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# Dimethyl Octamethyltricyclo[4.2.2.0$^{2,5}$]deca-3,7,9-triene-7,8-dicarboxylate (Cookson's Diester) Revisited: Cope Rearrangement and Epoxidation Site Selectivity

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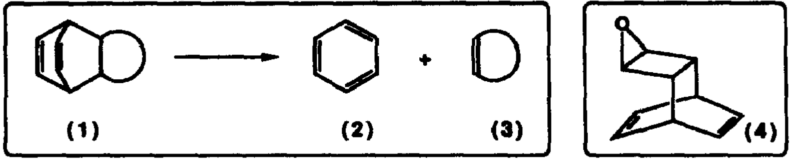
***Abstract:*** Dimethyl octamethyltricyclo[4.2.2.0$^{2,5}$]deca-3,7,9-triene-7,8-dicarboxylate (Cookson's diester) (**8**) is rearranged thermally *via* a double Cope reaction to its ring-degenerate isomer (**14**). The structure of diester (**8**) (indirectly) and the rearrangement product (14) (directly) are placed on an unequivocal base by X-Ray structure analysis. AM1 semi-empirical calculations support the preferential formation of (**8**) from the reaction of DMAD with transient intermediate diene (**7**). Epoxidation studies (mCPBA) have been conducted and firm site selectivities determined. A correction is made to an earlier report on the epoxidation selectivity of (**18**).

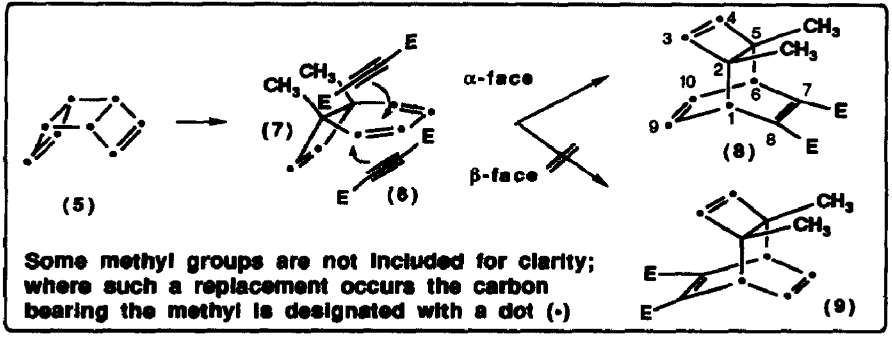
The retro Diels-Alder reaction is a recognised protocol for the thermal generation of strained olefins.[1a] In particular, the ejection of the unsaturated species (3) from 1,4-bridged benzenes (1) as outlined in Scheme 1 is especially facile as it is driven by the formation of an aromatic species (2) as co-product.[1b] Thus, in searching for a precursor suitable for the thermal generation of Dewar furans[2] we were attracted to cyclobutene epoxides of type (4) as a possible substrate. For this reason we investigated the epoxidation of Cookson's diester (**8**) as a route to tetramethyl Dewar furan and this is the topic of the present communication.



**Scheme 1:** *The retrodiene cleavage of 1,4-substituted benzenes as a thermal route to olefins*

Cookson's diester is prepared by heating dimethyl acetylenedicarboxylate (6) (DMAD) with tetramethylcyclobutadiene dimer (5) and the reaction is presumed to involve prior ring-opening of (5) to the bicyclo [4.2.0]octadiene (7) which serves as the diene for addition of the dienophile.[3] Two Diels-Alder adducts are formally possible depending on the $\pi$-facial selectivity of cycloaddition to the diene: addition of DMAD from the methyl-screened face (route a) yielding (8); addition of DMAD from the cyclobutene-screened face (route b) yielding (9) (Scheme 2). Cookson formulated the product as (8) although no evidence was given for the preference of this structure over the isomer (9).[4]

We were curious about which facial selectivity prevailed in the cycloaddition of DMAD to diene (7) since approach from either face is sterically restricted and it is not clear from an inspection of molecular models which would be preferred. We have addressed the specificity from a theoretical viewpoint by calculating the energy of the transition state for each approach at the AM1 semi-empirical level of theory.[5] The calculations gave an energy difference of 2.68 kcalmol$^{-1}$ in favour of the Cookson structure (8).[6]

