which was shown to consist of a single component by glpc. The crude hemiacetal was sufficiently pure for subsequent reactions. A small sample, recrystallized twice from acetone–hexane, gave hemiacetal of analytical purity: mp 174.5–178°; ir ($CHCl_3$) 3570–3360 cm^{-1} (broad OH), no absorption due to carbonyl in the 1700-cm^{-1} region.

Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.41; H, 8.60.

1β,4aβ-Dimethyl-3,4,4a,9,10,10aα-hexahydro-7-methoxy-1α-(2′-*m*-methoxyphenylethyl)-2(1H)-phenanthrone (24).—The general procedures followed in the subsequent experiments were similar to those which were used in the synthesis of the isomeric C-10aβ ketone **23**.

Grignard Addition.—To a solution of 0.04 mol of *m*-methoxyphenylmagnesium bromide in 60.0 ml of 2:1 ether–tetrahydrofuran was added 3.8 g (12.6 mmol) of the above hemiacetal in 50 ml of dry tetrahydrofuran. The red solution was heated at reflux for 6 hr, cooled, and then poured onto ice and solid ammonium chloride. The crude diol was isolated and purified by chromatography as previously described. This diol was carried onto the next experiment without characterization.

Hydrogenolysis.—A solution of the diol obtained in the previous experiment in 250 ml of methanol and 1.0 ml of 60% perchloric acid was stirred under 1 atm of hydrogen in the presence of 0.50 g of 10% palladium on charcoal. After the theoretical quantity of hydrogen was absorbed, the catalyst was filtered and the product was isolated as previously described. The resulting alcohol was used in the following oxidation without purification.

Oxidation.—The unpurified alcohol from the preceding experiment was dissolved in 125 ml of acetone and treated with 4.0 ml of Jones reagent[17] for 0.5 hr at 0°. The reaction was worked up in the previously described manner, and the resulting product was chromatographed on 150 g of alumina (Merck). Elution with 900 ml of 50% benzene–ligroin afforded material which on trituration in cold ether gave 4.33 g (88% from lactone **22**) of the colorless, crystalline ketone **23**, mp 108–111°. Recrystallization of a small sample from methanol for analysis afforded material which melted at 109.5–111°: ir ($CHCl_3$) 1700 (C=O), 1610 and 1500 (aromatic bands), and 1035 cm^{-1} ($ArOCH_3$); nmr ($CDCl_3$) δ 1.16 (s, 3, C-1β CH_3), 1.25 (s, 3, C-4aβ CH_3), and 3.80 (s, 6, 2 $ArOCH_3$).

Anal. Calcd for $C_{26}H_{32}O_3$: C, 79.56; H, 8.22. Found: C, 79.43; H, 8.20.

3,10-Dimethoxy-6aβ,12bβ-dimethyl-5,6,6a,6bα,7,8,12b,13-octahydropicene (26).—A solution of 2.163 g (5.52 mmol) of ketone **24** and 0.80 g of *p*-toluenesulfonic acid monohydrate in 500 ml of toluene was heated at reflux under a Dean–Stark water separator in a nitrogen atmosphere. The progress of the reaction was followed by glpc. After 31 hr, all of the ketone had been transformed to a single product which was stable to further acid treatment. The reaction mixture was cooled, washed with 10% aqueous potassium hydroxide solution, water until neutral, and saturated brine solution, and dried (Na_2SO_4). Removal of the solvent at reduced pressure yielded a crystalline residue which on trituration with methanol afforded 1.90 g (97%) of the pentacyclic olefin **26**, mp 185–188°. Recrystallization of a small sample from ethanol–benzene for analysis gave material melting at 188.5–191°: ir (Nujol) 1650 (weak C=C), 1610, 1574, and 1500 (aromatic bands), and 1030 and 1040 cm^{-1} ($ArOCH_3$); nmr ($CDCl_3$) δ 1.00 (s, 3, C-6aβ CH_3), 1.32 (s, 3, C-12bβ CH_3), 3.78 (s, 6, 2 $ArOCHH_3$), 5.91 (m, 1, C-14 **H**), 6.67 (m, 2, C-4 and C-9 **H**), 7.27 (d, 1, J = 9.0 Hz, C-12 **H**), and 7.43 (d, 1, J = 9.0 Hz, C-1 **H**).

Anal. Calcd for $C_{26}H_{30}O_2$: C, 83.38; H, 8.07. Found: C, 83.24; H, 8.05.

Registry No.—**11**, 21343-29-3; **12**, 21347-62-6; **13**, 21347-63-7; **14**, 21347-64-8; **16**, 21371-73-3; **17**, 21373-64-8; **18**, 21347-65-9; **19**, 21347-66-0; **20**, 21347-67-1; **21**, 21347-68-2; **22**, 21371-74-4; **23**, 21347-69-3; **24**, 21347-70-6; **25**, 21343-13-5; **26**, 21343-14-6; **27**, 21343-15-7; **28**, 21343-16-8; **29**, 21343-17-9; methyl ester of **16**, 21343-18-0; ethyl ester of **17**, 21343-19-1; 1α,4aβ-dimethyl-7-methoxy-1,2α,3,4,4a,9-hexahydro-2β-hydroxy-1-α-phenanthreneacetic acid, 21343-20-4; methyl ester of **21**, 21343-21-5; lactone of **16**, 21343-22-6; methyl ester of **18**, 21343-23-7; 1β-4aβ-dimethyl-7-methoxy-1,2,3,-4,4a,9,10,10aβ-octahydro-2-oxo-1α-phenanthreneacetic acid, 21343-24-8; free acid of **28**, 21343-25-9; methyl 1β,4aβ-dimethyl-2,2-ethylenedithio-7-methoxy-1,2,3,4,4a,9,10,10aα-octahydro-1α-phenanthreneacetate, 21343-26-0; corresponding diol of **20**, 21343-27-1; N-methyl 1β,4aβ-dimethyl-2β-hydroxy-7-methoxy-1,2α,3,4,4a,9,10,10aα-octahydro-1α-phenanthreneacetamide, 21343-28-2.

Experiments Directed toward the Total Synthesis of Terpenes. XVI. The Structure and Stereochemistry of Two Decahydropicene Derivatives

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Received January 14, 1969

The conversion of the *cis,syn*-octahydropicene **5** and the *trans,anti*-octahydropicenes **12a** and **12b** to the *cis,-syn,cis*-decahydropicene **7** and *trans,anti,trans*-decahydropicenes **16a** and **16b** is described. In the former case, the structure and stereochemistry of the ketone **7** was established by single-crystal X-ray structural analysis of the derived bromo ketone **8**. While the stereochemistry of the latter series of ketones **16a** and **16b** is that required for the synthesis of the triterpene alnusenone **1**, the yield in the transformation was too low to make either material a viable synthetic intermediate.

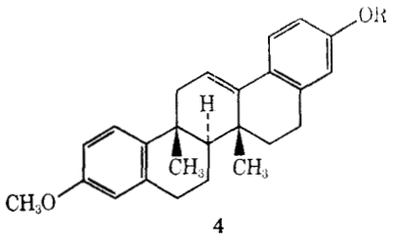
In the preceding paper in this series,[3] a plan was presented for the construction of the pentacyclic triterpene alnusenone (**1**) which entailed the construction of the trimethyl decahydropicene derivative (**2**). One approach to the synthesis of this key intermediate **2** envisaged the introduction of the angular methyl group at C-14a through methylation of the ketone **3** derived by oxidation of the pentacyclic olefin **4**. The preparation of three stereoisomers of this latter material **4** was initially accomplished,[3] and the results of the further transformations of two of these stereoisomeric olefins is the subject of the present report.

(1) This research program was made possible by a grant (GP 4978) from the National Science Foundation. The X-ray work was supported by a grant (USPHS GM 12121) from the National Institutes of Health. The authors gratefully acknowledge this support.

(2) Research Fellow of the National Institute of General Medical Sciences of the U. S. Public Health Service.

(3) R. E. Ireland, D. A. Evans, D. Glover, G. Rubottom, and H. Young, *J. Org. Chem.*, **35**, 3717 (1969).

As before,[3] in order to simplify the problems that attend the crucial carbon skeletal construction phase of the work, the initial investigations were carried out with derivatives of the olefin **4** that bore two methoxy substituents (**4**, R = CH_3) on the aromatic rings rather



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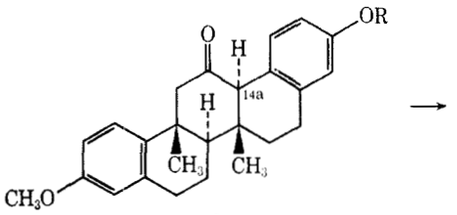

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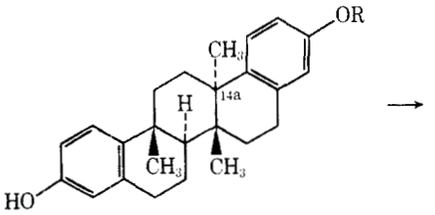

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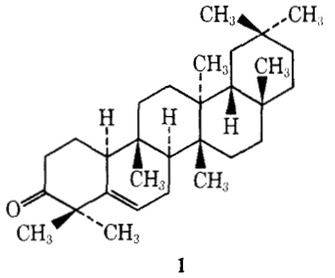

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than the more complex system in which the two aromatic rings bore oxygen substituents that would allow for the ultimately necessary differentation of the two terminal rings. Chronologically, the more readily available pentacyclic olefin and hence the first one investigated was later (*vide infra*) shown to be the *cis,syn* isomer **5**.[3] It was through the study of this isomer that the information required for the construction of the desired *trans,anti* isomer **4** became available.

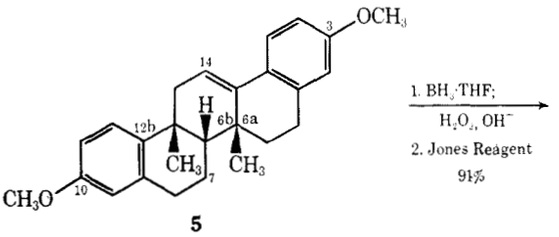
cis,syn,cis **Series.**—The olefin **5** was found to undergo efficient oxidation to the ketone **6** through the intermediate C-14 alcohol obtained on hydroboration.[4] The ketone that initially resulted from mild Jones oxidation[5] was a mixture of stereoisomers about the C-14a position, but after mild base treatment only the *cis,syn,trans* isomer **6** remained. See Chart I.

