4,5-O-Substituted Phenanthrenes from Cyclophanes. The Total Synthesis of Cannithrene II[1]

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A new procedure for the synthesis of phenanthrenes with oxygen substitution at positions 4 and 5 (**9b–f**) has been developed. It is based on the regioselective cyclization of the conformationally rigid *cis*-stilbene moiety of a suitable cyclophane (**8b–f**). These cyclophanes (**8b–f**) were obtained by the intramolecular reductive carbonyl coupling of compounds **7b–f** by active titanium. This new approach was successfully applied to obtain cannithrene II (**10**).

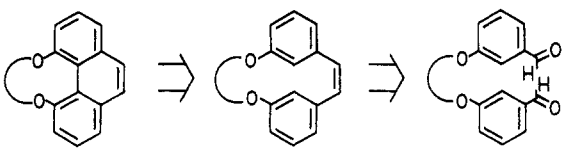
The phenanthrene nucleus is present in a great number of natural substances,[2] some of them having valuable chemotherapeutic properties, which has resulted in considerable efforts being made to synthesize them.[3] Despite the various approaches now available, there exists no efficient method for the preparation of a phenanthrene substituted at positions 4 and 5 as in **1**. The main obstacle lies in the steric hindrance between the two substituents resulting in a low yield for the key cyclization step when approached from stilbene precursors.[4]

We wish to report here a new synthesis of 4,5-O-substituted phenanthrenes in which the above difficulty is overcome by the previous strategic construction of the cyclophane **2** (Scheme I),[5] which can be prepared from the dicarbonylic compound **3** by using a titanium-induced carbonyl coupling[6] under high dilution conditions.[7] The availability of a fairly rigid *cis*-stilbene moiety in **2** allows its regioselective oxidative photocyclization to the 4,5-substituted phenanthrene **1** in good yield.

Results and Discussion

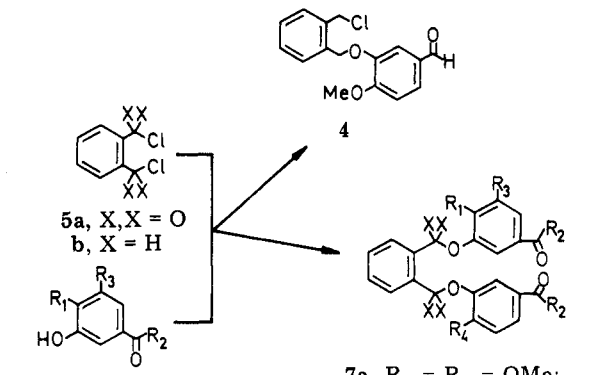
Synthesis of Phenanthrenes 9b–e. The moiety bridging the oxygens in compounds **1–3** should conform to two conditions: (a) It should be easily removed. (b) It should withstand the strong reducing power of the active titanium used in the carbonyl coupling. Our earlier finding that carboxylic esters can resist the conditions used to reductively couple benzaldehyde or acetophenones[8] prompted us to synthesize the dicarbonylic compound **7a** (Scheme II) by reacting the sodium salt of isovanillin (**6a**) with phthalylchloride (**5a**). Unfortunately, after trying

Scheme I



1 **2** **3**

Scheme II



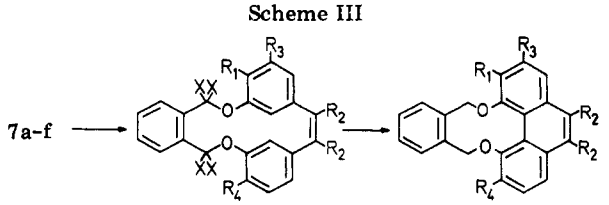
4

5a, X,X = O
b, X = H

6a, R_1 = OMe; R_2 = R_3 = H
b, R_1 = R_2 = R_3 = H
c, R_1 = R_3 = H; R_2 = Me
d, R_1 = R_2 = H; R_3 = OMe

7a, R_1 = R_4 = OMe; R_2 = R_3 = H; X,X = O
b, R_1 = R_4 = OMe; R_2 = R_3 = X = H
c, R_1 = R_2 = R_3 = R_4 = X = H
d, R_1 = R_3 = R_4 = X = H; R_2 = Me
e, R_1 = OMe; R_2 = R_3 = R_4 = X = H
f, R_1 = R_2 = X = H; R_3 = R_4 = OMe

Scheme III



8 **9**

a, R_1 = R_4 = OMe; R_2 = R_3 = H, X,X = O
b, R_1 = R_4 = OMe; R_2 = R_3 = X = H
c, R_1 = R_2 = R_3 = R_4 = X = H
d, R_1 = R_3 = R_4 = X = H; R_2 = Me
e, R_1 = OMe; R_2 = R_3 = R_4 = X = H
f, R_1 = R_2 = X = H; R_3 = R_4 = OMe

(1) Presented in part at the 19th Biannual Meeting of the Spanish Royal Society of Chemistry, Santander, Sept, 1982. A preliminary communication on the synthesis of cannithrene II has been published: Castedo, L.; Saá, J. M.; Suau, R.; Tojo, G. *Tetrahedron Lett.* **1983**, *24*, 5419.

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various conditions, only a 10% yield of cyclophane **8a** from the dicarbonyl diester **7a** could be obtained with a 5-fold molar excess of Ti^0 under high dilution. The ester linkages presumably do not resist the great excess of Ti^0 necessary to efficiently effect the intramolecular reductive coupling.[9]

A successful result was obtained when the ester groups were replaced by ether groups. Compound **7b** was then synthesized from the potassium salt of **6a** and 1,2-bis(chloromethyl)benzene (**5b**)[10] and treated with a 20-fold molar excess of Ti^0 under high dilution conditions. This led to a 65% yield of cyclophane **8b** (Scheme III).

