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Stereoselective Total Synthesis of Topographically Constrained Designer Amino Acids: 2', 6'-Dimethyl-β-methyltyrosines

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Abatract : The constrained aromatic α-amino acid 2', 6'-dimethyl-β-methyl tyrosine (*Figure 1*) was designed to provide specific local constraints to peptides or peptide mimetics. We report here methods for the total asymmetric synthesis of all four stereoisomers. The precursors used were α,β-unsaturated acid derivatives, (2*E*) 3-(4')-methoxy-2',6'-dimethyl-2-propenoic acid (**5**) and crotonyl chloride (**6**). In order to introduce chirality at both the α- and the β-positions of the amino acids, optically pure 4-phenyl-2-oxazolidinones (Xc) were coupled to **5** and **6**. The key steps for the synthesis were: (**1**) a Michael type addition using either methylmagnesium bromide/copper (I) bromide-dimethyl sulfide complex or 4-methoxy-2,6-dimethylphenylmagnesium bromide / copper (I) bromide-dimethyl sulfide complex as nucleophiles; (**2**) an asymmetric bromination of the α-position of the *N*-acyloxazolidinones using di(*n*-butyl)boron triflate/DIEA/NBS as reagents at low temperature. In both cases, the stereoselectivies and yields were excellent; (**3**) amination was achieved in nearly quantative yield by treating the bromides with azide exchange resin via an S_N2 mechanism. (Electrophilic azidation using 2,4,6-triisopropylsulfonyl azide also was achieved). The excellent stereoselectivity (80-98% ee/de) and overall yield (30- 60%) made these optically pure amino acids available in amounts practical for peptide synthesis and further conformational and structure-activity relationship studies of various peptide analogues.

INTRODUCTION

One of the most practical approaches for designing receptor-selective peptide and peptido-mimetic ligands with high potency and specific biological properties is to apply global and/or local constraints to polypeptides.[1] For the design of polypeptides with local topographic constraints, we have utilized β-branched phenylalanine, tyrosine and other aromatic amino acid analogues in several biologically active peptides.[2] The utilization of topographically constrained analogues provides valuable information and new insights about how these amino acid residues are involved in the binding of peptides to their receptors and in signal transduction.[2] Very recently, we have synthesized a series of highly constrained tyrosine derivatives, 2', 6'-dimethylphenyl-β-methyltyrosines (TMTs), which have been incorporated into δ opioid peptide agonists. The remarkable differences in binding affinities and bioactivities of these δ opioid peptides, which differ only from one another in having different isomers of this amino acid in their sequences, provide new insights into the preferred topography of the tyrosine residue and its effect on binding to receptors and subtypes.[3]

The 2', 6'-dimethylphenyl-β-methyltyrosines are of particular interest and importance because by incorporating methyl substituents in the 2' and 6' positions of tyrosine's side chain aromatic ring and of the β-position as well, not only is the χ_1 torsional angle of the amino acid side chain constrained, but the χ_2 torsional angle also becomes highly restricted (*Figure 1*). Model building studies and steric considerations suggested that a high barrier of rotation would exist about the C_β-C_γ bond. Indeed, temperature dependent dynamic NMR studies have shown[4] that the energy barrier for rotation of the dimethyl substituted phenyl ring in the title compounds is 14-20 kcal/mol. This substantial but not rigid restriction of the torsion angles may offer certain advantages for ligands to recognize their receptors and may result in a better binding fit. We report here methods for the total synthesis of all four isomers of 2', 6'-dimethylphenyl-β -methyltyrosine in quantities

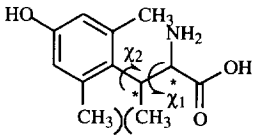


Figure 1. Methyl substitutions caues restrictions of rotation about the torsional angles of 2', 6'-dimethylphenyl-β-methyltyrosines, * indicates the location of the chiral center.

sufficient for structural, conformational and dynamic studies, and for incorporation into peptides.

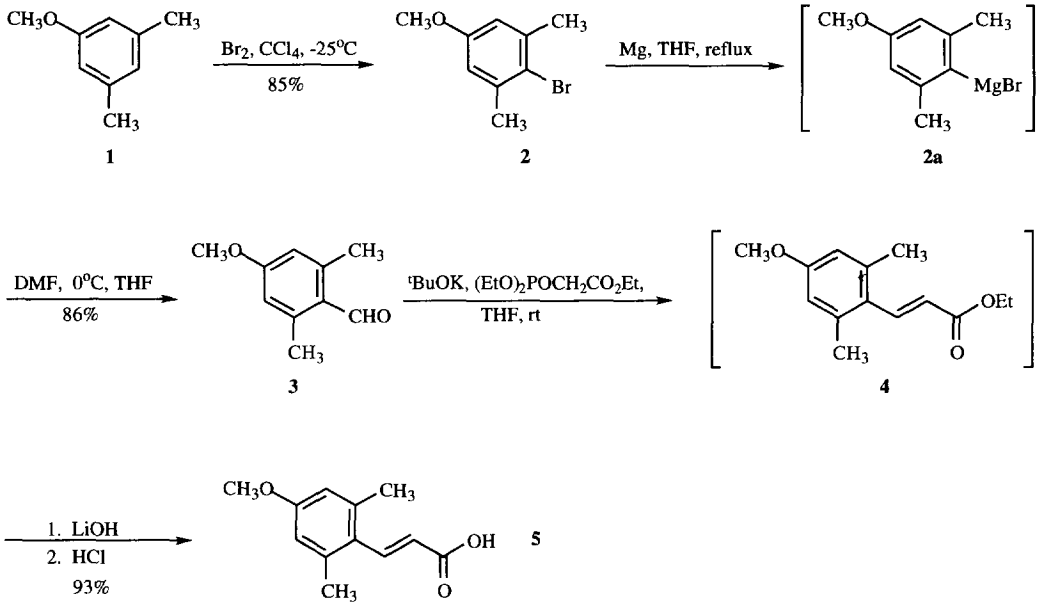
RESULTS AND DISCUSSION

The precursors selected for these syntheses were 2*E*-3-(4'-methoxy-2', 6'-dimethylphenyl)-2-propenoic acid (**5**) or commercially available crotonyl chloride (**6**). Acid **5** was prepared by literature methods[5] with modifications such that the stereochemistry of the carbon-carbon double bond was exclusively *trans* as determined by proton NMR. Thus, 3, 5-dimethylanisole (**1**) was used as starting material for preparing **5** (*Scheme 1*). Electrophilic addition of bromine to substituted anisole **1** was carried out without catalyst and occurred exclusively at the *para* position to the 4-methoxy group, although this position is the most hindered (*Scheme 1*). Bromide **2** was converted to the corresponding Grignard reagent (without initiator) and condensed with dimethylformamide to provide aldehyde **3**. Aldehyde **3** underwent a Wittig reaction with triethylphosphonoacetate in the presence of potassium *tert*-butoxide to afford 2*E*-3-(4'-methoxy-2',6'-dimethylphenyl)-2-propenoate (**4**), which was then subjected to basic hydrolysis followed by acidification to afford acid **5**. Compared to the previously reported method for synthesizing this acid,[5] the route developed here for the synthesis of **5** has many advantages. The overall yields are high, the entire synthesis requires less time to perform, chromatography is not required, and all reactions can readily be carried out on scales of 40-50 grams, although larger scale should be possible.

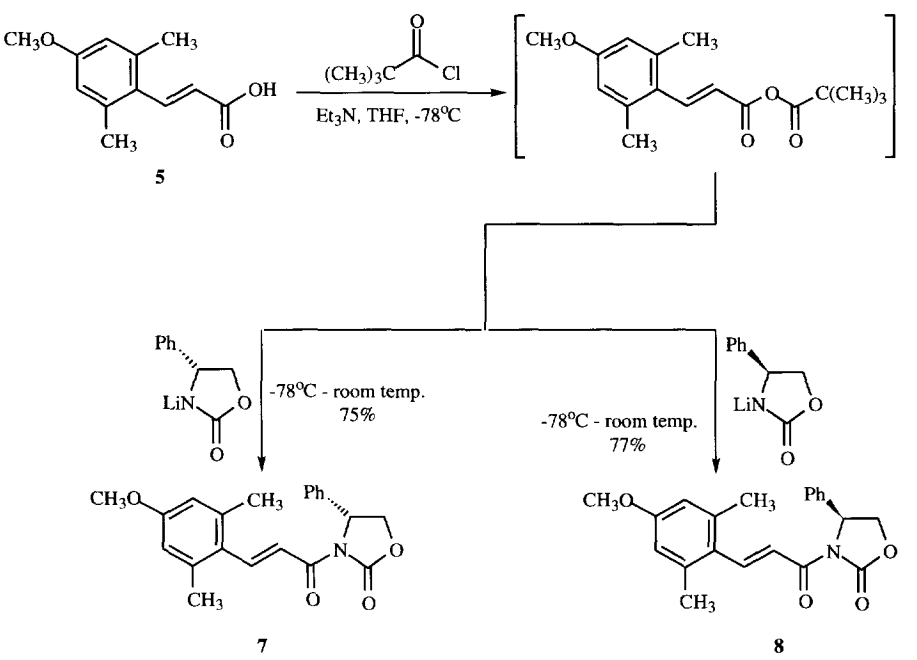
Previously we have reported extensive studies on the asymmetric synthesis of β-methylphenylalanine, β-methyltyrosine and β-methyltryptophan derivatives.[6-9] In some of these studies, we used optically pure 4-phenyl-2-oxazolidinones as chiral auxiliaries suitable for introducing a chiral center at the β-position of the α,β-unsaturated acid.[8,9] This method was adopted for the synthesis reported here. Thus, optically pure 4-phenyl-2-oxazolidinones were converted to their lithium salts at low temperature by treatment with *n*-BuLi, and were coupled to the activated mixed anhydride of acid **5** (obtained by treatment of **5** with pivaloyl chloride) to afford enatiomerically pure *N*-acyl-4-phenyl-2-oxazolidinones **7** or **8** (*Scheme 2*). The *N*-acyl-oxazolidinones **9** and **10** can also be prepared via a similar mixed anhydride pathway using crotonic acid. However, better yields of **9** and **10** were observed when they were prepared directly from the acid chloride **6** (*Scheme 3*).[8b]

The Michael-like additions (*Scheme 4*) were carried out at -10° to -4°C to prevent the formation of polymer by-products. For maximum yields (86%-95%) and good asymmetric induction, the Grignard reagent/cuprous bromide systems in THF/$(CH_3)_2S$ have proven to be the best in our hands. The asymmetric 1,4-addition was shown to occur almost exclusively from the face opposite of the phenyl group of the oxazolidinone chiral auxiliary. It is believed that the carbonyl groups and the enolate oxygen anion in **7** - **10** are complexed by a metal ion during the conjugate addition.[10-12] Any loss of asymmetric control may be

