

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

Alicia Boto,^{*[a]} Yolanda De León,^[a] Juan Antonio Gallardo,^[a] and Rosendo Hernández^{*[a]}

Keywords: Alkaloids / Amino acids / Nitrogen heterocycles / Radical reactions / Spiro compounds

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.

(© Wiley-VCH Verlag GmbH & Co. KGaA, 69451 Weinheim, Germany, 2005)

Introduction

Alkaloids have attracted a much interest both from the synthetic and the pharmacological standpoints.^[1] The anti-tumour 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]

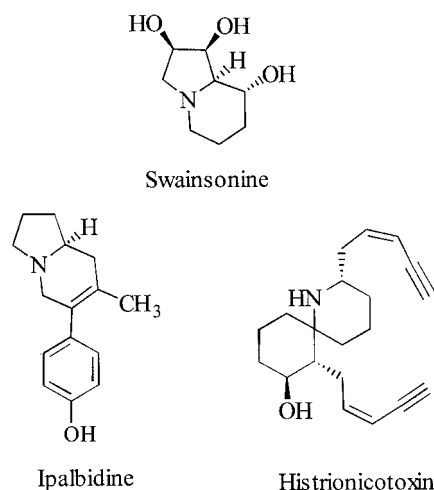
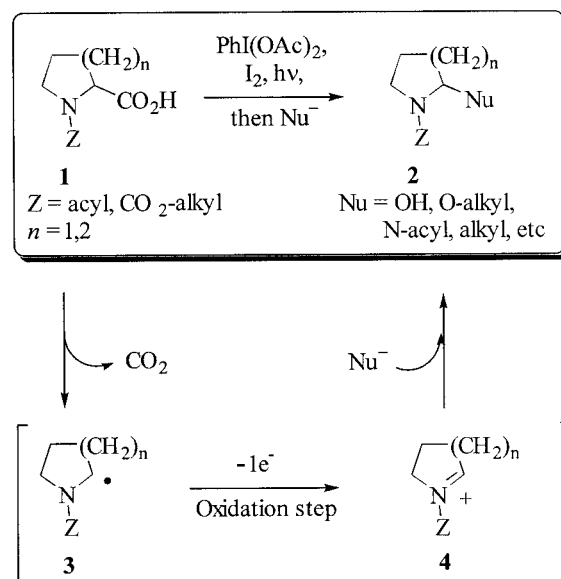


Figure 1. Bioactive alkaloids.

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 ($\text{Nu} = \text{alkyl}$) as the key step is reported herein.

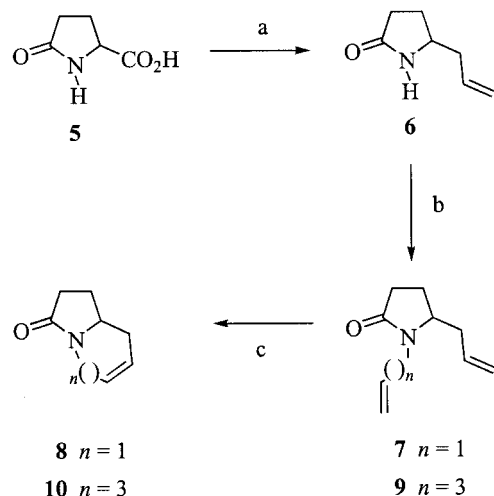
Results and Discussion

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

[a] Instituto de Productos Naturales y Agrobiología CSIC, Avda. Astrofísico Francisco Sánchez 3, 38206 La Laguna, Tenerife, Spain
Fax: +34-922-260-135
E-mail: alicia@ipna.csic.es
rhernandez@ipna.csic.es

(such as swainsonine, Figure 1) are potent glycosidase inhibitors and possess antitumoural, antiviral or hypoglycaemic 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.



