Pergamon

Tetrahedron Letters 40 (1999) 8477–8481

TETRAHEDRON LETTERS

Kinetic and thermodynamic control in the intramolecular hydroxyl capture of seleniranium ions

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Received 19 July 1999; accepted 14 September 1999

Abstract

The formation of tetrahydrofurans and tetrahydropyrans by acid catalyzed cyclization of hydroxy selenides can be explained by kinetic and thermodynamic control. The tetrahydropyrans from the hybrid 7-*endo*/6-*exo* cyclization are the thermodynamic products of the acid catalyzed cyclization of hydroxy selenides **1**, whereas the tetrahydrofurans from the 5-*exo* cyclization are the kinetic products. © 1999 Elsevier Science Ltd. All rights reserved.

The stereoselective synthesis of cyclic ethers by hydroxyl capture of a thiiranium or seleniranium ion, during acid catalyzed cyclization of hydroxy sulfides or hydroxy selenides, is an interesting route to tetrahydrofurans and tetrahydropyrans.[1] Recently, using this methodology we realized the stereoselective synthesis of the tetrahydrofuran containing fragment of (−)-nonactic acid and the pamamycins,[1b] and the C15–C20 fragment of (+)-rolliniastatin 1.[1d]

In comparison with the hydroxy selenides, which have hardly been investigated, the acid catalyzed cyclization of hydroxy sulfides have been extensively studied by Warren's group.[1e–l]

During the course of our investigations we studied regiochemical control in the cyclization of hydroxy selenides such as **1** (Scheme 1). During acid catalyzed treatment, compounds **1** undergo a stereoconvergent elimination of water to give the intermediate ion **2**. In principle four modes of cyclization of the intermediate ion **2** are possible: (i) cyclization in the 6-*endo*/5-*exo*[1l] mode to give **3**; (ii) cyclization in the 4-*exo* mode to give **4**; (iii) cyclization in the 5-*exo* mode to give **5**; and (iv) cyclization in the 7-*endo*/6-*exo*[1j,k] mode to give **6**.

We treated the hydroxy selenides (**1**) with a catalytic amount of perchloric acid in dichloromethane at room temperature and quenched the reaction after 1 min. No starting material was recovered and we isolated tetrahydrofuran **5** by column chromatography and, unexpectedly, the diasteromeric structure **7**[2] in almost the same yield.

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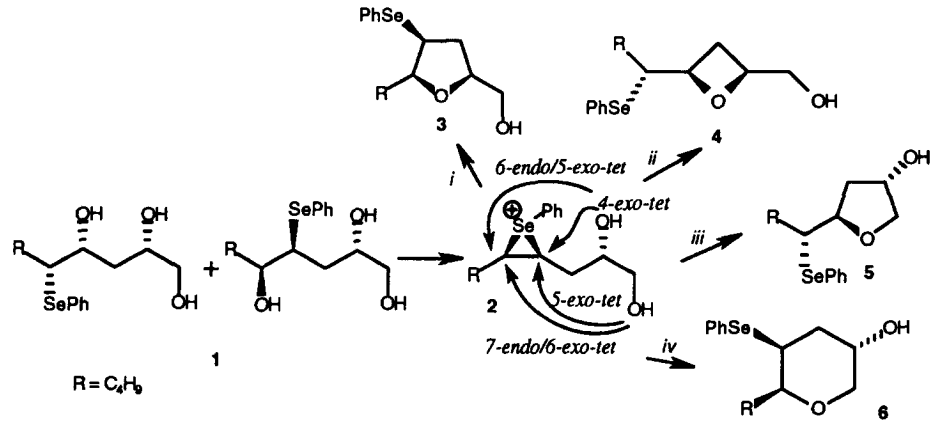
PII: S0040-4039(99)01779-7

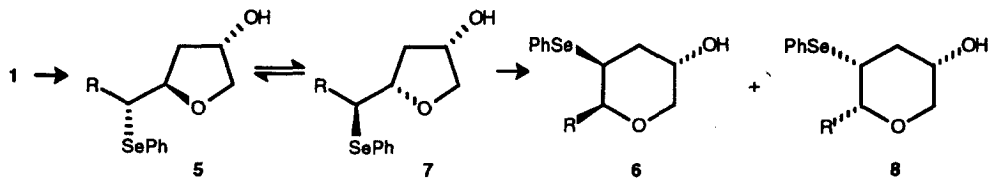


Scheme 1.

