The Structure, Stereochemistry, and Genesis of α-Caryophyllene Alcohol (Apollan-11-ol)[1,2]

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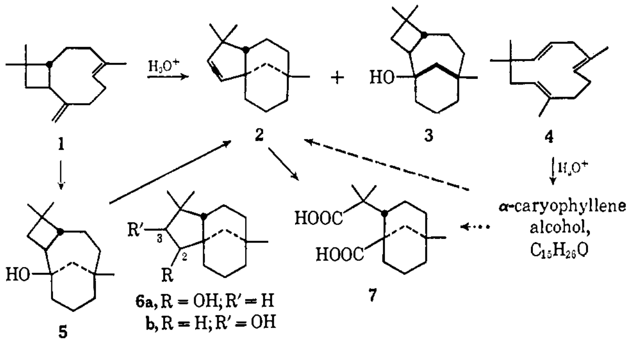
Abstract: A complete chemical structure proof is presented for α-caryophyllene alcohol ($C_{15}H_{26}O$), which is formed on acid cyclization of commercial caryophyllene. Previous information on the oxidation and dehydration of α-caryophyllene alcohol was found to be erroneous. A novel feature of our degradation scheme was tactical application of nitrite photolysis (Barton reaction) to introduce remote functional groups. The OH group in α-caryophyllene alcohol was shown to be secondary, on a five-membered ring, and flanked by fully substituted carbons. Irradiation of its nitrite ester followed by hydrolysis of the derived oxime gave a keto-alcohol with the new carbonyl group (B) in a 1,4-relationship and in a separate five-membered ring. During nitrite irradiation the original C–O bond epimerized to the epi configuration. Repetition of the nitrite photolysis–hydrolysis sequence on the keto-alcohol introduced another ketone group (C) which was shown, by alkaline cleavage reactions, to be separated from B by a single carbon carrying a *gem* dimethyl group. Nmr of several compounds in the series revealed four quaternary methyl groups, two of which are equivalent in α-caryophyllene alcohol and in the symmetrically functionalized derivatives. The facts uniquely define the tricyclic skeleton, including stereochemistry at ring junctions and at the alcoholic carbon. Cyclization with D_2SO_4 revealed that α-caryophyllene alcohol arises not from caryophyllene, but from humulene. The name *apollane* is suggested for the mesoid, tricyclic hydrocarbon on which α-caryophyllene alcohol is based.

The cyclization of caryophyllene (**1**) with sulfuric acid in aqueous acetic acid, first reported by Wallach and Walker,[3] gives among other products[4a] clovene and caryolan-1-ol,[4b] which are now known to have structures **2** and **3**, respectively.[5] In 1922 Asahina and Tsukamoto conducted the reaction with sulfuric acid in ether and, after basification, obtained the same two compounds; but on reacidification and steam distillation a third product ($C_{15}H_{26}O$; mp 117°) was isolated in low yield. The new compound, presumed to have been liberated from a sulfate ester, had $[\alpha]D \pm 0°$, was saturated, gave a phenylurethan (mp 180°, $[\alpha]D \pm 0°$) and was trivially named α-caryophyllene alcohol.[6]

In 1930 Bell and Henderson[7] reported that dehydration of α-caryophyllene alcohol (*e.g.*, with P_2O_5 or oxalic acid) gave a liquid olefin regarded as clovene, and that chromic acid oxidation of α-caryophyllene alcohol gave in *ca.* 30% yield clovenic acid (mp 187°), which was thermally converted to an anhydride (mp 49.5°). These two crystalline compounds (whose structures are now known to be **7** and its cyclic anhydride) were said to be identical (melting point and mixture melting point) with those obtainable by oxidation of clovene.[8] In the light of these facts and current knowledge on caryophyllene and its transformation products, formula **6a** (either epimer) was suggested as a possibility for α-caryophyllene alcohol,[5a] but both epimers were subsequently ruled out by synthesis.[9] At the start of our work, three obvious structures remained that could account for the facts; these were **6b** (either epimer) and the tertiary alcohol **5**, which is thought to be an intermediate[5b] in the acid rearrangement of caryophyllene (**1**) to clovene (**2**). However, in exhaustive attempts to verify Bell and Henderson's work, we could under no circumstances obtain clovene by dehydration or clovenic acid by oxidation.[10] Therefore, we undertook an *ab initio* study that eventually led us to propose for α-caryophyllene alcohol structure **33a**,[2b] which was also deduced independently by X-ray crystallography.[11] The present paper describes experiments that define the complete constitution and show



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[1] We are grateful to The National Institutes of Health (Grant No. GM 06304) for major support of this research and to the Alfred P. Sloan Foundation for a Fellowship to A. N., which originally helped launch our work in this area.

[2] For preliminary communications of portions of this work see: (a) A. Nickon, J. R. Mahajan, and F. J. McGuire, *J. Org. Chem.*, **26**, 3617 (1961); (b) A. Nickon, F. J. McGuire, J. R. Mahajan, B. Umezawa, and S. A. Narang, *J. Amer. Chem. Soc.*, **86**, 1437 (1964).

[3] O. Wallach and W. Walker, *Ann.*, 271, 285 (1892).

[4] (a) W. Parker, R. A. Raphael, and J. S. Roberts, *Tetrahedron Lett.*, 2313 (1965); (b) formerly called β-caryophyllene alcohol. For reviews of caryophyllene chemistry see: A. Nickon, *Perfum. Essent. Oil Rec.*, **45**, 149 (1954); J. L. Simonsen and D. H. R. Barton, "The Terpenes," Vol. III, Cambridge University Press, London, 1952, p 39; Vol. V, 1957, p 517; P. de Mayo, "Mono- and Sesquiterpenoids" in "The Chemistry of Natural Products," K. W. Bentley, Ed., Vol. II, Interscience Publishers, Inc., New York, N. Y., 1959, p 286.

[5] (a) D. H. R. Barton, T. Bruun, and A. S. Lindsey, *J. Chem. Soc.*, 2210 (1952); (b) A. Aebi, D. H. R. Barton, A. W. Burgstahler, and A. S. Lindsey, *ibid.*, 4659 (1954), and references cited therein; (c) A. W. Lutz and E. B. Reid, *ibid.*, 2265 (1954).

[6] Y. Asahina and T. Tsukamoto, *J. Pharm. Soc. Japan*, 484, 463 (1922); *ibid.*, **491**, 1202 (1929).

[7] J. Bell and G. G. Henderson, *J. Chem. Soc.*, 1971 (1930).

[8] L. Ruzicka and D. T. Gibson, *Helv. Chim. Acta*, **14**, 570 (1931).

[9] D. H. R. Barton and A. Nickon, *J. Chem. Soc.*, 4665 (1954).

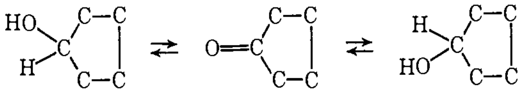
[10] We are unable to account for their findings, which were unquestioned[6] but are now obviously erroneous in view of our structure for α-caryophyllene alcohol.

[11] K. W. Gemmell, W. Parker, J. S. Roberts, and G. A. Sim, *J. Amer. Chem. Soc.*, **86**, 1438 (1964).

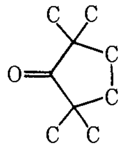
that α-caryophyllene alcohol arises not from caryophyllene[5a,7] as supposed but from its companion sesquiterpene humulene (**4**).[12,13]

Results

α-Caryophyllene alcohol (henceforth abbreviated α-alcohol) was oxidized with CrO_3 to a ketone (α-ketone) whose carbonyl band (1742 cm^{-1}) indicated strain comparable to that in a five-membered ring (partial structure **9**). Reduction with sodium in 2-propanol regenerated α-alcohol (**8**; 87%) whereas hydrogenation (Pt–EtOAc–$HClO_4$) gave in about equal amounts α-alcohol and a liquid, isomeric alcohol (designated epi-α-alcohol, **10**) which was characterized as a crystalline 3,5-dinitrobenzoate. Oxidation of the epi alcohol to α-ketone confirmed that the two alcohols are epimers; very likely α-alcohol is the more stable.



8 **9** **10**



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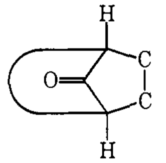

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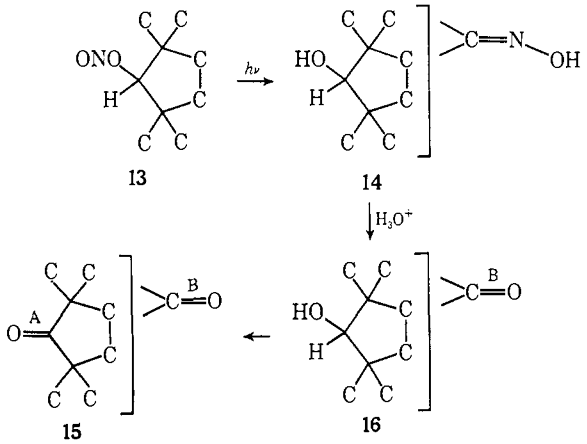
α-Ketone was recovered when subjected to a variety of tests for enolizable hydrogens including attempted bromination, Claisen and aldol condensations, and oxidation with selenious acid. When refluxed in MeOD–NaOMe there was no evidence (ir) for deuterium incorporation. Consequently, positions adjacent to the carbonyl are either fully substituted (**11**) or contain bridgehead hydrogens (*e.g.*, **12**) whose enolization is precluded by Bredt's rule.[14] That the former situation is correct became clear from the nmr spectra of esters (*e.g.*, benzoate, 3,5-dinitrobenzoate, nitrite) of the epimeric alcohols because the signal for the low-field proton attached to the oxygenated carbon was a singlet in *both* the α and epi α series. Because methods for stepwise degradation of fully substituted ketones are limited we gave attention to the possibility of remote functionalization, and Barton's elegant reaction involving photolysis of nitrite esters[15] was explored with ultimate success as follows.

