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REACTIVITY OF (3-CHLORO-2-METHYLENECYCLOALKYL)PALLADIUM CHLORIDE DIMERS: A PALLADIUM MEDIATED RING HOMOLOGATION--FUNCTIONALIZATION APPROACH TO THE AR-7-7 SKELETON OF COLCHICINE

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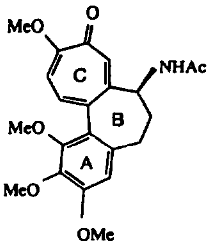
SUMMARY: A palladium mediated ring homologation--functionalization approach to the Ar-7-7 tricyclic skeleton of colchicine from 1-arylcyclohexenes is described. This methodology involves the chloropalladation of 1-aryl-7-methylenebicyclo[4.1.0]heptanes to afford aryl substituted (3-chloro-2-methylenecycloheptyl)palladium chloride dimers. Reaction of the π-allyl complexes with one equivalent of malonate anion gives a cycloheptadiene product. Subsequent reduction and intramolecular acylation yields the Ar-7-7 skeleton.

The tricyclic alkaloid colchicine (*1*) is the active principle of the toxic meadow saffron (*colchicum automnale*).[1] It has been used as a gout suppressant, as a treatment for glaucoma[2] and in cancer research as an antimitotic agent.[3] More recently, it is undergoing preclinical trials as an HIV inhibitor.[4] These desirable biological properties derive from the slow, irreversible 1:1 binding of colchicine to the tubulin protein, which inhibits *in vivo* microtubule formation.[5] Substantial experimental evidence has established that there are two distinct binding sites which individually recognize the A and the C rings of colchicine,[6] while the exact nature of the B ring's contribution to the tubulin binding site is unknown.[7] For example, the A-C linked molecule 2-methoxy-5-(2',3',4'-trimethoxyphenyl)tropone (*2*) binds rapidly and reversibly to tubulin.[8] Obviously, the availability of a series of rationally designed colchicine analogs bearing a modified B ring would be of value to the elucidation of the colchicine-tubulin binding mechanism. However, of the numerous syntheses of colchicine,[9] there is only one reported synthesis of a derivative with a six-membered B ring.[10] We herein report on a palladium mediated ring homologation--functionalization approach to the colchicine skeleton.



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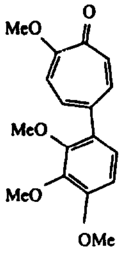

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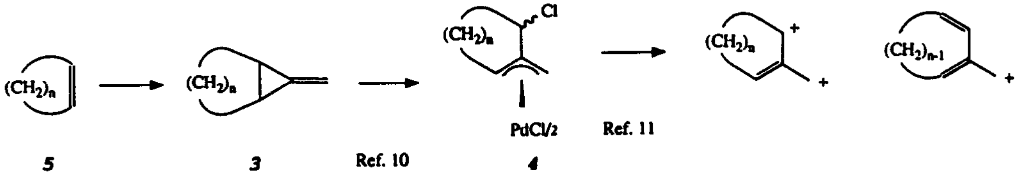
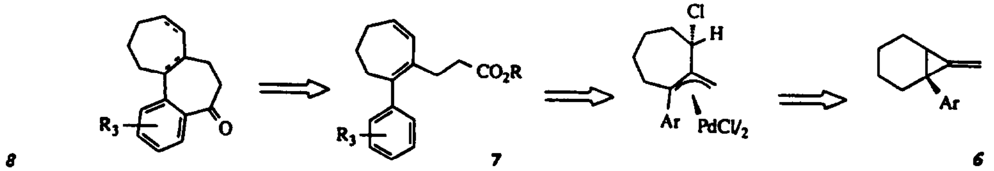
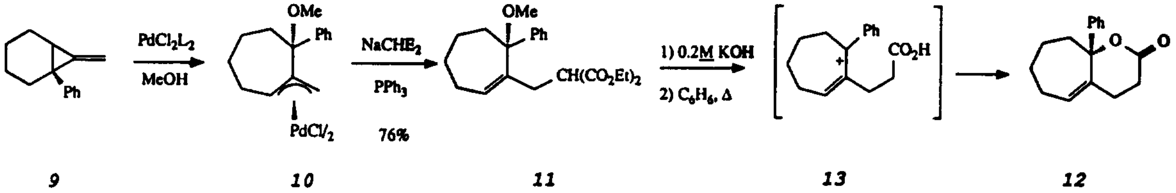
We have recently demonstrated that the chloropalladation of ω-methylenebicyclo[n.1.0]-alkanes *3* affords the (3-chloro-2-methylenecycloalkyl)palladium chloride dimers *4* in excellent yield.[11] Further, we have shown that compounds ***4*** may serve as either "trimethylenemethane dication" synthons or "isoprenyl monocation" synthons under the appropriate reaction conditions.[12] Since the precursors ***3*** may be prepared from the corresponding cycloalkene ***5*** in two steps, this sequence of reactions constitutes an efficient overall ring homologation--functionalization methodology. Thus, the general synthetic strategy for the construction of the Ar-7-7 skeleton of colchicine involves *i)* the chloro- or alkoxy-palladation of an 1-aryl-7-methylenebicyclo[4.1.0]heptane ***6***, *ii)* reaction of the product as an "isoprenyl monocation" synthon to generate a substituted arylcycloheptadiene **7**, and *iii)* subsequent intramolecular acylation to form the central B ring (***8***).[13]



