An Allyltitanium Derived from Acrolein 1,2-Dicyclohexylethylene Acetal and (η^2-propene)Ti(O-*i*-Pr)$_2$ as a Chiral Propionaldehyde Homoenolate Equivalent that Reacts with Imines with Excellent Stereoselectivity. An Efficient and Practical Access to Optically Active γ-Amino Carbonyl Compounds

Sentaro Okamoto, Xin Teng, Shintaro Fujii, Yuuki Takayama, and Fumie Sato*

Contribution from the Department of Biomolecular Engineering, Tokyo Institute of Technology, 4259 Nagatsuta-cho, Midori-ku, Yokohama, Kanagawa 226-8501, Japan

Received December 1, 2000

Abstract: A chiral allyltitanium compound **2**, prepared in situ by the reaction of optically active acrolein 1,2-dicyclohexylethylene acetal (**3**) with (η^2-propene)Ti(O-*i*-Pr)$_2$ (**1**), reacts with a variety of acyclic and cyclic imines **4** in a regiospecific way to afford α-addition products **5** as a mixture of the *E*- and *Z*-isomers in good combined yield, where the former is predominant in a ratio of 92:8 to >95:5. The mixture of (*E*)- and (*Z*)-**5** and pure (*E*)-**5** which could be isolated in several cases were respectively converted to the corresponding β-amino ester **6** to confirm the absolute configuration and enantiomeric purity. The ee of the newly formed asymmetric center of **5** is more than 78% for the mixture of (*E*)- and (*Z*)-**5** and more than 96% for pure (*E*)-**5**. By taking advantage of the versatility of the vinyl ether moiety in **5**, optically active γ-amino aldehydes **8**, γ-amino aldehyde acetals **7** and **10**, γ-amino acids **9**, β-amino esters **6**, and pyrrolidinoisoquinolines **12** were readily prepared. In the reaction of **2** with optically active α-silyloxyimine **4n**, remarkable double stereodifferentiation was observed; thus, the reaction of **2** derived from (*S,S*)- or (*R,R*)-**3** provided *syn*- and *anti*-**5n** in a ratio of 55:45 or 0:100, respectively. Meanwhile, the stereochemistry of the product in the reaction of **2** with β-silyloxyimine **4o** was controlled mainly by **2**. Thus, the reaction of β-silyloxyimine **14** with **2** derived from **1** and (*R,R*)-**3** afforded γ-silyloxyimine **15** with 92% diastereoselectivity, from which 4-amino-6-hydroxypentadecanal dimethyl acetal (**13**), a key intermediate for the synthesis of batzelladine D, was synthesized.

Introduction

Chiral cyclic and acyclic amines bearing a stereogenic center at the α-position are widely distributed in nature and include many biologically important molecules, and thus, their asymmetric synthesis has attracted much interest. Diastereo- or enantioselective addition reaction of carbanions with imines and imine derivatives affords an attractive access to these compounds;[1,2] however, the scope and a variety of this kind of reaction have been considerably limited in comparison with the corresponding reaction with aldehydes and ketones. This is due to the inability of certain nucleophiles to add to imino compounds, coupled with the propensity of basic reagents to preferentially abstract protons α to the imino group. For example, although many homoenolate synthons, including their chiral form, which react selectively with carbonyl compounds, have been reported and have been widely used in organic synthesis,[3] to the best of our knowledge, only one achiral homoenolate equivalent has been reported to react with imines.[4] Thus, Fang et al. generated a dithio-substituted crotyllithium from 2-propenyl-1,3-dithiane and *n*-BuLi and showed that it reacted with aldimines to afford the corresponding ketene dithioacetals exclusively. However, the synthetic utility and scope of the reaction have remained unexplored, and development of the reagent to a chiral form seems difficult.

Recently, we have reported a new efficient method for preparing allyltitanium complexes by the reaction of allylic alcohol derivatives with a divalent titanium reagent (η^2-

(1) Reviews for the asymmetric nucleophilic addition reactions to imines: Enders, D.; Reinhold: U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895. Denmark, S. E.; Nicaise, O. J.-C. *Chem. Commun.* **1996**, 999. Bloch, R. *Chem. Rev.* **1998**, *98*, 1407. Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069. Kleinman, E. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, p 893.

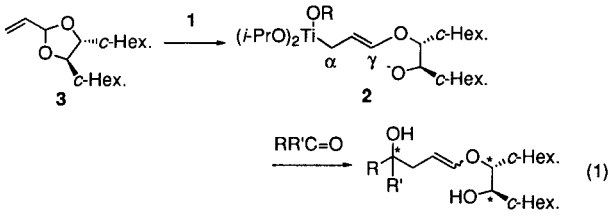
(2) Most recent examples: Sato, I.; Kodaka, R.; Shibata, T.; Hirokawa, Y.; Shirai, N.; Ohtake, K.; Soai, K. *Tetrahedron: Asymmetry*, **2000**, *11*, 2271. Saito, S.; Hatanaka, K.; Yamamoto, H. *Org. Lett.* **2000**, *2*, 1891. Kobayashi, S.; Ishitani, H. *Chirality* **2000**, *12*, 540. Hamada, T.; Mizojiri, R.; Urabe, H.; Sato, F. *J. Am. Chem. Soc.* **2000**, *122*, 7138. Hanessian, S.; Griffin, A. M.; Cantin, L.-D. *Chirality* **2000**, *12*, 342. García Ruano, J. L.; Alcudia, A.; del Prado, M.; Barros, D.; Maestro, M. C.; Fernández, I. *J. Org. Chem.* **2000**, *65*, 2856. Alvaro, G.; Grepioni, F.; Grilli, S.; Maini, L.; Martelli, G.; Savoia, D. *Synthesis* **2000**, 581. Porter, J. R.; Wirschun, W. G.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 2657. Vachal, P.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 867. Roland, S.; Mangeney, P. *Eur. J. Org. Chem.* **2000**, 611. Cossy, J.; Pévet, I.; Meyer, C. *Synlett* **2000**, 122. Miyabe, H.; Ushiro, C.; Ueda, M.; Yamakawa, K.; Naito, T. *J. Org. Chem.* **2000**, *65*, 176.

(3) Reviews: Kuwajima, I.; Nakamura, E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, p 441. Kuwajima, I.; Nakamura, E. *Top. Curr. Chem.* **1990**, *155*, 1. Ryu, I.; Sonoda, N. *Synth. Org. Chem., Jpn.* **1985**, *43*, 112. Werstiuk, N. H. *Tetrahedron* **1983**, *39*, 205. Katritzky, A. R.; Piffl, M.; Lang, H.; Anders, E. *Chem. Rev.* **1999**, *99*, 665. See also: Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 932. Review for chiral homoenolate equivalents: Ahlbrecht, H.; Beyer, U. *Synthesis* **1999**, 365.

(4) Fang, J.-M.; Chen, S. T.; Chen, I.-H. *J. Organomet. Chem.* **1990**, *398*, 219.

10.1021/ja004140k CCC: $20.00
Published on Web 03/24/2001

propene)Ti(O-*i*-Pr)$_2$ (**1**),[5] readily generated in situ from Ti(O-*i*-Pr)$_4$ and 2 equiv of *i*-PrMgX, which proceeds via an oxidative addition pathway.[6] The resulting allyltitaniums react with aldehydes and ketones at the γ-position exclusively to provide homoallylic alcohols. During these studies we found that the allyltitanium **2** obtained from **1** and chiral acrolein 1,2-dicyclohexylethylene acetal (**3**) reacts with aldehydes and ketones at the α- rather than the γ-position highly selectively as shown in eq 1.[7] In all cases, the resulting α-addition product



RR'C=O	Regio-selectivity	*E*:*Z*	Total Yield, %
PhCHO	90%	75:25	95
EtCHO	93%	66:34	85
Et_2C=O	>97%	87:13	84

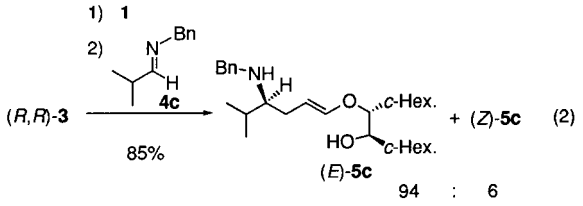
consists of a mixture of inseparable *E*- and *Z*-enol ethers, and the ^{13}C NMR analysis of the mixture indicated that the chiral induction at the newly generated asymmetric center was low (see Supporting Information). These results strongly indicated that **2** works as a convenient homoenolate equivalent, but not as an efficient chiral homoenolate equivalent for the reaction with carbonyl compounds.

As allyltitaniums also react with imines smoothly, we then turned our attention to the reaction of **2** with imines, in anticipation of developing for the first time a propionaldehyde homoenolate equivalent that can react with imines. Furthermore, we had some expectation of attaining high chiral induction because the reaction of allyltitaniums with imines proceeds with far better stereoselectivity than that of the reaction with aldehydes.[6b,d,h]

We have now found that **2** works as an efficient chiral homoenolate equivalent that reacts with a variety of imines, thus opening an easy access to optically active γ-amino carbonyl compounds.[8]

Results and Discussion

Reaction of 2 with Imines. The reaction of **2** derived from (*R*,*R*)-**3** with imine **4c**, prepared from 2-methylpropanal and benzylamine, proceeds smoothly and in a regiospecific way to afford 85% yield of the α-addition product **5c** as a mixture of *E*- and *Z*-enol ethers in a ratio of 94:6 (eq 2), and from which

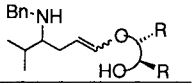
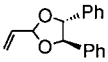
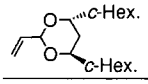


pure (*E*)-**5c** was isolated in 70% yield by column chromatography. The mixture of (*E*)- and (*Z*)-**5c** itself as well as the pure (*E*)-**5c** was respectively converted into the known methyl 3-amino-4-methylpentanoate (**6c**) by conventional methods, and the configuration of a stereogenic center bearing an amino group as well as the enantiomeric excess (ee) was determined (vide infra). To our surprise as well as to our delight, the ee of **6c** derived from the mixture was 88% and that of pure (*E*)-**5c**, which has the structure depicted in eq 2, was very high, reaching 98%.

With this finding, to see whether **3** is the optimum acetal or not, we investigated the reaction of **4c** with allyltitaniums derived from **1** and a few acrolein chiral acetals other than **3** such as 1,2-dimethyethylene and 1,2-diphenylethylene acetal, and 1,3-dicyclohexylpropylene acetal.[9] As revealed from Table 1, which summarizes the results, the allyltitanium **2** derived from **3** was found to work as the most efficient chiral propionaldehyde homoenolate equivalent; the diastereoselectivity judged by ^{1}H NMR analysis of the corresponding main product and the overall ee value of **5** (shown in Table 1) were the highest for the reaction with **3**.

We then investigated the reaction of **2** with various imines other than **4c**, and the results are summarized in Table 2. It can be seen from the table that a variety of acyclic and cyclic aldimines reacted with **2** with excellent selectivity similarly to secondary aldimine **4c**. These aldimines involve methylimines (entry 1), primary alkylimines (entry 2), arylimines (entries 5−7), five-membered cyclic imines (entry 9), and six-membered cyclic imines including 3,4-dihydroisoquinolines (entries 10−12). Tertiary alkylimines and acyclic ketimines, however, did not react with **2**, presumably due to their larger steric requirement (entries 4 and 8). In contrast to acyclic ketimines, cyclic ketimine **4m** reacted smoothly with **2** (entry 13), probably owing to its strained dehydropiperidine structure. It is worth noting that the ee of the product **5m** was higher than that of **5l** (entry 12), the reaction product of aldimines having a similar structure,

Table 1.

Acetal	Product(s), 		
	Yield, %	*E* : *Z*	Overall ee at C*-N
3	85	94 : 6	88
	78	95 : 5	47
	72	95 : 5	52
	85	80 : 20	72

(5) Reviews for the synthetic utility of **1**: Sato, F.; Urabe, H.; Okamoto, S. *Pure Appl. Chem.* **1999**, *71*, 1511. Sato, F.; Urabe, H.; Okamoto, S. *J. Synth. Org. Chem. Jpn.* **1998**, *56*, 424. Sato, F.; Urabe, H.; Okamoto, S. *Synlett* **2000**, 753. Sato, F.; Urabe, H.; Okamoto, S. *Chem. Rev.* **2000**, *100*, 2835.

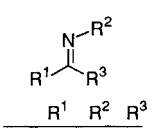
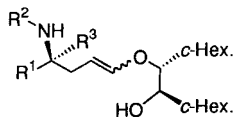
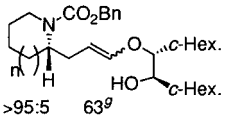
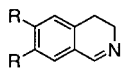
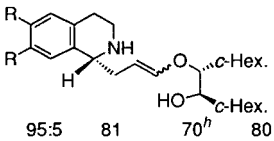
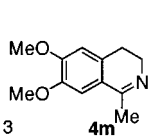
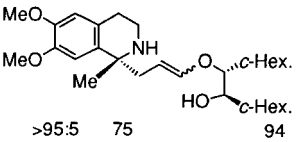
(6) (a) Kasatkin, A.; Nakagawa, T.; Okamoto, S.; Sato, F. *J. Am. Chem. Soc.* **1995**, *117*, 3881. (b) Gao, Y.; Sato, F. *J. Org. Chem.* **1995**, *60*, 8136. (c) Kasatkin, A.; Sato, F. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2848. (d) Hikichi, S.; Gao, Y.; Sato, F. *Tetrahedron Lett.* **1997**, *38*, 2867. (e) Teng, X.; Kasatkin, A.; Kawanaka, Y.; Okamoto, S.; Sato, F. *Tetrahedron Lett.* **1997**, *38*, 8977. (f) Teng, X.; Okamoto, S.; Sato, F. *Tetrahedron Lett.* **1998**, *39*, 6927. (g) Matsuda, S.; An, D. K.; Okamoto, S.; Sato, F. *Tetrahedron Lett.* **1998**, *39*, 7513. (h) Okamoto, S.; Fukuhara, K.; Sato, F. *Tetrahedron Lett.* **2000**, *41*, 5561. (i) Okamoto, S.; Sato, F. *J. Organomet. Chem.* In press.

(7) These results strongly indicate that the allyltitanium **2** is in equilibrium with its internal titanium form (depicted in Scheme 1, vide infra) and the reaction with the carbonyl compounds proceeds mainly through this internal form.

