JOC Article

Concise and Stereocontrolled Synthesis of Pseudo-C_2-symmetric Diamino Alcohols and Triamines for Use in HIV Protease Inhibitors

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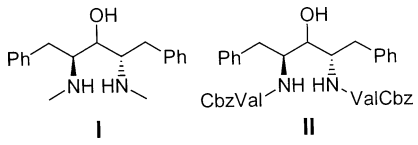
A new protocol is described for the stereocontrolled synthesis of pseudo-C_2-symmetric core units of interest as candidates for HIV protease inhibition. Addition of unbranched and branched organolithium reagents to cyanohydrins from L-phenylalaninal and L-isoleucinal, followed by in situ reduction of the intermediate imines and CHT deprotection under MW irradiation, led to 1,3-diamino alcohols **6a** and **8a** as the major products in satisfactory to good yields. The first preparation of a previously unreported pseudo-C_2-symmetric triamino derivative was accomplished expeditiously via high-yielding nitro-Mannich addition of the silylnitronate, from 2-phenyl-1-nitroethane, to the PMP imine derived from L-phenylalaninal. Reduction of the nitro group in the moderately unstable nitro diamine adduct, followed by chromatographic separation of the required diastereoisomer and CHT debenzylation under MW irradiation, led to the 2-PMP-protected triamine **19** isolated as a bis(sulfonamide).

Introduction

Inhibitors of HIV-protease are effective against the proliferation of HIV-1 infection in vitro. On the basis of the inherent symmetry of the protease homodimer, C_2-symmetric and pseudo-C_2-symmetric molecules have been designed, synthesized, and demonstrated to be potent inhibitors. The hypothesis that the C_2-symmetric inhibitors comprised of a key diamino unit flanked by acyl groups would be recognized and bound by this homodimeric retroviral protease led to a great deal of synthetic efforts aimed at the synthesis of stereochemically defined molecules possessing the diamino diol and the diamino alcohol cores. A complementary interest in the synthesis of these compounds lies moreover on their ability to act as multidentate chiral ligands able to impart asymmetry to transition and main group elements.[1]



The synthesis of a series of pseudo-C_2-symmetric inhibitors derived from the core diamine **I**, culminating in the identification of the highly selective and efficient A-74704 (**II**),[2] has been reported in which the key steps are the 2C-homologation of phenylalaninal and a double-bond epoxidation.[3]

Moreover, other efficient syntheses of **I** based on the SAMP/RAMP hydrazone method[4] and starting from N-Boc hydroxylactams have been published in which the absolute stereochemistry was derived from an amino acid source.[5] More recently a stereochemically flexible entry to the 1,3-diamino propanol units has been devised via organometallic addition of chiral aldehydes to nitrones leading to a diamino alcohol stereotriad.[6] Furthermore, a synthetic protocol was proposed on the basis of a ruthenium-catalyzed asymmetric reduction of a bis-cinnamic acid derivative.[7]

We now report an alternative approach to this diamino alcohol core unit by using a concise synthetic route starting from easily available nonracemic materials.

[†] Università di Bologna.
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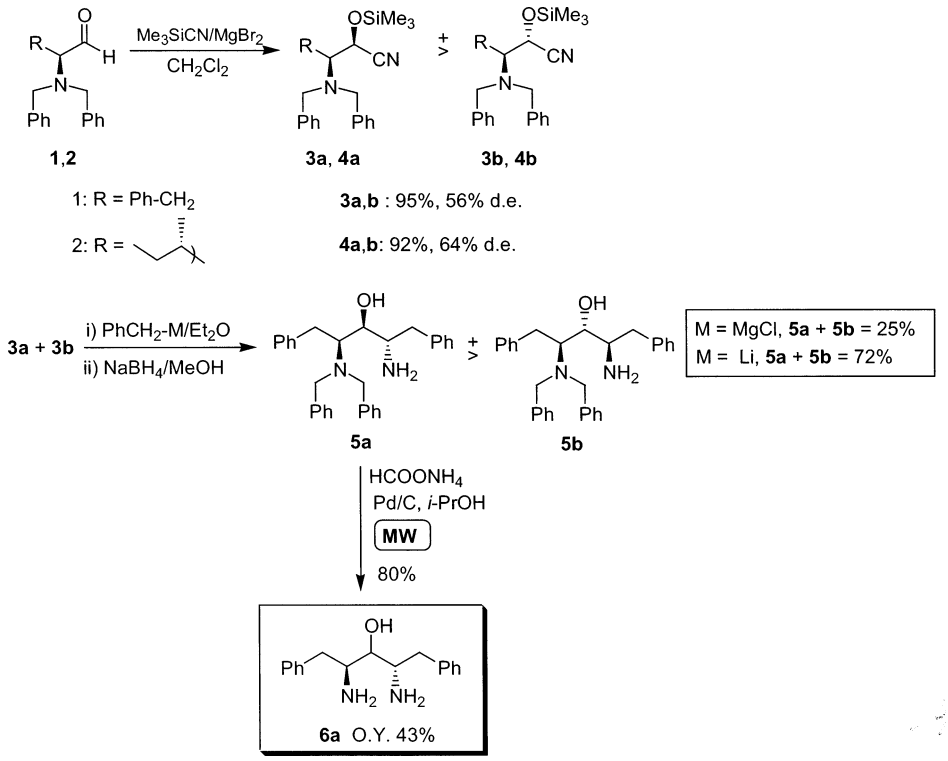
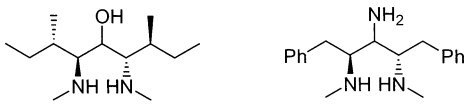
SCHEME 1



Since desirable features in an HIV protease inhibitor would include hydrophobic sites to project into the specific pockets of the enzyme[8] and hydrogen-bond donors to interact with the carbonyl of Gly-27,[9] we have also addressed our efforts toward the synthesis of structural variants **III** and **IV** of the core key unit present in the inhibitor A-74704.

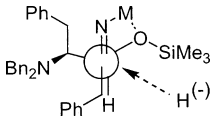


III **IV**

Results and Discussion

A linear pathway, shown in Scheme 1, was adopted. The key to the success of this approach was the ability to produce the protected cyanohydrins **3** and **4** in good overall yields and to induce their reactivity with the suitable organometallic reagents. Accordingly, *N*,*N*-dibenzyl-protected phenylalaninal **1**[10] obtained from L-phenylalanine, by sequential protection, $LiAlH_4$ reduction, and Swern oxidation, subjected to addition of Me_3SiCN in the presence of $MgBr_2$, led to **3a** + **3b** in 95% overall yields and with 56% de; in an analogous way, isoleucinal[11] led to **4a** + **4b** in 92% overall yield and 64% de.

These results showing a prevalence of the chelation-controlled adduct, matched well with those previously obtained by Reetz.[12] By virtue of its symmetry characteristic, the central carbon (C_3) of **I** is not stereogenic. However, even though control of the stereochemistry at that center would not be a requirement for the stereoselective syntheses of type **I** derivatives, its role in determining the configuration at C_4 must be recognized. To avoid risk of decomposition on silica gel, the diastereomeric mixture of **3a** + **3b** was used as such with the aim of performing the separation at a more advanced stage of the synthetic sequence. Since trimethylsilyl-protected cyanohydrins are usually stable under Grignard conditions,[13] a benzylmagnesium chloride addition was first carried out on **3a** + **3b** as depicted in Scheme 1 followed by the one-pot reduction of the intermediate imine.



