Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron
Tetrahedron 60 (2004) 1505–1511

Rhodium(II) catalyzed intramolecular insertion of carbenoids derived from 2-pyrrolyl and 3-indolyl α-diazo-β-ketoesters and α-diazoketones

Erick Cuevas-Yañez,[a,*] Joseph M. Muchowski[b] and Raymundo Cruz-Almanza[a,†]

[a]*Instituto de Química, UNAM. Circuito Exterior, Ciudad Universitaria, Coyoacán, 04510 México, DF, Mexico*
[b]*Department of Chemistry, Roche Palo Alto, 3431 Hillview Avenue, Palo Alto, CA 94304-1320, USA*

Received 24 July 2003; revised 8 December 2003; accepted 8 December 2003

Abstract—α-Diazo-β-ketoesters and α-diazoketones derived from 2-pyrrolylacetic, 2-pyrrolylpropionic, 3-indolylacetic and 3-indolylpropionic acids afforded carbenoid derived cyclization products on treatment with catalytic rhodium(II) acetate.

1. Introduction

The first intramolecular carbenoid insertions at C-2 of pyrroles were described by Muchowski, et al.[1] and shortly thereafter by Jefford and coworkers.[2] The Jefford group extensively studied the Rh(II) catalyzed process using α-diazoketones as the carbenoid precursors, demonstrated that it was high yielding process and utilized it to synthesize several naturally occurring indolizine derivatives.[3]

In connection with other projects, we some time ago initiated studies on the insertion of α-keto carbenoids into the C-3H of pyrroles, no examples of which were then known, as well as into the C-2H of indoles. A recent publication of Capretta and Salim,[4] which describes examples of both processes, causes us to disclose our results in this area.

The pyrrolyl α-diazo-β-ketoesters **6** and **7** were generated (ca. 65%) by a diazo transfer reaction on the β-ketoesterers **4** and **5** with *p*-toluenesulfonylazide.[5] These β-ketoesters were obtained when the nitriles **2**[6] and **3** were reacted with excess ethyl bromoacetate and zinc.[7] The pyrrolepropionitrile **3** was obtained by catalytic hydrogenation of the acrylonitrile **1**, which in turn was prepared from 1-methylpyrrole-2-aldehyde and triphenylphosphanylidene acetonitrile.[8]

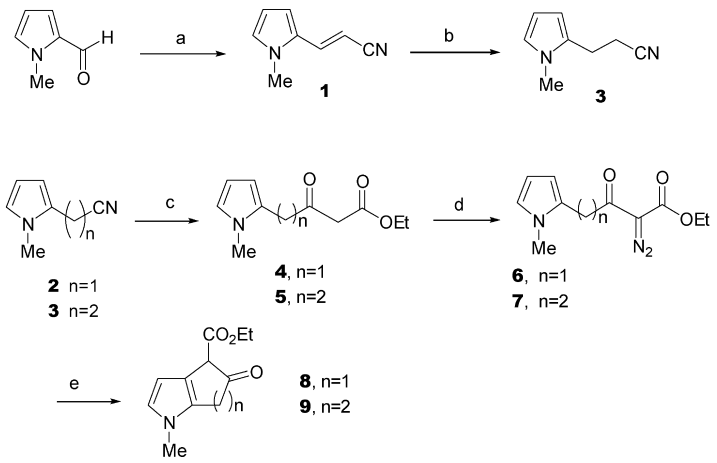
The α-diazo-β-ketoesters **6** and **7** were unaffected by catalytic rhodium(II) acetate in dichloromethane, even at reflux temperature. Conversion of these compounds into the expected bicyclic ketones **8** and **9** did occur, however (ca. 50% yields), in 1,2-dichloroethane at reflux temperature (bp 72 °C in Mexico City). It is not clear what factors control the rate of these reactions given that related β-ketoester carbenoid insertions into aromatic CH bonds are reported to require 1,2-dichloroethane at reflux temperature,[9] whereas others take place at room temperature.[10] It is noteworthy that the cyclization of the carbenoids derived from indoles **10** and **11** also require 1,2-dichloroethane at reflux temperature (see below) (Scheme 1).

The indolyl α-diazo-β-ketoesters **10** and **11** were obtained (ca. 50%) from the acid chlorides of indole-3-acetic and indole-3-propionic acids (oxalyl chloride/−65 °C) and ethyl diazoacetate containing an equivalent of triethylamine using a modification of a procedure described by Bestmann and Kolm.[11] Rhodium(II) catalyzed decomposition of the diazo compounds **10** and **11** ($ClCH_2CH_2Cl$/reflux) generated the anticipated tricyclic ketones **12** (55%) and **13** (52%) as the major products in each case (Scheme 2).

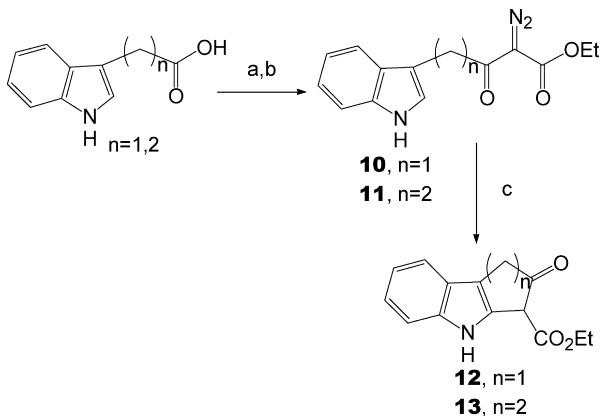
Additionally, some α-diazoketones derived from 2-pyrrolylacetic, 2-pyrrolylpropionic, 3-indolylacetic and 3-indolylpropionic acids were explored. The pyrrole-2-alkanoic acids **17**, **18** and **20** used in this study were prepared by adaptations of literature methodology. Thus, the pyrrole-2-acetic acids **17** and **18** were obtained by alkaline hydrolysis[12] of the nitriles **2** and **16**, which in turn were derived from the ammonium salts of the Mannich bases **14** and **15** and sodium cyanide.[6] Pyrrole-2-propionic acid **20** was obtained by catalytic reduction and subsequent hydrolysis of the acrylate derivative **19**, which was prepared

Keywords: Rhodium carbenoids; α-diazo-β-ketoesters; α-diazoketones; Insertion pyrrol,indol.
* Corresponding author. Tel.: +52-56-224408; fax: +52-56-162217; e-mail address: erick.cuevas@correo.unam.mx
† Deceased on October, 2003.

