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CYCLIC POLYEPOXIDES

SYNTHETIC, STRUCTURAL AND BIOLOGICAL ASPECTS†

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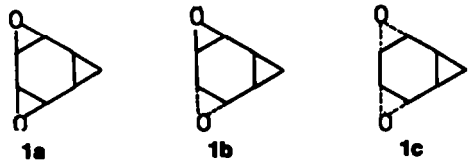
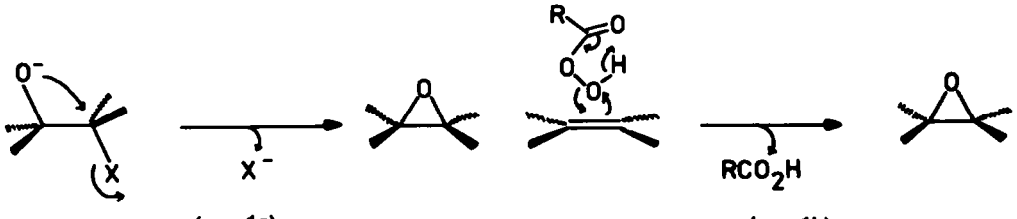
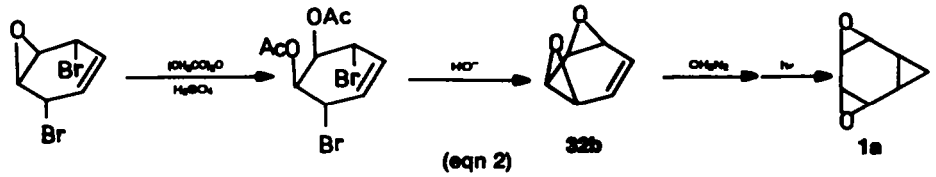
INTRODUCTION

Let us illustrate our title with a concrete example, namely the three stereoisomeric norcaradiene diepoxides 1a–c. Besides the intriguing structural features that these fascinating molecules portray, our example permits us to introduce the synthetic methodology that has become available for their stereospecific preparation and convey their biological importance.





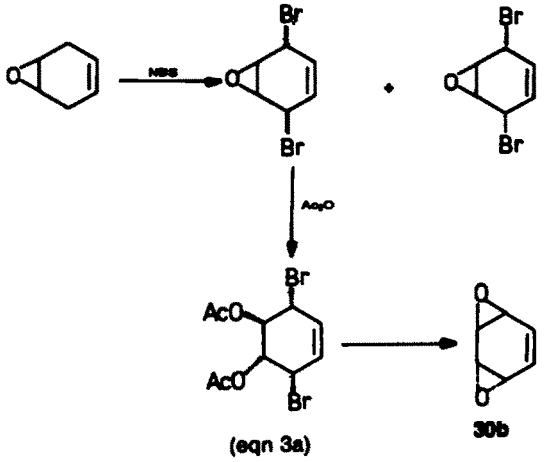
(eqn 1a) (eqn 1b)



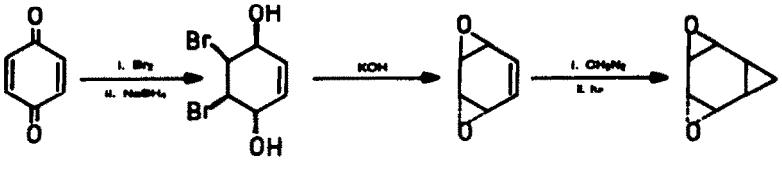
(eqn 2) 32b 1a

†This article is dedicated to Prof. Dr. Emanuel Vogel of the University of Cologne in appreciation for his pioneering contributions in this field.
‡NIH Career Awardee, 1975–80.

For the stereoisomers **1a** and **1b** the classical epoxide synthesis (eqn 1)[1] was utilized, consisting of either base-catalyzed nucleophicic cyclization of *trans*-halohydrins or their derivatives (eqn 1a) and/or peracid epoxidation of olefins (eqn 1b). For example, the all *syn*-isomer **1a** was obtained according to the synthetic sequence outlined in eqn (2).[2,3] Of course, the dibromo-epoxide starting material in eqn (2) was obtained by peracid epoxidation of 1,4-cyclohexadiene, followed by NBS bromination of the mono-epoxide.[4] The stereoisomer **1b** was first prepared in an analogous manner (eqn 3a)[3] and more recently substantially simplified and improved (eqn 3b).[5]



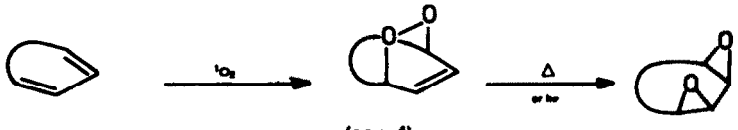
(eqn 3a)



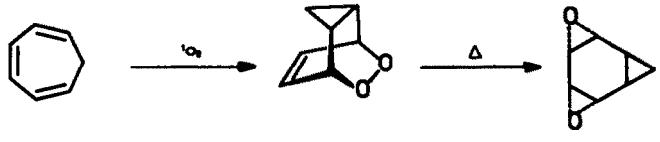
30b (1b

(eqn 3b)

The third isomer **1c** was recently prepared via an entirely different synthetic strategy, whose basic transformations are outlined in eqn (4). Thus, singlet oxygenation of the conjugated cyclodiene and thermal or photochemical rearrangement of the intermediary endoperoxide affords the diepoxide conveniently and efficiently.[6] This stereospecific route must lead to the *syn* arrangement of the epoxide rings. Thus, singlet oxygenation of 1,3,5-cycloheptatriene afforded 3.5% of the norcaradiene endo-peroxide, which heated at 100° rearranged quantitatively to the diepoxide stereoisomer **1c** (eqn 5).[7]



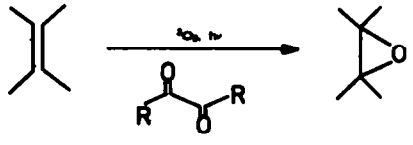
(eqn 4)



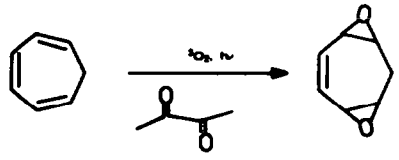
1c

(eqn 5)

Another potentially promising preparative method for polyepoxides is the novel photosensitized oxidation of olefins (eqn 6).[8] Possibly the formation of the diepoxide 2 in the photosensitized oxidation of 1,3,5-cycloheptatriene (eqn 7)[9] may have occurred in this way.



(eqn 6)



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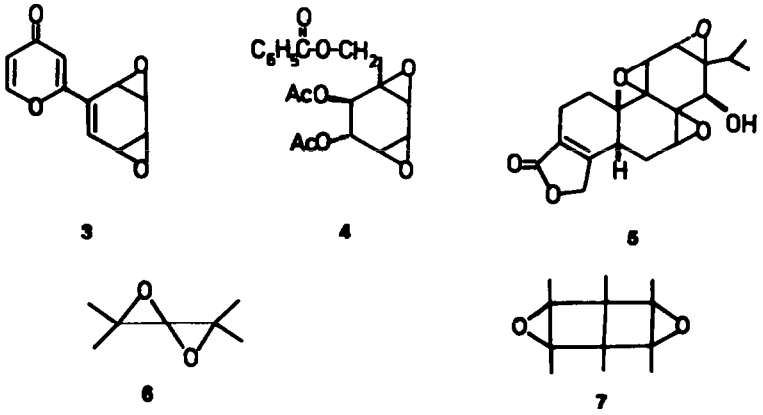


3 4 5

6 7

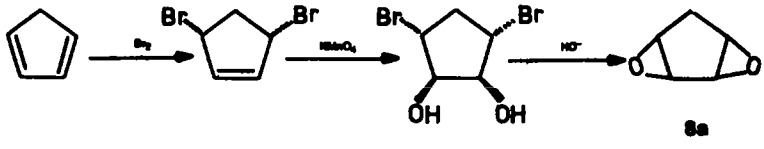
(eqn 7)

From the few examples cited above, mentioned merely to serve as an appetizer, the synthetic challenge and structural uniqueness and novelty of polyepoxides should be quite obvious. However, still more significant and valuable are their biological involvement. To illustrate their diverse cytotoxic nature, we single out for the time being the antimicrobial LL-Z1220 3,[10] isolated from culture filtrate of undertermined fungal species, the carcinoma-inhibiting crotepoxide 4,[11] isolated from the fruit of the plant *Croton macrostachys* and from the leaves and stem of *Piper futokadzura*, and the antileukemic triptolide 5,[12] isolated from an alcoholic extract of *Tripterygium wilfordii* Hook F. Clearly these natural products are of great pharmacological value.

In view of the structural diversity, synthetic challenge, and biological importance inherent with the polyepoxides, we decided to write this comprehensive but critical report. We have limited ourselves to those systems which at least formally are derived from the conjugated cyclic polyenes. Spiro systems 6, formally derived from cumulated polyenes,[13] or polyepoxides 7 derived formally from isolated cyclic polyenes,[14] will not be specifically covered. We commence with the cyclopentane diepoxides.

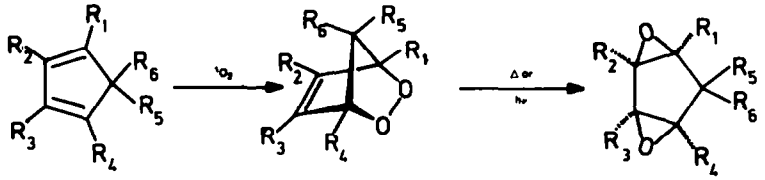
Cyclopentane diepoxides

The *syn* isomer 8 of the parent skeleton was made[15] by the classical method (eqn 8), utilizing the dibromo diol as precursor.[16] In view of the appreciable ring strain, ring opening reactions of **8a** take place readily. Alternatively, the parent diepoxide **8a** could be made by the thermal endoperoxide-diepoxide rearrangement (eqn 9), affording necessarily the *syn* isomer, but in low yield.[17] The endoperoxide precursor **9a** was first prepared by Schenck and Dunlap[18] and fully characterized. Similarly, the substituted endoperoxides **9b–h** were photo-isomerized into the substituted diepoxides **8b–h** in high yields.[19]



8a

(eqn 8)

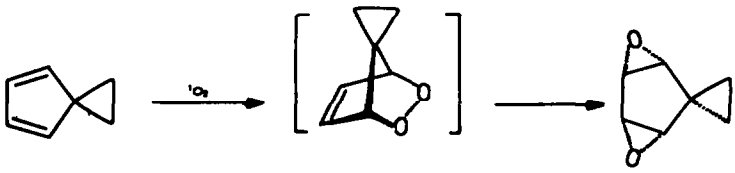


9 8

a: R_{1-6} = H (7%)
b: $R_{1,2}$ = C_6H_5; $R_{3,5,6}$ = H, R_4 = CH_3 (60%)
c: $R_{1,2}$ = C_6H_5; $R_{3,5,6}$ = H, R_4 = COOH (10%)
d: $R_{1,2}$ = C_6H_5; $R_{3,5,6}$ = H, R_4 = CO_2Me (70%)
e: R_{1-4} = C_6H_5; $R_{5,6}$ = H (95%)
f: R_{1-4} = C_6H_5; R_5 = H; R_6 = C_2H_5 (83%)
g: R_{1-5} = C_6H_5; R_6 = H (70%)
h: R_{1-5} = C_6H_5; R_6 = CH_3 (60%)

