Modified Guanidines as Potential Chiral Superbases. 3. Preparation of 1,4,6-Triazabicyclooctene Systems and 1,4-Disubstituted 2-Iminoimidazolidines by the 2-Chloro-1,3-dimethylimidazolinium Chloride-Induced Cyclization of Guanidines with a Hydroxyethyl Substituent

Toshio Isobe,[†,‡] Keiko Fukuda,[‡] Kentaro Yamaguchi,[§] Hiroko Seki,[§] Tatsuhiro Tokunaga,[§] and Tsutomu Ishikawa*[,†]

Faculty of Pharmaceutical Sciences and Chemical Analysis Center, Chiba University, 1-33 Yayoi, Inage, Chiba 263-8522, Japan, and Central Research Laboratory, Shiratori Pharmaceutical Co. Ltd., 6-11-24 Tsudanuma, Narashino, Chiba 275-0016, Japan

benti@p.chiba-u.ac.jp

Received May 15, 2000

Simple preparation methods of modified guanidines have been explored as potential chiral superbases. Thus, 3,7,8-trisubstituted and 3,6,7,8-tetrasubstituted 1,4,6-triazabicyclooctene systems were prepared from (1*S*,2*S*)-1,2-diphenylethylenediamine through stepwise 2-chloro-1,3-dimethylimidazolinium chloride (DMC)-induced cyclizations of protected thioureas to the corresponding 2-iminoimidazolidines and then of 2-(2-hydroxyethylimino)imidazolidines to the bicyclic systems. Linear guanidines with a 2-hydroxyethyl functional group were prepared by the reaction of carbodiimides with 2-amino alcohols. Reaction of linear-type guanidines with DMC followed by base treatment afforded 1,4-disubstitued 2-iminoimidazolidines. Furthermore, another type of 1,4,6-triazabicyclooctene was also prepared through double DMC-induced cyclization of guanidines with two 2-hydroxyethyl substituents.

Introduction

Due to their strongly basic character,[1] guanidines can be considered as superbases[2] and, although chiral guanidines are expected to have potential as asymmetric reagents, their limited use[3] in asymmetric synthesis as chiral auxiliaries is due mainly to the absence of simple preparation methods. In the preceding papers[4] we reported the preparation of modified guanidines containing a 2-iminoimidazolidine ring as potential chiral superbases. In this paper we present the preparation of three kinds of bicyclic guanidines, 3,7,8-trisubstituted **11**, 3,6,7,8-tetrasubstituted **20**, and 3,6,8-trisubstituted 1,4,6-triazabicyclooctene systems **41** and **44** by the 2-chloro-1,3-dimethylimidazolinium chloride (DMC)[5]-induced cyclization of hydroxyethyl-substituted guanidines as the key step. In addition 1,4-disubstituted 2-iminoimidazolidines **30**−**35** have also been prepared by the similar DMC-induced cyclization.

Results and Discussion

Preparation of 3-Substituted (7*S*,8*S*)-7,8-Diphenyl-1,4,6-triazabicyclo[3.3.0]oct-4-enes (3,7,8-Trisubstituted Bicyclic Guanidines) 11. 3-Substituted (7*S*,8*S*)-7,8-diphenyl-1,4,6-triazabicyclo[3.3.0]oct-4-enes (3,7,8-trisubstituted bicyclic guanidines) **11** were prepared from 2-amino alcohols **1** through eight-step sequences as shown in Scheme 1, in which DMC played important roles in both the dehydrosulfination and the chlorination reactions. The results obtained in each step are given in Table 1.

Optically active *tert*-butyldimethylsilyl (TBDMS)-protected hydroxyethyl isothiocyanates **4** were prepared from the corresponding 2-amino alcohols **1** by the DMC-induced dehydrosulfide reaction[5c] of triethylammonium dithiocarbamates **3** after protection of the hydroxy group in **1** through steps 1−3. Treatment of **4** with monoethoxycarbonylated (1*S*,2*S*)-1,2-diphenylethylenediamine[4b] **5** afforded thiourea derivatives **6** (step 4), which were subjected to the DMC-induced cyclization[4b] to give protected 2-iminoimidazolidines **7** smoothly (step 5).

We have shown that DMC can be used for the chlorination of primary alcohols.[5a] Application of this reaction to 2-hydroxyethyl-substituted guanidines **8** was expected to produce cyclized guanidines **10** through spontaneous intramolecular displacement of chlorinated compounds **9**. Treatment of **7** with DMC in boiling acetonitrile

[†] Faculty of Pharmaceutical Sciences, Chiba University.
[‡] Shiratori Pharmaceutical Co. Ltd.
[§] Chemical Analysis Center, Chiba University.

(1) Yamamoto, Y.; Kojima, S. *The Chemistry of Amidines and Imidates*; Patai, S.; Rappoport, Z., Eds.; John Wiley & Sons Inc.: New York, 1991; Vol. 2, pp 485−526.
(2) Costa, M.; Chiusoli, G. P.; Taffurelli, D.; Dalmonego, G. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1541−1546.
(3) (a) For the nitroaldol (Henry) reaction, see Chinchilla, R.; Najera, C.; Sanchez-Agullo, P. *Tetrahedron: Asymmetry* **1994**, *5*, 1393−1402. (b) For the Strecker reaction, see Iyer, M. S.; Gigstad, K. M.; Namdev, N. D.; Lipton, M. *J. Am. Chem. Soc.* **1996**, *118*, 4910−4911. Corey, E. J.; Grogan, M. J. *Org. Lett.* **1999**, *1*, 157−160. (c) For Michael reaction, see Alcazar, V.; Moran, J. R.; deMendoza, J. *Tetrahedron Lett.* **1995**, *36*, 3941−3944. Ma, D.; Cheng, K. *Tetrahedron: Asymmetry* **1999**, *10*, 713−719. Howard-Jones, A.; Murphy, P. J.; Thomas, D. A. Caulkett, P. W. R. *J. Org. Chem.* **1999**, *64*, 1039−1041.
(4) (a) Isobe, T.; Fukuda, K.; Ishikawa, T. *J. Org. Chem.* **2000**, *65*, 7770−7773. (b) Isobe, T.; Fukuda, K.; Tokunaga, T.; Seki, H.; Yamaguchi, K.; Ishikawa, T. *J. Org. Chem.* **2000**, *65*, 7774−7778.
(5) (a) Isobe, T.; Ishikawa, T. *J. Org. Chem.* **1999**, *64*, 5832−5835. (b) Isobe, T.; Ishikawa, T. *J. Org. Chem.* **1999**, *64*, 6984−6988. (c) Isobe, T.; Ishikawa, T. *J. Org. Chem.* **1999**, *64*, 6989−6992.

10.1021/jo000746f CCC: $19.00
Published on Web 10/21/2000

Scheme 1

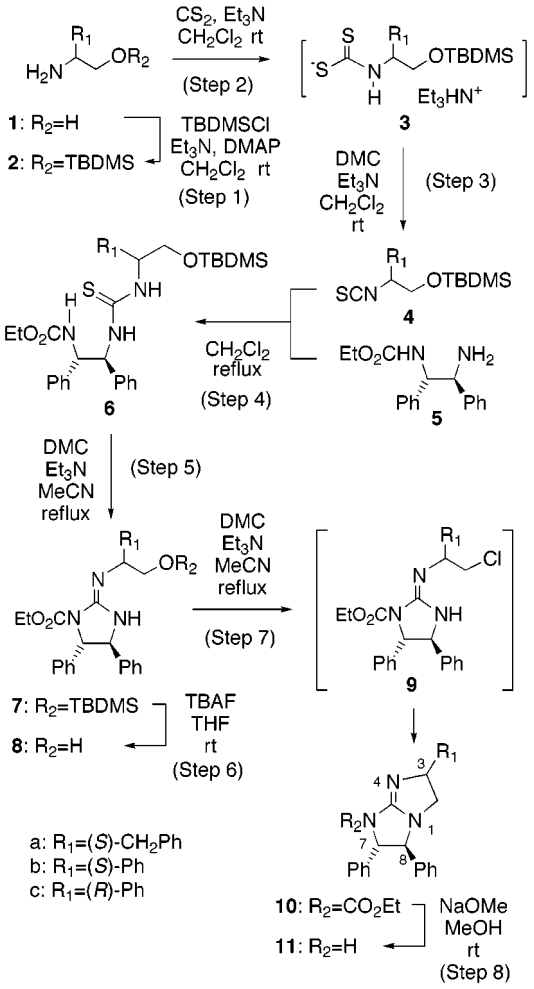


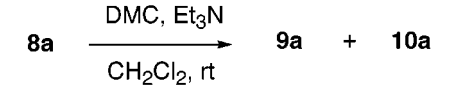
Table 1. Result of Each Step in Scheme 1 for the Preparation of 3,7,8-Trisubstituted Bicyclic Guanidines 11

