9th International Electronic Conference on Synthetic Organic Chemistry. ECSOC-9. 1-30 November 2005.

http://www.usc.es/congresos/ecsoc/9/ECSOC9.HTM & http://www.mdpi.net/ecsoc/

[A032]

ENANTIOPURE TETRAHYDROFURANOLS BY RADICAL CYCLIZATION REACTIONS. A SIMPLE ENTRY INTO ISODIDEOSSINUCLEOSIDES

F. Marini, M. Tiecco, L. Testaferri, S. Sternativo, C. Santi, L. Bagnoli and A. Temperini

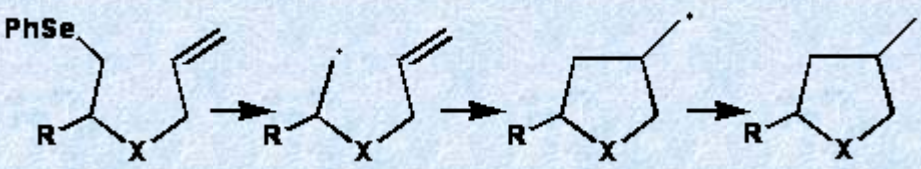
Dipartimento di Chimica e Tecnologia del Farmaco, Sezione di Chimica Organica, Università di Perugia, Italy. E-mail: marini@unipg.it

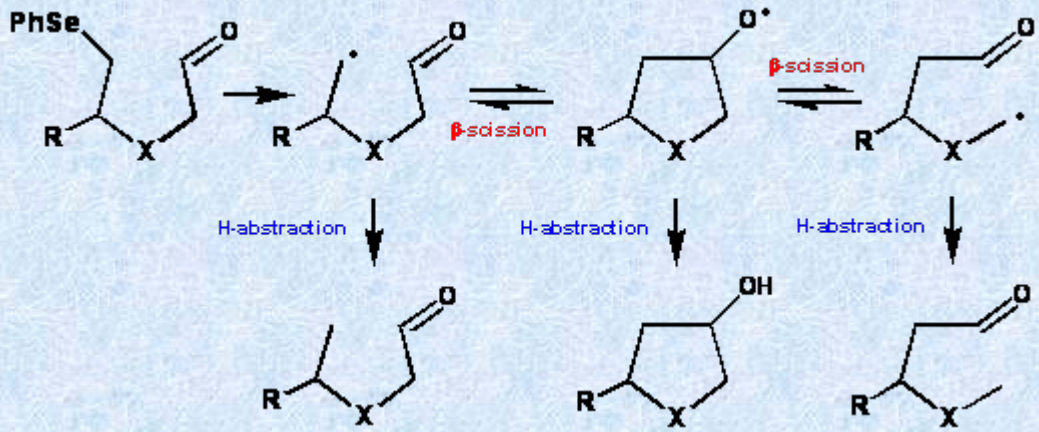
Introduction:

Organoselenium chemistry can be successfully employed for the stereoselective synthesis of heterocyclic compounds. In the last few years our research group has been involved in the preparation of enantiopure or enantiomerically enriched heterocyclic compounds by using electrophilic cyclization reactions promoted by enantiopure selenium reagents. A number of heterocycles have been prepared in high yields and with excellent diastereoselectivities.[1] However, other selenium containing compounds can find useful application for the preparation of heterocyclic compounds, also in the optically active form. In fact, readily available phenyl selenides give ring closure reactions through easy manipulations of the phenylseleno group. For example, they generate heterocyclic compounds by intramolecular nucleophilic substitution after conversion of the phenylseleno group into a better leaving group such as a selenone or a selenonium ion.[2]

Phenyl selenides are also good precursors of carbon radicals, so that heterocyclic compounds can be formed by intramolecular addition of these radicals to a C-C double bond (Scheme 1). These reactions have been extensively studied and several tetrahydrofurans and pyrrolidines have been prepared in high yields. [3] Similar cyclizations which involve a C-O double bond are much less explored. The few examples reported in the literature indicate that, although the carbonyl group is an excellent radical acceptor, the trapping of the intermediate cyclic alkoxy radical, particularly if 5-membered, is not always easy because of its rapid b-scission. [4,5]

