Stereoselective Synthesis of *Threo* and *Erythro* β-Hydroxy and β-Disubstituted-β-Hydroxy α-Amino Acids

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Optically pure N-protected serine aldehyde equivalents can be prepared by the protection of the carboxylic group of serine by a cyclic ortho ester. Alkylation of *N*-Cbz-, *N*-Fmoc- or *N*-Boc-protected serine with oxetane tosylate **1** or bromide **2** gives the corresponding oxetane esters **4a**−**c** which can easily be converted to the cyclic ortho esters **5a**−**c**. A variety of unusual *threo* β-hydroxy amino acids have been synthesized by Grignard addition to these optically pure serine aldehyde equivalents. The *erythro* diastereomers can be obtained by oxidation of the initial *threo* adduct followed by reduction with $LiBH_4$. Also described is a general approach for the diastereoselective synthesis of optically pure β,β-dialkyl-β-hydroxy α-amino acids. These highly substituted amino acids are prepared by a sequence of Grignard addition to the optically active serine aldehyde equivalent, followed by oxidation of the initial adduct, and a second Grignard addition to the resulting ketone. The hydroxy adduct is obtained with very high diastereoselectivity (84−96% de). All four diastereomers can be selectively synthesized by varying the order of the Grignard additions and the chirality of the initial synthon. Removal of the protecting groups can be effected in very mild conditions, giving excellent yields of highly substituted amino acids in high diastereomeric purity.

Introduction

β-Hydroxy α-amino acids are an important class of compounds due to their inherent biological activities[1] and as structural components of more complex biomolecules.[2] β-Hydroxy α-amino acids have also been used as intermediates in the synthesis of other compounds,[3] such as β-lactams[4] and β-fluoro amino acids.[5] While many β-monoalkyl-β-hydroxy α-amino acids have been isolated from natural sources,[1,2] β-hydroxyvaline is the only example of a naturally occurring β-dialkyl-substituted compound[6] and is found in aureobasidins,[7] luzupeptins,[8] and tigemonam.[9] Recent reports describe the use of β-branched amino acids as "topographically constrained" analogues for incorporation in biologically active peptides.[10] In that context β-dialkyl-β-hydroxy α-amino acids are of particular interest due to the bioactivity demonstrated by many β-hydroxy α-amino acids.

A number of elegant approaches have been described for the asymmetric synthesis of various β-hydroxy α-amino acids in their optically pure forms.[11] Many of these methods involve derivatization of glycine equivalents attached to chiral templates which often require harsh conditions for their removal. Although some of these methods give good stereoselectivity, most often only one of the isomers at the β-carbon can be obtained.[12] On the other hand, very few syntheses of the disubstituted derivatives have been reported, even though they are theoretically accessible by the addition of glycine enolate equivalents to ketones.[13] These compounds are highly susceptible to dehydration, and protecting group removal often results in decomposition.[13] Recently, Shao and Goodman reported an efficient synthesis of β-hydroxyvaline but the overall strategy does not permit the stereoselective introduction of different alkyl groups at the β-carbon.[14]

We previously reported a new route for the synthesis of an enantiomerically pure serine aldehyde equivalent in which the carboxylic acid is protected as a trioxabicyclo[2.2.2] ortho (OBO) ester and the amine function is protected with Fmoc.[15] The serine aldehyde is a stable solid which undergoes a number of classical carbonyl addition (Grignard, Reformatsky, Wittig) reactions with little or no epimerization at the α-carbon.[15] In this paper we report a major improvement in the preparation of the precursor serine oxetane ester which allows for its large scale production with three different commonly used α-amino protecting groups. We also describe the synthesis of both *threo* and *erythro* diastereomers of several other β-hydroxy amino acids in which the amine is protected as the Fmoc, Cbz, or Boc derivative. In all cases Grignard addition to the aldehyde results in the protected *threo* β-hydroxy α-amino acids; oxidation of the initial adduct to the ketone followed by reduction with $LiBH_4$ provides the *erythro* diastereomers. Finally, we describe a significant extension of this approach to the stereoselective synthesis of β-disubstituted-β-hydroxy α-amino acids by a second Grignard addition to the *N*-Cbz or *N*-Fmoc-protected ketone intermediate. The stereochemistry at the carbinol center is controlled by the order of addition of the two desired alkyl substituents. In each case the protecting groups are easily removed, allowing for the synthesis of sensitive amino acids. This paper further demonstrates the versatility and practicality of the serine aldehyde equivalent for the synthesis of a wide range of β-hydroxy α-amino acids from D- or L-serine.

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Results

Synthesis of the Oxetane Ester. In the previous procedure,[15] the Fmoc-protected 4-methyl-2,6,7-trioxabicyclo[2.2.2] ortho (OBO) ester **5a** was prepared by the boron trifluoride catalyzed rearrangement of the corresponding 3-methyl-3-(hydroxymethyl)oxetane ester **4a**, itself prepared by the condensation of 3-methyl-3-(hydroxymethyl)oxetane[16] mediated by DCC and DMAP with Fmoc-serine. Although the yields for the esterification reaction were excellent (80−85%), the reaction required an excess of oxetane alcohol and chromatography on silica gel to obtain a pure product.[15] Trace amounts of the diimide or urea also affected the yields of the $BF_3{\cdot}Et_2O$-catalyzed rearrangement of the oxetane ester to the OBO ester. We found that the desired oxetane esters **4a**−**c** are much more conveniently prepared by alkylation of the N-protected serine carboxylates **3a**−**c** by the corresponding oxetane tosylate **1** or bromide **2**. The tosylate **1** is prepared using standard conditions as a stable crystalline material in 90−95% yield. The oxetane bromide **2** can be prepared in a number of ways from 3-methyl-3-(hydroxymethyl)oxetane with bromine/triphenylphosphine[17] or carbon tetrabromide/triphenylphosphine[18] or by displacement of the corresponding tosylate **1** with sodium bromide in acetone.[19] The oxetane bromide **2** may be distilled from these reactions but slowly decomposed upon standing. The best yields for the alkylation reaction were obtained using the cesium salt of Cbz-L-serine **3b** or Cbz-L-threonine **7b** with oxetane bromide **2** (85−90%). However, the preferred method is alkylation with oxetane tosylate **1** in DMF in the presence of sodium iodide (10 mol %), as distillation and storage of the sensitive oxetane bromide **2** is avoided (Scheme 1). In these latter conditions, the Cbz oxetane

(2) For example, D-*allo*-threonine is found in antibiotics such as the katanosins[2a,b] or accuminatum,[2c] while *β*-hydroxytyrosine and/or *β*-phenylserine is/are present in antibiotics such as vancomycin,[2d−f] chloramphenicol,[2g] bouvardin,[2h] orienticins,[2i] chloroorienticins,[2j] risocetins,[2k] hypeptin,[2l] katanosins,[2a,b] and a number of other cyclic peptides (avoparcin, teicoplanin, actaplanin, parvodicin, actinoidin, and chloropolysporin).[1a] *β*-Hydroxyleucine is present in lysobactin,[2m] katanosins,[2a,b] hypeptin,[2l] azinothricin,[2n] and leucinostatin A.[2o,p] *β*-Hydroxyhomotyrosine is found in echinocandin D,[2q] while *β*-hydroxyasparagine is present in katanosins[2a,b] and hypeptin.[2l] Both *β*-hydroxyproline and *β*-hydroxyaspartic acid have been isolated from empedopeptin,[2r] and *β*-hydroxyaspartic acid is also believed to play a role in blood clotting proteins.[2s] *β*-Hydroxyglutamine has been found in antibiotics such as neopeptin[2t] and acitulins[2u] while *β*-hydroxyglutamic acid is used to mimic glutamic acid, which plays an important role in the central nervous system.[2v] MeBmt is a critical component of the immunosuppressant cyclosporin.[2w] (a) Kato, T.; Hinoo, H.; Terui, Y.; Kikuchi, J.; Shoji, J. *J. Antibiot.* **1988**, *41*, 719−725. (b) Shoji, J.; Hinou, H.; Matsumoto, K.; Hattori, T.; Yoshida, T.; Matsuura, S.; Kondo, E. *J. Antibiot.* **1988**, *41*, 713−719. (c) Carr, S. A.; Block, E.; Costello, C. E. *J. Org. Chem.* **1985**, *50*, 2854−2858. (d) Williams, D. H. *Acc. Chem. Res.* **1984**, *17*, 364−369. (e) Harris, C. M.; Kopecka, H.; Harris, T. M. *J. Am. Chem. Soc.* **1983**, *105*, 6915−6922. (f) Nagarajan, R.; Schabel, A. A.; Occolowitz, J. L.; Counter, F. T.; Ott, J. L. *J. Antibiot.* **1988**, *41*, 1431−1458. (g) Chênevert, R.; Thiboutot, S. *Synthesis* **1989**, 444−446. (h) Joland, S. D.; Hoffmann, J. J.; Torrance, S. J.; Wiedhopf, R. M.; Cole, J. R.; Arora, S. K.; Bates, R. B.; Gargiulo, R. L.; Kriek, G. R. *J. Am. Chem. Soc.* **1977**, *99*, 8040−8044. (i) Tsuji, N.; Kobayashi, M.; Kamigauchi, T.; Yoshimura, Y.; Terui, Y. *J. Antibiot.* **1988**, *41*, 819−822. (j) Tsuji, N.; Kobayashi, M.; Kamigauchi, T.; Y.; Terui, Y. *J. Antibiot.* **1988**, *41*, 1506−1523. (k) Selva, E.; Goldstein, B. P.; Ferrari, P.; Paalanza, R.; Riva, E.; Berti, M.; Borghi, A.; Beretta, G.; Scott, R.; Cassani, G.; Arioli, V.; Denaro, M. *J. Antibiot.* **1988**, *41*, 1243−1252. (l) Shoji, J.; Hinoo, H.; Hattori, T.; Hirooka, K.; Kimura, Y.; Yoshida, T. *J. Antibiot.* **1989**, *42*, 1460−1464. (m) Tymiak, A. A.; McCormick, J. J.; Unger, S. E. *J. Org. Chem.* **1989**, *54*, 1149−1157. (n) Maehr, H.; Liu, C.-M.; Palleroni, N. J.; Smallheer, J.; Todaro, L.; Williams, T. H.; Blount, J. F. *J. Antibiot.* **1986**, *39*, 17−25. (o) Fukushima, K.; Arai, T.; Mori, Y.; Tsuboi, M.; Suzuki, M. *J. Antibiot.* **1983**, *36*, 1613−1630. (p) Cerrini, S.; Lamba, D.; Scatturin, A.; Ughetto, G. *Biopolymers* **1989**, *28*, 409−420. (q) Traber, V. R.; Keller-Juslén, C.; Loosli, H.-R.; Kuhn, M.; Wartburg, A. *Helv. Chim. Acta* **1979**, *62*, 1252−1267. (r) Sugawara, K.; Numata, K.-I.; Konishi, M.; Kawaguchi, H. *J. Antibiot.* **1984**, *37*, 958−964. (s) Ohlin, A.-K.; Landes, G.; Bourdon, P.; Oppenheimer, C.; Wydro, R.; Stenflo, J. *J. Biol. Chem.* **1988**, *263*, 19240−19248. (t) Ubakata, M.; Uramoto, M.; Isono, K. *Tetrahedron Lett.* **1984**, *25*, 423−427. (u) Bewley C. A.; He, H.; Williams, D. H.; Faulkner, J. D. *J. Am. Chem. Soc.* **1996**, *118*, 4314−4321. (v) Cotman, C. W.; Iverson, L. L. *Trends Neurosci.* **1987**, *10*, 263−265. (w) Schreiber, S. L. *Science* **1991**, *251*, 283−287.

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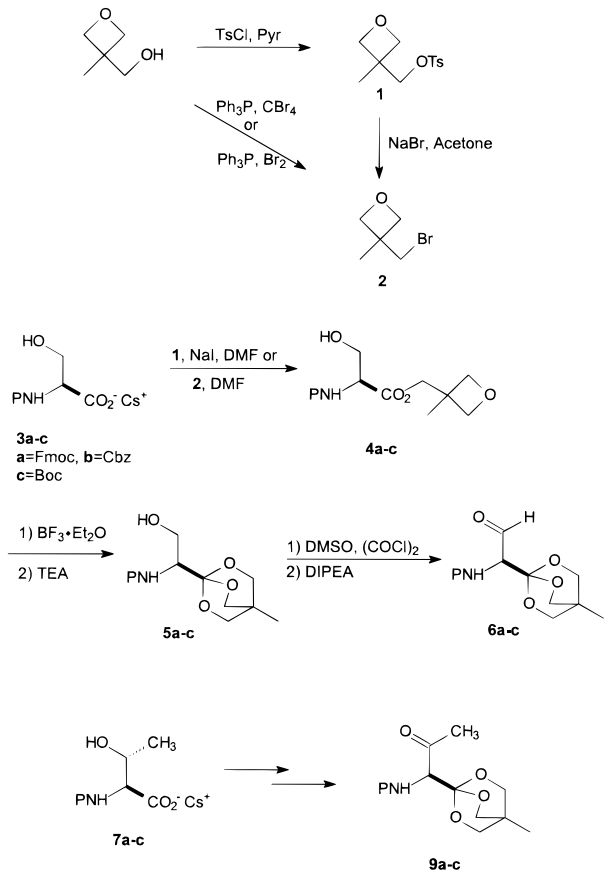
(11) Both the 2*S*,3*S*/2*R*,3*R* (*anti*, *erythro*, or *allo*-Thr analogues) and 2*S*,3*R*/2*R*,3*S* (*syn* or *threo* Thr analogues) diastereomers can be selectively synthesized using Rapoport's serine derivative,[11a,b] Evans' oxazolidinone glycine enolate,[11c−e] or Garner's aldehyde.[11f−h] See also references within ref 1a and 11i−m for other approaches. (a) Maurer, P. J.; Takahata, H.; Rapoport, H. *J. Am. Chem. Soc.* **1984**, *106*, 1095−1098. (b) Roemmele, R. C.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 1866−1875. (c) Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1986**, *108*, 6757−6761. (d) Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1987**, *109*, 7151−7157. (e) Evans, D. A.; Sjogren, E. B.; Weber, A. E.; Conn, R. E. *Tetrahedron Lett.* **1987**, *28*, 39−42. (f) Garner, P.; Park, J. M. *J. Org. Chem.* **1987**, *52*, 2361−2364. (g) Coleman, R. S.; Carpenter, A. J. *Tetrahedron Lett.* **1992**, *33*, 1697−1700. (h) Garner, P.; Park, J. M. *J. Org. Chem.* **1990**, *55*, 3772−3787. (i) Duthaler, R. O. *Tetrahedron* **1994**, *50(6)*, 1539−1650. (j) Sunazuka, T.; Nagamitsu, T.; Tanaka, H.; Omura, S. *Tetrahedron Lett.* **1993**, *34*, 4447−4448. (k) Jackson, R. F. W.; Palmer, N. J.; Wyhtes, M. J.; Clegg, W.; Elsegood M. R. J. *J. Org. Chem.* **1995**, *60*, 6431−6440. (l) Easton, C. J.; Hutton, C. A.; Roselt, P. D.; Tiekink, E. R. T. *Tetrahedron* **1994**, *50*, 7327−7340. (m) Hughes P. F.; Smith, S. H.; Olson, J. T. *J. Org. Chem.* **1994**, *59*, 5799−5802. (n) Cardillo, G.; Tolomeli, A.; Tomasini, C.; *Tetrahedron* **1995**, *51*, 11831−11840.

(12) Most glycine enolate equivalents tend to produce the *threo*/*syn* stereochemistry upon addition to aldehydes, with no possibility of obtaining the other diastereomer. Note that two chiral centers are formed in these additions, with very high selectivity usually observed at the α-center and variable selectivity at the carbinol center. Seebach's oxazolidinone[12a,b] and imidazolidinone,[12c,d] Schöllkopf's bis-lactim ether,[12e] and the Ni(II) glycine Schiff base enolate of Belokon et al.[12f] all add to aldehydes and ketones to give the *threo* diastereomer, while the glycine boron enolate equivalent derived from Williams' oxazinone produces the *erythro* isomer.[12g,h] (a) Seebach, D.; Müller, S. G.; Gysel, U.; Zimmermann, J. *Helv. Chim. Acta* **1988**, *71*, 1303−1318. (b) Blaser, D.; Seebach, D. *Liebigs Ann. Chem.* **1991**, 1067−1078. (c) Seebach, D.; Juaristi, E.; Miller, D. D.; Schickli, C.; Weber, T. *Helv. Chim. Acta* **1987**, *70*, 237−261. (d) Fitzi, R.; Seebach, D. *Tetrahedron* **1988**, *44*, 5277−5292. (e) Schöllkopf, U. *Pure Appl. Chem.* **1983**, *55*, 1799−1806. (f) Belokon, Y. N.; Bulychev, A. G.; Vitt, S. V.; Struchkov, Y. T.; Batsanov, A. S.; Timofeeva, T. V.; Tsyryopkin, V. A.; Ryzhov, M. G.; Lysova, L. A.; Bakhmutov, V. I.; Belikov, V. M. *J. Am. Chem. Soc.* **1985**, *107*, 4252−4259. (g) Reno, D. S.; Lotz, B. T.; Miller, M. J. *Tetrahedron Lett.* **1990**, *31*, 827−830. (h) Williams, R. M.; Im, M.-N.; Cao, J. *J. Am. Chem. Soc.* **1991**, *113*, 6976−6981.

Scheme 1



ester **4b** is obtained as a crystalline solid in 75−80% yield, while the corresponding Fmoc derivative **4a** was obtained in 65−70% yield. The Boc derivative **4c** was obtained in 66% yield as an oil which crystallized upon standing. The formation of the ortho esters **5a** and **5b** from the oxetane esters **4a** and **4b** is performed as described previously in CH_2Cl_2 with a catalytic amount of $BF_3{\cdot}Et_2O$ (2−5 mol %) for the Fmoc and Cbz derivatives, which were obtained in 90−95% yield after recrystallization. The more acid sensitive Boc derivative **5c** is obtained in 66% yield after chromatography. Similar yields are obtained for the threonine derivatives **7a**−**c**. Oxidation under Swern conditions of **5a**−**c** gave the parent aldehydes **6a**−**c** in 90−95% yields. Comparable yields were also obtained for the L-threonine derivatives **7a**−**c** under analogous conditions.

Table 1. Addition of CH_3MgBr to P-Ser(ald) OBO Esters 6a and 6b

entry	P	solvent	temp (°C)	yield (%)	diastereoselectivity *threo:erythro*
1	Fmoc	CH_2Cl_2	25	63	83:17
2	Fmoc	Et_2O/CH_2Cl_2	25	74	84:16
3	Fmoc	Et_2O/CH_2Cl_2	−78	51	96:4
4	Fmoc	THF	25	70	81:19
5	Fmoc	THF	−78	63	83:17
6	Cbz	CH_2Cl_2	25	52	82:18
7	Cbz	CH_2Cl_2	−78	61	96:4
8	Cbz	Et_2O/CH_2Cl_2	−78	60	97:3
9	Cbz	THF	25	73	80:20
10	Cbz	THF	−78	95	74:26
11	Boc	Et_2O/CH_2Cl_2	−78	61	85:15

Synthesis of the *Threo* β-Hydroxy Amino Acids. We have reexamined the conditions for the addition of MeMgBr with the Fmoc and Cbz derivatives **6a** and **6b** in a wide range of solvents, concentrations, reagent stoichiometry, and temperature. Yields and diastereoselectivities were essentially the same for the Fmoc, Cbz, and Boc groups. Excesses of reagents from 250 to 600 mol % had little or no effect on yields or diastereoselectivies. The best results, in terms of yields and diastereoselectivities, were obtained with CH_3MgBr (400 mol %) at −78 °C in a mixture of Et_2O/CH_2Cl_2 (1:1) and the serine aldehyde **6a** or **6b**, resulting in protected L-threonines **9a** and **9b** in 60% yield with a *threo* (2*S*,3*R*): *erythro* (2*S*,3*S*) ratio of 97:3 and >99% ee (Table 1). Higher yields (80−85%) are obtained if the reaction is carried out at room temperature in the same solvent conditions or in THF, but lower diastereoselectivity is observed (84:16). Higher yields (95%) are also obtained at −78 °C with the corresponding organocerium reagent, but the diastereoselectivity is significantly lower (74:26). Reaction of **6a**−**c** with a number of other Grignard reagents leads to the corresponding protected β-hydroxy amino acids **10a**−**17a**, and **10b**−**11b**, and **10c**−**11c** (Scheme 2). The *threo* diastereomer was again produced preferentially and generally with better diastereoselectivities (98:2 for PhMgBr and 95:5 for EtMgBr) (Table 2). Organocuprate addition (Me_2CuLi) gives **9a** with 94:6 *threo*:*erythro* selectivity, but the product is completely racemic and the yield is low.

