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1976

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CAMPHORAE: CHIRAL INTERMEDIATES FOR THE TOTAL
SYNTHESIS OF STEROIDS

by

Federico Carlos Aréjola Gaeta

A THESIS SUBMITTED
IN PARTIAL FULFILLMENT OF THE
REQUIREMENTS FOR THE DEGREE OF

Doctor of Philosophy

Thesis Director's Signature:

A handwritten signature in black ink, appearing to read "Robert V. Stevens", written over a horizontal line.

Houston, Texas

December, 1976

DEDICATION

To my loving wife Terenia for her support,
encouragement, and hard work during the last four
and a half years. Also to my parents and family
who provided me boundless opportunity.

ACKNOWLEDGEMENTS

It is indeed an honor and a pleasure to have worked so closely with Robert Velman Stevens, a man who I respect and admire. His genius provided a formidable problem, and his guidance coupled with the freedom of expression extended to me have made the present work a reality.

I also would like to extend my gratitude to those coworkers who made the past few years pleasant, and to Fred Wudl, my first research director, who first recognized in me the desire and potential to become a good chemist.

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ARTZENDANA, ZORTZENDA

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INTRODUCTION

Steroids are a class of compounds generally possessing four fused rings. In a formal sense they could be considered derivatives of the hydrocarbon 1,2-cyclopentanoperhydrophenanthrene (1); hence the first three rings (A-C) are usually six-membered, while the fourth (D) is five-membered. Inspection of the skeleton of (1) reveals the awesome presence of six contiguous asymmetric centers (i.e. at the ring fusions) bringing the number of possible isomers to 2^6 or 64!

In addition, further substitutions on the remaining sites would augment this number exponentially. As will be seen, these compounds exhibit a wide variety of functionalization.

A common feature of many steroids is the trans-anti-trans-anti-trans backbone shown by the heavy line in (2) (5α -androstane, $R=CH_3$). Examination of a molecular model for such a substance reveals that it is rigid with as few eclipsing interactions as possible, thus gaining in thermodynamic stability. The trans terminology refers to the geometrical disposition of the AB, BC, and CD ring fusions, whereas anti relates to the 9,10- and 8,14-geometries.

The numbering system in (1) is self-explanatory but, in addition,

the 10- and 13-positions often bear functional groups other than hydrogen (usually a methyl group), and these are numbered 19- and 18- respectively. The spatial arrangement of a steroid molecule (such as (2)) dictates that there be two faces. By convention, groups on the "top" face such as R are referred to as being " β ", while those on the opposite face are " α ".

Other commonly found geometries among steroidal compounds may be typified by the estrogen (3), androgen (4), and coprostan (5) skeletons. It should be noted that in the latter, the AB ring fusion is cis creating a definite "corner" in the molecule. As a consequence of the rigidity of systems such as (2), (3), and (4) it can

be predicted with great certainty what conformations certain substituents will have (i.e. axial or equatorial). For example, in testosterone (4) the 13β -methyl group is axial since it is part of a conformationally rigid system. On the other hand, the 17β -hydroxyl is considered to be quasi-equatorial due to a somewhat more relaxed conformational requirement in a pseudorotating (and, therefore, much less rigid) D ring.

Steroid compounds are ubiquitous in most living organisms, and play vital roles in their development and maintenance. It is beyond the scope of this writing to undertake a discussion of the mechanism of action of these substances. The reader is directed to more specialized publications dealing with this important aspect of the steroid field.¹

As noted previously, steroids have certain common skeletal characteristics. Moreover, these substances can be further classified by the nature and position of their substituents into a number of principal families. Since much of their chemistry has been reviewed by the Fiesers² in their outstanding account "Steroids", it would not be appropriate to embark in any detailed discussion. Rather, we shall restrict ourselves only to those aspects of their chemical features which give rise to the different families.

The simplest of the steroids are those which contain one or two aromatic rings (usually the A or AB rings). Representative of this class are the estrogens of which estrone (3) and equilinenin (6) are of particular importance being female sex hormones for mammals.

A considerably more complex family of steroids comprises the androgens, which are the male sex-hormones of mammals. Testosterone (4), for example, in contrast to the previous class of steroids has six contiguous asymmetric centers, and a C-10 β -methyl substituent.

A steroid class of comparable complexity to the androgens are the progestogens, of which progesterone (7), the hormone of pregnancy, is a representative example. The corticosteroids (e.g. cortisone (8)) are also representative of this class. A distinguishing feature of these compounds is the presence of a two-carbon side chain at C-17. In addition, the corticosteroids exhibit a hydroxyl or keto function at C-11.

The principal precursor from a biogenetic point of view of all the above classes of steroids is cholesterol (9). The sterols are

9 10 11

present in both animal and plant organisms, and can be distinguished by the lengthening of the C-17 side chain. Other steroids bearing a long C-17 side chain are the bile acids, of which cholic acid (10) is representative.

An increasingly important sterol from a commercial standpoint is stigmasterol (11). It is found in large concentrations in soybeans, and a degradation procedure to progesterone (7) has been known for years.² A schematic representation of this process is shown on the next page.

DEGRADATION OF STIGMASTEROL TO PROGESTERONE

There is a group of steroids that exhibit cardiac action, for instance digitoxigenin (15) and bufalin (16). These contain a γ - or δ -lactone moiety for a side-chain at C-17. A sapogenin which is also of commercial importance is diosgenin (17). Its isolation from yams, and its degradation by Marker² to pregnenolone acetate (21) have been responsible for the establishment of a chemical industry in Mexico. Regulations on the import of this substance by the Mexican government in recent times has provided impetus to develop a commercial process based on stigmasterol (11) (vide supra).

Finally, other types of plant steroids are represented by the alkaloids conessine (22) and solanidine (23).

MARKER DEGRADATION OF DIOSGENENIN TO PREGNENOLONE ACETATE

The biosynthesis of steroids was suggested as arising from squalene-2,3-oxide (24) in two independent publications by Stork³ and Eschenmoser.⁴ This stereoelectronic theory which predicted the correct cyclization of squalene oxide to produce in a totally stereospecific manner lanosterol (25) became known as the Stork-Eschenmoser hypothesis. It is remarkable that a polyolefin with no asymmetric centers gives rise to a molecule with no less than seven! In this respect, enzymatic control of the reaction has to be of paramount importance. The template-like action of the enzyme lanosterol cyclase has been suggested to maintain the steroidal ring B carbon atoms in a boat form. The correctness of this hypothesis has been demonstrated

(in vitro) in a series of elegant papers by van Tamelen⁵ and Johnson⁶, who developed an approach to the total synthesis of steroids based on the cyclization of synthetic polyolefins somewhat resemblant of squalene.

The biosynthetic pathways to squalene have been somewhat elucidated, and Cornforth⁷ has written a review on the subject. Two matters of controversy are (a) the difficulty of asserting a definitive pathway to the known squalene precursor presqualene alcohol pyrophosphate (27) from two molecules of trans-trans-farnesyl pyrophosphate (26); and (b) a rationale for the efficient conversion of (27) to squalene (28) in vivo under solvolytic conditions which in vitro afford complex mixtures of products. To this end a number of competent workers have expended a great deal of time and energy,⁸ and their studies have not been completed.

Total steroid synthesis has been a fertile area in organic chemistry since the early 1930's when structures for many of these substances were elucidated. The literature on the total synthesis of steroids is massive, and, therefore only those references which bear the greatest significance to this thesis will be dealt with in any detail. Furthermore, the recent publication⁹ of three comprehensive monographs on the subject makes it unnecessary to pursue the matter any further than needed. The merits of carrying out total syntheses have been discussed previously by Stevens¹⁰ from a scientific as well as philosophical point of view.

In an area of organic synthesis so formidably challenging as the steroid field, there are a number of problems which can be clearly defined. With regard to steroids, some of these problems are listed below:

- (a) the C,D-trans-fused ring junction;
- (b) the trans-anti-trans-anti-trans skeletal arrangement;
- (c) introduction of oxygen functionality at C-11;
- (d) introduction of functionality at C-17;
- (e) the feasibility of synthesizing a variety of steroids from a common intermediate;
- (f) the stereochemistry of the C-10 methyl group;
- (g) the length of the synthesis;
- (h) the synthesis of optically active steroids.

As will be demonstrated (vide infra) any approach that embodies an efficient solution to these problems is worthy of the highest consideration. Some of the problems mentioned have general solutions ((b), (c), (d), (e), and (f) above), provided that sound retrosynthetic planning is used in the preparation of intermediary precursors (cf. historical section).

In this thesis an approach to the synthesis of steroids is presented which takes advantage of the natural chirality of (-)-camphor (29). Hence, our approach takes advantage of (a) the natural chirality of camphor, and (b) the topological arrangement of its substituents (Figure 1). By employing known methods of functionalizing camphor

we have synthesized the key (-)-ketoester (31) from the previously reported (-)- π -bromocamphor ($\pi=C-9$) (30). Beckmann fragmentation of oxime (32) afforded the optically active cyanoester (33), which underwent smooth cyclization to produce chirally pure hydriindanone (34). As will be seen, (34) can be synthesized in a relatively few number of steps.

As can be seen, dione (37) results from heating of a mixture of cis-, and trans-fused diketones resulting in epimerization of the cis-fused material to the thermodynamically more stable trans-fused isomer (37). The trans-fused decalin system was visualized as capable of being transformed into a tetracyclic D-homosteroid which, in turn, could be subjected to D-ring contraction, forming the desirable C,D-trans-fused steroid (Scheme II).

The cyclization of (39) to (40) was a very low yielding process, and very sensitive^{11e} to impurities found in AlCl_3 . Hence, if the reaction was run with ordinary reagent the exclusive product formed was the trans-anti-cis-methoxyhydrochryseneone (40a).^{11a} A further point to be made on this approach regards the lack of stereospecificity

of the Dieckmann condensation (i.e. (41) $\rightarrow$ (42)). This complication makes the approach unattractive as a method of synthesizing steroids.

Absence of an angular methyl group at C-13 is obvious in the above scheme, and its introduction should be accomplished at some stage unless one desires 18-norsteroids (13-desmethyl). Johnson addressed himself to this matter by further utilizing the ketone (40) (Scheme III). Condensation of the tetracyclic ketones (40) and (40a) with benzaldehyde led to the corresponding benzylidene derivatives (43) and (43a). The ensuing angular methylation was accomplished with potassium tert-butoxide in its conjugate acid as the solvent and iodomethane. Unfortunately, the trans-C,D isomer was the minor product; nevertheless, the mixture could be carried through the steps delineated in Scheme II to produce the three isomers (45), (46), and (47) of O-methylestrone.

(Scheme III)

Although the above approaches to the total synthesis of steroids have major drawbacks, they helped pave the way for the monumental effort which was to be undertaken by Johnson and his collaborators

during their next decade. Their work can be considered as consisting of five phases: (1) preparation of tetracyclic intermediates; (2) reduction of these to the desired trans-anti-trans-isomers; (3) reduction of the aromatic ring; (4) angular methylation and D-ring contraction; and (5) further functionalization of the steroid nucleus.

A primary objective in Johnson's continuing steroid saga was the synthesis of tetracyclic intermediates with varying degrees of unsaturation. This unsaturation was desired in order to further manipulate these substances in a manner conducive to a trans-anti-trans skeletal arrangement. Since the previous approach was unsatisfactory, a new one was originated which also utilized naphthalene derivatives as building blocks for preformed C,D-rings. The methoxytetralone (49) had been prepared previously¹³ from 1,6-dihydroxynaphthalene dimethyl ether (48), and utilized by Robinson¹⁴ in his synthesis of epi-androsterone.

Annulation of a 3-pentanone unit onto (49) was accomplished by means of Mannich base (50) in the presence of methoxide ion, generating anion (51). This intermediate was capable of further annulation with methyl vinyl ketone (Scheme IV). This resulted in an elegant synthesis of tetracycle (52), thus completing the first stage of Johnson's

hydrochrysene approach.¹⁵

(Scheme IV)

Johnson's next synthetic goal^{15a, 16} was elaborating pathways which, utilizing (**52**), would lead to the trans-anti-trans-skeletal arrangement of steroids. Catalytic hydrogenation of the dienolether (**53**), obtained by treatment of (**52**) with triethylorthoformate in the presence of acid, gave a good yield of (**54**). Conditions for this transformation were quite specific (6% palladium on strontium carbonate) and, after hydrolysis of the $\Delta^{2,3}$ -enol ether, attention was focused on reduction of the $\Delta^{8,9}$ -double bond of (**55**) (Scheme V). Since reduction of (**55**) by hydrogen (mediated by poisoned metal catalysts)

(Scheme V)

afforded the trans-anti-cis-arrangement (as expected), a method of choice was obviated by the observation of Wilds and Nelson¹⁷ that such systems on dissolving metal reduction afforded primarily thermodynamic products. On ketalization of (55), the Wilds-Nelson procedure was applied and, after hydrolysis of the ketal, ketone (56) was obtained. Thus, a remarkable series of transformations efficiently gave rise to four contiguous asymmetric centers culminating this aspect of Johnson's approach.

