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[D002]

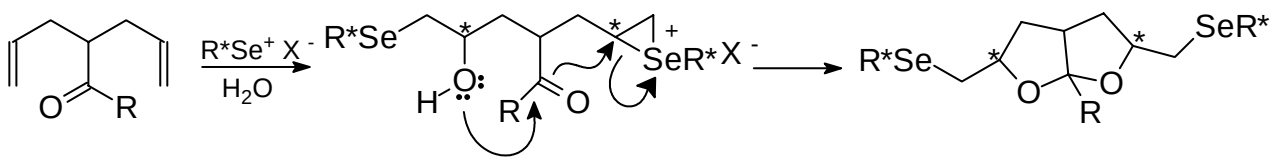
SELENIUM PROMOTED ENANTIOSELECTIVE SYNTHESIS OF SPIROKETALS

Luana Bagnoli, Marcello Tiecco, Lorenzo Testaferri, Catalina Scarponi, Andrea Temperini, Francesca Marini and Claudio Santi

Dipartimento di Chimica e Tecnologia del Farmaco, Sezione di Chimica Organica, Università di Perugia, 06123 Perugia, Italy

1. Introduction

In the last few years our research group has been deeply involved in the synthesis of several types of heterocyclic compounds in an enantiomerically enriched or pure form using very efficient chiral non racemic organoselenium reagents.[1] At the same time the synthesis of enantiomerically pure substituted heterocycles was effected starting from commercially available enantiopure compounds[2] and using simple conversions promoted by electrophilic phenylselenium reagents.[3,4] Using this methodology and starting from the commercially available (*R*)-(+)-2,2-dimethyl-1,3-dioxolane-4-carboxaldehyde, by means of two consecutive selenium promoted cyclizations, the tetrahydrofuro[3,4-*b*]pyrans and tetrahydrofuro[3,4-*b*]furans could be easily obtained as pure enantiomers.[5] On the other hand we have recently reported the synthesis of the related enantiomerically pure perhydrofuro[2,3-*b*]furans by means of a double cyclization of bis-alkenylketones promoted by the enantiopure camphorselenenyl sulphate, in the presence of water.[6] (Scheme 1)

