JOC The Journal of Organic Chemistry

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Samarium Iodide-Mediated Reformatsky Reactions for the Stereoselective Preparation of β-Hydroxy-γ-amino Acids: Synthesis of Isostatine and Dolaisoleucine

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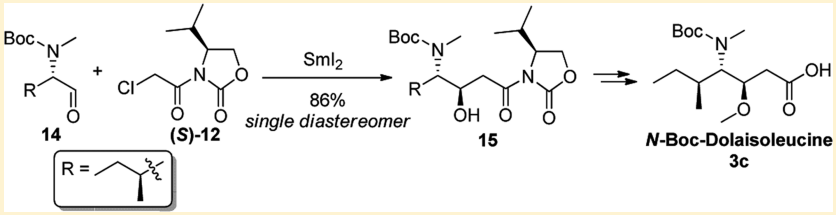
Supporting Information



ABSTRACT: The synthesis of β-hydroxy-γ-amino acids via SmI_2-mediated Reformatsky reactions of α-chloroacetyloxazolidinones with aminoaldehydes is reported. Diastereoselective coupling is demonstrated to depend on the absolute configuration of the Evans chiral auxiliary employed in the reaction, allowing *erythro* or *threo* products to be obtained selectively. The potential utility of the methodology is exemplified by the facile synthesis of biologically relevant *N*-Boc-isostatine (**2b**) and *N*-Boc-dolaisoleucine (**3c**).

Nonproteinogenic amino acids containing β-hydroxy-γ-amino acid motifs comprise a biologically important class of agents that includes (3*S*,4*S*)-4-amino-3-hydroxy-6-methylheptanoic acid (statine, **1**), a component of aspartic protease inhibitors such as peptstatine[1] and (3*S*,4*R*,5*S*)-4-amino-3-hydroxy-5-methylheptanoic acid (isostatine, **2a**), found in the cytotoxic didemnin cyclodepsipeptides.[2] Additional examples are (3*S*,4*R*,5*S*)-3-methoxy-5-methyl-4-(methylamino)heptanoic acid (dolaisoleucine or "Dil", **3a**) and (2*R*,3*R*)-3-methoxy-2-methyl-3-((*S*)-pyrrolidin-2-yl)propanoic acid (dolaproine or "Dap", **4**), both of which are key constituents of cytotoxic peptides, including dolastatin 10,[3] as well as (2*S*,3*S*,4*R*)-4-amino-3-hydroxy-2-methylpentanoic acid (**5**), a component of the antineoplastic glycopeptide, bleomycin B2 (Figure 1).[4]

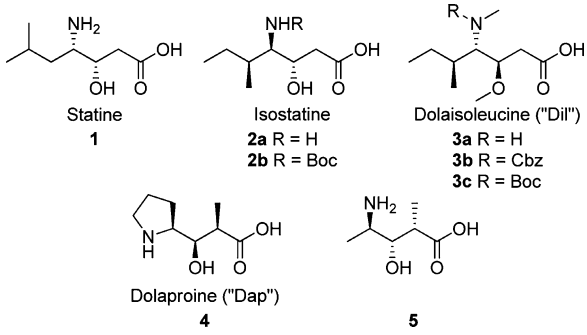


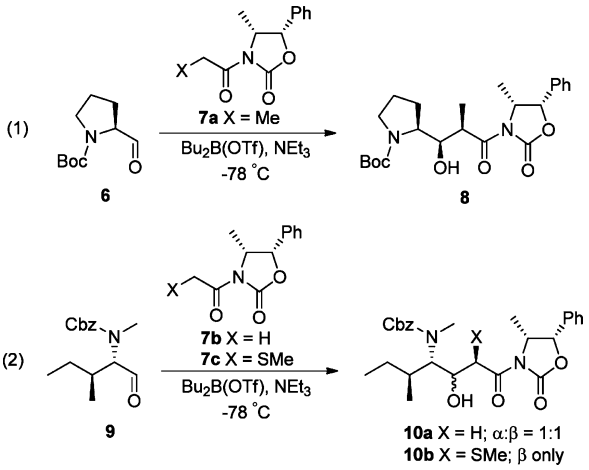
Figure 1. Structures of β-hydroxy-γ-amino acids discussed in the text.

Several synthetic methodologies have been reported for the stereoselective syntheses of β-hydroxy-γ-amino acids (reviewed in ref 5). Of particular note for the preparation of analogues such as **4**[6] and **5**[7] that contain substituents at the α-position are "double stereo-differentiating"[8] aldol reactions of amino aldehydes with chiral acyloxazolidinones, where nascent α-functionality within the auxiliary facilitates chirality transfer. As shown in Scheme 1 (eq 1), the aldol addition of propanoyloxazolidinone **7a** to *N*-Boc-(*S*)-prolinal **6** provides the Dap precursor **8** as a single diastereomer. In contrast, similar chemistry applied to the preparation of products that lack α-substituents can result in significantly less effective stereoinduction. This is exemplified by the synthesis of *N*-Cbz Dil (**3b**) through the reaction of *N*-Cbz-*N*-methyl (*S*)-isoleucinal (**9**) with the boron enolate of acetyloxazolidinone **7b**, where a near complete lack of stereocontrol is observed at the β-hydroxyl center of the resulting product **10a** (Scheme 1, eq 2).[9] In this latter example, limitations imposed by the absence of an α-substitutent can be overcome through a two-step process involving the aldol reaction of a methylthio-containing acyloxazolidinone (**7c**), which yields a thiomethyl group at the α-position (**10b**) that facilitates chirality transfer to the β-hydroxyl center. Once the stereodirecting role of the thiomethyl group has been achieved, it can be removed reductively to provide the desired final product, *N*-Cbz Dil (**3b**).[9]

Metal-catalyzed Reformatsky reactions between aldehydes or ketones and compounds containing α-halo carbonyls can provide an alternate approach to the synthesis of β-hydroxy