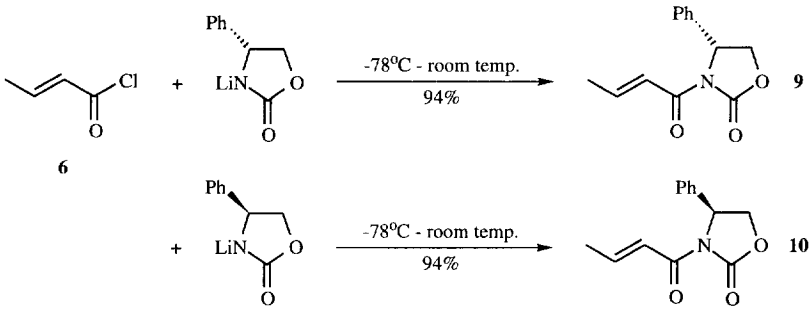
Scheme 1



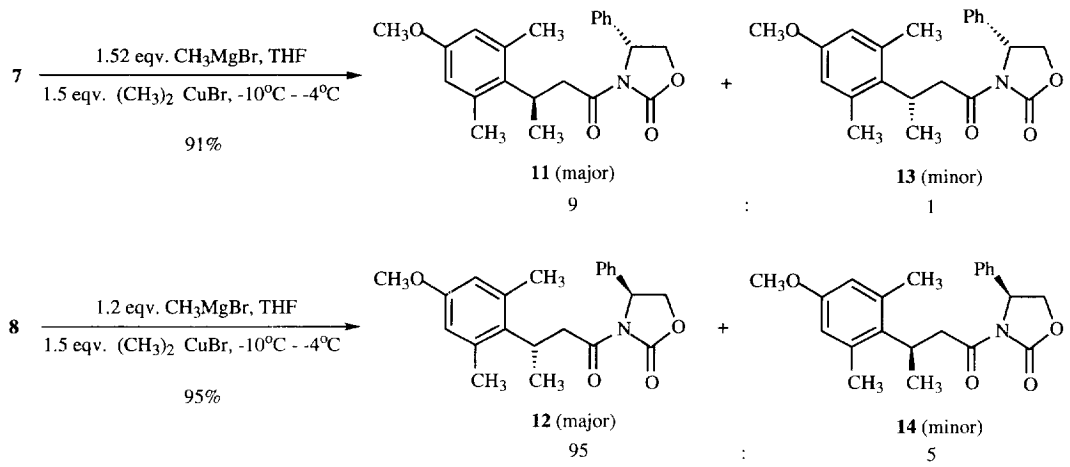
Scheme 2



Scheme 3

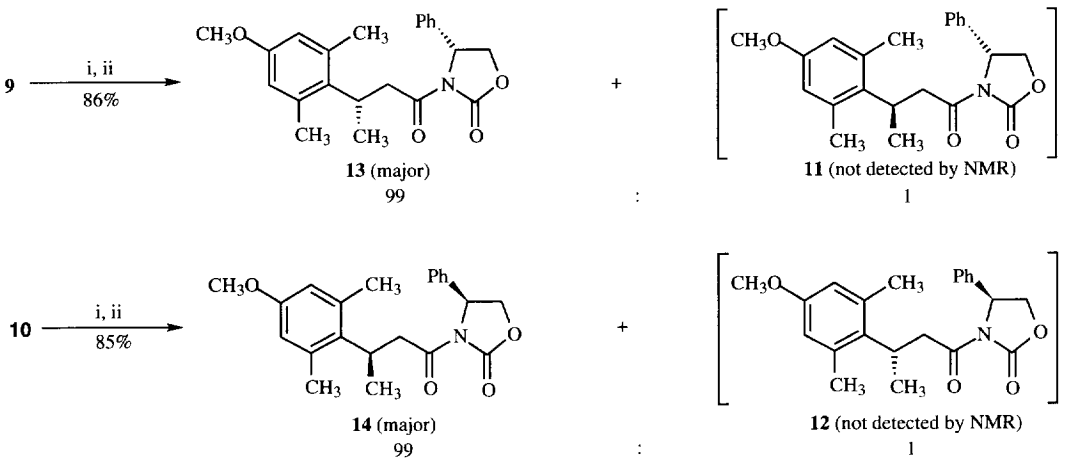


Scheme 4



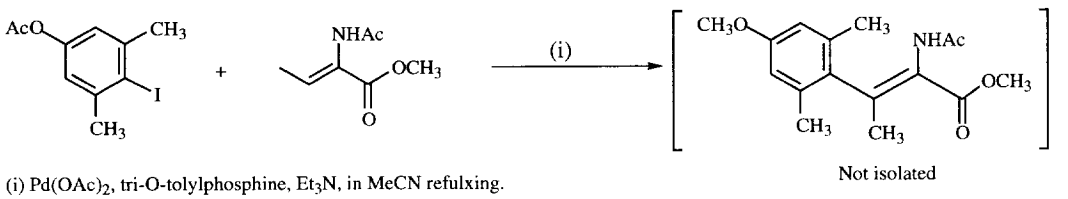
caused by rotation about the C_α-C_β bond. The predominant isomers, **11** and **12**, could be obtained indiastereomerically pure form by fractional recrystallization. More than 3 equivalents of Grignard reagents were shown to reduce the yield of the 1,4-adducts. It is possible that some of the excess Grignard reagent may result in partial cleavage of the chiral auxiliary from the *N*-acyl-4-phenyl-2-oxazolidinones **7-10** accounting for the slightly less than quantitive yield. To our knowledge, this is the first example of excellent stereocontrolled Michael-type additions in a sterically hindered system with high yields using either methylmagnesiumbromide / dimethylcopper bromide or 2, 6-dimethyl-4-methoxyphenylmagnesium bromide/dimethyl copper bromide as nucleophilic reagents. When we used methylmagnesium as Grignard reagent to react with α,β-unsaturated *N*-acyl-4-phenyl-2-oxazolidinones **7** and **8**, the ratio of major products **11** and **12** over the minor products **13** and **14** were $\geq$ 9:1 in both cases as determined by integration of the β-methyl protons in the NMR (see Experimental Section). We were especially interested to see the results of 1,4-addition of the Grignard reagent, 2, 6-dimethyl-4-methoxyphenylmagnesium bromide (**2a**, Scheme 1) to *N*-crotonyl-oxazolidinones **9** and **10** (*Scheme 5*). In these cases, we did not observe any of adducts **11** and **12** in the crude product within the limits of detection by proton NMR (250 MHz). The major adducts **13** and **14** could be isolated and

Scheme 5



(i) 2.4 eqv. $(CH_3)_2S$ CuBr, -10°C - -4°C; (ii) 2 eqv. **2a**, THF.

Scheme 6



(i) $Pd(OAc)_2$, tri-O-tolylphosphine, Et_3N, in MeCN refulxing.

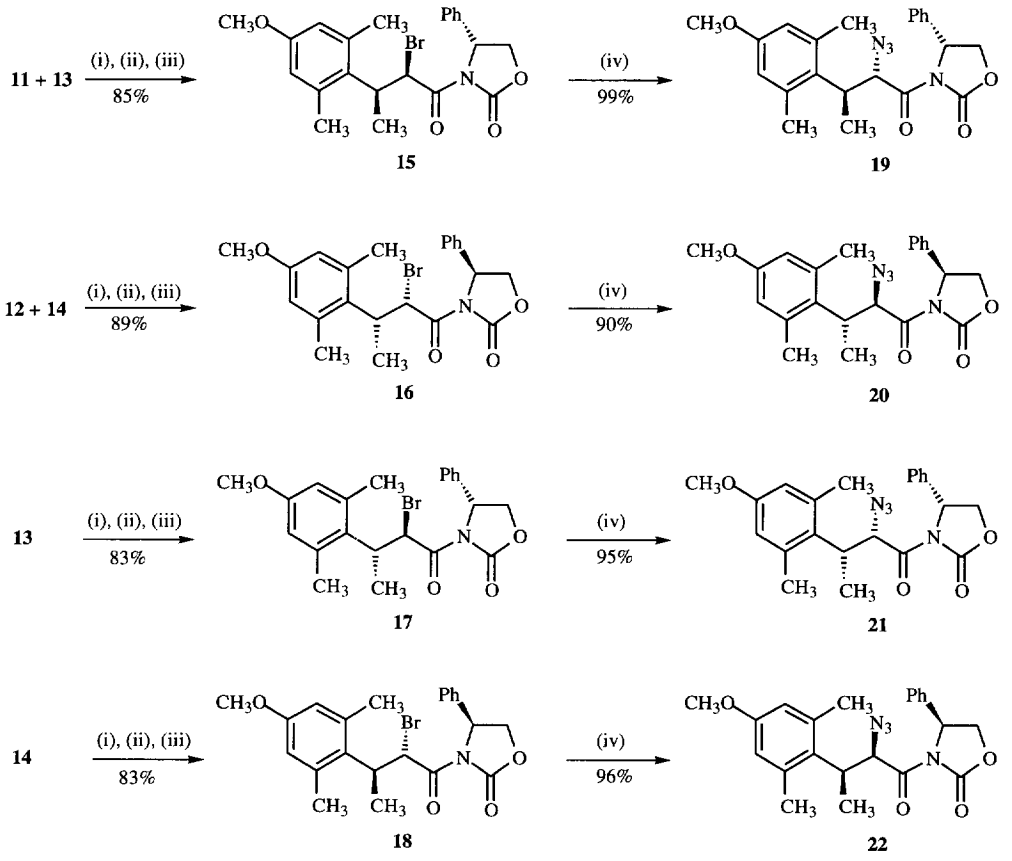
purified by gravity column chromatography. Undoubtedly, the absolute stereocontrol induced by the 4-phenyl-2-oxazolidinone chiral auxiliary was due to the bulky size of the aromatic Grignard reagent which is much larger than methylmagnesium bromide. Again the clean stereocontrol was achieved by attack from the opposite side of the phenyl moiety in the chiral auxiliary. The diastereoisomeric mixtures can be brominated without separation (*Scheme 7*).

It is surprising to us that these additions can be carried out without problems arising from steric hindrance. On the other hand, we have experienced difficulty in carrying out a Heck coupling reaction in a similar system (*Scheme 6*). In order to synthesize a dehydro-form of 2', 6'-dimethyl-β-methyltyrosine, we tried to couple 4-iodo-3,5-dimethylphenyl acetate and *N*-acetyl-2-dehydrothreonine methylester under normal Heck coupling conditions, but only starting materials were isolated. Since in another case, 4-iodo-3,5-dimethylphenyl acetate can be coupled to 2-acetamidoacrylate easily under the same conditions (this reaction was repeatable in our hands),[13] obviously steric effect may take an important role in this system, and the Michael-type addition we carried out could overcome this steric-hinderance problem.

The 4-phenyl-3-[3-(4'-methoxy-2', 6'-dimethylphenylbutanoyl]-2-oxazolidinones **11-14** were treated with 1.1-1.2 equivalents of diisopropylethylamine and 1.05 equivalents of di(*n*-butyl)boron triflate at -78°C and warmed up to 0°C to generate the more stable *Z*-enolate (*Scheme 7*). After re-cooling to -78°C, the enolates were transferred to a -78°C slurry of 1.1 equivalents of *N*-bromosuccinimide in dry dichloromethane. The isolated yields ranged from 85-89%. The attack of the enolate ion by the electrophilic agent occurred quantitatively from the side opposite of the phenyl group attached to the oxazolidinone ring. We did not observe any diastereoisomers within the limits of NMR detection (see the Experimental Section). Although diastereoisomeric mixtures of the Michael adducts were used as starting materials for the bromination reaction, they can be separated easily by column chromatography as bromides with chirality differences only at the β-carbons. X-ray crystallographic structures of bromides **17** and **18** were obtained to confirm the suggested absolute stereochemistry.[14] Attempts to obtain the crystal structure of bromides **15** and **16** were unsuccessful.

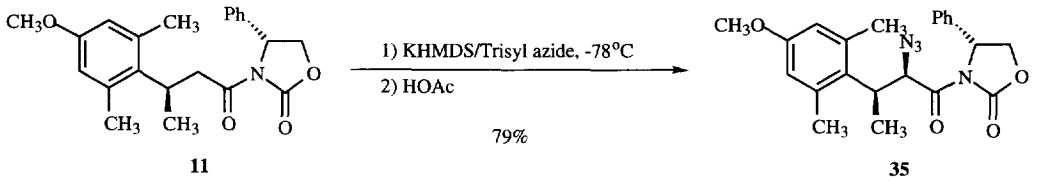
Azide formation was achieved by displacement of the bromides **15-18** with nucleophilic azide via an

Scheme 7

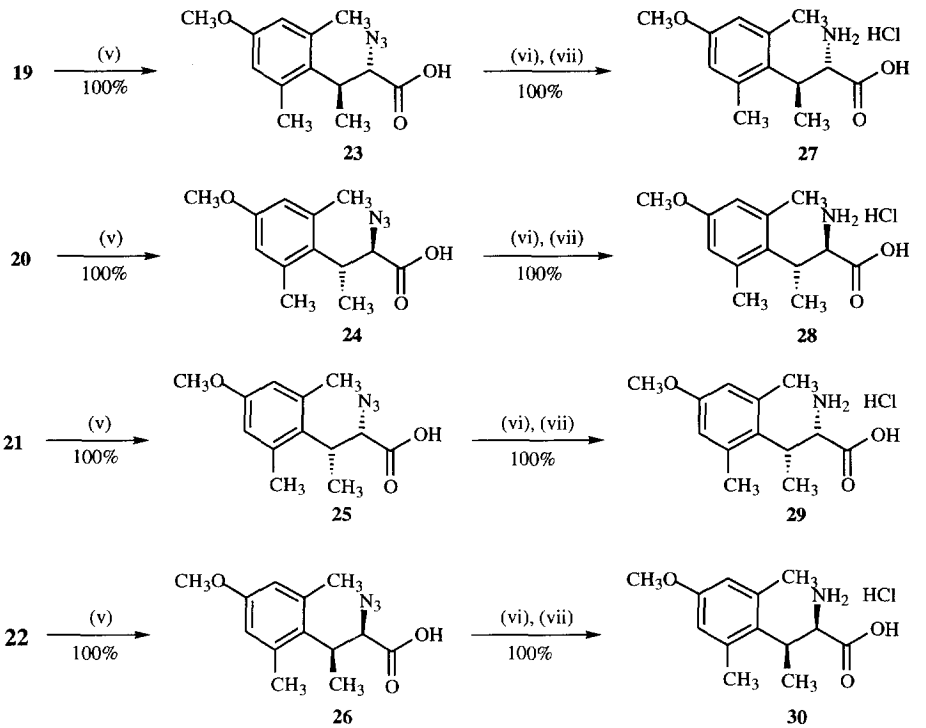


(i) 1.05 eqv. $(^{n}Bu)_2BOTf$, DIEA, -78°C; (ii) 1.1 eqv. NBS; (iii) Column chromatography; (iv) Amberlite IR-400 azide exchange resin, 9 days at room temp. in CH_3CN.

