A Simple Route to α-Substituted-β-Amino Ester Precursors of Carbapenem Antibiotics

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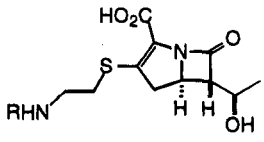
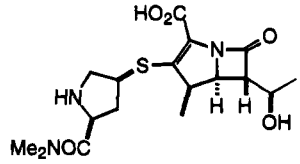
A three-step process is presented for the preparation of α-substituted-β-amino esters which can serve as precursors to a key intermediate in carbapenem synthesis. The pivotal reaction in this sequence involves a highly diastereoselective conjugate addition reaction. Two series of alkenoates bearing a stereogenic substituent attached to C2 were prepared and their conjugate addition reactions with benzylamine studied under several different sets of conditions. Conjugate addition of benzylamine to alkenoates **7a** and **7d**, in methanol at room temperature, gave adducts **8a** and **8d** with virtually complete *anti*-diastereoselectivity. These two β-amino esters bear the correct relative stereochemistry and side chain to serve as precursors for carbapenem antibiotic synthetic intermediates. The role of the allylic substituents of the alkenoates **7a–e** in determining the stereochemical outcome of these additions is discussed. These conjugate additions were explored further by the preparation and conjugate addition reactions of the α,β-disubstituted alkenoates **15a** and **15b**. It was found that the presence of a β-substituent led to a dramatic reduction in yield although the same *anti*-diastereoselectivity was maintained. The relative stereochemistry of the adducts was established by examination of the relevant coupling constants in the ^{1}H NMR spectra of their tetrahydro-1,3-oxazine derivatives.

Introduction

Much attention has been paid to the synthesis of the therapeutically useful carbapenem antibiotics including thienamycin,[1] imipenem[2] and, in particular β-methyl derivatives[3] such as meropenem.[4] These last derivatives are important as the presence of the β-methyl substituent confers significantly improved chemical and metabolic stability.



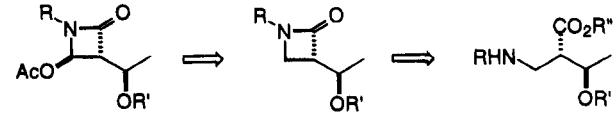
R = H, Thienamycin
R = CH=NH, Imipenem



Meropenem (SM-7338)

The 4-acyloxy-3-(1-alkoxyethyl)-2-azetidinone system, **1** (Scheme 1) has proved to be a popular intermediate in carbapenem synthesis.[5] This intermediate is readily available from 2-azetidinone **2** by oxidation of C4.[6] 2-Azetidinones like **2** could be generated from α-substituted-β-amino esters such as **3**.[7] In this paper we demonstrate a simple method for synthesizing **3** in racemic form from readily available precursors.[8] The pivotal reaction is a highly diastereoselective conjugate addition reaction.[9,10]

Scheme 1. Retrosynthesis of 4-Acetoxy-3-(1-hydroxyethyl)-2-azetidinones



1 **2** **3**

Results and Discussion

The first step in the sequence involved Baylis–Hillman coupling of a propenoate with the series of aldehydes given in Scheme 2.[11] Yields varied between 57 and 97%. After some initial experimentation it was found that the conjugate addition of benzylamine to **4a–4f** in methanol at room temperature gave the best results (Scheme 2, Table 1). The results from the use of three other sets of

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(1) A-Schönberg, G.; Arison, B. H.; Hensens, O. D.; Hirshfield, J.; Hoogsteen, K.; Kaczka, E. A.; Rhodes, R. E.; Kahan, J. S.; Kahan, F. M.; Ratcliffe, R. W.; Walton, E.; Ruswinkle, L. J.; Morin, R. B.; Christensen, B. G. *J. Am. Chem. Soc.* **1978**, *100*, 6491.

(2) (a) Leanza, W. J.; Wildonger, K. J.; Miller, T. W.; Christensen, B. G. *J. Med. Chem.* **1979**, *22*, 1435. (b) Kropp, H.; Sundelof, J. G.; Hajdu, R.; Kahan, F. M. *Antimicrob. Agents Chemother.* **1982**, *22*, 62.

(3) Shih, D. H.; Baker, F.; Cama, L.; Christensen, B. G. *Heterocycles* **1984**, *21*, 29.

(4) Sunagawa, M.; Matsumura, H.; Inoue, T.; Fukasawa, M.; Kato, M. *J. Antibiot.* **1990**, *43*, 519.

(5) (a) Uyeo, S.; Hikaru, I. *Tetrahedron Lett.* **1994**, *35*, 4377. (b) Choi, W.-B.; Churchill, H. R. O.; Lynch, J. E.; Thompson, A. S.; Humphrey, G. R.; Volante, R. P.; Reider, P. J.; Shinkai, I. *Tetrahedron Lett.* **1994**, *35*, 2275. (c) Murayama, T.; Yoshida, A.; Kobayashi, T.; Miura, T. *Tetrahedron Lett.* **1994**, *35*, 2271. For references up to 1992, see Bender, D. R.; DeMarco, A. M.; Melillo, D. G.; Riseman, S. M.; Shinkai, I. *J. Am. Chem. Soc.* **1992**, *57*, 2411, footnotes 3 and 4.

(6) (a) Murahashi, S.; Saito, T.; Naota, T.; Kumobayashi, H.; Akutagawa, S. *Tetrahedron Lett.* **1991**, *32*, 5991. (b) Mori, M.; Kagechika, K.; Tojima, K. O.; Shibasaki, M. *Tetrahedron Lett.* **1988**, *29*, 1409. (c) Murahashi, S.; Naota, T.; Kuwabara, T.; Saito, T.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1990**, *112*, 7820. (d) Murahashi, S.; Saito, T.; Naota, T.; Kumobayashi, H.; Akutagawa, S. *Tetrahedron Lett.* **1991**, *32*, 2145. (e) Mori, M.; Kagechika, K.; Sasai, H.; Shibasaki, M. *Tetrahedron* **1991**, *47*, 531.

(7) See Wang, W.-B.; Roskamp, E. J.; *J. Am. Chem. Soc.* **1993**, *115*, 9417 and references cited therein.

(8) All compounds described in this work are racemic. For simplicity only one enantiomeric series (with a β side-chain alkoxy group) is shown throughout this paper. For the production of enantiomerically enriched "Baylis–Hillman" starting materials, see Basavaiah, D.; Rao, P. Dharma *Synth. Commun.* **1994**, *24*, 917.

(9) For a preliminary communication of part of this work see: Perlmutter, P.; Tabone, M. *Tetrahedron Lett.* **1988**, *29*, 949.

(10) For another approach to carbapenem synthesis which involves diastereoselective conjugate additions, see Tsukuda, N.; Shimada, T.; Gyoung, Y. S.; Asao, N.; Yamamoto, Y. *J. Org. Chem.* **1995**, *60*, 143.

(11) (a) Baylis, A. B.; Hillman, M. E. German Patent 2155113 (May 1992), *Chem. Abstr.* **1972**, *77*, 34174q. (b) For a review of this reaction, see: Drewes, S. E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653.

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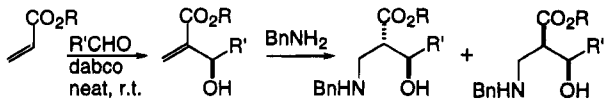
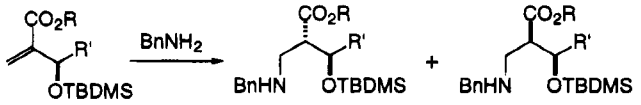
Scheme 2. Preparation and Benzylamine Additions of Alkenoates 4a–f



4a-f 5a-f (*anti*) 6a-f (*syn*)

	R	R'
a	CH_3	CH_3
b	CH_3	CH_2CH_3
c	CH_3	$CH(CH_3)_2$
d	t-Bu	CH_3
e	CH_3	Ph
f	CH_3	2-Fur

Scheme 3. Benzylamine Additions to Alkenoates 7a–f



7a-f 8a-f (*anti*) 9a-f (*syn*)

	R	R'
a	CH_3	CH_3
b	CH_3	CH_2CH_3
c	CH_3	$CH(CH_3)_2$
d	t-Bu	CH_3
e	CH_3	Ph
f	CH_3	2-Fur

reaction conditions for these additions are included in Table 1. The additions proceeded in excellent yield but with modest diastereoselectivity, typically ~4:1, in favor of the *anti*-diastereomers (**5a–f**). The worst selectivity (57:43) for the additions run in methanol was for alkenoate **4c** which bears a branched (isopropyl) side chain. Heating the reaction in tetrahydrofuran led to a reversal of selectivity with the *syn*-diastereomers being produced in ratios ranging from ~67:33 (entry 19) to 86:14 (entry 12). Very similar results were obtained by simply heating a neat mixture of the two reactants at 70 °C for 2 h (cf. entries 5 and 6, 15 and 16, 19 and 20).

In order to determine the influence on diastereoselectivity of an ether protecting group we prepared *tert*-butyldimethylsilyl ethers **7a–f**. Remarkably, additions of benzylamine to these ethers gave significantly improved diastereoselectivity while maintaining high chemical yields (Scheme 3, Table 1 entries 21–24, 26–29, 31–32). In many cases the *anti*-diastereomer was formed exclusively.

