Marguerite, Quebec, Canada, Butterworths, London, 1971, pp 413–453; *Pure Appl. Chem.*, No. 4, 28 (1971). (b) W. D. Celmer in "Biogenesis of Antibiotic Substances," Z. Vaněk and Z. Hošťalek, Ed., Academic Press, New York, N. Y., 1965, Chapter 10.
(4) T. J. Perun, *J. Org. Chem.*, **32**, 2324 (1967).
(5) P. H. Jones, T. J. Perun, E. K. Rowley, and E. J. Baker, *J. Med. Chem.*, **15**, 631 (1972).
(6) The authors are grateful to Dr. T. J. Perun for suggesting the use of this reagent.
(7) P. Kurath, P. H. Jones, R. S. Egan, and T. J. Perun, *Experientia*, **27**, 362 (1971).
(8) J. R. Martin, R. S. Egan, T. J. Perun, and A. W. Goldstein, *Tetrahedron*, **29**, 935 (1973).
(9) R. S. Egan, Ph.D. Thesis, University of Illinois Medical Center, 1971.
(10) DBU is extremely caustic and should be used with care. Tests with rabbits have shown it to be instantly destructive of eye tissue.
(11) N. L. Oleinick and J. W. Corcoran, *J. Biol. Chem.*, **244**, 727 (1969).
(12) Obtained from several runs.

Studies on Resin Acids. IX. Synthesis and Stereochemistry of 6-Ketoabietatrienes[1]

John W. Huffman* and J. J. Gibbs

Department of Chemistry and Geology, Clemson University, Clemson, South Carolina 29631

Received March 26, 1974

In an effort to explore the stereochemistry of 6-ketoabieta-8,11,13-trienes, 18-nor-5β-abieta-8,11,13-trien-6-one (**8**), 19-nor-5β-abieta-8,11,13-trien-6-one (**14**), 19-norabieta-8,11,13-trien-6-one (**3**), and abieta-8,11,13-trien-6-one (**1**) have been prepared. 19-Norabieta-8,11,13-triene (**7**) was converted to ketone **8** by the sequence oxidation to 18-norabieta-8,11,13-trien-7-one (**5**), reduction to the 7β-ol (**6**), dehydration to 18-norabieta-6,8,11,13-tetraene (**4**), oxidation to a mixture of glycols, and dehydration to **8**. 19-Norabieta-8,11,13-trien-6-one (**3**) was prepared by a similar route using 19-norabieta-8,11,13-trien-7-one (**19**) as starting material and also by isomerization of 19-nor-5β-abieta-8,11,13-trien-6-one (**14**). Ketone **14** was obtained by oxidation of 19-nor-5β-abieta-8,11,13-trien-6β-ol (**15**), which was the principal alcoholic product from the hydroboration–oxidation of 18-norabieta-4,8,11,13-tetraene (**9**). Prolonged treatment of **9** with diborane, followed by oxidation, gave a mixture of 19-nor-5β-abieta-8,11,13-trien-7α- and -7β-ol (**17** and **18**). Abieta-8,11,13-trien-6-one (**1**) was prepared from abieta-8,11,13-triene (**23**) by the method used for the synthesis of ketones **3** and **8**. The mechanism of the anomalous hydroboration of **9** and the conformations of the various 6-ketones are discussed.

Several naturally occurring compounds, among them taxodione[2] and maytenoquinone,[3] have been isolated which contain a keto group in the 6 position of an abietane ring system. In addition to these compounds, and their derivatives, the parent compound abieta-8,11,13-trien-6-one (**1**) has been prepared,[4] as have a few other structurally related ketones.[5] In the compounds of this type in which the stereochemistry about the A–B ring fusion has been discussed, it has been either shown or assumed that the stable ring juncture is trans. However, ketones similar to **1** are essentially 9-methyl-1-decalone systems, in which it is known that there is very little energy difference between the cis and trans isomers,[6] and in the trans isomer of **1** there is also a severe axial–axial interaction between the β-methyl group (C-19) at C-4 and the angular methyl. It would thus appear that for ketones such as **1** the cis isomer should be more stable. In order to explore this apparent stereochemical inconsistency, the synthesis of **1** has been reinvestigated, and the preparation of the 18- and 19-nor ketones (**2** and **3**) and their stereochemical preferences at C-5 studied.

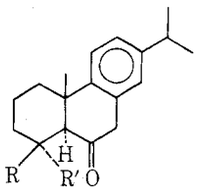
The obvious precursor of the 18-nor ketone (**2**), 18-norabieta-6,8,11,13-tetraene (**4**), was prepared from 18-norabieta-8,11,13-trien-7-one (**5**)[7] by hydride reduction to the 7β-ol (**6**) which gave olefin **4** on dehydration with toluenesulfonic acid in benzene. In order to ensure that no isomerization at C-5 had occurred under the conditions of the dehydration, olefin **4** was reduced to18-norabieta-8,11,13-triene (**7**).[8] The attempted direct conversion of ketone **5** to the olefin by reaction with toluenesulfonylhydrazine, followed by methyllithium,[9] gave a complex mixture containing no hydrocarbon.

Although olefins similar to **4** have been converted to the 6-ketones by various procedures,[4,5a] in our hands these did not prove efficient and an alternative route was chosen, which entailed oxidation of **4** to a stereoisomeric mixture of cis glycols using sodium chlorate–osmium tetroxide,[10] followed by treatment with hot formic acid to give the 6-ketone.

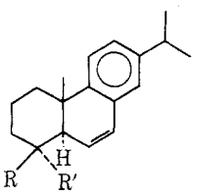
The nmr spectrum of the product ketone shows a secondary methyl signal at δ 0.84 with a coupling constant of 5 Hz, indicating that this group is equatorial,[11] consistent only with a cis A–B ring fusion and a steroidal conformation of these rings.[12] It is thus aparent that the product of this sequence is 18-nor-5β-abieta-8,11,13-trien-6-one (**8**), and that during the reaction with formic acid, isomerization to the more stable cis isomer has occurred.

19-Norabietatrien-6-one (**3**) was initially obtained *via* a fortuitous series of reactions resulting from the investigation of the hydroboration–oxidation of 18-norabieta-4,8,11,13-tetraene (**9**). It has been reported that hydroboration–oxidation of the mixture of olefins obtained by lead tetraacetate decarboxylation of abieta-8,11,13-trien-18-oic acid (dehydroabietic acid) affords, in addition to other products, 19-nor-5β-abieta-8,11,13-trien-7-one (**10**).[7] It was suggested that this ketone was probably derived from olefin **9** *via* 19-nor-5β-abieta-8,11,13-triene (**11**); however, this could not be confirmed. In subsequent work, attempts were made to obtain a homogeneous sample of hydrocarbon **9**; however, a practical method for preparation of this compound by acid-catalyzed isomerization of the mixture of olefins obtained from dehydroabietic acid could not be accomplished.[12b]

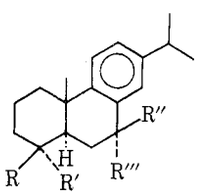
Attempted separation of a mixture of **9** and 18-nor-5β-abieta-3,8,11,13-tetraene (**12**)[12] by reaction with bis(3-methyl-2-butyl)borane, which has been utilized to separate trisubstituted from tetrasubstituted olefins, gave residual hydrocarbons with essentially the same composition as the starting mixture.[13] Both olefins apparently react with the reagent at nearly the same rate, and 18-nor-5β-abieta-8,11,13-trien-3α-ol (**13**),[12b] arising from olefin **12**, was isolated from the reaction. When the mixture of olefins from the decarboxylation of dehydroabietic acid[7] was treated



