An Improved Synthesis of (4*S*,5*S*)-2-Phenyl-4-(methoxycarbonyl)-5-isopropyloxazoline from (*S*)-Phenylglycinol

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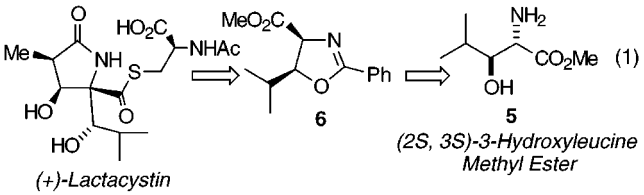
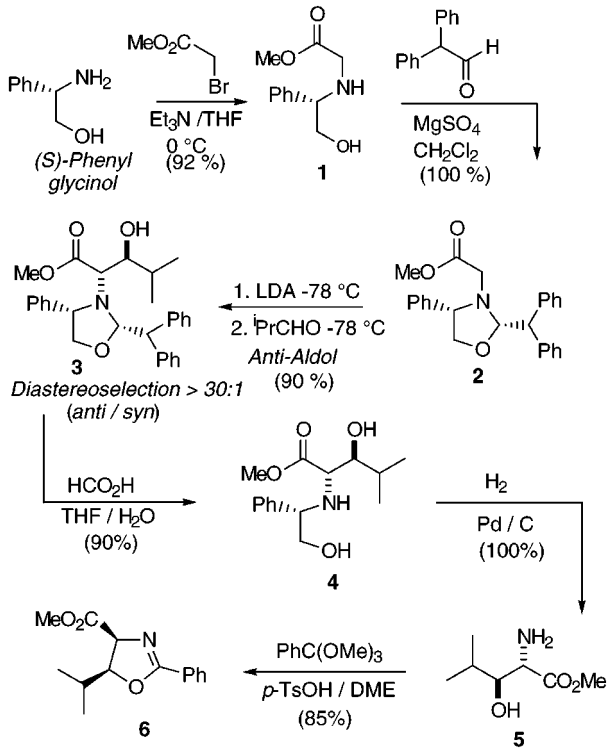
Introduction

(4*S*,5*S*)-2-Phenyl-4-(methoxycarbonyl)-5-isopropyloxazoline (**6**) is a useful chiral auxiliary for the stoichiometric, asymmetric aldol reaction. This auxiliary has been utilized in asymmetric alkylation reactions[1] and more recently in asymmetric aldol reactions aimed at the synthesis of the neurotrophic agent, (+)-lactacystin (eq 1).[2] Currently, the most efficient approach to oxazoline **6** requires 10 steps with an overall yield of 60% from (*E*)-4-methyl-2-penten-1-ol.[2a] The central issue in the preparation of **6** relies on the asymmetric synthesis of the 3-hydroxyleucine derivative **5**. 3-Hydroxyleucine has attracted considerable attention as an amino acid component of numerous peptide antibiotics such as azinothricin,[3] telomycin,[4] and lysobacin.[5] More recently, it has been sought after as a key synthon in the synthesis of (+)-lactacystin and its analogues.



To develop an efficient synthesis of oxazoline **6**, we first needed to devise a concise and stereoselective synthesis of hydroxyleucine **5**. Numerous approaches to the 3-hydroxyleucine synthon **5** have been reported. However, they either lack the flexibility to prepare the various isomers, require the preparation of a chiral catalyst system, or are prohibitively lengthy for large scale preparations.[6] As part of a program aimed at the synthesis of (+)-lactacystin, as well as its analogues, we required an efficient method for the preparation of multiple grams of the (2*S*,3*S*)-isomer of 3-hydroxyleucine methyl ester. Herein we describe an efficient and concise approach to the synthesis of (2*S*,3*S*)-hydroxyleucine methyl ester (**5**) employing commercially available materials utilizing an underdeveloped *anti*-selective aldol reaction between a oxazolidine-based chiral glycine enolate and isobutyraldehyde.

