Pergamon

Tetrahedron Vol. 50, No. 37, pp. 10909-10922, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4020/94 $7.00+0.00

0040-4020(94)00675-X

Asymmetric Synthesis of β-Aminotetralins by Electrophilic Amination

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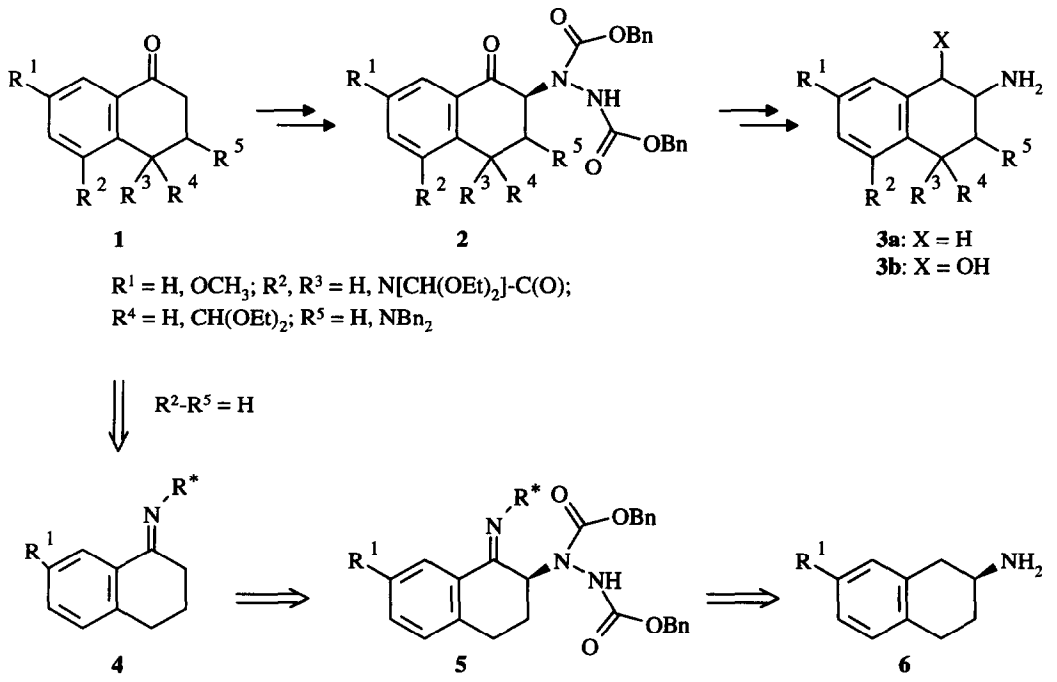
Abstract: An effective synthesis of β-aminotetralins (**6**) including an asymmetric electrophilic amination by di-t-butyl azodicarboxylate is reported. Depending on the chiral auxiliaries *(S)*-**7a-d**, the central intermediates **9** and **10** could be isolated in 62-80% de. Subsequent hydrolysis and reductive degradation resulted in the nonracemic final products **6** (57-84% ee). Separation of the diastereomeric intermediates by chromatography makes possible the synthesis of optically pure products. An induction model for the asymmetric amination is provided.

The electrophilic amination of chiral ketene acetal derivatives was described as an effective method for the synthesis of α-amino acids.[1] Recently, we reported the electrophilic amination of ketone enolates by dibenzyl azodicarboxylate, which constitutes a practical approach to conformationally constrained analogs of the neurotransmitters dopamine or serotonin.[2] Depending on the reduction and work up conditions, either the β-aryl amines **3a** or, highly diastereoselectively, the cis- or trans-amino alcohols **3b** were accessible from the corresponding α-aryl ketones **1** when the protected hydrazino ketones **2** served as central intermediates (Scheme 1). As an extension we envisioned to control not only the relative but also the absolute configuration by a chiral auxiliary. Herein, we describe the results of a study designed to show the versatility of that method by an asymmetric variant of the electrophilic amination.

For the sake of an asymmetric α-alkylation, chiral enamines or their salts were often employed as enolate equivalents.[3] Chiral enamines were also chosen for amination with alkyl azidoformate and (ethoxycarbonyl)nitrene.[4] The first asymmetric α-amination of prochiral ketone enolates with a chiral

α-chloro-α-nitroso reagent was recently reported by Oppolzer.[5] Our approach has been to focus on the preparation of the chiral imines **4** starting from the α-tetralones **1a,b** and various enantiomerically pure amino ethers. These imines should be deprotonated, then treated with dibenzyl azodicarboxylate and finally transformed to nonracemic β-aminotetralins **6**.

Scheme 1

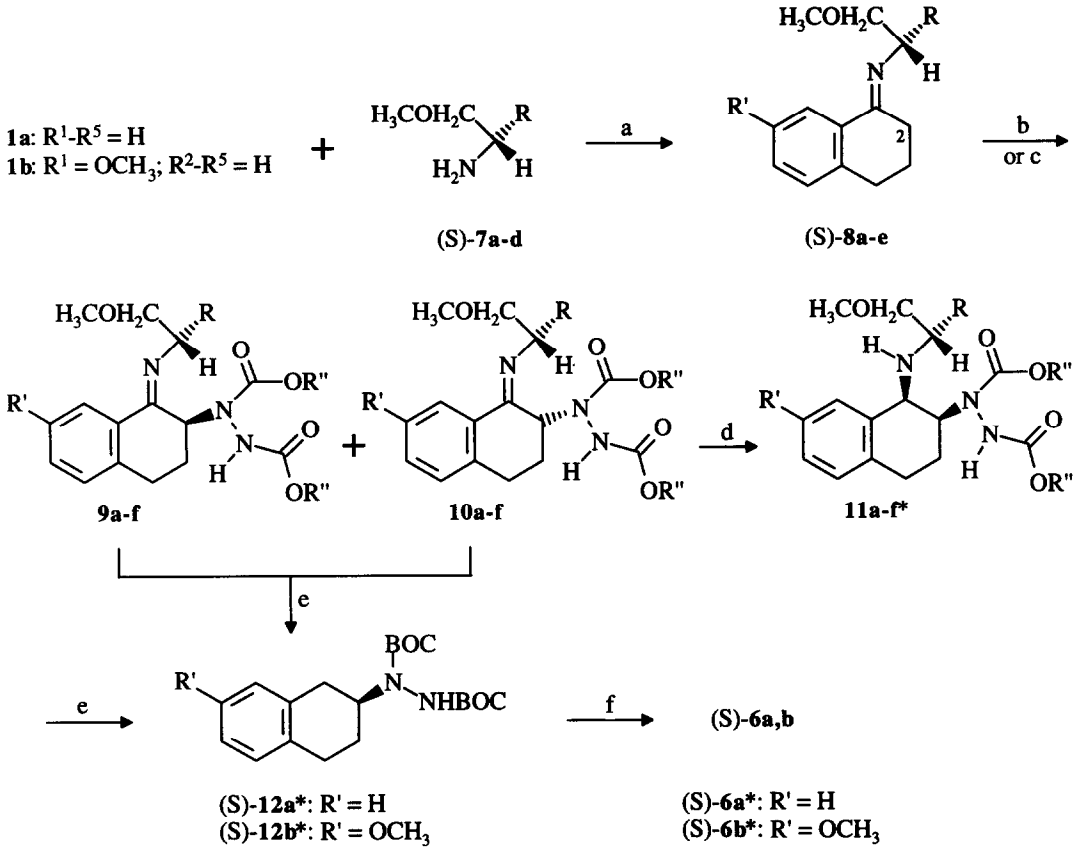


Using trifluoroacetic acid as a catalyst, the chiral imine *(S)*-**8a** was easily obtained from α-tetralone (**1a**) and the chiral amino ether *(S)*-**7a**.[6,7] A significant nuclear Overhauser effect between the methine proton of the chiral group and the protons 2-H_2 revealed that the imine *(S)*-**8a** is present in the (E)-configuration.

Deprotonation of the imine *(S)*-**8a** with lithium diisopropylamide (LDA) at -35 °C afforded an azaenolate, which was diastereoselectively attacked at -78° C by the electrophilic dibenzyl azodicarboxylate (DBAD). The reaction furnished **9f,10f** as a 7:3 mixture of diastereomers (determined by HPLC analysis of the crude product). The major isomer **9f** could be enriched by flash chromatography and characterized by ^{1}H-NMR spectroscopy (DMSO-d_6, 100 °C). However, we did not succeed in a complete separation of the diastereomers, since **9f** was partially converted into **10f** on the silica gel column.[8]

Due to an imine-enamine tautomerism *(S)*-**8a** can be successfully subjected to the electrophilic amination process without previous deprotonation.[9] Thus, *(S)*-**8a** reacted with DBAD in THF to give **9f,10f** (75:25) in 72% yield.

