Preparation of 5-unsubstituted 4-formylpyrrole-2-carboxylates and conversion to cycloalkano-oligopyrroles †

Yumiko Fumoto,[a] Hidemitsu Uno,[b] Satoshi Ito,[a] Yuka Tsugumi,[a] Maki Sasaki,[a] Yukiko Kitawaki[a] and Noboru Ono *[a]

[a] *Department of Chemistry, Faculty of Science, Ehime University, Matsuyama 790-8577, Japan. Fax: +81(89)9279590. E-mail: ononbr@dpc.ehime-u.ac.jp*
[b] *Advanced Instrumentation Center for Chemical Analysis, Ehime University, Matsuyama 790-8577, Japan*

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Ethyl 4-formylpyrrole-2-carboxylates were prepared from nitroacetaldehyde dimethyl acetal in 9–50% yields using the Barton–Zard reaction. These formylpyrroles were successfully transformed to cycloalkano-oligopyrroles. The conformation of cyclononatripyrroles in $CDCl_3$ was found to be a crown form based on the NMR analysis, while cyclododecatetrapyrroles were in two interconverting boat and chair conformations.

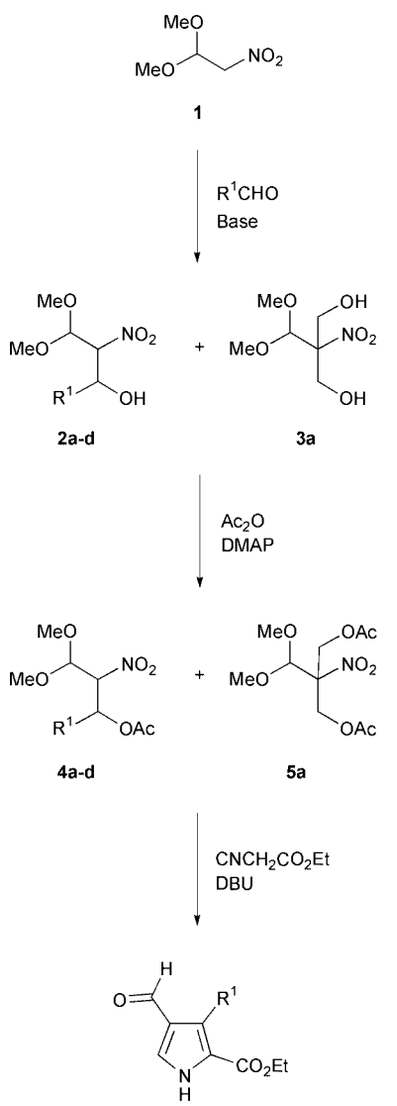
Introduction

Recently, calixarenes,[1] cyclophanes[2] and cyclotriveratrylene derivatives[3] have been extensively studied as host molecules capable of binding or including neutral, anionic and cationic substances. Their interesting ability to form supramolecular complexes such as caviplexes[4] is expected to reveal new chemical or physical functions. These host molecules are usually prepared by simple oligocyclic condensation of arylmethyl units utilizing the electron-rich nature of phenol, resorcinol and veratrole, respectively. Similarly, pyrroles have been successfully utilized for the construction of host molecules, and the binding ability of the so-called calixpyrroles toward anions, metals and neutral molecules have been extensively studied by Sessler's and Floriani's groups.[5,6] The pyrrole ring is very electron-rich and capable of reacting easily with electrophiles even if the ring is already substituted by an electron-withdrawing group. In contrast to the calixpyrroles, the properties of cycloalkano-oligopyrroles,[7] pyrrole versions of cyclotriveratrylenes, have not been investigated, although macrocyclic oligopyrroles are thought to be promising candidates for the recognition of negatively charged substances by the acidic NH groups and for the formation of caviplexes[4] by the variety in the possible choice of substituents on the pyrrole ring. The slow growth of studies in this area is due to the lack of a reliable method to access the macrocycles: easily accessible α-hydroxymethylpyrroles tend to oligomerize at the α-positions, even if the other α-position is occupied by a substituent, and no simple method for the preparation of α-unsubstituted β-hydroxymethylpyrroles has been reported. Moreover, contrary to the conformation of cyclotriveratrylenes, the reported conformations of cyclononatripyrroles[7a] and cyclononatriindoles[7b] are ambiguous. In this paper, we report an efficient method to access the β-hydroxymethylpyrroles and their oligocyclization leading to cycloalkano-oligopyrroles.