0040–4020/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.12.019



Scheme 1. *Reagents and conditions*: (a) Ph_3PCHCN, toluene/CH_2Cl_2, reflux, 36 h; (b) H_2, Pd/C, MeOH, RT, 6 h; (c) $BrCH_2CO_2Et$, Zn, THF, reflux, 8 h; (d) TsN_3, Et_3N, CH_2Cl_2, RT, 12 h; (e) $Rh_2(OAc)_4$, $ClCH_2CH_2Cl$, reflux, 3 h.



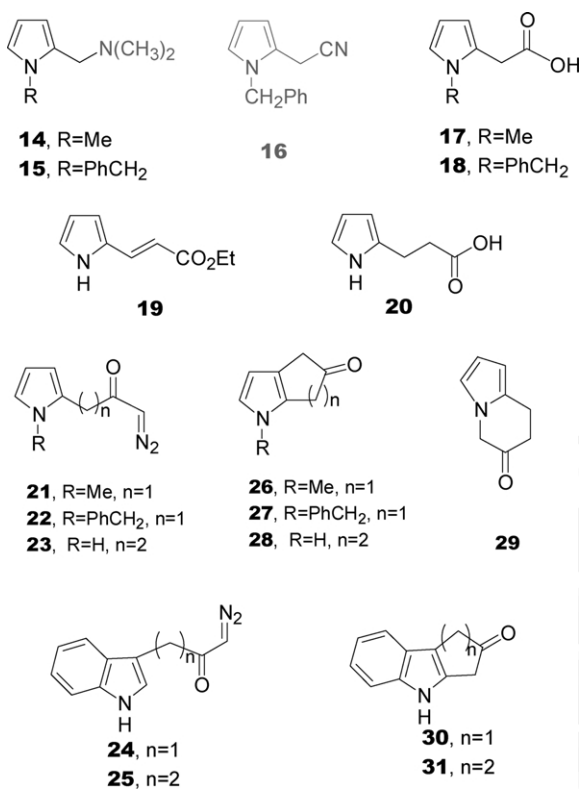
Scheme 2. *Reagents and conditions*: (a) oxalyl chloride, DMAP, THF, −65 °C. 30 min; (b) ethyl diazoacetate, Et_3N, −65 °C for 30 min and 12 h at RT; (c) $Rh_2(OAc)_4$, $ClCH_2CH_2Cl$, reflux, 3 h.

from pyrrole-2-aldehyde and the mono ethyl ester of malonic acid.[13]

The pyrrolyl diazoketones **21**–**23** were prepared (60–85%) by addition of excess ethereal diazomethane at 0 °C to an ethereal solution of the mixed ethyl carbonic–carboxylic anhydrides generated in situ at 0 °C. Exposure of the diazo compounds **21** and **22** to catalytic amounts of rhodium(II) acetate in dichloromethane solution at room temperature afforded the expected bicyclic ketones **26** and **27** respectively, as the only isolable products in 55–60% yields.

However, the α-diazobutanone **23** gave a mixture of ketones **28** (30% yield) and **29** (15% yield) derived from intramolecular insertion into the C-3H and N–H bonds of the pyrrole ring. This product ratio was independent of both the reaction temperature and the catalyst concentration. On the other hand, Capretta and Salim[4] report a 2.7:1 ratio of N–H to C-3H insertion for both the α-diazopropanone **23** (n=1) and the corresponding indole analog. Although the formation of both **28** and **29** was expected, the preferential formation of the CH insertion product **28**, was not. We are currently carrying out mechanistic studies on these seemingly counterintuitive results.

The indolyl diazoketones **24**[14] and **25** were prepared (70–



85%) from the commercially available carboxylic acids in a manner identical to that used for the synthesis of the 2-pyrrolyl analogs **21**–**23**. Rhodium(II) catalyzed decomposition of the diazo compound **24** (CH_2Cl_2/RT) and **25** ($ClCH_2CH_2Cl$/reflux) generated the anticipated tricyclic ketones **30** (70%) and **31** (82%) as the major products in each case.

In summary, this report shows that appropriately constituted 2-pyrrolyl and 3-indolyl-α-diazo-β-ketoesters and α-diazo alkanones are efficiently converted into bicyclic and tricyclic 5- and 6-membered ketones. These last results display alternative synthesis methodologies to obtain diverse pyrrolyl and indolyl diazo compounds, which complement and extend the results of Capretta and Salim.[4] In addition, all the cyclic ketones described herein

are useful points of departure enroute to certain natural products, and the cyclic β-ketoesters are particularly interesting in this regard because of the facility which further regiospecific chemical elaborations can be effected.

2. Experimental

2.1. General

The starting materials were purchased from Aldrich Chemical Co. and were used without further purification. The N-alkylated pyrroles were prepared according to the literature.[15] Solvents were distilled before use; ether and tetrahydrofuran (THF) were dried over sodium using benzophenone as indicator. Diazomethane was prepared from *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (Diazald®) using a minimum amount of water and ethanol as cosolvent, and dried over KOH pellets before use. Silica gel (230–400 mesh) and neutral alumina were purchased from Merck. Silica plates of 0.20 mm thickness were used for thin layer chromatography. Melting points were determined with a Fisher–Johns melting point apparatus and they are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded using a Varian Gemini 200, the chemical shifts (δ) are given in ppm relative to TMS as internal standard (0.00). For analytical purposes the mass spectra were recorded on a JEOL JMS-5X 10217 in the EI mode, 70 eV, 200 °C via direct inlet probe. Only the molecular and parent ions (*m*/*z*) are reported. IR spectra were recorded on a Nicolet Magna 55-X FT instrument.

