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Practical Enantioselective Synthesis of β-Substituted-β-amino Esters

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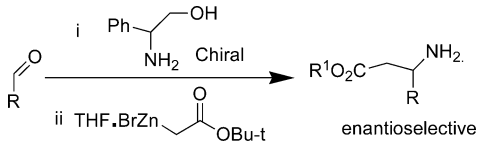
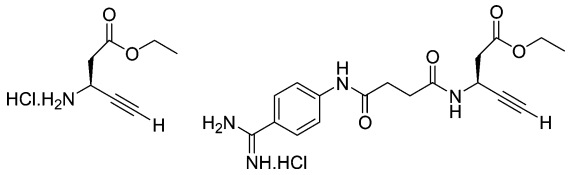
Received January 27, 2005



A practical, large-scale synthesis of a β-amino ester **1** was developed. A chiral imine derived from (*S*)-phenylglycinol and 3-trimethylsilylpropanal was coupled with the Reformatsky reagent **3** with high diastereoselectivity (de > 98%) to give (*SS*)-**4a** as the major isomer. The amino alcohol residue of the coupling product **4** was oxidatively cleaved with sodium periodate in the presence of methylamine. An unusual selective oxidative cleavage of the (*SS*)-isomer was observed and the imine **6** was obtained with ee > 99% while the (*RS*)-**4b** isomer was not cleaved. Reaction with *p*-toluenesulfonic acid monohydrate allowed for the hydrolysis of the imine and the isolation of the amine as its salt. The title compound **1** was then obtained by transesterification, desilylation, and hydrochloride salt formation in a one-pot process. The method was successfully applied toward the synthesis of a wide variety of β-amino esters.

Introduction

The development of enantioselective syntheses of β-amino acids is of constant interest in organic chemistry[1] due to the importance of this subunit in biologically active compounds. Our interest in this field stemmed from the need of an efficient scaleable synthesis of the alkyne derivative **1**, a key intermediate in the preparation of Xemilofiban, a platelet aggregation inhibitor.[2]



1 Xemilofiban

Early routes to **1** involved the synthesis of a racemic precursor followed by either formation of a Mandelate ester and chromatographic separation[2,3] or a resolution with Mandelic acid.[4] However, the inefficient resolution associated largely with the difficulty of recycling the undesired enantiomer made the method expensive and tedious for a manufacturing synthesis of **1**. Alternatively, **1** could be prepared also by transformation of aspartic acid[5] or by an enzymatic resolution method.[6] Our strategy

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10.1021/jo050177h CCC: $30.25
Published on Web 06/03/2005

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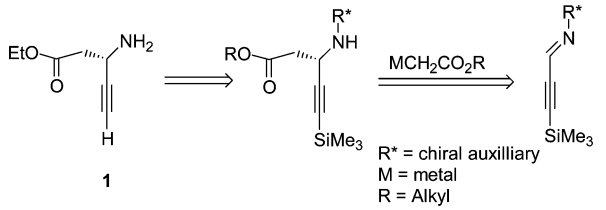
SCHEME 1



involved the diastereoselective 1,2 addition of an organometallic reagent to a chiral imine as shown in Scheme 1.

The 1,2-addition of organometallic reagents to chiral imine for the preparation of enantioenriched amines has received considerable attention.[7] While this methodology has been mostly used to generate chiral amines, it has also been used in the preparation β-amino esters.[8] To our knowledge, only a few examples of alkynyl β-amino ester preparation have been reported.[8f−h] Similarly, there are few examples of the application of this methodology to prepare chiral propargylic amines.[9] Among the methods of interest for the synthesis of β-amino acids, the addition of Reformatsky-type reagents to chiral imines or oxazolidines derived from phenylglycinol[8a−d] or to chiral sulfonyl imines[1d,10] is very attractive due to the high stereoselectivity often observed. Drawbacks of these methodologies are that the methods described usually involve conditions or reagents generally not suitable for large-scale synthesis or are incompatible with the alkyne functionality. Herein, we report the development of a practical and scalable synthesis using the Reformatsky reaction methodology and its generalization to a wide variety of β-amino esters.

Results and Discussion

The imine **2a** was prepared from phenylglycinol and 3-trimethylsilyl-2-propynal in THF in the presence of $MgSO_4$ or in toluene followed by the azeotropic removal of water by distillation. The imine was isolated by precipitation with heptane. It is interesting to note that the imine in solution presented variable syn/anti ratios of isomers in equilibrium with a mixture of oxazolidines isomers depending on the nature of the solvent used for NMR. In a slightly acidic solvent such as $CDCl_3$, the syn/anti ratio was 2/1 with up to 20% of oxazolidine isomers detectable. The anti form is increased in a nonacidic solvent like THF or in polar solvents such as NMP. The anti/syn ratios were 4/1 at 20 °C in THF-d_8 or 94/6 at 20 °C (96/4 at −10 °C) in NMP-d_9. Only traces of oxazolidines were then observed. This type of solvent-dependent equilibrium is typical for aryl-imines derived from amino alcohols.[11] Noteworthy is that the imines of 3-trimethylsilylpropynal and (S)-valine methyl ester[12] or α-methylbenzylamine[13] were reported as a mixture of anti and syn isomers. The imine **2b** derived from α-methylbenzylamine was prepared and used as a reference to compare with the imine **2a**. As described in the literature[13] the imine **2b** was obtained as a mixture of isomers (anti/syn, 3/2 in $CDCl_3$) and the major isomer was confirmed as an anti isomer via a nOe study (see the Experimental Section), ^{1}H NMR, and ^{13}C NMR.[14] The conformation of the major isomer in **2a** was assumed to be anti based on this study.

SCHEME 2

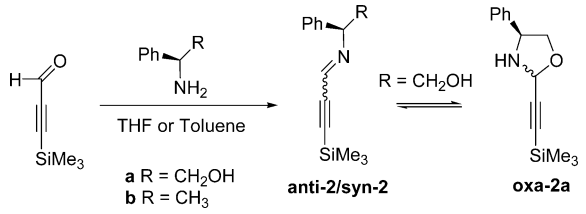


TABLE 1. Ratio of Isomer *anti*-2/*syn*-2/oxa-2a in Solution

entry	R	^{1}H NMR solvent/*T*	*anti*-**2**/*syn*-**2**	oxa-**2a** (%)
1	CH_2OH	$CDCl_3$/25 °C	2/1	20
2		THF-d_8/25 °C	4/1	traces
3		NMP-d_9/25 °C	94/6	traces
4		NMP-d_9/−10 °C	96/4	traces
6	CH_3	$CDCl_3$	3/2	NA[a]

[a] NA: not applicable.

To study the preparation of **4a** from imine **2a**, the reagent of choice appeared to us to be the Reformatsky reagent **3** ($BrZnCH_2CO_2tBu$·THF), as it was reported to be a reasonably stable isolable well-characterize solid as a dimer form.[15] While this reagent was easily prepared on a gram scale and was well characterized, a multikilogram preparation had not been described. We reinvestigated this synthesis to optimize the preparation and isolation conditions. Activation of zinc was performed in situ in THF with dibromoethane at reflux temperature[16a] or with trimethylsilyl chloride[16b] at 22 °C. The reagent was then formed at 50 °C by the controlled addition of *tert*-butyl bromoacetate to a stirred suspension of the activated zinc. Such conditions led to higher yield and adequate exothermic control of the reaction upon

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SCHEME 3

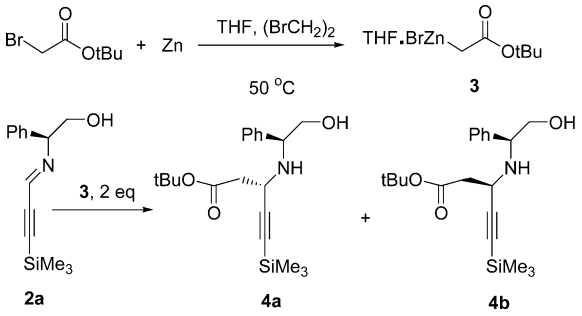


TABLE 2. Selectivity of the Coupling

entry	solvents	conditions	T (°C)	t (h)	% de
1	THF	A[a]	20	5	60−80
2	DMF	A	−5	1	96
3	DMF/THF 20%	A	0	1	80
4	DMF/THF 40%	A	0	1	70
5	DMSO	A	10	1	97
6	DMSO/THF 20%	A	0	1	79
7	NMP	A	−10	1	95
8	NMP	B[b]	−10	1	95 to 98[c]
8	NMP/THF 25%	A	−10	0.5	80[d]
9	DMAc	B	20	7	70
10	1,4-dioxane	A	20	20	90

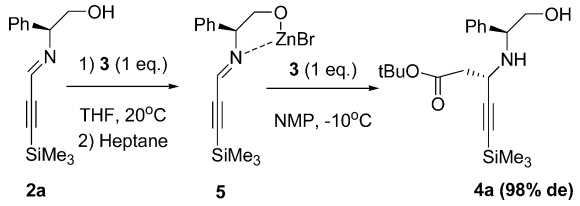
[a] Condition A: a solution of imine **2a** (1 equiv) was added to a solution of **3** (2 equiv) at the given temperature. Reaction were quenched with a solution of NH_4Cl and HCl. [b] Condition B: solid **3** (2 equiv) was added to the solution of imine **2a** at the given temperature. Reactions were quenched with a solution of NH_4Cl and HCl. [c] Yield for **4a**-*SS* isomer isolated by chromatography on silica gel was 84%. [d] Yield determined by GC quantitation with an external standard of 90%.

scale-up. Compound **3** was then isolated as a solid after precipitation from the reaction mixture upon cooling. The solid reagent could be stored at −20 °C and was found to be stable at that temperature for at least 6 months. Alternatively, THF was removed under reduced pressure or by decantation and replaced with the coupling reaction solvent (NMP, DMF, or DMSO) and use directly in solution. The solution of the reagent was found to be less stable and could only be stored for several hours at subzero temperatures.

Coupling reactions were performed initially in THF with excess of the solid Reformatsky reagent **3**. Results showed that the reaction proceeded with medium to low selectivity, long reaction times (over 5 h at 22 °C), and incomplete conversion (Table 2, entry 1) to give a mixture of diastereoisomers **4a/4b**.

Polar solvents were then screened in an attempt to increase the solubility of the reagent and to enhance the rate and the selectivity of the reaction. When the reaction was performed in polar aprotic solvents such as DMF, DMSO, or NMP, the reaction was found to proceed in a dose controlled manner with a higher diastereoselectivity. Surprisingly when the reaction was performed in a mixture of those polar solvents with THF, the selectivity dropped significantly. DMF was found to react readily with the Reformatsky reagent while NMP reacted only slowly at room temperature and insignificantly at low temperatures (below 0 °C).[17] Elimination to form an ene-yne byproduct was observed to a great extent in DMSO due to the higher operating temperature associated with this solvent.[18] NMP, therefore, became the solvent of

SCHEME 4

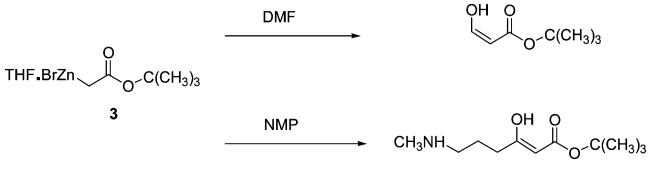


choice for this reaction. Finally, optimal conditions were identified when the reagent was added to the imine **2a** in NMP at −10 °C as shown in Scheme 4. Diastereoselectivity of 95−98% was then achieved.

