Solvent and ligand effects on selective mono- and dilithiation of 1-(chlorophenyl)pyrroles and 1-(methoxyphenyl)pyrroles †

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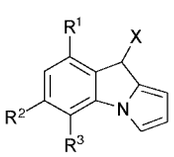
Novel methods for site-selective lithiation of 1-(chlorophenyl)pyrroles and 1-(methoxyphenyl)pyrroles are described. Mono- or dilithiations are governed by change of both the temperature and the solvent from tetrahydrofuran to diethyl ether. Regioselectivities could be influenced by the quality of the metallating agent. Thus, 1-(4-chlorophenyl)pyrrole was dilithiated with activated butyllithium at 0 °C to afford a valuable intermediate in a pyrrolobenzoxazepine synthesis.

Introduction

Multifunctionalized derivatives of 1-phenylpyrrole are known potent biologically active compounds. Cytostatic mytomycine derivatives[1] (**1**), central nervous system (CNS)-active pyrrolobenzoxazepines[2] (**2**), the neopyrrolomycine[3] **3** and analogous antibiotics and fungicides[3] are among the known pharmaceutically interesting compounds.



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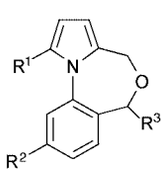

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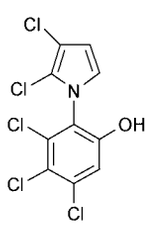
R^1,R^2,R^3 = Me, OMe
X = OH, CH_2CONH_2



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Site-selective metallation methods would be useful tools for the synthesis of these molecules. On the other hand, 1-(substituted phenyl)pyrroles are quite interesting models for the investigation of the directing effects during metallation. The pyrrole ring is suitable for α metallation, while it works as an *ortho*-directing group connected to the benzene ring and this latter aromatic ring contains (an)other directing substituent(s) in different positions. Mono- and dimetallations of 1-alkylpyrroles have been extensively studied by Chakrabarti[4] and Chadwick.[5] However, few articles have discussed the metallation of 1-arylpyrroles. Selective α lithiation of 1-phenylpyrrole was observed first by Shirley,[6] and α,2 dilithiation of the same molecule was published by Cheeseman.[7] Recently, we have reported on the regioselective monolithiation of 1-(methoxyphenyl)pyrroles controlled by the appropriate application of the di- or tridentate activating agents (*N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) or *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (PMDTA) in tetrahydrofuran (THF) at −75 °C.[8] Site-selective monolithiation of 1-(fluorophenyl)pyrroles[9] and of 1-[(trifluoromethyl)-phenyl]pyrroles[10] has also been reported by our laboratory.

Regiocontrolled metallation of *ortho*, *meta* and *para* isomers of 1-(bromophenyl)pyrroles (**4**, **9**, **18**) and of 1-(chlorophenyl)-pyrroles (**5**, **10**, **19**) is a new challenge. First of all, metal halogenide elimination may easily occur during *ortho* metallation. In addition, the electronic, steric and complex-forming abilities of the halogen substituents are different from those of the OMe group.

On the other hand, α,2 dilithiation of the model compounds would be useful for simultaneous functionalization of the pyrrole and the benzene rings, yielding valuable intermediates for the synthesis of biologically active compounds (such as **1**, **2** or **3**). Substituents like Cl, Br or OMe may influence the outcome of such reactions depending on their characters. Therefore, comparison of dilithiations of the OMe-substituted 1-phenylpyrroles (**6**, **11** and **20**) with the same reactions of the halogen-containing model compounds is also interesting both from theoretical and practical points of view.

Results and discussion

Consecutive treatment of the *ortho*-, *meta*- and *para*-substituted 1-phenylpyrroles **4**–**6**, **9**–**11**, **18**–**20** with organometallic base and solid CO_2 provided mono- and dicarboxylic acids as mixtures or sole products depending on the reaction conditions used. The reactions and the structures of the isolated products are shown in Schemes 1–3. The reagents, product ratios and yields are collected in Tables 1 and 2.