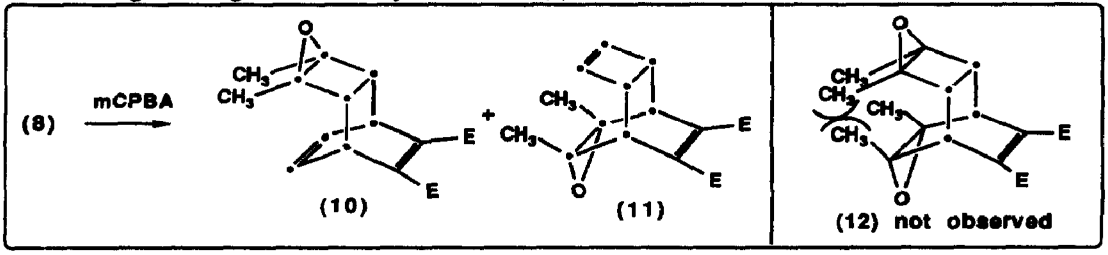


**Some methyl groups are not included for clarity; where such a replacement occurs the carbon bearing the methyl is designated with a dot (•)**

**Scheme 2:** *Facial selectivity in the cycloaddition of diene (5) with DMAD (6)*

Treatment of Cookson's diester with mCPBA yields a mixture of two mono epoxides: major isomer, 63% yield, m.p. 145-146 °C, $^{1}H$ nmr $\delta$ 0.92, 1.26, 1.31, 1.60, 4xC-$CH_3$, 3.69, O-$CH_3$ ; minor isomer, 36% yield, m.p. 114-115 °C, $^{1}H$ nmr $\delta$ 0.88, 1.21, 1.46, 1.84, 4xC-$CH_3$, 3.68 O-$CH_3$ (Scheme 3).[7] These $^{1}H$ nmr data confirmed the $C_2$-symmetry of each product but were not diagnostic for either structure.[8] Mass spectrometry was more helpful as the base peak in the spectrum of the major isomer occurred at *m/z* 108 corresponding to loss of tetramethylcyclobutadiene while in the minor isomer it occurred at *m/z* 124 corresponding to loss of tetramethyl Dewar furan. This located the epoxide at the cyclobutene site and supported structure (10) for the minor epoxide. The major epoxide is therefore assigned structure (11) where attack has occurred at the external face of the $\Delta^{9,10}$ $\pi$-bond of Cookson's diester (8). No attack occurs on the electron-deficient, ester-substituted $\pi$-bond in this or any of the following epoxidation reactions.

This interpretation was confirmed by the results from a single crystal X-Ray structure determination on monoepoxide (10) (Fig. 1a).[9] This shows that the epoxide is outward facing and attached to the cyclobutane ring. Further, the cyclobutane bears an *anti*-relationship with the ester-substituted $\pi$-bond which thereby confirms the original assignment made by Cookson as (8).



**Scheme 3:** *Epoxidation of Cookson's diester (8) with mCPBA*

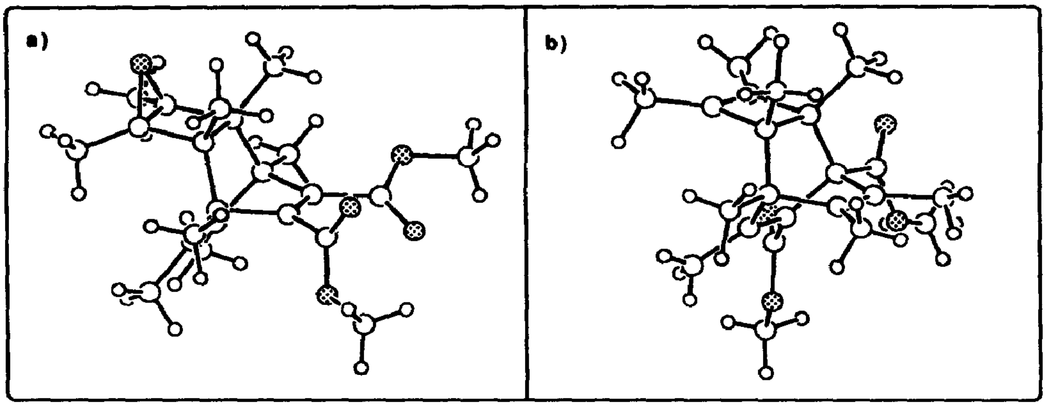
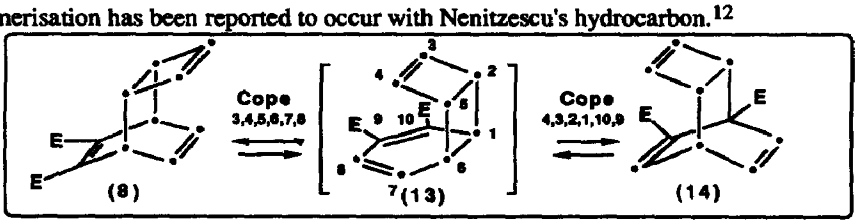