1, R = R′ = CH_3
2, R′ = CH_3; R′ = H
3, R = H; R′ = CH_3

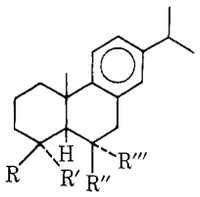


4, R = CH_3; R′ = H
21, R = H; R′ = CH_3
22, R = R′ = CH_3

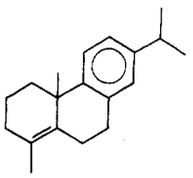


5, R = CH_3; R′ = H; R″ = R‴ = O
6, R = CH_3; R′ = R‴ = H; R″ = OH
7, R = CH_3; R′ = R″ = R‴ = H
19, R = H; R′ = CH_3; R″ = R‴ = O
20, R = R‴ = H; R′ = CH_3; R″ = OH

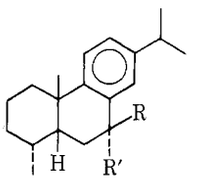
23, R = R′ = CH_3; R″ = R‴ = H
24, R = R′ = CH_3; R″ = H; R‴ = $OCOCH_3$
25, R = R′ = CH_3; R″ = H; R‴ = OH
26, R = R′ = CH_3; R″ = R‴ = O



8, R = CH_3; R′ = H; R″ = R‴ = O
14, R = H; R′ = CH_3; R″ = R‴ = O
15, R = R‴ = H; R′ = CH_3; R″ = OH
27, R = R′ = CH_3; R″ = R‴ = O



9



10, R = R′ = O
11, R = R′ = H
17, R = H; R′ = OH
18, R = OH; R′ = H

with bis(3-methyl-2-butyl)borane, there was obtained a mixture of **9** (41%) and 18-norabieta-3,8,11,13-tetraene (**12**, 5α H, 58%), from which **9** could be obtained by selective periodate–permanganate oxidation of the 3-olefin.[14]

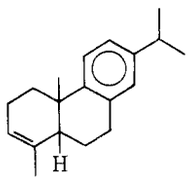
With a method available for the preparation of modest quantities of olefin **9**, uncontaminated by its isomers, the hydroboration–oxidation was carried out under the conditions reported previously.[7,12b] From this reaction there was obtained by careful chromatography an oily secondary alcohol in 43% yield. Controlled oxidation of this alcohol with Jones reagent afforded an unstable nonconjugated ketone,[15] the nmr spectrum of which permitted an unequivocal assignment of structure and stereochemistry. The C-10 methyl appears at δ 1.20, indicating that this compound almost certainly has a cis A–B ring fusion, with a steroidal conformation.[12] The secondary methyl group at C-4 appeared as a doublet (J = 7 Hz) at extremely high field (δ 0.52), which can only be accounted for by a cis ring fusion with the methyl group lying below the plane of the aromatic ring. The C-7 benzyl protons appear as an AB quartet (J = 20 Hz) at quite low field (δ 3.22 and 3.65), indicating that the carbonyl group is at C-6. The C-5 proton is a clear doublet at δ 2.38, with a coupling constant of 5 Hz consistent with a dihedral angle of approximately 60° between H-4 and H-5.[16] The only structure consistent with these data is 19-nor-5β-abieta-8,11,13-trien-6-one (**14**), which must exist in conformation **14a**.

Acid-catalyzed isomerization of **14** afforded 19-norabieta-8,11,13-trien-6-one (**3**), which has an equatorial secondary methyl group, as indicated by a coupling constant of 5 Hz for these protons.[11] The other spectral properties of this compound are in agreement with the assigned structure (see Experimental Section).

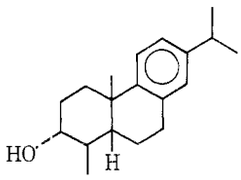
Since oxidation of the alcohol isolated from the hydroboration–oxidation sequence gave ketone **14**, this alcohol must be 19-nor-5β-abieta-8,11,13-trien-6β-ol (**15**), derived from olefin **9** by hydroboration, elimination to 19-norabieta-5,8,11,13-tetraene (**16**), and readdition of diborane. Although the thermal isomerization of alkylboranes is well known,[17a] there exist only a few examples of this type of reaction under mild conditions (*i.e.*, room temperature).[17b-e] The stereochemistry of **15** is based on the established stereochemistry of the derived ketone (**14**) and the fact that hydroboration is a stereospecific cis process.[18,19] The nmr spectrum of **15** shows a very low field (δ 1.38) angular methyl signal indicating a nonsteroidal conformation about the A–B ring fusion,[12] which is confirmed by the observation that the secondary methyl signals show a normal chemical shift (δ 1.09) with a coupling constant of 5 Hz, characteristic of an equatorial methyl group.[11]

When the hydroboration of **9** was carried out for a prolonged period, alcohol **15** could not be detected, but an inseparable mixture of two compounds was obtained as the only isolable, alcoholic product. That these were the epimeric 19-nor-5β-abieta-8,11,13-trien-7α- and -β-ols (**17** and **18**) was shown by the nmr spectrum of the mixture, which shows two C-10 methyl signals at δ 1.35 and 1.38, an equatorial secondary methyl signal at δ 0.96 (J = 6 Hz), and two low-field carbinol protons, a quasi-equatorial 7α proton (7β-ol) as a triplet (J_{app} = 3 Hz) at δ 4.48 and a quasi-axial 7β proton as a multiplet ($W_{1/2}$ = 19 Hz) at δ 4.00. Integration of the relative intensities of these protons indicated that the ratio of **18** to **17** was 3:2. Jones oxidation of the mixture afforded 19-nor-5β-abieta-8,11,13-trien-7-one (**10**).[7]

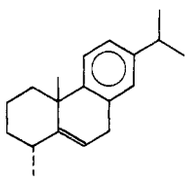
Although addition–elimination readdition sequences under mild hydroboration conditions have been reported previously,[17b-e] two successive such sequences is unusual. The stereochemical outcome of the first step of these reactions appears anomalous in that it involves attack of diborane from the more hindered β face of the molecule in contrast to the usually accepted mode of addition of this reagent. The most plausible mechanism for the general reaction of diborane with olefins is that suggested recently by Jones[20] which proposes the rapid, reversible formation of a π complex, followed by a rate-determining concerted conversion of this intermediate to the reaction products. Although the initial π complex derived from **9** should be formed more readily from the relatively unhindered α face of the molecule, the energy of activation leading to a 5α product, with an axial (4β) methyl group, would be considerably greater than that leading to a 5β-substituted product, in which there is no incipient axial–axial interaction between the secondary and angular methyl groups in the transition state. Also, the orientation of diborane in the initial π complex, assuming β attack, would almost certainly favor addition of boron at C-5, owing to the axial–axial interaction with the angular methyl group if boron were to



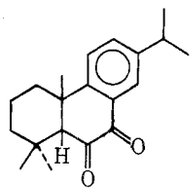
12



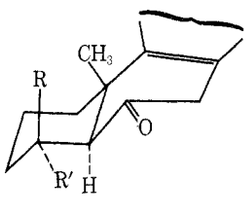
13



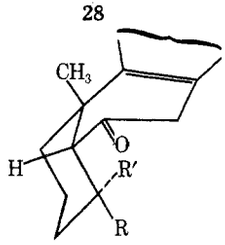
16



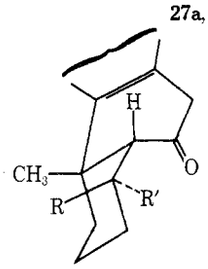
28



1a, R = R′ = CH_3
2a, R = CH_3; R′ = H
3a, R = H; R′ = CH_3



8a, R = CH_3; R′ = H
14a, R = H; R′ = CH_3
27a, R = R′ = CH_3



14b, R = H; R′ = CH_3
27b, R = R′ = CH_3

add from the β face of the molecule at C-4. The explanation for the β stereospecificity in the addition of diborane to 16 is not as apparent, however; examination of models of this olefin indicates that the α face of this molecule is concave and that attack from the β side may be preferred for that reason.