Scheme 2



* Only the major isomer is shown

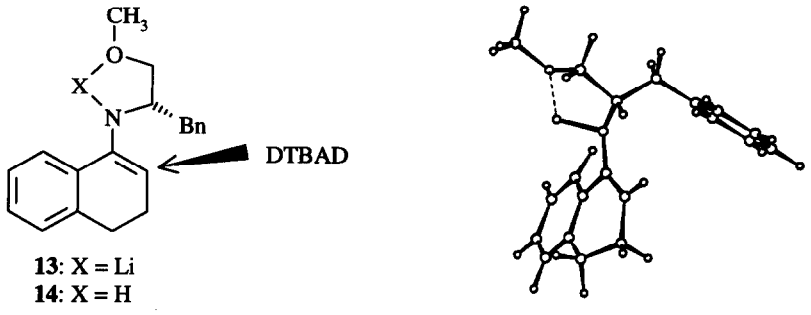
	7	8	9, 10	11
a: R = benzyl	-	R' = H	R' = H, R" = t-butyl	R' = H, R" = t-butyl
b: R = isobutyl	-	R' = H	R' = H, R" = t-butyl	R' = H, R" = t-butyl
c: R = isopropyl	-	R' = H	R' = H, R" = t-butyl	R' = H, R" = t-butyl
d: R = t-butyl	-	R' = H	R' = H, R" = t-butyl	R' = H, R" = t-butyl
e: R = isopropyl	---	R' = OCH_3	R' = OCH_3, R" = t-butyl	R' = OCH_3, R" = t-butyl
f: R = benzyl	---	---	R' = H, R" = benzyl	R' = H, R" = benzyl

a) TFA, toluene, reflux. b) 1. LDA, THF, -35 °C; 2. R"O_2C-N=N-CO_2R", THF, -78 °C.
c) R"O_2C-N=N-CO_2R", THF, RT. d) $NaBH_3CN$, glacial acetic acid, MeOH, RT. e) Pd/C, H_2 (12 - 15 bar), EtOH, 70 - 75 °C. f) 1. TFA/CH_2Cl_2 (1:1); 2. Raney-Ni, H_2 (50 bar), MeOH, RT.

Analogous reactions were accomplished with di-t-butyl azodicarboxylate (DTBAD). Thus deprotonation of *(S)*-**8a** with LDA, followed by amination with DTBAD, afforded the α-hydrazino imi-

nes **9a,10a** in a 86:14 ratio (yield: 86%). Similar results were obtained for the variant without LDA-deprotonation (**9a:10a** = 87:13, yield: 84%).[10]

In the course of the synthesis, the position 2 of the major isomer **9a** turned out to be *(S)*-configurated. Thus, the attack of the electrophile had predominantly occurred from the si-face (front side). The diastereoselection can be explained by the model shown in Figure 1.



13: X = Li
14: X = H

Figure 1. Induction model of the electrophilic attack (left), three-dimensional representation of **13** (right)

The asymmetric induction can be rationalized by a transition state, which is structurally related to the chelated Li-azaenolate conformer **13** characterized by the disposition of the benzyl group behind the azaallyl plane. Since the bottom side would then be protected, the attack of the electrophile (DTBAD) should predominantly occur from the front side. This assumption was confirmed by computional studies. Figure 1 shows the three-dimensional representation of **13** based on force field calculations and subsequent geometry optimization by MNDO.[11,12] The antiperiplanar disposition of the N,Li bond and the C,C double bond is confirmed by a recently described X-ray analysis of a SAMP based Li-hydrazone.[13] Due to a hydrogen bonding between the nitrogen proton and the oxygen atom of the methoxy group, an analogous structure can be postulated for the enamine **14**.

The following steps of the synthesis aimed at a reductive removal of the chiral auxiliary and a degradation of the hydrazino group. Thus, the hydrazino imines **9a,10a** and **9f,10f** could be easily reduced with $NaBH_3CN$/HOAc to give predominantly the cis-isomers **11a** and **11f**. The configuration of **11a** and **11f** was determined by the coupling constants and 2 D spectra. The reaction could also be conducted with BH_3·THF in lower yields, whereas our attempts with $NaBH_4$, $LiAlH_4$, $Li(Et)_3BH$ or $(^iBu)_2AlH$ failed.

Subsequently, the degradation of the protected hydrazines and the removal of the chiral auxiliary were investigated. Hydrolysis of **11f** by Pd/C-H_2 (for the activated benzylic positions) and Ra-Ni, H_2 (N,N-cleavage) resulted in decomposition. We assume that an intermediately formed hydrazino amine with a free $NHNH_2$ group decomposed under the more drastic conditions required for the removal of the chiral auxiliary. This problem was nonexistent for the degradation reactions of the BOC substituted analog **11a** with a hydrazine protection resistant to rather drastic conditions for the removal of *(S)*-**7a**. Starting from **11a**, the chiral auxiliary could be removed by Pd/C-H_2 in ethanol to give *(S)*-**12a** (77% yield; 54% recovery of the chiral auxiliary *(S)*-**7a**), when an H_2-pressure of 12 bar

and 70 °C was required. It is worthy to note, that *(S)*-**12a** can be also synthesized directly from the hydrazino imines **9a,10a** under the same reaction conditions. Thus, the synthesis was shortened, and the yield increased to 84%. However, this method does not allow a separation of the diastereomers at the intermediate stage of the protected hydrazino amine **11a**.

Finally, the degradation of the protected hydrazine *(S)*-**12a** to the amine *(S)*-**6a** was achieved by removal of the BOC groups with trifluoroacetic acid / dichloromethane (1:1), followed by reduction with Raney-Ni/H_2 (50 bar) in methanol. The optical rotation of **6a** proved its predominant *(S)*-configuration.[14] In consequence, the major products of the preliminary stages are also *(S)*-configurated in position 2.

In order to determine the enantiomeric excess of **6a**, the crude final product was subjected to derivatisation with *(R)*-phenylethyl isocyanate, followed by an analysis of the obtained diastereomers with the aid of HPLC. This was done after having conducted the complete reaction sequence without separation of particular diastereomers at the individual stages. The enantiomeric excess for *(S)*-**6a** amounted to 58% or 57%, depending on the cleavage method employed (Table 1).

In order to improve the asymmetric induction, we also employed the chiral amino ethers *(S)*-**7b-d**[7,15] derived from leucine, valine and t-leucine as alternative directing groups. Thus, the condensation reaction of **1a** with the methoxy amines **7b-d** gave the imines **8b-d** in 73-84% yield. The amination products **9b-d,10b-d** were easily prepared by treatment of *(S)*-**8b-d** with DTBAD in THF at room temp. The resulting selectivities ranged between 6.7:1 and 9:1. All the measurements of the crude products, i.e. before chromatographic purification, afforded lower ratios of isomers (Table 1). Therefore, we assumed that, due to a imine-enamine tautomerism under the influence of silica gel, it comes to an empimerisation which results in a equilibrium of the imines. Alternatively, **9b,c,10b,c** have been prepared via LDA deprotonation (method b).[16]

^{1}H-NMR coupling constants of **9a-e** indicated a prefered axial orientation of the protected hydrazino group ($^3J_{2,3a} \cong {}^3J_{2,3b} < 4.5$ Hz). This observation can be rationalized by the 1,3 allylic strain[17] between the hydrazino substituent and the chiral auxiliary which disfavors an equatorial disposition (Figure 2). The observed conformations are in accordance with free energy values based on force field calculations.

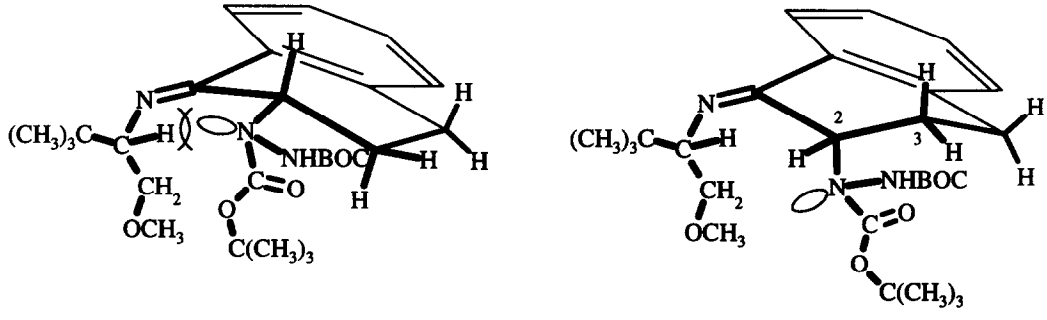


Figure 2. Three-dimensional representation of **9d** with equatorially (left) and axially (right) orientated hydrazino group

The reductive degradation of the substituted imines **9b-d,10b-d** to the amine *(S)*-**6a** via the hydrazino amines **11b-d** lead to 1%-2% epimerisation at C-2, probably due to an imine-enamine equilibrium[8] or a reversibility of the DTBAD addition. Starting from **9a,10a**, the epimerisation amounted to 11%. The alternative way, including the one-step removal of the chiral auxiliaries, produced only slightly lower values of enantiomeric excess, except for the auxiliary *(S)*-**7b** (Table 1).