Results and discussion

Preparation of 4-formylpyrrole-2-carboxylates 6

Since hydroxymethyl- and alkoxymethyl-pyrroles are thought to be unstable, the corresponding formylpyrroles were chosen as the first target compounds. The Barton–Zard pyrrole synthesis[8] was used for the preparation of the 4-formylpyrroles (Scheme 1). The starting material, nitroacetaldehyde dimethyl



Scheme 1 **a**: R^1 = H; **b**: R^1 = Me; **c**: R^1 = Ph; **d**: R^1 = *p*-BrC_6H_4.

† Experimental procedures for the preparation of compounds **6a**, **6b**, **6d**, **10b**, **10d**, **11b** and **11d** are available as supplementary data. For direct electronic access see http://www.rsc.org/suppdata/p1/b0/b003360j/

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Table 1 Synthesis of 4-formylpyrrole-2-carboxylates **6**

Comp.	R^1	Nitro aldol reaction conditions	Yield of **6** (%)[a]
a	H	A	9
b	Me	B	50
c	Ph	C	31
d	*p*-BrC_6H_4	C	13

[a] The yield was based on the starting nitro acetal **1**.

acetal (**1**), was readily prepared from methyl orthoformate and nitromethane by the reported procedure.[9] The nitro acetal **1** easily reacted with acetaldehyde with the aid of Amberlyst A-21 (condition B)[10] to give the β-nitro alcohol **2b** in 83% yield. A similar reaction of **1** with formalin using Et_3N gave a mixture of the desired **2a** and bishydroxymethylated by-product **3a**. Since the presence of **3a** did not interfere with the following reactions, this mixture was used without separation and the calculated yield of **2a** was 50%. On the other hand, poor results were obtained in the reaction of **1** with aromatic aldehydes under similar conditions. After several trials, use of Et_3N, TBSCl, and TBAF was found to be effective.[11] Thus, the reaction of **1** with benzaldehyde and *p*-bromobenzaldehyde gave β-nitro alcohols **2c** and **2d** in 56% and 35% yield, respectively (condition C).

β-Nitro alcohols **2a–d** were transformed to β-acetoxy nitro compounds **4a–d** by acetylation with Ac_2O in the presence of DMAP. The acetoxy nitro compounds **4b–d** reacted with ethyl isocyanoacetate in the presence of DBU to give 4-formylpyrrole-2-carboxylates **6b–d** in good yields after acidic work-up (Scheme 1, Table 1). In the reaction of **4a**, however, the corresponding pyrrole **6a** having no substituent at the 3-position was obtained in lower yield than in other cases. A similar difficulty was reported in preparations of 3-unsubstituted pyrroles by the Barton–Zard method.[8]

Reaction of ethyl 4-formylpyrrole-2-carboxylates 6

The formyl group at the 4-position of the pyrroles was easily converted to a hydroxymethyl group in quantitative yields by treatment with $NaBH_4$ in THF at 0 °C (Scheme 2). When 4-hydroxymethylpyrrole **7c** was treated with toluene-*p*-sulfonic acid in the presence of ethanol and thiophenol, dehydration followed by nucleophilic attack occurred to give 4-ethoxymethyl- and 4-phenylthiomethyl-pyrroles **8** and **9** in 79% and 62% yields, respectively. On the other hand, when the 4-(hydroxymethyl)pyrroles **7b–d** were treated with toluene-*p*-sulfonic acid in the absence of a nucleophile, oligocyclization took place to give mixtures of cyclononatripyrroles **10b–d**, cyclododecatetrapyrroles **11b–d** and a small amount of by-products. Separation of the macrocycles **10** and **11** was problematic. To our surprise, the macrocycles **10** and **11** could not be separated either preparative gel permeation chromatography (GPC) or recrystallization. For **10c** and **11c** only, separation of these two macrocycles was achieved by repeated column chromatography. Pure **10c** and **11c** were obtained in 58% and 7% yields, respectively.