(eqn 9)

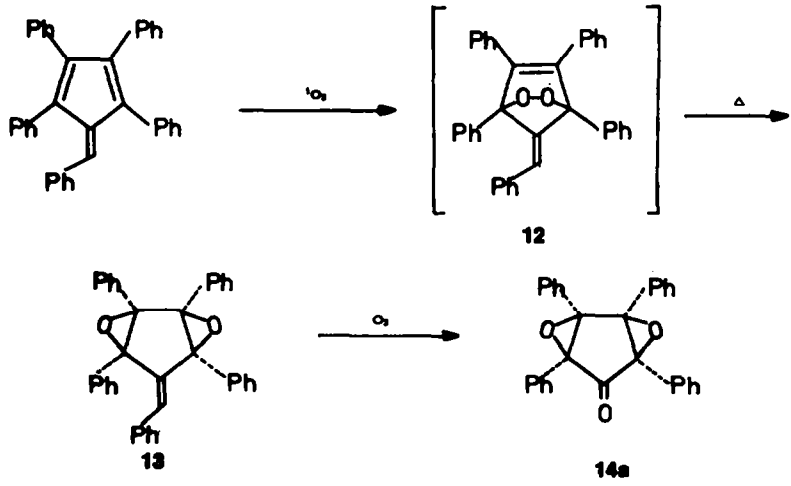
Photooxygenation of the spirocyclopentadiene at 0–5° in $CHCl_3$ gave the rather unstable endoperoxide **10**, which rearranged *in situ* to the interesting diepoxide **11** (eqn 10),[20] isolated in 48% yield. Photooxygenation at room temperature did not lead to the desired diepoxide **11**.



10 11

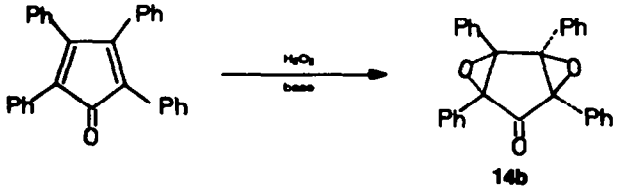
(eqn 10)

Fulvenes have been favorite substrates for singlet oxygenation,[21] but except for the pentaphenyl derivative (eqn 11a), the endoperoxides **12** did not lead to the corresponding diepoxides **13**.[22] Complex rearrangement products were observed instead, which implicate the intervention of the endoperoxide **12**.



12 13 14a

(eqn 11a)



14b

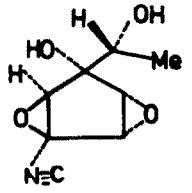
(eqn 11b)

By ozonolysis the fulvene diepoxide **13** could be converted to the cyclopentadienone diepoxide **14a**.[23] The correspondir g endoperoxide was claimed in the enzymic oxygenation of the dienone,[24] but had to be retracted.[25] The *anti*-isomer **14b** was prepared as shown in eqn (11b).[24]

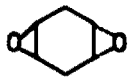
The amazing fungal metabolite trichoveridine **15** was isolated from the culture filtrate of *Trichodema sp.*, and determined to possess the diepoxide structure of a five-membered ring skeleton with an isocyanide functionality.[26] The *anti* configuration of the two epoxide rings clearly implies that its metabolic history must involve the classical pathway rather than an endoperoxide–diepoxide rearrangement. No other natural products containing the cyclopentane diepoxide structure appear to be reported.

Cyclohexane systems

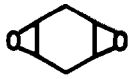
Diepoxides. One of the earliest cyclic diepoxides to be characterized was the *anti* isomer **16a**, prepared by peracid epoxidation[27] of 1,3-cyclohexadiene (eqn 12). The *syn* isomer **16b** was observed via the endoperoxide–diepoxide transformation (eqn 13), either by heating or by irradiation at 366 nm.[28]



15



17a



17b

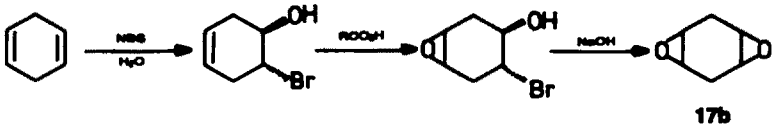
16a

(eqn 12)

16b

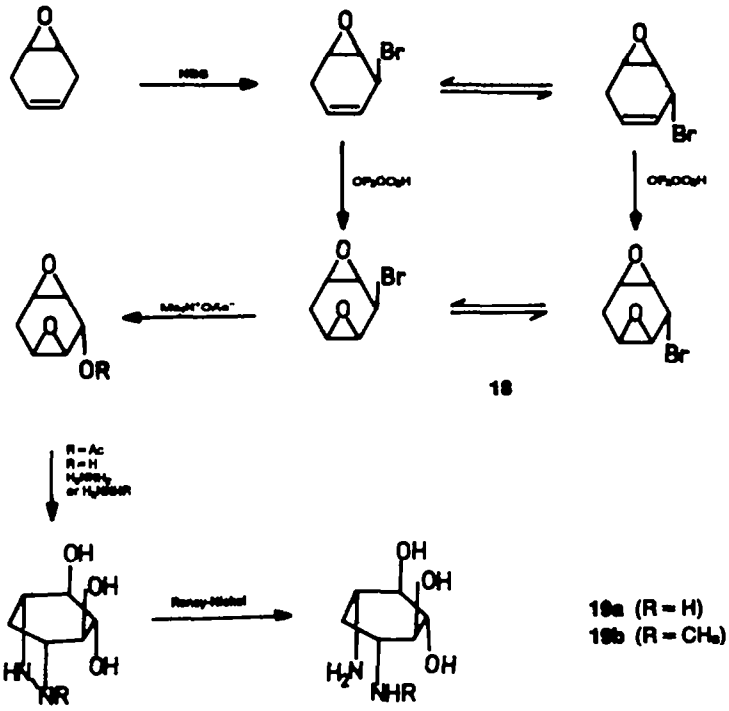
(eqn 13)

Of interest are the structurally related diepoxide isomers **17a** and **17b** since they serve as valuable synthons for the preparation of antibiotics. Thus, peracid epoxidation of 1,4-cyclohexadiene affords a mixture of **17a** and **17b**, from which the *anti* isomer **17a** could be isolated and characterized.[29] Apparently the *syn* isomer **17b** is too labile and difficult to isolate. However, via the classical route (eqn 14) it was possible to obtain it.[29b] As expected the *anti* isomer **17a** has a zero dipole moment, while the *syn* isomer has a $\mu = 3.8$D.[29b]



17b

(eqn 14)

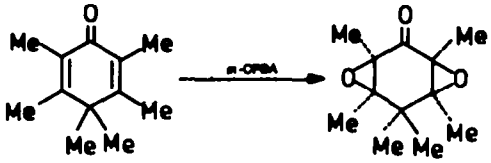


18

19a (R = H)
19b (R = CH_3)

(eqn 15)

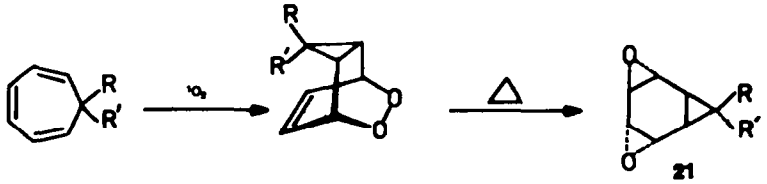
Prinzbach *et al.*[30] employed this synthetic methodology for the preparation of derivatives of streptamin and hyosamin antibiotics in which the bromodiepoxide *syn* isomer **18** served as synthon (eqn 15). Structure **19a** represents 2-desoxystreptamin and **19b** (±)-hyosamin. Clearly, the synthetic convenience of these diepoxides in fixing the complex stereochemistry is of great preparative value in natural product chemistry.



20

(eqn 16)

A synthetically intriguing example is the functionalized diepoxide **20**, prepared by peracid epoxidation of the corresponding dienone (eqn 16).[31] What is unusual in this example is that normally conjugated enones resist epoxidation by peracids.



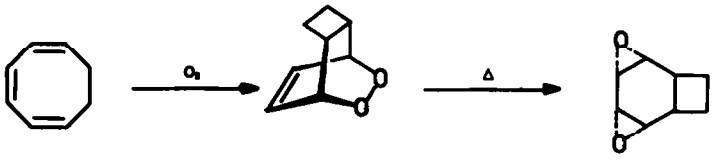
21

	Literature
a: R = H; R′ = CO_2Me	32a
b: R = H; R′ = CN	32b, c
c: R = CN; R′ = H	32c
d: R = Ph; R′ = H	32d
e: R = CHO; R′ = H	32d
f: R = CH_3; R′ = H	32e

(eqn 17)

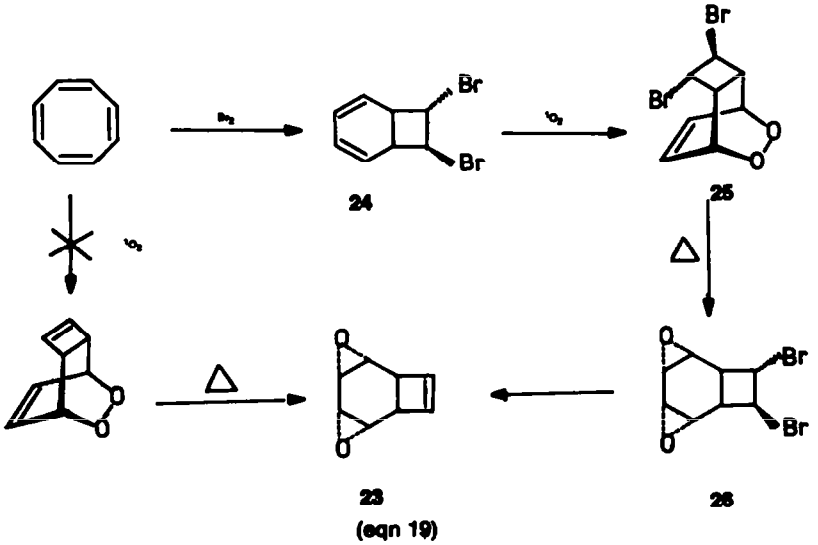
In the Introduction we mentioned already the structurally more complex isomeric norcaradiene diepoxides 1a–c, in order to set the stage. Furthermore, a number of substituted derivatives 21 have been prepared via the endoperoxide–diepoxide rearrangement (eqn 17).[32] Structurally these norcaradiene dipoxides 21 are extremely interesting because the isomers with the *anti* configuration of the epoxide rings with respect to the cyclopropane ring possess a locked-in planar cyclohexane conformation, as suggested by inspection of Dreiding models. X-ray analysis of the carbomethoxy (21a)[32a] and cyano (21b)[36b] have confirmed these structural features.[32c,d]

The structurally related cyclohexane diepoxide 22 with an annexed cyclobutane ring was prepared by singlet oxygenation of 1,3,5-cyclooctatriene and thermal isomerization of the stable endoperoxide (eqn 18).[33] Unfortunately cyclooctatetraene is inert towards singlet oxygenation[34] so that the potentially valuable diepoxide 23 cannot be prepared via the synthetic sequence of eqn (18). However, in the singlet oxygenation of the dibromide 24, prepared from cyclooctatetraene by bromine addition, the diepoxide 26 was reported as side product (eqn 19).[35] We confirmed[36] that it was derived from the endoperoxide 25 by thermal rearrangement. Debromination of 26 is presently being attempted as a convenient route to the hitherto unknown diepoxide 23 (eqn 19),[36] thereby circumventing the lack of reactivity of cyclooctateraene towards singlet oxygen.