It was not necessary to block the C-13 methylene group in the ketone **6** in order to realize methylation at the desired angular C-14a position by virtue of the greater ease of enolate formation toward the latter, more acidic site. The pure, methylated ketone **7** was readily available in 50% yield after potassium *t*-butoxide catalyzed enolization of the ketone **6** and then addition of methyl iodide. As a result of the subsequent delineation of the undesired stereochemical arrangement of this isomer, no effort was made to increase this yield.

At this point in the synthetic process, the four centers of asymmetry of the key intermediate pentacyclic derivative **2** had been established and firm verification of both structure and stereochemistry were desired. No chemically convenient method was available, for this determination for the synthetic scheme had been highly stereoselective throughout and isomeric intermediates were not available in quantity for comparison. In particular, the methylation reaction that generated the ketone **7** had produced no detectable (nmr) amount of an isomeric methylated ketone; the balance of the reaction product was shown to be unmethylated starting ketone **6** (probably a result of O methylation). This structural and stereochemical problem appeared ideally suited to the methods of single-crystal X-ray structural analysis. Accordingly, in order to obtain a derivative of the methylated ketone **7** that would facilitate the X-ray analysis, a bromine atom was introduced in the molecule by bromination with phenyltrimethylammonium tribromide (PTAB)[6] in tetrahydrofuran. A

CHART I

SYNTHESIS OF 14-KETO-3,10-DIMETHOXY-6aβ,12bβ,14aβ-TRIMETHYL-5,6,6a,6bβ,7,8,12b,13,14,14a-DECAHYDROPICENE (**7**)



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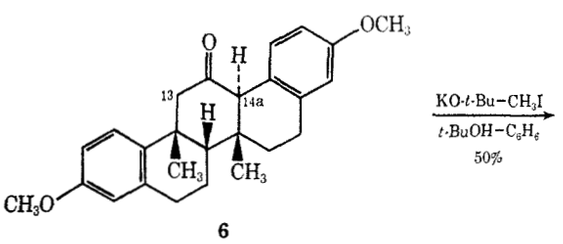

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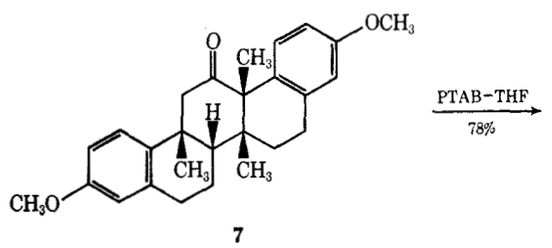

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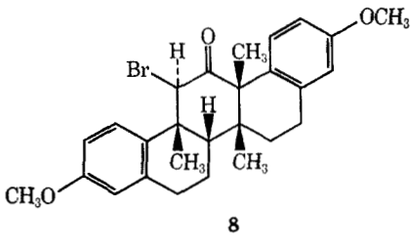

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(4) G. Zweifel and H. C. Brown, *Org. Reactions*, **13**, 1 (1963).

(5) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, **39** (1946); see also C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

(6) J. Jacques, A. Marquet, and B. Tchoubar, *Bull. Soc. Chim. Fr.*, 511 (1965).

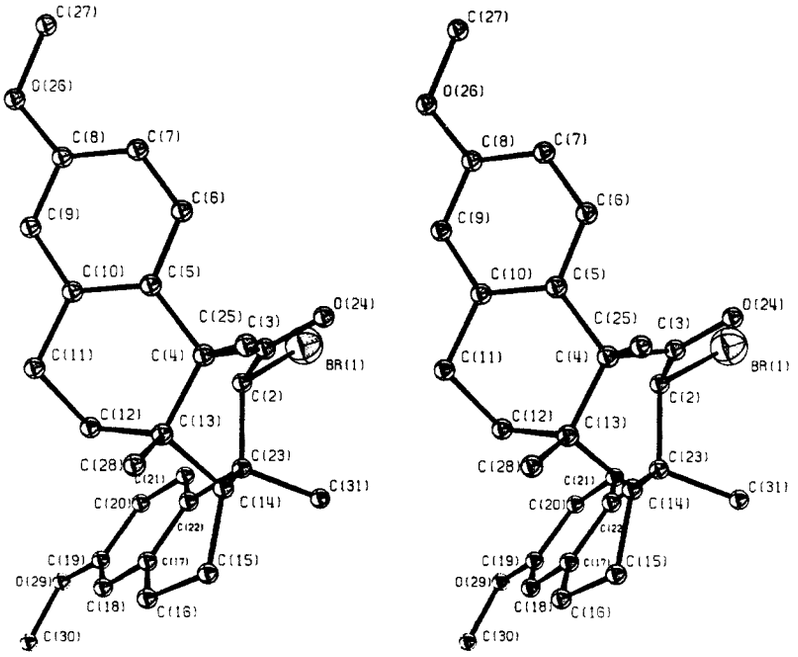
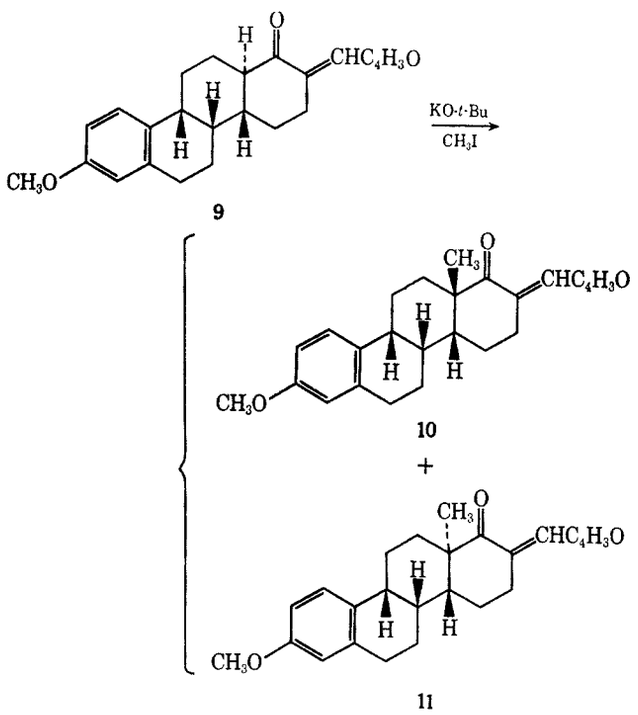


Figure 1.—Stereoformula of pentacyclic bromo ketone 8.

crystalline monobromo ketone **8**, which after careful purification was available in 78% yield, was found quite adequate for the X-ray analysis. This structural analysis[7] showed unequivocally that the bromo ketone **8** (and hence the methylated ketone **7** from which it was derived) possessed the undesired *cis,syn,cis* skeletal arrangement[7] (Figure 1). This structure suggests that the undesired stereochemical orientation about both the C-6b and C-14a carbon atoms is the result of the catalytic hydrogenation of the 6b(7) double bond at the tricyclic stage.[3] It is this reaction that establishes the *cis,syn* backbone of the pentacyclic olefin **5**, and there is adequate precedence that angular methylation of a polycyclic molecule with these stereochemical features leads to the predominate formation of the *cis,syn,cis* isomer. Thus, Johnson and coworkers[8] found that methylation of the tetracyclic derivative **9** resulted in the preponderant formation of the *cis* isomer **10**, and only a very low yield of the *trans* isomer **11**. On this basis, the undesired β orientation of the C-14a methyl group in the methylated ketone **7** is more logically a consequence of the *cis,syn* backbone of the starting ketone **6** than of any intrinsic factor that favors the formation of the unwanted *cis* fusion between the C and D rings. This conclusion leaves unanswered the important question of whether the two axially oriented methyl groups at C-6a and C-12b in the stereoisomeric *trans,anti,trans* ketone **3** would so sterically hinder the β face of the molecule that the methylation would result in the stereoselective introduction of an α-oriented methyl group at C-14a.

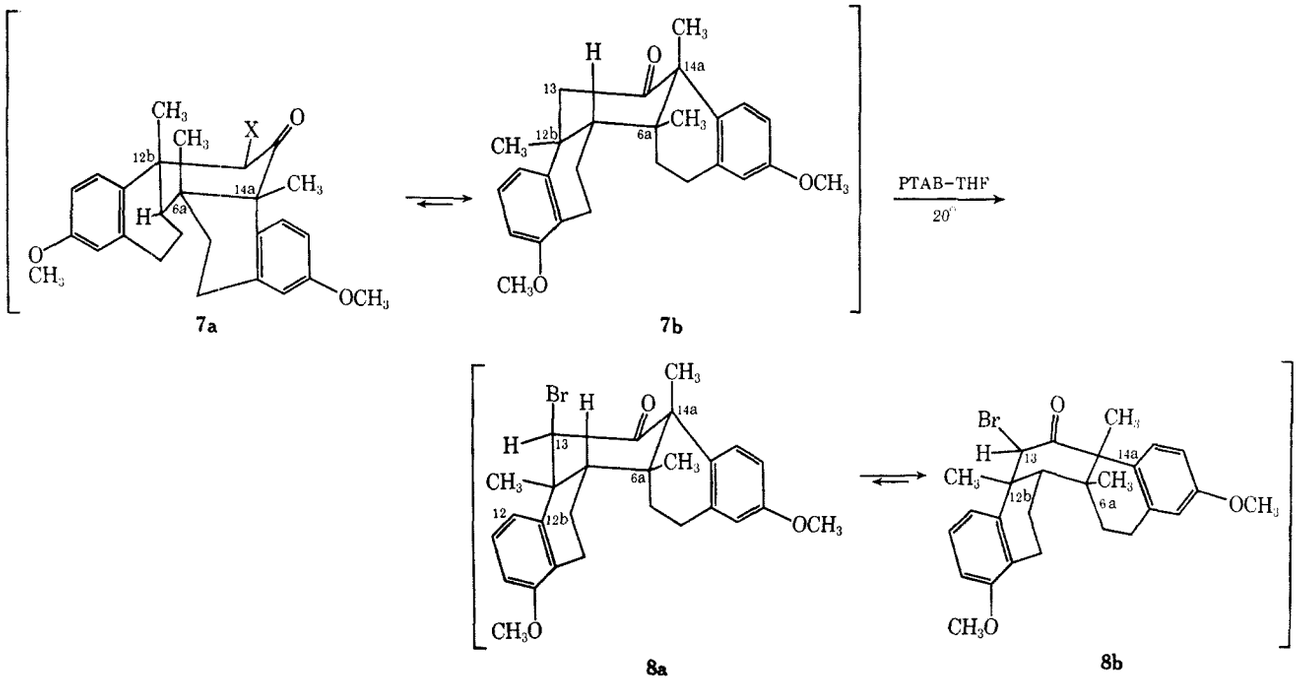
Another interesting facet of the structure derived for the bromo ketone **8** devolves from the orientation of the C-13 bromine substituent. Inspection of the structure shown in Figure 1 for the bromo ketone **8** shows that



the bromine-containing ring (ring C) has taken the *boat conformation* and that the β-oriented bromine atom is in a boat–equatorial conformation (**8b**). The potential conformational flexibility of the *cis,syn,cis* configuration makes possible at least two other conformations for this bromo ketone **8**—namely, **7a** (X = Br) and **8a**—that might be preferred by the molecule in solution in contrast to the crystalline state. It is possible to exclude conformation **8a** on both theoretical and spectral grounds. The severe 1,3-diaxial C-13 Br–C-14a CH_3 interaction is known[8] to destabilize this arrangement, and the observed shift of the carbonyl stretching frequency in the infrared on conversion of the methylated ketone **7** (1705 cm^{-1}) to the bromo ketone **8**

(7) Complete experimental detail (Document NAPS-00647) from ASIS National Auxiliary Publications Service, c/o CCM Information Corp., 909 3rd Ave., New York, N. Y. 10022; remit $1.00 for microfiche or $3.00 for photocopy.