Conformational consideration of cycloalkano-oligopyrroles

In the NMR spectrum of **10c** in $CDCl_3$ at 27 °C, the three pairs of methylene protons appeared at δ 3.55 and δ 3.98 as a pair of doublets (AB-quartet), which did not coalesce even at 50 °C, and only one set of resonances for the ethyl ester and phenyl groups was observed. These facts suggest that this macrocycle exists in one rigid conformation, where each of the ester and phenyl groups is equivalent. Therefore, the macrocycle is deduced to be in the crown conformation with C_3 symmetry. The macrocycle, of course, exists as a mixture of enantiomers, one of which is shown in Fig. 1. Although the precise $\Delta H^{\ddagger}$

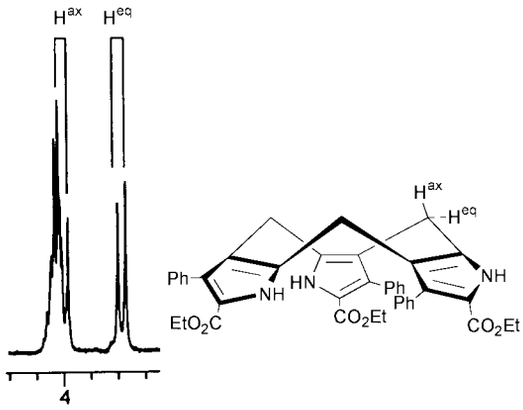
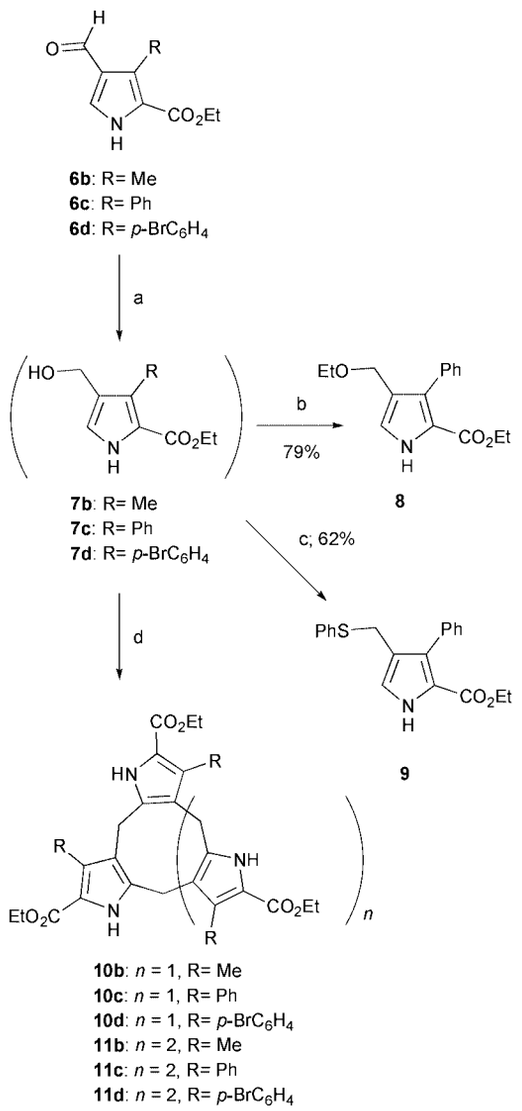


Fig. 1 The methylene proton region of the ^1H NMR spectrum of **10c** at 50 °C in $CDCl_3$ and the crown conformation of cyclononatripyrrole **10c**.



