case of the enantiomer (*R,R*) (leading to lactones **2** and **3**), this portion of the molecule could adopt two orientations (position 3 and 4), although one (position 4) would be favored over the other because of some electronic interactions with the active site.[20]

Experimental Section

General Procedures and Materials. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$. FID gas chromatography (GC) analyses were performed using a capillary column (OV-1701, 25 m). Separations by flash chromatography were achieved with Merck silica gel, and separations by HPLC were carried out with a Si60 column (1-in. diameter) using hexane/ether (70/30–20 mL/min).

Acinetobacter NCIB 9871 was a generous gift from Prof. C. T. Walsh and *Acinetobacter* TD63 from Prof. P. W. Trudgill. Stock cultures were grown on nutrient agar at 30 °C, stored at 4 °C, and subcultured at monthly intervals.

Ketone **1a** was purchased from Merck. Catalytic reduction of **1a** (H_2, atmospheric pressure, 5% Pd/C, AcOEt) led to ketone **1b**. Ketones **1c–e** were obtained from the corresponding olefins by [2 + 2] cycloaddition of dichloroketene (generated in situ from trichloroacetyl chloride according to the procedure of Mehta and Rao),[21] followed by dechlorination (zinc and acetic acid).[22] The IR and ^1H NMR spectra of compounds **1c**,[23a] **1d**,[23b] and **1e**[23a] were identical with those previously reported.

Typical Biotransformation Experiment. A 1-L minimal mineral medium culture[4] with 2 g of *cis/trans*-1,2-cyclohexanediol (Prolabo) as only carbon source was used. Cells were grown for 15 h at 30 °C in a 2-L fermentor with vigorous aeration and stirring at 400 rpm. At the end of the growth period, the temperature was lowered to 25 °C[24] and pH was adjusted to 7.1. Additional cyclohexanediol (0.25 g) and, for *Acinetobacter* NCIB 9871, tetraethylpyrophosphate (200 mg) as a hydrolase inhibitor,[4] was added. After 45 min, 1 g of ketone dissolved in 5 mL of EtOH was added. The progress of the reaction was followed by periodic analysis of aliquots (1 mL) by capillary GC using tetradecane as an internal standard. After completion of the reaction (2–6 h), the biotransformation medium was acidified (pH 1) and extracted with dichloromethane (continuous extraction, 24 h). Products, which were all liquids, were purified by flash chromatography and/or bulb-to-bulb distillation.

The lactones **2a,b,d,e** and **3a–e** were identified by comparison of their IR and ^1H and ^{13}C NMR spectra with those already described in the literature (cf. Table I for references).

(1*S*,6*R*)-(−)-8-Oxabicyclo[4.3.0]non-2-en-7-one (2c):[16d] IR (neat) 1760 cm^{-1}; ^1H NMR δ 1.1–1.98 (m, 7 H), 2.20 (m, 1 H), 2.42 (m, 1 H), 2.63 (m, 1 H), 3.95 (d, 1 H), 4.20 (m, 1 H); ^{13}C NMR δ 186.5 (C=O), 130.7 (CH), 125.2 (CH), 72.0 (CH_2), 38.0 (CH), 35.4 (CH), 21.1 (CH_2), 19.8 (CH_2). Anal. Calcd for $C_6H_{10}O_3$: C, 69.54; H, 7.30. Found: C, 69.24; H, 7.42.

The assessments of enantiomeric excesses were made utilizing NMR spectroscopy in the presence of a shift reagent, $Eu(tfc)_3$, according to the method of Jakovac and Jones.[25] In some cases, the optical purities and ee's of unsaturated lactones were determined on the corresponding saturated compounds obtained by hydrogenation over a Pd/C catalyst. The absolute configurations of the lactones were determined on the basis of previously published results (cf. Table I for references).

The racemic lactones **3a–e** were prepared by chemical Baeyer–Villiger oxidation (H_2O_2–AcOH) at 0 °C.[26] The racemic lactones **2b** and **2e** are obtained after reduction of the corresponding anhydrides using $NaBH_4$.[27]

Acknowledgment. We thank the Groupement Scientifique "Arômes et Bioconversions" managed by the CNRS, the Ministère de la Recherche, and the Société Nationale Elf-Aquitaine (Sanofi-BioIndustries) for financial support of this research and the attribution of a research grant to one of us (V.A.). Dr. Lizzani-Cuvelier and Prof. R. Fellous (Laboratoire de Chimie des Arômes, Nice, France) are greatly acknowledged for having performed the various ee determinations by GC analysis as well as Ms. M. Noailly (Faculté de Pharmacie, Marseille) for running the 200-MHz NMR spectra. Dr. A. Archelas is sincerely thanked for interesting and stimulating discussions and for help.

Registry No. **1a**, 62182-73-4; **1b**, 138124-04-6; **1c**, 52466-03-2; **1d**, 137917-81-8; **1e**, 109660-29-9; **2a**, 128946-78-1; **2b**, 121960-86-9; **2c**, 138124-05-7; **2d**, 88586-06-5; **2e**, 89395-29-9; **3a**, 43119-28-4; **3b**, 43119-29-5; **3c**, 43119-25-1; **3d**, 124094-64-0; **3e**, 74708-16-0.

