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SYNTHETIC STUDIES OF DIDEMNINS. III.

SYNTHESES OF STATINE AND ISOSTATINE STEREOISOMERS

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Abstract: *The stereoselectivity of the reduction of β-keto ester precursors leading to several stereoisomers of statine and isostatine was investigated. As a result, a short and highly stereoselective route to the isomer of isostatine found in the didemnins, (3S,4R,5S)-isostatine, was devised.*

The didemnins (Figure 1) are a group of macrocyclic depsipeptides isolated from tunicates collected in the waters off the coasts of such countries as Columbia, Mexico, Honduras, Panama, and Guadeloupe.[1,2] These interesting marine natural products exhibit promising biological activity as anticancer[3], antiviral[4], and immunosuppresive[5] agents. Because of their biological significance, several investigators have reported their efforts toward the syntheses of these cyclic depsipeptides.[6] The original structural elucidation of the didemnins did not provide rigorous

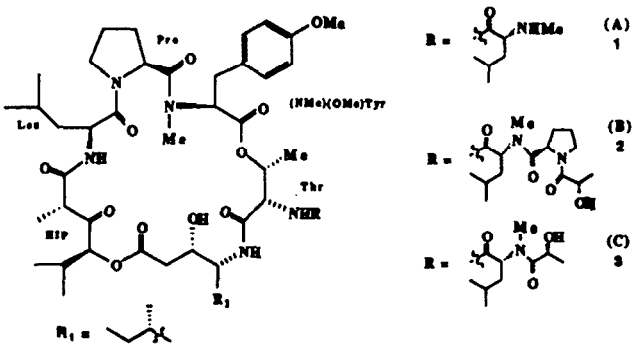
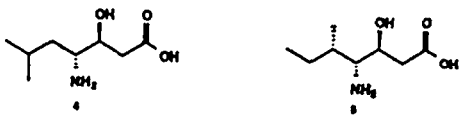


Figure 1. Structures of the Didemnins A, B, and C.

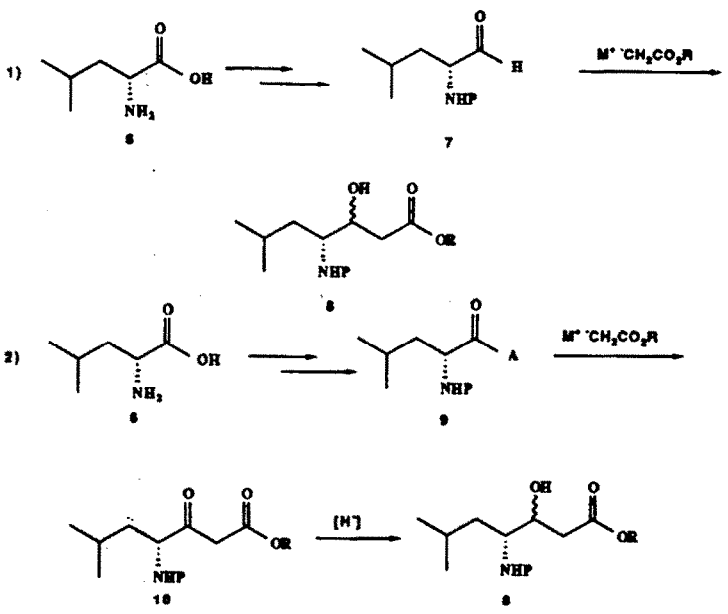
proof that the proposed (3S,4R) stereoisomer of statine (4) was the correct amino acid.[1] In fact, subsequent high field NMR studies by other investigators suggested that some stereoisomer of isostatine was present in the didemnins.[2] Eventually, synthesis of the didemnins with either 4 or (3S,4R,5S)-isostatine (5) incorporated into the depsipeptide ring provided conclusive proof that indeed 5 was the amino acid with the correct absolute configuration.[6a]



One of the most common approaches to statine and its various stereoisomers (Scheme 1, equation 1) involves an aldol condensation on a suitably protected leucinal derivative (7).[7] This strategy has been used to produce statine stereoisomers in studies concerning the structural elucidation and the synthesis of the didemnins.[1,6a] However, this approach suffers from several drawbacks such as extensive initial functional group interconversion from leucine to leucinal, poor stereoselectivity in the aldol condensation, and chance of racemization of the α-amino aldehyde.[7a]

A more attractive route[8,9] (Scheme 1, equation 2) involves direct activation of the carboxylic functionality of leucine followed by alkylation with suitable enolates to produce the corresponding β-keto esters (10). These β-keto esters can be reduced stereoselectively to produce various mixtures of chromatographically separable diastereomers. However, all previous investigations concerning the synthesis of statine by this approach, have produced the β-keto ester in poor to moderate yield, and no extensive study on the optimization of the stereoselective reduction has been reported.[8]

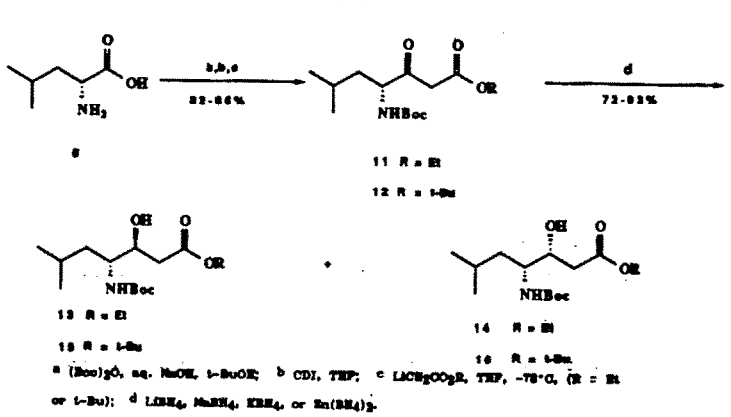
Scheme 1



We have very recently reported an improved procedure for the synthesis of (3S,4R)-statine from D-leucine *via* stereoselective reduction of β-keto esters such as 10, in connection with the synthesis of the didemnins.[9] We now wish to describe our results for the optimization of the stereoselective reduction and expansion of the methodology in devising a highly stereoselective route to (3S,4R,5S)-isostatine (5) from D-alloisoleucine.

The synthetic studies began as outlined in Scheme 2.[9] Readily available D-leucine (6) was protected under standard conditions by treatment with di-*tert*-butyldicarbonate (BOC_2O) in aqueous base to produce BOC-D-leucine.

Scheme 2

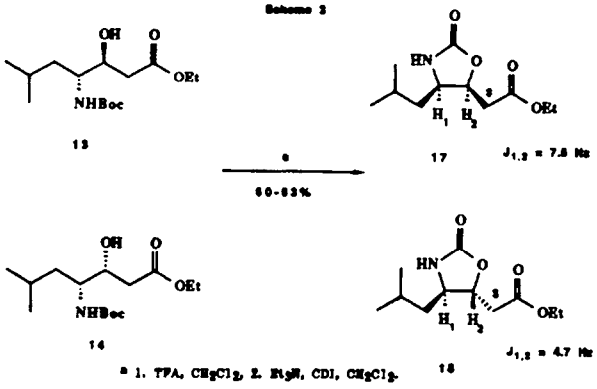


[a] $(Boc)_2O$, aq. NaOH, t-BuOH; [b] CDI, THF; [c] $LiCH_2CO_2R$, THF, -78°C, (R = Et or t-Bu); [d] $LiBH_4$, $NaBH_4$, KBH_4, or $Zn(BH_4)_2$.

