17-Hydroxy-3-methoxy-19-nor-17α-pregna-1,3,5(10),20-tetraene-20,21-dicarboxylic Acid Anhydride (6). An 8 *N* chromic acid solution (6.55 ml) was added slowly to a solution of **3a** (500 mg) in acetone (25 ml) at 10–12°. After stirring for 15 min at room temperature, the excess oxidant was decomposed by the addition of *i*-PrOH. H_2O was added and the solution was evaporated almost to dryness. The residue was extracted with Et_2O and CH_2Cl_2. The organic phase was washed to neutrality ($NaHCO_3$, H_2O), dried ($MgSO_4$), and evaporated. Crystallization of the crude reaction product from $CHCl_3$–Et_2O and then acetone–Et_2O afforded **6** as a pale yellow solid (175 mg, 35%): mp 227–228°; [α]D +96.9°. Anal. ($C_{23}H_{26}O_5$) C, H.

17-Hydroxy-3-methoxy-19-nor-17α-pregna-1,3,5(10)-triene-20,21-dicarboxylic Acid Anhydride (7). A mixture of the maleic anhydride **6** (10 g), $CHCl_3$ (200 ml), AcOH (500 ml), and Zn dust (50 g) was stirred at room temperature for 1 hr. The metal was filtered and washed with $CHCl_3$. The filtrate was thoroughly washed with H_2O, dried ($MgSO_4$), and evaporated. Crystallization of the residue from $CHCl_3$–Et_2O afforded **7** (2.1 g, 21%): mp 234–235°; [α]D +69.9° ($CHCl_3$). Anal. ($C_{23}H_{28}O_5$) C, H.

This product is not very stable and is readily converted into the acid lactone **8a**.

17-Hydroxy-3-methoxy-19-nor-17α-pregna-1,3,5(10)-triene-20,21-dicarboxylic Acid Anhydride (7). A mixture of the dride **7** (8.9 g) was dissolved in 0.1 *N* NaOH. Upon acidification with 1 *N* HCl (100 ml), the solid which formed was filtered, washed with H_2O, and dried. This solid was boiled in the presence of Et_2O for 5 min to yield the acid lactone **8a** (6.72 g, 75%). The analytical sample was obtained from acetone: mp 233–234° dec; [α]D +21.3°. Anal. ($C_{23}H_{28}O_5$) C, H.

17-Hydroxy-3-methoxy-19-nor-17α-pregna-1,3,5(10)-triene-20,21-dicarboxylic Acid γ-Lactone Methyl Ester (8b). Esterification of the acid lactone **8a** in a conventional manner with CH_2N_2 afforded the methyl ester 8b (73%): mp 135–136° (MeOH); [α]D +10.5° ($CHCl_3$). Anal. ($C_{24}H_{30}O_5$) C, H.

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Synthesis and Antiinflammatory Activity of Some 1,6-Methano[10]annuleneacetic Acids†

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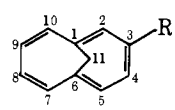
Some new approaches to the 1,6-methano[10]annulene system are described. The routes were used to prepare 1,6-methano[10]annulene-3-acetic acid and the α-methyl analog. The compounds showed antiinflammatory and analgesic activity, though less than that of the corresponding naphthalene compounds; the possible effect of the chirality of the annulene on the observed biological activity is discussed.

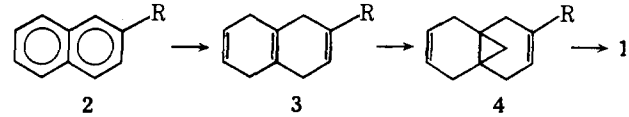
The antiinflammatory activity of arylacetic acids, in which activity is maintained despite wide variations in the nature of the aryl group, has prompted considerable recent research into this class of compounds.[1] In view of the antiinflammatory activity reported[2] for a number of naphthylacetic acids, and also of the spatial similarities between naphthalene and 1,6-methano[10]annulene **1a**,[3] we have synthesized 1,6-methano[10]annulene-3-acetic acid and the α-methyl analog. The syntheses incorporate some novel and efficient approaches to the annulene system.



