Synthesis of Alkaloid Analogues from α-Amino Acids by One-Pot Radical Decarboxylation/Alkylation

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A mild, one-pot methodology to obtain α-substituted nitrogen heterocycles from commercial amino acids is reported. This versatile procedure has been applied to the synthesis of different alkaloid analogues in good to excellent yields.

Introduction

Alkaloids have attracted a much interest both from the synthetic and the pharmacological standpoints.[1] The antitumour agent swainsonine[2] (Figure 1), the non-addictive analgesic ipalbidine[3] and the poisonous histrionicotoxin[4] exemplify the variety of structures and biological activities. In order to study structure-activity relationships (SAR) many alkaloid analogues have been prepared, and in many cases new synthetic strategies have been developed.[1]

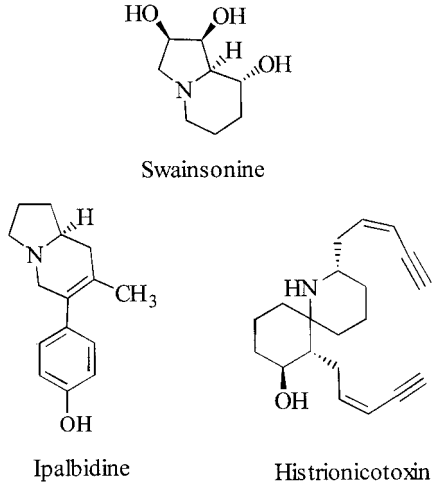
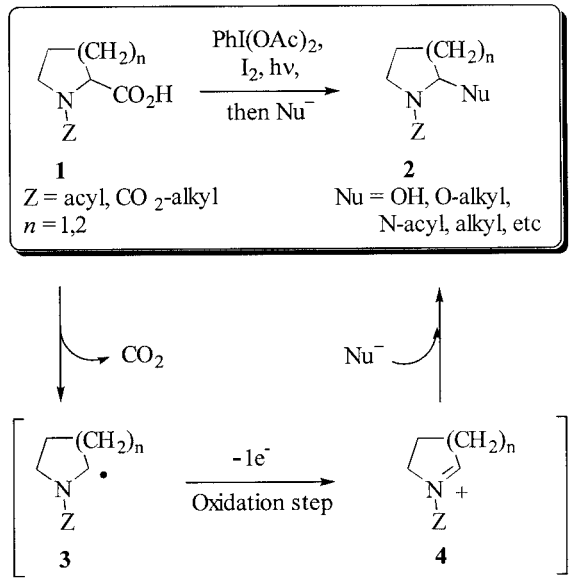


Figure 1. Bioactive alkaloids.

In recent reports from our group, α-amino acids **1** (Scheme 1) were used as starting materials in the synthesis of substituted nitrogen heterocycles **2**.[5] The key step was a radical decarboxylation, which generated a carbon radical **3**. This radical was oxidized in situ to an acyliminium ion **4**, which could be trapped by different nucleophiles[6] to yield the α-substituted heterocycles **2**.



Scheme 1. Synthesis of functionalised pyrrolidines (n = 1) and piperidines (n = 2) by oxidative radical decarboxylation of α-amino acids.

We reasoned that the resulting α-substituted heterocycles **2** would be useful intermediates to obtain alkaloids or their analogues. The synthesis of indolizidine and spirobicyclic alkaloid analogues using a tandem decarboxylation/alkylation reaction (Nu = alkyl) as the key step is reported herein.

Results and Discussion

In recent years, many efforts have been devoted to the synthesis of indolizidine alkaloids since several of them

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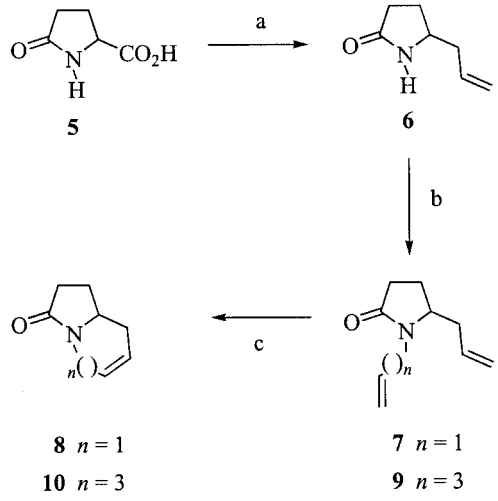
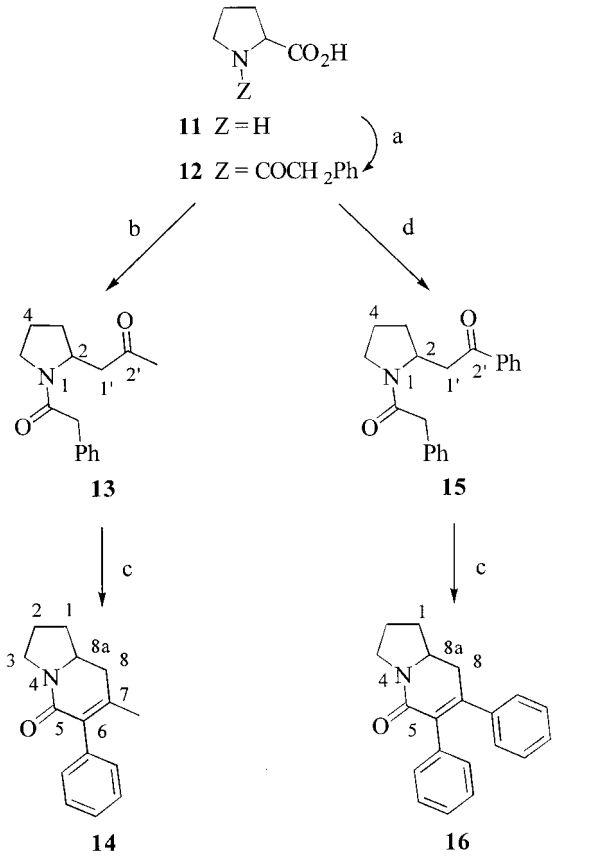
(such as swainsonine, Figure 1) are potent glycosidase inhibitors and possess antitumoural, antiviral or hypoglucaemic activities.[2] However, they also have important side-effects or limited bioavailability. In order to overcome these problems, different synthetic analogues have been developed.

The indolizidine core can be synthesised in three steps starting from commercial pyroglutamic acid **5** (Scheme 2). When the amino acid **5** was treated with DIB/iodine, followed by addition of boron trifluoride and allyltrimethylsilane, the 2-allylpyrrolidinone **6**[5d] was obtained in excellent yield. *N*-Allylation afforded the diene **7**,[7] which underwent olefin metathesis to give the indolizidine **8**[7a] in good global yield.



Scheme 2. Synthesis of analogues of indolizidine alkaloids. Reagents and conditions: (a) DIB, I_2, CH_2Cl_2, 3 h; then $BF_3{\cdot}OEt_2$, allylTMS, 0 °C to room temp., 4 h, 81%; (b) NaH, DMF, 0 °C, 0.5 h; then $CH_2{=}CHCH_2Br$ or $CH_2{=}CHCH_2CH_2CH_2Br$, 67% for **7**, 63% for **9**; (c) (benzylidene)dichlorobis(tricyclohexylphosphane) ruthenium(II) (cat.), CH_2Cl_2, reflux, 80% for **8**, 81% for **10**.

yield. Treatment of **13** with base gave the 6,7-disubstituted indolizodinone **14** in excellent yield.



Scheme 3. Synthesis of ipalbidine and septicine analogues. Reagents and conditions: (a) $ClCOCH_2Ph$, THF/$NaHCO_3$ (aq. satd.), room temp., 10 h, 76%; (b) DIB, I_2, CH_2Cl_2, 3 h; then $BF_3{\cdot}OEt_2$, isopropenyl acetate, 0 °C to room temp., 4 h, 58%; (c) *t*BuOK, *t*BuOH, reflux, 12 h, 99% for **14**, 82% for **16**; (d) DIB, I_2, CH_2Cl_2, 3 h; then $BF_3{\cdot}OEt_2$, $PhC(OTMS){=}CH_2$, 0 °C to room temp., 4 h, 50%.

In order to obtain derivatives with different ring sizes, the pyrrolidinone **6** was treated with sodium hydride and 5-bromo-1-pentene. The resultant diene **9** underwent olefin metathesis to yield the bicyclic compound **10**,[7a] which contains an eight-membered ring. Although rather unusual, the bicyclo[3.0.6] system can be found in alkaloids with potent biological activity, such as the manzamines.[8]

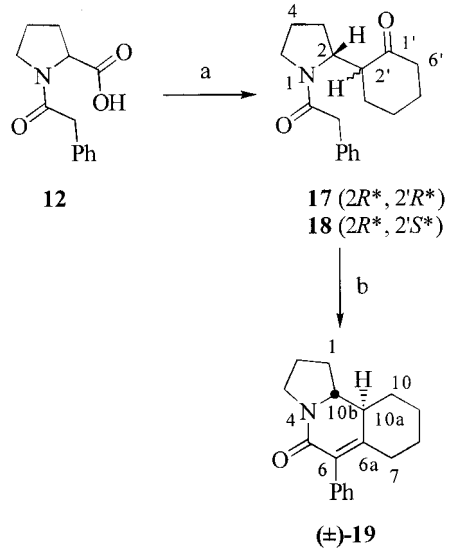
The indolizidine core can also be found in phenanthroline or *seco*-phenanthroline alkaloids. The analgesic ipalbidine[3] (Figure 1) has already been mentioned, and other members of this family present promising antitumoural activity.[9,10] The synthesis of analogues to study the SAR has been undertaken by several groups.

