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Synthesis of [1]Benzopyrano[4,3-*b*]pyrrol-4(1*H*)-ones from *N*(α)-(2-Oxo-2*H*-1-benzopyran-4-yl)Weinreb α-Aminoamides

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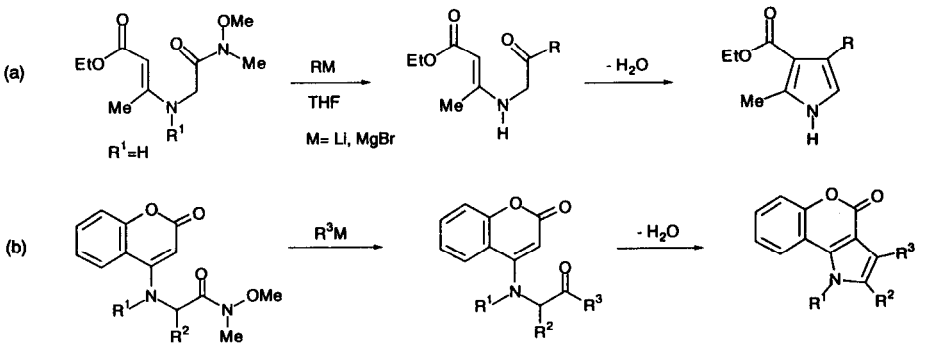
Abstract. *N*(α)-(2-Oxo-2H-1-benzopyran-4-yl)Weinreb-α-aminoamides were prepared from 4-chlorocoumarin and α-aminoacid derivatives. Their reaction with organometallic compounds (RLi or RMgBr) and subsequent cyclization of ketones thus obtained, give [1]benzopyrano[4,3-*b*]pyrrol-4(1*H*)-ones. Starting from proline derivatives, simultaneously with the pyranone-pyrrole fusion, we establish an interesting procedure for the formation of pyrrolizines. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Knorr pyrrole synthesis; Weinreb amides; [1]Benzopyrano[4,3-*b*]pyrrole; Pyrrolizine.

Introduction

In a recent paper[1] we established an original and versatile method for the synthesis of pyrroles by reaction of ethyl 3-(*N*-methoxy-methylcarbamoyl)methylaminocrotonates with organometallic compounds and subsequent cyclization of the resulting α-vinylaminoketones (Scheme 1, a). In the above procedure only secondary enamines were used (R^1=H). These facilitate the selective reaction of the organometallic compound with the Weinreb amide group without attacking the ester group.



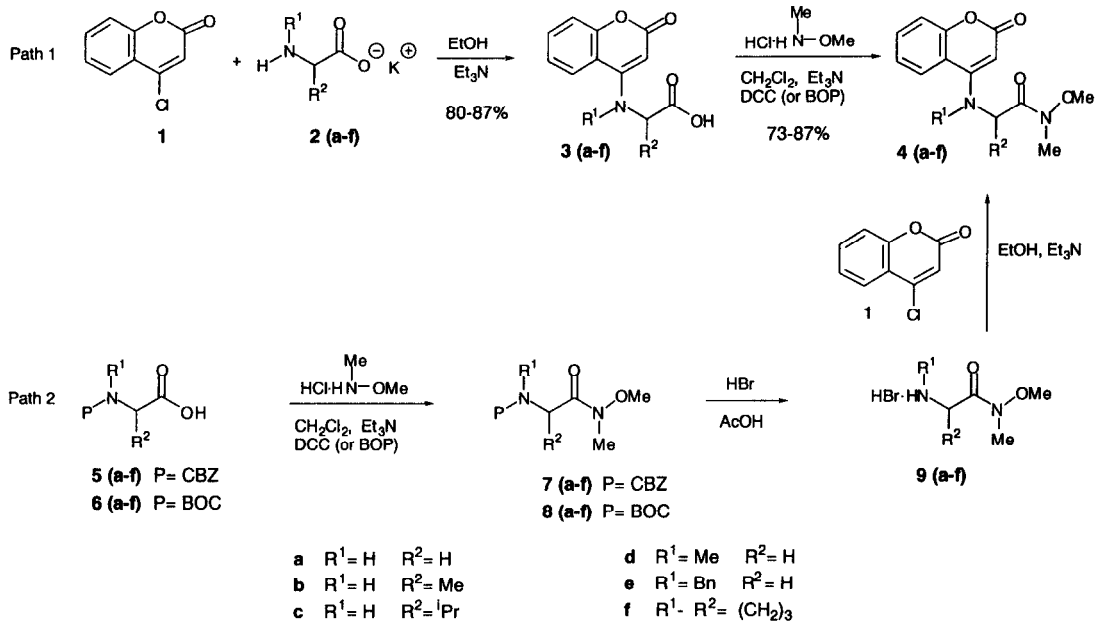
Scheme 1

PII: S0040-4020(99)00802-9

In this paper, we apply the same method to the obtention of [1]benzopyrano[4,3-*b*]pyrrol-4(1*H*)-ones starting from the corresponding 4-aminocoumarin derivatives (Scheme 1, b). We have extended the study to tertiary enamines ($R^1 \neq H$) whose reactivity towards organometallic compounds is different.[2-4] We have chosen the 4-aminocoumarin derivatives because they are more stable substrates than the β-aminocrotonates in acid medium[5] and because they lead to fused heterocycles which are interesting for their potential biological activity.[6-8]

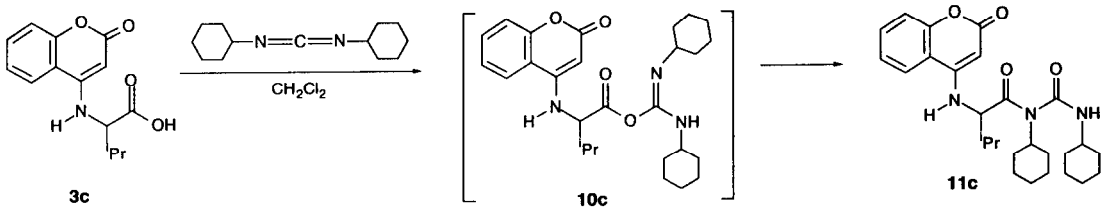
Preparation of *N(α)*-(2-Oxo-2*H*-1-benzopyran-4-yl)Weinreb-α-Aminoamides

We have compared two alternative procedures for the preparation of *N(α)*-(2-Oxo-2*H*-1-benzopyran-4-yl)Weinreb-α-aminoamides **4a-f** from 4-chlorocoumarin **1** and α-aminoacid derivatives (Scheme 2). In both paths the nitrogenated substituent is incorporated in the benzopyranone by a process of addition conjugated-elimination, but they differ in sequential order.



Scheme 2

In Path 1, the 4-chlorocoumarin **1** reacts with the potassium salts **2** in ethanol/triethylamine to give good yields of *N*-(2-Oxo-2*H*-1-benzopyran-4-yl)-α-aminoacids **3** (Table 1). When R^2 is slightly bulky (*e.g.* R^2= H, Me), the treatment of **3** with 1,3-dicyclohexylcarbodiimide (DCC) and *N,O*-dimethylhydroxylamine in dichloromethane successfully allowed us to obtain Weinreb amides **4**. If R^2 is bulky (*e.g.* R^2= ^{i}Pr), the principal reaction is a rearrangement of the *O*-acylisourea **10** to the *N*-acylurea **11**[9] (Scheme 3). In the latter case (benzotriazol-1-yloxyl)tris(dimetilamino)phosphonium hexafluorophosphate (BOP) should be used as coactivating reactant (Table 1).