The selectivity in this type of reaction is often explained by the formation of an organometallic chelate giving a conformationally rigid structure and allowing for the addition of the organometallic reagent on the less hindered face.[7] We were able to isolate such an intermediate by taking advantage of the poor reactivity in THF. Thus after reaction of 1 equiv of reagent **3** and imine **2a** in THF, no reaction was observed and it was possible to isolate the chelate **5** after precipitation with heptane. IR spectra of compound **5** showed a clear difference from the imine **2a** with a shift of the imine band from 1709 to 1720 cm^{-1} and a disappearance of the OH band. Broad peaks characterized ^1H NMR of **5** in THF-d_8 although ^1H NMR in NMP-d_9 or DMF-d_7 showed similar spectra to the imine **2a**. Reaction of this isolated chelate with an additional equivalent of reagent **3** in NMP provided compounds **4a/4b** with selectivity comparable to previous reactions starting from imine **2a** and isolated reagent **3** in NMP.

As stated above, the reaction performed in THF did not proceeded with the addition of 1 equiv of reagent **3** and proceeded slowly upon the addition of another equivalent of **3** with low selectivity (Figure 1). In contrast, when the reaction was performed in NMP, after the addition of 1 equiv of reagent, the reaction was 50% complete with high diastereoselectivity and was complete after the addition of the second equivalent of **3** (Figure 2). Mixing the sequence as shown in Scheme 4 (i.e. adding the first equivalent of **3** in THF and the second equivalent of **3** in NMP) gave comparable selectivity. This suggests that the intermediate was the same in either solvent. One equivalent of reagent **3** was necessary to consume the hydroxyl proton in both cases to yield the intermediate **5**. This had greater reactivity in NMP and reacted spontaneously with a second equivalent of the reagent **3**. The origin of the difference in selectivity and reactivity when the reaction is performed in a polar solvent like NMP vs THF may be speculated. One explanation is the

(17) The Reformatsky reagent was found to react with DMF and NMP as shown below. This side reaction is, however, avoided in NMP at temperatures below 0 °C.



(18) This was also observed in the reaction of zinc enolate with imine: Van Maanen, H. L.; Johan, H. K.; Jastrzebski, J. T. B. H.; van Koten, G. *Recl. Trav. Chim. Pays-Bas* **1994**, *113*, 567.

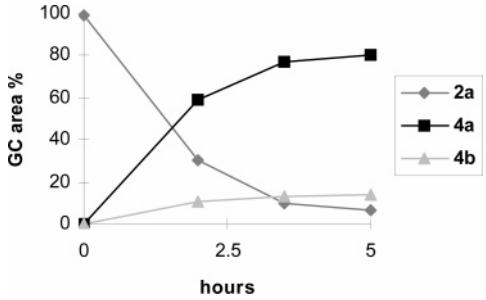


FIGURE 1. Formation of **4a/4b** in THF. Imine **2a** (1 equiv) and reagent **3** (2 equiv) were mixed together in THF.

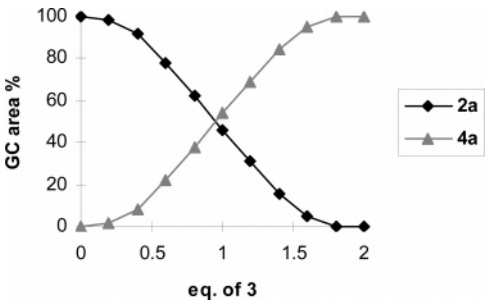
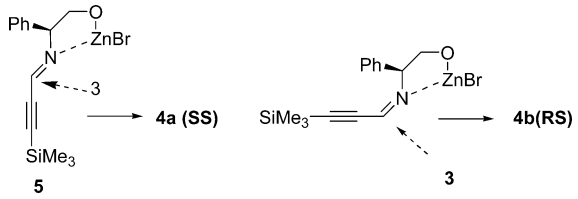


FIGURE 2. Formation of **4a** in NMP. Reagent **3** (2 equiv) was added in portions at −10 °C to imine **2a** (1 equiv).

preponderance of the anti conformer in NMP (Table 1). The syn conformation of the imine would lead to the (*SR*)-**4b** isomer (minor) assuming a rigid structure for the chelate, whereas the anti isomer would lead to the major isomer (*SS*)-**4a**. Higher selectivity should therefore be observed in NMP, where mostly the anti form of the imine **2a** was observed. Another probable factor is the change in the reagent structure, from a dimeric form in THF to a monomeric form in a polar aprotic solvent, as proposed in the literature.[15b] This could explain the increased reactivity observed in such solvents as the monomeric species has been demonstrated by calculation to be the likely reactive species for a simple Reformatsky coupling.[19]



The stereochemistry of the new asymmetric center was determined by comparison of the final compound **1** with material prepared by transformation of aspartic acid.[5] The SS selectivity is in good agreement with similar transformations of chiral imines by an organometallic reagent.[7]

The effect of the chiral auxiliary was briefly studied. When the coupling was performed with imine **2b** derived from methylbenzylamine, poor selectivity reactivity with the reagent **3** in THF or NMP was observed. This result

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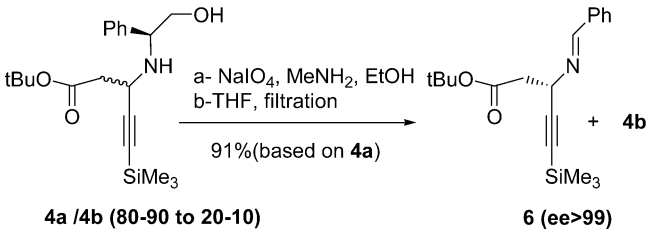
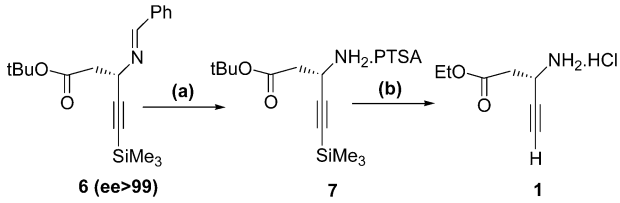
SCHEME 5



SCHEME 6[a]



[a] Reagents and conditions: (a) PTSA (1 equiv), THF, heptane, (94%); (b) (1) PTSA, ethanol, reflux, (2) $NaHCO_3$, MTBE, (3) NaOEt, ethanol, rt, 1.5 h, (4) precipitation with HCl, (5) recrystallization ACN, MTBE (77.7% overall yield).

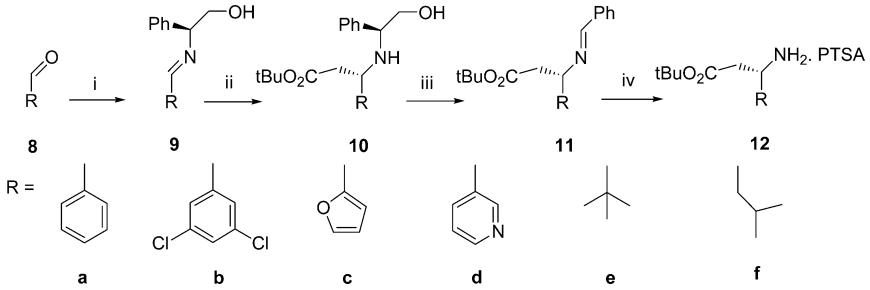
supports the idea that an imino-alcohol residue was critical for the formation of a chelate in order to obtain good selectivity and good reactivity.

The presence of the alcohol residue offers the advantage of a removal of the auxiliary by oxidative cleavage. The presence of the alkynyl group precludes hydrogenolysis as a cleavage method. Oxidative cleavage protocols described in the literature usually involve the use of lead tetraacetate in dichloromethane or methanol. This reagent due to its toxicity and the need to dispose of the lead containing waste stream is generally avoided in a pharmaceutical manufacturing setting. There are few reports of the oxidative cleavage of amino-alcohol with periodic acid[20] or sodium periodate,[11] usually with low yield for the latter.

The oxidative cleavage with periodate and periodic acid was studied with a mixture of**4a/4b**. Periodic acid gave typically a very complicated reaction mixture in our hands, so our attention focused on the use of sodium periodate. As previously described in the literature when using periodic acid,[20] we quickly identified the need for using a formaldehyde scavenger such as methylamine to avoid the formation of an oxazolidine as a major byproduct (reaction of the amino alcohol residue in **4a/4b** with benzaldehyde, the byproduct of the cleavage). As shown in Scheme 5, the reaction was performed by reacting a mixture of isomers **4a/4b** (80−90/20−10) with sodium periodate in the presence of methylamine in ethanol/water. To our surprise we found that the major isomer (*SR*)-**4a** reacted preferentially under the reaction conditions and the minor isomer (*RR*)-**4b** was left intact (or partially consumed) in solution. The oxidative cleavage proceeded therefore as a kinetic resolution. The imine **6** and the sodium iodate salts cocrystallized as the reaction proceeded and the product was isolated as a mixture of inorganic salts and **6** and the unreacted diastereoisomer **4b** was washed out in the mother liquor. The imine **6** was then separated from the salts by dissolution in THF and removal of the salts by filtration. Imine **6** was

(20) Chang, Z.-Y.; Coates, R. M. *J. Org. Chem.* **1990**, *55*, 3475.

SCHEME 7[a]



[a] Reagents and conditions: (i) (*S*)-phenylglycinol, $MgSO_4$, toluene; (ii) **3** (2 equiv), NMP/THF, −5 °C (**9a** to **9d**) or DMSO, rt (**9e** and **9f**); (iii) $NaIO_4$, MeOH, $MeNH_2$ for **10a** to **10d** and $Pb(OAc)_4$ for **10e** and **10f**, MeOH; (iv) pTSA, EA.

TABLE 3.

entry	R	9	10	12[a]
1	a	88.9%[b]	not isolated	63%
2	b	Not isolated	not isolated	49%
3	c	91.4%[b]	70.5% (isolated)	55%
4	d	93.3%[b]	not isolated	65%
5	e	not isolated	not isolated	43%
6	f	not isolated	85%*	NA

[a] Overall isolated yield from imines **9** (3 steps) or aldehyde **8**. [b] Isolated from heptane slurry.

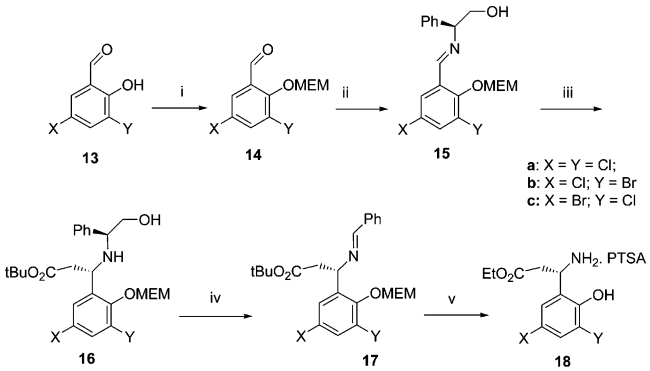
obtained with ee > 99% and a yield of 91% based on the major isomer **4a**.

