6060 *J. Org. Chem.* **1997,** *62,* 6060−6063

Synthesis and Diatropicity of *trans-N*-Cyclohexyl-2′,5′,10b,10c-tetramethylpyrrolo[3,4-*e*]-10b,10c-dihydropyrene. The First Example of an Iso[17]annulenopyrrole

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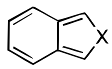
Received March 10, 1997

Aromaticity is a fundamental concept discussed in many aspects of chemistry.[1−3] The general criteria for heteroaromaticity are, however, not fully defined, although many qualitative and quantitative approaches have been reported to describe the aromatic character in heterocyclic compounds.[3−5] Contradictory results are sometimes observed among different theoretical approaches. Reports[6] based on the discussion of resonance energy, for example, indicate that the order of decrease in aromaticity is accepted as thiophene > pyrrole > furan. More recently, Bird's heteroaromaticity index[7] and Katritzky's independent "classical" and "magnetic" aromaticity scales,[8] however, strongly suggest that pyrrole is more aromatic than thiophene.

The fusion of these 5-membered heterocycles at their 3,4-positions to unsaturated carbocycles (*i.e*, isoannelation)[9] is also of special interest. Theoretical estimations of the topological resonance energy per π-electron have been reported[10] for several linear heteropolycycles to correlate their "percentage benzene character per π-electron". In each series of **1**, **2**, and **3**, nitrogen is shown to be the most effective heteroatom resulting in the most aromatic heteropolycycle. Oxygen is always the least ideal. None of the members of the 18π **3** has been isolated, and thus, the above order of aromaticity could not be verified experimentally. The syntheses of iso[17]annulenofuran[11] **4**[12] and iso[17]annulenothiophene[11] **5**[13] have, however, been reported. The difference in chemical shifts between the internal and external protons of **4** and **5** are <0.35 ppm, indicating that there is hardly any detectable ring current (aromatic character) in these systems. The bisdehydroiso[17]annulenofuran **6**[14] and iso[17]annulenofurans **7**[15] and **8**[16] on the other hand show experimentally observable diatropicity (aromaticity). It is apparent that an isoannelated heterocycle should be held geometrically rigid to maximize the extent of π-delocalization, thus allowing its diatropicity (aromaticity) to be investigated effectively. Going from **7** to **8** results in a decrease in diatropicity due to unfavorable steric interactions and, thus, a deviation from molecular planarity, with the external methyl groups located in the bay regions in **8**. The iso[17]annulenofuran **8** exhibits only <7% of the ring current observed in the parent [14]annulene **12**.[16] Before this work, there was no known example of an iso[17]annulenopyrrole.[11] It would thus be interesting to determine experimentally whether a significant increase in diatropicity (aromaticity) is observed going from **8** to **10** (or a derivative) similar to that predicted theoretically going from **3a** to **3c**. We wish to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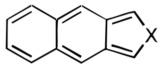
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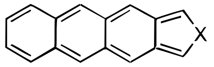
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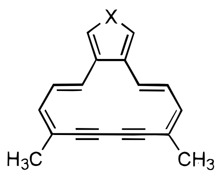
b, X = S
c, X = NH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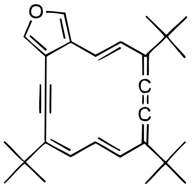
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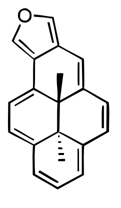
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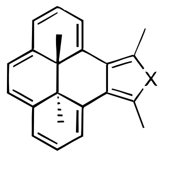
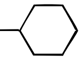

8, X = O
9, X = S
10, X = NH
11, X = N—

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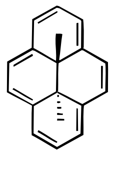
describe in this paper the synthesis and diatropicity of the iso[17]annulenopyrrole **11**.

