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HIGHLY STEREOSELECTIVE DOUBLE MICHAEL CYCLIZATION OF 1-PHENYLSULFINYL AND SULFONYL ANALOGUES OF THE NAZAROV REAGENT

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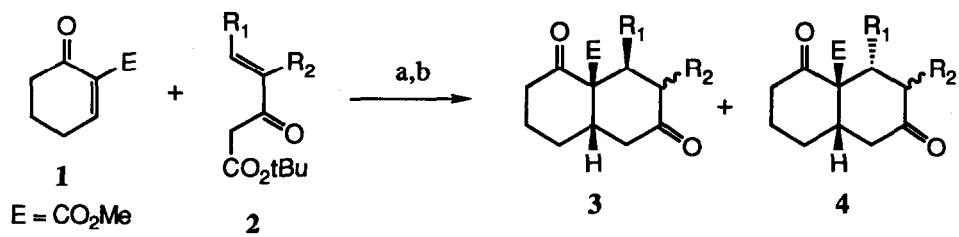
ABSTRACT : The base-catalyzed double Michael addition of the ß-keto sulfoxide **5** with 2-carbomethoxy-2-cyclohexenone (**1**) proceeds, after elimination of the sulfoxide moiety during chromatography on silica, to give the dehydrodecalin adduct **6** with high stereoselectivity.

The Diels-Alder cycloaddition or double Michael cyclization of substituted Nazarov reagents like **2** with 2-carbomethoxy-2-cyclohexenone (**1**)[2] leads to *cis*-decalins with a high degree of stereoselectivity (Scheme 1).[3] The orientation of the alkyl group at C_9 (steroid numbering) is solvent dependent. In polar solvents such as DMF and acetonitrile, for R_1 = Me and R_2 = H, the reaction was shown to proceed, at least in part, via a double Michael addition and compounds **3** and **4** were formed in ratios of 1:1 and 3:1, respectively.

However, in solvents like chloroform and dichloromethane, the reaction proceeded solely via a Diels-Alder cycloaddition, and ratios of **3** to **4** better than 99:1 were obtained.[3] A wide variety of substituted Nazarov reagents (R_1 = R_2 = alkyl, -$(CH_2)_4$-, etc...) undergo cycloaddition with **1** to give *cis*-decalins or polycyclic compounds.[4,5] In all cases the reaction proceeds with high stereoselectivity to give the *cis-cis* stereochemistry at C_5, C_9, and C_{10}.

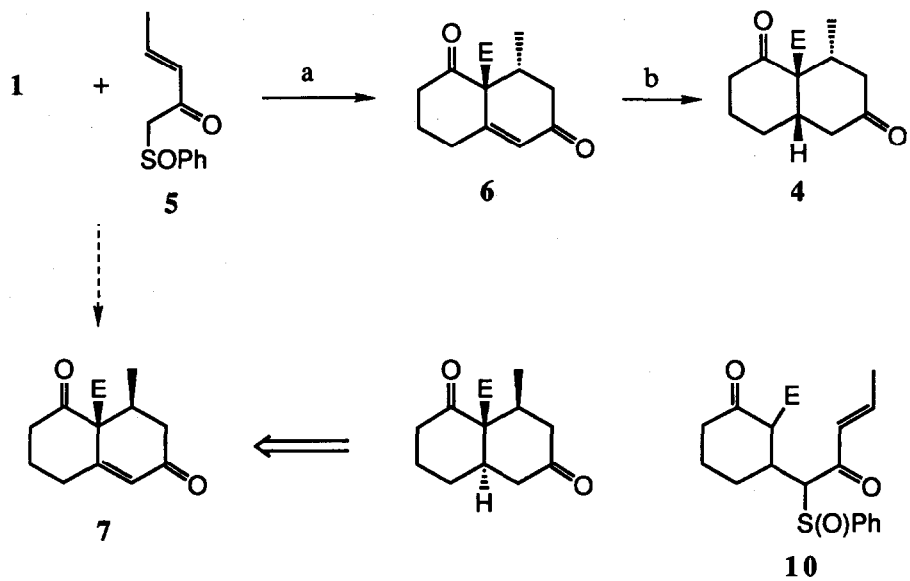


1 E = CO_2Me **2** **3** **4**

SCHEME 1 (a) Cs_2CO_3 in $CHCl_3$ 2 h, r.t. (b) pTsOH, benzene, reflux, 2 h.

We decided to look at the reaction of 1-phenylsulfinyl analogues of the Nazarov reagent, such as **5**, and 2-carbomethoxy-2-cyclohexenone (**1**), to gain entry to *trans*-decalin systems via the reduction of unsaturated compounds such as **7** (Scheme 2). Indeed it was thought that the phenylsulfoxide group could easily undergo elimination after the cycloaddition had taken place, to afford the corresponding unsaturated decalin system. A dissolving metal reduction in liquid ammonia would then afford the desired *trans*-decalin.[6] The preparation of the ß-keto sulfoxide **5** was easily achieved by the condensation of the anion of methylphenylsulfoxide (LDA, THF, -78°C)[7] with methyl crotonate.