(8) For a preliminary account of this work, see: Teng, X.; Takayama, Y.; Okamoto, S.; Sato, F. *J. Am. Chem. Soc.* **1999**, *121*, 11916.

(9) Reviews for use of C_2-symmetric diols as a chiral auxiliary: Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581. Alexakis, A.; Mangeney, P. *Tetrahedron*: *Asymmetry*, **1990**, *1*, 477.

Table 2. Asymmetric Addition Reaction of the Allyltitanium Compound **2** Derived from **1** and **3** with Imines **4**

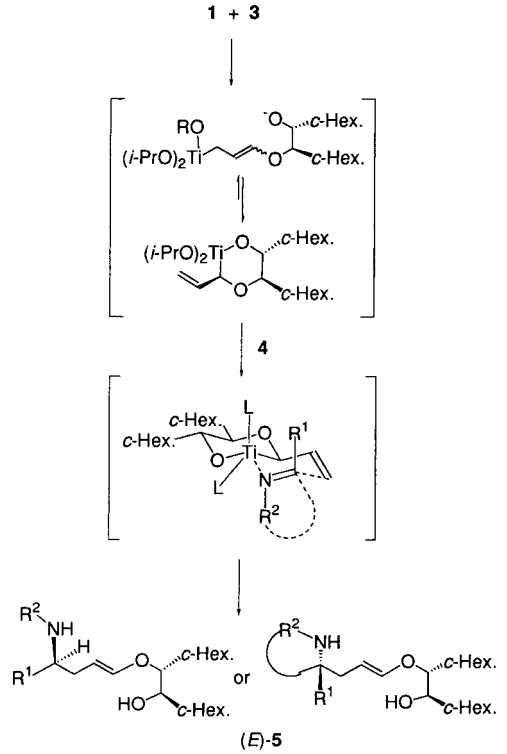
Entry	Imine **4**	Adducts **5**[a]			Ee at C*-N, %[d]	
			Isolated Yield, %[c]			
		E:*Z*[b]	The *EZ* mixture	Pure (*E*)-**5**	Overall[e]	Pure (*E*)-**5**
						
	R^1 R^2 R^3					
1	**4a** ; Me Bn H	92:8	84		83	
2	**4b** ; *n*-Pr Bn H	94:6	81		85	
3	**4c** ; *i*-Pr Bn H	94:6	85	70	88	98
4	**4d** ; *t*-Bu Bn H	-	trace		-	
5	**4e** ; Ph Bn H	93:7	82	40	86	96
6	**4f** ; Ph *n*-Pr H	95:5	85		88	
7	**4g** ; Ph Ph H	95:5	71		>85	
8[f]	**4h** ; Ph Bn Me	-	trace		-	
						
9	**4i** ; n = 0	>95:5	63[g]		78	
10	**4j** ; n = 1	>95:5	66[g]		89	
						
11	**4k** ; R = H	95:5	81	70[h]	80	98[i]
12	**4l** ; R = OMe	95:5	81		81	
						
13	**4m**	>95:5	75		94	

[a] No γ-addition product was observed. Absolute configuration was determined for **5a**−**c**,**e**,**k**,**m** (see Supporting Information), and, in other cases, was speculated in analogy with them. [b] Determined by ^{1}H NMR analysis. [c] Unless otherwise indicated, **5** was isolated by column chromatography. [d] Determined after conversion to **6** for entries 1−7 or to **10** for entries 9−13 (see Schemes 2 and 3). [e] Ee of **6** or **10** derived from the mixture of (*E*)- and (*Z*)-**5**. [f] **4h** was an 18:1 mixture of *E* and *Z* isomers. [g] Isolated as the *N*-benzyloxycarbonyl derivative. [h] Isolated by recrystallization after column chromatography. [i] Ee of **10k** derived from recrystallized (*E*)-**5k**.

although it is widely observed that the asymmetric nucleophilic addition reaction with ketimines usually affords lower ee than that attained with aldimines.[1,10] In addition to **5c**, pure (*E*)-**5e** and -**5k** could be easily isolated by column chromatography or recrystallization, respectively, and the corresponding ee of which was more than 96%. For the other entries in Table 2, the separation of (*E*)- and (*Z*)-**5** is difficult or tedious; however, even in these cases, use of the mixture for further elaboration is synthetically attractive because of the high level of ee that is attainable.

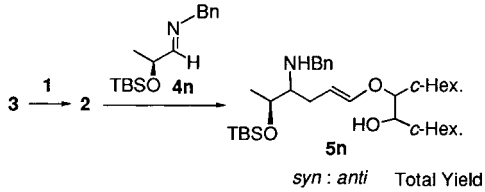
The predominant production of (*E*)-**5** with the absolute configuration depicted in Table 2, the sense of which should be noted to be different between acyclic and cyclic imines, can be explained by assuming that the allyltitanium complex generated from **1** and **3** would exist mostly as an internal titanium derivative that can be stabilized by chelation, rather than as the primary derivative,[11] and the reaction with imines proceeds preferentially via the most stable transition state, as

Scheme 1



shown in Scheme 1, which has a *trans*-fused chair−chair conformation.[12]

Reaction of 2 with α- and *β*-Alkoxy Imines. Properly functionalized 1,2- and 1,3-alkoxyamines (β- or γ-alkoxyamines) can serve as key intermediates for the synthesis of biologically active compounds.[13] We were, therefore, interested in the reaction of **2** with optically active α- or β-alkoxyimines such as **4n** and **4o** (eqs 3 and 4). In these reactions, since the electrophile (imine) and the nucleophile (allyltitanium) are both chiral, double asymmetric differentiation was expected.[14] For the reaction with α-silyloxyimine **4n** remarkable double asymmetric differentiation was observed. Thus, as shown in eq 3,



(3)

	syn : *anti*	Total Yield
(*S*,*S*)-**3**	0 : 100	83
(*R*,*R*)-**3**	55 : 45	78

while the reaction of **4n**[15] having (*S*)-configuration with **2** derived from (*S*,*S*)-**3** proceeded with complete diastereoselec-

(10) For example, see: Hanessian, S.; Yang, R.-Y. *Tetrahedron Lett.* **1996**, *37*, 8997. Nakamura, K.; Hirai, A.; Nakamura, E. *J. Am. Chem. Soc.* **1996**, *118*, 8489.

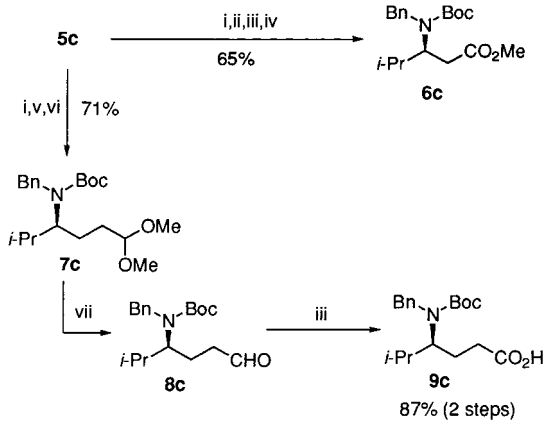
(11) A similar stabilization of allyltitaniums by intramolecular chelation or coordination has been reported, see: Hanko, R.; Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 372. Weidmann, B.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 31. Roder, H.; Helmchen, G.; Peters, E.-M.; Peters, K.; von Schnering, H.-G. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 898. Zubaidha, P. K.; Kasatkin, A.; Sato, F. *Chem. Commun.* **1996**, 197. See also ref 6f.

(12) Yamamoto, Y.; Nishii, S.; Maruyama, K.; Komatsu, T.; Ito, W. *J. Am. Chem. Soc.* **1986**, *108*, 7778.

(13) Leading references: (a) Sakaitani, M.; Ohfune, Y. *J. Am. Chem. Soc.* **1990**, *112*, 1150. (b) Ishimaru, K.; Tsuru, K.; Yabuta, K.; Wada, M.; Yamamoto, Y.; Akiba, K. *Tetrahedron* **1996**, *52*, 13137.

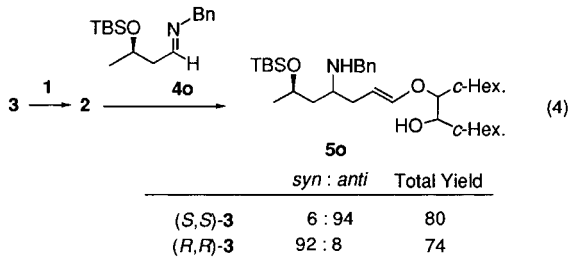
(14) Double stereodifferentiation of the reaction of a chiral imine with a chiral allylmetal reagent has been reported; see: Hallett, D. J.; Thomas, E. J. *J. Chem. Soc., Chem. Commun.* **1995**, 657.

Scheme 2[a]



[a] Conditions: (i) $(Boc)_2O$, Et_3N, THF; (ii) O_3, Me_2S, CH_2Cl_2; (iii) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH−H_2O; (iv) MeI, $NaHCO_3$, DMF; (v) Ac_2O, pyridine, DMAP catalyst; (vi) *p*-TsOH catalyst, MeOH; (vii) TFA, CH_2Cl_2−H_2O.

tivity to afford **5n** with *anti*-stereochemistry exclusively, the reaction with **2** derived from (*R*,*R*)-**3** gave a diastereomeric mixture of **5n** in a ratio of 55:45.[16] In contrast, as shown in eq 4, little double stereodifferentiation was observed for the



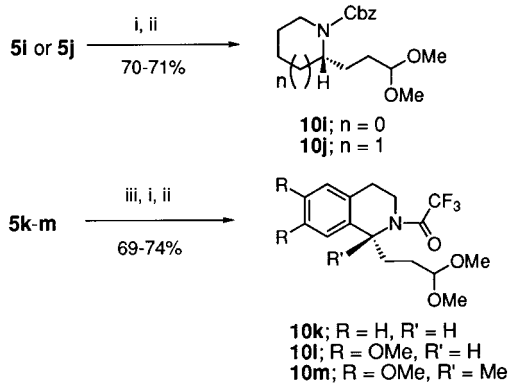
(4)

	syn : *anti*	Total Yield
(*S*,*S*)-**3**	6 : 94	80
(*R*,*R*)-**3**	92 : 8	74

reactions with a β-silyloxyimine **4o**[15] and the stereochemistry was controlled mainly by **2**; thus, the reaction affords either *syn*- or *anti*-**5o** with more than 92% diastereoselectivity. As the resulting products have an enol ether moiety that allows further elaboration, a new efficient entry to optically active β−alkoxyamines with *anti*-stereochemistry and γ-alkoxyamines with either *syn*- or *anti*-stereochemistry has conclusively been opened up.

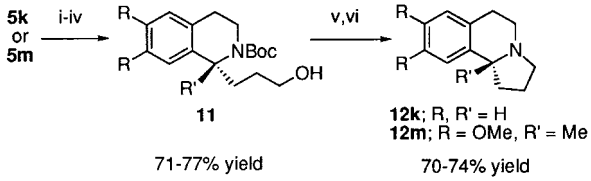
Synthetic Transformation of the Addition Products 5 and Preparation of a Key Intermediate for the Synthesis of Batzelladine D. By taking advantage of the reactivity of the enol ether functionality, the products **5** could be readily transformed into a variety of aminocarbonyl compounds.[17] As represented by the reaction of **5c** shown in Scheme 2, after protection of **5** as the *N*-Boc-*O*-acetyl derivative, it was readily

Scheme 3[a]



[a] Conditions: (i) Ac_2O, pyridine; (ii) *p*-TsOH catalyst, MeOH; (iii) $(CF_3CO)_2O$, Et_3N, CH_2Cl_2.

Scheme 4[a]



[a] Conditions: (i) $(Boc)_2O$, Et_3N, CH_2Cl_2; (ii) Ac_2O, pyridine; (iii) TFA, CH_2Cl_2−H_2O; (iv) $NaHBH_4$, EtOH; (v) MsCl, Et_3N, CH_2Cl_2; (vi) TFA, CH_2Cl_2 and then quenched with saturated aqueous $NaHCO_3$.

converted into the corresponding γ-amino aldehyde dimethyl acetal **7** by acidic methanolysis.[18] Acidic hydrolysis of the resulting **7** afforded the γ-amino aldehyde **8** which, in turn, was converted to the γ-amino acid **9** by oxidation with sodium chlorite. The compound **5** can also be converted to β-amino ester **6**[19] by conventional reaction sequence. Similarly, from the cyclic amines **5i**−**m** the corresponding N-protected γ-amino aldehyde dimethyl acetals **10i**−**m**[20] were readily prepared (Scheme 3).

From the compounds **5k** and **5m**, optically active pyrrolidinoisoquinolines, the structure of which exists in plant alkaloids,[21] could be easily synthesized as shown in Scheme 4. Thus, the *N*-Boc-*O*-acetyl derivatives of **5k** and **5m** were successively treated with TFA and H_2O in CH_2Cl_2 and then $NaBH_4$ in EtOH to provide the corresponding alcohols **11k** and **11m** which, in turn, were converted to the corresponding known pyrrolidinoisoquinolines **12k** and **12m**,[22] respectively, by deprotective cyclization after mesylation.

We also carried out the synthesis of 4-amino-6-hydroxypentadecanal dimethyl acetal (**13**), which is a key intermediate for the Overman synthesis of an *anti*-HIV polyguanidine alkaloid Batzelladine D (Scheme 5).[23] Thus, the optically active β-silyl-

(15) Imines **4n** and **4o** were prepared according to the reported procedure: Yamamoto, Y.; Komatsu, T.; Maruyama, K. *J. Chem. Soc., Chem. Commun.* **1985**, 814. Cainell, G.; Giacomini, D.; Mezzina, E.; Panunzio, M.; Zarantonello, P. *Tetrahedron Lett.* **1991**, *32*, 2967. See also ref 13b.

(16) The reaction of **4n** with allyltitanium derived from acrolein 1,1,2,2-tetramethylethylene acetal afforded the corresponding *anti*- and *syn*-adducts in a ratio of 90:10.