Results and Discussion

(a) Synthesis. 2,5-Diarylfurans are known to undergo acid-catalyzed hydrolysis to afford the corresponding 1,4-diketones, which could be cyclized again to form either 2,5-diarylthiophenes or 2,5-diarylpyrroles.[17] A potential route to the pyrrole-annelated thiacyclophane **15**, and perhaps the thiophene-annelated thiacyclophane **14**, was using the furan-annelated thiacyclophane **13**[16] as a precursor. In all our attempts, compound **13** was, however, very resistant to hydrolysis and failed to yield the 1,4-diketone **17**. Treatment of the reported 1,4-diketone **18**[16] with either P_2S_5[18] or sulfur melt[19] surprisingly yielded the furan **19** instead of the thiophene **20**. The sulfur-containing reagents served as a dehydrating agent but failed to achieve deoxygenation.[19] Reaction of **18** with ammonium acetate gave a low yield of the pyrrole **21**. An attempt to convert the dichloride **21** to a dinitrile (for subsequent functional transformations, see the later discussion on **22**) by the von Braun reaction[20] was, however, unsuccessful due to thermal decomposition resulting in noncharacterizable products.



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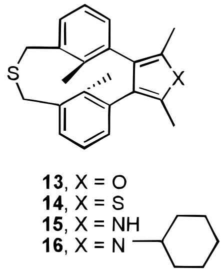
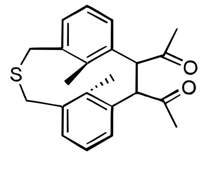


13, X = O
14, X = S
15, X = NH
16, X = N



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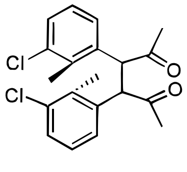

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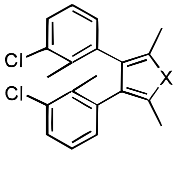
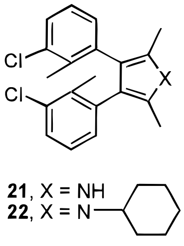
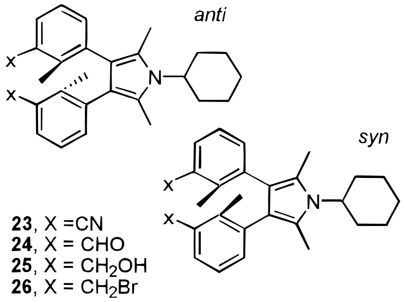


19, X = O
20, X = S



21, X = NH
22, X = N

Protection of the NH function in **21** was thus required. Treating the diketone **18** in cyclohexylamine, which has a sufficiently high boiling point, gave the diarylpyrrole **22** in a high yield. Conversion of **22** to **26** was achieved with minor modifications via a similar sequence of reactions reported for the syntheses of the corresponding diarylfurans.[16] The optimized overall yield of dibromide **26** was about 30%. The existence of *anti* and *syn* conformers in this series of compounds is evident by the resolution of the corresponding pairs of methyl groups on the pyrrole and/or benzene rings. A study of the rotation barriers in these compounds will be discussed later.



23, X =CN
24, X = CHO
25, X = CH_2OH
26, X = CH_2Br

The methyl protons on the pyrrole rings (see later discussion on assignment) of **26** appear as two singlets at δ 2.05 and 2.11 in a 1:1 ratio. An intramolecular coupling reaction of **26** using sodium sulfide under high dilution conditions[21] led to the isolation of only a low yield (20%) of the *anti*-thiacyclophane **16** with no detectable amount of the corresponding *syn* isomer. The *anti* stereochemistry of **16** is supported by a high-field signal at δ 0.89 for the internal methyl protons shielded by the opposite benzene rings.

