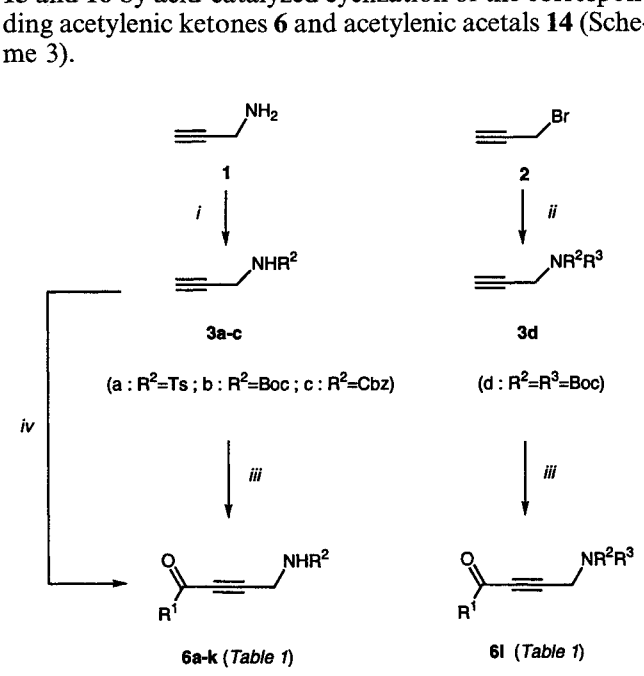
A New Approach to the Synthesis of *N*-Protected 2- and 5-Substituted 3-Halopyrroles

Thierry Masquelin, Daniel Obrecht*
Pharma Research, F. Hoffmann-La Roche AG, CH-4002 Basel, Switzerland
Received 16 August 1994; revised 4 November 1994

A new and efficient method for the preparation of *N*-protected 5- and 2-substituted 3-bromopyrroles **15** and **16** via acid-catalyzed cyclization of the corresponding acetylenic ketones **6** and acetylenic acetals **14** has been found (Scheme 3). Using this methodology, rapid and quite general access to highly substituted pyrroles, which are known to exhibit a number of interesting biological activities, has been established.

In recent years, significant attention has been focused on the synthesis of pyrroles and their derivatives because many naturally occurring pyrroles are known to possess biological activity. Specially designed pyrroles have found applications in the pharmaceutical field[1,2] and also in polymer technology.[3] During the last decades, several methods have been developed for the preparation of pyrroles, the most versatile of which was described by Trofimov.[4] This approach stimulated fresh interest in pyrrole chemistry which has resulted in a number of publications in this area.[5-8] Among the large family of pyrroles, several efforts have focused on the development of methodologies for the synthesis of substituted pyrrolecarboxylates,[9-12] arylpyrroles and heteroarylpyrroles.[13] Since 3-halo 5-membered heterocyclic derivatives can be easily substituted in various ways, their preparation is currently of great interest. Recently, a new route to 3-halofurans by acid-catalyzed cyclization of acetylenic ketones and acetylenic acetals was described.[14] We have now extended these studies to provide a novel general synthesis of the *N*-protected 5- and 2-substituted 3-halopyrroles **15** and **16** by acid-catalyzed cyclization of the corresponding acetylenic ketones **6** and acetylenic acetals **14** (Scheme 3).



i: protection; *ii*: KNR^2R^3, DMF; *iii*: a) LDA, THF, -78°C, b) HMPT, R^1-CHO (**4a-g, i-k**), c) MnO_2, CH_2Cl_2 (*Method A*); *iv*: a) LDA, THF, -78°C, b) HMPT, R^1-CO-NMe(OMe) (**5f,g**) (*Method B*).

Scheme 1

The acetylenic ketones **6** were conveniently prepared in good yields using two different procedures (Scheme 1).

The *N*-protected propargylamines **3a–c** were easily obtained by standard methods and in good yields from α-propynylamine **(1)**, whereas **3d** was obtained from 2-propynylbromide **(2)** and potassium di-*tert*-butyliminodicarboxylate in dimethylformamide (DMF). Treatment of the desired *N*-protected propynylamines **3** with 2.5 equivalents of freshly prepared lithium diisopropylamide (LDA) solution in tetrahydrofuran (THF) and hexamethylphosphorous triamide (HMPT) at −78 °C, followed by addition of the corresponding aldehyde **4** and oxidation of the intermediate alcohols with manganese(IV) oxide (MnO_2) in dichloromethane, gave the acetylenic ketones **6a–e** and **g–l** in good overall yields after purification of the intermediates when necessary (Scheme 1; Table 1; Method A). Alternatively, the *N*-protected propynylamines **3a,d** could be treated with 2.5 equivalents of freshly prepared LDA solution in THF/HMPT at −78 °C as above to afford the intermediate dianions, which reacted with the *N*-methoxy-*N*-methylamides **5**[15] giving the corresponding acetylenic ketones **6f,g** (Scheme 1; Table 1; Method B). In cases where the carboxylic acid chlorides were readily available, Method B gave slightly better overall yields.

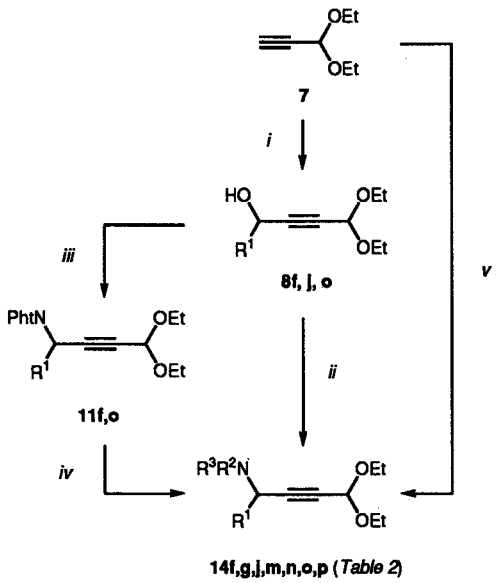
Table 1. Synthesis of Acetylenic Ketones **6a–l**

4/5	R^1	R^2	R^3	Method	Product	Yield (%)
4a	2-furyl	Ts	H	A	**6a**	62
4b	3-furyl	Ts	H	A	**6b**	53
4c	2-thienyl	Ts	H	A	**6c**	65
4d	3-thienyl	Ts	H	A	**6d**	61
4e	2-(*N*-Ts)-pyr[a]	Ts	H	A	**6e**	39
5f	*t*-Bu	Cbz	H	B	**6f**	73
4g	Ph	Ts	H	A	**6g**	75
5g	Ph	Ts	H	B	**6g**	75
4g	Ph	Boc	H	A	**6h**	65
4i	$(MeO)_3C_6H_2$	Boc	H	A	**6i**	45
4j	C_8H_{17}	Boc	H	A	**6j**	65
4k	PhCH=CH	Boc	H	A	**6k**	47
4g	Ph	Boc	Boc	A	**6l**	65

[a] pyr = pyrrole.

The key acetylenic acetals **14** were synthesized by three different routes as shown in Scheme 2.

Treatment of the commercially available 3,3-diethoxyprop-1-yne (**7**) with butyllithium (BuLi) in THF at −78 °C,[14] followed by addition of the corresponding aldehydes **4f,j,o** gave the acetylenic alcohols **8f** and **8j,o**[14] in good yields (Method C; see experimental section). Addition of methanesulfonyl chloride in the presence of triethylamine to the acetylenic alcohol **8j** afforded the corresponding mesylate **9j** in 93 % yield, which after treat-



i: a) BuLi, THF, -78°C, b) R^1-CHO (**4f,j,o**) (*Method C*) ; *ii*: a) MsCl, Et_3N (→ **9j**), b) Boc_2NH (**10**), KtBuO, DMF (*Method D*) ; *iii*: a) DEAD, $P(\Phi)_3$, THF,phthalimide (*Method E*) ; *iv*: a) NH_2NH_2, EtOH (→ **12f,o**), b) protection ; *v*: a) BuLi, THF, -78°C, b) R^1-CH=NR^2 (**13g,n**) (*Method F*).

Scheme 2

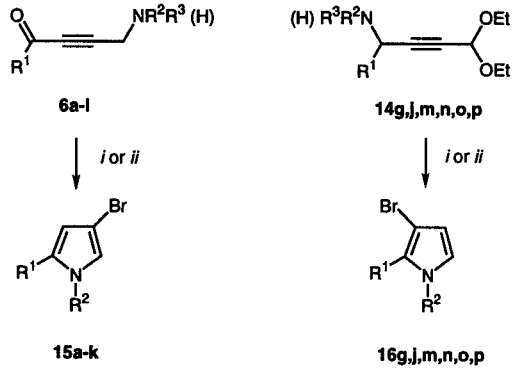
ment with *t*-BuOK and di-*tert*-butyliminodicarboxylate (**10**) in DMF at 70 °C gave the acetylenic acetal **14j** in 56% yield (Method D; Table 2). Alternatively, we used the reaction of the acetylenic alcohols **8f,o** with phthalimide, triphenylphosphine and diethylazodicarboxylate (DEAD)[16] at room temperature to conveniently synthesize the phthalimide intermediates **11f,o** in good yields (Method E; see experimental section). Subsequent reaction of **11f,o** with 1 N ethanolic hydrazine solution at 80 °C, followed by protection of the free amine intermediates **12f,o** using standard methods, afforded the *N*-protected acetylenic acetals **14f,m,o,p** in good overall yields (Method E; Table 2). In the search for other routes, the synthesis of the acetylenic acetals **14g,n** were also conveniently achieved in good to excellent yields by the addition of the lithium acetylide of 3,3-diethoxyprop-1-yne (prepared by reaction of **7** with BuLi in THF at − 78 °C) to the corresponding *N*-tosylimines **13g,n** (generated from aldehydes **4g,k** using toluenesulfonamide and boron trifluoride–diethyl ether complex ($BF_3 \cdot Et_2O$) (see experimental section; Method F; Table 2) in the presence of zinc chloride.[17–19]

Table 2. Synthesis of Acetylenic Acetals **14f,g,j,m,n,o,p**

8/13	R^1	R^2	R^3	Method	Product	Yield (%)
8f	*t*-Bu	Cbz	H	E	**14f**	62
13g	Ph	Ts	H	F	**14g**	74
8j	C_8H_{17}	Boc	Boc	D	**14j**	56
8f	*t*-Bu	Ts	H	E	**14m**	40
13n	PhCH=CH	Ts	H	F	**14n**	96
8o	C_5H_{11}	Boc	H	E	**14o**	85
8o	C_5H_{11}	Cbz	H	E	**14p**	83

In cases where the *N*-tosylimines **13** were readily available, we preferred Method F because they are easier to handle and generally gave slightly better overall yields.