(20) This hypothesis could explain the difference of behavior observed between the five-membered ring compounds **1a,b** and the six-membered ring compounds **1c,d**. **1a** and **1b** could not adopt the position 3, because these molecules, more concave than the six-membered ring, would be partially situated in the "forbidden zone" (dotted cube).

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Reactivity of (3-Chloro-2-methylenecycloalkyl)palladium Chloride Dimers: A Palladium-Mediated Ring Homologation–Functionalization Approach to 4-Aryltropones Related to Colchicine

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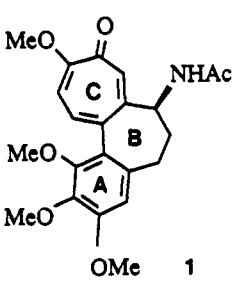
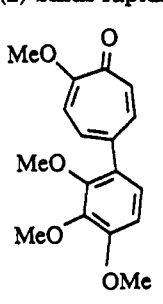
The tricyclic alkaloid colchicine (**1**) is the active principle of the toxic meadow saffron (*colchicum automnal*).[1] It has been used as a treatment for gout,[2] glaucoma,[3] and HIV-1 and -2.[4] The slow, irreversible 1:1 binding of colchicine to the tubulin protein inhibits in vivo microtubule formation.[5] There are two distinct binding sites which individually recognize the A and the C rings of colchicine.[6] Thus, the A–C linked molecule 2-methoxy-5-(2′,3′,4′-trimethoxyphenyl)tropone (**2**) binds rapidly and



1



2

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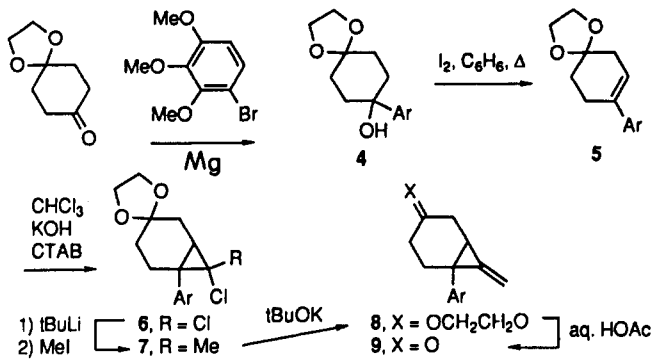
0022-3263/92/1957-1309$03.00/0

Scheme I

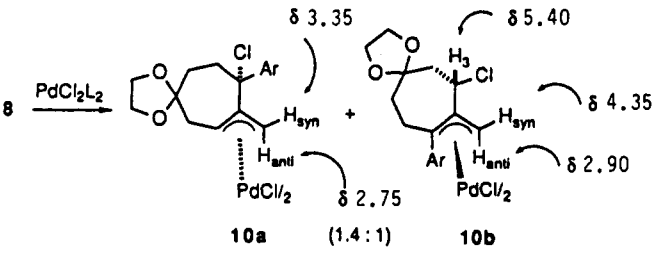


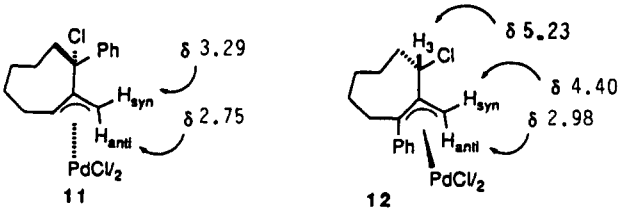
reversibly to tubulin.[7a] More recently, other A–C linked compounds have demonstrated significant tubulin polymerase inhibitory activity.[7b-d] Recent synthetic efforts toward colchicine have focused on ring expansion routes to generate the tropolonic C ring.[8] Our efforts in this area have led to the preparation of the AR-7-7 skeleton of colchicine using a ring homologation–functionalization methodology.[9] This strategy involves (i) chloropalladation of 1-aryl-7-methylenebicyclo[4.1.0]heptane,[10] (ii) reaction of the resultant π-allyl palladium product as an "isopropenyl monocation" synthon[11] to generate a substituted arylcycloheptadiene, and (iii) subsequent intramolecular acylation to form the central B ring. However, these previous studies have indicated the problems associated with attempts to cyclize a substrate with a partially oxidized C ring. We herein report on a palladium-mediated ring homologation–functionalization route to 4-aryltropones related to **2**.

Results and Discussion[12]

Formation of a tropone C ring required a protected carbonyl functionality on the cyclohexene ring of **5**. Thus, the methylenebicyclo[4.1.0]heptane precursor **8** was prepared as indicated in Scheme I. Addition of the Grignard reagent derived from 1-bromo-2,3,4-trimethoxybenzene[13] to cyclohexanedione monoethyleneketal followed by dehydration gave the precursor for ring homologation–functionalization. Of particular note is the lack of reactivity of olefin **5** with (1-chloroethyl)carbene, generated from the reaction of 1,1-dichloroethane with *n*-butyllithium.[14] The two-step procedure involving PTC addition of dichlorocarbene[15] followed by lithium–halogen exchange and methylation[16] proved to be a suitable alternative. Dehydrochlorination[14] of the mixture of diastereoisomers **7** gave the ketal-protected methylenebicyclo[4.1.0]heptanone **8**. The ketal protecting group could be removed without disruption of the methylenecyclopropane moiety to give **9**.

