Synthesis of Polysubstituted Pyrroles from Nitroso-Diels–Alder Cycloadducts

Géraldine Calvet, Nicolas Blanchard, Cyrille Kouklovsky*

Laboratoire de Synthèse des Substances Naturelles, ICMMO, UMR 8615, Batiment 410, Université d'Orsay, 91400 Orsay, France
Fax +33(1)69154679; E-mail: cykouklo@icmo.u-psud.fr

Received 2 May 2005

Dedicated with much respect and admiration to Professor Steven V. Ley, FRS, on the occasion of his 60th birthday

Abstract: Nitroso-Diels–Alder cycloaddition of various dienes combined with a straightforward sequence including N–O bond cleavage and oxidation reaction of the resulting (*Z*)-γ-aminoenone (or enal) leads to polysubstituted pyrrolic units.

Key words: nitroso-Diels–Alder reactions, oxidations, pyrroles, ring closure

The chemistry of the pyrrole nucleus has been under close investigation due to the occurrence of this unique heterocycle in naturally and/or biologically active compounds.[1] Numerous methods for the synthesis of pyrroles have been reported in the literature and can be classified, for example, according to the bond disconnections (Figure 1).[1a–c] The N–C2 disconnection method includes cyclization reactions,[2] metal-mediated cyclization reactions (catalytic[3] or non-catalytic[4]), and N–H insertion reactions.[5] The classical Knorr and Hantzch pyrrole synthesis (N–C2, C3–C4 disconnections) or the Paal–Knorr cyclocondensation (N–C2, N–C5 disconnections) are still the object of active research aimed at increased efficiency and simplicity.[6] New methods for the synthesis of pyrroles include multicomponent reactions based on Stetter (or sila-Stetter) Paal–Knorr domino processes[7] or the sequential rearrangement of enol-protected propargylic alcohols.[8] Cycloadditions (involving C2–C3, C4–C5 disconnections) of azomethine ylides,[9] isonitriles,[10] or oxazolium oxides (münchnones)[11] are also an important class of reactions which allow a straightforward access to polysubstituted pyrroles. Recently, a metathesis reaction[12] (with ruthenium trichloride as co-catalyst)[13] has been studied, allowing the efficient conversion of diallylamines to 3-pyrrolines, which could be dehydrogenated in situ to pyrrole.

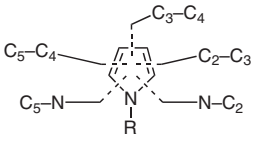
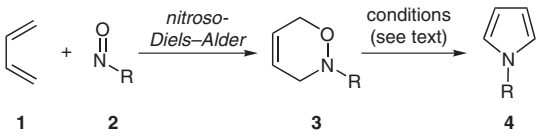


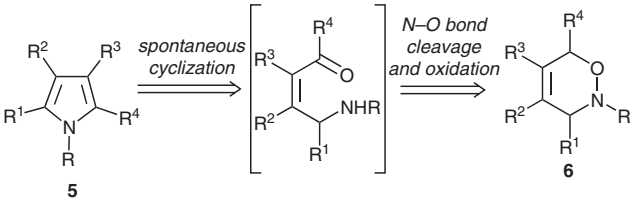
Figure 1 Bond disconnections for pyrrole synthesis

Contraction of an existing heterocyclic ring into pyrrole has also been reported. In this regard, 1,2-diazines[14] or 3,6-dihydro-1,2-oxazines **3** can be viewed as direct precursors. The latter are easily obtained by nitroso-Diels–Alder cycloaddition of electron-rich 1,3-dienes **1** with nitroso dienophiles **2** (Scheme 1).[15] These cycloadducts can be converted into pyrrole **4** photochemically (when R = Ar);[16] under high temperature and pressure;[17] ruthenium or rhodium catalysis,[18] Lewis acid,[19] Brönsted acid,[20] or silica gel activation;[21] fluoride-mediated desilylation of 6-silyl-3,6-dihydro-1,2-oxazine;[22] or base-mediated rearrangement of 3,6-dihydro-1,2-oxazine bearing an electron withdrawing group in the 6-position.[23] These methods suffer either from a lack of generality, drastic conditions, or require very specific substitution of the nitroso-Diels–Alder cycloadduct.



Scheme 1 Literature synthesis of pyrroles **4** from 3,6-dihydro-1,2-oxazines **3**[16–23]

To the best of our knowledge, no systematic studies have been reported to explore the scope of pyrrole formation from diversely substituted dihydrooxazine **6** under mild conditions. The latter can be viewed as a latent pyrrole: a simple two-step sequence, namely N–O bond cleavage followed by an oxidation–spontaneous cyclization reaction, should lead directly to pyrrolic units (Scheme 2). Since substitution of the starting 1,3-diene directly translates into the pyrrole, this approach should also be quite flexible. Moreover, regiochemical control during the [4+2] cycloaddition step is not considered to be an issue. In continuation of our interest in nitroso-Diels–Alder cycloadditions,[24] we would like to report a general and straightforward access to the pyrrole nucleus from cycloadducts **6**.



R = acyl
R^1, R^2, R^3, R^4 = H, alkyl, aryl

Scheme 2 A straightforward two-step synthesis of polysubstituted

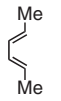
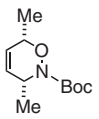
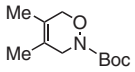
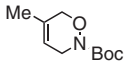
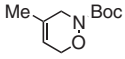
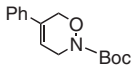
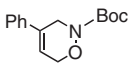
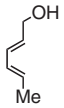
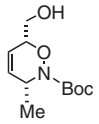
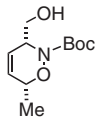
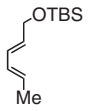
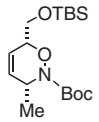
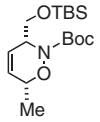
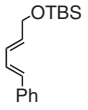
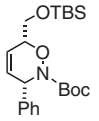
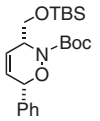
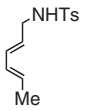
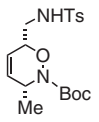
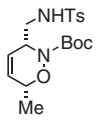
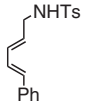
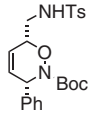
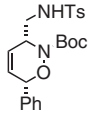
SYNTHESIS 2005, No. 19, pp 3346–3354
Advanced online publication: 04.11.2005
DOI: 10.1055/s-2005-918457; Art ID: C04905SS

pyrroles **5** from 3,6-dihydro-1,2-oxazines **6**

We first examined the cycloaddition reaction of the nitroso dienophile derived from *tert*-butyl-*N*-hydroxycarbamate with mono- or disubstituted 1,3-dienes **7a–i**. The substitution of these dienes was chosen as representative of alkyl groups (**7a–c**), aromatic group (**7d**), hydroxymethyl (**7e–g**), and aminomethyl functions (**7h–i**). Two sets of oxidation conditions were evaluated according to the diene solubility: $NaIO_4$, MeOH, 0 °C (conditions A) or Bu_4NIO_4, CH_2Cl_2, 0 °C (conditions B)[25] (Scheme 3, Table 1).