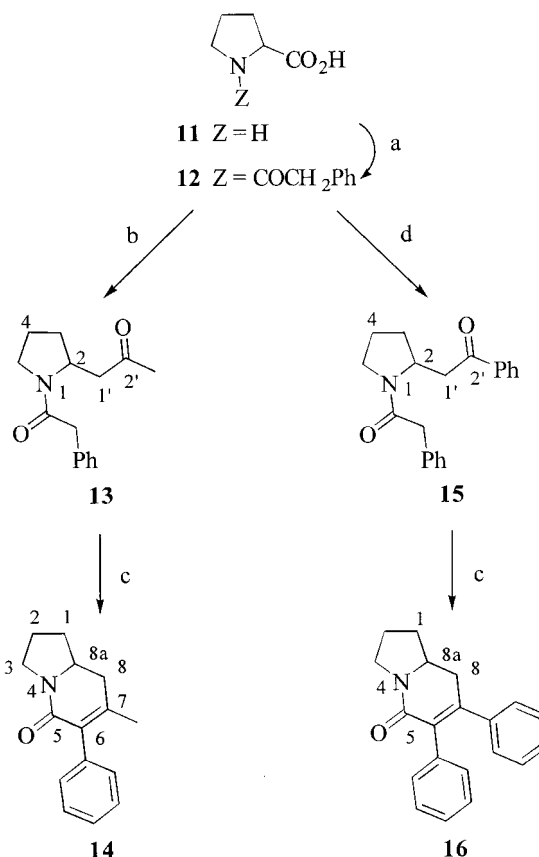
Scheme 2. Synthesis of analogues of indolizidine alkaloids. Reagents and conditions: (a) DIB, I₂, CH₂Cl₂, 3 h; then BF₃·OEt₂, allylTMS, 0 °C to room temp., 4 h, 81%; (b) NaH, DMF, 0 °C, 0.5 h; then CH₂=CHCH₂Br or CH₂=CHCH₂CH₂Br, 67% for **7**, 63% for **9**; (c) (benzylidene)dichlorobis(tricyclohexylphosphane) ruthenium(II) (cat.), CH₂Cl₂, reflux, 80% for **8**, 81% for **10**.

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/I₂, followed by addition of boron trifluoride–diethyl ether and isopropenyl acetate to give the (±)-norhygrine derivative **13** in good

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

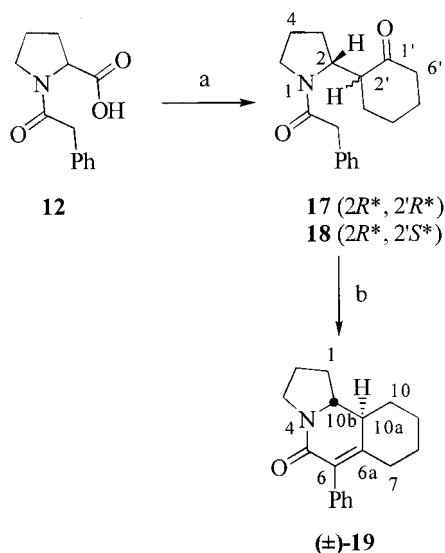


Scheme 3. Synthesis of ipalbidine and septicine analogues. Reagents and conditions: (a) ClCOCH₂Ph, THF/NaHCO₃ (aq. satd.), room temp., 10 h, 76%; (b) DIB, I₂, CH₂Cl₂, 3 h; then BF₃·OEt₂, isopropenyl acetate, 0 °C to room temp., 4 h, 58%; (c) *t*BuOK, *t*BuOH, reflux, 12 h, 99% for **14**, 82% for **16**; (d) DIB, I₂, CH₂Cl₂, 3 h; then BF₃·OEt₂, PhC(OTMS)=CH₂, 0 °C to room temp., 4 h, 50%.

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/I₂, 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 $\text{BF}_3 \cdot \text{OEt}_2$, 1-(trimethylsilyloxy)cyclohexene, 0°C to room temp., 4 h, 68%, (**17/18** = 3:2); (b) $t\text{BuOK}$, $t\text{BuOH}$, 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 ^1H NMR spectra,^[13,14] the ($2R^*, 2'R^*$) configuration was tentatively assigned to the major product **17**, and the ($2R^*, 2'S^*$) 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 ($\pm$)-**19** could be isolated (21%).

