

189. The Formation of Bridged Bicyclic 1,2,4-Trioxanes by Intramolecular Capture of β -Hydroperoxy Cations

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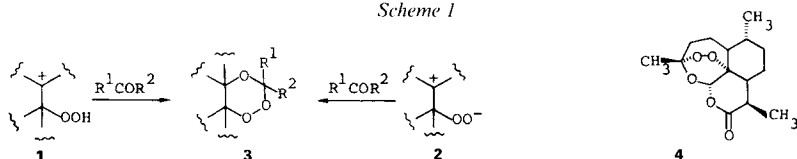
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The 1,4-endoperoxide, prepared from 3-(4-methylnaphth-1-yl)propanal by photo-oxygenation in CH_2Cl_2 , gave on treatment with *Amberlyst-15*[®], 3,10b-epidioxy-2,3,4a,10b-tetrahydro-6-methyl-1*H*-naphtho[2,1-*b*]pyran in 85% yield. Its structure was determined by X-ray crystal structure analysis. The 1,2,4-trioxane moiety is locked in a twist-boat conformation with *trans* fusion to the parent six-membered ring. The 1,4-endoperoxides of the methyl, butyl, and phenyl ketone analogues of the aforementioned aldehyde underwent similar acid-catalyzed rearrangement to the corresponding bridged bicyclic trioxanes in 94, 47, and 48% yields, respectively.

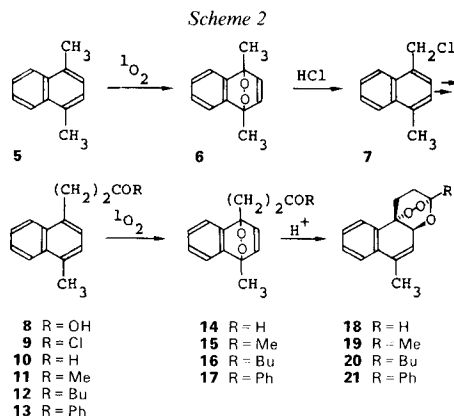
Introduction. – We have recently shown that β -hydroperoxy cations **1**, zwitterionic peroxides **2** and their structural equivalents can be captured in intermolecular fashion by aldehydes and ketones to give a wide variety of 1,2,4-trioxanes **3** [1]. The intramolecular version of these annulations has not been examined, although the crucial step of two recent syntheses of qinghaosu (**4**) did involve the internal construction of the trioxane ring [2] [3]. Apart from this specific example, the formation of bridged bicyclic 1,2,4-trioxanes is confined to serendipitous cases involving cycloaddition of singlet or triplet molecular oxygen to dienes and photoexcited quinones, respectively [4]. Consequently,

Scheme 1



we decided to investigate the conditions for preparing bridged bicyclic 1,2,4-trioxanes. In this paper, we describe the intramolecular capture of β -hydroperoxy cations by suitably placed aldehyde and ketone groups. The molecules selected to produce such cations are the 1,4-endoperoxides of 3-(4-methylnaphth-1-yl)propanal and their methyl, butyl, and phenyl ketone analogues **14–17**. Protonation is expected to generate the hydroperoxy allylic cations (*e.g.* **27**) which will be available for capture by the pendent carbonyl function.

Results. – The experimental design takes advantage of the property of the 1,4-dimethylnaphthalene moiety to undergo iterative peroxidation. Photo-oxygenation of 1,4-dimethylnaphthalene (**5**) afforded the well-known 1,4-endoperoxide **6** [5]. Demolition of the peroxide bridge with HCl/H₂O gave 1-(chloromethyl)-4-methylnaphthalene (**7**) in quantitative yield [6]. Homologation of the activated CH₃ group in **7** provided the propionic-acid derivative **8** which was converted to the acyl chloride **9** [7]. Reduction of **9** with bis(triphenylphosphine)copper(I) tetrahydridoborate [8] gave the desired aldehyde **10** in 75% yield. Direct treatment of **8** with MeLi furnished the methyl ketone **11** in 59% yield. Similarly, the action of BuLi and PhLi on **8** [9] gave the corresponding butyl and phenyl ketones **12** and **13** in 51 and 29% yield, respectively.



The photo-oxygenation of **10–13** using methylene blue as sensitizer at 0° in CH₂Cl₂ generated the 1,4-endoperoxides **14–17** in quantitative yields. The endoperoxides were then treated *in situ* with Amberlyst-15® at –15° with stirring. In every case, rearrangement occurred to the bridged bicyclic 1,2,4-trioxane. The propanal-substituted endoperoxide **14** gave a single, new tetracyclic molecule, 3,10b-epidioxy-2,3,4a,10b-tetrahydro-6-methyl-1*H*-naphtho[2,1-*b*]pyran (**18**) in quantitative yield after 3 h. A sample suitable for X-ray analysis was obtained by slow recrystallization from CH₂Cl₂/hexane at –30°. The resulting relative structure showed that the trioxane ring had been formed uniquely to give the *trans* junction with the parent ring (*Figure*).