(17) Recent reviews for syntheses of β-amino acids, see: (a) Juaristi, E.; Lopez-Ruiz, H. *Curr. Med. Chem.* **1999**, *6*, 983. (b) Yamamoto, Y.; Asao, N.; Tsukada, N. *Adv. Asymmetric Synth.* **1998**, *3*, 1. (c) *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, 1997. Synthesis of optically active γ-amino acids attracts current interest; see: (d) Smrcina, M.; Majer, P.; Majerová, E.; Guerassina, T. A.; Eissenstat, M. A. *Tetrahedron* **1997**, *53*, 12867 and references therein. For the biological importance of γ-amino acids, see: (e) Nanavati, S. M.; Silverman, R. B. *J. Am. Chem. Soc.* **1991**, *113*, 9341. (f) Burke, J. R.; Silverman, R. B. *J. Am. Chem. Soc.* **1991**, *113*, 9329. See also ref 17d.

(18) Treatment of a crude mixture including **7** and the monoacetate of 1,2-dicyclohexylethandiol with NaOH in MeOH followed by column chromatography after extractive workup gave **7** in 70% yield and 1,2-dicyclohexylethandiol in 63% yield.

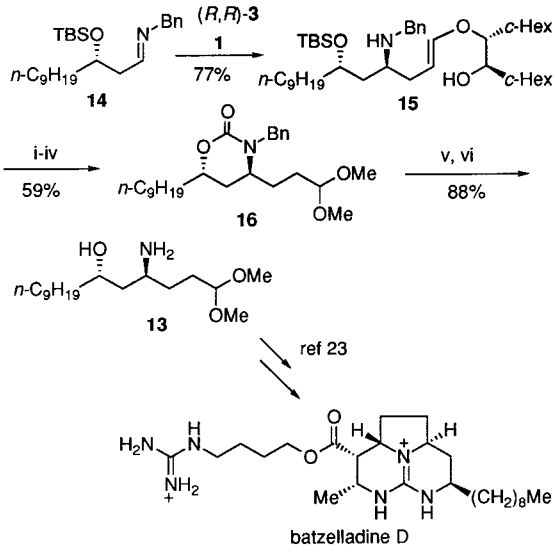
(19) Ee of **6c** was confirmed by ^1H NMR analysis after conversion to the corresponding MTPA amides. The absolute configuration was determined by conversion of the corresponding *N*-Cbz derivative and comparison of its $[\alpha]_D$ value with that reported. See Supporting Information.

(20) Ee of **10** thus obtained was determined by HPLC analysis with use of a chiral column.

(21) Boekelheide, V. *Alkaloids* **1960**, *7*, 201. Hill, R. K. *Alkaloids* **1967**, *9*, 483.

(22) The spectroscopic data of **12k** and **12m** thus prepared were in good agreement with those reported, and their absolute configuration was determined by comparison of their $[\alpha]_D$ values with those reported: (a) Lee, Y. S.; Kang, D. W.; Lee, S. J.; Park, H. *J. Org. Chem.* **1995**, *60*, 7149. (b) Meyers, A. I.; Gonzalez, M. A.; Struzka, V.; Akahane, A.; Guiles, J.; Warmus, J. S. *Tetrahedron Lett.* **1991**, *32*, 5501.

Scheme 5[a]



[a] Conditions: (i) CbzCl, *i*-Pr_2NEt, CH_2H_2; (ii) Ac_2O, DMAP catalyst, pyridine; (iii) *p*-TsOH catalyst, MeOH; (iv) NaH, THF; (v) Li, liquid NH_3−THF; (vi) KOH, H_2O, EtOH.

oxyimine **14**[24] reacted with **2** derived from (*R,R*)-**3** to afford *anti*-adduct **15** with 92% diastereoselectivity in 77% total yield, which was then converted to **13** in 52% overall yield via **16** by the conventional protection/deprotection reaction sequence. Although the diastereoselectivity of the resulting **13** was 92% due to the difficulty of separating each diastereomer of **15**, the synthesis seems to be attractive because the stereochemistry and the functionalities required for the preparation of **13** can be introduced by the one-step reaction.

Conclusions

We have now succeeded in developing, for the first time, a chiral homoenolate equivalent that reacts with a variety of acyclic and cyclic imines with excellent stereoselectivity, thus allowing an efficient preparation of various kinds of optically active γ-amino carbonyl compounds. Since the reagent is easy to prepare from readily available and inexpensive starting materials, the reaction is practical and will find numerous applications in organic synthesis.

Experimental Section

General. ^1H and ^{13}C NMR spectra were taken on a Varian Gemini-2000 spectrometer at 300 and 75 MHz, respectively. $CDCl_3$ was used as the solvent. Chemical shifts are reported in parts per million (δ value) from Me_4Si (δ 0 ppm for ^1H) or based on the middle peak of the solvent ($CDCl_3$) (δ 77.00 ppm for ^{13}C NMR) as an internal standard. Signal patterns are indicated as br s, broad singlet; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Coupling constants (*J*) are given in hertz. Analytical thin-layer chromatography (TLC) was performed on aluminum sheets precoated with silica gel (Merck, Kieselgel 60 F_{254}). Visualization was accomplished by UV light (254 nm), $KMnO_4$, and/or vanillin. Infrared (IR) spectra were recorded on a JASCO A-230 spectrometer and are reported in wavenumbers (cm^{-1}). Optical rotation was measured on a JASCO DIP-370 digital polarimeter. Enantiomeric excess values were determined by HPLC analysis with use of chiral columns or by ^1H NMR analysis of MTPA amides. Elemental analysis was performed on a Elementar Vario-EL. Ti(O-*i*-Pr)$_4$ was distilled and stored under argon. *i*-PrMgCl was prepared as a 1.20−1.50 M ethereal solution from *i*-PrCl and magnesium turnings by the usual procedure, titrated, and stocked under argon atmosphere. All reactions sensitive to oxygen or moisture were conducted under an argon or nitrogen atmosphere in a flame-dried flask.

Acrolein (*R,R*)-1,2-Dicyclohexylethylene Acetal (3). To a solution of (1*R*,2*R*)-(−)-1,2-dicyclohexyl-1,2-ethanediol (2.26 g, 10 mmol, Aldrich) and *p*-toluenesulfonic acid hydrate (30 mg) in dichloromethane (40 mL) was added dropwise acrolein diethyl acetal (1.7 mL, 13 mmol) at 0 °C. The resulting solution was stirred at room temperature for 2 h and then quenched by addition of saturated aqueous $NaHCO_3$ (40 mL). The organic layer was separated and the aqueous layer was extracted with ether (2 × 15 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by passing through a short silica gel column (hexanes/ether = 3/1) to give **3** as a colorless oil (2.50 g, 95%): $[\alpha]^{26}_D$ +28.5 (*c* 1.10, $CHCl_3$); IR (neat) 2924, 2852, 1449, 1346, 1103, 983, 933, 891 cm^{-1}; ^1H NMR δ 0.95−2.00 (m, 22H, C_6H_{11}), 3.62 (dd, *J* = 5.1, 6.6 Hz, 1H, $C_6H_{11}CHO$), 3.67 (t, *J* = 5.3 Hz, 1H, $C_6H_{11}CHO$), 5.22 (d, *J* = 6.6 Hz, 1H, CH_2=CHC*H*), 5.34 (d, *J* = 10.2 Hz, 1H, CH_2=CHCH), 5.46 (d, *J* = 16.8 Hz, 1H, CH_2=CHCH), 5.82 (ddd, *J* = 6.6, 10.2, 16.8 Hz, 1H, CH_2=C*H*CH); ^{13}C NMR δ 25.77, 25.88, 26.05, 26.09, 26.33 (two carbons), 28.11, 28.40, 29.58, 29.68, 40.60, 41.46, 83.30, 83.63, 103.13, 120.31, 135.39. Anal. Calcd for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found: C, 77.45; H, 10.71.

Typical Procedure for the Reactions in Tables 1 and 2. (*E*)-(4*S*)-4-(*N*-Benzyl)amino-1-[(1*R*,2*R*)-2-hydroxy-1,2-dicyclohexylethyl]oxy-5-methyl-1-hexene (5c) (eq 2 and entry 3 in Table 2): To a solution of the acetal **3** (305 mg, 1.153 mmol) and Ti(O-*i*-Pr)$_4$ (443 μL, 1.50 mmol) in ether (3 mL) was added dropwise *i*-PrMgCl (2.34 mL, 1.28 M in ether, 3.0 mmol) at −50 °C and the resulting mixture was stirred for 1.5 h at −50 to −40 °C. To this was added a solution of *E*-2-methylpropanal *N*-benzylimine (**4c**) (242 mg, 1.5 mmol) in ether (2 mL) at −40 °C. The mixture was allowed to warm to room temperature over 4 h and then quenched by addition of saturated aqueous $NaHCO_3$ (ca. 100 μL). The mixture was filtered through a pad of Celite with ether. The filtrate was concentrated under reduced pressure and the residue was dried by azeotropical removal of water with THF to give a crude mixture. On ^1H NMR analysis of the crude mixture no γ-addition product was observed. The crude residue was purified by a rapid column chromatography on silica gel eluted with hexanes, ether, and triethylamine to give a mixture of (*E*)- and (*Z*)-**5c** (total 405 mg, 85% yield) in a ratio of 94:6. Further purification by repeated column chromatography gave pure (*E*)-**5c** (344 mg, 70% yield): IR (neat) 3447, 2926, 2853, 1666, 1450, 1384, 1261, 1166, 1041, 924, 734, 698 cm^{-1}; ^1H NMR δ 0.89 (d, *J* = 6.9 Hz, 3H, CH_3CH), 0.91 (d, *J* = 6.6 Hz, 3H, CH_3CH), 0.88−2.00 (m, 24H, C_6H_{11}, CH_3CH, CH_2CH=CH), 2.07 (dddd, *J* = 1.2, 4.5, 6.6, 14.1 Hz, 1H, CH_2CH=CH), 2.30 (dt, *J* = 8.1, 4.5 Hz, 1H, CHN), 3.25−3.43 (m, 2H, $C_6H_{11}CH$), 3.72 (d, *J* = 13.2 Hz, 1H, $C_6H_5CH_2$), 3.77 (d, *J* = 13.2 Hz, 1H, $C_6H_5CH_2$), 4.81 (ddd, *J* = 6.6, 8.1, 12.0 Hz, 1H, CH_2CH=CH), 6.10 (d, *J* = 12.0 Hz, 1H, CH_2CH=C*H*), 7.16−7.40 (m, 5H, C_6H_5); ^{13}C NMR δ 17.86, 18.86, 26.10, 26.16, 26.18, 26.46, 26.49, 28.11, 28.25, 28.83, 29.63, 29.75, 29.77, 39.69, 40.44, 52.03, 62.27, 74.85, 85.70, 102.27, 126.64, 128.01, 128.18, 140.84, 149.46. Anal. Calcd for $C_{28}H_{45}NO_2$: C, 78.64; H, 10.61; N, 3.28. Found: C, 78.27; H, 10.22; N, 3.40. The selected ^1H NMR data for (*Z*)-**5c**: (300 MHz, $CDCl_3$) δ 4.23 (dt, *J* = 6.3, 7.2 Hz, 1H, CH_2CH=CH), 6.07 (d, *J* = 6.3 Hz, 1H, CH=C*H*O).

(*E*)-(4*R*)-4-(*N*-Benzyl)amino-1-[(1*R*,2*R*)-2-hydroxy-1,2-dicyclohexylethyl]oxy-1-pentene (5a) [entry 1 in Table 2]: The reaction of **3** with **4a** gave a mixture of (*E*)- and (*Z*)-**5a** (total 84% yield) in a ratio of 92:8. The following data were selected for (*E*)-**5a** from the spectra obtained with use of a mixture of *E*- and *Z*-isomers: ^1H NMR δ 0.88−2.08 (m, 24H, C_6H_{11}, CH_2CH=CH), 1.07 (d, *J* = 6.3 Hz, 3H, CH_3), 2.64 (sixtet, *J* = 6.3 Hz, 1H, CH_3CHN), 3.25−3.44 (m, 2H, $C_6H_{11}CH$), 3.71 (d, *J* = 12.9 Hz, 1H, $C_6H_5CH_2$), 3.84 (d, *J* = 12.9 Hz, 1H, $C_6H_5CH_2$), 4.82 (dt, *J* = 12.0, 7.8 Hz, 1H, CH_2CH=CH), 6.12 (d, *J* = 12.0 Hz, 1H, CH_2CH=C*H*), 7.15−7.38 (m, 5H, C_6H_5); ^{13}C NMR δ 20.15, 26.09, 26.16, 26.19, 26.44, 26.48, 28.22, 28.80, 29.76, 29.78, 35.06, 39.68, 40.41, 51.48, 52.48, 74.84, 85.72, 101.46, 126.71, 127.93, 128.27, 140.45, 149.77. The selected ^1H NMR data for (*Z*)-**5a**: δ 4.17−4.28 (m, 1H, CH_2CH=CH). IR (neat) 3412, 2924, 2852, 1665, 1450,

(23) Cohen, F.; Overman, L. E.; Ly Sakata, S. K. *Org. Lett.* **1999**, *1*, 2169.

(24) Prepared from (*S*)-(+)-epichlorohydrine through a six-step reaction sequence, see Supporting Information.

1376, 1170, 1146, 924, 732, 697 cm^{-1}. Anal. Calcd for $C_{26}H_{41}NO_2$: C, 78.15; H, 10.34; N, 3.51. Found: C, 77.93; H, 10.36; N, 3.57 (measured using a mixture of *E*- and (*Z*)-**5a**).

