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Synthesis of 2,4,6-trisubstituted tetrahydropyrans via 6-*exo* selenoetherification of unsaturated alcohols

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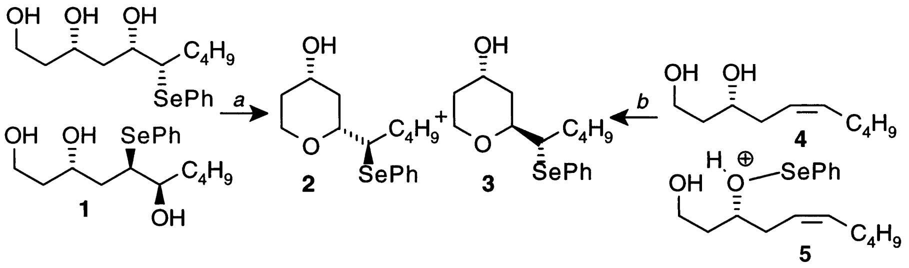
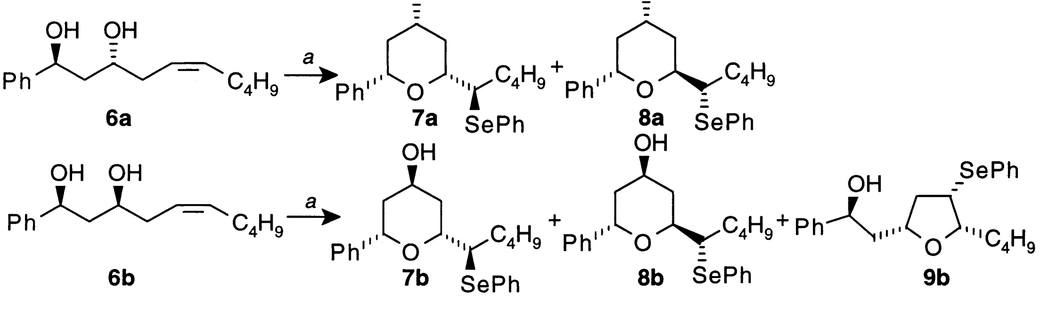
Abstract—Stereoselectivity, regioselectivity and yields in the 6-*exo* selenoetherification of four unsaturated diols were found to depend on the stereochemistry of the diols and on the presence of an oxygen atom close to the intermediate seleniranium ring. Silica gel was useful in order to obtain good yields. Reactions performed both under kinetic and thermodynamic control led to the same products. © 2001 Elsevier Science Ltd. All rights reserved.

In recent years we have been interested in the stereoselective synthesis of oxygenated heterocyclic rings via the intermediate formation of a seleniranium ion.[1] It is well established that when an electrophilic seleno species, such as $PhSe^+$, attacks a C–C double bond carrying a tethered nucleophile, such as a hydroxyl group, the seleniranium ion formed undergoes an intramolecular attack leading to the oxygenated heterocyclic ring. It is well known that chiral carbon atoms present in the three-membered seleniranium ring racemize quite readily during the reaction.[2] For instance, when we treated a mixture of hydroxy selenides **1** with a catalytic amount of perchloric acid in dichloromethane (via a), we found a 75:25 mixture of tetrahydropyrans **2** and **3**. A 33:67 ratio of tetrahydropyrans **2** and **3** was observed when we carried out the reaction under kinetic conditions (via b). We propose that the epimerization takes place through the intermediate oxonium ion **5** (Scheme 1).[1d]



Scheme 1. *Reagents*: (a) $HClO_4$ (cat.), CH_2Cl_2, 25°C; (b) PhSeCl, K_2CO_3, CH_2Cl_2, −78°C.



Scheme 2. *Reagents*: (a) PhSeCl, K_2CO_3, CH_2Cl_2, −78–25°C, 24 h, **7a** (60%), **8a** (5%), **7b** (50%), **8b** (<1%), **9b** (10%).