Regiocontrol was then observed since the reaction took place exclusively in the 5-*exo* mode. Neither 4-*exo* or *endo/exo* products were formed.[3] However, no stereoselectivity was observed; indeed, the stereoselectivity that should follow cyclization of the seleniranium ion **2** was lost.

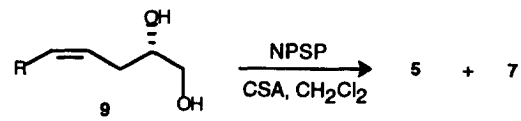
Surprisingly, if the reaction was not quenched immediately we observed, by TLC, the disappearance of the two spots corresponding to the tetrahydrofurans **5** and **7** and the appearance of two other spots. The reaction was complete after 30 min. Separation by column chromatography gave the two tetrahydropyrans **6** and **8** in good overall yield (80%) and with a 68:32 ratio. The structure of these products was proven by the usual spectroscopic and analytical techniques.[4]

Resubjecting compound **5** or **7** to the reaction conditions (i.e., cat. $HClO_4$) initially led to their equilibration and they then disappeared to give the two tetrahydropyrans **6** and **8** (68:32) (Scheme 2). Resubjecting compound **6** or **8** to the above conditions saw no equilibration.



Scheme 2.

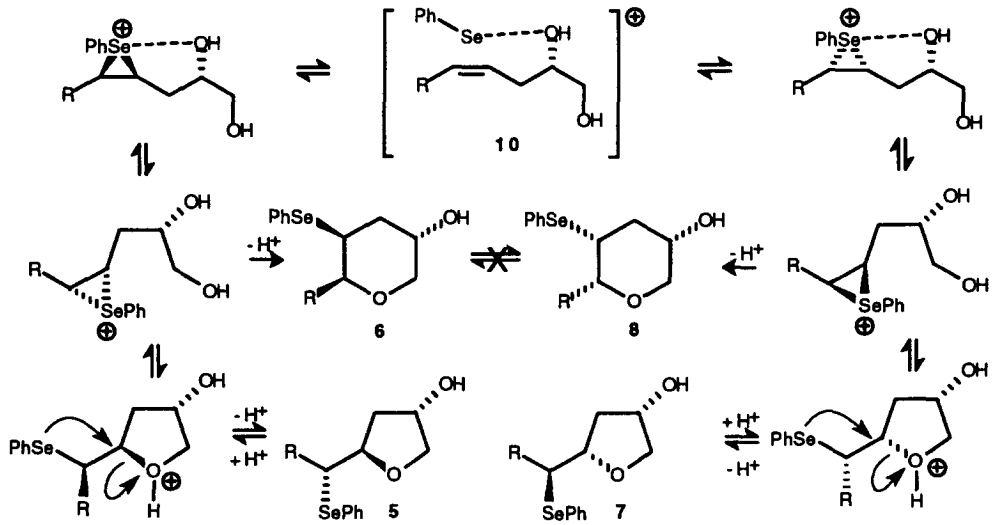
In order to gain deeper insight into this reaction mechanism, we removed, by reduction with tributyltin hydride and AIBN, the phenylselanyl group in compound **5**: no equilibration occurred. Moreover, no equilibration occurred when the hydroxyl group in the 3-position was protected as a benzyl ether. So, both the phenylselanyl group and the OH group play an important role in the equilibration reaction. Carrying out the reaction under kinetic control (i.e., we performed the reaction between the alkene **9** and *N*-phenylselenophthalimide, NPSP,[6] as carrier of the electrophilic phenylseleno species $PhSe^+$) we isolated compounds **5** and **7** in 62% and 37% yield, respectively (Scheme 3).