For example, whereas addition of benzylamine to **4a** gave adducts **5a** and **6a** in a ratio of 82:18 (entry 1), similar addition to **7a**, the TBDMS ether of **4a**, provided only the *anti* isomer **8a** in 82% isolated yield (entry 21).

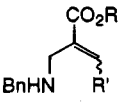
Several other trends also emerged from this study. Heating the additions of benzylamine to **4a–f** in methanol generally reduced selectivity for the *anti*-isomer. However this had little effect on the high selectivity observed in additions to the silyl ethers **7a–f**. Running

Table 1. Conjugate Addition of Benzylamine to Alkenoates 4a–f and 7a–f

entry	alkenoate	reaction conditions[a]	time (h)	product(s)	ratio **5:6**	yield (%)
1	**4a**	A	41	**5a** and **6a**	82:18	97
2	**4a**	B	4	**5a** and **6a**	82:18	87
3	**4a**	C	28	**5a** and **6a**	27:73	71
4	**4b**	A	90	**5b** and **6b**	79:21	77
5	**4b**	C	96	**5b** and **6b**	31:69	66
6	**4b**	D	2	**5b** and **6b**	31:69	76
7	**4c**	A	182	**5c** and **6c**	57:43	59
8	**4c**	B	71	**5c** and **6c**	33:67	53
9	**4c**	C	42	**5c** and **6c**	23:77	70
10	**4d**	A	43	**5d** and **6d**	77:23	56
11	**4d**	B	21	**5d** and **6d**	75:25	50
12	**4d**	C	28	**5d** and **6d**	14:86	72
13	**4e**	A	16	**5e** and **6e**	82:18	94
14	**4e**	B	8	**5e** and **6e**	68:32	80
15	**4e**	C	40	**5e** and **6e**	22:78	92
16	**4e**	D	2	**5e** and **6e**	22:78	92
17	**4f**	A	21	**5f** and **6f**	83:17	68
18	**4f**	B	5	**5f** and **6f**	67:33	58
19	**4f**	C	26	**5f** and **6f**	33:67	95
20	**4f**	D	2	**5f** and **6f**	37:63 (**8:9**)	93
21	**7a**	A	72	**8a** and **9a**	>95:5	82
22	**7a**	A	192	**8a** and **9a**	95:5	75
23	**7a**	B	18	**8a** and **9a**	95:5	83
24	**7a**	C	96	**8a** and **9a**	83:17	19[b]
25	**7b**	B	45	**8b** and **9b**	95:5	44[c]
26	**7c**	A	240	**8c** and **9c**	95:5	47[d]
27	**7c**	B	192	**8c** and **9c**	95:5	24[e]
28	**7d**	A	72	**8d** and **9d**	>95:5	58
29	**7d**	B	24	**8d** and **9d**	95:5	64[f]
30	**7d**	C	48	**8d** and **9d**	n.r.	
31	**7e**	A	96	**8e** and **9e**	95:5	92
32	**7f**	A	72	**8f** and **9f**	95:5	84

[a] Method A: 1 equiv of each reactant, methanol, 25 °C; method B: as for method A, but heated at reflux; method C: as for method B, tetrahydrofuran as solvent; method D: 1 equiv of each reactant at, 70 °C. [b] **10a** was obtained in 27% yield. [c] **10b** was obtained in 35% yield. [d] **10c** was obtained in 32% yield. [e] **10c** was obtained in 36% yield. [f] **10d** was obtained in 19% yield.

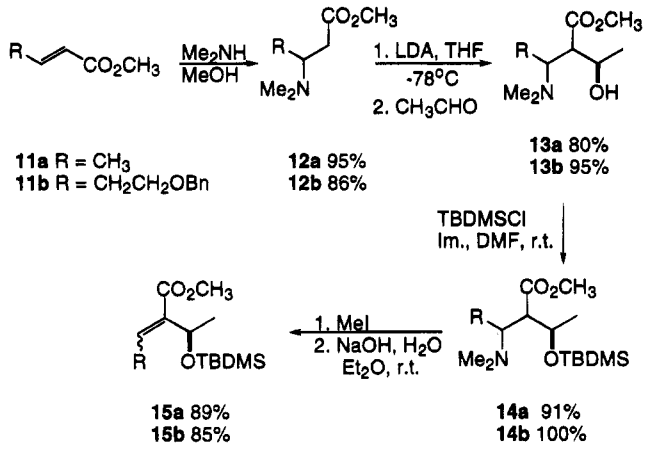
the additions to **4a–f** in refluxing tetrahydrofuran reversed the selectivity, favoring the *syn*-isomer in each case. (Heating was necessary as no addition occurred in tetrahydrofuran at room temperature). This reversal was most pronounced in the reactions of **4d**, a result which suggests that the use of sterically-demanding esters may afford *syn*-diastereomers with good selectivity. Where such influences were allowed to compete, namely a *tert*-butyl ester (*syn*-selectivity) and a TBDMS ether (*anti*-selectivity), no reaction occurred (entry 30). Reactions of silyl ethers **7a–d** which were heated generated significant quantities of addition/elimination byproducts **10a–d** (for example, entries 24–27 and 29).



10a-d

Conjugate Additions to β-Substituted Alkenoates. Although methods exist for the introduction of carbon-based substituents at C4 of 2-azetidinones it was of interest to establish whether or not such substituents could be incorporated into the 2-azetidinone precursors. In this study the most obvious way to achieve this was first to prepare β-substituted alkenoates. As the Baylis–Hillman procedure fails for the coupling of crotonates to aldehydes, we chose to apply the sequence outlined in Scheme 4. Dimethylamine was added to a solution of

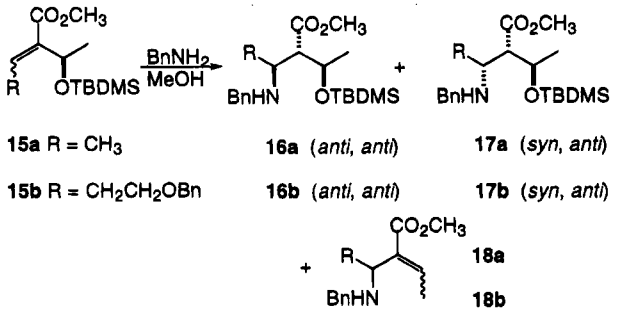
Scheme 4. Synthesis of α,β-Disubstituted Alkenoates



11a R = CH_3 **12a** 95% **13a** 80%
11b R = CH_2CH_2OBn **12b** 86% **13b** 95%

15a 89% **14a** 91%
15b 85% **14b** 100%

Scheme 5. Benzylamine Additions to Alkenoates 15a and 15b



15a R = CH_3 **16a** (*anti, anti*) **17a** (*syn, anti*)

15b R = CH_2CH_2OBn **16b** (*anti, anti*) **17b** (*syn, anti*)

18a

18b

Alkenoate	Benzylamine (equiv.)	Reaction time (h)	Temperature (°C)	Yield (%)	16:17:18
15a	1	146	rt	24	8:14:2
15a	1	71	65	51	1:1:1
15a	5	68	65	76	1:1:1
15b	1	140	65	14	1:1:4
15b	5	76	65	32	1:1:2

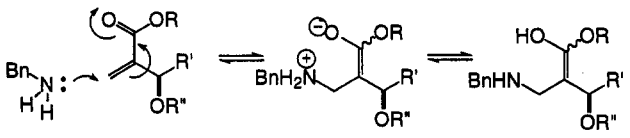
α,β-unsaturated esters **11a** and **11b**[12] in methanol.[13] Reaction of the corresponding enolates of **12a** and **12b** with acetaldehyde gave the aldols **13a** and **13b** in good yields. Attempts to regenerate the double bond at this stage led to a retroaldol reaction followed by elimination of dimethylamine. Thus it was necessary to protect the hydroxyl group before attempting the elimination reaction. Protection of **13a** and **13b** as their TBDMS ethers **14a** and **14b**, respectively, followed by quaternization of the amine and base-promoted elimination gave the desired α,β-unsaturated esters **15a** and **15b** in high yield with only a trace of the retroaldol/elimination product being observed in the case of **14b**.

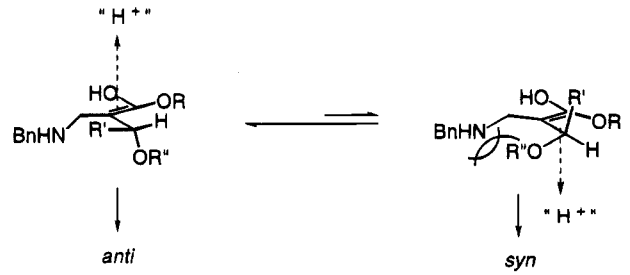
The best results for the addition to **15a** were obtained in refluxing methanol using five equivalents of benzylamine (Scheme 5). Significant amounts of addition/elimination product **18a** were formed. The addition proceeded to some extent at room temperature over several days with only very small amounts of **18a** being produced. However the yields were not useful. Consistent with the results obtained for additions to **7a–f**, only the *anti* diastereomeric adducts (with respect to the ester and silyloxy substituents) were obtained in these additions. There was no significant selectivity observed at the β-carbon.

Not surprisingly, addition is more difficult where there is increased steric demand at the β-carbon. Thus addition of benzylamine to **15b**, which bears a larger, more functionalized β-substituent, gave very poor yields of the desired adducts **16b** and **17b**. Rather the major product was the addition/elimination product **18b** (as well as some recovered **15b**). No reaction was observed if the addition to **15b** was run at room temperature.