As pointed out previously, a phase of this work required that methods of reduction be developed for compounds such as (56) in order

to obtain precursors transformable into a steroid. Reduction of the aromatic nucleus was best accomplished by alkali metals in ammonia in the presence of an acid (Scheme VI). Hence, reduction of (56) with

(Scheme VI)

lithium in liquid ammonia in the presence of ethanol afforded a mixture of enone-alcohols (57) and (58) in a ratio of two to three, respectively. That two isomers were formed was of no consequence since they could be reduced further to the ketone (59) in good yield using 10% palladium on charcoal. However, in order to achieve a desirable C,D-trans-geometry in the reduction of (57) a catalytic amount of base was required. An obvious question at that time must have been the intriguing possibility

of reducing the tetracyclic material (52) obtained from "double-barrel" annulation of methyl vinyl ketone and its equivalent (50) onto the C,D-precursor (49). This was accomplished in good yield (Scheme VI) by an extension of work previously described. It must have been a gratifying experience for Johnson's research group to obtain these results, particularly since the overall yield of ($\pm$)-18-nor-D-homoepiandrosterone (59) from (52) was on the order of 30%, without purification of the intermediates - indeed, a remarkable accomplishment.¹⁸

Introduction of an angular (C₁₃) methyl group was perhaps the most frustrating aspect of this classic piece of work.^{11a, 18, 19} Condensation of (59) with furfural followed by protection of the alcohol as the tetrahydropyranyl ether proceeded satisfactorily (Scheme VII). Angular methylation was then accomplished with methyl iodide and base, and as before (cf. Scheme III) an epimeric mixture obtained with a ratio of desired (60) to undesired (61) ketones of one to two, respectively. The ring contraction was again effected in much the same manner as before (cf. Scheme III). Overall, the yield of ($\pm$)-epiandrosterone (63) from 5-methoxy-2-tetralone (49) was 1%; that of the "unnatural" isomer ((64), 13 α -CH₃) was 3%. This completed synthetic efforts directed towards the synthesis of a full-fledged steroid molecule.

As can be seen, introduction of a 13 β -methyl group is not an easy task. One could say, in fact, that this has been the gloom and doom of many a steroid synthesis. It is not unusual, then, to note that this type of reaction has been the subject of numerous investigations²⁰ (vide infra). Johnson devoted some time to this as well.²¹ Reasoning that removal of the C-11 axial hydrogen would lessen steric hindrance

(Scheme VII)

towards attack from the β -position, Johnson synthesized the $\Delta^{9,11}$ -
 analog of (**59**) (i.e. **65**). Introduction of a " β " methyl group at C-13
 in (**65**) to yield 13,14-trans-fused (**66**) was quite facile.

The final phase of Johnson's steroid synthesis that will be discussed deals with development of methods which introduce oxygen substituents at C-11.^{19b, 22} Reduction of (56) followed by acetylation provided the key intermediate (67). The reaction of systems such as (67) with lead tetraacetate was known²³ to proceed selectively at C-12 to afford complex mixtures of acetoxy derivatives. Heating of the mixture in acetic acid provided the conjugated olefin (68) (Scheme VIII) in good yield. Oxidation of (68) with a variety of peracids yielded the 11,12-epoxide (68a) which was carried on to the next step without isolation. Dissolving-metal reduction of this compound gave a mixture of 11 β -(31%) and 11 α -alcohols (11%), (70) and (71). Alternatively, triol (69) could be obtained by treatment of the crude epoxide (68a) with acetic acid and subsequent base hydrolysis. Hydrogenolysis of (69) afforded the 11 β -alcohol (70). In addition, pyrolysis of epoxide (68a) afforded the 11-keto compound (72) in moderate yield. Further manipulations of these materials (i.e. reduction, methylation, and ring contraction) afforded (±)-3 β ,11 β -dihydroxyandrostan-17-one (73) and the corresponding 13 α -methyl isosteroid (74). The level of complexity at this stage had risen to eight asymmetric centers, climaxing the last

(Scheme VIII)

stage of Johnson's hydrochrysene approach. Further additions to and modifications of this approach led to the synthesis of steroidal precursors which made it possible to synthesize a virtually limitless number of natural (racemic) steroids. Later work focused on the synthesis of testosterone,²⁴ progesterone,²⁵ aldosterone,²⁶ cholesterol,²⁷ and the steroidal alkaloids conessine^{20a, 25b} and veratramine.²⁸

Other research groups have made use of the hydrochrysene approach, notably those of Kutney,²⁹ and Nagata.³⁰ However, in the interest of space these efforts will only receive the honorable mention given. Nagata's approach is also of a historical interest since it laid a background for the development of his important contributions on the

hydrocyanation reaction.³¹

A unique and elegant approach to a non-aromatic steroid is that of Woodward and collaborators.³² These investigators opted, as well, to begin their synthesis with a preformed C,D-intermediate (78) (Scheme IX). The synthesis of this material was accomplished rapidly by first reacting 4-methoxytoluquinone (75) with butadiene. Although the initial adduct was of course cis-fused, recrystallization from aqueous base afforded the trans-fused dione (76) in an excellent overall yield. Reduction with lithium aluminum hydride (LAH) gave initially a diol, which on acid treatment produced enone alcohol (77). Removal of the hydroxyl group was subsequently accomplished with zinc and acetic anhydride.

(Scheme IX)

Annulation of ring B onto (78) was accomplished by ethyl vinyl ketone (EVK) in the presence of base after activation of (78) via its hydroxymethylene derivative (Scheme X). At this stage the isolated double bond in (79) was osmylated, and the resulting diol (mainly β -diol) converted into the acetonide (80). By this method, the ratio of β to α diols produced was four to one; this ratio was tremendously improved in favor of the β if the, now famous, cis-hydroxylation procedure (silver acetate-iodine in moistened acetic acid) was employed.³³ Catalytic hydrogenation of (80) selectively reduced the prototypical $\Delta^{11,12}$ -double bond (the presence of an A ring is assumed for the purpose of labelling such positions as in the case of an actual steroid). The resulting enone (81) was then condensed with acrylonitrile after blocking the C-6 methylene against carbanion formation. As exemplified by other syntheses (vide infra) the introduction of an A ring in the case of C-10-methyl steroids is not a trivial process, and in this case two isomers (83) and (84) were obtained in a ratio of two to one, respectively. Note that the ratio favors the unnatural configuration of the side chain.

Separation of the isomers (83) and (84) was easily accomplished, and on refluxing with acetic anhydride containing a catalytic amount of sodium acetate, the enol lactone (85) was isolated. Reaction of (85) with methyl magnesium bromide afforded the homosteroid (86). All that remained to be done now was to effect a ring contraction. This transformation was accomplished in two stages. The first stage was the known cleavage of vicinal diols by periodic acid. The intermediate dialdehyde produced was then cyclized unidirectionally by piperidine acetate to produce the steroid (87). This material could

(Scheme X)

be carried on to a number of other steroids and, in a formal sense, represented a general synthetic approach.³⁴

The unidirectionality of the piperidine acetate cyclization is a most striking observation, and is representative of an unwritten formalism (at least to our knowledge) in organic synthesis which dictates that, in general, the directionality in condensations of this type is such as to produce the α,β -unsaturated carbonyl compound resulting from attack on the least hindered electrophilic center.

A major advantage of the Woodward synthesis over those previously described (vide supra) is the unambiguous stereochemical disposition of the C-13 (β) methyl group. Unfortunately, the introduction of an A ring is non-stereospecific if the C-10 β -methyl steroids are desired. A number of efforts have been made to improve the overall scheme, but without significant success. An interesting approach, which was only partially successful, was that of a Monsanto group.³⁵ Their contribution basically showed that the C-10 angular methyl group could be introduced with higher selectivity after D-ring contraction, and in the presence of an A ring fragment.

Syntheses of tricyclic enones analogous to (88) are an attractive target, and the subject of several independent investigations. One such effort was expended by Ireland³⁶ (Scheme XI). The tris-cyanoketal (91) could be synthesized in good yield from 2-methyl-5-keto-1-hexene (90) by standard chemical means. Cyclization of (91) by successive treatment with potassium tert-butoxide followed by strong acid workup, and esterification with methanolic hydrochloric acid, provided (92) in good yield. Reduction of the dienol acetate of (92) with sodium borohydride provided an epimeric mixture (C-9 and C-17) of (93).

Catalytic hydrogenation of the mixture followed by saponification and Jones oxidation afforded a mixture of trans-(major product) and cis-hydrindanones (94). Bromination of (94) followed by hydrazone formation (2,4-dinitrophenylhydrazone), and cleavage³⁷ with methyl pyruvate afforded the enone (95) in good yield.

Ten years ago a group at Columbia University headed by Gilbert Stork described³⁸ a novel approach to the total synthesis of steroids utilizing isoxazole intermediates. Reaction of octalin-dione (96) with isoxazole (97) via the dienolate of (96) produced the intermediate (98) after reduction of the C-17a ketone and hydrogenation with palladium on charcoal in the presence of base (Scheme XII). Raney nickel reduction of the isoxazole nucleus followed by base induced condensation with the concomitant loss of an acetyl group led to enone (99). Here was made the important discovery that on reductive alkylation of enone (99) (lithium in ammonia, followed by methyl iodide) the exclusive product formed was the C-10 β -methyl-seco-D-homosteroid (100). Ketal hydrolysis and base catalyzed condensation afforded the homosteroid (101). This material on ring contraction by a procedure resembling the Demjanov rearrangement (after some simple manipulations) afforded (+)-progesterone (7). The key contributions of this work (reductive alkylation and usage of isoxazoles (such as (97)) as methyl vinyl ketone equivalents) have proved to be very useful in organic synthesis.

(Scheme XIII)

One of several³⁹ approaches developed by Danishefsky for the total synthesis of steroids is that delineated in Scheme XIII. The triketone (104) obtained from 2-methyl-1,3-cyclopentanedione and enone (103) was condensed with (105) in two stages (base, followed by acid) to afford (107). The intermediate (106) was not isolated, but tert-butyl esters were mandatory in order to avoid poly-condensed materials. The Wichterle reaction has been well explored by Lansbury⁴⁰ and coworkers, and its application to (107) afforded the dienone (108). Base catalyzed condensation of (108), in turn, produced the tetracyclic trienone (109). Efforts directed at methylating C-10 showed that this could be accomplished in good yield to produce (110). Unfortunately, a considerable amount of C-10 α -methyl isomer (unnatural) was also formed (not shown). Further elaboration of this scheme provided other steroidal intermediates; however, the question of the trans-fusion between rings C and D was not solved at this stage. It appears that the process is only applicable to the synthesis of 19-norsteroids, which are important medicinally.

(Scheme XIII)

In recent years, a major effort has been expended to synthesize C,D-steroidal intermediates that are chiral or, at least, optically enriched. Such intermediates can be generated in three ways: (a) by resolution, (b) asymmetric induction, and (c) by the use of optically active starting materials. Of these the first is the least desirable since the maximum yield attainable is 50%. The latter of the two remaining methods is nowadays more practical if the starting materials are readily available, but the concept of asymmetric induction is most fascinating.

A French group⁴¹ has reported a microbiological reduction of the prochiral trione (114) synthesized from 2-methyl-1,3-cyclopentanedione and the enone (113). The mold *Rhizopus arrhizus* reduces (114) in good yield to the monoalcohol (115), which can be converted to optically active enone (116) on acid treatment (Scheme XIV). In this respect, the induction of asymmetry is performed by Mother Nature.

Hoffmann-La Roche, a long-time leader among the pharmaceutical industry in basic research directed towards the total synthesis of steroids, has been instrumental in bringing to the light two superbly elegant examples of asymmetric induction. This topic has been the subject of a review⁴² and textbook.⁴³ Initially, impetus for this research came from the observation that if 2-methyl-1,3-cyclopentanedione was refluxed in pyridine-toluene with enone (117) a good yield of the diastereomeric materials (118) and (119) was obtained. However, enol ether ($\pm$)-(118) was by far the predominant species produced⁴⁴ (Scheme XV). Later, optically active (117) was synthesized (7(S)-hydroxy-1-nonene-3-one), and on condensation with the dione afforded a good yield of (-)-(118) with very high optical purity.⁴⁵ This exemplifies transfer of asymmetry to a prochiral center during the course of the reaction by a reagent possessing a dissymmetric center. The synthesis of optically active (117) could be efficiently accomplished by microbiological reduction of δ -oxoheptanoic acid using Cladosporium butyri followed with the addition of vinylmagnesium chloride.⁴⁵ Since the enone was not very stable, it was found convenient to use the corresponding Mannich base (117a). Unfortunately, the microbiological reduction was not general for other more highly substituted ketoacids, and a second scheme was developed (Scheme XVI). Reaction of glutaraldehyde with a variety of Grignard reagents provided a mixture of lactols which could be oxidized by silver oxide to the lactones (121b,c). Attack on the lactones by vinylmagnesium chloride afforded racemic hydroxyenones (117b,c). At this stage a clever plan to separate the enantiomeric forms of (117b,c) was devised. Instead of using diethylamine to form the Mannich base (in analogy with (117a)) the optically

(Scheme XV)

(Scheme XVI)

active forms of α -methylbenzylamine were used, and a separable diastereomeric mixture of (122b,c) and (123b,c) obtained.⁴⁶ A number of syntheses have been realized⁴⁷ for many commercially important steroids

using the chiral intermediates described above.

A remarkable contribution from another Hoffmann-La Roche group is that due to Hajos⁴⁸ and coworkers. Their approach embodied the transfer of asymmetry by a chiral catalyst onto a prochiral center. In short, they found that the triketone (124) could be condensed in extremely high chemical, as well as optical, yield to the ketol (125). This phenomenal task was accomplished by the natural aminoacid proline in dimethylformamide (DMF). A laborious mechanistic interpretation

has been provided, concluding with the suggestion that (-)-proline adds to one of the carbonyl groups on the cyclopentane ring. The addition can then be followed by intramolecular attack from an enol in the side-chain. The ketol (125) was easily dehydrated to the enone (126) during the process of recrystallization from ether, and shown

to be identical to authentic material prepared by a Schering⁴⁹ group using a different route. The soundness of this approach is likely to be a cornerstone in the area of asymmetric induction.