In line with previous findings[14] highlighting the very high *erythro* selectivity in the sodium borohydride reduction of the intramolecularly chelated magnesiated imines, a mixture of two distinct diastereomeric *N*,*N*-dibenzyl-protected diamino alcohols **5a** and **5b** was obtained from this reaction though in modest yields (25% yield, 56% de). On the other hand, the use of benzyllithium from

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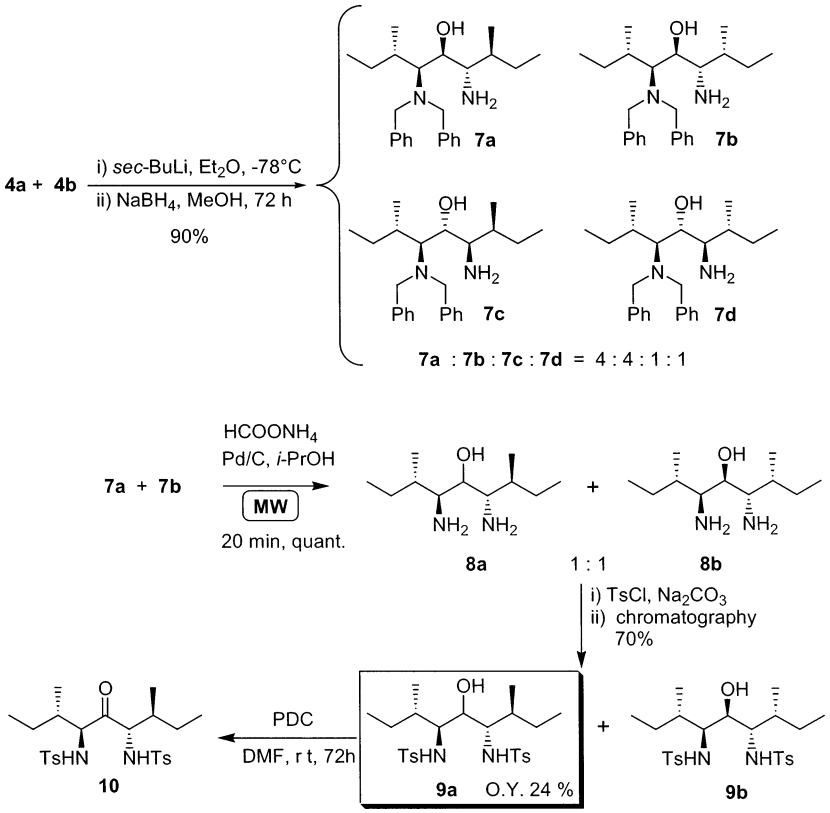
SCHEME 2



toluene, *n*-BuLi, and TMEDA led to a substantial improvement, the diamino alcohols **5a** and **5b** being isolated in a 78:22 ratio and 72% overall yields from **3a** + **3b**. Following this latter procedure, separation of the major optically active amino alcohol **5a** from the precursor of the *meso* form **5b** by silica gel chromatography, followed by removal of the protection at nitrogen by catalytic hydrogen transfer (CHT) methodology under MW irradiation,[15] afforded in quantitative yield the diamino alcohol **6a** with the structure and the stereochemistry of the desired core unit **I** (43% overall yield from **1**).

The synthesis of the isoleucine derivative was carried out (Scheme 2) by using small variations of the previously described sequence. For the addition to the cyano group in **4a**,**b**, *sec*-BuLi was the reagent of choice, no reaction at all being observed with the corresponding Grignard reagent. After in situ $NaBH_4$ reduction of the intermediate imine, adducts were obtained in 90% yield. This reduction is expected to occur giving rise to two couples of diastereoisomers in a 4:1 ratio whose stereochemistry should account, as in the previous case, for an anti relationship between the preexisting hydroxy moiety and the newly created amino function, in line with a chelation-controlled pathway. Diastereoisomers **7a** and **7b** coming from the major OTMS-cyanohydrin could be separated as a 1:1 mixture from the minor components in 72% combined yields by column chromatography.

After CHT removal of the protection at nitrogen, **8a** and **8b** could be separated by column chromatography only after derivatization (70% yield) of the free diamino alcohols into the corresponding sulfonamides: the ^{1}H and ^{13}C NMR spectra of these two isomers (**9a** and **9b**) present both sets of signals for the two sides of the chain, thus excluding the presence of a *meso* form. The product with a higher R_f (**9a**, R_f = 0.60, 1/1 EtOAc/hexane) was then oxidized at the alcoholic function: the ^{1}H and ^{13}C NMR spectra of this ketone (**10**) present only one set of signals for the two branches of the chain, thus demonstrating the pseudo-C_2-symmetry of its precursor, the diamino alcohol **9a** (24% from **4a** + **4b**).

With a convenient synthesis of **6a** and **9a** in hand, we turned our attention to the assembly of the vicinal triamine **IV**. The widely investigated 1,2-diamine structural motif is important in biologically active products, in medicinal chemistry, and more recently for use as chiral auxiliaries and chiral ligands in asymmetric catalysis.[16] Unfortunately, there are very few reports on the synthesis of stereodefined triamines despite their importance in a variety of physiological processes[17] and their ability to serve as versatile ligands for catalytic applications.[18] Addition of trimethylsilyl cyanide to the imine derived from the phenylalaninal in the presence of a Lewis acid ($MgBr_2$) occurred smoothly to give the

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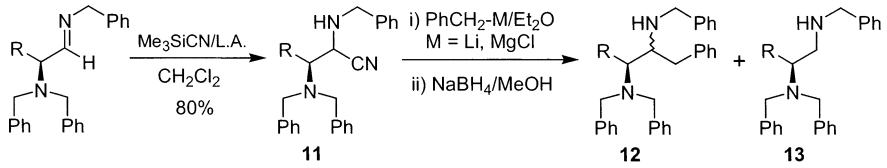
SCHEME 3



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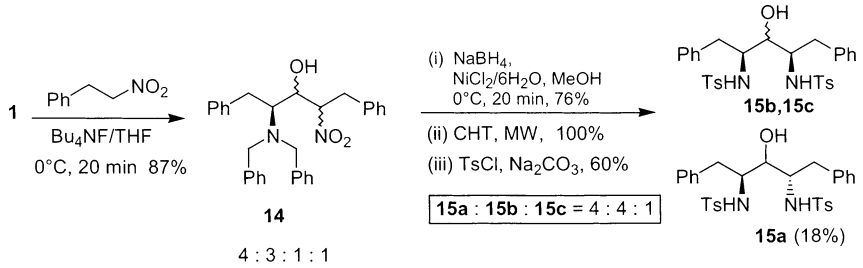

expected α-aminonitrile **11** in 80% yield.[19] However, in line with the previously observed[20] lability of α-aminonitriles toward basic reagents, when the Strecker adduct (**11**) was subjected to addition of benzylmagnesium chloride or benzyllithium, the cyano group was predominantly substituted by the benzyl group (Scheme 3), leading to compound **12** together with variable amounts of the diamine **13** from the in situ reduction of the starting imine formed from the α-aminonitrile via HCN elimination.

An alternative convergent approach to **IV** was therefore envisaged on the basis of the Henry or nitroaldol reaction, one of the classical name reactions in organic synthesis that have seen increasing in utilization.[21] Recently, several examples of the nitro-Mannich reaction have been reported disclosing a suitable entry to the stereoselective synthesis of 1,2-diamines.[22] On these grounds the reaction of 2-phenylnitroethane, used as a synthetic equivalent of an α-amino carbanionic synthon (**V**), was performed with suitable electrophiles.

V

For the sake of comparison with the procedure outlined in Scheme 1, we first applied this approach to the synthesis of **6a**. Reaction of the nitronate, generated in situ by TBAF deprotonation of 2-phenylnitroethane[23] with phenylalaninal, led (Scheme 4) after chromatography to a mixture of four diastereoisomers of **14** in a 4:3:1:1 ratio and in 87% combined yields. Compared to the synthesis previously reported in Scheme 1, this latter procedure, though more straightforward and high yielding, is hampered by the low stereoselectivity of the coupling. Moreover, attempts at performing the one-step NO_2 reduction−deprotection with thermal or MW-induced CHT were unsuccessful. For this reason, reduction of the nitro group was performed at first by using the $NaBH_4/NiCl_2 \cdot 6H_2O$ combination as a reducing system,[24] leading in 76% yield to a diastereomeric mixture of the protected diamino alcohols. The subsequent CHT deprotection occurred smoothly and afforded in quantitative yield the stereotriad of one optically active and two *meso* diamino alcohols in a 4:4:1 ratio, respectively. From this mixture, after derivatization to sulfonamides and column chromatography, compound **15a** could be isolated in 18% overall yield from **1**.

