Synthetic Studies toward Complex Diterpenoids. 16.[1] A Novel Synthetic Route to the Carbocyclic Skeleta of Stemodin and Stemarin by Acid-Catalyzed Intramolecular C-Alkylation and Rearrangement Reactions

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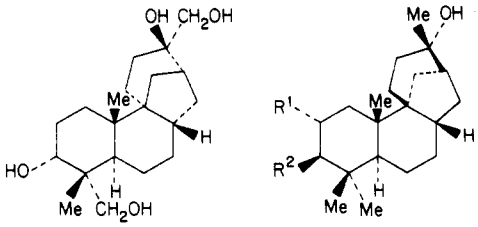
A simple strategy, involving an intramolecular C-alkylation and regiospecific rearrangement, is described leading to a highly efficient stereospecific synthesis of (±)-7-methoxy-12-methyl-2,3,3aβ,4,5,9b-hexahydro-2β,9bβ-prop-2-eno-1*H*-benz[*e*]indene (**13**) and (±)-7-methoxy-2-methyl-3,4,4a,9,10,10aβ-hexahydro-3β,4aβ-ethanophenanthrene (**14**), incorporating respectively the B/C/D ring systems of stemodin and stemarin-type diterpenoids through a common intermediate, (±)-2β-methyl-7-methoxy-11-oxo-1,2,3,4,4a,9,10,10aβ-octahydro-2α,4aα-ethanophenanthrene (**12**). The efficacy of a new acid-catalyzed intramolecular C-alkylation reaction developed pertaining to the synthesis of **12** has been further demonstrated by the synthesis of (±)-2β-methyl-7-methoxy-10-oxo-1,2,3,4,4a,9aβ-hexahydro-2α,4aα-ethanofluorene (**20**) from easily accessible starting material. The transformations of the bridged ketones **12** and **20** to the respective cis dicarboxylic acids **23** and **26** are reported.

The antiviral tumor-inhibiting fungal metabolite aphidicolin (**1**)[2] and its C-9 and C-12 isomeric stemodane derivatives (**2a–d**)[3] are members of a class of diterpenes having an unusual tetracyclic framework. Stemarin (**3**),[3b]



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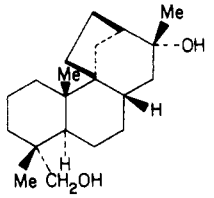
2a, $R^1=R^2=H$
b, $R^1=OH$; $R^2=H$
c, $R^1=O$; $R^2=H$
d, $R^1=H$; $R^2=OH$



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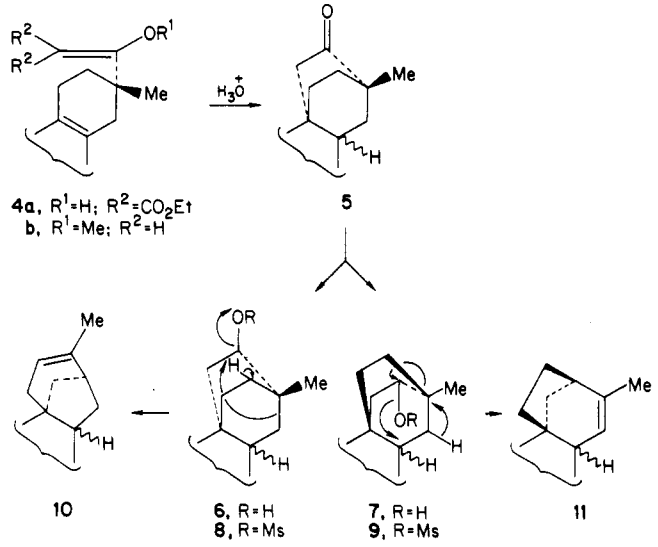
which occurs with the stemodane group in *Stemodia maritama* L. represents another interesting C/D-ring variant of diterpenes. These compounds have been the subject of much recent synthetic efforts. Total syntheses of **1**,[4] **2a**,[5] **2b,c**,[6] **2d**,[7] and **3**[8] have recently been achieved by a number of groups, and a few other approaches to the same molecules have also been reported.[9]

Scheme I



4a, $R^1=H$; $R^2=CO_2Et$
b, $R^1=Me$; $R^2=H$

5

10

6, R=H
8, R=Ms

7, R=H
9, R=Ms

11

In conjunction with our synthetic interests in complex bioactive diterpenes using intramolecular alkylation reactions,[10] we have been exploring a biogenetic-type[11] syn-

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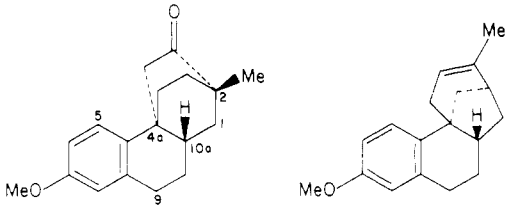
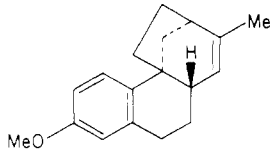
thetic approach (Scheme I) for the construction of the C/D-ring systems of the aforementioned diterpenes through easily accessible intermediates involving the following two stages: (i) formation of bicyclo[2.2.2]octan-2-one systems **5** by an intramolecular cationic angular alkylation[12] in substrates such as **4a** or **4b** (ii) regiospecific Wagner–Meerwein-type rearrangement[13] of epimeric alcohols **6** and **7**, derivable in principle from **5**, through mesylates **8** and **9**, leading to olefins **10** and **11**, respectively, incorporating the C/D-ring systems of aphidicolin/stemodane and stemarin.

The successful realization of a part of our objective, leading to a remarkably simple and potentially useful method for intramolecular α-tert-alkylation,[14] resulting in the synthesis of the tetracyclic bicyclo[2.2.2]octanone **12** was reported[15] in a preliminary communication in 1978. Subsequently, we also achieved[16] the transformation of **12** to the key tetracyclic intermediates **13** and **14**, incorporating the B/C/D-ring carbocyclic systems with aromatized ring A related to **2** and **3**. The recent reports of biogenetic-like total syntheses of **1** and **2d** by van Tamelen et al.[4e,7] and particularly those of 2-deoxystemodinone (**2a**)[5] and **3**[8] by Kelly et al. through rearrangements of some tetracyclic bicyclo[2.2.2]octanols, prepared by entirely different routes, prompted us to describe herein the details of our own work at this stage.