Examination of molecular models led us to believe that the transformation of **8b** into phenanthrene **9b** should be straightforward, since in the conformationally rigid stilbene **8b** the p orbitals involved in the required photochemically produced disrotatory cyclization leading eventually to the phenanthrene **9b** are apparently very close in space. Actually, when **8b** was irradiated in the presence of an oxidant under standard conditions[3] (I_2, O_2), a sluggish transformation took place, giving rise to a complex mixture. Proton NMR analysis of this mixture showed, to our surprise, the presence of signals corresponding to the dicarbonylic compound **7b**. This result can be explained assuming that the triplet oxygen in its ground state, which is present in the solution, is excited to its singlet state by some sensitizer. The reactive species O_2 ($^1\Delta_g$) thus formed can undergo 2 + 2 addition to the stilbene central bond of compound **8b** to give a dioxetane, which decomposes to **7b**. While a great number of phenanthrenes have successfully been prepared by oxidative photocyclization from a stilbene, examples of singlet oxygen reacting with stilbenes do exist,[11] especially when dealing with electron-rich olefins, with which O_2 ($^1\Delta_g$) is known to react faster.[12] In some instances these unwanted reactions caused by singlet oxygen have been avoided by using Cu^{2+} instead of O_2 as oxidant,[11a] but when we irradiated stilbene **8b** under various conditions, in the presence of I_2 and a Cu^{2+} salt such as $CuSO_4$, $CuCl_2$, or $Cu(AcO)_2$, no phenanthrene was formed. This was presumably due to the fact that whereas **8b** can only be dissolved in apolar organic solvents, the Cu^{2+} salts used are only soluble in polar solvents. We were unable to find a solvent or solvent mixture capable of dissolving simultaneously **8b** and any of the above Cu^{2+} salts. This problem was overcome by the use of Cu^{2+} decanoate, which was found to be very soluble in organic solvents such as benzene or CH_2Cl_2 and is easily made by simply pouring aqueous $CuSO_4$ over a solution of sodium decanoate kept at 80 °C. When a diethyl ether solution[13] of cyclophane **8b** was irradiated in the presence of I_2 and 5 equiv of Cu^{2+} decanoate, a clean reaction took place, giving rise to a mixture of the desired phenanthrene **9b** and the starting compound, from which **9b** could be isolated in 51% yield by crystallization. This new approach to the 4,5-*O*-substituted phenanthrenes was also applied to the syntheses of phenanthrenes **9c** and **9d**, starting from 3-hydroxybenzaldehyde (**6b**) and 3-hydroxyacetophenone (**6c**), respectively.

We then carried out research to extend this approach to the syntheses of asymmetrical phenanthrenes. We found that when the sodium salt of the phenol **6a** was treated with 3 equiv of dichloride **5b** in DMF (Scheme III), a 73% yield of monochloride **4** was obtained after column chromatography of the reaction mixture to separate it from the accompanying **7b** and **5b**. Compound **4** was transformed to the asymmetric dicarbonyl compound **7e** by reaction with the potassium salt of 3-hydroxybenzaldehyde (**6b**). When the dicarbonyl compound **7e** was subjected to reductive coupling followed by photocyclization, the asymmetric 4,5-*O*-substituted phenanthrene **9e** was obtained.

Synthesis of Cannithrene II (10). Δ^9-Tetrahydrocannabinol is the main cause of the physiological effects of Cannabis. However, these complex effects cannot be completely explained solely by the presence of cannabinoids.[14] L. Crombie et al. have recently discovered a new phenolic phenanthrene in the acidic extract of the leaves of Cannabis sativa.[15] This compound was identified as 4,5-dihydroxy-3,7-dimethoxyphenanthrene (cannithrene II) by single-crystal X-ray analysis of its diacetate. The synthesis of cannithrene II (**10**) is thus of interest, for this phenanthrene could be engaged in some of the biological properties of crude extracts of Cannabis leaves.

Cannithrene II was thought likely to be obtainable by the catalytic hydrogenation of the phenanthrene compound **9f**, which may be derived from monochloride **4** and 3-hydroxy-5-methoxybenzaldehyde (**6d**) by the phenanthrene synthesis described above. Efficient synthesis of cannithrene II (**10**) demanded the easy production of the simple compound **6d**, but previous syntheses of **6d** have involved long multistep procedures with low overall yields.[16] We found that the action of 3 equiv of sodium ethanethiolate on a not too concentrated refluxing solution[17] of commercially available 3,5-dimethoxybenzaldehyde gave rise to its selective monodemethylation. When the reaction is performed in the standard way,[18] the ethanethiol formed in the presence of aqueous HCl causes the rapid formation of the diethyl thioacetal of the benzaldehyde **6d**, in spite of the great excess of water. This can be avoided by pouring the DMF solution resulting from the reaction on a mixture of aqueous acetic acid and formaline, which allows a 73% yield of **6d** to be obtained.

3-Hydroxy-5-methoxybenzaldehyde (**6d**) was converted into the cyclophane **8b** via **7f** by using the same series of reactions which allowed the conversion of 3-hydroxybenzaldehyde into **8e**. Compound **8f**, unlike cyclophanes **8b–e** (with which it was necessary to use Cu^{2+}) could be cyclized by irradiation in the presence of I_2 and O_2 to the phenanthrene **9f** in 73% yield, a discrepancy for which we can at present offer no explanation. Reductive cleavage of the cyclic ether in **9f** and simultaneous reduction of the 9,10-double bond by catalytic hydrogenation in acidic dioxane–ethanol resulted in a 90% yield of cannithrene II (**10**), whose identity was fully confirmed by direct comparison with a natural sample.