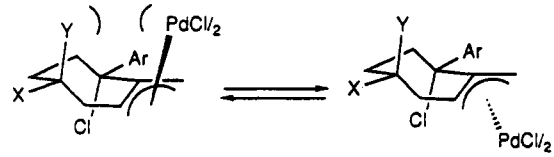
Chloropalladation of **8** gave a mixture of **10a** and **10b** (1.4:1 ratio as determined by integration of the H_{syn} resonance signals of each). The structure of **10a** was assigned





by comparison of its ^{1}H NMR spectroscopic data with that of the known complex **11**.[10a] In particular, the chemical shifts for H_{syn} and H_{anti} of **10a** (δ 3.35 and 2.75, respectively) are similar to those of the corresponding signals for **11** (δ 3.29 and 2.75, respectively).[10a] Likewise, the structure of **10b** was assigned by comparison of its ^{1}H NMR spectroscopic data with that of the known complex **12**.[10a] In particular, the chemical shifts for H_{syn}, H_{anti}, and H_3 or **10b** (δ 4.35, 2.90, and 5.40, respectively) are similar to those of the corresponding signals for **12** (δ 4.40, 2.98, and 5.23, respectively).[10a]

The relative stereochemistry at the π-allyl C1 carbon and at C3 for **10a** and for the parent (3-chloro-2-methylene-3-phenylcycloheptyl)palladium chloride dimer (**13a**)[10] are different (**10a** = 1*R**,3*S**; **13a** = 1*S**,3*S**). Both com-



plexes **10a** and **13a** adopt structures in which the 3-aryl substituent is equatorial and the 3-chloro substitutent is axial. This conformer avoids allylic $A^{1,3}$ strain[17] between the chlorine atom and the 2-methylene substituent.[18] The difference in relative stereochemistry of **10a** and **13a** is rationalized on the following basis: complex **13a** (Cl and Pd anti periplanar) is more stable than **13a'** since this orientation avoids steric interactions between Cl and Pd, while complex **10a** (Cl and Pd syn periplanar) is more stable than **10a'** since this orientation avoids 1,3-diaxial interactions between the Pd metal and one of the ethylene ketal oxygens.[19]

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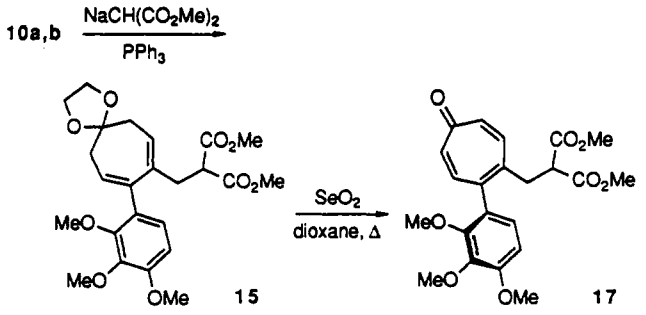
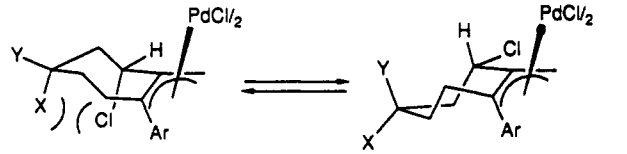
(18) The equatorial 3-aryl substituent presents less allylic $A^{1,3}$ strain since it may twist perpendicular to the plane of the plane of the π-allyl.

(19) Structures **10a** and **10a'**, and similarly **13a** and **13a'**, are related by $\eta^3 \rightarrow \eta^1 \rightarrow \eta^3$ interconversion. This interconversion is known to be a facile process for certain π-allyl palladium complexes.[20]

Scheme II



While the relative stereochemistry at the π-allyl C1 carbon and at C3 for **10b** and for the parent (3-chloro-2-methylene-1-phenylcycloheptyl)palladium chloride dimer (**13b**)[10] are the same (1*R**,3*S**), the two structures differ

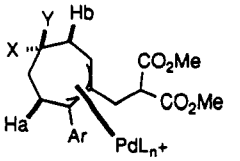


10b' X = Y = OCH_2CH_2O, Ar = $(MeO)_3C_6H_2$ **10b**
13b X = Y = H, Ar = C_6H_5 **13b'**

with respect to the conformation of the 7-membered ring pseudochair (**10b** = Cl-eq; **13b** = Cl-ax). This difference is rationalized on the following basis: complex **13b** adopts a Cl-axial conformation to avoid allylic $A^{1,3}$ strain with the 2-methylene substituent, while complex **10b** adopts a Cl-equatorial conformation in order to avoid 1,3-diaxial interactions between the chlorine atom and one of the ethylene ketal oxygens.