The imine was hydrolyzed in the presence of *p*-toluenesulfonic acid (PTSA) monohydrate and the amine **7** was isolated as the PTSA salt by precipitation from THF/heptane. Thus mixing a solution of **6** in THF with PTSA (1 equiv) followed by addition of heptane led quickly to the precipitation of **7**, which was isolated by filtration in quantitative yield. Compound **1** was then obtained by successive treatment of **7** with an excess of PTSA in EtOH, neutralization followed by reaction with sodium ethoxide in ethanol, and precipitation of **1** with HCl and recrystallization from acetonitrile. This succession of transformations was performed without isolation and achieves sequentially the transesterification and the desilylation followed by formation and isolation of the hydrochloride salt as shown in Scheme 6. The title compound **1** was obtained in 77.7% yield.

With that background in hand, the preparations of several β-amino acids were demonstrated and are summarized in Scheme 7 and in Table 3. ^1H NMR of the products of the Reformatsky coupling **10** determined the diastereoselectivities of the syntheses. The stereochemistry of the final products was assigned by similarity with the alkynyl derivative.

The imines **9a**−**f** were easily prepared from the corresponding aryl, heterocyclic, and alkyl aldehydes **8a**−**f** by reaction with (*S*)-phenylglycinol in toluene in the presence of $MgSO_4$. The coupling of aryl imines **9a** and **9b** or heterocyclic imines **9c** and **9d** with **3** to the corresponding adducts **10a**−**d** proceeded with high yields and high diastereoselectivities in NMP/THF at −5 °C (no diastereoisomers were detected by ^1H NMR). Interestingly, while in the case of the alkynyl derivative a mixture of diastereoisomers was obtained when using a solution of reagent **3** in NMP/THF, in the aromatic derivative, no loss of selectivity was observed. The β-amino esters **12a**−**d** were then prepared with sodium

SCHEME 8[a]



[a] Reagents and conditions: (i) K_2CO_3, DMF, MEMCl; (ii) (*S*)-phenylglycinol, $MgSO_4$, toluene; (iii) **3** (2 equiv), NMP/THF, −5 °C; (iv) $Pb(OAc)_4$·MeOH; (v) (1) pTSA, EtOH, (2) THF/heptane precipitation.

periodate and methylamine in ethanol followed by formation of the corresponding pTSA salt with *p*-toluenesulfonic acid monohydrate.

The transformation of alkyl imines **9e** and **9f** to their corresponding β-amino esters proved to be more delicate. The corresponding imines were found to be less reactive than previously encountered for unsaturated derivative. Higher temperature (room temperature vs −5 °C), longer reaction time (over 20 h), and an excess of reagent **3** were required. DMSO was chosen as preferred solvent as to avoid reaction of NMP with **3**.[17] Thus, using DMSO as solvent, in both cases studied, the selectivity of the coupling was very high. In addition, the sodium periodate procedure did not perform efficiently for the oxidative cleavage in the case of the *tert*-butyl derivative and was not attempted in the case of **10f**. Lead tetraacetate in MeOH was used successfully replacing sodium periodate in the preparation of **12e**. It could be noted that in the case of the alkyl derivatives, hydrogenolysis could be used rather than the oxidative method.

After demonstrating the generality of the Reformatsky coupling method with aryl, alkynyl, and alkyl derivatives, our attention focuses on the preparation of 3-amino-3-(3,5-dihalo-2-hydroxyphenyl)propionic acid ethyl ester **18** as shown in Scheme 8**.** Our interest in that material stemmed from a need of multigram to kilogram quantities of that type of β-amino acid for the development of novel API acting as $\alpha V\beta_3$ integrin inhibitors.[21]

(21) Holzemann, G. *IDrugs* **2001**, *4*, 72.

TABLE 4.

X, Y	14	18[a]
a	89%	49%
b	88%	45%, >99% ee[b]
c	95%	33%, >99% ee[b]

[a] Overall yield from **14**. [b] Determined by Chiral LC.

The obvious starting materials were commercially available 3,5-dihalosalicyladehydes. Initially the imine derived from 3,5-dichlorosalicyladehyde and phenylglycinol was prepared and tested. However, as expected, reaction of that imine with reagent **3** failed to give any product.

The MEM group was chosen as the phenol-protecting group of choice throughout the syntheses based on the potential ease of removal under acidic condition.[22] The MEM derivative **14a**−**c** of 3,5-dihalosalicylaldehydes **13a**−**c** were easily prepared with MEMCl and K_2CO_3 in DMF. The use of K_2CO_3 instead of NaH typically used for this kind of protection allowed us to have an easily scalable process. The imines **15a**−**c** were prepared following the typical procedure from (*S*)-phenylglycinol. Addition of 2 equiv of Reformatsky reagent **3** to imine **15** in NMP at −5 °C led to the coupling product with high diastereoselectivity to give the corresponding products **16a**−**c**. The oxidative cleavage of the amino-alcohol residue in the coupled products **16a**−**c** with the standard sodium periodate procedure, while giving the desired product,[23] proved to be more difficult than previously encounter to carry through the final β-amino acids. Lead acetate in methanol was, however, used successfully to afford accordingly the corresponding imines **17a**−**c**.

Last, having to prepare the ethyl ester, a one-step process was devised to allow the MEM deprotection, the imine hydrolysis, and the transesterification and the crystallization of the final product to occur simultaneously. These transformations were achieved by refluxing the crude imines isolated from the oxidative cleavage in ethanol in the presence of *p*-toluenesulfonic acid monohydrate. The resulting deprotected ethyl esters were then precipitated out of solution and isolated as pTSA salts **18a**−**c** with high purity and high ee (Table 4). As for the examples **12a**−**e** described above, the β-amino esters **18a**−**c** were prepared in high overall yields and high chiral purity without isolation and purification of intermediates.

The process for the preparation of **18b** was further optimized for pilot plant scale-up and was reported in a separate paper.[24]

Conclusions

We have demonstrated a highly stereoselective and scalable method to prepare the β-alkynyl-β-amino acid ester **1**. An unusual stereodifferentiation during an oxidative cleavage of a mixture of diastereoisomers was observed. We also demonstrated that the method is fairly general for the preparation of a wide range of β-amino esters **12** and **18**. The method was easily applied to various derivatives without excessive optimization and changes in the process with good overall yield. The β-amino esters **12** and **18** were obtained with high purity and high ee from the corresponding aldehyde without purification of the intermediates.

Experimental Section

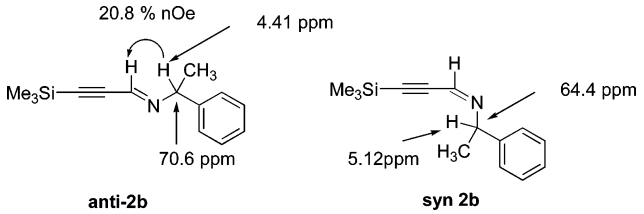
3-(Trimethylsilyl)-2-propynal was obtained by custom synthesis neat or as a solution in MTBE in 96% purity. The other reagents were obtained from commercial sources and used without purification. The solvents MTBE, EA, toluene, THF, and ethanol 2B (denatured with 5% toluene) were used as technical grade without purification. NMP (HPLC grade) was purchased and used without further drying. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer. DSC (Differential Scan Calorimetry) was run in a closed pan from room temperature to 300 °C (at 10 °C/min). GCs were obtained with use of a HP1 column 10 m × 0.53 mm i.d. 2.65 μm film (detector temperature 260 °C; injector temperature 240 °C, FID detection; 50 °C, 5 min hold time; ramp to 250 °C at 15 °C/min, hold 10 min). Chiral LC's were obtained on a chiracel OF column with a mobile phase of hexane/*n*-butanol (99/1) at a flow rate of 1.0 mL/min and UV detection at 210 nm. Reactions were performed under an atmosphere of dry nitrogen unless otherwise stated.

(α*S*)-[[3-(Trimethylsilyl)-2-propynylidene]amino]benzeneethanol (2a). To a slurry of l-phenylglycinol (10.00 g, 72.9 mmol) in toluene (55 mL), at ambient temperature, was added 1.05 equiv of 3-(trimethylsilyl)-2-propynal (9.66 g, 76.5 mmol) at such a rate as to keep the temperature below 30 °C. The mixture was stirred at ambient temperature for 1 h. The water was azeotropically removed with toluene under reduced pressure to a final weight of 28.2 g (1.5 × the expected yield). At room temperature and with stirring heptane (75 mL) was added and the mixture was cooled to −10 °C for 8 h. Filtration of the solids by suction followed by a heptane rinse of the cake and air-drying produced the solid imine **2a** in 80% yield (15.00 g) in 4:1 ratio of anti to syn isomers (as determined by ^{1}H NMR in THF-d_8) or 94/6 ratio of anti to syn isomer (as determined by ^{1}H NMR in NMP-d_9). Mp 78−80 °C; ^{1}H NMR (THF-d_8) anti-isomer, δ 0.20 (s, 9H), 3.61 (t, J = 6.3 Hz, 1H), 3.95 (t, J = 6.3 Hz, 1H), 4.18 (t, J = 6.3 Hz, 1H), 7.17 (tt, J = 7.3 and 1.4 Hz, 1H), 7.25 (complex t, J = 7.3 Hz, 2H), 7.35 (complex d, J = 7.3 Hz, 2H), 7.57 (s, 1H); ^{1}H NMR (THF-d_8) syn-isomer, δ 0.22 (s, 9H), 3.63−3.76 (complex band, 3H), 5.01 (m, 1H), 7.16 (tt, J = 7.3 and 1.4 Hz, 1H), 7.23 (complex t, J = 7.3 Hz, 2H), 7.33 (complex d, J = 7.3 Hz, 2H), 7.56 (d, 1H); ^{1}H NMR (NMP-d_9) anti-isomer, δ 0.20 (s, 9H), 3.56−3.69 (m, 2H), 4.33 (dd, 1H), 5.15 (broad, 1H), 7.23−7.28 (m, 1H), 7.31−7.40 (m, 4H), 7.72 (s, 1H); ^{1}H NMR (NMP-d_9) syn-isomer, δ 0.22 (s, 9H), 7.67 (s, 1H), 5.0−5.1 (m, 1H), other signals are overlapped by the anti-isomer; ^{13}C NMR (THF-d_8) anti-isomer, δ −0.3, 67.9, 79.3, 96.5, 103.5, 127.9, 128.2, 129, 141.9, 145.4; ^{13}C NMR (THF-d_8) syn-isomer, δ −0.4, 68.6, 73.2, 98.2, 103.6, 127.7, 128.6, 128.9, 142.4, 143.3: IR 1610, 2370, 2340, 3390, 3610 cm^{-1}. Anal. Calcd for C_{14} H_{19}NOSi: C, 68.52; H, 7.80; N, 5.71. Found: C, 68.59; H, 7.52; N, 5.71.

