Stereoselective Synthesis and Binding Properties of Novel Concave-Shaped Indolizino[3,4-*b*]quinolines

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Dedicated to Professor Dr. Horst Kunz, University of Mainz, on the Occasion of his 60th Birthday

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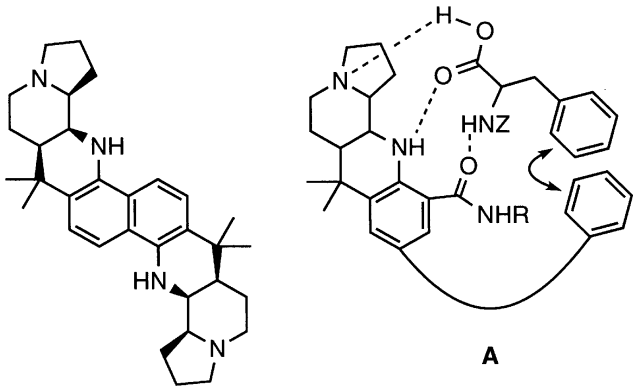
Abstract. Novel *all-cis*-configurated indolizino[3,4-*b*]quinoline receptors **3**, **4** were prepared *via* diastereoselective Lewis acid-catalyzed cyclization of *N*-arylimines **6**, **7** as the key step. In order to obtain the indolizino[3,4-*b*]quinoline derivative **21** without a *gem*-dimethyl group at C-7, an *N*-arylimine precursor **18** bearing a vinyldisilane terminus was prepared in **8** steps from *L*-prolinol **15**. In contrast to the known β-effect of silyl groups cyclization of **18** proceeded via an α-carbenium ion species to give the diastereomeric products **19**, **20**, which were desilylated to **21**, **22**. The association constants for receptors **2**–**4** and **21** decreased in the order **21** > **2** > **4** > **3** for both acetic acid and *N*-Z-phenylalanine as substrates.

Supramolecular chemistry and the design of novel artificial receptors are among the most actively pursued research topics in recent years [1]. Particularly the binding of carboxylic acids [2, 3] and amino acids [4] is intensively investigated with the aim to mimic enzymes and transport proteins. We have previously discovered that concave-shaped azapolycyclic systems **1** bearing two indolizino[3,4-*b*]quinoline moieties were easily accessible *via* Lewis acid-catalyzed cyclizations of *N*-arylimines (Scheme 1) [5]. However, initial binding studies suffered from a serious drawback that is the occurrence of several competing association processes. In order to avoid such difficulties and to learn more about the parent indolizino[3,4-*b*]quinoline system we decided to investigate the molecular recognition properties of simpler systems. The following derivatives **2**–**4** were chosen as model compounds. It was anticipated that compounds **2**–**4** should display similar binding properties for simple carboxylic acids such as acetic acid. However, the presence of additional substituents on the aromatic ring of indolizino[3,4-*b*]quinolines **3**, **4** should lead to increased association constants with aromatic amino acids such as phenylalanine due to additional π-stacking interactions and hydrogen bonding (A) as compared to the parent compound **2**. The results towards the synthesis and molecular recognition properties are reported below.



A

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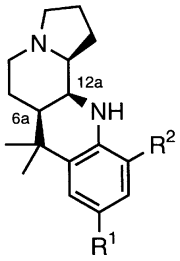

2 $R^1 = R^2 = H$

3 R^1 = O Ph $R^2 = H$

4 $R^1 = H$ $R^2 = CONHPh$

Scheme 1 Indolizino[3,4-*b*]quinoline receptors

Results and Discussion

Following our previously established strategy [6] *L*-prolinal-derived aldehyde **5** was condensed with aniline derivatives **6** or **7** in the presence of molecular sieves to the corresponding imines, which were subsequently treated with $EtAlCl_2$ to yield the tetracyclic indolizino [3,4-*b*]quinolines **3**, **8**, **9** (Scheme 2). Depending on the substitution pattern of the aniline derivatives **6**, **7** varying mixtures of *all-cis*- and *all-trans*-diastereomers were obtained during the cyclization. When 4-(3-phenylpropyloxy)aniline **6** was employed, the cyclization procee-

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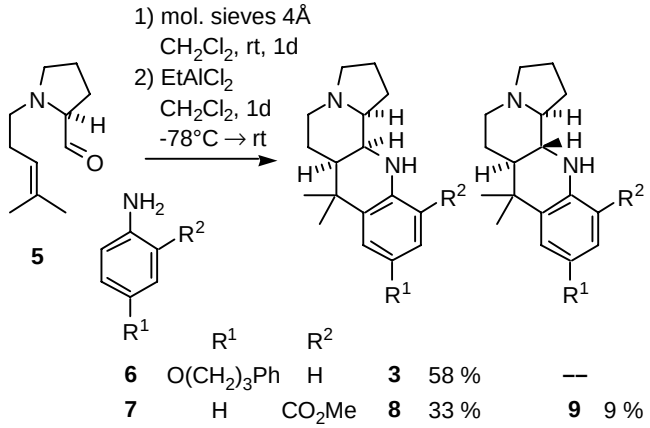
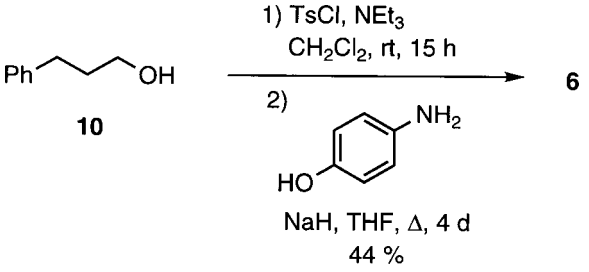
ded with high diasteroselectivity yielding 58% of the *cis*-product **3** as a single stereoisomer. As shown in Scheme 3 compound **6** was prepared from 3-phenylpropanol **10** *via* tosylation and nucleophilic displacement with 4-hydroxyaniline [7]. In contrast, methyl 2-aminobenzoate **7** gave 33% of the *all-cis*-product 8 and 9% of the corresponding *all-trans*-diastereomer **9** [8].