Scheme 3

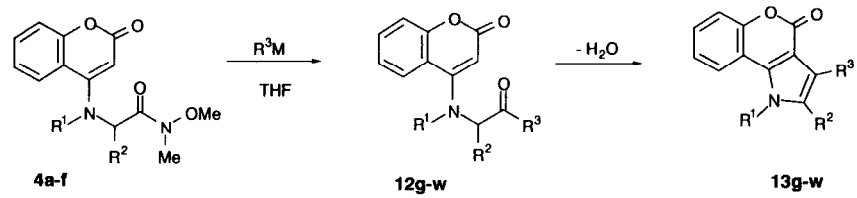
In Path 2, starting from protected α-aminoacids **5**, **6** and *N,O*-dimethylhydroxylamine hydrochloride the Weinreb amides **7** and **8**[10] can be prepared according to the procedures previously described.[11] Their deprotection with hydrogen bromide (33% in acetic acid)[12] leads to *N*-methoxy-*N*-methyl-α-aminoamide hydrobromides **9**. These react with 4-chlorocoumarin **1** in ethanol/triethylamine to give **4** with yields which vary between 50-80% (Table 1).

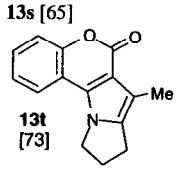
Table 1. Preparation of compounds **3** and **4**.

Start	R^1	R^2	Conditions	Product (%)
2a	H	H	Et_3N, EtOH, 55°C → reflux, 16 h	**3a** (81)
2b	H	Me	Et_3N, EtOH, 55°C → reflux, 16 h	**3b** (82)
2c	H	^{i}Pr	Et_3N, EtOH, 55°C → reflux, 16 h	**3c** (85)
2d	Me	H	Et_3N, EtOH, 55°C → reflux, 16 h	**3d** (80)
2e	Bn	H	Et_3N, EtOH, 55°C → reflux, 16 h	**3e** (86)
2f	R^1-R^2= $(CH_2)_3$		Et_3N, EtOH, 55°C → reflux, 16 h	**3f** (87)
3a	H	H	DCC, Et_3N, CH_2Cl_2, 0°C → r.t., 4 h	**4a** (73)
9a	H	H	Et_3N, EtOH, 55°C, 24 h	**4a** (60)
3b	H	Me	DCC, Et_3N, CH_2Cl_2, 0°C → r.t., 4 h	**4b** (85)
9b	H	Me	Et_3N, EtOH, 55°C, 24 h	**4b** (52)
3c	H	^{i}Pr	DCC, Et_3N, CH_2Cl_2, 0°C → r.t., 4 h	**4c** (<10), **11c** (72)
3c	H	^{i}Pr	BOP, Et_3N, CH_2Cl_2, 0°C → r.t., 2 h	**4c** (79)
9c	H	^{i}Pr	Et_3N, EtOH, 55°C, 24 h	**4c** (55)
3d	Me	H	DCC, Et_3N, CH_2Cl_2, 0°C → r.t., 4 h	**4d** (87)
9d	Me	H	Et_3N, EtOH, 55°C, 24 h	**4d** (48)
3e	Bn	H	DCC, Et_3N, CH_2Cl_2, 0°C → r.t., 4 h	**4e** (71)
3f	R^1-R^2= $(CH_2)_3$		DCC, Et_3N, CH_2Cl_2, 0°C → r.t., 4 h	**4f** (76)

Of the two previously mentioned paths for the preparation of *N*(α)-(2-Oxo-2*H*-1-benzopyran-4-yl)Weinreb-α-aminoamides **4a-f**, it is advisable to follow the first one, given that it uses cheaper reactants,[13] requires one stage less[10] and the yields are greater.

Table 2. Reaction of **4** with organometallic compounds. Cyclization of **12** to **13**.

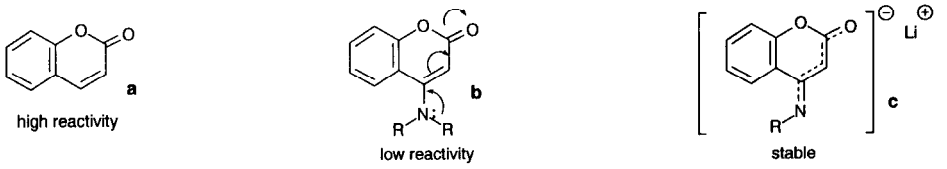


	Reaction with organometallic compounds								Cyclization	
Start	R^3-M	Ratio	T (°C)	Time (min)	R^1	R^2	R^3	**12** (%)	Method[a]	**13** (%)[b] [%][c]
4a	PhMgBr	1 : 3	-5	45	H	H	Ph	**12g** (65)	A	**13g** (75)
4a	MeLi	1 : 3	-5	30	H	H	Me	**12h** (60)	A	**13h** (92)
4a	^{i}PrMgBr	1 : 3	0	45	H	H	^{i}Pr	**12i** (68)	A	**13i** (81)
4a		1 : 3	-10	10	H	H		**12j** (63)	A	**13j** (80)
4b	PhMgBr	1 : 3	-5	55	H	Me	Ph	**12k** (85)	A	**13k** (72)
4b	MeLi	1 : 3	-5	60	H	Me	Me	**12l** (88)	A	**13l** (69)
4c	MeLi	1 : 3	0	45	H	^{i}Pr	Me	**12m** (92)	A	**13m** (76)
4d	PhLi	1 : 2	-50	35	Me	H	Ph	**12n** (51)	B	**13n** (88)
4d	MeLi	1 : 1.5	-40	20	Me	H	Me	**12o** (76)	C	**13o** (80) [78]
4d	BuLi	-[d]	-[d]	-[d]	Me	H	Bu	**12p** (0)		
4d	BuC≡CLi	1 : 2	-50	30	Me	H	BuC≡C	**12q** (-[e])	C	**13q** [80]
4e	PhLi	1 : 2	-60	20	Bn	H	Ph	**12r** (-[e])	C	**13r** [<15][f]
4e	MeLi	1 : 1.8	-40	20	Bn	H	Me	**12s** (-[e])	C	**13s** [65]
4f	MeLi	1 : 1.5	-40	15	R^1-R^2 = $(CH_2)_3$		Me	**12t** (-[e])	C	 **13t** [73]
4f	BuLi	-[d]	-[d]	-[d]	R^1-R^2 = $(CH_2)_3$		Bu	**12u** (0)		
4f	BuC≡CLi	1 : 2	-40	30	R^1-R^2 = $(CH_2)_3$		BuC≡C	**12v** (-[e])	C	**13v** [81]
4f	H_2C=CHLi	1 : 2	-50	30	R^1-R^2 = $(CH_2)_3$		H_2C=CH	**12w** (-[e])	C	**13w** [59]

(a) Methods: A EtONa/EtOH, B AcOH/H_2O, C Silica gel/ $CHCl_3$. (b) Yield from **12**. (c) Yield from **4** (one–pot synthesis). (d) Various conditions were tried without success. (e) Cyclized to **13**, without isolating **12**. (f) Estimated from NMR spectra of the reaction mixture. Unisolated

Reaction of *N*(α)-(2-Oxo-2*H*-1-benzopyran-4-yl)-*N*-methoxy-*N*-methyl-α-aminoamides with Organometallic Compounds

When he amides **4a-c**, with R^1=H, react with an equimolar amount of the organometallic compound (R^3MgBr or R^3Li), they form a conjugate anion (Scheme 4, **c**) which deactivates the lactone. If an excess of reagent is used, only the *N*-methoxy-*N*-methylcarboxamide group is transformed into a carbonyl group (Table 2). Normally, a strict control of the temperature and proportion of reagents is unnecessary to obtain satisfactory yields. It should be pointed out that compounds such as **12k-m**, with $R^2 \neq$ H, are difficult to obtain from the corresponding α-aminoketones. Their reaction with 4-chlorocoumarin (**1**) lead preferably to processes of autocondensation instead of conjugated addition-elimination.[14]



Scheme 4. Reactivity [15] of the coumarin (**a**), 4-dimethylaminocoumarin (**b**) and 4-methylaminocoumarin (**c**) towards methyllithium in THF at –40°C.

