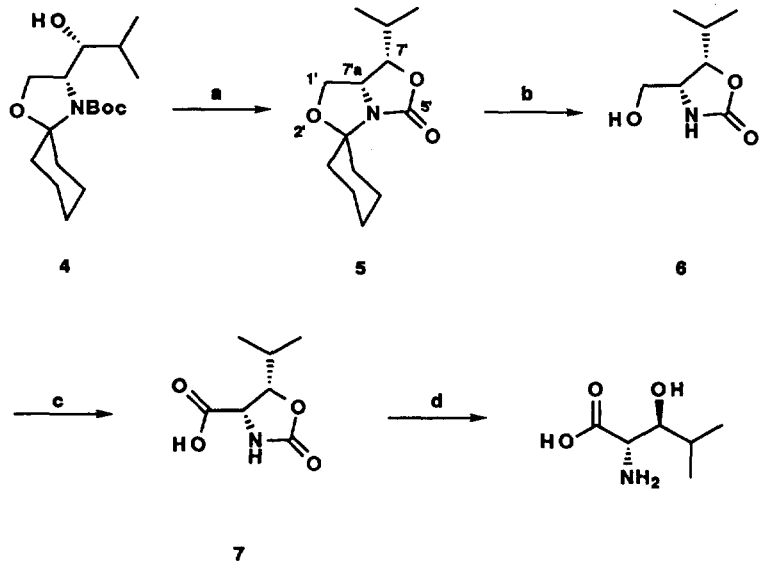
Treatment of the alcohol **4** with triflic anhydride allowed for the formation of the spirobicyclic compound **5**[9] in good yield (Scheme 2). It is believed that this triflate-mediated cyclization occurs with inversion *via* participation of the urethane carbonyl. Supporting evidence for the formation of the *erythro* product was obtained from the coupling constants of **5** and the oxazolidinones **6** and **7** ($J_{7'\text{-}7'a}$ 7.8 Hz for **5**, $J_{4\text{-}5}$ 6.8 Hz for **6** and $J_{4\text{-}5}$ 8.5 Hz for **7**).[10] Similar rearrangements have previously been reported in the formation of oxazolines from tosyl and chlorosulfinyl derivatives of *N*-benzoyl-β-hydroxy amino acids[11a] and of oxazolidones from N-Boc, O-tosyl derivatives of amino alcohols.[11b]



(a) i) MeOH, $SOCl_2$; ii) $(Boc)_2O$, Et_3N, CH_2Cl_2 (94 %). (b) cyclohexanone, TsOH, PhH, reflux, 40h, Soxhlet, 4Å mol. sieves (82 %). (c) i) LiCl, $NaBH_4$, 0-25 °C, THF, EtOH (92 %); ii) Dess-Martin periodinane (75 %). (d) isopropylmagnesium chloride, THF, -78 °C (66 %).

Scheme 1

Hydrolysis of the spirobicyclic compound **5** was achieved with boron trifluoride-acetic acid complex to afford oxazolidinone **6**. Subsequent Jones oxidation yielded the oxazolidinone carboxylic acid **7** which was subjected to hydrolysis, and treatment of the corresponding amino acid salt with an ion exchange resin afforded (2*S*, 3*S*)-3-hydroxyleucine as a white solid.[12]



(a) Tf_2O, CH_2Cl_2, 2,6-di^{t}Bu-4-MePy, 0-25 °C (83 %). (b) BF_3.2HOAc, MeOH (80 %). (c) Jones oxidation (74 %). (d) i) 5N HCl, 100 °C; ii) Dowex-50W (200-400) (99 %).

Scheme 2

The described strategy utilizes high yielding steps and may be employed to provide any of the diastereomers of 3-hydroxyleucine. By using either L- or D-serine as the chiral precursor and by exploiting the efficient epimerization in the conversion of *erythro*- to *threo*-oxazolidinone carboxylic acids developed by Ōmura,[2e] the other diastereoisomers could be obtained.

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Dedicated to Professor Ivar Ugi on the occasion of his 65th birthday.