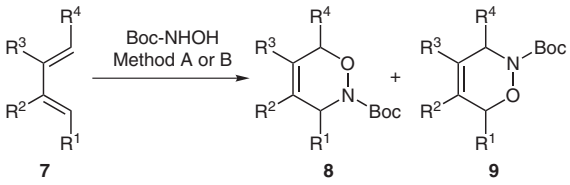
Symmetrical 1,3-dienes were reacted first (Table 1, entries 1 and 2). In line with previous work, the corresponding cycloadducts **8a** and **8b** were obtained with moderate to good yields. Dissymmetrical 1,3-dienes **7c–i** were then submitted to the nitroso-Diels–Alder cycloaddition (Table 1, entries 3–9). Good yields of the corresponding cycloadducts were obtained, except for **8c**, as has been previously noted. The regioisomeric ratios ranges from

Table 1 Synthesis of 3,6-Dihydro-1,2-oxazines **8** and **9** by Nitroso-Diels–Alder Cycloaddition

Entry	Diene	Cycloadducts		Yield[a]	Ratio **8/9**
1	 **7a**[b]	 **8a**[c]		Conditions A: 84%	–
2	 **7b**	 **8b**		Conditions A: 42%	–
3	 **7c**	 **8c**	 **9c**	Conditions A: 25% Conditions B: 38%	45:55
4	 **7d**	 **8d**	 **9d**	Conditions A: 80% Conditions B: 84%	20:80
5	 **7e**	 **8e**	 **9e**	Conditions B: 80%	67:33
6	 **7f**	 **8f**	 **9f**	Conditions A: 51% Conditions B: 97%	87:13
7	 **7g**	 **8g**	 **9g**	Conditions B: 74%	2:98
8	 **7h**	 **8h**	 **9h**	Conditions B: 89%	73:27
9	 **7i**	 **8i**	 **9i**	Conditions B: 67%	2:98

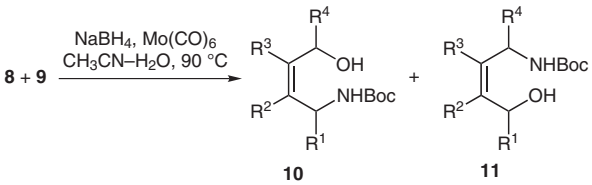
[a] Isolated yield. Conditions A: $NaIO_4$, MeOH, 0 °C; Conditions B: Bu_4NIO_4, CH_2Cl_2, 0 °C to r.t.
[b] As commercially available 70:30 (*E,E*)/(*Z,E*) mixture.
[c] With 20% *trans* isomer.

55:45 (Table 1, entry 3) to 2:98 (Table 1, entries 7 and 9), depending on the diene. The structure of each regioisomer was unambiguously deduced from multidimensional NMR experiments (HMBC and HSQC). The presence of a phenyl substituent on C2 in diene **7d** led to an increase in the regioisomeric ratio of the corresponding cycloadducts compared to the C2-methyl substituted dienes **7c** (Table 1, entries 4 and 3, 20:80 vs. 45:55). That the phenyl moiety was a stronger directing group than the methyl group in this cycloaddition was confirmed with 1,3-dienes **7g** and **7i**. The regioisomeric ratio of nitroso-Diels–Alder cycloadducts was 87:13 and 73:27 with 5-methyl-1,3-dienes **7f** and **7h** (Table 1, entries 6 and 8) whereas a 2:98 ratio was observed with 5-phenyl-1,3-dienes **7g** and **7i** (Table 1, entries 7 and 9). It has been previously shown for the nitroso-Diels–Alder cycloaddition that a substituent at the C1-position had a stronger directing effect than a substituent at C2.[26]



Scheme 3

3,6-Dihydro-1,2-oxazines **8a–i** and **9c–i** were then subjected to N–O bond cleavage, mediated by $Mo(CO)_6$ in aqueous acetonitrile.[27] The corresponding (*Z*)-hydroxycarbamate were obtained as mixture of regioisomers, in good yields (Scheme 4, Table 2).

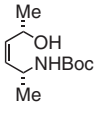
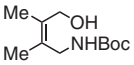
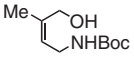
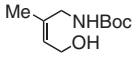
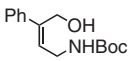
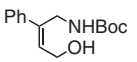
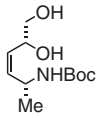
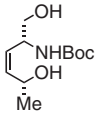
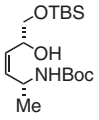
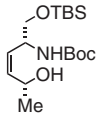
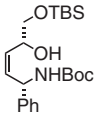
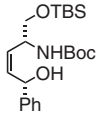
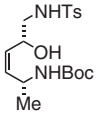
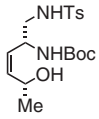
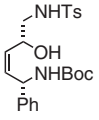
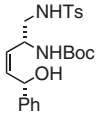


Scheme 4

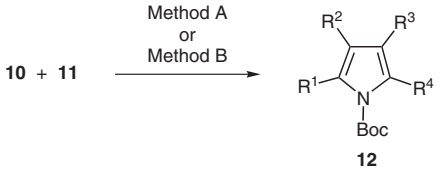
Hydroxycarbamates **10a–d** and **11c–d** were oxidized with MnO_2 in dichloroethane (Table 3, conditions A); a smooth oxidation occurred, followed by a spontaneous cyclization reaction. In some cases, it was necessary to heat the reaction mixture to promote the ring closure. Both 2,5- and 3,4-disubstituted pyrroles **12a** and **12b** were obtained in 60% isolated yield under these conditions (Table 3, entries 1 and 2). Monosubstituted pyrrole could also be obtained in good yield (Table 3, entry 3) except in the case of the 3-phenyl substitution which proved detrimental to the yield (Table 3, entry 4, conditions A, 28%). Hydroxycarbamates **10e** and **11e**, possessing a primary alcohol moiety, led to a complex mixture of products (Table 3, entry 5).

In some cases, pyrrole synthesis by MnO_2 oxidation proved unsuccessful. When hydroxycarbamates **10g** and **11g** (Table 2, entry 7) were treated with MnO_2 at 30 °C, a clean conversion to the corresponding (*Z*)-γ-aminoenone took place (89% yield). However, the latter decomposed under neutral, acidic, or basic cyclization conditions (MnO_2, CH_2C_{12}, 90 °C; anhyd HCl, CH_2Cl_2[2d] KHMDS, THF, –78 °C). Therefore, a second set of oxidation conditions using Dess–Martin periodinane was evaluated (Table 3, conditions B). Reactions were generally cleaner and better yields were obtained (Table 3, entry 4, 28% under conditions A, compared to 98% under conditions B; entry 6, 47% under conditions A, compared to 68% under conditions B). Under these modified conditions the sensitive pyrrole **12g** was obtained in 69% yield at 45 °C (Table 3, entry 7). The yield dropped to 33% when the oxidation took place at 90 °C, highlighting the sensitive nature of the transient (*Z*)-γ-aminoenone and/or pyrrole **12g**

Table 2 N–O Bond Cleavage of 3,6-Dihydro-1,2-oxazines **8** and **9**

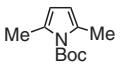
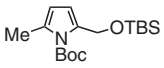
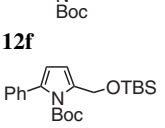
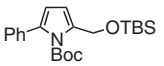
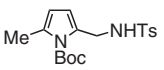
Entry	Oxazine	Carbamates **10** and **11**		Yield
1	**8a**			67%
		10a		
2	**8b**			81%
		10b		
3	**8c** + **9c**			65%
		10c	**11c**	
4	**8d** + **9d**			76%
		10d	**11d**	
5	**8e** + **9e**			60%
		10e	**11e**	
6	**8f** + **9f**			70%
		10f	**11f**	
7	**8g** + **9g**			85%
		10g	**11g**	
8	**8h** + **9h**			85%
		10h	**11h**	
9	**8i** + **9i**			68%
		10i	**11i**	

(vide supra). It is interesting to note that **10h** and **11h** led to the same pyrrole in different yields. Regioisomer **10h** leads to **12h** in quantitative yield whereas **11h** gave only a 51% yield (Table 3, entry 8). Pyrrole **12i** was obtained in 61% yield, allowing further functionalization of the phenyl or tosylamino moieties (Table 3, entry 9).



Scheme 5

Table 3 Synthesis of Pyrroles **12** from Carbamates **10** and **11**

Entry	Carbamates **10** and **11**	Pyrrole **12**	Yield[a]
1	**10a**	 **12a**	Conditions A: 60%
2	**10b**	 **12b**	Conditions A: 60%
3	**10c** + **11c**	 **12c**	Conditions A: 63%
4	**10d** + **11d**	 **12d**	Conditions A: 28% Conditions B: 98%
5	**10e** + **11e**	–	[b]
6	**10f** + **11f**	 **12f**	Conditions A: 47% Conditions B: 68%
7	**10g** + **11g**	 **12g**	Conditions B: 69%
8	**10h** + **11h**	 **12h**	Conditions B: 100%[c] Conditions B: 51%[d]
9	**10i** + **11i**	 **12i**	Conditions B: 61%

[a] Isolated yield of pyrrole; Conditions A: MnO_2, 1,2-dichloroethane, 30 °C; Conditions B: Dess–Martin periodinane, CH_2Cl_2–H_2O, 90 °C.
[b] Complex mixture of products was obtained.
[c] Carbamate **10h** alone was used as starting material.
[d] Carbamate **11h** alone was used as starting material.