Tab. 1: Diastereomeric excess of the imines **9a-d** and enantiomeric excess of the amines **6a,b** without separation of the minor isomers (determined by HPLC).

Starting ketone	Chiral auxiliary	Amination product (% de)		Final product (% ee)[a]
		Method b	Method c	
1a	*(S)*-**7a**	**9a,10a** (72)	**9a,10a** (76, 74[b])	*(S)*-**6a** (58, 57[c])
1a	*(S)*-**7b**	**9b,10b** (76)	**9b,10b** (74, 64[b])	*(S)*-**6a** (72, 52[c])
1a	*(S)*-**7c**	**9c,10c** (62, 38[b])	**9c,10c** (76, 58[b])	*(S)*-**6a** (73, 71[c])
1a	*(S)*-**7d**	**9d,10d** (46[b])	**9d,10d** (80, 74[b])	*(S)*-**6a** (76)
1b	*(S)*-**7c**			*(S)*-**6b** (84, 56[c])

[a] Determined after derivatisation with *(R)*-phenylethyl isocyanate
[b] Crude product
[c] Removal of the auxiliary by method d and e

The highest enantiomeric excess (76%) was achieved with the aid of the chiral auxiliary *(S)*-**7d** including the bulky t-butyl group. However, *(S)*-**7d** is less accessible since it is not a derivative of a proteinogenic amino acid. Therefore, from the preparative point of view, the amino ethers *(S)*-**7b** and *(S)*-**7c** also play an important role.

The complete reaction sequence could be run as well starting from 7-methoxy-1-tetralone (**1b**), when *(S)*-**7c** was used as a directing group. The synthesis via the hydrazino amine **11e** gave an enantiomeric excess of 84%, whereas the direct hydrogenolysis of the hydrazino imines **9e,10e** afforded only 56% ee. The enantiomeric excess was determined after derivatisation with *(R)*-phenylethyl isocyanate. A comparison of the α_D-values showed that **6b** was predominantly produced *(S)*-configurated.[18]

In order to obtain enantiomerically pure products, the resulting mixtures of diastereomers must be separated at an intermediate stage. Whereas the major diastereomer could not be separated by flash chromatography at the stage of the hydrazino imines **9,10**, we achieved a complete purification (de > 99%) of the hydrazino amine **11c** with the aid of preparative HPLC. This provides an efficient approach to the synthesis of enantiomerically pure aminotetralins, since for the following reaction steps no epimerisation or racemisation is to be expected.

EXPERIMENTAL

General: Tetrahydrofuran and toluene were distilled from sodium immediately before use. Diisopropylamine was distilled from CaH_2. All liquid reagents were also purified by distillation. Unless otherwise noted, reactions were conducted under dry nitrogen. Concentration of final product solutions was performed in vacuo with a rotatory evaporator.- Flash chromatography: 230 - 400 mesh silica gel.- Melting points: Büchi melting point apparatus, uncorrected.- IR: Perkin-Elmer Infrared Spectrophotometer 1600 FT-IR. MS: Varian CH 7 and 5989 A Mass Spectrometer with 59980 B particle beam LC/MS interface (Hewlett Packard).- NMR: Jeol 400 JNM-GX Spectrometer, 400 MHz, tertramethylsilane as internal standard.- Elementar analyses: Heraeus CHN Rapid instrument.- HPLC: columns: LiChrosorb® Si 60, LiChrospher® 100 RP-18; UV detector: Merck-Hitachi 655 A (254 nm), UV photodiodes-array detector: LKB 2140 Rapid spectral detector (LKB-Bromma); pump: Merck-Hitachi L-6000 and L-6200; integrator: Merck-Hitachi D 2000.- Preparative HPLC: column: LiChrosorb® Si 60; detector: Bischoff Spectrophotometric Detector 8201; pump: Knauer HPLC pump 64; integrator: Waters Data Module.- HPLC-MS: HPLC system: HP 1050 with variable UV-VIS-detector and integrator; MS: HP 5989 LC/MS-system with particle beam interface (Hewlett Packard).

(*S*)-(E)-1-Methoxy-3-phenyl-N-(1,2,3,4-tetrahydro-1-naphthyliden)-2-propylamine [(*S*)-8a]:

A mixture of (*S*)-**7a** [7] (1.38 g, 8.34 mmol), α-tetralone (1.23 g, 8.34 mmol) and trifluoroacetic acid (32 µl, 0.42 mmol) in 50 ml toluene was refluxed for 22 h in a system with a Dean-Stark trap for azeotropic removal of water. Removal of the solvent and distillition of the oily residue gave 2.2 g (88%) of (*S*)-**8a** as a yellow oil, Kugelrohr: 140 - 145 °C (0.5 torr).- $[\alpha]_D^{23}$ = -202.6° (c = 2.11, $CHCl_3$; Lit.[7]: $[\alpha]_D^{23}$ = -207.9° (c = 6.64, $CHCl_3$)).- IR (NaCl): 2925, 1630, 1125 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.51 - 1.62 (m, 1 H, 3-H_a), 1.69 - 1.78 (m, 1 H, 3-H_b), 1.92 (ddd, *J* = 16.1/8.1/4.7 Hz, 1 H, 2-H_a), 2.42 (ddd, *J* = 16.1/8.8/4.4 Hz, 1 H, 2-H_b), 2.64 - 2.74 (m, 2 H, 4-H_2), 2.77 (dd, *J* = 13.2/8.8 Hz, 1 H, CH_2phenyl), 3.03 (dd, *J* = 13.2/4.4 Hz, 1 H, CH_2phenyl), 3.37 (s, 3 H, OCH_3), 3.50 (dd, *J* = 9.5/7.3 Hz, 1 H, OCH_2), 3.60 (dd, *J* = 9.5/5.1 Hz, 1 H, OCH_2), 4.06 - 4.13 (m, 1 H, NCH), 7.08 - 7.29 (m, 8 H, aromat.), 8.23 (d, *J* = 7.3 Hz, 1 H, 8-H).- MS: m/z = 293 (M^+).- $C_{20}H_{23}NO$ (293.4) Calcd.: C 81.87 H 7.90 N 4.77 Found.: C 81.75 H 7.99 N 4.80.

(*S*)-(E)-1-Methoxy-4-methyl-N-(1,2,3,4-tetrahydro-1-naphthyliden)-2-pentylamine [(*S*)-8b]:

A mixture of (*S*)-**7b** [7] (1.42 g, 10.84 mmol), α-tetralone (1.27g, 8.7 mmol) and trifluoroacetic acid (34 µl, 0.44 mmol) in 50 ml toluene was treated and worked up as described for (*S*)-**8a** to give 1.89 g (84%) of (*S*)-**8b** as a yellow oil, Kugelrohr: 98 - 102 °C (0.08 torr).- $[\alpha]_D^{23}$ = -57.4° (c = 1.19, $CHCl_3$).- IR (NaCl): 2925, 1630, 1150 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 0.85 (d, *J* = 6.6 Hz, 3 H, CHCH_3), 0.91 (d, *J* = 6.6 Hz, 3 H, CHCH_3), 1.41 (ddd, *J* = 14/10.3/4 Hz, 1 H, CH_2CH$(CH_3)_2$), 1.51 - 1.61 (m, 2 H, CH_2CH$(CH_3)_2$), 1.91 - 1.98 (m, 2 H, 3-H_2), 2.58 (ddd, *J* = 16.1/7.3/5.9 Hz, 1 H, 2-H_a), 2.76 (ddd, *J* = 16.1/7.3/5.9 Hz, 1 H, 2-H_b), 2.84 (t, *J* = 6.2 Hz, 2 H, 4-H_2), 3.31 (s, 3 H, OCH_3), 3.39 (dd, *J* = 9.5/7.5 Hz, 1 H, OCH_2), 3.49 (dd, *J* = 9.5/4.4 Hz, 1 H, OCH_2), 3.96 - 4.02 (m, 1 H, NCH), 7.13 (d, *J* = 7.3 Hz, 1 H, 5-H), 7.21 (t, *J* = 7.3 Hz, 1 H, 7-H), 7.27 (t, *J* = 7.3 Hz, 1 H, 6-H), 8.21 (d, *J* = 7.3 Hz, 1 H, 8-H).- MS: m/z = 259 (M^+).- $C_{17}H_{25}NO$ (259.4) Calcd.: C 78.72 H 9.71 N 5.40 Found: C 78.51 H 10.13 N 5.43.