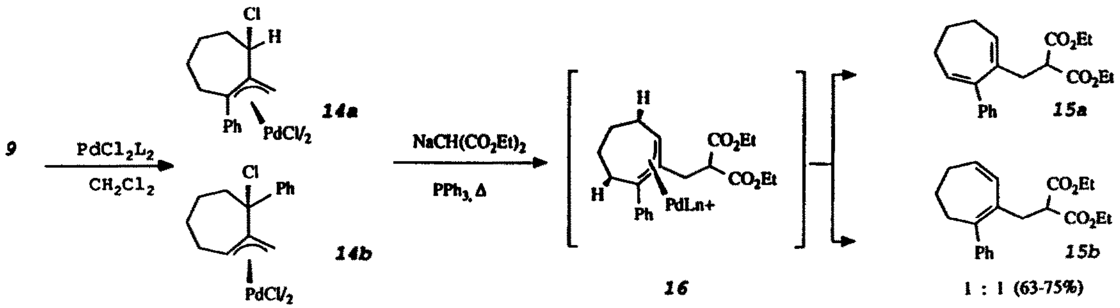


RESULTS AND DISCUSSION[14]

As previously reported, the reaction of (±)-7-methylene-1-phenylbicyclo[4.1.0]heptane (***9***) with palladium chloride (MeOH, 65°C) affords the π-allyl complex ***10***.[15,16] Reaction of compound ***10*** with one equivalent of diethylmalonate anion gives the expected diester ***11*** in good yield. Unfortunately, this compound proved unsuitable for elaboration into the tricyclic skeleton. Saponification-decarboxylation of ***11*** gave the lactone ***12*** as the only isolable product. Presumably, the conditions for decarboxylation are sufficiently vigorous to effect cyclization via the benzylic/allylic cation (***13***).

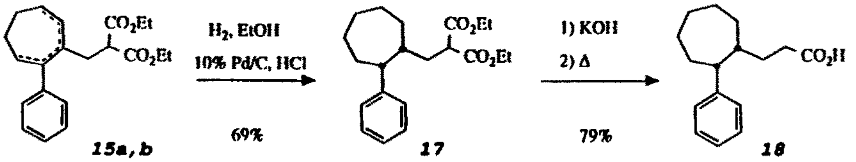


The chloropalladation of ***9*** in CH_2Cl_2 gives a mixture of the isomeric π-allyls ***14a*** and ***b***, which are separable by fractional crystallization.[15,16] In the presence of PPh_3, either ***14a*** or ***b*** reacts with one equivalent of diethylmalonate anion, to produce a mixture of cycloheptadienes ***15a*** and ***b*** (1:1, 63-75%). The isomeric cycloheptadienes were identified by ^1H NMR spectroscopy. Notably, the signals for the olefinic protons of ***15a*** appear as a pair of triplets, due to coupling of two adjacent protons each; while the olefinic proton signals of ***15b*** appear as a doublet (J = 11.2) and a doublet of triplets (J = 11.2, 5.6). Analysis by GC/MS gave a single, broad peak with the corresponding parent ion (m/z = 342).

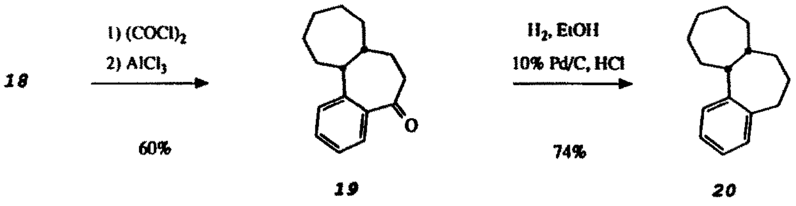


Isolation of identical product mixtures from the reaction of isomeric π-allyls ***14a*** and ***b*** suggests the involvement of a common intermediate. We propose that the reaction of ***14a*** or ***b*** proceeds via initial nucleophilic attack at the exocyclic terminus, followed by oxidative addition of Pd(0) into the resultant isomeric allylic chlorides to yield the same π-allyl species (***16***). The product mixture arises via β-hydride elimination of the unsymmetrical intermediate ***16***.