(8) W. S. Johnson, I. A. David, H. C. Dehm, R. J. Highet, E. W. Warnhoff, W. D. Wood, and E. T. Jones, *J. Amer. Chem. Soc.*, **80**, 661 (1958).



(1718 cm^{-1}) implies[9] that even in solution ($HCCl_3$) the C-13 bromine substituent bears a near-eclipsed conformational relationship to the C-14 carbonyl group. Further, it is possible to show by nmr spectroscopy that conformation **7a** (X = H) is not a valid representation for the methylated ketone **7**—and hence, conformation **7a** (X = Br) is an unlikely depiction of the bromoketone **8** in solution. This may be done through an evaluation of the direction of the benzene-induced solvent shift (Δ)[10] of the C-14a angular methyl group. If conformation **7a** (X = H) were the preferred arrangement for the methylated ketone **7** in solution, a negative[10] Δ value would be expected for the equatorial C-14a methyl group, while the axial C-14a methyl group in conformation **7b** would be manifest in a positive Δ value. The observed positive Δ value of 6.0 Hz ($\delta^{DCCl_3}_{C\text{-}14a\ CH_3}$ 92 Hz − $\delta^{C_6H_6}_{C\text{-}14a\ CH_3}$ 86 Hz) clearly indicates that the best representation of the methylated ketone **7** is conformation **7b**, where only the C-14a methyl group is axially oriented and the C-6a and C-12b methyl groups are equatorially disposed toward ring C. These observed spectral characteristics of the ketones **7** and **8** serve to verify the validity of the crystal structure analysis of the bromo ketone **8**, and the intuitive conclusion that, in the flexible *cis,syn,cis* configuration, the 1,3-diaxial relationship between the C-6a and C-12b methyl groups in conformation **7a** (X = H)—as well as **7a** (X = Br)—will distabilize this arrangement relative to conformation **7b**. It seems reasonable to propose, then, that both the methylation of the starting ketone **6** and the bromination of the methylated ketone **7** take place through stereoelectronically preferred axial attack of the enolate and enol of the two ketones, respectively,[11] where the reactive conformation most closely resembles that shown by conformation **7b**. It is interesting to note that, under the bromination conditions used for the conversion of the methylated ketone **7** to the bromo ketone **8**, no isomerization of the initial kinetic bromination product was observed. This may be due to the mild character of the reaction conditions or to the fact that the β-oriented bromine substituent is, indeed, the thermodynamically as well as the kinetically preferred product. An α- (equatorial) oriented C-13 bromine substituent in an all-chair conformation similar to **8a** would experience a severe *peri* interaction[12] with the aromatic C-12 hydrogen which would materially destabilize this arrangement. This could result in an isomeric equilibrium mixture that favored the β-oriented bromine in conformation **8b**.

trans,anti,trans **Series.**—Attention was next turned to the oxidation and subsequent methylation of the *trans,anti* olefin **12a**, the structure and stereochemistry of which was firmly established through the relationship of the synthetic sequence used to that of the *cis,syn* isomer **5**.[3] It was surprising to find that the olefin **12a** was completely inert to hydroboration. Even after allowing the olefin **12a** to remain in contact with a tenfold excess of diborane in tetrahydrofuran or diglyme for a period of 1 week, a 95% recovery of the starting olefin **12a** was realized. There are very few cases[4] of olefins that are too hindered to undergo the addition of diborane, and the structure of the olefin **12a** does not suggest that it fits in this group.

An alternative method of effecting the desired transformation was, however, found in the oxidation of the olefin **12a** with *m*-chloroperbenzoic acid in methylene chloride at 0°. Even this process exhibited some unexpected characteristics, as a variety of ketonic products were formed. From the crude oxidation product there was isolated a 44% yield of a mixture of the *trans, anti,*-

(9) E. J. Corey, *J. Amer. Chem. Soc.*, **75**, 4832 (1953).

(10) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Systems," Holden-Day, Inc., San Francisco, Calif., 1966; P. C. Cherry, W. R. T. Cottrel, G. D. Meakins, and E. E. Richards, *J. Chem. Soc.*, 187 (1967).

(11) J. C. Jacques and J. Levisalle, *Bull. Soc. Chim. Fr.*, 1866 (1962); C. Djerassi, N. Finch, R. C. Cookson, and C. W. Bird, *J. Amer. Chem. Soc.*, **82**, 5488 (1960).

(12) For an analogous evaluation of a similar *peri* interaction, see S. G. Levine, N. H. Eudy, and E. C. Farthing, *Tetrahedron Lett.*, 1517 (1963); A. D. Cross, E. Denot, R. Acevedo, R. Urquiza, and A. Bowers, *J. Org. Chem.*, **29**, 2195 (1964).

trans ketone **14a** (37%) and the *trans,anti,cis* ketone **15a** (63%). An additional product, which was produced in 37% yield, was identified as the hydroxy ketone **13**. Attempts to suppress the formation of this latter product by variations in the reaction conditions and quantity of oxidant were unsuccessful. In addition to these three major products, there were also formed minor amounts of an isomeric hydroxy ketone and some diols that were not further characterized. There was no evidence for the expected oxide among the products formed, even after short reaction times when unreacted olefin **12a** was recovered. It therefore appears that the initially formed oxide is rapidly rearranged to the ketone mixture, which in turn is further oxidized by the *m*-chloroperbenzoic acid to the observed hydroxy ketones. Inasmuch as the hydroxy ketone **13** was identified as a major product of the reaction when incomplete oxidation of the olefin **12a** was observed, it appears that the ketones **14a** and **15a** are oxidized at least as fast (if not faster) as the starting olefin **12a**. See Chart II.

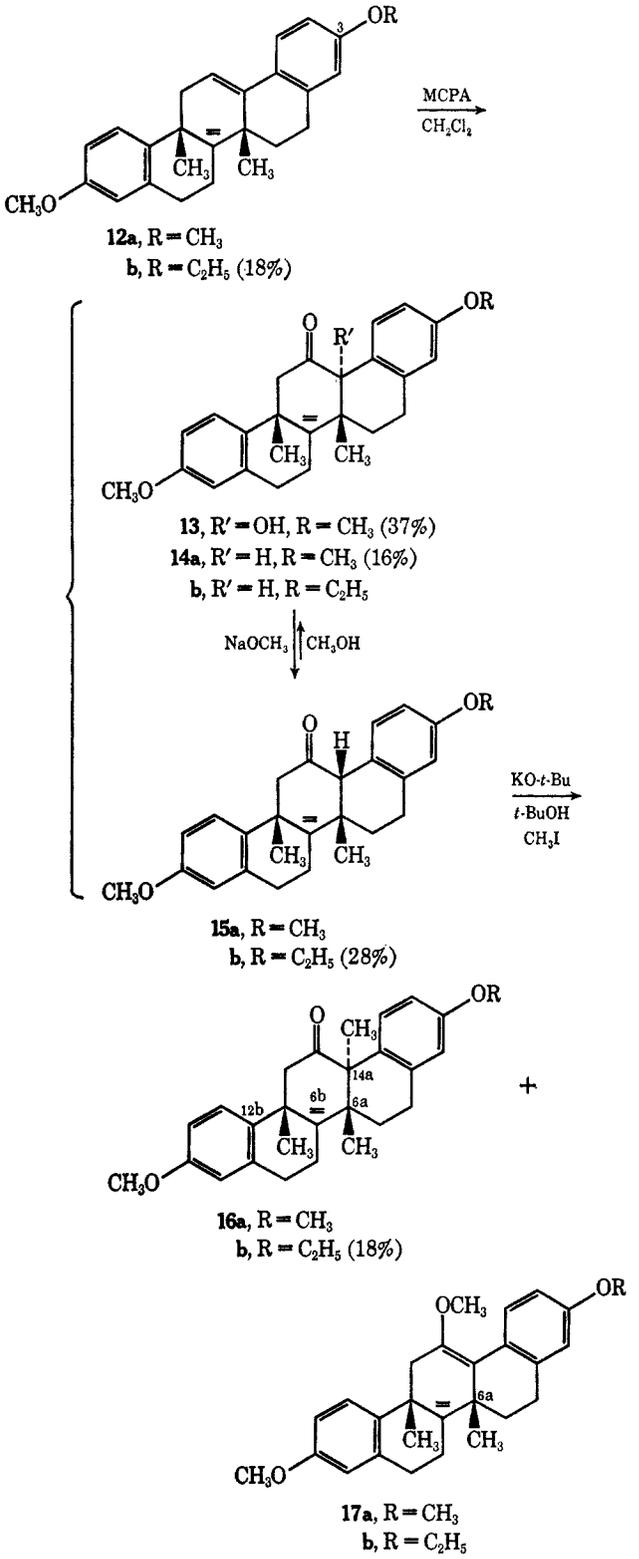
The isomeric ketones **14a** and **15a** could not be separated by fractional crystallization, but, on treatment with sodium methoxide in methanol, this original mixture was converted to an equilibrium mixture that consisted of 95% of the *trans,anti,cis* ketone **15a** and 5% of the *trans,anti,trans* ketone **14a**. The stereochemical assignments made here are elaborated below. For the moment, the equilibration of these two ketones serves to justify the conclusion that they are simply isomers about the C-14a position, and thus the mixture of the two may be used in further studies.

