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Stereoselective Synthesis of 1,4,4a,9a-Tetrahydro-9-fluorenone Bearing *trans* Angular Substituents

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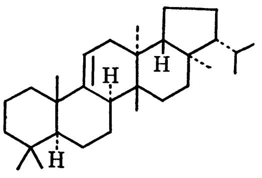
An intramolecular Friedel-Crafts reaction of 2-methyl-1-phenyl-1,2,3,6-tetrahydrophthalic anhydride **6** followed by methylation afforded new types of fluorenones bearing *trans* angular substituents, 4a-carbomethoxy-*trans*-9a-methyl-1,4,4a,9a-tetrahydro-9-fluorenone **7** and 3-hydroxy-*trans*-9a-methyl-9-oxo-1,2,3,4,4a,9a-hexahydrofluoren-*cis*-4a-carboxylic anhydride **10**.

A number of triterpenes are found to have polycyclic systems bearing *trans* substituents at the angular positions, as exemplified by the C/D ring system of fernene **1**.[1] A few reports have appeared concerning the methods for building up such *trans* fused cyclic systems, *e.g.*, hydrocyanation,[2] olefinic cyclization,[3] and the cleavage of a cyclopropane ring.[4] In the preceding paper[5] we have reported upon the acid-catalyzed cyclization of the cyclohexenone **2**, which gives rise to the *cis*-dimethylphenanthrenone **3**.



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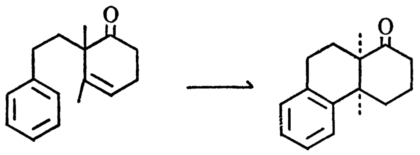


2 **3**

We report here a new method for the stereoselective synthesis of a tricyclic system carrying *trans* angular substituents using a Diels-Alder reaction and an intramolecular Friedel-Crafts reaction.

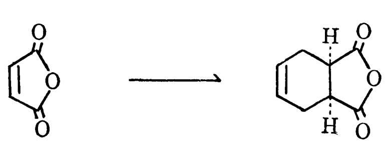
The Diels-Alder reaction of maleic anhydride and butadiene is well known to produce stereoselectively *cis*-1,2,3,6-tetrahydrophthalic anhydride. The same reaction of the anhydride **4** and butadiene affords the hydrophenanthrene derivative **5**,[5] in which the two functional groups are also oriented in a *cis* sense at the ring junctions. Thus, the cycloaddition reaction is suitable for synthesis of alicyclic compounds with two functional groups in a *cis* relation. We have devised the synthesis of polycyclic compounds having *trans* angular substituents from the *cis*-intermediate produced by a Diels-Alder reaction.

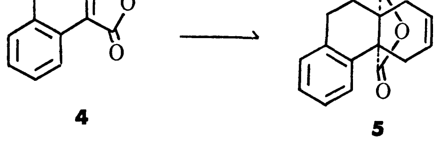
Results and Discussion

A Diels-Alder reaction of phenylmethylmaleic anhydride[6] and butadiene (or 3-sulfolene[7]) at 200 °C afforded the adduct **6** (mp 99.5—100 °C). Treatment of the anhydride **6** with aluminum chloride in carbon disulfide, followed by methylation with diazomethane, afforded the fluorenone **7** in 40% yield accompanied by three reaction products, the structures of which will be clarified later. The NMR spectrum of **7** shows two singlets at 1.05 (3H, angular methyl) and 3.48 (3H, $-COOCH_3$), in addition to a broad singlet at 5.8 (2H, olefinic protons) ppm. The IR (1710 and 1600 cm^{-1}) and UV (245 and 288 nm) spectra are consistent with the indanone chromophor of **7**. The structure was also verified by a further transformation; the ester **7** was reduced with lithium aluminum hydride in ether to give the diol **8**. The benzylic hydroxyl group was selectively oxidized on treatment with manganese dioxide[8] in methylene chloride to afford the crystalline hydroxy ketone **9**, which gives analytical datum and spectroscopic properties consistent with the proposed structure.