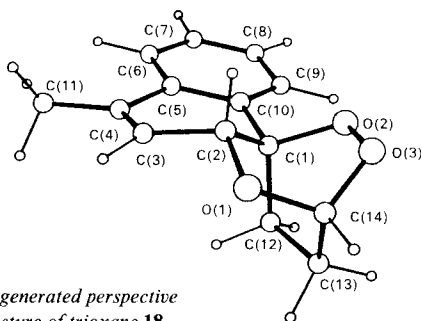


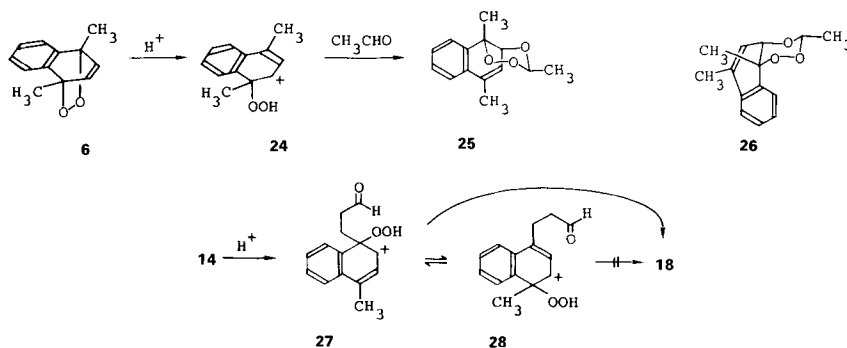
Figure. Computer-generated perspective drawing of the structure of trioxane **18**

In a similar manner, the methyl-ketone- and butyl-ketone-substituted endoperoxides **15** and **16** were converted quantitatively into the 3-methyl and 3-butyl derivatives **19** and **20**, respectively, of 3,10b-epidioxo-2,3,4a,10b-tetrahydro-6-methyl-1*H*-naphtho[2,1-*b*]pyran. The phenyl-ketone-substituted endoperoxide **17** proved less reactive; acid catalysis furnished 48% of the appropriate phenyl trioxane **21**.

In order to get a measure of the efficiency and nature of intramolecular capture, a competition experiment was performed with the methyl-ketone-substituted endoperoxide **15** using excess acetaldehyde as external electrophile. Only the tricyclic trioxane **22** was formed as a pair of diastereoisomers (see below, *Scheme 4*). In another experiment using **15** and acetone as the external trap, a 1:1 mixture of both the tetracyclic and tricyclic trioxanes **19** and **23** was obtained (see below, *Scheme 4*).

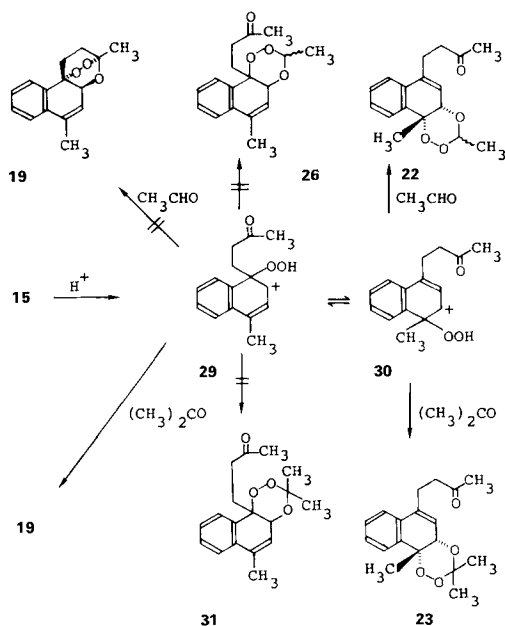
Discussion. – We have already reported that the protonation of certain endoperoxides, exemplified by **6**, produces β -hydroperoxy-allylic cations [1a] [6]. Despite the absence of hard evidence for **24**, its intermediacy is inferred from the formation of a pair of diastereoisomeric trioxanes **25** and **26** when acetaldehyde is present [1a] [10] (*Scheme 3*). Incorporation of the carbonyl function by the hydroperoxy group and the stable cationic center occurs in the expected electronic sense to create the trioxane ring in a unique way. As the acetaldehyde molecule can adopt two limiting orientations, the new CH_3 substituent is introduced in either the *cis* or *trans* configuration. The construction of the trioxane ring admits of no such ambiguity. It is formed exclusively with *cis* fusion to the parent ring.

