Pergamon

Tetrahedron 55 (1999) 4153–4166

TETRAHEDRON

A New Synthesis of Alkyl 1-Alkyl-2-methylpyrrole-3-carboxylates by Ring Transformation of 2-Chloro-2-acetimidoylbutyrolactones

Bart Kesteleyn,[1] Erick Rosas Alonso,[1] Christian Stevens,[1] Yves Dejaegher,[1] Maria Peristeropoulou,[1] Tuyen Nguyen Van,[1] Oleg Kulinkovich [2] and Norbert De Kimpe*,[1]

[1]Department of Organic Chemistry, Faculty of Agricultural and Applied Biological Sciences, University of Gent, Coupure Links 653, B-9000 Gent, Belgium

[2]Department of Organic Chemistry, Belarussian State University, Fr. Skaryny Avenue 4, 220050 Minsk, Belarus

Received 3 November 1998; revised 14 January 1999; accepted 28 January 1999

Abstract: Reaction of 2-chloro-2-acetimidoylbutyrolactones with sodium methoxide or sodium ethoxide in the corresponding alcohol provides a facile one-step synthesis of methyl or ethyl 1-alkyl-2-methylpyrrole-3-carboxylates from readily available starting materials.

Dedicated to Prof. Dr. Henk van der Plas on the occasion of his 70th birthday

INTRODUCTION

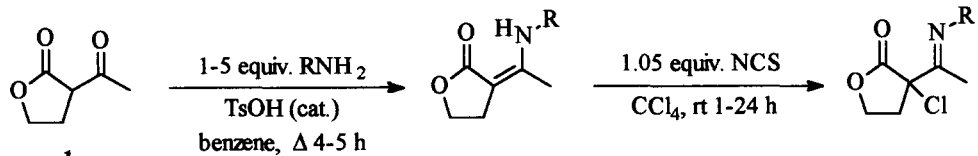
Pyrrole syntheses have always attracted considerable attention in organic chemistry due to the importance of the pyrrole skeleton as a characteristic subunit in natural products and physiologically active compounds.[1-3] Several pyrroles show interesting physiological activities in agrochemistry[3] ranging from fungicidal activity (e.g. uncoupling of the oxidative phosphorylation initiated by phenylpyrroles),[4] herbicidal activity (e.g. 2-benzoylpyrroles)[5] to insecticidal activity (e.g. 2-arylpyrroles).[6] The introduction of a substituent at the 3-position of the pyrrole ring is of importance in the synthesis of natural products, while these pyrroles are not easily accessible.[2] Only a few methods allow the synthesis of 3-(methoxycarbonyl)pyrroles, e.g. 1,3-dipolar cycloadditions of acetylenes to azomethine ylides[7] or to münchnones,[8] addition of 2-cyanoaziridines to alkynes,[9] reaction of ethyl acetoacetate with 1,2-dibromoethyl acetate and benzylamine in the presence of excess sodium hydride[10] and haloform reaction of 3-acetyl-1-tosylpyrrole using bromine and aqueous sodium hydroxide followed by N-deprotection.[11] In this paper, a new straighforward synthetic strategy towards the synthesis of methyl and ethyl 1-alkyl-2-methylpyrrole-3-carboxylates is presented.

RESULTS AND DISCUSSION

A series of methyl 1-alkyl-2-methylpyrrole-3-carboxylates **4** was synthesized from the corresponding 2-chloro-2-acetimidoylbutyrolactones **3** upon treatment with 3 equivalents of 2 M sodium methoxide in methanol under reflux for 2 h. The reaction produced a lot of tar-like products but the pyrroles **4** were obtained in pure

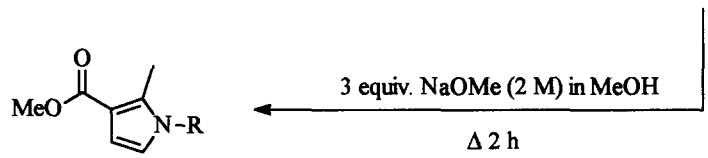
0040-4020/99/$ - see front matter
PII: S0040-4020(99)00108-8

form from the reaction mixtures in isolated yields of 20-25% after flash chromatography. Despite the low yields, this ring transformation is an attractive synthesis of functionalised pyrroles due to the fact that the readily available starting materials are converted in essentially one step to the title pyrroles. The ease by which this process occurs competes very well with the known procedures for the synthesis of pyrrole-3-carboxylic acid derivatives. As outlined in Scheme 1, 2-chloro-2-acetimidoylbutyrolactones **3** are readily accessible from the commercially available 2-acetylbutyrolactone **1**. Condensation of 2-acetylbutyrolactone **1** with a primary amine under reflux in benzene, using a catalytic amount of *p*-toluenesulfonic acid and water removal by azeotropic distillation, resulted in the 2-acetimidoylbutyrolactones **2**, which occurred entirely as the enamino ester tautomer. The enamino compounds **2** were then reacted with 1 equivalent of *N*-chlorosuccinimide in carbon tetrachloride at room temperature to give the 2-chloro-2-acetimidoylbutyrolactones **3** in mostly excellent yields.



1

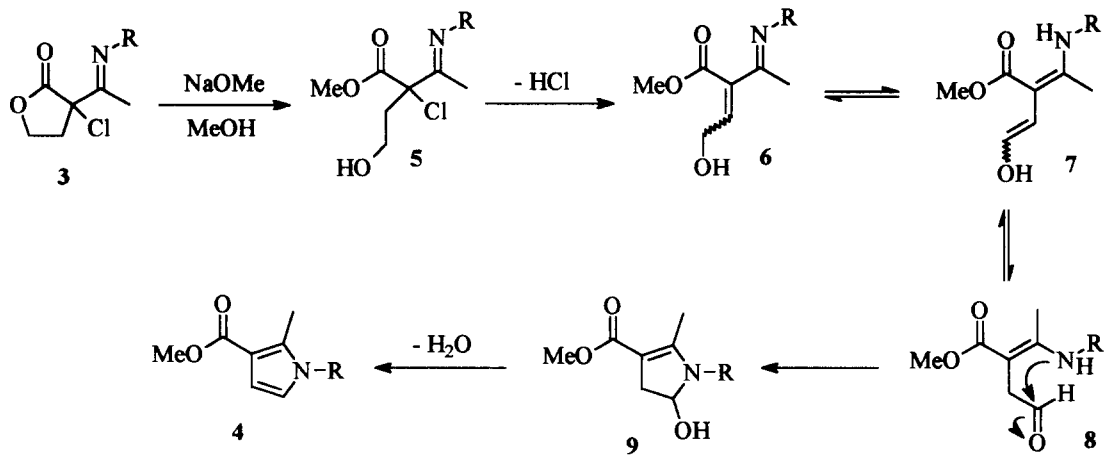
2	**3**
2a: R = isopropyl (98%)	**3a** (96%)
2b: R = n-propyl (93%)	**3b** (97%)
2c: R = *sec*-butyl (98%)	**3c** (95%)
2d: R = cyclohexyl (97%)	**3d** (98%)
2e: R = benzyl (70%)	**3e** (95%)
2f: R = phenyl (76%)	**3f** (96%)
2g: R = phenylethyl (90%)	**3g** (71%)
2h: R = 2-(4-chlorophenyl)ethyl (84%)	**3h** (94%)
2i: R= 2-(3,4-dimethoxyphenyl)ethyl (91%)	**3i** (97%)



4a: R = isopropyl (23%)
4b: R = cyclohexyl (25%)
4c: R = phenylethyl (23%)
4d: R = 2-(4-chlorophenyl)ethyl (22%)
4e: R = 2-(3,4-dimethoxyphenyl)ethyl (20%)

Scheme 1

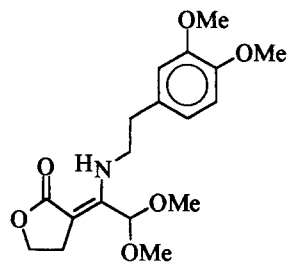
The mechanism of the pyrrole synthesis is presumed to start via opening of the lactone moiety of compound **3** by nucleophilic attack of methoxide anion followed by dehydrochlorination of the intermediate iminoester **5** (or vice versa) to give compound **6**. Then, a rearrangement of the conjugated double bonds leads to enaminoester **7**. Intramolecular condensation of the tautomeric aldehyde **8** and subsequent dehydration of the intermediate hemiaminal **9** would then result in pyrroles **4**.



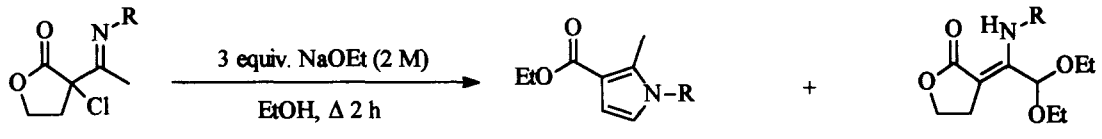
Scheme 2

As could be predicted from this reaction mechanism, N-benzyl-2-chloro-2-acetimidoylbutyrolactone **3e** could not be transformed into the corresponding pyrrole, probably as a result of competitive deprotonation at the benzylic position. 2-Chloro-2-acetimidoylbutyrolactone **3f** (R = phenyl) as well gave only a complex reaction mixture upon reaction with sodium methoxide in methanol under reflux. Surprisingly, in the case of N-alkyl-2-chloro-2-acetimidoylbutyrolactones **3b** (R = n-propyl) and **3c** (R = sec-butyl), and in contrast to the isopropyl derivative **3a**, reaction with 3 equivalents of 2 M sodium methoxide in methanol, again gave only complex reaction mixtures.