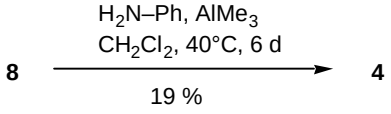


Scheme 2 Synthesis of aniline derivative (**3**), (**8**) and (**9**)



Scheme 3 Synthesis of aniline derivative (**6**)

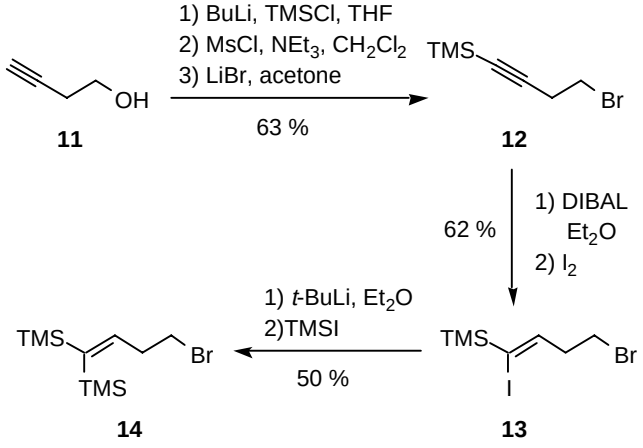
The *all-cis*-configurated methyl ester **8** was further converted to the anilide **4** using Weinreb's conditions (Scheme 4) [9]. Although the amidation proceeded with rather low yield [10], it was considered advantageous as compared to the activation *via* acid chlorides, because the latter ones interfered with the remaining amino groups.



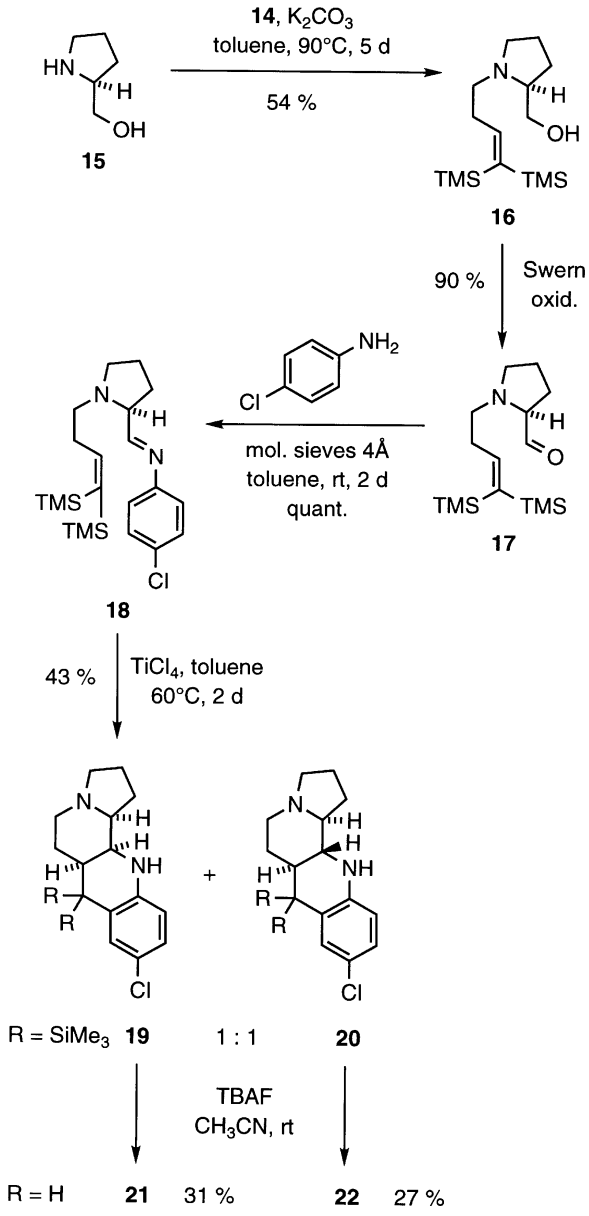
Scheme 4 Amidation of methyl ester (**8**)

From inspection of molecular models we concluded that *all-cis*-configurated indolizino[3,4-*b*]quinolines without a *gem*-dimethyl group at C-7 should lead to improved binding constants due to a sterically less encumbered binding site. Although direct cyclization of a derivative of **5** with a terminal alkene moiety seemed an attractive approach to such unsubstituted indolizino[3,4-*b*]quinoline, this route was not possible. According to earlier mechanistic studies [11] the Lewis acid-catalyzed cyclization of *N*-arylimines follows a stepwise pathway, i.e. a sequence of iminium ion cyclization followed by intramolecular Friedel–Crafts type alkylation of the resulting carbenium ion and final tautomerization. Consequently, the reaction requires at least on cation stabilizing group at the alkene terminus [12].

In order to circumvent this problem we *reasoned* that two trimethylsilyl groups at the terminal alkene carbon atom should stabilize the intermediate cation and might be removed at a later stage of the synthesis. This approach might seem somewhat risky because it is well known that silyl groups stabilize carbenium ions at the β-position due to $(\sigma\text{-p})\pi$ hyperconjugation [13]. However, there was some precedence by Overman [14], who observed the stereospecific acetal-initiated cyclization of vinylsilanes to tetrahydropyranes with concomitant formation of α-silyl cations. We therefore attempted the synthesis of a precursor bearing a vinyldisilane moiety and its subsequent Lewis acid-catalyzed cyclization. As shown in Scheme 5 the terminal carbon at the alkyne **11** was protected with trimethylsilyl according to a modified procedure by Negishi [15]. Mesylation of the hydroxy group and Finkelstein reaction gave the bromide **12** [16]. Following Negishi's protocol hydroalumination of **12** with DIBAL followed by trapping with iodine yielded iodovinylsilane **13** [15]. Replacement of the iodide by trimethylsilyl gave vinyldisilane **14**, which was coupled with prolinol **15** in the presence of K_2CO_3



