Chlorotitanium Enolate Addition to Aldimines: A Stereoselective Route to α-Oxy-β-substituted-β-amino Esters

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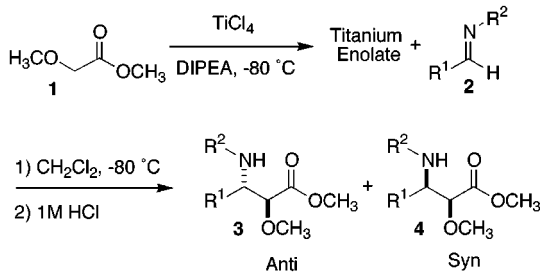
β-Amino acids, although far less abundant in nature than their α-analogues, nevertheless hold an important place in pharmacology.[1] The β-lactam antibiotics are the best known class of medicinally important β-amino acid derivatives.[2] Recently, attention has been focused on the ability of peptides composed of β-amino acids to adopt predictable and reproducible folding patterns similar to those observed for α-amino acid peptides.[3] Thus, new methods for the preparation of this useful class of molecules are constantly being pursued.[4]

As the β-amino ester side chain of Taxol, the phenylisoserine derivatives have attracted considerable synthetic interest.[5] We have been particularly interested in developing a stereoselective, one-step approach to this class of molecules. There are two general strategies for the preparation of these compounds: (a) direct coupling of the C_2-C_3 bond, or (b) the functional transformation of the C_2-C_3 positions of cinnamic acid derivatives. An attractive approach, which has received little attention, is the direct coupling of the chlorotitanium enolates of glycolate esters to aldimines.

In a pair of engaging papers in 1992, two groups independently reported that the aldol reaction between chlorotitanium enolates of O-protected aryl thioglycolates and various aldehydes cleanly afforded the α,β-dihydroxy thioesters in excellent yields.[6] Both groups demonstrate that these aldol reactions lead predominately to the anti isomer. The Cozzi group further demonstrated that the relative stereochemical outcome of these reactions depended on the steric bulk of the O-protecting group, with the smaller group (benzyl) leading to the anti (**a**) diastereomer and the larger (TBDMS) to the syn (**s**).[6b] Here we report the extension of this chemistry to the addition of the chlorotitanium enolates of methyl methoxyacetate[7] to aldimines. These coupling reactions afford, in a single step, the α-oxy-β-substituted-β-amino esters with good to excellent diastereoselectivety for the anti isomer[8] and comparable yields (Scheme 1).

Scheme 1



To effect the synthesis of the β-amino esters, methyl methoxyacetate was readily enolized in CH_2Cl_2 by treatment with $TiCl_4$ and diisopropylethylamine (DIPEA) at −80 °C, followed by transfer of the violet enolate solution to 0.5 mol equiv of the imine in CH_2Cl_2 at −80 °C. This resulted in generally excellent yields of the β-amino esters (Scheme 1 and Table 1). In most cases, the **a**:**s** ratios were determined on the crude materials by HPLC. In all cases, however, the diastereomers were easily distinguishable by 200-MHz ^{1}H NMR spectroscopy. The configuration of ester **3g**, the major product of imine **2g**, was confirmed to be the anti isomer by X-ray structure determination. Serendipitously, the minor product of imine **2f**, ester **4f**, spontaneously crystallized. This product was isolated, and the configuration was also confirmed by X-ray to be the syn isomer.[9] The results of our structural studies gave us great confidence in assigning the anti configuration to the major isomers on the basis of chemical shift, coupling constant trends,[10] and common HPLC behavior of the products.[11]

We have first explored the effect of imine substitution. As can be seen from these data, these reactions lead to

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(3) For examples, see: (a) Seebach, D.; Overhand, M.; Kühnle, F. N. M.; Martinoni, B.; Oberer, L.; Hommel, U.; Widmer, H. *Helv. Chim. Acta* **1996**, *79*, 913−941. (b) Appela, D. H.; Christianson, L. A.; Karle, I. L.; Powel, D. R.; Gellman, S. H. *J. Am. Chem. Soc.* **1996**, *118*, 13071−13072.

