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Diterpenoid Total Synthesis, an A → B → C Approach. VIII. Introduction of Oxygen at Carbon-11. Total Synthesis of (±)-Carnosic Acid Dimethyl Ether and (±)-Carnosol Dimethyl Ether[1]

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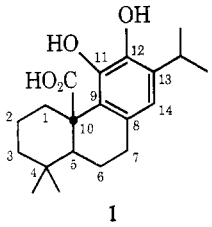
Total syntheses of the title compounds are described. Condensation of 10-carbethoxy-4,4-dimethyl-*trans*-7-decalone (**4**)[2] with ethyl formate followed by DDQ dehydrogenation produces the 8-formyl-Δ^8-7-octalone **6**, which is the key intermediate. Michael addition of *tert*-butyl acetoacetate or *tert*-butyl isovalerylacetate to **6** followed by acid-catalyzed *tert*-butyl ester cleavage, decarboxylation, and cyclodehydration of the resulting adducts affords trans-syn-cis tricyclic enediones **8a** and **8b**, which are dehydrogenated to 7-keto-12-phenols **9a** and **9b**, respectively. Hydrogenolysis of **9b** leads to 12-phenol **10a**, into which an 11-methoxy substituent was introduced by coupling with *p*-nitrobenzenediazonium chloride, O-methylation, sodium dithionite reduction, diazotization, and methanolysis to produce **14**. Ester cleavage (*t*-BuOK–Me_2SO) affords (±)-carnosic acid dimethyl ether. Alternatively, Michael addition of 1-methylsulfinyl-4-methyl-2-pentanone to **6** produces an adduct **22** which was subjected to Pummerer rearrangement, enol etherification, base-catalyzed cyclization, and O-methylation to afford **25b**. Hydrogenolysis gives **14**, while treatment with sodium borohydride followed by sodium hydride gives (±)-carnosol dimethyl ether. On exposure to hydrochloric acid in dimethyl sulfoxide, adduct **22** cyclizes with sulfoxide elimination, giving **9b**. Preparation of **4** by hydrogenation of the corresponding octalone is discussed, and the by-products sometimes encountered are identified as **28, 29, 30, 31, 33,** and **34**. Lactone **32** is described in connection with structure determination of **30**.

One of the advantages of the general A → B → C approach to diterpenoid synthesis which we have described[1a,3] is its potential for direct adaptability to construction of terpenoids containing a functional group rather than methyl at the angular position. Such a system is exemplified by carnosic acid (**1**)[4,5] and its derivatives carnosol (**2**)[6–10] (picrosalvin[7]) and rosmaricine (**3**).[5,11] Although the



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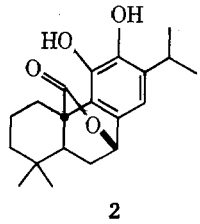

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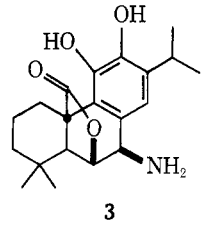

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latter two of these substances now appear to be artifacts from isolation rather than natural products,[5] the unusual state of oxidation at the angular position in carnosic acid and the interesting niche which has been proposed for it or analogous angular acids in diterpenoid biosynthesis[8] led us to investigate the total synthesis of such substances.

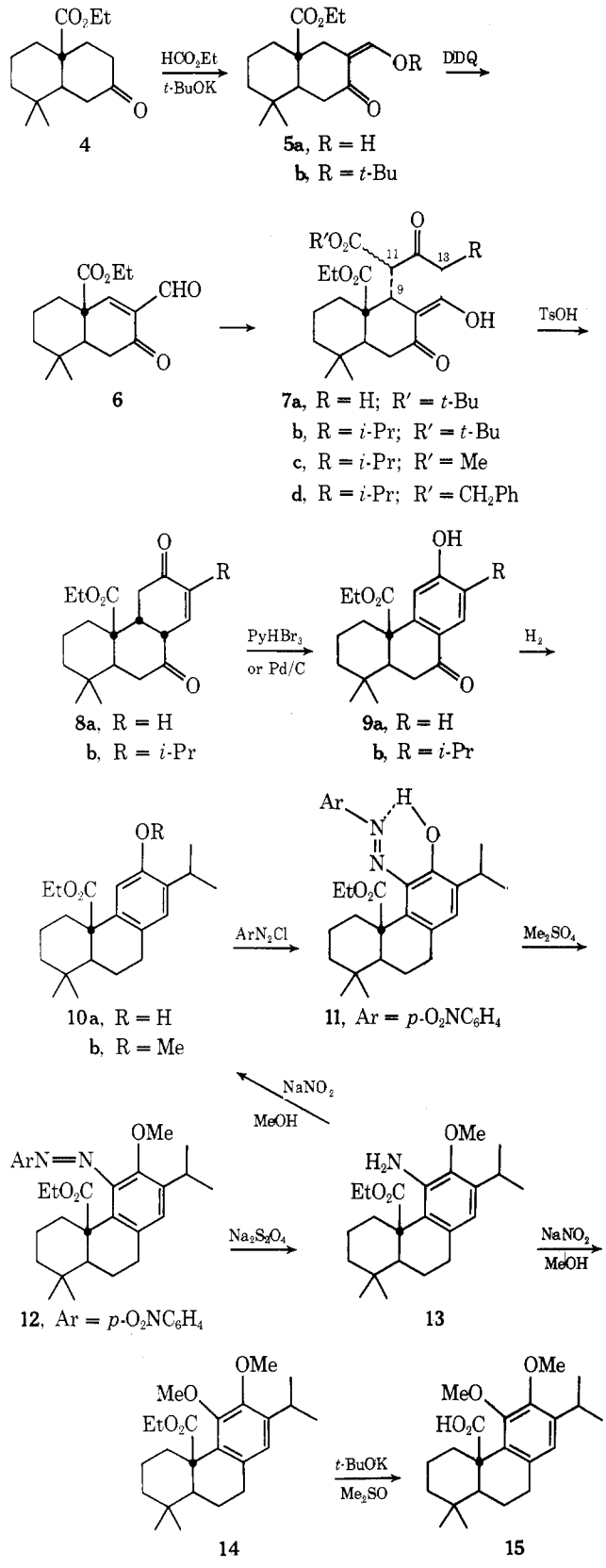
The A/B Ring System. The ideal bicyclic starting point for extension of this general synthetic plan[3] to the carnosic acid system is 10-carbethoxy-4,4-dimethyl-*trans*-7-decalone (**4**),[2] which contains both the appropriate oxidation level at the angular carbon and the necessary configuration of the A/B ring fusion. Preparation of this keto ester by an efficient and stereoselective route has already been reported.[12] Several improvements in the reactions leading to its synthetic progenitor, the corresponding Δ^5-7-octalone,[12] have subsequently been discovered and are recorded in the Experimental Section; they have raised the overall yield of the octalone to 87% from 6-carbethoxy-2,2-dimethylcyclohexanone. Some difficulties were encountered in reproducing the hydrogenation of this octalone to decalone **4**, but, as will be described later in this paper, these problems are largely circumvented by adjusting the solvent for the reduction.

Conversion of decalone **4** to the corresponding 8-formyl-Δ^8-7-octalone (**6**), the principal intermediate for attachment of ring C, followed the usual path[1a,3] (Scheme I). As anticipated,[1a] condensation of the decalone with ethyl formate affords its 8-hydroxymethylene derivative **5a**[13] to the exclusion of the 6-hydroxymethylene isomer. Dehydrogenation of enol **5a** by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)[1a,14] was found to be considerably improved by acetic acid catalysis, and under carefully controlled conditions this reaction leads to formyl enone **6** in 92% yield.

With the angular carboxyl in place and the skeletal configuration under control at this early stage of the synthesis, the major structural feature requiring attention in extension of the general synthetic scheme[3] to carnosic acid and its derivatives is the 11-hydroxyl group which is present in those natural products. Two fundamental approaches have been examined for obtaining such 11,12-dioxygenated systems rather than the 12-hydroxy compounds which were the objectives of initial work.[1a,3,15] In the first, an 11 oxygen is introduced into an 11-unsubstituted intermediate after ring C has been constructed. In the second, the C-ring elaboration scheme is varied so as to obtain an 11 functional group as an integral part of the ring extension sequence.

Carnosic Acid through 11-Unsubstituted Intermediates. As a model for the initial C-ring construction sequence, aldehyde **6** was treated with the sodium enolate of *tert*-butyl acetoacetate in benzene[3] or dimethyl sulfoxide

Scheme I



(Scheme I). ^{1}H NMR spectra of the crude adducts, which are formed rapidly and in high yield in either solvent, show two acetyl resonances, two *tert*-butyl resonances, and resonances from two different 9,11-proton systems, but otherwise are in accord with expectation for structure **7a,** as are their ir spectra. Thus two diastereomers of the adduct are produced, in relative amounts which depend on reaction conditions, as has subsequently been found common for such reactions. Evidence that these products differ in configuration at C-11 but that both correspond to a β configuration of the 9 hydrogen will be presented and discussed in a subsequent paper.[16] Reaction of the crude adduct mixture with *p*-toluenesulfonic acid in acetic acid[1a,3] affords a product with the correct ir and ^{1}H NMR spectroscopic properties[16] for enedione **8a,** and this is converted in 35% yield to phenolic ketone **9a** by dehydrogenation over 30% palladium on carbon with maleic acid as a hydrogen acceptor.[1a,17]

Analogous Michael addition of the sodium enolate of *tert*-butyl isovalerylacetate[1a] to aldehyde **6** affords adduct **7b,** again as a mixture of C-11[16] diastereomers. While one of these adducts could be obtained in pure form by fractional crystallization, for synthetic purposes the mixture was not separated, but was directly exposed to *p*-toluenesulfonic acid in glacial acetic acid to induce *tert*-butyl ester cleavage, decarboxylation, and cyclodehydration, with formation of the trans-syn-cis[16] tricyclic enedione **8b** in 80% yield from aldehyde **6.** By this time use of pyridinium bromide perbromide in acetic acid as a superior technique for C-ring aromatization had been discovered,[1a] and treatment of enedione **8b** with this reagent affords keto phenol **9b** in 90% yield. Hydrogenolysis over palladium on carbon leads to the phenolic ester **10a.** As a measure of the efficiency of this C-ring elaboration sequence, the overall yield from decalone **4** to phenol **10a** is 64%.

Introduction of the C-11 oxygen function followed the sequence utilized by Brieskorn et al.[8] for conversion of ferruginol to 11-hydroxyferruginol (Scheme I). Use of methanol rather than ethanol as solvent for coupling *p*-nitrobenzenediazonium chloride with phenol **10a** is highly advantageous, for the latter solvent is a much more effective reductant in this system than is the former,[18] and converts much of the diazonium salt to nitrobenzene before it can attack the phenol. Consequently yields of azo phenol **11** are 89% in methanol vs. 50% in ethanol. Like the corresponding ferruginol derivative,[8] this phenol is hydrogen bonded to the azo group as indicated by the absence of characteristic OH ir absorption; the same interaction is also probably responsible for its abnormally intense long wavelength uv absorption (480 nm, ϵ 8200, for phenol **11,** compared with 485 nm, ϵ 1000, for the corresponding ether **12**).[19]

Reaction of the azo phenol with dimethyl sulfate affords its methyl ether as a 4:1 mixture of chromatographically separable products. The major component, a red, crystalline solid, was completely characterized to conform to the assigned structure **12.** The minor substance, a purple oil, was not obtained in pure form, but its ir spectrum shows functional group absorptions identical with those of the major product, and sodium dithionite reduction of the 4:1 mixture produces amino ether **13** quantitatively. Thus we believe that both methylation products correspond to the azo ether constitution and represent stereoisomers about the N=N bond. It is, of course, not surprising that azo phenol **11** is not an analogous isomer mixture, for in that case only the anti isomer can be stabilized by intramolecular hydrogen bonding; such association is not possible for either of the ethers, and the syn ether becomes more competitive with the anti ether in stability.