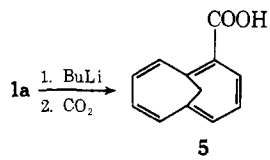
1a, R = H
b, R = CH_2COOCH_3
c, R = $CH(CH_3)COOCH_3$
d, R = CH_2COOH
e, R = $CH(CH_3)COOH$
f, R = CN
1g, R = $COOCH_3$
h, R = COOH
i, R = CH_2OH
j, R = CH_2Cl
k, R = CH_2CN

Chemistry. Since electrophilic substitution has been reported to yield almost exclusively the 2-substituted derivatives,[4] the desired 3-substituted compounds were first synthesized by a modification of the abbreviated synthesis of the parent hydrocarbon which was developed in these laboratories.[5] This synthesis, shown in Scheme I, R = H, is, at least in principle, applicable to 2-substituted naphthalenes in which the substituent R is compatible with Birch reduction, Simmons–Smith methylenation, and dichlorodicyano-*p*-benzoquinone (DDQ) oxidation. Accordingly, 2-naphthylacetic acid and 2-(2-naphthyl)propionic acid were each

Scheme I



2a–4a, R = H
2b–4b, R = CH_2COOH
2c–4c, R = $CH(CH_3)COOH$
2d–4d, R = CH_2CH_2OH

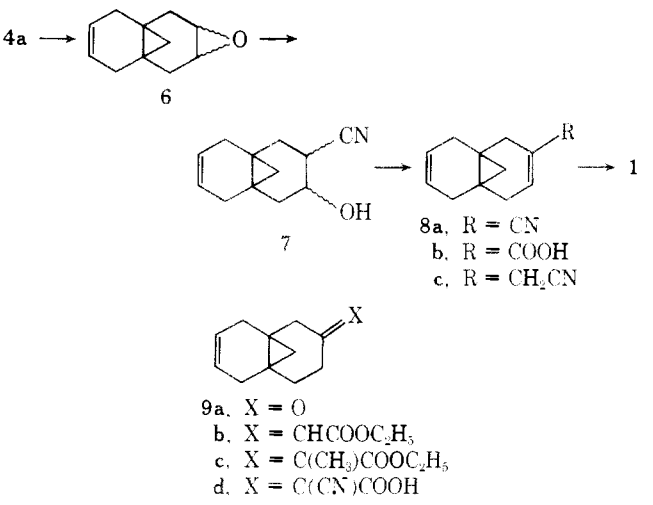


†Contribution No. 445 from the Syntex Institute of Organic Chemistry.

subjected to Birch reduction to give in good yield the isotetralin derivatives **3b** and **3c**. Modified Simmons–Smith reaction[6] on the latter compounds gave a high degree of regioselective addition (ca. 50 and 75% of the total reaction products, respectively) to the tetrasubstituted double bond, thus affording **4b** and **4c**. Interestingly, Simmons–Smith reaction on the alcohol **3d**, obtained by reduction of **3b** was less regioselective than that on the carboxylic acid, and when the methyl ester of **3b** was used as substrate an even more complex mixture of products, containing little of the desired adduct, was obtained. This result indicates that a carboxyl group can efficiently deliver the iodozinc methylene iodide intermediate of the methylenation and, in this case, is far superior to the corresponding alcohol which, based on ample precedent,[7] was expected to be the substrate of choice. Despite the selective addition, however, purification of the products **4b** and **4c** was difficult, and thus the partially purified products were esterified and oxidized with DDQ to the annulene derivatives **1b** and **1c**. Chromatography then furnished the purified esters which were hydrolyzed to the corresponding acids **1d** and **1e**. The annulenepropionic acid was obtained as a mixture of diastereomers because of the presence of the chiral substituted annulene moiety and the asymmetric α-carbon substituent. The diastereomeric ratio, determined by the NMR signal of the methyl group, was ca. 2:1, presumably indicating a preferential formation of one diastereomer during the Simmons–Smith reaction. (In fact, examination of Dreiding models shows that one of the two possible intermediates for delivery of the postulated carboxyl-coordinated methylenation reagent suffers considerable nonbonded interaction between the side-chain methyl group and the olefinic 4-hydrogen. The product derived from this intermediate is therefore assigned to be the minor one.)