Scheme 3



A similar mechanistic argument may be advanced for the endoperoxides **14**–**17**. As an example, the simplest member **14**, on protonation, will similarly open to the β -hydroperoxy cation, but as the 1,4 substituents are different, two isomers **27** and **28** will be produced (*Scheme 3*). Only one of them, **27**, can be productive in the intramolecular cyclization mode. Obviously, in the isomeric cation **28**, the hydroperoxy and aldehyde groups are too far apart to react with each other and the cationic center. The fact that all endoperoxides **14**–**17**, with the possible exception of the phenyl derivative **17**, rearranged in high yield to the tetracyclic trioxanes probably means that the isomeric β -hydroperoxy cations **27** and **28** obtained from **14** and the corresponding analogues derived from **15**–**17** are in equilibrium. As the bridged bicyclic trioxane progressively forms, so the geometrically unfavorable hydroperoxide, *e.g.* **28**, is depleted.

Scheme 4

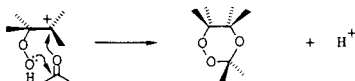


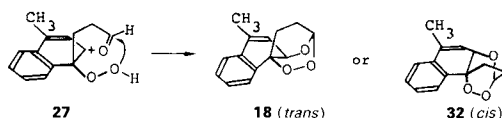
Evidence in favor of such an equilibrium is provided by the competition experiments with the methyl-ketone derivative **15**. Although the competition is doubly unfair in that the external nucleophile is in excess and is more electrophilic when it is acetaldehyde, the formation of just the tricyclic trioxane **22** as a pair of epimers is significant (*Scheme 4*). Protonation of **15** undoubtedly gives the pair of hydroperoxy cations **29** and **30**. The overwhelming presence of the more potent electrophile preferentially captures the non-intramolecular candidate ion **30**. Despite the entropic factors favoring **29**, the equilibrium shifts rapidly towards **30** so that **29** has neither time to collapse intramolecularly to **19** nor time to react intermolecularly to **26**.

When the weaker electrophile acetone is used, protonation of **15** gives the same ions **29** and **30** which now have more or less equal chances to compete with each other as attested by the formation of both the intramolecular and intermolecular products **19** and **23** (*Scheme 4*). Interestingly enough, no intermolecular product **31** arises from the intramolecular candidate ion **29**, which is entirely intercepted by its own ketonic appendage. Again, the formation of **31** is presumably precluded for entropy reasons.

The ring fusion in the intermolecular products **22** and **23** is *cis*. The reason is that the creation of the 1,2,4-trioxane ring from a free β -hydroperoxy cation and carbonyl partner passes through a preferred *cis* transition state (*Scheme 5*). When the two partners

Scheme 5. *cis*-Transition State for Formation of a 1,2,4-Trioxane from a β -Hydroperoxy Cation and a Carbonyl Partner

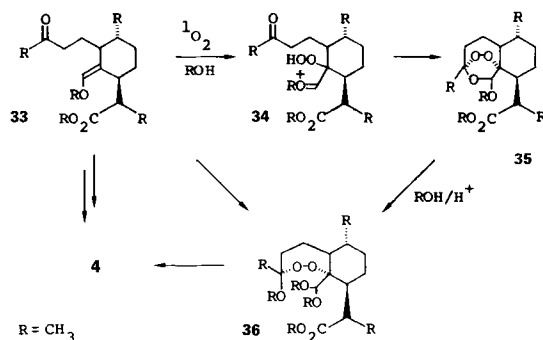


Scheme 6. Cyclization of Cation **27** to give either the *trans*- or *cis*-Fused Trioxane **18** and **32**

are tethered, then the optimal geometry for charge annihilation may be different. Indeed, inspection of a *Dreiding* model of the cation **27** derived from the endoperoxide **14** reveals that two cyclization modes are possible (Scheme 6). If the hydroperoxy group initially attacks the carbonyl group, the resulting tetrahedral oxido anion could affix itself to the upper or lower face of the cationic center. Consequently, the new bridged bicyclic entity could contain the trioxane ring in a *trans* (**18**) or a *cis* (**32**) fusion with respect to the original six-membered ring. Alternatively, the carbonyl group could add first to the cationic center, followed by attack of the hydroperoxy group. Whatever the timing of events, the critical step appears to be the construction of the pyran ring which prefers to occur in a *cis* process. Experimentally, only **18** is formed in which the pyran part is *cis*-fused, therefore, obliging the C–O bonds of the trioxane ring to be fixed *trans* to the dihydronaphthalene moiety. No trace of the *cis*-fused trioxane **32** is found.