The direct synthesis of an ipalbidine analogue was carried out according to Scheme 3. Commercial proline **11** reacted with phenylacetyl chloride to afford the proline derivative **12**.[11] The latter was treated with DIB/I_2, followed by addition of boron trifluoride–diethyl ether and isopropenyl acetate to give the (±)-norhygrine derivative **13** in good

In a similar way, an analogue of the *seco*-phenanthroline alkaloid septicine[12] was readily synthesised. Thus, when the proline derivative **12** was treated with DIB/I_2, and then boron trifluoride–diethyl ether and phenyl(trimethylsilyloxy)ethene were added, the phenone derivative **15** was obtained. This product underwent reaction with *t*BuOK in refluxing *t*BuOH to yield the septicine analogue **16**[12k] in very good yield.

It should be noted that other substituents can be introduced into the bicyclic core by using other cyclic amino acids as substrates or by varying the amido and ketone chains, thus offering a versatile route to many analogues.

This strategy also offers a direct route to polycyclic systems. For instance, when proline derivative **12** was treated under the usual decarboxylation/alkylation conditions with 1-(trimethylsilyloxy)cyclohexene as nucleophile, the cyclohexyl derivatives **17** and **18** (Scheme 4) were obtained as an inseparable diastereomer mixture (**17**/**18** = 3:2, according to the NMR spectra at 25 °C) in 68% yield.



Scheme 4. Synthesis of polycyclic compounds. Reagents and conditions: (a) DIB, I_2, CH_2Cl_2, 3 h; then $BF_3{\cdot}OEt_2$, 1-(trimethylsilyloxy)cyclohexene, 0 °C to room temp., 4 h, 68%, (**17**/**18** = 3:2); (b) *t*BuOK, *t*BuOH, reflux, 12 h, 81% for the isomeric olefinic mixture, 21% for **19** purified from the mixture.

To confirm that compounds **17** and **18** are diastereomers and not rotamers, the NMR spectra at 26 °C and 60 °C were compared. Although the resolution improved on heating, no coalescence or significant shifts of the signals were observed, and the ratio **17**/**18** remained constant. This behaviour indicates that compounds **17** and **18** are diastereomers and not rotamers. According to the coupling constants observed in the ^{1}H NMR spectra,[13,14] the (2*R**,2′*R**) configuration was tentatively assigned to the major product **17**, and the (2*R**,2′*S**) configuration to the minor diastereomer **18**.

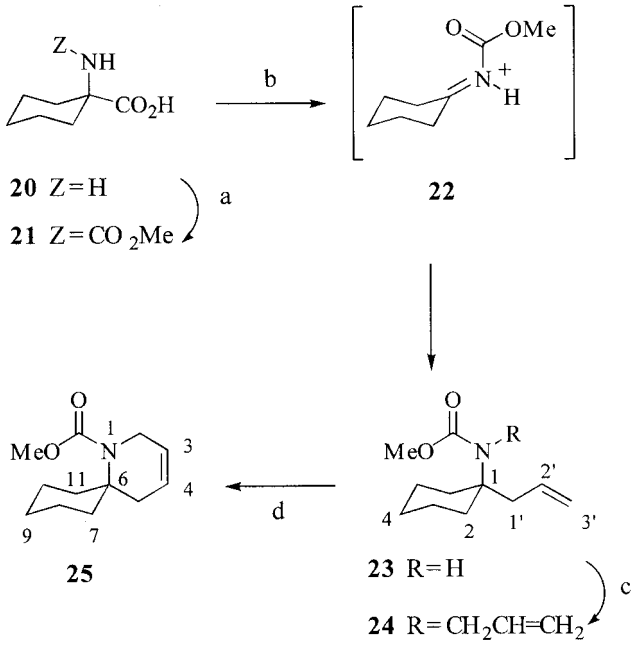
To generate a polycyclic core, the mixture of diastereomers **17** and **18** was submitted to an aldol condensation under thermodynamic conditions. A mixture of isomeric olefinic products was obtained (81% estimated yield[15]), from which the tricyclic conjugated amide (±)-**19** could be isolated (21%).

The (10a*S**,10b*R**) configuration was assigned to product **19** according to the coupling constants observed in the ^{1}H NMR spectrum, and by comparison with the *J* values calculated for the minimum-energy conformations of the possible diastereomers.[14,16]

The formation of compound (±)-**19** was achieved in two steps from a common amino acid derivative. Other polycyclic systems could be generated by using different cyclic or polycyclic silyl enol ethers as nucleophiles. Although the cyclohexanone derivatives **17** and **18** could not be separated, in other cases separation of the decarboxylation/alkylation products would be possible, or stereoselectivity could be induced.

Other alkaloids that have attracted much interest are the azaspirocyclic compounds (such as histrionicotoxin,[4] Figure 1), due not only to their unusual structure but also to the potent biological activities (immunosuppressant,[17] antiinflammatory,[18] cytotoxic activities,[19] etc.) associated with many of them.[20]

A synthetic approach to the heterobicyclic core was devised using the commercial amino acid **20** (Scheme 5) as starting material. Its methyl carbamate **21**[21] was treated under the decarboxylation/allylation conditions to generate the tertiary *N*-acyliminium ion **22**, which reacted with the nucleophile to give the allyl derivative **23**.



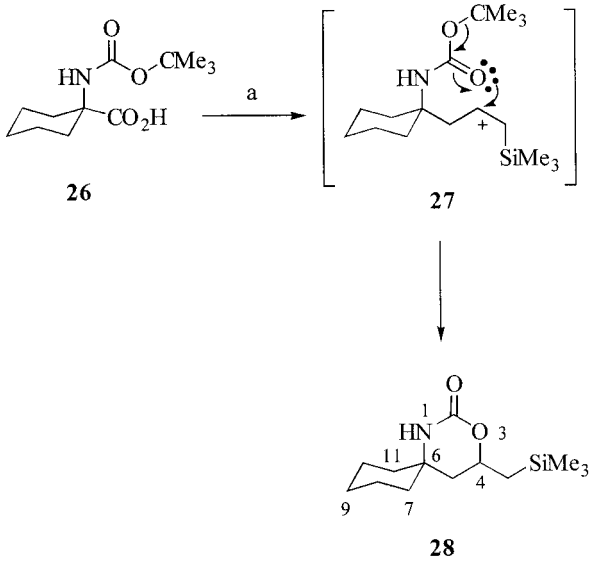
Scheme 5. Synthesis of the azaspirocyclic core. Reagents and conditions: (a) $ClCO_2Me$, THF/$NaHCO_3$ (aq. satd.), room temp., 18 h, 72%; (b) DIB, I_2, CH_2Cl_2, room temp., 3 h, then 0 °C, allyltrimethylsilane, $BF_3{\cdot}OEt_2$, 61%; (c) NaH, DMF, 0 °C, 1 h, then allyl bromide, 4 h, 88%; (d) (benzylidene)dichlorobis(tricyclohexylphosphane)ruthenium(II) (cat.), CH_2Cl_2, reflux, 94%.

This reaction is remarkable since the use of tertiary acyliminium ions in synthesis has been restricted until recently.[22] In some cases, their generation was difficult, whereas in other cases the addition of nucleophiles was hampered due to steric hindrance or other problems. In our case, the first problem was avoided by using the acid **21** as a stable precursor of the acyliminium intermediate. To our satisfaction, the addition of the nucleophile also proceeded in good yields.

The allyl derivative **23** underwent *N*-allylation to yield the diene **24**, and subsequent ring-closing metathesis afforded the spirocyclic system **25** in excellent yield. This bicyclic system is present in bioactive natural products such as histrionicotoxin.[4]

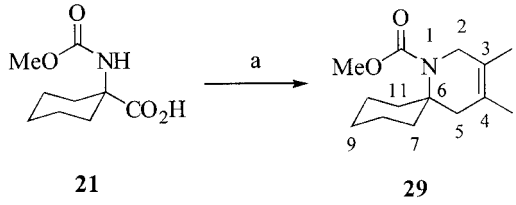
By replacing the nitrogen protecting group, we can alter the reaction outcome and obtain different spirocyclic compounds. Thus, when the methyl carbamate in **21** was replaced by a BOC group (substrate **26**,[23] Scheme 6), a one-pot decarboxylation/alkylation/cyclisation took place. The reaction intermediate **27** evolved by nucleophilic addition

of the carbamate oxygen and concomitant loss of the *tert*-butyl group,[24] affording the spirocyclic carbamate **28** in 61% global yield. The spirocyclic carbamates are structural analogues of spirocyclic lactams, and both kinds of compounds may be bioisosters.



Scheme 6. Synthesis of the spirocyclic carbamate **28**. Reagents and conditions: (a) DIB, I_2, CH_2Cl_2, room temp., 3 h; then 0 °C, allyltrimethylsilane, $BF_3{\cdot}OEt_2$, 61%.