(*E*)-(4*R*)-4-(*N*-Benzyl)amino-1-[(1*R*,2*R*)-2-hydroxy-1,2-dicyclohexylethyl]oxy-1-heptene (5b) [entry 2 in Table 2]: The reaction of **3** with **4b** gave a mixture of (*E*)- and (*Z*)-**5b** (total 81% yield) in a ratio of 94:6. The following data were selected for (*E*)-**5b** from the spectra obtained by using a mixture of *E*- and *Z*-isomers: ^{1}H NMR δ 0.90 (t, J = 6.6 Hz, 3H, C*H*$_3$CH$_2$), 0.95−2.02 (m, 27H, C$_6$H$_{11}$, CH$_3$C*H*$_2$C*H*$_2$, C*H*$_2$CH═CH), 2.04−2.16 (m, 1H, C*H*$_2$CH═CH), 2.45−2.56 (m, 1H, CHN), 3.27−3.44 (m, 2H, C$_6$H$_{11}$C*H*), 3.73 (d, J = 12.9 Hz, 1H, C$_6$H$_5$C*H*$_2$), 3.78 (d, J = 12.9 Hz, 1H, C$_6$H$_5$C*H*$_2$), 4.83 (ddd, J = 6.9, 8.7, 12.0 Hz, 1H, CH$_2$C*H*═CH), 6.11 (d, J = 12.0 Hz, 1H, CH$_2$CH═C*H*), 7.15−7.40 (m, 5H, C$_6$H$_5$); ^{13}C NMR δ 14.47, 19.02, 26.10, 26.12, 26.18, 26.21, 26.46, 26.49, 28.21, 28.80, 29.78, 31.81, 36.14, 39.72, 40.45, 51.28, 56.65, 74.86, 85.70, 101.38, 126.70, 127.99, 128.24, 140.59, 149.63. The selected ^{1}H NMR data for (*Z*)-**5b**: δ 4.23 (dt, J = 6.3, 7.5 Hz, 1H, CH$_2$C*H*═CH), 6.09 (d, J = 6.3 Hz, 1H, CH═C*H*O). IR (neat) 3422, 2924, 2852, 1666, 1450, 1168, 924, 732, 698 cm^{-1}. Anal. Calcd for $C_{28}H_{45}NO_2$: C, 78.64; H, 10.61; N, 3.28. Found: C, 78.71; H, 10.84; N, 3.16 (measured using the mixture of (*E*)- and (*Z*)-**5b**).

(*E*)-(4*S*)-4-(*N*-Benzyl)amino-1-[(1*R*,2*R*)-2-hydroxy-1,2-dicyclohexylethyl]oxy-4-phenyl-1-butene (5e) [entry 5 in Table 2]: The reaction of **3** with **4e** gave a mixture of (*E*)- and (*Z*)-**5e** (total 82% yield) in a ratio of 93:7. Further purification of the mixture by repeated column chromatography gave pure (*E*)-**5e** in 40% yield. For the *E*-isomer: ^{1}H NMR δ 0.90−1.90 (m, 22H, C$_6$H$_{11}$), 2.15 (dt, J = 14.1, 8.7 Hz, 1H, C*H*$_2$CH═CH), 2.26 (dt, J = 14.1, 6.0 Hz, 1H, C*H*$_2$CH═CH), 3.22−3.40 (m, 2H, C$_6$H$_{11}$C*H*), 3.51 (d, J = 13.5 Hz, 1H, C$_6$H$_5$C*H*$_2$), 3.58 (dd, J = 5.4, 8.1 Hz, 1H, C$_6$H$_5$C*H*NH), 3.67 (d, J = 13.5 Hz, 1H, C$_6$H$_5$C*H*$_2$), 4.78 (ddd, J = 6.3, 9.3, 12.3 Hz, 1H, CH$_2$C*H*═CH), 6.09 (d, J = 12.3 Hz, 1H, CH$_2$CH═C*H*), 7.18−7.40 (m, 10H, C$_6$H$_5$); ^{13}C NMR δ 25.86, 25.90, 25.97, 26.26, 26.28, 27.97, 28.60, 29.56, 29.60, 36.84, 39.54, 40.23, 51.51, 62.42, 74.73, 85.68, 101.40, 126.84, 127.01, 127.33, 128.10, 128.37, 140.70, 144.04, 150.24. Anal. Calcd for $C_{31}H_{43}NO_2$: C, 80.65; H, 9.39; N, 3.03. Found: C, 80.53; H, 9.26; N, 2.95. The selected ^{1}H NMR data for (*Z*)-**5e**: δ 4.18 (dt, J = 8.4, 6.3 Hz, 1H, CH$_2$C*H*═CH), 6.04 (d, J = 6.3 Hz, 1H, CH═C*H*O). IR (neat) 3450, 2926, 2852, 1665, 1451, 1165, 926, 700 cm^{-1}.

(*E*)-(4*S*)-4-(*N*-Propyl)amino-1-[(1*R*,2*R*)-2-hydroxy-1,2-dicyclohexylethyl]oxy-4-phenyl-1-butene (5f) [entry 6 in Table 2]: The reaction of **3** with **4f** gave a mixture of (*E*)- and (*Z*)-**5f** (total 85% yield) in a ratio of 95:5. The following data were selected for (*E*)-**5f** from spectra obtained by using a mixture of *E*- and *Z*-isomers: ^{1}H NMR δ 0.86 (t, J = 7.5 Hz, 3H, CH$_3$), 0.90−1.95 (m, 24H, C$_6$H$_{11}$, CH$_3$C*H*$_2$), 2.14 (dt, J = 13.8, 9.0 Hz, 1H, C*H*$_2$CH═CH), 2.25 (dt, J = 13.8, 5.7 Hz, 1H, C*H*$_2$CH═CH), 2.39 (t, J = 7.5 Hz, 2H, CH$_3$CH$_2$C*H*$_2$N), 3.25−3.42 (m, 2H, 2C$_6$H$_{11}$C*H*), 3.52 (dd, J = 5.4, 7.8 Hz, 1H, C$_6$H$_5$C*H*N), 4.80 (ddd, J = 6.6, 9.3, 12.3 Hz, 1H, CH$_2$C*H*═CH), 6.11 (d, J = 12.3 Hz, 1H, CH$_2$CH═C*H*), 7.17−7.40 (m, 5H, C$_6$H$_5$); ^{13}C NMR δ 11.65, 23.16, 25.89, 25.95, 26.01, 26.30, 28.04, 28.69, 29.57, 29.62, 36.80, 39.58, 40.29, 49.66, 63.33, 74.78, 85.69, 101.55, 126.89, 127.21, 128.31, 144.41, 150.22. The selected ^{1}H NMR data for (*Z*)-**5f**: δ 4.16−4.28 (m, 1H, CH$_2$C*H*═CH). IR (neat) 3422, 2925, 2852, 1664, 1450, 1166, 926, 758, 701 cm^{-1}. Anal. Calcd for $C_{27}H_{43}NO_2$: C, 78.40; H, 10.48; N, 3.39. Found: C, 78.25; H, 10.40; N, 3.65 (measured using the mixture of (*E*)- and (*Z*)-**5f**).

(*E*)-(4*S*)-4-(*N*-Phenyl)amino-1-[(1*R*,2*R*)-2-hydroxy-1,2-dicyclohexylethyl]oxy-4-phenyl-1-butene (5g) [entry 7 in Table 2]: The reaction of **3** with **4g** gave a mixture of (*E*)- and (*Z*)-**5g** (total 71% yield) in a ratio of 95:5. The following data were selected for (*E*)-**5g** from the spectra obtained with use of a mixture of *E*- and *Z*-isomers: ^{1}H NMR δ 0.90−1.95 (m, 22H, C$_6$H$_{11}$), 2.25−2.50 (m, 2H, C*H*$_2$CH═CH), 3.30−3.45 (m, 2H, C$_6$H$_{11}$C*H*), 4.20 (br s, 1H, N*H*), 4.27 (t, J = 6.2 Hz, 1H, CHN), 4.77 (dt, J = 12.3, 7.8 Hz, 1H, CH$_2$C*H*═CH), 6.16 (d, J = 12.3 Hz, 1H, CH$_2$CH═C*H*), 6.47 (d, J = 7.8 Hz, 2H, C$_6$*H*$_5$N), 6.62 (t, J = 7.5 Hz, 1H, C$_6$H$_5$N), 7.08 (t, J = 7.5 Hz, 2H, C$_6$H$_5$N), 7.18−7.40 (m, 5H, C$_6$H$_5$C); ^{13}C NMR δ 26.10, 26.14, 26.20, 26.29, 26.45, 26.49, 28.13, 28.73, 29.82, 37.00, 39.64, 40.47, 57.70, 74.88, 85.79, 100.02, 113.40, 117.20, 126.28, 126.77, 128.37, 128.94, 143.37, 147.20, 150.24. The selected peaks for (*Z*)-**5g**: ^{1}H NMR δ 4.17 (dt, J = 6.3, 8.4 Hz, 1H, CH$_2$C*H*═C), 6.04 (d, J = 6.3 Hz, 1H, C═CHO). IR (neat) 3410, 2926, 2853, 1664, 1602, 1502, 1450, 1316, 1263, 1164, 927, 748, 700 cm^{-1}. The diastereoselectivity of the addition reaction was determined by conversion of a mixture of (*E*)- and (*Z*)-**5g** to the corresponding acetal, 4-phenyl-4-(*N*-phenyl)-amino-1-butanal (*R*,*R*)-1,2-dicyclohexylethylene acetal, and its ^{1}H and ^{13}C NMR analyses: To a stirred solution of **5g** (60.0 mg, 0.134 mmol) in chloroform (1.34 mL) was added 1 N HCl (0.5 mL). After 1 h at room temperature, the reaction mixture was quenched with saturated aqueous NaHCO$_3$ and extracted with Et$_2$O (3 × 5 mL). The combined extracts were washed with brine, dried over MgSO$_4$, filtered, and concentrated in vacuo. The residue was passed through a short silica gel column to give the cyclic acetal as a colorless oil (52.7 mg, 88%). The diastereomeric ratio of the resulting acetal was determined to be >85%: selected peaks for major and minor isomers; ^{1}H NMR δ 3.611 (s) vs 3.605 (s) [measured by ^{1}H−^{1}H homo-decoupling experiments with irradiating allylic methylene protons], and ^{13}C NMR δ 83.524 vs 83.467, 83.077 vs 83.024.

(*E*)-3-[(2*S*)-*N*-Benzyloxycarbonyl-2-pyrrolidinyl]-1-[(1*R*,2*R*)-2-hydroxy-1,2-dicyclohexylethyl]oxy-1-propene (5i) [entry 9 in Table 2]: ^{1}H NMR (65 °C) δ 0.93−2.40 (m, 28H, C$_6$*H*$_{11}$, C*H*$_2$C*H*$_2$, C*H*$_2$CH═CH), 3.24−3.54 (m, 4H, C*H*$_2$N, C$_6$H$_{11}$C*H*O), 3.73−3.90 (m, 1H, C*H*N), 4.80 (dt, J = 12.0, 8.1 Hz, 1H, CH$_2$C*H*═CH), 5.10 (d, J = 12.6 Hz, 1H, C$_6$H$_5$C*H*$_2$), 5.16 (d, J = 12.6 Hz, 1H, C$_6$H$_5$C*H*$_2$), 6.07 (d, J = 12.0 Hz, 1H, CH$_2$CH═C*H*), 7.20−7.40 (m, 5H, C$_6$*H*$_5$); ^{13}C NMR (65 °C) δ 26.24, 26.28, 26.35, 26.61, 26.63, 28.35, 28.91, 29.94, 40.07, 40.90, 46.94, 58.17, 66.62, 75.03, 85.55, 100.97, 127.72, 127.75, 128.33, 137.26, 149.64, 154.75; IR (neat) 3449, 3032, 2923, 2851, 1700, 1449, 1414, 1359, 1171, 1106, 923, 768, 732, 697 cm^{-1}. Anal. Calcd for $C_{29}H_{43}NO_4$: C, 74.16; H, 9.23; N, 2.98. Found: C, 74.52; H, 9.25; N, 3.22.

(*E*)-3-[(2*S*)-*N*-Benzyloxycarbonyl-2-piperidyl]-1-[(1*R*,2*R*)-2-hydroxy-1,2-dicyclohexylethyl]oxy-1-propene (5j) [entry 10 in Table 2]: ^{1}H NMR (65 °C) δ 0.90−1.95 (m, 28H, C$_6$*H*$_{11}$, C*H*$_2$C*H*$_2$C*H*$_2$), 2.10 (dt, J = 7.2, 14.1 Hz, 1H, C*H*$_2$CH═CH), 2.19 (dt, J = 7.2, 14.1 Hz, 1H, C*H*$_2$CH═CH), 2.82 (dt, J = 2.1, 12.9 Hz, 1H, C*H*$_2$N), 3.27−3.43 (m, 2H, C*H*O), 3.95−4.30 (m, 2H, C*H*$_2$N, C*H*N), 4.79 (dt, J = 7.8, 12.0 Hz, 1H, CH$_2$C*H*═CH), 5.09 (d, J = 12.9 Hz, 1H, C$_6$H$_5$C*H*$_2$), 5.14 (d, J = 12.9 Hz, 1H, C$_6$H$_5$C*H*$_2$), 6.11 (d, J = 12.0 Hz, 1H, CH$_2$CH═C*H*), 7.20−7.41 (m, 5H, C$_6$*H*$_5$); ^{13}C NMR (65 °C) δ 18.88, 25.51, 26.20, 26.30, 26.32, 26.37, 26.60, 26.62, 27.18, 28.15, 28.70, 30.00, 39.54, 40.00, 40.76, 51.67, 66.94, 75.08, 85.65, 101.55, 127.67, 127.69, 128.32, 137.23, 149.30, 155.62; IR (neat) 3448, 3033, 2925, 2853, 1685, 1423, 1352, 1258, 1172, 1040, 730, 697 cm^{-1}. Anal. Calcd for $C_{30}H_{45}NO_4$: C, 74.50; H, 9.38; N, 2.90. Found: C, 74.58; H, 9.62; N, 3.09.

(*E*)-3-[(1*R*)-1,2,3,4-Tetrahydroisoquinol-1-yl]-1-[(1*R*,2*R*)-2-hydroxy-1,2-dicyclohexylethyl]oxy-1-propene (5k) [entry 11 in Table 2]: Recrystallized from hexanes−ether: mp 54−55 °C; $[\alpha]^{26}_D$ +63.9 (*c* 1.07, CHCl$_3$) (98% ee); ^{1}H NMR δ 0.90−2.23 (m, 24H, NH, OH, C$_6$*H*$_{11}$), 2.31 (dt, J = 8.7, 14.1 Hz, 1H, C*H*$_2$CH═CH), 2.49 (ddd, J = 3.6, 7.2, 14.4 Hz, 1H, C*H*$_2$CH═CH), 2.67−2.92 (m, 2H, ArC*H*$_2$), 2.97 (ddd, J = 6.0, 7.2, 12.3 Hz, 1H, C*H*$_2$NH), 3.22 (dt, J = 5.1, 12.3 Hz, 1H, C*H*$_2$NH), 3.28−3.47 (m, 2H, C$_6$H$_{11}$C*H*), 3.93 (dd, J = 3.3, 8.4 Hz, 1H, C*H*NH), 4.84 (ddd, J = 7.2, 8.4, 12.0 Hz, 1H, CH$_2$C*H*═CH), 6.19 (d, J = 12.0 Hz, 1H, CH$_2$CH═C*H*), 7.00−7.23 (m, 4H, Ar); ^{13}C NMR δ 26.11, 26.18, 26.25, 26.44, 26.47, 28.15, 28.69, 29.76, 30.04, 34.13, 39.58, 40.42, 40.93, 55.53, 74.82, 85.99, 100.95, 125.56, 125.80, 125.93, 129.09, 135.23, 138.44, 150.37. Anal. Calcd for $C_{26}H_{39}NO_2$: C, 78.54; H, 9.89; N, 3.52. Found: C, 78.23; H, 10.13; N, 3.34.