Since the reaction of regioisomerically substituted (3-chloro-2-methylenecycloheptyl)palladium chloride dimers **10a** and **10b** with malonate anion was anticipated to converge through a single intermediate **14**,[21] separation of the two isomers was not attempted. Treatment of a mixture of **10a** and **10b** with 1 equiv of sodium dimethyl malonate in the presence of triphenylphosphine gave a single cycloheptadiene product **15** (Scheme II). The structure of **15** was assigned on the basis of its ^1H NMR spectral data. In particular, each of the two olefinic resonance signals (δ 5.84 and 6.10) appears as a triplet (J = 7 Hz each). Exclusive formation of **15** indicates that β-hydride elimination of the intermediate **14** only occurs from the hydrogen β to the more substituted terminus of the cycloheptenyl π-allyl (i.e., only H_a). We have previously found that reaction of a mixture of **13a** and **13b** under similar reaction conditions (proceeding via intermediate **16**) gave a 1:1 mixture of cycloheptadienes. This mixture arises from hydride elimination at the two β-positions of the π-allyl intermediate **16** (i.e., both H_a and H_b). While it is clear that the difference in reactivity for intermediates **14** and **16** is due to the presence of the ethylene ketal, the exact nature by which this functionality effects the course of β-hydride elimination is ambiguous.

A one-pot deketalization–oxidation of **15** with selenium dioxide gave the tropone **17** in 50% yield.[22] The structural



14, X=Y= OCH_2CH_2O, Ar = $(MeO)_3C_6H_2$
16, X=Y= H, Ar = C_6H_5

assignment for **17** is based upon its spectral data. In particular, the carbonyl ν_{CO} (1736 and 1628 cm^{-1}) and ^{13}C NMR chemical shift (δ 186.8) are characteristic of the polar nature of this functional group in the tropone ring. It is also of interest to note that the ^1H NMR spectrum of **17** contains five methoxy singlets, thus indicating that the two methoxy esters are chemically nonequivalent. Since molecule **17** does not contain a tetrahedral chiral carbon, then the two ester functionalitites are diastereotopic due to the "biaryl chirality" about the aryl-to-tropone bond.

In summary, the palladium-mediated ring homologation–functionalization methodology has been successfully applied to the synthesis of 4-aryltropones related to colchicine. In order to proceed to the tropolone ring required for colchicine-like tubulin binding activity, further oxidation of the tropone ring is required.[23]

Experimental Section[24]

4-(Ethylenedioxy)-1-(2′,3′,4′-trimethoxyphenyl)cyclohexanol (4). To magnesium turnings (2.17 g, 89 mmol) was added a solution of 4-bromo-1,2,3-trimethoxybenzene[13] (**3**; 22.15 g, 89 mmol) in THF (45 mL). The suspension was stirred and warmed at 60 °C until the Grignard formation began and was then allowed to stand without heating until the Mg had reacted. The flask was cooled to rt, and a solution of 1,4-cyclohexandione–monoethyleneketal (13.93 g, 89 mmol) in THF (90 mL) was added dropwise over the period of 1 h. The milky solution was stirred for 20 h. The reaction was then quenched by the addition of H_2O (100 mL), and the resultant mixture was extracted with Et_2O (4 × 100 mL). The combined organic layers were washed with 10% aqueous NaOH (100 mL) and with H_2O (100 mL). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure. Kugelrohr distillation at 140–150 °C (0.20 mm Hg) afforded **4** as a light yellow oil: 18.28 g (63%); IR (neat) 3700–3100 s, 1610 m, 1105 s, 925 m, 850 w, 820 m cm^{-1}; 60-MHz ^1H NMR (CCl_4) δ 1.6–2.3 (m, 8 H), 3.54 (br s, 1 H), 3.6–4.1 (m, 13 H), 6.42 and 6.86 (2d, J_{AB} = 8 Hz, 2 H). This product was used in the next step without further purification or characterization.

4-(Ethylenedioxy)-1-(2′,3′,4′-trimethoxyphenyl)cyclohexene (5). A solution of **4** (25.0 g, 77 mmol) and I_2 (0.05 g) in benzene (60 mL) was heated at reflux for 36 h, with azeotropic removal of H_2O by a Dean-Stark trap. The solution was cooled and washed with saturated aqueous $NaHSO_3$ (60 mL). The aqueous layer was washed with benzene (60 mL). The combined benzene layers were dried ($MgSO_4$) and evaporated under pressure. The residue was recrystallized (Et_2O) to give **5** as a colorless solid: 22.1 g (94%); mp 40–41 °C; IR (Nujol) 3039 m, 3010 s, 2910 m, 1598 m, 1495 s, 1484 s, 1295 s, 1110 s cm^{-1}; 300-MHz ^1H NMR ($CDCl_3$) δ 1.77 (t, J = 7 Hz, 2 H), 2.44 (br s, 2 H), 2.59 (br m, 2 H), 3.84, 3.85, 3.97, and 4.02 (4s, 13 H), 5.64 (m, 1 H), 6.62 and 6.87 (2d, J_{AB} = 8.5 Hz, 2 H); 15-MHz $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 28.2, 31.3, 36.0, 55.7, 60.5, 64.0, 107.1, 107.4, 122.7, 123.1, 130.1, 133.8, 142.0, 151.0, 152.4; GC/MS 306 (M^+, 50), 220 (100), 205 (78), 189 (62). Anal. Calcd for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24. Found: C, 66.72; H, 7.17.