If $R^1 \neq$H (compounds **4d-f**), the electron-donating character of the tertiary amino group in C4 only partially deactivates the reactivity of the α,β-unsaturated lactone (Scheme 4, **b**). Working conditions must be rigourously controlled if we wish to achieve the selective reaction of the Weinreb amide group without modifying the lactone. At –40°C in tetrahydrofuran, the yields depend fundamentally on the organolithium[16] reagent used: results are good for methyl-, 1-hexynyl- or vinyllithium; very variable for phenyllithium and negligible for butyllithium (Table 2).

As regards the results obtained in the reaction stage of **4** with organometallic compounds, we may conclude that our synthetic procedure maintains its general application and versatility when R^1= H. The method is also valid if $R^1 \neq$ H, although greater limitations present themselves (*e.g.* with BuLi) and in some cases the individual optimisation of the reaction conditions will be necessary.

Cyclization of α-Vinylaminoketones 12 to [1]Benzopyrano[4,3-*b*]pyrrol-4(1*H*)-ones 13

The cyclization conditions from **12g-w** to pyrroles **13g-w** not only depend on the reactivity of the carbonyl group, but also on the nature of R^1. Thus, the treatment with sodium ethoxide/ethanol gives good yields starting from **12g-m** (R^1=H), but not from **12n-w** ($R^1 \neq$H) which lack N-H hydrogens capable of activating the nucleophile of the enamine in basic medium. In the latter, whose tertiary enamine is more resistent to acid hydrolysis, good yields are obtained when refluxed with acetic acid/water (3:1). When $R^1 \neq$H, the thermal cyclization of **12n-w** can also be successfully obtained by reflux in chloroform in the presence of silica gel.The

one-pot procedure (from **4** to **13**), without isolation and purification of the ketone intermediates **12**, is generally advantageous in all cases.

The pyrrolizines **13t,v,w**, obtained from proline derivatives, suggest an interesting extrapolation of the procedure for the synthesis of fused bicyclic compounds with bridged nitrogen atoms.

Experimental

Melting points were measured on a Reichert-Jung Thermo Galen and are uncorrected. IR spectra were obtained on a Perkin Elmer 1720 X spectrometer. NMR spectra were recorded on a Bruker AC300 spectrometer, and chemical shifts are given downfield from $SiMe_4$ as an internal standard; ^{13}C-NMR spectra were carried out with complete ^1H decoupling and the assignments were made by additional DEPT experiments. Mass spectra were measured on a Hewlett-Packard 5988A mass spectrometer.

The starting compounds were purchased from the usual suppliers or synthesized by literature procedures. The 4-chlorocoumarin **1**[17] was obtained from 4-hydroxycoumarin and $POCl_3$. The *N*-methoxy-*N*-methyl-α-aminoamides **9** (hydrobromide derivatives) were prepared from their corresponding BOC-α-aminoamides **8**[11] (or CBZ-α-aminoamides **7**) by deprotection with HBr in AcOH (33%) and precipitation in dry ether.[12]

Preparation of acids 3 from 4-chlorocoumarin 1 and potassium salt 2. A mixture of 4-chlorocoumarin **1** (2g, 11 mmol), α-aminoacid potassium salt **2** (16.4 mmol) and Et_3N (1.53 ml, 11 mmol) in 40 cm^3 of ethanol was stirred for 15 h at 55ºC, plus an additional hour in reflux. The solvent was then evaporated, and the residue was dissolved in the minimum volume of water and 10 cm^3 of dichloromethane. The aqueous layer was decanted, cooled in an ice-water bath and acidified with hydrochloric acid[18] (pH~3), until the complete precipitation of **3**. The precipitate was filtered, washed with water and recrystallized from methanol.

The chemical yields and the physical and spectral characteristics of these products are given below.

N-(2-0xo-2H-1-benzopyran-4-yl)glycine (**3a**): 81%, colorless crystals, mp. 145ºC. IR (KBr) 3318, 1709, 1665, 1608, 1551, 1261, 1206, 943, 748 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ = 4.05 (d, J=5.0, 2H), 5.04 (s, 1H), 7.30-7.98 (m, 4H), 8.00 (d, J=5.0, 1H, NH), 12.98 (br, 1H, OH); ^{13}C NMR (75.4 MHz, DMSO-d_6) δ = 43.87 (CH_2), 82.56 (CH), 114.93 (C), 117.11 (CH), 122.40 (CH), 123.62 (CH), 132.18 (CH), 153.14 (C), 153.60 (C), 161.54 (C), 170.73 (C); MS: m/z 219 (M^+, 90), 146 (100). (Found: C, 60.28; H, 4.16; N, 6.40. $C_{11}H_9NO_4$ requires C, 60.27; H, 4.14; N, 6.39%).

N-(2-0xo-2H-1-benzopyran-4-yl)alanine (**3b**): 82%, colorless crystals, mp. 242ºC. IR (KBr) 3319, 1741, 1650, 1628, 1601, 1539, 1478, 1268, 1178, 810, 770, 749 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ = 1.51 (d, J=7.1, 3H), 4.25 (m, J=7.1, 1H), 5.03 (s, 1H), 7.30-8.21 (m, 4H), 7.62 (d, J=7.1, 1H, NH), 13.40 (br, 1H, OH); ^{13}C NMR (75.4 MHz, DMSO-d_6) δ = 17.10 (CH_3), 50.94 (CH), 82.90 (CH), 114.24 (C), 116.98 (CH), 122.94 (CH), 123.41 (CH), 132.15 (CH), 153.03 (C), 153.06 (C), 161.48 (C), 173.76 (C); MS: m/z 233 (M^+, 36), 188 (100). (Found: C, 61.70; H, 4.74; N, 5.99. $C_{12}H_{11}NO_4$ requires C, 61.80; H, 4.75; N, 6.01%).

N-(2-0xo-2H-1-benzopyran-4-yl)valine (**3c**): 85%, colorless crystals, mp. 243ºC. IR (KBr) 3350, 1730, 1668, 1625, 1600, 1542, 1480, 1258, 1192, 802, 765 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ = 0.99 (d, J=6.7, 3H), 1.03 (d, J=6.7, 3H), 2.30 (m, J=8.1 and 6.7, 1H), 3.78 (d.d, J=8.1 and 7.8, 1H), 5.13 (s, 1H),

7.29-8.31 (m, 4H), 7.45 (d, J=7.8, 1H, NH), 13.04 (br, 1H, OH); ^{13}C NMR (75.4 MHz, DMSO-d_6) δ = 19.09 (CH_3), 19.60 (CH_3), 29.46 (CH), 62.30 (CH), 83.07 (CH), 114.20 (C), 116.96 (CH), 123.07 (CH), 123.40 (CH), 132.19 (CH), 153.03 (C), 153.40 (C), 161.43 (C), 172.93 (C); MS: m/z 261 (M^+, 54), 133 (100). (Found: C, 64.41; H, 5.81; N, 5.39; $C_{14}H_{15}NO_4$ requires C, 64.36; H, 5.79, N, 5.36 %).

N-(2-0xo-2H-1-benzopyran-4-yl)sarcosine (**3d**): 80%, colorless crystals, mp. 138°C. IR (KBr) 1686, 1594, 1545, 1400, 1343, 1256, 1192, 932, 921, 744 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ = 3.04 (s, 3H), 4.16 (s, 2H), 5.46 (s, 1H), 7.27-7.73 (m, 4H), 13.06 (br, 1H, OH); ^{13}C NMR (75.4 MHz DMSO-d_6) δ = 40.93 (CH_3), 55.59 (CH_2), 93.10 (CH), 115.59 (C), 117.50 (CH), 123.62 (CH), 125.53 (CH), 131.85 (CH), 153.73 (C), 159.34 (C), 161.12 (C), 170.81 (C); MS: m/z 233 (M^+, 73), 188 (100). (Found: C, 61.85; H, 4.78; N, 5.99. $C_{12}H_{11}NO_4$ requires C, 61.80; H, 4.75; N, 6.01%).

