Cyclopropane-Annelated Azaoligoheterocycles by Ti-Mediated Intramolecular Reductive Cyclopropanation of Cyclic Amino Acid Amides[‡]

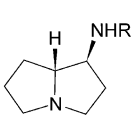
Martina Gensini and Armin de Meijere*[a]

Abstract: Starting from pyrrole- and indole-2-carboxylic acids **5a** and **5b**, the tri- and tetracyclic *N*,*N*-dibenzylcyclopropylamines **7a** and **7b** have been synthesized in 52 and 33% overall yield, respectively. The synthesis of the enantiopure tetracyclic diamine **10** has been achieved applying the established set of reactions to *N*-*tert*-butoxycarbonylindoline-2-carboxylic acid (**8**) in 46% overall yield. The amide **15** could not be prepared in the same way starting from the *N*-*tert*-butoxycarbonylproline **11**. In fact, in the allylation step the stereogenic center was deprotonated and the doubly alkylated amide **13** was formed. However, the desired intermediate **15** could be obtained from L-proline in 49% yield performing first the *N*-allylation step, then the introduction of the amide function. From **15**, the cyclopropane-annelated pyrrolizidine **16** was obtained in 70% yield as a mixture of (1a*S*,6a*S*,6b*R*)-**16** and (1a*R*,6a*S*,6b*S*)-**16** diastereoisomers in a ratio of 1:2.9.

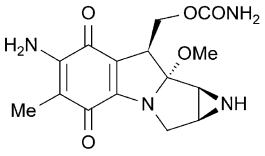
Keywords: alkaloids · cyclopropanation · N heterocycles · titanium

Introduction

Pyrrolizidine and indolizidine heterocycles are quite common skeletons in natural compounds.[1–7] Some examples are the alkaloid (+)-Absouline (**1**; R = (*E*)-*p*-(OMe)cinnamoyl-)[8] and the Mitomycine antibiotics, among which for example Mitomycine C (**2**) is clinically used as an antitumor agent.[9] In the last decade, many groups have been engaged in the stereocontrolled synthesis of the heterocyclic skeleton of such natural compounds.[7,9,10] We envisaged the possibility of employing our amide variant[11,12] of the Kulinkovich reaction[12,13] to prepare cyclopropane-annelated pyrrolizidine and indolizidine skeletons from *N*-alkylpyrrole and *N*-alkylindole carboxamides, just as Sato et al. converted pyrrole- and indole-2-carboxylic acid methyl esters to tri- and tetracyclic cyclopropanols.[14] As we have previously demonstrated, a variety of 1-amino-3-azabicyclo[3.1.0]hexane derivatives can be obtained by this Ti-mediated intramolecular reductive cyclopropanation of appropriate *N*,*N*-dialkylcarboxamides, which are readily available from natural amino acids or bromoacetyl bromide by simple transformations.[15,16] Here we report the intramolecular aminocyclopropanation of the *N*-allyl group in *N*,*N*-dialkylamides of type **3** leading to tricyclic and tetracyclic systems of type **4** as cyclopropane-annelated analogues of natural skeletons such as in **1** and **2** (Scheme 1).

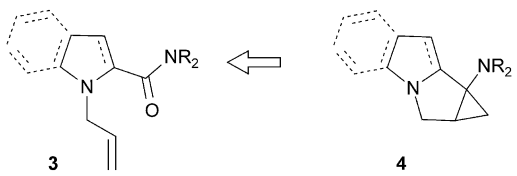


(+)-Absouline, **1**



Mitomycine C, **2**

The *N*,*N*-dibenzylamides **6a** and **6b** were prepared from pyrrole- and indole-2-carboxylic acids (**5a** and **5b**) by treatment with dibenzylamine, dicyclohexylcarbodiimide (DCC), and hydroxybenzotriazole (HOBT),[17] and then with allyl



3 **4**

Scheme 1. Strategy for the synthesis of cyclopropane-annelated pyrrolizidine and indolizidine systems.

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[‡] Cyclopropyl Building Blocks for Organic Synthesis, Part 94. Part 93 see: S. I. Kozhushkov, A. Leonov, A. de Meijere, *Synthesis* **2003**, 956–958. Part 92: N. Moszner, F. Zeuner, U. K. Fischer, V. Rheinberger, A. de Meijere, V. Bagutski, *Macromol. Rapid Commun.* **2003**, *24*, 269–273.

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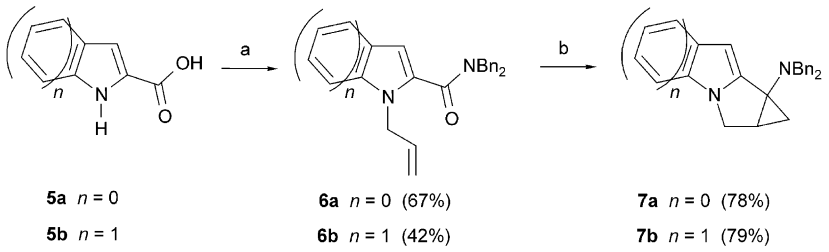
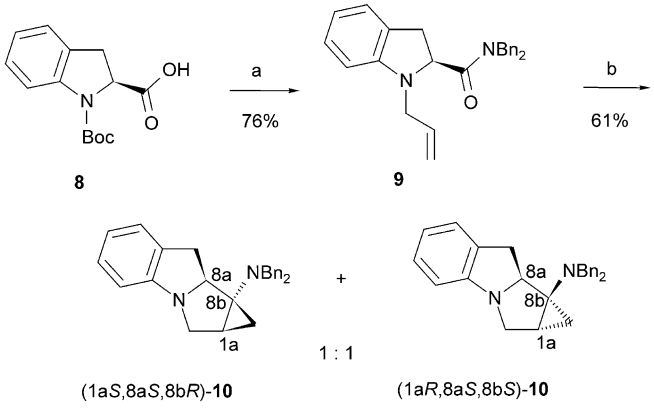
bromide and potassium carbonate[18] in 67 and 42% overall yield, respectively. The amides **6a** and **6b** were treated with cyclohexylmagnesium bromide (5 equiv) in the presence of methyltitanium triisopropoxide (1.50 equiv) to give the tetracyclic amines **7a** and **7b** in 78 and 79% yield, respectively (Scheme 2).



Scheme 2. a) 1) 1 $HNBn_2$, DCC, HOBT, CH_2Cl_2, 20°C, 2 d; 2) allyl bromide, K_2CO_3, MeCN, 60°C, 16 h. b) cHexMgBr, [MeTi(O*i*Pr)$_3$], THF, 20°C, 12 h.