Steps	Time (h) / Yields[a] (%)		
	R_1= (*S*)-CH_2Ph	(*S*)-Ph	(*R*)-Ph
1	21 / 100	41 / 100	24 / 94
2[b]	2 / -	1 / -	1 / -
3	48 / 96	1 / 82	1.2 / 85
4	20 / 98	23 / 83	25 / 100
5	13 / 88	12 / 67	24 / 74
6	1.5 / 96	5 / 86	3 / 100
7	see Table 2	3 / 58[c]	17 / 40[d]
8	3 / 89	2 / 88	20 / 100

[a]Isolated, non-optimized yields. [b]The product was used for a next step without purification. [c]A deprotected product **11** was also given in 30% yield. [d]No trials for isolation of other products.

(MeCN) in the presence of triethylamine (Et_3N) after selective deprotection of the TBDMS group afforded the desired bicyclic systems **10** in moderate yields (steps 6 and 7). Removal of the ethoxycarbonyl group with sodium methoxide (MeONa) gave 3-substituted 7,8-diphenyl-1,4,6-triazabicyclooctenes as 3,7,8-trisubstituted bicyclic guanidines **11** (step 8).

Table 2. Reaction of 8a with DMC in CH_2Cl_2 at rt in Step 7 in Scheme 1



Runs	Et_3N (M eq)	Time (h)	Yields[a] (%)	
			9a	**10a**
1	1.5	1	47	38
2	1.5	7.5	35	48
3	3.5	30	6	57

[a]Isolated, non-optimized yields.

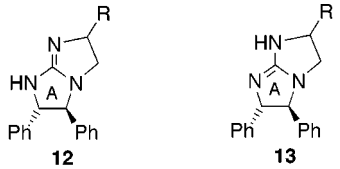


Figure 1. Possible imino- **12** and amino-type isomers **13** of 3,7,8-trisubstituted bicyclic guanidines based on a diphenyl-substituted ring (A).

Simple chlorination[5a] of the hydroxyl group in **8** in the step 7 was also observed in addition to desired cyclization when the reaction was carried out at room temperature. The results, when **8a** derived from (*S*)-phenylalaninol (**1a**) was used as a substrate, are shown in Table 2. The product ratio of a chlorinated product **9a** and bicyclic guanidine **10a** was dependent upon both the amount of Et_3N used and reaction time. Thus, the reaction using a limited amount of Et_3N (1.5 mol equiv) at room temperature for 1 h produced **9a** in slightly higher yield (run 1 in Table 2). Alternatively, **10a** resulted mainly given on treatment with excess of Et_3N for longer periods (30 h) (run 3 in Table 2).

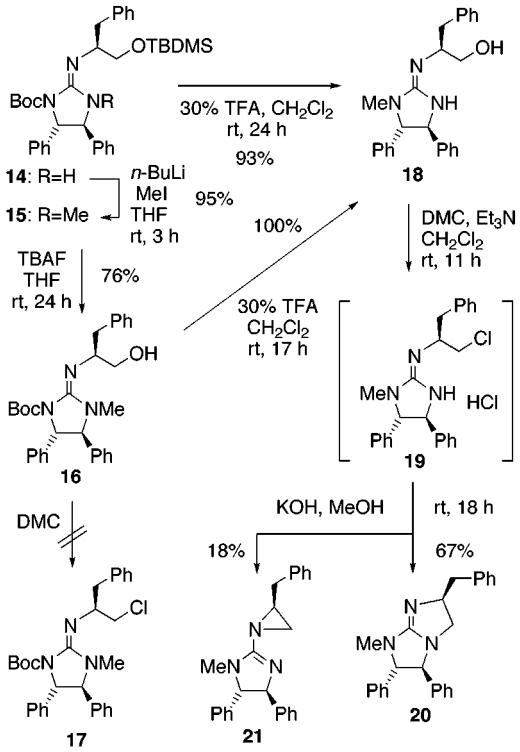
In bicyclic systems **11** two isomers[6] of an imino-type **12** and an amino-type **13** based on a diphenyl-substituted ring (A) are theoretically possible as discussed in the Part 2[4b] of this series (Figure 1). X-ray crystallographic analysis of the (3*R*)-phenyl derivative **11c** (See Supporting Information) suggested that these systems preferred an imino isomer such as **12** in a solid state.

Preparation of (3*S*,7*S*,8*S*)-3-Benzyl-7,8-diphenyl-6-methyl-1,4,6-triazabicyclo[3.3.0]oct-4-ene (3,6,7,8-Tetrasubstituted Bicyclic Guanidine) (20). (3*S*,7*S*,8*S*)-3-Benzyl-7,8-diphenyl-6-methyl-1,4,6-triazabicyclo [3.3.0]-oct-4-ene (**20**) was prepared as a representative of 3,6,7,8-tetrasubstituted bicyclic guanidines by *N*-methylation before construction of bicyclic systems (Scheme 2). Treatment of the *tert*-butoxycarbonyl (Boc)-protected 2-imino-imidazolidine **14**[7] with methyl iodide in the presence of

(6) Tanatani, A.; Yamaguchi, K.; Azumaya, I.; Fukutomi, R.; Shudo, K.; Kagechika, H. *J. Am. Chem. Soc.* **1998**, *120*, 6433−6442.

(7) **14** was prepared from (1*S*,2*S*)-1,2-diphenylethylenediamine by three sequential reactions of thioamidation with an isothiocyanate **4a**, protection with Boc group, and the DMC-induced cyclization according to a similar procedure shown in Scheme 1 (see Supporting Information).

Scheme 2



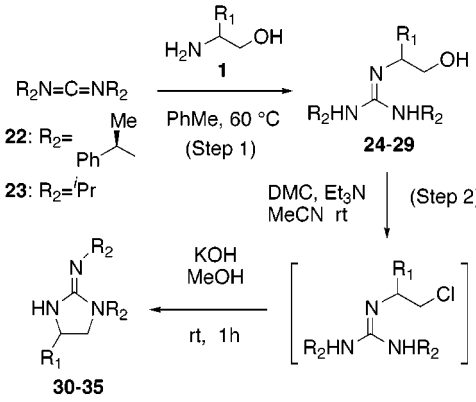
base gave an *N*-methylated product **15**. Introduction of a methyl group on the ring nitrogen was deduced by inspection of its NMR spectra including HMBC experiments (see Supporting Information). Furthermore, this deduction was supported by chemical evidence that an aziridine **21** was formed as an alternative product in the DMC-induced cyclization of a guanidine **18** derived from **15** (vide infra).

Displacement[5a] of the oxygen function in **15** by a chlorine atom using DMC was investigated on *O*-deprotected product **16**, but complete recovery of **16** was observed. The presence of Boc and methyl groups on the ring nitrogens of **16** could be acting to block the approach of the reagent because smooth displacement was observed in the case of ethoxycarbonylated **8** (see Scheme 1). Thus, both protecting groups on **15** were removed before cyclization. Stepwise deprotection of *N*- and *O*-functions in **15** with tetra-*n*-butylammonium fluoride (TBAF) followed by 30% trifluoroacetic acid (TFA) in dichloromethane (CH_2Cl_2) or simultaneous deprotection with TFA afforded **18**.