Multicomponent mixtures formed instead of the desired products when the bromine-containing **4** and **9** substrates were consecutively treated with lithium 2,2,6,6-tetramethylpiperidide (LiTMP) and solid CO_2. Failure of these reactions is due to the special ease of elimination of lithium bromide from the *ortho*-lithiated derivatives of **4** and **9**. Metallation and consecutive carboxylation of the *para* isomer **18** afforded acid **21** as the main product, but we could not avoid formation of **22** even when 20% excess of 2,2,6,6-tetramethylpiperidine (TMP) was used related to the amount of butyllithium. The selectivity completely changed when a stronger base, potassium *tert*-butoxide-activated LiTMP (LiTMP–KOR), was the reagent in

† Electronic supplementary information (ESI) available. Details of molecular modelling, yields, melting or boiling points, spectroscopic data of the starting materials **4**–**6**, **9**–**11**, **18**–**20** and the known products **12**, **14**, **16**, **22**–**25**, **27**, **28**, **30**. See http://www.rsc.org/suppdata/p1/b1/b100008j/

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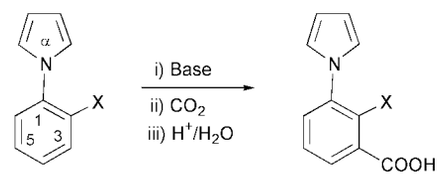
the presence of the tridentate PMDTA ligand (Table 1, entry 12). The high selectivity of this reaction can be explained by the stabilizing effect of PMDTA on the organometallic intermediate of **23** and by the simultaneous fast elimination of alkali bromide from the organometallic intermediate of **21** (if it was formed).

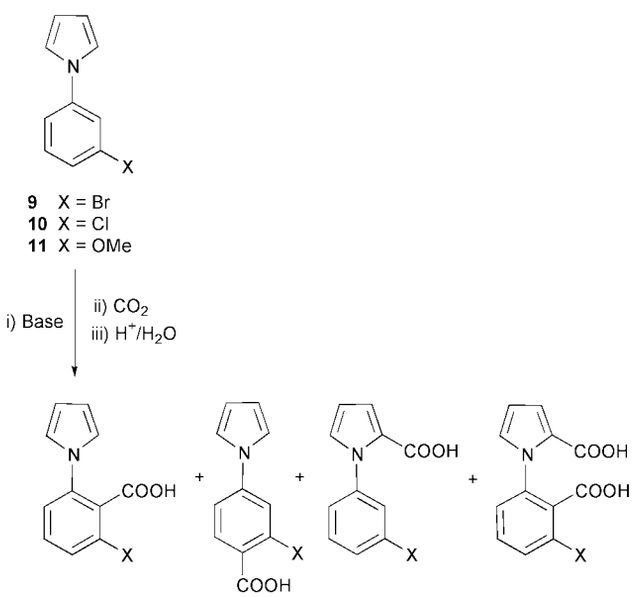
Much higher yields were achieved during lithiation and carboxylation of the chloro-substituted compounds (**5**, **10** and **19**). The C–Cl bond was stable enough at −75 °C; neither halogen–lithium exchange nor elimination of lithium chloride was observed using butyllithium (BuLi) or its activated complexes (BuLi–TMEDA and BuLi–PMDTA) in THF. The yields of the isolated carboxylic acids **7**, **12** and the mixture of **24** and **25** increased together with the reactivity of the metallating agent. Change of TMEDA to PMDTA did not influence the regioselectivities during metallation of **5** and **10**; monocarboxylic acids **7** and **12** were isolated as sole products, respectively (Table 1, entries 2–4 and 7–9). A strong competition between the C-2 and C-3 positions (activated by the chloro and the pyrrolo substituents, respectively) was observed when **19** was treated with the above-mentioned bases and mixtures of **24** and **25** were isolated.



4 X = Br
5 X = Cl
6 X = OMe

7 X = Cl
8 X = OMe

Scheme 1



9 X = Br
10 X = Cl
11 X = OMe

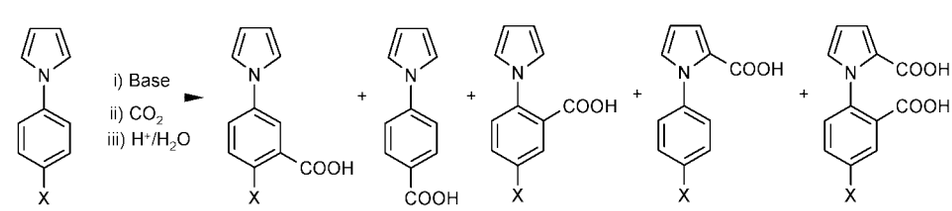
12 X = Cl
13 X = Cl
14 X = OMe
15 X = OMe
16 X = OMe
17 X = OMe