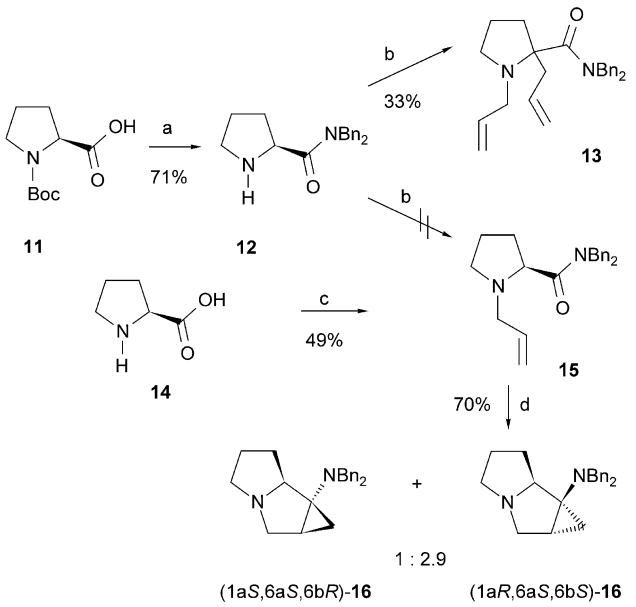
The obvious success of these reductive cyclizations led to the idea to apply this same protocol to indoline and proline derivatives of types **9** and **15** in order to access enantiopure cyclopropane-annelated analogues of the alkaloid **1**. Sato and co-workers[14] reported that *N*-allylproline methyl ester did not undergo intramolecular hydroxycyclopropanation, and attributed this failure to an energetically disfavored transition state for ring closure. Since a fused aromatic ring in the starting material might favor the ring closure, the indoline derivative **9** was tested first. Applying an established set of reactions to *N*-(*tert*-butoxycarbonyl)indoline-2-carboxylic acid (**8**) the *N*-allyl-(*N*,*N*-dibenzyl)carboxamide **9** was obtained in 76% yield. Under the conditions employed for **6a**,**b**, the amide **9** was converted to the tetracyclic cyclopropylamine **10** in 61% yield, obtained as a 1:1 mixture of diastereomers, which could be separated by column chromatography (Scheme 3).

Treatment of L-*N*-(*tert*-butoxycarbonyl)proline (**11**) with dibenzylamine, dicyclohexylcarbodiimide, and hydroxybenzotriazole,[17] followed by deprotection with trifluoroacetic acid[19] gave the proline amide **12** in 71% overall yield.



Scheme 3. a) 1) $HNBn_2$, DCC, HOBT, CH_2Cl_2, 20°C, 2 d; 2) TFA, CH_2Cl_2, 20°C, 12 h; 3) allyl bromide, K_2CO_3, MeCN, 60°C, 16 h; b) cHexMgBr, [MeTi(O*i*Pr)$_3$], THF, 20°C, 12 h.

When the latter was treated with allyl bromide and potassium carbonate,[18] the doubly allylated amide **13** was obtained instead of the expected **15** (Scheme 4). It is surprising that, under the reaction conditions employed, that is with potassium carbonate as a base at 60°C, **12** apparently must be deprotonated at the stereogenic center, and the allylation at C-2 (proline numbering) occurred with complete racemization, as revealed by the optical activity measurement $[\alpha]_D^{20} = 0.0$ (c = 1.0, $CHCl_3$). Not even a trace of the desired product **15** could be detected. Usually, deprotonation at the α-position of proline derivatives can only be brought about with much stronger bases such as lithium diisopropylamide.[20]



Scheme 4. a) 1) $HNBn_2$, DCC, HOBT, CH_2Cl_2, 20°C, 2 d; 2) TFA, CH_2Cl_2, 20°C, 12 h; b) Allyl bromide, K_2CO_3, MeCN, 60°C, 16 h; c) 1) Allyl bromide, KOH, *i*PrOH, 40°C, 22 h; 2) $HNBn_2$, DCC, HOBT, CH_2Cl_2, 20°C, 1 d; d) cHexMgBr, [MeTi(O*i*Pr)$_3$], THF, 20°C, 12 h.

The *N*-allylprolineamide **15** could, however, be prepared by treatment of L-proline (**14**) with allyl bromide and potassium hydroxide in 2-propanol,[21] then with dibenzylamine, dicyclohexylcarbodiimide, and hydroxybenzotriazole[17] in 49% overall yield. The titanium-mediated intramolecular reductive cyclopropanation of the latter afforded the tricyclic cyclopropylamine **16** in 70% yield as a mixture of diastereoisomers (ratio 1:2.9). They could be separated by column chromatography and assigned as (1a*S*,6a*S*,6b*R*)-**16**/(1a*R*,6a*S*,6b*S*)-**16** on the basis of their ^{1}H NMR spectra (Scheme 4).

The absolute configuration of the minor diastereoisomer (1a*S*,6a*S*,6b*R*)-**16** was assigned on the basis of an X-ray crystal structure analysis relative to the known absolute configu-

ration of the used (*S*)-proline (Figure 1).[22] Apparently, (1a*S*,6a*S*,6b*R*)-**16** has the same relative configuration as the natural alkaloid (±)-Absouline (**1**).

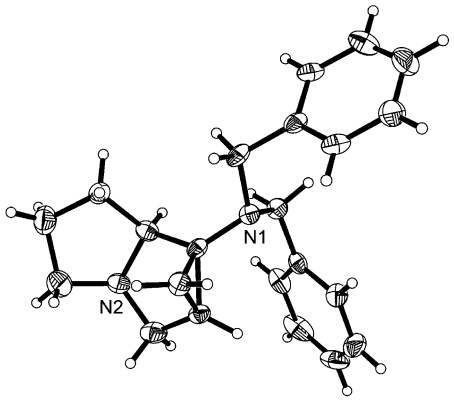


Figure 1. Molecular structure of compound (1a*S*,6a*S*,6b*R*)-**16** in the crystal.[22]

Since the *N*-benzyl groups can easily be removed from *N,N*-dibenzylcyclopropylamines such as **16**,[11c] the latter may be used to prepare a cyclopropane-annelated analogue of the natural product. This and the other new intramolecular variants of the titanium-mediated reductive cyclopropanation of amide carbonyl groups[11] once again demonstrate the synthetic utility of this highly efficient methodology.[12]

Experimental Section

General: ^{1}H and ^{13}C NMR: Spectra were recorded at 250, 300 (^{1}H), and 62.9, 75.5 [^{13}C, additional DEPT (distortionless enhancement by polarization transfer)] MHz on Bruker AM 250 and AMX 300 instruments in $CDCl_3$ solution, if not otherwise specified, $CHCl_3/CDCl_3$ as internal reference; δ in ppm, J in Hz. IR: Bruker IFS 66 (FT-IR) instrument, measured as KBr pellets, oils between KBr plates. MS (EI): Finnigan MAT 95 spectrometer. Optical rotations: Perkin-Elmer 241 digital polarimeter, 1 dm cell. M.p.: Büchi 510 capillary melting point apparatus, values are uncorrected. TLC: Macherey-Nagel precoated sheets, 0.25 mm Sil G/UV_{254}. Column chromatography: Merck silica gel, grade 60, 230–400 mesh. Starting materials: Anhydrous diethyl ether and THF were obtained by distillation from sodium/benzophenone, CH_2Cl_2 and DMF from CaH_2 and acetonitrile from P_4O_{10}. Compounds were prepared according to published procedures. Cyclohexylmagnesium bromide was prepared from cHexBr and Mg in Et_2O, [MeTi(O*i*Pr)$_3$] from MeLi and [ClTi(O*i*Pr)$_3$] in Et_2O, [ClTi(O*i*Pr)$_3$] from $TiCl_4$ and [Ti(O*i*Pr)$_4$] in Et_2O. All other chemicals were used as commercially available (Merck, Acrõs, BASF, Bayer, Hoechst, Degussa AG, and Hüls AG). All reactions were performed under an argon atmosphere. Organic extracts were dried over $MgSO_4$.