A Wittig rearrangement of **16** in the presence of *n*-butyllithium followed by methyl iodide quench gave the ring-contracted product **27** in high yield (96%). The *anti* stereochemistry is again confirmed by a shielded signal at δ 0.58 for the internal methyl protons. The pseudoequatorial stereochemistry of the methylsulfanyl group is suggested by the absence of deshielding of the adjacent methyl protons on the benzene ring, thus the unresolved signal for all six internal methyl protons. Remethylation of **27** with dimethoxycarbonium fluoroborate provided the corresponding sulfonium salt, which when treated with potassium *tert*-butoxide at room temperature afforded compound **28**. The structure of **28** is supported by a shielded signal at δ 1.23 and a singlet at δ 6.41 for the internal methyl and bridge-olefinic protons, respectively. The first example of an iso[17]annulenopyrrole, namely compound **11**, was then obtained by irradiation of a solution of **28** in thoroughly degassed benzene with UV light at 254 nm. A purple solution was obtained after irradiation for 1 h, and the presence of **11** was clearly indicated by two new singlets at δ −0.42 (internal methyl protons) and 2.82 (external methyl protons) in a 1:1 ratio

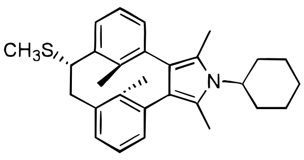


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Table 1. Proton Chemical Shifts of the Internal and External Methyl Protons in Compounds 22−26 in $CDCl_3$ and $C_6D_5NO_2$

	in $CDCl_3$		in $C_6D_5NO_2$	
compd	protons A[a]	protons B[b]	protons A[a]	protons B[b]
22	2.02, 2.07	2.17, 2.10	2.17, 2.15	2.25, 2.19
23	2.11, 2.03	2.31, 2.19	2.20, 2.18	2.41, 2.34
24	2.12, 2.09	2.46, 2.32	2.21, 2.19	2.58, 2.51
25	2.03, 1.98	2.10	2.18, 2.12	2.27, 2.22
26	2.11, 2.05	2.13	2.17, 2.15	2.26, 2.24

[a] Methyl protons on pyrrole. [b] Methyl protons on benzene.

in the ^{1}H NMR spectrum of the mixture. A similar spectrum was observed when a solution of **28** was warmed to about 80 °C for several hours. However, no complete conversion of **28** to **11** could be observed under either thermal or photochemical conditions. Decomposition of **11** was apparent in attempts involving longer reaction times.

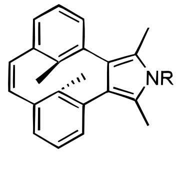
(b) Rotational Barriers. The conformational behavior of 1,2-di-*o*-tolylbenzene and its 3′,3″-disubstituted derivatives has been investigated by dynamic ^{1}H NMR studies.[22] The 3,4-diaryl derivatives of five-membered heteroaromatic rings in principle are expected to involve lower rotational energy barriers than those in the corresponding 1,2-diarylbenzenes. With the presence of the 2,5-dimethyl groups in the pyrrole ring in compounds **22**−**26** the rotational energy barriers in the this series are, however, expected to increase significantly. The methyl signals would serve as good probes for the dynamic ^{1}H NMR studies of **22**−**26**. Assignments of these protons are thus required. The methyl protons on the benzene rings in compounds **22**−**24**, respectively, are expected to be deshielded by the anisotropic effects of the adjacent Cl, CN, and CHO functions. On the other hand, chemical shifts of the methyl protons on the pyrrole ring would be very similar. The methyl proton signals are thus assigned accordingly (Table 1).