12

13



14

Results and Discussion

Preparation of the Bridged Ketones 12a and 20. The acid chloride obtained from the known acid **15a**,[17] on treatment with diethyl ethoxymagnesium malonate[18] gave **16a**, the substrate for intramolecular cationic cyclization. Reaction of **16a** with a mixture of CH_3CO_2H, H_2SO_4, and H_2O (40:7:10, v/v) at room temperature followed by refluxing (optimized condition for cyclization) gave the crystalline bridged ketone **12** as the only isolable product in excellent overall yield from **15a**. Similarly, the hydrofluorene analogue **19a**, obtained from the acid **18a**,[1] under identical reaction conditions afforded the bridged ketone **20**, which incorporates the carbocyclic skeleton of the antheridium-inducing factor A_{An}.[19] In contrast, refluxing **16a** and **19a** with a mixture of CH_3CO_2H–H_2SO_4–H_2O (8:1:5, v/v)[20] afforded only methyl ketones **17a** and **21a**, respectively. The keto diesters **16b**, **16c**,[20] and **19b**, prepared from the corresponding acids **15b**,[21] **15c**, and **18b**,[20] respectively, on attempted cyclization under the above conditions afforded only the corresponding methyl ketones **17b**, **17c**,[20] and **21b**[20] in good yields. From these and a large number of related experiments it appear that the acid-catalyzed cyclization of β-keto diester substrates such as **16a** and **19a** is extremely sensitive and depends considerably upon their structures and the reaction conditions. Although detailed ^{13}C NMR data[22] of **12** (see Experimental Section) using $Yb(DPM)_3$ shift reagent failed to give conclusive evidence regarding the stereochemical assignment at C-10a, this could be achieved by its further transformation to the dicarboxylic acid **23** (Scheme II). Thus, oxidation[23] of **12** with SeO_2 afforded diketone **22**, which on treatment[24] with alkaline H_2O_2 gave **23** in excellent overall yield. The A/B-trans-ring fusion of the diester **24** could be elucidated by comparison of its ^{13}C NMR chemical shifts with those of *trans*- and *cis*-methyl 1,2,3,4,4a,9,10,10a-octahydrophenanthrene-4a-carboxylates.[25]

While the analytical and spectral data are in complete agreement with structure **20** (see Experimental Section), the stereochemistry of this bridged ketone is based upon its mode of formation[26] in analogy to the octahydrophenanthrene system (**12**). The ^1H NMR spectral data (see Experimental Section) for diketones **25**, obtained in excellent yield by oxidation of **20**, also supports the assigned stereochemistry for these compounds. Oxidative

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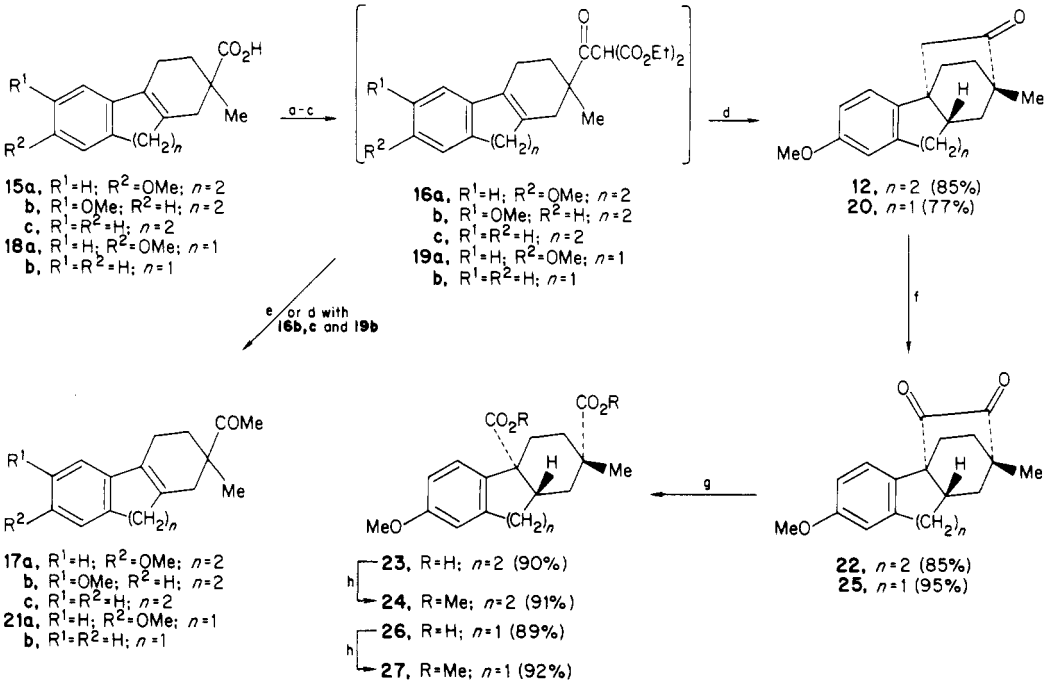
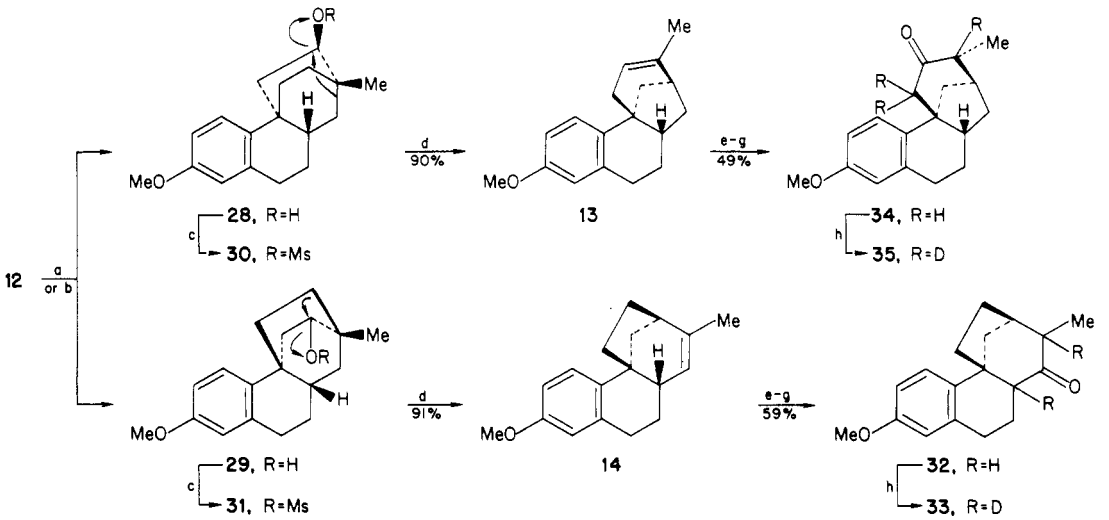
(26) It seems that the first step in the acid-catalyzed intramolecular angular alkylation reaction of β-keto diesters **16a** and **19a** is the formation of highly stabilized epimeric benzylic cations (cf. Kuo, C. H.; Taub, D.; Wendler, N. L. *J. Org. Chem.* **1968**, *33*, 3126). In the absence of a *p*-methoxy stabilizing group in the aromatic ring, such cations either do not form or exist in negligible concentrations under protic acid catalysis. This point has been proved by persistent failure in the attempted cyclization reactions of β-keto diester substrates having no *p*-methoxy group in the aromatic ring (e.g., **16b**, **16c**, and **19b**). It is known that the acid-catalyzed decarbethoxylation of similar β-keto diesters to β-keto esters is a facile process.[27] Although we have failed to identify the products in the initial step in the alkylation process, it can be reasonably assumed that both the protonated β-keto diester enolates from **16a** or **19a** as well as the β-keto ester enolates, produced by their decarbethoxylation, possibly take part in the carbon–carbon bond formation reaction.[28] The most notable feature in the reaction of **16a** and **19a** is essentially the exclusive formation of the trans-oxoethano-bridged fused products **12** and **20**, respectively, with regard to the newly generated asymmetric center. Examination of the molecular models of the intermediate from **16a** with C-10aβ and C-10aα (cf. **12**) hydrogen respectively suggests that only in the former case the π-orbital of the sp^2-hybridized C-4a center can overlap with the enolate moiety. Such overlapping is sterically impossible in the latter cation. Similar explanation is also valid for **19a**.