Encouraged by the above results, we turned finally to the assembly of the backbone **IV**. To this end, a three-step sequence was devised on the basis of the use of imine **16** as the 4-methoxyphenyl (PMP) group can be easily removed using CAN[25] and favors the coordination of the imine nitrogen with a Lewis acid.[22a] The reaction sequence took place as shown in Scheme 5. Addition of the silylnitronate[26] to the imine **16** was screened for different Lewis acids. After several attempts, the best route involved the use of catalytic (5%) $Sc(OTf)_3$.[27] Although this Lewis acid turned out to be efficient at catalyzing the addition of the silyl nitronate to the PMP-imine, the diastereomeric ratio was poor. The nitroadducts could be isolated in 68% yield after column chromatography as a mixture of two diastereoisomers **17a**,**b** (60:40, ^{1}H NMR). On a second run, to avoid the already reported retro-Henry reaction[22a] that partially occurred on silica gel, the crude adducts **17a**,**b** were directly subjected to reduction using the $NaBH_4/NiCl_2$-based protocol.[24] After separation on deactivated silica, the protected triamines **18a** and **18b** could be isolated as single diastereoisomers in 66% overall yield starting from the imine **16**.

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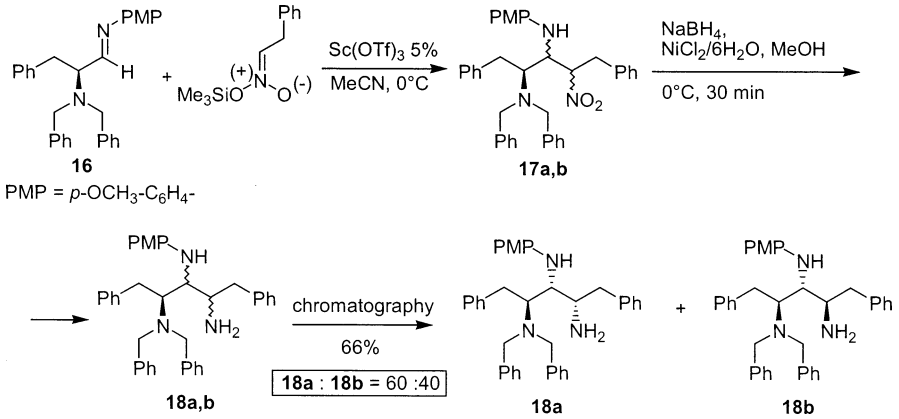
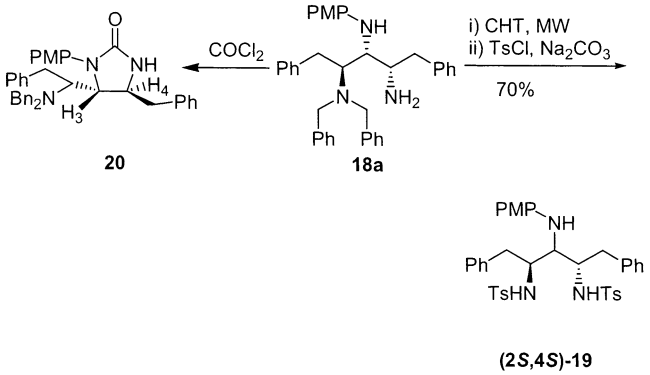
SCHEME 5



SCHEME 6



From X-ray analysis, the configuration of the minor diastereoisomer **18b**[28] was established to be (2*S*,3*R*,4*R*), thus making this compound a precursor of the *meso* triamine (2*S*,3*s*,4*R*). CHT debenzylation of the major component **18a**, followed by TsCl derivatization, afforded the optically active compound **19** in 70% isolated yield, thus allowing assignment of the (*S*) configuration at C_4 (Scheme 6). Finally, the stereochemistry at C_3 of **18a** was tentatively assigned by means of NOE experiments on its cyclic derivative **20**, which suggested a trans relationship between H_3 and H_4.

Conclusion

In summary the results presented here provide a practical and stereoselective synthesis of the enantiopure pseudo-C_2-symmetric 1,3-diamino-2-propanol units **6a** and **8a**. The explored overall process may serve as one of the most practical synthetic methods of these core key units because of its directness and operational simplicity. A stereoselective nitro-Mannich reaction based on an enantiomerically pure imine gave access to the novel triamino derivative **19**. All of these products can be diastereomerically enriched with standard chromatography and selectively deprotected.

Experimental Section

General Methods. Unless otherwise noted, all reagents were obtained from commercial suppliers and used without further purification. Reactions were conducted in oven-dried (120 °C) glassware under a positive pressure of Ar. Microwave-induced reactions were performed on a monomode apparatus (maximum power = 300 W, frequency = 2.45 GHz). Transfer of anhydrous solvents or mixtures was accomplished with oven-dried syringes/septum techniques. THF was distilled from sodium/benzophenone just prior to use and stored under Ar. Et_2O was distilled from phosphorus pentoxide. CH_2Cl_2 was passed through basic alumina and distilled from CaH_2 prior to use. Light petroleum ether refers to the fraction with a boiling range of 40−60 °C. Powdered 4 Å molecular sieves were activated under vacuum at 220 °C for 6 h before use. Protected phenylalaninal **1**,[10] PMP-imine **16**,[29] and isoleucinal **2**[11] were prepared following literature procedures starting from L-phenylalanine and L-isoleucine. Benzyllithium was prepared at room temperature as a toluene solution from *n*-BuLi (1.6 M in hexanes, 2.95 mL) and dry toluene (9.20 mL) containing TMEDA (1.10 mL). 2-Phenylnitroethane[30] and trimethylsilyl-2-phenyl-ethylnitronate[26] were prepared according to literature procedures. Thin-layer chromatography (TLC) was performed on plastic plates coated with (0.20 mm) silica gel 60 F_{254}. Column chromatography was carried out on 70−230 mesh silica gel. Melting points were uncorrected. ^1H and ^{13}C NMR spectra were recorded at 300 and 400 MHz and 75 and 100 MHz, respectively. Chemical shifts were reported in the δ scale relative to an internal reference of TMS (0 ppm). The coupling constants (*J*) values are given in Hz. ^{13}C NMR spectral assignments were performed by use of DEPT experiments. The manufacturer's software was used for DEPT, gradient-enhanced COSY, as well as for the inversely detected gradient-selected heteronuclear correlations gHMBC and gHSQC. Mass spectra (MS) were obtained at an ionizing voltage of 70 eV (EIMS) or with an electrospray ionization source (ESIMS). All ESIMS spectra were performed using MeOH as the solvent. Optical rotations were obtained at 20 ± 2 °C. In the characterization of new compounds, oily products were characterized by accurate mass measurements [high-resolution mass spectra (HRMS)] because of the small scales used for their preparations. The originality of all compounds was checked by a CAS online structure search.

(2*R*,3*S*)- and (2*S*,3*S*)-3-*N*,*N*-Dibenzylamino-4-phenyl-2-trimethylsilanyloxy Butyronitrile (3a and 3b). To a solution of freshly prepared aldehyde **1** (2.00 g, 6.10 mmol) in dry CH_2Cl_2 (40 mL), cooled to −20 °C and magnetically stirred under Ar, were subsequently added $MgBr_2$ (1.23 g, 6.67 mmol) and TMSCN (0.90 mL, 6.67 mmol). After stirring at −20 °C for 4 h, the mixture was poured into H_2O; the layers were separated, and the aqueous layer was extracted three times with Et_2O. The combined organic extracts were washed with brine, dried (Na_2SO_4), and filtered. Evaporation of the solvents gave 2.49 g (95%) of a pale yellow oil, mainly constituted by

(28) CCDC 195390 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via the Internet at www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. Fax: +44 1223 336033. E-mail: deposit@ccdc.cam.ac.uk).

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3a and **3b** in a 78:22 ratio (^{1}H NMR). Crude product was used in the subsequent reaction with no further purification: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40−7.00 (m, 15H_{min}, 15H_{maj}), 4.48 (d, J = 6.3 Hz, 1H_{min}), 4.35 (d, J = 3.9 Hz, 1H_{maj}), 4.10 (d, J = 13.8 Hz, 2H_{maj}), 3.72 (s, 4H_{min}), 3.58 (d, J = 13.8 Hz, 2H_{maj}), 3.39 (m, 1H_{min}), 3.19−3.08 (m, 1H_{min}, 1H_{maj}), 3.07−2.97 (m, 1H_{min}, 2H_{maj}), 0.18 (s, 9H_{min}), 0.15 (s, 9H_{maj}); ^{13}C NMR ($CDCl_3$, 75 MHz) δ [minor isomer in brackets] 139.3 (s), [138.9 (s)], 138.7 (s), [129.4 (d)], 129.2 (d), 128.9 (d), [128.8 (d)], 128.5 (d), [128.4 (d)], 128.3 (d), 127.0 (d), [126.4 (d)], 119.7 (s), 64.2 (d), [63.2 (d)], [62.8 (d)], 62.0 (d), 55.2 (t), [54.8 (t)], [33.2 (t)], 30.2 (t), −0.4 (q); IR ν_{max} (thin layer, NaCl plate) 2240, 1250, 1090 cm^{-1}; EIMS m/z 428 (M^+), 413, 402, 337, 300, 91.

