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One Pot Michael Addition, Vinylsulfone Isomerization and Alkynyl to Alkenyl Triple Bond Reduction. Synthesis of a Carbasugar Related to Rancinamycin III

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Dedicated to Prof. Henry Rapoport

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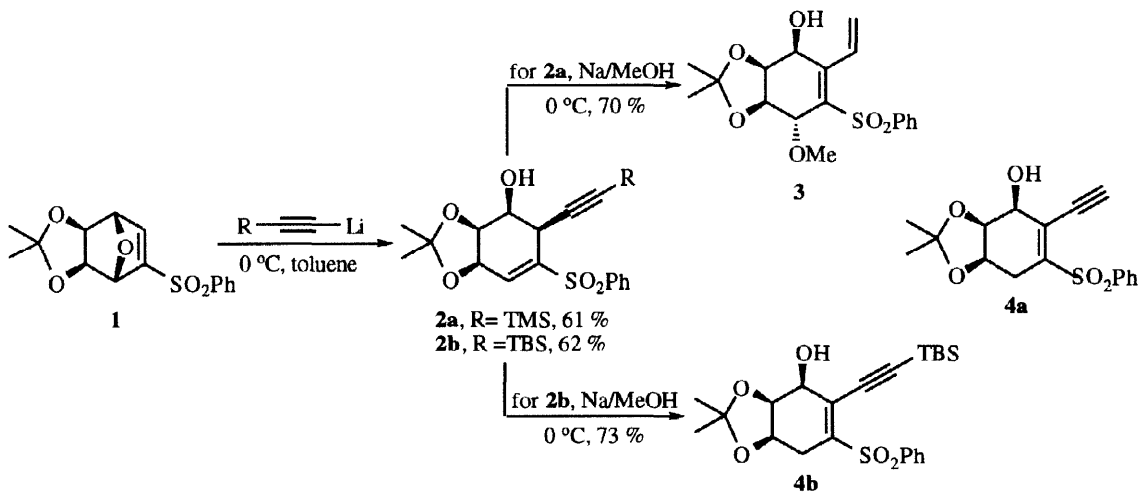
Abstract: Cyclohexenylsulfones **2** show a different behaviour in their reactions with Na/MeOH system depending on the nature of protecting groups R. In the case of R= TMS, the observed sequence Michael addition-vinylsulfone isomerization-alkynyl to alkenyl reduction has been used for the synthesis of a carbasugar related to the antibiotic Rancinamycin III.

In connection with some studies concerning the synthetic application of functionalized cyclohexenylsulfones **2** obtained by S_N2' ring opening of oxanorbornenic derivatives **1** by reaction with lithium acetylides,[1] we have studied the reaction of sulfones **2a** and **2b** with Na/MeOH system in order to achieve the transformation **2** to **4**. In this way, we have observed a different behaviour of both compounds **2a** and **2b** depending on the nature of the substituent R attached to the exocyclic triple bond (Scheme 1).



Scheme 1

Thus, reaction of **2b** with Na, MeOH at 0 °C gave the expected conjugated sulfone **4b**. However, in the case of **2a** in the same conditions, one pot sequence Michael addition of methoxide to the vinylsulfone moiety with concommitant vinylsulfone isomerization and triple to double bond reduction was observed. It should be pointed out that the use of other basic reagents, such as NaH in THF at 0 °C, affords exclusively sulfones **4a** and **4b**, starting from **2a** and **2b**, respectively.