In conclusion, we have shown that protected 3,6-dihydro-1,2-oxazines can be viewed as latent pyrroles. Benefits include the wide scope of the nitroso-Diels–Alder cycloaddition combined with a straightforward sequence including N–O bond cleavage and oxidation reaction of the resulting (*Z*)-γ-aminoenone (or enal) leading directly to the desired pyrrole. Two sets of oxidation conditions have been successfully applied: MnO_2 or Dess–Martin periodinane according to the sensitivity of the reactants and/or the products. Owing to the mild conditions required and the diversity of substitution attainable, this transformation should prove useful for the synthesis of polysubstituted pyrrolic units.

All reactions were conducted in flame-dried or oven dried glassware under an atmosphere of dry nitrogen. All solvents were purified before use unless otherwise indicated. THF, Et_2O, and toluene were distilled over Na/benzophenone ketyl anion under argon. CH_2Cl_2 was distilled over CaH_2 under argon. All other reagents were purchased and used without further purification. Analytical TLC was performed on Kieselgel 60 F_{254} glass precoated with 0.25 mm of silica gel. Flash chromatography was performed on Kieselgel 60 (230–400 mesh) silica gel. IR spectra were recorded as thin films on NaCl plates using a Perkin-Elmer Spectrum One FT-IR spectrophotometer. ^{1}H NMR spectra were measured at 360 MHz on a Bruker AC360, at 250 MHz on a Bruker AC250 or AM250 and at 200 MHz on a Brucker AC200 using $CDCl_3$ as solvent. Chemical shifts are reported to 0.01 ppm precision with coupling constants reported to 0.1 Hz precision using residual $CHCl_3$ (7.27 ppm) as an internal reference. MS were measured on a MAT 95S Finnigan-Thermo spectrometer at the Institut de Chimie Moléculaire d'Orsay (ICMMO) Mass Spectrometry Laboratory. Elemental analyses were performed at the ICSN, CNRS, Gif sur Yvette, France. Spectroscopic data were in agreement with literature data for compounds **8a**,[28] **8c**,[29] **9c**,[29] **10a**,[24] **10b**,[24] **11c**,[31] **12a**,[2d] and **12c**.[30]

Nitroso-Diels–Alder Cycloaddition – Method A; Typical Procedure

To a soln of 2,6-hexadiene **7a** (*E*,*E*/*E*,*Z* = 70:30 as determined by ^{1}H NMR analysis of the commercial compound, 0.27 mL, 2.3 mmol) in MeOH (15 mL) at 0 °C was added portionwise $NaIO_4$ (497 mg, 2.3 mmol) and BocNHOH (310 mg, 2.3 mmol) over 4 h. The reaction mixture was stirred at 0 °C for 2 h and then quenched with a sat. aq soln of $Na_2S_2O_3$ (10 mL). The aqueous phase was extracted with EtOAc (3 × 20 mL), the combined organic phases were washed with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated. The crude oil was purified by flash chromatography (heptane–EtOAc, 90:10) to give **8a** (412 mg, 84%) as a colorless oil.

Nitroso-Diels–Alder Cycloaddition – Method B; Typical Procedure

To a soln of diene **7h** (603 mg, 2.4 mmol) and BocNHOH (320 mg, 2.4 mmol) in CH_2Cl_2 (7 mL) at 0 °C was added a soln of Bu_4NIO_4 (520 mg, 1.2 mmol) in CH_2Cl_2 (5 mL) dropwise over 40 min. The reaction mixture was stirred at 0 °C for 1.5 h and at r.t. for 2 h before being quenched with a sat. aq $Na_2S_2O_3$ soln (5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), the combined organic phases were washed with brine (15 mL), dried over $MgSO_4$, filtered, and concentrated. The crude oil was purified by flash chromatography (heptane–EtOAc, 90:10) to give **8h** (32.2 mg) and a mixture of **8h** and **9h** (782 mg, 89% combined yield) as colorless oils.

tert-Butyl 4,5-Dimethyl-3,6-dihydro-2*H*-1,2-oxazine-2-carboxylate (8b)

R_f 0.27 (heptane–EtOAc, 90:10).

IR: 2979, 2930, 1728, 1708, 1393, 1368, 1239, 1173, 1140, 1089, 865 cm^{-1}.

^{1}H NMR (benzene-d_6, 250 MHz): δ = 4.03 (s, 2 H), 3.86 (s, 2 H), 1.42 (s, 6 H, CH_3-4, CH_3-5), 1.24 (s, 9 H, 3 × CH_3).

^{13}C NMR (benzene-d_6, 100 MHz): δ = 155.2, 147.9, 123.2, 122.3, 84.5, 80.6, 70.9, 48.6, 28.3, 27.1, 14.9, 13.4.

***tert*-Butyl 5-Methyl-3,6-dihydro-2*H*-1,2-oxazine-2-carboxylate (8c)**

Isolated as a mixture with **9c**; R_f 0.22 (heptane–EtOAc, 90:10).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.54 (m, 1 H, H-4), 4.24 (br s, 2 H, H-6), 4.02 (br s, 2 H, H-3), 1.65 (s, 3 H, CH_3-5), 1.49 (s, 9 H, 3 × CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 154.8 or 154.7 (CO), 131.3 or 130.0 (C-5), 116.2, 81.3, 70.9, 44.5, 28.0, 18.0.

***tert*-Butyl 4-Methyl-3,6-dihydro-2*H*-1,2-oxazine-2-carboxylate (9c)**

Isolated as a mixture with **8c**; R_f 0.22 (heptane–EtOAc, 90:10).

IR: 1728, 1704, 1393, 1367, 1243, 1165, 1102, 858, 760 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.54 (m, 1 H, H-5), 4.35 (br s, 2 H, H-6), 3.93 (m, 2 H, H-3), 1.72 (s, 3 H, CH_3-4), 1.49 (s, 9 H, 3 × CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 154.8 or 154.7 (CO), 131.3 or 130.0 (C-5), 117.8, 81.3, 67.7, 48.3, 28.0, 19.5.

***tert*-Butyl 5-Phenyl-3,6-dihydro-2*H*-1,2-oxazine-2-carboxylate (8d)**

R_f 0.23 (heptane–EtOAc, 90:10).

IR: 2978, 1704, 1367, 1246, 1165, 749, 693 cm^{-1}.

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 7.36–7.26 (5 H, Ar), 6.19 (m, 1 H, H-4), 4.78 (dd, *J* = 4.0, 2.0 Hz, 2 H, H-6), 4.25 (dd, *J* = 9.2, 4.0 Hz, 2 H, H-3), 1.52 (s, 9 H, 3 × CH_3).

^{13}C NMR ($CDCl_3$, 90 MHz): δ = 154.9, 136.5, 134.5, 128.6, 127.9, 124.7, 118.4, 81.7, 69.2, 45.1, 28.2.

***tert*-Butyl 4-Phenyl-3,6-dihydro-2*H*-1,2-oxazine-2-carboxylate (9d)**

R_f 0.23 (heptane–EtOAc, 90:10).

IR: 2978, 1704, 1367, 1246, 1165, 749, 693 cm^{-1}.

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 7.39–7.28 (5 H, Ar), 6.19 (m, 1 H, H-5), 4.61 (dd, *J* = 5.3, 2.6 Hz, 2 H, H-6), 4.48 (dd, *J* = 4.0, 2.1 Hz, 2 H, H-3), 1.52 (s, 9 H, 3 × CH_3).

^{13}C NMR ($CDCl_3$, 90 MHz): δ = 154.9, 137.1, 133.1, 128.6, 127.9, 124.7, 120.0, 81.7, 68.1, 46.2, 28.2.

MS (ESI, Na^+): *m*/*z* (%) = 545.3 ([2 M + Na]$^+$, 36), 284.2 ([M + Na]$^+$, 100), 162.1 (68).