(4) For a further review of β-amino acid synthesis, see: D. C. Cole *Tetrahedron* **1994**, *50*, 9517−9582.

(5) For a comprehensive review, see the other chapters in *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, 1996.

(6) (a) Mukai, C.; Kim, I. J.; Hanaoka, M. *Tetrahedron: Asymmetry* **1992**, *3*, 1007−1010. (b) Annunziata, R.; Cinquini, M.; Cozzi, F.; Borgia, A. L. *J. Org. Chem.* **1992**, *57*, 6339−6342.

(7) Cozzi and co-workers, in ref 6b, use only TEA as the base and report that alkoxy esters such as methyl (benzyloxy)acetate do not enolize. However, M. Bilodeau in his thesis (Bilodeau, M. T. Ph.D. Thesis, Harvard University, November 1993.) reported that methyl (methoxy)acetate is enolizable if DIPEA is used as base. Further, we have found that several other alkoxy esters, including methyl (benzyloxy)acetate, are enolized if DIPEA rather than TEA is used as base.

(8) (a) Our results are complimentary to those of Ellman and co-workers in which they obtain the syn-products via the addition of the lithium−titanium-ate enolate of methyl propanoate to a chiral *tert*-butanesulfanyl imine. Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 12−13. (b) Kobayashi and co-workers have reported an enantioselective preparation of both syn and anti β-amino esters via the addition of an α-*O*-benzylsilylketeneacetal to aldimines using a chiral bis-1,1′-bi-2-naphthol zirconium catalyst. In several cases their system was able to achieve anti:syn ratios of 92:8, with ee's as high as 96%. Kobayahi, S.; Haruro, I.; Ueno, M. *J. Am. Chem. Soc.* **1998**, *120*, 431−432.

(9) Crystal structures and refinement data for esters **3g** and **4f** are available in the Supporting Information.

(10) For example, the anti isomers generally feature larger C*H*(NHR)-C*H*(OMe) *J* values. Also, the C*H*(OMe) generally resonates at lower field in anti isomers than in syn.

(11) In all cases where separation was possible the anti isomer eluted prior to the syn.

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Table 1. Effect of Imine Substitution on Yield and Diastereoselectivity

imine	R^1	R^2	yield (%)[c]	dr (**a**:**s**)
2a	Ph	*o*-ClPh	83	93:7[e]
2b	Ph	*o*-EtPh	73	92:8
2c	Ph	PMP[a]	77	79:21
2d	Ph	*p*-NO_2Ph	52	77:23[e]
2e	Ph	Ph	70	78:22
2f	Ph	OMP[b]	95	94:6
2g	*p*-ClPh	OMP	95	95:5
2h	PMP[a]	OMP	84	94:6
2i	*p*-CH_3Ph	OMP	95	92:8
2j	*β*-naphthyl	OMP	87	92:8
2k	furanyl	OMP	95	95:5
2l	*tert*-Bu	OMP	NR[d]	

[a] *p*-Methoxyphenyl. [b] *o*-Methoxyphenyl. [c] Isolated yield. [d] No Reaction. [e] Determined by ^{1}H NMR of the crude reaction mixture.

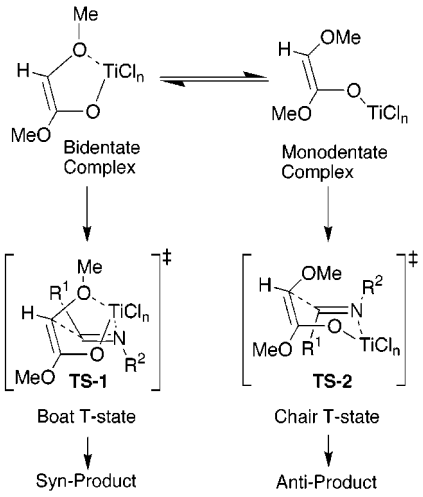
the formation of the anti ester with generally excellent diastereoselectivity. These results appear to be dependent on the nature of the imine substituents. Two observations are of particular interest: (1) the presence of an *ortho*-substituent other than hydrogen, on the R^2 group of the imine leads to excellent anti selectivity (avg: 93:7) and, (2) the nonenolizable alkyl imine **2l**, is completely unreactive under our conditions.