Scheme 1



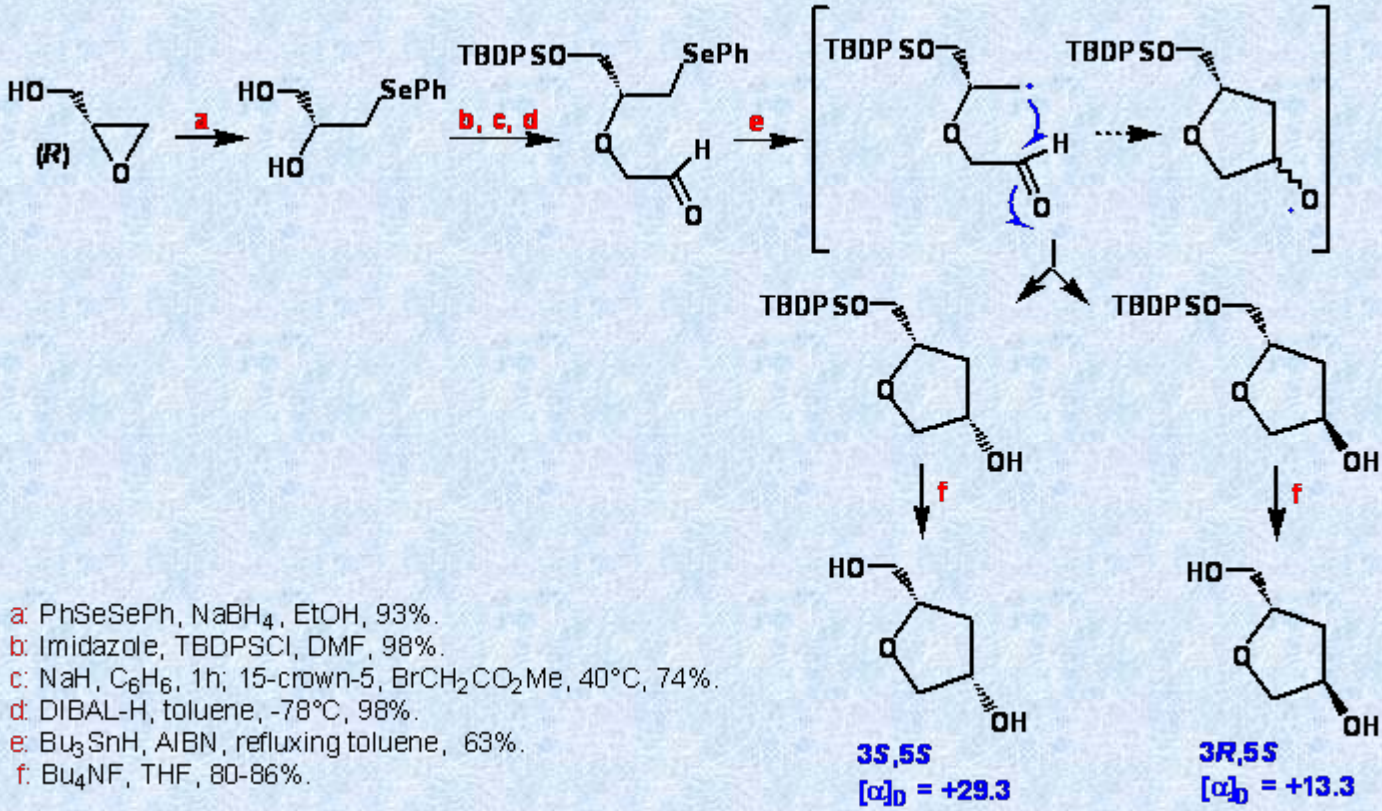


We now report that radical cyclization reactions involving a carbonyl group can be successfully employed for the synthesis of enantiopure tetrahydrofuranols. The starting (2-phenylselenoethoxy)aldehydes have been easily prepared from commercially available enantiopure epoxides or chlorohydrins.