(*R*)-α-Methyl-*N*-[3-(trimethylsilyl)-2-propylidene]benzenemethanamine (2b). To a solution of (*R*)-methylbenzylamine (1.28 mL, 10.0 mmol) in toluene (8 mL), at ambient temperature, was added 3-(trimethylsilyl)-2-propynal (1.27 g, 10 mmol) at such a rate as to keep the temperature below 35 °C. The mixture was stirred at ambient temperature for 0.5 h. $MgSO_4$ (1 g) was added to the solution and the slurry was stirred at 22 °C for 2 h, filtered, and concentrated under reduced pressure to afford an oil (2.21 g, 96.5% yield) containing imine **2b** in 3:2 ratio of anti to syn isomers (as determined

(22) Green, T. W.; Wuts, P. G. *Protective Group in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999; pp 41 and 268 for the MEM group.
(23) The sodium periodate process was later successfully optimized for **15b** and was reported in ref 24.
(24) Clark, J. D.; Weisenburger, G. A.; Anderson, D. K.; Colson, P.-J.; Edney, A. D.; Gallagher, D. J.; Kleine, H. P.; Knable, C. M.; Lantz, M. K.; Moore, C. M. V.; Murphy, J. B.; Rogers, T. E.; Ruminski, P. G.; Shah, A. S.; Storer, N.; Wise, B. E. *Org. Process Res. Dev.* **2004**, *8*, 51.

by ^{1}H NMR and NOE experiments in $CDCl_3$); ^{1}H NMR ($CDCl_3$) anti-isomer, δ 0.22 (s, 9H), 1.55 (d, 3H, J = 7.7 Hz), 4.41 (dt, 1H, J = 6.6 Hz), 7.57 (d, 1H, J = 0.6 Hz); ^{1}H NMR ($CDCl_3$) syn-isomer, δ 0.26 (s, 1H), 1.51 (d, 3H, J = 6.6 Hz), 5.12 (dt, 1H, J = 5.3 Hz), 7.51 (d, 1H, J = 1.4 Hz); ^{1}H NMR ($CDCl_3$) anti/syn-isomer, δ 7.22 to 7.40 (m, overlapping peaks); ^{13}C NMR ($CDCl_3$) anti-isomer, δ 0.0, 24.1, 70.6, 98.3, 101.1, 126.7, 127.2, 128.5, 143.7; ^{13}C NMR ($CDCl_3$) syn-isomer, δ 0.0, 24.1, 64.4, 96.5, 104.4, 126.8, 127, 128.4, 144.5; IR 1610, 2370, 2340, 3390, 3610 cm^{-1}. Anal. Calcd for $C_{14}H_{19}NSi$: C, 73.30; H, 8.35; N, 6.11; Found: C, 73.29; H, 8.81; N, 5.95.



BrZnCH$_2$CO$_2$t-Bu·THF (3). Method A: Preparation of a Solution in NMP/THF. Step A: A 4 L jacketed flask, fitted with a condenser, temperature probe, and a mechanical stirrer, was charged with Zn metal (180.0 g, 2.77 mol, 30−100 mesh) and THF (1.25 L). With stirring, 1,2-dibromoethane (4.74 mL, 0.055 mol) was added to the vessel via a syringe. The suspension of zinc in THF was heated to reflux (65 °C) and maintained at this temperature for 1 h. The mixture was cooled to 50 °C before charging the *tert*-butyl bromoacetate (488.0 g, 369 mL, 2.5 mol) over a 1.5 h time period. Controlled reagent addition was performed with a 50 mL syringe and syringe pump (addition rate set at 4.1 mL/min). A temperature of 50 ± 5 °C was maintained during the addition (self-heating). It is important to determine that the formation of the reagent is initiated to avoid any accumulation of unreacted *tert*-butyl bromoacetate, leading potentially to a strong exotherm and foaming of THF. The reaction mixture was allowed to stir at 50 °C for 1 h after the addition was complete. The reaction mixture was allowed to cool to 25 °C, and the agitation was turned off to allow the precipitate to settle (the product precipitates from THF solution at 31 °C). The THF mother liquor was removed by decantation into a 2 L round-bottom flask under partial vacuum (20 mmHg) with a dip tube (coarse fritted glass filter). This removed 65% of THF from the vessel, then 800 mL of NMP was added and agitation was resumed for 5 min at 25 °C. The reaction mixture was transferred to another vessel by filtration to remove the remaining zinc to afford about 1.5 L of green/orange solution. The titer of the solution was found to be 1.57 M with a molar yield of 94% of **3** (see below for titration method).

Step B: Titration Method. A 1.0 mL aliquot of the Reformatsky-NMP/THF solution was removed from the reaction mixture via syringe and added to a 25 mL round-bottom flask that contained a preweighed amount of benzaldehyde (250−300 mg) and a magnetic stir bar, under a nitrogen atmosphere. The reaction mixture was stirred for 30 min at room temperature. To the flask were added aqueous NH_4Cl (29 wt %, 5.0 mL) and methyl *tert*-butyl ether (5.0 mL). The resulting mixture was stirred for 5 min at room temperature. The agitation was stopped and the layers were allowed to separate over 5 min. A 1.0 mL aliquot of the organic layer was removed and diluted to 25 mL with MTBE in a volumetric flask. This solution was subjected to gas chromatography (GC) analysis with use of a HP-1 10 m column. Standard solutions of benzaldehyde in MTBE at concentrations of 0.04, 0.01, and 0.002 M are co-injected with the sample. The sample concentration was determined from the linearity plot of the standard solutions and the sample GC peak area. The concentration of the Reformatsky solution was determined by using the following calculation:

amount of remaining benzaldehyde = concentration of sample (g/L) × 50 × 5/2

titer (mol/L) = (preweighed amount of benzaldehyde − amount remaining)/106

yield = mol/L × (total volume of solution/theoretical 100% yield)

Method B: Preparation of Solid Reagent (3). Zn metal (176.0 g, 2.69 mol, 30−100 mesh) and THF (1.25 L) were charged into a l L, three-necked, round-bottomed flask that was fitted with a condenser, temperature probe, and mechanical stirrer. With stirring, trimethylsilyl chloride (3.25 mL, 0.060 mol) was added to the vessel via syringe. The suspension of zinc in THF was stirred at room temperature for 1 h. *tert*-Butyl bromoacetate (500 g, 2.56 mol) was then added dropwise to bring the temperature to 50 °C and maintain that temperature ±5 °C with cooling over a 1 h time period. Controlled reagent addition was performed with a 50 mL syringe and syringe pump. The reaction mixture was allowed to stir at 50 °C for 40 min after the addition was complete. The reaction mixture was allowed to cool to 10 °C to precipitate the reagent as a white solid. The reagent was colleted by filtration with use of a pressure filter (extra coarse). The cake was washed three times with THF (3 × 200 mL) and dried on the filter with a stream of N_2 to afford **3** as a white powder (690 g, 81% yield). Analyses of **3** were consistent with literature data.[15b]

1,1-Dimethylethyl (3*S*)-[(2-Hydroxy-(1*S*)-phenylethyl)-amino]-5-(trimethylsilyl)-4-pentynoate (4a). Method A. A solution of the product of **3** in NMP/THF (2.6/1, 1.5 L, 1.57 M, 2.4 mol), prepared as above, was charged in a 4 L flask (jacketed, 4 ports fitted with mechanical stirrer, Teflon coated temperature probe, and addition funnel). The solution was cooled to −10 °C and a solution of imine of **2a** (220.0 g, 0.96 mol) in NMP (0.250 L) was added after 30 min while the temperature was maintained at −3 °C. After total conversion (less than 1% of starting material), a mixture of ammonium chloride aqueous solution (1.0 L, 29 wt %) and 2 N HCl (0.5 L) was added in 15 min from −10 to 13 °C. The mixture was warmed to 25 °C and MTBE (1.0 L) was added. The mixture was stirred for 30 min and the layers were separated. The aqueous layer was extracted with MTBE (0.5 L). The organic layers were combined and washed successively with a solution of NH_4Cl (29 wt %, 0.5 L), H_2O (0.5 L), and a saturated solution of NaCl (0.5 L) and were concentrated under reduced pressure to afford an orange oil (366 g) containing the title compound **4a** (84 wt. %, 91% yield determined by GC quantitation) and 1,1-dimethylethyl (3*R*)-[(2-hydroxy-(1*S*)-phenylethyl)amino]-5-(trimethylsilyl)-4-pentynoate (**4b**) mixture obtained with 80% de as determined by chiral HPLC. Samples of the two isomers were separated by preparative chiral HPLC for analytical purposes.

Data for **4b**: ^{1}H NMR ($CDCl_3$, TMS) δ 0.16 (s, 9H), 1.45 (s, 9H), 2.52 (dd (AB), J = 15.3 and 5.6 Hz, 1H), 2.56 (dd (AB), J = 15.3 and 5.6 Hz, 1H), 3.55 (dd, J = 7.7 and 5.6 Hz, 1H), 3.59 (dd, J = 10.7 and 8.5 Hz, 1H), 3.74 (dd, J = 10.8 and 4.5 Hz, 1H), 4.15 (dd, J = 8.4 and 4.5 Hz, 1H), 7.27−7.34 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 0.1, 28.1, 42.2, 44.9, 67.2, 67.5, 80.9, 88.6, 105.0, 127.7, 128.5, 139.7, 170.1; DSC 79.68 °C (endo 71.68 J/g), 237.33 °C (exo 169.0 J/g); $[\alpha]^{25}_D$ +179.3 (*c* 0.36, $CHCl_3$); IR (MIR) 2167, 1735 cm^{-1}; UV max (nm) 204 (abs 0.37). Microanal. Calcd for $C_{20}H_{31}NO_3Si$: C, 66.44; H, 8.64; N, 3.87. Found: C, 66.34; H, 8.88; N, 3.89.

Data for **4a**: ^{1}H NMR ($CDCl_3$, TMS) δ 0.09 (s, 9H), 1.46 (s, 9H), 2.49 (dd (AB), J = 15.6 and 8.6 Hz, 1H), 2.59 (dd (AB), J = 15.6 and 5.1 Hz, 1H), 3.59 (dd, J = 11.1 and 6.5 Hz, 1H), 3.77 (dd, J = 11.1 and 4.5 Hz, 1H), 3.89 (dd, J = 8.7 and 5.1 Hz, 1H), 3.97 (dd, J = 8.7 and 5.1 Hz, 1H), 7.24−7.36 (m, 5H); ^{13}C NMR ($CDCl_3$) δ −0.1, 28.1, 42.3, 46.2, 62.1, 65.5, 81.2, 88.3, 105.9, 127.3; DSC 252.27 °C (exo 342.3 J/g); $[\alpha]^{25}_D$ −5.6 (*c* 1.024, $CHCl_3$); IR (neat) 2167, 1735 cm^{-1}; UV max (nm) 205

(abs 0.33). Microanal. Calcd for C_{20} $H_{31}NO_3Si$: C, 66.44; H, 8.64; N, 3.87. Found: C, 66.22; H, 8.82; N, 3.85.