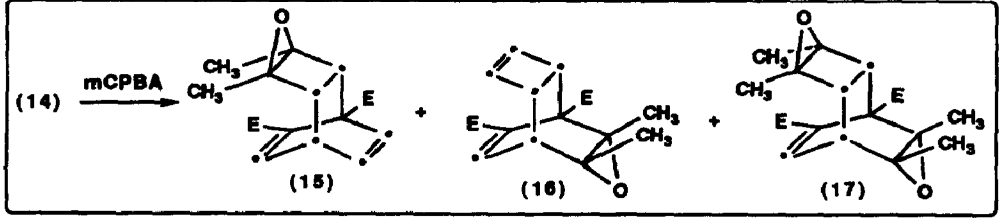
Fig 1. Molecular structures of a) the monoepoxide (**10**) and b) the rearranged ester (**14**) as determined by single crystal X-Ray structure analysis.

Cookson's diester is thermally rearranged[10] to an isomer which $^1H$ n.m.r shows no longer retains $C_2$-symmetry.[11] The structure of the new isomer was determined by X-Ray techniques (Fig. 1b)[9] and shown to have the same carbon skeleton as Cookson's diester, however the substituents were unsymmetrically positioned. Formation of (**14**) is rationalised by the double Cope rearrangement shown in Scheme 4. An analogous isomerisation has been reported to occur with Nenitzescu's hydrocarbon.[12]



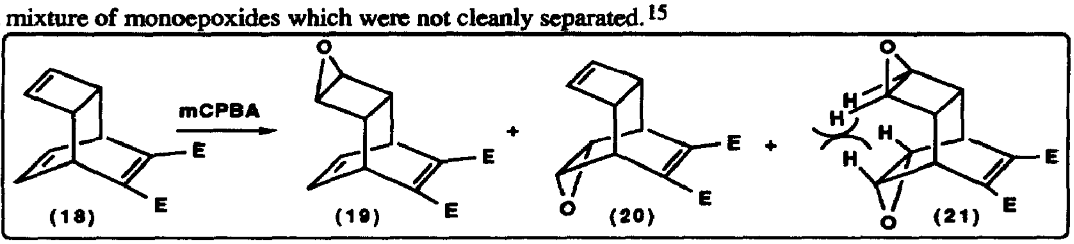
**Scheme 4:** *Cope rearrangement of Cookson's diester (8) to rearranged diester (14)*

Epoxidation of rearranged diester (**14**) with mCPBA produces a mixture of two monoepoxides as well as a bisepoxide. Separate experiments show that the bisepoxide is formed by further epoxidation of either monoepoxide. The epoxidation assignments are again dependant upon mass spectrometry results: the major epoxide (**15**) showing a base peak at *m/z* 124 corresponding to loss of tetramethyl Dewar furan. The fact that the rearranged isomer (**14**) forms a bisepoxide while Cookson's diester does not, is indicative of the prohibitive steric interaction between the two sets of methyl substituents when forced into the cavity between *syn*-related epoxides, cf. (**12**). The transoid relationship of the two epoxide functionalities in (**17**) avoids this.



**Scheme 5:** *Site selectivity in the epoxidation (mCPBA) of rearranged diester (14)*

Epoxidation of Nenitzescu's diester (**18**) was also studied under the mCPBA conditions. Here again two mono epoxides and a bisepoxide were produced. The major epoxide (60%, m.p. 101-102°C) was assigned the cyclobutene epoxide structure (**19**)[13]; the minor epoxide (21%, m.p 63-64 °C) was assigned structure (**20**) and the bisepoxide (18%, m.p. 158-159 °C) structure (**21**). It is apparent that H,H interaction in the cavity between the *syn*-related epoxides is not nearly as severe as Me,Me interaction and so bisepoxidation is possible. An earlier report[14] on the epoxidation of (**18**) using monoperphthalic acid suggested that only the cyclobutene epoxide (**19**) was formed. The low m.p. reported for their product (m.p. 96 °C) indicates that it may have been a mixture of monoepoxides which were not cleanly separated.[15]