The extensive chromatography involved in this sequence was inconvenient and so, in order to produce further quantities of the target compounds, some alternative syntheses were examined. Attempted reaction between the annulene **1a** and ethyl diazoacetate, under either thermal, photochemical, or acid-catalyzed conditions, gave none of the desired product **1b**. An attempt to produce 1,6-methano-[10]annulene-3-carboxylic acid, a convenient precursor for both target compounds, by lithiation–carbonation of the hydrocarbon was also unsuccessful. Treatment of **1a** with *n*-butyllithium–tetramethylethylenediamine in hexane gave a deep red solution of an anion, but carbonation produced only the known[4] 2-carboxylic acid **5** (60%). The 3- and 11-carboxylic acids were not formed. However, it was found that the desired 3-substituted annulenes could be efficiently obtained by the reaction shown in Scheme II. Epoxidation of the readily available[5] diene **4a** produced mainly the monoepoxide mixture **6** which, upon treatment with potassium cyanide in ethylene glycol[8] and subsequent dehydration, afforded the unsaturated nitrile **8a**. This compound was oxidized with DDQ to the 3-cyanoannulene **1f** or, alternatively, was hydrolyzed to the carboxylic acid **8b** which was esterified and oxidized to 3-carbomethoxy-1,6-methano[10]annulene (**1g**). Base hydrolysis of either the ester or the nitrile furnished the 3-carboxylic acid **1h** which was homologated to the 3-acetic acid. A stepwise homologation was necessary since the acetic acid was not obtained from several attempted Arndt–Eistert reactions. The homologation was carried out by reduction of the carboxylic acid with diborane to give the carbinol **1i** which was treated with thionyl chloride to yield the benzylic chloride **1j**. Reaction of the latter with sodium cyanide in dimethyl sulfoxide, followed by base hydrolysis, provided the alternative route to the 3-acetic acid. The epoxide **6** also provided two other approaches to 3-substituted [10]annulenes.

Scheme II



Reduction with lithium aluminum hydride followed by Jones oxidation produced the ketone **9a**[9] which, when subjected to a Wittig reaction with carboethoxymethylidene- or carboethoxyethylidenetriphenylphosphorane, gave the acrylic esters **9b** and **9c** in good yield. DDQ oxidation, however, afforded the corresponding annuleneacetic and annulenepropionic esters in only 5 and 20% yield, respectively. Alternative methods for conversion of the acrylic esters to the annulenes were not explored. The ketone **9a** also underwent condensation with cyanoacetic acid, catalyzed by ammonium acetate,[10] and the product decarboxylated pyrolytically to produce the acetonitrile **8c** which, upon DDQ oxidation, also afforded **1k**, though in overall yield of only 20% from the ketone.

Biological Results.[‡] The acetic and propionic acids were tested by oral administration in antiinflammatory (carrageenan-induced rat paw edema[11]) and analgetic (mouse writhing[12] or Randall–Sellito[13]) assays. The results are shown in Table I. It can be seen that both annulene compounds showed less antiinflammatory activity than the corresponding naphthalene compounds [2-naphthylacetic acid and *dl*-2-(2-naphthyl)propionic acid have antiinflammatory activities of 0.6[2a] and 0.3[§] times phenylbutazone, respectively]. The fact that the 3-acetic acid **1d** is a *dl* mixture may have diminished the observed activity since it is likely that the enantiomers have different biological activities. In the case of the propionic acid (**1e**), which consisted of two diastereomeric pairs (see Chemistry section), the dilution of the active compound(s) by possibly inactive isomers would be more accentuated. However, in view of the activities observed, no attempt was made to separate diastereomers or enantiomers in this series.