Our choice of the *o*-methoxyphenyl (OMP) group was prompted by the observation that an *ortho*-substituent on the imine R^2 group leads to higher anti selectivity, and our recent experience in the preparation of *β*-amino esters as the sole products via the addition of (methoxycarbonyl)methyl zinc bromide to aldimines derived from *o*-methoxyaniline.[12] In addition, the OMP group, like the PMP group, is easily removed by mild CAN oxidation[8b,13a] or $AgNO_3$/$(NH_4)S_2O_8$.[13b]

The nature of the chlorotitanium enolate is uncertain[14] and demands caution in proposing models of stereoselection. However, it would be expected that the (*Z*)-titanium enolate could be formed exclusively by the intramolecular chelation between the oxygen of the methyloxy group and that of the carbonyl group through the titanium.[15] Therefore, the stereoselecivity difference between imines with and without an R^2 *ortho* substituent suggests different transition states.

Our working hypothesis is that for the *Z*-enolate an equilibrium with the titanium is established between a bidentate complex and a monodentate complex (Scheme 2).[16] The syn isomer results from the bidentate chelate through the boatlike transition-state, **TS-1**.[17] The anti isomer results from the monodentate complex through the Zimmerman−Traxler chair-type transition-state, **TS-2**.[18,19]

Scheme 2



We would expect the bidentate complex to predominate in the equilibrium.[16] Thus, we rationalize the observed stereoselectivity in the following way: the R^2 group of the imine experiences greater crowding in the endo position of the boatlike **TS-1**, which is relieved in the chair-type **TS-2**. Increasing the steric demand of the R^2 group by the addition of an *ortho* substituent further increases these interactions in the already crowded bicyclic **TS-1** system. Additionally, we feel that the experiments with imines **2a** (*o*-chloro, **a**:**s** 93:7) and **2b** (*o*-ethyl, **a**:**s** 92:8), buttress our steric argument and likely rule out any significant contribution from electronic or chelation effects due to the presence of the OMP group.[20]

In summary, we have demonstrated that the chlorotitanium enolate of methyl methoxyacetate adds to relatively unactivated aldimines, affording the α-oxy-*β*-substituted-*β*-amino esters as the sole products. These reactions are diastereoselective, affording the anti isomers of these α,*β*-substituted *β*-amino esters in generally excellent yields. Experiments to elucidate the mechanism and expand the scope of this chemistry are ongoing. The results of these and other experiments will be reported in due course.

Experimental Section

General. Melting points were measured in open capillary tubes and are uncorrected. Elemental analyses, were performed by Atlantic Microlabs of Norcross, GA, and low- and high-resolution mass spectra were performed by the Mass Spectrometry Service of the University of Illinois. ^{1}H NMR spectra were determined at 200 MHz, and ^{13}C NMR spectra were determined at 50 MHz. Chemical shifts are expressed in parts per million (*δ* units) downfield from tetramethylsilane used as an internal reference. Analytical HPLC was carried out using a Zorbax

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(17) Both Hanaoka (ref 6a) and Cozzi (ref 6b) propose bidentate boatlike transition states in which the aldehyde oxygen coordinates with the titanium atom resulting in *anti*-aldol products. While our results seem to be at odds with those of Hanaoka and Cozzi, we do not think they are. It is important to note that contrary to an aldehyde substrate, our *E*-imine substrates are restricted to only one binding mode. Thus, a boatlike transition state places the R^1 substituent in an *exo* environment, leading to the syn isomer. If the relative imine orientation is reversed, a boat-type complex is not possible.

(18) Assuming a *Z*-enolate, a Zimmerman−Traxler chair-type **TS** model leading to the anti ester is precisely in accord with the Zimmerman−Traxler chair-type **TS** model proposed by Ellman and co-workers, ref 8a, leading to the syn-ester, via an *E*-enolate.