The structure of ketone **3**, obtained from the hydroboration–oxidation sequence, was confirmed by its synthesis *via* essentially the same route used for the preparation of 18-norabieta-8,11,13-trien-6-one (**2**). Borohydride reduction of 19-norabieta-8,11,13-trien-7-one (**19**) gave 19-norabieta-8,11,13-trien-7β-ol (**20**), which on dehydration afforded 19-norabieta-6,8,11,13-tetraene (**21**). Osmium tetroxide oxidation of **21**, followed by treatment of the mixed glycols with hot formic acid, gave ketone **3**, identical with that obtained from olefin **9** by the method described above.

Although the preparation of abieta-8,11,13-trien-6-one (**1**) from abieta-6,8,11,13-tetraene (**22**) by treatment with perbenzoic acid has been described,[4] and although a similar route has been used in the preparation of a related 6-ketone,[5a] experience in the preparation of ketone **2** indicated that not only was this not a particularly effective route for the preparation of **1**, but that the reported synthesis of olefin **22**[4] was probably not suitable for the preparation of quantities of this material.

Abieta-6,8,11,13-tetraene (**22**) was prepared most readily by a modification of the route used for the synthesis of olefins **4** and **21**. Lead tetraacetate oxidation of abieta-8,11,13-triene (**23**)[21] gave 7α-acetoxyabieta-8,11,13-triene (**24**), which on hydrolysis or metal hydride reduction afforded abieta-8,11,13-trien-7α-ol.[4] Pyrolysis of acetate **24** gave olefin **22**, although in poor yield, as did dehydration of the corresponding alcohol (**25**) with either phosphoryl chloride–pyridine or dimethyl sulfoxide.[22] As in the case of the preparation of olefins **4** and **21**, dehydration with toluenesulfonic acid–benzene gave the desired product (**22**) in acceptable yield. In contrast to the failure of the tosylhydrazone of ketone **5** to give an olefinic product, this reaction proceeded smoothly, although in mediocre yield when carried out on abieta-8,11,13-trien-7-one (**26**). The conversion of olefin **22** to abieta-8,11,13-trien-6-one (**1**) was carried out in the manner described above for the preparation of the 18-nor 5β-ketone (**2**). The initial preparation of this compound afforded a single ketone as expected from the reports of the earlier workers.[2-5] The nmr spectrum of this compound shows three methyl signals at δ 1.11, 1.17, and 1.32 which is consistent only with a trans-fused ketone of structure **1**.[12] The absence of a high-field methyl signal clearly contraindicates a cis steroidal ring fusion, which was expected if isomerization had occurred during dehydration. Attempted repetition of the dehydration of the glycols derived from olefin **22**, however, gave a mixture of three products, two of which were an inseparable mixture of **1** and, based on spectral data, the C-5 epimer of **1**, 5β-abieta-8,11,13-trien-6-one (**27**). The nmr spectrum of this mixture shows no high-field methyl signal, indicating that ketone **27** must exist preferentially in a nonsteroidal conformation, which is confirmed by the presence of a methyl signal at δ 1.56.[12] The third component of the mixture was an unstable yellow solid which showed the characteristic infrared absorptions of an α-diketone. The mass spectrum gave a parent ion at *m/e* 298, and the nmr spectrum has a methyl signal at δ 0.44. These data are consistent only with structure **28**, 5β-abieta-8,11,13-triene-6,7-dione, which must exist in a steroidal conformation and which is probably derived from ketone **27** by air oxidation. Acid-catalyzed isomerization of trans ketone **1** afforded the same mixture of cis and trans ketones obtained from the formic acid dehydration.

Although the conformational preferences of the various 6-substituted abietatriene derivatives described above seem secure based on their nmr spectra, several of these conformations are unexpected based on first-order conformational principles. As expected for the 6-ketone derived from 18-norabieta-8,11,13-triene, the cis isomer (**8**) is more stable than the trans (**2**). In the trans isomer (**2a**), there exists a severe axial–axial interaction between C-19 and the angular methyl group, which is relieved in the steroidal conformer of the cis isomer (**8a**).

It would be expected that19-nor-5β-abieta-8,11,13-trien-6-one (**14**) would exist as the nonsteroidal conformer (**14b**), in which the secondary methyl group is equatorial. However, the nmr spectrum of this compound clearly indicates that it is in the steroidal conformation, with an axial methyl group (**14a**). Examination of models shows that in the nonsteroidal conformation (**14b**), there exists a rather considerable steric interaction between C-18 and the carbonyl group. In contrast to the other 6-ketones in this series, the two benzylic protons at C-7 in ketone **14** are magnetically nonequivalent (δ 3.22 and 3.65). This difference in chemical shift can only be explained if the carbonyl group is not equidistant from each proton. These data are only consistent with a half-boat conformation for ring B, which relieves the rather severe interaction between C-19 and C-7 which exists in the half-chair conformer.

In the case of 19-nor-5β-abieta-8,11,13-trien-6β-ol (**15**), the precursor of ketone **14**, the nmr spectrum indicates that the compound is in the nonsteroidal conformation, and examination of models discloses that with an sp^3 hybrid car-

Experimental Section[24]

18-Norabieta-8,11,13-trien-7-one (6). – This material was prepared as previously described, however, the ketone, originally reported as an oil, gave crystals, mp ~6–8° on standing. The other properties of this compound were identical to those reported earlier.[7]

18-Norabieta-8,11,13-trien-7α-ol (6a). – To a stirred solution of 3 ml of a 70% solution of sodium bis(2-methoxyethoxy) aluminum hydride (Red-Al) in benzene, dissolved in 20 ml of dry ether, was added slowly a solution of 1.059 g of 18-norabieta-8,11,13-trien-7-one (6) in 20 ml of dry ether. The solution was stirred at 25° under nitrogen for 4 hr. Excess hydride was decomposed with crushed ice and the inorganic salts dissolved in water. The reaction mixture was extracted with ether and the extracts dried, filtered, and evaporated to give 0.813 g (76%) of pale yellow gum which crystallized on standing. Recrystallization from hexane gave the analytical sample, mp 105–112°; $[\alpha]_D^{23}$ 1.01 (d, J=7Hz, C-4 methyl), 1.23 (s, C-10 methyl), 4.82 (m, H-7), 7.39 (br s, H-14).

Anal. Calcd for $C_{19}H_{28}O$: C, 83.77; H, 10.36. Found: C, 83.93; H, 10.40.

18-Norabieta-5,8,11,13-tetraene (8). – A solution of 0.332 g of 18-norabieta-8,11,13-trien-7α-ol (6) in 25 ml of benzene was treated with 0.35 g of *p*-toluenesulfonic acid and heated at reflux, using a Dean-Stark trap, for 1 hr. After cooling, the solution was washed with successive portions of saturated sodium bicarbonate and saturated sodium chloride. The benzene layer was dried over magnesium sulfate, filtered, and evaporated to give 0.287 g of yellow oil. The crude product was dissolved in pentane and filtered through Merck alumina. Elution with pentane gave 0.237 g (67%) of colorless oil; ir 3.42μ; nmr 1.01 (d, J=7Hz, C-5 methyl), 1.04 (s, C-10 methyl), 5.78 (q, $J_{6,7}$=9.5Hz, $J_{5,7}$=3Hz, H-6), 6.40 (c, $J_{6,7}$ = 9Hz, H-7); mass spectrum *m/e* (rel intensity) 254 (100), 239 (55), 225 (8), 211 (15), 197 (58), 183 (15).[26]

A 0.048 g sample of the above material was hydrogenated (platinum oxide–ethanol, 50 psi, 25° for 10 min). The nmr spectrum of the hydrogenated product and comparative gas chromatography on an OV-17 column showed the hydrogenated material was 18-norabieta-8,11,13-triene (7).