(*E*)-3-[(1*R*)-6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinol-1-yl]-1-[(1*R*,2*R*)-2-hydroxy-1,2-dicyclohexylethyl]oxy-1-propene (5l) [entry 12 in Table 2]: For the *E*-isomer: ^{1}H NMR δ 0.90−1.90 (m, 22H, C$_6$*H*$_{11}$), 2.28 (dt, J = 8.7, 14.1 Hz, C*H*$_2$CH═CH), 2.46 (ddd, J = 3.0, 7.5, 14.1 Hz, 1H, C*H*$_2$CH═CH), 2.60−2.82 (m, 2H, ArC*H*$_2$), 2.93 (dt, J = 6.0, 12.6 Hz, 1H, C*H*$_2$NH), 3.19 (dt, J = 5.4, 12.6 Hz, 1H, C*H*$_2$-NH), 3.32 (dd, J = 3.6, 6.3 Hz, 1H, C$_6$H$_{11}$C*H*), 3.40 (dd, J = 3.6, 6.0 Hz, 1H, C$_6$H$_{11}$C*H*), 3.77−3.90 (m, 1H, C*H*NH), 3.85 (S, 6H, C*H*$_3$O), 4.85 (ddd, J = 7.5, 8.7, 12.3 Hz, 1H, CH$_2$C*H*═CH), 6.20 (d, J = 12.3 Hz, 1H, CH$_2$CH═C*H*), 6.57 (s, 1H, Ar), 6.64 (s, 1H, Ar); ^{13}C NMR δ 25.94, 26.00, 26.07, 26.26, 26.29, 27.88, 28.46, 29.41, 29.60, 29.63,

34.03, 39.47, 40.29, 40.83, 55.12, 55.73, 55.90, 74.80, 86.09, 100.96, 109.17, 111.79, 127.57, 130.60, 147.23, 147.40, 150.68. The selected peaks for the *Z*-isomer: ^{1}H NMR δ 4.21 (q, J = 6.9 Hz, 1H, CH_2CH═CH), 6.12 (d, J = 6.0 Hz, 1H, CH_2CH═C*H*). IR (neat) 3204, 2924, 2845, 1663, 1509, 1449, 1258, 1166, 1113, 1038, 923, 853, 729 cm^{-1}.

(*E*)-3-[(1*R*)-6,7-Dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinolyl]-1-[(1*R*,2*R*)-2-hydroxy-1,2-dicyclohexylethyl]oxy-1-propene (5m) [entry 13 in Table 2]: For the *E*-isomer: ^{1}H NMR δ 0.90−2.10 (m, 22H, C_6H_{11}), 1.37 (s, 3H, CH_3C), 2.15 (dd, J = 9.3, 14.1 Hz, 1H, CH_2CH═CH), 2.53 (dd, J = 6.0, 14.1 Hz, 1H, CH_2CH═CH), 2.56−2.72 (2H, m, ArCH_2), 2.93−3.18 (m, 2H, CH_2NH), 3.27−3.42 (m, 2H, $C_6H_{11}CH$), 3.85 (s, 6H, CH_3O), 4.65 (ddd, J = 6.9, 9.0, 12.0 Hz, 1H, CH_2CH═CH), 6.15 (d, J = 12.0 Hz, 1H, CH_2CH═C*H*), 6.53 (s, 1H, Ar), 6.65 (s, 1H, Ar); ^{13}C NMR δ 25.87, 25.89, 26.00, 26.26, 28.05, 28.65, 29.21, 29.54, 29.60, 30.03, 38.08, 38.79, 39.51, 40.30, 40.58, 54.73, 55.65, 56.02, 74.75, 85.70, 99.91, 109.08, 111.65, 127.39, 134.80, 147.20, 147.32, 150.71. The selected peak for the *Z*-isomer: ^{1}H NMR δ 6.08 (d, J = 6.9 Hz, 1H, CH_2CH═C*H*).

(*E*)-(4*R*,5*S*)-5-(*tert*-Butyldimethylsilyl)oxy-4-benzylamino-1-[(1*S*,2*S*)-2-hydroxy-1,2-dicyclohexylethyl]oxy-1-hexene (*anti*-5n) [eq 3]: ^{1}H NMR δ 0.02 (s, 3H, $SiCH_3$), 0.04 (s, 3H, $SiCH_3$), 0.87 (s, 9H, *t*-Bu), 0.92−2.17 (m, 24H, C_6H_{11}, allylic CH_2), 1.14 (d, J = 6.3 Hz, 3H, CH_3), 2.49 (dt, J = 4.2, 6.6 Hz, 1H, CHN), 3.30−3.42 (m, 2H, CHC_6H_{11}), 3.74−3.91 (m, 3H, CH_2Ph, CHOSi), 4.85 (dt, J = 12.0, 8.1 Hz, 1H, CH_2CH═CHO), 6.10 (d, J = 12.0 Hz, 1H, CH═C*H*O), 7.19−7.34 (m, 5H, Ph); ^{13}C NMR δ −4.99, −4.70, 17.86, 18.18, 25.72, 25.87, 25.90, 25.98, 26.26, 28.06, 28.64, 29.56, 39.51, 40.33, 52.18, 62.86, 69.91, 74.75, 85.55, 101.79, 126.75, 128.16, 128.31, 140.94, 149.36; IR (neat) 3430, 2926, 1666, 1450, 1386, 1254, 1166, 1004, 836, 775 cm^{-1}. Anal. Calcd for $C_{33}H_{57}NO_3Si$: C, 72.87; H, 10.56; N, 2.58. Found: C, 72.95; H, 10.90; N, 2.69.

(*E*)-(4*R*,6*R*)-6-(*tert*-Butyldimethylsilyl)oxy-4-benzylamino-1-[(1*S*,2*S*)-2-hydroxy-1,2-dicyclohexylethyl]oxy-1-heptene (*anti*-5o) [eq 4]: Data for the *anti*-*E*-isomer: ^{1}H NMR δ 0.03 and 0.04 (2s, 6H, $SiCH_3$), 0.86 (s, 9H, *t*-Bu), 0.94−1.98 (m, 24H, C_6H_{11}, CH_2), 1.10 (d, J = 6.0 Hz, 3H, CH_3), 1.99−2.45 (m, 2H, allylic CH_2), 2.64−2.73 (m, 1H, CHN), 3.31−3.43 (m, 2H, $C_6H_{11}CH$), 3.69 (d, J = 12.9 Hz, 1H, CH_2Ph), 3.80 (d, J = 12.9 Hz, 1H, CH_2Ph), 3.97−4.08 (m, 1H, CHOSi), 4.83 (dt, J = 12.3, 7.5 Hz, 1H, CH_2CH═CH), 6.11 (d, J = 12.3 Hz, 1H, CH═C*H*O), 7.18−7.41 (m, 5H, Ph); ^{13}C NMR δ −4.98, −4.51, 17.86, 23.77, 25.74, 25.88, 25.92, 26.00, 26.28, 28.03, 28.63, 29.58, 32.16, 39.56, 40.32, 43.80, 51.18, 54.04, 66.51, 74.81, 85.56, 101.36, 126.80, 128.13, 128.25, 128.34, 140.91, 149.75.

(*E*)-(4*S*,6*R*)-6-(*tert*-Butyldimethylsilyl)oxy-4-benzylamino-1-[(1*R*,2*R*)-2-hydroxy-1,2-dicyclohexylethyl]oxy-1-heptene (*syn*-5o) [eq 4]: Data for the *syn*-*E*-isomer: ^{1}H NMR δ 0.02 and 0.04 (2s, 6H, $SiCH_3$), 0.86 (s, 9H, *t*-Bu), 0.92−2.22 (m, 26H, C_6H_{11}, CH_2), 1.11 (d, J = 6.0 Hz, 3H, CH_3), 2.56−2.74 (m, 1H, CHN), 3.32−3.44 (m, 2H, $C_6H_{11}CHO$), 3.72 (d, J = 13.5 Hz, 1H, CH_2Ph), 3.77 (d, J = 13.5 Hz, 1H, CH_2Ph), 3.88−3.98 (m, 1H, CHOSi), 4.75−4.88 (m, 1H, CH_2CH═CH), 6.10 (d, J = 12.0 Hz, 1H, CH═C*H*O), 7.16−7.34 (m, 5H, Ph); ^{13}C NMR δ −4.86, −4.34, 17.85, 24.29, 25.73, 25.90, 25.97, 26.25, 26.27, 28.01, 28.62, 29.58, 31.70, 39.57, 40.28, 44.11, 51.01, 54.11, 66.45, 74.78, 85.76, 101.15, 126.77, 128.12, 128.27, 128.33, 140.89, 150.00.

Typical Procedure for the Conversion of 5 to the β- and γ-Amino Carbonyl Compounds 6, 7, 8, and 9 (Scheme 2). Methyl (*S*)-3-(*N*-*tert*-butyloxycarbonyl-*N*-benzyl)amino-4-methylpentanoate (6c): A mixture of **5c** (215 mg, 0.504 mmol), Et_3N (0.14 mL), Boc_2O (0.23 mL, 1.0 mmol), and THF (5 mL) was stirred at 50 °C for 12 h. After addition of water (15 mL), the mixture was extracted with ether (2 × 10 mL). The combined extracts were washed with brine (15 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was passed through a short silica gel column with hexanes and ether and concentrated in vacuo. The resulting residue was dissolved in CH_2Cl_2 (methanol-free, 10 mL). Ozone gas (1.5 g/(h·air)) was passed at a rate of gentle bubbling through the solution at −78 °C. After consumption of the substrate was checked by TLC analysis, ozone was stopped and argon was bubbled for 20 min at −78 °C to remove excess ozone, and then dimethyl sulfide (0.5 mL) was added. The mixture was allowed to warm to room temperature over 2 h and stirring was continued for an additional 10 h. The mixture was concentrated in vacuo. The resulting residue was diluted with *tert*-butyl alcohol (10 mL) and 2-methyl-2-butene (2.5 mL). To this was added dropwise a solution of $NaClO_2$ (416 mg, 4.6 mmol) and NaH_2PO_4−$2H_2O$ (538 mg, 3.45 mmol) in water (4.2 mL). The mixture was stirred overnight at room temperature and concentrated under reduced pressure. The residue was diluted with ether (10 mL), acidified (pH 6) by addition of aqueous 0.5 N HCl, and extracted with ether (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, concentrated in vacuo, and chromatographed on silica gel (hexanes−ether) to give 3-(*N*-Boc-*N*-benzyl)amino-4-methylpentanoic acid (113 mg), which was converted into its methyl ester **6c** (100 mg, 60% yield) by treatment with MeI (0.11 mL) in the presence of $NaHCO_3$ (59 mg) in DMF (3.5 mL) at room temperature for 12 h: $[\alpha]_D^{25}$ −34.9 (*c* 0.88, $CHCl_3$) for **6c** derived from the 94:6 mixture of (*E*)- and (*Z*)-**5c**; $[\alpha]_D^{25}$ −40.7 (*c* 1.32, $CHCl_3$) for **6c** derived from pure (*E*)-**5c**; ^{1}H NMR (65 °C) δ 0.76 (d, J = 6.6 Hz, 3H, $(CH_3)_2CHCH$), 0.87 (d, J = 6.9 Hz, 3H, $(CH_3)_2CHCH$), 1.45 (s, 9H, $C(CH_3)_3$), 1.90−2.10 (m, 1H, $(CH_3)_2CHCH$), 2.54 (dd, J = 5.1, 15.6 Hz, 1H, CH_2COOCH_3), 2.64 (dd, J = 8.4, 15.6 Hz, 1H, CH_2COOCH_3), 3.52 (s, 3H, $COOCH_3$), 3.70−3.87 (m, 1H, CHN), 4.29 (d, J = 15.6 Hz, 1H, $C_6H_5CH_2$), 4.45 (d, J = 15.6 Hz, 1H, $C_6H_5CH_2$), 7.15−7.35 (m, 5H, C_6H_5); ^{13}C NMR (65 °C) δ 20.12, 20.30, 28.56, 31.69, 37.28, 50.89, 51.37, 61.65, 79.87, 126.83, 127.99, 128.10, 139.24, 155.70, 172.15; IR (neat) 2965, 2874, 1741, 1688, 1453, 1435, 1365, 1252, 1163, 982, 868, 771, 733, 701 cm^{-1}.

Methyl (*R*)-3-(*N*-*tert*-butyloxycarbonyl-*N*-benzyl)aminobutanoate (6a): 61% yield from a mixture of (*E*)- and (*Z*)-**5a**; $[\alpha]_D^{23}$ −22.5 (*c* 1.03, $CHCl_3$); ^{1}H NMR (65 °C) δ 1.16 (d, J = 6.9 Hz, 3H, CH_3CHN), 1.45 (s, 9H, $C(CH_3)_3$), 2.43 (dd, J = 7.2, 15.0 Hz, 1H, CH_2COOCH_3), 2.68 (dd, J = 6.9, 15.0 Hz, 1H, CH_2COOCH_3), 3.61 (s, 3H, $COOCH_3$), 4.12−4.32 (m, 1H, CHN), 4.30 (d, J = 15.6 Hz, 1H, $C_6H_5CH_2$), 4.49 (d, J = 15.6 Hz, 1H, $C_6H_5CH_2$), 7.15−7.38 (m, 5H, C_6H_5); ^{13}C NMR (65 °C) δ 19.28, 28.76, 40.26, 49.68, 50.75, 51.60, 80.18, 127.02, 127.47, 128.44, 139.67, 155.51, 171.84; IR (neat) 2975, 2975, 1739, 1689, 1451, 1407, 1365, 1253, 1165, 1029, 866, 736, 701 cm^{-1}.