Treatment of **18** with DMC led to only conversion into the corresponding chlorine-substituted product **19**, despite smooth cyclization to bicyclic systems **10** from the protected guanidines **8** as mentioned above (see Scheme 1), indicating undesired formation of hydrochloride salt of a guanidyl function. Thus, base treatment after chlorination of **18** with DMC without isolation of an intermediate **19** afforded expectedly 3,6,7,8-tetrasubstituted bicyclic guanidine **20** in 67% yield (Scheme 2).

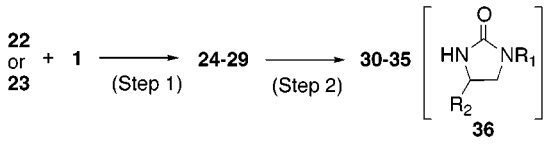
Alternative cyclization of **19** involving participation of the external nitrogen leading an aziridine **21** was observed as a reaction path (18%). However, aziridine cyclization did not occur when protected guanidines **8** were used as substrates in the DMC-induced cyclization. These facts suggest that cyclization paths could be controlled by the electronic character of substituents on guanidyl nitrogen atoms.

Scheme 3



R_1=(*S*)-PhCH$_2$, (*R*)-PhCH$_2$, (*S*)-^{i}Pr, or (*R*)-Ph

Table 3. Preparation of 1,4-Disubstituted 2-Iminoimidazolidines 30−35 through Linear-Type Guanidines 24−29



Runs	R_1	R_2	Step 1			Step 2		
				Time (h)	Yield[a] (%)		Time[b] (h)	Yield[c] (%)
1	(*S*)-PhCH$_2$		**24**	9	89	**30**	3	82
2	(*R*)-PhCH$_2$		**25**	15	88	**31**	18	80
3	(*S*)-^{i}Pr		**26**	11	22	**32**	8	93
4	(*R*)-Ph		**27**	16	90	**33**	4	94
5	(*S*)-PhCH$_2$	^{i}Pr	**28**	17	41	**34**	5	98
6	(*R*)-Ph	^{i}Pr	**29**	25	30	**35**	5	87

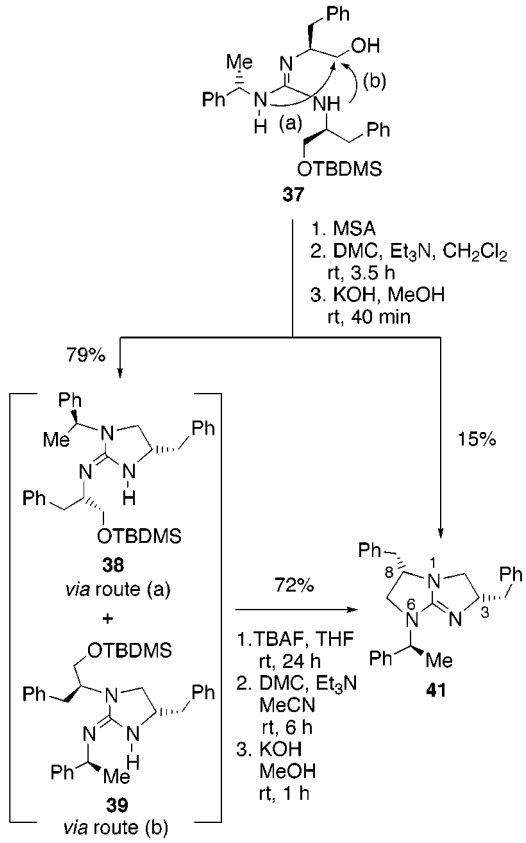
[a] Isolated, non-optimized yields. In some cases over-reaction to cyclization was observed. Thus, 1,4-disubstituted imidazolidinones **36** were given in 11, 12, 63, and 19% yields, respectively, in runs 1, 2, 3, and 6. On the other hand in the case of run 5 a 2-iminoimidazolidine **34** was produced in 10% yield in addition to the corresponding hydrolyzed product (11%).[b] For the chlorination. [c] Isolated, non-optimized yields after rwo steps of chlorination and hydrolysis.

Preparation of Linear-type Guanidines 24−29 with a 2-Hydroxyethyl Group and 1,4-Disubstituted 2-Iminoimidazolidines 30−35. Linear-type guanidines **24−29** with a 2-hydroxyethyl function and the corresponding cyclized guanidines **30−35** were prepared as shown in Scheme 3 and Table 3. The linear-type guanidines **24−29**, which could be also used as chiral superbases, were synthesized by reaction of carbodiimides with 2-amino alcohols **1**. We used di[(*S*)-1-phenylethyl]carbodiimide[8] (**22**) and commercially available diisopropylcarbodiimide (**23**) as carbodiimide substrates.

Heating carbodiimides **22** or **23** and amino alcohols **1** in toluene at 60 °C gave **24−29** in moderate to good yields (step 1 in Table 3). In some cases 1,4-disubstituted imidazolidinones **36**, the hydrolyzed products of the

(8) Chinchilla, R.; Najera, C.; Sanchez-Agullo, P. *Tetrahedron: Asymmetry* **1994**, *7*, 1393−1402.

Scheme 4



2-iminoimdazolidines, were obtained as coproducts in runs 1 (11%), 2 (12%), 3 (63%), and 6 (19%). On the other hand the cyclized guanidine **34** (10%) was also formed, together with the urea derivative (11%) in the case of run 5. Stirring a solution of **24**−**29** in MeCN with DMC at room temperature in the presence of Et_3N followed by base treatment afforded 1,4-disubstituted 2-iminoimidazolidines **30**−**35** in good to excellent yields[9] (step 2 in Table 3).

Preparation of 6-Substituted (3*S*,8*S*)-3,8-Dibenzyl-1,4,6-triazabicyclo[3.3.0]oct-4-enes (3,6,8-Trisubstituted Bicyclic Guanidines) 41 and 44. 6-Substituted (3*S*,8*S*)-3,8-dibenzyl-1,4,6-triazabicyclo[3.3.0]oct-4-enes **41** and **44** were prepared as an alternative type of bicyclic guanidine from hydroxyethyl-substituted guanidines by a similar DMC-induced cyclization. 6-[(*S*)-1-Phenylethyl] derivative **41** was derived from linear guanidine **37**[10] (Scheme 4). Production of highly polar substances, one possible compound of which appeared to correspond to biguanidinium salt **40** (Figure 2), was observed when **37** was treated with DMC in a preliminary experiment. Therefore, we preprotected the strongly basic guanidyl nitrogen using methanesulfonic acid (MSA) resulting in salt formation. Subsequent treatments with DMC and potassium hydroxide afforded an inseparable 1:1 mixture of isomeric guanidines **38** and

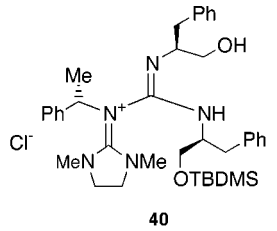
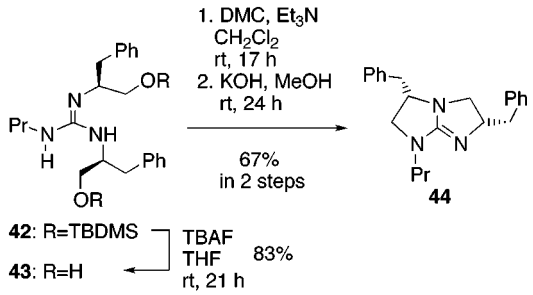


Figure 2. One of three possible biguanidium chlorides formed by the reaction of a linear-type guanidine **37** and DMC.

Scheme 5



39 in 79% combined yield along with bicyclic guanidine **41** (15% yield). After *O*-deprotection, the mixture was subjected to the second DMC-induced cyclization followed by base treatment to afford **41** in 72% yield.

Alternatively, the same type of the bicyclic guanidine **44** was directly prepared from a protected guanidine **42**[11] in good overall yield by the DMC-induced cyclization of a linear-type guanidine **43** with two free 2-hydroxyethyl functions (Scheme 5).

