Synthesis of two Conformationally Restricted Piperazine Scaffolds for Combinatorial Chemistry

Till Opatz[a]

Dedicated to Professor Johann Mulzer on the occasion of his 60th birthday

Keywords: Combinatorial chemistry / Nitrogen heterocycles / Piperazines / Protecting groups / Scaffolds

Piperazines are widely used as central elements in the construction of bioactive molecules. Herein, the short synthesis of two chiral 2,6-bridged piperazines possessing orthogonally stable protecting groups from readily available starting materials is described. It is suggested that these molecules may be used as conformationally restricted scaffolds for the combinatorial synthesis of drug-like compounds.

Introduction

The piperazine ring is a common pharmacophore found in a large number of drugs for the treatment of disorders of the central nervous system associated with imbalances in dopaminergic, cholinergic or serotonergic signal transmission. Among these CNS active agents are antipsychotics such as trifluoperazine (**1**), antidepressants such as clozapin (**2**) and anticonvulsants such as ropizine (**3**) (Figure 1).

The piperazine moiety is also contained in antihypertensive agents such as prazosine, calcium channel blockers such as flunarizine (**4**), H_1-blockers such as oxatomide, and the anti-ulcer agent esaprazole (**5**).[1] Because of its prevalence in the field of pharmacologically active compounds, it is regarded as a privileged structural element for the construction of drug-like molecules.[2−5] Whereas the synthesis of simple 1,4-disubstituted piperazines has received considerable attention, only a comparatively small number of *C*-substituted derivatives have been prepared and evaluated for their pharmacological properties. Nevertheless, the synthesis of conformationally restricted bicyclic piperazines could be an interesting approach to gain insight into the influence of ring conformation on biological activity.[6]

The preparation of hexahydro-1,5-imino-3-benzazocines from dipeptide aldehyde acetals by *N*-acyliminium ion chemistry has been reported by Kurihara and Mishima and has recently been taken up by Hiemstra et al., but there have not yet been any reports on the construction of diamine scaffolds for combinatorial chemistry based on this efficient method.[7−10] Therefore, the preparation of the selectively deprotectable chiral non-racemic piperazines **6** and **7** from Fmoc−L-phenylalanine and Fmoc−L-tyrosine *tert*-butyl ether was undertaken (Figure 2).

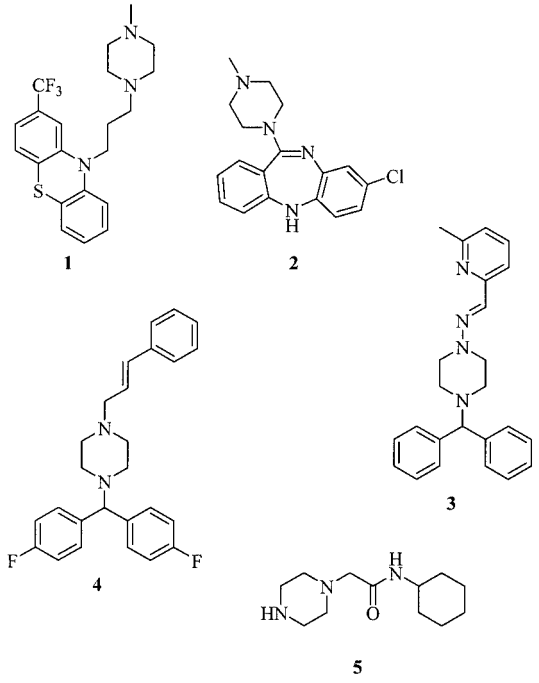


Figure 1. Some drugs containing the piperazine ring

Apart from its general use as a rigid scaffold for the construction of potentially bioactive products, a more specific application for the silyloxy-iminobenzazocine **7** could be the synthesis of opioid mimetics. Various cyclic 2-phenylalkylamines possessing a phenolic hydroxy group in *meta*-

[a] Institut für Organische Chemie, Johannes Gutenberg-Universität Mainz,
Duesbergweg 10−14, 55128 Mainz, Germany
Fax: (internat.) + 49-6131-39-24786
E-mail: opatz@uni-mainz.de