Preparation of *N,N*-dibenzylcarboxamides—General procedure 1 (GP 1): Dibenzylamine ($HNBn_2$, 12.5 mmol) was added dropwise to a suspension of dicyclohexylcarbodiimide (DCC, 12.5 mmol), hydroxybenzotriazole (HOBT, 5.00 mmol), and the respective carboxylic acid (5.00 mmol) in anhydrous CH_2Cl_2 (10 mL). The mixture was stirred at ambient temperature for two days. EtOAc (10 mL) was added, the mixture was filtered through Celite, and the solvent was removed under reduced pressure. EtOAc (10 mL) was added, the organic phase was washed with 5% aqueous HCl solution (10 mL), brine (10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel.

***N,N*-Dibenzyl-1*H*-pyrrole-2-carboxamide**: *N,N*-Dibenzyl-1*H*-pyrrole-2-carboxamide (1.31 g, 89%) was obtained from pyrrole-2-carboxylic acid (**5a**, 556 mg, 5.00 mmol), DCC (2.60 g, 12.5 mmol), HOBT (676 mg, 5.00 mmol), and $HNBn_2$ (2.4 mL, 12.5 mmol) according to GP 1, as a colorless solid. R_f (Et_2O/hexane 1:1) = 0.38; m.p. 140–144 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 11.41 (br s, 1H; NH), 7.48–7.18 (m, 10H; H_{ar}), 6.93–6.91 (m, 1H; 5-H), 6.50–6.48 (m, 1H; 3-H), 6.18–6.16 (m, 1H; 4-H), 4.89 ppm (s, 4H; CH_2Ph); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 163.6 (C=O), 136.8 (2 C_{ar}), 128.9 (CH_{ar}), 128.8 (3 CH_{ar}), 127.5 (4 CH_{ar}), 126.9 (2 CH_{ar}), 124.1 (C_{ar}), 122.1 (CH_{ar}), 112.7 (CH_{ar}), 109.7 (CH_{ar}), 47.6 ppm (2 CH_2; CH_2Ph); IR (KBr): $\tilde{\nu}$ = 3258, 3030, 2905, 1600, 1576, 1424, 1129 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%): 290 (30) [M^+], 199 (70) [$M^+ - C_7H_7$], 106 (100), 91 (52) [$C_7H_7^+$]; elemental analysis calcd (%) for $C_{19}H_{18}N_2O$ (290.37): C 78.59, H 6.25; found: C 78.38, H 6.42.

Preparation of *N*-allylheterocycles—General procedure 2 (GP 2): Allyl bromide (0.57 mmol) was added dropwise at 0 °C to a suspension of the respective azaheterocycle (0.41 mmol) and K_2CO_3 (0.82 mmol) in anhydrous MeCN (8.0 mL). After the addition was complete, the reaction mixture was stirred at 60 °C for 16 h. EtOAc (5.0 mL) and saturated aqueous $NaHCO_3$ solution (5.0 mL) were added, the organic phase was separated, washed with brine (10 mL), and dried over $MgSO_4$. After evaporation of the solvent under reduced pressure the crude product was purified by column chromatography on silica gel.

1-Allyl-*N,N*-dibenzyl-pyrrole-2-carboxamide (6a): The amide **6a** (1.11 g, 75%) was obtained from *N,N*-dibenzyl-1*H*-pyrrole-2-carboxamide (1.30 g, 4.48 mmol), K_2CO_3 (1.24 g, 8.97 mmol), and allyl bromide (0.50 mL, 6.27 mmol) according to GP 2 as a colorless oil. R_f (Et_2O/hexane 1:2) = 0.46; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.41–7.24 (m, 10H; H_{ar}), 6.82–6.80 (m, 1H; 5-H), 6.42 (dd, J = 1.6, 3.8 Hz, 1H; 3-H), 6.10–5.97 (m, 2H; C*H*=CH_2, 4-H), 5.20–5.01 (m, 2H; CH=CH_2), 4.95–4.91 (m, 2H; CH_2CH=CH_2), 4.74 ppm (s, 4H; CH_2Ph); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 163.6 (C=O), 137.0 (2 C_{ar}), 136.4 (CH; *C*H=CH_2), 135.3 (3 CH_{ar}), 128.7 (3 CH_{ar}), 127.4 (4 CH_{ar}), 125.9 (CH_{ar}), 124.4 (C_{ar}), 116.5 (CH_2; CH=*C*H_2), 112.6 (CH_{ar}), 107.1 (CH_{ar}), 50.7 (2 CH_2), 49.0 ppm (CH_2); IR (film): $\tilde{\nu}$ = 3029, 2925, 1623, 1464, 1240, 987, 734 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%): 330 (91) [M^+], 239 (22) [$M^+ - C_7H_7$], 134 (100), 106 (61), 91 (56) [$C_7H_7^+$]; HRMS (EI) calcd for $C_{22}H_{22}N_2O$ [M^+] 330.1732, found 330.1732.

Ti-mediated intramolecular reductive cyclopropanation of *N,N*-dibenzylcarboxamides—General procedure 3 (GP 3): Cyclohexylmagnesium bromide (cHexMgBr, 5.00 mmol) was added dropwise at ambient temperature to a well stirred solution of *N,N*-dialkylcarboxamide (1.00 mmol) and methyltitanium triisopropoxide ([MeTi(O*i*Pr)$_3$], 1.50 mmol) in anhydrous THF (30 mL). After the addition was complete, the mixture was stirred for 12 h, then poured into ice-cold water (10 mL), and stirred for an additional 1 h. The mixture was filtered through Celite, the aqueous phase was extracted with Et_2O (3 × 50 mL), and the combined ethereal phases were washed with saturated aqueous $NaHCO_3$ solution (50 mL), brine (50 mL), and dried over $MgSO_4$. The solvent was removed and the residue was purified by column chromatography on silica gel.

