JOC Article

Novel Syntheses of Enantiopure Hexahydroimidazo[1,5-*b*]isoquinolines and Tetrahydroimidazo[1,5-*b*]isoquinolin-1(5*H*)-ones via Iminium Cation Cyclizations

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Condensations of chiral diamines **11a**−**c** with benzotriazole and formaldehyde gave benzotriazolyl intermediates **12a**−**c**; similar condensations of α-amino-amides **10a**−**c** with benzotriazole and paraformaldehyde gave **14a**−**c**. Subsequent treatment of **12a**−**c** and **14a**−**c** with $AlCl_3$ led to enantiopure tricyclic 1,2,3,5,10,10a-hexahydroimidazo[1,5-*b*]isoquinolines **1a**−**c** and 2,3,10,10a-tetrahydroimidazo[1,5-*b*]isoquinolin-1(5*H*)-ones **15a**−**c**, respectively, via Lewis acid promoted iminium cation cyclizations.

Introduction

Following our recent syntheses of optically active imidazolidines **6** from *N*-Boc-α-amino acids,[1] we have now developed routes to novel tricyclic 1,2,3,5,10,10a-hexahydroimidazo[1,5-*b*]isoquinolines **1** and 2,3,10,10a-tetrahydroimidazo[1,5-*b*]isoquinolin-1(5*H*)-ones **2**. The nearest known analogues of **1** and **2** are 10,10a-dihydroimidazo-[1,5-*b*]isoquinoline-1,3(2*H*,5*H*)-diones **3**, which are of interest as inhibitors of inflammation,[2a,b] apoprotein B-100 biosynthesis,[2c] and matrix-degrading metalloproteinase.[2d]

Parent compound **3** ($R^1 = R^2 = R^3 = H$) was obtained by cyclization of 1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid with KOCN.[2a,b] Significant synthetic activity to prepare derivatives of **3** has involved (i) *N*-alkylation of **3** ($R^1 = R^2 = R^3 = H$) with *N*-(2-chloroethyl)-piperidine;[2a,b] (ii) Mannich condensation of **3** ($R^1 = R^2 = R^3 = H$) with formaldehyde and secondary amines;[3] and (iii) modification of **3** ($R^1 = H$, alkyl, or Ph, $R^2 = R^3 = H$) via bromination and nucleophilic substitutions.[2c,4] Additional analogues of **3** have been made by (iv) solid phase supported intramolecular cyclization of *N*-CBZ-α-amino-amides.[5] No previous reports have been found for the preparation of compounds of type **1** and **2**.

Optically active imidazolidines **6** were synthesized by Mannich condensations of chiral diamines **4** with benzotriazole and formaldehyde, followed by the nucleophilic substitutions of the benzotriazolyl group in **5**.[1] Previous syntheses of 1,4-dihydro-3(2*H*)-isoquinolinones,[6a] tetrahydro[1,3]oxazolo[3,4-*b*]isoquinolin-3-ones,[6b] and tetrahydroisoquinolines[6c] by intramolecular cyclizations utilizing Lewis acid-activated benzotriazole as a leaving group suggested a route to **1** by iminium cation Lewis acid-promoted cyclizations of intermediates **5** (Scheme 1). Success of the methodology led to its extension to prepare 2,3,10,10a-tetrahydroimidazo[1,5-*b*]isoquinolin-1(5*H*)-ones **2**.

Results and Discussion

Preparation of Chiral Diamines 11a−c from *N*-Boc-Phe-OH (7). *N*-Boc-α-amino-amides **9a**−**c** were readily obtained from optically active *N*-Boc-Phe-OH (**7**) and primary amines **8a**−**c** (R = *p*-$CH_3C_6H_4$, *c*-C_6H_{11}, or $PhCH_2$) by using the mixed anhydride method.[7] We previously used excess HCl/EtOAc to remove the *N*-Boc protection group (usually needs 12−24 h until the disappearance of **9**).[1,7a] We now find that 8 equiv of CF_3COOH in dry CH_2Cl_2 efficiently removes *N*-Boc in 2−5 h giving the α-amino-amides **10a**−**c** in ≥88% yields. Treatment of **10a**−**c** with 6 equiv of $LiAlH_4$ in refluxing THF for 2 days afforded chiral diamines **11a**−**c** in ≥90% yields. Intermediates **9a**−**c**, **10a**−**c**, and **11a**−**c** were all used as crude products for the subsequent reactions.

Syntheses of 1,2,3,5,10,10a-Hexahydroimidazo-[1,5-*b*]isoquinolines 1a−c. Mannich condensation of

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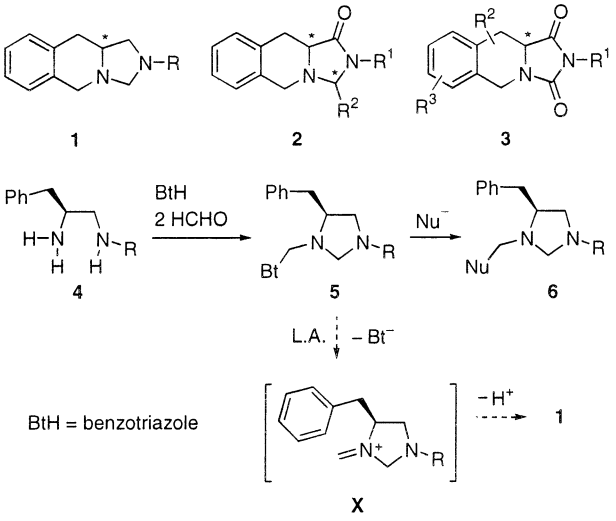
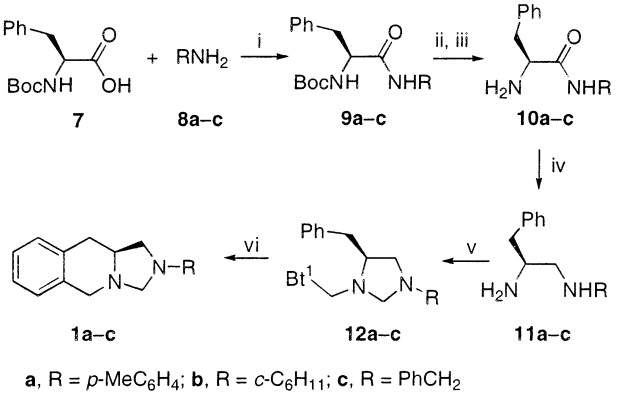
SCHEME 1



SCHEME 2[a]



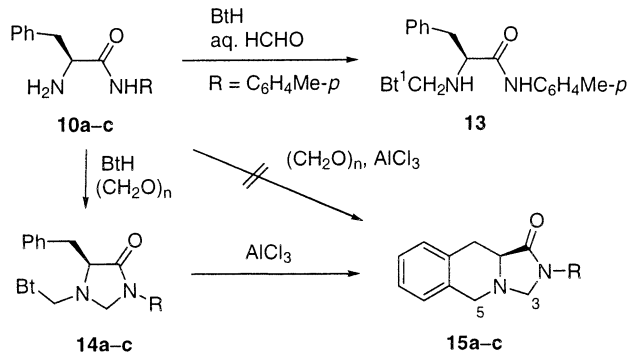
[a] Conditions: (i) ClCOOBu-*i*, *N*-methylmorpholine; (ii) CF_3COOH; (iii) aq NaOH; (iv) $LiAlH_4$; (v) BtH, 2 HCHO (aq); (vi) $AlCl_3$.

chiral diamines **11a**−**c** with 1 equiv of benzotriazole and 2 equiv of formaldehyde (37% aqueous solution) in an aqueous solution at 25 °C gave benzotriazolyl intermediates **12a**−**c** in 93%, 96%, and 90% yields, respectively. Compounds **12a**,**c** were obtained solely as benzotriazol-1-yl isomers; **12b** was obtained as a mixture of Bt^1 and Bt^2 isomers in ca. 26:1 ratio.