Scheme 2 *Reagents*: a, $NaBH_4$, EtOH; b, EtOH, *p*-TsOH, $CHCl_3$; c, PhSH, *p*-TsOH, $CHCl_3$; d, *p*-TsOH, $CHCl_3$.

value for the ring flipping could not be estimated, the value was far in excess of 63 kJ mol^{-1}. A similar NMR behaviour was reported for tribenzocyclononanes and the crown motif was confirmed.[12] The $\Delta H^{\ddagger}$ for the conformational barrier was reported to be *ca.* 108–117 kJ mol^{-1}.[13] On the other hand, unambiguous conformational determination was not possible from the reported data for the cyclononatripyrroles obtained by the condensation of 3,4-unsubstituted pyrroles with formalin, because the signal due to the methylene protons was reported to

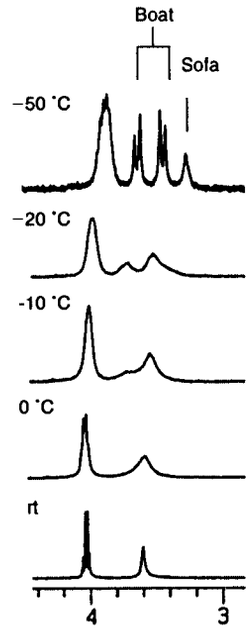


Fig. 2 The ^{1}H NMR spectra of methylene protons of cyclododecatetrapyrrole **11c** in CD_2Cl_2 at the indicated temperatures.

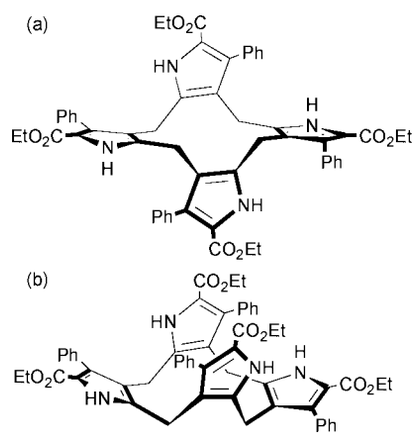


Fig. 3 (a) Chair and (b) boat conformations of cyclododecatetrapyrrole **11c**.

be a broad singlet even at −40 °C. This differing NMR behaviour could be due to the difference in the substitution pattern on the pyrrole ring.

In contrast to the rigid macrocycle **10c**, the methylene absorption of **11c** appeared as a rather broader singlet (δ 3.60) at room temperature in CD_2Cl_2, and this signal became broader as the temperature was lowered (Fig. 2). At −50 °C, two conformers were observed and the methylene protons appeared as a pair of doublets (δ 3.64 and δ 3.81) and a new broad singlet. The coalescence temperature between the two conformers was *ca.* −20 °C in $CDCl_3$ and −10 °C in CD_2Cl_2. The integral ratios of the methylene signals at −50 °C were *ca.* 3:2 in $CDCl_3$ and 6:1 in CD_2Cl_2. The ΔG values between the two conformers at −40 °C in $CDCl_3$ and CD_2Cl_2 were 0.79 and 3.47 kJ mol^{-1}, respectively. The new broad singlet signal did not coalesce even at −90 °C in CD_2Cl_2. These facts suggest that there are two stable conformations of macrocycle **11c** in $CDCl_3$ and CD_2Cl_2 (Fig. 3). The structures of similar tetrabenzocyclododecanes have been fully explored by ^{1}H NMR analysis.[14] Dodecamethoxytribenzocyclododecane exists as two conformers, boat and chair conformers, in $CDCl_3$ and $C_6D_5NO_2$ even at 25 °C. The aromatic protons in each conformer appeared as a pair of singlets in both solvents. The equilibrium concentration of the boat and chair (sofa) conformers depended on the solvent polarity. The boat conformation has C_2 symmetry and the chair conformation has C_i. In **11c**, the chair conformer should be less polar because the dipolar moments of the functional groups are counterbalanced with each other. The more stable conformation whose equilibrium concentration increases in CD_2Cl_2 (more polar than $CDCl_3$) would be a boat form in which the methylene protons appeared as a pair of doublets at the low temperature.

Conclusion

We report an efficient synthesis of 4-formylpyrroles **6a**–**d** *via* Barton–Zard reaction, which are difficult to prepare by other methods. The conformation of macrocycle **10c** in $CDCl_3$ is, as expected, the locked crown form with C_3 symmetry. Since the inversion energy is calculated to be over 63 kJ mol^{-1} by ^{1}H NMR analysis, it appears that the chirality of macrocycle **10c** is stable enough for the macrocycle to be a promising candidate for recognition of chiral molecules. On the other hand, the macrocycle **11c** exists as two interconverting boat and chair conformers at −50 °C.