When 2-chloro-2-{N-[2-(3,4-dimethoxyphenyl)ethyl]acetimidoyl}butyrolactone **3i** was reacted with 3 equivalents of 2 M sodium methoxide in methanol, a substantial side-product appeared in the reaction mixture. After isolation by flash chromatography, it was identified as the enaminolactone dimethyl acetal **10** (yield 14%). The same type of acetals **12** were also formed as substantial side-products of the present pyrrole synthesis from the reaction of 2-chloro-2-acetimidoylbutyrolactones **3** with 3 equivalents of 2 M sodium ethoxide in ethanol under reflux for 2h. These side-products **12** were separated from the ethyl 1-alkyl-2-methylpyrrole-3-carboxylates **11** by means of flash chromatography (Scheme 3).



10

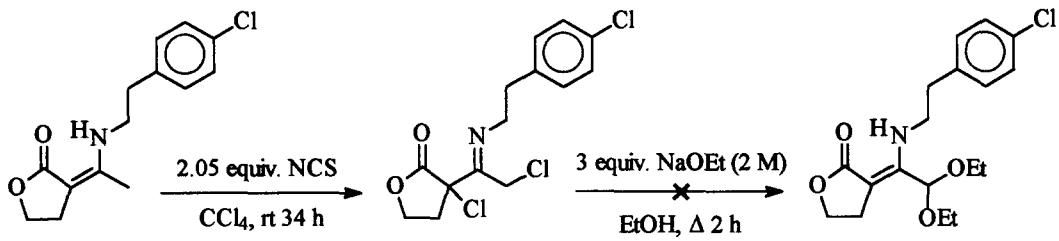


3

11a: R = isopropyl (18%) **12a** (5%)
11b: R = cyclohexyl (29%) **12b** (18%)
11c: R = phenylethyl (21%) **12c** (12%)
11d: R = 2-(3,4-dimethoxyphenyl)ethyl (23%) **12d** (28%)

Scheme 3

It was first believed that these 2-acetimidoylbutyrolactone acetals **12** would be formed as a result of double nucleophilic substitution by ethoxide of dichlorinated acetimidoylbutyrolactones present in the reaction mixture as side-products from the chlorination reaction. Therefore, such a dichlorinated 2-acetimidoylbutyrolactone **13** (Scheme 4) was prepared by reaction of 2-acetimidoylbutyrolactone **2h** with 2 equivalents of *N*-chlorosuccinimide in carbon tetrachloride but the lactone, upon treatment with 3 equivalents of 2 M sodium ethoxide in ethanol under reflux, gave only a complex reaction mixture in which no trace of compound **14** was detected. No suitable mechanistic explanation could be given for this double substitution reaction, accounting for an oxidation process. One possible explanation could be a self chlorination of compound **3**, bearing in mind the electropositive nature of the chlorine situated between the lactone and the imidoyl moieties.



2h **13** (100%) **14**

Scheme 4

In conclusion, a series of methyl and ethyl 1-alkyl-2-methylpyrrole-3-carboxylates **4** and **11** was synthesized from the corresponding 2-chloro-2-acetimidoylbutyrolactones **3** in a one-step procedure by treatment with sodium methoxide or sodium ethoxide in the corresponding alcohol. The yields of alkyl pyrrole-3-carboxylates **4** and **11** are rather low but the pyrroles were isolated in pure form. The advantage of the present pyrrole synthesis stems from its simplicity, utilising only three steps from commercially available 2-acetylbutyrolactone.

EXPERIMENTAL PART

General. ^{1}H NMR spectra (270 MHz) and ^{13}C NMR spectra (68 MHz) were run with a Jeol JNM-EX 270 NMR spectrometer. Peak assignments were performed by the aid of the DEPT technique, 2D-COSY spectra and HETCOR spectra. IR spectra were obtained from a Perkin Elmer model 1310 Spectrometer while mass spectra were measured with a Varian MAT 112 spectrometer (70 eV). Melting points were measured with a Büchi 535 apparatus. Flash chromatography was carried out on a glass column with ACROS silica gel (particle size 0.035-0.07 mm, pore diameter ca. 6 nm). TLC was performed on silica gel plates Kieselgel $60F_{254}$ (layer thickness 0.25 mm). All solvents and reagents were obtained from commercial suppliers and were used without purification. Stock solutions of 2 M sodium methoxide in methanol and 2 M sodium ethoxide in ethanol were prepared by reaction of sodium metal in the respective alcohols.

General procedure for the synthesis of 2-[1-(*N*-alkylamino)ethylidene]butyrolactones (2). To a solution of 2-acetylbutyrolactone **1** and 1 equivalent of a primary amine (in the case of isopropylamine, *n*-propylamine and *sec*-butylamine, 5 equivalents were used) in benzene (10% w/v), a catalytic amount of *p*-toluenesulfonic acid was added and the mixture was heated under reflux for 4-5 h with azeotropic distillation of water by means of a Dean-Stark apparatus. Then the solvent was evaporated under reduced pressure. The crude 2-acetimidoylbutyrolactones **2** were used as such in the next step. Most of the enaminoesters **2** were purified by recrystallisation, while compound **2a** was distilled under vacuo. Compound **2b** and **2c** decomposed upon vacuum distillation.

2-[1-(*N*-Isopropylamino)ethylidene]butyrolactone (**2a**)

Yield 98% (crude product). Distillation (bp 90°C / 0.15 mmHg) gave **2a** as a colourless oil, yield 49%. ^{1}H NMR ($CDCl_3$) : δ 1.22 (6H, d, J=6.3 Hz, $CH(C\underline{H}_3)_2$), 1.96 (3H, s, $C=CC\underline{H}_3$), 2.82 (2H, t, J=7.9 Hz, $OCH_2C\underline{H}_2$), 3.68 (1H, septet, J=6.3 Hz, $C\underline{H}(CH_3)_2$), 4.26 (2H, t, J=7.9 Hz, OCH_2), 8.13 (1H, broad s, NH). ^{13}C NMR ($CDCl_3$) : δ 16.28 ($C=C\underline{C}H_3$), 24.06 ($CH(\underline{C}H_3)_2$), 26.58 ($OCH_2\underline{C}H_2$), 44.49 ($\underline{C}H(CH_3)_2$), 65.03 (OCH_2), 84.37 ($\underline{C}=CN$), 156.15 ($C=\underline{C}N$), 173.98 (C=O). IR (NaCl) ν_{max} : 3240 (NH), 1690 (C=O), 1615 (C=C) cm^{-1}. MS *m/z* (%) : 169(M^+, 61), 154(100), 136(10), 126(14), 110(20), 96(18), 69(27), 58(51), 43(53). Anal. Calcd. for $C_9H_{15}NO_2$: C 63.88%, H 8.93%, N 8.28%. Found C 63.52%, H 8.77%, N 8.22%.

2-[1-(*N*-Propylamino)ethylidene]butyrolactone (**2b**)

Yield 93% (crude product). This compound decomposed upon distillation. ^{1}H NMR ($CDCl_3$) : δ 0.96 (3H, t, J=7.3 Hz, $CH_2C\underline{H}_3$), 1.56 (2H, sextet, J=7.3 Hz, $C\underline{H}_2CH_3$), 1.94 (3H, s, $C=CC\underline{H}_3$), 2.83 (2H, t, J=7.9 Hz, $OCH_2C\underline{H}_2$) 3.18 (2H, t, J=7.3 Hz, NCH_2), 4.25 (2H, t, J=7.9 Hz, OCH_2), 8.25 (1H, broad s, NH). ^{13}C NMR ($CDCl_3$) : δ 10.89 ($CH_2\underline{C}H_3$), 15.92 ($C=C\underline{C}H_3$), 23.39 ($\underline{C}H_2CH_3$), 26.14 ($OCH_2\underline{C}H_2$), 44.39 (NCH_2), 64.73 (OCH_2), 83.99 ($\underline{C}=CN$), 156.93 ($C=\underline{C}N$), 173.73 (C=O). IR (NaCl) ν_{max} : 3272 (NH), 1683 (C=O), 1607 (C=C) cm^{-1}. MS *m/z* (%) : 169(M^+, 41), 141(8), 140(100), 122(17), 112(14), 111(10), 110(12), 96(16), 94(9), 82(16), 69(14), 68(11), 67(12), 53(14), 44(8), 43(17), 42(42), 41(30).

2-[1-(*N-sec*-Butylamino)ethylidene]butyrolactone (**2c**)

Yield 98% (crude product).This compound decomposed upon distillation. ^{1}H NMR ($CDCl_3$) : δ 0.93 (3H, t, J=7.3 Hz, CH_2CH_3), 1.17 (3H, d, J=6.8 Hz, $CHCH_3$), 1.52 (2H, quintet, J=6.8 Hz, CH_2CH_3), 1.95 (3H, s, $C=CCH_3$), 2.83 (2H, t, J=7.9 Hz, OCH_2CH_2), 3.45 (1H, sextet, J=6.8 Hz, $CHCH_3$), 4.25 (2H, t, J=7.9 Hz, OCH_2), 8.14 (1H, s, NH). ^{13}C NMR ($CDCl_3$) : δ 9.49 (CH_2CH_3), 15.58 ($C=CCH_3$), 21.01 ($CHCH_3$), 25.75 (OCH_2CH_2), 29.98 (CH_2CH_3), 49.15 (NCH), 64.21 (OCH_2), 83.43 (C=CN), 155.90 (C=CN), 173.15 (C=O). IR (NaCl) ν_{max} : 3297 (NH), 1683 (C=O), 1615 (C=C) cm^{-1}. MS *m/z* (%) : 183(M^+, 23), 168(11), 155(9), 154(100), 110(11), 69(18), 68(11), 44(11), 42(29), 41(29).