After a great deal of experimental variation of reaction conditions, solvent and base, it was found that the optimum yield of C-methylated ketone **16a** was produced when the mixture of ketones **14a** and **15a** were treated with potassium *t*-butoxide and then methyl iodide in *t*-butyl alcohol. In more nonpolar solvents, the yield of O-methylated product **17a** seemed to be increased and variation of the cation from potassium to lithium, magnesium, or sodium resulted in higher portions of unmethylated starting ketones. Even with potassium *t*-butoxide in *t*-butyl alcohol, the spectroscopically (nmr) determined yield of C-methylated material **16a** was only 22%, while the O-methylated product **17a** was formed in 36% (O/C ratio 1.63) and the unmethylated starting ketones **14a** and **15a** were recovered in 42% yield. There was no evidence in this or any other crude methylation product for the formation of the C-14a epimeric methylated ketone. As is shown below, the C/D *cis* and *trans* fused isomers may readily be detected on the basis of the chemical shift of the C-6a methyl protons in the nmr spectrum. The lack of a signal due to the C-6a methyl group in a C/D *cis* system indicates that less than 5% of this isomer could be present in the crude product. Therefore, that part of the methylation reaction that takes place at C-14a does so with a high degree of stereoselectivity.

Isolation of a pure sample of the C-methylated product **16a** was possible—albeit in very low yield—by thick layer chromatography of the reaction product on silica gel. The O-methylated ether **17a** was also isolated and identified from the product mixture, but was more readily prepared in higher yield by methylation of the mixture of ketones **14a** and **15a** in dimethoxyethane in the presence of sodium hydride.

CHART II

SYNTHESIS OF 14-KETO-3,10-DIMETHOXY-6aβ,12bβ,14aα-TRIMETHYL-5,6,6a,6bα,7,8,12b,13,14a-DECAHYDROPICENE (**16a**)



In connection with the preparation of these picene derivatives for the proposed conversion to alnusenone (**1**) type derivatives, the olefin **12b** was prepared by a scheme identical with that[3] used for the preparation of the olefin **12a**, except that *m*-ethoxyphenylmagnesium bromide replaced the earlier *m*-methoxyphenylmagnesium bromide in the later stages.[3] It was planned to achieve the necessary differentiation[3] of the two aro-

matic rings by selective cleavage[13] of the ring-A methyl ether in the presence of the ring-E ethyl ether. As expected, virtually no differences in reactivity were observed between the C-3 methoxy and ethoxy series in the transformations under consideration. However, a concerted effort was made to maximize the yields of isolated products in the C-3 ethoxy series, inasmuch as it was this sequence that was to form an integral part of the total synthesis of alnusenone (**1**).

The oxidation of the ethoxy olefin **12b** was accomplished as described above, and after direct crystallization of the ketones **14b** and **15b** from the crude oxidation product in 38% yield, the mother liquors, which contained principally the hydroxy ketone corresponding to **13**, were reduced with lithium aluminum hydride. The resulting diol mixture was not purified further, but stirred with aqueous hydrochloric acid in order to effect a pinacol–pinacolone-type rearrangement. Again the crude product was not extensively purified, but oxidized with Jones reagent[5] in order to convert any C-14 monohydroxy material that remained to the ketones **14b** or **15b**. From this crude product it was then possible to isolate an additional 29% of the mixture of ketones **14b** and **15b** by fractional crystallization. Thus, by these manipulations the overall conversion of the ethoxy olefin **12b** to the ethoxy ketone mixture, **14b** and **15b** was increased to a more reasonable 67%. It was possible in the case of the ethoxy ketone mixture to separate the *trans,anti,trans* isomer **14b** from the *trans,anti,cis* isomer **15b** by thick layer chromatography on silica gel. Both isomers were obtained in a pure state, and, through analysis of their nmr spectra, a conclusion concerning their stereochemistry could be derived (*vide infra*). As was observed in the C-3 methoxy series, a mixture of the two ethoxyketones **14b** and **15b** was isomerized almost quantitatively to the *trans,anti,cis* isomer **15b**.

The methylation of the ethoxy ketones **14b** and **15b** was then pursued. Inasmuch as earlier investigations had established that under the optimum C-methylation conditions (potassium *t*-butoxide–*t*-butyl alcohol–methyl iodide), the only by-products were the O-methylated material and unmethylated starting ketone, the methylation of the ethoxy ketones was carried out three times under these conditions with an intervening aqueous hydrochloric acid hydrolysis step in order to reconvert the O-methylation product **17b** back to the starting ethoxy ketones **14b** and **15b**. By fractional crystallization of the final reaction product, it was possible to isolate an 18% yield of the pure C-methylated ethoxy ketone **16b** as well as a sample of the O-methylated material **17b**. Thus, through what appeared to be the best reaction conditions available, the overall yield of the desired methylated ethoxy ketone **16b** from the ethoxy olefin **12b** was a very disappointing 12%. Further synthetic transformations of this material toward the desired triterpenoid objective have been deferred pending an investigation of alternate synthetic schemes aimed at the introduction of the C-14a methyl group but by circumvention of these latter two steps. The fact that only the desired 14aα orientation of this methyl group was observed in the present work provides impetus for this continuing effort.

(13) Preliminary observations by J. Bolen and G. Eggart in these laboratories.

Stereochemistry in the *trans,anti,trans* **Series.**—The stereochemical assignments made for the C-methylated ketones **16a**—and hence, **16b** as well—remain to be justified. The configurations indicated about C-6a, C-6b, and C-12b result from the earlier[3] definition of these positions by comparison with materials in the known[3,7] *cis,syn,cis* series. The configuration about the C-14a position results from a consideration of the direction of the benzene-induced solvent shift (Δ)[10] of the C-14a methyl group in the nmr spectra of these ketones (Table I). The observed positive solvent

TABLE I

SOLVENT EFFECTS ON THE ANGULAR METHYL RESONANCES OF DECAHYDROPICENE DERIVATIVES

Compd	Angular methyl	δ in $CDCl_3$, Hz	δ in C_6H_5, Hz	Δ, Hz
16a	C-6a	49.5	47.0	2.5
	C-12b	74.0	67.5	6.5
	C-14a	87.0	82.0	5.0
13	C-6a	48.0		
	C-12b	74.0		
14a	C-6a	48.5		
	C-12b	74.0		
15a	C-6a	66.0	58.0	8.0
	C-12b	77.0	74.0	3.0

shift, Δ, of 4.5 Hz for the C-14a methyl group implies that it is in an axial conformation with respect to the carbonyl group in ring C. This conformation may only be accommodated by the assigned *trans,anti,trans* backbone for the ketone **16a** in which the C-14a methyl group is α oriented.

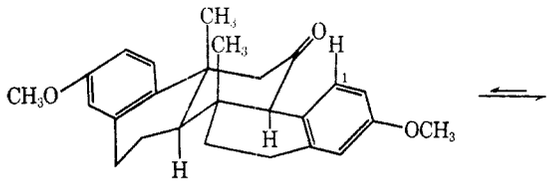
The nmr spectral characteristics of the *trans,anti,trans*-methylated ketone **16a** serve as a standard through which it is also possible to establish the stereostructures of the hydroxy ketone **13** and the isomeric unmethylated ketones **14a** and **15a**. The C-6a and C-12b methyl resonances of the hydroxy ketone **13** and the unmethylated ketone **14a** occur at virtually identical positions with those of the same two methyl groups in the *trans,anti,trans*-methylated ketone **16a**. Inasmuch as different chemical shifts for these two methyl groups—particularly for the C-6a methyl group—are found in the spectrum of the isomeric unmethylated ketone **15a**, it seems reasonable to assign the hydroxy ketone **13** and the unmethylated ketone **14a** to the *trans,anti,trans* series and the isomeric unmethylated ketone **15a** to the *trans,anti,cis* series.

Independent confirmation of these assignments is available from the infrared spectrum of the hydroxy ketone **13**. Normal stretching frequencies are observed for both the C-14a hydroxyl group (3595 cm^{-1}) and the C-14 carbonyl group (1710 cm^{-1}) in the solution spectrum of the hydroxy ketone **13**. Had the C-14a hydroxyl group been β (equatorial) oriented relative to the carbonyl-bearing C ring, the hydrogen bonding that would have occurred between the two groups would have been manifest in lower stretching frequencies for each than was observed.[14] The observed normal absorptions of the hydroxyl and carbonyl groups indicate that there is no intramolecular hydrogen bonding—a situation that can best be explained by the α (axial)

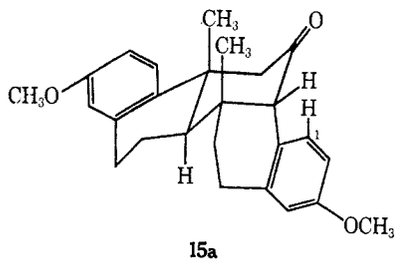
(14) H. B. Henbest and B. J. Lovell, *J. Chem. Soc.*, 1965 (1957); A. R. H. Cole and G. T. A. Muller, *ibid.*, 1224 (1959).

orientation of the hydroxyl group and hence the *trans,anti,trans* stereostructure for the hydroxy ketone **13**.

An interesting aspect of these stereochemical conclusions is that the *trans,anti,trans* backbone present in the ketone **14a** is configurationally *less stable* than the *trans,anti,cis* arrangement of the ketone **15a**, for an ethoxide-catalyzed equilibration of the two ketones leads almost quantitatively to the latter ketone **15a**. At first sight this might seem unreasonable, but inspection of the molecular models of the two stereochemical arrangements reveals that there is indeed good reason for the observation. In the *trans,anti,trans* ketone **14a**, the *trans* C/D ring fusion introduces a severe *peri*



14a



15a

interaction between the C-1 hydrogen and the C-14 carbonyl oxygen. This interaction is relieved in the *trans,anti,cis* ketone **15a**, where the aromatic ring is now joined to the carbonyl-containing C ring by an axially oriented bond. The axial character of the aromatic ring is not so severe in this conformationally fixed molecule as it would be in a molecule where the aromatic ring was free to rotate. Indeed, in the ketone **15a** the face of the aromatic E ring is presented to the α side of the molecule, and therefore, 1,3-diaxial interactions expected of an axial substituent are reduced to a minimum. These considerations make the greater configurational stability of the *trans,anti,cis* ketone **15a** relative to its *trans,anti,trans* isomer **14a** appear plausible and provide a theoretical basis for the stereochemical assignments made on the basis of spectral observations.