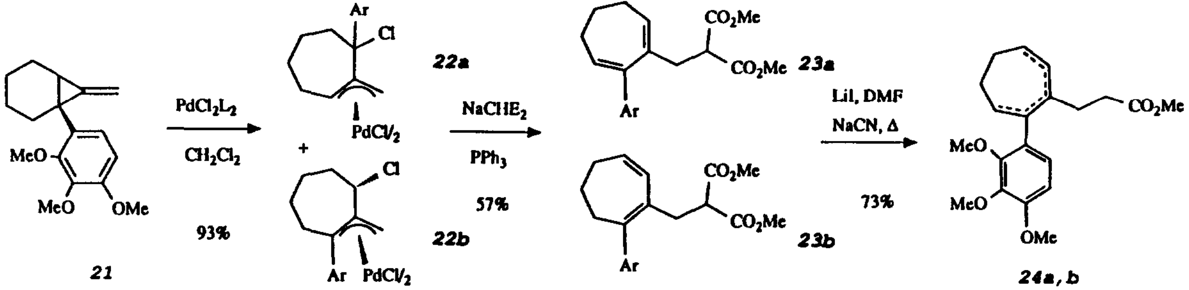
Attempts to separate the mixture were unsuccessful, however, separation proved unnecessary since catalytic hydrogenation of the mixture afforded a single product (***17***). The product was assigned the *cis* stereochemistry on the basis of ^{1}H NMR spectroscopy. Notably, the benzylic proton appears as a doublet of triplets (J = 11.1, 4.3). The large doublet coupling indicates that the benzylic proton is coupled to only one other *trans* proton. Saponification-decarboxylation of diester ***17*** gave (2-phenylcycloheptyl)propanoic acid ***18***.



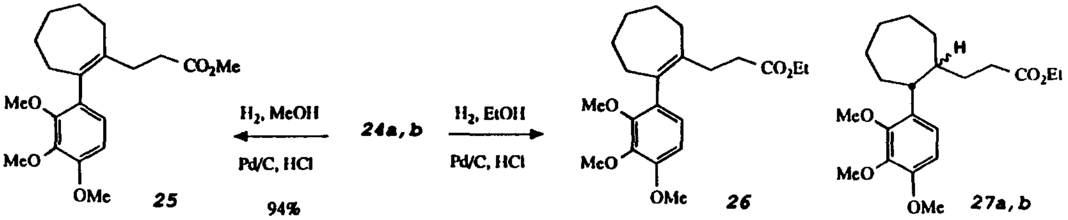
Conversion of ***18*** into the known[13a] tricyclic ketone ***19*** was accomplished in a one-pot procedure involving initial treatment with neat oxalyl chloride, followed by $AlCl_3$ in CH_2Cl_2. While Friedel-Crafts cyclization for the formation of seven-membered rings is generally less facile than formation of six- and five-membered rings,[17] the product is obtained in good yield. This may be due, in part, to the constraints upon bond rotation which the C ring places on the system.[18] Reduction of the benzylic ketone proceeded in good yield to give the hydrocarbon ***20***.



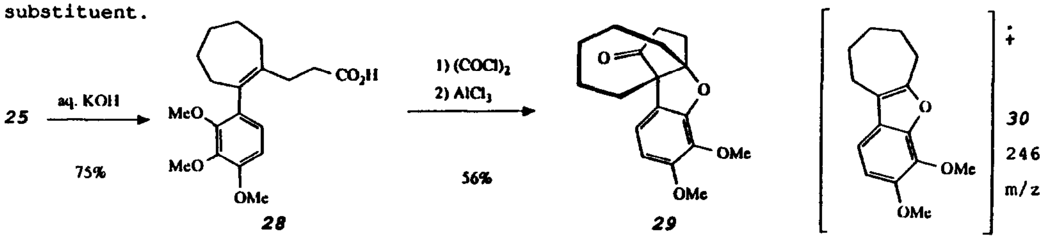
The 2,3,4-trimethoxy substituted A ring of colchicine is a prerequisite for tubulin binding activity.[5] Thus, along the lines of our proposed synthetic strategy, the preparation of colchicine would require an intramolecular acylation at a position *meta* to two *ortho-para* directing substituents. In order to examine the viability of this route, the synthesis of ***32*** was undertaken. The chloropalladation of **21** gives **22a** and **22b** in excellent yield (1.6:1 ratio).[16] Treatment of the mixture of **22a** and **b** with sodio dimethylmalonate in the presence of PPh_3 gave a mixture of cycloheptadienes **23a** and **23b**. Decarbomethoxylation of the mixture gave a mixture of cycloheptadiene esters **24a,b**.