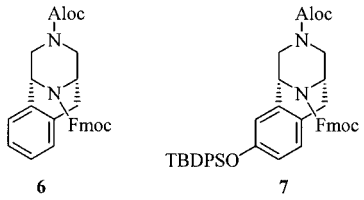


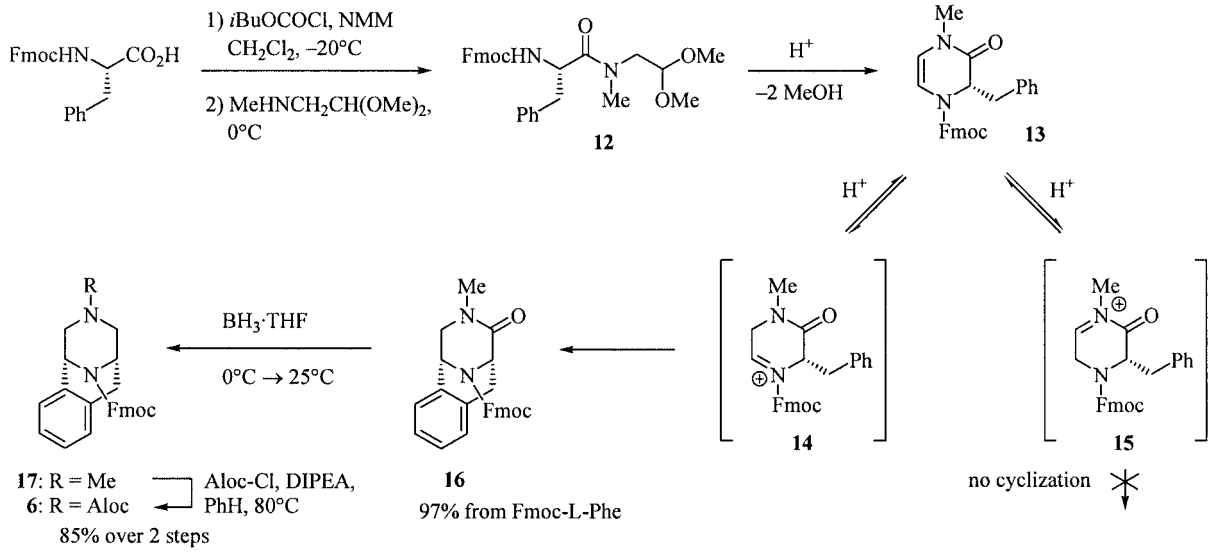
Figure 2. Selectively deprotectable iminobenzazocine scaffolds

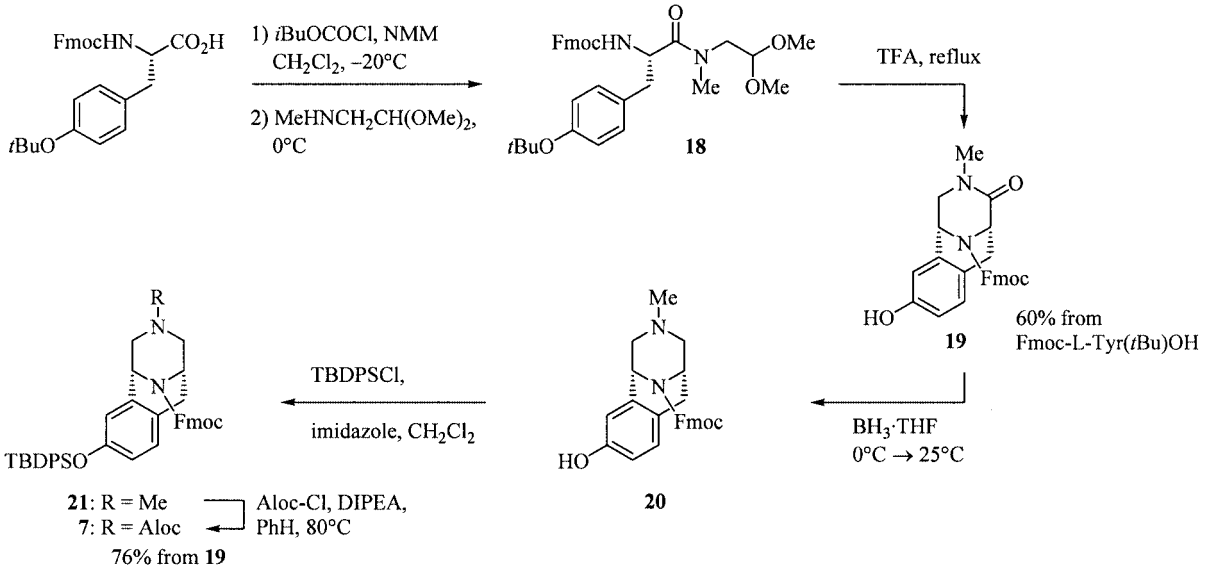
or *para*-position, such as the partial μ-opioid agonists dezocine (**8**, Dalgan®),[11,12] metazocine (**9**),[13] profadol (**10**)[14] and meptazinol (**11**, Meptid®, Nestan®;[15] Figure 3), exhibit analgesic activity through a morphine-like mechanism.[1,16]

Since scaffold **7** shares this structural feature with the drugs described, its derivatives might possess an affinity to opioid receptors.

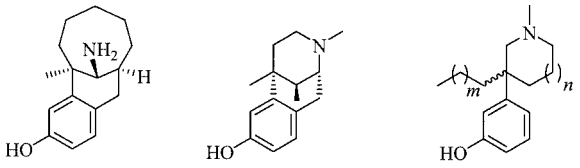
Results and Discussion

Amide **12** was prepared from Fmoc−L-phenylalanine by condensation with commercially available *N*-(methylamino)acetaldehyde dimethyl acetal, using isobutyl chloroformate as the coupling reagent and *N*-methylmorpholine as an activating base.[17] A low reaction temperature was





Scheme 1. Preparation of the iminobenzazocine scaffolds



8 **9** **10**: $m = 1, n = 0$ **11**: $m = 0, n = 2$

Figure 3. Opioid receptor ligands

kept to suppress racemization in this step.[18] TFA-catalysed cyclization of amide **12** to iminobenzazocinone **16** proceeded through intermediate formation of 3-benzyl-3,4-dihydro-2-pyrazinone **13**, yielding the bicyclic product **16** upon heating at reflux in neat TFA (97% from Fmoc−L-Phe).[7,8,19,20] This reaction proceeds via the cyclic acyliminium ion **14**, the result of protonation at C6. Although protonation at C5 to afford the isomeric acyliminium ion **15** is possible, no cyclization occurs in this case.