(13) A number of syntheses of racemic β-hydroxyvaline have been reported.[13a−j] The first synthesis of optically active material was by addition of Schöllkopf's bis-lactim ether to acetone, with condensation proceeding in 98% yield, but deprotection to the free amino acid in only 49% yield under "carefully controlled" conditions to prevent dehydration.[13k] Seebach's imidazolidinone has also been added to acetone, with 62% yield for the condensation, but only 30% yield for deprotection.[12d] Addition of Belokon's Ni(II) glycine Schiff base enolate to acetone provides the best yield (56%) of β-hydroxy-L-valine that has been reported.[13l] Protected β-hydroxyvaline has also been synthesized by hydroxylation of valine, with unreported yield.[13m] The only report of a glycine enolate equivalent addition to an asymmetric ketone is of Schöllkopf's bis-lactim ether to methylphenyl ketone, which gave the adduct in 91% yield with >95% ee at the α-center, but only 38% de at the carbinol (β-) center. Deprotection was not described.[13n] (a) Rüfenacht, K. *Helv. Chim. Acta* **1952**, *93*, 762−764. (b) Schöberl, A.; Ernsberger, A. *Naturwiss* **1966**, *53*, 107−109. (c) Oh-hashi, J.; Harada, K. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 2287−2289. (d) Edwards, G. W.; Minthorn, M. L. *Can. J. Biochem.* **1968**, *46*, 1227−1230. (e) Berse, C.; Bessette, P. *Can. J. Chem.* **1971**, *49*, 2610. (f) Shanzer, A.; Somekh, L.; Butina, D. *J. Org. Chem.* **1979**, *44*, 3967−3969. (g) Broxterman, H. J. G.; Liskamp, R. M. J. *Recl. Trav. Chem. Pays-Bas* **1991**, *110*, 46−52. (h) Kurome, T.; Inami, K.; Inoue, T.; Ikai, K.; Takesako, K.; Kato, I.; Shiba, T. *Tetrahedron* **1996**, *52*, 4327−4336. (i) Jao, E.; Cooper, A..B.; Rane, D. F.; Saksena, A. K.; Desai, J.; Wang, L.; Girijavallabhan, V. M.; Ganguly, A. K. *Terahedron Lett.* **1996**, *37*, 5661−5664. (j) Stoll, A.; Petrzilka, T. *Helv. Chim. Acta* **1952**, *35*, 589−607. (k) Schöllkopf, U.; Nozulak, J.; Groth, U. *Synthesis* **1982**, 868−870. (l) Belokon, Y. N.; Chernoglazova, N. I.; Kochetkov, C. A.; Garbalinskaya, N. S.; Belikov, V. M. *J. Chem. Soc., Chem. Commun.* **1985**, 171−172. (m) Easton, C. J.; Hutton, C. A.; Tan, E. W.; Tiekink, E. R. T. *Tetrahedron Lett.* **1990**, *31*, 7059−7062. (n) Schöllkopf, U.; Groth, Gull, M. R.; Nozulak, J. *Liebigs Ann. Chem.* **1983**, 1133−1151.

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(16) The oxetane alcohol is commercially available but is easily prepare on 10 mol scale and obtained as an oil (65% yield) according to the procedure reported by Corey. Corey, E. J.; Raju, N. *Tetrahedron Lett.* **1983**, *24*, 5571−5574.

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(19) The oxetane bromide **2** otained by this procedure is sufficiently pure to be used without distillation.

Scheme 2

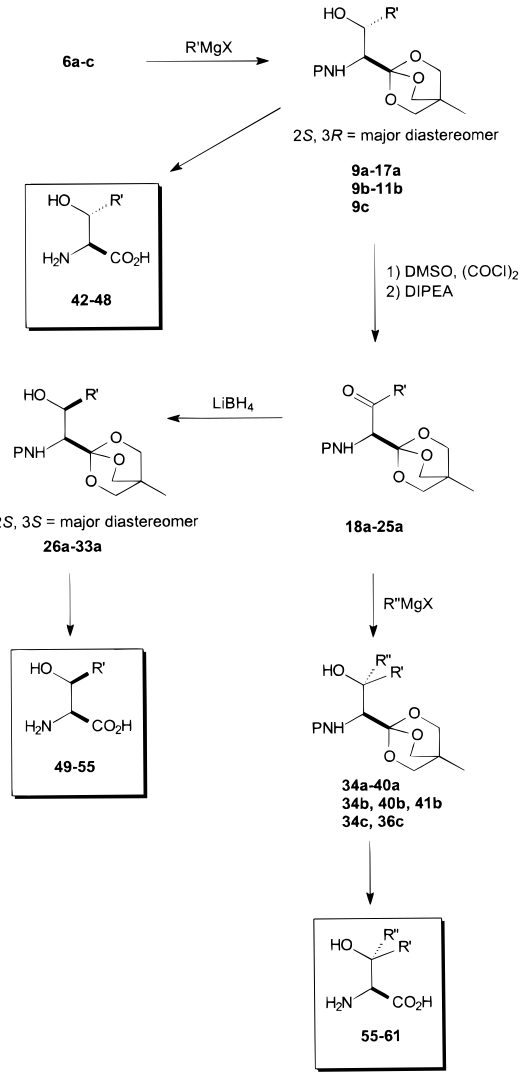

Table 2. Yields and Diastereomeric Ratios of Grignard Addition to P-Ser(ald) OBO Ester with RMgBr

entry	product	P	R	temp (°C)	yield (%)	diastereoselectivity
1	**10a**	Fmoc	Et	25	61	88:12
2	**10a**	Fmoc	Et	−78	45	93:7
3	**11a**	Fmoc	Ph	25	85	83:17
4	**11a**	Fmoc	Ph	−78	56	86:14
6	**12a**	Fmoc	*n*-Bu	25	58	82:10
7	**13a**	Fmoc	vinyl	25	45	86:14
8	**14a**	Fmoc	allyl	25	70	70:30
9	**15a**	Fmoc	4-PhOCH$_3$	25	61	88:12
10	**16a**	Fmoc	cyclohexyl	25	35	86:14
11	**17a**	Fmoc	CD$_3$	−78	45	95:5
12	**10b**	Cbz	Et	25	51	86:14
13	**10b**	Cbz	Et	−78	59	92:8
14	**11b**	Cbz	Ph	25	73	84:16
15	**11b**	Cbz	Ph	−78	77	92:8

Synthesis of *Erythro* Isomers. The β-hydroxy adducts can be oxidized under Swern conditions to give the corresponding ketones **18a**−**25a**, **18b**, and **20b** in very good yields. The lowest yield was obtained with vinylserine **22a**. Oxidation of allylserine **14a** gave the corresponding ketone **23a** in 52% yield but also gave 17% of the isomerized α,β-unsaturated product. The protected ketones can be purified by chromatography on silica gel without racemization, and a greater excess of reagent can be employed during the oxidation than with the more sensitive protected serine substrate **5a**. Reduction of the ketones (LiBH$_4$, −78 °C) regenerates the β-hydroxy amino acids **26a**−**33a**, but with the opposite configuration at the β-carbon.[15] Diastereoselectivity varies from 91:9 *erythro* (2*S*,3*S*):*threo* (2*S*,3*R*) for the threonine derivative **26a** to >98:<2 *erythro* (2*S*,3*S*):*threo* (2*S*,3*R*) for phenylserine derivative **28a** and anisoleserine derivative **32a** (Table 3). The selectivity can be reversed if Zn(BH$_4$)$_2$[15b] is used as the reducing agent, giving 32:68 *erythro* (2*S*,3*S*):*threo* (2*S*,3*R*) when **18a** is reduced. The diastereomeric ratios can be determined by integration of the urethane protons in the ^{1}H NMR spectra of the protected amino acids or by integration of the α-protons of the deprotected products. If the *erythro* β-methyl diastereomer is desired, the necessary methyl ketone substrate **6a** is available in four steps and 60−70% yield from threonine.[15]

Table 3. Yields and Diastereomeric Ratios for the LiBH$_4$ Reduction of Fmoc-Protected Ketone Ortho Ester 19a−26a[a]

entry	starting ketone	P	R′	product	yield[a] (%)	diastereoselectivity *threo:erythro*
1	**18a**	Fmoc	Me	**26a**[b]	100	9:91
2	**19a**	Fmoc	Et	**27a**	75	7:93
3	**20a**	Fmoc	Ph	**28a**	94	2:98
4	**21a**	Fmoc	*n*-Bu	**29a**	71	7:93
5	**22a**	Fmoc	vinyl	**30a**	78	15:85
6	**23a**	Fmoc	allyl	**31a**	69	6:94
7	**24a**	Fmoc	4-PhOCH$_3$	**32a**	85	1:99
8	**25a**	Fmoc	cyclohexyl	**33a**	68	7:93

[a] Isolated yield after chromatography. [b] Experimental result reported previously.[15b]

Synthesis of β-Dialkyl-β-hydroxy α-Amino Acids. Addition of MeMgBr (400 mol %, 25 °C) to Fmoc-, Cbz-, or Boc-L-Thr(ket)-OBO esters **18a**−**c** in THF results in protected L-β-hydroxyvalines **34a**−**c** in 95% yield. When isotopically labeled CD$_3$MgI is employed, **35a** is obtained with 95:5 *threo* (2*S*,3*R*):*erythro* (2*S*,3*S*). Even higher selectivity of 99:1 is observed when bulkier PhMgBr is added to the methyl ketone **18a**−**18b** (Table 4). The corresponding *erythro* isomers are obtained by addition of MeMgX to ketones **19a**−**24a** and **20b**, which are prepared from the Grignard adduct of the aldehydes **6a** or **6b** followed by oxidation. Diastereoselectivity remains high for addition of MeMgI to the ethyl ketone **19a** but is reduced for addition of MeMgI to the bulkier anisole ketone **24a**.

Deprotection. Removal of the protecting groups from the Fmoc β-hydroxy derivatives is accomplished by a three-step "one-pot" procedure as described previously.[15] The protected amino acid is first treated with piperidine (20% in CH$_2$Cl$_2$), then reacted with aqueous trifluoroacetic acid in CH$_2$Cl$_2$, and finally hydrolyzed with Cs$_2$CO$_3$ (500 mol %, MeOH:H$_2$O, 1:1.5) in 75−95% yield. The iodotrimethylsilane (TMSI) deprotection procedure reported earlier[15] was found to give inconsistent results with the Fmoc protecting group but works very well with all the Cbz derivatives.

Alternatively the Cbz group is first removed by hydrogenolysis, followed by TFA ring opening of the OBO ester and then followed by base hydrolysis. The Boc derivatives can be fully deprotected by initial treatment with TFA followed by base hydrolyis as described above. Purification by anion exchange chromatography (Bio-Rad AG 1-X4) was found to be more convenient than the equivalent cation exchange procedure. The enantiomeric and diastereomeric purity of the amino acid was deter-

Table 4. Yields and Diastereoselectivities of Grignard Addition of R^2MgX to Fmoc, Cbz, and Boc Protected Ketone Ortho Esters

ketone substrate	P	R^1	added substituent R^2	product	diastereoslectivity *threo:erythro*	yield (%)
18a	Fmoc	CH_3	CH_3	**34a**		75
18b	Cbz	CH_3	CH_3	**34b**		85
18a	Fmoc	CH_3	CD_3	**35a**	95:5	73
18a	Fmoc	CH_3	Et	**36a**	98:2	72
18a	Fmoc	CH_3	4-$PhOCH_3$	**37a**	97:3	58
19a	Fmoc	Et	CH_3	**38a**	3:97	75
24a	Fmoc	4-$PhOCH_3$	CH_3	**39a**	8:92	75
18b	Cbz	CH_3	Ph	**40b**	99:1	84
20b	Cbz	Ph	CH_3	**41b**	1:99	92
18c	Boc	CH_3	CH_3	**34c**		72
18c	Boc	CH_3	Et	**36c**	97:3	75

mined by HPLC analysis after derivatization of the free amine with *o*-phthaladehyde (OPA) and *N*-isobutyryl-L-cysteine (*N*-*i*-Bu-L-Cys).[15,20] Additional characterization of the free amino acid was provided by electrospray mass spectrometry, which gives less fragmentation compared to FAB-MS and allows the molecular ion to be observed without dehydration.

Discussion

The Grignard additions to the aldehydes **6a**−**c** proceed in good yields, even with highly hindered reagents such as cyclohexylmagnesium chloride. The steric bulk of the Grignard reagent does not consistently affect diastereoselectivity, but lower temperature gave better de although in generally lower yields. Similar yields were observed with the Cbz and Boc derivatives. The main byproduct from these reactions is recovered aldehydes **6a**−**c**.[21] Use of excess Grignard reagent does not increase the yield of product or lead to decomposition of the unreacted protected aldehyde. The recovered aldehyde retains its enantiomeric purity,[22] suggesting that enolization is not responsible for preventing quantitative reaction. Surprisingly, there is little cleavage of the Fmoc group in the presence of excess reagent. It is possible that the urethane nitrogen proton is abstracted by the Grignard reagent at a rate competitive with nucleophilic addition, with the resulting carbamate anion strongly disfavoring carbonyl attack or Fmoc cleavage. Grignard addition to ketones **18a**, **19a**, **24a** and **18b**, **20b** gave better diastereoselectivities and yields than that to the corresponding aldehyde.

The high levels of diastereoselectivity observed in the additions to the carbonyl of this acyclic system appear to be induced by the bulk of the OBO ester protecting group and are consistent with a nonchelation-controlled

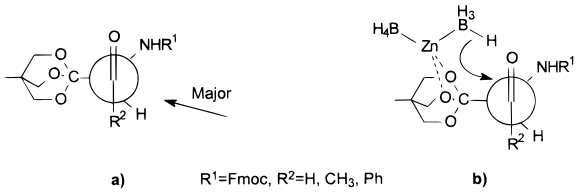

Figure 1. Felkin−Anh model (a) predicting direction of nonchelation-controlled attack on the side chain carbonyl and (b) predicting direction of chelation-controlled $Zn(BH_4)_2$ reduction.

Felkin−Anh attack[23] (Figure 1a) from the face opposite to the OBO ester blocking group (*re* face attack). This analysis is supported by the reversal in reduction diastereoselectivity observed when the chelating reagent $Zn(BH_4)_2$[15b] was used (Figure 1b). The enhanced diastereoselectivity observed with the increasing size of the ketone substituent in the reduction step and in the second Grignard addition also agrees with the Felkin−Anh model predictions.

The high 95:5 *threo:erythro* ratio observed in the synthesis of 4,4,4-$^2H_3$-L-β-hydroxyvaline **57** is particularly noteworthy as most other synthetic methods, which rely upon addition of a glycine enolate equivalent to a ketone, would not discriminate between the two faces of isotopically substituted acetone. This results in the *threo* diastereomer if the higher priority substituent is added in the second Grignard addition. The diastereomeric ratios can be determined by integration of the β-methyl resonances in the ^1H NMR spectra of both the protected amino acids and the deprotected products. The relative stereochemistry of the products was determined by comparison of the ^1H and ^{13}C NMR spectra with the spectra of the corresponding monosubstituted adducts. For example, in Fmoc-Thr-OBO ester **9a**, the γ-methyl group resonates at δ 1.13/18.99 ppm in the $^1H/^{13}C$ NMR spectra, in Fmoc-*allo*-Thr-OBO ester at δ 1.18/19.18 ppm.[15b] The two methyl groups in protected β-hydroxyvaline **34a** appear at δ 1.21/26.77 ppm and 1.34/28.18 ppm. When one of these methyl groups is replaced by CD_3, the remaining resonance is observed at δ 1.33/28.06 ppm. Thus, the methyl group already present in the Fmoc-Thr(ket)-OBO ester **18a** moves to a position equivalent to the "*erythro*" methyl group of Fmoc-L-*allo*-Thr-OBO, while the methyl group resulting from Grignard addition occupies the "*threo*" position. Analogous differ-

(20) Brückner, H.; Wittner, R.; Godel, H. *J. Chromatogr.* **1989**, 476, 73−82. Difficulty was observed in obtaining good yields of *N*-*i*-Bu-L-Cys without racemization when the procedure reported by Brückner, Wittner, and Godel was used (4−5% racemization observed). Reaction of L-Cys_2 in 2:1 H_2O: dioxane with 10 equiv of NaOH and 5 equiv of isobutyryl chloride for 10 min was found to give much better yields of $(N$-*i*-Bu-L-$Cys)_2$ with minimal racemization (<0.2%). Reduction with Zn/2 N HCl gave the desired *N*-*i*-Bu-L-Cys.

(21) If separation of the unreacted aldehyde by flash column chromatography is difficult, the aldehyde can be reduced to the alcohol with $NaBH_4$.

(22) The aldehyde is not enantiomerically stable to the silica column chromatography required to separate it from the Grignard addition product. To ascertain its enantiomeric purity, the crude adduct solution was treated with $NaBH_4$. The resulting Fmoc-Ser OBO ester **5a** is chromatographically stable, and its optical rotation can then be compared to authentic material.

(23) For a summary of various carbonyl addition models, see: (a) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 2−72. (b) For a disussion of Anh's model, see: Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145−163.

ences are observed in the spectra of the free amino acids, though there is a reversal in the relative chemical shifts of the "*threo*" and "*erythro*" methyls, so that the "*erythro*" methyl in *threo* 4,4,4-$^2H_3$-L-β-hydroxyvaline **57** is at the higher field values (δ 1.12/25.92 ppm) of the two methyls in β-hydroxyvaline **56** (δ 1.37/30.11, 1.15/26.02 ppm).

Deprotection occurs under mild conditions, giving the recrystallized free β-hydroxy amino acids in 18−50% overall yield from Fmoc-, Cbz-, and Boc-protected Ser-OBO esters **6a**−**c** for the *threo* isomers and 7−35% for the *erythro* isomers, with little racemization at the α-carbon (>95% ee). The mildness of the deprotection is illustrated by the high yields obtained with the aromatic β-hydroxy amino acids and with the disubstituted β-hydroxy amino acids. Other procedures often report poor yields for the deprotection step of this class of compounds.[24] Yields and diastereoselectivities of the deprotected amino acids compare favorably to the best of previously published syntheses for *threo* β-ethylserine (β-hydroxynorvaline)[25] and both *threo* and *erythro* β-phenylserine[26] and β-anisoleserine.[27] The synthesis of deprotected *erythro* β-ethylserine, and both *threo* and *erythro* β-cyclohexylserine,[28] β-vinylserine,[29] and β-allylserine,[30] has not previously been reported. This synthetic approach allows for the introduction of isotopically labeled substituents, either at the Grignard addition step or at the reduction of the intermediate ketones. The yield of β-hydoxyvaline (37% from Fmoc-Thr-OBO ester **9a**) also compares favorably to the best previous synthesis of this compound (Belokon et al., 56%[12f] and Goodman[14]). 4,4,4-$^2H_3$-L-β-Hydroxyvaline **57**, β-hydroxyisoleucine **58**, and β-anisolethreonine **59** have not been previously reported.

Conclusion

In summary, we describe a new strategy for the stereoselective synthesis of β-hydroxy α-amino acids from a chiral serine equivalent protected as a cyclic ortho ester. Both L- and D-amino acid derivatives can be obtained starting directly from the commercially available L- or D-serine respectively, allowing for all four diastereomers to be selectively synthesized. Both C and H isotopes can be stereospecifically incorporated. The precursor oxetane ester can be prepared on a large scale without chromatography with Fmoc and Cbz as the amine protecting group. Future work will explore the addition of more complex side chains and the use of modified reagents to improve or reverse organometallic addition diastereoselectivities. We also describe the extension of this strategy for amino acid synthesis to the preparation of the di-β-substituted-β-hydroxy class of compounds, including β-hydroxyvaline and β-hydroxyisoleucine. While only β-methyl-β-substituted-β-hydroxy α-L-amino acids were synthesized in this study, all four diastereomers of any disubstituted derivative should be accessible by Grignard addition of the desired substituents in the appropriate order to either D- or L-protected-Ser(ald)-OBO esters **6a**−**c**. Removal of the hydroxyl function to yield β-dialkyl-substituted amino acids should be feasible,[31] as should other types of addition to the OBO ester-protected ketone. Incorporation of some of these β-hydroxy amino acids in peptides is underway.

Experimental Section

General. See ref 15a. NMR spectra were recorded in $CDCl_3$ (referenced to TMS at 0.00 ppm for ^1H, to $CDCl_3$ at 77.00 ppm for ^{13}C or D_2O (referenced to *2,2,3,3-d*$_4$-3-(trimethylsilyl)propionic acid, sodium salt at 0.00 ppm for both ^1H and ^{13}C) on a Bruker AC-200 or AM-250 spectrometer. $CDCl_3$ used for NMR samples containing an ortho ester was prefiltered through basic alumina to remove traces of acid. TLC was carried out on Merck aluminum backed silica gel 60 F_{254}, with visualization by UV, ninhydrin solution (2% in EtOH), or I_2. TLC solvent systems commonly used: A, 1:1 EtOAc:hex; B, 3:1 EtOAc:hex; C, 1:1:1:1 H_2O:EtOAc:*n*-BuOH:MeOH.

Typical Procedure for Grignard Addition to the Protected Aldehydes 6a−c and Ketones 18a−c, 19a, 24a, and 20b. Crude aldehyde or ketone (1.0 mmol assuming 100% yield in the oxidation) was dissolved in dry Et_2O under N_2. A solution of RMgX in Et_2O (Aldrich, 1.0−3.0 M, 2.5−4 equiv) was added quickly by syringe at −78 °C and stirred vigorously. After 5 min the reaction was quenched by pouring into 100 mL of 5% NH_4Cl. CH_2Cl_2 (100 mL) was added, and the organic layer was separated, washed with 3% NH_4Cl (1 × 100 mL) and brine (1 × 100 mL), dried ($MgSO_4$), and evaporated to dryness. The colorless solid foam was purified by flash column chromatography (silica gel, 1:1 EtOAc:hex, loaded in CH_2Cl_2). Diastereomeric ratios were determined by integration of the appropriate protons in the ^1H NMR spectra.

Typical Procedure for Reduction of Ketones. Crude Fmoc/OBO ester protected ketone (0.25 mmol) and $LiBH_4$ (2.5 mmol, 1000 mol %) were cooled to −78 °C in a 50 mL flask under N_2. A 1.5:1 solution of CH_2Cl_2:CH_3OH (15 mL, cooled to −78 °C) was added, and the solution was stirred at −78 °C for 10−20 h, until complete by TLC. After being warmed to room temperature, the solution was poured into 5% NH_4Cl (50 mL) and CH_2Cl_2 (25 mL) was added. The organic layer was separated, washed with 5% NH_4Cl (1 × 50 mL) and saturated NaCl (1 × 50 mL), dried ($MgSO_4$), and evaporated to dryness. The colorless solid foam was purified by flash column chromatography (silica gel, 1:1 EtOAc:hex, loaded in CH_2Cl_2). Diastereomeric ratios were determined by integration of the urethane protons in the ^1H NMR spectra.

General Procedure for Removal of Protecting Groups. The Fmoc and OBO ester protecting groups were removed by a three-step procedure (piperidine, aqueous TFA, aqueous

(24) Aromatic adducts of bis-lactim ether enolates hydrolyze to the methyl ester in 46−66% yield.[12e] Schöllkopf, U.; Beulshausen, T. *Liebigs Ann. Chem.* **1989**, 223−225. Phenylserine obtained from an imidazolidinone enolate was hydrolyzed in 54% yield.[12c]

(25) The D-*threo* isomer of β-ethylserine has been prepared in 70% overall yield with >98% de from a chiral oxazolidinone template.[12b]

(26) L-*threo*-β-Phenylserine has been prepared via an oxazolidinone in 76% yield with >98% de.[12b] Evans' methodology has been applied to the synthesis of both *threo* and *erythro* β-phenylserine in 50% overall yield and >98% de: Lago, M. A.; Samanen, J.; Elliott, J. D. *J. Org. Chem.* **1992**, *57*, 3439−3496. Many other glycine enolate equivalent additions to benzaldehyde have been reported, but few describe the deprotection of the adduct to the free amino acid.

