Enantioselective Approach Towards Potential Substance P Antagonists via Hetero-Ene Reaction of Phenylglycine Derivatives

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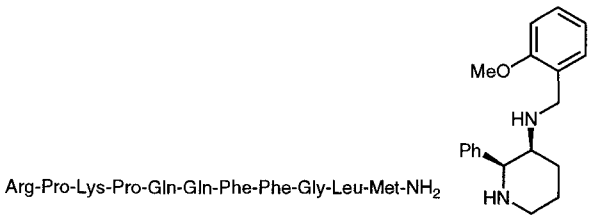
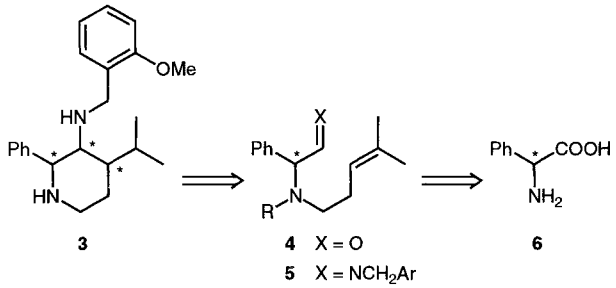
Phenylglycine methyl ester **7** can be converted in a four-step sequence to the aldehyde **11**. Lewis acid catalyzed hetero-ene reaction of **11** gave a mixture of 3-hydroxy-2-phenylpiperidines **14a,b** with high diastereoselectivity. The major diastereomer **14a** was further transformed into 4-isopropyl-3-(2-methoxybenzylamino)-2-phenylpiperidine **(19)**, a compound structurally related to a substance P antagonist, in five steps via azide displacement and reductive amination.

The undecapeptide substance P **1**, which was first isolated in 1931 from horse brain and intestine,[1] belongs to the tachykinin family of neurotransmitters which are related by a homologous N-terminal sequence: Phe-XXX-Gly-Leu-Met-NH_2. Various studies showed that substance P is involved in the transmission of pain signals and the initiation of inflammatory responses.[2,3] In addition substance P has several other biological effects like smooth muscle contraction, secretion from exocrine and endocrine glands, vasodilation, increased vascular permeability (neurogenic inflammation) and regulation of immune responses.[4-6] Therefore substance P antagonists may be useful as novel analgetics[7] and as anti-inflammatory agents in the treatment of migraine[8] and rheumatoid arthritis.[9] With respect to the potential pharmacological properties several nonpeptidic substance P antagonists[10] have been synthesized by others, from which the racemic 3-amino-2-phenylpiperidine CP-99,994 **2** turned out to be the most potent one.[11-13]



Substance P **1** CP-99,994 **2**

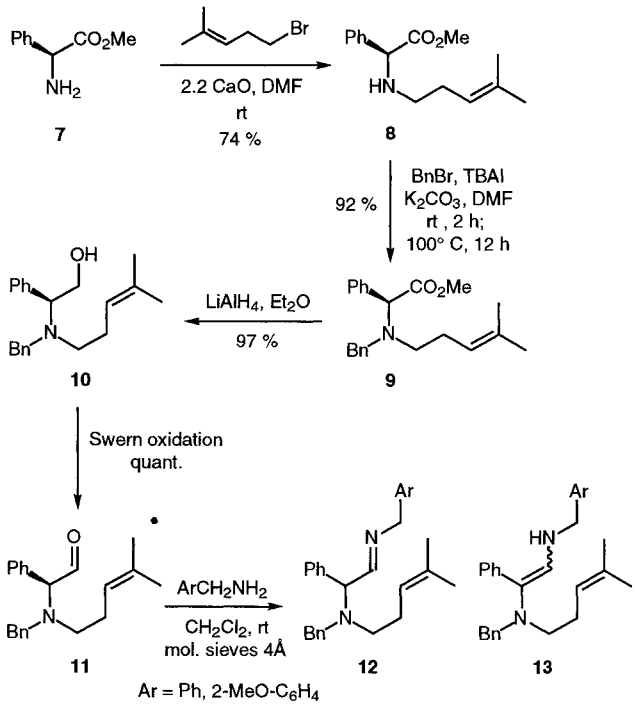
Recently we reported a diastereoselective synthesis of 8-aminoindolizidines[14] and highly substituted 3-aminopiperidines[15] by imino-ene reaction of amino acid derivatives.[16] We reasoned that a related strategy, i.e. hetero-ene reaction of either the aldehyde **4** or the imine **5** of phenylglycine **6** should lead to the 2,3,4-trisubstituted piperidine **3**, a close analogue of compound **2** (Scheme 1). It was anticipated that the decreased conformational flexibility of **3** as compared to **2**, which is caused by the additional substituent in the 4-position, should eventually result in an increased receptor affinity. In this paper the enantioselective synthesis of compound **3** is described.