The synthesis of the 3-bromopyrroles of types **15** and **16** (Scheme 3) was achieved in good to excellent yields by treatment of the acetylenic ketones **6a–l** and the acetylenic acetals **14g,j,m,n,o,p**, respectively, with 33% hydrogen bromide/acetic acid in dichloromethane (Method G; Table 3), or 2–4 N aqueous hydrobromic acid in toluene at temperatures ranging from room temperature to 60 °C (Method H; Table 3).



i: HBr-AcOH (33%), CH_2Cl_2, 0°-r.t (*Method G*) ; *ii*: HBr_{aq} (2-4N), toluene, r.t.-60° (*Method H*).

a: R^1 = 2-furyl, R^2 = Ts; **b**: R^1 = 3-furyl, R^2 = Ts; **c**: R^1 = 2-thienyl, R^2 = Ts; **d**: R^1 = 3-thienyl, R^2 = Ts; **e**: R^1 = *N*-Ts-pyrrolyl, R^2 = Ts; **f**: R^1 = *t*Bu, R^2 =Cbz; **g**: R^1 = Ph, R^2 = Ts ; **h**: R^1 = Ph, R^2 = Boc ; **i**: R^1 = 3,4,5-$(MeO)_3C_6H_2$, R^2 = Boc; **j**: R^1 = C_8H_{17}, R^2 = Boc; **k**: R^1 = Ph-CH=CH, R^2 = Boc; **l**: R^1 = Ph, R^2 = Boc, R^3 = Boc; **m**: R^1 = *t*Bu, R^2 = Ts; **n**: R^1 = Ph-CH=CH, R^2 = T ; **o**: R^1 = C_5H_{11}, R^2 = Boc; **p**: R^1 = C_5H_{11}, R^2 = Cbz; **q**: R^1 = C_8H_{17}, R^2 = Boc, R^3 = Boc.

Scheme 3

Table 3. Synthesis of *N*-Protected 5- and 2-Substituted 3-Halopyrroles **15** and **16**

6/14	R^1	R^2	R^3	Method	Product	Yield (%)
6a	2-furyl	Ts	H	G	**15a**	97
6b	3-furyl	Ts	H	G	**15b**	94
6c	2-thienyl	Ts	H	G	**15c**	94
6d	3-thienyl	Ts	H	G	**15d**	89
6e	2-(*N*-Ts)-pyr[a]	Ts	H	G	**15e**	91
6f	*t*-Bu	Cbz	H	G/H	**15f**	92/96
6g	Ph	Ts	H	G	**15g**	82
6h	Ph	Boc	H	G	**15h**	89
6i	$(MeO)_3C_6H_2$	Boc	H	G	**15i**	87
6j	C_8H_{17}	Boc	H	G	**15j**	66
6k	PhCH=CH	Boc	H	G	**15k**	95
6l	Ph	Boc	Boc	G	**15h**	96
14g	Ph	Ts	H	G	**16g**	96
14j	C_8H_{17}	Boc	Boc	G	**16j**	64
14m	*t*-Bu	Ts	H	G	**16m**	[b]
14n	PhCH=CH	Ts	H	H	**16n**	89
14o	C_5H_{11}	Boc	H	G	**16o**	64
14p	C_5H_{11}	Cbz	H	G	**16p**	92

[a] pyr = pyrrole.

[b] No cyclization occured under the reaction conditions. We isolated *N*-[(*Z*)-2-bromo-1-*tert*-butyl-4-oxobut-2-enyl]-4-methylbenzenesulfonamide in 90% yield.

The present strategy allows us to synthesize regioselectively the isomeric *N*-protected 2- and 5-substituted 3-halopyrroles as shown in Scheme 3. The high degree of regioselectivity is the result of the regioselective β-addition of hydrogen bromide to the acetylenic ketone moiety.[14]

In conclusion, acetylenic ketones **6** and acetylenic acetals **14** have been shown to be useful precursors for a new and efficient synthetic route to various *N*-protected 2- and 5-substituted 3-bromopyrroles. The cyclization yields are largely independent of the substituents R^1, R^2, and R^3 as long as they are compatible with the acidic reaction conditions. Since 3-bromopyrroles can be easily substituted, the present work constitutes a novel general synthesis of highly substituted pyrroles.

Further applications of this type of cyclization to the synthesis of interesting heterocycles will be reported in due course.

All reactions with air or moisture sensitive reactants and solvents were carried out in oven- or flame-dried glassware under a positive pressure of dry Ar. Reaction solvents and liquid reagents were purified before use. EtOH was distilled under Ar, THF from Na with benzophenone ketyl as indicator, CH_2Cl_2 from powdered CaH_2, DMF over ninhydrin and kept over 4 Å molecular sieves. All other reactants were "reagent-grade" unless described otherwise. Anal. TLC: 2.5 × 10 cm precoated TLC plates, SiO_2 60F-254, layer thickness 0.25 mm (E. Merck & Co., Darmstadt, Germany). Flash chromatography (FC): E. Merck $SiO_2$60 (70–230 Mesh ASTM); according to reference 20. Mp: Büchi-SMP-20 apparatus; uncorrected. IR: Nicolet-7199 Ft-IR spectrometer; solids in KBr pellets, liquids as thin films; characteristic bands in cm^{-1}. ^1H NMR spectra: Bruker-AC-250 apparatus, at 250 MHz; in DMSO or $CDCl_3$; TMS as internal standard; chemical shift of signal centers and ranges in ppm (δ), *J* in Hz. MS: Finnigan MS9-AEI or Mat90; *m/z* (rel.-%). Satisfactory microanalyses were obtained for compounds **8f**: C + 0.09, H + 0.12; **3c, 6h–l, 11f,o, 12o, 14f,p**: C ± 0.26, H ± 0.26, N ± 0.26; **3a, 6a–g, 13n, 14g,m, 15d,h**: C ± 0.29, H ± 0.21, N ± 0.25, S ± 0.28; **15a–c,e,g, 16g,h**: C ± 0.18, H ± 0.26, N ± 0.21, S ± 0.28, Br ± 0.15; **15f, 16o,p**: C ± 0.33, H ± 0.28, N ± 0.19, Br ± 0.12; **14j**: C – 0.03, H – 0.02, N – 0.20; **15i**: C – 0.27, H – 0.23, N – 0.05, Br + 0.12.

tert-Butyl prop-2-ynylcarbamate **3b**[21] and 1-tosylpyrrol-2-ylcarbaldehyde **4e**[22] were prepared following literature procedures. Derivatives **5f, 5g**,[23] and **8j, 8o**[14] were prepared according to literature procedure respectively. Aldehydes **4a–d,f,g,i–k** are commercially available.

General Procedures:

Method A:

To a stirred solution of diisopropylamine (1.7 mL, 11.95 mmol) in dry THF (20 mL), was added BuLi solution (1.6 M in hexane, 7.5 mL, 11.95 mmol) at 0 °C. The mixture was stirred for 15 min at 0 °C, cooled to – 78 °C, and *N*-tosylpropynylamine **(3a)** (1.0 g, 4.78 mmol) was added, followed by HMPT (3 mL). After stirring for 2 h at – 78 °C, aldehyde **4** (7.12 mmol) was added. The resulting mixture was stirred for 30 min at – 78 °C, allowed to slowly warm to 0 °C, stirred at 0 °C and quenched with sat. $NaHCO_3$ (30 mL), ice and Et_2O (50 mL). The aqueous layer was extracted with Et_2O (50 mL), the combined organic fractions were washed with brine (50 mL), dried (Na_2SO_4) and the solvents were removed. The residue was chromatographed on silica gel (if necessary) (Et_2O/hexane 2:1), dissolved in CH_2Cl_2 (10 mL) and added to a mechanically stirred suspension of MnO_2 (15 g) in CH_2Cl_2 (50 mL) at 0 °C. The mixture was stirred for 15 min at 0 °C, allowed to warm to r.t., stirred at r.t., filtered through Decalite and the solvents were removed. The acetylenic ketones **6** were purified as indicated in the corresponding description.

Method B:

To a stirred solution of diisopropylamine (6.6 mL, 47.7 mmol) in dry THF (100 mL), BuLi solution (1.6 M in hexane, 29.8 mL, 47.7 mmol) was added at 0 °C. The mixture was stirred for 15 min at 0 °C then cooled to – 78 °C, followed by the addition of the *N*-protected propynylamine **3** (15.9 mmol) and HMPT (5 mL). The reaction mixture was stirred for 2 h at – 78 °C then for 30 min at – 40 °C, followed by the addition of the corresponding *N*-methoxy-*N*-methylamide **5** (20.7 mmol).[23] The resulting mixture was stirred at – 40 °C, then allowed to slowly warm to 0 °C, stirred at 0 °C for 2 h and quenched with 0.5 N aq HCl (100 mL), ice, and Et_2O (200 mL). The combined organic fractions were washed with water (100 mL) brine (100 mL), dried ($MgSO_4$) and the solvents were removed. The residue was purified as indicated in the corresponding description.

Method C:

To a stirred solution of 3,3-diethoxyprop-1-yne **(7)** (7.16 mL, 50.0 mmol) in THF (150 mL), BuLi solution (1.6 M in hexane, 34.4 mL, 55.0 mmol) was added under Ar at – 78 °C. After stirring for 30 min at – 78 °C, freshly distilled aldehyde **4** (55.0 mmol) was added. The reaction mixture was allowed to slowly warm up to 0 °C, stirred at 0 °C for 1 h, then poured onto sat. aq $NaHCO_3$ (120 mL), ice and Et_2O (200 mL). The organic phase was washed with brine (100 mL), dried ($MgSO_4$) and the solvents were evaporated. The residue was purified as indicated in the corresponding description.

Method D:

To a stirred mixture of **8** (1.0 g, 3.70 mmol) and of triethylamine (0.77 mL, 5.52 mmol) in CH_2Cl_2 (12 mL), was added under Ar at 0 °C, mesyl chloride (0.38 mL, 5.18 mmol). The reaction mixture was stirred for 2 h at 0 °C and poured onto ice, 1 N aq. NaH_2PO_4 (10 mL) and Et_2O (20 mL). The organic layer was washed with brine (10 mL), dried ($MgSO_4$) and the solvents removed. The residue was purified as indicated, affording the corresponding mesylate **9**. To a stirred suspension of di-*tert*-butyl iminodicarboxylate **(10)** ($R^2 = R^3$ = Boc) (Fluka, 0.99 g, 4.56 mmol) and *t*-BuOK (0.48 g, 4.26 mmol) in DMF (10 mL) was added at r.t. under Ar a solution of mesylate **9** (1.06 g, 3.04 mmol) in DMF (3 mL). The reaction mixture was heated for 1 h at 70 °C, cooled to r.t. and poured onto ice and Et_2O/hexane (1:1, 50 mL). The organic layer was washed with brine (20 mL), dried ($MgSO_4$) and the solvents were removed. The residue was purified as indicated in the corresponding description.