Scheme 8



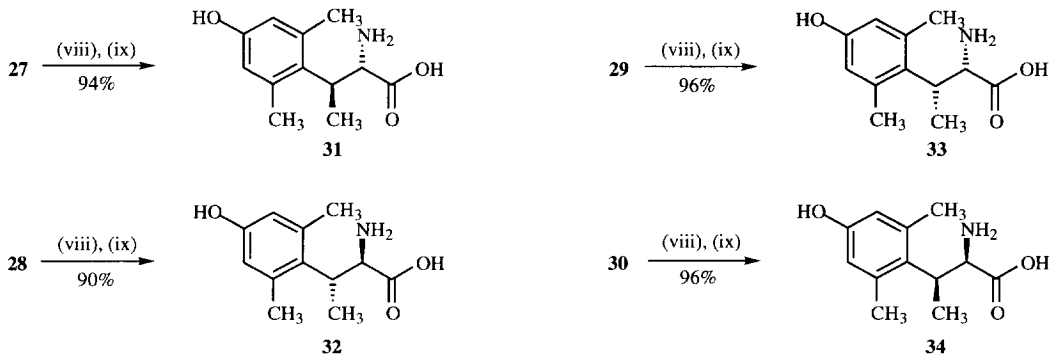
Scheme 9



(v) LiOH, H_2O_2, 0°C, 2hr; (vi) H_2 / 10% Pd-C, 35 psi, 24hr; (vii) 6N HCl (aq).

S_N2 mechanism (*Scheme 7*). The yields were nearly quantitative in all cases. We tried both tetrabutylammonium azide and azide exchange resin as nucleophiles. For safety reasons[15] and convenience of work-up/separation, we finally chose the azide exchange resin as the azidation reagent. No epimerization at the α-carbon was observed in any of the cases, although a drawback is the long reaction times (7-10 days). Attempts at direct azidation by treating the Michael adduct **11** with potassium hexamethyldisilazide (KHDMS) and 2,4,6-triisopropylsulfonyl azide (trisyl azide, an electrophilic azide) at low temperature was examined, the reaction proceeded with 94% de, but only in a moderate 79% yield (*Scheme 8*).[16] The advantage of electrophilic direct azidation using a (+)-N_3 synthon, tiisopropylsulfonyl azide, is to shorten the entire

Scheme 10



(viii) F_3CSO_3H, thioanisole, -4 - 0°C in CF_3COOH; (ix) ion exchange.

synthetic route significantly. We may also eventually obtain *L*- and *D*-TMT isomers by just using one optically pure chiral auxiliary. Attempts of asymmetric direct azidation of the Michael adduct **11** using a radical approached (N_3 radical was generated by sodium azide and ammonium cerium nitrate at -20°C in acetonitrile[17]) were not successful.

The chiral auxiliaries were hydrolytically removed from **19-22** under basic conditions in quantitative yields (*Scheme 9*),[6-9,16] and were recovered for further use. Optically pure azido acids **23-26** were reduced to the corresponding amines by standard catalytic hydrogenation in the presence of hydrochloric acid to give the hydrochloride salts of *O*-protected tyrosine derivatives **27-30** in high yields. No racemization was observed during the reduction step.

The *O*-methoxy protecting group of the α-amino acids **27-30** was removed by trifluoromethanesulfonic acid (TFMSA) and thioanisole in trifluoroacetic acid at low temperature via a "push and pull" mechanism[18] to give the tyrosine derivatives (*Scheme 10*). Although the trifluoromethanesulfonic acid (TFMSA) / thioanisole / TFA conditions seemed to be harsh, no racemization was observed under our experimental conditions, and the reaction time was significantly shortened. The final 2', 6'-dimethylphenyl-β-methyltyrosines **31-34** were purified by ion exchange chromatography and examined by reverse phase chiral tlc. No optical isomeric contamination was observed. We observed that large amounts of heat were released when we tried to wash the final TMTs off the ion-exchange resin with 5% ammonium hydroxide solution, so a jacketed column with recycling ice-water was used as an ion-exchange column.

In conclusion, we have developed an asymmetric synthesis of the four stereoisomers of 2', 6'-dimethyl-β-methyltyrosine (**31-34**) that could be extended to a general synthesis of other β-branched aromatic α-amino acids. Utilization of optically active 4-phenyl-2-oxazolidinones as a chiral auxiliary affords excellent chiral induction at both the α- and β-carbons of α, β-unsaturated acids. Further applications of 4-phenyl-2-oxazolidinones to the asymmetric synthesis of nonproteogenic α-amino acids are under investigation in our laboratory as are electrophilic and radical azidation.

EXPERIMENTAL

General. All reagents, unless otherwise noted, were purchased from Aldrich Chemical Co. and were used without further purification except for triethylamine and acetonitrile (distilled from CaH_2 under argon and stored over CaH_2). Crotonyl chloride was distilled under argon before use. Triisopropylsulfonyl azide was synthesized as described in literature.[20] Amberlite azide exchange resin was purchased from Aldrich Chemical Co. The following solvents were freshly distilled and stored under argon prior to use: THF from Na/benzophenone ketyl, CH_2Cl_2 from CaH_2. Water was distilled and deionized before use. All reactions, unless otherwise noted were carried out under the protection of argon; the reaction temperatures listed are the bath temperatures. All reaction containers were flame dried under vacuum before use. Melting points were determined in open capillary tubes with a Thomas-Hoover melting point apparatus and are uncorrected. ^1H and ^{13}C-NMR spectra were recorded on superconducting instruments operating at 250 MHz or 300 MHz spectrometers in $CDCl_3$, D_2O or CD_3OD as solvent. Optical rotations were taken on an Autopol III polarimeter using a 1.0 dm cell. Infrared spectra were taken on an Perkin Elmer FT-IR spectrometer. Mass spectra were determined on Hewlett Packard 5988A or Hewlett Packard 5970 mass spectrometer. Column chromatography was performed using Aldrich silica gel 60, 230-400 mesh ASTM. Solvents for chromatography were used without further purification. Analytical tlc was performed on Merck precoated Kieselgel 60 F-254 plates, and the chiral reverse phase tlc plates (Chiralplate®) were purchased from Aldrich. Detections were made using either I_2, ninhydrin, or UV light. A jacketed column with the inside diameter of 1 inch and length of 18 inch was purchased from ACE Glass. Elemental analysis was done by Desert Analytics Co., Tucson, Arizona. High resolution mass spectra were obtained from the Mass Spectroscopy Facility at the College of Pharmacy, University of Arizona, and the Mass Spectroscopy Service Laboratory, Department of Chemistry, The University of Minnesota, Minneapolis.

4-Bromo-3,5-dimethylanisole (2). 3,5-Dimethylanisole (**1**, 87.5 mL, 619 mmol) was dissolved in 1.0 L of carbon tetrachloride. The mixture was cooled to -25°C, and a solution of bromine (35.0 mL, 679 mmol) in carbon tetrachloride (200 mL) was added over 8 hrs, until the bromine color persisted. The solution was allowed to warm to room temperature, poured into water (1.0 L) and stirred for 1.5 hrs. The aqueous and organic phases were separated and the aqueous phase was extracted with ethyl ether (3 x 200 mL). The combined organic phases were dried over anhydrous magnesium sulfate, filtered, the solvents removed by rotary evaporation, and the residue oil vacuum distilled to yield 113.5 g (85%) of the product as a clear colorless liquid. Tlc R_f = 0.41 (9:1, hexanes : ethyl acetate, v/v). Bp 64°C, 2.1 torr. ^1H NMR ($CDCl_3$, TMS): δ 6.60 (s, 2H, aromatic hydrogens), 3.71 (s, 3H, $-OCH_3$), 2.35 (s, 6H, $-CH_3$). ^{13}C NMR ($CDCl_3$): δ 157.9, 138.8, 118.0, 113.6, 55.0, 23.9. CIMS: m/e (relative intensity) 215.00 (M^++1, 100). Anal. Calcd for $C_9H_{11}BrO$: C, 50.26; H, 5.15, Br, 37.15. Found: C, 49.95; H, 5.11; Br, 37.15.

4-Methoxy-2,6-dimethylbenzaldehyde (3). A mixture of 4-bromo-3,5-dimethylanisole (**2**, 68.0 g, 316 mmol), polished magnesium strips (9.0 g, 158 mmol) and freshly distilled THF (1.0 L) was gently heated. The heat was removed until the reaction ceased to reflux. The black colloidal suspension was reheated to reflux for 4 hrs and then recooled to 0°C. A solution of anhydrous dimethylformamide (28.7 mL, 371 mmol) in freshly distilled THF (30 mL) was added to the above suspension dropwise over 20 min. The grey suspension was allowed to warm to room temperature and stirred for 1 hr. The reaction was quenched by

decanting the reaction solution into a saturated ammonium chloride solution (1 L). The reaction flask was washed with additional THF (2 x 30 mL) which was decanted into the above ammonium chloride solution. The aqueous and organic phases were separated, and the aqueous phase was extracted with ethyl ether (3 x 200 mL). The combined organic phases were dried over anhydrous magnesium sulfate, filtered, and the solvents removed by rotary evaporation. The residue, a yellow oil, was further dried *in vacuo*, to give a yellow solid (96%). The crude product was recrystallized from hexanes at -20°C (44.9 g, 86%). The product was of satisfactory purity (^{1}H NMR pure) for use in the next reaction. A sample was further purified by distillation (Bp 104°C, 5 torr) and recrystallized from hexanes at -20°C. Tlc R_f = 0.24 (9:1, hexanes : ethyl acetate, v/v), 2,4-DNP (+). Mp 44.0-45.5°C (lit. 40-41°C).[5] ^{1}H NMR ($CDCl_3$, TMS): δ 10.47 (lit. 10.40, s, 1H), 6.58 (lit. 6.51, s, 2H), 3.48 (lit. 3.77, s, 3H), 2.60 (lit. 2.53, s, 6H). ^{13}C NMR ($CDCl_3$): δ 191.5, 162.6, 144.4, 125.9, 114.8, 55.2, 21.0. CIMS: m/e (relative intensity) 165.00 (M^++1, 100). Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 73.01 (lit. 73.19); H, 7.52 (lit. 7.47).

(2*E*)-Ethyl 3-(4'-methoxy-2', 6'-dimethylphenyl)-2-propenoate (4). To a solution of potassium tert-butoxide (53.1 g, 450 mmol), triethyl phosphonoacetate (93 mL, 450 mmol) in freshly distilled THF (1.2 L), was added 4'-methoxy-2',6'-dimethylbenzaldehyde **3** (41.4 g, 252 mmol) in one portion at room temperature. The solution thickened considerably after a few min and the reaction was stirred at room temperature for 2 hrs. A small amount of this material was removed from the reaction mixture and purified by column chromatography for characterization. Tlc R_f = 0.27 (9:1, hexanes : ethyl acetate, v/v). Mp 68.0-69.0°C. ^{1}H NMR ($CDCl_3$, TMS): δ 7.83 (d, 1H, J = 16.3 Hz, Ar-CH=CH-), 6.60 (s, 2H, aromatic 3',5' hydrogens), 6.02 (d, 1H, J = 16.3 Hz, Ar-CH=CH-), 4.26 (q, 2H, J = 7.1 Hz, -O-*CH*$_2$-CH_3), 3.77 (s, 3H, -OCH_3), 2.35 (s, 6H, Ar-CH_3s), 1.34 (t, 3H, 7.1 Hz, -OCH_2-*CH*$_3$). ^{13}C NMR ($CDCl_3$): δ 167.1, 159.2, 142.5, 138.9, 126.1, 121.9, 113.7, 60.2, 54.9, 21.5, 14.2. CIMS: m/e (relative intensity) 235.05 (M^++1, 100). Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.76; H, 7.93.