Scheme 5 Synthesis of 4,4-bistrimethylsilyl-1-bromo-3-butene (**14**)



Scheme 6 Synthesis of indolizino[3,4-*b*]quinolines (**21**), (**22**)

to give aminoalcohol **16** in 54% yield [17] (Scheme 6). Swern oxidation of **16** [18] followed by condensation of the resulting aldehyde **17** with 4-chloroaniline yielded the imine **18**, which was further cyclized in the presence of $TiCl_4$ at elevated temperatures [19] to give a (1:1) mixture of diastereomers **19**, **20**. Unfortunately, chromatographic separation of **19**, **20** was not possible at this stage and thus the mixture was submitted to fluoride-induced desilylation [20], which proceeded without any event. After flash chromatography the *all-cis*- and *all-trans*-diastereomers **21** and **22** were isolated in 31% and 27% yield respectively.

Binding constants of compounds **2**–**4** and **21** with acetic acid and *N*-*Z*-phenylalanine (*Z*-Phe–OH) were determined by ^{1}H NMR titration [21] assuming a (1:1) complexation mode. When a complexation occurred, a shift of the signal corresponding to the 12a-H of the indolizino[3,4-*b*]quinoline was observed. Analysis of the NMR data according to the Benesi–Hildebrand equation [22] yielded the association constants K_a, which are summarized in Table 1. A similar trend was observed for the binding of acetic acid and *N*-Z-phenylalanine by the different receptors. The association constants decreased in the order **21** > **2** > **4** > **3**. However, whereas the binding strengths of the receptors towards *N*-Z-phenylalanine differ by a factor of 200, the corresponding K_a values for acetic acid differ only by a factor of 2 [23].

Table 1 Association constants K_a of indolizino[3,4-*b*]quinolines **2**–**4**, **21** with acetic acid and *N*-Z-L-phenylalanine [a])

Receptor	HOAc K_a [l mol^{-1}]	Z-Phe-OH K_a [l mol^{-1}]
2	84	1153
3	41	98
4	69	442
21	99	1920

[a]) K_a values were obtained by ^{1}H NMR titration. For details see Experimental part.

Several conclusions can be drawn from these results. Increased binding strength of the indolizino[3,4-*b*]quinoline skeleton was indeed obtained by decreasing the steric hindrance at C-7 (compare **2** with **21** in Table 1). This effect was even more pronounced for the binding of the *N*-protected amino acid as compared to the sterically less encumbered acetic acid. The increased K_a values of compounds **2**–**4**, **21** for the complexation of *N*-Z-phenylalanine as compared to acetic acid indicate an additional stabilizing π–π interaction between the aromatic moiety of the receptor and the amino acid. However, attaching additional substituents at the indolizino[3,4-*b*]quinoline which are capable of further hydrogen bonding and π–π interaction as in compounds **3**, **4** proved to be deleterious and lead to a decrease of the K_a values [24]. Overall, indolizino[3,4-*b*]quinoline **21** without a *gem*-dimethyl group at C-7 turned out to be the best receptor for acidic substrates within this series. Compound **21** was available via a Lewis acid-catalyzed cyclization of an *N*-arylimine tethered to a vinyldisilane followed by desilylation. Further synthetic applications of this exception of the β-silicon effect are currently under investigation.

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Experimental

All reactions were carried out under argon by 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 products were visualized with UV light or a solution of phosphomolybdic acid in EtOH (5%, v/v). Flash chromatography [21] was carried out with Merck silica gel 60 (230–400 mesh). – NMR spectra: Bruker AM 400 (400 MHz ^{1}H, 100 MHz ^{13}C), Bruker DRX 400 (400 MHz ^{1}H, 100 MHz ^{13}C) and Bruker AC 200 (200 MHz ^{1}H, 50 MHz ^{13}C). Multiplets in ^{13}C NMR spectra were determined by DEPT and APT experiments. – Melting points: Rheometric Scientific DSC-SP differential scanning calorimeter. – IR spectra: Nicolet 320 FT-IR spectrometer. – Mass spectra: Finnigan Model MAT 8430 (EI). – GC-mass spectra: Carlo Erba HRGC 5160 coupled with a Finnigan MAT 4515 (EI, 40 eV). – Compound **2** was prepared according to ref. [6]. – 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). Temperature program: 80 °C with 16 °C min^{-1} until 300 °C.

4-(3-Phenylpropyloxy)aniline (**6**)

To a solution of 3-phenylpropanol (**10**) (2.72 g, 20.0 mmol) in CH_2Cl_2 (50 mL) were added triethylamine (4.46 g, 44.0 mmol) and tosyl chloride (4.20 g, 22.0 mmol) and the mixture was stirred overnight at room temp. Then the mixture was washed with sat. NH_4Cl (3 × 50 mL), sat. $NaHCO_3$ (50 mL) and concentrated to give 5.77 g (16.0 mmol, 80%) of a crude product, which was used without further purification. To a suspension of NaH (444 mg, 18.5 mmol) in THF (50 mL) was added dropwise 4-aminophenol (1.83 g, 16.8 mmol) and the mixture was stirred for 15 min. Then was added a solution of crude tosylate in THF (20 mL) and the resulting mixture was refluxed for 3 d. After cooling to room temp. the solution was slowly poured in H_2O (150 mL). The mixture was extracted with CH_2Cl_2 (150 mL) and the combined organic layers were dried over $MgSO_4$ and evaporated. Flash chromatography of the crude product on SiO_2 (hexanes/$CHCl_3$/NEt_3 10:5:1) yielded 2.03 g (8.94 mmol, 53%) of a pale brown, crystalline solid; *m.p.* 50 °C. – IR (film) ν/cm^{-1} = 3403, 1631, 1510, 824, 744, 724, 697. – ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.29–7.16 (m, 5H, 2''-H, 3''-H, 4''-H, 5''-H, 6''-H), 6.75–6.60 (m, 4H, 2-H, 3-H, 5-H, 6-H), 3.88 (t, J = 6.4 Hz, 2H, 1'-H), 3.40 (s, 2H, NH_2), 2.79 (t, J = 7.4 Hz, 2H, 3'-H), 2.06 (dt, J = 7.4/6.4 Hz, 2H, 2'-H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm = 152.2, 141.6 (C-1, C-4), 139.9 (C-1''), 128.5, 128.3, 125.8, 116.4, 115.7 (C-2, C-3, C-5, C-6, C-2'', C-3'', C-4'', C-5'', C-6''), 67.6 (C-1'), 32.1, 30.9 (C-2', C-3'). – MS (70 eV); *m/z* (%): 227 (62, M$^+$), 109 (100), 108 (25), 92 (4), 91 (40), 80 (15), 77 (3), 65 (9). $C_{15}H_{17}NO$ Calcd.: 227.1310; Found: 227.1310 (MS).