Scheme 2

The weaker, lithium amide-type base (LiTMP) reacted with the chloro compounds (**5**, **10** and **19**) in different ways: compounds **5** and **19** could be transformed—after solid-CO_2 quenching—into acids **7** and **24**, respectively, with complete regioselectivity and in good yields. The *meta* isomer **10** underwent parallel lithiation on both halogen-adjacent positions (C-2 and C-4) with LiTMP, therefore a 1 : 2 mixture of **12** and **13** was isolated after the reaction with solid CO_2. The C-2 position is sterically more crowded than the C-4 position, but the bulkiness of LiTMP alone does not explain the result since BuLi–TMEDA and BuLi–PMDTA are also bulky reagents and we obtained the C-2 acid **12** regioselectively and in a high yield using these bases (Table 1, entries 8–10).

Change of the temperature from −75 °C to 0 °C and of the solvent from THF to diethyl ether resulted in significant differences in the metallation reactions. The lithio derivatives of the 1-(bromophenyl)pyrroles **4**, **9** and **18** and of the *ortho* and *meta* 1-(chlorophenyl)pyrroles (**5** and **10**) were unstable under these conditions; we could not isolate any halogen-containing mono- or dicarboxylic acid from these reactions. However, 1-(4-chlorophenyl)pyrrole **19** underwent α,2 dimetallation even when only one equivalent butyllithium was added to the model compound (Table 2, entry 7). The yield of the isolated dicarboxylic acid **26** became three–four-times higher when two equivalents of butyllithium was used even in THF at 0 °C (entry 9). Metallation with two equivalents of BuLi–TMEDA gave the best result in this series of experiments (Table 2, entry 10) while the reaction with BuLi–PMDTA yielded—after solid-CO_2 quenching—a mixture of monocarboxylic (**25**) and dicarboxylic (**26**) acids. It has to be mentioned that we could not isolate any α-substituted product from this reaction. (This is in accord with the monolithiation reactions at −75 °C, Table 1, entries 13–15.)

For comparison, monolithiations of the OMe-group-containing model compounds (**6**, **11** and **20**) were also accomplished at 0 °C. Two-fold excess of BuLi–TMEDA was necessary for *ortho* metallation of **6**, providing the monocarboxylic acid **8** with reasonable yield (Table 2, entry 1). During metallation of **11** and **20** *ortho* lithiation occurred (products **14** and **27**) with BuLi–TMEDA reagent, but the thermodynamically favored α lithiation dominated in the presence of PMDTA (formation of acids **16** and **28**, respectively). In diethyl ether, the consecutive reactions of **11** with BuLi–PMDTA and solid CO_2 resulted in a mixture of **16** and **17**. Appearance of the dicarboxylic acid **17** might be due to the co-ordination of the α-lithiated compound with another molecule of base and in this aggregate hydrogen–lithium exchange could occur at the activated C-2 position. Better solvation in THF prevents the α-lithiated compound from forming such a type of aggregate, therefore clean α lithiation of **11** could be achieved even at 0 °C. The dicarboxylic acid **17** formed in good yield when **11** was treated with two equivalents amount of BuLi–TMEDA in diethyl ether at 0 °C followed by quenching with solid CO_2 (Table 2, entry 6).



18 X = Br
19 X = Cl
20 X = OMe

21 X = Br
24 X = Cl
27 X = OMe

22

23 X = Br
25 X = Cl

28 X = OMe

26 X = Cl
29 X = OMe

Scheme 3

Table 1 Reagents and results of the consecutive lithiation and carboxylation reactions in THF at −75 °C