(2*E*) 3-(4'-Methoxy-2', 6'-dimethylphenyl)-2-propenoic acid (5). To a slurry containing crude ester **4** was added methanol (400 mL) and water (400 mL). Lithium hydroxide monohydrate (75 g, 1.8 mol, 4 eq) was added and the reaction stirred overnight. Volatiles were removed by rotary evaporation and the aqueous layer, now containing a white precipitate, was diluted to 1.5 L with water and gently heated to dissolve solids. The warm solution was washed with chloroform (3 x 200 mL) and acidified to pH = 1 with 6N hydrochloric acid. The white solid was filtered, washed with water (1 L) and dried *in vacuo* in the presence of P_2O_5. The off-white solid weighed 48.6 g (93%). The product was used for the next reaction without further purification. A small amount of the product was recrystallized from ethyl acetate and hexanes for analysis. Tlc R_f = 0.22 (70:30:1, hexanes : ethyl acetate : acetic acid, v/v/v). Mp 174.5-175.5°C. ^{1}H NMR ($CDCl_3$, TMS): δ 7.98 (d, 1H, J = 16.3 Hz, Ar-CH=*CH*-), 6.63 (s, 2H, aromatic 3',5' hydrogens), 6.08 (d, 1H, J = 16.4 Hz, -*CH*=CH-CO_2H), 3.80 (s, 3H, -OCH_3), 2.40 (s, 6H, Ar-CH_3s). ^{13}C NMR ($CDCl_3$): δ 172.5, 159.6, 145.0, 139.4, 125.7, 120.7, 113.9, 55.1, 21.7. CIMS: m/e (relative intensity) 207.20 (M^++1, 100), 189.05 (26.5). Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 70.18; H, 6.78.

(4*S*)- and (4*R*)-4-Phenyl-2-oxazolidinone. These two chiral auxiliaries were prepared according to literature procedures with modifications.[8,9,21,22]

General Methods for the Synthesis of 7, 8. These compounds were prepared using a procedure for coupling of the precursor acids **5** to the chiral auxiliaries using mixed anhydrides.[6-9]

To a stirred, -78°C pre-cooled solution of (2*E*) 3-(4'-methoxy-2',6'-dimethylphenyl)propenoic acid (**5**, 6.50 g, 31.5 mmol) in dry THF (650 mL) was added triethylamine (5.3 mL, 37.8 mmol, 1.2 eq) via syringe, followed by pivaloyl chloride (4.3 mL, 34.9 mmol, 1.1 eq). The suspension was stirred for 15 min at -78°C, 0°C for 45 min, and then recooled to -78°C. The suspension was then transferred via cannula to a stirring slurry of the lithiated 4(*S*)-4-phenyl-2-oxazolidinone at -78°C [prepared 20 min in advance at -78°C by the addition of n-BuLi (1.6 M in hexanes, 18.0 mL, 28.8 mmol) to a solution of the 4(*S*)-4-phenyl-2-oxazolidinone (4.70 g, 28.8 mmol) in freshly distilled tetrahydrofuran (120 mL)]. The resulting suspension was stirred at -78°C for 20 min and at room temperature for 2 hrs. The reaction was quenched by the addition of saturated NH_4Cl aqueous solution (70 mL). Volatiles were removed by rotary evaporation and the residual aqueous slurry was extracted with chloroform (3 x 110 mL). The combined extracts were washed with diluted aqueous $NaHCO_3$ solution (3 x 70 mL), dried over anhydrous $MgSO_4$, filtered, rotary evaporated to dryness and stored *in vacuo*. The crude product was chromatographed on silica gel using 2:8, ethyl acetate:hexanes (v/v) as eluent solvent. An analytical sample was rechromatographed and recrystallized in hexanes/ethyl acetate for charaterization in both cases.

3(2*E*), 4 (*R*) - 3 - [(4' - Methoxy - 2', 6'- dimethylphenyl) - 1 -oxopropenoyl] - 4- phenyl - 2 - oxazolidinone (7). Yield 75%. Tlc R_f = 0.29 (3:7, EtOAc : Hexanes, v/v). Mp 158.5-160.0 °C. ^1H NMR ($CDCl_3$) TMS : δ 8.00 (d, J=16.0 Hz, 1H, Ar-CH=C-), 7.56 (d, J=16.0 Hz, 1H, -C=CH-CO-), 7.44 - 7.31 (m, 5H, oxazolidinone aromatic hydrogens), 6.61 (s, 2H, aromatic 3',5' hydrogens), 5.55 (dd, J=8.7 Hz, 3.9 Hz, 1H, oxazolidinone Ph-CH-), 4.73 (t, J=8.6 Hz, 1H, oxazolidinone -CH_2-*/pro R*), 4.32 (dd, J=8.7 Hz, 3.9 Hz, 1H, oxazolidinone -CH_2-*/pro S*), 3.79 (s, 3H, Ar-OCH_3), 2.40 (s, 6H, Ar-2', 6'-CH_3). ^{13}C NMR ($CDCl_3$) : δ 161.5, 159.6, 153.8, 144.0, 140.1, 139.2, 129.1, 128.6, 126.0, 125.9, 119.7, 114.1, 69.9, 57.9, 55.0, 22.0. IR (KBr, cm^{-1}): 2963, 2911, 1764, 1670, 1615, 1599, 1568, 1475, 1384, 1349, 1300, 1198, 1150, 975, 851, 760, 706. MS: m/e (relative intensity) 352.05 (M^++1, 100), 189.05 (14). $[\alpha]^{22}_D$ = -26.1° (c 1.05 $CHCl_3$). Anal. Calcd for $C_{21}H_{21}NO_4$: C, 71.78; H, 6.02; N, 3.99. Found: C, 72.03; H, 6.06; N, 4.00.

3(2*E*), 4 (*S*) - 3 -[(4' - Methoxy- 2', 6' - dimethylphenyl) - 1 - oxopropenoyl] - 4 - phenyl-2-oxazolidinone (8). Yield 77%. Tlc R_f = 0.64 (1:1, EtOAc : Hexanes, v/v). Mp 157.5-158.0 °C. ^1H NMR ($CDCl_3$) TMS: δ 8.00 (d, J=16.0 Hz, 1H, Ar-CH=C-), 7.56 (d, J=16.0 Hz, 1H, -C=CH-CO-), 7.40 - 7.37 (m, 5H, oxazolidinone aromatic hydrogens), 6.61 (s, 2H, aromatic 3',5' hydrogens), 5.55 (dd, J=8.8 Hz, 4.0 Hz, 1H, oxazolidinone Ph-CH-), 4.74 (t, J=8.8 Hz, 1H, oxazolidinone -CH_2-*/pro R*), 4.32 (dd, J=8.8 Hz, 4.0 Hz, 1H, oxazolidinone -CH_2-*/pro S*), 3.79 (s, 3H, Ar-OCH_3), 2.41 (s, 6H, Ar-2', 6'-CH_3). ^{13}C NMR ($CDCl_3$) : δ 165.1, 159.6, 153.8, 144.0, 140.1, 139.2, 129.1, 128.6, 126.0, 125.9, 119.7, 114.1, 69.9, 57.9, 55.0, 22.0. IR (KBr, cm^{-1}): 2963, 2911, 1764, 1670, 1615, 1599, 1475, 1384, 1349, 1198, 1150, 975, 851, 760, 706. MS: m/e (relative intensity) 352.00 (M^++1, 64), 207.05 (4), 179.15 (100), 164.00 (80). $[\alpha]^{25}_D$ = + 32.0° (c 0.29, $CHCl_3$). Anal. Calcd for $C_{21}H_{21}NO_4$: C, 71.78; H, 6.02; N, 3.99. Found: C, 71.73; H, 5.89; N, 4.03.

General Methods for the Synthesis of 9 and 10. These compounds were prepared using a procedure for coupling of the acid chloride **6** to the optically pure 4-phenyl-2-oxazolidinone, and was similar to that previously reported.[8]

Freshly distilled crotonyl chloride **6** (21.08 mL, 220 mmol) was dissolved in freshly distilled tetrahydrofuran (80 mL), and the solution was cooled to -78°C. In a separate 2 L round bottom flask with a magnetic stirbar, 4(*R*)-4-phenyl-2-oxazolidinone (32.64 g, 200 mmol) was dissolved in freshly distilled tetrahydrofuran (500 mL) and was cooled to -78°C, then n-BuLi (150 mL, 1.6 M in hexanes, 240 mmol) was added via syringe. The mixture was stirred for 20 min and the crotonyl chloride solution was transferred to the lithiated oxazolidinone via cannula. The resulting solution was stirred for 30 min at -78°C and 1.5 hrs at room temperature before quenching the reaction by the addition of saturated NH_4Cl aqueous solution (150 mL). Volatiles were removed by rotary evaporation. The resulting aqueous slurry was diluted with water (200 mL) and extracted with ethyl acetate (3 x 150 mL). The combined organic layers were washed with saturated sodium bicarbonate solution (2 x 150 mL), and brine (150 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to dryness by rotary evaporation. The crude product was purified by column chromatography using 30% ethyl acetate in hexanes (v/v) as the eluant. An analytical sample was rechromatographed and recrystallized in hexanes/ethyl acetate for characterization in both cases.

3(2*E*), 4(*R*)-3-(1-Oxo-2-butenyl)-4-phenyl-2-oxazolidinone (9). Yield 94% and contained a 96:4 ratio of *E* : *Z* isomers by proton NMR. Mp 77-79°C. ^{1}H NMR ($CDCl_3$) TMS: δ 7.40-7.25 (m, 6H), 7.15-6.90 (m, 1H), 5.47 (dd, J=8.8, 3.9 Hz, 1H), 4.67 (t, J=8.8 Hz, 1H), 4.24 (dd, J=8.8, 3.9 Hz, 1H), 1.92 (d, J=6.7 Hz, 3H). IR (KBr, cm^{-1}): 2990, 1785, 1690, 1640, 1340, 1190, 715. MS: m/e (relative intensity) 231.0 (M^++1, 5), 69 (100). $[\alpha]^{22}_D$ = -111.8° (c 1.08, $CHCl_3$). Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.25; H, 5.67; N, 6.13.

3(2*E*), 4(*S*)-3-(1-Oxo-2-butenyl)-4-phenyl-2-oxazolidinone (10). Yield 90% and no *Z* isomer was observed by proton NMR. Mp 74.5-75.5°C. ^{1}H NMR ($CDCl_3$) TMS: δ 7.42-7.24 (m, 6H), 7.16-7.02 (m, 1H), 5.48 (dd, J=8.7, 3.9 Hz, 1H), 4.69 (t, J=8.8 Hz, 1H), 4.26 (dd, J=8.9, 3.9 Hz, 1H), 1.93 (d, J=5.6 Hz, 3H). ^{13}C NMR ($CDCl_3$) : δ 164.4, 159.6, 153.7, 147.3, 139.0, 129.1, 128.6, 125.8, 121.6, 69.9, 57.7, 18.5. IR (KBr, cm^{-1}): 2973, 1779, 1685, 1657, 1634, 1472, 1457, 1439, 1392, 1329, 1229, 1211, 1085, 964, 714, 695. MS: m/e (relative intensity) 231.0 (M^++1, 40), 69 (100). $[\alpha]^{22}_D$ = +113.4° (c 1.085, $CHCl_3$). Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.52; H, 5.67; N, 6.13.

General Procedure for the Preparation of the Organo-copper Reagents. To a suspension of magnesium turnings (2.91 g, 120 mmol, 1.1 eqv.) in dry THF (50 mL) was added the 4-bromo-3,5-dimethylanisole (23.5 g, 109 mmol) and bromoethane (0.80 mL, 11 mmol). The mixture were heated with stirring to reflux for 4 hrs, was cooled to -4°C, and then transferred via cannula to a -40°C stirring slurry of copper (I) bromide-dimethyl sulfide complex (11.23 g, 53.8 mmol) in freshly distilled THF (130 mL) and anhydrous dimethylsulfide (65 mL). The grey mixture (mixture **A**) was warmed to -10°C and was ready for the conjugate additions. In the case of MeMgBr, a commercial solution (3.0 M in ethyl ether, 7.5 mL, 22.5 mmol) was added by syringe to a solution of $CuBr{\cdot}(CH_3)_2S$ complex (4.58 g, 22.0 mmol) in freshly distilled THF (50 mL) and anhydrous dimethylsulfide (20 mL) at -4°C. The resulting yellow-greenish mixture (mixture **B**) was stirred for 10 min at -4°C and used for the conjugate addition at the given temperature.

General Procedure for Conjugate Additions. The procedure was slightly different depending on the substrate used. For **11** and **12**, a typical procedure as follows. A solution of the α,β-unsaturated

acyloxazolidinone **7** (5.20 g, 14.8 mmol) in freshly distilled THF (25 mL) was added dropwise to mixture **B** over 60 min at -4°C and the resulting mixture was stirred for an additional 90 min at -4°C. Then the reaction mixture was warmed up to room temperature and stirred overnight. The reaction was quenched by slow addition of saturated NH_4Cl (aq.) (70 mL) and stirred for 30 min. The phases were separated, the organic phase was set aside while the aqueous phase was extracted with ethyl ether (50 mL x 3). The combined organic phases were washed with saturated NH_4Cl (aq.) (30 mL x 3), water (30 mL x 3), brine (30 mL) and dried over anhydrous $MgSO_4$. The drying agent was filtered, the solvent was evaporated off, and the diastereoisomeric mixture was purified by column chromatography (3:7, EtOAc : Hexanes, v/v). Analytical samples were rechromatographed and fractionally recrystallized for characterization. For the preparation of **13** and **14**, a typical procedure was as follows. A solution of the α,β-unsaturated acyloxazolidinone **9** (8.5 g, 36.6 mmol) in freshly distilled THF (65 mL) was added dropwise to the organocopper solution **A** at -10°C, within a period of 1 hr. The suspension was slowly warmed to room temperature over 1.5 hr and stirred at the room temperature overnight. The quenching, workup, and purification procedures were similiar to the preparation of **11** and **12**.