Results and discussion

Scheme 2 illustrates the preparation of the two enantiopure *cis* and *trans* 5-(hydroxymethyl)tetrahydrofuran-3-ols starting from (*R*)-glycidol. The first step of the sequence is the regiospecific opening of the epoxide which generates a dihydroxyselenide. After selective protection of the primary alcohol, the hydroxyselenide was transformed into the corresponding alkoxyester by treatment with methyl bromoacetate. A controlled reduction with DIBAL-H generated the aldehyde. As reported in the scheme all these reactions occur in good to excellent yields. The enantiopure aldehyde was then submitted to radical cyclization. Preliminary experiments were carried out in order to optimize this step. Different solvents, reaction temperatures and hydrogen donors were examined and the best yield was obtained using a slight excess of Bu_3SnH in refluxing toluene. None of the b-scission products was present in the crude mixture and the indicated enantiopure diastereomeric tetrahydrofuranols were produced with a 63% yield in almost equal amounts. Lower yields were observed by using other hydrogen donors, such as Ph_3SnH or $(Me_3Si)_3SiH$, or by adding Bu_3SnH in large excess or by a slow addition. The two diastereoisomers, after chromatographic separation, were deprotected by treatment with tetrabutylammonium fluoride. The spectroscopic data and the optical rotations of the formed compounds were in good agreement with those reported in the literature.[6]

Scheme 2

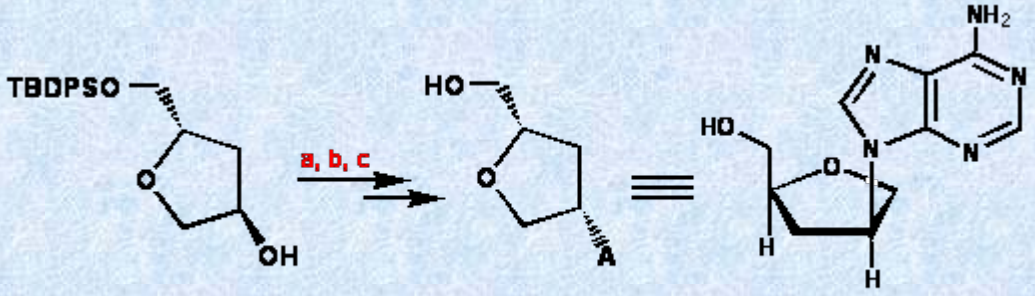


a: $PhSeSePh$, $NaBH_4$, EtOH, 93%.
b: Imidazole, TBDPSCl, DMF, 98%.
c: NaH, C_6H_6, 1h; 15-crown-5, $BrCH_2CO_2Me$, 40°C, 74%.
d: DIBAL-H, toluene, -78°C, 98%.
e: Bu_3SnH, AIBN, refluxing toluene, 63%.
f: Bu_4NF, THF, 80-86%.

These tetrahydrofuranols are useful intermediates in the synthesis of isonucleosides, usually prepared by multi-step sequences from carbohydrates.

Isonucleosides constitute a novel class of antiviral agents which have attracted great interest.[6,7] Besides their strong and selective anti-HIV and anti-HSV activities, this class of nucleosides possesses an high stability toward acids and a good resistance to enzymatic deamination.

