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CHIRAL 1,3-OXATHIANES VIA STEREOSELECTIVE ADDITION-CYCLIZATION OF HYDROXYTHIOLS TO ELECTRON-POOR ACETYLENES

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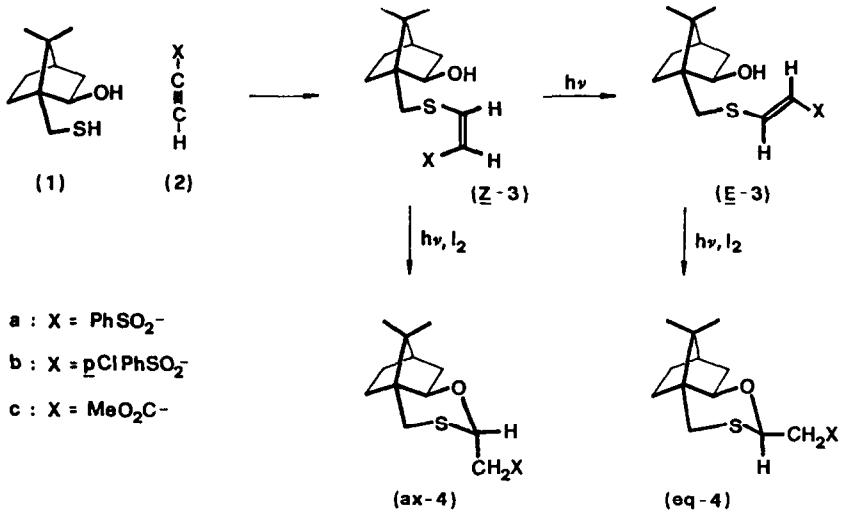
Summary: A novel preparation of chiral 1,3-oxathianes via nucleophilic addition of hydroxythiols to electron-poor acetylenes, followed by iodine catalyzed photoinduced cyclization is reported. The stereochemical outcome of the reaction is determined with a conformational study based on n.O.e. ^{1}H-NMR differential spectroscopy experiments.

The utilization of chiral 1,3-oxathianes in the asymmetric synthesis of optically active hydroxyaldehydes is currently investigated by Eliel and coworkers.[1] Their synthetic strategy entails condensation of a chiral hydroxythiol with formaldehyde and subsequent reaction of the carbanion derived by the resulting oxathiane with a carbonyl compound. Herewith we report on a different approach to chiral 1,3-oxathianes based on nucleophilic addition of the thiol group of an hydroxythiol to an electron-poor acetylene, followed by a photoinduced intramolecular cyclization of the resulted Michael adduct. The obtained products contain versatile functionalities which may be amenable to further asymmetric manipulations.

Scheme 1 shows the complete synthetic sequence starting from the Eliel hydroxythiol 1, readily available from lithium aluminium hydride reduction of commercial (1S)-d-10-camphorsulfonyl chloride.[2] Morpholine catalyzed Michael addition of **1** to benzenesulfonyl-acetylene (2a) (CH_2Cl_2, 0°C, overnight, 85% yield) gives stereospecifically the vinyl sulfide Z-**3a**, which in chloroform or dichloromethane, in the presence of a catalytic quantity of iodine and exposed to the sunlight for few hours, affords a mixture of the two cyclized axial (ax-**4a**) and equatorial (eq-**4a**) 1,3-oxathianes in quantitative yield (from NMR). The two diastereoisomeric 1,3-oxathianes has been separated by radial chromatography (silica gel; petrol ether : ethyl-acetate 98:2 eluant) and independently characterized. The individual



Scheme 1

structures were assigned on the basis of their spectral data and their stereochemical identities were attributed with the help of n.O.e. ^{1}H-NMR differential spectroscopy. Figure 1 reports the data which are relevant for the assignment of the stereochemistry. The numbers give the % n.O.e. enhancements upon irradiation of the connected nucleus.[3] Cross experiments may give different answers because of efficient relaxation mechanisms associated with some nuclei. The configurational assignments are unambiguous; furthermore the n.O.e. results can be fully accounted for assuming a predominant chair conformation in the case of eq-**4a**, while both chair and tub conformations are significantly populated in ax-**4a**, in agreement with simple steric considerations.

If the reaction is monitored at partial conversion, variable amounts of the trans form (E-3) can be detected together with the final products ax-**4** and eq-**4**. This observation suggested that the two products could arise from two stereospecific paths dictated by

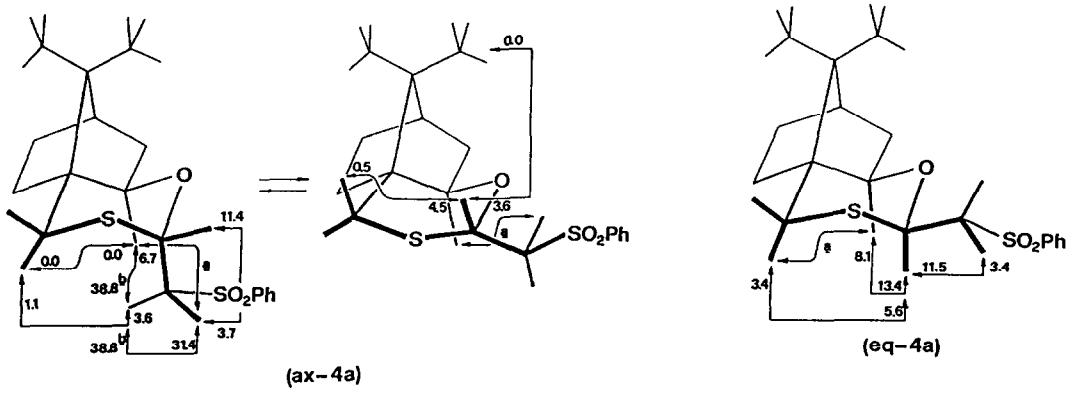


Figure 1. Selected n.O.e. values for oxathianes **4a**. [a] Isochronous or almost isochronous resonances. [b] From multiple irradiation of isochronous resonances.