***N,N*-Dibenzyl-1,1a,2,6b-tetrahydrocyclopropa[1,2-*a*]pyrrolizin-6b-ylamine (7a)**: The amine **7a** (224 mg, 78%) was obtained from the amide **6a** (300 mg, 908 μmol), [MeTi(O*i*Pr)$_3$] (327 mg, 1.36 mmol) and cHexMgBr (4.6 mL, 4.60 mmol, 1.0 M solution in Et_2O) according to GP 3 as a colorless oil. R_f (hexane/Et_2O 5:1) = 0.74; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.37–7.18 (m, 10H; H_{ar}), 6.50–6.42 (m, 1H; H_{ar}), 6.25–6.20 (m, 1H; H_{ar}), 5.90–5.84 (m, 1H; H_{ar}), 4.11 (d, J = 13.2 Hz, 2H; CH_2Ph), 3.96 (d, J = 13.2 Hz, 2H; CH_2Ph), 3.59–3.50 (m, 2H; NCH_2CH), 1.38–0.84 (m, 2H; cPr), 0.72 ppm (ps t, J = 4.6 Hz, 1H; cPr); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 139.8 (C_{ar}), 136.0 (C_{ar}), 131.9 (C_{ar}), 129.3 (4 CH_{ar}), 128.1 (4 CH_{ar}), 126.9 (2 CH_{ar}), 113.5 (CH_{ar}), 111.2 (CH_{ar}), 99.7 (CH_{ar}), 57.7 (2 CH_2; CH_2Ph), 49.7 (C; cPr), 47.9 (CH_2; N*C*H_2CH), 29.6 (CH; cPr), 23.8 ppm (CH_2; cPr); IR (film): $\tilde{\nu}$ = 3028, 2924, 1530, 1392, 745 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%): 314 (1) [M^+], 223 (14) [$M^+ - C_7H_7$], 197 (61), 106 (38), 91 (100) [$C_7H_7^+$]; HRMS (EI) calcd for $C_{22}H_{22}N_2$ [M^+] 314.1783, found 314.1783; elemental analysis calcd (%) for $C_{22}H_{22}N_2$ (314.43): C 84.04, H 7.05; found C 84.24, H 7.27.

***N,N*-Dibenzyl-1*H*-indole-2-carboxamide**: *N,N*-Dibenzyl-1*H*-indole-2-carboxamide (1.10 g, 95%) was obtained from $HNBn_2$ (1.6 mL, 8.55 mmol), DCC (1.76 g, 8.55 mmol), HOBT (462 mg, 3.42 mmol), and indole-2-car-

boxylic acid (**5b**, 551 mg, 3.42 mmol) in CH_2Cl_2 (30 mL) according to GP 1 as a colorless oil, which was used for the subsequent reaction without further purification.

1-Allyl-*N*,*N*-dibenzyl-1*H*-indole-2-carboxamide (6b): Compound **6b** (545 mg, 44%) was obtained from *N*,*N*-dibenzyl-1*H*-indole-2-carboxamide (1.10 g, 3.23 mmol), allyl bromide (0.40 mL, 4.79 mmol), and K_2CO_3 (945 mg, 6.84 mmol) according to GP 2 as a colorless solid. R_f (Et_2O/hexane 1:2) = 0.53; m.p. 121–128 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.56–7.07 (m, 14H; H_{ar}), 6.70 (s, 1H; 3-H), 6.09–5.94 (m, 1H; C*H*=CH_2), 5.13–4.91 (m, 4H; CH_2Ph, CH_2CH=CH_2), 4.73 ppm (s, 4H; CH_2Ph, CH_2CH=CH_2); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 165.1 (C=O), 137.6 (C_{ar}), 136.6 (C_{ar}), 136.1 (CH; *C*H=CH_2), 134.1 (2 CH_{ar}), 131.0 (C_{ar}), 128.8 (2 C_{ar}), 127.6 (3 CH_{ar}), 126.4 (2 CH_{ar}), 123.5 (2 CH_{ar}), 121.7 (2 CH_{ar}), 120.4 (2 CH_{ar}), 116.5 (CH_2; CH=*C*H_2), 110.3 (CH_{ar}), 103.7 (CH; C-3), 47.0 (CH_2), 46.6 ppm (2 CH_2); IR (KBr): $\tilde{\nu}$ = 3064, 3029, 2917, 1630, 1523, 1451, 1244, 962 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%): 380 (100) [M^+], 196 (17), 184 (81), 157 (55), 91 (62), 56 (29); elemental analysis calcd (%) for $C_{26}H_{24}N_2O$ (380.49): C 82.07, H 6.36; found: C 81.86, H 6.59.

***N*,*N*-Dibenzylindolo[1,2-*a*]cyclopropa[1,2-*c*]pyrrolidin-8b-ylamine (7b)**: The amine **7b** (204 mg, 79%) was obtained from the *N*,*N*-dibenzylamide **6b** (270 mg, 710 μmol), [MeTi(O*i*Pr)$_3$] (256 mg, 1.06 mmol) and cHexMgBr (3.5 mL, 3.50 mmol, 1.0 M solution in Et_2O) according to GP 3 as a colorless oil. R_f (hexane/Et_2O 10:1) = 0.55; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.66–7.62 (m, 1H; H_{ar}), 7.36–7.12 (m, 13H; H_{ar}), 6.33 (s, 1H; H_{ar}), 4.15 (d, *J* = 13.0 Hz, 2H; CH_2Ph), 4.03 (d, *J* = 13.0 Hz, 2H; CH_2Ph), 3.70 (d, *J* = 10.1 Hz, 1H; NC*H*HCH), 3.61 (dd, *J* = 5.0, 10.0 Hz, 1H; NC*H*HCH), 1.59?1.49 (m, 1H; cPr), 1.37–1.32 (m, 1H; cPr), 0.85 ppm (ps t, *J* = 5.0 Hz, 1H; cPr); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 143.2 (C_{ar}), 139.6 (2 C_{ar}), 132.7 (C_{ar}), 132.6 (C_{ar}), 129.2 (4 CH_{ar}), 128.1 (4 CH_{ar}), 127.1 (2 CH_{ar}), 120.5 (CH_{ar}), 120.4 (CH_{ar}), 119.2 (CH_{ar}), 108.9 (CH_{ar}), 93.4 (CH_{ar}), 57.8 (2 CH_2; CH_2Ph), 49.6 (CH_2; NCH_2CH), 45.8 (C; cPr), 30.6 (CH; cPr), 24.2 ppm (CH_2; cPr); IR (film): $\tilde{\nu}$ = 3024, 2928, 1510, 1398, 1114 cm^{-1}; MS (EI): *m*/*z* (%): 364 (1) [M^+], 273 (100), 168 (6), 91 (32); elemental analysis calcd (%) for $C_{26}H_{24}N_2$ (364.49): C 85.68, H 6.64; found: C 85.44, H 6.50.

(*S*)-*N*,*N*-Dibenzyl-1-(*tert*-butoxycarbonyl)-2,3-dihydroindole-2-carboxamide: (*S*)-*N*,*N*-Dibenzyl-1-(*tert*-butoxycarbonyl)-2,3-dihydroindole-2-carboxamide (1.50 g, 89%) was obtained from the acid **8** (1.00 g, 3.80 mmol), DCC (1.96 g, 9.50 mmol), HOBT (513 mg, 3.80 mmol), and $HNBn_2$ (1.8 mL, 9.50 mmol) according to GP 1 as a colorless oil. R_f (hexane/Et_2O 2:1) = 0.35; $[\alpha]_D^{20}$ = −72.0 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$, observed as a major/minor rotamer mixture): δ = 7.23–6.80 (m, 14H; H_{ar}), 5.28–5.10 (m, 1H; 2-H), 4.90–4.64 (m, 2H; CH_2Ph), 4.58–4.41 (m, 2H; CH_2Ph), 3.25–2.91 (m, 2H; 3-H), 1.63 [s, 9H, major; C(CH_3)$_3$], 1.41 ppm [s, 9H, minor; C(CH_3)$_3$]; ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 175.5 (C=O), 157.2 (C_{ar}), 155.3 (C=O), 137.1 (2 C_{ar}), 130.2 (C_{ar}), 129.8 (2 CH_{ar}), 129.2 (2 CH_{ar}), 129.0 (2 CH_{ar}), 128.6 (2 CH_{ar}), 127.7 (CH_{ar}), 127.3 (2 CH_{ar}), 126.8 (CH_{ar}), 122.2 (CH_{ar}), 114.8 (CH_{ar}), 79.7 [*C*(CH_3)$_3$], 59.1 (CH; C-2), 50.1 (CH_2; CH_2Ph), 49.8 (CH_2; CH_2Ph), 49.2 (CH_2; C-3), 28.4 ppm [3 CH_3; C(*C*H_3)$_3$]; MS (EI, 70 eV): *m*/*z* (%): 442 (14) [M^+], 342 (15), 224 (7), 118 (100), 91 (23) [$C_7H_7^+$].