(27) L-*threo*-β-Anisoleserine has been obtained in 94% de and 35% yield by benzylic oxidation of a protected tyrosine derivative [Shimamoto, K.; Ohfune, Y. *Tetrahedron Lett.* **1988**, *29*, 5177−5180] and in 68% yield with >98% de via an oxazolidinone enolate.[12b]

(28) Racemic β-cyclohexylserine has been prepared in 75% yield with 62:38 *threo*:*erythro* selectivity by the condensation of trimethylsilyl glycine Schiff base enolate with cyclohexane carboxaldehyde: (a) van der Werf, A. W.; Kellogg, R. M.; van Bolhius, F. *J. Chem. Soc., Chem. Commun.* **1991**, 682−683. The D-*erythro*-*N*,*N*-dialkyl and L-*erythro* azide analogues have been prepared via epoxide intermediates: (b) Chong, J. M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1560−1563. (c) Saito, S.; Takahashi, N.; Ishikawa, T.; Moriwake, T. *Tetrahedron Lett.* **1991**, *32*, 667−670. An enzymatic synthesis with serine hydroxymethyltransferase gave 11% yield, with undetermined stereochemistry.[1b]

(29) The D-*threo* ethyl ester of β-vinylserine has been prepared in 48% yield with >97% de by a chiral titanium complex catalyzed addition of a protected glycine lithium enolate to propenal: Bold, G.; Duthaler, R. O.; Riediker, M. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 497−498.

(30) Both vinyl and allyl adducts of other serine aldehyde equivalents have been reported, but the corresponding free amino acids have not been prepared.[11b,g]

(31) Williams, R. M.; Im, M.-N.; Cao, J. *J. Am. Chem. Soc.* **1991**, *113*, 6976−6981.

Cs_2CO_3) as previously reported.[15] The basic Cs_2CO_3 solution was filtered, then loaded directly onto an anion-exchange resin column (Bio-Rad AG 1-X4 100−200 mesh, hydroxide form), washed with H_2O, and eluted with 1 N AcOH. Diastereomeric ratios were determined by integration of the α-protons in the ^{1}H NMR spectra or by HPLC analysis after derivatization with *o*-phthaladehyde and *N*-isobutyryl-L-cysteine (Waters 125A 8 × 100 mm μ-Bondapak C_{18} Radial-Pak cartridge column, 2 mL/min; 100% 30 mM sodium acetate buffer, pH 6.5; various linear gradients to a buffer:MeOH combination; detection at 338 nm). The Cbz/OBO were removed simultaneously with TMSI, and the product was purified by ion exchange. The Boc/OBO were removed first by treatement with aqueous 95:5 TFA:H_2O and then base hydrolyzed with Cs_2CO_3 as for the Fmoc procedure.

3-Methyl-3-(toluenesulfonyloxymethyl)oxetane, Oxetane Tosylate, 1. Tosyl chloride (57.20 g, 0.3 mol) was dissolved in dry pyridine (400 mL) under argon. 3-Methyl-3-(hydroxymethyl)oxetane (20.4 g, 0.2 mol) was added slowly, and the solution was stirred for 1.5 h. Crushed ice (400 g) was then added to the vigorously stirring mixture, which was allowed to stir for an additional 0.5 h. The white precipitate was then collected on Whatman filter paper # 1 and washed with cold H_2O. The product was dried under high vacuum to obtain the white powder of oxetane tosylate (49.11 g, 92%): mp 49.5−51 °C; TLC (2:3, EtOAc:hexane) R_f = 0.42; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.81 (d, J = 8.2 Hz, 2H), 7.37 (d, J = 8.2 Hz, 2H), 4.37 (m, 4H), 4.11 (s, 2H), 2.46 (s, 3H), 1.31 (s, 3H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 145.1, 132.8, 129.9, 127.9, 78.9, 74.2, 39.3, 21.6, 20.6; HRMS (FAB) calcd for (M + H^+) $C_{12}H_{16}O_4S$ 256.0769, found 256.0774. Anal. Calcd for $C_{12}H_{16}O_4S$: C, 56.23; H, 6.29. Found: C, 56.33; H, 6.44.

3-Methyl-3-(bromomethyl)oxetane, Oxetane Bromide, 2. Procedure A. 3-Methyl-3-(hydroxymethyl)oxetane (50.0 mL, 0.50 mol) and carbon tetrabromide (182.9 g, 0.55 mol) were dissolved in CH_2Cl_2 (500 mL) and cooled to 0 °C under argon. Triphenylphosphine (157.8 g, 0.60 mol) was added in portions. The reaction was warmed to room temperature and stirred for a further 20 min under argon. The CH_2Cl_2 was removed in vacuo, and Et_2O (500 mL) was added to the mixture. The crude product was filtered through Celite to remove some of the byproduct Ph_3PO. The filtrate was then concentrated to a viscous liquid, and hexane (500 mL) was added. The mixture was filtered once more through Celite to remove most of the byproduct Ph_3PO. The filtrate was concentrated to obtain a viscous yellow oil. The crude product was distilled under vacuum with a fractionation column. Oxetane bromide **2** was collected as a viscous liquid in 95−99% (81.0 g) yield: bp 62−64 °C/10 mmHg; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 4.46−4.38 (d+d, J = 6.3 Hz, 4H), 3.65 (s, 2H), 1.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 80.5, 41.3, 40.5, 22.3; IR (neat) 2960, 1453, 1233; MS (ESI, *m*/*z*) 157. Anal. Calcd for C_5H_9BrO: C, 36.39; H, 5.50. Found: C, 36.50; H, 5.70.

Procedure B. A solution of bromine (10.2 mL, 0.2 mol) in 50 mL of CH_2Cl_2 at 0 °C was slowly added to a stirred solution of oxetane alcohol (20.4 g, 0.20 mol), triphenylphosphine (63.0 g, 0.24 mol), and pyridine (39 mL, 0.48 mol) in 200 mL of CH_2Cl_2. The mixture was stirred at room temperature for 1 h. The solvent was removed under reduced pressure. To the residue was added Et_2O (400 mL), the mixture was then filtered through Celite, and the filtrate was evaporated in vacuo. Hexanes (200 mL) was then used to rinse the remaining solids. The final filtrate was concentrated and distilled to give the product **2** (22.7 g, 69%).

Procedure C. 3-Methyl-3-(toluenesulfonyloxymethyl)oxetane **1** (25.0 g, 97.53 mmol) and NaBr (50.18 g, 0.49 mol, 5.0 equiv) were suspended in dry acetone (250 mL) under dry nitrogen and refluxed for 30 h. The solution was first filtered, and decolorizing charcoal was added. The solution was filtered, and the acetone was evaporated in vacuo to give a colorless thick oil (14.8 g, 92%) which does not need further purification.

***N*-(9-Fluorenylmethyloxycarbonyl)-L-serine 3-Methyl-3-(hydroxymethyl)oxetane Ester, Fmoc-Ser Oxetane Ester, 4a. Procedure A.** Fmoc-Ser (2.00 g, 6.11 mmol) was suspended in distilled H_2O (20 mL). Cs_2CO_3 (1.00 g, 3.05 mmol) was added in three portions, and the reaction was stirred vigorously. After 20 min the solution was concentrated to a thick oil using a rotary evaporator at 45 °C connected to a vacuum pump and then lyophilized for 24 h. The resulting white solid was dissolved in dry DMF (20 mL), and oxetane bromide **2** (1.09 mL, 7.64 mmol) was then added. The reaction mixture was stirred under nitrogen at room temperature for 24 h. DMF was removed using a rotary evaporator at 45 °C connected to a pump. The white crude product was dissolved in EtOAc (100 mL), washed with 5% $NaHCO_3$ (1 × 100 mL), 3% NH_4Cl (2 × 100), saturated NaCl (1 × 100 mL), dried ($MgSO_4$), and evaporated to dryness. The crude product was redissolved in CH_2Cl_2 and filtered through Celite to remove a white solid. The filtrate was concentrated to obtain a white solid in 64% (1.60 g) yield and compared to an authentic sample.[15a] TLC (3:1 EtOAc:hexane), R_f = 0.40; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.28−7.82 (m, 8H), 5.81 (d, J = 7.6 Hz, 1H), 4.38−4.67 (m, 9H,) 4.28 (t, J = 7.6 Hz, 1H), 4.10−4.24 (m, 1H), 3.89−4.05 (m, 1H), 2.95 (t, J = 6.0 Hz, 1H), 1.33 (s, 3H).

***N*-Benzyloxycarbonyl-L-serine 3-Methyl-3-(hydroxymethyl)oxetane Ester, Cbz-Ser Oxetane Ester, 4b. Procedure B.** Cbz-L-Ser (11.36 g, 0.047 mol) and Cs_2CO_3 (9.19 g, 0.028 mol, 0.6 eq) were combined and dissolved in H_2O (100 mL). The water was then removed in vacuo, and the resulting oil was lyophilized for 12 h to give a white foam. To this foam were added oxetane tosylate (12.65 g, 0.049 mol) and NaI (1.41 g, 9.8 mmol, 0.2 equiv) which were then taken up in DMF (350 mL) and allowed to stir under Ar for 48 h. The DMF was then removed in vacuo, and the resulting solid was dissolved in EtOAc (600 mL) and H_2O (200 mL), extracted with 10% $NaHCO_3$ (2 × 100 mL) and saturated NaCl (1 × 100 mL), and dried over $MgSO_4$. The solvent was removed under reduced pressure to yield a yellow oil which was recrystallized from ethyl acetate and hexanes to yield colorless rodlike crystals in 78% yield (11.85 g): mp 70−70.5 °C; $[\alpha]^{20}_D$ = −8.5 (c = 1.04, EtOAc); TLC (2:1, EtOAc:hexane), R_f = 0.34; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.28−7.34 (br m, 5H), 5.89 (d, J = 7.9 Hz, 1H), 5.12 (s, 2H), 4.38−4.56 (m, 6H), 4.04−4.13 (br m, 2H), 3.84−3.93 (br m, 1H), 3.22 (t, J = 6.0 Hz, 1H), 1.28 (br s, 3H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 170.6, 156.2, 136.1, 128.5, 128.1, 128.0, 79.4, 68.9, 67.1, 63.2, 56.3, 39.5, 20.7; IR (cast fron $CHCl_3$) 3330, 2958, 2877, 1714, 1531, 1214, 1061, 978, 752. Anal. Calcd for $C_{16}H_{21}NO_6$: C, 59.43; H, 6.55; N, 4.33. Found: C, 59.44; H, 6.61; N, 4.31.

***N*-Benzyloxycarbonyl-L-serine 3-Methyl-3-(hydroxymethyl)oxetane Ester, Cbz-Ser Oxetane Ester, 4b.** As in **4a**, procedure A using Cbz-Ser (30.0 g, 0.12 mol). The product was then crystallized from EtOAc and hexane to obtain an 85% (34.56 g) yield of colorless rodlike crystals: mp 70−70.5 °C; $[\alpha]^{20}_D$ = −8.5 (c = 1.04, EtOAc); TLC (2:1 EtOAc:hexane), R_f = 0.34. Anal. Calcd for $C_{16}H_{21}NO_6$: C, 59.43; H, 6.55; N, 4.33. Found: C, 59.44; H, 6.61; N, 4.31.

***N*-*tert*-Butyloxycarbonyl-L-serine 3-Methyl-3-(hydroxymethyl)oxetane Ester, Boc-Ser Oxetane Ester, 4c.** As in **4b**, procedure B was repeated on Boc-L-Ser **3c** (5.0 g, 0.024 mol). After extraction, the crude product was purified by flash chromatography (1:1, EtOAc:hex) to yield the ester in 66% yield (4.32 g) which crystallized upon standing: $[\alpha]^{20}_{578}$ = −15.4 (c = 1.02, EtOAc); TLC (solvent A) R_f = 0.33; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 5.47 (br d, J = 8.0 Hz, 1H), 4.47 (d, J = 6.1 Hz, 1H), 4.43 (d, J = 6.1 Hz, 1H), 4.35−4.27 (m, 4H), 4.07−3.57 (m, 3H), 3.01 (br s, 1H), 1.36 (s, 9H), 1.24, (s, 3H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 171.0, 155.6, 80.1, 79.8, 68.8, 63.1, 55.8, 39.3, 28.2, 20.7; IR (neat) 3386, 2970, 1746, 1713, 1509, 1367, 1163, 1060; HRMS (FAB) calcd for (M + H^+) $C_{13}H_{24}NO_6$ 290.1604, found 290.1594. Anal. Calcd for $C_{13}H_{23}NO_6$: C, 53.78; H, 8.33; N, 4.83. Found: C, 53.97; H, 8.62; N, 5.06.

Fmoc-L-serine OBO Ester, 5a. General procedure for rearrangement to trioxabicyclo[2.2.2]oxetane given in ref 15a.

1-[*N*-Benzyloxycarbonyl-(1*S*)-1-amino-2-hydroxyethyl]-4-methyl-2,6,7-trioxabicyclo[2.2.2]oxetane, Cbz-L-Ser OBO Ester, 5b. Procedure A. Cbz-Ser oxetane ester **4b** (15.0 g, 46.2 mmol) was dissolved in dry CH_2Cl_2 (450 mL) and cooled to 0 °C under Ar. $BF_3{\cdot}Et_2O$ (0.11 mL, 0.93 mmol) was diluted in CH_2Cl_2 (5.0 mL) and added to the reaction flask. The reaction was allowed to warm to room temperature and was checked by TLC. After 6 h, Et_3N (1.29 mL, 9.25 mmol) was added and the reaction was stirred for an additional 30 min before being concentrated to a thick oil. The crude product was redissolved in EtOAc (400 mL), washed with 3% NH_4Cl (2 × 250 mL) and saturated NaCl (1 × 250 mL), dried ($MgSO_4$), and evaporated to dryness. The reaction yielded a colorless thick oil in 95% (14.2 g) yield. The clear colorless oil was crystallized from EtOAc to give rodlike shiny crystals in 93% (13.6 g) yield: mp = 103.5−105.0 °C; $[\alpha]^{20}_D = -24.8$ (c = 1.00, EtOAc); TLC (3:1 EtOAc:hexane), R_f = 0.37; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.29−7.38 (m, 5H), 5.33 (d, J = 8.8 Hz, 1H), 5.10−5.18 (m, 2H), 3.61−3.95 (m, 9H), 2.57 (m, 1H), 0.81 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 156.3, 136.4, 128.4, 128.1, 128.0, 108.4, 72.7, 66.9, 61.9, 55.2, 30.5, 14.2. Anal. Calcd for $C_{16}H_{21}NO_6$: C, 59.43; H, 6.55; N, 4.33. Found: C, 59.60; H, 6.77; N, 4.22.

(1*S*)-1-[1-*N*-(*tert*-Butyloxycarbonyl)-(1*S*)-1-amino-2-hydroxyethyl]-4-methyl-2,6,7-trioxabicyclo[2.2.2]-octane, Boc-L-Ser OBO Ester, 5c. As for **5b**, procedure A using Boc-L-Ser oxetane ester **4c** (5.0 g, 0.0183 mol). The residue was purified by flash chromatography (silica gel, 4:1 CH_2Cl_2:EtOAc) to give a light yellow oil (3.35 g) in 67% yield: $[\alpha]^{20}_{578} = -41.8$ (c = 1.00, EtOAc); TLC (4:1 CH_2Cl_2:EtOAc) R_f = 0.47; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 5.05 (d, J = 7.7 Hz, 1H), 3.90 (s, 6H), 3.85−3.62 (m, 3H), 2.65 (br s, 1H), 1.42 (s, 9H), 0.79 (s, 3H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 165.6, 80.2, 72.5, 68.6, 60.5, 55.3, 39.7, 28.3, 14.5; IR (neat) 3386, 2975, 1694, 1515, 1367, 1164, 1055. Anal. Calcd for $C_{13}H_{23}NO_6$: C, 53.78; H, 8.33; N, 4.83. Found: C, 54.02; H, 8.61; N, 5.02.

1-[*N*-Fluorenyloxycarbonyl-(1*S*)-1-amino-2-oxoethyl]-4-methyl-2,6,7-trioxabicyclo[2.2.2]oxetane, Fmoc-L-serine Aldehyde, 6a. See ref 15a.

1-[*N*-Benzyloxycarbonyl-(1*S*)-1-amino-2-oxoethyl]-4-methyl-2,6,7-trioxabicyclo[2.2.2]oxetane, Cbz-L-Ser(ald) OBO Ester, 6b. Cbz-Ser OBO ester **5b** (9.04 g, 27.86 mmol) was dissolved in freshly distilled CH_2Cl_2 (80 mL) under Ar and cooled to −78 °C in flask 1. Oxalyl chloride (3.89 mL, 44.58 mmol, 1.60 equiv) was added to CH_2Cl_2 (120 mL) in a separate round-bottom flask (flask 2) under Ar and cooled to −78 °C. Dry DMSO (7.03 mL, 91.94 mmol, 3.30 equiv) was added to the oxalyl chloride solution (flask 2), and the mixture was stirred at −78 °C for 15 min. The alcohol solution was transferred slowly by cannula to flask 2 over a period of 45 min and then rinsed with CH_2Cl_2 (50 mL). The resulting cloudy, white mixture was stirred for 1.5 h at −78 °C. DIPEA (24.27 mL, 0.14 mol, 5.0 equiv) was added and the solution stirred for 30 min at −78 °C and 10 min at 0 °C. Ice-cold CH_2Cl_2 (250 mL) was added, and the solution was washed with ice-cold 3% NH_4Cl (3 × 250 mL) and saturated NaCl (1 × 250 mL), dried ($MgSO_4$), and evaporated to dryness. The reaction yielded a slightly yellowish solid in 96% (8.68 g) yield. The enantiomeric purity of Cbz-Ser(ald) OBO ester was determined by chiral shift ^{1}H NMR studies. Cbz-Ser(ald) OBO ester **6b** (10 mg) was dissolved in benzene-d_6. Eu(hfc)$_3$ (100 μL, 50 mg/mL in benzene-d_6) was added to obtain the ^{1}H NMR spectrum at 250 MHz. The purity was observed to be 97−99% ee. **6b**: $[\alpha]^{20}_D = -99.3$ (c = 1.03, EtOAc); TLC (3:1 EtOAc:hexane) R_f = 0.60; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 9.69 (s, 1H), 7.30−7.38 (m, 5H), 5.34 (d, J = 9.2 Hz, 1H), 5.10−5.15 (m, 2H), 4.61 (d, J = 8.9 Hz, 1H), 3.94 (s, 6H), 0.83 (s, 3H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 195.6, 156.1, 136.1, 128.4, 128.1, 107.1, 72.8, 67.2, 63.2, 30.8, 14.2; HRMS (FAB) calcd for (M + H$^+$) $C_{16}H_{20}O_6N$ 322.12906, obsd 322.12854. Anal. Calcd for $C_{16}H_{19}O_6N$: C, 59.75; H, 5.96; N, 4.36. Found: C, 59.41; H, 5.68; N, 4.52.

1-[*N*-*tert*-Butyloxycarbonyl-(1*S*)-1-amino-2-oxoethyl]-4-methyl-2,6,7-trioxabicyclo[2.2.2]oxetane, Boc-L-Ser(ald) OBO Ester, 6c. The Swern oxidation was carried out on Boc-Ser OBO ester **5c** (1.12 g, 3.87 mmol) following the procedure for **6b**. After extraction, the solvent was removed under reduced pressure to yield a light-colored foam (1.10 g) in 99% yield: $[\alpha]^{20}_{578} = -44.8$ (c =1.02, CH_2Cl_2); TLC (solvent A) R_f = 0.58; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 9.64 (s, 1H), 5.07 (br d, J = 7.8 Hz, 1H), 4.48 (d, J = 7.8 Hz, 1H), 3.91 (s, 6H), 1.41 (s, 9H), 0.79 (s, 3H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 195.7, 155.6, 107.3, 80.1, 72.8, 63.3, 30.9, 28.2, 14.3; IR (cast from CH_2Cl_2) 3374, 2973, 1716, 1506, 1166, 1046; HRMS (FAB) calcd for (M + H$^+$) $C_{13}H_{22}NO_6$ 288.1447, found 288.1425. Anal. Calcd for $C_{13}H_{21}NO_6$: C, 53.78; H, 8.33; N, 4.83. Found: C, 53.98; H, 8.56; N, 4.89.

***N*-9-Fluorenylmethylyoxylcarbonyl-L-threonine 3-Methyl-3-(hydroxymethyl)oxetane Ester, Fmoc-Thr Oxetane Ester, 8a.** As for **4a**, procedure A using Fmoc-Thr (5.3 g, 15.5 mmol). The residue was purified by chromatography (3:1 EtOAc/hexane) to give the oxetane ester **8a** (3.58 g, 54%): mp 46−48 °C; $[\alpha]^{20}_D = -18.4$ (c = 1.00, EtOAc); TLC (3:1 EtOAc:hexane) R_f = 0.52, (5:1, CH_2Cl_2:EtOAc) R_f = 0.21; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.79−7.29 (m, 8H), 5.67 (d, J = 8.0 Hz, 1 H), 4.59−4.42 (m, 9H), 4.25 (t, J = 7.0 Hz, 1H), 4.13 (d, J = 11.3 Hz, 1H), 2.86 (br s, 1H), 1.29−1.26 (s+d, 6H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 171.1, 156.7, 143.7, 143.5, 141.1, 127.6, 126.9, 124.9, 119.8, 79.3, 68.6, 67.7, 67.0, 59.4, 47.0, 39.3, 20.7, 19.8; IR (Nujol mull) 3355, 1720, 1457, 1377, 1079, 739; HRMS (FAB) calcd for (M + H$^+$) $C_{24}H_{28}NO_6$ 426.1917, found 426.1920. Anal. Calcd for $C_{24}H_{27}NO_6$: C, 67.75; H, 6.40; N, 3.29. Found: C, 67.88; H, 6.31; N, 3.23.

