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# Stereoselective Synthesis of Four Stereoisomers of β-Methoxytyrosine, a Component of Callipeltin A

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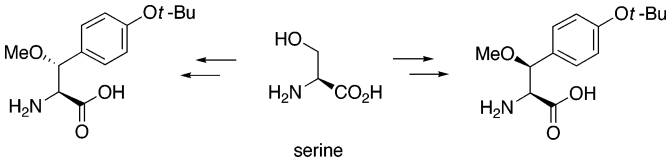
*Received November 30, 2004*




Callipeltin A is a novel cyclic depsipeptide that selectively inhibits the cardiac sodium/calcium exchanger and is therefore of interest as a regulator of myocardial contractility. The stereochemistry of β-methoxytyrosine, one of the amino acids contained within the marine natural product, could not be determined. In an effort to elucidate the stereochemistry of this moiety, a stereoselective synthesis of four stereoisomers of β-methoxytyrosine from (*S*)- and (*R*)-serine was accomplished.

## Introduction

The presence of β-methoxy amino acids in biologically active natural products has stimulated interest in the synthesis of these unusual amino acids. Callipeltin A, a novel cyclic depsipeptide, was isolated by Zampella et al.[1,2] in 1996 from a shallow water sponge of the genus *Callipelta* collected in the waters off New Caledonia (Figure 1). Callipeltin A was reported to have moderate antiviral, antifungal anti-HIV properties. More recently, this natural product was shown to be a selective and powerful inhibitor of the cardiac sodium/calcium exchanger making it of interest as a regulator of myocardial contractility.[3,4]

Papuamide A, another novel cyclic depsipeptide isolated by Boyd et al.[5] from the marine sponge genus *Theonella* collected in Papua New Guinea, has shown significant cytotoxicity against a number of human cancer lines. Papuamide A is also known to inhibit the infection of human T-lymphoblastanoid cells by HIV-1. Callipeltin A and papuamide A contain a variety of unusual amino acids but β-methoxytyrosine is a component of both, and in each instance the stereochemistry of the β-methoxytyrosine was undetermined because of decomposition during degradation studies. The combination of interesting biological activity, unusual amino acids, and complex molecular architecture has attracted the interest of several research groups in the synthesis of callipeltin A[6−8] and papuamide A.[9−11] In our investigations toward the synthesis of callipeltin A, we have previously reported the synthesis of 3,4-dimethylglutamine[12] and 3-hydroxy-2,4,6-trimethylheptanoic acid.[13] However, the stereochemistry of the β-methoxytyrosine remained a problem. Any effort to use total synthesis as a method to determine the relative and absolute stereochemistry of the β-methoxytyrosine would require access to synthetically useful quantities of all four possible stereoisomers of β-methoxytyrosine. Recently, two groups

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(11) Makino, K.; Okamoto, N.; Hara, O.; Hamada, Y. *Tetrahedron: Asymmetry* **2001**, *12*, 1757−1762.

(12) Liang, B.; Carroll, P. J.; Joullie, M. M. *Org. Lett.* **2000**, *2*, 4157−4160.

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10.1021/jo047876z CCC: $30.25 
Published on Web 03/23/2005

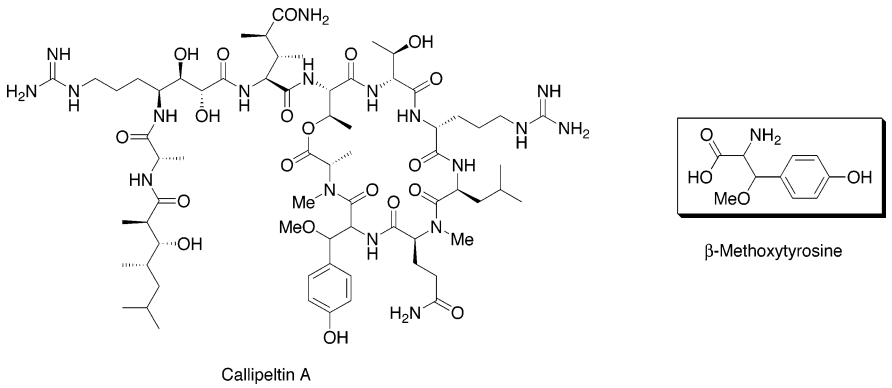
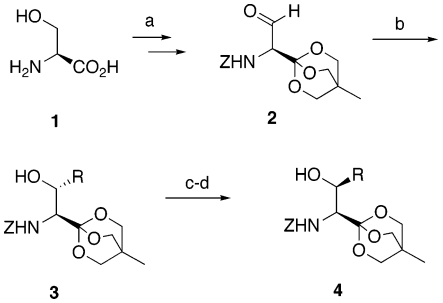



**FIGURE 1.** Callipeltin A and β-methoxytyrosine.

**SCHEME 1. Lajoie's Method**[a]



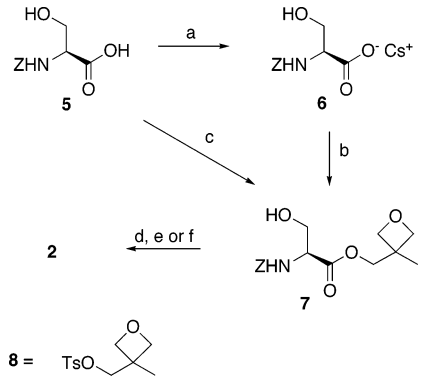
[a] Reagents and conditions: (a) ref 16; (b) RMgX; (c) DMSO, oxalyl chloride, TEA; (d) $LiBH_4$.

have completed syntheses of all four stereoisomers of β-methoxytyrosine based on two different methods.[9,14] While a variety of synthetic methods exist for the synthesis of β-hydroxy and β-methoxy amino acids, all have a number of shortcomings including poor stereoselectivity, limited substrate scope, and harsh reaction conditions. We now report a simple synthesis of all four stereoisomers of β-methoxytyrosine from serine based on the work of Lajoie.

## Results and Discussion

Our initial investigation focused on the use of a general route that would allow for the synthesis of multigram quantities of all four stereoisomers of β-methoxytyrosine. Previously we had utilized Garner's aldehyde as a chiral serine aldehyde equivalent but found the levels of asymmetric induction to vary greatly among a variety of organometallic nucleophiles.[15] Lajoie and co-workers developed a serine aldehyde equivalent **2** from serine (**1**), which seemed to solve the problem of limited asymmetric induction (Scheme 1).[16] Addition of a variety of Grignard reagents exhibited a large degree of diastereoselectivity consistent with nonchelation-controlled Felkin−Anh addition to give β-hydroxy amino acid intermediate **3**. Additionally, Lajoie's serine aldehyde equivalent also allowed for the synthesis of the opposite diastereomer **4** by a simple oxidation to the β-keto intermediate followed by reduction, which occurs under Felkin−Anh control to give **4**.