	Starting material			Product	
Entry	No.	X	Base (equivalents)	No. (ratio)[a]	Yield (%)[b]
1	**4**	Br	LiTMP (1)		[c]
2	**5**	Cl	BuLi (1)	**7**	18
3	**5**	Cl	BuLi–TMEDA (1)	**7**	54
4	**5**	Cl	BuLi–PMDTA (1)	**7**	55
5	**5**	Cl	LiTMP (1)	**7**	59
6	**9**	Br	LiTMP (1)		[c]
7	**10**	Cl	BuLi (1)	**12**	69
8	**10**	Cl	BuLi–TMEDA (1)	**12**	58
9	**10**	Cl	BuLi–PMDTA (1)	**12**	75
10	**10**	Cl	LiTMP (1)	**12** + **13** (1 : 2)	34
11	**18**	Br	LiTMP (1)	**21** + **22** (2 : 1)	32
12	**18**	Br	LiTMP–KOR + PMDTA (1)	**23**	17
13	**19**	Cl	BuLi (1)	**24** + **25** (1 : 3)	58
14	**19**	Cl	BuLi–TMEDA (1)	**24** + **25** (1 : 3)	64
15	**19**	Cl	BuLi–PMDTA (1)	**24** + **25** (1 : 1)	66
16	**19**	Cl	LiTMP (1)	**24**	67

[a] Compositions of the isolated crude products were determined by ^{1}H NMR. [b] Yields of the isolated products. [c] Multicomponent mixtures formed. In the case of **9**, only 1-(3-carboxyphenyl)pyrrole was isolated (20%) from the mixture in spite of the excess of TMP (20% relative to butyllithium).

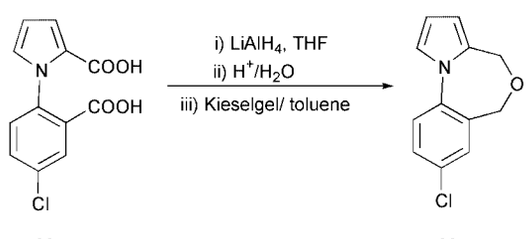
Table 2 Reagents and results of the consecutive lithiation and carboxylation reactions at 0 °C

	Starting material			Product	
Entry	No.	X	Base (equiv.), solvent[a]	No. (ratio)[b]	Yield (%)[c]
1	**6**	OMe	BuLi–TMEDA (2), Et_2O	**8**	55[d]
2	**11**	OMe	BuLi (1), Et_2O	**14** + **15** (1 : 3)	24
3	**11**	OMe	BuLi–TMEDA (1), Et_2O or THF	**14**	62[d]
4	**11**	OMe	BuLi–PMDTA (1), Et_2O[e]	**16** + **17** (2 : 1)	62
5	**11**	OMe	BuLi–PMDTA (1), THF	**16**	68
6	**11**	OMe	BuLi–TMEDA (2), Et_2O	**17**	88
7	**19**	Cl	BuLi (1), Et_2O	**26**	14
8	**19**	Cl	BuLi (2), Et_2O	**26**	51
9	**19**	Cl	BuLi (2), THF	**26**	55
10	**19**	Cl	BuLi–TMEDA (2), Et_2O	**26**	70
11	**19**	Cl	BuLi–PMDTA (2), Et_2O	**25** + **26** (4 : 3)	49
12	**20**	OMe	BuLi–TMEDA (2), Et_2O	**27** + **29** (1 : 1)	72
13	**20**	OMe	BuLi–TMEDA (1), THF	**27**	67[d]
14	**20**	OMe	BuLi–PMDTA (1), Et_2O	**28**	32
15	**20**	OMe	BuLi–PMDTA (2), Et_2O	**29**	66

[a] Et_2O:diethyl ether, THF:tetrahydrofuran. [b] Compositions of the isolated crude products were determined by ^{1}H NMR. [c] Yields of the isolated products. [d] The yields were >95% when D_2O was used as electrophilic reagent. [e] The metallation was carried out at −20 °C.

In the reaction of **20** with BuLi–TMEDA, a 1 : 1 mixture of **27** and **29** could be isolated after solid-CO_2 quenching. Clean α lithiation was accomplished with BuLi–PMDTA in diethyl ether to afford **28**, and the pure dicarboxylic acid **29** was formed when two equivalents of BuLi–PMDTA were used (Table 2, entries 14 and 15).

Efficient preparation of dicarboxylic acid **26** was the starting point of the novel, convenient synthesis of a known, CNS-active pyrrolobenzoxazepine[2] (**30**, Scheme 4). In the two-step



26 **30**

Scheme 4

synthesis the dicarboxylic acid **16** was reduced to the diol, then this was treated with silica gel. Silica is acidic enough to promote elimination of water under mild conditions. In this way, **30** could be prepared conveniently while the known methods (use of P_2O_5 or other strong acid) initiate serious side-reactions of the pyrrole moiety.

