Stereoselective Synthesis of MeBmt and Methyl (4*R*,5*S*)-5-Isopropyl-2-phenyloxazoline-4-carboxylate by a Pd-Catalyzed Equilibration

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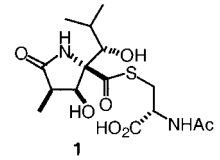
Introduction

Lactacystin (**1**), isolated in 1991,[1] has been a target of intense study recently due to its highly potent and selective inhibition of the 20 S proteasome.[2,3] The first total synthesis of **1** was reported by the Corey group in 1992, and subsequent evolution of the synthesis and the preparation of the equally potent lactone analogue **2** have been described.[4] A variety of other synthetic approaches have appeared utilizing chiral sources such as D-glucose,[5] D-glutamic acid,[6] and an allylic alcohol derived from a Sharpless asymmetric epoxidation.[7] The 3-hydroxyleucine derivative, oxazoline **3**, has been employed as a key intermediate in the total synthesis of lactacystin. Omura and Smith[8] prepared **3** from (*E*)-4-methyl-3-penten-1-ol, also via Sharpless epoxidation, in 10 steps with 41% overall yield. Another route utilized a Sharpless asymmetric dihydroxylation of methyl 4-methyl-2-pentenoate with 70% ee, which could be improved to >99% ee by one recrystallization.[9] The Panek group has recently communicated a more direct route from *p*-bromophenyl (*E*)-4-methyl-2-pentenoate utilizing an asymmetric aminohydroxylation reaction.[10] Regioselectivity was 7:1 favoring the α-amino ester with 87% ee. And more recently, a chiral auxiliary-directed conjugate addition of *O*-benzylhydroxylamine (80% de), followed by aziridine formation, and ring opening, afforded a similar hydroxyleucine derivative.[11]

MeBmt (**4**), another unusual α-amino-*β*-hydroxy acid, is an important constituent of cyclosporin.[12] The first synthesis of MeBmt from L-(+)-diethyl tartrate was reported by Wenger in 1983.[13] Since then, a number of synthetic approaches have appeared relying on asymmetric aldol reactions,[14] opening of chiral epoxides,[15] or beginning with natural chiral building blocks (D-isoascorbic acid,[16] L-glutamic acid,[17] D-2-deoxyribose,[18] D-glucose,[19] and D-serine[20]). Most recently, a stereoselective radical addition to a 2-oxazolone heterocycle was reported.[21]



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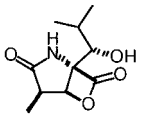

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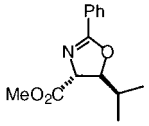

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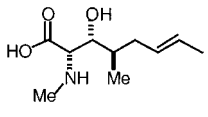

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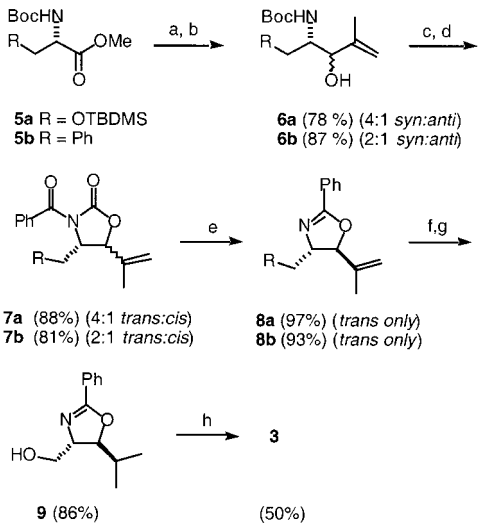
Scheme 1. Preparation and Isomerization of 2-Propenyloxazolines[a]



[a] Key: (a) DIBAL-H, Tol; (b) 2-propenylmagnesium bromide, THF; (c) NaH, THF; (d) PhCOCl, NaH, THF; (e) 0.5 mol % $Pd_2(dba)_3CHCl_3$, 2 mol % dppp, THF, 45 °C; (f) $(PH_3P)_3RhCl$, H_2, PhH; (g) TBAF, THF; (h) cat. CrO_3, HIO_5, then CH_2N_2.

As part of our program to synthesize aminohydroxy acids, we have shown that diastereomeric mixtures of 5-vinyloxazolidinones derived from α-amino acids undergo palladium-catalyzed oxazoline formation by ring opening, loss of CO_2, and subsequent cyclization. Thermodynamic equilibration via π-allyl inversion afforded predominantly trans diastereomers in ratios up to 16:1.[22] We anticipated that the more sterically encumbered 2-propenyl group should present even greater selectivity and the resulting oxazoline could be utilized as a common intermediate for the preparation of a variety of novel aminohydroxy acids. We report herein our investigation and application of this methodology to the asymmetric synthesis of the title compounds.

Results and Discussion

Preparation and Isomerization of 2-Propenyloxazolines. To study the equilibration of 5-(2-propenyl)-oxazolines, the oxazolidinones **7a** and **7b** were prepared from their respective *N*-BOC-protected amino esters as shown in Scheme 1. Diisobutylaluminum hydride reduction of this ester followed by the addition of 2-propenylmagnesium bromide to the crude aldehyde afforded the alcohols **6a** and **6b** with modest diastereoselectivity (syn/anti 4:1 and 2:1, respectively).[23] Cyclization of the alcohol onto the BOC carbonyl was accomplished by stirring with NaH in THF, and acylation afforded the desired oxazolidinones **7a** and **7b**. We were gratified to find that the palladium-catalyzed oxazoline formation and equilibration reaction provided oxazolines **8a** and **8b** with excellent yield and diastereoselectivity (single isomer).[24] The reaction was amenable to scale-up. Thus, the serine derivative **7a** was efficiently transformed into **8a** on greater than a 5 g scale in 4 h utilizing only 0.5 mol % $Pd_2(dba)_3CHCl_3$ and 2 mol % bis(diphenylphosphino)-propane (dppp). Given this success, even lower catalyst levels should be attainable (vide infra).