Finally, in order to obtain other spirocyclic compounds in one step, a new tandem decarboxylation/hetero-Diels–Alder reaction was developed[25,26] (Scheme 7). To our satisfaction, when the substrate **21** was treated with DIB and iodine followed by addition of boron trifluoride and 2,3-dimethylbutadiene, the interesting spirocyclic compound **29** was obtained in 42% yield. This variation illustrates the versatility of this methodology for the synthesis of different classes of alkaloid analogues.



Scheme 7. One-pot decarboxylation/aza-Diels–Alder reaction. Reagents and conditions: (a) DIB, I_2, room temp., 2 h; then 0 °C, 2,3-dimethylbutadiene, $BF_3{\cdot}OEt_2$, 42%.

Conclusions

The tandem decarboxylation/alkylation reaction is a versatile and efficient process to obtain key intermediates in alkaloid synthesis. The reaction has been applied to the synthesis of analogues of bioactive indolizidine and azaspirocyclic alkaloids. The development of a new one-pot decarboxylation/Diels–Alder reaction illustrates the versatility of this methodology.

Experimental Section

General Remarks: Commercially available reagents and solvents were of analytical grade or were purified by standard procedures prior to use. All reactions involving air- or moisture-sensitive materials were carried out under nitrogen. The spray reagents for TLC analysis were 0.5% vanillin in H_2SO_4/EtOH (4:1) or 0.25% ninhydrin in ethanol. Merck silica gel 60 PF was used for TLC analysis and 0.063–0.2 mm silica gel was used for column chromatography. NMR spectra were determined in $CDCl_3$ solution using TMS as an internal standard, unless otherwise stated. For some compounds, a mixture of two rotamers was observed at room temperature, which caused broadening or splitting of the NMR signals. The rate of rotamer interconversion usually increased on heating, and in many cases only one rotamer could be detected at 60–70 °C. When the NMR resolution improved significantly on heating, the spectra at 60–70 °C are described. Abbreviations: arom. = aromatic protons or carbon atoms; BOC = *tert*-butyl carbamate; c.s. = complex signal; DIB = (diacetoxyiodo)benzene; DMF = dimethylformamide; SAR = structure-activity relationship; THF = tetrahydrofuran; TMS = trimethylsilyl; AllylTMS = allyltrimethylsilane. Compounds **6**,[5d] **7**–**10**,[7a] **12**[11] and **26**[23] have been reported previously.

General Procedure for the Tandem Decarboxylation/Alkylation Reaction: DIB (2.0 mmol) and iodine (1.0 mmol, unless otherwise stated) were added to a solution of the starting acid (1.0 mmol) in dry CH_2Cl_2 (15 mL) under nitrogen. The reaction mixture was stirred at room temperature in sunlight for the time stated in the scheme captions. Afterwards, it was cooled to 0 °C and $BF_3{\cdot}OEt_2$ (2 mmol) and the nucleophile (5 mmol) were added dropwise. The reaction mixture was allowed to reach room temperature and was stirred for another 4 h. It was then poured into an aqueous 10% sodium thiosulfate ($Na_2S_2O_3$)/saturated $NaHCO_3$ solution and extracted with CH_2Cl_2. The organic layer was washed with brine, dried with Na_2SO_4, filtered and the solvents were evaporated under vacuum. The residue was purified by chromatography on silica gel (hexanes/EtOAc) to yield the purified reaction product(s).

1-[1-(Phenylacetyl)-2-pyrrolidinyl]acetone (13): The general decarboxylation/alkylation procedure with I_2 (0.5 equiv.) afforded product **13** (58%) as a syrup. IR ($CHCl_3$): $\tilde{\nu}$ = 1711 cm^{-1}. ^1H NMR (500 MHz, 70 °C): δ = 1.70 (m, 1 H, 3-H_a), 1.86 (m, 2 H, 4-H_2), 2.02 (m, 1 H, 3-H_b), 2.09 (s, 3 H, CH_3CO), 2.40 (m, 1 H, 1′-H_a), 3.10 (d, J = 14.8 Hz, 1 H, 1′-H_b), 3.42 (m, 2 H, 5-H_2), 3.61 (s, 2 H, CH_2Ph), 4.39 (m, 1 H, 2-H), 7.24 (m, 5 H, arom.) ppm. ^{13}C NMR (125.7 MHz, 70 °C): δ = 24.1 (CH_2, 4-C), 30.0 (CH_2, 3-C), 30.4 (CH_3), 42.5 (CH_2, *C*H_2Ph), 47.1 (CH_2, 1′-C, *C*H_2CO), 47.3 (CH_2, 5-C), 54.0 (CH, 2-C), 126.7 (CH, arom.), 128.5 (2×CH, arom.), 128.9 (2×CH, arom.), 135.0 (C, arom.), 169.5 (C, CO), 207.1 (C, CO) ppm. MS (EI, 70 eV): *m*/*z* (%) = 245 (14) [M^+], 202 (27) [M^+ – $COCH_3$], 154 (20) [M^+ – CH_2Ph], 126 (56) [M^+ – $COCH_2$Ph], 91 (87) [CH_2Ph], 70 (100) [M^+ + H – CH_2COCH_3 – $COCH_2$Ph]. HRMS (EI, 70 eV): calcd. for $C_{15}H_{19}NO_2$ 245.1416; found 245.1397; calcd. for $C_{13}H_{16}NO$ 202.1232; found 202.1201; calcd. for $C_8H_{12}NO_2$ 154.0868; found 154.0858; calcd. for $C_7H_{12}NO$ 126.0919; found 126.0911. $C_{15}H_{19}NO_2$ (245.32): calcd. C 73.44, H 7.81, N 5.71; found C 73.59, H 8.18, N 5.93.

7-Methyl-6-phenyl-2,3,8,8a-tetrahydro-5(1*H*)-indolizinone (14): *t*BuOK (167 mg, 1.5 mmol) was added to a solution of compound **13** (125 mg, 0.5 mmol) in dry *tert*-butyl alcohol (5 mL) and the reaction mixture was refluxed under nitrogen for 8 h. It was then partially concentrated under vacuum, poured into 10% aqueous HCl and extracted with EtOAc. The organic layer was dried with sodium sulfate, filtered and the solvents were evaporated under vac-

uum. The residue was purified by column chromatography on silica gel (hexanes/EtOAc, 90:10) to afford the indolizinone **14** (115 mg, 99%) as white crystals. M.p. 69.9–70.6 °C (from EtOAc/*n*-hexane). IR ($CHCl_3$): $\tilde{\nu}$ = 1650, 1612 cm^{-1}. ^1H NMR (500 MHz): δ = 1.62 (dddd, J = 7.1, 10, 12, 12 Hz, 1 H, 1-H_a), 1.76 (s, 3 H, CH_3C=), 1.80 (m, 1 H, 2-H_a), 2.00 (m, 1 H, 2-H_b), 2.22 (m, 1 H, 1-H_b), 2.35 (ddd, J = 1.2, 13.1, 16.6 Hz, 1 H, 8-H_a), 2.40 (dd, J = 5.5, 16.5 Hz, 1 H, 8-H_b), 3.49 (ddd, J = 7.5, 9.8, 11.9 Hz, 1 H, 3-H_a), 3.60 (ddd, J = 2.3, 9.1, 11.7 Hz, 1 H, 3-H_b), 3.77 (m, 1 H, 8a-H), 7.17 (d, J = 7.2 Hz, 2 H, arom.), 7.25 (dd, J = 7.4, 7.6 Hz, 1 H, arom.), 7.31 (dd, J = 7.2, 7.5 Hz, 2 H, arom.) ppm. ^{13}C NMR (125.7 MHz): δ = 21.4 (CH_3, 7-Me), 23.0 (CH_2, 2-C), 33.7 (CH_2, 1-C), 37.2 (CH_2, 8-C), 44.5 (CH_2, 3-C), 55.3 (CH, 8a-C), 126.8 (CH, arom.), 127.6 (2×CH, arom.), 130.2 (2×CH, arom.), 132.3 (C, arom.), 136.1 (C, 6-C), 143.7 (C, 7-C), 163.7 (C, CO) ppm. MS (EI, 70 eV): m/z (%) = 227 (96) [M^+], 158 (100) [OCC(Ph)=C(Me)CH_2]. HRMS (EI, 70 eV): calcd. for $C_{15}H_{17}NO$ 227.1310; found 227.1283; calcd. for $C_{11}H_{10}O$ 158.0732; found 158.0745. $C_{15}H_{17}NO$ (227.31): calcd. C 79.26, H 7.54, N 6.16; found C 79.25, H 7.54, N 6.14.