Received: October 12, 2011
Published: December 2, 2011

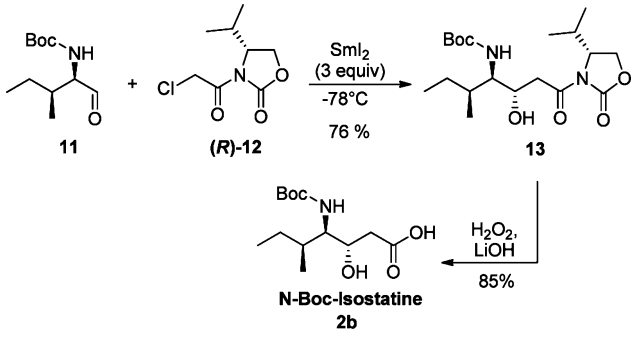
Scheme 1. Aldol Reaction Strategies for the Construction of Dap Precursor 8 (eq 1)[6] and Dil Precursors 10a,b (eq 2)[9] Employing Chiral Auxiliaries in the Presence (7a and 7c) and Absence (7b) of α-Functionality



derivatives.[10] However, literature pertaining to the synthesis of β-hydroxy-γ-amino acids by asymmetric Reformatsky reactions employing oxazolidinone chiral uxiliaries is significantly less extensive than for asymmetric aldol reactions. These protocols often involve substituents at the α-position, as exemplified by the synthesis of Dap (**4**) via a cobalt−phosphine complex-directed Reformatsky reaction.[11] Therefore, we noted with interest the ability of SmI_2 to mediate Reformatsky reactions of haloacetyloxazolidinones with aldehydes to form β-hydroxy adducts in high stereoselectivity without the necessity of α-substituents (for example, see ref 12). As reported herein, in order to examine the potential utility of this chemistry for the preparation of β-hydroxy-γ-amino acids lacking α-substituents, we applied SmI_2-catalyzed Reformatsky chemistry to the synthesis of *N*-Boc-protected isostatine (**2b**) and Dil (**3c**).

The synthesis of **2b** began with the known aldehyde **11**, which was obtained from commercially available *N*-Boc-D-*allo*-isoleucine.[2,13] We were pleased to observe that the addition of a mixed solution of aldehyde **11** and α-chloroacetyloxazolidinone (*R*)-**12**[12d] to an excess (3 equiv) of SmI_2[14] resulted in the formation of the secondary alcohol **13** as a single diastereomer (Scheme 2). Removal of the chiral auxiliary under oxidative

Scheme 2. Synthesis of *N*-Boc-isostatine (2b)

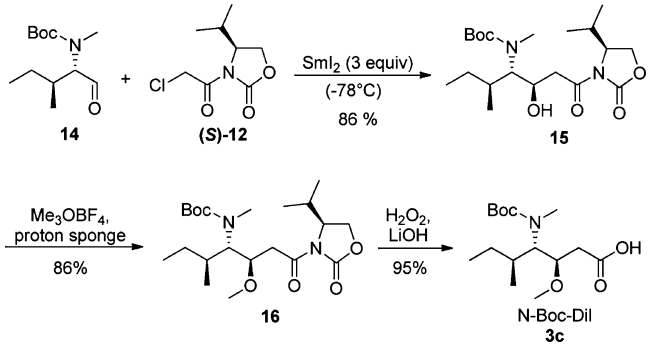


conditions[11] provided *N*-Boc-isostatine (**2b**) as a 3:1 mixture of conformers, as indicated by NMR. The optical rotation of the product and the spectral properties of the major conformer agreed well with literature values.

The differentiation of conformers vs stereoisomers was made using NMR. COSY analysis displayed two distinct CH_γ−NH correlations and NOESY analysis revealed a same-phase (relative to the diagonal) crosspeak between the two NH signals.[15] This same-phase crosspeak arises from the *conformational exchange* of a single diastereomer. The presence of two diastereomers would not display such a NH−NH crosspeak.

The synthesis of *N*-Boc-Dil (**3c**) started with *N*-Boc-*N*-methylisoleucinal **14**. This was obtained from commercially available *N*-Boc-*N*-methylisoleucine[9] in a manner analogous to that used to convert *N*-Boc-D-*allo*-isoleucine to *N*-Boc-D-*allo*-isoleucinal (**13**). As noted above, while isostatine and Dil share the same relative β,γ-*erythro* stereochemistry, they are enantiomeric. Accordingly, α-chloroloacetyloxazolidinone (*S*)-**12**[12] was used in the Sm-mediated Reformatsky coupling with aldehyde **14**. Under similar reaction conditions as above, successful coupling was again realized to provide the secondary alcohol **15** as a single diastereomer in good yield (Scheme 3).

Scheme 3. Synthesis of *N*-Boc-Dil (3c)



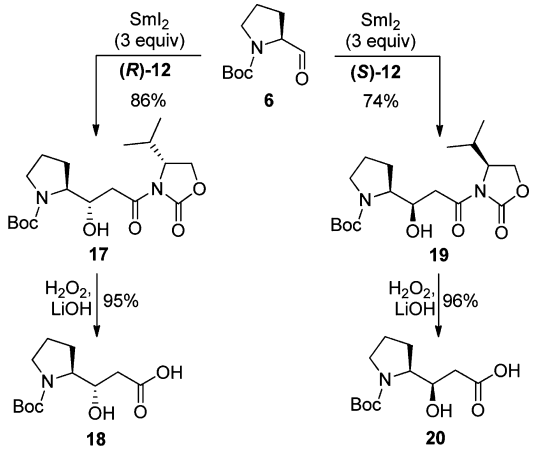
Subsequent O-methylation using trimethyloxonium tetrafluoroborate[2] and oxidative removal of the chiral auxiliary yielded *N*-Boc-Dil (**3c**), having spectral and optical properties matching literature values.[3]

The stereochemical outcome of the Sm^{II}-mediated formation of Reformatsky products **13** and **15** presumably depends highly on the nature of the chiral auxiliary Sm-enolate complex. However additions of achiral lithium enolates to (*S*)-prolinal derivatives have also been shown to be highly diastereoselective.[16] To determine whether the selectivities observed with the Sm^{II}-mediated Reformatsky reactions to form products **13** and **15** are derived from the chirality of the Sm^{III} enolate (ie. auxiliary control) or from preferential approach of a Sm^{III} enolate to a low energy conformation of the aldehyde (i.e., Felkin addition),[16] we coupled *N*-Boc-(*S*)-prolinal (**6**) to both α-chloroacetyloxazolidinones (*R*)-**12** and (*S*)-**12** using the above reaction conditions (Scheme 4).