In order to help rationalization of the observed reactivities and selectivities, molecular modelling and quantum chemical calculations were also carried out. Details of the calculations are reported in the deposited Supplementary Data. These data may be helpful for prediction of *ortho* lithiation adjacent to the halogen or OMe group. However, the solvent- and ligand-dependent site selectivities as well as the formation of the dilithiated species (intermediates of dicarboxylic acids **17**, **26** and **29**) indicate the complexity of these reactions. Detailed investigations have confirmed[11] that lithium (in the complex BuLi–TMEDA) may co-ordinate to the OMe group of anisole-type molecules (Ar-H), but this intermediate does not account for the facilitated *ortho* lithiation as such.[11] Instead, it has been shown by *ab initio* calculations[12] and systematic kinetic measurements[12,13] that TMEDA-activated butyllithium may react in a dimeric form of structure $(BuLi)_2(TMEDA)_2$. The transition structures of stoichiometry $[(BuLi)_2(TMEDA)_2$-$(Ar\text{-}H)]^{\ddagger}$ as well as formation of triple ions in the rate-limiting steps have been discussed by Collum and co-workers.[12] On the other hand, they have demonstrated that activating ligands and solvents may influence both the rate and the mechanism of metallations by correlated solvation. Thus, construction of a cogent mechanistic model is difficult.[14]

Conclusions

In summary, highly selective methods for mono- and dimetallation of (bromo)-, chloro- and methoxy-substituted 1-phenylpyrroles have been developed. Thus 1-(chlorophenyl)pyrroles could be lithiated with activated butyllithium at low temperature with good yields.

Special effects influenced the metallations in diethyl ether at 0 °C. Site-selective monolithiation of 1-(2-methoxyphenyl)-pyrrole **6** could be achieved with two equivalents of BuLi–TMEDA, only. Selective dimetallations of *meta* and *para* methoxy analogs (**11** and **20**) with two equivalents of BuLi–PMDTA and efficient α,2 dilithiation of 1-(4-chlorophenyl)-pyrrole **19** were also accomplished. In the latter case, simple butyllithium or its TMEDA-activated form was suitable for dimetallation. Synthetic utility of these metallation reactions was demonstrated by the preparation of a pyrrolobenzoxazepine derivative.

Experimental

Generalities

All commercial starting materials were purchased from Fluka AG and Merck-Shuchardt and were used without further purification. Butyllithium was supplied by Chemetall GmbH Lithium Division, Frankfurt. Anhydrous diethyl ether and THF were obtained by distillation from sodium wire after the characteristic blue color of *in situ*-generated sodium diphenylketyl had been found to persist. TMEDA and PMDTA were also distilled from sodium wire before use. The concentration of the butyllithium solution was determined by the double-titration method.[15] All experiments were carried out in Schlenk flasks under dry nitrogen atmosphere. Solid CO_2–acetone-baths were used to achieve −75 °C during metallation reactions. NMR spectra were recorded in deuteriochloroform or hexadeuteriodimethyl sulfoxide solution at 250 MHz. Chemical shifts refer to tetramethylsilane ($\delta = 0$ ppm); coupling constants (J) are given in Hz. Assignments for the proton signals are given in all cases; the numbers and greek letters refer to the numbering of the carbon skeleton (shown in Scheme 2).

Compounds **4**–**6**, **9**–**11**, **18**–**20** are known from the literature. These materials were prepared from the corresponding substituted aniline and *cis*,*trans*-2,5-dimethoxytetrahydrofuran in glacial acetic acid according to Gross' general procedure.[16] Several end-products (**12**, **14**, **16**, **22**–**25**, **27**, **28**, **30**) are also known from the literature. The yields, physical and spectroscopic data of all the above-mentioned products are available in the deposited Supplementary Data.

Metallation (general procedure)

