Condensed Cyclic and Bridged-Ring Systems. 8.[1] Factors Influencing the Stereochemistry of the Products in the Acid-Catalyzed Cyclialkylation Reactions of Some Substituted β-Phenylethylcyclohexene and -cyclohexanol Derivatives

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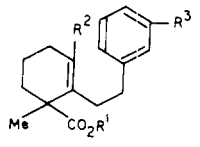
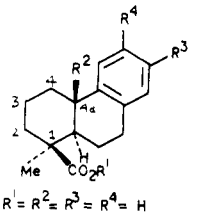
The distributions of the four possible racemic octahydrophenanthrene derivatives (**4**, **18**, **19**, and **20**) in the cyclialkylation reaction products from ethyl 1-methyl-2-(β-phenylethyl)cyclohex-2-enecarboxylate (**1a**), the corresponding exo double-bond isomer **1b**, and the epimeric lactones of 2-(β-phenylethyl)-3-hydroxy-1-methylcyclohexane-1-carboxylic acid (**17a** and **17b**) using H_2SO_4–HOAc, PPA, and $AlCl_3$–HCl have been investigated. The diastereomeric cyclic acids were analyzed by ^1H NMR spectroscopy and GC of their methyl esters, and were also separated by preparative procedures. H_2SO_4–HOAc and PPA catalyzed cyclizations of 3β-hydroxy-1α,3α-dimethyl-2β-(2′-phenylethyl)cyclohexane-1β-carboxylic acid (1 → 3)-lactone (**10a**) are also described. Based on these experimental data and their comparison with the previously reported results on the formation of the diastereomeric octahydrophenanthrene derivatives **5** and **11a** through similar cyclialkylation reactions, consistent mechanisms for these stereochemical results have been advanced.

The acid-catalyzed intramolecular cyclialkylation reaction constitutes one of the simplest and most widely used methods for the synthesis of ring C aromatic diterpenoid resin acids and various diterpenoid intermediates.[2-18] In 1939, Haworth and Barker first reported[3] the cyclization of β-phenylethylcyclohexene derivatives **1**, **2**, and **3** with an



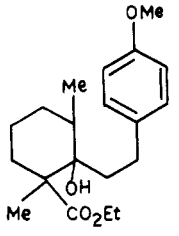
1a, R^1 = Et; R^2 = R^3 = H
2, R^1 = Et; R^2 = Me; R^3 = H
3, R^1 = Et; R^2 = Me, R^3 = i-Pr



4, R^1 = R^2 = R^3 = R^4 = H
5, R^1 = R^3 = R^4 = H, R^2 = Me
6, R^1 = R^4 = H; R^2 = Me; R^3 = i-Pr
8, R^1 = Et; R^2 = Me; R^3 = H; R^4 = OMe
9, R^1 = R^3 = H; R^2 = Me; R^4 = OMe

H_2SO_4–HOAc mixture and obtained directly the corresponding tricarbocyclic acids **4**, **5**, and **6**, respectively, as a single diastereomer in each case. The stereochemistries of these acids are represented as assigned by the later workers.

King, King, and Topliss[7] identified the major product[19] from the PPA-induced cyclization of **7** as (±)-ethyl *O*-methylpodocarpate (**8**) and correlated this with the corresponding acid **9**, prepared independently by Bhattacharyya[5] and Haworth et al.[4] Our own investigations[9] on the PPA-catalyzed cyclization of a mixture of lactone **10** epimers and ester **2** (R^1 = Me) revealed that out of the four possible racemic octahydrophenanthrene derivatives, only the trans and cis diastereomeric acids **5** and **11a** (and the corresponding esters) are formed in this reaction. This and related studies[10] established the stereochemistry of the acids **5** and **6**. Parham and coworkers[6] reported the conversion of the keto lactone **12** with $AlCl_3$–HCl to a single keto acid **13** (56% yield), the stereochemistry of which has been assigned from the studies[9] mentioned above. Dehydroabietic acid (**14a**)[20] (or the nitrile **14b**[21]), on treatment with $AlCl_3$ in boiling benzene, is transformed to mostly the cis acid, the enantiomer of **11a** (or the nitrile **11b**), along with a very small amount of **15a**[21b] (or the nitrile **15b**) by a cleavage–recylization process and the loss of the isopropyl group.



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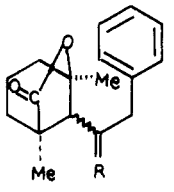
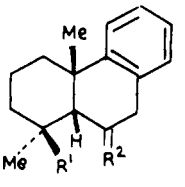
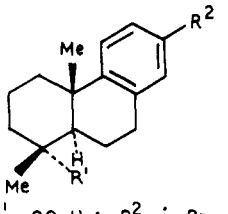


10, R = H_2
12, R = O



11a, R^1 = CO_2H; R^2 = H_2
11b, R^1 = CN; R^2 = H_2
13, R^1 = CO_2H; R^2 = O



14a, R^1 = CO_2H; R^2 = i-Pr
14b, R^1 = CN; R^2 = i-Pr
15a, R^1 = CO_2H; R^2 = H
15b, R^1 = CN; R^2 = H

The results of these and related cyclialkylation reactions are quite revealing with respect to the stereochemical nature of the products. Thus, the H_2SO_4–HOAc cyclization method of Haworth is highly stereoselective[3-5,12-15] and results in the formation of the trans product (e.g., **5**) related to podocarpic acid; PPA- or P_2O_5-induced cyclizations may lead to a mixture[7-10] of the trans and cis isomers **5** and **11a** (or the related aromatic substituted derivatives) or only the latter,[17] depending upon the nature of the substrates,[22] and the $AlCl_3$–HCl catalyzed cyclization[6] or cleavage–recyclization[20,21] again appears to be highly stereoselective, generating mainly the 5-*epi*-podocarpic acid systems (e.g., **11a**). The possible mechanisms suggested in our earlier publications[9,10,23] to explain the influence of the *gem*-methylcarboxyl functionality in controlling the stereochemistry of the products from the PPA cyclization of **2** (R^1 = Me), **10**, and similar systems and by Wenkert[21] and Dodson[24] for the $AlCl_3$–HCl catalyzed reactions could partly account for certain specific cases. More recently Ireland and co-workers[25] have advanced a unified

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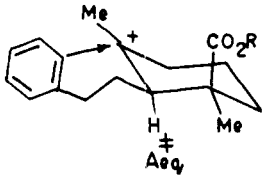
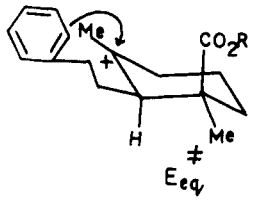
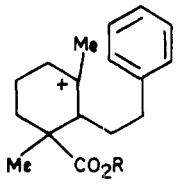
Table I. Distribution of the Diastereomeric Acids 4, 18, 19, and 20 in the Cyclialkylation Reactions of 17a, the 17b–17a (3:1) Mixture, and the 1a–1b (3:7) Mixture with Different Catalysts

starting material	cyclization catalyst	yield,[a] %	ratio of the diastereomers[b,c] 4	18	19	20
17a	H_2SO_4–HOAc	60[d]	2	1	*e*	*e*
	$AlCl_3$–HCl	67[f]	1	2	5	2
	PPA	70[d]	1	20	*e*	*e*
17b–17a (3:1)	H_2SO_4–HOAc	60[d]	2	1	*e*	*e*
	$AlCl_3$–HCl	65[g]	1	3	6	2
	PPA	69[d]	3	1	*e*	*e*
1a–1b (3:7)	H_2SO_4–HOAc	30[h]	80	13	*e*	7
	$AlCl_3$–HCl	58[i]	14	33	35	18
	PPA	43[j]	(3)[k]	(18)[k]	*e*	*e*