Treatment of **6** with oxazolidinones (*R*)-**12** and (*S*)-**12** provided the alcohols **17** and **19**, respectively (Scheme 4). Oxidative removal of the chiral auxiliaries gave the corresponding diastereomeric β-hydroxyacids **18** and **20**, respectively. Spectral analysis confirmed that the stereochemical outcome of the Sm^{II}-mediated Reformatsky coupling was indeed controlled by the chirality of the auxiliary employed in the reaction, allowing *threo* (**17**; dr 5:1) or *erythro* (**19**; dr 14:1) products to be obtained selectively. It should be noted that chiral induction by α-amino aldehydes generally favors the *erythro* products.[16] This preference accounts for the difference in selectivity observed in the formation of *threo* product **17** (dr 5:1) vs

dx.doi.org/10.1021/jo202091r | J. Org. Chem. 2012, 77, 733−738

Scheme 4. Stereoselective Synthesis of (*R*)- and (*S*)-β-Hydroxy-γ-amino Acids Derived from *N*-Boc-(*S*)-prolinal (6)



erythro product **19** (dr 10:1). Utilizing the appropriate chiral auxiliary can enhance this preference (*erythro*/*threo* = 10:1 vs 4:1[16a]) or reverse it (*erythro*/*threo* = 1:5).

In summary, the SmI_2-mediated Reformatsky coupling of amino aldehydes with α-chloroacetyloxazolidinones has been successfully applied to the synthesis of the β-hydroxy-γ-amino acids *N*-Boc-isostatine (**2b**) and *N*-Boc-dolaisoleucine (**3c**). The stereochemical outcomes of the reactions are controlled by the absolute configuration of the chiral auxiliaries used, allowing the selective formation of *erythro* or *threo* products. These results should serve as a general method for the construction of β-hydroxy-γ-amino acids that enables the synthesis of both natural and unnatural peptide sequences for biological evaluation.

EXPERIMENTAL SECTION

General Information. Reactions were stirred magnetically under an argon atmosphere, unless otherwise noted, and reagents were purchased from commercial sources and used without further purification. Solvents were removed by rotary evaporation under reduced pressure and silica gel chromatography was performed using flash silica gel (230−400 mesh, 40−60 μm particle size). Anhydrous solvents were obtained commercially and used without further drying. Infared (IR) measurements were made using a Fourier transform infared spectrometer equipped with an ATR probe. NMR measurements were performed at 25 °C (unless otherwise noted) at either 400 or 500 MHz. When required, NMR spectra were acquired at elevated temperatures, specified within the reported data and in the spectral parameters.

***N*-Boc-D-*allo*-isoleucinal (11).** To a solution of *N*-Boc-D-*allo*-isoleucine (1 g, 4.32 mmol) in THF (4.32 mL), at −10 °C under argon, was added *N*-methylmorpholine (0.475 mL, 4.32 mmol), followed by isobutyl chloroformate (0.568 mL, 4.32 mmol). After being stirred at −10 °C (10 min), the reaction mixture was filtered (glass fritted funnel) to remove the precipitate and the filtrate cooled to −10 °C. A solution of $NaBH_4$ (0.245 g, 6.49 mmol) in H_2O (2.2 mL) was then added over 5 min. Upon complete addition, the reaction was diluted with H_2O (5 mL) and extracted with EtOAc (3 × 30 mL). The organic phase was dried (Na_2SO_4) and concentrated in vacuo.[13] The crude residue was diluted with DMSO (4.3 mL) under argon, and NEt_3 (3.01 mL, 21.60 mmol) was added. The mixture was stirred at room temperature (15 min) before being cooled to 0 °C. SO_3−pyridine complex (3.438 g, 21.60 mmol) was added, and the mixture was stirred at 0 °C (45 min). The reaction was halted by the addition of H_2O (30 mL). The mixture was extracted with Et_2O (3 × 60 mL), and the organic phases were washed, successively, with 10% aqueous citric acid, H_2O, saturated aqueous $NaHCO_3$, and brine (20 mL each). All aqueous phases were back extracted with Et_2O (1 × 50 mL). Combined organic fractions were dried (Na_2SO_4), concentrated in vacuo and chromatographed over silica gel to afford **11** (706 mg, 3.3 mmol, 76% yield) as a colorless oil. Spectroscopic data for compound **11** matched that previously reported.[17]

Samarium Iodide (SmI_2). Using standard anhydrous techniques, with careful exclusion of oxygen, to a round-bottomed flask was added a dry mixture of samarium metal (99.9% purity, 40 mesh, 3.76 g, 25.00 mmol; 1.25 equiv) and diiodine (5.08 g, 20 mmol) under argon. The flask containing the dry mixture was then quickly evacuated and argon backfilled (3×), anhydrous THF (200 mL) was added via cannula, the flask was wrapped in aluminum foil, and the mixture was stirred at room temperature (4 h). The SmI_2 obtained in this fashion is deep green-blue in color with a nominal concentration of 0.1 M. When protected from light and stored under argon, this stock solution is stable over a period of approximately 1 week without any appreciable loss of activity.

General Procedure (A) for SmI_2-mediated Reformatsky Coupling. To a dry round-bottomed flask, evacuated and backfilled with argon (3×) at −78 °C, was added freshly prepared SmI_2 (3 equiv) followed by a solution of aldehyde (1.2 equiv) and α-chloroacetyloxazolidinone (1 equiv) in dry THF (0.3 M), dropwise via syringe. The transfer was quantitated with additional THF, and the mixture was stirred at −78 °C (5 min). The reaction was terminated by bubbling O_2 through the solution to quench residual Sm^{II} (indicated by a change in color from blue-green Sm^{II} to yellow Sm^{III}). A solution of saturated aqueous NH_4Cl was then added at −78 °C, and the mixture was brought to room temperature and further diluted with aqueous NH_4Cl. The mixture was extracted with Et_2O, and the combined organic phases were washed thoroughly with 15% aqueous $Na_2S_2O_3$, dried (Na_2SO_4), and concentrated in vacuo. The resulting crude residue was purified by silica gel chromatography to provide the desired coupled products (see below).