(*S*)-*N*,*N*-Dibenzyl-2,3-dihydro-1*H*-indole-2-carboxamide: Trifluoroacetic acid (1.3 mL, 17.0 mmol) was added dropwise to a well-stirred solution of (*S*)-*N*,*N*-dibenzyl-1-(*tert*-butoxycarbonyl)-2,3-dihydroindole-2-carboxamide (1.50 g, 3.39 mmol) in CH_2Cl_2 (20 mL) at ambient temperature. The reaction mixture was stirred at ambient temperature for 12 h, then cooled in an ice bath while a saturated aqueous $NaHCO_3$ solution (20 mL) was carefully added. The organic phase was separated, washed with saturated aqueous $NaHCO_3$ solution (2×20 mL), brine (20 mL), and dried over $MgSO_4$. The product (1.12 g, 95%) was obtained as a colorless oil, which was used without further purification. $[\alpha]_D^{20}$ = −64.0 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ? = 7.45–7.12 (m, 12H; H_{ar}), 6.81–6.76 (m, 2H; H_{ar}), 4.98 (d, *J* = 14.6 Hz, 1H; CH*H*Ph), 4.75–4.65 (m, 2H, 2-H; CH*H*Ph), 4.42–4.25 (m, 3H, NH; CH_2Ph), 3.44 (dd, *J* = 10.6, 15.7 Hz, 1H; 3-H), 3.25 ppm (dd, *J* = 6.4, 15.7 Hz, 1H; 3-H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 174.1 (C=O), 156.1 (2 C_{ar}), 136.9 (CH_{ar}), 135.7 (2 C_{ar}), 128.8 (3 CH_{ar}), 128.4 (CH_{ar}), 127.9 (2 CH_{ar}), 127.6 (CH_{ar}), 127.3 (CH_{ar}), 126.7 (2 CH_{ar}), 124.3 (CH_{ar}), 119.9 (CH_{ar}), 111.5 (CH_{ar}), 58.2 (CH; C-2), 49.1 (CH_2; CH_2Ph), 48.2 (CH_2; CH_2Ph), 35.5 ppm (CH_2; C-3); MS (EI, 70 eV): *m*/*z* (%): 342 (8) [M^+], 270 (29), 189 (19), 155 (28), 118 (100), 90 (48).

(*S*)-*N*,*N*-Dibenzyl-1-allyl-2,3-dihydroindole-2-carboxamide (9): The amide **9** (1.13 g, 90%) was obtained from (*S*)-*N*,*N*-dibenzyl-2,3-dihydro-1*H*-indole-2-carboxamide (1.12 g, 3.27 mmol), K_2CO_3 (940 mg, 6.80 mmol), and allyl bromide (0.40 mL, 4.75 mmol) according to GP 2 as a colorless oil. R_f (Et_2O/hexane 1:2) = 0.31; $[\alpha]_D^{20}$ = −36.0 (*c* = 0.35, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.98 (m, 12H; H_{ar}), 6.68–6.51 (m, 2H; H_{ar}), 5.91–5.75 (m, 1H; C*H*=CH_2), 5.25–5.10 (m, 2H; CH=CH_2), 4.83 (d, *J* = 14.5 Hz, 1H; CH_2Ph), 4.65–4.49 (m, 4H, 2-H; CH_2Ph), 3.98 (dd, *J* = 5.0, 15.7 Hz, 1H; 3-H), 3.73 (dd, *J* = 7.4, 15.7 Hz, 1H; 3-H), 3.27–3.04 ppm (m, 2H; CH_2CH=CH_2); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 172.9 (C=O), 156.4 (C_{ar}), 151.1 (C_{ar}), 137.2 (C_{ar}), 136.4 (C_{ar}), 133.4 (CH; *C*H=CH_2), 129.0 (2 CH_{ar}), 128.7 (2 CH_{ar}), 128.5 (2 CH_{ar}), 127.8 (2 CH_{ar}), 127.6 (CH_{ar}), 126.6 (CH_{ar}), 126.5 (CH_{ar}), 124.1 (CH_{ar}), 118.3 (CH_{ar}), 117.9 (CH_2; CH=CH_2), 107.4 (CH_{ar}), 63.6 (CH; C-2), 50.1 (CH_2; CH_2Ph), 49.4 (CH_2; CH_2Ph), 48.7 (CH_2; *C*H_2CH=CH_2), 34.1 ppm (CH_2; C-3); IR (film): $\tilde{\nu}$ = 3030 cm^{-1}, 2925, 1657, 1453, 1208, 747; MS (EI, 70 eV): *m*/*z* (%): 382 (8) [M^+], 270 (10), 158 (100), 117 (20); elemental analysis calcd (%) for $C_{26}H_{26}N_2O$ (382.51): C 81.64, H 6.85; found: C 81.58, H 6.97.

(1a*S*,8a*S*,8b*R*)- and (1a*R*,8a*S*,8b*S*)-*N*,*N*-Dibenzyl-8,8a-dihydroindolo[1,2-*a*]cyclopropa-[1,2-*c*]pyrrolidin-8b-ylamine (10): The amine **10** (223 mg, 61%) was obtained from the amide **9** (382 mg, 1.00 mmol), Me-Ti(O*i*Pr)$_3$ (361 mg, 1.50 mmol) and cHexMgBr (5.0 mL, 5.00 mmol, 1.0 M solution in Et_2O) according to GP 3 in a (1a*S*,8a*S*,8b*R*)-**10**/(1a*R*,8a*S*,8b*S*)-**10** ratio of 1:1.