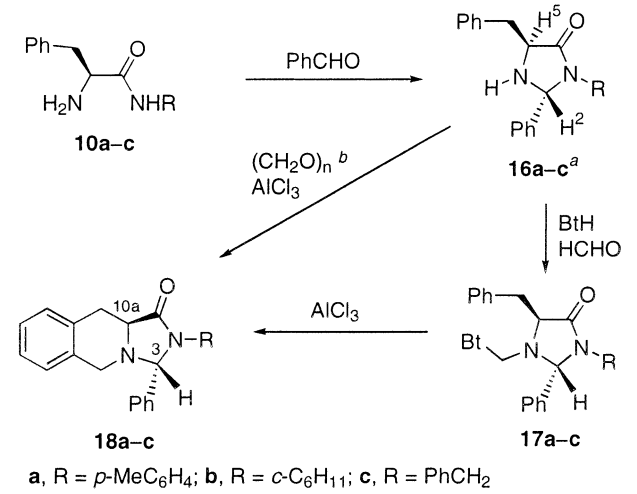
Treatment of crude **12a**−**c** with 3 equiv of $AlCl_3$ in refluxing CH_2Cl_2 afforded 2-substituted-1,2,3,5,10,10a-hexahydroimidazo[1,5-*b*]isoquinolines **1a**−**c** (Scheme 2). The structures of **1a**−**c** are clearly supported by their ^1H, ^{13}C NMR spectra and microanalyses. Lewis acid $AlCl_3$ facilitates loss of the benzotriazolyl anion to form an iminium cation, which then undergoes intramolecular cyclization to afford **1a**−**c**.

Syntheses of 2,3,10,10a-Tetrahydroimidazo[1,5-*b*]-isoquinolin-1(5*H*)-ones 15a−c (cf. Scheme 3). The reaction of α-amino-amide **10a** with benzotriazole and formaldehyde in aqueous solution at 25 °C did not produce the desired cyclized compound **14a**; instead acyclic **13** was obtained in 92% yield, due to the lower nucleophilic activity of amide nitrogen. Therefore, stronger conditions using azeotropic distillation with paraformaldehyde were applied and Bt intermediates **14a**−**c** were prepared in 92%, 91%, and 94% yields, respectively.

SCHEME 3



SCHEME 4[a]



[a] For *trans*-**16a**, the *cis*-**16′a** was isolated in 31% yield. [b]This route resulted in a mixture of *trans*-**18a**−**c** and *cis*-**18′a**−**c** in a ratio range from 4:1 to 5:1.

Attempts to purify **14a**−**c** by column chromatography failed due to their significant decomposition on silica gel. Therefore, compounds **14a**−**c** were used directly for the subsequent cyclizations.

The subsequent treatment of **14a**−**c** with 3 equiv of $AlCl_3$ in refluxing CH_2Cl_2 furnished 2,3,10,10a-tetrahydroimidazo[1,5-*b*]isoquinolin-1(5*H*)-ones **15a**−**c** in 82%, 83%, and 78% yields, respectively. The structures of **15a**−**c** are clearly supported by their ^1H, ^{13}C NMR spectra and microanalyses. The two methylene protons at the 5-position in **15a**−**c** appear at 3.7−4.0 ppm as a typical AB system with ca. 14 Hz coupling constant.

We attempted direct treatment of α-amino-amide **10a** with excess paraformaldehyde in the presence of $AlCl_3$, but could not isolate any desired tricyclic **15a**. This result proves the necessity of using benzotriazole.

Syntheses of Chiral 3-Substituted-2,3,10,10a-tetrahydroimidazo[1,5-*b*]isoquinolin-1(5*H*)-ones 18a−c (cf. Scheme 4). We further investigated the modification of 2,3,10,10a-tetrahydroimidazo[1,5-*b*]isoquinolin-1(5*H*)-ones **15** at the 3-position. In agreement with the previous reactions of α-amino-amides and aldehydes,[8] we obtained

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16b,**c** as the sole trans-isomers; however, *trans*-**16a** was isolated in 38% yield together with the corresponding *cis*-**16′a** in 31% isolated yield. The absolute configurations of *trans*-**16a**−**c** and *cis*-**16′a** were determined by NOE experiments. For example, strong positive NOE effect between H(2) (5.81 ppm, s) and H(5) (4.00 ppm, t) in **16′a** confirms its cis-configuration. For *trans*-**16a**−**c**, no positive NOE effect was observed between H(2) and H(5); however, small but distinct NOE effects between H(2) and PhCH_2 at the 5-position prove their trans-configurations.

Reaction of **16a**−**c** with benzotriazole and aqueous formaldehyde readily gave Bt intermediates **17a**−**c**, which were directly treated with $AlCl_3$ to furnish enantiopure *trans*-3-substituted-2,3,10,10a-tetrahydroimidazo-[1,5-*b*]isoquinolin-1(5*H*)-ones **18a**−**c**. The same route from *cis*-**16′a** led to enantiopure *cis*-**18′a**. The ^{1}H NMR spectra show that NC*H*N (5.68 ppm, d) in *trans*-**18a** appears at a lower field than NC*H*N (5.32 ppm, d) in *cis*-**18′a**. The positive NOE effect of H(3) and H(10a) in **18′a** also confirms its cis-configuration.

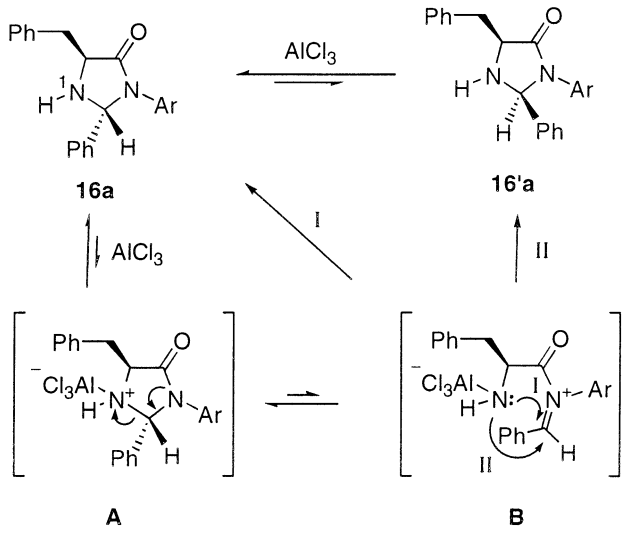
We attempted reactions of **16a**−**c** with paraformaldehyde and $AlCl_3$ in the absence of benzotriazole. The crude NMR spectra of the products show a mixture of *trans*-**18a**−**c** and *cis*-**18′a**−**c** in a ratio ranging from 4:1 to 5:1. It is impossible to separate *trans*-**18a**−**c** and *cis*-**18′a**−**c** by column chromatography due to their very close retention factors on alumina or silica gel TLC plate. This result indicates the possible Lewis acid-promoted ring opening and closing of the five-membered ring in **16a**−**c**. We further treated *trans*-**16a** with $AlCl_3$ only, and did observe the formation of *cis*-**16′a** in 1:4 ratio. Therefore, we believe that the nitrogen at the 1-position may coordinate with $AlCl_3$ to form intermediate **A**, which undergoes ring opening to generate an iminium cation intermediate **B**. The lone electron pair of the nitrogen in **B** attacks the iminium cation from above (I) or below (II) the plane, leading to *trans*-**16a** and *cis*-**16′a**, respectively.

