

Photochemical Rearrangement of 2-Phenylthio-1,3-cyclohexanediols to Deoxysugars. Application to a Stereospecific Synthesis of (+)-*cis*-Rose Oxide.

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ABSTRACT: The present paper reports the stereospecific synthesis of (+)-*cis*-rose oxide, the unnatural isomer of the fragrant oil isolated from Bulgarian roses and Bourbon geraniums. The synthesis serves to illustrate the potential of a new photochemical rearrangement of carbocycles to deoxysugars reported earlier. © 1998 Elsevier Science Ltd. All rights reserved.

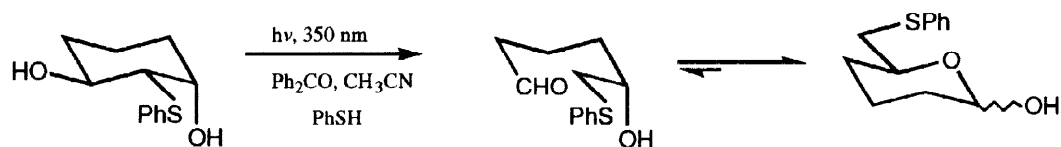
Sometime ago, we reported on the photosensitized redox cleavage of cyclic 2-phenylthioalcohols.¹ This new reaction provided an interesting and useful methodology to carry out the indirect redox cleavage of the olefinic bond (Scheme 1).

Scheme 1



Later studies showed that when an additional hydroxyl is present in the 3-position i.e. in the case of 2-phenylthio-1,3-cyclohexane- or cyclopentanediois, the rearrangement leads to deoxysugars² (Scheme 2).

Scheme 2

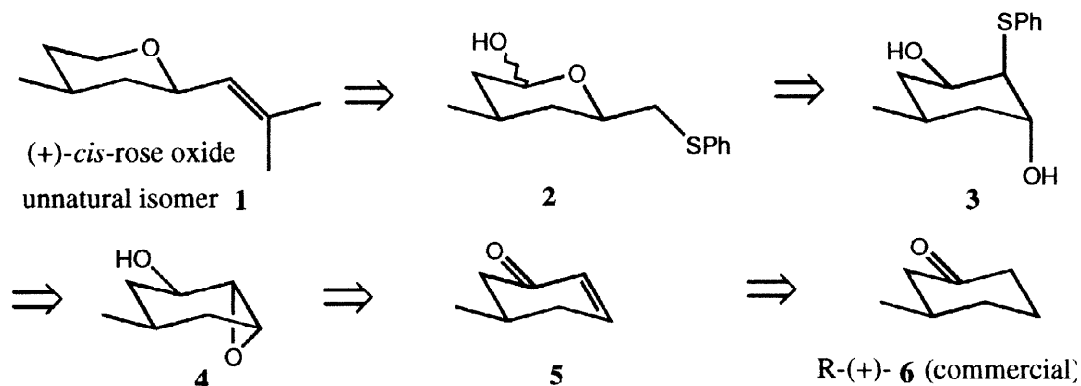


One fortunate limitation of the reaction, as was shown previously,² is that cleavage is highly inefficient in the case of *trans*-diaxial 2-phenylthioalcohols whereas it is most efficient in a *cis* relationship, which should allow for regiocontrol in the cleavage of conformationally rigid 2-phenylthio-1,3-cyclohexanediols of appropriate stereochemistry. This interesting regiocontrol in the cleavage reaction was put to the test in a total synthesis of (+)-*cis*-rose oxide, the unnatural isomer of

the well known fragrant oil isolated from Bulgarian roses in 1959³ and Bourbon geraniums in 1961.⁴ Since then, a number of syntheses were reported.⁵⁻¹⁰ Unfortunately, most of these approaches based on the use of terpenes as starting material lead to *cis-trans* mixtures of *cis* rose oxide. In 1978, however, Ogawa reported the first stereospecific synthesis of natural (-)-*cis*-rose oxide using D-glucose as starting material.¹¹ More recently, Fronza *et al.*¹² reported a stereoselective synthesis of (+)-*cis*-rose oxide based on the Baker's yeast reduction of an appropriately substituted δ -keto acid.

Our approach, based on the above novel rearrangement, is totally different from any ever published as the following retrosynthetic analysis shows (Scheme 3). A key requisite in the sequence as explained previously, is that the 2-phenylthio-1,3-diol array be in a *trans* (a,a)-*cis* relationship in order to ensure regiocontrol in the photorearrangement of the carbocycle to the corresponding deoxysugar.