Preparation of (4*R*,5*S*)-2-Phenyl-4-(methoxycarbonyl)-5-isopropyloxazoline (3). The oxazoline **8a** was employed in the synthesis of the hydroxyleucine derivative **3** (Scheme 1). Hydrogenation using Wilkinson's catalyst followed by desilylation with tetrabutylammonium fluoride (TBAF) gave alcohol **9**. Subsequent oxidation with catalytic chromium trioxide/periodic acid[25] and treatment with diazomethane afforded the title compound in moderate yield.

Synthesis of MeBmt. The oxazoline *ent*-**8a**, prepared in an analogous fashion from the D-serine derivative *ent*-**5a**, served as an intermediate for the synthesis of MeBmt. As shown in Scheme 2, hydroboration with 9-BBN followed by a Suzuki coupling protocol[26] with (*E*)-1-bromopropene afforded the chain-extended oxazoline **10** as a 5.5:1 mixture of diastereomers. Deprotection of the silyl ether gave the alcohol **11** as a solid that could be recrystallized from ether/hexane to enhance the diastereomeric purity (dr 16:1, 59% yield; 31% isolated from mother liquor, dr 1.7:1). Hydrolysis of the oxazoline under acidic conditions yielded the ammonium hydrochloride benzoate, which, upon neutralization in the presence of di-*tert*-butyl dicarbonate, resulted in the formation of the *N*-BOC-aminodiol monobenzoate **12** in high yield. Protection of the primary alcohol to provide **13** was followed by methylation of the nitrogen and methanolysis of the benzoate to give **14** via cyclization of the alkoxide onto the BOC group. Oxidation and esterification afforded the known ester **15**,[14a,g] which was subsequently hydrolyzed with KOH[13] to afford MeBmt as the free aminohydroxy acid.

Conclusion

We have demonstrated that the palladium-mediated epimerization of 5-(2-propenyl)oxazolines affords complete stereocontrol of vicinal amino and hydroxy functionalities via a thermodynamic equilibration. This provides a facile and practical route to amino alcohol derivatives in stereochemically pure form without relying on intricate chelation controlled additions.[23] The oxazoline **8a** was utilized in an expedient and efficient synthesis of **3**, a key intermediate for the synthesis of lactacystin. MeBmt was synthesized from *ent*-**8a** utilizing a key hydroboration/Suzuki coupling protocol. Considering the synthetic utility of unnatural amino acids in organic synthesis, unsaturated oxazolines **8a** and **8b** are valuable intermediates for the preparation of novel amino acids.

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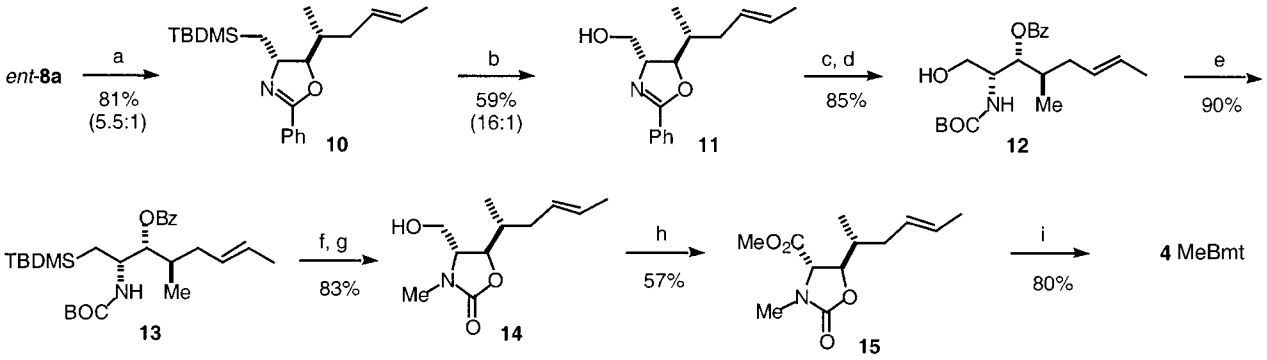
Scheme 2. Preparation of MeBMT[a]



[a] Key: (a) 9-BBN, THf; (ii) (*E*)-1-bromopropene, $Pd(PPh_3)_4$ (cat.), THF; (b) TBAF, THF, then recryst; (c) 2 N HCl, THF; (d) $NAHCO_3$, BOC_2O; (e) TBDMSCl, imidazole; (f) NaH, MeI; (g) NaOMe, MeO; (h) PDC, DMF then CH_2N_2; (i) 2 N KOH.