Scheme II[a]



[a] (a) NaOMe, C_6H_6; (b) $(COCl)_2$, C_6H_6; (c) $OEtMgCH(CO_2Et)_2$, Et_2O; (d) CH_3CO_2H-H_2SO_4-H_2O (40:7:10), room temperature 16 h reflux, 7 h; (e) CH_3CO_2H-H_2SO_4-H_2O (8:1:5), reflux, 7 h; (f) SeO_2, Ac_2O, 160 °C; (g) H_2O_2 (30%), NaOH (10%), *t*-BuOH, then HCl; (h) CH_2N_2, Et_2O.

Scheme III[a]



[a] (a) B_2H_6, THF, 2 h; (b) $NaBH_4$, EtOH; (c) CH_3SO_2Cl, NEt_3, CH_2Cl_2; (d) neutral alumina, petroleum ether (bp 60–80 °C); (e) B_2H_6, THF, H_2O; (f) H_2O_2 (30%), H_2O, NaOH; (g) Jones reagent, CH_3COCH_3; (h) NaOMe, MeOD.

cleavage of **25** gave diacid **26** in excellent yield, which was converted to the respective diester **27**.

Rearrangement of Bicyclo[2.2.2]octanol Intermediates. With the successful development of an efficient intramolecular alkylation route to bicyclo[2.2.2]octanone **12**, we examined the skeletal rearrangement of derived alcohols **28** and **29**. Reduction of **12** with diborane in THF (Scheme III) and $NaBH_4$ in ethanol gave mixtures of **28** (mp 118 °C) and **29** (mp 126 °C) in 22:78 and 1:1 ratios, respectively, in good yield. This epimeric pair of alcohols could be partially separated by fractional crystallization, but the stereochemistry of these alcohols could not be assigned even by extensive ^{13}C NMR studies[22] using shift reagents. In spite of considerable effort, we failed to produce crystals of these epimeric alcohols amenable to X-ray crystallographic analyses. The configurations of the lower and the higher melting alcohols have been assigned as **28** and **29**, respectively, on the basis of the corresponding rearrangement products **13** and **14** (see Scheme III).

Rearrangement of the crude mesylate (**30**) of alcohol **28** by chromatography on neutral alumina gave a single olefin **13**. The rearrangement of **30** → **13** evidently is controlled by the stereoallignment of the migrating bond[5,13] relative to the leaving OMs group. Repeating the rearrangement of the higher melting alcohol **29** under an identical condition through the unstable mesylate **31** afforded the rearranged tetracyclic olefin **14** (mp 62 °C) in excellent yield.

Although the ^1H NMR spectral data for the tetracyclic olefins **13** and **14** are consistent with the assigned structures, these are not adequate to distinguish one from the other. Initially, attempts were made to settle this question through X-ray crystallographic analysis of the crystalline olefin **14**. Unfortunately, this crystal was found to be unsuitable for simple crystallographic methods. The as-

signed structures **14** and **13** have been confirmed by the following transformations. Hydroboration–oxidation of olefin **14** (Scheme III) afforded a mixture of diastereomeric carbinols, which was directly oxidized to a mixture of two epimeric ketones. From this, one crystalline isomer (**32**) (stereochemistry of Me is uncertain) could be separated in 52% yield, which exhibited a methyl doublet at δ 0.97 (J = 6 Hz). Deuterium exchange of **32** with $NaOCH_3$ in CH_3OD and determination of the extent of deuteration by mass spectrometry indicated the incorporation of two deuterium atoms. This was confirmed by the ^1H NMR spectrum of deuterated ketone **33**, which exhibited a methyl singlet at δ 0.97, and integration indicated the decrease in two protons. The assigned structure of **32** has been further confirmed by the detailed mass spectral analysis of the nondeuterated and the deuterated ketones (see Experimental Section).

Hydroboration–oxidation of the isomeric olefin **13** followed by oxidation of the intermediate carbinols with Jones reagent afforded a stereochemically homogeneous ketone (**34**) (mp 130 °C) in 49% yield. The preferred stereochemistry for the methyl group in **34** has been tentatively assigned from the examination of molecular models. Unlike the facile deuteration of ketone **32**, deuteration of the boat-locked isomeric ketone **34** was extremely slow. Treatment of **34** with $NaOCH_3$ in CH_3OD at room temperature for 40–60 h gave very little deuteration. However, refluxing the mixture for 28 h under N_2 gave deuterated ketone **35** (incorporating d_1–d_3) (mp 92–95 °C), which exhibited a methyl singlet at δ 0.98 along with the doublet for the nondeuterated ketone **34**. Mass spectral analysis of this deuterated ketone showed the incorporation of upto 11% of 3 equiv of deuterium (see Experimental Section). The extreme steric congestion and nonenolizability[29] of the C=O group in **34** is possibly responsible for the slow deuterium exchange.

The structures of the isomeric ketones **32** and **34** were finally established by the mass spectral fragmentation patterns (see Experimental Section).

Establishment of the structures of the ketones **32** and **34** leads to the complete structural assignments to the respective olefins **14** and **13** and the key alcohol substrates **29** and **28** from which these were derived. The transformations of the olefins related to **13** and **14** to the tertiary carbinols corresponding to the ring-D functionalities of stemodin and stemarin have already been achieved by Kelly et al.,[5,8] and the generation of ring-A functionalities from these intermediates are in progress.

Conclusion

The objectives of the present investigation have been realized in developing a new acid-catalyzed intramolecular angular alkylation leading to a simple *p*-methoxyphenyl substituted bicyclo[2.2.2]octan-2-one[16] as well as oxo-2,4a-ethanohydrophenanthrene and hydrofluorene derivatives. These intermediates can be utilized for stereospecific generation of the difficulty accessible quaternary[30,31] dicarboxylic acid functionality. The biogenetically modelled regiospecific rearrangement of two epimeric tetracyclic bridged bicyclo[2.2.2]octanols provides a simple and a highly efficient synthetic route to the complex carbocyclic skeleta of stemodane and stemarin diterpenoids.

Experimental Section

The compounds described are all racemates. Melting points, taken in open capillary, are uncorrected. ^1H NMR spectra were run at 60 MHz, ^{13}C NMR spectra at 25.2 MHz. Column chromatography was performed on neutral aluminum oxide "Standardized for chromatographic analysis according to Brockmann". Petroleum ether refers to the fraction with boiling point of 60–80 °C. GLC was performed on a 20 × $^1/_8$ in. 10% UCW-982 column with N_2 as the carrier gas.