3(3*R*), 4(*R*) 3-[3-(4'-Methoxy-2',6'-dimethylphenyl)-1-oxobutyl]-4-phenyl-2-oxazolidinone (11). Yield 91% and was a 9:1 mixture of diastereoisomers by proton NMR. The diasteroisomeric product was recrystallized from ethyl acetate and hexanes to obtain **11** (yield after recrystallization, 75%) as a single isomer. Mp 99.5-101.0°C; ^{1}H NMR ($CDCl_3$) TMS: δ 7.33 (m, 3H, chiral auxiliary aromatic hydrogens), 7.24 (m, 2H, chiral auxiliary aromatic hydrogens), 6.52 (s, 2H, aromatic 3',5' hydrogens), 5.36 (dd, J=8.7, 3.7 Hz, 1H, oxazolidinone Ar-CH-), 4.60 (t, J=8.6 Hz, 1H, oxazolidinone -CH_2-/*pro R*), 4.23 (dd, J=8.7, 3.9 Hz, 1H, oxazolidinone -CH_2-/*pro S*), 3.86 (m, 1H, H-C_β), 3.74 (s, 3H, Ar-OCH_3), 3.41 (s, 1H, CH_α), 3.39 (d, J=1.1 Hz, 1H, CH_α'), 2.43 (s, broad, 3H, Ar-CH_3), 2.32 (s, broad, 3H, Ar-CH_3'), 1.25 (d, J=7.3 Hz, 3H, C_β-CH_3). ^{13}C NMR ($CDCl_3$) : δ 171.2, 152.7, 137.9, 133.6, 129.1, 128.6, 125.8, 115.4, 113.7, 69.8, 57.6, 54.9, 40.8, 30.1, 29.7, 21.8, 19.2. IR (KBr, cm^{-1}): 2970, 1770, 1600, 1460, 1360, 1180, 1140, 850. MS: m/e (relative intensity) 368.20 (M^++1, 100), 367.20 (28), 232.05 (28), 163.05 (40). $[\alpha]_D^{22}$ = -88.5° (c 1.07, $CHCl_3$). Anal. Calcd for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 71.95; H, 6.80; N, 3.86.

3(3*S*), 4(*S*) 3-[3-(4'-Methoxy-2',6'-dimethylphenyl)-1-oxobutyl]-4-phenyl-2-oxazolidinone (12) Yield 95% and was a 95:5 mixture of diastereomers by proton NMR. The material was recrystallized from ethyl acetate and hexanes to obtain **12** (yield after recrystallization, 85%) as a single isomer. Mp 104.0-104.5°C; ^{1}H NMR ($CDCl_3$) TMS: δ 7.37-7.34 (m, 3H, chiral auxiliary aromatic hydrogens), 7.24 (m, 2H, chiral auxiliary aromatic hydrogens), 6.52 (s, broad, 2H, aromatic 3',5' hydrogens), 5.37 (dd, J=8.7, 3.7 Hz, 1H, oxazolidinone Ar-CH-), 4.62 (t, J=8.8 Hz, 1H, oxazolidinone -CH_2-/*pro R*), 4.24 (dd, J=8.8, 3.7 Hz, 1H, oxazolidinone -CH_2-/*pro S*), 3.84 (m, 1H, H-C_β), 3.75 (s, 3H, Ar-OCH_3), 3.42 (s, 1H, CH_α), 3.39 (dd, J=7.3, 1.5 Hz, 1H, CH_α'), 2.44 (s, broad, 3H, Ar-CH_3), 2.33 (s, broad, 3H, Ar-CH_3'), 1.25 (d, J=7.3 Hz, 3H, C_β-CH_3). ^{13}C NMR ($CDCl_3$) : δ 171.9, 157.1, 139.0, 137.8, 133.8, 129.1, 128.6, 125.8, 115.2, 115.1, 113.7, 69.8, 57.6, 54.9, 40.7, 40.5, 29.9, 29.7, 21.8, 19.2. IR (KBr, cm^{-1}): 2990, 2971, 1767, 1698, 1603, 1487, 1474, 1458, 1327, 1182, 1143, 1069, 850, 761, 723, 702. MS: m/e (relative intensity) 368.05 (M^++1, 4), 367.05 (14), 189.05 (16), 163.05 (100). $[\alpha]_D^{25}$ = +95.6° (c 0.39, $CHCl_3$). Anal. Calcd for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 71.90; H, 6.78; N, 3.76.

3(3*S*), 4(*R*) 3-[3-(4'-Methoxy-2',6'-dimethylphenyl)-1-oxobutyl]-4-phenyl-2-oxazolidinone (13). Yield 84% and was a single diastereomer by proton NMR. The diasteroisomeric product was recrystallized from ethyl acetate and hexanes to obtain **13** as a single isomer. Mp 99.5-101.0°C; ^{1}H NMR ($CDCl_3$) TMS: δ 7.30 (m, 3H, chiral auxiliary aromatic hydrogens), 7.12 (m, 2H, chiral auxiliary aromatic hydrogens), 6.49 (s, 2H, aromatic 3',5' hydrogens), 5.41 (dd, J=8.7, 3.9 Hz, 1H, oxazolidinone Ar-CH-), 4.66 (t, J=8.7 Hz, 1H, oxazolidinone -CH_2-*/pro R*), 4.22 (dd, J=8.7, 3.9 Hz, 1H, oxazolidinone -CH_2-*/pro S*), 3.82 (m, 1H, H-C_β), 3.75 (s, 3H, Ar-OCH_3), 3.41 (dd, J=16.2, 6.2 Hz, 1H, CH_α), 3.36 (dd, J=16.2, 8.6 Hz, 1H, CH_α'), 2.44 (s, broad, 3H, Ar-CH_3), 2.22 (s, broad, 3H, Ar-CH_3'), 1.28 (d, J=7.3 Hz, 3H, C_β-CH_3). ^{13}C NMR ($CDCl_3$) : δ 175.3, 152.7, 139.7, 133.6, 129.1, 128.6, 125.6, 115.5, 114.0, 69.8, 57.5, 54.9, 40.8, 30.1, 29.7, 22.0, 19.2. IR (KBr, cm^{-1}): 2920, 1790, 1700, 1600, 1450, 1310, 1200, 1070, 760. MS: m/e (relative intensity) 368.05 (M^++1, 100), 232.05 (31), 162.95 (78). $[\alpha]_D^{22}$ = -15.6° (c 1.20, $CHCl_3$). Anal. Calcd for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 71.90; H, 7.00; N, 3.90.

3(3*R*), 4(*S*) 3-[3-(4'-Methoxy-2',6'-dimethylphenyl)-1-oxobutyl]-4-phenyl-2-oxazolidinone (14). Yield 85% and was a single diastereomer by proton NMR. The product was recrystallized from ethyl acetate and hexanes to obtain **14** as a single isomer. Mp 135.0-136.0°C; ^{1}H NMR ($CDCl_3$) TMS: δ 7.30 (m, 3H, chiral auxiliary aromatic hydrogens), 7.12 (m, 2H, chiral auxiliary aromatic hydrogens), 6.50 (s, 2H, aromatic 3',5' hydrogens), 5.41 (dd, J=8.7, 3.9 Hz, 1H, oxazolidinone Ar-CH-), 4.67 (t, J=8.8 Hz, 1H, oxazolidinone -CH_2-*/pro R*), 4.22 (dd, J=8.7, 3.9 Hz, 1H, oxazolidinone -CH_2-*/pro S*), 3.80 (m, 1H, H-C_β), 3.75 (s, 3H, Ar-OCH_3), 3.40 (dd, J=7.3, 3.2 Hz, 1H, CH_α), 3.38 (dd, J=7.3, 5.4 Hz, 1H, CH_α'), 2.44 (s, broad, 3H, Ar-CH_3), 2.23 (s, broad, 3H, Ar-CH_3'), 1.28 (d, J=7.2 Hz, 3H, C_β-CH_3). ^{13}C NMR ($CDCl_3$) : δ 175.1 157.1, 153.7, 138.9, 137.7, 133.7, 129.1, 128.5, 125.6, 115.2, 113.8, 69.8, 57.6, 54.9, 40.6, 30.1, 29.7, 27.6, 21.7, 19.2. IR (KBr, cm^{-1}): 2986, 2938, 1777, 1697, 1601, 1480, 1469, 1449, 1382, 1352, 1306, 1145, 1071, 850, 764, 721, 703. MS: m/e (relative intensity) 368.35 (M^++1, 5), 163.25 (100). $[\alpha]_D^{22}$ = +16.8° (c 1.038, $CHCl_3$). Anal. Calcd for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 72.01; H, 6.85; N, 3.81.

General Procedure for Asymmetric Bromination of *N*-Acyloxazolidinones. A typical procedure is illustrated by the preparation of 3(2*R*,3*S*), 4(*R*) 3-[2-bromo-3-(4'-methoxy-2',6'-dimethylphenyl)-1-oxobutyl]-4-phenyl-2-oxazolidinone, **15**.

A solution of 3.87 g (10.53 mmol) of *N*-acyloxazolidinone **11** in 50 mL of dichloromethane was cooled to -78°C, then 2.20 mL (12.64 mmol, 1.2 eq) of freshly distilled diisopropylethylamine and 11.06 mL of di-n-butylborontriflate (1M solution in CH_2Cl_2, 11.05 mmol, 1.05 eq) were added via syringe. Meanwhile in another dry 100 mL 3-neck round bottom flask, a suspension of 2.06 g of recrystallized *N*-bromosuccinimide (11.58 mmol) in freshly distilled dichloromethane (35 mL) was cooled to -78°C. The boron enolate solution was transferred to the *N*-bromosuccinimide suspension at -78°C via cannula. The resulting mixture was stirred at -78°C for 2 hrs and warmed up to -4°C. Then, it was quenched with a 0.5 M sodium bisulfate solution (20 mL). The mixture was warmed up to room temperature and was stirred for 30 min. The phases were separated, the organic layer was set aside, and the aqueous layer was extracted by dichloromethane (25 mL x 2). The combined organic phases were washed with 0.5 M sodium bisulfate solution (50 mL), 1N sodium thiosulfate solution (50 mL x 3), water (50 mL), and brine (50 mL). The organic layer was then dried over anhydrous $MgSO_4$, filtered, evaporated to give the crude bromide as a yellow solid which was further purified

by column chromatography (2:8, EtOAc: Hexanes v/v). An analytical sample was recrystallized from hexanes-ethyl acetate mixture for characterization.

3 (2*R* , 3*S*), 4(*R*) 3-[2-Bromo-3-(4'-methoxy-2',6'-dimethylphenyl)-1-oxobutyl]-4-phenyl-2-oxazolidinone (15). Yield 85%. Tlc R_f = 0.50 (3:7, EtOAc:Hexanes, v/v). Mp 172.0-173.5°C. ^{1}H NMR ($CDCl_3$) TMS: δ 7.38-7.23 (m, 5H, chiral auxiliary aromatic hydrogens), 6.53 (m, 3H, aromatic 3',5'-hydrogens and -CHBr-), 5.13 (dd, J=8.7, 3.6 Hz, 1H, oxazolidinone Ph-CH-), 4.46 (t, J=8.7 Hz, 1H, oxazolidinone -CH_2-/*proR*), 4.10 (dd, J=8.7, 3.6 Hz, 1H, oxazolidinone -CH_2-/*proS*), 3.92-3.84 (m, 1H, C_βH), 3.71 (s, 3H, Ar-OCH_3), 2.41 (s, 3H, Ar-CH_3), 2.35 (s, 3H, Ar-CH_3'), 1.51 (d, J=7.3 Hz, 3H, C_β-CH_3). ^{13}C NMR ($CDCl_3$) : δ 167.4, 157.5, 152.7, 139.3, 137.8, 137.0, 130.3, 129.0, 128.7, 125.5, 115.3, 114.1, 69.8, 57.4, 54.8, 47.8, 36.9, 21.8, 26.1, 17.3. IR (KBr, cm^{-1}): 2980, 1790, 1700, 1600, 1480, 1310, 1060, 700. MS: m/e (relative intensity) 448.00 (M^++3, 100), 446.00 (M^++1, 100), 366.05 (30), 163.05 (60). $[\alpha]_D^{22}$ = -94.0° (c 1.01, $CHCl_3$). Anal. Calcd for $C_{22}H_{24}NO_4Br$: C, 59.20; H, 5.42; N, 3.14. Found: C, 58.87; H, 5.34; N, 3.10.

