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Syntheses of Optically Active Tetrahydro-1*H*-pyrrolo[1,2-*a*]imidazol-2-ones and Hexahydroimidazo[1,2-*a*]pyridin-2(3*H*)-ones

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The reactions of (2*S*)-2-amino-2-substituted-*N*-(4-nitrophenyl)acetamides **16a**−**c**, succindialdehyde (**13**), and benzotriazole afforded enantiopure (3*S*,5*R*,7a*R*)-5-(1*H*-1,2,3-benzotriazol-1-yl)-3-substituted-1-(4-nitrophenyl)tetrahydro-1*H*-pyrrolo[1,2-*a*]imidazol-2-ones **17a**−**c**, which were converted by sodium borohydride into (3*S*,7a*R*)-3-substituted-1-(4-nitrophenyl)tetrahydro-1*H*-pyrrolo[1,2-*a*]imidazol-2-ones **18a**−**c**. Chiral (2*S*)-2-amino-2-substituted-*N*-(4-methylphenyl)acetamides **12a**−**d**, easily prepared in two steps from *N*-Boc-α-amino acids **10a**−**d**, similarly reacted with glutaraldehyde (**20**) and benzotriazole to generate 5-benzotriazolyl-3-substituted-hexahydroimidazo[1,2-*a*]pyridin-2(3*H*)-ones **21a**−**d**, which were converted by sodium borohydride directly into optically active 3-substituted-hexahydroimidazo[1,2-*a*]pyridin-2(3*H*)-ones **22a**−**d**.

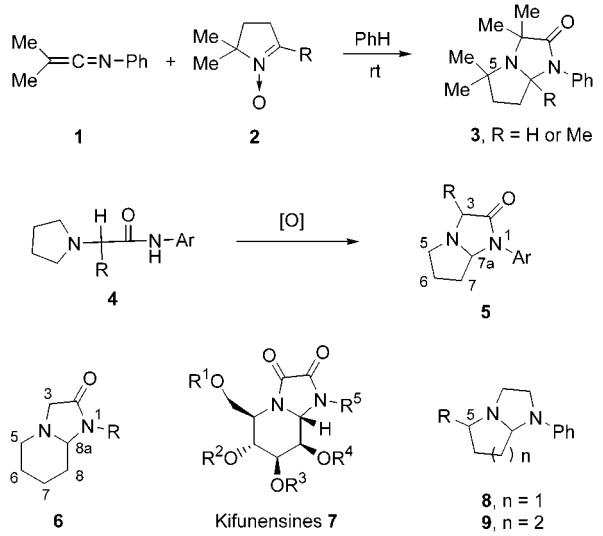
Introduction

Tetrahydro-1*H*-pyrrolo[1,2-*a*]imidazol-2-ones are biologically active as central nervous system depressants, sedatives, and anticonvulsants.[1] The known routes to tetrahydro-1*H*-pyrrolo[1,2-*a*]imidazol-2-ones are (i) the reaction of dimethylketene-*N*-phenylimine (**1**) with cyclic nitrones **2**[2] and (ii) the oxidative cyclizations of pyrrolidin-1-ylacetamide and α-(pyrrolidin-1-yl)propionamide **4** with mercuric acetate, potassium hexacyanoferrate(III), or potassium permanganate[3] (Scheme 1). No synthesis of an optically active compound was reported by any of the previous methods.

No published synthesis of hexahydroimidazo[1,2-*a*]-pyridin-2(3*H*)-ones **6** was found, although the corresponding dioxo structures, kifunensines **7**, which show promising immunomodulatory activity in α-mannosidase inhibition,[4] have been studied in detail by Kayakiri, Hashimoto, et al.,[5] and the parent was synthesized by Rouden and Hudlicky.[4a]

We recently reported reactions of succindialdehyde or glutaraldehyde with benzotriazole and *N*-phenylethylenediamine leading to 1-phenyl-5-(benzotriazol-1-yl)-hexahydro-1*H*-pyrrolo[1,2-*a*]imidazole **8** (R = Bt[1]) or 1-phenyl-5-benzotriazolyloctahydroimidazo[1,2-*a*]pyridine **9** (R = Bt), respectively.[6] The Bt group at the 5-position in these intermediates 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 **8** [R = alkyl, aryl, allyl, CH_2COR', and $P(O)(OEt)_2$] or 1-phenyl-5-substituted-octahydroimidazo-[1,2-*a*]pyridines **9** (R groups same as those in **8**). These

SCHEME 1



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results suggested the use of chiral α-amino amides instead of *N*-phenylethylenediamine to control the new chiral center at the 7a-position in **5** or 8a-position in **6**. We now document the syntheses of novel optically active 3-substituted-tetrahydro-1*H*-pyrrolo[1,2-*a*]imidazol-2-ones **18a**−**c** and 3-substituted-hexahydroimidazo[1,2-*a*]-pyridin-2(3*H*)-ones **22a**−**d**.

