JOC*Note*

[4+2] Cycloaddition of 2-Substituted 1,2-Dihydropyridines with Nitrosobenzene: Asymmetric Synthesis of *trans*-2-Substituted 3-Amino-1,2,3,6-tetrahydropyridines

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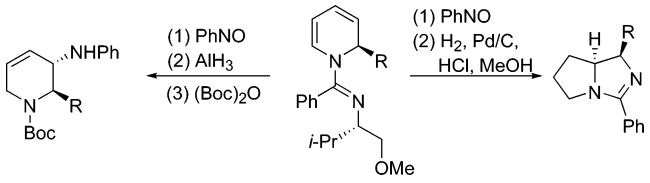

A new methodology for the stereoselective synthesis of *trans*-2-substituted 3-amino-1,2,3,6-tetrahydropyridines is reported. The preparation of these 3-aminopiperidines is achieved by cycloaddition of nitrosobenzene with 2-substituted 1,2-dihydropyridines followed by chemoselective reduction of the cycloadducts. Enantioenriched 1,2-dihydropyridine derivatives are easily prepared from pyridine and a chiral amide following a previous report from our laboratories. Moreover, the in situ hydrogenation of these cycloadducts over palladium in a solution of hydrogen chloride in methanol led to tetrahydropyrroloimidazoles.

The piperidine subunit is one of the most prominent pharmacophores found in biologically active compounds. The development of stereocontrolled syntheses of substituted piperidines has been the focus of many studies during the past decade.[1] Many 2,3-disubstituted piperidines are known to exhibit unique biological activities,[2] therefore creating a great demand for the efficient synthesis of this motif.

We have recently reported that organomagnesium and diorganozinc nucleophiles readily add to pyridinium imidates bearing a valinol-derived auxiliary to afford 2-subtituted 1,2-dihydropyridines with excellent regio- and diastereocontrol.[3] In an effort to extend the scope of this methodology toward the synthesis of polysubstituted piperidines, we further reported an expedient approach to *cis*-2,3-disubtituted piperidines. These piperidines were synthesized by diastereoselective hydrogenation of 2,3-disubtituted 1,2-dihydropyridines, which were prepared by nucleophilic addition to 3-substituted pyridinium imidates. Two substance P antagonists, (−)-L-733,061 (**1**) and (−)-CP-99,994 (**2**), were successfully prepared using this methodology.[4] In the initial attempts toward the synthesis of **1** and **2**, we found that hydrogenation of the dihydropyridine derivative **5** over palladium afforded 2-phenyl-3-triisopropylsilylpiperidinol **6** with a *trans*-2,3 relative stereochemistry, without any trace of the *cis* stereoisomer (Scheme 1). However, not only were the yields unsatisfactory, but the corresponding 1,2,5,6-tetrahydropyridine **7** was also isolated in similar yield as a result of an incomplete hydrogenation. The use of harsher conditions was unsuccessful, as the aromatic rings of **7** were hydrogenated faster than the enol ether. Numerous attempts to improve this result failed. A new route to access the 2,3-*trans* stereoisomer of 2,3-disubstituted piperidines was required and is reported in this Note.

To circumvent this problem, it was envisioned that the introduction of the 3-substituent could be achieved at a later stage. To this end, we turned our attention to a [4+2] cycloaddition,[5] since many 1,2-dihydropyridines have been efficiently transformed into highly substituted piperidines by relying on such a strategy.[6,7] We focused on nitrosoarenes[8,9] as reactive dienophiles to introduce the required stereocenter at C-3, which would be unveiled upon reductive opening of the bicyclic system.

We first chose to investigate the cycloaddition reaction between 2-phenyl-1,2-dihydropyridine **8a** and nitrosobenzene. When the reaction was carried out with equimolar

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(1) For recent reviews on the stereoselective synthesis of piperidines, see: (a) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701−1729. (b) Felpin, F.-X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, 3693−3712. (c) Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953−2989. For a recent review on dihydropyridines, see: (d) Lavilla, R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1141−1156.