As mentioned earlier, a research group headed by Danishefsky at the University of Pittsburg has long been active in developing new methodology applicable to the steroid field. Mindful of the work of Hajos, these workers⁵⁰ were able to cyclize the prochiral intermediate (127) to (128) in good chemical, and optical, yield. The conditions necessary for this transformation were similar to those used by the Schering group⁴⁹ (trione, L-phenylalanine, acetonitrile, and a catalytic amount of perchloric acid).

In this section we have tried to show some of the problems and solutions associated with total synthesis in the steroid field. During the investigations, not only have new chemical reactions been discovered and modified, but extremely delicate and selective methods of transforming chemical species have been developed. The increasing number of scientific publications in this area are evidence that these problems continue to demand the creativity of modern organic chemists.

RESULTS AND DISCUSSION

As mentioned in the introduction our starting material for the synthesis of chiral steroidal precursors is (-)-camphor. The driving force behind the original utilization of this substance arose out of a need to develop new methodology for the total synthesis of cobyric acid (129) (vitamin B₁₂). Inspection of this marvelous molecule

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reveals that the care which Mother Nature has taken to protect the periphery of the molecule from oxidation is at the same time a synthetic chemist's nightmare. Not only are there nine asymmetric centers in the ligand, but six of them are contiguous. The prospect of synthesizing such a substance is indeed a highly stimulating proposition. However, any such project, if it is to succeed, must consider that to achieve this goal the use of optically active starting materials and or intermediates is of unquestionable necessity. Bearing this in mind it became apparent that construction of the ligand could be related, in principle, to the synthesis of the four cyclopentenones (130A-D) (note, $A \equiv B$), and that if these were chiral a feasible entry into the macrocyclic skeleton of vitamin B₁₂ would be realized.

A cyclopentenone (131) bearing a close structural similarity of (130) can be obtained from the microbiological degradation of camphor by Pseudomonad strain P, although the conversion is not efficient.⁵¹

The methodology involved in the conversion of these cyclopentenones into the ligand precursors (132A-D) and (133) has been previously elaborated.⁵²

If a synthesis of (130) that is capable of taking advantage of the built-in chirality found in (-)-camphor (29) could be developed, such would incorporate the asymmetric centers in rings (130A-C) in the correct relative and absolute configurations shown. Furthermore, employment of the enantiomeric (+)-camphor (134) could provide the synthesis of the remaining cyclopentenone (130D) (cf. p. 54).

The functionalization of camphor has been known for over eighty years.⁵³ Although there have been numerous misinterpretations in the literature regarding the chemistry of camphor, recent clarifications⁵⁴ have considerably alleviated the situation. The sulfonation of camphor by fuming and concentrated sulfuric acids was first reported by Kipping and Pope⁵⁵ in 1893. They discovered that by using the former reagent they obtained a sulfonic acid (136) isomeric to the one formed (137) with concentrated sulfuric acid. Furthermore, they made the astonishing discovery that if (+)-camphor (134) was employed the resulting sulfonic acids (136, 137) were racemic, whereas (+)- α -bromocamphor (135) yielded the corresponding sulfonic acids (138, 139) in optically active form (Scheme XVII). Unfortunately, they were not able to assign the correct absolute configuration to these derivatives, but they did assign a correct relative one. This problem was not unique to them, and was perhaps worsened by the random assignment by Hueckel of (+)-camphor (134) to its enantiomeric structure (29). It took some forty years to correct this mistake,⁵⁶ and it is still not completely removed from some classical texts.⁵⁷ These derivatives of camphor were denominated as π -substituted camphors for the "pyrogenic" nature that they exhibited in the reaction leading to their formation. It is interesting to note that upon prolonged reaction of camphor with concentrated sulfuric acid massive rearrangement and oxidation (air) occurs to produce "camphren", better known as 3,4-dimethylacetophenone. This product was known to Kipping and Pope, but a structure not assigned. A mechanistic interpretation of these results has been set forth by Meyer^{54a} and Vaughan^{54b} in the case of sulfonation, and by Noyce^{58a} and Roberts^{58b} for latter rearrangement.

a = H₂SO₄
b = Fum. H₂SO₄ or
ClSO₃H

(Scheme XVII)

The reactions must proceed through norbornyl-type carbonium ions. Whether these ions are classical or non-classical will not be dealt with here.⁵⁹ However, for the sake of clarity, they will be depicted as classical (Scheme XVIII). Thus, a ketone such as camphor is capable of producing a carbonium ion (134a) which through a series of equilibria may produce the cations (134b) and (134c). These are capable of deprotonating, and by electrophilic attack on a sulfonating agent produce the corresponding (sulfonic) acids. The selective formation of one sulfonic acid over another is one which hinges on the particular set of conditions chosen for the reaction. Therefore, one may speculate that under milder conditions (i.e. concentrated sulfuric acid) the cation (134b) is generated in low concentrations, so that its progeny (134c) is formed very slowly, leading to sulfonation at C-10. Under more vigorous conditions (fuming sulfuric acid, or chlorosulfonic acid) a higher concentration of (134b), and hence more (134c) may be produced, resulting in sulfonation at C-9. This may simply reflect a difference between thermodynamic and kinetic control of the reaction. Racemization of camphor in this medium indicated that perhaps some carbonium ion involved is capable of giving rise to two enantiomeric cations. This can be demonstrated by proposing an intermediate (134d) which is capable of undergoing a 2,6-hydride shift - a facile process in the norbornyl series. The shift undoubtedly would lead to racemized product. If the analogous cation (135d) from reaction with α -bromo-(+)-camphor is considered, it is easy to see that such a species is stabilized by a bromine atom which may make the 2,6-hydride shift unlikely on electronic as well as steric grounds. The reaction leading to the π -sulfonic acid is a regiospecific transformation,

(Scheme XVIII)

affording only the sulfonic acid anti to the ketone. It may be ascribed to the observation made by Finch and Vaughan^{54b} in the course of some labelling experiments performed with bornane derivatives. They found that exo-methyl shifts (i.e. (134b) $\rightarrow$ (134c) took place in precedence over the corresponding endo-shifts.

The rearrangement of camphor on prolonged treatment with sulfuric acid to produce 3,4-dimethylacetophenone (141) was shown by Noyce to proceed with the intermediacy of fenchone (140). A few years later Roberts showed the latter to rearrange to the aromatic species, and a mechanism was suggested based on labelling experiments.

A final point to be made with regard to reactions of camphor in super-acid media is exemplified in a publication by Jacquesy and coworkers⁶⁰ where they claim that in hydrofluoric acid - antimony pentafluoride camphor yields 1,4-dimethylbicyclo[2.2.2]octan-2-one (142a) (12%), 2,4-dimethyl-5-ethylcyclohex-2-ene-1-one (142b) (27%), and 1,4-dimethylbicyclo[3.2.1]oct-3-ene-2-one (142c) (20%).

Having set the stage for functionalizing camphor at a position remote from the carbonyl group, Kipping and Pope were able to synthesize efficiently a number of halogenated derivatives. They also showed that chlorosulfonic acid was the reagent of choice for functionalizing the " π " (C-9) position. Neutralization of α -bromocamphor- π -sulfonic acid with ammonia yielded a non-hygroscopic ammonium salt, which on reduction with zinc dust followed by halogenation with a phosphoric halide afforded camphor- π -sulfonyl halide. This material was transformed to the corresponding optically active π -bromocamphor on heating (Scheme XIX). With this precedent in mind, Japanese workers were able to dispose of a number of steps by carrying out a direct bromination of camphor at the π -position with bromine in chlorosulfonic acid.⁶¹

(Scheme XIX)

In addition, they investigated the halogenation using the common agents bromine, iodine, and chlorine (Table I). These results showed that the best entry into the π -substituted camphor skeleton could be achieved by bromination of α -bromocamphor in chlorosulfonic acid. In the late 1950's E. J. Corey's laboratory performed some minor modifications on the Japanese procedure, and using π -bromocamphor were able to synthesize⁶² a number of santalene sesquiterpenes. These workers were also the first to show definitive proof that bromination in chlorosulfonic acid yielded only the anti-substituted product in optically active form. Subsequent reduction of the α - π -dibromo-(+)-camphor in methylene chloride with

DIRECT π -HALOGENATION OF CAMPHOR

No.	$(+), X = H$	$Y = Cl$	A or B	$(\pm), X = H, Y = Cl$	Yield
1.	$(+), X = H$	$Y = Cl$	A or B	$(\pm), X = H, Y = Cl$	30%
2.	$(+), X = H$	$Y = Br$	B	$(\pm), X = H, Y = Br$	45%
3.	$(+), X = H$	$Y = Br$	A	$(+), X = H, Y = Br$	50%
4.	$(+), X = H$	$Y = I$	A	$(\pm), X = H, Y = I$	6.5%
5.	$(+), X = Cl$	$Y = Cl$	A or B	$(+), X = Y = Cl$	25%
6.	$(+), X = Cl$	$Y = Br$	A	$(+), X = Cl, Y = Br$	50%
7.	$(+), X = Cl$	$Y = Br$	B	$(+), X = Cl, Y = Br$	27%
8.	$(+), X = Br$	$Y = Cl$	A	$(+), X = Br, Y = Cl$	60%
9.	$(+), X = Br$	$Y = Br$	B	$(+), X = Y = Br$	70%
10.	$(+), X = Br$	$Y = I$	A	$(+), X = Br, Y = I$	13%

(Table I)

zinc and anhydrous hydrogen bromide was shown to produce π -bromo-(+)-camphor in a yield greater than 90%^{62a} (Scheme XX). Alternatively,

(Scheme XX)

the reduction may be achieved with refluxing N,N-dimethylaniline,⁶³ but we found Corey's method to be advantageous.

Remembering that our goal was the synthesis of cyclopentenones (130A-D), and knowing how to functionalize camphor without loss of chirality, we began to rationalize efficient syntheses of (130). Since (130A) and (130B) are identical it seemed to us that a synthesis of this compound would be more fruitful for a start (Scheme XXI).

(Scheme XXI)

Unfortunately, the starting material for this synthesis is the enantiomer of (+)- π -bromocamphor. Whereas this would normally be solved by carrying out the transformations on (-)-camphor, a natural product itself, the price of this substance was sufficiently prohibitive that we felt (+)-camphor would be better suited for our initial studies.

We recognized in the structure of (130) a feature which might allow us to construct trans-fused hydrindanes with a methyl substituent at the ring junction. This is easily visualized by joining the adjacent side-chains on the five-membered ring. An obvious use for such compounds would be in the steroid field, where recent advances had shown their utility (cf. historical section). As a model study we designed a series of experiments which tested the feasibility of the hypothesis in a rapid and efficient fashion (Scheme XXII).

(Scheme XXII)

To our delight we discovered that α -bromo-(+)-camphor was commercially available and inexpensive, although it was a congener of (+)-camphor and, therefore, not of its desired enantiomer.

We launched our investigations in the steroid field by synthesizing π -bromo-(+)-camphor by Corey's procedure. Having accomplished this transformation we met our first stumbling block. On repeated attempts to add methyllithium to (144) in a variety of solvents we obtained only small amounts of (152), recovering a great deal of starting material. Granted that camphor is a hindered ketone we expected the reaction to be sluggish. But even with the use of prolonged reaction times and large excesses of organometallic reagent we were unsuccessful at preparing (152) in significant quantity. We reasoned that methyllithium was reacting with camphor as a base, and began searching the literature for alternatives. Indeed, methyllithium does not add to camphor significantly,⁶⁴ but methylmagnesium iodide does.⁶⁵ Finnish workers⁶⁵ had reported that on addition of methylmagnesium iodide to camphor the exclusive product formed was 2-endo-methyl-2-exo-bornanol, in good yield. We were not able to reproduce these results with π -bromocamphor at first. Part of the problem was that this Grignard reaction was carried out by the former workers in a rather unconventional manner, and when we initiated this study the key reference^{65d} did not have any of the experimental details needed. The unconventional nature of this reaction, as found in a latter publication,^{65e} calls for the slow addition of the ketone in anhydrous ether, to a reaction vessel containing magnesium turnings and neat methyl iodide. When we tried this method it proved satisfactory although somewhat on the dangerous side. However, in the mean time

we had been successful in achieving the same transformation using methylmagnesium iodide etherate-complex in methylene chloride solvent. This procedure is in itself somewhat unusual, but is well preceded.⁶⁶ Furthermore, this Grignard reagent (as the etherate complex) is not only readily soluble in methylene chloride, but safer as well since the presence of a highly inflammable solvent (such as ether) is eliminated. Our experience with this solvent system indicates a higher reactivity of the Grignard reagent toward nucleophilic addition. Unlike Maelkoe (who used camphor), we obtained mixtures of 2-endo-methyl-2-exo-9-borbornanol and 2-exo-methyl-2-endo-9-borbornanol as evidenced by the n.m.r. spectrum of chromatographed material. The work up of this reaction was sensitive to the conditions used.

Acidic conditions afforded the exocyclic olefin (157) obtained by dehydration of the alcohol (152). In fact, this 3^o alcohol was even sensitive to the drying agent used to remove traces of water from the organic solvent. Upon drying with magnesium sulfate a considerable amount of (157) was observed. From that point on, we used potassium carbonate as the drying agent for this work up. In addition to the

carbinol obtained, the product mixture contained varying amounts (about 20%) of starting material, which was easily removed by oximation⁶⁷ with hydroxylamine in the presence of potassium hydroxide, and partition of the basic mixture between organic and aqueous phases. In this manner we were able to obtain the desired carbinol (152) in 80% yield.