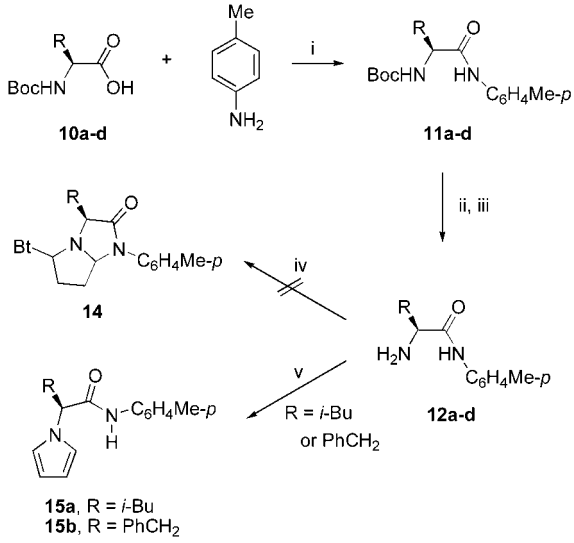
Results and Discussion

Preparation of Chiral α-Amino Amides 12a−d from *N*-Boc-α-amino Acids 10a−d. Although (2*S*)-2-amino-2-substituted-*N*-(4-nitrophenyl)acetamides **16a**−**c** are commercially available, apparently a convenient general method for the preparation of chiral α-amino amides **12** has not been described. Douat et al. recently prepared *N*-Boc- and *N*-(*Z*)-α-amino acylmorpholines by coupling the corresponding amino acids with morpholine, using conventional activation (phosphorium or uronium salts, chloroformates, DCC/HOBt).[7] We now show that isobutyl chloroformate together with *N*-methylmorpholine converts *N*-Boc-α-amino acids **10a**−**d** to the mixed anhydrides, and the subsequent addition of *p*-methylaniline affords the *N*-Boc-α-amino amides **11a**−**d** in excellent yields. The structures of **11a**−**d** are supported by their ^{1}H and ^{13}C NMR spectra and microanalyses. Treatment of crude *N*-Boc-α-amino amides **11a**−**d** with HCl/EtOAc at room temperature removed the Boc protection to generate the α-amino amide hydrochloride salts, which were converted by aqueous NaOH into the free bases α-amino amides **12a**−**d** in 81−92% yields (Scheme 2). α-Amino amides **12a**−**d** were used for the subsequent cyclizations without further purification.

Preparation of 5-(1*H*-1,2,3-Benzotriazol-1-yl)-3-substituted-tetrahydro-1*H*-pyrrolo[1,2-*a*]imidazol-2-ones 17a−c Followed by Reduction with $NaBH_4$. Reaction of commercially available (2*S*)-2-amino-2-substituted-*N*-(4-nitrophenyl)acetamides **16a**−**c** with succindialdehyde (**13**; 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 5-(1*H*-1,2,3-benzotriazol-1-yl)-3-substituted-tetrahydro-1*H*-pyrrolo[1,2-*a*]imidazol-2-ones **17a**−**c**, which were recrystallized from $CHCl_3$/hexanes to give single diastereoisomers in 91%, 84%, and 90% yields, respectively (Scheme 3). The stereochemistry of **17a**−**c** was determined by NOE NMR experiments. Using **17a** as an example, the ^{1}H NMR spectrum shows that H(3), H(7a), and H(5) appear at 3.89 ppm (q), 5.84 ppm (t), and 6.08 ppm (t), respectively. A significant positive NOE effect was observed between H(3) and H(5); no NOE effect was observed between H(7a) and either H(3) or H(5). Furthermore, a positive NOE effect was observed between H(7a) and the annual methyl group (1.25 ppm, d) in **17a**. Thus, NOE analysis demonstrates that in **17a** H(3) and H(5) are in a *cis*-orientation while H(3) and H(7a) are in a *trans*-orientation. Very similar NOE results observed for **17b,c** prove the same configuration as that of **17a**.

We previously reported that the benzotriazolyl group can be substituted with hydrogen by sodium borohydride.[8] Reduction of **17a** with 3 equiv of $NaBH_4$ in dry

SCHEME 2



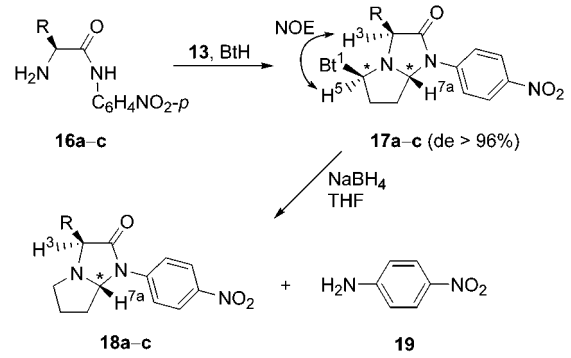
i) ClCOOBu-*i*, *N*-methylmorpholine; ii) HCl/EtOAc; iii) NaOH (1M)

iv) succindialdehyde (**13**), benzotriazole (BtH); v) **13**

Entry	R	Y (%) of **11**	Y[a] (%) of **12**
a	Me	88	81
b	*i*-Pr	94	92
c	*i*-Bu	94	89
d	$PhCH_2$	94	85

[a] Isolated yields based on *N*-Boc-α-amino amides **11**.

SCHEME 3



a, R = Me; **b**, R = *i*-Bu; **c**, R = $PhCH_2$

THF at room temperature for 24 h gave a mixture of **17a**, the desired product **18a**, and a byproduct, 4-nitroaniline (**19**), in a 3.3:2.3:1 ratio, determined by the ^{1}H NMR spectrum. Structure **19** was confirmed by GC−MS [MS (EI) *m*/*z* 138 (M^+) for **19**] and NMR spectra after separation on column chromatography. Treatment of this mixture with an additional 2 equiv of $NaBH_4$ at room

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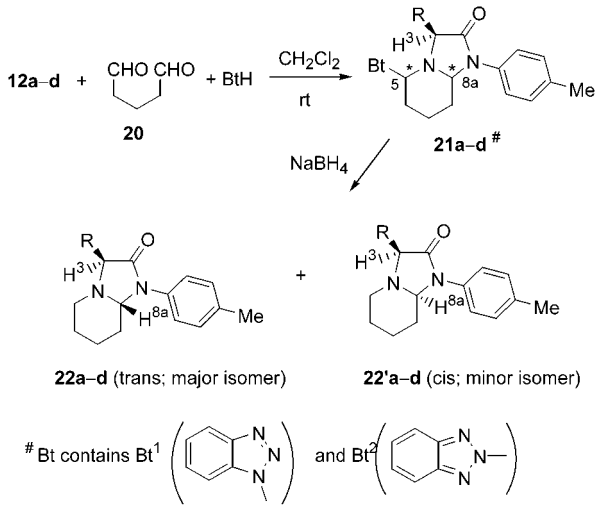
SCHEME 4