(2*R*,3*S*,4*S*)- and (2*S*,3*S*,4*S*)-3-*N*,*N*-Dibenzylamino-4-methyl-2-trimethylsilanyloxy Hexanenitrile (4a and 4b). Compounds **4a** and **4b** were obtained (92%) in a 82:18 ratio (^{1}H NMR) as a pale yellow oil following the procedure used for **3**, starting from aldehyde **2**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.30−7.10 (m, 10H_{min}, 10H_{maj}), 4.68 (d, J = 3.3 Hz, 1H_{min}, 1H_{maj}), 3.82 (d, J = 13.8 Hz, 2H_{maj}), 3.77 (d, J = 13.5 Hz, 2H_{min}), 3.66 (d, J = 13.5 Hz, 2H_{maj}), 3.55 (d, J = 13.5 Hz, 2H_{min}), 2.70 (dd, J = 4.8 Hz, J = 7.8 Hz, 1H_{min}), 2.53 (dd, J = 3.3 Hz, J = 9.3 Hz, 1H_{maj}), 2.00−1.70 (m, 2H_{min}, 2H_{maj}), 1.10−0.90 (m, 1H_{min}, 1H_{maj}), 0.88 (d, J = 6.6 Hz, 3H_{min}), 0.80 (d, J = 6.9 Hz, 3H_{maj}), 0.70 (t, J = 7.5 Hz, 3H_{maj}), 0.65 (t, J = 7.5 Hz, 3H_{min}), 0.17 (s, 9H_{min}), 0.13 (s, 9H_{maj}); ^{13}C NMR ($CDCl_3$, 75 MHz) δ [minor isomer in brackets] 139.4 (s), [139.0 (s)], 129.2 (d), 128.2 (d), 127.0 (d), 120.3 (s), 64.7 (d), [64.0 (d)], 61.7 (d), [61.2 (d)], 54.9 (t), [54.7 (t)], 34.5 (d), [32.8 (d)], [26.9 (t)], 26.1 (t), 16.1 (q), [15.2(q)], 10.9 (q), −0.3 (q); IR ν_{max} (thin layer, NaCl plate) 2234, 1256, 1096 cm^{-1}; EIMS m/z 394 (M^+), 379, 337, 266, 91.

(2*S*,3*S*,4*S*)- and (2*S*,3*R*,4*R*)-4-Amino-2-*N*,*N*-dibenzylamino-1,5-diphenyl Pentan-3-ol (5a and 5b). To a cooled (−78 °C) solution of **3** (1.14 g, 2.66 mmol) in dry Et_2O (30 mL), under Ar, was added a solution of BnLi in toluene (4.72 mmol). The reaction mixture was stirred at −78 °C for 1 h, and then MeOH (20 mL) was added, followed by $NaBH_4$ (0.505 g, 13.30 mmol). The resulting suspension was allowed to warm to room temperature and stirred for 72 h; then, the reaction was quenched with water, followed by HCl 10% (pH ≈ 2, clear solution), and the mixture was left under stirring for 30 min. After alkalanization with 3 M aqueous NaOH (pH ≈ 9), the two layers were separated, and the aqueous layer was extracted three times with EtOAc. The combined organic extracts were washed with brine, dried ($NaSO_4$), and filtered. Evaporation of the solvents gave a crude product containing **5a** and **5b** in a 78:22 ratio (^{1}H NMR). Silica gel chromatography (97/3 $CHCl_3$/MeOH) gave 684 mg of **5a** and 178 mg of **5b** (72% overall yield), as white solids.

(2*S*,3*S*,4*S*)-5a: mp = 53−55 °C; $[\alpha]_D^{20}$ +22 (*c* 1.16, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40−7.00 (m, 18H), 6.60−6.55 (m, 2H), 4.05 (d, J = 12.9 Hz, 2H), 3.84 (dd, J = 2.3 Hz, J = 8.2 Hz, 1H), 3.45 (d, J = 12.9 Hz, 2H), 3.25 (dd, J = 4.7 Hz, J = 13.9 Hz, 1H), 3.20−3.10 (m, 1H), 2.85−2.80 (m, 1H), 2.75 (dd, J = 8.1 Hz, J = 14.0 Hz, 1H), 2.50−2.30 (bs, 3H), 2.15 (dd, J = 9.7 Hz, J = 13.7 Hz, 1H), 2.05 (dd, J = 4.3 Hz, J = 13.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.9 (s), 139.1 (s), 138.6 (s), 129.3 (d), 129.2 (d), 128.8 (d), 128.6 (d), 128.3 (d), 127.5 (d), 126.4 (d), 126.0 (d), 74.0 (d), 60.0 (d), 54.4 (d), 53.9 (t), 36.6 (t), 32.3 (t); IR ν_{max} (thin layer, NaCl plate) 3597, 3369 cm^{-1}; EIMS m/z 451 (MH^+) 359, 330, 300, 240, 120, 91. Anal. Calcd for $C_{31}H_{34}N_2O$: C, 82.63; H, 7.61; N, 6.22. Found: C, 82.58; H, 7.49; N, 6.35.

(2*S*,3*R*,4*R*)-5b: mp = 218 °C; $[\alpha]_D^{20}$ −14 (*c* 0.997, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40−7.22 (m, 18H), 6.95 (m, 2H), 3.96 (dd, J = 3.7 Hz, J = 5.6 Hz, 1H), 3.70 (d, J = 13.8 Hz, 2H), 3.55 (d, J = 13.8 Hz, 2H), 3.20 (dt, J_t =3.4 Hz, J_d = 11.1 Hz, 1H), 3.11−2.92 (m, 3H) 2.39 (dd, J = 2.8 Hz, J = 13.6 Hz, 1H), 2.30 (bs, 1H), 2.10 (dd, J = 11.0 Hz, J = 13.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 141.8 (s), 139.6 (s), 139.0 (s), 129.6 (d), 129.0 (d), 128.2 (d), 126.9 (d), 126.2 (d), 125.7 (d), 74.5 (d), 60.8 (d), 54.5 (t), 54.2 (d), 35.6 (t), 32.7 (t); IR ν_{max} (thin layer, NaCl plate) 3587, 3368 cm^{-1}; EIMS m/z 359, 300, 240, 120, 91. Anal. Calcd for $C_{31}H_{34}N_2O$: C, 82.63; H, 7.61; N, 6.22. Found: C, 82.74; H, 7.53; N, 6.12.

(2*S*,4*S*)-2,4-Diamino-1,5-diphenyl Pentan-3-ol (6a). Pd/C 10% was weighed (44 mg) in a microwave reactor and immediately covered with *i*-PrOH (1 mL). A solution of **5a** (100 mg, 0.22 mmol) in *i*-PrOH (3 mL) was added, followed by $HCOONH_4$ (84 mg, 1.33 mmol). After 20 min of irradiation (30 W with stirring), the mixture was allowed to cool to room temperature and then filtered through a Celite pad. The pad was washed with MeOH; then, the solvents were evaporated, and the crude was purified by chromatography on silica gel (85/15 $CHCl_3$/MeOH) affording 48 mg (80%) of compound **6a**[31] as a white solid: mp = 136−138 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.20−7.05 (m, 10H), 3.40−3.36 (m, 2H), 3.20−3.07 (m, 1H), 3.00 (dd, J = 3.3, J = 13.3, 1H), 2.95 (dd, J = 4.5, J = 13.3, 1H), 2.62 (dd, J = 9.5, J = 13.3, 1H), 2.50 (dd, J = 9.9, J = 13.3, 1H), 1.50−1.00 (br s, 5H); EIMS m/z 271 (MH^+), 179, 150, 120, 91; ESIMS m/z 271 ($M + H^+$).