A new synthesis of 4,5-substituted phenanthrenes has been developed and applied to the synthesis of cannithrene II (**10**). Further investigations are in progress to widen the range of this new pathway to 4,5-disubstituted phenan-

(9) In our previous experiments,[8] in which intermolecular couplings were dealt with, good yields of coupled products were obtained with only a 4-fold excess of Ti^0.

(10) In this and other reactions we found that 1,2-bis(bromomethyl)benzene is equally effective, but we do not recommend its use because of its lachrymatory properties.

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(13) Other solvents tried, such as benzene, acetonitrile, acetone, pyridine, and THF, were less effective.

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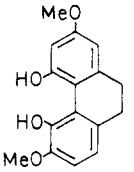
(15) Crombie, L.; Crombie, W. M. L. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1455.

(16) (a) Mauther, F. *J. Prak. Chem.* **1927**, *116*, 314. (b) Späth, E.; Kromp, K. *Chem. Ber.* **1941**, *74*, 1424.

(17) Use of a highly concentrated solution here leads to a Cannizzaro reaction.

(18) Baht, M. V.; Kulkarni, S. U. *Synthesis* **1983**, 249.

threnes for the preparation of aporphine alkaloids and other natural phenanthrenes.



10

Experimental Section

General Procedures. All melting points are uncorrected and refer to products crystallized from EtOH–CH_2Cl_2 unless otherwise stated. Proton NMR were obtained on a Varian CFT-20 (80 MHz) or a Bruker WM-250 (250 MHz) with $CDCl_3$ as solvent and Me_4Si as internal standard. Mass spectra were recorded with a Kratos MS-25 instrument at 70 eV ionizing energy. IR spectra were recorded with a PYE UNICAM 1100 spectrometer with KBr pellets unless otherwise stated and UV spectra were recorded with a PYE UNICAM 1700.

Tetrahydrofuran was distilled under Ar from sodium benzophenone ketyl radical immediately prior to use. *N,N*-Dimethylformamide was dried by low-pressure distillation from CaH_2 and stored over molecular sieves 4A. K_2CO_3 was dried heating at 180 °C in vacuo. The Zn–Cu couple was obtained by using the procedure of McMurry et al.[6] All sensitive materials were handled under inert atmosphere in a dry box or Schlenk apparatus.

Preparation of Dialdehyde 7a. NaH (108 mg, 3.6 mmol) (80% weight oil dispersion) was introduced in a flask purged with Ar and washed twice with THF. THF (2 mL) and a solution of 500 mg (3.29 mmol) of 3-hydroxy-4-methoxybenzaldehyde (**6a**) in 4 mL of DMF were then slowly added. When the evolution of hydrogen ceased, a solution of 400 mg (1.97 mmol) of 1,2-benzenedicarbonyl dichloride (**5a**) in 2 mL of THF was added. The mixture was left stirring at room temperature overnight. The resulting solution was concentrated to half its volume in a rotatory evaporator, poured into water, and extracted with CH_2Cl_2. The organic phase was dried (Na_2SO_4) and the solvent removed in vacuo, leaving a residue which was purified by crystallization from EtOH–CH_2Cl_2 and gave 630 mg (88%) of compound **7a**: mp 140–141 °C; IR 1765, 1700 cm^{-1}; ^1H NMR (80 MHz) δ 9.85 (s, 2 H, ArC*H*O), 8.2–7.6 (m, 8 H, ArH), 7.11 (d, 2 H, J = 8.1 Hz, ArH), 3.90 (s, 6 H, CH_3OAr); MS, m/e (relative intensity) 434 (M^+, 0.05), 283 (94), 152 (69), 151 (72), 133 (23), 104 (85), 76 (100), 50 (83).

Anal. Calcd for $C_{24}H_{18}O_8$: C, 66.36; H, 4.18. Found: C, 66.16; H, 4.14.

Reductive Coupling of Dialdehyde 7a. A mixture of 580 mg (3.76 mmol) of $TiCl_3$, 670 mg (10.32 mmol) of Zn–Cu couple,[6] and 76 mL of THF was refluxed for 1 h under Ar. Immediately afterward, without stopping the reflux, a solution of 280 mg (0.64 mmol) of dialdehyde **7a** in 20 mL of THF was slowly dripped in. After 9 h, when the addition was complete, the reflux was continued for another 13 h. To the cooled reaction mixture abundant silica gel (Merck type 60 for column chromatography) was added, the solvent was evaporated in the rotatory evaporator, and the residue incorporated at the top of a short silica gel column. Elution with CH_2Cl_2 gave 82 mg of cyclophane **8a**, which was further purified by preparative chromatography on silica gel, eluting with CH_2Cl_2. After crystallizing from EtOH–CH_2Cl_2, a final 27 mg (10%) of **8a** was obtained: mp 227–228 °C; IR 1755 cm^{-1}; ^1H NMR (80 MHz) δ 8.0–7.4 (AA′XX′, 4 H, J = 5.7 and 3.2 Hz, xylyl aromatic protons), 7.13 (d, 2 H, J = 2.0 Hz, ArH), 6.98 (dd, 2 H, J = 8.3 and 2.8 Hz, ArH), 6.77 (d, 2 H, J = 8.3 Hz, ArH), 6.36 (s, 2 H, ArC*H*=C*H*Ar), 3.77 (s, 6 H, CH_3OAr); MS, m/e (%) 402 (M^+, 25), 272 (4), 152 (19), 139 (18), 104 (69), 76 (100), 50 (56).