Scheme 3



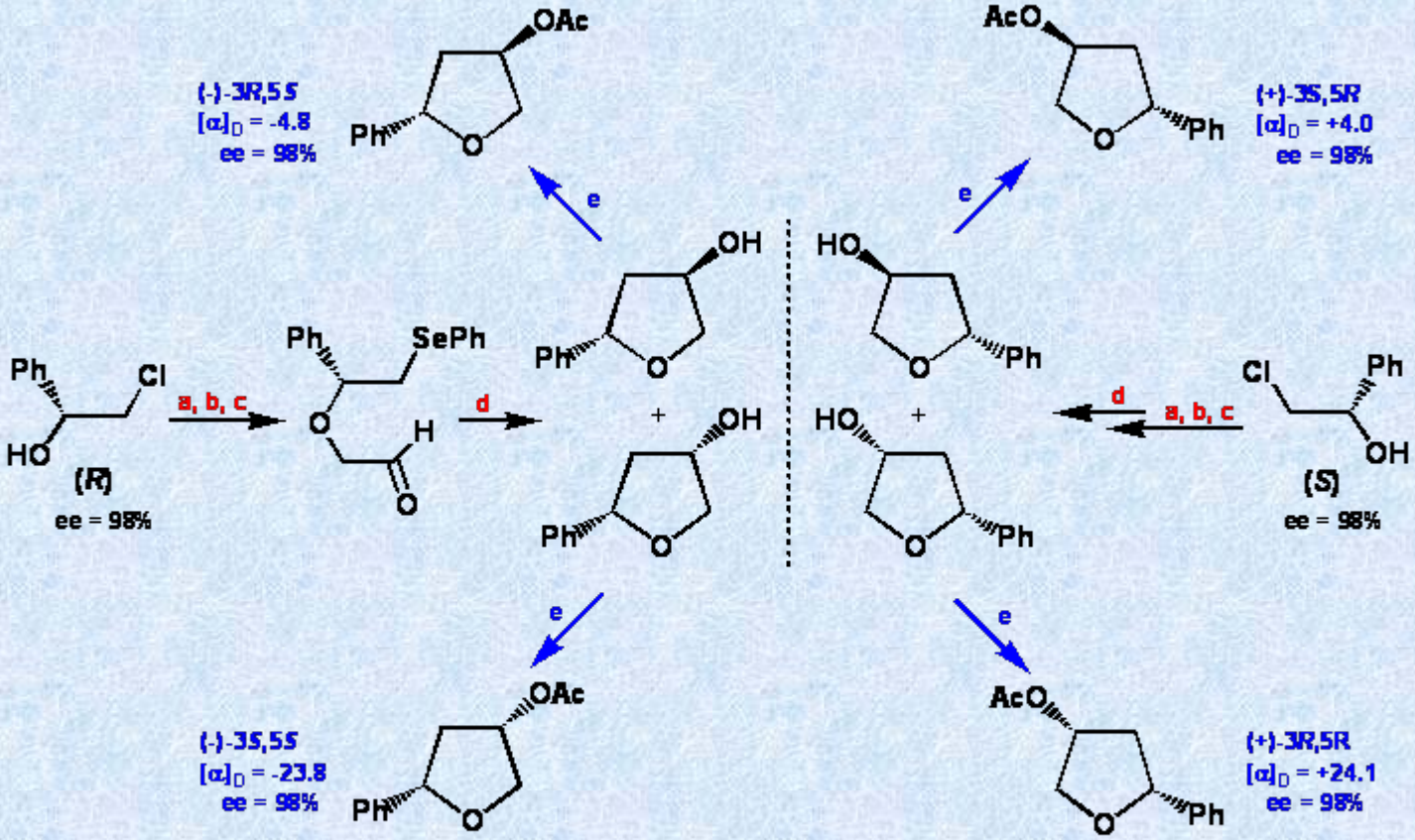
a: MsCl, DMAP, Et_3N, 81%. b: Adenine (=A), 18-crown-6, K_2CO_3, DMF, 63%. c: TBAF, THF, 100%.

Scheme 3 describes the facile conversion of the protected (3*R*,5*S*)-5-(hydroxymethyl)tetrahydrofuran-3-ol into the (*S*,*S*)-*iso*-ddA by nucleophilic substitution of the hydroxyl group after its activation as mesylate.[6]

Scheme 4 refers to the preparation of enantiopure 5-phenyl-3-tetrahydrofuranols. The nucleophilic substitution by sodium phenyl selenolate of the commercially available (*R*)-2-chloro-1-phenylethanol generates the hydroxyselenide. This approach is more convenient than the opening of the corresponding (*R*)-styrene oxide which is not regiospecific. The next steps proceed in moderate to good yields. The diastereomeric tetrahydrofuranols were obtained in pure form by medium pressure liquid chromatography after conversion into the corresponding acetates. The synthetic sequence has been repeated starting from the (S)-chlorohydrin in order to obtain the enantiomeric *trans* and *cis* tetrahydrofuranols. Scheme 4

shows the measured optical rotations and the enantiomeric excesses determined by HPLC using a chiral column.

Scheme 4



a: $PhSeSePh, NaBH_4$, THF-HMPA, 40°C, 90%. b: NaH, C_6H_6, 1h;15-Crown-5, $BrCH_2CO_2Me$, 40°C, 75%. c: DIBAL-H, toluene, -78°C, 80%. d: Bu_3SnH, AIBN, refluxing toluene, 50-60%. e: AcCl, Pyr., THF, 60-80%.