Diazotization and methanolysis converts amino ether **13** into three compounds. The predominant product is the desired ethyl (±)-carnosate dimethyl ether (**14**), with ir and ^{1}H NMR spectra superimposable on those of a sample of the (+) enantiomer prepared by diethyl sulfate esterification of (+)-carnosic acid dimethyl ether.[20] Accompanying it are significant amounts of the 12-monomethoxy derivative

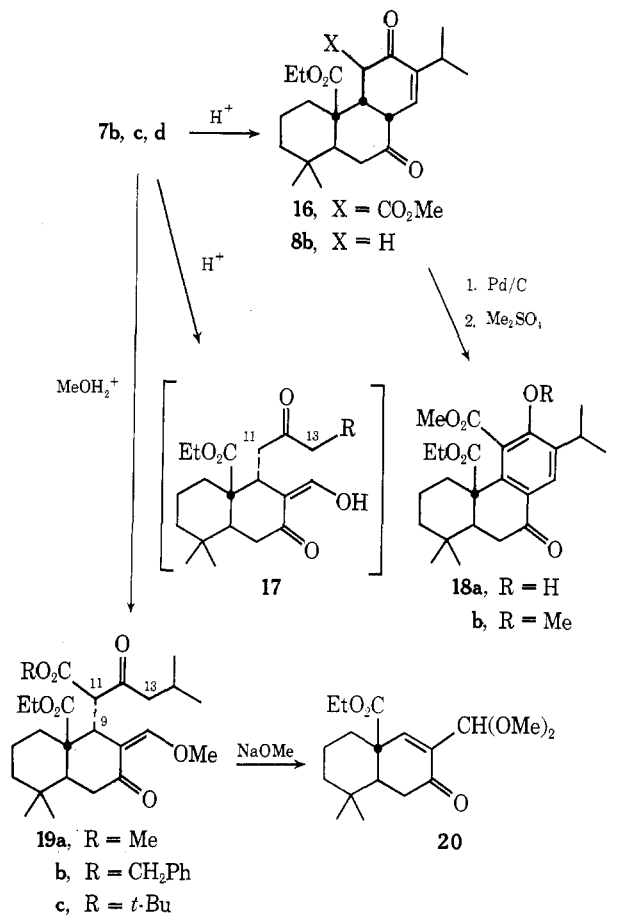
10b and 12-monophenol **10a** in a 3:2 ratio. The latter was identified by comparison with the sample obtained earlier in this synthesis, and the former was independently prepared by methylation of that phenol. These substances obviously result from reductions of the diazonium group which are competitive with its methanolysis,[18] with methanol serving as the reductant in production of at least **10b** and perhaps both compounds; whether the unusual formation of the phenol precedes, follows, or accompanies the reduction process (for example, with the *o*-methoxy group serving as an intramolecular reductant) was not established.

Inasmuch as extreme steric hindrance would be expected to render saponification of the angular ester very slow,[12] cleavage to acid **15** was carried out by potassium *tert*-butoxide in dimethyl sulfoxide,[21] conditions which could in the case of ethyl esters involve an elimination to form ethylene by way of attack at β carbon of the ethyl group, a much more exposed site than the carbonyl carbon. Whether such a mechanism is involved was not examined, but synthetically the reaction follows the desired course, smoothly producing (±)-carnosic acid dimethyl ether (**15**) in 80% yield. Like the synthetic ester this substance has ir and ^{1}H NMR properties indistinguishable from those of the naturally derived sample,[20] the structure of which is thus confirmed by total synthesis as well as by degradative work. Inasmuch as the dextrorotatory dimethyl ether has been demethylated by boron tribromide,[5] the present research lacks only resolution of the racemic dimethoxy acid to constitute a formal total synthesis of carnosic acid itself.

Carnosol and Carnosic Acid through 11-Substituted Intermediates. Although the foregoing synthesis attained the desired goal, preparation of the 11,12-dioxygenated diterpenoid system, the general C-ring elaboration sequence seemed susceptible to major strategic improvement. At the stage of Michael adducts **7** a functional substituent already exists at the 11 position, and the synthesis involved its removal followed by several steps to reintroduce a function at the same point. Much more efficient, obviously, would be either a pathway in which the 11 substituent of an adduct such as **7** is retained during cyclization so it can be subsequently converted to the required hydroxyl, or a sequence in which the 11 substituent is replaced by the necessary oxygen prior to cyclization. Several routes designed to incorporate these features have been examined, and although only one has thus far been carried to fruition, certain results from others have provided important information regarding properties of adducts like **7** and their derivatives.

The first alternative involves use of adducts similar to **7b** in which the potential 11 substituent will be stable during cyclization and can later be selectively manipulated even in the presence of the angular carbethoxy group. The corresponding methyl and benzyl ester adducts **7c** and **7d** were potential candidates to satisfy these criteria, and each is produced as a mixture of two 11 diastereomers[16] by addition of the appropriate β-keto ester to aldehyde **6**. However, their acid-catalyzed cyclization to 11-substituted enediones such as **16** (Scheme II) is not readily accomplished. Standard conditions for conversion of *tert*-butyl ester **7b** to enedione **8b** leave methyl ester **7c** largely unaltered, and with benzyl ester **7d** produce a substantial quantity of the decarbobenzoxylated enedione **8b**. Thus, although they are often less acid sensitive than their *tert*-butyl counterparts, for this purpose benzyl esters are still too reactive to survive any of the acidic conditions which we have found to induce cyclization. These results strongly suggest that ester cleavage and decarboxylation of the *tert*-butyl esters precede cyclization, which occurs with intermediacy of the unisolated ketones **17**. Cyclization prior to decarboxylation is undoubtedly inhibited because formation of the requisite 12,13-enol competes poorly with formation of a conjugated 11,12-enol.

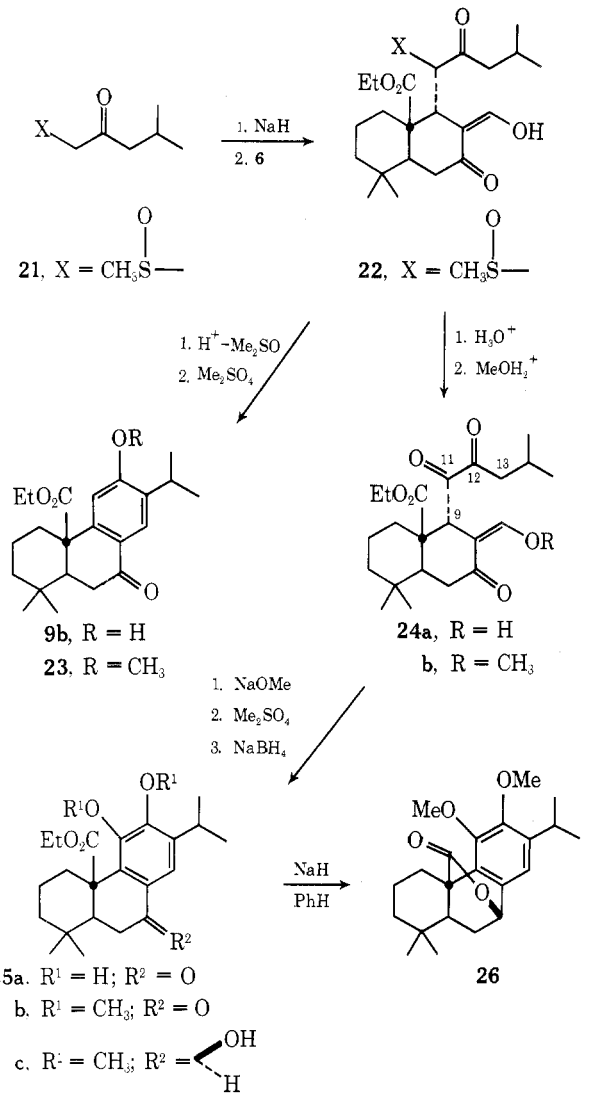
Scheme II



Longer exposure of methyl ester **7c** to acid also leads to formation of enedione **8b**, but in this instance it is not clear whether loss of the carbomethoxy group occurs before or after cyclization, for use of a short reaction time but a much greater acid concentration produces a complex mixture which spectroscopically appears to contain several isomers of the 11-carbomethoxy enedione **16**. A keto phenol with ir, uv, and ^{1}H NMR absorption appropriate for structure **18a** (including only one ArH and one OCH_3) can be isolated after dehydrogenation of such mixtures over palladium on carbon, and subsequent reaction with dimethyl sulfate produces a substance with *two* methoxyls and *one* ethoxyl (^{1}H NMR), as expected for ether diester **18b**. Thus this process apparently *can* allow retention of the 11-carbomethoxy substituent. Inasmuch as yields in the aromatization are undoubtedly capable of improvement (these investigations predated recognition of pyridinium bromide perbromide as the preferred reagent for such transformations[1a]), the sequence holds considerable potential for use under appropriate circumstances. However, it was not pursued in the present system after preliminary experiments indicated that a C-11 methyl ester would be difficult to distinguish chemically from the angular ethyl ester in spite of the steric hindrance of the latter. The 11-ester is also very hindered, and a variety of attempts to chemically differentiate the two functions were unsuccessful.

Base- rather than acid-catalyzed cyclodehydration of an adduct such as **7** does not occur under conditions which would permit retention of an 11-ester function, of course,

Scheme III



because both the hydroxymethylene proton and the C-11 proton are much more acidic than the C-13 proton which requires abstraction to initiate the appropriate aldol reaction. Furthermore, removal of the hydroxymethylene proton can lead to reversal of the Michael addition by which the adduct is produced, and in fact this is the primary result from protracted exposure of adduct **7c** to several basic reagents.

This particular retro-Michael process should be blocked in the corresponding hydroxymethylene enol ethers **19.** In spite of the fact that deprotonation at C-11 would still be seriously competitive with that at C-13 in such derivatives, the possibility of bringing about the necessary intramolecular Michael addition–elimination sequence was examined in order to learn if an unfavorable equilibrium for C-13 deprotonation of the enol ether could be offset by a favorable equilibrium for C-8 deprotonation of the vinylogous β-diketone system in the potential cyclization product **16.** Acid-catalyzed enol etherification of the adducts occurs rapidly and efficiently, even without loss of the acid-sensitive *tert*-butyl group in the case of **7b,** with the methyl enol ethers **19a–c** usually being produced as mixtures of two C-11 diastereomers.[16] However, these derivatives do not cyclize in base. Treatment of ether **19a** with sodium methoxide in either methanol or dioxane leads primarily to loss of the side chain and formation of acetal **20,** identified through its alternate preparation by reaction of aldehyde **6** with methanolic acid. Apparently the nucleophilic methoxide ion attacks enol ether **19a** at the methoxymethylene carbon, and the less basic β-keto ester enolate departs in a process resembling the SN2′ mechanism. This undesirable reaction is avoided by using a bulkier and thus less nucleophilic base such as potassium *tert*-butoxide in benzene, but that reagent still does not engender cyclization; it simply leaves enol ether **19a** unchanged after 62 h at room temperature. Other basic systems we examined also failed to induce the transformation of interest.

The key to the second major strategic alternative for completion of the 11,12-dihydroxy diterpenoid system lies in selecting a C-ring synthon of general structure **21** such that the group X can first serve to activate its α carbon for enolate formation and then, in the adduct **22,** is subject to simple transformation into an oxygen substituent (Scheme III). Ideally this new substituent would be a keto group, so that in compounds like **24** enolization of the 12-ketone would of necessity be toward C-13, and aldol cyclodehydration would lead directly to the dihydroxy aromatic system. Furthermore, the presence of an 11-ketone should allow epimerization of the C-9 side chain to the thermodynamically preferred β (equatorial) configuration in future extensions of the synthetic pathway to C-hydroaromatic substances.