N-Benzyl-N-(2-oxo-2H-1-benzopyran-4-yl)glycine (**3e**): 86%, colorless crystals, mp. 205°C. IR (KBr) 1730, 1685, 1633, 1606, 1547, 1421, 1370, 1232, 1207, 762, 751, 697 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ = 4.17 (s, 2H), 4.68 (s, 2H), 5.56 (s, 1H), 7.25-7.71 (m, 9H), 13.09 (br, 1H, OH); ^{13}C NMR (75.4 MHz, DMSO-d_6) δ = 53.84 (CH_2), 55.54 (CH_2), 95.87 (CH), 115.94 (C), 117.50 (CH), 123.78 (CH), 124.78 (CH), 127.36 (2 CH), 127.47 (CH), 128.72 (2 CH), 131.90 (CH), 136.61 (C), 153.62 (C), 158.48 (C), 160.87 (C), 170.71 (C); MS: m/z 309 (M^+, 17), 91 (100). (Found: C, 69.83; H, 4.90; N, 4.52. $C_{18}H_{15}NO_4$ requires C, 69.89; H, 4.89; N, 4.53%).

N-(2-0xo-2H-1-benzopyran-4-yl)proline (**3f**): 87%, colorless crystals, mp. 105°C. IR (KBr) 1699, 1651, 1604, 1541, 1417, 1350, 1232, 1207, 758 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ = 1.96 (m, 3H), 2.39 (m, 1H), 3.80 (m, 1H), 3.86 (m, 1H), 4.65 (t, J=6.9, 1H), 5.07 (s, 1H), 7,25-8.03 (m, 4H), 12,91 (br, 1H, OH); ^{13}C NMR (75.4 MHz, DMSO-d_6) δ = 24.57 (CH_2), 30.55 (CH_2), 53.23 (CH_2), 63.01 (CH), 87.28 (CH), 115.89 (C), 117.49 (CH), 123.29 (CH), 125.87 (CH), 131.73 (CH), 153.66 (C), 155.12 (C), 161.02 (C), 173.17 (C); MS: m/z 259 (M^+, 14), 214 (100). (Found: C, 64.80; H, 5.07; N, 5.38. $C_{14}H_{13}NO_4$ requires C, 64.87; H, 5.05; N, 5.40%).

Preparation of Weinreb amides 4 from acids 3. To a cooled (0ºC) solution of **3** (10 mmol), *N,O*-dimethylhydroxylamine hydrochloride (1.46 g, 15 mmol) and triethylamine (1.94 cm^3, 1.4 mmol) in 70 cm^3 of dichloromethane was added dropwise a solution of 1,3-dicyclohexylcarbodiimide[19] (2.27 g, 11 mmol) in 10 cm^3 of dichloromethane. The mixture was stirred at 20°C for 4h and then was added 0.5 cm^3 of acetic acid in order to eliminate the excess of DCC. The precipitate of 1,3-dicyclohexylurea was filtered and the solution washed with water (2 x 70 cm^3). The organic layer was dried (Na_2SO_4) and evaporated under reduced presure. The residue was recrystallized from dichloromethane/ether, or chromatographed on silica gel using dichloromethane/tetrahydrofuran (5:1) as eluent.

The following compounds were thus prepared.

N-(2-0xo-2H-1-benzopyran-4-yl)glycine N´-methoxy-N´-methylamide (**4a**): 73%, colorless crystals, mp. 206°C. IR (KBr) 3346, 1687, 1669, 1618, 1608, 1558, 1484, 1335, 1265, 1249, 1199, 981, 943, 783 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ = 3.15 (s, 3H), 3.78 (s, 3H), 4.26 (d, J=5.6, 2H), 5.04 (s, 1H), 7.32-8.02 (m, 4H), 7.82 (t, J=5.6, 1H, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 32.44 (CH_3), 43.06 (CH_2), 61.67 (CH_3), 84.54 (CH), 113.92 (C), 117.70 (CH), 120.47 (CH), 123.47 (CH), 131.87 (CH), 151.83 (C), 153.43 (C),

162.84 (C), 168.44 (C); MS: m/z 262 (M^+, 18), 174 (100). (Found: C, 59.61; H, 5.40; N, 10.65. $C_{13}H_{14}N_2O_4$ requires C, 59.54; H, 5.38; N, 10.68%).

N-(2-0xo-2H-1-benzopyran-4-yl)alanine N′-methoxy-N′-methylamide (**4b**): 85%, colorless crystals, mp. 191°C. IR (KBr) 3377, 1706, 1693, 1641, 1615, 1606, 1559, 1542, 1483, 1198, 1184, 982, 953, 819, 765, 753 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 1.53 (d, J=6.7, 3H), 3.31 (s, 3H), 3.85 (s, 3H), 4.60 (m, J=6.7 and 5.9, 1H), 5.24 (s, 1H), 6.69 (d, J=5.9, 1H, NH), 7.16-7.59 (m, 4H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 17.28 (CH_3), 32.47 (CH_3), 48.41 (CH), 61.81 (CH_3), 84.00 (CH), 114.09 (C), 117.64 (CH), 120.79 (CH), 123.40 (CH), 131.86 (CH), 151.56 (C), 153.44 (C), 163.15 (C), 172.63 (C); MS: m/z 276 (M^+, 16), 188 (100). (Found: C, 60.99; H, 5.81; N, 10.09. $C_{14}H_{16}N_2O_4$ requires C, 60.86; H, 5.84; N, 10.14%).

N-(2-0xo-2H-1-benzopyran-4-yl)valine-N′-methoxy-N′-methylamide (**4c**): 79%, colorless crystals, mp. 160°C. IR (KBr) 3363, 1705, 1684, 1650, 1619, 1559, 1469, 1449, 1387, 1194, 998, 932, 769, 746 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 1.01 (d, J=6.5, 3H), 1.03 (d, J=6.5, 3H), 2.25 (m, J=6.5 and 5.9, 1H), 3.25 (s, 3H), 3.78 (s, 3H), 4.52 (dd, J=5.9 and 8.7, 1H), 5.41 (s, 1H), 6.02 (d, J=8.7, 1H, NH), 7.22-7.56 (m, 4H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 17.90 (CH_3), 19.69 (CH_3), 32.16 (CH_3), 32.19 (CH), 56.59 (CH), 61.64 (CH_3), 84.42 (CH), 114.20 (C), 117.82 (CH), 120.34 (CH), 123.47 (CH), 131.93 (CH), 152.65 (C), 153.53 (C), 163.09 (C), 171.58 (C); MS: m/z 304 (M^+, 8), 216 (100). (Found: C, 63.08; H, 6.64; N, 9.17. $C_{16}H_{20}N_2O_4$ requires C, 63.15; H, 6.62; N, 9.20%).

N-(2-0xo-2H-1-benzopyran-4-yl)sarcosine N′-methoxy-N′-methylamide (**4d**): 87%, colorless crystals, mp. 135°C. IR (KBr) 1690, 1602, 1550, 1408, 1350, 1248, 1200, 937, 794, 759 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 3.10 (s, 3H), 3.28 (s, 3H), 3.70 (s, 3H), 4.28 (s, 2H), 5.62 (s, 1H), 7.20-7.63 (m, 4H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 32.43 (CH_3), 40.73 (CH_3), 55.27 (CH_2), 61.48 (CH_3), 94.82 (CH), 116.00 (C), 117.87 (CH), 123.20 (CH), 125.00 (CH), 131.39 (CH), 154.19 (C), 160.25 (C), 162.48 (C), 169.16 (C); MS: m/z 276 (M^+, 10), 188 (100).). (Found: C, 60.94; H, 5.86; N, 10.09. $C_{14}H_{16}N_2O_4$ requires C, 60.86; H, 5.84; N, 10.14%).