Conclusions

It was found that guanidines with a 2-hydroxyethyl function can be easily converted into cyclized guanidines by treatment with DMC. Although limited synthesis of these specialized guanidines were described in the present paper, preparation methods based upon the DMC-induced cyclization should be widely applicable to the preparation of similar types of guanidines with different substituents by use of appropriate 2-amino alcohols. In addition, successful preparation of cyclic guanidines induced by DMC resulted in uncovering further utility of DMC[5] as a reagent in organic synthesis.

Modified guanidines may be promising basic catalysts for green chemistry[12] because of their recycling potential, easy handling, and expected safety.[13] We have examined their possibility as chiral auxiliaries in asymmetric synthesis and reported their application to alkylative esterification[14] of benzoic acid with racemic phenylethyl

(9) In these reaction schemes (5*S*)-3-[(*S*)-1-phenylethyl]-2-[(*S*)-1-phenylethylimino]-1,3-diazabicyclo[3.3.0]octane, which had been prepared in the Part 1[4a] in this series, was obtained from di[(*S*)-1-phenylethyl]carbodiimide in 61% overall yield when (*S*)-prolinol was used as the 2-amino alcohol unit (see Supporting Information).

(10) This guanidine was prepared by the reaction of an unsymmetrical carbodiimide derived from a protected amino alcohol **2a** and (*S*)-phenylethylisothiocyanate with (*S*)-phenylalaninol (**1a**) (see Supporting Information).

(11) This guanidine was prepared by reaction of a symmetrical carbodiimide derived from (*S*)-phenylalaninol (**1a**) with propylamine (see Supporting Information).

(12) Anastas, P. T.; Warner, J. C. *Green Chemistry*: *Theory and Practice*; Oxford University Press: Oxford, 1998.

(13) Although there are no data on the toxicity of modified guanidines prepared here, the presence of guanidyl functions including an 2-iminoimidazolidine ring in a range of pharmaceutical products such as clonidine, a cardiovascular drug, allows us to deduce that they are likely to be nontoxic (see Greenhill, J. V.; Lue, P. *Progress in Medicinal Chemistry*;Ellis, G. P.; Luscombe, D. K., Eds; Elsevier Science Publishers: New York, 1993; Vol. 30, Chapter 5).

(14) Isobe, T.; Fukuda, K.; Ishikawa, T. *Tetrahedron Asymmetry*, **1998**, *9*, 1729−1735.

bromide. Their utilities as chiral superbases for asymmetric synthesis[15] will be reported elswhere.

Experimental Section

General. Melting points are uncorrected. ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$ with TMS as an internal reference unless otherwise stated. UV spectra were measured in MeOH. Organic extract was dried over $MgSO_4$ or Na_2SO_4 and evaporated under reduced pressure. Columns for chromatography contained silica gel 60 (SiO_2) (70−230 mesh ASTM; Merck) or NH-type silica gel (NH−SiO_2) (Chromatorex NH-DM1020; Fuji Silysia Chemical Ltd.), and TLC proceeded on silica gel GF_{254} (Merck).

A Typical Procedure for Protection of 2-Amino Alcohols 1 (step 1 in Table 1): (*S*)-1-Benzyl-2-(*tert*-butyldimethylsilyloxy)ethylamine (2a). A solution of TBDMSCl (16.0 g, 106 mmol) in CH_2Cl_2 (96 mL) was dropped to a stirred solution of (*S*)-phenylalaninol (**1a**) (16.1 g, 106 mmol), Et_3N (21.5 g, 213 mmol), and 4-(dimethylamino)pyridine (2.60 g, 21.3 mmol) in CH_2Cl_2 (160 mL). The whole was stirred at room temperature for 21 h, poured into water, and extracted with CH_2Cl_2. The residue obtained from the organic extract was purified by column chromatography (SiO_2, $CHCl_3$ to $CHCl_3$−MeOH = 50:1) gave **2a** (28.2 g, quant) as colorless oil; UV λ_{max} 208.0 (ϵ 8100) nm; $[\alpha]^{23}_D$ −3.6 (*c* 1.00, $CHCl_3$); ^{1}H NMR δ 0.06 (s, 6H), 0.91 (s, 9H), 1.40 (br s, 2H), 2.50 (dd, *J* = 13.4, 8.2 Hz, 1H), 2.79 (dd, *J* = 13.4, 5.3 Hz, 1H), 3.05−3.13 (m, 1H), 3.44 (dd, *J* = 9.7, 6.6 Hz, 1H), 3.58 (dd, *J* = 9.7, 4.4 Hz, 1H), 7.19−7.32 (m, 5H); ^{13}C NMR δ −5.5, 18.2, 25.8, 40.4, 54.3, 67.4, 126.1, 128.3, 129.2, 139.1; HRFABMS *m*/*z*:266.1935 (M + H$^+$, $C_{15}H_{28}NOSi$ requires *m*/*z* 266.1940).

A Typical Procedure for Preparation of Isothiocyanates 4[4b] (steps 2 and 3 in Table 1): (*S*)-1-Benzyl-2-(*tert*-butyldimethylsilyloxy)ethylisothiocyanate (4a). A solution of **2a** (8.01 g, 30.2 mmol), Et_3N (7.33 g, 72.6 mmol), and CS_2 (2.30 g, 30.2 mmol) in CH_2Cl_2 (100 mL) was stirred at room temperature for 2 h, and to the resulting solution was dropped a solution of DMC (6.13 g, 36.3 mmol) in CH_2Cl_2 (30 mL). The whole was stirred at room temperature for 48 h and evaporated. Purification of the residue by column chromatography (SiO_2, hexanes−EtOAc = 20:1) gave **4a** (8.91 g, 96%) as colorless oil; IR (neat) ν_{max} 2100, 1125, 830 cm^{-1}; UV λ_{max} 247.2 (ϵ 1300), 204.0 (12100) nm; $[\alpha]^{22}_D$ −77.0 (*c* 1.00, $CHCl_3$); ^{1}H NMR δ 0.10 (s, 3H), 0.11 (s, 3H), 0.95 (s, 9H), 2.89 (dd, *J* = 13.6, 7.9 Hz, 1H), 3.01 (dd, *J* = 13.6, 5.7 Hz, 1H), 3.65 (dd, *J* = 10.1, 5.3 Hz, 1H), 3.70 (dd, *J* = 10.1, 4.8 Hz, 1H), 3.81−3.89 (m, 1H), 7.21−7.37 (m, 5H); ^{13}C NMR δ −5.4, 18.2, 25.8, 38.2, 61.1, 64.3, 127.1, 128.6, 129.3, 133.1, 136.5; HRFABMS *m*/*z* 308.1489 (M + H$^+$, $C_{16}H_{26}NOSSi$ requires *m*/*z* 308.1504).

A Typical Procedure for Preparation of Thioureas 6[4b] (step 4 in Table 1): *N*-[(*S*)-1-Benzyl-2-(*tert*-butyldimethylsilyloxy)ethyl]-*N*′-[(*1S*,*2S*)-1,2-diphenyl-2-(ethoxycarbonylamino)ethyl]thiourea (6a). A mixture of **4a** (9.11 g, 29.7 mmol) and 1,2-diphenyl-*N*-ethoxycarbonylethylenediamine (**5**) (8.43 g, 29.7 mmol) in CH_2Cl_2 (178 mL) was refluxed for 20 h and evaporated. Purification of the residue by column chromatography (SiO_2, $CHCl_3$) gave **6a** (17.2 g, 98%) as amorphous mass; IR (neat) ν_{max} 1685, 1525, 1255, 1115, 1045 cm^{-1}; UV λ_{max} 207.2 (ϵ 33900) nm; $[\alpha]^{20}_D$ −26.9 (*c* 1.00, $CHCl_3$); ^{1}H NMR δ 0.03 (s, 6H), 0.91 (s, 9H), 1.22 (t, *J* = 7.1 Hz, 3H), 2.66 (br s, 1H), 2.87 (br s, 1H), 3.48−3.58 (m, 2H), 4.10 (q, *J* = 7.1 Hz, 2H), 4.50 (br s, 1H), 4.95 (t, *J* = 8.8 Hz, 1H), 5.54 (br s, 1H), 5.81 (br s, 1H), 6.13 (br s, 1H), 7.03−7.26 (m, 15H); ^{13}C NMR δ −5.6, 14.4, 18.2, 25.8, 36.4, 61.0, 61.4, 62.1, 63.1, 126.3, 127.4, 127.5, 127.8, 128.3, 128.4, 129.3, 137.8, 138.4, 157.2, 181.5. Anal. Calcd for $C_{33}H_{45}N_3O_3SSi$: C, 66.97; H, 7.66; N, 7.10. Found: C, 66.97; H, 7.69; N, 7.02.