The oxidation of bornyl alcohols with one-electron oxidizing

agents is well known,⁶⁸ and reactions of such bicyclic alcohols with Ceric Ammonium Nitrate (CAN) clearly demonstrate that oxidative cleavage is the preferred mode of oxidation.^{68a} Thus, rapid combination of a bromoalcohol (152) solution in acetonitrile with two equivalents of CAN in acetonitrile - water (1:2, v/v) solution at 55°C immediately produces the deep-red coloration of the $\text{Ce}^{\text{IV}}\text{-O}$ complex. The coloration changes in seconds to a faint yellow solution. Workup of the reaction after one minute (see experimental) affords an orange oil which exhibits spectroscopic properties attributable to bromoketone (153).

Attempts to purify (153) by distillation were only partially successful since considerable decomposition occurred under the conditions. This apparent lack of stability may be attributable to the presence of small amounts of thermally labile⁶⁹ nitrate esters produced by ligand exchange. A closer examination of the infrared spectra of crude and purified materials revealed that, in the latter, the 1648 cm^{-1} and 1250 cm^{-1} bands of nitrate esters were absent. Attempts to purify (153) by (a) distillation in the presence of silica gel,⁷⁰ (b) base-induced elimination,⁷¹ or (c) zinc reduction (of the N-O bond) followed by elimination⁷² were met by little success. Chromatography on silica gel was the only appropriate purification method.

A mechanistic interpretation of the oxidative cleavage has been set forth by Trahanovsky^{68a} (Scheme XXIII). The first step of the reaction involves a rapid equilibrium leading to formation of a Ce^{IV} -alcohol red complex followed by irreversible cleavage of the C1-C2 bond. The resulting radical can be oxidized to the cation (by a second electron-transfer process) which on loss of a proton produces (153). Certain observations published by Kochi⁷³ suggest that substitution products in the oxidation of radicals result from ligand-exchange reactions whereas elimination products result from electron transfer. Since the metal is highly nitrated under the reaction conditions⁷⁴ it seems reasonable to expect nitrate ester formation to arise by ligand-exchange. The realization that two olefinic products ((153) and (158)) should be obtained from this reaction suggested that a lower reaction temperature might favor production of (158) somewhat. Our interest in such a compound lies in the expectation that by cleavage of the double bond a precursor to the 17-keto steroids be produced. We found that at 0°C one indeed observed production of (153) and (158) in a ratio of approximately three to two, respectively; further lowering of the temperature did not change this ratio. These results are in accord with similar observations made by Brown⁷⁵ in the elimination of 1-methyl-1-chlorocyclopentane. The suggestion can be made that at higher temperatures (55°C) one only observes endocyclic olefin (153) because the exocyclic isomer is isomerized under the acidic reaction conditions.

(Scheme XXIII)

Our failure to obtain (153) in good yields led us to seek alternate synthetic pathways. We tried Ceric Ammonium Sulphate (CAS) but it was insoluble in ordinary solvents, and in every case only starting material was recovered. An approach which caught our attention was the possibility of oxidizing the olefin (157) with thallic nitrate or acetate. We reasoned that if the initial organothallium compound (157a) was formed its decomposition⁷⁶ might lead to the enol ether or acetate (159) (Scheme XXIV). Such an enol acetate would be expected to generate the enolate anion necessary for cyclization to (154) when treated with methyl lithium. Unfortunately, the oxidation

(Scheme XXIV)

step failed. Lead tetraacetate is also known⁶⁸ to oxidize norbornyl alcohols with concomitant cleavage, but we were less successful with this reagent than with CAN. On consideration of the known reactions of camphor and its derivatives, it occurred to us that we should be able to obtain (153) from the addition of methyllithium to the Beckmann fragmentation product (161) of π -bromocamphoroxime (160) after hydrolysis of the imine (Scheme XXV). It is well known that camphoroxime undergoes Beckmann rearrangement in an "abnormal" manner⁷⁷ (this process is often referred to in the literature as a Beckmann rearrangement of the second order). We like to refer to this process as the

(Scheme XXV)

Beckmann fragmentation. Oximation of π -bromocamphor with excess hydroxylamine hydrochloride in pyridine proceeded smoothly, and fragmentation (160) with p-toluenesulfonyl chloride (p-TsCl) in pyridine^{77e} at 50°C afforded a mixture of nitriles (161) and (162) in 70% yield. The ratio of (161) to (162) was approximately three to two, respectively. This is the same ratio of olefinic isomers as obtained from the CAN oxidation of (152) at 0°C. We were somewhat concerned at one point with the possibility of having syn and anti oximes (160). If we had a mixture we would have expected the syn-oxime not to undergo rearrangement. Fleming and Woodward⁷⁸ in their study of oxime tosylates derived from homoepicamphor showed that this geometry was unreactive. However, the n.m.r. spectrum of π -bromocamphoroxime did not indicate the presence of more than one isomer. This is in further

agreement with a report by Roberts⁷⁹ that the ^{13}C -n.m.r. spectrum of camphoroxime is that of only anti-oxime. The addition of methyllithium to (161) and (162) proceeded in good yield, but great care had to be taken during hydrolysis of the resulting imine. After acidic workup we only had the endocyclic double bond isomer (153). By coincidence, we discovered several examples in the literature where organometallic reagents had been added to nitriles, and the resulting imine anions treated with excess reagent to produce dianionic species capable of being trapped by alkylating agents.⁸⁰ The reactions were run in a mixture of tetrahydrofuran and hexamethylphosphoramide. This seemed attractive to us since we expected formation of dianion (163) to be followed by intramolecular displacement of bromide (Scheme XXVI) producing (154). This, however, was not the case. The only product observed (153) was that of addition to the cyano group. We also

(Scheme XXVI)

considered, as an alternative, the photochemical decomposition of the nitrite ester of (152). But, after considering the known⁸¹ analog (164), the variety of products formed and the low yields made the reaction unattractive.

With a reliable synthesis of (153) we embarked on a series of experiments which would test the feasibility of intramolecular displacement of bromine to produce the steroidal C,D-intermediate (154). We realized that this would not be easy since the bromide was primary, but neopentyl and, therefore, hindered. Nevertheless, there are a few examples in the literature of intramolecular displacements at neopentyl centers by enolate anions of methyl ketones.⁸² The low yields obtained in these reactions were inconsequential at the time since we were

primarily interested in obtaining positive results.

This phase of our research was a complete and dismal failure. Under a variety of bases and conditions we obtained no products recognizable as (154), or as being derived from the hydrindanone. We also attempted cyclization via the enamine (165) to no avail. The n.m.r. spectra of crude reaction products showed a preponderance of starting material (153) along with an unknown polyolefinic substance (tar) which was uncharacterized. Such material could come from intramolecular fragmentation (Scheme XXVII).

(Scheme XXVII)

Disappointed with these findings we turned our attention to suitable alternatives. One such alternative, which seemed like a "sure-fire" method, is delineated below (Scheme XXVIII).

(Scheme XXVIII)

Although this approach is somewhat longer than the previous one (cf. Scheme XXII) it is, nevertheless, worthy of consideration for at least two reasons. First, since the A and B rings of a steroid must somehow be attached to the C,D-intermediate, it is clear that if such a process is to involve enolate chemistry, the enone (172) is by far a more suitable intermediate than (154). This expectation is based on an

extension of arguments used in decalone chemistry. In general, the regioselectivity observed in enolate formation of 3-decalones (steroid numbering) is dependent on the stereochemistry of the ring fusion.⁸³ Formation of the $\Delta^{3,4}$ -enolate is kinetically favored with a cis-ring fusion, whereas the $\Delta^{2,3}$ -enolate is formed most rapidly in the corresponding trans-fused isomer. Secondly, an intermediate such as (172)

exhibits additional versatility in that, after functionalization at C-9 (i.e. C-9 of the corresponding steroid derived from (172)), the $\Delta^{11,12}$ double bond can be utilized to generate corticosteroid intermediates.

The displacement of bromide (144) was known⁸⁴ to occur with sodium acetate in refluxing acetic acid, but this seemed to be a rather brutal procedure in view of what is now known about nucleophilic displacements in polar aprotic solvents. Furthermore, we envisaged the possibility of carrying out a displacement on the 3° carbinol (152), and the acidic conditions used by the Indian workers were clearly unacceptable (Scheme XXIX). We, therefore, proceeded as planned and were delighted to find that displacements on both (144) and (152) with potassium acetate in dimethyl sulfoxide (DMSO) proceeded cleanly and in excellent yields to produce, after saponification, the alcohols (167) and (174), respectively. Incidentally, these results completely ruled out the

(Scheme XXIX)

possibility of converting the bromide (144) to aldehyde (168) by the known⁸⁵ oxidation of primary halides to aldehydes with dimethyl sulfoxide. Oxidation of (167) with the Collins⁸⁶ reagent, using the Ratcliffe-Rodehorst^{86b} modification, afforded ketoaldehyde (168) in nearly quantitative yield. This particular reagent was chosen for its mildness and high selectivity. Nevertheless, when we attempted to oxidize (174) in the same fashion tars were obtained. Other methods of oxidation were also considered. Attempted oxidation of (174) with CAN was not clean, affording a multitude of products. We also investigated the decomposition of alkyl hypochlorites⁸⁷ as a viable method of oxidizing alcohols to ketones. As a model study we carried out an oxidation on (-)-borneol (175) with hypochlorous acid generated in situ from household bleach and acetic acid. In the absence of light we observed production of small amounts of (-)-camphor (29), whereas if light (room lighting) was allowed to penetrate the reaction vessel fragmentation products (176) were formed (Scheme XXX). Our interest

(Scheme XXX)

in the oxidation of (-)-borneol (175) to (-)-camphor (29) is more than just a passing one, for the cost of the alcohol is considerably less than that of (-)-camphor. Being somewhat confident that (173) and (174) might undergo oxidative cleavage, we made several attempts under varying conditions and reagents to obtain "clean" oxidation. However, we were unsuccessful in our pursuits and obtained complex mixtures of products which were not identified. Nonetheless, as a result of our investigations, we developed a procedure⁸⁸ which allowed us to produce large quantities of (-)-camphor from (-)-borneol in a quantitative yield using tert-butyl hypochlorite.

After realizing the peculiarities associated with tertiary alcohol (174) we concentrated our efforts, again, on Scheme XXVIII. Formation of the monodimethylacetal (169) of π -oxocamphor (168) (methanol, trimethylorthoformate in the presence of a catalytic amount of p-toluenesulfonic acid) was selective, and high-yielding. Reaction of (169) with methylmagnesium iodide in a variety of solvent systems was disappointing, affording a variety of products easily identifiable.

This result could be explained by assuming intervention of Lewis acids arising from a Schlenk-type equilibrium.⁸⁹ To avoid undesirable attack at the π -position we prepared the cyclic acetals (179) and (180) (Scheme XXXI). The addition of methylmagnesium iodide to (179) and

(Scheme XXXI)

(180) was even more sluggish than in the reaction with π -bromocamphor (144). We did manage, however, to secure enough of the carbinols (181) and (182) to study their oxidation with CAN. Oxidation of 3° alcohols (181) and (182) with CAN afforded the ketoacetals (183) and (184) which had limited stability under the reaction conditions. We observed small amounts of aldehyde in the n.m.r. spectra of crude (183). However,

deprotection, to be followed by aldol condensation, left a great deal to be desired (Scheme XXXII). To make a long story short, the conditions necessary to remove the protecting group afforded a complex mixture of compounds which were not fully identified. Our feeling is that generation of a carbonium ion, which is both neopentyl and homo-allylic, during hydrolysis of the protecting group was responsible for the *melée*. Notwithstanding, some condensation products may have been present as evidenced by olefinic proton signals in the n.m.r. attributable to a cyclohexenone. The signals, however, were due to a very minor component. This series of experiments completed this phase of our research.

(Scheme XXXII)

We have shown so far that camphor can be functionalized at the π -(C9)-position, and fragmented to produce substituted cyclopentenones. Since the cyclopentenones which we have so far synthesized appear to be incapable of intramolecular closure, we turned our interest to elaborating substituted cyclopentenones which would not have to undergo intramolecular displacement at a neopentyl site (Scheme XXXIII).

(Scheme XXXIII)

Compounds such as (187) and (188) would be expected to alkylate electrophiles unequivocally at the C-8 position of a steroid. This is, of course, advantageous from the point of view of total steroid synthesis, and the merits of synthesizing such intermediates has been

dealt with previously. Their precursors (i.e. (185) or (186)) should be preparable from suitably functionalized camphor derivatives by application of methods described earlier.

Clearly, if one is to synthesize compounds such as (189) and (190) the C-9 (π) position of camphor (134) must be extended by an additional acetate unit. Retrosynthetic planning indicates that introduction of a two-carbon unit bearing a terminal carboxylate function can, in principle, be achieved by a multitude of ways (Scheme XXXIV).

(Scheme XXXIV)

The generation and utilization of ethyl lithioacetate and tert-butyl lithioacetate have been previously discussed.⁹⁰ The reactions of ethyl or tert-butyl lithioacetate with π -bromocamphor (144) afforded only starting material and the corresponding acetoacetic ester from self-condensation. The iodide (191) was prepared and found to be equally unreactive (Scheme XXXIV). To avoid the problems accompanying enolization in (144) or (191) the corresponding 1,3-dioxolanes were tested - these failed, as well.