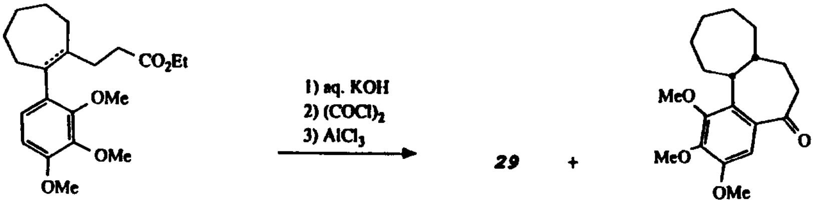
Reduction of **24a,b** with H_2 (47 psi, 144 h) and 10% Pd/C in anhydrous *methanol* gave only the cycloheptene ester **25**. Reduction of **24a,b** with H_2 and 10% Pd/C in absolute *ethanol* with a trace of HCl gave a mixture cycloheptene ethyl ester **26** and *cis* and *trans*-cycloheptane ethyl esters **27a** and **b** (ca. 1:1:1 ratio). The product mixture was characterized by ^1H NMR and GC/MS; **26** exhibits a characteristic singlet for its two aromatic protons, while **27a** and **27b** each exhibit distinct AB quartets. Attempts to separate the mixture or to force the reduction to completion were unsuccessful.



Saponification of **25** gave the cycloheptenyl propanoic acid **28** in good yield. Treatment of **28** with $(COCl)_2$ followed by $AlCl_3$ gave the propellanone **29**. This novel product was identified by spectroscopic means. Notably, the carbonyl ν_{co} and ^{13}C NMR chemical shift are indicative of a cyclopentanone ring. In addition, the most abundant MS fragment (m/z = 246) corresponds to formation of cycloheptenylbenzofuran **30**. The propellanone presumably arises via electrophilic attack on the cycloheptene ring followed by intramolecular capture of the cation by the *ortho* methoxy substituent.



Saponification of the mixture of **26**, **27a** and **27b** gave **28**, **31a** and **31b**. This mixture was subjected to the one-pot acylation conditions to give a separable mixture of propellanone **29** (24%) and the known[13c] tricyclic ketone **32** (23%).



26, 27a,b **32**

The structures of the Ar-7-7 tricyclic skeletons **19** and **32** are both assigned as *cis* by comparison of their physical data to literature values.[13] In addition, the benzylic resonance signal of each is not split by a large coupling as would be expected for the *trans* isomers. It is not possible to rationalize the splitting patterns of the diastereotopic protons α to the carbonyl by a single conformer, and it is thus likely that the NMR spectra represent a weighted average of a number of structures. The conformational flexibility of models of the *cis*-Ar-7-7 ring system has been previously noted.[13c] In addition, MM2 calculations of **19** and **32** indicate a number of low energy structures, conformationally different about the B and C rings, which are all within ±2 kcal/mole. In comparison, the B ring of colchicine is conformationally rigid.[19]

Reduction of the cycloheptadiene rings of **15** and **23** might seem antithetical in a synthetic scheme for colchicine, since this ring would eventually become the highly oxidized tropolonic C ring. However, the formation of lactone **12** and propellanone **29** are indicative of the potential problems associated with a partially oxidized C ring. Further oxidation of the cycloheptadiene ring to a tropone ring has been achieved and will be reported in due course.

EXPERIMENTAL

General Data. All IR spectra were recorded on a Perkin Elmer 700 spectrometer and were calibrated against the 1601 cm^{-1} peak of polystyrene. All 60 MHz ^1H NMR and 15 MHz $^{13}C\{^1H\}$ NMR spectra were recorded on a Varian EM360L or a JEOL FX60Q spectrometer; chemical shifts are reported in ppm downfield of TMS and couplings are reported in hertz. All 300 MHz ^1H NMR spectra were recorded on a GE QE-300 spectrometer. All GC/MS were recorded on a Hewlett Packard 5890 instrument with a 5970 mass selective detector and are reported as m/z (% rel. intensity). Melting points were obtained using a Mel-Temp melting point apparatus and are uncorrected. Microanalyses were sent to Midwest Microlab, LTD., Indianapolis, IN. High resolution mass spectra were obtained from the Midwest Center for Mass Spectrometry, an NSF Regional Instrumentation Facility.