(19) Our model predicts that increasing the Lewis basicity of the α-oxygen of the glycolate would be expected to stabilize the formation of the boat **TS** and thus increase the relative percentage of the syn ester. To test this we generated the enolate of methyl glycolate using 2 equiv of DIPEA, which was added to imine **2g** at −80 °C. The subsequent **a**:**s** ratio observed for ester adducts was 50:50**,** in accord with our model (unpublished results from these laboratories).

(20) It is interesting to note that while the steric demands of the R^2 substituent appear to be of importance to the mode of stereoselection, the same does not appear to be so for the R^1 group. Increasing the steric demand of the R^1 group (**2j**, R^1 = *β*-naphthyl) does not significantly effect the diastereoselection (**a**:**s**, 92:8).

SB-C18 4.6 mm × 25 mm column. A reverse phase acetonitrile (ACN)−water solvent system was used, with ACN as the eluting solvent. Four solvent gradients were used to achieve diastereomer separation and are detailed in the Supporting Information. All enolate reactions were run under N_2. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride under N_2 immediately prior to use. All other commercially available reagents and solvents were used without further purification unless otherwise noted. In all cases, 1 h was allowed for the formation of the titanium enolates. Enolates were reacted with imines for 1 h, unless otherwise indicated.

General Procedure. Methyl 3-[(2-Methoxyphenyl)amino]-2-methoxy-3-(4-methoxyphenyl)propanoate (3h). To a stirred solution of methyl methoxyacetate (**1**) (2.0 mmol) in CH_2Cl_2 (6.0 mL) cooled at −78 °C was added, dropwise, 2.1 mL of a 1.0 M solution of $TiCl_4$ in CH_2Cl_2 (2.1 mmol). After 5 min, DIPEA (400 μL, 2.2 mmol) was added dropwise affording a violet solution indicative of enolate formation. After 1 h the enolate solution was transferred via cannula to a stirred solution of the aldimine (1.0 mmol) in CH_2Cl_2 at −78 °C. After 1 h the reaction was quenched with the addition of approximately 10 mL of aqueous 1 M HCl. The organic phase was separated, washed sequentially with 25 mL of water and brine, dried with $MgSO_4$, filtered, and concentrated in vacuo to afford 0.40 g as a brown oil, which was purified by column chromatography, to afford 0.31 g (84%) of **3h** as a yellow oil. **Note:** Column chromatography should be done within a day or two of the workup or the crude products turn a deep forest green (due presumably to residual titanium salts). Chromatography of the deep green products results in considerable decrease in yields: R_f = 0.19 (SiO_2, 5% Et_2O/CH_2Cl_2); IR (thin film); 3419, 1750 cm^{-1}; 200 MHz ^1H NMR; δ 7.23 (d, 2H, J = 9.0), 6.81 (d, 2H, J = 9.0), 6.74−6.62 (m, 3H), 6.45 (dd, 1H, J = 7.0 Hz, J = 2.0 Hz), 5.30 (d, 1H, J = 8.0 Hz), 4.80 (dd, 1H J = 8.0 Hz, J = 5.0 Hz), 4.18 (d, 1H, J = 5.0), 3.89 (s, 3H), 3.76 (s, 3H), 3.67 (s, 3H), 3.44 (s, 3H); 50 MHz ^{13}C NMR; δ 170.9, 159.1, 147.2, 136.2, 130.3, 128.6, 121.1, 117.1, 113.8, 111.5, 109.6, 83.7, 56.2, 58.4, 55.5, 55.1, 51.9; HRMS, calcd for $C_{19}H_{23}NO_5$ 345.1576, found 345.1574; HPLC (gradient #1, flow rate = 1.0 mL/min): t_R = 8.8 min (major diastereomer), t_R = 9.2 min (minor diastereomer); minor isomer **4a** (syn) C*H*(OMe) signal: 200 MHz ^1H NMR; δ 4.08 (d, J = 3.0 Hz).