Experimental Section[15]

cis,syn,cis **Series. 3,10-Dimethoxy-6aβ,12bβ-dimethyl-5,6,-6a,6bβ,7,8,12b,13-octahydro-14(14aαH)-picenone (6).**—To a solution of 406 mg (1.08 mmol) of olefin **5** in 10 ml of dry tetrahydrofuran was added 2.0 ml of a 0.83 *M* borane–tetrahydrofuran solution with stirring under a nitrogen atmosphere. The reaction was allowed to stand for 16 hr at room temperature. The excess borane was decomposed by the careful addition of water to the well-stirred, ice-cooled reaction mixture. The reaction mixture was successively treated with 2.0 ml of 2.5 *N* aqueous sodium hydroxide and 1.0 ml of 30% hydrogen peroxide over a period of 5 min at 0°, and the solution was stirred for 2 hr while it warmed to room temperature. The reaction mixture was diluted to 200 ml with benzene and the benzene layer was separated and washed with 25 ml of 5 *N* aqueous sulfuric acid and with water until neutral. The organic layer was dried over sodium sulfate and concentrated at reduced pressure. The crude product, obtained as a crystalline mixture of isomeric alcohols, was oxidized without further purification.

A stirred, ice-cooled solution of the above crude alcohols in 40 ml of acetone was treated with 0.5 ml of 8.0 *N* chromium trioxide in sulfuric acid. The reaction was stirred for 0.5 hr at 0° and then poured into an ice–water mixture. The aqueous solution was extracted with two 100-ml portions of 1:1 ether–benzene. The organic layer was washed with water until neutral, dried over sodium sulfate, and evaporated to dryness at reduced pressure. There was obtained 400 mg of a pale yellow crystalline solid. The crude product was chromatographed on 15 g of alumina (Merck), and the desired material was eluted with 150 ml of 85% benzene–ligroin. The crystalline column fractions which were combined and triturated with ether gave 384 mg (91%) of the ketone **6** as colorless prisms, mp 180–182°. Two additional crystallizations from acetone–hexane afforded colorless needles: mp 182–183.5°; ir ($CHCl_3$) 1715 (C=O), 1615 and 1500 (aromatic ring), 1249, and 1035 cm^{-1} (CH_3OAr); nmr ($CDCl_3$) δ 1.09 (s, 3, C-6aβ CH_3), 1.35 (s, 3, C-12bα CH_3), and 3.72 (s, 3, 2 $ArOCH_3$).

Anal. Calcd for $C_{26}H_{30}O_3$: C, 79.97; H, 7.74. Found: C, 80.08; H, 7.97.

Base Equilibration of Ketone 6.—A solution of 14 mg (0.036 mmol) of the ketone **6** in 2 ml of tetrahydrofuran and 5 ml of absolute methanol was stirred under a nitrogen atmosphere in the presence of 1–2 mg of sodium methoxide for a 40-hr period. The reaction was diluted to 50 ml with benzene, and the solution was washed four times with water and then once with saturated brine. The organic layer was dried over sodium sulfate and evaporated to dryness at reduced pressure, and the crystalline residue was heated at 50° (0.1 mm) for 2 hr to remove the last traces of volatile material. Analysis of this material by nmr spectroscopy showed that the major component in the mixture was the ketone **6**. In addition to this material, two new methyl resonances at 1.27 and 1.47 ppm were taken to indicate the presence of the epimeric *cis,syn,cis* ketone. The ratio of the *cis,syn,trans* ketone **6** to the presumed *cis,syn,cis* ketone, as judged by the ratio of these methyl resonances, was 10:1. An independent check on the stereochemical assignment of the *cis,syn,trans* ketone **6** was possible through measurement of the half line widths of the C-6aβ and C-12bβ methyl resonances relative to tetramethylsilane in chloroform (Table II). These values are in good agreement with the values for *cis*- and *trans*-10-methyldecalin derivatives which have been determined by Williamson and coworkers.[16]

TABLE II

	$W_{1/2}$, cps	TMS $W_{1/2}$, cps	$\Delta W_{1/2}$, cps
C-6aβ CH_3	1.55	0.76	0.79
C-12bβ CH_3	1.15	0.76	0.39

3,10-Dimethyl-6aβ,12bβ,14aβ-trimethyl-5,6,6a,6bβ,7,8,12b,13-octahydro-14(14aH)-picenone (7).—To a solution of 536 mg (13.7 g-atoms) of potassium in 10 ml of dry *t*-butyl alcohol and 5 ml of dry benzene under a nitrogen atmosphere was added a solution of 1.32 g (3.37 mmol) of ketone **6** in 5 ml of dry benzene. The contents were refluxed for 0.5 hr, cooled to room temperature, and quenched with 1.5 ml of methyl iodide. After the mixture was stirred for 12 hr, it was treated with 10.0 ml of 10% aqueous hydrochloric acid, and the aqueous solution was extracted with 200 ml of 1:1 ether–benzene. The organic layer was washed three times with water and then dried over sodium sulfate. Evaporation of the solvent at reduced pressure gave 1.4 g of a crystalline residue. The methylated ketone **7** was separated from

(15) All melting points were determined on a Kofler hot stage and are uncorrected. All boiling points are uncorrected. Infrared spectra were taken on a Perkin-Elmer infrared spectrometer Model 237B and ultraviolet spectra were taken on a Cary recording spectrometer Model 11M. Nuclear magnetic resonance spectra were taken on a Varian Associates Model A-60A nuclear magnetic resonance spectrometer. Ligroin, unless otherwise noted, refers to the petroleum ether fraction boiling in the range of 30–60°. All gas chromatographic analyses were carried out on an F & M Model 810 gas chromatograph which was equipped with a 6-ft 5% silicon gum rubber (SE-30) on Chromosorb P support. The term "dry tetrahydrofuran" refers to purification of the commercial material by distillation from lithium aluminum hydride under anhydrous conditions. "Dry benzene" was obtained by distillation of the solvent from calcium hydride. All microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich.

(16) K. L. Williamson, T. Howell, and T. Spencer, *J. Amer. Chem. Soc.*, **88**, 325 (1966).

the starting ketone **6** by preparative thin layer chromatography on 20 × 20 × 0.2 cm alumina plates after three successive elutions with 1:1 ether–hexane. In this manner, 690 mg (51%) of the methylated ketone **7** was isolated as colorless prisms, mp 126–128°. The balance of the material from the reaction was starting material. No other isomeric methylated ketone could be isolated. Recrystallization of the product from methanol yielded material of analytical purity: mp 126–128°; ir ($CHCl_3$) 1701 (C=O), 1610, 1576, 1550 (aromatic ring), and 1030 cm^{-1} (Ar-OCH_3); nmr ($CDCl_3$) δ 1.02 (s, 3, C-6aβ CH_3), 1.28 (s, 3, C-12bβ CH_3), 1.53 (s, 3, C-14aβ CH_3), 3.69 and 3.72 (2 s, 6, 2 $ArOCH_3$), 7.19 (d, 1, J = 8.5 Hz, C-12 H), and 7.15 (d, 1, J = 9.0 Hz, C-1 H); nmr (C_6H_6) δ 0.834 (s, 3, C-6aβ CH_3), 1.18 (s, 3, C-12bβ CH_3), and 1.43 (s, 3, C-14aβ CH_3); mass spectrum (70 eV) *m/e* 404, 230, 188, 173.

Anal. Calcd for $C_{27}H_{32}O_3$: C, 80.16; H, 7.97. Found: C, 80.06; H, 7.96.

13β-Bromo-3,10-dimethoxy-6aβ,12bβ,14aβ-trimethyl-5,6,6a,-6bβ,7,8,12b,13-octahydro-14(14a*H*)-picenone (8).—To a solution of 41.7 mg (0.103 mmol) of the ketone **7** in 5 ml of dry tetrahydrofuran was added 41.3 mg (0.110 mmol) of PTAB.[6] The reaction was stirred at room temperature for 4 hr and then diluted with 100 ml of water. The aqueous solution was extracted with ether, and the organic layer was washed with water and dried over sodium sulfate. Removal of the solvent under reduced pressure afforded a white crystalline residue. This material was purified by preparative thin layer chromatography on a 20 × 20 × 0.2 cm silica gel plate which was developed with 10% ether–benzene. The developed chromatogram showed the presence of two components in the crude reaction mixture. The faster moving component (R_f 0.74) was isolated and gave 38 mg of the crystalline bromo ketone **8**. Recrystallization of this material from methanol–acetone afforded 26 mg of white prisms, mp 193–197°. The slower moving component (R_f 0.44) was isolated and gave 11 mg of crystalline starting ketone **7**. The yield of bromo ketone **8** based on recovered ketone **7** was 78%. Two additional crystallizations of the bromo ketone **8** from methanol–acetone afforded orthorhombic crystals, mp 194–196°, which were suitable for X-ray analysis:[7] ir ($CHCl_3$) 1718 (C=O), 1610, 1575, 1490 (aromatic ring), and 1240 and 1035 ($ArOCH_3$).

Anal. Calcd for $C_{27}H_{31}BrO_3$: C, 67.07; H, 6.46. Found: C, 67.26; H, 6.33.

***trans,anti,trans* Series. 3-Ethoxy-10-methoxy-6aβ,12bβ-dimethyl-5,6,6a,6bα,7,8,12b,13-octahydropicene (12b).**—The procedure described previously[3] for the preparation of the dimethoxy analog **12a** was followed exactly, except that the Grignard reagent was prepared from 3-bromophenetole instead of 3-bromoanisole. Thus, under a nitrogen atmosphere, a solution of 2.00 g (6.6 mmol) of the tricyclic lactol[3] in 30 ml of anhydrous tetrahydrofuran was added dropwise with stirring to a refluxing solution of 3-ethoxyphenylmagnesium bromide [prepared from 4.00 g (19.8 mmol) of 3-bromophenetole and 0.47 g (19.8 mg-atoms) of magnesium] in 10 ml of anhydrous ether and 15 ml of anhydrous tetrahydrofuran. After the addition was complete (0.5 hr), the slightly turbid solution was heated under reflux for 6 hr and then cooled and poured into an ice-chilled aqueous ammonium chloride solution. The product was isolated by ether, extracted as described earlier,[3] and chromatographed on 100 g of alumina (Merck). After an initial wash with 400 ml of benzene, the expected diol (2.80 g) was eluted with 350 ml of 9:1 ether–methanol. This material was obtained as a solidified foam, and the bulk was not further purified, but used directly in the subsequent transformations. A small sample, crystallized first from ether–ligroin and then acetone–ligroin, afforded the analytical sample: mp 132–134°; ir ($CHCl_3$) 3600 and 3400 (free and H-bonded OH), and 1615 and 1500 cm^{-1} (aromatic absorption); nmr ($CDCl_3$) δ 1.0 (s, 3, C-1β CH_3), 1.175 (s, 3, C-4aβ CH_3), 1.40 (t, 3, J = 7.0 Hz, $ArOCH_3$), 3.75 (s, 3, $ArOCH_3$), 4.02 (q, 2, J = 7.0 Hz, $ArOCH_2CH_3$), and 4.25 (s, 2, OH).