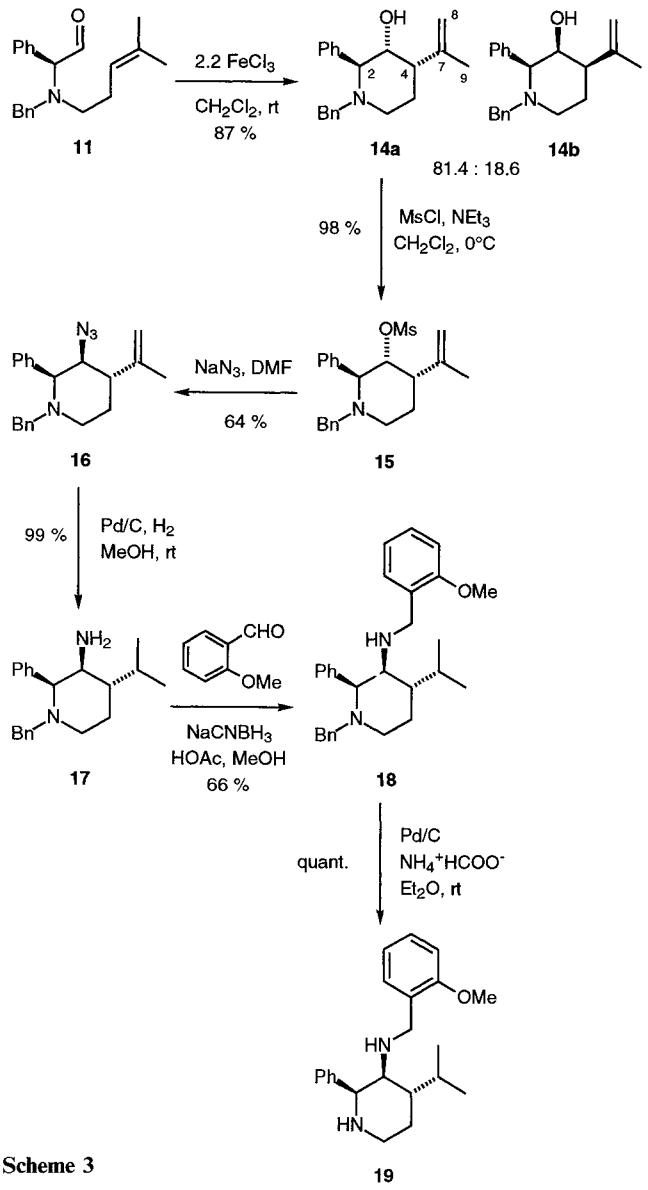
3 **4** X = O **5** X = NCH_2Ar **6**

Scheme 1

The central intermediate in our approach was the aldehyde **11**, whose synthesis could be achieved in a straightforward four-step sequence. As outlined in Scheme 2 starting from L-phenylglycine methyl ester (**7**) the *N*-alkylated product **8** was obtained in 74% yield by treatment with 4-methylpent-3-enyl bromide in the presence of CaO in DMF. By using benzyl bromide and stoichiometric amounts of TBAI and K_2CO_3 in DMF **8** could be converted to the *N*-benzylated amino acid derivative **9** in 92% yield. Reduction with $LiAlH_4$ followed by Swern oxidation[17] gave the aldehyde **11** in 66% overall yield (from **7**). In an attempt to convert the aldehyde **11** to the corresponding imine **12**, the aldehyde **11** was treated with benzylamine or 2-methoxybenzylamine in CH_2Cl_2 in the presence of powdered molecular sieves 4 Å,[14,18] and the reaction was monitored by ^1H NMR. However, immediate formation of a complex mixture of the imine **12** and *E*/*Z* isomers of enamine **13** was observed.[19] That means the stereochemical information of the amino acid is lost during this step due to tautomerization. In order to circumvent this problem, the aldehyde **11** was directly cyclized in the presence of Lewis acids.[20] Hetero-ene reaction of **11** with $FeCl_3$ gave two diastereomeric 3-hydroxy-2-phenylpiperidines **14a,b** (Scheme 3) in a ratio of 81.4:18.6 (determined by GC) in 87% yield, from which the major isomer **14a** could be separated by flash chromatography. Our efforts to obtain the 3-azidopiperidine **16** directly from the 3-hydroxypiperidine **14a** under Mitsunobu conditions by using the zinc azide pyridine complex recently described by Rollin[21] were not successful. The hydroxy group in compound **14a** is probably sterically too hindered to undergo a nucleophilic displacement under S_N2 conditions. Therefore the hydroxypiperidine **14a** was treated with mesyl chloride and triethylamine to give the mesylate **15**, which was then converted to the azide **16**. Catalytic hydrogenation gave the 3-aminopiperidine **17** in almost quantitative yield. Subsequent reductive amination of compound **17** with *o*-methoxybenzaldehyde in the presence of sodium cyanoborohydride and acetic acid gave piperidine derivative **18**.[22] The



Scheme 2



Scheme 3

enantiomeric purity of **14a** and **18** (>98% ee) was determined by ^1H NMR (200 MHz) using one molar equivalent of (−)-(*R*)-1-(9-anthryl)-2,2,2-trifluoroethanol as shift reagent and a racemic sample of **14a** as reference.[23]

The relative configuration of the *N*-benzyl protected piperidine **18** was established by COSY- and HMQC-NMR experiments.[24] The coupling patterns for 2-H (d at δ = 3.98, $J_{2,3}$ = 3.6 Hz), 3-H (dd at δ = 2.54, $J_{3,4}$ = 4.8 Hz, $J_{2,3}$ = 3.6 Hz) and 4-H (dddd at δ = 2.28, $J_{5eq,4}$ = 9.6 Hz, $J_{3,4}$ = 4.8 Hz, $J_{5ax,4}$ = 4.8 Hz, $J_{4,7}$ = 1.8 Hz) indicated a *cis* relationship for 2-H/3-H and a *trans* configuration for 3-H/4-H. This assignment was confirmed by 1D-NOE experiments. Irradiation of 3-H resulted in an enhancement of the signal for 2-H and vice versa, whereas irradiation of 4-H gave no enhancement for the 2-H or 3-H absorption.

Finally, the desired piperidine **19** could be obtained by using a transfer hydrogenation (Pd on carbon/ammonium formate in Et_2O) in quantitative yield.[11]

In conclusion an enantioselective synthesis of the potential substance P antagonist 4-isopropyl-3-(2-methoxybenzylamino)-2-phenylpiperidine **(19)** was developed, which gave the desired target compound in 10 steps and 24% overall yield starting from L-phenylglycine methyl ester **(7)**. As a key reaction a diastereoselective Lewis acid catalyzed hetero-ene reaction of aldehyde **11** was used. Investigations on the pharmacological properties of compound **19** are now in progress.