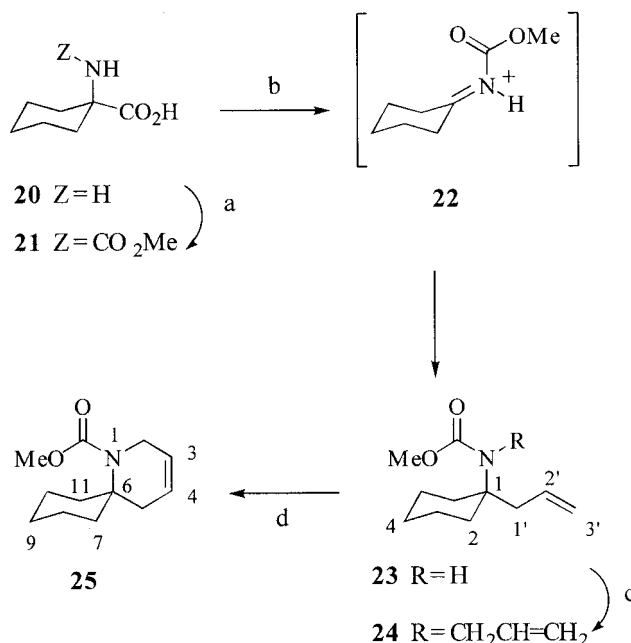
The ($10aS^*, 10bR^*$) configuration was assigned to product **19** according to the coupling constants observed in the ^1H NMR spectrum, and by comparison with the J values calculated for the minimum-energy conformations of the possible diastereomers.^[14,16]

The formation of compound ($\pm$)-**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/alkylation conditions to generate the tertiary N -acyliminium ion **22**, which reacted with the nucleophile to give the allyl derivative **23**.



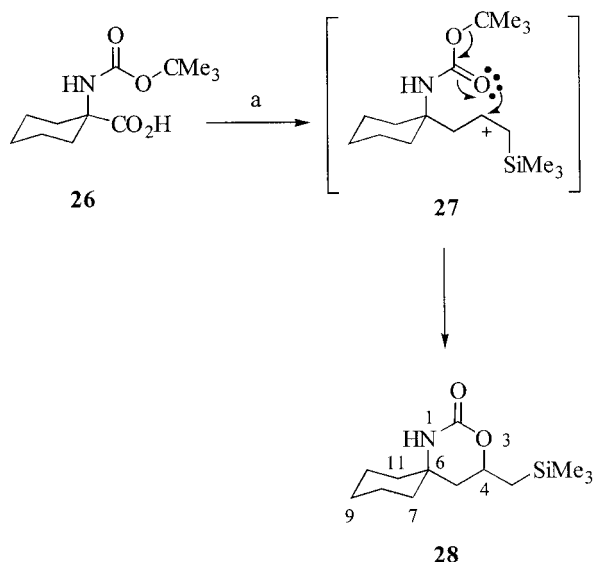
Scheme 5. Synthesis of the azaspirocyclic core. Reagents and conditions: (a) ClCO_2Me , $\text{THF}/\text{NaHCO}_3$ (aq. satd.), room temp., 18 h, 72%; (b) DIB, I_2 , CH_2Cl_2 , room temp., 3 h, then 0°C , allyltrimethylsilane, $\text{BF}_3 \cdot \text{OEt}_2$, 61%; (c) NaH , DMF, 0°C , 1 h, then allyl 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]