Scheme 1



Results and Discussion

Our preparation of 3-hydroxyleucine methyl ester **5** is outlined in Scheme 1 and makes use of an *anti*-selective aldol reaction of chiral oxazolidine **2** derived from (*S*)-phenylglycinol.[7] Preparation of the oxazolidine auxiliary began with the *N*-alkylation of (*S*)-phenylglycinol[8] with methyl bromoacetate to afford **1**. Condensation of **1** with diphenylacetaldehyde and anhydrous magnesium sulfate at ambient temperature afforded the 2,4-disubstituted oxazolidine **2** as a single diastereomer[9] which serves as the chiral glycine equivalent for the subsequent aldol. The *anti*-selective aldol reaction between the lithium enolate of the phenylglycinol derived oxazolidine **2** with

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(8) Prepared by reduction of (*S*)-phenylglycine with $NaBH_4/H_2SO_4$ see: Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1992,** *33*, 5517−5518.

(9) The relative stereochemical assignment of the C2 center of the phenylglycinol derived oxazolidines has been established to be a *cis*-relationship based on recent ^1H NMR studies: see Arseniyadis, S.; Huang, P. Q.; Morellet, N.; Beloeil, J.-C.; Husson, H.-P. *Heterocycles* **1990**, *31*, 1789−1799 and references therein.

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isobutyraldehyde afforded the aldol product **3** as a single diastereomer (de > 30:1 *anti*/*syn*). The aldol bond construction of such α-amino esters have been shown to exhibit high levels of anti stereoselection (simple diastereoselectivity).[10] Such literature precedent warranted an investigation into the use of phenylglycinol derived oxazolidine **2** for the preparation of the chiral isopropyloxazoline **6**. The stereochemical outcome of this aldol condensation is critically dependent on the geometry of the glycine enolate. However, there are conflicting literature precedents regarding the conformational preference of such glycine enolates.[11] The high levels of *anti*-stereoselection observed in this aldol reaction would require either a chairlike transition state via the *E(O)*-enolate or a twist-boat transition structure via the *Z(O)*-enolate. While the steric bulk of the auxiliary favors the (*E*) geometry, the potential for internal coordination of the amine moiety to the lithium counterion may predispose the glycine enolate to the (*Z*) geometry. Studies are ongoing to determine the operative enolate configuration with oxazolidine **2**. Amino alcohol **3** was then treated with formic acid to hydrolyze the oxazolidine. Subsequent heterogeneous hydrogenation to remove the phenylglycinol derived amino protecting group afforded the (2*S*,3*S*)-3-hydroxyleucine methyl ester **5**.[12] Finally, treatment of **5** with trimethyl orthobenzoate in the presence of *p*-toluenesulfonic acid affords the *cis*-oxazoline **6**.[13] The virtues of this approach are apparent from the following: (i) the concise nature of the synthetic sequence, (ii) the auxiliary is prepared from readily available and inexpensive chiral pool materials with high optical purity, (iii) preparation of the auxiliary and deprotection steps, which include acid-promoted hydrolysis of oxazolidine and hydrogenation of the benzylic *N*-protecting group, are conducted under mild reaction conditions which in principle makes the synthesis readily scaled to gram quantities of oxazoline, (iv) the (2*R*,3*R*)-antipode can be accessed by using the (*R*)-phenylglycinol derived auxiliary.

Conclusion

In summary, multigram quantities of (2*S*,3*S*)-3-hydroxyleucine methyl ester and resulting oxazoline **6** can be readily prepared in 63% overall yield with high enantiomeric purity using the concise sequence described above. Additionally, only intermediates **3** and the final product **6** require chromatographic purification; all other intermediates can be recrystallized or carried through the sequence without purification, enhancing the operational aspects of this approach for large scale synthesis. Application of the synthesis of oxazoline **6** to the synthesis of (+)-lactacystin and its analogues will be reported at a later time.