3 (2*S* , 3*R*), 4(*S*) 3-[2-Bromo-3-(4'-methoxy-2',6'-dimethylphenyl)-1-oxobutyl]-4-phenyl-2-oxazolidinone (16). Yield 89%. Tlc R_f = 0.24 (1:4, EtOAc:Hexanes, v/v). Mp 150.0-151.0°C. ^{1}H NMR ($CDCl_3$) TMS: δ 7.41-7.26 (m, 5H, chiral auxiliary aromatic hydrogens), 6.55-6.47 (m, 3H, aromatic 3',5'-hydrogens and -CHBr-), 5.20 (dd, J=8.6, 3.6 Hz, 1H, oxazolidinone Ph-CH-), 4.53 (t, J=8.7 Hz, 1H, oxazolidinone -CH_2-/*proR*), 4.16 (dd, J=8.7, 3.4 Hz, 1H, oxazolidinone -CH_2-/*proS*), 3.96-3.82 (m, 1H, C_βH), 3.75 (s, 3H, Ar-OCH_3), 2.42 (s, 3H, Ar-CH_3), 2.38 (s, 3H, Ar-CH_3'), 1.51 (d, J=7.3 Hz, 3H, C_β-CH_3). ^{13}C NMR ($CDCl_3$) : δ 167.0, 157.6, 152.8, 137.8, 137.1, 130.3, 129.1, 128.8, 125.6, 115.3, 114.1, 69.9, 57.4, 54.9, 47.8, 37.0, 21.9, 21.7, 17.4. IR (KBr, cm^{-1}): 2970, 2361, 2342, 1783, 1705, 1653, 1603, 1560, 1457, 1385, 1305, 1210, 1150, 1068, 758, 705. MS: m/e (relative intensity) 448.00 (M^++3, 1.6), 446.00 (M^++1, 2.2), 366.15 (12), 309.9 (9), 163.20 (100). $[\alpha]_D^{25}$ = +87.9° (c 1.16, $CHCl_3$). Anal. Calcd for $C_{22}H_{24}NO_4Br$: C, 59.20; H, 5.42; N, 3.14. Found: C, 58.82; H, 5.27; N, 2.78.

3 (2*R* , 3*R*), 4(*R*) 3-[2-Bromo-3-(4'-methoxy-2',6'-dimethylphenyl)-1-oxobutyl]-4-phenyl-2-oxazolidinone (17). Yield 83%. Tlc R_f = 0.48 (3:7, EtOAc:Hexanes, v/v). Mp 186.0-187.5°C. ^{1}H NMR ($CDCl_3$) TMS: δ 7.45-7.29 (m, 5H, chiral auxiliary aromatic hydrogens), 6.56 (s, 2H, aromatic 3',5'-hydrogens), 6.44 (d, J=11.9 Hz, 1H, -CHBr-), 5.54 (dd, J=8.9, 5.0 Hz, 1H, oxazolidinone Ph-CH-), 4.77 (t, J=8.7 Hz, 1H, oxazolidinone -CH_2-/*proR*), 4.29 (dd, J=8.9, 5.0 Hz, 1H, oxazolidinone -CH_2-/*proS*), 4.12-3.98 (m, 1H, C_βH), 3.76 (s, 3H, Ar-OCH_3), 2.47 (s, 3H, Ar-CH_3), 2.31 (s, 3H, Ar-CH_3'), 1.31 (d, J=7.3 Hz, 3H, C_β-CH_3). ^{13}C NMR ($CDCl_3$) : δ 168.8, 157.5, 153.0, 138.6, 137.6, 137.4, 131.2, 129.2, 128.9, 125.8, 115.4, 113.6, 69.8, 57.9, 54.9, 46.2, 36.2, 21.9, 21.3, 16.8. IR (KBr, cm^{-1}): 2970, 1780, 1710, 1600, 1480, 1370, 1300, 1200, 1060, 700. MS: m/e (relative intensity) 448.00 (M^++3, 100), 446.00 (M^++1, 100), 366.05 (30), 163.05 (60). $[\alpha]_D^{22}$ = -1.5° (c 1.03, $CHCl_3$). Anal. Calcd for $C_{22}H_{24}NO_4Br$: C, 59.20; H, 5.42; N, 3.14. Found: C, 59.23; H, 5.52; N, 3.01.

3 (2*S* , 3*S*), 4(*S*) 3-[2-Bromo-3-(4'-methoxy-2',6'-dimethylphenyl)-1-oxobutyl]-4-phenyl-2-oxazolidinone (18). Yield 83%. Tlc R_f = 0.17 (1:4, EtOAc:Hexanes, v/v). Mp 192.0-193.0°C. ^{1}H NMR ($CDCl_3$) TMS: δ 7.45-7.36 (m, 5H, chiral auxiliary aromatic hydrogens), 6.56 (s, 2H, aromatic 3',5'-hydrogens), 6.44 (d, J=12.0 Hz, 1H, -CHBr-), 5.54 (dd, J=8.9, 5.0 Hz, 1H, oxazolidinone Ph-CH-), 4.78 (t,

J=8.9 Hz, 1H, oxazolidinone -CH_2-/*proR*), 4.29 (dd, J=8.9, 5.0 Hz, 1H, oxazolidinone -CH_2-/*proS*), 4.12-3.99 (m, 1H, C_βH), 3.76 (s, 3H, Ar-OCH_3), 2.48 (s, 3H, Ar-CH_3), 2.31 (s, 3H, Ar-CH_3'), 1.28 (d, J=7.3 Hz, 3H, C_β-CH_3). ^{13}C NMR ($CDCl_3$) : δ 168.8, 157.5, 153.0, 138.6, 137.6, 131.2, 129.2, 128.9, 125.8, 115.4, 113.6, 69.9, 57.9, 54.9, 46.2, 36.2, 22.0 21.3, 16.8. IR (KBr, cm^{-1}): 2975, 1782, 1703, 1605, 1487, 1456, 1394, 1370, 1337, 1310, 1213, 1194, 1150, 1071, 764, 704. MS: m/e (relative intensity) 448.00 (M^++3, 2.3), 446.00 (M^++1, 2.1), 366.05 (3.0), 163.15 (100). $[\alpha]_D^{25}$ = +1.75° (c 1.14, $CHCl_3$). Anal. Calcd for $C_{22}H_{24}NO_4Br$: C, 59.20; H, 5.42; N, 3.14. Found: C, 59.42; H, 5.12; N, 2.82.

General Procedure for Azide Displacement; Illustrated by the Preparation of 3(2*S*,3*S*), 4(*R*) 3-[2-Azido-3-(4'-methoxy-2',6'-dimethylphenyl)-1-oxobutyl]-4-phenyl-2-oxazolidinone (19). 3(2*R*,3*S*), 4(*R*) 3-[2-Bromo-3-(4'-methoxy-2',6'-dimethylphenyl)-1-oxobutyl]-4-phenyl-2-oxazolidinone (**15**, 2.20 g, 4.93 mmol) was dissolved in 50 mL acetonitrile (freshly distilled over anhydrous $MgSO_4$). Amberlite IR-400 azide exchange resin (11.03 g, 41.90 mmol, 8.5 eq) was added and the reaction mixture was stirred gently for 9 days. The resin was filtered and washed with acetonitrile (25 mL x 4). The filtrate was concentrated to an off white solid which was then chromatographed (3:7, EtOAc:Hexanes, v/v). A small sample was recrystallized from hexanes-ethyl acetate mixture for characterization.

3 (2*S* , 3*S*), 4(*R*) 3-[2-Azido-3-(4'-methoxy-2',6'-dimethylphenyl)-1-oxobutyl]-4-phenyl-2-oxazolidinone (19). Yield 99%. Tlc R_f = 0.42 (3:7, EtOAc:Hexanes, v/v). Mp 121.0-121.5°C. ^{1}H NMR ($CDCl_3$) TMS: δ 7.44-7.36 (m, 5H, chiral auxiliary aromatic hydrogens), 6.75 (m, 2H, aromatic 3',5'-hydrogens), 5.82 (d, J=11.6 Hz, 1H, -CHN_3-), 5.52 (dd, J=8.6, 3.5 Hz, 1H, oxazolidinone Ph-CH-), 4.72 (t, J=8.6 Hz, 1H, oxazolidinone -CH_2-/*proR*), 4.38 (dd, J=8.6, 3.5 Hz, 1H, oxazolidinone -CH_2-/*proS*), 3.76 (s, 3H, Ar-OCH_3), 3.76-3.66 (m, 1H, C_βH), 2.49 (s, 3H, Ar-CH_3), 2.31 (s, 3H, Ar-CH_3'), 1.05 (d, J=7.2 Hz, 3H, C_β-CH_3). ^{13}C NMR ($CDCl_3$) : δ 171.0, 157.7, 153.4, 138.8, 138.4, 137.8, 129.3, 129.0, 126.1, 115.6, 114.1, 70.1, 60.2, 58.0, 54.9, 37.1, 21.8, 21.5, 15.6. IR (KBr, cm^{-1}): 2970, 2090, 1790, 1700, 1600, 1450, 1200. MS: m/e (relative intensity) 409.20 (M^++1, 1), 381.20 (9), 366.05 (6), 190.05 (15), 163.05 (100). $[\alpha]_D^{22}$ = -48.7° (c 1.24, $CHCl_3$). Anal. Calcd for $C_{22}H_{24}N_4O_4$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.57; H, 5.91; N, 13.53.

3 (2*R* , 3*R*), 4(*S*) 3-[2-Azido-3-(4'-methoxy-2',6'-dimethylphenyl)-1-oxobutyl]-4-phenyl-2-oxazolidinone (20). Yield 90%. Tlc R_f = 0.41 (3:7, EtOAc:Hexanes, v/v). Mp 111.5-112.0°C. ^{1}H NMR ($CDCl_3$) TMS: δ 7.48-7.35 (m, 5H, chiral auxiliary aromatic hydrogens), 6.58 (m, 2H, aromatic 3',5'-hydrogens), 5.83 (d, J=11.6 Hz, 1H, -CHN_3-), 5.53 (dd, J=8.6, 3.5 Hz, 1H, oxazolidinone Ph-CH-), 4.79 (t, J=8.8 Hz, 1H, oxazolidinone -CH_2-/*proR*), 4.40 (dd, J=9.0, 3.5 Hz, 1H, oxazolidinone -CH_2-/*proS*), 3.76 (s, 3H, Ar-OCH_3), 3.76-3.63 (m, 1H, C_βH), 2.50 (s, 3H, Ar-CH_3), 2.32 (s, 3H, Ar-CH_3'), 1.06 (d, J=7.2 Hz, 3H, C_β-CH_3). ^{13}C NMR ($CDCl_3$) : δ 175.4, 171.0, 138.9, 138.4, 137.8, 129.3, 129.1, 126.2, 115.6, 114.1, 70.1, 60.2, 58.1, 55.0, 37.3, 21.9, 21.6, 15.7. IR (KBr, cm^{-1}): 2964, 2091, 1767, 1700, 1630, 1597, 1484, 1451, 1204, 1153, 1068, 766, 700. MS: m/e (relative intensity) 409.25 (M^++1, 0.6), 381.25 (6), 366.15 (3) 190.15 (18), 163.00 (100). $[\alpha]_D^{22}$ = +49.1° (c 1.24, $CHCl_3$). Anal. Calcd for $C_{22}H_{24}N_4O_4$: C, 64.69; H, 5.92; N, 13.72. Found: C, 65.01; H, 5.82; N, 13.56.

3 (2*S* , 3*R*), 4(*R*) 3-[2-Azido-3-(4'-methoxy-2',6'-dimethylphenyl)-1-oxobutyl]-4-phenyl-2-oxazolidinone (21). Yield 95%. Mp 102.5-103.5°C. ^{1}H NMR ($CDCl_3$) TMS: δ 7.22-7.10 (m, 3H, chiral

auxiliary aromatic hydrogens), 6.61-6.58 (m, 2H, chiral auxiliary aromatic hydrogens), 6.52 (s, broad, 1H, aromatic 3'-hydrogen), 6.25 (s, broad, 1H, aromatic 5'-hydrogen), 5.73 (d, J=11.6 Hz, 1H, -CHN_3-), 5.34 (dd, J=8.9, 4.9 Hz, 1H, oxazolidinone Ph-CH-), 4.72 (t, J=8.9 Hz, 1H, oxazolidinone -CH_2-*proR*), 4.61 (dd, J=8.9, 4.3 Hz, 1H, oxazolidinone -CH_2-*proS*), 3.78 (s, 3H, Ar-OCH_3), 3.77 (m, 1H, C_βH), 2.49 (s, 3H, Ar-CH_3), 1.93 (s, 3H, Ar-CH_3'), 1.48 (d, J=7.3 Hz, 3H, C_β-CH_3). ^{13}C NMR ($CDCl_3$) : δ 168.9, 156.5, 138.1, 137.3, 136.3, 127.9, 127.3, 127.1, 124.3, 114.0, 113.6, 68.8, 59.0, 56.4, 53.8, 34.6, 20.9, 20.2, 18.0. IR (KBr, cm^{-1}): 2965, 2100, 1790, 1690, 1600, 1450, 1310, 1200, 710. MS: m/e (relative intensity) 409.20 (M^++1, 15), 366.20 (40), 163.1 (100). $[\alpha]_D^{22}$ = -41.9° (c 1.01, $CHCl_3$). Anal. Calcd for $C_{22}H_{24}N_4O_4$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.93; H, 5.83; N, 13.50.