(3*S*,4*S*,5*S*,6*S*,7*S*)- and (3*S*,4*S*,5*S*,6*S*,7*R*)-6-Amino-4-*N*,*N*-dibenzylamino-3,7-dimethyl Nonan-5-ol (7a and 7b). Following the procedure used for **5a** and **5b**, compounds **7a** and **7b** were obtained as a white solid in 72% yield in a 1:1 mixture after chromatography on silica gel: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40−7.15 (m, 20H), 4.05 (d, J = 13.0 Hz, 4H), 3.85 (dd, J = 3.0 Hz, J = 6.3 Hz, 1H), 3.78 (dd, J = 3.8 Hz, J = 5.3 Hz, 1H), 3.50 (d, J = 13.0 Hz, 2H), 3.42 (d, J = 14.0 Hz, 2H), 2.70 (dd, J = 2.9 Hz, J = 6.8 Hz, 2H), 2.60 (dd, 1H), 2.50 (t, J = 3.5 Hz, 1H), 2.30 (br s, 6H), 2.10−1.90 (m, 2H), 1.50−0.50 (m, 34H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.5 (s), 139.3 (s), 129.3 (d), 129.2 (d), 128.3 (d), 128.0 (d), 127.1 (d), 127.0 (d), 71.9 (d), 71.2 (d), 60.5 (d), 60.4 (d), 58.3 (d), 57.4 (d), 54.9 (t), 54.6 (t), 34.9 (d), 34.4 (d), 33.2 (d), 32.4 (d), 30.0 (t), 29.4 (t), 27.8 (t), 23.3 (t), 17.1 (q), 16.9 (q), 16.9 (q), 13.5 (q), 12.8 (q), 12.6 (q), 11.7 (q), 11.6 (q); EIMS m/z 382 (M^+), 354, 308, 297, 267, 240, 91, 86, 65, 41.

(3*S*,4*S*,6*S*,7*S*)- and (3*S*,4*S*,5*r*,6*S*,7*R*)-4,6-Diamino-3,7-dimethyl Nonan-5-ol (8a and 8b). Following the procedure used for **6a**, compounds **8a** and **8b** were obtained in quantitative yield and in a 1:1 ratio as a white solid; crude **8** was used in the subsequent step with no further purification: ^{1}H NMR (CD_3OD, 300 MHz) δ 5.00 (br s, 10H), 3.90 (dd, J = 1.5 Hz, J = 8.1 Hz, 1H), 3.80 (dd, J = 1.8 Hz, J = 8.7 Hz, 1H), 3.08 (dd, J = 3.0 Hz, J = 8.4 Hz, 1H), 3.00 (dd, J = 3.6 Hz, J = 8.1 Hz, 1H), 2.95 (m, 2H), 2.23−1.18 (m, 12H), 1.18−1.08 (m, 24H); ^{13}C NMR (CD_3OD, 75 MHz) δ 71.9 (d), 71.3 (d), 58.8 (d), 55.8 (d), 55.5 (d), 39.0 (d), 38.9 (d), 36.2 (d), 35.4 (d), 28.1 (t), 26.1 (t), 23.4 (t), 16.6 (q), 15.7 (q), 15.6 (q), 12.4 (q), 12.0 (q), 11.9 (q), 11.2 (q); ESIMS m/z 203 ($M + H^+$).

(3*S*,4*S*,6*S*,7*S*)- and (3*S*,4*S*,5*r*,6*S*,7*R*)-3,7-Dimethyl-4,6-di-(*p*-toluensulfonylamino) Nonan-5-ol (9a and 9b). To a stirred solution of **8** (100 mg, 0.50 mmol) in H_2O/THF (1/2 v/v, 1.5 mL) were sequentially added Na_2CO_3 (300 mg, 2.80 mmol) and TsCl (220 mg, 1.15 mmol). After 4 h of stirring at room temperature, the resulting biphasic mixture was diluted with Et_2O and H_2O. The layers were separated, and the aqueous layer was extracted twice with Et_2O. The combined organic extracts were washed twice with H_2O, dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The crude product was then purified, and the two isomers were separated by chromatography on silica gel (4/1 EtOAc/*n*-hexane), affording 89 mg of **9a** and 91 mg of **9b** as white solids (70% overall yield).

(3*S*,4*S*,6*S*,7*S*)-9a: mp = 57−58 °C; $[\alpha]_D^{20}$ −43 (*c* 0.270, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.78 (d, J = 8.1 Hz, 2H), 7.76 (d, J = 8.1 Hz, 2H), 7.32 (d, J = 7.3 Hz, 2H), 7.29 (d, J = 7.5 Hz, 2H), 5.52 (d, J = 9.9 Hz, 1H), 5.07 (d, J = 8.7 Hz, 1H), 3.68 (dd, J = 1.8 Hz, J = 4.2 Hz, 1H), 3.27 (m, 1H), 3.18 (m, 1H), 2.40 (s, 3H), 2.38 (s, 3H), 1.60−1.05 (m, 5H), 1.00−0.60 (m, 14H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.6 (s), 143.4 (s), 138.0

(31) Analytic and spectroscopic data are in agreement with the literature: ref 5a.

(s), 137.9 (s), 129.7 (d), 129.6 (d), 127.2 (d), 69.4 (d), 61.9 (d), 57.2 (d), 38.6 (d), 35.5 (d), 25.2 (t), 25.1 (t), 21.5 (q), 16.2 (q), 15.2 (q), 11.7 (q), 11.1 (q); IR ν_{max} (thin layer, NaCl plate) 3463, 3293, 1331, 1160 cm^{-1}; EIMS *m*/*z* 510 (M^+), 270, 240, 155, 91; ESIMS *m*/*z* 533 ($M + Na^+$). Anal. Calcd for $C_{25}H_{38}N_2O_5S_2$: C, 58.79; H, 7.50; N, 5.49. Found: C, 58.88; H, 7.59; N, 5.41.

(3*S*,4*S*,5*r*,6*S*,7*R*)-9b: mp = 53−54 °C; $[\alpha]_D^{20}$ −40 (*c* 0.385, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.75 (d, *J* = 8.1 Hz, 2H), 7.73 (d, *J* = 8.1 Hz, 2H), 7.27 (d, *J* = 7.8 Hz, 2H), 7.25 (d, *J* = 7.5 Hz, 2H), 5.55 (d, *J* = 9.9 Hz, 1H), 5.07 (d, *J* = 8.7 Hz, 1H), 3.58 (t, *J* = 4.4 Hz, 1H), 3.27 (quint, *J* = 4.2 Hz, 1H), 3.18 (quint, *J* = 4.8 Hz, 1H), 2.41 (s, 3H), 2.39 (s, 3H), 1.60−1.50 (m, 1H), 1.38−0.80 (m, 4H), 0.80−0.60 (m, 14H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.5 (s), 143.4 (s), 138.0 (s), 137.9 (s), 129.6 (d), 127.1 (d), 127.1 (d), 70.7 (d), 59.1 (d), 58.4 (d), 37.5 (d), 34.6 (d), 27.0 (t), 24.2 (t), 21.5 (q), 15.4 (q), 11.8 (q), 11.1 (q); IR ν_{max} (thin layer, NaCl plate) 3450, 3320, 1333, 1159 cm^{-1}; EIMS *m*/*z* 510 (M^+), 270, 240, 91. Anal. Calcd for $C_{25}H_{38}N_2O_5S_2$: C, 58.79; H, 7.50; N, 5.49. Found: C, 58.83; H, 7.42; N, 5.38.