Experimental

Unless otherwise noted, NMR spectra were obtained with a JEOL GSX-270 or JMN-400 spectrometer at ambient temperature by using $CDCl_3$ as solvent and TMS as internal standard for ^{1}H and ^{13}C. *J* Values are given in Hz. Mass spectra and HRMS were measured with a Hitachi M80B-LCAPI spectrometer under the following ionizing conditions (20 eV for EI and 70 eV for HRMS, high boiling perfluorokerosine as a standard). Column chromatography and TLC were carried out using C-200 (Wakogel) and Kieselgel 60 F254 (Merk), respectively. Tetrahydrofuran was distilled from sodium benzophenone ketyl under an inert atmosphere. Chloroform was washed with water to remove EtOH, dried with Na_2SO_4 and distilled from CaH_2 under an inert atmosphere. EtOH was distilled from CaH_2 under an inert atmosphere. Other commercially available materials were used without further purification. Ethyl isocyanoacetate was prepared from ethyl *N*-formylglycinate using $POCl_3$ and triethylamine.[15] Nitro acetal **1** was prepared from nitromethane and orthoformate according to the literature procedure as a pale yellow liquid: 63–65 °C (10 mmHg).[9] Experimental procedures for the preparation of **6a**, **6b**, **6d**, **10b**, **10d**, **11b** and **11d** are given in the Supplementary data.

Ethyl 4-formyl-3-phenylpyrrole-2-carboxylate (6c)

To a stirred solution of $Bu_4NF{\cdot}3H_2O$ (7.5 mL, 7.5 mmol) in THF (12 mL) at 0 °C were sequentially added nitro compound **1** (4.05 g, 30 mmol), benzaldehyde (2 mL, 20 mmol), Et_3N (2.8 mL, 20 mmol) and a solution of ^{t}BuMe$_2$SiCl (4.5 g, 30 mmol) in THF (20 mL). After 2 h, the reaction mixture was filtered through a Celite pad, which was washed with EtOAc (3 × 50 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with water (5 × 50 mL) and brine (30 mL), dried over Na_2SO_4 and concentrated. The residue was chromatographed on silica gel (20%, EtOAc–hexane) to give 4.49 g (62%) of crude 1,1-dimethoxy-2-nitro-3-phenylpropan-3-ol (**2c**) as an orange liquid: ν_{max}(neat)/cm^{-1} 3471, 2941, 2841 and 1554; δ_H 3.13 (d, 1H, J = 8.3, major isomer), 3.43 (s, 3H, major isomer), 3.44 (s, 3H, minor isomer), 3.45 (s, 3H, major isomer), 3.47 (s, 3H, minor isomer), 3.62 (d, 1H, J = 1.9, minor isomer), 4.50 (d, 1H, J = 7.3, minor isomer), 4.70 (m, 1H, both isomers), 5.03 (d, 1H, J = 7.3, major isomer), 5.13 (dd, 1H, J = 7.3, 1.9, minor isomer) and 5.26 (dd, 1H, J = 8.3, 4.2, major isomer); δ_C 54.6, 54.9, 55.6, 55.9, 71.9, 73.2, 91.1, 92.1, 101.9, 103.2, 125.6, 126.9, 128.6, 128.7, 128.8 and 129.1.

To a stirred solution of the crude nitro alcohol **2c** (4.49 g, 18.6 mmol) in THF (10 mL) were added acetic anhydride (1.8 mL) and DMAP (0.01 g) at 0 °C. The mixture was warmed to