A Typical Procedure for Preparation of *N*,*O*-Diprotected 2-Iminoimidazolidines 7[4b] (step 5 in Table 1): (4*S*,5*S*)-2-[(*S*)-1-Benzyl-2-(*tert*-butyldimethylsilyloxy)ethylimino]-4,5-diphenyl-1-ethoxycarbonylimidazolidine (7a). A mixture of **6a** (4.53 g, 7.67 mmol), Et_3N (2.32 g, 23.0 mmol), and DMC (1.56 g, 9.20 mmol) in MeCN (100 mL) was refluxed for 13 h, poured into water, and extracted with CH_2Cl_2. The residue obtained from the organic extract was purified by column chromatography (SiO_2, hexanes−EtOAc = 5:1) gave **7a** (3.76 g, 88%) as a colorless oil; IR (neat) ν_{max} 3380, 1710, 1640, 1130 cm^{-1}; UV λ_{max} 207.2 (ϵ 35400) nm; $[\alpha]^{22}_D$ −37.5 (*c* 1.00, $CHCl_3$); ^{1}H NMR δ 0.09 (s, 3H), 0.10 (s, 3H), 0.93 (t, *J* = 7.1 Hz, 3H), 0.96 (s, 9H), 3.00 (dd, *J* = 13.4, 7.1 Hz, 1H), 3.07 (dd, *J* = 13.4, 8.6 Hz, 1H), 3.67 (dd, *J* = 9.9, 3.1 Hz, 1H), 3.81 (dd, *J* = 9.9, 4.4 Hz, 1H), 3.94 (q, *J* = 7.1 Hz, 2H), 4.31 (br s, 1H), 4.75 (s, 2H), 7.11 (d, *J* = 6.4 Hz, 2H), 7.21−7.35 (m, 13H); ^{13}C NMR δ −5.5, −5.4, 13.8, 18.3, 25.9, 37.4, 54.9, 61.8, 62.9, 70.0, 73.9, 125.7, 126.07, 126.10, 127.2, 127.5, 128.2, 128.5, 128.7, 129.6, 138.6, 142.7, 144.7, 153.1; HRFABMS *m*/*z* 558.3156 (M + H$^+$, $C_{33}H_{44}N_3O_3Si$ requires *m*/*z* 558.3152).

A Typical Procedure for Preparation of *O*-Deprotected 2-Iminoimidazolidines 8 (step 6 in Table 1): (4*S*,5*S*)-2-[(*S*)-1-Benzyl-2-hydroxyethylimino]-4,5-diphenyl-1-ethoxycarbonylimidazolidine (8a). A 1 M solution of TBAF in THF (8.78 mL, 8.78 mmol) was dropped to a solution of **7a** (3.76 g, 6.75 mmol) in THF (17 mL), and the whole was stirred at room temperature for 1.5 h. The reaction mixture was poured into 5% NaOH aqueous solution and extracted with CH_2Cl_2. The residue obtained from the organic extract was purified by column chromatography (SiO_2, hexane−EtOAc = 1:1) gave **8a** (2.87 g, 96%) as a colorless viscous oil; IR (neat) ν_{max} 3350, 1710, 1635 cm^{-1}; UV λ_{max} 207.2 (ϵ 28100) nm; $[\alpha]^{21}_D$ −22.9 (*c* 1.00, $CHCl_3$); ^{1}H NMR δ 0.89 (t, *J* = 7.1 Hz, 3H), 2.94 (dd, *J* = 13.7, 8.3 Hz, 1H), 3.08 (dd, *J* = 13.7, 6.0 Hz, 1H), 3.75 (dd, *J* = 11.3, 5.7 Hz, 1H), 3.81 (dd, *J* = 11.3, 3.1 Hz, 1H), 3.86−3.96 (m, 2H), 4.10−4.16 (m, 1H), 4.77 (s, 2H), 7.10−7.35 (m, 15H); ^{13}C NMR δ 13.7, 37.6, 57.1, 62.1, 65.8, 70.2, 73.2, 125.8, 125.9, 126.5, 127.4, 127.7, 128.5, 128.7, 128.8, 129.4, 138.1, 142.2, 143.9, 153.1, 154.3; HRFABMS *m*/*z* 444.2293 (M + H$^+$, $C_{27}H_{30}N_3O_3$ requires *m*/*z* 444.2287).

A Typical Procedure for the DMC−Induced Cyclization of Protected Hydroxyethylguanidines 8 (step 7 in Table 1): On the (*S*)-Benzyl Derivative 8a (run 2 in Table 2). To a stirred mixture of **8a** (2.87 g, 6.48 mmol) and DMC (1.64 g, 9.72 mmol) in CH_2Cl_2 (30 mL) was added Et_3N (0.98 g, 9.72 mmol) at room temperature, and then the whole was stirred at room temperature for 7.5 h, poured into water, and extracted with CH_2Cl_2. The residue obtained from the organic extract was purified by column chromatography (SiO_2, hexanes−EtOAc = 1:3 to $CHCl_3$−MeOH = 20:1) gave two products. **(i) (4*S*,5*S*)-2-[(*S*)-1-Benzyl-2-chloroethylimino]-4,5-diphenyl-1-ethoxycarbonylimidazolidine (9a).** Obtained as a less polar colorless oil (1.06 g, 35%); IR (neat) ν_{max} 3360, 1710, 1645 cm^{-1}; UV λ_{max} 206.4 (ϵ 24100) nm; $[\alpha]^{21}_D$ −11.9 (*c* 1.00, $CHCl_3$); ^{1}H NMR δ 0.94 (t, *J* = 6.4 Hz, 3H), 3.07 (dd, *J* = 13.6, 7.7 Hz, 1H), 3.13 (dd, *J* = 13.6, 6.8 Hz, 1H), 3.63 (dd, *J* = 11.2, 3.2 Hz, 1H), 3.95−4.00 (m, 3H), 4.49−4.63 (m, 1H), 4.76 (d, *J* = 4.2 Hz, 1H), 4.78 (d, *J* = 4.2 Hz, 1H), 7.11−7.37 (m, 15H); ^{13}C NMR δ 13.8, 37.9, 46.5, 53.9, 62.2, 70.1, 74.0, 125.8, 126.1, 126.7, 127.4, 127.7, 128.6, 128.7, 128.8, 129.5, 137.3, 142.4, 144.1, 152.7; HRFABMS *m*/*z* 462.1964 (M + H$^+$, $C_{27}H_{29}ClN_3O_2$ requires *m*/*z* 462.1948), 464.1931 (M + 2 + H$^+$, $C_{27}H_{29}ClN_3O_2$ requires *m*/*z* 464.1932). **(ii) (3*S*,7*S*,8*S*)-3-Benzyl-7,8-diphenyl-6-ethoxycarbonyl-1,4,6-triazabicyclo[3.3.0]oct-4-ene (10a).** Obtained as a more polar colorless oil (1.32 g, 48%); IR (neat) ν_{max} 1745, 1715, 1660 cm^{-1}; UV λ_{max} 207.2 (ϵ 25200) nm; $[\alpha]^{22}_D$ +45.1 (*c* 1.00, $CHCl_3$); ^{1}H NMR δ 1.11 (t, *J* = 7.0 Hz, 3H), 2.87−3.01 (m, 3H), 3.19 (dd, *J* = 13.5, 4.4 Hz, 1H), 4.01 (d, *J* = 5.7 Hz, 1H), 4.09−4.25 (m, 2H), 4.71−4.76 (m, 1H), 5.04 (d, *J* = 5.7 Hz, 1H), 6.94−6.97 (m, 2H), 7.19−7.36 (m, 13H); ^{13}C NMR δ 13.9, 41.3, 50.3, 62.4, 67.6, 71.8, 73.5, 125.98, 126.01, 126.5, 127.99, 128.02, 128.3, 128.5, 128.7, 129.3, 137.1, 138.4, 139.2, 151.0, 160.8; HRFABMS *m*/*z* 426.2156 (M + H$^+$, $C_{27}H_{28}N_3O_2$ requires *m*/*z* 426.2182).