(2) For examples of biologically active *trans*-2,3-disubstituted piperidines, see: (a) Desideri, N.; Galli, A.; Sestili, J.; Stein, M. L. *Arch. Pharm.* **1992**, *325*, 29−34. (b) Kobayashi, S.; Ueno, M.; Suzuki, R.; Ishitani, H.; Kim, H.-S.; Wataya, Y. *J. Org. Chem.* **1999**, *64*, 6833−6841. For examples of biologically active *cis*-2,3-disubstituted piperidines, see: (c) Harrison, T.; Williams, B. J.; Swain, C. J.; Ball, R. G. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2545. (d) Desai, M. C.; Lefkowitz, S. L.; Thadeio, P. F.; Longo, K. P.; Snider, R. M. *J. Med. Chem.* **1992**, *35*, 4911.

(3) Charette, A. B.; Grenon, M.; Lemire, A.; Pourashraf, M.; Martel, J. *J. Am. Chem. Soc.* **2001**, *123*, 11829−11830.

(4) Lemire, A.; Grenon, M.; Pourashraf, M.; Charette, A. B. *Org. Lett.* **2004**, *6*, 3517−3520.

(5) For reviews, see: (a) Dell, C. P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3873−3905. (b) Tietze, L. F.; Kettschau, G. *Top. Curr. Chem.* **1997**, *189*, 1−120.

(6) (a) For an enantioselective reaction, see: Takenaka, N.; Huang, Y.; Rawal, V. H. *Tetrahedron* **2002**, *58*, 8299−8305. (b) For a diastereoselective reaction, see: dos Santos, D. C.; de Freitas Gil, R. P.; Gil, L.; Marazano, C. *Tetrahedron Lett.* **2001**, *42*, 6109−6111. (c) For a racemic reaction, see: Arakawa, Y.; Murakami, T.; Ozawa, F.; Arakawa, Y.; Yoshifuji, S. *Tetrahedron* **2003**, *59*, 7555−7563. (d) For an intramolecular reaction, see: Comins, D. L.; Brooks, C. A.; Al-awar, R. S.; Goehring, R. R. *Org. Lett.* **1999**, *1*, 229−231. (e) For reaction with a *N*-tosylpyridone, see: Lorthiois, E.; Meyyappan, M.; Vasella, A. *Chem. Commun.* **2000**, 1829−1830.

(7) For a review on stereocontrolled additions to di- and tetrahydropyridines, see: Kumar, R.; Chandra, R. *Adv. Heterocycl. Chem.* **2001**, *78*, 269−313.

(8) For reviews on *C*-nitroso compounds, see: (a) Lee, J.; Chen, L.; West, A. H.; Richter-Addo, G. B. *Chem. Rev.* **2002**, *102*, 1019−1065. (b) Adam, W.; Krebs, O. *Chem. Rev.* **2003**, *103*, 4136−4146. For an enantioselective hetero-Diels−Alder reaction, see: (c) Yamamoto, Y.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 4128−4129.

(9) For reactions with dihydropyridines, see: (a) Knaus, E. E.; Avasthi, K. *Can. J. Chem.* **1980**, *58*, 2447−2451. (b) Dubey, S. K.; Knaus, E. E. *J. Org. Chem.* **1985**, *50*, 2080−2086. For use in the synthesis of racemic diaminosugar derivatives, see: (c) Augelmann, G.; Streith, J.; Fritz, H. *Helv. Chim. Acta* **1985**, *68*, 95−103. (d) Streith, J.; Defoin, A. *Synlett* **1996**, 189−200.