Anal. Calcd for $C_{27}H_{36}O_4$: C, 76.38; H, 8.55. Found: C, 76.39; H, 8.53.

The remainder of the crude diol (2.67 g) was hydrogenated in the manner described earlier[3] over 250 mg of 10% palladium on carbon in 120 ml of methanol containing 0.5 ml of 60% aqueous perchloric acid. After 5 hr, the absorption of hydrogen had ceased, the catalyst was removed by filtration, and the reaction mixture was worked up as before.[3] The bulk of the resulting colorless oil (2.33 g) was not further purified, but subjected directly to oxidation with Jones reagent.[5] A small sample was crystallized twice from ether and afforded an analytically pure sample of the monoalcohol: mp 88–89°; ir ($CHCl_3$) 3600 (OH) and 1615 and 1500 cm^{-1} (aromatic absorption); nmr ($CDCl_3$) δ 1.00 (s, 3, C-1β CH_3), 1.20 (s, 3, C-4aβ CH_3), 1.38 (t, 3, J = 7.0 Hz, $ArOCH_2CH_3$), 3.75 (s, 3, $ArOCH_3$), and 4.03 (q, 2, J = 7.0 Hz, $ArOCH_2CH_3$).

Anal. Calcd for $C_{27}H_{36}O_3$: C, 79.37; H, 8.88. Found: C, 79.18; H, 8.81.

The crude monoalcohol from the above experiment (2.18 g) was dissolved in 50 ml of dry acetone and treated with 4.0 ml of Jones reagent[5] at 0°. Excess oxidant was judged to be present as a result of the red-brown coloration that was maintained for 10 min. After the usual work-up procedure,[3] there was obtained a crude yellow oil (2.3 g) which was chromatographed on 100 g of alumina (Merck). After an initial wash of the column with 400 ml of 50% benzene–ligroin, the desired ketone was eluted as a colorless oil (1.95 g) with 400 ml of 75% benzene–ligroin. This material could not be induced to crystallize, and the bulk of the chromatographically pure ketone was submitted directly to the acid-catalyzed cyclization conditions.

A solution of 1.65 g (4.06 mmol) of the above ketone in 350 ml of toluene containing 0.60 g (3.15 mmol) of *p*-toluenesulfonic acid monohydrate was heated at reflux under a Dean–Stark water separator for 9.5 hr. After this period, no starting ketone could be detected on gas chromatographic analysis[15] of the reaction mixture at 300°. The reaction mixture was treated as before,[3] and after crystallization of the crude, crystalline product (1.525 g) from benzene–ethanol, there was obtained 1.330 g (78% overall) of the pentacyclic diether, mp 185–187°. The analytical sample, obtained after two further crystallizations of a proton of this material from the same solvent pair, melted at 187–188°: ir ($CHCl_3$) 1650 (C=C), 1610, and 1500 cm^{-1} (aromatic absorption); nmr ($CDCl_3$ δ 0.99 (s, 3, C-6aβ CH_3), 1.31 (s, 3, C-12b CH_3), 1.38 (t, 3, J = 7.0 Hz, $ArOCH_2CH_3$), 3.75 (s, 3, $ArOCH_3$), 4.02 (q, 2, J = 7.0 Hz, $ArOCH_2CH_3$), and 5.95 (m, 1, C-15 H).

Anal. Calcd for $C_{27}H_{32}O_2$: C, 83.46; H, 8.30. Found: C, 83.37; H, 8.27.

3,10-Dimethoxy-6aβ,12bβ-dimethyl-5,6,6a,6bα,7,8,12b,13-octahydro-14(14aβH)-picenone (15a).—To a stirred, ice-cooled solution of 0.500 g (1.33 mmol) of olefin **12a** in 15 ml of methylene chloride was added 145 mg of *m*-chloroperbenzoic acid. After the mixture had stirred for 1.5 hr, all of the peracid had been consumed, and an additional 145 mg of peracid was added. Stirring was continued for 1.5 hr, another charge of 100 mg of peracid was added, and stirring was continued for an additional 1.5 hr. The course of the reaction was followed by tlc on silica gel, and the reaction was quenched when all of the starting material had been consumed. The reaction mixture was diluted with 200 ml of ether and extracted with 10% aqueous potassium carbonate and water until neutral. After the organic layer was dried over sodium sulfate and the solvents were removed at reduced pressure, a pale yellow oil was obtained which was shown by tlc on silica gel to be a mixture of at least three products. An infrared spectrum of this mixture showed the presence of a strong carbonyl band at 1705 cm^{-1} as well as hydroxyl bands at 3595 cm^{-1}. A partial separation of this mixture was realized by preparative thick layer chromatography on silica gel plate (0.2 × 40 × 20 cm) by elution with 10% ether–benzene. One band, R_f 0.74, 4 mg, was shown by infrared spectroscopy to be the starting olefin **12a**. Another band, R_f 0.40, was obtained as a semicrystalline solid, yield 240 mg. Crystallization of this material from ethanol afforded 200 mg (37%) of the hydroxy ketone **13**, mp 198–203°. Several recrystallizations of this substance from 1:1 ethanol–benzene afforded the analytically pure hydroxy ketone **13**: mp 201.5–204.5°; ir ($CHCl_3$) 3595 (free, nonbonded OH[14]) and 1710 cm^{-1} (ketone C=O not involved in H bonding[14]); nmr ($CDCl_3$) δ 0.80 (s, 3, C-6aβ CH_3), 1.23 (s, 3, C-12bβ CH_3), 3.77 (s, 6, 2 $ArOCH_3$), 6.65 (m, 2, C-4 H and C-9 H), 7.07 (d, 1, J = 9.0 Hz, C-12 H), and 7.50 (d, 1, J = 8.0 Hz, C-1 H).

Anal. Calcd for $C_{26}H_{30}O_4$: C, 76.82; H, 7.44. Found: C, 76.78; G, 7.46.

The third band, R_f 0.57, was obtained as a semicrystalline solid which, on trituration with cold ether, afforded 229 mg (44%) of an epimeric mixture of the ketones **15a** and **14a** in a ratio of 1.7:1 as determined by nmr spectroscopy. Equilibration of this mixture with sodium methoxide in methanol afforded a new mixture of these ketones **15a** and **14a** in the ratio of 19:1 as judged from the nmr spectrum. A pure sample of the *trans*,-

anti,cis ketone **15a**, obtained after several crystallizations of this material from acetone–hexane, melted in the range of 158–160°: ir ($CHCl_3$) 1690 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.12 (s, 3, C-6aβ CH_3), 1.30 (s, 3, C-12bβ CH_3), 3.44 (s, 1, C-14aβ H), and 3.70 (s, 6, 2 $ArOCH_3$).

Anal. Calcd for $C_{26}H_{30}O_3$: C, 79.97; H, 7.74. Found: C, 80.08; H, 7.67.

The *trans,anti,trans* ketone **14a** was never obtained in pure form from this oxidation. However, the strong signals in the nmr spectrum of the initial oxidation product that were associated with this ketone **14a** could be deduced through a comparison of the spectrum of the mixture and that of the pure *trans,anti,cis* ketone **15a**: nmr ($CDCl_3$) δ 0.81 (s, 3, C-6aβ CH_3), 1.28 (s, 3, C-12bβ CH_3), and 3.76 (s, 6, 2 $ArOCH_3$). Analysis of the composition of mixtures of these two ketones **15a** and **14a** was readily accomplished through the integrated intensities of the C-6aα CH_3 resonances of each ketone.

3-Ethoxy-10-methoxy-6aβ,12bβ-dimethyl-5,6,6a,6bα,7,8,12b,-13-octahydro-14(14aβH)-picenone (15b).—By a procedure identical with that described above for the oxidation of the dimethoxypentacyclic olefin **12a**, 2.00 g of the ethoxymethoxypentacyclic olefin **12b** was oxidized at 0° with a total of 1.80 g of *m*-chloroperbenzoic acid (80% purity) in 100 ml of methylene chloride over a period of 5 hr. Crystallization of the crude oxidation product from methylene chloride–ligroin afforded 945 mg of a mixture, mp 145–149°, consisting primarily of the two ketones **15b** and **14b** together with some hydroxyl-bearing impurity which was considered to be the ketol that corresponded to **13**. Recrystallization of the material from the same solvent pair afforded 782 mg (38%) of a mixture of the epimeric ketones **15b** and **14b** in two crops of 138 mg, mp 175–178°, and 644 mg, mp 145–150°. Careful recrystallization of the first crop material two times from methylene chloride–ether afforded an analytically pure sample of the *trans,anti,trans* ketone **14b**: mp 180–181°; ir ($CHCl_3$) 1710 (C=O), 1605, and 1500 cm^{-1} (aromatic absorption); nmr ($CDCl_3$) δ 0.80 (s, 3, C-6aβ CH_3), 1.26 (s, 3, C-12bβ CH_3), 1.38 (t, 3, J = 7.0 Hz, $ArOCH_2CH_3$), 3.76 (s, 3, $ArOCH_3$), and 4.00 (q, 2, J = 7.0 Hz, $ArOCH_2CH_3$).

Anal. Calcd for $C_{27}H_{32}O_3$: C, 80.16; H, 7.97. Found: C, 80.14; H, 7.97.

Equilibration of a sample of the second crop material with sodium methoxide in methanol–tetrahydrofuran produced a mixture that was again rich in the *trans,anti,cis* ketone **15b**, as judged from both tlc on silica gel and comparative nmr spectroscopy. After several crystallizations of this material from methylene chloride–ether, an analytically pure sample of the *trans,anti,-cis* ketone **15b**, mp 156–157°, was obtained: ir ($CHCl_3$) 1703 (C=O), 1615, and 1500 cm^{-1} (aromatic absorption); nmr ($CDCl_3$) δ 1.10 (s, 3, C-6aβ CH_3), 1.29 (s, 3, C-12bβ CH_3), 1.35 (t, 3, J = 7.0 Hz, $ArOCH_2CH_3$), 3.73 (s, 3, $ArOCH_3$), and 3.97 (q, 2, J = 7.0 Hz, $ArOCH_2CH_3$).