18-Nor-5β-abieta-8,11,13-trien-6-one (9). – To a stirred solution of 0.696 g of sodium chlorate and a few crystals of osmium tetroxide in 15 ml of water was added 0.445 g of 18-norabieta-5,8,11,13-tetraene (8) in 5 ml of tetrahydrofuran. The reaction mixture was stirred at 25° for 6 hr and an additional 0.750 g of sodium chlorate was added. Stirring was continued at 25° for 14 hr when 25 ml of 20% sodium bisulfite solution was added and stirring continued an additional 1.5 hr. The reaction mixture was taken up in chloroform and the organic layer was washed with water, dried, filtered and evaporated to give 0.427 g of black gum which was dissolved in 40 ml of water and 2 ml of 30% sodium hydroxide solution. The mixture was heated at reflux for 16 hr after which the solvent was removed under vacuum and the product taken up in ether. The ether layer was washed with water, dried and the solvent removed to give 0.342 g of yellow gum, ir 5.97μ; the nmr shows no olefinic protons. This material is a mixture of the 6α, 7α and 6β, 7β-diols and was used in the subsequent step without purification.

A solution of 0.295 g of the mixed glycols in 10 ml of 98% formic acid was heated at reflux for 45 min. After cooling, the reaction mixture was poured over crushed ice and extracted with ether. The ether extracts were washed with water then with saturated sodium bicarbonate, dried and the solvent removed to give 0.265 g of brown oil which was dissolved in benzene and chromatographed on Woelm silica gel, Activity I. Elution with benzene–10% ethyl acetate gave 0.126 g of brown oil which was dissolved in benzene and filtered through Merck acid washed alumina. Elution with benzene gave 0.120 g (25%) of ketone 9 as an unstable pale yellow oil which was homogeneous to tlc (Silica Gel-G–benzene); ir 3.36 and 5.84μ; nmr (CCl$_4$) 0.84 (d, J=5Hz, C-4 methyl), 1.08 (s, C-10 methyl), 3.61 (br, s, H-7); ORD: ϕ_{698} +998, ϕ_{336} +1210, ϕ_{334} +1434; mass spectrum *m/e* (rel intensity) 270 (59), 255 (100), 237 (56), 227 (10), 213 (10), 201 (23), 195 (17), 185 (17).[26]

Abieta-4,8,11,13-tetraene (9). – A solution of 19.11 g of the mixture of olefins obtained from dehydroabietic acid via lead tetraacetate decarboxylation[7,27] in 15 ml of tetrahydrofuran was added slowly to a solution of bis(3-methyl-2-butyl) borane prepared from 7.26 g of boron trifluoride etherate, 7.10 g of 2-methyl-2-butene and 1.43 g of sodium borohydride in 35 ml of tetrahydrofuran.[28] The reaction mixture was stirred at room temperature 2 hr, 20 ml of water were added dropwise, followed by 15 ml of 10% aqueous sodium hydroxide. To this mixture was then added slowly 15 ml of 30% hydrogen peroxide and the reaction mixture stirred at room temperature overnight. The aqueous layer was drawn off, extracted with ether, the ethereal extract was combined with the original organic phase and the combined extracts washed with brine, dried, and the solvents removed at reduced pressure to give a yellow oil. This oil was taken up in hexane and filtered through 200 g of Merck alumina. Elution with hexane gave 4.71 g of a mixture, which contained by glc 41% abieta-4,8,11,13-tetraene (9) and 59% 18-norabieta-8,11,13-tetraene (12, 30-X). This hydrocarbon mixture was dissolved in 300 ml of *t*-butanol and added to a solution of 5.40 g of potassium permanganate, 25 g of sodium metaperiodate and 21 g of potassium carbonate in 850 ml of water. The reaction mixture was stirred at room temperature 84 hr, sodium metabisulfite was added until the reaction was colorless and the mixture was concentrated *in vacuo* to a small volume. After cooling, the residue was extracted with three portions of ether, which was combined, washed with brine, dried and the solvent removed at reduced pressure to give a pale yellow oil. This oil was taken up in hexane and filtered through Merck alumina to give 2.45 g of 18-norabieta-4,8,11,13-tetraene (9) contaminated with 13% of another hydrocarbon which, based on glc data, was one of the 16 or 19-norabietatrienes. The spectral properties of the reaction product were identical to those of a sample prepared previously.[7]

When 6.67 g of a mixture of 43% 18-norabieta-4,8,11,13-tetraene (9) and 57% 18-nor-5β-abieta-3,6,11,13-tetraene[12b] (10) was treated with bis(3-methyl-2-butyl) borane there was obtained 4.24 g of a mixture containing 42% olefin 9, 58% olefin 10 and 0.750 g of a mixture of alcohols from which 0.099 g of 18-nor-5β-abieta-8,11,13-trien-3β-ol (11),[12b] mp and mmp, 135–136° could be isolated.

Hydroboration of 18-norabieta-4,8,11,13-tetraene (9). A. – To a solution of 0.500 g of olefin 9 (87% purity, see above) in 10 ml of dry tetrahydrofuran containing 0.85 g of lithium aluminum hydride and maintained at 0° was added dropwise 1.0 ml of boron trifluoride etherate in 15 ml of tetrahydrofuran. The reaction mixture was stirred at 0° for one hr and at ambient temperature for an additional 2 hr. The excess diborane was decomposed by the dropwise addition of ice water, 15 ml of 10% aqueous sodium hydroxide were added, the reaction mixture was cooled to 0° and 12 ml of 30% hydrogen peroxide were added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 18 hr. The aqueous layer was drawn off and extracted with two portions of ether which were combined with the original tetrahydrofuran solution, washed with brine, dried, and the solvent removed to give 0.548 g of almost colorless oil. This oil was dissolved in hexane and chromatographed on 30 g of Woelm activity II neutral alumina. Elution with hexane gave 0.047 g (9%) of a mixture of approximately equal portions of two norabietа-8,11,13-trienes. On the basis of nmr and glc data these are 18 and 19-nor-5β-abieta-8,11,13-triene.[12b] Elution with benzene–methylene chloride gave 0.191 (43%) of 19-nor-5β-abieta-8,11,13-trien-6β-ol (13) as a colorless oil: ir 2.98μ; nmr 1.09 (d, J=5Hz, C-4 methyl), 2.73 (t, J_{app} 7Hz, 12Hz, H-7), 4.05 (q, J_{app} 7Hz, 12Hz, H-6); mass spectrum *m/e* (rel intensity) 272 (13), 270 (52), 257(58), 255 (100), 254 (37), 239 (65), 237 (40), 221 (33), 199 (31), 197 (65), 187 (91). For analysis a small sample of this material was rechromatographed under the conditions described above.

Anal. Calcd for $C_{19}H_{30}O$: C, 83.77; H, 10.36. Found: C, 83.66; H, 10.36.

The later fractions eluted with the same solvent system gave an additional 0.050 g of impure 13, which on the basis of nmr data (see below) was contaminated with the 7-ols (17 and 18).