(*S*)-(E)-1-Methoxy-3-methyl-N-(1,2,3,4-tetrahydro-1-naphthyliden)-2-butylamine [(*S*)-8c]:

A mixture of (*S*)-**7c** [7] (2.58 g, 22 mmol), α-tetralone (2.57 g, 17.6 mmol) and trifluoroacetic acid (67 µl, 0.88 mmol) in 60 ml toluene was refluxed for 44 h and worked up as described for (*S*)-**8a** to give 3.33 g (77%) of (*S*)-**8c** as a yellow oil, Kugelrohr: 100 °C (0.3 torr).- $[\alpha]_D^{23}$ = -48.9° (c = 1.91, $CHCl_3$).- IR (NaCl): 2930, 1635, 1115 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 0.85 (d, *J* = 7.3 Hz, 3 H, CHCH_3), 0.88 (d, *J* = 6.6 Hz, 3 H, CHCH_3), 1.81 - 1.92 (m, 3 H, 3-H_2, C$H(CH_3)_2$), 2.48 (ddd, *J* = 16.1/7.3/5.1 Hz, 1 H, 2-H_a), 2.63 (ddd, *J* = 16.1/7.3/5.9 Hz, 1 H, 2-H_b), 2.76 (t, *J* = 6.2 Hz, 2 H, 4-H_2),

3.23 (s, 3 H, OCH_3), 3.36 (dd, J = 9.5/7.3 Hz, 1 H, OCH_2), 3.56 (dd, J = 9.5/4.4 Hz, 1 H, OCH_2), 3.61 (ddd, J = 10.3/7.3/4.4 Hz, 1 H, NCH), 7.06 (d, J = 7.3 Hz, 1 H, 5-H), 7.14 (t, J = 7.3 Hz, 1 H, 7-H), 7.20 (ddd, J = 7.3/7.3/1.5 Hz, 1 H, 6-H), 8.17 (d, J = 7.3 Hz, 1 H, 8-H).- MS (CI): m/z = 246 ([M + H]$^+$).- $C_{16}H_{23}NO$ (245.4) Calcd.: C 78.32 H 9.45 N 5.71 Found: C 78.35 H 9.64 N 5.72.

(*S*)-(E)-1-Methoxy-3,3-dimethyl-N-(1,2,3,4-tetrahydro-1-naphthyliden)-2-butylamine [(*S*)-8d]:

A mixture of (*S*)-**7d** [15] (0.93 g, 6.9 mmol), α-tetralone (0.86 g, 5.9 mmol) and trifluoroacetic acid (23 µl, 0.3 mmol) in 45 ml toluene was refluxed for 32 h and worked up as described for (*S*)-**8a** to give 1.11 g (73%) of (*S*)-**8d** as a yellow oil, Kugelrohr: 90 °C (0.04 torr).- $[\alpha]_D^{23}$ = -50.0° (c = 1.95, $CHCl_3$).- IR (NaCl): 2950, 1635, 1120 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 0.95 (s, 9 H, $C(CH_3)_3$), 1.87 - 1.99 (m, 2 H, 3-H_2), 2.53 (ddd, J = 16.1/8.1/5.1 Hz, 1 H, 2-H_a), 2.75 (ddd, J = 16.1/8.1/5.1 Hz, 1 H, 2-H_b), 2.83 (t, J = 5.9 Hz, 2 H, 4-H_2), 3.25 (s, 3 H, OCH_3), 3.40 (dd, J = 8.8/8.1 Hz, 1 H, OCH_2), 3.59 (dd, J = 8.1/2.9 Hz, 1 H, OCH_2), 3.72 (dd, J = 8.8/2.9 Hz, 1 H, NCH), 7.13 (d, J = 7.3 Hz, 1 H, 5-H), 7.20 - 7.29 (m, 2 H, 6-H, 7-H), 8.29 (d, J = 8.1 Hz, 1 H, 8-H).- MS: m/z = 259 (M$^+$).- $C_{17}H_{25}NO$ (259.4) Calcd.: C 78.72 H 9.71 N 5.40 Found: C 78.36 H 9.88 N 5.65.

(*S*)-(E)-1-Methoxy-3-methyl-N-(1,2,3,4-tetrahydro-7-methoxy-1-naphthyliden)-2-butylamine [(*S*)-8e]

A mixture of (*S*)-**7c** [7] (645 mg, 5.5 mmol), 7-methoxy-1-tetralone (775 mg, 4.4 mmol) and trifluoroacetic acid (17 µl, 0.22 mmol) in 40 ml toluene was refluxed for 21 h and worked up as described for (*S*)-**8a** to give 1.10 g (91%) of (*S*)-**8e** as a yellow oil, Kugelrohr: 140 °C (0.04 torr).- $[\alpha]_D^{23}$ = -28.3° (c = 2.3, $CHCl_3$).- IR (NaCl): 2935, 1635, 1115 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 0.92 (d, J = 6.6 Hz, 3 H, $CHC\underline{H}_3$), 0.96 (d, J = 6.6 Hz, 3 H, $CHC\underline{H}_3$), 1.88 - 1.98 (m, 3 H, $C\underline{H}(CH_3)_2$, 3-H_2), 2.50 - 2.57 (m, 1 H, 2-H_a), 2.62 - 2.73 (m, 1 H, 2-H_b), 2.77 (t, J = 5.9 Hz, 2 H, 4-H_2), 3.31 (s, 3 H, $CH_2OC\underline{H}_3$), 3.44 (dd, J = 8.8/8.1 Hz, 1 H, OCH_2), 3.63 (dd, J = 9.5/4.4 Hz, 1 H, OCH_2), 3.68 - 3.72 (m, 1 H, NCH), 3.83 (s, 3 H, $COCH_3$), 6.88 (dd, J = 8.1/2.9 Hz, 1 H, 7-H), 7.05 (d, J = 8.1 Hz, 1 H, 5-H), 7.83 (d, J = 2.9 Hz, 1 H, 6-H).- MS: m/z = 275 (M$^+$).- $C_{17}H_{25}NO_2$ (275.4) Calcd.: C 74.14 H 9.15 N 5.09 Found: C 74.17 H 9.22 N 4.98.

Di-tert-butyl 1-{(*S*)-(Z)-1,2,3,4-tetrahydro-1-[(*S*)-1-benzyl-2-methoxyethylimino]-2-naphthyl}-1,2-hydrazinedicarboxylate (9a)
Di-tert-butyl 1-{(*R*)-1,2,3,4-tetrahydro-1-[(*S*)-1-benzyl-2-methoxyethylimino]-2-naphthyl}-1,2-hydrazinedicarboxylate (10a)

a) To a solution of diisopropylamine (0.28 ml, 2 mmol) in 15 ml THF n-BuLi (1.25 ml, 1.6 M in hexane) was added at -78 °C. The mixture was stirred for 15 min at 0 °C and then cooled to -35 °C. (*S*)-**8a** (586 mg, 2 mmol) in 6 ml THF was added over 15 min, and the mixture was stirred for 1 h. The solution was then cooled to -78 °C and a precooled solution (-78 °C) of di-t-butyl azodicarboxylate (690 mg, 3 mmol) in 8 ml THF was added. After 3 min, the mixture was treated with 10% aqueous NH_4Cl and extracted with ether. The organic layer was dried ($MgSO_4$), the solvent evaporated and the residue purified by flash chromatography (petroleum ether - EtOAc, 7:1) to give 898 mg (86%) of **9a/10a** (mixture of diastereomers) as a yellowish solid.- b) To a solution of (*S*)-**8a** (36 mg, 0.123 mmol) in 4 ml THF di-t-butyl azodicarboxylate (37 mg, 0.16 mmol) was added at room temp. After stirring for 24 h, the mixture was evaporated and purified as described for a) to give 54 mg (84%) of **9a/10a** as a yellowish solid. Ratios **9a/10a**: see table 1.- IR (KBr): 3300, 2980, 1750, 1705, 1630, 1155 cm^{-1}.- ^{1}H-NMR (major isomer **9a**, DMSO-d_6, 100 °C): δ (ppm) = 1.44 (s, 9 H, $C(CH_3)_3$), 1.45 (s, 9 H, $C(CH_3)_3$), 1.91 - 1.96 (m, 1 H, 3-H_a), 2.27 - 2.31 (m, 1 H, 3-H_b), 2.60 - 2.75 (m, 2 H, 4-H_a, $C\underline{H}_2$phenyl), 2.96 (m, 1 H, $C\underline{H}_2$phenyl), 3.20 (s, 3 H, OCH_3), 3.29 - 3.31 (m, 1 H, 4-H_b), 3.58 - 3.66 (m, 2 H, OCH_2), 4.02 - 4.05 (m, 1 H, NCH), 4.42 (br. s, 1 H, 2-H_{eq}), 6.95 - 7.26 (m, 9 H, aromat.).- MS: m/z = 524 ([M + H]$^+$).- $C_{30}H_{41}N_3O_5$ (523.7) Calcd.: C 68.81 H 7.89 N 8.02 Found: C 68.85 H 8.04 N 7.83.