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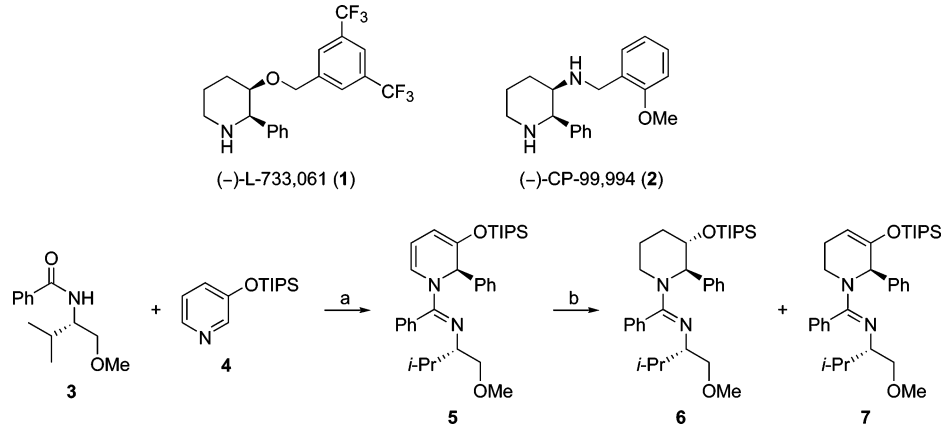
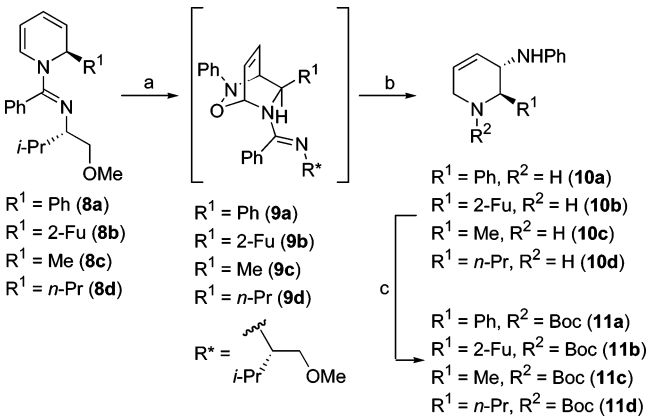
SCHEME 1[a]



[a] Reagents and conditions: (a) amide **3**, pyridine **4** (3 equiv), Tf_2O, CH_2Cl_2, −40 °C to rt, then PhMgBr, −78 °C (57%); (b) H_2 (1 atm), Pd 10%/C, MeOH, rt (**6**: 26%; **7**: 36%).

SCHEME 2[a]



[a] Reagents and conditions: (a) nitrosobenzene, benzene, rt; (b) AlH_3, Et_2O, 0 °C to rt; (c) $(Boc)_2O$, THF, 2.0 M NaOH, rt (**8a**: 89%; **8b**: 68%; **8c**: 71%; **8d**: 55%, 3 steps).

quantities, formation of [2,2,2]-bicycloadduct **9a** was observed in 90% conversion within an hour (Scheme 2). No further increase in conversion was observed beyond this point, and partial degradation to 2-phenylpyridine and other decomposition products appeared over time. Two equivalents of nitrosobenzene were found to be necessary to obtain >95% conversion to adduct **9a**. Early attempts to purify the hetero-Diels−Alder adduct over silica gel resulted in decomposition. This was circumvented by pretreating the silica gel with triethylamine, which allowed the isolation of a mixture of **9a** and starting material **8a** in a 3:1 ratio, respectively. This suggested that an equilibrium existed between **8a** and **9a**;[10] therefore, we favored an approach involving the in situ reduction of **9a**. When *N*-nitrosopyrrolidine was used as the heterodienophile, no reaction occurred after 2 days with 1.2 to 6 equiv of *N*-nitrosopyrrolidine.