Methyl 3-[(2-Chlorophenyl)amino]-2-methoxy-3-phenylpropanoate (3a). Reaction time = 12 h. The crude product is a brown oil and isolated as a yellow oil, isolated yield: 83%: R_f = 0.17 (SiO_2, 25% hexane/CH_2Cl_2); IR (Thin Film); 3403, 1754 cm^{-1}; 200 MHz ^1H NMR; δ 7.32−7.26 (m, 6H), 6.98 (dt, 1H, J = 7.0 Hz, J = 1.0 Hz), 6.59 (dt, 1H, J = 7.0 Hz, J = 1.0 Hz), 6.47 (dd, 1H, J = 8.0 Hz, J = 5.0 Hz), 5.53 (d, 1H, J = 8.0 Hz), 4.86 (dd, 1H J = 8.0 Hz, J = 5.0 Hz), 4.20 (d, 1H, J = 5.0 Hz), 3.67 (s, 3H), 3.46 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 170.5, 142.3, 137.6, 129.1, 128.5, 128.0, 127.7, 127.4, 119.8, 117.9, 112.7, 83.5, 59.3, 58.9, 52.0; HRMS, calcd for $C_{17}H_{16}ClNO_3$ 319.0970, found 319.0968. Minor isomer **4a** (syn) C*H*(OMe) signal: 200 MHz ^1H NMR; δ 4.08 (d, J = 3.0 Hz).

Methyl 3-[(2-Ethylphenyl)amino]-2-methoxy-3-phenylpropanoate (3b). The crude product is a brown oil and isolated as a yellow oil, isolated yield: 73%: R_f = 0.15 (SiO_2, 25% hexane/CH_2Cl_2); IR (thin film); 3429, 1743 cm^{-1}; 200 MHz ^1H NMR; δ 7.35−7.26 (m, 5H), 7.08−6.91 (m, 2H), 6.69−6.61 (m, 1H), 6.4 (dd, 1H, J = 8.0 Hz, J = 1.0 Hz), 4.87 (s, 1H), 4.19 (d, 1H, J = 4.0 Hz), 3.62 (s, 3H), 3.43 (s, 3H), 2.61 (q, 2H, J = 7.0 Hz), 1.31 (t, 3H, J = 7.0 Hz); 50 MHz ^{13}C NMR; δ 170.9, 143.8, 138.5, 128.5, 128.2, 128.0, 127.8, 127.3, 126.9, 117.6, 111.5, 83.7, 59.1, 59.0, 51.9, 24.2, 13.0; HRMS, calcd for $C_{19}H_{23}NO_3$ 313.1678, found 313.1678. HPLC (gradient # 3): t_R = 11.7 min (major diastereomer), t_R = 12.0 min (minor diastereomer). Minor isomer **4b** (syn) C*H*(OMe) signal: 200 MHz ^1H NMR; δ 4.08 (d, J ≤ 2.0 Hz).

Methyl 3-[(4-Methoxyphenyl)amino]-2-methoxy-3-phenylpropanoate (3c). The crude product is a brown oil which slowly crystallizes and isolated as a pale yellow oil which slowly crystallizes, isolated yield: 77%: mp = 84−86 °C; R_f = 0.26 (SiO_2, 2.5/37.5/60% ether/Hexane/CH_2Cl_2); IR (Thin Film); 3391, 1752 cm^{-1}; 200 MHz ^1H NMR; δ 7.36−7.23 (m, 5H), 6.70 (d, 2H, J = 9.0 Hz), 6.57 (d, 2H, J = 9.0 Hz), 4.75 (d, 1H, J = 5.0 Hz), 4.20 (d, 1H, J = 5.0 Hz), 3.69 (s, 3H), 3.62 (s, 3H), 3.44 (s, 3H); 50 MHz ^{13}C NMR; δ 170.8, 152.3, 140.6, 138.2, 128.4, 127.8, 127.4, 115.5, 114.7, 83.4, 60.2, 59.0, 55.6, 51.8. An analytical sample was recrystallized from 95% ethanol as white needles. Anal. Calcd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.69; H, 6.79; N, 4.37; HRMS, calcd for $C_{18}H_{21}NO_4$ 315.1471, found 315.1471. HPLC (gradient #3): t_R = 7.1 (major diastereomer), t_R = 7.8 (minor diastereomer). Minor isomer **4c** (syn) C*H*(OMe) signal: 200 MHz ^1H NMR; δ 4.03 (d, J = 3.0 Hz).