[a] Crude solid acids in cases of **17a** and the **17b–17a** mixture, and total acidic product after alkaline hydrolysis and sublimation from the **1a–1b** mixture. [b] Determined from ^1H NMR (at 100 MHz) and GC of the methyl esters by CH_2N_2 esterification of the crude acidic products followed by filtration through a short neutral alumina column with 1:1 petroleum–benzene; in $CDCl_3$ the C-1 methyl singlet appears at δ 1.29, 1.19, 1.21, and 1.38, respectively, for **21, 22, 23,** and **24** relative to Me_4Si ($\delta = 0$); GC analyses were carried out on a Shemadzu GC-5AP-TFE instrument using FID with N_2 as carrier gas on two columns. Column A: 1.5% OV-1 on Shemalite W (4 mm × 2 m) at a temperature of 160 °C and an injection temperature of 210 °C; retention times (R_t) for **21, 22, 23,** and **24** are 9.41, 9.22, 10.81, and 9.97 min, respectively. Column B: OV-17 on Shemalite W (4 mm × 1.8 m) at 160 °C; R_t = 9.83, 9.75, 12.04, and 10.64 min, respectively, for **21, 22, 23,** and **24.** [c] Average of at least two runs. [d] GC of methyl ester showed a single peak at R_t = 9.2–9.4 min on column A and R_t = 9.8–9.9 min on column B. [e] Could not be detected by ^1H NMR or GC. [f] GC of methyl ester on column A showed three peaks: R_t = 9.4, 9.95, and 10.85 min in a ratio of 35:17:48, corresponding to a **21** and **22** mixture, **24,** and **23,** respectively. [g] GC of methyl ester on column A showed three peaks: R_t = 9.4, 9.97, and 10.90 min in a ratio of 33:17:50, corresponding to a **21** and **22** mixture, **24,** and **23,** respectively. [h] Acidic product directly obtained from the reaction product; GC of methyl ester on column A showed two major peaks (98%) with R_t = 9.4 and 9.95 min in a ratio of 90:8, corresponding to a **21** and **22** mixture and **24,** and an unidentified product (~2%) with R_t above 11 min. [i] GC of methyl ester on column A showed three major peaks (95%) with R_t = 9.3, 10.0, and 10.8 min in a ratio of 47:17:36, corresponding to a **21** and **22** mixture, **24,** and **23,** respectively. [j] GC of methyl ester on column A showed a major peak (87%) with R_t = 9.3 min, corresponding to a **21** and **22** mixture, and two other unknown esters (~13%) with R_t above 11 min; the ^1H NMR spectrum showed two additional singlets at δ 1.11 and 1.13 besides the C-1 Me signal for **21** and **22.** [k] Based on isolated yield.







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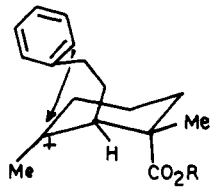
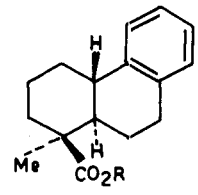
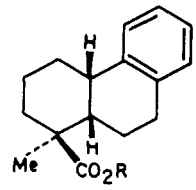
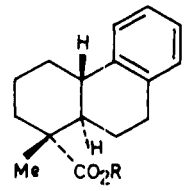




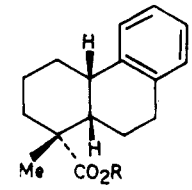
4, R = H
21, R = Me



18, R = H
22, R = Me



19, R = H
23, R = Me



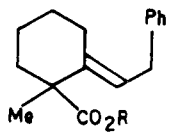
20, R = H
24, R = Me

mechanism to explain the observed stereochemistry of the products in these (and similar) cyclialkylation reactions. This mechanism considered the contribution of one or more of the three energetically probable conformations, such as $A^{\ddagger}_{eq}$, $E^{\ddagger}_{eq}$, and $A^{\ddagger}_{ax}$, of the intermediate carbonium in **16** (generated from the different substrates) in the transition states. The essence of Ireland's proposal, that torsional strain in these transition states plays a dominating role over the steric strains in deciding the stereochemical outcome of the cyclization products, has been questioned by Harding.[26] Furthermore, this mechanism cannot adequately account for the remarkable effects of the cyclization reagents, as well as the structure of the substrates, on the observed stereochemistry of the products. It is quite possible, in fact, that different mechanisms predominate under different conditions of catalysts and even of structure and stereochemistry of the substrates.

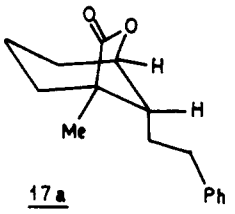
We report[27] here a study concerning the nature of the three commonly used cyclization reagents, H_2SO_4–HOAc, PPA, and $AlCl_3$–HCl, on the stereochemical distributions of the epimeric hydrophenanthrene derivatives **4, 18, 19,** and **20** (Table I) in cyclizations of two diastereomeric lactones **17a** and **17b** as well as a mixture of the isomeric unsaturated esters **1a** and **1b.** We have also investigated H_2SO_4–HOAc and PPA cyclizations of the lactone **10a.** These results are discussed in the context of the effects of cyclization reagents and the structure and stereochemistry of the substrates on the observed stereochemical course of the cyclization reactions in the corresponding methyl analogues, e.g., **2, 10,** and related substrates.

Results

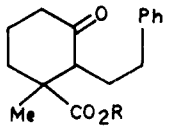
Synthesis of Starting Materials and Products. The stereocontrolled syntheses of the four diastereomeric acids



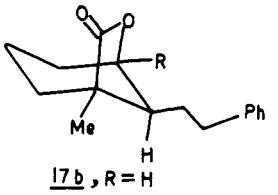
1b, R = Et
1c, R = H
1d, R = Me



17a



25, R = H
25a, R = Me



17b, R = H
10a, R = Me

4, 18, 19, and 20 and the respective methyl esters 21, 22, 23, and 24 required for identification of the products have been reported in detail.[28] The diastereomeric lactone mixture **17a–17b** was prepared in 40–44% yield by $NaBH_4$ reduction of keto acid **25**[9] in alkaline solution followed by treatment with boiling dilute sulfuric acid. The proportion of **17a** and **17b** varied from 55:45 to 45:55 (GC) in different preparations. Although the two epimers could not be separated by TLC, fractional crystallization of the mixtures partly removed the pure epimer **17a.** The other epimer could only be isolated as a 3:1 eutectic mixture of **17b** and **17a.** This mixture was used in the cyclization studies and stereochemical assignment. The stereochemistry of these epimeric lactones was established through ^{13}C NMR (see Experimental Section).

The synthesis of the unsaturated ester substrate **1a** by treatment of ethyl 1-methyl-2-oxocyclohexanecarboxylate with an excess of β-phenylethylmagnesium bromide followed by dehydration of the crude carbinol with $KHSO_4$ according to the reported procedure of Haworth,[3] in fact, gave a mixture of double-bond isomeric esters **1a** and **1b** in a ratio of 30:70 (GC) in ~95% purity. Alkaline hydrolysis of the mixture according to the reported procedure[3] afforded only one crystalline acid, the exo double-bond isomer **1c.** The structure (the double-bond stereochemistry is uncertain) of this has been established from the ^1H NMR spectrum of the corresponding methyl ester **1d** (diazomethane). Since in the original work[3] Haworth used the 3:7 mixture of **1a** and **1b,** we also repeated our cyclization studies with the same substrate.