Method E:

To a stirred solution of the acetylenic alcohol **8** (10.0 mmol) in THF (80 mL) were added under Ar at 0 °C phthalimide (2.21 g, 15.0 mmol), triphenylphosphine (2.89 g, 11.0 mmol) and (slowly) diethylazodicarboxylate (DEAD) (2.09 g, 12.0 mmol). After stirring at 0 °C for 1 h and overnight at r.t. the reaction mixture was poured onto ice and extracted with hexane/Et_2O (1:1, 120 mL). The organic layer was washed with water (100 mL), brine (100 mL), dried ($MgSO_4$), the solvents were evaporated and the residue purified as indicated in the corresponding description.

Method F:

To a stirred solution of 3,3-diethoxyprop-1-yne **(7)** (0.72 mL, 5.0 mmol) in THF (15 mL), BuLi solution (1.6 M in hexane, 3.13 mL, 5.28 mmol) was added under Ar at – 78 °C. The mixture was stirred for 30 min at – 78 °C, followed by addition of the corresponding *N*-tosylimine **13g,n** (3.33 mmol)[17,24] respectively and $ZnCl_2$ solution (1.0 M in Et_2O, 5.7 mL). The reaction mixture was stirred for further 30 min at – 78 °C, allowed to slowly warm to 0 °C, stirred at 0 °C for 5 h and poured onto sat. aq NH_4Cl (15 mL), ice and Et_2O (30 mL). The organic phase was washed with brine (15 mL), dried ($MgSO_4$), the solvents were evaporated and the residue was purified as indicated in the corresponding description.

Method G:

To a stirred solution of acetylenic ketone **6** or acetylenic acetal **14** (2.35 mmol) in CH_2Cl_2 (20 mL) was added a solution of 33% HBr–AcOH (0.56 mL) at 0 °C. The mixture was stirred for 15 min at 0 °C, warmed to r.t. and quenched with sat. $NaHCO_3$ (20 mL), ice and Et_2O (50 mL). The organic phase was washed with brine (20 mL), dried ($MgSO_4$) and the solvents were removed. The residue was chromatographed on silica gel, distilled under reduced pressure or recrystallized as indicated, affording pure **15** or **16** derivatives.

Method H:

To a stirred solution of acetylenic ketone **6** or acetylenic acetal **14** (10.0 mmol) in toluene (30 mL), 2–4 N aq HBr (10 mL) was added at r.t. The reaction mixture was stirred at r.t., warmed to 60 °C for 2–4 h, cooled to r.t., diluted with Et_2O (50 mL) and poured onto ice. The aqueous phase was extraced with Et_2O (50 mL), the combined organic fractions were washed with brine (50 mL) and the solvents removed. The residue was chromatographed on silica gel, distilled under reduced pressure or recrystallized as indicated.

N-Protected Prop-2-ynylamines 3:

N-Tosylprop-2-ynylamine **(3a)**:

To a stirred solution of tosyl chloride (Fluka, 20.0 g, 0.105 mol) in CH_2Cl_2 (100 mL) was added dropwise at 0 °C under Ar pyridine (10.5 mL). To this mixture was added prop-2-ynylamine **(1)** (Fluka, 6.4 mL, 0.099 mol) over 10 min. The mixture was stirred at 0 °C for 30 min, then 4-dimethylaminopyridine (DMAP) (0.5 g, 4.09 mmol) was added to the orange suspension. After the addition, the mixture was allowed to warm to r.t., stirred at r.t. overnight and quenched with 0.5 N aq HCl (80 mL), ice and Et_2O (100 mL). The organic layer was washed with brine (100 mL), dried ($MgSO_4$) and the solvents were removed. The residue was chromatographed on silica gel (Et_2O/hexane 1:2 to 2:1) affording **3a** as a white solid; yield: 18.8 g (90%), mp 73.5–74 °C.

IR (KBr): ν = 3433w, 3270s, 2110w, 1596m, 1437m, 1325s, 116 s, 814m cm^{-1}.

^1H NMR (DMSO-d_6): δ = 8.04 (t, J = 5.9 Hz, NH); 7.68 (d, J = 7.5 Hz, 2 arom. H); 7.38 (d, J = 7.5 Hz, 2 arom. H); 3.65–3.6 (dd, J = 5.9, 2.5 Hz, C≡C–CH_2); 3.05 (t, J = 5.9 Hz, C≡C–H); 2.38 (s, Ar–CH_3).

MS: m/z (%) = 209 (M^+), 155 (20), 145 (28), 139 (15), 130 (29), 118 (38), 116 (13), 91 (100), 89 (10), 77 (10), 65 (50), 63 (10), 54 (80), 39 (22).

Benzyl Prop-2-ynylcarbamate **(3c)**:

To a stirred solution of *N*-(benzyloxycarbonyloxy)succinimide (Fluka, 30.0 g, 0.12 mol) in CH_2Cl_2 (300 mL) was added under Ar at 0 °C prop-2-ynylamine (**1**, 8.44 mL, 0.13 mol). The reaction mixture was stirred for 30 min at 0 °C and overnight at r.t., quenched with 2 N aq HCl (100 mL), ice and CH_2Cl_2 (100 mL). The combined organic layers were dried ($MgSO_4$) and the solvents removed. The residue was chromatographed on silica gel (Et_2O/hexane 1:1) affording **3c** as a white solid; yield: 20.6 g (91%), mp 35–36 °C.

IR (KBr): ν = 3341s, 3233s, 2120w, 1668s, 1528m, 1458w, 1349w, 1281s, 1140w, 1052w, 976m, 893m cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.4–7.25 (m, 5 arom. H); 5.13 (s, 2 aliph. H); 4.95 (br. s, NH); 4.05–3.95 (m, C≡C–CH_2); 2.24 (t, J = 2.5 Hz, C≡C–H).

MS: m/z (%) = 189 (M^+), 108 (30), 91 (100), 79 (18), 77 (18), 65 (322), 39 (54).

Di-tert-butyl Prop-2-ynyliminodicarboxylate **(3d)**:

To a stirred suspension of freshly prepared potassium di-*tert*-butyliminodicarboxylate[25] (12.1 g, 46 mmol) in DMF (120 mL) was added under Ar at 0 °C a solution of prop-2-ynyl bromide (**2**, Fluka, 5.2 mL, 69 mmol) in DMF (20 mL). The reaction mixture was stirred for 30 min at 0 °C and for 3 h at r.t., the solvent removed and the residue poured onto ice, H_2O (100 mL) and Et_2O (120 mL). The organic layer was washed with brine (100 mL), dried ($MgSO_4$) and the solvents were evaporated. The residue was chromatographed on silica gel (Et_2O/hexane 1:7) to give **3d** as a white solid; yield: 9.64 g (82%), mp 29–30 °C.

IR (KBr): ν = 3265w, 2975w, 2936w, 2120, 1794w, 1750s, 1720s, 1457w, 1368s, 1342s, 1148s, 1119s, 853 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 4.35 (d, J = 2.4 Hz, C≡C–CH_2); 2.19 (t, J = 2.4 Hz, C≡C–H); 1.53 (s, 2 *t*-Bu).

MS: m/z (%) = 256 (5, M^+), 173 (10), 161 (100), 117 (50).

Acetylenic Ketones 6:

N-(4-Furan-2-yl-4-oxobut-2-ynyl)-4-methylbenzenesulfonamide **(6a)**:

A solution of **3a** (1.0 g, 4.78 mmol) in THF was treated according to Method A with furan-2-carbaldehyde (**4a**, 0.62 mL, 7.12 mmol). Compound **6a** was obtained as a white crystalline product after recrystallization from EtOAc/hexane 1:2; yield: 0.90 g (62%), mp 115.5–116 °C.

IR (KBr): ν = 3435w, 3304w, 2251w, 1636s, 1557s, 1326s, 115s, 817m cm^{-1}.

^1H NMR (DMSO-d_6): δ = 8.28 (t, J = 5.9 Hz, NH); 8.1–8.05 (m, 1 fur. H); 7.72 (d, J = 7.5 Hz, 2 arom. H); 7.31 (d, J = 7.5 Hz, 2 arom. H); 7.3–7.25 (m, 1 fur. H); 6.8–6.75 (m, 1 fur. H); 4.08 (d, J = 5.0 Hz, C≡C–CH_2); 2.25 (s, Ar–CH_3).

MS: m/z (%) = 303 (M^+), 210 (16), 155 (20), 145 (30), 106 (14), 95 (28), 65 (30), 39 (16).

N-(4-Furan-3-yl-4-oxobut-2-ynyl)-4-methylbenzenesulfonamide **(6b)**:

A solution of **3a** (2.5 g, 0.012 mol) in THF was treated according to Method A with furan-3-carbaldehyde (**4b**, 1.4 mL, 0.02 mol). Compound **6b** was obtained as a white crystalline product after recrystallization from EtOAc/hexane 1:2; yield: 1.89 g (53%), mp 114–115 °C.

IR (KBr): ν = 3438w, 3206m, 2223w, 1645m, 1614s, 1507s, 1338s, 1161s, 868w, 807w cm^{-1}.

^1H NMR (DMSO-d_6): δ = 8.3–8.25 (m, 1 fur. H); 8.23 (t, J = 5.8 Hz, NH); 7.9–7.8 (m, 1 fur. H); 7.72 (d, J = 7.5 Hz, 2 arom. H); 7.28 (d, J = 7.5 Hz, 2 arom. H); 6.75–6.7 (m, 1 fur. H); 4.06 (d, J = 5.8 Hz, C≡C–CH_2); 2.24 (s, Ar–CH_3).

MS: m/z (%) = 303 (10, M^+), 210 (12), 155 (16), 148 (30), 139 (10), 106 (20), 95 (35), 91 (100), 65 (25), 39 (20).

N-(4-Oxo-4-thiophen-2-ylbut-2-ynyl)-4-methylbenzenesulfonamide **(6c)**:

A solution of **3a** (1.0 g, 4.78 mmol) in THF was treated according to Method A with thiophene-2-carbaldehyde (**4c**, 0.66 mL, 7.18 mmol). Compound **6c** was obtained as a white crystalline product after recrystallization from EtOAc/hexane 1:2; 0.98 g (65%), mp 154–154.5 °C.

IR (KBr): ν = 3438w, 3180m, 2234w, 1618m, 1596s, 1513w, 1333s, 1160s, 837w cm^{-1}.