**SCHEME 2. Synthesis of Chiral (2*S*)-Serine Aldehyde**[a]



[a] Reagents and conditions: (a) $Cs_2CO_3$, $H_2O$, then lyophilize, 100%; (b) **8**, NaI, DMF, 71%; (c) **8**, TEA, TBAI, DMF, 88%; (d) $BF_3{\cdot}Et_2O$, $CH_2Cl_2$, 79%; (e) DMSO, $(COCl)_2$, then DIPEA, 99%; (f) Dess−Martin periodinane, 94%.

Our synthesis of Lajoie's serine aldehyde equivalent utilized a slightly modified approach to the previously published method (Scheme 2).[17] The initial alkylation of Cbz-(2*S*)-serine cesium salt **6** with oxetane tosylate **8** proceeded as reported to give **7**, but the preparation of the Cbz-(2*S*)-serine cesium salt **6** was tedious because of the need to lyophilize the material to complete dryness, which limited the amount of material that could be prepared at one time. We found that combining Cbz-(2*S*)-serine **5**, the oxetane tosylate **8**, triethylamine, and a catalytic amount of tetrabutylamine iodide in DMF and heating to 70 °C overnight gave the desired (2*S*)-serine oxetane ester **7**, which was identical in all respects to the compound reported by Lajoie. The formation of the ortho ester was performed as previously described by the addition of catalytic $BF_3{\cdot}Et_2O$ to give the ortho ester. Oxidation of the β-hydroxy group was accomplished by Swern oxidation to give the desired (2*S*)-aldehyde **2**. The oxidation could also be accomplished with Dess−Martin periodinane in the presence of $NaHCO_3$ to give the desired aldehyde with slightly diminished *enantiomeric*

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(15) Williams, L.; Zhang, Z. D.; Shao, F.; Carroll, P. J.; Joullie, M. M. *Tetrahedron* **1996**, *52*, 11673−11694.
(16) Blaskovich, M. A.; Lajoie, G. A. *J. Am. Chem. Soc.* **1993**, *115*, 5021−5030.
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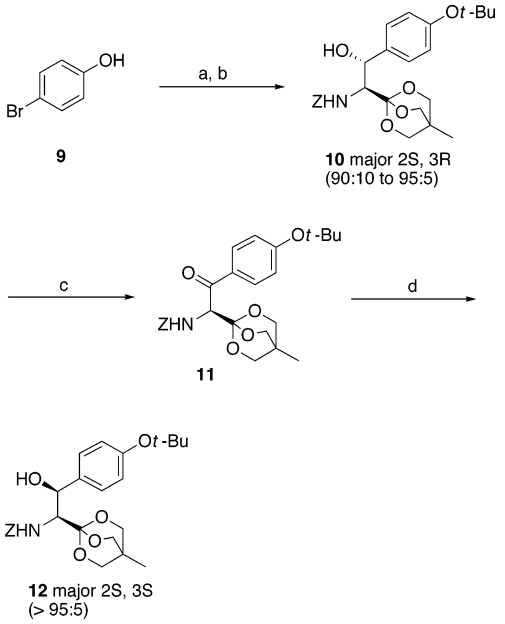
**SCHEME 3. Grignard Addition**[a]

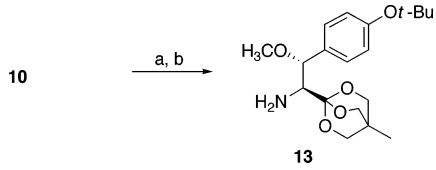



[a] Reagents and conditions: (a) isobutylene, PTSA, $CH_2Cl_2$, 83%; (b) Mg turnings, $I_2$, THF, then **2**, 1:1 $CH_2Cl_2$:$Et_2O$, 65%; (c) Dess–Martin periodinane, 94%; (d) $LiBH_4$, THF, 96%.

*excess* (91–94%) compared to the results from the Swern oxidation (96–98%), but the method was found to be somewhat easier to perform on larger scale than the Swern oxidation used by Lajoie.

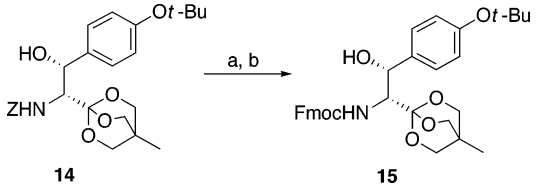
The next step was the preparation of a suitably protected Grignard reagent for addition into the chiral (2*S*)-serine aldehyde **2**. Lajoie had shown that *p*-anisyl MgBr[18] could successfully be added to the desired chiral aldehyde but we thought that deprotection of a phenyl methyl ether at a late stage could be problematic given the inherent instability of the *β*-methoxytyrosine residue in callipeltin A. We chose a *tert*-butyl ether as a protecting group for the phenolic hydroxyl group, which would be easier to remove and able to withstand the conditions necessary for the formation of the desired Grignard. 4-Bromophenol **9** was exposed to condensed isobutylene and an acid catalyst to provide the protected derivative. *p*-Toluenesulfonic acid (PTSA) gave the highest yields of the desired 4-bromophenol-*tert*-butyl ether (Scheme 3). Surprisingly, the use of a catalytic amount of concd $H_2SO_4$[19,20] was found to give a mixture of O- and C-2-alkylated products. Additionally, the use of *tert*-butyl chloride and zinc gave exclusively the C2-alkylation product in our hands.[21] Formation of the 4-*tert*-butylphenol ether Grignard proceeded smoothly followed by addition to the Cbz-(2S)-serine aldehyde **2** under Lajoie's conditions to give **10** in a 65% yield of a 90:10 to 95:5 (2*S*,3*R threo/2S,3S erythro*) as a mixture of inseparable diastereomers that were separable at a later point (vida infra). Having accessed the *threo* diastereomer in good yield we sought to synthesize the (2*S*,3*S*) *erythro* diastereomer. Intermediate **10** was oxidized with Dess–Martin periodinane to give ketone **11**, which was reduced using $LiBH_4$ to give **12** in a greater than 5:95 (2*S*,3*R threo/2S,3S erythro)* ratio of diastereomers. To further corroborate the formation of each diastereomer, two derivatives were prepared for X-ray crystal analysis. The *β*-methoxy derivative (vide infra) of the (2*S*,3*R*) intermediate **10** was deprotected by hydrogenolysis to yield amine **13** (Scheme 4), which gave crystals suitable for X-ray examination. The Cbz group of *β*-hydroxy (2*R*,3*R*) intermediate **14** was removed by hydrogenolysis and reprotected with Fmoc-Cl to give *β*-methoxytyrosine intermediate **15** (Scheme 5), which gave crystals suitable from X-ray examination. The X-ray structures of both derivatives confirmed the relative stereochemistry of the *threo* and *erythro* diastereomers.