Di-tert-butyl 1-{*(S)*-(Z)-1,2,3,4-tetrahydro-1-[*(S)*-1-methoxymethyl-3-methylbutylimino]-2-naphthyl}-1,2-hydrazinedicarboxylate (9b)
Di-tert-butyl 1-{*(R)*-1,2,3,4-tetrahydro-1-[*(S)*-1-methoxymethyl-3-methylbutylimino]-2-naphthyl}-1,2-hydrazinedicarboxylate (10b)

a) To a solution of *(S)*-**8b** (195 mg, 0.75 mmol) in 12 ml THF di-t-butyl azodicarboxylate (230 mg, 1 mmol) was added at room temp. After stirring for 24 h, the mixture was evaporated and purified by flash chromatography (petroleum ether - EtOAc, 86:14) to give 313 mg (85%) of **9b/10b** (mixture of diastereomers) as a yellowish solid. The major isomer **9b** could be enriched by flash chromatography (petroleum ether - EtOAc, 9:1).- b) To a solution of freshly prepared LDA (0.92 ml, 0.33 M in THF) in 2 ml THF a solution of *(S)*-**8b** (78 mg, 0.3 mmol) in 3 ml THF was added dropwise at -35 °C, and the mixture was stirred for 1 h. The solution was then cooled to -78 °C and a precooled solution (-78 °C) of di-t-butyl azodicarboxylate (92 mg, 0.4 mmol) in 8 ml THF was added. After 3 min the mixture was treated with 10% aqueous NH_4Cl and extracted with ether. The organic layer was dried ($MgSO_4$), the solvent evaporated and the residue purified as described for a) to give 120 mg (82%) of **9b/10b** as a yellowish solid. Ratios **9b/10b**: see table 1.- IR (NaCl): 3300, 2930, 1745, 1705, 1630, 1155 cm^{-1}.- ^{1}H-NMR (major isomer **9b**, DMSO-d_6, 100 °C): δ (ppm) = 0.86 (d, J = 6.6 Hz, 3 H, $CHC\underline{H}_3$), 0.88 (d, J = 5.9 Hz, 3 H, $CHC\underline{H}_3$), 1.28 (s, 9 H, $C(CH_3)_3$), 1.32 - 1.44 (m, 3 H, $C\underline{H}_2C\underline{H}(CH_3)_2$), 1.41 (s, 9 H, $C(CH_3)_3$), 1.90 - 1.96 (m, 1 H, 3-H_a), 2.20 - 2.25 (m, 1 H, 3-H_b), 2.60 (br. d, J = 16.9 Hz, 1 H, 4-H_a), 3.11 - 3.19 (m, 1 H, 4-H_b), 3.29 (s, 3 H, OCH_3), 3.45 - 3.55 (m, 2 H, OCH_2), 3.86 (m-centered, 1 H, NCH), 5.08 (br. s, 1 H, 2-H_{eq}), 7.12 (t, J = 8.1 Hz, 1 H, 7-H), 7.17 (d, J = 7.7 Hz, 1 H, 5-H), 7.24 (t, J = 7.7 Hz, 1 H, 6-H), 8.05 (d, J = 8.1 Hz, 1 H, 8-H).- MS (CI): m/z = 490 ([M + H]$^+$).- $C_{27}H_{43}N_3O_5$ (489.7) Calcd.: C 66.23 H 8.85 N 8.58 Found: C 66.08 H 8.61 N 8.63.

Di-tert-butyl 1-{*(S)*-(Z)-1,2,3,4-tetrahydro-1-[*(S)*-1-methoxymethyl-2-methylpropylimino]-2-naphthyl}-1,2-hydrazinedicarboxylate (9c)
Di-tert-butyl 1-{*(R)*-1,2,3,4-tetrahydro-1-[*(S)*-1-methoxymethyl-2-methylpropylimino]-2-naphthyl}-1,2-hydrazinedicarboxylate (10c)

a) *(S)*-**8c** (184 mg, 0.75 mmol) was treated and worked up as described for **9b** a) (using petroleum ether - EtOAc, 87:13, for flash chromatography) to give 303 mg (85%) **9c/10c** (mixture of diastereomers) as a yellowish oil. The major isomer **9c** could be enriched by flash chromatography.- b) *(S)*-**8c** (123 mg, 0.5 mmol) in 5 ml THF, LDA (1.5 ml, 0.33 M in THF) in 4 ml THF and di-t-butyl azodicarboxylate (150 mg, 0.65 mmol) was treated and worked up as described for **9b** b). Purification: see a). Ratios **9c/10c**: see table 1.- IR (NaCl): 3300, 2975, 1745, 1700, 1155 cm^{-1}.- ^{1}H-NMR (major isomer **9c**, DMSO-d_6, 100 °C): δ (ppm) = 0.85 (d, J = 7.3 Hz, 3 H, $CHC\underline{H}_3$), 0.89 (d, J = 7.3 Hz, 3 H, $CHC\underline{H}_3$), 1.28 (s, 9 H, $C(CH_3)_3$), 1.41 (s, 9 H, $C(CH_3)_3$), 1.77 - 1.86 (m, 1 H, $C\underline{H}(CH_3)_2$), 1.89 - 1.96 (m, 1 H, 3-H_a), 2.19 - 2.23 (m, 1 H, 3-H_b), 2.59 - 2.63 (m, 1 H, 4-H_a), 3.10 - 3.18 (m, 1 H, 4-H_b), 3.29 (s, 3 H, OCH_3), 3.56 - 3.60 (m, 3 H, NCH, OCH_2), 5.06 (m-centered, 1 H, 2-H_{eq}), 7.12 (d, J = 7.3 Hz, 1 H, 5-H), 7.19 (t, J = 8.1 Hz, 1 H, 7-H), 7.25 (t, J = 7.3 Hz, 1 H, 6-H), 8.07 (d, J = 8.1 Hz, 1 H, 8-H).- MS (CI): m/z = 476 ([M + H]$^+$).- $C_{26}H_{41}N_3O_5$ (475.6) Calcd.: C 65.66 H 8.69 N 8.83 Found: C 65.51 H 8.87 N 8.77.

Di-tert-butyl 1-{*(S)*-(Z)-1,2,3,4-tetrahydro-1-[*(S)*-1-methoxymethyl-2,2-dimethylpropylimino]-2-naphthyl}-1,2-hydrazinedicarboxylate (9d)
Di-tert-butyl 1-{*(R)*-1,2,3,4-tetrahydro-1-[*(S)*-1-methoxymethyl-2,2-dimethylpropylimino]-2-naphthyl}-1,2-hydrazinedicarboxylate (10d)

To a solution of *(S)*-**8d** (130 mg, 0.5 mmol) in 10 ml THF di-t-butyl azodicaroxylate (460 mg, 2 mmol) was added at room temp. After stirring for 48 h the mixture was evaporated and purified by flash chromatography (petroleum ether - EtOAc, 85:15) to give 209 mg (85%) of **9d/10d** (mixture of diastereomers) as a yellowish oil. Ratios **9d/10d**: see table 1. The major isomer **9d** could be enriched

by flash chromatography.- IR (NaCl): 3290, 2975, 1745, 1700, 1155 cm^{-1}.- ^{1}H-NMR (major isomer **10d**, DMSO-d_6, 100 °C): δ (ppm) = 0.90 (s, 9 H, $CHC(C\underline{H}_3)_3$), 1.27 (s, 9 H, $OC(CH_3)_3$), 1.43 (s, 9 H, $OC(CH_3)_3$), 1.89 - 1.96 (m, 1 H, 3-H_a), 2.17 - 2.24 (m, 1 H, 3-H_b), 2.57 - 2.63 (m, 1 H, 4-H_a), 3.10 - 3.18 (m, 1 H, 4-H_b), 3.28 (s, 3 H, OCH_3), 3.45 (dd, *J* = 8.1/2.9 Hz, 1 H, OCH_2), 3.60 - 3.70 (m, 2 H, OCH_2, NCH), 5.10 (t, *J* = 4.4 Hz, 1 H, 2-H_{eq}), 7.13 (d, *J* = 7.3 Hz, 1 H, 5-H), 7.17 (t, *J* = 7.3 Hz, 1 H, 7-H), 7.25 (ddd, *J* = 7.3/7.3/1.5 Hz, 1 H, 6-H), 8.11 (d, *J* = 8.1 Hz, 1 H, 8-H).- MS (CI): m/z = 490 ($[M + H]^+$).- $C_{27}H_{43}N_3O_5$ (489.7) Calcd.: C 66.23 H 8.85 N 8.58 Found: C 66.21 H 8.83 N 8.44.