^1H NMR (DMSO-d_6) δ = 8.3 (t, J = 5.8 Hz, NH); 8.15–8.1 (m, 1 thioph. H); 7.76 (d, J = 7.5 Hz, 2 arom. H); 7.75–7.65 (m, 1 thioph. H); 7.3–7.25 (m, 2 arom. H/1thioph. H); 4.11 (d, J = 5.8 Hz, C≡C–CH_2); 2.21 (s, Ar–CH_3).

MS: m/z (%) = 319 (10, M^+), 226 (12), 164 (32), 155 (16), 136 (14), 111 (40), 92 (20), 91 (100), 90 (10), 80 (12), 65 (36), 53 (10), 39 (26).

N-[4-Oxo-4-thiophen-3-ylbut-2-ynyl]-4-methylbenzenesulfonamide **(6d)**:

A solution of **3a** (2.0 g, 9.85 mmol) in THF was treated according to Method A with thiophene-3-carbaldehyde (**4d**, 1.31 mL, 0.014 mol). Compound **6d** was obtained as a white crystalline product after recrystallization from EtOAc/hexane 1:2 yield: 1.85 g (61%), mp 104.5–105 °C.

IR (KBr): ν = 3435w, 3186m, 2232w, 1634m, 1612s, 1508s, 1332s, 1160s, 853w, 817w cm^{-1}.

^1H NMR (DMSO-d_6): δ = 8.3–8.2 (m, NH/1 thioph. H); 7.72 (d, J = 7.5 Hz, 2 arom. H); 7.7–7.65 (m, 1 thioph. H); 7.4–7.35 (m, 1 thioph. H); 7.27 (d, J = 7.5 Hz, 2 arom. H); 4.1 (d, J = 5.0 Hz, C≡C–CH_2); 2.22 (s, Ar–CH_3).

MS: m/z (%) = 319 (14, M^+), 226 (10), 164 (35), 155 (14), 136 (12), 11 (46), 106 (20), 91 (100), 90 (14), 80 (16), 65 (28), 53 (10), 39 (22).

N-[4-(1-Tosylpyrrol-2-yl)-4-oxobut-2-ynyl]-4-methylbenzenesulfonamide (**6e**):

A solution of **3a** (0.43 g, 2.03 mmol) in THF was treated according to Method A with **4e**[22] (0.76 g, 3.05 mmol). Compound **6e** was obtained as a pale brown crystalline product after FC on silica gel (Et_2O/hexane/$CHCl_3$ 3:1:1); yield: 0.36 g (39%), mp 148–149°C.

IR (KBr): ν = 3425w, 3326m, 2230w, 1636s, 1612s, 1595m, 1338s, 1163s, 814w cm^{-1}.

^1H NMR (DMSO-d_6): δ = 8.21 (t, J = 5.8 Hz, NH); 8.05–7.95 (m, 1 pyr. H); 7.83 (d, J = 7.5 Hz, 2 arom. H); 7.68 (d, J = 7.5 Hz, 2 arom. H); 7.45 (d, J = 7.5 Hz, 2 arom. H); 7.25 (d, J = 7.5 Hz, 2 arom. H); 7.15–7.1 (m, 1 pyr. H); 6.55–6.5 (m, 1 pyr. H); 4.01 (d, J = 5.8 Hz, C≡C–CH_2); 2.39 (s, Ar–CH_3); 2.2 (s, Ar–CH_3).

MS: m/z (%) = 456 (M^+), 301 (10), 237 (102), 155 (38), 139 (12), 92 (20), 91 (100), 90 (14), 65 (22).

Benzyl (5,5-Dimethyl-4-oxohex-2-ynyl)carbamate (**6f**):

A mixture of **3c** (3.0 g, 15.9 mmol) and *N*-methoxy-*N*-2,2-dimethylpropanamide[23] (**5f**, 3.0 g, 20.7 mmol) in THF was treated according to Method B to give, after FC on silica gel (Et_2O/hexane 3:2), **6f** as a pale yellow oil; yield: 3.2 g (73%).

IR (film): ν = 3327m, 3034w, 2965w, 2932w, 2218w, 1708s, 1670s, 1525m, 1457w, 1355w, 1248s, 1129m, 1044w, 749w cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.4–7.3 (m, 5 arom. H); 5.14 (s, Ar–CH_2); 5.05 (br s, NH), 4.19 (d, J = 5.7 Hz, C≡C–CH_2); 1.18 (s, *t*-Bu).

MS: m/z (%) = 273 (M^+), 124 (35), 91 (100), 81 (10), 57 (54), 41 (18).

N-[4-Oxo-4-phenylbut-2-ynyl]-4-methylbenzenesulfonamide (**6g**):

A mixture of **3a** (1.0 g, 4.78 mmol) and of *N*-methoxy-*N*-methylbenzamide (**5g**, 1.18 g, 7.17 mmol) in THF was treated according to Method B to give, after FC on silica gel (Et_2O/hexane 3:2), **6g** as a pale yellow solid; yield: 1.12 g (75%), mp 127–128°C.

IR (KBr): ν = 3129m, 3055w, 2955w, 2880w, 2238w, 2204w, 1622s, 1592m, 1574m, 1449m, 1339m, 1279s, 1113m, 1070w, 805w, 711m, 685 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.95–7.9 (m, 2 arom. H); 7.85–7.75 (m, 2 arom. H); 7.65–7.6 (m, 1 arom. H); 7.5–7.4 (m, 2 arom. H); 7.3–7.2 (m, 2 arom. H); 4.98 (t, J = 6.8 Hz, NH); 4.16 (d, J = 6.8 Hz, C≡C–CH_2); 2.25 (s, Ar–CH_3).

MS: m/z (%) = 313 (12, M^+), 220 (10), 158 (40), 105 (50), 91 (100), 77 (34), 65 (25), 51 (12).

A solution of **3a** (10.0 g, 47.8 mmol) in THF was treated according to Method A with freshly distilled benzaldehyde (**4g**, 7.25 mL, 71.7 mmol) to give, after FC on silica gel eluting with (Et_2O/hexane 1:1) and recrystallization from EtOAc/hexane, **6g** as a pale yellow crystalline product; yield: 11.23 g (75%), mp 127–128°C.

IR, MS, ^1H NMR data in close agreement to those described above.

tert-Butyl 4-Oxo-4-phenylbut-2-ynylcarbamate (**6h**):

Compound **3b** (1.0 g, 6.44 mmol) in THF was treated according to Method A with freshly distilled benzaldehyde (**4g**) to give, after FC on silica gel (Et_2O/hexane 1:2) and crystallization from EtOAc/hexane, **6h** as a white solid; yield: 1.09 g (65%), mp 78–79°C.

IR (KBr): ν = 3368m, 3060w, 2967w, 2226w, 1688s 1650s, 1520s, 1450w, 1367w, 1294m, 1285s, 170m, 1099w, 699s cm^{-1}.

^1H NMR ($CDCl_3$): δ = 8.2–8.05 (m, 2 arom. H); 7.65–7.55 (m, 1 arom. H); 7.55–7.4 (m, 2 arom. H); 4.92 (t, J = 6.5 Hz, NH); 4.24 (d, J = 6.5 Hz, C≡C–CH_2); 1.48 (s, *t*-Bu).

MS: m/z (%) = 259 (M^+), 203 (22), 186 (16), 147 (20), 130 (22), 115 (24), 105 (42), 77 (24), 57 (100), 41 (30).

tert-Butyl 4-Oxo-4-(3,4,5-trimethoxyphenyl)but-2-ynylcarbamate (**6i**):

A mixture of **3b** (5.0 g, 32.22 mmol) and of 3,4,5-trimethoxybenzaldehyde (**4i**, 7.59 g, 38.66 mmol) in THF was treated according to Method A to give, after FC on silica gel (EtOAc/hexane 1:2) and crystallization from Et_2O/hexane, **6i** as a pale yellow solid; yield: 5.1 g (45%), mp 106–107°C.

IR (KBr): ν = 3365m, 3000w, 2970w, 2939w, 2228w, 1714s, 1638s, 1586w, 1523m, 1500m, 1465m, 1367m, 1329s, 1267m, 1164m, 1131m, 995w, 740w cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.95–7.90 (m, 2 arom. H); 7.85–7.75 (m, 2 arom. H); 7.65–7.6 (m, 1 arom. H); 7.45–7.35 (m, 2 arom. H); 4.92 (br. s, NH); 4.22 (d, J = 5.9 Hz, C≡C–CH_2); 3.94–3.93 (2 s, 3 CH_3O); 1.47 (s, *t*-Bu).

MS: m/z (%) = 349 (20, M^+), 293 (100), 276 (30), 249 (20), 195 (18), 168 (30), 57 (70), 41 (22).

tert-Butyl 4-Oxododec-2-ynylcarbamate (**6j**):

A mixture of **3b** (2.4 g, 15.46 mmol) and nonanal (**4j**, 2.6 mL, 18.65 mmol) in THF was treated according to Method A to give, after FC on silica gel (Et_2O/hexane 1:4), **6j** as a colourless oil; yield: 0.96 g (65%).

IR (film): ν = 3344m, 2928w, 2856w, 2220w, 1720s, 1674s, 1521m, 1458w, 1277m, 1249m, 1166s, 1048w cm^{-1}.

^1H NMR ($CDCl_3$): δ = 4.76 (br. s, NH); 4.1 (d, J = 6.0 Hz, C≡C–CH_2); 2.54 (t, J = 7.3 Hz, CH_2CO); 1.75–1.55 (m, 2 aliph. H); 1.55–1.15 (m, 10 aliph. H); 1.46 (s, *t*-Bu); 0.95–0.8 (m, CH_3).

MS: m/z (%) = 295 (M^+), 141 (30), 57 (100), 41 (34).

tert-Butyl (E)-4-Oxo-6-phenylhex-5-en-2-ynylcarbamate (**6k**):

A mixture of **3b** (3.0 g, 19.23 mmol) and cinnamic aldehyde (**4k**, 3.41 mL, 27.1 mmol) in THF was treated according to Method B to give, after FC on silica gel (Et_2O/hexane 1:2) and crystallization from hexane, **6k** as a pale yellow solid; yield: 2.6 g (47%), mp 96.5–97°C.

IR (KBr): ν = 3360m, 3060w, 2978w, 2935w, 2223w, 1692s, 1634s, 1519s, 1448w, 1367w, 1286m, 1251s, 1149m, 982w, 781m cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.83 (d, J = 16.1 Hz, 1 vyn. H); 7.65–7.55 (m, 2 arom. H); 7.5–7.4 (m, 3 arom. H); 6.77 (d, J = 16.1 Hz, 1 vyn. H); 4.89 (br. s, NH); 4.19 (d, J = 5.8 Hz, C≡C–CH_2); 1.48 (s, *t*-Bu).

MS: m/z (%) = 285 (M^+), 229 (40), 212 (36), 168 (36), 141 (20), 131 (38), 57 (100), 41 (30).