While lithium aluminum hydride proved to be unsatisfactory in the reduction of adduct **9a**, alane was found to be an effective reagent for the desired transformation.[11] The latter reduction provided 1,2,3,6-tetrahydropiperidine **10a** in excellent yield (95% by ^{1}H NMR, based on internal standard), but separation of **10a** from the *N*-benzyl-*O*-methylvalinol chiral auxiliary residue proved difficult. Both compounds coelute by silica gel chromatography under various solvent systems, and the hydrochloride salt of **10a** decomposes. It was found that isolation of the mono-*tert*-butoxycarbonyl (Boc) derivative was far easier, affording diastereomerically pure (>98% de) and enantioenriched (98% ee) **11a** in 89% yield over 3 steps. Along with **11a** was isolated *N*-benzyl-*N*-Boc-*O*-methylvalinol (45%) as well as its demethylated derivative (32%, see the Experimental Section), and both were easily separable upon flash chromatography. This facile 3-step sequence was then applied to 2-substituted-1,2-dihydropyridines **8b**−**d**, which afforded **11b**−**d** in 68%, 71%, and 55% yields, respectively. We were pleased to obtain **11c** as a crystalline solid and analysis of the X-ray crystal structure proved unambiguously the *trans* relation between the 2-substituent and the 3-amino group on the piperidine ring (see the Supporting Information). The chemoselective alane reduction of the hetero-Diels−Alder products **9** efficiently reduced the aminal function, the N−O bond, as well as the amidine group, in one step, leading directly to **10**. The Δ-4,5-alkene functionality remained on the piperidine, allowing for further functionalization or reduction. Interestingly, the reduction of **9** to **10** drives the equilibrium, as neither **8** nor any of its reduced forms were found in the crude reaction mixture. One drawback of the methodology is that a nondeprotectable phenylamine is obtained. The use of *p*-methoxynitrosobenzene would allow for oxidative deprotection of the obtained aniline with ceric ammonium nitrate.[12] The use of *N*-acyl or *N*-carbamoyl nitroso compounds as heterodienophile will reverse the regioselectivity of the cycloaddition.[9b,d]

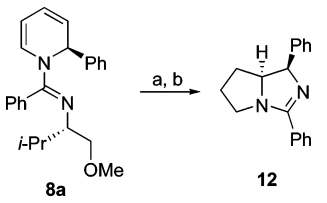
During our investigation of the reduction of **9a** to **10a**, we found that hydrogenation of **9a** over palladium on charcoal in a solution of hydrogen chloride in methanol produced a totally unexpected compound in 61% isolated yield, based on the molecular weight (LCMS-APCI). This compound did not bear the chiral auxiliary, nor the phenyl hydroxylamine subunit. After extensive NMR

(10) This equilibrium has been observed on a similar system, see ref 9c.

(11) See ref 4 for use of AlH_3 in the reduction of amidines.

(12) Yao, S.; Saaby, S.; Hazell, R. G.; Jørgensen, K. A. *Chem. Eur. J.* **2000**, *6*, 2435−2448.

SCHEME 3[a]



[a] Reagents and conditions: (a) nitrosobenzene, benzene, rt; (b) H_2 (1 bar), 10% Pd/C, 0.3 M HCl/MeOH, rt (61%, 2 steps).

studies (COSY, NOESY, HMBC, HMQC), it became clear that this compound was (1*R*,7a*S*)-1,3-diphenyl-5,6,7,7a-tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazole (**12**; Scheme 3). No other diastereoisomer was observed, and the enantiomeric purity of **12** was 82% ee, thus it was clear that racemization occurred to some extent during this process.

A mechanism consistent with the formation of this product is shown in Scheme 4. Many of the steps are interchangeable, but the end product is the same. The partial racemization observed could occur by epimerization of the phenyl-substituted carbon adjacent to the imine produced after the cleavage of the bicycloadduct. However, if a different mechanism operates, one could propose a competition of a S_N1 and S_N2 process under the strongly acidic conditions. This reaction establishes a new approach for the preparation of enantioenriched 2-substituted pyrrolidines bearing an α-chiral secondary amine. The generality, the scope, and mechanistic aspects of this reaction are under investigation in our laboratories.