2.1.1. Preparation of 3-(1-methylpyrrol-2-yl)propionitrile (3). A solution of triphenylphosphanylidene acetonitrile[8] (7.78 g, 25.8 mmol) in CH_2Cl_2 (20 mL) was added to a solution of 1-methylpyrrole-2-aldehyde[16] (0.76 g, 6.98 mmol) in toluene (50 mL). The resulting mixture was refluxed under a nitrogen atmosphere for 36 h. The mixture was cooled to room temperature and the solvent was removed in vacuo. Purification by column chromatography (SiO_2, hexane/AcOEt 8:2) afforded the pyrrole acrylonitrile **1** (0.74 g, 80%) as a colorless oil. IR ($CHCl_3$, cm^{-1}) 2949, 2210, 1615; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.67 (s, 3H), 5.46 (d, 1H), 5.52 (d, 1H), 6.18 (m, 2H), 6.78 (t, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 37.9, 101.6, 107.1, 108.0, 116.5, 117.4, 117.7, 131.3. MS [EI+] *m*/*z* (RI%): 132 $[M]^+$ (100), 131 $[M-H]^+$ (40). HRMS (EI^+): for $C_8H_8N_2$ calcd 132.0687, found 132.0690.

The pyrrole acrylonitrile **1** was dissolved in anhydrous MeOH (50 mL) and hydrogenated (760 mm) over Pd/C (0.08 g) for 6 h. The catalyst was removed by filtration and the solvent was evaporated to give the crude pyrrole propionitrile **3** (0.68 g, 90%) as a colorless oil which was used without purification. IR ($CHCl_3$, cm^{-1}) 2924, 2246, 1494; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.64 (t, 2H), 2.96 (t, 2H), 3.56 (s, 3H), 5.98m, 1H), 6.07 (m, 1H), 6.59 (t, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.6, 24.8, 37.6, 106.1, 108.0, 116.5, 117.7, 131.3. MS [EI+] *m*/*z* (RI%): 134 $[M]^+$ (50), 94 $[M-CH_2CN]^+$ (100). HRMS (FAB^+): for $C_8H_{11}N_2$ calcd 135.0922, found 135.0919.

2.2. Preparation of pyrrolyl-β-ketoesters

Typical procedure. To a suspension of zinc dust (0.32 g, 5 mmol) in refluxing anhydrous THF (3 mL) under a nitrogen atmosphere was added 4 drops of ethyl bromoacetate (0.055 mL, 0.08 g, 0.5 mmol). After the appearance of the green color, the pyrrolyl nitrile (1 mmol) was added in 1 portion, and ethyl bromoacetate (0.43 mL, 0.66 g, 4 mmol) was injected by syringe pump over 1 h and the mixture was refluxed for additional 8 h. The dark solution was cooled to 0 °C and it was treated with 10% aqueous HCl (1 mL) for 30 min. The mixture was concentrated in vacuo, diluted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4 and purified by column chromatography (SiO_2, hexane/AcOEt 8:2).

2.2.1. 4-(1-Methylpyrrol-2-yl)-3-oxo-butyric acid ethyl ester (4). Colorless oil (63%). IR ($CHCl_3$, cm^{-1}) 2985, 1732, 1316; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.26 (t, 3H), 2.61 (s, 2H), 3.44 (s, 3H), 3.79 (s, 2H), 4.18 (q, 2H), 6.02 (m, 1H), 6.08 (m, 1H), 6.60 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.0, 40.5, 49.2, 59.0, 106.5, 107.1, 122.1, 131.2, 171.1, 194.8; MS [EI+] *m*/*z* (RI%): 209 $[M]^+$ (20), 94 $[M-COCH_2CO_2Et]^+$ (100). HRMS (EI^+): for $C_{11}H_{15}NO_3$ calcd 209.1052, found 209.1056.

2.2.2. 5-(1-Methylpyrrol-2-yl)-3-oxo-pentanoic acid ethyl ester (5). Colorless oil (58%). IR ($CHCl_3$, cm^{-1}) 2940, 1728; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.27 (t, 3H), 2.85 (t, 2H), 3.19 (t, 2H), 3.42 (s, 2H), 3.56 (s, 3H), 4.21 (q, 2H), 5.93 (m, 1H), 6.06 (m, 1H), 6.52 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.2, 15.3, 33.8, 37.6, 49.4, 59.4, 106.2, 107.0, 121.9, 131.0, 171.0, 194.0; MS [EI+] *m*/*z* (RI%): 223 $[M]^+$ (5), 180 $[M-C_2H_3O]^+$ (50), 94 $[M-COCH_2CO_2Et]^+$ (100). HRMS (EI^+): for $C_{12}H_{17}NO_3$ calcd 223.1208, found 223.1210.

2.3. Preparation of pyrrolyl-α-diazo-β-ketoesters by diazo transfer reaction

Typical procedure. An ice-cold solution of pyrrolyl-β-ketoester (1 mmol) in CH_2Cl_2 (5 mL) was treated with triethylamine (0.27 mL, 0.20 g, 2 mmol) and *p*-toluenesulfonyl azide (0.197 g, 1 mmol) and the mixture was stirred under a nitrogen atmosphere at room temperature overnight. The solvent was removed in vacuo, the solid residue was triturated with ether (20 mL) and the mixture including the insoluble residue was washed successively with a 20% aqueous NaOH (3×20 mL). The red ethereal phase was dried over Na_2SO_4, and the solvent was removed in vacuo. The final product was purified by column chromatography (SiO_2, hexane/AcOEt 8:2).

2.3.1. 2-Diazo-4-(1-methylpyrrol-2-yl)-3-oxo-butyric acid ethyl ester (6). Red oil (52%). IR ($CHCl_3$, cm^{-1}) 2987, 2139, 1725; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.26 (t, 3H), 2.42 (s, 2H), 3.64 (s, 3H), 4.24 (q, 2H), 5.79 (m, 1H), 5.98 (m, 1H), 6.62 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.2, 40.5, 59.6, 72.0, 106.4, 107.0, 122.0, 131.1, 171.2, 205.0. MS [EI+] *m*/*z* (RI%): 235 $[M]^+$ (5), 94 $[M-COCH_2CO_2Et]^+$ (100). HRMS (EI^+): for $C_{11}H_{13}N_3O_3$ calcd 235.0957, found 235.0954.