2-[1-(*N*-Cyclohexylamino)ethylidene]butyrolactone (**2d**)

Yield 97% (crude product). Recrystallisation from dichloromethane gave **2d** as a white powder, mp 72.5-76°C, yield 50%. ^{1}H NMR ($CDCl_3$) : δ 1.15-1.92 (10H, m, $(CH_2)_5$), 1.95 (3H, s, $C=CCH_3$), 2.82 (2H, t, J=7.9 Hz, OCH_2CH_2), 3.25-3.35 (1H, m, CHN), 4.25 (2H, t, J=7.9 Hz, OCH_2), 8.27 (1H, d, J=7.6 Hz, NH). ^{13}C NMR ($CDCl_3$) : δ 16.30 ($C=CCH_3$), 24.69 (2C) and 25.37 and 34.30 (2C) ($(CH_2)_5$), 26.61 (OCH_2CH_2), 51.50 (CHN), 65.05 (OCH_2), 84.28 (C=CN), 156.13 (C=CN), 173.98 (C=O). IR (KBr) ν_{max} : 3420 (NH), 1675 (C=O), 1605 (C=C) cm^{-1}. MS *m/z* (%) : 209(M^+, 44), 166(50), 128(100), 98(21), 84(23), 69(23), 67(19), 55(27), 44(22), 41(33). Anal. Calcd. for $C_{12}H_{19}NO_2$: C 68.87%, H 9.15%, N 6.69%. Found C 68.69%, H 8.89%, N 6.85%.

2-[1-(*N*-Benzylamino)ethylidene]butyrolactone (**2e**)

Recrystallisation from dichloromethane gave **2e** as a white powder, mp 100.9-101.4°C, yield 70%. ^{1}H NMR ($CDCl_3$) : δ 1.89 (3H, s, $C=CCH_3$), 2.83 (2H, t, J=7.9 Hz, OCH_2CH_2), 4.27 (2H, t, J=7.9 Hz, OCH_2), 4.42 (2H, d, J=6.6 Hz, NCH_2), 7.23-7.36 (5H, m, C_6H_5), 8.66 (1H, broad s, NH). ^{13}C NMR ($CDCl_3$) : δ 16.39 ($C=CCH_3$), 26.49 (OCH_2CH_2), 46.70 (NCH_2), 65.21 (OCH_2), 86.05 (C=CN), 126.59 and 127.31 and 128.77 and 138.88 (C_6H_5), 156.98 (C=CN), 174.12 (C=O). IR (KBr) ν_{max} : 3300 (NH), 1680 (C=O), 1620 (C=C) cm^{-1}. MS *m/z* (%) : 217(M^+, 51), 202(6), 172(8), 158(13), 131(9), 106(28), 104(12), 92(14); 91(100), 65(23), 40(17). Anal. Calcd. for $C_{13}H_{15}NO_2$: C 71.87%, H 6.96%, N 6.45%. Found C 72.15%, H 6.98%, N 6.55%.

2-[1-(*N*-Phenylamino)ethylidene]butyrolactone (**2f**)

Recrystallisation from dichloromethane gave **2f** as a pink powder, mp 74.7-77.4°C, yield 76%. ^{1}H NMR ($CDCl_3$) : δ 2.02 (3H, s, $C=CCH_3$), 2.91 (2H, t, J=7.6 Hz, OCH_2CH_2), 4.35 (2H, t, J=7.6 Hz, OCH_2), 7.05 (2H, d, J=7.6 Hz) and 7.15 (1H, t, J=7.6 Hz) and 7.31 (2H, m) (C_6H_5). 9.98 (1H, s, NH). ^{13}C NMR ($CDCl_3$) : δ 17.72 ($C=CCH_3$), 26.45 (OCH_2CH_2), 65.34 (OCH_2), 89.27 (C=CN), 124.22 and 124.85 and 129.13 and 139.15 (C_6H_5), 153.53 (C=CN), 173.89 (C=O). IR (KBr) ν_{max} : 1680 (C=O), 1635 (C=C) cm^{-1}. MS *m/z* (%) : 203(M^+, 100), 202(26), 188(12), 184(10), 175(33), 158(22), 157(16), 156(15), 144(57), 130(33), 118(46), 117(18), 93(50), 65(20), 51(36), 42(21), 41(19), 40(15). Anal. Calcd. for $C_{12}H_{13}NO_2$: C 70.92%, H 6.45%, N 6.89%. Found C 70.77%, H 6.68%, N 6.81%.

2-{1-[*N*-(2-Phenylethyl)amino]ethylidene}butyrolactone (**2g**)

Recrystallisation from benzene gave **2g** as a yellow powder, mp 78-79°C, yield 90%. ^{1}H NMR ($CDCl_3$) : δ 1.82 (3H, s, $C=CCH_3$), 2.77-2.87 (4H, m, OCH_2CH_2 and NCH_2CH_2), 3.44 (2H, ~q, J= ~6.9 Hz, $NHCH_2$), 4.26 (2H,

t, J=7.9 Hz, OCH_2), 7.18-7.31 (5H, m, C_6H_5), 8.34 (1H, broad s, NH). ^{13}C NMR ($CDCl_3$) δ : 16.03 (C=C$\underline{C}H_3$), 26.35 ($OCH_2\underline{C}H_2$), 37.22 ($NCH_2\underline{C}H_2$), 44.64 (NCH_2), 64.98 (OCH_2), 84.82 ($\underline{C}$=CN), 126.47 (2x) and 128.46 (2x) and 128.68 (5x =CH), 138.37 (=C_{quat}), 156.73 (C=$\underline{C}$N), 173.91 (C=O). IR (KBr) ν_{max} : 3287 (NH), 1682 (C=O), 1612 (C=C) cm^{-1}. MS *m/z* (%) : 231(M^+, 24), 140(100), 122(17), 112(10), 69(7), 53(8), 42(10). Anal. Calcd. for $C_{14}H_{17}NO_2$: C 72.70%, H 7.41%, N 6.06%. Found C 72.54%, H 7.65%, N 6.01%.

2-{1-[*N*-(2-(4-Chlorophenyl)ethyl)amino]-1-ethylidene}butyrolactone (**2h**)

Recrystallisation from benzene gave **2h** as a yellow powder, mp 88-89°C, yield 84%. ^1H NMR ($CDCl_3$) : δ 1.81 (3H, s, C=CCH_3), 2.75-2.83 (4H, m, $NCH_2\underline{CH_2}$ and $OCH_2\underline{CH_2}$), 3.42 (2H, q, J=6.9 Hz, NCH_2), 4.26 (2H, t, J=7.9 Hz, OCH_2), 7.12 (2H, d, J=8.6 Hz, C_6H_4), 7.28 (2H, d, J=8.6 Hz, C_6H_4), 8.31 (1H, broad s, NH). ^{13}C NMR ($CDCl_3$) : δ 16.16 (C=C$\underline{C}H_3$), 26.42 ($OCH_2\underline{C}H_2$), 36.64 ($NCH_2\underline{C}H_2$), 44.55 ($NHCH_2$), 65.10 (OCH_2), 85.27 ($\underline{C}$=CN), 128.71 and 130.15 (4x =CH), 132.45 and 136.93 (2x =C_{quat}), 156.49 (C=$\underline{C}$N), 174.05 (C=O). IR (KBr) ν_{max} : 3288 (NH), 1678 (C=O), 1614 (C=C) cm^{-1}. MS *m/z* (%) : 265(M^+, 8), 164(12), 151(36), 140(100), 122(13), 112(4), 94(5), 77(5), 69(7), 42(8), 40(33). Anal. Calcd. for $C_{14}H_{16}NO_2Cl$: C 63.28%, H 6.07%, N 5.27%. Found C 63.02%, H 5.88%, N 5.33%.

2-{1-[*N*-(2-(3,4-Dimethoxyphenyl)ethyl)amino]ethylidene}butyrolactone (**2i**)

Recrystallisation from benzene gave **2i** as a white powder, mp 112-113°C, yield 91%. ^1H NMR ($CDCl_3$) : δ 1.79 (3H, s, C=CCH_3), 2.76-2.82 (4H, m, $OCH_2\underline{CH_2}$ and $NCH_2\underline{CH_2}$), 3.43 (2H, ~q, J= ~6.7 Hz, $NHC\underline{H_2}$), 3.86 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 4.26 (2H, t, J=7.9 Hz, OCH_2), 6.73-6.83 (3H, m, C_6H_3), 8.35 (1H, broad s, NH). ^{13}C NMR ($CDCl_3$) : δ 16.23 (C=C$\underline{C}H_3$), 26.52 ($OCH_2\underline{C}H_2$), 36.95 ($NCH_2\underline{C}H_2$), 45.05 ($NHCH_2$), 55.89 (OCH_3), 55.92 (OCH_3), 65.12 (OCH_2), 84.87 ($\underline{C}$=CN), 111.41 and 112.25 and 120.75 (3x =CH), 131.19 (=C_{quat}), 147.78 and 148.96 (2x =$\underline{C}$-OCH_3), 156.87 (C=$\underline{C}$N), 174.07 (C=O). IR (KBr) ν_{max} : 3280 (NH), 1683 (C=O), 1610 (C=C) cm^{-1}. MS *m/z* (%) : 291(M^+, 10), 164(14), 140(100), 122(11), 112(5), 53(7), 42(9), 41(9), 40(8). Anal. Calcd. for $C_{16}H_{21}NO_4$: C 65.96%, H 7.27%, N 4.81%. Found C 65.88%, H 7.05%, N 4.68%.