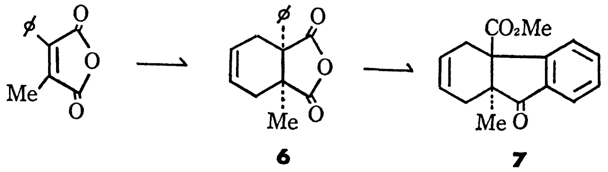
The angular substituents in these compounds (**7**–**9**) are necessarily located in the *trans* relationship because of the *cis* arrangement of the two carbonyls in the anhydride **6**.

Three other crystalline substances were also isolated from the Friedel-Crafts reaction products of the an-



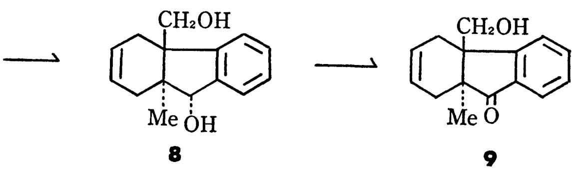


4 **5**



6 **7**

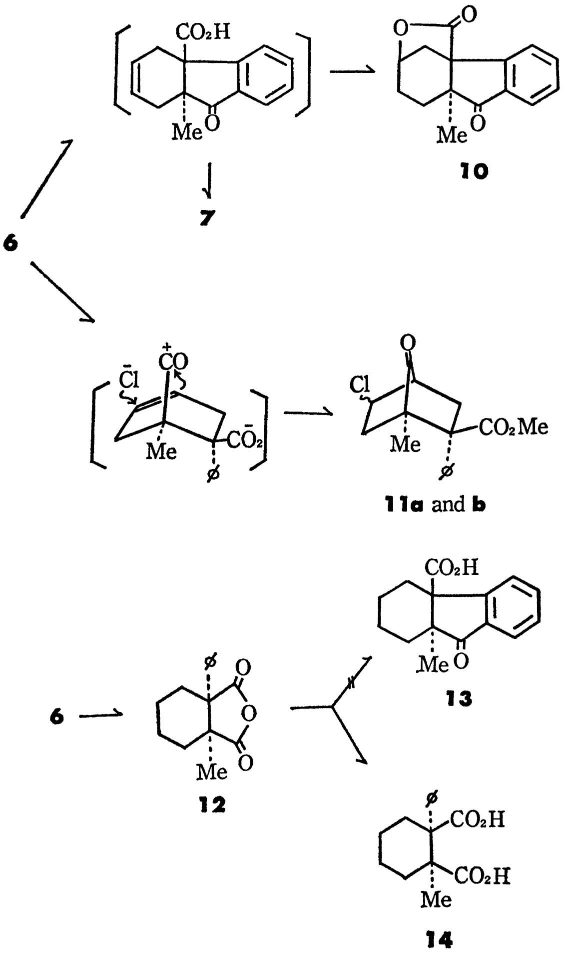
+ Three products



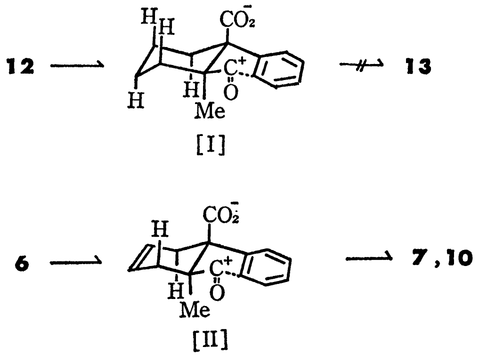
8 **9**

hydride **6**. The IR spectrum of the first crystals (40% from **6**) shows bands at 1765 and 1712 cm^{-1} and the UV spectrum exhibits absorption maxima at 247 and 290 nm, suggesting the presence of a γ-lactone and an indanone chromophor. The NMR spectrum exhibits a sharp singlet at 1.22 due to an angular methyl group and a 1H-multiplet at 4.95 ppm attributable to the proton attached to the carbinyl carbon atom of the lactone. From these properties the structure **10** was assigned for the first crystals, and this was further supported by physicochemical analyses.