(3*S*,4*S*,6*S*,7*S*)-3,7-Dimethyl-4,6-di-(*p*-toluensulfonylamino) Nonan-5-one (10). To a stirred solution of **9a** (35 mg, 0.069 mmol) in DMF (2 mL) was added PDC (132 mg, 0.35 mmol). The reaction mixture was left standing at room temperature for 72 h, with stirring, and then H_2O and EtOAc were added. The layers were separated, and the organic layer was washed with H_2O and brine and then dried (Na_2SO_4). After filtration and evaporation of the solvents, the crude product was purified by preparative TLC (7/3 *n*-hexane/EtOAc), affording 21 mg (60%) of compound **10** as a white solid: mp = 164−165 °C; $[\alpha]_D^{20}$ +126 (*c* = 0.980, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.62 (d, *J* = 8.4 Hz, 4H), 7.20 (d, *J* = 9.9 Hz, 4H), 5.27 (d, *J* = 8.7 Hz, 2H), 3.93 (dd, *J* = 2.7 Hz, *J* = 8.7 Hz, 2H), 2.28 (s, 6H), 1.60 (m, 2H), 0.87 (d, *J* = 6.9 Hz, 6H), 0.78−0.60 (m, 2H), 0.60 (t, *J* = 6.5 Hz, 6H), 0.30−0.20 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 223.2 (s), 143.7 (s), 129.6 (d), 127.3 (d), 64.2 (d), 37.5 (d), 22.5 (t), 21.5 (d), 16.1 (q), 11.7 (q); IR ν_{max} (thin layer, NaCl plate) 3331, 1716, 1343, 1161 cm^{-1}; ESIMS *m*/*z* 531 ($M + Na^+$). Anal. Calcd for $C_{25}H_{36}N_2O_5S_2$: C, 59.03; H, 7.13; N, 5.51. Found: C, 59.11; H, 7.26; N, 5.39.

(2*S*,3*S*,4*S*)-, (2*S*,3*R*,4*S*)-, (2*R*,3*S*,4*S*)-, and (2*R*,3*R*,4*S*)-4-*N*,*N*-Dibenzylamino-1,5-diphenyl-2-nitro Pentan-3-ol (14). To a stirred solution of TBAF·*x*H_2O (730 mg, 2.80 mmol) in THF (60 mL), cooled to 0 °C, was added 2-phenylnitroethane (450 mg, 2.98 mmol) in THF (8 mL) and, after 5 min, a solution of aldehyde **1** (670 mg, 2.09 mmol) in THF (15 mL). After 20 min of stirring at the same temperature, the mixture was poured onto saturated $NaHCO_3$ and extracted three times with Et_2O. The organic extracts were then washed with brine, dried (Na_2SO_4), filtered, and evaporated. Chromatography on silica gel (95/5 *n*-hexane/EtOAc) gave 872 mg (87%) of a colorless oil constituted by the four stereoisomers of **14** in a 4:3:1:1 ratio (^{1}H NMR analysis of the α-nitro protons): ^{1}H NMR ($CDCl_3$) δ 7.50−6.80 (m, 20H), 5.30−2.40 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 140.8 (s), 140.1 (s), 139.2 (s), 138.8 (s), 138.6 (s), 135.5 (s), 135.1 (s), 129.3 (d), 129.2 (d), 129.1 (d), 128.9 (d), 128.8 (d), 128.8 (d), 128.6 (d), 128.6 (d), 128.5 (d), 128.4 (d), 128.3 (d), 127.8 (d), 127.5 (d), 127.1 (d), 126.9 (d), 126.7 (d), 126.6 (d), 126.2 (d), 90.9 (d), 90.8 (d), 90.4 (d), 90.2 (d), 73.1 (d), 73.0 (d), 70.8 (d), 61.1 (d), 60.8 (d), 60.2 (d), 59.4 (d), 54.8 (t), 54.5 (t), 53.6 (t), 36.9 (t), 35.7 (t), 32.9 (t), 32.4 (t), 32.0 (t), 31.8 (t), 31.4 (t), 30.8 (t); IR ν_{max} (thin layer, NaCl plate) 3350, 1551, 1372 cm^{-1}; EIMS *m*/*z* 481 (MH^+), 389, 371, 342, 300, 238, 181, 104, 91.

(2*S*,3*S*,4*S*)-, (2*S*,3*R*,4*R*)-, (2*S*,3*S*,4*R*)-, and (2*S*,3*R*,4*S*)-4-Amino-2-*N*,*N*-dibenzylamino-1,5-diphenyl Pentan-3-ol (5). To a stirred solution of compound **14** (280 mg, 0.58 mmol) in MeOH (13 mL), cooled to 0 °C, was added $NiCl_2$·6H_2O (344 mg, 1.45 mmol), followed by $NaBH_4$ (365 mg, 9.61 mmol). The resulting dark suspension was stirred at the same temperature for 20 min, and then the reaction was quenched with water and HCl 10% (pH ≈ 2). After alkalanization with NaOH 3M (pH ≈ 9), the product was extracted three times with EtOAc. The organic extracts were washed with brine, dried (Na_2SO_4), and filtered. Evaporation of the solvents gave 200 mg (76%) of a mixture of four diastereoisomers of **5** as a white solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.50−7.05 (m, 20H) 4.10−1.80 (m, 14H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 142.2 (s), 141.8 (s), 140.2 (s), 139.9 (s), 139.6 (s), 139.2 (s), 138.6 (s), 129.6 (d), 129.3 (d), 129.0 (d), 128.4 (d), 128.3 (d), 128.1 (d), 127.9 (d), 127.1 (d), 126.9 (d), 126.5 (d), 126.3 (d), 126.0 (d), 125.7 (d), 74.5 (d), 74.0 (d), 73.1 (d), 71.6 (d), 61.0 (d), 60.7 (d), 60.5 (d), 60.2 (d), 59.9 (d), 54.4 (t), 54.3 (t), 54.1 (d), 53.7 (t), 53.3 (d), 53.1 (t), 52.3 (d), 42.0 (t), 40.6 (t), 36.1 (t), 35.5 (t), 32.6 (t), 32.2 (t), 31.8 (t), 31.7 (t); EIMS *m*/*z* 451 $(MH)^+$, 359, 300, 240, 210, 120, 91.

(2*S*,4*S*)-, (2*S*,3*r*,4*R*)-, and (2*S*,3*s*,4*R*)-2,4-*N*,*N*-Diamino-1,5-diphenyl Pentan-3-ol (6). Following the procedure used for **6a**, the three diastereoisomers of **6**[31] were obtained in quantitative yield as a white solid; the crude product was used in the subsequent step with no further purification: ^{1}H NMR (CD_3OD, 300 MHz) δ 7.40−7.10 (m, 10H), 3.60−3.10 (m, 3H), 3.00−2.60 (m, 4H); ^{13}C NMR (CD_3OD, 75 MHz) δ 139.1 (s), 138.9 (s), 138.7 (s), 131.0 (d), 130.8 (d), 130.7 (d), 130.4 (d), 130.2 (d), 130.1 (d), 128.5 (d), 128.4 (d), 128.3 (d), 128.2 (d), 128.1 (d), 128.0 (d), 75.0 (d), 69.8 (d), 68.5 (d), 58.9 (d), 58.3 (d), 57.5 (d), 54.9 (d), 41.1 (t), 40.0 (t), 39.1 (t), 38.9 (t); ESIMS *m*/*z* 271 ($M + H^+$).

(2*S*,4*S*)-, (2*S*,3*r*,4*R*)-, and (2*S*,3*s*,4*R*)-1,5-Diphenyl-2,4-[di-(*p*-toluensulfonylamino)] Pentan-3-ol (15a, 15b and 15c). Following the procedure used for compounds **9**, the three diastereoisomers of **6** were reacted with TsCl affording, after separation by preparative TLC (9/1 $CHCl_3$/EtOAc), **15a**, **15b**, and **15c** as white solids in 60% overall yield and 4:4:1 ratio (^{1}H NMR of the crude).

(2*S*,4*S*)-15a: mp = 94−96 °C; $[\alpha]_D^{20}$ −44 (*c* 0.460, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.76 (d, *J* = 8.4 Hz, 2H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.31 (br d, *J* = 8.4 Hz, 2H), 7.10−6.89 (m, 10H), 6.69 (d, *J* = 7.2 Hz, 2H), 5.40 (d, *J* = 9.2 Hz, 1H), 5.05 (d, *J* = 9.2 Hz, 1H), 3.76 (m, 1H), 3.62 (m, 1H), 3.49 (m, 1H), 2.78 (dd, *J* = 13.4 Hz, *J* = 9.7 Hz, 1H), 2.60 (dd, *J* = 14.2 Hz, *J* = 7.8 Hz, 1H), 2.50−2.44 (m, 2H), 2.43 (s, 3H), 2.39 (s, 3H), 1.80 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.8 (s), 143.2 (s), 136.8 (s), 136.3 (s), 129.9 (d), 129.6 (d), 129.2 (d), 128.9 (d), 128.6 (d), 128.5 (d), 127.1 (d), 126.9 (d), 126.7 (d), 126.4 (d), 70.0 (d), 58.3 (d), 55.1 (d), 37.0 (t), 36.4 (t), 21.6 (q), 21.5 (q); IR ν_{max} (thin layer, NaCl plate) 3370, 1338, 1158 cm^{-1}; ESIMS *m*/*z* 601 ($M + Na^+$). Anal. Calcd for $C_{31}H_{34}N_2O_5S_2$: C, 64.33; H, 5.92; N, 4.84. Found: C, 64.41; H, 5.82; N, 4.95.