A 1-(substituted phenyl)pyrrole **4**–**6**, **9**–**11**, **18**–**20** (10.0 mmol) and the activating agent (10.0 mmol, TMEDA: 1.16 g; PMDTA: 1.73 g, or the double amount) were dissolved in dry THF or diethyl ether (25.0 ml) and cooled to 0 or −75 °C. Buthyllithium (11.0 mmol; 7.3 ml or the double amount) in hexane was added dropwise to the solution. When LiTMP was used as a base, it was prepared from TMP (13.0 mmol, 1.83 g) and butyllithium (11.0 mmol, 7.3 ml) before addition of the model compound. The reaction mixture was stirred for 60 min (in the case of **6** 15 min), then was poured into a solid CO_2–diethyl ether slurry. At 20 °C, 20 ml of water was added, the phases were separated, and the aqueous solution was washed with diethyl ether (3 × 15 ml). The aqueous solution was acidified with 10% aq. citric acid. The product precipitated from the solution in the form of an oil or as crystals. In the case of the oil the aqueous phase was extracted with dichloromethane (3 × 25 ml). The collected dichloromethane solutions were dried over sodium sulfate and concentrated *in vacuo*. The residue was treated with hexane to give crystalline material. The yields and compositions are given in Tables 1 and 2. Analytical samples of the products were recrystallized; the type of solvent is given below. When D_2O was the electrophile, the organic phase of the reaction mixture was collected after hydrolysis, then was dried, and concentrated *in vacuo*. The position of the inserted deuterium was observed by ^1H NMR spectroscopy.

1-(4-Bromo-3-carboxyphenyl)pyrrole 21. Mp 138–142 °C (from hexane) (Found: C, 49.61; H, 3.12; N, 5.17. $C_{11}H_8BrNO_2$ requires C, 49.65; H, 3.03; N, 5.26%); ν_{max}(KBr)/cm^{-1} 3446 (OH), 1710, 1648 (CO); δ_H($CDCl_3$) 6.38 (2H, t, J 1.9, β- + β′-H), 7.10 (2H, t, J 1.9, α- + α′-H), 7.42 (1H, dd, J 8.6, 2.5, 6-H), 7.75 (1H, d, J 8.6, 5-H), 8.03 (1H, d, J 2.5, 2-H).

1-(3-Carboxy-2-chlorophenyl)pyrrole 7. Mp 156–157 °C (from dichloromethane) (Found: C, 59.63; H, 3.71; N, 6.48. $C_{11}H_8ClNO_2$ requires C, 59.61; H, 3.64; N, 6.32%); ν_{max}(KBr)/cm^{-1} 3446 (OH), 1696 (CO); δ_H($CDCl_3$) 6.36 (2H, t, J 2.1, β- + β′-H), 6.88 (2H, t, J 2.1, α- + α′-H), 7.43 (1H, t, J 7.9, 5-H), 7.50 (1H, dd, J 7.9, 2.0, 6-H), 7.88 (1H, dd, J 7.9, 2.0, 4-H).

1-(4-Carboxy-3-chlorophenyl)pyrrole 13. Mp 166–168 °C (from dichloromethane–hexane) (Found: C, 59.62; H, 3.61; N, 6.32. $C_{11}H_8ClNO_2$ requires C, 59.61; H, 3.64; N 6.32%); ν_{max}(KBr)/cm^{-1} 3446 (OH), 1708 (CO); δ_H($CDCl_3$) 6.40 (2H, t, J 2.0, β- + β′-H), 7.15 (2H, t, J 2.0, α- + α′-H), 7.36 (1H, dd, J 8.9, 2.5, 6-H), 7.52 (1H, d, J 2.5, 2-H), 8.10 (1H, d, J 8.9, 5-H).

1-(2-Carboxy-4-chlorophenyl)pyrrole-2-carboxylic acid 26. Mp 173–174 °C (from chloroform) (Found: C, 54.32; H, 3.03; N, 5.27. $C_{12}H_8ClNO_4$ requires C, 54.26; H, 3.04; N, 5.27%); ν_{max}(KBr)/cm^{-1} 3445 (OH), 1706 (CO); δ_H(DMSO-d_6) 6.25 (1H, dd, J 4.0, 2.4, β′-H), 6.90 (1H, dd, J 4.0, 1.8, β-H), 7.04 (1H, t-like dd, J 2.4, 1.8, α-H), 7.36 (1H, d, J 8.7, 6-H), 7.68 (1H, dd, J 8.7, 2.5, 5-H), 7.85 (1H, d, J 2.5, 3-H).

1-(3-Carboxy-2-methoxyphenyl)pyrrole 8. Mp 104–106 °C (from hexane) (Found: C, 66.26; H, 5.11; N, 6.38. $C_{12}H_{11}NO_3$ requires C, 66.33; H, 5.11; N, 6.45%); ν_{max}(KBr)/cm^{-1} 3434 (OH), 1693 (CO); δ_H($CDCl_3$) 3.49 (3H, s, OMe), 6.40 (2H, t, J 2.1, β- + β′-H), 7.03 (2H, t, J 2.1, α- + α′-H), 7.35 (1H, t, J 7.9, 5-H), 7.59 (1H, dd, J 7.8, 2.0, 6-H), 8.18 (1H, dd, J 8.0, 2.0, 4-H).