(3*S*,4*R*,5*S*)-4-*tert*-Butyl carbamate-3-hydroxy-1-((*R*)-4-isopropyl-2-oxazolidinone-3-yl)-5-methyl-1-oxoheptanone (13). The general procedure "A" outlined above was followed using SmI_2 (9.29 mL, 0.929 mmol, 3 equiv), *N*-Boc-D-*allo*-isoleucinal (**11**) (80 mg, 0.372 mmol, 1.2 equiv) and α-chloroacetyloxazolidinone (*R*)-**12** (63.7 mg, 0.310 mmol). The product residue was chromatographed over silica gel to afford alcohol **13** (90.4 mg, 0.234 mmol, 76%) as a colorless oil: TLC R_f = 0.27 (40% EtOAc/hexane); α_D^{25} (*c* 2.5, $CHCl_3$) = (−) 38.27; ^{1}H NMR (25 °C, 500 MHz, $CDCl_3$) δ 4.49−4.45 (m, 2H), 4.31 (t, *J* = 8.6 Hz, 1H), 4.20 (dd, *J* = 9.0, 2.6 Hz, 1H), 3.95 (bs, 0.1H), 3.86 (ddd, *J* = 14.9, 8.5, 3.3 Hz, 0.9H), 3.69 (td, *J* = 9.6, 3.5 Hz, 1H), 3.58 (d, *J* = 8.1 Hz, 1H), 3.34 (dd, *J* = 17.4, 6.6 Hz, 1H), 3.04 (dd, *J* = 17.4, 3.3 Hz, 1H), 2.38−2.31 (m, 1H), 1.97 (ddd, *J* = 13.8, 6.9, 3.6 Hz, 1H), 1.44 (s, 1H), 1.41 (s, 8H), 1.38−1.30 (m, 1H), 1.26−1.19 (m, 1H), 0.92 (d, *J* = 7.0 Hz, 3H), 0.92−0.87 (m, 3H), 0.88 (d, *J* = 6.9 Hz, 3H), 0.85 (d, *J* = 6.9 Hz, 3H); ^{1}H NMR (75 °C, 500 MHz, DMSO-d_6) δ 4.59 (bs, 1H), 4.41−4.36 (m, 1H), 4.31 (t, *J* = 8.6 Hz, 1H), 4.28−4.27 (m, 1H), 4.25 (dd, *J* = 8.9, 3.0 Hz, 1H), 3.03 (bs, 1H), 2.92 (dd, *J* = 15.9, 3.4 Hz, 1H), 2.66 (s, 3H), 2.25−2.18 (m, 1H), 1.89−1.81 (m, 1H), 1.50 (bs, 1H), 1.40 (s, 9H), 1.07−1.00 (m, 1H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.87 (d, *J* = 7.0 Hz, 3H), 0.85 (t, *J* = 7.5 Hz, 3H), 0.82 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (25 °C, 125 MHz, $CDCl_3$) δ 173.6, 156.4, 154.04, 79.5, 69.6, 63.8, 58.6, 56.1, 37.7, 33.7, 28.8, 28.3, 27.1, 18.0, 14.9, 13.1, 11.7; IR (neat film, cm^{-1}) 3371, 2963, 1783, 1697, 1236; HRMS (MALDI - TOF) calcd for $C_{19}H_{34}N_2O_6$ $[M + Na]^+$ 409.2315, found 409.2327.

***N*-Boc-*N*-methylisoleucinal (14).** To a solution of *N*-Boc-*N*-Me-isoleucine (2.94 g, 12 mmol) in dry THF (8.4 mL) at 0 °C was added BH_3−THF complex (1.0 M in THF, 18 mL, 1.5 equiv) dropwise via syringe. The reaction solution was stirred at 0 °C (2 h) and then room temperature (1 h). The reaction was halted by the slow addition of H_2O (20 mL), and the mixture was extracted with EtOAc (3 × 50 mL). The organic phase was washed, successively, with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL). Removal of the solvent in vacuo afforded the crude amino alcohol as a viscous clear oil which was diluted with DMSO (10.81 mL) and NEt_3 (7.53 mL, 54.0 mmol) under argon. The mixture was stirred at room temperature

dx.doi.org/10.1021/jo202091r | J. Org. Chem. 2012, 77, 733−738

(15 min) then cooled to 0 °C. SO_3–pyridine complex (8.60 g, 54.0 mmol) was added and the mixture was stirred at 0 °C (45 min). The reaction was halted by the addition of H_2O (50 mL). The mixture was extracted with Et_2O (3 × 100 mL), and the organic phase was washed, successively, with 10% aqueous citric acid, water, saturated aqueous $NaHCO_3$, and brine (15 mL each). All aqueous phases were backwashed with Et_2O (1 × 40 mL). Combined organic fractions were dried with Na_2SO_4 and concentrated in vacuo. The residue was eluted through a short plug of silica gel to afford **14** (2.061 g, 8.99 mmol, 75% yield) as a colorless oil. Spectroscopic data for compound **14** matched that previously reported.[6]