***N*-Benzyloxycarbonyl-L-threonine 3-Methyl-3-(hydroxymethyl)oxetane Ester, Cbz-Thr Oxetane Ester, 8b.** As for **4a**, procedure A using Cbz-Thr (0.12 mol). A clear yellowish oil was obtained in 98−100% (39.5 g) yield. The product was crystallized from EtOAc as rodlike crystals in 98% (38.9 g) yield: mp = 49−51 °C; $[\alpha]^{20}_D = -18.2$ (c = 1.12, EtOAc); TLC (3:1 EtOAc:hexane) R_f = 0.46; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.32−7.36 (m, 5H), 5.66 (d, J = 8.9 Hz, 1H), 5.14 (s, 2H), 4.40−4.57 (m, 7H), 4.13 (d, J = 11.2, 1H), 2.82 (d, J = 4.9 Hz, 1H), 1.28 (s, 3H), 1.26 (d, J = 8.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 171.2, 156.7, 136.0, 128.5, 128.2, 128.0, 79.4, 68.8, 67.9, 67.1, 59.5, 39.6, 20.7, 19.9. Anal. Calcd for $C_{17}H_{23}O_6N$: C, 60.52; H, 6.87; N, 4.15. Found: C, 60.42; H, 7.04; N, 4.18.

***N*-*tert*-Butyloxycarbonyl-L-threonine 3-Methyl-3-(hydroxymethyl)oxetane Ester, Boc-Thr Oxetane Ester, 8c.** As for **4b**, procedure B using Boc-L-Thr (5.0 g, 0.023 mol). The product was purified by flash chromatography (1:1, EtOAc:hex) to yield the ester as a white solid in 73% yield (4.32 g): mp 69−71 °C; $[\alpha]^{20}_{578} = -24.5$ (c = 1.04, EtOAc); TLC (solvent A) R_f = 0.21; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.40 (br d, J = 9.2 Hz, 1H), 4.54 (d, J = 6.1 Hz, 2H), 4.50 (d, J = 6.1 Hz, 2H), 4.44 (d, J = 6.1 Hz, 1H), 4.42 (d, J = 6.1 Hz, 1H), 4.40 (br d, J = 6.3 Hz, 1H), 4.30 (d, J = 9.2 Hz, 1H), 3.01 (br s, 1H), 1.36 (s, 9H), 1.27, (s, 3H), 1.21 (d, J = 6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 171.6, 155.8, 80.1, 79.5, 68.6, 68.0, 59.0, 39.7, 28.3, 20.8, 20.0; IR (cast in CH_2Cl_2) 3386, 2975, 1694, 1515, 1367, 1164, 1055; HRMS (FAB) calcd for (M + H$^+$) $C_{14}H_{26}NO_6$ 304.1761, found 304.1769. Anal. Calcd for $C_{13}H_{23}NO_6$: C, 53.78; H, 8.33; N, 4.83. Found: C, 53.91; H, 8.52; N, 5.03.

1-[*N*-Fluorenyloxycarbonyl-(1*S*,2*R*)-1-amino-2-hydroxypropyl]-4-methyl-2,6,7-trioxabicyclo[2.2.2]-oxetane, Fmoc-L-Thr OBO Ester, 9a. As for **5b**, procedure A using Fmoc-Thr oxetane ester (3.44 g, 8.09 mmol) in 80 mL of dry CH_2Cl_2 at room temperature. The oily residue was purified by chromatography (5:1 CH_2Cl_2:EtOAc) to provide the product (3.0 g, 87%) as a white foam: mp 184−186 °C; $[\alpha]^{20}_D = -12.8$ (c = 1.01, EtOAc); TLC (5:1 CH_2Cl_2:hexane) R_f = 0.47; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.78−7.28 (m, 8H), 5.36 (br d, J = 10.1 Hz, 1H), 4.43−4.35 (m, 3H), 4.27 (t, J = 7.1 Hz, 1H), 3.95 (s, 6H), 3.76 (d, J = 10.5 Hz, 1H), 2.95 (br s, 1H), 1.13 (d, J = 6.3 Hz, 3H), 0.83 (s, 3H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 156.8, 144.0, 143.7, 141.1, 127.5, 126.8, 125.0, 119.8, 108.6, 72.5, 66.7, 65.0, 57.6, 47.0, 30.5, 18.9, 14.1. IR (Nujol mull) 3518, 3455, 1736, 1509, 1455, 1199, 1051, 740; HRMS (FAB) calcd for (M + H$^+$) $C_{24}H_{28}NO_6$ 426.1916, found 426.1952. Anal. Calcd for $C_{24}H_{27}NO_6$: C, 67.75; H, 6.40; N, 3.29. Found: C, 68.00; H, 6.58; N, 3.28.

1-[*N*-Benzyloxycarbonyl-(1*S*,2*R*)-1-amino-2-hydroxypropyl]-4-methyl-2,6,7-trioxabicyclo[2.2.2]oxetane, Cbz-L-Thr OBO Ester, 9b. As for **5b**, procedure A using Cbz-Thr oxetane ester (36.30 g, 0.11 mol). The reaction yielded a colorless thick oil in 95−99% (34.75 g) yield. Enantiomeric purity of >99% ee was determined by HPLC using a Chiradex chiral column, indicating little or no racemization during coupling of Cbz-Thr and oxetane bromide **2**. The colorless oil was crystallized from EtOAc and hexane to give white flakes in 94% (34.11 g) yield: mp = 117.0−118.0 °C; $[\alpha]^{20}_D = -12.1$ ($c = 1.06$, EtOAc); TLC (3:1 EtOAc:hexane) $R_f = 0.40$; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.27−7.38 (m, 5H), 5.33 (d, $J = 10.3$ Hz, 1H), 5.07−5.20 (m, 2H), 4.36 (m, 1H), 3.93 (s, 6H), 3.75 (m, 1H), 2.88 (s, 1H), 1.12 (d, $J = 6.4$ Hz, 3H), 0.82 (s, 3H); ^{13}C NMR ($CDCl_3$), 63 MHz) δ 156.9, 136.5, 128.4, 127.9, 108.7, 72.7, 66.8, 65.1, 57.9, 30.6, 18.9, 14.3. Anal. Calcd for $C_{17}H_{23}O_6N$: C, 60.52; H, 6.87; N, 4.15. Found: C, 60.29; H, 6.82; N, 3.94.

HPLC Analysis. A solution of Cbz-Thr OBO ester (5 mg/mL) in MeOH was prepared. The solution (5 μL) was injected onto a Hewlett-Packard LiChroCART 250-4 ChiraDex column (particle size 5 μm and pore diameter of 100 Å). The column was operated at flow rate of 0.8 mL/min with 50:50 MeOH and H_2O and detection at 215 nm. The retention times were determined using various solutions on Cbz-DL-Thr OBO ester, with elution time of 16.4 min for the D-isomer and 18.3 min for the L-isomer.

1-[*N*-*tert*-Butyloxycarbonyl-(1*S*,2*R*)-1-amino-2-hydroxypropyl]-4-methyl-2,6,7-trioxabicyclo[2.2.2]-oxetane, Boc-L-Thr OBO Ester, 9c. As for **5b**, procedure A using Boc-L-Thr oxetane ester (4.182 g, 13.79 mmol). The product was purified by flash chromatography (4:1 CH_2Cl_2:EtOAc) to give a white solid (2.84 g) in 68% yield: mp 128−129 °C; $[\alpha]^{20}_{578} = -15.2$ ($c = 1.04$, CH_2Cl_2); TLC (4:1, CH_2Cl_2:EtOAc) $R_f = 0.39$; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 5.06 (br d, $J = 10.4$ Hz, 1H), 4.31 (q, $J = 6.4$ Hz, 1H), 3.89 (s, 6H), 3.63 (d, $J = 10.4$ Hz, 1H), 2.88, (br s, 1H), 1.42 (s, 9H), 1.06, (d, $J = 6.4$ Hz, 3H), 0.7 (s, 3H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 156.3, 108.8, 79.2, 72.6, 65.3, 57.1, 30.5, 28.3, 26.7, 18.9, 14.3; IR (cast from CH_2Cl_2) 3386, 2975, 1715, 1506, 1365, 1169, 1049; HRMS (FAB) calculated for (M + H^+) $C_{14}H_{26}NO_6$ 304.1761, found 304.1732. Anal. Calcd for $C_{14}H_{25}NO_6$: C, 55.43; H, 8.30; N, 4.61. Found: C, 55.63; H, 8.56; N, 4.92.

1-[*N*-*tert*-Butyloxycarbonyl-(1*S*,2*R*)-1-amino-2-hydroxypropyl]-4-methyl-2,6,7-trioxabicyclo[2.2.2]-oxetane, Boc-L-Ser(Me)-OBO Ester, 9c. Grignard addition to Boc-L-Ser(ald) OBO ester **6c** (0.478 g, 1.66 mmol) was carried out using MeMgBr as in the typical procedure. Toluene (20 mL) was used as the solvent. The product was purified by flash chromatography (4:1 CH_2Cl_2:EtOAc) to give a light oil in 0.307 g yield (61%). The diastereometric ratio of 85:15 *threo*:*erythro* was determined using ^{1}H NMR integration of the *threo* β-CH_3 at δ 1.12−1.07 ppm and the *erythro* β-CH_3 at δ 1.21−1.14 ppm in the crude product: TLC (4:1 CH_2Cl_2:EtOAc) $R_f = 0.39$ (*threo*), 0.34 (*erythro*); $[\alpha]^{20}_{578} = -15.4$ ($c = 1.01$, CH_2Cl_2); TLC (4:1 CH_2Cl_2:EtOAc) $R_f = 0.39$; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 5.06 (br d, $J = 10.4$ Hz, 1H), 4.31 (q, $J = 6.4$ Hz, 1H), 3.89 (s, 6H), 3.63 (d, $J = 10.4$ Hz, 1H), 2.88, (br s, 1H), 1.42 (s, 9H), 1.06, (d, $J = 6.4$ Hz, 3H), 0.7 (s, 3H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 171.6, 155.8, 80.1, 79.5, 68.6, 68.0, 59.0, 39.7, 28.3, 20.8, 20.0; IR (cast from CH_2Cl_2) 3386, 2975, 1694, 1515, 1367, 1164, 1055; HRMS (FAB) calcd for (M + H^+) $C_{14}H_{26}NO_6$ 304.1761, found 304.1769. Anal. Calcd for $C_{14}H_{25}NO_6$: C, 53.78; H, 8.33; N, 4.83. Found: C, 54.08; H, 8.66; N, 5.16.

1-[*N*-(9-Fluorenylmethyloxycarbonyl)-(1*S*,2*R*)-1-amino-2-hydroxybutyl]-4-methyl-2,6,7-trioxabicyclo[2.2.2]-octane, Fmoc-(2*S*,3*R*)-β-ethylserine OBO Ester, 10a. Et-MgBr (Aldrich, 3.0 M in Et_2O) was added to crude Fmoc-L-Ser(ald)-OBO ester **6a** (0.426 g, 1.02 mmol) to give 0.272 g (61% yield from **5a**) of **10a** after flash column chromatography. Integration of the carbamate proton signals in the ^{1}H NMR spectrum indicated a 88:12 *threo* (2*S*,3*R*):*erythro* (2*S*,3*S*) ratio. Recrystallization (Et_2O/hexane) produced 0.178 g (40%) of colorless crystals, with a 94:6 *threo*:*erythro* ratio, as determined by ^{1}H NMR spectroscopy. If the addition was done at −78 °C, the yield decreased to 43% for the crude product, with an increased diastereoselectivity (to 93:7 *threo*:*erythro* by NMR analysis of the crude protected derivative). A substantial quantity of aldehyde (37%) was recovered: mp 138−139 °C; $[\alpha]^{25}_D = -11.3$ ($c = 1.13$, EtOAc); TLC (Solvent A) $R_f = 0.46$ (*threo*), 0.39 (*erythro*); ^{1}H NMR ($CDCl_3$, 250 MHz) major isomer = *threo* (94%), minor = *erythro* (6%) δ 7.76−7.25 (m, 8H), 5.05 (d, $J = 10.2$ Hz, 0.06H), 5.37 (d, $J = 10.2$ Hz, 0.94H), 4.65 (d, $J = 6.5$ Hz, 2H), 4.26 (t, $J = 7.1$ Hz, 1H), 4.07 (t, $J = 6.9$ Hz, 1H), 3.94 (s, 6H), 3.87 (t, $J = 10.2$ Hz, 1H), 2.96 (s, 1H), 1.62−1.32 (m, 2H), 0.94 (t, $J = 7.4$ Hz, 3H), 0.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 156.7, 144.4, 143.9, 141.2, 127.5, 126.9, 125.1, 119.8, 108.3, 72.7, 70.7, 66.8, 56.0, 47.2, 30.6, 25.9, 14.2, 10.0; IR (cast from CH_2Cl_2) 1720, 1106, 1050, 1014, 987, 760, 739 cm^{-1}; MS (CI, CH_4) *m*/*z* 440 (MH^+, 100), 422 ($MH^+ - 18$, 78), 395 ($MH^+ - 45$, 32), 381 ($MH^+ - 59$, 84); HRMS (CI, CH_4) calcd for (M + H^+) $C_{25}H_{30}NO_6$ 440.2073, found 440.2075. Anal. Calcd for $C_{25}H_{29}NO_6$: C, 68.32; H, 6.65; N, 3.19. Found: C, 68.19; H, 6.87; N, 3.22.

Deprotection of 10a: (2*S*,3*R*)-β-Ethylserine (β-hydroxynorvaline), 42. Fmoc-L-β-ethylserine-OBO ester **10a** (0.194 g, 0.441 mmol) was deprotected to give 0.0503 g (86%) of product **42** after ion exchange chromatography. ^{1}H NMR integration of the α-CH proton indicated an 80:20 *threo* (2*S*,3*R*):*erythro* (2*S*,3*S*) ratio. Recrystallization (H_2O/acetone) gave 0.0312 g (53%) of colorless crystals, also with a 80:20 *threo* (2*S*,3*R*):*erythro* (2*S*,3*S*) ratio as determined by ^{1}H NMR spectroscopy. Derivatization followed by analysis by HPLC also indicated a 80:20 ratio, with 98.4% ee. Retention times of the *threo* and *erythro* isomers were identical to standards prepared from D,L-β-hydroxynorvaline (Sigma, contained 98:2 *threo*:*erythro* mixture; linear gradient over 45 min to 40:60 buffer:MeOH; diastereomers formed by derivatization, *threo* L-a.a. at 34.0 min, by *threo* D-a.a. at 34.9 min, by *erythro* L-a.a. at 38.9 min, and by *erythro* D−a.a. at 39.9 min): mp 215−216 °C (dec); TLC (solvent C) $R_f = 0.48$; ^{1}H NMR (D_2O, 200 MHz) major isomer = *threo* (80%), minor = *erythro* (20%) δ 3.90 (dt, $J = 4.9$, 8.2 Hz, 1H), 3.75 (d, $J = 3.7$ Hz, 0.2H), 3.57 (d, $J = 4.4$ Hz, 0.8H), 1.63−1.37 (m, 2H), 0.90 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (D_2O, 50.3 MHz) δ 175.8, 174.6, 74.1, 73.6, 62.1, 61.6, 29.3, 27.2, 12.8, 12.2 Anal. Calcd for $C_5H_{11}NO_3$: C, 45.10; H, 8.34; N, 10.52. Found: C, 44.98; H, 8.24; N, 10.39.

1-[*N*-(9-Fluorenylmethyloxycarbonyl)-(1*S*,2*R*)-1-amino-2-hydroxyhexyl]-4-methyl-2,6,7-trioxabicyclo[2.2.2]-octane, Fmoc-(2*S*,3*R*)-β-*n*-butylserine OBO Ester, 12a. *n*-BuMgCl (Aldrich, 2.0 M in Et_2O) was added to crude Fmoc-L-Ser(ald)-OBO ester **6a** (0.627 g, 1.44 mmol) to give 0.377 g (56% yield from **5a**) of **12a** after flash column chromatography. The crude product was treated with $NaBH_4$ before chromatography to reduce unreacted Fmoc-Ser(ald)-OBO ester and simplify purification. Integration of the carbamate proton signals in the ^{1}H NMR spectrum indicated a 82:18 *threo* (2*S*,3*R*):*erythro* (2*S*,3*S*) ratio. Recrystallization (Et_2O/hexane) produced 0.178 g (45%) of colorless crystals, with a 90:10 *threo*:*erythro* ratio, as determined by ^{1}H NMR spectroscopy: mp 130−131 °C; $[\alpha]^{25}_D = -8.7$ ($c = 1.23$, EtOAc); TLC (solvent A) $R_f = 0.50$ (*threo*), 0.52 (*erythro*); ^{1}H NMR ($CDCl_3$, 200 MHz) major isomer = *threo* (90%), minor = *erythro* (10%) δ 7.77−7.25 (m, 8H), 5.39 (d, $J = 10.3$ Hz, 0.9H), 4.42−4.38 (m, 2H), 4.30−4.13 (m, 2H), 3.94 (s, 6H), 3.84 (d, $J = 10.3$ Hz, 1H), 2.95 (s, 0.9H), 1.59−1.31 (br m, 6H), 0.88 (br t, $J = 6.7$ Hz, 3H), 0.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 156.7, 144.1, 143.8, 141.2, 127.5, 126.9, 125.1, 125.1, 119.8, 108.9, 72.7, 69.1, 66.8, 56.4, 47.1, 32.6, 30.5, 27.7, 22.5, 14.2, 13.9; IR (cast from CH_2Cl_2) 1720, 1047, 1016, 759, 737 cm^{-1}; MS (EI, 70 eV) *m*/*z* 467 (M^+, 3), 423 ($M^+ - 44$, 6), 410 ($M^+ - 57$, 9), 381 ($M^+ - 86$, 84); HRMS (EI, 70 eV) calcd for $C_{27}H_{33}O_6N$ 467.2308, found 467.2305 (M^+). Anal. Calcd for $C_{27}H_{33}O_6N$: C, 69.36; H, 7.13; N, 3.00. Found: C, 69.16; H, 7.24; N, 2.99.

Deprotection of 12a: (2*S*,3*R*)-β-*n*-Butylserine, 43. Fmoc-L-β-*n*-butylserine OBO ester **12a** (0.124 g, 0.266 mmol) was deprotected to give 0.0437 g (>100%) of product **43** after ion exchange chromatography. ^{1}H NMR integration of the α-CH proton indicated a 85:15 *threo* (2*S*,3*R*):*erythro* (2*S*,3*S*) ratio.

Recrystallization (H_2O/acetone) gave 0.0116 g (27%) of colorless crystals as a first crop, with a 67:33 *threo* (2*S*,3*R*): *erythro* (2*S*,3*S*) ratio as determined by ^{1}H NMR spectroscopy. A second crop of 0.0115 g (27%) was also obtained with a 95:5 *threo*:*erythro* ratio. Derivatization followed by analysis by HPLC also indicated a 67:33 ratio, with 99.0% ee, and 96:4, with 99.1% ee, for the two crops (linear gradient over 5 min to 65:35 buffer:MeOH, followed by linear gradient to 50:50 buffer:MeOH at 65 min; diastereomers formed by *threo* L-a.a. at 34.8 min, by *threo* D-a.a. at 36.3 min, by *erythro* L-a.a. at 49.5 min, and by *erythro* D-a.a. at 52.1 min): mp 215−216 °C (dec); TLC (solvent C) R_f = 0.73; ^{1}H NMR (D_2O, 200 MHz) major isomer = *threo* (95%), minor = *erythro* (5%) δ 3.92 (dt, J = 8.6, 4.4 Hz, 1H), 3.69 (d, J = 3.7 Hz, 0.05H), 3.49 (d, J = 4.5 Hz, 0.95H), 1.55−1.10 (br m, 6H), 0.76 (t, J = 6.4 Hz, 3H); ^{13}C NMR (D_2O, 50.3 MHz) δ 175.8, 72.4, 62.0, 35.6, 29.8, 24.4, 15.9. Anal. Calcd for $C_7H_{15}NO_3$: C, 52.16; H, 9.40; N, 8.69. Found: C, 51.98; H, 9.31; N, 8.45.

1-[*N*-(9-Fluorenylmethyloxycarbonyl)-(1*S*,2*R*)-1-amino-2-hydroxybut-3-enyl]-4-methyl-2,6,7-trioxabicyclo-[2.2.2]octane, Fmoc-(2*S*,3*R*)-β-vinylserine OBO Ester, 13a. VinylMgBr (Aldrich, 1.0 M in THF) was added to crude Fmoc-L-Ser(ald) OBO ester **6a** (0.440 g, 1.03 mmol) to give 0.152 g (34% yield from **5a**) of **13a** after flash column chromatography. Integration of the carbamate proton signals in the ^{1}H NMR spectrum indicated a 86:14 *threo* (2*S*,3*R*): *erythro* (2*S*,3*S*) ratio. Recrystallization attempts (Et_2O/hexane, EtOAC/hexane) were unsuccessful.: mp 73−82 °C; $[\alpha]^{20}_D$ = −4.6 (c = 0.42, EtOAc); TLC (solvent A) R_f = 0.29 (*threo*), 0.29 (*erythro*); ^{1}H NMR ($CDCl_3$, 200 MHz) major isomer = *threo* (86%), minor = *erythro* (14%) δ 7.78−7.26 (m, 8H), 5.79 (ddd, J = 16.7, 11.0, 5.3 Hz), 5.39 (d, J = 16.7 Hz, 1H), 5.37 (d, J = 11.0 Hz, 1H), 5.18 (d, J = 10.5 Hz, 0.86H), 5.04 (d, J = 9.6 Hz, 0.14H), 4.74 (d, J = 4.7 Hz, 1H), 4.51−4.21 (m, 3H), 4.07−3.92 (m, 1H), 3.97 (s, 6H), 3.12 (s, 1H), 0.84 (s, 3H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 156.6, 144.1, 143.0, 141.2, 136.2, 127.5, 126.9, 125.2, 119.8, 116.2, 108.7, 72.7, 69.9, 66.9, 56.8, 47.2, 30.7, 14.3; IR (cast from CH_2Cl_2) 1716, 1048, 1018, 990, 759, 740 cm^{-1}; MS (CI, CH_4) m/z 438 (MH^+, 90), 420 (MH^+ − 18, 53), 410 (MH^+ − 28, 23), 381 (MH^+ − 57, 100); HRMS (CI, CH_4) calcd for $C_{25}H_{28}NO_6$ 438.1916, found 438.1910 (MH^+). Anal. Calcd for $C_{25}H_{27}NO_6$: C, 68.63; H, 6.22; N, 3.20. Found: C, 68.54; H, 6.34; N, 3.08.