The lactone epimer **10a** was prepared in 46% yield by reaction of keto ester **25a**[9] with an excess of methylmagnesium iodide followed by treatment with refluxing *p*-toluenesulfonic acid in benzene, partial alkaline hydrolysis of the resulting mixture, and subsequent relactonization. The stereochemistry of this lactone has been assigned from an analogy of the preparation of a similar lactone with identical stereochemistry[23,29] as well as from the results of its cyclizations to be mentioned in the latter part of this paper.

Results of Cyclizations. The conditions and products of the cyclizations of the lactone **17a,** the **17a–17b** mixture, and of the unsaturated ester **1a–1b** mixture are outlined in Table I.

A part of the crude crystalline acidic product isolated from each of the cyclization reactions of the lactones was esterified with ethereal diazomethane and in some cases purified by filtration through a short column of neutral alumina for GC and ^1H NMR analyses. GC analyses of known mixtures of the four epimeric methyl esters **21–24** in different proportions showed only three peaks corresponding to a mixture of **21** and **22** and the individual diastereomers **23** and **24** in two different columns. However, the C-1 methyl singlets of the methyl esters showed sufficient separation in the ^1H NMR spectra[28a] for quantitative evaluations of these mixtures to the extent of a maximum deviation of ±2.5% in an average of three experiments. Taken together, these analytical methods provided sufficient information regarding distribution of the diastereomeric cyclization products arising from lactones **17a** and **17b.** Some important observations were made in the PPA-catalyzed cyclizations of the lactone **17a** and the **17b–17a** mixture. It was found that if the reaction is continued for more than 15–20 min at 80–85 °C or above, substantial decarboxylation occurs, leading to nonacidic products.

Only the crystalline acidic products were analyzed in the cyclization products from the 7:3 mixture of **1b** and **1a** with H_2SO_4–HOAc. The neutral fractions from this reaction were found to be complex mixtures containing mostly the decarboxylated compounds, alkaline hydrolysis of which gave very little acidic products. The $AlCl_3$–HCl and PPA catalyzed cyclizations of the unsaturated ester mixture resulted in, in addition to the major neutral products, some solid acidic products. The neutral fractions were hydrolyzed, the solid acidic materials from each of these reactions were mixed with the acidic products obtained directly from the cyclization experiments, purified by sublimation, and the corresponding methyl esters (diazomethane) were analyzed by ^1H NMR and GC (Table I). The PPA-catalyzed cyclizations of the **1b–1a** mixture produced substantial amounts of decarboxylated products along with some unidentified acidic products (~13% by GC). Analysis of these products by ^1H NMR could not be used since the unidentified products showed peaks in the regions of the quaternary methyl singlets of the epimeric hydrophenanthrene esters. The total amount (~87%) of the esters **21** and **22,** however, could be estimated from GC (Table I). In some of these reactions the pure epimeric hydrophenanthrene acids could be separated partially, particularly in the products containing predominantly one epimer (e.g., H_2SO_4–HOAc cyclization). Column chromatography of the methyl ester mixture could only separate the ester **21** from the remaining epimers. The differences[28a] between the saponification rates of **21** and **22** from the remaining two epimers **23** and **24** were also utilized for their partial separation. None of these methods are totally satisfactory, but by a combination of these it was possible to achieve separation of different diastereomers at least to a certain extent. Only the epimer **24,** detected in the ^1H NMR and GC analyses of the cyclization product from $AlCl_3$–HCl, could not be separated from the mixture by these methods.

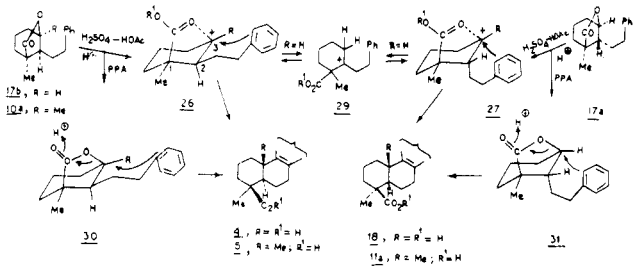
The cyclization of the pure diastereomeric lactone **10a** with H_2SO_4–HOAc under standard reaction conditions gave a single epimeric acid (**5**) in 67% yield. The stereochemical homogeneity of this acid was confirmed by direct IR and ^1H NMR comparisons of the methyl ester of the crude acid with a corresponding authentic sample. Similarly, PPA-catalyzed cyclization of **10a** produced the same acid (**5**) in 72% yield.

Discussion

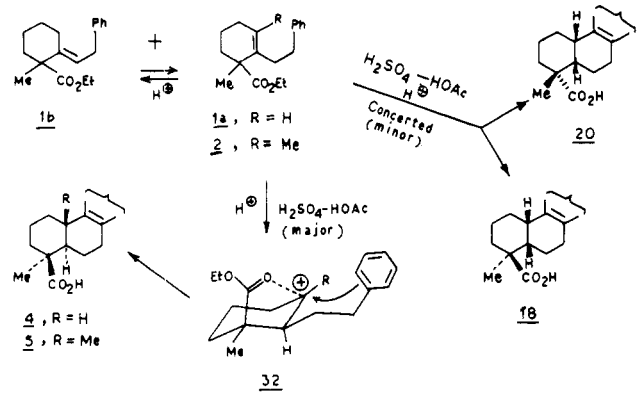
The data recorded in Table I indicate that the stereochemistry in the cyclizations of **17a, 17b,** and **1b–1a** induced by H_2SO_4–HOAc (Haworth cyclization) and by PPA is kinetically controlled[23,29] and is, in general, compatible with the results observed with the corresponding 3-methyl analogues, for example **2, 7,** and **10a.** The stereochemical outcome from the reversible $AlCl_3$–HCl catalyzed cyclizations of **17a, 17b,** and the **1b–1a** mixture is, on the other hand, significantly different from that observed[6,11] in the compounds containing the methyl group, e.g., compound **12.**

The results of the H_2SO_4–HOAc catalyzed cyclizations of

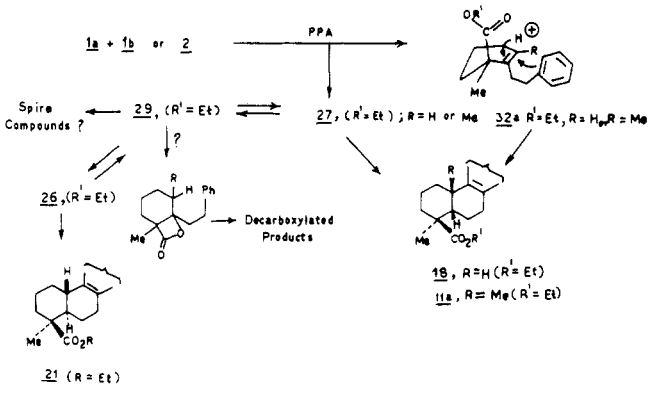
Scheme I



Scheme II



Scheme III

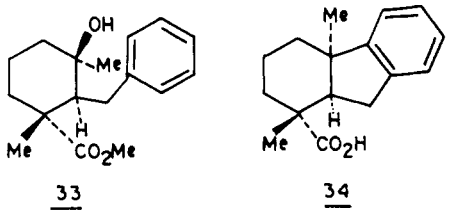


the lactones **17a** and the **17b–17a** mixture indicate that each of these gives the same mixture of products, a 2:1 ratio of **4** and **18**. The unsaturated esters, the **1a–1b** mixture, produce, however, an ca. 8:1 mixture of **4** and **18**. Furthermore, isomer **20** is also a product from cyclization of this mixture, but not of lactones **17a, 17b**. The difference in behavior of these substrates with regard to the stereochemical distribution of products shows that possibly similar mechanisms are not operating in these cyclizations. The formation of the acid **4** and **18** mixture from **17a** and **17b** can be visualized as arising from the carbonyl-participating cations **26** (R = R^1 = H) and **27** (R = R^1 = H), derived through protonation of the lactones, which may undergo a rapid preequilibration involving the tertiary cation **29** (R^1 = H). The contribution of the transition state involving an equatorial side chain (**26**) over that of the axial analogue (**27**) is reflected in the products. The validity of the foregoing analysis is further supported by the H_2SO_4–HOAc catalyzed cyclization of the lactone **10a**, where the exclusive product is the *trans*-acid **5** (Scheme I).