(3*S*,4*R*,5*S*)-4-((*tert*-Butoxycarbonyl)amino)-3-hydroxy-5-methylheptanoic Acid (*N*-Boc-isostatine, 2b). To a solution of amide **13** (50 mg, 0.129 mmol) in 3:1 THF/H_2O (0.35 mL) at 0 °C was added 50% aqueous H_2O_2 (0.056 mL, 0.776 mmol) followed by LiOH–H_2O (14.13 mg, 0.336 mmol). The mixture was stirred at 0 °C (3 h), and then excess peroxide was quenched by the addition of 1.5 N aqueous Na_2SO_3 (1 mL, 1.5 mmol) at 0 °C, and the mixture was stirred at room temperature (overnight). The pH was adjusted to ∼9–10 by the addition of saturated aqueous $NaHCO_3$ and the free oxazolidinone side product was extracted using DCM. The aqueous phase was acidified to pH ∼2 using 1 N aqueous HCl and extracted with EtOAc . The combined EtOAc phases were dried (Na_2SO_4) and taken to dryness in vacuo to afford *N*-Boc-isostatine (**2b**) (30.3 mg, 0.11 mmol, 85%) as a colorless semisolid: α_D^{25} (*c* 1.25, $CHCl_3$) = (−) 7.5; ^{1}H NMR (25 °C, 500 MHz, $CDCl_3$, 2 conformers) δ 5.77 (NH, d, *J* = 10.6 Hz, 0.36H, minor conformer, exchanges), 4.51 (NH, d, *J* = 9.6 Hz, 0.64H, major conformer, exchanges), 3.95 (td, *J* = 8.1, 3.0 Hz, 1H), 3.65 (td, *J* = 9.7, 3.8 Hz, 0.66H, major), 3.58 (t, *J* = 8.6 Hz, 0.33H, minor), 2.70–2.62 (m, 1H), 2.57–2.47 (m, 1H), 1.92–1.85 (m, 1H), 1.47 (s, 3H, minor), 1.44 (s, 6H, major), 1.40–1.32 (m, 1H), 1.26–1.19 (m, 2H), 0.92 (t, *J* = 7.4 Hz, 3H), 0.89–0.85 (m, 3H); ^{13}C NMR (25 °C, 125 MHz, $CDCl_3$) δ major 176.65, 156.6, 80.0, 69.1, 56.8, 38.3, 33.9, 28.31, 27.0, 13.3, 11.6; minor 176.67, 157.8, 81.4, 68.5, 58.0, 39.2, 34.1, 28.26, 26.8, 12.8, 11.8; LRMS (ESI–negative mode) *m*/*z* 274 $[M - H]^-$, 310 $[M + {}^{35}Cl]^-$, 312 $[M + {}^{37}Cl]^-$; LRMS (ESI–positive mode) *m*/*z* 298 $[M + Na]^+$; HRMS (MALDI - TOF) calcd for $C_{13}H_{25}NO_5$ $[M + Na]^+$ 298.1630, found 298.1640.

(3*R*,4*S*,5*S*)-4-(*tert*-Butoxycarbonyl)(methyl)amino-3-hydroxy-1-((*S*)-4-isopropyl-2-oxazolidinone-3-yl)-5-methyl-1-oxoheptanone (15). The general procedure "A" outlined above was followed using SmI_2 (136 mL, 13.60 mmol, 3 equiv), *N*-Boc-*N*-Me-isoleucinal **14** (1.247 g, 5.44 mmol, 1.2 equiv), and α-chloroacetyloxazolidinone (*S*)-**12** (0.932 g, 4.53 mmol). The product residue was chromatographed over silica gel to afford alcohol **15** (1.54 g, 3.85 mmol, 86%) as a colorless oil: TLC R_f = 0.22 (35% EtOAc/hexane); α_D^{25} (*c* 2.6, $CHCl_3$) = (−) 38.71; ^{1}H NMR (25 °C, 500 MHz, DMSO-d_6) δ 4.84 (dd, *J* = 7.3, 28.7 Hz, 1H), 4.40–4.35 (m, 1H), 4.32–4.20 (m, 3H), 3.76 (bs, 1H), 2.99–2.85 (m, 1H), 2.91 (d, *J* = 6.2 Hz, 1H), 2.64 (s, 1.6H), 2.59 (s, 1.3H), 2.22–2.14 (m, 1H), 1.82 (m, 1H), 1.53–1.43 (m, 1H), 1.38 (s, 9H), 1.04–0.95 (m, 1H), 0.94–0.90 (m, 3H), 0.87–0.78 (m, 9H); ^{1}H NMR (75 °C, 500 MHz, DMSO-d_6) δ 4.61 (bs, 1H), 4.41–4.37 (m, 1H), 4.31 (t, *J* = 8.6 Hz, 1H), 4.29–4.23 (m, 1H), 4.25 (dd, *J* = 8.9, 2.8 Hz, 1H), 3.81–3.59 (m, 1H), 3.01 (bs, 1H), 2.92 (dd, *J* = 15.7, 3.1 Hz, 1H), 2.66 (s, 3H), 2.22 (dtd, *J* = 13.8, 6.9, 4.0 Hz, 1H), 1.86 (dd, *J* = 13.4, 6.7 Hz, 1H), 1.55–1.45 (m, 1H), 1.40 (s, 9H), 1.08–0.98 (m, 1H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.87 (d, *J* = 7.0 Hz, 3H), 0.88–0.84 (m, 3H), 0.82 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 °C, 125 MHz, d_6-DMSO) δ 170.7, 153.5, 78.1, 67.1, 63.3, 57.8, 40.6, 34.6, 34.2, 28.1, 27.7, 25.0, 17.1, 16.0, 14.5, 10.9; IR (neat film, cm^{-1}) 3458, 2964, 1780, 1684; HRMS (MALDI - TOF) calcd for $C_{20}H_{36}N_2O_6$ $[M + Na]^+$ 423.2471, found 423.2477.