Di-tert-butyl 4-Oxo-4-phenylbut-2-ynylimidodicarbonate (**6l**):

Compound **3d** (3.0 g, 19.23 mmol) in THF was treated according to Method A with freshly distilled benzaldehyde (**4g**) to give, after FC on silica gel (Et_2O/hexane 1:3) and crystallization from hexane, **6l** as a white solid; yield: 1.67 g (65%), mp 88–89°C.

IR (KBr): ν = 3064w, 2981m, 2935w, 2234w, 1794w, 1755s, 1700s, 1648s, 1598w, 1368s, 1340s, 1263s, 1228s, 1146s, 1121m, 852w cm^{-1}.

^1H NMR ($CDCl_3$): δ = 8.15–8.05 (m, 2 arom. H); 7.65–7.55 (m, 1 arom. H); 7.55–7.4 (m, 2 arom. H); 4.67 (s, C≡C–CH_2); 1.55 (s, 2 *t*-Bu).

MS: m/z (%) = 359 (M^+), 247 (12), 203 (20), 186 (10), 105 (14), 57 (100), 41 (14).

Acetylenic Alcohols 8f, 8j[14], 8o[14] and Mesylate 9j:

1,1-Diethoxy-5,5-dimethylhex-2-yn-4-ol (**8f**):

A mixture of 3,3-diethoxyprop-1-yne (**7**, 8.75 g, 68.3 mmol) and of pivaldehyde (**4f**, 8.3 mL, 75.1 mmol) in THF was treated according to Method C[14] to give, after bulb-to-bulb distillation under reduced pressure, **8f** as a colourless liquid; yield: 12.6 g (86%), bp 140°C, 0.2 mbar.

IR (film): ν = 3458w, 2975m, 2876w, 1475w, 1463w, 1365m, 1326w, 1140s, 1086m, 1052s, 1011s, 889w, 763 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 5.31 (d, J = 1.3 Hz, C≡C–CH($OEt)_2$); 4.09 (br. d, J = 4.3 Hz, CHOH); 3.8–3.55 (m, $2CH_2O$); 1.83 (br. d J = 4.3 Hz, OH); 1.24 (t, J = 7.1 Hz, $2CH_3$); 1.0 (s, *t*-Bu).

MS: m/z (%) = 213 ($M^+ - H$), 169 (20), 112 (100), 103 (14), 84 (40), 57 (94), 43 (36), 41 (26).

1,1-Diethoxy-4-mesyldodeca-7-yne (**9j**):

To a stirred mixture of **8j** (1.0 g, 3.70 mmol) and triethylamine (0.77 mL, 5.52 mmol) in CH_2Cl_2 (12 mL) was added under Ar at 0°C mesyl chloride (0.38 mL, 5.18 mmol). The reaction mixture was stirred for 2 h at 0°C and poured onto ice, 1 N aq NaH_2PO_4

(15 mL), Et_2O (20 mL). The organic layer was washed with brine (15 mL), dried ($MgSO_4$) and the solvents removed. The residue was purified by FC on silica gel (Et_2O/hexane 1:4) to give **9i** as a colourless oil; yield: 1.2 g (93%).

IR (Film): ν = 2929s, 2856m, 1462w, 1365s, 1330m, 1178s, 1151m, 1120m, 1089m, 1054s, 1015w, 906m, 826w cm^{-1}.

^1H NMR ($CDCl_3$): δ = 5.31 (d, J = 1.3 Hz, C≡C–CH($OEt)_2$); 5.25–5.15 (m, CH–OMs); 3.8–3.5 (m, $2CH_2O$); 3.12 (s, CH_3–SO_2); 2.0–1.8 (m, 2 aliph. H); 1.6–1.4 (m, 2 aliph. H); 1.4–1.15 (m, 10 aliph. H); 1.23 (t, J = 7.1 Hz, $2CH_3$); 0.95–0.8 (m, CH_3).

MS: m/z (%) = 347 ($M^+ - H$), 303 (22), 207 (30), 179 (40), 161 (20), 151 (26), 109 (38), 95 (46), 81 (100), 67 (40), 55 (62), 43 (72).

Phthalimides 11:

N-(1,1-Diethoxy-5,5-dimethylhex-2-yn-4-yl)isoindolin-1,3-dione **(11f)**:

A mixture of **8f** (4.0 g, 18.66 mmol) in THF was treated according to Method E to give, after FC on silica gel (EtOAc/hexane 1:7) and crystallization from hexane, **11f** as a white solid; yield: 4.5 g (70%), mp 71–72°C.

IR (KBr): ν = 2970m, 2930w, 2875w, 1768w, 1712s, 1607w, 1471w, 1382s, 1351m, 1326m, 1148m, 1089s, 1055s, 889w, 724 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.9–7.8 (m, 2 arom. H); 7.8–7.7 (m, 2 arom. H); 5.33 (d, J = 1.6 Hz, C≡C–CH($OEt)_2$); 4.93 (d, J = 1.6 Hz, CH–Npht); 3.9–3.7 (m, CH_2O); 3.7–3.5 (m, CH_2O); 1.24 (t, J = 7.1 Hz, $2CH_3$); 1.1(s, *t*-Bu).

MS: m/z (%) = 343 (M^+), 298 (18), 241 (100), 184 (20), 103 (46), 75 (20), 57 (24).

N-(1,1-Diethoxynon-2-yn-4-yl)isoindolin-1,3-dione **(11o)**:

A mixture of **8o** (4.0 g, 17.5 mmol) in THF was treated according to Method E to give, after FC on silica gel (Et_2O/hexane 1:4), **11o** as a colourless oil; yield: 5.73 g (92%).

IR (film): ν = 2970m, 2930m, 2873w, 1776w, 1718s, 1608w, 1467w, 1385s, 1348m, 1335m, 1150m, 1084s, 1052s, 1012 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.9–7.8 (m, 2 arom. H); 7.8–7.7 (m, 2 arom. H); 5.29 (d, J = 1.6 Hz, C≡C–CH($OEt)_2$); 5.15–5.05 (m, CH–Npht); 3.85–3.65 (m, CH_2O); 3.65–3.5 (m, CH_2O); 2.2–2.0 (m, 2 aliph. H); 1.5–1.15 (m, 6 aliph. H); 1.23–1.22 (2 t, J = 7.1 Hz, $2CH_3$); 0.95–0.8 (m, 3 aliph. H).

MS: m/z (%) = 356 ($M^+ - H$), 312 (100), 212 (18), 184 (24), 160 (32), 148 (22), 130 (40), 119 (30), 103 (38), 29 (40).

Acetylenic Amines 12f,o:

1-tert-Butyl-4,4-diethoxybut-2-ynylamine **(12f)**:

A mixture (3.61 g, 10.51 mmol) of **11f** in dioxane (10 mL) and 1 N ethanolic hydrazine solution (20 mL) was heated at 80°C for 24 h, then cooled to r.t. and mixed with a 2 N aq NaOH solution (10 mL) and Et_2O (20 mL). The organic layer was washed with brine (15 mL), dried ($MgSO_4$), and the solvents were removed. The residue was distilled under reduced pressure (bulb-to-bulb) to give **12f** as a colourless liquid; yield: 2.2 g (98%), bp 135°C/0.1 mbar.

IR (film): ν = 3384w, 3315w, 2975s, 2884m, 2242w, 1654w, 1479w, 1392w, 1139m, 1085m, 1052s, 1009m, 889w cm^{-1}.

^1H NMR ($CDCl_3$): δ = 5.29 (d, J = 1.4 Hz, C≡C–CH($OEt)_2$; 3.85–3.65 (m, CH_2O); 3.65–3.5 (m, CH_2O); 3.35–3.3 (m, CH–N); 1.24 (t, J = 7.1 Hz, $2CH_3$); 1.0 (s, *t*-Bu).

MS: m/z (%) = 213 (M^+), 156 (80), 128 (60), 103 (42), 100 (100), 84 (38), 82 (60), 75 (40), 57 (55), 54 (38), 47 (50).

4,4-Diethoxy-1-pentylbut-2-ynylamine **(12o)**:

A mixture of **11o** (5.47 g, 15.3 mmol) in dioxane (15 mL) and 1 N ethanolic hydrazine solution (30 mL) was heated at 80°C for 24 h, then cooled to r.t. and mixed with 2 N aq NaOH (15 mL) and Et_2O (20 mL). The organic layer was washed with brine (15 mL), dried ($MgSO_4$) and the solvents were removed. The residue was distilled under reduced pressure (bulb-to-bulb) to give **12o** as a colourless liquid; yield: 3.34 g (98%). bp 180°C/0.1 mbar.

IR (film): ν = 3371w, 3305w, 2975s, 2235w, 1461w, 1354w, 1327w, 1145m, 1118m, 1054s, 1009m, 891w cm^{-1}.

^1H NMR ($CDCl_3$): δ = 5.29 (d, J = 1.4 Hz, C≡C–CH($OEt)_2$); 3.8–3.5 (m, 5 aliph. H); 1.65–1.55 (m, 2 aliph. H); 1.55–1.25 (m, 6 aliph. H); 1.24 (t, J = 7.1 Hz, $2CH_3$); 0.95–0.8 (m, 3 aliph. H).

MS: m/z (%) = 226 ($M^+ - H$), 182 (10), 156 (100), 128 (60), 110 (22), 100 (85), 82 (50), 75 (40), 54 (34), 47 (22), 29 (42).

***N*-Tosylimines 13:**

N,N-Benzylidene-4-methylbenzenesulfonamide **(13g)**:

To a stirred mixture of 4-toluenesulfonamide (Fluka, 10.0 g, 58.4 mmol) and of freshly distilled benzaldehyde (**4g**, 6.2 g, 58.4 mmol) in toluene (150 mL) was added under Ar at r.t. $BF_3 \cdot Et_2O$ (0.58 mL). The reaction flask was equipped with a Dean–Stark apparatus and the mixture was refluxed for 12 h, then cooled to r.t. and poured onto ice, 2 N aq NaOH (50 mL) and toluene (50 mL). The organic phase was washed with brine (100 mL), dried ($MgSO_4$) and the solvents were removed. The residue was crystallized from EtOAc/hexane to give **13g** as a white solid; yield: 11.45 g (76%), mp 91–93°C.