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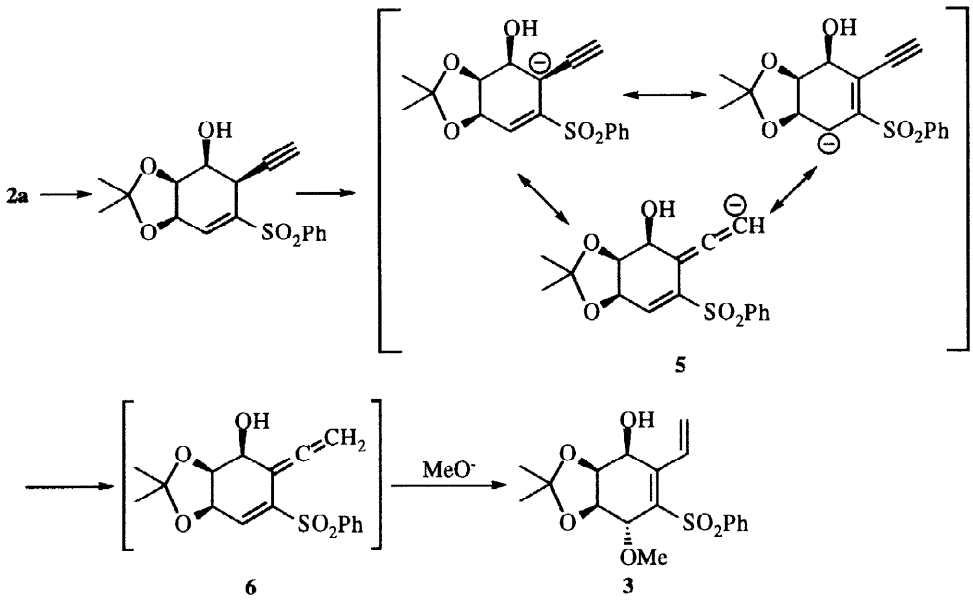
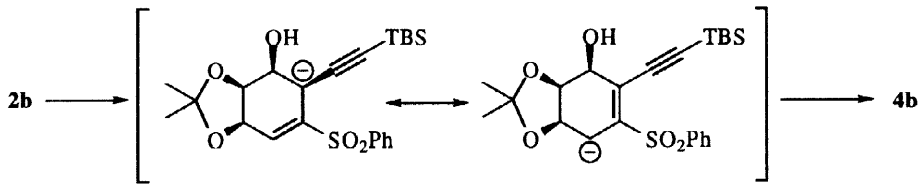
A probably reaction pathway for the transformation **2a** to **3** involves the previous deprotection of the acetylenic moiety to produce the tridentate anion **5**. Reprotonation at the terminal allenic position gives **6**[2] which after conjugate addition of methoxide anion affords, finally, compound **3** (Scheme 2).[3]



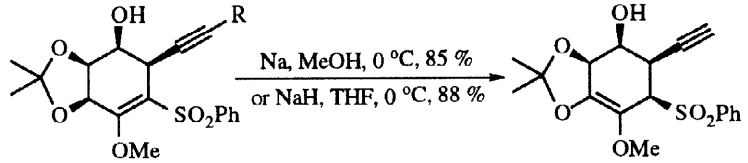
Scheme 2

In the case of **2b**, this compound does not undergo elimination of the TBS group and thus the alkyne-allene isomerization is prevented. Final protonation on the less hindered position of the ambidentate anion gives the conjugated enyne **4b** (Scheme 3).



Scheme 3

It should be pointed out that methoxysulfone **7a**[4] shows a different behaviour in Na/MeOH system. Thus, deprotection of TMS group and 1,3-hydrogen shift rendered the allylic sulfone **8**. In the same conditions, the analogous sulfone **7b** did not react (Scheme 4).



7a, R= TMS
7b, R= TBS

Scheme 4

Compound **3** has been used for the synthesis of carbasugar **9** related to the general structure of the antibiotic Rancinamycin III[5] and with a well defined stereochemistry in the four chiral centers (Figure 1).

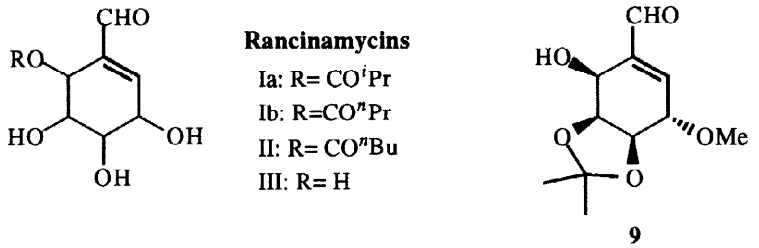
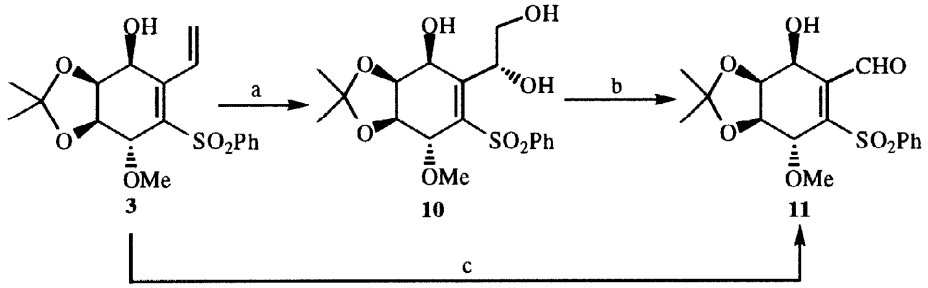