Anal. Calcd for $C_{27}H_{32}O_3$: C, 80.16; H, 7.97. Found: C, 79.97; H, 8.00.

The mother liquors from both the initial crystallization of the crude oxidation product and the recrystallization of the major crystalline product amounted to 1.3 g and were rich in hydroxyl-bearing components by infrared spectroscopy. These combined mother liquors were reduced with 300 mg of lithium aluminum hydride in 40 ml of tetrahydrofuran. After the reaction had stirred for 0.5 hr at 0° and then for 0.5 hr at room temperature, the excess hydride and alcoholates were decomposed by the addition of sufficient saturated aqueous sodium sulfate solution to produce a thick, flocculent precipitate (*ca.* 1.5 ml). The suspension was then treated with 40 ml of ether and stirred at room temperature for 16 hr. The solids were then separated by filtration through Celite, and the ethereal filtrate was evaporated to dryness at reduced pressure. The infrared spectrum of the resulting oily residue, which amounted to 1.22 g, showed the absence of any carbonyl absorption in the 1700-cm^{-1} region and the presence of strong hydroxyl absorption in the 3500-cm^{-1} region.

This crude mixture of alcohols was dissolved in 100 ml of ether and stirred for 20 hr at room temperature under a nitrogen atmosphere with 100 ml of 10% aqueous hydrochloric acid. The ethereal layer was then separated, washed with water and twice with saturated brine, and dried (Na_2SO_4). Removal of the solvent at reduced pressure afforded a clear, colorless oil that amounted to 1.2 g and which was not further purified but dissolved in 50 ml of dry acetone and treated at 0° with excess (maintenance of red-brown coloration) Jones reagent.[5] After dilution of the reaction mixture with 100 ml of water, the product was isolated by extraction with two 50-ml portions of ether. The ethereal extracts were combined and washed successively with 10% aqueous potassium carbonate (two 25-ml portions) and saturated brine (two 25-ml portions) and dried (Na_2SO_4). Evaporation of the solvent at reduced pressure left 1.1 g of a slightly yellow oil, which deposited 502 mg (24%), mp 145–150°, of a mixture of the ketones **15b** and **14b** on crystallization from ether.

The mother liquors from this crystallization were concentrated and chromatographed on two 0.2 × 20 × 20 cm silica gel thick layer plates. Continuous elution for 3 hr in benzene served to separate the components sufficiently such that elution of the two middle bands, R_f 0.40 and 0.50, with ethyl acetate afforded an additional 108 mg (5.2%), mp 148–152°, of the ketone mixture.

Thus, the total overall yield of the desired epimeric mixture of ketones **15b** and **14b** by this oxidation sequence was 1.392 g (67%).

3,10-Dimethoxy-6aβ,12bβ,14aα-trimethyl-5,6,6a,6bα,7,8,12b,-13-octahydro-14(14aH)-picenone (16a).—To a solution of 174 mg (0.45 mmol) of a mixture of the ketones **14a** and **15a** in 25 ml of dry benzene under a nitrogen atmosphere was added 2.0 ml of 0.856 *N* potassium *t*-butoxide in *t*-butyl alcohol. The reaction mixture was stirred at room temperature for 0.5 hr, and 0.21 ml (3.4 mmol) of methyl iodide was added *via* a syringe. The solution was allowed to stir at room temperature for 16 hr under a nitrogen atmosphere, and then diluted with 150 ml of ether. The ethereal solution was washed with water; the organic layer was separated and washed with saturated brine and then dried (Na_2SO_4). Evaporation of the solvent at reduced pressure afforded a colorless oil which was purified by thick layer chromatography on a 0.2 × 20 × 20 cm silica gel plate. Two successive elutions with 12% ether–benzene separated the product mixture into three bands. Elution of the material from the first band, R_f 0.78, with ethyl acetate and trituration of this material with cold ether afforded 29 mg (16%) of the O-methylated product **17a**, mp 157–160°, as a colorless solid. Recrystallization from ethanol gave material of analytical purity: mp 159.5–161°; ir ($CHCl_3$) 1638, 1610, and 1500 cm^{-1}; nmr ($CDCl_3$) δ 0.925 (s, 3, C-6aβ CH_3), 1.38 (s, 3, C-12b CH_3), 3.47 (s, 3, C-14 OCH_3), 3.78 (s, 6, 2 $ArOCH_3$), 6.65 (m, 2, C-4 H and C-9 H), 7.27 (d, 1, J = 8.0 Hz, C-12 H), and 7.84 (d, 1, J = 8.5 Hz, C-1 H).

Anal. Calcd for $C_{27}H_{32}O_3$: C, 80.16; H, 7.97. Found: C, 80.26; H, 7.97.

From the second band, R_f 0.52, was isolated a semicrystalline solid, 29 mg, by elution with ethyl acetate. This material was shown by nmr spectroscopy to be a mixture of the *trans*-methylated ketone **16a** (75%) and the unalkylated ketone **15a** (25%). After two crystallizations of this material from ethanol, a pure sample of the *trans,anti,trans* ketone **16a** was obtained as colorless prisms: mp 182–184°; ir ($CHCl_3$) 1705 (C=O), 1615, 1500 (aromatic absorption), 1240, and 1035 cm^{-1} ($ArOCH_3$); nmr ($CDCl_3$) δ 0.825 (s, 3, C-6aβ CH_3), 1.23 (s, 3, C-12bβ CH_3), 1.44 (s, 3, C-14aα CH_3); nmr (C_6H_6) δ 0.783 (s, 3, C-6aβ CH_3), 1.127 (s, 3, C-12bβ CH_3), and 1.370 (s, 3, C-14aα CH_3).

Anal. Calcd for $C_{27}H_{32}O_3$: C, 80.16; H, 7.97. Found: C, 80.35; H, 7.97.

The third band, R_f 0.34, was isolated as a crystalline solid by elution with ethyl acetate and melted over the broad range of 180–203°. Two crystallizations from ethanol–benzene afforded 300 mg of a crystalline solid, mp 201.5–204.5°. This material was shown to be the *trans,anti,trans*-hydroxy ketone **13** by direct comparison with an authentic sample. This substance was never encountered again during subsequent alkylation experiments.

The Effect of Solvent on the Methylation of the Ketones 14a and 15a. A.—To a solution of 117 mg (3.0 g-atoms) of potassium in 13 ml of dry *t*-butyl alcohol under a nitrogen atmosphere was added with stirring a solution of 50.0 mg (0.13 mmol) of the mixture of ketones **14a** and **15a** in 2.0 ml of dry benzene, and the reaction mixture was then stirred for 0.5 hr. After the addition of 1.0 ml of methyl iodide, the solution was allowed to stand at room temperature for 20 hr. An additional 3 ml of methyl iodide was then added, and the reaction mixture was stirred and heated at reflux for 1 hr. After cooling, the suspension was diluted with 150 ml of benzene and extracted with an aqueous sodium thiosulfate solution. The organic layer was separated and washed several times with water and the dried over sodium sulfate. Removal of the solvent at reduced pressure afforded a colorless oil which was heated (50°) under high vacuum (0.05 mm) for

2 hr to remove all volatile material. The product mixture was analyzed by nmr spectroscopy through comparing the relative areas of the C-6aβ CH_3 resonances of the three components (Table III).

TABLE III

C-6aβ CH_3 resonance, ppm	Component	%
1.12	Unmethylated ketone **15a**	42
0.925	Enol ether **17a**	36
0.825	Methylated ketone **16a**	22

B.—To a slurry of 170 mg (1.52 mmol) of potassium *t*-butoxide in 15 ml of benzene containing 1.1 ml (1.52 mmol) of *t*-butyl alcohol under a nitrogen atmosphere was added 50 mg (0.13 mmol) of the mixture of ketones **14a** and **15a** in 2 ml of benzene. The reaction mixture was allowed to stir for 0.5 hr at 25°, and 1.0 ml of methyl iodide was added. After this supension had stirred at room temperature for 20 hr, 3.0 ml of methyl iodide was added, and the mixture was refluxed for 1 hr. The products were isolated and analyzed (Table IV) in the manner described in part A.

TABLE IV

C-6aβ CH_3 resonance, ppm	Component	%
1.12	Unmethylated ketone **15a**	21
0.925	Enol ether **17a**	60
0.825	Methylated ketone **16a**	17

There was no evidence for an isomeric methylated ketone (C/D *cis* fused) in either of these experiments, as all the quaternary methyl resonances could be assigned to known products.

3-Ethoxy-10-methoxy-6aβ,12bβ,14aα-trimethyl-5,6,6a,6bα,-7,8,12b,13-octahydro-14(14aH)-picenone (16b).—To a solution of 7.5 g (0.067 mmol) of potassium *t*-butoxide in 75 ml of dry *t*-butyl alcohol under a nitrogen atmosphere was added with stirring 500 mg (1.24 mmol) of a mixture of ketones **14b** and **15b**, mp 145–150°, and the mixture was stirred at room temperature for 2 hr. To this red-brown solution was added 10 ml of methyl iodide, and the resulting mixture was then stirred at room temperature for 15 hr. The suspension was then poured into ice–water, and the aqueous mixture was extracted four times with methylene chloride (total of 300 ml used). The combined methylene chloride extracts were washed with water and saturated brine and dried (Na_2SO_4). Evaporation of the solvent at reduced pressure afforded a light yellow oil (525 mg), the nmr spectrum of which showed signals due to C-methylated, O-methylated, and unmethylated ketones.

This crude methylation product was not further purified, but was dissolved in 60 ml of ethanol and treated with 30 ml of 10% aqueous hydrochloric acid, and the resulting solution was heated at reflux under a nitrogen atmosphere for 2 hr. The reaction mixture was then cooled, and most of the ethanol was removed by evaporation at reduced pressure on the rotary evaporator. The resulting aqueous suspension was extracted two times with 50-ml portions of 1:1 ether–benzene, and the combined organic extracts were washed successively with 30 ml of 10% aqueous potassium carbonate solution, 30 ml of water, and two 15-ml portions of saturated brine, and dried (Na_2SO_4). Removal of the solvents on the rotary evaporator at reduced pressure left 510 mg of a yellow oil which exhibited no signal for the O-methylated product in its nmr spectrum.