Attempts to Synthesize 1,2a,3,4a,5,9b-Hexahydrobenzo[*g*]imidazo[2,1,5-*cd*]indolizin-4(2*H*)-one (23). We recently reported reaction of succindialdehyde (**19**) with benzotriazole and *N*-phenylethylenediamine leading to 1-phenyl-5-(benzotriazol-1-yl)hexahydro-1*H*-pyrrolo-[1,2-*a*]imidazole **20**. The benzotriazolyl group at the 5-position in **20** is readily removed by nucleophilic substitutions with Grignard reagents, allylsilanes, silyl enol ethers, or triethyl phosphite to furnish novel 1-phenyl-5-substituted-hexahydro-1*H*-pyrrolo[1,2-*a*]imidazoles **21** [Nu = alkyl, aryl, allyl, and P(O)(OEt)$_2$] (Scheme 6).[9] Since chiral diamines **11a**−**c** were readily obtained in high yields, our initial idea intended to use chiral diamine **11a** instead of *N*-phenylethylenediamine, to control the two new chiral centers at the 5- and 7a-positions. Subsequent treatment of Bt intermediates **22** was supposed to undergo intramolecular cyclizations at the tethered phenyl group to give **23**.

Reaction of chiral diamines **11a** with succindialdehyde (**19**, obtained by treatment of 2,5-dimethoxytetrahydrofuran with 0.1 M HCl) and benzotriazole in CH_2Cl_2 at room temperature for 24 h readily afforded Bt intermediates **22** as single enantiomers in 81% yield (Scheme 6).

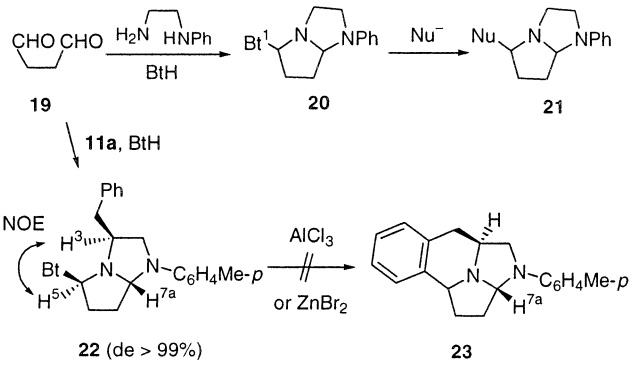
(9) Katritzky, A. R.; Qiu, G.; He, H.-Y.; Yang, B. *J. Org. Chem.* **2000**, *65*, 3683.

SCHEME 5[a]



[a] Ar = *p*-MeC_6H_4; reflux of only *trans*-**16a** resulted in a mixture of *trans*-**16a** and *cis*-**16′a** in ca. 4:1 ratio.

SCHEME 6



The stereochemistry of **22** was determined by NOE NMR experiments. ^{1}H NMR spectra of **22** show that H(3), H(7a), and H(5) appear at 3.7 (multiplet), 5.1 (doublet−doublet), and 6.0 ppm (triplet), respectively. A significant positive NOE effect was observed between H(3) and H(5), and no NOE effect was observed between H(7a) with either H(3) or H(5). Thus, NOE analysis demonstrates that H(3) and H(5) in **22** are in cis-orientation, while H(3) and H(7a) are in trans-orientation.

Treatment of **22** with 2 equiv of $AlCl_3$ or $ZnBr_2$ did not afford the desired **23**, but gave a decomposed mixture possibly due to the labile NCHN moiety in the presence of a Lewis acid.

In summary, starting from easily available *N*-Boc-α-amino acids, we have developed an efficient method for the preparation of novel enantiopure 1,2,3,5,10,10a-hexahydroimidazo[1,5-*b*]isoquinolines **1a**−**c**, 2,3,10,10a-tetrahydroimidazo[1,5-*b*]isoquinolin-1(5*H*)-ones **15a**−**c**, and **18a**−**c** via Lewis acid-promoted iminium cation intramolecular cyclizations.

Experimental Section

^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded in $CDCl_3$ (with TMS for ^{1}H and chloroform-*d* for ^{13}C as the internal reference). Column chromatography was performed

on silica gel (200−425 mesh). All of the reactions were carried out under nitrogen.

General Procedure for the Preparation of Chiral α-Amino-amides 10a−c and Diamines 11a−c from *N*-Boc-Phe-OH (7). α-Amino-amides **10a−c** and diamines **11a−c** were prepared from *N*-Boc-Phe-OH (**7**) and primary amines **8a−c** according to our recent paper.[1,7a,10]

General Procedure for the Preparation of Benzotriazolyl intermediates 12a−c. A mixture of a diamine **11a−c** (3.0 mmol), BtH (0.36 g, 3.0 mmol), and formaldehyde (37% aqueous solution, 0.49 g, 6 mmol) in CH_3OH/H_2O (10 mL/5 mL) was stirred at 25 °C for 4 h. The precipitate formed was filtered and washed with cool Et_2O to give **12a−c**, which was used directly for the subsequent reactions. For microanalyses and optical activity, crude **12a−c** was recrystallized from appropriate solvents.

Data for 1-{[(5*S*)-5-benzyl-3-(4-methylphenyl)tetrahydro-1*H*-imidazol-1-yl]methyl}-1*H*-1,2,3-benzotriazole (12a): white microcrystals (from EtOH); yield 93%; mp 94−95 °C; $[\alpha]^{25}_D$ +1.8 (*c* 1.70, $CHCl_3$); ^{1}H NMR δ 2.21 (s, 3H), 2.74 (dd, *J* = 13.2, 8.3 Hz, 1H), 3.08 (t, *J* = 7.6 Hz, 1H), 3.22−3.31 (m, 2H), 3.58−3.63 (m, 1H), 4.24, 4.39 (AB, *J* = 5.0 Hz, 2H), 5.56, 5.67 (AB, *J* = 13.7 Hz, 2H), 6.35 (d, *J* = 8.4 Hz, 2H), 6.98 (d, *J* = 8.1 Hz, 2H), 7.22−7.40 (m, 6H), 7.48 (d, *J* = 3.6 Hz, 2H), 8.05 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR δ 20.3, 39.2, 52.2, 61.2, 63.7, 68.2, 109.7, 112.3, 120.0, 124.0, 126.4, 126.6, 127.7, 128.6, 129.0, 129.7, 133.5, 138.1, 144.0, 146.0. Anal. Calcd for $C_{24}H_{25}N_5$: C, 75.17; H, 6.57; N, 18.26. Found: C, 74.95; H, 6.77; N, 18.29.