2-Phenyl-1-[1-(phenylacetyl)-2-pyrrolidinyl]ethanone (15): General decarboxylation/alkylation procedure (50%); syrup. IR ($CHCl_3$): $\tilde{\nu}$ = 1678, 1632, 1599 cm^{-1}. ^1H NMR (500 MHz): δ = 1.83 (m, 1 H, 3-H_a), 1.88 (m, 1 H, 4-H_a), 1.90 (m, 2 H, 3-H_b + 4-H_b), 2.71 (dd, J = 10.3, 14.7 Hz, 1 H, C$H_a$$H_b$COPh), 3.44 (ddd, J = 7.8, 8.1, 9.3 Hz, 1 H, 5-H_a), 3.50 (m, 1 H, 5-H_b), 3.67 (s, 2 H, COCH_2Ph), 3.90 (dd, J = 3.0, 15.0 Hz, 1 H, CH$_a$$H_b$COPh), 4.58 (m, 1 H, 2-H), 7.26 (dd, J = 8.2, 8.5 Hz, 1 H, arom.), 7.28 (d, J = 7.4 Hz, 2 H, arom.), 7.33 (dd, J = 7.4, 7.4 Hz, 2 H, arom.), 7.45 (dd, J = 7.5, 7.9 Hz, 2 H, arom.), 7.54 (dd, J = 7.4, 7.4 Hz, 1 H, arom.), 8.10 (d, J = 7.2 Hz, 2 H, arom.) ppm. ^{13}C NMR (125.7 MHz): δ = 23.8 (CH_2, 4-C), 29.3 (CH_2, 3-C), 42.1 (CH_2, CH$_2$COPh), 42.4 (CH_2, COCH$_2$Ph), 47.2 (CH_2, 5-C), 54.7 (CH, 2-C), 126.7 (CH, arom.), 128.3 (2×CH, arom.), 128.5 (4×CH, arom.), 128.9 (2×CH, arom.), 133.0 (CH, arom.), 134.6 (C, arom.), 136.5 (C, arom.), 169.6 (C, CO), 198.8 (C, CO) ppm. MS (EI, 70 eV): m/z (%) = 307 (8) [M^+], 202 (11) [M^+ – COPh], 188 (73) [M^+ – $COCH_2Ph$], 105 (100) [PhCO], 91 (65) [PhCH$_2$]. HRMS (EI, 70 eV): calcd. for $C_{20}H_{21}NO_2$ 307.1572; found 307.1585; calcd. for $C_{12}H_{14}NO$ 188.1075; found 188.1091; calcd. for C_7H_5O 105.0340; found 105.0357. $C_{20}H_{21}NO_2$ (307.39): calcd. C 78.15, H 6.89, N 4.56; found C 78.26, H 7.12, N 4.40.

6,7-Diphenyl-2,3,8,8a-tetrahydro-5(1*H*)-indolizinone (16): The same procedure as reported for compound **17** afforded the indolizinone **16** (82%) as a colourless oil. IR ($CHCl_3$): $\tilde{\nu}$ = 1651 cm^{-1}. ^1H NMR (500 MHz): δ = 1.73 (m, 1 H, 1-H_a), 1.89 (m, 1 H, 2-H_a), 2.09 (m, 1 H, 2-H_b), 2.29 (ddd, J = 5.3, 5.5, 12.0 Hz, 1 H, 1-H_b), 2.77 (dd, J = 13.2, 16.4 Hz, 1 H, 8-H_a), 2.83 (dd, J = 5.1, 16.4 Hz, 1 H, 8-H_b), 3.60 (m, 1 H, 3-H_a), 3.71 (dd, J = 10.4, 11.3 Hz, 1 H, 3-H_b), 3.97 (m, 1 H, 8a-H), 7.01 (m, 2 H, arom.), 7.09 (m, 2 H, arom.), 7.13 (m, 6 H, arom.) ppm. ^{13}C NMR (100.6 MHz): δ = 23.2 (CH_2, 2-C), 33.7 (CH_2, 1-C), 37.5 (CH_2, 8-C), 44.7 (CH_2, 3-C), 55.7 (CH, 8a-C), 126.7 (CH, arom.), 127.4 (CH, arom.), 127.5 (2×CH, arom.), 127.9 (2×CH, arom.), 128.3 (2×CH, arom.), 131.1 (2×CH, arom.), 133.2 (C, arom.), 135.9 (C, arom.), 140.3 (C, 6-C), 145.2 (C, 7-C), 163.9 (C, CO) ppm. MS (EI, 70 eV): m/z (%) = 289 (60) [M^+], 288 (100) [M^+ – H], 220 (66) [OCC(Ph)=C(Ph)CH_2]. HRMS (EI, 70 eV): calcd. for $C_{20}H_{19}NO$ 289.1467; found 289.1503; calcd. for $C_{20}H_{18}NO$ 288.1388; found 288.1420; calcd. for $C_{16}H_{12}O$ 220.0888; found 220.0914. $C_{20}H_{19}NO$ (289.38): calcd. C 83.01, H 6.62, N 4.84; found C 83.08, H 6.96, N 4.77.

Mixture of Diastereomers (2*R,2′*R**)- and (2*R**,2′*S**)-2′-[1-(Phenylacetyl)-2-pyrrolidinyl]cyclohexanone (17 and 18):** The general decarboxylation/alkylation procedure with I_2 (0.5 equiv.) afforded a diastereomer mixture of **17** and **18** (3:2; 68%) as orange oil. IR ($CHCl_3$): $\tilde{\nu}$ = 1703, 1630 cm^{-1}. ^1H NMR (500 MHz, 60 °C): Major diastereomer (2*R**,2′*R**): δ = 1.42 (ddd, J = 3.2, 11.8, 12.0 Hz, 1 H, 3′-H_a), 1.50–2.00 (c.s., 7 H, 3-H_a + 4-H_2 + 5′-H_a + 4′-H_2 + 3′-H_b), 2.14 (ddd, J = 7.9, 7.9, 8.2 Hz, 1 H, 3-H_b), 2.17 (ddd, J = 7.8, 7.9, 8.0 Hz, 1 H, 5′-H_b), 2.28 (m, 2 H, 6′-H_2), 3.30 (ddd, J = 6.9, 7.1, 10.1 Hz, 1 H, 5-H_a), 3.37 (ddd, J = 4.8, 4.9, 11.8 Hz, 1 H, 2′-H), 3.49 (ddd, J = 6.9, 7.0, 10 Hz, 1 H, 5-H_b), 3.63 (s, 2 H, CH_2Ph), 4.58 (ddd, J = 4.3, 4.7, 8.4 Hz, 1 H, 2-H), 7.15–7.30 (c.s., 5 H, arom.). Minor diastereomer (2*R**,2′*S**): δ = 1.56 (m, 1 H, 3′-H_a), 1.50–2.00 (c.s., 8 H, 3-H_2 + 4-H_2 + 5′-H_a + 4′-H_2 + 3′-H_b), 2.24 (m, 1 H, 5′-H_b), 2.41 (m, 2 H, 6′-H_2), 3.06 (ddd, J = 5.8, 5.8, 11.6 Hz, 1 H, 2′-H), 3.56 (m, 2 H, 5-H_2), 3.61 (s, 2 H, CH_2Ph), 4.22 (ddd, J = 6.1, 6.1, 7.5 Hz, 1 H, 2-H), 7.15–7.30 (c.s., 5 H, arom.) ppm. ^{13}C NMR (125.7 MHz, 60 °C; mixture of two diastereomers, the signals for each diastereomer could not be assigned, since they are of similar intensity): δ = 24.2/24.4 (CH_2, 4-C or 4′-C), 24.7/24.8 (CH_2, 4-C or 4′-C), 26.8/26.9 (CH_2, 3-C or 5′-C or 3′-C), 26.8/27.2 (CH_2, 3-C or 5′-C or 3′-C), 27.4/27.9 (CH_2, 3-C or 5′-C or 3′-C), 41.8/42.5 (CH_2, 6′-C), 42.5/42.8 (CH_2, CH_2Ph), 47.7/48.0 (CH_2, 5-C), 51.4/52.2 (CH, 2′-C), 56.9/57.8 (CH, 2-C), 126.6/126.7 (CH, arom.), 128.4 (2×CH, arom.), 128.9 (2×CH, arom.), 135.1/135.2 (C, arom.), 169.8 (C, CO), 211.0/211.2 (C, CO) ppm. MS (EI, 70 eV): m/z (%) = 285 (13) [M^+], 188 (10) [M^+ – cyclohexanone], 166 (30) [M^+ – $COCH_2Ph$], 91 (92) [CH_2Ph], 70 (100) [M^+ + H – cyclohexanone – $COCH_2Ph$]. HRMS (EI, 70 eV): calcd. for $C_{18}H_{23}NO_2$ 285.1729; found 285.1691; calcd. for $C_{12}H_{14}NO$ 188.1075; found 188.1013; calcd. for $C_{10}H_{16}NO$ 166.1232; found 166.1187; calcd. for C_7H_7 91.0548; found 91.0498; calcd. for C_4H_8N 70.0657; found 70.0617. $C_{18}H_{23}NO_2$ (285.39): calcd. C 75.76, H 8.12, N 4.91; found C 75.59, H 8.44, N 4.61.