The sulfoxide grouping appeared to neatly satisfy these requirements, and thus we examined Michael addition of the sodium enolate of 1-methylsulfinyl-4-methyl-2-pentanone (**21**) to keto aldehyde **6.** Within 25 min at room temperature in dimethyl sulfoxide this reaction forms adduct **22** in quantitative yield as a mixture of two separable crystalline diastereomers. These adducts are believed to differ in configuration only at C-11 or at sulfur, because both diastereomers lead to the same α-diketone **24a** when asymmetry at C-11 is destroyed under conditions where the C-9 configuration is not altered (see below). They are assigned the 9β-H configuration in analogy to the keto ester adducts.[16]

Pummerer rearrangement[22] of either adduct or their mixture quantitatively produces α-diketone **24a.** When this reaction was carried out in a fully deuterated solvent system (D_2O–acetic acid-d_1), the C-9 H singlet at τ 5.42 in the ^1H NMR spectrum of the α-diketone was not appreciably diminished in relative intensity, indicating that little or no deuterium is incorporated at that point and that thus little or no enolization of the product toward C-9 occurs under these conditions. Accordingly this α-diketone has the same 9 configuration as does its precursor **22.**

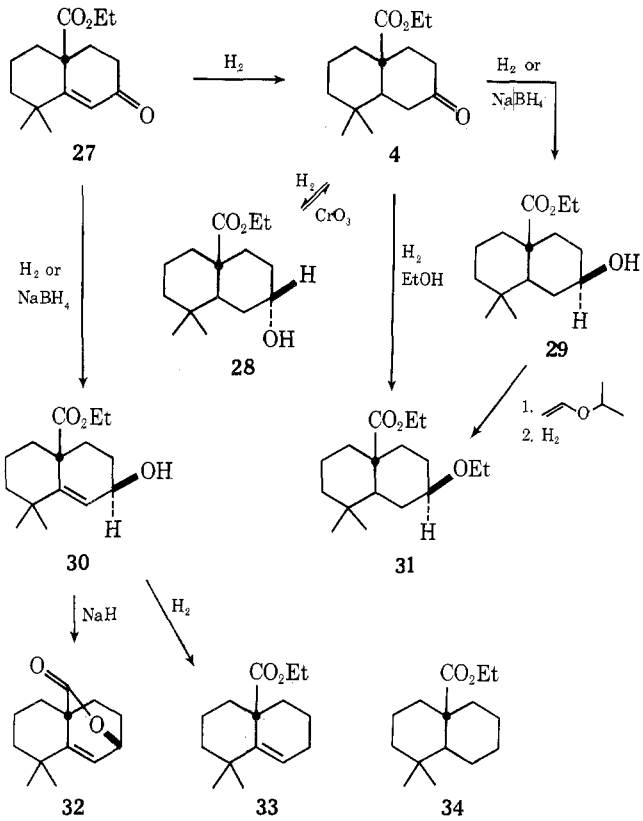
For reasons that are not clear, exposure of the α-diketone to *p*-toluenesulfonic acid in acetic acid does not bring about cyclization under conditions which presumably convert the related 12-monoketone **17** to enedione **8b.** However, unlike the enol ethers of β-keto ester adducts (**19**), in this system the corresponding hydroxymethylene enol ether **24b** is devoid of protons substantially more acidic than that at C-13, and the side chain at C-9 is now in a functional state which is incapable of anionic departure in an SN2′ reaction. Thus the reactions which interfere with base-catalyzed ring closure of the former systems have been blocked, and ether **24b,** which is formed in methanolic *p*-toluenesulfonic acid without enol etherification at the α-diketo function, readily undergoes the expected Michael cyclization, elimination, and aromatization in methanolic sodium methoxide, producing keto catechol **25a** in 73% yield. Methylation followed by hydrogenolysis affords ethyl (±)-carnosate dimethyl ether identical with the sample prepared by the earlier sequence. As a comparison of the two routes, we would note that from the bicyclic aldehyde **6** to this dimethoxy ester the first pathway proceeds in 28% yield over eight steps whereas the latter involves six steps with an overall yield of 53%.

A further advantage of the β-keto sulfoxide sequence is that the 7-keto group need not be removed until after the C-ring functionality is intact, and consequently that carbonyl is available for manipulation should 7-functional substances like carnosol or rosmaricine be synthetic targets. For example, sodium borohydride reduction of dimethoxy ketone **25b** stereoselectively affords the 7β-hydroxy derivative **25c**, which upon exposure to potassium *tert*-butoxide in benzene[4] is converted to (±)-carnosol dimethyl ether (**26**). The racemic lactone has identical ir and ^{1}H NMR spectroscopic properties with those of a naturally derived sample,[23] confirming the assigned structural relationships.

Finally, the β-keto sulfoxide adducts prove to be promising not only for synthesis of the 11,12-dioxygenated systems which were the main goal of this research, but also for substances such as the ferruginol types, etc., where only 12 hydroxylation is required.[1a] Exposure of adduct **22** to concentrated hydrochloric acid in dimethyl sulfoxide brings about not the Pummerer rearrangement but an acid-catalyzed cyclization with elimination of the methylsulfinyl group, to directly produce the 7-keto 12-phenol **9b** in 97% yield. This product was identified by comparison of its methyl ether with that of the keto phenol prepared earlier from adduct **7b** by the two-step sequence cyclization–aromatization. Study of the sequence of events in this conversion, most notably whether elimination precedes or follows cyclization, is presently incomplete. Nonetheless, its potential synthetic utility is obvious.

Hydrogenation of 10-Carbethoxy-4,4-dimethyl-Δ^5-7-octalone (27). Early in this paper we mentioned that difficulties were encountered in attempts to reproducibly prepare decalone **4** by hydrogenation of octalone **27** in ethanol over palladium on carbon catalysts. This reaction has been unusually erratic. In some instances the decalone is produced in high yield with only traces of by-products, as described earlier.[12] On numerous occasions, however, with no intentional differences in conditions but with different commerical samples of catalyst, the rate of hydrogen uptake has not changed radically after absorption of 1 equiv and ketone **4** has been accompanied by substantial quantities of other reduction products (Scheme IV). These substances, which vary considerably in relative amounts from run to run, have been identified as ethyl ether **31** (often the predominant by-product and sometimes the major component of the reduction mixture),[24] 7α- and 7β-*trans*-decalols **28** and **29** (the former never in more than trace amounts), and 7β-octalol **30**, as well as the previously described octalin **33**[12,25] and decalin **34**.[12] The constitution and configuration of ether **31**, which is also produced nearly quantitatively by hydrogenation of either octalone **27** or decalone **4** in the presence of acid, are verified by its alternate synthesis (Scheme IV) from hydroxy ester **29**, the structure of which was substantiated earlier.[26] Jones oxidation[27] of hydroxy ester **28** affords *trans*-decalone **4**, which confirms the α orientation of its 5 hydrogen and thereby demonstrates that it differs from the 7β-hydroxy isomer **29** only in configuration at C-7. Although octalol **30** has not been isolated from the abnormal hydrogenation products, ^{1}H NMR spectra of these mixtures often contain all of the resonances characteristic of the octalol formed by sodium borohydride reduction of enone **27**. Treatment of this octalol with sodium hydride produces a lactone (**32**), and inasmuch as this reaction must involve intramolecular attack of a 7β-alkoxide on the 10-ethoxycarbonyl group[12,26] it confirms assignment of the 7β-hydroxy configuration to the octalol;[28] this assignment is also in accord with the existence of a 2.5-Hz spin coupling, and thus a ca. 90° dihedral angle,[29] between the 6 and 7 protons in the octalol and several derivatives.

Scheme IV



Apparently at least two competitive pathways are involved in the early stages of hydrogenation of octalone **27**, one leading to decalone **4** which becomes the probable source of ether **31**[30] and decalols **28** and **29**,[31] and the other producing octalol **30** and thence the octalin and decalin.[12,32] The relative rates of all these processes are obviously critically dependent on undefined properties of the catalyst which vary among samples, rendering the reaction of capricious synthetic utility. It is nonetheless significant that none of the products corresponds to a cis ring fusion, and but for the very small amount of 7α-decalol **28**, hydrogen attachment at C-7 is also α; thus the various reduction reactions all involve selective approach of catalyst from the less hindered α face of the ring system.[34] Efforts to characterize the precise nature and sequence of the various reduction steps and the properties of the catalyst which so dramatically control their relative rates, or to perfect the reduction in ethanol, were not pursued, however, after it was found that in ethyl acetate the octalone is usually hydrogenated almost exclusively (ca. 95%) to the decalone.

Experimental Section

General procedures and techniques were the same as described earlier.[1a] Unless otherwise specified, HCl, NaOH, KOH, $NaHCO_3$, K_2CO_3, and Na_2CO_3 solutions were aqueous. Brine refers to saturated aqueous NaCl. General procedures for isolation of reaction products are abbreviated as follows: (A) the specified organic solution was washed with the indicated sequence of aqueous solutions followed by water or brine and dried ($MgSO_4$ unless otherwise specified), and solvent was removed either in vacuo or by evaporation on the steam bath under a stream of dry N_2; (B) the indicated aqueous mixture was thoroughly extracted with the specified organic solvent followed by the steps in procedure A; (C) the reaction mixture was added to water followed sequentially by the steps in procedures B and A.

10-Carbethoxy-4,4-dimethyl-Δ^5-octalone-7 (27) was prepared as described earlier.[12] The yield of distilled 2-carbethoxy-2-(3′-ketobutyl)-6,6-dimethylcyclohexanone was 93% when methyl vinyl ketone was distilled as well as dried just before use, and the yield in its cyclodehydration to octalone **27** was 93% when the pyr-

rolidine:diketone molar ratio was increased to 3.3, the aqueous extract was acidified with three times the prescribed amount[12] of concentrated HCl, and base treatment of the aqueous extract[1a] was included in the isolation procedure.

10-Carbethoxy-4,4-dimethyl-5α-decalone-7 (4). Hydrogenation of 6.25 g (0.025 mol) of **27**, mp 69.5–70.5 °C, over 267 mg of 30% Pd/C in 130 ml of EtOAc at 1 atm required 1.25 h, after which H_2 absorption ceased. Isolation as described[12] afforded 5.98 g (95%) of recrystallized **4**, mp 45–46 °C (lit.[12] mp 45–46.5 °C).

10-Carbethoxy-4,4-dimethyl-8-hydroxymethylene-5α-decalone-7 (5a). To a stirred solution of 5.7 g (0.15 g-atom) of K in 120 ml of dry *t*-BuOH was added 5.7 g (22.6 mmol) of **4**, mp 45–46 °C; 10 min later 10 ml (0.12 mol) of ethyl formate (dried over K_2CO_3 and distilled from P_2O_5, bp 50–52 °C) in 10 ml of *t*-BuOH was added dropwise during 25 min. After 4.5 h the solution had become very viscous and 14 ml of glacial HOAc was quickly added. Isolation C (ether and $CHCl_3$; water and $NaHCO_3$ wash) afforded 6.25 g (100%) of **5a** as a pale yellow viscous oil, the ^1H NMR spectrum of which showed no resonances attributable to major contamination: uv max (95% EtOH) 272 nm (ε 1640); (base) 312 nm (ε 4400);[35] ir ($CHCl_3$) 1710, 1665, 1640, 1580 cm^{-1}; ^1H NMR ($CDCl_3$) τ −4.28 (s, broad, 1 H), 1.90 (s, 1 H), ca. 5.90 and 6.00 (m,[36] 2 H), 8.82 (t, J = 7 Hz, 3 H), 9.08 (s, 3 H), 9.22 (s, 3 H). Attempted purification by crystallization, sublimation, or chromatography led to decomposition, so the crude material was used in further work.

When concentrated HCl was used to acidify the reaction mixture, **5a** was accompanied by 5–20% (^1H NMR integration of the *tert*-butyl resonance) of the **8-*tert*-butoxymethylene derivative 5b.** This substance was isolated from a Florisil chromatogram of the mother liquors from the subsequent oxidation. Recrystallization from petroleum ether–$CHCl_3$ afforded **5b** as long, white needles: mp 108–109 °C; uv max (95% EtOH or base) 277 nm (ε 15 500); (acid) 273 nm (ε 10 100); (base, after acid) 312 nm (ε 11 300); ir ($CHCl_3$) 1715, 1670, 1580 cm^{-1}; ^1H NMR ($CDCl_3$) τ 2.40 (m, 1 H), ca. 5.90 and 5.94 (m,[36] 2 H), 8.68 (s, 9 H), 8.82 (t, J = 7 Hz, 3 H), 9.12 (s, 3 H), 9.23 (s, 3 H).

Anal. Calcd for $C_{20}H_{32}O_4$: C, 71.39; H, 9.59. Found: C, 71.64; H, 9.30.

10-Carbethoxy-4,4-dimethyl-8-formyl-5α-Δ⁸-octalone-7 (6). To a solution of 6.35 g (22.6 mmol) of crude **5a** (no contamination detectable by ^1H NMR) and 51 drops (ca. 18 mmol) of glacial HOAc in 55 ml of dioxane was quickly added 5.05 g (22.3 mmol) of DDQ (mp 213–215 °C dec), and the mixture was stirred for 5.5 min. Solvent was rapidly removed in vacuo at ca. 23° and the residual gum was thoroughly extracted with seven 30-ml portions of petroleum ether–$CHCl_3$ (6:1) which were combined with 50 ml of ether, washed with $NaHCO_3$ until the washings were colorless, dried, and evaporated in vacuo to produce 6.41 g (102%) of yellow semisolid which was washed with cold ether to give 5.80 g (92%) of **6**, mp 93–94 °C. Recrystallization from $CHCl_3$–petroleum ether (bp 30–60 °C) afforded yellowish crystals: mp 92–93.5 °C; uv max (95% EtOH) 245 nm (ε 5100); (base) 302 nm (ε 20 500); ir ($CHCl_3$) 1720, 1700, 1680, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) τ 0.00 (s, 1 H), 2.78 (s, 1 H), 5.87 (q, J = 7 Hz, 2 H), 8.77 (t, J = 7 Hz, 3 H), 9.07 (s, 3 H), 9.18 (s, 3 H).

Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 69.11; H, 8.00.