Experimental Section

***N*-[(1*E*)-[(1*S*,4*R*,6*R*)-2,6-Diphenyl-3-oxa-2,5-diazabicyclo-[2.2.2]oct-7-en-5-yl](phenyl)methylene]-*N*-[(1*S*)-1-(methoxymethyl)-2-methylpropyl]amine (9a).** Nitrosobenzene (24 mg, 0.22 mmol) and dihydropyridine derivative **8a** (40 mg, 0.11 mmol) were dissolved in C_6D_6 (1 mL) and charged in an oven-dried NMR tube and the resultant golden-brown solution was left to stand for 2 h at room temperature: ^{1}H NMR (C_6D_6, 400 MHz) δ 7.33 (br s, 4H), 7.21 (br m, 3H), 7.11 (br m, 5H), 6.93 (m, 2H), 6.84 (t, J = 7.2 Hz, 1H), 5.97 (s, 1H), 5.90 (br m, 1H), 5.42 (br s, 1H), 5.40 (t, J = 6.6 Hz, 1H), 4.44 (s, 1H), 3.09 (m, 2H), 2.81 (s, 3H), 2.74 (br s, 1H), 1.77 (m, 1H), 1.01 (d, J = 6.8 Hz, 3H), 0.88 (d, J = 6.8 Hz, 3H); ^{13}C NMR (C_6D_6, 75 MHz) δ 158.4, 152.0, 141.2, 135.0, 130.9, 129.3, 129.3, 129.1 (2C), 129.0 (2C), 128.7, 128.3 (2C), 127.8 (2C), 127.3 (2C), 123.0, 122.8, 118.1 (2C), 76.2, 64.3, 63.6, 59.2, 58.8, 31.2, 20.7, 18.6; FTIR (neat) 3062, 3029, 2958, 2927, 2873, 1634, 1597, 1489, 1452, 1377, 1344, 1301, 1113, 1019, 846, 757, 700 cm^{-1}; LRMS (APCI) calcd for $C_{30}H_{34}N_3O_2$ (M + H)$^+$ 468.3, found 468.2.