General procedure for the synthesis of 2-chloro-2-[1-(*N*-alkylimino)ethyl]butyrolactones (3). A mixture of 2-acetimidoylbutyrolactone **2** and 1.05 equivalents of *N*-chlorosuccinimide in carbon tetrachloride (10% w/v) was stirred at room temperature for 1-24 h. The progress of the reaction was followed by TLC. Then the succinimide precipitate was separated by filtration and the solvent was evaporated under reduced pressure. The crude 2-chloro-2-acetimidoylbutyrolactones **3** (purity > 95%) were used as such in the next step.

2-Chloro-2-[1-(*N*-isopropylimino)ethyl]butyrolactone (**3a**)

Yield 96% (crude product). Distillation (bp 50-56°C / 0.01 mmHg) gave **3a** as a colourless oil, yield 66%. ^1H NMR ($CDCl_3$) : δ 1.09 (3H, d, J=6.3 Hz, $CH(C\underline{H_3})_2$), 1.11 (3H, d, J=6.3 Hz, $CH(C\underline{H_3})_2$), 2.14 (3H, s, CH_3C=N), 2.45-2.58 and 3.34-3.44 (each 1H, each m, $OCH_2\underline{CH_2}$), 3.70 (1H, septet, J=6.3 Hz, $C\underline{H}(CH_3)_2$), 4.22-4.30 and 4.37-4.45 (each 1H, each m, OCH_2). ^{13}C NMR ($CDCl_3$) : δ 13.42 ($\underline{C}H_3C$=N), 22.98 and 23.04 ($CH(\underline{C}H_3)_2$), 36.39 ($OCH_2\underline{C}H_2$), 51.36 ($\underline{C}H(CH_3)_2$), 65.97 (OCH_2), 69.13 (CCl), 159.06 (C=N), 172.32 (C=O), IR (NaCl) ν_{max} : 1770 (C=O), 1650 (C=C) cm^{-1}. MS *m/z* (%) : no M^+, 202/4(M^+-1, 19), 188/90(2), 168(13),

144/6(2), 120(7), 108(3), 84(37), 67(5), 42(19). Anal. Calcd. for $C_9H_{14}NO_2Cl$: C 53.08%, H 6.93%, N 6.88%. Found C 53.40%, H 6.89%, N 6.87%.

2-Chloro-2-[1-(*N*-propylimino)ethyl]butyrolactone (**3b**)

Yield 97% (crude product). This compound decomposed upon distillation. ^{1}H NMR ($CDCl_3$) : δ 0.94 (3H, t, J=7.0 Hz, CH_2CH_3), 1.65 (2H, sextet, J=7.0 Hz, CH_2CH_3), 2.14 (3H, s, CH_3C=N), 2.47-2.59 and 3.18-3.40 (each 1H, each m, OCH_2CH_2), 3.29 (2H, t, J=7.0 Hz, NCH_2), 4.24-4.32 and 4.40-4.46 (each 1H, each m, OCH_2). ^{13}C NMR ($CDCl_3$) : δ 11.47 (CH_2CH_3), 13.49 (CH_3C=N), 23.09 (CH_2CH_3), 35.99 (OCH_2CH_2), 53.01 (NCH_2), 65.34 (OCH_2), 68.89 (CCl), 161.55(C=N), 171.77 (C=O). IR (NaCl) ν_{max} : 1778 (C=O), 1656 (C=N) cm^{-1}. MS *m/z* (%) : no M^+, 168(M^+-Cl), 140(2), 120(2), 102(2), 98(2), 94(4), 89(2), 85(5), 84(51), 82(2), 75(2), 68(2), 67(3), 65(3), 55(3), 53(6), 43(22), 42(100).

2-Chloro-2-[1-(*N-sec*-butylimino)ethyl]butyrolactone (**3c**)

Yield 95% (crude product). This compound decomposed upon distillation. ^{1}H NMR ($CDCl_3$) : δ 1.05 (3H, t, J=6.0 Hz, CH_2CH_3), 1.17 (2H, d, J=6.6 Hz, $CHCH_3$), 1.45-1.57 (2H, m, CH_2CH_3), 2.14 (3H, s, CH_3C=N), 2.47-2.54 and 3.34-3.45 (each 1H, each m, OCH_2CH_2), 3.40-3.49 (1H, m, NCH), 4.22-4.31 and 4.45-4.55 (each 1H, each m, OCH_2). ^{13}C NMR ($CDCl_3$) : δ 10.44 (CH_2CH_3), 13.26 (CH_3C=N), 20.24 ($CHCH_3$), 30.32 (OCH_2CH_2), 36.34 (CH_2CH_3), 57.02 (NCH), 65.63 (OCH_2), 69.11 (CCl), 159.48 (C=N), 173.76 (C=O). IR (NaCl) ν_{max} : 1778 (C=O), 1655 (C=N) cm^{-1}. MS *m/z* (%) : no M^+, 182(M^+-Cl, 8), 154(2), 144(1), 126(2), 122(4), 120(9), 118(2), 109(1), 108(5), 102(2), 98(37), 94(2), 82(3), 68(4), 67(7), 65(4), 57(27), 56(3), 55(5), 53(6), 43(5), 42(100).

2-Chloro-2-[1-(*N*-cyclohexylimino)ethyl]butyrolactone (**3d**)

Yield 98% (crude product). This compound decomposed upon distillation. ^{1}H NMR ($CDCl_3$) : δ 1.21-1.40 (6H, m) and 1.42-1.66 (2H, m) and 1.69-1.79 (2H, m) ($(CH_2)_5$), 2.14 (3H, s, CH_3C=N), 2.45-2.58 (1H, m, OCH_2CH_2), 3.32-3.42 (2H, m, OCH_2CH_2 and NCH), 4.21-4.28 and 4.32-4.44 (each 1H, each m, OCH_2). ^{13}C NMR ($CDCl_3$) δ : 13.46 (CH_3C=N), 24.22 (2x) and 25.66 and 32.92 (2x), ($(CH_2)_5$), 36.46 (OCH_2CH_2), 59.39 (CHN), 65.95 (OCH_2), 69.24 (CCl), 159.15 (C=N), 172.36 (C=O). IR (NaCl) ν_{max} : 1780 (C=O), 1650 (C=N) cm^{-1}. MS *m/z* (%) : no M^+, 208(M^+-Cl, 33), 128(7), 124(32), 120(15), 98(4), 84(9), 83(100), 67(8), 55(42), 42(23), 42(21).

2-Chloro-2-[1-(*N*-benzylimino)ethyl]butyrolactone (**3e**)

Recrystallisation from ether gave **3**[e] as a white powder, mp 35.5-36°C, yield 95%. ^{1}H NMR ($CDCl_3$) : δ 2.27 (3H, s, CH_3C=N), 2.50-2.61 and 3.40-3.50 (each 1H, each m, OCH_2CH_2), 4.26-4.34 and 4.39-4.47 (each 1H, each m, OCH_2), 4.56 (2H, s, NCH_2), 7.32-7.35 (5H, m, C_6H_5). ^{13}C NMR ($CDCl_3$) : δ 14.88 (CH_3C=N), 36.23 (OCH_2CH_2), 55.38 (NCH_2), 65.89 (OCH_2), 68.89 (CCl), 126.92 and 127.46 (2x) and 128.50 (2x) and 139.15 (C_6H_5), 163.50 (C=N), 171.95 (C=O). IR (KBr) ν_{max} : 1770 (C=O), 1650 (C=N) cm^{-1}. MS *m/z* (%) : no M^+, 250(1), 216(23), 187(1), 170(1), 157(1), 132(2), 106(2), 91(100), 65(12). Anal. Calcd. for $C_{13}H_{14}NO_2Cl$: C 62.03%, H 5.61%, N 5.56%. Found C 61.76%, H 5.45%, N 5.44%.

2-Chloro-2-[1-(*N*-phenylimino)ethyl]butyrolactone (**3f**)

Yield 96% (crude product). Distillation (bp 121-127°C / 0.05 mmHg) gave **3f** as a colourless oil, yield 64%. ^{1}H NMR ($CDCl_3$) : δ 2.17 (3H, s, CH_3C=N), 2.58-2.69 and 3.45-3.56 (each 1H, each m, $OCH_2C\underline{H}_2$), 4.40-4.55 (2H, m, OCH_2), 6.70 (2H, d, J=7.6 Hz) and 7.11 (1H, t, J=7.6 Hz) and 7.34 (2H, t, J=7.6 Hz) (C_6H_5). ^{13}C NMR ($CDCl_3$) : δ 16.28 ($\underline{C}H_3C$=N), 36.44 ($OCH_2\underline{C}H_2$), 65.97 (OCH_2), 68.32 (CCl), 118.76 (2x) and 124.33 and 129.11 (2x) and 149.22 (C_6H_5), 164.92 (C=N), 171.50 (C=O). IR (KBr) ν_{max} : 1775 (C=O), 1650 (C=N) cm^{-1}. MS *m/z* (%) : 237/9(M^+, 16), 202(8), 158(6), 143(8), 119(24), 118(100), 91(1), 77(47), 51(18). Anal. Calcd. for $C_{12}H_{12}NO_2Cl$: C 60.64%, H 5.09%, N 5.89%. Found C 60.55%, H 5.29%, N 5.87%.

