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Rearrangement of α-Bromocamphoric Anhydride. 2. Competitive Mechanisms in the Formation of Laurolenic Acid[1,2a-c]

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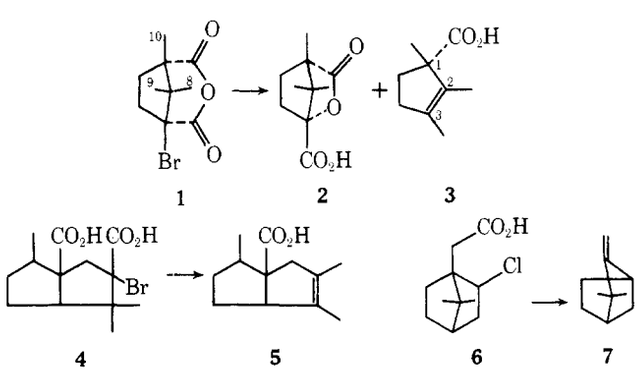
α-Bromocamphoric anhydride (1) is converted by aqueous sodium carbonate into camphanic acid (2) and the rearranged product laurolenic acid (3). L(+)-α-Bromocamphoric anhydride-*8,8,8-d*$_3$ was prepared from L(−)-camphor-*8,8,8-d*$_3$ by oxidation with selenium dioxide and then hydrogen peroxide, followed by bromination. Rearrangement of this labeled anhydride produces L(−)-laurolenic acid in which 71% of the CD_3 group is located at the 1 position and 29% is at the 3 position. In conjunction with earlier work, these results indicate that the rearrangement is not unimechanistic, but follows at least two competitive pathways. One of these involves loss of the carboxyl γ to the bromine by a path which is concerted with migration of the 8-methyl to the initially brominated carbon. Another process involves loss of the α-carboxyl, but the present results do not determine whether or not this is also concerted with the stereoselective 8-methyl migration. Even if it is, concerted γ-decarboxylation predominates over concerted α-decarboxylation. Optically and isotopically pure L(−)-camphor-*8,8,8-d*$_3$ was prepared in 41% overall yield from L(−)-8-apoisoborneol-7-carboxylic acid lactone by lithium aluminum deuteride reduction to L(+)-8-hydroxyisoborneol-*8,8-d*$_2$ (**17**-d_2), selective preparation of the 8-benzoate, Jones oxidation and saponification to afford L(−)-8-hydroxycamphor-*8,8-d*$_2$ (**25**-d_2), treatment with phosphorus tribromide to produce the 8-bromo ketone, and tri-*n*-butyltin deuteride reduction. Small amounts of the 2,8-dibenzoate **20** and the 2-monobenzoate **21** are by-products of the benzoylation, the latter being converted to carboxy ester **29** in the oxidation step. Conversion of the undeuterated diol **17** to ketol **25** by selective 8-tritylation, Sarett oxidation, and hydrolysis of keto trityl ether **23** is also described. 2-Hydroxy- and 2-keto-8-*p*-toluenesulfonates **22** and **26** are both converted by lithium aluminum hydride into cyclic ether **30**, which is also produced by attempted tosylation of **17** at room temperature.

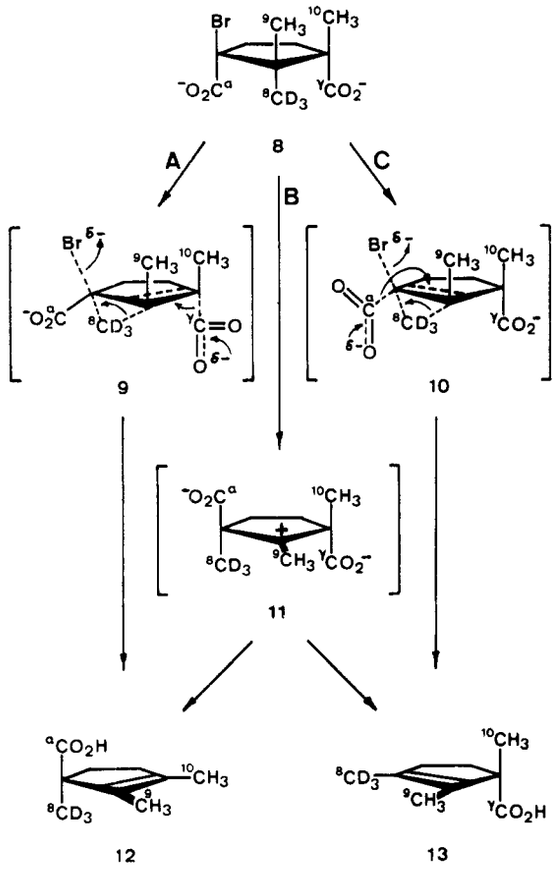
One of the most striking molecular rearrangements of organic chemistry is the solvolytic conversion of α-bromocamphoric anhydride (1) to laurolenic acid (3), first reported by Fittig and Woringer in 1885.[3] This unsaturated acid accompanies the major unrearranged product, camphanic acid (2),



in about 15% yield when the solvolysis is conducted at pH 11,[4] and its formation involves the unusual combination of bromide loss, 1,2-methyl migration, and decarboxylation of an α- or γ-bromo acid. Other examples of potentially analogous reactions are extremely rare, but include the rearrangement of bromonorcedrenedicarboxylic acid (an α-bromo acid, **4** → **5**)[5] and of 2-chloro-1-apocamphaneacetic acid (a γ-bromo acid, **6** → **7**).[6] A few related base-catalyzed rearrangements of α-bromo acids not accompanied by decarboxylation are also known.[7]

Some time ago we became interested in the mechanism of this peculiar reaction, particularly in the stereoselectivity of methyl migration and in the regioselectivity of decarboxylation. Owing to the particular juxtaposition of functional groups in the camphoric acid system, the latter is not intuitively obvious as it is in the cases of **4** and **6**. In an earlier paper we reported the results of research showing that the methyl migration which occurs during formation of laurolenic acid is completely stereoselective and therefore concerted with bromide loss, and that neither an α-lactone (or its mechanistic equivalent), a carbene, nor camphanic acid is involved in the rearrangement.[1] It is also known that the rearrangement product is at least 96% optically pure[8] and has the same configuration at C-1 as does the bromo anhydride from which it is derived.[1,8-10] These results limit the mechanistic possibil-

Scheme I



ities to pathways such as those depicted in Scheme I or related processes,[1] but shed no light on the decarboxylation stages of the reaction. They leave unanswered questions as to whether carboxyl loss is specific or statistical, whether carboxyl loss is also concerted with methyl rearrangement, which carboxyl is lost, and whether an intermediate such as the protio analogue of carbonium ion **11**, with equivalent carboxylates or carboxyls, can be involved. We have now completed a further examination of this reaction, and herein report results which show that carboxyl loss is *neither* specific *nor* statistical, so that at least two pathways are followed during decarboxylation and at least one of them involves a concerted loss of carbon dioxide.

These aspects of the rearrangement have been studied by labeling the 8-methyl of bromocamphoric anhydride[11] with deuterium and determining the location of the deuteriomethyl group in the resulting laurolenic acid. This labeled methyl is the group which migrates in the reaction,[1] so its ultimate location serves to mark the carbon which initially held the bromine. The direct question then, of course, is simply whether that carbon has retained or lost its carboxyl.