The tertiary amide moiety of **16** can be reduced in a fast and clean reaction with borane−THF without affecting the carbamate group.[21] Surprisingly, the hydrolytic destruction of the borane complex of the resulting tertiary amine took much longer than the reduction itself, which was complete after less than one hour. The obtained *N*-methylamine **17** was then subjected to *N*-demethylation with allyl chloroformate and Hünig's base in benzene at reflux to furnish the doubly protected scaffold **6** in 85% yield.[22,23] The proton and carbon NMR spectra of **6** revealed the presence of four conformers, due to slow rotation about both CO−*N* bonds.[24] The triply protected phenol **7**, the hydroxy derivative of scaffold **6**, was prepared from Fmoc−L-tyrosine *tert*-butyl ether in an analogous sequence, the *tert*-butyl group being cleaved under the conditions used for the cyclization of dimethyl acetal **18** to iminobenzazocinone **19**. Although no trapping reagent for the generated *tert*-butyl cations could be added, realkylation at the *ortho* position of the phenol ring occurred only to a small extent as judged by TLC. After borane reduction of the amide moiety and acid hydrolysis of the resulting borane complex, the hydroxy group of the resulting *N*-methylamine **20** was protected as the TBDPS ether. Finally, *N*-demethylation with allyl chloroformate furnished the triply protected scaffold **7**.

Conclusion

In summary, a short synthesis of the divalent scaffold **6** and the trivalent scaffold **7** from simple starting materials through ring closure of cyclic acyliminium ions has been achieved. The protecting groups chosen are orthogonally stable, and so their selective removal and the subsequent introduction of substituents in any order is possible.

Experimental Section

General Remarks: All reactions were carried out in dried glassware under argon unless stated otherwise. Solvents were distilled under argon from suitable drying agents (CH_2Cl_2 from calcium hydride, THF from Na/benzophenone). Analytical TLC was performed on aluminium-backed TLC plates coated with silica 60 F_{254} (E. Merck). Compounds were viewed under UV light (254 nm) and/or by dipping the plates into an alkaline $KMnO_4$ solution and heating. Column chromatography was performed on silica gel (40−63 μm, E. Merck). Optical rotations were measured with a Perkin−Elmer 241 polarimeter. NMR spectra were recorded with Bruker AC 300, AMX 400 or DRX 600 spectrometers; chemical shifts were referenced to the residual solvent peak ($CHCl_3$, δ_H = 7.24 ppm, $\delta_{C,central}$ = 77.0 ppm). ESI-MS spectra were measured with a Navigator instrument (ThermoQuest) at a cone voltage of 70 V with a flow rate of 0.75 mL/min acetonitrile/water (70:30 v/v) and a nitrogen flow of 300 L/h. A Basic-Marathon autosampler was employed for sample injection (20 μL at 0.1 g/L in acetonitrile). ESI-HMRS analyses were performed with a Micromass Q-TOF Ultima-III with a Lockspray interface and sodium formate as an external reference, FD-MS spectra were recorded with a Finnigan MAT 95 (desorption voltage 5 kV, heater current 10 mA/min). IR spectra were measured with a Perkin−Elmer 1760X FTIR spectrometer.