(6aS,12aS,12bS)-1,2,3,5,6,6a,7,12,12a,12b-decahydro-7,7-dimethyl-9-(3-phenyl-propyloxy)indolizino[8,7-b]quinoline (**3**)

A flame-dried Schlenk tube was charged with molecular sieve pellets 4Å (10 g), CH_2Cl_2 (25 mL) and 4-(3-phenylpropyloxy)aniline (**6**) (2.11 g, 9.30 mmol). Then was added aldehyde **5** and the mixture was stirred for 2 d at room temp. The molecular sieves was removed by filtration *via* Celite. After cooling the filtrate to –78 °C $EtAlCl_2$ (26.0 mL, 26.0 mmol, 1 M solution in *n*-hexane) was added dropwise and the cooling bath was removed. The mixture was stirred for another 2 d at room temp. and then poured into ice-cold 2 M NH_4F solution (300 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. After purification by flash chromatography on SiO_2 (hexanes/$CHCl_3$/NEt_3 10:5:1) 2.11 g (5.41 mmol, 58%) of a brown oil was isolated as a single diastereomer. – $[\alpha]^{22}_D$ = +144.8 (c = 1.00; CH_2Cl_2). – IR (film) ν/cm^{-1} = 3342, 1604, 1501, 963, 867, 807, 746, 700. – ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.29–7.15 (m, 5H, 2''-H, 3''-H, 4''-H, 5''-H, 6''-H), 6.75 (d, J = 3.0 Hz, 1H, 8-H), 6.58 (dd, J = 8.8/3.0 Hz, 1H, 10-H), 6.51 (d, J = 8.8 Hz, 1H, 11-H), 3.88 (t, J = 6.4 Hz, 2H, 1'-H), 3.64 (s, 1H, 12a-H), 3.62 (s, br, 1H, N<u>H</u>), 3.10–3.07 (m, 2H, 3-H$_{eq}$, 5-H$_{eq}$), 2.79 (t, J = 7.6 Hz, 2H, 3'-H), 2.09–2.01 (m, 4H, 2'-H, 12b-H, 2-H$_{eq}$), 1.98–1.92 (m, 1H, 5-H$_{ax}$), 1.85–1.73 (m, 4H, 3-H$_{ax}$, 2-H$_{ax}$, 1-H$_{eq}$, 1-H$_{ax}$), 1.55–1.52 (m, 1H, 6-H$_{eq}$), 1.30–1.24 (m, 2H, 6a-H, 6-H$_{ax}$), 1.31, 1.26 (s, 6H, 13-H, 14-H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm = 151.3 (C-9), 141.7 (C-11a), 136.5 (C-7a), 130.6 (C-1''), 128.4, 128.2 (C-2'', C-3'', C-5'', C-6''), 125.7 (C-4''), 116.5 (C-11), 113.0, 112.8 (C-8, C-10), 67.6 (C-1'), 67.2 (C-12b), 54.1, 52.5 (C-3, C-5), 46.9, 45.0 (C-12a, C-6a), 35.6 (C-7), 33.8, 26.3 (C-13, C-14), 32.2, 31.1 (C-2', C-3'), 24.9, 22.9, 21.0 (C-1, C-2, C-6). – MS (70 eV); *m/z* (%): 390 (100, M$^+$), 375 (35), 306 (56), 278 (14), 202 (6), 160 (11), 97 (10), 84 (62). $C_{26}H_{34}N_2O$ Calcd.: 390.2670; Found: 390.2670 (MS).

Methyl (6aS,12aS,12bS)-1,2,3,5,6,6a,7,12,12a,12b-decahydro-7,7-dimethylindolizino-[8,7-b]quinoline-11-carboxylate (**8**)

Following the procedure described for 3 methyl 2-aminobenzoate (**7**) (1.51 g, 10.0 mmol) and aldehyde **5** (1.83 g, 10.0 mmol) were converted to the corresponding imine, which was immediately cyclized in the presence of $EtAlCl_2$. After hydrolysis and aqueous work-up the crude product contained a (4:1) mixture of diastereomers **8** and **9**, which could be separated by flash chromatography on SiO_2 (hexanes/$CHCl_3$/NEt_3 20:1:1) to yield .05 g (3.34 mmol, 33%) of the *all-cis* product **8** as the first fraction and 280 mg (0.89 mmol, 9%) of the *all-trans* product **9** as the second fraction. Pale yellow solid, *m.p.* 99 °C. – $[\alpha]^{22}_D$ = +3.5 (c = 1.00; CH_2Cl_2). – IR (film) ν/cm^{-1} = 3356, 1680, 1600, 1587, 1511, 755, 746. – ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 8.25 (s, br, 1H, NH), 7.70 (dd, J = 8.4/1.5 Hz, 1H, 10-H), 7.24 (dd, J = 7.4/1.5 Hz, 1H, 8-H), 6.45 (dd, J = 8.4/7.4 Hz, 1H, 9-H), 3.84 (m, 1H, 12a-H), 3.82 (s, 3H, OCH_3), 3.12–3.08 (m, 2H, 3-H$_{eq}$, 5-H$_{eq}$), 2.08–2.01 (m, 2H, 12b-H, 2-H$_{eq}$), 1.98–1.55 (m, 7H, 5-H$_{ax}$, 3-H$_{ax}$, 2-H$_{ax}$, 1-H$_{eq}$, 1-H$_{ax}$, 6-H$_{eq}$, 6-H$_{ax}$), 1.40 (m, 1H, 6a-H), 1.36, 1.20 (s, 6H, 13-H, 14-H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm = 169.5 (C=O), 147.0 (C-11), 130.4, 129.2 (C-9, C-10), 129.1 (C-11a), 113.4 (C-8), 108.3 (C-7a), 67.1 (C-12b), 54.0, 52.4 (C-3, C-5), 51.3 (OCH_3), 46.7 (C-12a), 43.2 (C-6a), 35.7 (C-7), 32.6, 26.1 (C-14, C-13), 25.4, 23.3, 21.0 (C-1, C-2, C-6). – MS (70 eV); *m/z* (%): 314 (24, M$^+$), 299 (8), 283 (4), 230 (12), 202 (8), 198 (8), 170 (12), 97 (18),