Nitrosation of α-alcohol gave a crystalline nitrite (**13**; ν 1650, 1623, 928 cm^{-1}), which reverted to the parent alcohol on saponification. Irradiation of **13** in benzene isomerized it to a photoproduct **14** (40–67%)[16] acid hydrolysis of which gave a keto alcohol (**16**; $C_{15}H_{24}O_2$ ν 3630, 3500, 1730; no aldehydric H *via* nmr). From the known structural specificity of the Barton reaction,[15] the new carbonyl group (B) is 1,4 to the alcoholic carbon; and the carbonyl absorption suggests that B is also in a five-membered ring. This last conclusion was supported by oxidation of **16** to its diketone **15** in which carbonyls A and B are superposed at 1739 cm^{-1}. That the two functional groups are not 1,3 to each other, and therefore not in the same ring, was shown by complete recovery of **15** after reflux in ethanolic potassium hydroxide.



13 **14** **15** **16**

We repeated the nitrite photolysis sequence to introduce a third functional group. The keto alcohol **16** was converted to a crystalline keto nitrite (**17**) which on irradiation deposited a photoproduct (isomer I), which could not be satisfactorily recrystallized. However, dilute acid converted it to a form (isomer II, **18**; ν 1727, 1647) that was readily crystallized and analyzed. Presumably we are dealing with a nitroso dimer → oxime change, or *syn-anti* oxime isomerization, but the point is not critical because vigorous acid hydrolysis of either isomer in the presence of levulinic acid produced, in addition to an unidentified oil, the same crystalline diketo alcohol (**20**; $C_{15}H_{22}O_3$; no aldehydic H *via* nmr).[17] This diketo alcohol showed two unequal carbonyl bands (ν 1751 medium, 1706 strong) whose marked intensity difference suggested that the new carbonyl (C) is close enough to B to undergo vibrational coupling, a situation that is not uncommon for cyclic 1,3-diketones.[18,19] From the stringent six-membered cyclic transition state of the Barton reaction[20] it follows that C, like B, must

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[12] (a) S. Dev, *Tetrahedron*, **9**, 1 (1960); (b) V. Benesova, V. Herout, and F. Sorm, *Collect. Czech. Chem. Commun.*, **26**, 1832 (1961); (c) M. D. Sutherland and O. J. Waters, *Aust. J. Chem.*, **14**, 596 (1961); (d) A. T. McPhail, R. I. Reed, and G. A. Sim, *Chem. Ind.* (London), 976 (1964); (e) J. A. Hartsuck and I. C. Paul, *ibid.*, 977 (1964); (f) R. P. Hildebrand and M. D. Sutherland, *Aust. J. Chem.*, **14**, 272 (1961).

[13] For example, the commercial caryophyllene in this study contained *ca.* 10–15% humulene and traces of several unknown components (total <5%). Typical yields of α-caryophyllene alcohol were 3–5%.

[14] F. S. Fawcett, *Chem. Rev.*, **47**, 219 (1950).

[15] (a) D. H. R. Barton, J. M. Beaton, L. E. Geller, and M. M. Pechet, *J. Amer. Chem. Soc.*, **82**, 2640 (1960); (b) for reviews see A. L. Nussbaum and C. H. Robinson, *Tetrahedron*, **17**, 35 (1962); M. Akhtar, *Advan. Photochem.*, **2**, 263 (1964).

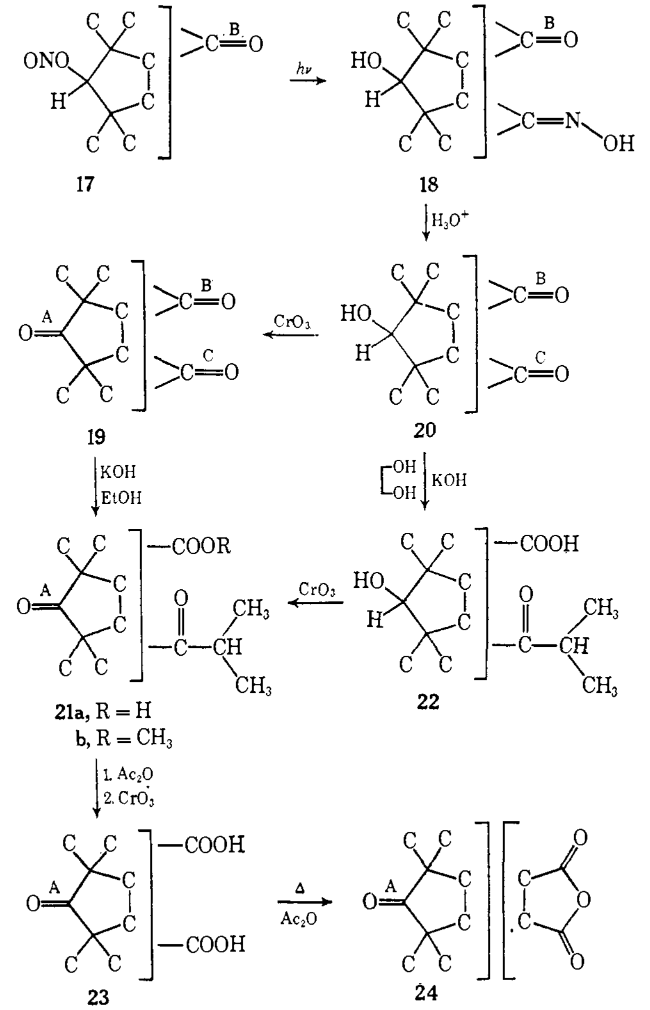
[16] This photoproduct was converted to an isomer on treatment with Ac_2O–Py followed by saponification. The two isomers have different ir spectra, melting points, and solubilities but give the same keto alcohol on acid hydrolysis. They could be *syn-anti* oxime isomers, but the infrared spectra (KBr) were not definitive and low solubility precluded nmr study. Possibly the initial photoproduct is a nitroso dimer, and its isomer an oximino alcohol. For discussion the initial photoproduct is formulated as an oximino alcohol in partial structure **14**.

[17] This compound was originally obtained reproducibly in a crystalline form, mp 136–136.5°, but later only as a form with mp 149–149.5°. Both forms were separately characterized, had identical ir spectra in solution, and identical glpc behavior. Eventually we were not able to prepare the lower melting form and believe it may no longer be obtainable in our laboratory, which has been microscopically seeded with the higher melting point form.

[18] (a) P. F. Donovan, S. A. Liebman, and S. D. Koch, *J. Org. Chem.*, **28**, 2451 (1963); (b) 2,2,5,5-tetramethylcyclohexane-1,3-dione similarly shows two unequal carbonyl peaks (1727, 1698 in CS_2; 1730, 1698 in CCl_4; 1727, 1692 in $CHCl_3$). We thank Dr. J. Hudec (University of Southampton) for providing this compound for infrared study.

[19] At this stage we did not dismiss the possibility that intramolecular H bonding or hemiacetal formation was responsible for the positions and relative intensities of the carbonyl bands.

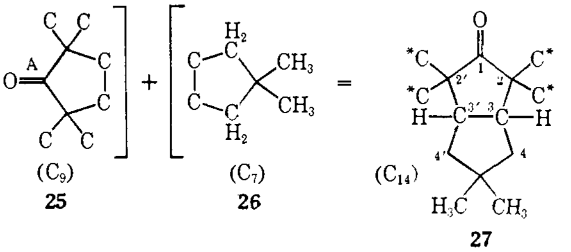
[20] For the first recorded exception (a seven-membered transition state) see D. H. R. Barton and J. R. Hanson, *Chem. Commun.*, 117 (1965); see also J. R. Hanson, *Tetrahedron*, **22**, 1701 (1966).

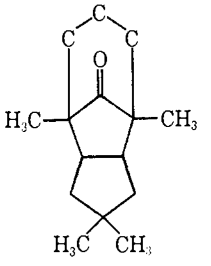


be in a 1,4 relation to A, and the following experiments reveal that B and C are also 1,3 to each other and share the same five-membered ring.

Treatment of the diketo alcohol **20** with potassium hydroxide gave a hydroxy keto acid **22** (no loss in carbon), which was directly oxidized to a diketo acid **21a**, whose methyl ester (**21b**) showed three carbonyl peaks at 1748 (carbonyl A), 1730 (COOMe), and 1704 (open-chain unstrained ketone) and had three enolizable hydrogens (2.49 D incorporated with MeOD–NaOMe). The nmr absence of aldehydic H confirmed that the unstrained carbonyl in **21b** is ketonic and that the alkali treatment of **20** had opened a cyclic 1,3-diketone and not a cyclic 1,2-diketone. The same diketo acid **21a** was obtained by another sequence, which involved oxidation of diketo alcohol **20** to a triketone **19** followed by alkaline cleavage. Importantly, the nmr of ester **21b** revealed that a $-CH(CH_3)_2$ group had been created by the alkaline cleavage, because the *gem* dimethyl unit appears as a six-proton doublet at δ 1.23 ($J \sim 7.5$ Hz), and the isopropyl hydrogen appears as a one-proton septet at δ 3.76 ($J \sim 7.5$ Hz).[21] If carbonyls B and C are indeed in the same five-membered ring it follows that the COOMe group and the isopropyl ketone chain in **21b** must be attached to contiguous carbons, and this corollary was confirmed by a vigorous chromic acid oxidation on the diketo ester **21b**. The product was a keto dicarboxylic acid (**23**; $C_{12}H_{10}O_5$), which had lost the three-carbon isopropyl unit, and which was separately dehydrated to a cyclic anhydride **24** whose carbonyl pattern (1865, 1795; 1745 for A) is typical of five-membered anhydrides.[22]

With the knowledge that carbonyls B and C were derived from CH_2's *via* 1,4-functionalization sequences the facts require in α-ketone the presence of the C_9 unit **25** and the C_7 unit **26**, with *two carbons* in common, and uniquely define their mode of attachment as in the C_{14} fragment **27**.[23a] At this stage hydrogens may be attached to C-3 and C-3′ to account for the three enolizable protons in **21b**.