2.3.2. 2-Diazo-5-(1-methylpyrrol-2-yl)-3-oxo-pentanoic acid ethyl ester (7). Red oil (65%). IR ($CHCl_3$, cm^{-1}) 2939, 2138, 1715; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.25 (t, 3H), 2.85 (t, 2H), 2.92 (t, 2H), 3.61 (s, 3H), 4.20 (q, 2H), 5.82 (m, 1H), 6.00 (m, 1H), 6.51 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.3, 19.5, 33.7, 59.4, 71.1, 106.2, 107.0, 121.9, 131.0, 171.0, 204.0; MS [EI+] *m/z* (RI%): 249 $[M]^+$ (10), 94 $[M-CH_2COCH_2CO_2Et]^+$ (100). HRMS (EI^+): for $C_{12}H_{15}N_3O_3$ calcd 249.1113, found 249.1119.

2.4. Cyclization of pyrrolyl-α-diazo-β-ketoesters

Typical procedure. A solution of pyrrolyl-α-diazo-β-ketoester (1 mmol) in dry 1,2-dichloroethane (10 mL) was treated with $Rh_2(OAc)_4$ (2 mg) under a nitrogen atmosphere and the resulting mixture was heated at reflux for 3 h. The reaction mixture was cooled to room temperature and the solvent was removed in vacuo. The final product was purified by column chromatography (SiO_2, hexane/AcOEt 8:2).

2.4.1. 1-Methyl-5-oxo-1,4,5,6-tetrahydrocyclopenta[*b*]-pyrrole-4-carboxylic acid ethyl ester (8). Colorless oil (54%). IR ($CHCl_3$, cm^{-1}) 2986, 1731; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.29 (t, 3H), 3.40 (s, 2H), 3.63 (s, 3H), 4.12 (q, 2H), 4.16 (s, 1H) 5.92 (d, 1H), 6.70 (d, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.1, 40.8, 40.9, 60.1, 60.6, 108.4, 119.0, 122.9, 133.3, 171.0, 215.0; MS [EI+] *m/z* (RI%): 207 $[M]^+$ (5), 134 $[M-CO_2Et]^+$ (40), 29 $[CH_2CH_3]^+$ (100). HRMS (EI^+): for $C_{11}H_{13}NO_3$ calcd 207.0895, found 207.0897.

2.4.2. 1-Methyl-5-oxo-4,5,6,7-tetrahydroindole-4-carboxylic acid ethyl ester (9). Colorless oil (57%). IR ($CHCl_3$, cm^{-1}) 2929, 1726; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.25 (t, 3H), 2.85 (t, 2H), 2.92 (t, 2H), 3.61 (s, 3H), 4.11 (q, 2H), 4.16 (s, 1H) 6.05 (d, 1H), 6.55 (d, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.1, 22.1, 38.2, 40.8, 60.1, 60.5, 108.3, 118.9, 122.8, 133.1, 171.0, 210.2; MS [EI+] *m/z* (RI%): 221 $[M]^+$ (10), 149 $[M-C_3H_4O_2]^+$ (65), 148 $[M-CO_2Et]^+$ (100). HRMS (EI^+): for $C_{12}H_{15}NO_3$ calcd 221.1052, found 221.1057.

2.5. Preparation of indolyl-α-diazo-β-ketoesters

Typical procedure. A dry ice-cold solution of the acid (1 mmol) in freshly distilled THF (10 mL) was treated successively with oxalyl chloride (0.087 mL, 0.127 g, 1 mmol) and 4-(dimethylamino)pyridine (0.012 g, 0.1 mmol), the mixture was stirred under a nitrogen atmosphere for 30 min at −65 °C. The mixture was treated with ethyl diazoacetate (0.105 mL, 0.114 g, 1 mmol) and triethylamine (0.139 mL, 0.101 g, 1 mmol) at −65 °C. The stirring was continuing for additional 2 h under nitrogen atmosphere at −65 °C and the reaction was allowed to warm to room temperature overnight. The solvent was removed in vacuo and the product was purified by column chromatography (SiO_2, hexane/AcOEt 8:2).

2.5.1. 2-Diazo-4-(indol-3-yl)-3-oxobutyric acid ethyl ester (10). Red oil (50%). IR ($CHCl_3$, cm^{-1}) 3479, 2987, 2154, 1725, 1716; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.28 (t, 3H), 3.80 (s, 2H), 4.31 (q, 2H), 7.09–7.26 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.8, 30.9, 61.5, 71.0, 107.4, 111.2, 118.6, 119.7, 122.2, 123.3, 127.0, 136.0, 177.7, 213.6; MS [EI+] *m/z* (RI%): 271 $[M]^+$ (5), 243 $[M-N_2]^+$ (5), 175 $[M-COCN_2CO]^+$ (65), 130 $[M-COCN_2CO_2Et]^+$ (100). HRMS (EI^+): for $C_{14}H_{13}N_3O_3$ calcd 271.0957, found 271.0963.

2.5.2. 2-Diazo-4-(indol-3-yl)-3-oxopentanoic acid ethyl ester (11). Red oil (50%). IR ($CHCl_3$, cm^{-1}) 3480, 2927, 2145, 1720, 1712; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.27 (t, 3H), 2.70 (t, 2H), 3.07 (t, 2H), 4.26 (q, 2H), 6.97–7.33 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.9, 20.3, 34.5, 61.9, 71.0, 111.1, 114.1, 118.2, 118.7, 121.4, 121.6, 126.9, 136.0, 177.7, 213.6; MS [EI+] *m/z* (RI%): 285 $[M]^+$ (2), 284 $[M-H]^+$ (5), 130 $[M-CH_2COCN_2CO_2Et]^+$ (100). HRMS (EI^+): for $C_{15}H_{15}N_3O_3$ calcd 285.1113, found 285.1117.

2.6. Cyclization of indolyl α-diazo-β-ketoesters

Typical procedure. A solution of indolyl diazo compound (1 mmol) in dry 1,2-dichloroethane (10 mL) was treated with $Rh_2(OAc)_4$ (2 mg) under a nitrogen atmosphere and the resulting mixture was heated at reflux for 3 h. The reaction mixture was cooled to room temperature and the solvent was removed in vacuo. The final product was purified by column chromatography (SiO_2, hexane/AcOEt 8:2).