Experimental Section

Melting points were taken on a Fisher-Johns apparatus and are not corrected. Infrared (ir) frequencies refer to liquid films unless otherwise indicated. Ultraviolet (uv) spectra were taken in EtOH. NMR spectra were taken in $CDCl_3$ at 60 or 100 MHz. Coupling constants (J) are in hertz: s = singlet; d = doublet; dd = double doublet; q = quartet; m = multiplet; br = broad. Microanalyses were within ±0.4% of theory. Column and thin-layer chromatographies were performed with Merck silica gel. All reactions were performed under N_2. Gas–liquid chromatography (GLC) was carried out on two columns: A, 12 ft × 3 mm 10% OV 17; B, 6 ft × 3 mm 3% XE 60. We wish to thank V. Hayashida, R. Leibrand, M. L. Maddox, and J. Nelson for analytical and spectroscopic data.

[‡]We thank W. Rooks II and A. Tomolonis, Syntex Institute of Biological Sciences, and Dr. A. P. Roszkowski, Syntex Institute of Clinical Medicine, for providing the results.

[§]Unpublished results from these laboratories.

Table I. Pharmacological Activities

Compound	Dose, mg/kg	Relative potencies: Antiinflammatory,[a] phenylbutazone = 1	Relative potencies: Analgetic,[a] aspirin = 1
1d	2.8–11	0.2 (0.1–0.5)	
1d	200		<0.2[b]
1d sodium salt	200		<0.2[b]
1e	2.8–11	<0.1	
1e	100		<0.5[b]
1e sodium salt	18		Active[c]

[a]The free acids were dissolved in a solvent consisting of sodium chloride (0.9%), sodium carboxymethylcellulose 7LP (0.5%), polysorbate 80 (0.4%), and benzyl alcohol (0.9%) in water. The salts were dissolved in water. [b]Mouse writhing assay (ref 12). [c]Randall–Sellito assay (ref 13); the activity was of short duration (less than 2 hr).

A. Birch Reductions. (i) 1,4,5,8-Tetrahydro-2-naphthylacetic Acid (3b). Sodium (32 g, 1.39 mol) was added to 2-naphthylacetic acid (20 g, 0.108 mol) in Et_2O (100 ml), EtOH (85 ml), and NH_3 (800 ml). The mixture was stirred at reflux until the blue color faded. Water (250 ml) was added and the mixture warmed to room temperature. The residue was acidified with 18% HCl and the product filtered off, washed (H_2O), dried, and recrystallized from MeOH to give **3b** (12.9 g, 65% yield): mp 173–175°; NMR 2.58 (allylic H), 3.03 (CH_2CO), and 5.73 ppm (olefinic H). Anal. ($C_{12}H_{14}O_2$) C, H.

(ii) 2-(1,4,5,8-Tetrahydro-2-naphthyl)propionic Acid (3c). The above reduction was carried out on 2-(2-naphthyl)propionic acid to afford **3c** (70% yield): mp 118–120° (aqueous MeOH); NMR 1.30 (d, J = 7 Hz, CH_3), 2.55 (allylic H), 3.17 (q, J = 7 Hz, $CHCH_3$), and 5.73 ppm (olefinic H). Anal. ($C_{13}H_{16}O_2$) C, H.

B. 2-(1,4,5,8-Tetrahydro-2-naphthyl)ethanol (3d). The methyl ester of **3b** (210 mg, 1.07 mM) was added to Et_2O (15 ml) containing lithium aluminum hydride ($LiAlH_4$) (100 mg, 3.4 mM) and the mixture stirred for 30 min. Excess hydride was destroyed (EtOAc, MeOH, dilute HCl) and the ethereal layer washed, dried, and evaporated to afford **3d** which was recrystallized from hexane–Et_2O: yield 83 mg (45%); mp 68–69°. Anal. ($C_{12}H_{16}O$) C, H.