Methyl (*R*)-3-(*N*-*tert*-butyloxycarbonyl-*N*-benzyl)aminohexanoate (6b): 65% yield from a mixture of (*E*)- and (*Z*)-**5b**; $[\alpha]_D^{28}$ −22.8 (*c* 1.42, $CHCl_3$); ^{1}H NMR (65 °C) δ 0.80 (t, J = 7.2 Hz, 3H, CH_3CH_2), 1.11−1.27 (m, 2H, CH_3CH_2), 1.35−1.68 (m, 2H, $CH_3CH_2CH_2$), 1.45 (s, 9H, $C(CH_3)_3$), 2.42 (dd, J = 6.6, 15.0 Hz, 1H, CH_2COOCH_3), 2.60 (dd, J = 7.5, 15.0 Hz, 1H, CH_2COOCH_3), 3.58 (s, 3H, $COOCH_3$), 4.07−4.24 (m, 1H, CHN), 4.30 (d, J = 15.6 Hz, 1H, $C_6H_5CH_2$), 4.44 (d, J = 15.6 Hz, 1H, $C_6H_5CH_2$), 7.16−7.38 (m, 5H, C_6H_5); ^{13}C NMR (65 °C) δ 13.76, 19.76, 28.56, 35.73, 38.89, 49.66, 51.38, 54.72, 79.91, 126.85, 127.64, 128.17, 139.42, 155.64, 171.77; IR (neat) 2960, 2872, 1739, 1691, 1454, 1408, 1365, 1247, 1164, 1016, 868, 734, 701 cm^{-1}.

Methyl (*S*)-3-(*N*-*tert*-butyloxycarbonyl-*N*-benzyl)amino-3-phenylpropionate (6e): 52% yield from a mixture of (*E*)- and (*Z*)-**5e**; $[\alpha]_D^{26}$ −79.2 (*c* 1.18, $CHCl_3$) for **6e** derived from pure (*E*)-**5e**; $[\alpha]_D^{26}$ −70.8 (*c* 1.28, $CHCl_3$) for **6e** derived from the mixture of (*E*)- and (*Z*)-**5e**; ^{1}H NMR (65 °C) δ 1.41 (s, 9H, $C(CH_3)_3$), 2.89 (dd, J = 7.8, 15.9 Hz, 1H, CH_2COOCH_3), 2.95 (dd, J = 7.8, 15.9 Hz, 1H, CH_2COOCH_3), 3.55 (s, 3H, $COOCH_3$), 4.14 (d, J = 15.6 Hz, 1H, $C_6H_5CH_2$), 4.46 (d, J = 15.6 Hz, 1H, $C_6H_5CH_2$), 5.61 (t, J = 7.5 Hz, 1H, CHN), 7.05−7.35 (m, 10H, C_6H_5); ^{13}C NMR (65 °C) δ 28.49, 37.68, 49.10, 51.57, 56.65, 80.38, 126.78, 127.39, 127.45, 127.49, 128.13, 128.33, 139.22, 139.71, 155.66, 171.06; IR (neat) 2975, 1741, 1689, 1453, 1402, 1365, 1252, 1163, 975, 867, 743, 699 cm^{-1}.

Methyl (*S*)-3-(*N*-*tert*-butyloxycarbonyl-*N*-propyl)amino-3-phenylpropionate (6f): 60% yield from a mixture of (*E*)- and (*Z*)-**5f**; $[\alpha]_D^{24}$ −62.5 (*c* 1.32, $CHCl_3$); ^{1}H NMR (65 °C) δ 0.73 (t, J = 7.5 Hz, 3H, CH_3CH_2), 1.20−1.60 (m, 2H, CH_3CH_2), 1.44 (s, 9H, $C(CH_3)_3$), 2.99 (t, J = 7.8 Hz, 2H, $CH_3CH_2CH_2N$), 3.01 (d, J = 7.5 Hz, 2H, CH_2COOCH_3), 3.65 (s, 3H, $COOCH_3$), 5.51 (t, J = 7.5 Hz, 1H, C_6H_5CHN), 7.15−7.45 (m, 5H, C_6H_5); ^{13}C NMR (65 °C) δ 11.41, 22.69, 28.52, 37.74, 47.66, 51.62, 56.55, 79.74, 127.06, 127.32, 128.29, 140.20, 155.37, 171.26; IR (neat) 2970, 2874, 1741, 1686, 1453, 1405, 1365, 1250, 1154, 966, 864, 770, 700 cm^{-1}.

Methyl (3*R*,4*S*)-3-(*N*-*tert*-butyloxycarbonyl-*N*-benzyl)amino-4-(*tert*-butyldimethylsiloxy)pentanoate (*anti*-6n): a white solid; mp 66.0−67.0 °C; $[\alpha]_D^{27}$ +46.2 (*c* 0.216, $CHCl_3$); ^{1}H NMR (65 °C) δ

0.02 (s, 6H, $SiCH_3$), 0.86 (s, 9H, Si-*t*-Bu), 0.96 (d, J = 6.0 Hz, 3H, CH_3), 1.46 (s, 9H, O-*t*-Bu), 2.65 (dd, J = 7.8, 15.9 Hz, 1H, CH_2CO_2), 2.79 (dd, J = 4.2, 15.9 Hz, 1H, CH_2CO_2), 3.52 (s, 3H, OCH_3), 3.84−4.12 (m, 2H, CHO, CHN), 4.37 and 4.49 (2d, J = 15.6, 15.6 Hz, 2H, CH_2Ph), 7.15−7.30 (m, 5H, Ph); ^{13}C NMR (65 °C) δ −4.52, −3.91, 18.05, 21.26, 25.97, 28.60, 35.30, 51.29, 51.54, 61.76, 70.20, 80.10, 126.89, 128.13 (four carbons), 139.15, 155.66, 172.18; IR 2925, 2854, 1730, 1696, 1410, 1366, 1251, 1171, 1133, 1072, 1053, 1000, 834, 777 cm^{-1}. Anal. Calcd for $C_{24}H_{41}NO_5Si$: C, 63.82; H, 9.15; N, 3.10. Found: C, 63.75; H, 9.26; N, 3.09. The selected peaks for *syn*-**6n**: ^{1}H NMR (65 °C) δ 1.19 (d, J = 6.3 Hz, 3H, CH_3), 2.46−2.64 (m, 2H, CH_2CO_2), 3.51 (s, 3H, OCH_3), 4.05−4.21 (m, 1H, CHO), 4.38 (q, J = 5.9 Hz, 1H, CHN), 4.54 (d, J = 15.9 Hz, 1H, CH_2Ph), 4.63 (d, J = 15.9 Hz, 1H, CH_2Ph). The relative stereochemistries were confirmed by conversion to β-(BnNH)-γ-valerolactone by sequential treatment with TFA, CH_2Cl_2 and then NaH, THF and its NOE experiments on ^{1}H NMR: ^{1}H NMR δ 1.40 (d, J = 6.3 Hz, 3H, CH_3), 2.37 (dd, J = 6.0, 17.7 Hz, 1H, CH_2CO_2), 2.57 (dd, J = 7.5, 17.7 Hz, 1H, CH_2CO_2), 3.18−3.26 (m, 1H, CHN), 3.80 (s, 2H, CH_2Ph), 4.33−4.50 (m, 1H, CHO), 7.22−7.38 (m, 5H, Ph).

Methyl (3*S*,5*R*)-3-(*N*-*tert*-butyloxycarbonyl-*N*-benzyl)amino-5-(*tert*-butyldimethylsiloxy)hexanoate (*anti*-6o): ^{1}H NMR (65 °C) δ 0.02 and 0.03 (2s, 6H, $SiCH_3$), 0.88 (s, 9H, Si-*t*-Bu), 1.07 (d, J = 6.0 Hz, 3H, CH_3), 1.47 (s, 9H, O-*t*-Bu), 1.62−1.88 (m, 2H, CH_2), 2.51 (dd, J = 5.7, 15.3 Hz, 1H, CH_2CO_2), 2.68−2.80 (m, 1H, CH_2CO_2), 3.58 (s, 3H), 3.67−3.77 (m, 1H, CHO), 4.09−4.22 (m, 1H, CHN), 4.28 (d, J = 15.6 Hz, 1H, CH_2Ph), 4.53 (d, J = 15.6 Hz, 1H, CH_2Ph), 7.16−7.34 (m, 5H, Ph); ^{13}C NMR (65 °C) δ −4.97, −4.53, 17.89, 23.28, 25.80, 28.40, 38.38, 43.23, 51.22, 52.69, 66.10, 80.00, 127.08, 127.87, 128.40, 139.46, 155.50, 172.07. The relative stereochemistries were confirmed by conversion to the corresponding β-(BnNH)-δ-caprolactone by sequential treatment with TFA, CH_2Cl_2 and then NaH, THF and its NOE experiments on ^{1}H NMR: ^{1}H NMR δ 1.37 (d, J = 6.3 Hz, 3H, CH_3), 1.72 (ddd, J = 4.8, 10.8, 14.4 Hz, 1H, CH_2), 1.89 (dt, J = 14.4, 3.6 Hz, 1H, CH_2), 2.45 (ddd, J = 1.2, 5.4, 16.8 Hz, 1H, CH_2CO_2), 2.69 (dd, J = 5.1, 16.8 Hz, 1H, CH_2CO_2), 3.23−3.31 (m, 1H, CHN), 3.77 (s, 2H, CH_2Ph), 4.72−4.85 (m, 1H, CHO), 7.21−7.39 (m, 5H, Ph).

Methyl (3*R*,5*R*)-3-(*N*-*tert*-butyloxycarbonyl-*N*-benzyl)amino-5-(*tert*-butyldimethylsiloxy)hexanoate (*syn*-6o): ^{1}H NMR (65 °C) δ 0.02 and 0.04 (2s, 6H, $SiCH_3$), 0.88 (s, 9H, Si-*t*-Bu), 0.96 (d, J = 6.0 Hz, 3H, CH_3), 1.48 (s, 9H, O-*t*-Bu), 1.54−1.76 (m, 2H, CH_2), 2.51 (dd, J = 6.3, 15.0 Hz, 1H, CH_2CO_2), 2.69 (dd, J = 8.1, 15.0 Hz, 1H, CH_2CO_2), 3.59 (s, 3H, OCH_3), 3.53−3.67 (m, 1H, CHO), 4.15 (br s, 1H, CHN), 4.35−4.52 (m, 2H, CH_2Ph), 7.17−7.35 (m, 5H, Ph); ^{13}C NMR (65 °C) δ −4.72, −4.23, 17.90, 23.83, 25.85, 28.42, 39.29, 43.98, 50.46, 51.25, 53.00, 66.85, 80.04, 127.12, 127.90, 128.43, 139.65, 155.75, 172.03. The relative stereochemistries were confirmed by conversion to the corresponding β-(BnNH)-δ-caprolactone by sequential treatment with TFA, CH_2Cl_2 and then NaH, THF and its NOE experiments on ^{1}H NMR: ^{1}H NMR δ 1.40 (d, J = 6.3 Hz, 3H, CH_3), 1.33−1.56 (m, 1H, CH_2), 2.14−2.24 (m, 1H, CH_2), 2.33 (dd, J = 9.0, 17.1 Hz, 1H, CH_2CO_2), 2.84 (ddd, J = 1.5, 6.0, 17.1 Hz, 1H, CH_2CO_2), 3.09−3.22 (m, 1H, CHN), 3.81 (s, 2H, CH_2Ph), 4.36 (ddq, J = 3.0, 12.9, 6.3 Hz, 1H, CHO), 7.23−7.40 (m, 5H, Ph).

(*S*)-4-[*N*-(*tert*-Butyloxycarbonyl)-*N*-benzyl]amino-5-methylhexanal dimethyl acetal (7): To a solution of the crude *N*-Boc derivative of **5c** (215 mg, 0.504 mmol), prepared by the procedure described above for the synthesis of **6c**, in pyridine (5 mL) were added DMAP (ca. 15 mg) and Ac_2O (0.24 mL) and the resulting mixture was stirred at room temperature overnight. After addition of brine (20 mL), the mixture was extracted with hexanes (2 × 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated, and chromatographed by passing through a short silica gel column to give an *N*-Boc-*O*-Ac derivative of **5c**, which was treated with a catalytic amount of *p*-TsOH (ca. 15 mg) in MeOH (6.3 mL) to afford a mixture of the titled compound and (*R*,*R*)-1,2-dicyclohexyl-1,2-ethandiol monoacetate. The resulting mixture was refluxed with aqueous 3 N NaOH (0.5 mL) in MeOH (2.5 mL) for 6 h. After cooling to room temperature, the mixture was extracted with hexanes (2 × 15 mL), dried over $MgSO_4$, concentrated under reduced pressure, and chromatographed on silica gel to give **7** (128 mg, 70% yield) and (*R*,*R*)-1,2-dicyclohexyl-1,2-ethandiol (72 mg, 63% recovered). **7**: $[\alpha]^{25}_D$ −14.6 (*c* 0.70, $CHCl_3$) for **7** prepared from a mixture of (*E*)- and (*Z*)-**5c** (overall 88% ee.); ^{1}H NMR (65 °C) δ 0.81 (d, J = 6.3 Hz, 3H, $(CH_3)_2$CH), 0.92 (d, J = 6.3 Hz, 3H, $(CH_3)_2$CH), 1.44 (s, 9H, C$(CH_3)_3$), 1.20−1.90 (m, 5H, $(CH_3)_2$C*H*, CH_2CH_2), 3.18 (s, 3H, OCH_3), 3.22 (s, 3H, OCH_3), 3.40−3.80 (br, 1H, C*H*N), 4.07 (br s, 1H, C*H*$(OCH_3)_2$), 4.24 (d, J = 13.5 Hz, 1H, $C_6H_5CH_2$), 4.37 (d, J = 13.5 Hz, 1H, $C_6H_5CH_2$), 7.18−7.40 (m, 5H, C_6H_5); IR (neat) 2964, 2829, 1688, 1454, 1408, 1388, 1365, 1250, 1166, 1064, 951, 735, 701 cm^{-1}.