The crude product was then treated with 1,1'-carbonyldiimidazole (CDI) in THF to produce the corresponding imidazolide[10] which was not isolated but treated directly with either ethyl or *tert*-butyl lithioacetate at -78°C to produce, after workup and purification, the β-keto esters (11 and 12) in 86% and 82% overall yield from D-leucine, respectively. Several different reagents under various conditions, were tried for the stereoselective reduction of the chiral α-amino carbonyl compounds 11 and 12, including the bulky reducing reagents disiamylborane[11] and lithium tri-*tert*-butoxyaluminohydride.[12] Chiral reducing reagents using N,N'dibenzoylcystine,[13] pinene,[14] and glucofuranose[15] as chiral auxiliaries were also examined as well as microbial reductions using yeast.[16] The bulky hydride reagents produced the reduced products in low yields. None of the chiral reducing reagents provided the high enantioselection in these systems as they have exhibited with other substrates. The microbial reductions provided products in low yields and with poor stereoselection.

Finally, we found that common, readily available borohydride reagents gave the best overall results with respect to yields, purification, and stereoselectivity. We therefore examined a periodic trend of these borohydride reagents [$LiBH_4$, $NaBH_4$, KBH_4, and $Zn(BH_4)_2$], under various conditions, in order to optimize the stereoselectivity of the reduction. As shown in Scheme 2, reduction of β-keto ester 11 with these reagents produced the corresponding β-hydroxy esters in moderate to excellent yields (72-93% yield) as mixtures of chromatographically separable diastereomers (13 and 14). The *erythro* product 13 [having the desired (3S,4R) stereochemistry] was the major product regardless of the reducing reagent.[17] Reduction of compound 12 produced diastereomers 15 and 16 again with the *erythro* product 15 as the major isomer. The purity of the isolated products was determined by comparison of rotation values and gas chromatographic analyses. The absolute stereochemistry of diastereomers 13 and 14 was determined as shown in Scheme 3. Treatment of either pure 13 or 14 with trifluoroacetic acid (TFA) effected removal of the BOC protecting group.

Scheme 3

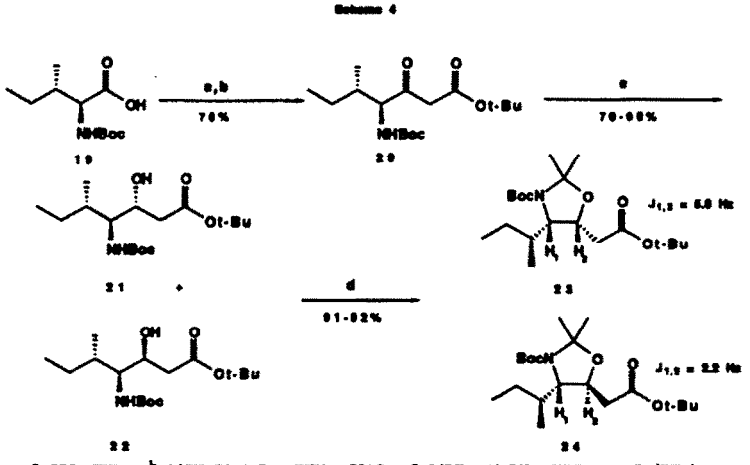


[a] 1. TFA, CH_2Cl_2, 2. Et_3N, CDI, CH_2Cl_2.

Subsequent neutralization of the trifluoroacetate ammonium salt with triethylamine and further treatment with CDI in methylene chloride, produced the oxazolidinones 17 and 18. Decoupling experiments on 17 and 18 allowed determination of the relative configurations at the 3 and 4 positions of statine. Thus, decoupling at the protons labeled 3 in compounds 17 and 18, allowed determination of the coupling constants between ring protons 1 and 2. For the oxazolidinone 17, derived from compound 13, the coupling constant was 7.5Hz, thereby suggesting a *cis* relationship and confirming the (3S,4R) assignment. The coupling constant between the ring protons in

oxazolidinone 18, derived from the assigned (3R,4R) isomer 14, was 4.7Hz which is indicative of a *trans* relationship, thus confirming the (3R,4R) assignment. The results of these decoupling experiments are in good agreement with values obtained from decoupling experiments on other oxazolidine systems used to determine the absolute stereochemistry of statine derivatives.[8a,18]

The approach described was then expanded to develop a synthetic route to several isomers of isostatine. Using readily available BOC-L-isoleucine (19) as a precursor (Scheme 4), produced the corresponding β-keto ester 20, after activation with CDI and alkylation with *tert*-butyl lithioacetate. Reduction of the keto group in 20, with the aforementioned reducing reagents, produced mixtures of chromatographically separable diastereomers (21 and 22), in yields ranging from 70–90%. Compound 21 was always produced as the major product. The absolute stereochemistry was again determined by decoupling experiments on oxazolidines derived from the pure isolated β-hydroxy esters. Thus, treatment of either pure 21 or 22 with 2-methoxypropene in dimethylformamide, in the presence of *p*-toluenesulfonic acid, produced oxazolidines 23 and 24, respectively. Decoupling experiments showed that the coupling constant between the ring protons in 23 was 5.0 Hz while

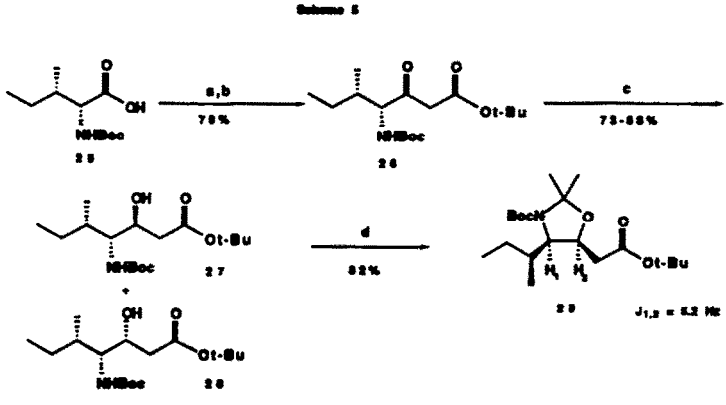


Scheme 4

[a] CDI, THF; [b] $LiCH_2CO_2t$-Bu, THF, -78°C; [c] $LiBH_4$, $NaBH_4$, KBH_4, or $Zn(BH_4)_2$;
[d] 2-methoxypropene, TsOH, DMF.

that in 24 was 2.2Hz, suggesting a *cis* and *trans* relationship respectively. These results confirmed the assignments of (3R,4S,5S) for 21 and (3S,4S,5S) for 22.