Deprotection of 13a: (2*S*,3*R*)-β-Vinylserine, 44. Fmoc-L-β-vinylserine OBO ester **13a** (0.0808 g, 0.186 mmol) was deprotected to give 0.0205 g (84%) of product **44** after ion exchange chromatography. ^{1}H NMR integration of the β-CH proton indicated a 85:15 *threo* (2*S*,3*R*):*erythro* (2*S*,3*S*) ratio. Recrystallization attempts (H_2O/acetone, H_2O/EtOH) were unsuccessful, as the product kept oiling out. The crude product had an 84:16 *threo* (2*S*,3*R*):*erythro* (2*S*,3*S*) ratio as determined by derivatization followed by analysis by HPLC, with 98.2% ee (linear gradient over 60 min to 50:50 buffer:MeOH; diastereomers formed by derivatization, *threo* L-a.a. at 38.8 min, by *threo* D-a.a. at 40.8 min, by *erythro* L-a.a. at 44.5 min, and by *erythro* D-a.a. at 46.9 min). **44**: TLC (solvent C) R_f =0.46; ^{1}H NMR (D_2O, 250 MHz) major isomer = *threo* (85%), minor = *erythro* (15%): δ 5.82 (ddd, J = 16.8, 10.9, 5.5 Hz, 1H), 5.34 (d, J = 16.8 Hz, 1H), 5.25 (d, J = 10.9 Hz, 1H), 4.58 (br m, 1H), 3.81 (d, J = 4.0 Hz, 0.15H), 3.65 (d, J = 3.8 Hz, 0.85H); ^{13}C NMR (D_2O, 63 MHz) *threo* isomer δ 174.7, 138.1, 135.7, 120.8, 122.0 72.9, 61.7.,61.2.

1-[*N*-(9-Fluorenylmethyloxycarbonyl)-(1*S*,2*R*)-1-aminopent-4-en-2-ol]-4-methyl-2,6,7-trioxabicyclo-[2.2.2]octane, Fmoc-(2*S*,3*R*)-β-allylserine OBO Ester, 14a. AllylMgBr (Aldrich, 1.0 M in Et_2O) was added to crude Fmoc-L-Ser(ald) OBO ester **6a** (0.666 g, 1.51 mmol) to give 0.478 g (70% yield from **5a**) of **15a** after flash column chromatography. The crude product was treated with $NaBH_4$ before chromatography to reduce unreacted Fmoc-Ser(ald) OBO ester and simplify purification. The diastereomer ratio could not be determined by integration of the carbamate proton signals in the ^{1}H NMR spectrum as the *erythro* carbamate proton was hidden under the *threo* and *erythro* terminal alkene protons. However, ^{13}C NMR peak heights indicated a 70:30 *threo* (2*S*,3*R*):*erythro* (2*S*,3*S*) ratio. Recrystallization attempts (Et_2O/hexane, EtOAc/hexane) were unsuccessful: mp 61−67.5 °C; $[\alpha]^{20}_D$ = −10.5 (c = 1.04, EtOAc); TLC (Solvent A) R_f = 0.41, 0.39; ^{1}H NMR ($CDCl_3$, 200 MHz) cannot differentiate *threo*/*erythro* isomers: δ 7.78−7.25 (m, 8H), 5.93−5.73 (m, 1H), 5.36 (d, J = 10.4 Hz, 1H, *threo* N*H*), 5.16−5.06 (m, 2H), 4.44−4.4 (m, 4H), 3.94 (s, 6H), 3.88 (d, J = 10.3 Hz, 1H), 2.96 (s, 1H), 2.34−2.07 (m, 2H), 0.83 (s, 3H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) major isomer = *threo* (70%), minor = *erythro* (30%), *threo* δ 156.6, 144.1, 143.8, 141.2, 135.2, 134.1, 127.5, 126.9, 125.1, 125.0, 119.9, 117.7, 116.9, 108.8, 72.7, 70.9,68.9, 66.8, 55.8, 57.7, 47.2, 57.7, 37.7, 37.4, 30.6, 14.3; IR (cast from CH_2Cl_2) 1720, 1641, 1082, 1047, 1013, 761, 739 cm^{-1}; MS (CI, CH_4) m/z 452 (MH^+, 100), 434 (MH^+ − 18, 67), 409 (MH^+ − 43, 31), 381 (MH^+ − 71, 67); HRMS (CI, CH_4) calcd for $C_{26}H_{30}NO_6$ 452.2073, found 452.2079 (MH^+). Anal. Calcd for $C_{26}H_{29}NO_6$: C, 69.16; H, 6.47; N, 3.10. Found: C, 69.15; H, 6.50; N, 2.96.

Deprotection of 14a: (2*S*,3*R*)-β-Allylserine, 45. Fmoc-L-β-allylserine OBO ester **14a** (0.179 g, 0.385 mmol) was deprotected to give 0.0548 g (98%) of product **45** after ion exchange chromatography. ^{1}H NMR integration of the α-CH proton indicated a 72:28 *threo* (2*S*,3*R*):*erythro* (2*S*,3*S*) ratio. Recrystallization (H_2O/acetone) gave 0.0212 g (38%) of colorless crystals as a first crop, with a 67:33 *threo* (2*S*,3*R*):*erythro* (2*S*,3*S*) ratio as determined by ^{1}H NMR. A second crop of 0.0176 g (32%) was also obtained with a 77:23 *threo*:*erythro* ratio. Derivatization followed by analysis by HPLC also indicated a 68:32 ratio, with 99.4% ee, and 79:21, with 99.0% ee, for the two crops (linear gradient over 1 min to 90:10 buffer:MeOH, followed by linear gradient to 50:50 buffer:MeOH at 55 min; diastereomers formed by *threo* L-a.a. at 42.0 min, by *threo* D-a.a. at 43.7 min, by *erythro* L-a.a. at 49.4 min, and by *erythro* D-a.a. at 51.0 min). **45**: mp 215−217 °C (dec); TLC (solvent C) R_f = 0.61; ^{1}H NMR (D_2O, 200 MHz) major isomer = *threo* (77%), minor = *erythro* (23%): δ 5.74 (ddt, J = 17.1, 10.2, 6.9 Hz, 1H), 5.08 (dd, J = 17.1, 0.7 Hz, 1H), 5.07 (dd, J = 10.1, 0.7 Hz, 1H), 4.04 (dt, J = 4.8, 7.9 Hz, 1H), 3.76 (d, J = 3.6 Hz, 0.23H), 3.58 (d, J = 4.4 Hz, 0.77H), 2.37−2.09 (m, 2H); ^{13}C NMR (D_2O, 63 MHz): δ 174.2, 136.9, 136.4, 121.0, 121.4, 71.9, 61.8, 61.4, 40.7, 38.6. Anal. Calcd for $C_6H_{11}O_3N$: C, 49.65; H, 7.65; N, 9.65. Found: C, 49.44; H, 7.46; N, 9.71.

1-[*N*-(9-Fluorenylmethyloxycarbonyl)-(1*S*,2*R*)-1-amino-2-(3-methoxybenzyl)-2-ethanol]-4-methyl-2,6,7-trioxa-bicyclo[2.2.2]octane, Fmoc-(2*S*,3*R*)-β-anisoleserine OBO Ester, 15a. A 1.9 M solution of *p*-anisylMgBr in Et_2O was prepared from 4-bromoanisole and Mg and was added to a solution of crude Fmoc-L-Ser(ald) OBO ester **6a** (0.636 g, 1.49 mmol) to give 0.548 g (71% yield from **5a**) of **15a** after flash column chromatography, with partial resolution of diastereomers. The crude product was treated with $NaBH_4$ before chromatography to reduce unreacted Fmoc-Ser(ald) OBO ester and simplify purification. ^{1}H NMR integration of the carbamate or methyl ether protons indicated an overall 89:11 *threo* (2*S*,3*R*):*erythro* (2*S*,3*S*) ratio. Recrystallization (Et_2O/hexane) gave 0.375 g (49%) of colorless crystals, with a 97:3 *threo*:*erythro* ratio, as determined by ^{1}H NMR: mp 143.5−144.5 °C; $[\alpha]^{20}_D$ = −37.1 (c = 1.02, EtOAc); TLC (solvent A) R_f = 0.37 (*threo*), 0.28 (*erythro*); ^{1}H NMR ($CDCl_3$, 200 MHz) major isomer = *threo* (97%), minor = *erythro* (3%) δ 7.76−7.24 (m, 10H), 6.79 (d, J = 8.7 Hz, 2H), 5.51 (d, J = 10.4 Hz, 0.97H), 5.32 (br s, 1H), 4.34−4.08 (m, 3H), 4.06 (d, J = 10.4 Hz, 1H), 3.98 (s, 6H), 3.68 (s, 3H), 3.40 (d, J = 1.3 Hz, 1H), 0.83 (s, 1H); ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 158.7, 156.2, 144.0, 141.1, 132.1, 127.4, 126.9, 125.1, 119.8, 113.5, 108.7, 72.7, 70.3, 66.9, 58.5, 55.0, 47.0, 30.6, 14.2; IR (cast from CH_2Cl_2) 1724, 1613, 1515, 1453, 1246, 1195, 1081, 1048, 1024, 989, 760, 739 cm^{-1}; MS (CI, isobutane) m/z 518 (MH^+, 0.2), 500 (MH^+ − 18, 7), 412 (MH^+ − 106, 2), 381 (MH^+ − 137, 100); HRMS (CI, isobutane) calcd for $C_{30}H_{32}NO_7$ 518.2179, found 518.2174 ($M + H^+$). Anal. Calcd for $C_{30}H_{31}NO_7$: C, 69.62; H, 6.05; N, 2.71. Found: C, 69.43; H, 6.20; N, 2.71.

Deprotection of 15a: (2*S*,3*R*)-β-Anisoleserine, 46. Fmoc-β-anisoleserine OBO ester **15a** (0.0855 g, 0.165 mmol) was deprotected to give 0.0351 g (101%) of product **46** after ion

exchange chromatography. ^{1}H NMR integration of the α-CH proton indicated a 92:8 *threo* (2*S*,3*R*):*erythro* (2*S*,3*S*) ratio. Recrystallization (H_2O/acetone) gave 0.0168 g (71%) of colorless crystals with a >99:<1 *threo*:*erythro* ratio. Derivatization followed by analysis by HPLC indicated a 99.8:0.2 ratio, with >95% ee. Only partial separation of the *threo* diastereomers was obtained (2/3 base line separation), and no resolution of the *erythro* isomers (linear gradient over 5 min to 85:15 buffer: MeOH, followed by linear gradient to 70:30 buffer:MeOH at 200 min; diastereomers formed by *threo* L-a.a. at 125.5 min, by *threo* D-−a.a. at 130.0 min, by *erythro* L-a.a. and *erythro* D-a.a. at 182.0 min). **46**: mp 207 °C (dec); TLC (solvent C) R_f = 0.66; ^{1}H NMR (D_2O, 250 MHz) major isomer = *threo* (>99%), minor = *erythro* (<1%), *threo* isomer δ 7.29 (d, *J* = 8.5 Hz, 2H), 6.93 (d, *J* = 8.5 Hz, 2H), 5.11 (d, *J* = 4.7 Hz, 1H), 3.76 (d, *J* = 4.7 Hz, 1H), 3.73 (s, 3H); ^{13}C NMR (D_2O, 63 MHz) δ 174.8, 161.7, 134.5, 130.1, 117.1, 73.8, 63.6, 58.2. Anal. Calcd for $C_{10}H_{13}O_4N$: C, 56.87; H, 6.22; N, 6.63. Found: C, 56.74; H, 6.31; N, 6.60.

1-[*N*-(9-Fluorenylmethyloxycarbonyl)-(1*S*,2*R*)-1-amino-2-cyclohexyl-2-ethanol]-4-methyl-2,6,7-trioxabicyclo-[2.2.2]octane, Fmoc-(2*S*,3*R*)-β-cyclohexylserine OBO Ester, 16a. CyclohexylMgCl (Aldrich, 2.0 M in Et_2O) was added to crude Fmoc-L-Ser(ald) OBO ester **6a** (0.426 g, 1.02 mmol) to give 0.225 g (33% yield from **5a**) of **16a** after flash column chromatography, with partial resolution of the *threo* and *erythro* diastereomers. The crude product was treated with $NaBH_4$ before chromatography to reduce unreacted Fmoc-Ser(ald) OBO ester and simplify purification. Integration of the carbamate proton signals in the ^{1}H NMR spectrum indicated an overall 84:16 *threo* (2*S*,3*R*):*erythro* (2*S*,3*S*) ratio. Recrystallization (Et_2O/hexane) of the pure *threo* fractions produced 0.084 g (12%) of colorless crystals, with a >99.5:<0.5 *threo*:*erythro* ratio, as determined by ^{1}H NMR: mp 160−161.5 °C; $[\alpha]^{20}_D$ = −9.4 (*c* = 1.03, EtOAc); TLC (solvent A) R_f = 0.61 (*threo*), 0.54 (*erythro*); ^{1}H NMR ($CDCl_3$, 200 MHz) major isomer = *threo* (>99.5%), minor = *erythro* (<0.5%) δ 7.78−7.25 (m, 8H), 5.41 (d, *J* = 10.3 Hz, 1H), 4.41−4.24 (m, 3H), 4.04 (d, *J* = 10.3 Hz, 1H), 3.94 (s, 6H), 3.82 (d, *J* = 9.0 Hz, 1H), 3.05 (d, *J* = 1.4 Hz, 1H), 2.06 (br d, *J* = 15.3 Hz, 1H), 1.70 (br t, *J* = 12.0 Hz, 4H), 1.48−0.88 (br m, 6H), 0.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 156.4, 144.1, 143.9, 141.2, 127.5, 126.9, 125.2, 125.1, 119.8, 109.1, 73.4, 72.7, 66.8, 53.8, 47.1, 39.4, 30.5, 29.4, 28.5, 26.3, 25.9, 25.8, 14.2; IR (cast from CH_2Cl_2) 1722, 1048, 1020, 738 cm^{-1}; MS (CI, CH_4) *m*/*z* 494 (MH^+, 38), 476 (MH^+ − 18, 31), 449 (MH^+ − 45, 17), 381 (MH^+ − 113, 100); HRMS (CI, CH_4) calcd for (M + H^+) $C_{29}H_{36}NO_6$ 494.2542, found 494.2537. Anal. Calcd for $C_{29}H_{35}NO_6$: C, 70.57; H, 7.15; N, 2.84. Found: C, 70.46; H, 7.16; N, 2.86.

Deprotection of 16a: (2*S*,3*R*)-β-Cyclohexylserine, 47. Fmoc-L-β-cyclohexylserine OBO ester **16a** (0.0773 g, 0.157 mmol) was deprotected to give 0.0451 g (>100%) of product **47** after ion exchange chromatography. ^{1}H NMR integration of the α-CH proton indicated a >99:<1 *threo* (2*S*,3*R*):*erythro* (2*S*,3*S*) ratio. Recrystallization (H_2O/acetone) gave 0.0162 g (55%) of colorless crystals with a >99:<1 *threo* (2*S*,3*R*):*erythro* (2*S*,3*S*) ratio as determined by ^{1}H NMR. Derivatization followed by analysis by HPLC indicated a 99.7:0.3 ratio. The *threo* D- and L-diastereomers could not be separated (linear gradient over 5 min to 65:35 buffer:MeOH, followed by linear gradient to 50:50 buffer:MeOH at 80 min; diastereomers formed by *threo* L-a.a. and *threo* D-a.a. at 58.6 min, by *erythro* L-a.a. at 70.2 min, and by *erythro* D-a.a. at 72.3 min; the *threo* L-a.a. and D-a.a diastereomers were not resolved even with a linear gradient over 200 min to 50:50 buffer:MeOH; diastereomers formed by *threo* L-a.a. and *threo* D-a.a. at 184.6 min). **47**: mp 216−217 °C (dec); TLC (solvent C) R_f =0.70; ^{1}H NMR (D_2O, 200 MHz) δ major isomer = *threo* (>99%), minor = *erythro* (<1%) δ 3.74 (d, *J* = 3.3 Hz, 1H), 3.69 (br dd, *J* = 8.0, 3.5 Hz, 1H), 1.81 (br d, *J* = 12.9 Hz, 1H), 1.75−0.86 (br m, 10H); ^{13}C NMR (D_2O, 50.3 MHz) δ 176.3, 76.9, 59.0, 42.3, 31.5, 31.0, 28.4, 28.1, 27.9. Anal. Calcd for $C_9H_{17}O_3N$: C, 57.73; H, 9.17; N, 7.48. Found: C, 57.89; H, 9.32; N, 7.28.

1-[*N*-(9-Fluorenylmethyloxycarbonyl)-(1*S*,2*R*)-1-amino-3,3,3-d_3-2-propanol]-4-methyl-2,6,7-trioxabicyclo[2.2.2]-octane, Fmoc-γ-$^2H_3$-L-Thr-OBO Ester, 17a. A 2.0 M solution of CD_3MgI in Et_2O was prepared from CD_3I (MSD Isotopes, >99.5 atom % D) and Mg and was added to a solution of crude Fmoc-L-Ser(ald) OBO ester **6a** (0.364 g, 0.890 mmol) at −78 °C to give 0.172 g (45% yield from **5a**) of **17a** after flash column chromatography and 0.082 g (22%) of recovered aldehyde (racemic). Integration of the carbamate proton signals in the ^{1}H NMR spectrum indicated a 95:5 *threo* (2*S*,3*R*):*erythro* (2*S*,3*S*) ratio. Recrystallization of the protected derivative (EtOAc/hexane) gave the *threo* isomer in 96% de (38% yield): mp 176.5−178.5 °C; $[\alpha]^{20}_D$ = −13.3 (*c* = 0.91, EtOAc); TLC (solvent A) R_f = 0.24 (*threo*), (solvent B) R_f = 0.49; ^{1}H NMR ($CDCl_3$, 250 MHz) major isomer = *threo* (98%), minor = *erythro* (2%) δ 7.76−7.25 (m, 8H), 5.39 (br d, *J* = 10.3 Hz, 0.98H), 5.05 (br d, *J* = 9.8 Hz, 0.02H), 4.46−4.15 (m, 4H), 3.93 (s, 6H), 3.77 (d, *J* = 10.4 Hz, 1H), 2.94 (br s, 1H), 0.80 (s, 3H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 156.9, 144.1, 143.9, 141.2, 127.5, 126.9, 125.1, 119.8, 108.7, 72.7, 66.9, 65.0, 57.7, 47.2, 30.5, 19−17 (weak m, 18.07, *J* = 20 Hz), 14.2; MS (EI, 70 eV) *m*/*z* 428 (M^+, 8), 410 (M^+ − 18, 8), 381 (M^+ − 47, 100); IR (cast from CH_2Cl_2) 1718, 1050, 1022, 761, 739 cm^{-1}; HRMS (EI, 70 eV) calcd for $C_{24}H_{24}D_3NO_6$ 428.2027, found 428.2024 (M^+). Anal. Calcd for $C_{24}H_{24}D_3NO_6$: C, 67.28; H + D, 7.07; N, 3.27. Found: C, 67.00; H + D, 6.89; N, 3.24.

Deprotection of 17a: γ-$^2H_3$-L-(2*S*,3*R*)-Threonine, 48. Fmoc-γ-$^2H_3$-L-Thr-OBO ester **17a** (0.111 g, 0.259 mmol) was deprotected to give 0.030 g (93%) of product **48** after ion exchange chromatography. ^{1}H NMR integration of the α-CH proton indicated a 97:3 *threo* (2*S*,3*R*):*erythro* (2*S*,3*S*) ratio. Recrystallization (H_2O/acetone) gave 0.026 g (80%) of colorless crystals, also with a 97:3 *threo* (2*S*,3*R*):*erythro* (2*S*,3*S*) ratio as determined by ^{1}H NMR. Derivatization followed by analysis by HPLC indicated a 98:2 ratio of labeled L-Thr:L-*allo*-Thr, with 99.1% ee. Retention times were identical to standards prepared from L-Thr (25.3 min), D-Thr (26.3 min), L-*allo*-Thr (30.3 min), and D-*allo*-Thr (31.0 min) (linear gradient over 35 min to 45:55 buffer:MeOH). **48**: mp 227−230 °C (dec); TLC (solvent C) R_f = 0.35; ^{1}H NMR (D_2O, 250 MHz) major isomer = *threo* (97%), minor = *erythro* (3%) δ 4.11 (d, *J* = 4.7 Hz, 1H), 3.71 (d, *J* = 3.5 Hz, 0.03H), 3.45 (d, *J* = 4.8 Hz, 0.97H); ^{13}C NMR (D_2O, 62.7 MHz) δ 175.5, 68.5, 63.1, 21.4−19.7 (very weak m). Anal. Calcd for $C_4H_6D_3O_3N$: C, 39.33; H + D, 9.92; N, 11.47. Found: C, 39.59; N, 11.51.

1-[*N*-*tert*-Butyloxycarbonyl-(1*S*)-1-amino-2-oxopropyl]-4-methyl-2,6,7-trioxabicyclo[2.2.2]oxetane, Boc-L-Thr-(ket) OBO Ester, 18c. The Swern oxidation was performed on Boc-L-Thr OBO ester (0.90 g, 2.97 mmol) as in **6b**, to give Boc-L-Thr(ket) OBO ester **18c** in quantitative yield, 0.885 g (98.9%), as a yellow oil: $[\alpha]^{20}_{578}$ = −107.1 (*c* = 1.51, EtOAc); TLC (solvent A) R_f = 0.58; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 5.37 (br d, *J* = 8.3 Hz, 1H), 4.46 (d, *J* = 8.3 Hz, 1H), 3.89 (s, 6H), 2.28 (s, 3H) 1.39 (s, 9H), 0.79 (s, 3H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 201.6, 156.6, 107.3, 80.1, 72.8, 63.3, 30.9, 29.8, 28.2, 14.3; IR (cast from CH_2Cl_2) 2972, 2883, 1716, 1506, 1362, 1167, 1045; HRMS (FAB) calcd for (M + H^+) $C_{14}H_{24}NO_6$ 302.1604, found 302.1593. Anal. Calcd for $C_{14}H_{23}NO_6$: C, 55.80; H, 7.69; N, 4.64. Found: C, 56.01; H, 7.96; N, 4.86.