temperature for 24 h resulted in a ratio of **17a**, **18a**, and **19** of 0.5:1:1. When the reaction was carried out with 8 equiv of $NaBH_4$ in 48 h, the ratio became 0.05:0.37:1. The higher temperature (70 °C in 28 h with 3 equiv of $NaBH_4$) caused ring opening of **17a** and gave a low proportion of **18a**. We later found that this reaction was almost completed by using 4 equiv of $NaBH_4$ in THF at 40 °C for 36 h (a ratio of **17a**, **18a**, and **19** of 0.5:3.3:1). Compounds **18a**−**c** and **19** are difficult to separate by silica gel column chromatography due to their very close R_f values. However, **18a**−**c** and **19** were separated by neutral alumina column chromatography, and **18a**−**c** were isolated in 48%, 42%, and 51% yields, respectively. For **18a**, partial racemization occurred (de 69%), and a positive NOE effect between H(7a) and the annual methyl group confirms the major diastereoisomer as a *trans*-isomer.

Reactions of α-amino amides **12c,d** with succindialdehyde (**13**) and benzotriazole in CH_2Cl_2 did not give the desired fused ring system **14**; instead *N*-substituted pyrroles **15a,b** were obtained in 57% and 48% yields, respectively. We later found that **15a,b** were also obtained from **12c,d** in 59% and 55% yields, respectively, in the absence of benzotriazole (Scheme 2). Reactions of 2,5-dimethoxytetrahydrofuran with primary amines under acidic conditions have been developed as a general method to produce *N*-substituted pyrroles.[9] After acid hydrolysis of 2,5-dimethoxytetrahydrofuran with 0.1 M HCl, we neutralized the mixture with 0.5 M NaOH to pH ca. 8 and then added **12c** and BtH, but still failed to obtain the desired **14**. In the absence of exhaustive mechanistic studies, the weaker acidity of the amide hydrogen (−$CONHC_6H_4Me$-*p*) in **12c,d** than that of −$CONHC_6H_4NO_2$-*p* in **16a**−**c** may reflect the electron-releasing *p*-methyl group in **12c,d** and the strong electron-withdrawing *p*-nitro group in **16a**−**c**.

Syntheses of 5-Benzotriazolyl-3-substituted -hexahydroimidazo[1,2-*a*]pyridin-2(3*H*)-ones 21a−d. Reactions of α-amino amides **12a**−**d**, glutaraldehyde (**20**; 50% aqueous solution), and benzotriazole in CH_2Cl_2 at room temperature for 24 h afforded solid 5-benzotriazolyl-3-substituted-hexahydroimidazo[1,2-*a*]pyridin-2(3*H*)-ones **21a**−**d** (Scheme 4). Attempts to obtain pure **21** by column chromatography (silica gel) failed due to significant decomposition of these Bt intermediates. Compounds **21a**−**d** were therefore used directly for the subsequent reactions. The complex ^{1}H NMR spectra, due to mixtures of Bt^1 and Bt^2 isomers and some byproducts, made it difficult to establish the relative stereochemistry at the 5- or 8a-position in Bt intermediates **21**; thus, we report only the crude ^{1}H NMR spectral data for the major diastereoisomers. It is interesting to point out that one methyl group (in *i*-Bu) in **21c** appears at −0.10 ppm as a doublet obviously due to its significant shielding by the benzotriazolyl ring system. We also reacted **12c** with glutaraldehyde in the absence of benzotriazole and did not obtain any fused ring compounds.

TABLE 1. Isolated Yields and Optical Activities for 22 (*trans*) and 22′ (*cis*)

		22 (*trans*)		**22′** (*cis*)	
22, **22′**	R	yield[a] (%)	$[\alpha]^{25}_D$	yield[a] (%)	$[\alpha]^{25}_D$
a	Me	48 (57[b])	−12.5	11	+103.3
b	*i*-Pr	58	−44.3	*c*	
c	*i*-Bu	42 (47[b])	−26.5	7	+79.1
d	$PhCH_2$	49	−18.1	*c*	

[a] Isolated yields based on α-amino amides **12a**−**d**. [b] Yield obtained with 1% Et_3N eluent, and only a trace amount of the corresponding *cis*-isomer was isolated. [c] No detectable amount of the product was isolated.

Syntheses of Optically Active Hexahydroimidazo-[1,2-*a*]pyridin-2(3*H*)-ones 22 or 22′ via Reduction of 21a−d with $NaBH_4$. Treatment of crude 5-benzotriazolyl-3-substituted-hexahydroimidazo[1,2-*a*]pyridin-2(3*H*)-ones **21a**−**d** with sodium borohydride (2 equiv based on α-amino amides **12a**−**d**) in dry THF at room temperature overnight removed the benzotriazolyl group to give crude optically active hexahydroimidazo[1,2-*a*]-pyridin-2(3*H*)-ones **22a**−**d** (Scheme 4). The isolated yields of **22** (*trans*) or **22′** (*cis*) depend on the nature of the R groups in **12** and the conditions of column chromatography (cf. Table 1).

The structures for **22** or **22′** are clearly supported by their ^{1}H and ^{13}C NMR spectra, NOE experiments, and microanalyses or HRMS results. In the ^{1}H NMR spectra, H(8a) in **22** or **22′**, always at the lowest field in the aliphatic region, can be easily confirmed by its strong positive NOE effect with the aromatic hydrogens in the *p*-methylphenyl group. For **22a**−**d**, when H(8a) was irradiated, no distinct NOE effect was observed for H(3) in any compound; conversely, irradiation of H(3) gave no positive NOE for H(8a). This result suggests that H(8a) and H(3) in **22a**−**d** are located in a *trans*-orientation. The *trans*-configurations for **22a,b,d** were confirmed by positive NOE effects observed between H(8a) and the annular methyl group (for **22a**), the two methyl groups (for **22b**), or $PhCH_2$ (for **22d**). For *cis*-isomers **22′a,c**, a significant positive NOE effect was observed between H(8a) and H(3) in each compound, thus demonstrating their *cis*-orientation. It is noteworthy that the chemical shifts for H(8a) and H(3) in *trans*-isomers **22a,c** appear at a lower field as compared to those in *cis*-isomers **22′a,c**.