HRMS-ESI: *m*/*z* calcd for $C_{15}H_{19}NO_3Na$ [M + Na]$^+$: 284.1257; found: 284.1259.

***tert*-Butyl 6-Hydroxymethyl-3-methyl-3,6-dihydro-2*H*-1,2-oxazine-2-carboxylate (8e)**

R_f 0.14 (heptane–EtOAc, 70:30).

IR: 3428, 1651, 1369 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.81 (ddd, *J* = 10.2, 4.4, 2.2 Hz, 1 H), 5.66 (d, *J* = 10.2 Hz, 1 H), 4.57 (br m, 1 H, H-6), 4.33 (br m, 1 H, H-3), 3.85 (br s, 1 H, OH), 3.62 (d, *J* = 5.1 Hz, 2 H, CH_2OH), 1.42 (s, 9 H, 3 × CH_3), 1.22 (d, *J* = 6.7 Hz, 3 H, CH_3-3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 154.4, 129.6, 124.1, 81.4, 78.5, 63.2, 50.4, 28.1, 17.8.

MS (ESI, Na^+): *m*/*z* (%) = 196.0 ([M + Na]$^+$, 100).

HRMS-ESI: *m*/*z* calcd for $C_{11}H_{19}NO_4Na$ [M + Na]$^+$: 252.1206; found: 252.1209.

***tert*-Butyl 3-Hydroxymethyl-6-methyl-3,6-dihydro-2*H*-1,2-oxazine-2-carboxylate (9e)**

R_f 0.18 (heptane–EtOAc, 70:30).

IR: 3430, 1683, 1704, 1695, 1369, 1164 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.81 (d, *J* = 10.4 Hz, 1 H), 5.77 (ddd, *J* = 10.4, 3.8, 1.8 Hz, 1 H), 4.64 (m, 1 H), 4.46 (m, 1 H), 3.77–3.71 (2 H, CH_2OH), 2.36 (br s, 1 H, OH), 1.48 (s, 9 H, 3 × CH_3), 1.24 (d, *J* = 6.8 Hz, 3 H, CH_3-6).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 155.1, 131.2, 130.2, 81.9, 72.3, 63.3, 56.1, 28.2, 18.7.

MS (ESI, Na^+): *m*/*z* (%) = 252.1 ([M + Na]$^+$, 100), 196 (75).

HRMS-ESI: *m*/*z* calcd for $C_{11}H_{19}NO_4Na$ [M + Na]$^+$: 252.1206; found: 252.1209.

***tert*-Butyl 6-[(*tert*-Butyldimethylsilyl)oxy]methyl-3-methyl-3,6-dihydro-2*H*-1,2-oxazine-2-carboxylate (8f)**

R_f 0.37 (heptane–EtOAc, 90:10).

IR: 2957, 2930, 1728, 1704, 1393, 1367, 1313, 1256, 1174, 1118, 839, 778 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.85 (ddd, *J* = 10.2, 4.4, 2.2 Hz, 1 H), 5.76 (d, *J* = 10.2 Hz, 1 H), 456 (br s, 1 H, H-6), 4.43 (br s, 1 H, H-3), 3.75 (dd, *J* = 10.7, 5.6 Hz, 1 H, CH*H*OSi), 3.59 (dd, *J* = 10.7, 5.4 Hz, 1 H, C*H*HOSi), 1.48 (s, 9 H, 3 × CH_3), 1.28 (d, *J* = 6.8 Hz, 3 H, CH_3-3), 0.88 (s, 9 H, 3 × CH_3), 0.06 (s, 6 H, 2 × CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 154.4, 129.3, 124.8, 81.1, 77.6, 63.7, 50.1, 28.3, 25.8, 18.2, 18.0, –5.4, –5.5.

MS (ESI, Na^+): *m*/*z* (%) = 366.2 ([M + Na]$^+$, 46), 310.2 (31), 244.2 (100).

HRMS-ESI: *m*/*z* calcd for $C_{17}H_{33}NO_4SiNa$ [M + Na]$^+$: 366.2071; found: 366.2084.

***tert*-Butyl 3-[(*tert*-Butyldimethylsilyl)oxy]methyl-6-methyl-3,6-dihydro-2*H*-1,2-oxazine-2-carboxylate (9f)**

R_f 0.34 (heptane–EtOAc, 90:10).

IR: 2931, 2858, 1704, 1367, 1255, 1111, 838, 777 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.91 (ddd, *J* = 10.3, 4.2, 1.9 Hz, 1 H), 5.77 (d, *J* = 10.3 Hz, 1 H), 4.62 (m, 1 H), 4.42 (m, 1 H), 3.81 (dd, *J* = 9.8, 7.5 Hz, 1 H, CH*H*OSi), 3.66 (dd, *J* = 9.8, 6.9 Hz, 1 H, C*H*HOSi), 1.48 (s, 9 H, 3 × CH_3), 1.24 (d, *J* = 6.8 Hz, 3 H, CH_3-6), 0.89 (s, 9 H, 3 × CH_3), 0.06 (s, 6 H, 2 × CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 154.3, 130.4, 123.9, 81.2, 72.5, 63.8, 55.3, 28.3, 25.8, 18.8, 18.3, –5.4 (2 C).

MS (ESI, Na^+): *m*/*z* (%) = 366.2 ([M + Na]$^+$, 100), 310.1 (69), 266.1 (44)

HRMS-ESI: *m*/*z* calcd for $C_{17}H_{33}NO_4SiNa$ [M + Na]$^+$: 366.2071; found: 366.2080.

***tert*-Butyl 3-[(*tert*-Butyldimethylsilyl)oxy]methyl-6-phenyl-3,6-dihydro-2*H*-1,2-oxazine-2-carboxylate (9g)**

R_f 0.22 (heptane–EtOAc, 98:2).

IR: 2955, 2929, 2857, 1706, 1368, 1254, 1170, 1105, 837, 777, 716, 698 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.38–7.33 (5 H), 6.09 (ddd, *J* = 10.5, 4.3, 2.0 Hz, 1 H), 5.98 (ddd, *J* = 10.4, 10.4, 1.2 Hz, 1 H), 5.52 (br s, 1 H, H-6), 4.57 (br s, 1 H, H-3), 3.94 (dd, *J* = 9.9, 7.4 Hz, 1 H, CH*H*OSi), 3.81 (dd, *J* = 9.9, 6.8 Hz, 1 H, C*H*HOSi), 1.54 (s, 9 H, 3 × CH_3), 0.93 (s, 9 H, 3 × CH_3), 0.10 (s, 6 H, 2 × CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 154.3, 137.0, 128.7, 128.6, 128.4, 128.0, 124.6, 81.1, 78.1, 63.8, 55.5, 28.2, 25.7, 18.1, –5.4, –5.6.

MS (ESI, Na^+): *m*/*z* (%) = 428.4 ([M + Na]$^+$, 42), 306.3 (100).

HRMS-ESI: *m*/*z* calcd for $C_{22}H_{35}NO_4SiNa$ [M + Na]$^+$: 428.2228; found: 428.2229.

tert-Butyl 3-Methyl-6-(tosylamino)methyl-3,6-dihydro-2*H*-1,2-oxazine-2-carboxylate (8h)

R_f 0.28 (heptane–EtOAc, 70:30).

IR: 3267, 2978, 1699, 1369, 1329, 1161, 1119, 816, 665 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.74 (d, *J* = 8.0 Hz, 2 H), 7.30 (d, *J* = 8.0 Hz, 2 H), 5.86 (ddd, *J* = 10.4, 4.4, 2.0 Hz, 1 H), 5.62 (d, *J* = 10.4 Hz, 1 H), 5.13 (br s, 1 H, NH), 4.57 (br s, 1 H, H-6), 4.39 (br s, 1 H, H-3), 3.24 (ddd, *J* = 13.2, 7.3, 3.2 Hz, 1 H, CH*H*N), 3.01 (ddd, *J* = 13.2, 7.1, 5.4 Hz, 1 H, CH*H*N), 2.42 (s, 3 H, C*H*$_3$Ph), 1.49 (s, 9 H, 3 × CH_3), 1.25 (d, *J* = 6.8 Hz, 3 H, CH_3-3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 154.2, 143.4, 136.8, 130.6, 129.7, 127.0, 123.9, 81.9, 75.8, 50.5, 45.1, 28.2, 21.5, 18.0.