Data for 1-{[(5*S*)-5-benzyl-3-cyclohexyltetrahydro-1*H*-imidazol-1-yl]methyl}benzotriazole (12b): obtained as a mixture of Bt^1 and Bt^2 isomers in 26:1 ratio, and NMR data are reported for the major Bt^1 isomer; white needles (from EtOH); yield 96%; mp 94−95 °C; $[\alpha]^{25}_D$ +30.5 (*c* 1.64, $CHCl_3$); ^{1}H NMR δ 1.02−1.14 (m, 5H), 1.53−1.67 (m, 5H), 1.90 (br s, 1H), 2.41 (dd, *J* = 8.8, 6.8 Hz, 1H), 2.65−2.77 (m, 2H), 2.99 (dd, *J* = 13.4, 6.1 Hz, 1H), 3.43−3.48 (m, 1H), 3.70 (s, 2H), 5.31, 5.49 (AB, *J* = 13.5 Hz, 2H), 7.20−7.48 (m, 8H), 8.04 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR δ 24.4, 24.6, 25.8, 31.6, 31.7, 41.1, 56.3, 61.4, 61.5, 65.1, 72.3, 109.8, 119.8, 123.8, 126.3, 127.3, 128.4, 129.1, 133.4, 138.8, 145.8. Anal. Calcd for $C_{23}H_{29}N_5$: C, 73.57; H, 7.78; N, 18.65. Found: C, 73.94; H, 8.17; N, 18.77.

Data for 1-{[(5*S*)-3,5-dibenzyltetrahydro-1*H*-imidazol-1-yl]methyl}-1*H*-1,2,3-benzotriazole (12c): white microcrystals (from EtOH); yield 90%; mp 81−82 °C; $[\alpha]^{25}_D$ +40.8 (*c* 1.87, $CHCl_3$); ^{1}H NMR δ 2.34 (dd, *J* = 9.4, 6.5 Hz, 1H), 2.67−2.81 (m, 2H), 2.92 (dd, *J* = 13.2, 6.6 Hz, 1H), 3.42, 3.52 (AB, *J* = 13.2 Hz, 2H), 3.52−3.60 (m, 1H), 3.62, 3.70 (AB, *J* = 6.3 Hz, 2H), 5.38, 5.43 (AB, *J* = 13.6 Hz, 2H), 7.12−7.45 (m, 13H), 8.05 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR δ 41.3, 57.8, 58.6, 61.8, 65.5, 73.9, 109.8, 119.8, 123.8, 126.3, 127.0, 127.3, 128.2, 128.3, 128.4, 129.2, 133.4, 138.3, 138.8, 145.9. Anal. Calcd for $C_{24}H_{25}N_5$: C, 75.17; H, 6.57; N, 18.26. Found: C, 75.03; H, 6.32; N, 18.30.

General Procedure for the Preparation of 1,2,3,5,10,-10a-Hexahydroimidazo[1,5-*b*]isoquinolines 1a−c. A mixture of **12a−c** (1.0 mmol) and anhydrous $AlCl_3$ (0.40 g, 3.0 mmol) was refluxed in dry CH_2Cl_2 (20 mL) for 12 h. After cooling, the reaction mixture was added to CH_2Cl_2 (30 mL), washed with 2 M NaOH and brine, and dried over anhydrous K_2CO_3. After removal of the solvent in vacuo, the crude product was purified by column chromatography with hexanes/EtOAc (3:1 to 1:1) as an eluent to give **1a−c**.

Data for (10a*S*)-2-(4-methylphenyl)-1,2,3,5,10,10a-hexahydroimidazo[1,5-*b*]isoquinoline (1a): colorless microcrystals (from hexanes/$CHCl_3$); yield 76%; mp 189−190 °C; $[\alpha]^{25}_D$ −50.3 (*c* 1.68, $CHCl_3$); ^{1}H NMR δ 2.26 (s, 3H), 2.91−3.06 (m, 3H), 3.24 (t, *J* = 8.2 Hz, 1H), 3.62−3.70 (m, 2H), 3.84 (d, *J* = 3.6 Hz, 1H), 4.18 (d, *J* = 14.4 Hz, 1H), 4.60 (d, *J* = 3.6 Hz, 1H), 6.45 (d, *J* = 8.5 Hz, 2H), 7.05−7.19 (m, 6H); ^{13}C NMR 20.3, 33.2, 52.8, 53.0, 59.2, 71.1, 111.3, 125.3, 126.0, 126.5, 126.8, 129.1, 129.7, 133.5, 134.0, 144.3. Anal. Calcd for $C_{18}H_{20}N_2$: C, 81.78; H, 7.63; N, 10.60. Found: C, 81.31; H, 8.18; N, 10.71.

Data for (10a*S*)-2-cyclohexyl-1,2,3,5,10,10a-hexahydroimidazo[1,5-*b*]isoquinoline (1b): colorless prism (from hexanes/$CHCl_3$); yield 77%; mp 101−102 °C; $[\alpha]^{25}_D$ −35.5 (*c* 1.66, $CHCl_3$); ^{1}H NMR δ 1.24 (br s, 5H), 1.56−1.62 (m, 1H), 1.74 (br s, 2H), 1.88 (br s, 2H), 2.31 (br s, 1H), 2.63 (t, *J* = 8.4 Hz, 1H), 2.76−2.93 (m, 3H), 3.17 (dd, *J* = 8.4, 5.5 Hz, 1H), 3.43 (d, *J* = 4.6 Hz, 1H), 3.56, 4.02 (AB, *J* = 14.3 Hz, 2H), 4.03 (d, *J* = 4.6 Hz, 1H), 7.04−7.26 (m, 4H); ^{13}C NMR δ 24.7, 24.8, 26.0, 31.6, 32.2, 33.5, 52.9, 56.0, 58.8, 62.2, 74.1, 125.7, 126.2, 126.7, 129.0, 134.4, 134.8. Anal. Calcd for $C_{17}H_{24}N_2$: C, 79.64; H, 9.44; N, 10.93. Found: C, 79.94; H, 9.69; N, 10.87.

Data for (10a*S*)-2-benzyl-1,2,3,5,10,10a-hexahydroimidazo[1,5-*b*]isoquinoline (1c): white needles (from hexanes/EtOH); yield 85%; mp 73−74 °C; $[\alpha]^{25}_D$ −30.3 (*c* 1.77, $CHCl_3$); ^{1}H NMR δ 2.64 (t, *J* = 8.7 Hz, 1H), 2.77−2.95 (m, 3H), 3.21 (dd, *J* = 8.7, 5.7 Hz, 1H), 3.43, 3.93 (AB, *J* = 5.4 Hz, 2H), 3.55, 3.99 (AB, *J* = 14.2 Hz, 2H), 3.84 (s, 2H), 7.04−7.16 (m, 4H), 7.23−7.39 (m, 5H); ^{13}C NMR δ 33.5, 52.6, 59.0, 59.1, 60.6, 76.5, 125.9, 126.4, 126.7, 127.0, 128.3, 128.5, 128.9, 134.4, 134.7, 139.4. Anal. Calcd for $C_{18}H_{20}N_2$: C, 81.78; H, 7.63; N, 10.60. Found: C, 81.52; H, 7.37; N, 10.65.