Di-tert-butyl 1-{*(S)*-(Z)-1,2,3,4-tetrahydro-7-methoxy-1-[*(S)*-1-methoxymethyl-2-methylpropylimino]-2-naphthyl}-1,2-hydrazinedicarboxylate (9e)
Di-tert-butyl 1-{*(R)*-1,2,3,4-tetrahydro-7-methoxy-1-[*(S)*-1-methoxymethyl-2-methylpropylimino]- 2-naphthyl}-1,2-hydrazinedicarboxylate (10e)

To a solution of *(S)*-**8e** (207 mg, 0.75 mmol) in 13 ml THF was added di-t-butyl azodicaroxylate (690 mg, 3 mmol) at room temp. After stirring for 20 h, the mixture was evaporated and purified by flash chromatography (petroleum ether - EtOAc, 85:15) to give 293 mg (77%) of **9e/10e** (mixture of diastereomers) as a yellowish oil. The major isomer **9e** could be enriched by flash chromatography.- IR (NaCl): 3300, 2975, 1745, 1705, 1155 cm^{-1}.- ^{1}H-NMR (major isomer **9e**, DMSO-d_6, 100 °C): δ (ppm) = 0.86 (d, *J* = 6.6 Hz, 3 H, $CHC\underline{H}_3$), 0.90 (d, *J* = 6.6 Hz, 3 H, $CHC\underline{H}_3$), 1.30 (s, 9 H, $C(CH_3)_3$), 1.42 (s, 9 H, $C(CH_3)_3$), 1.81 - 1.90 (m, 2 H, $C\underline{H}(CH_3)_2$, 3-H_a), 2.18 - 2.21 (m, 1 H, 3-H_b), 2.54 - 2.58 (m, 1 H, 4-H_a), 3.07 (br. d, *J* = 11.7 Hz, 1 H, 4-H_b), 3.30 (s, 3 H, $CH_2OC\underline{H}_3$), 3.56 (br. s, 1 H, NCH), 3.61 (br. s, 2 H, OCH_2), 3.74 (s, 3 H, $COCH_3$), 5.05 (br. s, 1 H, 2-H_{eq}), 6.89 (d, *J* = 8.8 Hz, 1 H, 6-H), 7.07 (d, *J* = 8.8 Hz, 1 H, 5-H), 7.63 (s, 1 H, 8-H).- MS (CI): m/z = 506 ($[M + H]^+$).- $C_{27}H_{43}N_3O_6$ (505.7) Calcd.: C 64.13 H 8.57 N 8.31 Found: C 64.20 H 8.29 N 8.33.

Di-tert-butyl 1-{*(S)*-(Z)-1,2,3,4-tetrahydro-1-[*(S)*-1-benzyl-2-methoxyethylimino]-2-naphthyl}-1,2-hydrazinedicarboxylate (9f)
Di-tert-butyl 1-{*(R)*-1,2,3,4-tetrahydro-1-[*(S)*-1-benzyl-2-methoxyethylimino]-2-naphthyl}-1,2-hydrazinedicarboxylate (10f)

a) To a solution of diisopropylamine (112 µl, 0.8 mmol) in 6 ml THF was added n-BuLi (0.8 ml, 1.6 M in hexane) at -78 °C. The mixture was stirred for 15 min at 0 °C and then cooled to -35°C. The chiral imine *(S)*-**8a** (234 mg, 0.8 mmol) in 6 ml THF was added over 10 min and the mixture was stirred for 1 h. The solution was then cooled to -78 °C and a precooled solution (-78 °C) of dibenzyl azodicarboxylate (360 mg, 1.2 mmol) in 8 ml THF was added. After 3 min, the mixture was treated with 10 % aqueous NH_4Cl and extracted with ether. The organic layer was dried ($MgSO_4$), the solvent evaporated and the residue purified by flash chromatography (petroleum ether - EtOAc, 8:2) to give 314 mg (66%) of **9f/10f** (mixture of diastereomers, crude product: **9f/10f** = 7:3) as a yellow oil. The major isomer **9f** could be enriched by flash chromatography (petroleum ether - EtOAc, 85:15).- b) To a solution of *(S)*-**8a** (33 mg, 0.11 mmol) in 4 ml THF was added dibenzyl azodicarboxylate (45 mg, 0.15 mmol) at 0 °C. After stirring at 0 °C for 1 h the mixture was evaporated and purified as described for a) to give 47 mg (72%) **9f/10f** (mixture of diastereomers, **9f/10f** = 3:1) as a yellow oil.- IR (NaCl): 3265, 2940, 1755, 1720, 1630, 1220 cm^{-1}.- ^{1}H-NMR (major isomer **9f**, DMSO-d_6, 100 °C): δ (ppm) = 1.27 (br. d, *J* = 13.9 Hz, 1 H, 3-H_a), 1.91 (br. d, *J* = 13.9 Hz, 1 H, 3-H_b), 2.32 (br. d, *J* = 17.6 Hz, 1 H, 4-H_a), 2.56 - 2.59 (m, 1 H, $CHC\underline{H}_2$phenyl), 2.96 (m, 2 H, 4-H_b, $CHC\underline{H}_2$phenyl), 3.24 (s, 3 H, OCH_3), 3.53 - 3.57 (m, 2 H, $C\underline{H}_2OCH_3$), 4.03 (m-centered, 1 H, NCH), 4.45 (m-centered, 1 H, 2-H), 4.93 (s, 2 H, $OC\underline{H}_2$phenyl), 5.09 (s, 2 H, $OC\underline{H}_2$phenyl), 6.98 - 7.31 (m, 18 H, aromat.), 8.03 (d, *J* = 7.3 Hz, 1 H, 8-H).- MS (CI): m/z = 592 ($[M + H]^+$).- $C_{36}H_{37}N_3O_5$ (591.7) Calcd.: C 73.08 H 6.30 N 7.10 Found: C 73.50 H 6.25 N 6.72.

Di-tert-butyl 1-{(1*R*,2*S*)-1,2,3,4-tetrahydro-1-[(*S*)-1-benzyl-2-methoxyethylamino]-2-naphthyl}-1,2-hydrazinedicarboxylate (11a)

A mixture of **9a/10a** (733 mg, 1.4 mmol), $NaBH_3CN$ (264 mg, 4.2 mmol) and glacial acetic acid (0.35 ml, 5.6 mmol) in 35 ml methanol was stirred for 2 h at room temp. Then the mixture was concentrated, treated with satd. aqueous $NaHCO_3$ and extracted with ether. The organic layer was dried ($MgSO_4$), evaporated and the residue was purified by flash chromatography (petroleum ether - EtOAc, 88:12) to give 611 mg (83%) of **11a** (mixture of diastereomers) as a colorless solid.- IR (NaCl): 3280, 2980, 1735, 1700, 1155 cm^{-1}.- ^{1}H-NMR (major isomer **11a**, DMSO-d_6, 100 °C): δ (ppm) = 1.40 (s, 9 H, $C(CH_3)_3$), 1.42 (s, 9 H, $C(CH_3)_3$), 1.77 (br. s, 1 H, 3-H_a), 1.97 - 2.09 (m, 1 H, 3-H_b), 2.58 - 2.63 (m, 1 H, CH_2phenyl), 2.72 - 2.83 (m, 3 H, 4-H_2, CH_2phenyl), 3.03 (m-centered, 1 H, NCH), 3.25 - 3.27 (m, 2 H, OCH_2), 3.27 (s, 3 H, OCH_3), 4.01 (s, 1 H, 1-H), 4.18 (br. d, *J* = 8.8 Hz, 1 H, 2-H), 7.00 - 7.27 (m, 9 H, aromat.), 8.13 (br. s, 1 H, NH).- MS (CI): m/z = 526 ($[M + H]^+$).- $C_{30}H_{43}N_3O_5$ (525.7) Calcd.: C 68.54 H 8.24 N 7.99 Found: C 68.45 H 8.42 N 7.92.