Similar results were obtained when BOC-D-alloisoleucine (25) (Scheme 5) was used as the amino



Scheme 5

[a] CDI, THF; [b] $LiCH_2CO_2t$-Bu, THF, -78°C; [c] $LiBH_4$, $NaBH_4$, KBH_4, or $Zn(BH_4)_2$;
[d] 2-methoxypropene, TsOH, DMF.

acid precursor. However, in this case, reduction of the derived β-keto ester 26 produced one diastereomer in high excess over the other. The β-hydroxy ester 27 was produced as the major isomer regardless of the reducing agent used. Compound 27 was assigned the (3S,4R,5S) configuration based on previous results. Compound 28 was produced in such a small amount that it was never isolated for full characterization. Oxazolidine 29 was derived from 27 and decoupling experiments showed that the coupling constant between the ring protons in 29 was 5.2 Hz. These results are indicative of a *cis* relationship and therefore confirm the (3S,4R,5S) assignment.

The results of the stereoselective reductions are shown in Figure 2. The aforementioned

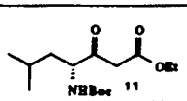
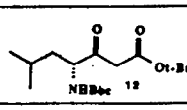
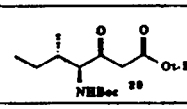
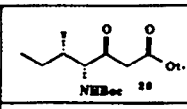
				
$LiBH_4$	(4eq, THF, 0.5h -78°C) 87% 1:1.7	(4eq, THF, 0.5h, -78°C) 93% 1:1.7	(4eq, THF, 0.75h, -78°C) 90% 1:1.5	(4eq, THF, 0.75h, -78°C) 88% 1:5.2
$NaBH_4$	(3.5eq, EtOH, 1h, 0°C) 83% 1:3.0	(3.5eq, EtOH, 1h, 0°C) 83% 1:3.0	(3.5eq, EtOH, 1h, 0°C) 82% 1:7.1	(3.5eq, EtOH, 4h, rt) 80% 1:9.3
KBH_4	(3.5eq, EtOH, 1h, 0°C) 80% 1:7.1	(3.5eq, EtOH, 1h, 0°C) 88% 1:3.7	(4eq, EtOH, 20h, rt) 83% 1:10.6	(4eq, EtOH, 4h, rt) 89% 1:10.5
$Zn(BH_4)_2$	(5eq, Et_2O, 0.5h, 0°C) 72% 1:2.9	(5eq, Et_2O, 0.5h, 0°C) 75% 1:4.1	(5eq, Et_2O, 0.5h, 0°C) 70% 1:4.6	(5eq, Et_2O, 0.5h, 0°C) 73% 1:6.9

Figure 2. Results From the Stereoselective Reduction of the β-keto esters.

β-keto esters 11, 12, 20 and 26 were reduced with $LiBH_4$, $NaBH_4$, KBH_4, and $Zn(BH_4)_2$ using similar if not identical conditions for each individual reagent. The corresponding β-hydroxy esters were produced in moderate to excellent yields as mixtures of chromatographically separable diastereomers, as outlined previously. Examination of these results reveals several periodic trends. In general, the stereoselectivity increased for the reduction of the β-keto esters in going from $LiBH_4$ to KBH_4 and then decreases for $Zn(BH_4)_2$. Overall, the reduction of the isostatine precursors (20 and 26) showed greater stereoselectivity (>10:1 for KBH_4) than for the statine precursors (11 and 12). Reduction with KBH_4 in ethanol gave the greatest stereoselectivity. These results can be rationalized by considering the proposed transition state models by which these chiral α-amino carbonyl compounds (11, 12, 20, and 26) undergo reduction. A review by Tramontini[17] concerning the stereoselective reduction of chiral amino carbonyl compounds proposes a cyclic transition state such as I (Figure 3) for the reduction of chiral α-amino systems.[17]

However, spectral data (UV and NMR) suggests that the β-keto esters 11, 12, 20, and 26 may be easily enolized. Thus, in the enol form transition state models such as II (for 11 and 12) and III (for 20 and 26) shown in Figure 3, are possible.

These cyclic transition states could be formed by chelation of boron between the protected amino group and the enolized oxygen. Hydride attack could then occur either intramolecularly or intermolecularly at the β-position on the least hindered face as determined by the butyl appendage. Reduction of these models would account for several of the experimental results. The *erythro* product would always be produced as the major isomer. This is borne out by our

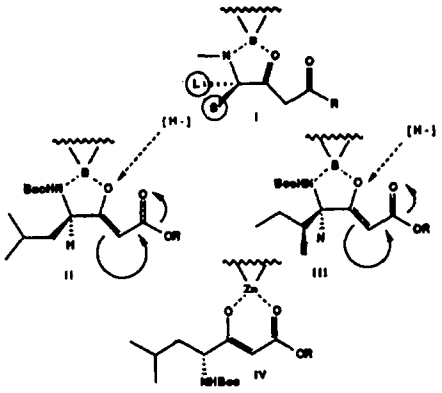


Figure 3. Transition State Models

empirical data. Greater stereoselectivity would be expected in going from $LiBH_4$ to $NaBH_4$ to KBH_4 due to the decrease in reactivity of the reducing reagent. The less reactive borohydride reagent would allow more time for the formation of the cyclic transition state before reduction of the keto group in the acyclic form. One would also expect greater stereoselectivity in the reduction of the isostatine precursors due to the fact that the transition state model (III) has a methyl group closer to the point of hydride attack than in the statine precursor transition state model (II), thus creating greater asymmetric induction. The lack of stereoselectivity in the $Zn(BH_4)_2$ reductions can be accounted for by considering the known chelation of zinc to β-carbonyl compounds[19] as in IV (Figure 3). This chelation would interfere with transition states II and III, and therefore decrease the stereoselectivity. Several five and six-membered heterocyclic amino acid boranes similar to proposed models II and III have actually been synthesized and isolated.[20]

Compound **27**, of course, has the desired (3S, 4R, 5S) stereochemistry that is needed for the isostatine isomer found in the didemnins. Thus, a highly stereoselective route to this unusual amino acid has been achieved. Application of this methodology to the synthesis of the didemnins has been developed and the results of this investigation will be reported shortly.