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Indeed, it has been reported that selenium can interact with nearby heteroatoms.[3] In some cases, the existence of this intramolecular interaction has been demonstrated by theoretical calculations, as well as by crystal structure determinations and by NMR spectroscopy.[4]

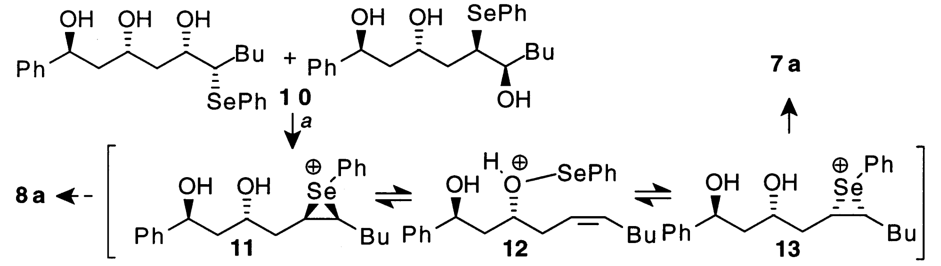
The main aspects of this communication are the kinetic and thermodynamic control observed in selenoetherification and the evidence for the formation of stable seleniranium ions in dichloromethane solution during the cyclization leading to substituted tetrahydropyrans. We have considered the stereoselective synthesis of 2,4,6-trisubstituted tetrahydropyran rings, investigating the behaviour of four unsaturated alcohols (**6a**–**d**)[5] with PhSeCl. The additional substituent (Ph) should give more conformational restriction and higher selectivity in the cyclization process.

Treatment of **6a** under kinetic conditions afforded a 93:7 mixture of **7a** and **8a** in 65% yield. The reaction was carried out at −78°C for 2 h then at 25°C for 22 h (Scheme 2). In order to establish the thermodynamic product, we investigated cyclization of the mixture of hydroxy selenides **10**[5] with a catalytic amount of perchloric acid. The reaction, that in principle should give **8a** through **11**, after the stereoconvergent elimination of water, again gave **7a** in 85% yield as a consequence of the very fast equilibration of the seleniranium ions **11** and **13** (Scheme 3).

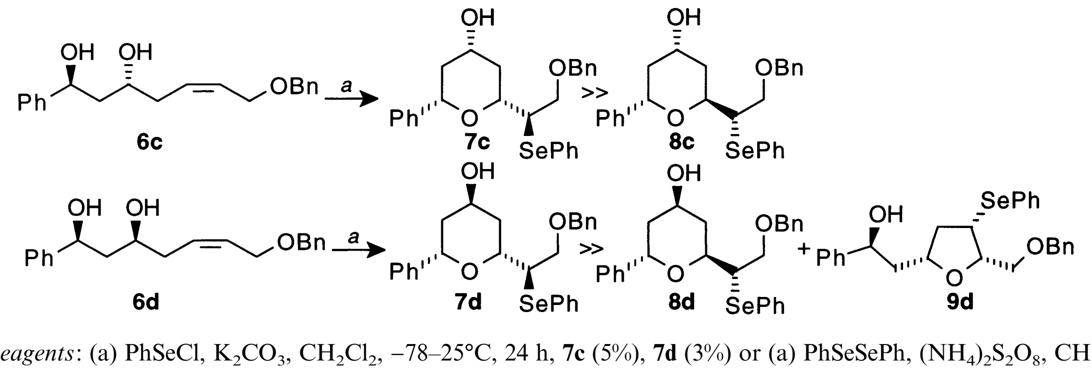
Compound **6b** gave, after 2 h at −78°C then 22 h at 25°C, a 5:1 ratio of tetrahydropyran **7b** and tetrahydrofuran **9b** in 60% yield. The presence of compound **9b** can be explained by assuming the intermediacy of a partial chair-like transition state in which the $PhCH(OH)CH_2$ group lies in the equatorial position. In order to overcome the problem of the presence of **9b** we studied the cyclization of compound **6d**. The presence of the CH_2OBn group should avoid the formation of the *endo* product (Scheme 4).[1c]

However, compound **6d** behaved differently; indeed, carrying out the reaction as above we isolated only a 3% yield of **7d** and we recovered **6d** in 89% yield with several unidentified products, although, at −78°C, the TLC showed a big spot as compound **7d**. When the reaction mixture was promptly chromatographed after 2 h at −78°C, we isolated **7d** in 35% yield and **6d** in 40% yield.[6] In order to obtain a higher yield of **7d** we used phenylselenenyl sulfate in dry acetonitrile for 30 h at room temperature.[7] In this way we obtained **7d** in 57% yield and starting material (5%). Similarly, **6c** gave **7c** (5%) and starting material (63%) when treated with $PhSeCl/K_2CO_3$ from −78 to 25°C for 24 h, whereas we obtained **7c** in 64% yield together with 9% of starting material when we used the phenylselenenyl sulfate. Compound **6c** was also treated with $PhSeCl/K_2CO_3$ in dry acetonitrile; after 24 h at 25°C we isolated **7c** in 15% yield and starting material.