General Procedure for the Preparation of Benzotriazolyl Intermediates 13 and 14a−c. Using the same procedure as for the preparation of **12a−c**, reaction of **10a** with benzotriazole and aqueous formaldehyde (1 or 2 equiv) led to **13**.

Data for (2*S*)-2-[(1*H*-1,2,3-benzotriazol-1-ylmethyl)-amino]-*N*-(4-methylphenyl)-3-phenylpropanamide (13): white microcrystals (from CH_3OH); yield 92%; mp 136−137 °C; $[\alpha]^{25}_D$ −74.5 (*c* 1.76, $CHCl_3$); ^{1}H NMR δ 2.32 (s, 3H), 2.70 (br s, 1H), 2.79 (dd, *J* = 13.8, 8.7 Hz, 1H), 3.01 (dd, *J* = 14.1, 4.8 Hz, 1H), 3.61 (dd, *J* = 8.4, 4.5 Hz, 1H), 5.41−5.53 (m, 2H), 6.87−6.89 (m, 2H), 7.08−7.14 (m, 5H), 7.33−7.40 (m, 4H), 7.44 (d, *J* = 7.8 Hz, 1H), 8.04 (d, *J* = 8.7 Hz, 1H), 8.67 (s, 1H); ^{13}CNMR δ 20.8, 39.0, 60.9, 61.3, 108.8, 119.7, 120.1, 124.1, 127.0, 127.8, 128.6, 128.7, 129.4, 132.5, 134.1, 134.6, 135.9, 146.0, 170.2. Anal. Calcd for $C_{23}H_{23}N_5O$: C, 71.67; H, 6.01; N, 18.17. Found: C, 71.60; H, 6.25; N, 18.29.

A mixture of **10a−c** (2.0 mmol), BtH (0.48 g, 4.0 mmol), and paraformaldehyde (0.18 g, 6.0 mmol) with *p*-TsOH·H_2O (0.08 g, 0.4 mmol) was refluxed in benzene (25 mL) with a Dean−Stark apparatus for 2 h. After cooling, benzene was evaporated and toluene (25 mL) was added, and then the mixture was refluxed for another 1 h. The mixture was washed with 2 M NaOH. The aqueous phase was extracted with EtOAc and the combined organic phase was washed with water and brine and dried over anhydrous K_2CO_3. Removal of solvent in vacuo gave the crude **14a−c**, which were directly used for the subsequent reactions. Attempts to purify **14a−c** failed due to their significant decomposition on silica gel.

Data for (5*S*)-1-(benzotriazolylmethyl)-5-benzyl-3-(4-methylphenyl)tetrahydro-4*H*-imidazol-4-one (14a): obtained as a mixture of Bt^1 and Bt^2 isomers in 3:1 ratio, and NMR data are reported for the major Bt^1 isomer; yellowish oil; yield 92%; ^{1}H NMR δ 2.29 (s, 3H), 3.09 (dd, *J* = 14.2, 7.4 Hz, 1H), 3.35 (dd, *J* = 14.2, 3.9 Hz, 1H), 3.91 (dd, *J* = 7.3, 3.8 Hz, 1H), 4.63, 4.85 (AB, *J* = 5.6 Hz, 2H), 5.41 (s, 2H), 7.06−7.46 (m, 12H), 8.04 (d, *J* = 8.2 Hz, 1H).

Data for (5*S*)-1-(benzotriazolylmethyl)-5-benzyl-3-cyclohexyltetrahydro-4*H*-imidazol-4-one (14b): obtained as a mixture of Bt^1 and Bt^2 isomers in 4:1 ratio, and NMR data are reported for the major Bt^1 isomer; yellowish oil; yield 91%; ^{1}H NMR δ 0.90−1.40 (m, 6H), 1.50−1.80 (m, 4H), 2.95 (dd, *J* = 13.9, 7.4 Hz, 1H), 3.24 (dd, *J* = 13.8, 3.4 Hz, 1H), 3.70−3.81 (m, 2H), 4.21, 4.43 (AB, *J* = 5.6 Hz, 2H), 5.31 (d, *J* = 4.8 Hz, 2H), 7.11 (d, *J* = 8.1 Hz, 1H), 7.27−7.45 (m, 7H), 8.04 (d, *J* = 8.1 Hz, 1H).

(10) Katritzky, A. R.; He, H.-Y.; Verma, A. K. *Tetrahedron: Asymmetry* **2002**, *13*, 933.

Data for (5*S*)-1-(benzotriazolylmethyl)-3,5-dibenzyltetrahydro-4*H*-imidazol-4-one (14c): obtained as a mixture of Bt^1 and Bt^2 isomers in 5:1 ratio, and NMR data are reported for the major Bt^1 isomer; pale brown oil; yield 94%; ^{1}H NMR δ 3.04 (dd, J = 14.0, 6.8 Hz, 1H), 3.29 (dd, J = 14.0, 3.7 Hz, 1H), 3.87−3.90 (m, 1H), 4.09, 4.57 (AB, J = 10.7 Hz, 2H), 4.11−4.13 (m, 1H), 4.32 (d, J = 5.2 Hz, 1H), 5.35 (s, 2H), 6.91−6.93 (m, 2H), 7.11−7.45 (m, 11H), 8.05 (d, J = 8.1 Hz, 1H); ^{13}C NMR δ 37.4, 44.9, 62.9, 63.3, 65.1, 109.1, 120.0, 124.2, 126.8, 127.5, 127.7, 127.9, 128.5, 128.7, 130.0, 133.4, 134.9, 137.3, 145.7, 170.6.

General Procedure for the Preparation of 2,3,10,10a-Tetrahydroimidazo[1,5-*b*]isoquinolin-1(5*H*)-ones 15a−c. Treatment of crude **14a−c** with 3 equiv of $AlCl_3$ afforded **15a−c** with use of the same procedure as for the preparation of **1a−c**. The isolated yields of **15a−c** were based on α-amino-amides **10a−c**.

Data for (10a*S*)-2-(4-methylphenyl)-2,3,10,10a-tetrahydroimidazo[1,5-*b*]isoquinolin-1(5*H*)-one (15a): colorless needles; yield 82%; mp 185−186 °C; $[\alpha]^{25}_D$ −62.7 (*c* 1.66, $CHCl_3$); ^{1}H NMR δ 2.32 (s, 3H), 3.04−3.21 (m, 2H), 3.38−3.43 (m, 1H), 3.83, 4.05 (AB, J = 14.0 Hz, 2H), 4.48 (dd, J = 4.8, 1.6 Hz, 1H), 4.76 (d, J = 5.0 Hz, 1H), 7.10−7.21 (m, 6H), 7.44 (d, J = 8.5 Hz, 2H); ^{13}C NMR δ 20.8, 29.9, 52.3, 61.4, 69.6, 119.2, 126.2, 126.6, 126.9, 129.4, 129.5, 133.3, 133.7, 134.5, 135.0, 170.9. Anal. Calcd for $C_{18}H_{18}N_2O$: C, 77.67; H, 6.52; N, 10.06. Found: C, 77.28; H, 6.54; N, 10.10.

