## **Reactions of an Endoperoxide with Chiral Ketones. Diastereoselective Formation of 1,2,4-Trioxanes and 1,3-Dioxolanes**

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Abstract. 1,4-Diphenylcyclopent-2-ene 1,4-endoperoxide on catalysis with trimethylsilyl trifluoromethanesulfonate reacted with (-)-menthone in a doubly diastereoselective manner to yield two tricyclic 1,2,4trioxanes having the 35,55,65 and 3R,5R,6R configurations respectively. The corresponding pair of 1,3dioxolanes arising by Baeyer-Villiger-type rearrangement was also formed.

The synthesis and chemistry of 1,2,4-trioxanes are of growing importance<sup>1</sup> in view of the potent antimalarial properties of artemisinin, a naturally-occurring member<sup>2</sup> of this hitherto little known class of heterocycles.<sup>3</sup> We have previously shown that the reaction of endoperoxides with aldehydes and ketones provides a convenient method for preparing a variety of trioxanes.<sup>4</sup> We now report that the products obtained depend crucially on the kind of ketone used, especially if it is chiral.



The normal course is exemplified by the interaction of 1,4-diphenylcyclopent-2-ene 1,4-endoperoxide (1) with acetone (2). Catalysis with amberlyst-15 or trimethylsilyl trifluoromethanesulfonate (TMSOTf) in methylene chloride at  $-78^{\circ}$  cleanly affords the *cis*-fused 1,2,4-trioxane 3 as a racemic mixture in high yield as the sole product (Scheme 1). However, repetition of this experiment using (-)-menthone (4) as the carbonyl



7243

partner led to an entirely different result. After 4 h of reaction time, four products were isolated in 56% yield. Two were 1,2,4-trioxanes (5 and 6), while the other two (7 and 8) were 1,3-dioxolanes in which an oxygen atom had undergone insertion into the bond between the ring and one of the phenyl substituents<sup>5</sup> (Scheme 2).

As usual, the elucidation of the structure of these products by NMR spectroscopy was not possible owing to the invisibility of the oxygenated rings. Fortunately, three of them (5, 6 and 7) gave crystals suitable for X-ray enabling their absolute configurations to be determined<sup>6</sup> (Fig.). The structures of 5 and 6 are revealing. They both contain the identical menthone ring, but the two cis-fused bicylic trioxane entities as well as the spirocyclic carbon atoms are enantiomerically related to each other. Equally significant is the configuration of the *cis*-fused dioxolane ring in 7, which is the same as that in trioxane 5. The accompanying dioxolane 8 is inferred to have the same configuration as trioxane 6.



Fig. X-ray structures of compounds 5, 6 and 7.

These results can be rationalized in terms of the equilibrating R- and S-trimethylsilylperoxy cations 9 and 10 which are generated from 1 by reaction with TMSOTf. Although 9 and 10 can combine with (-)menthone to give four possible trioxanes, only two were actually formed. In other words, the chirality of 4 has totally controlled the orientation of 9 and 10 in the transition state (Scheme 3). The R-configured peroxide 9 first attacks the silylated carbonyl function but only on its si face. The resulting trimethylsiloxy group then combines with the attached cyclopentenyl cation on its si face to create the 1,2,4-trioxane ring having the all-S configuration (5). Contrariwise, the peroxide of the S configuration (10) is constrained to attack exclusively the re face of the carbonyl function. Subsequent annihilation of charge produces the all-R trioxane 6.

The 1,3-dioxolanes 7 and 8 are secondary products. Comparison of the configurations of the *cis*-fused moleties reveals that 7 and 8 have arisen by stereospecific rearrangement of the trioxanes 5 and 6 respectively. Evidently, silylation of the peroxide entity in 5 and 6 caused the 1,2 migration of the adjacent phenyl group.<sup>7</sup>



Other chiral ketones behaved similarly towards the endoperoxide 1. (+)-Nopinone (13) gave four products in 85% yield (Scheme 4)<sup>8</sup>. The main product was identified as a trioxane (14). Its configuration, determined by X-ray,<sup>9</sup> established that (+)-nopinone had acted just like (-)-menthone by selectively capturing the R-trimethylsilyl peroxide 9 on the si face of its carbonyl function. The counterpart of this reaction, namely the incorporation of the S-trimethylsilyl peroxide 10 on the re face of 13 undoubtedly occurred, but the expected trioxane 15, although initially present, could not be isolated. Nonetheless, proof for the intermediacy of 15 was furnished by the product of its rearrangement, the dioxolane 17, which was isolated. The strucure of 17 was extrapolated from that of the companion dioxolane 16, which arose by partial rearrangement of the major product 14.