IR, MS, ^1H NMR spectroscopic data identical to the literature.[24]

(E)-Styryl-4-methylbenzenesulfonamide **(13n)**:

To a stirred mixture of 4-toluenesulfonamide (Fluka, 17.0 g, 0.10 mol) and of freshly distilled cinnamic aldehyde (**4k**, 12.6 mL, 0.10 mol) in toluene (300 mL) was added under Ar, $BF_3 \cdot Et_2O$ (0.2 mL). The reaction flask was equipped with a Dean–Stark apparatus and the mixture was refluxed for 4 h, cooled to r.t. and poured onto ice, 2 N aq NaOH (150 mL) and toluene (200 mL). The organic phase was washed with brine (200 mL), dried ($MgSO_4$) and the solvents were removed. The residue was crystallized from EtOAc/hexane to give **13n** as a pale yellow solid; yield: 23.8 g (82%), mp 117–118°C.

IR (KBr): ν = 3048w, 2924w, 1622s, 1579s, 1448w, 1314s, 1288w, 1154s, 1089m, 926w, 854w, 773s, 739m, 682s, 583m, 553m cm^{-1}.

^1H NMR ($CDCl_3$): δ = 8.78 (d, J = 9.4 Hz, CH=N–Ts); 7.86 (d, J = 8.4 Hz, 2 arom. H); 7.6–7.4 (m, 5 arom. H/1 allyl H); 7.34 (d, J = 8.4 Hz, 2 arom H); 7.05–6.9 (dd, J = 9.4, 15.8 Hz, 1allyl H); 2.44 (s, Ar–CH_3).

MS: m/z (%) = 285 (M^+), 155 (10), 130 (100), 91 (70), 77 (15), 65 (18).

Acetylenic Acetals 14f,g,j,m,n,o,p:

Benzyl N-(1-tert-Butyl-4,4-diethoxybut-2-ynyl)carbamate **(14f)**:

To a stirred solution of (1.0 g, 4.69 mmol) of **12f** in CH_2Cl_2 (15 mL) was added under Ar at 0°C a solution of (Fluka, 1.40 g, 5.63 mmol) *N*-(benzyloxycarbonyloxy)succinimide in CH_2Cl_2 (3 mL). The reaction mixture was stirred for 30 min. at 0°C, then for 1.5 h at r.t. and poured onto ice, sat. aq $NaHCO_3$ (15 mL) and Et_2O (20 mL). The organic layer was washed with brine (20 mL), dried ($MgSO_4$) and the solvents were removed. The residue was purified by FC on silica gel (Et_2O/hexane 1:2) to give **14f** as a colourless oil; yield: 1.45 g (89%).

IR (film): ν = 3324w, 2972m, 2884w, 2251w, 1720s, 1705s, 1528m, 1455w, 1396w, 1325w, 1236s, 1127s, 1052s, 698w cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.4–7.3 (m, 5 arom H); 5.28 (d, J = 1.4 Hz, C≡C–CH($OEt)_2$); 5.11 (s, $PhCH_2O$); 4.94 (br. d, J = 9.0 Hz, NH); 4.39 (d, J = 9.0 Hz, CH–NH); 3.8–3.65 (m, CH_2O); 3.65–3.5 (m, CH_2O); 1.22 (t, J = 7.1 Hz, $2CH_3$); 0.98 (s, *t*-Bu).

MS: m/z (%) = 347 (M^+), 246 (10), 245 (10), 103 (20), 91 (100), 57 (20).

N-(4,4-Diethoxy-1-phenylbut-2-ynyl)-4-toluenesulfonamide **(14g)**:

A mixture of **7** (0.83 mL, 5.79 mmol) and **13g** (1.0 g, 3.86 mmol) in THF was treated according to Method F to give, after flash chromatography on silica gel (Et_2O/hexane 1:2) and crystallization from Et_2O/hexane, **14g** as a white solid; yield: 1.1 g (74%), mp 66.5–67.5°C.

IR (KBr): ν = 3260m, 3032w, 2978w, 1597w, 1495w, 1427w, 1320m, 1157s, 1091m, 1053s, 814w, 673s cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.8–7.7 (m, 2 arom. H); 7.5–7.4 (m. 2 arom. H); 7.4–7.25 (m. 5 arom. H); 5.41 (d, J = 8.7 Hz, CH–NH); 5.05 (d, J = 1.3 Hz, C≡C–CH(OEt)$_2$); 4.91 (br. d, J = 8.7 Hz, NH); 3.65–3.4 (m, 2CH_2O); 2.43 (s, Ar–CH_3); 1.18 (t, J = 6.2 Hz, 2CH_3).

MS: m/z (%) = 386 (M^+ – H), 341 (10), 187 (80), 158 (82), 144 (30), 130 (36), 115 (80), 103 (40), 91 (100), 77 (24), 65 (24).

Di-tert-butyl N-(4,4-Diethoxy-1-octylbut-2-ynyl)imidodicarbonate **(14j)**:

A solution of mesylate **9j** (1.06 g, 3.04 mmol) in DMF (3 mL) was treated according to Method D to give, after FC on silica gel (Et_2O/hexane 1:15) dodec-4-en-2-ynal diethyl acetal (as a 3:2 mixture of E/Z isomers by ^{1}H NMR); yield: 0.20 g (26%), and **14j** as a colourless oil; yield: 0.86 g (60%).

IR (film): ν = 2975m, 2929s, 2857w, 1789w, 1749s, 1708s, 1457w, 1365s, 1345m, 1307w, 1151s, 1124s, 1058m, 1012w cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 5.28 (d, J = 1.4 Hz, C≡C–CH(OEt)$_2$); 5.15–5.05 (m, CH–NH); 3.8–3.65 (m, CH_2O); 3.65–3.5 (m, CH_2O); 2.0–1.8 (m, 2 aliph. H); 1.51 (s, 2 t-Bu); 1.4–1.15 (m, 12 aliph. H); 1.22 (t, J = 7.8 Hz, 2CH_3); 0.95–0.8 (m, CH_3).

MS: m/z (%) = 469 (M^+), 268 (10), 103 (10), 57 (100), 41 (20).

N-(1-tert-Butyl-4,4-diethoxybut-2-ynyl)-4-toluenesulfonamide **(14m)**:

To a stirred solution of **12f** (0.10 g, 0.48 mmol) in CH_2Cl_2 (4 mL) were added under Ar at 0 °C a catalytic amount of DMAP, pyridine (Fluka, 0.50 mL, 0.63 mmol) and tosyl chloride (Fluka, 0.11 g, 0.58 mmol). The reaction mixture was stirred at r.t. and poured onto ice, 0.5 N aq HCl (2 mL). The organic layer was washed with brine (5 mL), dried ($MgSO_4$) and the solvents were removed. The residue was purified by FC on silica gel eluting with (Et_2O/hexane 1:1) to give **14m** as a white solid; yield: 0.10 g (58%).

IR (KBr): ν = 3275m, 2975m, 2886w, 2221w, 1598w, 1478w, 1324s, 1164s, 1142s, 1053s, 816m, 675m cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.8–7.7 (m, 2 arom. H); 7.5–7.4 (m. 2 arom. H); 4.87 (d, J = 1.4 Hz, C≡C–CH(OEt)$_2$); 4.47 (br. d, J = 9.0 Hz, NH); 3.85–3.8 (dd, J = 9.0, 1.4 Hz, CH–NH); 3.55–3.45 (m, 2CH_2O); 2.47 (s, Ar–CH_3); 1.18–1.13 (t, J = 7.1 Hz, 2CH_3); 0.99 (s, t-Bu).

MS: m/z (%) = 368 (M^+), 322 (10), 310 (16), 266 (10), 265 (42), 172 (14), 171 (10), 155 (40), 139 (46), 111 (10), 110 (100), 103 (64), 91 (66), 82 (44), 75 (16), 65 (12), 57 (44), 54 (14), 41 (18), 29 (22).

(E)-N-(4,4-Diethoxy-1-styrylbut-2-ynyl)-4-toluenesulfonamide **(14n)**:

A mixture of **7** (3.0 mL, 21.0 mmol) and N-tosylimine (**13n**, 5.0 g, 17.52 mmol) in THF was treated according to Method F to give, after FC on silica gel (Et_2O/hexane 1:1) and crystallization from Et_2O/hexane, **14n** as a white solid; yield: 6.95 g (96%), yield: mp 68–70 °C.

IR (KBr): ν = 3261s, 3029w, 2977w, 2889w, 1598w, 1440m, 1338s, 1158s, 1092m, 1051s, 912w, 753w, 675 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.85–7.75 (m, 2 arom. H); 7.35–7.2 (m. 8 arom. H); 6.71 (d, J = 15.7 Hz, 1 allyl H); 6.1–6.0 (m, 1 allyl H); 5.07 (d, J = 1.2 Hz, C≡C–CH(OEt)$_2$); 5.05–4.95 (m, CH–NH); 4.73 (br. d, J = 8.7 Hz, NH); 3.65–3.4 (m, 2CH_2O); 2.41 (s, Ar–CH_3); 1.2 (t, J = 7.2 Hz, 2CH_3).

MS: m/z (%) = 413 (M^+), 368 (20), 367 (20), 258 (38), 212 (40), 184 (80), 156 (40), 103 (54), 91 (100), 77 (18), 75 (24), 65 (18), 47 (24).

tert-Butyl N-(4,4-Diethoxy-1-pentylbut-2-ynyl)imidocarbonate **(14o)**:

To a stirred solution of **12o** (1.0 g, 4.40 mmol) in CH_2Cl_2 (15 mL) was added under Ar at 0 °C a solution (Fluka, 1.35 g, 6.19 mmol) of di-*tert*-butyl dicarbonate in CH_2Cl_2 (5 mL). The reaction mixture was stirred for 30 min at 0 °C, then overnight at r.t. and poured onto ice, sat. aq $NaHCO_3$ (10 mL) and Et_2O (20 mL). The organic layer was washed with brine (15 mL), dried ($MgSO_4$) and the solvents were removed. The residue was purified by FC on silica gel (Et_2O/hexane 1:4) to give **14o** as a colourless oil; yield: 1.37 g (95%).

IR (film): ν = 3341w, 2965m, 2931m, 2873m, 2251w, 1715s, 1519m, 1455w, 376m, 1329w, 1246w, 1161s, 1052s, 1015w cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 5.27 (d, J = 1.3 Hz, C≡C–CH(OEt)$_2$); 4.75–4.6 (m, CH–NH); 4.55–4.4 (m, NH); 3.8–3.65 (m, CH_2O); 3.65–3.5 (m, CH_2O); 1.7–1.55 (m, 2 aliph. H); 1.5–1.15 (m, 6 aliph. H); 1.44 (s, t-Bu); 1.22 (t, J = 7.8, 2CH_3); 0.95–0.8 (m, CH_3).

MS: m/z (%) = 327 (M^+), 226 (20), 200 (20), 156 (20), 57 (100), 41 (22).