10-Carbethoxy-4,4-dimethyl-8-hydroxymethylene-9α-(1′-carbo-*tert*-butoxy-2′-oxopropyl)-5α-decalone-7 (7a). Sodium hydride (9.3 mg, 0.39 mmol, as 16 mg of a 58% mineral oil dispersion) was added to a solution of 70 mg (0.44 mmol) of *tert*-butyl acetoacetate[37] in 8 ml of C_6H_6 in a N_2 atmosphere; after gas evolution ceased (ca 20 min) 100 mg (0.36 mmol) of **6** was added. After 10 min 3 drops of glacial HOAc were added and isolation C ($CHCl_3$) afforded 146 mg (92%) of two isomers of **7a** as a pale yellow, viscous oil: ir ($CHCl_3$) 1738 (sh), 1718, 1642, 1587 cm^{-1}; ^1H NMR ($CDCl_3$) τ −4.58 (s, broad, 1 H), 1.90 (s, 1 H), ca. 5.90 and 6.00 (m,[36] 2 H), 6.32 and 6.50 (AB, J = 7.5 Hz, isomer A) and 6.33 (s, isomer B) (total 2 H), 7.77 (s, isomer B) and 7.95 (s, isomer A) (total 3 H), 8.53 (s, isomer A) and 8.63 (s, isomer B) (total 9 H), 8.83 (t, J = 7 Hz, 3 H), 9.03 (s, 3 H), 9.17 (s, 3 H); relative intensities of the resolved signals from isomers A and B were in the approximate ratio of 3:1.

Alternatively, NaH (8.0 mg of a 58% dispersion in mineral oil, 0.19 mmol) was added to a solution of 57 mg (0.36 mmol) of *tert*-butyl acetoacetate in 4 ml of Me_2SO and after 15 min 50 mg (0.18 mmol, mp 90–92 °C) of **6** was added. After 5 min 3 drops of glacial HOAc were added and the mixture was processed as above to afford 79 mg (100%) of **7a** as pale yellow crystals (by ^1H NMR a 3:1 mixture of C-11 isomers, B preponderant). Recrystallization from pentane afforded 35 mg of pure isomer B as matted white crystals, mp 110–111 °C.

Anal. Calcd for $C_{24}H_{36}O_7$: C, 66.03; H, 8.31. Found: C, 65.89; H, 8.24.

10-Carbethoxy-17-nor-5α,8β,9β-podocarp-13-ene-7,12-dione (8a). A 162-mg (0.37 mmol) sample of crude **7a** was treated with 30 mg of TsOH in 4 ml of glacial HOAc for 1 h at 110 °C. The mixture was cooled, diluted with ether and water, and neutralized with solid Na_2CO_3. Isolation B (ether) afforded 99 mg (78%) of mostly crystalline **8a**, further purification of which was not attempted: ir ($CHCl_3$) 1712, 1685, 1625 cm^{-1}; ^1H NMR ($CDCl_3$) τ 2.95 (dd, J = 10 and 6 Hz, 1 H), 3.85 (d, J = 10 Hz, 1 H), ca. 5.70 and 5.80 (m,[36] 2 H), 6.22 (t, J = 5 Hz, 1 H), 6.55 (t, J = 14 Hz, 1 H), 8.68 (t, J = 7 Hz, 3 H), 9.08 (s, 3 H), 9.17 (s, 3 H).

10-Carbethoxy-12-hydroxy-17-norpodcarpa-8,11,13-trien-7-one (9a). A solution of 99 mg (0.31 mmol) of crude **8a** and 38 mg (0.21 mmol) of maleic acid in 5 ml of 80% EtOH containing 80 mg of 30% Pd/C was refluxed for 13 h under N_2, cooled, filtered, diluted with ether, and washed with 5% $NaHCO_3$. The phenol was extracted into 1% NaOH. Acidification followed by isolation B (ether) left 37 mg (37%) of residue which was sublimed, affording **9a** as a colorless glass which did not crystallize and was thus characterized only spectrally: ir ($CHCl_3$) 3610, 3300, 1720, 1670, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) τ 5.98 (q, J = 7 Hz, 2 H), 8.90 (t, J = 7 Hz, 3 H), 9.07 (s, 3 H), 9.15 (s, 3 H).

10-Carbethoxy-4,4-dimethyl-8-hydroxymethylene-9-(1′-carbo-*tert*-butoxy-2′-oxo-4′-methylpentyl)-5α-decalone-7 (7b). This adduct was prepared as described for **7a**, using 113 mg of a 58% NaH dispersion in mineral oil (2.7 mmol), 540 mg (2.70 mmol) of *tert*-butyl isovalerylacetate, bp 94–99 °C (0.7–0.9 mm),[1a] and 500 mg (1.80 mmol) of **6**, mp 93–94 °C, in 40 ml of C_6H_6. Reaction was quenched with 1 ml of glacial HOAc after 20 min, and 1.13 g of crude **7b** was isolated as described for **7a** with the addition of a $NaHCO_3$ wash of the $CHCl_3$ solution. This product was contaminated with *tert*-butyl isovalerylacetate but not by **6** (^1H NMR assay). A sample was washed with and recrystallized from pentane to afford an analytical sample of a 2:1 mixture of C-11 isomers[16] of **7b** (integration of the *tert*-butyl resonance) as white needles: mp 105–127 °C; uv max (95% EtOH) 288 nm (ε 7600); (base) 306 nm (ε 16 000); ir ($CHCl_3$) 1735 (sh), 1715, 1635, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) τ −4.65 (s, broad, 1 H), 1.87 (s, 1 H), ca. 5.90 and 6.00 (m,[36] 2 H), 6.33 (s, 2 H), 8.55 (s, isomer A) and 8.65 (s, isomer B) (total 9 H), 8.83 (t, J = 7 Hz, 3 H), 9.02–9.17 (12 H).

Anal. Calcd for $C_{27}H_{42}O_7$: C, 67.76; H, 8.85. Found: C, 67.74; H, 8.83.

Recrystallization from $CHCl_3$–petroleum ether (bp 30–60 °C) afforded colorless prisms, mp 121–123 °C, which appeared (^1H NMR) to be mainly the preponderant isomer (B): uv max (95% EtOH) 285 nm (ε 7000); ir ($CHCl_3$) 1735 (sh), 1715, 1640, 1590 cm^{-1}.

Anal. Calcd for $C_{27}H_{42}O_7$: C, 67.76; H, 8.85. Found: C, 67.57; H, 8.87.

10-Carbethoxy-17-nor-5α,8β,9β-abiet-13-ene-7,12-dione (8b). Crude **7b** (5.20 g, contaminated with *tert*-butyl isovalerylacetate, ca. 4.3 g, 9.0 mmol of available adduct assuming quantitative addition to 9.0 mmol of **6**) and 67 mg of TsOH in 70 ml of glacial HOAc was heated under reflux for 3 h and cooled, 200 mg of NaOAc was added, and solvent was distilled in vacuo to provide a yellow gum which was partitioned between $CHCl_3$ and water. Isolation B ($CHCl_3$, $NaHCO_3$ wash) provided a residue which was washed thoroughly with cold pentane to afford 2.52 g (78% based on **6**) of **8b** as white needles, mp 134–135.5 °C. Recrystallization from EtOAc provided the analytical sample: mp 135–135.5 °C; uv max (95% EtOH) 232 nm (ε 9000); (base) 255 nm (ε 7600), 440 (20 000); ir ($CHCl_3$) 1710, 1675 cm^{-1}; ^1H NMR ($CDCl_3$) τ 3.28 (dd, J = 6 and 1 Hz, 1 H), ca. 5.73 and 5.83 (m,[36] 2 H), 6.27 (t, J = 5 Hz, 1 H), 8.70 (t, J = 7 Hz, 3 H), 8.97 (d, J = 7 Hz, 3 H), 9.02 (d, J = 7 Hz, 3 H), 9.10 (s, 3 H), 9.17 (s, 3 H).

Anal. Calcd for $C_{22}H_{32}O_4$: C, 73.29; H, 8.95. Found: C, 73.52; H, 8.94.

10-Carbethoxy-12-hydroxy-17-norabieta-8,11,13-trien-7-one (9b). Aromatization was conducted as described for (±)-sugiol,[1a] using 2.00 g (5.55 mmol) of **8b**, mp 134.5–135.5 °C, and 1.79 g (5.75 mmol) of pyridinium bromide perbromide, mp 132 °C dec, in 120 ml of glacial HOAc. After 30 min isolation C ($CHCl_3$, $NaHCO_3$ wash) provided 2.19 g of white, amorphous solid which was washed with cold pentane to afford 1.79 g (90%) of **9b**, mp 176–180 °C. Recrystallization from EtOAc gave **9b** as a white powder: mp 184–185 °C; uv max (95% EtOH) 238 nm (ε 20 000), 290 (13 900); (base) 257 nm (ε 13 100), 349 (30 000); ir ($CHCl_3$) 3590, 3350 (br), 1715, 1665,

1600, 1575, 1500, 1460 cm^{-1}; ^1H NMR ($CDCl_3$) τ 1.85 (s, 1 H), 2.07 (s, 1 H), 3.08 (s, 1 H), ca. 5.96 and 6.00 (m,[36] 2 H), 8.77 (d, J = 7 Hz, 6 H), 8.88 (t, J = 7 Hz, 3 H), 9.05 (s, 3 H), 9.13 (s, 3 H).

Anal. Calcd for $C_{22}H_{30}O_4$: C, 73.70; H, 8.43. Found: C, 73.57; H, 8.33.

10-Carbethoxy-12-hydroxy-17-norabieta-8,11,13-triene (10a). A mixture of 598 mg (1.67 mmol) of **9b**, mp 176–180 °C, 105 mg of 30% Pd/C, and 1 drop of concentrated H_2SO_4 in 40 ml of EtOAc was hydrogenated at 1 atm for 2 h and filtered, 100 mg of catalyst and 1 drop of H_2SO_4 were added, and hydrogenation was repeated for 2 h.[38] Filtration and isolation A afforded 576 mg (99%) of **10a** as a fine white powder, mp 129–132 °C, which was recrystallized from pentane–EtOAc to afford white prisms: mp 134–135 °C; uv max (95% EtOH) 286 nm (ϵ 3500); (base) 305 nm (ϵ 4600); ir ($CHCl_3$) 3585, 3410 (br), 1710 cm^{-1}; ^1H NMR ($CDCl_3$) τ 3.15 (s, 1 H), 3.25 (s, 1 H), 3.58 (s, 1 H), 6.00 (q, J = 7 Hz, 2 H), 8.82 (d, J = 7 Hz, 6 H), 8.90 (t, J = 7 Hz, 3 H), 9.03 (s, 3 H), 9.18 (s, 3 H).

Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.37. Found: C, 76.89; H, 9.26.

10-Carbethoxy-11-*p*-nitrophenylazo-12-hydroxy-17-norabieta-8,11,13-triene (11). The procedure follows one of Brieskorn et al.[8] A solution of 400 mg (2.90 mmol) of *p*-nitroaniline, mp 147–148 °C, in 3.0 ml of concentrated HCl was diluted with 1.5 ml of water and cooled to 0 °C, and an ice-cold solution of 200 mg (2.90 mmol) of $NaNO_2$ in 1.0 ml of water was slowly added with vigorous stirring. After 15 min at 0 °C this solution was added over 5 min to a solution of 1.0 g (0.43 g-atom) of Na in 75 ml of MeOH containing 385 mg (1.12 mmol) of **10a**, mp 130–133 °C, to afford a deep blue solution which was stirred for 45 min at 0 °C, diluted with 150 ml of water, and acidified with glacial HOAc. Isolation B ($CHCl_3$, $NaHCO_3$ wash) afforded 910 mg of red oil which was filtered through 20 g of Al_2O_3 with pentane and 10% ether–pentane to produce 510 mg (92%) of red oil. Rechromatography afforded 18 mg of $PhNO_2$ followed by 490 mg (89%) of **11** as a deep red glass which crystallized from pentane as red needles: mp 154–155 °C; uv max (95% EtOH) 380 nm (ϵ 19 700), 480 (8200); (base) 380 nm (ϵ 16 000), 515 (8300); ir ($CHCl_3$) 1710, 1525, 1345 cm^{-1}; ^1H NMR ($CDCl_3$) τ ca. 1.67 and 2.05 (m, A_2B_2, J_{ortho} = 9 Hz, 4 H), 2.97 (s, 1 H), 5.95 (q, J = 7 Hz, 2 H), 8.77 (d, J = 7 Hz, 6 H), 8.88 (t, J = 7 Hz, 3 H), 9.00 (s, 3 H), 9.13 (s, 3 H).

Anal. Calcd for $C_{28}H_{35}N_3O_5$: C, 68.13; H, 7.15; N, 8.51. Found: C, 68.57; H, 7.40; N, 8.80.