7,7-Dichloro-4-(ethylenedioxy)-1-(2′,3′,4′-trimethoxyphenyl)bicyclo[4.1.0]heptane (6). To a solution of **5** (5.00 g, 16.3 mmol) and cetyltrimethylammonium bromide (0.06 g, 0.2 mmol) in $CHCl_3$ (100 mL) was added 50% aqueous NaOH (50 mL). The biphasic solution was vigorously stirred with a mechanical stirrer for 1 h at 30 °C. The yellow solution was diluted

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(21) Nucleophilic attack at the unsubstituted allylic terminus of either isomer **10a** or **10b**, followed by oxidative addition of the resultant allylic chlorides, was anticipated to afford the same π-allyl intermediate **14**.[9,11]

(22) It is not clear which step occurs first, deketalization or oxidation; however, cycloheptadienones are known to undergo oxidation by SeO_2 to form tropones: Nozoe, T. *Non-Benzenoid Aromatic Compounds*; Ginsberg, D., Ed.; Interscience: New York, 1959; Chapter 7, pp 339–464. Lloyd, D. *Carbocyclic Non-Benzenoid Aromatic Compounds*; Elsevier: New York, 1966; Chapter 6, pp 117–161.

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with H_2O (100 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 75 mL), and the combined organic extracts were washed with H_2O (100 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (100 mL) and filtered through a bed of silica gel (230–400 mesh). The solvent was evaporated under reduced pressure to afford **6** as a cream solid: 4.98 g (78%); mp 112–113 °C; IR (Nujol) 3010 w, 2994 s, 1598 w, 1427 s, 1284 s, 1276 s, 1253 m cm^{-1}; 60-MHz ^1H NMR (CCl_4) δ 1.1–2.4 (m, 7 H), 3.78 (s, 3 H), 3.80 (s, 4 H), 3.85 (s, 3 H), 4.02 (s, 3 H), 6.40 and 6.70 (2d, J_{AB} = 8 Hz, 2 H); 15-MHz $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 27.4, 29.1, 30.3, 32.1, 34.6, 55.9, 60.5, 61.1, 64.4, 70.7, 106.3, 108.0, 122.7, 129.0, 141.8, 152.7, 153.4; GC/MS 370 ($M^{37}Cl^+$ – Cl, 4), 368 ($M^{35}Cl^+$ – Cl, 6), 353 (23), 231 (10), 99 (100). Anal. Calcd for $C_{18}H_{22}O_5Cl_2$: C, 55.53; H, 5.70. Found: C, 55.64; H, 5.77.

7-Chloro-4-(ethylenedioxy)-1-(2′,3′,4′-trimethoxyphenyl)-7-methylbicyclo[4.1.0]heptane (7). To a solution of **6** (4.00 g, 10.3 mmol) and HMPA (20 mL, 0.11 mol) in THF (200 mL) cooled in an ether/liquid N_2 bath (–95 °C) was added, via syringe, a solution of *t*-BuLi (13.3 mL, 1.7 M, 23 mmol) over a period of 15 min. The colorless solution became a dark brown color. The solution was stirred for 5 min, and CH_3I (3.2 mL, 51 mmol) was added over a period of 5 min. The brown solution turned yellow. The solution was stirred at –95 °C for 15 min and then allowed to warm to rt and stirred for 18 h. The reaction mixture was diluted with H_2O (200 mL) and extracted with Et_2O (4 × 50 mL). The combined organic extracts were washed with H_2O (100 mL), dried ($MgSO_4$), and evaporated. The crude product was purified by flash chromatography using hexanes/ethyl acetate (3:1) as eluant. Evaporation of the product fractions gave a mixture of diastereomers **7** (ca. 1:1) as a colorless solid: 3.13 g (88%); mp 81–83 °C; IR (Nujol) 3023 w, 2991 s, 1598 w, 1495 m, 1466 m, 1234 s, 1216 s, 1197 s, 1103 s cm^{-1}; 60-MHz ^1H NMR (CCl_4) δ 0.9–2.4 (m) and 1.30 and 1.75 (2s, total 10 H), 3.70, 3.83 and 3.95 (3 br s, 13 H), 6.42 and 6.77 (2d, J_{AB} = 8 Hz, 2 H); 15-MHz $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 19.2, 26.7, 26.7, 27.9, 28.7, 29.0, 29.3, 29.5, 30.4, 36.5, 30.8, 31.8, 43.2, 51.1, 54.9, 55.8, 60.4, 60.9, 63.6, 64.0, 64.3, 105.8, 106.1, 106.5, 107.1, 108.0, 108.7, 109.1, 123.0, 124.2, 124.5, 128.0, 129.9, 131.6, 141.8, 152.7; GC/MS 370 ($M^{37}Cl^+$, 3), 368 ($M^{35}Cl^+$, 7), 333 (32), 231 (15), 216 (9), 99 (100), 55 (11). Anal. Calcd for $C_{19}H_{25}O_5Cl$: C, 61.87; H, 6.83. Found: C, 61.90; H, 6.68. The ratio of diastereoisomers (ca. 1:1) was determined by GC/MS and by the intensity of the cyclopropylmethyl resonance signals.