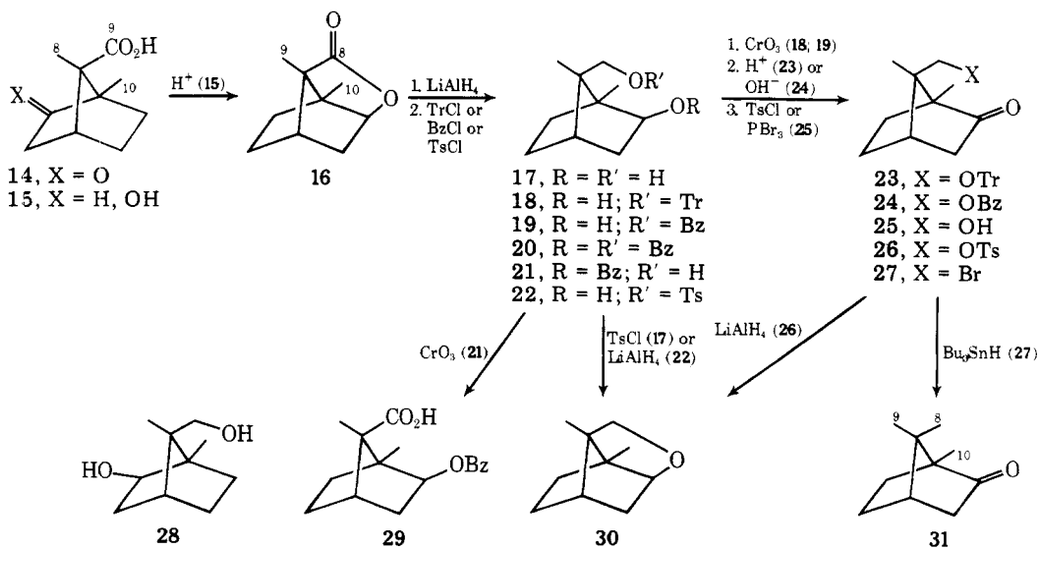
Synthesis of L(−)-Camphor-*8,8,8-d*$_3$ and L(+)-α-Bromocamphoric Anhydride-*8,8,8-d*$_3$. Preparation of the necessary labeled bromo anhydride required availability of the correspondingly labeled camphor. Although for this study the optical purity of the anhydride was not important, in connection with other research we needed a series of 8-deuterated camphor derivatives which were high in optical purity as well as containing complete and specific deuterium substitution for one, two, or all three of the 8-hydrogen atoms, respectively. Therefore a synthesis which could satisfy all of these requirements was developed (Scheme II).

The sequence is initiated with conversion of D(+)-camphor into D(+)-isoketopinic acid (**14**) as described earlier,[1,12-14] a transformation which is known to proceed with complete retention of configuration.[1,15] In order to transmogrify this keto acid into a substance with a reducible function in the 8 rather than the 9 position, advantage was taken of the known rearrangement of the corresponding hydroxy acid **15** to lactone **16**.[14] This process, which occurs by way of a 2,6-hydride shift,[14] actually brings about the necessary interchange of carbons 8 and 9 by converting the ring system functionality from the D to the L enantiomeric series.[16] Although the point had apparently not been previously substantiated, it is clear from the present work that subtle rearrangements which induce partial racemization do not intervene during lactone formation, for the L-camphor ultimately derived from this lactone proves to be optically pure.[17]

Conversion of the racemate of lactone **16** into camphor has been described by Finch and Vaughan[18] and by Rodig and Sysko,[19] and our sequence for conducting this transformation starts in a similar manner with lithium aluminum hydride reduction to form the 2,8-diol **17**. However, for a variety of reasons including not only a desire for high yields, but also for ease of manipulation of intermediates and purification of products and particularly for specificity and efficiency in the incorporation of deuterium as well as protium into the products, many of the subsequent stages in our synthesis differ from those reported earlier.[18,19]

The potentially direct route for removing the primary hydroxyl of diol **17** by means of the selective changes OH → OTs

Scheme II



→ H, in analogy with the procedure used with the isomeric anti diol **28**,[1] was discarded when we, too, found that cyclic ether **30** is difficult to reproducibly avoid as a by-product of the monotosylation,[18,19] and that in any event it is the main product from lithium aluminum hydride reduction of not only hydroxy tosylate **22**[18,19] but also keto tosylate **26**. Attempted reductive cleavage of this ether to isoborneol using lithium aluminum hydride–aluminum chloride[20] was unsuccessful, so the facile formation of ether **30** could not be turned to advantage.

The foregoing results augured ill for sequences utilizing lithium aluminum deuteride as the source of the final deuterium on C-8 without elaborate protection of the 2-oxygen function, and we preferred not to chance the possibility of hydrogen–deuterium exchange at various points in the molecule which might threaten to accompany catalytic replacement of an 8 substituent by molecular deuterium. Accordingly attention was turned to preparation of ketol **25** and examination of the sequence OH → Br → H, where a trialkyltin hydride or deuteride could be used for the last reductive step in the presence of a 2-keto group.[21] Selective Jones oxidation of diol **17** to ketol **25** was not explored in view of the reported poor yield,[18] and exposure to *N*-bromoacetamide produced lactone **16** rather than bringing about the normal preferential oxidation of the secondary alcohol.[22] However, diol **17** is selectively protected at the primary hydroxyl by either tritylation or benzoylation, and oxidation of either derivative followed by deprotection readily produces ketol **25**. We preferred the route through benzoyl derivatives, since it sometimes proved difficult to purify the hydroxy trityl ether **18**. Although benzoylation of the diol affords small amounts of diester **20** and the isomeric hydroxy ester **21** in addition to the required hydroxy ester **19**, these by-products are not troublesome. The diester is easily separated from the 11:1 mixture of hydroxy esters by chromatography, and in the oxidation step residual hydroxy ester **21** is converted to the acid **29** which can be removed by extraction. These techniques afford ketol **25** in 68% yield from diol **17**. Use of mesitoyl chloride rather than benzoyl chloride in an effort to improve the selectivity in monoacylation of **17** showed no advantage to lie with the more hindered acylating agent.

Ketol **25** is converted to bromo ketone **27**[23] by phosphorus tribromide,[18] and reduction by tri-*n*-butyltin hydride affords L(−)-camphor (**31**).[26] This product is optically pure (±4%, the uncertainty in our rotation measurements), as thus must be all of its predecessors.[17] The overall yield from lactone **16**, the crucial steps for deuterium introduction, is 41%, which compares favorably with the 16[18] and 43%[19] reported for other sequences, and with the 45% for conversion of methyl D-isoketopinate to optically pure D-camphor-*9,9,9-d*$_3$.[1]

Repetition of the sequence **16** → **17** → **19** → **24** → **25** → **27** → **31** with use of lithium aluminum deuteride and tri-*n*-butyltin deuteride in the appropriate reduction steps affords optically pure L-camphor-*8,8,8-d*$_3$ containing at least 97.5% of the d_3 species according to mass spectrometric analysis. ^{1}H NMR spectra of this product and all of its deuterated predecessors and progeny contain appropriate features[1] for location of all deuterium atoms specifically on the 8 carbon. These spectra, together with those obtained earlier from 9-deuterio derivatives,[1] have allowed unequivocal assignments of the methyl resonances in these compounds; assignments are listed in the Experimental Section and confirm earlier proposals concerning camphor and camphorquinone.[27]

It may be noted that by use of the isotopic reagent in one or the other but not both of the reduction steps the d_1 and d_2 derivatives will be available in equivalent optical and isotopic purity. Thus this sequence and that described earlier[1] make accessible optically pure camphor derivatives with mono-, di-, or trideuteration of either methyl-8 or methyl-9.[28] Undoubtedly one or the other sequence could also be adapted for deuteration of methyl-10 if the need should arise for samples with greater or more specific deuterium incorporation at that site than can be obtained by way of the 10-chloro sulfoxide.[24]

8-Labeled bromo anhydride for the rearrangement experiment was prepared by sequential oxidations of L(−)-camphor-*8,8,8-d*$_3$ with selenium dioxide and alkaline hydrogen peroxide, followed by bromination, as described earlier for the unlabeled and 9-labeled analogues.[1] Phosphorus tribromide–bromine has proven preferable to phosphorus pentachloride–bromine[1] for the bromination step, because on some occasions the latter reagent leads to significant amounts of unbrominated camphoric anhydride as a by-product.

Rearrangement of the 8-Labeled Bromo Anhydride. Rearrangement of the labeled bromo anhydride under conditions identical with those used in the previous study[1] affords labeled laurolenic acid (**3**-d_3) and labeled camphanic acid (**2**-d_3). The latter is devoid of τ 8.98 methyl resonance but has equal 3-proton intensity methyl resonances at τ 8.86 and 8.90, just as that from base treatment of the *9,9,9-d*$_3$ anhydride has 3-proton methyl resonances at τ 8.86 and 8.98 but none at 8.90.[1] These observations are all in accord with a mechanism for formation of the lactonic acid **2** which involves simple intramolecular displacement of bromide by the carboxylate which is γ to it, the τ 8.86, 8.90, and 8.98 resonances of camphanic acid being respectively those of the former 10-methyl, 9-methyl, and 8-methyl of the bromo anhydride.