Method B. Reformatsky reagent **3** (60.0 g, 0.18 mmol) was added in 10 portions to a solution of imine **2a** (21.0 g, 0.086 mol) in NMP (100.0 mL) at −10 °C while maintaining an internal temperature of 7.5 ± 2.5 °C. The reaction was monitored by GC. After addition the mixture was stirred 2 h at −10 °C. A mixture of a saturated solution of ammonium chloride (75 mL) and HCl 37% (6.0 mL) was added to the solution at −10 °C and the mixture was warmed up to 22 °C. The mixture was extracted with MTBE (2 × 100.0 mL). The organic layers were combined and washed successively with a saturated solution of Ammonium hydroxide (100.0 mL), water (100.0 mL), and a saturated solution of NaCl (100.0 mL), dried with Na_2SO_4, filtered, and concentrated under reduce pressure to afford an orange oil containing a mixture of isomer **4a/4b** (30.92 g, 97.6/2.4) as determined by GC. The crude reaction mixture was purified by chromatography on silica gel (250 g, elution withheptane 80%/ethyl acetate 20%) to afford **4a** (25.91 g, 83.7%) as a pale yellow oil. Analyses were consistent with the above description for **4a**. Microanal. Calcd for C_{20} $H_{31}NO_3Si$: C, 66.44; H, 8.64; N, 3.87. Found: C, 66.2; H, 8.64; N, 3.70.

Preparation of Zinc Chelate (5). Reagent **3** solid (3.32 g, 10.0 mmol) was added in 2 min to a solution of imine **2a** (2.45 g, 10 mmol) in THF (30.0 mL), which was then cooled to 0 °C to form an homogeneous orange solution. The mixture was stirred at 0 °C for 30 min and heptane was added. Precipitation occurred and the slurry was stirred at 0 °C for 20 min. The solids were filtered off under N_2 and washed with heptane (20 mL) and dried in a pressure filter under N_2 (2 Psi) and vacuum to afford **5** (2.13 g, 55%) as a pale orange solid. GC trace analysis of a sample quenched with ammonium chloride showed only imine **2**. DSC 262.33 °C (exo 402.1 J/g); IR (MIR) 1720 cm^{-1}. Microanal. Calcd for $C_{14}H_{18}BrNOSiZn$: C, 43.15; H, 4.68; N, 3.59; Br, 20.51. Found: C, 42.93; H, 4.68; N, 3.61; Br, 20.86.

Formation of 4 from 2 through the Isolation of Zinc Chelate (5). The Reformatsky reagent **3** (16.6 g, 50.0 mmol) was added to a solution of imine **2a** (12.25 g, 50.0 mmol) in THF (100.0 mL) at 0 °C. After 5 min, the reaction mixture was held to 22 °C. Additional THF (100 mL) was added and the solution was filtered through a coarse sintered glass filter and the filtrate was concentrated under reduced pressure to afford an orange solid (22.3 g) containing **5**. The residue was taken up in NMP (100 mL). The solution was cooled to −10 °C and a second equivalent of **3** (16.6 g, 50.0 mmol) was added as a solid by portions while maintaining the temperature at −7.5(±2.5) °C. The mixture was stirred at −10 °C for 2.5 h and held at 5 °C for 1 h. An additional 1.5 g of reagent **3** was added and after 20 min, a solution of NH_4Cl (20 wt % in water, 100 mL) was added while maintaining a temperature of 5(±5) °C followed by MTBE (100 mL). The layers were separated and the aqueous layer was extracted with MTBE (100 mL). The combined MTBE layers were washed with a solution of NH_4Cl (20 wt %), water, and brine, dried with Na_2SO_4, filtered, and concentrated under reduced pressure to afford an orange oil containing a mixture of **4a/4b** (16.7 g, ratio of 97.4/2.6) and a trace of recovered imine **2a** (2%) as determined by GC.

1,1-Dimethyl (3*S*)-[(Phenylmethylene)amino-5-trimethylsilyl]-4-pentynoate (6). $NaIO_4$ (77.0 g, 0.36 mol) was charged into a 500 mL flask followed by water (330 mL) and the mixture was stirred for 30 min at 25 °C. A solution of 1,1-dimethyl (3*S*)-[(2-hydroxy-(1*S*)-phenylethyl)amino]-5-(trimethylsilyl)-4-pentynoate (**4a**) (116.3 g, 86 wt %, 0.277 mol) in ethanol (520 mL) was charged into a 1 L flask (4 ports, jacketed, fitted with mechanical stirrer and Teflon coated temperature probe) purged with N_2, followed by addition of a solution of methylamine (40 wt %, 24 mL, 0.278 mol). After 5 min of stirring at 25 °C, a slurry of $NaIO_4$ in water was added portion wise while maintaining a temperature below 35 °C (32 ± 2 °C). After complete addition, conversion was complete and the mixture was cooled to 3 °C and held at this temperature for 3 h. The mixture was filtered on an ace-glass pressure filter (extra coarse, 600 mL) and the cake was dried for 3.5 h under a N_2 vacuum (Karl-Fisher analysis showed 5.60% H_2O remaining). The cake containing a mixture of the title compound and iodate salt was charged into a 500 mL flask and toluene (THF can also be used) (130 mL) was added. After 30 min of stirring at 30 °C, the mixture was filtered. The cake was washed twice with toluene (THF can also be used) (2 × 50 mL). The three fractions were combined and partially concentrated to a weight of 161 g containing 53.3 wt % of the title compound (determined by GC quantitation) with a yield of 92% and a chiral purity of 99.9% (determined by chiral HPLC). A sample was isolated for full characterization by concentration of the solution: ^{1}H NMR ($CDCl_3$, TMS) δ 0.20 (s, 9H), 1.45 (s, 9H), 2.66 (dd (AB), J = 15.0 and 7.0 Hz, 1H), 2.80 (dd (AB), J = 15.0 and 7.7 Hz, 1H), 4.83 (dt, J = 7.6 and 1.7 Hz, 1H), 7.38−7.44 (m, 3H), 7.74−7.77 (m, 2H), 8.56 (d, J = 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 0.1, 28.1, 43.2, 56.5, 80.8, 92.5, 103.2, 128.5, 128.6, 130.9, 135.9, 161.8, 169.6; DSC: 72.22 °C (endo 112.4 J/g); $[\alpha]^{25}_D$ −35.5 (*c* 1.16, $CHCl_3$); IR (MIR) 2174, 1728, 1641 cm^{-1}; UV max (nm) 205 (abs 1.004), 248 (abs 0.655). Microanal. Calcd for C_{19} $H_{27}NO_2Si$: C, 68.75; H, 8.65; N, 4.33. Found: C, 69.10; H, 8.43; N, 4.33.

1,1-Dimethylethyl (3*S*)-Amino-5-(trimethylsilyl)-4-pentynoate 4-Methylphenylsulfonate Salt (7). A solution of **6** (123.3 g, 0.374 mol) in dry THF (350 mL) was prepared. *p*-Toluenesulfonic acid monohydrate (71.2 g, 0.374 mol) was charged to a 4 L jacketed reaction vessel under nitrogen. An overhead stirrer with a 10 cm Teflon stir blade was attached. A thermocouple thermometer was put in place. The reactor jacket was cooled to 0 °C. The solution of **6** was added via an addition funnel over 5 min with stirring at 250 rpm. The reaction temperature rose to 10 °C. The addition funnel was rinsed with THF (300 mL). After stirring for 15 min the mixture became homogeneous. The stirring rate was increased to 350 rpm. Heptane (1360 mL) was added over 5 min. The product crystallized and the agitation was increased to 540 rpm. The solvent was distilled from the reactor under vacuum under the following conditions. An oil pump connected to a vacuum regulator was used to adjust the vacuum to 45 mmHg. The jacket temperature was set to 20 °C and a dry ice/2-propanol condenser with a 2 L receiving flask was used to collect the distillate. The distillate collected was 900 mL. The reactor was placed under a nitrogen atmosphere and additional heptane (900 mL) was added. The slurry was cooled to 2 °C. The solids were collected on a 10 cm coarse glass fritted filter with a vacuum. The reaction vessel was rinsed by adding heptane (500 mL) and THF (50 mL) with stirring. The reaction mixture was cooled to 10 °C and added to the filter. The cake was washed with heptane (3 × 300 mL) and dried by using a combination of vacuum and nitrogen flow for 4.5 h to produce **7** (145.9 g, 94%); mp 142 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.32 (br, s, 3H), 7.79 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 8.0 Hz, 2H), 4.40 (dd, J = 8.0 and 6.0 Hz, 1H), 2.89 (dd, J = 17.0 and 8.0 Hz, 1H), 2.76 (dd, J = 17.0 and 5.0 Hz, 1H), 2.36 (s, 3H), 1.41 (s, 9H), 0.10 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.6, 141.6, 140.2, 128.8 (2C), 126.1 (2C), 98.5, 92.7, 82.0, 40.6, 38.6, 27.9 (3C), 21.3, −0.5 (3C). Anal. Calcd for C_{19} $H_{31}NO_5SSi$: C, 55.17; H, 7.55; N, 3.39. Found: C, 55.27; H, 7.27; N, 3.34.

Ethyl (3S)-Amino-5-(trimethylsilyl)-4-pentynoate Hydrochloride Salt (1). A solution of **7** (500.0 g, 1.21 mol) and *p*-toluenesulfonic acid monohydrate (69.5 g, 0.365 mol) in ethanol 2B (930 mL) was heated to reflux and held for 4 h. Reaction completion was determined by GC. The reaction mixture was concentrated under reduced pressure. MTBE (1200 mL) was charged to the concentrate with stirring to complete dissolution. A 26 wt/wt % of potassium bicarbonate aqueous solution (1387.0 g) was added to the MTBE solution. The biphasic mixture was stirred for 15 min. The aqueous layer was back-extracted with MTBE (700 mL). The combined organic layers were extracted a second time with a 26 wt/wt

% of potassium bicarbonate aqueous solution (306.0 g). The organic layer was concentrated under reduce pressure. Water was removed azeotropically with ethanol 2B (900 mL) under reduced pressure. An 87.3% yield of the desired silyl protected ethyl ester free amine is typically obtained (1.06 mol in this experiment). To the concentrate was charged ethanol 2B (600 mL), followed by 21 wt % of sodium ethoxide (in ethanol denatured with 5% toluene) (39.6 mL, 0.106 mol, 0.1 equiv sodium ethoxide). The reaction solution was allowed to cool to room temperature and stirred for 1.5 h. Desilylation completion was determined by GC. In a separate vessel was charged ethanol 2B (720 mL), followed by acetyl chloride (81.6 mL, 1.15 mol, 1.1 equiv). This addition was carried out over 20 min, not allowing the temperature to rise above 45 °C. The solution was then cooled to 20−25 °C. The resulting hydrogen chloride/ethyl acetate/ethanol solution was charged to the desilylation reaction mixture. A 5 °C exotherm was observed. The reaction was cooled to 25 °C with stirring over a 30 min period and then stirred at 25 °C for an additional 30 min. The reaction mixture was concentrated under reduced pressure. The concentrate was cooled to room temperature and toluene (920 mL) was added. The mixture was stirred for 20 min and then concentrated under reduced pressure. Toluene (920 mL) was added to the concentrate and the solution was stirred for 20 min. Solids were collected by filtration and dried to afford crude **1** (184.94 g, 86.1% yield).