2.6.1. 2-Oxo-1,2,3,4-tetrahydrocyclopenta[*b*]indole-3-carboxylic acid ethyl ester (12). White solid (55%). Mp 145–147 °C (ether–hexane). IR ($CHCl_3$, cm^{-1}) 3479, 2987, 1725, 1716; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.28 (t, 3H), 3.80 (s, 2H), 4.31 (q, 2H), 4.73 (s, 1H), 7.09–7.26 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.8, 30.9, 61.5, 63.6, 107.4, 111.2, 118.6, 119.7, 122.2, 123.3, 127.0, 136.0, 177.7, 213.6; MS [EI+] *m/z* (RI%): 243 $[M]^+$ (2), 242 $[M-H]^+$ (5), 130 $[M-COCCO_2Et]^+$ (100). HRMS (EI^+): for $C_{14}H_{13}NO_3$ calcd 243.0895, found 243.0896.

2.6.2. 2-Oxo-2,3,4,9-tetrahydrocarbazole carboxylic acid ethyl ester (13). White solid (52%). Mp 156 °C (ether–hexane). IR ($CHCl_3$, cm^{-1}) 3480, 2929, 1721, 1711; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.27 (t, 3H), 2.75 (t, 2H), 3.10 (t, 2H), 4.22 (q, 2H), 4.67 (s, 1H), 6.99–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.0, 20.3, 34.5, 61.9, 68.0, 111.1, 114.5, 118.5, 119.3, 121.4, 122.0, 127.0, 136.2, 178.9, 213.0; MS [EI+] *m/z* (RI%): 257 $[M]^+$ (5), 130 $[M-CH_2COCCO_2Et]^+$ (100). HRMS (EI^+): for $C_{15}H_{15}NO_3$ calcd 257.1052, found 257.1057.

2.7. Preparation of dimethylaminomethylpyrroles

Typical procedure. A mixture of 37% aqueous formaldehyde (9 mL, 3.6 g, 0.12 mol) and dimethylamine hydrochloride (9.78 g, 0.12 mol) was added with stirring to the pyrrole (0.10 mol) at a rate such that the reaction temperature did not exceed 60 °C. The stirring was continued a further 2 h. At the end of this time, 20% NaOH (15 mL) and H_2O (40 mL) were added and the product was extracted with ether (3×20 mL). The organic layers were combined, they were washed with saturated NaCl solution (50 mL) and dried over Na_2SO_4. The solvent was removed in vacuo, and the residue was purified by distillation under a reduced pressure.

2.7.1. 1-Methyl-2-(dimethylaminomethyl)pyrrole (14). Colorless oil (71%). Bp 58 °C/5 mm. IR (film, cm^{-1}) 3404, 2971, 2941, 2812; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.18 (s, 6H), 3.32 (s, 2H), 3.62 (s, 3H), 6.00 (m, 2H), 6.57 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 37.7, 41.7, 41.7, 58.2, 108.6, 108.7, 121.1, 121.2; MS [EI+] *m/z* (RI%): 138 $[M]^+$ (40), 94 $[M-(CH_3)_2N]^+$ (100). HRMS (EI^+): for $C_8H_{14}N_2$ calcd 138.1157, found 138.1159.

2.7.2. 1-Benzyl-2-(dimethylaminomethyl)pyrrole (15). Colorless oil (52%). Bp 110 °C/5 mm. IR (film, cm^{-1}) 3400, 2970, 2938, 2824; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.15 (s, 6H), 3.30 (s, 2H), 3.59 (s, 3H), 5.09 (s, 2H), 6.13 (m, 2H), 6.67 (m, 1H). ^{13}C NMR (CDCl3, 50 MHz) δ 41.4, 41.4, 51.5, 58.0, 107.6, 109.8, 122.7, 126.3, 126.4, 127.2, 127.4, 128.4, 128.5, 137.5. MS [EI+] *m/z* (RI%): 208 $[M]^+$ (35), 164 $[M-(CH_3)_2N]^+$ (25), 91 $[PhCH_2]^+$ (100). HRMS (EI^+): for $C_{14}H_{18}N_2$ calcd 214.1470, found 214.1475.

2.8. Preparation of pyrrole acetic acids

Typical procedure. Iodomethane (7.47 mL, 17.04 g, 0.12 mol) was added slowly to a stirred and cooled (0 °C) solution of 2-(dimethylaminomethyl)pyrrole (0.1 mol) in acetone (5 mL/g pyrrole) maintained in a nitrogen atmosphere, at a rate such that the reaction temperature did not exceed 4 °C. When the addition was completed, the solution was stirred at room temperature for 1 h, then the solvent was removed and a solution of NaCN (14.7 g, 0.3 mol) in H_2O (150 mL) and EtOH (50 mL) was added and the resulting solution was heated at reflux overnight. The reaction mixture was cooled to room temperature, and the solvent was removed in vacuo, then, H_2O was added and the product was extracted with ether. The extract was washed with saturated NaCl solution and after drying the solvent was removed in vacuo and the product was purified by distillation under a reduced pressure (100 °C/5 mm). The pyrroleacetonitriles (**2** and **16**) were mixed with a solution of KOH (6 equiv.) H_2O (1.5 mL/mmol pyrroleacetonitrile) and EtOH (3.0 mL/mmol pyrroleacetonitrile) and the mixture was heated at reflux overnight. The reaction mixture was cooled to room temperature and the solvent was removed in vacuo, then H_2O was added and the resulting solution was acidified with 10% HCl solution to pH=1. The product was extracted with ethyl acetate (3×50 mL), the extract was washed and dried over Na_2SO_4, the solvent was removed in vacuo and the product was purified by crystallization.

2.8.1. 1-Methylpyrrol-2-yl acetic acid (17). White solid (70%). Mp 135 °C (ether–hexane). IR (KBr, cm^{-1}) 3465, 3339, 1660, 1624; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.57 (s, 2H), 3.65 (s, 3H), 6.07 (m, 2H), 6.61 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 39.4, 41.8, 108.6, 108.7, 121.1, 121.2, 178.0. MS [EI+] *m/z* (RI%): 139 $[M]^+$ (50), 94 $[M-COOH]^+$ (100). HRMS (FAB^+): for $C_7H_{10}NO_2$ calcd 140.0712, found 140.0719.