The ^{1}H NMR spectrum of the labeled laurolenic acid contains the allylic methyl multiplet (ca. τ 8.41, 2-methyl plus 3-methyl)[1] and the quaternary 1-methyl singlet (τ 8.77)[1] in the intensity ratio of 86:14. Inasmuch as our earlier work has shown that 100% of the 9-methyl remains at C-2 (allylic) in laurolenic acid, this ^{1}H NMR result indicates that the ratio of *protonic* 3-methyl to *protonic* 1-methyl in the laurolenic acid derived from 8-labeled anhydride is 72:28. In view of the breadth and overlap of the C-2 and C-3 methyl resonances, and the possibility that they might overlap slightly with ring proton resonances in the spectrum of the unsaturated acid itself, this quantitative result was checked by conversion of the acid to its bromo lactone.[1,29] Integration of the three sharp methyl singlets in the spectrum of this derivative[1] showed their relative intensities to be 99 (τ 8.38, 2-CH_3):71 (τ 8.50, 3-CH_3):30 (τ 8.75, 1-CH_3). The excellent agreement of the 3-methyl:1-methyl resonance intensity ratio between this bromo lactone and the labeled acid from which it was derived requires that the τ 8.50 and 8.75 resonances of bromo lactone correspond to the τ 8.41 and 8.77 resonances of the unsaturated acid, respectively. This information confirms our earlier assignment of chemical shifts to the bromo lactone,[1] because both the chemical shift of the τ 8.41 resonance of the acid and its breadth due to homoallylic spin coupling demonstrate its allylic nature, which requires its assignment to the 2- and 3-methyls.

Comparison of the *m/e* 125 and 128 ions in mass spectra of the unlabeled and labeled bromo lactones ($C_7H_9O_2$ or $C_8H_{13}O$; no significant molecular ion appears in the spectrum) shows the latter to indeed contain at least 96% of the d_3 species.

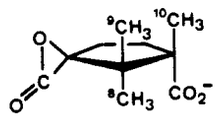
Discussion

This result and the earlier one show that while 100% of methyl 9 from the anhydride becomes the 2-methyl of laurolenic acid, 71% of methyl 8 becomes the 1-methyl and 29% becomes the 3-methyl. Thus under these reaction conditions the rearrangement products are the isotopic isomers **12** and **13** (Scheme I) in a 71:29 ratio, and loss of the carboxyl which was originally γ to the bromine predominates over loss of the α-carboxyl.

One immediate conclusion which follows is that rear-

rangement of the intermediate dianion 8[1] does *not* proceed exclusively through a species with equivalent carboxyls such as carbonium ion **11** (path B of Scheme I), which would require distribution of the labeled methyl to be 50:50 modified only slightly by any secondary deuterium isotope effects.[30] Likewise, the rearrangement does not proceed by a single concerted path, such as path A or path C, which would require exclusive loss of a particular carboxyl. More than one sequence is involved. It is possible that as much as 58% of the product is formed through a symmetric species (**11**, etc.), accounting for all of the 3-CD_3 acid **13** and a corresponding amount of the 1-CD_3 substance **12**, but even if this is the case there is an additional 42% of the product formed by specific loss of the γ-carboxyl. On the other hand, the result is equally consistent with a situation in which no laurolenic acid is produced through a system with equivalent carboxyls like **11**, but in which there are two (or more) competitive concerted pathways, the predominant one (71%) involving γ-carboxyl loss and a minor one (29%) involving specific α-carboxyl loss. Or, of course, all three processes could be operating to appropriate intermediate extents. In any event, this reaction is not completely analogous to either the bromonorcedrenedicarboxylic acid case (**4**, α-decarboxylation) nor the chloroapocamphaneacetic acid case (**6**, γ-decarboxylation), but shows characteristics of both.

Thus far we have considered the decarboxylation only in terms of intermediates with two free carboxylate groups (Scheme I), but the possible intervention of lactonic species must also be examined. Of course the γ-lactone camphanic acid (**2**) was excluded earlier by the observation that it is not converted to laurolenic acid under these conditions.[1] α-Lactones **32** and **33** can be discarded on mechanistic grounds, the



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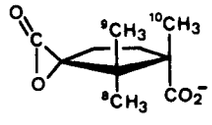

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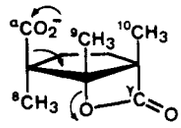

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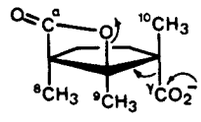

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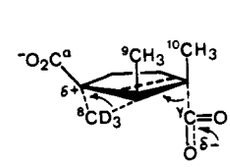
former because its formation would involve displacement of bromide with retention of configuration and the latter because its rearrangement would require methyl migration with retention of configuration at the migration terminus.[1] However, β-lactones **34** and **35** are not so readily dismissed.[31] In principle either could be individually produced by attack of the appropriate carboxylate on the cationic center which is developing at C-2 as the methyl group migrates, and the two of them could be generated in equal amounts[30] from cation **11**. Subsequent decarboxylative anti elimination as indicated would lead to laurolenic acid (**13** and **12**, respectively).[32] Actual intermediacy of these two lactones in any fraction of decarboxylation which occurs by way of cation **11** remains an open question, for their transient presence as equimolecular progeny of the latter is allowed but not required by the available data. On the other hand, independent genesis of lactone **35** seems quite improbable. Before the α-carboxylate oxygen can approach C-2 closely enough to start formation of the C-2–O bond of this β-lactone, methyl migration and inversion of configuration at the migration terminus must be nearly complete. If there were a need for the C-2 center to undergo nucleophilic collapse with a carboxylate oxygen before it reaches the fully charged state of **11**, it should be able to do so at a much earlier point in the reaction by bonding to the geometrically available γ-carboxylate, thereby affording **34** rather than **35**. We therefore feel that sequences for specific γ-decarboxylation through lactone **35** are not worthy of further consideration. Even though such purely geometric constraints do not similarly militate against preferential formation of lactone **34**, that process is also less than completely satisfying as a probable participant in the reactions under discussion. It requires that the γ-carboxylate attack the face of C-2 from which the migrating methyl is departing, and analogous β-lactonizations with retention of configuration do not occur in related reactions such as the solvolysis of *cis*-2-bromocyclopentanecarboxylic acid.[33] Nonetheless, we do not feel that this is a sufficiently strong argument to entirely exclude the possibility of selective α-decarboxylation by a route through lactone **34**.

Among the points which are more or less clear[30] regarding the decarboxylation mechanisms is that there is a process for specific γ-carboxyl loss. Of the possibilities we have considered, the most probable is direct decarboxylation concerted with methyl migration, by a route which resembles path A of Scheme I. The present data do not indicate whether this decarboxylation is also concerted with bromide loss, involving a transition state like **9** as is shown in Scheme I, or whether it only begins after completion of that bond rupture (e.g., through an alternative transition state such as **36**). They



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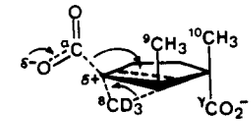

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simply show that loss of this carboxylate begins before methyl migration is completed with formation of a symmetric ion **11**. The other processes which could hypothetically lead to specific γ-decarboxylation are cycloreversion of lactone **34**, which should not occur under these conditions,[32-34] and β-decarboxylative elimination of lactone **35**, which should not be selectively generated in this system (see above).

The mechanism 8 → (**9** or **36**) → **12** corresponds to a syn 1,2 elimination with the migrating methyl as the leaving nucleophile. Such a stereochemical result is by no means uncommon for concerted eliminations from cyclopentane systems, with CO_2 as the departing electrophile[33] as well as with proton.[35] One should not, however, extrapolate the propensity of bromocamphorate to undergo syn γ-decarboxylation in preference to α-decarboxylation to the general case. Just as concerted 1,2-elimination reactions show a favored conformational relationship between the leaving groups (near coplanarity, either anti or syn), these decarboxylative rearrangements may well have a preferred geometry between the γ-carboxyl and the migrating alkyl group which is satisfied in the five-membered ring but would not be met in certain other structures. Even in the present instance the energy difference between transition states for γ-decarboxylation and α-decarboxylation is only about 0.6 kcal/mol (less if the latter proceeds through **11**). Thus if in a different system such conformational or other structural factors inhibited or precluded γ-decarboxylation, α-decarboxylation could easily become the predominant or sole process. This is, of course, vividly demonstrated in the cedrene series (**4** → **5**), where γ-decarboxylation is impossible. Finally it should be noted that the present example gives no information about the reactivity of a γ-carboxyl which is oriented trans to the migrating alkyl group. One would suspect that if such a carboxyl

could attain an approximately anti-coplanar conformation with respect to the migrating group, it would also be readily lost.