Scheme 3.

In order to rationalize the experimental results we propose an equilibration pathway as outlined in Scheme 4. The key step in this equilibration was the stabilization of the selenium electrophile and/or the

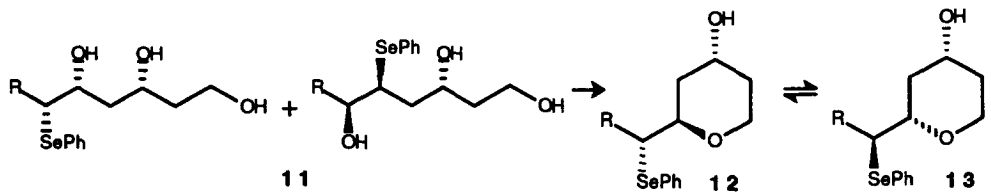
seleniranium ion by means of the hydroxyl group nearest to the reaction centre.[5] The smaller the residue on the oxygen of the hydroxyl group nearest to the reaction centre (H compared with Bn), the better the interaction with the selenium atom. The presence of compounds **5** and **7** from **9** is in agreement with the participation of intermediate species **10** in the equilibrium (Scheme 4) that leads to the two diastereomeric seleniranium ions which give the THF rings. While the formation of **5** and **7** was reversible, the formation of **6** and **8** was not reversible.



Scheme 4.

From our results we can argue that when the phenylselanyl group was in an exocyclic position, the products easily equilibrated under acidic conditions. When the phenylselanyl group was in an endocyclic position no equilibration occurred. As a matter of fact, both compound **3**[1d] and compounds **6** and **8** were found to be stable under the reaction conditions, whereas compound **5** easily equilibrated and compound **4** was not detected.[7]

By analogy to the behaviour of compound **5**, the tetrahydropyran **12**, obtained by cyclization of hydroxy selenides **11**, in acid solution, readily interconverted to **13** giving a 25/75 equilibrium mixture of **12** and **13** (Scheme 5).[8]

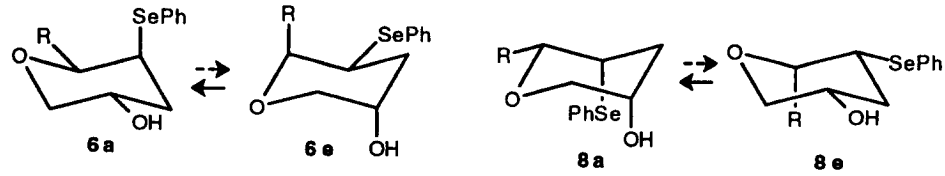


Scheme 5.

The behaviour of compounds **5**, **7**, **12** and **13** in acid solution can be ascribed to the fact that these rearrangments proceed via a loose S_N2 transition state; when the phenylselanyl group was in an exocyclic position, rotation around the C–C bond of the side chain allows alignment of Se, C2 and the protonated heterocyclic oxygen atom at the required 180° (see Scheme 4). This situation is not possible when the phenylselanyl group is in an endocyclic position.

Actually, compounds **6** and **8** can exist in several conformations, and could reach a conformation in which the Se, C2 and the protonated heterocyclic oxygen atom are almost aligned at the required 180° as

in **6e** and **8e** (Scheme 6). NMR analysis showed that these compounds exist in a conformation in which the phenylselanyl group lies in an axial position that does not allow the alignment at the required 180°.



Scheme 6.

The absence of rearrangment of these compounds, however, indicated that conformations **6e** and **8e** do not possess the stereoelectronic requirements that allow the equilibration in our reaction conditions. Indeed, the intramolecular attack of the phenylselanyl group on C2 should cause a severe distorsion of the THP ring.