C. Simmons–Smith Reactions. (i) 3b (1.0 g, 0.00525 mol), cuprous chloride (0.7 g, 0.0071 mol), zinc dust (Mallinckrodt) (1.5 g, 0.023 mol), CH_2I_2 (4.52 g, 0.019 mol), and Et_2O (200 ml) were refluxed for 10 hr. Saturated NH_4Cl and then dilute HCl were added and the Et_2O layer was separated, washed (aqueous Na_2SO_3, H_2O), and dried. Excess ethereal diazomethane was then added and the solution evaporated to yield a product (1.13 g) shown by GLC (column A, 200°) to contain 53% of one component. The crude product was chromatographed on silica gel (50 g) (2:1 hexane–Et_2O) so as to isolate the major component (0.5 g, 82% pure). The NMR spectrum was consistent with the methyl ester of **4b**.

(ii) Using the same proportions and procedure as in (i) above, **3c** (1.0 g) was converted to a crude product (1.08 g) containing 75% of one component (GLC column A, 210°). Chromatography as in (i) produced **4c** methyl ester (0.64 g, 84% pure).

(iii) Similar methylenations were performed on the alcohol **3d** and on the methyl ester of **3b**. The crude products after starting material was consumed were analyzed by GLC. The largest single product from **3d** comprised 30% of the total (GLC column A, 210°) and from **3b** methyl ester 21% of the total (GLC column A, 200°).

D. (i) 1,6-Methano[10]annulene-3-acetic Acid (1d). 4b methyl ester (0.5 g, 82% pure, 0.0023 mol) from C (i) above was refluxed in dioxane (10 ml) containing DDQ (0.85 g, 0.0037 mol) for 3 hr. The mixture was poured into H_2O and extracted with Et_2O. The ethereal solution was dried and evaporated to give a residue which was chromatographed on silica gel (15 g) (4:1 hexane–Et_2O). The annulene-containing fractions (275 mg) were rechromatographed on two 1 m × 1.3 mm preparative TLC plates (6:1 hexane–Et_2O) to give 1b as an oil (180 mg, 47% yield): NMR −0.36 (11 H), 3.63 (OCH_3), 3.72 (CH_2CO), and 6.9–7.6 ppm (arom H).

The ester was refluxed for 8 hr in 1:1 EtOH–10% aqueous NaOH (8 ml). Water and Et_2O were added; the aqueous layer was acidified (dilute HCl) and extracted with Et_2O. The extract was dried and evaporated to give 1d which was recrystallized from aqueous MeOH: yield 90 mg (50%); mp 86–88°; uv 259, 299 nm (ϵ 58,400, 5500); ir 1710, 1690 cm^{-1}; NMR −0.40 (11 H), 3.65 (CH_2CO), 6.9–7.5 (arom H), and ~11.3 ppm (carboxyl H). Anal. ($C_{13}H_{12}O_2$) C, H.

(ii) 2-(1,6-Methano[10]annulen-3-yl)propionic Acid (1e). Similar DDQ oxidation of **4c** methyl ester (0.6 g, 84% pure) from C (ii) above gave after chromatography **1c** (150 mg, 26% yield) as an oil: NMR −0.38 (11 H), 1.50, 1.52, 1.58, 1.60 (dd, J = 8 Hz, $CHCH_3$), 3.62, 3.64 (OCH_3), 3.74, 3.82, 3.89, 3.97 (q, J = 8 Hz, $CHCH_3$), and 6.9–7.6 ppm (m, arom H).

Base hydrolysis as described above gave 1e (120 mg, 85% yield) as a gum: NMR −0.39 (11 H), 1.49, 1.52, 1.56, 1.58 (dd, J = 8 Hz, $CHCH_3$), 3.73, 3.80, 3.87, 3.94 (q, J = 8 Hz, $CHCH_3$), 6.9–7.6 (arom H), and ~10.7 ppm (carboxyl H). (The integration of the methyl signals indicated a diastereomeric ratio of ca. 2:1.)