(*S*)-4-[*N*-(*tert*-Butyloxycarbonyl)-*N*-benzyl]amino-5-methylhexanal (8): The acetal **7** (94 mg, 0.258 mmol) prepared above was treated with trifluoroacetic acid (0.074 mL) in CH_2Cl_2 (0.3 mL) and water (0.074 mL) at room temperature for 2 h. After addition of aqueous saturated $NaHCO_3$ (2 mL), the mixture was extracted with hexanes (3 × 5 mL).The combined extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude aldehyde **8** (90 mg), which was subjected to the next reaction without further purification. The ^{1}H NMR date observed with the crude product: ^{1}H NMR (65 °C) δ 0.84 (d, J = 6.6 Hz, 3H, CH_3), 0.96 (d, J = 6.6 Hz, 3H, CH_3), 1.46 (s, 9H, *t*-Bu), 1.55−2.30 (m, 5H, CH, CH_2), 3.20−3.70 (br s, 1H, CHN), 4.24 (d, J = 14.7 Hz, 1H, CH_2Ph), 4.39 (d, J = 14.7 Hz, 1H, CH_2Ph), 7.15−7.40 (m, 5H), 9.45 (s, 1H, Ph).

(*S*)-4-[*N*-(*tert*-Butyloxycarbonyl)-*N*-benzyl]amino-5-methylhexanoic Acid (9): The aldehyde **8** obtained above was diluted with *tert*-butyl alcohol (5.4 mL) and 2-methyl-2-butene (1.3 mL). To this was added dropwise a solution of $NaClO_2$ (214 mg, 2.37 mmol) and NaH_2PO_4−$2H_2O$ (271 mg, 1.78 mmol) in water (2.2 mL). The mixture was stirred overnight at room temperature and concentrated under reduced pressure. The residue was diluted with ether (6 mL), acidified (pH 4) by addition of aqueous 0.5 N HCl, and extracted with ether (3 × 8 mL). The combined organic layers were dried over $MgSO_4$, concentrated in vacuo, and purified by column chromatography on silica gel (hexanes−ether) to afford the γ-amino acid **9** (75 mg) in 87% overall yield (two steps): $[\alpha]^{25}_D$ −19.5 (*c* 1.38, $CHCl_3$); ^{1}H NMR (65 °C) δ 0.81 (d, J = 6.6 Hz, 3H, $(CH_3)_2$CH), 0.94 (d, J = 6.3 Hz, 3H, $(CH_3)_2$CH), 1.45 (s, 9H, C$(CH_3)_3$), 1.60−2.30 (m, 5H, $(CH_3)_2$C*H*, CH_2CH_2), 3.20−3.80 (br, 1H, C*H*N), 4.23 (d, J = 15.0 Hz, 1H, $C_6H_5CH_2$), 4.39 (d, J = 15.0 Hz, 1H, $C_6H_5CH_2$), 7.12−7.40 (m, 5H, C_6H_5); ^{13}C NMR (65 °C) δ 20.30, 20.54, 25.79 (br), 28.55, 31.21, 31.46, 48.52 (br), 63.50 (br), 80.05, 126.98, 128.22, 139.40, 156.67, 177.95; IR (neat) 3189, 2973, 1724, 1686, 1454, 1411, 1366, 1252, 1163, 1006, 910, 734, 701 cm^{-1}. Anal. Calcd for $C_{19}H_{29}NO_4$: C, 68.03; H, 8.71; N, 4.18. Found: C, 67.92; H, 8.79; N, 3.96.

(*S*)-2-(3,3-Dimethoxypropyl)pyrrolidine benzylcarbamate (10i): $[\alpha]^{25}_D$ −30.8 (*c* 0.84, $CHCl_3$) (78% ee); ^{1}H NMR (65 °C) δ 1.35−2.02 (m, 8H, CH_2), 3.28 (s, 6H, OCH_3), 3.30−3.55 (m, 2H, CH_2N), 3.80−3.93 (m, 1H, C*H*N), 4.30 (br s, 1H, C*H*OCH_3), 5.10 (d, J = 12.6 Hz, 1H, $C_6H_5CH_2$), 5.15 (d, J = 12.6 Hz, 1H, $C_6H_5CH_2$), 7.22−7.40 (m, 5H, C_6H_5); ^{13}C NMR (65 °C) δ 23.60, 29.49, 29.60, 30.58, 46.57, 52.79, 53.03, 57.52, 66.64, 104.81, 127.69, 127.75, 128.31, 137.21, 154.88; IR (neat) 2952, 2882, 2829, 1701, 1451, 1412, 1359, 1190, 1102, 1076, 919, 753, 698 cm^{-1}. Anal. Calcd for $C_{17}H_{25}NO_4$: C, 66.43; H, 8.20; N, 4.56. Found: C, 66.07; H, 8.11; N, 4.80. Ee was determined to be 78% by HPLC analysis (CHIRALCEL OD-H, Hexane/*i*-PrOH 95/5, 0.60 mL/min, retention times, 15.4/17.2 min, respectively).

(*S*)-2-(3,3-Dimethoxypropyl)piperidine benzylcarbamate (10j): $[\alpha]^{27}_D$ −31.6 (*c* 0.74, $CHCl_3$) (89.5% ee); ^{1}H NMR (65 °C) δ 1.50−1.85 (m, 10H, CH_2), 2.84 (dt, J = 2.7, 13.2 Hz, 1H, CH_2N), 3.27 (s, 6H, OCH_3), 4.05 (dd, J = 3.3, 13.2 Hz, 1H, CH_2N), 4.20−4.37 (m, 1H, C*H*N), 4.32 (t, J = 5.4 Hz, 1H, C*H*$(OMe)_2$), 5.12 (s, 2H, PhCH_2), 7.20−7.42 (m, 5H, Ph); ^{13}C NMR (65 °C) δ 19.09, 24.77, 25.69, 28.70, 29.65, 39.28, 50.94, 52.87, 53.05, 67.00, 104.61, 127.70, 127.72, 128.33, 137.18, 155.51; IR (neat) 2936, 2870, 2829, 1697, 1425, 1354, 1259, 1125, 1070, 912, 733, 698 cm^{-1}. Ee was determined to be 89.5% by HPLC analysis (CHIRALCEL OD-H, Hexane/*i*-PrOH 95/5, 0.52 mL/min, retention times, 13.3/14.8 min, respectively).

(*R*)-1-(3,3-Dimethoxypropyl)-1,2,3,4-tetrahydroisoquinoline trifluoroacetylamide (10k): A mixture of rotamers was obtained in a ratio of 83:17. For a major rotamer: ^{1}H NMR δ 1.54−2.03 (m, 4H,

CH_2), 2.87 (dt, J = 16.2, 3.6 Hz, 1H, ArCH_2), 3.04 (ddd, J = 5.7, 11.1, 16.8 Hz, 1H, ArCH_2), 3.31 (s, 3H, OCH_3), 3.32 (s, 3H, OCH_3), 3.64 (ddd, J = 5.2, 11.4, 15.3 Hz, 1H, CH_2N), 3.95−4.10 (m, 1H, CH_2N), 4.39 (t, J = 5.4 Hz, 1H, C*H*OMe), 5.55 (t, J = 7.5 Hz, 1H, CHN), 7.10−7.30 (m, 4H, Ar); ^{13}C NMR δ 29.12, 31.25, 39.48, 39.53, 52.99, 53.31, 53.91, 104.00, 116.50 (q, ^1J (C,F) = 285.8 Hz), 126.55, 127.00, 127.22, 128.66, 132.25, 135.89, 156.07 (q, ^{2}J (C,F) = 35.3 Hz). The selected peaks of a minor rotamer: ^{1}H NMR δ 4.33 (t, J = 5.4 Hz, 1H, C*H*OMe), 4.47 (ddd, J = 2.4, 6.6, 13.2 Hz, 1H, CH_2N), 4.92 (t, J = 6.9 Hz, 1H, C*H*N). IR (neat) 2953, 2832, 1685, 1458, 1386, 1269, 1198, 1141, 1068, 948, 930, 765, 744, 675 cm^{-1}. Anal. Calcd for $C_{16}H_{20}F_3NO_3$: C, 58.00; H, 6.08; N, 4.23. Found: C, 58.37; H, 4.42; N, 6.00. Ee was determined to be 80.2% (minor rotamer) and 79.8% (major rotamer) by HPLC analysis (CHIRALCEL OD-H, Hexane/*i*-PrOH 95/5, 0.60 mL/min, retention times, 8.6/9.2 min (minor) and 12.7/15.5 min (major), respectively).

(*R*)-1-(3,3-Dimethoxypropyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline trifluoroacetylamide (10*l*): A mixture of rotamers was obtained in a ratio of 84:16. For a major rotamer: ^{1}H NMR δ 1.52−2.00 (m, 4H, CH_2), 2.77 (ddd, J = 2.7, 3.6, 15.9 Hz, 1H, ArCH_2), 3.04 (ddd, J = 5.4, 11.4, 15.9 Hz, 1H, ArCH_2), 3.32 (s, 3H, OCH_3), 3.33 (s, 3H, OCH_3), 3.60 (ddd, J = 4.5, 11.7, 15.3 Hz, 1H, CH_2N), 3.85 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.95−4.10 (m, 1H, CH_2N), 4.40 (t, J = 5.4 Hz, 1H, C*H*OMe), 5.48 (t, J = 7.8 Hz, 1H, CHN), 6.58 (s, 1H, Ar), 6.61 (s, 1H, Ar); ^{13}C NMR δ 28.77, 29.08, 31.10, 39.41 (q, J (C,F) = 3.7 Hz), 52.91, 53.44, 53.47, 55.92, 56.05, 104.00, 109.79, 111.02, 116.50 (q, ^1J (C,F) = 285.9 Hz), 124.16, 127.86, 147.70, 147.96, 156.00 (q, ^2J (C,F) = 35.2 Hz). The selected peaks of a minor rotamer: ^{1}H NMR δ 4.34 (t, J = 5.4 Hz, 1H, C*H*OMe), 4.49 (ddd, J = 2.4, 6.6, 13.2 Hz, 1H, CH_2N), 4.85 (t, J = 6.9 Hz, 1H, C*H*N). IR (neat) 2935, 2835, 1684, 1612, 1520, 1465, 1371, 1254, 1198, 1119, 1069, 921, 858, 755 cm^{-1}. Ee was determined to be 81% for **10*l*** derived from a mixture of *E*- and *Z*-**5l** by HPLC analysis (CHIRALCEL OD-H, Hexane/*i*-PrOH 95/5).

(*R*)-1-Methyl-1-(3,3-dimethoxypropyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline trifluoroacetylamide (10m): ^{1}H NMR δ 1.00−1.40 (m, 2H, CH_2CH(OCH$_3$)$_2$), 1.72 (dt, J = 3.9, 14.1 Hz, 1H, CH_2CH$_2$CH(OCH$_3$)$_2$), 1.79 (s, 3H, CH_3C), 2.70 (1H, ddd, J = 3.0, 4.5, 15.9 Hz, ArCH_2), 2.88 (1H, ddd, J = 3.9, 7.5, 15.6 Hz, ArCH_2), 3.06 (s, 3H, CH(OCH_3)$_2$), 3.12−3.31 (m, 1H, CH_2CH$_2$CH(OCH$_3$)$_2$), 3.20 (s, 3H, CH(OCH_3)$_2$), 3.41 (ddd, J = 2.7, 10.2, 13.5 Hz, 1H, CH_2N), 3.80−3.95 (m, 1H, CH_2N), 3.87 (s, 6H, ArOCH_3), 4.21 (dd, J = 4.8, 6.9 Hz, 1H, C*H*(OCH$_3$)$_2$), 6.56 (s, 1H, Ar), 6.74 (s, 1H, Ar); ^{13}C NMR δ 26.04, 26.41, 29.78, 34.73, 42.87, 51.54, 52.54, 55.85, 56.11, 64.75, 103.47, 108.75, 110.28, 116.39 (q, ^1J (C,F) = 287.4 Hz), 127.30, 132.37, 147.38, 148.08, 155.89 (q, ^2J (C,F) = 34.4 Hz). Anal. Calcd for $C_{28}H_{43}NO_4$: C, 56.29; H, 6.46; N, 3.45. Found: C, 56.27; H, 6.49; N, 3.41. Ee was determined to be 94% ee by HPLC analysis (CHIRALCEL OD-H, Hexane/*i*-PrOH 95/5, 0.51 mL/min, retention times, 15.6/16.3 min, respectively).

Synthesis of Pyrrolidinoisoquinolines 12 (Scheme 4). (*R*)-1-(3-Hydroxypropyl)-1,2,3,4-tetrahydroisoquinoline *tert*-butyl carbamate (11k): A mixture of 5k (300 mg, 0.754 mmol), Et_3N (210 μL, 1.51 mmol), Boc_2O (347 μL, 1.51 mmol), and THF (7.5 mL) was stirred at room temperature for 12 h. After addition of water (20 mL), the mixture was extracted with ether (2 × 15 mL). The combined extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was passed through a short silica gel column (hexanes−ether) and concentrated in vacuo. To a solution of the residue in pyridine (7.5 mL) were added DMAP (ca. 20 mg) and Ac_2O (356 μL, 3.77 mmol), and the resulting mixture was stirred at room temperature overnight. After addition of brine (25 mL), the mixture was extracted with hexanes (2 × 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated, and chromatographed by passing through a short silica gel column to give the *N*-Boc-*O*-Ac derivative of 5k which was treated with trifluoroacetic acid (0.27 mL) in CH_2Cl_2 (1.1 mL) and H_2O (0.27 mL) at room temperature for 2 h to afford a crude residue of aldehyde. To this in EtOH (1.5 mL) was added $NaBH_4$ (57 mg, 1.50 mmol) at 0 °C. After 1 h at room temperature, the solution was quenched by addition of water (5 mL). The mixture was extracted with Et_2O (3 × 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated, and purified by column chromatography to give 11k (170 mg, 77%) as a colorless oil: $[\alpha]^{27}_D$ −60.7 (*c* 0.42, $CHCl_3$); ^{1}H NMR (65 °C) δ 1.47 (s, 9H, C(CH_3)$_3$), 1.55−1.92 (m, 4H, CH_2CH_2CH$_2$OH), 2.72 (dt, J = 16.2, 4.2 Hz, 1H, ArCH_2), 2.90 (ddd, J = 6.0, 9.9, 15.9 Hz, 1H, ArCH_2), 3.27 (ddd, J = 4.2, 9.9, 13.8 Hz, 1H, CH_2N), 3.69 (dt, J = 1.5, 6.6 Hz, 2H, CH_2OH), 3.86−4.14 (m, 1H, CH_2N), 5.12 (br s, 1H, C*H*N), 7.02−7.20 (m, 4H, Ar); ^{13}C NMR (65 °C) δ 28.65, 28.69, 29.65, 33.66, 38.24, 54.43, 62.78, 79.81, 125.98, 126.42, 127.09, 128.76, 134.25, 138.20, 155.04; IR (neat) 3436, 2976, 2929, 2867, 1691, 1422, 1365, 1295, 1166, 1121, 1065, 1039, 945, 757 cm^{-1}.