MS (ESI, Na^+): *m*/*z* (%) = 405.2 ([M + Na]$^+$, 96), 283.2 (100).

HRMS-ESI: *m*/*z* calcd for $C_{18}H_{26}NO_5SNa$ [M + Na]$^+$: 405.1455; found: 405.1462.

tert-Butyl 6-Methyl-3-(tosylamino)methyl-3,6-dihydro-2*H*-1,2-oxazine-2-carboxylate (9h)

Isolated as a mixture with **8h**; R_f 0.26 (heptane–EtOAc, 70:30).

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 7.75 (d, *J* = 8.1 Hz, 2 H), 7.30 (d, *J* = 8.1 Hz, 2 H), 5.81 (d, *J* = 10.4 Hz, 1 H), 5.71 (ddd, *J* = 10.4, 4.3, 1.9 Hz, 1 H), 4.83 (m, 1 H, NH), 4.59 (m, 1 H, H-6 or H-3), 4.48 (m, 1 H, H-3 or H-6), 3.17 (ddd, *J* = 9.3, 5.0, 2.0 Hz, 2 H, CH_2N), 2.42 (s, 3 H, C*H*$_3$-Ph), 1.54 (s, 9 H, 3 × CH_3), 1.22 (d, *J* = 6.8 Hz, 3 H, CH_3-3).

^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 154.0, 143.4, 136.8, 131.7, 129.7, 127.1, 122.7, 82.4, 72.3, 65.9, 45.0, 28.3, 18.7, 15.3.

tert-Butyl 6-Phenyl-3-(tosylamino)methyl-3,6-dihydro-2*H*-1,2-oxazine-2-carboxylate (9i)

R_f 0.31 (heptane–EtOAc, 70:30).

IR: 3278, 2978, 1704, 1395, 1369, 1331, 1161, 1094, 815, 757, 700, 662 cm^{-1}.

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 7.72 (d, *J* = 8.3 Hz, 2 H), 7.36–7.29 (7 H), 6.01 (d, *J* = 10.3 Hz, 1 H), 5.93 (ddd, *J* = 10.4, 4.1, 2.3 Hz, 1 H), 5.49 (m, 1 H, H-6), 4.99 (m, 1 H, NH), 4.60 (m, 1 H, H-3), 3.25 (t, *J* = 6.0 Hz, 2 H, CH_2N), 2.40 (s, 3 H, CH_3-Ph), 1.52 (s, 9 H, 3 × CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 154.5, 143.2, 136.8, 136.4, 129.5, 129.4, 129.0, 128.5, 128.2, 126.9, 123.9, 82.3, 78.0, 53.0, 45.0, 28.1, 21.3.

MS (ESI, Na^+): *m*/*z* (%) = 467.3 ([M + Na]$^+$, 79), 411.2 (47), 345.3 (100).

HRMS-ESI: *m*/*z* calcd for $C_{23}H_{28}N_2O_5SNa$ [M + Na]$^+$: 467.1611; found: 467.1619.

N–O Bond Cleavage; Typical Procedure

To a soln of **8g** (626 mg, 1.54 mmol) in CH_3CN–H_2O (7:1, 12 mL) was added $Mo(CO)_6$ (653 mg, 2.47 mmol). After 10 min at r.t., $NaBH_4$ (29 mg, 0.77 mmol) was added and the suspension was heated at 90 °C overnight. The reaction mixture was cooled and Et_2O (10 mL) was added. The suspension was filtered through a bed of celite and thoroughly rinsed with Et_2O (3 × 5 mL). The filtrate was concentrated and the crude oil was purified by flash chromatography (heptane–EtOAc, 85:15 to 80:20) to give **11g** (535 mg, 85%) as a colorless oil.

tert-Butyl (*Z*)-4-Hydroxy-3-phenylbut-2-en-1-yl Carbamate (10d)

Isolated as a minor isomer as a mixture with **11d**.

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 7.49 (d, *J* = 6.8 Hz, 2 H), 7.36–7.26 (3 H), 5.78 (t, *J* = 7.8 Hz, 1 H, H-2), 4.98 (s, 1 H), 4.55 (s, 1 H), 3.94 (dd, *J* = 7.8, 6.1 Hz, 2 H, H-1), 3.74 (s, 1 H), 1.42 (s, 9 H, 3 × CH_3).

tert-Butyl (*Z*)-4-Hydroxy-2-phenylbut-2-en-1-yl Carbamate (11d)

IR: 3332, 1689, 1514, 1367, 1251, 1166, 767, 698 cm^{-1}.

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 7.38–7.26 (m, 5 H), 6.10 (t, *J* = 6.8 Hz, 1 H, H-3), 4.87 (s, 1 H), 4.34 (d, *J* = 7.3 Hz, 2 H), 4.21 (d, *J* = 5.9 Hz, 2 H), 1.38 (s, 9 H, 3 × CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 156.2, 140.2, 139.3, 129.7, 128.6, 127.7, 126.6, 80.0, 58.0, 38.8, 28.3.

MS (ESI, Na^+): *m*/*z* (%) = 286.3 ([M + Na]$^+$, 64), 230.2 (45), 186.2 (24).

HRMS-ESI: *m*/*z* calcd for $C_{15}H_{21}NO_3Na$ [M + Na]$^+$: 286.1414; found: 286.1420.

tert-Butyl (2*S*,5*S*)-(*Z*)-6-(_tert_-Butyldimethylsilyl)oxy-5-hydroxyhex-3-en-2-yl Carbamate (10f)

R_f 0.28 (heptane–EtOAc, 80:20).

IR: 3334, 2957, 2931, 1689, 1520, 1367, 1252, 1174, 1115, 1055, 837, 778 cm^{-1}.

^{1}H NMR ($CDCl_3$, 360 MHz): δ = 5.51 (dd, app. br t, *J* = 9.2 Hz, 1 H, H-4), 5.31 (br t, *J* = 10.1 Hz, 1 H, H-3), 4.58–4.50 (3 H, H-5, H-2, OH or NH), 3.97 (br s, 1 H, OH or NH), 3.65 (m, 1 H, H-6), 3.57 (dd, *J* = 9.4, 5.6 Hz, 1 H, H-6), 1.42 (s, 9 H, 3 × CH_3), 1.18 (d, *J* = 6.8 Hz, 3 H, H-1), 0.89 (s, 9 H, 3 × CH_3), 0.08 (s, 6 H, 2 × CH_3).

^{13}C NMR ($CDCl_3$, 90 MHz): δ = 155.4, 134.5, 130.7, 79.9, 67.4, 66.8, 44.0, 28.4, 25.9, 21.1, 18.3, –5.3 (2 C).

MS (ESI, Na^+): *m*/*z* (%) = 713.5 ([2 M + Na]$^+$, 4), 368.2 ([M + Na]$^+$, 100), 246.2 (12).

HRMS-ESI: *m*/*z* (%) calcd for $C_{17}H_{35}NO_4SiNa$ [M + Na]$^+$: 368.2228; found: 368.2242.

tert-Butyl (2*S*,5*S*)-(*Z*)-1-(_tert_-Butyldimethylsilyl)oxy-5-hydroxyhex-3-en-2-yl Carbamate (11f)

Isolated as a mixture with **10f**.

^{1}H NMR ($CDCl_3$, 360 MHz): δ = 5.58 (dd, app. br t, *J* = 9.5 Hz, 1 H), 5.37 (dd app. t, *J* = 10.3 Hz, 1 H), 4.69–4.66 (2 H), 4.11 (m, 1 H), 3.70 (dd, *J* = 9.7, 4.0 Hz, 1 H, H-1), 3.56 (m, 1 H, H-1), 1.40 (s, 9 H, 3 × CH_3), 1.22 (d, *J* = 6.1 Hz, 3 H, H-6), 0.88 (s, 9 H, 3 × CH_3), 0.08 (s, 6 H, 2 × CH_3).