N-Benzyl-N-(2-oxo-2H-1-benzopyran-4-yl)glycine N′-methoxy-N′-methylamide (**4e**): 71%, colorless crystals, mp. 115°C. IR (KBr) 1704, 1690, 1670, 1604, 1414, 1222, 1193, 938, 740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 3.20 (s, 3H), 3.59 (s, 3H), 4.24 (s, 2H), 4.79 (s, 2H), 5.63 (s, 1H), 7.12-7.68 (m, 9H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 32.39 (CH_3), 51.61 (CH_2), 56.30 (CH_2), 61.44 (CH_3), 96.41 (CH), 116.24 (C), 118.06 (CH), 123.46 (CH), 124.63 (C), 127.44 (2 CH), 127.89 (CH), 129.06 (2 CH), 131.52 (CH), 136.03 (C), 154.29 (C), 159.50 (C), 162.49 (C), 168.98 (C); MS: m/z 325 (M^+, 6), 91 (100). (Found: C, 68.19; H, 5.70; N, 7.92. $C_{20}H_{20}N_2O_4$ requires C, 68.17; H, 5.72; N, 7.95%).

N-(2-0xo-2H-1-benzopyran-4-yl)proline N′-methoxy-N′-methylamide (**4f**): 76%, colorless crystals, mp. 152°C. IR (KBr) 1682, 1591, 1539, 1419, 1359, 1257, 1194, 999, 930, 775 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 1.95 (m, 2H), 2.09 (m, 1H), 2.36 (m, 1H), 3.09 (s, 3H), 3.75 (s, 3H), 3.83 (m, 1H), 3.90 (m, 1H), 4.93 (t, J=6.5, 1H), 5.11 (s, 1H), 7.06-7.83 (m, 4H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 24.64 (CH_2), 30.08 (CH_2), 32.37 (CH_3), 53.24 (CH_2), 60.98 (CH), 61.47 (CH_3), 87.88 (CH), 115.95 (C), 117.63 (CH), 122.45 (CH), 125.19 (CH), 130.91 (CH), 153.93 (C), 154.92 (C), 162.37 (C), 171.83 (C); MS: m/z 302 (M^+, 5), 214 (100). (Found: C, 63.49; H, 6.03; N, 9.30. $C_{16}H_{18}N_2O_4$ requires C, 63.56; H, 6.00; N, 9.27%).

1,3-dicyclohexyl-1-(2-(2-0xo-2H-1-benzopyran-4-yl)-3-methylbutanoyl)urea (**11**): colorless crystals, mp. 126°C. IR (KBr) 1673, 1612, 1550 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 0.89 (d, J=6.7, 3H), 0.94 (d, J=6.7, 3H), 1.05-2.15 (m, 20H), 2.35 (m, J=6.7 and 6.1, 1H), 3.81 (m, 1H), 4.30 (m, 1H), 4.64 (dd, J=8.4 and 6.1, 1H), 5.08 (s, 1H), 6.09 (d, J=8.4, 1H, NH), 6.87-7.35 (m, 4H), 8.53 (d, J=8.1, 1H, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 16.27 (CH_3), 20.40 (CH_3), 25.17 (CH_2), 25.30 (CH_2), 25.40 (2 CH_2), 26.01 (2 CH_2), 29.66 (CH_2), 31.55 (CH_2), 32.40 (CH and CH_2), 32.56 (CH_2), 50.82 (CH), 55.34 (CH), 57.66 (CH), 83.81 (CH), 113.84 (C), 117.90 (CH), 119.82 (CH), 123.64 (CH), 131.55 (CH), 152.69 (C), 152.86 (C), 153.00 (C), 163.64 (C), 168.68 (C); MS: m/z 467 (M^+, 1), 216 (100). (Found: C, 69.22; H, 8.00; N, 9.03. $C_{27}H_{37}N_3O_4$ requires C, 69.34; H, 7.98; N, 8.99%).

Preparation of Weinreb amides 4 from 4-chlorocoumarin 1 and hydrobromides 9. A mixture of 4-chlorocoumarin **1** (2 g, 11 mmol), hydrobromide **9** (12 mmol) and triethylamine (3.06 cm^3, 22 mmol) in anhydrous ethanol (40 cm^3) was stirred at 55°C for 24h. The solvent was then evaporated and the residue was dissolved in dichloromethane/water (1:1, 150 cm^3). The aqueous layer was extracted with dichloromethane (2 x 50 cm^3) and the combined organic layer was dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel using dichloromethane/tetrahydrofuran (5:1) as eluent (yields in Table 1).

Reaction of Weinreb amides 4 with organometallic compounds. Preparation of carbonyl intermediates 12. To a magnetically stirred solution of amides **4a-e** (2.22 mmol) in 35 cm^3 of dry tetrahydrofuran was added dropwise (10 min) the organometallic compound under nitrogen (see Table 2). At the end of the reaction (monitored by TLC), the mixture was hydrolyzed with cooled hydrochloric acid (1N). The organic layer was decanted, washed with water, dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel using dichloromethane/tetrahydrofuran (6:1) as eluent (**12g-n**). The carbonyl compounds **12o-w** were not isolated[20] and the concentrate underwent cyclization treatment.

4-(2-Oxo-2-phenyl-ethylamino)-2H-1-benzopyran-2-one (**12g**): 65%, colorless crystals, mp. 237°C (lit.,[14] 236-237°C). IR (KBr) 3328, 3279, 1700, 1657, 1607, 1557, 1484, 1452, 1251, 1222, 1199, 947, 766, 755 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ = 4.93 (d, J=5.5, 2H), 5.15 (s, 1H), 7.24-8.24 (m, 10H); ^{13}C NMR (75.4 MHz, DMSO-d_6) δ = 48.92 (CH_2), 82.82 (CH), 114.39 (C), 117.02 (CH), 122.36 (CH), 123.53 (CH), 128.13 (2 CH), 128.85 (2 CH), 132.05 (CH), 133.89 (CH), 134.74 (C), 153.09 (C), 153.53 (C), 161.46 (C), 194.63 (C); MS: m/z 279 (M^+, 13), 105 (100). (Found: C, 73.18; H, 4.68; N, 5.01. $C_{17}H_{13}NO_3$ requires C, 73.11; H, 4.69; N, 5.01%).

4-(2-Oxo-propylamino)-2H-1-benzopyran-2-one (**12h**): 60%, colorless crystals, mp. 181°C (lit.,[14] 181-182°C). IR (KBr) 3389, 1690, 1620, 1609, 1561, 1536, 1264, 937, 762, 752 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 2.38 (s, 3H), 4.14 (d, J=4.0, 2H), 5.22 (s, 1H), 6.23 (br, 1H, NH), 7.24-7.61 (m, 4H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 27.47 (CH_3), 51.96 (CH_2), 84.67 (CH), 113.78 (C), 117.68 (CH), 120.46 (CH), 123.64 (CH), 132.02 (CH), 151.72 (C), 153.39 (C), 162.92 (C), 201.56 (C); MS: m/z 217 (M^+, 43), 174 (100). (Found: C, 66.46; H, 5.12; N, 6.43. $C_{12}H_{11}NO_3$ requires C, 66.35; H, 5.10; N, 6.45%).

4-(3-Methyl-2-oxo-butylamino)-2H-1-benzopyran-2-one (**12i**): 68%, colorless crystals, mp. 161°C. IR (KBr) 3307, 1670, 1614, 1555, 1259, 1195, 763 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 1.25 (d, J=6.9, 6H),

2.81 (m, J=6.9, 1H), 4.18 (d, J=4.0, 2H), 5.23 (s, 1H), 6.31 (br, 1H, NH), 7.26-7.60 (m, 4H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 18.26 (2 CH_3), 39.13 (CH), 49.43 (CH_2), 84.88 (CH), 113.94 (C), 117.83 (CH), 120.45 (CH), 123.66 (CH), 132.05 (CH), 151.74 (C), 153.55 (C), 162.85 (C), 207.92 (C); MS: m/z 245 (M^+, 12), 174 (100). (Found: C, 68.63; H, 6.16; N, 5.69. $C_{14}H_{15}NO_3$ requires C, 68.56; H, 6.16; N, 5.71%).