Scheme 3

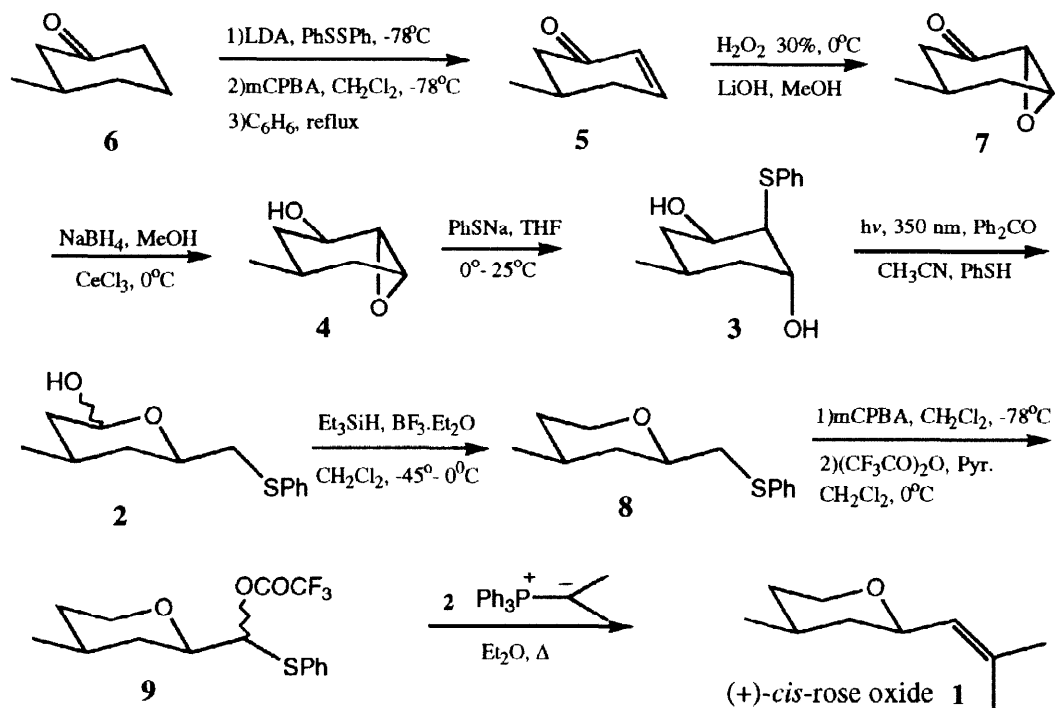


More specifically, the target (+)-*cis*-rose oxide 1 should readily be accessible from the precursor deoxysugar 2 *via* deoxygenation of the anomeric hydroxyl group followed by Pummerer rearrangement of the corresponding sulfoxide and hydrolysis of the resulting α -trifluoroacetoxy thioether to the aldehyde. A Wittig reaction on the latter should yield the desired *cis*-rose oxide 1. The precursor deoxysugar 2 itself should be accessible in the key photochemical rearrangement from the 5-methyl-2-phenylthio-1,3-cyclohexanediol carbocycle 3 where stereochemistry of the 2-phenylthio-1,3-diol array is dictated by the regiocontrol desired in the cleavage as explained above. The latter should be easily accessible from the *trans*-epoxyalcohol 4 in view of the well known Fürst-Plattner rule.¹³ Finally, the *trans*-epoxyalcohol 4 should be attainable *via* the stereocontrolled epoxidation of 5-methylcyclohexenone 5 followed by the stereocontrolled reduction of the resulting epoxy ketone by the Luche method.¹⁴ The enone 5 itself is a known compound which can regioselectively be prepared from commercially available R-(+)-3-methylcyclohexanone 6.

The actual synthesis proceeded according to plan as shown in Scheme 4. The first step of the sequence required the regioselective introduction of a double bond α to the ketone and this specific case had already been reported by Oppolzer^{15a} using the Trost^{15b} method. Compound 5 was thus obtained in a 50% yield for the three steps. The second modification involving the stereoselective epoxidation of enone 5 is also known¹⁶ on the racemic ketone and it yielded the desired epoxy ketone 7 in a 60% yield. Stereoselective reduction of the latter to give the *trans*-epoxy alcohol 4 was accomplished in a 71%

yield by the Luche method,¹⁴ as first applied to epoxy ketones by Rücker.¹⁷ *Trans*-diaxial opening of the epoxide¹³ in **4**, to yield the 2-phenylthio-1,3-diol carbocycle **3** of appropriate stereochemistry for the regioselective photochemical rearrangement, was accomplished in 51% yield.

Scheme 4



The key photochemical step was then carried out by irradiating in a Rayonet Photochemical Reactor and monitoring the reaction by tlc as long as the separation remained sharp and only one reaction product of the substrate appeared. This corresponded to about 30% conversion. The desired deoxysugar **2** was then isolated and the unreacted product reirradiated. This procedure yielded on average 50-55% of deoxysugar **2** as a 1:1 mixture of the two anomeric forms.

Termination of the synthesis was carried out by first reducing the anomeric hydroxyl by the Kraus procedure¹⁸ to obtain tetrahydropyran **8** in an 87% yield and carrying out a modified Pummerer rearrangement¹⁹ to furnish the α -trifluoroacetoxy thioether **9** essentially quantitatively. Hydrolysis of the latter unfortunately yielded only small amounts of the desired aldehyde because of the small amounts of material being processed and the volatility of the compound. In order to circumvent this problem, precursor **9** was treated with two equivalents of Wittig reagent to yield the desired (+)-*cis*-rose oxide **1** as sole product of the reaction. The synthetic material gave a proton nmr spectrum and an optical rotation in perfect accord with those reported in the literature.^{11,12} The success of the present endeavor therefore illustrates the potential and usefulness of this new methodology in organic synthesis.

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