**SCHEME 4. Synthesis of (2*S*,3*R*) X-ray Derivative**[a]




[a] Reagents and conditions: (a) $Me_3O^+$ $BF_4^-$, Proton Sponge, 4 Å mol. sieves, $CH_2Cl_2$, 77%; (b) Pd/C, $H_2$, 72%.

**SCHEME 5. Synthesis of (2*R*,3*R*) X-ray Derivative**[a]




[a] Reagents and conditions: Pd/C, $H_2$; (b) Fmoc-Cl, $NaHCO_3$, $H_2O$, 60%, over two steps.

**TABLE 1. Methylation Conditions**

| base | electrophile | *T* (°C) | yield (%) |
|---|---|---|---|
| NaH | MeI | 0 | 0 |
| LiHMDS | $Me_2SO_4$ | −78 | 0 |
| $Ag_2O$ | MeI | 50 | 0 |
| DTBMP[a] | MeOTf | 0 | trace |
| Proton Sponge | $Me_3O^+BF_4^-$ | rt | 77 |

[a] 2,6-Di-*tert*-butyl-4-methylpyridine.

Having accomplished a diastereoselective synthesis of both *β*-hydroxytyrosine derivatives we sought to methylate the remaining *β*-hydroxyl group. Our initial attempts using traditional methods were unsuccessful. Exposure of either **10** or **12** to a variety of strong bases and methylating reagents led to decomposition of the starting material (Table 1). In an effort to circumvent strong basic conditions, iodomethane and silver(I) oxide were tried but only gave starting material. Using more potent electrophiles in combination with weak bases afforded some improvement. Exposure to methyl triflate and 2,6-di-*tert*-butyl-4-methylpyridine gave a trace amount of product accompanied by decomposition of the starting material. A search of the literature revealed that in instances where traditional methylation conditions fail the use of Meerwein's trimethyl oxonium salt was successful. Using

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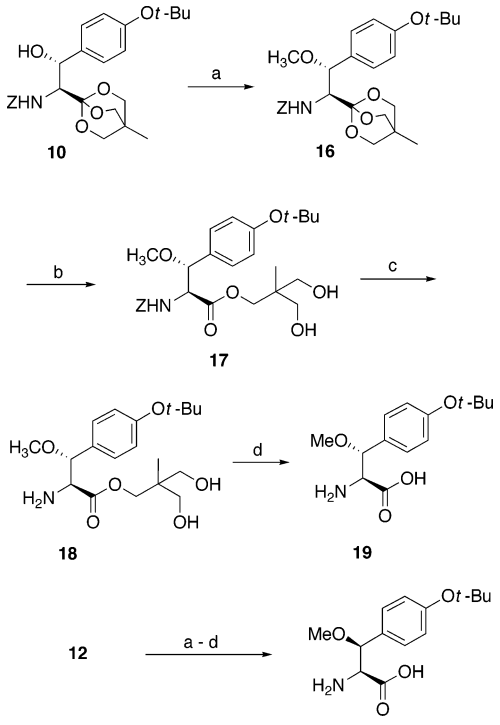
(21) Bandgar, B. P.; Kasture, S. P. *J. Chem. Res., Synop.* **2000**, 252–253.

**SCHEME 6. Methylation and Deprotection of (2*S*,3*R*)- and (2*S*,3*S*)-β-Methoxytyrosine**[a]




[a] Reagents and conditions: (a) $Me_3O^+$ $BF_4^-$, Proton Sponge, 4 Å mol. sieves, $CH_2Cl_2$, 77%; (b) 1:1:1 dioxane:HOAc:$H_2O$, 98%; (c) Pd/C, $H_2$, MeOH, quantitative; (d) IRA-400($OH^-$), dioxane, $H_2O$, 76%, over two steps.

conditions developed by Ireland,[22] with $Me_3O^+$ $BF_4^-$, Proton Sponge, and 4 Å molecular sieves, the hydroxyl group was methylated in good yield to give **16** (Scheme 6).

To complete the synthesis of both diastereomers of β-methoxytyrosine the selective removal of both the Cbz and ortho ester protecting groups was needed. Following Lajoie's conditions the Cbz group was removed using 10% Pd/C under 1 atm of hydrogen. The resulting amine was then treated with aqueous TFA to hydrolyze the ortho ester. The reaction proceeded slowly and was unselective causing removal of the *tert*-butyl ether. Treatment with base and purification according to Lajoie's conditions allowed for the complete deprotection of both the ortho ester and *tert*-butyl ether. It was clear that the *tert*-butyl ether could be removed without decomposition of the amino acid as this will be necessary during a total synthesis. To avoid reprotecting the phenolic hydroxy group more selective deprotection conditions were needed to allow for opening of the ortho ester in the presence of the *tert*-butyl ether. It became clear that the ortho ester was more acid sensitive than originally presumed. Exposure of any intermediates that contain both a Cbz and ortho ester protecting group to trace amounts of acid in deuterated chloroform or silica gel lead to partial opening of the ortho ester. It was believed that a strong acid such as TFA was required because the unprotected primary amine was acting as an internal base.[23] Initial protonation of the primary amine causes further protonation of the ortho ester to be unfavorable. Exposure of the Cbz-protected amine **16** to a 1:1:1 mixture of dioxane/HOAc/$H_2O$ for 10 min allowed for selective quantitative opening of the ortho ester in the presence of the *tert*-butyl ether to give **17**. At this point it was found that any remaining amounts of the undesired diastereomers could also be separated by chromatography. Hydrogenolysis of the remaining Cbz group was accomplished using standard conditions to give diol **18**. Finally the remaining ester could be removed in a simple one step procedure. An aqueous solution of diol **18** in dioxane was treated with IRA-400($^-$OH) cation ion-exchange resin overnight and then purified to give *threo tert*-butyl protected (2*S*,3*R*)-β-methoxytyrosine **19** in good yield. The same methylation and deprotection scheme was applied to the *erythro* diastereomer **12** with similar results to provide *erythro tert*-butyl-protected (2*S*,3*S*)-β-methoxytyrosine **20** (Scheme 6). The remaining two enantiomers of β-methoxytyrosine derived from (*R*)-serine were synthesized using the same procedures to afford the desired (2*R*,3*S*)-β-methoxytyrosine and its diastereomer (2*R*,3*R*)-β-methoxytyrosine with similar stereoselectivity and chemical yield.

In conclusion, we have successfully completed the synthesis of all four stereoisomers of β-methoxytyrosine utilizing Lajoie's chiral serine aldehyde equivalent. Both *threo* and *erythro* diastereomers of (2*S*)- and (2*R*)-β-methoxytyrosine can be selectively synthesized from (*S*)- and (*R*)- serine, respectively. Further investigations into the synthesis of a variety of architecturally more complex β-hydroxy amino acids are currently underway in this laboratory utilizing this method.