All reactions were carried out under an Ar atmosphere using standard Schlenk technique. Solvents were dried and deoxygenated by standard procedures. Analytical TLC was performed on precoated Merck Si 254 F plates (0.25 mm thickness) and visualized with a solution of phosphomolybdic acid in EtOH (5%, v/v). Flash chromatography was carried out with Merck silica gel 60 (230–400 mesh). NMR spectra: Bruker AC 200 P (200 MHz-^1H, 50 MHz-^{13}C) and Varian Unity-plus (600 MHz-^1H, 150 MHz-^{13}C). Multiplets in ^{13}C NMR spectra were determined by DEPT and APT experiments.[25] Melting points (uncorrected): Gallenkamp melting point apparatus. IR spectra: Nicolet 5DXC FT-IR spectrometer. Optical rotations (1 dm-cells, 1 mL capacity, r.t.): Perkin Elmer Model 241 polarimeter. Mass spectra: Finnigan Model MAT 312 (EI), Finnigan Model MAT 8230 (CI, reactant gas: NH_3). GC analysis: HP5 fused silica capillary column (ID 0.32 mm, length 25 m), HPU2 fused silica capillary column (ID 0.2 mm, length 25 m). 4-Methylpent-3-enyl bromide was prepared according to ref. 26.

(*S*)-*N*-(4-Methylpent-3-enyl)phenylglycine Methyl Ester (8):
To a solution of (*S*)-phenylglycine methyl ester **(7)** (24.8 g, 0.15 mol) in anhyd DMF (300 mL) were subsequently added CaO (18.5 g, 0.33 mol) and 4-methylpent-3-enyl bromide (24.4 g, 0.15 mol) and the remaining suspension was stirred at r.t. for 5 days. After dilution with Et_2O (200 mL), Celite (5.0 g) was poured under vigorous stirring into the mixture, which was then filtered through a short column (eluent: Et_2O). The combined filtrates and washings were poured into ice-H_2O (500 mL). Extraction with Et_2O (4 × 200 mL), followed by drying ($MgSO_4$) and evaporation of the solvent yielded a yellow oil, which was further purified by flash chromatography

on silica gel (hexanes/EtOAc 10:1 then 4:1) to give 27.4 g (74%) of a yellow oil; $[\alpha]_D^{22}$ + 50.8 (c = 1.00; $CHCl_3$).

IR (film): ν = 1739, 1454, 1436, 1206, 1168, 698 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.22–7.06 (m, 5H, Ph), 4.91 (dd, J = 7.2 Hz, 1H, 3′-H), 4.20 (s, 1H, 2-H), 3.45 (s, 3H, CO_2CH_3), 2.49–2.27 (m, 2H, 1′-H), 2.02 (q, J = 7.1 Hz, 2H, 2′-H), 1.90 (s br, 1H, NH), 1.50 (d, J = 0.8 Hz, 3H, 5′-H), 1.43 (s, 3H, 6′-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.1 (CO), 138.0 (C-i), 133.3 (C-4′), 128.3, 127.6, 127.1 (CH_{aryl}), 121.4 (C-3′), 65.2 (CO_2CH_3), 51.7 (C-2), 47.2 (C-2′), 28.4 (C-1′), 25.4 (C-5′), 17.5 (C-6′).

MS (EI): m/z (%) = 247 (M+1, 6), 232 (3), 188 (28), 178 (100), 149 (91), 121 (77), 106 (32), 91 (47), 83 (35), 77 (30), 67 (17), 55 (71).

HRMS (CI) calcd. for $C_{15}H_{21}NO_2$ 247.1572, found 247.1565.

Anal. calcd. for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.90; H, 8.76; N, 5.76.

(*S*)-*N*-Benzyl-*N*-(4-methylpent-3-enyl)phenylglycine Methyl Ester (9):

To a solution of ester **8** (7.41 g, 30.0 mmol) in anhyd DMF (30 mL) was sucessively added K_2CO_3 (4.14 g, 30.0 mmol), tetrabutylammonium iodide (11.1 g, 30.0 mmol) and then BnBr (5.13 g, 30.0 mmol). The resulting mixture was stirred at r.t. for 4 h and then heated to 100 °C for 48 h. The dark brown mixture was then diluted with toluene (100 mL) and azeotropically codistilled (3 times) under high vacuum. The remaining brown solid was diluted in pentane (20 mL) and purified by flash chromatography over silica gel (hexanes/EtOAc 95:5) to give 9.28 g (92%) of a colorless oil; $[\alpha]_D^{22}$ + 25.2 (c = 1.00; $CHCl_3$).

IR (film): ν = 1739, 1452, 1433, 1023, 1164, 1132, 698 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.29–7.08 (m, 10H, 2 × Ph), 4.83 (dd, J = 7.2 Hz, 1H, 3′-H), 4.54 (s, 1H, 2-H), 3.70 (d, J = 14.3 Hz, 1H, NCH_2Ph), 3.63 (s, 3H, CO_2CH_3), 3.59 (d, J = 14.3 Hz, 1H, NCH_2Ph), 2.49 (dd, J = 6.7 Hz, 2H, 1′-H), 2.04–1.91 (m, 2H, 2′-H), 1.51–1.37 (s, 3H, 6′-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.7 (CO), 140.0, 137.1 (C-i), 132.3 (C-4′), 128.7, 128.6, 128.2, 128.1, 127.7, 126.8 (CH_{aryl}), 122.0 (C-3′), 67.5 (CO_2CH_3), 54.9 (NCH_2Ph), 51.3 (C-2), 50.2 (C-2′), 26.4 (C-1′), 25.6 (C-5′), 17.5 (C-6′).