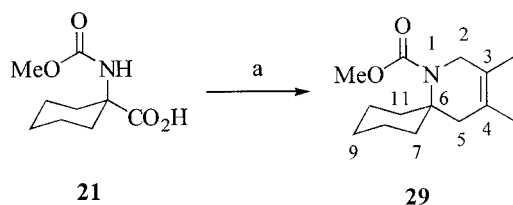
By replacing the nitrogen protecting group, we can alter the reaction outcome and obtain different spirocyclic compounds. Thus, when the methyl carbamate in **21** was replaced by a BOC group (substrate **26**,^[23] Scheme 6), a one-pot decarboxylation/alkylation/cyclisation took place. The reaction 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, I₂, CH₂Cl₂, room temp., 3 h; then 0 °C, allyltrimethylsilane, BF₃·OEt₂, 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, I₂, room temp., 2 h; then 0 °C, 2,3-dimethylbutadiene, BF₃·OEt₂, 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 H₂SO₄/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 CDCl₃ 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 CH₂Cl₂ (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 BF₃·OEt₂ (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 (Na₂S₂O₃)/saturated NaHCO₃ solution and extracted with CH₂Cl₂. The organic layer was washed with brine, dried with Na₂SO₄, 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 I₂ (0.5 equiv.) afforded product **13** (58%) as a syrup. IR (CHCl₃): $\tilde{\nu}$ = 1711 cm⁻¹. ¹H NMR (500 MHz, 70 °C): δ = 1.70 (m, 1 H, 3-H_a), 1.86 (m, 2 H, 4-H₂), 2.02 (m, 1 H, 3-H_b), 2.09 (s, 3 H, CH₃CO), 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-H₂), 3.61 (s, 2 H, CH₂Ph), 4.39 (m, 1 H, 2-H), 7.24 (m, 5 H, arom.) ppm. ¹³C NMR (125.7 MHz, 70 °C): δ = 24.1 (CH₂, 4-C), 30.0 (CH₂, 3-C), 30.4 (CH₃), 42.5 (CH₂, CH₂Ph), 47.1 (CH₂, 1'-C, CH₂CO), 47.3 (CH₂, 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⁺ – COCH₃], 154 (20) [M⁺ – CH₂Ph], 126 (56) [M⁺ – COCH₂Ph], 91 (87) [CH₂Ph], 70 (100) [M⁺ + H – CH₂COCH₃ – COCH₂Ph]. HRMS (EI, 70 eV): calcd. for C₁₅H₁₉NO₂ 245.1416; found 245.1397; calcd. for C₁₃H₁₆NO 202.1232; found 202.1201; calcd. for C₈H₁₂NO₂ 154.0868; found 154.0858; calcd. for C₇H₁₂NO 126.0919; found 126.0911. C₁₅H₁₉NO₂ (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*)-indolizidine (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 (CHCl₃): $\tilde{\nu}$ = 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, CH₃C=), 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. ¹³C NMR (125.7 MHz): δ = 21.4 (CH₃, 7-Me), 23.0 (CH₂, 2-C), 33.7 (CH₂, 1-C), 37.2 (CH₂, 8-C), 44.5 (CH₂, 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)CH₂]. HRMS (EI, 70 eV): calcd. for C₁₅H₁₇NO 227.1310; found 227.1283; calcd. for C₁₁H₁₀O 158.0732; found 158.0745. C₁₅H₁₇NO (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 (CHCl₃): $\tilde{\nu}$ = 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, CH₂H_bCOPh), 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, COCH₂Ph), 3.90 (dd, J = 3.0, 15.0 Hz, 1 H, CH_aH_bCOPh), 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. ¹³C NMR (125.7 MHz): δ = 23.8 (CH₂, 4-C), 29.3 (CH₂, 3-C), 42.1 (CH₂, CH₂COPh), 42.4 (CH₂, COCH₂Ph), 47.2 (CH₂, 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⁺ – COCH₂Ph], 105 (100) [PhCO], 91 (65) [PhCH₂]. HRMS (EI, 70 eV): calcd. for C₂₀H₂₁NO₂ 307.1572; found 307.1585; calcd. for C₁₂H₁₄NO 188.1075; found 188.1091; calcd. for C₇H₅O 105.0340; found 105.0357. C₂₀H₂₁NO₂ (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(1H)-indolizinone (16): The same procedure as reported for compound **17** afforded the indolizinone **16** (82%) as a colourless oil. IR (CHCl₃): $\tilde{\nu}$ = 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. ¹³C NMR (100.6 MHz): δ = 23.2 (CH₂, 2-C), 33.7 (CH₂, 1-C), 37.5 (CH₂, 8-C), 44.7 (CH₂, 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)CH₂]. HRMS (EI, 70 eV): calcd. for C₂₀H₁₉NO 289.1467; found 289.1503; calcd. for C₂₀H₁₈NO 288.1388; found 288.1420; calcd. for C₁₆H₁₂O 220.0888; found 220.0914. C₂₀H₁₉NO (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 (2R*,2'R*)- and (2R*,2'S*)-2'-[1-(Phenylacetyl)-2-pyrrolidinyl]cyclohexanone (17 and 18): The general de-