^{13}C NMR ($CDCl_3$, 90 MHz): δ = 156.0, 136.8, 127.8, 80.0, 64.9, 62.0, 49.1, 28.3, 25.8, 22.3, 18.2, –5.6 (2 C).

tert-Butyl (2*S*,5*S*)-(*Z*)-5-Hydroxy-5-phenyl-1-(_tert_-butyldimethylsilyl)oxyhex-3-en-2-yl Carbamate (11g)

IR: 3442, 1692, 1493, 1367, 1253, 1171, 1101, 837, 778, 700 cm^{-1}.

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 7.42–7.25 (m, 5 H), 5.80 (dd, *J* = 10.5, 9.0 Hz, 1 H), 5.67 (d, *J* = 9.3 Hz, 1 H), 5.53 (t, *J* = 10.5 Hz, 1 H), 5.18 (br d, *J* = 6.0 Hz, 1 H), 4.64 (m, 1 H), 3.78 (dd, *J* = 10.1, 3.6 Hz, 1 H, CH*H*OSi), 3.61 (dd, *J* = 10.1, 3.9 Hz, 1 H, C*H*HOSi), 1.46 (s, 9 H, 3 × CH_3), 0.91 (s, 9 H, 3 × CH_3), 0.07 (s, 6 H, 2 × CH_3).

^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 156.1, 143.0, 135.3, 128.3, 127.1, 126.0, 80.3, 68.3, 64.8, 49.1, 28.4, 25.8, 18.3, –5.5.

MS (ESI, Na^+): *m*/*z* (%) = 430.4 ([M + Na]$^+$, 60), 290.3 (100).

HRMS-ESI: *m*/*z* calcd for $C_{22}H_{37}NO_4SiNa$ [M + Na]$^+$: 430.2384; found: 430.2389.

***tert*-Butyl (2*S*,5*S*)-(*Z*)-6-Tosylamino-5-hydroxyhex-3-en-2-yl Carbamate (10h)**

R_f 0.26 (heptane–EtOAc, 60:40).

IR: 3364, 2978, 1683, 1516, 1506, 1328, 1161, 914, 815, 734 cm^{-1}.

^1H NMR ($CDCl_3$, 360 MHz): δ = 7.70 (d, *J* = 8.3 Hz, 2 H), 7.24 (d, *J* = 8.3 Hz, 2 H), 5.41–5.34 (m, 2 H, H-4, OH or NH), 5.20 (t, *J* = 10.4 Hz, 1 H, H-3), 4.89–4.82 (m, 2 H, NH, OH), 4.53 (m, 1 H, H-5), 4.32 (br s, 1 H, H-2), 3.02 (ddd, *J* = 12.3, 7.8, 3.5 Hz, 1 H, H-6), 2.84 (ddd, *J* = 12.3, 7.6, 4.6 Hz, 1 H, H-6), 2.35 (s, 3 H, C*H*$_3$Ph), 1.33 (s, 9 H, 3 × CH_3), 1.09 (d, *J* = 6.8 Hz, 3 H, H-1).

^{13}C NMR ($CDCl_3$, 90 MHz): δ = 155.6, 143.1, 136.8, 135.3, 129.5, 129.1, 126.9, 80.0, 64.5, 47.6, 43.6, 28.1, 21.3, 20.1.

MS (ESI, Na^+): *m*/*z* (%) = 407.3 ([M + Na]$^+$, 100), 184.2 (43).

HRMS-ESI: *m*/*z* calcd for $C_{18}H_{28}N_2O_5SNa$ [M + Na]$^+$: 407.1611; found: 407.1621.

***tert*-Butyl (2*S*,5*S*)-(*Z*)-1-Tosylamino-5-hydroxyhex-3-en-2-yl Carbamate (11h)**

R_f 0.28 (heptane–EtOAc, 60:40).

IR: 3364, 2978, 1683, 1516, 1506, 1328, 1161, 914, 815, 734 cm^{-1}.

^1H NMR ($CDCl_3$, 250 MHz): δ = 7.72 (d, *J* = 8.3 Hz, 2 H), 7.29 (d, *J* = 8.3 Hz, 2 H), 5.64–5.53 (m, 2 H), 5.26 (d, *J* = 7.5 Hz, 1 H), 5.13 (t, *J* = 10.4 Hz, 1 H), 4.58–4.44 (m, 2 H), 4.05 (br s, 1 H), 2.97 (t, *J* = 6.4 Hz, 2 H, H-1), 2.41 (s, 3 H, C*H*$_3$Ph), 1.38 (s, 9 H, 3 × CH_3), 1.18 (d, *J* = 6.5 Hz, 3 H, H-6).

^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 156.0, 143.6, 137.8, 136.6, 129.8, 127.3, 126.9, 80.4, 62.3, 47.7, 46.1, 28.2, 22.4, 21.5.

MS (ESI, Na^+): *m*/*z* (%) = 407.3 ([M + Na]$^+$, 100), 250.2 (22), 184.2 (29).

HRMS-ESI: *m*/*z* calcd for $C_{18}H_{28}N_2O_5SNa$ [M + Na]$^+$: 407.1611; found: 407.1622.

***tert*-Butyl (2*S*,5*S*)-(*Z*)-5-Hydroxy-5-phenyl-1-tosylaminohex-3-en-2-yl Carbamate (11i)**

R_f 0.25 (heptane–EtOAc, 80:20).

IR: 3362, 2978, 1689, 1516, 1328, 1161, 1093, 815, 743, 701, 662 cm^{-1}.

^1H NMR ($CDCl_3$, 250 MHz): δ = 7.70 (d, *J* = 7.8 Hz, 2 H), 7.32–7.24 (7 H), 5.74 (dd, *J* = 10.8, 9.3 Hz, 1 H), 5.65 (t, *J* = 6.4 Hz, 1 H), 5.50 (d, *J* = 8.8 Hz, 1 H), 5.34 (d, *J* = 7.0 Hz, 1 H), 5.23 (t, *J* = 10.4 Hz, 1 H), 4.63 (m, 1 H), 4.40 (br s, 1 H), 3.01–2.92 (2 H), 2.39 (s, 3 H, C*H*$_3$Ph), 1.41 (s, 9 H, 3 × CH_3).

^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 156.0, 143.6, 142.6, 136.5, 136.2, 129.8, 128.4, 127.8, 127.3, 126.9, 126.0, 80.4, 68.5, 47.7, 46.0, 28.3, 21.4.

MS (ESI, Na^+): *m*/*z* (%) = 469.3 ([M + Na]$^+$, 100), 329.3 (23).

HRMS-ESI: *m*/*z* calcd for $C_{23}H_{30}N_2O_5SNa$ [M + Na]$^+$: 469.1768; found: 469.1772.

***tert*-Butyl 2,5-Dimethyl-1*H*-Pyrrole-1-carboxylate (12a) – Method A; Typical Procedure**

To a soln of **10a** (55.4 mg, 0.26 mmol) in CH_2Cl_2 (2.6 mL) was added MnO_2 (1.12 g, 12.9 mmol) and the resulting suspension was stirred at 30 °C overnight. The reaction mixture was filtered through a bed of celite and rinsed with CH_2Cl_2 (3 × 5 mL). The filtrate was concentrated and the crude oil was purified by flash chromatography (heptane–EtOAc, 95:5) to give **12a** (29.8 mg, 60%) as a colorless oil.

R_f 0.13 (heptane).

IR: 2978, 2930, 1739, 1371, 1335, 1313, 1125 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 5.80 (s, 2 H, H-3, H-4), 2.39 (s, 6 H, CH_3-2, CH_3-5), 1.60 (s, 9 H, 3 × CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 150.5, 131.2, 110.1, 83.2, 28.1, 16.5.

MS (ESI, Na^+): *m*/*z* (%) = 413.2 ([2 M + Na]$^+$, 100), 219.1 (32), 138 (53), 118 (32).