The reaction between **5** and **1**, catalyzed by cesium carbonate, proceeded smoothly in dichloromethane to give, after chromatography on silica gel[8] a 70% yield of a single bicyclic product.[9] We expected the relative stereochemistry of the adduct to be that shown for **7** based on the results obtained with ß-keto esters like **2**.

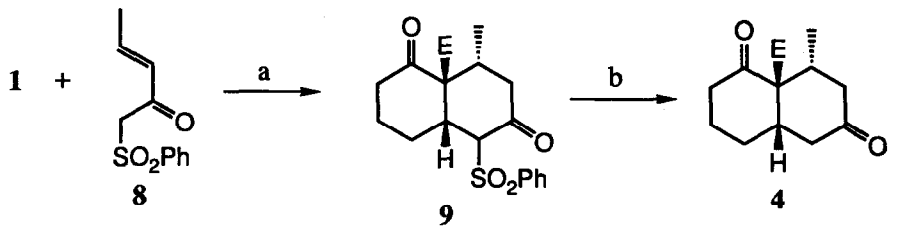


SCHEME 2 (a) Cs_2CO_3, CH_2Cl_2, 2h, r.t., then SiO_2 (b) H_2, Pd/C, EtOAc

To our surprise, hydrogenation (H_2 / Pd-C, EtOAc, r.t., 12 h) of this bicyclic compound furnished a 13:1 ratio of the known dione **4**,[10,11] and a second bicyclic product, in a combined chemical yield of 60% (Scheme 2). This indicated that the product formed in the reaction of **5** and **1** had in fact the structure shown for **6**. The spectral data for the minor isomer resulting from the hydrogenation did not correspond to those of compound **3**. Although it seems reasonable to think that this

minor isomer would result from the α-face attack of hydrogen to give the *trans*-decalin, we could not secure its structure due to our inability to isolate it in pure form.

Also, reaction of ß-ketosulfone **8** and **1** afforded bicyclic adduct **9** in 45% yield, which was reduced with aluminium amalgam[12] to give **4** as the sole product in 48% yield (79% based on recovered starting material) (Scheme 3). ß-Keto sulfone **8** was in turn prepared in 81% yield from the oxidation of ß-keto sulfoxide **5** with *m*-chloroperbenzoic acid in dichloromethane. The reaction between **8** and **1** was, however, slower and more sluggish.



SCHEME 3 (a) Cs_2CO_3, CH_2Cl_2, 6h, r.t. (b) Al / Hg, THF:H_2O (9:1)

Unlike the reaction of ß-keto ester **2** with **1**, the stereoselectivity in the reaction of **5** and **1** proved to be independent of the solvent used, and only isomer **6** could be detected when the condensation was performed in the polar solvent DMF. The reaction can in principle proceed through a double Michael addition or Diels-Alder mechanism.[13] To probe the reaction mechanism, we carried out the condensation of **5** and **1** at lower temperature. After 1.5 hours in dichloromethane, at 0°C, we isolated the monoadduct **10** in 46% yield along with 32% starting material. This result is consistent with a double Michael addition mechanism.

In acetonitrile at -5°C, the monoadduct **10**, the bicyclic compound **6**, and the starting sulfoxide **5**, were isolated in 17%, 24%, and 26% yield respectively. No reaction could be observed at lower temperatures, in either solvent. In the latter case we cannot exclude the possibility that the reaction proceeds partly through a cycloaddition mechanism. However, the isolation of compound **6** more likely reflects a faster rate of ring closure in acetonitrile. When the monoadduct **10** was submitted to the usual reaction conditions (Cs_2CO_3, 25°C) in either solvents, a ~ 60% yield of the bicyclic adduct **6** could be obtained as the sole product.

In conclusion, the double Michael addition-cyclization of 1-phenylsulfinyl-3-penten-2-one **5** and 2-carbomethoxy-2-cyclohexenone (**1**) is in effect analogous to a Robinson annulation reaction done under mild conditions. It is complementary to the

cycloaddition of substituted Nazarov reagents like **2** and could prove useful in the synthesis of a variety of naturally occurring compounds. The reason for the reversal of stereochemistry at C_9 is at present unknown and further experiments will be required to determine the exact mechanistic role of the sulfinyl and sulfonyl group in this reaction.[14]

References and Notes

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(8) The elimination of the phenylsulfoxide proceeded on the silica gel during chromatography. Compound **6** can be recrystallized from a 3 : 1 mixture of hexanes - ethyl acetate.

(9) None of the isomer **7** could be detected after chromatography. Compound **6** was shown to be >99% pure by G.C. analysis after chromatography.

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