Di-tert-butyl 1-{(1*R*,2*S*)-1,2,3,4-tetrahydro-1-[(*S*)-1-methoxymethyl-3-methylbutylamino]-2-naphthyl}-1,2-hydrazinedicarboxylate (11b)

A mixture of **9b/10b** (367 mg, 0.75 mmol), $NaBH_3CN$ (189 mg, 3 mmol) and glacial acetic acid (0.21 ml, 3.75 mmol) in 20 ml methanol was stirred for 3 h at room temp. and worked up as described for **11a** (using petroleum ether - EtOAc, 85:15 - 8:2) to give 611 mg (83%) of **11b** (mixture of diastereomers) as a colorless solid.- IR (KBr): 3270, 2960, 1745, 1690, 1175 cm^{-1}.- ^{1}H-NMR (major isomer **11b**, DMSO-d_6, 140 °C): δ (ppm) = 0.69 (d, *J* = 6.6 Hz, 3 H, $CHCH_3$), 0.80 (d, *J* = 6.6 Hz, 3 H, $CHCH_3$), 1.21 - 1.27 (m, 2 H, $CH_2CH(CH_3)_2$), 1.41 (s, 9 H, $C(CH_3)_3$), 1.43 (s, 9 H, $C(CH_3)_3$), 1.48 - 1.56 (m, 1 H, $CH(CH_3)_2$), 1.82 - 1.85 (m, 1 H, 3-H_a), 2.09 - 2.19 (m, 1 H, 3-H_b), 2.76 - 2.80 (m, 2 H, 4-H_a, NCH), 2.94 (dd, *J* = 16.9/6.6 Hz, 1 H, 4-H_b), 3.26 - 3.31 (m, 2 H, OCH_2), 3.31 (s, 3 H, OCH_3), 3.99 (br. s, 1 H, 1-H), 4.18 (br. d, *J* = 11.7 Hz, 1 H, 2-H_{ax}), 7.04 - 7.13 (m, 3 H, aromat.), 7.22 (d, *J* = 7.3 Hz, 1 H, aromat.), 7.92 (br. s, 1 H, NH).- MS: m/z = 492 (M^+).- $C_{27}H_{45}N_3O_5$ (491.7) Calcd.: C 65.96 H 9.23 N 8.55 Found: C 66.22 H 9.30 N 8.55.

Di-tert-butyl 1-{(1*R*,2*S*)-1,2,3,4-tetrahydro-1-[(*S*)-1-methoxymethyl-2-methylpropylamino]-2-naphthyl}-1,2-hydrazinedicarboxylate (11c)

A mixture of **9c/10c** (266 mg, 0.56 mmol), $NaBH_3CN$ (141 mg, 2.24 mmol) and glacial acetic acid (0.16 ml, 2.8 mmol) in 20 ml methanol was stirred for 3 h at room temp. and worked up as described for **11a** (using petroleum ether - EtOAc, 85:15) to give 232 mg (87%) of **11c** (mixture of diastereomers) as a colorless solid. The major isomer was separated by preparative HPLC (LiChrosorb® Si 60; n-hexane - EtOAc, 85:15; 20 ml/min). Colorless solid, m. p. 138 - 139 °C.- $[\alpha]_D^{23}$ = -38.1° (c = 0.84, $CHCl_3$).- IR (KBr): 3260, 2970, 1735, 1700, 1170 cm^{-1}.- ^{1}H-NMR (DMSO-d_6, 100 °C): δ (ppm) = 0.71 (d, *J* = 6.6 Hz, 3 H, $CHCH_3$), 0.79 (d, *J* = 6.6 Hz, 3 H, $CHCH_3$), 1.40 (s, 9 H, $C(CH_3)_3$), 1.42 (s, 9 H, $C(CH_3)_3$), 1.79 (m-centered, 2 H, $CH(CH_3)_2$, 3-H_a), 2.09 - 2.18 (m, 1 H, 3-H_b), 2.55 - 2.57 (m, 1 H, NCH), 2.74 - 2.80 (m, 1 H, 4-H_a), 2.91 - 2.95 (m, 1 H, 4-H_b), 3.21 - 3.26 (m, 1 H, OCH_2), 3.31 (s, 3 H, OCH_3), 3.36 (dd, *J* = 10.3/4.4 Hz, 1 H, OCH_2), 3.96 (s, 1 H, 1-H), 4.16 (dd, *J* = 11.0/2.9 Hz, 1 H, 2-H_{ax}), 7.05 - 7.13 (m, 3 H, aromat.), 7.20 (d, *J* = 7.3 Hz, 1 H, aromat.).- MS (CI): m/z = 478 ($[M + H]^+$).- $C_{26}H_{43}N_3O_5$ (477.7) Calcd.: C 65.38 H 9.07 N 8.80 Found: C 65.23 H 9.09 N 8.70.

Di-tert-butyl 1-{(1*R*,2*S*)-1,2,3,4-tetrahydro-1-[(*S*)-1-methoxymethyl-2,2-dimethylpropylamino]-2-naphthyl}-1,2-hydrazinedicarboxylate (11d)

A mixture of **9d/10d** (215 mg, 0.44 mmol), $NaBH_3CN$ (113 mg, 1.8 mmol) and glacial acetic acid (0.13 ml, 2.3 mmol) in 16 ml methanol was stirred for 18 h at room temp. and worked up as described for **11a** (using petroleum ether - EtOAc, 85:15) to give 134 mg (62%) of **11d** (mixture of diastereomers) as a colorless solid.- IR (KBr): 3320, 2980, 1740, 1705, 1150 cm^{-1}.- ^{1}H-NMR (major isomer **11d**, DMSO-d_6, 100 °C): δ (ppm) = 0.69 (s, 9 H, $CHC(CH_3)_3$), 1.41 (s, 9 H, $OC(CH_3)_3$), 1.43 (s, 9 H,

$OC(CH_3)_3$), 1.79 (m-centered, 1 H, 3-H_a), 2.20 - 2.27 (m, 1 H, 3-H_b), 2.38 (br. s, 1 H, NCH), 2.74 - 2.82 (m, 1 H, 4-H_a), 2.94 - 2.98 (m, 1 H, 4-H_b), 3.30 (s, 3 H, OCH_3), 3.38 (dd, J = 10.3/4.4 Hz, 1 H, OCH_2), 3.55 (dd, J = 10.3/4.4 Hz, 1 H, OCH_2), 4.07 (br. s, 1 H, 1-H), 4.17 (ddd, J = 11.0/4.4/3.7 Hz, 1 H, 2-H_{ax}), 7.02 - 7.13 (m, 3 H, aromat.), 7.18 (d, J = 6.6 Hz, 1 H, aromat.).- MS (CI): m/z = 492 ([M + H]$^+$).- $C_{27}H_{45}N_3O_5$ (491.7) Calcd.: C 65.96 H 9.23 N 8.55 Found.: C 65.81 H 9.25 N 8.65.

Di-tert-butyl 1-{(1*R*,2*S*)-1,2,3,4-tetrahydro-7-methoxy-1-[(*S*)-1-methoxymethyl-2-methylpropylamino]-2-naphthyl}-1,2-hydrazinedicarboxylate (11e)

A mixture of **9e/10e** (293 mg, 0.58 mmol), $NaBH_3CN$ (145 mg, 2.3 mmol) and glacial acetic acid (0.17 ml, 3 mmol) in 17 ml methanol was stirred for 5.5 h at room temp. and worked up as described for **11a** (using petroleum ether - EtOAc, 85:15) to give 192 mg (65%) of **11e** (mixture of diastereomers) as a colorless solid.- IR (KBr): 3285, 2960, 1740, 1700, 1160 cm^{-1}.- ^{1}H-NMR (major isomer **11e**, DMSO-d_6, 100 °C): δ (ppm) = 0.76 (d, J = 6.6 Hz, 3 H, $CHC\underline{H}_3$), 0.82 (d, J = 6.6 Hz, 3 H, $CHC\underline{H}_3$), 1.40 (s, 9 H, $C(CH_3)_3$), 1.42 (s, 9 H, $C(CH_3)_3$), 1.77 (m-centered, 1 H, 3-H_a), 1.86 (m-centered, 1 H, $C\underline{H}(CH_3)_2$), 2.03 - 2.14 (m, 1 H, 3-H_b), 2.59 (br. s, 1 H, NCH), 2.65 - 2.69 (m, 1 H, 4-H_a), 2.82 - 2.86 (m, 1 H, 4-H_b), 3.10 (m-centered, 1 H, OCH_2), 3.32 (s, 3 H, $CH_2OC\underline{H}_3$), 3.35 - 3.37 (m, 1 H, OCH_2), 3.71 (s, 3 H, $COCH_3$), 3.91 (s, 1 H, 1-H), 4.15 - 4.18 (m, 1 H, 2-H), 6.71 (d, J = 8.1 Hz, 1 H, 6-H), 6.79 (s, 1 H, 8-H), 6.96 (d, J = 8.8 Hz, 1 H, 5-H).- MS (CI): m/z = 508 ([M + H]$^+$).- $C_{27}H_{45}N_3O_6$ (507.6) Calcd.: C 63.88 H 8.93 N 8.28 Found: C 63.86 H 8.99 N 8.26.