(10a*S,10b*R**)-6-Phenyl-2,3,7,8,9,10,10a,10b-octahydropyrrolo[2,1-*a*]isoquinoline-5(1*H*)-one (19):** Same procedure as for compound **17**. Starting from a 3:2 mixture of diastereomers **17**/**18** (142 mg, 0.50 mmol), a mixture of isomeric tricyclic compounds was obtained (108 mg, 81%) from which pure compound **19** (28 mg, 21%) was isolated as a syrup by Chromatotron chromatography (toluene/EtOAc, 98:2). IR ($CHCl_3$): $\tilde{\nu}$ = 1719, 1641 cm^{-1}. ^1H NMR (500 MHz): δ = 1.65 (m, 3 H, 1-H_a + 2-H_a + 8-H_a), 1.76 (m, 1 H, 8-H_b), 1.83 (m, 3 H, 7-H_a + 9-H_2), 2.05 (m, 3 H, 2-H_b + 10-H_2), 2.31 (m, 2 H, 10a-H + 1-H_b), 2.51 (d, J = 15.2 Hz, 1 H, 7-H_b), 3.41 (ddd, J = 5.6, 10.9, 11.7 Hz, 1 H, 10b-H, CHN), 3.52 (ddd, J = 8, 10, 10 Hz, 1 H, 3-H_a), 3.68 (dd, J = 9.2, 9.6 Hz, 1 H, 3-H_b), 7.15 (d, J = 7.1 Hz, 2 H, arom.), 7.26 (dd, J = 7.1, 7.6 Hz, 1 H, arom.), 7.34 (dd, J = 7.5, 7.6 Hz, 2 H, arom.) ppm. ^{13}C NMR (100.6 MHz): δ = 22.8 (CH_2, 2-C), 24.3 (CH_2, 8-C) 25.3 (CH_2, 9-C), 30.3 (CH_2, 7-C), 30.8 (CH_2, 10-C), 32.7 (CH_2, 1-C), 42.6 (CH, 10a-C), 44.9 (CH_2, 3-C), 61.5 (CH, 10b-C), 126.8 (CH, arom.), 127.7 (2×CH, arom.), 130.3 (2×CH, arom.), 131.2 (C, 6-C), 136.2 (C, arom.), 149.0 (C, 6a-C), 163.7 (C, CO) ppm. MS (EI, 70 eV): m/z (%) = 267 (100) [M^+], 198 (35) [M^+ – pyrrolidine]. HRMS (EI, 70 eV): calcd. for $C_{18}H_{21}NO$ 267.1623; found 267.1635; calcd. for $C_{14}H_{14}O$ 198.1045; found 198.1071. $C_{18}H_{21}NO$ (267.37): calcd. C 80.86, H 7.92, N 5.24; found C 80.43, H 8.03, N 5.19.

1-[(Methoxycarbonyl)amino]cyclohexanecarboxylic Acid (21): Commercial 1-aminocyclohexanecarboxylic acid (**20**) (1.35 g, 10 mmol) was added to a biphasic mixture of THF (15 mL) and a saturated aqueous $NaHCO_3$ solution (15 mL) at 0 °C. Methyl chloroformate was then injected dropwise (1.0 mL, 1.22 g, 13 mmol). The reaction mixture was allowed to reach room temperature and was then stirred for 18 h, after which it was carefully acidified with 2 M aqueous HCl and extracted with EtOAc. The organic layer was dried

with sodium sulfate, filtered and the solvents were evaporated under vacuum to yield acid **21** (1.47 g, 72%) as a white crystalline solid. M.p. 178–179 °C. IR ($CHCl_3$): $\tilde{\nu}$ = 3441, 1723 cm^{-1}. ^1H NMR (500 MHz, CD_3OD): δ = 1.27 (m, 1 H, 4-H_a), 1.49 (m, 4 H, 3-H_2 + 5-H_2), 1.55 (m, 1 H, 4-H_b), 1.75 (ddd, J = 4.1, 11.4, 13.6 Hz, 2 H, 2-H_a + 6-H_a), 1.95 (m, 2 H, 2-H_b + 6-H_b), 3.55 (s, 3 H, OMe) ppm. ^{13}C NMR (100.6 MHz, CD_3OD): δ = 22.4 (2×CH_2, 3-C + 5-C), 26.5 (CH_2, 4-C), 33.5 (2×CH_2, 2-C + 6-C), 52.2 (CH_3, OMe), 60.1 (C, 1-C), 158.5 (C, CO), 178.5 (C, CO) ppm. MS (EI, 70 eV): m/z (%) = 169 (4) [M^+ – HOMe], 156 (100) [M^+ – COOH]. HRMS (EI, 70 eV): calcd. for $C_8H_{11}NO_3$ 169.0739; found 169.0746; calcd. for $C_8H_{14}NO_2$ 156.1025; found 156.0990. $C_9H_{15}NO_4$ (201.22): calcd. C 53.70, H 7.52, N 6.96; found C 53.61, H 7.68, N 6.83.

Methyl 1-Allylcyclohexylcarbamate (23): The general decarboxylation/alkylation procedure with I_2 (0.5 equiv.) afforded product **23** (61%) as a syrup. IR ($CHCl_3$): $\tilde{\nu}$ = 3441, 1723, 1509 cm^{-1}. ^1H NMR (400 MHz): δ = 1.15–1.60 (m, 8 H, 2-H_a + 6-H_a + 4-H_2 + 3-H_2 + 5-H_2), 1.93 (m, 2 H, 2-H_b + 6-H_b), 2.44 (d, J = 7.3 Hz, 2 H, CH_2C=C), 3.56 (s, 3 H, OMe), 4.46 (br. s, 1 H, NH), 5.02 (m, 2 H, 3′-H_2), 5.73 (m, 1 H, 2′-H) ppm. ^{13}C NMR (100.6 MHz): δ = 21.5 (2×CH_2, 3-C + 5-C), 25.6 (CH_2, 4-C), 34.7 (2×CH_2, 2-C + 6-C), 42.5 (CH_2, 1′-C), 51.4 (CH_3, OMe), 54.4 (C, 1-C), 117.9 (CH_2, 3′-C), 133.7 (CH, 2′-C), 155.1 (C, CO) ppm. MS (EI, 70 eV): m/z (%) = 197 (<1) [M^+], 156 (100) [M^+ – $CH_2CH{=}CH_2$]. HRMS (EI, 70 eV): calcd. for $C_{11}H_{19}NO_2$ 197.1416; found 197.1455; calcd. for $C_8H_{14}NO_2$ 156.1025; found 156.1071. $C_{11}H_{19}NO_2$ (197.28): calcd. C 66.97, H 9.71, N 7.10; found C 66.61, H 10.01, N 7.30.

Methyl *N*-Allyl-*N*-(1-allylcyclohexyl)carbamate (24): A solution of the allyl derivative **23** (100 mg, 0.51 mmol) in dry DMF (3 mL) was added dropwise to a suspension of NaH (50% dispersion in mineral oil, 72 mg, 1.5 mmol) in dry DMF (3 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 0.5 h and then allyl bromide (60 μL, 88 mg, 0.73 mmol) was slowly injected. The solution was allowed to reach room temperature and stirring was continued for another 4 h. The mixture was then cooled to 0 °C and methanol (0.5 mL) was added dropwise to destroy unreacted NaH. The solution was poured into aqueous saturated sodium hydrogencarbonate and extracted with Et_2O. The organic layer was dried and concentrated as usual, and the residue was purified by column chromatography on silica gel (hexanes/EtOAc, 95:5) to afford the diene **24** (105 mg, 88%) as a syrup. IR ($CHCl_3$): $\tilde{\nu}$ = 1693 cm^{-1}. ^1H NMR (500 MHz): δ = 1.32 (m, 1 H, 4-H_a), 1.40–1.60 (m, 5 H, 4-H_b + 3-H_2 + 5-H_2), 1.82 (ddd, J = 3.0, 10.0, 12.7 Hz, 2 H, 2-H_a + 6-H_a), 1.99 (m, 2 H, 2-H_b + 6-H_b), 2.64 (d, J = 7.4 Hz, 2 H, 1′-H_2), 3.64 (s, 3 H, OMe), 3.89 (d, J = 5.5 Hz, 2 H, 1′′-H_2, NCH_2C=C), 5.03 (m, 4 H, 3′-H_2 + 3′′-H_2), 5.70 (m, 1 H, 2′-H), 5.84 (m, 1 H, 2′′-H) ppm. ^{13}C NMR (100.6 MHz): δ = 22.6 (2×CH_2, 3-C + 5-C), 25.6 (CH_2, 4-C), 34.7 (2×CH_2, 2-C + 6-C), 38.6 (CH_2, 1′-C), 47.0 (CH_2, 1′′-C), 51.9 (CH_3, OMe), 61.7 (C, 1-C), 114.9 (CH_2, 3′-C or 3′′-C), 117.5 (CH_2, 3′-C or 3′′-C), 134.6 (CH, 2′-C), 137.5 (CH, 2′′-C), 156.7 (C, CO) ppm. MS (EI, 70 eV): m/z (%) = 237 (5) [M^+], 236 (32) [M^+ – H], 196 (100) [M^+ – $CH_2CH{=}CH_2$]. HRMS (EI, 70 eV): calcd. for $C_{14}H_{23}NO_2$ 237.1729; found 237.1704; calcd. for $C_{14}H_{22}NO_2$ 236.1651; found 236.1662; calcd. for $C_{11}H_{18}NO_2$ 196.1338; found 196.1333. $C_{14}H_{23}NO_2$ (237.34): calcd. C 70.85, H 9.77, N 5.90; found C 70.74, H 9.75, N 5.76.