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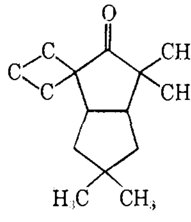

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Location of the fifteenth carbon and the third ring is most easily done by consideration of the number of $C-CH_3$ groups, whose sharp, high-field signals make them readily identified by nmr. In fact, several of the compounds showed unequivocally the presence of four quaternary CH_3 groups. For example, diketone **15** shows sharp singlets (3 H each) at δ 0.95, 1.00, 1.03, and 1.07; and the oxime of α-ketone has the singlets at δ 0.90, 0.95, 1.04, 1.40. Since two quaternary CH_3's are already accounted for by the *gem*-dimethyl unit in **27**, two of the starred carbons in **27** as well as the fifteenth carbon must be part of the third ring. Only two arrangements, **28** and **29**, are possible for the complete C_{15} skeleton. That the mesoid structure **28** is the correct one became evident at several stages in our degradation scheme because whenever the functionality permitted a plane of symmetry, two of the CH_3 signals became equivalent and two were nonequivalent. For example, in α- and epi-α-alcohol and all their esters, in α-ketone, and in the diketo alcohol **20**, two CH_3's appear as a 6-proton singlet and the remaining two as separate 3-proton singlets. These facts are readily understandable in terms of **28**, whereas skeleton **29** would re-

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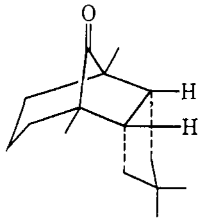
[21] The terminal components of the multiplet are not clearly discernible above background but the relative intensities of the remaining five peaks accord with theory for a septet (1:6:15:20:15:6:1) rather than a quintet (1:4:6:4:1). The diketo acid (partial structure **21a**, full structure **39a**) showed the same characteristics.

[22] (a) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, John Wiley & Sons, Inc., New York, N. Y., 1958; (b) K. Nakanishi, "Infrared Absorption Spectroscopy, Practical," Holden-Day, Inc., San Francisco, Calif., 1962.

[23] (a) Every other possible way of combining **25** and **26** *via* one or two common atoms was considered and can be ruled out by one or more of the facts; (b) chemical arguments in favor of a symmetrical skeleton included the absence of regioselective isomers in the initial Barton sequence, in the 1,3-diketone cleavage, and in the Baeyer–Villiger oxidation of α-ketone to be described.

quire an extraordinary number of coincidences to explain the CH_3 patterns.[23b]

Stereochemistry. On the question of skeletal stereochemistry, we note that only three types of ring fusions are possible for skeleton **28**, and two of these are illustrated in **30** and **31** (the third has the angular hydrogens *trans* to each other). Our nitrite photolyses results uniquely support **31** because only this stereoisomer is geometrically capable of functionalization at *both* sites B and C by the intramolecular Barton reaction.



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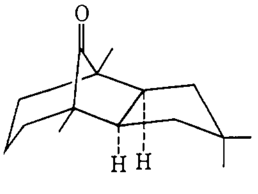

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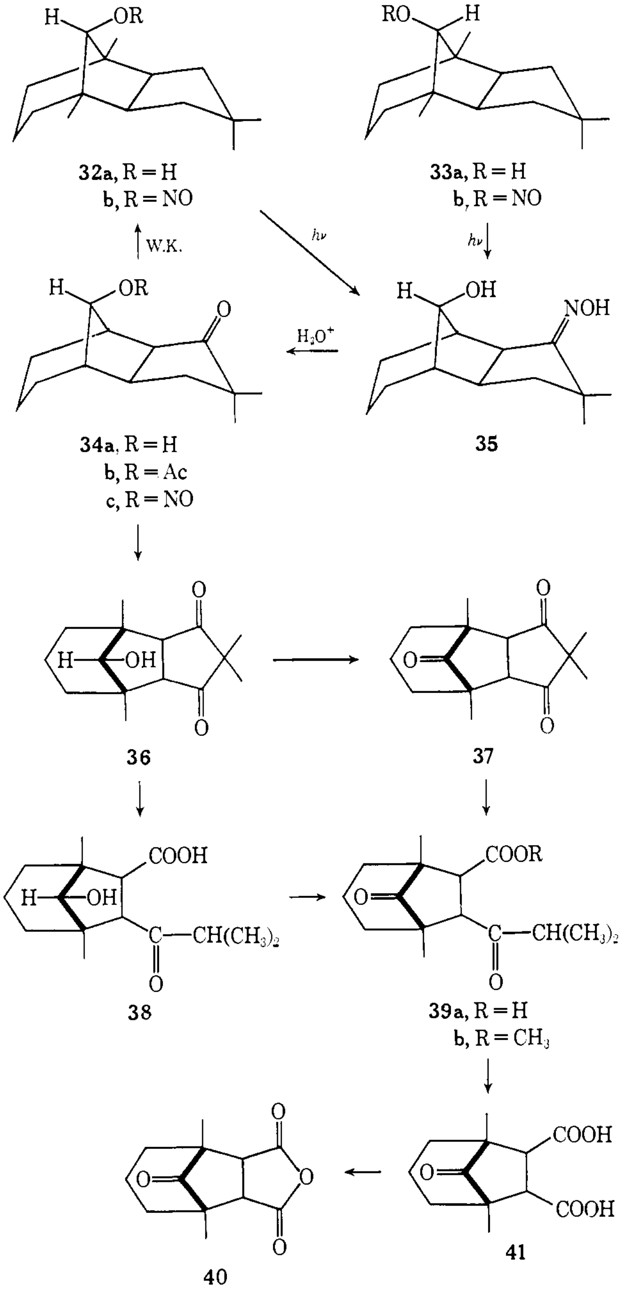
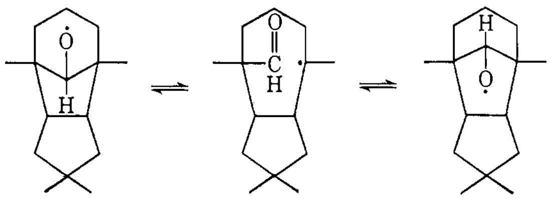
The final point to settle is the configuration of the OH group in α-alcohol and its epimer, and in this connection an unprecedented anomaly was discovered concerning the Barton reaction. We noted earlier that irradiation of α-nitrite (**13**) gave an oximino alcohol **14** and ultimately a keto alcohol **16**. To test this sequence in the epi series, we converted epi-α-alcohol to a crude, liquid nitrite (ν 1642, 1621, 915) from which epi-α-alcohol was regenerated by saponification. Surprisingly, irradiation of the epi nitrite gave the *same* oximino alcohol (50–60% yield) **14** as was obtained from α-nitrite, identified by melting point, mixture melting point, ir, and also by hydrolysis to the same keto alcohol **16**. These findings establish that a C–O bond epimerization had occurred during irradiation of one of the nitrites.



After irradiation the C–O bond must necessarily be oriented toward the newly functionalized ring, and the derived products (partially formulated as **14**, **16**) can be assigned complete structures as shown respectively in **35** and **34a**. That the OH group in these products has the epi configuration was shown by Wolff–Kishner reduction of keto alcohol **34a**, which gave epi-α-alcohol (**32a**). Consequently it is α-nitrite that undergoes C–O epimerization to the epi configuration, and these facts lead to complete structures **33a** for α-alcohol and to **36** and **37** for diketo alcohol and triketone represented earlier by partial structures **20** and **19**. This was the first recorded case[2a] of C–O bond inversion in nitrite photolysis,[24] and a reasonable gross scheme for epimerization is shown in Scheme I. The rupture of a ring bond in cycloalkoxy radicals has ample analogy[25] and a reclosure after conformational rotation of the aldehyde unit could interconvert the α- and epi-α-alkoxy radicals, of which only the latter can consummate the Barton reactions.[26]

Scheme I



With complete structures in hand we can now describe some miscellaneous transformations encountered in this work. When α-ketone (**42**) was treated with sodium amide in xylene (Haller–Bauer cleavage) an anomalous product $C_{30}H_{48}N_2$ was obtained in place of the expected amide. We believe the compound to be the corresponding azine **43** based on ir (ν 1650; no N–H), uv (221 nm, ε 12,037; 246 nm, ε 1670) and acid hydrolysis, which regenerated α-ketone. Although there is precedent for azine production under Haller–Bauer conditions[27] we have no mechanistic information on its formation.