***tert*-Butyl (2*R*,3*S*)-3-Anilino-2-phenyl-3,6-dihydropyridine-1(2*H*)-carboxylate (11a).** Nitrosobenzene (71 mg, 0.663 mmol) and dihydropyridine derivative **8a** (200 mg, 0.555 mmol) were charged in an oven-dried, 10-mL round-bottomed flask then dissolved in benzene (4 mL), and the resultant golden-brown solution was stirred for 2 h at room temperature. In a separate flame-dried 50-mL round-bottomed flask, lithium aluminum hydride (253 mg, 6.66 mmol) was suspended in Et_2O (8 mL), the solution was cooled to 0−5 °C by means of an ice−water bath, followed by slow addition of aluminum chloride (6 mL of a 0.37 M solution in Et_2O, 2.22 mmol), and the light gray suspension was stirred for 15 min. The previously prepared solution of cycloadduct (**9a**) was diluted with Et_2O (6 mL) and slowly added to the freshly prepared alane suspension via a syringe. The resultant light-yellow suspension was then warmed to room temperature and stirred for 16 h. The reaction was quenched by slow addition of the resultant suspension to a heavily stirred biphasic solution of Et_2O (50 mL), saturated aqueous sodium−potassium tartrate (50 mL), and 2.0 M aqueous NaOH (1.5 mL). After 3 h of vigorous stirring, two clear phases were obtained and separated. The aqueous phase was extracted with CH_2Cl_2 (4 × 25 mL), and the organic phases were combined, dried over potassium carbonate, filtered, and concentrated under reduced pressure, which afforded 282 mg of a yellow-orange oil. The oily residue and di-*tert*-butyl dicarbonate (484 mg, 2.22 mmol) were charged in a 25-mL, round-bottomed flask then dissolved in THF (2.5 mL) and 2.0 M aqueous NaOH (2.5 mL), and the resultant mixture was stirred for 60 min. The reaction mixture was extracted with CH_2Cl_2 (4 × 10 mL), and the organic phases were combined, dried over sodium sulfate, filtered, and concentrated under reduced pressure, which afforded 530 mg of an orange oil. Flash chromatography of the oily residue was performed using EtOAc/hexane (gradient 0:100−10:90), which afforded 173 mg of **11a** (89%) as a colorless oil: R_f 0.24 (EtOAc/hexane, 15:85); $[\alpha]^{20}_D$ 16.7 (*c* 2.22, C_6H_6); ^{1}H NMR (C_6D_6, 400 MHz) δ 7.31 (br s, 2H), 7.20−7.12 (m, 3H), 7.12−7.02 (m, 2H), 6.71 (t, J = 7.3 Hz, 1H), 6.43 (d, J = 7.8 Hz, 2H), 5.76 (br s, 1H), 5.71 (br s, 1H), 5.38 (dq, J = 10.0, 2.0 Hz, 1H), 4.57 (br m, 1H), 4.26 (br s, 1H), 3.62 (br s, 1H), 3.22 (d, J = 19.0 Hz, 1H), 1.29 (s, 9H); ^{1}H NMR (C_6D_6, 400 MHz, 70 °C) δ 7.33 (d, 2H), 7.20−7.12 (m, 3H), 7.12−7.03 (m, 2H), 6.69 (tt, J = 7.3, 0.9 Hz, 1H), 6.57 (dd, J = 8.6, 0.9 Hz, 2H), 5.77 (br m, 2H), 5.47 (dqd, J = 10.2, 1.8, 0.7 Hz, 1H), 4.50 (br d, J = 8.6 Hz, 1H), 4.27 (br s, 1H), 3.61 (br s, 1H), 3.27 (dq, J = 19.2, 2.3 Hz, 1H), 1.32 (s, 9H); ^{13}C NMR (C_6D_6, 75 MHz) δ 155.5, 147.2 (2C), 139.8, 129.7, 128.8 (2C), 128.1, 127.8 (2C) 127.6, 124.6, 118.3, 114.0 (2C), 79.7, 54.8, 49.5, 40.1, 28.3 (3C); FTIR (neat) 3369, 2975, 2930, 1691, 1658, 1602, 1500, 1413, 1364, 1308, 1254, 1168, 1119, 749, 695 cm^{-1}; LRMS (APCI) calcd for $C_{22}H_{27}N_2O_2$ (M + H)$^+$ 351.2, found 351.1. The enantiomeric purity of **11a** was determined as 98% ee by HPLC analysis (Chiralpak AD-H, 95:5 *n*-hexane:*i*-PrOH, 1.0 mL/min: (−)-**11a**, t_r = 7.7 min; (+)-**11a**, t_r = 10.9 min).