84 (100), 69 (8).
$C_{19}H_{26}N_2O_2$ Calcd.: 314.1990; Found: 314.1990 (MS).

Methyl (6aS,12aR,12bS)-1,2,3,5,6,6a,7,12,12a,12b-decahydro-7,7-dimethylindolizino-[8,7-b]quinoline-11-carboxylate (**9**)

Pale yellow solid; *m.p.* 141 °C. – $[\alpha]^{22}_D = -146.0$ (c = 1.00; CH_2Cl_2). – IR (film) ν/cm^{-1} = 3342, 1678, 1590, 1511, 752, 741. – ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 8.13 (s, br, 1H, NH), 7.73 (dd, *J* = 7.9/1.5 Hz, 1H, 10-H), 7.36 (dd, *J* = 7.4/1.5 Hz, 1H, 8-H), 6.51 (dd, *J* = 7.4/7.9 Hz, 1H, 9-H), 3.83 (s, 3H, OCH_3), 3.23 (ddd, *J* = 10.8/3.9/2.4 Hz, 1H, 5-H$_{eq}$), 3.14 (ddd, *J* = 8.4/8.4/1.5 Hz, 1 H, 3-H$_{eq}$), 3.06 (dd, *J* =9.8/9.8 Hz, 1H, 12a-H), 2.30–2.18 (m, 2H, 12b-H, 2-H$_{eq}$), 2.13 (ddd, *J* = 11.8/11.8/2.5 Hz, 1H, 5-H$_{ax}$), 1.97–1.57 (m, 6H, 3-H$_{ax}$, 2-H$_{ax}$, 1-H$_{eq}$, 1-H$_{ax}$, 6-H$_{eq}$, 6a-H), 1.41–1.37 (m, 1H, 6-H$_{ax}$), 1.34, 1.10 (s, 6H, 13-H, 14-H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm = 169.4 (C=O), 146.7 (C-11), 132 (C-11a), 130.6, 129.3 (C-8, C-10), 113.9 (C-9), 108.3 (C-7a), 69.1 (C-12b), 54.3 (C-12a), 53.7, 52.1 (C-3, C-5), 51.4 (OCH_3), 44.7 (C-6a), 34.8 (C-7), 26.3, 26.2 (C-14, C-13), 28.0, 24.4, 21.3 (C-1, C-2, C-6). – MS (70 eV); *m/z* (%): 314 (37, M$^+$), 299 (8), 230 (12), 198 (8), 169 (8), 97 (12), 84 (100), 69 (6).
$C_{19}H_{26}N_2O_2$ Calcd.: 314.1990; Found: 314.1990 (MS).

(6aS,12aS,12bS)-1,2,3,5,6,6a,12,12a,12b-Decahydro-7,7-dimethylindolizino[8,7-b]-quinoline-11-(N-phenyl)-carboxamide (**4**)

To a solution of aniline (521 mg, 5.50 mmol) in CH_2Cl_2 (40 mL) was added dropwise over 30 min $AlMe_3$ (2.75 mL, 5.50 mmol, 2 M solution in CH_2Cl_2) and the resulting mixture was stirred for 15 min. Then was added methyl ester **8** (1.57 g, 5.00 mmol) and the mixture was heated for 6 d at 40 °C. After cooling to room temp. the mixture was slowly poured into ice-cold 2N HCl (100 mL). The pH was adjusted to **9** by addition of conc. NH_3 and then the mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed *in vacuo*. Purification of the crude product by flash chromatography on SiO_2 (hexanes/$CHCl_3$/NEt_3 5:10:1) yielded 350 mg (0.93 mmol, 19%) of a pale yellow solid; *m.p.* 223 °C. – $[\alpha]^{22}_D = -38.2$ (c = 1.00; CH_2Cl_2). – IR (film): ν/cm^{-1} = 3424, 3402, 3389, 1656, 1593, 1520, 1497, 757, 749, 691. – ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.92, 7.78 (s, br, 2H, CONH, NH), 7.54 (d, *J* = 7.4 Hz, 2H, 17-H), 7.34 (dd, *J* = 7.4/7.4 Hz, 2H, 3''-H), 7.32, 7.24 (dd, *J* = 8.4/1.0 Hz, 2H, 8-H, 10-H), 7.10 (dt, *J* = 7.4/1.0 Hz, 1H, 4''-H), 6.52 (dd, *J* = 8.4/8.4 Hz, 1H, 9-H), 3.81 (s, 1H, 12a-H), 3.10–3.07 (m, 2H, 3-H$_{eq}$, 5-H$_{eq}$), 2.12–1.72 (m, 7H, 12b-H, 2-H$_{eq}$, 5-H$_{ax}$, 3-H$_{ax}$, 2-H$_{ax}$, 1-H$_{eq}$, 1-H$_{ax}$), 1.59 (m, 1H, 6-H$_{eq}$), 1.37, 1.22 (m, 2H, 6a-H, 6-H$_{ax}$), 1.40, 1.20 (s, 6H, 13-H, 14-H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm = 168.3 (C=O), 145.7 (C-11a), 138.2 (C-11), 130.1 (C-7a), 128.9 (C-3'), 129.3, 125.3 (C-8, C-10), 124.0 (C-4'), 120.5 (C-2'), 114.0 (C-9), 67.1 (C-12b), 53.9, 52.3 (C-3, C-5), 46.7 (C-12a), 43.3 (C-6a), 35.8 (C-7), 32.9, 26.1 (C-14, C-13), 25.4, 23.3, 21.0 (C-1, C-2, C-6). – MS (70 eV); *m/z* (%): 375 (51, M$^+$), 360 (20), 291 (42), 263 (7), 198 (28), 170 (18), 141 (17), 122 (10), 97 (19), 84 (100), 69 (9).
$C_{24}H_{29}N_3O$ Calcd.: 375.2310; Found: 375.2310 (MS).

