Heteroatom Chemistry
Volume 15, Number 6, 2004

# A Simple, Convenient and Expeditious Approach to Cineol

Zorica M. Bugarčić, Jelena D. Dunkić, and Biljana M. Mojsilović

*Department of Chemistry, Faculty of Science, University of Kragujevac, Radoja Domanovića 12, P.O. Box 60, 34 000 Kragujevac, Serbia*

*Received 25 June 2004*

ABSTRACT: *A convenient two-step protocol preparation of cineol (1-isopropyl-4-methyl-7-oxabicyclo-[2,2,1]heptane) from α-terpineol (p-menth-1-en-8-ol) is reported. The phenylselenoetherification of α-terpineol with PhSeX (X = Cl, Br, I) as a key step is described. α-Terpineol reacts with PhSeX to form the corresponding phenylselenoether in short reaction time and in quantitative yield. A subsequent reduction with $Bu_3SnH$ to cineol proceeds in high yield (98%)* © 2004 Wiley Periodicals, Inc. Heteroatom Chem 15:468–470, 2004; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20044

## *INTRODUCTION*

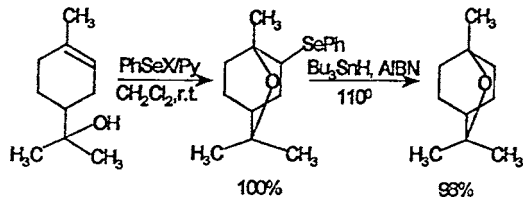
Cyclofunctionalization of unsaturated alcohols is a very popular reaction providing easy access to cyclic ether products [1–6]. In many respects, selenocyclofunctionalization has the advantage that the introduction of the heteroatom, the manipulation of the obtained product, and the removal of the function are facilitated by simple and mild condition required [5–7]. This methodology has been extended to more complex system having alcohol and double bond functions.

Cyclization of unsaturated alcohols leading to cyclic ethers is well documented in the literature as convenient pathways in the synthesis of natural-products and related compounds [8]. During the past years, cyclic ethers have attracted considerable attention due to their occurrence in several groups of natural compounds exhibiting important biological activities [9]. These units can be found in monocyclic or polycyclic compounds, fused with other cyclic ethers or forming spiro systems [10]. The presence of molecules with oxygenated heterocycles in nature is receiving considerable attention considering their capacity of modification of the transport of the $Na^+$, $K^+$, and $Ca^{2+}$ cations through lipid membranes [11–14]. This activity is responsible for their antibiotic [11], neurotoxic [15,16], antiviral [17], and cytotoxic action [18,19] and as growth regulators [11,20,21] or inhibitors of the level of cholesterol in blood [22].

In the past few years, attention has been focused on the synthesis of the substituted tetrahydropyranes and tetrahydrofuranes as key starting materials for the preparation of numerous heterocyclic compounds including physiologically active products. Tetrahydropyrans are commonly encountered substructures in many natural products showing interesting biological properties; the most prominent of these being polyether antibiotics such as monensin, narasin, and tetronomycin [11]. Hence, of particular importance is the discovery of the appropriate experimental conditions under which phenylselenocyclization of alkenols would readily be accomplished in synthetically useful yields, regardless of the reagent used. This prompted us to examine a methodology for the synthesis of these systems. In recent years, we have studied intramolecular cyclization of some $\Delta^4$- and $\Delta^5$-alkenols by means of

*Correspondence to:* Z. M. Bugarčić; e-mail: zoricab@kg.ac.yu.
Contract grant sponsor: Ministry of Science, Technology and Development, Republic of Serbia.
Contract grant number: 1254.

phenylselenyl halides [23], PhSeX (X = Cl, Br). Intramolecular heterocyclization is the main reaction in the case of all investigated primary and secondary alkenols, while tertiary alkenols, under the same experimental conditions, are not converted into cyclic products at all by PhSeBr and in a small amount with PhSeCl.




SCHEME 1

## *RESULTS AND DISCUSSION*

Recently, we presented an approach to cyclic ethers from tertiary alkenols using PhSeX (X = Cl, Br) in the presence of pyridine [24]. The procedure works smoothly resulting in quantitative formation of the cyclic ethers. Prompted by this finding, we considered it synthetically interesting and profitable for our purposes to extend this method to other representative alkenols in order to describe a general procedure for a rapid and efficient cyclization reaction of alkenols with phenylselenyl halides [25,26]. Various substituted tetrahydrofuran and tetrahydropyran rings were obtained that depended on the structure of the starting alkenols. Oxidative or reductive elimination of phenylseleno group gave different unsaturated or saturated ethers that are constutuents of many natural and biological active products. In particular, our attention focused on the development of a general synthetic route for the preparation of cineol. It is a matter of fact that cineol (eucalyptol) has a widespread use (in cough syrups and expectorants, in perfumery, and flavoring). Available methods for the preparation of cineol require more steps in the synthetic process with unsatisfactory yields [27,28], or isolation from natural products [29]. The most common approach involves phenylselenoetherification of α-terpineol and a subsequent reduction with $Bu_3SnH$ or by catalytic hydrogenation ($H_2$, Pd/C, or Ra/Ni in THF at room temperature).

The cyclization step was carried out by addition of 1 equivalent of PhSeX (X = Cl, Br, I) at room temperature to a $CH_2Cl_2$ solution of α-terpineol and pyridine (in ratio 1:1), and cyclic ether bearing PhSe group was obtained in quantitative yield (100%). Reduction of this cyclic ether (elimination of PhSe group) with $Bu_3SnH$ in toluene at 110°C in the presence of AIBN gave a 98% yield of the cineol (see Scheme 1). When the removing of PhSe group was performed by catalytic hydrogenation with Ra/Ni in THF at room temperature, the yield of cineol was lower (94%).