Finally, we conclude that the cyclization of hydroxy selenides **1** is governed by both kinetic and thermodynamic factors:

(i) 5-*exo-tet* cyclization is preferred to the hybrid 6-*endo*/5-*exo-tet* cyclization;
(ii) 5-*exo-tet* cyclization is preferred to the hybrid 7-*endo*/6-*exo-tet* cyclization;
(iii) the oxetane **4** derived from the 4-*exo* cyclization was never observed;
(iv) the tetrahydropyrans derived from the hybrid 7-*endo*/6-*exo-tet* cyclization, disfavoured by Baldwin's rules, are the thermodynamic products of the acid catalyzed cyclization;
(v) the tetrahydrofurans coming from the pure 5-*exo* cyclization equilibrate rapidly to the tetrahydropyrans under the acid catalyzed reaction conditions;
(vi) no equilibration occurs between the tetrahydropyrans in the presence of acid;
(vii) no equilibration occurs between the tetrahydrofurans and the tetrahydropyrans in the absence of acid.

The formation of the tetrahydropyrans can be regarded as a new way for the synthesis of 2,5-disubstituted THP rings, after removal of the phenylselanyl group. Further investigations have to be made in order to understand scope and limitations of this reaction.

Acknowledgements

This investigation has been supported by the University of Palermo (funds for selected research topics).

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2. Previously[1d] we erroneously attributed to compound **7** the structure of THF **3** coming from the 6-*endo*/5-*exo-tet* cyclization.

3. It should be reminded that when the primary hydroxyl group is protected (TIPS or TBS) only the 6-*endo*/5-*exo* cyclization takes place.[1c,d]
4. Compound **6**: ^{1}H NMR (250 MHz) δ: 0.88 (t, 3H, *J*=6.8 Hz), 1.23–1.38 (m, 4H), 1.55–1.92 (m, 3H), 2.20 (br s, 1H), 2.40–2.46 (m, 1H), 3.19 (dd, 1H, *J*=9.9 and 9.9 Hz), 3.37–3.44 (m, 1H), 3.49–3.52 (m, 1H), 4.05 (ddd, 1H, *J*=6.8, 4.9 and 1.9 Hz), 4.12–4.24 (m, 1H), 7.25–7.28 (m, 3H), 7.52–7.60 (m, 2H); ^{13}C NMR δ: 13.9, 22.5, 27.9, 33.6, 39.5, 47.1, 63.7, 72.7, 80.1, 127.4, 129.1, 129.9, 134.2. Compound **8**: ^{1}H NMR (250 MHz) δ: 0.91 (t, 3H, *J*=6.7 Hz), 1.28–1.42 (m, 4H), 1.60–1.67 (m, 1H), 1.76–1.83 (m, 1H), 2.12 (ddd, 1H, *J*=15, 4.1 and 3.8 Hz), 2.25–2.35 (m, 1H), 2.50 (br s, 1H), 3.40–3.44 (m, 1H), 3.40–3.51 (m, 1H), 3.66 (dd, 1H, *J*=12.1 and 1.6 Hz), 3.78–3.81 (m, 1H), 4.00–4.06 (m, 1H), 7.27–7.32 (m, 3H), 7.59–7.66 (m, 2H); ^{13}C NMR δ: 14.0, 22.5, 27.7, 34.1, 34.3, 43.9, 66.0, 73.7, 80.4, 127.9, 128.5, 129.2, 135.2.
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6. Nicolaou, K. C.; Petasis, N. A.; Claremon, D. A. *Tetrahedron* **1985**, *41*, 4835–4841.
7. A similar oxetane with an exocyclic phenylsulfanyl group, responsible for 20–30% of the kinetic product, was never observed during the acid catalyzed cyclization of an hydroxy sulfide, because it readily rearranged to the corresponding THF with the phenylsulfanyl group in an endocyclic position.[1f]
8. Gruttadauria, M.; Lo Meo, P.; Noto, R. *Tetrahedron* **1999**, in press.