EXPERIMENTAL

General

All solvents used were reagent grade. Anhydrous ether, tetrahydrofuran (THF), and benzene were distilled from sodium and benzophenone. Methylene chloride and N,N-dimethylformamide (DMF) were distilled from calcium hydride. Dioxane and anhydrous ethanol were used without further purification. Melting points were determined with a Thomas-Hoover melting point apparatus. They are expressed in degrees Centigrade (°C) and are uncorrected. Optical rotations were measured by a Perkin-Elmer Model 241 polarimeter at the sodium line. Proton magnetic resonance spectra (^{1}H NMR) were recorded on a Bruker WM 250 (250 MHz) or a 500 (500 MHz) Fourier transform spectrometer. Decoupled carbon magnetic resonance spectra (^{13}C NMR) were recorded on a Bruker 500 MHz Fourier transform spectrometer. Chemical shifts are measured in parts per million (δ) relative to tetramethylsilane (TMS) as an internal standard. Coupling constants (J values) are in Hertz (Hz). Multiplicities are designated as singlet (s), broad singlet (brs), doublet (d), triplet (t), quartet (q), and multiplet (m). Infrared spectra (IR) were obtained on a Perkin-Elmer Model 281B spectrometer. Solid samples were analyzed as chloroform solutions in sodium chloride cells. Liquids or oils were analyzed as neat films between sodium chloride plates or as chloroform solutions in sodium chloride cells. Absorptions are reported in wave numbers (cm^{-1}) and their intensities are designated as strong (s), medium (m), and weak (w), and only the most prominent or characteristic absorptions are noted. The spectra taken on the Perkin-Elmer Model 281B spectrometer, are calibrated against the 1601 cm^{-1} band of polystyrene. Analytical thin layer chromatography (tlc) was performed on silica gel plates (0.25 cm) precoated with a fluorescent indicator. Visualization was effected with ultraviolet light, ninhydrin (3% w/v) in 95% ethanol containing 2% acetic acid, and phosphomolybdic acid reagent (7% w/v) in 95% ethanol. High resolution mass spectra (HRMS) were obtained on a Hitachi-Perkin Elmer RMH-2 high resolution double focusing, electron impact spectrometer or a Vacuum Generator's V.G. 7070H spectrometer interfaced with a Kratos DS-50-S data system. Elemental analyses were performed by Desert Analytics Organic Microanalysis Labs, Tucson, Arizona. Gas chromatographic analysis was done on a Hewlett Packard 5890 gas chromatograph on a HP-1 crosslinked methyl silicone gum capillary column (25 m x 0.2 mm).

Preparation of β-Keto Esters.
Ethyl and tert-Butyl (R)-4-(carboxyamino)-6-methyl-3-oxoheptanoate 4-tert-butyl ester (11 and 12).

To a suspension of D-leucine (6) (0.20 g; 1.52 mmol) in dioxane (1.22 mL) and water (0.60 mL), stirring at 0°C, was added 1N aqueous sodium hydroxide (3.2 mL) and di-*tert*-butyl dicarbonate (0.67 g; 3.07 mmol). The resulting mixture was warmed to room temperature and stirred for a total of 15 h. The reaction was washed with pentane (2 x 10 mL), and the pentane layer was extracted with saturated aqueous sodium bicarbonate (3 x 5 mL). The combined aqueous layers were cooled to 0°C and acidified to pH 1 by litmus with 1N potassium hydrogen sulfate. The resulting aqueous solution was extracted with ether (4 x 20 mL), and the combined organic layers washed with brine (1 x 10 mL), dried (Na_2SO_4), and concentrated *in vacuo* to produce N-*tert*-butoxycarbonyl-D-leucine (0.368g, crude quantitative yield). The crude product was then azeotropically dried with benzene (3 x 10 mL) and diluted with THF (5.0 mL). To the solution was added 1,1'-carbonyldiimidazole (0.272g; 1.68 mmol) with stirring at room temperature. After stirring for approximately 10 min., the reaction was cooled to -78°C and treated with ethyl lithioacetate (6.4 mL of a 0.77 M solution in THF; 4.93 mmol) [made by adding ethyl acetate (0.5 mL; 5.12 mmol) to lithium diisopropylamine (5.87 mL of a 0.84 M solution in THF; 4.96 mmol] *via* a canula with efficient stirring. The resulting reaction became very thick, and a white precipitate formed. The reaction was stirred at -78°C for 0.5 h when it was quenched at -78°C with saturated aqueous ammonium chloride (5 mL) and warmed to room temperature. The reaction mixture was then diluted with ether (50 mL) and water was added until all solids were dissolved. The organic and aqueous layers were separated and the organic layers were washed sequentially with 5% aqueous HCl (1 x 10 mL) and 5% aqueous $NaHCO_3$ (1 x 10 mL). The combined aqueous layers were extracted with ether (3 x 10 mL). The organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to produce the crude product which was purified by silica gel column chromatography using 10, 15, 20, 25% ether in petroleum ether solvent gradient system to afford 11 (0.36g; 86% yield from 6) as an oil which solidified upon refrigeration (m.p. 38-40°C). Compound 12 was obtained in 82% yield from D-leucine as described above except that *tert*-butyl lithioacetate was used instead of ethyl lithioacetate.

Compound 11 displayed the following spectral characteristics: $[\alpha]^{26}_D$ + 19.46° (c 1.3, $CHCl_3$), $[\alpha]^{19}_D$ + 52.66° (c 1.39, MeOH). Literature value[8c] for L-isomer $[\alpha]^{20}_D$ -49.5° (c 1.0, MeOH). HRMS calcd for $C_{15}H_{28}NO_5$ (M^+ +H): 302.1967. Found: 302.1971. Anal. Calcd for $C_{15}H_{27}NO_5$: C, 59.76; H, 9.03; N, 4.65. Found: C, 59.70; H, 9.24; N, 4.51. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 12.08 (s, C=C-OH, enol resonance), 5.13 (s, C=C-H, enol resonance), 4.96 (1H, d, J=6.9, NH), 4.35 (1H, m, NCH), 4.20 (2H, q, J=7.1, OCH_2), 3.55 (2H, m, (O)CCH_2C(O), 1.80-1.50 (3H, m, CH and CH_2), 1.45 (9H, s, BOC), 1.28 (3H, t, J=7.1, CH_2CH_3), 0.97 - 0.93 (6H, m, isopropyl). IR (neat): 3400 (m), 2900 (s), 2280 (w), 1760 (s), 1530 (s), 1490 (s), 1380 (s), 1180 (s), 1050 (s), 750 (s). cm^{-1}.

Compound 12 displayed the following spectral characteristics: $[\alpha]^{21}_D$ + 39.46 (c 2.23, MeOH). HRMS calcd for $C_{17}H_{32}NO_5$ (M^+ + H): 330.2280. Found 330.2278. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 12.23 (s, C=C-OH, enol resonance), 5.05 (s, C=C-H, enol resonance), 4.96 (1H, d, J=7.7 NH), 4.40 (1H, m, NCH), 3.47 (2H, m, (O)CCH_2C(O)), 1.80 - 1.55 (3H, m, CH and CH_2), 1.47 (9H, s, OtBu), 1.45 (9H, s, BOC), 0.97 - 0.93 (6H, m, isopropyl). IR (neat): 3380 (m), 2900 (s), 1750 (s), 1720 (s), 1520 (2), 1460 (m), 1380 (s), 1260 (s), 1180 (s), 760 (m) cm^{-1}.

tert-Butyl (4S, 5S) and (4R, 5S)-4-(carboxy amino)-5-methyl-3-oxoheptanoate, 4-tert-butyl ester (20) and (26).