(3*R*,4*S*,5*S*)-4-*tert*-Butoxycarbonyl)(methyl)amino-1-((*S*)-4-isopropyl-2-oxazolidinone-3-yl)-3-methoxy-5-methyl-1-oxoheptanone (16). A mixture of alcohol **15** (304 mg, 0.76 mmol) and molecular sieves (4 Å, oven-dried, 300 mg) was diluted with anhydrous 1,2-dichloroethane (1.12 mL) under an argon atmosphere and stirred (20 min). The mixture was cooled to 0 °C prior to the sequential addition of proton sponge [1,8-bis(dimethylamino)-naphthalene; 423 mg, 1.97 mmol, 2.6 equiv] and trimethyloxonium tetrafluoroborate (281 mg, 1.90 mmol, 2.5 equiv). The mixture was brought to room temperature, sealed under argon, and stirred (48 h). The mixture was filtered through Celite and concentrated in vacuo, and the residue was chromatographed over silica gel to afford methyl ether **16** (271 mg, 0.66 mmol, 86%) as a colorless oil: TLC R_f = 0.42 (35% EtOAc/hexane); α_D^{20} (*c* 0.9, $CHCl_3$) = (+) 36.0; ^{1}H NMR (25 °C, 400 MHz, DMSO-d_6, two conformers) δ 4.41–4.36 (m, 1H), 4.34–4.26 (m, 2H), 4.03–3.85 (m, 2H), 3.26 (s, 1.6H), 3.23 (s, 1.4H), 3.08–3.02 (m, 2H), 2.62 (s, 1.7H), 2.60 (s, 1.3H), 2.22–2.13 (m, 1H), 1.84–1.71 (m, 1H), 1.38 (s, 9H), 1.41–1.34 (m, 1H), 1.08–0.95 (m, 1H), 0.89 (d, *J* = 6.6 Hz, 3H), 0.87–0.82 (m, 6H), 0.79 (m, 3H); ^{1}H NMR (60 °C, 400 MHz, DMSO) δ 4.42–4.37 (m, 1H), 4.33 (t, *J* = 8.5 Hz, 1H), 4.27 (dd, *J* = 8.9, 2.9 Hz, 1H), 4.00–3.93 (m, 1.4H), 3.85 (bs, 0.4H), 3.26 (s, 3H), 3.14–3.00 (m, 2H), 2.64 (s, 3H), 2.26–2.15 (m, 1H), 1.84–1.73 (m, 1H), 1.45–1.38 (m, 1H), 1.39 (s, 9H), 1.04 (m, 1H), 0.92 (d, *J* = 6.7 Hz, 3H), 0.87 (d, *J* = 7.0 Hz, 3H), 0.86–0.82 (m, 3H), 0.81 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (60 °C, 100 MHz, DMSO-d_6, major conformer) δ 170.4, 153.7, 76.9, 63.3, 57.9, 37.3, 33.2, 27.8, 25.3, 17.2, 15.8, 14.5, 10.4; IR (neat film, cm^{-1}) 2965, 1777, 1688, 1150; HRMS (MALDI - TOF) calcd for $C_{21}H_{38}N_2O_6$ $[M + Na]^+$ 437.2628, found 437.2632.

(3*R*,4*S*,5*S*)-4-((*tert*-Butoxycarbonyl)(methyl)amino)-3-methoxy-5-methylheptanoic Acid (*N*-Boc-Dolaisoleucine, 3c). To a solution of carbamate **16** (261 mg, 0.548 mmol) in a 1:1 mixutre of THF/H_2O (1.26 mL), under argon and at 0 °C, was added 50% aqueous H_2O_2 (0.114 mL, 1.972 mmol) over 5 min. The resultant solution was stirred (5 min), LiOH–H_2O (36.8 mg, 0.876 mmol) was added, and stirring was continued at 0 °C (3 h). The reaction was quenched by the addition of Na_2SO_3 (276 mg, 2.191 mmol, 4 equiv) in H_2O (1.5 mL, 1.46 M), and the mixture was stirred at room temperature (overnight). The mixture was concentrated in vacuo, and the resulting aqueous slurry was washed with DCM. The aqueous phase was acidified to pH ∼2 using 37% aqueous HCl and extracted with EtOAc. The original DCM extracts were again extracted with 5% NaOH (10 mL), and the aqueous layer was acidified and extracted (EtOAc) as before. The DCM organic phases were dried (Na_2SO_4) and concentrated in vacuo to afford recovered chiral auxiliary (64 mg, 90%). The combined EtOAc organic phases were dried (Na_2SO_4) and taken to dryness in vacuo to afford **3c** (158 mg, 0.52 mmol, 95%) as a viscous oil: α_D^{19} (*c* 2.5, $CHCl_3$) = (−) 10.9; ^{1}H NMR (25 °C, 400 MHz, $CDCl_3$) δ 4.02–3.80 (m, 2H), 3.38 (s, 3H), 2.67 (s, 3H), 2.60–2.43 (m, 2H), 1.82–1.69 (m, 1H), 1.51–1.40 (m, 1H), 1.43 (s, 9H), 1.12–1.02 (m, 1H), 0.94 (d, *J* = 5.9 Hz, 3H), 0.87 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (25 °C, 100 MHz, $CDCl_3$) δ 176.5 and 176.4, 156.6, 80.1 and 79.6, 78.3, 60.9 (br), 57.7 and 57.6, 37.1 and 36.9, 34.9 (br) and 34.5, 28.39 and 28.35, 25.9 and 25.7, 16.2 and 16.1, 11.28; HRMS (MALDI - TOF) calcd for $C_{15}H_{29}NO_5$ $[M + Na]^+$ 326.1943, found 326.1916.