3 (2*R* , 3*S*), 4(*R*) 3-[2-Azido-3-(4'-methoxy-2',6'-dimethylphenyl)-1-oxobutyl]-4-phenyl-2-oxazolidinone (22). Yield 96%. Mp 105.5-106.0°C. ^{1}H NMR ($CDCl_3$) TMS: δ 7.26-7.10 (m, 3H, chiral auxiliary aromatic hydrogens), 6.62-6.58 (m, 2H, chiral auxiliary aromatic hydrogens), 6.52 (s, broad, 1H, aromatic 3'-hydrogen), 6.25 (s, broad, 1H, aromatic 5'-hydrogen), 5.73 (d, J=11.6 Hz, 1H, -CHN_3-), 5.35 (dd, J=8.9, 4.9 Hz, 1H, oxazolidinone Ph-CH-), 4.63 (t, J=8.9 Hz, 1H, oxazolidinone -CH_2-*proR*), 4.09 (dd, J=8.9, 4.9 Hz, 1H, oxazolidinone -CH_2-*proS*), 3.79 (s, 3H, Ar-OCH_3), 3.82-3.72 (m, 1H, C_βH), 2.50 (s, 3H, Ar-CH_3), 1.94 (s, 3H, Ar-CH_3'), 1.48 (d, J=7.3 Hz, 3H, C_β-CH_3). ^{13}C NMR ($CDCl_3$) : δ 171.6, 169.9, 157.6, 153.1, 139.0, 137.3, 136.3, 128.9, 128.3, 125.3, 115.0, 114.6, 69.8, 60.1, 57.5, 54.8, 35.6, 21.9, 21.2, 16.0. IR (KBr, cm^{-1}): 2955, 2105, 1780, 1692, 1602, 1383, 1305, 1201, 710. MS: m/e (relative intensity) 409.0 (M^++1, 6), 366.0 (40), 163.2 (100). $[\alpha]_D^{23}$ = +40.59° (c 1.01, $CHCl_3$). Anal. Calcd for $C_{22}H_{24}N_4O_4$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.68; H, 5.84; N, 13.51.

General Procedure for the Hydrolysis of 3-(α-Azidoacyl)-4-phenyl-2-oxazolidinones; Illustrated by the Preparation of (2*S*,3*S*) 2-Azido-3-(4'-methoxy-2',6'-dimethylphenyl)butanoic acid (23). The azidoacyl-oxazolidinone **19** (2.0 g, 4.9 mmol) was dissolved in THF (60 mL) and water (20 mL). The mixture was cooled to -4°C and 30 % hydrogen peroxide (3.4 mL, 30 mmol) was added via syringe over 5 min. A solution of lithium hydroxide (0.44 g of lithium hydroxide monohydrate, 10.5 mmol in 3 mL water) was then added dropwise over 10 min. The reaction was stirred at 0°C for 2 hrs and was quenched with 1.3 M sodium sulfite solution (30 mL). The mixture was warmed up to room temperature and stirred for 30 min. Volatiles were removed by rotary evaporation and the aqueous phase was extracted with dichloromethane (40 mL x 3) to remove the chiral auxiliary. The remaining aqueous phase was cooled to 0°C and acidified to *ca.* pH = 1.5 with aqueous 6N HCl and was extracted with dichloromethane (40 mL x 3). The colorless extracts were dried over anhydrous sodium sulfate, filtered and concentrated to yield the product as an off-white solid.

(2*S*,3*S*) 2-Azido-3-(4'-methoxy-2',6'-dimethylphenyl)butanoic acid (23). Yield 100%. Tlc R_f = 0.26 (20:79:1, EtOAc:Hexanes:AcOH, v/v/v). Mp 55.0-57.0°C. ^{1}H NMR ($CDCl_3$) TMS: δ 6.61 (s, broad, 1H, aromatic 3'-hydrogen), 6.57 (s, broad, 1H, aromatic 5'-hydrogen), 4.27 (d, J=11.5 Hz, 1H, -CHN_3), 3.78 (s, 3H, Ar-OCH_3), 3.75 (m, 1H, C_βH), 2.42 (s, 3H, Ar-CH_3), 2.40 (s, 3H, Ar-CH_3'), 1.38 (d, J=7.2 Hz, 3H, C_β-CH_3). ^{13}C NMR ($CDCl_3$) : δ 176.6, 157.8, 138.8, 137.4, 129.3, 115.7, 114.1, 65.2, 54.9, 36.7, 21.8, 21.6, 16.5. IR (KBr, cm^{-1}): 2970, 2100, 1720, 1600, 1490, 1307, 1150, 1070, 840. High Resolution-CIMS calcd for $C_{13}H_{17}N_3O_3$: 264.13480 (M^++1). Found: m/e 264.1328. $[\alpha]_D^{22}$ = -17.0° (c 0.82, $CHCl_3$).

(2*R*,3*R*) 2-Azido-3-(4'-methoxy-2',6'-dimethylphenyl)butanoic acid (24). Yield 100%. Tlc R_f = 0.33 (2.5:6.5:1, EtOAc:Hexanes:AcOH, v/v/v). Mp 77.0-77.5°C. ^{1}H NMR ($CDCl_3$) TMS: δ 6.62 (s, broad, 1H, aromatic 3'-hydrogen), 6.58 (s, broad, 1H, aromatic 5'-hydrogen), 4.26 (d, J=11.5 Hz, 1H, -CHN_3), 3.78 (s, 3H, Ar-OCH_3), 3.75 (m, 1H, C_βH), 2.41 (s, 3H, Ar-CH_3), 2.40 (s, 3H, Ar-CH_3'), 1.37 (d, J=7.2 Hz, 3H, C_β-CH_3). ^{13}C NMR ($CDCl_3$) : δ 176.3, 157.8, 138.9, 129.3, 115.7, 114.1, 65.2, 55.0, 36.8, 22.0, 21.6, 16.5. IR (KBr, cm^{-1}): 2970, 2100, 1720, 1600, 1490, 1307, 1150, 1070, 840. High Resolution-CIMS calcd for $C_{13}H_{17}N_3O_3$: 263.12699. Found: m/e 263.1261. $[\alpha]_D^{25}$ = +16.6° (c 1.10, $CHCl_3$).

(2*S*,3*R*) 2-Azido-3-(4'-methoxy-2',6'-dimethylphenyl)butanoic acid (25). Yield 100%. Oil. ^{1}H NMR ($CDCl_3$) TMS: δ 9.83 (s, 1H, -CO_2H), 6.53 (s, 2H, aromatic 3',5'-hydrogens), 4.14 (d, J=10.4 Hz, 1H, -CHN_3), 3.75 (s, 3H, Ar-OCH_3), 3.65 (m, 1H, C_βH), 2.38 (s, broad, 3H, Ar-CH_3), 2.29 (s, broad, 3H, Ar-CH_3'), 1.44 (d, J=7.0 Hz, 3H, C_β-CH_3). ^{13}C NMR ($CDCl_3$) : δ 175.4, 157.6, 138.3, 138.2, 128.8, 115.2, 114.7, 65.0, 54.8, 36.5, 21.7, 21.6, 15.8. IR (KBr, cm^{-1}): 2970, 2100, 1720, 1600, 1490, 1307, 1150, 1070, 840. High Resolution-CIMS calcd for $C_{13}H_{17}N_3O_3$: 264.13480 (M^++1). Found: m/e 264.1330. $[\alpha]_D^{22}$ = +84.8° (c 1.66, $CHCl_3$).

(2*R*,3*S*) 2-Azido-3-(4'-methoxy-2',6'-dimethylphenyl)butanoic acid (26). Yield 99%. Oil. ^{1}H NMR ($CDCl_3$) TMS: δ 8.07 (s, 1H, -CO_2H), 6.53 (s, 2H, aromatic 3',5'-hydrogens), 4.15 (d, J=10.4 Hz, 1H, -CHN_3), 3.76 (s, 3H, Ar-OCH_3), 3.62 (m, 1H, C_βH), 2.39 (s, broad, 3H, Ar-CH_3), 2.29 (s, broad, 3H, Ar-CH_3'), 1.44 (d, J=7.2 Hz, 3H, C_β-CH_3). ^{13}C NMR ($CDCl_3$)) : δ 175.1, 157.7, 138.4, 138.3, 128.9, 115.4, 114.3, 65.1, 54.9, 36.6, 21.8, 16.0. IR (KBr, cm^{-1}): 2964, 2103, 1742, 1600, 1485, 1305, 1260, 1150, 1071, 858, 601. High Resolution-CIMS calcd for $C_{13}H_{17}N_3O_3$: 264.1354 (M^++1). Found: m/e 264.1330. $[\alpha]_D^{23}$ = -84.3° (c 1.065, $CHCl_3$).

General Procedure for the Reduction of Azido Acids; Illustrated by Preparation of (2*S*,3*S*) 2-Amino-3-(4'-methoxy-2',6'-dimethylphenyl)butanoic acid hydrochloride (27). (2*S*,3*S*) 2-Azido-3-(4'-methoxy-2',6'-dimethylphenyl)butanoic acid **23** (1.00 g, 3.8 mmol) was dissolved in glacial acetic acid (48 mL) and water (24 mL). The solution was de-gased with argon bubbled for 45 min, and then 10% palladium on activated carbon (0.1 g) was added, the mixture was bubbling with argon for another 20 min. The reaction mixture was washed with hydrogen 3 times and was charged with hydrogen (36 psi) and shaken for 24 hrs. The catalyst was filtered, and the volatiles was removed by rotary evaporation. To the remaining aqueous phase was added 6 mL of 6N HCl solution. It was then evaporated, frozen and lyophilized to give 1.14 g of an off-white solid.

(2*S*,3*S*) 2-Amino-3-(4'-methoxy-2',6'-dimethylphenyl)butanoic acid hydrochloride (27). Yield 100%. Tlc R_f = 0.63 (4:1:1, acetonitrile:methanol:water, v/v/v, RP chiral plate). Mp 109.5-111.5°C. ^{1}H NMR (D_2O) : δ 6.52 (m, 2H, aromatic 3',5'-hydrogens), 3.91(d, J=11.5 Hz, 1H, -C_αH), 3.57 (s, 3H, Ar-OCH_3), 3.28 (m, 1H, C_βH), 2.21 (s, 3H, Ar-CH_3), 2.13 (s, 3H, Ar-CH_3'), 1.16 (d, J=7.3 Hz, 3H, C_β-CH_3). IR (KBr, cm^{-1}): 2970, 1600, 1490, 1310. High Resolution-CIMS calcd for $C_{13}H_{19}NO_3$: 238.14431 (M^++1). Found: m/e 238.1466. $[\alpha]_D^{22}$ = -31.9° (c 0.63, MeOH).

(2*R*,3*R*) 2-Amino-3-(4'-methoxy-2',6'-dimethylphenyl)butanoic acid hydrochloride (28). Yield 100%. Oil. Tlc R_f = 0.44 (4:1:1, acetonitrile:methanol:water, v/v/v, RP chiral plate). ^{1}H NMR (CD_3COD) : δ 6.44 (m, 2H, aromatic 3',5'-hydrogens), 4.07(d, J=11.20 Hz, 1H, -C_αH), 3.54 (s, 3H, Ar-OCH_3), 3.36 (m, 1H, C_βH), 2.23 (s, 3H, Ar-CH_3), 2.16 (s, 3H, Ar-CH_3'), 1.22 (d, J=7.3 Hz, 3H, C_β-CH_3). ^{13}C NMR (CD_3COD) : δ 176.8, 172.2, 159.9, 129.0 117.4, 115.7, 57.5, 55.5, 54.9, 50.0, 37.8, 21.7, 20.8, 20.5, 17.3. IR (KBr, cm^{-1}): 2970, 1600, 1490, 1310. High Resolution-CIMS calcd for $C_{13}H_{19}NO_3$: 238.14431 (M^++1). Found: m/e 238.1447. $[\alpha]_D^{25}$ = +32.1° (c 0.95, MeOH).