Methyl 3-[(4-Nitrophenyl)amino]-2-methoxy-3-phenylpropanoate (3d). The crude product is a brown oil and isolated as a yellow/orange oil, isolated yield: 52%; R_f = 0.20 (SiO_2, 5% hexane/CH_2Cl_2); IR (thin film); 3476, 3373, 1744 cm^{-1}; 200 MHz ^1H NMR; δ 8.01 (d, 2H, J = 9.0 Hz), 7.30 (m, 5H), 6.52 (d, 2H, J = 9.0 Hz), 5.70 (d, 1H, J = 7.0 Hz), 4.90 (dd, 1H, J = 7.0 Hz, J = 5.0 Hz), 4.21 (d, 1H, J = 5.0 Hz), 3.61 (s, 3H), 3.49 (s, 3H); 50 MHz ^{13}C NMR; δ 170.9, 151.8, 138.8, 136.5, 128.8, 128.5, 127.2, 126.1, 112.2, 82.7, 59.0, 58.6, 52.0; HRMS, calcd for $C_{17}H_{18}N_2O_5$ 330.1216, found 330.1208. Minor isomer **4d** (syn) C*H*(OMe) signal: 200 MHz ^1H NMR; δ 4.07 (d, J = 3.0 Hz).

Methyl 3-(Phenylamino)-2-methoxy-3-phenylpropanoate (3e). The crude products are a yellow/brown solid, the isolated products are a pale yellow crystalline solid, isolated yield: 70%; mp = 73−75 °C; R_f = 0.16 (SiO_2, 25% hexane/CH_2Cl_2); IR (thin film); 3401, 1743 cm^{-1}; 200 MHz ^1H NMR; δ 7.33−7.23 (m, 5H), 7.10 (t, 2H, J = 8.0 Hz), 6.67 (t, 1H, J = 8.0 Hz), 6.89 (d, 2H, J = 8.0 Hz), 4.82 (bd, 2H, J = 4.0 Hz), 4.19 (d, 1H, J = 4.0 Hz), 3.62 (s, 3H), 3.45 (s, 3H); 50 MHz ^{13}C NMR; δ 170.9, 146.5, 148.2, 129.2, 128.5, 127.9, 127.4, 118.0, 114.0, 83.4, 59.2, 59.0, 51.9. Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91; found: C, 71.38; H, 6.64; N, 4.77. HPLC (gradient #3): t_R = 8.2 (major diastereomer), t_R = 8.7 (minor diastereomer). Minor isomer **4e** (syn) C*H*(OMe) signal: 200 MHz ^1H NMR; δ 4.03 (d, J = 3.0 Hz).

Methyl 3-[(2-Methoxyphenyl)amino]-2-methoxy-3-phenylpropanoate (3f). The crude product is a brown oil and isolated as a brown oil, isolated yield: 95%. R_f = 0.12 (SiO_2, 30% hexane/CH_2Cl_2); IR (Thin Film); 3416, 1744 cm^{-1}; 200 MHz ^1H NMR; δ 7.31−7.21 (m, 5H), 6.78−6.58 (m, 3H), 6.45 (dd, 1H, J = 7.0 Hz, J = 2.0 Hz), 4.75 (bs, 1H), 4.83 (d, 1H, J = 5.0 Hz), 4.21 (d, 1H, J = 5.0 Hz), 3.89 (s, 3H), 3.65 (s, 3H), 3.44 (s, 3H); 50 MHz ^{13}C NMR; δ 170.8, 147.2, 138.4, 136.2, 128.4, 127.8, 127.5, 121.1, 117.2, 111.4, 109.6, 83.7, 59.1, 59.0, 55.6, 51.8; HRMS, calcd for $C_{18}H_{21}NO_4$ 315.1471, found 315.1479. HPLC (gradient #4): t_R = 7.1 (major diastereomer), t_R = 7.8 (minor diastereomer). Minor isomer **4f** (syn) spontaneously crystallized from the crude mixture; 200 MHz ^1H NMR; δ 7.39−7.22 (m, 5H), 6.77−6.55 (m, 3H), 6.32 (dd, 1H, J = 7.0 Hz, J = 2.0 Hz), 5.36 (d, 1H, J = 8.0 Hz), 4.75 (dd, 1H, J = 8.0 Hz, J = 3.0 Hz), 4.06 (d, 1H, J = 3.0 Hz), 3.88 (s, 3H), 3.71 (s, 3H), 3.34 (s, 3H).