All organometallic reactions were run under an atmosphere of nitrogen. Spectrograde solvents were used without further purification except for diethylether and tetrahydrofuran (THF) which were distilled from sodium- and potassium-benzophenone ketyl respectively, dimethylsulfoxide (DMSO) which was refluxed over CaH_2 before distillation, and methylene chloride which was distilled from phosphorus pentoxide. The term "flash chromatography" refers to the procedure of Still, Kahn, and Mitra.[20]

The π-allyl palladium complexes **10, 14a, 14b, 22a,** and **22b** were prepared as previously described.[15,16]

3-Methoxy-3-phenyl-2-[2',2'-di(carboethoxy)ethane]-cycloheptene (**11**). To a solution of **10** (0.30 g, 0.84 mmol) and triphenylphosphine (0.44 g, 1.68 mmol) in THF (50 mL) under N_2 was added, via syringe, a freshly prepared solution of sodium diethylmalonate (from diethylmalonate, 0.14 g, 0.84 mmol, and excess NaH) in THF (15 mL). The yellow reaction mixture initally turned yellow green, and then red-brown and was stirred at 23 C for 24 h. The solvent was removed under reduced pressure and the resultant red oil was dissolved in CH_2Cl_2 (80 mL) and washed twice with H_2O (40 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was separated by flash chromatography (hexanes:CH_2Cl_2/1:1). The product fractions were distilled (kugelrohr) under high vacuum to give a colorless oil (0.24 g, 0.64 mmol, 76%): bp 160 C/0.07 mm Hg; IR (cm^{-1}, neat) 1740s, 780s, 710s; 60 MHz ^1H NMR ($CDCl_3$) δ 7.3-7.0 (m, Ar*H*), 5.94 (t, $J = 6.1$), 4.15 (q, $J = 7.1$), 3.59 (t, $J = 7.5$, $CH(CO_2Et)_2$), 3.27 (s, OCH_3), 2.6-1.0 (m, 10H), 1.22 (t, $J = 7.1$); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 169.5, 143.2, 139.9, 132.0, 127.8, 127.1, 85.9, 61.2, 51.5, 50.6, 35.1, 33.1, 25.9, 24.7, 21.9, 14.1.

Attempted saponification/decarboxylation of ***11***. To an aqueous KOH solution (200 mL, 0.2 M) was added the diester ***11*** (0.24 g, 0.64 mmol). The reaction mixture was stirred for 48 h, and extracted with ether (2 x 50 mL). The aqueous layer was acidified with dilute aqueous H_2SO_4, and extracted with CH_2Cl_2 (2 x 75 mL). The combined organic extracts were concentrated, dissolved in C_6H_6 (50 mL) and heated at a gentle reflux for 21 h. The solvent was removed under reduced pressure and the residue was distilled (kugelrohr) under high vacuum to afford ***12*** as a colorless oil (0.11 g, 0.45 mmol, 68%): bp 120-130 C/0.05 mm Hg; IR (cm^{-1}, neat) 1750s, 760m, 710m; 60 MHz ^1H NMR ($CDCl_3$) δ 7.5-7.1 (m, Ar*H*), 6.05 (t, $J = 6.3$), 2.6-2.0 (m, 8H), 1.8-1.3 (m, 4H); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 174.2, 141.6, 135.5, 129.4, 128.6, 128.1, 126.3, 91.1, 40.8, 30.6, 29.1, 26.4, 25.4, 22.3.

1-Phenyl-2-[2',2'-di(carboethoxy)ethane]-1,3-cycloheptadiene (***15a***) and 2-phenyl-3-[2',2'-di(carboethoxy)ethane-1,3-cycloheptadiene (***15b***). To a solution of ***14a*** (0.76 g, 2.10 mmol) and triphenylphosphine (1.10 g, 4.21 mmol) in THF (70 mL) under N_2 at reflux, was added, via syringe, a freshly prepared solution of sodium diethylmalonate (2.1 mmol) in THF (15 mL). The reaction mixture initally turned cloudy, and then red (30 min). After 24 h, the reaction mixture was cooled and the solvent removed under reduced pressure. The resultant red oil was dissolved in CH_2Cl_2 (80 mL) and washed twice with H_2O (40 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was separated by flash chromatography (hexanes:ethyl acetate/4:1). The product fractions were distilled (kugelrohr) under high vacuum to give a mixture of dienes ***15a/b*** (0.49 g, 1.43 mmol, 68%): bp 130-145 C/0.06 mm Hg; IR (cm^{-1}, neat) 1740s, 1610w, 1220s, 770m, 710m; 300 MHz ^1H NMR ($CDCl_3$) δ 7.4-7.1 (m, Ar*H*), 6.37 (t, $J = 6.7$), 6.25 (t, $J = 6.7$), 6.07 (td, $J = 5.6, 11.2$), 5.88 (d, $J = 11.2$), 4.08, 4.07 (two qt's), 3.34, 3.26 (two t's, $J = 7.6$ and 7.7 respectively), 2.70, 2.68 (two d's, $J = 7.6$ and 7.7 respectively), 2.4-1.9 (m, 6H), 1.20, 1.17 (two t's); GC/MS [m/z(%)] 342(20), 251(14), 222(21), 182(100), 167 (68), 141 (34), 91(30).