2-Chloro-2-{1-[*N*-(2-phenylethyl)imino]ethyl}butyrolactone (**3g**)

Yield 71% (crude product). This compound decomposed upon distillation. ^{1}H NMR ($CDCl_3$) : δ 2.01 (3H, s, CH_3C=N), 2.45-2.59 and 3.24-3.34 (each 1H, each m, $OCH_2C\underline{H}_2$), 2.96 (2H, t, J=6.9 Hz, $NCH_2C\underline{H}_2$), 3.59 (2H, t, J=6.9 Hz, $NC\underline{H}_2CH_2$), 4.15-4.42 (2H, m, $OC\underline{H}_2CH_2$), 7.18-7.32 (5H, m, C_6H_5). ^{13}C NMR ($CDCl_3$) : δ 14.11 ($\underline{C}H_3C$=N), 36.28 and 36.66 ($NCH_2\underline{C}H_2$ and $OCH_2\underline{C}H_2$), 53.32 ($N\underline{C}H_2CH_2$), 65.64 (OCH_2), 68.95 (CCl), 126.18, 128.32 (2x), 128.86 (2x) (5 x =CH), 139.91 (=C_{quat}), 162.75 (C=N), 172.00 (C=O). IR (NaCl) ν_{max} : 1775 (C=O), 1657 (C=N) cm^{-1}. MS *m/z* (%) : 265(M^+, 1), 230(8), 208(5), 182(23), 174(38), 146(13), 140(11), 105(100), 91(18), 77(13), 53(12), 43(12), 39(11).

2-Chloro-2-{1-[*N*-(2-(4-chlorophenyl)ethyl)imino]ethyl}butyrolactone (**3h**)

Yield 94% (crude product). This compound decomposed upon distillation. ^{1}H NMR ($CDCl_3$) : δ 2.04 (3H, s, CH_3C=N), 2.46-2.56 and 3.21-3.31 (each 1H, each m, $OCH_2C\underline{H}_2$), 2.94 (2H, ~t , J= ~6.8 Hz, $NCH_2C\underline{H}_2$), 3.56 (2H, ~t, J= ~6.8Hz, $NC\underline{H}_2CH_2$), 4.10-4.21 and 4.40-4.49 (each 1H, each m, $OC\underline{H}_2CH_2$), 7.11-7.30 (4H, m, C_6H_4). ^{13}C NMR ($CDCl_3$) : δ 14.25 ($\underline{C}H_3C$=N), 36.07 and 36.48 ($NCH_2\underline{C}H_2$ and $OCH_2\underline{C}H_2$), 53.01 (NCH_2), 65.68 (OCH_2), 69.24 (CCl), 128.45 (2x) and 130.39 (2x) (4x =CH), 131.95 and 138.62 (2x =C_{quat}), 163.23 (C=N), 172.04 (C=O). IR (NaCl) ν_{max} : 1778 (C=O), 1655 (C=N) cm^{-1}. MS *m/z* (%) : 299/301(M^+, 2), 264(9), 180(10), 176(31), 174(97), 141(33), 139(100), 130(5), 125(15), 111(14), 103(34), 94(12), 89(23), 77(18), 53(14), 43(26), 39(10).

2-Chloro-2-{1-[*N*-(2-(3,4-dimethoxyphenyl)ethyl)imino]ethyl}butyrolactone (**3i**)

Yield 97% (crude product). This compound decomposed upon distillation. ^{1}H NMR ($CDCl_3$) : δ 2.03 (3H, s, CH_3C=N), 2.51-2.60 and 3.24-3.31 (each 1H, each m, $OCH_2C\underline{H}_2$), 2.92 (2H, ~t, J= ~7.0 Hz, $NCH_2C\underline{H}_2$), 3.59 (2H, ~t, J= ~7.0 Hz, $NC\underline{H}_2CH_2$), 3.88 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 4.03-4.29 and 4.36-4.44 (each 1H, each m, $OC\underline{H}_2CH_2$), 6.72-6.83 (3H, m, 3x =CH). ^{13}C NMR ($CDCl_3$) : δ 13.89 ($\underline{C}H_3C$=N), 36.10 and 36.36 ($NCH_2\underline{C}H_2$ and $OCH_2\underline{C}H_2$), 53.40 ($N\underline{C}H_2CH_2$), 55.70 (OCH_3), 55.74 (OCH_3), 65.39 (OCH_2), 69.07 (CCl), 111.07 and 112.17 and 120.56 (3x =CH), 132.49 (=C_{quat}), 147.28 and 148.59 (2x =$\underline{C}$-OCH_3), 162.71 (C=N), 171.12 (C=O). IR (NaCl) ν_{max} : 1780 (C=O), 1655 (C=N) cm^{-1}. MS *m/z* (%) : 325/27(M^+, 1), 122(19), 120(58), 99(10), 91(8), 86(22), 84(35), 75(6), 56(8), 51(15), 49(46), 43(100), 41(13).

Synthesis of 2-chloro-2-{1-[*N*-(2-(4-chlorophenyl)ethyl)imino]-2-chloroethyl}butyrolactone 13. A mixture of 3-{1-[*N*-(2-(4-chlorophenyl)ethyl)amino]ethylidene}butyrolactone **2h** (1.5 mmol, 0.40 g) and *N*-chlorosuccinimide (3.075 mmol, 0.42 g) in carbon tetrachloride (10 ml) was stirred at room temperature for 34 h. Then the succinimide precipitate was separated by filtration and the solvent was evaporated under reduced pressure to afford the crude 2-chloro-2-{1-[*N*-(2-(4-chlorophenyl)ethyl)amino]-2-chloroethyl}butyrolactone **13** (0.50 g, 100%) which was used as such in the next step. ^{1}H NMR ($CDCl_3$) : δ 2.98 (2H, t, J=6.9 Hz, $NCH_2C\underline{H}_2$), 3.21-3.38 and 3.72-3.94 (each 1H, each m, $OCH_2C\underline{H}_2$), 3.79 (2H, t, J=6.9 Hz, NCH_2), 4.11 (1H, d, J=12.2 Hz, C<u>H</u>HCl), 4.31 (1H, d, J=12.2 Hz, CH<u>H</u>Cl), 4.19-4.31 and 4.39-4.49 (each 1H, each m, OCH_2), 7.12-7.29 (4H, m, C_6H_4). ^{13}C NMR ($CDCl_3$) : δ 32.37 (CH_2Cl), 35.40 and 36.17 ($OCH_2\underline{C}H_2$ and $NCH_2\underline{C}H_2$), 53.01 (NCH_2), 65.27 (OCH_2), 67.78 (CCl), 128.03 (2x =CH), 130.00 (2x =CH), 131.56 (=C_{quat}), 137.75 (=C_{quat}), 159.32 (C=N), 170.98 (C=O). Anal. Calcd. for $C_{14}H_{14}NO_2Cl_3$: C 50.25%, H 4.22%, N 4.19%. Found C 50.13%, H 4.05%, N 4.22%.

General procedure for the synthesis of methyl and ethyl 1-alkyl-2-methylpyrrole-3-carboxylates 4 and 11 and 2-[1-(*N*-alkylamino)-2,2-dialkoxyethylidene]butyrolactones 10 and 12. At 0°C, 3 equivalents of a 2 M solution of sodium methoxide in methanol or a 2 M solution of sodium ethoxide in ethanol was added dropwise to a 2-chloro-2-acetimidoylbutyrolactone **5**. The resulting suspension was heated under reflux for 2 h, the reaction was quenched by the addition of water, extracted with dichloromethane, dried ($MgSO_4$) and evaporated under reduced pressure. The pyrroles **4** and **11** and the acetals **10** and **12** were isolated by flash chromatography.

<u>Methyl 1-isopropyl-2-methylpyrrole-3-carboxylate (**4a**)</u>

Flash chromatography (Rf = 0.35, ethyl acetate/hexane 20/80) gave **4a** as a yellow oil, yield 23%. ^{1}H NMR ($CDCl_3$) : δ 1.40 (6H, d, J=6.6 Hz, $CH(C\underline{H}_3)_2$), 2.54 (3H, s, CH_3C=C), 3.78 (3H, s, CH_3O), 4.33 (1H, septet, J=6.6 Hz, $C\underline{H}(CH_3)_2$), 6.54 (1H, d, J=3.3 Hz, C<u>H</u>=CHN), 6.61 (1H, d, J=3.3 Hz, CH=C<u>H</u>N). ^{13}C NMR ($CDCl_3$) : δ 10.66 ($\underline{C}H_3C$=C), 23.17 ($CH(\underline{C}H_3)_2$), 46.94 ($\underline{C}H(CH_3)_2$), 50.55 (CH_3O), 109.51 (<u>C</u>H=CHN), 111.32 (=$\underline{C}CH_3$), 115.08 (CH=<u>C</u>HN), 134.86 (=$\underline{C}CO_2CH_3$), 166.09 (C=O). IR (NaCl) ν_{max} : 1700 (C=O) cm^{-1}. MS *m/z* (%) : 181(M^+, 100), 166(36), 150(61), 138(8), 124(38), 122(24), 108(92), 107(39), 80(20), 79(17), 59(11), 53(23), 43(20), 41(20). Anal. Calcd. for $C_{10}H_{15}NO_2$: C 66.27%, H 8.34%, N 7.73%. Found C 66.25%, H 8.45%, N 7.76%.