General Procedure for the Preparation of Dicarbonyl Compounds 7b–d. A mixture of 470 mg (3.41 mmol) of K_2CO_3, 1.74 mmol of the corresponding phenol (**6a**, **6b**, or **6c**), and 5 mL of dry DMF was stirred magnetically at room temperature for 6 h in a stoppered flask. After adding 152 mg (0.87 mmol) of 1,2-bis(chloromethyl)benzene (**5b**),[10] the flask was again stoppered and left stirring at room temperature for 24 h. The following products were worked-up as follows.

Compound 7b. Water was added and the precipitate filtered, washed with water, and vacuum dried to give a 92% yield from 3-hydroxy-5-methoxybenzaldehyde (**6a**): mp 157–159 °C; IR 1695 cm^{-1}; ^1H NMR (80 MHz) δ 9.80 (s, 2 H, ArC*H*O), 7.5–7.3 (m, 8 H, ArH), 6.90 (d, 2 H, J = 8.6 Hz, ArH), 5.34 (s, 4 H, ArCH_2Ar′), 3.88 (s, 6 H, CH_3OAr); MS, m/e (%) 406 (M^+, 2), 255 (16), 227 (19), 152 (57), 151 (65), 104 (100), 91 (61), 81 (34), 77 (57), 51 (83).

Anal. Calcd for $C_{24}H_{22}O_6$: C, 70.92; H, 5.46. Found: C, 71.04; H, 5.45.

Compound 7c. As **7b**. A 93% yield was obtained from 3-hydroxybenzaldehyde (**6b**): mp 67–68 °C; IR 1695 cm^{-1}; ^1H NMR (80 MHz) δ 9.94 (s, 2 H, ArC*H*O), 7.5–7.2 (m, 12 H, ArH), 5.24 (s, 4 H, ArCH_2OAr′); MS, m/e (%) 346 (M^+, 1), 224 (37), 225 (56), 197 (41), 179 (32), 169 (34), 122 (5), 104 (100), 91 (92), 78 (52).

Anal. Calcd for $C_{22}H_{18}O_4$: C, 76.28; H, 5.24. Found: C, 75.99; H, 5.21.

Compound 7d. Plenty of water was added and the solution extracted with CH_2Cl_2. The organic phase was washed with water, dried (Na_2SO_4), and concentrated in the rotatory evaporator, giving an oil which crystallized on standing. A 89% yield was obtained from 3-hydroxyacetophenone (**6c**): mp 87–89 °C; IR 1685 cm^{-1}; ^1H NMR (80 MHz) δ 7.6–7.1 (m, 12 H, ArH), 5.22 (s, 4 H, ArCH_2OAr′), 2.56 (s, 6 H, ArCOCH_3); MS, m/e (%) 374 ($M^{+\prime}$ 1), 238 (5), 197 (13), 136 (1), 135 (0.5), 104 (13), 91 (9), 78 (9), 43 (100).

Anal. Calcd for $C_{24}H_{22}O_4$: C, 76.98; H, 5.92. Found: C, 76.79; H, 5.99.

Preparation of Monochloride 4. NaH (660 mg, 22 mmol) (80% oil dispersion) and 40 mL of DMF were introduced in a flask previously purged with Ar. While the solution was magnetically stirred, 3.04 g (20 mmol) of 3-hydroxy-4-methoxybenzaldehyde (**6a**) were slowly added. When the evolution of hydrogen ceased, 10.5 g (60 mmol) of 1,2-bis(chloromethyl)benzene (**5b**) was introduced and the flask was stoppered and left with magnetic stirring at room temperature for 16 h. After pouring in 50 mL of CH_2Cl_2, the resulting solution was washed with a 5% NH_4Cl aqueous solution (4 × 100 mL), the aqueous phase was extracted with CH_2Cl_2 (3 × 25 mL), and the combined organic phases were dried (Na_2SO_4). Solvent removal in vacuo left an oil shown by TLC to be a mixture of **5b**, **7b**, and **4**, which were separated by column chromatography on silica gel (150 g). Elution with CH_2Cl_2 gave 7.2 g of starting 1,2-bis(chloromethyl)benzene (**5b**) followed by 4.25 g (73% based on **6a**) of monochloride **4**: mp 92.5–93 °C; IR 1690 cm^{-1}; ^1H NMR (80 MHz) δ 9.84 (s, 1 H, ArC*H*O), 7.6–7.0 (m, 7 H, ArH), 5.29 (s, 2 H, ArCH_2OAr′), 4.77 (s, 2 H, ArCH_2Cl), 3.94 (s, 3 H, CH_3OAr); MS, m/e (%) 292 (M^+ + 2, 19), 290 (M^+, 56), 255 (2), 227 (4), 141 (94), 139 (100), 119 (5), 104 (27), 103 (25), 91 (8), 78 (13), 77 (18).

Anal. Calcd for $C_{16}H_{15}O_3Cl$: C, 66.10; H, 5.20; Cl, 12.19. Found: C, 66.13; H, 5.20; Cl, 12.05.