10 °C and stirred for 18 h. Aqueous saturated $NaHCO_3$ (10 mL) and EtOAc (20 mL) were added. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with water (2 × 20 mL) and brine (20 mL), dried over Na_2SO_4 and concentrated to give 4.06 g (77%) of crude 1-acetoxy-3,3-dimethoxy-2-nitro-1-phenylpropane (**4c**) as a yellow oil: ν_{max}(neat)/cm^{-1} 2939, 2841, 1753 and 1558; δ_H 2.07 (s, 3H, major isomer), 2.15 (s, 3H, minor isomer), 3.23 (s, 3H, major isomer), 3.37 (s, 3H, minor isomer), 3.38 (s, 3H, major isomer), 3.42 (s, 3H, minor isomer), 4.58 (d, 1H, J = 6.8, major isomer), 4.65 (d, 1H, J = 7.8, minor isomer), 4.99 (dd, 1H, J = 7.8, 6.8, major isomer), 5.10 (dd, 1H, J = 7.8, 6.0 minor isomer), 6.26 (d, 1H, J = 6.0, minor isomer), 6.29 (d, 1H, J = 7.8, major isomer) and 7.37 (m, 5H); δ_C (typical signals) 20.8, 20.9, 54.6, 55.8, 55.03, 56.0, 72.0, 72.8, 88.5, 90.3, 101.1, 101.5, 153.1, 154.6, 155.0, 155.8, 156.0, 169.0 and 169.9.

To a stirred solution of the crude β-nitro acetate **4c** (4.06 g, 14.3 mmol) in anhydrous THF (20 mL) were added dropwise ethyl isocyanoacetate (1.5 mL, 14.5 mmol) and DBU (4.1 mL, 29 mmol) at 0 °C. After the mixture was warmed to 10 °C and stirred for 18 h, 1 mol L^{-1} HCl (10 mL) and $CHCl_3$ (10 mL) were added. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (3 × 20 mL). The combined organic layers were washed with saturated $NaHCO_3$ (20 mL), water (3 × 20 mL) and brine (20 mL), dried over Na_2SO_4 and concentrated. The residue was chromatographed on silica gel (10%, EtOAc–hexane) to give crude **6c**. Recrystallization from EtOAc–hexane afforded 1.91 g (55%) of pure **6c** as yellow crystals: mp 83–84 °C; ν_{max}(neat)/cm^{-1} 3268 and 1672; δ_H 1.15 (t, 3H, J = 7.1), 4.2 (q, 2H, J = 7.1), 7.4 (m, 5H), 7.65 (d, 1H, J = 3.4) and 9.65 (s, 1H); δ_C 14.0, 60.8, 120.6, 125.1, 126.1, 127.7, 127.9, 130.7, 131.5, 133.1, 160.6 and 187.0; MS (EI) 243 (M$^+$, 67%), 196 (100) and 169 (89). Anal. Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.23; H, 5.49; N, 5.82%.

Ethyl 4-ethoxymethyl-3-phenylpyrrole-2-carboxylate (8)

To a stirred solution of the formyl pyrrole **6c** (100 mg, 0.41 mmol) in EtOH (8 mL) was added $NaBH_4$ (150 mg, 4 mmol) at 0 °C. After 3 h, 1 mol L^{-1} HCl was added (pH = 7–8) and then $CHCl_3$ (20 mL) was added. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (3 × 10 mL). The combined organic layers were washed with saturated $NaHCO_3$ (20 mL), water (3 × 10 mL) and brine (30 mL), dried over Na_2SO_4 and concentrated to give crude ethyl 4-hydroxymethyl-3-phenylpyrrole-2-carboxylate (**7c**). To a stirred solution of crude **7c** in EtOH (1 mL) was added *p*-TsOH (16.0 mg). After 11 h, water (10 mL) and $CHCl_3$ (20 mL) were added. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (3 × 30 mL). The combined organic layers were washed with saturated $NaHCO_3$ (20 mL), water (3 × 10 mL) and brine (20 mL), dried over Na_2SO_4 and concentrated. The residue was chromatographed on silica gel (20%, EtOAc–hexane) to give 69 mg (62%) of **8** as a yellow oil: mp 65 °C; ν_{max}(neat)/cm^{-1} 3309, 2954, 2885 and 1689; δ_H 1.17 (t, 3H, J = 6.8), 1.21 (t, 3H, J = 6.8), 3.44 (q, 2H, J = 6.8), 4.16 (q, 2H, J = 6.8), 4.24 (s, 2H), 6.99 (d, 1H, J = 2.9), 7.37 (m, 5H) and 9.61 (br s, 1H); δ_C 13.9, 15.1, 60.0, 63.9, 65.2, 119.0, 122.0, 122.2, 126.8, 127.2, 130.4, 131.1, 133.9 and 161.3; MS (EI) 273 (M$^+$, 54%), 244 (46), 229 (62), 198 (530, 182 (100) and 154 (45); HRMS calcd for M$^+$ ($C_{16}H_{19}NO_3$): 273.1365, found 273.1351.