An estimation of the energy barrier for the anti $\rightleftharpoons$ syn interconversion process in **22**−**26** could be obtained from the coalescence temperature method.[22,23] The high-temperature ^{1}H NMR studies were carried out using $C_6D_5NO_2$ in which the two pairs of methyl proton signals are resolved in each of the compounds **22**−**26**. An appreciable dependence of the frequency separation ($\Delta\nu$) of the two pairs of methyl signals on temperature was, however, observed. Thus, the chemical shift difference ($\Delta\nu$) at the coalescence temperature (T_c) was calculated by extrapolating a linear plot of the $\Delta\nu$ values observed at *ca.* 75−105 °C where the rate of the site exchange is expected to be slow within the NMR time scale. Although the $\Delta\nu$ values are small in several cases (Table 2), separate analyses of the two pairs of methyl signals could be carried out that collectively should give a reasonably reliable estimation of the transition-state free energy at coalescence, $\Delta G_c^\ddagger$ (Table 2). The energy barriers to rotation in **22**−**26** of 95−100 kJ mol^{-1} (Table 2) are 25−30 kJ mol^{-1} higher than those observed in the corresponding diarylbenzenes **29**.[22] The additional steric effects induced by the 2,5-dimethyl groups on the pyrrole ring going from the transition state **30** to **31** are clearly the key factor resulting in an increase in energy barriers to rotation.

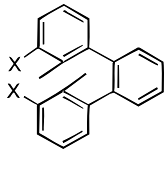
Table 2. Dynamic NMR Data for the Barriers to Rotation in Compounds 22−26

		$\Delta\nu$ at T_c (Hz)[a,b]		T_c (°C)		$\Delta G_c^\ddagger$ (kJ mol^{-1})	
compd	X	A[c]	B[d]	A[c]	B[d]	A[c]	B[d]
22	Cl	1.5	4.8	140	163	97.5 ± 1.5	98.8 ± 0.5
23	CN	1.0	4.1	125	145	95.1 ± 2.4	95.2 ± 0.6
24	CHO	1.5	5.2	142.5	165	98.0 ± 1.5	99.0 ± 0.5
25	CH_2OH	1.5	3.1	143	158	98.1 ± 1.6	99.2 ± 0.8
26	CH_2Br	1.0	0.3	140	140	98.7 ± 2.2	100.3 ± 2.8

[a] Data obtained from spectra determined using ca. 25 mg of sample in 0.5 mL of $C_6D_5NO_2$. [b] Calculated by linear extrapolation to T_c of the chemical shift differences observed at 75−105 °C. [c] Methyl protons on pyrrole. [d] Methyl protons on benzene.



28 ($R = C_6H_{11}$)



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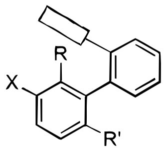

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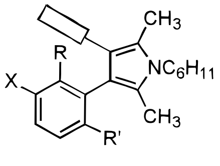

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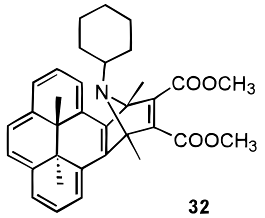
(c) Isoannelation and Diatropicity. The shielded internal methyl protons (δ −0.42) and the deshielded external methyl protons (δ 2.82) are both indicative of an appreciable diamagnetic ring current in the 18π marcroring in **11**. Pyrrole is known to behave as a poor 1,3-diene and only undergoes Diels−Alder reactions with very reactive dienophiles such as benzyne.[24] The isoannelated benzo- and naphthopyrroles **1c** and **2c**, however, form Diels−Alder adducts readily with a series of dienophiles.[25] Treatment of **28** with dimethyl acetylenedicarboxylate in refluxing benzene (during which thermal conversion of **28** to **11** occurred) gave the Diels−Alder adduct **32** in a good yield. The internal methyl protons in **32** appear as two singlets at δ −3.45 and −3.81, indicating a significantly higher diatropicity in the 14π macroring in **32**.



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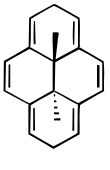

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Qualitatively, there is a large decrease in ring current effect going from **32** or the parent dihydropyrene **12** (δCH_3 = −4.25)[26] to the iso[17]annulenopyrrole **11**. Using **12** and the nonaromatic compound **33** (δCH_3 =

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0.97)[27] as reference systems and assuming that proton shielding is proportional to ring current,[16,28] **11** exhibits only about 27% of the ring current of **12**. The ring current of **11** is, however, about 20% stronger than that of the furano system **8**.[16] In the calculation of the topological resonance energy of the heteroaromatic systems **1a**−**3a** and **1c**−**3c**,[10] going from the nitrogen series to the corresponding members of the oxygen series results in a decrease of >30% of aromatic character of benzene per π electron. Using diatropicity (ring current) as a parameter for aromatic character, our experimental result has, however, indicated a significantly smaller difference in the ability of oxygen and nitrogen in contributing to the aromaticity of an isoannelated heteroaromatic system.