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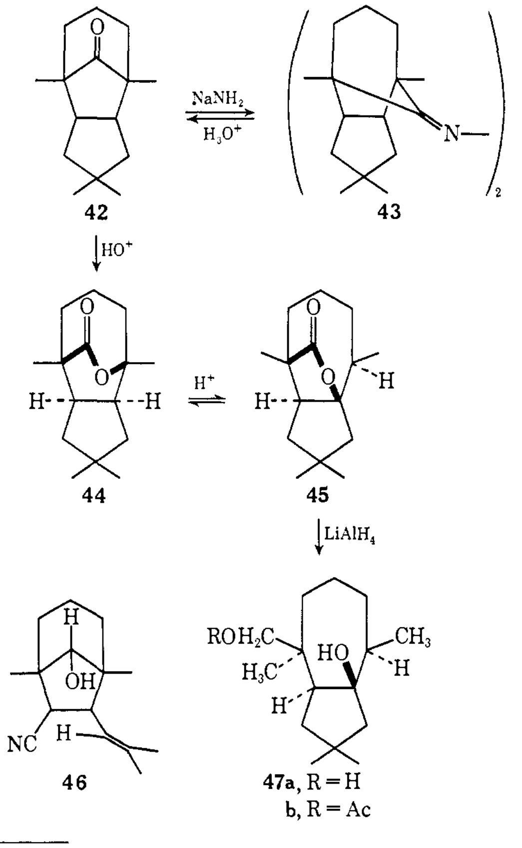
[24] (a) A second example has been recently found [H. Suginome, N. Sato, and T. Masamune, *Tetrahedron Lett.*, **16**, 1557 (1967)]. Several cases of C–O epimerizations in $Pb(OAc)_4$ treatment of alcohols are now known [K. Heusler, J. Kalvoda, G. Anner, and A. Wettstein, *Helv. Chim. Acta*, **46**, 352 (1963); G. B. Spero, J. L. Thompson, W. P. Schneider, and F. Kagan, *J. Org. Chem.*, **28**, 2225 (1963)].

[25] For leading references see footnotes 15b and 24, also M. Akhtar and S. Marsh, *J. Chem. Soc.*, *C*, 937 (1966); P. Kabasakalian and E. R. Townley, *J. Org. Chem.*, 27, 3562 (1962).

[26] Mechanistic studies of this C–O inversion are in progress (A. Bosch and R. Ferguson, unpublished results).

[27] G. W. Kenner, M. J. T. Robinson, C. M. B. Taylor, and B. R. Webster, *J. Chem. Soc.*, 1756 (1962).

Baeyer–Villiger oxidation of α-ketone (**42**) with perbenzoic acid in HOAc–H_2SO_4 gave a mixture from which we isolated two isomeric lactones. One of these was the expected δ lactone (**44**; ν 1742), and the other was a γ-lactone (ν 1767), which must necessarily be a secondary transformation product. When separately treated with sulfuric acid in acetic acid each lactone was equilibrated to a mixture (*ca.* 30:70, respectively) of the two, and this finding indicated that the acid medium during the Baeyer–Villiger reaction produces the γ- from the δ-lactone and that no profound skeletal reorganization is involved in the isomerization.[28] Reduction of the γ-lactone with lithium aluminum hydride gave a diol which formed a monoacetate. That the unacetylated OH is tertiary was indicated (a) by recovery of the monoacetate on attempted oxidation with Sarett's reagent and (b) by the nmr absence of low-field hydrogens other than those associated with the $-CH_2-OR$ unit, the methylene group of which appears as a typical AB quartet ($J \sim 11$ Hz). That one of the CH_3 groups in the diol is no longer quaternary is indicated in the nmr by a 12-proton count in the C–CH_3 region comprised of three-sharp methyl singlets and a "filled in"[29] region amounting to 3 protons between two of these signals. In the simplest interpretation of these facts we formulate the γ-lactone as **45** (derived by acid rearrangement of δ-lactone **44**) and the diol and its monoacetate as **47a** and **b**. Molecular models indicate that the geometry is suitable for the **44** $\rightleftarrows$ **45** interconversion.



42 **43** **44** **45** **46**

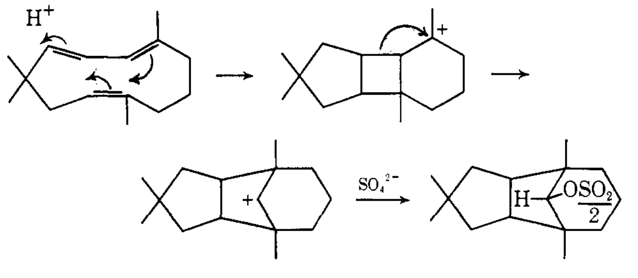
47a, R = H
b, R = Ac

In the light of the full structure for oximino alcohol **35**, we can now assign a reasonable structure to a by-product that was isolated when ethanol was present in the acid hydrolysis of the oxime. This by-product (**46**) is a hydroxy nitrile (ν KBr 3448, 2232), contains one olefinic H (δ 5.62) and two geminal, allylic methyl groups (δ 1.62, 1.79) in addition to two quaternary methyls (δ 0.92, 1.30). Its derivation from **35** by an abnormal Beckmann reaction is readily understandable.

Genesis of α-Alcohol. Because of Bell and Henderson's report that α-alcohol was convertible to clovene and clovenic acid (optically active compounds!) it was generally accepted that caryophyllene was the progenitor.[4,5] Although the plane of symmetry in α-alcohol precludes optical activity, the possibility still remained that it arises from caryophyllene (rather than from an inactive precursor such as humulene). However, any reasonable mechanism requires the exocyclic CH_2 in caryophyllene to become a C–CH_3 in α-alcohol and this provided a basis for an experimental test. When commercial caryophyllene was cyclized with D_2SO_4 in ether the derived α-alcohol contained 2.74 *d*. Importantly, the CH_3 absorption pattern in the 1395–1360 cm^{-1} ir region and in the δ 0.8–1.1 nmr region are identical in detail with those regions in the spectra of nondeuterated α-alcohol. These results establish the absence of the structural unit $-CH_2D$ and rule out caryophyllene or isocaryophyllene[30] as the progenitor. Humulene (**4**) is the only other constituent present in sufficient quantity to account for the α-alcohol, and indeed we obtained higher yields (*e.g.*, 24%) from pure humulene.[13,31]

The mechanism for transformation of humulene to α-alcohol is not known, but a reasonable sequence (Scheme II) involves shift of a tricyclic double bond into conjugation followed by transannular closure to a 5–4–6 tricyclic skeleton and then expansion of the four-membered ring.[32] In detail this scheme is grossly oversimplified because for D$^+$ cyclization it predicts the incorporation of two deuterium atoms (one to shift the double bond and the other to initiate the ring closure),

Scheme II



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(28) (a) Drs. W. Parker and J. S. Roberts (University of Glasgow) have informed us that they treated α-ketone with trifluoroperacetic acid and isolated three lactones, two of which proved identical with our δ and γ-lactones. We are grateful to them for this information and for comparison spectra; (b) for examples of δ- to γ-lactone isomerizations see: G. Buchi and I. M. Goldman, *J. Amer. Chem. Soc.*, **79**, 4741 (1957); J. Meinwald, M. C. Seidel, and B. C. Cadoff, *ibid.*, **80**, 6303 (1958).

(29) F. A. L. Anet, *Can. J. Chem.*, **39**, 2262 (1961); G. V. Smith and P. J. Trotter, *J. Org. Chem.*, **28**, 2450 (1963); E. W. Garbisch, Jr., and D. B. Patterson, *J. Amer. Chem. Soc.*, **85**, 3228 (1963).

(30) A. Aebi, D. H. R. Barton, and A. S. Lindsey, *J. Chem. Soc.*, 3124 (1953).

(31) (a) On acid hydration of humulene (*ca.* 95% pure) S. Dev [*Curr. Sci.* (India), **20**, 296 (1961)] obtained an alcohol mp 116° suggested to be α-caryophyllene alcohol. Dr. Dev kindly sent us details as well as a sample of his compound and we confirmed its identity with α-alcohol by melting point, mixture melting point, and ir comparison; (b) W. Parker and J. S. Roberts (private communication) have also obtained higher yields of α-alcohol from pure humulene.

(32) The scheme is written for compactness and does not imply any particular sequence of events or specific intermediates. However, our deuterium results rule out isomerizations or intermediates involving *exocyclic* methylene units. Similar genesis was envisaged by E. J. Corey and S. Nozoe in their synthesis of α-alcohol [*J. Amer. Chem. Soc.*, **87**, 5733 (1965)].

whereas our deuterated α-alcohol (total 1.74 *d*) had species with up to seven deuteriums per molecule! Clearly a variety of proton exchanges and olefinic intermediates can intervene.

Asahina and Tsukamoto suggested that α-alcohol exists as a sulfate ester, which is hydrolyzed during the steam distillation of the acidified mixture.[6] Parker and Roberts have isolated a sulfate ($C_{30}H_{50}O_4S$; mp 137–138°) from the reaction mixture[33] but it remained to be established whether this was the sulfate of α-alcohol or of some precursor that could isomerize to α-alcohol during the acid work-up. We settled this last point by converting α-alcohol to a sulfate ester (see Scheme II) identical with that of Parker and Roberts.

In accord with Barton's recommendation[5b] to remove confusion of α,β-stereochemical nomenclature with trivial names in this field, to circumvent cumbersome systematic nomenclature, and to remove the erroneous implication of a genetic link with caryophyllene we propose that the saturated tricyclic hydrocarbon on which α-caryophyllene alcohol is based be henceforth called *apollane*.[34]

Experimental Section[35]

Caryophyllene (1). Commercial caryophyllene (Dodge and Olcott Inc., N. Y.) was extracted with dilute sodium hydroxide solution, washed with water, dried and distilled: bp 127–129.5° (15–17 mm); α-11° (*c* 4.43); $n^{21.5}$D 1.4998; ν (neat) 1631, 1381, 1364, 883, 877, 840, 822, 812. Typically it contained *ca.* 80% caryophyllene, 15% humulene, and numerous minor components (<5%) by glpc on Castorwax at 170° (Golay capillary).