4-(2-(1,3-Dithiolan-2-yl)-2-oxo-ethylamino)-2H-1-benzopyran-2-one (**12j**): 63%, colorless crystals, mp. 190°C. IR (KBr) 3258, 1657, 1602, 1550, 1242, 1194, 745 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ = 1.84 (m, 2H), 2.04 (m, 1H), 2.65 (m, 2H), 3.06 (m, 2H), 4.49 (d, J=6.0, 2H), 4.92 (s, 1H), 5.11 (s, 1H), 7.32-8.02 (m, 4H), 8.02 (br, 1H, NH); ^{13}C NMR (75.4 MHz, DMSO-d_6) δ = 24.75 (CH_2), 25.34 (2 CH_2), 42.41 (CH), 48.55 (CH_2), 82.44 (CH), 114.31 (C), 117.05 (CH), 122.37 (CH), 123.56 (CH), 132.12 (CH), 153.08 (C), 153.51 (C), 161.42 (C), 198.52 (C); MS: m/z 321 (M^+, 12), 161 (100). (Found: C, 56.25; H, 4.69; N, 4.34. $C_{15}H_{15}NO_3S_2$ requires C, 56.06; H, 4.70; N, 4.36%).

4-(1-Methyl-2-oxo-2-phenyl-ethylamino)-2H-1-benzopyran-2-one (**12k**): 85%, colorless crystals, mp. 161°C. IR (KBr) 3325, 1660, 1605, 1542, 1358, 1260, 1183, 770 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.59 (d, J=6.9, 3H), 5.24 (m, J=6.9 and 6.1, 1H), 5.42 (s, 1H), 6.74 (d, J=6.1, 1H, NH), 7.27-8.06 (m, 9H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 18.67 (CH_3), 52.38 (CH), 84.48 (CH), 114.24 (C), 117.90 (CH), 120.59 (CH), 123.62 (CH), 128.78 (2 CH), 129.22 (2 CH), 132.02 (CH), 133.21 (C), 134.59 (CH), 151.14 (C), 153.69 (C), 163.06 (C), 198.01 (C); MS: m/z 293 (M^+, 20), 188 (100). (Found: C, 73.64; H, 5.13; N, 4.79. $C_{18}H_{15}NO_3$ requires C, 73.71; H, 5.15; N, 4.78%).

4-(1-Methyl-2-oxo-propylamino)-2H-1-benzopyran-2-one (**12l**): 88%, colorless crystals, mp. 140°C. IR (KBr) 3320, 1650, 1607, 1545, 1195, 942, 795, 760 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.55 (d, J=7.0, 3H), 2.36 (s, 3H), 4.30 (m, J=7.0 and 5.5, 1H), 5.22 (s, 1H), 6.50 (d, J=5.5, 1H, NH), 7.25-7.63 (m, 4H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 16.45 (CH_3), 26.26 (CH_3), 56.64 (CH), 84.33 (CH), 114.04 (C), 117.74 (CH), 120.52 (CH), 123.56 (CH), 131.96 (CH), 151.08 (C), 153.50 (C), 162.90 (C), 205.69 (C); MS: m/z 231 (M^+, 19), 188 (100). (Found: C, 67.54; H, 5.65; N, 6.04. $C_{13}H_{13}NO_3$ requires C, 67.51; H, 5.67; N, 6.06%).

4-(1-Isopropyl-2-oxo-propylamino)-2H-1-benzopyran-2-one (**12m**): 92%, colorless crystals, mp. 160°C. IR (KBr) 3290, 1710, 1658, 1612, 1537, 815, 740 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.00 (d, J=7.0, 3H), 1.03 (d, J=7.0, 3H), 2.30 (s, 3H), 2.39 (m, J=7.0 and 4.1, 1H), 4.18 (dd, J=7.3 and 4.1, 1H), 5.26 (s, 1H), 6.15 (d, J=7.3, 1H, NH), 7.25-7.64 (m, 4H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 17.83 (CH_3), 19.45 (CH_3), 27.93 (CH_3), 30.38 (CH), 66.56 (CH), 84.63 (CH), 114.16 (C), 117.62 (CH), 120.51 (CH), 123.56 (CH), 131.90 (CH), 152.65 (C), 153.34 (C), 162.99 (C), 206.08 (C); MS: m/z 259 (M^+, 12), 216 (100). (Found: C, 69.51; H, 6.63; N, 5.39. $C_{15}H_{17}NO_3$ requires C, 69.48; H, 6.61; N, 5.40%).

4-(N-Methyl-2-oxo-2-phenyl-ethylamino)-2H-1-benzopyran-2-one (**12n**): 51%, colorless crystals, mp. 131°C (lit.,[14] 130-131°C). IR (KBr) 1699, 1599, 1551, 1224, 751 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.10 (s, 3H), 4.82 (s, 2H), 5.59 (s, 1H), 7.11-7.96 (m, 9H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 40.74 (CH_3), 60.56 (CH_2), 94.88 (CH), 115.82 (C), 117.77 (CH), 123.28 (CH), 124.65 (CH), 127.76 (2 CH), 128.89 (2 CH), 131.38 (CH), 134.10 (CH), 134.56 (C), 154.06 (C), 160.12 (C), 162.28 (C), 194.02 (C); MS: m/z 293 (M^+, 8), 188 (98), 77(100). (Found: C, 73.61; H, 5.17; N, 4.79. $C_{18}H_{15}NO_3$ requires C, 73.71; H, 5.15; N, 4.78%).

4-(N-Methyl-2-oxo-propylamino)-2H-1-benzopyran-2-one (**12o**): 76%, colorless crystals, mp. 113°C. IR (KBr) 1715, 1675, 1597, 1547, 1405, 935, 760 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 2.23 (s, 3H), 3.03 (s, 3H), 4.18 (s, 2H), 5.60 (s, 1H), 7.22-7.49 (m, 4H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 27.40 (CH_3), 40.76 (CH_3), 63.98 (CH_2), 95.46 (CH), 115.88 (C), 118.03 (CH), 123.43 (CH), 124.62 (CH), 131.62 (CH), 154.21 (C), 160.07 (C), 162.46 (C), 203.31 (C); MS: m/z 231 (M^+, 20), 188 (100).). (Found: C, 67.44; H, 5.69; N, 6.08. $C_{13}H_{13}NO_3$ requires C, 67.51; H, 5.67; N, 6.06%).

Cyclization of 12g-m to pyrroles 13g-m. Method A. A mixture of **12g-m** (5 mmol) and NaOEt (0.34g, 5 mmol) in ethanol (30 cm^3) was stirred at room temperature for 2 h, and then refluxed for 1 h. The mixture was cooled to room temperature, hydrolyzed with ice water and neutralized, yielding a solid which was washed with water. The product was recrystallized (dichloromethane/diethyl ether) or chromatographed on silica gel using dichloromethane or dichloromethane/pentane (10:1) as eluent.

The following compounds were thus prepared.

3-Phenyl-[1]benzopyrano[4,3-b]pyrrol-4(1H)-one (**13g**): 75%, colorless crystals, mp. 327°C (lit.,[14] 326°C). IR (KBr) 3112, 1679, 1578, 1066, 798, 744, 698 cm^{-1}; ^1H NMR (80 MHz, DMSO-d_6) δ = 7.20-8.10 (m, 10H), 12.70 (br, 1H, NH); ^{13}C NMR (75.4 MHz DMSO-d_6) δ = 104.5 (C), 113.7 (C), 116.6 (CH), 121.3 (CH), 122.5 (CH), 124.1 (CH), 124.4 (C), 126.5 (CH), 128.0 (2 CH), 128.5 (2 CH), 128.9 (CH), 136.3 (C), 136.5 (C), 151.1 (C), 157.8 (C); MS: m/z 261 (M^+, 100). (Found: C, 78.21; H, 4.23; N, 5.38. $C_{17}H_{11}NO_2$ requires C, 78.15; H, 4.24; N, 5.36%).