MS (EI): m/z (%) = 337 (M, 1), 278 (6), 268 (33), 260 (3), 149 (31), 121 (32), 105 (9), 91 (100), 83 (9), 77 (14), 65 (26), 55 (27).

MS (CDI): m/z (%) = 338 (M + 1, 100), 268 (9).

HRMS (DCI) calcd. for $C_{22}H_{27}NO_2$ + H 338.2120, found 338.2079.

Anal. calcd. for $C_{22}H_{27}NO_2$: C, 78.30; H, 8.06; N, 4.15. Found: C, 78.05; H, 8.15; N, 4.21.

(*S*)-*N*-Benzyl-*N*-(4-methylpent-3-enyl)phenylglycinol (10):

To an ice-cooled suspension of $LiAlH_4$ (1.18 g, 30.3 mmol) in anhyd Et_2O (40 mL) was added dropwise ester **9** (9.28 g, 27.5 mmol) in anhyd Et_2O (15 mL). Then the ice-bath was removed and the resulting suspension was stirred at r.t. for 22 h and then carefully hydrolyzed by addition of EtOAc (151 mL) and H_2O (56 mL). Stirring was continued for another 1 h and then were added H_2O (200 mL) and Et_2O (200 mL). After separation of the organic layer, the aqueous layer was extracted with Et_2O (200 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated to yield 8.24 g (97%) of a colorless oil, which was used without further purification; $[\alpha]_D^{22}$ + 48.5 (c = 1.00; $CHCl_3$).

IR (film): ν = 3442, 1452, 1028, 699 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.26–7.09 (m, 10H, 2 × Ph), 4.96 (dd, J = 7.2 Hz, 1H, 3′-H), 4.09–3.77 (m, 2H, 1-H), 3.80 (d, J = 13.7 Hz, 1H, NCH_2Ph), 3.50 (dd, J = 9.4/3.5 Hz, 1H, 2-H), 3.07 (d, J = 13.7 Hz, 1H, NCH_2Ph), 3.09–2.98 (s br, 1H, OH), 2.68–2.52 (m, 1H), 2.27–2.03 (m, 3H, 1′-H, 2′-H), 1.60 (s, 3H, 5′-H), 1.48 (s, 3H, 6′-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 139.4, 135.9 (C-i), 133.1 (C-4′), 128.9, 128.7, 128.3, 128.1, 127.7, 127.0 (CH_{aryl}), 122.0 (C-3′), 63.9 (C-2), 60.4 (C-1), 54.0 (NCH_2Ph), 48.9 (C-2′), 26.8 (C-1′), 25.6 (C-5′), 17.7 (C-6′).

MS (EI): m/z (%) = 309 (M, 1), 291 (M-H_2O, 4), 278 (6), 240 (22), 222 (6), 187 (7), 178 (6), 149 (7), 120 (43), 103 (21), 91 (100), 77 (19), 65 (25), 55 (29).

HRMS (EI) calcd. for $C_{21}H_{25}N$ (M-H_2O) 291.1987, found 291.1979.

Anal. calcd. for $C_{21}H_{27}NO_2$: C, 81.51; H, 8.79; N, 4.53. Found: C, 81.27; H, 9.04; N, 4.52.

(*S*)-*N*-Benzyl-*N*-(4-methylpent-3-enyl)phenylglycinal (11):

A solution of DMSO (3.51 g, 45.0 mmol) in CH_2Cl_2 (4 mL) was added dropwise over 30 min at −45 °C to a solution of oxalyl chloride (2.85 g, 22.5 mmol) in anhyd CH_2Cl_2 (31 mL). After stirring for 15 min a solution of alcohol **10** (4.02 g, 13.0 mmol) in anhyd CH_2Cl_2 (20 mL) was added dropwise over 2.5 h and the resulting mixture was stirred for another 4 h at −45 °C. Then was added Et_3N (13.0 mL) over 30 min and the mixture was warmed to r.t. and stirred for another 1 h. The mixture was washed with H_2O (3 × 100 mL), dried (Na_2SO_4) and evaporated to yield 3.99 g (quant.) of a pale brown oil (97% pure by GC), which was immediately used for further reactions; $[\alpha]_D^{22}$ − 7.8 (c = 1.00; $CHCl_3$).

IR (film): ν = 1729, 1635, 1598, 1452, 699 cm^{-1}.

^1H NMR (200 MHz, C_6D_6): δ = 9.55 (d, J = 3.2 Hz, 1H, CHO), 7.42–7.06 (m, 10H, 2 × Ph), 4.89 (dd, J = 7.2 Hz, 1H, 3′-H), 4.17 (d, J = 3.2 Hz, 1H, 2-H), 3.65 (d, J = 14.1 Hz, 1H, NCH_2Ph), 3.39 (d, J = 14.1 Hz, 1H, NCH_2Ph), 2.59–2.25 (m, 2H), 2.11–1.97 (m, 2H, 1′-H, 2′-H), 1.53 (s, 3H, 5′-H), 1.38 (s, 3H, 6′-H).

^{13}C NMR (50 MHz, C_6D_6): δ = 199.1 (CHO), 139.4, 134.9 (C-i), 132.6 (C-4′), 129.7, 129.1, 128.9, 128.6, 128.5, 127.4 (CH_{aryl}), 122.1 (C-3′), 76.0 (C-2), 55.3 (NCH_2Ph), 46.6 (C-2′), 25.7 (C-5′), 25.1 (C-1′), 17.6 (C-6′).

MS (DCI): m/z (%) = 308 (M + 1, 14), 294 (88), 235 (14), 218 (23), 190 (100), 154 (5), 120 (9), 108 (7).