A portion of the crude **1** (80.0 g) was recrystallized from acetonitrile/MTBE. To crude **1** (80 g) was added acetonitrile (400 mL). The mixture was heated to reflux and the resulting heated opaque yellow solution was filtered through Celite (20 g, Celite had been washed with hot acetonitrile). The filtrate was concentrated under vacuum to remove 195 mL of solvent. The concentrated solution was cooled to 45 °C. To the solution was added MTBE (195 mL). The resulting opaque mixture was then heated to reflux, cooled to 50 °C, and then stirred for 15 min. The mixture was then cooled to 40 °C and then held for 15 min. The mixture was then allowed to cool to 22 °C and filtered. The resulting solids were dried on the filter for 10 min, then under high vacuum for 2 h, providing **1** (72.18 g).

^{1}H NMR (d_6-DMSO) δ 1.21 (t, J = 7 Hz, 3H), 2.84 (dd, J = 16 and 9 Hz, 1H), 3.03 (dd, J = 16 and 5 Hz, 1H), 3.70 (d, J = 2 Hz, 1H), 4.13 (q, J = 7 Hz, 2H), 4.31 (m, 1H), 8.82 (s, 3H); ^{13}C NMR (d_6-DMSO) δ 13.9, 37.6, 38.4, 60.7, 77.9, 78.6, 168.4; DSC 125−131 °C (endo 107.2 J/g); $[\alpha]^{25}_D$ −6.7; IR (MIR) 3252, 2128, 1726 cm^{-1}. Microanal. Calcd for $C_7H_{12}NO_2Cl$: C, 47.33; H, 6.81; N, 7.89; Cl, 19.96. Found: C, 47.15; H, 6.84; N, 7.99; Cl, 19.55.

General Method A (Imine Preparation). (*S*)-Phenylglycinol (1 equiv) was then added at once (endothermic reaction) to a solution of aldehyde (1 equiv) in toluene or THF (10 mL/g of (*S*)-phenylglycinol) at room temperature. After 30 min at 22 °C, $MgSO_4$ was added. The mixture was stirred for 2 h at 22 °C then filtered on a coarse fritted filter and the cake was washed with toluene or THF. The filtrate and washes were concentrated under reduce pressure to afford a crude containing the desired imine. The crude was used directly in the coupling reaction except when specified.

General Method B (Reformatsky Coupling Reaction). A solution of crude imine **9** or **15** in NMP was prepared under nitrogen and then added in 30 min to a solution of reagent **1** (2.2 equiv) in NMP/THF (when **3** was prepared and used as a titrated solution), NMP or DMSO (when the reagent **3** was used as solid, 2 mL/g of **3**) at −10 °C while the temperature was maintained at −5 °C. The mixture was stirred for 3 h at −8(±3) °C or until the reaction was complete and then cooled to −10 °C. A mixture of 2 N HCl solution/saturated solution of NH_4Cl (1/2 v/v, 2.4 mL/g of **1**) was added in 10 min (exothermic, temperature typically rose from −10 to 7 °C). MTBE (2−2.4 mL/g of **1**) was added and the mixture was stirred for 30 min at 23 °C. Stirring was stopped and the layers were separated. The aqueous layer was extracted with MTBE (1 mL/g of **1**). The two organic layers were combined and washed successively with a saturated solution of NH_4Cl (1 mL/g of **3**), DI water (1 mL/g of **3**), and saturated sodium chloride solution (1 mL/g of **3**). The organic layer was dried with $MgSO_4$, filtered, and concentrated to afford a crude oil containing the desired product **10** (from **9**) or **16** (from **15**) as a single diastereoisomer. The material was used directly in the oxidative cleavage (general method C or D) except when specified.

General Method C (Oxidative Cleavage with Sodium Periodate). Methylamine (40 wt % in water, 1.1 to 1.2 equiv) was added to a solution of crude ester **10** in ethanol (4 mL/g of crude ester **10**). A slurry of $NaIO_4$ (1.2−1.3 equiv) in water (2 mL/g of crude ester **10**) was then added by portion while maintaining the temperature below 30 °C. An additional portion of $NaIO_4$ could be added as specified if the reaction did not complete and the mixture was heated to 30 °C for 0.5 h. The mixture was cooled to 25 °C, concentrated under reduce pressure, and taken up in MTBE (as needed) and the residual solids were filtered off. The layers were separated and the organic layer was washed with water, dried with $MgSO_4$, filtered, and concentrated to afford an oil that was used directly in the salt formation.

General Method D (Oxidative Cleavage with Lead Acetate). Lead tetraacetate (1 equiv) was added in one portion to a solution of crude ester **10** or **16** (1 equiv) in methanol (15 mL/g of crude ester **10** or **16**) at 0 °C. Addition was exothermic and the temperature goes up to 4 °C. The reaction mixture was stirred for 3 h at 0 °C and then 15% aqueous NaOH (1.5 mL/g of crude ester) was added to the reaction mixture while maintaining the temperature below 5 °C. Methanol was removed under reduced pressure on rotovap. An additional portion of 15% aqueous NaOH (60 mL/g of crude ester **10** or **16**) was added and the reaction mixture was extracted 3× with ethyl acetate (3 mL/g of crude ester **10** or **16**) and washed 2× with DI water (2 mL/g of crude ester **10** or **16**) and 2× with a saturated NaCl solution (1 mL/g of crude ester **10** or **16**) then dried over anhydrous $MgSO_4$. It was then filtered over Celite and concentrated under reduced pressure to give an oil containing the desired product **11** or **17**.

General Procedure E (Isolated pTSA Tbutyl Ester Salts 12). A solution of *p*-toluenesulfonic acid monohydrate (calcd 1 equiv vs crude imine **11**) in THF (1.5 mL/g of pTSA·H_2O) was added to a solution of crude imine **11** in THF (2.5 mL/g of crude imine **11**). After 5 min, heptane (5 mL/g of crude imine) was added and after a few minutes heavy salt precipitation occurred. Additional heptane was added if needed and the slurry was stirred for 0.5 h after precipitation then the salt was filtered off and the cake was washed twice with heptane/THF 20 to 30 vol % (5 mL/g of crude imine). The solids were then dried under vacuum/nitrogen flow as needed and collected to afford the desired β-amino ester **12** as a pTSA salt.

General Procedure F (Isolated pTSA Ethyl Ester Salts 18). *p*-Toluenesulfonic acid monohydrate (1.3 equiv) was added to a solution of crude **17** (1 equiv) in absolute ethanol (2 mL/g of crude **17**). The reaction mixture was then heated to reflux for 8 h after which solvent was removed under reduced pressure. Residual solid was taken up in THF (1 mL/g of crude **17**) and THF was then stripped off under reduced pressure. Residue was dissolved in fresh THF (1 mL/g of crude **17**) and dissolved on warming to 40 °C. Heptane, ethyl acetate ,or THF as specified was added and reaction mixture was cooled to 30 °C. A thick slurry precipitated out and was filtered with the aid of a THF/heptane solution. Solid was washed with acetone or a mixture of THF 30%/heptane and dried under vacuum at 40 psi under a blanket of nitrogen at 48−49 °C for 16 h to afford **18** as a white solid.

(3*S*)-3-Amino-3-phenylpropionic Acid *tert*-Butyl Ester *p*-Toluene-4-sulfonic Acid (12a). Following the general procedure A, crude **9a** was prepared (40.07 g, 88.9%) from (*S*)-phenylglycinol (27.44 g, 0.20 mol) and benzaldehyde **2a** (21.75 g, 0.205 mol).

Following the general procedure B, crude **10a** (33.24 g, 97.3%) was prepared as a yellow oil solidifying on standing as a single diastereoisomer as determined by ^{1}H NMR and ^{13}C NMR from **1** (160 mL of 1.378 M solution in NMP/THF, 3/2)) and a portion of crude imine **9a** (22.53 g, 0.1 mol).

Following general procedures C and E, **12a** (19.28 g) was isolated as a white solid from a portion of crude **10a** (27.37 g, calcd 0.075 mol), $NaIO_4$ (19.57 g, 0.091 mol), $MeNH_2$ (40 wt % aqueous solution, 5.56 mL, 0.077 mol), and pTSA·H_2O (10.72 g, 0.057 mol) with heptane as a nonsolvent. ^{1}H NMR (d_6-DMSO, TMS) δ 1.26 (s, 9H), 2.29 (s, 3H), 2.81 (dd, 1H, J = 9.2, 15.6 Hz), 2.99 (dd, J = 5.8, 15.8 Hz), 4.55 (m, 1 Hz), 7.11 (d, 2H, J = 8.1 Hz), 7.38 to 7.49 (m, 8H), 8.31 (s (broad), 3H); ^{13}C NMR (d_6-DMSO, TMS) (ppm) 20.8, 27.5, 51.2, 80.8, 125.5, 127.7, 128.2, 128.6, 128.9, 136.4, 138.0, 145.0, 168.1; $[\alpha]^{25}_D$ −2.5 (c 0.91, $CHCl_3$); IR (MIR) (cm^{-1}) 1725. Microanal. Calcd for $C_{20}H_{27}NO_5S$: C, 61.05; H, 6.92; N, 3.56; S, 8.15. Found: C, 60.13; H, 7.03; N, 3.53; S, 8.46.

(3*S*)-3-Amino-3-(3,5-dichlorophenyl)propionic Acid *tert*-Butyl Ester *p*-Toluene-4-sulfonic Acid Salt (12b). Following the general procedure A, **9b** was prepared as crude (27.00 g, pale yellow oil) from (*S*)-phenylglycinol (11.44 g, 0.086 mol) and 3,5-dichlorobenzaldehyde (**8b**) (15.0 g, 0.086 mol).

Following the general procedure B, crude **10b** (35.2 g) was prepared as an orange oil solidifying on standing as a single diastereoisomer as determined by ^{1}H NMR and ^{13}C NMR from **3** (165 mL of 1.15 M solution in NMP/THF (3/2), 0.189 mol) and a portion of crude imine **9b** (25.39 g, calcd 0.086 mol).

Following general procedures C and E, **12b** (25.1 g) was isolated as a ivory solid from crude **10b**, $NaIO_4$ (25.92 g, 0.112 mol and 2 portions of 6.0 g, 0.026 mol), $MeNH_2$ (40 wt % aqueous solution, 8.9 mL, 0.1 mol), and pTSA·H_2O (13.6 g, 0.072 mol) with heptane as nonsolvent.