B. – The hydroboration of 0.463 g of olefin 9 was carried out as described above, however, the reaction with diborane was allowed to proceed for 18 hr. Isolation of the reaction products in the usual manner gave 0.427 g of a viscous oil. This oil was taken up in hexane and chromatographed on 30 g of Woelm neutral alumina, Activity II. Elution with hexane gave 0.154 g of starting olefin, while benzene–methylene chloride (4 to 1) gave 0.125 g (32%, based on starting material consumed) of a mixture of 19-nor-5β-abieta-8,11,13-trien-7α and 7β-ols (17 and 18) as a colorless oil. Although this material was homogeneous to tlc (silica gel-G, benzene–ethyl acetate, 8 to 1), the nmr spectrum clearly showed the presence of two alcohols: ir: 2.93, 6.23μ; nmr 0.92 (d, J=6Hz, C-4 methyl), 1.35, 1.38 (s, C-10 methyls), 4.00 (m $W_{1/2}$ 19Hz, 72H, 0.4 protons), 4.46 (t, J_{app} 5Hz, 7αH, 0.6 protons); mass spectrum *m/e* (rel intensity) 272 (60), 258 (14), 257 (51), 254 (17), 240 (20), 239 (100), 229 (36), 211 (16), 201 (43), 197 (60), 186 (36), 182 (23), 162 (42), 159 (36), 141 (46).

19-Nor-5β-abieta-8,11,13-trien-6-one (14). – To a solution of 0.126 g of 19-nor-5β-abieta-8,11,13-trien-6β-ol (13) in 7 ml of acetone at 0° was added dropwise 0.47 ml (1.05 equiv.) of Jones reagent. The reaction mixture was stirred at 0° for 5 min, methanol was added to destroy the excess oxidizing agent and the reaction mixture was poured into water. The resulting suspension was extracted with two portions of ether, the ethereal extracts were combined, washed with water and brine, dried and the solvent removed at reduced pressure to give 0.100 g (80%) of ketone 14 as an unstable pale yellow oil, which was homogeneous to tlc (silica gel G, benzene); ir 5.87, 6.22μ; nmr 0.92 (d, J=7Hz, C-4 methyl), 1.20 (s, C-10 methyl), 2.38 (t, J=5Hz, H-5), 3.22 (d, J=20Hz, H-7), 3.65 (d, J=20Hz, H-7); ORD (c = 0.000953): ϕ_{700} – 703; ϕ_{316} + 920; ϕ_{304} + 1540; ϕ_{317} + 2200; ϕ_{300} 0; $[\phi]_{298}$ – 11200; mass spectrum *m/e* (rel intensity) 270 (75), 255 (21), 235 (100), 236 (12), 237 (58), 227 (21), 201 (88), 200 (21), 199 (25), 185 (21), 157 (33), 185 (38).[26]

19-Norabieta-8,11,13-trien-7β-ol (20). – To a solution of 0.370 g of 19-norabieta-8,11,13-trien-7-one (19)[12] in 20 ml of 95% ethanol was added 1.0 g of sodium borohydride. The mixture was heated at reflux 2.5 hr, cooled, poured into water and extracted with three portions of ether. The ether extracts were washed first with water, then with brine, dried and the solvent removed to give 0.327 g (88%) of alcohol 20 as a pale yellow glass which was essentially homogeneous to tlc (silica-gel-G, benzene–ethyl acetate 8 to 1), ir 2.85μ; nmr 0.92 (d, J=6Hz, C-4 methyl), 1.13 (s, C-10 methyl), 4.70 (m, H-7). For analysis, a small sample of the compound was dissolved in benzene and chromatographed on Woelm activity II neutral alumina. Elution with benzene–methylene chloride gave the analytical sample as a colorless glass.

Anal. Calcd for $C_{19}H_{30}O$: C, 83.77; H, 10.36. Found: C, 83.84; H, 10.44.

19-Norabieta-5,8,11,13-tetraene (21). – To a solution of 0.307 g of alcohol 20 in 25 ml benzene was added 0.340 g of toluenesulfonic acid. The reaction was carried out and the product isolated as described above for the preparation of 18-norabieta-5,8,11,13-tetraene (8). Chromatography on Merck alumina gave 0.194 g (69%) of colorless oil which was homogeneous to tlc (silica gel-G, hexane); nmr 0.98 (d, J=5Hz, C-4 methyl), 1.00 (s, C-10 methyl), 5.88 (q, $J_{6,7}$=8Hz, $J_{6,5}$=2Hz, H-6), 6.40 (q, $J_{6,7}$=8Hz, $J_{5,7}$=3Hz).

Anal. Calcd for $C_{19}H_{28}$: C, 89.70; H, 10.30. Found: C, 89.55; H, 10.43

19-Norabieta-5,8,11,13-trien-6-one (22). A. – To a solution of 0.084 g of ketone (14) in 5 ml of diglyme was added 0.5 ml of 2 *N* hydrochloric acid and the mixture was heated on the steam bath 1 hr. The reaction mixture was poured into water and extracted with two portions of ether, the ethereal extracts were combined, washed with water, 10% aqueous sodium bicarbonate and brine, dried and the solvent removed to give 0.054 g (64%) of ketone 22 as a yellow oil. This material was combined with 0.041 g from a previous run, dissolved in benzene and filtered through 5 g of Merck acid washed alumina to give 0.069 g of pure (tlc) ketone as an unstable, pale yellow oil: ir 5.81, 6.23μ; nmr 0.92 (d, J=5Hz, C-4 methyl), 0.95 (s, C-10 methyl), 2.21 (br s, H-5), 3.36 (br s, H-7); ORD (c = 0.000358): ϕ_{700} + 1,320; ϕ_{340} + 2,000; ϕ_{328} + 3,000; ϕ_{296} – 4,900; mass spectrum *m/e* (rel intensity) 270 (50), 255 (100), 254 (43), 239 (43), 237 (64), 197 (21), 195 (19), 184 (29).[26]

B. – To a solution of 1.112 g of 19-norabieta-5,8,11,13-tetraene (21) in 25 ml of pyridine was added 1.00 g of osmium tetroxide. The reaction mixture was stirred at room temperature for 52 hr; 30 ml of 10% aqueous sodium bisulfite and 15 ml of pyridine were added. After stirring 2 hr, the reaction mixture was poured into water and extracted with two portions of methylene chloride. The extracts were combined, washed with water, three portions of 10% hydrochloric acid and again with water. After drying and removing the solvent there was obtained 1.133 g of a mixture of diols as a pale yellow glass, which was used in the subsequent step without purification.

A solution of 1.004 g of the mixed diols in 30 ml of 98% formic acid was heated at reflux and the product isolated as described above in the preparation of 18-nor-5β-abieta-8,11,13-trien-6-one. After chromatography there was obtained 0.569 g of ketone 23 as a pale yellow oil. This material was identical to that described in part A.

19-Nor-5β-abieta-8,11,13-trien-7-one (19). – To a solution of 0.077 g of the mixture of 7α and 7β-ols (17 and 18) described above in 5 ml of acetone was added, with stirring at 0°, 0.150 ml (1.05 equiv.) of Jones' reagent. The reaction mixture was stirred at 0° for 10 min, methanol was added and the mixture diluted with water and extracted with two portions of ether. The ethereal extracts were combined, washed with brine, dried and the solvent removed to give 0.044 g (57%) of ketone 19 as a colorless oil which crystallized on standing. Recrystallization from hexane gave white crystals mp 97–100°, mmp 99–101°, UV, 254 nm (4.04), 302 (3.32). The infrared spectrum was identical to that of material reported previously.[7]

7β-Acetoxyabieta-8,11,13-triene (24). – To a solution of ~.16 g of abieta-8,11,13-triene (23) in 32 ml of glacial acetic acid was added 3.0 g of lead tetraacetate and the mixture heated on a steam bath. After 2 hr an additional 4.0 g of lead tetraacetate was added and heating was continued 2 hr. The reaction mixture was diluted with water and extracted with ether. The ether layer was washed with successive portions of water and 5% sodium bicarbonate solution until the washings were basic to litmus, dried and the solvent removed to give 4.27 g of dark yellow oil. The crude product was dissolved in hexane and chromatographed on Merck acid washed alumina. Elution with hexane gave 1.758 g (35%) of acetate 24 as a colorless oil which crystallized on standing. Recrystallization from methanol–water gave white needles, m.p. 127–128° (dec.), ir 3.45 and 5.86μ; nmr 0.88 (s, C-4 methyls), 1.21 (s, C-10 methyl), 5.64 (t, J=5Hz, H-7).