E. Lithiation–Carbonation of 1,6-Methano[10]annulene. Tetramethylethylenediamine (1.11 g, 0.0096 mol) and 1.6 M n-butyllithium in hexane (6.2 ml, 0.0099 mol) were mixed and stirred for 15 min at 0° 1,6-Methano[10]annulene (1a) (1.11 g, 0.0084 mol) in hexane (5 ml) was added. A deep red color developed immediately. After 15 min a rapid stream of dry CO_2 was passed in until the red color had been discharged. Ether and dilute HCl were added. The organic layer was extracted with Na_2CO_3 solution, acidified (dilute HCl), and extracted with Et_2O. The extract was washed, dried, and evaporated to afford 1,6-methano[10]annulene-2-carboxylic acid (**5**) (890 mg, 61% yield) identical in all respects with a sample prepared by the published procedure.[4]

F. 1,6-Methano[10]annulene-3-carboxylic Acid (1h). (i) Epoxidation of 4a. Bicyclo[4.4.1.$0^{1,6}$]undeca-3,8-diene (2.82 g, 0.019 mol) was dissolved in dry CH_2Cl_2 (50 ml) and cooled to −80°; m-chloroperbenzoic acid (75% pure, 4.53 g, 0.02 mol) in CH_2Cl_2 (50 ml) was added. The mixture was warmed to room temperature and left 3 hr, then poured into aqueous Na_2CO_3. The organic layer was washed (aqueous Na_2SO_3, water), dried, and evaporated. The residue was chromatographed on silica gel (100 g). Elution with n-pentane yielded unchanged **4a** (500 mg), and with n-pentane–20% Et_2O the epoxide mixture **6** (1.8 g, 58% yield) was obtained: NMR 0.3–1.3 (two AB q, ratio ca. 1:1, 11 H), 1.4–2.6 (aliphatic H), 2.9–3.1 (allylic H), and ~5.5 ppm (olefinic H).

(ii) Unsaturated Nitrile 8a. The epoxides **6** (1.1 g, 0.0067 mol) and NaCN (1.1 g, 0.022 mol) were heated to 60° in ethylene glycol (30 ml) for 24 hr.[8] The mixture was poured into H_2O and extracted with EtOAc. The extract was washed and dried and the product 7 (1.08 g, 84% yield; ir 3400, 2200 cm^{-1}) was dissolved in dry C_6H_6 (15 ml) and thionyl chloride (1 ml) was added; the mixture was refluxed for 1 hr and then evaporated to dryness. The residue was dissolved in DMF (5 ml) and 1,5-diazabicyclo[4.3.0]non-5-ene (2 ml) was added. After 1 hr, H_2O and Et_2O were added. The organic layer was washed (dilute HCl, H_2O), dried, and evaporated to give 3-cyanobicyclo[4.4.1.$0^{1,6}$]undeca-3,8-diene (**8a**) (740 mg, 76% yield) which was recrystallized from hexane: mp 44–46.5°; ir (Nujol mull) 2200, 1630 cm^{-1}. Anal. ($C_{12}H_{13}N$) C, H.

(iii) 3-Cyano-1,6-methano[10]annulene (1f). **8a** (250 mg, 0.0015 mol) was refluxed in dioxane (20 ml) with DDQ (1.1 g, 0.0048 mol) for 8 hr. The mixture was cooled and added to pentane (500 ml), the solution filtered through silica gel (~10 g), and the eluate evaporated to yield **1f** (198 mg, 82% yield) which was recrystallized from Et_2O–hexane: mp 60–62°; uv 263, 311 nm (ϵ 61,400, 7500); ir (Nujol mull) 2190 cm^{-1}; NMR −0.44, −0.35, −0.25, −0.16 (AB q, J = 9 Hz, 11 H), 7.1–7.7 (m, arom H), and 7.83 ppm (s, 2 H). Anal. ($C_{12}H_9N$) C, H.