To a solution of N-tert-butoxycarbonyl-L-isoleucine (19) (0.523 g; 2.26 mmol) [azeotropically dried with benzene (3x5 mL)] in THF (7.6 mL) was added 1,1'-carbonyldiimidazole (0.48 g, 2.96 mmol) with stirring at room temperature. After stirring for 15 min, the reaction was cooled to -78°C and treated with tert-butyl lithioacetate (10.14 mL of a 0.90 M solution in THF; 9.13mmol) [made by adding tert-butylacetate (1.30 mL, 9.65 mmol) to lithium diisopropylamine (8.86 mL) of a 1.03 M, solution in the THF; 9.11 mmol] dropwise with efficient stirring. The resulting thick white reaction mixture was stirred at -78°C for 0.5 h when it was quenched at -78°C with aqueous saturated ammonium chloride (10 mL) and warmed to room temperature. The reaction was then diluted with ether (50 mL), and water added until all solids in the reaction mixture were dissolved. The organic and aqueous layers were separated and the organic layers were washed sequentially with 5% aqueous HCl (1x10 mL) and 5% aqueous $NaHCO_3$ (1x10 mL). The combined aqueous layers were then extracted with ether (3 x 20 mL), and the organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The resulting residue was purified by column chromatography on silica gel using 25% ether in petroleum ether as eluant to afford pure 20 (0.568g, 76% yield) as a colorless oil. Compound 26 was obtained from N-tert-butoxycarbonyl -D-alloisoleucine (25) in 79% yield using the identical protocol.

Compound 20 displayed the following spectral characteristics: $[\alpha]^{25}_D$ + 16.52° (c 9.64, $CHCl_3$). HRMS calcd for $C_{17}H_{31}NO_5$ (M^+): 329.2202. Found: 329.2189. Anal. Calcd for $C_{17}H_{31}NO_5$: C, 61.96; H, 9.49; N, 4.25. Found: C, 61.98; H, 9.62; N, 4.07. ^1H NMR (250 MHz, $CDCl_3$) δ: 12.27 (s, C=C-OH, enol resonance), 5.10 (1H, d, J=8.9, NH), 5.03 (s, C=C-H, enol resonance), 4.35 (1H, dd, J=4.3 and 8.9, NCH), 3.45 (2H, m, (O)CCH_2C(O), 1.96 (1H, m, CH), 1.60 - 1.25 (1H, m, CH_2), 1.47 (9H,s, OtBu), 1.44 (9H, s, BOC), 0.99 (3H, d, J=6.8, HCC$\underline{H}_3$), 0.90 (3H, t, J=7.3, $CH_2C\underline{H}_3$). IR (neat): 3380 (m), 2900 (s), 1700 - 1750 (s), 1520 (s), 1470 (s), 1380 (s), 1250 (s), 1170 (s), 750 (m) cm^{-1}.

Compound 26 displayed the following spectral characteristics: $[\alpha]^{24}_D$ - 38.88° (c, 2.32, $CHCl_3$). HRMS calcd for $C_{17}H_{31}NO_5$: 329.2202. Found: 329.2188. Anal. Calcd for $C_{17}H_{31}NO_5$: C, 61.96; H, 9.49; N, 4.25. Found C, 61.92; H, 9.72; N, 4.49. ^1H NMR (250 MHz, $CDCl_3$) δ: 12.31 (s, C=C-OH, enol resonance), 5.08 (1H, d, J=8.8, NH), 5.04 (s, C=C-H, enol resonance), 4.49 (1H, dd, J=2.9 and 8.8, NCH), 3.44 (2H, m, (O)CCH_2C(O)), 2.00 (1H, m, CH), 1.60 - 1.15 (2H, m, CH_2), 1.47 (9H, s, OtBu), 1.44 (9H, s, BOC), 0.97 (3H, t, J=7.3, $CH_2C\underline{H}_3$), 0.77 (3H, d, J=6.8, $CHC\underline{H}_3$) IR (neat): 3380 (m), 2900 (s), 1700 - 1760 (s), 1500 (s), 1460 (s), 1380 (s), 1160 (s), 760 (m) cm^{-1}.

Reductions of β-Keto Esters.
Ethyl (3S, 4R) and (3R, 4R)-4-(carboxyamino)-3-hydroxy-6-methylheptanoate, 4-tert-butyl ester (13) and (14). tert-Butyl (3S, 4R) and (3R, 4R)-4-(carboxyamino)-3-hydroxy-6-methylheptanoate 4-tert-butyl ester (15) and (16). tert-Butyl (3R, 4S, 5S) and (3S, 4S, 5S)-4-(carboxyamino) -3-hydroxy-5-methylheptanoate, 4-tert-butyl ester (21) and (22) and tert-Butyl (3S, 4R, 5S)-4-(carboxyamino)-3-hydroxy-5-methyl heptanoate, 4-tert-butyl ester (27).

The β-hydroxy esters were produced by reduction of the corresponding β-keto esters using the following procedures. The experimental is given in detail for the formation of compounds 13 and 14, and the procedure may vary with regard to reaction time, temperature, or amount of reducing reagent for compounds 15, 16, 21, 22, or 27 as outlined in Figure 2. Ratios were determined by gas chromatography.

Lithium Borohydride Reductions.

To a solution of compound 11 (0.112 g; 0.37mmol) [azeotropically dried with benzene (3x5 mL)] in THF (1.24 mL) was added lithium borohydride (0.75 mL of a 2M solution in THF; 1.5 mmol) dropwise with stirring at -78°C. The reaction was stirred for 0.5 h when it was quenched with 5% aqueous HCl (5 mL). The reaction was warmed to room temperature and diluted with ether (20 mL). The organic and aqueous layers were separated, and the aqueous layer was extracted with ether (3x5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to provide the crude alcohol which was purified by silica gel column chromatography using 55% ether in petroleum ether as eluant to afford a mixture of diastereomers 13 and 14 as a colorless oil (0.098 g; 87%). Compounds 13 and 14 were separated by silica gel column chromatography using 15% ethyl acetate in petroleum ether as eluant. Diastereomers 15 and 16 were produced in 93% yield from compound 12 and purified by silica gel column chromatography using 40% ether in petroleum ether as eluant. The diastereomers were separated using 10% ethyl acetate in petroleum ether. Diastereomers 21 and 22 were produced in 90% yield from compound 20, and compounds 27 and 28 were obtained in 88% yield from compound 26. The crude products were purified by column chromatography using 35% ether in petroleum ether and the purified diastereomeric mixture separated using 10% ethyl acetate in petroleum ether.

Sodium Borohydride Reductions.

To a solution of compound 11 (0.123 g; 0.409 mmol) [azeotropically dried with benzene (3x5 ml)] in ethanol (2.0 mL) was added $NaBH_4$ (0.54 g; 1.43 mmol) with stirring at 0°C. The reaction was stirred at 0°C for 1h, when it was then quenched with glacial acetic acid until the pH of the reaction mixture was 7 (litmus). The resulting solution was diluted with ethanol (4 mL) and warmed with stirring to room temperature. The reaction was then concentrated *in vacuo* to produce a white solid which was diluted with a 1:1 mixture of water and ethyl acetate (20 mL). The layers were separated, and the aqueous phase was extracted with ethyl acetate (3x5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to afford the crude product which was purified by column chromatography, using 55% ether in petroleum ether as

eluant on silica gel, to provide a diastereomeric mixture of 13 and 14 as a colorless oil (0.103 g; 83% yield). Compounds 15 and 16 were obtained as described above from compound 12 in 83% yield. The crude reaction mixture was purified by silica gel column chromatography using 40% ether in petroleum ether as the eluant. The diastereomers were separated using 10% ethyl acetate in petroleum ether as eluant. Diastereomers 21 and 22 were produced in 82% yield from compound 20 and compounds 27 and 28 were derived in 80% yield from β-keto ester 26. The crude products were purified by column chromatography using 40% ether in petroleum ether as eluant. The purified diastereomeric mixtures were separated using 10% ethyl acetate in petroleum ether.