Experimental Section

^{1}H NMR spectra were recorded on a 400 MHz spectrometer at ambient temperature. ^{13}C NMR spectra were recorded on a 75.5 Hz spectrometer at ambient temperature. Chemical shifts are reported in parts per million relative to chloroform (^{1}H, δ 7.24; ^{13}C, δ 77.0), acetone (^{1}H, δ 2.05; ^{13}C, δ 29.92), or methanol (^{1}H, δ 3.31; ^{13}C, δ 49.15). All ^{13}C NMR spectra were recorded with complete proton decoupling. Infrared spectra were recorded on a FT-spectrophotometer. Optical rotations were recorded on a digital polarimeter at 589 nm. High resolution mass spectra were obtained in the Boston University Mass Spectrometry Laboratory. Analytical thin-layer chromatography was performed on 0.25 mm silica gel 60-F plates. Flash chromatography was performed as previously described.[14] Melting points were determined on a Thomas-Hoover apparatus. When specified as "anhydrous", solvents were distilled and/or stored over 4 Å sieves prior to use. All reactions were carried out in oven-dried glassware under a dry argon atmosphere. Tetrahydrofuran was freshly distilled under argon from sodium/benzophenone ketyl. Dichloromethane (CH_2Cl_2) and diisopropylamine were distilled from calcium hydride. Isobutyraldehyde was distilled from calcium sulfate and stored over 4 Å sieves. The (*S*)-phenylglycine, methyl bromoacetate, diphenylacetaldehyde, trimethyl orthobenzoate, and dimethoxyethane were purchased from Aldrich and used as received. The anhydrous magnesium sulfate was purchased from J. T. Baker and used as received.

***N*-(Methylacetyl)-(*S*)-phenylglycinol (1).** To a solution of (*S*)-phenylglycinol (10.0 g, 72.9 mmol) in 300 mL of dry THF (0.25 M) at 0 °C was added triethylamine (12.3 mL, 87.6 mmol, 1.2 equiv) followed by dropwise addition of a solution of methyl bromoacetate (7.6 mL, 80.2 mmol, 1.1 equiv) in THF (80 mL, 1 M). The reaction mixture was warmed to room temperature over a 10 h period and subsequently diluted with saturated NH_4Cl solution (60 mL). The reaction mixture was extracted with Et_2O (3 × 25 mL), dried ($MgSO_4$), and concentrated in vacuo to afford a white solid. Purification is accomplished either by recrystallization from 1:1 EtOAc/PE or on SiO_2 (50% EtOAc/PE) to afford **1** as a white solid (14.0 g, 92%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.25 (m, 5H), 3.78−3.75 (m, 1H), 3.70 (dd, 1H, J_1 = 4.4 Hz, J_2 = 4.0 Hz), 3.65 (s, 3H), 3.60−3.55 (m, 1H), 3.35 and 3.25 (ABq, 2H, J_{AB} = 17.6 Hz), 2.49 (s, br, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 173.0, 140.0, 127.8, 127.3, 66.9, 64.2, 51.8, 48.3; IR (neat) ν_{max} 3384, 2954, 1718, 1646; CIMS (NH_3 gas) 210.1, 178.1, 118.1, 91.0; CIHRMS M + H^+ (calculated for $C_{11}H_{16}NO_3$): 210.1130, found: 210.1117; $[\alpha]^{23}_D$ = −80.7° (*c* = 1.23, $CHCl_3$); mp = 69−70 °C.

(2*S*,4*S*)-2-(Diphenylmethyl)-3-*N*-(methylacetyl)-4-phenyloxazolidine (2). To a solution of *N*-(methylacetyl)-(*S*)-phenylglycinol (**1**) (14.0 g, 67.0 mmol) in CH_2Cl_2 (260 mL, 0.25 M) was added diphenylacetaldehyde (13.0 mL, 73.8 mmol, 1.1 equiv) followed by the addition of anhydrous magnesium sulfate (8.0 g, 67.0 mmol, 1.0 equiv). The reaction mixture was stirred at ambient temperature for 12 h and subsequently diluted with H_2O (200 mL). The reaction mixture was extracted with Et_2O (3 × 25 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification is accomplished either by recrystallization from 1:3 EtOAc/PE or on SiO_2 (10% EtOAc/PE) to afford **2** as a light yellow solid (25.8 g, 100%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52−7.25 (m, 13H), 7.16−7.13 (m, 2H), 5.55 (d, 1H, *J* = 4.0 Hz), 4.37 (dd, 1H, J_1 = 6.8 Hz, J_2 = 7.2 Hz), 4.26 (d, 1H, *J* = 4.0 Hz), 4.19−4.15 (m, 1H), 3.62 (s, 3H), 3.35−3.28 (m, 2H), 3.19 (d, 1H, *J* = 17.6 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.0, 141.7, 140.6, 138.8, 132.4, 130.0, 129.2, 129.0, 128.5, 128.4, 127.8, 127.6, 126.5, 126.4, 73.7, 65.3, 55.4, 51.3, 48.7; IR (neat) ν_{max} 3027, 1740, 1600, 1451; CIMS (NH_3 gas) 388.3, 220.1, 192.1, 132.1; CIHRMS M + H^+ (calculated for $C_{25}H_{26}NO_3$): 388.1913, found: 388.1939; $[\alpha]^{23}_D$ = +2.8° (*c* = 1.14, $CHCl_3$); mp = 58−60 °C.