[(9*H*-Fluoren-9-yl)methyl] (1*R*,9*S*)-11-Methyl-10-oxo-11,13-diazatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-triene-13-carboxylate (16): *N*-Methylmorpholine (3.41 mL, 31.0 mmol) was added to a stirred suspension of Fmoc−L-phenylalanine (10 g, 25.8 mmol) in dry CH_2Cl_2 (50 mL) and the resulting clear solution was cooled to −20 °C in an ice/NaCl bath. Isobutyl chloroformate (3.68 mL, 28.4 mmol) was added, and the mixture was stirred at −20 °C for 5 min. *N*-(Methylamino)acetaldehyde dimethyl acetal (4.97 mL, 38.7 mmol) was added to the turbid mixture, and the reaction mixture was warmed up to 0 °C. After stirring for 3 h at that temperature, the mixture was poured into a saturated aqueous solution of $NaHCO_3$ (200 mL) and the product was extracted twice with CH_2Cl_2 (50 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated in vacuo. The resulting viscous yellowish oil was passed over a column of silica with ethyl acetate containing 1% ethyldimethylamine. Evaporation of the eluent in vacuo gave the tertiary amide **12** (13.07 g, not completely dry) as a colourless, viscous oil sufficiently pure for the subsequent cyclization. A portion of amide **12** (12.84 g) was dissolved in trifluoroacetic acid (130 mL), and the mixture was heated at reflux until TLC indicated complete conversion (ca. 6 h). The reaction mixture was poured onto ice (1 L) and the acid was neutralised by portionwise addition of $NaHCO_3$ (150 g). The product was extracted with CH_2Cl_2 (3 × 100 mL), the combined organic layers were dried over Na_2SO_4, and the solvent was evaporated in vacuo to afford iminobenzazocinone **16** (10.47 g, 97%) as a slightly pinkish foam. $[\alpha]_D^{25}$ = −24.2 (*c* = 1.0, $CHCl_3$). R_f (EtOAc) = 0.38. ^{1}H NMR, COSY (400 MHz, $CDCl_3$): δ = 2.77 (s, 1.2 H, NCH_3^x), 2.82 (s, 1.8 H, NCH_3^y), 2.96−3.20 (m, 3 H, H_2-8^{x+y}, $H12b^{x+y}$), contained in this multiplet: 3.17 (d, J_{gem} = 11.5 Hz, 0.6 H, $H12b^y$), 3.67 (dd, J_{gem} = 11.5, J_{vic} = 4.7 Hz, 0.4 H, $H12a^x$), 3.91 (dd, J_{gem} = 11.5, J_{vic} = 4.7 Hz, 0.6 H, $H12a^y$), 4.18−4.24 (br. m, 1 H, Fmoc−CH^{x+y}), 4.43−4.53 (m, 1.6 H, OCH_2-b^{x+y}, OCH_2-a^y), 4.65 (dd, J_{gem} = 10.8, J_{vic} = 5.9 Hz, 0.4 H, OCH_2-a^x), 4.78−4.83 (m, 0.6 H, $H9^y$), 4.93 (br. pseudo-d, *J* = 6.0 Hz, 0.4 H, $H9^x$), 4.99 (br. pseudo-d, *J* = 4.7 Hz, 0.4 H, $H1^x$), 5.38 (br. pseudo-d, *J* = 4.7 Hz, 0.6 H, $H1^y$), 6.98−7.77 (several m, 12 H, Ar−H^{x+y}) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$), HMQC, HMBC (100.6 MHz, $CDCl_3$): δ = 31.47 ($C8^x$), 32.11 ($C8^y$), 34.01 (NMe^x), 34.20 (NMe^y), 47.20 (Fmoc−$C9^y$), 47.30 (Fmoc−$C9^x$), 49.04 ($C1^y$), 49.89 ($C1^x$), 52.51 ($C9^x$), 53.26 ($C9^y$), 56.10 ($C12^y$), 56.36 ($C12^x$), 66.93 (OCH_2^x), 67.60 (OCH_2^y), 119.78, 119.94, 120.03 (Fmoc−$C4,5^{x+y}$), 124.61, 124.69, 124.78

(Fmoc−C1,8^{x+y}), 126.07, 126.40, 126.51, 126.66, 126.90, 127.03, 127.60, 127.73, 127.81, 127.89 (C3 − C5^{x+y}, Fmoc−C2,3,6,7^{x+y}), 129.21 (C6^{y}), 129.45 (C6^{x}), 132.70 (C7^{y}), 133.13 (C7^{x}), 134.05 (C2^{x}), 134.27 (C2^{y}), 141.21, 141.27, 141.33 (Fmoc−C4a,b^{x+y}), 143.34, 143.48, 143.57, 143.64 (Fmoc−C8a,9a^{x+y}), 153.18 (Fmoc−CO^{x}), 153.58 (Fmoc−CO^{y}), 167.65 (CO^{y}), 167.93 (CO^{x}) ppm. Note: The indices x and y denote the minor and the major rotamer, respectively. ESI-MS: *m*/*z* (%) = 488.27 (21) [M + Na + MeCN]$^+$, 447.23 (100) [M + Na]$^+$, 179.08 (49) [fluorenylmethyl]$^+$. ESI-HRMS: calcd. for $C_{27}H_{24}N_2O_3$ + H$^+$: 425.1865, found 425.1853. IR (film): $\tilde{\nu}$ = 3016, 2947, 1705, 1656, 1452, 1427, 1324, 1298, 1230, 1124, 1030, 757, 742 cm^{-1}.