Methyl 3-[(2-Methoxyphenyl)amino]-2-methoxy-3-(4-chlorophenyl)propionate (3g). The crude product is a brown oil which slowly crystallizes and isolated as a pale yellow oil which slowly crystallizes, isolated yield: 95%; mp: 99−101 °C; R_f = 0.23 (SiO_2, 40% hexane/CH_2Cl_2); IR (thin film); 3416, 1753 cm^{-1}; 200 MHz ^1H NMR; δ 7.25 (s, 4H), 6.79−6.61 (m, 3H), 6.40, (dd, 1H, J = 7.0 Hz, J = 2.0 Hz), 5.31 (d, 1H, J = 8.0 Hz), 4.81 (dd, 1H, J = 8.0 Hz, J = 5.0 Hz), 4.19 (d, 1H, J = 5.0 Hz), 3.89 (s, 3H), 3.68 (s, 3H), 3.45 (s, 3H); 50 MHz ^{13}C NMR; δ 170.5, 147.1, 136.9, 135.7, 133.4, 128.8, 128.4, 121.0, 117.4, 111.4, 109.5, 83.3, 59.1, 58.3, 55.5, 51.9. Anal. Calcd for $C_{18}H_{20}NO_4Cl$: C, 61.80; H, 5.76; N, 4.00. Found: C, 61.78; H, 5.86; N, 3.91. HPLC (gradient #3): t_R = 12.5 (major diastereomer), t_R = 13.5 (minor diastereomer). Minor isomer **4g** (syn) spontaneously crystallized from a dilute 95% ethanol solution; mp: 163−164 °C; 200 MHz ^1H NMR; δ 7.32 (d, 2H, J = 9.0 Hz), 7.26 (d, 2H, J = 9.0 Hz), 6.78−6.58 (m, 3H), 6.28, (dd, 1H, J = 8.0 Hz, J = 2.0 Hz), 5.34 (d, 1H, J = 8.0 Hz), 4.85 (dd, 1H, J = 8.0 Hz, J = 3.0 Hz), 4.02 (d, 1H, J = 3.0 Hz), 3.88 (s, 3H), 3.73 (s, 3H), 3.35 (s, 3H).

Methyl 3-[(2-Methoxyphenyl)amino]-2-methoxy-3-(4-methylphenyl)propanoate (3i). The crude product is a brown oil and isolated as a light brown oil which slowly crystallizes. Isolated yield: 95%; mp: 83−85 °C; R_f = 0.17 (SiO_2, 25% hexane/CH_2Cl_2); IR (thin film); 3416, 1755 cm^{-1}; 200 MHz ^1H NMR; δ 7.19 (d, 1H, J = 8.0 Hz), 7.07 (d, 1H, J = 8.0 Hz), 6.78−6.58 (m, 3H), 6.45 (dd, 1H, J = 7.0 Hz, J = 2.0 Hz), 5.32 (d, 1H, J = 7.0 Hz), 4.80 (dd, 1H, J = 7.0 Hz, J = 5.0 Hz), 4.19 (d, 1H, J = 5.0 Hz), 3.88 (s, 3H), 3.67 (s, 3H), 3.43 (s, 3H), 2.28 (s, 3H); 50 MHz ^{13}C NMR; δ 170.8, 147.0, 137.1, 136.1, 135.1, 129.0, 127.2, 121.0,