## Experimental Section

**3-(Methyloxetane-3-yl)methyl 2-Benzyloxycarbonylamino-3-hydroxypropanoate [(2*S*)-7].** Cbz-(*S*)-Serine **5** (50.00 g, 0.21 mol), 3-methyl-3-(tosylmethyl)oxetane **8** (53.57 g, 0.21 mol), tetrabutylammonium iodide (3.70 g, 0.01 mol), TEA (23.54 g, 0.23 mol), and DMF (100 mL) were combined in an oil bath and slowly heated to 70 °C overnight. The reaction was allowed to cool to room temperature, and the DMF was removed under reduced pressure. The remaining residue was dissolved in 1.00 L of EtOAc, washed twice with 1.0 N HCl, water, saturated $NaHCO_3$, and brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the remaining residue was purified by flash silica gel chromatography (gradient 50−100% EtOAc/hexanes) to give **7** as a pale yellow oil that solidified upon standing (60.1 g, 88%): mp 68−69 °C; $[\alpha]^{20}_D = -6.5$ ($c = 1.00$, $CHCl_3$); TLC (2:1 EtOAc/hexanes) $R_f = 0.36$; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 7.27−7.33 (m, 5H), 6.06 (d, $J = 8.1$ Hz, 1H), 5.10 (s, 2H), 4.46−4.51 (m, 3H) 4.31−4.38 (m, 3H), 4.10 (d, $J = 11.1$ Hz, 1H), 4.00−4.02 (m, 1H), 3.83−3.85 (m, 1H), 3.55 (t, $J = 5.8$, 1H), 1.26 (s, 3H); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 171.2, 156.8, 136.6, 128.9, 128.6, 128.5, 79.8, 69.4, 67.5, 63.3, 56.8, 39.8, 21.2; IR (thin film) 3378 br, 2962 m, 1720 s, 1528 m, 1456 m, 1380 w, 1341 m, 1214 m, 1063 m, 979 m; HRMS (EI) *m/z* calcd for $C_{16}H_{21}O_6N$ 323.1368, found 323.1363.

**1-[*N*-Benzyloxycarbonyl-(2*S*)-1-amino-2-hydroxyethyl]-4-methyl-2,6,7-trioxabicyclo[2.2.2]oxetane, Cbz-L-Ser OBO Ester.** This compound was prepared according to the procedure of Lajoie.[17]

**Preparation and Determination of Enantiomeric Purity of 2-(4-Methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)-**

(22) Ireland, R. E.; Liu, L. B.; Roper, T. D.; Gleason, J. L. *Tetrahedron* **1997**, *53*, 13257−13284.

(23) Dodd, D. S.; Oehlschlager, A. C. *J. Org. Chem.* **1992**, *57*, 2794−2803.

**2-benzyloxycarbonylaminoethanal [(2S)-2].** Ester **7** (250 mg, 0.77 mmol) was dissolved in 10 mL of $CH_2Cl_2$, and then $NaHCO_3$ (323 mg, 3.85 mmol) was added, followed by Dess−Martin periodinane. The reaction was stirred for 10 min, and then the organic layer was washed with a mixture of 1:1 satd $Na_2S_2O_3$/satd $NaHCO_3$ and water and then dried over $MgSO_4$ to provide an off-white solid (232 mg, 94%). The spectral data matched that reported by Lajoie et al.[17] NMR chiral shift analysis was performed as previously described as by Lajoie et al.[17] The purity was 91−94% ee.

**1-Bromo-4-*tert*-butoxybenzene.** In a glass pressure reaction vessel were placed 4-bromophenol **9** (50.00 g, 0.29 mol), 50 mL of $CH_2Cl_2$, and *p*-toluenesulfonic acid monohydrate (0.50 g, 0.003 mol). Approximately 50 mL of liquefied isobutylene was added with a gas condenser. The reaction was sealed and allowed to warm to room temperature with stirring overnight. The isobutylene was allowed to slowly evaporate at room temperature, and the remaining solution was diluted with 500 mL of $Et_2O$. The organic layer was washed with1 N NaOH, 5% $NH_4Cl$, and brine and dried over $MgSO_4$ and the solvent reduced in vacuo. The residue was quickly purified by flash silica gel chromatography to give a clear oil that slowly crystallized upon standing (55.11 g, 83%). The crude residue was pure by $^1$H NMR but if it was not purified, the 4-bromophenol-*tert*-butyl ether **9** slowly decomposed to the starting material over time: mp 36−37 °C; TLC (2.5% EtOAc/hexanes) 0.47; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 7.36 (d, $J$ = 8.6, 2H), 6.86 (d, $J$ = 8.6, 2H), 1.33 (s, 9H); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 154.4, 131.8, 125.9, 116.1, 78.9, 28.7; IR (thin film) 2997 m, 1582 w, 1486 s, 1366 m, 1240 s, 1161 s, 1070 m, 1008 m, 894 m, 847 m; HRMS (EI) *m/z* calcd for $C_{10}H_{13}OBr$ 228.0150, found 228.0155.

**Benzyl (1*S*)-2-(4-*tert*-Butoxyphenyl)-2-hydroxy-1-(4-methyl-2.6,7-trioxabicyclo[2.2.2]octan-1-yl)ethylcarbamate [(2*S*,3*R*)-10].** Magnesium turnings (3.01 g, 0.124 mol) were placed in a flame-dried round-bottomed flask fitted with a condenser and pressure addition funnel. THF was added to just cover the magnesium turnings, approximately 10 mg of $I_2$ was added, and then a solution of 4-bromophenol-*tert*-butyl ether **9** (28.41 g, 0.124 mol) dissolved in 90 mL of THF was added dropwise. After the addition was complete the reaction was refluxed for 1 h. At this point the magnesium had been consumed and the reaction was cooled to room temperature. The crude Cbz-(2*S*)-Ser(ald) OBO ester **2** (0.031 mol assuming 100% yield of the aldehyde from the oxidation) was dissolved in 400 mL of a 1:1 solution of $CH_2Cl_2$/$Et_2O$ and cooled to 0 °C. A Grignard solution was cannulated into this solution, and the mixture was allowed to stir for 5 min at 0 °C. The reaction was then quenched with 5% $NH_4Cl$ and diluted with $Et_2O$. The organic layer was separated, washed with 5% $NH_4Cl$, water, and brine, and dried over $MgSO_4$. The residue was dissolved in 250 mL of EtOAc and then added to a solution of $NaBH_4$ (0.33 g, 0.06 mol) in 200 mL of EtOH. The reaction was stirred for 15 min at room temperature to remove any residual ester **2**. The reaction was then quenched with 5% $NH_4Cl$, diluted with $Et_2O$, washed with water and brine, and dried over $MgSO_4$, and the solvent was reduced in vacuo. The remaining residue was purified by flash silica gel chromatography (gradient 35 to 50% EtOAc/hexanes) to give a pale yellow oil that solidified slowly upon standing (9.51 g, 65%). The diastereomeric ratio of 92:8 (2*S*,3*R threo*/2*S*,3*S erythro*) was determined by integration of the N−H carbamate proton signals in the $^1$H NMR spectrum: mp 57−59 °C; $[\alpha]^{20}_D = -20.6$ ($c$ = 0.70, $CHCl_3$); TLC (1:1 EtOAc/hexane) $R_f$ = 0.33; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 7.23−7.26 (m, 7H), 6.90 (d, $J$ = 8.5, 2H), 5.41(d, $J$ = 10.3, 1H), 5.24 (s, 1H), 4.91−5.01 (m, 2H), 4.06 (d, $J$ = 10.3, 1H), 3.98 (s, 6H), 3.33 (s, 1H), 1.31 (s, 9H), 0.84 (s, 3H); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 156.2, 154.6, 136.7, 134.9, 128.3, 127.9, 127.8, 126.5, 123.8, 108.9, 78.2, 72.8, 70.5, 66.6, 58.4, 30.7, 28.9, 14.3; IR (thin film) 3507 w, 3448 w, 3354 w, 2974 m, 2884 m, 1725 s, 1602 w, 1508 w, 1390 m, 1366 m, 1231 s, 1155 s, 1049 s, 1020 s, 984 m, 896 m, 732 m, 696 m; HRMS (EI) *m/z* calcd for $C_{26}H_{33}O_7NNa$ 494.2154, found 494.2140.