Preparation of Dialdehyde 7e. A mixture of 97 mg (0.80 mmol) of 3-hydroxybenzaldehyde (**6b**), 220 mg (1.60 mmol) of K_2CO_3, and 6 mL of DMF was stirred at room temperature for 6 h in a stoppered flask. Monochloride **4** (232 mg, 0.80 mmol) was added and the reaction was left for a further 24 h at room temperture. The product was worked-up in the same way as compound **7b** to give a 98% yield of dialdehyde **7e**: mp 96–97.5 °C (EtOH); IR 1700 cm^{-1}; ^1H NMR (80 MHz) δ 9.94 (s, 1 H, ArC*H*O), 9.80 (s, 1 H, ArC*H*O), 7.6–7.1 (m, 10 H, Ar*H*), 6.95 (d, 1 H, J = 8.6 Hz, ArH), 5.30 (s, 2 H, ArCH_2OAr′), 5.28 (s, 2 H, ArCH_2OAr′), 3.90 (s, 3 H, CH_3OAr); MS, m/e (%) 370 (M^+, 8), 255 (3), 277 (5), 225 (21), 197 (34), 179 (28), 169 (28), 152 (13), 151 (17), 122 (6), 121 (17), 104 (100), 91 (35), 78 (55).

Anal. Calcd for $C_{23}H_{20}O_5$: C, 73.39; H, 5.35. Found: C, 73.04; H, 5.45.

3-Hydroxy-5-methoxybenzaldehyde (6d). Ethanethiol (7 mL) was slowly injected into a magnetically stirred mixture of 2.08 g (69.3 mmol) of NaH (80% weight oil dispersion) and 50 mL of DMF cooled in an ice–water bath. Once the evolution of hydrogen ceased, the solution was refluxed under Ar for an hour to eliminate the excess ethanethiol. 3,5-Dimethoxybenzaldehyde (3.84 g, 23.1 mmol) and 90 mL of DMF were added, and the solution was refluxed again under Ar for an hour and worked-up by successively adding a saturated aqueous NaCl solution (700 mL), 26% formaline (70 mL), and acetic acid (130 mL). The

resulting solution was thoroughly extracted with ethyl acetate, the organic phase was dried (Na_2SO_4), and the solvent eliminated in vacuo. The remaining crude dark syrup was purified in a column of silica gel (70 g), eluting with CH_2Cl_2–EtOH (50:1), to obtain 2.58 g (73%) of 3-hydroxy-5-methoxybenzaldehyde (**6d**): mp 129–130 °C (water) (lit.[16a] mp 130–131 °C); IR 3225 (broad), 1685 cm^{-1}; ^1H NMR (80 MHz) δ 9.88 (s, 1 H, ArC*H*O), 6.98 (m, 2 H, ArH), 6.67 (t, 1 H, J = 2.3 Hz, ArH), 5.46 (broad singlet, 1 H, ArO*H*), 3.84 (s, 3 H, CH_3OAr); MS, m/e (%) 152 (M^+, 100), 151 (57).

Preparation of Dialdehyde 7f. NaH (464 mg, 15.5 mmol) (80% weight oil dispersion) was introduced in a flask previously purged with Ar. The hydride was washed twice with 5 mL of petroleum ether and DMF (30 mL) was added. 3-Hydroxy-5-methoxybenzaldehyde (**6d**) (1.96 g, 12.9 mmol) was then slowly introduced into the well-stirred suspension. Once the evolution of hydrogen was over, 3.76 g (12.9 mmol) of monochloride **4** were added and the mixture was left stirring under Ar at room temperature for 13 h. Compound **7f** was crystallized from the crude mixture after adding ca. 11 mL of water. It was filtered, washed with ethanol, and dried in vacuo to yield 3.67 g (70% yield) of pure dialdehyde **7f**. A further quantity of 0.54 g (10%) (80% combined yield) was isolated from the mother liquors by adding water, extracting the mixture with CH_2Cl_2, drying (Na_2SO_4), concentrating the organic layer, and purifying the resulting residue by column chromatography (SiO_2, 60 g, CH_2Cl_2): mp 127–129 °C; IR 1700 cm^{-1}; ^1H NMR (80 MHz) δ 9.87 (s, 1 H, ArC*H*O), 9.80 (s, 1 H, ArC*H*O), 7.6–6.9 (m, 9 H, Ar*H*), 6.77 (t, 1 H, J = 2.3 Hz, Ar*H*), 5.28 (s, 4 H, benzylic protons), 3.90 (s, 3 H, CH_3OAr), 3.81 (s, 3 H, CH_3OAr); MS, m/e (%) 406 (M^+, 7), 255 (100).

Anal. Calcd for $C_{24}H_{22}O_6$: C, 70.92; H, 5.46. Found: C, 71.20; H, 5.39.

General Procedure for the Preparation of Cyclophanes 8b–f by Reductive Coupling of the Corresponding Dicarbonyl Compounds 7b–f. $TiCl_3$ (7.65 g, = 52 mmol), 7.95 g of Zn–Cu couple,[6] and 200 mL of THF were transferred under inert atmosphere to a flask previously purged with Ar. This mixture was refluxed for 1 h, and then, without stopping the reflux, a solution of 2.5 mmol of starting compound (**7b–f**) in 200 mL of THF was dripped into the titanium suspension, as steadily as possible, via a dropping funnel. Addition was finished in 8 h and the reflux was kept up under Ar for another 13 h. Most of the THF was removed in the rotatory evaporator, a saturated solution of K_2CO_3 was added, and the resulting mixture was thoroughly extracted with CH_2Cl_2. The collected organic phases were dried (Na_2SO_4) and the solvent was evaporated, leaving crude cyclophanes **8b–f** as syrups which were purified by preparative chromatography on silica gel, eluting with CH_2Cl_2 to obtain the corresponding products.