The observed stereoselectivity in the H_2SO_4–HOAc catalyzed cyclization of the **1a–1b** mixture is explicable on the basis of a stabilized intermediate cation **32** (R = H) through the ester-participated protonation of **1a**, which undergoes direct ring closure and *O*-alkyl cleavage[30] to acid **4** along with possibly the formation of the lactone **17b**. The latter gives rise to a mixture of **4** and **18** (Scheme I). The minor epimers **18** and **20** may also originate from a concerted protonation–cyclization[31] of **1a** followed by hydrolysis of the ester group. A similar type of mechanism involving the cation **32** (R = Me) may be used to explain the stereochemistry of the products in the Haworth cyclization of **2** to **5** (Scheme II).

The PPA-induced cyclization reactions of both the phenylethylcyclohexanol (or -hexene) or the respective methyl-substituted precursors, for example **17a**, the **17a–17b** and **1a–1b** mixtures, **2**, and **10**, are *stereospecific* as far as the cis stereochemistry of the C-1 carboxy and C-4a angular (phenanthrene numbering, see **4**) substituents are concerned in the corresponding products **4** and **18** or **5** and **11a**. The stereochemical distributions[9,17] of the cis- and trans-A/B diastereomers appear to depend considerably upon the nature of the substrates.[2,8,16] The reactivity of the aromatic ring may also have some effect on the stereochemical distributions of the cis and trans ring-fused products in the PPA cyclization reactions. The present results from the PPA-catalyzed cyclizations of the diastereomeric lactones **17a**, the **17b–17a** mixture, and the epimeric methyl-substituted lactone **10a** clearly indicate the high stereoselectivities in the products retaining the original stereochemistry of the C-2 phenylethyl side chain in the respective products. The major paths in these cyclizations may be concerted routes involving **30** (R = H or Me), **31**, and/or through the carbonyl-participating carbocations **26** (R = R^1 = H), **27** (R = R^1 = H), and **26** (R = Me, R^1 = H), respectively, in which the ring closure step is much faster than deprotonation–reprotonation or other equilibration pathways under the mild reaction conditions (Scheme I). The complete reversal of the stereochemistry of the products in the PPA cyclization of **10a** (leading completely to *trans*-acid **5**) and the unsaturated ester **2** (leading to the ester of *cis*-acid **11a**) reported by Barnes[17] can be best explained by a concerted protonation–cyclization of ester **2** through the intermediate **32a** (R^1 = Et, R = Me) in which the carbonyl group of the ester directs the protonation (Scheme III). In other substrates, where both cis and trans products have been found, the cyclohexyl cations (as shown in Scheme I for the lactones) can rationally explain the products. The complexity of the PPA-induced cyclization products from the unsaturated ester mixture **1a–1b** possibly originates through the tertiary cyclohexyl cation **29** leading to spiro compounds as have been observed[2] in other cases. The low yields of the hydrophenanthrene acids in the cyclization of the unsaturated esters may be explained by β-lactone formation[29] through this cation followed by decarboxylation.

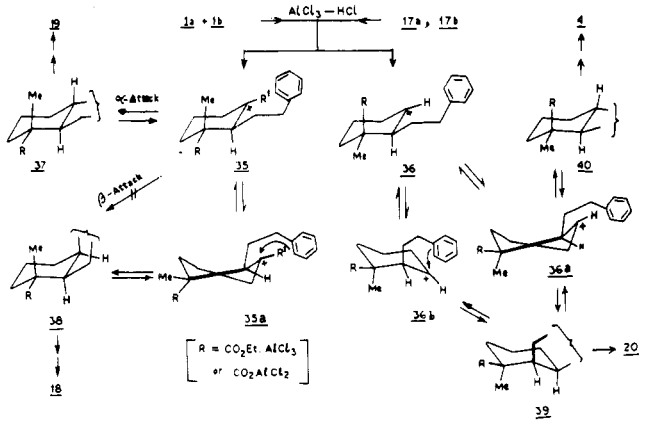
High stereoselectivity in a PPA cyclization has also been observed[23,29] in the cyclization of **33** to give **34** as the only



product in 59% yield, and a similar mechanism has been proposed for this process.

Although the stereochemical nature of the cyclization products from $AlCl_3$–HCl reflects the reversibility of the process and depends upon the stability of the final products, the possible distribution of the diastereomeric products (Table I) from the lactone **17a**, the **17b–17a** lactone mixture, and the **1a–1b** unsaturated ester mixture may also be explained[29] by considering their mode of formation in analogy with similar systems reported by us. The first step in $AlCl_3$–HCl catalyzed cyclizations of these substrates involves the formation of

Scheme IV



several carbocations, which have a comparatively high longevity in the strong Lewis acid medium.[32] In these cations, as suggested by Wenkert,[21a] the $AlCl_3$-complexed bulky carboxylate[33] or ester[34] group should lead mainly to **35** (R^1 = H) with equatorial orientation of this group along with the less favored cation **36.** The cyclohexyl cation **35** (R^1 = H) may give rise to the energetically favored diastereomeric systems **37** and **38.** The equatorial attack (α attack) by the phenyl group in **35** → **37** is free from any severe steric effect, but the strong 1,3-diaxial interaction between the methyl and the approaching phenyl group in **35** → **38,** in case of an axial attack (β attack), can be avoided by the assumption of a twist form such as **35a** (R^1 = H) relieving the steric strain and at the same time providing a better geometry for the σ complex as suggested for an analogous cyclization.[35] Similarly, a twist conformation **36a** of the cation **36** may undergo cyclization to **39** through a quasi-axial attack. The cyclization of **36b,** generated through conformational inversion of **36,** may also be an equally important path to **39.** The minor epimer **4** originates from **36a** and/or **36** through the less stable intermediate **40** (Scheme IV).

The reversibility of the aforementioned sequence has been proved qualitatively by prolonged treatment of the esters **21** and **24** with $AlCl_3$–HCl.

The arguments developed here can be extended for explaining the $AlCl_3$-catalyzed isomerization of dehydroabietic acid (**14a**) (or the nitrile **14b**) and the stereospecificity in the cyclization of the keto lactone **12** to **13.** The intermediate carbocations, similar to **35** (R^1 = Me), generated from **14a** and **12** can give rise to the corresponding cyclized acids **11a** and **13** through nucleophilic attack by the aromatic ring in the respective twist conformers **35a** from the quasi-axial direction in preference to the quasi-equatorial one. This type of analysis is further supported from the observation of important difference between the demethyl analogues **1a–1b** mixture, **17a,** and **17b,** with **14a** and **12,** in the absence of the epimeric hydrophenanthrene acids, related to **4** and **20** from the latter substrates, which would require intermediate carbocations with the bulky $AlCl_3$-complexed group in the axial conformation and the C-3 methyl group interacting in the transition states.