4-(Ethylenedioxy)-1-(2′,3′,4′-trimethoxyphenyl)-7-methylenebicyclo[4.1.0]heptane (8). To a stirred solution of *t*-BuOK (0.32 g, 3.26 mmol) in DMSO (10 mL) heated to 60–70 °C was added dropwise over a period of 10 min a solution of **7** (0.40 g, 1.09 mmol) in DMSO (8 mL). The solution was heated at 65 °C for 120 h. The solution was cooled to rt and diluted with H_2O (200 mL). The aqueous solution was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with H_2O (75 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification of the oily brown residue by flash chromatography using hexanes/ethyl acetate (5:1) as eluant gave **8** as a colorless oil: 0.22 g (73%); 300-MHz ^1H NMR ($CDCl_3$) δ 1.58 (m, 3 H), 1.94 (dd, *J* = 1.6, 14.1 Hz, 1 H), 2.09 (dt, *J* = 13.1, 4.6 Hz, 1 H), 2.24 (m, 2 H), 3.81 (s, 3 H), 3.85, (s, 3 H), 3.98 (s and m, 7 H), 5.57 (d, *J* = 1.2 Hz, 1 H), 5.66 (d, *J* = 2.4 Hz, 1 H), 6.54 and 6.97 (2d, *J* = 8.4 Hz, 2 H); 15-MHz $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 21.0, 24.9, 29.6, 30.7, 33.6, 56.6, 61.3, 61.5, 64.7, 64.9, 104.0, 106.9, 107.0, 108.4, 124.2, 131.7, 143.0, 143.8, 153.3, 153.9; GC/MS 332 (M^+, 11), 301 (88), 231 (23), 215 (100), 128 (18), 115 (23), 99 (42). Anal. Calcd for $C_{19}H_{24}O_5$: C, 68.66; H, 7.28. Found: C, 68.39; H, 7.16.

1-(2′,3′,4′-Trimethoxyphenyl)-7-methylenebicyclo[4.1.0]-heptan-4-one (9). A solution of **8** (1.99 g, 5.99 mmol) in THF (25 mL), glacial acetic acid (15 mL), and H_2O (10 mL) was headed to reflux for 1 h. The reaction mixture was cooled to rt, diluted with H_2O (150 mL), and neutralized with solid $NaHCO_3$. The aqueous mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with H_2O (75 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification of the residue by flash chromatography using $CHCl_3$/ethyl acetate (20:1) as eluant followed by recrystallization (Et_2O) gave **9** as a colorless solid: 1.56 g (90%); mp 103–104 °C; IR ($CHCl_3$) 1712 s, 1598 m cm^{-1}; 300-MHz ^1H NMR ($CDCl_3$) δ 1.82 (m, 1 H), 2.16 (dt, *J* = 12.3, 4.0 Hz, 1 H), 2.3–2.5 (m, 3 H), 2.79 (dd, *J* = 18.5, 2.4 Hz, 1 H), 2.93 (dd, *J* = 18.5, 4.8 Hz, 1 H), 3.84, 3.87, 3.99 (three s, 9 H), 5.70 (d, *J* = 1.2 Hz, 1 H), 5.81 (d, *J* = 2.4 Hz, 1 H), 6.57 and 6.97 (2d, *J* = 8.5 Hz, 2 H); 75-MHz $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 20.2, 24.8, 27.7, 37.7, 38.3, 56.0, 60.6, 60.8, 106.7, 107.0, 123.4, 129.1, 139.0, 142.4, 153.2, 209.9; GC/MS 288 (M^+, 13), 257 (100), 215 (58), 184 (13), 115 (19), 77 (13). Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.81; 6.99. Found: C, 70.65; H, 7.11.

Chloropalladation of 8. To a solution/suspension of $PdCl_2(CH_3CN)_2$ (0.04 g, 0.16 mmol) in CH_2Cl_2 (50 mL) was added **8** (0.06 g, 0.18 mmol). The solution was stirred at rt for 1 h during which time the brownish red color turned a golden yellow. The solvent was removed under reduced pressure. The resultant yellow solid was washed with hexanes (3 × 50 mL), and the solid was then purified by flash chromatography using $CHCl_3$ as eluant. Evaporation of the product fractions gave a mixture of **10a** and **10b** (1.4:1 ratio as determined by integration of their H_{syn} resonance signals) as a bright yellow solid: 0.07 g, (85%); mp >200 °C dec; 300-MHz ^1H NMR ($CDCl_3$) δ 1.2–2.7 (m), 2.75 (br s, H_{anti} **10a**), 2.90 (br s, H_{anti} **10b**), 3.35 (br s, H_{syn} **10a**), 3.80–4.15 (m), 4.35 (br s, H_{syn} **10b**), 5.40 (br d, *J* = 10 Hz, H_3 **10b**), 6.00–6.15 (m), 6.50–6.85 (m), 7.15–7.30 (m), 7.70–7.85 (m). Due to the thermal instability of this mixture[25] satisfactory elemental analysis could not be obtained. Anal. Calcd for $[C_{19}H_{24}O_5Cl_2Pd]_2$: C, 44.77; H, 4.75. Found: C, 43.72; H, 4.61.