11-Allyl 13-[(9*H*-Fluoren-9-yl)methyl] (1*R*,9*S*)-11,13-Diazatricyclo-[7.3.1.0^{2,7}]trideca-2,4,6-triene-11,13-dicarboxylate (6): A stirred solution of **16** (1 g, 2.36 mmol) in dry THF (30 mL) was cooled to 0 °C in an ice bath. A solution of borane in THF (1 M, 9.4 mL, 9.4 mmol) was added, and the mixture was stirred at 0 °C for 20 min. The solution was warmed up to 25 °C and stirring was maintained until TLC indicated complete conversion (ca. 25 min). The reaction was stopped by slow addition of a saturated aqueous solution of citric acid (10 mL), and the mixture was stirred for 18 h at 25 °C.[25] Since hydrolysis of the amine-borane complex was still not complete, the mixture was heated at 45 °C for 2 h and was then stirred for 3d at 25 °C. The solution was made alkaline by addition of a saturated aqueous $NaHCO_3$, and the product was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, and the solvent was evaporated in vacuo to afford iminobenzazocine **17** (1.22 g, not completely dry) as a colourless oil. Since **17** has an Fmoc group and a basic nitrogen, it was directly converted into the N-Aloc derivative. Amine **17** was dissolved in dry benzene (50 mL), and after addition of allyl chloroformate (2.5 mL, 23.4 mmol) the mixture was stirred for 15 h at 60 °C. Since TLC still showed the presence of unchanged starting material, ethyldiisopropylamine (404 μL, 2.36 mmol) was added and the mixture was stirred for 6 h at 70 °C. The solvent was removed in vacuo and the residue was coevaporated with benzene (2 × 10 mL). The residue was dissolved in diethyl ether (100 mL), and the solution was washed with water, saturated aq. $NaHCO_3$, HCl (0.5 N) and brine. The ethereal solution was dried over Na_2SO_4, and the solvent was evaporated in vacuo to afford crude iminobenzazocine **6** as a weakly brownish oil (1.38 g). The crude product was purified by flash chromatography on silica gel with cyclohexane/ethyl acetate (3:1) as the eluent to yield pure **6** as a colourless foam (959 mg, 85%). $[\alpha]_D^{25}$ = −34.3 (*c* = 1.0, $CHCl_3$). R_f (EtOAc) = 0.60. ^{1}H NMR, COSY (400 MHz, $CDCl_3$): δ = 2.64−2.85 (m, 1 H, H8b), 2.90−3.30 (m, 3 H, H8a, H10b, H12b), 3.87−4.62 (m, 8 H, H10a, H12a, 2 × OCH_2, Fmoc−CH, H9), 4.81 (br. pseudo-d, J_{trans} = 17.2 H, 0.7 Hz, CH_2=), 4.92−5.03 (m, 1.2 H, H1, CH_2=), 5.09−5.24 (m, 1.1 H, H1, CH_2=), 5.40−5.51 (m, 0.7 H, allyl = CH−), 5.68−5.81 (m, 0.3 H, allyl =CH−), 6.95−7.79 (several m, 12 H, Ar−H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$), HMQC (100.6 MHz, $CDCl_3$): δ = 30.93, 31.11, 31.47, 31.59 (C8), 45.98, 46.36, 46.86 (C9), 47.23, 47.39 (Fmoc−C9), 49.25, 49.45, 49.56, 50.07 (C10, C12), 50.95, 51.87 (C1), 65.69, 65.93 (Aloc−OCH_2), 67.00, 67.10 (Fmoc−OCH_2), 116.71, 117.40 (CH_2=), 119.87, 119.95 (Fmoc−C4,5), 124.66, 124.82 (Fmoc−C1,8), 125.84, 125.89, 126.18, 126.21, 126.50, 126.91, 126.96, 127.00, 127.22, 127.40, 127.57, 127.61, 127.68, 128.08, 128.17, 128.48 (C3−C6, Fmoc−C2,3,6,7), 132.55, 132.78 (allyl −CH=), 134.03, 134.09, 134.59 (C2,7), 141.23, 141.31, 141.36 (Fmoc−C4a,b), 143.59, 143.73, 143.79 (Fmoc−C8a,9a), 154.09 (Fmoc−CO), 155.06, 155.40 (Aloc-CO) ppm. ESI-MS: *m*/*z* (%) = 503.25 (100) [M + Na]$^+$, 179.07 (78) [fluorenylmethyl]$^+$. ESI-HRMS: calcd. for $C_{30}H_{28}N_2O_4$ + Na: 503.1947, found 503.1958. IR (film): $\tilde{\nu}$ = 3018, 2899, 1698, 1451, 1428, 1325, 1310, 1251, 1113, 759, 740 cm^{-1}. Note: The complete assignment of all signals in the NMR spectra was not undertaken due to the presence of two pairs of rotamers.