(iv) 1,6-Methano[10]annulene-3-carboxylic Acid (1h). 1f (210 mg, 0.0013 mol) was refluxed in EtOH (15 ml) and H_2O (15

ml) containing KOH (540 mg, 0.0096 mol) for 2 hr. Water and Et_2O were added. The aqueous layer was acidified (dilute HCl) and extracted with Et_2O. The extract was dried and evaporated to give **1h** which was recrystallized from aqueous MeOH: yield 150 mg (60%); mp 145–146°; uv 263, 312 nm (ε 47,700, 6200); NMR −0.31, −0.23, −0.20, −0.11 (AB q, J = 9 Hz, 11 H), 7.1–7.7 (m, arom H), 7.97, 8.06 (d, J = 9 Hz, 4 H), and 8.44 ppm (br s, 1 H). Anal. ($C_{12}H_{10}O_2$) C, H.

(v) The acid **1h** was also obtained by the sequence **8a** to 8b to **1g** to **1h** as follows. **8a** (510 mg) was hydrolyzed as in (iv) above to give 8b (445 mg, 87% yield): mp 182–183° (aqueous MeOH). Anal. ($C_{11}H_{14}O_2$) C, H. 8b (550 mg) was treated with ethereal diazomethane to produce the methyl ester which was oxidized with DDQ as described in (iii) above to give after chromatography on silica gel (6:1 hexane–Et_2O) (10 g) 3-carbomethoxy-1,6-methano-[10]annulene (**1g**) as an oil (380 mg, 70% yield): NMR −0.43 (11 H), 3.70 (CH_3O), 6.7–7.4 (m, arom H), 7.62, 7.78 (d, J = 9 Hz, 4 H), and 8.02 (2 H). The ester **1g** (380 mg) was hydrolyzed as in (iv) above to give the acid **1h** (321 mg, 89% yield).

G. Homologation of 1h to 1,6-Methano[10]annulene-3-acetic Acid. To the methyl ester **1g** (460 mg, 0.0024 mol) in Et_2O (50 ml) was added $LiAlH_4$ (250 mg, 0.0066 mol). After 1.5 hr excess hydride was decomposed. The solution was washed (dilute HCl, water), dried, and evaporated to give **1i** (400 mg, 95%) as an oil: ir 3250 cm^{-1}; NMR −0.35 (11 H), 1.8–2.0 (OH), 4.78 (CH_2O), and 6.9–7.6 ppm (m, arom H). This material was dissolved in dry C_6H_6 (60 ml) and thionyl chloride (3.5 ml) was added. After 30 min the solution was evaporated to give the unstable chloromethyl compound **1j** which was immediately dissolved in DMSO (1 ml) and added to a stirred mixture of NaCN (2.0 g) and DMSO (15 ml) and left for 25 min. Water and Et_2O were added; the ethereal solution was washed (aqueous Na_2CO_3, H_2O), dried, and evaporated to give **1k** as an oil (400 mg, 94%): ir 2220 cm^{-1}; NMR −0.38 (11 H), 3.85 (CH_2CN), and 6.9–7.6 ppm (m, arom H). The product was refluxed in EtOH (5 ml) and H_2O (45 ml) containing KOH (1.0 g) for 12 hr. The cooled solution was extracted with Et_2O, then acidified (dilute HCl), and reextracted with Et_2O. The extract was dried and evaporated to give **1d** (350 mg, 85%) identical with that obtained in D (i) above.

H. 2-(1,6-Methano[10]annulene-3-yl)propionic Acid from 1b. 1b (400 mg, 0.0019 mol) was added to diglyme (20 ml) followed by sodium hydride (50 mg, 0.0021 mol). The solution was heated to 100° for 45 min; then MeI (0.57 g, 0.0038 mol) was added. The temperature was raised to 120° for 3 hr. Water and Et_2O were added and the ethereal layer was washed, dried, and evaporated to yield a light brown gum (417 mg) which was chromatographed on 3 × 1 m × 0.25 mm preparative TLC plates (2:1 hexane–EtOAc) and the main band removed to give **1c** (300 mg, 70%) as a colorless oil. The NMR spectrum was identical with that given in D (ii) above except that the side-chain methyl signals indicated a ca. 1:1 diastereomeric mixture.