Dimethyl [[5-(Ethylenedioxy)-2-(2′,3′,4′-trimethoxyphenyl)-2,7-cycloheptadien-1-yl]methyl]propanedioate (15). To a solution of **10a/b** (0.41 g, 0.81 mmol) and triphenylphosphine (0.85 g, 3.24 mmol) in THF (40 mL) heated at reflux was added, via syringe, a solution of sodium dimethyl malonate (0.97 mmol, freshly prepared from excess NaH and dimethyl malonate) in THF (15 mL). The yellow solution turned cloudy upon addition of the malonate anion. The reaction mixture was heated for 24 h, during which time the color became a reddish brown. The solution was cooled and concentrated under reduced pressure. A solution of the residue in CH_2Cl_2 (75 mL) was washed with H_2O (2 × 50 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification of the residue by flash chromatography using hexanes/ethyl acetate (2:1) as eluant gave **15** as a colorless solid: 0.27 g (73%); mp 112–113 °C; IR ($CHCl_3$) 3050 m, 3005 m, 2957 s, 2885 s, 1725 s, 1596 s, 1495 s, 1461 s, 1337 s, 1284 s, 1153 s cm^{-1}; 60-MHz ^1H NMR ($CDCl_3$) δ 2.37 (m, 4 H), 2.62 (br d, *J* = 7 Hz, 2 H), 3.35 (t, *J* = 7 Hz, 1 H), 3.65, 3.70, 3.83, 3.90 (4s, 19 H), 5.84 (t, *J* = 7 Hz, 1 H), 6.10 (t, *J* = 7 Hz, 1 H), 6.63 and 6.90 (2d, J_{AB} = 8.5 Hz, 2 H); 15-MHz $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 34.5, 37.8, 51.1, 52.3, 55.9, 60.8, 61.0, 64.2, 107.4, 124.5, 126.7, 127.3, 129.8, 139.7, 140.5, 151.6, 153.4, 169.2; GC/MS 462 (M^+, 100), 431 (43), 331 (88), 259 (61), 258 (59), 228 (25), 227 (54), 103 (72), 73 (39). Anal. Calcd for $C_{24}H_{30}O_9$: C, 62.33; H, 6.54. Found: C, 62.21; H, 6.51.

Dimethyl [[3-(2′,3′,4′-trimethoxyphenyl)-7-oxo-1,3,5-cycloheptatrien-4-yl]methyl]propanedioate (17). To a solution of **15** (0.08 g, 0.17 mmol) in dioxane (10 mL) was added SeO_2 (0.038 g, 0.35 mmol). The reaction mixture was heated at reflux for 16 h, cooled, filtered through filter-aid and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (40 mL), washed with saturated aqueous $NaHCO_3$ (35 mL) and with H_2O (35 mL), dried ($MgSO_4$), and concentrated. Purification of the residue by flash chromatography using ethyl acetate/hexanes (2:1) as eluant gave **17** as a yellow oil: 0.040 g (50%); IR ($CHCl_3$) 2957 m, 1736 s, 1628 s, 1595 m, 1575 s, 1488 s, 1464 s, 1437 m, 1297 s, 1266 s, 1242 s, 1213 s, 1105 s, 1087 s, 1016 m, 927 m, 893 s cm^{-1}; 300-MHz ^1H NMR ($CDCl_3$) δ 3.02 (d, *J* = 7 Hz, 2 H), 3.48 (t, *J* = 7 Hz, 1 H), 3.64, 3.65, 3.77, 3.89, 3.91 (five s, 15 H), 6.74 and 6.79 (2d, J_{AB} = 8 Hz, 2 H), 6.89 (dd, *J* = 4, 12 Hz, 1 H), 6.98 (dd, *J* = 4, 12 Hz, 1 H), 7.05 (d, *J* = 12 Hz, 1 H), 7.16 (d, *J* = 12 Hz, 1 H); 75-MHz $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 36.4, 51.4, 52.7, 56.1, 61.0, 61.1, 107.6, 123.5, 128.3, 138.8, 140.0, 141.2, 142.5, 143.2, 144.3, 150.2, 154.1, 168.7, 186.8. Anal. Calcd for $C_{22}H_{24}O_8$: C, 63.45; H, 5.81. Found: C, 63.35; H, 5.90.

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Ipso Nitration of *p*-*tert*-Butylcalix[4]arenes

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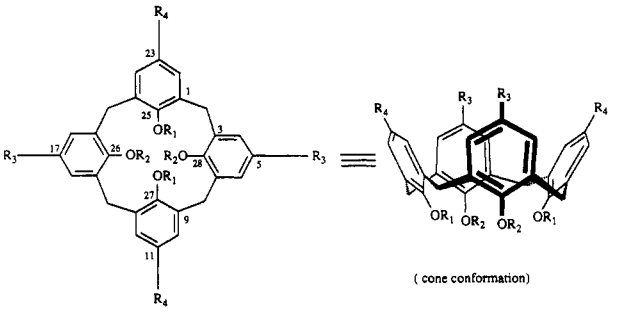
Functionalized calixarenes represent an important class of compounds that can complex cations and neutral molecules.[1,2] Calix[4]arenes can easily be functionalized both at the phenolic OH groups (lower rim) and, after (partial) removal of *tert*-butyl groups, at the para positions of the phenol rings (upper rim). Several methods have been reported for the (selective) introduction of nitro groups at the upper rim viz. direct nitration of free para positions[3,4] and replacement of *p*-sulfonate moieties.[5] Calix[4]arenes having one or two nitro groups at the upper rim have also been prepared by a stepwise synthesis.[6,7] In this paper we describe the (selective) introduction of one or more nitro groups by direct replacement of (a) *tert*-butyl group(s) via an ipso aromatic nitration.[8] After reduction these compounds are important starting materials for molecular receptors based on calixarenes.