The displacement by iodide ion on π -bromocamphor had been reported previously by Corey.^{54d} Their procedure called for a twenty five-fold excess of sodium iodide in a large amount of dimethylsulfoxide (DMSO) as the solvent. These conditions provided a good yield of (191). In addition, substantial amounts of π -hydroxycamphor (167) were formed. As an alternative, we executed the reaction with anhydrous potassium iodide in freshly distilled dimethylformamide (DMF) (Scheme XXXV). Using these conditions we discovered that only a three-fold excess of potassium iodide was needed since this reagent is extremely soluble in DMF, whereas the bromide (resulting from the displacement) is not, and precipitates out of solution. We also had to resort to high temperatures (as did Corey) to achieve a desirable reaction rate. The ketalization of π -iodocamphor is very sluggish, and at best proceeds to the extent of 85% completion. We reasoned that the bulk of the iodide might be responsible for this effect. Therefore, we investigated the alternate route in Scheme XXXV which consists of ketalization of (144) followed by iodide displacement. Unfortunately, this route offered no advantage. If one looks at the mass spectra of (191), (192), and (193) (electron impact studies) it becomes

(Scheme XXXV)

intuitively obvious that π -iodocamphor-1,3-dioxolane (193) should be a superb electrophile. At intensities two hundred and fifty times greater than those needed to observe a molecular ion for π -iodocamphor (191) or π -bromocamphor-1,3-dioxolane (192) one could still not see the molecular ion of (193), but rather the ion corresponding to loss of iodine. Further attempts to displace iodide (193) with lithioethoxyacetylene or lithium acetylide-ethylenediamine complex were also futile. The last experiment was particularly disappointing in view of positive results obtained by Erman⁹¹ in the displacement of π -bromotricyclene. We knew the π -position to be difficultly accessible, but

had hoped that these reagents would not be overly bulky. At this stage we abandoned any hope of carrying out the displacement at room temperature with the reagents described above.

A recent report by Grieco⁹² on the displacement of iodide (194) by sodium p-toluenesulfinate in DMF, at high temperatures (135-140°C), suggested that we take advantage of such an intermediate to further functionalize π -bromocamphor (144). A substance such as (195) could be alkylated (base, followed by an electrophile), and desulfurized using lithium and ethylamine. We applied Grieco's procedure to π -bromocamphor-1,3-dioxolane (192), and obtained in good yield the sulfone (197). Oddly enough we never had occasion to further utilize this compound.

Concurrent work on the displacement of π -iodocamphor-1,3-dioxolane (**193**) with the sodium salt of dimethylmalonate in DMF at high temperatures had given us a new direction.

While searching the chemical literature for known reactions of camphor and related compounds we came across an interesting series of articles by Bhattacharyya and coworkers⁹³ who claimed that π -bromotricyclene could be displaced by malonate ion. We were intrigued by

their find, but their yield was not in accord with the principles which have guided our synthetic planning. This may have been due to the unusual conditions reported (xylene, high temperature, pressure). Nevertheless, we explored the possibility of carrying out such a transformation, but under conditions favorable for an $\text{S}_{\text{N}}2$ displacement. Our initial studies with π -bromo-, and π -iodocamphor using several (5-10) equivalents of malonate were unsuccessful. At this point we made the crucial decision to "load" the reaction in a manner which would facilitate transformation of a π -halocamphor to a π -acetate system (propionate sidechain): (a) we chose as our alkylating agent π -iodocamphor-1,3-dioxolane (193); (b) we carried out the reaction with ten equivalents of the sodium salt of dimethylmalonate; (c) we used the minimum amount of solvent (DMF) which would dissolve our materials at reflux temperature; and (d) we added a small amount (approximately 10%) of 18-crown-6. The use of crown ethers to generate so-called "naked anions" has been dealt with previously,⁹⁴ and the potential use in our

system was eminently reasonable. The reaction was run exactly as specified above, at reflux temperature, for three days. On workup, to our delight, we discovered that not only had the reaction proceeded in high yield, but one of the carbomethoxy groups had vanished as well! Displacement had obviously taken place, and under the conditions we were observing decarbomethoxylation. We did not know at the time whether decarbomethoxylation had been promoted by the presence of crown ether,⁹⁵ high reaction temperature,⁹⁶ or attack on the diester by iodide ion released in the reaction.⁹⁷ Whatever the reason we were astounded. This reaction was to pave the way not only for our general approach to steroids, but was applicable, as well, toward the synthesis of a ring D (130D) precursor of vitamin B12. Having synthesized (198) the protecting group was easily removed by exchange in wet acetone with a catalytic amount of p-toluenesulfonic acid (Scheme XXXVI).

(Scheme XXXVI)

After preparation of the ketoester (199), in high yield, we were confident that reduction to the hydroxyester (189) with sodium borohydride would proceed without problems. However, the long history bearing out a lack of reactivity of this keto group once again came to light, and the reaction proceeded with uncontrollable over-reduction to produce the epimeric diols (200) as well as the desired hydroxyesters (189a) and (189b). This complication was in part due to the large excess of sodium borohydride needed to reduce ketones of this type. Finally,

we were able to reduce (199) to a 10:1 mixture of exo:endo alcohols in excellent yield using triisobutylaluminum in benzene, at room temperature. It should be pointed out that little is known about the scope and limitations of this reagent. The effect of steric hindrance

plagued us once more. The aluminum alkoxide produced after reduction of the keto group was difficult to hydrolyze. Acidic conditions were unsatisfactory, and basic ones hydrolyzed the ester, as well. We finally found that the method of choice consisted in refluxing the reaction mixture with wet (approximately 10% water) methanol, overnight. The predominantly exo-hydroxyester (**189**) was oxidized with CAN in 75% aqueous acetic acid⁹⁸ to produce the aldehydoester (**185**) in a moderate yield (Scheme XXXVII). We again were ready to test the feasibility of synthesizing a C,D-steroidal precursor. Hence, we treated a small amount of (**185**) with methoxide. The n.m.r. spectrum of the crude reaction product showed complete absence of a formyl or enol proton, and the infrared (i.r.) spectrum showed the presence of a saturated

carbonyl group. Unfortunately, mass spectral analysis did not show a molecular ion or pattern for the desired hydroxymethylene compound (187) or its deformedylated derivative (154). Other conditions were also

(Scheme XXXVII)

tried unsuccessfully. We should like to point out that to our knowledge, this would have been the first example of an intramolecular condensation between an aldehyde and an ester to produce a hydroxymethylene ketone. After this series of experiments we had exhausted our supply of ketoester (199), and rather than continue with these derivatives of (+)-camphor (134), we focused our attention on the enantiomeric (-)-camphor series. It should be recalled that the steroidal C,D-precursors with the natural absolute configuration can be related to (-)-camphor (29).

Preparation of $(-)\text{-}\pi\text{-bromocamphor}$ (30) was accomplished in the same manner as its enantiomer. However, the $(-)\text{-}\alpha\text{-bromocamphor}$ (201) was synthesized^{54a} rather than purchased, and the requisite $(-)\text{-camphor}$ (29) prepared from oxidation of $(-)\text{-borneol}$ (175) with tert-butyl hypochlorite⁸⁸ (Scheme XXXVIII). The $(-)\text{-}\pi\text{-iodocamphor}$ (203) and its

(Scheme XXXVIII)

corresponding 1,3-dioxolane (204) were also prepared and subsequently reacted with dimethylmalonate anion (DMM) (Scheme XXXIX). The results of these investigations revealed that one could perform the displacement on the iodoketal (204) (but not the bromoketal (205)) using potassium carbonate as the base in DMF and 18-crown-6. We also discovered that the sodium-salt of dimethylmalonate (generated with sodium or sodium hydride) was suitable for the displacement in the absence of crown ether. Finally, we were also successful at displacing (-)- π -iodocamphor (203), in good yield (without crown ether), thus eliminating the protection and deprotection steps. Of further interest was the find of trace amounts of ketodiester (207) on examination of crude

(Scheme XXXIX)

reaction mixtures by the technique of gas chromatography-mass spectroscopy combined. All the materials synthesized in this sequence of reactions were examined by polarimetry, except for (206), and found to be optically active (cf. experimental). The reason for not examining (206) is that the great care necessary to protect the dioxolane group during workup was not worth the trouble. Furthermore, the specific rotations of the ketoester (131) produced by displacement of (-)- π -iodocamphor or its dioxolane, followed by deprotection, were identical. This specific rotation was also identical in magnitude, but opposite in sign, to that found for the enantiomeric ketoester (199). All other compounds described thus far gave satisfactory rotations. The π -haloketals (204) and (205) had very low specific rotations.^{54e} The possibility of racemization was ruled out, however, by reversion to the ketones (203) and (30), respectively, and determination of their rotation. In this instance, we feel that the low rotations were due to a weakness of the chromophore in the π -haloketals versus the π -haloketones.

Relying on what has already been described about the properties of camphoroximes in the Beckmann rearrangement, we thought it expeditious to oximate ketoester (31) and subject the product (32) to Beckmann fragmentation (Scheme XL). As in the case of π -bromocamphoroxime (160) the rearrangement proceeded smoothly yielding a mixture of nitriles (33) and (208) in a ratio of 3:2 (again), respectively.

(Scheme XL)

We investigated the possibility of carrying out the rearrangement under acidic conditions, but found that lactone (211) was additionally formed. Lactone formation was also observed attempting to isomerize the exocyclic olefin (208) to its isomer (33) with 90% formic acid.

Lactone (211) must arise from trapping of the 3° carbonium ion by the ester function. Interestingly, compound (208) may be isomerized to (33) with trifluoroacetic acid (TFA), under anhydrous conditions, without lactonization. In addition, the olefinic isomers (33) and (208) could be easily separated by medium pressure liquid chromatography (MPLC).

The condensation of a nitrile with an ester was not one familiar to us at the time, and we had certain misgivings about the course of such a reaction. A quick search of the literature, however, demonstrated that although such transformations have not been very popular among organic chemists they are, nevertheless, general.⁹⁹ The major products from these condensation reactions are, in every case that we found, the α -cyanoketones; unfortunately, we were not able to find an example of an intramolecular condensation. This obviously did not

deter us, and by treating a mixture of (33) and (208) with potassium tert-butoxide in THF we were able to synthesize the bicyclic intermediates (34) and (209) (Scheme XL) in good yield. From that point on, however, we carried out the cyclization reaction with the endocyclic isomer (33) only, since isomerization of (209) to (34) proceeded with the production of an additional product tentatively identified as (210). The suggestion that (210) may be the side product observed is based on direct analogy from the steroid literature.¹⁰⁰ It obviously involves a 1,2-methyl shift in the carbonium ion generated by the acidic conditions, followed by deprotonation yielding a thermodynamically more stable tetrasubstituted double bond. The driving force in this process also must be due to the unfavorable trans-fused geometry of the ring junction.

Preliminary investigations on the annulation of hydrindanone (34) with methyl vinyl ketone proved to be fruitful from the start. As precedent, we were aware of a publication by Japanese workers¹⁰¹ on the annulation of hydrindanone (212) with dienone (213) to produce the triketone (214). Furthermore, we also found a useful procedure¹⁰² for

annulating methyl vinyl ketone onto an α -cyanoketone. Treatment of (34) with a catalytic amount of sodium ethoxide in ethanol-benzene, at room temperature, yielded the tricyclic enone (216) as well as ketol (215b) in good yield (Scheme XLI). We reasoned that failure to achieve

(Scheme XLI)

complete elimination to the enone (216) was probably due to steric effects in the elimination of hydroxide from (215b). The isomeric ketol (215a) is part of a conformationally rigid system, where the hydroxyl group occupies an axial position. Trans-diaxial elimination of this intermediate can, therefore, be recognized as proceeding with celerity. Conversely, if ketol (215b) is to undergo a similar trans-diaxial elimination the cage-like conformation that the intermediate must achieve indicates that approach to the axial C-10 hydrogen will

be obstructed. Unfortunately, ketol (215b) is expected to be formed in preponderance in this reaction since it results by attack from the least hindered α -face. It occurred to us that maximization of the yield of enone (216) could be done in two ways. The first is obviated

by assuming that formation of ketol (215b) should be reversible. Hence, on prolonged reaction times we indeed observed more favorable yields of enone versus ketol. However, the length of time necessary to carry out this transformation was prohibitive in view of the desired deadline for completing this work. Therefore, we sought a more rapid method for obtaining the required results. The steroid literature is replete with examples dealing with the dehydration of alcohols.¹⁰³ We tried several of these finding that the reactions were all slow, and that phosphorous oxychloride-pyridine showed promise of being the reagent of choice. This series of experiments completed the work described in this thesis.

Inspection of our approach to the total synthesis of steroids, in our opinion, demonstrates its efficiency. The possibilities of extending the uses of hydrindanone (34) and enone (216) to produce a variety of steroids are definitely attractive ones. In conclusion, we would be less than candid if we were not to state that our synthesis compares well to those in the literature.

EXPERIMENTAL

Melting points were taken on a Fisher-Johns melting point apparatus or a Melt-Temp hot-stage apparatus (sealed tubes), and are uncorrected. Boiling points are uncorrected, as well. Infrared spectra were obtained on a Beckmann IR-8 or 4210 spectrometers. Proton magnetic resonance spectra were recorded in deuteriochloroform solution using tetramethylsilane (TMS) as the internal standard on a Varian A56/60A spectrometer operating at 60 HMz. All chemical shifts reported are in parts per million (ppm) downfield from TMS. Mass spectra were taken on a Consolidated Electrodynamics Corp. 21-110B high resolution mass spectrometer, or a Finnigan 3300 quadrupole GC-mass spectrometer equipped with a 6100 data system. Column chromatography operations were carried out at medium pressures (30-90 psi) using Woelm silica gel, type 206, 0.032-0.063 mm. Gas chromatography (VPC) was performed on a Hewlett-Packard 5700A gas chromatograph using a thermal conductivity detector and He as the carrier gas. Rotations were determined on a JASCO DIP-4 digital polarimeter.