Experimental Section

Melting points are uncorrected. ^{1}H NMR spectra were recorded in $CDCl_3$ on a 90 or 300 MHz spectrometer with Me_4Si as internal standard. Coupling constants (J) are given in Hz. Mass spectra were obtained using EI ionization at 70 eV. UV photolysis was carried out in a Rayonet photochemical reactor (254 nm, 400 W). Microanalyses were performed by the Microanalytical Laboratory of the Department of Chemistry, National University of Singapore.

2,5-Dimethyl-3,4-bis(3-chloro-2-methylphenyl)pyrrole (21). Ammonium acetate (107 mg, 1.39 mmol) was added to a solution of **18**[16] (250 mg, 0.69 mmol) in 95% ethanol (10 mL). The reaction mixture was then brought to reflux for 3 h. Dichloromethane and water were added to the mixture. The organic layer was separated, washed, dried, and evaporated. The crude product was chromatographed on silica gel using dichloromethane/hexane (1:2) as eluant to give **21**: 105 mg (44%). Recrystallization from hexane yielded colorless crystals of **21**: mp 156−158 °C; ^{1}H NMR δ 7.72 (br s, 1H, exchanged with D_2O), 6.8−7.2 (m, 6H), 2.12 (s, 6H), 2.08 (s, 6H); IR (KBr) 3355 (NH) cm^{-1}; MS m/z 345 (M^+, 60), 344 (40), 343 (100), 328 (33), 293 (11). Anal. Calcd for $C_{20}H_{19}Cl_2N$: C, 69.77; H, 5.56; N, 4.07. Found: C, 69.70; H, 5.49; N, 4.00.

***N*-Cyclohexyl-2,5-dimethyl-3,4-bis(3-chloro-2-methylphenyl)pyrrole (22).** The diketone **18**[16] (100 mg, 0.28 mmol) was added to cyclohexylamine (5 mL). The reaction mixture was heated at reflux for 3 h and then cooled, washed with 1 N HCl, and extracted with dichloromethane. The crude product was chromatographed on silica gel using dichloromethane as an eluant to afford **22**: 110 mg (94%). Recrystallization from hexane gave colorless crystals of **22**: mp 180−182 °C; ^{1}H NMR δ 6.6−7.2 (m, 6H), 3.94−4.10 (m, 1H), 2.10, 2.17 (s, ratio 1:1, total 6H), 2.02, 2.07 (s, ratio 1:1, total 6H), 1.94 (br s, 10H); MS m/z 425 (M^+, 100), 410 (12), 382 (10), 343 (27), 328 (23), 215 (13). Anal. Calcd for $C_{26}H_{29}Cl_2N$: C, 73.23; H, 6.85; N, 3.28. Found: C, 73.24; H, 6.94; N, 3.51.

***N*-Cyclohexyl-2,5-dimethyl-3,4-bis(3-cyano-2-methylphenyl)pyrrole (23).**[29] Recrystallization (benzene/*n*-hexane) yielded colorless crystals of **23** (65%): mp 190−192 °C; ^{1}H NMR δ 7.0−7.45 (m, 6H), 4.04−4.13 (m, 1H), 2.19, 2.31 (s, ratio 1:1, total 6H), 2.03, 2.11 (s, ratio 1:1, total 6H), 1.95 (br s, 10H); IR (KBr) 2220 ($C{\equiv}N$) cm^{-1}; MS m/z 407 (M^+, 100), 325 (75), 310 (27). Anal. Calcd for $C_{28}H_{29}N_3$: C, 82.52; H, 7.17; N, 10.31. Found: C, 82.50; H, 7.01; N, 9.98.

