Highly diastereoselective photooxygenation of chiral 1,2-dihydronaphthalenes: evidence for a common intermediate in the ene reaction and the [4 + 2] cycloaddition

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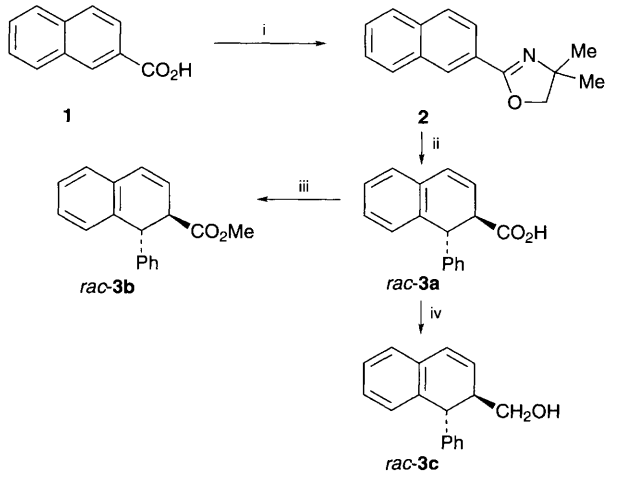
The photooxygenation of chiral 1,2-dihydronaphthalenes exhibits a very high degree of stereoselectivity, which provides evidence for a common intermediate with perepoxide geometry.

The reaction of singlet oxygen ($^1O_2$) with alkenes provides a valuable and convenient route to oxygen-functionalised products.[1] The major reaction pathway for alkenes with allylic hydrogen atoms is the ene reaction to form allylic hydroperoxides,[2] while conjugated dienes react preferentially by [4 + 2] cycloaddition to yield endoperoxides.[3] The diastereomeric course of both reaction modes has been studied intensively in recent years[4] and a high degree of stereoselection has been observed for oxygenation of chiral allylic alcohols, amines and stannanes.[5] Recently, we were able to substantiate the directing propensities of carboxylic acids, esters and homoallylic alcohols in the $^1O_2$ ene reaction of chiral cyclohexadienes.[6] In connection with the synthesis of podophyllotoxin,[7] it was of interest to extend our methodology to the photooxygenation of chiral 1,2-dihydronaphthalenes. Although the reaction of singlet oxygen with achiral indenes and dihydronaphthalenes has been studied previously,[8] no examples of chiral derivatives exist in the literature.

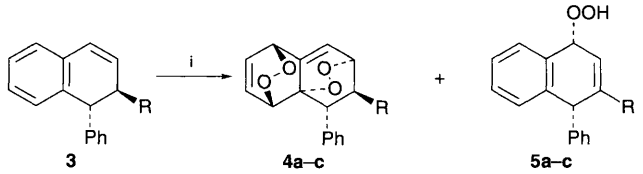
The synthesis of the chiral carboxylic acid **3a** was conveniently accomplished by the Meyers oxazoline method (Scheme 1).[9] Thus, 2-naphthoic acid **1** was transformed into the oxazoline **2** in good yield.[10] Addition of phenyllithium afforded, after quenching with trifluoroacetic acid and cleavage of the auxiliary, the hitherto unknown 1,2-dihydronaphthalene **3a** as a single diastereomer. The high *trans* selectivity is due to rapid and complete epimerisation at the 2-position and is in accordance with nucleophilic additions to 1-naphthyloxazolines.[10] To study the influence of different substituents on the photooxygenation, the carboxylic acid **3a** was transformed into the ester **3b** and homoallylic alcohol **3c** in excellent yields (Scheme 1).