Origins of Stereoselection in the Conjugate Additions. Standing a solution of either of the diastereomerically pure adducts **5e** or **6e** in methanol at 20 °C resulted in negligible isomerization. However, heating these same solutions to reflux led to significant equilibration. Most of the TBDMS ethers (**8a–d**) were stable in methanol, even at reflux. Only pure *anti*-**8e** equilibrated with **9e** in refluxing methanol. The *syn*-diastereomer **9e** was essentially unaffected under these conditions. Hence all the additions at room temperature in methanol were under kinetic control. (The reactions which were run neat or in tetrahydrofuran had to be heated in order for the reaction to proceed. Consequently the ratios of diastereomers obtained reflect the equilibrium ratio under these conditions).

For the kinetically-controlled additions the point at which the stereoselectivity is determined is during protonation of, most likely, either an enol or a solvated enolate. By assuming that the most populated conformation of enol or enolate has the hydrogen eclipsing (or close to eclipsing) the double bond, then protonation occurs from the less-hindered face leading to the *anti* diastereomer. Hence an increase in the size of R″ should lead to a greater preference for the *anti* isomer if reaction is through **A** rather than **B**. This is indeed what was found (additions to alcohols **4a–g** were less selective than those to the corresponding silyl ethers **7a–f**). The situation for alkenoates **15a** and **15b** is necessarily more complicated due to the presence of an extra stereocenter generated after addition of benzylamine. Remarkably this doesn't diminish the *anti*-selectivity of this process.



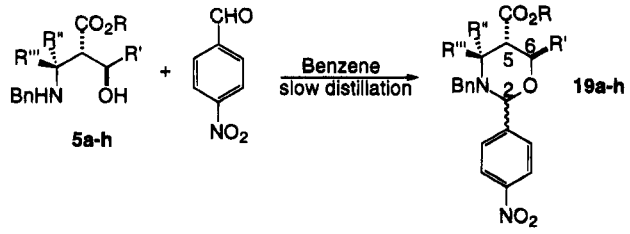


A **B**

Proof of Stereochemistry. The relative stereochemistry of the purified conjugate adducts from the addition of benzylamine to TBDMS ethers was established by measuring $J_{5,6}$ of their corresponding 1,3-oxazine derivatives **19a–h**. These were prepared by condensation of

(12) Eiter, K.; Trusicheit, E. *Annalen* **1962**, *658*, 65.
(13) It was found that the use of methanol, rather than diethyl ether, gave much better yields in this addition reaction. See Cambon, A.; Giacomoni, J.-C.; Rouvier, E. *Bull. Soc. Chim. Fr.* **1971**, 1717.

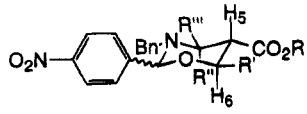
Scheme 6. Preparation of 1,3-Oxazine Derivatives 19a–h



	R	R'	R''	R'''
a	CH_3	CH_3	H	H
b	CH_3	CH_2CH_3	H	H
c	CH_3	$CH(CH_3)_2$	H	H
d	t-Bu	CH_3	H	H
e	CH_3	Ph	H	H
f	CH_3	2-Fur	H	H
g	CH_3	CH_3	CH_3	H
h	CH_3	CH_3	H	CH_3

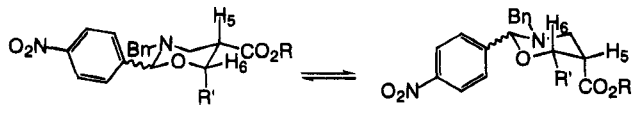
amino alcohols **5a–h** with 4-nitrobenzaldehyde using conditions described by Fodor[14] (Scheme 6).

Although this introduces a new stereocenter, at C2, $J_{5,6}$ was unaffected and was at least 10 Hz in all cases. If one assumes a chair conformation to dominate in solution then this clearly establishes the *trans* relationship in each oxazine derivative and an *anti* relationship (as shown throughout this paper) for each corresponding benzylamine adduct.



19a-h

Conversion of the *syn*-diastereomers **6a–f** to their corresponding 1,3-oxazines **20a–f**, respectively, gave products whose value for $J_{5,6}$ varied between 2.4 and 6.7 Hz, which is consistent with *cis* substitution at C5 and C6 and hence *syn* stereochemistry for **6a–f**.



20a-f

Conclusions

In summary we have demonstrated a simple three-step process for the stereoselective preparation of β-amino esters bearing a variety of side chains including that suitable for carbapenem antibiotics.

Experimental Section

Melting points are uncorrected. Kugelrohr (bulb to bulb) distillation temperatures are oven temperatures (ot) and serve only as a guide. Microanalyses were performed by the Australian National Analytical Laboratory, Melbourne. Acetaldehyde was distilled from anhydrous calcium sulfate prior to use. Sodium hydride (60% dispersion in oil) was washed with anhydrous petroleum ether prior to use. Benzene and toluene were dried with calcium hydride, distilled, and stored over sodium wire. Dichloromethane was distilled from calcium hydride and stored over 4 Å molecular sieves. Methanol was distilled from its magnesium alkoxide and stored over 4 Å molecular sieves. Diisopropylamine was distilled from sodium, stored over potassium hydroxide, and distilled prior to use. Dimethylformamide (DMF) was dried with barium oxide, decanted, distilled from calcium hydride, and stored over 4 Å molecular sieves. Anhydrous diethyl ether (ether) was dried with calcium chloride, distilled, and stored over sodium wire. Triethylamine was distilled from sodium, stored over calcium hydride, and distilled prior to use. AR grade tetrahydrofuran (THF) was stored over sodium wire and benzophenone and then distilled prior to use. Ethyl acetate was distilled from anhydrous potassium carbonate. Petroleum ether was distilled from calcium chloride and refers to the hydrocarbon fraction boiling between 60–70 °C. Chlorotrimethylsilane (TMSCl) was stirred with calcium hydride, distilled, and stored over polyvinylpyridine. All chromatography was carried out on SiO_2. Compounds **4a**[11a] and **4d–f**[15] were prepared according to literature methods.

General Procedure for the Preparation of 2-(1-Hydroxyalkyl)propenoates.[16,17] Diazabicyclo[2.2.2]octane (0.56 g, 5 mmol) was added to a mixture of the appropriate aldehyde (0.1 mol) and alkyl propenoate (0.15 mol), and the reaction mixture was then allowed to react at room temperature until ^{1}H NMR spectrocopic analysis revealed that all the aldehyde had reacted (generally several days). The reaction mixture was then dissolved in ether (20 mL), washed with water (3 × 5mL), and dried (Na_2SO_4) and the ether removed in vacuo. The residue was then distilled under reduced pressure in the presence of a small quantity of hydroquinone.[18]

Methyl 3-Hydroxy-2-methylenepentanoate (4b). Bp 125 °C/16 mm (71%). IR (film) 3320bs, 1720s, 1635w cm^{-1}. ^{1}H NMR δ 6.24 (d, J 1.0 Hz, 1H), 5.81 (t, J 1.1 Hz, 1H), 4.33 (t, J 6.4 Hz, 1H), 3.78 (s, 3H), 2.65 (bs, 1H), 1.77–1.61 (m, 2H), 0.95 (t, J 7.4 Hz, 3H). MS m/z 144 (M$^+$, 0.1%), 83 (100). Anal. Calcd for $C_7H_{12}O_3$: C, 58.3; H, 8.3. Found: C, 58.0; H, 8.6.

Methyl 3-Hydroxy-4-methyl-2-methylenepentanoate (4c). Bp 99–107 °C/18 mm (68%). IR (film) 3400bs, 1720s, 1635m cm^{-1}. ^{1}H NMR δ 6.26 (d, J 1.3 Hz, 1H), 5.77 (t, J 1.1 Hz, 1H), 4.07 (d, J 6.9 Hz, 1H), 3.78 (s, 3H), 2.49 (bs, 1H), 1.92 (p, J 6.9 Hz, 1H), 0.96 (d, J 6.9 Hz, 3H), 0.87 (d, J 6.9 Hz, 3H). MS m/z 141 (100%). Anal. Calcd for $C_8H_{14}O_3$: C, 60.7; H, 8.9. Found: C, 60.7; H, 9.0. A reaction time of 13 weeks was required to achieve the yield quoted. Heating the reaction mixture to 50 °C gave the required product in 57% yield after 5 weeks.

General Procedure for the Silylation of Alcohols 4a–f.[19] (Dimethylamino)pyridine (0.04 mmol) was added to a mixture of the appropriate alcohol (**4a–f**, 1 mmol), *tert*-butyldimethylsilyl chloride (TBDMSCl) (1.2 mmol), and triethylamine (1.2 mmol) in anhydrous DMF (2 mL). The mixture was then stirred at room temperature for 16–18 h. The reaction mixture was then added to ether (10 mL), washed with water (4 × 5 mL), and dried (Na_2SO_4) and the ether removed in vacuo. The required product was isolated using flash column chromatography or reduced pressure distillation of the residue in the presence of a small quantity of hydroquinone.