(*R*)-1-Methyl-1-(3-hydroxypropyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline *tert*-butyl carbamate (11m): 71% yield from **5m**; a colorless oil; $[\alpha]^{26}_D$ +60.1 (*c* 1.52, $CHCl_3$); ^{1}H NMR (65 °C) δ 0.98−1.80 (m, 3H, CH_2CH_2CH$_2$OH), 1.51 (s, 9H, C(CH_3)$_3$), 1.69 (S, 3H, CH_3C), 2.59 (dt, J = 15.9, 3.9 Hz, 1H, ArCH_2), 2.76 (ddd, J = 3.6, 9.6, 14.7 Hz, 1H, ArCH_2), 2.98−3.14 (m, 1H, CH_2CH$_2$CH$_2$OH), 3.31 (ddd, J = 3.0, 9.9, 12.6 Hz, 1H, CH_2N), 3.40−3.54 (m, 2H, CH_2OH), 3.84 (s, 6H, CH_3O), 4.00 (dt, J = 12.6, 4.2 Hz, 1H, CH_2N), 6.52 (s, 1H, Ar), 6.75 (s, 1H, Ar); ^{13}C NMR (65 °C) δ 27.79, 28.76, 30.41, 38.31, 42.37, 56.06, 56.61, 61.85, 63.04, 79.86, 110.54, 111,17, 129.04, 134.80, 147.62, 148.22, 155.01; IR (neat) 3447, 2974, 2935, 2870, 1677, 1518, 1465, 1366, 1257, 1164, 1075, 1021, 913, 859, 798, 773, 732 cm^{-1}.

Pyrrolidino[*a*]-1,2,3,4-tetrahydroisoquinoline (12k): To a solution of **11k** prepared above and Et_3N (162μL, 1.17 mmol) in CH_2Cl_2 (1.20 mL) was added MsCl (90.3 μL, 1.17 mmol) at 0 °C. The mixture was stirred at room temperature for 6 h. After addition of aqueous saturated $NaHCO_3$, the mixture was extracted with Et_2O (3 × 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford a crude oil that was treated with trifluoroacetic acid (1.5 mL) in CH_2Cl_2 (1.5 mL) at room temperature for 1 h. After neutralization with aqueous saturated $NaHCO_3$, the mixture was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed on silica gel to give **12k** (70 mg, 70%) as a colorless oil: ^{1}H NMR δ 1.65−2.04 (m, 3H, CH_2CH_2CHN), 2.28−2.42 (m, 1H, CH_2CHN), 2.51 (q, J = 8.4 Hz, 1H, CH_2N), 2.63 (dt, J = 4.8, 10.2 Hz, 1H, CH_2N), 2.82 (dt, J = 16.2, 3.0 Hz, 1H, ArCH_2), 3.02−3.27 (3H, CH_2N, ArCH_2), 3.40 (dd, J = 7.5, 8.7 Hz, 1H, C*H*N), 7.00−7.20 (m, 4H, Ar); ^{13}C NMR δ 22,24, 28.74, 30.21, 48.57, 53.41, 63.46, 125.45, 125.58, 125.82, 128.29, 134.08, 138.87; IR (neat) 3018, 2938, 2872, 2784, 2731, 1492, 1451, 1376, 1323, 1284, 1162, 1116, 1039, 911 cm^{-1}. The absolute configuration of **12k** thus obtained was confirmed to be *R* by comparison of its $[\alpha]_D$ value ($[\alpha]^{28}_D$ +112.8 (*c* 0.96, MeOH)) with that reported for the (*S*)-isomer [lit.[22a] for 100% ee: $[\alpha]^{22}_D$ −101.7 (*c* 2.0, MeOH)].

Pyrroridino[*a*]-1-methyl-1,2,3,4-terahydroisoquinoline (12m): 74% yield from **11m**; a colorless oil; ^{1}H NMR δ 1.42 (s, 3H, CH_3C), 1.58−1.92 (m, 2H, CH_2CH_2CH$_2$N), 2.00−2.18 (m, 2H, CH_2CH$_2$CH$_2$N), 2.45 (ddd, J = 2.7, 4.2, 15.9 Hz, 1H, CH_2N), 2.80−3.12 (m, 4H, ArCH_2, CH_2CH$_2$CH_2N), 3.22 (ddd, J = 5.1, 11.1, 13.5 Hz, 1H, CH_2N), 3.84 (s, 3H, CH_3O), 3.86 (s, 3H, CH_3O), 6.53 (s, 1H, Ar), 6.65 (s, 1H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.34, 23.46, 30.09, 40.31, 42.94, 50.34, 55.78, 56.05, 62.29, 109.63, 110.98, 125.64, 135.67, 146.83, 147.34; IR (neat) 2962, 2931, 2862, 16.9, 1510, 1464, 1357, 1254, 1211, 1167, 1078, 996, 858, 770 cm^{-1}. The absolute configuration of **12m** thus obtained was confirmed to be *R* by comparison of its $[\alpha]_D$ value ($[\alpha]^{26}_D$ +40.1 (*c* 1.36, $CHCl_3$); $[\alpha]^{28}_D$ +40.6 (*c* 1.32, THF); $[\alpha]^{29}_D$ +43.1 (*c* 1.20, EtOH)) with that reported for the (*R*)-isomer [lit.[22b] for 74% ee; $[\alpha]_D$ +42].

Preparation of Overman's Intermediate (13) for Synthesizing Batzelladine D [Scheme 4]. (*R*,*R*)-1,2-Dicyclohexyl-2-hydroxyethyl (1*E*,4*S*,6*S*)-4-*N*-benzylamino-6-(*tert*-butyldimethylsilyl)oxypentadec-1-enyl ether (15): To a solution of acrolein (*R*,*R*)-1,2-dicyclohexylethylene acetal (**3**) (153 mg, 0.58 mmol) and Ti(O-*i*-Pr)$_4$ (0.257 mL, 0.87 mmol) in ether (2.5 mL) was added *i*-PrMgCl (2.18 mL, 0.80 M in ether, 1.74 mmol) at −50 °C and the resulting mixture was stirred for 1.5 h at −50 to −40 °C. To this was added (*S*)-3-(*tert*-butyldimethylsilyl)oxydodecanal *N*-benzylimine (**14**)[24] (1.15 mL, 0.4 M in ether, 0.46 mmol) at −40 °C and the mixture was allowed to warm to

room temperature over 3 h. After addition of saturated aqueous $NaHCO_3$ (0.3 mL), NaF (1 g), and Celite (1 g), the mixture was filtered through a pad of Celite, concentrated in vacuo, and chromatographed on silica gel to provide **15** (240 mg) in 77% yield. ^{1}H NMR δ 0.02 and 0.03 (2s, 6H), 0.86 (s, 9H), 0.88 (t, J = 4.5 Hz, 3H), 0.92−2.14 (m, 42H), 2.62−2.70 (m, 1H), 3.29−3.43 (m, 2H), 3.68 (d, J = 12.9 Hz, 1H), 3.72−3.90 (m, 1H), 3.80 (d, J = 12.9 Hz, 1H), 4.82 (dt, J = 12.0, 7.5 Hz, 1H), 6.10 (d, J = 12.0 Hz, 1H), 7.17−7.35 (m, 5H); the selected peaks of ^{13}C NMR δ −4.8, −4.6, 13.9, 17.8, 22.5, 25.0, 29.6, 31.7, 32.2, 37.0, 39.5, 40.2, 40.7, 51.1, 53.8, 70.5, 74.7, 85.5, 101.3, 126.7, 128.1, 128.3, 140.8, 149.7. Selected peak for *syn*-diastereomer: ^{1}H NMR δ 6.22 (d, J = 12.3 Hz, 1H).

***N*-Cbz-*O*-Ac derivative of 15:** To a solution of **15** (422 mg, 0.63 mmol) in CH_2Cl_2 (2.5 mL) were added *i*-Pr_2NEt (0.33 mL) and benzyl chloroformate (0.77 mL, 30% in toluene, 1.26 mmol) and the mixture was stirred for 1 h at ambient temperature. After addition of saturated aqueous $NaHCO_3$ (10 mL), the mixture was extracted with ether (1 × 10 mL), dried over $MgSO_4$, concentrated in vacuo, and chromatographed on silica gel to afford the *N*-Cbz derivative of **15** (396 mg) in 78% yield. The mixture of this compound (273 mg, 0.34 mmol) thus obtained, pyridine (3.4 mL), Ac_2O (0.232 mL), and 4-*N*,*N*-(dimethylamino)pyridine (12 mg) was stirred for 20 h at room temperature. After addition of brine (16 mL), the mixture was extracted with hexanes (2 × 15 mL), dried over $MgSO_4$, concentrated in vacuo, and chromatographed on silica gel to give the *N*-Cbz-*O*-Ac derivative of **15** (272 mg) in 95% yield. ^{1}H NMR (65 °C) δ −0.01 (s, 6H), 0.86 (s, 9H), 0.82−2.24 (m, 45H), 2.04 (s, 3H), 3.42 (t, J = 5.4 Hz, 1H), 3.48 (m, 1H), 3.82 (m, 1H), 4.40 (d, J = 15.9 Hz, 1H), 4.48 (dm J = 15.9 Hz, 1H), 4.75 (dt, J = 12.3, 7.2 Hz, 1H), 4.93 (t, J = 5.4 Hz, 1H), 5.13 (d, J = 12.3 Hz, 1H), 5.22 (d, J = 12.3 Hz, 1H), 5.95 (d, J = 12.3 Hz, 1H), 7.16−7.41 (m, 10H).

(4*S*,6*S*)-3-Benzyl-4-(3,3-dimethoxy)propyl-6-nonyltetrahydro-1,3-oxazin-2-one (16): The mixture of the *N*-Cbz-*O*-Ac derivative of **15** (272 mg, 0.322 mmol), *p*-TsOH (10 mg), and methanol (3.1 mL) was stirred for 2 h at ambient temperature. After addition of saturated aqueous $NaHCO_3$ (6 mL), the mixture was extracted with hexanes (2 × 6 mL), dried over $MgSO_4$, concentrated, and chromatographed on silica gel to provide (4*R*,6*S*)-4-(*N*-benzyl-*N*-benzyloxycarbonyl)amino-6-hydroxypentadecanal dimethyl acetal (146 mg) in 86% yield. To a solution of the resulting dimethyl acetal (146 mg, 0.277 mmol) in THF (0.5 mL) was added NaH (20 mg, 50% in oil, 0.42 mmol) at 0 °C and the mixture was stirred for 1.5 h at room temperature. After addition of brine (2 mL), the mixture was extracted with hexanes (2 × 5 mL), dried over $MgSO_4$, concentrated, and chromatographed on silica gel to provide **16** (107 mg, 92% yield). ^{1}H NMR (65 °C) δ 0.88 (t, J = 6.3 Hz, 3H), 1.12−1.88 (m, 22H), 3.16−3.26 (m, 1H), 3.29 and 3.30 (2s, 6H), 4.09 (d, J = 15.3 Hz, 1H), 4.26 (t, J = 5.1 Hz, 1H), 4.32 (m, 1H), 5.11 (d, J = 15.3 Hz, 1H), 7.18−7.40 (m, 5H); ^{13}C NMR (65 °C) δ 13.8, 22.4, 24.7, 27.2, 29.1, 29.2, 29.3, 29.4, 30.7, 31.7, 35.3, 50.3, 52.4, 53.1, 53.2, 73.4, 104.4, 126.9, 127.5, 128.0, 128.5, 128.6, 137.6, 154.2; IR (neat) 2925, 2854, 1686, 1448, 1362, 1253, 1227, 1129, 1075, 756 cm^{-1}.

(4*S*,6*S*)-4-Amino-6-hydroxypentadecanal dimethyl acetal (13): A solution of **16** (107 mg, 0.255 mmol) in THF (3.5 mL) was cooled to −78 °C and to this was introduced NH_3 until the total volume reached ca. 7 mL. To the mixture was added metal Li (16 mg) and the resulting blue solution was stirred for 1 h at −78 °C. After addition of methanol (0.2 mL) and then saturated aqueous $NaHCO_3$ (2 mL), the mixture was extracted with ethyl acetate (2 × 5 mL), dried over $MgSO_4$, concentrated, and passed through a pad of silica gel to give (4*S*,6*S*)-4-(3,3-dimethoxy)propyl-6-nonyltetrahydro-1,3-oxazin-2-one (78 mg) in 93% yield: ^{1}H NMR (65 °C) δ 0.84 (t, J = 6.6 Hz, 3H), 1.10−1.89 (m, 22H), 3.29 and 3.30 (2s, 6H), 3.43 (m, 1H), 4.27 (m, 1H), 4.32 (t, J = 5.1 Hz, 1H), 6.62 (br s, 1H); ^{13}C NMR (65 °C) δ 13.9, 22.4, 24.8, 28.5, 29.1, 29.2, 29.3, 29.5, 30.8, 31.3, 31.7, 34.5, 47.9, 53.0, 53.4, 74.1, 104.3, 154.7. A mixture of (4*S*,6*S*)-4-(3,3-Dimethoxy)propyl-6-nonyltetrahydro-1,3-oxazin-2-one (78 mg, 0.236 mmol) and KOH (120 mg), H_2O (0.5 mL), and EtOH (2 mL) was heated to reflux for 12 h. After being cooled to room temperature, the mixture was concentrated in vacuo and diluted with THF (4 mL). After addition of Et_3N (0.5 mL) and solid NH_4Cl (100 mg), the mixture was filtered through a pad of Celite. The filtrate was concentrated and diluted with THF (3 mL). The mixture was passed through a pad of Chromatorex NH-gel (DM1020, Fuji Silysia Chemical Ltd.) and concentrated in vacuo to give **13** (68 mg) in 95% yield. The spectroscopic data (^{1}H and ^{13}C NMR) of compound **13** thus obtained were in good agreement with those reported in the literature.[23]

Acknowledgment. We thank the Ministry of Education, Culture, Sports, Science and Technology (Japan) for financial support.

Supporting Information Available: Experimental procedure for the reaction of eq 1, spectral data of cyclic acetals and adducts shown in Table 1, procedure for determination of ee and absolute configuration of **6**, and procedure for preparation of imine **14** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA004140K