carboxylation/alkylation procedure with I₂ (0.5 equiv.) afforded a diastereomer mixture of **17** and **18** (3:2; 68%) as orange oil. IR (CHCl₃): $\tilde{\nu}$ = 1703, 1630 cm⁻¹. ¹H NMR (500 MHz, 60 °C): Major diastereomer (2R*,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-H₂ + 5'-H_a + 4'-H₂ + 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'-H₂), 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, CH₂Ph), 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 (2R*,2'S*): δ = 1.56 (m, 1 H, 3'-H_a), 1.50–2.00 (c.s., 8 H, 3-H₂ + 4-H₂ + 5'-H_a + 4'-H₂ + 3'-H_b), 2.24 (m, 1 H, 5'-H_b), 2.41 (m, 2 H, 6'-H₂), 3.06 (ddd, J = 5.8, 5.8, 11.6 Hz, 1 H, 2'-H), 3.56 (m, 2 H, 5-H₂), 3.61 (s, 2 H, CH₂Ph), 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. ¹³C 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 (CH₂, 4-C or 4'-C), 24.7/24.8 (CH₂, 4-C or 4'-C), 26.8/26.9 (CH₂, 3-C or 5'-C or 3'-C), 26.8/27.2 (CH₂, 3-C or 5'-C or 3'-C), 27.4/27.9 (CH₂, 3-C or 5'-C or 3'-C), 41.8/42.5 (CH₂, 6'-C), 42.5/42.8 (CH₂, CH₂Ph), 47.7/48.0 (CH₂, 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⁺ – COCH₂Ph], 91 (92) [CH₂Ph], 70 (100) [M⁺ + H – cyclohexanone – COCH₂Ph]. HRMS (EI, 70 eV): calcd. for C₁₈H₂₃NO₂ 285.1729; found 285.1691; calcd. for C₁₂H₁₄NO 188.1075; found 188.1013; calcd. for C₁₀H₁₆NO 166.1232; found 166.1187; calcd. for C₇H₇ 91.0548; found 91.0498; calcd. for C₄H₈N 70.0657; found 70.0617. C₁₈H₂₃NO₂ (285.39): calcd. C 75.76, H 8.12, N 4.91; found C 75.59, H 8.44, N 4.61.

