The Reactions of Singlet Oxygen and the Triphenyl Phosphite–Ozone Adduct with Germacrene

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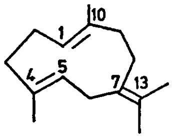
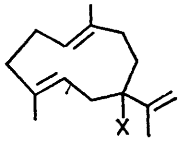
Summary In contrast to epoxidation, germacrene (**1**) reacts with $^1O_2$ at the exocyclic double bond faster than at the strained endocyclic double bonds, but with $(PhO)_3PO_3$, germacrene is attacked at the most strained double bond and forms an endocyclic allyl alcohol in contrast to the exocyclic isomers formed in the $^1O_2$ reaction.

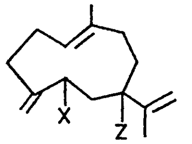
Previously we have shown[1] that oxidation of (**1**) with one mole of peracetic acid yields the 1,10-, 4,5-, and 7,13-monoxides in the ratio 30:70:2; these unexpected results have been rationalised on the basis of relief, in the transition state, of the sp^2–sp^2 torsional strain present in the endocyclic double bonds. The similar reactivity patterns in epoxidation and peroxidation have been noted previously,[2] and it has been suggested[3] that the formation of allylic hydroperoxides from olefins and singlet oxygen involves a perepoxide intermediate. If the singlet oxygen reaction involved the rate-determining formation of a perepoxide intermediate similar relative reactivities of the double bonds of (**1**) might be expected; in addition, possible internal nucleophilic attack on the perepoxide by the other endocyclic double bond could occur, so leading to cyclisation.[4]



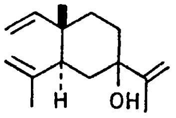
(1)



(2) X = OH
(3) X = O₂H



(4) X = Z = OH
(5) X = =O; Z = OH
(6) X = Z = O₂H



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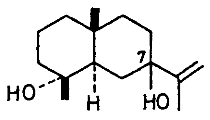
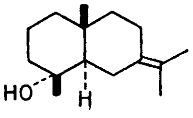
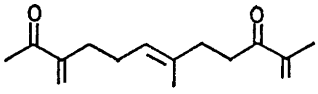


(8A,B)

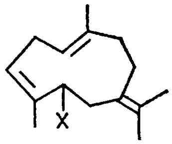


(9)

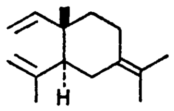
Reaction of (**1**) with singlet oxygen,† followed by sodium borohydride reduction of the reaction mixture gave the alcohols (**2**) [ν_{max} 3450, 900 cm^{-1}; τ ($CDCl_3$) 8·63 (s, 3H), 8·48 (s, 3H), 8·18 (s, 3H), 5·35 (s, 1H), 5·00 (s, 1H) and (**4**) [ν_{max} 3400, 900 cm^{-1}, τ ($CDCl_3$) 8·35 (s, 3H), 8·22 (s, 3H), 5·72 (m, 1H), 5·20—4·67 (5H)] characterised as its 3,5-dinitrobenzoate. The presence of a 1,5-diene system in (**2**) was established by pyrolysis to (**7**) [ν_{max} 900 cm^{-1}; τ ($CDCl_3$) 9·04 (s, 3H), 8·26 (s, 3H), 8·18 (s, 3H), 5·40 (m, 1H), 5·25 (m, 3H), 5·00 (m, 2H), 4·11 (dd, 1H, *J* 16 and 10 Hz)] and the structure confirmed by acid catalysed cyclisation of (**2**) to two isomeric diols (**8A**) [τ ($CDCl_3$) 9·18 (s, 3H), 9·02 (s, 3H), 8·24 (s, 3H), 5·35 (s, 1H), 5·08 (s, 1H)] and (**8B**) [τ ($CDCl_3$) 9·09 (s, 3H), 8·94 (s, 3H), 8·22 (s, 3H), 5·03 (m, 1H), 4·94 (s, 1H)] in a 9:1 ratio. That these isomers are epimeric at C-7 follows from their preparation (2:1 ratio) from (**9**)[5] by reaction with singlet oxygen followed by sodium borohydride reduction. Manganese dioxide oxidation of (**4**) gave (**5**) [λ_{max} (C_6H_{12}) 225 nm (ϵ 4600); ν_{max} 3400, 1670 cm^{-1}; τ (CCl_4) 8·42 (s, 3H), 8·22 (s, 3H), 7·53 (d, 1H, *J* 16 Hz), 7·10 (d, 1H, *J* 16 Hz), 5·25 (s, 1H), 5·22 (s, 1H), 4·80 (m, 1H), 4·73 (s, 1H), 4·67 (s, 1H)]. The AB quartet in the n.m.r. spectrum of (**5**) (confirmed by decoupling) excludes the alternative structure derived by reaction at the C-1–C-10 bond. Complete confirmation of structure (**5**) came from retro-aldolisation to (**10**) [λ_{max} (C_6H_{12}) 216 nm (ϵ 9750); ν_{max} 1680, 1620 cm^{-1}; τ ($CDCl_3$) 8·43 (s, 3H), 8·20 (s, 3H), 7·88 (s, 3H), 4·98 (t, 1H), 4·38 (s, 2H), 4·12 (s, 2H); M^+ 234], characterised as its bis-semicarbazone.