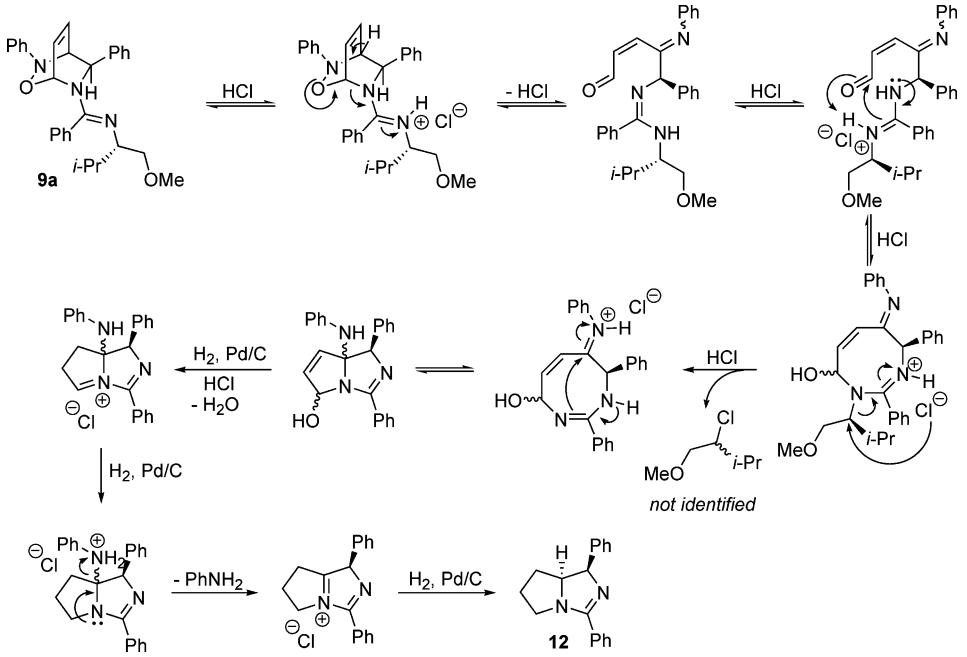
From the same reaction mixture was isolated 76 mg of ***tert*-butyl benzyl[(1*S*)-1-(methoxymethyl)-2-methylpropyl]carbamate (or *N*-benzyl-*N*-Boc-*O*-methylvalinol)** (45%) as a colorless oil: R_f 0.40 (EtOAc/hexane, 15:85); $[\alpha]^{20}_D$ −12.4 (*c* 1.23, C_6H_6); ^{1}H NMR (C_6D_6, 400 MHz, 70 °C) δ 7.34 (d, J = 7.4 Hz, 2H), 7.18−7.11 (m, 2H) 7.06 (t, J = 7.4 Hz, 1H), 4.51 (br m, 1H), 4.32 (d, J = 15.6, 1H), 3.82 (br s, 1H), 3.43 (br m, 1H), 3.34 (dd, J = 10.2, 3.7 Hz, 1 H), 2.90 (s, 3H), 1.94 (br m, 1H), 1.38 (s, 9H), 0.84 (m, 6H); ^{13}C NMR (C_6D_6, 100 MHz, 70 °C) δ 156.7, 141.4, 128.6 (3C), 127.1 (2C), 79.6, 74.0, 63.8, 58.5, 50.4, 29.3, 28.9 (3C), 20.8 (2C); FTIR (neat) 3435, 2974, 2930, 1690, 1454, 1409, 1389, 1249, 1166, 1113, 772, 734, 700 cm^{-1}; LRMS (APCI) calcd for $C_{18}H_{30}NO_3$ (M + H)$^+$ 308.2, found 308.2. Anal. calcd for $C_{18}H_{29}NO_3$: C, 70.32; H, 9.51; N, 4.56. Found: C, 70.45; H, 9.58; N, 4.62.

From the same reaction mixture was isolated 52 mg of ***tert*-butyl benzyl[(1*S*)-1-(hydroxymethyl)-2-methylpropyl]carbamate (or *N*-benzyl-*N*-Boc-valinol)**[13] (32%) as a colorless oil: R_f 0.15 (EtOAc/hexane, 15:85); $[\alpha]^{20}_D$ −20.1 (*c* 2.66, C_6H_6); ^{1}H NMR (C_6D_6, 400 MHz, 70 °C) δ 7.29 (d, J = 7.4 Hz, 2H), 7.18−7.11 (m, 2H), 7.06 (t, J = 7.4 Hz, 1H), 4.32 (d, J = 15.4, 1H), 4.21 (br m, 1H), 3.66 (br m, 2H), 3.27 (br m, 1H), 2.19 (br s, 1H), 1.37 (s, 9H), 1.67 (d, J = 1.6 Hz, 3H), 0.83 (d, J = 1.8 Hz, 3H); ^{13}C NMR (C_6D_6, 100 MHz, 70 °C) δ 157.5, 140.5, 129.0 (3C), 127.7 (2C), 80.3, 68.2, 63.9, 52.3, 28.8 (3C), 28.2, 20.8, 20.7; FTIR (neat) 3436, 2972, 2875, 1668, 1605, 1455, 1411, 1367, 1250, 1166, 1110, 1076, 865, 737, 701 cm^{-1}; LRMS (APCI) calcd for $C_{17}H_{28}NO_3$ (M + H)$^+$ 294.2, found 294.1. Anal. calcd for $C_{17}H_{27}NO_3$: C, 69.59; H, 9.28; N, 4.77. Found: C, 69.43; H, 9.28; N, 4.78.