15b: mp = 172−174 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.54 (d, *J* = 8.4 Hz, 4H), 7.18 (d, *J* = 8.2 Hz, 4H), 7.10−7.00 (m, 6H), 6.88 (dd, *J* = 7.8 Hz, *J* = 1.5 Hz, 4H), 4.80 (d, *J* = 8.4 Hz, 2H), 3.80 (m, 2H), 3.70 (m, 1H), 3.23 (br d, *J* = 5.1 Hz, 1H), 2.90 (dd, *J* = 13.8 Hz, *J* = 7.8 Hz, 2H), 2.65 (dd, *J* = 13.8 Hz, *J* = 4.5 Hz, 2H), 2.42 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 140.5 (s), 137.3 (s), 135.9 (s), 129.8 (d), 129.6 (d), 128.7 (d), 127.0 (d), 126.7 (d), 76.5 (d), 56.6 (d), 35.8 (t), 21.6 (q); IR ν_{max} (thin layer, NaCl plate) 3360, 1340, 1160 cm^{-1}; ESIMS *m*/*z* 601 ($M + Na^+$). Anal. Calcd for $C_{31}H_{34}N_2O_5S_2$: C, 64.33; H, 5.92; N, 4.84. Found: C, 64.29; H, 5.85; N, 4.91.

15c: mp = 137−139 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.65 (d, *J* = 8.6 Hz, 4H), 7.25 (d, *J* = 8.1 Hz, 4H), 7.19−7.03 (m, 6H), 6.80 (d, *J* = 6.8 Hz, 4H), 4.90 (d, *J* = 9.6 Hz, 2H), 3.60 (m, 2H), 3.30 (br t, *J* = 5.3 Hz, 1H), 2.75 (dd, *J* = 13.4 Hz, *J* = 7.7 Hz, 2H), 2.43 (s, 6H), 2.43 (dd, *J* = 13.4 Hz, *J* = 6.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.5 (s), 136.1 (s), 129.4 (d), 128.6 (d), 127.0 (d), 126.6 (d), 70.6 (d), 56.2 (d), 37.3 (t), 21.5 (q); IR ν_{max} (thin layer, NaCl plate) 3375, 1339, 1160 cm^{-1}; ESIMS *m*/*z* 601 ($M + Na^+$). Anal. Calcd for $C_{31}H_{34}N_2O_5S_2$: C, 64.33; H, 5.92; N, 4.84. Found: C, 64.48; H, 6.03; N, 4.75.

(2*S*,3*S*,4*S*)- and (2*S*,3*S*,4*R*)-N^2,N^2-(Dibenzyl)-N^3-(4-methoxyphenyl)-4-nitro-1,5-diphenyl-2,3-pentanediamine (17a and 17b). $Sc(OTf)_3$ (0.074 g, 0.15 mmol) and trimethylsilyl 2-phenylnitronate (0.80 g, 3.64 mmol) were added to a stirred

solution of **16** (1.30 g, 3.00 mmol) in dry CH_3CN (15 mL) at 0 °C. The resulting mixture was stirred for 2 h at 0 °C; then, the reaction was quenched with H_2O, and the mixture was extracted three times with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo, affording a yellow solid in quantitative yield, mainly constituted by the two diastereoisomers **17a** and **17b** in a 60:40 ratio (^{1}H NMR), which were used in the subsequent step with no further purification. An analytical sample for the distereomeric mixture **17a**,**b** was obtained in 68% yield by chromatography on silica gel: ^{1}H NMR (C_6D_6, 400 MHz) δ 7.66−7.12 (m, 20H_{maj}, 20H_{min}), 7.02 (d, J = 8.7 Hz, 2H_{maj}, 2H_{min}), 6.68 (d, J = 9.3 Hz, 2H_{min}), 6.52 (d, J = 8.7 Hz, 2H_{maj}), 5.7 (m, 1H_{maj}, 1H_{min}), 4.85 (m, 1H_{min}), 4.05 (m, 1H_{maj}), 4.00 (d, J = 10.2 Hz, 2H_{min}), 3.85 (d, J = 10.2 Hz, 2H_{maj}), 3.78 (m, 1H_{maj}, 1H_{min}), 3.66 (s, 3H_{maj}), 3.65 (d, J = 10.2 Hz, 2H_{maj}), 3.64 (s, 3H_{min}), 3.63 (d, J = 10.2 Hz, 2H_{min}), 3.43 (m, 1H_{maj}, 1H_{min}), 3.5−2.7 (m, 4H_{maj}, 4H_{min});^{13}C NMR (C_6D_6, 100 MHz) δ 152.9 (s), 152.6 (s), 141.3 (s), 140.7 (s), 140.5 (s), 140.4 (s), 139.5 (s), 139.2 (s), 136.4 (s), 136.2 (s), 129.3 (d), 129.2 (d), 129.1 (d), 129.0 (d), 128.7 (d), 128.6 (d), 128.5 (d), 127.4 (d), 127.2 (d), 126.9 (d), 126.3 (d), 126.1 (d), 115.4 (d), 115.3 (d), 114.3 (d), 90.3 (d), 90.0 (d), 64.0 (d), 62.1 (d), 60.0 (d), 57.7 (d), 55.3 (q), 55.3 (t), 55.3 (q), 54.4 (t), 37.6-(t), 33.9 (t), 33.1 (t), 33.0 (t); IR ν_{max} (thin layer, NaCl plate) 3030, 1513, 1246 cm^{-1}; ESIMS m/z 586 (M + H$^+$).

(2*S*,3*R*,4*S*)- and (2*S*,3*R*,4*R*)-*N*^{2},*N*^{2}-Dibenzyl-*N*^{3}-(4-methoxyphenyl)-1,5-diphenyl-2,3,4-pentanetriamine (18a and 18b). $NiCl_2$·$6H_2O$ (99 mg, 0.42 mmol) and $NaBH_4$ (16 mg, 4.2 mmol) were added to a cooled solution (−20 °C) of the crude diastereomeric mixture **17a**,**b** (102 mg, 0.17 mmol) in MeOH (6 mL). The resulting mixture was left at 0 °C for 30 min with stirring, and then the reaction was quenched with H_2O followed by HCl 10% (pH ≈ 2). After alkalanization with NaOH 3M (pH ≈ 9), the product was extracted three times with $CHCl_3$. The organic extracts were washed with brine, dried (Na_2SO_4), and filtered. ^{1}H NMR spectra of the crude reaction mixture showed the presence of two diastereoisomers of **18** in a 60:40 ratio. Chromatography on deactivated (1% Et_3N) silica gel (9/1 CH_2Cl_2/EtOAc) afforded the major diastereoisomer **18a** as a yellow brown oil and the minor diastereoisomer **18b** as a pale yellow solid in 66% overall yield.