2-Phenyl-1-[2',2'-di(carboethoxy)ethane]cycloheptane (***17***). A solution of dienes ***15a*** and ***b*** (0.13 g, 0.32 mmol) and 10% Pd/C (0.05 g) in absolute ethanol (20 mL) containing one drop of conc. HCl was shaken in a Parr apparatus, under H_2 (50 psi), for 48 h. The reaction mixture was filtered, and the filtrate concentrated under reduced pressure. The residue was taken up in ether (50 mL) and washed with aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The residue was distilled (kugelrohr) under high vacuum to afford ***17*** as a colorless oil (0.09 g, 0.22 mmol, 69%): bp 120-140°C/0.13 mm Hg; IR (cm^{-1}, neat) 1735s, 1250s, 760m, 705m; 300 MHz ^1H NMR ($CDCl_3$) δ 7.3-7.1 (m, Ar*H*), 4.15 (br q, $J = 7.0$, OCH_2CH_3), 3.14 (dd, $J = 5.8, 9.4$, $CH(CO_2Et)_2$), 2.97 (td, $J = 4.3, 11.1$, C*H*Ph), 2.0-1.4 (m), 1.25, 1.20 (two triplets, $J = 7.0$, OCH_2CH_3); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 169.8, 169.2, 146.0, 128.1, 125.8, 61.2, 61.0, 50.5, 48.9, 40.8, 31.2, 30.0, 29.5, 27.1, 26.5, 14.0; Anal. Calcd for $C_{21}H_{30}O_4$: C, 72.80; H, 8.72. Found: C, 72.34; H, 8.51.

3-(2'-Phenylcycloheptyl)propanoic acid (***18***). To an aqueous KOH solution (100 mL, 0.2 M) was added the diester ***17*** (0.09 g, 0.22 mmol). The reaction mixture was stirred for 24 h, acidified with dilute aqueous HCl, extracted with CH_2Cl_2 (2 x 25 mL). The combined organic extracts were stirred with SiO_2 for 16 h. The supernant was dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The residue was distilled (kugelrohr) under reduced pressure to afford ***20*** as a gummy oil (0.05 g, 0.20 mmol, 79%): bp 90-110 C/0.10 mm Hg; IR (cm^{-1}, neat) 3600-2500br, 1715s, 760m, 710m; 60 MHz ^1H NMR ($CDCl_3$) δ 9.6 (br s, COO*H*), 7.3-7.1 (m, Ar*H*), 3.05 (br m, C*H*Ph), 2.2-1.3 (m); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 174.9, 145.5, 128.1, 126.0, 49.8, 48.7, 40.7, 31.3, 30.7, 29.6, 27.0, 26.1; Anal. Calcd for $C_{16}H_{22}O_2 \cdot 1/2H_2O$: C, 71.47; H, 9.18. Found: C, 71.55; H, 8.81.

cis-5,6,7,7a,8,9,10,11,12,12a-Decahydrobenzo[a]heptalen-5-one (***19***). Carboxylic acid ***18*** (0.22 g, 0.89 mmol) was treated with excess oxalyl chloride (0.50 mL). After stirring at room temperature for 30 min, the reaction mixture was diluted with CH_2Cl_2 (5 mL) and the solvents were evaporated under reduced pressure. The resulting brown oil was dissolved in CH_2Cl_2 (15 mL) and anhydrous $AlCl_3$ (0.12 g, 0.89 mmol) was added. The solution was stirred under N_2 overnight. To the reaction mixture was added H_2O (30 mL) and the resultant mixture was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The residue was distilled (kugelrohr) under high vacuum to afford ***19*** as a pale oil (0.12 g, 60%): bp 75-85 C/0.075 mm Hg; IR (cm^{-1}, $CHCl_3$) 1673s, 1598m, 1448s, 1287m, 1264m, 1242m (lit.[13a] bp 160-180 C/3 mm Hg; IR 1285m, 1263m, 1235m); 300 MHz ^1H NMR ($CDCl_3$) δ 7.6-7.1 (m, Ar*H*, 4H), 3.14 (m, $J = 5.2$, benzylic *H*), 2.82 (ddd, $J = 2.9, 8.4, 18.2$, 1H), 2.55 (ddd, $J = 3.7, 9.5, 18.2$, 1H), 2.21 (m, 1H), 2.0-1.1 (m, 13H); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 208.3, 143.8, 139.6, 131.5, 127.8, 127.6, 126.4, 46.0, 40.4, 40.1, 32.2, 32.1, 30.1, 28.9, 27.8, 27.5; GC/MS [m/z(%)] 228(75), 185(42), 159(100), 131(81), 129(66), 128(62), 115(88), 91(58), 77(51).