Little can be concluded about the process which is involved in α-decarboxylation, other than that it exists and energetically is not greatly inferior to the γ-decarboxylation route. It may proceed through the 2 cation **11**, accompanied by an equivalent amount of γ-decarboxylation (either with or without prior β-lactonization to **34** and **35**). It may proceed by a concerted path in which the γ-carboxyl is not at all involved, such as path C of Scheme I or its counterpart in which bromide departure precedes the onset of decarboxylation (cf. **37**). Or it may proceed through selective formation and decomposition of lactone **34** as discussed above. Analogous paths are also open to the cedrene analogue.

Experimental Section

All reactions were conducted in a N_2 atmosphere. Melting points, corrected for stem exposure, were determined in sealed evacuated capillaries unless marked (o) to indicate open capillaries. Spectra were obtained using Perkin-Elmer Model 337 (IR) and Varian A-60 or Bruker HFX-90 (90 MHz) (^{1}H NMR) spectrometers. The ^{1}H NMR solvent was $CDCl_3$ unless otherwise stated, with Me_4Si as internal standard. Chemical shifts (τ), multiplicities (s, d, t for singlet, doublet, triplet; m for unanalyzed multiplet), coupling constants (J, in hertz), and the number of protons are listed for prominent resonances. Methyl resonance assignments, where indicated, are based on peak absences from spectra of the 8-d_3 and 9-d_3[1] analogues. Mass spectra were obtained on a Hitachi RMU-6E double focusing spectrometer at an ionization potential of 80 eV, with direct solid introduction unless marked (v) to indicate vaporization of a volatile solid into the liquid introduction system; data are in the form *m/e* (% base peak intensity). Column chromatographic separations employed a 30–50:1 w/w ratio of absorbent to substrate, and eluent fractions of approximately half the column volume or less. Microanalyses were by Alfred Bernhardt, Mulheim, Germany (indicated B), or Spang Laboratory, Ann Arbor, Mich. (S). Optical rotations were observed in 95% EtOH unless indicated otherwise, on a Rudolph Model 80 polarimeter with a 2-dm tube, and are considered accurate to $[\alpha]$ ±1.5°. When no temperature is specified, operations were conducted at room temperature, ca. 23 °C. Unless otherwise specified, HCl, NaOH, KOH, $NaHCO_3$, K_2CO_3, and Na_2CO_3 solutions were aqueous; brine refers to saturated aqueous NaCl. General procedures for isolation of reaction products are abbreviated as follows: (A) the indicated mixture was thoroughly extracted with the specified organic solvent, which was washed with the indicated sequence of aqueous solutions followed by water or brine, dried ($MgSO_4$ or Na_2SO_4), and removed in vacuo; (B) the mixture was added to water followed by the steps in procedure A.

L(−)-8-Apoisoborneol-7-carboxylic Acid Lactone (16). Optically pure **14**, mp 251.8–252.3 °C, $[\alpha]^{25}$D +6.0° (*c* 0.99) [lit. mp 257–258,[1] 249–250 °C;[36] $[\alpha]^{23}$D +5.9° (*c* 0.90),[1] $[\alpha]^{27}$D +3.2° (*c* 5.0, absolute EtOH)[36]], obtained from D(+)-camphor (Eastman white label), mp 177–178 °C, $[\alpha]^{28}$D +40.3° (*c* 1.02) [lit. mp 178–179 °C;[1] $[\alpha]^{20}$D + 40.2° (*c* 1.0),[37] $[\alpha]^{20}$D + 47.3° (*c* 50),[37] $[\alpha]^{23}$D +49.5° (*c* 1.2)[1]], as described earlier,[1] was reduced by $NaBH_4$ and crude **15** was treated with F_3CCO_2H according to the procedures of Corey et al.[14] Lactone **16** was obtained as colorless prisms in 75–80% yield after sublimation at 90–100 °C (10 mm) without prior recrystallization. Resublimed **16** has mp 195–196 °C (lit. 190–196 °C,[14] D isomer 190–191 °C,[38] racemate 192–194 °C[13,19]); $[\alpha]^{25}$D −111.8° (*c* 0.99) [lit.[16a] D isomer $[\alpha]^{19}$D + 116.8° (*c* 2.1, absolute EtOH)]; IR ($CHCl_3$) 1765 cm^{-1}; ^{1}H NMR τ 5.83 (d, J = 3 Hz, 1 H), 8.92 (s, 3 H), 8.95 (s, 3 H); mass spectrum *m/e* 166 (4), 138 (36), 95 (64), 94 (100).

L(+)-8-Hydroxyisoborneol (17). The procedure was adapted from that of Finch and Vaughan.[18] A solution of 4.99 g (0.0301 mol) of **16**, mp 195–196 °C, in 30 ml of tetrahydrofuran (THF; freshly distilled from $LiAlH_4$) was added dropwise to a stirred slurry of 4.30 g (0.113 mol) of $LiAlH_4$ in 80 ml of dry THF, stirred at reflux for 24 h, and cooled. Excess hydride was destroyed by sequential addition of 4.3 ml of water, 4.3 ml of 15% NaOH, and 12 ml of water. Filtration and isolation B (ether) provided 5.05 g (99%) of crude **17**. Sublimation afforded 4.87 g (96%) of **17** as white rosettes: mp 259.5–260.5 °C (lit.[18,19] racemate 273–276 °C); $[\alpha]^{29}$D +38.4° (*c* 1.08); IR ($CHCl_3$) 3620, 3400 cm^{-1} (broad); ^{1}H NMR τ 6.20 and 6.48 (AB, J = 11 Hz, 2 H), 6.43 (m, 1 H), 6.98 (s, 2 H, exchanges with D_2O), 9.07 (s, 3 H), 9.12 (s, 3 H); mass spectrum *m/e* 152 (6), 109 (16), 108 (100), 95 (67), 94 (33), 93 (30), 67 (19), 55 (22).

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.58; H, 10.59. Found (B): C, 70.32; H, 10.51.

L(+)-8-Hydroxyisoborneol-8,8-d_2 (17-d_2) was prepared in an identical manner by using $LiAlD_4$ (Metal Hydrides, Inc.) as the reductant. Diol **17**-d_2 has mp 250.0–250.3 °C; IR ($CHCl_3$) 3620, 3400 (broad), 2190, 2095 cm^{-1}; ^{1}H NMR like that of **17** without the τ 6.20 and 6.48 AB quartet; mass spectrum *m/e* 154 (5), 153 (5), 110 (30), 109 (93), 108 (22), 95 (100), 94 (58), 93 (19), 69 (21), 67 (15), 55 (22).

L(−)-2,8-Epoxybornane (30). A. From Diol 17. A solution of 80 mg (0.46 mmol) of **17**, mp 259.5–260.5 °C, and 154 mg (0.807 mmol) of TsCl, mp 71–72 °C, in 5 ml of dry pyridine was stirred for 25 h and diluted with 150 ml of 0.5 N HCl and 50 ml of pentane. Isolation A (pentane) left 60 mg (86%) of **30** as an oil. Fractional sublimation afforded 50 mg (72%) of pure **30** as white rosettes: mp 135–136 °C (lit. racemate 164–167,[18] 172–174 °C[19]); $[\alpha]^{23}$D −22.0° (*c* 1.10); IR (CCl_4) 1045, 1005 cm^{-1}; ^{1}H NMR (CCl_4) τ 6.28 and 6.52 (AB, J = 8 Hz, 2 H), 6.32 (d, J = 3 Hz, 1 H), 9.03 (s, 3 H), 9.13 (s, 3 H).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found (B): C, 79.00; H, 10.54.