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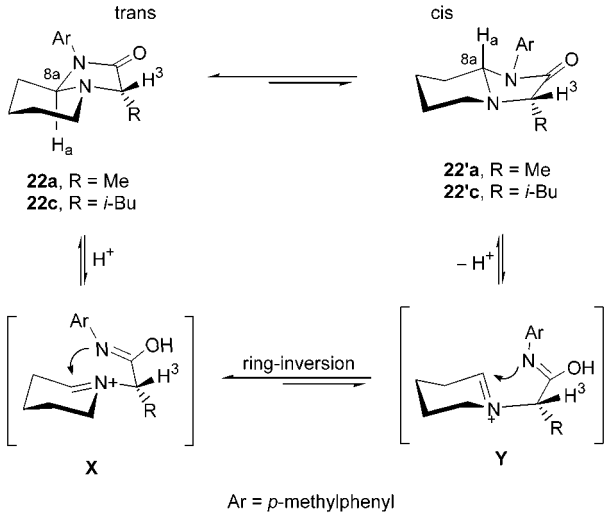

FIGURE 1.

After we confirmed the structures of the *trans*-isomers **22** and *cis*-isomers **22′**, careful comparison of the ^{1}H NMR spectra showed that crude **22a**−**d** (before column chromatography) were obtained as only *trans*-isomers. After column chromatography on silica gel, **22b** and **22d** were obtained as single diastereoisomers in 58% and 49% yields, respectively. However, purification of *trans*-isomers **22a,c** by column chromatography (silica gel, eluent hexanes/EtOAc) resulted in the formation of *cis*-isomers **22′a,c**, probably because of the weak acidity of silica gel. Furthermore, when we subjected pure *trans*-isomer **22a (**100 mg) to column chromatography (15 g of silica gel using 5:1 hexanes/EtOAc as an eluent), we recovered most of **22a** (88 mg) and isolated *cis*-isomer **22′a** (8 mg). Stirring of *trans*-isomer **22a** (80 mg) in hexanes/EtOAc (1:1, 15 mL) with silica gel (2 g) overnight formed a mixture with the *cis*-isomer **22′a** in a ratio of **22′a**:**22a** = 1:4.8, as determined by the ^{1}H NMR spectra. Treatment of pure *trans*-**22a** with neutral Al_2O_3 instead of silica gel gave a mixture of *trans*-**22a** and *cis*-**22′a** in a 9:1 ratio. Using silica gel, washed with a mixture of hexanes/EtOAc/Et_3N (10:1:0.1) to ca. pH 8 for the flash column chromatography of pure **22a**, gave only traces of **22′a**, and most of the **22a** was unchanged. Repetition of the preparation of **22a,c** using flash column chromatography with 1% Et_3N eluent improved the yields of **22a,c** from 48% and 42% to 57% and 47%, respectively. We also assessed the stability of the final products. Using **22a** and **22′a** as examples, no changes in the ^{1}H NMR spectra were observed for each compound in chloroform-*d* for 3 days at room temperature, and no obvious change for each compound in chloroform-*d* overnight at ca. 50 °C.

On the basis of the above experimental results, we believe that the C(8a)−N(1) bonds in *trans*-isomers **22a,c** can be broken on weak acidic silica gel to form the iminium cation and an α-hydroxyimine transient intermediate, **X**, via protonation of the amide carbonyl. Due to the equilibrium between **X** and **Y** by ring inversion, the lone electron pair of N(1) in **X** or **Y** subsequently attacks the iminium cation from the equatorial direction to form *trans*-isomers **22a,c** or *cis*-isomers **22′a,c** (Figure 1). The coupling constants for H(8a) (from 7.2 to 10.2 Hz) indicate their axial positions, as the larger substituents at the 8a-position prefer to locate at equatorial positions. According to our previous discussion[6] and other related reports,[10] the major conformation for **22** or **22′** is ring-*trans* due to its significantly lower energy than that of the ring-*cis* conformation.

In summary, we have developed a novel route to synthesize optically active 3-substituted-tetrahydro-1*H*-pyrrolo[1,2-*a*]imidazol-2-ones **18a**−**c** and 3-substituted-hexahydroimidazo[1,2-*a*]pyridin-2(3*H*)-ones **22a**−**d** via the reduction of 5-benzotriazolyl-3-substituted-tetrahydro-1*H*-pyrrolo[1,2-*a*]imidazol-2-ones **17a**−**c** and 5-benzotriazolyl-3-substituted-hexahydroimidazo[1,2-*a*]pyridin-2(3*H*)-ones **21a**−**d** with sodium borohydride. Bt intermediates **17a**−**c** were obtained by the reaction of succindialdehyde (**13**) with benzotriazole and (2*S*)-2-amino-2-substituted-*N*-(4-nitrophenyl)acetamides **16a**−**c**. Similarly, Bt intermediates **21a**−**d** were prepared by the reaction of glutaraldehyde (**20**), benzotriazole, and (2*S*)-2-amino-2-substituted-*N*-(4-methylphenyl)acetamides **12a**−**d**, readily available in two steps from *N*-Boc-α-amino acids **10a**−**d**.