(1a*S*,8a*S*,8b*R*)-10: Colorless oil; R_f (Et_2O/hexane 1:5) = 0.66; $[\alpha]_D^{20}$ = −7.7 (*c* = 0.35, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.37–6.97 (m, 12H; H_{ar}), 6.65 (t, *J* = 7.1 Hz, 1H; H_{ar}), 6.34 (d, *J* = 8.1 Hz, 1H; H_{ar}), 4.74 (ddd, *J* = 1.5, 5.2, 8.8 Hz, 1H; 2-H), 3.97 (d, *J* = 13.5 Hz, 2H; CH_2Ph), 3.80 (d, *J* = 13.5 Hz, 2H; CH_2Ph), 3.32–3.28 (m, 2H; 1-H), 3.15 (dd, *J* = 3.5, 11.3 Hz, 1H; 6-H), 3.00 (d, *J* = 11.3 Hz, 1H; 6-H), 1.03–0.97 (m, 1H; cPr), 0.64–0.58 (m, 1H; cPr), 0.18 ppm (ps t, *J* = 5.0 Hz, 1H; cPr); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 143.2 (C_{ar}), 139.9 (2 C_{ar}), 130.1 (C_{ar}), 128.9 (4 CH_{ar}), 128.1 (4 CH_{ar}), 127.5 (CH_{ar}), 127.0 (2 CH_{ar}), 124.4 (CH_{ar}), 118.5 (CH_{ar}), 109.2 (CH_{ar}), 60.8 (CH; C-2), 57.1 (2 CH_2; CH_2Ph), 55.3 (C; cPr-C), 53.1 (CH_2; C-6), 33.1 (CH_2; C-1), 28.1 (CH; cPr), 14.0 ppm (CH_2; cPr); IR (film): $\tilde{\nu}$ = 3026, 2920, 1480, 1263, 1028, 749 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%): 366 (47) [M^+], 275 (100) [M^+−C_7H_7], 170 (48), 91 (84) [$C_7H_7^+$]; HRMS (EI): calcd for $C_{26}H_{26}N_2$ [M^+] 366.2096, found 366.2096.

(1a*R*,8a*S*,8b*S*)-10: Colorless oil, R_f (Et_2O/hexane 1:5) = 0.33; $[\alpha]_D^{20}$ = −3.3 (*c* = 0.3, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ? = 7.08–7.34 (m, 12H; H_{ar}), 6.87 (t, *J* = 7.4 Hz, 1H; H_{ar}), 6.69 (d, *J* = 7.7 Hz, 1H; H_{ar}), 3.71 (s, 2H; CH_2Ph), 3.69 (s, 2H; 2 CH_2Ph), 3.56 (dd, *J* = 7.8, 16.0 Hz, 1H; 1-H), 3.90 (dd, *J* = 8.2 Hz, 1H; 2-H), 3.22–3.28 (m, 2H; 6-H), 2.83 (dd, *J* = 9.0, 16.0 Hz, 1H; 1-H), 1.82–1.90 (m, 1H; cPr), 1.30 (dd, *J* = 4.8, 9.1 Hz, 1H; cPr), 0.75 ppm (ps t, *J* = 4.7 Hz, 1H; cPr); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 154.3 (C_{ar}), 140.1 (2 C_{ar}), 133.1 (C_{ar}), 128.7 (3 CH_{ar}), 128.2 (4 CH_{ar}), 127.4 (CH_{ar}), 126.9 (3 CH_{ar}), 124.4 (CH_{ar}), 121.2 (CH_{ar}), 113.9 (CH_{ar}), 72.7 (CH; C-2), 56.9 (2 CH_2; CH_2Ph), 56.4 (CH_2; C-6), 55.0 (C; cPr), 33.1 (CH_2; C-1), 28.6 (CH; cPr), 21.0 ppm (CH_2; cPr); IR (film): $\tilde{\nu}$ = 3016 cm^{-1}, 2919, 1462, 1257, 1027, 769; MS (EI, 70 eV): *m*/*z* (%): 366 (24) [M^+], 275 (100) [M^+−C_7H_7], 170 (48), 130 (47), 91 (84) [$C_7H_7^+$]; HRMS (EI) calcd for $C_{26}H_{26}N_2$ [M^+] 366.2096, found 366.2096.

(*S*)-*N*,*N*-Dibenzyl-1-(*tert*-butoxycarbonyl)-2-pyrrolidinecarboxamide: (*S*)-*N*,*N*-Dibenzyl-1-(*tert*-butoxycarbonyl)-2-pyrrolidinecarboxamide (2.85 g, 72%) was obtained from proline **11** (2.15 g, 10.0 mmol), DCC (5.16 g, 25.0 mmol), HOBT (1.35 g, 10.0 mmol), and $HNBn_2$ (4.8 mL, 25.0 mmol) according to GP 1 as a colorless solid. R_f (cyclohexane/EtOAc 1:1) = 0.42; m.p. 128–131 °C; $[\alpha]_D^{20}$ = +28.8 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$, observed as a major/minor rotamer mixture): δ = 7.37–7.20 (m, 10H; H_{ar}), 4.89–4.80 (m, 1H; 2-H), 4.74–4.60 (m, 2H; CH_2Ph), 4.50–4.40 (m, 2H; CH_2Ph), 3.66–3.41 (m, 2H; 5-H), 2.04–1.81 (m, 4H; 3,4-H), 1.50 [s, 9H, minor; C(CH_3)$_3$], 1.38 ppm [s, 9H, major; C(CH_3)$_3$]; ^{13}C NMR (62.9 MHz, $CDCl_3$, observed as a major/minor rotamer mixture): δ = 174.0 (C=O), 155.3 (C=O), 137.2 (C_{ar}), 136.5 (C_{ar}), 128.9 (2 CH_{ar}), 128.8 (2 CH_{ar}), 128.5 (CH_{ar}), 127.9 (CH_{ar}), 127.5 (CH_{ar}), 126.8 (CH_{ar}), 126.7 (2 CH_{ar}), 79.9 [C, major; *C*(CH_3)$_3$], 79.4 [C, minor; *C*(CH_3)$_3$], 56.4 (CH, minor; C-2), 56.0 (CH, major; C-2), 50.2 (CH_2, major; CH_2Ph), 49.7 (CH_2, minor; CH_2Ph), 49.0 (CH_2, major; CH_2Ph), 48.8 (CH_2, minor; CH_2Ph), 47.0 (CH_2; C-5), 31.5 (CH_2, minor; C-3), 30.2 (CH_2, major; C-3), 28.5 [CH_3, major; C(*C*H_3)$_3$], 28.4 [CH_3, minor; C(*C*H_3)$_3$], 24.5 (CH_2, major; C-4), 23.4 ppm (CH_2, minor; C-4); IR (KBr): $\tilde{\nu}$ = 3030, 2973, 1684,

1651, 1403, 1164, 706 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 394 (2) [M^+], 303 (21) [$M^+-C_7H_7$], 170 (36), 114 (100), 91 (83) [$C_7H_7^+$], 70 (96); elemental analysis calcd (%) for $C_{24}H_{30}N_2O_3$ (394.52): C 73.07, H 7.67; found: C 72.83, H 7.46.