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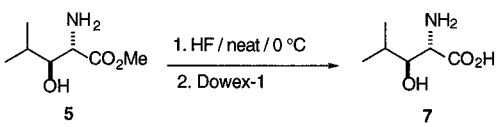
(12) The absolute stereochemistry of **5** was determined by conversion to (2*S*,3*S*)-3-hydroxyleucine (**7**) via the following sequence:



5 **7**

Optical rotation and mp for compound **7**: $[\alpha]^{23}_D$ = +37.2° (*c* = 0.40, 1 N aq HCl) {lit. $[\alpha]^{20}_D$ = +35.0° (*c* = 0.41, 1 N aq HCl)}, mp = 219−221 °C (lit. mp = 218−222 °C); see ref 4.

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***Anti*-Aldol Product (3).** To a cooled solution of (2*S*,4*S*)-2-(diphenylmethyl)-3-*N*-(methylacetyl)-4-phenyloxazolidine (**2**) (10.0 g, 25.8 mmol) at −78 °C in 260 mL THF (0.1 M) was added dropwise lithium diisopropylamide (28.4 mmol, 1.1 equiv). The bright orange solution was stirred at −78 °C for 1 h, after which time a solution of isobutyraldehyde (2.8 mL, 31.0 mmol, 1.2 equiv) in THF (31 mL, 1.0 M) was added. The light yellow solution was stirred at −78 °C for an additional 1 h and subsequently diluted with $NaHCO_3$ solution and warmed to room temperature. The reaction mixture was extracted with EtOAc (3 × 25 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification on SiO_2 (5% → 20% EtOAc/PE) afforded **3** as a light yellow oil, single diastereomer (de > 30:1) (10.7 g, 90%): ^{1}H NMR (400 MHz, acetone-d_6) δ 7.61−7.18 (m, 13H), 7.08−7.00 (m, 2H), 5.30 (d, 1H, J = 5.2 Hz), 4.85 (t, 1H, J = 6.0 Hz), 4.40 (d, 1H, J = 4.8 Hz), 4.15 (t, 1H, J = 6.2 Hz), 3.70 (s, 3H), 3.64−3.58 (m, 2H), 3.42−3.38 (m, 2H), 1.63−1.58 (m, 1H), 0.60 (d, 3H, J = 6.4 Hz), 0.28 (d, 3H, J = 6.8 Hz); ^{13}C NMR (75.5 MHz, acetone-d_6) δ 173.1, 144.6, 143.2, 142.1, 130.8, 129.8, 129.3, 128.8, 128.5, 128.3, 127.6, 127.2, 127.1, 98.1, 74.7, 74.5, 66.2, 61.5, 56.0, 51.3, 28.6, 19.9, 15.0; IR (neat) ν_{max} 3461, 3028, 1727, 1601, 1452; CIMS (NH_3 gas) 460.3, 293.2, 264.2, 220.1, 167.1; CIHRMS M + H^+ (calculated for $C_{29}H_{34}NO_4$): 460.2488, found: 460.2452; $[\alpha]^{23}_D$ = +17.8° (c = 2.42, $CHCl_3$).

(2*S*,3*S*)-2-*N*-((*S*)-Phenylglycinyl)-3-hydroxyleucine Methyl Ester (4). A dilute solution of aldol product **3** (10.7 g, 23.3 mmol) in a 3:1:1 mixture of THF/H_2O/formic acid (230 mL, 0.1 M) was stirred at ambient temperature for 24 h and subsequently diluted portionwise with $NaHCO_3$ solution to pH 7 (100 mL). The reaction mixture was extracted with EtOAc (3 × 25 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification is accomplished either by recrystallization from 1:1 EtOAc/PE or on SiO_2 (50% → 100% EtOAc/PE) to afford **4** as a white solid (5.2 g, 80%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.26 (m, 5H), 3.83−3.77 (m, 2H), 3.69−3.66 (m, 1H), 3.62−3.59 (m, 1H), 3.57−3.41 (m, 2H), 3.42 (s, 3H), 2.48 (s, br, 2H), 1.77−1.72 (m, 1H), 0.99 (d, 3H, J = 6.8 Hz), 0.90 (d, 3H, J = 6.4 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 174.1, 140.0, 128.5, 127.8, 127.2, 77.8, 66.3, 63.7, 61.4, 51.6, 30.8, 19.2, 18.2; IR (neat) ν_{max} 3400, 1710, 1640, 1400; CIMS (NH_3 gas) 282.2, 250.2, 191.0, 183.0, 104.0; CIHRMS M + H^+ (calculated for $C_{15}H_{24}NO_4$): 282.1705, found: 282.1703; $[\alpha]^{23}_D$ = +43.9° (c = 1.63, $CHCl_3$); mp = 70−72 °C.