(10aS*,10bR*)-6-Phenyl-2,3,7,8,9,10,10a,10b-octahydropyrrolo-[2,1-*a*]isoquinoline-5(1H)-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 (CHCl₃): $\tilde{\nu}$ = 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-H₂), 2.05 (m, 3 H, 2-H_b + 10-H₂), 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. ¹³C NMR (100.6 MHz): δ = 22.8 (CH₂, 2-C), 24.3 (CH₂, 8-C), 25.3 (CH₂, 9-C), 30.3 (CH₂, 7-C), 30.8 (CH₂, 10-C), 32.7 (CH₂, 1-C), 42.6 (CH, 10a-C), 44.9 (CH₂, 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 C₁₈H₂₁NO 267.1623; found 267.1635; calcd. for C₁₄H₁₄O 198.1045; found 198.1071. C₁₈H₂₁NO (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 NaHCO₃ 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 (CHCl₃): $\tilde{\nu}$ = 3441, 1723 cm⁻¹. ¹H NMR (500 MHz, CD₃OD): δ = 1.27 (m, 1 H, 4-H_a), 1.49 (m, 4 H, 3-H₂ + 5-H₂), 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. ¹³C NMR (100.6 MHz, CD₃OD): δ = 22.4 (2 × CH₂, 3-C + 5-C), 26.5 (CH₂, 4-C), 33.5 (2 × CH₂, 2-C + 6-C), 52.2 (CH₃, 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 C₈H₁₁NO₃ 169.0739; found 169.0746; calcd. for C₈H₁₄NO₂ 156.1025; found 156.0990. C₉H₁₅NO₄ (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 I₂ (0.5 equiv.) afforded product **23** (61%) as a syrup. IR (CHCl₃): $\tilde{\nu}$ = 3441, 1723, 1509 cm⁻¹. ¹H NMR (400 MHz): δ = 1.15–1.60 (m, 8 H, 2-H_a + 6-H_a + 4-H₂ + 3-H₂ + 5-H₂), 1.93 (m, 2 H, 2-H_b + 6-H_b), 2.44 (d, J = 7.3 Hz, 2 H, CH₂C=C), 3.56 (s, 3 H, OMe), 4.46 (br. s, 1 H, NH), 5.02 (m, 2 H, 3'-H₂), 5.73 (m, 1 H, 2'-H) ppm. ¹³C NMR (100.6 MHz): δ = 21.5 (2 × CH₂, 3-C + 5-C), 25.6 (CH₂, 4-C), 34.7 (2 × CH₂, 2-C + 6-C), 42.5 (CH₂, 1'-C), 51.4 (CH₃, OMe), 54.4 (C, 1-C), 117.9 (CH₂, 3'-C), 133.7 (CH, 2'-C), 155.1 (C, CO) ppm. MS (EI, 70 eV): m/z (%) = 197 (<1) [M⁺], 156 (100) [M⁺ – CH₂CH=CH₂]. HRMS (EI, 70 eV): calcd. for C₁₁H₁₉NO₂ 197.1416; found 197.1455; calcd. for C₈H₁₄NO₂ 156.1025; found 156.1071. C₁₁H₁₉NO₂ (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 μ L, 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 hydrogen carbonate and extracted with Et₂O. 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 (CHCl₃): $\tilde{\nu}$ = 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-H₂ + 5-H₂), 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'-H₂), 3.64 (s, 3 H, OMe), 3.89 (d, J = 5.5 Hz, 2 H, 1''-H₂, NCH₂C=C), 5.03 (m, 4 H, 3'-H₂ + 3''-H₂), 5.70 (m, 1 H, 2'-H), 5.84 (m, 1 H, 2''-H) ppm. ¹³C NMR (100.6 MHz): δ = 22.6 (2 × CH₂, 3-C + 5-C), 25.6 (CH₂, 4-C), 34.7 (2 × CH₂, 2-C + 6-C), 38.6 (CH₂, 1'-C), 47.0 (CH₂, 1''-C), 51.9 (CH₃, OMe), 61.7 (C, 1-C), 114.9 (CH₂, 3'-C or 3''-C), 117.5 (CH₂, 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⁺ – CH₂CH=CH₂]. HRMS (EI, 70 eV): calcd. for C₁₄H₂₃NO₂ 237.1729; found 237.1704; calcd. for C₁₄H₂₂NO₂ 236.1651; found 236.1662; calcd. for C₁₁H₁₈NO₂ 196.1338; found 196.1333. C₁₄H₂₃NO₂ (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 CH₂Cl₂ (5 mL), and the reaction mixture was heated under reflux for 2 h. It was then poured into a saturated aqueous NaHCO₃ solution and extracted with CH₂Cl₂. The or-