α-Caryophyllene Alcohol (33a). (a) From Crude Caryophyllene. Caryophyllene was hydrated in H_2SO_4–ether according to Asahina and Tsukamoto[6] as modified by Lutz and Reid.[5c] After removal of clovene (2) and caryolan-1-ol (3) crude α-alcohol was obtained by steam distillation of the reacidified mixture. Crystallization from acetone gave mp 118–120° (3–5% yield). For analysis it was recrystallized as plates from petroleum ether and sublimed at 70° (0.1 mm); mp 118.5–119.5° (lit.[6] 117°) α ± 0° (*c* 3.99); ν 3623, 3484 (free and bonded OH), 1381, 1377, 1362 (*gem* dimethyl and C–CH_3); nmr δ 0.87 (s, 6), 0.90 (s, 3), 1.05 (s, 3), 3.30 (s, 1, *CH*–O).

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.03; H, 11.82.

The derived **phenylurethan** was crystallized from petroleum ether and sublimed; mp 181–181.5° (lit.[6] 180°).

Anal. Calcd for $C_{22}H_{31}NO_2$: C, 77.37; H, 9.15; N, 4.10. Found: C, 77.48; H, 9.12; N, 4.12.

The **benzoate** was prepared by 16-hr reflux with benzoyl chloride in dry pyridine. The product, initially oily, was obtained crystalline by alumina chromatography. The analytical sample was obtained as plates from aqueous methanol and finally sublimed at *ca.* 60°; mp 63.5–65°; ν 1730; nmr δ 0.87 (s, 6), 0.93 (s, 3), 1.12 (s, 3), 5.01 (s, 1, *CH*–O).

Anal. Calcd for $C_{22}H_{30}O_2$: C, 80.93; H, 9.26. Found: C, 81.18; H, 9.32.

The **3,5-dinitrobenzoate** was obtained similarly and was crystallized as needles from petroleum ether. Sublimation gave mp 176.5–177°; ν 1736; nmr δ 0.88 (s, 6), 0.96 (s, 3), 1.15 (s, 3), 5.08 (s, 1, *CH*–O).

Anal. Calcd for $C_{22}H_{28}N_2O_6$: C, 63.44; H, 6.78. Found: C, 63.55; H, 6.76.

(b) From Humulene. Humulene (>99% pure) was isolated from a commercial "caryophyllene" mixture (Glidden Co., humulene content *ca.* 60%) by precipitation as the silver nitrate adduct and regeneration.[12f] Hydration gave α-alcohol in 12–24% yields.

Attempted Oxidations and Dehydrations of α-Alcohol. Following the procedures of Bell and Henderson[7] we were unable to get clovenic acid (7) as a product of oxidation with chromic acid. Controls showed that we could have isolated as little as 1% and we had no difficulty in getting the acid by oxidation of authentic clovene. Similarly, all attempts to convert α-alcohol to clovene with $POCl_3$, P_2O_5, or PCl_5, were unsuccessful.

α-Ketone (42). Chromium trioxide (8.0 g) was added to concentrated sulfuric acid (7 ml) and the mixture was diluted to 30 ml with water. This solution was added during 20 min to a stirred solution (kept at 30 ± 2°) of α-alcohol (25 g) in acetone (175 ml). After an additional 15 min the bulk of the acetone was evaporated at 20°. Addition of water gave the crude ketone which had mp 40–41° (23.5 g, 95%) after crystallization from methanol at 0°. The analytical sample was sublimed at 25° (0.1 mm); mp 40.5–41.5°; α ± 0° (*c* 3.39); ν 1742, 1385, 1381, 1368; nmr δ 0.93 (s, 6), 0.97 (s, 3), 1.00 (s, 3).

Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.83; H, 10.79.

Comparable results were obtained with sodium dichromate dihydrate in acetic acid or with CrO_3 in pyridine.[36]

The **2,4-dinitrophenylhydrazone** crystallized as small needles from ethyl acetate–methanol; mp 158.5–159°.

Anal. Calcd for $C_{21}H_{28}N_4O_4$: C, 62.98; H, 7.05. Found: C, 62.88; H, 6.90.

The **oxime** was crystallized from petroleum ether; mp 173.5–175° dec; ν 1681; nmr δ 0.90, 0.95, 1.04, 1.40 (all s, 3).

Anal. Calcd for $C_{15}H_{25}NO$: C, 76.54; H, 10.71. Found: C, 76.38; H, 10.71.

Reduction of α-Ketone. (a) With Sodium in Isopropyl Alcohol. Conventional reduction and work-up gave the crude alcohol which was chromatographed on alumina. Benzene elution gave an 87% yield of α-alcohol (mp 117.5–119°) identified by mixture melting point and by infrared comparison.

(b) Catalytic Hydrogenation. The ketone (402 mg) in ethyl acetate (20 ml) containing perchloric acid (5 drops of 60% aqueous solution) was hydrogenated over prereduced platinum oxide (99 mg) for 6 hr. The product was chromatographed over alumina and eluted with benzene–petroleum ether (1:4). Liquid epi-α-alcohol (215 mg, 53%) was eluted early, followed by slow emergence of α-alcohol (178 mg, 44%, mp 116–119°) identified by mixture melting point and infrared. The epi-α-alcohol **32a**, ν 3650, 1383, 1377, 1366, nmr δ 0.90 (s, 3), 1.00 (s, 6), 1.05 (s, 3), 3.22 (s, 1, *CH*–O), has a shorter retention time on glpc (Carbowax; 196°) than α-alcohol and has differences in fingerprint absorption. Epi-α-alcohol, which could be solidified on a cold finger, was heated in pyridine with 3,5-dinitrobenzoyl chloride (2 hr). The crude **3,5-dinitrobenzoate** was chromatographed on alumina, was crystallized as small cubes from petroleum ether, and was sublimed at 124° for analysis; mp 129.5–130.5°; ν 1736; nmr δ 0.97 (s, 6), 1.00 (s, 3), 1.25 (s, 3), 5.03 (s, 1, *CH*–O).

Anal. Calcd for $C_{22}H_{28}N_2O_6$: C, 63.44; H, 6.78. Found: C, 63.19; H, 6.64.

Oxidation of Epi-α-alcohol. This liquid epimer was oxidized at room temperature with sodium dichromate dihydrate in acetic acid or with chromic acid in acetone as described for α-alcohol. Work-

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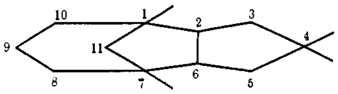
(33) We thank Drs. Parker and Roberts for providing this information and for a comparison sample of their sulfate.

(34) This name is prompted by the rocket-like symmetry of the structure and the historic July 1969 moon flight of Apollo-11. The systematic title is 1,4,4,7-tetramethyltricyclo[$5.3.1.0^{2,6}$]undecane.



(35) Unless specified otherwise, the following information applies. Melting points are corrected. Infrared spectra were recorded on carbon tetrachloride solutions with a Perkin-Elmer Model 21 instrument equipped with sodium chloride optics. Band positions are in cm^{-1}. Fisher Scientific Co. alumina (80–200 mesh) was used for column chromatography. Sublimations were conducted under the vacuum of an oil diffusion pump. Elemental analyses were performed by Mr. J. Walter. The drying agent was $MgSO_4$ or Na_2SO_4. Optical rotations refer to the sodium D line taken on chloroform solutions at room temperature. Petroleum ether refers to the fraction bp 66–75°. Nmr were recorded in $CDCl_3$ and peaks are expressed in δ units (parts per million downfield from internal tetramethylsilane) followed by multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet) and proton count. Except where assigned otherwise, nmr signals are those due to CH_3 groups. Trifluoroacetic acid or D_2O were used to identify and to remove splitting by OH, whose position is not listed in the assignments. "Oxidation solution" refers to that prepared from chromium trioxide (4.0 g) and concentrated sulfuric acid (3.5 ml) made up to 15 ml with water. Ultraviolet spectra were taken on a Beckman Recording spectrophotometer, Model DK-2.

(36) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Amer. Chem. Soc.*, **75**, 422 (1953).

up gave α-ketone (in high yields) identified by infrared, melting point, and mixture melting point comparisons with authentic material.

Attempted Enolization Reactions of α-Ketone. The ketone was recovered after treatment with (a) ethyl formate and sodium hydride in benzene at reflux; (b) benzaldehyde in ethanolic KOH; (c) selenious acid in acetic acid at reflux; (d) bromine in acetic acid containing a drop of aqueous hydrobromic acid; (e) concentrated sulfuric acid in acetic acid (*ca.* 1:1 volume). Also, attempted deuterium exchange by 42-hr reflux in methanol-O-*d* containing dissolved sodium gave ketone whose intense infrared spectrum (CCl_4) in a 5-mm cell showed no absorption in the 2400–2100 region (C–D stretching).[37]

α-Alcohol Nitrite (33b). (a) Sodium nitrite (10.0 g) was added during 2.5 hr to a stirred solution of α-alcohol (10.0 g) in acetic acid (120 ml) and carbon tetrachloride (20 ml) maintained at 10–15° under nitrogen. The reaction mixture was kept an additional 1.5 hr at 10°, was diluted with cold water, and was extracted with ether. The ether extracts were washed successively with water, sodium carbonate solution, and water, and were dried. Evaporation with a stream of nitrogen left α-nitrite and α-alcohol as a mixture that solidified in the cold. When brought to room temperature the nitrite liquefied while most of the α-alcohol stayed solid and was removed by suction filtration. Several repetitions of the cooling–thawing–filtration process removed most of the α-alcohol (0.7 g) and left 10.0 g of the nitrite as faint yellow needles that liquefy around room temperature. The oily nitrite was used for subsequent photolysis as well as for preparation of an analytical specimen by crystallization (with some difficulty) from a small volume of hexane in the cold; mp 25–26°; ν 1650, 1623 (*anti* and *syn* ON=O), 928; nmr δ 0.83 (s, 6), 0.96 (s, 3), 1.13 (s, 3), 5.16 (s, 1, *CH*–O).