<u>Methyl 1-cyclohexyl-2-methylpyrrole-3-carboxylate (**4b**)</u>

Flash chromatography (Rf = 0.40, ethyl acetate/hexane 20/80) gave **4b** as yellow needles, yield 25%, mp 57.6°C (ether/pentane). 1.18-1.98 (10H, m, $(CH_2)_5$), 2.54 (3H, s, CH_3C=C), 3.78 (3H, s, CH_3O), 3.84 (1H, m, CHN). 6.53 (1H, d, J=3.3 Hz, C<u>H</u>=CHN), 6.60 (1H, d, J=3.3 Hz, CH=C<u>H</u>N). ^{13}C NMR ($CDCl_3$) : δ 10.84 ($\underline{C}H_3C$=C), 25.37 and 25.84 (2x) and 33.93 (2x) ($(CH_2)_5$) 50.62 (CHN), 55.20 (CH_3O), 109.34 (<u>C</u>H=CHN), 111.30 (=$\underline{C}CH_3$), 115.96 (CH=<u>C</u>HN), 135.00 (=$\underline{C}CO_2CH_3$), 166.09 (C=O). IR (KBr) ν_{max} : 1700 (C=O) cm^{-1}. MS *m/z* (%) : 221(M^+, 98), 206(33), 190(27), 178(14), 174(12), 166(22), 162(26), 140(85), 139(55), 124(30), 108(100), 107(58), 94(17), 80(26), 67(20), 55(53), 53(23), 41(41). Anal. Calcd. for $C_{13}H_{19}NO_2$: C 70.56%, H 8.65%, N 6.33%. Found C 70.39%, H 8.76%, N 6.45%.

Methyl 2-methyl-1-(2-phenylethyl)pyrrole-3-carboxylate (**4c**)

Flash chromatography (Rf = 0.20, ethyl acetate/hexane 20/80) gave **4c** as a brown oil, yield 23%. ^{1}H NMR ($CDCl_3$) : δ 2.35 (3H, s, CH_3), 2.97 (2H, t, J=7.3 Hz, $NCH_2\underline{C}H_2$), 3.78 (3H, s, OCH_3), 4.03 (2H, t, J=7.3 Hz, NCH_2), 6.41 (1H, d, J=3.3 Hz, NCH=C<u>H</u>), 6.50 (1H, d, J=3.3 Hz, NC<u>H</u>=CH), 7.03-7.05 and 7.20-7.23 (5H, m, C_6H_5). ^{13}C NMR ($CDCl_3$) : δ 11.13 ($\underline{C}H_3C$=C), 38.06 ($NCH_2\underline{C}H_2$), 48.69 ($N\underline{C}H_2CH_2$), 51.07 ($O\underline{C}H_3$), 109.92 (NCH=<u>C</u>H), 112.04 (=<u>C</u>CH$_3$), 120.16 (N<u>C</u>H=CH), 129.16 (5x =CH), 136.20 (=<u>C</u>CO$_2$CH$_3$), 138.19 (=C_{quat}), 167.0 (C=O). IR (NaCl) ν_{max} : 1693 (C=O) cm^{-1}. MS *m/z* (%) : 243(M^+, 37), 200(14), 178(12), 171(95), 169(100), 166(27), 152(48), 127(27), 125(81), 110(82), 104(25), 90(33), 86(45), 77(12), 70(15), 58 (31), 54(95), 45(30), 41(41). Anal. Calcd. for $C_{15}H_{17}NO_2$: C 74.05%, H 7.04%, N 5.76%. Found C 73.66%, H 7.12%, N 5.88%.

Methyl 1-[2-(4-chlorophenyl)ethyl]-2-methylpyrrole-3-carboxylate (**4d**)

Flash chromatography (Rf = 0.30, ethyl acetate/hexane 20/80) gave **4d** as a brown oil, yield 22%. ^{1}H NMR ($CDCl_3$) : δ 2.35 (3H, s, CH_3), 2.94 (2H, t , J=7.4 Hz, $NCH_2\underline{C}H_2$), 3.78 (3H, s, OCH_3), 4.03 (2H, t , J=7.4 Hz, $NC\underline{H}_2CH_2$), 6.37 (1H, d , J=2.7 Hz, NCH=C<u>H</u>), 6.49 (1H, d , J=2.7 Hz, NC<u>H</u>=CH), 6.92-6.96 and 7.20-7.31 (each 2H, each m, C_6H_4). ^{13}C NMR ($CDCl_3$) : δ 10.71 ($\underline{C}H_3C$=C), 36.89 ($NCH_2\underline{C}H_2$), 47.96 ($N\underline{C}H_2CH_2$), 50.66 (OCH_3), 109.58 (NCH=<u>C</u>H), 111.90 (=<u>C</u>CO$_2$CH$_3$), 119.71 (N<u>C</u>H=CH), 128.79 (2x) and 130.06 (2x) (4x =CH), 132.78 (=C_{quat}), 135.44 (=<u>C</u>CH$_3$), 136.14 (=C_{quat}), 165.91 (C=O). IR (NaCl) ν_{max} : 1694 (C=O) cm^{-1}. MS *m/z* (%) : 277(M^+, 75), 246(16), 168(6), 152(100), 140(16), 138(35), 125(10), 108(17), 103(14), 92(8), 85(8), 77(10), 59(17), 57(17), 43(15), 40 (17). Anal. Calcd. for $C_{15}H_{16}NO_2Cl$: C 64.87%, H 5.81%, N 5.04%. Found C 64.99%, H 5.89%, N 5.07%.

Methyl 1-[2-(3,4-dimethoxyphenyl)ethyl]-2-methylpyrrole-3-carboxylate (**4e**)

Flash chromatography (Rf = 0.21 ethyl acetate/hexane 20/80) gave **4e** as brown crystals, yield 20%, mp 76-79°C. ^{1}H NMR ($CDCl_3$) : δ 2.33 (3H, s, CH_3), 2.90 (2H, t, J=6.9 Hz, $NCH_2\underline{C}H_2$), 3.76 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.86 (3H, s, CO_2CH_3), 4.01 (2H, t, J=6.9 Hz, $NC\underline{H}_2CH_2$), 6.37 (1H, d, J=1.9 Hz, $C_6\underline{H}_5$), 6.41 (1H, d, J=2.9 Hz, NCH=C<u>H</u>), 6.50 (1H, d, J=2.9 Hz, NC<u>H</u>=CH), 6.60 (1H, dd, J_1=7.2 Hz, J_2=1.9 Hz, $C_6\underline{H}_5$), 6.78 (1H, d, J=7.2 Hz, $C_6\underline{H}_5$). ^{13}C NMR ($CDCl_3$) : δ 10.65 ($\underline{C}H_3C$=C), 37.02 ($NCH_2\underline{C}H_2$), 48.30 ($N\underline{C}H_2CH_2$), 50.91 ($CO_2\underline{C}H_3$), 55.67 and 55.76 (2x OCH_3), 109.40 (<u>C</u>H=CHN), 111.20 and 111.86 and 120.61 (3x =CH), 111.60 (=<u>C</u>CH$_3$), 119.71 (CH=<u>C</u>HN), 130.17 (=C_{quat}), 135.60 (=<u>C</u>CO$_2$CH$_3$), 147.83 and 148.81 (2x =<u>C</u>-OCH$_3$), 165.85 (C=O). IR (NaCl) ν_{max} : 1694 (C=O) cm^{-1}. MS *m/z* (%) : 303(M^+, 6), 229(9), 183(35), 151(100), 107(5), 94(4), 77(3), 40(5). Anal. Calcd. for $C_{17}H_{21}NO_4$: C 67.31%, H 6.78%, N 4.62%. Found C 67.15%, H 6.68%, N 4.55%.

2-{1-[*N*-(2-(3,4-Dimethoxyphenyl)ethyl)amino]-2,2-dimethoxyethylidene}butyrolactone (**10**)

Flash chromatography (RF = 0.26, ethyl acetate/hexane 20/80) gave **10** as a brown oil, yield 14%. ^{1}H NMR ($CDCl_3$) : δ 2.16-2.23 and 2.36-2.51 (each 1H, each m, $OCH_2\underline{C}H_2$), 2.77-2.85 (2H, m, $NCH_2\underline{C}H_2$), 3.28-3.54 (2H, m, NCH_2), 3.45 (3H, s, OCH_3), 3.66 (3H, s, OCH_3), 3.70-3.98 (2H, m, OCH_2), 3.87 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 4.91 (1H, s, $C\underline{H}(OCH_3)_2$), 6.75-6.84 (3H, m, C_6H_3), 8.54 (1H, broad s, NH). ^{13}C NMR ($CDCl_3$) : δ 22.88 ($OCH_2\underline{C}H_2$) 36.75 ($NCH_2\underline{C}H_2$) 44.35 ($N\underline{C}H_2CH_2$) 50.62 and 54.70 and 55.74 and 55.89 (4x OCH_3),

57.79 ($O\underline{C}H_2CH_2$), 88.21 ($\underline{C}$=CN), 93.46 ($\underline{C}H(OCH_3)_2$), 111.34 and 112.13 and 120.54 (3x =CH), 131.38 (=C_{quat}), 147.40 (=$\underline{C}$-OMe), 148.92 (=$\underline{C}$-OMe), 152.99 (C=$\underline{C}$N), 170.40 (C=O). IR (NaCl) ν_{max} : 1657 (C=O), 1606 (C=C) cm^{-1}. MS *m/z* (%) : 351(M^+, 15), 321(5), 289(4), 200(37), 169(12), 168(100), 164(18), 152(13), 108(8), 80(4), 40(5). Anal. Calcd. for $C_{18}H_{25}NO_6$: C 62.52%, H 7.17%, N 3.99%. Found C 62.34%, H 7.08%, N 3.66%.