2.8.2. 1-Benzylpyrrol-2-yl acetic acid (18). White solid (40%). Mp 122 °C (ether–hexane). IR (film, cm^{-1}) 3201, 3032, 2929, 1645; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.52 (s, 2H), 5.09 (s, 2H), 6.14 (m, 2H), 6.67 (m, 1H), 7.00–7.31 (m, 5H); ^{13}C NMR (CDCl3, 50 MHz) δ 39.0, 50.9, 107.7, 109.8, 122.6, 126.2, 126.2, 127.2, 127.3, 128.2, 128.3, 137.5, 179.1; MS [EI+] *m/z* (RI%): 215 $[M]^+$ (30), 170 $[M-COOH]^+$ (20), 91 $[PhCH_2]^+$ (100). HRMS (EI^+): for $C_{13}H_{13}NO_2$ calcd 215.0946, found 215.0947.

2.8.3. Preparation of 3-(pyrrol-2-yl)propionic acid (20). Pyrrole-2-aldehyde (1 g, 10.3 mmol) was mixed with hydrogen ethyl malonate (2.78 g, 21 mmol) in pyridine (10 mL) and piperidine (0.5 mL) and the mixture was warmed at 50 °C with stirring for 48 h and 80 °C for 24 h. 10% HCl (150 mL) was added, the product was extracted with ether, the organic phase was washed with aqueous Na_2CO_3 and dried over Na_2SO_4, and the solvent was removed in vacuo. Purification by distillation under reduced pressure afforded the 3-(pyrrol-2-yl)acrylic acid ethyl ester **19** as colorless oil. Bp 120 °C/5 mm. IR ($CHCl_3$, cm^{-1}) 3463, 1695; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.21 (t, 3H), 4.20 (q, 2H), 5.94 (d, 3H), 5.99 (d, 1H), 6.18 (m, 1H), 6.28 (m, 1H), 6.91 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.1, 22.6, 105.9, 107.9, 116.1, 123.4, 131.1, 142.8, 165.9; MS [EI+] *m/z* (RI%): 165 $[M]^+$ (100). HRMS (EI^+): for $C_9H_{11}NO_2$ calcd 165.0790, found 165.0792. Compound **19** may be used without purification.

The crude acrylic ester **19** was dissolved in anhydrous MeOH (75 mL) and hydrogenated (760 mm) over 10% Pd/C (0.1 g) for 6 h. The catalyst was removed by filtration and the solvent was evaporated. Distillation of the product afforded the ethyl propionic ester, as a colorless oil. Bp 100 °C/5 mm. IR ($CHCl_3$, cm^{-1}) 3462, 1732; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.25 (t, 3H), 2.74 (t, 2H), 3.09 (t, 2H), 4.13 (q, 2H), 6.08 (m, 1H), 6.13 (m, 1H), 6.81 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.1, 22.6, 41.0, 59.1, 105.9, 107.9, 116.1, 131.1, 171.5; MS [EI+] *m/z* (RI%): 167 $[M]^+$ (10), 94 $[M-CO_2Et]^+$ (100). HRMS (EI^+): for $C_9H_{13}NO_2$ calcd 167.0946, found 165.0745.

The ethyl propionic ester was added to a solution of K_2CO_3 (2 equiv.) in H_2O (6 mL) and EtOH (24 mL) and the mixture was heated at reflux overnight. The mixture was cooled at room temperature, the solvent was removed and H_2O (50 mL) was added, the solution was acidified with 10% HCl solution to pH=1, the product was extracted with ethyl acetate, the organic phase was washed, dried and the solvent was evaporated in vacuo. Crystallization afforded the pyrrolepropionic acid **20** in 40% global yield. Mp 138 °C (ether). IR ($CHCl_3$, cm^{-1}) 3479, 3060, 1712; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.78 (t, 2H), 3.12 (t, 2H), 6.01 (m, 2H), 6.68 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 22.5, 40.9, 105.9, 107.9, 116.1, 131.1, 176.3; MS [EI+] *m/z* (RI%): 139 $[M]^+$ (50), 94 $[M-COOH]^+$ (100). HRMS (EI^+): for $C_7H_9NO_2$ calcd 139.0633, found 139.0639.

2.9. Preparation of pyrrolyldiazoketones

Typical procedure. An ice-cold solution of the acid (1 mmol) in freshly distilled ether was treated successively with ethyl chloroformate (0.10 mL, 0.11 g, 1.1 mmol) and *N*-methylmorpholine (0.10 mL, 0.10 g, 1 mmol), the mixture was stirred under nitrogen atmosphere for 15 min at 0 °C, then an ether solution of diazomethane (10 mmol) from *N*-methyl-*N*-nitroso-4-toluenesulfonamide (3.06 g, 14.3 mmol) was added at 0 °C. A vigorous evolution of

nitrogen occurred, and the mixture was allowed to warm to room temperature overnight. The solvent was removed in vacuo and the product was purified by column chromatography (alumina activity III, hexane/AcOEt 95:5).

2.9.1. 1-Diazo-3-(1-methylpyrrol-2-yl)propanone (21). Orange oil (80%). IR (film, cm^{-1}) 2105, 1738, 1637; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.53 (s, 3H), 3.59 (s, 2H), 5.13 (s, 1H), 6.02 (m 1H), 6.07 (t, 1H, J_{3-4}=3.5 Hz), 6.60 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 39.4, 41.8, 52.4, 108.6, 108.7, 121.1, 121.2, 195.2; MS [EI+] *m/z* (RI%): 163 $[M]^+$ (77), 135 $([M-N_2]^+$ (10), 94 $[M-COCHN_2]^+$ (100).HRMS (FAB^+): for $C_8H_{10}N_3O$ calcd 164.0824, found 164.0834.