Acid-Catalyzed Intramolecular Alkylation Reaction of the β-Keto Diester 16a. (A) Preparation of 2β-Methyl-7-methoxy-11-oxo-1,2,3,4,4a,9,10,10aβ-octahydro-2α,4aα-ethanophenanthrene (12). The dry sodio salt[10c] of acid **15a**[17] (4 g, 14.8 mmol) was suspended in anhydrous benzene (75 mL) containing pyridine (0.5 mL) and cooled in an ice bath, and oxalyl chloride (6 mL, 68.7 mmol) was added slowly with stirring. The mixture was stirred while cooling for 0.5 h and at 60 °C for 1 h and filtered. The filtrate was evaporated under vacuum and the residue was taken up in 100 mL of anhydrous Et_2O. A solution of diethyl ethoxymagnesium malonate,[18] prepared from 4.8 g (20 mmol) of magnesium, 32 mL of diethyl malonate, and 22 mL of ethanol in the presence of a catalytic amount of CCl_4 in 100 mL of Et_2O, was added slowly to the stirred ether solution of the crude acid chloride with salt–ice bath cooling. Stirring was continued for 2 h with cooling and then for 12 h at room temperature. The mixture was added to 400 mL of ice-cold 2 N H_2SO_4. The Et_2O layer was separated, and the aqueous layer was extracted with Et_2O (2 × 50 mL). The combined Et_2O solution and the Et_2O extracts were washed with H_2O, 5% aqueous Na_2CO_3, and again with H_2O and dried (Na_2SO_4). Removal of Et_2O afforded a mixture of the β-keto diester **16a** and diethyl malonate. To this mixture was added a mixture of CH_3CO_2H (160 mL), concentrated H_2SO_4 (28 mL), and H_2O (40 mL), and the resulting solution was left under N_2 for 16 h at room temperature followed by reflux for 7 h. The reaction mixture was diluted to 600 mL with H_2O and extracted with Et_2O (4 × 100 mL). The ethereal extract was washed with H_2O, 10% aqueous NaOH, and again with H_2O and dried (Na_2SO_4). Removal of Et_2O afforded a solid (3.84 g), mp 110–115 °C, which on chromatography over neutral alumina (30 g) with petroleum ether–benzene (95:5) as eluent followed by crystallization from petroleum ether gave **12** as white needles (3.39 g, 85%): mp 137 °C; IR ($CHCl_3$) 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.99 (3 H, s, Me), 1.1–2.03 (9 H, m), 2.06–2.43 (partially resolved quartet centered at 2.23 and 2.28, 2 H, $COCH_2$, J_{AB} = 9 Hz), 2.65–2.90 (9 H, m, $ArCH_2$), 3.70 (3 H, s, $ArOCH_3$), 6.53–7.25 (3 H, m, Ar H); mass spectrum, m/z (relative intensity) 270 (M^+, 70), 255 (5), 227 (10), 186 (100); ^{13}C NMR ($CDCl_3$) δ 215.7 (C_{11}), 157.1 (C_7), 137.0 (C_{8a}), 133.5 (C_{4b}), 127.1 (C_5), 112.9 (C_8), 112.2 (C_6), 54.7 (OMe), 48.2 (C_{12}), 42.7 (C_2), 38.2 (C_1), 37.7 (C_{4a}), 35.9 (C_{10a}), 33.7 (C_4), 30.9 (C_3), 30.2 (C_9), 27.0 (C_{10}), 19.5 (C_1-Me); molar shifts with $Yb(DPM)_3$ 110.0 (C_{11}), 47.0 (C_{12}), 46.0 (C_1), 36.5 (C_1-Me), 26.0 (C_3), 25.0 (C_1), 21.0 (C_{4a}), 18.0 (C_4), 17.0 (C_{10a}), 8.5 (C_{10}), 7.0 (C_{4b}), 4.5 (C_9), 4.0 (C_{8a}), 3.3 (C_5), 3.0 (C_7)8 2.5 (C_8), 2.0 (OMe), and 1.3 (C_6). Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.98; H, 8.20. Found: C, 80.09; H, 8.17.

(B) The crude **16a**, prepared from **15a** (4 g, 14.8 mmol), after removal of the excess diethyl malonate under vacuum, on refluxing with a mixture of CH_3CO_2H–H_2SO_4–H_2O (8:1:5, v/v) for 7 h, gave the liquid methyl ketone **17a** (3.82 g, 95%): IR 1700, 1605 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.07 (3 H, s), 1.5–2.46 (11 H, m, containing a sharp Me s for $COCH_3$ at 2.0), 2.50–2.80 (2 H, m), 3.67 (3 H, s), 6.34–7.1 (3 H, m). Anal. Calcd for $C_{18}H_{22}O$: C, 79.98; H, 8.20. Found: C, 80.12; H, 8.27.

(C) Attempted cyclization of the crude β-keto diester **16a** admixed with diethyl malonate, with CH_3CO_2H–H_2SO_4–H_2O

(27) (a) Riegel, B.; Lilienfeld, W. M. *J. Am. Chem. Soc.* **1945**, *67*, 1273. (b) Baker, B. R.; Schaub, R. E.; Williams, J. H. *J. Org. Chem.* **1952**, *17*, 116.

(28) It is worthy to note here that while the *de*methoxy methyl ketone **16c** on interactions with trimethyl and triethyl orthoformates in the presence of $HClO_4$ (70%) gave entirely different products (ref 20), the *p*-methoxy methyl ketones **17a** and the respective hydrofluorene analogue **21a** on reaction with trimethyl orthoformate under similar conditions gave the tetracyclic bridged ketones **12** and **20**, respectively (~50% yield), evidently through the respective protonated enol ethers [B. C. Ranu and R. Dasgupta, unpublished results].

(29) Yamada, K.; Manabe, S.; Kyotani, Y.; Suzuki, M.; Hirata, Y. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 186.

(30) Ghatak, U. R.; Chakrabarty, S. *J. Org. Chem.* **1976**, *41*, 1089.

(31) For a review, see: Martin, S. *Tetrahedron* **1980**, *36*, 419.

(40:7:10, v/v) and (70:7:20 v/v), under reflux for 7 h afforded a mixture of the bridged ketone **12** and the methyl ketone **17a** in the isolated yields of 72% and 12% and 34% and 55%, respectively.

Preparation and Attempted Intramolecular C-Alkylation of the β-Keto Diester 16b. 2-Acetyl-2-methyl-6-methoxy-1,2,3,4,9,10-hexahydrophenanthrene (17b). The crude β-keto diester **16b** admixed with the excess of diethyl malonate, prepared through the acid chloride from **15b**,[21] was treated directly with a mixture of CH_3CO_2H (140 mL), concentrated H_2SO_4 (28 mL), and H_2O (40 mL) and left under N_2 for 16 h at room temperature, following which it was refluxed for 7 h. Usual workup gave a liquid which on chromatography over neutral alumina (25 g) yielded in the petroleum ether elutes the liquid ketone **17b** (3.28 g, 81%): IR (neat) 1700, 1602 cm^{-1}; UV (EtOH) λ_{max} 268 nm (log ε 4.20); ^1H NMR (CCl_4) δ 1.10 (3 H, s, CH_3), 1.67–2.75 (13 H, m, consisting of a Me s for $COCH_3$ at 2.01), 3.68 (3 H, s, $ArOCH_3$), 6.33–6.93 (3 H, m). Anal. Calcd for $C_{18}H_{22}O_2$: C,79.98; H, 8.20. Found: C, 79.84; H, 8.16.