**Benzyl (1*S*)-2-(4-*tert*-Butoxyphenyl)-2-oxo-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)ethylcarbamate [(2*S*)-11].** Cbz-(2*S*, 3*R*)-$\beta$-hydroxytyrosine OBO ester **10** (490 mg, 1.04 mmol) was dissolved in 10.0 mL of $CH_2Cl_2$, and then $NaHCO_3$ (665 mg, 7.80 mmol) was added followed by Dess−Martin periodinane (660 mg, 1.56 mmol). The reaction was stirred at room temperature for 10 min and judged to be complete by TLC. The reaction was diluted with $Et_2O$, washed with a mixture of 1:1 satd $Na_2S_2O_3$/satd $NaHCO_3$ and water, and then dried over $MgSO_4$ and the solvent reduced in vacuo. The residue was purified by flash silica gel chromatography (gradient 30 to 40% EtOAc/hexanes + 0.1% TEA) to give a pale yellow oil (459 mg, 94%): $[\alpha]^{20}_D = -30.0$ ($c$ = 0.50, $CHCl_3$); TLC (1:1 EtOAc/hexane) $R_f$ = 0.53; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 8.00 (d, $J$ = 8.6, 2H), 7.33−7.34 (m, 5H), 7.01 (d, $J$ = 8.7, 2H), 5.94 (d, $J$ = 9.4, 1H), 5.54 (d, $J$ = 9.4, 1H), 5.09 (s, 2H), 3.86 (s, 6H), 1.43 (s, 9H), 0.75 (s, 3H); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 193.5, 160.7, 155.8, 136.2, 131.1, 130.6, 128.3, 128.0, 127.9, 121.5, 107.2, 79.5, 72.8, 66.9, 57.0, 30.5, 28.8, 14.2; IR (thin film) 2447 w, 2976 m, 2881 m, 1726 s, 1685 s, 1597 s, 1509 s, 1354 m, 1312 m, 1230 s, 1159 s, 1049 s, 1007 s, 897 m. 849 w, 734 m; HRMS (EI) *m/z* calcd for $C_{26}H_{31}O_7NNa$ 492.1998, found 492.1996.

**Benzyl (1*S*)-2-(4-*tert*-Butoxyphenyl)-2-hydroxy-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)ethylcarbamate [(2*S*,3*S*)-12].** Cbz-(2*S*)-$\beta$-ketotyrosine OBO ester **11** (4.70 g, 10.0 mmol) was dissolved in 75 mL of $CH_2Cl_2$, diluted with 225 mL of MeOH under argon, and then cooled to −78 °C. Then a solution of 2.0 M $LiBH_4$ in THF (10 mL, 20.0 mmol) was added dropwise, and the reaction was allowed to stir at −78 °C for 8 h and slowly warmed to room temperature. The reaction was then diluted with 600 mL of $CH_2Cl_2$ and then quenched with 5% $NH_4Cl$, the organic layer was separated, and the aqueous layer was extracted twice with $CH_2Cl_2$. The organic layers were combined, washed with 5% $NH_4Cl$ and brine, and dried over $MgSO_4$. The solvent was reduced in vacuo to yield a white solid (4.53 g, 96%). A diastereomeric ratio greater than 5:95 (2*S*,3*R threo*/2*S*,3*S erythro*) was determined by integration of the N−H carbamate proton signals in the $^1$H NMR spectrum: mp 186−188 °C; $[\alpha]^{20}_D = -43.0$ ($c$ = 0.58, $CHCl_3$); TLC (1:1 EtOAc/hexanes) $R_f$ = 0.25; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 7.25−7.33 (m, 5H), 7.15 (d, $J$ = 7.0, 2H), 6.92 (d, $J$ = 8.4, 2H), 4.88 (s, 2H), 4.79−4.81 (m, 2H), 4.17 (dd, $J$ = 8.5, 1.8, 1H), 4.11 (d, $J$ = 1.4, 1H), 3.95 (br s, 6H), 1.31 (s, 9H), 0.84 (s, 3H); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 155.7, 154.9, 136.3, 135.0, 128.4, 128.1, 127.9, 127.8, 123.7, 108.7, 78.3, 73.9, 72.7, 66.6, 58.6, 30.7, 28.8, 14.3; IR (thin film) 3502 w, 3339 w, 2973 m, 2887 m, 1719 s, 1529 m, 1508 m, 1398 m, 1286 m, 1238 m, 1194 m, 1164 m, 1044 m, 955 s; HRMS (EI) *m/z* calcd for $C_{26}H_{33}O_7N_1Na_1$ 494.2155, found 494.2146.