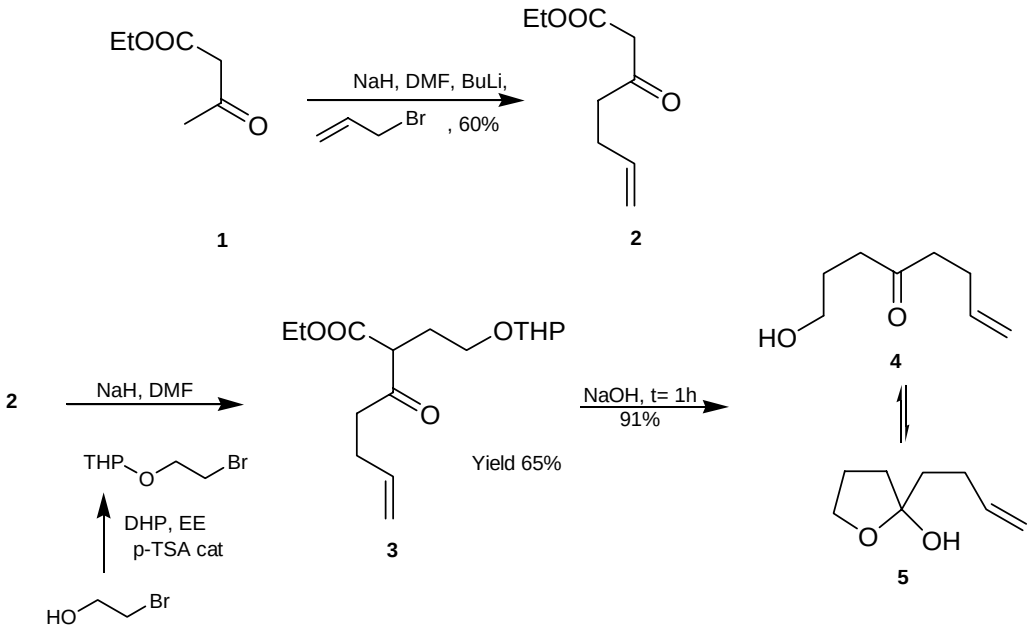


Scheme 1

2. Results and discussion

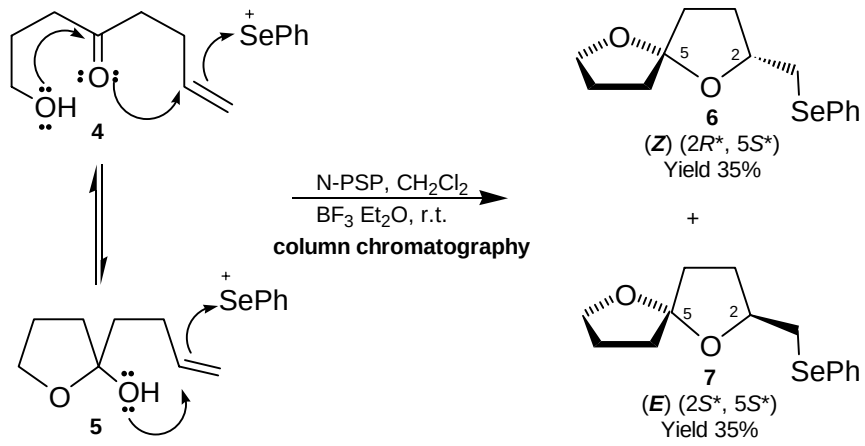
We now report that using a similar approach the synthesis of enantiomerically pure 2-substituted-1,6-dioxaspiro[4.4]nonane can be easily effected starting from 1-hydroxyoct-7-en-4-one. The enantioselective synthesis of these chiral spiroketals has a considerable importance since these nuclei are the subunits of many biologically active natural products.[7] Moreover, the control of the stereochemistry at their spiro center is also a challenging problem.[8]

The starting product of the present investigation was easily prepared starting from commercial available ethyl-3-oxobutanoate **1**. The reaction sequence consisted in two consecutive alkylation reactions to obtain the ketone **3**, which after hydrolysis provided 1:2 mixture of the hydroxyketone **4** and the hemiacetal **5**. (Scheme 2)



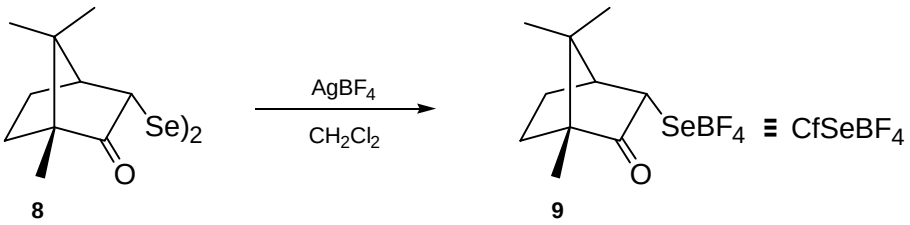
Scheme 2

In order to dispose of the racemic 2-substituted-1,6-dioxaspiro[4.4]nonanes **6** and **7** (Scheme 3) to be used as reference compounds we have preliminarly carried out the cyclization reaction of the mixture of **4** and **5** with the N-phenylselenophthalimide (N-PSP) in the presence of BF_3 as catalyst [7] at room temperature. This reaction produced a 1:1 mixture of the *Z* and *E* isomers **6** and **7**, which were separated by medium pressure liquid chromatography.