Experimental Section

General Procedure for the Preparation of Chiral *N*-Boc-α-Amino Amides 11a−d. To a cold solution (−15 °C) of *N*-Boc-α-amino acids **10a**−**d** (10 mmol) and 4-methylmorpholine (1.01 g, 10 mmol) in dry THF (30 mL) was added dropwise isobutyl chloroformate (1.36 g, 10 mmol) in dry THF (5 mL) over 15 min. After the mixture was stirred for another 15 min, 4-methylaniline (1.07 g, 10 mmol) was added. Then the mixture was allowed to slowly warm to room temperature and stirred overnight. After evaporation of the solvent in vacuo, the residue was diluted with EtOAc and the organic phase was washed with 10% aq Na_2CO_3, 0.1 M HCl, and brine and dried over anhydrous Na_2SO_4. Evaporation of the solvents gave crude *N*-Boc-α-amino amides **11a**−**d**, which were used for the subsequent acid hydrolysis without further purification. For microanalysis purposes, **11a**−**d** were recrystallized from the appropriate solvents.

Data for *tert*-Butyl *N*-[(1*S*)-1-Methyl-2-oxo-2-(4-toluidino)ethyl]carbamate (11a): colorless plates (from $CHCl_3$/hexanes); yield 88%; mp 121−122 °C; $[\alpha]^{25}_D = -45.1$ (*c* 1.63, EtOH); ^{1}H NMR δ 8.57 (br s, 1H), 7.37 (d, J = 8.3 Hz, 2H), 7.05 (d, J = 8.1 Hz, 2H), 5.37−5.28 (m, 1H), 4.37 (br s, 1H), 2.28 (s, 3H), 1.45 (s, 9H), 1.43 (d, J = 8.7 Hz, 3H); ^{13}C NMR δ 171.2, 156.0, 135.3, 133.6, 129.2, 119.9, 80.3, 50.7, 28.3, 20.8, 18.0. Anal. Calcd for $C_{15}H_{22}N_2O_3$: C, 64.73; H, 7.97; N, 10.06. Found: C, 64.84; H, 8.13; N, 10.02.

General Procedure for the Preparation of Chiral α-Amino Amides 12a−d from *N*-Boc-α-amino Amides 11a−d. To a stirred solution of *N*-Boc-α-amino amides **11a**−**d** (3 mmol) in EtOAc (15 mL) was added HCl in EtOAc (ca. 1 M, 15 mL). The mixture was stirred at room temperature until TLC showed the disappearance of the starting material (usually 10−20 h). Then the mixture was treated with 1 M aq NaOH and extracted with EtOAc. The organic phase was washed with brine and dried over anhydrous K_2CO_3. Evaporation of the solvent in vacuo gave the crude products **12a**−**d**, which were used for the subsequent reactions without further purification. For microanalysis purposes, **12a**−**d** were recrystallized from appropriate solvents.

Data for (2*S*)-2-Amino-*N*-(4-methylphenyl)propanamide (12a): colorless plates (from EtOAc); yield 81%; mp 60−61 °C; $[\alpha]^{25}_D = +13.8$ (*c* 1.37, EtOH); ^{1}H NMR δ 9.39 (s,

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1H), 7.48 (d, J = 8.3 Hz, 2H), 7.11 (d, J = 8.1 Hz, 2H), 3.62 (q, J = 7.0 Hz, 1H), 2.30 (s, 3H), 1.93 (s, 2H), 1.42 (d, J = 7.0 Hz, 3H); ^{13}C NMR δ 173.4, 135.2, 133.5, 129.4, 119.4, 51.1, 21.5, 20.8. Anal. Calcd for $C_{10}H_{14}N_2O$: C, 67.39; H, 7.92; N, 15.72. Found: C, 67.24; H, 7.80; N, 15.67.

General Procedure for the Preparation of *N*-Substituted Pyrroles 15a,b. A mixture of 2,5-dimethoxytetrahydrofuran (0.26 g, 2 mmol) and HCl aqueous solution (0.1 M, 8 mL) was heated to 100 °C for 0.5 h and then cooled to room temperature. A solution of **12c,d** (2 mmol) in CH_2Cl_2 (20 mL) was added and stirred at room temperature for 16 h. The reaction mixture was washed with 2 M aq 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 (2:1) as an eluent to give **15a,b**.

Data for (2*S*)-4-Methyl-*N*-(4-methylphenyl)-2-(1*H*-pyrrol-1-yl)pentanamide (15a): colorless prisms (from the column); yield 59%; mp 107−108 °C; $[\alpha]^{25}_D$ = −22.0 (*c* 1.67, $CHCl_3$); ^{1}H NMR δ 7.21 (d, J = 8.4 Hz, 2H), 7.05 (d, J = 8.3 Hz, 2H), 6.90 (br s, 1H, NH), 6.78 (dd, J = 2.0, 2.0 Hz, 2H), 6.31 (dd, J = 2.0, 2.0 Hz, 2H), 4.70 (dd, J = 11.3, 4.5 Hz, 1H), 2.27 (s, 3H), 2.24−2.00 (m, 2H), 1.60−1.42 (m, 1H), 0.94 (d, J = 6.5 Hz, 3H), 0.93 (d, J = 6.7 Hz, 3H); ^{13}C NMR δ 169.6, 134.5, 134.3, 129.4, 120.1, 119.9, 110.1, 62.3, 40.0, 24.7, 23.1, 21.1, 20.8. Anal. Calcd for $C_{17}H_{22}N_2O$: C, 75.52; H, 8.20; N, 10.36. Found: C, 75.22; H, 8.36; N, 10.17.

Procedure for the Synthesis of (3*S*,5*R*,7a*R*)-5-(1*H*-1,2,3-Benzotriazol-1-yl)-3-substituted-1-(4-nitrophenyl)tetrahydro-1*H*-pyrrolo[1,2-*a*]imidazol-2-ones 17a−c. A mixture of 2,5-dimethoxytetrahydrofuran (0.40 g, 3 mmol) and 0.1 M HCl aqueous solution (12 mL) was heated to 100 °C for 0.5 h and then cooled to room temperature. A solution of benzotriazole (0.36 g, 3 mmol) and (2*S*)-2-amino-2-substituted-*N*-(4-nitrophenyl)acetamides **16a−c** (2.5 mmol) in CH_2Cl_2 (40 mL) was added and stirred at 25 °C for 24 h. The reaction mixture was washed with 1 M aq NaOH solution, and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent in vacuo gave a solid, which was recrystallized from $CHCl_3$/hexanes to afford essentially a single diastereoisomer, **17a−c**.