3-Methyl-[1]benzopyrano[4,3-b]pyrrol-4(1H)-one (**13h**): 92%, colorless crystals, mp. 286°C (lit.,[14] 285-286°C). IR (KBr) 3145, 1695, 1581, 1465, 1207, 1039, 746 cm^{-1}; ^1H NMR (80 MHz, DMSO-d_6) δ = 2.30 (s, 3H), 7.04 (d, J=1.0, 1H), 7.20-8.02 (m, 4H), 12.50 (br, 1H, NH); ^{13}C NMR (75.4 MHz DMSO-d_6) δ = 10.7 (CH_3), 106.8 (C), 114.1 (C), 116.7 (CH), 118.4 (C), 121.1 (CH), 121.2 (CH), 123.9 (CH), 128.3 (CH), 134.9 (C), 151.2 (C), 158.6 (C); MS: m/z 199 (M^+, 100). (Found: C, 72.31; H, 4.55; N, 7.00. $C_{12}H_9NO_2$ requires C, 72.36; H, 4.55; N, 7.03%).

3-Isopropyl-[1]benzopyrano[4,3-b]pyrrol-4(1H)-one (**13i**): 81%, colorless crystals, mp. 225°C. IR (KBr) 3155, 1680, 1509, 1208, 1038, 1010, 779, 740 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ = 1.25 (d, J=6.8, 6H), 3.27 (m, J=6.8, 1H), 7.05 (d, J=1.5, 1H), 7.29-8.02 (m, 4H), 12.35 (br, 1H, NH); ^{13}C NMR (75.4 MHz DMSO-d_6) δ = 23.22 (2 CH_3), 25.06 (CH), 105.60 (C), 113.97 (C), 116.60 (CH), 118.62 (CH), 121.07 (CH), 123.88 (CH), 128.33 (CH), 131.16 (C), 135.24 (C), 151.11 (C), 158.08 (C); MS: m/z 227 (M^+, 54), 212 (100). (Found: C, 74.01; H, 5.78; N, 6.18. $C_{14}H_{13}NO_2$ requires C, 73.99; H, 5.77; N, 6.16%).

3-(1,3-Dithiolan-2yl)-[1]benzopyrano[4,3-b]pyrrol-4(1H)-one (**13j**): 80%, colorless crystals, mp. >300°C. IR (KBr) 3227, 1692, 1462, 1043, 751 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ = 1.74 (m, 1H), 2.12 (m, 1H), 2.89 (m, 2H), 3.08 (m, 2H), 5.85 (s, 1H), 7.43 (s, 1H), 7.33-8.06 (m, 4H), 12.81 (br, 1H, NH); ^{13}C NMR (75.4 MHz DMSO-d_6) δ = 24.91 (CH_2), 31.48 (2 CH_2), 40.06 (CH), 104.51 (C), 113.58 (C), 116.82 (CH), 121.40 (CH), 121.81 (C), 123.20 (CH), 124.24 (CH), 128.92 (CH), 134.65 (C), 151.17 (C), 157.60 (C); MS: m/z 305 (M+2, 3), 303 (M^+, 31), 228 (100). (Found: C, 59.40; H, 4.34; N, 4.64. $C_{15}H_{13}NO_2S_2$ requires C, 59.37; H, 4.32; N, 4.62%).

2-Methyl-3-phenyl-[1]benzopyrano[4,3-b]pyrrol-4(1H)-one (**13k**): 72%, colorless crystals, mp. >310ºC. IR (KBr) 3228, 1686, 1500, 1100, 973, 750, 700 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ = 2.34 (s, 3H), 7.35-8.02 (m, 9H), 12.56(br, 1H, NH); ^{13}C NMR (75.4 MHz DMSO-d_6) δ = 11.69 (CH_3), 105.44 (C), 113.57 (C), 116.60 (CH), 119.86 (C), 120.93 (CH), 124.01 (CH), 126.26 (CH), 127.62 (2 CH), 128.36 (CH), 130.27 (2 CH), 130.99 (C), 133.23 (C), 134.28 (C), 150.94 (C), 157.48 (C); MS: m/z 275 (M+, 100). (Found: C, 78.49; H, 4.78; N, 5.06. C18H13NO2 requires C, 78.53; H, 4.76; N, 5.09%).

2,3-Dimethyl-[1]benzopyrano[4,3-b]pyrrol-4(1H)-one (**13l**): 69%, colorless crystals, mp. >330ºC. IR (KBr) 3271, 1698, 1542, 1520, 1213, 1035, 750 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ = 2.20 (s, 3H), 2.25 (s, 3H), 7.29-7.91 (m, 4H), 12.16(br, 1H, NH); ^{13}C NMR (75.4 MHz DMSO-d_6) δ= 9.32 (CH_3), 10.57 (CH_3), 107.06 (C), 113.58 (C), 113.95 (C), 116.65 (CH), 120.66 (CH), 123.92 (CH), 127.80 (CH), 129.74 (C), 133.16 (C), 150.89 (C), 158.48 (C); MS: m/z 213 (M^+, 100). (Found: C, 73.26; H, 5.23; N, 6.58. $C_{13}H_{11}NO_2$ requires C, 73.22; H, 5.20; N, 6.57%).

2-Isopropyl-3-methyl-[1]benzopyrano[4,3-b]pyrrol-4(1H)-one (**13m**): 76%, colorless crystals, mp. 284ºC. IR (KBr) 3265, 1682, 1453, 1200, 1032, 1004, 758 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ = 1.28 (d, J=7.0, 6H), 2.25 (s, 3H), 3.13 (m, J=7.0, 1H), 7.28-8.11 (m, 4H), 11.82 (br, 1H, NH); ^{13}C NMR (75.4 MHz DMSO-d_6) δ = 9.30 (CH_3), 22.14 (2 CH_3), 24.97 (CH), 107.00 (C), 112.00 (C), 114.02 (C), 116.62 (CH), 121.12 (CH), 123.77 (CH), 127.86 (CH), 133.40 (C), 139.67 (C), 150.89 (C), 158.58 (C); MS: m/z 241 (M^+, 38), 226 (100). (Found: C, 74.77; H, 6.24; N, 5.79. $C_{15}H_{15}NO_2$ requires C, 74.67; H, 6.27; N, 5.80%).

Cyclization of 12n to *1-Methyl-3-phenyl-[1]benzopyrano[4,3-b]pyrrol-4(1H)-one* (13n). Method B. The compound **12n** (0.75 g, 2.55 mmol) was refluxed in 30 cm^3 of acetic acid/water (3:1) for 6 h. When the reaction, which was monitored by TLC, was completed, the mixture was poured into water yielding a colorless solid which was filtered off, washed with aqueous $NaHCO_3$ and recrystallized from methanol; yield: 0.60 g (88%) of **13n**. Colorless crystals, mp. 215ºC (lit.,[14] 214-215ºC). IR (KBr) 1695, 1502, 1064, 754, 698 cm^{-1}; ^1H NMR (300 MHz $CDCl_3$) δ = 4.12 (s, 3H), 6.90 (s, 1H), 7.25-8.00 (m, 9H); ^{13}C NMR (75.4 MHz DMSO-d_6) δ = 37.61 (CH_3), 105.59 (C), 114.11 (C), 117.03 (CH), 122.01 (CH), 123.00 (C), 124.12 (CH), 126.61 (CH), 127.89 (2 CH), 128.72 (3 CH), 128.81 (CH), 132.91 (C), 134.79 (C), 151.12 (C), 157.88 (C); MS: m/z 275 (M^+, 100). (Found: C, 78.46; H, 4.77; N, 5.08. $C_{18}H_{13}NO_2$ requires C, 78.53; H, 4.76; N, 5.09%).