1-(2-Methoxy[3-^{2}H]phenyl)pyrrole. Oil, δ_H($CDCl_3$) 3.81 (3H, s, OMe), 6.30 (2H, t, J 2.0, β- + β′-H), 6.99 (2H, t, J 2.0, α- + α′-H), 7.00 (1H, t, J 7.8, 5-H), 7.27 (1H, dd, J 7.8, 1.7, 4-H), 7.30 (1H, dd, J 7.8, 1.7, 6-H).

1-(4-Carboxy-3-methoxyphenyl)pyrrole 15. Mp 118–120 °C (from hexane) (Found: C, 66.38; H, 5.15; N, 6.43. $C_{12}H_{11}NO_3$ requires C, 66.33; H, 5.11; N, 6.45%); ν_{max}(KBr)/cm^{-1} 3433 (OH), 1710 (CO); δ_H($CDCl_3$) 4.04 (3H, s, OMe), 6.39 (2H, t-like m, J 2.0, β- + β′-H), 6.92–7.20 (4H, m, 2-, 6-, α- + α′-H), 8.19 (1H, d, J 7.8, 5-H).

1-(2-Carboxy-3-methoxyphenyl)pyrrole-2-carboxylic acid 17. Mp 146–148 °C (from chloroform–hexane) (Found: C, 59.73; H, 4.30; N, 5.45. $C_{13}H_{11}NO_5$ requires C, 59.77; H, 4.24; N, 5.36%); ν_{max}(KBr)/cm^{-1} 3428 (OH), 1713, 1654 (CO); δ_H(DMSO-d_6) 3.85 (3H, s, OMe), 6.19 (1H, dd, J 3.9, 2.8, β′-H), 6.75 (1H, dd, J 3.9, 2.0, β-H), 6.82 (1H, d, J 7.7, 4-H), 6.88 (1H, dd, J 2.8, 2.0, α′-H), 7.13 (1H, d, J 7.7, 6-H), 7.36 (1H, t, J 7.7, 5-H).

1-(2-Carboxy-4-methoxyphenyl)pyrrole-2-carboxylic acid 29. Mp 171–172 °C (from chloroform–hexane) (Found: C, 59.82; H, 4.31; N, 5.43. $C_{13}H_{11}NO_5$ requires C, 59.77; H, 4.24; N, 5.36%); ν_{max}(KBr)/cm^{-1} 3430 (OH), 1686, 1654 (CO);

δ_H(DMSO-d_6) 3.83 (3H, s, OMe), 6.19 (1H, dd, *J* 3.5, 2.9, β′-H), 6.88 (1H, dd, *J* 3.5, 1.9, β-H), 6.96 (1H, dd, *J* 2.9, 1.9, α′-H), 7.15 (1H, dd, *J* 8.2, 3.0, 5-H), 7.23 (1H, d, *J* 8.2, 6-H), 7.35 (1H, d, *J* 3.0, 3-H).

Synthesis of 8-chloro-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepine[2] 30

A solution of **26** (3.8 mmol, 0.84 g) in THF (10 ml) was added dropwise to a suspension of lithium aluminium hydride (9.4 mmol, 0.35 g) in THF (30 ml) at 0 °C. The mixture was stirred for 30 min at 0 °C, then for 10 h at 25 °C. After addition of distilled water (2 ml) the THF solution was decanted and the precipitate was washed with diethyl ether (4 × 20 ml). The collected organic phases were dried and the solvent was evaporated *in vacuo*. The oily residue was crude diol 1-[4-chloro-2-(hydroxymethyl)phenyl]-2-(hydroxymethyl)pyrrole[2] (yield 90%). The diol (3.4 mmol, 0.81 g) was dissolved in toluene (16 ml), silica gel (3 g) was added to the solution, and the mixture was stirred at 70 °C for 5 h. The reaction mixture was concentrated *in vacuo*. Column chromatography of the residue (silica gel; eluent: hexane–ethyl acetate 4 : 1) gave tricycle **30** as an oil (0.41 g, 55%).[2]

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