Experimental Section

General Methods. All reactions were carried out under an inert atmosphere of dry nitrogen. Reagents were obtained commercially and used as provided unless otherwise noted. $Pd_2dba_3CHCl_3$ (dba = dibenzylidineacetone) was prepared as described previously.[27] Reaction solvents were freshly distilled under nitrogen from standard drying agents prior to use. NMR spectra were recorded on JEOL 400, 270 MHz or Varian Inova 500, 400, or 300 MHz instruments. Chemical shifts are reported in ppm relative to residual solvent as internal standard. Elemental analyses were obtained from MHW Laboratories. Optical rotations were recorded on a JASCO-DIP-370 polarimeter. Melting points were uncorrected.

(4*S*)-4-*tert*-Butoxycarbonylamino-5-*tert*-butyldimethylsilyloxy-2-methylpent-1-en-3-ol (6a). DIBAL-H (35 mL, 1.5 M in toluene, 53 mmol) was added dropwise over a period of 1 h into a solution of ester **5a** (7.0 g, 21 mmol) in toluene (100 mL) at −78 °C. The reaction was allowed to stir at −78 °C for 2 h, and methanol (15 mL) was added dropwise at the same temperature. After warming to 0 °C, the reaction mixture was poured into a solution of saturated aqueous sodium potassium tartrate (250 mL) and ethyl acetate (150 mL) and stirred for 30 min. The organic layer was separated, and the aqueous layer was further extracted with ethyl acetate (2 × 100 mL). The combined organic extracts were washed with water and brine, dried over $MgSO_4$, and concentrated to afford the crude aldehyde. To the crude aldehyde in THF (100 mL) at 0 °C was added a solution of 2-propenylmagnesium bromide (prepared freshly from magnesium (1.53 g, 63 mmol) and 2-bromopropene (5.6 mL, 63 mmol) in THF (75 mL) and the mixture stirred at ambient temperature for 20 h. The reaction was quenched with saturated aqueous NH_4Cl solution and extracted with ether (3 × 100 mL). The organic layer was washed with water and brine, dried over $MgSO_4$, concentrated, and purified by column chromatography over silica gel (1:16 ethyl acetate/hexane) to afford the alcohol **6a** (5.67 g, 78%) as a colorless oil in a 4:1 mixture of syn and anti isomers, respectively: ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.10 (bs, 0.2H, anti), 5.05 (bs, 0.8H, syn), 5.02 (bs, 0.2H, anti), 4.98 (m, 0.8H, syn), 4.91 (bs, 0.8H, syn), 4.90 (m, 0.2H, anti), 4.32 (bs, 0.8H, syn), 4.25−4.14 (m, 2H, syn and anti), 3.92−3.60 (m, 6H, syn and anti), 3.47 (bs, 2H, syn and anti), 1.73 (s, 0.6H, anti), 1.72 (s, 2.4H, syn), 1.43 (s, 1.8H, anti), 1.41 (s, 7.2H, syn), 0.88 (s, 7.2H, syn), 0.875 (s, 1.8H, anti), 0.06 (s, 4.8H, syn), 0.05 (s, 0.6H, anti), 0.04 (s, 0.6H, anti); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 156.4 (syn), 155.9 (anti), 144.8 (anti), 144.0 (syn), 111.8 (syn and anti), 79.4 (syn), 77.7 (anti), 75.5 (syn and anti), 65.3 (syn), 63.3 (anti), 52.5 (syn), 51.5 (anti), 28.5 (syn), 28.4 (anti), 25.9 (syn), 25.7 (anti), 19.1 (syn and anti), 18.2 (anti), 18.1 (syn), −5.5 (syn), −5.6 (anti); IR (neat film) 3446, 1710, 1502 cm^{-1}. Anal. Calcd for $C_{17}H_{35}NO_4Si$: C, 59.09; H, 10.21; N, 4.05. Found: C, 58.81; H, 10.10; N, 4.17.

(4*S*)-4-*tert*-Butoxycarbonylamino-2-methyl-5-phenylpent-1-en-3-ol (6b): colorless oil (yield 87%) (2:1 mixture of syn and anti); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.4−7.1 (m, 10H, syn and anti), 5.07 (s, 0.33H, anti), 5.02 (s, 0.67H, syn), 4.98 (s, 0.33H, anti), 4.91 (s, 0.67H, syn), 4.82 (d, J = 8.1 Hz, 0.67H, syn), 4.71 (d, J = 6.7 Hz, 0.33H, anti), 4.19 (s, 0.33H, syn), 4.05−3.78 (m, 4H, syn and anti), 2.96−2.52 (m, 4H, syn and anti), 1.80 (s, 1H, anti), 1.68 (s, 2H, syn), 1.37 (s, 6H, syn), 1.33 (s, 3H, anti); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 156.4 (syn), 155.9 (anti), 145.5 (syn), 144.9 (anti), 138.6 (syn and anti), 129.5 (anti), 129.4 (syn), 128.5 (syn), 128.4 (anti), 126.4 (syn), 126.2 (anti), 112.3 (anti), 111.5 (syn), 79.4 (syn and anti), 74.7 (syn and anti), 54.0 (syn), 53.8 (anti), 38.50 (syn), 34.4 (anti), 28.4 (syn and anti), 19.2 (anti), 19.1 (syn); IR (neat film) 3420, 2978, 1691, 1498, 1367, 1170 cm^{-1}. Anal. Calcd for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65; N, 4.81. Found: C, 70.09; H, 8.36; N, 4.92.