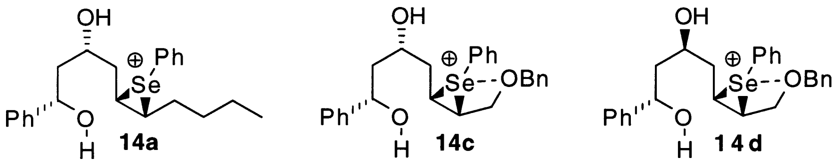
On the basis of these observations we suggest that at −78°C the tetrahydropyran ring is not present but we have an appreciable concentration of a sufficiently stable seleniranium ion that on contact with silica gel is transformed into the final tetrahydropyran ring **7c**,**d** (Scheme 5).



Scheme 3. *Reagents*: (a) $HClO_4$ (cat.), CH_2Cl_2, 25°C, 5 min, **7a** (85%).



Scheme 4. *Reagents*: (a) PhSeCl, K_2CO_3, CH_2Cl_2, −78–25°C, 24 h, **7c** (5%), **7d** (3%) or (a) PhSeSePh, $(NH_4)_2S_2O_8$, CH_3CN, 25°C, 30 h, **7c** (64%), **7d** (57%) or (a) PhSeCl, K_2CO_3, CH_2Cl_2, silica gel, −78–25°C, 2 h, **7c** (68%), **7d** (61%).



Scheme 5.

The higher stabilities of the seleniranium ions **14c**,**d** could be attributed to the Se–OBn interaction, absent in **14a**. Then **14a** should be more reactive. Actually **14a** could be stabilized by the interaction between the selenium atom and the hydroxyl group, but we have evidence that this interaction plays a more important role when the oxygen atom is closer to the seleniranium ring.[8] Seleniranium ions **14c**,**d** may be stable at −78°C, but when the solution is allowed to warm at room temperature, instead of the ring closure to **7c**,**d**, we observed the formation of **6c**,**d** probably because, as **14c**,**d** are more stable, they survive sufficiently to undergo the intermolecular attack of the nucleophilic chloride ion on the seleniranium ring. The use of phenylselenenyl sulfate in acetonitrile gave good yields of the cyclized products probably because the sulfate ion is not a good nucleophile. The solvent plays a minor role, indeed in acetonitrile the Se–OBn interaction is still operative, as demonstrated by the poor yield of the cyclization of **6c**. Considering our hypothesis that at −78°C we have the intermediate seleniranium ion that is probably transformed into the tetrahydropyran by silica gel, we quenched the reaction, performed on **6c** with PhSeCl and K_2CO_3, after 2 h at −78°C, by adding silica gel to the reaction mixture. The mixture was allowed to warm to room temperature and stirred for 20 min and then evaporated under reduced pressure. Column chromatography gave **7c** in 68% yield with several minor unidentified products; no starting material was found. In the same way compound **6d** gave the tetrahydropyran **7d** in 61% yield. No tetrahydrofuran **9d** was found. The reaction with compound **6c** was also realized by adding the PhSeCl solution to a suspension of silica gel, K_2CO_3 and **6c** at −78°C. The reaction was stirred at this temperature for 20 min then allowed to warm to room temperature. Column chromatography gave again the final product with the same yield.

The reactions with silica gel are in agreement with our hypothesis; the OH groups of the silica gel are able to destroy the Se–OBn interaction as a consequence of the coordination of the ethereal oxygen atom, destabilizing in this way **14c**,**d** and then allowing their closure to **7c**,**d**. In conclusion, the 6-*exo* selenoetherification of unsaturated alcohols proceeds with high diastereoselectivity to 2,6-*cis*-trisubstituted tetrahydropyrans when the reaction is carried out both under kinetic and thermodynamic conditions. Although Se–O interactions are well documented,[3b,9] our findings represent one further and clear way to demonstrate the existence of these interactions. Moreover, to the best of our knowledge, these reactions are the first examples of the use of silica gel in selenoetherification.[10] This chemistry will be used in order to prepare natural products containing 2,4,6-trisubstituted tetrahydropyran rings.

Acknowledgements

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