Figure 1

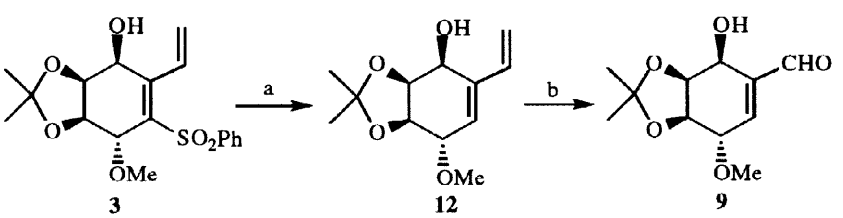
Bishydroxilation of **3** afforded 55 % of **10** after column chromatography.[6] $NaIO_4$ oxidation of diol **10** produced aldehyde **11**. Also, oxidation of **3** with $NaIO_4$ and $RuCl_3$ gave directly **11**. At this stage, desulfonylation of **11** was not possible and under a variety of experimental conditions, extensive decomposition of the starting material was observed (Scheme 5).



Reagents and conditions: a) OsO_4, $NOMe_3 \cdot 2H_2O$, acetone:H_2O 8:1, 55 %. b) $NaIO_4$, THF:H_2O 1:1, 71 %. c) $NaIO_4$, $RuCl_3 \cdot H_2O$, CH_3CN:CCl_4:H_2O 3:3:4, 67 %.

Scheme 5

Therefore, we decided to change the order of experimental operations. In this way, desulfonylation of **3** was achieved using Na-Hg to give **12**. Finally, direct oxidation of exocyclic double bond in **12** with $NaIO_4$, $RuCl_3$ afforded **9**[7] (Scheme 6).



Reagents and conditions: a) Na-Hg, , Na_2HPO_4, MeOH, -20 °C to rt, 80 %. b) $NaIO_4$, $RuCl_3 \cdot H_2O$, CH_3CN:CCl_4:H_2O 3:3:4, 50 %.

Scheme 6

In summary, an interesting, unprecedent transformation of alkynylcyclohexenylsulfones such as **2** was achieved involving a Michael addition, vinylsulfone isomerization and triple bond reduction. This transformation has been used for the synthesis of carbasugar **9** related to Rancinamycin III. Alternatively, vinylsulfone isomerization was observed depending on the nature of the substituent attached to the alkynyl moiety. Other useful transformations are now under active research in our laboratory.

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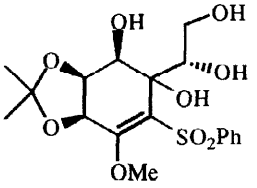
References and notes.

1. a) Arjona, O.; de Dios, A.; Fernández de la Pradilla, R.; Plumet, J.; Viso, A. *J. Org. Chem.* **1994**, *59*, 3906-3916. b) Aceña, J. L.; Arjona, O.; Iradier, F.; Plumet, J. *Tetrahedron Lett.* **1996**, *37*, 105-106.
2. For a general account on the alkyne-allene isomerism, see: J. March in "Advanced Organic Chemistry. Reactions, Mechanism and Structure". 4th Ed. John Wiley, **1992**, pp. 582-583.
3. This reaction pathway appears to be reminiscent of those proposed for organocopper reagents mediated 1,6-additions to alkenynones and alkenylnoates: Frederick, M. A.; Hulce, M.; *Tetrahedron* **1997**, *53*, 10197-10277. See pp. 10204-10206.
4. Compounds **7** were prepared by Diels-Alder cycloaddition of 2-methoxyfuran and *trans*-1,2-*bis*-(phenylsulfonyl)-ethylene followed by chemical elaboration of the resulting adducts. Full details wil be given elsewhere.
5. a) Argoudelis, A. D.; Pike, T. R.; Sprague, R. W.; *J. Antibiot.* **1976**, *29*, 777-786. b) Argoudelis, A. D.; Sprague, R. W.; Mizsak, S. A.; *J. Antibiot.* **1976**, *29*, 787-796.
6. A 18 % yield of compound **13** has been found in bishydroxylation of compound **3**.
7. All new compounds showed spectroscopic and analytical data consistent with the assigned structures. In the case of ^{1}H-RMN, selective decoupling experiments were used for stereochemical determination.



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