**[2-(4-*tert*-Butoxyphenyl)-2-hydroxy-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]oct-1-yl)ethyl]carbamic Acid 9*H*-Fluoren-9-ylmethyl Ester [(2*R*,3*R*)-15].** Compound (2*R*,3*R*)-**12** (1.00 g) was dissolved in 25 mL of EtOAc, and 50 mL of EtOH was then added. After 0.20 g (20 wt %) of 10% Pd/C was added, the mixture was stirred under a hydrogen atmosphere for 12 h. The mixture was then passed though a pad of Celite, and the filtrate was concentrated to give 0.56 g of crude intermediate. Then, 0.20 g crude product (0.59 mmol), 0.18 g of Fmoc-Cl (0.71 mmol), and a catalytic amount DMAP were dissolved in 10 mL of dry $CH_2Cl_2$, 0.1 mL of $NEt_3$ was added dropwise, and the mixture was allowed to stir for 12 h. The mixture was diluted with 30 mL of EtOAc and 10 mL of aqueous 5% $NH_4Cl$ solution. The organic layer was separated, washed with 5% $NH_4Cl$, saturated $NaHCO_3$, and brine, dried with $Na_2SO_4$, and concentrated. The crude product was purified by flash silica gel chromatography (gradient 30−40% EtOAc/hexanes) to give a pale yellow solid (0.19 g, 60%). The solid was recrystallized in a mixture of EtOAc/hexanes to give

crystals suitable for X-ray examination: mp 168−169 °C; $[\alpha]^{20}_D = -45.2$ ($c = 0.71$, $CHCl_3$); TLC (1:1 EtOAc/hexanes) = 0.35; $^1$H NMR 7.71−7.73 (d, $J = 7.5$ Hz, 2H), 7.24−7.50 (m, 8H), 6.86−6.88 (d, $J = 8.4$ Hz, 2H), 4.83−4.88 (m, 2H), 4.16−4.20 (m, 1H), 4.02−4.10 (m, 2H), 3.97 (s, 6H), 1.64 (s, br, 1H), 1.18 (s, 9H), 0.83 (s, 3H); $^{13}$C NMR 155.7, 155.0, 144.0, 143.9, 141.2, 141.1, 134.9, 128.1, 127.5, 126.9, 125,2, 125.1, 123.5, 119.8, 108.7, 78.2, 73.8, 72.8, 66.9, 58.6, 47.0, 30.7, 28.7, 14.2; IR 3452 w, 2972 s, 2883 s, 1722 s, 1609 m, 1512 s, 1451 m, 1397 m, 1327 m, 1239 s, 1164 s, 1049 s, 1007 s, 902 s, 739 s; *m/z* calcd for $C_{33}H_{37}O_7NNa$ 582.2468, found 582.2445.

**2-(4-*tert*-Butoxyphenyl)-2-methoxy-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)-1-benzyloxycarbonylaminoethane [(2*S*,3*R*)-16].** In a flame-dried round-bottomed flask containing 6.0 g of 4 Å molecular sieves under argon were added $CH_2Cl_2$ (300 mL), ester **10** (5.64 g, 11.97 mmol), Proton Sponge (10.26 g, 47.88 mmol), and then $Me_3O^+$ $BF_4^-$ (5.31 g, 35.90 mmol). The reaction was stirred vigorously at room temperature and monitored by TLC. The reaction was complete after 6 h. The reaction was then diluted with 750 mL of EtOAc and filtered through Celite. The Celite pad was washed twice with EtOAc. The filtrate was then washed twice with 10% $CuSO_4$, 5% $NH_4Cl$, satd $NaHCO_3$, and brine and dried over $MgSO_4$. The solvent was reduced in vacuo. The residue was then purified by flash silica gel chromatography (gradient 30 to 40% EtOAc/hexanes + 0.1% TEA) to give a pale pink oil (4.49 g, 77%): $[\alpha]^{20}_D = -46.3$ ($c = 1.50$, $CHCl_3$); TLC (1:1 EtOAc/hexane) $R_f = 0.49$; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 7.29−7.35 (m, 5H), 7.17 (d, $J = 8.3$, 2H), 6.88 (d, $J = 8.3$, 2H), 5.46 (d, $J = 10.3$, 1H), 5.06 (d, $J = 12.5$, 1H), 4.96 (d, $J = 12.5$, 1H), 4.61 (s, 1H), 3.96 (d, $J = 9.5$, 1H), 3.92 (s br, 6H), 3.27 (s, 3H), 1.32 (s, 9H), 0.81 (s, 3H); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 156.2, 154.8, 137.0, 134.8, 128.3, 128.1, 127.8, 127.1, 123.7, 108.4, 79.3, 78.2, 72.8, 66.4, 59.4, 57.4, 30.7, 28.9, 14.4; IR (thin film) 3460 w, 3366 w, 2978 m, 2931 m, 2873 m, 1725 s, 1608 w, 1508 w, 1396 m, 1361 m, 1302 m, 1232 s, 1161 s, 1102 m, 1049 s, 1014 s, 891 m; HRMS (EI) *m/z* calcd for $C_{27}H_{35}O_7N_1Na_1$ 508.2311, found 508.1302

**2-(4-*tert*-Butoxyphenyl)-2-methoxy-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)-1-aminoethane [(2*S*,3*R*)-13].** Ester **16** (153 mg, 0.32 mmol) was dissolved in 5 mL of EtOAc and then diluted with 5 mL of EtOH and transferred to a hydrogenation flask containing 10% Pd/C (20 mg). The flask was evacuated under reduced pressure and filled with hydrogen twice. The reaction was shaken under 40 psi of hydrogen gas for 4 h. The reaction was filtered through a pad of Celite, and the Celite pad was washed 2 × 10 mL of EtOAc. The filtrate was then reduced in vacuo to yield a pale yellow viscous oil that crystallized slowly upon standing. The crude solid was purified by flash silica gel chromatography (1:1 acetone/hexanes with 1% TEA) to give a pale yellow solid (81 mg, 72%): mp 133−135 °C; $[\alpha]^{20}_D = -6.4$ ($c = 0.77$, $CHCl_3$); TLC (1:1 acetone/hexanes + 1% TEA) $R_f = 0.47$; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 7.22 (d, $J = 8.4$, 2H), 6.94 (d, $J = 8.5$, 2H), 4.43 (d, $J = 4.7$, 1H), 3.83 (m, 6H), 3.26 (s, 3H), 3.02 (d, $J = 4.6$, 1H), 1.34 (s, 9H), 0.77 (s, 3H); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 154.4, 135.8, 127.6, 123.5, 108.7, 81.7, 78.1, 61.1, 57.0, 30.5, 28.9, 14.4; IR (thin film) 3582 w, 3399 w, 2972s, 2923 s, 2862 s, 2826 m, 1730 w, 1608 m, 1578 w, 1504 s, 1468 m, 1394 m, 1350 m, 1279 m, 1232 s, 1161 s, 1096 s, 1055 s, 1013 s, 924 m, 895 s; HRMS (EI) *m/z* calcd for $C_{19}H_{29}O_5N_1$ 351.2045, found 351.2044.