Like qinghaosu (**4**), the 1,2,4-trioxane ring in **18** is locked in a twist-boat conformation with an axis of *pseudo*-C₂ symmetry passing through the C(1)–C(2) and O(3)–C(14) bonds (Figure). Among the structures determined by X-ray, compound **18** now brings the number of 1,2,4-trioxanes adopting twist-boat conformations to five, all others preferring the chair conformation [11].

Scheme 7



The present results have relevance to the key step of the recently published synthesis of qinghaosu (**4**), which involves the (*Z*)-enol ether **33** [2] [3] (Scheme 7). On photo-oxygenation in MeOH followed by acid treatment, **33** gave **4** in poor yield (30%). In one instance, an intermediate peroxide **36** was isolated which was subsequently converted to **4**. What was and is still not known is the nature of the first formed intermediate. However, it can now be surmised that the β -hydroperoxy cation **34** is a likely candidate. Intramolecular cyclization in the manner described above should afford the tricyclic 1,2,4-trioxane **35** which, on methanolysis, would logically give the relay peroxide **36**.

Further experiments on the details of this postulated mechanism are under way and will be reported elsewhere.

We thank the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases for support of this work. We also thank Messrs J.-P. Saulnier and A. Pinto for performing the NMR experiments.

Experimental Part

1. *General.* Solvents used were Merck anal. grade. Column chromatography: Merck silica gel 60 (70–230 mesh) and Fluka Florisil (100–200 mesh). TLC and prep. TLC: Merck silica gel 60 F_{254} (0.2 mm and 2 mm, resp.). M.p.: Reichert hot-stage microscope; uncorrected. IR spectra (cm^{-1}): Perkin-Elmer-681 spectrometer. ^1H - and ^{13}C -NMR spectra: at 360 and 90.6 MHz, resp., Bruker-FT-360 spectrometer; chemical shifts in ppm downfield from tetramethylsilane and coupling constants J in Hz. MS (m/z): CH-4-MAT and Finnigan-GC/MS-4023 instruments using the INCOS data system. Elemental analyses were carried out by Dr. H. Eder, Service de microchimie, Institut de chimie pharmaceutique, University of Geneva.

2. *Starting Materials.* 3-(4-Methylnaphth-1-yl)propionic acid (**8**) (^1H -NMR (CD_3COCD_3): 2.64 (s, 3 H); 2.72 (t , $J = 8$, 2 H); 3.38 (t , $J = 8$, 2 H); 7.26 (d , $J = 7$, 1 H); 7.31 (d , $J = 7$, 1 H); 7.55 (m , 2 H); 8.05 (m , 1 H); 8.13 (m , 1 H)) was prepared [7] from 1-(chloromethyl)-4-methylnaphthalene (**7**) [6].

3-(4-Methylnaphth-1-yl)propionyl chloride (**9**) was prepared from **8** as follows. Freshly distilled SOCl_2 (1.5 ml) was added to **8** (190.8 mg, 0.89 mmol) and heated at 100° for 3 h. Extraction with hexane followed by filtration gave **9** as yellow crystals, m.p. 69° (193.5 mg, 93%). ^1H -NMR (CDCl_3): 2.65 (s, 3 H); 3.22 (m , 4 H); 7.23–8.38 (m , 6 H) [7].

3. 3-(4-Methylnaphth-1-yl)propanal (**10**). To a stirred soln. of **9** [9] (1.1287 g, 4.85 mmol) and Ph_3P (2.8 g, 10 mmol) in acetone (20 ml), bis(triphenylphosphine)copper(I) tetrahydridoborate [10] (3 g, 5 mmol) was added at r.t. After 2 h the mixture was filtered, washed with Et_2O and evaporated. The residue was extracted with CH_3OH , the resulting soln. evaporated, and the residue redissolved in CHCl_3 (6 ml). The CHCl_3 soln. was stirred over finely powdered CuCl for 30 min, then filtered, the CHCl_3 evaporated, and the residue extracted with Et_2O . The Et_2O soln. was evaporated to yield a yellow-green oil which by prep. TLC (silica gel F_{254} , hexane/ CH_2Cl_2 25:75 gave **10** as pale yellow crystals, m.p. 41° (725 mg, 75%). IR (CCl_4): 1725 ($\text{C}=\text{O}$). ^1H -NMR (CDCl_3): 2.7 (s, 3 H); 2.92 (t , $J = 8$, 2 H); 3.43 (t , $J = 8$, 2 H); 7.28 (m , 2 H); 7.55 (m , 2 H); 8.05 (m , 2 H); 9.85 (t , $J = 1$, 1 H). MS: 198 (53, M^+), 165 (15), 155 (100), 142 (30), 128 (17), 115 (25), 77 (10), 63 (12), 51 (12). Anal. calc. for $\text{C}_{14}\text{H}_{14}\text{O}$ (198.28): C 84.80, H 7.13; found: C 84.60, H 7.14.