Methyl 1-Azaspiro[5.5]undec-3-ene-1-carboxylate (25): A catalytic amount (20 mg) of (benzylidene)dichlorobis(tricyclohexylphosphane)ruthenium(II) was added to a solution of diene **24** (90 mg, 0.38 mmol) in dry CH_2Cl_2 (5 mL), and the reaction mixture was heated under reflux for 2 h. It was then poured into a saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. The organic layer was dried and concentrated as usual, and the residue was purified by column chromatography on silica gel (hexanes/EtOAc, 90:10) to afford the azaspiro compound **25** (74 mg, 94%) as a syrup. IR ($CHCl_3$): $\tilde{\nu}$ = 1696.1 cm^{-1}. ^1H NMR (500 MHz): δ = 1.25–1.40 (m, 3 H, 7-H_a + 11-H_a + 9-H_a), 1.40–1.70 (m, 5 H, 9-H_b + 8-H_2 + 10-H_2), 2.13 (m, 2 H, 5-H_2), 2.52 (m, 2 H, 7-H_b + 11-H_b), 3.64 (s, 3 H, OMe), 4.00 (dd, J = 2.5, 2.5 Hz, 2 H, 2-H_2), 5.66 (m, 1 H, 3-H or 4-H), 5.70 (m, 1 H, 3-H or 4-H) ppm. ^{13}C NMR (100.6 MHz): δ = 22.5 (2×CH_2, 8-C + 10-C), 26.3 (CH_2, 9-C), 35.3 (2×CH_2, 7-C + 11-C), 36.0 (CH_2, 5-C), 43.4 (CH_2, 2-C), 51.9 (CH_3, OMe), 57.2 (C, 6-C), 125.0 (CH, 3-C or 4-C), 125.2 (CH, 3-C or 4-C), 156.6 (C, CO) ppm. MS (EI, 70 eV): m/z (%) = 209 (92) [M^+], 194 (30) [M^+ – Me], 166 (100) [M^+ – H – $CH_2CH_2CH_2$]. HRMS (EI, 70 eV): calcd. for $C_{12}H_{19}NO_2$ 209.1416; found 209.1405; calcd. for $C_{11}H_{16}NO_2$ 194.1181; found 194.1209; calcd. for $C_9H_{12}NO_2$ 166.0868; found 166.0866. $C_{12}H_{19}NO_2$ (209.29): calcd. C 68.87, H 9.15, N 6.69; found C 68.90, H 9.47, N 7.05.

4-[(Trimethylsilyl)methyl]-3-oxa-1-azaspiro[5.5]undecan-2-one (28): General decarboxylation/alkylation procedure (61%). White solid; m.p. 139.6–141.4 °C (from EtOAc/*n*-hexane). IR ($CHCl_3$): $\tilde{\nu}$ = 3427, 1691 cm^{-1}. ^1H NMR (500 MHz): δ = 0.07 (s, 9 H, $SiMe_3$), 0.92 (dd, J = 8.2, 14.5 Hz, 1 H, CH_aH$_b$TMS), 1.18 (dd, J = 6.4, 14.5 Hz, 1 H, CH$_a$$H_b$TMS), 1.40–1.70 (m, 11 H), 1.97 (d, J = 14 Hz, 1 H), 4.41 (m, 1 H, 4-H, CHO), 5.78 (br. s, 1 H, NH) ppm. ^{13}C NMR (100.6 MHz): δ = –0.9 [3×CH_3, $Si(CH_3)_3$], 21.9 (2×CH_2, 8-C + 10-C), 24.1 (CH_2, CH$_2$TMS), 25.1 (CH_2, 9-C), 37.8 (CH_2, 5-C or 7-C or 11-C), 40.2 (CH_2, 5-C or 7-C or 11-C), 40.5 (CH_2, 5-C or 7-C or 11-C), 52.6 (C, 6-C), 72.6 (CH, 4-C), 154.8 (C, CO) ppm. MS (EI, 70 eV): m/z (%) = 255 (11) [M^+], 240 (5) [M^+ – CH_3], 214 (49) [M^+ – $CH_2CH{=}CH_2$], 168 (100) [M^+ – H – CO_2 – $CH_2CH_2CH_2$]. HRMS (EI, 70 eV): calcd. for $C_{13}H_{25}NO_2Si$ 255.1655; found 255.1710; calcd. for $C_{12}H_{22}NO_2Si$ 240.1439; found 240.1438; calcd. for $C_{10}H_{20}NO_2Si$ 214.1263; found 214.1324; calcd. for $C_9H_{18}NSi$ 168.1209; found 168.1206. $C_{13}H_{25}NO_2Si$ (255.43): calcd. C 61.13, H 9.87, N 5.48; found C 60.97, H 10.22, N 5.23.

Methyl 3,4-Dimethyl-1-azaspiro[5.5]undec-3-ene-1-carboxylate (29): DIB (805 mg, 2.5 mmol) and iodine (127 mg, 0.5 mmol) were added to a solution of acid **21** (200 mg, 1.0 mmol) in dry CH_2Cl_2 (15 mL) under nitrogen. The reaction mixture was stirred at room temperature in sunlight for 2 h. Afterwards, it was cooled to 0 °C and 2,3-dimethylbutadiene (1.13 mL, 0.82 g, 10 mmol) and $BF_3{\cdot}OEt_2$ (0.25 mL, 0.28 g, 1.97 mmol) were added dropwise. The reaction mixture was allowed to reach room temperature and was stirred for another 4 h. It was then poured into an aqueous 10% sodium thiosulfate ($Na_2S_2O_3$)/saturated $NaHCO_3$ solution and extracted with CH_2Cl_2. The organic layer was dried and concentrated as usual and the residue was purified by chromatography on silica gel (hexanes/EtOAc, 98:2) to yield the azaspiro compound **29** (99 mg, 42%) as a syrup. IR ($CHCl_3$): $\tilde{\nu}$ = 1697 cm^{-1}. ^1H NMR (500 MHz): δ = 1.29 (m, 2 H, 7-H_a + 11-H_a), 1.47 (m, 6 H, 8-H_2 + 9-H_2 + 10-H_2), 1.59 (s, 3 H, Me_a-C=), 1.62 (s, 3 H, Me_b-C=), 2.05 (s, 2 H, CCH_2C=), 2.45 (m, 2 H, 7-H_b + 11-H_b), 3.61 (s, 3 H, OMe), 3.79 (br. s, 2 H, 2-H_2, NCH_2C=) ppm. ^{13}C NMR (125.7 MHz): δ = 15.9 (CH_3), 18.9 (CH_3), 22.8 (2×CH_2, 8-C + 10-C), 26.0 (CH_2, 9-C), 34.6 (2×CH_2, 7-C + 11-C), 41.2 (CH_2, 5-C, CCH_2C=), 47.7 (CH_2, 2-C, NCH_2C=), 51.9 (CH_3, OMe), 57.8 (C, 6-C), 124.1 (C, 3-C or 4-C), 124.7 (C, 3-C or 4-C), 156.3 (C, CO) ppm. MS (EI, 70 eV): m/z (%) = 237 (100) [M^+], 222 (32) [M^+ – Me]. HRMS (EI, 70 eV): calcd. for $C_{14}H_{23}NO_2$ 237.1729; found 237.1736; calcd. for $C_{13}H_{20}NO_2$ 222.1494; found 222.1496. $C_{14}H_{23}NO_2$ (237.34): calcd. C 70.85, H 9.77, N 5.90; found C 70.86, H 10.01, N 6.03.

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[1] For recent reviews on alkaloids, see: a) P. Laurent, J. C. Braekman, D. Daloze, J. Pasteels, *Eur. J. Org. Chem.* **2003**, 2733–2734; b) S. M. Weinreb, *Acc. Chem. Res.* **2003**, *36*, 59–60; c) R. M. Williams, R. J. Cox, *Acc. Chem. Res.* **2003**, *36*, 127–139; d) J. P. Michael, *Nat. Prod. Rep.* **2004**, *21*, 650–688; e) J. R. Lidell, *Nat. Prod. Rep.* **2002**, *19*, 773–781. See also: f) A. Elbein, R. I. Molyneux, in *The Alkaloids, Chemical and Biological Perspectives* (Ed.: S. W. Pelletier), Wiley, New York, **1990**, vol. 5, pp. 1–54.

[2] a) J. P. Michael, *Nat. Prod. Rep.* **2004**, *21*, 625–649; b) V. H. Lillelund, H. H. Jensen, X. Laing, M. Bols, *Chem. Rev.* **2002**, *102*, 515–553; c) J. P. Michael, "Simple Indolizidine and Quinolizidine Alkaloids", in *The Alkaloids, Chemistry and Pharmacology* (Ed.: G. Cordell), Academic Press, New York, **2001**, vol. 55, pp. 91–258; d) N. Asano, R. J. Nash, R. J. Molyneux, G. W. J. Fleet, *Tetrahedron: Asymmetry* **2000**, *11*, 1645–1680; e) D. L. Zechel, S. G. Withers, *Acc. Chem. Res.* **2000**, *33*, 11–18; f) A. El Nemr, *Tetrahedron* **2000**, *56*, 8579–8629, and references cited therein.

[3] For articles on ipalbidine and synthetic analogues, see: a) T. Honda, H. Namiki, H. Nagase, H. Mizutani, *Tetrahedron Lett.* **2003**, *44*, 3035–3038; b) M. Ikeda, J. Shikaura, N. Maekawa, K. Daibuzono, H. Teranishi, Y. Teraoka, N. Oda, H. Ishibashi, *Heterocycles* **1999**, *50*, 31–34; c) C. Vogel, S. J. Danishefsky, *J. Org. Chem.* **1986**, *51*, 3915–3916, and references cited therein.

[4] Histrionicotoxin: a) C. J. Smith, A. B. Holmes, N. J. Press, *Chem. Commun.* **2002**, 1214–1215; b) E. C. Davidson, M. E. Fox, A. B. Holmes, S. D. Roughley, C. J. Smith, G. M. Williams, J. E. Davies, P. R. Raithby, J. P. Adams, I. T. Forbes, N. J. Press, M. Thompson, *J. Chem. Soc., Perkin Trans. 1* **2002**, 1494–1514, and references cited therein.