Cyclization of 12o-w to pyrroles 13o-w Method C. The previously mentioned reaction mixtures of **12o-w** (approximately 2.2 mmol) and silica gel (5 x, w/w) in chloroform (30 cm^3) were heated in a rotary evaporator, slowly distilling the solvent (45 min). The silica gel was filtered off and washed thoroughly with hot acetone. The solvent was removed *in vacuo*, and the concentrate was recrystallized from methanol or chromatographed on silica gel using dichloromethane/pentane (10:1) as eluent.

The following compounds were thus prepared.

1,3-Dimethyl-[1]benzopyrano[4,3-b]pyrrol-4(1H)-one (**13o**): 78%, colorless crystals, mp. 148ºC. IR (KBr) 1729, 1510, 1200, 1048, 1028, 759 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ = 2.23 (s, 3H), 3.97 (s, 3H), 6.91 (s, 1H), 7.20-8.10 (m, 4H); ^{13}C NMR (75.4 MHz DMSO-d_6) δ = 10.32 (CH_3), 36.79 (CH_3), 107.81 (C), 114.30 (C), 116.91 (CH), 117.42 (C), 121.39 (CH), 123.81 (CH), 127.62 (CH), 127.89 (CH), 133.11 (C),

151.09 (C), 158.01 (C); MS: m/z 213 (M^+, 100). (Found: C, 73.27; H, 5.17; N, 6.60. $C_{13}H_{11}NO_2$ requires C, 73.22; H, 5.20; N, 6.57%).

3-(1-Hexynyl)-1-methyl-[1]benzopyrano[4,3-b]pyrrol-4(1H)-one (**13q**): 80%, colorless crystals, mp. 125°C. IR (KBr) 1723, 1504, 1213, 1048, 745 cm^{-1}; ^1H NMR (300 MHz $CDCl_3$) δ = 0.92 (t, J=7.1, 3H), 1.49 (m, 2H), 1.58 (m, 2H), 2.42 (t, J=6.9, 2H), 3.92 (s, 3H), 6.80 (s, 1H), 7.14-7.73 (m, 4H); ^{13}C NMR (75.4 MHz $CDCl_3$) δ = 13.54 (CH_3), 19.32 (CH_2), 21.87 (CH_2), 30.72 (CH_2), 37.58 (CH_3), 71.65 (C), 92.85 (C), 104.16 (C), 109.58 (C), 113.82 (C), 117.42 (CH), 120.62 (CH), 123.59 (CH), 128.26 (CH), 131.85 (CH), 133.45 (C), 151.58 (C), 157.34 (C); MS: m/z 279 (M^+, 100). (Found: C, 77.32; H, 6.16; N, 5.03. $C_{18}H_{17}NO_2$ requires C, 77.40; H, 6.13; N, 5.01%).

1-Benzyl-3-methyl-[1]benzopyrano[4,3-b]pyrrol-4(1H)-one (**13s**): 65%, colorless crystals, mp. 261°C (lit.,[6b] 262-263°C). IR (KBr) 1718, 1510, 1456, 1199, 1045, 1029, 746, 738, 703 cm^{-1}; ^1H NMR (300 MHz $CDCl_3$) δ = 2.45 (s, 3H), 5.53 (s, 2H), 6.69 (s, 1H), 7.04-7.55 (m, 9H); ^{13}C NMR (75.4 MHz $CDCl_3$) δ = 10.96 (CH_3), 52.79 (CH_2), 109.69 (C), 114.39 (C), 117.85 (CH), 120.12 (C), 121.10 (CH), 123.77 (CH), 125.97 (2 CH), 126.48 (CH), 128.10 (2 CH), 129.25 (2 CH), 134.08 (C), 135.88 (C), 152.07 (C), 159.43 (C); MS: m/z 289 (M^+, 12), 91 (100). (Found: C, 78.85; H, 5.25; N, 4.83. $C_{19}H_{15}NO_2$ requires C, 78.87; H, 5.23; N, 4.84%).

8,9-Dihydro-7-methyl-[1]benzopyrano[3,4-b]pyrrolyzin-6(6H,10H)-one (**13t**): 73%, colorless crystals, mp. 237°C. IR (KBr) 1708, 1535, 1504, 1456, 1198, 1112, 991, 763 cm^{-1}; ^1H NMR (300 MHz $CDCl_3$) δ = 2.27 (s, 3H), 2.66 (m, 2H), 2.82 (dd, J=7.0 and 7.7, 2H), 4.27 (t, J=7.1, 2H), 7.16-7.61 (m, 4H); ^{13}C NMR (75.4 MHz $CDCl_3$) δ = 10.13 (CH_3), 21.87 (CH_2), 27.81 (CH_2), 46.63 (CH_2), 110.27 (C), 111.24 (C), 114.56 (C), 117.31 (CH), 119.96 (CH), 123.50 (CH), 127.30 (CH), 129.94 (C), 139.42 (C), 151.31 (C), 163.07 (C); MS: m/z 239 (M^+, 100). (Found: C, 75.27; H, 5.50; N, 5.84. $C_{15}H_{13}NO_2$ requires C, 75.30; H, 5.48; N, 5.85%).

8,9-Dihydro-7(1-hexynyl)-[1]benzopyrano[3,4-b]pyrrolyzin-6(6H,10H)-one (**13v**): 81%, colorless crystals, mp. 152°C. IR (KBr) 1718, 1510, 1452, 1095, 743 cm^{-1}; ^1H NMR (300 MHz $CDCl_3$) δ = 0.94 (t, J=7.2, 3H), 1.50 (m, 2H), 1.57 (m, 2H), 2.43 (t, J=6.9, 2H), 2.61 (m, J=7.5 and 7.2, 2H), 2.84 (t, J=7.5, 2H), 4.18 (t, J=7.2, 2H), 6.97-7.39 (m, 4H); ^{13}C NMR (75.4 MHz $CDCl_3$) δ = 13.62 (CH_3), 19.49 (CH_2), 21.88 (CH_2), 22.77 (CH_2), 27.03 (CH_2), 30.93 (CH_2), 47.22 (CH_2), 72.12 (C), 93.14 (C), 96.02 (C), 111.49 (C), 113.36 (C), 116.93 (CH), 119.91 (CH), 123.46 (CH), 127.66 (CH), 129.62 (C), 146.48 (C), 151.00 (C), 157.59 (C); MS: m/z 305 (M^+, 100). (Found: C, 78.69; H, 6.30; N, 4.58. $C_{20}H_{19}NO_2$ requires C, 78.66; H, 6.27; N, 4.59%).

8,9-Dihydro-7-vinyl-[1]benzopyrano[3,4-b]pyrrolyzin-6(6H,10H)-one (**13w**): 59%, colorless crystals, mp. 196°C. IR (KBr) 1713, 1504, 1451, 1108, 1039, 992, 765, 750 cm^{-1}; ^1H NMR (300 MHz $CDCl_3$) δ = 2.66 (m, 2H), 2.85 (t, J=7.5, 2H), 4.18 (t, J=7.3, 2H), 5.11 (dd, J=11.3 and 1.5, 1H), 5.30 (dd, J=18.0 and 1.5, 1H), 7.13 (dd, J=18.0 and 11.3, 1H), 7.06-7.48 (m, 4H); ^{13}C NMR (75.4 MHz $CDCl_3$) δ = 23.92 (CH_2), 27.31 (CH_2), 46.37 (CH_2), 109.13 (C), 112.82 (CH_2), 112.91 (C), 113.77 (C), 116.96 (CH), 119.98 (CH), 123.55 (CH), 127.51 (CH), 128.11 (CH), 129.92 (C), 140.00 (C), 150.97 (C), 158.81 (C); MS: m/z 251 (M^+, 100). (Found: C, 76.58; H, 5.19; N, 5.55. $C_{16}H_{13}NO_2$ requires C, 76.49; H, 5.21; N, 5.57%).

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