Intramolecular C-Alkylation of the β-Keto Diester 19a. (A) 2β-Methyl-7-methoxy-10-oxo-1,2,3,4,4a,9aβ-hexahydro-2α,4aα-ethanofluorene (20). The acid **18a**[1] (4 g, 15.5 mmol) was converted to the β-keto diester **19a** through the acid chloride following the procedure described for **16a**. The crude mixture of β-keto diester and diethyl malonate thus obtained was mixed with 228 mL of a solution of CH_3CO_2H, concentrated H_2SO_4, and H_2O (40:7:10, v/v), and the resulting mixture was left under N_2 for 16 h at room temperature followed by reflux for 7 h. Workup of the reaction mixture with Et_2O according to the aforementioned procedure afforded a semisolid mass. The crude product on chromatography through neutral alumina with petroleum ether–benzene (90:10) followed by crystallization from Et_2O petroleum ether afforded **20** (3.09 g, 77%), mp 112 °C; IR ($CHCl_3$) 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.0 (3 H, s, Me), 1.30–3.13 (11 H, m), 3.73 (3 H, s, $ArOCH_3$), 6.56–7.10 (3 H, m, ArH); mass spectrum, *m/z* (relative intensity) 254 (M^+, 36), 241 (3), 213 (6), 172 (100). Anal. Calcd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.67; H, 7.80.

(B) The attempted cyclization of the crude **19a**, prepared from **18a** (4 g, 15.5 mmol), by refluxing for 7 h with a mixture of CH_3CO_2H (32 mL), concentrated H_2SO_4 (4 mL), and H_2O (20 mL) under N_2 afforded, after usual workup, the methyl ketone **21a** (2.95 g, 77%): bp 190–195 °C (0.1 mmHg) (bath temperature): IR (neat) 1700, 1608 cm^{-1}; UV (EtOH) λ_{max} 272 nm (log ε 4.15); ^1H NMR (CCl_4) δ 1.16 (3 H, s, CH_3), 1.60–2.82 (9 H, m, consisting a Me s for $COCH_3$ at 2.08), 3.12 (2 H, br s, $ArCH_2$), 3.72 (3 H, s, $ArOCH_3$), 6.50–6.98 (3 H, m, ArH). Anal. Calcd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.96. Found: C, 79.49; H, 7.81.

Selenium Dioxide Oxidation of 12. 2β-Methyl-7-methoxy-11,12-dioxo-1,2,3,4,4a,9,10,10aβ-octahydro-2α,4aα-ethanophenanthrene (22). A mixture of the ketone **12** (400 mg, 1.48 mmol) and freshly sublimed and powdered SeO_2 (800 mg, 7.2 mmol) in acetic anhydride (15 mL) was refluxed with stirring under N_2 for 8 h at 160 °C in an oil bath. The cooled solution was diluted with Et_2O (100 mL) and the etheral solution was filtered free of precipitated selenium. The filtrate was repeatedly washed with 5% aqueous $NaHCO_3$ until free from acid followed by washing with H_2O and dried (Na_2SO_4). Removal of Et_2O afforded a yellow solid which after crystallization from THF–petroleum ether (bp 40–60 °C) gave pure **22** (400 mg, 95%): mp 182 °C; IR ($CHCl_3$) 1740, 1720, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.18 (3 H, s, CH_3), 1.33–2.50 (9 H, m), 2.70–2.96 (2 H, m, $ArCH_2$), 3.77 (3 H, s, $ArOCH_3$), 6.63–7.03 (3 H, m, Ar H). Anal. Calcd for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 75.90; H, 7.13.

2β-Methyl-7-methoxy-1,2,3,4,4a,9,10,10aβ-octahydrophenanthrene-2α,4aα-dicarboxylic Acid (23). To a solution of the diketone **22** (200 mg, 0.7 mmol) in *t*-BuOH (10 mL) was added with stirring 30% H_2O_2 solution (10 mL) followed by 10% aqueous NaOH (25 mL) dropwise. After stirring for 30 min, a second aliquot of 30% hydrogen peroxide solution (10 mL) followed by 10% aqueous NaOH (25 mL) was added dropwise. The mixture was stirred for an additional 1 h, and the excess peroxide was then decomposed by addition of a small amount of Pd–C (10%) catalyst and the solution filtered. The filtrate was extracted with Et_2O (2 × 30 mL). The basic aqueous part was then acidified with ice-cold 6 N HCl. The precipitated acid was extracted with $CHCl_3$. The dried ($CaCl_2$) $CHCl_3$ extracts on evaporation under vacuum afforded a solid which was crystallized from THF–petroleum ether (bp 40–60 °C) to give pure acid **23** (200 mg, 90%): mp 212 °C; IR ($CHCl_3$) 3500, 1710 cm^{-1}. Anal. Calcd for $C_{18}H_{22}O_5$: C, 67.91; H, 6.97. Found: C, 67.90; H, 6.92.

Dimethyl 2β-Methyl-7-methoxy-1,2,3,4,4a,9,10,10aβ-octahydrophenanthrene-2α,4aα-dicarboxylate (24). The diacid **23** (100 mg) was treated with excess CH_2N_2 in Et_2O for 15 min. After removal of the excess Et_2O, the crude ester was dissolved in petroleum ether and filtered through a small bed of neutral alumina. Evaporation of the solvent followed by crystallization of the residue from petroleum ether yielded the pure diester **24** (100 mg, 91%): mp 114 °C; IR ($CHCl_3$) 1725 cm^{-1}; ^1H NMR (CCl_4) δ 1.22 (3 H, s, Me), 1.40–2.20 (9 H, m), 2.60–3.00 (2 H, m, $ArCH_2$), 3.55 (3 H, s, CO_2CH_3), 3.62 (3 H, s, CO_2CH_3), 3.70 (3 H, s, $ArOCH_3$), 6.50–7.33 (3 H, m, Ar H); ^{13}C NMR ($CDCl_3$) δ 178.5 (C_{12}), 173.8 (C_{11}), 158.9 (C_7), 138.8 (C_{8a}), 130.7 (C_{4b}), 127.8 (C_5), 113.6 (C_8), 111.9 (C_6), 55.0 (OMe), 51.6* (C_{11} ester Me), 51.5* (C_{12} ester Me), 48.8 (C_{4a}), 41.7 (C_2), 37.6 (C_{10a}), 37.5 (C_1), 32.0† (C_3), 31.9† (C_4), 29.2 (C_9), 25.2 (C_{10}), and 21.2 (Me) [* and † denote interchangeable chemical shifts]; mass spectrum, *m/z* (relative intensity) 346 (M^+, 10), 287 (100), 227 (70). Anal. Calcd for $C_{20}H_{26}O_5$: C, 69.34; H, 7.57. Found: C, 69.17; H, 7.59.