22

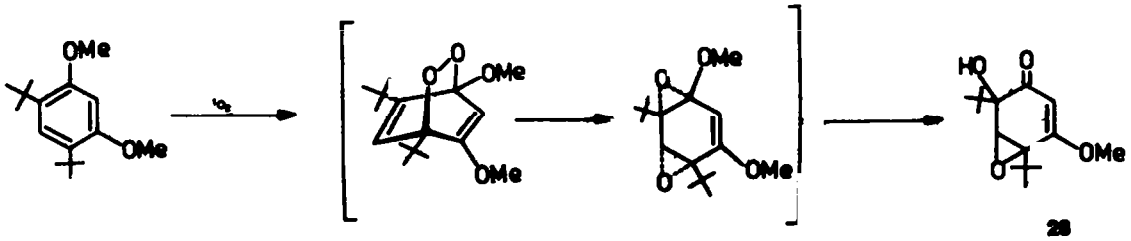
(eqn 18)



24 25 23 26

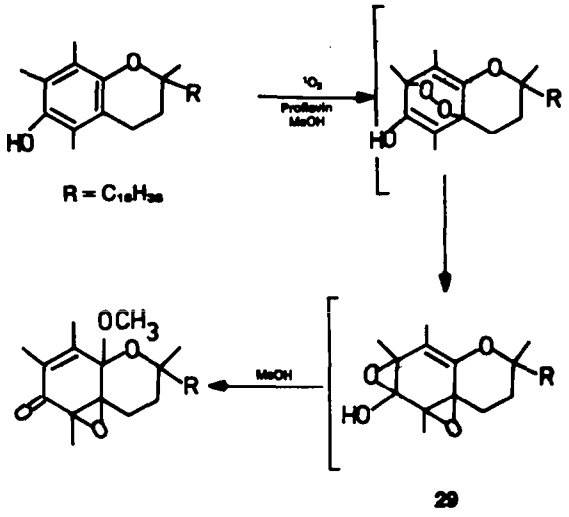
(eqn 19)

Normally benzene derivatives are also inert towards singlet oxygen. When highly substituted with electron donors, e.g. 1,3-di-t-butyl-4,6-dimethoxybenzene, then singlet oxygenation does take place leading to the labile endoperoxide 27 (eqn 20).[37] The latter rearranges *in situ* to the epoxy-enone 28, presumably via the unstable diepoxide.

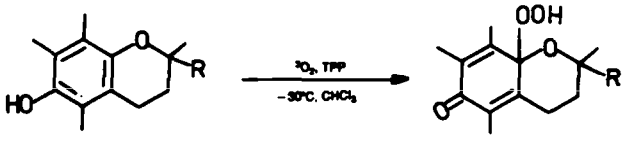


27 28

(eqn 20)



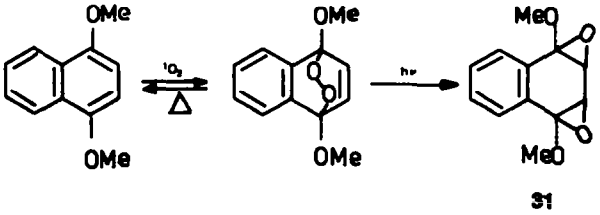
(eqn 21a)



(eqn 21b)

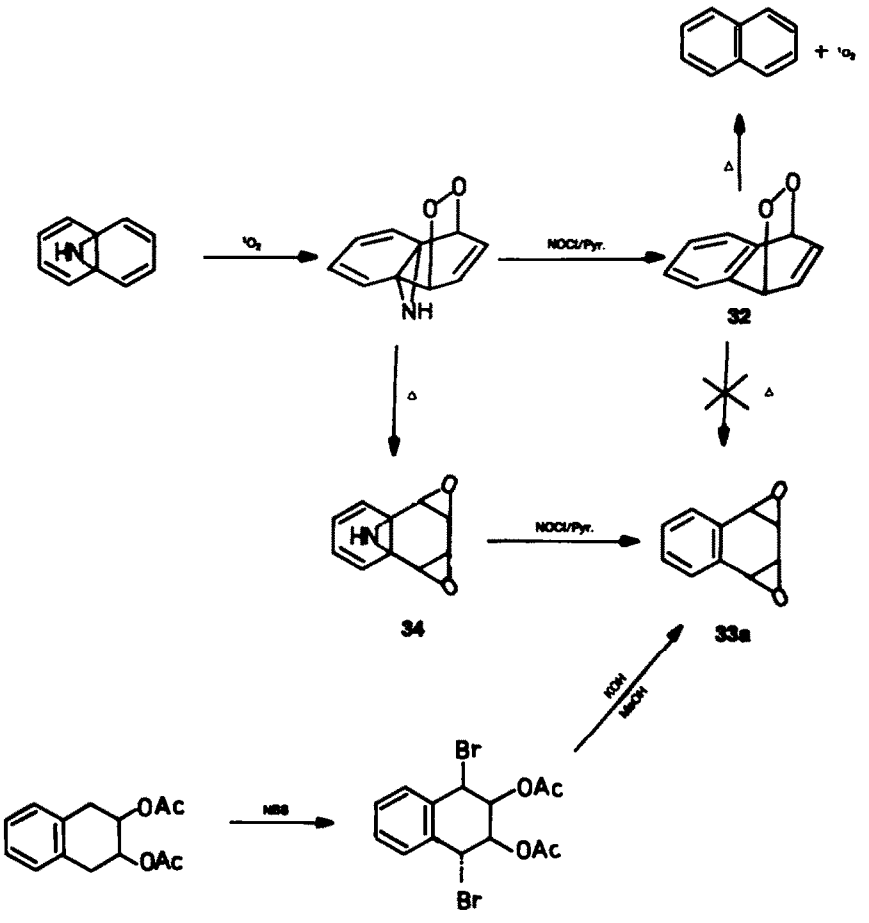
30a 30b

Furthermore, in the photooxygenation of α-tocopherol (Vitamin E) the benzene diepoxide **29** has been postulated as intermediate (eqn 21)[38a] However, very recently Foote *et al.*[38b] reexamined the photooxygenation of tocopherol more carefully and showed that the hydroperoxyenone in eqn (21b) was the precursor to the final products rather than the benzene diepoxide **29** in eqn (21a). Yet, as we have already stated in the Introduction, the isomeric benzene diepoxides **30a** and **30b**, the precursors to the isomeric norcaradiene diepoxides **1a** (eqn 2) and **1b** (eqn 3), respectively, can be prepared by classical methods, circumventing the necessity of singlet oxygenation of the unreactive benzene.



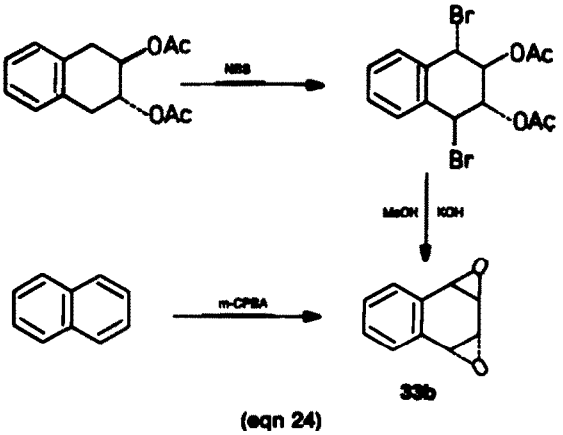
(eqn 22)

Naphthalenes are considerably more reactive towards singlet oxygen. Thus, the 1,4-dimethoxynaphthalene affords the expected endoperoxide which on photolysis is cleanly transformed into the naphthalene diepoxide **31** (eqn 22).[39] On heating, on the other hand, the endoperoxide reverts to starting material rather than rearranging into the diepoxide **31**. Similar observations have been made with methylated naphthalene.[40] Also Vogel *et al.* showed[41] that the parent naphthalene endoperoxide **32** gave naphthalene and $^1O_2$ on heating (eqn 23), rather than the desired *syn* naphthalene diepoxide **33a**. All that was necessary was to reverse the timing in releasing the imino vise. Thus, when the imino endoperoxide was first isomerized thermally into its imino-diepoxide **34**, nitrogen extrusion led to the desired **33a** (eqn 23).[42]



(eqn 23)

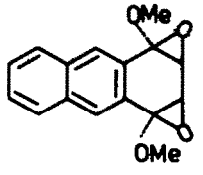
Analogous to the *syn*-isomer **33a** (eqn 23), the naphthalene *anti*-diepoxide **33b** could be prepared in 1–2% yield via the classical method shown in eqn (24).[42] Surprisingly, under appropriate conditions naphthalene is directly converted into its *anti*-diepoxide **33b** by treatment with *m*-chloroperbenzoic acid (eqn 24).[43] Obviously, this synthetic convenience opens up new vistas for the preparation of aromatic diepoxides.



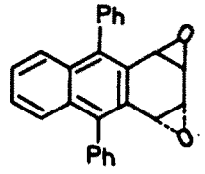
(eqn 24)

In the anthracene series the *syn*-1,4-diepoxide **35a** was prepared by singlet oxygenation of 1,4-dimethoxyanthracene and thermal rearrangement of the 1,4-endoperoxide,[39a,44] while the *anti*-diepoxide **35b** was conveniently prepared by direct epoxidation of 9,10-diphenylanthracene with *m*-chloroperbenzoic acid.[43] In the case of 9,10-endoperoxides **36**, thermolysis or photolysis leads to the unstable anthracene diepoxides **37** which suffer deep-seated further rearrangements (eqn 25). However, with

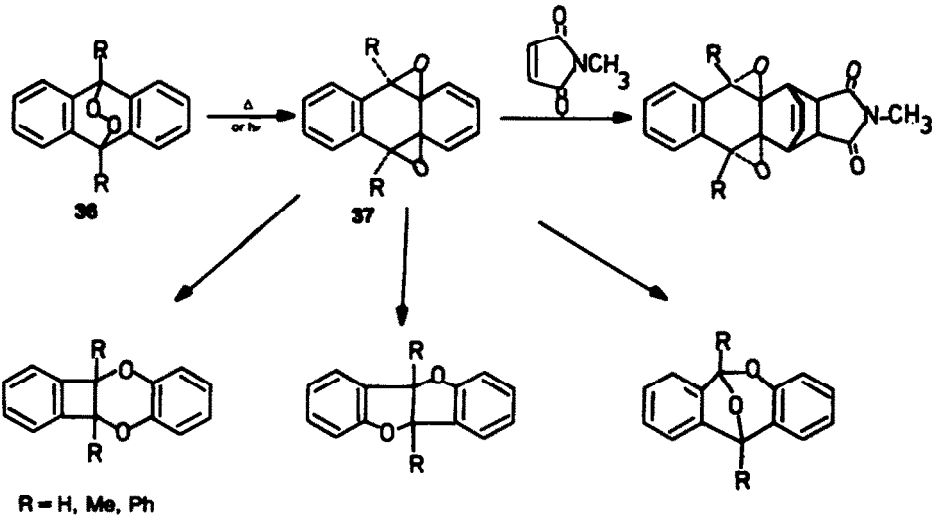
N-methylmaleimide the transient diepoxides **37** could be trapped.[45] A similar fate was suffered by the naphthacene diepoxide **38** and the benzanthracene dieopxide **39**, intermediates derived from the thermolysis[46] and photolysis[47] of the respective endoperoxides.