These results constitute an unusual example of a pair of complementary diastereoselective reactions between a prochiral endoperoxide and a chiral ketone. The observed spiro-peracetalization entails the mutually controlled assembly of three new chiral centers and is reminiscent of the enantiodifferentiated acetalization of racemic 1,3-diols by (-)-menthone.<sup>10</sup> Synthetic applications are under study and will be reported elsewhere.

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- 5) Compounds 5-8 were formed in a ration of 3:3:3:1 and separated by flash chromatography (Silica, CH<sub>2</sub>Cl<sub>2</sub> : cyclohexane, 1:5). Although 5, 6 and 7 were obtained pure, 8 was admixed with some 7; all gave acceptable elemental analyses.
- 6) Crystallographic data for 5, 6, and 14 have been deposited with the Cambridge Crystallographic Data Center. The structures were solved by direct methods (Multan-87) and refined by full-matrix least-sqares (X-TAL 3.0). *Trioxane* 5, recrystallized from EtOH : C<sub>27</sub>H<sub>32</sub>O<sub>3</sub>, Mr = 404.5, m.p. 103-106<sup>+</sup>, Orthorhombic, P2<sub>1</sub>2<sub>1</sub>2<sub>1</sub>, a = 6.1715(10), b = 16.811(2), c = 21.836(3) Å, V = 2265.5(6) Å<sup>3</sup>, Z = 4, D<sub>c</sub> = 1.19 grcm<sup>-3</sup>, Fooo = 872, µ(MoKα) = 0.071 mm<sup>-1</sup>. R = 0.064 (ωR = 0.036; ω = 1/σ<sup>2</sup>(Fo)) for 1109 observed reflections (1Fo1> 4σ (Fo)). *Trioxane* 6, recrystallized from EtOH : C<sub>27</sub>H<sub>32</sub>O<sub>3</sub>, Mr = 404.5, m.p. 105-110<sup>+</sup>, Monoclinic, P2<sub>1</sub>, a = 10.070(2), b = 6.3263(7), c = 18.471(3) Å, β = 103.70(1)<sup>+</sup>, V = 1143.2(3) Å<sup>3</sup>, Z = 2, D<sub>c</sub> = 1.18 gr·cm<sup>-3</sup>, Fooo = 436, µ(MoKα) = 0.070 mm<sup>-1</sup>. R = 0.067 (ωR = 0.030; ω = 1/σ<sup>2</sup>(Fo)) for 1215 observed reflections (1Fo1> 4σ (Fo)). *Dioxolane* 7, recrystallized from EtOH : C<sub>27</sub>H<sub>32</sub>O<sub>3</sub>, Mr = 404.5, m.p. 111-114<sup>+</sup>, Monoclinic, P2<sub>1</sub>, a = 9.4284(7), b = 18.8451(12), c = 20.484(3) Å, β = 99.96(1)<sup>+</sup>, V = 3584.7(6) Å<sup>3</sup>, Z = 6, D<sub>c</sub> = 1.12 gr·cm<sup>-3</sup>, Fooo = 1308. Of the three molecules of the asymmetric unit, two were considerably disordered around the menthyl moiety, while the third showed large atomic displacement parameters and some distortion of the geometrical parameters. Consequently, the crystallographic data have not been deposited. Nevertheless, the whole structure could be elucidated as shown in the Fig.
- For a related rearrangement see: C.W. Jefford, J.C. Rossier, J. Boukouvalas, J. Chem. Soc., Chem. Commun. 1987, 1713
- 8) Compounds 14-17 were formed in a ration of 8:2:3:3 and separated (see ref. 5, for conditions). Compounds 14, 16 and 17 were isolated and gave analytical data consistent with the depicted structures.
- 9) Trioxane 14, recrystallized from EtOH :  $C_{26}H_{28}O_3$ , Mr = 388.5, m.p. 85-90°, Orthorhombic,  $P2_12_12_1$ , a = 6.1799(6), b = 13.9999(13), c = 24.173(2) Å, V = 2091.4(3) Å<sup>3</sup>, Z = 4, D<sub>c</sub> = 1.23 gr cm<sup>-3</sup>, Fooo = 832,  $\mu$ (MoK $\alpha$ ) = 0.074 mm<sup>-1</sup>. R = 0.062 ( $\omega$ R = 0.040;  $\omega$  =  $1/\sigma^2$ (Fo)) for 1433 observed reflections (1Fo1> 4 $\sigma$  (Fo)).
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