Methyl 3-(((1,1-Dimethylethyl)dimethylsilyl)oxy)-2-methylenebutanoate (7a). Bp 66–68 °C/0.9 mm (69%). IR (film) 1720s, 1630m cm^{-1}. ^{1}H NMR δ 6.19 (t, J 1.7 Hz, 1H),

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5.96 (t, J 1.7 Hz, 1H), 4.69 (qt, J 6.2, 1.7 Hz, 1H), 3.58 (s, 3H), 1.27 (d, J 6.2 Hz, 3H), 0.90 (s, 9H), 0.07 (s, 3H), 0.03 (s, 3H). MS m/z 243 ($M^+ - 1$, 3%) 73 (100). Anal. Calcd for $C_{12}H_{24}O_3Si$: C, 59.0; H, 9.9. Found: C, 59.3; H, 10.3.

Methyl 3-(((1,1-Dimethylethyl)dimethylsilyl)oxy)-2-methylenepentanoate (7b). Bp 120–130 °C (oven)/18 mm (78%). IR (film) 1722s, 1631w cm^{-1}. ^1H NMR δ 6.24 (m, 1H), 5.91 (m, 1H), 4.60 (bt, J 5.0 Hz, 1H), 3.75 (s, 3H), 1.77–1.57 (m, 1H), 1.55–1.35 (m, 1H), 0.90 (s, 9H), 0.86 (t, J 7.7 Hz, 3H), 0.07 (s, 3H), 0.03 (s, 3H). MS (methane CI) m/z 259 ($M^+ + 1$, 67%) 127 (100). Anal. Calcd for $C_{13}H_{26}O_3Si$: C, 60.5; H, 10.1. Found: C, 60.2; H, 10.4.

Methyl 3-(((1,1-Dimethylethyl)dimethylsilyl)oxy)-4-methyl-2-methylenepentanoate (7c). Bp 115 °C (oven)/5 mm (78%). IR (film) 1721s, 1632m cm^{-1}. ^1H NMR δ 6.29–6.26 (m, 1H), 5.84 (m, 1H), 4.44 b(d, J 3.5 Hz, 1H), 3.75 (s, 3H), 1.77 (dh, J 6.7, 3.5 Hz, 1H), 0.91 (d, J 6.7 Hz, 3H), 0.90 (s, 9H), 0.75 (d, J 6.7 Hz, 3H), 0.05 (s, 3H), −0.07 (s, 3H). MS (methane CI) m/z 273 ($M^+ + 1$, 0.1%), 215 (100). Anal. Calcd for $C_{14}H_{28}O_3Si$: C, 61.8; H, 10.3. Found: C, 62.2; H, 10.3.

1,1-Dimethylethyl 3-(((1,1-Dimethylethyl)dimethylsilyl)oxy)-2-methylenebutanoate (7d). Bp 66–68 °C/0.9 mm (69%). IR (film) 1710s, 1630w cm^{-1}. ^1H NMR δ 6.07 (dd, J 2.0, 1.1 Hz, 1H), 5.85 (t, J 2.0 Hz, 1H), 4.64 (bq, J 6.2 Hz, 1H), 1.49 (s, 9H), 1.26 (d, J 6.2 Hz, 3H), 0.90 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H). MS m/z 285 ($M^+ - 1$, 0.5%), 57 (100). Anal. Calcd for $C_{15}H_{30}O_3Si$: C, 62.9; H, 10.5. Found: C, 63.2; H, 10.4.

Methyl 3-(((1,1-Dimethylethyl)dimethylsilyl)oxy)-2-methylene-3-phenylpropanoate (7e). The product (R_f 0.81) was isolated (99%) using flash column chromatography, eluant: ether/petroleum ether 1:4. IR (film) 1723s, 1629m cm^{-1}. ^1H NMR δ 7.35–7.25 (m, 5H), 6.24 (d, J 1.6 Hz, 1H), 6.09 (d, J 1.6 Hz, 1H), 5.61 (s, 1H), 3.68 (s, 3H), 0.88 (s, 9H), 0.06 (s, 3H), −0.11 (s, 3H). MS m/z 291 ($M^+ - 15$, 2%) 89 (100). Anal. Calcd for $C_{17}H_{26}O_3Si$: C, 66.6; H, 8.6. Found: C, 66.7; H, 8.6.

Methyl 3-(((1,1-dimethylethyl)dimethylsilyl)oxy)-3-(2-furyl)-2-methylenepropanoate (7f). Bp 128 °C (oven)/3 mm (81%). IR (film) 1725s, 1630w cm^{-1}. ^1H NMR δ 7.25 (dd, J 1.7, 0.8 Hz, 1H), 6.29 (t, J 1.5 Hz, 1H), 6.19 (dd, J 3.2, 1.8 Hz, 1H), 6.07 (s, 1H), 6.06 (m, 1H), 5.59 (s, 1H), 3.62 (s, 3H), 0.80 (s, 9H), 0.02 (s, 3H), −0.11 (s, 3H). MS m/z 295 ($M^+ - 1$, 2%), 73 (100). Anal. Calcd for $C_{15}H_{24}O_4Si$: C, 60.8; H, 8.2. Found: C, 60.6; H, 8.2.

Conjugate Additions. Four methods were employed in the additions of benzylamine to 2-(1-hydroxyalkyl)- and 2-(((1-((1,1-dimethylethyl)dimethylsilyl)oxy)alkyl)propenoates. Method A. A solution of a propenoate (1 mmol) and benzylamine (1 mmol) in methanol (2 mL) was allowed to react at room temperature until analysis by analytical TLC indicated that the reaction was complete. Chromatography on silica gel then provided pure diastereomers. Method B. As for method A with the exception that the reaction mixture was heated to reflux. Method C. As for method B with the exception that anhydrous THF was used as the reaction solvent. Method D. As for method A with the exception that solvent was omitted and the reaction was heated to 70 °C. Refer to Table 1 in Results and Discussion for the outcome of the use of these different methods.

***anti-* and *syn*-Methyl 2-[(Benzylamino)methyl]-3-hydroxybutanoates (5a and 6a).** Purification by column chromatography (eluant ether/petroleum ether 2:1) gave **5a** (R_f 0.35) and **6a** (R_f 0.19) as pale yellow oils. **5a** IR (film) 3300bm, 1735s cm^{-1}. ^1H NMR δ 7.37–7.26 (m, 5H), 4.16 (p, J 6.3 Hz, 1H), 3.71 (s, 2H), 3.63 (s, 3H), 3.03 (dd, J 12.3, 6.7 Hz, 1H), 2.94 (dd, J 12.3, 4.0 Hz, 1H), 2.41 (ddd, J 6.7, 6.3, 4.0 Hz, 1H), 1.18 (d, J 6.3 Hz, 3H). MS m/z 238 ($M^+ + 1$, 1%), 91 (100). Anal. Calcd for $C_{13}H_{19}NO_3$: C, 65.8; H, 8.0; N, 5.9. Found: C, 65.8; H, 8.0; N, 5.7. **6a** IR (film) 3350bm, 1730s cm^{-1}. ^1H NMR δ 7.36–7.21 (m, 5H), 4.14 (dq, J 6.5, 3.9 Hz, 1H), 3.79 (d, J 13.3 Hz, 1H), 3.73 (d, J 13.3 Hz, 1H), 3.69 (s, 3H), 3.14 (bs, 2H), 3.09 (dd, J 12.2, 5.6 Hz, 1H), 2.87 (dd, J 12.2, 5.6 Hz, 1H), 2.65 (dt, J 5.6, 3.9 Hz, 1H), 1.22 (d, J 6.5 Hz, 3H). MS m/z 237 (M^+, 0.2%), 91 (100). Anal. Calcd for $C_{13}H_{19}NO_3$: C, 65.8; H, 8.0. Found: C, 65.9; H, 8.3.

***anti-* and *syn*-1,1-Dimethylethyl 3-((benzylamino)methyl)-3-hydroxybutanoates (5d and 6d).** Purification by column chromatography (eluant ether/petroleum ether 1:1) gave diastereomers **5d** (R_f 0.46) and **6d** (R_f 0.25) as a colorless oil and a colorless solid, respectively. Recrystallization from ether/petroleum ether gave **6d** as colorless microneedles, mp 76 °C. **5d** IR (film) 3290bm, 1725s cm^{-1}. ^1H NMR δ 7.37–7.26 (m, 5H), 4.17 (p, J 6.4 Hz, 1H), 3.80 (d, J 13.1 Hz, 1H), 3.76 (d, J 13.1 Hz, 1H), 3.65 (bs, 2H), 3.05–3.02 (m, 2H), 2.35 (dt, J 6.4 4.9 Hz, 1H), 1.45 (s, 9H), 1.20 (d, J 6.4 Hz, 3H). MS m/z 279 (M^+, 0.5%), 91 (100). Anal. Calcd for $C_{16}H_{25}NO_3$: C, 68.8; H, 9.0 ; N, 5.0. Found: C, 69.1; H, 8.6; N, 4.8. **6d** IR (Nujol) 3300bm, 1725s cm^{-1}. ^1H NMR δ 7.38–7.20 (m, 5H), 4.14 (dq, J 6.5, 3.6 Hz, 1H), 3.78 (s, 2H), 3.09 (dd, J 12.2, 6.0 Hz, 1H), 2.95 (bs, 2H), 2.83 (dd, J 12.2, 5.2 Hz, 1H), 2.56 (ddd, J 6.0, 5.2, 3.6 Hz, 1H), 1.47 (s, 9H), 1.24 (d, J 6.5 Hz, 3H). MS m/z 279 (M^+, 1%), 91 (100). Anal. Calcd for $C_{16}H_{25}NO_3$: C, 68.8; H, 9.0 ; N, 5.0. Found: C, 69.1; H, 8.7; N, 5.0.