***tert*-Butyl 2-(*tert*-Butyldimethylsilyloxymethyl)-5-Methyl-1*H*-pyrrole-1-carboxylate (12f) – Method B; Typical Procedure**

To a soln of **10f** and **11f** (73.2 mg, 0.21 mmol) in CH_2Cl_2 (4.2 mL) was added Dess–Martin periodinane (180 mg, 0.42 mmol) and the resulting suspension was stirred at 90 °C for 8 h. The reaction mixture was cooled and poured into a sat. aq soln of $NaHCO_3$ (5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL), the combined organic phases were washed with a sat. aq soln of $Na_2S_2O_3$ (10 mL), dried over $MgSO_4$, filtered, and concentrated. The crude oil was purified by flash chromatography (heptane–EtOAc, 98:2) to give **12f** (47 mg, 68%) as colorless oil.

R_f 0.40 (heptane–EtOAc, 95:5).

IR: 2980, 1767, 1716, 1369, 1153 cm^{-1}.

^1H NMR ($CDCl_3$, 250 MHz): δ = 6.06 (d, *J* = 2.7 Hz, 1 H), 5.84 (d, *J* = 2.7 Hz, 1 H), 4.81 (s, 2 H, CH_2O), 2.38 (s, 3 H, CH_3-5), 1.58 (s, 9 H, 3 × CH_3), 0.91 (s, 9 H, 3 × CH_3), 0.05 (s, 6 H, 2 × CH_3).

^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 150.1, 135.0, 110.4, 109.8, 83.4, 60.6, 28.0, 25.9, 18.5, 16.2, –5.3.

MS (ESI, Na^+): *m*/*z* (%) = 348.2 ([M + Na]$^+$, 100), 301.2 (41), 275.1 (57), 231.1 (38).

***tert*-Butyl 3,4-Dimethyl-1*H*-pyrrole-1-carboxylate (12b)**

Prepared under conditions A; yield: 60%; R_f 0.10 (heptane).

IR: 2980, 2934, 1738, 1402, 1345, 1254 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 6.94 (s, 2 H, H-2, H-5), 1.98 (s, 6 H, CH_3-3, CH_3-4), 1.57 (s, 9 H, 3 × CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 148.9, 122.7, 117.0, 82.6, 28.0, 10.1.

MS (ESI, Na^+): *m*/*z* (%) = 413.2 ([2 M + Na]$^+$, 68), 301 (28), 250 (45), 234 (100), 178 (55), 150 (48), 134 (51).

***tert*-Butyl 3-Methyl-1*H*-pyrrole-1-carboxylate (12c)**

Prepared under conditions A; yield: 63%.

IR: 3151, 1741, 1343, 1251, 972 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.13 (t, *J* = 2.5 Hz, 1 H, H-2 or H-5), 6.97 (m, 1 H, H-5 or H-2), 6.05 (m, 1 H, H-4), 2.06 (s, 3 H, CH_3-3), 1.58 (s, 9 H, 3 × CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 148.9, 122.4, 119.9, 117.1, 114.0, 83.1, 28.0, 11.9.

***tert*-Butyl 3-Phenyl-1*H*-pyrrole-1-carboxylate (12d)**

Prepared under conditions B; yield: 98%; R_f 0.24 (heptane–EtOAc, 98:2).

IR: 1743, 1392, 1355, 1142, 975 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.55 (d, *J* = 6.8 Hz, 4 H), 7.43 (t, *J* = 6.8 Hz, 2 H), 7.35 (m, 1 H, H-2 or H-5), 6.59 (m, 1 H, H-4), 1.65 (s, 9 H, 3 × CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 148.8, 134.3, 128.7, 127.8, 126.6, 125.5, 120.9, 115.7, 110.4, 83.8, 28.0.

MS (EI): *m*/*z* (%) = 243.1 ([M]$^+$, 9), 143.0 (100), 115 (34), 57 (65).

HRMS-EI: *m*/*z* (%) calcd for $C_{23}H_{30}N_2O_5SNa$ [M]$^+$: 243.1254; found: 243.1265.

***tert*-Butyl [2-(*tert*-Butyldimethylsilyl)oxy]methyl-5-phenyl-1*H*-pyrrole-1-carboxylate (12g)**

Prepared under conditions B; yield: 69%; R_f 0.45 (heptane–EtOAc, 95:5); mp < 50 °C (waxy solid).

IR: 2930, 1737, 1339, 1313, 1256, 1148, 1061, 838, 777, 698 cm^{-1}.

^1H NMR ($CDCl_3$, 250 MHz): δ = 7.29–7.21 (m, 5 H), 6.20 (d, *J* = 3.5 Hz, 1 H), 6.08 (d, *J* = 3.5 Hz, 1 H), 4.87 (s, 2 H, CH_2O), 1.21 (s, 9 H, 3 × CH_3), 0.90 (s, 9 H, 3 × CH_3), 0.07 (s, 6 H, 2 × CH_3).

^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 149.8, 136.6, 135.5, 135.2, 128.7, 127.6, 126.8, 112.4, 110.0, 83.5, 59.9, 27.3, 25.9, 18.3, –5.3.

MS (ESI, Na^+): *m*/*z* (%) = 410.2 ($[M + Na]^+$, 100), 301.2 (27).

HRMS-ESI: *m*/*z* calcd for $C_{22}H_{33}NO_3SiNa$ $[M + Na]^+$: 410.2122; found: 410.2118.

Anal. Calcd for $C_{22}H_{33}NO_3Si$: C, 68.17; H, 8.58; N, 3.61. Found: C, 68.19; H, 8.58; N, 3.46.

***tert*-Butyl 2-(Tosylamino)methyl-5-methyl-1*H*-pyrrole-1-carboxylate (12h)**

Prepared under conditions B; yield: 100% (from **10h**), 51% (from **11h**); R_f 0.43 (heptane–EtOAc, 70:30); mp 73 °C.

IR: 3304, 1733, 1392, 1338, 1260, 1163, 1129, 1093, 850, 814, 790, 737 cm^{-1}.

^1H NMR ($CDCl_3$, 250 MHz): δ = 7.57 (d, *J* = 8.1 Hz, 2 H), 7.16 (d, *J* = 8.1 Hz, 2 H), 5.91 (d, *J* = 3.2 Hz, 1 H), 5.67–5.61 (m, 2 H), 4.21 (d, *J* = 6.5 Hz, 2 H, CH_2N), 2.37 (s, 3 H, CH_3-Ar), 2.18 (s, 3 H, CH_3-5), 1.53 (s, 9 H, 3 × CH_3).

^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 150.3, 142.4, 137.7, 132.3, 129.7, 129.5, 129.1, 126.7, 113.6, 110.6, 84.4, 41.7, 27.8, 21.3, 16.5.

MS (ESI, Na^+): *m*/*z* (%) = 387.2 ($[M + Na]^+$, 100).

HRMS-ESI: *m*/*z* calcd for $C_{18}H_{24}N_2O_4SNa$ $[M + Na]^+$: 387.1349; found: 387.1353.

Anal. Calcd for $C_{18}H_{24}N_2O_4S$: C, 59.32; H, 6.64; N, 7.69. Found: C, 59.30; H, 6.71; N, 7.50.

***tert*-Butyl 2-(Tosylamino)methyl-5-phenyl-1*H*-pyrrole-1-carboxylate (12i)**

Prepared under conditions B; yield: 61%; R_f 0.25 (heptane–EtOAc, 80:20).

IR: 3305, 1732, 1371, 1318, 1149, 1693, 812, 759, 735, 700 cm^{-1}.

^1H NMR ($CDCl_3$, 250 MHz): δ = 7.65 (d, *J* = 8.3 Hz, 2 H), 7.32–7.26 (m, 3 H), 7.19 (d, *J* = 8.0 Hz, 2 H), 7.08 (d, *J* = 7.5 Hz, 2 H), 6.08 (d, *J* = 2.9 Hz, 1 H), 5.93 (d, *J* = 2.9 Hz, 1 H), 5.83 (dd, app. t, *J* = 6.6 Hz, 1 H, NH), 4.29 (d, *J* = 7.3 Hz, 2 H, CH_2N), 2.34 (s, 3 H, CH_3-Ar), 1.12 (s, 9 H, 3 × CH_3).