**3-Hydroxy-2-(hydroxymethyl)-2-methylpropyl 2-Benzyloxycarbonylamino-3-(4-*tert*-butoxyphenyl)-3-methoxypropanoate, [(2*S*,3*R*)-17].** Cbz-(2*S*,3*R*)-β-methoxytyrosine OBO ester **16** (2.72 g, 5.61 mmol) was dissolved in dioxane (10 mL) and then diluted with glacial acetic acid (10 mL) and water (10 mL). The reaction was allowed to stir at room temperature for 10 min. TLC showed no starting material, and the solvent was removed under reduced pressure to yield a yellow oil. The crude material was then purified by flash silica gel chromatography (gradient 66 to 100% EtOAc/hexanes) to give a pale yellow oil (2.76 g, 98%): $[\alpha]^{20}_D = -35.6$ ($c = 1.60$, $CHCl_3$); TLC (2:1 EtOAc/hexane) $R_f = 0.37$; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 7.26−7.36 (m, 5H), 7.18 (d, $J = 8.4$, 2H), 6.96 (d, $J = 8.6$, 2H), 5.58 (d, $J = 8.6$, 1H), 4.97−5.04 (m, 2H), 4.72 (d, $J = 3.5$, 1H), 4.48 (dd, $J = 3.6$, 8.5, 1H), 4.19−4.25 (m, 2H), 3.47−3.53 (m, 4H), 3.23 (s, 3H), 2.81 (br s, 2H), 1.35 (s, 9H), 0.81 (s, 3H); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 171.1, 156.2, 155.7, 136.1, 131.0, 128.5, 128.1, 128.0, 127.8, 127.4, 123.9, 82.1, 78.6, 67.9, 67.4, 67.3, 67.0, 57.2, 40.7, 28.8, 16.8; IR (thin film) 3340 br, 2975 m, 2881 w, 1725 s, 1607 w, 1506 s, 1456 m, 1366 w, 1300 m, 1237 s, 1162 s, 1097 m, 1057 s, 896 m, 698 m; HRMS (EI) *m/z* calcd for $C_{27}H_{37}O_8N_1Na_1$ 526.2417, found 526.2443.

**3-Hydroxy-2-(hydroxymethyl)-2-methypropyl 2-Amino-3-(4-*tert*-butoxyphenyl)-3-methoxypropanoate [(2*S*,3*R*)-18].** Ester **17** (2.76 g, 5.48 mmol) was dissolved in 50 mL of MeOH and transferred to a hydrogenation flask containing 10% Pd/C (0.28 g). The hydrogenation vessel was evacuated and filled with hydrogen twice. The reaction was shaken under 40 psi of hydrogen for 4 h. The reaction mixture was filtered through a pad of Celite, and the Celite pad was washed 2 × 50 mL of MeOH. The filtrate was then reduced in vacuo to yield a pale yellow viscous oil and was used directly in the next step without further purification (2.2 g, 109%): $[\alpha]^{20}_D = -20.3$ ($c = 2.9$, $CHCl_3$); $^1$H NMR (DMSO, 500 MHz) $\delta$ 7.10 (d, $J = 8.3$, 2H), 6.89 (d, $J = 8.4$, 2H), 4.37 (d, $J = 4.8$, 1H), 4.01 (d, $J = 11.0$, 1H), 3.92 (d, $J = 11.0$, 1H), 3.51 (d, $J = 4.8$, 1H), 3.29−3.34 (m, 4H), 3.12 (s, 3H), 1.25 (s, 9H), 0.65 (s, 3H); $^{13}$C NMR (DMSO, 125 MHz) $\delta$ 172.6, 155.1, 131.8, 127.3, 123.7, 84.0, 78.3, 67.1, 65.9, 65.7, 60.5, 56.8, 40.2, 28.5, 16.4; IR (thin film) 3371 br, 2976 s, 2879 s, 1736 s, 1606 s, 1506 s, 1469 m, 1391 m, 1366 m, 1236 br, 1162 br, 1093 s, 1051 s, 897 s, 755 s; HRMS (EI): *m/z* calcd for $C_{19}H_{31}O_6N_1Na_1$ 392.2049, found 392.2051.

**2-Amino-3-(4-*tert*-butoxyphenyl)-3-methoxypropanoic Acid [(2*S*,3*R*)-19].** The crude (2*S*,3*R*) ester **18** (2.2 g) was dissolved in 20 mL of dioxane and then diluted with 20 mL of water, and to this solution was added 18 mL of freshly prepared IRA-400 ($OH^-$). The solution was shaken overnight. The resin and solution were transferred to a column and then washed with $H_2O$ and eluted with 1.0 M HOAc. The fractions were tested with ninhydrin for the presence of the amino acid. All positive ninhydrin fraction were combined and reduced to give an off-white solid (1.11 g, 76% over two steps): mp 178−180 °C dec; $[\alpha]^{20}_D = -56.4$ ($c = 0.50$, $H_2O$); $^1$H NMR (DMSO, 500 MHz) $\delta$ 7.24 (d, $J = 8.4$, 2H), 6.96 (d, $J = 8.4$, 2H), 4.67 (d, $J = 4.7$, 1H), 3.30 (d, $J = 4.7$, 1H), 3.17 (s, 3H), 1.32 (s, 9H); $^{13}$C NMR (DMSO, 125 MHz) $\delta$ 168.5, 155.6, 133.7, 128.5, 124.1, 82.0, 78.7, 60.6, 57.6, 29.5; IR (KBr pellet) 2977 br s, 1607 s, 1508 s, 1391 s, 1237 m, 1088 s, 890 s; HRMS (EI) *m/z* calcd for $C_{14}H_{21}O_4N_1Na_1$ 290.1368, found 290.1368.

**2-(4-*tert*-Butoxyphenyl)-2-methoxy-1-(4-methyl-2.6,7-trioxabicyclo[2.2.2]octan-1-yl)-1-benzyloxycarbonylaminoethane [(2*S*,3*S*)-16].** Ester **12** (2.00 g, 4.25 mmol) was methylated using the same procedure for Cbz-(2*S*,3*R*)-β-methoxytyrosine OBO ester **16** to give a pale pink oil (1.48 g, 72%): $[\alpha]^{20}_D = 7.16$ ($c = 1.02$, $CHCl_3$); TLC (1:1 EtOAc/hexane) $R_f = 0.42$; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 7.24−7.35 (m, 5H), 7.18 (d, $J = 8.4$, 2H), 6.90 (d, $J = 8.4$, 2H), 5.09 (s, 2H), 4.74 (d, $J = 10.7$, 1H), 4.60 (d, $J = 3.7$, 1H), 4.44 (dd, $J = 3.7$, 10.7, 1H), 3.75−3.80 (m, 6H), 3.28 (s, 3H), 1.33 (s, 9H), 0.75 (s, 3H); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 156.2, 154.7, 136.7, 133.0 128.6, 128.3, 127.9, 127.8, 123.1, 107.7, 80.8, 78.1, 72.4, 66.6, 57.3, 56.8, 30.5, 28.8, 14.3; IR (thin film) 3452 w, 2974 m, 2878 m, 1732 s, 1607 w, 1506 s, 1456 w, 1396w, 1364 m, 1307 w, 1234 m, 1218 m, 1162 s, 1096 m, 1052 s, 1013 s; HRMS (EI) *m/z* calcd for $C_{27}H_{35}O_7N_1Na_1$ 508.2311, found 508.2291