2β-Methyl-7-methoxy-10,11-dioxo-1,2,3,4,4a,9aβ-hexahydro-2α,4aα-ethanofluorene (25). The ketone **20** (200 mg, 0.78 mmol) was oxidized by refluxing with SeO_2 (340 mg, 3.06 mmol) and acetic anhydride (3.4 mL) for 16 h to afford **25** (200 mg, 95%): mp 160 °C; ^1H NMR ($CDCl_3$ δ 1.16 (3 H, s, CH_3), 1.50–2.70 (7 H, m), 2.73–3.00 (2 H, m), two partially resolved ABX systems at 2.85 (J_{AB} = 10 Hz, J_{AX} = 3 Hz) and 3.07 (J_{AB} = 3 Hz), 3.80 (3 H, s, $ArOCH_3$), 6.7–7.12 (3 H, m, Ar H). Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.38; H, 6.67.

2β-Methyl-7-methoxy-1,2,3,4,4a,9aβ-hexahydrofluorene-2α,4aα-dicarboxylic Acid (26). The diketone **25** (100 mg, 0.37 mmol) in *t*-BuOH (3 mL) was oxidized with 30% H_2O_2 (6 mL) in the presence of 10% aqueous NaOH (20 mL) to the dicarboxylic acid **26** (100 mg, 89%): mp 230 °C; IR ($CHCl_3$) 1695 cm^{-1}. Anal. Calcd for $C_{17}H_{20}O_5$: C, 67.09; H, 6.62. Found: C, 67.10; H, 6.59.

Dimethyl 2β-Methyl-7-methoxy-1,2,3,4,4a,9aβ-hexahydrofluorene-2α,4aα-dicarboxylate (27). The diacid **26** (100 mg) was esterified with excess CH_2N_2 in Et_2O and the crude dimethyl ester was purified to afford 98 mg (92%) of **27**: mp 71 °C; IR ($CHCl_3$) 1700 cm^{-1}; ^1H NMR (CCl_4) δ 1.27 (3 H, s, Me), 1.57–3.30 (9 H, m), 3.53 (3 H, s, CO_2CH_3), 3.67 (3 H, s, CO_2CH_3), 3.71 (3 H, s, $ArOCH_3$), 6.43–7.10 (3 H, m, Ar H). Anal. Calcd for $C_{19}H_{22}O_5$: C, 69.07; H, 6.71. Found: C, 69.16; H, 6.81.

Reduction of the Ketone 12 to the Epimeric Alcohols 28 and 29. (A) With Diborane. Diborane gas [generated from $NaBH_4$ (1.5 g, 39.6 mmol) and $BF_3{\cdot}Et_2O$ (6 mL, 48.7 mmol) in diglyme (6 mL)] was bubbled through a cold (0 °C) solution of the ketone **12** (2 g, 7.4 mmol) in anhydrous THF (25 mL) for 2 h under a slow stream of N_2. The solution was decomposed by careful addition of H_2O in cold (0 °C) and extracted with Et_2O after saturation with NaCl. The ethereal extract was washed with brine and dried (Na_2SO_4). Removal of solvent afforded a mixture (1.61 g, 80%) of epimeric alcohols **29** and **28** in a ratio of ~78:22 (from methyl signals in ^1H NMR). Fractional crystallization of this mixture from Et_2O–petroleum ether afforded the major epimer **29** (1.22 g, 61%) [mp 126 °C; IR 3300, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (3 H, s, CH_3), 1.10–2.36 (12 H, m), 2.50–2.93 (2 H, m, $ArCH_2$), 3.53–3.66 (1 H, m, CH(OH)), 3.77 (3 H, s, $ArOCH_3$), 6.46–7.20 (3 H, m, Ar H). Anal. Calcd for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.41; H, 8.86] and the minor epimer **28** (352 mg, 17%) [mp 118 °C; IR 3300, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (3 H, s, CH_3), 1.28–2.41 (12 H, m), 2.50–2.83 (2 H, m, $ArCH_2$), 3.50 [1 H, br d, *J* = 4 Hz, C*H*(OH)], 3.73 (3 H, s, $ArOCH_3$), 6.48–7.26 (3 H, m, Ar H). Anal. Calcd for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.62; H, 8.94].

(B) With $NaBH_4$. To a magnetically stirred solution of the ketone **12** (945 mg, 3.5 mmol) in EtOH (28 mL) was added $NaBH_4$ (455 mg, 12 mmol) in one lot. Stirring was continued for 3 h and left overnight (total 18 h). On the next day, the reaction mixture was poured into ice-cold 10% HCl (70 mL) and the resulting solution was extracted with Et_2O. The ethereal extract was washed with brine and dried (Na_2SO_4). Removal of Et_2O afforded a solid (860 mg, 91%) which was found to be a ~1:1 mixture (from ^1H NMR) of the two epimeric alcohols **28** and **29**. Fractional crys-

tallization of this crude solid from Et_2O petroleum ether afforded **29** (240 mg, 25%), mp and mmp 126 °C with sample described above, and **28** (238 mg, 25%), mp and mmp 118 °C, with the sample described above.

Rearrangement of 28: 7-Methoxy-12-methyl-2,3,3aβ,4,5,9b-hexahydro-2β,9bβ-prop-2-eno-1*H*-benz[*e*]indene (13). To a magnetically stirred, cold (0 °C) solution of the carbinol **28** (250 mg, 0.92 mmol) in anhydrous CH_2Cl_2 (15 mL) and NEt_3 (0.5 mL, 3.5 mmol) freshly distilled CH_3SO_2Cl (0.25 mL, 3.2 mmol) was added dropwise. After being stirred for 30 min at 0 °C, the reaction mixture was quenched with ice-cold H_2O. The organic layer was separated, washed with H_2O, and dried ($CaCl_2$). Removal of the solvent under reduced pressure afforded a light brown liquid which was chromatographed on a column of neutral alumina (10 g). Elution with petroleum ether afforded the unsaturated hydrocarbon **13** (209 mg, 90%) as a thick liquid which was further purified by evaporative distillation, bp (bath temperature) 145–150 °C (0.35 mmHg); homogeneous in GLC at column temperature 170 °C, with t_R 6.5 min; IR (neat) 2920, 2860, 2840, 1610, 1500, 1450, 1280, 1260, 1250, 1230, 1200, 1165, 1155, 1130, 1050, 815, and 800 cm^{-1}; ^1H NMR (CCl_4) δ 1.00–2.77 (15 H, m), including a CH_3 d at 1.71 (J = 2 Hz), 3.73 (3 H, s, $ArOCH_3$), 5.10 (1 H, m, vinyl), 6.33–6.70 (2 H, m, Ar H), 7.07 (1 H, d, J = 8 Hz, Ar H). Anal. Calcd for $C_{18}H_{22}O$: C, 84.99; H, 8.72. Found: C, 84.91; H, 9.00.