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3. Reviews on cyclopeptide alkaloids can be found in: (a) Joullié, M. M.; Nutt, R.; *Alkaloids: Chemical and Biological Perspectives*, vol 3, ed. S.W. Pelletier, Wiley, NY, 1985: pp. 113-168. (b) Schmidt, U.; Lieberknecht, A.; Haslinger E.; *The Alkaloids*, vol 26, ed. A. Brossi, Acad. Press, NY, 1985; pp. 299-326;.
4. Garner, P.; Park, J. M. *Org. Synth.* **1991**, *70*, 18-28 and references therein.
5. Spectroscopic data of 4-*tert*-butyl 3-methyl 1-oxa-4-azaspiro[4.5]decane-(3*R*)-3,4-dicarboxylate **2**: R_f 0.31 (EtOAc-petroleum ether 20%, v/v); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.50-4.30 (m, 1H), 4.11-3.90 (m, 2H), 3.66 (s, 3H), 2.41-1.47 (m, 9H), 1.32 and 1.40 (s, 9H), 1.00-1.25 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 150.6, 96.0, 80.2, 66.0, 58.6, 52.1, 32.8, 32.0, 28.2, 24.2, 23.5, 23.4; IR (CH_2Cl_2) 2960 (s), 2880 (m), 1760 (s), 1700 (s), 1450 (m), 1440 (m), 1400 (s), 1370(s), 1290(m), 1240 (m), 1180 (s), 1140 (m), 1090 (m), 910 (m) cm^{-1}; MS (CI, NH_3) calcd for $C_{15}H_{25}NO_5$: m/z 299.1733, found 299.1742; 299 M^+ (12), 244 (8), 226 (12), 199 (43), 170 (23), 156 (100), 140 (8); $[\alpha]_D^{25}$ +39.8° (*c* 3.4, $CHCl_3$); Anal. Calcd for $C_{15}H_{25}NO_5$: C, 60.17; H, 8.42; N, 4.68. Found: C, 59.94; H, 8.58; N, 4.49.
6. Spectroscopic data of *tert*-butyl (3*R*)-3-formyl-1-oxa-4-azaspiro[4.5]decane-4-carboxylate **3**: R_f 0.26 (EtOAc-petroleum 7%, v/v); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.50 (d, J=18 Hz, 1H), 4.35-3.92 (m, 3H), 2.55-1.95 (m, 2H), 1.01-1.78 (m, 17H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.8, 151.3, 96.3, 96.3, 81.0, 64.6, 63.9, 41.9, 34.0, 31.3, 28.2, 27.0, 24.5, 23.2; IR ($CHCl_3$) 2970 (m), 2930 (s), 2860 (w), 1720 (m), 1700 (s), 1450 (w), 1390 (s), 1370 (s), 1170 (m), 1120 (m), 1070 (m) cm^{-1}; MS (CI, NH_3) calcd for $C_{14}H_{23}NO_4$: m/z 269.1627, found 269.1621; 270 MH^+ (14), 269 (26), 240 (30), 214 (74), 196 (25), 169 (53), 140 (100); $[\alpha]_D^{25}$ +66.0° (*c* 1.57, $CHCl_3$); Anal. Calcd for $C_{14}H_{23}NO_4$: C, 62.42; H, 8.61; N, 5.20. Found: C, 62.00; H, 9.08; N, 4.49.
7. Spectroscopic data of *tert*-butyl (3*R*)-3-[(1*R*)-1-hydroxy-2-methylpropyl]-1-oxa-4-azaspiro[4.5]-

decane-4-carboxylate **4**: m.p. 130°; R_f 0.54 (EtOAc-petroleum ether 13%, v/v); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.30 (d, J =15 Hz, 1H), 4.10-3.30 (m, 4H), 2.80-2.02 (m, 2H), 1.75-1.25 (m, 16H), 1.20-0.75 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.5, 99.0, 79.2, 76.1, 64.9, 45.5, 35.8, 31.0, 29.2, 28.4, 28.3, 27.0, 24.9, 23.4, 22.5, 20.4, 14.2; IR ($CHCl_3$) 3400 (m), 2970 (s), 2920 (s), 1700 (m), 1650 (s), 1480 (w), 1450 (w), 1400 (s), 1360 (m), 1170 (m), 1130 (m), 1090 (w), 1000 (w), 900 (w) cm^{-1}; MS (CI, NH_3) calcd for $C_{17}H_{31}NO_4$: m/z 313.2253, found 313.2246; 313 (23) 259 (12), 258 (68), 241 (26), 214 (38), 213 (56), 170 (100), 140 (98), 123 (20); $[\alpha]_D^{25}$ +48.7° (*c* 1.43, $CHCl_3$); Anal. Calcd for $C_{17}H_{31}NO_4$: C, 65.13; H, 9.97; N, 4.47. Found: C, 64.73; H, 10.27; N, 4.30.

8. A full account of the synthesis of 3-hydroxyleucine together with the synthesis of other related building blocks within the chiral pool will be published in due course.

9. Spectroscopic data of (7'*S*, 7'a*R*)-dihydro-7'-isopropylspiro[cyclohexane-1,3'-[1*H*, 3*H*, 5*H*]oxazolo-[3,4-*c*]oxazol]-5'-one **5**: m.p. 98°; R_f 0.57 (EtOAc-petroleum ether 20%, v/v); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.25 (m, 1H), 4.15 (dd, J=10.4, 7.8 Hz, 1H), 3.93 (dd, J=8.1, 6.6 Hz, 1H), 3.65 (m, 1H), 2.43 (m, 1H), 1.90-1.41 (m, 9H), 1.31 (m, 1H), 1.08 (d, J=6.7 Hz, 3H), 0.85 (d, J=6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.2, 96.5, 79.9, 63.1, 60.6, 37.6, 31.9, 29.5, 24.9, 23.6, 23.1, 19.8, 18.0; IR (film) 2960 (m), 1738 (s) cm^{-1}; MS (CI, NH_3) calcd for $C_{13}H_{22}NO_3$: m/z 240.1599, found 240.1606; 257 $(M+NH_4)^+$ (5), 240 $(M+H)^+$ (100), 196 (5), 152 (5); $[\alpha]_D^{28}$ +36.0° (*c* 0.5, $CHCl_3$); Anal. Calcd for : C, 65.25; H, 8.84; N, 5.85. Found: C, 65.14; H, 8.78; N, 5.90.

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12. $[\alpha]_D^{25}$ + 35.0° (*c* 1.0, H_2O) {lit.[2e] +37.0° (*c* 1.0, H_2O)}; the sample proved identical in all other aspects to that provided by Professor S. Ōmura.

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