***anti*-Methyl 2-((benzylamino)methyl-3-(((1,1-dimethylethyl)dimethylsilyl)oxy)butanoate (8a).** Purification by column chromatography (eluant ether/petroleum ether 1:2.5) gave **8a** (R_f 0.52) and *E*-methyl 2-((benzylamino)methyl)-2-butenoate **10a** (R_f 0.29) as colorless oils. **8a** IR (film) 3334bw, 1732s cm^{-1}. ^1H NMR δ 7.31–7.23 (m, 5H), 4.08 (p, J 6.4 Hz, 1H), 3.78 (s, 2H), 3.69 (s, 3H), 2.94 (dd, J 11.8, 9.2 Hz, 1H), 2.88 (dd, J 11.8, 4.5 Hz, 1H), 2.62 (ddd, J 9.2, 6.4, 4.5 Hz, 1H), 1.66 (bs, 1H), 1.15 (d, J 6.4 Hz, 3H), 0.84 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H). MS m/z 351 (M^+, 1%), 91 (100). Anal. Calcd for $C_{19}H_{33}NO_3Si$: C, 65.0; H, 9.4; N, 4.0. Found: C, 65.0; H, 9.4; N, 3.8. **10a** IR (film) 3322bw, 1713s, 1651m cm^{-1}. **(*E*)-10a** ^1H NMR δ 7.46 −7.24 (m, 5H), 7.06 (q, J 7.2 Hz, 1H), 3.79 (s, 5H), 3.52 (s, 2H), 1.95 (bs, 1H), 1.85 (d, J 7.2 Hz, 3H). **(*Z*)-10a** ^1H NMR δ 7.46 −7.24 (m, 5H), 6.27 (qt, J 7.2, 0.8 Hz, 1H), 3.82 (s, 3H), 3.81 (s, 2H), 3.46 (t, J 1.0 Hz, 2H), 2.08 (dd, J 7.2, 0.9 Hz, 3H), 1.95 (bs, 1H). MS m/z 219 (M^+, 1%), 91 (100). Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.2; H, 7.8; N, 6.4. Found: C, 71.0; H, 7.8; N, 6.2.

***anti*-1,1-Dimethylethyl 2-((benzylamino)methyl)-3-(((1,1-dimethylethyl)dimethylsilyl)oxy)butanoate (8d).** Purification by column chromatography (eluant ether/petroleum ether 1:3) gave **8d** (R_f 0.36) and 1,1-dimethylethyl 2-(benzylamino)-2-butenoate (**10d**) (R_f 0.10) as colorless oils. **8d** IR (film) 3345bw, 1723s cm^{-1}. ^1H NMR δ 7.32–7.18 (m, 5H), 3.96 (dq, J 7.4, 6.2 Hz, 1H), 3.83 (d, J 13.3 Hz, 1H), 3.74 (d, J 13.3 Hz, 1H), 2.86 (d, J 6.9 Hz, 1H), 2.51 (dt, J 7.4, 6.9 Hz, 1H), 2.17 (s, 1H), 1.45 (s, 9H), 1.15 (d, J 6.2 Hz, 3H), 0.84 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H). MS m/z 393 (M^+, 1%), 91 (100). Anal. Calcd for $C_{22}H_{39}NO_3Si$: C, 67.2; H, 9.9; N, 3.6. Found: C, 66.8; H, 9.9; N, 3.6. **10d** IR (film) 3346bw, 1698s, 1649m cm^{-1}. **(*E*)-10d** ^1H NMR δ 7.38 −7.21 (m, 5H), 6.95 (q, J 7.2 Hz, 1H), 3.79 (s, 2H), 3.47 (s, 2H), 1.85 (s, 1H), 1.82 (d, J 7.2 Hz, 3H), 1.52 (s, 9H). **(*Z*)-10d** ^1H NMR δ 7.38 −7.21 (m, 5H), 6.15 (qt, J 7.2, 0.9 Hz, 1H), 3.78 (s, 2H), 3.40 (t, J 0.9 Hz, 2H), 2.03 (dt, J 7.2, 0.9 Hz, 3H), 1.85 (s, 1H), 1.49 (s, 9H). MS m/z 261 (M^+, 0.1%), 91 (100). Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.6; H, 8.8, N, 5.4. Found: C, 73.3; H, 9.0; N, 5.2.

Methyl 3-(*N*,*N*-Dimethylamino)-2-(1-(((1,1-dimethylethyl)-dimethylsilyl)oxy)ethyl)butanoate (14a). *n*-Butyllithium (2.5 M in hexane, 18.2 mL, 45.4 mmol) was added to a stirred solution of diisopropylamine (6.4 mL, 45.4 mmol) in anhydrous THF (120 mL) at −10 °C (dry ice/acetone). After stirring for 10 min the solution was cooled to −70 °C and a solution of methyl 3-(*N*,*N*-dimethylamino)butanoate, (**12a**) (5.49 g, 37.9 mmol) in THF (10 mL) was added dropwise. Stirring was continued for 15 min and then acetaldehyde (2.5 mL, 45.4 mmol) in THF (10 mL) was added over a period of 5 min and stirring was continued for a further 15 min. The reaction was quenched with 10% aqueous ammonium chloride (10 mL), and the reaction mixture was allowed to warm to room temperature. The mixture was added to ether (100 mL), washed with water (3 × 20 mL), and dried (Na_2SO_4) and the solvent removed in vacuo. The resulting crude oil was placed under high vacuum to remove any remaining water. The crude product **12a** was then dissolved in anhydrous DMF (20 mL), imidazole (6.19 g, 91.0 mmol) and TBDMSCl (6.87 g, 45.5 mmol) were added, and the mixture was stirred for 22 h. The

mixture was taken up in ether (20 mL), washed with water (4 × 10 mL), and dried (Na_2SO_4) and the ether removed in vacuo. Kugelrohr distillation yielded the four diastereomers of compound **13a** (8.38 g, 73%) as a colorless liquid, bp (ot) 84 °C/0.5 mm. IR (film) 1741s cm^{-1}. ^1H NMR δ 4.25 (p, J 6.1 Hz, 1H), 4.15 (p, J 6.3 Hz, 1H), 4.01 (dq, J 6.3, 4.2 Hz, 1H), 3.93 (p, J 6.2 Hz, 1H), 3.64 (s, 3H), 3.06 (dq, J 10.6, 6.7 Hz, 1H), 2.82–2.92 (m, 1H), 2.67–2.74 (m, 1H), 2.49 (dd, J 8.5, 5.7 Hz, 1H), 2.44 (dd, J 10.6, 4.2 Hz, 1H), 2.17 (s, 3H), 2.16 (s, 3H), 1.21 (d, J 6.2 Hz, 3H), 1.20 (d, J 6.3 Hz, 3H), 1.19 (d, J 6.3 Hz, 3H), 0.84–0.90 (m, 6H), 0.09 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H). MS m/z 288 (M^+ − 15, 2%), 72 (100). Anal. Calcd for $C_{15}H_{33}NO_3Si$: C, 59.4; H, 10.9; N, 4.6. Found: C, 59.8; H, 10.8; N, 4.6.

(*E*/*Z*)-Methyl 2-(1-(((1,1-Dimethylethyl)dimethylsilyl)oxy)ethyl)-2-butenoate (15a). A solution of methyl 2-(1-(((1,1-dimethylethyl)dimethylsilyl)oxy)ethyl)-3-(*N*,*N*-dimethylamino)butanoate (7.32 g, 24.2 mmol) and methyl iodide (7.6 mL) in absolute methanol (8 mL) was allowed to react at room temperature in the absence of light in a sealed vessel for 21 h. Methanol and excess methyl iodide were removed in vacuo to give a solid colorless residue which was then dissolved in ether (20 mL). Aqueous 1 M sodium hydroxide (25 mL) was added, and the mixture was stirred for 40 min at room temperature. The ether solution was decanted, and the aqeous solution was extracted once with ether (10 mL). The combined organic solutions were dried (Na_2SO_4), and the ether was removed in vacuo to yield a colorless liquid. Distillation gave **15a** as a 1:1 mixture of the *E* and *Z* isomers (5.55 g, 89%), bp (oven) 107 °C/23 mm. IR (film) 1712s, 1615m cm^{-1}. *E*-isomer ^1H NMR δ 6.84 (q, J 7.5 Hz, 1H), 4.96 (q, J 6.5 Hz, 1H), 3.76 (s, 3H), 2.03 (d, J 7.5 Hz, 3H), 1.39 (d, J 6.5 Hz, 3H), 0.91 (s, 9H), 0.09 (s, 3H). 0.03 (s, 3H). *Z*-isomer ^1H NMR δ 6.37 (qd, J 7.5, 1.4 Hz, 1H), 4.66 (qt, J 6.2, 1.4 Hz, 1H), 3.79 (s, 3H), 2.00 (dd, J 7.5, 1.4 Hz, 3H), 1.28 (d, J 6.2 Hz, 3H), 0.93 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H). MS (methane CI) m/z 260 (M^+ + 2, 1%), 259 (M^+ + 1, 1%), 72 (100). Anal. Calcd for $C_{13}H_{26}O_3Si$: C, 60.5; H, 10.1. Found: C, 60.2; H, 10.1.