Conclusions

The present investigations have provided illustrations of the effects of changes in cyclization conditions and/or of stereochemistry and structure of the substrates on the stereochemical course in the cyclization reactions of 1-*gem*-methyl (1 → 3)-lactone and carboxylic ester substituted 2β-phenylethylcyclohexanol and -cyclohexene derivatives. The origin of the observed high stereoselectivity in these reactions, as well as that reported for other substrates, has been supported both by experimental results and possible mechanistic analyses. In particular, the results obtained above also emphasize the importance of selecting the open chain substrates which may control the yield and stereochemistry of the final products.

Experimental Section

General Procedure. Melting points were determined in open capillary tubes on a sulfuric acid bath and are uncorrected. The identity of known compounds was established by mixture melting points (mmp) and IR comparisons in $CHCl_3$ solutions on a Perkin-Elmer Model-21 spectrometer. TLC plates were coated with silica gel G (Merck, 200 mesh) having a thickness of ~0.2 mm, and spots were located by exposing the dried plates in I_2 vapor. Routine ^1H NMR spectra were taken on a Varian T60 A spectrometer. The ^1H NMR analyses of the cyclization products were carried out on a Varian HA 100 spectrometer in $CDCl_3$ and C_6D_6 solutions, and compositions of the epimeric compounds were determined by the integration values of the methyl singlets and assigned by comparison with known mixtures of the epimeric esters. GC analyses were obtained on a Shemadzu GC-5AP-TFE apparatus using FID and N_2 as carrier gas on 1.5% OV-1 on Shemalite W (4 mm × 2 m) or 1.5% OV-17 on Shemalite W (4 mm × 1.8 m) columns at 160 °C (column temperature) and an injection temperature of 210 °C through the courtesy of (the late) Dr. Akira Tahara and Dr. M. Shimagaki, The Institute of Physical and Chemical Research, Wako-Shi, Saitama, Japan. Microanalyses were performed by Mrs. C. Dutta of this laboratory. Petroleum ether and petroleum refer to the fractions with bp 40–60 and 60–80 °C, respectively. The general workup procedure was to extract the aqueous layer with ether (3–5 times); the combined ethereal extracts were washed with water (two times) and saturated sodium chloride solution (once) and then dried (Na_2SO_4), filtered, and concentrated in vacuo.

Preparation of Reference Cyclized Products. The pure 1-methyl-1-carboxy-1,2,3,4,4a,9,10,10a-octahydrophenanthrene diastereomers **4** [mp 189–190 °C (lit.[28a] mp 189–190 °C)], **18** [mp 205–207 °C (lit.[28a] mp 205–206 °C)], **19** [mp 209–210 °C (lit.[28a] mp 209–210 °C)], and **20** [mp 193–194 °C (lit.[28a] mp 193–194 °C)] and the corresponding methyl esters **21** [mp 78–79 °C (lit.[28a] mp 78–79 °C)], **22** [bp (bath temperature) 168–170 °C (0.2 mm) [lit.[28a] bp 165–175 °C (0.2 mm)]], **23** [mp 54–55 °C (lit.[28a] mp 54–55 °C)], and **24** [mp 83–84 °C (lit.[28a] mp 83–84 °C)] were prepared by procedures as reported earlier.[28a] The significant ^1H NMR data of the diastereomeric methyl esters and the retention times (R_t) from GC on two different columns are given in Table I.

3β-Hydroxy-1α-methyl-2α-(2′-phenylethyl)cyclohexane-1-β-carboxylic Acid (1 → 3)-Lactone (17a) and 3β-Hydroxy-1α-methyl-2β-(2′-phenylethyl)cyclohexane-1β-carboxylic Acid (1 → 3)-Lactone (17b). To a cold stirred solution of 20.8 g (0.08 mol) of the keto acid **25**[9] in 20 mL of ethanol and 19 mL of water containing 3.5 g of sodium hydroxide was added 4.8 g (0.1 mol) of sodium borohydride in small portions, and the mixture was left overnight at room temperature. The ice-cooled reaction mixture was decomposed with 60 mL of 12 N sulfuric acid, when a waxy solid separated. The mixture was then heated to reflux for 2 h. The cooled reaction mixture was extracted with ether, washed repeatedly with 5% sodium carbonate solution and water, and dried. Evaporation of the solvent and distillation of the residual oil afforded 8.50 g (44%) of a thick colorless liquid: bp 160–165 °C (0.4 mm); IR 1765 cm^{-1}; TLC in benzene–methanol (9:1) showed two overlapping spots; the ^1H NMR spectrum showed two methyl singlets in a ratio of 55:45. This ratio varied in different preparations from 50:50 to 45:55. Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.66; H, 8.25. Found: C, 79.00; H, 8.38.

On keeping in the cold, the lactone mixture solidified. Trituration with petroleum ether and recrystallization from ether–petroleum ether afforded the pure (^1H NMR and GC) epimeric lactone **17a,** mp 84–85 °C (2.5 g, 12%), as colorless cubes: IR 1770 cm^{-1}; ^1H NMR (100 MHz) δ ($CDCl_3$) 1.10 (s, 3 H, C-1 CH_3), 1.40–2.0 (complex m, 8 H, $-CH_2-$ protons), 2.15 (br m, 1 H, -CH<), 2.66 (m, 2 H, $PhCH_2-$), 4.62 (m, 1 H, -CH–O), 7.0 (br s, 5 H, C_6H_5); by decoupling the benzylic protons, a doublet at δ 2.15 ($J_{2,3}$ = 6 Hz) for C-2 H was observed. Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.52; H, 8.34.

Repeated recrystallization of the mother liquors after separation of **17a** afforded colorless prisms: 1.45 g (7%); mp 72 °C; IR 1768 cm^{-1}; ^1H NMR δ 1.10 (s) and 1.05 (s) in a ratio of ca. 1:3. GC analysis on a 6 ft × ⅛ in. column packed with 3% SE-52 on Chromosorb W with N_2 as a flow gas at a column temperature of 195 °C showed the presence of **17b** and **17a** in a ratio of 3:1 with very close retention times in increasing order. Further separation of this mixture was not possible, and this material was used for the cyclization reactions. Stereochemical assignment by ^{13}C NMR was also made on this mixture.

The ^{13}C NMR spectral data of the epimeric lactones **17a** and **17b** and their assignments obtained through the courtesy of Professor E. Wenkert are summarized in the structures shown in Figure 1.

Ethyl 1-Methyl-2-(2′-phenylethylidene)cyclohexanecarboxylate (1b) and Its Endo Double-Bond Isomer (1a). Grignard reagent, prepared from 50 g of β-phenylethyl bromide and 6.75 g of magnesium in 300 mL of anhydrous ether, was inversely added over a period of 1 h to an ice-cooled, stirred solution of 25 g of ethyl 1-methyl-2-oxocyclohexanecarboxylate, and the reaction was carried out following exactly the procedure of Haworth et al.[3] The crude carbinol was dehydrated by heating it with 70 g of fused potassium hydrogen sulfate for 1.5 h according to the reported[3] method to afford, after distillation, a mixture of 16.3 g of the unsaturated esters **1b** and **1a,** bp 140–145 °C (0.5 mm) [lit.[3] bp 160–163 °C (3 mm)]. GC analysis in OV-1 at 160 °C showed two major components (~95%) with R_t = 7.92 and 8.33 min in a ratio of ca. 70:30. Three minor components had R_t = 3.7–4.2 min. The ^1H NMR spectrum in CCl_4 showed two singlets at δ 1.20 and 1.25 overlapped with the triplets of $-CO_2CH_2CH_3$ with shoulders at δ 1.01 and 1.30, benzylic protons at δ 2.75 (m) for **1a** and at δ 3.39 (d, J = 7 Hz) for the corresponding protons of **1b,** overlapping quartets at δ 4.05 (J = 7 Hz), olefinic protons at δ 5.25–5.50 (m), and aromatic protons at δ 7.0 (br s).