2.9.2. 1-Diazo-3-(1-benzylpyrrol-2-yl)propanone (22). Orange oil (63%). IR ($CHCl_3$, cm^{-1}) 2104, 1745, 1638; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.49 (s, 2H), 5.02 (s, 2H), 5.06 (s, 1H), 6.09 (m, 1H), 6.15 (t, 1H, J_{3-4}=3.46 Hz), 6.71 (m, 1H)7.0–7.3 (m, 5H); ^{13}C NMR (CDCl3, 50 MHz) δ 39.0, 50.5, 53.9, 107.6, 109.8, 122.7, 126.3, 126.4, 127.2, 127.4, 128.4, 128.5, 137.5, 192.0; MS [EI+] *m/z* (RI%): 239 $[M]^+$ (15), 211 $[M-N2]^+$ (10), 170 $[M-COCHN2]^+$ (55), 91 $[PhCH_2]^+$ (100). HRMS (FAB^+): for $C_{14}H_{14}N_3O$ calcd 240.1139, found 240.1137.

2.9.3. 1-Diazo-4-(pyrrol-2-yl)-butan-2-one (23). Orange oil (70%). IR ($CHCl_3$, cm^{-1}) 3478, 2976, 2109, 1730; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.73 (t, 2H), 2.95 (t, 2H), 6.10 (m, 2H), 6.66 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 22.5, 40.9, 55.1, 105.9, 107.9, 116.1, 131.1, 195.5; MS [EI+] *m/z* (RI%): 163 $[M]^+$ (10), 94 $[M-COCHN_2]^+$ (100).HRMS (FAB^+): for $C_8H_{10}N_3O$ calcd 164.0824, found 164.0833.

2.10. Cyclization of pyrrolyldiazopropanones

Typical procedure. A solution of the diazopropanone (1 mmol) in dry CH_2Cl_2 (5 mL) was stirred with $Rh_2(OAc)_4$ (2 mg) under a nitrogen atmosphere at room temperature. After 2 h, the mixture was evaporated in vacuo and purified by column chromatography (SiO_2, hexane/AcOEt 8:2).

2.10.1. 1-Methyl-4,6-dihydrocyclopenta[*b*]pyrrol-5-one (26). Colorless oil (60%). IR (film, cm^{-1}) 2925, 2854, 1738; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.56 (s, 2H), 3.58 (s, 3H), 3.69 (s, 2H), 6.04 (d, 1H, J_{4-5}=2.7 Hz), 6.56 (d, 1H, J_{5-4}=2.76 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 37.9, 40.8, 40.9, 108.6, 119.3, 122.9, 131.2, 215.2; MS [EI+] *m/z* (RI%): 135 $[M]^+$ (40), 134 $[M-H]^+$ (100). HRMS (EI^+): for C_8H_9NO calcd 135.0684, found 135.0686.

2.10.2. 1-Benzyl-4,6-dihydrocyclopenta[*b*]pyrrol-5-one (27). Colorless oil (55%). IR ($CHCl_3$, cm^{-1}) 2956, 2927, 1724; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.50 (s, 2H), 4.56 (s, 2H), 5.01 (s, 2H), 6.10 (d, 1H, J_{4-5}=2.74 Hz), 6.65 (d, 1H, J_{5-4}=2.72 Hz), 7.0–7.3 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 32.5, 40.7, 52.2, 109.5, 119.5, 122.8, 126.4, 127.1, 127.8, 128.6, 128.8, 131.0, 137.3, 215.4; MS [EI+] *m/z* (RI%): 211 $[M]^+$ (5), 210 $[M-H]^+$ (100). HRMS (EI^+): for $C_{14}H_{13}NO$ calcd 211.0997, found 211.0999.

2.11. Reaction of 1-diazo-4-(2-pyrrolyl)-2-butanone (23) with rhodium(II) acetate

The procedure was similar to that used in the cyclization of pyrrolyldiazopropanones. Column chromatography (SiO_2, hexane/AcOEt 9:1) afforded the compounds **28** and **29**.

2.11.1. 1,4,6,7-Tetrahydroindol-5-one (28). White solid (30%). Mp 137 °C. IR (film, cm^{-1}) 3476, 2920, 1711; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.68 (t, 2H), 2.97 (t, 2H), 3.40 (s, 2H), 5.98 (d, 1H, J_{4-5}=2.7 Hz), 6.68 (d, 1H, J_{5-4}=2.76 Hz), 8.01 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 22.2, 38.3, 39.0, 107.4, 114.2, 117.7, 124.7, 210.7; MS [EI+] *m/z* (RI%): 135 $[M]^+$ (100), 134 $[M-H]^+$ (10).HRMS (FAB^+): for $C_8H_{10}NO$ calcd 136.0762, found 136.0751.

2.11.2. 7,8-Dihydroindolizin-6-one (29). Colorless oil (15%). IR (film, cm^{-1}) 2958, 1724; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.70 (t, 2H), 3.06 (t, 2H), 4.52 (s, 2H), 5.98 (dd, 1H), 6.17 (d, 1H), 6.58 (d, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.8, 38.1, 54.8, 104.7, 108.9, 118.8, 128.0, 205.9; MS [EI+] *m/z* (RI%): 135 $[M]^+$ (40), 134 $[M-H]^+$ (75), 80 $[M-CH_2COCH]^+$ (100).HRMS (FAB^+): for $C_8H_{10}N_3O$ calcd 136.0762, found 136.0774.

2.12. Preparation of indolyl diazoalkanones 24 and 25

The procedure was similar to that used in the preparation of pyrrolyldiazoketones.

2.12.1. 1-Diazo-3-(indol-3-yl)propanone (24). Orange oil (84%). IR ($CHCl_3$, cm^{-1}) 3477, 2108, 1735, 1633; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.77 (s, 2H), 5.17 (s, 1H), 7.1–7.3 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 37.9, 54.3, 108.5, 111.3, 118.8, 119.9, 122.4, 123.4, 127.2, 136.2, 194.2; MS [EI+] *m/z* (RI%): 199 $[M]^+$ (10), 171 $[M-N_2]^+$ (11), 130 $[M-COCHN_2]^+$ (100). HRMS (EI^+): for $C_{11}H_9N_3O$ calcd 199.0746, found 199.0743.