Anal. Calcd for $C_{15}H_{25}NO_2$: C, 71.67; H, 10.03. Found: C, 72.06; H, 10.14.

(b) A cold solution of dinitrogen tetroxide (0.6 ml) in 4 ml of methylene chloride was slowly added (20 min) to a cold (−5 to −10°) stirred mixture of α-alcohol (0.50 g), anhydrous sodium acetate (1.0 g), and methylene chloride (7 ml). After addition, the cold mixture was stirred an additional 1 hr, and pyridine (0.6 ml) was added. After concentration under vacuum at 0° water was added, and the mixture was extracted with ether, which was washed, dried, and evaporated as before to leave α-nitrite (0.5 g) as a pale yellow oil.

α-Nitrite regenerated α-alcohol (85%) on saponification with ethanolic potassium hydroxide. Exposure of the ester to air also gradually reverts it to the parent alcohol.

Epi-α-nitrite (32b). Epi-α-alcohol (1.5 g, from chromatography) in glacial acetic acid (15 ml) was treated with sodium nitrite (1.5 g) at 10° as described above for α-alcohol. After work-up of the ether extract the infrared spectrum of the light yellow, liquid nitrite (1.4 g) showed no OH and had ν 1642, 1621 (*anti* and *syn* ON=O), 915 (useful to distinguish from α-nitrite); nmr δ 0.85 (s, 6), 0.92 (s, 3), 1.07 (s, 3). This material was used directly for photolysis, and a portion was separately saponified with ethanolic potassium hydroxide to regenerate epi-α-alcohol, identified by infrared comparison. Epi-α-nitrite (0.28 g) was also obtained from epi-α-alcohol (0.25 g) by the N_2O_4 procedure.

Irradiation of Nitrites. Formation of Photoproduct. (a) **From** α-**Nitrite.** A solution of α-nitrite (7.3 g) in thiophene free benzene (200 ml) under nitrogen in a Pyrex flask equipped with a condenser was irradiated externally with the filament unit of a 250-W Hg lamp (General Electric H250-A5) placed as close as possible so that its heat brought and maintained the solution at reflux. A solid began to appear after *ca.* 40 min, and the irradiation was continued for a total of 75 min. The photoproduct (mp 224.5–226° dec, 4.2 g) was collected and the filtrate was concentrated and irradiated 30 min to give a second crop (mp 223–225° dec, 0.7 g); total 4.9 g (67%). Recrystallization from dioxane gave the photoproduct as shining needles, mp 226.5–227° (dec, varies with rate of heating) ν (KBr) 3600–3200, 1632. It was sublimed at 130° for analysis.

Anal. Calcd for $C_{15}H_{25}NO_2$: C, 71.61; H, 10.03; N, 5.57. Found: C, 71.75; H, 10.37; N, 5.59.

In numerous repetitions we tried different Hg light sources, internal irradiation, cooling the solution, and varying the irradiation time. The yields of precipitate were typically *ca.* 35–60%. Purity of the nitrite, sufficient intensity of irradiation, and a nitrogen atmosphere appeared to be the most important factors. In general some α-alcohol could be recovered from the irradiation mother liquor. Prior to being recrystallized, dried, or sublimed, the photoproduct showed a band at ν 685, which may represent occluded benzene.

(b) **From Epi-α-nitrite.** A dry benzene (80 ml) solution of the epi nitrite (1.4 g) in a Pyrex flask was irradiated externally as described in part a. Solid began to precipitate in *ca.* 30 min and the irradiation was continued a total of 2 hr. The precipitate (0.7 g, 50%) was collected and washed with benzene; mp 224.5–225.5° dec, undepressed by the photoproduct from α-nitrite. Their infrared spectra (KBr) were identical when compared prior to, and after, crystallization. Repetitions of the irradiation gave yields up to 64%.

Isomerization of Photoproduct to Oximino Alcohol 35. A solution of the photoproduct (mp 224–225° dec, 0.10 g) from α- or epi-α-nitrite in dry pyridine (5 ml) and acetic anhydride (5 ml) was refluxed 2 hr. The solvent was removed under vacuum and the gummy residue was heated with ethanolic potassium hydroxide (20 ml, 0.5 *N*) for 1 hr. After concentration to 10 ml, the solution was diluted with water and extracted with ether. Work-up left solid **35** which was crystallized from ethyl acetate; mp 204–205° (0.05 g); ν (KBr) 3530, 3400–3050, 1668.

Anal. Calcd for $C_{15}H_{25}NO_2$: C, 71.61; H, 10.03: Found: C, 71.40; H, 9.93.

Hydrolysis of Photoproducts to Keto Alcohol (34a). A mixture of the photoproduct (2.2 g) from α-nitrite, acetone (42 ml), water (8 ml), and concentrated hydrochloric acid (2.0 ml) was refluxed 70 hr. The mixture was filtered, the filtrate was concentrated, diluted with water, and extracted with ether. Normal work-up followed by crystallization from hexane gave a total of 1.2 g; mp 97.5–99°. The analytical sample of the keto alcohol was obtained from hexane and final sublimation; mp 98.5–99.5°; ν 3630, 3500, 1730; nmr δ 1.04 (s, 6), 1.07 (s, 3), 1.20 (s, 3), 2.16 (s, *CH*–O).

Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 75.98; H, 10.33.

Similar hydrolysis of the photoproduct from epi-α-nitrite or of the oximino alcohol **35** from isomerization of the photoproduct gave the same keto alcohol **34a**, identified by melting point, mixture melting point, and infrared spectral comparisons. Processing the mother liquors (*e.g.*, by column chromatography) gave a by-product (nitrile **46**), which was better obtained by a procedure to be described later.

Acetylation of Keto Alcohol 34a. A solution of the keto alcohol **34a** (0.48 g) in pyridine (2.0 ml) and acetic anhydride (2.0 ml) was refluxed 18 hr. Conventional work-up gave a thick oil that slowly crystallized. Sublimation at 80° (0.25 mm) gave 0.42 g of solid, mp 76–78° The analytical sample of **34b** was obtained by recrystallization from petroleum ether (bp 30–40°) and a final sublimation; mp 79–80.5°; ν 1733, 1230, 1031; ν (KBr) 1730, 1239, 1031; nmr δ 0.97 (s, 3), 1.02 (s, 9), 2.01 (s, 3, $COCH_3$), 4.62 (s, 1, *CH*–O).

Anal. Calcd for $C_{17}H_{26}O_3$: C, 73.34; H, 9.41. Found: C, 73.57; H, 9.38.

Oxidation of Keto Alcohol 34a to its Diketone. An oxidation solution[35] was added dropwise to the keto alcohol (0.10 g) in acetone (2 ml) until the green mixture became yellow (total reagent added *ca.* 0.12 ml; 1.1 equiv). After 5 min the acetone was evaporated and water was added. Trituration gave crystals that were collected, washed, and dried; mp 97–99° (0.09 g). For analysis the diketone was crystallized from hexane and finally sublimed at *ca.* 90° (0.3 mm); mp 98.5–100° (strongly depressed by **34a**); ν 1739 (not sharp); nmr δ 0.95, 1.00, 1.03, 1.07 (all s, 3).

Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 77.00; H, 9.49.

Wolff–Kishner Reduction of Keto Alcohol 34a. The keto alcohol (0.10 g), commercial anhydrous hydrazine (95 + %; 0.5 ml), and absolute ethanol (1.0 ml) containing dissolved sodium (0.05 g) were sealed in a tube under nitrogen and heated at 215 ± 5° for 20 hr. Normal work-up gave a nearly colorless residue (0.1 g) whose ir spectrum resembled closely that of epi-α-alcohol. It was converted directly to the 3,5-dinitrobenzoate by treatment with 3,5-dinitrobenzoyl chloride (0.15 g) in dry pyridine (1.0 ml) on the steam bath for 3 hr. Work-up gave 0.15 g of ester whose ir (KBr) was essentially identical with that of authentic **epi-α-alcohol 3,5-dinitrobenzoate.** Recrystallization from ether gave mp 126.5–127.5° undepressed by an authentic sample.

Nitrosation of Keto Alcohol 34a. Procedure a. A cold solution of dinitrogen tetroxide (0.08 ml) in methylene chloride was slowly added to a stirred, cold (−5 to −10°) suspension of keto alcohol (0.10 g) and anhydrous sodium acetate (0.18 g) in methylene chlo-

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(37) R. N. Jones, A. R. H. Cole, and B. Nolin, *J. Amer. Chem. Soc.*, 74, 5662 (1952).

ride. After 1 hr in the cold, the mixture stood overnight at room temperature. Evaporation of the solvent under vacuum, addition of water, extraction with ether, and normal work-up gave the keto nitrite **34c** as an oil that solidified when cooled (0.12 g). Recrystallization from methanol (charcoal) gave colorless needles, mp 73.5–74°; ν 1727 ($C=O$), 1650, 1626 (*anti* and *syn* $ON=O$), 696; nmr δ 0.95 (s, 3), 1.05 (s, 9). 4.90 (s, 1, *CH*–O).