Compound 8b: 65% yield; mp 174–175 °C; IR 1610, 1520, 1270, 1140 1020 cm^{-1}; ^1H NMR (80 MHz) δ 7.4–6.7 (m, 10 H, ArH), 6.35 (s, 2 H, ArC*H*=C*H*Ar), 5.09 (s, 4 H, ArCH_2OAr), 3.92 (s, 6 H, CH_3OAr); MS, m/e (%) 374 (M^+, 38), 152 (8), 139 (15), 128 (23), 104 (100), 91 (13), 78 (48); UV (CH_2Cl_2) λ_{max} 290 (log ε 4.01), 330 (3.80) nm.

Anal. Calcd for $C_{24}H_{22}O_4$: C, 76.98; H, 5.92. Found: C, 76.95; H, 5.78.

Compound 8c: 62% yield; mp 153–154 °C; IR (CCl_4) 1610, 1500, 1480, 1460, 1440, 1260 cm^{-1}; ^1H NMR (80 MHz) δ 7.5–6.7 (m, 12 H, ArH), 6.52 (s, 2 H, ArC*H*=C*H*Ar), 4.99 (s, 4 H, ArCH_2OAr); MS, m/e (%) 314 (M^+, 96), 152 (17), 128 (14), 104 (100), 91 (15), 78 (50); UV (CH_2Cl_2) λ_{max} 250 (log ε 4.02, sh), 300 (3.77) nm.

Anal. Calcd for $C_{22}H_{18}O_2$: C, 84.05; H, 5.77. Found: C, 83.62; H, 5.63.

Compound 8d: 78% yield; mp 173–174 °C; IR 1608, 1580, 1490, 1480, 1450, 1260 cm^{-1}; ^1H NMR (80 MHz) δ 7.5–6.6 (m, 10 H, aromatic + olefinic protons), 6.23 (d, 2 H, J = 1.9, aromatic protons ortho to the ether oxygen and the double bond), 4.74 (s, 4 H, ArCH_2OAr'), 2.02 (s, 6 H, =CArCH_3); MS, m/e (%) 342 (M^+, 100), 327 (10), 138 (13), 195 (20), 165 (23), 152 (16), 104 (82), 91 (13), 78 (37); UV (CH_2Cl_2) λ_{max} 255 (log ε 4.04), 280 (3.83) nm.

Anal. Calcd for $C_{24}H_{22}O_2$: C, 84.17; H, 6.47. Found: C, 84.05; H, 6.27.

Compound 8e: 57% yield; mp 110–111 °C; IR 2840, 1605, 1580, 1570, 1510, 1440, 1410, 1270, 1150, 680 cm^{-1}; ^1H NMR (80 MHz) δ 7.3–7.2 (m, 10 H, ArH), 6.83 (d, 1 H, J = 9.8 Hz, aromatic proton ortho to the methoxy substituent), 6.42 (s, 2 H, ArC*H*=C*H*Ar'), 5.05 (s, 4 H, ArCH_2OAr'), 3.91 (s, 3 H, CH_3OAr); MS, m/e (%) 344 (M^+, 100), 329 (2), 141 (19), 137 (21), 115 (24), 104 (95), 103 (29), 91 (13), 78 (33); UV (CH_2Cl_2) λ_{max} 248 (log ε 4.10), 290 (3.94), 328 (3.77 nm.

Anal. Calcd for $C_{23}H_{20}O_3$: C, 80.21; H, 5.85. Found: C, 80.70; H, 5.70.

Compound 8f: 65% yield; mp 151–153 °C; IR 1605, 1585, 1520, 1430, 1270, 1215, 1040, 1030 cm^{-1}; ^1H NMR (250 MHz) δ 7.46–7.40 (symmetric multiplet, 2 H, ArH), 7.27–7.22 (symmetric multiplet, 2 H, ArH), 6.92 (d, 1 H, J = 2.1 Hz, ArH), 6.79 (d, 1 H, J = 8.3 Hz, ArH), 6.73 (dd, 1 H, J = 8.3, 2.1 Hz, ArH), 6.50 (t, 1 H, J = 2.3 Hz, ArH), 6.47–6.45 (m, 1 H, ArH), 6.42 (d, 1 H, J = 12.1 Hz, ArC*H*=), 6.35 (d, 1 H, J = 12.1 Hz, ArC*H*=), 6.35–6.33 (m, 1 H, ArH), 5.05 (s, 2 H, ArCH_2OAr'), 5.03 (s, 2 H, ArCH_2OAr'), 3.90 (s, 3 H, CH_3OAr), 3.75 (s, 3 H, CH_3OAr); MS, m/e (%) 374 (M^+, 46), 359 (4), 343 (3), 270 (7), 139 (12), 128 (14), 115 (11), 104 (100), 103 (31), 78 (35); UV (CH_2Cl_2) λ_{max} 275 (log ε 3.95), 287 (3.95), 313 (3.82, sh) nm.

Anal. Calcd for $C_{24}H_{22}O_4$: C, 76.98; H, 5.92. Found: C, 76.99; H, 5.63.

Preparation of Cu(II) Decanoate. A hot solution of 2.898 g (11.6 mmol) of $CuSO_4 \cdot 5H_2O$ in 20 mL of water was added over a stirred solution of 0.928 g (23.2 mmol) of NaOH and 3.99 g (23.2 mmol) of decanoic acid in 30 mL of water at 80 °C. A blue precipitation of Cu(II) decanoate immediately formed. The suspension was stirred for 2 h at 80 °C to complete the reaction and the precipitate was filtered, washed with hot water, and vacuum dried to yield 4.87 g (98% yield) of Cu(II) decanoate as a light bluish powder: mp 261–263 °C (absolute ethanol); IR 2920, 2850, 1590, 1410 cm^{-1}; ^1H NMR (80 MHz) 1–1.5 (m).