4,4-Bistrimethylsilyl-1-bromo-3-butene (**14**)

To a cooled solution of 3-butyne-1-ol 11 (7.01 g, 0.10 mol) in THF (500 mL) was dropwise added *n*-BuLi (125 mL, 0.20 mol, 1.6 M solution in *n*-hexane) at –78 °C and the resulting mixture was stirred for 1 h at that temp. Then was added trimethylsilylchloride (22.8 g, 0.21 mol) and the mixture was slowly warmed to room temp. over 2 h. After hydrolysis with H_2O (150 mL) and separation of the layers, the aqueous layer was extracted with Et_2O (3 × 150 mL). The combined organic layers were washed with sat. $NaHCO_3$ (100 mL) and brine (100 mL) and dried over $MgSO_4$. After evaporation of the solvent 13.9 g (97.0 mmol, 98%) of a colourless liquid was obtained, which was dissolved in CH_2Cl_2 (100 mL) and treated with NEt_3 (29.7 g, 0.29 mol). The mixture was cooled to 0 °C, methanesulfonyl chloride (11.8 g, 0.10 mol) was added dropwise, the mixture was stirred for 2 h at 0 °C, the cooling bath was removed and stirring was continued for 3 h at room temp. Then the mixture was diluted with Et_2O (100 mL), washed with sat. NH_4Cl (200 mL) and H_2O (200 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was dissolved in acetone (100 mL), treated with LiBr (25.1 g, 0.29 mol) and refluxed for 15 h. After cooling to room temp. the mixture was poured into H_2O (200 mL), the layers were separated and the aqueous layer was extracted with Et_2O (2 × 200 mL). The combined organic layers were washed with sat. $NaHCO_3$ (200 mL), H_2O (200 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the crude product by flash chromatography on SiO_2 yielded 12.9 g (63.0 mmol, 64%) of compound **12** as a colourless oil. To a solution of 1-bromo-4-trimethylsilyl-3-butyne **12** (12.3 g, 60.0 mmol) in Et_2O (100 mL) was dropwise added DIBAL (11.8 mL, 66.0 mmol) and the resulting mixture was heated for 2 h at 40 °C. After cooling to –78 °C a solution of iodine (18.3 g, 72.0 mmol) in THF (50 mL) was added dropwise and the resulting mixture was warmed to 0 °C and slowly hydrolyzed with ice-cold 3N HCl (200 mL). The layers were separated and the aqueous layer was extracted with *n*-pentane (200 mL). The combined organic layers were washed with sat. $NaHCO_3$ (3 × 200 mL), sat. $Na_2S_2O_3$ (200 mL) and brine (200 mL), dried over $MgSO_4$ and concentrated *in vacuo*. After purification by destillation (*b.p.* 90 °C/0.1 mbar) 12.3 g (36.9 mmol, 62%) of compound **13** was obtained as a colourless liquid. To a cooled solution of 4-bromo-1-iodo-1-trimethylsilyl-1-butene **13** (8.99 g, 27.0 mmol) in Et_2O (30 mL) was dropwise added *t*-BuLi (35.3 mL, 55.4 mmol, 1.53 M solution in *n*-pentane) at –78 °C and stirring was continued for 2 h. Then was added dropwise trimethylsilyliodide (5.41 g, 27.0 mmol) and the mixture was warmed to room temp. over 2 h and hydrolyzed with H_2O (50 mL). The layers were separated and the aqueous layer was extracted with Et_2O (100 mL). The combined organic layers were washed with sat. $NaHCO_3$ (100 mL) and brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Destillation of the crude product (*b.p.* 110 °C/8 mbar) yielded 3.77 g (13.5 mmol, 50%) of compound **14** a colourless liquid.

(2S)-2-Hydroxymethyl-N-(4,4-bistrimethylsilyl-3-buten)pyrrolidine (**16**)