(4*S*)-3-Benzoyl-4-*tert*-butyldimethylsilyloxymethyl-5-(2-propenyl)oxazolidin-2-one (7a). To a suspension of NaH (1.32 g, 60% in mineral oil, 33 mmol) in THF (30 mL) at 0 °C was added a solution of the alcohol **6a** (5.67 g, 16 mmol) in THF (90 mL), and the mixture was allowed to stir at room temperature for 12 h. It was cooled to 0 °C, and benzoyl chloride (2.3 mL, 20 mmol) was added dropwise. After being stirred for 1 h at room temperature, the reaction mixture was carefully quenched with water and extracted with ether (3 × 100 mL). The combined organic extracts were washed with water and brine, dried over $MgSO_4$, concentrated, and purified by column chromatography over silica gel (graduated from 1:12 to 1:7, ethyl acetate/hexane) to yield the oxazolidinone **7a** (5.45 g, 88%) as a colorless oil in a 4:1 mixture of trans and cis isomers, respectively: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65−7.59 (m, 4H, cis and trans), 7.56−7.5 (m, 2H, cis and trans), 7.46−7.39 (m, 4H, cis and trans), 5.29 (bs, 1H, cis), 5.17 (bs, 2H, cis and trans), 5.07 (bs, 0.8H, trans), 5.06 (d, J = 6.5 Hz, 0.2H, cis), 4.96 (d, J = 4.8 Hz, 0.8H, trans), 4.61 (m, 0.2H, cis), 4.37 (dt, J = 4.3, 2.2 Hz, 0.8H, trans), 4.16 (dd, J = 10.5, 4.3 Hz, 0.2H, cis), 4.12 (dd, J = 10.8, 4.3 Hz; 0.8H, trans), 3.78 (dd, J = 10.8, 2.5 Hz, 0.8H, trans), 3.74 (dd, J = 10.5, 1.6 Hz, 0.2H, cis), 1.86 (s, 0.6H, cis), 1.83 (s, 2.4H, trans), 0.9 (s, 7.2H, trans), 0.83 (s, 1.8H, cis), 0.08 (s, 2.4H, trans), 0.04 (s, 2.4H, trans), 0.01 (s, 0.6H, cis), 0.0 (s, 0.6H, cis); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 170.0 (trans), 169.8 (cis), 153.1 (trans), 153.0 (cis), 140.4 (trans), 136.2 (cis), 133.5 (cis), 133.3 (trans), 132.4 (trans), 132.1 (cis), 129.0 (trans), 128.8 (cis), 128.0 (trans), 127.9 (cis), 114.8 (trans), 114.5 (cis), 79.7 (cis), 79.0 (trans), 60.5 (trans), 60.1 (trans), 59.4 (cis), 58.7 (cis), 25.9 (trans), 25.8 (cis), 19.5 (cis), 18.2 (trans), 18.1 (cis), 17.0 (trans), −5.4 (trans), −5.5 (trans), −5.6 (cis); IR (neat film) 2930, 2858, 1790, 1680, 1469, 1325, 1112 cm^{-1}. Anal. Calcd for $C_{20}H_{29}NO_4Si$: C, 63.97; H, 3.73; N. 7.78. Found: C, 63.89; H, 3.73; N, 7.59.

(4*S*)-3-Benzoyl-4-benzyl-5-(2-propenyl)oxazolidin-2-one (7b): colorless oil (yield 81%) (2.4:1 mixture of trans and cis); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67−7.17 (m, 20H, trans and cis), 5.34 (s, 0.3H, cis), 5.20 (s, 0.3H, cis), 5.07−4.95 (m, 0.6H, cis), 4.99 (s, 0.7H, trans), 4.97 (s, 0.7H, trans), 4.74 (d, J = 4.5 Hz, 0.7H, trans), 4.60 (ddd, J = 8.1, 4.6, 3.5 Hz, 0.7H, trans), 3.37 (dd, J = 13.7, 3.2 Hz, 0.7H, trans), 3.14 (dd, J = 13.7, 4.3 Hz, 0.3H, cis), 3.08 (dd, J = 13.7, 8.6 Hz, 0.7H, trans), 2.94 (dd, J = 13.7, 7.7 Hz, 0.3H, cis), 1.57 (s, 2.1H, trans), 1.53 (s, 0.9H,

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cis); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 170.0 (trans), 169.4 (cis), 152.9 (trans), 152.7 (cis), 140.1 (trans), 136.7 (cis), 136.6 (cis), 135.1 (trans), 133.4 (trans), 133.3 (cis), 132.5 (trans), 132.4 (cis), 130.1 (trans), 129.9 (cis), 129.2 (cis), 129.1 (cis), 129.0 (trans), 128.6 (cis), 128.1 (trans), 128.0 (cis), 127.6 (trans), 127.0 (cis), 115.6 (cis), 114.6 (trans), 80.5 (cis), 80.0 (trans), 59.7 (trans), 59.1 (cis), 37.6 (trans), 34.4 (cis), 19.3 (cis), 17.0 (trans); IR (neat film) 1788, 1680, 1448, 1309 cm^{-1}. Anal. Calcd for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96; N, 4.36. Found: C, 75.00; H, 6.02; N, 4.47.