[5] a) A. Boto, R. Hernández, E. Suárez, *J. Org. Chem.* **2001**, *66*, 7796–7803; b) A. Boto, R. Hernández, E. Suárez, *Tetrahedron Lett.* **2000**, *41*, 2495–2498; c) A. Boto, R. Hernández, E. Suárez, *Tetrahedron Lett.* **2000**, *41*, 2899–2902; d) A. Boto, R. Hernández, E. Suárez, *J. Org. Chem.* **2000**, *65*, 4930–4937, and references cited therein.

[6] For reviews concerning acyliminium ions, see: a) J. Royer, M. Bonin, L. Micouin, *Chem. Rev.* **2004**, *104*, 2311–2352; b) A. Padwa, S. K. Bur, D. M. Danca, J. D. Ginn, S. M. Lynch, *Synlett* **2002**, 851–862; c) W. N. Speckamp, M. J. Moolenaar, *Tetrahedron* **2000**, *56*, 3817–3856; d) A. Padwa, *Chem. Commun.* **1998**, 1417–1424; e) M. Arend, B. Westermann, N. Risch, *Angew. Chem. Int. Ed.* **1998**, *37*, 1045–1070; f) J. Utley, *Chem. Soc. Rev.* **1997**, *26*, 157–167; g) H. De Koning, M. J. Moolenaar, H. Hiemstra, W. N. Speckamp, in *Studies in Natural Products Chemistry* (Ed.: Atta-ur-Rahman), Elservier, Amsterdam, **1993**, vol. 13, pp. 473–518; h) H. Hiemstra, W. N. Speckamp, in *Comprehensive Organic Chemistry* (Eds.: B. M. Trost, I. Fleming), Pergamon Press, Oxford, **1991**, vol. 2, pp. 1047–1082; i) L. E. Overman, D. J. Ricca, in *Comprehensive Organic Chemistry* (Eds.: B. M. Trost, I. Fleming), Pergamon Press, Oxford, **1991**, vol. 2, pp. 1007–1046; j) H. De Koning, W. N. Speckamp, in *The Alkaloids* (Ed.: A. Brossi), Academic Press, New York, **1988**; vol. 32, pp. 271–339; k) D. J. Hart, in *The Alkaloids: Chemical and Biological Perspective* (Ed.: S. W. Pelletier), Wiley, New York, **1988**, vol. 6, pp. 227–296.

[7] a) Indolizidines: C. A. Tarling, A. B. Holmes, R. E. Markwell, N. D. Pearson, *J. Chem. Soc., Perkin Trans. 1* **1999**, 1695–1702; b) M. D. Groaning, A. I. Meyers, *Chem. Commun.* **2000**, 1027–1028.

[8] For reviews on the manzamine alkaloids, see: a) J. F. Hu, M. T. Hamann, R. Hill, M. Kelly, *The Alkaloids* **2003**, *60*, 207–285; b) E. Magnier, Y. Langlois, *Tetrahedron* **1998**, *54*, 6201–6258. For other articles on this bicyclic system, see: c) P. G. Reddy, B. Verghese, S. Baakaran, *Org. Lett.* **2003**, *5*, 583–586; d) W. H. Pearson, D. A. Hutta, W.-K. Fang, *J. Org. Chem.* **2000**, *65*, 8326–8332; e) L. Manzoni, L. Belvisi, C. Scolastico, *Synlett* **2000**, 1287–1288; f) L. M. Beal, K. D. Moeller, *Tetrahedron Lett.* **1998**, *39*, 4639–4642; g) G. L. Milligan, C. J. Mossman, J. Aubé, *J. Am. Chem. Soc.* **1995**, *117*, 10449–10495; h) H. E. Schoemaker, T.-J. Boer-Terpstra, J. Dijkink, W. N. Speckamp, *Tetrahedron* **1980**, *36*, 143–148.

[9] a) For reviews which detail the biological activities (including antitumoural activity) of these alkaloids, see: I. R. C. Bick, W. Sinchai, in *The Alkaloids* (Ed.: R. H. F. Manske), Academic Press, New York, **1981**, vol XIX, chapter 3; b) M. Suffness, G. A. Cordell, in *The Alkaloids* (Ed.: A. Brossi), Academic Press, Orlando, **1985**, vol. 25, pp. 3–355.

[10] Tyloforine: S. Lebrun, A. Couture, E. Deniau, P. Grandclaudon, *Tetrahedron* **1999**, *55*, 2659–2670.

[11] Phenylacetylproline (**12**): a) D. J. Abraham, D. M. Gazze, P. E. Kennedy, M. Mokotoff, *J. Med. Chem.* **1984**, *27*, 1549–1559; b) T. A. Gudasheva, T. A. Voronina, R. U. Ostrovskaya, N. I. Zaitseva, N. A. Bondarenko, V. K. Briling, L. S. Asmakova, G. G. Rozantsev, S. B. Seredenin, *J. Med. Chem.* **1998**, *41*, 284–290; c) N. Balasubramanian, D. R. StLaurent, M. E. Federici, N. A. Meanwell, J. J. Wright, W. A. Schumacher, S. M. Seilar, *J. Med. Chem.* **1993**, *36*, 300–303; d) F. R. Pfeiffer, P. A. Chambers, E. E. Hilbert, P. W. Woodward, D. M. Ackermann, *J. Med. Chem.* **1984**, *27*, 325–341.

[12] For articles on septicine and synthetic analogues, see: a) V. M. Sharma, K. V. A. Seshu, C. V. Krishna, P. Prasanna, V. C. Sekhar, A. Venkateswarlu, S. Rajagopal, R. Ajaykumar, D. S. Deevi, N. V. S. Rao-Mamidi, R. Rajagopalan, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1679–1682; b) A. Padwa, S. M. Sheehan, C. S. Staub, *J. Org. Chem.* **1999**, *64*, 86–95; c) H. J. Kim, U. C. Yoon, Y.-S. Jung, N. S. Park, E. M. Cederstrom, P. S. Mariano, *J. Org. Chem.* **1998**, *63*, 860–863; d) S.-K. Kim, E. Cederstrom, D. C. Ferri, P. S. Mariano, *Tetrahedron* **1996**, *52*, 3195–3222; e) B. R. Verxa, K. Yang, H. W. Moore, *Tetrahedron* **1994**, *50*, 6173–6180; f) See also: H. Iida, Y. Watanabe, M. Tanaka, C. Kibayashi, *J. Org. Chem.* **1984**, *49*, 2412–2418; g) T. F. Buckley, H. Rapoport, *J. Org. Chem.* **1983**, *48*, 4222–4232; h) N. A. Khatri, H. F. Schmitthenner, J. Shringarpure, S. M. Weinreb, *J. Am. Chem. Soc.* **1981**, *103*, 6387–6393; i) D. W. Bhakuni, V. Mangla, *Tetrahedron* **1981**, *37*, 401–407; j) T. Iwashita, M. Suzuki, T. Kusumi, H. Kakisawa, *Chem. Lett.* **1980**, 383–386; k) T. R. Govindachari, N. Viswanathan, *Tetrahedron* **1970**, *26*, 715–719.

[13] Selected experimental coupling constants for compound **17** are $J_{2,2'}$ = 4.5 Hz, and $J_{2,3}$ = 4.7, 8.2 Hz, and for compound **18** $J_{2,2'}$ = 6.0 Hz, and $J_{2,3}$ = 6.1, 7.5 Hz. The *J* values were also calculated for the minimum-energy conformations of both diastereomers. For instance, the coupling constants for the (2*R*,2′*R*) diastereomer are $J_{2,2'}$ = 3.6 Hz, and $J_{2,3}$ = 6.5, 10.7 Hz, and for the (2*R*, 2′*S*) diastereomer $J_{2,2'}$ = 11.1 Hz, and $J_{2,3}$ = 8.0, 9.1 Hz. It must be taken into account that free rotation around the C2–C2′ bond is possible, and hence the experimental constants may not completely match those calculated for the minimum-energy conformations.

[14] Theoretical coupling constants were calculated over the minimised structures (MMFF force field) for all possible isomers, by using the Karplus–Altona equation implemented in the Macromodel 7.0 program. See: C. A. G. Haasnoot, F. A. A. M. de Leeuw, C. Altona, *Tetrahedron* **1980**, *36*, 2783–2792.

[15] The elemental analysis of the mixture and the elemental analysis of the pure tricyclic compound **19** corresponded to an empirical formula $C_{18}H_{21}NO$. The ^{13}C NMR spectrum of the mixture resembles that of compound **19**, and shows olefinic

(C) signals corresponding either to another diastereomer or to double-bond position isomers. The estimated 81% yield was calculated from the weight of the mixture isolated after column chromatography.

[16] The experimental coupling constants for compound (±)-**19** were $J_{10a,10b}$ = 10.9 Hz and $J_{10b,1}$ = 5.6, 11.7 Hz. The *J* values were also calculated for the minimum-energy conformations of the possible diastereomers, and were $J_{10a,10b}$ = 11.0 Hz and $J_{10b,1}$ = 5.6, 11.3 Hz for the (10a*S**,10b*R**) isomer, and $J_{10a,10b}$ = 5.3 Hz and $J_{10b,1}$ = 5.1, 11.6 Hz for the (10a*R**,10b*R**) diastereomer.