10-Carbethoxy-11-*p*-nitrophenylazo-12-methoxy-17-norabieta-8,11,13-triene (12). According to the Brieskorn et al. procedure[8] a solution of 600 mg (1.22 mmol) of amorphous **11** (no impurities detectable by ^1H NMR) and 1.2 ml (12.4 mmol) of Me_2SO_4 in 120 ml of dry acetone was refluxed for 16 h over 25 g of anhydrous K_2CO_3. Filtration and distillation of solvent in vacuo left a deep purple oil which was chromatographed on 20 g of Al_2O_3 to give a first fraction (pentane and 10% C_6H_6–pentane) of 407 mg of red glass which appeared (^1H NMR) to be pure **12** and a second fraction (25% ether–pentane) of 83 mg (79% total) of deep purple glass which had ir ($CHCl_3$) 1705, 1590, 1525, 1335 cm^{-1}. The red isomer was rechromatographed and crystallized from pentane to afford an analytical sample of **12** as light red needles, mp 121–122 °C. Recrystallization from 95% EtOH afforded dark red prisms: mp 137–137.5 °C; uv max (95% EtOH) 279 nm (ϵ 14 500), 347 (11 200), 485 (1000); ir ($CHCl_3$) 1710, 1605, 1590, 1530, 1345 cm^{-1}; ^1H NMR ($CDCl_3$) τ ca. 1.68 and 1.97 (m, A_2B_2, J_{ortho} = 9 Hz, 4 H), 2.97 (s, 1 H), 6.03 (q, J = 7 Hz, 2 H), 6.47 (s, 3 H), 8.77 (d, J = 7 Hz, 6 H), 8.97 (t, J = 7 Hz, 3 H), 9.02 (s, 3 H), 9.20 (s, 3 H).

Anal. Calcd for $C_{29}H_{37}N_3O_5$: C, 68.61; H, 7.35; N, 8.28. Found: C, 68.86; H, 7.28; N, 8.46.

10-Carbethoxy-11-amino-12-methoxy-17-norabieta-8,11,13-triene (13). According to the general Brieskorn et al. procedure[8] a mixture of 590 mg (1.16 mmol) of amorphous **12** (chromatographed isomer mixture, no impurities detectable by ^1H NMR) and 9.5 g (54.6 mmol) of $Na_2S_2O_4$ in 140 ml of 95% EtOH was brought to reflux and enough water (ca. 70 ml) was added to form a homogeneous solution which was refluxed for 3 h. Isolation C ($CHCl_3$) afforded 558 mg of brown gum. Filtration through 10 g of Al_2O_3 with 1:1 hexane–C_6H_6 gave 436 mg (100%) of white solid, recrystallization of which from cyclohexane afforded 409 mg (94%) of pure **13** as white plates, mp 143–144 °C. The analytical sample had mp 143.5–144 °C; uv max (95% EtOH) 297 nm (ϵ 2900); (acid) 282 nm (ϵ 2300), 295 (ϵ 2300); ir ($CHCl_3$) 3455, 3370, 1690, 1615 cm^{-1}; ^1H NMR ($CDCl_3$) τ 3.65 (s, 1 H), 5.70 (s, broad, 2 H), 5.93 (q, J = 7 Hz, 2 H), 6.35 (s, 3 H), 8.80 (d, J = 7 Hz, 3 H), 8.82 (d, J = 7 Hz, 3 H), 8.83 (t, J = 7 Hz, 3 H), 9.02 (s, 3 H), 9.18 (s, 3 H).

Anal. Calcd for $C_{23}H_{35}NO_3$: C, 73.95; H, 9.44; N, 3.75. Found: C, 73.93; H, 9.14; N, 4.03.

Ethyl (±)-Carnosate Dimethyl Ether (14). The procedure follows one of Brieskorn et al.[8] A solution of 100 mg (0.268 mmol) of **13**, mp 143–144 °C, in 22 ml of absolute MeOH was acidified with 17 drops of concentrated H_2SO_4, cooled to 5 °C, and mixed with a solution of 25 mg (0.36 mmol) of $NaNO_2$ in 3 ml of MeOH. The mixture was kept at 5 °C for 15 min, allowed to warm to ca. 23 °C, refluxed for 30 min, cooled, and neutralized with $NaHCO_3$. Isolation B ($CHCl_3$) afforded 120 mg of crude product.

The crude products from several experiments (880 mg), all of which had similar ^1H NMR spectra, were chromatographed on 15 g of Al_2O_3 and eluted with cyclohexane, cyclohexane–C_6H_6 (9:1, 3:1, 1:1, and 1:3), and C_6H_6. The first two fractions (210 mg) consisted of 40% **10b** and 60% **14** (GLC, 250°). Fractions 3–7 (370 mg) were 97% **14** and 3% **10b.** Fractions 8–10 contained 120 mg of **10b** and **14** and 30 mg of **10a.**

Pure **10b** (15% total yield estimated from GLC) was identical (ir) with the authentic sample described below.

Phenol **10a** (10% total yield estimated from GLC) was purified by crystallization and recrystallization from pentane–EtOAc, mp 133–135 °C, ir identical with that of the sample described above.

Fractions 3–7 slowly crystallized at room temperature. Two recrystallizations from MeOH afforded **14** (60% total yield estimated from GLC) as white needles: mp 89.5–90°; spectral properties (ir, ^1H NMR) indistinguishable from those of a sample prepared from (+)-**15**; uv max (95% EtOH) 276 nm (ϵ 610); ir ($CHCl_3$) 1715 cm^{-1}; ^1H NMR ($CDCl_3$) τ 3.35 (s, 1 H), ca. 5.85 and 5.95 (m,[36] 2 H), 6.28 (s, 3 H), 6.33 (s, 3 H), 8.78 (t, J = 7 Hz, 3 H), 8.80 (d, J = 7 Hz, 6 H), 9.03 (s, 3 H), 9.18 (s, 3 H).

Anal. Calcd for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 74.49; H, 9.42.

Ethyl (+)-Carnosate Dimethyl Ether (14). A 100-mg (0.27 mmol) sample of (+)-carnosic acid dimethyl ether[20] was refluxed for 12 h with 50 mg (9.3 mmol) of Et_2SO_4 and 2 g of anhydrous K_2CO_3 in 10 ml of dry acetone, filtered, evaporated, taken up in ether, washed with dilute NH_4OH, dried, and concentrated. Filtration through acidic Al_2O_3 with C_6H_6 and a few drops of ether afforded (+)-**14** as a colorless oil; GLC (250 °C) showed a single peak; ir and ^1H NMR identical with those of the synthetic racemate.

10-Carbethoxy-12-methoxy-17-norabieta-8,11,13-triene (10b). Phenol **10a** (205 mg, 0.596 mmol, mp 128–133 °C) was methylated as described for **11**, using 8 g of anhydrous K_2CO_3 and 0.5 ml of Me_2SO_4 in 40 ml of dry acetone. The crude product from removal of acetone was taken up in $CHCl_3$–ether. Isolation A (dilute NH_4OH wash) gave 210 mg of pale yellow solid which was recrystallized from 95% EtOH to afford 198 mg (93%) of **10b** as colorless plates, mp 65–66 °C. The analytical sample had mp 66–66.5 °C; uv max (95% EtOH) 240 nm (ϵ 7100), 281 (ϵ 3800), 288 (ϵ 3700); ir ($CHCl_3$) 1705 cm^{-1}; ^1H NMR ($CDCl_3$) τ 3.13 (s, 1 H), 3.25 (s, 1 H), 6.00 (q, J = 7 Hz, 2 H), 6.30 (s, 3 H), 8.83 (d, J = 7 Hz, 6 H), 8.90 (t, J = 7 Hz, 3 H), 9.03 (s, 3 H), 9.18 (s, 3 H).

Anal. Calcd for $C_{23}H_{34}O_3$: C, 77.05; H, 9.65. Found: C, 77.42; H, 9.64.

(±)-Carnosic Acid Dimethyl Ether (15). A solution of 105 mg (0.270 mmol) of (±)-**14** (98% pure by GLC) and 0.50 g of freshly prepared *t*-BuOK in 5 ml of Me_2SO was heated for 2 h at ca. 95 °C, poured onto ice, acidified with 1.5 ml of concentrated HCl, and extracted with $CHCl_3$–ether which was extracted with 1% NaOH. The basic extract was acidified with concentrated HCl, and isolation B ($CHCl_3$) provided 90 mg (92%) of pale yellow solid. Recrystallization from 95% EtOH afforded 80 mg (82%) of (±)-**15** as white prisms, mp 226–228 °C. The analytical sample had mp 230.5–231.5 °C; ir and ^1H NMR identical with those of (+)-**15**;[20] uv max (95% EtOH) 276 nm (ϵ 700); ir ($CHCl_3$) 3000 (br), 1690 cm^{-1}; ^1H NMR ($CDCl_3$) τ 3.35 (s, 1 H), 6.28 (s, 3 H), 6.37 (s, 3 H), 8.82 (d, J = 7 Hz, 6 H), 9.05 (s, 3 H), 9.18 (s, 3 H).

Anal. Calcd for $C_{22}H_{32}O_4$: C, 73.29; H, 8.95. Found: C, 73.46; H, 8.96.

Methyl Isovalerylacetate. Methyl α-isovalerylacetoacetate was prepared by the procedure described for the analogous *tert*-butyl ester.[1a] The diketo ester was obtained from methyl acetoacetate, bp 170 °C, in 63% yield as a colorless oil: bp 110–111 °C (0.7 mm); ir (film) 1710 cm^{-1}; ^1H NMR (CCl_4) τ 6.27 (s, 3 H), 7.72 (s, 3 H), 9.07 (d, J = 7 Hz, 6 H). A MeOH solution of this diketo ester was treated with a catalytic amount of base for 12 h as described for preparation of the corresponding *tert*-butyl ester[1a] to provide 63% of methyl isovalerylacetate as a colorless liquid: bp 85–87 °C (1.25 mm); ir (film) 1745, 1705 cm^{-1}; ^1H NMR (CCl_4) τ 5.07 (s, 1

H, enol), 6.33 (s, 3 H, enol), 6.37 (s, 3 H, keto), 6.63 (s, 2 H, keto), 9.08 (d, J = 7 Hz, 6 H).

Anal. Calcd for $C_8H_{14}O_3$: C, 60.73; H, 8.92. Found: C, 60.94; H, 9.09.

10-Carbethoxy-4,4-dimethyl-8-hydroxymethylene-9-(1'-carbomethoxy-2'-oxo-4'-methylpentyl)-5α-decalone-7 (7c). An 850-mg (5.40 mmol) sample of methyl isovalerylacetate, bp 85–87 °C (1.25 mm), in 50 ml of Me_2SO was treated with 226 mg of a 58% NaH dispersion in mineral oil (5.40 mmol) for 30 min, 1.00 g (3.60 mmol) of **6**, mp 93–94 °C, was quickly added, and stirring was continued for 30 min. The yellow solution was acidified with 1 ml of glacial HOAc, diluted with 150 ml of water, and extracted with ether which was washed with 20% K_2CO_3. The potassium salt which formed at the interface was separated, dissolved in 50 ml of water, and acidified with concentrated HCl. Isolation B (ether; water and $NaHCO_3$ wash) afforded 750 mg (48%) of **7c** as a light yellow oil. A mixture of aldehyde **6**,[39] starting β-keto ester, and mineral oil was recovered from the initial ether extracts. Crude **7c** crystallized from cold petroleum ether (bp 30–60 °C), and three washings with the same solvent provided an analytical sample of a ca. 1:1 mixture of isomers (^1H NMR integration of the OCH_3 resonance) as a white powder: mp 75–95 °C; uv max (95% EtOH) 285 nm (ε 6900); (base) 285 nm (ε 18 000), 304 (18 000); ir ($CHCl_3$) 1740 (sh), 1720, 1645, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) τ 1.88 (s, broad, 1 H), 5.92 and 5.95 (q's each J = 7 Hz, total 2 H), 6.27 and 6.43 (s's, total 3 H), 8.83 (t, J = 7 Hz, 2 H), 9.02 (s, 3 H), 9.07 (d, J = 7 Hz, 6 H), 9.17 (s, 3 H).

Anal. Calcd for $C_{24}H_{36}O_7$: C, 66.03; H, 8.31. Found: C, 66.22; H, 8.05.

Benzyl Isovalerylacetate. Benzyl acetoacetate, bp 156–158 °C (10 mm), was acylated with isovaleryl chloride, bp 116–116.5 °C, as described for the corresponding *tert*-butyl ester.[1a] Attempted distillation resulted in decomposition, so the crude product (90% yield; ^1H NMR showed no resonance from major impurities) was used directly: ^1H NMR (CCl_4) τ 2.73 (s, 5 H), 4.87 (s, 2 H), 7.82 (s, 3 H), 9.18 (d, J = 7 Hz, 6 H). Base cleavage was conducted as described for preparation of methyl isovalerylacetate. The benzyl β-keto ester was obtained in 69% yield as a colorless liquid: bp 160–161 °C (1.0 mm); ir (film) 1740, 1710 cm^{-1}; ^1H NMR (CCl_4) τ 2.78 (s, 5 H), 4.97 (s, 2 H), 6.72 (s, 2 H), 9.17 (d, J = 7 Hz, 6 H).

Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.57; H, 7.92.

10-Carbethoxy-4,4-dimethyl-8-hydroxymethylene-9-(1'-carbobenzoxy-2'-oxo-4'-methylpentyl)-5α-decalone-7 (7d). This adduct was prepared as described for **7c** using 22 mg of a 58% NaH dispersion in mineral oil (0.54 mmol), 122 mg (0.540 mmol) of benzyl isovalerylacetate, bp 160–161 °C (1.0 mm), and 100 mg (0.360 mmol) of **6**, mp 93–94 °C, in 8 ml of Me_2SO. Preliminary isolation involved addition of 5 drops of glacial HOAc and 10 ml of water, extraction with ether, washing with water, extraction into 1% NaOH, and acidification with 5% HCl. Final isolation (method B, ether, water and $NaHCO_3$ wash) provided 141 mg (76%) of light yellow oil which contained ca. 75% **7d** and 25% **6** (^1H NMR assay).[39] This adduct was used without further purification: ^1H NMR ($CDCl_3$) τ 1.90 (s, broad, 1 H), 2.72 (s, 5 H), 4.85 (s, 2 H), 5.05 (s, 2 H), 5.97 (m, 2 H).

10-Carbethoxy-11-carbomethoxy-5α,8β,9β-17-norabiet-13-ene-7,12-dione (16). A solution of 333 mg (0.76 mmol) of crude **7c** and 150 mg of TsOH in 4 ml of glacial HOAc was heated for 2 h at 100 °C and processed as in the preparation of **8a** to yield 284 mg (85%) of a mixture of products as an oil with ir ($CHCl_3$) 1720, 1670, 1600 cm^{-1}. The ^1H NMR spectrum contained several absorptions in the OCH_3, OCH_2, CCH_3, and vinyl regions, suggesting the presence of several isomers of **16**. This material was used directly in the next reaction.

10-Carbethoxy-11-carbomethoxy-12-hydroxy-17-norabieta-8,11,13-trien-7-one (18a). A mixture of 323 mg (0.77 mmol) of crude **16** (oil), 100 mg (0.87 mmol) of maleic acid, and 150 mg of 30% Pd/C in 15 ml of 80% ethanol was heated to reflux under N_2, solvent was slowly removed in vacuo during ca. 1 h, and the residue was heated at 100 °C for 1 h, suspended in ether, filtered, and washed with 5% $NaHCO_3$. The phenol was extracted into 1% NaOH and isolated as described for **9a**. The semisolid residue, 115 mg (35%), was sublimed to afford **18a** as a colorless glass. Crystallization could not be effected, so **18a** was characterized spectrally only: uv max (95% EtOH) 239, 282 nm; ir ($CHCl_3$) 1730, 1670, 1600, and 1570 cm^{-1}; ^1H NMR ($CDCl_3$) τ 1.92 (s, 1 H), ca. 5.80 and 5.93 (m,[36] 2 H), 6.15 (s, 3 H), 8.74 (d, J = 7 Hz, 3 H), 8.77 (d, J = 7 Hz, 3 H), 8.80 (t, J = 7 Hz, 3 H), 9.07 (s, 3 H), 9.10 (s, 3 H).

10-Carbethoxy-11-carbomethoxy-12-methoxy-17-norabieta-8,11,13-trien-7-one (18b). A mixture of 104 mg (0.29 mmol) of crude **18a**, 3.5 g of anhydrous K_2CO_3, and 10 drops of Me_2SO_4 in 15 ml of dry acetone was refluxed for 12 h, cooled, filtered, and concentrated. The residue was chromatographed with C_6H_6 on silica gel to afford 98 mg (92%) of ether **18b** as a slightly yellow oil which could not be induced to crystallize and was therefore characterized only spectrally: ir ($CHCl_3$) 1725, 1672, 1585 cm^{-1}; ^1H NMR ($CDCl_3$) τ 1.87 (s, 1 H), 5.90 (q, J = 7 Hz, 2 H), 6.12 (s, 3 H), 6.22 (s, 3 H), 8.75 (d, J = 7 Hz, 3 H), 8.77 (d, J = 7 Hz, 3 H), 8.83 (t, J = 7 Hz, 2 H), 9.05 (s, 3 H), 9.15 (s, 3 H). TLC (1:1 C_6H_6–$CHCl_3$) showed only one spot.

10-Carbethoxy-4,4-dimethyl-8-methoxymethylene-9-(1'-carbomethoxy-2'-oxo-4'-methylpentyl)-5α-decalone-7 (19a). A solution of 308 mg (0.707 mmol) of **7c**, mp 75–95 °C, and 51 mg of TsOH in 25 ml of absolute MeOH was refluxed for 20 min, cooled, treated with 200 mg of NaOAc, and concentrated in vacuo. The residual gum was distributed between water and ether, and isolation B (ether, 1% NaOH wash) afforded 321 mg (100%) of **19a** as a colorless oil, a 3:1 mixture of C-11 epimers (^1H NMR integration of the vinyl resonance). Crystallization from and washing with petroleum ether and recrystallization from petroleum ether–EtOAc provided a sample of the minor isomer as white needles: mp 116–117 °C; uv max (95% EtOH) 269 nm (ε 11 000); ir ($CHCl_3$) 1750, 1715, 1675, 1595 cm^{-1}; ^1H NMR ($CDCl_3$) τ 2.92 (s, 1 H), 5.92 (q, J = 7 Hz, 2 H), 6.00 (d, J = 8 Hz, 1 H), 6.25 (s, 3 H), 6.27 (s, 3 H), 8.80 (t, J = 7 Hz, 3 H), 9.08 (s, 3 H), 9.12 (d, J = 7 Hz, 6 H), 9.20 (s, 3 H).

The combined mother liquors from the above crystallization were left at ca. 23 °C for 24 h and the crystalline product was washed with cold petroleum ether and recrystallized from petroleum ether–EtOAc to give a pure sample of the major isomer as white prisms: mp 105–106 °C; uv max (95% EtOH) 269 nm (ε 13 000); ir ($CHCl_3$) 1740 (sh), 1720, 1675, 1595 cm^{-1}; ^1H NMR ($CDCl_3$) τ 2.85 (s, 1 H), 5.90 (q, J = 7 Hz, 2 H), 5.95 (d, J = 5 Hz, 1 H), 6.22 (d, J = 4 Hz, 1 H), 6.28 (s, 3 H), 6.43 (s, 3 H), 8.80 (t, J = 7 Hz, 3 H), 9.02 (s, 3 H), 9.12 (s, 3 H), 9.15 (d, J = 7 Hz, 6 H).

10-Carbethoxy-4,4-dimethyl-8-methoxymethylene-9-(1'-carbobenzoxy-2'-oxo-4'-methylpentyl)-5α-decalone-7 (19b). Crude **7d** (141 mg, contaminated with ca. 25% of **6**) was converted to its methyl enol ether as described for **7c**, using 10 mg of TsOH in 10 ml of dry MeOH. The crude product (135 mg, ca. 93% based on available **7d**) consisted of a 3:2 mixture of isomers of **19b** (^1H NMR integration of the OCH_3 resonances) containing ca. 25% of **20** (identified by comparison of the extraneous ^1H NMR peaks with the spectrum of an authentic sample) from the aldehyde contaminant: ^1H NMR ($CDCl_3$) τ 2.70 (s, 5 H), 2.92 (s, isomer A) and 2.98 (s, isomer B) (total 1 H), 4.83 (s, isomer B) and 4.90 and 5.17 (AB, J = 12 Hz, isomer A) (total 2 H), 5.95 (q, J = 7 Hz, 2 H), 6.30 (s, isomer B) and 6.42 (s, isomer A) (total 3 H), 8.83 (t, J = 7 Hz, 3 H), 9.13 (m, 12 H), and resonance from **20**.

10-Carbethoxy-4,4-dimethyl-8-methoxymethylene-9-(1'-carbo-*tert*-butoxy-2'-oxo-4'-methylpentyl)-5α-decalone-7 (19c). Adduct **7b** (1.421 g, 3.03 mmol, mp 110–125 °C) was converted to its methyl enol ether as described for **7c**, using 32 mg of TsOH in 25 ml of dry MeOH for 10 min to afford 1.345 g (90%) of a crude 5:1 mixture of isomers of **19c** (^1H NMR integration of the =CH and OCH_3 resonances). Washing with cold petroleum ether and recrystallization from petroleum ether–EtOAc afforded the major isomer as white prisms: mp 125–126 °C; ir ($CHCl_3$) 1740 (sh), 1715, 1670, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) τ 2.85 (d, J = 0.6 Hz, 1 H), 5.93 (q, J = 7 Hz, 2 H), 5.98 (d, J = 5 Hz, 1 H), 6.28 (s, 3 H), 6.38 (d, J = 5 Hz, 1 H), 8.62 (s, 9 H), 8.82 (t, J = 7 Hz, 3 H), 9.05 (d, J = 7 Hz, 6 H), 9.10 (s, 3 H), 9.22 (s, 3 H).

Anal. Calcd for $C_{28}H_{44}O_7$: C, 68.26; H, 9.01. Found: C, 68.33; H, 8.97.

10-Carbethoxy-4,4-dimethyl-8-dimethoxymethyl-Δ⁸-5α-octalone-7 (20). Formyl enone **6** (110 mg, 0.360 mmol) was treated with 8 mg of TsOH in 10 ml of dry MeOH as described for enol etherification of **7c** to give 111 mg (95%) of pure (^1H NMR assay) **20** as a yellow oil: ir (film) 1725, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) τ 3.32 (d, J = 1 Hz, 1 H), 4.77 (d, J = 1 Hz, 1 H), 5.88 (q, J = 7 Hz, 2 H), 6.68 (s, 3 H), 6.75 (s, 3 H), 8.78 (t, J = 7 Hz, 3 H), 9.10 (s, 3 H), 9.20 (s, 3 H).

1-Methylsulfinyl-4-methylpentan-2-one (21). The procedure follows one by Moore.[40] A mixture of 8.3 g of a 58% NaH dispersion in mineral oil (0.20 mol of NaH) and 280 ml of Me_2SO was heated for 2 h at 66° under N_2, cooled to 20 °C, and 13.02 g (0.10 mol) of ethyl isovalerate, bp 134 °C,[41] was added over 15 min. The

solution was stirred for 30 min, poured into 300 g of ice water containing 52.5 g of NH_4Cl, and extracted with $CHCl_3$ which was concentrated in vacuo. The residual oil in 30 ml of ether was extracted with six 15-ml portions of water which were saturated with NaCl, extracted with six 15-ml portions of $CHCl_3$, dried, and evaporated in vacuo to produce 10.4 g of yellow oil. Distillation through a short-pass distillation head packed with glass wool afforded a forerun (0.75 g) of Me_2SO, followed by 8.35 g (52%) of **21**: bp 103–108 °C (0.3 mm); ir (film) 1700 cm^{-1}; ^1H NMR ($CDCl_3$) τ 6.15 and 6.23 (AB, J = 14 Hz, 2 H), 7.35 (s, 3 H), 9.07 (d, J = 7 Hz, 6 H).[41]

10-Carbethoxy-4,4-dimethyl-8-hydroxymethylene-9-(1′-methylsulfinyl-2′-oxo-4′-methylpentyl)-5α-decalone-7 (22). This adduct was prepared as described for **7c**, using 226 mg of a 58% dispersion of NaH in mineral oil (5.40 mmol), 880 mg (5.40 mmol) of **21**, bp 103–108 °C (0.3 mm), and 1.00 g (3.60 mmol) of **6** in 50 ml of dry Me_2SO. Formation of the homogeneous enolate solution required 30 min and a 25-min reaction time was allowed before acidification with 1.5 ml of HOAc. Isolation as described for adduct **7b** provided 1.71 g (100%) of white semisolid. This was taken up in $CHCl_3$, extracted with 1% NaOH to remove the adduct from mineral oil, and acidified with 5% HCl to afford 1.581 g (99%) of a 1:1 mixture of stereoisomers (^1H NMR assay) of **22**, free of **6** or **21** (^1H NMR). A sample was washed thoroughly with cold ether and recrystallized from $CHCl_3$ to afford one isomer as a white powder: mp 167–168 °C; uv max (95% EtOH) 277 nm (ϵ 8500); (base) 310 nm (ϵ 15 500); ir ($CHCl_3$) 1710, 1635, 1580 cm^{-1}; ^1H NMR ($CDCl_3$) τ 1.87 (s, 1 H), 5.88 (d, J = 4 Hz, 1 H), ca. 5.88 and 5.98 (m,[36] 2 H), 6.75 (d, J = 4 Hz, 1 H), 7.60 (s, 3 H), 8.85 (t, J = 7 Hz, 3 H), 9.02 (d, J = 7 Hz, 6 H), 9.02 (s, 3 H), 9.15 (s, 3 H).