Dibenzyl 1-{(1*R*,2*S*)-1,2,3,4-tetrahydro-1-[(*S*)-1-benzyl-2-methoxyethylamino]-2-naphthyl}-1,2-hydrazinedicarboxylate (11f)

A mixture of **9f/10f** (300 mg, 0.52 mmol), $NaBH_3CN$ (96 mg, 1.53 mmol) and glacial acetic acid (0.14 ml, 2.5 mmol) in 20 ml methanol was treated and worked up as described for **11a** (using petroleum ether - EtOAc, 8:2) to give 245 mg (81%) of **11f** (mixture of diastereomers) as a colorless oil.- IR (NaCl): 3260, 2930, 1750, 1710 cm^{-1}.- ^{1}H-NMR (major isomer **11f**, DMSO-d_6, 140 °C): δ (ppm) = 1.85 (m-centered, 1 H, 3-H_a), 2.02 - 2.12 (m, 1 H, 3-H_b), 2.59 - 2.79 (m, 4 H, 4-H_2, $CHC\underline{H}_2$phenyl), 3.07 - 3.26 (m, 3 H, $C\underline{H}_2OCH_3$, NCH), 3.20 (s, 3 H, OCH_3), 4.07 (br. s, 1 H, 1-H), 4.29 - 4.33 (m, 1 H, 2-H), 5.04 - 5.12 (m, 4 H, 2 $OC\underline{H}_2$phenyl), 6.98 - 7.28 (m, 19 H, aromat.), 8.05 (br. s, 1 H, NH).- MS (CI): m/z = 594 ([M + H]$^+$).- $C_{36}H_{39}N_3O_5$ (593.7) Calcd.: C 72.83 H 6.62 N 7.08 Found: C 72.74 H 6.68 N 7.11.

(*S*)-Di-tert-butyl 1-(1,2,3,4-tetrahydro-2-naphthyl)-1,2-hydrazinedicarboxylate [(*S*)-12a]

a) A mixture of the amine **11a** (**b**, **c**, **d**) (0.3 - 0.7 mmol) and 10% Pd/C (60 - 150 mg) in 7 - 10 ml ethanol was stirred for 5 h at 70 °C under H_2-pressure (12 bar). Then it was filtered (Celite® AFA), and concentrated. The residue was purified by flash chromatography (petroleum ether - EtOAc, 9:1).- b) A mixture of the imines **9a** (**b**, **c**)/**10a** (**b**, **c**) (0.1 - 0.4 mmol) and 10% Pd/C (20 - 70 mg) in 5 - 8 ml ethanol was stirred for 5 h at 70 °C under H_2-pressure (12 bar). Then it was filtered (Celite® AFA) and concentrated. The residue was purified by flash chromatography (petroleum ether - EtOAc, 9:1). Colorless solid, m. p. 146 °C, IR (KBr): 3275, 2980, 1745, 1675 cm^{-1}.- ^{1}H-NMR (DMSO-d_6, 140 °C): δ (ppm) = 1.42 (s, 18 H, 2 $C(CH_3)_3$), 1.71 - 1.76 (m, 1 H, 3-H_a), 1.96 (m-centered, 1 H, 3-H_b), 2.83 - 2.85 (m, 4 H, 1-H_2, 4-H_2), 4.21 - 4.23 (m, 1 H, 2-H), 7.02 (m-centered, 4 H, aromat.), 8.15 (s, 1 H, NH).- MS (CI): m/z = 363 ([M + H]$^+$).- $C_{20}H_{30}N_2O_4$ (362.5) Calcd.: C 66.27 H 8.34 N 7.73 Found: C 66.49 H 8.51 N 7.65.

Table 2: Yields, enantiomeric excess and optical rotation of *(S)*-**12a**

Initial products	Yield (%)	ee (%)	$[\alpha]_D^{23}$ (c, $CHCl_3$)
11a	77	58	-16.3° (1.0)
11b	85	72	-23.1° (3.5)
11c	77	73	-24.4° (3.0)
11d	85	76	-25.9° (4.5)
9a/10a	84	57	-16.2° (0.6)
9b/10b	64	52	-18.3° (3.3)
9c/10c	67	71	-23.5° (5.3)

(*S*)-Di-tert-butyl 1-(1,2,3,4-tetrahydro-7-methoxy-2-naphthyl)-1,2-hydrazinedicarboxylate [(*S*)-12b]

A mixture of **11e** (mixture of diastereomers, 117 mg, 0.23 mmol) and 10% Pd/C (60 mg) in 7 ml ethanol was stirred for 10 h at 75 °C under H_2-pressure (15 bar). Then it was filtered (Celite® AFA) and concentrated. The residue was purified by flash chromatography (petroleum ether - EtOAc, 87:13) to give 73 mg (81%) of *(S)*-**12b** as a colorless solid, m. p. 64 °C.- $[\alpha]_D^{23}$ = -22.1° (c = 3.65, $CHCl_3$), 84 % ee.- b) A mixture of **9e/10e** (205 mg, 0.4 mmol) and 10% Pd/C (75 mg) in 8 ml ethanol was stirred for 5 h at 70 °C under H_2-pressure (15 bar). Then it was worked up as described for a) to give 131 mg (83%) of *(S)*-**12b** as a colorless solid.- IR (KBr): 3325, 2980, 1745, 1705, 1160 cm^{-1}.- ^{1}H-NMR (DMSO-d_6, 100 °C): δ (ppm) = 1.42 (s, 18 H, 2 $C(CH_3)_3$), 1.61 - 1.72 (m, 1 H, 3-H_a), 1.92 (m-centered, 1 H, 3-H_b), 2.71 - 2.80 (m, 4 H, 1-H_2, 4-H_2), 3.70 (s, 3 H, OCH_3), 4.16 - 4.22 (m, 1 H, 2-H), 6.59 (s, 1 H, 8-H), 6.64 (d, *J* = 8.1 Hz, 1 H, 6-H), 6.94 (d, *J* = 8.1 Hz, 1 H, 5-H), 8.38 (br. s, 1 H, NH).- MS (CI): m/z = 393 ($[M + H]^+$).- $C_{21}H_{32}N_2O_5$ (392.5) Calcd.: C 64.26 H 8.22 N 7.14 Found: C 63.92 H 8.31 N 7.40.

(*S*)-(1,2,3,4-Tetrahydro-2-naphthyl)amine [(*S*)-6a][14]

To a solution of *(S)*-**12a** (109 mg, 0.3 mmol) in 3 ml CH_2Cl_2 3 ml of trifluoroacetic acid was added at 0 °C. After stirring for 1 h at room temp., the mixture was treated with 5 ml CCl_4 and evaporated (2x). The residue was dried, dissolved in 6 ml methanol and treated with Raney-Ni (140 mg, methanol wet). Subsequently the mixture was stirred for 4 h under H_2-pressure (50 bar). After filtration and addition of 2 N HCl (2 ml) the solution was extracted with ether. The aqueous layer was basified with 2 N NaOH and extracted with ether. The organic layer was dried ($MgSO_4$), and the solvent was evaporated to give 40 mg (81 %) of *(S)*-**6a** as a colorless oil with spectral characteristics, consistent with those reported.[2,14]- $[\alpha]_D^{23}$ = -47.3° (c = 0.8), 57% ee [ref.[19]: $[\alpha]_D^{21}$ = -94.2 (neat); ref.[20]: $[\alpha]_D^{24}$ = -35.2 (neat); ref.[14]: hydrochloride: $[\alpha]_D^{20}$ = -65.2° (c = 1, H_2O)]. In order to determine the enantiomeric excess, a solution of *(S)*-**6a** in THF was treated with 1 equivalent of *(R)*-phenylethyl isocyanate (HPLC analysis: LiChrosorb® Si 60, diisopropyl ether/n-hexane - EtOAc, 8:5:2.1, 2 ml/min). Enantiomeric excess: see table 1.

(*S*)-(1,2,3,4-Tetrahydro-7-methoxy-2-naphthylamine [(*S*)-6b][18]

(S)-**12b** (79 mg, 0.2 mmol) was treated and worked up as described for *(S)*-**6a** to give 17 mg (49%) of *(S)*-**6b** as a colorless oil with spectral characteristics, consistent with those reported.[2,18]- $[\alpha]_D^{23}$ = -66.4° (c = 0.85, $CHCl_3$), 84 % ee. In order to determine the enantiomeric excess, a solution of *(S)*-**6a** in THF was treated with 1 equivalent of *(R)*-phenylethyl isocyanate (HPLC analysis: LiChrosorb® Si 60, diisopropyl ether/n-hexane - EtOAc, 8:5:2.5, 2.5 ml/min).

Acknowledgments: The financial support of the Deutsche Forschungsgemeinschaft (DFG) and the Fonds der Chemischen Industrie are gratefully acknowledged.

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(Received in Germany 1 *July* 1994; *revised* 29 *July* 1994; *accepted* 1 *August* 1994)