A 5-g amount of the above ester mixture was saponified by refluxing with 100 mL of a 20% methanolic potassium hydroxide solution for 18 h according to Haworth[3] to afford 4.2 g of a solid acidic product, which on repeated recrystallization from petroleum ether afforded pure acid **1c,** mp 108–109 °C (lit.[3] mp 97–98 °C assigned this as the endocyclic double-bond isomer **1a**). Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.43; H, 8.42.

A portion of this acid was converted to the corresponding methyl ester **1d** with ethereal diazomethane, and the ester gave the following spectral data: IR 1715 cm^{-1}; ^1H NMR δ (CCl_4) 1.26 (s, 3 H, $\geqslant CCH_3$), 1.5–2.7 (complex m, 8 H), 3.38 (d, 2 H, $=CHCH_2Ph$), 3.60 (s, 3 H, $-COOCH_3$), 5.37 (br t, J = 8 Hz, 1 H, $=CHCH_2-$), 7.1 (br s, 5 H, C_6H_5). GC on OV-17 at 160 °C showed a single peak with R_t = 3.66 min.

3β-Hydroxy-1α,3α-dimethyl-2β-(2′-phenylethyl)cyclohexane-1β-carboxylic Acid (1 → 3)-Lactone (10a). The crude product from the condensation of methylmagnesium iodide (prepared from 1 g of magnesium in 50 mL of ether) with 5 g of the keto ester **25a** according to the procedure reported[9] earlier was refluxed in 200 mL of benzene containing 500 mg of p-toluenesulfonic acid monohydrate for 8 h using a water trap. The crude product was distilled to afford a light yellow thick oil: 4.6 g; bp 160–170 °C (0.2 mm); IR 1765 (very strong) and 1725 (medium) cm^{-1}. This mixture was refluxed for 2 h with a solution of 2.5 g of potassium hydroxide in 25 mL of water and 25 mL of ethanol. Most of the ethanol was removed in vacuo, and the residue, after being diluted with water, was extracted with ether. The aqueous alkaline layer was acidified with an excess of concentrated hydrochloric acid and heated on a steam bath for 15 min. The cooled reaction mixture was extracted with ether. The ethereal extracts were washed with 1% sodium hydroxide solution and water. The residual brown liquid, after removal of ether, was distilled to afford 2.50 g (46%), bp 145–150 °C (0.2 mm), of a colorless thick liquid, which on trituration with petroleum ether gave the crystalline lactone **10a,** mp 73–74 °C. It showed a single spot in TLC in benzene–methanol (9:1). On recrystallization from petroleum ether it gave an analytically pure sample as colorless needles: mp 74–75 °C; IR 1765 cm^{-1}; UV λ_{max} (EtOH) 253 nm (log ε 2.93), 259 (2.44); ^1H NMR δ (CCl_4) 1.18 (s, 3 H, C-1 CH_3), 1.42 (s, 3 H, C-3 CH_3), 1.63–1.85 (complex m, 9 H), 2.62 (m, 2 H, $-CH_2Ph$), 7.01 (br s, 5 H, C_6H_5). Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.53. Found: C, 79.00; H, 8.66.

Cyclization Experiments with Lactone 17a. H_2SO_4–HOAc Catalyzed Cyclization of 17a. In a typical experiment, 200 mg of the lactone **17a** in 1.8 mL of acetic acid and 0.2 mL of concentrated sulfuric acid was refluxed on an oil bath for 6 h. The dark brown reaction mixture was poured into ice water and extracted with ether. The ethereal extracts were thoroughly extracted with 3% aqueous potassium hydroxide solution and water and dried. The removal of ether left a small amount of a yellow liquid (IR 1765 cm^{-1}) which was not investigated further. The aqueous alkaline layer was acidified with 6 N hydrochloric acid, and subsequent ether extraction afforded 120 mg (60%) of a light yellow solid. This acid was esterified with an excess of ethereal diazomethane. The crude ester was dissolved in 25 mL of 1:1 petroleum–benzene and filtered through a short column of acid-washed alumina (2 g). The colorless ester (116 mg) was subjected to ^1H NMR and GC analyses (Table I).

$AlCl_3$–HCl Catalyzed Cyclization of 17a. A solution of 300 mg of **17a** in 5 mL of anhydrous thiophene-free benzene was added slowly to a stirred refluxing suspension of powdered resublimed anhydrous aluminum chloride (1.0 g) in 10 mL of anhydrous thiophene-free benzene into which dry HCl gas was bubbled at the rate of about three bubbles per second. The addition was completed in about 30 min, and the HCl flow through the boiling reaction mixture was continued for an additional 1.5 h. The reddish brown mixture was allowed to stir at room temperature for 30 min and was finally decomposed by pouring it into ice and concentrated hydrochloric acid. The benzene layer was separated, and the aqueous layer was extracted with ether. The combined organic extracts were repeatedly extracted with 3% aqueous potassium hydroxide solution and water and dried. On removal of the solvent ~80 mg of a dark brown oil was left, which showed the absence of a carbonyl band in IR. The combined basic aqueous extracts were acidified with 6 N hydrochloric acid, and the acidic material was isolated by ether extraction to afford a light yellow solid (220 mg, 67%). This was esterified with diazomethane and purified as described above to give 210 mg of a colorless liquid ester which was subjected to ^1H NMR and GC analyses (Table I).

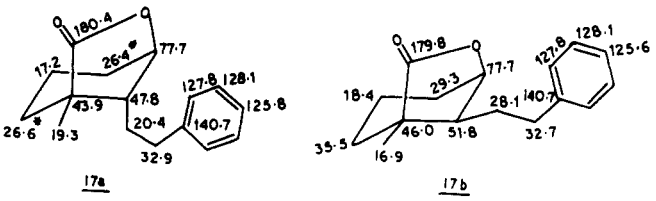


Figure 1. ^{13}C NMR spectral data of **17a** and **17b.** Values are in δ (Me_4Si = 0.0), and asterisks denote interchangeable assignments.

PPA-Catalyzed Cyclization of 17a. To a well-stirred homogeneous solution of PPA, prepared from 3 g of phosphorus pentoxide and 2 mL of 89% w/w phosphoric acid and cooled to about 20 °C by placing the reaction flask in a cold water bath was added 400 mg of **17a** in a lot. The cold water was replaced by boiling water, and the temperature of the water bath was maintained at 80–85 °C for 10–15 min. The reaction mixture was decomposed with ice, and 280 mg (70%) of a colorless solid acidic product, mp 185–190 °C, was isolated by the usual workup procedure. A portion of this acid was esterified with diazomethane and subjected to ^1H NMR and GC analyses (Table I). The remaining acid, on recrystallization from ethyl acetate, afforded pure acid **18,** mp and mmp 205–206 °C.

When the PPA cyclization of **17a** was continued for longer periods of time or at a higher temperature, considerable decarboxylation was observed, leading mostly to neutral products.

Cyclizations of the diastereomeric lactones 17b and 17a (3:1) mixture were carried out with H_2SO_4–HOAc, $AlCl_3$–HCl, and PPA on a 200-mg scale following the aforementioned procedures for **17a,** and the results are given in Table I.