116.9, 111.3, 109.4, 83.6, 59.0, 58.5, 55.4, 51.7, 21.0; HRMS, calcd for $C_{19}H_{23}NO_4$ 329.1627, found 329.1621; HPLC (gradient #3): $t_R = 10.7$ (major diastereomer), $t_R = 11.5$ (minor diastereomer). An analytical sample was recrystallized from 95% ethanol as colorless prisms. Anal. Calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.22; H, 7.06; 4.25. Minor isomer **4i** (syn) C*H*(OMe) signal: 200 MHz ^{1}H NMR; δ 4.03 (d, $J \leq 2.0$ Hz).

Methyl 3-[(2-Methoxyphenyl)amino]-2-methoxy-3-naphthylpropanoate (3j). The crude product is a yellow oil which slowly crystallizes and isolated as pale yellow oil which slowly crystallizes as fine yellow needles. Isolated yield: 87%; mp = 103−105 °C; $R_f = 0.17$ (SiO_2, 25% hexane/CH_2Cl_2); IR (thin film); 3414, 1744 cm^{-1}; 200 MHz ^{1}H NMR; δ 7.80−7.75 (m, 4H), 7.49−7.40 (m, 3H), 6.78−6.57 (m, 3H), 6.47 (dd, 1H, $J = 7.0$ Hz, $J = 2.0$ Hz), 5.47 (bs, 1H), 4.98 (d, 1H, $J = 5.0$ Hz), 4.28 (d, 1H, $J = 5.0$ Hz), 3.91 (s, 3H), 3.63 (s, 3H), 3.45 (s, 3H); 50 MHz ^{13}C NMR; δ 170.9, 147.2, 136.3, 136.2, 133.3, 133.2, 128.2, 128.1, 127.7, 126.7, 126.0, 125.9, 125.3, 121.1, 117.3, 111.5, 109.6, 83.9, 59.3, 59.2, 55.6, 52.0. HPLC (gradient #2): $t_R = 13.3$ (major diastereomer), $t_R = 14.3$ (minor diastereomer). An analytical sample was recrystallized from 95% ethanol as fine white needles. Anal. Calcd for $C_{22}H_{23}NO_4$: C, 72.31; H, 6.34; N, 3.71. Found: C, 72.34; H, 6.29; 3.71. Minor isomer **4j** (syn) C*H*(OMe) signal: 200 MHz ^{1}H NMR; δ 4.15 (d, $J = 4.0$ Hz).

Methyl 3-[(2-Methoxyphenyl)amino]-2-methoxy-3-(2-furanyl)propanoate (3k). Crude product is dark red oil and is isolated as a red oil, isolated yield: 95%: $R_f = 0.11$ (SiO_2, 100% CH_2Cl_2); IR (thin film); 3402, 1754 cm^{-1}; 200 MHz ^{1}H NMR; δ 7.33 (m, 1H), 6.87−6.62 (m, 5H), 6.28−6.24 (m, 1H), 5.03 (d, 1H, $J = 4.0$ Hz), 4.21 (d, 1H, $J = 4.0$ Hz), 3.86 (s, 3H), 3.75 (s, 3H), 3.46 (s, 3H); 50 MHz ^{13}C NMR; δ 170.7, 151.8, 147.4, 142.1, 135.9, 121.1, 117.9, 111.6, 110.3, 110.0, 108.0, 81.6, 56.6, 55.5, 53.6, 52.0. HRMS, calcd for $C_{16}H_{19}NO_5$ 305.1263, found 305.1257; HPLC (gradient #3): $t_R = 7.8$ (major diastereomer), $t_R = 8.4$ (minor diastereomer). Minor isomer **4k** (syn) C*H*(OMe) signal: 200 MHz ^{1}H NMR; δ 4.30 (d, $J \leq 1.0$ Hz).

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Supporting Information Available: Experimental procedure and characterization data for the aldimine **2l**, representative β-amino ester ^{1}H NMR and ^{13}C NMR spectra, and the crystal structures and refinement data for esters **3g** and **4f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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