Data for (3*S*,5*R*,7a*R*)-5-(1*H*-1,2,3-Benzotriazol-1-yl)-3-methyl-1-(4-nitrophenyl)tetrahydro-1*H*-pyrrolo[1,2-*a*]-imidazol-2-one (17a): colorless needles; yield 91%; de > 99%; mp 174−175 °C; $[\alpha]^{25}_D$ = +62.7 (*c* 1.38, $CHCl_3$); ^{1}H NMR δ 8.32 (d, J = 9.2 Hz, 2H), 8.12 (d, J = 8.2 Hz, 1H), 7.81 (d, J = 8.2 Hz, 1H), 7.78 (d, J = 9.0 Hz, 2H), 7.54 (dd, J = 7.5, 7.5 Hz, 1H), 7.43 (dd, J = 7.4, 7.4 Hz, 1H), 6.08 (t, J = 6.8 Hz, Bt^{1}C*H*N, 1H), 5.84 (t, J = 4.9 Hz, NC*H*N, 1H), 3.89 (q, J = 7.1 Hz, NC*H*CO, 1H), 2.93−2.81 (m, 1H), 2.81−2.69 (m, 1H), 2.62−2.52 (m, 1H), 2.23−2.11 (m, 1H), 1.25 (d, J = 7.2 Hz, 3H); ^{13}C NMR δ 173.5 (C=O), 146.9, 144.1, 142.1, 131.5, 127.5, 124.9, 124.3, 120.4, 119.9, 110.7, 81.5, 77.7, 62.0, 30.0, 29.9, 18.0. Anal. Calcd for $C_{19}H_{18}N_6O_3$: C, 60.31; H, 4.79; N, 22.21. Found: C, 59.98; H, 4.94; N, 21.91.

General Procedure for the Synthesis of (3*S*,7a*R*)-3-substituted-1-(4-nitrophenyl)tetrahydro-1*H*-pyrrolo[1,2-*a*]imidazol-2(3*H*)-ones 18a−c. To a solution of **17a−c** (1.2 mmol) in dry THF (15 mL) was added $NaBH_4$ (0.18 g, 4.8 mmol), and the mixture was stirred at 40 °C for 36 h. After evaporation of the solvent in vacuo, the residue was diluted with EtOAc. The organic phase was washed with 1 M aq NaOH and brine and dried over anhydrous Na_2SO_4. After removal of the solvent in vacuo, the residue was purified by neutral Al_2O_3 (60−325 mesh) column chromatography with hexanes/EtOAc (4:1) as an eluent to afford **18a−c**. The R_f value for the byproduct 4-nitroaniline (**19**) is 0.33 (hexanes:EtOAc = 2:1; alumina TLC plate).

Data for 3-Methyl-1-(4-nitrophenyl)tetrahydro-1*H*-pyrrolo[1,2-a]imidazol-2(3*H*)-one (18a): obtained as a mixture of diastereoisomers, and NMR data are reported for its major isomer (3*S*,7a*R*); yellow microcrystals; R_f = 0.51 (hexanes:EtOAc = 2:1; alumina TLC plate); yield 48%; de 69%; mp 87−88 °C; ^{1}H NMR δ 8.26 (d, J = 9.3 Hz, 2H), 7.74 (d, J = 9.3 Hz, 2H), 5.47 (dd, J = 6.5, 3.8 Hz, NC*H*N, 1H), 3.57 (q, J = 7.1 Hz, NC*H*CO, 1H), 3.28 (dt, J = 9.8, 5.2 Hz, 1H), 2.79 (dt, J = 9.8, 7.5 Hz, 1H), 2.46−2.36 (m, 1H), 1.98−1.89 (m, 2H), 1.87−1.79 (m, 1H), 1.40 (d, J = 7.1 Hz, 3H); ^{13}C NMR δ 174.9 (C=O), 143.6, 142.9, 124.7, 119.6, 78.9, 63.1, 54.6, 31.2, 24.0, 17.8. Anal. Calcd for $C_{13}H_{15}N_3O_3$: C, 59.75; H, 5.80; N, 16.08. Found: C, 59.66; H, 5.92; N, 16.03.

Data for (3*S*,7a*R*)-3-Isobutyl-1-(4-nitrophenyl)tetrahydro-1*H*-pyrrolo[1,2-*a*]imidazol-2(3*H*)-one (18b): colorless flakes; R_f = 0.64 (hexanes:EtOAc = 2:1; alumina TLC plate); yield 42%; de 95%; mp 131−132 °C; $[\alpha]^{25}_D$ = −52.1 (*c* 1.83, $CHCl_3$); ^{1}H NMR δ 8.25 (d, J = 9.3 Hz, 2H), 7.73 (d, J = 9.3 Hz, 2H), 5.45 (dd, J = 6.0, 3.9 Hz, NC*H*N, 1H), 3.51 (dd, J = 9.6, 5.4 Hz, NC*H*CO, 1H), 3.28 (dt, J = 9.3, 4.8 Hz, 1H), 2.77 (dt, J = 9.0, 7.9 Hz, 1H), 2.47−2.36 (m, 1H), 2.00−1.88 (m, 3H), 1.84−1.73 (m, 1H), 1.58−1.52 (m, 2H), 0.99 (d, J = 6.7 Hz, 3H), 0.98 (d, J = 6.7 Hz, 3H); ^{13}C NMR δ 175.1 (C=O), 143.5, 143.1, 124.6, 119.6, 79.1, 66.2, 55.5, 40.9, 31.3, 25.0, 24.2, 23.2, 21.4. GC−MS (EI) *m*/*z* 303 (M^+). Anal. Calcd for $C_{16}H_{21}N_3O_3$: C, 63.35; H, 6.98; N, 13.85. Found: C, 63.38; H, 7.34; N, 13.87.