(2*S*,3*S*)-3-Hydroxyleucine Methyl Ester (5). A dilute solution of (2*S*,3*S*)-2-*N*-((*S*)-phenylglycinyl)-3-hydroxyleucine methyl ester (**4**) (5.0 g, 17.8 mmol) in anhydrous MeOH (350 mL, 0.050 M) was treated with 10% Pd−C (1.0 g, 20 wt %). The suspension was stirred under 1 atm of hydrogen for 24 h. The resulting suspension was filtered through Celite, washed with MeOH, and concentrated in vacuo. Purification is accomplished either by recrystallization from 1:1 EtOAc/PE or on SiO_2 (50% → 100% EtOAc/PE) to afford **5** as a white solid (2.8 g, 100%): ^{1}H NMR (400 MHz, CD_3OD) δ 4.12−4.06 (m, 1H), 3.85 (s, 3H), 3.70−3.67 (m, 1H), 2.85 (s, br, 3H), 1.78−1.74 (m, 1H), 1.02 (d, 3H, J = 4.0 Hz), 1.01 (d, 3H, J = 4.4 Hz); ^{13}C NMR (75.5 MHz, CD_3OD) δ 129.6, 80.4, 57.9, 52.5, 31.7, 20.3, 18.7; IR (neat) ν_{max} 3433, 1646, 1457; CIMS (NH_3 gas) 162.1, 154.1, 112.1, 104.0; CIHRMS M + H^+ (calculated for $C_7H_{15}NO_3$): 162.1130, found: 162.1117; $[\alpha]^{23}_D$ = +10.5° (c = 0.39, MeOH); mp = 100−103 °C (MeOH).

(4*S*,5*S*)-2-Phenyl-4-(methoxycarbonyl)-5-isopropyloxazoline (6). To a solution of (2*S*,3*S*)-3-hydroxyleucine methyl ester (**5**) (1.00 g, 6.2 mmol) in dimethoxyethane (120 mL, 0.5 M) was added *p*-toluenesulfonic acid (0.56 g, 6.2 mmol, 1.0 equiv) followed by trimethyl orthobenzoate (3.20 mL, 18.6 mmol, 3.0 equiv). The reaction mixture was refluxed 4 h and subsequently diluted with H_2O (20 mL). The reaction mixture was extracted with $CHCl_3$ (3 × 25 mL), dried ($MgSO_4$), and concentrated in vacuo to afford the crude oxazoline. Purification on SiO_2 (10% EtOAc/PE) afforded **6** as a light yellow oil (1.35 g, 85%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99−7.96 (m, 2H), 7.48−7.46 (m, 1H), 7.41−7.38 (m, 2H), 4.65 (t, 1H, J = 7.2 Hz), 4.55 (d, 1H, J = 7.2 Hz), 3.79 (s, 3H), 1.95−1.93 (m, 1H), 1.01 (d, 3H, J = 6.8 Hz), 0.98 (d, 3H, J = 6.8 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 172.0, 165.7, 131.7, 128.5, 128.3, 127.1, 87.2, 71.2, 52.6, 32.4, 17.4, 17.2; IR (neat) ν_{max} 2963, 2877, 1740, 1646, 1581, 1451; CIMS (NH_3 gas) 247.1, 188.1, 105.0, 49.0, 30.0; CIHRMS M^+ (calculated for $C_{14}H_{17}NO_3$): 247.1208, found: 247.1220; $[\alpha]^{23}_D$ = −105.7° (c = 1.32, $CHCl_3$).

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Supporting Information Available: ^{1}H and ^{13}C spectral data for all reaction products (12 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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