**3-Hydroxy-2-(hydroxymethyl)-2-methylpropyl 2-Benzyloxycarbonylamino-3-(4-*tert*-butoxyphenyl)-3-methoxypropanoate [(2*S*,3*S*)-17].** Ester (2*S*,3*S*)-**16** (1.41 g, 2.90 mmol) was deprotected in the same manner as (2*S*,3*R*)-**16** to give a yellow oil (1.37 g, 94%): $[\alpha]^{20}_D = 13.7$ ($c = 1.13$, $CHCl_3$);

TLC (2:1 EtOAc/hexane) $R_f = 0.40$; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 7.25−7.36 (m, 5H), 7.19 (d, $J$ = 8.2, 2H), 6.98 (d, $J$ = 8.2, 2H), 5.45 (d, $J$ = 8.4, 1H), 5.05 (s, 2H), 4.63 (t, $J$ = 6.0, 1H), 4.48 (d, $J$ = 5.4, 1H), 4.20 (d, $J$ = 11.1, 1H), 4.04 (d, $J$ = 11.2, 1H), 3.45 (s br, 4H), 3.23 (s, 3H), 2,79 (s br, 2H), 1.35 (s, 9H), 0.73 (s, 3H); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 170.8, 155.8, 155.8, 136.0, 130.9, 128.5, 128.2, 128.1, 127.5, 123.9, 83.0, 78.7, 67.7, 67.1, 59.1, 57.4, 40.5, 28.8, 16.7; IR (thin film) 3434 br, 2976 m, 2881 m, 1718 s, 1607 m, 1506 s, 1456 m, 1390 m, 1366 m, 1237 s, 1211 s, 1161 s, 1101 s, 1051 s, 971 m, 897 m, 735 m, 698 m; HRMS (EI) *m/z* calcd for $C_{27}H_{37}O_8N_1Na_1$ 526.2417, found 526.2426.

**3-Hydroxy-2-(hydroxymethyl)-2-methypropyl 2-Amino-3-(4-*tert*-butoxyphenyl)-3-methoxypropanoate [(2*S*,3*S*)-18].** This ester (1.37 g, 2.72 mmol) was deprotected in the same manner as (2*S*,3*R*)-**17** to give a yellow oil (1.02 g, 102%) that was used without further purification: $[\alpha]^{20}_D = 25.3$ ($c$ = 1.11, $CHCl_3$); $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 7.20 (d, $J$ = 8.3, 2H), 6.97 (d, $J$ = 8.4, 2H), 4.61 (br s, 5H), 4.26 (d, $J$ = 10.9, 1H), 4.03 (d, $J$ = 4.6, 1H), 3.89 (d, $J$ = 10.9, 1H), 3.40−3.48 (m, 4H), 3.25 (s, 3H), 1.33 (s, 9H), 0.68 (s, 3H); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 170.2, 155.7, 130.4, 127.7, 123.9, 82.6, 78.6, 67.9, 66.3, 65.8, 59.1, 57.2, 40.4, 28.8, 16.8; IR (thin film) 3371 br s, 2976 br, 2935 s, 1739 s, 1607 m, 1506 s, 1470 m, 1391 w, 1366 m, 1237 s, 1161 s, 1096 s, 1048 m, 897 m, 733 m; HRMS (EI) *m/z* calcd for $C_{19}H_{31}O_6N_1Na_1$ 392.2049, found 392.2051.

**2-Amino-3-(4-*tert*-butoxyphenyl)-3-methoxypropanoic Acid [(2*S*,3*S*)-20].** The (2*S*,3*S*)-isomer (1.02 g crude) was deprotected in the same manner as (2*S*,3*R*)-**18** to give an off-white solid (622 mg, 81% over two steps): mp 212−215 °C dec; $[\alpha]^{20}_D = 35.2$ ($c$ = 0.25, $H_2O$); $^1$H NMR (DMSO, 500 MHz) $\delta$ 7.21 (d, $J$ = 8.4, 2H), 6.91 (d, $J$ = 8.3, 2H), 4.73 (d, $J$ = 3.7, 1H), 3.64 (d, $J$ = 3.6, 1H), 3.39 (br s, 3H), 3.21 (s, 3H), 1.30 (s, 9H); $^{13}$C NMR (DMSO, 125 MHz) $\delta$ 167.1, 154.7, 130.5, 128.2, 122.8, 81.1, 77.8, 58.3, 56.4, 28.6; IR (KBr pellet) 3425 br w, 3061 br m, 2977 s, 2555 br s, 1609 s, 1508 s, 1404 m, 1365 m, 1313 m, 1237 m, 1163 m, 1094 s, 890 s, 860 m; HRMS (EI) *m/z* calcd for $C_{14}H_{21}O_4N_1Na_1$ 290.1368, found 290.1373.

**2-Amino-3-(4-*p*-phenol)-3-methoxypropanoic Acid (2*S*,3*R*).** Amine **13** (298 mg, 0.85 mmol) was dissolved in 10 mL of 50% aqueous TFA. The reaction was allowed to stir at room temperature for 15 min and reduced in vacuo. The residue was dissolved in 5 mL of MeOH and 5 mL of $H_2O$, and 13.8 mL of 10% (wt/vol) $Cs_2CO_3$ solution (4.25 mmol, 5.0 equiv) was added. The reaction was stirred for 2 days at room temperature. Reaction was acidified to a pH <3 with 2 N HCl. The solution was loaded on to a cation-exchange column (Amberlite FPC11, hydrogen form) eluted with water until pH = 5 and then eluted with 4% $NH_4OH$; all ninhydrin positive fractions were collected and reduced in vacuo to yield an off-white solid (115 mg, 71%): mp 158−160 °C dec; $[\alpha]^{20}_D = -28.6$ ($c$ = 0.25, $H_2O$); $^1$H NMR ($D_2O$, 500 MHz) $\delta$ 7.33 (d, $J$ = 8.5, 2H), 6.99 (d, $J$ = 8.6, 2H), 4.63 (d, $J$ = 5.9, 1H), 3.70 (d, $J$ = 5.9, 1H), 3. 35 (s, 3H); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 175.2, 160.9, 157.1, 129.0, 116.3, 82.5, 61.8, 57.2, 33.0; IR (KBr pellet) 2978 m br, 1609 s, 1508 m, 1404 m, 1366 m, 1313 m, 1237 m, 1164 m, 1093 s; HRMS (EI) *m/z* calcd for $C_{10}H_{14}O_4N$ 212.0922, found 212.0930.

**Acknowledgment.** We thank the NSF (CHEM-0130958) for partial support of this work.

**Supporting Information Available:** General procedures, complete spectroscopic data, and $^1$H and $^{13}$C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO047876Z