Anal. Calcd for $C_{22}H_{32}O_2$: C, 80.44; H, 9.82. Found: C, 80.22; H, 9.86.

In subsequent experiments the crude product was hydrolyzed directly to the 7-ol.

Abieta-8,11,13-trien-7α-ol (25). A. – To a solution of 0.904 g of acetate 24 in 25 ml of 5% methanolic potassium hydroxide was heated at reflux for 4 hr. The reaction mixture was poured into water and extracted with ether. The ether extracts were washed with water, dried, and the solvent removed to give 0.645 g (82%) of alcohol 25 as a colorless oil; ir 2.98μ, nmr 0.91 (s, C-4a methyl), 1.10 (s, C-10 methyl), 1.20 (s, C-4a methyl), 4.58 (W-7). Although this compound was previously reported as a solid, mp 78–80°,[7] in our hands it failed to crystallize.

B. – To a solution of 0.665 g of acetate 24 in 15 ml of dry ether was added 1.5 ml of Red-Al in benzene. The reaction mixture was stirred under nitrogen for 4 hr, the excess Red-Al was destroyed with ice and the reaction mixture poured into water. The aqueous layer was drawn off, extracted with ether, and the ethereal extracts combined and washed with water. After drying, the solvents were removed to give 0.527 g (91%) of alcohol 25, identical to that prepared in part A above.

10

Abieta-6,8,11,13-tetraene (25). A. - To a solution of 1.58 g of alcohol 25 in 10 ml of dry pyridine was added dropwise 2.0 ml of phosphoryl chloride. The reaction mixture was heated on a steam bath for 1 hr, diluted with water, and extracted with three 10 ml portions of ether. The extracts were combined, washed with 6N hydrochloric acid, dried over magnesium sulfate, filtered, and evaporated to give 0.850 g (17%) of colorless oil; ir 3.44, 6.05μ; nmr 0.93 (s, C-10 methyl), 1.01 (s, C-4 methyls), 5.68 (q, $J_{5,6}$=2Hz, $J_{6,7}$=9.5 Hz, H-7), 6.13 (t, $J_{5,7}$=2Hz, $J_{6,7}$ =9Hz, H-7). This material has been reported as a solid, mp 203°,[4] however, in our hands it did not crystallize at 0°.

B. - A solution of 0.850 g of alcohol 25 in 2 ml of dimethylsulfoxide was heated at 155° for 14 hr. After cooling the reaction mixture was poured into water and extracted with hexane. The extracts were dried, filtered and the solvent removed to give 0.042 g (28%) of colorless oil, identical to the material prepared above.

C. - A 0.285 g sample of acetate 24 was pyrolyzed under nitrogen at 155° for 10 min. After cooling, the reaction products were dissolved in hexane and the solution washed with successive portions of water and 5% aqueous sodium hydroxide. The hexane extracts were dried and the solvent removed to give 0.203 g (35%) of colorless oil the infrared and nmr spectra of which are identical to those reported in A above.

D. - To a stirred solution of 1.56 g of p-toluenesulfonylhydrazine in 25 ml of dry tetrahydrofuran was added 2.00 g of abieta-8,11,13-trien-7-one (26) and 5 drops of concentrated hydrochloric acid. The mixture was stirred and heated at reflux for 13 hr then cooled to 5°. To the cold stirred mixture was added 10 ml of methyllithium over a 30 min period. After 15 min an additional 8 ml of methyllithium was added and stirring continued for 30 min at 5°. Excess methyllithium was decomposed with crushed ice and the reaction mixture was extracted with hexane. The extracts were dried and evaporated to give 1.56 g of yellow oil. Chromatography on Merck neutral alumina and elution with hexane gave 0.750 g (40%) of colorless oil identical to the material described in part A.

11

E. - A solution of 2.10 g of alcohol 25 in 40 ml of benzene was added to a solution of 0.837 g of p-toluenesulfonic acid in 10 ml of benzene. The reaction was carried out and the product isolated as described above for the preparation of 18-norabieta-6,8,11,13-tetraene (4). Chromatography on Merck alumina gave 1.03 g (52%) of a very pale yellow oil identical to the material described in part A.

Abieta-8,11,13-trien-6-one (5). - The preparation of ketone 5 was carried out in the same manner as described for the preparation of 18-nor-5β-abieta-8,11,13-trien-6-one (8). From 0.501 g of olefin 26, there was obtained as a crude product 0.183 g of a greenish yellow gum. This material was dissolved in hexane and chromatographed on Merck acid washed alumina. Elution with hexane gave 0.100 g of pale yellow oil which was not homogeneous to tlc. Rechromatography of 0.086 g of this material on Woelm acidic alumina, Activity II, and elution with hexane-benzene (2:1) gave 0.033 g of ketone 5 as an unstable pale yellow oil which was homogeneous to tlc (silica gel-benzene); ir 5.84μ(reported, 5.83μ[4]); nmr 1.11 (s, C-4 methyl), 1.17 (s, C-10 methyl), 1.32 (s, C-4 methyl), 2.42 (br, s, H-5), 3.61 (br s, H-7), ORD: C=0.00225. a_{328} + 8463; mass spectrum, m/e (rel intensity) 284 (56), 269 (100), 251 (11), 241 (17), 227 (33), 213 (22), 199 (39), 197 (22). Although this material has been reported as a solid, mp 40°,[4] in our hands it failed to crystallize.

When an attempt was made to repeat this experiment using 0.364 g of diol mixture in 15 ml of 98% formic acid there was obtained 0.345 g of greenish yellow gum. This material was dissolved in hexane and chromatographed on Merck acid washed alumina. Elution with hexane gave 0.130 g of yellow oil, while elution with benzene gave 0.087 g of dark yellow oil. Neither fraction was homogeneous to tlc. The fractions were combined, dissolved in hexane and rechromatographed on Woelm silica gel, Activity I.

12

Elution with hexane-benzene (1:1) gave 0.054 g of a mixture of ketones 5 and 27 as a pale yellow oil which showed two spots of almost identical R_f on tlc (silica gel-benzene); ir 5.40 and 5.84μ; nmr 1.11 (s, C-4 methyl, 3a), 1.14 (s, C-10 methyl, 3a), 1.32 (s, C-4 methyl, 3a), 1.48 (s, C-4 methyl, 3b), 1.96 (s, C-10 methyl, 3b). 2.42 (br, s, H-5), 3.51 (br, s, H-7); mass spectrum, m/e (rel intensity) 284 (87), 269 (100, 241 (27), 227 (70), 199 (73).