Oxidation of Et Grignard Adduct 10a: 1-[*N*-(9-Fluorenylmethyloxycarbonyl)-(1*S*)-1-amino-2-oxobutyl]-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane, Fmoc-L-β-ethylserine(ket) OBO Ester 19a. Fmoc-L-β-ethylserine OBO ester **10a** (0.273 g, 0.622 mmol) was oxidized and purified under standard conditions to give 0.231 g (85%) of colorless solid, a portion of which was recrystallized (Et_2O/hexane): mp 68−71 °C; $[\alpha]^{20}_D$ = −31.8 (*c* = 1.57, EtOAc); TLC (solvent A) R_f = 0.53; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.77−7.26 (m, 8H), 5.74 (d, 1H, *J* = 8.9 Hz), 4.64 (d, 1H, *J* = 8.9 Hz), 4.37−4.4 (m, 3H), 3.93 (s, 6H), 2.87 (dq, 1H, *J* = 18.3, 7.3 Hz,), 2.53 (dq, 1H, *J* = 18.3, 7.2 Hz), 1.07 (t, 3H, *J* = 7.2 Hz), 0.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 205.5, 155.9, 143.9, 143.8, 141.2, 127.5, 127.0, 125.2, 119.8, 106.9, 72.9, 67.2, 62.2, 47.0, 35.7, 30.6, 14.4, 7.4; IR (cast from CH_2Cl_2) 1718, 1081, 1046, 1017, 761, 740 cm^{-1}; MS (EI, 70 eV) *m*/*z* 437 (M^+, 25), 380

($M^+ - 57$, 47); HRMS (EI, 70 eV) calcd for $C_{25}H_{27}NO_6$ 437.1838, found 437.1833 (M^+). Anal. Calcd for $C_{25}H_{27}NO_6$: C, 68.64; H, 6.23; N, 3.20. Found: C, 68.82; H, 6.51; N, 3.07.

1-[*N*-(9-Fluorenylmethyloxycarbonyl)-(1*S*)-1-amino-2-oxohexyl]-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane, Fmoc-L-*β*-butylserine(ket) OBO Ester 21a. Fmoc-L-*β*-*n*-butylserine OBO ester **12a** (0.202 g, 0.432 mmol) was oxidized and purified under standard conditions to give 0.201 g (100%) of colorless solid. Recrystallization (Et_2O/hexane) gave 0.160 g (80%) of product: mp 92−94 °C; $[\alpha]^{20}_D = -54.7$ ($c = 1.63$, EtOAc); TLC (solvent A) R_f =0.66; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.77−7.25 (m, 8H), 5.73 (d, J = 8.9 Hz, 1H), 4.64 (d, J = 9.0 Hz, 1H), 4.37−4.4 (m, 3H), 3.93 (s, 6H), 2.82 (dt, J = 17.5, 7.5 Hz, 1H), 2.55 (dt, J = 17.4, 7.1 Hz, 1H), 1.59 (quint, J = 7.4 Hz, 2H), 1.27 (sext, J = 7.3 Hz, 2H), 0.90 (t, J = 7.2 Hz, 3H), 0.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 205.0, 155.9, 143.9, 143.8, 141.1, 127.5, 126.9, 125.2, 119.8, 106.9, 72.8, 67.1, 62.2, 47.0, 42.1, 30.6, 25.5, 22.1, 14.1, 13.8; IR (cast from CH_2Cl_2) 1722, 1512, 1047, 1022, 1005, 761, 741 cm^{-1}; MS (EI, 70 eV) *m*/*z* 465 (M^+, 6), 421 ($M^+ - 44$, 2), 380 ($M^+ - 85$, 8); HRMS (EI, 70 eV) calcd for $C_{27}H_{31}NO_6$ 465.2152, found 465.2145 (M^+). Anal. Calcd for $C_{27}H_{31}NO_6$: C, 69.66; H, 6.73; N, 3.01. Found: C, 69.70; H, 6.53; N, 3.05.

1-[*N*-(9-Fluorenylmethyloxycarbonyl)-(1*S*)-1-amino-2-oxo-3-butenyl]-4-methyl-2,6,7-trioxabicyclo[2.2.2]-octane, Fmoc-L-*β*-vinylserine(ket) OBO Ester 22a. Fmoc-L-*β*-vinylserine OBO ester **13a** (0.185 g, 0.422 mmol) was oxidized and purified under standard conditions to give 0.075 g (41%) of colorless solid, a portion of which was recrystallized (Et_2O/hexane) to give 0.027 g of product: mp 113−115 °C; $[\alpha]^{20}_D = -36.2$ ($c = 0.83$, EtOAc); TLC (solvent A) $R_f = 0.53$; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.77−7.25 (m, 8H), 6.69 (dd, J = 17.3, 10.2 Hz, 1H), 6.37 (dd, J = 17.3, 1.2 Hz, 1H), 5.81 (d, J = 9.0 Hz, 1H), 5.77 (dd J = 10.2, 1.2 Hz, 1H), 4.88 (d, J = 9.1 Hz, 1H), 4.37−4.4 (m, 3H), 3.92 (s, 6H), 0.79 (s, 3H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 193.7, 155.9, 143.8, 141.2, 134.4, 128.9, 127.5, 127.0, 125.2, 119.8, 107.1, 72.9, 67.2, 61.0, 47.0, 30.7, 14.4; IR (cast from CH_2Cl_2) 1725, 1706, 1612, 1047, 1008, 988, 761, 739 cm^{-1}; MS (CI, CH_4) *m*/*z* 436 (MH^+, 100), 391 ($MH^+ - 45$, 15), 380 ($MH^+ - 56$, 18); HRMS (CI, CH_4) calcd for $C_{25}H_{26}NO_6$ 436.1760, found 436.1754 (MH^+). Anal. Calcd for $C_{25}H_{25}NO_6$: C, 68.96; H, 5.80; N, 3.22. Found: C, 68.72; H, 6.01; N, 3.21.

1-[*N*-(9-Fluorenylmethyloxycarbonyl)-(1*S*)-1-amino-2-oxo-4-pentenyl]-4-methyl-2,6,7-trioxabicyclo[2.2.2]-octane, Fmoc-L-*β*-allylserine(ket) OBO Ester 23a. Fmoc-L-*β*-allylserine OBO ester **14a** (0.426 g, 0.944 mmol) was oxidized and purified under standard conditions to give 0.222 g (52%) of the desired product, 0.072 g (17%) of a product where the alkene has isomerized into conjugation with the ketone, and 0.035 g (8%) of recovered starting alcohol. A portion of product was recrystallized (Et_2O/hexane): mp 55−58 °C; $[\alpha]^{20}_D$ = 55.6 ($c = 1.04$, EtOAc); TLC (solvent A) $R_f = 0.53$; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.77−7.25 (m, 8H), 6.05−5.85 (m, 1H), 5.72 (d, J = 8.9 Hz, 1H), 5.19 (dd, J = 9.6, 1.3 Hz, 1H), 5.14 (dd, J = 17.1, 1.4 Hz, 1H), 4.70 (d, J = 8.9 Hz, 1H), 4.37−4.4 (m, 3H), 3.93 (s, 6H), 3.57 (dd, J = 17.7, 6.6 Hz, 1H), 3.37 (dd, J = 17.6, 7.0 Hz, 1H), 0.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 202.6, 155.9, 143.8, 143.8, 141.1, 130.1, 127.5, 127.0, 125.1, 119.8, 118.8, 106.9, 72.9, 67.2, 62.0, 47.0, 46.8, 30.6, 14.2; IR (cast from CH_2Cl_2) 1721, 1641, 1642, 1047, 1007, 761, 742 cm^{-1}; MS (EI, 70 eV) *m*/*z* 449 (M^+, 45), 405 ($M^+ - 44$, 15), 380 ($M^+ - 69$, 64); HRMS (EI, 70 eV) calcd for $C_{26}H_{27}NO_6$ 449.1838, found 449.1831 (M^+). Anal. Calcd for $C_{26}H_{27}NO_6$: C, 69.48; H, 6.07; N, 3.12. Found: C, 69.57; H, 6.09; N, 3.05.

Isomerized Oxidation Product: 1-[*N*-(9-Fluorenylmethyloxycarbonyl)-(*E*)-(1*S*)-1-amino-2-oxo-4-pentenyl]-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.77−7.26 (m, 8H), 7.01 (dq, J = 15.5, 6.9 Hz, 1H), 6.43 (dd, J = 15.6, 1.5 Hz, 1H), 5.82 (d, J = 9.2 Hz, 1H), 4.83 (d, J = 9.1 Hz, 1H), 4.37−4.4 (m, 3H), 3.92 (s, 6H), 1.92 (dd, J = 6.9, 1.3 Hz, 3H), 0.80 (s, 3H); ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 193.1, 155.9, 144.1, 143.8, 141.1, 130.0, 127.5, 126.9, 126.0, 119.8, 107.2, 72.8, 67.1, 60.7, 47.0, 30.6, 18.4, 14.4.

1-[*N*-(9-Fluorenylmethyloxycarbonyl)-(1*S*)-1-amino-2-(4-methoxybenzyl)-2-oxoethyl]-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane, Fmoc-L-*β*-anisoleserine(ket) OBO Ester 24a. Fmoc-L-*β*-anisoleserine OBO ester **15a** (0.357 g, 0.690 mmol) was oxidized and purified under standard conditions to give 0.288 g (81%) of colorless solid. Recrystallization attempts (Et_2O/hexane, EtOAc/hexane) were unsuccessful: mp 93−96 °C; $[\alpha]^{20}_D = -26.6$ ($c = 0.94$, EtOAc); TLC (solvent A) $R_f = 0.45$; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.07 (d, J = 8.9 Hz, 2H), 7.76−7.25 (m, 8H), 6.93 (d, J = 8.9 Hz, 2H), 6.04 (d, J = 9.5 Hz, 1H), 5.59 (d, J = 9.5 Hz, 1H), 4.36−4.19 (m, 3H), 3.88 (s, 6H), 3.85 (s, 3H), 0.75 (s, 1H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 193.1, 163.7, 155.8, 143.8, 141.1, 131.9, 129.3, 127.5, 126.9, 125.2, 119.8, 113.4, 107.3, 72.8, 67.2, 56.9, 55.3, 47.0, 30.6, 14.1; IR (cast from CH_2Cl_2) 1724, 1681, 1600, 1574, 1512, 1222, 1181, 1049, 1031, 1009, 910, 846, 761, 734 cm^{-1}; MS (EI, 70 eV) *m*/*z* 515 (M^+, 4), 471 ($M^+ - 44$, 1); HRMS (EI, 70 eV) calcd for $C_{30}H_{29}NO_7$ 515.1944, found 515.1940 (M^+). Anal. Calcd for $C_{30}H_{29}NO_7$: C, 69.89; H, 5.68; N, 2.17. Found: C, 69.64; H, 5.69; N, 2.39.

1-[*N*-(9-Fluorenylmethyloxycarbonyl)-(1*S*)-1-amino-2-cyclohexyl-2-oxoethyl]-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane, Fmoc-L-*β*-cyclohexylserine(ket) OBO Ester 25a. Fmoc-L-*β*-cyclohexylserine OBO ester **16a** (0.252 g, 0.511 mmol) was oxidized and purified under standard conditions to give 0.185 g (74%) of colorless solid. Recrystallization (Et_2O/hexane) gave 0.145 g (58%) of product: mp 154.5−155.5 °C; $[\alpha]^{20}_D = -47.3$ ($c = 1.82$, EtOAc); TLC (solvent A) $R_f = 0.68$; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.77−7.25 (m, 8H), 5.75 (d, J = 9.2 Hz, 1H), 4.80 (d, J = 9.3 Hz, 1H), 4.36−4.4 (m, 3H), 3.93 (s, 6H), 2.83 (tt, J = 11.1, 3.0 Hz, 1H), 2.07−1.03 (br m, 10 H), 0.80 (s, 3H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 208.3, 155.7, 143.9, 143.8, 141.1, 127.5, 126.9, 125.2, 119.8, 107.1, 72.9, 67.1, 60.4, 49.9, 47.0, 30.6, 29.2, 26.9, 26.0, 25.7, 25.1, 14.2; IR (cast from CH_2Cl_2) 1720, 1048, 1025, 1005, 987, 760, 739 cm^{-1}; MS (EI, 70 eV) *m*/*z* 491 (M^+, 6), 475 ($M^+ - 16$, 2), 380 ($M^+ - 111$, 3); HRMS (EI, 70 eV) calcd for $C_{29}H_{33}NO_6$ 491.2308, found 491.2305 (M^+). Anal. Calcd for $C_{29}H_{33}NO_6$: C, 70.86; H, 6.78; N, 2.85. Found: C, 71.00; H, 7.00; N, 2.93.

1-[*N*-(9-Fluorenylmethyloxycarbonyl)-(1*S*,2*S*)-1-amino-2-hydroxybutanol]-4-methyl-2,6,7-trioxabicyclo[2.2.2]-octane, Fmoc-(2*S*,3*S*)-*β*-ethylserine OBO Ester, 27a. Ketone **19a** (0.101 g, 0.231 mmol) was reduced with $LiBH_4$ to give 0.079 g of crude product with a 93:7 *erythro*:*threo* ratio. Purification gave 0.044 g (45%) of colorless solid. Recrystallization (EtOAc/hexane) gave 0.037 g (38%) of crystals, with a >99.5:<0.5 *erythro*:*threo* ratio: mp 151.5−152 °C; $[\alpha]^{20}_D$ = −41.0 ($c = 1.28$, EtOAc); TLC (solvent A) $R_f = 0.39$ (*erythro*); ^{1}H NMR ($CDCl_3$, 200 MHz) major isomer = *erythro* (>99.5%), minor = *threo* (<0.5%) δ 7.78−7.25 (m, 8H), 5.05 (d, J = 10.2 Hz, 1H), 4.44−4.21 (m, 3H), 3.93 (s, 6H), 3.88 (dd, J = 10.0, 7.4 Hz, 1H), 3.78−3.64 (m, 1H), 3.46 (s, 1H), 1.72−1.53 (m, 1H), 1.53−1.32 (m, 1H), 0.97 (t, J = 7.4 Hz, 3H), 0.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 156.4, 144.1, 143.8, 141.2, 127.5, 126.9, 125.0, 119.9, 108.9, 72.6, 72.5, 66.7, 57.6, 47.2, 30.5, 26.0, 14.2, 9.7; IR (cast from CH_2Cl_2) 1720, 1045, 1002, 761, 736 cm^{-1}; MS (EI, 70 eV) *m*/*z* 439 (M^+, 3), 410 ($M^+ - 29$, 11), 381 ($M^+ - 58$, 100); HRMS (EI, 70 eV) calcd for $C_{25}H_{29}NO_6$ 439.1995, found 439.1990 (M^+). Anal. Calcd for $C_{25}H_{29}NO_6$: C, 68.32; H, 6.65; N, 3.19. Found: C, 68.50; H, 6.83; N, 3.21.

Deprotection of 27a: (2*S*,3*S*)-*β*-Ethylserine, 49. Fmoc-L-*β*-ethylserine OBO ester **27a** (0.0359 g, 0.082 mmol) was deprotected to give 0.0127 g (>100%) of product **49** after ion exchange chromatography. ^{1}H NMR integration of the α-CH proton indicated a 94:6 *erythro* (2S,3*S*):*threo* (2*S*,3*R*) ratio. Recrystallization (H_2O/acetone) gave 0.0095 g (87%) of colorless crystals, also with a 94:6 *erythro* (2S,3*S*):*threo* (2*S*,3*R*) ratio as determined by ^{1}H NMR. Derivatization followed by analysis by HPLC indicated a 95:5 ratio of *erythro* (2S,3*S*):*threo* (2*S*,3*R*), with 94.0% ee (conditions as for *threo* isomer **10a**). **49**: mp 215−216 °C (dec); TLC (solvent C) $R_f = 0.58$; ^{1}H NMR (D_2O, 200 MHz) major isomer = *erythro* (94%), minor = *threo* (6%) δ 3.88 (dt, J = 3.7, 6.6 Hz, 1H), 3.72 (d, J = 3.7 Hz, 0.94H), 3.53 (d, J = 4.4 Hz, 0.06H), 1.41 (quintet, J = 7.2 Hz, 2H),

0.87 (t, J = 7.4 Hz, 3H); ^{13}C NMR (D_2O, 50.3 MHz) δ 174.3, 74.0, 61.9, 27.3, 12.7.

1-[*N*-(9-Fluorenylmethyloxycarbonyl)-(1*S*,2*S*)-1-amino-2-phenyl-2-hydroxyethyl]-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane, Fmoc-L-(2*S*,3*S*)-phenylserine OBO Ester, 28a. Synthesis of Fmoc-L-(2*S*,3*S*)-phenylserine OBO ester **28a** and its subsequent deprotection to L-(2*S*,3*S*)-phenylserine **50** is outlined in ref 15a.

1-[*N*-(9-Fluorenylmethyloxycarbonyl)-(1*S*,2*S*)-1-amino-2-hydroxyethyl]-4-methyl-2,6,7-trioxabicyclo-[2.2.2]octane, Fmoc-(2*S*,3*S*)-β-*n*-Butylserine OBO Ester, 29a. Ketone **21a** (0.116 g, 0.240 mmol) was reduced to give 0.095 g of crude product with a 93:7 *erythro* (2*S*,3*S*):*threo* (2*S*,3*R*) ratio. Purification gave 0.080 g (71%) of a colorless solid. Recrystallization (EtOAc/hexane) gave 0.057 g (51%) of crystals, with a 97:3 *erythro*:*threo* ratio: mp 161−162 °C; $[\alpha]^{20}_D$ = −42.5 (c = 1.42, EtOAc); TLC (solvent A) R_f = 0.52 (*erythro*); ^{1}H NMR ($CDCl_3$, 200 MHz) major isomer = *erythro* (97%), minor = *threo* (3%) δ 7.78−7.25 (m, 8H), 5.08 (d, J = 9.7 Hz, 1H), 4.43−4.22 (m, 3H), 3.93 (s, 6H), 3.86 (d, J = 9.7 Hz, 1H), 3.89−3.68 (m, 1H), 3.43 (d, J = 3.8 Hz, 1H), 1.75−1.13 (br m, 6H), 0.89 (br t, J = 6.9 Hz, 3H), 0.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 156.4, 144.0, 143.8, 141.2, 127.5, 126.9, 125.0, 119.8, 108.8, 72.6, 71.3, 66.7, 57.9, 47.1, 32.8, 30.5, 27.5, 22.6, 14.2, 14.0; IR (cast from CH_2Cl_2) 1719, 1519, 1046, 1004, 760, 736 cm^{-1}; MS (EI, 70 eV) m/z 467 (M^+, 2), 410 (M^+ − 57, 8), 381 (M^+ − 86,100); HRMS (EI, 70 eV) calcd for $C_{27}H_{33}NO_6$ 467.2308, found 467.2305 (M^+). Anal. Calcd for $C_{27}H_{33}NO_6$: C, 69.36; H, 7.13; N, 3.00. Found: C, 69.15; H, 7.21; N, 3.01.

Deprotection of 29a: (2*S*,3*S*)-β-*n*-Butylserine, 51. Fmoc-L-β-*n*-butylserine OBO ester **29a** (0.0680 g, 0.145 mmol) was deprotected to give 0.0314 g (>100%) of product **51** after ion exchange chromatography. ^{1}H NMR integration of the α-CH proton indicated an 85:15 *erythro* (2S,3S):*threo* (2*S*,3*R*) ratio. Recrystallization (H_2O/acetone) gave 0.0113 g (48%) of colorless crystals as a first crop, with a 93:7 *erythro* (2*S*,3*S*):*threo* (2*S*,3*R*) ratio as determined by ^{1}H NMR spectroscopy. A second crop of 0.0089 g (38%) was also obtained with a 91:9 *threo*:*erythro* ratio. Derivatization followed by analysis by HPLC indicated a 95:5 and 91:9 ratio of *erythro* (2*S*,3*S*):*threo* (2*S*,3*R*), with 99.1% and 99.4% ee for the two crops (conditions as for *threo* isomer **43**). **51**: mp 223−224 °C (dec); TLC (solvent C) R_f = 0.75; ^{1}H NMR (D_2O, 200 MHz) major isomer = *erythro* (93%), minor = *threo* (7%) δ 3.96 (dt, J = 4.4, 3.8 Hz, 1H), 3.69 (d, J = 3.7 Hz, 0.93H), 3.55 (d, J = 4.4 Hz, 0.07H), 1.52−1.10 (m, 6H), 0.75 (t, J = 6.8 Hz, 3H); ^{13}C NMR (D_2O, 50.3 MHz) δ 174.6, 72.3, 62.4, 35.6, 30.3, 24.4, 15.9. Anal. Calcd for $C_7H_{15}O_3N$: C, 52.16; H, 9.40; N, 8.69. Found: C, 51.98; H, 9.31; N, 8.45.