(*S*)-*N*,*N*-Dibenzyl-2-pyrrolidinecarboxamide (12): Trifluoroacetic acid (0.50 mL, 6.34 mmol) was added dropwise to a well stirred solution of (*S*)-*N*,*N*-dibenzyl-1-(*tert*-butoxycarbonyl)-2-pyrrolidinecarboxamide (480 mg, 1.22 mmol) in CH_2Cl_2 (20 mL) at ambient temperature. The reaction mixture was stirred at ambient temperature for 12 h, then cooled in an ice bath while a saturated aqueous $NaHCO_3$ solution (20 mL) was carefully added. The organic phase was separated, washed with a saturated aqueous $NaHCO_3$ solution (2×20 mL), brine (20 mL), and dried over $MgSO_4$. The product (355 mg, 99%) was obtained as a colorless oil, which was used without further purification. $[\alpha]_D^{20}=-77.0$ ($c=0.50$, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta=7.34$–7.15 (m, 10H; H_{ar}), 4.91 (d, $J=14.8$ Hz, 1H; CH*H*Ph), 4.58 (d, $J=23.5$ Hz, 1H; CH*H*Ph), 4.34 (d, $J=23.5$ Hz, 1H; CH*H*Ph), 4.25 (d, $J=14.8$ Hz, 1H; CH*H*Ph), 3.99–3.94 (m, 1H; 2-H), 3.29–3.19 (m, 1H; 5-H), 2.91 (s, 1H; NH), 2.86–2.77 (m, 1H; 5-H), 2.08–1.98 (m, 1H), 1.84–1.69 ppm (m, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta=174.8$ (C=O), 137.0 (C_{ar}), 136.0 (C_{ar}), 129.0 (2 CH_{ar}), 128.6 (2 CH_{ar}), 128.1 (2 CH_{ar}), 127.8 (CH_{ar}), 127.4 (CH_{ar}), 126.6 (2 CH_{ar}), 58.5 (CH; C-2), 49.1 (CH_2; CH_2Ph), 48.1 (CH_2; CH_2Ph), 47.9 (CH_2; C-5), 31.4 (CH_2; C-3), 26.6 ppm (CH_2; C-4).

(±)-*N*,*N*-Dibenzyl-1,2-diallyl-2-pyrrolidinecarboxamide (13): Compound **13** (1.32 g, 33%) was obtained from the amine **12** (3.15 g, 10.7 mmol), K_2CO_3 (3.00 g, 21.7 mmol), and allyl bromide (1.40 mL, 16.1 mmol) according to GP 1 as a colorless oil. R_f (hexane/Et_2O 10:1) = 0.48; $[\alpha]_D^{20}=0.0$ ($c=1.0$, $CHCl_3$); ^{1}H NMR (300 MHz, $C_2D_2Cl_4$ at 100°C): $\delta=7.38$–7.15 (m, 10H; H_{ar}), 6.11–5.97 (m, 1H; NCH_2CH=CH_2), 5.78–5.63 (m, 1H; CCH_2CH=CH_2), 5.19–4.98 (m, 6H; CH_2Ph, CCH_2CH=CH_2, NCH_2CH=CH_2), 4.60 (d, $J=18.5$ Hz, 2H; CH_2Ph), 3.56–3.45 (m, 1H), 3.21–3.09 (m, 2H), 2.90 (dd, $J=7.3$, 13.1 Hz, 1H), 2.70–2.61 (m, 1H; $CCHCH$=CH_2), 2.39–2.20 (m, 2H; 3-H, $CCHCH$=CH_2), 2.18–2.03 (m, 1H), 1.84–1.78 ppm (m, 2H); ^{13}C NMR (75.5 MHz, $C_2D_2Cl_4$ at 100°C): $\delta=174.6$ (C=O), 137.6 (2 C_{ar}), 136.5 (CH; NCH_2CH=CH_2), 136.2 (CH; CCH_2CH=CH_2), 128.2 (4 CH_{ar}), 127.2 (4 CH_{ar}), 126.7 (2 CH_{ar}), 116.8 (CH_2; NCH_2CH=CH_2), 115.7 (CH_2; CCH_2CH=CH_2), 65.2 (C; C-2), 51.9 (2 CH_2), 50.0 (CH_2), 49.7 (CH_2; NCH_2CH=CH_2), 37.1 (CH_2; CCH_2CH=CH_2), 32.3 (CH_2; C-3), 21.7 ppm (CH_2; C-4); IR (film): $\tilde{\nu}=$ 3067, 2977, 2812, 1633, 1413, 1190, 916 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 374 (<1) [M^+], 150 (100), 91 (14) [$C_7H_7^+$].

(*S*)-1-Allylproline hydrochloride: A mixture of L-proline (**14**, 20.0 g, 174 mmol) and KOH (29.2 g, 521 mmol) in isopropanol (100 mL) was heated at 40°C for 30 min, then allyl bromide (18 mL, 208 mmol) was added and the solution stirred at the same temperature for 19 h. Hydrochloric acid (22 mL of a 37% aq. solution) and $CHCl_3$ (100 mL) were added, the mixture was stirred for 3 h and then filtered. After removal of the solvent under reduced pressure a yellow solid was obtained and washed several times with acetone. The product (18.3 g, 55%) was obtained as a colorless solid. M.p. 205–209°C; $[\alpha]_D^{20}=-60.2$ ($c=1.0$, MeOH); ^{1}H NMR (250 MHz, CD_3OD): $\delta=5.84$–5.67 (m, 1H; C*H*=CH_2), 5.41–5.26 (m, 2H; CH=CH_2), 3.94 (dd, $J=6.7$, 9.5 Hz, 1H; 2-H), 3.78–3.58 (m, 2H; CH_2CH=CH_2), 3.52–3.42 (m, 1H; 5-H), 3.08–2.96 (m, 1H; 5-H), 2.35?2.24 (m, 1H), 2.01–1.70 ppm (m, 3H); ^{13}C NMR (62.9 MHz, CD_3OD): $\delta=172.0$ (C=O), 128.8 (CH; *C*H=CH_2), 125.8 (CH_2; CH=*C*H_2), 68.1 (CH; C-2), 58.3 (CH_2), 55.5 (CH_2), 29.8 (CH_2), 23.9 ppm (CH_2); IR (KBr): $\tilde{\nu}=3480$, 3004, 2849, 1734, 1444, 1226, 953 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 155 (2) [M^+], 110 (100), 70 (18), 41 (33).

(*S*)-*N*,*N*-Dibenzyl-1-allyl-2-pyrrolidinecarboxamide (15): The amide **15** (4.65 g, 89%) was obtained from (*S*)-1-allylproline hydrochloride (3.00 g, 15.6 mmol), DCC (3.40 g, 16.5 mmol), HOBT (2.22 g, 16.4 mmol), and $HNBn_2$ (4.5 mL, 23 mmol) according to GP 1 as a colorless oil. R_f (Et_2O) = 0.30; $[\alpha]_D^{20}=-75.0$ ($c=1.0$, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta=7.39$–7.12 (m, 10H; H_{ar}), 5.98–5.85 (m, 1H; C*H*=CH_2), 5.16–4.97 (m, 2H; CH=CH_2), 4.74 (d, $J=14.6$ Hz, 1H; CH_2Ph), 4.49–4.41 (m, 4H; CH_2Ph, 2-H), 3.50–3.34 (m, 2H; CH_2CH=CH_2), 3.25–3.18 (m, 1H; 5-H), 3.01 (dd, $J=7.3$, 13.1 Hz, 1H; 5-H), 2.35–2.25 (m, 1H), 2.04?1.87 (m, 2H), 1.76–1.71 ppm (m, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta=173.8$ (C=O), 137.3 (C_{ar}), 136.6 (C_{ar}), 135.8 (CH; *C*H=CH_2), 128.7 (2 CH_{ar}), 128.4 (2 CH_{ar}), 128.3 (2 CH_{ar}), 127.4 (CH_{ar}), 127.2 (CH_{ar}), 126.3 (2 CH_{ar}), 116.8 (CH_2; CH=*C*H_2), 63.5 (CH; C-2), 57.3 (CH_2; CH_2Ph), 53.1 (CH_2; CH_2Ph), 49.0 (CH_2; *C*H_2CH=CH_2), 48.1 (CH_2; C-5), 29.6 (CH_2), 22.8 ppm (CH_2); IR (film): $\tilde{\nu}=3030$, 2972, 1651, 1453, 1211, 732 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 334 (2) [M^+], 110 (100), 91 (10), 41 (33); elemental analysis calcd (%) for $C_{22}H_{26}N_2O$ (334.46): C 79.00, H 7.84; found: C 78.89, H 7.64.