4. 4-(4-Methylnaphth-1-yl)butan-2-one (**11**). To a vigorously stirred suspension of **8** (183.2 mg, 0.855 mmol) in Et_2O (16 ml) at -78° , a 1.6M soln. of MeLi [9] in Et_2O (1.3 ml, 2.08 mmol) was added dropwise over 20 min. The reaction was monitored by TLC (R_f of **11** 0.54, CH_2Cl_2) and judged complete after 3 h. The pink suspension was acidified with 1N aq. HCl (2 ml), cooled with ice, and then extracted with Et_2O (3×10 ml). The combined extracts were dried (MgSO_4) and evaporated to give a colorless solid which, by recrystallization from EtOH , gave **11** as colorless crystals, m.p. 65° (133.3 mg, 73%). IR (CH_2Cl_2): 1700 ($\text{C}=\text{O}$). ^1H -NMR (CDCl_3): 2.16 (s, 3 H); 2.67 (s, 3 H); 2.88 (t , $J = 8$, 2 H); 3.35 (t , $J = 8$, 2 H); 7.22 (s, 2 H); 7.55 (m , 2 H); 8.04 (m , 2 H). Anal. calc. for $\text{C}_{15}\text{H}_{16}\text{O}$ (212.31): C 84.85, H 7.61; found: C 84.91, H 7.35.

5. 1-(4-Methylnaphth-1-yl)heptan-3-one (**12**). The acid **8** (189.8 mg, 0.886 mmol) was converted to **12** using 1.6M BuLi in Et_2O (3 ml, 4.8 mmol) in the same way as for preparing **11**. A colorless solid was obtained, **12**, after recrystallization from EtOH , m.p. $33\text{--}34^\circ$ (114.2 mg, 51%). IR (CCl_4): 1715 ($\text{C}=\text{O}$). ^1H -NMR (360 MHz, CDCl_3): 0.88 (t , $J = 8$, 3 H); 1.29 (*sext.*, $J = 8$, 2 H); 1.55 (*quint.*, $J = 8$, 2 H); 2.38 (t , $J = 8$, 2 H); 2.66 (s, 3 H); 2.82 (t , $J = 8$, 2 H); 3.33 (t , $J = 8$, 2 H); 7.21 (s, 2 H); 7.51 (m , 2 H); 8.01 (m , 2 H). Anal. calc. for $\text{C}_{18}\text{H}_{22}\text{O}$ (254.40): C 84.97, H 8.73; found: C 84.79, H 8.76.

6. 3-(4-Methylnaphth-1-yl)-1-phenylpropanone (**13**). The acid **8** (2.0 g, 9.334 mmol) was converted to **13** using 2M PhLi in THF (25.3 ml, 50.6 mmol) as for **11**. A yellow oil was obtained (4.19 g) which, by chromatography over silica gel (CH_2Cl_2 /hexane 3:1) gave **13** as a white solid, m.p. 80° (266 mg, 74%). IR (CCl_4): 1695 ($\text{C}=\text{O}$). ^1H -NMR (360 MHz, CDCl_3): 2.65 (s, 3 H); 3.42 (m , 2 H); 7.27 (m , 2 H); 7.40 (m , 2 H); 7.52 (m , 3 H); 7.92 (m , 2 H); 8.40 (m , 2 H). Anal. calc. for $\text{C}_{20}\text{H}_{18}\text{O}$ (274.38): C 87.54, H 6.63; found: C 87.53, H 6.52.

7. *3,10b-Epidioxy-2,3,4a,10b-tetrahydro-6-methyl-1H-naphtho[2,1-b]pyran (18)*. A soln. of **10** (55.5 mg, 0.28 mmol) and methylene blue (18 mg) in CH_2Cl_2 (60 ml) was irradiated by 2 500-W Na lamps while O_2 was passed through the soln. at 0° for 3 h. The progress of the reaction was monitored by TLC of the starting aldehyde (R_f 0.65, CH_2Cl_2). The *3-(1,4-epidioxy-1,4-dihydro-4-methylnaphth-1-yl)propanal (14)* was formed in quantitative yield as judged by $^1\text{H-NMR}$. $^1\text{H-NMR}$ (CDCl_3): 1.88 (s, 3 H); 2.70 (m, 2 H); 2.89 (m, 2 H); 6.72 (d, $J = 8$, 1 H); 6.77 (d, $J = 8$, 1 H); 7.25–7.34 (m, 4 H); 9.91 (s, 1 H).