(2*S*,3*R*,4*S*)-18a: $[\alpha]_D^{20}$ +11 (c = 1.215, $CHCl_3$); ^{1}H NMR (C_6D_6, 400 MHz) δ 7.3−6.9 (m, 20H), 6.79 (d, J = 8.9 Hz, 2H), 6.44 (d, J = 8.9 Hz, 2H), 4.42 (bd, J = 9.0 Hz, 1H), 3.88 (bt, J = 7.5 Hz, 1H), 3.65 (d, J = 13.6 Hz, 2H), 3.40 (s, 3H), 3.30 (bd, J = 13.5 Hz, 3H), 3.05 (dd, J = 14.1 Hz, J = 4.5 Hz, 1H), 2.90 (dd, J = 14.1 Hz, J = 7.2 Hz, 1H), 2.60 (dd, J = 13.3 Hz, J = 6.6 Hz, 1H), 2.42 (dd, J = 13.3 Hz, J = 8.1 Hz, 1H); ^{13}C NMR (C_6D_6, 100 MHz) δ 151.8 (s), 143.9 (s), 142.9 (s), 140.2 (s), 139.7 (s), 129.5 (d), 129.4 (d), 128.5 (d), 128.4 (d), 128.3 (d), 127.1 (d), 126.3 (d), 125.7 (d), 115.3 (d), 113.9(d), 58.6 (d), 55.4 (q), 54.7 (t), 52.7 (d), 41.8 (t), 33.6 (t); ESIMS m/z 556 (M + H$^+$).

(2*S*,3*R*,4*R*)-18b: mp = 135−145 °C (EtOH); $[\alpha]_D^{20}$ −13 (c = 1.03, $CHCl_3$); ^{1}H NMR (C_6D_6, 400 MHz) δ 7.25 (d, J = 7.5 Hz, 2H), 7.23−6.98 (m, 16H), 6.86 (d, J = 7.5 Hz, 2H), 6.81 (d, J = 8.9 Hz, 2H), 5.89 (d, J = 8.9 Hz, 2H), 3.82 (m, 1H), 3.74 (d, J = 14.0 Hz, 2H), 3.55 (d, J = 14.0 Hz, 2H), 3.40 (s, 3H), 3.35 (m, 1H), 3.26 (m, 1H), 3.11 (d, J = 10.3 Hz, 1H), 2.96 (dd, J = 14.0 Hz, J = 6.6 Hz, 1H), 2.73 (dd, J = 14.0 Hz, J = 6.4 Hz, 1H), 2.67 (dd, J = 13.3 Hz, J = 13.3 Hz, 1H), 1.96 (dd, J = 13.3 Hz, J = 10.6 Hz, 1H); ^{13}C NMR (C_6D_6, 100 MHz) δ 152.3 (s), 142.5 (s), 141.5 (s), 140.1 (s), 140.0 (s), 129.5 (d), 129.2 (d), 128.4 (d), 128.4 (d), 128.3 (d), 127.0 (d), 115.2 (d), 114.4 (d), 61.2 (d), 60.5 (d), 55.7 (d), 55.4 (q), 54.7 (t), 40.7 (t), 33.4 (t); ESIMS m/z 556 (M + H$^+$). Anal. Calcd for $C_{38}H_{41}N_3O$: C, 82.12; H, 7.44; N, 7.56. Found: C, 82.21; H, 7.38; N, 7.49.

(2*S*,4*R*)-*N*^{3}-(4-Methoxyphenyl)-1,5-diphenyl-2,3,4-pentanetriamine. Following the procedure used for **6a**, the title compound was obtained in quantitative yield as a thick yellow oil and used in the next step with no further purification: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.50−7.30 (m, 10H), 6.75 (d, J = 8.7 Hz, 2H), 6.55 (d, J = 8.7 Hz, 2H), 3.80 (s, 3H), 3.83−3.78 (m, 1H), 3.70−3.60 (m, 1H), 3.40−3.20 (m, 1H), 3.0−2.4 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 151.5 (s), 142.5 (s), 139.1 (s), 138.9 (s), 129.4 (d), 129.0 (d), 128.5 (d), 128.5 (d), 128.2 (d), 126.3 (d), 115.0 (d), 114.0 (d), 58.7 (d), 55.8 (q), 55.4 (d), 52.4 (d), 42.2 (t), 41.4 (t); ESIMS m/z 398 (M + Na$^+$).

(2*S*,4*R*)-*N*^{3}-(4-Methoxyphenyl)-1,5-diphenyl-*N*^{2},*N*^{4}-(di-*p*-toluensulfonyl)-2,3,4-pentanetriamine (19). Following the procedure used for compounds **9**, use of crude (2*S*,4*R*)-*N*^{3}-(4-methoxyphenyl)-1,5-diphenyl-2,3,4-pentanetriamine as a starting material afforded compound **19** in 70% yield after chromatography on silica gel (97/3 CH_2Cl_2/Et_2O) as a white solid: mp = 92−94 °C; $[\alpha]_D^{20}$ −66 (c = 1.048, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.79 (d, J = 6.0 Hz, 2H), 7.57 (d, J = 8.4 Hz, 2H), 7.40−6.90 (m, 10H), 6.71 (d, J = 6.3 Hz, 2H), 6.58 (d, J = 9.0 Hz, 2H), 6.50 (d, J = 6.9 Hz, 2H), 6.10 (d, J = 8.7 Hz, 2H), 5.95 (d, J = 10.2 Hz, 1H), 4.95−4.80 (br s, 1H), 4.98−3.80 (m, 2H), 3.70 (s, 3H), 3.72−3.65 (m, 1H), 3.18 (br s, 1H), 2.67−2.60 (m, 2H), 2.50 (dd, J = 9.3 Hz, J = 13.8 Hz, 1H), 2.42 (s, 3H), 2.36 (s, 3H), 2.27 (dd, J = 13.5 Hz, J = 5.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 152.5 (s), 144.1 (s), 142.9 (s), 140.5 (s), 138.1 (s), 136.8 (s), 136.7 (s), 130.1 (d), 129.6 (d), 129.3 (d), 128.7 (d), 128.6 (d), 128.5 (d), 127.3 (d), 126.9 (d), 126.8 (d), 126.2 (d), 115.4 (d), 114.6 (d), 57.3 (d), 55.6 (q), 54.7 (d), 53.7 (d), 40.1 (t), 38.5 (t), 21.6 (q), 21.5 (q); IR ν_{max} (thin film, NaCl plate) 3352, 3250, 1333, 1158 cm^{-1}; ESIMS m/z 706 (M + Na$^+$). Anal. Calcd for $C_{38}H_{41}N_3O_5S_2$: C, 66.74; H, 6.04; N, 6.14. Found: C, 66.69; H, 6.13; N, 6.18.

(4*S*,5*S*)-5-[(1*S*)-1-*N*,*N*-Dibenzylamino-2-phenylethyl]-4-benzyl-1-(4-methoxyphenyl)-tetrahydro-2*H*-imidazol-2-one (20). To a stirred solution of **18a** (44 mg, 0.07 mmol) in CH_2Cl_2 (3 mL), cooled to 0 °C, was added a 20% solution of phosgene in toluene (0.055 mL, 0.10 mmol), followed by Et_3N (0.030 mL, 0.21 mmol). The reaction mixture was left standing at room-temperature overnight, with stirring, and then CH_2Cl_2 was added, followed by H_2O and NaOH 6M (1 mL). The two layers were separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated. Purification by preparative TLC (light petroleum/EtOAc) afforded 14 mg of **20** as a thick colorless oil: $[\alpha]_D^{20}$ −25 (c = 0.645, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40−7.10 (m, 22H), 6.75 (d, J = 9.0 Hz, 2H), 4.50 (s, 1H), 4.00−3.90 (br d, J = 6.3 Hz, 1H), 3.80 (s, 3H), 3.80−3.70 (m, 1H), 3.68 (d, J = 13.8 Hz, 2H), 3.50−3.40 (m, 1H), 3.47 (d, J = 13.8 Hz, 2H), 2.90−2.60 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.9 (s), 156.0 (s), 139.9 (s), 139.3 (s), 136.7 (s), 132.6 (s), 129.3 (d), 129.2 (d), 128.9 (d), 128.9 (d), 128.5 (d), 128.3 (d), 127.1 (d), 127.0 (d), 126.3 (d), 123.1 (d), 114.2 (d), 63.4 (d), 62.2 (d), 55.5 (q), 54.9 (t), 54.7 (d), 42.7 (t), 33.4 (t); IR ν_{max} (thin film, NaCl plate) 1706 cm^{-1}; ESIMS m/z 582 (M + H$^+$). The trans configuration was elucidated by NOE experiments. Saturation of the resonance at 3.9−4.0 ppm (H_3) produced a significant increase in the intensity of the aromatic proton signal at 7.2 ppm (25%), whereas it was not possible to detect any positive NOE effect on the H_4 signal at 3.80−3.70 ppm.

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