(4*S*,5*S*)-4-*tert*-Butyldimethylsilyloxymethyl-2-phenyl-5-(2-propenyl)oxazoline (8a). $Pd_2(dba)_3CHCl_3$ (75 mg, 0.07 mmol) and dppp (120 mg, 0.29 mmol) were taken in a Schlenk tube, evacuated, and flushed with nitrogen. THF (10 mL) was added, and the mixture was stirred at ambient temperature until the deep red solution turned yellow (15 min). A solution of the oxazolidinone **7a** (5.45 g, 14.5 mmol) in THF (50 mL) was added, and the reaction was stirred at 50 °C. After 4 h, the reaction was concentrated and purified by column chromatography over silica gel (1:19, ethyl acetate/hexane) to afford the oxazoline **8a** (4.69 g, 97%) as a colorless oil: $[\alpha]^{25}_D = +2.2$ (c = 1.18, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01−7.95 (m, 2H), 7.51−7.38 (m, 3H), 5.04 (t, J = 0.7 Hz, 1H), 4.97 (d, J = 5.9 Hz, 1H), 4.88 (t, J = 1.4 Hz, 1H), 4.05 (dt, J = 6.4, 3.8 Hz, 1H), 3.89 (dd, J = 10.2, 3.8 Hz, 1H), 3.66 (J = 10.2, 6.7 Hz, 1H), 1.74 (s, 3H), 0.85 (s, 9H), 0.07 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 164.1, 143.6, 131.4, 128.4, 128.4, 127.8, 111.7, 85.0, 73.2, 65.0, 25.9, 18.3, 17.1, −5.2, −5.3; IR (neat film) 2930, 1649, 1450, 1221 cm^{-1}. Anal. Calcd for $C_{19}H_{29}NO_2Si$: C, 68.84; H, 8.82; N, 4.22. Found: C, 69.05; H, 8.82; N, 4.21.

(4*S*,5*S*)-4-Benzyl-2-phenyl-5-(2-propenyl)oxazoline (8b): colorless oil (yield 93%); $[\alpha]^{25}_D = +38.6$ (c = 2.32, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05−7.95 (m, 2H), 7.5−7.18 (m, 8H), 4.73 (s, 2H), 4.72 (d, J = 5.9 Hz, 1H), 4.24 (dt, J = 8.3, 5.9 Hz, 1H), 3.23 (dd, J = 13.8, 5.4 Hz, 1H), 2.76 (dd, J = 13.7, 8.3 Hz, 1H), 1.51 (s, 3H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 163.3, 143.1, 137.7, 131.5, 129.8, 128.6, 128.5, 128.4, 127.8, 126.7, 112.0, 86.6, 73.0, 42.3, 16.7; IR (neat film) 1649, 1494, 1450, 696. cm^{-1}. Anal. Calcd for $C_{19}H_{19}NO$: C, 82.28; H, 6.90; N, 5.05. Found: C, 81.98; H, 6.99; N, 5.04.

(4*S*,5*S*)-5-isopropyl-4-Hydroxymethyl-2-phenyloxazoline (9). To a solution of the oxazoline **8a** (1.16 g, 3.5 mmol) in benzene (15 mL) was added $(PPh_3)_3RhCl$ (33 mg, 0.04 mmol). The mixture was shaken under H_2 at 55 psi. After 12 h, one more portion of the catalyst $(PPh_3)_3RhCl$ (33 mg, 0.04 mmol) was added and shaking continued under H_2 for 24 h. The reaction mixture was filtered through Florisil and concentrated to afford the saturated oxazoline in quantitative yield as a colorless oil: ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.95−7.85 (m, 2H), 7.5−7.32 (m, 3H), 4.34 (t, J = 5.9 Hz, 1H), 4.0 (m, 1H), 3.84 (dd, J = 10, 4 Hz, 1H), 3.57 (dd, J = 10, 7.1 Hz, 1H), 1.85 (m, 1H), 0.98 (d, J = 6.7 Hz, 3H), 0.95 (d, J = 6.7 Hz, 3H), 0.84 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 164.2, 131.3, 128.3, 128.3, 128.1, 87.5, 70.6, 65.5, 32.5, 25.9, 18.3, 17.6, 17.4, −5.2. The hydrogenated oxazoline was dissolved in dry THF (10 mL) and treated with tetrabutylammonium fluoride (TBAF) (3.85 mL, 1 M in THF) at ambient temperature. After 1 h, the reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (3 × 25 mL). The combined organic layer was washed with brine, dried over $MgSO_4$, concentrated, and recrystallized from ether/hexane (1:2) to afford alcohol **9** as white crystalline solid: mp 146 °C; $[\alpha]^{25}_D = -115.5$ (c = 0.64, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92−7.88 (m, 2H), 7.49−7.41 (m, 1H), 7.40−7.31 (m, 2H), 4.29 (t, J = 6.7 Hz, 1H), 4.03 (m, 1H), 3.95 (dd, J = 11.5, 3.1 Hz, 1H), 3.57 (dd, J = 11, 3.5 Hz, 1H), 1.90 (m, 1H), 1.74 (bs, 1H), 1.01 (d, J = 6.7 Hz, 3H), 0.96 (d, J = 7 Hz, 3H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 164.9, 131.3, 128.3, 128.2, 127.3, 86.2, 71.0, 64.6, 32.3, 17.65, 17.4; IR (neat film) 3192, 2957, 2870, 1649, 1450, 1371, 1344 cm^{-1}. Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.70; H, 7.15; N, 6.32