1-[*N*-(9-Fluorenylmethyloxycarbonyl)-(1*S*,2*S*)-1-aminobut-3-en-2-ol]-4-methyl-2,6,7-trioxabicyclo[2.2.2]-octane, Fmoc-(2*S*,3*S*)-β-vinylserine OBO Ester, 30a. Ketone **22a** (0.044 g, 0.100 mmol) was reduced to give 0.048 g of crude product. Purification by flash column chromatography gave 0.034 g (78%) of colorless solid with an 85:15 *erythro* (2*S*,3*S*):*threo* (2*S*,3*R*) ratio, as determined by ^{1}H NMR integration of the terminal alkene protons. A small amount of reduced alkene (0.12 equiv) was also evident in the ^{1}H NMR. Recrystallization (EtOAc/hexane) gave 0.012 g (27%) of crystals, with a 94:6 *erythro*:*threo* ratio: mp 141−153 °C; $[\alpha]^{20}_D$ = −57.0 (c = 1.71, EtOAc); TLC (solvent A) R_f = 0.29. ^{1}H NMR ($CDCl_3$, 200 MHz) major isomer = *erythro* (94%), minor = *threo* (6%) δ 7.78−7.26 (m, 8H), 5.92 (ddd, J = 17.0, 10.6, 6.3 Hz, 1H), 5.42 (s, 0.06H), 5.30 (br d, J = 17.2 Hz, 0.94H), 5.17 (br d J = 10.4 Hz, 1H), 5.04 (d, J = 9.8 Hz, 1H), 4.51−4.21 (m, 4H), 4.03−3.84 (m, 1H), 3.95 (s, 6H), 3.51 (s, 1H), 0.84 (s, 3H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 156.4, 143.9, 143.8, 141.2, 136.9, 127.5, 126.9, 125.0, 119.8, 116.6, 108.6, 72.6, 66.8, 58.1, 47.1, 30.5, 14.2; IR (cast from CH_2Cl_2) 1721, 1646, 1082, 1047, 1006, 761, 741 cm^{-1}; MS (EI, 70 eV) m/z 437 (M^+, 2), 419 (M^+ − 18, 1), 381 (M^+ − 56, 100); HRMS (EI, 70 eV) calcd for $C_{25}H_{27}NO_6$ 437.1838, found 437.1833 (M^+). Anal. Calcd for $C_{25}H_{28}NO_6$: C, 68.63; H, 6.22; N, 3.20. Found: C, 68.85; H, 5.92; N, 3.18.

Deprotection of 30a: (2*S*,3*S*)-β-Vinylserine, 52. Fmoc-L-β-vinylserine OBO ester **30a** (0.0209 g, 0.0482 mmol) was deprotected to give 0.0085 g (>100%) of product **52** after ion exchange chromatography. ^{1}H NMR integration of the α-CH proton indicated a 93:7 *erythro* (2*S*,3*S*):*threo* (2*S*,3*R*) ratio. Recrystallization (H_2O/acetone) gave 0.004 g (60%) of colorless crystals, with a 92:8 *erythro* (2*S*,3*S*):*threo* (2*S*,3*R*) ratio as determined by ^{1}H NMR. Derivatization followed by analysis by HPLC indicated a 98:2 ratio of *erythro* (2*S*,3*S*):*threo* (2*S*,3*R*), with 98.6% ee. **52**: mp 230−240 °C (dec); TLC (solvent C) R_f = 0.44; ^{1}H NMR (D_2O, 250 MHz) major isomer = *erythro* (92%), minor = *threo* (8%) δ 5.72 (ddd, J = 17.0, 10.7, 5.5 Hz, 1H), 5.33 (d, J = 17.2 Hz, 1H), 5.26 (d, J = 10.5 Hz, 1H), 4.61 (dd, J = 5.5, 4.4 Hz, 1H), 3.79 (d, J = 4.1 Hz, 0.92H), 3.71 (d, J = 3.7 Hz, 0.08H); ^{13}C NMR (D_2O, 63 MHz) δ 174.0, 135.7, 121.9, 72.9, 61.8.

1-[*N*-(9-Fluorenylmethyloxycarbonyl)-(1*S*,2*S*)-1-amino-2-hydroxy-4-pentenyl]-4-methyl-2,6,7-trioxabicyclo-[2.2.2]octane, Fmoc-(2*S*,3*S*)-β-allylserine OBO Ester, 31a. Ketone **23a** (0.099 g, 0.220 mmol) was reduced to give 0.083 g of crude product with a 94:6 *erythro* (2*S*,3*S*):*threo* (2*S*,3*R*) ratio, as determined by ^{1}H NMR integration of the carbamate protons (the *erythro* carbamate proton remains hidden under the alkene protons, but the *threo* carbamate proton is distinct, and can be used to quantify minor amounts). Purification gave 0.069 g (69%) of product, and 0.05 g (5%) of the reduced ketone with the alkene isomerized to the 4,5 position. Recrystallization (EtOAc/hexane) gave 0.055 g (55%) of crystals, with a >99.5:<0.5 *erythro*:*threo* ratio: mp 140.5−141.5 °C; $[\alpha]^{20}_D$ = −39.7 (c = 1.52, EtOAc); TLC (solvent A) R_f = 0.39 (*erythro*); ^{1}H NMR ($CDCl_3$, 200 MHz) major isomer = *erythro* (>99.5%), minor = *threo* (<0.5%) δ 7.78−7.25 (m, 8H), 6.01−5.80 (m, 1H), 5.14−5.04 (m, 3H), 4.45−4.21 (m, 3H), 3.93 (s, 6H), 3.98−3.80 (m, 2H), 3.48 (s, 1H), 2.44−2.14 (m, 2H), 0.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 156.4, 144.0, 143.7, 141.2, 135.1, 127.5, 126.9, 125.0, 119.9, 116.8, 108.7, 72.6, 70.9, 66.7, 57.7, 47.2, 37.7, 30.5, 14.2; IR (cast from CH_2Cl_2) 1719, 1640, 1045, 1003, 913, 761, 737 cm^{-1}; MS (EI, 70 eV) m/z 451 (M^+, 4), 381 (M^+ − 70, 94); HRMS (EI, 70 eV) calcd for $C_{26}H_{29}NO_6$ 451.1995, found 451.1988 (M^+). Anal. Calcd for $C_{26}H_{29}NO_6$: C, 69.16; H, 6.47; N, 3.10. Found: C, 69.06; H, 6.61; N, 3.11.

Deprotection of 31a: (2*S*,3*S*)-β-Allylserine, 53. Fmoc-L-β-allylserine OBO ester **31a** (0.0519 g, 0.115 mmol) was deprotected to give 0.0161 g (96%) of product **53** after ion exchange chromatography. ^{1}H NMR integration of the α-CH proton indicated a 90:10 *erythro* (2*S*,3*S*):*threo* (2*S*,3*R*) ratio. Recrystallization (H_2O/acetone) gave 0.0140 g (84%) of colorless crystals with a 91:9 *erythro* (2*S*,3*S*):*threo* (2*S*,3*R*) ratio as determined by ^{1}H NMR spectroscopy. Derivatization followed by analysis by HPLC indicated a 93:7 ratio of *erythro* (2*S*,3*S*):*threo* (2*S*,3*R*), with 98.8% ee. **53**: mp 219−220 °C (dec); TLC (solvent C) R_f = 0.62; ^{1}H NMR (D_2O, 200 MHz) major isomer = *erythro* (91%), minor = *threo* (9%) δ 5.87−5.67 (m, 1H), 5.15−5.03 (m, 2H), 4.61−4.04 (m, 1H), 3.76 (d, J = 3.7 Hz, 0.91H), 3.57 (d, J = 4.5 Hz, 0.09H), 2.29−2.19 (m, 2H); ^{13}C NMR (D_2O, 62.7 MHz): δ 174.2, 136.8, 121.0, 71.8, 61.8, 38.6.

1-[*N*-(9-Fluorenylmethyloxycarbonyl)-(1*S*,2*S*)-1-amino-2-(4-methoxyphenyl)-2-hydroxyethyl]-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane, Fmoc-(2*S*,3*S*)-β-anisoleserine OBO Ester, 32a. Ketone **24a** (0.066 g, 0.128 mmol) was reduced to give 0.070 g of crude product. Purification gave 0.056 g (85%) of colorless solid with a >99:<1 *erythro* (2*S*,3*S*):*threo* (2*S*,3*R*) ratio. Recrystallization (EtOAc/hexane) gave 0.043 g (65%) of crystals, with a >99.5:<0.5 *erythro*:*threo* ratio. **32a**: mp 220−220.5 °C; $[\alpha]^{20}_D$ = −64.1 (c = 1.08, EtOAc); TLC (solvent A) R_f =0.28 (*erythro*); ^{1}H NMR ($CDCl_3$, 200 MHz) major isomer = *erythro* (>99.5%), minor = *threo* (<0.5%) δ 7.75−7.20 (m, 10H), 6.82−6.75 (m, 2H), 4.89−4.67 (m, 2H), 4.39−3.92 (m, 4H), 4.06 (d, J = 1.2 Hz, 1H), 3.98 (s, 6H), 3.59 (s, 3H), 0.85 (s, 1H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 159.1, 155.7, 144.1, 143.7, 141.2, 141.0, 132.8, 128.8, 127.5, 126.9, 126.8, 125.2, 125.0, 119.8, 113.4, 108.7, 73.7, 72.8, 66.9, 58.6, 54.9, 46.9, 30.7, 14.2; IR (cast from CH_2Cl_2) 1723, 1613, 1516, 1246, 1047, 1005, 761, 742 cm^{-1}; MS (CI, isobutane) m/z 518 (MH^+, 2), 500 (MH^+ − 18, 40), 381 (MH^+ − 137, 100); HRMS

(CI, CH_4) calcd for $C_{30}H_{32}NO_7$ 518.2179, found 518.2174 (MH^+). Anal. Calcd for $C_{30}H_{31}NO_7$: C, 69.62; H, 6.05; N, 2.71. Found: C, 69.43; H, 6.20; N, 2.71.

Deprotection of 32a: (2*S*,3*S*)-β-Anisoleserine, 54. Fmoc-L-β-anisoleserine OBO ester **32a** (0.0479 g, 0.0925 mmol) was deprotected to give 0.0222 g (>100%) of product **54** after ion exchange chromatography. ^{1}H NMR integration of the α-CH proton indicated a 98:2 *erythro* (2*S*,3*S*):*threo* (2*S*,3*R*) ratio. Recrystallization (H_2O/acetone) gave 0.0166 g (85%) of colorless crystals with a >99:<1 *erythro* (2*S*,3*S*):*threo* (2*S*,3*R*) ratio. Derivatization followed by analysis by HPLC indicated a 99.1:0.9 ratio of *erythro* (2*S*,3*S*):*threo* (2*S*,3*R*), with undetermined % ee as the *erythro* isomers could not be separated. **54**: mp 165−168 °C (dec); TLC (solvent C) R_f = 0.68; ^{1}H NMR (D_2O, 200 MHz) major isomer = *erythro* (>99%), minor = *threo* (<1%) δ 7.24 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 5.21 (d, *J* = 4.2 Hz, 1H), 3.96 (d, *J* = 4.3 Hz, 1H), 3.74 (s, 3H); ^{13}C NMR (D_2O, 62.7 MHz) δ 173.9, 161.9, 132.2, 130.5, 117.0, 73.5, 63.1, 58.2. Anal. Calcd for $C_{10}H_{13}NO_3$: C, 56.87; H, 6.22; N, 6.63. Found: C, 56.87; H, 6.50; N, 6.43.

1-[*N*-(9-Fluorenylmethyloxycarbonyl)-(1*S*,2*S*)-1-amino-2-cyclohexyl-2-ethanol]-4-methyl-2,6,7-trioxabicyclo-[2.2.2]octane, Fmoc-(2*S*,3*S*)-β-cyclohexylserine OBO ester, 33a. Ketone **25a** (0.096 g, 0.195 mmol) was reduced to give 0.082 g of crude product with a 93:7 *erythro* (2*S*,3*S*):*threo* (2*S*,3*R*) ratio. Purification by flash column chromatography gave 0.066 g (68%) of colorless solid. Recrystallization (EtOAc/hexane) gave 0.023 g (24%) of crystals, with a >95:<5 *erythro*:*threo* ratio. **33a**: mp 82−84 °C; $[\alpha]^{20}_D$ = −43.3 (*c* = 1.70, EtOAc); TLC (solvent A) R_f = 0.54 (*erythro*); ^{1}H NMR ($CDCl_3$, 200 MHz) major isomer = *erythro* (>95%), minor = *threo* (<5%) δ 7.79−7.26 (m, 8H), 5.01(d, *J* = 10.6 Hz, 1H), 4.42−4.24 (m, 3H), 4.02 (dd, *J* = 10.7, 8.2 Hz, 1 H), 3.95 (s, 6H), 3.58−3.44 (m, 2H, on D_2O exchange simplifies to 3.55, dd, *J* = 8.2, 3.3 H), 1.78−1.13 (br m, 11H), 0.83 (s, 3H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 156.1, 144.1, 141.2 127.6, 126.9, 125.0, 119.9, 109.3, 75.2, 72.7, 66.7, 54.9, 47.1, 39.8, 30.5, 30.1, 26.7, 26.4, 26.2, 25.7, 14.2; IR (cast from CH_2Cl_2) 1721, 1045, 1004, 735 cm^{-1}; MS (CI, CH_4) *m*/*z* 494 (MH^+, 19), 449 (MH^+ − 45, 28), 381 (MH^+ − 113, 100); HRMS (CI, CH_4) calcd for $C_{29}H_{36}NO_6$ 494.2542, found 494.2537 (MH^+). Anal. Calcd for $C_{29}H_{35}NO_6$: C, 70.57; H, 7.15; N, 2.84. Found: C, 70.34; H, 7.36; N, 2.86.

Deprotection of 33a: (2*S*,3*S*)-β-Cyclohexylserine, 55. Fmoc-L-β-cyclohexylserine OBO ester **33a** (0.0330 g, 0.067 mmol) was deprotected to give 0.0143 g (>100%) of product **55** after ion exchange chromatography. ^{1}H NMR integration of the α-CH proton indicated a >99:<1 *erythro* (2*S*,3*S*):*threo* (2*S*,3*R*) ratio. Recrystallization (H_2O/acetone) gave 0.0081 g (65%) of colorless crystals with a >99:<1 *erythro* (2*S*,3*S*):*threo* (2*S*,3*R*) ratio as determined by ^{1}H NMR. Derivatization followed by analysis by HPLC indicated a 99.5:0.5 ratio of *erythro* (2*S*,3*S*):*threo* (2*S*,3*R*), with 93.8% ee. **55**: mp 216−217 °C (dec); TLC (solvent C) R_f = 0.75; ^{1}H NMR (D_2O, 200 MHz) major isomer = *erythro* (>99%), minor = *threo* (<1%): δ 3.82 (d, *J* = 3.1 Hz, 1H), 3.52 (dd, *J* = 8.9, 3.1 Hz, 1H), 1.85−1.57 (br m, 6H), 1.25−0.78 (br m, 5H); ^{13}C NMR (D_2O, 50.3 MHz) δ 174.6, 77.7, 59.6, 42.2, 31.6, 28.5, 27.9, 22.8. Anal. Calcd for $C_9H_{17}NO_3$: C, 57.73; H, 9.15; N, 7.48. Found: C, 57.79; H, 9.25; N, 7.59.

1-[*N*-(9-Fluorenylmethyloxycarbonyl)-(1*S*)-1-amino-2-methyl-2-oxopropyl]-4-methyl-2,6,7-trioxabicyclo-[2.2.2]octane, Fmoc-L-β-hydroxyvaline OBO Ester, 34a. MeMgBr (Aldrich, 3.0 M in Et_2O, 3.5 equiv) was added quickly by syringe to a vigorously stirred solution of Fmoc-L-Thr(ket)-OBO ester **18a** (0.186 g, 0.438 mmol, prepared as previously reported[15a]) dissolved in dry Et_2O (20 mL) under N_2. Workup and purification gave 0.135 g (70%) of colorless solid and 0.025 g (13%) of recovered ketone. Recrystallization attempts were unsuccessful. **34a**: mp 67−71 °C; $[\alpha]^{20}_D$ = −26.3 (*c* = 1.22, EtOAc); TLC (solvent A) R_f = 0.28, (solvent B) R_f = 0.56; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.76−7.25 (m, 8H), 5.34 (d, *J* = 10.5 Hz, 1H), 4.47−4.17 (m, 3H), 3.91 (s, 6H), 3.84 (d, *J* = 10.5 Hz, 1H), 3.43 (br s, 1H), 1.34 (s, 3H), 1.21 (s, 3H,), 0.80 (s, 3H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 156.7, 144.1, 143.0, 141.2, 127.5, 126.9, 125.1, 119.8, 109.3, 72.4, 72.3, 66.7, 60.5, 47.2, 30.4, 28.1, 26.7, 14.2; IR (cast from CH_2Cl_2) 1721, 1049, 1022, 1009, 990, 761, 736 cm^{-1}; MS (EI, 70 eV) *m*/*z* 439 (M^+, 1), 424 (M^+ − 15, 19), 395 (M^+ − 4, 2), 381 (M^+ − 58, 100); HRMS (EI, 70 eV) calcd for $C_{25}H_{29}NO_6$ 439.1995, found 439.1986. Anal. Calcd for $C_{25}H_{29}NO_6$: C, 68.32; H, 6.66; N, 3.19. Found: C, 68.13; H, 6.72; N, 3.03.

Deprotection of 34a: L-β-Hydroxyvaline, 56. Fmoc-β-hydroxyvaline OBO ester **34a** (0.140 g, 0.317 mmol) was deprotected to give 0.017 g (>100%) of the product **56** as a white solid. Recrystallization (H_2O/acetone) gave 0.008 g (55%) of colorless crystals. Derivatization followed by analysis by HPLC indicated 99.8% ee (linear gradient over 1 min to 90:10 buffer:MeOH, then linear gradient to 50:50 buffer:MeOH at 55 min; diastereomer formed by L-a.a. at 40.8 min, by D-a.a. at 42.4 min). **56**: mp 197−198 °C (dec) (lit.[14] mp >254 °C, ^{1}H NMR agrees with that reported by Shao and Goodman); TLC (solvent C) R_f = 0.46; ^{1}H NMR (D_2O, 200 MHz) δ 3.52 (s, 1H), 1.37 (s, 3H), 1.15 (s, 3H); ^{13}C NMR (D_2O, 50.3 MHz) δ 174.9, 72.6, 66.2, 30.1, 26.0; MS (ESI) *m*/*z* 134 (MH^+). Anal. Calcd for $C_5H_{11}NO_3$: C, 45.10; H, 8.34; N, 10.52. Found: C, 44.96; H, 8.22; N, 10.36.

Deprotection of 34b: L-β-Hydroxyvaline, 56. Cbz-β-hydroxyvaline OBO ester **34b** (0.250 g, 0.71 mmol) was stirred in TMSI (1.01 mL, 7.11 mmol) at room temperature for 12 h. Et_2O (25 mL) was added and the solution extracted with 0.5 M NaOH (2 × 25 mL). The aqueous fractions were combined, washed with Et_2O (1 × 25 mL), acidified to pH 3 with 1 M HCl, and concentrated to dryness. The crude product was purified by cation exchange column chromatography (Bio-Rad AG 50W-X8 100−200 mesh, H^+ form) to give the product **56** as a white solid in 95% (89 mg) yield. Anal. Calcd for $C_5H_{11}NO_3$: C, 45.10; H, 8.34; N, 10.52. Found: C, 44.93; H, 8.24; N, 10.47.

1-[*N*-(9-Fluorenylmethyloxycarbonyl)-(1*S*,2*R*)-1-amino-2-methyl-3,3,3-*d*$_3$-2-hydroxypropyl]-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane, Fmoc-4,4,4-$^2H_3$-(2*S*,3*R*)-β-Hydroxyvaline OBO Ester, 35a. A 2.0 M solution of CD_3MgI in Et_2O was prepared from CD_3I (MSD Isotopes, >99.5 atom % D) and Mg and was added to a solution of Fmoc-L-Thr(ket) OBO ester **18a** (0.392 g, 0.926 mmol) to give 0.300 g (73%) of **35a** after flash column chromatography and 0.041 g (10%) of recovered ketone. Recrystallization of the protected derivative (Et_2O/hexane) gave 0.238 g, (58%) with a 95:5 ratio of *threo*(2*S*,3*R*):*erythro* (2*S*,3*S*), as determined by integration of the two methyl group signals (assuming no residual signal from labeled methyl group). **35a**: mp 94−96 °C; $[\alpha]^{20}_D$ = −23.9 (*c* = 0.87, EtOAc); TLC (solvent A) R_f = 0.28, (solvent B) R_f = 0.52; ^{1}H NMR ($CDCl_3$, 200 MHz) major isomer = *threo* (95%), minor = *erythro* (5%) δ 7.77−7.26 (m, 8H), 5.36 (d, *J* = 10.4 Hz, 1H), 4.48−4.20 (m, 3H), 3.90 (s, 6H), 3.84 (d, *J* = 10.5 Hz, 1H), 3.42 (s, 1H), 1.33 (s, 2.85H), 1.20 (s, 0.15H), 0.79 (s, 3H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 156.6, 144.1, 143.8, 141.1, 127.4, 126.8, 125.0, 119.8, 109.2, 72.3, 72.1, 66.7, 60.3, 47.1, 30.3, 28.0, 26.6, 27−25 (very weak m, centered at 25.90, *J* = 18.8 Hz), 14.1; IR (cast from CH_2Cl_2) 3527, 3437, 3319, 3059, 2233, 1722, 1450, 1327, 1233, 1046, 1000, 887 cm^{-1}; MS (EI, 70 eV) *m*/*z* 442 (M^+, 2), 427 (M^+ − 15, 13), 424 (M^+ − 18, 12), 398 (M^+ − 44, 5), 381 (M^+ − 61, 100); HRMS (EI, 70 eV) calcd for $C_{25}H_{26}D_3O_6N$ 442.2183, found 442.2170 (M^+). Anal. Calcd for $C_{25}H_{26}D_3O_6N$: C, 67.86; H + D, 7.30; N, 3.17. Found: C, 67.61; H + D, 6.53; N, 3.05.