35a



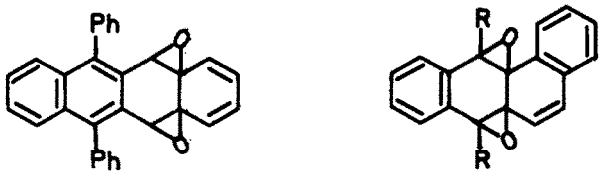
35b



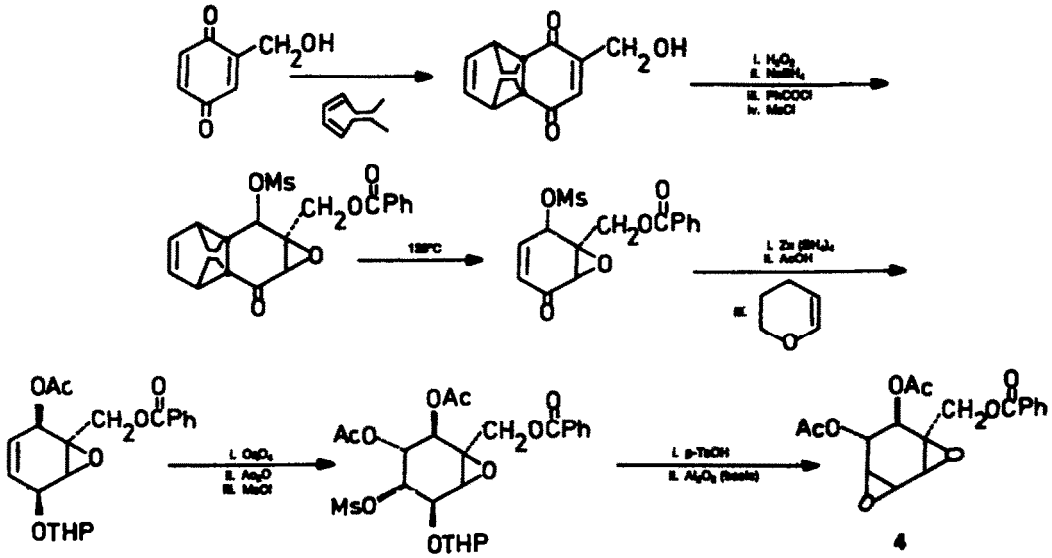
36 **37**

R = H, Me, Ph

(eqn 25)

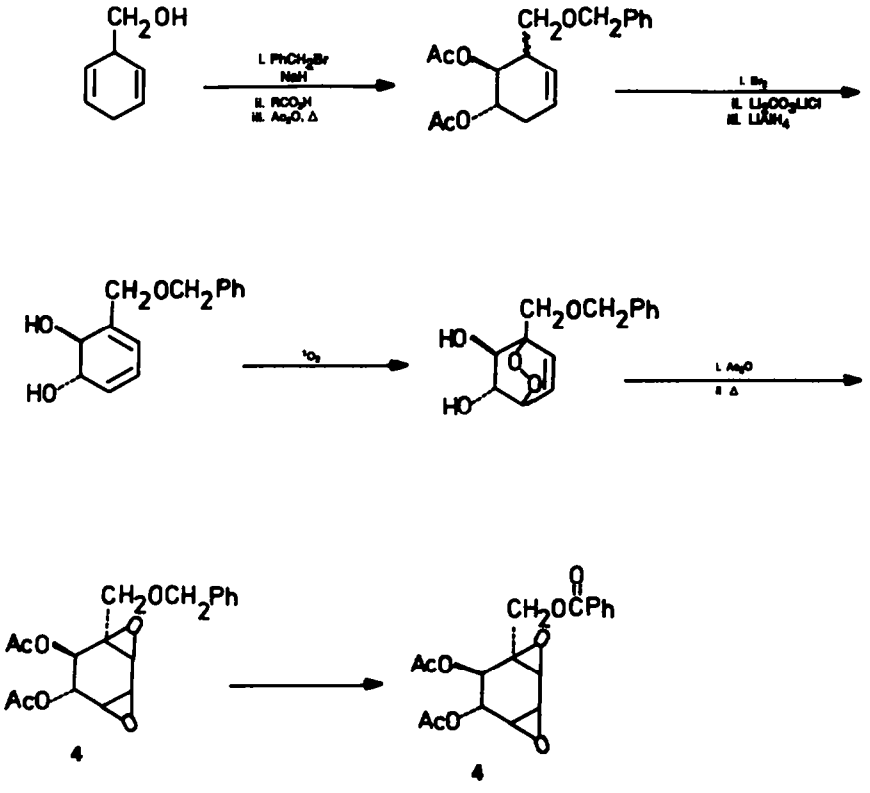


38 **39**

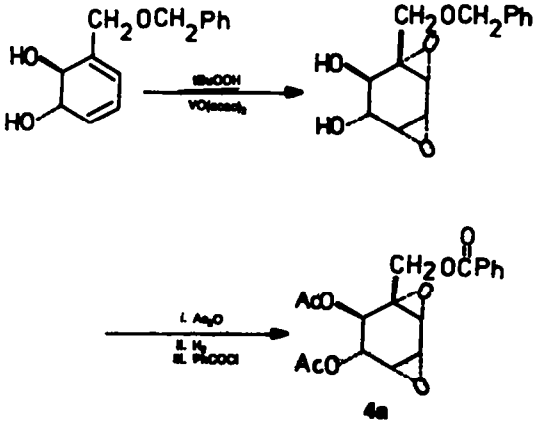


(eqn 26)

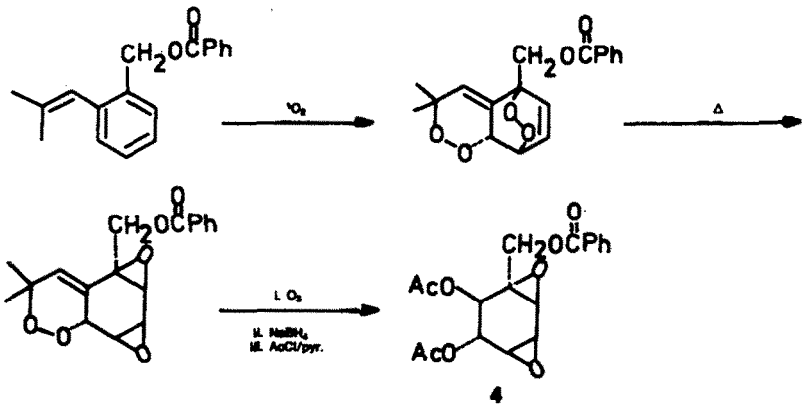
Of the cyclohexane diepoxide of biological interest we have mentioned already the crotepoxide **4**, first discovered by Kupchan *et al.*[11] Since then a number of research groups have devised synthetic pathways to this important antitumor agent. The first of these, reported by Oda *et al.*,[48] employed a classical pathway to obtain the diepoxide skeleton (eqn 26). A second approach by White *et al.*[49] utilized the endoperoxide–diepoxide rearrangement to fix the *syn* stereochemistry (eqn 27). A low yield of isocrotepoxide **4a** could be obtained by diepoxidation of the diol **40** with t-butyl hydroperoxide in the presence of $VO(acac)_2$ catalyst (eqn 28).[49] The third synthesis of crotepoxide was accomplished via the sequence outlined in eqn (29).[50]



(eqn 27)



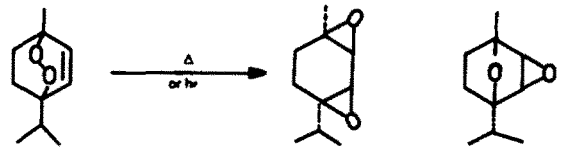
(eqn 28)



4

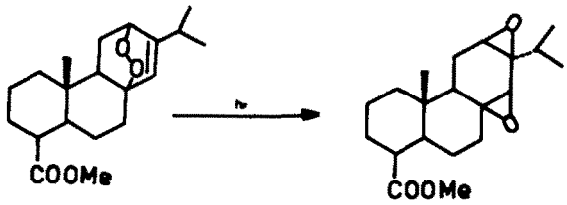
(eqn 29)

The conversion of ascaridole 41 into its diepoxide 42 (eqn 30) represents the first recognized example of the synthetically valuable and versatile endoperoxide–diepoxide rearrangement.[51] At the high temperature required to effect this rearrangement, the diepoxide 42 can further rearrange in the isomer 43. However, under the mild photolysis conditions at 366 nm,[28] ascaridole is cleanly converted into the diepoxide 42, avoiding such complications. Similarly the endoperoxide of levopimarate was transformed into its diepoxide 44 in 31% yield on photolysis (eqn 31).[28] Also the natural product β-damascenon, the essential oil derived from Manila tabaco, could be converted into the diepoxide 45 via the thermal endoperoxide–diepoxide rearrangement (eqn 32a).[52]



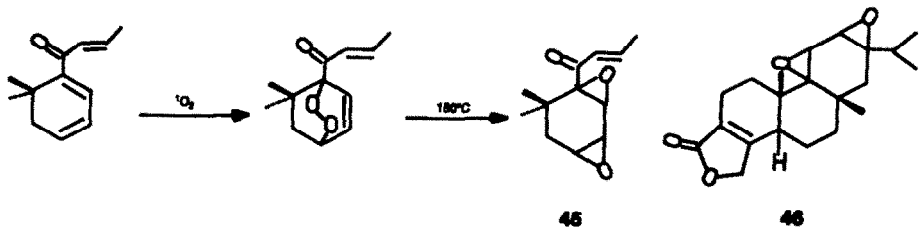
41 42 43

(eqn 30)



44

(eqn 31)

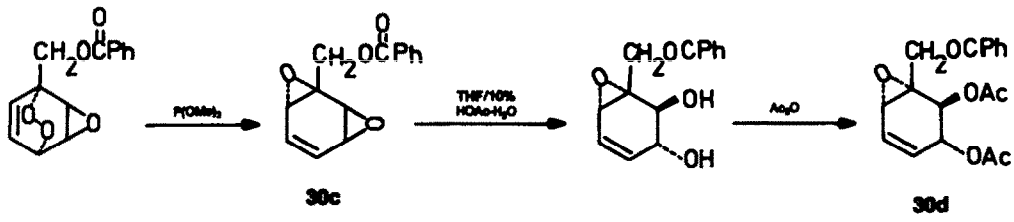


45 46

(eqn 32a)

The novel diterpene diepoxide 46, known as stemolide and closely related to the antileukemic triptolide 5, was isolated recently from the leaves of *Stemodia maritima*.[53]