B. From Keto Tosylate 26. A solution of 114 mg (0.370 mmol) of **26**, mp 109–110 °C (see below), in 25 ml of THF was treated with 14.2 mg (3.80 mmol) of $LiAlH_4$ and refluxed for 12 h. Excess hydride was destroyed by dropwise addition of water followed by 5 ml of concentrated NaOH, and isolation A (ether) followed by fractional sublimation afforded 47 mg (82%) of **30**, mp 135–136 °C, identical with the sample described above.

L(−)-8-Hydroxycamphor *p*-Toluenesulfonate (26). A cold (0 °C) solution of 63 mg (0.38 mmol) of **25**, mp 230–233 °C (preparation described below), in 1 ml of dry pyridine was treated with 76 mg (0.39 mmol) of TsCl and stirred at 0 °C for 2 h and at ca. 23 °C for 0.5 h. Isolation B (ether; 5% $NaHCO_3$ and 1% HCl washing) afforded 117 mg (97%) of **26** as a yellow oil. Recrystallization from ether–hexane yielded 96 mg (80%) of pure **26** as colorless needles: mp 109–110 °C (lit.[19] racemate 73–74 °C); $[\alpha]^{23}$D −69.7° (*c* 0.68); IR ($CHCl_3$) 1733 cm^{-1}; ^{1}H NMR τ 2.27 and 2.68 (A_2B_2, J_{AB} = 8 Hz, 4 H), 6.30 (s, 2 H), 7.57 (s, 3 H), 8.97 (s, 3 H), 9.13 (s, 3 H).

Anal. Calcd for $C_{17}H_{22}O_4S$: C, 63.32; H, 6.87; S, 9.94. Found (B): C, 63.51; H, 6.64; S, 9.86.

L(+)-8-Hydroxyisoborneol 8-Benzoate (19). A solution of 4.34 g (0.0310 mol) of BzCl (Eastman white label) in 15 ml of PhH (distilled from P_2O_5) was added dropwise to a stirred solution of 4.80 g (0.0282 mol) of **17**, mp 259.5–260.5 °C, in 2.68 g (0.0338 mol) of pyridine (distilled from BaO) and 250 ml of PhH. The stirred solution was heated under reflux for 47 h (pyridine hydrochloride precipitated), cooled, and washed sequentially with brine, 10% $NaHCO_3$, and brine. Each aqueous wash was extracted with ether, and the combined organic phases were dried (Na_2SO_4) and evaporated in vacuo to afford 8.37 g of an oily mixture of esters which was chromatographed on Baker silica gel (60–200 mesh) using cyclohexane–ether mixtures.

The 13:1 cyclohexane–ether fractions afforded 1.68 g (16%) of **20** as a semisolid, the ^{1}H NMR spectrum of which was identical with that of a purified sample. A portion was recrystallized from pentane to afford pure **dibenzoate 20** as colorless prisms: mp 71.5–72.0 °C; $[\alpha]^{24}$D +28.5° (*c* 1.10); IR ($CHCl_3$) 1715 cm^{-1} (broad); ^{1}H NMR τ 1.95–2.23 and 2.58–2.97 (m, 10 H), 5.07 (t, J = 5 Hz, 1 H), 5.26 and 5.65 (AB, J = 11.5 Hz, 2 H), 8.88 (s, 3 H), 8.91 (s, 3 H); mass spectrum *m/e* 136 (9), 109 (23), 105 (100), 77 (67).

Anal. Calcd for $C_{24}H_{26}O_4$: C, 76.17; H, 6.92. Found (S): C, 76.31; H, 6.84.

The 5:1 and 4:1 cyclohexane–ether fractions afforded 6.61 g (85%) of a mixture of **19** and **21**, mp 90–94 °C, the former preponderant [ca. 11:1 estimated from the result of the oxidation described below or from integration of the 2-H resonances at τ 5.20 (**21**) and 6.37 (**19**) in the spectrum of the corresponding d_2 sample]. Recrystallization of an early fraction from ether–pentane afforded an analytical sample of **19** as white rosettes: mp 100.2–100.8 °C; $[\alpha]^{27}$D +16.8° (*c* 1.00); IR ($CHCl_3$) 3610, 3500 (broad), 1715 cm^{-1}; ^{1}H NMR τ 2.03–2.20 and 2.57–2.88 (m, 5 H), 5.28 and 5.78 (AB, J = 11.5 Hz, 2 H), 6.37 (m, 1 H), 8.98 (s, 3 H), 8.98 (s, 3 H); mass spectrum *m/e* 152 (35), 109 (24), 108 (100), 105 (73), 95 (28), 93 (27), 77 (32).

Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found (B): C, 74.24; H, 8.14.

Reaction of 5.16 g (0.0307 mol) of diol **17** in PhH with 5.76 g (0.0313 mol) of mesitoyl chloride,[39] bp 65–67 °C (1.5 mm), and 3.20 ml (0.0412 mol) of pyridine by the same procedure at ca. 23 °C produced a mixture of the corresponding mesitoyl esters, chromatography of which afforded 1.57 g (11%) of the **2,8-dimesitoate** as an oil, 1.41 g (15%) of a nearly 50:50 mixture of the 2- and 8-monomesitoates, and 4.46 g

(48%) of the **8-monomesitoate.** Recrystallization of the latter from ether–pentane afforded colorless needles: mp 103–105 °C; $[\alpha]^{28}D$ +11.5° (*c* 1.00); IR ($CHCl_3$) 3630, 3500 (broad), 1720 cm^{-1}; ^1H NMR τ 3.18 (s, 2 H), 5.13 and 5.82 (AB, J = 11.5 Hz, 2 H), 6.35 (m, 1 H), 7.72 (s, 9 H), 9.03 (s, 6 H); mass spectrum *m/e* 147 (79), 119 (32), 108 (50), 95 (23), 93 (36), 91 (49), 84 (49), 54 (45), 41 (100).

Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.90; H, 8.93. Found (B): C, 75.88; H, 8.58.

L(+)-8-Hydroxyisoborneol 8-Benzoate-*8,8-d*$_2$ (19-*d*$_2$) was prepared in an identical manner from **17-*d*$_2$**, and has mp 100.0–100.8 °C; IR ($CHCl_3$) 3610, 3500 (broad), 2150, 2050, 1715 cm^{-1}; ^1H NMR like that of **19** without the τ 5.28 and 5.78 AB quartet; mass spectrum *m/e* 154 (50), 110 (45), 109 (100), 105 (78), 95 (46), 77 (51).

L(−)-8-Benzoyloxycamphor (24). A cold (4 °C) solution of 6.44 g (0.0234 mol) of mixed hydroxy esters **19** and **21** (chromatographed) in 500 ml of Me_2CO (distilled from $KMnO_4$) was treated with 11.7 ml (0.0466 molar equiv of Cr^{VI}) of Jones reagent[40] (a solution of 2.68 g of CrO_3 in 2.30 ml of concentrated H_2SO_4 diluted to 10 ml with water) in one portion with vigorous stirring. The mixture was brought to ca. 23 °C over 3 h, neutralized with 1% NaOH, concentrated to 150 ml, and diluted with 1.6 l. of brine. Isolation A (ether; 1% NaOH washing) afforded 5.78 g (91%) of **24.** Recrystallization from ether–pentane produced pure **24** as white rosettes: mp 102.8–103.5 °C; $[\alpha]^{26}D$ −21.3° (*c* 0.94); IR ($CHCl_3$) 1740, 1720 cm^{-1}; ^1H NMR τ 2.07–2.23 and 2.53–2.87 (m, 5 H), 5.97 (s, 2 H, broad), 8.87 (s, 3 H), 8.98 (s, 3 H); mass spectrum *m/e* 272 (5), 167 (9), 122 (6), 107 (8), 105 (100), 77 (15).

Anal. Calcd for $C_{17}H_{20}O_3$: C, 74.98; H, 7.39. Found (B): C, 75.18; H, 7.38.

The basic extract was acidified to pH 1 with concentrated HCl. Isolation A (ether) afforded 0.513 g (8%) of **8-apoisoborneol-7-carboxylic acid benzoate (29),** mp 98–99 °C. Recrystallization from pentane produced pure **29** as white plates: mp 197.5–198.0 °C; $[\alpha]^{28}D$ +41.7° (*c* 0.96); IR ($CHCl_3$) 3500, 3100 (broad), 1760, 1680 cm^{-1}; ^1H NMR τ −0.67 (broad s, 1 H), 2.17–2.37 and 2.65–3.00 (m, 5 H), 5.21 (m, 1 H), 8.77 (s, 3 H), 8.80 (s, 3 H); mass spectrum *m/e* 122 (100), 105 (100), 77 (76), 51 (38).

Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found (S): C, 71.19; H, 6.81.

Similar oxidation of a mixture of the corresponding monomesitoic esters afforded 91% of **L-8-mesitoyloxycamphor** as an oil, evaporative distillation of which (bath temperature 150 °C, 0.05 mm) produced the analytical sample as a clear oil: IR ($CHCl_3$) 1745, 1725 cm^{-1}; ^1H NMR τ 3.25 (s, 2 H), 5.98 (s, 2 H), 7.75 (s, 9 H), 8.92 (s, 3 H), 9.05 (s, 3 H); mass spectrum *m/e* 147 (100), 119 (41), 91 (62), 55 (52), 41 (51).

Anal. Calcd for $C_{20}H_{26}O_3$: C, 76.40; H, 8.33. Found (B): C, 76.33; H, 8.34.

The basic extract from this oxidation afforded 9% of **L-8-apoisoborneol-7-carboxylic acid mesitoate,** recrystallization of which from pentane produced colorless plates of the pure acid: mp 175.5–176.0 °C; IR ($CHCl_3$) 3520, 3200 (broad), 1715 cm^{-1} (broad); ^1H NMR τ 0.23 (broad s, 1 H), 3.39 (s, 2 H), 5.21 (m, 1 H), 7.83 (s, 9 H), 8.88 (s, 3 H), 9.00 (s, 3 H); mass spectrum *m/e* 95 (22), 94 (35), 55 (22), 43 (100).

Anal. Calcd for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found (S): C, 72.59; H, 7.90.

L(−)-8-Benzoyloxycamphor-*8,8-d*$_2$ (24-*d*$_2$) was prepared identically from **19-*d*$_2$**, and has mp 234.0–235.0 °C; IR ($CHCl_3$) 2200, 1740, 1720 cm^{-1}; ^1H NMR like that of **24** without the τ 5.97 singlet; mass spectrum *m/e* 274 (11), 169 (23), 124 (17), 109 (26), 105 (100), 77 (38).

L(+)-8-Hydroxyisoborneol 8-Triphenylmethyl Ether (18). A solution of 226 mg (1.33 mmol) of **17,** mp 261–262 °C, and 395 mg (1.43 mmol) of Ph_3CCl, mp 113–115 °C, in 2 ml of dry pyridine was warmed on a steam bath for 0.5 h and held at ca. 23 °C for 12 h. Isolation B (ether) afforded 498 mg (91%) of crude **18** as a yellow gum. Recrystallization from ether–hexane produced 469 mg (85%) of pure **18** as colorless crystals: mp 154–155 °C; $[\alpha]^{23}D$ +36.8° (*c* 1.12); IR ($CHCl_3$) 3665, 3500 cm^{-1}; ^1H NMR τ 2.40–2.95 (m, 15 H), 6.52 and 6.98 (AB, J = 10 Hz, 2 H), 6.62 (m, 1 H), 8.93 (s, 3 H), 9.18 (s, 3 H).

Anal. Calcd for $C_{29}H_{32}O_2$: C, 84.42; H, 7.81. Found (B): C, 84.41; H, 7.89.

L(−)-8-Hydroxycamphor Triphenylmethyl Ether (23). A cold (0 °C) solution of 175 mg (0.425 mmol) of **18,** mp 154–155 °C, in 10 ml of dry pyridine was added to a cold (0 °C) solution of 500 mg of CrO_3 in 5 ml of pyridine.[41] After 9 h at ca. 23 °C, isolation B (ether) afforded 158 mg (78%) of a yellow gum. Recrystallization from ether–hexane produced 136 mg (67%) of **23** as colorless crystals: mp 124–125 °C; $[\alpha]^{25}D$ −21.3° (*c* 0.84); IR ($CHCl_3$) 1730 cm^{-1}; ^1H NMR τ 2.50–2.90 (m, 15 H), 7.12 and 7.32 (AB, J = 10 Hz, 2 H), 8.87 (s, 3 H), 9.25 (s, 3 H).

Anal. Calcd for $C_{29}H_{30}O_2$: C, 84.81; H, 7.36. Found (B): C, 84.56; H, 7.39.

L(−)-8-Hydroxycamphor (25). A. From Benzoate 24. A solution of 5.77 g (0.0209 mol) of **24,** mp 102.8–103.5 °C, in 250 ml of 10% methanolic KOH was heated at reflux for 30 h, cooled, concentrated to 150 ml, and diluted with brine. Isolation A (ether) left 3.40 g (97%) of **25** as a white solid. Recrystallization from cyclohexane–ether produced 3.08 g (88%) of **25** as white needles: mp 233–234 °C (lit. D isomer 233–234 °C,[38b] racemate 232–234 °C[18]); $[\alpha]^{28}D$ −24.9° (*c* 1.07), $[\alpha]^{26}D$ −32.6° (*c* 3.00, absolute EtOH) [lit.[38b] D isomer $[\alpha]^{15}D$ +40.7° (*c* 3.07, absolute EtOH)]; IR ($CHCl_3$) 3620, 3450, 1750 cm^{-1}; ^1H NMR τ 6.67 (broad s, 2 H), 7.70 (s, 1 H, exchanges with D_2O), 8.95 (s, 3 H), 9.11 (s, 3 H); mass spectrum *m/e* 168 (2), 108 (100), 95 (34), 93 (63), 67 (41), 55 (42).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found (S): C, 71.13; H, 9.83.

B. From Trityl Ether 23. A solution of 105 mg (0.612 mmol) of **23,** mp 124–125 °C, in 25 ml of saturated methanolic HCl was stirred for 6 h. Isolation B (ether; 5% $NaHCO_3$ washing) afforded 38 mg of crude **25,** mp 184–193 °C. Recrystallization from hexane produced 31 mg (93%) of **25** as colorless crystals, mp 230–233 °C, identical (IR, ^1H NMR) with the product from procedure A.

L(−)-8-Hydroxycamphor-*8,8-d*$_2$ (25-*d*$_2$) was prepared in an identical manner from **24-*d*$_2$**. Ketol **25-*d*$_2$** has mp 233.0–234.0 °C; IR ($CHCl_3$) 3620, 3450, 2170, 2070, 1750 cm^{-1}; ^1H NMR like that of **25** without the τ 6.67 singlet; mass spectrum *m/e* 170 (5), 109 (100), 95 (60), 94 (47), 69 (22), 67 (23), 55 (20).

L(−)-8-Bromocamphor (27). The procedure is modified from that of Finch and Vaughan.[18] To an ice-cold stirred solution of 2.21 g (0.0135 mol) of **25,** mp 233–234 °C, in 10 ml of PhBr was added 2.0 ml (0.0169 mol) of quinoline (distilled from Zn dust) followed by 1.00 ml (0.0150 mol) of PBr_3 (Eastman White Label). After 30 min the ice bath was removed and the yellowish mixture was heated at 130–140 °C for 24 h, cooled, diluted with 25 ml of ether followed by 20 ml of 5% HCl, stirred for 30 min, and diluted with ether. Isolation A (ether) left a residual PhBr solution which was chromatographed through a 2.2 × 65 cm column of Baker silica gel (60–200 mesh) with cyclohexane–ether mixtures to afford 2.20 g (73%) of **27,** mp 80–81 °C. Recrystallization from pentane produced pure **27** as colorless needles: mp 84.5–85.0 °C (lit. 121.5–122.5 °C,[14] racemate 120–122 °C,[18] D isomer 83–85 °C[25]);[23] $[\alpha]^{26}D$ −72.5° (*c* 0.81) [lit. $[\alpha]^{26}D$ −95° (solvent and concentration not reported),[14] D isomer $[\alpha]D$ +76.7° (*c* 4.08)[25]];[23] IR ($CHCl_3$) 1745 cm^{-1}; ^1H NMR τ 6.90 (broad s, 2 H), 8.87 (s, 3 H), 9.08 (s, 3 H); mass spectrum *m/e* 151 (2), 109 (19), 108 (28), 107 (23), 95 (11), 93 (17), 91 (12), 81 (31), 67 (42), 41 (100).