cis-5,6,7,7a,8,9,10,11,12,12a-Decahydrobenzo[a]heptalene (***20***). A solution of ketone ***19*** (0.07 g, 0.31 mmol) and 10% Pd/C (0.025 g) in absolute ethanol (25 mL) containing one drop of conc. HCl, was shaken in a Parr apparatus, under H_2 (45 psi) for 24 h. The reaction mixture was filtered and the solvent removed under reduced pressure. The residue was dissolved in ether (50 mL) and washed with saturated aqueous $NaHCO_3$ (2 x 25 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The residue was distilled (kugelrohr) under high vacuum to afford ***20*** as a clear oil (0.05 g, 0.23 mmol, 74%): bp 70-80 C/0.05 mm Hg; IR (cm^{-1}, $CHCl_3$) 2922s, 1500w, 1442m; 60 MHz ^1H NMR ($CDCl_3$) δ 7.05 (br s, Ar*H*, 4H), 3.1-2.7 (br m, 3H), 2.2-1.1 (m, 15H); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 147.7, 141.5, 130.2, 128.6, 126.0, 125.7, 51.1, 41.2, 36.5, 35.9, 33.2, 30.8, 28.2, 27.6, 26.6; GC/MS [m/z(%)] 214(86), 186(14), 157(44), 143(55), 129(100), 115(46), 104(29), 91(37); Anal. Calcd for $C_{16}H_{22}$: C, 89.65; H, 10.35. Found: C, 87.52; H, 9.93.

1-(2',3',4'-Trimethoxyphenyl)-2-[2',2'-di(carbomethoxy)ethane]-1,3-cycloheptadiene (***23a***) and 2-(2',3',4'-trimethoxyphenyl)-3-[2',2'-di(carbomethoxy)ethane]-1,3-cycloheptadiene (***23b***) were prepared from the reaction of ***21a,b*** with sodio dimethylmalonate in the presence of PPh_3 in a manner similar to the preparation of ***15a,b***. The residue was separated by flash chromatography (hexanes:ethyl acetate/3:1). The product fractions were distilled (kugelrohr) under high vacuum to afford a mixture of dienes ***23a,b*** as a pale oil (57%): bp 95-110 C/0.075 mm Hg; IR (cm^{-1}, $CHCl_3$) 1720s, 1596m; 60 MHz ^1H NMR (CCl_4) δ 6.73, 6.52 (AB q, *J* = 8, Ar*H*, 2H), 6.1 (m, 2H), 3.77, 3.72, 3.67 (three s, 9H), 3.60 (s, 6H), 3.2 (m, 1H), 2.43 (d, *J* = 8), 2.3-1.7 (m, 6H); GC/MS [m/z(%)] 404(77), 273(39), 272(100), 257(27), 242(35), 241(94); Anal. Calcd. for $C_{22}H_{28}O_7$: C, 65.33; H, 6.98. Found: C, 65.23; H, 6.84.

Decarbomethoxylation of ***23a,b***. To a solution of ***23a,b*** (0.61 g, 1.51 mmol) in DMF (15 mL) was added NaCN (0.09 g, 1.81 mmol) and $LiI:3H_2O$ (0.85 g, 4.53 mmol). The solution was warmed to 120 C under N_2 and stirred for 20 h. The brown solution was cooled, diluted with H_2O (80 mL), and extracted with CH_2Cl_2 (2 x 50 mL). The combined extracts were washed with H_2O, 10% aqueous HCl and saturated aqueous $NaHCO_3$. The organic solution was dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The resulting oil was purified by flash chromatography (hexanes:ethyl acetate/4:1) to afford ***24a,b*** as a clear oil (0.38 g, 1.09 mmol, 73%): IR (cm^{-1}, neat) 1728s, 1596m; 60 MHz ^1H NMR (CCl_4) δ 6.60 (m, 2H), 5.89 (m, 2H), 5.89 (m, 2H), 3.80, 3.78, 3.68, 3.52 (four s, 12H), 2.3-1.9 (m, 10H); GC/MS [m/z(%)] 346(100), 273(20), 272(23), 257(17), 241(30); Anal. Calcd. for $C_{20}H_{26}O_5$: C, 69.34; H, 7.56. Found: C, 69.29; H, 7.57.