This material was again not further purified but subjected *twice more* to identical methylation and hydrolysis conditions as those described above. After the last of these operations, there remained 525 mg of a yellow oil which deposited 145 mg of a crystalline solid on trituration with ether. After two further crystallizations of this sample from ethanol, there was obtained 93 mg (18%) of the C-methylated ketone **16b**, mp 187–189°. After one further crystallization of a sample of this material from ethanol, an analytically pure specimen of the ketone **16a** was obtained: mp 192–193°; ir ($CHCl_3$) 1705 (C=O), 1615 and 1500 (aromatic absorption), and 1240 cm^{-1} (ArOR); nmr ($CDCl_3$) δ 0.82 (s, 3, 6aβ CH_3), 1.24 (s, 3, C-12bβ CH_3), 1.44 (s, 3, C-14aα CH_3), 3.75 (s, 3, $ArOCH_3$), and 4.0 (q, 2, J = 7.0 Hz, $ArOCH_2CH_3$).

Anal. Calcd for $C_{28}H_{34}O_3$: C, 80.35; H, 8.19. Found: C, 80.27; H, 8.15.

On preparative thick layer chromatography of the combined mother liquors from all of the above crystallizations on a 0.2 × 20 × 20 cm silica gel plate in 4:1 benzene–ether, there was isolated a large fraction (219 mg) of material that appeared from nmr spectroscopy to be a mixture of methylated and unmethylated ketones. From this fraction, on crystallization from ether–ligroin, it was possible to isolate 60 mg of a mixture of unmethylated ketones **14b** and **15b**. The remainder of the material could not be further purified and remained an oil.

From an earlier experiment in which only one methylation sequence was performed and the hydrolysis step was omitted, a sample of the pure O-methylated pentacyclic ether **17b** was isolated by preparative thick layer chromatography on silica gel in benzene. Crystallization of this material from ether–ligroin afforded the analytically pure specimen of the enol ether **17b**: mp 135–136°; ir ($CHCl_3$) 1648, 1605, and 1500 cm^{-1}; nmr ($CDCl_3$) δ 0.925 (s, 3, C-6aβ CH_3), 1.39 (s, 3, C-12b CH_3), 3.48 (s, 3, C-14 OCH_3), 3.79 (s, 3, $ArOCH_3$), and 4.06 (q, 2, J = 7.0 Hz, $ArOCH_2CH_3$).

Anal. Calcd for $C_{28}H_{34}O_3$: C, 80.35; H, 8.19. Found: C, 80.30; H, 8.15.

X-Ray Analysis of Bromo Ketone 8.—A precession camera survey revealed that the resulting prismatic crystals belonged to space group Pbca. Sodium chloride calibrated precession photographs established the cell dimensions. Results of the survey are summarized in Table V.

TABLE V

DETAILS OF CRYSTAL SURVEYS

Solvent system	Acetone
a (Å) = 11.413 ± 0.002	
b (Å) = 17.654 ± 0.003	
c (Å) = 22.547 ± 0.004	
Systematic extinctions	$0kl$: k odd
	$h0l$: l odd
	$hk0$: h odd
Space group	Pbca
Molecules/unit cell	8
Density calculation	1.412 g/cm³
Density observed	1.40 g/cm³
Number reflections	2332
Nonzero reflections	2297

Intensity data to a resolution of 1 Å (maximum sin θ/λ = 0.5) were collected on a Supper–Phillips–Datex diffractometer using nickel-filtered copper radiation and a proportional counter. A Φ scan technique was employed, background was counted for 10 sec at each end of the scan, and the scan rate was 1°/minute in Φ. A single-check reflection (230) that was monitored every 30 reflections showed no decay and was well within counter statistics.

The diffractometer output was processed using subprograms of the CRYRM crystallographic computer system.[17] The processing included corrections for background and for Lorentz and polarization effects. It also included calculation of the F^2 value and its standard deviation for each of the 2332 reflections (35 reflections had zero intensity). The standard deviations were assigned on the basis of the following equation, where S is the

$$\sigma^2(I) = S + (B_1 + B_2)\alpha^2 + (dS)^2$$

scan count, B_1 and B_2 are the background counts, d is an empirical constant equal to 0.02, and $\alpha = n/2mt$ where n is the scan range, m is the scanning speed, and t is the time for background count in seconds. Finally, the data were placed on an absolute scale by means of Wilson statistics.[18]

Determination and Refinement of Structure.—The trial structure was derived by the usual Patterson and Fourier techniques in three dimensions. Full matrix least-squares refinement of the coordinates, isotropic temperature factors (bromine anisotropic), and scale factor reduced the R index to 30.5%. A difference Fourier revealed at this point that one carbon atom has been mis-

(17) D. J. Duchamp, American Crystallographers Association Meeting, Bozeman, Mont., paper B-14, 1964, p 29.

(18) A. J. C. Wilson, *Nature*, **150**, 152 (1942).

placed. Correction of this coordinate and further refinement reduced the R index to 11.0%. A difference Fourier indicated no misplaced or missing Br, C, or O atoms. The difference Fourier was also used to locate the hydrogen atoms. The addition of the hydrogen atoms and five anisotropic temperature factors[19] to the refinement reduced the R index to its final value of 9.0%.

Results of X-Ray Analysis.—The structure obtained in the analysis was stereographically plotted (Figure 1) using the ORTEP computer program of C. K. Johnson.[20] An estimate of errors in positional parameters, bond lengths, and bond angles are summarized in Table VI.[21] Owing to limitations in space, other pertinent crystallographic data and parameters cannot be listed here. F tables, atomic coordinates, temperature factors, bond angles, and distances have been filed with NAPS.[7]

TABLE VI
DATA FIT AND DEVIATIONS

Final R index	0.090
Standard deviations[a] of coordinates	
Br	0.001 Å
C, O	0.006 Å
Uncertainties in C–O–Br bond lengths	0.01 Å
Uncertainties in C–O–Br bond angles	0.5°

[a] Standard deviations in the coordinates were derived from the residuals and the diagonal elements of the inverse matrix of the final least-squares cycle.

Registry No.—**6**, 21436-28-2; **7**, 21436-29-3; **8**, 21436-30-6; **12b**, 21436-31-7; **13**, 21436-32-8; **14a**, 21436-33-9; **14b**, 21436-34-0; **15a**, 21436-35-1; **15b**, 21436-36-2; **16a**, 21436-37-3; **16b**, 21436-38-4; **17a**, 21436-39-5; **17b**, 21436-40-8.

(19) Anisotropic temperature factors for atoms Br(1), O(24), O(26), C(27), O(29), and C(30) were used during refinement since these atoms displayed the largest isotropic temperature factors.

(20) C. K. Johnson, ORTEP, ORNL-3794, Oak Ridge National Laboratories, Oak Ridge, Tenn.

(21) Error estimates involving the hydrogen positions have not been made since no effort was made to refine their coordinates rigorously. Moreover, any error estimate involving even well-refined hydrogen positions is at best dubious.

Synthesis and Conformational Analysis of Tricyclic Ring-C Aromatic 20-Nor Diterpenoid Resin Acid Analogs

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Received October 31, 1968

A simple synthesis of the tricyclic unsaturated acid **8** and its conversion into lactone **9** is described. All four possible racemates of ring-C aromatic 20-nor diterpenoid resin acid analogs **1**, **2**, **3**, and **4** have been synthesized by catalytic and chemical reduction of **8** and **9**. Lithium–ammonia reduction of the benzylic lactone **9** proceeds with retention of configuration at C-12 to give *trans* acid **1**, while catalytic hydrogenation of **9** proceeds with inversion at C-12 to give *cis* acid **3**. Lithium–ammonia reduction of **8** yields *trans* acid **2** exclusively, whereas catalytic hydrogenation of **8** gives 75% *cis* acid **3** and 9% *cis* acid **4**. Some chemical and conformational properties of **1**, **2**, **3**, and **4** are reported. In contrast to the corresponding *cis* resin acid analogs where the conformation of ring A is "steroid," ring A for the *cis* acids **3** and **4** is "nonsteroid."

The first synthesis of a 20-*nor* resin acid analog was achieved by Haworth and Barker.[2] These authors obtained a compound, mp 187–188°, from a sulfuric acid–acetic acid catalyzed cyclization of **5**, but could not assign stereochemistry to it. Mori and coworkers[3] later established the stereochemistry of Haworth's acid as **1**.

When Mori's publication appeared, we were prompted to report a portion of our work in a preliminary communication.[4] As part of our synthetic studies[5-7] of diterpenoids related to rosenonolactone and gibberellin, we had synthesized the four possible racemates of tricyclic ring-C aromatic 20-nor diterpenoid resin acid analogs **1**, **2**, **3**, and **4**.

At about the same time Tahara and Hirao[8] reported the conversion of dehydroabietic acid to the *enantiomers* of **1** and **3** and conformational studies of some derivatives of the *cis* acid **3**. Dasgupta and Antony[9] also had developed a synthesis of racemic acid **3**.

The present paper describes in detail the synthesis of the racemic acids **1**, **2**, **3**, and **4** and presents data on conformational–configurational relationships in these compounds.

Synthesis of Intermediates.—Compound **7** could be prepared in 77% yield by cyclization of the keto ester **6**[10] in concentrated sulfuric acid–benzene solution.[11] Attempted cyclodehydration of **6** with polyphosphoric acid under various conditions,[7] however, failed to produce pure **8**. Saponification of **7** yielded the corresponding acid **8** in almost quantitative yield. The structures of **7** and **8** were assigned from the electronic spectra and secured when **8** was dehydrogenated to 1-methylphenanthrene.

Lactonization of **8** with concentrated sulfuric acid at −10° proceeded cleanly to **9**[12] (Scheme I) as shown by the single carbonyl band at 1760 cm^{-1} in the infrared spectrum. We have assigned a *trans* A/B ring junction to lactone **9**, as a molecular model (Dreiding)

(1) To whom inquiries regarding this work should be made: Calcutta, India.

(2) R. D. Haworth and R. L. Barker, *J. Chem. Soc.*, 1299 (1939).

(3) K. Mori, M. Matsui, and H. Tanaga, *Tetrahedron*, **22**, 885 (1966).

(4) U. R. Ghatak, A. K. Banerjee, N. R. Chatterjee, and J. Chakravarty, *Tetrahedron Lett.*, 247 (1967).

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(10) U. R. Ghatak, D. K. Datta, and S. C. Ray, *J. Amer. Chem. Soc.*, **82**, 1728 (1960).

(11) B. R. T. Keene and K. Schofield, *J. Chem. Soc.*, 3181 (1957).

(12) Mori, *et al.*[3] have described a different method for the synthesis of lactone **9**. They assigned a *trans* A/B ring junction to lactone **9** on the basis that a monoketo derivative is obtained on chromic acid oxidation of **9**.