***N*-Cyclohexyl-2,5-dimethyl-3,4-bis(3-formyl-2-methylphenyl)pyrrole (24).**[29] Chromatography (dichloromethane/*n*-hexane (1:1)) on silica gel gave colorless crystals of **24** (89%): mp 162−164 °C; ^{1}H NMR 10.25, 10.21 (s, ratio 1:1, total 2H), 7.0−7.7 (m, 6H), 3.87−4.20 (m, 1H), 2.32, 2.46 (s, ratio 1:1, total 6H), 2.09, 2.12 (s, ratio 1:1, total 6H), 2.04 (br s, 10H); IR (KBr) 1685 ($C{=}O$) cm^{-1}; MS m/z 413 (M^+, 100), 398 (12), 385 (23), 370 (13), 331 (13), 316 (12), 303 (16). Anal. Calcd for $C_{28}H_{31}NO_2$: C, 81.32; H, 7.55; N, 3.39. Found: C, 81.13; H, 7.42; N, 3.48.

***N*-Cyclohexyl-2,5-dimethyl-3,4-bis[3-(hydroxymethyl)-2-methylphenyl]pyrrole (25).**[29] Recrystallization (benzene) afforded colorless crystals of **25** (76%): mp 112−114 °C; ^{1}H NMR δ 6.9−7.1 (m, 6H), 4.11−3.85 (m, 1H), 2.10 (s, 6H), 1.98, 2.03 (s, ratio 1:1, total 6H), 1.94 (br s, 10H), 1.63 (s, 2H); IR (KBr) 3450 (OH) cm^{-1}; MS m/z 417 (M^+, 100), 402 (10), 325 (12); M_r calcd for $C_{28}H_{35}NO_2$ 417.2668, found (MS) 417.2660.

***N*-Cyclohexyl-2,5-dimethyl-3,4-bis[3-(bromomethyl)-2-methylphenyl]pyrrole (26).**[29] Recrystallization (benzene/*n*-hexane) gave colorless crystals of **26** (72%): mp 158−160 °C; ^{1}H NMR δ 6.8−7.1 (m, 6H), 4.48, 4.46 (s, ratio 1:1, total 4H), 3.95−4.11 (m, 1H), 2.13 (s, 6H), 2.05, 2.11 (s, ratio 1:1, total 6H), 1.94−1.96 (m, 10H); MS m/z 541 (M^+, 36), 463 (36), 462 (100), 380 (29), 300 (27), 270 (28), 229 (18). Anal. Calcd for $C_{28}H_{33}Br_2N$: C, 61.89; H, 6.12; N, 2.58. Found: C, 62.25; H, 6.30; N, 2.66.

***anti*-*N*-Cyclohexyl-8,16,2′,5′-tetramethyl-1-thia-[3.2]metacyclo[9,10-*c*]pyrrole (16).**[30] Chromatography (dichloromethane/*n*-hexane (1:2)) on silica gel yielded colorless crystals of **16** (20%): mp 261−263 °C; ^{1}H NMR δ 6.9−7.2 (m, 6H), 3.99−4.14 (m, 1H), 3.65, 3.81 (AB q, J = 12.9, 4H), 2.48 (s, 6H), 2.03 (br s, 10H), 0.89 (s, 6H); MS m/z 415 (M^+, 100), 300 (12). Anal. Calcd for $C_{28}H_{33}NS$: C, 80.91; H, 8.00; N, 3.37. Found: C, 81.18; H, 8.25; N, 3.48.