To the resulting soln. of **14** (62.3 mg, 0.27 mmol), *Amberlyst-15** (0.4 g) was added with stirring at -15° . After 3 h, the soln. was filtered over *Celite* and evaporated to give **18** (53 mg, 85%; quantitative conversion according to $^1\text{H-NMR}$). Recrystallization was effected from CH_2Cl_2 /hexane at -30° for several days: colorless crystals of **18**, m.p. $99-100^\circ$. $^1\text{H-NMR}$ (CDCl_3): 1.95 (m, 1 H); 2.10 (dd, $J = 2$, 1.5, 3 H); 2.16 (m, 1 H); 2.30 (m, 1 H); 2.47 (m, 1 H); 5.24 (m, 1 H); 5.42 (dd, $J = 2$, 0.75, 1 H); 5.80 (t, $J = 1.5$, 1 H); 7.22–7.35 (m, 4 H). Anal. calc. for $\text{C}_{14}\text{H}_{14}\text{O}_3$ (230.28): C 73.03, H 6.14; found: C 72.89, H 6.34.

8. *Crystallographic Data of 18*. Orthorhombic, $a = 6.942(1)$, $b = 12.421(2)$, $c = 13.114(2)$ Å, space group $P2_12_12_1$, $Z = 4$, $d_c = 1.352$ g·cm $^{-3}$. The lattice parameters and intensities were measured at r.t. on an automatic

Table 1. *Crystallographic Coordinates for 18 and Equivalent Isotropic Temperature Factors* U_{eq} ($\times 10^3$ Å 2). E.s.d. in parentheses^a.

	<i>x</i>	<i>y</i>	<i>z</i>	U_{eq}
O(1)	0.4461(9)	0.1288(6)	0.8912(5)	67.7(25)
O(2)	0.4008(10)	0.3566(5)	0.8460(4)	63.9(23)
O(3)	0.4868(10)	0.3070(6)	0.9392(5)	80(3)
C(1)	0.3773(11)	0.2678(6)	0.7717(6)	41(3)
C(2)	0.2965(13)	0.1736(8)	0.8293(7)	56(3)
C(3)	0.2166(13)	0.0892(7)	0.7572(7)	58(3)
C(4)	0.1273(12)	0.1144(7)	0.6736(6)	49(3)
C(5)	0.1173(12)	0.2319(7)	0.6450(5)	39(3)
C(6)	−0.0031(13)	0.2648(9)	0.5651(6)	59(3)
C(7)	−0.0029(16)	0.3755(9)	0.5360(7)	67(4)
C(8)	0.1104(15)	0.4470(7)	0.5826(7)	61(4)
C(9)	0.2344(14)	0.4125(7)	0.6598(7)	59(3)
C(10)	0.2361(10)	0.3078(7)	0.6918(6)	41(3)
C(11)	0.0281(16)	0.0342(7)	0.6086(7)	73(4)
C(12)	0.5748(11)	0.2441(7)	0.7285(6)	47(3)
C(13)	0.7114(11)	0.2307(8)	0.8202(7)	55(3)
C(14)	0.5803(15)	0.2112(9)	0.9133(7)	66(4)

^a) The numbering of atoms is that shown in the Figure.

Table 2. *Bond Lengths (Å) and Relevant Torsional Angles for 18*. E.s.d. in parentheses.

O(1)–C(2)	1.431(11)	C(4)–C(5)	1.509(12)	C(14)–O(1)–C(2)–C(1)	26.4(9)
O(1)–C(14)	1.414(13)	C(4)–C(11)	1.481(13)	C(2)–O(1)–C(14)–O(3)	43.5(9)
O(2)–O(3)	1.494(9)	C(5)–C(6)	1.402(12)	C(2)–O(1)–C(14)–C(13)	−77.8(9)
O(2)–C(1)	1.481(10)	C(5)–C(10)	1.395(11)	C(1)–O(2)–O(3)–C(14)	22.5(8)
O(3)–C(14)	1.397(13)	C(6)–C(7)	1.427(16)	O(3)–O(2)–C(1)–C(2)	43.8(8)
C(1)–C(2)	1.501(12)	C(17)–C(8)	1.335(15)	O(3)–O(2)–C(1)–C(12)	−76.4(7)
C(1)–C(10)	1.519(11)	C(8)–C(9)	1.397(14)	O(2)–O(3)–C(14)–C(13)	48.4(9)
C(1)–C(12)	1.513(11)	C(9)–C(10)	1.367(13)	O(2)–C(1)–C(2)–O(1)	−73.6(8)
C(2)–C(3)	1.517(13)	C(12)–C(13)	1.540(12)	C(12)–C(1)–C(2)–O(1)	43.2(9)
C(3)–C(4)	1.298(13)	C(13)–C(14)	1.541(13)	O(2)–C(1)–C(12)–C(13)	50.3(8)
				C(2)–C(1)–C(12)–C(13)	−66.5(9)
				C(1)–C(12)–C(13)–C(14)	17.6(9)
				C(12)–C(13)–C(14)–O(1)	50.2(9)
				C(12)–C(13)–C(14)–O(3)	−72.2(9)