Methyl (4*R*,5*S*)-5-Isopropyl-2-phenyloxazoline-4-carboxylate (3). To a solution of the alcohol **9** (686 mg, 3.13 mmol) in CH_3CN (10 mL) at room temperature was added a solution of H_5IO_6 (2.14 g, 9.40 mmol) and CrO_3 (16 mg, 0.16 mmol) in CH_3CN (20 mL) over a period of 15 min, and the mixture was allowed to stir for 30 min. It was diluted with water (20 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was treated with a solution of diazomethane in ether (freshly prepared from *N*-methyl-*N*-nitrosourea[28]) to afford the methyl ester. The product was purified by column chromatography over silica gel (1:4, ethyl acetate/hexane) to yield the ester **3** (382 mg, 50%) as a pale yellow oil: $[\alpha]^{25}_D = -111.3$ (c = 0.68, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.0−7.95 (m, 2H), 7.5−7.35 (m, 3H), 4.67 (t, J = 6.8 Hz, 1H), 4.56 (d, J = 7.3 Hz, 1H), 3.80 (s, 3H), 1.95 (m, 1H), 1.02 (d, J = 6.7 Hz, 3H), 0.99 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 172.2, 165.8, 131.9, 128.6, 128.4, 127.2, 87.2, 71.4, 52.8, 32.5, 17.5, 17.4; IR (neat film) 2962, 1743, 1643, 696 cm^{-1}. Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.84; H, 6.99; N, 5.60.

(4*R*,5*R*)-4-*tert*-Butyldimethylsilyloxymethyl-5-((*E*,1*R*)-1-methyl-3-pentenyl)-2-phenyloxazoline (10). To a solution of oxazoline *ent*-**8a** (1.67 g, 5.1 mmol) in THF (5 mL) at 0 °C was added 9-BBN (20.2 mL, 0.5 M solution in THF), and the mixture was stirred at room temperature. After 3 h, 2 N NaOH (10 mL) followed by a THF (3 mL) solution of $Pd(PPh_3)_4$ (58 mg, 0.05 mmol) and 1-bromopropene (0.52 mL, 6.1 mmol) was added. The mixture was heated at 55−60 °C for 4 h. The reaction mixture was cooled to room temperature and extracted with ether (3 × 50 mL). The combined organic layer was washed with water and brine, dried over $MgSO_4$, concentrated, and purified by column chromatography over silica gel (1:19 ethyl acetate:hexane). The product was further purified by bulb-to-bulb distillation to yield pure oxazoline **10** (1.53 g, 81%) as a 5.5:1 mixture of diastereomers. $[\alpha]^{25}_D = +58.5$ (c = 1.44, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) (major isomer) δ 7.96−7.86 (m, 2H), 7.48−7.32 (m, 3H), 5.52−5.34 (m, 2H), 4.40 (dd, J = 6.7, 5.6 Hz, 1H), 4.02 (m, 1H), 3.81 (dd, J = 10.1, 3.7 Hz, 1H), 3.58 (dd, J = 10.1, 6.7 Hz, 1H), 2.23 (m, 1H), 1.90 (m, 1H), 1.78 (m, 1H), 1.63 (d, J = 6.5 Hz, 3H), 0.88 (d, J = 7 Hz, 3H), 0.83 (s, 9H), 0.04 (s, 3H), 0.00 (s, 3H); (minor isomer, characteristic peaks) δ 4.50 (t, J = 5.2 Hz, 1H), 3.86 (dd, J = 10.1, 4 Hz, 1H), 3.54 (dd, J = 10.1, 7.4 Hz, 1H), 2.19 (m, 1H), 1.66 (m, 1H), 0.84 (s, 9H), 0.05 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) (major isomer) δ 164.30, 131.42, 128.94, 128.47, 128.44, 127.14, 86.25, 70.72, 65.54, 37.80, 35.25, 26.06, 26.05, 18.47, 18.23, 14.42, −5.09, −5.11,; (minor isomer, characteristic peaks) δ 164.60, 129.30, 128.25, 85.90, 71.06, 65.65, 38.21, 36.11, 18.44, 18.21, 13.95, −5.13. IR (neat film) 1649, 1604, 1462, 1282 cm^{-1}. Anal. Calcd for $C_{22}H_{35}NO_2Si$: C, 70.73; H, 9.44; N, 3.75. Found: C, 70.93; H, 9.35; N, 3.81.

(4*R*,5*R*)-4-Hydroxymethyl-5-((*E*,1*R*)-1-methyl-3-pentenyl)-2-phenyloxazoline (11). To a solution of oxazoline **10** (689 mg, 1.85 mmol) in THF (5 mL) was added TBAF (2.2 mL, 1 M in THF). After being stirred at room temperature for 30 min, the reaction mixture was diluted with water and extracted ethyl acetate (3 × 25 mL). The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was recrystallized from ether (3 mL) and hexane (12 mL) to afford the alcohol **11** (280 mg, 59%) as 16:1 mixture of diastereomers: mp 128 °C; $[\alpha]^{25}_D = +118.6$ (c = 1.16, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92−7.78 (m, 2H), 7.48−7.3 (m, 3H), 5.54−5.36 (m, 2H), 4.38 (t, J = 7 Hz, 1H), 4.06 (dt, J = 7, 4 Hz, 1H), 3.96 (dd, J = 11.5, 3.5 Hz, 1H), 3.57 (dd, J = 11.5, 5 Hz, 1H), 3.14 (bs, 1H), 2.3−2.22 (m, 1H), 2.0−1.79 (m, 2H), 1.67 (dd, J = 6, 1 Hz, 3H), 0.9 (d, J = 7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.03, 131.56, 128.50, 128.47, 128.41, 127.53, 85.0, 71.04, 64.92, 37.73, 35.51, 18.26, 14.18; IR (neat film) 3194, 1651, 1465, 1375 cm^{-1}. Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 73.78; H, 8.44; N, 5.40. The mother liqour was concentrated and purified by column chromatography over silica gel (3:2 ethyl acetate/hexane) to yield more alcohol **11** (150 mg, 31%, dr = 1.7:1).