***anti*-*N*-Cyclohexyl-8,16,2′,5′-tetramethyl-1-(methylsulfanyl)[2.2]metacyclo[9,10-*c*]pyrrole (27).**[30] Chromatography (dichloromethane/*n*-hexane (1:2)) on silica gel gave colorless crystals of **27** (96%): mp 121−123 °C; ^{1}H NMR δ 6.9−7.7 (m, 6H), 3.97−4.13 (m, 1H), 3.81 (t, J = 2.9, 1H), 3.11 (dd, J = 2.9, 3.2, 1H), 2.58 (dd, J = 2.9, 3.2, 1H), 2.54 (s, 6H), 2.14 (s, 3H), 2.03 (br s, 10H), 0.58 (s, 6H); MS m/z 429 (m^+, 51), 399 (12), 382 (41), 367 (47), 366 (100), 352 (42), 284 (33), 270 (23); M_r calcd for $C_{29}H_{35}NS$ 429.2490, found (MS) 429.2489.

***anti*-*N*-Cyclohexyl-8,16,2′,5′-tetramethyl[2.2]-metacyclo[9,10-*c*]pyrrole-1-ene (28).**[30] Chromatography (cyclohexane) on silica gel gave gray (due to a minute amount of **11**) crystals of **28** (33%): mp 153−155 °C; ^{1}H NMR δ 6.7−7.2 (m, 6H), 6.41 (s, 2H), 3.82−4.15 (m, 1H), 2.51 (s, 6H), 2.01 (br s, 10H), 1.23 (s, 6H); MS m/z 381 (M^+, 30), 366 (100), 351 (78), 336 (12), 283 (78), 268 (91), 226 (25). Anal. Calcd for $C_{28}H_{31}N$: C, 88.14; H, 8.19; N, 3.67. Found: C, 87.84; H, 8.32; N, 3.38.

Photochemical Valence Isomerization of 28 To Give 11. A solution of **28** in benzene (5 mL) in a quartz cell was irradiated with UV light at 254 nm for 1 h. A dark purple solution was obtained. The solvent was rapidly removed, and the sample contained a mixture of **11** and **28** in a 1:8 ratio based on the integration ratios of the two pairs of methyl signals in the ^{1}H NMR spectrum: δ 6.7−7.2 (m, 6H), 6.41 (s, 2H), 3.82−4.15 (m, 1H), 2.82, 2.51 (s, ratio 1:8, total 6H), 2.01 (br s, 10H), 1.23, −0.42 (s, ratio 8:1, total 6H).

Diels−Alder Reaction between 11 and Dimethyl Acetylenedicarboxylate. Dimethyl acetylenedicarboxylate (0.50 g, 3.52 mmol) was added to a solution of **28** in benzene (15 mL). The reaction mixture was then brought to reflux for 15 h. The solvent was removed, and the crude product was chromatographed on silica gel using dichloromethane as an eluant to give green crystals of **32**: 24 mg (73%); mp 78−79.5 °C; ^{1}H NMR δ 7.8−8.8 (m, 8H), 3.62 (s, 3H), 3.58 (s, 3H), 1.47 (br s, 10H), −3.45 (s, 3H), −3.81 (s, 3H); IR (KBr) 1720 ($C{=}O$) cm^{-1}; MS m/z 523 (M^+, 11), 508 (18), 366 (98), 351 (69), 284 (47), 283 (53), 269 (100), 268 (84) 226 (36). Anal. Calcd for $C_{34}H_{37}NO_4$: C, 77.98; H, 7.12; N, 2.67. Found: C, 77.66; H, 7.10; N, 2.92.

Acknowledgment. This work was supported (RP910649) by the National University of Singapore (NUS). P.C. thanks the NUS for the Research Studentship. Assistance from the technical staff of the Department of Chemistry, NUS, is gratefully acknowledged.

JO970430G

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[29] Reaction conditions for the series of functional group transformations going from **22** to **26** were similar to those reported for the furano[16] and/or benzo[22] series.

[30] The cyclization−Wittig rearrangement−Hofmann elimination sequence going from **16** → **27** → **28**(**11**) was similar to that reported for the furano[16] series.