HRMS (CDI) calcd. for $C_{21}H_{25}NO$ + H 308.2014, found 308.2014.

(2*S*,3*R*,4*S*)-*N*-Benzyl-3-hydroxy-4-isopropenyl-2-phenylpiperidine (14a):

To an ice-cooled solution of aldehyde **11** (3.59 g, 11.7 mmol) in anhyd CH_2Cl_2 (330 mL) was added dropwise over 40 min $FeCl_3$ (29.2 mL of a 1.0 M solution in Et_2O) and the remaining brown solution was stirred at r.t. for 35 h. Then the mixture was quenched by addition of 2 N NaOH (300 mL) and extracted with CH_2Cl_2 (4 × 200 mL). The combined organic layers were washed with brine (500 mL), dried ($MgSO_4$) and evaporated to yield a brown oil (mixture of diastereomers **14a**:**14b** = 81.4:18.6), which was purified by flash chromatography on silica gel (hexanes/EtOAc/Et_3N 94:5:1) to give 2.55 g (71%) of an orange oil as the first fraction; $[\alpha]_D^{22}$ + 3.7 (c = 100; $CHCl_3$).

IR (film): ν = 3556, 3469, 1644, 1494, 1452, 1091, 1070, 1029, 763, 701 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.42–7.03 (m, 10H, 2 × Ph), 4.74 (s, broad, 2H, 8-H), 3.57 (d, J = 13.5 Hz, 1H, NCH_2Ph), 3.42 (dd, J = 10.0/8.6 Hz, 1H, 3-H), 3.04–2.68 (m, 3H), 2.72 (d, J = 13.5 Hz, 1H, NCH_2Ph), 2.20–1.87 (m, 3H), 1.61 (s, 3H, 9-H), 1.76–1.43 (m, 1H, 2-H, 4-H, 5-H, 6-H, OH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 146.2 (C-7), 141.3, 139.4 (C-i), 128.7, 128.6, 128.5, 128.1, 127.8 (CH_{aryl}), 112.6 (C-8), 74.8 (C-3), 74.4 (C-2), 59.1 (NCH_2Ph), 52.2 (C-6), 51.9 (C-4), 29.0 (C-5), 21.9 (C-9).

MS (EI): m/z (%) = 307 (M, 20), 289 (M-H_2O, 18), 276 (7), 222 (25), 216 (70), 194 (22), 171 (20), 118 (41), 91 (100), 69 (36), 55 (37).

HRMS (EI) calcd. for $C_{21}H_{25}NO$ 307.1936, found 307.1944. Anal. calcd. for $C_{21}H_{25}NO$: C, 82.04; H, 8.20; N, 4.56. Found: C, 82.06; H, 8.19; N, 4.55.

(2*S*,3*S*,4*R*)-*N*-Benzyl-3-hydroxy-4-isopropenyl-2-phenylpiperidine (14b):

Flash chromatography of **14a,b** gave 575 mg (16%) of a yellow oil as the second fraction; $[\alpha]_D^{22}$ + 8.7 (c = 1.00; $CHCl_3$).

IR (film): ν = 3483, 3346, 1646, 1494, 1452, 700 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.39–7.07 (m, 10H, 2 × Ph), 4.74

(d, J = 1.0 Hz, 1 H, 8a-H), 4.64 (s, 1 H, 8b-H), 3.75 (d, J = 13.7 Hz, 1 H, NCH_2Ph), 3.65 (s br, 1 H, 3-H), 3.22 (d, J = 1.5 Hz, 1 H, 2-H), 2.91 (dd, J = 10.3/7.4 Hz, 1 H, 6-H_e), 2.76 (d, J = 13.7 Hz, 1 H, NCH_2Ph), 2.16–2.03 (m, 1 H), 1.93–1.81 (m, 4 H, 4-H, 5-H, 6-H_a, OH), 1.63 (s, 3 H, 9-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 146.0 (C-7), 140.8, 138.9 (C-i), 128.5, 128.4, 128.3, 128.0, 127.3, 126.7 (CH_{aryl}), 111.1 (C-8), 72.9 (C-3), 70.8 (C-2), 59.2 (NCH_2Ph), 52.8 (C-6), 48.0 (C-4), 23.6 (C-5), 21.8 (C-9).

MS (EI): m/z (%) = 307 (M, 14), 277 (13), 262 (15), 222 (20), 216 (41), 199 (21), 171 (18), 118 (26), 91 (100), 71 (25), 55 (31).

HRMS (EI) calcd. for $C_{21}H_{25}NO$ 307.1936, found 307.1924.

Anal. calcd. for $C_{21}H_{25}NO$: C, 82.04; H, 8.20; N, 4.56. Found: C, 82.10; H, 8.22; N, 4.53.

(2*S*,3*R*,4*S*)-*N*-Benzyl-4-isopropenyl-3-mesyloxy-2-phenylpiperidine (15):

To an ice-cooled solution of hydroxypiperidine **14a** (1.20 g, 3.90 mmol) and Et_3N (501 mg, 4.95 mmol) in CH_2Cl_2 (7.8 mL) was added dropwise over 30 min mesyl chloride (524 mg, 4.57 mmol) and the orange solution was stirred for 3 h at 0 °C and then poured onto ice. After separation of the layers, the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL), the combined organic layers were washed with brine (100 mL), dried ($MgSO_4$) and evaporated to yield 1.47 g (98 %) of a dark yellow oil (97 % pure by GC); $[\alpha]_D^{22}$ − 1.4 (c = 1.00; $CHCl_3$).