Rearrangement of 29: 7-Methoxy-2-methyl-3,4,4a,9,10,10aβ-hexahydro-3β,4aβ-ethanophenanthrene (14). To a magnetically stirred, cold (0 °C) solution of the alcohol **29** (1 g, 3.67 mmol) in anhydrous CH_2Cl_2 (50 mL) and NEt_3 (2.0 mL, 14.3 mmol) was added freshly distilled CH_3SO_2Cl (1 mL, 12.9 mmol) dropwise during 1 min. After being stirred for 15 min at 0 °C, the reaction mixture was quenched with ice-cold H_2O. The organic layer was separated and washed thoroughly with H_2O and dried ($CaCl_2$). The brownish residue after removal of the solvent was chromatographed through a column of neutral alumina (30 g). Elution with petroleum ether afforded the rearranged hydrocarbon **14** (853 mg, 91%) as a waxy solid which was crystallized from petroleum ether (bp 40–60 °C): mp 62 °C; homogeneous in GLC (t_R 7.5 min) at column temperature 170 °C; IR (KBr) 2940, 2850, 1610, 1500, 1320, 1260, 1240, 1170, and 1040 cm^{-1}; ^1H NMR (CCl_4) δ 1.52–2.37 (13 H, m), including a CH_3 d at 1.67 (J = 2 Hz), 2.53–3.90 (2 H, m, $ArCH_2$), 3.66 (3 H, s, $ArOCH_3$), 5.00 (1 H, m, vinylic), 6.30–6.70 (2 H, m, ArH), and 7.10 (1 H, d, J = 9 Hz, Ar H). Anal. Calcd for $C_{18}H_{22}O$: C, 84.99; H, 8.72. Found: C, 84.90; H, 8.92.

7-Methoxy-2-methyl-1(*H*),2,3,4,4a,9,10,10a-octahydro-3β,4aβ-ethanophenanthren-1-one (32). Diborane gas [generated from $NaBH_4$ (400 mg, 10.5 mmol) and BF_3·Et_2O (2 mL, 16.2 mmol) in diglyme (2 mL)] was bubbled through a cold (0 °C) solution of the olefin **14** (250 mg, 0.98 mmol) in anhydrous THF (10 mL) during 2 h, under a slow stream of N_2. The reaction mixture was decomposed by careful addition of H_2O in cold (0–5 °C), followed by addition of 3 N aqueous NaOH (10 mL). To this solution, cooled to 10–15 °C was added 30% H_2O_2 (6 mL) dropwise with stirring. Stirring in the cold was continued for an additional 30 min; then a second lot of 30% H_2O_2 (4 mL) was added similarly. The bath temperature was gradually raised to room temperature and the reaction mixture was allowed to stand overnight followed by extraction with Et_2O. The Et_2O extract was washed with H_2O and dried (Na_2SO_4). Removal of solvent afforded a mixture of epimeric carbinols as a thick liquid (242 mg) which was directly oxidized in $(CH_3)_2CO$ (10 mL) at 5–10 °C by Jones reagent[32] (0.35 mL, 0.93 mmol) with stirring for 45 min. The reaction mixture was diluted with H_2O and extracted with Et_2O after saturation with NaCl. The ethereal extract was washed with 5% aaqueous $NaHCO_3$ and H_2O and dried (Na_2SO_4). The semisolid mass, after removal of the solvent, was chromatographed on a column of neutral alumina (10 g). Elution with petroleum ether afforded a gummy solid (156 mg, 59%) which was crystallized from petroleum ether (bp 40–60 °C) to afford one of the two epimers of the ketone **32** (137 mg, 52%): mp 110 °C; homogeneous in GLC (column temperature 170 °C) with t_R 15.5 min; IR (KBr) 2940, 2840, 1700, 1610, 1500, 1460, 1420, 1370, 1300, 1280, 1260, 1240, 1160, 1130, 1050, 1035, 890, 850, 810 cm^{-1}; ^1H NMR (CCl_4) δ 0.97 (3 H, d, J = 6 Hz, $CHCH_3$), 1.18–2.90 (13 H, m), 3.72 (3 H, s, $ArOCH_3$), 6.43–6.67 (2 H, m, Ar H) and 7.10 (1 H, d, J = 8 Hz, Ar H); mass spectrum, m/z (relative intensity) 270 (M^+, 85), 269 (35), 241 (23), 239 (33), 214 (23), 213 (43), 200 (100), 199 (15), 173 (20), 172 (33), 171 (25), 159 (28), 158 (23), 141 (23), 129 (35), 128 (45), 127 (18), 121 (10), 116 (18), 115 (63), 103 (10), 102 (10), 91 (20), 77 (13), 69 (50). Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 80.11; H, 8.34.

7-Methoxy-12α-methyl-2,3,3aβ,4,5,9b-hexahydro-2β,9bβ-propano-1*H*-benz[*e*]inden-11-one (34). Hydroboration of the unsaturated hydrocarbon **13** (199 mg, 0.78 mmol) with diborane gas [generated from $NaBH_4$ (400 mg, 10.5 mmol) and BF_3·Et_2O (2 mL, 16.2 mmol) in diglyme (2 mL)] in THF (8 mL) for 2 h, followed by treatment with 30% H_2O_2 (10 mL) and 3 N aqueous NaOH (10 mL) according to the condition described for **14**, afforded a mixture of epimeric alcohols as a thick liquid (183 mg). This was directly oxidized with Jones reagent (0.3 mL, 0.8 mmol) in $(CH_3)_2CO$ (10 mL) for 1 h. Workup of the reaction mixture with Et_2O afforded a semisolid material which on chromatography through neutral alumina (15 g) with benzene–petroleum ether (1:3) as eluent followed by crystallization from Et_2O afforded the ketone **34** (105 mg, 49%): mp 130 °C; homogeneous in GLC (column temperature 170 °C) with t_R 12.7 min; IR (KBr) 2990, 2970, 2940, 2915, 2840, 1700, 1610, 1500, 1470, 1450, 1375, 1360, 1340, 1315, 1285, 1260, 1210, 1165, 1125, 1040, 905, 855, 840, 820 cm^{-1}; ^1H NMR (CCl_4) δ 0.98 (4 H, d, J = 6 Hz, $CHCH_3$ and 1 CH_2 proton m), 1.10–2.83 (12 H, m), 3.71 (3 H, s, $ArOCH_3$), 6.36–6.73 (2 H, m, Ar H), 7.10 (1 H, d, J = 8 Hz, Ar H); mass spectrum, m/z (relative intensity) 270 (M^+, 54), 200 (22), 199 (71), 198 (100), 197 (16), 141 (31), 129 (11), 128 (14), 115 (17). Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 80.03; H, 8.24.