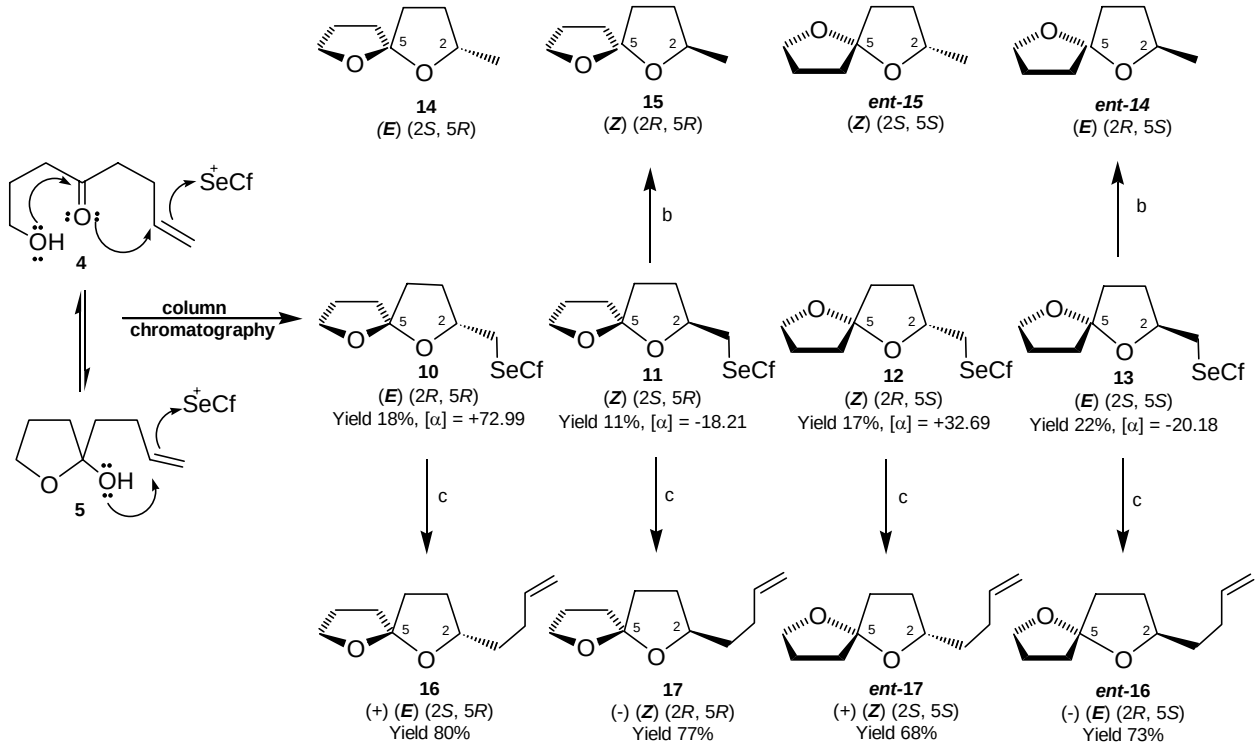
Scheme 3

The same synthetic sequence was then employed for the cyclizations of **4** and **5** promoted by the camphorselenenyl tetrafluoroborate **9**, generated from the reaction of the camphor diselenide[9] **8** with silver tetrafluoroborate in dichloromethane at -50°C and the suspension was stirred at the same temperature for 30 min.[10] The starting products **4** and **5** were added and the temperature was allowed to slowly reach room temperature. Stirring was continued for 20 h and the reaction was then quenched with a 10% $NaHCO_3$ solution and extracted with dichloromethane.



Scheme 4

The results of this cyclization reaction are reported in Scheme 5. A mixture of the two *E* diastereisomers **10** and **13** and of the two *Z* diastereoisomers **11** and **12**, was obtained. These were separated by medium pressure liquid chromatography. The enantiopure selenides are presented in the Scheme in the same order in which they are eluted from the chromatographic column.



a: $CfSe)_2$, $AgBF_4$, CH_2Cl_2, T = -50°C to r.t.; b: Ph_3SnH, AIBN, C_6H_6, reflux, t=1h; c: Bu_3Sn, AIBN,C_6H_6, reflux, t=6h

Scheme 5

The reductive deselenenylation and deselenenylation with allylation reactions were employed to assign the *E* and *Z* configurations at the four diastereoisomers **10**-**13**. The reductive deselenenylations with Ph_3SnH and AIBN were complicated by the volatility and the instability of the deselenenylated products. However the NMR spectra of the crude reaction mixtures of the products **15** and ***ent*-14**, obtained from **11** and **13**, were in perfect agreement with the data reported in the literature for the racemic 2-methyl-1,6-dioxaspiro[4.4]nonane with configuration *Z* and *E* respectively.[7,11,12]

The camphorselenyl group was then substituted by an allyl function using allyl-tributylstannane in the presence of AIBN. The two allylation products deriving from the two diastereoisomers **10** and **13** presented identical NMR spectra suggesting that they are the two enantiomers **16** and ***ent*-16**, having the *E* configuration. The diastereoisomers **11** and **12** gave two other allylation products which presented identical NMR spectra. Thus, the structures **17** and ***ent*-17**, having the *Z* configuration was attributed to these two enantiomers.

Attribution of structure **16** and structure ***ent*-16** to the dextrorotatory and to the levorotatory enantiomers respectively, and the structures **17** and ***ent*-17** to the levorotatory and to the dextrorotatory enantiomers respectively are at present only tentative.

3. Conclusions

The great advantage of the present method consists in the use of chiral non racemic organoselenium reagents and hence in the preparation of the 1,6-dioxaspiro[4.4]nonane in enantiomerically pure form in a one pot reaction. The present simple procedure can have general application since it can be applied to the cyclization of several hydroxyketones thus leading to differently spiro compounds. Moreover, the presence of the organoselenium function in the cyclization products allows the introduction of several other groups to be easily effected.

Acknowledgements

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4. References

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