(2*S*,3*R*) 2-Amino-3-(4'-methoxy-2',6'-dimethylphenyl)butanoic acid hydrochloride (29). Yield 100%. Tlc R_f = 0.51 (4:1:1, acetonitrile:methanol:water, v/v/v, RP chiral plate). Mp 110.0-113.0°C. ^{1}H NMR (D_2O) : δ 6.44 (s, 2H, aromatic 3',5'-hydrogens), 3.85(d, J=11.0 Hz, 1H, -C_αH), 3.51 (s, 3H, Ar-OCH_3), 3.44 (m, 1H, C_βH), 2.12 (s, broad, 6H, Ar-CH_3), 1.19 (d, J=7.3 Hz, 3H, C_β-CH_3). ^{13}C NMR (D_2O, 1,4-dioxane) : δ 180.5, 163.5, 145.5, 121.8, 120.6, 74.2, 73.2, 61.7, 42.5, 27.6, 21.7. IR (KBr, cm^{-1}): 3450, 2970, 1603, 1400, 1310, 1150, 1070. High Resolution-CIMS calcd for $C_{13}H_{19}NO_3$: 238.14431 (M^++1). Found: m/e 238.1490. $[\alpha]_D^{22}$ = +62.53° (c 0.84, MeOH).

(2*R*,3*S*) 2-Amino-3-(4'-methoxy-2',6'-dimethylphenyl)butanoic acid hydrochloride (30). Yield 99%. Tlc R_f = 0.41 (4:1:1, acetonitrile:methanol:water, v/v/v, RP chiral plate). Mp 118.5-120.0°C. ^{1}H NMR (D_2O) : δ 6.48 (s, 2H, aromatic 3',5'-hydrogens), 4.15 (d, J=11.3 Hz, 1H, -C_αH), 3.55 (s, 3H, Ar-OCH_3), 3.53 (m, 1H, C_βH), 2.21 (s, broad, 3H, Ar-CH_3), 2.07 (s, broad, 3H, Ar-CH_3), 1.26 (d, J=7.2 Hz, 3H, C_β-CH_3). ^{13}C NMR (D_2O, 1,4-dioxane) : δ 171.7, 157.1, 138.8, 115.2, 115.0, 113.6, 56.2, 55.0, 35.7, 20.6, 15.0. IR (KBr, cm^{-1}): 3437, 2934, 1738, 1680, 1601, 1485, 1307, 1146, 1070, 853.. High Resolution-CIMS calcd for $C_{13}H_{19}NO_3$: 238.14431 (M^++1). Found: m/e 238.1439. $[\alpha]_D^{23}$ = -63.73° (c 1.02, MeOH).

General Procedure for the Hydrolysis of Methyl Ethers and Ion-exchange Purification of the Final Amino Acids; Illustrated by the Preparation of (2*S*,3*S*) 2-Amino-3-(2',6'-dimethyl-4'-hydroxyphenyl)butanoic Acid (31). 1.15 (g) of (2*S*,3*S*) 2-Amino-3-(4'-methoxy-2',6'-dimethylphenyl)butanoic acid (**27**, 4.85 mmol) was dissolved in trifluoroacetic acid (50 mL). The solution was cooled to -4°C, thioanisole (3.98 mL, 33.92 mmol, 7 eq) was added and stirred for 10 min., finally trifluoromethanesulfonic acid (6.43 mL, 72.69 mmol, 15 eq) was added via syringe. The light yellow cloudy solution was stirred at 0° to -4°C for 30 min. Volatiles were removed by rotary evaporation. The residue was a dark red-brownish tar and was dissolved in 100 mL of water. The solution was loaded on an ion-exchange column (2.5 cm x 46 cm) with Amberlite IR-120 (H^+) resin (150 g). The column was washed with water until the eluant was neutral. The amino acid was washed out with 5% NH_4OH solution, this process was monitored by tlc. Fractions containing the product were combined, evaporated to remove excess NH_4OH, frozen and lyophilized to give 1.02 g of this title compound as off-white solid.

(2*S*,3*S*) 2-Amino-3-(2',6'-dimethyl-4'-hydroxyphenyl)butanoic Acid (31). Yield 94%. Tlc R_f = 0.69 (acetonitrile:methanol:water, 4:1:1, v/v/v; RP chiral plate). Mp 153.0-156.0°C dec. ^{1}H NMR (D_2O) : δ 6.41 (s, 2H, aromatic 3',5'-hydrogens), 4.17 (d, J=11.0 Hz, 1H, C_αH), 3.36 (m, 1H, C_βH), 2.16, (s, 3H, Ar-CH_3), 2.08 (2, 3H, Ar-CH_3'), 1.14 (d, J=7.4 Hz, 3H, C_β-CH_3). ^{13}C NMR (D_2O) : δ 171.4, 154.5, 143.9, 138.4, 131.3, 127.9, 117.5, 113.2, 57.4, 34.4, 18.4, 14.6. IR (KBr, cm^{-1}) 2980, 1730, 1610, 1490, 1300, 1210.

High Resolution - CIMS calcd for $C_{12}H_{17}NO_3$: 224.12866 (M^++1). Found: 224.1264. $[\alpha]^{22}_D$= -35.36° (c 0.51, MeOH). The N^{α}-Boc amino acid was prepared, purified and analyzed as previously reported.[3]

(2*R*,3*R*) 2-Amino-3-(2',6'-dimethyl-4'-hydroxyphenyl)butanoic Acid (32). Yield 90%. Tlc R_f = 0.60 (acetonitrile:methanol:water, 4:1:1, v/v/v; RP chiral plate). Mp 168.0-170.0°C dec. ^{1}H NMR (D_2O) : δ 6.39-6.32 (s, broad, 2H, aromatic 3',5'-hydrogens), 3.86 (d, J=11.6 Hz, 1H, C_{α}H), 3.23 (m, 1H, C_{β}H), 2.14, (s, 3H, Ar-CH_3), 2.06 (2, 3H, Ar-CH_3'), 1.12 (d, J=7.3 Hz, 3H, C_{β}-CH_3). ^{13}C NMR (D_2O) : δ 174.4, 157.0, 140.6, 139.0, 128.8, 118.7, 116.9, 59.9, 38.1, 21.8, 21.6, 18.3, 17.4. IR (KBr, cm^{-1}) 3417, 2972, 1729, 1712, 1649, 1632, 1612, 1503, 1469, 1307, 1201, 1137, 1030, 857, 722. High Resolution - CIMS calcd for $C_{12}H_{17}NO_3$: 224.12866 (M^++1). Found: 224.1275. $[\alpha]^{22}_D$= +35.49° (c 0.71, MeOH).

(2*S*,3*R*) 2-Amino-3-(2',6'-dimethyl-4'-hydroxyphenyl)butanoic Acid (33). Yield 96%. Hygroscopic solid. Tlc R_f = 0.61 (acetonitrile:methanol:water, 4:1:1, v/v/v; RP chiral plate). ^{1}H NMR (D_2O) : δ 6.36 (s, 2H, aromatic 3',5'-hydrogens), 4.11 (d, J=11.3 Hz, 1H, C_{α}H), 3.50 (m, 1H, C_{β}H), 2.15, (s, 3H, Ar-CH_3), 2.02 (2, 3H, Ar-CH_3'), 1.23 (d, J=7.2 Hz, 3H, C_{β}-CH_3). ^{13}C NMR (D_2O) : δ 171.4, 153.9, 138.9, 128.7 116.7, 115.1, 56.1, 35.8, 20.8, 20.6, 15.2. IR (KBr, cm^{-1}) 3430, 3030, 1740, 1600, 1520, 1300, 1150. High Resolution - CIMS calcd for $C_{12}H_{17}NO_3$: 224.12866 (M^++1). Found: 224.1261. $[\alpha]^{22}_D$= +46.6° (c 0.79, MeOH).

(2*R*,3*S*) 2-Amino-3-(2',6'-dimethyl-4'-hydroxyphenyl)butanoic Acid (34). Yield 96%. Tlc R_f = 0.49 (acetonitrile:methanol:water, 4:1:1, v/v/v; RP chiral plate). Mp 175.0-178.0°C dec. ^{1}H NMR (D_2O) : δ 6.36 (s, 2H, aromatic 3',5'-hydrogens), 3.85 (d, J=11.0 Hz, 1H, C_{α}H), 3.44 (m, 1H, C_{β}H), 2.11, (s, broad, 6H, Ar-CH_3), 1.20 (d, J=7.2 Hz, 3H, C_{β}-CH_3). ^{13}C NMR (D_2O) : δ 174.0, 153.5, 139.0, 138.9, 130.2, 116.7, 115.6, 58.4, 35.8, 20.8, 20.6, 15.1. IR (KBr, cm^{-1}) 3415, 2971, 1719, 1591, 1503, 1469, 1402, 1305, 1201, 1146. High Resolution - CIMS calcd for $C_{12}H_{17}NO_3$: 224.12866 (M^++1). Found: 224.1281. $[\alpha]^{22}_D$= -42.8° (c 0.50, MeOH).

Preparation of 3(2*R*,3*S*), 4(*R*) 3-[2-Azido-3-(4'-methoxy-2',6'-dimethylphenyl)-1-oxobutyl]-4-phenyl-2-oxazolidinone (35). To 5 mL of dry THF stirred at -78°C was added potassium hexamethyldisilazide (KHMDS, 3.12 mL, 0.5 M in toluene, 1.1 eq.). The resulting solution was stirred at -78°C for 20 min, and was added via cannula to a precooled (-78°C) solution of **11** (0.5 g, 1.36 mmol) in dry THF (4 mL). The mixture was stirred at -78°C for 30 min. To the above solution was added via cannula a precooled (-78°C) solution of 2,4,6-triisopropylsulfonyl azide (0.59 g, 1.19 mmol, 1.4 eq.) in dry THF (6 mL). 2,4,6-Triisopropylsulfonyl azide was prepared according to a literature method.[20] After 3 min, the reaction was quenched with glacial acetic acid (0.7 mL). The reaction mixture was warmed to room temperature and stirred for 5 hrs. The reaction mixture was partitioned between dichloromethane (100 mL) and diluted brine (50 mL). The aqueous phase was washed with dichloromethane (3 x 30 mL). The combined organic phases was washed with saturated $NaHCO_3$ solution (2 x 30 mL) and dried over anhydrous $MgSO_4$. The drying agent was filtered and the solvent was evaporated. The crude product, a yellow solid, was purified by gravity column chromatography using 5% to 12% ethyl acetate in hexanes (v/v) as eluant. The purified product weighed 0.44 g and was a yellow solid. A small sample was recrystallized from hexanes-ethyl acetate mixtures for characterization (yellow plate-like crystals).

3(2*R*,3*S*), 4(*R*) 3-[2-Azido-3-(4'-methoxy-2',6'-dimethylphenyl)-1-oxobutyl]-4-phenyl-2-oxazolidinone (35). Yield 79% and was a 97:3 mixture of diastereomers by integration of $C_{\alpha}H$ in proton NMR. Tlc R_f = 0.35 (3:7, EtOAc:Hexanes, v/v). Mp 113.0-113.5°C. ^1H NMR ($CDCl_3$) TMS: δ 7.41-7.32 (m, 3H, chiral auxiliary aromatic hydrogens), 7.22-7.18 (m, 2H, chiral auxiliary aromatic hydrogens), 6.56 (d, J = 3.41 Hz, 2H, aromatic 3',5'-hydrogens), 5.46 (d, J=11.5 Hz, 1H, -CHN_3-), 4.94 (dd, J=8.0, 2.9 Hz, 1H, oxazolidinone Ph-CH-), 4.19 (t, J=8.3 Hz, 1H, oxazolidinone -CH_2-*/proR*), 4.10 (dd, J=8.7, 2.9 Hz, 1H, oxazolidinone -CH_2-*/proS*), 3.78 (m, 1H, $C_{\beta}H$), 3.76 (s, 3H, Ar-OCH_3), 2.45 (s, 3H, Ar-CH_3), 2.34 (s, 3H, Ar-CH_3'), 1.52 (d, J=7.3 Hz, 3H, C_{β}-CH_3). ^{13}C NMR ($CDCl_3$) : δ 169.7, 157.8, 152.9, 139.1, 138.5, 138.1, 129.3, 129.2, 129.1, 128.8, 125.5, 125.4, 115.3, 114.2, 70.2, 61.1, 57.9, 55.0, 36.1, 22.3, 21.8, 16.2. IR (KBr, cm^{-1}): 2971, 2098, 1787, 1691, 1601, 1453, 1303, 1193, 1037, 705. MS: m/e (relative intensity) 409.20 (M^++1, 10), 366.05 (100), 163.05 (81). $[\alpha]_D^{23}$ = -235.7° (c 0.67, $CHCl_3$). Anal. Calcd for $C_{22}H_{24}N_4O_4$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.98; H, 5.81; N, 13.80.

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