(-)-Camphor (29), Method A. To a solution of 10.4 ml (0.13 mole) of anhydrous pyridine in 250 ml of reagent grade methylene chloride were added 6.00 g (0.06 mole) of chromium trioxide. The mixture was stirred at room temperature for 15 min. under an inert atmosphere. At this time 1.54 g (0.01 mole) of (-)-borneol (175) was added neat to the deep burgundy colored solution. At once a black precipitate began to deposit on the walls of the reaction vessel. Stirring was continued for 1.5 hr. The crude reaction mixture was filtered through Alcoa

alumina. The reaction vessel was rinsed with an additional 100 ml of methylene chloride, and this solution filtered as well. The organic layers were combined and washed with 1N HCl to remove any remaining pyridine. The organic layer was dried with magnesium sulfate, filtered, and the solvent evaporated to afford 1.32 g of a white solid (87%). Recrystallization from hexane afforded (-)-camphor (29) identical with authentic material; m.p. 174-176°C (sealed tube); $[\alpha]_D^{20} = -38.1^\circ$ (c = 11.8, CH₃OH); i.r. 1750 cm⁻¹.

Method B.⁸⁸ In a dry 1000 ml three-neck round bottom flask, equipped with a drying tube, addition funnel, thermometer, and magnetic stirrer were placed 69.3 g (0.45 mole) of (-)-borneol (175) and 600 ml of anhydrous, freshly distilled, tert-butanol. The mixture was stirred to dissolve the borneol, and 72.9 g (76 ml, 0.67 mole) of tert-butyl hypochlorite added over a 15 min. period. The reaction temperature was maintained at 20-25°C. After addition of hypochlorite the reaction was allowed to stir at room temperature for an hour. Removal of the solvent affords a white solid which is sufficiently pure for the next transformation, provided that not more than a trace of tert-butanol remain. The yield of (-)-camphor (29) is essentially quantitative. This method is far superior to the previous one, particularly for large scale preparations.

(-)-3-Bromocamphor (201).^{54a} In a 500 ml three-neck round bottom flask, fitted with a dropping funnel, condenser, thermometer, and a magnetic stirrer, were placed 68 g (0.45 mole) of (-)-camphor (29) and 150 ml of glacial acetic acid. The mixture was warmed to 80°C (a homogeneous solution resulted), and a solution of 32 ml (93.5 g, 0.585 mole)

of bromine in 32 ml of acetic acid added dropwise over a 3 hr. period. Additional stirring for 4 hr. completed the reaction (vpc on a 4' x $\frac{1}{4}$ " carbowax 20M column at 190°C). The reaction was cooled, and poured into a 1000 ml beaker containing ca. 200 ml of ice. The crude product precipitates out of solution. The white solid was filtered and recrystallized from 95% ethanol. Three more crops of crystals may be obtained by concentrating the mother liquors to yield 79.5 g (77%) of (-)-3-bromocamphor (201). Alternatively, petroleum ether (b.p. 30-60°C) may be used in the recrystallization: m.p. 75-78°C, $[\alpha]_D^{20} = -132^\circ$ (c = 5.3, CH₃OH) (lit., $[\alpha]_D^{23} = +125^\circ$, c = 1.0 for the enantiomeric form); i.r. 1760, 1388, 1374 cm⁻¹; n.m.r. 4.62 (d, J = 4.5 Hz), 1.08 (s), 0.96 (s), 0.94 (s).

(+)-3,9-Dibromocamphor (145). We followed the procedure of Corey and coworkers⁶² without any modifications, and found satisfactory physical properties for this compound; m.p. 150-152°C; $[\alpha]_D^{29} = +98.5^\circ$ (c = 1.3, CHCl₃) (lit. $[\alpha]_D = 98.8^\circ$, c = 4.0, CHCl₃); i.r. 1760 cm⁻¹; n.m.r. 4.57 (d, J = 4.5 Hz), 3.68 (d, hpfs, * J = 10.5 Hz), 3.31 (d, J = 10.5 Hz), 1.10 (s), 1.02 (s). Our yields varied from 54% to 72% of theory.

(-)-3,9-Dibromocamphor (202). Same as above, $[\alpha]_D^{29} = -98.5^\circ$ (c = 1.3, CHCl₃).

* hpfs = hyperfine splitting

(+)-9-Bromocamphor ((+)- π -bromocamphor) (144), Method A. We again followed the procedure of Corey and coworkers⁶² without modifications, and found satisfactory physical properties for this molecule: m.p. = 80-90°C (mixture of crops); $[\alpha]_D^{29} = +115^\circ$ (c = 1.21, CHCl₃) (lit. $[\alpha]_D = +116^\circ$, c = 6.0, CHCl₃); i.r. 1750 cm⁻¹; n.m.r. 3.52 (d, hpfs, J = 10.5 Hz), 3.11 (d, J = 10.5 Hz), 0.97 (s), 0.91 (s).

Method B.⁶³ A solution of (+)-3,9-dibromocamphor (145) (10 g, 33 mmoles) in 75 ml of N,N-dimethylaniline (free of monomethylaniline) was refluxed under an inert atmosphere for 24 hr. The reaction exhibited varied coloration during this time. The initially formed yellow "complex" turned green, dark blue, violet, and finally red-brown. A small amount of light blue sublimate deposited on the upper walls of the reaction flask during the initial stages of the reaction, and became clear towards the end. After refluxing for 24 hr. the mixture was allowed to cool to room temperature and dissolved in 150 ml of ether. The solution was washed with 80 ml of chilled conc. HCl, followed by three, 250 ml, washes with water. Dehydration of the organic solution, filtration, and solvent evaporation afforded 6 g of slightly yellow colored solid (80%). Several recrystallizations from hexane afforded 5 g (67%) of pure (+)- π -bromocamphor (144); m.p. = 85-89°C. Method A was found to be a superior method.

(-)- π -Bromocamphor (30), Method A. Same procedure followed as for (+)- π -bromocamphor (144): $[\alpha]_D^{29} = -115^\circ$ (c = 1.21, CHCl₃).

Method B. Not tried

(+)- π -Iodocamphor (191), Method A. The procedure used by Corey and coworkers⁶² was tried, but found to be less satisfactory than our own: m.p. = 62-63°C; $[\alpha]_D^{29} = +139^\circ$ (c = 0.878, CHCl₃) (yield = 75%). The spectral properties of this compound were in close agreement with those reported by Money and coworkers.^{54f}

Method B. In a 500 ml three-neck round bottom flask, fitted with a magnetic stirrer, condenser, and addition funnel were placed 83.0 g (0.5 mole) of dry pulverized KI in 300 ml of anhydrous DMF. Under a positive pressure of N₂ gas, the reaction temperature was brought to 100-110°C (bath temp.), and a clear yellow solution resulted. To the reaction was added a solution of 23.1 g (0.1 mole) of (+)- π -bromocamphor (144) in 25 ml of DMF (rapidly). The reaction became cloudy instantly, and a precipitate resulted shortly (KBr). Heating was continued for 4 hr.. At this time an aliquot was removed, and vpc showed approximately 98% completion. Our experience has been that the reaction can be stopped here. After allowing the reaction to cool to room temperature, it was poured into a separatory funnel containing 150 ml of water. The remaining solid (in the reaction vessel) was dissolved with additional water and added to the funnel. The mixture was extracted three times with 100 ml of light petroleum ether (b.p. 30-60°C). The combined organic layers were boiled with some decolorizing charcoal and filtered while hot through MgSO₄. An additional 30 ml of solvent were used to rinse the flask. The resulting solution was concentrated to ca. 50 ml and allowed to cool. Colorless needles were obtained. Two crops were collected to afford 25.3 g of (+)- π -iodocamphor (91%), that contained only a trace of starting material (vpc on a 8' x $\frac{1}{4}$ " 5% FFAP column at 220°C); m.p. 62.5-63°C (lit. 56°C);

$[\alpha]_D^{29} = +139^\circ$ ($c = 0.878$, CHCl_3). The spectral properties of this compound were in close agreement with those previously reported. This method is superior to that used by Corey and coworkers.⁶²

(-)- π -Iodocamphor (203), Method A. Not tried

Method B. Identical procedure to that found above for (-)- π -bromocamphor (30): $[\alpha]_D^{29} = -139^\circ$ ($c = 0.878$, CHCl_3).

(+)- π -Bromocamphor-1,3-dioxolane (192). The following procedure typifies the general reaction. One equivalent of ketone ((+)- π -bromocamphor (144)) was refluxed with 10 equivalents of ethylene glycol, and a quantity of solvent corresponding to ten times the weight of ketone with a catalytic amount of p-toluenesulfonic acid. A Dean-Stark trap was used to collect the water formed in this reaction. Reflux time was approximately 30 hr. Aliquots showed that the reaction stops at about 85-90% completion, and cannot be driven any further by the methods that we tried. The reaction was worked up by allowing it to cool, and adding it to a 5% solution of NaHCO_3 . Separation of layers was followed by a wash of the aqueous with an equivalent amount of solvent. The organic layers were combined, dried with Na_2SO_4 and filtered. Evaporation of the solvent afforded material balance of approximately 85% purity (15% ketone) (vpc on 8' x $\frac{1}{4}$ " 10% OV-17, 220°C). For (+)- π -bromocamphor-1,3-dioxolane (192): b.p. $93-98^\circ\text{C}$ at 0.25-0.3 mm; $[\alpha]_D^{29} = +1.23^\circ$ ($c = 10.0$, CHCl_3) (lit. $[\alpha]_D^{24} = +1.2^\circ$, $c = 7.46$, CHCl_3). The spectral properties of this compound were equivalent to those previously reported.^{54f}

(-)- π -Bromocamphor-1,3-dioxolane (205).^{54f} Same procedure as above using (-)- π -bromocamphor (30) instead: $[\alpha]_D^{29} = -1.2^\circ$ (c = 7.46 CHCl₃).

(-)- π -Iodocamphor-1,3-dioxolane (193), Method A. The same procedure as that for the displacement of (+)- π -bromocamphor (144) with KI, except, of course, substituting (+)- π -bromocamphor-1,3-dioxolane (192): yield = 85%, other 15% is starting material. Physical properties of (193): b.p. 111-113°C at 0.3-0.4 mm; $[\alpha]_D^{29} = -2.21^\circ$ (c = 10.0, CHCl₃) - note that (-)- π -iodocamphor-1,3-dioxolane is related to the (+)-camphor series. The spectral properties of this compound are in agreement with those previously reported.^{54f}

Method B. The material could also be prepared by forming the ketal directly from (+)- π -iodocamphor (191).

(+)- π -Iodocamphor-1,3-dioxolane (204), Methods A and B. See above for general methods, using instead (-)- π -bromocamphor-1,3-dioxolane (205) or (-)- π -iodocamphor (203). Physical properties of (204): b.p. 111-113°C at 0.3-0.4 mm; $[\alpha]_D^{29} = +2.21^\circ$ (c = 10.0, CHCl₃). The spectral properties of this compound are in agreement with those previously reported.^{54f}

2-Methyl-9-bromo-2-bornanol (152). To 33.1 g (1.36 moles) of Mg⁰ turnings in 150 ml of freshly distilled anhydrous ether (distilled from sodium benzophenone ketyl) were added, slowly, 85.0 ml (194 g, 1.36 mole) of iodomethane under an inert atmosphere. The reaction needed to be cooled periodically. When formation of the Grignard

reagent ceased, the solvent was evaporated under reduced pressure until a thick gray paste remained. Then 300 ml of anhydrous dichloromethane were introduced, and the solution filtered through a fritted funnel under a slight nitrogen pressure. This solution of Grignard reagent was then added dropwise to a solution of (+)- π -bromocamphor (144) (63.0 g, 0.273 mole) in 100 ml of dichloromethane. After addition was complete, the reaction was refluxed for 40 hr. The reaction was worked up by pouring into water, and extracting the aqueous phase with ether several times. The combined organic layers were dried using K_2CO_3 . If $MgSO_4$ was used instead, its slight acidity was sufficient to dehydrate the alcohol to the exocyclic methylene compound (157). After evaporation of the solvent, 69.1 g of crude material were obtained. This contained substantial amounts of starting material (ca. 20-30%) and was treated directly with 64 g of hydroxylamine hydrochloride and 80 g of KOH in 1000 ml of 95% ethanol. The mixture was refluxed for 3 hr., cooled, and extracted with ether (additional water added to dissolve the inorganic salts). Dehydration of the combined ethereal layers was again accomplished by K_2CO_3 . Evaporation of the solvent afforded 35.0 g of pure (152) (52% yield). This yield was on the low side - the usual is on the order of 70-80%; m.p. 77.5-78.5°C; i.r. 3260 (m) free OH; n.m.r. 3.65 (d, hpfs, $J = 10.5$ Hz, 1.5 Hz), 3.19 (d, $J = 10.5$ Hz), 1.29 (s) and 1.27 (s) for the two epimers, 1.22 (s), 0.87 (s). Mass spectrum: m/e 246, 248 (M^+); m/e 228, 230 (M^+ less H_2O); m/e 167 (M^+ less Br); m/e 149 (M^+ less H_2O , Br).

2-Methylene-9-bromobornane (157). As mentioned above the acid catalyzed dehydration of (152) was very facile, producing the exocyclic

methylene compound (157). Since we were not particularly interested in preparing this compound, only incomplete spectral data is available: i.r. 3100, 1657 cm^{-1} ; n.m.r. 4.65 (m, $J = 3$ Hz), 3.58 (d, hpfs, $J = 10.5$ Hz), 3.17 (d, $J = 10.5$ Hz), 0.92 (s).