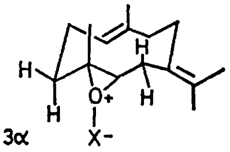
(10)



(11) X = OH
(12) X = OAc
(13) X = H



(14)



(15)

The total yield of (**2**) + (**4**) (*ca.* 50—60%) is fairly constant but the ratio (**2**):(**4**) varied from 3·2—0·6 with increasing time of reaction, implying that a major portion of (**6**) was derived by further reaction of (**3**) rather than by the reverse order of reaction. Crude measurements of $-d(\mathbf{1})/dt$

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† $^1O_2$ was produced using methylene blue as sensitiser.

and $-\mathrm{d}(\mathbf{2})/\mathrm{d}t$ (9:2) support this if it is accepted that the reactivity of the endocyclic double bonds of (**1**) are similar to those of (**2**). From the reaction of (**2**) with singlet oxygen the diol (**4**) (40%) could be isolated after reduction. To test whether the change of hybridisation at C-7 had altered the relative reactivities of the endocyclic double bonds, (**2**) was treated with one mole of peracetic acid. The monoxide mixture obtained could not be separated but acid-catalysed cyclisation showed it to consist of 48—71% of the 1,10- and 52—29% of the 4,5-monoxides, demonstrating a slight change in the relative reactivities.‡

The qualitative picture which emerges from these data is that the isopropylidene double bond of (**1**) is *ca.* 9 times more reactive than the endocyclic double bonds rather than the factor of *ca.* 30—50 expected[6] from comparison with unstrained models. This suggests that relief of sp^2–sp^2 torisional strain is a factor in this reaction but that it does not have the dominant effect observed in epoxidation. These results can be interpreted to favour an 'ene' mechanism but certainly do not establish it.

The triphenyl phosphite–ozone adduct has been shown to be a source of singlet oxygen[7] above −35°. It has also been established that the complex can react with some olefins below this temperature to give products identical to those obtained from singlet oxygen.[8] The triphenyl phosphite–ozone adduct reacts with (**1**) at −45°. After reduction of the reaction mixture with lithium aluminium hydride the alcohol (**11**) (50%) [$\nu_{\max}$ 3440 cm^{-1}; τ (CDCl$_3$) 8·32 (s, 12H), 5·0 (m, 2H)] was isolated and characterised as a crystalline 3,5-dinitrobenzoate. The alcohol (**11**) was converted into the acetate (**12**) which on reduction with lithium in ammonia yielded (**11**) (35%) and a mixture (28:38:34) (28%) of three hydrocarbons, the minor component being identified by g.l.c. as (**1**). This was confirmed by preparation of the palladium chloride complex of γ-elemene§ (**14**) from the mixture. The two remaining hydrocarbons were not rearranged by the treatment with palladium chloride–benzonitrile complex and this, coupled with the 1:1 ratio observed for the vinylic (τ 5·0) and bis-allylic (τ 7·3) protons suggested that these hydrocarbons had the constitution (**13**). The constitution of (**11**) was firmly established by ozonolysis followed by sodium borohydride reduction to give trimethylene glycol (21%).

We were unable to detect either of the products formed in the singlet oxygen–(**1**) reaction in the triphenyl phosphite–ozone peroxidation; thus both the predominant position of attack and the allyl system formed differ. The attack on the endocyclic double bond could be due to strain relief in the transition state or to increased hindrance to reaction at the exocyclic bond. However, the formation of an endocyclic allyl hydroperoxide (which is almost certainly more strained than the isomer with the exocyclic double bond) is more significant. An interpretation which accounts for the product is approach of the reagent from the less hindered sector of the double bond (*syn* to CH_2–H) and formation of an intermediate (**15**) containing a trivalent O atom with the third substituent *syn* to CH_2–H. If O inversion is slow¶ compared to further electrocyclic rearrangement then the geometrically most accessible hydrogen is 3α; the methyl hydrogens are completely inaccessible.

If the singlet oxygen reaction involves an intermediate perepoxide the rate of inversion of which is slow compared to further reaction then it is difficult to understand why with (**1**) and caryophyllene (strained *trans* double bond) no endocyclic isomers are formed while *cis*-caryophyllene yields only endocyclic isomers.[9] On the basis of an 'ene' mechanism these results are more readily interpretable.

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‡ The composition was based on the assumption that 1,10-oxides cyclise to bicyclo[4,4,0]decanes while the 4,5-oxide yields bicyclo-[5,3,0]decanes, see ref. 4.

§ This metal-catalysed Cope rearrangement occurs readily at room temperature.

¶ Analogy with the increased barriers observed for nitrogen inversion by bonding to an electronegative group and in aziridines suggest that this might be so.

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