Anal. Calcd for $C_{20}H_{22}O_4Cu$: C, 59.16; H, 9.43. Found: C, 59.14; H, 9.64.

General Procedure for the Irradiation of Cyclophanes 8b–f with I_2–Cu(II) as the Oxidant System. A solution of 1.41 mmol of the corresponding cyclophane **8b–f**, 5.72 g (7.05 mmol) of Cu(II) decanoate, and 350 mg of I_2 in 500 mL of deoxygenated Et_2O was irradiated for 24 h with a 450-W Hanovia medium-pressure mercury lamp equipped with a Pyrex filter (except compound **8f**, which was irradiated for only 2 h). The solution was washed with a sodium thiosulfate solution (20% in water) to eliminate the peroxides, concentrated ammonia, and water. It was dried (Na_2SO_4) and the solvent eliminated in the rotatory evaporator, leaving a residue which was worked-up as indicated below to obtain the following phenanthrenes.

Compound 9b. The residue was purified by preparative chromatography on silica gel plates, eluting with CH_2Cl_2. A band consisting of a mixture of **9b** plus the starting compound **8b** was extracted and a 51% yield of phenanthrene **9b** was isolated by crystallization from EtOH: mp 144–145 °C; IR 2840, 1610, 1590, 1540, 1280, 1120 cm^{-1}; ^1H NMR (80 MHz) δ 7.6–7.2 (m, 10 H, ArH), 5.66 (s, 4 H, ArCH_2OAr'), 3.99 (s, 6 H, CH_3OAr); MS, m/e (%) 372 (M^+, 100), 339 (34), 296 (29), 252 (88), 196 (27), 153 (29), 138 (27), 125 (30), 119 (4), 104 (54), 91 (11), 78 (36); UV (CH_2Cl_2) λ_{max} 264 (log ε 4.62), 308 (4.15), 321 (4.16), 362 (3.44), 382 (3.48) nm.

Anal. Calcd for $C_{24}H_{20}O_4$: C, 77.40; H, 5.41. Found: C, 77.65; H, 5.20.

Compound 9c. The resulting residue was worked-up in the same way as compound **9b**. A 58% yield of phenanthrene **9c** was obtained by crystallizing from EtOH the mixture of **9c** plus starting compound **8c**: mp 159–160 °C; IR 160, 1570, 1520, 1440, 1260 cm^{-1}; ^1H NMR (80 MHz) δ 7.6–7.2 (m, 12 H, ArH), 5.52 (s, 4 H, ArCH_2OAr'); MS, m/e (%) 312 (M^+, 100), 294 (31), 196 (19), 192 (9), 184 (42), 152 (91), 129 (70), 119 (9), 104 (67), 103 (40), 91 (13), 78 (43); UV (CH_2Cl_2) λ_{max} 248 (log ε 4.58), 288 (4.57), 320 (3.40), 340 (2.89), 354 (2.58) nm.

Anal. Calcd for $C_{22}H_{16}O_2$: C, 84.59; H, 5.16. Found: C, 84.18; H, 5.16.

Compound 9d. The resulting residue was purified by preparative chromatography on silica gel plates, eluting with CH_2Cl–benzene (3:1, v/v). Two bands were extracted, the more polar of the two consisting of starting compound **8d** (22% yield) and the less polar consisting of phenanthrene **9d** (67% yield, 86% yield after correcting for recovery of starting material): mp

208-209.5 °C (EtOH); IR 2900, 1600, 1570, 1520, 1450, 1260 cm^{-1}; ^1H NMR (80 MHz) δ 7.7-7.1 (m, 10 H, ArH), 5.47 (s, 4 H, $ArCH_2OAr'$), 2.59 (s, 6 H, $ArCH_3$); MS, *m/e* (%) 340 (M^+, 100), 325 (9), 224 (27), 220 (5), 212 (25), 205 (9), 181 (18), 179 (16), 165 (36), 129 (36), 119 (5), 104 (32), 103 (21), 78 (18); UV (CH_2Cl_2) λ_{max} 264 (log ε 4.48), 291 (4.55), 324 (3.96), 354 (2.98), 370 (2.90) nm.

Anal. Calcd for $C_{24}H_{20}O_2$: C, 84.68; H, 5.92. Found: C, 84.91; H, 5.97.

Compound 9e. The resulting residue was worked-up in the same way as compound **9d**, but with CH_2Cl_2 as eluent. Two bands were extracted, the more polar of the two consisting of starting compound **8e** (16% yield) and the less polar consisting of phenanthrene **9e** (54% yield, 64% after correcting for recovery of starting material): mp 229.5-230.5 °C (EtOH); IR 2845, 1600, 1580, 1520, 1440, 1270, 1140 cm^{-1}; ^1H NMR (80 MHz) δ 7.7-7.0 (m, 11 H, ArH), 5.70 (s, 2 H, $ArCH_2OAr'$), 5.47 (s, 2 H, $ArCH_2OAr'$), 4.04 (s, 3 H, CH_3OAr); MS, *m/e* (%) 342 (M^+, 100), 223 (54), 214 (21), 195 (28), 167 (23), 139 (51), 129 (40), 119 (12), 104 (49), 103 (30), 91 (12), 78 (28); UV (CH_2Cl_2) λ_{max} 262 (log ε 4.51), 294 (4.26), 320 (3.97), 346 (3.39), 374 (3.38) nm.

Anal. Calcd for $C_{23}H_{18}O_3$: C, 80.68; H, 5.30. Found: C, 80.53; H, 5.26.