(*S*)-*tert*-Butyl 2-((*S*)-1-Hydroxy-3-((*R*)-4-isopropyl-2-oxoxazolidin-3-yl)-3-oxopropyl)pyrrolidine-1-carboxylate (17) and (*S*)-*tert*-Butyl 2-((*R*)-1-Hydroxy-3-((*R*)-4-isopropyl-2-oxoxazolidin-3-yl)-3-oxopropyl)pyrrolidine-1-carboxylate (*epi*-17). The general procedure "A" outlined above was followed using SmI_2 (29.2 mL, 2.92 mmol, 3.0 equiv), *N*-Boc-prolinal **6** (233 mg, 1.168 mmol, 1.2 equiv), and (*R*)-**12** (200 mg, 0.973 mmol, 1.0 equiv). The product residue was chromatographed over silica gel to afford a mixture (310 mg, 0.84 mmol, 86%, dr 5:1) of alcohols **17** and ***epi*-17**: TLC R_f = 0.34 (55% EtOAc/hexane); α_D^{23} (*c* 1.4, $CHCl_3$) = (−) 94.5; **17** ^{1}H NMR (25 °C, 400 MHz, DMSO-d_6) δ 4.90 (s, 0.1H), 4.81 (d, *J* = 5.9 Hz, 0.9H), 4.39–4.32 (m, 1H), 4.33–4.22 (m, 2.3H), 4.12 (bs, 0.6H), 3.95–3.75 (m, 0.8H), 3.61 (bs, 0.1H), 3.37–3.28 (m, 1H), 3.26–2.99 (m, 1.7H), 2.99–2.60 (m, 1.3H), 2.27–2.12 (m, 1H), 1.94–1.77 (m, 2.8H), 1.75–1.63 (m, 1.2H), 1.40 (s, 1.7H), 1.38 (s, 7.3H), 0.85 (d, *J* = 7.0 Hz, 3H), 0.82–0.77 (m, 3H); ^{1}H NMR (60 °C, 400 MHz, DMSO-d_6) δ 4.68 (d, *J* = 5.2 Hz, 0.86H), 4.39–4.35 (m, 1H), 4.30 (t, *J* = 8.4 Hz, 1H), 4.25 (dd, *J* = 8.9, 3.1 Hz, 1H), 4.25–4.17 (m, 1H), 3.88 (bs, 0.86H), 3.42–3.33 (m, 1H), 3.24–3.14 (m, 1.4H), 3.04–2.82 (m, 1.6H), 2.26–2.17 (m, 1H), 1.90–1.81 (m, 3H), 1.75–1.68 (m, 1H), 1.40 (s, 7.7H), 0.86 (d, *J* = 7.1 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (60 °C, 100 MHz, DMSO-d_6) δ 171.4, 154.3, 78.8,

dx.doi.org/10.1021/jo202091r | *J. Org. Chem.* 2012, 77, 733–738

63.8, 58.4, 47.5, 28.8, 28.5, 27.2, 17.9, 15.2; IR (neat film, cm^{-1}) 2972, 2360, 1780, 1685; HRMS (MALDI - TOF) calcd for $C_{18}H_{30}N_2O_6$ $[M + K]^+$ 409.1741, found 409.1719. ***epi*-17**: diagnostic ^1H NMR peaks (60 °C, 400 MHz, DMSO-d_6) δ 4.73 (d, J = 5.7 Hz, 0.14H), 3.65 (bs, 0.14H), 2.73 (dd, J = 15.8, 3.3 Hz, 0.2H), 1.41 (s, 1.3H).

(*S*)-3-((*S*)-1-(*tert*-Butoxycarbonyl)pyrrolidin-2-yl)-3-hydroxypropanoic Acid (18). To a solution of carbamate **17** (70 mg, 0.189 mmol) in 4:1 THF/H_2O (1.08 mL, 0.175 M), at 0 °C, was added 50% aqueous H_2O_2 (39 μL, 0.680 mmol, 3.6 equiv) dropwise via syringe. A solution of LiOH–H_2O (12.70 mg, 0.302 mmol, 1.6 equiv) in H_2O (216 μL) was added, and stirring was continued at 0 °C (3 h). A solution of Na_2SO_3 (95 mg, 0.756 mmol, 4 equiv) in H_2O (518 μL, 1.46 M) was added, and the mixture was stirred at room temperature (overnight). The mixture was concentrated in vacuo, and the residue was diluted with 5% aqueous $NaHCO_3$ (10 mL). The aqueous phase was washed with DCM (2 × 10 mL, acidified to pH ~2 with 37% aqueous HCl and extracted with EtOAc. The original DCM washes were extracted with 5% aqueous $NaHCO_3$ (10 mL), and the aqueous layer was acidified and extracted with EtOAc. The DCM phases were dried (Na_2SO_4) and concentrated in vacuo to afford recovered chiral auxiliary (23 mg, 0.178 mmol, 94% recovered). The combined EtOAc phases were dried (Na_2SO_4) and taken to dryness in vacuo to afford a mixture (46.4 mg, 0.179 mmol, 95%, dr = 5:1) of acids **18** and **20** as a colorless oil: α_D^{20} (c 2.3, MeOH) = (−) 47.1; **18** ^1H NMR (25 °C, 400 MHz, DMSO-d_6) δ 4.27–4.17 (m, 0.45H), 4.17–4.07 (m, 0.55H), 3.85–3.75 (m, 0.84H), 3.39–3.25 (m, 1H), 3.24–3.11 (m, 1H), 2.32–2.19 (m, 1H), 2.13 (dd, J = 15.0, 9.3 Hz, 1H), 1.91–1.73 (m, 3H), 1.73–1.63 (m, 1H), 1.39 (s, 9H); ^1H NMR (65 °C, 400 MHz, DMSO-d_6) δ 4.23–4.08 (m, 1H), 3.86–3.79 (m, 0.83H), 3.41–3.31 (m, 1H), 3.22–3.12 (m, 1H), 2.28 (dd, J = 15.0, 4.0 Hz, 1H), 2.16 (dd, J = 15.1, 9.0 Hz, 1H), 1.89–1.76 (m, 3H), 1.74–1.64 (m, 1H), 1.41 (s, 9H); ^{13}C NMR (65 °C, 100 MHz, DMSO-d_6) δ 172.6, 154.2, 78.3, 68.9, 60.3, 46.8, 37.9, 27.9, 26.2, 23.2; IR (neat film, cm^{-1}) 3402, 2930, 2361, 1677, 1394; HRMS (MALDI - TOF) calcd for $C_{12}H_{21}NO_5$ $[M + Na]^+$ 282.1317, found 282.1318. **20**: diagnostic ^1H NMR peak (25 °C, 400 MHz, DMSO-d_6) δ 3.62–3.56 (m, 0.16H); diagnostic ^1H NMR peak (65 °C, 400 MHz, DMSO-d_6) δ 3.66–3.60 (m, 0.16H).