Cyclization of the 1:1 Mixture of Lactones 17a and 17b in Preparative Scale and Separation of the Products. H_2SO_4–HOAc Cyclization of the 17a and 17b (1:1) Mixture. The crude acid obtained from cyclization of 1 g of the **17a** and **17b** mixture in 9 mL of acetic acid and 1 mL of sulfuric acid was sublimed at 160–170 °C (0.3 mm) (bath temperature) to afford 570 mg (57%) of a light yellow solid. On repeated crystallization from methanol, it gave 60 mg of the acid **4,** mp 188–189 °C, alone or mixed with an authentic sample. The residual acid was esterified (diazomethane), and the crude methyl ester, on refluxing for 3 h with 1 g of potassium hydroxide solution in 10 mL of 50% v/v aqueous ethanol and following the standard workup, afforded 310 mg of the unhydrolyzed ester and 150 mg of a solid acidic product. On repeated crystallization from ethyl acetate–methanol, the crude acid gave 45 mg of pure acid **18,** mp 205–206 °C, alone or on admixture with an authentic sample. The recovered ester was chromatographed on acidic alumina (15 g). Petroleum ether–benzene (9:1) elution afforded 155 mg of the pure ester **21,** mp and mmp 78–79 °C. Further elution with petroleum ether–benzene (3:1 to 1:1) yielded 100 mg of a thick liquid ester fraction which on alkaline hydrolysis as described above yielded 89 mg of acid and 10 mg of neutral products. On repeated recrystallizations of the acid from ethyl acetate, another 20 mg of the pure acid **18,** mp 205–206 °C, was isolated. The residual acid and the neutral fraction could not be separated further.

The total yields of the isolated acids **4** (including the ester **21**) and **18** were 22 and 7%, respectively.

$AlCl_3$–HCl Catalyzed Cyclization of the 17a and 17b (1:1) Mixture. A solution of 2.1 g (9 mmol) of the mixture of **17a–17b** in 20 mL of anhydrous thiophene-free benzene was added slowly to a refluxing suspension of powdered sublimed anhydrous aluminum chloride (8 g, 60 mmol) in 40 mL of dry thiophene-free benzene into which dry hydrogen chloride gas was bubbled. The reaction was car-

ried out as described for **17a**, and the crude acidic product (1.80 g) was purified by sublimation at 165–180 °C (0.3 mm) (bath temperature) to afford a brown solid (1.51 g, 72%), which on repeated crystallizations from ethyl acetate yielded 350 mg of the acid **19**, mp and mmp 210–211 °C. The combined residual acids were esterified (diazomethane), and the crude ester was chromatographed on 40 g of acidic alumina and eluted as follows: (i) petroleum elutions (300 mL) afforded a light yellow liquid (110 mg); (ii) petroleum–benzene (9:1) yielded 140 mg of the crystalline ester **21**, mp and mmp 78–79 °C; (iii) the subsequent fractions eluted with petroleum–benzene (3:1, 250 mL; 1:1, 200 mL) and benzene (200 mL) yielded 610 mg of a thick liquid.

Fraction iii was hydrolyzed with 6 mL of 10% w/v potassium hydroxide solution in 25% v/v aqueous ethanol by refluxing for 3 h. The acidic fraction (340 mg) and the unhydrolyzed ester (240 mg) were isolated by the usual workup procedure. The crude acid, on sublimation at 160–170 °C (0.2 mm) (bath temperature), afforded a yellow-white solid, mp 150–158 °C. On repeated crystallizations from ethyl acetate, it afforded 70 mg of the acid **19**, mp and mmp 210–211 °C. The acidic products, mp 145–150 °C, from the mother liquor could not be separated further. The unhydrolyzed ester fraction (240 mg) was rehydrolyzed with 5 mL of 7% w/v potassium hydroxide solution in 95% v/v diethylene glycol–water by refluxing for 2 h under nitrogen. On working up a brown solid acidic product was obtained which on repeated crystallizations from ethyl acetate afforded 120 mg of acid **18**, mp and mmp 204–205 °C. The residual acid could not be fractionated further. The total yields of the isolated pure acids **19**, **4**, and **18** were 20, 6, and 6%, respectively.

Cyclization Experiments with the (3:7) Unsaturated Ester Mixture of 1a and 1b. H_2SO_4–HOAc Catalyzed Cyclization of the 1a–1b Mixture. A 1-g amount of the unsaturated ester mixture was refluxed for 6 h with 9 mL of glacial acetic acid and 1 mL of concentrated sulfuric acid. Workup of the reaction mixture afforded 410 mg of brown solid acidic product. This was sublimed at 165–180 °C (0.2 mm) (bath temperature) to afford 300 mg (30%) of white solid, mp 180–185 °C. This was esterified with diazomethane and subjected to ^1H NMR and GC analyses (Table I).

$AlCl_3$–HCl Catalyzed Cyclization of the 1a–1b Mixture. The ester mixture (5.4 g, 20 mmol) in 60 mL of dry thiophene-free benzene was cyclized with 15 g (110 mmol) of sublimed anhydrous aluminum chloride in benzene (100 mL) and dry hydrogen chloride under the same experimental conditions as described for lactone **17a**. After the usual workup, 4.1 g of a neutral fraction, bp 135–150 °C (0.6 mm), and 650 mg of a yellowish solid acidic product were obtained. The neutral fraction was rehydrolyzed with 50 mL of a 7% w/v potassium hydroxide solution in 95% v/v diethylene glycol–water by refluxing for 3 h. The dark brown solid acid (3.75 g) isolated from the hydrolysis was mixed with the acidic product obtained from the cyclization (total yield 80%) and purified by sublimation at 170–180 °C (0.5 mm) (bath temperature) to afford 2.82 g (58%) of light yellowish white solid. A portion of this acid was esterified (diazomethane) and subjected to ^1H NMR and GC analyses (Table I).

A 1.41-g amount of this acidic fraction was separated by a similar sequence to that described for the reaction of the **17a** and **17b** (1:1) mixture with $AlCl_3$–HCl to afford the pure acids **19**, **18**, and **4** (including ester **21**) in 18, 13, and 3% yields, respectively.

PPA-Catalyzed Cyclization of the 1a–1b Mixture. The ester mixture (5.0 g) was cyclized with PPA prepared from 16 g of phosphorus pentoxide and 12 mL of 89% w/w phosphoric acid at 65–70 °C (water bath) for 1 h followed by 15–20 min at 80–85 °C. The neutral fraction (4.70 g) isolated from the reaction was fractionated into three fractions: 1.3 g, boiling point up to 150 °C (6 mm), did not show any carbonyl band in the IR; 2.8 g, bp 125–145 °C (0.6 mm); and an acidic fraction (260 mg). The alkaline hydrolysis of the second fraction (2.8 g) with boiling 7% w/v potassium hydroxide solution in 95% v/v diethylene glycol–water for 3 h under nitrogen and workup afforded a light brown solid acid. The total yield of the acidic product is 2.06 g (43%). A portion of the combined acidic fractions was esterified (diazomethane), and the ester was subjected to ^1H NMR and GC analyses (Table I). However, no quantitative analysis of this mixture could be done in the ^1H NMR due to the additional peaks in the regions of the methyl singlets for the epimeric esters **21–24**.

The acidic products obtained in a similar reaction were fractionated by the combination of methods described above to afford the pure acids **18** and **4** (isolated as **21**) in 18 and 3% yields, respectively.