Partial reduction of ***24a,b***. A solution of dienes ***24a,b*** and 10% Pd/C in anhydrous methanol was shaken in a Parr apparatus, under H_2 (47 psi), for 144 h. The reaction mixture was worked up in the usual manner the resulting oil was purified by flash chromatography (hexanes:ethyl acetate/7:1) to afford ***25*** as a clear oil (94%): IR (cm^{-1}, $CHCl_3$) 1731s, 1596m; 60 MHz ^1H NMR (CCl_4) δ 6.50 (s, Ar*H*, 2H), 3.80 (br s, 9H), 3.52 (s, 3H), 2.5-2.1 (m, 8H), 1.9-1.4 (m, 6H); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 173.9, 152.3, 150.8, 142.5, 138.5, 137.3, 132.2, 123.5, 107.0, 60.9, 60.6, 56.0, 51.4, 36.4, 33.0, 32.7, 32.0, 26.9, 26.7; GC/MS [m/z(%)] 348(100), 219(55), 181(67), 168(55), 69(59). Extended reduction of the mixture ***24a,b*** in absolute ethanol in the presence of 10% Pd/C and HCl (1 drop) gave an inseparable mixture of ***26***, ***27a*** and ***27b*** (ca. 1:1:1 ratio by GC/MS).

3-[2-(2',3',4'-Trimethoxyphenyl)cycloheptenyl]propanoic acid (***28***). To an aqueous KOH solution (50 mL, 0.2 M) was added ***24*** (0.17 g, 0.49 mmol). The reaction mixture was heated at reflux for 30 h. The solution was cooled, acidified with dilute aqueous HCl and extracted with CH_2Cl_2 (2 x 25 mL). The organic extracts were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The resulting oil was purified by flash chromatography (methanol:hexanes/2:1) to afford ***25*** as a gummy oil (0.12 g, 0.36 mmol, 75%): IR (cm^{-1}, $CHCl_3$) 3200-2600br, 1599m; 60 MHz ^1H NMR ($CDCl_3$) δ 10.7 (br s, 1H), 6.5 (s, Ar*H*, 2H), 3.73 (br s, 6H), 3.70 (s, 3H), 2.4-2.0, 1.8-1.4 (m, 14H); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 179.4, 152.3, 150.8, 142.5, 138.1, 137.5, 132.1, 123.5, 107.1, 60.9, 60.7, 56.0, 36.4, 33.0, 32.7, 31.7, 26.9, 26.7.

Propellanone (***29***). The acid ***28*** was treated successively with $(COCl)_2$ and $AlCl_3$ in a fashion similar to the preparation of ***19***. The resulting brown oil was purified by flash chromatography (hexanes:ethyl acetate/5:1) to afford ***29*** as a clear oil (56%): IR (cm^{-1}, $CHCl_3$) 1734s; 60 MHz ^1H NMR (CCl_4) δ 6.52, 6.30 (AB q, *J* = 8, 2H), 3.77, 3.71 (two s, 6H), 2.6-1.2 (m, 14H); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 215.1, 153.2, 151.6, 132.9, 122.7, 117.9, 105.1, 101.1, 64.9, 60.6, 56.3, 39.0, 35.7, 34.9, 31.3, 24.7, 23.7; GC/MS [m/z(%)] 302(22), 247(16), 246(100), 231(36); Anal. Calcd. for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.33; H, 7.48.

cis-5,6,7,7a,8,9,10,11,12,12a-Decahydro-1,2,3-Trimethoxybenzo[a]heptalen-5-one (***32***). The mixture of ***26***, ***27a*** and ***27b*** was saponified by treatment with dilute aqueous KOH in a fashion similar to the preparation of ***18***. The product was a mixture of carboxylic acids ***28*** and ***31***. Treatment of this mixture with $(COCl)_2$ followed by $AlCl_3$ in a manner similar to the preparation of ***19*** gave a brown oil. Separation by flash chomatography (hexanes:ethyl acetate/7:1) gave ***32*** (23%) as a colorless oil followed by ***29*** (24%). ***32***: IR (cm^{-1}, $CHCl_3$) 1668s, 1593m; 300 MHz ^1H NMR ($CDCl_3$) δ 6.9 (s, Ar*H*, 1H), 3.85, 3.90 (two s, 9H), 3.60 (m, HW = 19, 1H), 2.95 (d, *J* = 7.5, 1H), 2.56 (dt, *J* = 15 and 4, 1H), 2.27 (m, 1H), 2.0-1.4 (m, 12H); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 206.3, 151.2, 150.1, 145.0, 134.6, 125.3, 107.6, 61.4, 60.8, 55.9, 40.0, 39.4, 38.5, 34.9, 32.4, 29.9, 29.1, 27.7, 25.6; GC/MS [m/z(%)] 318(100), 261(47), 247(21), 219(27); HRMS, m/z 318.1837 [calcd for $C_{19}H_{16}O_4$, 318.1831).

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