Ethyl 1-isopropyl-2-methylpyrrole-3-carboxylate (**11a**)

Flash chromatography (Rf = 0.11, ethyl acetate/hexane 5/95) gave **11a** as a yellow oil, yield 18%. ^1H NMR ($CDCl_3$) : δ 1.33 (3H, t, J=7.3 Hz, $OCH_2C\underline{H}_3$), 1.40 (6H, d, J=6.6 Hz, $CH(C\underline{H}_3)_2$), 2.54 (3H, s, CH_3C=C), 4.25 (2H, q, J=7.3 Hz, $OC\underline{H}_2CH_3$), 4.33 (1H, septet, J=6.6 Hz, $C\underline{H}(CH_3)_2$), 6.54 (1H, d, J=3.3 Hz, C$\underline{H}$=CHN), 6.58 (1H, d, J=3.3 Hz, CH=C$\underline{H}$N). ^{13}C NMR ($CDCl_3$) δ : 10.76 ($\underline{C}H_3C$=C), 14.56 ($OCH_2\underline{C}H_3$), 23.25 ($CH(\underline{C}H_3)_2$), 46.97 ($\underline{C}H(CH_3)_2$), 59.15 ($O\underline{C}H_2CH_3$), 109.59 ($\underline{C}$H=CHN), 111.75 (=$\underline{C}CH_3$), 115.06 (CH=$\underline{C}$HN), 134.75 (=$\underline{C}CO_2Et$), 165.75 (C=O). IR (NaCl) ν_{max} : 1690 (C=O) cm^{-1}. MS *m/z* (%) : 195(M^+, 75), 180(12), 166(75), 150(71), 125(23), 124(100), 108(91), 107(28), 106(32), 80(35), 67(16), 65(16), 53(38), 43(37), 41(33). Anal. Calcd. for $C_{11}H_{17}NO_2$: C 67.66%, H 8.78%, N 7.17%. Found C 67.89%, H 8.66%, N 7.02%.

Ethyl 1-cyclohexyl-2-methylpyrrole-3-carboxylate (**11b**)

Flash chromatography (Rf = 0.19, ethyl acetate/hexane 5/95) gave **11b** as a yellow powder, yield 29%, mp 56.7-57.7°C. ^1H NMR ($CDCl_3$) : δ 1.33 (3H, t, J=7.3 Hz, $OCH_2C\underline{H}_3$), 1.20-1.98 (10H, m, $(CH_2)_5$), 2.54 (3H, s, CH_3C=C), 3.75-3.85 (1H, m, CHN), 4.25 (2H, q, J=7.3 Hz, $OC\underline{H}_2CH_3$), 6.55 (1H, d, J=3.3 Hz, C$\underline{H}$=CHN), 6.60 (1H, d, J=3.3 Hz, CH=C$\underline{H}$N). ^{13}C NMR ($CDCl_3$) : δ 10.84 ($\underline{C}H_3C$=C), 14.57 ($OCH_2\underline{C}H_3$), 25.37 and 25.84 (2x) and 33.93 (2x) ($(CH_2)_5$), 55.15 (CHN), 59.14 ($O\underline{C}H_2CH_3$), 109.36 ($\underline{C}$H=CHN), 111.62 (=$\underline{C}CH_3$), 115.85 (CH=$\underline{C}$HN), 134.82 (=$\underline{C}CO_2Et_3$), 165.77 (C=O). IR (KBr) ν_{max} : 1690 (C=O) cm^{-1}. MS *m/z* (%) : 235(M^+, 92), 206(57), 190(51), 162(43), 154(67), 153(45), 126(43), 125(55), 124(100), 108(98), 107(52), 83(42), 82(53), 81(43), 80(46), 79(39), 67(39), 55(95), 53(49), 41(84). Anal. Calcd. for $C_{14}H_{21}NO_2$: C 71.46%, H 8.99%, N 5.95%. Found C 71.33%, H 8.72%, N 6.15%.

Ethyl 2-methyl-1-(2-phenylethyl)pyrrole-3-carboxylate (**11c**)

Flash chromatography (Rf = 0.23, ethyl acetate/hexane 20/80) gave **11c** as a brown oil, yield 21%. ^1H NMR ($CDCl_3$) : δ 1.31 (3H, t , J=7.3 Hz, $OCH_2C\underline{H}_3$), 2.36 (3H, s, C=CCH_3), 2.97 (2H, t, J=7.0 Hz , $NCH_2C\underline{H}_2$), 4.06 (2H, t, J=7.0 Hz, $NC\underline{H}_2CH_2$), 4.25 (2H, q, J=7.3 Hz, $OC\underline{H}_2CH_3$), 6.41 (1H, d, J=3.0 Hz, NCH=C$\underline{H}$), 6.51 (1H, d, J=3.0 Hz, NC$\underline{H}$=CH), 7.03-7.07 and 7.21-7.32 (5H, m, C_6H_5). ^{13}C NMR ($CDCl_3$) : δ 10.71 (C=C$\underline{C}H_3$), 14.01 ($OCH_2\underline{C}H_3$), 37.61 ($NCH_2\underline{C}H_2$), 48.23 (NCH_2), 59.19 ($O\underline{C}H_2CH_3$), 109.51 ($\underline{C}$H=CHN), 112.09 (=CCO_2Et), 119.61 (CH=$\underline{C}$HN), 126.85 and 128.66 (2x) and 128.69 (2x) (5x =CH), 135.40 (=$\underline{C}CH_3$), 137.75 (=C_{quat}), 165.61 (C=O). IR (NaCl) ν_{max} : 1688 (C=O) cm^{-1}. MS *m/z* (%): 257(M^+, 75), 212(23), 184(14), 166(58), 151(22), 140(52), 138(20), 111(11), 105(45), 104(49), 97(12), 94(24), 91(20), 84(14), 77(18), 71(19), 65(16), 57(35), 43(37), 40(100). Anal. Calcd. for $C_{16}H_{19}NO_2$: C 74.68%, H 7.44%, N 5.44%. Found C 74.75%, H 7.66%, N 5.53%.

Ethyl 1-[2-(3,4-dimethoxyphenyl)ethyl]-2-methylpyrrole-3-carboxylate (**11d**)

Flash chromatography (Rf = 0.22, ethyl acetate/hexane 20/80) gave **11d** as yellow crystals, yield 23%, mp 64-66°C. ^{1}H NMR ($CDCl_3$) : δ 1.33 (3H, t, J=7.1 Hz, OCH_2CH_3), 2.33 (3H, s, CH_3C=C); 2.9 (2H, t, J=6.9 Hz, NCH_2CH_2), 3.77 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 4.01 (2H, t, J=6.9 Hz, NCH_2), 4.25 (2H, q, J=7.1 Hz, OCH_2CH_3), 6.37 (1H, d, J=1.9 Hz, C_6H_3), 6.41 (1H, d, J=3.1 Hz, NCH=CH), 6.52 (1H, d, J=3.1 Hz, NCH=CH), 6.59 (1H, dd, J_1=9.2 Hz, J_2=1.9 Hz, C_6H_3), 6.78 (1H, d, J=9.2 Hz, C_6H_3). ^{13}C NMR ($CDCl_3$) : δ 11.00 (=C-CH_3), 14.00 (OCH_2CH_3), 37.14 (NCH_2CH_2), 49.00 (NCH_2), 55.79 and 55.90 (2x OCH_3), 59.23 (OCH_2CH_3), 109.58 (CH=CHN), 111.29 (=CCO_2Et), 111.32 and 111.97 and 120.72 (3x =CH), 119.71 (CH=CHN), 130.31 (=C_{quat}), 135.20 (=CCH3), 147.30 and 148.33 (2x =$COCH_3$), 163.02 (C=O). IR (NaCl) ν_{max} : 1688 (C=O) cm^{-1}. MS *m/z* (%) : 317(M^+,1), 240(2), 196(3), 169(4), 155(4), 141(5), 127(6), 111(9), 97(17), 85(31), 71(54), 68(22), 57(92), 55(33), 43(38), 40(100). Anal. Calcd. for $C_{18}H_{23}NO_4$: C 68.12%, H 7.30%, N 4.41%. Found C 68.01%, H 7.26%, N 4.56%.