**Scheme 6:** *Site selectivity in the epoxidation (mCPBA) of Nenitzescu's diester (18)*

## References and Notes

1. a) Ripoll, J.L.; Rouessac, A.; Rouessac, F. *Tetrahedron*, **1978**, *34*, 19. Kwart, H.; King, K.; *Chem. Rev.* **1968**, *68*, 415.
   b) Recent applications of retro Diels-Alder reaction include, *inter alia*, Gilchrist, T.L.; Wood, J.E.: *J. Chem. Soc. Perkin Trans 1*, **1992**, 9. Kimura, K.; Murata, K.; Otsuka, K.; Ishizuka, T.; Haratake, M.; Kunieda, T. *Tetrahedron Lett.* **1992**, *33*, 4461.
2. R.N.Warrener in "Advances in Theoretically Interesting Molecules" Vol 2, R.P. Thummel Ed., JAI Press Inc., Greenwich, Connecticut, 1992, pp 143-205.
3. Berkoff, C.E.; Cookson, R.C.; Hudec, J.; Williams, R.O. *Proc. Chem. Soc. (London)* **1961**, 312.
4. Thermal decomposition to dimethyl 3,4,5,6-tetramethyl phthalate was cited in support of the structure,[3] but this does not distinguish between these stereoisomers, nor in fact from (**14**).
5. Dewar, M.J.S.; Zoebisch, E.G.; Healy, E.F.; Stewart, J.J.P. *J. Amer. Chem. Soc.* **1985**, *107*, 3902.
6. Transition States were located using the Linear Synchronous Transit Method contained within the SPARTAN Molecular modelling package, and were rigorously shown to be maxima on the energy surface by the possession of exactly one imaginary frequency of vibration.
7. All compounds showed correct CH analytical data (± 0.4%). Physical properties of new compounds: (number of compound), m.p., yield: (**10**), 114-115°C, 36%; (**11**), 145-146°C, 63%; (**12**), 131-132°C, 60-80%; (**15**), 143-145°C, 72%; (**16**), 151-152°C, 21%; (**17**), 160-161°C, 7%; (**19**), 101-102°C (lit[10] 96°C), 60%; (**20**), 63-64°C, 21%; (**21**), 158-159°C, 18%.
8. Lack of proton coupling data and the similarity of methyl group chemical shifts makes stereochemical or even structural assignments difficult in these permethylated compounds.
9. Molecular structure the monoepoxide (**10**): monoclinic, space group $P2_1/c$, $a = 14.754(3)$, $b = 8.602(3)$, $c = 15.829(3)$ Å, $\beta = 102.05(1)^\circ$, $R = 0.043$ for 2411 observed data. Molecular structure of the rearranged diester (**14**): monoclinic, space group $P2_1/c$, $a = 16.013(6)$, $b = 7.597(3)$, $c = 17.059(7)$ Å, $\beta = 114.69(2)^\circ$, $R = 0.068$ for 1724 observed data.
10. Heating Cookson's diester (**8**) as a melt at 330-350°C or FVP at 470°C gives a 1:2 equilibrium mixture of (**11**):(**14**) plus some dimethyl 3,4,5,6-tetramethylphthalate.
11. Compound (**14**), m.p. 131-132 °C: $^1H$ n.m.r. ($CDCl_3$,TMS) : δ 0.84, s, 3H; 1.29, s, 3H; 1.39, q, *J* 1.3 Hz, 3H; 1.52, q, *J* 1.3 Hz, 3H; 1.64, q, *J* 1.2 Hz, 3H; 1.71, q, *J* 1.2 Hz, 3H; 1.92, s, 3H; 3.66, s, 6H.
12. Dinulescu, I.G.; Georgescu, E.G.; Stanescu, L.; Avram, M. *Tetrahedron Suppl.* **1980**, *47*, 55. Westberg, E.E.; Cain, E. N.; Masamune, S. *J. Amer. Chem. Soc.*, **1969**, *91*, 7512.
13. This assignment is supported by FVP studies which yield $C_4H_4O$ products together with dimethyl phthalate (see reference 2 for specific references)
14. Kozmin, A.S.; Yureva, N.M.; Kirin, V.N.; Bylina, G.S.; Luzikov, Yu.N.; Moiseenkov, A.M. *Zh. Org. Khim.* **1983**, *19*, 1543 (*J. Org. Chem. USSR* **1983**, 1390)
15. We have not repeated their reaction to confirm this premise, although we find that recrystallisation alone does not separate epoxides (**19**) and (**20**) and repeated chromatography (silica, radial chromatography, 5-15% EtAc in hexane) is required to obtain pure samples.

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