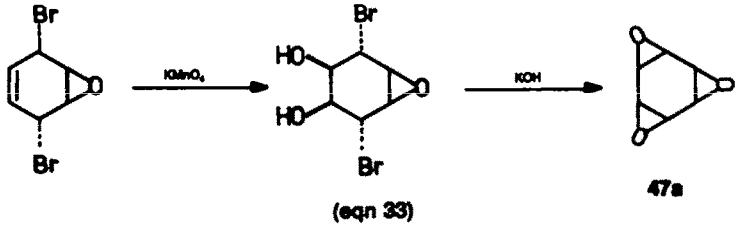
Finally, the benzene diepoxide 30c serves as important synthon in the preparation of the antileukemic senepoxide 30d a metabolite isolated from *Uvaria catocarpa* (eqn 32b).[54]



30c 30d

(eqn 32b)

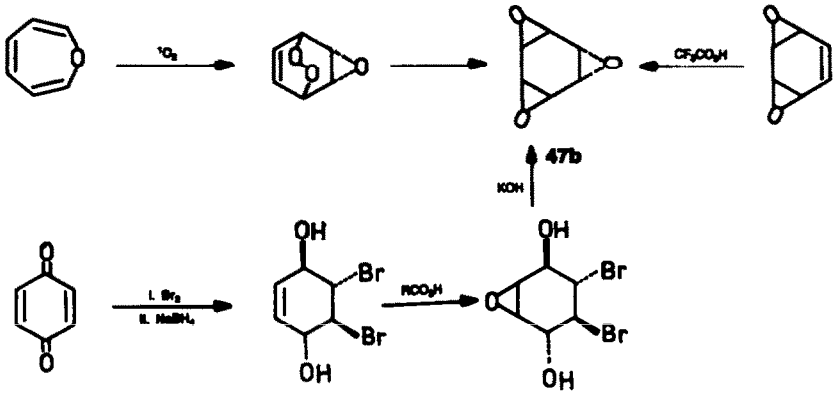
Triepoxides. Of the cyclohexane triepoxides, also known as benzene trioxides, the two stereoisomers **47a** and **47b** are possible and both have been synthesized. The *syn*-isomer **47a** was prepared by the classical method (eqn 33) simultaneously but independently by Vogel *et al.*[55] and by Schwesinger and Prinzbach.[56] The *anti*-isomer **47b** was synthesized in a number of ways. Again essentially simul-



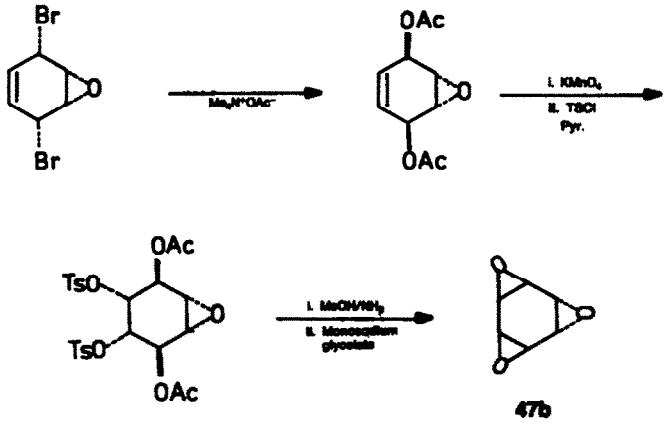
47a

(eqn 33)

taneously Vogel *et al.*[55] and Forster and Berchthold[57] prepared this isomer via the endoperoxide–diepoxide rearrangement starting from benzene oxide (eqn 34). Furthermore, direct trifluoroperacetic acid epoxidation of benzene diepoxide afforded **47b**;[55] however, a more convenient and improved method starting from *p*-benzoquinone was devised by Vogel *et al.*[5] (eqn 34). On the other hand, Prinzbach and coworkers employed the classical route shown in eqn (35).

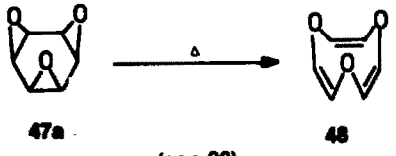


(eqn 34)



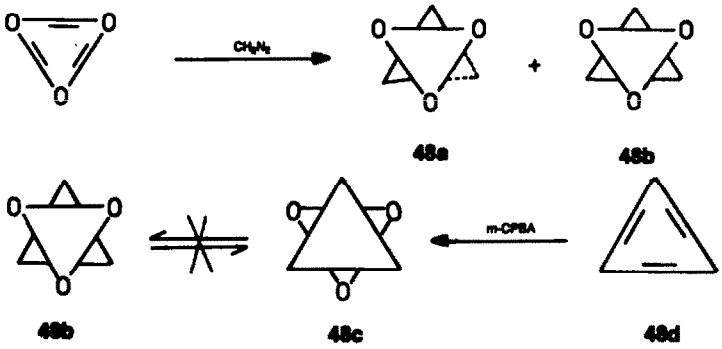
(eqn 35)

Besides their fascinating structural features, the benzene trioxides are of considerable mechanistic interest in regard to thermal valence isomerization. The *syn*-isomer **47a** opens up to the non-aromatic *cis,cis,cis*-1,4,7-trioxacyclononatriene **48** at 200° (eqn 36).[59] The activation parameters E_a and log A are given in Table 1 together with those for the benzene *syn*-diepoxide **30a**[60] and monoepoxide **49**.[61] Although the ring strain is progressively increased as the number of epoxide rings increases, the valence tautomerization becomes more difficult.



47a **48**

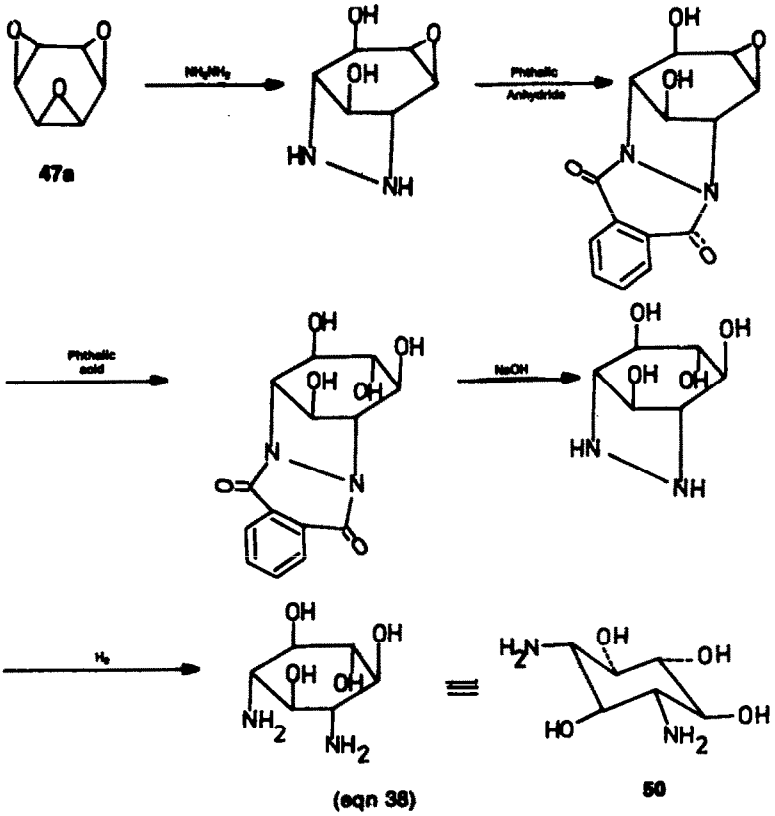
(eqn 36)



48a **48b** **48b** **48c** **48d**

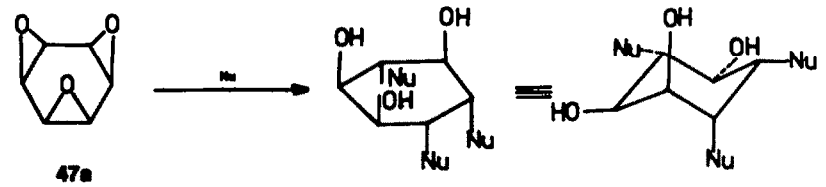
(eqn 37)

Prinzbach *et al.*[62] converted the ring-opened trioxide **48** via exhaustive cyclopropanation (eqn 37) into the cyclopropane isomers **48a** and **48b**, formed respectively as major and minor products. The isomers **48b** and **48c** did not interconvert even up to 400°. For confirmation, isomer **48c** was synthesized by peracid epoxidation of the corresponding triene (eqn 37). As expected, σ-bonds are more difficult to valence-isomerize than π-bonds under comparable structural situations.

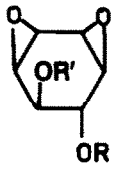


47a **50**

(eqn 38)



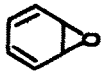
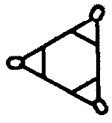
47a 51



R' = Ac; Ac; Ac; H; H; Me; Me
R = H; Ac; Ms; H; Ms; H; Ac

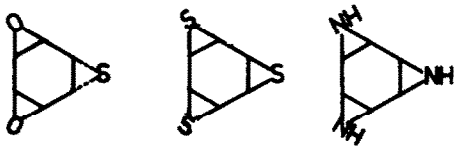
52 (eqn 39)

Table 1. Activation parameters for the thermal valence isomerization of the benzene oxides

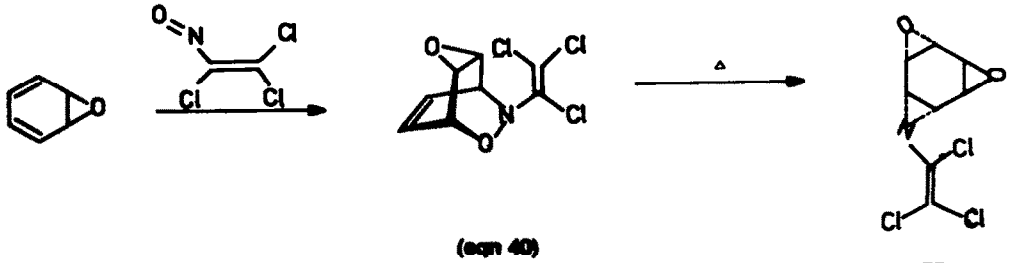
Oxide		E_a/kcal mol^{-1}	log A	Ref.
	49	9.1 ± 0.7	14.4 ± 1.1	61
	30a	27	13.9	60
	47a	42.3 ± 1.4	14.9 ± 0.6	59

The benzene trioxides **47** constitute valuable synthons for the stereospecific preparation of complex natural as well as unnatural molecules. For example, the total synthesis of streptamin **50** could be achieved by opening with a divalent nucleophile two of the epoxide rings of the *syn*-isomer **47a** (eqn 38).[64] Such absolute stereocontrol would be very difficult were it not for the epoxide vises of the benzene *syn*-trioxide **47a**. On the other hand, three-fold opening by a monovalent nucleophile of the epoxide rings in the *syn*-trioxide **47a** affords the (e,e,e,e,a,a)-isomer of the product **51** (eqn (39).[64] A number of 1,2:3,4-dianhydro-epi-inosit derivatives **52** could be prepared by opening of one of the epoxide rings of **47a** by monovalent nucleophiles.[65]

Other interesting molecules that could be prepared from the *syn*-trioxide synthon **47a** by nucleophilic epoxide ring-opening and subsequent nucleophilic ring-closure, include the thio-derivatives **53a**[66] and **53b**[67] and the aza-derivative **54**.[68] The substituted aza-derivative **55** was made via a completely different synthetic strategy (eqn 40), utilizing the singlet oxygen-type behavior of nitrosotrichloroethene.[69] Unquestionably, this novel method should be of considerable synthetic value.