Potassium Borohydride Reductions.

To a solution of compound 11 (0.134 g; 0.445 mmol) [azeotropically dried with benzene (3x5 mL)] in ethanol (2.2 mL) was added KBH_4 (0.084g, 1.56 mmol) with stirring at 0°C. The reaction was stirred for 1 h at 0°C, when it was quenched by adding glacial acetic acid dropwise at 0°C, until th pH of the reaction mixture was 7 (litmus). The quenched reaction was diluted with ethanol (10 mL) and warmed with stirring to room temperature. The reaction was then concentrated *in vacuo* to produce a white solid which was dissolved in a 1:1 mixture of water and ethyl acetate (20 mL). The organic and aqueous phases were separated, and the aqueous layers were extracted with ethyl acetate (3x5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The oily residue was purified by column chromatography, using 55% ether in petroleum ether as eluant on silica gel, to afford compounds 13 and 14 as a mixture of diastereomers (0.107 g, 80% yield). Diastereomers 13 and 14 were separated by column chromatography using 15% ethyl acetate in petroleum ether as eluant on silica gel. Compounds 15 and 16 were produced as described above from compound 12 in 88% yield and purified by silica gel column chromatography using 40% ether in petroleum ether as eluant. The diastereomers 15 and 16 were separated by silica gel column chromatography using 10% ethyl acetate in petroleum ether. Diastereomers 21 and 22 were produced as described (Figure 2) in 83% yield from compound 20, and diastereomers 27 and 28 from compound 26, in 89% yield. The crude products were purified by column chromatography using 40% ether in petroleum ether and the diastereomers were separated using 10% ethyl acetate in petroleum ether.

Zinc Borohydride Reductions.

To a solution of compound 11 (0.100 g; 0.333 mmol) [azeotropically dried with benzene (3x3 mL)] in ether (1.7 mL), stirring at 0°C, was added zinc borohydride (12.0 mL of a 0.14M solution; 1.68 mmol). The reaction was stirred at 0°C for 0.5h, when it was quenched with 5% aqueous HCl (10 mL). The reaction was warmed to room temperature and diluted with ether (30 mL). Additional 5% aqueous HCl was added with stirring until all solids dissolved. The ether and aqueous layers were separated, and the ether layer was washed with 5% aqueous $NaHCO_3$ (1x10 mL). The combined aqueous layers were extracted with ethyl acetate (3x10 mL). The combined ether layers were dried (Na_2SO_4) and concentrated *in vacuo* to provide the crude product. The oily residue was purified by silica gel column chromatography using 55% ether in petroleum ether as eluant to afford the pure product (0.073 g; 72% yield) as a diastereomeric mixture of 13 and 14. The diastereomers were separated using 15% ethyl acetate in petroleum ether as an eluant for silica column chromatography. Compounds 15 and 16 were produced in 75% yield from compound 12. The diastereomers 15 and 16 were separated using silica gel column chromatography with 10% ethyl acetate in petroleum ether as eluant after initial purification using 40% ether in petroleum ether. Reduction of compound 20 as described above, afforded diastereomers 21 and 22 in 70% yield, and reduction of 26 produced 27 and 28 in 73% yield. The crude products were purified by silica gel chromatography using 40% ether in petroleum ether, and the diastereomers were separated using 10% ethyl acetate in petroleum ether as eluant.

Compound 13 displayed the following physical characteristics $[\alpha]^{19}_D$ + 22.03° (c 1.77, MeOH) Lit. value for enantiomer $[\alpha]^{24}_D$ -23.2° (c 0.94, MeOH).[7c] M.p. 45-47°C. HRMS calcd for $C_{15}H_{30}NO_5$ (M^+ + H): 304.2124. Found: 304.2157. ^1H NMR (500 MHz, $CDCl_3$) δ: 5.01 (1H, d, J=8.4, NH), 4.16 (2H, q, J=7.1, OCH_2), 4.02 (1H, m, OCH), 3.80 (1H, s, OH), 3.66 (1H, m, NCH), 2.49 (2H, m, $CH_2C(O)$), 1.67 (1H, m, CH), 1.44, (9H, s, BOC), 1.35 (2H, m, CH_2), 1.27 (3H, t, J=7.1, OCH_2CH_3), 0.93 (6H, m, isopropyl). IR ($CHCl_3$): 3480 (s), 2980 (s), 2280 (w), 1720 (s), 1700 (s), 1520 (s), 1480 (m), 1460 (m), 1400 (s), 1380 (s), 1260 (s), 750 (s) cm^{-1}. ^{13}C NMR (500 MHz, $CDCl_3$) δ: 172.41 (C-1), 155.89 (BOC carbonyl), 78.94 (ester O-C), 71.08 (C-3), 60.38 (BOC O-C), 52.48 (C-4), 38.49 (C-2), 38.13 (C-5), 28.07 (BOC CH_3), 24.41 (C-6), 23.44 and 21.27 (isopropyl CH_3), 13.84 (ester CH_3).

Compound 14 displayed the following spectral characteristics: $[\alpha]^{21}_D$ + 39.87° (c 0.71, MeOH). Lit. value for enantiomer $[\alpha]^{24}_D$ -37.9 (c 0.84, MeOH).[7c] HRMS calcd for $C_{15}H_{30}NO_5$ (M^+ + H): 304.2124. Found: 304.2157. ^1H NMR (500 MHz, $CDCl_3$) δ: 4.90 (1H, d, J=9.7, NH), 4.16 (2H, q, J=7.1, OCH_2), 4.02 (1H, m, OCH), 3.63 (1H, m, NCH), 3.37 (1H, s, OH), 2.52 (2H, m, $CH_2C(O)$), 1.66 (1H, m, CH), 1.53 and 1.34 (2H, m, CH_2), 1.44 (9H, s, BOC), 1.27 (3H, t, J=7.1, OCH_2CH_3), 0.93 (6H, d, J=6.7, isopropyl). IR (neat): 3480 (s), 3400 (s), 2980 (s), 2280 (s), 1720 (s), 1700 (s), 1520 (s), 1480 (m), 1180 (s), 750 (s) cm^{-1}. ^{13}C NMR (500 MHz, $CDCl_3$) δ: 173.24 (C-1), 155.98 (BOC carbonyl), 79.02 (ester O-C), 69.60 (C-3), 60.66 (BOC O-C), 51.89 (C-4), 38.75 (C-2 and C-5), 28.27 (BOC CH_3), 24.63 (C-6), 22.94 and 22.14 (isopropyl CH_3), 14.03 (ester CH_3).