(1a*S*,6a*S*,6b*R*)- and (1a*R*,6a*S*,6b*S*)-*N*,*N*-Dibenzylperhydrocyclopropa[1,2-*a*]pyrrolizin-6b-ylamine (16): The amine **16** (224 mg, 70%) was obtained from (*S*)-*N*,*N*-dibenzyl-1-allyl-2-pyrrolidinecarboxamide (**15**, 334 mg, 1.00 mmol), [MeTi(O*i*Pr)$_3$] (370 mg, 1.54 mmol), and cHexMgBr (5.0 mL, 5.00 mmol, 1.0 M solution in Et_2O) according to GP 3 in a (1a*R*,6a*S*,6b*S*)-**16**/(1a*S*,6a*S*,6b*R*)-**16** ratio of 2.9:1. (1a*R*,6a*S*,6b*S*)-**16**: Colorless oil; R_f (CH_2Cl_2/MeOH 20:1) = 0.25; $[\alpha]_D^{20}=-21.6$ ($c=0.80$, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta=7.34$–7.15 (m, 10H; H_{ar}), 4.90 (m, 1H; 6a-H), 3.83 (d, $J=13.3$ Hz, 2H; CH_2Ph), 3.66 (d, $J=13.3$ Hz, 2H; CH_2Ph), 3.56–3.52 (m, 1H; 4-H), 3.46–3.40 (m, 1H; 2-H), 2.60 (d, $J=12.3$ Hz, 1H; 2-H), 2.50–2.04 (m, 4H; 4,5,6-H), 1.89–1.80 (m, 1H; 6-H), 1.17–1.10 (m, 1H; cPr), 1.00–0.94 (m, 1H; cPr), 0.59 ppm (ps t, $J=5.3$ Hz, 1H; cPr); ^{13}C NMR (250 MHz, $CDCl_3$): $\delta=139.4$ (2 C_{ar}), 128.9 (4 CH_{ar}), 128.2 (4 CH_{ar}), 127.1 (2 CH_{ar}), 62.4 (CH; C-6a), 57.0 (2 CH_2; CH_2Ph), 55.2 (CH_2; C-4), 54.3 (CH_2; C-2), 53.5 (C; cPr), 30.1 (CH; cPr), 29.4 (CH_2; C-6), 27.7 (CH_2; C-5), 19.3 ppm (CH_2; cPr); IR (film): $\tilde{\nu}=3020$, 2910, 1465, 1241, 1032 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 318 (6) [M^+], 250 (10), 227 (100) [$M^+-C_7H_7$], 124 (60), 91 (80) [$C_7H_7^+$]; HRMS (EI) calcd for $C_{22}H_{26}N_2$ [M^+] 318.2096, found 318.2096; elemental analysis calcd (%) for $C_{22}H_{26}N_2$ (318.46): C 82.97, H 8.23; found: C 82.73, H 8.08.

(1a*S*,6a*S*,6b*R*)-16: Colorless solid; R_f (CH_2Cl_2/MeOH 20:1) = 0.10; m.p. 148–151°C; $[\alpha]_D^{20}=-40.0$ ($c=0.25$, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta=7.35$–7.18 (m, 10H; H_{ar}), 4.24 (t, $J=7.3$ Hz, 1H; 6a-H), 3.79 (d, $J=13.3$ Hz, 2H; CH_2Ph), 3.70 (d, $J=13.3$ Hz, 2H; CH_2Ph), 3.03–2.89 (m, 2H; 2,4-H), 2.42–2.28 (m, 2H; 2,4-H), 2.24–2.22 (m, 1H; 5-H), 1.96–1.57 (m, 3H; 5,6-H), 1.04–0.97 (m, 1H; cPr), 0.80–0.71 (m, 1H; cPr), 0.26 ppm (t, $J=4.9$ Hz, 1H; cPr); ^{13}C NMR (250 MHz, $CDCl_3$): $\delta=140.1$ (2 C_{ar}), 128.9 (4 CH_{ar}), 128.0 (4 CH_{ar}), 126.8 (2 CH_{ar}), 61.4 (CH; C-6a), 57.9 (C; cPr), 57.1 (2 CH_2; CH_2Ph), 55.1 (CH_2; C-4), 54.3 (CH_2; C-2), 30.5 (CH; cPr), 29.8 (CH_2; C-6), 28.0 (CH_2; C-5), 19.1 ppm (CH_2; cPr); IR (film): $\tilde{\nu}=3018$ cm^{-1}, 2912, 1468, 1235, 1022; MS (EI, 70 eV): *m/z* (%): 318 (5) [M^+], 250 (1), 227 (100) [$M^+-C_7H_7$], 123 (18), 91 (75) [$C_7H_7^+$]; HRMS (EI) calcd for $C_{22}H_{26}N_2$ [M^+] 318.2096, found 318.2096.

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[22] Crystals of compound (1a*S*,6a*S*,6b*R*)-**16** were grown by slow evaporation of their solution in Et_2O. The X-ray single crystal data were collected on a Bruker CCD SMART 1 K diffractometer using graphite-monochromated $Mo_{K\alpha}$ radiation. The structure solutions and refinements on F^2 were performed with the Bruker SHELXTL program suite. (1a*S*,6a*S*,6b*R*)-**16**: $C_{22}H_{26}N_2$, crystal size $0.33\times0.07\times0.04\,mm^3$, orthorhombic, $a=6.1990(3)$, $b=14.5497(8)$, $c=20.0989(11)$ Å, $V=1812.79(17)$ Å^3, $Z=4$, space group $P2_12_12_1$, $T=120(2)$ K, $\rho=1.167\,g\,cm^{-3}$, intensities measured: 13907 ($2\theta_{max}=50°$), independent: 3194 ($R_{int}=0.1604$), 217 parameters refined, R_1 (all data) = 0.1363, wR_2 (all data) = 0.1082, Gof = 0.976, maximum and minimum residual electron density 0.180 and $-0.222\,e\,Å^{-3}$. CCDC-206103 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44)1223–336033; or email: deposit@ccdc.cam.ac.uk.

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