Benzyl N-(4,4-Diethoxy-1-pentylbut-2-ynyl)carbamate **(14p)**:

To a stirred solution of **12o** (1.0 g, 4.40 mmol) in CH_2Cl_2 (15 mL) was added under Ar at 0 °C a solution of N-(benzyloxycarbonyloxy)succinimide (Fluka, 1.32 g, 5.28 mmol) in CH_2Cl_2 (3 mL). The reaction mixture was stirred for 30 min at 0 °C, then for 2 h at r.t. and poured onto ice, sat. aq $NaHCO_3$ (10 mL) and Et_2O (20 mL). The organic layer was washed with brine (15 mL), dried ($MgSO_4$) and the solvents were removed. The residue was purified by FC on silica gel (Et_2O/hexane 1:4) to give **14p** as a colourless oil; yield: 1.48 g (93%).

IR (film): ν = 3341w, 2965m, 2931m, 2873m, 2251w, 1715s, 1519m, 1455w, 1376m, 1329w, 1246w, 1161s, 1052s, 1015w cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 5.27 (d J = 1.3 Hz, C≡C–CH(OEt)$_2$); 4.75–4.6 (m, CH–NH); 4.55–4.40 (m, NH); 3.8–3.65 (m, CH_2O); 3.65–3.5 (m, CH_2O); 1.7–1.55 (m, 2 aliph. H); 1.5–1.15 (m, 6 aliph. H); 1.44 (s, t-Bu); 1.22 (t, J = 7.8 Hz, 2CH_3); 0.95–0.8 (m, CH_3).

MS: m/z (%) = 361 (M^+), 226 (6), 166 (6), 91 (100).

N-Protected 2-Substituted 4-Bromopyrroles 15:

4-Bromo-2-furan-2-yl-1-tosylpyrrole **(15a)**:

A solution of **6a** (0.6 g, 1.97 mmol) in CH_2Cl_2 was treated according to Method G to give, after FC on silica gel (EtOAc/hexane 1:1), **15a** as a white solid; yield: 0.69 g (97%), mp 59–95.5 °C.

IR (KBr): ν = 3436w, 3141w, 1590w, 1510w, 1383s, 1173s, 812m cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 7.8–7.75 (m, 1 pyr. H); 7.75–7.7 (m, 1 pyr. H); 7.66 (d, J = 7.5 Hz, 2 arom. H); 7.42 ((d, J = 7.5 Hz, 2 arom. H); 6.7–6.65 (m, 1 fur. H); 6.65–6.6 (m, 1 fur. H); 6.6–6.55 (m, 1 fur. H); 2.38 (s, Ar–CH_3).

MS: m/z (%) = 366 (12, M^+), 213 (10), 212 (98), 210 (100), 184 (16), 182 (18), 131 (14), 103 (28), 91 (42), 76 (32), 65 (28), 50 (14), 39 (20).

4-Bromo-2-furan-3-yl-1-tosylpyrrole **(15b)**:

A solution of **6b** (0.71 g, 2.35 mmol) in CH_2Cl_2 was treated according to Method G to yield, after FC on silica gel (EtOAc/hexane 1:1), **15b** as a white solid; yield: 0.81 g (94%), mp 112–113 °C.

IR (KBr): ν = 3437w, 3160w, 1592w, 1530w, 1369 s, 1177 s, 810 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 7.75–7.7 (m, 2 pyr. H); 7.7–7.65 (m, 1 fur. H); 7.5 (d, J = 7.5 Hz, 2 arom. H); 7.38 (d, J = 7.5 Hz, 2 arom. H); 6.6–6.55 (m, 1 fur. H); 6.55–6.5 (m, 1 fur. H); 2.35 (s, Ar–CH_3).

MS: m/z (%) = 366 (18, M^+), 213 (10), 212 (96), 210 (100), 184 (22), 182 (20), 155 (10), 103 (30), 91 (64), 76 (30), 65 (34), 63 (10), 50 (18), 39 (20), 38 (16).

4-Bromo-1-tosyl-2-thiophen-2-ylpyrrole **(15c)**:

A solution of **6c** (0.94 g, 2.94 mmol) in CH_2Cl_2 was treated according to Method G to give, after FC on silica gel (EtOAc/hexane 1:1), **15c** as a white crystalline product; yield: 1.05 g (94%), mp 96–96.5 °C.

IR (KBr): ν = 3439w, 3158w, 1596w, 1485w, 1373s, 1172s, 813m, 706m cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 7.8–7.75 (m, 1 pyr. H); 7.65–7.6 (dd, J = 5.0, 1.5 Hz, 1 thioph. H); 7.41 (d, J = 7.5 Hz, 2 arom. H); 7.34 (d, J = 7.5 Hz, 2 arom. H); 7.15–7.05 (m, 2 thioph. H); 6.55–6.5 (m, 1 pyr. H); 2.35 (s, Ar–CH_3).

MS: m/z (%) = 382 (10, M^+), 229 (10), 228 (100), 226 (98), 147 (28), 120 (18), 91 (28), 65 (20), 39 (14).

4-Bromo-1-tosyl-2-thiophen-3-ylpyrrole **(15d)**:

A solution of **6d** (0.79 g, 2.47 mmol) in CH_2Cl_2 was treated according to Method G to give, after FC on silica gel (EtOAc/hexane 1:1), **15d** as a white solid; yield: 0.84 g (89%), mp 81–81.5°C.

IR (KBr): ν = 3434w, 3147w, 1590w, 1366s, 1174s, 795m cm^{-1}.

^1H NMR (DMSO-d_6): δ = 7.7–7.65 (m, 1 pyr. H); 7.6–7.5 (dd, J = 8.0, 3.0 Hz, 1 thioph. H); 7.45–7.4 (m, 1 thioph. H); 7.35–7.3 (m, 4 arom. H); 7.05–6.95 (dd, J = 5.0, 1.5 Hz, 1 thioph. H); 6.45–6.4 (m, 1 pyr. H); 2.35 (s, Ar–CH_3).

MS: m/z (%) = 382 (14, M^+), 228 (100), 220 (98), 147 (46), 120 (18), 91 (36), 65 (22), 39 (12).

4-Bromo-1,1'-bistosyl-2,2'-bipyrrole **(15e)**:

A solution of **6d** (0.57 g, 1.24 mmol) in CH_2Cl_2 was treated according to Method G to give, after FC on silica gel (Et_2O/hexane 1:1), **15e** as a white solid, yield: 0.58 g (91%), mp 186–187°C.

IR (KBr): ν = 3435w, 1596w, 1498w, 1373s, 1150s, 813m, 704m cm^{-1}.

^1H NMR (DMSO-d_6): δ = 7.8–7.75 (m, 1 pyr. H); 7.55–7.45 (m, 1 pyr. H/4 arom. H); 7.45–7.35 (m, 4 arom. H); 6.4–6.35 (m, 1 pyr. H); 6.1–6.05 (m, 2 py. H); 2.56 (s, 3 aliph. H); 2.37 (s, Ar–CH_3).

MS: m/z (%) = 519 (10, M^+), 365 (34), 363 (32), 155 (84), 91 (100), 65 (16).

Benzyl 4-Bromo-2-tert-butylpyrrole-1-carboxylate **(15f)**:

A solution of **6f** (1.5 g, 5.49 mmol) in CH_2Cl_2 was treated according to Method G to give, after FC on silica gel (Et_2O/hexane 1:10), **15f** as a white solid; 1.69 g (92%), mp 44–45°C.

IR (KBr): ν = 3170w, 3034w, 2965w, 2872w, 1759s, 1498w, 1460w, 1380m, 1360m, 1298s, 1248m, 1215m, 1189m, 1051s, 1029w, 912w, 700 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.45–7.35 (s, 5 arom. H); 7.29 (d, J = 2.0 Hz, 1 pyr. H); 6.08 (d, J = 2.0 Hz, 1 pyr. H); 5.32 (s, OCH_2–Ph); 1.39 (s, t-Bu).

MS: m/z (%) = 336 (M^+), 91 (100).

A solution of **6f** (0.84 g, 3.06 mmol) in toluene was treated according to Method H to give, after purification as described above **15f**; yield: 0.99 g (96%). Analytical data were in close agreement to those described above.

4-Bromo-2-phenyl-1-tosylpyrrole **(15g)**:

A solution of **6g** (2.34 g, 7.47 mmol) in CH_2Cl_2 was treated according to Method G to give, after FC on silica gel (Et_2O/hexane 1:5) and crystallization from Et_2O/hexane, **15g** as a white solid; yield: 2.30 g (82%), mp 91–92°C.

IR (KBr): ν = 3126w, 3052w, 2920w, 1596w, 1559w, 1467w, 1440w, 1370s, 1237m, 1176s, 1125s, 1090m, 1059m, 907m, 762m, 696m, 662m, 588 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.46 (d, J = 1.9 Hz, 1 pyr. H); 7.45–7.1 (m, 9 arom. H); 6.15 (d, J = 2.0 Hz, 1 pyr. H); 2.37 (s, Ar–CH_3).

MS: m/z (%) = 376 (20, M^+), 222 (100), 141 (56), 114 (14), 91 (38), 65 (14).

tert-Butyl 4-Bromo-2-phenylpyrrole-1-carboxylate **(15h)**:

A solution of **6h** (0.20 g, 0.77 mmol) in CH_2Cl_2 was treated according to Method G to give, after FC on silica gel (Et_2O/hexane 1:6) and crystallization from hexane, **15h** as a white crystalline product; yield: 0.22 g (89%) mp 68–69.5°C.

IR (KBr): ν = 3156 w, 3068 w, 2983 w, 1750 s, 1476 w, 1446 m, 1372 m, 1300 s, 1147 s, 1078 m, 1059 m, 984 w, 817 m, 645 w cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.4–7.35 (m, 6 arom. H); 6.18 (d, J = 2.0 Hz, 1 pyr. H); 1.35 (s, t-Bu).

MS: m/z (%) = 322 (M^+), 223 (30), 141 (24), 114 (12), 57 (100), 41 (38).

A solution of **6l** (0.30 g, 0.84 mmol) in CH_2Cl_2 was treated according to Method G to give, after purification as described above, **15h**; yield: 0.99 g (96%). Analytical data were in close agreement to those described above.

tert-Butyl 4-bromo-2-(3,4,5-trimethoxyphenyl)pyrrole-1-carboxylate **(15i)**:

A solution of **6i** (1.20 g, 3.43 mmol) in CH_2Cl_2 was treated according to Method G to give, after FC on silica gel (EtOAc/hexane 1:4) and crystallization from hexane, **15i** as a white crystalline product; yield: 1.22 g (87%), mp 98–99°C.

IR (KBr): ν = 3170w, 3101w, 2934w, 1748s, 1586m, 1483w, 1418 w, 1374m, 1310s, 1248m, 1133s, 1010w, 830w, 757w cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.33 (d, J = 2.0 Hz, 1 pyr. H); 6.54 (s, 2 arom. H); 6.2 (d, J = 2.0 Hz, 1 pyr. H); 3.67–3.65 (2 s, $3CH_3O$); 1.35 (s, t-Bu).