four-circle *Philips-PW1100* diffractometer with a graphite monochromator using MoK_α radiation. The structure was solved by direct methods using the MULTAN-80 program [12] and refined by full-matrix least-squares analysis using the X-ray system [13]. All coordinates of the H-atoms were calculated. The final *R* factor, based on the 624 reflections observed ($|F_o| \geq 3\sigma(F_o)$ and $|F_c| \geq 7$), was 0.056. The positional and thermal parameters are reported in Table 1 and the bond lengths and principal torsional angles in Table 2¹⁾.

9. *3,10b-Epidioxy-2,3,4a,10b-tetrahydro-3,6-dimethyl-1H-naphtho[2,1-b]pyran* (**19**). As for **18** with **11** (46.5 mg, 0.22 mmol), methylene blue (4 mg) in CH_2Cl_2 (10 ml) for 3.5 h. TLC monitoring of **15** (R_f 0.14, CH_2Cl_2). A quantitative yield of 4-(1,4-epidioxy-1,4-dihydro-4-methylnaphth-1-yl)butan-2-one (**15**) was obtained according to the ¹H-NMR of the mixture. ¹H-NMR (CDCl_3): 1.88 (s, 3 H); 2.22 (s, 3 H); 2.50–2.96 (m, 4 H); 6.72 (s, 2 H); 7.16–7.40 (m, 4 H).

To the resulting soln. of **15**, *Amberlyst-15*[®] (500 mg) was added with vigorous stirring at -10° . After 40 min (TLC monitoring of **19**; R_f 0.52, CH_2Cl_2), the soln. was filtered over *Celite* and evaporated to give **19** as a colorless liquid (53 mg, 94%). ¹H-NMR (CDCl_3): 1.44 (s, 3 H); 2.10 (dd, $J = 1.5, 3, 3$ H); 1.85–2.50 (m, 4 H); 5.22 (m, 1 H); 5.80 (m, 1 H); 7.24–7.34 (m, 4 H); irradiation at 5.8: dd at 2.10 $\rightarrow$ d ($J = 3$); irradiation at 5.22: m at 5.8 $\rightarrow$ q ($J = 1.5$) and dd at 2.1 $\rightarrow$ d ($J = 1.5$); irradiation at 2.1: m at 5.8 $\rightarrow$ d ($J = 2$) and m at 5.2 $\rightarrow$ t ($J = 1.5$). Anal. calc. for $\text{C}_{15}\text{H}_{16}\text{O}_3$ (244.31): C 73.75, H 6.60; found: C 73.53, H 6.73.

10. *3-Butyl-3,10b-epidioxy-2,3,4a,10b-tetrahydro-6-methyl-1H-naphtho[2,1-b]pyran* (**20**). The ketone **12** (200 mg, 0.786 mmol) was converted according to the above procedure into **20**. According to the ¹H-NMR of the mixture, the yield was ca. 95%. Chromatography over silica gel with CH_2Cl_2 gave **21** as a colorless oil (105 mg, 47%). 1-(1,4-Epidioxy-1,4-dihydro-4-methylnaphth-1-yl)heptan-3-one (**16**): ¹H-NMR (CDCl_3): 0.92 (m, 3 H); 1.16–1.70 (m, 4 H); 1.88 (s, 3 H); 2.40–2.92 (m, 6 H); 6.73 (s, 2 H); 7.30 (s, 4 H). *Trioxane* **20**: ¹H-NMR (CDCl_3): 0.92 (t, $J = 7, 3$ H); 1.32–1.50 (m, 4 H); 1.68 (m, 2 H); 1.88 (m, 1 H); 2.02 (m, 1 H); 2.08 (dd, $J = 2.5, 1.5, 3$ H); 2.23 (m, 1 H); 2.45 (m, 1 H); 5.20 (m, 1 H); 5.78 (t, $J = 1.5, 1$ H); 7.27 (m, 4 H). Anal. calc. for $\text{C}_{18}\text{H}_{22}\text{O}_3$ (286.40): C 75.49, H 7.76; found: C 75.26, H 7.93.