A Typical Procedure for Preparation of 3,7,8-Trisubstituted Bicyclic Guanidines 11 (step 8 in Table 1): (3*S*,7*S*,8*S*)-3-Benzyl-7,8-diphenyl-1,4,6-triazabicyclo[3.3.0]-

(15) During our research works, an effective asymmetric Strecker reaction catalyzed by C_2-symmetrical bicyclic guanidines was reported by Corey et al.[3b]

oct-4-ene (11a). A mixture of **10a** (1.59 g, 3.74 mmol) and 28% MeONa in MeOH (5.70 g, 29.5 mmol) in MeOH (35 mL) was stirred at room temperature, poured into water, and extracted with CH_2Cl_2. The residue obtained from the organic extract was purified by column chromatography ($NH-SiO_2$, $CHCl_3$) followed by recrystallization from MeCN gave **11a** (1.18 g, 89%) as colorless prisms, mp 156−157 °C; IR (neat) ν_{max} 1670 cm^{-1}; UV λ_{max} 206.4 (ϵ 40200) nm; $[\alpha]^{23}_D$ +10.4 (*c* 1.00, $CHCl_3$); ^1H NMR δ 2.82−2.93 (m, 2H), 2.95 (d, *J* = 8.1 Hz, 1H), 3.04 (dd, *J* = 8.2, 2.2 Hz, 1H), 3.94 (d, *J* = 9.0 Hz, 2H), 4.22−4.29 (m, 1H), 4.85 (d, *J* = 9.0 Hz, 1H), 5.16 (br s, 1H), 7.11−7.33 (m, 15H); ^{13}C NMR δ 42.0, 50.4, 64.0, 79.3, 126.3, 127.0, 127.1, 127.4, 127.7, 128.2, 128.4, 128.5, 129.3, 138.4, 139.0, 141.6, 168.1; FABMS *m/z* 354 (M + H^+). Anal. Calcd for $C_{24}H_{23}N_3$: C, 81.55; H, 6.56; N, 11.89. Found: C, 81.27; H, 6.50; N,11.83.

(4*S*,5*S*)-2-[(*S*)-1-Benzyl-2-(*tert*-butyldimethylsilyloxy)-ethylimino]-1-*tert*-butoxycarbonyl-4,5-diphenyl-3-methylimidazolidine (15). A 1.66 M solution of *n*-BuLi in THF (4.54 mL, 7.53 mmol) was dropped to a solution of **14** (3.67 g, 6.27 mmol) in THF (30 mL). After 10 min, methyl iodide (1.07 g, 7.53 mmol) was added, and the whole was stirred at room temperature for 3 h. The reaction mixture was quenched with water and extracted with CH_2Cl_2. The residue obtained from the organic extract was purified by column chromatography (SiO_2, hexanes−EtOAc = 1:1) followed by recrystallization from hexane gave **15** (3.58 g, 95%) as colorless prisms, mp 91−92 °C; IR (neat) ν_{max} 1740, 1725, 1670, 1150 cm^{-1}; UV λ_{max} 208.8 (ϵ 37000) nm; $[\alpha]^{22}_D$ −33.7 (*c* 1.00, $CHCl_3$); ^1H NMR δ -0.04 (s, 3H), 0.02 (s, 3H), 0.85 (s, 9H), 1.31 (s, 9H), 2.70 (s, 3H), 2.82 (dd, *J* = 12.8, 9.3 Hz, 1H), 3.27 (dd, *J* = 12.8, 3.3 Hz, 1H), 3.45−3.55 (m, 2H), 3.83−3.93 (m, 1H), 3.96 (d, *J* = 4.6 Hz, 1H), 4.72 (d, *J* = 4.6 Hz, 1H), 7.13−7.42 (m, 15H); ^{13}C NMR δ −5.1, 18.7, 26.1, 28.0, 32.5, 39.4, 62.1, 67.1, 68.3, 70.4, 81.6, 125.4, 126.0, 126.6, 127.6, 127.7, 128.2, 128.6, 129.0, 130.2, 140.3, 140.6, 141.8, 146.8, 152.9; HRFABMS *m/z* 600.3616 (M + H^+, $C_{36}H_{50}N_3O_3Si$ requires *m/z* 600.3621).

(4*S*,5*S*)-2-[(*S*)-1-Benzyl-2-hydroxyethylimino]-1-*tert*-butoxycarbonyl-4,5-diphenyl-3-methylimidazolidine (16). According to the procedure for *O*-deprotection mentioned above (step 6 in Table 1), a solution of **15** (7.89 g, 13.2 mmol) in THF (34 mL) was treated with a 1 M solution of TBAF in THF (17.1 mL, 17.1 mmol) at room temperature for 24 h. After workup purification of the crude prodcut by column chromatography (SiO_2, $CHCl_3$) gave **16** (4.85 g, 76%) as a colorless viscous oil; IR (neat) ν_{max} 3310, 1700, 1630, 1160 cm^{-1}; UV λ_{max} 207.2 (ϵ 26700) nm; $[\alpha]^{25}_D$ +144.6 (*c* 1.00, $CHCl_3$); ^1H NMR δ 1.45 (s, 9H), 2.70 (s, 3H), 2.71 (dd, *J* = 13.6, 8.1 Hz, 1H), 3.13 (dd, *J* = 13.6, 5.3 Hz, 1H), 4.08 (dd, *J* = 7.3, 5.9 Hz, 1H), 4.27−4.41 (m, 2H), 5.44 (d, *J* = 11.0 Hz, 1H), 5.61 (d, *J* = 11.0 Hz, 1H), 7.08−7.34 (m, 15H); ^{13}C NMR δ 28.5, 30.1, 43.2, 54.9, 64.1, 65.7, 73.1, 79.4, 126.3, 127.2, 127.7, 128.2, 128.4, 128.5, 129.1, 129.4, 135.7, 138.8, 140.4, 155.4, 163.5.

Preparation of (4*S*,5*S*)-2-[(*S*)-1-Benzyl-2-hydroxyethylimino]-4,5-diphenyl-1-methylimidazolidine (18): (a) From the Monoprotected Imidazolidine 16. A mixture of **16** (1.23 g, 2.54 mmol), TFA (6.0 g), and CH_2Cl_2 (14.0 g) was stirred at room temperature for 17 h, poured into 5% NaOH aqueous solution, and extracted with CH_2Cl_2. The residue obtained from the organic extract was purified by column chromatography (SiO_2, $CHCl_3$−MeOH = 50:1) gave **18** (0.98 g, quant) as colorless needles, mp 181−182 °C; IR (neat) ν_{max} 3270, 1605, 1100 cm^{-1}; UV λ_{max} 207.2 (ϵ 32900) nm; $[\alpha]^{24}_D$ −23.3 (*c* 1.00, $CHCl_3$); ^1H NMR δ 2.39 (s, 3H), 2.81 (dd, *J* = 13.2, 9.0 Hz, 1H), 2.90 (dd, *J* = 13.2, 4.2 Hz, 1H), 3.61−3.78 (m, 3H), 3.90 (d, *J* = 9.2 Hz, 1H), 4.26 (br s, 1H), 7.03−7.30 (m, 15H); ^{13}C NMR δ 31.5, 38.5, 53.6, 67.2, 71.1, 126.6, 126.6, 127.3, 127.4, 128.0, 128.3, 128.6, 128.7, 129.3, 139.0, 139.2, 141.9, 160.3. Anal. Calcd for $C_{25}H_{27}N_3O_3$: C, 77.89; H, 7.06; N, 10.90. Found: C, 78.10; H, 7.17; N, 10.62.