2.12.2. 1-Diazo-4-(indol-3-yl)butan-2-one (25). Orange oil (87%). IR ($CHCl_3$, cm^{-1}) 3481, 2110, 1732; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.72 (t, 2H), 3.11 (t, 2H), 5.15 (s, 1H), 6.99–7.45 (m, 5H), 7.61 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.6, 41.1, 54.6, 111.2, 114.3, 118.6, 119.4, 121.6, 121.6, 127.2, 136.4, 195.0; MS [EI+] *m/z* (RI%): 213 $[M]^+$ (10), 185 $[M-N_2]^+$ (15), 130 $[M-CH_2COCHN_2]^+$ (100). HRMS (EI^+): for $C_{12}H_{11}N_3O$ calcd 213.0902, found 213.0907.

2.12.3. Cyclization of 1-diazo-3-(indol-3-yl)propanone (24) with rhodium(II) acetate. The procedure was similar to that used in the cyclization of pyrrolyldiazopropanones. Purification by column chromatography (SiO_2, hexane/AcOEt 8:2) afforded 3,4-dihydrocyclopenta[*b*]indol-2-one **30** as white solid (70%). Mp 145 °C. IR ($CHCl_3$, cm^{-1}) 3477, 2916, 1753; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.49 (s, 2H), 3.78 (s, 2H), 7.1–7.3 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 39.2, 39.3, 111.1, 111.6, 118.8, 120.2, 121.9, 136.0, 136.0, 138.8, 214.2; MS [EI+] *m/z* (RI%): 171 $[M]^+$ (20), 143 $[M-CO]^+$ (30), 130 $[M-CHCO]^+$ (100).). HRMS (EI^+): for $C_{11}H_9NO$ calcd 171.0684, found 171.0697.

2.12.4. Cyclization of indolyl diazoketone 25. A solution of indolyl diazoketone **25** (1 mmol) in dry 1,2-dichloroethane (10 mL) was treated with $Rh_2(OAc)_4$ (2 mg) under a nitrogen atmosphere and the resulting mixture was heated at reflux for 3 h. The reaction mixture was cooled to room temperature and the solvent was removed in vacuo. Purification by column chromatography (SiO_2, hexane/AcOEt 8:2) afforded 1,3,4,9-tetrahydrocarbazol-2-one **31** as a white solid (82%). Mp 150 °C. IR ($CHCl_3$, cm^{-1}) 3481, 2957, 1732; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.74 (t, 2H), 3.12 (t, 2H), 3.68 (s, 2H), 7.0–7.3 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.6, 29.7, 34.7, 111.1, 114.9, 118.6, 119.2, 121.3, 122.0, 130.8, 136.2, 218.0; MS [EI+] *m/z* (RI%): 185 $[M]^+$ (5), 130 $[M-CHCH_2CO]^+$ (100). HRMS (EI^+): for $C_{12}H_{11}NO$ calcd 185.0841, found 185.0845.

Acknowledgements

Financial support from CONACyT (No. 37312-E) is gratefully acknowledged. The authors would like to thank R. Patiño, M. Adaya, A. Peña, E. Huerta, N. Zavala, C. Márquez, J. Pérez and L. Velasco for the technical support.

References and notes

1. (a) Galeazzi, E.; Guzman, A.; Piñedo, A.; Saldaña, A.; Torre, D.; Muchowski, J. M. *Can. J. Chem.* **1983**, *61*, 454. (b) Müller, P.; Polleux, P. *Helv. Chim. Acta* **1998**, *81*, 317.
2. Jefford, C. W.; Johncock, W. *Helv. Chim. Acta* **1983**, *66*, 2666.
3. (a) Jefford, C. W.; Kubota, T.; Zaslona, A. *Helv. Chim. Acta* **1986**, *69*, 2048. (b) Jefford, C. W.; Tang, Q.; Zaslona, A. *Helv. Chim. Acta* **1989**, *72*, 1749. (c) Jefford, C. W.; Tang, Q.; Zaslona, A. *J. Am. Chem. Soc.* **1991**, *113*, 3513. (d) Jefford, C. W.; Wang, J. B. *Tetrahedron Lett.* **1993**, *34*, 3119.
4. Capretta, A.; Salim, M. *Tetrahedron* **2000**, *56*, 8063.
5. Doyle, M. P.; McKervey, M. A.; Ye, T. Modern catalytic methods for organic synthesis with diazo compounds: from cyclopropanes to ylides; Wiley: New York, 1998; p 10.
6. (a) Herz, W.; Rogers;, J. *J. Am. Chem. Soc.* **1951**, *73*, 4921. (b) Herz, W.; Ditter, K.; Cristol, S. J. *J. Am. Chem. Soc.* **1947**, *69*, 1698.
7. Hannick, S. M.; Kishi, Y. *J. Org. Chem.* **1983**, *48*, 3833.
8. Tamiaki, H.; Kouraba, M. *Tetrahedron* **1997**, *53*, 10677.
9. Hashimoto, S.; Watanabe, N.; Ikegami, S. *J. Chem. Soc. Chem. Commun.* **1992**, 1508.
10. Zaragoza, F. *Tetrahedron* **1995**, *51*, 8829.
11. Bestmann, H. J.; Kolm, H. *Chem. Ber.* **1963**, *96*, 1948.
12. Carpio, H.; Cho, D.; Gallegra, P.; Halpern, O.; Koehler, R.; Maddox, M. L.; Muchowski, J. M.; Prince, A.; Tegg, D.; Thurber, T. C.; Van Horn, A. R.; Wren, D. *Can. J. Chem.* **1982**, *60*, 2295.
13. (a) Bates;, H. A.; Rapoport, H. *J. Am. Chem. Soc.* **1979**, *101*, 1259. (b) Volz, H.; Draese, R. *Tetrahedron Lett.* **1970**, *11*, 4917.
14. Franceschetti, L.; Garzon-Aburbeh, A.; Mahmoud, M. R.; Natalini, B.; Pellicciari, R. *Tetrahedron Lett.* **1993**, *34*, 3185.
15. Heany, H.; Ley, S. *J. Chem. Soc., Perkin Trans. 1* **1973**, 499.
16. 1-Methylpyrrole-2-aldehyde was prepared using the procedure described by Muchowski, J. M.; Solas, D. R. *J. Org. Chem.* **1984**, *49*, 203.