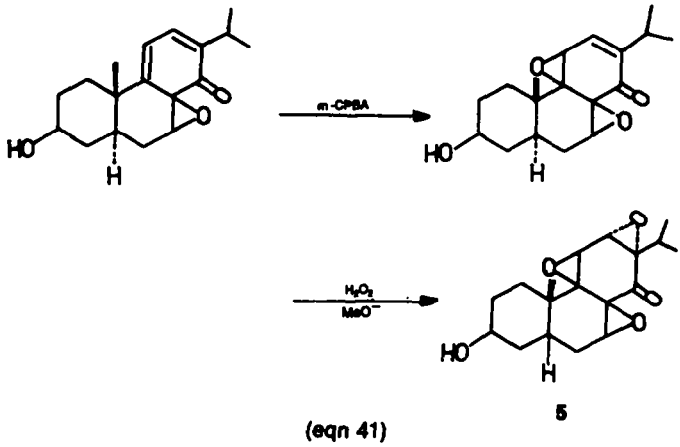


53a 53b 54



(eqn 40)

55



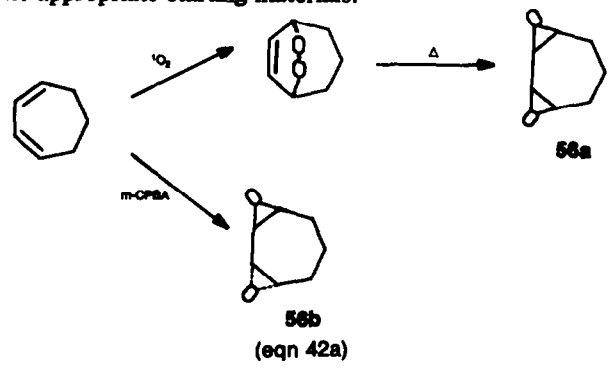
5

(eqn 41)

The natural triepoxide triptolide **5**, important for its antileukemic properties, was already mentioned in the Introduction. Its partial synthesis has recently been achieved as outlined in eqn (41),[70] using classical methods.

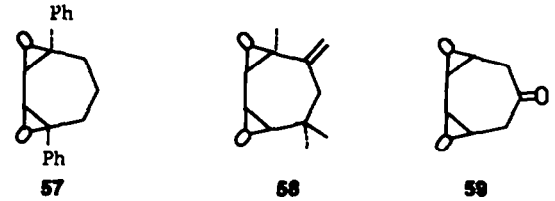
Cycloheptane di- and triepoxides

The isomeric parent diepoxides **56a** and **56b** are readily made from 1,3-cycloheptadiene. Thus, the *syn*-isomer **56a** was obtained[71] via the thermal rearrangement of the known[72] cycloheptadiene endoperoxide (eqn 42a), while the *anti*-isomer was produced by *m*-chloroperbenzoic acid epoxidation.[71] The derivatives **57**,[73] **58**[74] and **59**[75] were all prepared by the thermal endoperoxide–diepoxide route after singlet oxygenation of the appropriate starting materials.

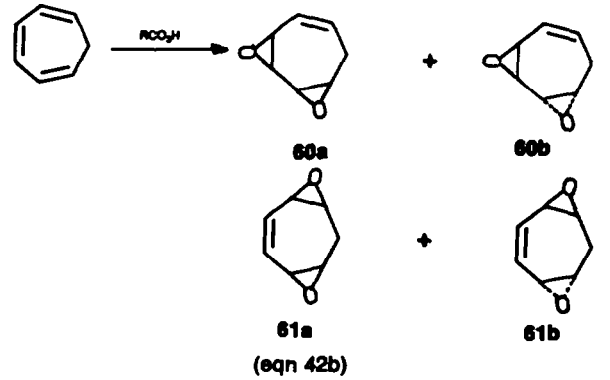


56a **56b**

(eqn 42a)



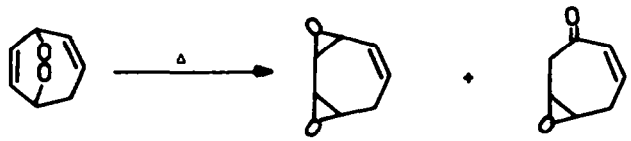
57 **58** **59**



60a **60b**

61a **61b**

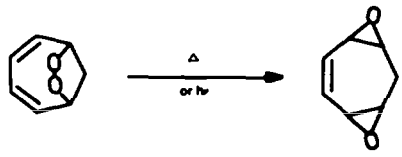
(eqn 42b)



62 60a 63

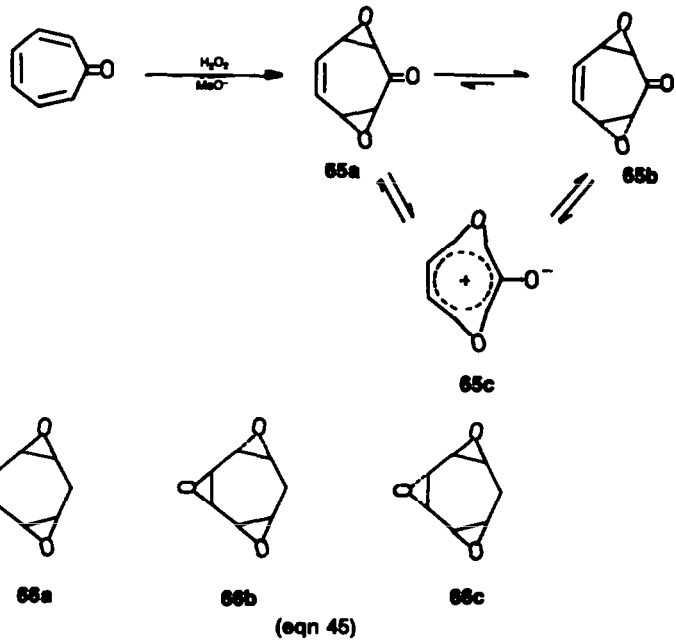
(eqn 43)

All the possible isomeric diepoxides **60** and **61** have been claimed in the peracid epoxidation of 1,3,5-cycloheptatriene (eqn 42b).[76] Unfortunately only the *anti*-isomer **60b** could be isolated and fully characterized. The *syn*-isomer **60a** could be prepared in 11% yield by thermal rearrangement of the endoperoxide **62** (eqn 43).[77] The low yield is due to the labile nature of endoperoxide **62**, rearranging to the enone epoxide **63**. The *syn*-isomer **61a** could be prepared by thermal (24% yield) or photochemical (56% yield) rearrangement of the endoperoxide **64** (eqn 44).[78]



64 61a

(eqn 44)

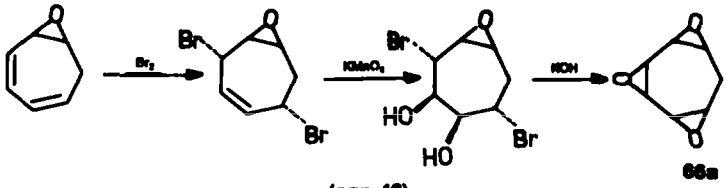


65a 65b 65c

66a 66b 66c

(eqn 45)

The tropone diepoxides **65a** and **65b** were prepared as a mixture by treatment of tropone with basic hydrogen peroxide (eqn 45).[79] The interesting feature about this system is the fact that initially the proportion of **65a** to **65b** was *ca.* 1:1 but with time under the basic conditions the *anti*-isomer **65b** predominated. It has been postulated that this novel epimerization is channeled through ring-opened dipolar intermediate **65c**.



66a

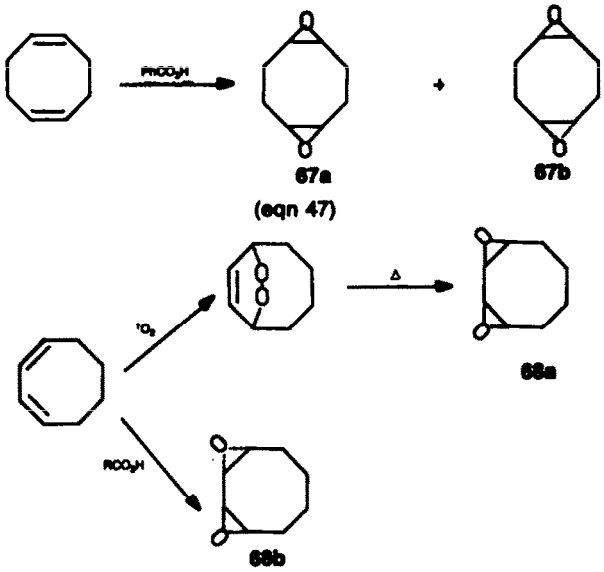
(eqn 46)

The structurally fascinating triepoxides **66** of cycloheptatriene are all known, prepared quite recently by stereospecific syntheses. Thus, via the classical route (eqn 46) the isomer **66a** was obtained.[76] The isomers **66b** and **66c** could be prepared from cycloheptatriene oxide and diepoxide **61a**, respectively via the endoperoxide-diepoxide rearrangement and by *m*-chloroperbenzoic acid epoxidation.[80]

Cyclooctane di- and triepoxides

An early report on diepoxides derived from the cyclooctane skeleton dates back to Cope *et al.*,[81] who showed that 1,5-cyclooctadiene leads to the diepoxide isomers **67a** and **67b** (eqn 47). Subsequently Benzel *et al.*[83] prepared the *syn*-isomer **67a** following Crandall's *et al.*[82] synthesis of the monoepoxide.

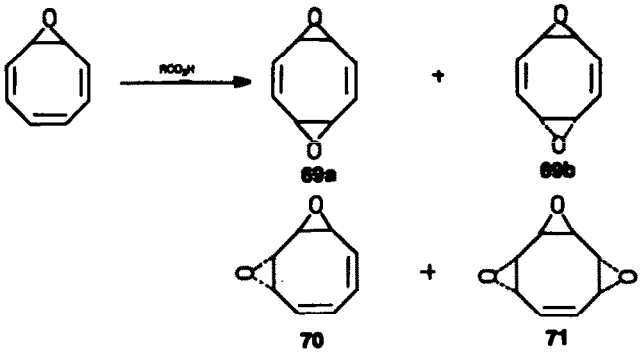
The *syn*-isomer **68a** was prepared by thermal rearrangement of the endoperoxide of 1,3-cyclooctadiene,[84] while the *anti*-isomer **68b** was made by peracid epoxidation[85] (eqn 48). A rather detailed variable temperature ^{13}CNMR study of the *anti*-isomer **68b** showed that the twist-boat and twist-boat-chair conformations prevailed.[86]