^{1}H NMR ($CDCl_3$, TMS) δ 1.26 (s, 9H), 2.37 (s, 3H), 2.84 (dd, 1H, J = 9.5, 16.3 Hz), 2.98 (dd, J = 5.1, 16.2 Hz), 4.53 (m, 1 Hz), 7.14 (d, 2H, J = 7.9 Hz), 7.19 (t = 1 H, J = 1.8 Hz), 7.32 (d, 2H, J = 8.1 Hz), 7.56 (d, 2H, J = 8.1 Hz), 8.43 (s (broad), 3H); ^{13}C NMR (d_6-DMSO, TMS) (ppm) 21.4, 27.8, 39.5, 51.4, 81.9, 125.8, 126.4, 129.1, 129.1, 135.2, 139.1, 140.6, 140.7, 168.1; $[\alpha]^{25}_D$ +37.4 (c 0.147, $CHCl_3$); IR (MIR) (cm^{-1}) 1726, 1587, 1567. Microanal. Calcd for $C_{20}H_{25}Cl_2NO_5S$: C, 51.95; H, 5.64; N, 3.01; Cl, 15.33; S, 7.02. Found: C, 51.65; H, 5.64; N, 3.01; Cl, 15.13; S, 7.02.

(3*S*)-3-Amino-3-furan-2-ylpropionic Acid *tert*-Butyl Ester *p*-Toluene-4-sulfonic Acid Salt (12c). Following the general procedure A, **9c** was prepared as crude (54.72 g, yellow solid, 91.4%) from (*S*)-phenylglycinol (38.16 g, 0.278 mol) and freshly distilled 3-furaldehyde (**8c**) (26.73 g, 0.278 mol) followed by slurry with heptane (100 mL), filtration, and drying under vacuum.

Following the general procedure B, crude **10c** (7.3 g) was prepared as an orange oil solidifying on standing as a single diastereoisomer as determined by ^{1}H NMR and ^{13}C NMR from **3** (43 mL of 1.36 M solution in NMP/THF (3/2), 0.058 mol) and a portion of crude imine **9c** (5.00 g, calcd 0.023 mol). The crude was purified by chromatography on silica gel, eluting with heptane/MTBE (2:1) to yield the desired product **10c** (5.43 g, 70.5%).

^{1}H NMR ($CDCl_3$, TMS) δ (ppm) 1.44 (s, 9H), 2.71−2.65 (m, 2H), 3.55 (dd, 1H, J = 12.0, 7.9 Hz), 3.79−3.75 (m, 2H), 4.25 (dd, 1 H, J = 7.7, 6.2 Hz), 6.07 (d, 1H, J = 3.2 Hz), 6.21 (dd, 1 H, J = 3.2, 1.8 Hz), 7.29−7.19 (m, 6H); ^{13}C NMR ($CDCl_3$, TMS) δ (ppm) 28.1, 40.7, 51.4, 61.7, 66.1, 81, 106.3, 109.9, 127.08, 127.4, 128.4, 141.4, 141.6, 155.3, 170.9; $[\alpha]^{25}_D$ +7.6 (c 0.983, $CHCl_3$); IR (MIR) (cm^{-1}) 3427, 2974, 2929, 2870, 1720, 1452, 1365, 1147. Microanal. Calcd for $C_{19}H_{25}NO_4$: C, 67.80; H, 7.86; N, 3.84 Found: C, 68.86; H, 7.60; N, 3.23.

Following general procedures C and E, **12c** (4.39 g, 78%) as a pale yellow solid was isolated from **10c**, $NaIO_4$ (3.55 g, 0.017 mol), $MeNH_2$ (40 wt % aqueous solution, 1.30 mL, 0.015 mol), and pTSA·H_2O (2.35 g, 0.0123 mol) with heptane as nonsolvent.

^{1}H NMR ($CDCl_3$, TMS) δ 1.32 (s, 9H), 2.35 (s, 3H), 2.96 (m, 2H), 4.72 (m (br), 1 H), 6.22 (dd, 1H, J = 3.3, 1.8 Hz), 7.12 (d, 2 H, J = 8 Hz), 7.22−7.23 (m, 1H), 7.67 (d, 2H, J = 8.1 Hz), 8.23 (s (broad), 3H); ^{13}C NMR (d_6-DMSO, TMS) (ppm) 21.3, 27.8, 36.8, 45.7, 81.7, 109.5, 110.6, 126.1, 128.8, 140.2, 141.5, 142.9, 148.6, 168.8. Microanal. Calcd for $C_{18}H_{25}NO_6S$: C, 56.30; H, 6.57; N, 3.65. Found: C, 55.08; H, 5.69; N, 3.83.

(3*S*)-3-Amino-3-pyridin-3-ylpropionic Acid *tert*-Butyl Ester *p*-Toluene-4-sulfonic Acid Salt (12d). Following the general procedure A, **9d** was prepared as crude (42.25 g, white solid, 93.3%) from (*S*)-phenylglycinol (27.96 g, 0.2 mol) and 3-pyridinecarbixaldehyde (**8d**) (21.96 g, 0.205 mol) followed by slurry with heptane (100 mL), filtration, and drying under vacuum.

Following the general procedure B, crude **10d** (27.85 g) was prepared as an orange oil as a single diastereoisomer as determined by ^{1}H NMR and ^{13}C NMR from **3** (121 mL of 1.36 M solution in NMP/THF (3/2), 0.164 mol) and a portion of crude imine **10d** (17.00 g, calcd 0.075 mol). In that example, additional back extractions after regular extractions were performed. A saturated solution of NH_4Cl (50 mL) was added to the aqueous layer followed by extraction with MTBE and the layers were separated. This was repeated a second time and the MTBE layers were combined, dried with $MgSO_4$, filtered, and concentrated

Following general procedures C and E, **12d** (19.28 g) was isolated as an ivory solid from crude **10d**, $NaIO_4$ (19.57 g, 0.091 mol), $MeNH_2$ (40 wt % aqueous solution, 5.56 mL, 0.077 mol), and pTSA·H_2O (10.72 g, 0.057 mol) with heptane as nonsolvent.

^{1}H NMR ($CDCl_3$, TMS) δ 1.24 (s, 9H), 2.35 (s, 3H), 2.90 (dd, 1H, J = 8.87, 16.6 Hz), 3.09 (dd, 1H, J = 5.8, 16.6 Hz), 4.71 (dd, 1 H, J = 6.0, 8.9 Hz), 7.09 (d, 1H, J = 7.9 Hz), 7.19 (d, 2 H, J = 4.9, 7.9 Hz), 7.57 (d, 2H, J = 8.1 Hz), 7.99 (dd, 1H, J = 1.7, 8.1 Hz), 8.46 (dd, 1H, J = 1.4, 5.0 Hz), 8.70 (d, 1H, 1.9 Hz); ^{13}C NMR ($CDCl_3$, TMS) (ppm) 21.3, 27.7, 48.9, 49.9, 81.9, 124.2, 125.8, 128.9, 132.5, 137.2, 140.5, 141.2, 148.3, 148.6, 168.3; $[\alpha]^{25}_D$ −1.5 (c 0.998, $CHCl_3$); IR (MIR) (cm^{-1}) 2116, 1721, 1540. Anal. Calcd for $C_{14}H_{26}N_2O_5S$: C, 57.15; H, 6.46; N, 6.44; S, 8.38. Found: C, 57.85; H, 6.64; N, 7.10; S, 8.13.

(3*S*)-3-Amino-4,4-dimethylpentanoic Acid *tert*-Butyl Ester *p*-Toluene-4-sulfonic Acid Salt (12e). Following the general procedure A, **9e** was prepared as crude (14.41 g, clear oil) from (*S*)-phenylglycinol (10.00 g, 0.073 mol) and trimethylacetaldehyde (**8e**) (6.59 g, 0.076 mol).

Following the general procedure B, crude **10e** (18.11 g) was prepared as a yellow oil as a single diastereoisomer as determined by ^{1}H NMR and ^{13}C NMR from **3** (57.50 g, 0.173 mol) and crude imine **9e** in DMSO at room temperature for 20 h.

Following general procedures D and E, **12e** (11.83 g) was isolated as a white solid from crude **12e**, $Pb(OAc)_4$ (23.40 g, 0.054 mol), and pTSA·H_2O (8.24 g, 0.043 mol). The pTSA salt was prepared from MTBE/heptane.

^{1}H NMR ($CDCl_3$, TMS) δ 1.01 (s, 9H), 1.41 (s, 1H), 2.35 (s, 3H), 2.55 (dd, 1H, J = 4.0, 17.7 Hz), 2.66 (dd, 1H, J = (0.0, 17.6 Hz), 3.28 (m, 1H), 7.15 (d, 2H), 7.75 (d, 2H), 7.80 (s (broad), 3H); ^{13}C NMR (CDCl3, TMS) (ppm) 21.3, 26, 27.9, 33.2, 33.8, 57.4, 82.1, 126.1, 139.9, 141.9, 170.9; $[\alpha]^{25}_D$ −24.7 (c 0.777, $CHCl_3$); IR (MIR) (cm^{-1}) 1718. Anal. Calcd for $C_{18}H_{31}NO_5S$: C, 57.64; H, 8.37; N, 3.58; S, 8.80. Found: C, 57.88; H, 8.37; N, 3.75; S, 8.58.

(3*S*)-3-(2-Hydroxy-(1*S*)-phenylethylamino)methylhexanoic Acid *tert*-Butyl Ester (10f). Following the general procedure A, **9f** was prepared as crude (15.14 g, clear oil) from (*S*)-phenylglycinol (10.00 g, 0.073 mol) and isobutyraldehyde (**8f**) (6.59 g, 0.076 mol).

Following the general procedure B, crude **10f** (19.4 g) was prepared as a yellow oil as a single diastereoisomer as determined by ^{1}H NMR and ^{13}C NMR from **3** (57.50 g, 0.173 mol) and crude imine **9f** in DMSO at room temperature for 20

h. Additional reagent **3** (11.47 g, 0.035 mol) was added and the mixture was stirred for an additional 20 h.

A portion of the crude (3 g) was purified by silica gel (elution heptane, 30% ethyl acetate) to afford the desired product **10f** (2.31 g) as a pale yellow oil.

^{1}H NMR ($CDCl_3$, TMS) δ 0.68 (d, 3H, J = 6.5 Hz), 0.83 (d, 3H, J = 6.5 Hz), 1.19 (m, 1H), 1.32 (m, 1H), 1.46 (s, 9H), 1.61 (s, 1H), 2.26 (dd, 1H, J = 5.70, 14.62 Hz), 2.38 (dd, 1H, J = 5.71, 14.57 Hz), 2.92 (m, 1H), 3.51 (dd, 1H, J = 10.75, 8.54 Hz), 3.69 (dd, 1H, 4.32, 10/72 Hz), 3.84 (dd, 1H, J = 8.49, 4.44 Hz), 7.23 to 7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, TMS) (ppm) 22.3, 24.7, 28.1, 40.4, 44.9, 50.5, 61.8, 67.0, 80.6, 127.3, 127.5, 128.5, 141.5, 171.9; $[\alpha]^{25}_D$ +49 (*c* 1.005, $CHCl_3$); IR (MIR) (cm^{-1}) 3428, 3331, 1721. Anal. Calcd for $C_{19}H_{31}NO_3$: C, 70.99; H, 9.72; N, 4.36. Found: C, 69.29; H, 9.75; N, 4.08.