MS: m/z (%) = 412 (M^+), 357 (10), 298 (16), 57 (100), 41 (16).

tert-Butyl 4-Bromo-2-octylpyrrole-1-carboxylate **(15j)**:

A solution of **6j** (0.62 g, 2.10 mmol) in CH_2Cl_2 was treated according to Method G to give, after FC on silica gel (Et_2O/hexane 1:20), **15j** as a colourless oil; yield: 0.495 (66%).

IR (film): ν = 2927s, 2854w, 1751s, 1568w, 1395w, 1310s, 1236w, 1159m, 1116w, 1073w, 851w cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.17 (d, J = 2.0 Hz, 1 pyr. H); 5.95 (d, J = 2.0 Hz, 1 pyr. H); 2.85–2.75 (m, 2 aliph. H); 1.65–1.5 (m, 2 aliph. H); 1.58 (s, t-Bu); 1.4–1.15 (m, 10 aliph. H); 0.95–0.8 (m, CH_3).

MS: m/z (%) = 359 (M^+), 158 (10), 57 (100), 41 (22).

tert-Butyl (E)-4-Bromo-2-styrylpyrrole-1-carboxylate **(15k)**:

A solution of **6k** (0.50 g, 1.75 mmol) in CH_2Cl_2 was treated according to Method G to give, after FC on silica gel (Et_2O/hexane 1:10), **15k** 0.58 g (95%) as an amorphous solid.

IR (KBr): ν = 3168 w, 2979 w, 1753 s, 1474 w, 1391 m, 1305 s, 1238 m, 1154 s, 1110 s, 1075 m, 961 m, 916 m, 740 m, 691 m cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.69 (d, J = 16.3 Hz, 1 vyn. H); 7.5–7.15 (m, 5 arom. H/1 pyr. H); 6.87 (d, J = 16.3 Hz, 1 vyn. H); 6.54 (d, J = 1.3 Hz, 1 pyr. H); 1.61 (s, t-Bu).

MS: m/z (%) = 349 (M^+), 158 (10), 167 (15), 57 (100), 41 (20).

N-Protected 2-Substituted 3-Bromopyrroles 16:

3-Bromo-2-phenyl-1-tosylpyrrole **(16g)**:

A solution of **14g** (0.40 g, 1.04 mmol) in CH_2Cl_2 was treated according to Method G to give, after FC on silica gel (EtOAc/hexane 1:5) and crystallization from hexane/Et_2O, **16g** as a pale yellow solid; yield: 0.38 g (96%), mp 90–91°C.

IR (KBr): ν = 3159w, 3127w, 1599w, 1499w, 1380m, 1367s, 1188s, 1174s, 1120s, 1056w, 817w, 769s, 744m, 694m, 668m, 578s cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.44 (d, J = 3.4 Hz, 1 pyr. H); 7.4–7.3 (m, 3 arom. H); 7.25–7.05 (m, 6 arom. H); 6.38 (d, J = 3.4 Hz, 1 pyr. H); 2.38 (s, Ar–CH_3).

MS: m/z (%) = 376 (30, M^+), 222 (80), 155 (20), 141 (100), 117 (20), 91 (90), 65 (32).

tert-Butyl 3-Bromo-2-octylpyrrole-1-carboxylate **(16j)**:

A solution of **14j** (0.50 g, 1.22 mmol) in CH_2Cl_2 was treated according to Method G to give, after FC on silica gel (hexane/Et_2O 25:1), **16j** as a colourless oil; yield: 0.28 g (64%).

IR (film): ν = 2928w, 2854w, 1748s, 1497w, 1459w, 1399m, 1315s, 1170m, 1128s, 918w, 851w cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.17 (d, J = 3.5 Hz, 1 pyr. H); 6.13 (d, J = 3.5 Hz, 1 pyr. H); 2.95–2.85 (m, 2 aliph. H); 1.59 (s, t-Bu); 1.6–1.45 (m, 2 aliph. H); 1.4–1.2 (m, 10 aliph. H); 0.95–0.8 (m, CH_3).

MS: m/z (%) = 358 (M^+), 303 (10), 178 (14), 160 (16), 57 (100), 41 (14).

(E)-3-Bromo-1-tosyl-2-styrylpyrrole **(16n)**:

A solution of **14n** (3.0 g, 7.25 mmol) in toluene was treated according to Method H to give, after FC on silica gel (Et_2O/hexane 1:15) and recrystallization from Et_2O/hexane, **16n** as a pale yellow solid; yield: 2.6 g (89%), mp 85–86.5°C.

IR (KBr): ν = 3143w, 3083w, 3028w, 2924w, 1595w, 1468w, 1386s, 1155m, 1174s, 1118m, 1029w, 967w, 719m, 669s, 536m cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.7–7.6 (m, 2 arom. H); 7.55–7.45 (m, 2 arom. H); 7.4–7.2 (m, 5 arom. H/1 pyr. H/1 vyn. H); 7.18 (d, J = 16.1 Hz, 1 vyn. H); 6.35 (d, J = 3.3 Hz, 1 pyr. H); 2.37 (s, Ar–CH_3).

MS: m/z (%) = 403 (20, $M^+ + H$), 401 (20, $M^+ - H$), 167 (100), 139 (10), 91 (10).

tert-Butyl 3-Bromo-2-pentylpyrrole-1-carboxylate (**16o**):

A solution of **14o** (1.32 g, 4.03 mmol) in CH_2Cl_2 was treated according to Method G to give, after FC on silica gel (hexane/Et_2O 10:1), **16o** as a colourless oil; yield: 0.82 g (64%).

IR (film): ν = 2958 w, 2931 w, 2863 w, 1747 s, 1556 w, 1497 w, 1399 w, 1371 m, 1319 s, 1256 w, 1165 m, 1127 s, 916 w, 847 w cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.17 (d, J = 3.5 Hz, 1 pyr. H); 6.13 (d, J = 3.5 Hz, 1 pyr. H); 2.95–2.85 (m, 2 aliph. H); 1.59 (s, t-Bu); 1.6–1.45 (m, 2 aliph. H); 1.4–1.25 (m, 4 aliph. H); 0.95–0.8 (m, CH_3).

MS: m/z (%) = 316 (M^+), 261 (14), 160 (22), 136 (10), 57 (100), 41 (10).

Benzyl 3-Bromo-2-pentylpyrrole-1-carboxylate (**16p**):

A solution of **14p** (1.45 g, 4.0 mmol) in CH_2Cl_2 was treated according to Method G to give, after FC on silica gel (hexane/Et_2O 10:1), **16p** as a colourless oil; yield: 1.29 g (92%).

IR (film): ν = 2945 w, 2929 w, 2861 w, 1752 s, 1552 w, 1487 w, 1407 w, 1379 m, 1306 s, 1216 w, 1127 m, 917 w, 697 w cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.45–7.3 (m, 5 arom. H); 7.22 (d, J = 3.5 Hz, 1 pyr. H); 6.15 (d, J = 3.5 Hz, 1 pyr. H); 5.34 (s, 2 aliph. H); 2.95–2.85 (m, 2 aliph. H); 1.59 (s, t-Bu); 1.6–1.45 (m, 2 aliph. H); 1.35–1.2 (m, 4 aliph. H); 0.95–0.8 (m, CH_3).

MS: m/z (%) = 350 (M^+), 91 (100).

We wish to thank our colleagues from F. Hoffmann-La Roche AG, for IR spectra (Mr. A. Bubendorf), NMR (Dr. W. Arnold), MS (Dr. W. Vetter and Mr. W. Meister), and elemental analyses (Dr. St. Müller and Mr. G. Nein). We would also like to thank Profs. K. Müller, H.-J. Hansen, J. Baldwin, F. Diederich, and A. Vasella for fruitful discussions.

(1) Sundberg, R.J. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A.R.; Rees, C.W., Eds.; Pergamon: New York, 1984; Vol. 4.
(2) Korostova, S.E.; Sobenima, L.N.; Nesterenko, R.N.; Aliev, I.A.; Mikhaleva, A.I. *Zh. Org. Khim.* **1984**, 1960.
(3) Niziurski-Mann, R.E.; Cava, M.P. *Heterocycles* **1992**, *34*, 2003.
(4) Trofimov, B.A.; Mikhaleva, A.I. *Khim. Geterotsikl. Soedin.* **1980**, 1299.
(5) Bean, G.P. In *The Chemistry of Heterocyclic Compounds*; Jones, R.A., Ed.; Wiley: New York, 1990; Vol. 48.
(6) Trofimov, B.A.; Mikhaleva, A.I. *Khim. Geterotsikl. Soedin.* **1987**, 1299.
(7) Trofimov, B.A. *Zh. Org. Khim.* **1986**, *23*, 1991.
(8) Trofimov, B.A. *Adv. Heterocycl. Chem.* **1990**, *51*, 178.
(9) Jackson, A.H.; Smith, K.M. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley: New York, 1973; Vol. 1.
(10) Lask, T.D.; Hoehner, M.C. *J. Heterocycl. Chem.* **1991**, *28*, 1671.
(11) Barton, D.H.R.; Zard, S.Z. *J. Chem. Soc., Chem. Commun.* **1985**, 1098.
(12) Dalton, C.R.; Kane, J.M.; Rampe, D. *Tetrahedron Lett.* **1992**, *33*, 5713.
(13) Katritzky, A.R.; Li, J.; Gordeev, M. *Synthesis* **1994**, 93.
(14) Obrecht, D. *Helv. Chim. Acta* **1989**, *72*, 447.
(15) Weinreb, S.M.; Nahm, S. *Tetrahedron Lett.* **1981**, 3815.
(16) Mitsunobu, O. *Synthesis* **1981**, 1.
(17) Barbot, F.; Miginiac, P. *Bull. Chem. Soc. Fr.* **1983**, 41.
(18) Boger, D.L.; Corbett, W.L. *J. Org. Chem.* **1992**, *57*, 4777.
(19) Trost, B.M.; Marrs, C. *J. Org. Chem.* **1991**, *56*, 6468.
(20) Still, W.C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(21) Metcalf, B.W.; Casara, P. *J. Chem. Soc., Chem. Commun.* **1979**, 119.
(22) Masquelin, T.; Broger, E.; Muller, K.; Schmid, R.; Obrecht, D. *Helv. Chim. Acta.* **1994**, *77*, 0000.
(23) Obrecht, D.; Weiss, B. *Helv. Chim. Acta* **1989**, *72*, 117.
(24) McKay, W.R.; Proctor, G.R. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2435.
(25) Jones, J.H.; Clarke, C.T.; Elliott, J.D. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1088.