Data for (3*S*,7a*R*)-3-Benzyl-1-(4-nitrophenyl)tetrahydro-1*H*-pyrrolo[1,2-*a*]imidazol-2(3*H*)-one (18c): colorless microcrystals; R_f = 0.52 (hexanes:EtOAc = 2:1; alumina TLC plate); yield 51%; de > 99%; mp 128−129 °C; $[\alpha]^{25}_D$ = −138 (*c* 1.79, $CHCl_3$); ^{1}H NMR δ 8.23 (d, J = 9.2 Hz, 2H), 7.55 (d, J = 9.2 Hz, 2H), 7.26−7.21 (m, 5H), 4.83 (dd, J = 6.2, 4.0 Hz, NC*H*N, 1H), 3.76 (dd, J = 6.6, 4.4, NC*H*CO, 1H), 3.18−2.96 (m, 3H), 2.64−2.59 (m, 1H), 2.28−2.17 (m, 1H), 1.87−1.78 (m, 2H), 1.69−1.59 (m, 1H); ^{13}C NMR δ 173.9 (C=O), 143.8, 142.8, 137.6, 129.6, 128.2, 126.7, 124.6, 119.9, 79.6, 69.7, 55.7, 38.7, 31.4, 24.0. Anal. Calcd for $C_{19}H_{19}N_3O_3$: C, 67.64; H, 5.68; N, 12.45. Found: C, 67.51; H, 5.78; N, 12.48.

General Procedure for the Preparation of 5-Benzotriazolyl-3-substituted-hexahydroimidazo[1,2-*a*]pyridin-2(3*H*)-ones 21a−d. A mixture of glutaraldehyde (0.60 g, 3 mmol, 50% aqueous solution), benzotriazole (0.39 g, 3.3 mmol), and **12a−d** (3 mmol) in CH_2Cl_2 (40 mL) was stirred at room temperature for 24 h. The reaction mixture was washed with 2 M aq NaOH solution, and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent in vacuo afforded **21a−d** as a solid. Attempts to purify **21** by column chromatography (silica gel) failed due to their decomposition on silica gel. Therefore, Bt intermediates **21a−d** were used for the following reactions as crude products.

General Procedure for the Preparation of 3-Substituted-hexahydroimidazo[1,2-*a*]pyridin-2(3*H*)-ones 21 or 21′ via Reduction of 21a−d with $NaBH_4$. To a solution of crude 5-benzotriazolyl-3-substituted-hexahydroimidazo[1,2-*a*]-pyridin-2(3*H*)-ones **21a−d** (prepared from 3.0 mmol of **12a−d**) in dry THF (40 mL) was added $NaBH_4$ (0.23 g, 6.0 mmol). The mixture was stirred overnight at room temperature. After evaporation of the solvent in vacuo, the residue was diluted with EtOAc. The organic phase was washed with 1 M aq NaOH and 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 (10−6:1) as an eluent to afford **22** or **22′**.

Data for (3*S*,8a*R*)-3-Methyl-1-(4-methylphenyl)hexahydroimidazo[1,2-*a*]pyridin-2(3*H*)-one (22a): colorless flakes (from the column); mp 75−76 °C; $[\alpha]^{25}_D$ = −12.5 (*c* 1.47, $CHCl_3$); R_f = 0.23 (hexanes:EtOAc = 1:1); ^{1}H NMR δ 7.30 (d, J = 8.2 Hz, 2H), 7.17 (d, J = 8.1 Hz, 2H), 4.76 [dd, J = 9.3, 3.0 Hz, 1H, H(8a)], 3.68 [q, J = 6.6 Hz, 1H, H(3)], 3.11−3.00 (m, 1H), 2.86 (ddd, J = 13.7, 10.8, 3.2 Hz, 1H), 2.33 (s, 3H), 1.96−1.88 (m, 1H), 1.88−1.73 (m, 1H), 1.63−1.35 (m, 4H), 1.30 (d, J = 6.6 Hz, 3H); ^{13}C NMR δ 173.2 (C=O), 135.4, 133.7,

129.6, 123.0, 74.4, 57.1, 45.6, 27.7, 21.9, 21.4, 20.9, 13.0. Anal. Calcd for $C_{15}H_{20}N_2O$: C, 73.74; H, 8.25; N, 11.46. Found: C, 73.36; H, 8.32; N, 11.65.

Data for (3*S*,8a*S*)-3-Methyl-1-(4-methylphenyl)hexahydroimidazo[1,2-*a*]pyridin-2(3*H*)-one (22′a): colorless flakes (from the column); mp 75−76 °C; $[\alpha]^{25}_D = +103.3$ (*c* 2.87, $CHCl_3$); $R_f = 0.42$ (hexanes:EtOAc = 1:1); ^{1}H NMR δ 7.18 (d, $J = 8.1$ Hz, 2H), 7.10 (d, $J = 8.1$ Hz, 2H), 3.97 [d, $J = 9.9$ Hz, 1H, H(8a)], 3.11 (d, $J = 10.5$ Hz, 1H), 2.93 [q, $J = 6.6$ Hz, 1 H, H(3)], 2.33 (s, 3H), 2.76 (dd, $J = 11.0$, 4.9 Hz, 1H), 2.03−1.83 (m, 2H), 1.78−1.55 (m, 2H), 1.20−1.54 (m, 5H); ^{13}C NMR δ 173.3 (C═O), 135.9, 133.0, 129.4, 124.5, 78.0, 60.1, 47.9, 28.6, 25.0, 22.8, 21.0, 14.0. Anal. Calcd for $C_{15}H_{20}N_2O$: C, 73.74; H, 8.25; N, 11.46. Found: C, 73.43; H, 8.61; N, 11.64.