Preparation of Methyl 5-(Benzyloxy)-2-(1-(((1,1-dimethylethyl)dimethylsilyl)oxy)ethyl)-2-pentenoate (15b). 1. (*E*/*Z*)-Methyl 5-(Benzyloxy)-2-pentenoate (11b). A mixture of 3-(benzyloxy)propanal[20] (8.25 g, 50.0 mmol) and ((methoxycarbonyl)methylene)triphenylphosphorane[12] (16.80 g, 50.0 mmol) in anhydrous benzene (300 mL) was heated at reflux for 46 h. The reaction was cooled to room temperature, petroleum ether (100 mL) added, and the mixture allowed to stand overnight. The mixture was filtered and the solvent removed in vacuo to give a pale yellow oil contaminated with some triphenylphosphine oxide. Column chromatography (eluant ether/petroleum ether 1:3) yielded a mixture of *E*- and *Z*-isomers of **11b** (in a 9.1 to 1 ratio, respectively) (10.72 g, 98%) as a colorless oil (R_f 0.56). Preparative thin layer chromatography on silica gel (eluant ether/petroleum ether 1:3) provided pure samples of the *E* and *Z* isomers for characterization. **(*E*)-11b** Oil. IR (film) 1724s, 1660m cm^{-1}. ^1H NMR δ 7.38–7.26 (m, 5H), 7.00 (dt, J 15.8, 7.0 Hz, 1H), 5.90 (dt, J 15.7, 1.6 Hz, 1H), 4.52 (s, 2H), 3.75 (s, 3H), 3.58 (t, J 6.5 Hz, 1H), 2.51 (ddt, J 6.6, 1.5 Hz, 1H). MS (methane CI) m/z 221 (M^+ + 1, 10%), 91 (100). Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.9; H, 7.3. Found: C, 71.2; H, 7.4. **(*Z*)-11b.** Oil. IR (film) 1722s, 1647m cm^{-1}. ^1H NMR δ 7.34–7.26 (m, 5H), 6.36 (dt, J 11.5, 7.2 Hz), 5.86 (dt, J 11.5, 1.9 Hz, 1H), 4.53 (s, 2H), 3.71 (s, 3H), 3.59 (t, J 6.3 Hz, 1H), 2.98 (ddt, J 7.0, 6.3, 1.8 Hz, 1H). MS (methane CI) m/z 221 (M^+ + 1, 4%), 91 (100). Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.9; H, 7.3. Found: C, 70.9; H, 7.6.

2. Methyl 5-(Benzyloxy)-3-(*N*,*N*-dimethylamino)-2-(1-(((1,1-dimethylethyl)dimethylsilyl)oxy)ethyl)-pentanoate (14b). *n*-Butyllithium (2.2 M in hexane, 5.3 mL, 11.6 mmol) was added to a stirred solution of diisopropylamine (1.64 mL, 11.6 mmol) in anhydrous THF (30 mL) at −10 °C (dry ice/acetone). After stirring for 15 min, the resulting solution was then cooled to −70 °C, a solution of **11b** (2.81 g, 10.6 mmol) in THF (8 mL) was added dropwise, and stirring was continued for a further 15 min. A solution of acetaldehyde (0.65 mL, 11.6 mmol) in THF (5 mL) was then added over a period of 5 min and stirring was continued for a further 20 min. The reaction was quenched with 10% aqueous ammonium chloride (10 mL) and the reaction mixture allowed to warm up to room temperature. The mixture was added to ether (40 mL) and washed with water (4 × 15 mL). The combined aqueous washings were extracted once with ether (15 mL), and the combined organic solutions were dried (Na_2SO_4). The solvent was removed in vacuo and the residue dried under high vacuum. The crude reaction mixture was then dissolved in anhydrous DMF (20 mL), imidazole (2.88 g, 42.4 mmol) and TBDMSCl (3.20 g, 21.2 mmol) were added, and the mixture was stirred at room temperature for 18 h. Water (5 mL) was then added, and the mixture was taken up in ether (30 mL), washed with water (4 × 15 mL), and dried (Na_2SO_4). The ether was removed in vacuo, and the required product was isolated using column chromatography (eluant ether/petroleum ether 1.5:1). **14b** (4.24 g, 95%) was obtained as a colorless oil (R_f 0.86). IR (film) 1737s cm^{-1}. ^1H NMR δ 7.35–7.26 (m), 4.15–3.65 (m), 3.63 (s), 3.59 (s), 3.57–3.39 (m), 2.98 (m), 2.79–2.68 (m), 2.25 (s), 2.19 (s), 1.88–1.79 (m), 1.79–1.71 (m), 1.23–1.17 (d), 0.85 (s), 0.04 (s), 0.03 (s). MS m/z 423 (M^+, 0.1%), 91 (100). Anal. Calcd for $C_{23}H_{41}NO_4Si$: C, 65.1; H, 9.9; N, 3.3 Found: C, 65.1; H, 9.8; N, 3.6

3. (*E*/*Z*)-Methyl 5-(Benzyloxy)-2-(1-(((1,1-dimethyethyl)dimethylsilyl)oxy)ethyl)-2-pentenoate (15b). A solution of **14b** (1.00 g, 2.36 mmol) and methyl iodide (0.74 mL) in absolute methanol (3 mL) was kept at room temperature in a sealed vessel, protected from light for 22 h. Methanol and excess methyl iodide were removed in vacuo yielding a gum which was next dissolved in ether (15 mL). Aqueous 1 M sodium hydroxide (2.5 mL) was added and the mixture stirred for 45 min. The ether solution was decanted and the aqueous solution was extracted once with ether (10 mL). The combined organic solutions were dried (Na_2SO_4), and the ether was removed in vacuo to give a pale yellow oil. Purification by column chromatography (eluant ether/petroleum ether 1:3) yielded (*E*)-methyl 5-(benzyloxy)-2-pentenoate (30 mg, 6%) (R_f 0.58) and the *E*- and *Z*-isomers of **15b** in a 2.2:1 ratio, respectively (0.76 g, 85%), as a colorless oil (R_f 0.69). IR (film)-1710s, 1648m cm^{-1}. **(*E*)-15b** ^1H NMR δ 7.35 −7.26 (m, 5H), 6.57 (t, J 7.4 Hz, 1H), 4.92 (q, J 6.4 Hz, 1H), 4.52 (s, 2H), 3.72 (s, 3H), 3.55 (t, J 6.6 Hz, 2H), 2.82 (dt, J 7.4, 6.6 Hz, 2H), 1.34 (d, J 6.4 Hz, 3H), 0.86 (s, 9H), 0.04 (s, 3H), −0.02 (s, 3H). **(*Z*)-15b** ^1H NMR δ 7.35 −7.26 (m, 5H), 6.35 (dt, J 6.3, 2.3 Hz, 1H), 4.63 (m, 1H), 4.51 (s, 2H), 3.73 (s, 3H), 3.55 (t, J 6.3 Hz, 2H), 2.76 (dt, J 6.1, 6.8 Hz, 2H), 1.24 (d, J 6.1 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H). MS (methane CI) m/z 379 (M^+ + 1, 1%), 91 (100). Anal. Calcd for $C_{21}H_{34}O_4Si$: C, 66.7; H, 9.0. Found: C, 67.0; H, 8.9.

***anti*,*anti*-Methyl 2-(1-(Benzylamino)ethyl)-3-(((1,1-dimethylethyl)dimethylsilyl)oxy)butanoate (16a).** IR (film) 3342w, 1733s cm^{-1}. ^1H NMR δ 7.40–7.25 (m, 5H), 4.18 (dq, J 8.6, 6.0 Hz, 1H), 3.85 (q(AB), J 13.1 Hz, 2H), 3.73 (s, 3H), 3.22 (dq, J 6.4, 5.6 Hz, 1H), 2.79 (dd, J 8.6, 5.6 Hz, 1H), 1.76 (bs, 1H), 1.21 (d, J 6.0 Hz, 3H), 1.15 (d, J 6.4 Hz, 3H), 0.87 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H). MS m/z 365 (M^+, 0.5%), 134 (100). Anal. Calcd for $C_{20}H_{35}NO_3Si$: C, 65.8; H, 9.6; N, 3.8. Found: C, 65.9; H, 9.4; N, 4.0.

***syn*,*anti*-Methyl 2-(1-(Benzylamino)ethyl)-3-(((1,1-dimethylethyl)dimethylsilyl)oxy)butanoate (17a).** IR (film) 3331w, 1732s cm^{-1}. ^1H NMR δ 7.41–7.25 (m, 5H), 4.30 (dq, J 7.2, 6.3 Hz, 1H), 3.97 (d, J 13.0 Hz, 1H), 3.73 (d, J 13.0 Hz, 1H), 3.72 (s, 3H), 3.19 (p, J 6.3 Hz, 1H), 2.61 (dd, J 7.2, 6.3 Hz, 1H), 2.25 (bs, 1H), 1.23 (d, J 6.3 Hz, 3H), 1.21 (d, J 6.3 Hz, 3H), 0.89 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H). MS m/z 365 (M^+, 0.5%), 134 (100). Anal. Calcd for $C_{20}H_{35}NO_3Si$: C, 65.8; H, 9.6; N, 3.8. Found: C, 66.1; H, 10.0; N, 4.0.