Anal. Calcd for $C_{23}H_{36}O_6S$: C, 62.70; H, 8.24. Found: C, 62.80; H, 8.17.

The mother liquors from the above purification were taken up in ether and cooled to −20 °C, and the precipitate was recrystallized from $CHCl_3$–ether to provide a sample of a second isomer as a white powder: mp 137–140 °C (comparison of the SCH_3 resonances indicated contamination with 5% of the first isomer); uv max (95% EtOH) 280 nm (ϵ 7200); (base) 309 nm (ϵ 15 000); ir ($CHCl_3$) 1710, 1640, 1580 cm^{-1}; ^1H NMR ($CDCl_3$) τ 1.48 (s, 1 H), ca. 5.86 and 5.96 (m,[36] 2 H), 6.37 and 6.58 (AB, J = 9 Hz, 2 H), 7.48 (s, 3 H), 8.83 (t, J = 7 Hz, 3 H), 8.97 (d, J = 7 Hz, 6 H), 9.05 (s, 3 H), 9.10 (s, 3 H).

10-Carbethoxy-4,4-dimethyl-8-hydroxymethylene-9-(1′,2′-dioxo-4′-methylpentyl)-5α-decalone-7 (24a). A solution of 430 mg (0.979 mmol) of an isomeric mixture of adducts **22**, mp 130–142 °C, in 12 ml of 50% aqueous HOAc was refluxed for 4 h[22] and diluted with 10 ml of brine. Isolation B ($CHCl_3$, water and $NaHCO_3$ wash) afforded 385 mg (100%) of **24a** as a bright yellow oil devoid of significant impurities (^1H NMR): ir ($CHCl_3$) 1705, 1635, 1580 cm^{-1}; ^1H NMR ($CDCl_3$) τ 1.93 (s, 1 H), 5.42 (s, 1 H), ca. 5.82 and 5.95 (m,[36] 2 H), 8.80 (t, J = 7 Hz, 3 H), 9.05 (d, J = 7 Hz, 6 H), 9.07 (s, 3 H), 9.22 (s, 3 H). The relative intensity of the C-9 H singlet at τ 5.42 was not significantly diminished in spectra of the product from conducting this reaction in 50% D_2O–DOAc.

10-Carbethoxy-4,4-dimethyl-8-methoxymethylene-9-(1′,2′-dioxo-4′-methylpentyl)-5α-decalone-7 (24b). A 245-mg (0.625 mmol) sample of crude **24a** was O-methylated as described for **7c** using 17 mg of TsOH in 15 ml of dry MeOH for 15 min to provide 231 mg (91%) of crude yellow solid. Recrystallization from petroleum ether gave 209 mg (82%) of **24b**, mp 84–86 °C. Further recrystallization provided an analytical sample as yellow plates: mp 87.5–88 °C; ir ($CHCl_3$) 1710, 1670, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) τ 2.78 (d, J = 1.5 Hz, 1 H), 5.22 (d, J = 1.5 Hz, 1 H), ca. 5.85 and 5.89 (m,[36] 2 H), 6.27 (s, 3 H), 8.77 (t, J = 7 Hz, 3 H), 9.05 (d, J = 7 Hz, 6 H), 9.12 (s, 3 H), 9.25 (s, 3 H).

Anal. Calcd for $C_{23}H_{34}O_6$: C, 67.95; H, 8.43; mol wt, 406. Found: C, 68.05; H, 8.37; mol wt, 406 (mass spectrum).

10-Carbethoxy-11,12-dihydroxy-17-norabieta-8,11,13-trien-7-one (25a). A solution of 490 mg (1.21 mmol) of **24b**, mp 84–86 °C, and 138 mg (2.54 mmol) of NaOMe in 20 ml of dry MeOH was refluxed for 6 h, acidified with glacial HOAc, and taken to dryness to afford a yellow gum which was taken up in 10 ml of ether. Isolation A (water and $NaHCO_3$ wash) left 440 mg (95%) of crude oil which was crystallized from cold petroleum ether to afford 225 mg of amorphous solid. Concentration of the mother liquors gave an additional 103 mg (73% total) of **25a**, mp 110–118 °C. Recrystallization from EtOAc provided pure **25a** as a white powder: mp 123–124 °C; uv max (95% EtOH) 237 nm (ϵ 17 500), 290 (11 300); (base) 262 nm (ϵ 10 700), 366 (24 700); ir ($CHCl_3$) 3505, 3310, 1710 (sh), 1675, 1615, 1570 cm^{-1}; ^1H NMR ($CDCl_3$) τ 2.27 (s, 1 H), 2.45 (s, 1 H), 3.38 (s, 1 H), ca. 5.78 and 5.82 (m,[36] 2 H), 8.75 (d, J = 7 Hz, 3 H), 8.78 (d, J = 7 Hz, 3 H), 8.78 (t, J = 7 Hz, 3 H), 9.00 (s, 3 H), 9.08 (s, 3 H).

Anal. Calcd for $C_{22}H_{30}O_5$: C, 70.56; H, 8.07. Found: C, 70.69; H, 8.08.

10-Carbethoxy-11,12-dimethoxy-17-norabieta-8,11,13-trien-7-one (25b). Diphenol **25a** (100 mg, 0.268 mmol, mp 110–118 °C) was methylated as described for **10a** using 0.25 ml of Me_2SO_4 and 2.0 g of K_2CO_3 in 5 ml of acetone for 7 h. Isolation as described for **10b** afforded 105 mg (98%) of **25b** as a pale yellow oil which crystallized from MeOH as white prisms (96 mg, 90%), mp 90–92 °C. Recrystallization from MeOH provided colorless prisms: mp 91–92 °C; uv max (95% EtOH) 224 nm (ϵ 25 400), 273 (13 400); ir ($CHCl_3$) 1720, 1680, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) τ 2.20 (s, 1 H), ca. 5.84 and 5.94 (m,[36] 2 H), 6.17 (s, 3 H), 6.33 (s, 3 H), 8.75 (d, J = 7 Hz, 3 H), 8.80 (d, J = 7 Hz, 3 H), 8.80 (t, J = 7 Hz, 3 H), 9.03 (s, 3 H), 9.13 (s, 3 H).

Anal. Calcd for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51. Found: C, 71.80; H, 8.61.

Ethyl (±)-Carnosate Dimethyl Ether (14). Hydrogenolysis of 80 mg (0.20 mmol) of **25b**, mp 90–92 °C, in 8 ml of EtOAc containing one drop of concentrated H_2SO_4 and 10 mg of 30% Pd/C required 45 min at 1 atm. Filtration (Celite) and isolation A ($NaHCO_3$ wash) afforded 75 mg (98%) of **14** as an oil which slowly crystallized. Recrystallization from MeOH provided pure **14**, mp 89–90 °C, identical (melting point, ir, ^1H NMR) with the sample described above.

Ethyl (±)-7β-Hydroxycarnosate Dimethyl Ether (25c). The procedure follows one of McChesney.[23] A mixture of 244 mg (0.608 mmol) of **25b**, mp 90–92 °C, and 360 mg (0.980 mmol) of $NaBH_4$ in 15 ml of 95% EtOH was stirred for 4 h and diluted with 15 ml of water and 25 ml of brine. Isolation B (ether) gave 240 mg (97%) of white solid, mp 110–114 °C. Recrystallization from petroleum ether–EtOAc afforded 261 mg (88%) of **25c** as white prisms, mp 115–116 °C. Pure **25c** had mp 116–117 °C; uv max (95% EtOH) 274 nm (ϵ 680); ir ($CHCl_3$) 3580, 3465 (br), 1720 cm^{-1}; ^1H NMR ($CDCl_3$) τ 2.75 (s, 1 H), 5.30 (broad t, J = 9 Hz, 1 H), ca. 5.81 and 5.93 (m,[36] 2 H), 6.27 (s, 3 H), 6.35 (s, 3 H), 8.75 (t, J = 7 Hz, 3 H), 8.78 (d, J = 7 Hz, 3 H), 8.80 (d, J = 7 Hz, 3 H), 9.03 (s, 3 H), 9.18 (s, 3 H).

Anal. Calcd for $C_{24}H_{36}O_5$: C, 71.26; H, 8.97. Found: C, 71.32; H, 8.99.

(±)-Carnosol Dimethyl Ether (26). The procedure follows one of Linde.[4] A solution of 74 mg (0.18 mmol) of **25c**, mp 115–116 °C, and 41 mg (0.37 mmol) of freshly prepared t-BuOK in 5 ml of dry C_6H_6 was stirred for 8 h, acidified with 3 drops of glacial HOAc, and diluted with brine. Isolation B (ether, $NaHCO_3$ wash) left 69 mg of white glass which was filtered through 5 g of Al_2O_3 with 1:1 petroleum ether–$CHCl_3$ to provide 53 mg (82%) of **26**, mp 150–154 °C. Recrystallization from dry MeOH afforded pure **26** as white prisms: mp 155–156 °C [lit.[4] mp for (+)-**26**, 155–156 °C]; uv max (95% EtOH) 272 nm (ϵ 930); ir ($CHCl_3$) 1740 cm^{-1}; ^1H NMR ($CDCl_3$) τ 3.17 (s, 1 H), 4.62 (dd, J = 2 and 4 Hz, 1 H), 6.22 (s, 3 H), 6.23 (s, 3 H), 8.80 (d, J = 7 Hz, 3 H), 8.82 (d, J = 7 Hz, 3 H), 9.08 (s, 3 H), 9.15 (s, 3 H); ir and ^1H NMR identical with those of (+)-**26**.[23]

Anal. Calcd for $C_{22}H_{30}O_4$: C, 73.70; H, 8.44. Found: C, 73.83; H, 8.36.

10-Carbethoxy-12-methoxy-17-norabieta-8,11,13-trien-7-one (23). A solution of 150 mg (0.341 mmol) of an isomeric mixture of adducts **22**, mp 130–142 °C, and 0.25 ml of concentrated HCl in 4 ml of Me_2SO was stirred for 14 h and diluted with 20 ml of 50% brine. Isolation B (4:1 ether–$CHCl_3$, $NaHCO_3$ wash) provided 119 mg (97%) of crude **9b**. This was refluxed for 12 h in 15 ml of dry acetone with 2.0 g of K_2CO_3 and 0.3 ml of Me_2SO_4. The neutral product was isolated as described for **10b** as 120 mg of yellow oil which was filtered through 10 g of Al_2O_3 with 1:1 petroleum ether–$CHCl_3$ to afford 81 mg (64%) of colorless oil which crystallized from petroleum ether. Recrystallization from MeOH provided **23** as colorless needles: mp 112.5–113 °C; uv max (95% EtOH) 281 nm (ϵ 16 800), 236 (ϵ 25 600); ir ($CHCl_3$) 1710, 1660, 1595, 1560, 1495 cm^{-1}; ^1H NMR ($CDCl_3$) τ 2.07 (s, 1 H), 3.17 (s, 1 H), ca. 5.94 and 6.01 (m,[36] 2 H), 6.13 (s, 3 H), 8.78 (d, J = 7 Hz, 3 H), 8.80 (d, J = 7 Hz, 3 H), 8.87 (t, J = 7 Hz, 3 H), 9.03 (s, 3 H), 9.12 (s, 3 H).

Anal. Calcd for $C_{23}H_{32}O_4$: C, 74.16; 8.66. Found: C, 74.07; H, 8.53.

10-Carbethoxy-12-methoxy-17-norabieta-8,11,13-triene (10b). Keto ester **23** (45 mg, 0.12 mmol, mp 112–113 °C) was hydrogenated for 45 min at 1 atm over 14 mg of 30% Pd/C in 10 ml of EtOAc containing 1 drop of concentrated H_2SO_4. Filtration and

isolation A ($NaHCO_3$ wash) gave 43 mg (100%) of white solid which was recrystallized from MeOH to afford pure **10b** as colorless plates, mp 64.5–65.5°, melting point, ir, ^1H NMR identical with those of the specimen described above.

By-Products from "Abnormal" Hydrogenation of Enone 27 in Ethanol. Hydrogenation of 24 g of **27**, mp 68–70 °C, at 1 atm over 300 mg of 30% Pd/C in 125 ml of 95% EtOH was intentionally allowed to proceed until H_2 uptake appeared to have stopped completely (ca. 1.5 molar equiv absorbed), in order to maximize the amounts of by-products sometimes detected by GLC and ^1H NMR in products from hydrogenation as described earlier.[12] Initial rapid absorption of approximately the theoretical amount of H_2 was followed by a period of slower but easily observable consumption, which was then followed by a long period of extremely slow absorption. The usual isolation[12] afforded an oil which was held at 80 °C and 0.025 mm for several hours (to remove EtOH erroneously believed to be present because ^1H NMR showed an "extra" OEt resonance) and chromatographed over 2 lb of Merck neutral Al_2O_3 (90 × 4 cm), with pentane, ether, $CHCl_3$, C_6H_6, MeOH, and mixtures thereof as eluents.