Elution with benzene gave 0.062 g of yellow oil which crystallized on standing. Recrystallization from hexane gave bright yellow crystals of 18-abieta-8,11,13-trien-6,7-dione (28) m.p. 89–91°; ir (CCl_4) 3.39, 5.81, 5.94μ; nmr 60.14 (s, C-4a-methyl), 1.01 (s, C-4β-methyl), 1.26 (s, C-10 methyl), 2.71 (br, s, H-5), 8.01 (d, J = 2H, H-14). Mass spectrum m/e (rel intensity) 298 (46), 283 (7), 270 (27), 255 (69), 239 (100), 211 (69). This material decomposed on attempted purification for analysis.

Isomerization of abieta-8,11,13-trien-6-one (5). - To a solution of 0.030 g of ketone 5 in 3 ml of diglyme was added 3.0 ml of 2N hydrochloric acid, the mixture was heated on a steam bath for 18 hr, poured into water and extracted with two portions of ether. The extracts were combined, washed with water, dried and evaporated to give 0.028 g of brown gum. The crude product was dissolved in benzene and chromatographed on Merck acid washed alumina. Elution with benzene gave 0.017 g of brown oil which shows two spots of nearly identical R_f value of tlc (silica gel-benzene). The spectral properties of this material were identical to those of the mixture of ketones 5 and 27 described above.

Acknowledgements. - The spectrophotometer and mass spectrometer were obtained through a National Science Foundation Research Instruments Grant. We thank T. F. Sanderson of Hercules, Inc., for a generous gift of dehydroabietonitrile.

bon at C-6, the equatorial methyl group at C-4 is gauche to both C-6 substituents, in contrast to the situation which prevails when C-6 is trigonal. As expected, ketone **14** proved unstable relative to the trans isomer (**3**) in which the secondary methyl group is equatorial (**3a**).

It was expected that if 5β-abieta-8,11,13-trien-6-one (**27**) could be obtained from the trans ketone, it would exist in the steroidal conformation (**27a**). However, the nmr data for the mixture of ketones obtained by isomerization clearly indicates that this is not the case, and that this compound exists in the nonsteroidal conformation (**27b**) in spite of the axial–axial methyl interaction. Although the reasons for this are not immediately obvious, a study of the models indicates that in **27b** with a half-boat conformation for ring B there exists a moderate interaction between the carbonyl group and C-19, while in the half-chair conformation there is a severe interaction between C-7 and C-18. Some confirmation for the latter conclusion is found in the fact that dione **28**, in which C-7 is trigonal, exists in the steroidal conformation.

Although the earlier workers[2–5] found no evidence for an equilibrium between cis and trans 6-ketones similar to **27** and **1**, it is quite apparent that such an equilibrium can be established under vigorous conditions. It was noted by Wenkert that xanthoperol, a 6,7-diketone similar to **28**, was resistant to enolization, owing to very unfavorable nonbonded interactions between C-18 and the oxygen at C-6 in the enol.[23] Similar interactions would exist in the enol derived from **1** or **27** in which the double bond is directed toward C-5, and we suggest that this steric inhibition of enolization which would cause isomerization is responsible for the reported observations regarding the stereochemistry at C-5 in ketones similar to **1**.[2–5]

Registry No.—**1**, 15372-59-5; **3**, 51820-96-3; **4**, 51838-79-0; **5**, 22566-08-1; **6**, 51820-97-4; **8**, 51820-98-5; **9**, 23963-77-1; **10**, 22566-11-6; **14**, 51820-99-6; **15**, 51829-69-7; **17**, 51821-00-2; **18**, 51821-01-3; **19**, 22566-09-2; **20**, 51821-02-4; **21**, 51821-03-5; **22**, 26906-88-7; **23**, 19407-28-4; **24**, 51821-04-6; **25**, 26920-02-5; **26**, 26920-03-6; **27**, 51821-05-7; **28**, 51821-06-8.

Miniprint Material Available. Full-sized photocopies of the miniprinted material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the mimiprinted and supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $4.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-2501.

References and Notes

(1) Part VIII: J. W. Huffman and J. J. Gibbs, *J. Org. Chem.*, **38**, 2732 (1973).
(2) S. M. Kupchan, A. Karim, and C. Marcks, *J. Amer. Chem. Soc.*, **90**, 5923 (1968).
(3) L. D. Martin, *Tetrahedron*, **29**, 2553 (1973).
(4) G. Defaye-Duchateau, *Bull. Soc. Chim. Fr.*, 1469 (1964).
(5) (a) K. Mori and Matsui, *Tetrahedron*, **26**, 3467 (1970); (b) R. C. Cambie and R. A. Franich, *Aust. J. Chem.*, **24**, 571 (1971).
(6) A. Ross, P. A. Smith, and A. S. Dreiding, *J. Org. Chem.*, **20**, 905 (1955).
(7) J. W. Huffman, *J. Org. Chem.*, **35**, 478 (1970).
(8) A. W. Burgstahler and J. N. Marx, *J. Org. Chem.*, **34**, 1562 (1969).
(9) (a) R. H. Shapiro and M. J. Heath, *J. Amer. Chem. Soc.*, **89**, 5734 (1967); (b) R. H. Shapiro and J. H. Duncan, *Org. Syn.*, **51**, 66 (1971).
(10) L. Blaha, J. Weichet, J. Zvachek, S. Smolik, and B. Kahac, *Collect. Czech. Chem. Commun.*, **25**, 237 (1960).
(11) F. Johnson, N. A. Starkousky, and W. D. Curowitz, *J. Amer. Chem. Soc.*, **87**, 3492 (1965).
(12) (a) E. Wenkert, A. Alonso, P. Beak, R. W. J. Carney, P. W. Jeffs, and J. D. McChesney, *J. Org. Chem.*, **30**, 713 (1965); (b) J. W. Huffman, *ibid.*, **37**, 17 (1972). The effect of steroidal *vs.* nonsteroidal conformations on the chemical shift of the angular methyl group in 5β-abieta-8,11,13-triene derivatives is also discussed in some detail in ref 7.
(13) R. S. Monson, "Advanced Organic Synthesis," Academic Press, New York, N. Y., 1971, p 37.
(14) C. R. Bennett, R. C. Cambie, R. A. Franich, and T. J. Fullerton, *Aust. J. Chem.*, **22**, 1711 (1969), have reported a similar selective oxidation, which could not be reproduced under their conditions (see Experimental Section). Although *a priori* one would expect that **9** and **12** could be separated in a similar manner, this mixture was inert to periodate–permanganate.
(15) The use of excess Jones reagent or dimethyl sulfoxide–acetic anhydride [D. J. Albright and L. Goldman, *J. Amer. Chem. Soc.*, **87**, 4214 (1965)] gave complex mixtures from which no ketone could be isolated.
(16) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, p 51.
(17) (a) H. C. Brown, "Hydroboration," W. A. Benjamin, New York, N. Y., 1962; (b) P. Pernelle and G. Ourisson, *J. Org. Chem.*, **30**, 1744 (1965); (c) W. Herz and J. Schmid, *ibid.*, **34**, 3464 (1969); (d) A. M. Krubiner, N. Gottfried, and E. P. Oliveto, *ibid.*, **33**, 1715 (1968); (e) B. E. Cross and P. L. Myers, *J. Chem. Soc. C*, 471 (1968).
(18) H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1972, pp 109–110, and many references therein.
(19) It might be argued that the 6-ol could be derived from a 6,8,11,13-abietatetraene. However, it has been reported (ref 4) that hydroboration of abieta-6,8,11,13-tetraene gives a mixture of 6- and 7-ols. Hydroboration of 18-norabieta-6,8,11,13-tetraene (**4**) gives the 7α-ol as the major product: J. W. Huffman and J. J. Gibbs, unpublished work.
(20) P. R. Jones, *J. Org. Chem.*, **37**, 1886 (1972). This author has pointed out that the generally accepted four-centered transition state mechanism for the hydroboration reaction suggested by Brown [ref 17a, p 145; see also H. C. Brown and G. Zweifel, *J. Amer. Chem. Soc.*, **82**, 4708 (1960); **83**, 2544 (1961)] has a significant symmetry barrier.