(b) From the Diprotected Imidazolidine 15. A mixture of **15** (2.00 g, 3.34 mmol), TFA (19.7 g), and CH_2Cl_2 (46.0 g) was similarly treated at room temperature for 24 h and workup gave **18** (1.19 g, 93%).

The DMC−Induced Cyclization of the Hydroxyethylguanidine 18. An unprotected hydroxyethylguanidine was converted into the hydrochloride salt by treatment of its benzene solution with an equimolar amount of 4 N HCl solution in EtOAc followed by evaporation and washing the residue with isopropyl ether. To a stirred mixture of the hydrochloride (0.99 g, 2.35 mmol) and DMC(0.80 g, 4.7 mmol) in CH_2Cl_2 (10 mL) was added Et_3N (0.95 g, 9.4 mmol) at room temperature, and then the whole was stirred at room temperature for 1 h. After evaporation the residue was dissolved in MeOH (30 mL), and then KOH (2.24 g, 0.4 mol) was added. The whole was stirred at room temperature for 18 h, poured into water, and extracted with CH_2Cl_2. The residue obtained from the organic extract was purified by column chromatography ($NH-SiO_2$, CH_2Cl_2) to give two products. **(i) (4*S*,5*S*)-2-[(*S*)-2-Benzylaziridin-1-yl]-4,5-diphenyl-1-methyl-2-imidazoline (21).** Obtained as less polar colorless needles (0.16 g, 18%), mp 118−119 °C; IR (neat) ν_{max} 1605 cm^{-1}; UV λ_{max} 207.2 (ϵ 38800) nm; $[\alpha]^{23}_D$ +53.7 (*c* 1.00, $CHCl_3$); ^1H NMR δ 2.20 (d, *J* = 3.5 Hz, 1H), 2.58 (d, *J* = 5.3 Hz, 1H), 2.66 (s, 3H), 2.75−2.83 (m, 2H), 3.16−3.24 (m, 1H), 4.17 (d, *J* = 9.4 Hz, 1H), 4.63 (d, *J* = 9.4 Hz, 1H), 7.14−7.37 (m, 15H); ^{13}C NMR δ 32.0, 33.6, 38.6, 40.4, 75.2, 78.4, 126.7, 126.9, 127.0, 127.1, 127.8, 128.3, 128.6, 128.7, 128.9, 137.9, 140.1, 143.6, 167.7; HRFABMS *m/z* 368.2124 (M + H^+, $C_{25}H_{26}N_3$ requires *m/z* 368.2127). **(ii) (3*S*,7*S*,8*S*)-3-Benzyl-7,8-diphenyl-6-methyl-1,4,6-triazabicyclo[3.3.0]oct-4-ene (20).** Obtained as more polar colorless needles (0.58 g, 67%), which were recrystallized from MeCN, mp 136−138 °C; IR (neat) ν_{max} 1660 cm^{-1}; UV λ_{max} 207.2 (ϵ 37200) nm; $[\alpha]^{23}_D$ +43.1 (*c* 1.00, $CHCl_3$); ^1H NMR δ 2.75 (s, 3H), 2.87 (t, *J* = 8.2 Hz, 1H), 2.92 (dd, *J* = 13.4, 8.4 Hz, 1H), 3.06 (dd, *J* = 13.4, 4.4 Hz, 1H), 3.10 (dd, *J* = 8.2, 1.8 Hz, 1H), 3.85 (d, *J* = 8.4 Hz, 1H), 4.27 (d, *J* = 8.4 Hz, 1H), 4.45−4.52 (m, 1H), 6.90−6.94 (m, 2H), 7.12−7.15 (m, 2H), 7.21−7.33 (m, 11H); ^{13}C NMR δ 30.9, 41.9, 51.3, 70.4, 70.8, 78.3, 126.0, 126.9, 127.8, 128.1, 128.2, 128.45, 128.51, 128.7, 129.5, 136.8, 137.6, 139.5, 168.3. Anal. Calcd for $C_{25}H_{25}N_3$: C, 81.71; H, 6.86; N, 11.44. Found: C, 81.58; H, 6.83; N,11.41.

A Typical Procedure for Preparation of Linear-type Guanidines 24−29 (step 1 in Table 3): *N*-[(*S*)-1-Benzyl-2-hydroxyethyl]-*N′*,*N″*-di[(*S*)-1-phenylethyl]guanidine (24). A mixture of a carbodiimide **22** (2.00 g, 8.00 mmol) and (*S*)-phenylalaninol **1a** (1.21 g, 8.00 mmol) in toluene (50 mL) was heated at 60 °C for 9 h. After evaporation, purification of the residue by column chromatography ($CHCl_3$ to $CHCl_3$−MeOH = 20:1) gave **24** (2.86 g, 89%) as colorless oil; IR (neat) ν_{max} 3430, 1620 cm^{-1}; UV λ_{max} 207.2 (ϵ 24100) nm; $[\alpha]^{26}_D$ +49.9 (*c* 1.00, $CHCl_3$); ^1H NMR δ 1.24 (d, *J* = 6.4 Hz, 6H), 2.36 (dd, *J* = 13.9, 9.7 Hz, 1H), 2.74 (dd, *J* = 13.9, 5.0 Hz, 1H), 3.37 (dd, *J* = 10.6, 8.2 Hz, 1H), 3.65 (dd, *J* = 10.6, 1.1 Hz, 1H), 3.81−3.88 (m, 1H), 4.08 (q, *J* = 6.4 Hz, 2H), 6.88−7.58 (m, 15H); ^{13}C NMR δ 25.4, 37.8, 53.2, 56.6, 68.8, 125.4, 126.3, 126.8, 128.4, 128.5, 128.8, 138.1, 145.1, 152.4; HRFABMS *m/z* 402.2549 (M + H^+, $C_{26}H_{32}N_3O$ requires *m/z* 402.2545).

An Example of the Preparation of 1,4-Disubstituted 2-Iminoimidazolidines 30−35 (step 2 in Table 3): (*S*)-4-Benzyl-1-[(*S*)-1-phenylethyl]-2-[(*S*)-1-phenylethylimino]-imidazolidine (30). According to the above DMC-induced cyclization of deprotected hydroxyethylguanidine the hydrochloride of **24** (2.79 g, 6.38 mmol) was treated with DMC (3.24 g, 19.2 mmol) and Et_3N (1.94 g, 1.92 mmol) in MeCN (50 mL) at room temperature for 3 h and then with KOH (2.63 g) in MeOH (100 mL) at room temperature for 1 h. Workup followed by purification by column chromatography ($NH-SiO_2$, $CHCl_3$) gave **30** (2.01 g, 82%) as colorless oil; IR (neat) ν_{max} 1645 cm^{-1}; UV λ_{max} 208.0 (ϵ 30600) nm; $[\alpha]^{23}_D$ −20.9 (*c* 1.00, $CHCl_3$); ^1H NMR δ 1.45 (d, *J* = 6.4 Hz, 3H), 1.70 (d, *J* = 6.4 Hz, 3H), 2.50 (dd, *J* = 13.6, 6.4 Hz, 1H), 2.63 (dd, *J* = 13.6, 3.3 Hz, 1H), 2.83 (dd, *J* = 9.4, 5.5 Hz, 1H), 3.37 (t, *J* = 9.4 Hz, 1H), 4.16 (m, 1H), 5.22−5.27 (m, 1H), 6.03 (q, *J* = 6.4 Hz, 1H), 6.57 (d, *J* = 7.1 Hz, 2H), 6.86 (d, *J* = 7.0 Hz, 2H), 6.96 (t, *J* = 7.3 Hz, 2H), 7.07−7.28 (m, 7H), 7.61 (dd, *J* = 6.3, 2.4 Hz, 2H), 8.99 (d, *J* = 7.0 Hz, 1H), 9.07 (s, 1H); ^{13}C NMR δ 16.7, 23.2, 39.8, 46.2, 52.2, 53.5, 54.4, 126.6, 126.7, 126.8, 127.5, 127.7, 128.5,

128.65, 128.73, 129.6, 135.0, 138.6, 143.0, 155.8; HRFABMS *m*/*z* 384.2410 (M + H^+, $C_{26}H_{30}N_3$ requires *m*/*z* 384.2440).