The second and third crystals (7% and 2% from **6**) were found to be isomers having molecular formula $C_{16}H_{17}O_3Cl$ from the consideration of their mass spectra (*m/e* 264, M^+-CO; 266, M^++2-CO [32% height of the 264 peak]) and analytical data. The presence of chlorine atom in each compound was also detected by a Beilstein test. The IR spectra of each substance gave a pair of carbonyl bands at around 1776 (strained carbonyl) and 1720 (ester) cm^{-1}; the NMR spectra suggest the presence of a quaternary methyl (1.48/1.34 ppm, s, 3H), methoxy (3.42/3.41 ppm, s, 3H), and monosubstituted phenyl (7.29/7.28 ppm, s, 5H) groups. The signal ascribable to the proton attached to the carbon bearing chlorine atom appears around 4.5 ppm, as a multiplet. The structures **11a** and **b** can be assigned to the isomeric pair which are formed by the attack of the acyl cation to the double bond, as shown in the following scheme.



It is noteworthy that the dihydroanhydride **12**, obtainable by hydrogenation of **6** on platinum oxide, does not give rise to the hexahydrofluorenone **13** by treating with aluminum chloride, but affords the diacid **14**. The molecular models indicate that interactions between the angular substituents and hydrogens destabilize the intermediate I. On the other hand, the absence of two hydrogen atoms at C-4 and 5 makes the intermediate II more stable and easier to cyclize.



Experimental

NMR spectra were obtained with a Hitachi H-60 instrument using TMS as an internal standard. All the infrared spectra were taken on a Hitachi EPI-3T spectrophotometer. Ultraviolet spectra were taken on a Hitachi EPS-3T. Melting points and boiling points are uncorrected.

2-Methyl-1-phenyl-1,2,3,6-tetrahydrophthalic Anhydride **6**. A solution of phenylmethylmaleic anhydride (3.76 g) and butadiene (10.8 g) in dry dioxane (12 ml) containing a small amount of hydroquinone was heated at 200 °C in a sealed tube for 65 hr. The tube was cooled in a Dry Ice-acetone bath and opened. The solvent was evaporated to afford a yellow residue, which was chromatographed on silica gel (200 g). Elution with benzene-hexane (4 : 6) gave the adduct **6** (1.24 g) followed by the recovered phenylmethylmaleic anhydride (0.87 g). The analytical sample of **6** was obtained by recrystallization from ethanol as needles, mp 99.5—100 °C; ν (KBr): 1855, 1780, 1210, 970, 760, 700 cm^{-1}; δ ($CDCl_3$): 0.98 (3H, s), 6.04 (2H, br. s), 7.28 (5H, s) ppm. Calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.83%. Found: C, 74.16; H. 5.80%.

Intramolecular Friedel-Crafts Reaction of the Tetrahydrophthalic Anhydride **6**. Finely powdered aluminum chloride (4.37 g) was added to a solution of the anhydride **6** (1.81 g) in dry carbon disulfide (500 ml) during 30 min with vigorous stirring under an atmosphere of nitrogen. The deep purple mixture was stirred at room temperature for 34 hr, and the solvent was removed on a rotary evaporator at 30 °C. Cold dilute hydrochloric acid (200 ml) was added to the dark red residue and the resulting light yellow oil was taken up in ether. The organic layer was separated and washed with aqueous sodium bicarbonate solution (150 ml), and dried over sodium sulfate. The ether was evaporated to give the crude γ-lactone **10** which was recrystallized from benzene (712 mg); mp 175—176 °C; ν (KBr): 1765, 1712 cm^{-1}; δ ($CDCl_3$): 1.22 (3H, s), 2.60 (2H, ABX, $J_{AB}=12$ Hz, $J_{AX}=5$ Hz), 4.95 (1H, br. t, $J=5$ Hz), 7.1—7.9 (4H, m) ppm. Calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.83%. Found: C, 74.09; H, 5.83%.

The aqueous layer was acidified with concentrated hydrochloric acid and extracted with several portions of ether.