Conclusions

Enantiopure (2-phenylselenoethoxy)aldehydes, prepared in three steps starting from commercial epoxides or chlorohydrins (ee>98%), afforded tetrahydrofuranols by 5-*exo*-*trig* radical cyclizations. In agreement with earlier observations[4b] these reactions are not diastereoselective but the enantiopure diastereomeric *cis* and *trans* tetrahydrofuranols can be easily separated by chromatography. These products can find useful applications in the preparation of natural or biologically active compounds as described for the isonucleosides. Similar reaction sequences affording more functionalized tetrahydrofuranols or nitrogen containing heterocycles are currently under investigation.

Financial support from MIUR -National Research Projects PRIN 2003 and FIRB 2001-, Consorzio CINMPIS and Perugia University -Progetti di Ateneo- is gratefully acknowledged.

References

[1] a) Tiecco, M.; Testaferri, L.; Marini, F.; Sternativo, S.; Bagnoli, L.; Santi, C.; Temperini, A.

Tetrahedron: Asymmetry **2001**, *12*, 1493. b) Tiecco, M.; Testaferri, L.; Marini, F.; Sternativo, S.; Santi, C.; Bagnoli, L.; Temperini, A. *Tetrahedron: Asymmetry* **2001**, *12*, 3053. c) Tiecco, M.; Testaferri, L. ; Bagnoli, L.; Purgatorio, V.; Temperini, A.; Marini, F.; Santi, C. *Tetrahedron: Asymmetry* **2001**, *12*, 3297.

[2] a) Tiecco, M.; Testaferri, L.; Temperini, A.; Bagnoli, L.; Marini, F.; Santi, C. *Chem. Eur. J*. **2004**, 1752. b) Tiecco, M.; Testaferri, L.; Marini, F.; Sternativo, S.; Santi, C.; Bagnoli, L.; Temperini, A. *Eur. J. Org. Chem*. **2005**, 543.

[3] a) Ericsson, C.; Engman, L. *Org. Lett.* **2001**, *3*, 3459. b) Berlin, S.; Ericsson, C.; Engman, L. *Org. Lett.* **2002**, *4*, 3. c) Gupta, V.; Besev, M.; Engman, L. *Tetrahedron Lett.* **1998**, *39*, 2429. d) Berlin, S.; Engman, L. *Tetrahedron Lett.* **2000**, *41*, 3701.

[4] These papers refer to the preparation of carbocyclic compounds starting from carbon radical generated from halogenides. a) Beckwith, A. L. J.; Hay, B. P. *J. Am. Chem. Soc.* **1989**, *111*, 2674. b) Beckwith, A. L. J.; Raner, K. D. *J. Org. Chem.* **1992**, *57*, 4954. c) Batey, R. A.; MacRay, D. B. *Tetrahedron Lett.* **1998**, 7267. d) Devin, P.; Fensterbank, L.; Malacria, M: *Tetrahedron Lett*. **1999**, *40*, 5511.

[5] Uchiyama, M.; Hirai, M.; Nagata, M.; Katoh, R.; Ogawa, R.; Ohta, A. *Tetrahedron Lett.* **2001**, *42*, 4653.

[6] Jung, M. E.; Kretschik, O. *J. Org. Chem.* **1998**, *63*, 2975.

[7] a) Nair, V.; Nuesca, Z. M. *J. Am. Chem. Soc.* **1992**, *114*, 7951. b) Huryn, D. M.; Sluboski, B. C.; Tam, S. Y.; Weigele, M.; Sim, I.; Anderson, B. D.; Mitsuya, H.; Broder, S. *J. Med. Chem.* **1992**, *35*, 2347. c) Jones, M. F.; Noble, S. A.; Robertson, C. A.; Store, R.; Highcock, R. M.; Lamont, R. B. *J. Chem. Soc. Perkin Trans. 1* **1992**, 1427. d) Diaz, Y.; Bravo, F.; Castillon, S. *J. Org. Chem.* **1999**, *64*, 6508. e) Yoo, S. J.; Kim, H. O.; Lim, Y.; Kim, J.; Jeong, L. S. *Bioorg. Med. Chem*. **2002**, *10*, 215. f) Nair, V.; Wenzel, T. ARKIVOC **2004**, (XIV) 128. (g). Nair, V.; Byoung, K. C.; Vadakkan, J. *Tetrahedron* **2004**, *60*, 10268.