Data for (10a*S*)-2-cyclohexyl-2,3,10,10a-tetrahydroimidazo[1,5-*b*]isoquinolin-1(5*H*)-one (15b): colorless microcrystals; yield 83%; mp 72−73 °C; $[\alpha]^{25}_D$ −89.8 (*c* 1.75, $CHCl_3$); ^{1}H NMR δ 1.03−1.16 (m, 1H), 1.23−1.42 (m, 4H), 1.66−1.82 (m, 5H), 2.98 (AB dd, J = 15.6, 9.6 Hz, 1H), 3.10 (AB dd, J = 15.6, 4.8 Hz, 1H), 3.28 (dd, J = 9.2, 4.8 Hz, 1H), 3.78, 3.96 (AB, J = 14.1 Hz, 2H), 3.90−3.95 (m, 1H), 4.04 (dd, J = 4.8, 2.1 Hz, 1H), 4.36 (d, J = 4.8 Hz, 1H), 7.08−7.10 (m, 1H), 7.17−7.20 (m, 3H); ^{13}C NMR δ 25.2, 25.2, 25.4, 29.8, 30.2, 30.6, 49.9, 52.3, 60.9, 65.1, 126.1, 126.5, 126.8, 129.3, 133.6, 133.9, 171.3; HRMS *m*/*z* calcd for $C_{17}H_{22}N_2O$ 270.1732 (M), found 270.1738. Anal. Calcd for $C_{17}H_{22}N_2O$: C, 75.52; N, 10.36. Found: C, 75.18; N, 10.32.

Data for (10a*S*)-2-benzyl-2,3,10,10a-tetrahydroimidazo-[1,5-*b*]isoquinolin-1(5*H*)-one (15c): colorless prism; yield 78%; mp 50−51 °C; $[\alpha]^{25}_D$ −64.8 (*c* 1.66, $CHCl_3$); ^{1}H NMR δ 3.10 (d, J = 6.6 Hz, 2H), 3.49 (t, J = 6.9 Hz, 1H), 3.77, 3.84 (AB, J = 14.5 Hz, 2H), 4.05 (dd, J = 5.2, 1.8 Hz, 1H), 4.12 (d, J = 5.0 Hz, 1H), 4.29, 4.65 (AB, J = 15.3 Hz, 2H), 7.02−7.15 (m, 3H), 7.16−7.27 (m, 6H); ^{13}C NMR δ 30.0, 44.8, 52.4, 60.4, 68.4, 126.3, 126.6, 127.0, 127.5, 127.6, 128.7, 129.2, 133.8, 134.4, 135.6, 172.3. Anal. Calcd for $C_{18}H_{18}N_2O$: C, 77.67; H, 6.52; N, 10.06. Found: C, 77.50; H, 6.83; N, 10.09.

General Procedure for the Preparation of 2,3,5-Trisubstituted-tetrahydro-4*H*-imidazol-4-ones 16a−c. A mixture of α-amino-amide **10a−c** (2.0 mmol), benzaldehyde (0.27 g, 2 mmol), and *p*-TsOH (0.4 mmol) was refluxed in CH_3OH (15 mL) with anhydrous Na_2SO_4 (3.0 g) for 12 h. After evaporation of CH_3OH in vacuo, the reaction mixture was diluted with EtOAc. The organic phase was washed with 2 M NaOH, water, and brine and dried over anhydrous K_2CO_3. After removal of solvent in vacuo, the residue was purified by column chromatography with hexanes/EtOAc (6:4) as an eluent to give *trans*-**16a**, *cis*-**16′a**, and *trans*-**16b**,**c**.

Data for (2*R*,5*S*)-5-benzyl-3-(4-methylphenyl)-2-phenyltetrahydro-4*H*-imidazol-4-one (16a): yellowish microcrystals; yield 38%; mp 106−107 °C; $[\alpha]^{25}_D$ −52.5 (*c* 1.86, $CHCl_3$); ^{1}H NMR δ 1.70 (br s, 1H), 2.24 (s, 3H), 3.09−3.21(m, 2H), 4.13 (t, J = 5.5 Hz, 1H), 5.55 (s, 1H), 7.03, 7.11 (AB, J = 8.5 Hz, 4H), 7.22−7.32 (m, 10H); ^{13}C NMR δ 20.8, 38.0, 60.2, 77.1, 122.0, 126.4, 126.8, 128.5, 128.8, 128.9, 129.4, 129.8, 134.2, 135.1, 137.3, 139.4, 173.7. Anal. Calcd for $C_{23}H_{22}N_2O$: C, 80.67; H, 6.48; N, 8.18. Found: C, 80.39; H, 6.51; N, 7.94.

Data for (2*S*,5*S*)-5-benzyl-3-(4-methylphenyl)-2-phenyltetrahydro-4*H*-imidazol-4-one (16′a): yellowish microcrystals; yield 31%; mp 97−98 °C; $[\alpha]^{25}_D$ −29.8 (*c* 1.58, $CHCl_3$); ^{1}H NMR δ 1.88 (br s, 1H), 2.20 (s, 3H), 3.17 (dd, J = 14.1, 4.8 Hz, 1H), 3.40 (dd, J = 14.1, 5.4 Hz, 1H), 4.00 (t, J = 4.6 Hz, 1H), 5.81 (s, 1H), 6.81 (d, J = 7.0 Hz, 2H), 6.98−7.33 (m, 12H); ^{13}C NMR δ 20.9, 36.6, 60.9, 77.2, 122.8, 127.0, 127.1, 128.8, 128.9, 129.1, 129.3, 129.9, 134.0, 135.3, 136.4, 138.5, 174.0. Anal. Calcd for $C_{23}H_{22}N_2O$: C, 80.67; H, 6.48; N, 8.18. Found: C, 80.40; H, 6.30; N, 8.28.

Data for (2*R*,5*S*)-5-benzyl-3-cyclohexyl-2-phenyltetrahydro-4*H*-imidazol-4-one (16b): colorless microcrystals; yield 69%; mp 92−93 °C; $[\alpha]^{25}_D$ −32.2 (*c* 1.81, $CHCl_3$); ^{1}H NMR δ 0.87−0.99 (m, 2H), 1.07−1.28 (m, 2H), 1.43−1.61 (m, 5H), 1.65−1.70 (m, 1H), 1.99 (br s, 1H), 2.90 (dd, J = 13.5, 7.5 Hz, 1H), 3.13 (dd, J = 13.6, 3.9 Hz, 1H), 3.53−3.64 (m, 1H), 4.07−4.11 (m, 1H), 5.16 (s, 1H), 7.20−7.34 (m, 10H); ^{13}C NMR δ 25.1, 25.6, 25.7, 29.9, 30.9, 38.7, 52.8, 59.7, 75.0, 126.4, 126.5, 128.3, 128.8, 129.0, 129.7, 137.8, 141.9, 173.6. Anal. Calcd for $C_{22}H_{26}N_2O$: C, 79.00; H, 7.84; N, 8.38. Found: C, 78.55; H, 7.99; N, 8.29.