Anal. Calcd for $C_{15}H_{23}NO_3$: C, 67.89; H, 8.74. Found: C, 68.02; H, 8.50.

Procedure b (for Larger Batches). A cold mixture of keto alcohol (2.5 g), anhydrous sodium acetate (4.5 g), and dinitrogen tetroxide (4 ml) in methylene chloride was stirred 1 hr and then dry pyridine (1 ml) was added. Work-up as in procedure a gave 2.4 g of keto nitrite **34c**.

Irradiation of Keto Nitrite 34c. A benzene (10 ml) solution of keto nitrite (0.10 g) under nitrogen in a Pyrex flask was externally irradiated as described above for α-nitrite. The heat of the lamp caused the solution to reflux and within 15 min a white solid began to appear. After 2.5 hr irradiation the solid (isomer I) was collected; 0.04 g, mp 204–205° dec, ν (KBr) 3497 (OH), 1727 ($C=O$), 1626 (?). In several repetitions, yields were 40–53% and in one run the product had mp 215–217° dec. During attempted recrystallization, the photoproduct partly decomposed, so it was converted to a stable isomeric form (isomer II) as follows.

A suspension of isomer I (0.10 g) in concentrated hydrochloric acid (0.5 ml), water (3 ml), and acetone (30 ml) was refluxed for 73 hr. Evaporation, extraction with ether and conventional work-up gave crude isomeric oximino keto alcohol (isomer II); mp 190–191° (0.07 g). The analytical sample was obtained by recrystallizations from benzene; mp 204–205°; ν ($CHCl_3$) 3546, 3205, 1727, 1647.

Anal. Calcd for $C_{15}H_{23}NO_3$: C, 67.89; H, 8.74; N, 5.25. Found: C, 68.25; H, 8.70; N, 5.13.

Diketo Alcohol 36. A suspension of either isomer I or isomer II (0.10 g) in 10% hydrochloric acid (4 ml), levulinic acid (10 ml),[38] and dioxane (20 ml) was refluxed 20 hr. After dilution with water, extraction with ether, and normal work-up the crude oil was chromatographed over alumina (5 g). Elution with benzene gave a yellow *oil* followed by crystalline diketo alcohol **36**, which had mp 133.5–134.5° (0.02 g) after one crystallization from hexane; ν (CS_2) 3521, 3205, 1751 (medium), 1706 (strong). The two $C=O$ peaks were at 1742, 1698 in $CHCl_3$ and at 1733, 1695 in KBr; nmr δ 1.08 (s, 3), 1.14 (s, 3), 1.22 (s, 6), 2.78 (s, 2, *CH*CO); 3.12 (s, 1, *CH*–O). The analytical sample (mp 136–136.5°) was obtained from hexane.

The results were reproduced with isomer I and isomer II but on one occasion the crystalline product **36** from chromatography (0.10 g from 0.44 g of isomer I) was obtained in a polymorphic form mp 149–149.5° (after crystallization from hexane). The low and high melting forms of **36** had identical ir spectra in solution and identical retention times on glpc. After appearance of the higher melting point form in our laboratory we were no longer able to get the lower melting point form.

Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: mp 136–136.5° form C, 72.26; H, 8.82; 149–149.5° form C, 71.64; H, 8.56.

The *oil* from the column chromatography remains unidentified. It had ν (CS_2) 3413, 1736, 1715, showed a single peak on glpc (silicone grease, 130°), and gave a positive iodoform test. It gave a 2,4-dinitrophenylhydrazone when refluxed 4 hr with the reagent in methanol containing concentrated hydrochloric acid; mp 135–136° (from methanol).

Anal. Calcd for $C_{12}H_{14}N_4O_6$ (310.36): C, 46.45; H, 4.55; N, 18.06. Found: C, 46.62, 46.70, 46.68; H, 4.32, 4.28, 4.79; N, 17.95, 17.97; mol wt 312.

Triketone 37. An oxidation solution[35] (0.4 ml) was added slowly to the diketo alcohol **36** (0.10 g) in acetone (8 ml) and the mixture was stirred 12 hr at room temperature. Conventional work-up and crystallization from hexane gave the triketone **37**; mp 131–131.5° (0.09 g). The analytical sample had mp 132°; ν (CS_2) 1745, 1718; nmr δ 0.87 (s, 3), 1.10 (s, 9), 3.06 (s, 2, *CH*CO); δ (CCl_4) 0.77 (s, 3), 1.03 (s, 6), 1.05 (s, 3), 2.90 (s, 2 *CH*CO).

Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.71; H, 7.98.

Alkaline Cleavage of Triketone 37. A solution of triketone (0.20 g), potassium hydroxide (0.50 g), water (10 ml), and ethanol (30 ml) was refluxed for 4 hr. Concentration, dilution with water, and ether extraction gave *ca.* 0.01 g of starting triketone. Acidification of the alkaline solution and normal ether work-up gave the diketo acid **39a** (0.19 g); one crystallization from benzene gave the analytical sample, mp 129–130° (no gas evolution even up to 212°); ν (CS_2) 3500–3030 (strong broad), 1748, 1701; nmr δ 1.07 (s, 6), 1.24 [d, 6, $HC(CH_3)_2$; J = 7.4 Hz], 2.80 [septet,[21] 1, $\mathit{H}C(CH_3)_2$; J = 7.4 Hz], 3.38, 3.59 (AB quartet, 2, vicinal tertiary hydrogens, J = 7.5 Hz).

Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.70; H, 8.20. Esterification with diazomethane gave the liquid **diketo acid methyl ester 39b**, which was vacuum distilled twice (bath temperature 145–155° at *ca.* 0.1 mm); ν (CS_2) 1748, 1733, 1706, 1206; one peak on glpc (silicone grease, 200°); nmr δ 1.00 (s, 3), 1.05 (s, 3), 1.23 [d, 6, $HC(CH_3)_2$; J = 7.5 Hz], 2.76 [septet,[21] 1, $\mathit{H}C(CH_3)_2$, J = 7.5 Hz], 3.42, 3.53 (AB quartet, 2, vicinal tertiary hydrogens, J = 7.5 Hz), 3.70 (s, 3, OCH_3).

Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.54; H, 8.63. Found: C, 68.93; H, 8.55.

Deuterium Exchange in Diketo Acid Methyl Ester 39b. The methyl ester (0.05 g) was refluxed 3 hr in methanol-O-*d* (1 ml) containing dissolved sodium (0.02 g). The solvent was evaporated, fresh methanol-O-*d* (1 ml) was added and reflux continued for 3.5 hr. Evaporation and ether work-up (D_2O and acidification with D_2SO_4) gave the diketo acid, which was converted to the methyl ester with diazomethane. After one vacuum distillation the methyl ester was refluxed for 6.5 hr in a solution of methanol-O-*d* (1 ml) and D_2O (1 ml) containing dissolved sodium (0.05 g). Work-up as before gave the diketo acid **39a**, which was crystallized twice from benzene–hexane; mp 128.5–129°. Assay by the ir–combustion method[39] gave 2.47 and 2.51 atom excess *d*.

Alkaline Cleavage of Diketo Alcohol 36. A solution of **36** (mp 136–136.5°; 0.025 g) and potassium hydroxide (0.05 g) in ethylene glycol (4 ml) was refluxed for 24 hr. After dilution with water and extraction of neutral material with ether the alkaline layer was acidified with dilute hydrochloric acid and extracted with ether to give the liquid hydroxy keto acid **38** (0.02 g), which did not crystallize even after chromatography over silica gel; ν 3500–2400, 1700. It was oxidized (1.5 hr) directly with chromium trioxide (0.008 g) and concentrated sulfuric acid (3 drops) in water to the diketo acid **39a**, identical in melting point (129–130°), mixture melting point, and infrared with the acid obtained by cleavage of the triketone **37**.

Oxidation of Diketo Ester 39b to Dicarboxylic Acid 41. An oxidation solution[35] (1.5 ml) was added dropwise to a cooled solution of ester **39b** (0.20 g) in acetic acid (2.0 ml) and acetic anhydride (2.5 ml) and then the stirred mixture was heated at 70° for 36 hr. The crude product was conventionally partitioned into a neutral and an oily acidic fraction. After being dried under vacuum for 12 hr the acidic product solidified; mp 255–256° (0.04 g) after repeated recrystallization from ethyl acetate; ν (KBr) 3500–2400, 1760, 1708.[40]

Anal. Calcd for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71. Found: C, 59.76; H, 6.72. Neutralization equivalent for dibasic acid: calcd, 120.1, found, 120.4.

Keto Anhydride 40. The dicarboxylic acid **41** (0 02 g) was refluxed for 6 hr with redistilled acetic anhydride (0.5 ml). Concentration under vacuum at room temperature and sublimation of the residue (0.1 mm; 170–180° bath temperature) followed by trituration with hexane–ether (to dissolve oily component) gave a solid that was resublimed and then recrystallized from hexane–ether (5:1); fine needles of anhydride **40**, mp 125–126° (0.01 g); ν (KBr) 1865, 1795 (five-membered anhydride) 1745 (five-membered $C=O$).

Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 65.17; H, 6.54.