(9*H*-Fluoren-9-yl)methyl (1*R*,9*S*)-4-Hydroxy-11-methyl-10-oxo-11,13-diazatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-triene-13-carboxylate (19): *N*-Methylmorpholine (341 μL, 3.10 mmol) was added to a stirred suspension of Fmoc−L-tyrosine *tert*-butyl ether (1.19 g, 2.59 mmol) in dry dichloromethane (5 mL) and the resulting clear solution was cooled to −20 °C in an ice/salt bath. Isobutyl chloroformate (368 μL, 2.84 mmol) was added dropwise to yield a milky suspension. After the mixture had been stirred at −20 °C for 5 min, (methylamino)acetaldehyde dimethyl acetal (497 μL, 3.87 mmol) was added and the reaction mixture was warmed up to 0 °C. After the mixture had been stirred for 1.5 h, TLC indicated complete conversion and the reaction mixture was quenched with aq. $NaHCO_3$ (50 mL). The resulting mixture was extracted with CH_2Cl_2 (2 × 50 mL), and the organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent in vacuo gave a viscous, colourless oil (1.61 g), which was purified by elution from a short column of silica gel with ethyl acetate containing 1% of ethyldimethylamine. Removal of the eluent in vacuo yielded the tertiary amide **18** (1.37 g) as a viscous, colourless oil. A portion of this product (1.33 g) was dissolved in trifluoroacetic acid (24 mL), and the mixture was heated at reflux until TLC indicated complete conversion (5 h). The reaction mixture was poured onto ice (100 mL), and the resulting suspension was extracted with ethyl acetate (100 mL). The organic layer was washed with aq. $NaHCO_3$ and dried over Na_2SO_4, and the solvent was evaporated in vacuo to furnish crude iminobenzazocinone **19** (1.14 g) as a tan-coloured amorphous solid. Purification by silica gel column chromatography with ethyl acetate/cyclohexane (2:1) gave **19** (670 mg, 60% from Fmoc−Tyr(*t*Bu)−OH) as a colourless foam. $[\alpha]_D^{25}$ = −16.2 (*c* = 1.0, $CHCl_3$). R_f (EtOAc) = 0.35. ^{1}H NMR, COSY, ROESY (600 MHz, $CDCl_3$): δ = 1.92 (br. s, 0.5 H, OH), 2.76 (s, 1.2 H, NCH_3^x), 2.82 (s, 1.8 H, NCH_3^y), 2.92−3.06 (m, 2.4 H, H_2-8^{x+y}, H12b^{x}), 3.15 (d, J_{gem} = 11.7 Hz, 0.6 H, H12b^{y}), 3.61 (dd, J_{gem} = 11.7, J_{vic} = 4.7 Hz, 0.4 H, H12a^{x}), 3.85 (dd, J_{gem} = 11.7, J_{vic} = 4.7 Hz, 0.6 H, H12a^{y}), 4.17−4.21 (br. m, 1 H, Fmoc−CH^{x+y}), 4.42−4.46 (m, 1 H, OCH_2-b^{x+y}), 4.50 (dd, J_{gem} = 10.6, J_{vic} = 6.5 Hz, 0.6 H, OCH_2-a^{y}), 4.66 (dd, J_{gem} = 10.9, J_{vic} = 5.9 Hz, 0.4 H, OCH_2-a^{x}), 4.79−4.81 (m, 0.6 H, H9^{y}), 4.88 (br. pseudo-d, *J* = 4.7 Hz, 0.4 H, H1^{x}), 4.92 (br. pseudo-d, *J* = 5.9 Hz, 0.4 H, H9^{x}), 5.27 (br. d, *J* = 4.7 Hz, 0.6 H, H1^{y}), 6.51 (d, J_{gem} = 2.5 Hz, 0.4 H, H3^{x}), 6.60 (d, J_{gem} = 2.4 Hz, 0.6 H, H3^{y}), 6.69−6.74 (m, 1 H, H5^{x+y}), 6.86−6.90 (m, 1 H, H6^{x+y}), 7.17−7.76 (several m, 8 H, Fmoc) ppm. ^{13}C NMR, HMQC, HMBC (150.9 MHz, $CDCl_3$): δ = 30.66 (C8^{x}), 31.37 (C8^{y}), 34.28 (NMe^{x}), 34.46 (NMe^{y}), 47.14 (Fmoc−CH^{y}), 47.29 (Fmoc−CH^{y}), 49.08 (C1^{y}), 49.89 (C1^{x}), 52.74 (C9^{x}), 53.45 (C9^{y}), 56.08 (C12^{y}), 56.33 (C12^{x}), 67.09 (OCH_2^x), 67.87 (OCH_2^y), 112.71 (C3^{x}), 112.91 (C3^{y}), 115.68 (C5^{x}), 115.76 (C5^{y}), 119.85, 120.01, 120.07, 120.11 (Fmoc−C4,5^{x+y}), 123.66 (C7^{y}), 124.03 (C7^{x}), 124.61, 124.73, 124.77, 124.87 (Fmoc−C1,8^{x+y}), 126.95, 127.07, 127.13 (Fmoc−C2,7^{x+y}), 127.67, 127.79, 127.82 (Fmoc−C3,6^{x+y}), 130.24 (C6^{y}), 130.40 (C6^{x}), 134.89 (C2^{x}), 135.04 (C2^{y}), 141.20, 141.26, 141.29, 141.39 (Fmoc−C4a,b^{x+y}), 143.26, 143.42, 143.48, 143.56 (Fmoc−C8a,9a^{x+y}), 153.32 (Fmoc−CO^{x}), 153.68 (Fmoc−CO^{y}), 155.07 (C4^{x}), 155.19 (C4^{y}), 168.32 (C10^{y}), 168.69 (C10^{x}) ppm. ESI-MS: *m*/*z* (%) = 504.23 (17) [M + Na + MeCN]$^+$, 463.25 (76) [M + Na]$^+$, 179.07 (100) [fluorenylmethyl]$^+$. ESI-HRMS: calcd. for $C_{27}H_{24}N_2O_4$ + Na: 463.1634, found 463.1635. IR (film): $\tilde{\nu}$ = 3279

(broad), 3017, 2932, 1705, 1640, 1504, 1451, 1429, 1339, 1300, 1222, 1122, 1032, 757, 742 cm^{-1}.