## *EXPERIMENTAL*

All reactions were carried out on a 1 mmol scale. To a magnetically stirred solution of alkenol (1 mmol) and pyridine (1 mmol) in dry $CH_2Cl_2$ (5 $cm^3$) was added solid PhSeCl (1.1 mmol, 0.212 g) or PhSeBr (1.1 mmol, 0.260 g) or PhSeI (1,1 mmol, 0.311 g) at room temperature. The reaction was completed in few minutes. The pale yellow solution was washed with 5 $cm^3$ 1 M HCl aqueous solution, saturated $NaHCO_3$, and then brine. The organic layer was dried ($Na_2SO_4$), concentrated, and chromatography was performed. The product was obtained after the elution of the traces of diphenyl diselenide from a silica gel /$CH_2Cl_2$ column. All the products were characterized and identified on the basis of their spectral data. The cyclic ether products were known compounds, and their spectral data had been given previously in the literature [30]. Reduction was performed according to the procedure described earlier [31].

## *REFERENCES*

[1] Mihailović, M. Lj. Lectures in Heterocyclic Chemistry, 1976, 3, S-111/A (suplementary issue of the J Heterocycl Chem 1974, 11, 771).
[2] Kalvoda, J.; Heusler, K. Synthesis 1971, 501.
[3] (a) Mihajlović, M. Lj.; Marinković, D.; Konstantinović, S.; Bugarčić, Z.; J Serb Chem Soc 1985, 50, 327; (b) Mihajlović, M. Lj.; Marinković, D.; Konstantinović, S.; Bugarčić, Z. J Serb Chem Soc 1986, 51, 1.
[4] Tien-Lay, L.; Wan-Hung, S.; Cheung, K. S.; Tam, S. W. J Org Chem 1985, 50, 3051.
[5] Schimdt, G. H.; Garratt, D. G. Chemistry of Double Bonded Functional Group; S. Patai, (Ed.); Wiley: New York, 1977; Vol. 2, Ch. 7.
[6] (a) Paulimer, C. Selenium Reagents and Intermediates in Organic Synthesis; Baldwin, I. E. (Ed.); Pergamon: New York, 1986; Vol. 4; (b) Chemistry of Organic Selenium and Tellurium Compounds; S. Patai (Ed.); Wiley: New York, 1987; Vol. 2.
[7] Tiecco, M. Electrophilic Selenium, Selenocyclizations, Top in Curr Chem 2000, 208, 7.
[8] Mugesh, G.; Du Mont, W. W.; Sies, H. Chemistry and Biologicaly Important Synthetic Organoselenium Compounds, Chem Rev 2001, 56.
[9] Yasumoto, T.; Murata, M. Chem Rev 1993, 93, 1897.
[10] Faulkner, D. J. Nat Prod Rep 1997, 14, 259.
[11] Wesley, J. W. Polyether Antibiotics Naturally Occurring Acid Ionophores; Vols I and II, Marcel Dekker: New York, 1982.
[12] Painter, G. R.; Presman, B. C. Top Curr Chem 1982, 101, 83.

[13] Still, W. C.; Hauck, P.; Kempf, D. Tetrahedron Lett 1987, 28, 2817.
[14] Smith, P. W.; Still, W. C. J Am Chem Soc 1988, 110, 7917.
[15] Shimizu, Y. Marine Natural Products; Vol I, Academic: New York, 1978; pp-1.
[16] Ellis, S. Toksikon 1985, 23, 469.
[17] Sakemi, S.; Higa, T.; Jefford, C. W.; Bernardinelli, G. Tetrahedron Lett 1986, 27, 4287.
[18] Suzuki, T.; Suzuki, A.; Furusaki, T.; Matsumoto, A.; Kato, A.; Imanaka, Y.; Kurosawa, E. Tetrahedron Lett 1985, 26, 1329.
[19] Corley, D. G.; Herb, R.; Moore, E.; Scheuer, P. J.; Paul, V. J. J Org Chem 1988, 53, 3644.
[20] Cohran, V. M. Physiology of Fungi; Wiley: New York, 1958.
[21] Schreiber, S. L.; Kelly, S. E.; Porco, J. A.; Sanmakia, T.; Suh, E. M. J Am Chem Soc 1988, 110, 6210.
[22] González, A. G.; Martin, J. D.; Martin, V. S.; Norte, M.; Pérez, R.; Ruano, J. Z.; Drexler, S. A.; Clardy, J. Tetrahedron 1982, 38, 1009.
[23] Konstantinovic, S.; Bugarcic, Z.; Milosavljevic, S.; Schroth, G.; Mihailovic M. Lj. Liebigs. Ann Chem 1992, 261.
[24] Mojsilovic, B.; Bugarcic, Z. Heteroat Chem 2001, 12, 475.
[25] Bugarcic, Z.; Gavrilovic, M. Monatsh Chem 2003, 134, 1359.
[26] Bugarcic, Z.; Mojsilovic, B. Heteroat Chem 2004, 15, 146.
[27] Brecknell, D. J.; Carman, R. M.; Garner, A. C. Aust J Chem 1997, 50, 35.
[28] Einhorn, J.; Einhorn, C.; Luche J. L. J Org Chem 1989, 54, 4480.
[29] Rieder, C.; Jaun, B.; Arigoni, D Helv Chim Acta 2000, 83, 2504.
[30] Liotta, D.; Zima, G. Tetrahedron Lett 1984. 25, 3525.
[31] Nicolaou, K. C.; Magolda, R. I.; Sipio, W. J.; Barnette, W. F.; Lysenko, Z.; Joullie, M. M. J Am Chem Soc 1980, 102, 3784.