I. (i) Tricyclo[4.4.1.0^{1,6}]undec-8-en-3-one (9a). The epoxide **6** (5.0 g, 0.031 mol) was added to $LiAlH_4$ (1.3 g, 0.034 mol) in Et_2O (150 ml). After 5 hr, excess $LiAlH_4$ was destroyed and the organic layer dried and evaporated to give tricyclo[4.4.1.0^{1,6}]undec-8-en-3-ol [4.9 g (96%); ir 3400 cm^{-1}] which was dissolved in acetone (50 ml) and 8 N Jones reagent was added, monitoring by TLC (2:1 hexane–EtOAc) until no alcohol remained. Water and Et_2O were added and the organic solution was washed (aqueous Na_2CO_3, H_2O), passed through silica gel (ca. 20 g), dried, and evaporated to yield **9a** (4.3 g, 88%): ir 1705 cm^{-1}; NMR 0.42, 0.52, 0.68, 0.78 (AB q, J = 10 Hz, 11 H), 1.9–2.7 (m, aliphatic H), and 2.5–2.65 ppm (olefinic H).

(ii) **Wittig Reactions of 9a.** **9a** (518 mg, 0.0032 mol) and carboethoxymethylidenetriphenylphosphorane (1.11 g, 0.0032 mol) were heated to 140° for 3.5 hr. The product was poured into Et_2O, filtered through silica gel (ca. 10 g), and evaporated. The product (0.8 g) was chromatographed on a 1 m × 1.3 mm preparative TLC plate (1:1 hexane–EtOAc) to afford the product **9b** (400 mg, 53%) as an oil. GLC (column B, 170°) indicated a 60:40 mixture of geometric isomers: NMR 0.32, 0.38, 0.55, 0.63 (AB q, J = 4 Hz, 11 H), 1.13, 1.25, 1.37 (t, J = 7 Hz, CH_2CH_3), 1.7–3.1 (m, aliphatic H), 3.95, 4.07, 4.18, 4.32 (q, J = 7 Hz, CH_2CH_3), 5.53 (br s, olefinic H), and 5.65 ppm (CHCOOEt).

Similarly, condensation of **9a** with carboethoxyethylidenetriphenylphosphorane (1 equiv) gave **9c** (65%) as a 2:1 geometric isomer mixture (determined by NMR integration): NMR 0.50, 0.79 (11 H), 1.1–1.5 (m, CH_2CH_3), 1.7–3.1 (aliphatic H), 2.20 (CH_3C=), 3.97, 4.07, 4.20, 4.30 (q, J = 10 Hz, CH_2CH_3), and 5.4–5.7 ppm (olefinic H).

DDQ oxidation of **9b** and **9c**, as described in D (i) above, gave after chromatography the ethyl esters of **1d** and **1e** in yields of 5 and 20%, respectively.

J. (i) Condensation of 9a with Cyanoacetic Acid.[10] **9a** (0.89 g, 0.0055 mol), cyanoacetic acid (0.43 g, 0.0051 mol), and ammonium acetate (15 mg) were refluxed for 6 hr in C_6H_6 (30 ml) using a water separator. Dilute KOH and Et_2O were added. The aqueous layer was washed with Et_2O, then acidified (dilute HCl), and extracted with Et_2O. The extract was dried and evaporated to give **9d** (380 mg, 30%) as a low melting solid: ir 3500–2700, 2200, 1720 cm^{-1}; NMR 0.30, 0.38, 0.67, 0.75 (AB q, J = 5 Hz, 11 H), 1.3–3.5 (m, aliphatic H), 5.47 (olefinic H), and 9.70 ppm (COOH).

(ii) Decarboxylation of 9d to 8c. **9d** (250 mg) was heated to 150–160° under vacuum (ca. 0.5 mm). An oil distilled out and was condensed in a Dry Ice trap. The product (100 mg, 47%) was impure (NMR, TLC). However, DDQ oxidation followed by chromatography as described in D (i) above gave the annuleneacetonitrile **1k** (35 mg, 18% overall).

References and Notes

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