The ethereal layer was washed with brine and dried over sodium sulfate. Removal of the ether under reduced pressure gave a brown oil; ν ($CHCl_3$): 3500—2400, 1770, 1730, 1700, 1605 cm^{-1}. The oil was dissolved in ethyl acetate–ether (1 : 2; 50 ml) and treated with excess diazomethane at 0 °C. After 3 hr the polymethylene was filtered away, and the filtrate was concentrated to afford a brown oil. Chromatography on silica gel (50 g) using benzene as eluent produced the ester **7** (700 mg) as a colorless oil; ν (film): 1730, 1710, 1600 cm^{-1}; δ ($CDCl_3$): 1.05 (3H, s), 3.48 (3H, s), 5.8 (2H, br. s), 7.0—8.0 (4H, m) ppm. Found: *m/e* 256.110. Calcd for $C_{16}H_{16}O_3$: 256.110.

Further elution with benzene gave the isomers **11a** and **b** as slightly yellow crystals; **11a** (155 mg); mp 125.5 °C; ν (KBr) 1776, 1732 cm^{-1}, δ ($CDCl_3$) 1.48 (3H, s), 3.42 (3H, s), 4.6 (1H, m), 7.29 (5H, m) ppm. Found: C, 65.59; H, 5.83%. Calcd for $C_{16}H_{17}O_3Cl$: C, 65.64; H, 5.85%. **11b** (40 mg); mp 140—141 °C; ν (KBr): 1776, 1713 cm^{-1}; δ ($CDCl_3$): 1.34 (3H, s), 3.41 (3H, s), 4.15 (1H, m), 7.28 (5H, s) ppm. Found: C, 65.59; H, 5.85%. Calcd for $C_{16}H_{17}O_3Cl$: C, 65.64; H, 5.85%.

4b-Hydroxymethyl-8a-methyl-4b,5,8,8a-tetrahydro-9-fluorenone ***9***. Lithium aluminum hydride (4 g) was added to a solution of the ester **7** (393 mg) in dry ether (100 ml), and the reaction mixture was refluxed overnight. The excess hydride was decomposed with water followed by the addition of 10% sodium hydroxide solution. After the precipitates were removed by filtration, the filtrate was concentrated into an oil (347 mg); ν ($CHCl_3$): 3560, 3430, 1180, 1070 cm^{-1}; δ ($CDCl_3$): 0.71 (3H, s), 3.50 (2H, ABq, $J_{AB}=10$ Hz), 5.09 (1H, s), 5.74 (2H, br. s), 6.9—7.6 (4H, m) ppm. The crude diol (250 mg) was dissolved in methylene chloride (50 ml) and stirred with active manganese dioxide (3 g) at room temperature for 3 hr. The manganese dioxide was removed by filtration and the filtrate was concentrated. The residual oil was crystallized with benzene to give needles (200 mg); mp 122—126 °C; δ ($CHCl_3$): 1.00 (3H, s), 3.48 (2H, s), 5.76 (2H, br. s), 7.0—8.0 (4H, m) ppm. Found: C, 78.90; H, 7.12%. Calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06%.

1-Methyl-2-phenyl-1,2,3,4,5,6-hexahydrophthalic Anhydride ***12***. A solution of the anhydride **6** (193 mg) in ethyl acetate (15 ml) was hydrogenated in the presence of platinum oxide (18 mg). After the catalyst was filtered away, the ethyl acetate was evaporated to give a crystalline residue (190 mg); mp 110—115 °C (cubes from benzene); ν (KBr): 1870, 1855, 1780 cm^{-1}. Found: C, 73.93; H, 6.66%. Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60%.

Attempted Cyclization of the Hexahydrophthalic Anhydride ***12***. A solution of the anhydride **12** (73 mg) and aluminum chloride (200 mg) in nitrobenzene (2 ml) was stirred at room temperature for 24 hr. Cold hydrochloric acid was added and the mixture was extracted with ether. Evaporation of the ether and removal of the nitrobenzene afforded the starting anhydride (20 mg). Continuous extraction of the aqueous layer with ether afforded the diacid **14** as a white powder (20 mg); ν (KBr): 3500—2400 (br.), 1710, 1695 cm^{-1}. The structure of the diacid **14** was confirmed by heating it with acetic anhydride for 4 hr. A quantitative yield of the anhydride **12** was obtained.

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