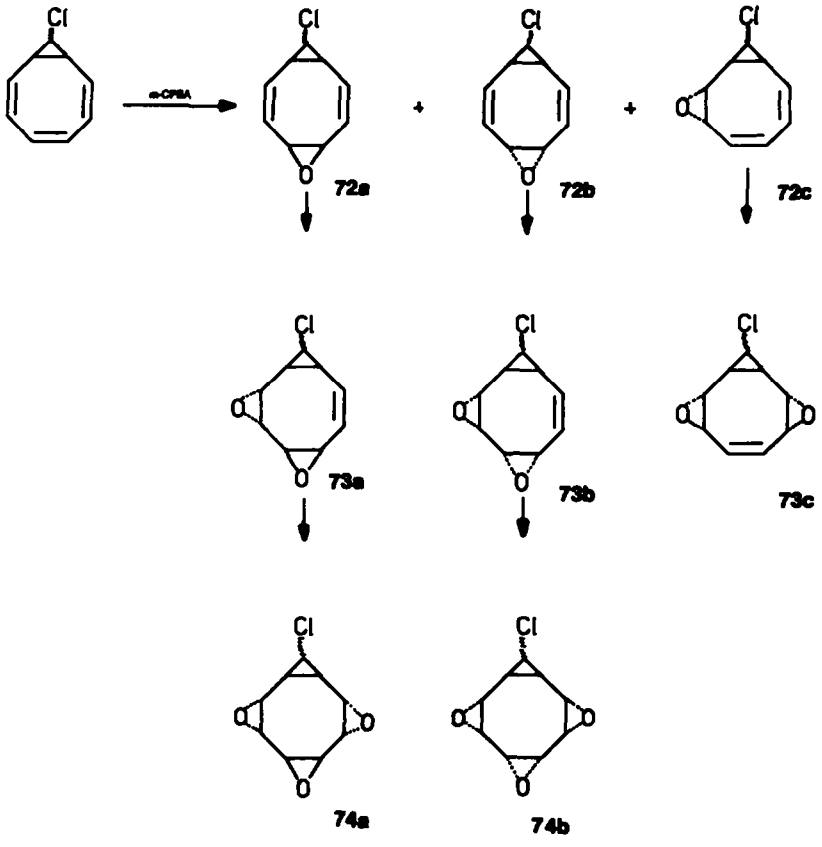
(eqn 47)

(eqn 48)

Polyepoxides derived from cyclooctatetraene were reported[87] in the peracid epoxidation of its monoepoxide. With *m*-chloroperbenzoic acid the diepoxides **69a,b** and **70** were obtained, while with trifluoroperacetic acid also the triepoxide **71** was observed (eqn 49). Finally, a similar study[88] but with chlorocyclopropane derivative of cyclooctatetraene (eqn 50) afforded first the monoepoxides **72a–c** and the diepoxide **73a**. Further epoxidation of the monoepoxides **72a–c** individually led to the remaining isomeric diepoxides **73b,c** and the triepoxides **74a,b**. As can be appreciated from this exhaustive investigation, the majority of the possible di- and triepoxides could be prepared. The obvious omissions are those isomers in which the epoxy rings are all *syn* to the cyclopropane ring. The endoperoxide–diepoxide rearrangement pathway should not be useful since even cyclooctatetraene monoepoxide resists singlet oxygenation, besides the wrong stereochemistry would result.[84]



(eqn 49)

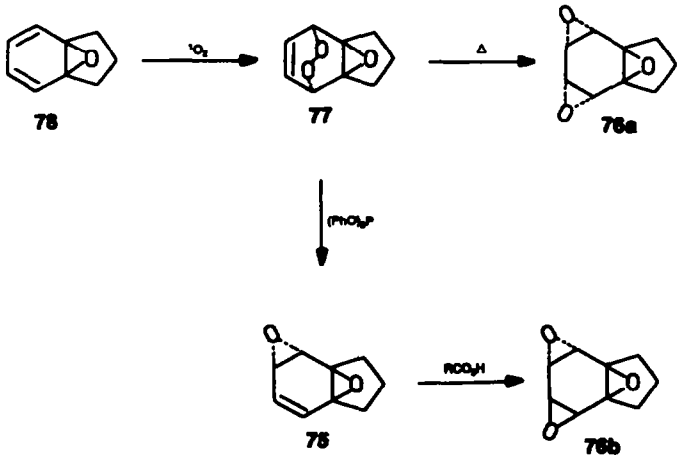


(eqn 50)

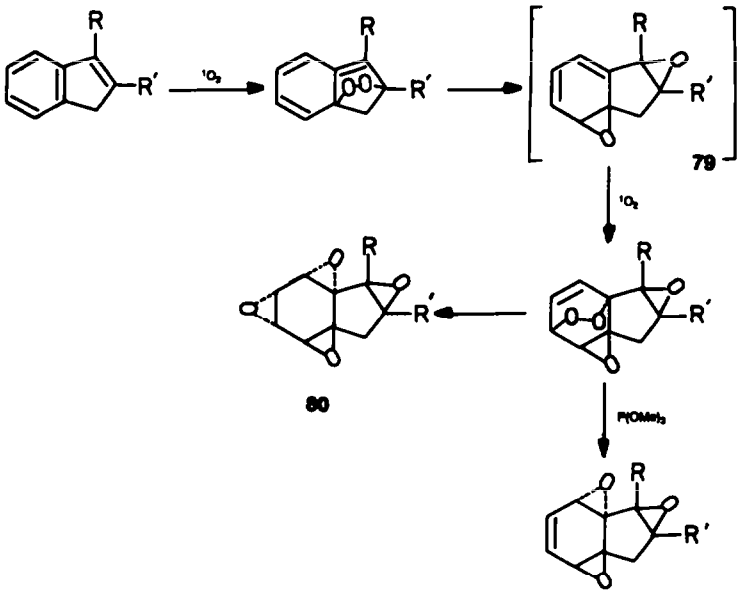
Odds and ends

In this section we take up those polyepoxide systems which do not fall very readily into our classification scheme. However, the examples to be reviewed here are no less intriguing and fascinating. First we take up the fused systems.

Fused systems. The indane diepoxide **75** and isomeric triepoxides **76a,b** were obtained from the endoperoxide **77** of indane monopoxide **78** (eqn 51).[89] Thermal isomerization of **77** led to **76a**, deoxygenation of **77** gave **75** which on epoxidation afforded **76b**.



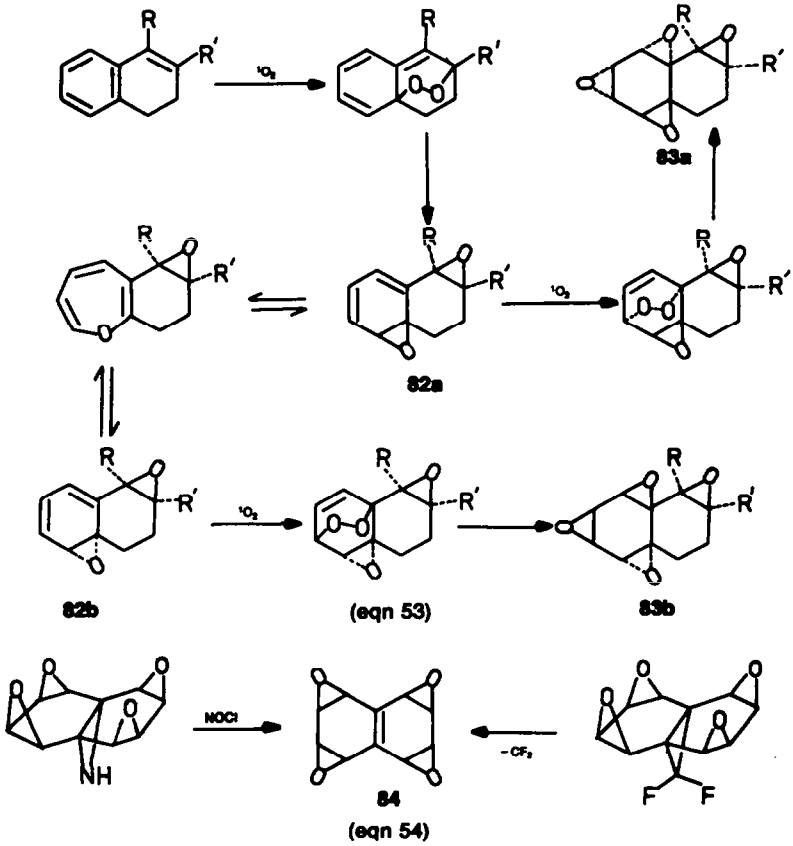
(eqn 51)



(eqn 52)

The singlet oxygenation of indenes is still more astounding (eqn 52).[90] The diepoxide **79**, rearrangement product of the initial endoperoxide, suffers *in situ* singlet oxygenation and the resulting endoperoxide again rearranges into the tetraepoxide **80** or is deoxygenated into the triepoxide **81**. Detailed ^{1}H and ^{13}C NMR analysis[90b] was of great assistance in the assignment of these complex structures.

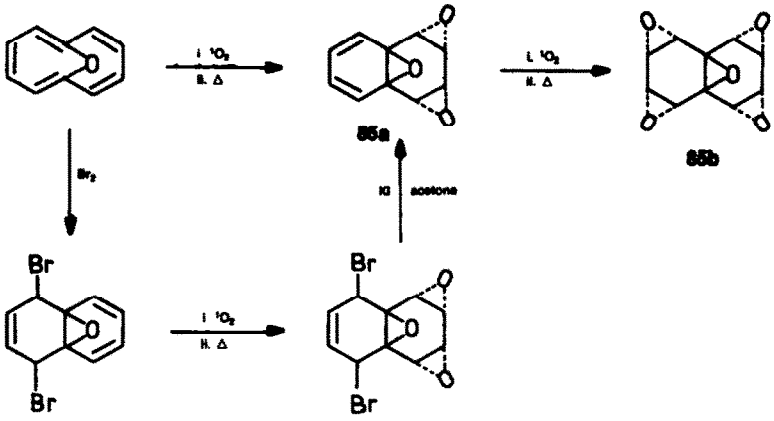
In the naphthalene series, the singlet oxygenation[91] of the 1,2-dihydro derivative (eqn 53) served as a fountain of entertaining polyepoxides. The initial endoperoxide rearranges to the diepoxide **82a** which isomerized via the oxepin into the diepoxide **82b**. Subsequent singlet oxygenation and rearrangement led to the isomeric tetraepoxides **83a** and **83b**, respectively.



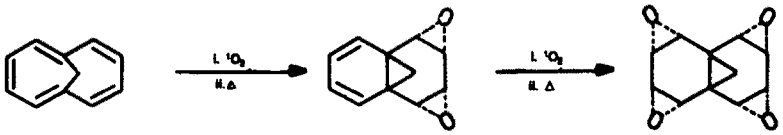
(eqn 53)

(eqn 54)

The symmetric naphthalene tetraepoxide **84** was prepared via the two independent routes shown in eqn (54).[42,92] In the first pathway denitrogenation with NOCl and in the second pathway thermal extrusion of CF_2 were used to obtain tetraepoxide **84**.