Data for (2*R*,5*S*)-3,5-dibenzyl-2-phenyltetrahydro-4*H*-imidazol-4-one (16c): colorless needles (from hexanes/EtOAc); yield 74%; mp 128−129 °C; $[\alpha]^{25}_D$ −19.7 (*c* 1.73, $CHCl_3$); ^{1}H NMR δ 2.15 (br s, 1H), 3.04 (AB dd, J = 13.8, 6.9 Hz, 1H), 3.16 (AB dd, J = 13.8, 4.2 Hz, 1H), 3.46, 5.02 (AB, J = 14.9 Hz, 2H), 4.17 (br s, 1H), 4.96 (s, 1H), 6.85−6.87 (m, 2H), 7.14−7.36 (m, 13H); ^{13}C NMR δ 38.1, 43.9, 59.8, 74.8, 126.7, 126.8, 127.5, 128.0, 128.5, 128.6, 129.1, 129.2, 129.8, 135.5, 137.2, 139.3, 173.6. Anal. Calcd for $C_{23}H_{22}N_2O$: C, 80.67; H, 6.48; N, 8.18. Found: C, 80.31; H, 6.63; N, 8.13.

General Procedure for the Preparation of Bt Intermediates 17a−c and 17′a. A mixture of **16a−c** or **16′a** (1.0 mmol), benzotriazole (0.14 g, 1.2 mmol), and formaldehyde (37% aqueous solution, 0.12 g, 1.5 mmol) was stirred in CH_3OH (15 mL) at 25 °C overnight. After evaporation of CH_3OH, EtOAc was added to the mixture. The organic phase was washed with 1 M NaOH aqueous solution, brine, and water and dried over anhydrous K_2CO_3. Removal of solvent in vacuo gave essentially pure **17a** and **17′a**, which were purified by recrystallization for analytical purposes. Attempt to purify **17b**,**c** (both obtained as sticky oil) by column chromatography (silica gel) failed, thus they were used directly for the subsequent reaction as crude products.

Data for (2*R*,5*S*)-1-(1*H*-1,2,3-benzotriazol-1-ylmethyl)-5-benzyl-3-(4-methylphenyl)-2-phenyltetrahydro-4*H*-imidazol-4-one (17a): white needles (from EtOH); yield 89%; mp 153−154 °C; $[\alpha]^{25}_D$ −20.4 (*c* 1.80, $CHCl_3$); ^{1}H NMR δ 2.19 (s, 3H), 3.30−3.43 (m, 2H), 4.46 (br s, 1H), 5.34, 5.65 (AB, J = 13.8 Hz, 2H), 5.45 (d, J = 2.1 Hz, 1H, NC*H*N), 6.84−6.97 (m, 5H), 7.08−7.32 (m, 12H), 7.98−8.01 (m, 1H); ^{13}C NMR δ 20.8, 36.3, 60.2, 63.2, 80.1, 109.7, 119.7, 123.6, 123.9, 126.8, 127.2, 128.0, 128.5, 128.8, 129.4, 129.6, 129.8, 132.3, 132.9, 135.9, 136.0, 136.7, 145.9, 170.6. Anal. Calcd for $C_{30}H_{27}N_5O$: C, 76.09; H, 5.75; N, 14.79. Found: C, 75.74; H, 6.01; N, 14.69.

Data for (2*S*,5*S*)-1-(benzotriazolylmethyl)-5-benzyl-3-(4-methylphenyl)-2-phenyltetrahydro-4*H*-imidazol-4-one (17′a): obtained as a mixture of Bt^1 and Bt^2 isomers in 17:1 ratio, and NMR data are reported for the major Bt^1 isomer; white prism (from EtOH); yield 85%; mp 197−198 °C; $[\alpha]^{25}_D$ −185 (*c* 1.56, $CHCl_3$); ^{1}H NMR δ 2.16 (s, 3H), 3.38 (AB dd, J = 14.0, 4.4 Hz, 1H), 3.47 (AB dd, J = 14.0, 4.4 Hz, 1H), 4.08 (br s, 1H), 5.34, 5.46 (AB, J = 14.8 Hz, 2H), 5.82 (s, 1H, NC*H*N), 6.84 (d, J = 8.2 Hz, 2H), 6.88−6.96 (m, 4H), 7.13−7.36 (m, 4H), 7.40−7.50 (m, 7H), 8.11 (d, J = 8.1 Hz, 1H); ^{13}C NMR δ 20.9, 36.9, 58.9, 61.6, 77.8, 108.8, 120.2, 124.2, 124.5, 126.8, 128.0, 128.4, 128.5, 128.9, 129.3, 129.4, 130.5, 132.5, 134.0, 136.3, 136.7, 137.1, 145.6, 169.5. Anal. Calcd for $C_{30}H_{27}N_5O$: C, 76.09; H, 5.75; N, 14.79. Found: C, 75.84; H, 5.96; N, 14.54.

(2*R*,5*S*)-1-(Benzotriazolylmethyl)-5-benzyl-3-cyclohexyl-2-phenyltetrahydro-4*H*-imidazol-4-one (17b): obtained as a mixture of Bt^1 and Bt^2 isomers in 10:1 ratio, and NMR data are reported for the major Bt^1 isomer; yellowish oil; yield 94%;

^{1}H NMR δ 0.85−1.07 (m, 2H), 1.12−1.26 (m, 2H), 1.40−1.72 (m, 6H), 3.20−3.30 (m, 2H), 3.40−3.60 (m, 1H), 4.40 (s, 1H), 5.15 (s, 1H), 5.24, 5.41 (AB, J = 13.6 Hz, 2H), 7.09−7.45 (m, 12H), 7.55 (d, J = 8.1 Hz, 1H), 8.03 (d, J = 8.1 Hz, 1H).

Data for (2*R*,5*S*)-1-(benzotriazolylmethyl)-5-benzyl-3-benzyl-2-phenyltetrahydro-4*H*-imidazol-4-one (17c): obtained as a mixture of Bt^1 and Bt^2 isomers in 7:1 ratio, and NMR data are reported for the major Bt^1 isomer; yellowish oil; yield 95%; ^{1}H NMR δ 3.21−3.35 (m, 2H), 4.60 (d, J = 3.3 Hz, 1H), 5.01−5.07 (m, 2H), 5.05 (d, J = 2.1 Hz, 1H), 5.30, 5.55 (AB, J = 14.2 Hz, 2H), 6.58 (d, J = 7.0 Hz, 2H), 6.90−7.38 (m, 16H), 7.95 (d, J = 8.1 Hz, 1H).

General Procedure for the Lewis Acid-Promoted Cyclization of 17a−c and 17′a. Using the same procedure as for the preparation of **1a−c**, treatment of **17a−c** and **17′a** with 3 equiv of $AlCl_3$ afforded **18a−c** and **18′a**. After workup, all of the products were obtained as essentially NMR pure solids which were recrystallized from EtOH for analytical purposes.

Data for (3*R*,10a*S*)-2-(4-methylphenyl)-3-phenyl-2,3,-10,10a-tetrahydroimidazo[1,5-*b*]isoquinolin-1(5*H*)-one (18a): colorless needles (from EtOH); yield 91%; mp 189−190 °C; $[\alpha]^{25}_D$ −79.2 (*c* 1.83, $CHCl_3$); ^{1}H NMR δ 2.22 (s, 3H), 3.14 (d, J = 6.9 Hz, 2H), 3.62, 3.81 (AB, J = 14.7 Hz, 2H), 4.02 (td, J = 7.0, 1.4 Hz, 1H), 5.68 (d, J = 1.4 Hz, 1H, NC*H*N), 7.00−7.08 (m, 3H), 7.15−7.28 (m, 5H), 7.32−7.39 (m, 5H); ^{13}C NMR δ 20.8, 30.0, 49.6, 58.3, 81.9, 122.4, 124.2, 126.3, 126.6, 127.0, 127.3, 128.8, 129.1, 129.4, 133.9, 134.0, 134.5, 135.3, 136.7, 172.3. Anal. Calcd for $C_{24}H_{22}N_2O$: C, 81.32; H, 6.26; N, 7.90. Found: C, 81.07; H, 6.53; N, 7.97.