Results and Discussion

Reaction of conformationally flexible 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetramethoxycalix[4]arene (**1**) with an excess (20 equiv) of 100% HNO_3 in a 1:1 mixture of dichloromethane and acetic acid for 2 h gave upon crystallization of the crude reaction mixture from ethanol the tetra-ipso-nitrated calix[4]arene **2** in 75% yield. According to the ^1H NMR spectrum, **2** exists as a 93:7 mixture of the partial cone and cone conformation with for the former characteristic absorptions for the methylene bridge protons at δ 4.11 and 3.45 (AB q) and 3.84 (s) and the typical singlet of one of the methoxy groups at δ 3.05. Shinkai et al.[9] described **2** as a complex mixture of conformational isomers (not further assigned) upon methylation of *p*-tetranitrocalix[4]arene. We have also reacted the other tetraalkylated calix[4]arenes **3**, **5**, and **7** (all in the cone conformation)[10] to give the tetranitrocalix[4]arenes **4**, **6**, and **8** (cone conformation) in yields of 67%, 76%, and 37%, respectively. Ipso nitration of the parent calix[4]arene **9** under the above-mentioned conditions failed probably due to the low solubility of the substrate.

Subsequently we studied the behavior of the *diametrically* dialkylated calix[4]arenes **10** and **12**. Treatment of **10** and **12** with about 5 equiv of 100% HNO_3 for only 5–10 min afforded selectively the 11,23-dinitrocalix[4]arenes **11** and **13** in 46% and 24% yield, respectively. Comparison of the NMR data of **11** and **13** with those of the starting compounds **10** and **12** and of the tetranitro compound **14** (vide infra) indicated that the ipso nitration had taken place exclusively at the para position of the phenolic units. Very characteristic in the ^1H NMR spectra is for instance the absorption of the OH group that shifts downfield from δ 7.91 (**10**) and δ 7.22 (**12**) to δ 9.50 and δ 8.99 in the "4-nitrophenol" derivatives **11** and **13**, respectively; in the corresponding tetranitro compound **14** the

Chart I



(cone conformation)

1 $R_1=R_2=Me$ $R_3=R_4=t\text{-}Bu$
3 $R_1=R_2=Pr$ $R_3=R_4=t\text{-}Bu$
5 $R_1=R_2=CH_2CH_2OEt$ $R_3=R_4=t\text{-}Bu$
7 $R_1=R_2=CH_2C(O)OEt$ $R_3=R_4=t\text{-}Bu$
9 $R_1=R_2=H$ $R_3=R_4=t\text{-}Bu$

2 $R_1=R_2=Me$ $R_3=R_4=NO_2$
4 $R_1=R_2=Pr$ $R_3=R_4=NO_2$
6 $R_1=R_2=CH_2CH_2OEt$ $R_3=R_4=NO_2$
8 $R_1=R_2=CH_2C(O)OEt$ $R_3=R_4=NO_2$

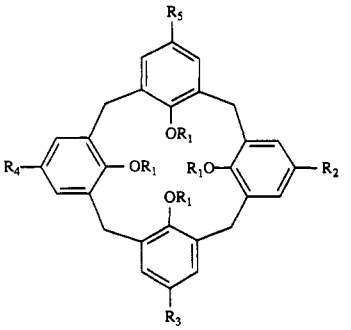
10 $R_1=H$, $R_2=Pr$ $R_3=R_4=t\text{-}Bu$
12 $R_1=H$, $R_2=CH_2C(O)OEt$ $R_3=R_4=t\text{-}Bu$

11 $R_1=H$, $R_2=Pr$, $R_3=t\text{-}Bu$, $R_4=NO_2$
13 $R_1=H$, $R_2=CH_2C(O)OEt$, $R_3=t\text{-}Bu$, $R_4=NO_2$
14 $R_1=H$, $R_2=Pr$, $R_3=R_4=NO_2$
15 $R_1=H$, $R_2=CH_2C(O)OEt$, $R_3=R_4=NO_2$

20 $R_1=H$, $R_2=Me$, $R_3=t\text{-}Bu$, $R_4=H$
21 $R_1=R_2=H$, $R_3=t\text{-}Bu$, $R_4=H$

22 $R_1=R_2=CH_2CH_2OEt$, $R_3=t\text{-}Bu$, $R_4=H$
23 $R_1=R_2=CH_2CH_2OEt$, $R_3=NO_2$, $R_4=H$

Chart II



16 $R_1=Pr$, $R_2=R_3=t\text{-}Bu$, $R_4=R_5=NO_2$
17 $R_1=Pr$, $R_2=R_4=t\text{-}Bu$, $R_3=R_5=NO_2$
18 $R_1=Pr$, $R_2=t\text{-}Bu$, $R_3=R_4=R_5=NO_2$
19 $R_1=CH_2CH_2OEt$, $R_2=R_3=R_4=t\text{-}Bu$, $R_5=NO_2$

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