To a suspension of K_2CO_3 (905 mg, 6.50 mmol) in toluene

(50 mL) were added *(S)*-prolinol (**15**) (505 mg, 5.00 mmol) and 4,4-bistrimethylsilyl-1-bromo-3-butene (**14**) (1.54 g, 5.50 mmol) and the mixture was heated at 90 °C for 4 d. After cooling to room temp. H_2O (100 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic layers were dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography on SiO_2 (*n*-hexane/*i*-propanol 6:1) to give 810 mg (2.70 mmol, 54%) as a yellow oil. – $[\alpha]^{22}_D = -34.8$ (c = 1.00; CH_2Cl_2). – IR (film) ν/cm^{-1} = 3307, 1569, 1249. – ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 6.57 (t, *J* = 6.9 Hz, 1H, 8-H), 3.64 (dd, *J* = 10.8/3.4 Hz, 1H, C<u>H</u>$_2$OH), 3.39 (dd, *J* = 10.8/2.4 Hz, 1H, C<u>H</u>$_2$OH), 3.24–3.17 (m, 1H, 5a-H), 2.88–2.78 (m,1H, 1'-H$_a$), 2.65–2.58 (m, 1H, 2-H), 2.49–2.32 (m, 3H, 1'-H$_b$, 2'-H), 2.32–2.25 (m, 1H, 5b-H), 1.92–1.85 (m, 1H, 3a-H), 1.85–1.70 (m, 3H, 3b-H, 4-H), 0.17, 0.08 (s, 18H, Si(CH$_3$)$_3$). – ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm = 154.6 (C-3'), 142.4 (C-4'), 64.7 (C-2), 61.6 (CH_2OH), 54.2 (C-5), 53.8 (C-1'), 35.0 (C-2'), 27.5 (C-3), 23.6 (C-4), 1.7, 0.2 (Si(CH$_3$)$_3$). – MS (70 eV); *m/z* (%): 300 (100, M$^+$ + H), 284 (9), 228 (14), 114 (21). $C_{14}H_{30}NOSi_2$ Calcd.: 284.1866 (M$^+$ – CH$_3$); Found: 284.1858 (MS).

(2S)- N-(4,4-bistrimethylsilyl-3-buten)pyrrolidine-2-carbaldehyde (**17**)

To a cooled solution of oxalylchloride (0.51 g, 4.00 mmol) in CH_2Cl_2 (20 mL) was added dropwise over 10 min at –50 °C dimethylsulfoxide (0.63 g, 8.00 mmol) in CH_2Cl_2 (4 mL) and stirring was continued for 10 min. Then alcohol **16** (598 mg, 2.00 mmol) in CH_2Cl_2 (2 mL) was added dropwise over 15 min and stirring was continued for 6 h at –50 °C. Triethylamine (1.75 mL) was added and the mixture was warmed to room temp., washed with H_2O (3 × 25 mL) and the organic layer was dried over $MgSO_4$ and concentrated to give a brown oil, which was immediately used without further purification. – $[\alpha]^{22}_D = -213.5$ (c = 1.00; CH_2Cl_2). – ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 9.43 (d, *J* = 3.9 Hz, 1H, CHO), 6.52 (t, *J* = 6.9 Hz, 1H, 3'-H), 3.24–3.20 (m, 1H, 5-H$_a$), 2.87 (ddd, *J* = 8.8/6.4/3.9 Hz, 1H, 2-H), 2.70–2.63 (m, 1H, 1'-H$_a$), 2.55–2.48 (m, 1H, 5-H$_b$), 2.43–2.30 (m, 3H, 1'-H$_b$, 2'-H), 2.00–1.95 (m, 1H, 3-H$_a$), 1.89–1.82 (m, 3H, 3-H$_b$, 4-H), 0.13, 0.04 (s, 18H, Si(CH$_3$)$_3$). – ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm = 203.2 (C=O), 154.0 (C-8), 142.4 (C-9), 72.1 (C-2), 55.0 (C-5), 54.1 (C-6), 35.1 (C-7), 26.4 (C-3), 24.0 (C-4), 1.7, 0.2 (Si(CH$_3$)$_3$).

(S)-[N-(4,4-Bistrimethyl-3-butenyl)pyrrolidin-2-methyliden]-(4-chlorphenylamine) (**18**)

To a suspension of molecular sieve pellets 4Å (2 g) in toluene (10 mL) were added 4-chloroaniline (254 mg, 2.00 mmol) and 596 mg (2.00 mmol) aldehyde **17** and the resulting mixture was stirred for 3 d at room temp. Molecular sieves was removed by filtration *via* Celite and the filtrate was immediately used without further purification. – $[\alpha]^{22}_D = -102.3$ (c = 1.00; CH_2Cl_2). – ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.67 (d, *J* = 6.6 Hz, 1H, HC=N), 7.29 (d, *J* = 8.8 Hz, 2H, 3''-H), 7.01 (d, *J* = 8.8 Hz, 2H, 2''-H), 6.56 (m, 1H, 3'-H), 3.30–3.24 (m, 1H, 4-H$_a$), 3.18–3.11 (m, 1H, 1-H), 2.84–2.76 (m, 1H, 1'-H$_a$), 2.48–2.41 (m, 3H, 2'-H, 1'-H$_b$), 2.36–2.29 (m, 1H, 4-H$_b$), 2.15–2.08 (m, 1H, 3-H$_a$), 1.92–1.84 (m, 3H, 2-H, 3-H$_b$), 0.14, 0.05 (s, 18H, Si(CH$_3$)$_3$). – ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm = 168.4 (C=N), 154.4 (C-3'), 149.8 (C-1''), 142.2 (C-4'), 131.4 (C-4''), 129.1, 122.1 (C-2'', C-3''), 68.7 (C-1), 54.6 (C-1'), 54.1 (C-4), 35.1 (C-2'), 29.1 (C-2), 23.4 (C-3), 1.74, 0.25 (Si(CH$_3$)$_3$).

(6aS,12aR/S,12bS)-7,7-Bistrimethylsilyl-9-chloro-1,2,3,5,6,6a,7,12,12a,12b-deca-hydroindolizino[8,7-b]quinoline (**19**, **20**)

To a solution of the imine **18** (2.00 mmol) in toluene (50 mL) was dropwise added $TiCl_4$ (5.20 mL, 5.20 mmol, 1 M solution in *n*-hexane) and the resulting mixture was heated at 60 °C for 2 d. After cooling to room temp. the mixture was poured into ice-cold 2 M NH_4F solution. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 200 mL) and the combined organic layers were dried over $MgSO_4$, evaporated and purified by flash chromatography on SiO_2 (hexanes/$CHCl_3$/NEt_3 15:1:1) to give 350 mg (0.86 mmol, 43%) of **19**, **20** as (1:1) mixture of diastereomers.