IR (film): ν = 1452, 1360, 1325, 1171, 955, 936, 701 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.42–7.04 (m, 10 H, 2 × Ph), 4.81 (s, 2 H, 8-H), 3.52 (d, J = 13.5 Hz, 1 H, NCH_2Ph), 3.12 (d, J = 9.1 Hz, 1 H, 3-H), 2.96–2.66 (m, 2 H), 2.70 (d, J = 13.5 Hz, 1 H, NCH_2Ph), 2.29 (ddd, J = 10.6/10.6/4.7 Hz, 1 H), 1.91 (ddd, J = 11.5/11.5/3.2 Hz, 1 H), 1.78 (s, 3 H, CH_3SO_2), 1.74–1.35 (m, 2 H, 2-H, 4-H, 5-H, 6-H), 1.65 (s, 3 H, 9-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 143.7 (C-7), 140.3, 138.9 (C-i), 128.8, 128.7, 128.4, 128.1, 126.8 (CH_{aryl}), 115.0 (C-8), 86.3 (SO_2CH_3), 73.1 (C-3), 58.4 (NCH_2Ph), 51.7 (C-2), 51.6 (C-6), 37.9 (C-4), 28.9 (C-5), 19.0 (C-9).

MS (CI): m/z (%) = 386 (M, 4), 326 (10), 308 (100), 290 (22), 285 (9), 216 (3), 200 (30), 106 (12).

(2*S*,3*S*,4*S*)-3-Azido-*N*-benzyl-4-isopropenyl-2-phenylpiperidine (16):

To a solution of mesylate **15** (1.46 g, 3.81 mmol) in anhyd DMF (20 mL) was added NaN_3 (2.48 g, 38.1 mmol) and the remaining mixture was heated at 100 °C for 20 h. After dilution with CH_2Cl_2 (200 mL), the mixture was washed with H_2O (200 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 200 mL) and the combined organic layers were washed with brine (500 mL), dried ($MgSO_4$) and evaporated to yield a brown oil, which was purified by flash chromatography on silica gel (hexanes/EtOAc/Et_3N 90:9:1) to yield 810 mg (64 %) of a yellow oil (99 % pure by GC); $[\alpha]_D^{22}$ − 22.6 (c = 1.00; $CHCl_3$).

IR (film): ν = 2099, 1495, 1452, 1261, 1028, 698 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.26–7.11 (m, 10 H, 2 × Ph), 4.49 (d, J = 6.0 Hz, 1 H, 3-H), 4.48 (s, 1 H, 8a-H), 4.38 (s, 1 H, 8b-H), 3.91 (d, J = 12.9 Hz, 1 H, NCH_2Ph), 3.52 (d, J = 12.9 Hz, 1 H, NCH_2Ph), 2.98–2.86 (m, 2 H, 2-H, 6-H_e), 2.70–2.64 (m, 1 H, 6-H_a), 2.41 (ddd, J = 9.4/9.4/6.4 Hz, 1 H, 4-H), 1.95–1.89 (m, 1 H, 5-H_e), 1.63–1.53 (m, 1 H, 5-H_a), 1.37 (s, 3 H, 9-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 147.4 (C-7), 138.9, 137.7 (C-i), 128.8, 128.2, 127.5, 127.2, 127.0 (CH_{aryl}), 110.0 (C-8), 73.5 (C-3), 67.9 (C-2), 59.8 (NCH_2Ph), 53.4 (C-6), 46.5 (C-4), 29.7 (C-5), 21.2 (C-9).

MS (EI): m/z (%) = 304 (M-N_2, 4), 289 (19), 274 (8), 248 (21), 200 (60), 184 (21), 158 (23), 132 (25), 103 (35), 91 (100), 77 (34), 65 (36), 55 (31).

MS (DCI): m/z (%) = 333 (M + 1, 100), 305 (2), 290 (2), 200 (73), 106 (51).

HRMS (DCI) calcd. for $C_{21}H_{24}N_4$ + H 333.2079, found 333.2062.

(2*S*,3*S*,4*S*)-3-Amino-*N*-benzyl-4-isopropyl-2-phenylpiperidine (17):

To a solution of azide **16** (546 mg, 1.65 mmol) in MeOH (15 mL) was added under Ar Pd on C (50 mg, 10 wt%) and the mixture was presaturated (3 times) with H_2 and then stirred under H_2 at 1 atm for 48 h at r.t. The mixture was filtered through Celite (1.0 g) via a fritted funnel and the solvent was evaporated to yield 503 mg (99 %) of a pale yellow oil (98 % pure by GC); $[\alpha]_D^{22}$ − 3.3 (c = 1.00; $CHCl_3$).

IR (film): ν = 3388, 1495, 1454, 700 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.30–7.05 (m, 10 H, 2 × Ph), 5.02 (s br, 2 H, NH_2), 4.05 (d, J = 3.2 Hz, 1 H, 3-H), 3.85 (d, J = 13.0 Hz, 1 H, NCH_2Ph), 3.61 (d, J = 13.0 Hz, 1 H, NCH_2Ph), 2.93–2.86 (m, 1 H), 2.71 (dd, J = 3.8 Hz, 1 H), 2.38–2.21 (m, 1 H), 1.85–1.56 (m, 1 H), 1.55–1.24 (m, 1 H), 0.79–0.69 (m, 2 H, 2-H, 4-H, 5-H, 6-H, 7-H), 0.39 (d, J = 6.6 Hz, 3 H, 8-H), 0.29 (d, J = 6.6 Hz, 3 H, 9-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 137.4 (2 × C-i), 129.3, 128.6, 128.5, 127.7, 126.9 (CH_{aryl}), 71.6 (C-3), 59.1 (NCH_2Ph), 56.5 (C-2), 53.8 (C-6), 43.6 (C-4), 30.8 (C-7), 26.2 (C-5), 20.7 (C-8), 18.6 (C-9).