Anal. Calcd for $C_{10}H_{15}BrO$: C, 51.96; H, 6.54. Found (S): C, 51.98; H, 6.56.

L(−)-8-Bromocamphor-*8,8-d*$_2$ (27-*d*$_2$) was prepared in an identical manner from **25-*d*$_2$**, and has mp 83.8–84.3 °C; IR ($CHCl_3$) 1745 cm^{-1}; ^1H NMR like that of **27** without the τ 6.90 singlet; mass spectrum *m/e* 153 (2), 109 (32), 108 (10), 95 (15), 93 (9), 81 (24), 69 (35), 41 (100).

L(−)-Camphor (31). The procedure was adapted from an analogous one of Kuivila et al.[21] To 800 mg (19.0 mmol) of $LiAlH_4$ in 50 ml of peroxide-free ether was added in one portion 15.0 g (46.2 mmol) of $(n\text{-}Bu)_3SnCl$ (Aldrich), and the mixture was stirred at reflux for 4 h, diluted with ether and 100 ml of cold saturated potassium sodium tartrate, and extracted with ether which was washed with brine, dried ($MgSO_4$), and removed in vacuo. The residual liquid was distilled at 76–78 °C (0.5 mm) [lit.[21a] 81 °C (0.9 mm)] to afford 8.12 g (60%) of $(n\text{-}Bu)_3SnH$. A solution of 4.50 g (0.0154 mol) of this hydride in 2 ml of ether was added with stirring to an ether solution of 2.84 g (0.0124 mol) of **27,** mp 84.5–85.0 °C, and the solution was stirred in the dark at ca. 23 °C for 24 h, diluted with pentane, washed with brine, dried ($MgSO_4$), and evaporated. Sublimation at 100 °C (752 mm) afforded 2.00 g (106%) of crude camphor, mp 167–172 °C, which was filtered through a 1.4 × 53 cm column of Woelm grade I Al_2O_3 with pentane to yield 1.66 g (87%) of L-camphor, mp 174–176 °C. A small portion was resublimed to afford a sample with mp 176.9–177.5 °C; $[\alpha]^{28}D$ −41.1° (*c* 1.04) [lit. mp 177–178 °C;[42] $[\alpha]^{25}D$ −42.0° (*c* 0.12, absolute EtOH);[42] $[\alpha]^{32}D$ −44.8° (*c* 1.82[17]]; IR ($CHCl_3$) 1740 cm^{-1}; ^1H NMR τ 9.04 (s, CH_3-9), 9.09 (s, CH_3-10), 9.17 (s, CH_3-8);[24,27] mass spectrum (v) *m/e* 152 (27), 137 (4), 109 (31), 108 (50), 95 (100), 81 (26), 69 (41), 55 (30), 41 (51).

L(−)-Camphor-*8,8,8-d*$_3$ (31-*d*$_3$) was prepared from **27-*d*$_2$** in an identical manner by using $LiAlD_4$ for reduction of $(n\text{-}Bu)_3SnCl$. The camphor-*d*$_3$ has mp 176.5–177.0 °C; IR ($CHCl_3$) 1740 cm^{-1}; ^1H NMR τ 9.04 (s, 3 H), 9.09 (s, 3 H); mass spectrum (v) *m/e* 155 (50), 140 (4),

137 (2), 112 (37), 111 (83), 98 (100), 95 (37), 81 (41), 69 (69), 58 (18), 55 (19), 44 (17), 41 (70).

Comparison of the mass spectrum of L-camphor-*8,8,8-d*$_3$ with that of D-camphor in the *m/e* 151–158 region indicated that the former contained 97.5% of the d_3 species, 2.5% of the d_2 species, and negligible amounts of d_1 and d_0 species, ±0.5% (average of 17 scans of each spectrum).[43]

Reduction of D-9-bromocamphor by tri-*n*-butyltin hydride[26] was carried out by the same procedure using 285 mg (1.23 mmol) of 9-bromocamphor, mp 93–95 °C,[1] and 657 mg (2.26 mmol) of the distilled hydride to afford 131 mg (70%) of crude (once sublimed) D-camphor, mp 161–167 °C.

L(+)-Camphorquinone-*8,8,8-d*$_3$. The procedure was identical with that described for preparation of the D(−)-protio analogue.[1] The diketone-d_3 has mp 198–199 °C (o); IR ($CHCl_3$) 1770, 1760 cm^{-1}; ^{1}H NMR τ 7.38 (d, J = 4.5 Hz, 1 H), 8.90 (s, CH_3-10), 8.93 (s, CH_3-9), no resonance at 9.07[1] (CH_3-8);[27] mass spectrum *m/e* 169 (6), 141 (13), 126 (7), 113 (9), 98 (98), 86 (88), 69 (100).

L(−)-Camphoric Acid-*8,8,8-d*$_3$. The procedure was identical with that described for preparation of the D-(+)-protio analogue.[1] The deuterated acid has mp 187–188 °C (o); IR (KBr) 2900 (broad), 1695 cm^{-1} (broad); ^{1}H NMR (CD_3COCD_3) τ 8.71 (s, CH_3-9), 8.75 (s, CH_3-10), no resonance at 9.12[1] (CH_3-8); mass spectrum *m/e* 157 (30), 139 (40), 112 (40), 111 (44), 71 (86), 70 (66), 69 (62), 41 (100).

D(−)-α-Bromocamphoric Anhydride (1). The procedure is modified from that of Meyer, Lobo, and McCarty.[1] A solution of 0.109 g (6.87 mmol) of Br_2 in 2.0 ml of CCl_4 was treated with 1.85 g (6.87 mmol) of PBr_3 (Eastman Yellow Label, freshly distilled, bp 167–168 °C) in one portion. After 10 min, 651 mg (3.26 mol) of camphoric acid [Eastman White Label, mp 186–187 °C (o)] was added and the mixture was heated at 70–75 °C for 4.5 h to afford a clear solution which was cooled to 60 °C, treated with 0.610 g (3.81 mmol) of Br_2 in one portion, and reheated at 70–75 °C for 7.5 h. The dark red solution was added to 25 g of ice, and the resulting suspension was stirred for 30 min. Isolation B (ether) afforded 773 mg (90%) of an 8.5:1 mixture of the bromo anhydride and camphoric anhydride (determined by integration of the τ 8.60–9.00 region of the ^{1}H NMR spectrum). Recrystallization from $CHCl_3$–ether afforded 537 mg (67%) of **1** as colorless, rhombic crystals: mp 216–217 °C (o) (lit.[1,4] 216 °C); IR ($CHCl_3$) 1820, 1775 cm^{-1}; ^{1}H NMR τ 8.62 (s, CH_3-10), 8.85 (s, CH_3-9), 8.93 (s, CH_3-8); mass spectrum *m/e* 175 (18), 173 (18), 137 (100), 109 (5), 94 (17), 93 (10), 69 (64).

This procedure also converted a 2:2:1 mixture of bromo anhydride, camphoric anhydride, and camphoric acid almost completely to the bromo anhydride.

L(+)-α-Bromocamphoric Anhydride-*8,8,8-d*$_3$ (1-d_3) was prepared from the deuterated camphoric acid in an identical manner, and has mp 216–217 °C (o); IR ($CHCl_3$) 1815, 1770 cm^{-1}; ^{1}H NMR τ 8.62 (s, 3 H), 8.85 (s, 3 H); mass spectrum *m/e* 178 (13), 176 (14), 175 (4), 173 (3), 140 (100), 112 (5), 97 (9), 96 (6), 94 (6), 93 (4), 69 (70).

Rearrangement of L(+)-α-Bromocamphoric Anhydride-*8,8,8-d*$_3$. A 0.525-g (1.97 mmol) sample of anhydride 1-d_3, mp 216–217 °C, was treated with 100 ml of 15% Na_2CO_3 in the manner described by Meyer, Lobo, and McCarty for the D-protio analogue.[1] This afforded 0.069 g (21%) of labeled laurolenic acid: IR ($CHCl_3$) 3300 (broad), 2200, 1700 cm^{-1}; ^{1}H NMR τ 8.41 (broad, 2-CH_3 and 3-CH_3), 8.77 (s, 1-CH_3). Repeated integration (32 scans) of the τ 8.41 and 8.77 resonances showed their relative intensities to be 85.8:14.2 ± 0.5, respectively.