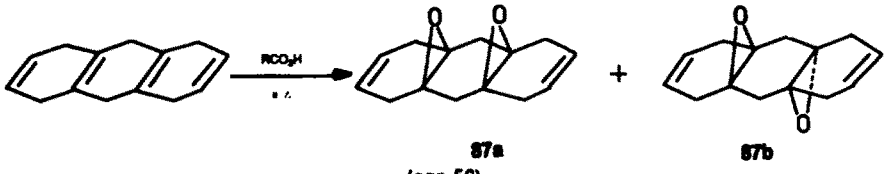


(eqn 55a)

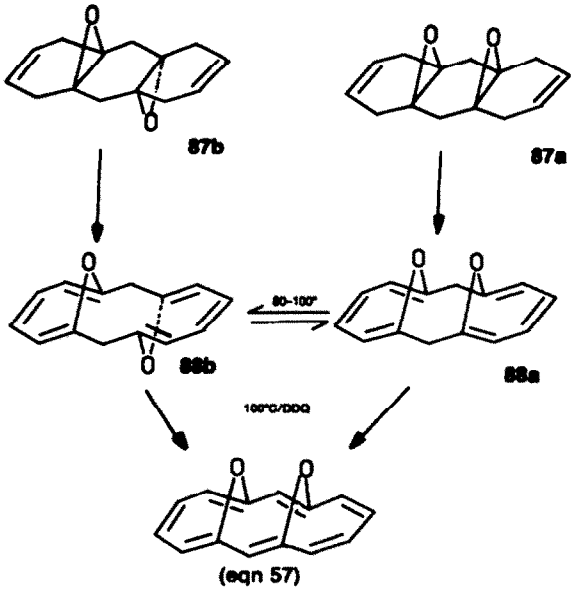


(eqn 55b)

The pentaepoxide **85** of naphthalene could be prepared[92] via the ingenious route shown in eqn (55a). Thus, singlet oxygenation of the ring-closed annulene and rearrangement of the endoperoxides leads to the triepoxide **85a**, which *in situ* singlet oxygenates and rearranges to the pentaepoxide **85b**. The triepoxide **85a** could be prepared alternatively via bromination, singlet oxygenation, rearrangement and debromination. Similarly, the tetraepoxide **86** could be prepared (eqn 55b).[93]



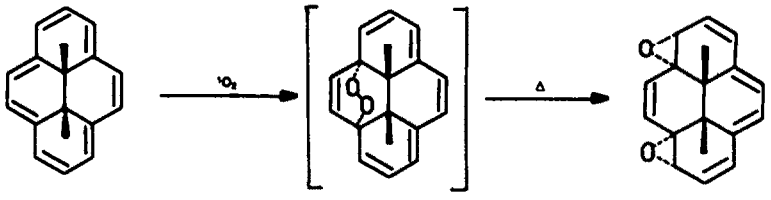
(eqn 56)



(eqn 57)

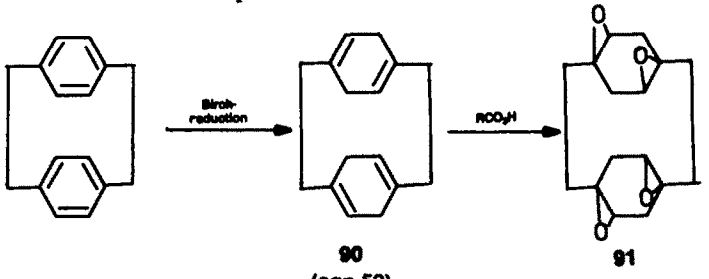
In the anthracene series, Vogel *et al.*[94] prepared the diepoxides **87a,b** by peracid epoxidation of the hexahydroanthracene (eqn 56). The interesting fact about these diepoxides is that they are valuable starting materials for the oxygen-bridged annulenes.[95] Thus, bromination and subsequent dehydrobromination of the 60:40 isomeric mixture of diepoxides **87a,b** generates the dioxepin isomers **88a,b** (eqn 57). Initially only the *syn*-isomer **88a** is formed from the isomeric mixture of diepoxides **87a,b** implying that these dioxepines can ring-invert. Indeed, this amazing process has been observed for **88** on heating to 80–100°.[95b] Furthermore, heating with DDQ at 100° dehydrogenates the isomeric **88a,b** exclusively to the *syn*- bisoxidoannulene (eqn 57).[95]

Kamp and Boekelheide[96] recently prepared the diepoxide **89** of 15,16-dimethyldihydropyrene (eqn 58) by singlet oxygenation and subsequent thermal isomerization. This unusual rearrangement of the endoperoxide is indeed fascinating.



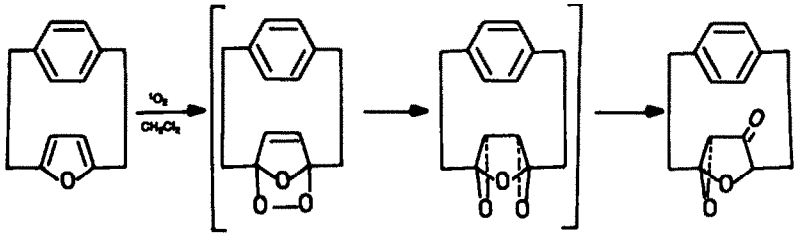
(eqn 58) **89**

Cyclophanes. Also the cyclophanes are valuable starting materials for unusual polyepoxides. For example, (2,2)-paracyclophane on Birch reduction affords the tetrahydro derivative **90** (eqn 59), which on exhaustive epoxidation leads to the tetrapoxide **91**.[97]



90 **91**

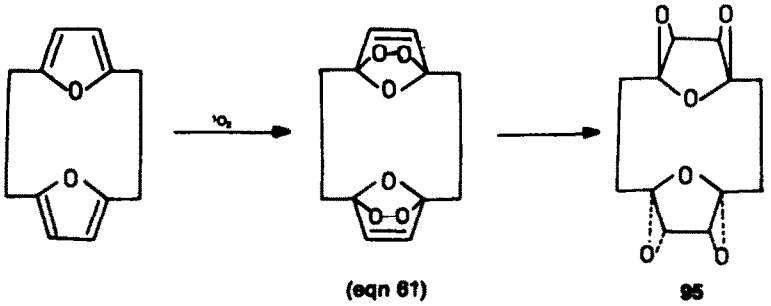
(eqn 59)



92 **93** **94**

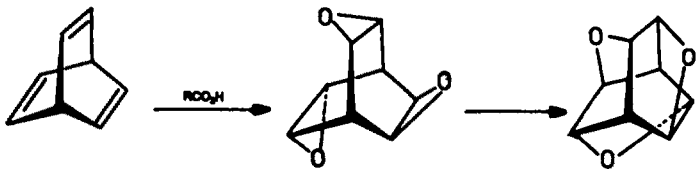
(eqn 60)

Similarly, the mixed cyclophane (eqn 60) on singlet oxygenation[98] leads to the endoperoxide **92**, which rearranges *in situ* to the ketoepoxide **94**, presumably via the diepoxide **93**. The tetraepoxide **95** was obtained in the singlet oxygenation of the furan cyclophane (eqn 61).[99] It is difficult to conceive more bizarre structures, clearly establishing the synthetic convenience of the endoperoxide-diepoxide process.



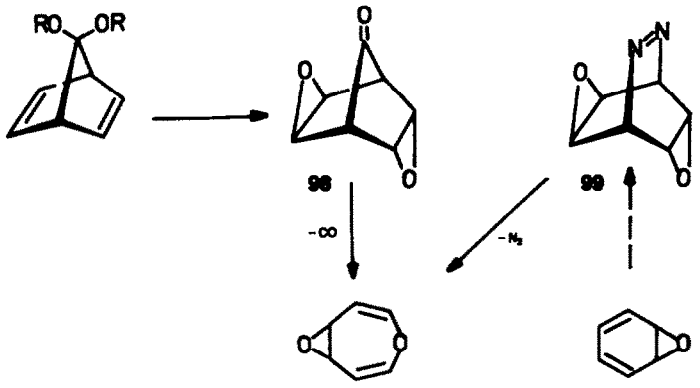
(eqn 61) **95**

Bicyclic systems. In this area the activity has been sporadic and much interesting work remains to be done. However, some eye-catching examples are known already. Thus, on exhaustive epoxidation[100] of barrelene (eqn 62) the triepoxide **96** was obtained. On heating the triepoxide **96** is converted in the truly incredible trioxide **97**, in which six tetrahydrofuran moieties are fused together resulting in a beautifully symmetrical molecule.



96 **97**

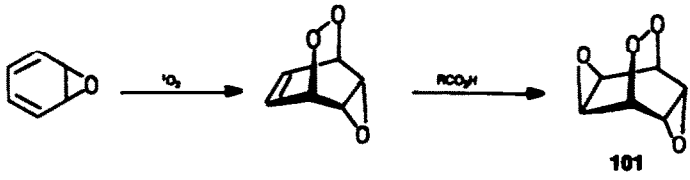
(eqn 62)



100

(eqn 63)

The keto-diepoxide **98**[101] and the azo-diepoxide **99**[102] are valuable precursors to the theoretically interesting oxepin epoxide **100** (eqn 63). The diepoxide **101** of the bicyclic peroxide (eqn 64) is also worth mentioning.[103]



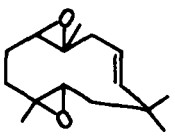
101

(eqn 64)

Larger rings. In this last section we have gathered information on polyepoxides derived from larger carbocyclic rings, especially terpene examples of natural origin. Thus, the humulene diepoxide **102** was isolated[104] from the sesquiterpene fraction of the wild ginger oil *Zingiber zerumbet*. On exhaustive epoxidation the triepoxide **103** of humulene was obtained.[104] The diepoxide **104** was obtained by epoxidation of zerumbone epoxide, which was isolated from *Zingiber zerumbet*.[105]

Coriamyrtin **105**, the main toxic principle of *Coriaria japonica*, was isolated and characterized by Okuda and students.[106] The cytotoxic sesquiterpene diepoxide **106** was isolated from alcoholic extracts of *Eupatorium rotundifolium L.* by Kupchan *et al.*[107] This natural diepoxide shows significant carcinoma inhibiting action and is of particular pharmacological value.

The diepoxide **107** was prepared by epoxidation of germacrone[108] because it was suspected as an important precursor for a number of carbobicyclic sesquiterpenoids. In fact, microbial epoxidation by *Cunninghamella blakeslecana* of germacrone into **107** took place with high efficiency. Finally, from a number of *Ligularia* species several sesquiterpene diepoxides **108** could be isolated and characterized.[109]



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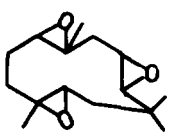

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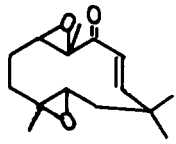
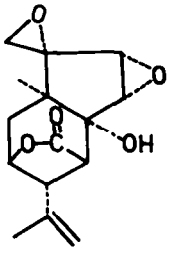


104



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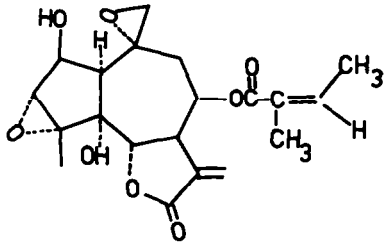

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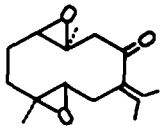
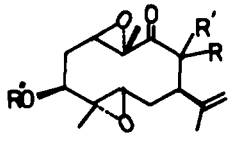


107



108

The amazing structural variety and beauty of the polyepoxides and the synthetic challenge that they represent to the organic chemists was emphasized in this Report. However, by far the most significant feature are the biomedical properties of the naturally occurring polyepoxides. Like the arene oxides, the potent carcinogenic intermediates formed *in situ* during the metabolysis of polycyclic aromatic hydrocarbons,[110] which have served an important role and major impetus in defining the mechanistic aspects of chemical carcinogenesis, we anticipate that the polyepoxides offer a similar stimulating and rewarding field for further investigation on all fronts.

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