11. *3,10b-Epidioxy-2,3,4a,10b-tetrahydro-3-phenyl-6-methyl-1H-naphtho[2,1-b]pyran* (**21**). The ketone **13** (205 mg, 9.11 mmol) was converted as above into **21**. The crude mixture was chromatographed on silica gel 60 F_{254} at -15° with CH_2Cl_2 giving **21** as a white solid, m.p. $134\text{--}136^\circ$ (109 mg, 48%). 3-(1,4-Epidioxy-1,4-dihydro-4-methylnaphth-1-yl)-1-phenylpropanone (**17**): ¹H-NMR (CDCl_3): 1.90 (s, 3 H); 2.84 (m, 2 H); 3.29–3.50 (m, 2 H); 6.75 (d, $J = 8, 1$ H); 6.80 (d, $J = 8, 1$ H); 7.25–7.40 (m, 4 H); 7.46 (t, $J = 7.5, 2$ H); 7.59 (t, $J = 7.5, 1$ H); 8.02 (d, $J = 7.5, 2$ H). *Trioxane* (**21**): ¹H-NMR (CDCl_3): 2.05 (m, 1 H); 2.12 (dd, $J = 1.5, 2, 3$ H); 2.26 (m, 1 H); 2.57–2.76 (m, 2 H); 5.44 (m, 1 H); 5.92 (m, 1 H); 7.25–7.45 (m, 7 H); 7.64 (m, 2 H). Anal. calc. for $\text{C}_{20}\text{H}_{18}\text{O}_3$ (306.38): C 78.40, H 5.93; found: C 78.37, H 5.88.

12. *Competition Experiments*. 12.1. 4-(cis-4a,10b-Dihydro-3,10b-dimethylnaphtho[2,1-e][1,2,4]trioxin-6-yl)butan-2-one (**22**). A soln. of **11** (72.6 mg, 0.342 mmol) in the presence of acetaldehyde (1.7 ml, 28 mmol) was treated as above for its conversion to **19**. The crude reaction mixture, according to its ¹H-NMR, consisted of essentially pure **22**. Prep. TLC with AcOEt /hexane 33:67 gave **22** as a yellow oil (35.9 mg, 36.4%). IR (CCl_4): 1726 (C=O). ¹H-NMR (CDCl_3): 1.16 (d, $J = 5.5, 3$ H); 1.22 (s, 3 H); 2.16 (s, 3 H); 2.64–2.93 (m, 4 H); 5.08 (d, $J = 6, 1$ H); 5.45 (q, $J = 5.5, 1$ H); 5.90 (d, $J = 6, 1$ H); 7.25–7.41 (m, 4 H); 7.68 (d, $J = 7.5, 1$ H). Anal. calc. for $\text{C}_{17}\text{H}_{20}\text{O}_4$ (288.37): C 70.80, H 7.00; found: C 70.59, H 7.21.

12.2. 4-(cis-4a,10b-Dihydro-3,3,10b-trimethylnaphtho[2,1-e][1,2,4]trioxin-6-yl)butan-2-one (**23**) and **19**. A soln. of **15** (200 mg, 0.8187 mmol) in CH_2Cl_2 (10 ml) was prepared from **11** by photo-oxygenation. Acetone (0.2 ml) and *Amberlyst-15*[®] (0.1 g) were added with stirring at -15° . Every 2 h a portion of acetone (0.2 ml) and *Amberlyst-15*[®] (0.1 g) was added, 3 times. After stirring for 8 h, the soln. was filtered and evaporated. According to the ¹H-NMR, the mixture contained **19** and **23** (5:4 ratio) in a combined yield of a least 80%. Pure **19** was obtained by chromatography over silica gel (CH_2Cl_2 ; 23 mg, 12%). Further passage over silica gel (CH_2Cl_2) followed by prep. TLC over silica gel F_{254} (CH_2Cl_2) gave pure **23** as a colorless oil (23 mg, 9.3%). ¹H-NMR (200 MHz, CDCl_3): 1.17 (s, 3 H); 1.25 (s, 3 H); 1.73 (s, 3 H); 2.15 (s, 3 H); 2.60–3.00 (m, 4 H); 4.31 (d, $J = 6, 1$ H); 5.83 (d, $J = 6, 1$ H); 7.25–7.45 (m, 3 H); 7.65–7.75 (m, 2 H). Anal. calc. for $\text{C}_{18}\text{H}_{22}\text{O}_4$ (302.40): C 71.49, H 7.35; found: C 71.20, H 7.18.

¹⁾ Observed and calculated structure factors may be obtained on request from G. B. Crystallographic data have been deposited with the *Cambridge Crystallographic Data Centre*, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, England.

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