Data for (3*S*,10a*S*)-2-(4-methylphenyl)-3-phenyl-2,3,-10,10a-tetrahydroimidazo[1,5-*b*]isoquinolin-1(5*H*)-one (18′a): colorless needles (from EtOH); yield 91%; mp 212.5−213 °C; $[\alpha]^{25}_D$ −83.9 (*c* 1.59, $CHCl_3$); ^{1}H NMR δ 2.22 (s, 3H), 3.22−3.35 (m, 2H), 3.44 (ddd, J = 10.8, 4.2, 2.2 Hz, 1H), 3.79 (s, 2H), 5.32 (d, J = 2.1 Hz, 1H, NC*H*N), 6.97−7.11 (m, 5H), 7.11−7.33 (m, 6H), 7.40−7.43 (m, 2H); ^{13}C NMR δ 20.9, 30.8, 50.6, 60.8, 82.7, 124.2, 126.1, 126.6, 126.8, 128.4, 128.9, 129.3, 129.4, 129.8, 133.3, 133.4, 133.7, 135.6, 136.1, 171.4. Anal. Calcd for $C_{24}H_{22}N_2O$: C, 81.32; H, 6.26; N, 7.90. Found: C, 81.07; H, 6.61; N, 8.04.

Data for (3*R*,10a*S*)-2-cyclohexyl-3-phenyl-2,3,10,10a-tetrahydroimidazo[1,5-*b*]isoquinolin-1(5*H*)-one (18b): white microcrystals (from EtOH); yield 78%; mp 150−151 °C; $[\alpha]^{25}_D$ −66.6 (*c* 1.79, $CHCl_3$); ^{1}H NMR δ 0.84−1.00 (m, 2H), 1.11−1.26 (m, 2H), 1.40−1.72 (m, 6H), 2.80−3.12 (m, 2H), 3.47, 3.64 (AB, J = 14.5 Hz, 2H), 3.60−3.70 (m, 1H), 3.86−3.91 (m, 1H), 5.19 (s, 1H, NC*H*N), 7.02 (d, J = 6.4 Hz, 1H), 7.12−7.41 (m, 8H); ^{13}C NMR δ 25.1, 25.6, 25.7. 30.1, 30.3. 31.1, 49.6, 52.4, 58.1, 79.4, 126.1, 126.5, 126.9, 127.4, 128.7, 129.0, 131.7, 134.1, 134.7, 138.8, 172.7; HRMS *m*/*z* calcd for $C_{23}H_{26}N_2O$ 346.2045 (M), found 346.2042. Anal. Calcd for $C_{23}H_{26}N_2O$: N, 8.09. Found: N, 8.05.

Data for (3*R*,10a*S*)-2-benzyl-3-phenyl-2,3,10,10a-tetrahydroimidazo[1,5-*b*]isoquinolin-1(5*H*)-one (18c): white needles; yield 78%; mp 108−109 °C; $[\alpha]^{25}_D$ +65.1 (*c* 1.23, $CHCl_3$); ^{1}H NMR δ 3.05 (dd, J = 15.2, 6.7 Hz, 1H), 3.22 (dd, J = 15.2, 4.8 Hz, 1H), 3.29, 4.99 (AB, J = 15.2 Hz, 2H), 3.58, 3.81 (AB, J = 15.2 Hz, 2H), 4.24 (br t, J = 4.7 Hz, 1H), 4.66 (d, J = 2.3 Hz, 1H, NC*H*N), 6.53 (d, J = 7.0 Hz, 2H), 7.02−7.39 (m, 12H); ^{13}C NMR δ 29.9, 43.4, 50.1, 59.2, 80.5, 126.5, 127.1, 127.2, 127.3, 127.5, 128.4, 128.5, 128.6, 128.8, 129.2, 134.6, 134.9, 135.6, 138.1, 172.9. Anal. Calcd for $C_{24}H_{22}N_2O$: C, 81.32; H, 6.26; N, 7.90. Found: C, 80.76; H, 6.38; N, 7.87.

Procedure for the Preparation of Bt Intermediate 22. A mixture of 2,5-dimethoxytetrahydrofuran (0.66 g, 5.1 mmol) and HCl aqueous solution (0.1 M, 20 mL) was heated to 100 °C for 45 min, then cooled to room temperature. CH_2Cl_2 (40 mL), benzotriazole (0.61 g, 5.1 mmol), and diamine **11a** (1.20 g, 5 mmol) were successively added and stirred at room temperature for 24 h. The reaction mixture was washed with 1 M NaOH and the aqueous phase was extracted with CH_2Cl_2. The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent in vacuo, the residue was purified by column chromatography with hexanes/EtOAc (3:1) as an eluent to give **22**. However, subsequent treatment of **22** with 2 equiv of $AlCl_3$ or $ZnBr_2$ did not afford the desired tetracyclic compound **23**.

Data for (3*S*,5*R*,7a*S*)-5-benzotriazolyl-3-benzyl-1-(4-methylphenyl)hexahydro-1*H*-pyrrolo[1,2-*a*]imidazole (22): obtained as a mixture of Bt^1 and Bt^2 isomers in 4.5:1 ratio, and NMR data are reported for the major Bt^1 isomer; colorless needles (from $CHCl_3$/Et_2O); mp 145−146 °C; $[\alpha]^{25}_D$ −4.2 (*c* 1.37, $CHCl_3$); ^{1}H NMR δ 2.06−2.17 (m, 1H), 2.29 (s, 3H), 2.45−2.64 (m, 5H), 3.18 (dd, J = 9.2, 4.0 Hz, 1H), 3.70−3.80 [m, 1H, H(3)], 3.85 (dd, J = 9.2, 6.5 Hz, 1H), 5.10 (dd, J = 5.3, 4.0 Hz, 1H, NC*H*N), 6.02 (t, J = 7.0 Hz, 1H, BtC*H*N), 6.58 (d, J = 8.3 Hz, 2H), 6.79−6.82 (m, 2H), 6.92−6.98 (m, 3H), 7.10 (d, J = 8.1 Hz, 2H), 7.32−7.36 (m, 2H), 7.61−7.64 (m, 1H), 8.00−8.03 (m, 1H); ^{13}C NMR δ 20.2, 30.6, 30.9, 41.0, 52.8, 63.7, 79.2, 81.6, 111.5, 113.5, 119.6, 123.6, 125.9, 126.7, 126.8, 127.8, 128.4, 129.7, 131.2, 137.8, 143.9, 146.6. Anal. Calcd for $C_{26}H_{27}N_5$: C, 76.25; H, 6.65; N, 17.10. Found: C, 76.05; H, 6.88; N, 17.03.

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