Data for (3*S*,8a*R*)-3-Isopropyl-1-(4-methylphenyl)hexahydroimidazo[1,2-*a*]pyridin-2(3*H*)-one (22b): colorless oil; $[\alpha]^{25}_D = -44.3$ (*c* 1.80, $CHCl_3$); $R_f = 0.48$ (hexanes:EtOAc = 3:1); ^{1}H NMR δ 7.27 (d, $J = 8.1$ Hz, 2H), 7.16 (d, $J = 8.4$ Hz, 2H), 4.92 [dd, $J = 7.2$, 3.6 Hz, 1H, H(8a)], 3.38 [dd, $J = 4.1$, 1.1 Hz, 1H, H(3)], 3.04−2.97 (m, 1H), 2.92−2.83 (m, 1H), 2.40−2.26 (m, 1H), 2.32 (s, 3H), 2.18−2.08 (m, 1H), 1.84−1.79 (m, 1H), 1.65−1.38 (m, 4H), 1.12 (d, $J = 6.9$ Hz, 3H), 1.04 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR δ 172.6 (C═O), 135.4, 133.9, 129.5, 123.3, 74.7, 68.0, 46.9, 29.1, 27.5, 21.8, 20.8, 20.8, 18.9, 18.4; HRMS *m*/*z* calcd for $C_{17}H_{25}N_2O$ 273.1967 (M + 1), found 273.1968. Anal. Calcd for $C_{17}H_{24}N_2O$: H, 8.88; N, 10.28. Found: H, 8.68; N, 10.35.

Data for (3*S*,8a*R*)-3-Isobutyl-1-(4-methylphenyl)hexahydroimidazo[1,2-*a*]pyridin-2(3*H*)-one (22c): colorless oil; $[\alpha]^{25}_D = -26.5$ (*c* 2.60, $CHCl_3$); $R_f = 0.33$ (hexanes:EtOAc = 3:1); ^{1}H NMR δ 7.25 (d, $J = 8.7$ Hz, 2H), 7.17 (d, $J = 8.4$ Hz, 2H), 4.87 [dd, $J = 7.2$, 3.6 Hz, 1H, H(8a)], 3.51 [t, $J = 6.5$ Hz, 1H, H(3)], 3.01−2.90 (m, 1H), 2.90−2.80 (m, 1H), 2.26 (s, 3H), 2.04−1.90 (m, 1H), 1.90−1.78 (m, 1H), 1.66−1.40 (m, 7H), 0.96 (d, $J = 6.9$ Hz, 6H); ^{13}C NMR δ 174.2 (C═O), 135.5, 133.8, 129.6, 123.4, 74.0, 61.8, 47.1, 36.8, 26.9, 25.1, 22.8, 22.7, 22.2, 21.0, 21.0. Anal. Calcd for $C_{18}H_{26}N_2O$: C, 75.48; H, 9.15; N, 9.78. Found: C, 75.58; H, 9.33; N, 10.18.

Data for (3*S*,8a*S*)-3-Isobutyl-1-(4-methylphenyl)hexahydroimidazo[1,2-*a*]pyridin-2(3*H*)-one (22′c): colorless oil; $[\alpha]^{25}_D = +79.1$ (*c* 2.33, $CHCl_3$); $R_f = 0.50$ (hexanes:EtOAc = 3:1); ^{1}H NMR δ 7.17 (d, $J = 8.7$ Hz, 2H), 7.09 (d, $J = 8.4$ Hz, 2H), 3.96 [d, $J = 9.6$ Hz, 1H, H(8a)], 3.10 (d, $J = 10.8$ Hz, 1H), 2.98−2.90 [m, 1H, H(3)], 2.35−2.24 (m, 4H), 2.10−1.22 (m, 9H), 0.99 (d, $J = 7.2$ Hz, 3H), 0.96 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR δ 173.3 (C═O), 135.6, 133.1, 129.3, 124.3, 77.7, 62.6, 48.0, 37.4, 28.7, 25.0, 24.9, 23.2, 22.7, 22.6, 20.9. Anal. Calcd for $C_{18}H_{26}N_2O$: C, 75.48; H, 9.15; N, 9.78. Found: C, 75.62; H, 9.52; N, 10.14.

Data for (3*S*,8a*R*)-3-Benzyl-1-(4-methylphenyl)hexahydroimidazo[1,2-*a*]pyridin-2(3*H*)-one (22d): colorless oil; $[\alpha]^{25}_D = -18.1$ (*c* 1.80, $CHCl_3$); $R_f = 0.43$ (hexanes:EtOAc = 3:1); ^{1}H NMR δ 7.33−7.24 (m, 4H), 7.24−7.18 (m, 1H), 7.16 (d, $J = 8.1$ Hz, 2H), 7.04 (d, $J = 8.4$ Hz, 2H), 3.94 [d, $J = 10.2$ Hz, 1H, H(8a)], 3.34 (dd, $J = 15.5$, 4.0 Hz, 1H), 3.34−3.26 [m, 1H, H(3)], 2.98 (dt, $J = 7.5$, 7.5 Hz, 1H), 2.92−2.82 (m, 1H), 2.32 (s, 3H), 2.26−2.14 (m, 1H), 1.94−1.74 (m, 2H), 1.62−1.50 (m, 2H), 1.42−1.12 (m, 2H); ^{13}C NMR δ 172.1 (C═O), 138.7, 136.0, 132.9, 129.5, 129.4, 128.0, 126.1, 124.6, 77.9, 65.3, 48.5, 36.1, 28.8, 25.0, 22.7, 21.0; HRMS *m*/*z* calcd for $C_{21}H_{25}N_2O$ 321.1967 (M + 1), found 321.1970. Anal. Calcd for $C_{21}H_{24}N_2O$: H, 7.55; N, 8.74. Found: H, 7.61; N, 8.66.

Supporting Information Available: Characterization data for compounds **11b**−**d**, **12b**−**d**, **15b**, **17b,c**, and **21a**−**d** and ^{1}H and ^{13}C spectra for **17a,c** and **18a,c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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