(*E*/*Z*)-Methyl 2-(1-(Benzylamino)ethyl)-2-butenoate (18a). IR (film) 3334bw; 1707s, 1638w cm^{-1}. (*E*)-isomer ^1H NMR δ 7.33–7.21 (m, 5H), 6.94 (q, J 7.2 Hz, 1H), 3.80 (q, 6.9 Hz, 1H), 3.75 (s, 3H), 3.75 (d, J 12.9 Hz, 1H), 3.60 (d, J 12.9 Hz, 1H), 2.48 (bs, 1H), 1.74 (d, J 7.2 Hz, 3H), 1.36 (d, J 6.9 Hz, 3H). (*Z*)-isomer ^1H NMR δ 7.33–7.21 (m, 5H), 6.13 (q, J 7.2 Hz), 3.78 (s, 3H), 3.77 (d, J 12.9 Hz, 1H), 3.61 (d, J 12.9

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Hz, 1H), 3.48 (q, J 6.8 Hz, 1H), 2.48 (bs, 1H), 1.97 (d, J 7.2 Hz, 3H), 1.27 (d, J 6.8 Hz, 3H). MS m/z (M^+ was not observed) 232 ($M^+ - 1$, 0.5%), 91 (100). Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.1; H, 8.2; N, 6.0. Found: C, 72.1; H, 8.2; N, 6.0.

Methyl 3-(Benzylamino)-5-(benzyloxy)-2-(1-(((1,1-dimethylethyl)dimethylsilyl)oxy)ethyl)pentanoate (16b and 17b). (Eluant ether/petroleum ether 1:2, R_f 0.69) IR (film) 3346w, 1732s cm^{-1}. Diastereomer A ^1H NMR δ 7.39–7.22 (m, 10H), 4.54 (s), 4.19 (dq, J 8.5, 6.0 Hz, 1H), 3.94 (d, J 13.0 Hz, 1H), 3.71 (s, 3H), 3.70 (d, J 12.9 Hz, 1H), 3.65 (t, J 6.5 Hz, 2H), 3.28–3.19 (m, 1H), 2.91 (dd, J 8.2, 5.1 Hz, 1H), 2.03–1.74 (m, 2H), 1.69 (s, 1H), 1.23 (d, J 6.0 Hz, 3H), 0.87 (s, 9H), 0.12 (s, 3H), 0.05 (s, 3H). Diastereomer B ^1H NMR δ 7.39–7.22 (m, 10H), 4.52 (d, J 12.0 Hz, 1H), 4.49 (d, J 12.1 Hz, 1H), 4.32 (dq, J 7.7, 6.1 Hz, 1H), 3.87 (d, J 12.8 Hz, 1H), 3.78 (d, J 12.4 Hz, 1H), 3.70 (s, 3H), 3.64 (t, J 6.5 Hz, 2H), 3.28–3.19 (m, 1H), 2.75 (dd, J 7.7, 5.6 Hz, 1H), 1.69 (s, 1H), 1.66–1.54 (m, 2H), 1.26 (d, J 6.1 Hz, 3H), 0.91 (s, 9H), 0.11 (s, 6H). MS m/z 485 (M^+, 0.5%), 91 (100). Anal. Calcd for $C_{28}H_{43}NO_4Si$: C, 69.3; H, 8.9; N, 2.9. Found: C, 69.0; H, 8.7; N, 2.8.

Methyl (*Z*)- and (*E*)-3-(Benzylamino)-5-(benzyloxy)-2-ethylenepentanoate (18b). (Eluant ether/petroleum ether 1:2, R_f 0.17). IR (film) 3344w, 1705s, 1638w cm^{-1}. *E*-isomer ^1H NMR δ 7.42–7.23 (m, 10 H), 7.07 (q, J 7.2 Hz, 1H), 4.48 (s, 1H), 3.82 (d, J 13.1 Hz, 1H), 3.77 (s, 3H), 3.66–3.59 (m, 2H), 3.62 (d, J 13.1 Hz, 1H), 3.50 (dd, J 7.7, 5.0 Hz, 1H), 2.28–2.17 (m, 3H), 1.74 (d, J 7.2 Hz, 3H). *Z*-isomer ^1H NMR δ 7.42–7.23 (m, 10 H), 6.11 (q, J 7.2 Hz, 1H), 4.52 (q (AB), J 11.9 Hz, 2H), 3.90 (t, J 7.5 Hz, 2H), 3.79 (s, 3H), 3.47 (dd, J 7.5, 5.0 Hz), 1H), 2.21 (bs, 1H), 2.08–1.87 (m, 2H), 1.98 (d, J 7.2 Hz, 3H). MS (methane CI) m/z 354 ($M^+ + 1$, 79%), 91 (100). (Found: C, 74.5; H, 7.7; N, 3.9. $C_{22}H_{27}NO_3$: C, 74.8; H, 7.7; N, 4.0%).

Fluoride-Mediated Cleavage of Silyl Ethers 16a and 17a.[21] Tetrabutylammonium fluoride (1 M in THF, 1.6 mL) was added to a stirred solution of the appropriate silyl ether (0.4 mmol) in anhydrous THF (5 mL) at −5 to −10 °C. Stirring was continued for 2–16.5 h (progress monitored by analytical TLC), and then water (5 mL) was added. The resulting mixture was then added to ether (10 mL), washed with water (3 × 5 mL), and dried (Na_2SO_4) and the solvent removed in vacuo. Preparative TLC on SiO_2 (eluant ether/petroleum ether) gave the pure desilylated product.

***syn,anti*-Methyl 2-(1-(Benzylamino)ethyl)-3-hydroxybutanoate (5g).** Purification by preparative TLC on SiO_2 (eluant ether/petroleum ether 1:1) Colorless oil. (R_f 0.28) (72%) IR (film) 3317bs, 1732s cm^{-1}. ^1H NMR δ 7.38–7.22 (m, 5H), 4.32 (p J 6.5 Hz, 1H), 4.20 (bs), 3.88 (q (AB), J 12.7 Hz, 2H), 3.70 (s, 3H), 3.24 (dq, J 6.6, 3.1 Hz, 1H), 2.53 (dd, J 6.6, 3.1 Hz, 1H), 1.29 (d, J 6.6 Hz, 3H), 1.18 (d, J 6.5 Hz, 3H). MS m/z 251 (M^+, 0.2%) 91 (100). Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.9; H, 8.4; N, 5.6. Found: C, 67.2; H, 8.3; N, 5.7.

***anti,anti*-Methyl 2-(1-(Benzylamino)ethyl)-3-hydroxybutanoate (5h).** Purification by preparative TLC on SiO_2 (eluant ether/petroleum ether 1.5:1) (R_f 0.42) (92%). Yellow oil. IR (film) 3295bs, 1732s cm^{-1}. ^1H NMR δ 7.33–7.27 (m, 5H), 4.08 (dq, J 9.1, 6.4 Hz, 1H), 3.99 (bs), 3.95 (q (AB), J 12.5 Hz, 2H), 3.68 (s, 3H), 3.19 (dq, J 10.1, 6.1 Hz, 1H), 2.23 (dd, J 10.1, 9.1 Hz, 1H), 1.17 (d, J 6.4 Hz, 3H), 1.11 (d, J 6.1 Hz, 3H). MS m/z 251 (M^+, 0.1%), 91 (100). Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.9; H, 8.4; N, 5.6. Found: C, 66.7; H, 8.4; N, 5.5.

Preparation of Tetrahydro-1,3-oxazines 19a–h and 20a–f. These tetrahydro-1,3-oxazines were prepared using an adaptation of the general method of Fodor and co-workers.[14] A solution of the appropriate amino alcohol (1 mmol) and 4-nitrobenzaldehyde (1 mmol) in anhydrous benzene (25 mL) was heated to reflux in a distillation apparatus equipped with a fractionating column. Benzene and water were removed by slow distillation, with more benzene being added as required, until analysis by analytical TLC indicated that the starting amino alcohol had been consumed. Excess benzene was then removed in vacuo, and the products were isolated from the residue using preparative TLC (eluant: ether/petroleum ether 1:1). The products were found to be epimeric at C2 of the oxazine ring, and separation of the epimers was effected in several cases.

5,6-*trans*-5-(Methoxycarbonyl)-6-methyl-2-(4-nitrophenyl)-3-benzyltetrahydro-1,3-oxazine (19a). R_f 0.82 (90%). IR ($CHCl_3$) 1730s cm^{-1}. Major C-2 epimer ^1H NMR δ 8.21 (d, J 8.7 Hz, 2H), 7.76 (d, J 8.7 Hz, 2H), 7.46–7.20 (m, 5H), 5.46 (s, 1H), 4.04 (dq, J 10.1, 6.1 Hz, 1H), 3.65 (s, 3H), 3.54 (q (AB), J 14.3 Hz, 2H), 3.24 (dd, J 13.4, 4.6 Hz, 1H), 3.12 (dd, J 13.4, 11.4 Hz, 1H), 2.81 (ddd, J 11.3, 10.1, 4.6 Hz, 1H), 1.37 (d, J 6.1 Hz, 3H). Minor C-2 epimer ^1H NMR δ 8.23 (d, J 8.9 Hz, 2H), 7.74 (d, J 8.9 Hz, 2H), 7.46–7.20 (m, 5H), 5.46 (s, 1H), 4.26 (q (AB), J 13.4 Hz, 2H), 3.86 (dq, J 10.1, 6.0 Hz, 1H), 3.58 (s, 3H), 3.10 (dd, J 14.1, 11.7 Hz, 1H), 3.06 (dd, J 14.1, 4.5 Hz, 1H), 2.85 (ddd, J 11.7, 10.1, 4.5 Hz, 1H), 1.28 (d, J 6.0 Hz, 3H). MS m/z 370 (M^+, 1%) 91 (100). Anal. Calcd for $C_{20}H_{22}N_2O_5$: C, 64.9; H, 6.0. Found: C, 65.0; H, 6.2.