MS (CDI): m/z (%) = 309 (M + 1, 100), 202 (33).

(2*S*,3*S*,4*S*)-*N*-Benzyl-4-isopropyl-3-*N*-(2-methoxybenzylamino)-2-phenylpiperidine (18):

To an ice-cooled solution of amine **17** (502 mg, 1.62 mmol) in anhyd MeOH (3.3 mL) was added $NaCNBH_3$ (61 mg, 0.97 mmol) and then 2-methoxybenzaldehyde (244 mg, 1.79 mmol) and the pH was adjusted to 6 by dropwise addition of HOAc. The ice-bath was removed and the green solution was stirred at r.t. for 24 h. Then the mixture was cooled to −15 °C and quenched by careful addition of K_2CO_3 solution (60 mL, 40 %). After extraction with Et_2O (3 × 100 mL), washing of the combined organic layers with brine (2 × 100 mL) and drying ($MgSO_4$) a yellow oil was obtained, which was further purified by flash chromatography over silica gel (hexanes/EtOAc/Et_3N 90:9:1) to give 461 mg (66 %) of colorless crystals; mp 124 °C; $[\alpha]_D^{22}$ − 17.5 (c = 1.00; $CHCl_3$).

IR (film): ν = 3550, 3478, 3412, 3306, 3083, 3060, 3024, 2959, 2928, 2852, 2781, 1639, 1617, 1599, 1491, 1453, 1238, 1120, 1029, 744, 698 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.47 (d, J = 7.2 Hz, 2 H, 2′-H, 6′-H), 7.34 (dd, J = 7.8 Hz, 2 H, 3′-H, 5′-H), 7.31–7.28 (m, 2 H), 7.25–7.22 (m, 5 H, 4′-H, Ph, 6‴-H), 7.21–7.18 (m, 1 H, 4‴-H), 6.89 (ddd, J = 7.2/7.2/0.6 Hz, 1 H, 5‴-H), 6.85 (d, J = 8.4 Hz, 1 H, 3‴-H), 3.98 (d, J = 13.2 Hz, 1 H, NCH_2Ph), 3.98 (d, J = 3.6 Hz, 1 H, 2-H), 3.83 (d, J = 13.2 Hz, 1 H, $HNCH_2Ar$), 3.79 (s, 3 H, OMe), 3.57 (d, J = 13.2 Hz, 1 H, $HNCH_2Ar$), 3.28 (d, J = 13.2 Hz, 1 H, NCH_2Ph), 2.80 (dd, J = 7.8/7.8 Hz, 1 H, 6-H_e), 2.54 (dd, J = 4.8/3.6 Hz, 1 H, 3-H), 2.28 (dddd, J = 9.6/4.8/4.8/1.8 Hz, 1 H, 4-H), 2.12 (ddd, J = 12.6/9.0/6.6 Hz, 1 H, 6-H_a), 1.66 (dddd, J = 12.6/12.6/10.2/7.2 Hz, 5-H_e), 1.48 (dd, J = 12.6/6.6 Hz, 1 H, 5-H_a), 0.64–0.59 (m, 1 H, 7-H), 0.53 (d, J = 6.6 Hz, 3 H, 8-H), 0.43 (d, J = 7.2 Hz, 3 H, 9-H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 157.7 (C-2‴), 141.7 (C-1′), 139.9 (C-i″), 129.9 (C-4‴), 129.1 (C-1‴), 129.1, 128.7, 128.0 (3 ×), 127.9 (CH_{aryl}), 126.6 (C-6‴), 120.2 (C-5‴), 110.2 (C-3‴), 73.2 (C-3), 61.8 (C-2), 58.7 (NCH_2Ph), 55.1 (OMe), 53.8 (C-6), 46.5 ($HNCH_2Ar$), 42.9 (C-4), 30.5 (C-7), 25.5 (C-5), 21.1 (C-9), 17.8 (C-8).

MS (EI): m/z (%) = 426 (M, 4), 346 (16), 289 (17), 248 (13), 200 (81), 134 (20), 121 (42), 91 (100), 65 (26).

HRMS (EI) calcd. for $C_{29}H_{34}N_2O$ 426.2671, found 426.2686.

Anal. calcd. for $C_{29}H_{34}N_2O$: C, 81.27; H, 8.47; N, 6.54. Found: C, 81.28; H, 8.35; N, 6.50.

(2*S*,3*S*,4*S*)-4-Isopropyl-3-*N*-(2-methoxybenzylamino)-2-phenylpiperidine (19):

To a solution of piperidine **18** (100 mg, 0.24 mmol) in Et_2O (5 mL) was added under Ar Pd on C (50 mg, 10 wt%) and ammonium formate (155 mg, 2.50 mmol) and the mixture was stirred for 2 h at r.t. The mixture was filtered through Celite (1.0 g) via a fritted funnel and the solvent was evaporated to yield 80 mg (quant.) of a colorless oil (98 % pure by GC); $[\alpha]_D^{22}$ − 8.7 (c = 1.00; $CHCl_3$).