11-Allyl 13-[(9*H*-Fluoren-9-yl)methyl] (1*R*,9*S*)-4-[*tert*-Butyl(diphenyl)silyloxy]-11,13-diazatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-triene-11,13-dicarboxylate (7): A solution of borane in THF (1 M, 3.64 mL, 3.64 mmol) was added at 0 °C to a stirred solution of **19** (320 mg, 726 μmol) in dry THF (15 mL). After 20 min, the solution was warmed up to room temperature. When TLC indicated complete conversion (40 min), the reduction was stopped by slow addition of a saturated aqueous solution of citric acid (2 mL). The resulting mixture was stirred for 4 d to destroy the rather stable amine borane adduct. The product was isolated by addition of aq. $NaHCO_3$ (50 mL), extraction with CH_2Cl_2 (2 × 25 mL), drying over Na_2SO_4 and removal of the solvent in vacuo. Amine **20** was obtained as colourless oil (344 mg, not completely dry) and since it contains both a sterically accessible amine and an Fmoc group, it was directly subjected to the subsequent silylation reaction without further purification. Crude **20** was dissolved in dry CH_2Cl_2 (10 mL) and after addition of *tert*-butyldiphenylsilyl chloride (570 μL, 2.18 mmol) and imidazole (74 mg, 1.09 mmol), the solution was stirred for 20 h at room temperature. The reaction mixture was partitioned between CH_2Cl_2 (30 mL) and aq. $NaHCO_3$ (50 mL), the organic layer was dried over Na_2SO_4, and the solvent was removed in vacuo to yield a colourless oil. The product was purified by silica gel column chromatography with petroleum ether/ethyl acetate (4:1 to 3:1) containing 0.8% ethyldimethylamine to yield silyl ether **21** (400 mg) as a colourless foam, which was directly converted into the *N*-Aloc derivative: ethyldiisopropylamine (515 μL, 3.01 mmol) and allyl chloroformate (642 μL, 6.02 mmol) were added to a stirred solution of **21** (400 mg) in dry benzene (15 mL), and the resulting clear solution was heated at 80 °C. After 30 h, TLC indicated a stagnating conversion, presumably due to complete decomposition of the chloroformate. Further portions of ethyldiisopropylamine (258 μL, 1.51 mmol) and allyl chloroformate (321 μL, 3.01 mmol) were added and the solution was stirred at 80 °C for 12 h. To complete the conversion, two more portions of the reagents (1.51 mmol base and 3.01 mmol chloroformate each) were added over a period of 5 h. The reaction mixture was concentrated by evaporation of the solvent in vacuo. To remove volatile impurities, the resulting solid was coevaporated with benzene (2 × 5 mL). The residue was partitioned between ethyl acetate and aq. $NaHCO_3$, the organic layer was washed with $KHSO_4$ (1 N) and aq. $NaHCO_3$ and, after drying over $MgSO_4$, the solvent was removed in vacuo. Purification of the crude product by flash chromatography on silica gel with petroleum ether/ethyl acetate (3:1) yielded iminobenzazocine **7** as a colourless foam (405 mg, 76% from **19**). $[\alpha]_D^{25} = -35.9$ ($c = 1.0$, $CHCl_3$). R_f (petroleum ether/EtOAc, 3:1) = 0.13. ^1H NMR, COSY (400 MHz, $CDCl_3$): δ = 1.10 (s, 4.1 H, *t*Bu), 1.14 (s, 4.9 H, *t*Bu), 2.52−2.72 (m, 1 H, H8b), 2.85−3.22 (m, 3 H, H10b, H12b, H8a), 3.75−4.60 (m, 8 H, H10a, H12a, 2 × OCH_2, Fmoc−CH, H9), 4.72−5.20 (m, 3 H, H9, CH_2=), 5.54−5.68 (m, 0.7 H, allyl −CH=), 5.70−5.82 (m, 0.3 H, allyl −CH=), 6.46−6.62 (m, 2 H, H3, H5), 6.65−6.80 (m, 1 H, H6), 7.18−7.79 (m, 18 H, 8 × Fmoc−H, 10 × Ph−H) ppm. ^{13}C NMR, DEPT (75.4 MHz, $CDCl_3$), HMQC (100.6 MHz, $CDCl_3$): δ = 19.43 (CMe_3), 26.52 (Me_3), 30.17, 30.38, 30.76, 30.85 (C8), 46.04, 46.16, 46.34 (C9), 47.24, 47.41 (Fmoc−C9), 49.17−49.57 (m, br), 49.84 (C10, C12), 50.87, 51.80 (C1), 65.75, 65.92 (Aloc−OCH_2), 66.99, 67.17 (Fmoc−OCH_2), 116.85, 117.25 (CH_2=), 116.61, 116.86, 118.85, 118.96 (C3, C5), 119.87, 119.96 (Fmoc−C4,5), 124.72, 124.88 (Fmoc−C1,8), 126.30, 126.81 (C7), 126.93, 127.03 (Fmoc−C2,7), 127.62, 127.73 (Fmoc−C3,6, 2 × Ph−C3,5), 128.64, 128.77, 129.08 (C6), 129.92 (br., 2 × Ph−C4), 132.65, 132.86 (allyl −CH=), 132.89 (2 × Ph−C1), 134.81, 134.91 (C2), 135.44, 135.53 (2 × Ph−C2,6), 141.26, 141.30, 141.33, 141.38 (Fmoc−C4a,5a), 143.61, 143.77 (Fmoc−C8a,9a), 153.45, 154.05, 155.03, 155.48 (C4, 2 × CO) ppm. FD-MS: *m*/*z* (%) = 735.5 [M + H]$^+$ (100). ESI-HRMS: calcd. for $C_{46}H_{46}N_2O_5$ + H: 735.3254, found 735.3237. IR (film): $\tilde{\nu}$ = 3015, 2931, 2894, 2858, 1702, 1612, 1502, 1429, 1312, 1293, 1264, 1248, 1156, 1111, 966, 833, 757, 741, 702 cm^{-1}. Note: The complete assignment of all signals in the NMR spectra was not undertaken due to the presence of two pairs of rotamers.