Compound 9f. The resulting residue was purified in a short column of silica gel, eluting with CH_2Cl_2, followed by crystallization from EtOH to obtain a 78% yield of phenanthrene **9f**: mp 215-217 °C; IR 2900, 1615, 1595, 1435, 1265, 1175, 1135, 825 cm^{-1}; ^1H NMR (80 MHz) δ 7.6-7.1 (m, 8 H, ArH), 6.74 (s, 2 H, ArH), 5.67 (s, 2 H, $ArCH_2OAr'$), 5.44 (s, 2 H, $ArCH_2OAr'$), 4.04 (s, 3 H, CH_3OAr), 3.88 (s, 3 H, CH_3OAr); MS, *m/e* (%) 372 (M^+, 100), 340 (15), 297 (14), 253 (81), 225 (21), 159 (21), 154 (19), 126 (21), 104 (38), 103 (23), 78 (23); UV (EtOH) λ_{max} 268 (log ε 4.50), 286 (4.52), 327 (3.87, sh), 354 (2.99), 374 (2.66) nm.

Anal. Calcd for $C_{24}H_{20}O_4$: C, 77.40; H, 5.41. Found: C, 77.32; H, 5.00.

Preparation of Phenanthrene 9f by Irradiation of Cyclophane 8f, with I_2-O_2 as the Oxidant System. A stirred solution of 650 mg (1.74 mmol) of cyclophane **8f** and 50 mg of I_2 in 500 mL of Et_2O was irradiated with a 450-W Hanovia medium-pressure mercury lamp through a Pyrex filter for 1 h. The solution was washed with a sodium thiosulfate solution to eliminate the peroxides and the solvent was removed in the rotatory evaporator. The residue was loaded on a silica gel column, which was eluted with CH_2Cl_2. In this way, after crystallizing from EtOH-CH_2Cl_2, 474 mg (73% yield) of phenanthrene **9f** was obtained.

Cannithrene II (10). Phenanthrene **9f** was (90 mg, 0.24 mmol) dissolved in 6 mL of dioxane. EtOH (10 mL), 10 mg of Pd/C (10%), and two drops of concentrated HCl were added. The solution was stirred for 18 h at room temperature under 760 mmHg of H_2. The catalyst was filtered and the solvent eliminated in vacuo. The residue was purified on a silica gel plate with CH_2Cl_2-EtOH (1:1, v/v) as eluent. In this way 59 mg (90% yield) of an oil identified as pure cannithrene II (**10**) by direct comparison (TLC, ^1H NMR, MS, UV) with a natural sample were obtained. A crystalline sample obtained by distillation of the oil (ca. 170 °C (3 mmHg)) followed by crystallization from Et_2O-hexane produced no depression of the melting point when mixed with a natural sample of cannithrene II.

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Registry No. **4**, 89052-09-5; **5a**, 88-95-9; **5b**, 612-12-4; **6a**, 621-59-0; **6b**, 100-83-4; **6c**, 121-71-1; **6d**, 57179-35-8; **7a**, 95912-29-1; **7b**, 95912-30-4; **7c**, 95912-31-5; **7d**, 95912-32-6; **7e**, 95912-33-7; **7f**, 89052-11-9; **8a**, 95912-34-8; **8b**, 95912-35-9; **8c**, 95912-36-0; **8d**, 95912-37-1; **8e**, 95912-38-2; **8f**, 95912-39-3; **9b**, 95912-40-6; **9c**, 95912-41-7; **9d**, 95912-42-8; **9e**, 95912-43-9; **9f**, 89052-08-4; **10**, 83016-16-4; 3,5-dimethoxybenzaldehyde, 7311-34-4; decanoic acid, 334-48-5; copper(II) decanoate, 28567-33-1.

Palladium-Catalyzed Dimerization of Allenes to 2,3-Bis(chloromethyl)butadienes. Synthesis of Conjugate Exocyclic Dienes

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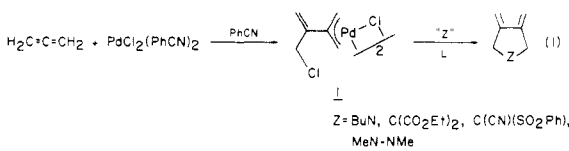
Treatment of allene with copper(II) chloride in the presence of palladium(II) chloride as catalyst (1%) produced 2,3-bis(chloromethyl)butadiene in good yield. Greater than 10 g of this material was produced in 24 h. 1-Phenylallene behaved in a similar manner, although in this case, mixtures of isomers were obtained. 1-*n*-Hexylallene underwent reaction to give an inseparable mixture of all possible regio- and stereoisomers of the coupling product. 1,1-Dimethylallene underwent polymerization, as did 1-ethoxyallene. 1-Bromoallene underwent a catalytic *trimerization*. The 2,3-bis(chloromethyl)-1,3-butadiene formed in the above catalytic reaction underwent reaction with a variety of bifunctional nucleophiles to produce five-, six-, and seven-membered rings containing exocyclic conjugated dienes.

Reaction of allene with dichlorobis(benzonitrile)palladium(II) in benzonitrile produces a high yield of a π-allylpalladium complex containing two units of allene connected at their central carbons.[1] We recently reported[2] the conversion of this complex into a variety of conjugated exocyclic dienes by reaction with "bifunctional" nucleophiles (eq 1). Although this led to the desired exocyclic dienes in fair yield, the range of nucleophiles was limited, and the process consumed a stoichiometric amount of palladium. To circumvent this problem, an approach to these same exocyclic dienes using only catalytic quantities of palladium salts was developed and is detailed herein.



Results and Discussion

π-Allylpalladium complexes are oxidatively cleaved to allylic chlorides by treatment with copper(II) chloride,[3]

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