Preparation of bromoketone (153), Method A. A solution of 5.46 g (22.1 mmoles) of 3° alcohol (152) in 25 ml of acetonitrile prewarmed to 55°C was rapidly mixed with a solution of 24.2 g (44.2 mmoles) of ceric ammonium nitrate (CAN) in 75 ml of 30% aqueous acetonitrile also prewarmed to 55°C. On mixing, a deep-red color was formed, which lasted only a few seconds. The resulting mixture was yellow in color, and was worked up after one minute by pouring it into 150 ml of chilled water. The aqueous mixture was washed three times with 50 ml of ether. The combined organic extracts were washed with 5% NaHCO_3 and saturated NaCl , followed by drying with MgSO_4 . Evaporation of the solvent afforded 5.36 g of crude product. This accounted for the material balance, but vpc showed it to be a complex mixture. The crude material was subjected to short-path distillation under reduced pressure (Kugelrohr) to afford 3.84 g of still another mixture although not as complex as the first (71%). In this instance vpc retention times showed that the major component (52%) was the desired one, and that one of the other components was the exocyclic methylene compound (157) described above: b.p. 100°C, 0.4 mm (vide infra); i.r. 3040, 1715 cm^{-1} ; n.m.r. 5.36 (m), 3.39 (s), 2.10 (s), 1.58 (m, $J = 1.5$ Hz), 0.91 (s). Mass spectrum: m/e 244, 246 (M^+); m/e 186, 188 (M^+ less acetone - McLafferty rearrangement); m/e 107 (M^+ less acetone, Br). If the reaction was run at 0°C one could observe the emergence of some exocyclic olefin isomer, which

had two sets of triplets with hyperfine splitting centered at 4.92 and 4.78, respectively.

Method B. To a solution of 2.6 g (11.4 mmoles) of bromonitrile (161) in 50 ml of anhydrous ether were added 5.18 ml of a 2.2M solution of MeLi in ether (11.4 mmoles) at -72°C under an inert atmosphere. The reaction turned reddish-orange. After 6 hr. an additional equivalent of MeLi was added, maintaining the reaction temperature at -72°C . The reaction was allowed to proceed for a total of 12 hr. at -72°C , then allowed to warm up to 0°C slowly over a period of 8 hr. The mixture was quenched with excess $\text{Na}_2\text{SO}_4 \cdot 10\text{H}_2\text{O}$, followed by 4N H_2SO_4 . The aqueous layer was extracted twice with ether. The combined layers were dried with MgSO_4 , filtered, and the solvent evaporated to afford a brown oil which was distilled affording 0.802 g (29%) of pure bromo-ketone (153): b.p. 100°C , 0.4 mm.

π -Bromocamphoroxime (160). To a solution of 35.0 g (0.151 mole) of π -bromocamphor in 50 ml of pyridine were added 42.1 g (0.606 mole) of $\text{NH}_2\text{OH} \cdot \text{HCl}$ in 50 ml of pyridine. The mixture was stirred at 50°C for 24 hr. The reaction was poured into ice-conc. HCl, and washed three times with 50 ml of ether. The combined ethereal layers were washed with brine, dried with MgSO_4 , and filtered. Evaporation of the solvent afforded 35.7 g (96%) of π -bromocamphoroxime (160): m.p. $124.5-125.5^{\circ}\text{C}$; i.r. $3400\text{ cm}^{-1}(\text{s})$, $1695\text{ cm}^{-1}(\text{w})$; n.m.r. 3.59 (d, hpfs, $J = 10.5\text{ Hz}$), 3.20 (d, $J = 10.5\text{ Hz}$), 1.05 (s), 1.02 (s) - it would appear that we only have anti-oxime .

Preparation of bromonitrile (161). To a solution of 9.65 g (39.2 mmoles) of π -bromocamphoroxime (160) in 75 ml of dry pyridine, under an inert atmosphere, was added a solution of 7.50 g (39.4 mmoles) of p-toluenesulfonyl chloride (pTsCl) in pyridine (10 ml). The reaction was allowed to stir for three days at room temperature, then poured into water. The aqueous phase was extracted three times with 50 ml of ether, and the combined organic layers washed with 1N HCl to remove any pyridine left. The organic layer was washed with 5% NaHCO₃, saturated NaCl, and dried over MgSO₄. Filtration and solvent evaporation afforded 6.10 g (68.3%) of bromonitriles (161) and (162). The product was sufficiently pure to be used in subsequent transformations. The crude product consisted of a mixture of endocyclic and exocyclic olefins in a ratio of 3:2, respectively: b.p. 99-103°C, 0.3 mm; i.r. 2240 cm⁻¹(m), 1650 cm⁻¹(w); n.m.r. 5.29 (m, endocyclic olefin), 4.92 and 4.78 (t with hpfs, exocyclic olefin), 3.37 (s), 3.34 (s), 1.62 (m, endocyclic isomer), 1.09 (s, exocyclic isomer), 1.02 (s, endocyclic isomer).

Attempts to cyclize bromoketone (153) to ketone (154). Numerous attempts were made to cyclize this material using a wide variety of bases, solvents, and conditions. All these experiments failed to provide the desired product, for which no evidence was found spectroscopically. It would not be feasible to present all the conditions tried in this experimental. We also tried to effect the cyclization using pyrrolidine (via the enamine), affording starting material and a complex mixture of other products. During this phase of research our department did not possess a Finnigan GC-mass spectrometer. If it

had, we may have been able to observe trace amounts of material. The situation being what it was, the mixtures were very difficult to separate by liquid chromatography.

π -Acetoxycamphor (166). A solution of 0.50 g (2.16 mmoles) of π -bromocamphor and 5 g (52.1 mmoles) of potassium acetate, in 15 ml of anhydrous DMSO was heated at 100-120°C under an inert atmosphere for 72 hr. The reaction was allowed to cool to room temperature and water added to dissolve the precipitated inorganic salts. Extraction with petroleum ether (b.p. 30-60°C) was followed by a wash of the organic layers with saturated NaCl. The combined organic layers were dried with MgSO₄, and after evaporation of the solvent 0.32 g of π -acetoxycamphor (166) (71%) obtained. The n.m.r. spectrum of crude (166) showed no starting material: b.p. 88-90°C, 0.5 mm; i.r. 1750-1735 cm⁻¹ (s, broad), 1240 cm⁻¹; n.m.r. 4.02 (non eq. H's, J = 11 Hz), 2.04 (s), 0.96 (s), 0.92 (s).

π -Hydroxycamphor (167). To a solution of 4.09 g (19.5 mmoles) of acetoxkyetone (166) in 450 ml of 95% ethanol were added 50 g of KOH pellets. The reaction mixture was refluxed for 30 min., then the solvent evaporated to one fourth the original volume. The resulting pasty material was poured into water and washed twice with 200 ml of ether. The combined organic layers were washed with saturated NaCl, and dried with MgSO₄. Evaporation of the solvent afforded an oily material which was recrystallized from dichloromethane yielding 3.0 g (92%) of pure π -hydroxycamphor (167): m.p. 233°C (sublimes); i.r. 3620 cm⁻¹(s), 3500 cm⁻¹, 1745 cm⁻¹; n.m.r. 3.63 (ABX, J = 11 Hz),

1.96 (s). Mass spectrum: m/e 168 (M^+), m/e 137 (M^+ less CH_2OH).

9-Acetoxy-2-methyl-2-bornanol (173). Following the same procedure as for π -acetoxycamphor (166) we used instead π -bromo-2-methyl-2-bornanol (152). The π -acetate in this series was formed in nearly quantitative yield. The material was used in the next experiment without purification: i.r. 3529 cm^{-1} (s), $1720\text{--}1750\text{ cm}^{-1}$ (s, broad); n.m.r. 3.97 (ABX, $J = 11\text{ Hz}$), 2.04 (s), 1.23 (s), 1.21 (s), 0.92 (s). Mass spectrum: m/e 166 (M^+ less HOAc), m/e 108 (M^+ less HOAc, acetone).

2-Methyl-2,9-bornanediol (174). The procedure for the hydrolysis of π -acetoxycamphor (166) was employed. The yields were on the order of 70%: m.p. $120\text{--}125^\circ\text{C}$ (sublimes); i.r. 3400 cm^{-1} (s); n.m.r. 3.5 (ABX, $J_{AB} = 11\text{ Hz}$), 1.22 (s, 2 CH_3 's), 0.90 (s). Mass spectrum: m/e 183 (M^+ less H), m/e 166 (M^+ less H_2O), m/e 108 (M^+ less H_2O , acetone).

π -Oxocamphor (168). We employed the same procedure as in Method A oxidation of (-)-borneol (175) to (-)-camphor (29). The yields were nearly quantitative in this transformation. The material could be recrystallized from benzene: i.r. $1748, 1725\text{ cm}^{-1}$; n.m.r. 8.96 (s), 1.32 (s), 1.18 (s). Mass spectrum: m/e 166 (M^+), m/e 109 (M^+ less H and acrolein from double McLafferty rearrangement).

Attempted oxidations of 2-methyl-2,9-bornanediol (174). Several attempts were made at the oxidation of this material with ceric ammonium nitrate. These reactions, as before, afforded complex mixtures that were not separable. Attempts were also made at oxidizing the compound

with tert-butyl hypochlorite (as in the case of (-)-borneol (175) to (-)-camphor (29), but these reactions also afforded complex mixtures. Finally, we attempted to oxidize the 1° alcohol selectively using the $\text{CrO}_3 \cdot (\text{pyr.})_2$ method (vide supra), but the reagent attacked both alcohol functions.

π -Oxocamphor dimethyl acetal (169). π -oxocamphor (168) (0.83 g, 5 mmoles) was treated with 15 ml of anhydrous methanol, 0.637 g (6 mmoles) of trimethyl orthoformate, and 50 mg of p-toluenesulfonic acid (tosic acid) for 10 hr. at R.T. The reaction mixture was poured into a NaHCO_3 solution, and washed with ether. The combined ethereal layers were dried with K_2CO_3 , and yielded 1.00 g of ketoacetal (94.3%) after evaporation of the solvent: i.r. 1750, 1060 cm^{-1} ; n.m.r. 4.31 (s), 3.52 (s), 3.50 (s), 0.99 (s), 0.87 (s).

Attempts to react π -oxocamphor dimethyl acetal (169) with methyl magnesium iodide. Formation of the Grignard reagent was done as usual, in ether. After formation, the solvent was evaporated and methylene chloride substituted in its place. The reagent was then added to the ketoacetal and the reaction refluxed for 40 hr. On workup a mixture of four products was obtained. It was comprised of starting material, desired product, and the product of attack on the acetal protecting group by the Grignard reagent. These materials were difficult to separate, but the n.m.r. spectrum of the mixture easily clarified their structures.

Preparation of the neopentyldiol monoacetal of π -oxocamphor (180),

Method A. A mixture of 1.24 g (5.85 mmoles) of dimethylacetal (169) and 0.61 g (5.85 mmoles) of neopentyl diol was refluxed in 50 ml of benzene containing a catalytic amount of tosic acid for 1 hr. After this time, the benzene was gradually distilled to 1/10 its original volume. Workup of the reaction mixture with NaHCO_3 solution (5%) and extraction with ether afforded 1.47 g of crystalline material after evaporation of the solvent (99.7%): i.r. 1745 cm^{-1} ; n.m.r. 4.46 (s), 3.62 (d, $J = 11\text{ Hz}$), 3.32 (d, $J = 11\text{ Hz}$), 1.15 (s), 0.97 (s), 0.92 (s), 0.71 (s). Mass spectrum: m/e 252 (M^+), m/e 115 (β -scission of acetal).

Method B. Alternatively, the material could be prepared directly from π -oxocamphor (168) and neopentyl diol in benzene, and a catalytic amount of tosic acid (cf. the synthesis of π -bromocamphor-1,3-dioxolane (192)). The yields were comparable.

Preparation of π -oxocamphor- π -1,3-dioxolane (179), Method A. By exchange from the dimethyl acetal (169) (see above), using ethylene glycol, in benzene, with a catalytic amount of tosic acid.

Method B. By direct formation from π -oxocamphor (168), ethylene glycol, benzene, and a catalytic amount of tosic acid (cf. preparation of π -bromocamphor-1,3-dioxolane). Distilled yield 87%: b.p. $98-100^\circ\text{C}$, 0.2 mm; i.r. 1750 cm^{-1} ; n.m.r. 4.90 (s), 3.85 (m), 1.03 (s), 0.80 (s). Mass spectrum: m/e 210 (M^+), m/e 73 (β -scission of acetal).

Preparation of methyl carbinol (182). Methyl magnesium iodide was prepared in ether as usual, then the solvent exchanged for 1:2 dichloromethane - benzene, respectively. To the Grignard reagent was

added the ketone (180) in benzene slowly (1.18 g, 4.67 mmol). The Grignard reagent was present in a five-fold excess. After addition of the ketone, the solution was refluxed for 82 hr. (bath temp. 80°C, reaction temp. 60°C). The reaction was then worked up with $\text{Na}_2\text{SO}_4 \cdot 10\text{H}_2\text{O}$ followed by more water. The organic layer was separated, and the aqueous reextracted twice with 200 ml portions of ether. The combined organic layers were dried with K_2CO_3 and the solvent evaporated to afford 1.28 g of oily material. Medium pressure chromatography on silica gel using 8:2 petroleum ether - ethyl acetate, respectively, afforded 0.331 g of pure 3° alcohol (26%): m.p. 105-106°C; i.r. 3600 cm^{-1} (m, sharp), a trace of ketone remained (1745 cm^{-1}); n.m.r. 4.42 (s), 3.59 (AB, $J = 11$ Hz), 3.29 (AB, $J = 11$ Hz), 1.26 (s), 1.22 (s), 1.18 (s), 0.98 (s), 0.72 (s). Mass spectrum: m/e 268 (M^+), m/e 253 (M^+ less CH_3), m/e 115 (β -scission of acetal).