2-[1-(*N*-Isopropylamino)-2,2-diethoxyethylidene]butyrolactone (**12a**)

Flash chromatography (Rf = 0.18, ethyl acetate/hexane 5/95) gave **12a** as a yellow oil, yield 5%. ^{1}H NMR ($CDCl_3$) : δ 1.18-1.31 (12H, m, $CH(CH_3)_2$ and 2x OCH_2CH_3), 2.17-2.26 and 2.39-2.53 (each 1H, each m, OCH_2CH_2), 3.47-3.66 (2H, m, $CH(CH_3)_2$ and $OCHHCH_3$), 3.83-3.95 (1H, m, $OCHHCH_3$), 3.69-3.76 and 3.96-4.01 (each 1H, each m, OCH_2CH_2), 4.06-4.19 (2H, m, OCH_2CH_3), 5.13 (1H, s, $CH(OCH_2CH_3)_2$), 8.46 (1H broad s, NH). ^{13}C NMR ($CDCl_3$) δ : 14.59 (OCH_2CH_3), 15.22 (OCH_2CH_3), 22.96 (OCH_2CH_2), 24.29 and 25.03 ($CH(CH_3)_2$), 43.95 ($CH(CH_3)_2$), 57.81 (OCH_2CH_3), 58.99 (OCH_2CH_3), 63.14 (OCH_2CH_2), 87.31 (C=CN), 92.31 ($CH(OCH_2CH_3)_2$), 152.63 (C=CN), 170.33 (C=O). IR (NaCl) ν_{max} : 1640 (C=O), 1600 (C=C) cm^{-1}. MS *m/z* (%) : 257(M^+, 96), 213(76), 212(82), 198(39), 196(100), 182(49), 168(32), 167(33), 166(89), 165(67), 140(33), 124(42), 97(43), 96(60), 69(36), 68(46), 43(71), 41(82). Anal. Calcd. for $C_{13}H_{23}NO_4$: C 60.68%, H 9.01%, N 5.44%. Found C 60.79%, H 9.18%, N 5.42%.

2-[1-(*N*-Cyclohexylamino)-2,2-diethoxyethylidene]butyrolactone (**12b**)

Flash chromatography (Rf = 0.28, ethyl acetate/hexane 5/95) gave **12b** as a yellow oil, yield 18%. ^{1}H NMR ($CDCl_3$) : δ 1.22-1.30 (6H, m, 2x OCH_2CH_3), 1.22-2.01 (10H m, $(CH_2)_5$), 2.17-2.25 and 2.39-2.50 (each 1H, each m, OCH_2CH_2), 3.21 (1H, broad m, CHN), 3.52-3.58 and 3.83-3.91 (each 1H, each m, OCH_2CH_3), 3.69-3.76 and 3.92-4.00 (each 1H, each m, OCH_2CH_2), 4.08-4.17 (2H, m, OCH_2CH_3), 5.11 (1H, s, $CH(OCH_2CH_3)_2$), 8.60 (1H broad s, NH). ^{13}C NMR ($CDCl_3$) δ : 14.61 (OCH_2CH_3), 15.20 (OCH_2CH_3), 22.98 (OCH_2CH_2), 24.96 and 25.01 and 25.48 and 34.47 and 35.20 ($(CH_2)_5$), 51.01 (CHN), 57.86 (OCH_2CH_2), 58.98 (OCH_2CH_3), 63.16 (OCH_2CH_3), 87.17 (C=CN), 92.34 ($CH(OCH_2CH_3)_2$), 152.67 (C=CN), 170.31 (C=O). IR (NaCl) ν_{max} : 1643 (C=O), 1598 (C=C) cm^{-1}. MS *m/z* (%) : 297(M^+, 96), 253(84), 252(58), 251(38), 222(45), 207(32), 206(65), 205(34), 178(81), 170(54), 142(36), 124(37), 114(56), 97(45), 96(44), 83(39), 69(37), 55(100), 41(87). Anal. Calcd. for $C_{16}H_{27}NO_4$: C 64.62%, H 9.15%, N 4.71%. Found C 64.89%, H 9.26%, N 4.62%.

2-{1-[*N*-(2-phenylethyl)amino]-2,2-diethoxyethylidene}butyrolactone (**12c**)

Flash chromatography (Rf = 0.30, ethyl acetate/hexane 20/80) gave **12c** as a yellow oil, yield 12%. ^{1}H NMR ($CDCl_3$) : δ 1.24-1.30 (6H, m, 2x OCH_2CH_3), 2.20-2.26 and 2.38-2.47 (each 1H, each m, OCH_2CH_2), 2.85-2.92

(2H, m, $NCH_2C\underline{H}_2$), 3.42-3.57 (2H, m, NCH_2), 3.71-3.91 (2H, m, $OC\underline{H}_2CH_2$), 4.10-4.16 (4H, m, 2x $OC\underline{H}_2CH_3$), 5.03 (1H, s, $C\underline{H}(OCH_2CH_3)_2$), 7.19-7.34 (5H, m , 5x =CH), 8.56 (1H, broad s, NH). ^{13}C NMR ($CDCl_3$) : δ 14.56 ($OCH_2\underline{C}H_3$), 15.27 ($OCH_2\underline{C}H_3$), 22.98 ($OCH_2\underline{C}H_2$), 37.32 ($NCH_2\underline{C}H_2$), 44.04 ($N\underline{C}H_2CH_2$), 57.83 ($O\underline{C}H_2CH_3$), 59.11 ($O\underline{C}H_2CH_3$), 63.09 ($O\underline{C}H_2CH_2$), 85.55 ($\underline{C}$=CN), 92.29 ($\underline{C}H(OCH_2CH_3)_2$), 126.52 and 128.68 and 128.61 (5x =CH), 138.88 (=C_{quat}), 152.97 (C=$\underline{C}$N), 170.13 (C=O). IR (NaCl) ν_{max} : 3271 (NH), 1655 (C=O), 1608 (C=C) cm^{-1}. MS *m/z* (%) : 319(M^+, 14), 274(9), 228(40), 182(100), 136(5), 105(20), 97(7), 91(8), 57(8), 43(7). Anal. Calcd. for $C_{18}H_{25}NO_4$: C 67.69%, H 7.89%, N 4.39%. Found C 67.56%, H 7.74%, N 4.35%.

2-{1-[*N*-(2-(3,4-dimethoxyphenyl)ethyl)amino]-2,2-diethoxyethylidene}butyrolactone (**12d**)

Flash chromatography (Rf = 0.28, ethyl acetate/hexane 20/80) gave **12d** as a yellow oil, yield 28%. ^{1}H NMR ($CDCl_3$) : δ 1.24 (3H, ~t, J = ~8 Hz, $OCH_2C\underline{H}_3$), 1.28 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 2.17-2.24 and 2.38-2.57 (each 1H, each m, $OCH_2C\underline{H}_2$), 2.79-2.82 (2H, m, $NCH_2C\underline{H}_2$), 3.31-3.54 (2H, m, NCH_2), 3.73-3.75 (2H, m, $OC\underline{H}_2CH_2$), 3.86 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 4.10-4.20 (4H, m, 2x $OC\underline{H}_2CH_3$), 5.03 (1H, s, $C\underline{H}(OCH_2CH_3)_2$) 6.78-6.81 (3H, m, C_6H_3), 8.57 (1H, broad s, NH). ^{13}C NMR ($CDCl_3$) : δ 14.56 ($OCH_2\underline{C}H_3$), 15.27 ($OCH_2\underline{C}H_3$), 22.97 ($OCH_2\underline{C}H_2$), 36.78 ($NCH_2\underline{C}H_2$), 44.24 (NCH_2), 55.76 and 55.92 (2x OCH_3), 57.83 ($O\underline{C}H_2CH_3$), 59.09 ($O\underline{C}H_2CH_3$), 63.07 ($O\underline{C}H_2CH_2$), 88.46 ($\underline{C}$=CN), 92.31 ($\underline{C}H(OCH_2CH_3)_2$), 111.43 and 112.18 and 120.52 (3x =CH), 131.52 (=C_{quat}), 147.69 and 148.93 (=$\underline{C}$-OCH_3), 153.01 (C=$\underline{C}$N), 170.11 (C=O). IR (NaCl) ν_{max} : 3280 (NH), 1657 (C=O), 1606 (C=C) cm^{-1}. MS *m/z* (%) : 379(M^+, 13), 334(5), 288(4), 228(31), 182(100), 164(18), 151(13), 108(6), 80(4), 40(5). Anal. Calcd. for $C_{20}H_{29}NO_6$: C 63.31%, H 7.70%, N 3.69%. Found C 63.24%, H 7.75%, N 3.85%.

Acknowledgement. The authors are indebted to INTAS (Grant 97-0217) and to the "Fund for Scientific Research Flanders" for financial support.

REFERENCES

1. *The Chemistry of Heterocyclic Compounds, Pyrroles*, Vol 1&2, Jones, R.A. Eds.; J. Wiley & Sons, New York, **1990**.
2. Pavri, N.P.; Trudell, M.L. *J. Org. Chem.* **1997**, *62*, 2649-2651 and references therein.
3. De Kimpe, N.; Abbaspour Tehrani, K.; Stevens, C.; De Cooman, P. *Tetrahedron* **1997**, *53*, 3693-3706.
4. Leroux, P. *Pesti Sci.* **1996**, *47*, 191-197.
5. Tsang, T.H. U.S. US 5,512,537 (Cl. 504-287; A01N43/46), 30 Apr 1996, Appl. 205,213, 2 Mar 1994; 7 pp. Chem. Abstr. **1996**, *125*, 3607p.
6. Hunt, D.A. *Pest. Sci.* **1996**, *47*, 201-202.
7. Padwa, A.; Haffmanns, G.; Tomas, M. *J. Org. Chem.* **1984**, *49*, 3314-3322.
8. Coppola, B.P.; Noe, M.C.; Schwartz, D.J., Abdon, R.L. II; Trost, B.M. *Tetrahedron* **1994**, *50*, 93-116.
9. Merah, B.; Texier, F. *Bull. Soc. Chim. France* II **1980**, 552-558.
10. Cambie, R.C.; Moratti, S.C.; Rutledge, P.S.; Woodgate, P.D. *Synth.Commun.* **1990**, *20*, 1923.
11. Catuiela, C.; Garcia, J.I. *Org. Prep. Proced. Int.* **1986**, *18*, 283.