Attempted Haller–Bauer[41] Cleavage of α-Ketone (42). Formation of Azine 43. A stirred mixture of α-ketone (1.1 g), dry xylene (35 ml), and commercial sodium amide (2.2 g, Farchan Research Laboratories) was refluxed for 26 hr (evolution of ammonia was evident). Water and ether were cautiously added to the cooled mixture and the combined ether–xylene extracts were washed with dilute hydrochloric acid and with brine and were dried. Evaporation *in vacuo* followed by recrystallizations from ethyl acetate gave white crystals, mp 124–137° (0.31 g). Chromatography on alumina

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(38) C. H. DePuy and B. W. Ponder, *J. Amer. Chem. Soc.*, **81**, 4629 (1959).

(39) J. L. Lambert, J. H. Hammons, J. A. Walter, and A. Nickon, *Anal. Chem.*, **36**, 2148 (1964).

(40) The possibility of a lactol structure for this keto diacid is not ruled out.

(41) (a) K. E. Hamlin and A. W. Weston, *Org. Reactions*, **9**, 1 (1957), (b) C. D. Gutsche and T. D. Smith, *J. Amer. Chem. Soc.*, 82, 4067 (1960).

gave 20 solid fractions with a 3–6° mp range between 129.5 and 136° and with ir spectra that were essentially identical. Recrystallization from ethyl acetate gave mp 130–134.5° (found: C, 82.74; H, 11.10) raised to 133–133.5° (softens 129.5°) after sublimation; ν 1650 (C=NN=C); no bands 3600–3200; uv (isooctane) 221 (ϵ 12,040), 246 (ϵ 1670) nm.

Anal. Calcd for $C_{30}H_{48}N_2$: C, 82.51; H, 11.08; N, 6.42. Found: C, 82.55; H, 11.09; N, 6.76.

Hydrolysis of Azine 43. The azine (0.07 g), acetic acid (2 ml), and concentrated hydrochloric acid (1 ml) were refluxed for 48 hr. Work-up with water and ether gave a crude product (0.05 g) whose ir was close to that of α-ketone. Treatment with warm methanolic 2,4-dinitrophenylhydrazine hydrochloride gave the corresponding derivative (0.05 g); mp 157–158°, after one crystallization from ethyl acetate–methanol, and undepressed by authentic α-ketone 2,4-dinitrophenylhydrazone.

Baeyer–Villiger Oxidation[42a] of α-Ketone (42). A stirred solution of α-ketone (9.4 g) in acetic acid (25 ml) cooled in ice was treated with perbenzoic acid[42b] (13.5 g) in acetic acid (50 ml). Concentrated sulfuric acid (40 ml) was added over a 15-min period while the temperature was kept at 10–20°. Acetic acid (15 ml) was added, the solution was stirred for an additional 1.5 hr at 5–10°, for 3 hr at room temperature, and then allowed to stand 42 hr. The dark maroon mixture was gradually added to sodium hydroxide (120 g) in ice–water (total volume 600 ml) and the solution (pH 6–7) was treated with acetic acid (15 ml) and extracted with ether. The ether was successively washed with aqueous ferrous sulfate, dilute sodium bicarbonate, dilute hydrochloric acid and brine, and was dried, treated with charcoal, and evaporated; 8.9 g of γ and δ-lactone mixture (estimated 3:2 *via* ir).

A lactone mixture (0.41 g) was chromatographed over alumina (15 g) and eluted with benzene–petroleum ether (1:9). Solid γ-lactone **45** was eluted early; mp 101.5–102.5°, small cubes (0.18 g) after several recrystallizatons from petroleum ether (bp 35–60°). For analysis it was sublimed at 68°; mp 101.5–103°; ν 1767 (1757 in KBr), γ-lactone;[22] nmr δ (pyridine) 0.92 (s, 3), 0.97 (s, 3), 0.97 (d, 3, CH-CH_3, J = 6.5 Hz), 1.12 (s, 3). The high-field component of the doublet is superposed on the 0.92 peak so that the observed area ratios are 4.5:3:1.5:3, respectively. A low-field signal (assigned to the ring junction hydrogen) appears at δ 2.65 as a pair of doublets (M part of ABM); J_{AM} = 10.5 Hz, J_{BM} = 7.5 Hz.

Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 76.42; H, 9.91.

Solid δ-lactone **44** (0.08 g) was eluted later and was recrystallized from petroleum ether (bp 35–60°) as small needles; mp 102–102.5°. Sublimation at 68° gave the analytical sample, mp 102–103°; ν 1742 (1721 in KBr), δ-lactone;[22] nmr δ 0.97, 1.07, 1.13, 1.29 (all s, 3).

Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 76.58; H, 10.08.

Interconversion of γ- and δ-Lactones. When either pure lactone **44** or **45** (0.02–0.05 g) was refluxed 3 hr in acetic acid (3 ml) containing concentrated sulfuric acid (1 drop), and the solution was worked up normally, the product consisted of a mixture in a ratio of *ca.* 70% γ-lactone:30% δ-lactone, as estimated by ir. For this estimate the overlapping carbonyl peaks were assumed to be symmetrical and equal in apparent integrated absorption.[43]

Reduction of γ-Lactone 45 to Diol 47. The γ-lactone (4.7 g) in dry ether (100 ml) was refluxed for 6 hr with lithium aluminum hydride (3.0 g). The mixture stood overnight at room temperature and was worked up with alkali by a reported general method.[44] The diol was recrystallized three times from benzene (mp 169–171°; 4.1 g) and sublimed at 124° for analysis; mp 168.5–170°; ν (1.04 × 10^{-3} M in 5-mm cells) 3650 free OH, 3484 (bonded OH); nmr δ 0.87 (s), 0.98 (s) and filled in portion in between (total 9), 1.14 (s, 3), 3.07, 3.56 (AB quartet, 2, CH_2–O; J_{gem} = 11.0 Hz).

Anal. Calcd for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74. Found: C, 75.16; H, 11.83.

The diol monoacetate **47b** was prepared by acetylation in pyridine and acetic anhydride (1:1) at room temperature for 49 hr. Work-up gave the liquid acetate (98%), which was distilled for analysis; bp 140° (3–4 mm); n^{18}D 1.4865; ν 3571 (sharp), 1745 (broad), 1218 (sp^2 C–O), 1029 (sp^3 C–O); nmr δ 0.98 (spike with a broad, high field shoulder, 9), 1.11 (s, 3), 3.96 (4.14 (AB quartet, 2, CH_2–O, J_{gem} = 11.5 Hz).

Anal. Calcd for $C_{17}H_{30}O_3$: C, 72.30; H, 10.71. Found: C, 72.50; H, 10.68.

Saponification of acetate **47b** with Claisen's alkali[45] regenerated diol **47a** in 95% yield. Attempted oxidation of acetate **47b** with CrO_3 in pyridine[36] led to virtually complete recovery of starting material.

Isolation of Nitrile 46 from Hydrolysis of Oximino Alcohol 35. A mixture of oximino alcohol **35** (0.60 g), acetone (15 ml), 95% ethanol (15 ml), and concentrated hydrochloric acid (1 ml) was refluxed for 70 hr. Evaporation, addition of water, and conventional work-up by ether extraction left a semisolid (0.50 g). Crystallization from ethyl acetate–hexane gave 0.08 g, mp 135–140°. Further crystallizations from ethyl acetate and a final sublimation (125–135° at 0.2 mm) afforded the analytical sample of **46**; mp 140–141.5°; ν (KBr) 3448 (sharp; intrabonded OH), 2232 (CN); nmr δ 0.92 (s, 3), 1.30 (s, 3), 1.62, 1.79 [each thick s, 3, C=C$(CH_3)_2$], 2.7–3.2 (m, 2, vicinal tertiary protons), 3.22 (s, 1, CH–O), 5.62 (d, 1, HC=C, J = 8Hz).

Anal. Calcd for $C_{15}H_{23}NO$: C, 77.20; H, 9.94. Found: C, 77.18; H, 9.94.

Sulfate Ester of α-Alcohol. α-Alcohol (0.5 g) was added slowly to fuming sulfuric acid (10.3 ml; 15–18% SO_3), which was cooled in Dry Ice. The red mixture stood overnight at room temperature, was heated on a steam bath for 1 hr, and when cool was poured onto ice. The mixture was made alkaline with dilute sodium hydroxide and was extracted with ether, work-up of which gave a red viscous oil (0.25 g). Chromatography over alumina (10 g, Woelm neutral grade I) gave some crystalline material preceded and followed by unidentified oils. The solid, in ether, was treated with charcoal and was crystallized from aqueous ethanol; mp 135–135.5°; nmr δ 0,89 (s, 3), 0.99 (s, 6), 1.06 (s, 3), 4.36 (s, 1, CH–O). It did not depress the melting point of, and its ir (KBr) was identical with, an authentic sample of α-alcohol sulfate (mp 137–138°).[33]

Acid Cyclization in Deuterated Medium. Anhydrous ether was shaken with D_2O and dried with $MgSO_4$. Caryophyllene (11.7 g) was slowly added (1 hr) to a solution of sulfuric acid-d_2 (30.3 g) in this ether (200 ml) cooled in an ice bath. After 2.5 hr in the cold, the mixture stood 46 hr at room temperature and was added to cold sodium hydroxide (55.1 g) in water (500 ml). Caryolanol and clovene were removed and the α-alcohol was isolated as reported.[5c,6] Crystallization from petroleum ether and sublimation gave mp 118–119°. Deuterium assay gave 2.75 (infrared[39]) 2.70, 2.76 (falling drop[46]) atom excess d. Mass spectral analysis gave 2% d_0, 14% d_1, 35% d_2, 23% d_3, 15% d_4, 7% d_5, 3% d_6, and 1% d_7 (total 2.74 d). In the 1395–1360 region of the ir and in the δ 0.8–1.1 region in the nmr the absorptions are identical in detail with those in natural abundance α-alcohol.

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