Deuteration of the Ketone 32. The ketone **32** (51 mg, 0.19 mmol) was stirred with a 2 M solution of $NaOCH_3$ [prepared by dissolving sodium (41 mg, 18 mmol) in CH_3OD (0.9 mL)] in CH_3OD under N_2 at room temperature (27–32 °C) for 42 h. The reaction mixture was decomposed with D_2O (2 mL) and extracted with Et_2O after saturation with NaCl. The ethereal extracts were washed with D_2O and dried (Na_2SO_4). Evaporation of the solvent left **33** (48 mg): mp 82–84 °C; IR (KBr) 2960, 2930, 2915, 2870, 2830, 1700, 1610, 1500, 1460, 1445, 1380, 1350, 1325, 1280, 1265, 1230, 1210, 1040, 915, 815 cm^{-1}; ^1H NMR (CCl_4) δ 0.97 (3 H, s), the integration showed a decrease of ~2 protons in the region 1.18–2.90, 3.72 (3 H, s), 6.43–6.67 (2 H, m, Ar H), 7.10 (1 H, d, J = 8 Hz, Ar H); mass spectrum, m/z (relative intensity) 272 ($M^+ - d_2$, 100), 271 ($M^+ - d_1$, 54), 270 (M^+, 25), 244 (22), 243 (54), 242 (66), 216 (22), 215 (72), 214 (30), 213 (20), 200 (28), 186 (20), 176 (29), 175 (28), 174 (30), 173 (20), 172 (19), 160 (26), 159 (20), 149 (18), 129 (18), 128 (17), 116 (16), 115 (16).

Deuteration of the Ketone 34. The ketone **34** (45 mg, 0.18 mmol) was stirred with a 2 M solution of $NaOCH_3$ [prepared by dissolving sodium (41 mg, 1.8 mmol) in CH_3OD (0.9 mL)] in CH_3OD at reflux for 28 h under N_2. The reaction mixture was worked up as described above for **33** to afford the deuterated ketones **35**-d_1–**35**-d_3 (46 mg): mp 92–95 °C; IR (KBr) 2990, 2970, 2920, 2850, 1700, 1610, 1500, 1470, 1450, 1375, 1340, 1320, 1260, 1245, 1170, 1135, 1125, 1040, 850, 820 cm^{-1}; ^1H NMR (CCl_4) exhibited a Me doublet (J = 6 Hz) with the singlet for **35** at 0.98, a br singlet at 1.27, 1.37–2.82 (m), 3.71 (3 H, s, OCH_3), 6.38–6.70 (2 H, m, Ar H), and 7.10 (1 H, d, J = 8); mass spectrum, m/z (relative intensity) 273 ($M^+ - d_3$, 4), 272 ($M^+ - d_2$, 6), 271 ($M^+ - d_1$, 4), 270 (M^+, 8), 200 (8), 199 (52), 198 (100), 197 (5), 183 (3), 173 (3), 171 (3), 167 (3), 159 (3), 158 (4), 149 (5), 141 (3), 129 (4), 128 (4), 115 (6).

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Registry No. (±)-**12**, 94840-94-5; (±)-**13**, 94751-71-0; (±)-**14**, 94751-72-1; (±)-**15a**, 53609-39-5; (±)-**15b**, 67661-78-3; (±)-**15c**, 94751-73-2; (±)-**16a**, 94751-74-3; (±)-**16b**, 94751-75-4; (±)-**16c**,

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Heterogeneous Catalysis of Glucose Mutarotation by Alumina in Dimethyl Sulfoxide. 2. Catalytic Activity of Various Aluminas, Effects of Inhibitors, and the Acid/Base Properties of the Active Sites

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The relative abilities of thermally treated aluminas to heterogeneously catalyze the mutarotaion of α-D-glucose have been studied in dimethyl sulfoxide at 25 °C. Heating of standard alumina to 150 °C, 600 °C, 800 °C, and 1100 °C results in reduced surface areas and catalytic activities. However, heating at 1250 °C produces a most effective, low surface area (6 M^2/g) alumina which, unlike the other aluminas, shows pseudo-first-order kinetics, does not become progressively deactivated, and irreversibly adsorbs little glucose. Kinetic inhibition of mutarotation is shown by added polyhydroxy compounds (e.g., inositol) but not by monohydroxylic (methanol) or aromatic additives. As shown by lack of an effect of added pyridine, and by the increased activity when the stronger base *n*-butylamine is added, the major catalytic sites on standard alumina are Brønsted acids rather than Lewis acids. However, the relative inhibition brought about when alumina is treated with carbon dioxide shows that the high catalytic activity of 1250 °C alumina is predominately due to basic sites produced by the thermal dehydration.

Although there are extensive and detailed kinetic studies of alumina as a catalyst for many reactions in the gas phase, few investigations of the kinetics of alumina-catalyzed reactions in liquid phases have been reported. Reports of the utility of solution reactions catalyzed by alumina,[1] together with interest in determining the general characteristics of some reactions using liquid suspensions of catalytic solids, have prompted this study of heterogeneous catalysis by alumina.

For determination of the characteristics of a heterogeneous alumina reaction relative to homogeneous catalysis in solution, a reaction that is well established in a homogeneous liquid phase, i.e., the mutarotation of glucose, was chosen for study in dimethyl sulfoxide (Me_2SO). A first report[2] has presented results showing that there are three types of adsorption sites for glucose on alumina, that the catalytically active site density on a widely available "standard" alumina is 5.4×10^{13} per cm^2, and that these sites have an activity about 9 times greater than that of hydronium ions under homogeneous conditions in water. However, this standard alumina slowly deactivates during the reaction and adsorbs a significant fraction (about 14%) of the glucose substrate.

We report here studies to determine the relative catalytic activities of various thermally treated aluminas and to obtain catalysts with less adsorption but with high activity. The alumina surface possesses many types of Lewis and Brønsted acidic and basic functional groups (e.g., Al^{3+}, $OH^{\delta+}$, $-O^-$, $-O^{\delta-}H$, and "defect sites")[3,4] which are all potential catalysts for glucose mutarotation.[5] By means of inhibitors, we have determined the acid/base characteristics of the active sites, i.e., whether this heterogeneous mutarotation occurs at centers which are Lewis or Brønsted acids/bases.

Results and Discussion

Thermal Treatment of Alumina. On heating a sample of alumina which has water adsorbed on the surface, first, some of the water molecules are desorbed and some react with the surface to form OH groups. As the sample is heated further, acidic and basic hydroxyl groups eliminate to form Lewis base and acid sites respectively.[6] Above 300 °C "defect sites", consisting of clusters of vacancies (Lewis acids) and neighboring oxide ions (Lewis bases) which are catalytically active in most gas-phase reactions, are formed.[3] At greater than 1100 °C, α-alumina, which is normally considered to be catalytically inactive, is formed.[4] The change in activity per unit surface area as the alumina is heated can therefore give information on the nature of the active sites. If only Lewis acid or basic oxide sites are catalytically active, an increase in activity per area will be observed; if only Brønsted acid or basic hydroxyl groups are active, there should be a decrease in activity.

Standard alumina was heated and the weight loss, surface area, and catalytic activity were determined to investigate the effect of thermal dehydration (see Table I). The results show that with standard alumina heated at up to 600 °C the catalytic activity decreases with increase in temperature. The previously reported main characteristics of the heterogeneous catalytic mutarotation,[2] i.e., curved first-order plots due to significant initial adsorption fol-

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