Cyclizations of Lactone 10a. 1,2,3,4,4a,9,10,10aα-Octahydro-1α,4aβ-dimethyl-1β-phenanthrenecarboxylic Acid [(±)-Deoxypodocarpic Acid] (5). (i) H_2SO_4–HOAc Catalyzed Cyclization. Lactone **10a** (300 mg) was refluxed for 6 h with a mixture of 3 mL of acetic acid and 0.3 mL of concentrated sulfuric acid. The dark brown mixture was worked up in the usual way to afford a light yellow solid acid (202 mg, 67%), mp 225–228 °C. A small portion of this acid was esterified with diazomethane, and the crude methyl ester was identical with an authentic sample[9] of (±)-methyl deoxypodocarpate with respect to IR, ^1H NMR, and TLC. A single recrystallization of the remaining acid from ethyl acetate afforded pure acid **5**, mp and mmp 233–234 °C alone or mixed with an authentic sample.[9]

(ii) PPA-Catalyzed Cyclization. To a well-stirred homogeneous solution of PPA, prepared from phosphorus pentoxide (3 g) and orthophosphoric acid (2 mL, 89% w/w), was added the lactone **10a** (500 mg) in one lot at 50 °C. The thick white reaction mixture was stirred for 1 h at 80–85 °C and worked up to afford a light yellow acid (361 mg, 72%), mp 228–230 °C. This, on one recrystallization from ethyl acetate, afforded colorless pure acid **5**, mp and mmp 233–234 °C with an authentic sample.

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Registry No.—**1a**, 69622-71-5; **1b**, 69622-72-6; **1c**, 69622-73-7; **1d**, 69622-74-8; **4**, 21995-83-5; **5**, 5708-75-8; **10a**, 69622-75-9; **17a**, 69622-69-1; **17b**, 69622-70-4; **18**, 21995-86-8; **19**, 21995-84-6; **20**, 13936-32-8; **21**, 5708-86-1; **22**, 21995-99-3; **23**, 21995-93-7; **24**, 21995-96-0; **25**, 57969-37-6; **25a**, 55732-04-2; β-phenylethyl bromide, 104-63-9; methyl iodide, 74-88-4; (±)-methyl deoxypodocarpate, 16957-27-0; ethyl 1-methyl-2-oxocyclohexanecarboxylate, 66088-37-7; ethyl 2-hydroxy-1-methyl-2-phenylethylcyclohexanecarboxylate, 69022-76-0; methyl 1,3-dimethyl-3-hydroxy-2-phenylethylcyclohexanecarboxylate, 69622-77-1.

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Transannular Reactions of Substituted Bicyclo[3.3.1]nonane-3-*endo*-carbonitriles: Synthesis of Bifunctional 4-Azahomoadamantanes[1a]

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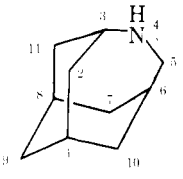
The synthesis of 2-*exo*-hydroxy-4-azahomoadamantanes has been accomplished employing three routes. Reactions have been studied that can lead to transannular cyclizations of the cyano group in substituted bicyclo[3.3.1]nonane-3-*endo*-carbonitriles. The nitrile function has been shown to participate in cyclizations under oxidizing and reducing conditions. 3-Azatricyclo[5.3.1.$0^{4,9}$]undec-5-ene (**16**), a representative of a new heterocyclic "cage" series, has been synthesized.

There has been considerable interest during the past decade in the synthesis and chemistry of adamantane-related "cage" compounds which are pharmacologically active.[2,3] Research in this area has naturally been extended to heterocyclic analogues of "cage" compounds.[3] Several derivatives of 4-azahomoadamantane (**1**) have been reported to show



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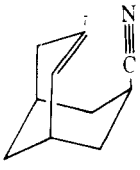
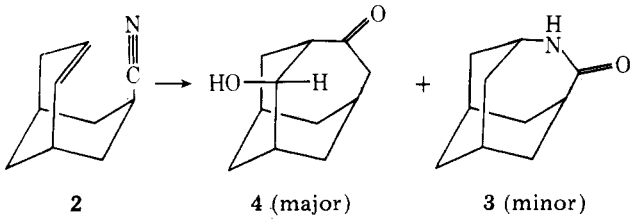


2

antiarrhythmic, hypoglycemic, and antiviral activity.[4-7] Most of the reported 4-azahomoadamantanes have been substituted at nitrogen (4 position) or across the 4–5 bridge.[4-7] There have also been a few examples of 4-azahomoadamantanes with substitution at the 3[8-10] and the 9 positions.[11]

The availability of bicyclo[3.3.1]-6-nonene-3-*endo*-nitrile (**2**) from adamantanone[12] led us to explore its usefulness as a precursor to 2-substituted 4-azahomoadamantanes as well as its behavior in transannular reactions. In principle, a nitrile may act as both an electrophile and a nucleophile in a given reaction.[13] Generation of an electrophilic center at C-7 of the bicyclo[3.3.1]nonane skeleton can lead to interception by the nitrile nitrogen and generate the 4-azahomoadamantane skeleton. Nucleophilic attack at the nitrile carbon can either *precede* or follow reaction of the nitrile nitrogen with the electrophilic center at C-7. In fact, Korsloot and Keizer have identified a small amount (2%) of 4-azahomoadamantan-5-one (**3**) from the reaction of **2** with 95% H_2SO_4.[14] This product could arise from initial protonation of the double bond followed by an intramolecular Ritter reaction. The major product, 3-*exo*-hydroxyadamantanone (**4**), is obviously formed by initial protonation of the nitrile followed by transannular double-bond participation. We wish to describe some transannular chemistry of nitrile **2** and several facile routes to 2-substituted 4-azahomoadamantanes as well as to a functionalized azatricycloundecane cage compound.

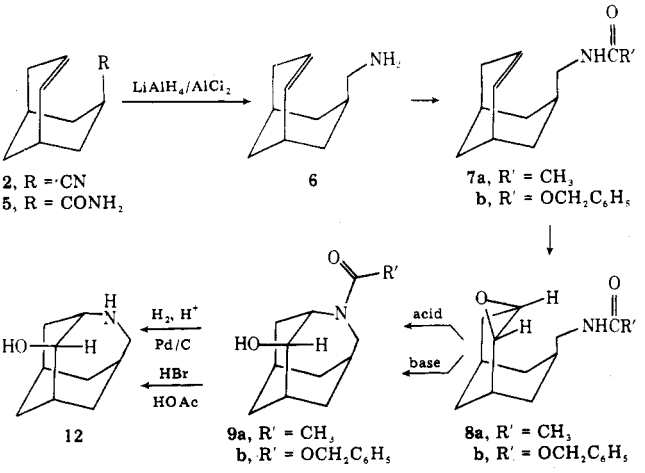


2 **4** (major) **3** (minor)

Results and Discussion

Three routes were devised for the transformation of the bicyclic unsaturated nitrile **2** into azahomoadamantane **12**. The first approach (Scheme I) was patterned after a sequence employed by Spurlock in the synthesis of 4-*exo*-hydroxy-2-azaadamantane[15] and served as an unambiguous route to **12**. Reduction of **2** with lithium aluminum hydride/aluminum chloride ($LiAlH_4/AlCl_3$, 1:1) to the *endo*-amine **6** proceeded in 76% yield and provided a good nucleophile before the epoxide leaving group was introduced on carbon.[16] Alternatively, **6** was obtained (70%) from $LiAlH_4$ reduction of the amide **5**. After the amine **6** was protected as the acetamide **7a** or the benzylcarbamate **7b**, *m*-chloroperbenzoic acid (MCPBA)

Scheme I



2, R = CN
5, R = $CONH_2$

6

7a, R' = CH_3
b, R' = $OCH_2C_6H_5$

12

9a, R' = CH_3
b, R' = $OCH_2C_6H_5$

8a, R' = CH_3
b, R' = $OCH_2C_6H_5$

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