[17] Immunosuppressant TAN1251C: a) M. Ousmer, N. A. Braun, C. Bavoux, M. Perrin, M. A. Ciufolini, *J. Am. Chem. Soc.* **2001**, *123*, 7534–7538, and references cited therein; b) H. Suzuki, N. Yamazaki, C. Kibayashi, *Tetrahedron Lett.* **2001**, *42*, 3013–3015; c) K. M. Brummond, J. Lu, *Org. Lett.* **2001**, *3*, 1347–1349; d) D. J. Wardrop, W. Zhang, *Org. Lett.* **2001**, *3*, 2353–2356, and references cited therein.

[18] Pinnaic acids: a) T. Huxford, N. A. Simpkins, *Synlett* **2004**, 2295–2298; b) I. Hayakawa, H. Arimoto, D. Uemura, *Heterocycles* **2003**, *59*, 441–444; c) J. D. White, P. R. Blakemore, E. A. Korf, A. F. T. Yokochi, *Org. Lett.* **2001**, *3*, 413–415; d) M. W. Carson, G. Kim, S. J. Danishefsky, *Angew. Chem. Int. Ed.* **2001**, *40*, 4453–4456; e) M. W. Carson, G. Kim, M. F. Hentemann, D. Trauner, S. J. Danishefsky, *Angew. Chem. Int. Ed.* **2001**, *40*, 4450–4452. For a related compound, halichlorine, see: f) R. A. Stockman, A. Sinclair, L. G. Arini, P. Szeto, D. L. Hughes, *J. Org. Chem.* **2004**, *69*, 1598–1602; g) D. Trauner, S. J. Danishefsky, *Tetrahedron Lett.* **1999**, *40*, 6513–6516.

[19] For antitumourals from the cephalotaxine family, see: a) Y. Koseki, H. Sato, Y. Watanabe, T. Nagasaka, *Org. Lett.* **2002**, *4*, 885–888; b) K. I. Booker-Milburn, L. F. Dudin, C. E. Anson, S. D. Guile, *Org. Lett.* **2001**, *3*, 3005–3008; c) L. F. Tietze, H. Schirok, *J. Am. Chem. Soc.* **1999**, *121*, 10264–10269.

[20] For other interesting examples, see: a) T. J. Greshock, R. L. Funk, *Org. Lett.* **2001**, *3*, 3511–3514, and references cited therein; b) P. Sun, C. Sun, S. M. Weinreb, *Org. Lett.* **2001**, *3*, 3507–3510; c) W. H. Pearson, Y. Mi, I. Young-Lee, P. Stoy, *J. Am. Chem. Soc.* **2001**, *123*, 6724–6725; d) D. Kim, P. J. Shim, J. Lee, C. W. Park, S. W. Hong, S. Kim, *J. Org. Chem.* **2000**, *65*, 4864–4870, and references cited therein; e) G. M. Williams, S. D. Roughley, J. E. Davies, A. B. Holmes, *J. Am. Chem. Soc.* **1999**, *121*, 4900–4901; f) S. P. Tanis, M. V. Deaton, L. A. Dixon, M. C. McMills, J. W. Raggon, M. A. Collins, *J. Org. Chem.* **1998**, *63*, 6914–6928.

[21] Acid **21**: S. Elmore, *Biochem. J.* **1965**, *94*, 563–564.

[22] For a good summary on the generation of tertiary acyliminium ions and related problems, see: a) L. Ollero, G. Mentink, F. P. T. J. Rutjes, W. N. Speckamp, H. Hiemstra, *Org. Lett.* **1999**, *1*, 1331–1334, and references cited therein. For recent applications of tertiary acyliminium ions in synthesis see: b) S. M. Allin, C. I. Thomas, J. E. Allard, M. Duncton, M. R. J. Elsegood, M. Edgar, *Tetrahedron Lett.* **2003**, *44*, 2335–2338; c) P. D. Bailey, K. M. Morgan, D. I. Smith, J. M. Vernon, *Tetrahedron* **2003**, *59*, 3369–3378; d) R. Malassene, E. Vanquelef, L. Toupet, J.-P. Hurvois, C. Moinet, *Org. Biomol. Chem.* **2003**, *1*, 547–551; e) A. Padwa, *Synlett* **2002**, 851–862; f) L. Planas, J. Pérard-Viret, J. Royer, M. Selkti, A. Thomas, *Synlett* **2002**, 1629–1632; g) E. Lete, N. Sotomayor, *Synlett* **2002**, 593–597; h) D. G. Vaidya, S. L. James, J. E. Allard, T. A. D. Smith, V. McKee, W. P. Martin, *Tetrahedron Lett.* **2002**, *43*, 3661–3664; i) C. M. Schuch, R. A. Pilli, *Tetrahedron: Asymmetry* **2000**, *11*, 753–764; j) S.-H. Kim, J. K. Cha, *Synthesis* **2000**, 2113–2116.

[23] Acid **26**: a) M. P. Paradisi, I. Torrini, G. P. Zecchini, G. Lucente, E. Gavuzzo, F. Mazza, G. Pochetti, *Tetrahedron* **1995**, *51*, 2379–2386; b) C. A. Fink, Y. Quiao, C. J. Berry, Y. Sakane, R. D. Ghai, A. J. Trapani, *J. Med. Chem.* **1995**, *38*, 5023–5030; c) A. Breveglieri, R. Guerrini, S. Salvadori, C. Bianchi, S. D. Bryant, M. Attila, L. H. Lazarus, *J. Med. Chem.* **1996**, *39*, 773–780; d) P. Hanson, G. Millhauser, F. Formaggio, M. Crisma, C. Toniolo, *J. Am. Chem. Soc.* **1996**, *118*, 7618–7625; e) S. Palacin, D. N. Chin, E. E. Simanek, J. C. McDonald, G. M. Whitesides, M. T. McBride, G. T. R. Palmore, *J. Am. Chem. Soc.* **1997**, *119*, 11807–11816; f) M. C. Evans, A. Pradhan, S. Venkatraman, W. H. Ojala, W. B. Gleason, R. K. Mishra, R. L. Johnson, *J. Med. Chem.* **1999**, *42*, 1441–1447; g) Z.-J. Yao, C. R. King, T. Cao, J. Kelley, G. W. A. Milne, J. H. Voigt, T. R. Burke, *J. Med. Chem.* **1999**, *42*, 25–35.

[24] C. Agami, F. Couty, *Tetrahedron* **2002**, *58*, 2701–2724.

[25] For a review on the aza-Diels–Alder reaction, see: D. L. Boger, S. N. Weinreb, *Hetero Diels–Alder Methodology in Organic Synthesis*, Academic, New York, **1987**.

[26] For recent articles on the aza-Diels–Alder reaction see: a) K. Makino, Y. Henmi, M. Terasawa, O. Hara, Y. Hamada, *Tetrahedron Lett.* **2005**, *46*, 555–558; b) O. G. Mancheño, R. G. Arrayás, J. C. Carretero, *J. Am. Chem. Soc.* **2004**, *126*, 456–457; c) A. Trifonova, P. G. Andersson, *Tetrahedron: Asymmetry* **2004**, *15*, 445–452; d) A. B. García, C. Valdés, M. P. Labal, *Tetrahedron Lett.* **2004**, *45*, 4357–4360; e) B. Alcaide, P. Almendros, J. M. Alonso, M. F. Aly, *Chem. Eur. J.* **2003**, *9*, 3415–3426; f) S. S. P. Chou, H.-C. Chiu, C.-C. Hung, *Tetrahedron Lett.* **2003**, *44*, 4653–4655; g) M. Shi, L. X. Shao, B. Xu, *Org. Lett.* **2003**, *5*, 579–582; h) J. Barluenga, C. Mateos, F. Aznar, C. Valdés, *Org. Lett.* **2002**, *4*, 1971–1974; i) P. D. Bailey, P. D. Smith, F. Pederson, W. Clegg, G. M. Rosair, S. J. Teat, *Tetrahedron Lett.* **2002**, *43*, 1067–1070; j) P. D. Bailey, P. D. Smith, K. M. Morgan, G. M. Rosair, *Tetrahedron Lett.* **2002**, *43*, 1071–1074; k) J. K. Ekegreen, S. A. Modin, D. A. Alonso, P. G. Andersson, *Tetrahedron: Asymmetry* **2002**, *13*, 447–449; l) K. Wojciechowski, S. Kosinski, *Eur. J. Org. Chem.* **2002**, 947–954; m) Y. Yuan, X. Li, K. Ding, *Org. Lett.* **2002**, *4*, 3309–3311; n) H. Mayr, A. R. Ofial, J. Sauer, B. Schmied, *Eur. J. Org. Chem.* **2000**, 2013–2020; o) S. Yao, S. Saaby, R. G. Hazell, K. A. Jørgensen, *Chem. Eur. J.* **2000**, *6*, 2435–2448; p) H. Steinhagen, E. J. Corey, *Angew. Chem. Int. Ed.* **1999**, *38*, 1928–1931; q) S. Yao, M. Johannsen, R. G. Hazell, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **1998**, *37*, 3121–3124; r) S. Kobayashi, S. Komiyama, H. Ishitani, *Angew. Chem. Int. Ed.* **1998**, *37*, 979–981; s) H. Waldman, *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 274–275.

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