different preferential conformations of the two isomeric vinyl sulfides Z-3 and E-3 as it is shown in Scheme 1. Indeed we synthetized pure E-3 by irradiation at 254 nm of Z-3 and, after exposure to the sunlight with a catalytic quantity of iodine, only the equatorial isomer eq-4 was obtained. The latter experiment is also demonstrative of the necessity of the iodine catalysis in the cyclization step.

A more precise knowledge of the conformations of Z-3 and E-3 in solution was gained with a detailed n.O.e. investigation on the two derivatives Z-3c and E-3c (Figure 2). As it could be expected from the steric outcome of the cyclization reactions, the preferred rotamer of the Z isomer presents the α-vinyl hydrogen syn to the dimethylmethano bridge of the camphor moiety, while in the E form the same vinyl hydrogen is anti. Hence, ring closure of the Z-form will result in the axial isomer, while the same reaction of the E form will give the equatorial product.

The reaction is influenced by several factors as irradiation source, solvent, temperature, presence or absence of oxygen and others. For example the change of the irradiation source brings about different ratios of ax-4 and eq-4, so that it is possible to drive efficiently the reaction to either product. From a synthetic point of view, the irradiation with a standard heat-lamp is relevant, as only the equatorial diastereoisomer 4 results. As it was confirmed by a separate experiment, the same product is obtained from the trans isomer, supporting the hypothesis that under the reaction conditions a previous cis-trans isomerization occurs. The concentration of oxygen is also critical as it efficiently inhibits the cyclization, allowing the cis-trans isomerization only. On the other hand, when the reaction is carried out under nitrogen or on degassed samples, mixtures of the two diastereoisomers are always formed. Hence the stereoselective preparation of eq-4 is best accomplished in open reactors. The cyclization is further inhibited by deuterium oxide or other proton sources; under these conditions only cis-trans isomerization occurs.

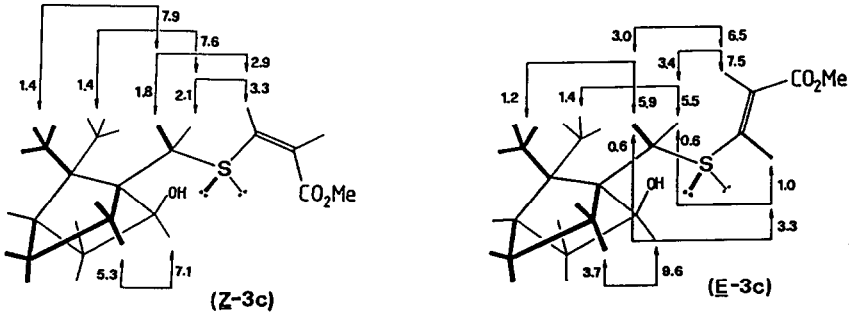
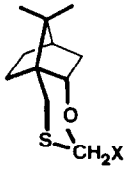
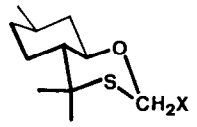


Figure 2. Preferred conformations of Z- and E-3c drawn on the basis of n.O.e. values.

The reaction of Scheme 1 seems to be general as it has been accomplished with the series of electron poor acetylenes **2a-c** and with other hydroxythiols, from which the corresponding 1,3-oxathianes **5** and **6** were obtained. The stereochemical outcome is analogous to that described in Scheme 1, suggesting that the rotameric conformational preference of the corresponding syn and anti vinyl sulfides is also similar.

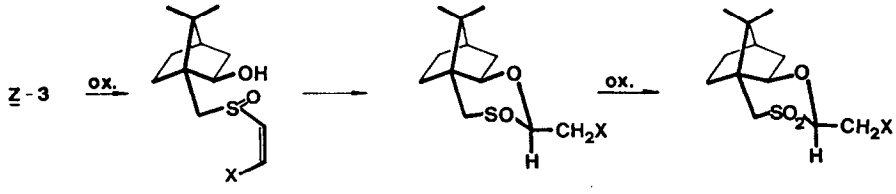


(5)



(6)

Related cyclization reactions occur on prolonged treatment with silica gel of the corresponding sulfoxides **7** which are obtained via a diastereoselective oxidation of the sulfides **3** and have already been utilized as efficient dienophiles in asymmetric Diels-Alder reactions.[4] The cyclization is stereospecific affording only one diastereoisomeric 1,3-oxathiane-S-oxide of equatorial configuration as shown by a n.O.e. investigation.[5] The cyclization of the sulfoxides does not occur with light in the presence of iodine under the conditions which cause cyclization of the sulfides. The corresponding sulfones do not cyclize



(7) **(8)** **(9)**

in either way, but the sulfone derivatives **9** can be easily obtained by oxidation of **4** or **8**. It has to be noted that whenever the photoinduced cyclization does not occur, cis-trans isomerization is observed.

We are currently trying to define the mechanism of these cyclizations as well as to utilize these reactions for asymmetric synthesis.

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