The **L(−) bromo lactone** of this labeled laurolenic acid was prepared as described[29] for the (+)-protio bromo lactone. It has mp 194.0–194.5 °C, identical with that of the corresponding D(+) lactone,[1,29] and shows IR ($CHCl_3$) 2350, 2215, 1790 cm^{-1}; ^{1}H NMR τ 8.38 (s, 2-CH_3), 8.50 (s, 3-CH_3), 8.75 (s, 1-CH_3); mass spectrum (v) *m/e* 128 (62), 112 (100), 96 (4), 94 (3), 93 (4), 91 (2). Repeated integration (64 scans) of the τ 8.38, 8.50, and 8.75 methyl resonances showed their intensity ratio to be 98.9 ± 1.7:71.2 ± 1.7:29.9 ± 1.0.

Comparison of the mass spectrum of the bromo lactone of this deuterated laurolenic acid with that of the bromo lactone of D(+)-laurolenic acid in the *m/e* region 124–130 showed the former to consist of 96.3% of the d_3 species, 2.6% of the d_2 species, 0.8% of the d_1 species, and 0.4% of the d_0 species, ±0.7% (average of 11 scans of each spectrum).[43]

In addition 0.197 g (49%) of **L(+)-camphanic acid-*d*$_3$** was obtained from the rearrangement. This was recrystallized from water to afford colorless needles: mp 200.0–200.3 °C; IR ($CHCl_3$) 3300 (broad), 2210, 1790, 1735 cm^{-1}; ^{1}H NMR τ 7.95 (m), 8.86 (s, CH_3-10), 8.90 (s, CH_3-9), no resonance at 8.98[1] (CH_3-8); mass spectrum *m/e* 173 (20), 155 (16), 141 (40), 112 (74), 86 (100), 43 (74), 41 (80).

Registry No.—**1**, 10333-96-7; **1**-d_3, 60966-74-7; **2**-d_3, 60966-75-8; **3**, 10333-98-9; **12**, 60934-69-2; **13**, 60934-70-5; **14**, 10334-07-3; **15**, 40724-61-6; **16**, 60966-76-9; **17**, 60966-77-0; **17**-d_2, 60934-71-6; **17** 2-monomesitoate, 60934-72-7; **17** 8-monomesitoate, 60934-73-8; **18**, 60966-78-1; **19**, 60934-74-9; **19**-d_2, 60949-92-0; **20**, 60934-75-0; **21**, 60934-76-1; **23**, 60966-79-2; **24**, 60934-77-2; **24**-d_2, 60934-78-3; **25**, 60966-80-5; **25**-d_2, 60966-81-6; **26**, 60966-82-7; **27**, 60966-83-8; **27**-d_2, 61008-83-1; **29**, 60934-79-4; **30**, 60966-84-9; **31**, 464-48-2; **31**-d_3, 60966-85-0; F_3CCO_2H, 76-05-1; $LiAlH_4$, 16853-85-3; $LiAlD_4$, 14128-54-2; L-8-mesitoyloxycamphor, 60934-80-7; L-8-apoisoborneol-7-carboxylic acid mesitoate, 60934-81-8; Ph_3CCl, 76-83-5; D-9-bromocamphor, 10293-09-1; tri-*n*-butyltin hydride, 688-73-3; D-camphor, 464-49-3; L(+)-camphorquinone-*8,8,8-d*$_3$, 61008-84-2; L(−)-camphoric acid-*8,8,8-d*$_3$, 60966-86-1; L(−)-laurolenic acid-d_3 bromo lactone, 10353-25-0.

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(16) Cf. (a) Y. Asahina and M. Ishidate, *Ber.*, **68**, 555 (1935), and (b) Y. Asahina, M. Ishidate, and T. Sano, *ibid.*, **69**, 343 (1936), for results which confirm the structure and configuration of the enantiomeric D-(+)-lactone. That the rearrangement product is indeed the (−) form is shown by the present work.[17]
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(30) This argument applies, of course, only to a symmetric ion **11**. The observed isotopic distribution *could* result from a mechanism in which C-2–methyl bond breaking and C-3–methyl bond formation are both complete prior to the start of decarboxylation or lactonization (see below), i.e., through an ion formally similar to **11**, provided that the two carboxylates are differently solvated, as could occur if some or all of the decarboxylation begins before solvent reorganization around **11** is complete. There is no evidence to exclude this as a viable alternative to the sequences proposed in the main discussion. Unequal isotope distribution could also result from an ion **11** in which there is preferential intramolecular "solvation" of the cationic C-2 by one of the carboxylates, as could occur if some or all of the decarboxylation begins before reorientation of the two carboxylates of **11** is complete. None of our evidence would distinguish this situation from the β-lactonizations which are discussed, so it is not considered separately here. Finally, unequal isotope distribution could also arise from an ion which in other respects is similar to **11**, but which is specifically monoprotonated at either the α- or γ-carboxylate, but this seems unlikely at pH 11 inasmuch as the second dissociation of the bromo diacid probably has a pK_a of about 6; cf. footnote 39 of ref 1.
(31) The three other stereoisomers of **34/35**, each of which must be examined as a pair of isotopic isomers differing in the location of methyls 8 and 10, are not considered because there is no apparent reasonable mechanism for their formation under these reaction conditions.
(32) Another hypothetical mode of decomposition of lactones **34** and **35** to laurolenic acid would be by [2 + 2] cycloreversion of the β-lactone system, but this is considered improbable because under comparable conditions simple β-lactones hydrolyze rather than expel CO_2 in such a manner. For example, at 100 °C in water *cis*-2-hydroxycyclopentanecarboxylic acid lactone affords no cyclopentene but only hydroxy acids.[33] Thermal cycloreversion of analogous β-lactones is normally observed only at higher temperatures and in the absence of a nucleophilic solvent; cf. ref 34.
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A Vanished Substituent Effect Predicted by the Kirkwood–Westheimer Electrostatic Field Model

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syn- (**2b**) and *anti-* (**3b**) *cis*-11,12,dichloro-9,10-dihydro-9,10-ethanoanthracene-1-carboxylic acids have been synthesized. Geometric assignments were made on the basis of their ^{13}C chemical shifts along with those of model compounds. The apparent pK_a's of **2b** and 9,10-dihydro-9,10-ethanoanthracene-1-carboxylic acid (**9b**) (previously reported by Stock) in aqueous ethanol are identical within experimental error. This result is predicted by the Kirkwood–Westheimer equation and is a consequence of the angular orientation of the dipole with respect to the site of ionization. The apparent pK_a of **3b** is approximately 0.47 units smaller than that of **9b**. These results are briefly discussed in terms of the Kirkwood–Westheimer electrostatic field model.

The Kirkwood–Westheimer expression[1] for calculating electrostatic effects of dipolar substituents upon acidities of carboxylic acids includes the angular orientation of the dipole with respect to the site of ionization (eq 1).

$$\log \frac{K}{K_0} = \frac{eu \cos \theta}{2.30\, kTR^2 D_E} \quad (1)$$

That both the sign and magnitude of dipolar substituent effects can be dependent upon the angular disposition of the dipole relative to the carboxylate group has been experimentally verified.[2]

An interesting consequence of this electrostatic model is the prediction that for a dipole oriented perpendicular to a line joining its midpoint to the ionizing proton, the substituent effect should vanish. That is, for $\theta = 90°$, $K = K_0$. We report here a case where the resultant dipole of a vicinal dichloride possesses this geometric characteristic.

Results

Methyl *syn-cis*-11,12-dichloro-9,10-dihydro-9,10-ethano-1-anthroate (**2a**) and the corresponding anti-cis dichloro isomer **3a** were prepared by the cycloaddition of *cis*-1,2-dichloroethene and 1-methyl anthroate (**1**). The isomers were separated by a combination of chromatography and crystallization. Progress in effecting the separation was followed by NMR monitoring of the relative intensities of the C_9 proton signals (peri to CO_2Me), the singlets for which lie downfield (δ 6.12 for **2a** and 5.73 for **3a**) from the remaining nonaromatic protons. The geometric assignments for **2a** and **3a** were made