Preparation of methyl carbinol (181). The same procedure as above was tried, and although some alcohol was formed, it was difficult to separate from the starting material, and from a third product. This could have been the exocyclic olefin. It had, nevertheless, a characteristic mass spectrum: m/e 226 (M^+), m/e 211 (M^+ less CH_3), m/e 73 (β -scission of acetal protecting group).

Oxidation of alcohol (182) with CAN. A solution of 100 mg (0.37 mmole) of alcohol (182) in 1.0 ml of CH_3CN prewarmed to 55°C was mixed with a solution of 0.409 g of CAN (0.746 mmole) in 1 ml of CH_3CN and 2 ml of water, also prewarmed to 55°C. The mixture was shaken for 1 min., then poured into water and extracted three times with 15 ml of

ether. The combined organic layers were washed with 5% NaHCO_3 , dried with Na_2SO_4 , and the solvent evaporated. An oily material was obtained. The n.m.r. of the crude product showed the presence of a small amount of methyl ketone, and a trace of aldehyde. The crude reaction product was refluxed with 6N HCl and some THF (for solubility purposes) for 6 hr. On workup, the n.m.r. showed little acetal, and little aldehyde. Thin layer chromatography showed at least four components. The material was subjected to basic conditions capable of inducing aldolization. After stirring at R.T. with KOH in ether for 7 hr, the i.r. showed a peak at 1680 cm^{-1} which could correspond to the desired enone, but it was very weak. The n.m.r. corroborated this observation, but evidence for the presence of the enone (172) was very weak.

Preparation of sulfone (197). The method of Grieco and coworkers was followed with (+)- π -bromocamphor-1,3-dioxolane (192) (1.14 g, 4.1 mmoles) to obtain 1.14 g oil (197) (79%): n.m.r. 7.43 (AA'BB'), 3.73 (m), 3.02 (AB, $J = 11\text{ Hz}$), 2.37 (s), 1.39 (s), 0.72 (s).

Preparation of ketalester (206). In a 50 ml three necked flask fitted with a condenser, dropping funnel, and a magnetic stirrer, 0.48 g of 50% NaH in mineral oil (10 mmoles) was washed free of oil with petroleum ether, and the reaction vessel evacuated and flushed three times with inert gas. Into the flask were introduced 6 ml of anhydrous DMF followed by 1.32 g (1.14 cc, 10 mmoles) of dimethyl malonate. The latter was added dropwise. The reaction with the NaH is, naturally, exothermic, but the reaction need not be cooled. Thus, the sodium salt goes into solution. The (+)- π -iodocamphor-1,3-dioxolane

(204) was added to the hot solution (0.644 g, 2 mmoles), and the reaction temperature brought to 150°C. The reaction was worked up after refluxing for 24 hr. (150°C, bath temp.) by pouring it into water and extracting twice with 50 ml of light petroleum ether (b.p. 30-68°C). The combined organic layers were dried with MgSO_4 , and the solvent evaporated. A great deal of dimethyl malonate remained, but this could be removed under reduced pressure and gentle heating. The product obtained was chromatographed at medium pressure (30-90 psi) on silica gel using 20% ethyl acetate - hexane as the solvent, affording 350 mg of ketalester (206) (65%): b.p. 120-128°C, 0.1-0.2 mm; i.r. 1740 cm^{-1} ; n.m.r. 3.85 (m), 3.67 (s), 1.02 (s), 0.81 (s). Mass spectrum: m/e 268 (M^+), m/e 237 (M^+ less OCH_3).

Preparation of (-)-ketoester (31), Method A. The ketalester (206) obtained in the previous experiment (200 mg, 0.75 mmole) was refluxed with 15 ml of moistened acetone and 50 mg of tosic acid for 1 hr. The reaction was then poured into 5% NaHCO_3 solution and extracted with light petroleum ether. Dehydration of the organic solution with MgSO_4 and evaporation of the solvent afforded 144 mg of a clear oil (97%): b.p. 113°C, 0.2 mm; $[\alpha]_D^{29} = -64.7^\circ$ ($c = 1.63$, CHCl_3); i.r. $1735\text{-}1750\text{ cm}^{-1}$ (s, broad); n.m.r. 3.69 (s), 0.93 (s), 0.82 (s). Mass spectrum: m/e 224 (M^+), m/e 193 (M^+ less OCH_3). HRMS for $\text{C}_{13}\text{H}_{20}\text{O}_3$: calculated 224.1412, found 224.1404.

Method B. In a 1000 ml three-neck flask, 17.23 g of 50% NaH in mineral oil were washed three times with 100 ml each of light petroleum ether to remove the oil. The remaining amounts of petroleum ether were removed at reduced pressure, and the reaction vessel flushed with

nitrogen gas. At this stage 450 ml of anhydrous DMF were introduced, and to the mixture added 47.4 g (41 ml, 0.359 mole) of dimethyl malonate, dropwise, over a period of 1 hr. The temperature of the reaction increased substantially, but this is helpful in solubilizing the malonate salt formed. After formation of the malonate anion, the temperature of the bath was increased to 150-160°C and 10 g (35.9 mmole) of (-)- π -iodocamphor (203) in 25 ml of DMF were added to the reaction. After 17 hr. of reflux there was a great mass of yellow solid in the reaction flask. This is usually an indication that the reaction has taken place. The mixture was allowed to cool to room temperature, then poured into ice-concentrated HCl, and extracted with light petroleum ether (b.p. 30-60°C) several times. The combined organic layers were dried with MgSO_4 , and the solvent evaporated to yield 7 g of oil containing some dimethyl malonate. Distillation afforded 4.0 g of ketoester (31) and 2.6 g of a higher boiling component which was not identified: b.p. 145°C, 0.3 mm. A GC-mass spectrum of the crude reaction product showed the presence of trace amounts of ketodiester (207). Mass spectrum: m/e 282 (M^+), m/e 251 (M^+ less OCH_3).

Preparation of hydroxyester (189). To a solution of 224 mg (1 mmole) of (+)-ketoester (199) (prepared in the same manner as (31)) in 8 ml of benzene was added 1 ml of a 1.036M solution (1.036 mmole) of triisobutylaluminum in benzene, at room temperature, under an inert atmosphere. The reaction was allowed to stir for 3 hr. followed by addition of 5 ml of methanol and 2 ml of water, and refluxing overnight (16 hr.). The aluminum salts (gel) were filtered through celite and the solvent evaporated. Since some water remained, this was removed

by extraction of the mixture with ether. The ether solution was dried with MgSO_4 , and the solvent evaporated to afford 201 mg of hydroxyester (90%). The material is a 10:1 epimeric mixture of exo- and endo-isomers, respectively: i.r. 3620, 1735 cm^{-1} ; n.m.r. 3.69 (s), 1.05 (s), 0.98 (s), 0.94 (s), 0.90 (s). The methine proton α to the OH is dwarfed by the 3.69 peak.

Reaction of hydroxyester (189) with CAN. To a solution of 150 mg (0.66 mmole) of hydroxyester in 10 ml of 75% aqueous HOAc were added 1.09 g (2.00 mmoles) of CAN (neat). The reaction was shaken vigorously for 30 min. at which time it was light yellow in appearance. The reaction was worked up by pouring it into brine and extracting twice with 25 ml of light petroleum ether. The combined organic layers were washed with 5% NaHCO_3 , dried with MgSO_4 , and evaporated to afford 65 mg (24%) of aldehydoester (185): i.r. 2710, 1740 cm^{-1} ; n.m.r. 9.76 (t), 5.34 (m), 3.68 (s), 1.60 (m), 0.88 (s).

Attempted cyclization of aldehydoester (185). The aldehydoester obtained in the previous experiment (65 mg, 0.29 mmole) was treated with a catalytic amount of NaOMe in MeOH at R.T. for 22 hr. The reaction was worked up by pouring it into 1N HCl and extracting with ether. The organic layer was dried with MgSO_4 , and the solvent evaporated. A brown oil was obtained, which consisted of starting material and several other components. Examination of this material by GC-mass spectroscopy did not show the presence of either the desired hydroxymethylene compound (187) or its deformylated derivative (154).

Preparation of (+)-oximinoester (32). A mixture of 3.89 g of (-)-ketoester (31) (17.4 mmoles), 6 g of $\text{NH}_2\text{OH}\cdot\text{HCl}$ (86 mmoles), and 25 ml of pyridine were stirred at 50°C for 2 days. The reaction was worked up by pouring into water, and extracting with ether. The aqueous phase was saturated with NaCl , and reextracted with ether. The combined ethereal layers were dried with MgSO_4 and the solvent evaporated to yield 3.61 g (87%) of an oil, which crystallized on standing. This material was sufficiently pure to use in the next experiment, however it could be recrystallized from ether: m.p. $88.5\text{--}89.5^\circ\text{C}$; $[\alpha]_{\text{D}}^{29} = +18.7^\circ$ ($c = 1.00$, CHCl_3); i.r. $3400\text{--}3500\text{ cm}^{-1}$ (s, broad), 1740 cm^{-1} (s), 1690 cm^{-1} (w); n.m.r. 3.67 (s), 1.04 (s), 0.82 (s). The n.m.r. spectrum did not show any evidence that we had syn oxime in the purified material or in the crude product. Mass spectrum: m/e 239 (M^+), m/e 208 (M^+ less OCH_3), m/e 222 (M^+ less OH), m/e 195 (M^+ less OH , HCN). HRMS for $\text{C}_{13}\text{H}_{21}\text{NO}_3$: calculated 239.1521, found 239.1531.

Preparation of cyanoester (33). To a solution of 2.39 g (10 mmoles) of oximinoester in 25 ml of dry pyridine was added a solution of 2.87 g (15 mmoles) of $p\text{-TsCl}$ in 25 ml of pyridine. The reaction was stirred at R.T. for a few minutes, then at 50°C for 24 hr. Workup as usual (cf. preparation of bromonitrile (161)) afforded 1.5 g (68%) of cyanoesters (33) and (208). The mixture consisted of endocyclic and exocyclic olefins in a ratio of 3:2, respectively. These materials were easily separated by medium pressure chromatography on silica gel using 20% ethyl acetate - hexane. The endocyclic isomer: $[\alpha]_{\text{D}}^{29} = -30.7^\circ$ ($c = 0.721$, CHCl_3); i.r. 2230, 1740 cm^{-1} ; n.m.r. 5.18 (m), 3.53 (s), 1.57 (m), 0.87 (s). Mass spectrum: m/e 221 (M^+), m/e 194 (M^+ less HCN),

m/e 180 (M^+ less CH_2CN). HRMS for $\text{C}_{13}\text{H}_{19}\text{NO}_2$: calculated 221.1416, found 221.1419. The exocyclic isomer: n.m.r. 4.79 (t, $J = 1.5$ Hz), 4.58 (t, $J = 1.5$ Hz), 3.52 (s), 0.87 (s). The exocyclic isomer could be converted to the endocyclic one by stirring the isomeric mixture (1.5 g) with 5 ml of trifluoroacetic acid (TFA) in methylene chloride (10 ml). The reaction was worked up by evaporating the solvent and the volatile reagent under reduced pressure. The residue was subsequently triturated with ether, washed once with 5% NaHCO_3 , dried with MgSO_4 , and the solvent evaporated. No material loss is observed, and only pure endocyclic olefin (33) observed: $[\alpha]_D^{29} = -30.7^\circ$ ($c = 0.721$, CHCl_3).

Preparation of (+)-hydrindanone (34). To a solution of 1.49 g (13.3 mmoles) of commercial potassium tert-butoxide in 50 ml of freshly distilled THF was added dropwise a solution of 1.47 g (6.65 mmoles) of (-)-cyanoester (33) in 20 ml of THF, at room temperature. After addition was complete, the reaction was allowed to stir for 15 min. at R.T., then poured into 1N HCl. The aqueous mixture was washed three times with 25 ml of ether. The combined organic layers were dried with MgSO_4 , filtered, and the solvent evaporated to afford 89 mg (70%) of (+)-hydrindanone (34). The product was recrystallized from ether: m.p. 130-131.5°C; $[\alpha]_D^{29} = +44.3^\circ$ ($c = 0.658$, CHCl_3); i.r. 3030 cm^{-1} (w), 2230 cm^{-1} (m), 1725 cm^{-1} (s), 1660 cm^{-1} (w); n.m.r. 5.4 (m), 3.67 (d, $J = 12.5$ Hz), 1.71 (m), 1.04 (s). Mass spectrum: m/e 189 (M^+), m/e 174 (M^+ less CH_3), m/e 134 (M^+ less CH_2CHCO , corroborated by base peak at m/e 55).

Preparation of tricyclic enone (216). To a solution of 50 mg (0.264 mmole) of cyanoketone (34) in 0.5 ml of benzene and 0.5 ml of a solution of 100 mg of Na⁰ in 100 ml of absolute ethanol were added 34 μ l of freshly distilled methyl vinyl ketone, under an inert atmosphere. The reaction was stirred for 19 hr., and then worked up with 1 ml of 1N HCl and ether. The organic layers collected from the previous extraction were dried with MgSO₄, and evaporation of solvent afforded 67 mg of a mixture of enone (216) and ketol (215b): i.r. 2220, 1683, 1627 cm⁻¹ (enone) - 3400, 2220, 1715 cm⁻¹ (ketol); n.m.r. 6.18 (m), 5.57 (m), 1.72 (m), 1.25 (s) (enone) - 5.57 (m), 1.72 (m), 1.25 (s) (ketol). Mass spectrum of enone: m/e 241, m/e 226 (M⁺ less CH₃). Mass spectrum of ketol: m/e 259 (M⁺), m/e 241 (M⁺ less H₂O), m/e 244 (M⁺ less CH₃).

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