Ethyl 3-phenyl-4-(phenylthiomethyl)pyrrole-2-carboxylate (9)

To a stirred solution of crude **7c** prepared from the formyl pyrrole **6c** (100 mg, 0.41 mmol) as above in anhydrous $CHCl_3$ (1 mL) was added thiophenol (0.04 mL, 0.4 mmol) in the presence of *p*-TsOH (16.0 mg). After the mixture was refluxed for 18 h, water (10 mL) and $CHCl_3$ (20 mL) were added. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (3 × 10 mL). The combined organic layers were washed with saturated $NaHCO_3$ (20 mL), water (3 × 10 mL) and brine (20 mL), dried over Na_2SO_4 and concentrated. The residue was chromatographed on silica gel ($CHCl_3$) to give crude **9**. Recrystallization from EtOAc–hexane afforded 86 mg (62%) of pure **9** as yellow crystals: mp 65 °C; ν_{max}(KBr)/cm^{-1} 3304, 2980, 1672 and 1292; δ_H 1.11 (t, 3H, J = 7.1), 3.90 (s, 2H), 4.14 (q, 2H, J = 7.33), 6.86 (d, 1H, J = 2.9), 7.27 (m, 10H) and 9.21 (br s, 1H); δ_C 14.0, 29.2, 60.1, 119.1, 120.8, 121.4, 126.1, 127.0, 127.6, 128.7, 129.6, 130.4, 130.7, 133.8, 136.6 and 161.0; MS (EI) 228 (M$^+$, 100%), 182 (98) and 154 (28). Anal. Calcd for $C_{20}H_{18}NO_2S$: C, 71.19; H, 5.68; N, 4.15. Found: C, 70.64; H, 5.81; N, 4.06%.

Triethyl 3,7,11-triphenylcyclonona[1,2-*b*:4,5-*b*′:7,8-*b*″]tripyrrole-2,6,10-tricarboxylate (10c) and tetraethyl 3,7,11,15-tetraphenylcyclododeca[1,2-*b*:4,5-*b*′:7,8-*b*″:10,11-*b*‴]tetrapyrrole-2,6,10,14-tetracarboxylate (11c)

To a stirred solution of crude **7c** prepared from the formyl pyrrole **6c** (100 mg, 0.41 mmol) as above in anhydrous $CHCl_3$ (1 mL) was added *p*-TsOH (16.0 mg). After for 18 h, water (10 mL) and $CHCl_3$ (20 mL) were added. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (3 × 10 mL). The combined organic layers were washed with saturated $NaHCO_3$ (20 mL), water (3 × 10 mL) and brine (20 mL), dried over Na_2SO_4 and concentrated. The residue was chromatographed on silica gel (20%, EtOAc–hexane) to give 77 mg (83%) of **10c** and 7 mg (7%) of **11c**. Recrystallization of both materials from EtOAc–hexane afforded pure **10c** and pure **11c**. **10c**: colorless crystals; mp 203–205 °C; ν_{max}(KBr)/cm^{-1} 3577, 2960 and 1678; δ_H 1.07 (t, 9H, J = 7.2), 3.55 (d, 3H, J = 15.1), 3.98 (d, 3H, J = 15.1), 4.05 (q, 6H, J = 7.2), 4.06 (m, 15H) and 7.72 (br s, 3H); MS (EI) 681 (M$^+$, 100%) and 608 (7). **11c**: colorless crystals; mp >300 °C; ν_{max}(KBr)/cm^{-1} 3440, 2979 and 1687; δ_H 1.10 (t, 12H, J = 6.8), 3.58 (br s, 8H), 4.07 (q, 8H, J = 6.8), 7.28 (m, 20H) and 7.99 (br s, 4H); MS (EI) 908 (M$^+$, 68%), 666 (100) and 241 (23). Anal. Calcd for $(C_{14}H_{13}NO_2)_n$ (mixture of **10c** and **11c**): C, 73.99; H, 5.77; N, 6.16. Found: C, 73.70; H, 6.00; N, 5.99%.

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