(3*S*,8*S*)-3,8-Dibenzyl-6-[(*S*)-1-phenylethyl]-1,4,6-triazabicyclo[3.3.0]oct-4-ene (41). According to the above DMC-induced cyclization of deprotected hydroxyethylguanidine **37** (23.4 g, 42.9 mmol) and Et_3N (13.0 g, 129 mmol) in CH_2Cl_2 (200 mL) containing MSA (4.12 g, 42.9 mmol) was treated with DMC (10.9 g, 64.4 mmol) at room temperature for 3.5 h and then with KOH (39.5 g) in MeOH (150 mL) at room temperature for 40 min. Workup followed by purification by column chromatography (NH−SiO_2, $CHCl_3$) gave an inseparable mixture (17.9 g, 79%) of **38** and **39** and a cyclized product **41** (2.47 g, 15%) as a less polar and a more polar compopnents, respectively, the former of which was further subjected to the DMC-induced cyclization as mentioned above.

The mixture (16.9 g, 32.1 mmol) was deprotected with a 1 M solution of TBAF in THF (50.3 mL, 50.3 mmol) in THF (98 mL) at room temperature for 24 h to give the guanidine (11.7 g, 88%) after purification by column chromatography (NH−SiO_2, $CHCl_3$). A part (7.16 g, 17.3 mmol) of it was treated with DMC (8.79 g, 52.0 mmol) and Et_3N (10.5 g, 104 mmol) in MeCN (207 mL) at room temperature for 6 h and then with KOH (20.7 g) in MeOH (311 mL) at room temperature for 1 h to afford **41** (5.62 g, 72%) as a colorless oil after purification by column chromatography (NH−SiO_2, CH_2Cl_2); IR (neat) ν_{max} 1655 cm^{-1}; UV λ_{max} 208.0 (ϵ 29900) nm; $[\alpha]^{27}_D$ −65.6 (*c* 1.00, $CHCl_3$); ^{1}H NMR δ 1.52 (d, *J* = 7.0 Hz, 3H), 2.54−2.63 (m, 2H), 2.68−2.77 (m, 2H), 2.84 (dd, *J* = 8.2, 2.9 Hz, 1H), 2.94−3.03 (m, 2H), 3.26−3.35 (m, 1H), 3.45 (dd, *J* = 8.6, 7.1 Hz, 1H), 4.27−4.35 (m, 1H), 5.11 (q, *J* = 7.0 Hz, 1H), 7.02 (d, *J* = 7.7 Hz, 2H), 7.18−7.38 (m, 13H); ^{13}C NMR δ 17.0, 38.8, 41.9, 51.3, 52.0, 52.1, 59.3, 71.1, 125.9, 126.6, 127.0, 127.3, 128.1, 128.4, 128.5, 129.1, 129.4, 137.6, 139.7, 140.8, 167.7; HRFABMS *m*/*z* 396.2420 (M + H^+, $C_{27}H_{30}N_3$ requires *m*/*z* 396.2440).

***N*,*N*′-Bis[(*S*)-1-benzyl-2-hydroxyethyl]-*N*″-propylguanidine (43).** According to the above deprotection method **42** (4.45 g, 7.45 mmol) in THF (19 mL) was treated with a 1 M solution of TBAF in THF (19.4 mL, 19.4 mmol) at room temperature for 21 h to give **43** (2.27 g, 83%) after purification by column chromatography (NH−SiO_2, $CHCl_3$); An amorphous mass; IR (neat) ν_{max} 3250, 1625 cm^{-1}; UV λ_{max} 206.4 (ϵ 18000) nm; $[\alpha]^{22}_D$ −139.8 (*c* 1.00, $CHCl_3$); ^{1}H NMR δ 0.67 (t, *J* = 7.3 Hz, 3H), 1.10−1.22 (m, 2H), 2.38−2.51 (m, 1H), 2.53 (dd, *J* = 11.3, 9.0 Hz, 2H), 2.65−2.73 (m, 1H), 2.80 (dd, *J* = 11.3, 3.3 Hz, 2H), 3.47−3.57 (m, 4H), 3.72 (d, *J* = 7.9 Hz, 2H), 7.05 (d, *J* = 6.4 Hz, 4H), 7.21−7.40 (m, 6H); ^{13}C NMR δ 10.7, 22.2, 37.0, 43.4, 57.2, 66.8, 126.4, 128.3, 128.7, 137.6, 156.3; HRFABMS *m*/*z* 370.2497 (M + H^+, $C_{22}H_{32}N_3O_2$ requires *m*/*z* 370.2495).

(3*S*,8*S*)-3,8-Dibenzyl-6-propyl-1,4,6-triazabicyclo[3.3.0]-oct-4-ene (44). According to the above DMC-induced cyclization of deprotected hydroxyethylguanidine the hydrochloride of **43** (2.27 g, 6.15 mmol) was treated with DMC (6.22 g, 68.8 mmol) and Et_3N (3.72 g, 36.8 mmol) in CH_2Cl_2 (40 mL) at room temperature for 17 h and then with KOH (8.24 g) in MeOH at room temperature for 24 h. Workup followed by purification column chromatography (NH−SiO_2, hexane-$CHCl_3$=1:1) gave **44** (1.38 g, 67%) as a colorless oil; IR (neat) ν_{max} 1655 cm^{-1}; UV λ_{max} 207.2 (ϵ 23000) nm; $[\alpha]^{25}_D$ −17.9 (*c* 1.00, $CHCl_3$); ^{1}H NMR δ 0.91 (t, *J* = 7.5 Hz, 3H), 1.49−1.61 (m, 2H), 2.55 (dd, *J* = 8.3, 8.0 Hz, 1H), 2.69 (dd, *J* = 13.3, 9.9 Hz, 1H), 2.74 (dd, *J* = 13.5, 6.2 Hz, 1H), 2.84 (dd, *J* = 13.5, 5.9 Hz, 1H), 2.85 (dd, *J* = 8.3, 2.4 Hz, 1H), 2.99 (dd, *J* = 13.3, 4.4 Hz, 1H), 3.15 (t, *J* = 7.0 Hz, 2H), 3.27−3.38 (m, 2H), 3.43−3.51 (m, 1H), 4.22−4.28 (m, 1H), 7.15−7.32 (m, 10H); ^{13}C NMR δ 11.2, 21.0, 39.4, 41.9, 47.2, 52.2, 56.5, 59.5, 71.4, 125.9, 126.7, 128.2, 128.6, 129.1, 129.4, 137.8, 139.9, 168.6; HRFABMS *m*/*z* 334.2293 (M + H^+, $C_{22}H_{28}N_3$ requires *m*/*z* 334.2283).

Supporting Information Available: Characterization data of compounds **(2, 4, 6−8, 10, 11)b**, **(2, 4, 6−8, 10, 11)c**, **14** and its synthetic intermediates, **25**−**29**, **31**−**35**, (5*S*)-3-[(*S*)-1-phenylethyl]-2-[(*S*)-1-phenylethylimino]-1,3-diazabicyclo[3.3.0]-octane and its synthetic intermediates, **37** and its synthetic intermediates, and **42** and its synthetic intermediates; ^{1}H and ^{13}C NMR charts of compounds **2a**, **4a**, **(7**−**10)a**, **15**, **16**, **21**, **24**, **30**, **41**, **43**, and **44**; 2D NMR charts of compound **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO000746F