(6aS,12aS,12bS)-9-Chloro-1,2,3,5,6,6a,7,12,12a,12b-deca-hydro-indolizino[8,7-b]quinoline (**21**)

To a solution of the (1:1) mixture of **19**, **20** (350 mg, 0.86 mmol) in acetonitrile (10 mL) was added dropwise a solution of TBAF (2.00 mL, 2.00 mmol, 1 M solution in THF) in acetonitril (6 mL) and the mixture was stirred overnight at room temp. Then 2N HCl (10 mL) was added and the pH was adjusted to **8** with conc. NH_3. The aqueous layers were extracted with CH_2Cl_2 (3 × 20 mL), the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the crude product by flash chromatography on SiO_2 (*n*-hexane/$CHCl_3$/NEt_3 10:1:1) yielded 70 mg (0.27 mmol, 31%) of the *all-cis*-product **21** as the first fraction and 60 mg (0.23 mmol, 27%) of the *all-trans*-product **22** as the second fraction. Colourless solid; *m.p.* 124 °C. – $[\alpha]^{22}_D = +150.7$ (c = 1.00; CH_2Cl_2). – IR (film) ν/cm^{-1} = 3442, 3399, 1600, 1493, 1082, 863, 812, 799. – ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 6.83–6.80 (m, 2H, 8-H, 10-H), 6.40 (dd, *J* = 9.1 Hz, 1H, 11-H), 3.67 (s, br, 1H N<u>H</u>), 3.36 (d, *J* = 2.0 Hz, 1H, 12a-H), 3.10–3.02 (m, 2H, 3-H$_a$, 5-H$_a$), 2.96 (dd, *J* = 16.7/5.8 Hz, 1H, 7-H$_a$), 2.40 (dd, *J* = 16.7/1.5 Hz, 1H, 7-H$_b$), 2.10–2.05 (m, 1H, 12b-H), 2.03–1.95 (m, 2H, 3-H$_b$, 5-H$_b$), 1.83–1.80 (m, 1H, 6a-H), 1.79–1.65 (m, 4H, 1-H, 2-H), 1.50 (dddd, *J* = 12.9/12.9/12.9/4.3 Hz, 1H, 6-H$_a$), 1.29 (dddd, *J* = 12.9/3.0/3.0/3.0 Hz, 1H, 6-H$_b$). – ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm = 142.1 (C-9), 129.2 (C-8), 126.4 (C-10), 121.5, 121.1 (C-7a, C-11a), 116.4 (C-11), 66.8 (C-12b), 54.1 (C-3), 52.4 (C-5), 50.0 (C-12a), 32.9 (C-7), 32.9 (C-6a), 26.0 (C-6), 24.9, 21.0 (C-1, C-2). – MS (70 eV): *m/z* (%) = 262 (23, M$^+$), 192 (4), 178 (3), 164 (22), 151 (2), 143 (2), 135 (2), 129 (4), 122 (4), 113 (3), 102 (2), 84 (100), 77 (2), 69 (15).
$C_{15}H_{19}N_2Cl$ Calcd.: 262.1237; Found: 262.1231 (MS).

(6aS,12aR,12bS)-9-Chloro-1,2,3,5,6,6a,7,12,12a,12b-deca-hydro-indolizino[8,7-b]-quinoline (**22**)

Colourless amorphous solid. – $[\alpha]^{22}_D = -167.9$ (c = 1.00; CH_2Cl_2). – IR (film) ν/cm^{-1} = 3397, 3388, 3336, 1603, 1580, 1494, 1088, 886, 807, 655. – ^{1}H NMR (400 MHz, $CDCl_3$):

δ/ppm = 6.93 (m, 2H, 8-H, 10-H), 6.43 (d, J = 9.1 Hz, 1H, 11-H), 3.77 (s, br, 1H, NH), 3.15–3.09 (m, 2H, 3-H_a, 5-H_a), 2.76 (dd, J = 9.1 Hz, 1H, 12a-H), 2.69 (dd, J = 16.4/4.8 Hz, 1H, 7-H_a), 2.52 (dd, J = 16.4/11.9 Hz, 1H, 7-H_b), 2.24–2.14 (m, 2H, 3-H_b, 5-H_b), 2.07–2.00 (m, 1H, 1/2-H_a), 1.92–1.72 (m, 4H, 6-H, 1/2-H_a, 12b-H), 1.62–1.45 (m, 3H, 6a-H, 1-H_b, 2-H_b). – ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm = 142.8 (C-9), 128.9, 126.6 (C-8, C-10), 122.9, 1218, (C-7a, C-11a), 115.3 (C-11), 68.0 (C-12b), 59.6 (C-12a), 53.8, 51.8 (C-3, C-5), 36.0 (C-6a), 33.4 (C-7), 31.1, 27.7 (C-1, C-2), 21.3 (C-6).

Determination of Association Constants by ^{1}H NMR Titration

First stock solutions of receptors **2**–**4** and **21** (0.02 M) and ligands HOAc and Z-Phe-OH (0.04 M) in $CDCl_3$ were prepared. Then ^{1}H NMR spectra of the receptors alone were recorded. For each receptor/ligand combination 14 NMR tubes were charged with 200 µL of the receptor stock solution. Then were added aliquots of the ligand stock solution (25, 50, 70, 85, 100, 115, 130, 150, 175, 200, 250, 300, 350, 400 µL) and $CDCl_3$ was added until the final volume was 1 mL. The chemical shift of 12a-H was measured for each sample. The observed complexation-induced shifts $\delta_0 - \delta_i$ of the 12a-H signal were analyzed according to the Benesi-Hildebrand equation [22]:

$$1/(\delta_0 - \delta_i) = 1/(\delta_0 - \delta_\infty) \cdot 1/K_a \cdot 1/[L] + 1/(\delta_0 - \delta_\infty)$$

where [L] is the ligand concentration, δ_0 is the initial chemical shift of 12a-H of the pure receptor, $\delta\infty$ is the chemical shift of 12a-H of the pure (1:1) complex and K_a is the association constant. A plot $1/(\delta_0 - \delta_i)$ versus 1/[L] gave a line from which K_a was calculated. Error limits of K_a values were ± 10% (from three measurements).

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