IR (film): ν = 3377, 1493, 1452, 699 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.26–6.96 (m, 7H, Ph, 4″-H, 6″-H), 6.72 (ddd, J = 7.4/7.4/1.0 Hz, 1H, 5″-H), 6.69 (d, J = 8.1 Hz, 1H, 3″-H), 3.66 (s, 3H, OMe), 3.59 (d, J = 13.5 Hz, 1H, $HNCH_2Ar$), 3.42 (d, J = 5.1 Hz, 1H, 2-H), 3.31 (d, J = 13.5 Hz, 1H, $HNCH_2Ar$), 2.99 (dd, J = 5.4/5.1 Hz, 1H, 3-H), 2.61–2.37 (m, 2H), 1.82 (s br, 2H, NH_2), 1.63–1.27 (m, 4H, 4-H, 5-H, 6-H, 7-H), 0.72 (d, J = 6.6 Hz, 3H, 8-H), 0.67 (d, J = 6.6 Hz, 3H, 9-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 157.7 (C-2″), 141.6 (C-i), 129.9 (C-4″), 131.7 (C-1″), 128.6, 128.1 (C-o, C-m), 128.0 (C-p), 127.0 (C-6″), 120.3 (C-5″), 110.1 (C-3″), 66.4 (C-2), 66.0 (C-3), 55.1 (OMe), 47.6 ($HNCH_2Ar$), 31.2 (C-7), 28.9 (C-5), 22.1 (C-9), 18.9 (C-8).

MS (DCI): m/z (%) = 339 (M + 1, 100), 320 (2), 226 (6), 112 (9).

HRMS (DCI) calcd. for $C_{22}H_{30}N_2O$ + H 339.2436, found 339.2441.

A sample of **19** was converted into the dihydrochloride by treatment with HCl in Et_2O. Anal. calcd. for $C_{22}H_{30}N_2O \cdot 2HCl$: C, 64.23; H, 7.84; N, 6.81. Found: C, 64.28; H, 7.81; N, 6.82.

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(1) von Euler, U.S.; Gaddum, J.H. *J. Physiol.* **1931**, *72*, 74.
(2) Nicoll, R.; Schenker, C.; Leeman, S.E. *Annu. Rev. Neurosci.* **1980**, *3*, 227.
(3) Otsuka, M.; Yanagisawa, M. *Trends Pharmacol. Sci.* **1987**, *8*, 506.
(4) Pernow, B. *Pharmacolog. Rev.* **1983**, *35*, 85.
(5) Payan, D.G.; Brewster, D.R.; Goetzl, E.J. *J. Immunol.* **1984**, *133*, 3260.
(6) Payan, D.G.; Brewster, D.R.; Goetzl, E.J. *J. Immunol.* **1983**, *131*, 1613.
(7) Otsuka, M.; Yanagisawa, M. *J. Physiol.* **1988**, *395*, 255.
(8) Moskowitz, M.A. *Trends Pharmacol. Sci.* **1992**, *13*, 307.
(9) Lotz, M.; Carsun, D.A.; Vaughan, J.H. *Science* **1987**, *235*, 893.
(10) Review of substance P antagonists: Lowe, J.A. *Drugs Future* **1992**, *17*, 1115.
(11) Desai, M.C.; Lefkowitz, S.L.; Thadeio, P.F.; Longo, K.P.; Snider, R.M. *J. Med. Chem.* **1992**, *35*, 4911.
(12) Rosen, T.; Seeger, T.F.; McLean, S.; Desai, M.C.; Guarino, K.J.; Bryce, D.; Pratt, K.; Heym, J.; Chalabi, P.M.; Windels, J.H.; Roth, R.W. *J. Med. Chem.* **1993**, *36*, 3197.
(13) Other 3-aminopiperidines: Diez, A.; Voldoire, A.; Lopez, I.; Rubralta, M.; Segarra, V.; Pages, L.; Palacios, J.M. *Tetrahedron* **1995**, *51*, 5143.
Desai, M.C.; Thadeio, P.F.; Lefkowitz, S.L. *Tetrahedron Lett.* **1993**, *34*, 5831.
(14) Laschat, S.; Grehl, M. *Angew. Chem.* **1994**, *106*, 475; *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 458.
Laschat, S.; Grehl, M. *Chem. Ber.* **1994**, *127*, 2023.
(15) Laschat, S.; Fröhlich, R.; Wibbeling, B. *J. Org. Chem.* **1996**, *61*, 2829.
(16) Review on imino-ene reactions: Borzilleri, R.M.; Weinreb, S.M. *Synthesis* **1995**, 347.
(17) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.
(18) Pawlenko, S. in *Houben-Weyl's Methoden der Organischen Chemie*, Müller, E., Ed.; Thieme: Stuttgart, 1990, Vol. E14b/1, p. 239.
(19) Characteristic NMR signals of **12** and **13** (mixture of *E*/*Z* isomers): ^{1}H NMR (200 MHz, C_6D_6): δ = 7.72 (s, HC=N), 4.97 and 4.90 [s, =CH(NHAr)]; ^{13}C NMR (50 MHz, C_6D_6): δ = 157.5 (HC=N), 111.1 and 110.3 [=CH(NHAr)].
(20) Reviews on carbonyl-ene reactions:
Mikami, K.; Terada, M.; Narisawa, S.; Nakai, T. *Synlett* **1992**, 255.
Mikami, K.; Shimizu, M. *Chem. Rev.* **1992**, *92*, 1021.
Snider, B.B. in *Comprehensive Organic Synthesis*; Trost, B.M., Ed.; Pergamon: Oxford, 1991; Vol. 2, p 527.
(21) Viaud, M.C.; Rollin, P. *Synthesis* **1990**, 130.
(22) Ando, A.; Shiorii, T. *Tetrahedron* **1989**, *45*, 4969.
(23) Pirkle, W.H.; Sikkenga, D.L.; Pavlin, M.S. *J. Org. Chem.* **1977**, *42*, 384.
(24) Heteronuclear multiple-quantum coherence (HMQC): Marion, D.; Ikura, M.; Tschudin, R.; Bax, A. *J. Magn. Reson.* **1989**, *85*, 393.
(25) Attached proton test (APT): Patt, S.; Shoolery, J. *J. Magn. Reson.* **1982**, *46*, 535.
(26) Biernacki, W.; Gdula, A. *Synthesis* **1979**, 37.