(21) M. Kitadani, A. Yoshikoski, Y. Kitahara, J. Campello, J. D. McChesney, D. J. Watts, and E. Wenkert, *Chem. Pharm. Bull.*, **18**, 407 (1970), have reported the preparation of this compound by the lithium aluminum hydride reduction of 18-tosyloxyabieta-8,11,13-triene; however, in our hands this reduction failed. Hydrocarbon **23** was prepared by Wolff–Kishner reduction of the aldehyde derived from dehydroabietic acid by a modification of the procedure described in ref 8.
(22) V. J. Traynelis and W. L. Hergenrother, *J. Org. Chem.*, **27**, 2377 (1962).
(23) E. Wenkert and B. G. Jackson, *J. Amer. Chem. Soc.*, **80**, 211 (1958).
(24) Melting points were determined on a Kofler hot stage and are uncorrected. Infrared spectra were taken as films or potassium bromide pellets on a Perkin-Elmer Model 137 spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian Associates Model A-60 spectrometer using deuteriochloroform as a solvent and tetramethylsilane as an internal standard. Signals are reported in parts per million relative to this standard (δ). Optical rotatory dispersion and circular dichroism measurements were made in methanol using a Jasco ORD/UV-5 spectropolarimeter. Glc data were obtained using an F and M Model 810 chromatograph with a 10 ft × 0.125 in. OV-17 on Chromosorb W column at a temperature of 260°. Mass spectra were determined using a Du Pont 21-4'0 mass spectrometer at 70 eV ionization potential. Unless otherwise noted, all compounds were homogeneous by tlc and/or glc.
(25) For this and all compounds in this series the isopropyl group appears as a doublet, J = 6–7 Hz, at δ 1.20 ± 0.05. H-15 is a multiplet centered in the region of δ 2.80.
(26) This compound was unstable, and satisfactory analyical data could not be obtained.
(27) J. W. Huffman and P. G. Arapakos, *J. Org. Chem.*, **30**, 1604 (1965).
(28) R. A. Benkeser and E. M. Kaiser, *J. Org. Chem.*, **29**, 955 (1964).

Synthesis of Prostaglandins by Conjugate Addition and Alkylation of a Directed Enolate Ion. 11-Deoxyprostaglandins[1]

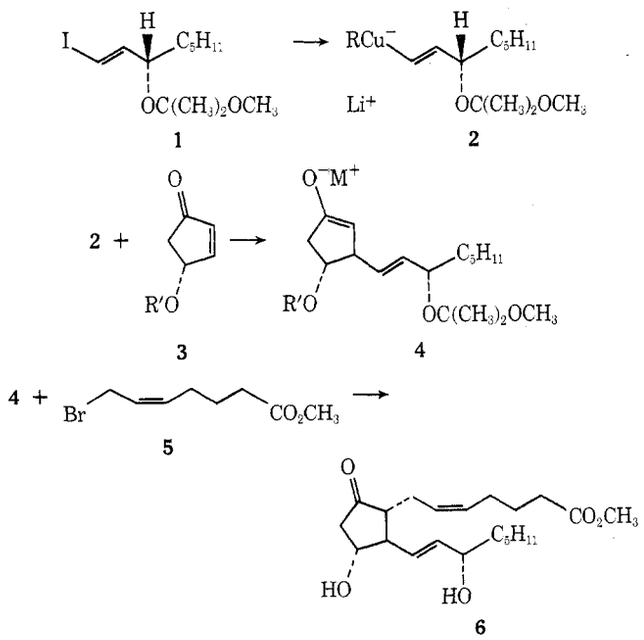
John W. Patterson, Jr.,* and John H. Fried

Institute of Organic Chemistry, Syntex Research, Palo Alto, California 94304

Received February 7, 1974

Bis[*trans*-3-(2'-methoxy-2'-prop-2'-oxy)-1-octenyl]copper lithium (**2**) has been added to cyclopent-2-enone and the resultant enolate ion converted to the silyl enol ether **8**. This silyl enol ether was then alkylated with methyl *cis*-7-bromooct-5-enoate to yield 11-deoxyprostaglandin E_2 methyl ester (**10**). By similar reactions (±)-5,6-dehydro-11-deoxyprostaglandin E_2 and (±)-11,15-deoxyprostaglandin E_2 methyl esters (**15** and **20**) were prepared.

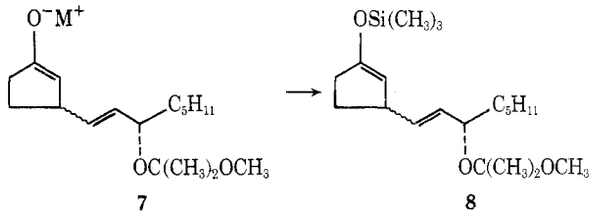
Conjugate addition of an organocopper reagent followed by alkylation of the resulting nonequilibrated enolate ion is a convenient method for converting α,β-unsaturated ketones to vicinally dialkylated ketones.[2,3] The use of the cuprate derived from 3-(*S*)-*trans*-1-iodo-1-octen-3-ol in prostaglandin synthesis *via* conjugate addition to 2-alkylated cyclopentenones has been actively investigated in these laboratories[4] and elsewhere.[5] With the goal of developing a short and converging synthesis of prostaglandins, we were interested in employing this conjugate addition in conjunction with an alkylation of the resultant enolate ion (**4**) to a protected 4-hydroxycyclopent-2-enone, *e.g.*, **3**, in



order to introduce both functionalized side chains characteristic of these natural products. Based on steric considerations, we expected that such an approach would give prostaglandins, incorporating mainly the trans,trans stereochemical relationship at carbons 8, 11, and 12, while the use of the cuprate **2** obtained from 3-(*S*)-*trans*-1-iodo-1-octen-3-ol methoxy isopropyl ether (**1**)[4] would establish the natural α configuration at C-15. Thus the prostaglandins resulting from such a sequence of reactions would be predominantly a mixture of PGE_2 (**6**) and 8,11,12-*epi*-PGE_2.[6]

We wish to describe here the application of this method to the synthesis of several 11-deoxyprostaglandins.

11-Deoxyprostaglandin E_2 (10).[7] Our initial attempts to alkylate enolate ion **7** obtained from the addition of achiral cuprate **2** (R = *trans*-CH=CHCH[OC-$(CH_3)_2OCH_3$]C_5H_{11}[4]), to cyclopent-2-enone were unsuccessful under a variety of conditions. Consequently, we turned to the expedient of trapping the enolate ion as the trimethylsilyl ether (**8**). This intermediate was not sufficiently stable for characterization or extensive purification. However, extraction of the trimethyl phosphite–copper iodide complex from a hexane solution of **8** with DMSO gave silyl ether **8** of adequate purity for the alkylation step.



In the alkylation procedure employed here, the achiral lithium enolate **7** (M = Li) was generated in liquid ammonia by reaction of silyl ether **8** with lithium amide. An excess of the alkylating agent, methyl *cis*-7-bromo-5-heptenoate (**9**), was added and, after a suitable period at −35°, the reaction was quenched with ammonium chloride. Aqueous acetic acid removed the methoxy isopropyl ether group, resulting in a mixture of (±)-11-deoxy-PGE_2 and (±)-11-deoxy-15-*epi*-PGE_2 methyl esters (**10** and **11**). By use of a fourfold ratio of allylic bromide to enolate ion