(1) Fractions 22–42 (5–10% ether–pentane) consisted of 9.3 g of **31** as a colorless, mobile oil, 99+% pure by GLC: ir (film) 1725 cm^{-1}; ^1H NMR ($CDCl_3$) τ 5.92 (q, J = 7 Hz, 2 H), 6.53 (q, J = 7 Hz, 2 H), ca. 6.78 (m, broad, 1 H), 8.77 (t, J = 7 Hz, 3 H), 8.87 (t, J = 7 Hz, 3 H), 9.10 (s, 3 H), 9.22 (s, 3 H).

Anal. Calcd for $C_{17}H_{30}O_3$: C, 72.30; H, 10.68. Found: C, 72.27; H, 10.52.

(2) Fractions 56–59 (ether) comprised 3.6 g of **4**, mp 44.2–45.8 °C.

(3) Fractions 69–75 (20% $CHCl_3$–ether and 10% C_6H_6–ether) comprised 140 mg of **28** as a yellowish oil which slowly solidified. Fractional vacuum sublimation in a horizontal tube afforded pure **28** as white microcrystals: mp 51–53 °C; ir ($CHCl_3$) 3615, 3450 (broad), 1710 cm^{-1}; ^1H NMR ($CDCl_3$) τ 5.80 (m, $W_{1/2} \simeq$ 7 Hz, 1 H), 5.90 (q, J = 7 Hz, 2 H), 8.75 (t, J = 7 Hz, 3 H), 9.13 (s, 3 H), 9.27 (s, 3 H).

Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.82; H, 10.30. Found: C, 70.55; H, 9.93.

(4) Fractions 80–81 (MeOH) comprised 4.0 g of **29** as a yellowish oil. Molecular distillation in a micro-Hickman flask (120 °C, 0.05 mm) afforded pure **29** as a colorless oil: ir (film) 3375 (broad), 1725 cm^{-1}; ^1H NMR ($CDCl_3$) τ ca. 5.86 and 5.90 (m,[36] 2 H), ca. 6.43 (m, broad, 1 H), 7.08 (s, 1 H), 8.73 (t, J = 7 Hz, 3 H), 9.10 (s, 3 H), 9.23 (s, 3 H). Ir, ^1H NMR, and GLC are identical with those of a sample *from $NaBH_4$ reduction of* **4**.[26]

Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.82; H, 10.30. Found: C, 70.72, H, 10.11.

10-Carbethoxy-4,4-dimethyl-7β-ethoxy-5α-decalin (31). The procedure follows one of Ireland et al.[42] A solution of 100 mg of $Hg(OAc)_2$ and 255 mg (1.00 mmol) of redistilled **29** in 10 ml of freshly distilled isopropyl vinyl ether, bp 51 °C, was gently refluxed for 6 h, K_2CO_3 (1.0 g) was added to inactivate the catalyst, and after 10 min at reflux the solution was decanted and evaporated under N_2 on the steam bath to afford an oil which was chromatographed over Al_2O_3 (Merck, 32 × 1 cm) in petroleum ether. The vinyl ether was eluted with 50 ml of 15% ether in pentane as 204 mg (73%) of a cloudy, mobile oil: ^1H NMR ($CDCl_3$) τ 3.67 (dd, J = 6.5 and 14 Hz, 1 H), 5.75 (dd, J = 1 and 14 Hz, 1 H), ca. 5.86 and 5.90 (m,[36] 2 H), 6.05 (dd, J = 1 and 6.5 Hz, 1 H), ca. 6.27 (m, broad, 1 H), 8.73 (t, J = 7 Hz, 3 H), 9.10 (s, 3 H), 9.23 (s, 3 H). The crude vinyl ether (204 mg, 0.728 mmol) was hydrogenated at 1 atm in 20 ml of 95% EtOH over 35 mg of 5% Rh/Al_2O_3. Theoretical H_2 uptake was very rapid. Filtration and evaporation afforded 100% of **31** (99+% pure by GLC) which was identical (ir, ^1H NMR, GLC) with the sample described above.

10-Carbethoxy-4,4-dimethyl-5α-decalone-7 (4). The procedure follows one of Djerassi et al.[43] Under N_2 0.12 ml of Jones reagent[27] (2.675 g of CrO_3 in 2.30 ml of concentrated H_2SO_4 diluted to 10.0 ml with water) was added rapidly with stirring to a cold solution (10–15 °C) of **28** (110 mg, 0.321 mmol) in 20 ml of acetone (redistilled from $KMnO_4$). After 5 min, isolation C (ether and $CHCl_3$, 5% $NaHCO_3$ wash) provided 100 mg (91%) of a yellow oil which solidified. Recrystallization afforded white crystals, mp 45–46 °C, identical (^1H NMR, mixture melting point) with authentic **4**.

10-Carbethoxy-4,4-dimethyl-Δ⁵-7β-octalol (30). A solution of 1.02 g (4.1 mmol) of **27**, mp 70–71 °C, and 1.51 g (40 mmol) of $NaBH_4$ in 150 ml of 95% EtOH was stirred for 2 h. Isolation C ($CHCl_3$, Na_2SO_4 drying) afforded 1.11 g (100%) of **30** as a brown oil which could not be crystallized or distilled without decomposition: ir (film) 3420, 1725, 1645 cm^{-1} (w); ^1H NMR ($CDCl_3$) τ 4.28 (d, J = 2.2 Hz, 1 H), ca. 5.80 and 5.92 (m,[36] 2 H), ca. 5.78 (m, broad, 1 H), 6.63 (s, 1 H), 8.73 (t, J = 7 Hz, 3 H), 8.90 (s, 3 H), 9.08 (s, 3 H). TLC, GLC, and ^1H NMR all indicated the absence of a second isomer or major amounts of contaminants.

10-Carboxy-4,4-dimethyl-Δ⁵-7β-octalol Lactone (32).[44] A mixture of 490 mg (1.94 mmol) of crude **30** and 53 mg of a 53% NaH–mineral oil dispersion (1.2 mmol of NaH) in 25 ml of C_6H_6 was stirred for 5 h in an N_2 atmosphere. Isolation C ($CHCl_3$, Na_2SO_4 drying) left 396 mg (93%, assuming presence of 25 mg of *mineral oil*) *of* **32** *as a colorless oil. Evaporative distillation* afforded an analytical sample: bp 119–122 °C (bath, 0.3 mm); ir (film) 1740, 1655 (w), 1620 cm^{-1} (w); ^1H NMR ($CDCl_3$) τ 3.88 (d, J = 5.5 Hz, 1 H), 4.95 (m, 1 H), 8.71 (s, 3 H), 8.73 (s, 3 H).

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found:[44] C, 75.68; H, 9.18.

Registry No.—**4**, 57593-80-3; **5a** 57593-81-4; **5b**, 57593-82-5; **6**, 57593-83-6; **7a** 11α-H epimer, 57593-84-7; **7a** 11β-H epimer, 57593-85-8; **7b** 11α-H epimer, 57593-86-9; **7b** 11β-H epimer, 57593-87-0; **7c** 11α-H epimer, 57593-88-1; **7c** 11β-H epimer, 57593-89-2; **7d** 11α-H epimer, 57607-04-2; **7d** 11β-H epimer, 57593-90-5; **8a**, 57593-91-6; **8b**, 57636-84-7; **9a**, 57593-92-7; **9b**, 57636-85-8; **10a**, 57636-86-9; **10b**, 57593-93-8; **11**, 57593-94-9; **12** syn isomer, 57593-95-0; **12** anti isomer, 57593-96-1; **13**, 57593-97-2; (+)-**14**, 57636-87-0; (±)-**14**, 10438-43-4; (+)-**15**, 20337-29-5; (±)-**15**, 20483-07-2; **16**, 57593-98-3; **18a**, 57593-99-4; **18b**, 57594-00-0; **19a** 11α-H epimer, 57594-01-1; **19a** 11β-H epimer, 57594-02-2; **19b** 11α-H epimer, 57594-03-3; **19b** 11β-H epimer, 57594-04-4; **19c** 11α-H epimer, 57594-05-5; **19c** 11β-H epimer, 57594-06-6; **20**, 57594-07-7; **21**, 16697-72-6; **22**, 20483-08-3; **23**, 57594-08-8; **24a**, 57594-09-9; **24b**, 57607-05-3; **25a**, 20483-10-7; **25b**, 20482-69-3; **25c**, 20482-68-2; **26**, 20483-06-1; **27**, 57594-10-2; **28**, 57594-11-3; **29**, 57594-12-4; **30**, 57594-13-5; **31**, 57594-14-6; **32**, 57594-15-7; *tert*-butyl acetoacetate, 1694-31-1; *tert*-butyl isovalerylacetate, 39140-54-0; methyl isovalerylacetate, 30414-55-2; methyl α-isovalerylacetoacetate, 57594-16-8; methyl acetoacetate, 105-45-3; benzyl isovalerylacetate, 57594-17-9; benzyl acetoacetate, 5396-89-4; isovaleryl chloride, 108-12-3; benzyl α-isovalerylacetoacetate, 57594-18-0.

References and Notes

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(16) Detailed consideration of data from several series of compounds which relates to the 9 configuration in adducts like **7** and their derivatives and to the double bond location and 8,9 configuration in enediones like **8**

will be included in the next paper of this series; cf. D. C. Shew and R. A. Manning, Ph.D. Dissertations, University of Arkansas, 1969 and 1971, respectively.
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(32) The observation that **33** was reduced only very slowly, if at all, at 1 atm over the limited number of Pd/C samples which were examined suggests that hydrogenolysis of **30** may proceed through a π-allyl adsorbed intermediate[33] to form a mixture of **33** and its unisolated Δ^6 isomer, with the latter rather than **33** being the precursor of decalin **34**.
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(36) This ethoxyl resonance shows distinct ABC_3 character with $J_{AB} = J_{AC} = 7$ Hz, but was not precisely analyzed; these chemical shifts are only estimated visually, ±0.02 ppm; cf. ref 25.
(37) We are grateful to the Eastman Chemical Co. for a generous gift of this material.
(38) We were unable to find conditions which would bring about this hydrogenolysis without sequential exposure to two fresh batches of catalyst.
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(44) This experiment was conducted by Mr. B. H. Fahoum; microanalysis by Spang Microanalytical Laboratory, Ann Arbor, Mich.

Sesquiterpene Lactones of *Eupatorium hyssopifolium*. A Germacranolide with an Unusual Lipid Ester Side Chain[1]

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The isolation and structure determination of three new closely related germacranolides, eupassopin, eupassopilin, and eupassofilin, from *Eupatorium hyssopifolium* L. are reported. Eupassofilin is highly unusual in being the first ester of D(−)-3-hydroxyoctadecanoic acid isolated from a higher plant. Generalizations for the ease of hydrolysis of five-carbon unsaturated ester side chains in germacranolides are presented.

Chemical examination of several *Eupatorium* species *sensu stricto*[2] has produced a number of cytotoxic and antitumor germacranolides and guaianolides.[3-7] In the present communication, we report the isolation and structure determination from *Eupatorium hyssopifolium* L. of three new noncrystalline germacranolides, eupassopin, eupassopilin, and eupassofilin, the last of which is linked in an unprecedented way to a D(−)-β-hydroxystearoyl ester side chain.[8]

For the sake of convenience we discuss first the structure of eupassopin (**1a**), $C_{20}H_{26}O_7$ (high-resolution mass spectrum), $[\alpha]D$ −137.5°, which was a conjugated γ-lactone of the type partially shown in A (ir bands at 1760 and 1650 cm^{-1}), as evidenced by the usual criteria of narrowly split doublets at 6.25 and 5.67 ppm (H_a and H_b) in the ^1H NMR spectrum (Table I) and the appropriate signals in the ^{13}C NMR spectrum, particularly the triplet at 122.8 ppm (Table II). D_2O exchange sharpened a two-proton AB system at 3.89 d and 3.75 d (J = 12 Hz) and a two-proton broad doublet at 4.24 ppm (J = 6 Hz); hence eupassopin appeared to contain two primary hydroxyl groups.

Acetylation of eupassopin indeed furnished a diacetate **1b** (two new acetate signals at 2.14 and 2.08 ppm), but while the two-proton broad doublet had moved downfield from 4.24 to 4.80 ppm as expected (see Table I), only one of