Compound 15 displayed the following physical characteristics. $[\alpha]^{24}_D$ + 19.75° (c 0.81, MeOH). M.p. 67-68.5°C. HRMS calcd for $C_{17}H_{33}NO_5$ (M^+): 331.2359. Found: 331.2316. Anal. Calcd. for $C_{17}H_{33}NO_5$: C, 61.59; H, 10.04; N, 4.23. Found: C, 61.74; H, 10.31; N, 4.48. ^1H NMR (500 MHz, $CDCl_3$) δ: 4.93 (1H, d, J=8.4, NH), 3.98 (1H, m, OCH), 3.66 (2H, m and s, NCH and OH), 2.39 (2H, m, $CH_2C(O)$), 1.67 (1H, m, CH), 1.46 (9H, s, OtBu), 1.44 (9H, s, BOC), 1.33 (2H, m, CH_2), 0.92 (6H, m, isopropyl). IR (neat): 3460 (m), 3380 (m), 2980 (s), 2280 (w), 1740 - 1700 (s), 1520 (m), 1460 (m), 1170 (m), 1050 (m) cm^{-1}. ^{13}C NMR (500 MHz, $CDCl_3$) δ: 171.93 (C-1), 155.85 (BOC carbonyl), 80.91

(ester O-C), 78.96 (BOC O-C), 71.11 (C-3), 52.39 (C-4), 39.10 (C-2), 38.39 (C-5), 28.17 (BOC CH_3), 27.85 (ester CH_3), 24.46 (C-6), 23.58 and 21.36 (isopropyl CH_3).

Compound 16 displayed the following physical characteristics: $[\alpha]^{23}_D$ + 45.00° (c 0.68, MeOH). HRMS calcd for $C_{17}H_{33}NO_5$ (M^+) 331.2359. Found: 331.2316. Anal. Calcd. for $C_{17}H_{33}NO_5$: C, 61.59; H, 10.04; N, 4.23. Found: C, 61.74; H, 10.31; N, 4.48. ^1H NMR (500 MHz, $CDCl_3$) δ: 4.95 (1H, d, J=9.6 NH), 3.99 (1H, m, OCH), 3.59 (2H, m and s, NCH and OH), 2.42 (2H, m, $CH_2C(O)$), 1.66 (1H, m, CH), 1.52 and 1.35 (2H, m, CH_2), 1.46 (9H, s, OtBu), 1.44 (9H, s, BOC), 0.93 (6H, m, isopropyl). IR (neat): 3460 (m), 3380 (m), 2980 (s), 2280 (w) 1740-1700 (s), 1520 (m), 1460 (m), 1410 (m), 1170 (m), 1050 (m) cm^{-1}. ^{13}C NMR (500 MHz, $CDCl_3$) δ: 172.61 (C-1), 155.91 (BOC carbonyl), 81.07 (ester O-C), 78.84 (BOC O-C), 69.95 (C-3), 51.80 (C-4), 41.67 (C-2), 39.71 (C-5), 28.26 (BOC CH_3), 27.93 (ester CH_3), 24.58 (C-6), 22.94 and 22.14 (isopropyl CH_3).

Compound 21 displayed the following physical characteristics: $[\alpha]^{24}_D$ + 7.63° (c 0.76, MeOH). M.p. 73 - 74°C. HRMS calcd for $C_{17}H_{33}NO_5$ (M^+): 331.2359. Found: 331.2324. $CH_2(O)$ ^1H NMR (500 MHz, $CDCl_3$) δ: 4.57 (1H, d, J=10.1, NH), 3.96 (1H, m, OCH), 3.54 (1H, m, NCH), 3.45 (1H, s, OH), 2.52 and 2.36 (2H, m, $CH_2(O)$, 1.83 (1H, m, CH), 1.61 and 1.01 (2H, m, CH_2), 1.46 (9H, s, OtBu), 1.44 (9H, s, BOC), 0.93 (6H, m, $2CH_3$). IR ($CHCl_3$): 3440 (s), 2980 (s), 2260 (w), 1750-1680 (s), 1510 (s), 1150 (s), 750 (s) cm^{-1}. ^{13}C NMR (500 MHz, $CDCl_3$) δ: 172.42 (C-1), 156.22 (BOC carbonyl), 80.96 (ester O-C), 79.11 (BOC O-C), 68.76 (C-3), 58.82 (C-4), 39.37 (C-2), 34.49 (C-5), 28.20 (BOC CH_3), 27.92 (ester CH_3), 23.03 (C-6), 16.15 (5-Me), 11.57 (C-7).

Compound 22 displayed the following physical characteristics: $[\alpha]^{24}_D$ + 38.51° (c 0.67, MeOH). HRMS calcd for $C_{17}H_{33}NO_5$ (M^+): 331.2359. Found: 331.2324. ^1H NMR (500 MHz, $CDCl_3$) δ: 4.97 (1H, d, J=10.1, NH), 4.23 (1H, m, $CH_2C(O)$, 3.33 (1H, brs, OH), 3.21 (1H, m, NCH), 2.46 and 2.36 (2H, m, $CH_2C(O)$) 1.59 (1H, m, CH), 1.55 and 1.16 (2H, m, CH_2), 1.46 (9H, s, OtBu), 1.45 (9H, s, BOC), 0.96 (3H, d, J=6.7, $CHCH_3$), 0.89 (3H, t, J=7.4, CH_2CH_3). IR ($CHCl_3$): 3440 (s), 2980 (s), 2260 (w), 1750 - 1680 (s), 1510 (s), 1150 (s), 750 (s) cm^{-1}, ^{13}C NMR (500 MHz, $CDCl_3$) δ: 172.95 (C-1), 156.21 (BOC carbonyl), 81.20 (ester O-C), 78.86 (BOC O-C), 66.85 (C-3), 58.00 (C-4), 40.06 (C-2), 36.46 (C-5), 28.32 (BOC CH_3), 28.00 (ester CH_3), 25.54 (C-6), 15.65 (5-Me), 11.06 (C-7).

Compound 27 displayed the following spectral characteristics: $[\alpha]^{23}_D$ - 8.75° (c 0.80, MeOH). HRMS calcd for $C_{17}H_{33}NO_5$ (M^+): 331.2359. Found: 331.2387. ^1H NMR (500 MHz, $CDCl_3$) δ: 4.54 (1H, d, J=9.3, NH), 3.87 (1H, m, OCH), 3.62 (1H, m, NCH), 3.42 (1H, s, OH), 2.54 and 2.41 (2H, m, CH_2 C(O)), 1.92 (1H, m, CH), 1.44 (9H, s, BOC), 1.43 (9H, s, OtBu), 1.35 and 1.21 (2H, m, CH_2), 0.93 (3H, m, $CHCH_3$), 0.86 (3H, m, CH_2CH_3). IR (neat): 3480 (m), 3000 (s), 1740-1700 (s), 1510 (m), 1410 (s), 1380 (s), 1250 (s), 1150 (s) 1080 (s), 770 (s) cm^{-1}. ^{13}C NMR (500 MHz, $CDCl_3$) δ: 172.61 (C-1), 155.95 (BOC carbonyl), 81.06 (ester O-C), 79.04 (BOC O-C), 68.93 (C-3), 56.48 (C-4) 39.59 (C-2), 33.82 (C-5), 28.21 (BOC CH_3), 27.94 (ester CH_3), 27.00 (C-6), 13.03 (5-Me), 11.59 (C-7).

Formation of the Oxazolidines.

Ethyl (4R, 5S)-4-sec-butyl-2-oxo-5-oxazolidineacetate 17 and Ethyl (4R, 5R)-4-sec-butyl-2-oxo-5-oxazolidineacetate 18.