5,6-*cis*-5-(Methoxycarbonyl)-6-methyl-2-(4-nitrophenyl)-3-benzyltetrahydro-1,3-oxazine (20a). R_f 0.46 (79%). IR (film) 1738s cm^{-1}. Major C-2 epimer ^1H NMR δ 8.21 (d, J 8.8 Hz, 2H), 7.74 (d, J 8.8 Hz, 2H), 7.30–7.17 (m, 5H), 4.91 (s, 1H), 3.92 (p, J 6.6 Hz, 1H), 3.73 (s, 3H), 3.43 (q (AB), J 13.8 Hz, 2H), 3.42 (dd, J 12.2, 2.2 Hz, 1H), 2.63 (dd, J 12.2, 3.7 Hz, 1H), 2.51–2.48 (m, 1H), 1.45 (d, J 6.6 Hz, 3H). Minor C-2 epimer ^1H NMR δ 8.22 (d, J 8.9 Hz, 2H), 7.77 (d, J 8.9 Hz, 2H), 7.30–7.17 (m, 5H), 5.50 (s, 1H), 4.63 (p, J 5.5 Hz, 1H), 3.68 (s, 3H), 3.65 (q (AB), J 14.0 Hz, 2H), 3.31–3.22 (m, 1H), 3.18–3.08 (m, 2H), 1.38 (d, J 6.1 Hz, 3H). MS m/z 370 (M^+, 3%), 91 (100). Anal. Calcd for $C_{20}H_{22}N_2O_5$: C, 64.9; H, 6.0; N, 7.6. Found: C, 64.9; H, 6.0; N, 7.9.

5,6-*trans*-5-((1,1-Dimethylethoxy)carbonyl)-6-methyl-2-(4-nitrophenyl)-3-benzyltetrahydro-1,3-oxazine (19d). R_f 0.84 (76%). IR (Nujol) 1715s cm^{-1}. Major C-2 epimer ^1H NMR δ 8.20 (d, J 8.8 Hz, 2H), 7.75 (d, J 8.8 Hz, 2H), 7.46–7.20 (m, 5H), 5.45 (s, 1H), 3.99 (dq, J 10.0, 6.1 Hz, 1H), 3.52 (q (AB), J 14.4 Hz, 2H), 3.20 (dd, J 13.4, 4.6 Hz, 1H), 3.11 (dd, J 13.4, 11.5 Hz, 1H), 2.66 (ddd, J 11.3, 10.0, 4.6 Hz, 1H), 1.43 (s, 9H), 1.38 (d, J 6.1 Hz, 3H). Minor C-2 epimer ^1H NMR δ 8.22 (d, J 8.8 Hz, 2H), 7.75 (d, J 8.8 Hz, 2H), 7.46–7.20 (m, 5H), 5.42 (s, 1H), 4.26 (q (AB), J 13.6 Hz, 2H), 3.80 (dq, J 10.1, 6.0 Hz, 1H), 3.12 (dd, J 14.1, 11.7 Hz, 1H), 3.00 (dd, J 14.1, 3.3 Hz, 1H), 2.69 (m, 1H), 1.35 (s, 9H), 1.30 (d, J 6.0 Hz, 3H). MS m/z 412 (M^+, 0.5%), 91 (100). Anal. Calcd for $C_{23}H_{28}N_2O_5$: C, 67.0; H, 6.8; N, 6.8. Found: C, 66.9; H, 7.1; N, 7.1.

5,6-*cis*-5-((1,1-Dimethylethoxy)carbonyl)-6-methyl-2-(4-nitrophenyl)-3-benzyltetrahydro-1,3-oxazine (20d). R_f 0.77 (63%). IR (Nujol) 1715s cm^{-1}. ^1H NMR δ 8.19 (d, J 8.4 Hz, 2H 7.53 (d, J 8.4 Hz, 2H), 7.32–7.18 (m, 5H), 5.46 (s, 1H), 4.61 (dq, J 6.7, 5.5 Hz, 1H), 3.63 (q (AB), J 13.9 Hz, 2H), 3.25–3.20 (m, 1H), 3.14 (d, J 13.1 Hz, 1H), 3.05 (dd, J 13.5, 5.3 Hz, 1H), 1.44 (s, 9H), 1.39 (d, J 6.7 Hz, 3H). MS m/z 412 (M^+, 2%), 91 (100). Anal. Calcd for $C_{23}H_{28}N_2O_5$: C, 67.0; H, 6.8; N, 6.8. Found: C, 67.3; H, 6.5; N, 6.9.

5,6-*cis*-5-((1,1-Dimethylethoxy)carbonyl)-6-methyl-2-(4-nitrophenyl)-3-benzyltetrahydro-1,3-oxazine (*epi*-20d). R_f 0.64 (23%). IR (Nujol) 1740s cm^{-1}. ^1H NMR δ 8.22 (d, J 8.8 Hz, 2H), 7.79 (d, J 8.8 Hz, 2H), 7.29–7.16 (m, 5H), 4.82 (s, 1H), 3.87 (dq, J 6.6, 2.5 Hz, 1H), 3.50 (q (AB), J 13.6 Hz, 2H), 3.41 (dd, J 12.1, 2.5 Hz, 1H), 2.54 (dd, J 12.1, 3.9 Hz, 1H), 2.40–2.37 (m, 1H), 1.45–1.44 (d, J 6.6 Hz, 3H), 1.44, (s, 9H). MS m/z 412 (M^+, 1%), 91 (100). Anal. Calcd for $C_{23}H_{28}N_2O_5$: C, 67.0; H, 6.8; N, 6.8. Found: C, 67.0; H, 6.9; N, 7.0.

4,5-*cis*-5,6-*trans*-5-(Methoxycarbonyl)-4,6-dimethyl-2-(4-nitrophenyl)-3-benzyltetrahydro-1,3-oxazine (19g). The product, a single C-2 epimer, was isolated using preparative TLC on SiO_2 (eluant 1:1 ether/petroleum ether) as a colorless gum (R_f 0.77) (52%). IR ($CHCl_3$) 1730s cm^{-1}. ^1H NMR δ 8.19 (d, J 8.7 Hz, 2H), 7.74 (d, J 8.7 Hz, 2H), 7.34–7.19 (m, 5H), 5.77 (s, 1H), 4.28 (dq, J 10.9, 6.0 Hz, 1H), 3.64 (s, 3H), 3.59 (q (AB), J 15.3 Hz, 2H), 3.51 (d, J 15.2 Hz, 1H), 3.38 (dq, J 7.1, 5.8 Hz, 1H), 2.95 (dd, J 10.8, 5.8 Hz, 1H), 1.40 (d, J 6.0 Hz,

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3H), 1.32 (d, J 7.1 Hz, 3H). MS m/z 384 (M^+, 2%), 91 (100). Anal. Calcd for $C_{21}H_{24}N_2O_5$: C, 65.6; H, 6.3; N, 7.3. Found: C, 65.3; H, 6.6; N, 7.0.

4,5-*trans*-5,6-*trans*-5-(Methoxycarbonyl)-4,6-dimethyl-2-(4-nitrophenyl)-3-benzyltetrahydro-1,3-oxazine (19h). R_f 0.87 (84%). Colorless microneedles (petroleum ether) mp 118 −119 °C. IR ($CHCl_3$) 1729s cm^{-1}. Major C-2 epimer ^1H NMR δ 8.00 (d, J 8.8 Hz, 2H), 7.62 (d, J 8.8 Hz, 2H), 7.13−7.02 (m, 5H), 5.56 (s, 1H), 4.03 (dq, J 10.2, 6.1 Hz, 1H), 3.73 (s, 3H), 3.70−3.64 (m, 1H), 3.57 (s, 2H), 2.48 (t, J 10.2 Hz, 1H), 1.34 (d, J 6.1 Hz, 3H), 1.07 (d, J 6.8 Hz, 3H). Minor C-2 epimer ^1H NMR δ 8.22 (d, J 8.9 Hz, 2H), 7.70 (dd, J 8.9, 0.9 Hz, 2H), 7.44−7.25 (m, 5H), 5.43 (s, 1H), 4.09 (q (AB), J 13.7 Hz, 2H), 1H), 3.87 (dq, J 10.5, 6.1 Hz, 1H), 3.63 (s, 3H), 3.35 (dq, J 10.5, 6.8 Hz, 1H), 2.55 (t, J 10.5 Hz, 1H), 1.25 (d, J 6.1 Hz, 3H), 1.23 (d, J 6.8 Hz, 3H). MS m/z 384 (M^+, 2%), 91 (100). Anal. Calcd for $C_{21}H_{24}N_2O_5$: C, 65.6; H, 6.3; N, 7.3. Found: C, 65.4; H, 6.2; N, 7.2.

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Supporting Information Available: The full listing of spectroscopic and microanalytical data for compounds **9a−f** as well as the diastereomers **b**, **c**, **e**, and **f** of compounds **5**, **6**, **8**, **10**, **19**, and **20** (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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