ganic 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 (CHCl₃): $\tilde{\nu}$ = 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-H₂ + 10-H₂), 2.13 (m, 2 H, 5-H₂), 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-H₂), 5.66 (m, 1 H, 3-H or 4-H), 5.70 (m, 1 H, 3-H or 4-H) ppm. ¹³C NMR (100.6 MHz): δ = 22.5 (2 × CH₂, 8-C + 10-C), 26.3 (CH₂, 9-C), 35.3 (2 × CH₂, 7-C + 11-C), 36.0 (CH₂, 5-C), 43.4 (CH₂, 2-C), 51.9 (CH₃, 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 – CH₂CH₂CH₂]. HRMS (EI, 70 eV): calcd. for C₁₂H₁₉NO₂ 209.1416; found 209.1405; calcd. for C₁₁H₁₆NO₂ 194.1181; found 194.1209; calcd. for C₉H₁₂NO₂ 166.0868; found 166.0866. C₁₂H₁₉NO₂ (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 (CHCl₃): $\tilde{\nu}$ = 3427, 1691 cm⁻¹. ¹H NMR (500 MHz): δ = 0.07 (s, 9 H, SiMe₃), 0.92 (dd, J = 8.2, 14.5 Hz, 1 H, CH_aH_bTMS), 1.18 (dd, J = 6.4, 14.5 Hz, 1 H, CH_aH_bTMS), 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. ¹³C NMR (100.6 MHz): δ = –0.9 [3 × CH₃, Si(CH₃)₃], 21.9 (2 × CH₂, 8-C + 10-C), 24.1 (CH₂, CH₂TMS), 25.1 (CH₂, 9-C), 37.8 (CH₂, 5-C or 7-C or 11-C), 40.2 (CH₂, 5-C or 7-C or 11-C), 40.5 (CH₂, 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⁺ – CH₃], 214 (49) [M⁺ – CH₂CH=CH₂], 168 (100) [M⁺ – H – CO₂ – CH₂CH₂CH₂]. HRMS (EI, 70 eV): calcd. for C₁₃H₂₅NO₂Si 255.1655; found 255.1710; calcd. for C₁₂H₂₂NO₂Si 240.1439; found 240.1438; calcd. for C₁₀H₂₀NO₂Si 214.1263; found 214.1324; calcd. for C₉H₁₈NSi 168.1209; found 168.1206. C₁₃H₂₅NO₂Si (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 CH₂Cl₂ (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 BF₃·OEt₂ (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 (Na₂S₂O₃)/saturated NaHCO₃ solution and extracted with CH₂Cl₂. 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 (CHCl₃): $\tilde{\nu}$ = 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-H₂ + 9-H₂ + 10-H₂), 1.59 (s, 3 H, Me_a-C=), 1.62 (s, 3 H, Me_b-C=), 2.05 (s, 2 H, CCH₂C=), 2.45 (m, 2 H, 7-H_b + 11-H_b), 3.61 (s, 3 H, OMe), 3.79 (br. s, 2 H, 2-H₂, NCH₂C=) ppm. ¹³C NMR (125.7 MHz): δ = 15.9 (CH₃), 18.9 (CH₃), 22.8 (2 × CH₂, 8-C + 10-C), 26.0 (CH₂, 9-C), 34.6 (2 × CH₂, 7-C + 11-C), 41.2 (CH₂, 5-C, CCH₂C=), 47.7 (CH₂, 2-C, NCH₂C=), 51.9 (CH₃, 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 C₁₄H₂₃NO₂ 237.1729; found 237.1736; calcd. for C₁₃H₂₀NO₂ 222.1494; found 222.1496. C₁₄H₂₃NO₂ (237.34): calcd. C 70.85, H 9.77, N 5.90; found C 70.86, H 10.01, N 6.03.

Acknowledgments

This work was supported by the Research Programmes PPQ2000-0728 and PPQ2003-01379 of the Plan Nacional de Investigación Científica, Desarrollo e Innovación Tecnológica, Dirección General de Investigación, Ministerio de Ciencia y Tecnología, Spain. We also acknowledge financial support from FEDER funds. Y. R. thanks the Gobierno de Canarias for a fellowship. We thank Dr. Ezequiel Quintana Morales for his help with molecular modelling.

- [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] Histronicotoxin: 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), Elsevier, 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 ($\pm$)-**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. Venkattraman, 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. Arayás, 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. Al-mendros, 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.

Received: February 18, 2005
Published Online: June 28, 2005