Deprotection of 35a: 4,4,4-$^2H_3$-(2*S*,3*R*)-β-Hydroxyvaline, 57. Fmoc-4,4,4-$^2H_3$-L-β-hydroxyvaline OBO ester **35a** (0.140 g, 0.317 mmol) was deprotected to give 0.040 g (92%) of the product **57** as a white solid: ^{1}H NMR integration of the methyl protons indicated a 95:5 *threo* (2*S*,3*R*):*erythro* (2*S*,3*S*) ratio. Recrystallization (H_2O/acetone) gave 0.032 g (75%) of colorless crystals, also with a 95:5 *threo* (2*S*,3*R*):*erythro* (2*S*,3*S*) ratio as determined by ^{1}H NMR. Derivatization followed by analysis by HPLC indicated 98.6% ee; there were no obvious differences due to the *threo* and *erythro* isomers, and retention times were identical to the Thr(CH_3) diastereomers (linear gradient over 1 min to 90:10 buffer:MeOH, then linear gradient to 50:50 buffer:MeOH at 55 min; diastereomers formed by

threo and *erythro* L-a.a. at 40.8 min, by *threo* and *erythro* D-a.a. at 42.4 min). **57**: mp 207−209 °C (dec); TLC (solvent C) R_f = 0.45; ^{1}H NMR (D_2O, 250 MHz) major isomer = *threo* (95%), minor = *erythro* (5%) δ 3.49 (s, 1H), 1.34 (s, 0.15H), 1.12 (s, 2.85H); ^{13}C NMR (D_2O, 62.7 MHz) δ 174.8, 72.4, 66.1, 30.8−28.2 (very weak m, *C*D_3), 25.9, MS (ESI) *m*/*z* 137 (MH^+). Anal. Calcd for $C_5H_8D_3NO_3$: C, 44.10; H + D, 10.38; N, 10.29. Found: C, 43.97; H + D, 8.19; N, 10.28.

1-[*N*-*tert*-Butyloxycarbonyl-(1*S*)-1-amino-2-butanol]-4-methyl-2,6,7-trioxabicyclo[2.2.2]oxetane, Boc-L-Thr(Me) OBO Ester, 35c. Addition of MeMgBr to Boc-L-Thr(ket) OBO ester **18a** (0.561 g, 1.86 mmol) as outlined in the typical procedure for Grignard addition. The product was purified by flash chromatography (4:1 CH_2Cl_2:EtOAc) to yield 0.424 g (72%) of a white solid: mp 80−81 °C; $[\alpha]^{20}_{578}$ = −67.0 (*c* = 1.55, EtOAc); TLC (4:1 CH_2Cl_2:EtOAc) R_f = 0.45; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 5.02 (br d, *J* = 10.6 Hz, 1H), 3.89 (s, 6H), 3.71 (d, *J* = 10.6 Hz, 1H), 3.38, (br s, 1H), 1.41 (s, 9H), 1.28 (s, 3H), 1.15 (s, 3H), 0.78 (s, 3H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 156.1, 109.3, 79.1, 72.5, 72.3, 59.8, 30.4, 28.3, 28.1, 26.6, 14.3; IR (neat) 3386, 2975, 1715, 1506, 1365, 1169, 1049; HRMS (FAB) calcd for (M + H^+) $C_{15}H_{28}NO_6$ 318.1917, found 318.1929. Anal. Calcd for $C_{15}H_{27}NO_6$: C, 56.77; H, 8.57; N, 4.41. Found: C, 56.98; H, 8.69; N, 4.73.

1-[*N*-(9-Fluorenylmethyloxycarbonyl)-(1*S*,2*R*)-1-amino-2-hydroxylmethyl-2-methyl]-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane, Fmoc-(2*S*,3*R*)-β-hydroxyisoleucine OBO Ester, 36a. EtMgBr (Aldrich, 3.0M in Et_2O, 3.0 equiv) was added quickly by syringe to a vigorously stirred solution of Fmoc-L-Thr(ket) OBO ester **18a** (0.397 g, 0.938 mmol) dissolved in dry CH_2Cl_2 (10 mL) and diluted with dry Et_2O (60 mL) under N_2. Workup and purification gave 0.305 g of white solid (72%), and 0.061 g (14%) of recovered ketone. ^{1}H NMR integration of the noncoupled methyl protons indicated a 98:2 *threo* (2*S*,3*R*):*erythro* (2*S*,3*S*) ratio. Recrystallization of the protected derivative (Et_2O/hexane) gave 0.233 g (55%) with a 99:1 ratio of *threo* (2*S*,3*R*): *erythro* (2*S*,3*S*), as determined by ^{1}H NMR spectroscopy: mp 71−73 °C; $[\alpha]^{20}_D$ = −19.6 (*c* = 1.09, EtOAc); TLC (solvent A) R_f = 0.38; ^{1}H NMR ($CDCl_3$, 250 MHz) major isomer = *threo* (99%), minor = *erythro* (1%) δ 7.77−7.26 (m, 8H), 5.31 (d, *J* = 10.1 Hz, 1H), 4.47−4.19 (m, 3H), 3.92 (s, 6H), 3.92−3.85 (m, 1H), 3.21 (s, 1H), 1.64−1.45 (m, 2H), 1.31 (s, 2.97H), 1.15 (s, 0.01H), 0.88 (t, *J* = 7.5 Hz, 3H), 0.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 156.6, 144.2, 143.8, 141.7, 127.4, 126.9, 125.1, 125.0, 119.8, 109.5, 74.5, 72.3, 66.7, 58.7, 47.2, 31.9, 30.3, 24.3, 14.2, 8.0; IR (cast from CH_2Cl_2) 1722, 1515, 1046, 1009, 761, 740 cm^{-1}; MS (EI, 70 eV) *m*/*z* 453 (M^+, 2), 438 (M^+ − 15, 14), 424 (M^+ − 29, 55), 409 (M^+ − 44, 6), 381 (M^+ − 72, 100); HRMS (EI, 70 eV) calcd for $C_{26}H_{31}NO_6$ 453.2151, found 453.2141 (M^+). Anal. Calcd for $C_{26}H_{31}NO_6$: C, 68.86; H, 6.90; N, 3.09. Found: C, 68.85; H, 6.97; N, 3.03.

Deprotection of 36a: (2*S*,3*R*)-β-Hydroxyisoleucine, 58. Fmoc-β-hydroxyisoleucine OBO ester **36a** (0.126 g, 0.277 mmol) was deprotected to give the product **58** as a white solid in 0.032 g (77%) yield. ^{1}H NMR integration of the α-CH or noncoupled methyl protons indicated a 97:3 *threo* (2*S*,3*R*): *erythro* (2*S*,3*S*) ratio. Recrystallization (H_2O/acetone) gave 0.010 g (25%) of colorless crystals as a first crop, with a >98.8:<0.2 *threo* (2*S*,3*R*): *erythro* (2*S*,3*S*) ratio as determined by ^{1}H NMR. A second crop of 0.008 g (20%) was also obtained. Derivatization followed by analysis by HPLC indicated a 99.4:0.6 ratio of *threo* (2*S*,3*R*):*erythro* (2*S*,3*S*), with 99.2% ee for the first crop and 99.0:1.0 for the second crop (linear gradient over 5 min to 80:20 buffer:MeOH, then linear gradient to 60:40 buffer:MeOH at 100 min; diastereomers formed by *threo* L-a.a. at 72.2 min, by *threo* D-a.a. at 78.1 min, by *erythro* L-a.a. at 68.2 min, and by *erythro* D-a.a. at 74.7 min). **58**: mp 225−235 °C (dec); TLC (solvent C) R_f = 0.54; ^{1}H NMR (D_2O, 200 MHz) major isomer = *threo* (>99.8%), minor = *erythro* (<0.2%) δ 3.48 (s, 1H), 1.69 (qt, *J* = 7.7 Hz, 1H), 1.53 (qt, *J* = 7.4 Hz, 1H), 1.04 (s, 3H), 0.83 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (D_2O, 50.3 MHz) δ 174.9, 72.9, 65.1, 34.6, 22.7, 9.4. Anal. Calcd for $C_6H_{13}NO_3$: C, 48.97; H, 8.93; N, 9.52. Found: C, 48.80; H, 8.85; N, 9.30.

1-[*N*-*tert*-Butyloxycarbonyl-(1*S*)-1-amino-2-butanol]-4-methyl-2,6,7-trioxabicyclo[2.2.2]oxetane, Boc-L-Thr(Et) OBO Ester, 36c. Addition of EtMgBr to Boc-L-Thr(ket) OBO ester **18c** (0.388 g, 1.29 mmol) as outlined in the typical procedure. The product was purified by flash chromatography (4:1 CH_2Cl_2:EtOAc) to yield 0.320 g (75%) of a white crystalline product. The diastereometric ratio of >95:<5 *threo*:*erythro* was determined using ^{1}H NMR integration of the threo α-CH at δ 1.23 ppm and the *erythro* α-CH at δ 1.19 ppm. **36c**: mp 87−88 °C; $[\alpha]^{20}_{578}$ = −31.8 (*c* = 1.06, EtOAc); TLC (4:1 CH_2Cl_2: EtOAc) R_f = 0.55; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 5.01 (br d, *J* = 10.3 Hz, 1H), 3.87 (s, 6H), 3.75 (d, *J* = 10.3 Hz, 1H), 3.18, (br s, 1H), 1.47 (q, *J* = 7.5 Hz, 2H), 1.41 (s, 9H), 1.23, (s, 3H), 0.84 (t, *J* = 7.5 Hz, 3H) 0.77 (s, 3H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 156.1, 109.6, 79.1, 74.7, 72.3, 58.3, 31.7, 30.4, 28.4, 24.3, 14.3, 8.0; IR (neat) 3380, 2975, 1715, 1505, 1362, 1169, 1051; HRMS (FAB) calcd for (M + H^+) $C_{16}H_{30}NO_6$ 332.2073, found 332.2061. Anal. Calcd for $C_{16}H_{29}NO_6$: C, 57.98; H, 8.85; N, 4.22. Found: C, 58.13; H, 9.02; N, 4.38.

Addition of Anisole MgBr to Fmoc-L-Thr(ket) OBO Ester 18a: 1-[*N*-(9-Fluorenylmethyloxycarbonyl)-(1*S*,2*R*)-1-amino-2-hydroxy-2-(*p*-methoxyphenyl)-2-propyl]-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane, Fmoc-(1*S*,2*R*)-β-anisolethreonine OBO Ester, 37a. A 2.3 M solution of *p*-anisylMgBr in Et_2O was prepared from 4-bromoanisole and Mg, and 5.0 equiv was added to a solution of Fmoc-L-Thr(ket) OBO ester **18a** (0.381 g, 0.901 mmol) dissolved in dry CH_2Cl_2 (2 mL) and diluted with dry Et_2O (60 mL) under N_2. Workup and purification gave 0.276 g of white solid (58%). ^{1}H NMR integration of either of the noncoupled methyl protons indicated a 98:2 *threo* (2*S*,3*R*):*erythro* (2*S*,3*S*) ratio. Recrystallization of the protected derivative (Et_2O/hexane) gave 0.233 g, (55%) with a 98:2 ratio of *threo* (2*S*,3*R*):*erythro* (2*S*,3*S*), as determined by ^{1}H NMR. **37a**: mp 155−156 °C; $[\alpha]^{20}_D$ = −45.1 (*c* = 1.70, EtOAc); TLC (solvent A) R_f = 0.37; ^{1}H NMR ($CDCl_3$, 200 MHz) major isomer = *threo* (98%), minor = *erythro* (2%) δ 7.77−7.21 (m, 10H), 6.82−6.75 (m, 2H), 5.33 (d, *J* = 10.2 Hz, 1H), 4.39−4.13 (m, 1H), 4.21 (d, *J* = 10.2 Hz, 1H), 4.13−4.01 (m, 2H), 3.99 (s, 1H), 3.93 (s, 6H), 3.73 (s, 0.06H), 3.63 (s, 2.94H), 1.66 (s, 2.94H), 1.50 (s, 0.06H), 0.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 158.0, 156.1, 144.1, 143.9, 141.2, 141.1, 137.9, 127.4, 126.9, 125.8, 125.3, 125.1, 119.7, 113.2, 109.6, 75.8, 72.5, 66.8, 60.3, 55.0, 47.0, 30.5, 29.5, 14.2; IR (cast from CH_2Cl_2) 1724, 1611, 1512, 1248, 1042, 1020, 760, 735 cm^{-1}; MS (CI, isobutane): *m*/*z* 514 (MH^+ − H_2O, 11), 381 (MH^+ − 151, 100); HRMS (CI, CH_4) calcd for $C_{31}H_{32}NO_7$ 530.2179, found 530.2190. Anal. Calcd for $C_{31}H_{33}NO_7$: C, 70.04; H, 6.27; N, 2.64. Found: C, 69.82; H, 6.41; N, 2.59.

Deprotection of 37a: (2*S*,3*R*)-β-Anisolethreonine, 59. Fmoc-β-anisolethreonine OBO ester **37a** (0.188 g, 0.354 mmol) was deprotected to give 0.064 g (79%) of a white solid **59**. ^{1}H NMR integration of the noncoupled methyl protons indicated a 96:4 *threo* (2*S*,3*R*):*erythro* (2*S*,3*S*) ratio. Recrystallization (H_2O/acetone) gave 0.016 g (20%) of colorless crystals as a first crop, with a >99:<1 *threo* (2*S*,3*R*):*erythro* (2*S*,3*S*) ratio as determined by ^{1}H NMR. A second crop of 0.20 g (25%) was also obtained, with a >99:<1 *threo* (2*S*,3*R*):*erythro* (2*S*,3*S*) ratio as determined by ^{1}H NMR. Derivatization followed by analysis by HPLC indicated a 98.2:1.8 ratio of *threo* (2*S*,3*R*): *erythro* (2*S*,3*S*), but enantiomeric purity could not be determined as the D,L-isomers were not resolved (linear gradient over 60 min to 20:80 buffer:MeOH; detection at 338 nm; diastereomers formed by *threo* D,L-a.a. at 39.3 min and by *erythro* D,L-a.a. at 36.5 min). **59**: mp 135−138 °C (dec); TLC (solvent C) R_f = 0.69; ^{1}H NMR (D_2O, 200 MHz) major isomer = *threo* (>99%), minor = *erythro* (<1%): δ 7.41−7.35 (m, 2H), 6.98−6.92 (m, 2H), 3.79 (s, 1H), 3.75 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (D_2O, 50.3 MHz) δ 174.4, 161.2, 138.7, 129.6, 116.9, 75.7, 66.2, 58.2, 28.4. Anal. Calcd for $C_{11}H_{15}O_4N$: C, 58.66; H, 6.73; N, 6.22. Found: C, 58.88; H, 7.06; N, 5.82.

1-[*N*-(9-Fluorenylmethyloxycarbonyl)-(1*S*,2*S*)-1-amino-2-hydroxybutyl-2-methyl]-4-methyl-2,6,7-trioxabicyclo-[2.2.2]octane, Fmoc-(2*S*,3*S*)-β-hydroxyisoleucine OBO Ester, 38a. A 2.0 M solution of MeMgI in Et_2O was prepared from MeI and Mg, and 4.0 equiv was added to a solution of

Fmoc-L-Ser(CO-Et) OBO ester **19a** (0.035 g, 0.079 mmol, prepared as previously reported[15a]) in dry Et_2O (4 mL), resulting in 0.012 g (33%) of **38a** after flash column chromatography and 0.007 g (20%) of recovered ketone. ^{1}H NMR integration of the noncoupled methyl protons indicated a >95:<5 *erythro* (2*S*,3*S*):*threo* (2*S*,3*R*) ratio. Recrystallization of the protected derivative (Et_2O/hexane) gave 0.0080 g (22%) with a 98:2 ratio of *erythro* (2*S*,3*S*):*threo* (2*S*,3*R*), as determined by ^{1}H NMR spectroscopy. **38a**: mp 88.5−91 °C; $[\alpha]^{20}_D = -23.3$ ($c = 0.92$, EtOAc); TLC (solvent A) $R_f = 0.38$; ^{1}H NMR ($CDCl_3$, 200 MHz) major isomer = *erythro* (98%), minor = *threo* (2%) δ 7.78−7.26 (m, 8H), 5.27 (d, $J = 10.6$ Hz, 1H), 4.46−4.21 (m, 3H), 3.92 (s, 6H), 3.93−3.87 (m, 1H), 3.41 (s, 1H), 1.66 (q, $J = 7.5$ Hz, 2H), 1.31 (s, 0.06H), 1.15 (s, 2.94H), 0.94 (t, $J = 7.4$ Hz, 3H), 0.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 156.6, 144.2, 143.9, 141.2, 127.5, 126.9, 125.1, 125.1, 119.9, 109.6, 74.6, 72.4, 66.7, 58.8, 47.2, 33.0, 30.4, 23.3, 14.2, 8.1; IR (cast from CH_2Cl_2) 1723, 1046, 1002, 760, 736 cm^{-1}; MS (EI, 70 eV) *m*/*z* 453 (M^+, 1), 438 ($M^+ - 15$, 7), 424 ($M^+ - 29$, 30), 409 ($M^+ - 44$, 2), 381 ($M^+ - 72$, 100); HRMS (EI, 70 eV) calcd for $C_{26}H_{31}O_6N$ 453.2151, found 453.2141. Anal. Calcd for $C_{26}H_{31}NO_6$: C, 68.86; H, 6.90; N, 3.09. Found: C, 68.61; H, 7.00; N, 2.89.

Deprotection of 38a: (2*S*,3*S*)-*β*-Hydroxyisoleucine, 60. Fmoc-*β*-hydroxyisoleucine OBO ester **38a** (0.0048 g, 0.011 mmol) was deprotected to give 0.0030 g (>100%) of a white solid **60**. ^{1}H NMR integration of the noncoupled methyl protons appeared to indicate a 88:12 *erythro* (2*S*,3*S*):*threo* (2*S*,3*R*) ratio. The lower diastereomeric purity observed compared to the protected starting material is likely due to use of recovered filtrate material from the recrystallization of the protected product. Recrystallization (H_2O/acetone) was unsuccessful due to the small quantities of product obtained. Derivatization followed by analysis by HPLC indicated a 92:8 ratio of *erythro* (2*S*,3*S*):*threo* (2*S*,3*R*), with 83.8% ee. **60**: TLC (solvent C) $R_f = 0.53$; ^{1}H NMR (D_2O, 200 MHz) major isomer = *erythro* (88%), minor = *threo* (12%) δ 3.54 (s, 0.88H), 3.51 (s, 0.12H), 1.6−1.3 (m, 2H), 1.26 (s, 2.64H), 1.07 (s, 0.36H), 0.83 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (D_2O, 50.3 MHz) δ 174.9, 74.9, 65.7, 31.9, 25.8, 9.7. Anal. Calcd for $C_6H_{13}NO_3$: C, 48.97; H, 8.90; N, 9.52. Found: C, 45.03; H, 9.01; N, 9.60.

1-[*N*-(9-Fluorenylmethyloxycarbonyl)-(1*S*,2*S*)-1-amino-2-hydroxy-2-(4-methoxyphenyl)-2-propyl]-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane, Fmoc-(1*S*,2*S*)-*β*-anisolethreonine OBO Ester, 39a. A 2.0 M solution of MeMgI in Et_2O was prepared from MeI and Mg, and 4.0 equiv was added to a solution of Fmoc-L-Ser(CO-anisole) OBO ester **24a** (0.052 g, 0.10 mmol) in dry Et_2O (4 mL), resulting in 0.022 g (41%) of **39a** after flash column chromatography and 0.021 g (29%) of recovered ketone. ^{1}H NMR integration of the noncoupled methyl protons indicated a 92:8 *erythro* (2*S*,3*S*):*threo* (2*S*,3*R*) ratio. Recrystallization of the protected derivative (Et_2O/hexane) gave 0.0073 g (14%) with a 96:4 ratio of *erythro* (2*S*,3*S*):*threo* (2*S*,3*R*), as determined by ^{1}H NMR spectroscopy. **39a**: mp 219−220 °C; $[\alpha]^{20}_D = -35.8$ ($c = 0.78$, EtOAc); TLC (solvent A) $R_f = 0.34$; ^{1}H NMR ($CDCl_3$, 250 MHz) major isomer = *erythro* (96%), minor = *threo* (4%) δ 7.77−7.26 (m, 10H), 6.80 (d, $J = 8.8$ Hz, 2H), 5.35 (d, $J = 10.5$ Hz, 1H), 4.43−4.14 (m, 3H), 4.19 (s, 1H), 3.94−3.70 (m, 1H), 3.76 (s, 6H), 3.73 (s, 3H), 1.66 (s, 0.12H), 1.50 (s, 2.88H), 0.74 (s, 3H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 158.0, 156.4, 144.0, 141.2, 138.3, 127.5, 126.9, 126.4, 125.1, 119.9, 112.7, 109.3, 75.8, 72.4, 66.9, 60.8, 55.1, 47.2, 30.3, 27.2, 14.1; IR (cast from CH_2Cl_2) 1719, 1610, 1513, 1453, 1248, 1182, 1083, 1043, 761, 739 cm^{-1}; MS (CI, isobutane): *m*/*z* 514 ($MH^+ - H_2O$, 9), 381 ($MH^+ - 151$, 100); HRMS (CI, CH_4) calcd for $C_{31}H_{32}NO_6$ 514.2229, found 514.2222 ($MH^+ - H_2O$).

Deprotection of 39a: (2*S*,3*S*)-*β*-Hydroxyanisolethreonine, 61. Fmoc-*β*-hydroxyanisolethreonine OBO ester **39a** (0.0058 g, 0.011 mmol) was deprotected to give 0.0053 g (>100%) of white solid **61**. ^{1}H NMR integration of the noncoupled methyl protons indicated a 85:15 *erythro* (2*S*,3*S*):*threo* (2*S*,3*R*) ratio. Recrystallization (H_2O/acetone) was unsuccessful due to the small quantities of product obtained. Derivatization followed by analysis by HPLC indicated an 87:13 ratio of *erythro* (2*S*,3*S*):*threo* (2*S*,3*R*), with undetermined % ee. **61**: TLC (solvent C) $R_f = 0.60$; ^{1}H NMR (D_2O, 200 MHz) major isomer = *erythro* δ 7.41−7.30 (m, 2H), 6.99−6.90 (m, 2H), 3.74 (s, 3H), 3.73 (s, 1H), 1.81 (s, 3H); ^{13}C NMR (D_2O, 50.3 MHz) δ 174.5, 164.3, 136.0, 130.0, 129.6, 117.0, 116.7, 75.7, 66.7, 58.2, 34.6. Anal. Calcd for $C_{11}H_{12}NO_4$: C, 59.45; H, 5.44; N, 6.30. Found: C, 59.61; H, 5.55; N, 6.51.

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