(2*R*,3*R*,4*R*)-2-*tert*-Butoxycarbonylamino-3-benzoyloxy-4-methyloct-6-enol (12). The alcohol **11** (217 mg, 0.84 mmol) was dissolved in THF (5 mL) and 2 N HCl (3 mL) and stirred at room temperature for 16 h. The reaction mixture was cooled in an ice bath, and solid $NaHCO_3$ (4 g) was added. Water (15 mL) was added followed by a solution of Boc_2O (365 mg, 1.68 mmol) in THF (3 mL). After being stirred at room temperature for 2 h,

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the solution was extracted with $CHCl_3$ (3 × 25 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, concentrated, and purified by column chromatography over silica gel (3:7 ethyl acetate/hexane) to afford **12** (271 mg, 85%) as a viscous liquid: $[\alpha]^{25}_D = +75.1$ ($c = 2.14$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.1−8.0 (m, 2H), 7.65−7.55 (m, 1H), 7.5−7.4 (m, 2H), 5.5−5.25 (m, 2H), 5.15 (dd, $J = 9$, 2.5 Hz, 1H), 4.65 (d, $J = 10$ Hz, 0.8H), 4.41 (d, $J = 8.5$ Hz, 0.2H, rotamer), 4.15 (m, 0.8 H), 4.03 (m, 0.2H, rotamer), 3.60 (dd, $J = 12$, 6 Hz, 1H), 3.33(dd, $J = 12$, 8 Hz, 1H), 2.93 (br, 1H), 2.24−1.9 (m, 3H), 1.57 (br, 3H), 1.48 (s, 0.2 × 9H), 1.42 (s, 0.8 × 9H), 1.01 (d, $J =$ 7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.39, 155.94, 133.75, 130.09, 128.80, 128.23, 127.69, 80.07, 76.9, 62.52, 52.52, 35.98, 34.36, 28.51, 18.15, 15.99; IR (neat film) 3450, 3406, 1707, 1504, 1273 cm^{-1}. Anal. Calcd for $C_{21}H_{31}NO_5$: C, 66.82; H, 8.28; N, 3.71. Found: C, 66.68; H, 8.10; N, 3.78.

(2*R*,3*R*,4*R*)-2-*tert*-Butoxycarbonylamino-3-benzoyloxy-1-*tert*-butyldimethylsiloxy-4-methyloct-6-ene (13). Compound **12** (750 mg, 1.99 mmol), TBDMSCl (360 mg, 2.39 mmol), and imidazole (163 mg, 2.39 mmol) were charged in a flask and kept under N_2. Dichloromethane (10 mL) was added, and the mixture was stirred at 10 °C for 2 h. The mixture was diluted with additional dichloromethane, washed with water and brine, dried over $MgSO_4$, concentrated, and purified by column chromatograpy over silica gel (1:24 ethyl acetate/hexane) to yield **13** (881 mg, 90%) as a colorless oil: $[\alpha]^{25}_D = +12.6$ ($c = 0.88$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09−8.01 (m, 2H), 7.61−7.54 (m, 1H), 7.5−7.44 (m, 2H), 5.48−5.34 (m, 2H), 5.28 (dd, $J = 6.3$, 4.8 Hz, 1H), 4.86 (d, $J = 10.5$ Hz, 1H), 4.1 (m, 1H), 3.65 (dd, $J =$ 10.5, 4.5 Hz, 1H), 3.6 (dd, $J = 10$, 5.5 Hz, 1H), 2.28−2.2 (m, 1H), 2.06−1.9 (m, 2H), 1.63 (d, $J = 5.5$ Hz, 3H), 1.38 (s, 9H), 1.00 (d, $J = 7$ Hz, 3H), 0.87 (s, 9H), 0.01(s, 3H), 0.0 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.30, 155.79, 133.16, 130.42, 129.98, 129.13, 128.58, 127.13, 79.57, 77.10, 63.46, 52.53, 35.15, 34.76, 28.51, 26.02, 18.41, 18.17, 16.37, −5.38; IR (neat film) 1722, 1496, 1269 cm^{-1}. Anal. Calcd for $C_{27}H_{45}NO_5Si$: C, 65.95; H, 9.22; N, 2.85. Found: C, 66.16; H, 9.21; N, 2.98.