^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 150.3, 142.7, 138.0, 134.9, 131.2, 129.2, 128.5, 127.6, 126.9, 113.6, 112.4, 84.5, 41.4, 27.1, 21.4.

MS (ESI, Na^+): *m*/*z* (%) = 449.2 ($[M + Na]^+$, 100), 393.1 (41), 355.0 (23).

HRMS-ESI: *m*/*z* calcd for $C_{23}H_{26}N_2O_4SK$ $[M + K]^+$: 465.1245; found: 465.1258.

Acknowledgment

We would like to thank Friederike Tewes for preliminary experiments. We thank the Ministère de la Recherche et de la Technologie for a grant (G.C.), the Université Paris-XI and the CNRS-UMR 8615 for financial support.

References

(1) (a) Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2491. (b) Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2849. (c) Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **1998**, 615. (d) Sundberg, R. J. In *Comprehensive Heterocyclic Chemistry II*, Vol. 2; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Pergamon: Oxford, **1996**, 119. (e) *Heterocyclic Chemistry*, 4th ed.; Joule, J. A.; Mills, K., Eds.; Blackwell Science: London, **2000**, Chap. 13. (f) Patterson, J. M. *Synthesis* **1976**, 281.

(2) (a) Nakamura, M.; Hara, K.; Sakata, G.; Nakamura, E. *Org. Lett.* **1999**, *1*, 1505. (b) Dieter, R. K.; Yu, H. *Org. Lett.* **2000**, *2*, 2283. (c) Benetti, S.; De Risi, C.; Marchetti, P.; Pollini, G. P.; Zanirato, V. *Synthesis* **2002**, 331. (d) Paulus, O.; Alcaraz, G.; Vaultier, M. *Eur. J. Org. Chem.* **2002**, 2565.

(3) (a) Ramanathan, B.; Keith, A. J.; Armstrong, D.; Odom, A. L. *Org. Lett.* **2004**, *6*, 2957. (b) Fürstner, A. *Synlett* **1999**, 1523. (c) Li, Y.; Marks, T. J. *J. Am. Chem. Soc.* **1998**, *120*, 1757. (d) Utimoto, K.; Miwa, H.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 4277.

(4) (a) Kel'in, A. V.; Sromek, A. W.; Gevorgyan, V. *J. Am. Chem. Soc.* **2001**, *123*, 2074. (b) Danks, T.; Velo-Rego, D. *Tetrahedron Lett.* **1994**, *35*, 9443.

(5) Wang, S.; Zhu, S. *Org. Lett.* **2003**, *5*, 745.

(6) (a) Nagafuji, P.; Cushman, M. *J. Org. Chem.* **1996**, *61*, 4999. (b) Banik, B. K.; Samajdar, S.; Banik, I. *J. Org. Chem.* **2004**, *69*, 213.

(7) (a) Braun, R. U.; Muller, T. J. J. *Synthesis* **2004**, 2391. (b) Bharadwaj, A. R.; Scheidt, K. A. *Org. Lett.* **2004**, *6*, 2465. (c) For a recent review, see: Balme, G. *Angew. Chem. Int. Ed.* **2004**, *43*, 6238.

(8) Tejedor, D.; Gonzalez-Cruz, D.; Garcia-Tellado, F.; Marrero-Tellado, J. J.; Rodriguez, M. L. *J. Am. Chem. Soc.* **2004**, *126*, 8390.

(9) Reisser, M.; Maas, G. *J. Org. Chem.* **2004**, *69*, 4913.

(10) (a) Takaya, H.; Kojima, S.; Murahashi, S.-I. *Org. Lett.* **2001**, *3*, 421. (b) Dijkstra, H. P.; ten Have, R.; van Leusen, A. M. *J. Org. Chem.* **1998**, *63*, 5332. (c) van Leusen, D.; van Leusen, A. M. *Org. React.* **2001**, *57*, 417.

(11) Dhawan, R.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2004**, *126*, 468.

(12) Yang, C.; Murray, W. V.; Wilson, L. J. *Tetrahedron Lett.* **2003**, *44*, 1783.

(13) Dieltiens, N.; Stevens, C. V.; De Vos, D.; Allaert, B.; Drozdzak, R.; Verpoort, F. *Tetrahedron Lett.* **2004**, *45*, 8995.

(14) Boger, D. L.; Boyce, C. W.; Labroli, M. A.; Sehon, C. A.; Jin, Q. *J. Am. Chem. Soc.* **1998**, *121*, 54.

(15) (a) Vogt, P. F.; Miller, M. J. *Tetrahedron* **1998**, *54*, 1317. (b) Tietze, L. F.; Kettschau, G. *Top. Curr. Chem.* **1997**, *189*, 1. (c) Streith, J.; Defoin, A. *Synlett* **1996**, 189. (d) Weinreb, S. M. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I.; Paquette, L. A., Eds.; Pergamon Press: New York, **1991**, 401.

(16) (a) Scheiner, P.; Chapman, O. L.; Lassila, J. D. *J. Org. Chem.* **1969**, *34*, 813. (b) Givens, R. S.; Choo, D. J.; Merchant, S. N.; Stitt, R. P.; Matuszewski, B. *Tetrahedron Lett.* **1982**, *23*, 1327.

(17) Ragaini, F.; Cenini, S.; Brignolli, D.; Gasperini, M.; Gallo, E. *J. Org. Chem.* **2003**, *68*, 460.

(18) (a) Okuro, K.; Dang, T.; Khumtaveeporn, K.; Alper, H. *Tetrahedron Lett.* **1996**, *37*, 2713. (b) Raigani, F.; Cenini, S.; Borsani, E.; Dompé, M.; Gallo, E. *Organometallics* **2001**, *20*, 3390.

(19) McClure, K. F.; Danishefsky, S. J. *J. Org. Chem.* **1991**, *56*, 850.

(20) Ring contraction of 6-trimethylsilyloxy substituted 3,6-dihydrooxazine: Shi, G.-Q.; Schlosser, M. *Tetrahedron* **1993**, *49*, 1445.
(21) Kresze, G.; Härtner, H. *Justus Liebigs Ann. Chem.* **1973**, 650.
(22) Kefalas, P.; Grierson, D. S. *Tetrahedron Lett.* **1993**, *34*, 3555.
(23) (a) Kresze, G.; Braun, H. *Tetrahedron Lett.* **1969**, 1743. (b) Defoin, A.; Fritz, H.; Geffroy, G.; Streith, J. *Tetrahedron Lett.* **1986**, *27*, 3135. (c) Firl, J.; Kresze, G. *Chem. Ber.* **1966**, *99*, 3695.
(24) Calvet, G.; Dussaussois, M.; Blanchard, N.; Kouklovsky, C. *Org. Lett.* **2004**, *6*, 2449.
(25) (a) Kirby, G. W.; Sweeny, J. G. *J. Chem. Soc., Chem. Commun.* **1973**, 704. (b) Emery, T.; Neilands, J. B. *J. Am. Chem. Soc.* **1960**, *82*, 4903.
(26) Leach, A. G.; Houk, K. N. *J. Org. Chem.* **2001**, *66*, 5192.
(27) (a) Cicchi, S.; Goti, A.; Brandi, A.; Guarna, A.; De Sarlo, F. *Tetrahedron Lett.* **1990**, *31*, 3351. (b) Zhang, D.; Süling, C.; Miller, M. J. *J. Org. Chem.* **1998**, *63*, 885.
(28) Defoin, A.; Joubert, M.; Heuchel, J.-M.; Strehler, C.; Streith, J. *Synthesis* **2000**, 1719.
(29) Tolman, V.; Hanus, J.; Sedmera, P. *Collect. Czech. Chem. Commun.* **1999**, *64*, 696.
(30) Davies, H. M. L.; Matasi, J. J.; Hodges, L. M.; Huby, N. J. S.; Thornley, C.; Kong, N.; Houser, J. H. *J. Org. Chem.* **1997**, *62*, 1095.
(31) Evidente, A.; Piccialli, G.; Sisto, A.; Ohba, M.; Honda, K.; Fuji, T. *Chem. Pharm. Bull.* **1992**, *40*, 1937.