(1*R*,7a*S*)-1,3-Diphenyl-5,6,7,7a-tetrahydro-1*H*-pyrrolo-[1,2-*c*]imidazole (12). Nitrosobenzene (71 mg, 0.663 mmol) and dihydropyridine derivative **8a** (200 mg, 0.555 mmol) were charged in a 10-mL, round-bottomed flask and dissolved in benzene (4 mL), and the resulting golden-brown solution was

(13) Márquez, F.; Montoro, R.; Llebaria, A.; Lago, E.; Molins, E.; Delgado, A. *J. Org. Chem.* **2002**, *67*, 308−311.

SCHEME 4



stirred for 2 h at room temperature. The solution was evaporated to dryness under reduced pressure, the obtained sticky residue was dissolved with 0.3 M HCl solution in MeOH (8 mL), and 10% Pd/C (40 mg, 37.6 μmol Pd) was added. The pale yellow solution was then stirred under an atmosphere of hydrogen for 18 h after which the resultant solution was poured into NaOH (2 M, 25 mL) and the resulting mixture extracted with CH_2Cl_2 (4 × 25 mL). Organic phases were combined, dried over sodium sulfate, filtered over activated charcoal/Celite, and concentrated under reduced pressure, which afforded 206 mg of an orange oil. Flash chromatography of the oily residue was performed using MeOH/CH_2Cl_2 (gradient 1:99−10:90), which afforded 90 mg of **12** (61%) as a colorless oil: R_f 0.16 (MeOH/CH_2Cl_2, 05:95); $[\alpha]^{20}_D$ −1.24 (*c* 1.13, C_6H_6); ^{1}H NMR (C_6D_6, 400 MHz) δ 8.06 (dd, J = 7.8, 1.5 Hz, 2H), 7.42 (d, J = 7.4 Hz, 2H), 7.28 (t, J = 7.5 Hz, 2H), 7.24−7.10 (m, 4H), 5.43 (d, J = 10.3 Hz, 1H), 4.00 (dd, J = 10.2 Hz, 7.7 Hz, 1H), 2.95 (t, J = 6.9 Hz, 2H), 1.15 (m, 2H), 0.90 (m, 2H); ^{13}C NMR (C_6D_6, 75 MHz) δ 169.2, 142.1 (2C), 132.8, 130.7 (2C), 129.7 (2C), 129.2, 128.2, 127.2 (2C), 70.4, 69.4, 50.8, 45.8, 27.7, 26.4; FTIR (neat) 3059, 3026, 2965, 2887, 1609, 1598, 1591, 1494, 1447, 1365, 1254, 1098, 1028, 782, 763, 720, 698 cm^{-1}; LRMS (APCI) calcd for $C_{18}H_{19}N_2$ (M + H)$^+$ 263.2, found 263.1. The enantiomeric purity of **12** was determined as 82% ee by HPLC analysis (Chiralpak AD-H, 89.1:10.0:0.9 hexane:*i*-PrOH:Et_2NH, 1.0 mL/min: (+)-**12**, t_r = 11.8 min; (−)-**12**, t_r = 14.3 min).

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Supporting Information Available: General information, experimental procedures, and characterization data for the synthesis of **4**−**7**, **8d**, and **11b**−**d**, and ^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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