Acknowledgments

The author is grateful to H. Kolshorn for the 2D NMR spectroscopic analyses.

[1] Database: *ChemIDplus*, Division of Specialized Information Services, National Library of Medicine, USA, http://chem.sis.nlm.nih.gov/chemidplus/.
[2] M. Y. Cha, B. C. Choi, K. H. Kang, A. N. Pae, K. I. Choi, Y. S. Cho, H. Y. Koh, H. Y. Lee, D. Jung, J. Y. Kong, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1327−1330.
[3] V. S. Goodfellow, C. P. Laudeman, J. I. Gerrity, M. Burkard, E. Strobel, J. S. Zuzack, D. A. McLeod, *Mol. Divers.* **1996**, *2*, 97−102.
[4] T. F. Herpin, G. C. Morton, A. K. Dunn, C. Fillon, P. R. Menard, S. Y. Tang, J. M. Salvino, R. F. Labaudiniere, *Mol. Divers.* **1998**, *4*, 221−232.
[5] I. Lewis, B. Rohde, M. Mengus, M. Weetall, S. Maida, R. Hugo, P. Lake, *Mol. Divers.* **2000**, *5*, 61−73.
[6] For the preparation of a chiral bicyclic piperazine carboxylate scaffold for the construction of cocaine analogues, see: S. Pichlmair, K. Mereiter, U. Jordis, *Tetrahedron Lett.* **2004**, *45*, 1481−1483.
[7] H. Kurihara, H. Mishima, *Heterocycles* **1982**, *17*, 191−199.
[8] J. J. N. Veerman, R. S. Bon, B. T. B. Hue, D. Girones, F. P. J. T. Rutjes, J. H. van Maarseveen, H. Hiemstra, *J. Org. Chem.* **2003**, *68*, 4486−4494.
[9] S. Shiotani, K. Mitsuhashi, *Yakugaku Zasshi* **1964**, *84*, 1032−1035.
[10] S. Shiotani, K. Mitsuhashi, *Yakugaku Zasshi* **1966**, *86*, 169−173.
[11] M. E. Freed, J. R. Potoski, E. H. Freed, G. L. Conklin, J. L. Malis, *J. Med. Chem.* **1973**, *16*, 595−599.
[12] J. L. Malis, M. E. Rosenthale, M. I. Gluckman, *J. Pharm. Exp. Ther.* **1975**, *194*, 488−498.
[13] E. L. May, E. M. Fry, *J. Org. Chem.* **1957**, *22*, 1366−1369.
[14] J. F. Cavalla, R. Jones, M. Welford, J. Wax, C. V. Vinder, *J. Med. Chem.* **1964**, *7*, 412−415.
[15] M. T. Rosseel, M. G. Bogaert, F. M. Belpaire, *Curr. Med. Res. Opin.* **1975**, *3*, 181−186.
[16] H. Buschmann, T. Christoph, E. Friderichs, C. Maul, B. Sundermann (Eds.), *Analgesics*, Wiley-VCH, Weinheim, **2002**.
[17] P. Stelzel, in *Synthese von Peptiden, 15/2* (Ed.: E. Wünsch), Georg Thieme Verlag, Stuttgart, **1974**, pp. 169−259.
[18] Attempts to determine the extent of racemization in the coupling step and the subsequent cyclization by chiral HPLC of compounds **6** and **7** were unsuccessful. It should, however, be noted that two samples of compound **16** prepared under different reaction conditions showed identical optical rotations.
[19] H. Uchida, T. Kato, K. Achiwa, *Chem. Pharm. Bull.* **1997**, *45*, 1228−1230.
[20] The dihydropyrazinone is already formed at room temperature, whereas the second cyclization requires elevated temperatures.
[21] W. J. Hoekstra, B. E. Maryanoff, B. P. Damiano, P. Andrade-

Gordon, J. H. Cohen, M. J. Costanzo, B. J. Haertlein, L. R. Hecker, B. L. Hulshizer, J. A. Kauffman, P. Keane, D. F. McComsey, J. A. Mitchell, L. Scott, R. D. Shah, S. C. Yabut, *J. Med. Chem.* **1999**, *42*, 5254−5265.
[22] J. Bonjoch, J.-C. Fernandez, N. Valls, *J. Org. Chem.* **1998**, *63*, 7338−7347.
[23] E. Magnier, Y. Langlois, C. Merienne, *Tetrahedron Lett.* **1995**, *36*, 9475−9478.
[24] The relative population of the rotamers about the CO−N bond of the Fmoc group is roughly 1:1, whereas there is a marked preference for one of the rotamers about the CO−N bond of the Aloc group (ratio 2:1). The assignment of the conformation of the inconsequential rotamers was not undertaken.
[25] V. Schanen, M. P. Cherrier, S. J. deMelo, J. C. Quirion, H. P. Husson, *Synthesis* **1996**, 833−837.

Received May 21, 2004