Scheme 1 *Reagents and conditions*: i, $SOCl_2$, then NEt_3, $H_2NCMe_2CH_2OH$, then $SOCl_2$, 78%; ii, PhLi, −78 °C, then CF_3CO_2H, then HCl, 100 °C, 83%; iii, CH_2N_2, 99%; iv, $LiAlH_4$, 90%

Photooxygenation of the chiral 1,2-dihydronaphthalenes **3** proceeded smoothly at −30 °C with tetraphenylporphine (TPP) as sensitiser. The diendoperoxides **4** and hydroperoxides **5** were obtained as sole products as a result of double [4 + 2] cycloaddition and ene reaction (Scheme 2). The product ratios were determined by ^1H NMR spectroscopy of the crude reaction mixture after evaporation of the solvent. Furthermore, both products are stable at room temperature and were isolated by silica gel column chromatography. This result is remarkable, since the photooxygenation of achiral 1,2-dihydronaphthalenes affords no diendoperoxides, but instead gives diepoxy endoperoxides by rearrangement even at low temperatures.[8c] Presumably, the product distribution is strongly influenced by the sensitiser, which was proposed for the photooxygenation of indenes.[8d,e] The complete assignment of the ^1H (500 MHz) and ^{13}C (125 MHz) NMR signals for all products was achieved by a combination of $^1H,^1H$-COSY, NOESY, HMQC and HMBC measurements. To elucidate the relative configuration of all stereocentres in the diendoperoxides **4** and hydroperoxides **5**, NOESY was the method of choice.

The moderate mode selectivities ([4 + 2] *versus* ene) can be rationalised by the influence of the substituents R. We recently established that the $^1O_2$ ene reaction of acids and esters is much slower than the addition to homoallylic alcohols.[6] Thus, in the case of dihydronaphthalenes **3a** and **3b**, the [4 + 2] cycloaddition can effectively compete with the ene reaction. Besides the modest mode selectivities, all reactions exhibit a very high degree of stereoselectivity, which is remarkable for photooxygenations of cyclic substrates. Furthermore, no substituent effects on the diastereomeric course of the reactions are observed. Thus, attack of singlet oxygen occurs exclusively *cis* to the phenyl group. This result seems to be contradictory to our previous finding,[6b] in which for cyclic substrates the ester and hydroxymethyl functionalities direct the attack of $^1O_2$ from opposite faces. The high stereoselectivities can only be



Scheme 2 *Reagents and conditions*: i, O_2, TPP, *hν*, CCl_4, −30 °C, >95%

rationalised in terms of attractive interactions between the terminal oxygen and the allylic hydrogen in an intermediate **6** with perepoxide geometry (Scheme 3). After hydrogen atom transfer the ene mode affords the hydroperoxides **5** (pathway **B**). Such favourable interactions were discussed previously in connection with the regioselectivity of singlet oxygen ene reactions.[11] On the other hand, the influence of allylic hydrogens on the stereochemical course of photooxygenations has been hitherto underestimated, although the directing propensities of various functional groups is well established.[5,6] Furthermore, it has been shown for cyclic substrates that the attack of $^1O_2$ can occur *trans* to the allylic hydrogen atom which has to be abstracted.[12]

Interestingly, the [4 + 2] cycloadditions show the same high degree of stereoselectivity as the ene reactions. Thus, the first equivalent of oxygen is added exclusively *cis* to the phenyl group to lead to the endoperoxides **7** (pathway **A**). This result is important from the mechanistic point of view, because it provides strong evidence for a common intermediate **6** for both reaction modes. At this point it is difficult to differentiate between a perepoxide,[13] a zwitterion[14] or a polarised exciplex,[15] but recently the latter was postulated as the most likely intermediate.[4b] Clearly, due to the observed attractive interaction to the allylic hydrogen, a diradical or synchronous mechanism cannot operate. Furthermore, if a concerted [4 + 2] cycloaddition of singlet oxygen were to take place, the sterically demanding phenyl group should direct the attack of $^1O_2$ from the opposite face.[16] Finally, the endoperoxides **7** undergo a fast second addition of singlet oxygen, which is again highly stereoselective. The attack occurs *trans* to the peroxide bridge, which is in accordance to the photooxygenation of indenes.[8d]

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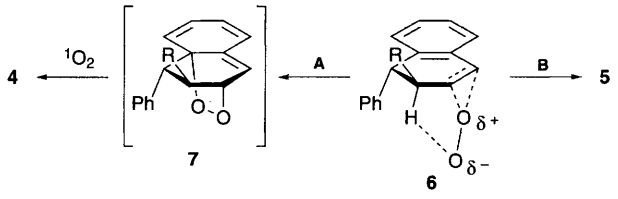

Scheme 3

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