3,5-Dichloro-2-(2-methoxyethoxymethoxy)benzaldehyde (14a). Potassium carbonate (powder, oven dried at 100 °C under vacuum, 8.28 g, 0.06 mol) was added to a solution of 3,5-dichlorosalicylaldehyde (**13a**) (11.46 g, 0.06 mol) in DMF (40 mL) at room temperature to give a bright yellow slurry. MEMCl (neat, 7.64 g, 0.061 mol) was then added while maintaining the bath temperature at 20 °C. Gas evolution is observe during the addition. The mixture was then stirred at 22 °C for 3 h and additional MEMCl (neat, 0.3 g) was added. The mixture was then stirred for an extra 0.5 h and poured into 200 mL of cold water to precipitate the product. The slurry was filtered on a pressure filter and the cake was washed with DI water (2 × 50 mL) and then dried under N_2/vacuum to afford **14a** (14.94 g, 89%) as a pale yellow solid. ^{1}H NMR ($CDCl_3$, TMS) δ 3.37 (s, 3H), 3.54 to 3.56 (m, 2H), 3.91 to 3.93 (m, 2H), 5.30 (s, 2H), 7.63 (d, 1H, J = 2.6 Hz), 7.73 (d, 1H, J = 2.6 Hz), 10.30 (s, 1H); ^{13}C NMR ($CDCl_3$, TMS) δ (ppm) 59.1, 70.1, 99.6, 126.6, 129.6, 130.8, 132.1, 135.4, 154.7, 188.3; DSC 31.17 °C (endo 83.12 J/g). Microanal. Calcd for $C_{11}H_{12}Cl_2O_4$: C, 47.34; H, 4.33; Cl, 25.40. Found: C, 47.15; H, 4.26; Cl, 25.16.

3-Bromo-5-chloro-2-(2-methoxyethoxymethoxy)benzaldehyde (14b). Following the procedure for **14a**, **14b** (182.4.0 g, 88%, off white solid) was prepared from potassium carbonate (powder, oven dried at 100 °C under vacuum, 94.1 g, 0.685 mol) and 3-chloro-5-bromosalicylaldehyde (**13b**) (150.0 g, 0.64 mol) and MEMCl (neat, 107.14 g, 0.86 mol) in DMF (750 mL). ^{1}H NMR ($CDCl_3$, TMS) δ (ppm) 3.38 (s, 3H), 3.55 to 3.57 (m, 2H), 3.92 to 3.94 (m, 2H), 5.30 (d, 2H), 7.79 (d, 1H, J = 2.68 Hz), 7.82 (d, 1H, J = 2.68 Hz); ^{13}C NMR ($CDCl_3$, TMS) δ (ppm) 59.1, 70.2, 71.5, 99.8, 118.9, 127.3, 131.3, 132.1, 138.3, 155.8, 188.5. Microanal. Calcd for $C_{11}H_{12}BrClO_4$: C, 40.82; H, 3.74; Br, 24.69; Cl, 10.95. Found: C, 40.53; H, 3.74; Br 23.60; Cl, 10.96.

5-Bromo-3-chloro-2-(2-methoxyethoxymethoxy)benzaldehyde (14c). Following the procedure for **14a**, **14c** (46.0 g, 95%, off white solid) was prepared from potassium carbonate (powder, oven dried at 100 °C under vacuum, 22.1 g, 0.16 mol) and 3-chloro-5-bromosalicylaldehyde (**13c**) (35.0 g, 0.15 mol) and MEMCl (neat, 25.0 g, 0.2 mol) in DMF (175 mL). ^{1}H NMR ($CDCl_3$, TMS) δ 3.35 (s, 3H), 3.54 to 3.56 (m, 2H), 3.91 to 3.93 (m, 2H), 5.30 (s, 2H), 7.77 (d, 1H), 7.85 (d, 1H), 10.30 (s, 1H); ^{13}C NMR ($CDCl_3$, TMS) δ (ppm) 59.1, 70.1, 71.5, 99.5, 117.9, 129.7, 129.8, 132.4, 138.1, 155.1, 188.2. Microanal. Calcd for $C_{11}H_{12}BrClO_4$: C, 40.82; H, 3.74; Br, 24.69; Cl, 10.95. Found: C, 40.64; H, 3.48; Br 24.67; Cl, 10.99.

(3*S*)-3-Amino-3-(3,5-dichloro-2-hydroxyphenyl)propionic Acid Ethyl Ester *p*-Toluene-4-sulfonic Acid Salt (18a). Following the general procedure A, **15a** was prepared as crude from (*S*)-phenylglycinol (17.20 g, 0.125 mol) and aldehyde **14a** (35 g, 0.125 mol).

Following the general procedure B, crude **16a** (66.26 g) was prepared as an orange oil solidifying on standing as a single diastereoisomer as determined by ^{1}H NMR and ^{13}C NMR from **3** (91.3 g, solid, 0.275 mol) in NMP and crude imine **15a**.

Following general procedures D and F, **18a** (7.40 g) was isolated as a salt containing 0.25 equiv of THF from a portion of crude **15a** (17.40 g, calcd 0.033 mol), $Pb(OAc)_4$ (15 g, 0.033 Mol), and pTSA·H_2O (6.3 g, 0.033 mol).

^{1}H NMR (d_6-DMSO, TMS) δ 1.12 (t, 3H, J = 7.1 Hz), 2.29 (s, 3H), 2.97 (dd, 1H, J = 7.4, 16.5 Hz), 3.04 (dd, J = 7.0, 16.5 Hz), 7.44 (d, 2H, J = 7.1 Hz), 7.48 (d, 2h, J = 8.1 Hz), 7.58 (2H, d, J = 2.5 Hz), 8.15 (s (broad), 3H) and THF 1.76 (m, 0.25 × 4H), 3.60 (m, 0.25 × 4H); ^{13}C NMR ($CDCl_3$, TMS) (ppm) 13.9, 21.4, 25.6, 36.3, 49.3, 61.4, 67.9, 123.5, 125.2, 125.5, 125.8, 128.9, 129.9, 140.6, 140.6, 149.2, 170.2 and THF 25.6, 67.9; $[\alpha]^{25}_D$ +6.7 (*c* 1.063, $CHCl_3$); IR (MIR) (cm^{-1}) 3146, 2981, 2904, 1724, 1596, 1472. Microanal. Calcd for $C_{18}H_{21}Cl_2O_6S$·$0.25C_4H_8O$: C, 48.73; H, 4.95; N, 2.99; Cl, 15.14. Found: C, 48.91; H, 4.95; N, 2.90; Cl, 14.95.

(3*S*)-3-Amino-3-(3-bromo-5-chloro-2-hydroxyphenyl)-propionic Acid Ethyl Ester *p*-Toluene-4-sulfonic Acid (18b). Following the general procedure A, **15b** was prepared as crude from (*S*)-phenylglycinol (54.86 g, 0.4 mol) and aldehyde **14b** (129.42 g, 0.4 mol).

Following the general procedure B, crude **16b** (221.0 g) was prepared as an orange oil as a single diastereoisomer as determined by ^{1}H NMR and ^{13}C NMR from **3** (332.0 g, 0.8 mol, solid) in NMP and crude imine **15b** in NMP.

Following general procedures D and F, **18b** (55 g as a white solid) was isolated as a salt containing 0.25 equiv of THF from a portion of crude **16b** (~111.0 g, calcd 0.2 mol), $Pb(OAc)_4$ (88.67 g, 0.2 mol), and pTSA·H_2O (50 0.0 g, 0.26 mol).

^{1}H NMR (d_6-DMSO, TMS) (ppm) 1.14 (t, 3H), 2.29 (s, 3H), 3.0 (m, 2H), 4.05 (q, 2H), 4.9 (t, 1H), 7.11 (d, 2H), 7.48 (dd, 3H), 7.70 (d, 1H), 8.35 (br s, 3H); ^{13}C NMR (DMSO, TMS) (ppm) 13.8, 20.8, 37.2, 45.8, 60.6, 112.5, 124.1, 125.5, 127.2, 127.6, 128.1, 132.2, 137.9, 145.2, 150.7, 168.98; DSC 146.19 °C (endo), 178.15 °C (endo, 68.66 J/g), 210.63 °C (exo); $[\alpha]^{25}_D$ +6.3 (*c* 1.110, MeOH); IR (MIR) (cm^{-1}) 3036, 2980, 2903, 2857, 1722, 1595, 1486, 1467, 1419, 1376. Microanal. Calcd for $C_{18}H_{21}BrClNO_6S$: C, 43.69; H, 4.27; N, 2.83; Br, 16.15; Cl, 7.16; S, 6.48. Found: C, 44.47; H, 4.46; N, 2.66; Br, 15.15; Cl, 7.05; S, 6.52.

(3*S*)-3-Amino-3-(5-bromo-3-chloro-2-hydroxyphenyl)-propionic Acid Ethyl Ester *p*-Toluene-4-sulfonic Acid (18c). Following the general procedure A **15c** (48.0 g) was prepared as a pale yellow oil from (*S*)-phenylglycinol (13.71 g, 0.1 mol) and aldehyde **14c** (32.35 g, 0.1 mol).

Following the general procedure B, crude **16c** (228.0 g) was prepared as an orange oil as a single diastereoisomer as determined by ^{1}H NMR and ^{13}C NMR from **3** (332.0 g, 0.8 mol, solid) in NMP and crude imine **15c** in NMP.

Following general procedures D and F, **18c** (38 g) was prepared as a white solid from a portion of crude ester **16c** (calcd 111.0 g, corrected for 0.2 mol), $Pb(OAc)_4$ (88.67 g, 0.2 mol), and pTSA·H_2O (50.0 g, 0.26 mol).

^{1}H NMR (DMSO, TMS) (ppm) 1.12 (t, 3H), 2.29 (s, 3H), 3.0 (m, 2H), 4.05 (q, 2H), 4.88 (t, 1H), 7.11 (d, 2H), 7.48 (d, 2H), 7.55 (d, 1H), 7.68 (1H, d), 8.35 (br s, 3H); ^{13}C NMR (DMSO, TMS) (ppm) 13.8, 20.8, 37.1, 45.6, 60.6, 110.6, 122.5, 125.4, 127.9, 128.1, 129.5, 131.9, 137.8, 145.3, 150.1, 168.9; $[\alpha]^{25}_D$ +4.2 (*c* 0.960, MeOH); IR (MIR) (cm^{-1}) 2922, 1726, 1621, 1591, 1494, 1471, 1413, 1376, 1324, 1286, 1237, 1207. Microanal. Calcd for $C_{18}H_{21}BrClNO_6S$: C, 43.69; H, 4.27; N, 2.83; Br, 16.15; Cl, 7.16; S, 6.48. Found: C, 43.40; H, 4.24; N, 2.73; Br, 16.40; Cl, 7.20; S 6.54.

Acknowledgment. The authors thank Teddy Albano, Daniel L. Sweeney, Patricia M. Finnegan, and the Physical Methodology Department for their analytical support.

JO050177H