(4*R*,5*R*)-4-Hydroxymethyl-3-methyl-5-((*E*,1*R*)-1-methyl-3-pentenyl)oxazolidin-2-one (14). To a suspension of NaH (147 mg, 3.67 mmol) in THF (3 mL) at 0 °C was added a solution of **13** (300 mg, 0.61 mmol) in THF (3 mL). After 15 min, methyl iodide (0.38 mL, 6.1 mmol) was added, and the mixture was stirred at room temperature for 2 days. The reaction was cooled, quenched with water, and extracted with ethyl acetate (3 × 25 mL). The combined organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated. The residue was dissolved in methanol (3 mL), and NaOMe (0.25 mL, 1.24 M in MeOH) was added. The mixture was heated at 55−60 °C for 24 h. The solution was cooled, concentrated, dissolved in 2 N HCl (6 mL) and THF (3 mL), and stirred at room temperature for 3 h. The solution was diluted with water and extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with water and brine, dried over $MgSO_4$, concentrated, and purified by column chromatography over silica gel (1:19 methanol/ethyl acetate) to yield oxazolidinone **14** (108 mg, 83%) as a white crystalline solid (mp 83−84 °C): $[\alpha]^{25}_D = +76.9$ ($c = 0.92$, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.52−5.43 (m, 1H), 5.4−5.31 (m, 1H), 4.19 (dd, $J = 6.8$, 5.4 Hz, 1H), 3.83 (dd, $J = 11.8$, 3.4 Hz, 1H), 3.59 (dd, $J = 11.9$, 3.5 Hz, 1H), 3.43 (dt, $J = 5.4$, 3.4 Hz, 1H), 2.89 (s, 3H), 2.40 (bs, 1H), 2.24−2.16 (m, 1H), 1.94−1.74 (m, 2H), 1.65 (dd, $J = 6.4$, 1.2 Hz, 3H), 0.9 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.87, 128.02, 127.92, 79.25, 61.55, 61.50, 37.61, 34.68, 29.39, 18.21, 14.07; IR (neat film) 3445, 1757, 1728, 1483 cm^{-1}. Anal. Calcd for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.98; N, 6.57. Found: C, 61.85; H, 9.02; N, 6.60.

Methyl (4*S*,5*R*)-3-Methyl-5-((*E*,1*R*)-1-methyl-3-pentenyl)-oxazolidin-2-one-4-carboxylate (15). Oxazolidinone **14** (108 mg, 0.51 mmol) and PDC (954 mg, 2.54 mmol) were dissolved in DMF (1.5 mL) and stirred at room temperature for 17 h. The reaction mixture was cooled, diluted with ether (10 mL), and acidified with 2 N HCl. The organic layer was separated, and the aqueous layer was further extracted with ether (2 × 15 mL). The combined organic extract was washed with brine, dried over $MgSO_4$, and concentrated. The residue was esterified with ethereal CH_2N_2 and purified by column chromatography over silica gel (2:3 ethyl acetate/hexane) to yield the ester **15** (70 mg, 57%) as a colorless liquid: $[\alpha]^{25}_D = +39.2$ ($c = 1.67$, CH_2Cl_2) [lit.[14g] $[\alpha]_D = +37.1$ ($c = 1.51$, CH_2Cl_2)]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.52−5.44 (m, 1H), 5.38−5.3 (m, 1H), 4.27 (dd, $J =$ 6.4, 4.7 Hz, 1H), 3.96 (d, $J = 5$ Hz, 1H), 3.81 (s, 3H), 2.90 (s, 3H), 2.23−2.15 (m, 1H), 1.98−1.82 (m, 2H), 1.65 (dd, $J = 6.4$, 1.3 Hz, 3H), 0.93 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.51, 157.58, 128.37, 127.51, 79.50, 61.96, 53.14, 37.81, 34.48, 30.32, 18.23, 14.06; IR (neat film) 1764, 1437, 1398, 1217, 1045 cm^{-1}. Anal. Calcd for $C_{12}H_{19}NO_4$: C, 59.74; H, 7.94; N, 5.81. Found: C, 59.70; H, 7.82; N, 5.72.

(*E*,2S,3*R*,4*R*)-2-Methylamino-3-hydroxy-4-methyl-6-octenoic Acid (MeBmt) (4). The hydrolysis of the oxazolidinone ester was carried out in a manner similar to that reported by Wenger.[13] A solution of oxazolidinone **15** (87 mg) in 2 N KOH (1.5 mL) was heated at 80−95 °C for 10 h, cooled to room temperature, and acidified with 1 N HCl to pH 5. The solution was concentrated to 1 mL, and the precipitate was filtered. The solid was recrystallized by first dissolving in hot ethanol/water (2 mL/1 mL respectively), filtered while hot, and then concentrated to 1 mL. The precipitated amino acid was filtered, washed with ethanol, and dried under vacuum to yield MeBmt (**4**) (58 mg, 80%) as a white solid (mp 234−236 °C) (lit.[13] mp 240−241 °C; lit.[20] mp 233 °C)): $\delta = +7.1$ ($c = 0.45$, 0.4 N HCl) (lit.[13] $\delta =$ +13.0 ($c = 0.46$, H_2O pH 7 phosphate Tritisol buffer) [lit.[20] $\delta =$ +12.2 ($c = 0.55$, H_2O pH 7 phosphate Tritisol buffer)]. Spectroscopic analysis was consistent with previous literature reports:[14f,15a] ^{1}H NMR (500 MHz, D_2O) δ 5.37 (dq, $J = 15.1$, 6.4 Hz, 1 H), 5.28 (dtq, $J = 15.1$, 7.8, 1.5 Hz, 1 H), 3.57 (dd, $J = 5.9$, 6.4 Hz, 1H), 3.45 (d, $J = 6.4$ Hz, 1 H), 2.53 (s, 3H), 2.08 (m, 1 H), 1.68 (dt, $J = 13.7$, 8.3 Hz, 1 H), 1.50 (m, 1 H), 1.45 (d, $J = 5.9$ Hz, 3 H), 0.74 (d, 6.8 Hz, 3 H).

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