To a solution of compound 13 (0.069 g; 0.23 mmol) in methylene chloride (0.5 mL) stirring at 0°C was added trifluoracetic acid (0.5 mL) *via* a syringe. The reaction was warmed to room temperature and stirred for 5 minutes when it was then diluted with anhydrous ether (20 mL) and concentrated to near dryness *in vacuo*. The remaining trifluoracetic acid was removed azeotropically with ether (3x5 mL). The residue containing the crude trifluoroacetate ammonium salt was azeotropically dried with benzene and diluted with methylene chloride (1.5 mL). This solution was then cooled to 0°C and treated with N, N-diisopropylethylamine (0.08 mL, 0.46 mmol) *via* a syringe followed by addition of 1,1'-carbonyldiimidazole (CDI) (0.08g; 0.49 mmol). The reaction was stirred 48 h when it was then diluted with methylene chloride (20 mL) and washed sequentially with 5% aqueous HCl (1x5 mL) and 5% aqueous $NaHCO_3$ (1x5 mL). The organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The oily residue was purified by column chromatography on silica gel, using 45% ethyl acetate in petroleum ether to afford 17 (0.033 g; 63% from 13). Compound 18 was produced in an identical manner as described above in 60% yield from compound 14.

Compound 17 displayed the following physical charateristics: $[\alpha]^{24}_D$ + 12.18° (c 1.1, MeOH). HRMS calcd for $C_{11}H_{19}NO_5$ (M^+): 299.1314. Found: 299.1300. ^1H NMR (500 MHz, $CDCl_3$) δ: 6.23 (1H, m, NH), 5.07 (1H, m, OCH), 4.19 (2H, q, J=7.1, OCH_2), 4.01 (1H, m, NCH), 2.81 (1H, dd, J=7.5 and 16.5, CHC(O) and 2.66 (1H, dd, J=6.9 and 16.5, CHC(O), 1.63 (1H, m, CH), 1.49 and 1.13 (2H, m, CH_2), 1.28 (3H, t, J=7.1, CH_2CH_3), 0.97 (3H, d, J=6.6, $CHCH_3$), 0.91 (3H, d, J=6.6, $CHCH_3$). IR (neat): 3300 (m), 2900 (s), 1740 (s), 1770 (s), 1480 (w), 1400 (s), 1200 (s), 1040 (m) cm^{-1}.

Compound 18 displayed the following physical characteristics: $[\alpha]^{24}_D$ + 66.7 (c 1.15, MeOH). HRMS calcd for $C_{11}H_{19}NO_5$ (M^+): 299.1314. Found: 299.1300. ^1H NMR (500 MHz, $CDCl_3$) δ: 5.45 (1H, m, NH), 4.56 (1H, m, OCH), 4.18 (2H, q, J=7.1, OCH_2), 3.62 (1H, m, NCH), 2.81 (1H, dd, J=6.4 and 16.2, CHC(O)) and 2.69 (1H, dd, J=6.7 and 16.2, CHC(O), 1.70 - 1.40 (3H, m, CH_2 and CH), 1.28 (3H, t, J=7.1, CH_2CH_3), 0.96-0.93 (6H, m, isopropyl). IR (neat): 3300 (m), 2900 (s), 1740 (s), 1770 (s), 1480 (w), 1400 (s), 1200 (s), 1040 (m) cm^{-1}.

tert-Butyl (4S, 5R)-2,2-dimethyl-4-[(S)-1-methylpropyl]-5-oxazolidineacetate 23. tert-butyl (4S, 5S)-2,2-dimethyl-4-[(S)-1-methylpropyl]-5-oxazolidineacetate 24 and tert-Butyl (4R, 5S) -2,2-dimethyl-4-[(S)-1-methylpropyl]-5-oxazolidineacetate 29.

To a stirred solution of compound **21** (0.027 g; 0.082 mmol) [azeotropically dried with benzene (3x5 mL)] in dimethylformamide (DMF) (0.42 mL) was added *p*-toluenesulfonic acid monohydrate (0.003g, 0.016 mmol) followed by 2-methoxypropene (0.02 mL, 0.21 mmol). The reaction was stirred at room temperature for 12 h. The reaction was then diluted with water (10 mL), and the resulting mixture extracted with ether (4x15 mL). The combined ether extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography, using 15% ether in petroleum ether as eluant to provide pure **23** (0.028g; 92% yield). Compound **24** was produced from compound **22** in 91% yield, and compound **29** from compound **27** in 82% yield by the same procedure.

Compound **23** displayed the following physical characteristics: $[\alpha]^{21}_D$ - 21.74° (c 1.55, $CHCl_3$). M.P. 58-59°C. HRMS calcd for $C_{20}H_{38}NO_5$ (M^+ + H): 372.2750. Found 327.2724. ^1H NMR (500 MHz, $CDCl_3$) δ: 4.43 (1H, m, OCH), 3.91 - 3.79 (1H, m, NCH), 2.59 (2H, m, $CH_2C(O)$), 1.40 - 1.60 (26H, CH_2, $C(CH_3)_2$, BOC, OtBu), 1.14 (1H, m, CH), 0.96 - 0.90 (6H, m, $CHCH_3$ and CH_2CH_3). IR ($CHCl_3$): 2900 (s), 1740 (s), 1690 (s), 1470 (m), 1410 (s), 1380 (s), 1310 (m), 1170 (m) cm^{-1}.

Compound **24** displayed the following physical characteristics: $[\alpha]^{22}_D$ - 17.53° (c 2.15, $CHCl_3$). HRMS calcd for $C_{20}H_{38}NO_5$ (M^+ +H): 372.2750. Found 327.2724. ^1H NMR (250 MHz, $CDCl_3$) δ: 4.35 (1H, m, OCH), 3.80 - 3.55 (1H, m, NCH), 2.62 - 2.42 (2H, m, $CH_2C(O)$), 2.05 - 1.00 (9H, m, CH_2, CH, $C(CH_3)_2$), 1.48 (9H, s, BOC), 1.46 (9H, s, OtBu), 0.94 - 0.89 (6H, $CHCH_3$ and CH_2CH_3). IR ($CHCl_3$), 2900 (s), 1740 (s), 1700 (s), 1470 (m), 1410 (s), 1380 (s), 1100 (m) cm^{-1}.

Compound **29** displays the following physical characteristics: $[\alpha]^{22}_D$ + 14.79° (c 1.42, $CHCl_3$). HRMS calcd for $C_{20}H_{38}NO_5$ (M^++H) 372.2750. Found 372.2724. ^1H NMR (250 MHz, $CDCl_3$); 4.43 (1H, m, OCH), 3.99 - 3.86 (1H, m, NHC), 2.57 (2H, m, $CH_2C(O)$), 1.72 - 1.10 (27H, m, CH_2, CH, BOC, OtBu, $C(CH_3)_2$), 0.94 - 0.88 (6H, m, $CHCH_3$, CH_2CH_3). IR ($CHCl_3$): 2900 (s), 1740 (s), 1700 (s), 1470 (m), 1410 (s), 1380 (s), 1250 (m), 1180 (s) cm^{-1}.

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