(*S*)-*tert*-Butyl 2-((*R*)-1-Hydroxy-3-((*S*)-4-isopropyl-2-oxooxazolidin-3-yl)-3-oxopropyl)pyrrolidine-1-carboxylate (19) and (*S*)-*tert*-Butyl 2-((*S*)-1-Hydroxy-3-((*S*)-4-isopropyl-2-oxooxazolidin-3-yl)-3-oxopropyl)pyrrolidine-1-carboxylate (*epi*-19). The general procedure "A" outlined above was followed using SmI_2 (29.200 mL, 2.92 mmol), *N*-Boc-prolinal **6** (233 mg, 1.168 mmol), and (*S*)-12 (200 mg, 0.973 mmol). The product residue was chromatographed over silica gel to afford pure alcohol **19** (272 mg, 0.75 mmol, 74%). An additional amount (71 mg) of **19** and *epi*-**19** was also obtained as a mixture (ratio **19**:*epi*-**19** = 53:47). **19**: TLC R_f = 0.35 (55% EtOAc/hexane); α_D^{22} (c 0.79, $CHCl_3$) = (+) 17.1; ^1H NMR (25 °C, 400 MHz, DMSO-d_6) δ 4.94–4.83 (m, 1H), 4.42–4.33 (m, 1H), 4.33–4.24 (m, 2H), 4.24–4.14 (m, 1H), 3.69–3.57 (m, 1H), 3.34–3.27 (m, 1H), 3.22–3.08 (m, 1H), 3.07–2.77 (m, 2H), 2.24–2.12 (m, 1H), 1.99–1.80 (m, 2H), 1.78–1.64 (m, 2H), 1.40 (s, 9H), 0.85 (d, J = 7.0 Hz, 3H), 0.79 (d, J = 6.9 Hz, 3H); ^1H NMR (60 °C, 400 MHz, DMSO-d_6) δ 4.75 (d, J = 5.0 Hz, 1H), 4.41–4.36 (m, 1H), 4.31 (t, J = 8.5 Hz, 1H), 4.26 (dd, J = 9.0, 3.1 Hz, 1H), 4.23–4.18 (m, 1H), 3.70–3.62 (m, 1H), 3.41–3.31 (m, 1H), 3.20–3.12 (m, 1.2H), 3.04–2.88 (m, 1.8H), 2.25–2.15 (m, 1H), 1.99–1.90 (m, 1H), 1.90–1.81 (m, 1H), 1.80–1.65 (m, 2H), 1.41 (s, 9H), 0.86 (d, J = 7.0 Hz, 3H), 0.81 (d, J = 6.9 Hz, 3H); ^{13}C NMR (60 °C, 100 MHz, DMSO-d_6) δ 170.5, 153.6, 78.1, 67.5, 63.2, 61.1, 57.7, 46.4, 28.2, 27.93, 25.2, 17.20, 14.56; IR (neat film, cm^{-1}) 3373, 2969, 2360, 1781, 1685; HRMS (MALDI - TOF) calcd for $C_{18}H_{30}N_2O_6$ $[M + Na]^+$ 393.2002, found 393.1994. *epi*-**19**: diagnostic ^1H NMR peaks (60 °C, 400 MHz, DMSO-d_6) δ 4.68 (d, J = 4.7 Hz), 3.86 (d, J = 3.5 Hz), 1.40 (s), 0.82 (d, J = 6.9 Hz); diagnostic ^{13}C NMR peaks (100 MHz, DMSO-d_6) δ 170.9, 153.8, 78.2, 57.9, 46.9, 28.3, 27.88, 26.5, 17.22, 14.61.

(*R*)-3-((*S*)-1-(*tert*-Butoxycarbonyl)pyrrolidin-2-yl)-3-hydroxypropanoic Acid (20). To a solution of carbamate **19** (70 mg, 0.189 mmol) in 4:1 THF:H_2O (1.08 mL, 0.175 M), at 0 °C, was added 50% aqueous H_2O_2 (39 μL, 0.680 mmol, 3.6 equiv) dropwise via syringe. A solution of LiOH-H_2O (12.70 mg, 0.302 mmol, 1.6 equiv) in H_2O (216 μL) was added and the reaction solution was stirred at 0 °C (3 h). To this solution was added a solution of Na_2SO_3 (95 mg, 0.756 mmol, 4 equiv) in H_2O (518 μL, 1.46 M) and the mixture was stirred at room temperature (overnight). The mixture was concentrated *in vacuo*, and the residue was diluted with 5% aqueous $NaHCO_3$ (10 mL) and washed with DCM (2 × 10 mL). The resulting aqueous layer was acidified to pH~2 using 37% aqueous HCl and extracted with EtOAc. The original DCM washes were extracted with 5% aqueous $NaHCO_3$ (10 mL), and the resultant aqueous layer was acidified and extracted with EtOAc. The DCM phases were dried (Na_2SO_4) and concentrated *in vacuo* to afford recovered chiral auxiliary (23 mg, 0.178 mmol, 94% recovered). The combined EtOAc phases were dried (Na_2SO_4) and taken to dryness *in vacuo* to afford acid **20** (46.8 mg, 0.18 mmol, 96%) as a pale red oil. α_D^{20} (c 2.3, $CHCl_3$) = (−) 46.3; ^1H NMR (65 °C, 400 MHz, d_6-DMSO) δ 4.14–4.06 (m, 1H), 3.66–3.60 (m, 1H), 3.38–3.29 (m, 1H), 3.20–3.10 (m, 1H), 2.28 (dd, J = 14.9, 4.2 Hz, 1H), 2.18 (dd, J = 14.8, 8.7 Hz, 1H), 1.97–1.81 (m, 2H), 1.77–1.64 (m, 2H), 1.41 (s, 9H); ^{13}C NMR (65 °C, 100 MHz, d_6-DMSO) δ 172.8, 153.7, 78.0, 67.8, 61.0, 61.0, 46.4, 39.8, 28.0, 25.0, 23.2; IR (neat film, cm^{-1}) 3397, 2972, 1676, 1401; HRMS (MALDI - TOF) calcd for $C_{12}H_{21}NO_5$ $[M + Na]^+$: 282.1317, found 282.1318.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^1H and ^{13}C NMR spectra for all compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENTS

We thank Dr. James Kelley and Christopher Lai (Chemical Biology Laboratory, NCI) for HRMS data and Dr. Joseph Barchi (Chemical Biology Laboratory, NCI) for NMR assistance. This work was supported in part by the Intramural Research Program of the NIH, Center for Cancer Research, NCI-Frederick, and the National Cancer Institute, National Institute of Health. The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government.

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