Pergamon

Tetrahedron Letters 43 (2002) 1669–1672

TETRAHEDRON LETTERS

Stereocontrolled approach to δ- and γ-lactones and 1,3-diols. The role of X^- ion in the selenolactonization

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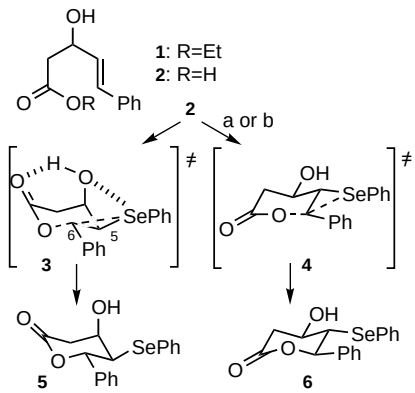
Received 21 December 2001; revised 9 January 2002; accepted 11 January 2002

Abstract—Two complementary approaches have been realized for the stereoselective synthesis of 4,6-disubstituted δ-lactones and 1,3-*anti* and *syn* diols. In the 6-*endo* selenolactonization the role of the X^- ion on the stereoselectivity is shown. Moreover, the highly stereoselective transformation of the 6-*endo* δ-lactone to the 5-*exo* γ-lactone is reported. © 2002 Elsevier Science Ltd. All rights reserved.

Lactones are not only found in the structures of many natural products, but they also constitute very useful synthetic intermediates, especially for the stereoselective synthesis of complex molecules. Halolactonization and selenolactonization are probably the most employed methods. In recent years we have been interested in the stereoselective synthesis of oxygenated heterocycles via the intermediate formation of a seleniranium ion.[1–5]

Here we report preliminary observations on the stereocontrolled synthesis of δ- and γ-lactones and 1,3-*anti* and *syn* diols. We used as model compounds for our study β-hydroxy ester **1** and β-hydroxy acid **2** that were readily prepared from cinnamaldehyde.

Hydroxy acid **2** was allowed to react with PhSeCl (1 equiv.) and potassium carbonate (3 equiv.) at −78°C in dichloromethane to give compounds **5** and **6** (Scheme 1).[6] We were disappointed to find poor results from this reaction. Indeed very low selectivity (determined by ^{1}H NMR) was found (Table 1, entry 1). However, increasing the amount of PhSeCl we found interesting results. The diastereoselectivity meaningfully increased when we used two equivalent of PhSeCl (entry 2). A further increase was observed with three equivalents of PhSeCl (entry 3). Obviously, it is not usual to find higher diastereoselectivities when the equivalent amount of reactant is increased. For example, increasing the amount of PhSeBr did not give a significantly different diastereoselectivity (entries 13–15).



Scheme 1. *Reagents and conditions*: (a) PhSeX, K_2CO_3, CH_2Cl_2, −78°C; (b) PhSeX, TBAX, K_2CO_3, CH_2Cl_2, −78°C.

However, it should be noted that when using one or two equivalents of PhSeBr higher diastereoselectivity was found compared with PhSeCl. In order to understand the role of the X^- counter ion we then realized the reaction using one equivalent of PhSeCl and one equivalent of TBAX (X = ClO_4, Cl, Br). With $TBAClO_4$ and TBACl (entries 4 and 5) the yield was poor, but interestingly, the diastereoselectivity was the same as observed when using two equivalents of PhSeCl (entry 2). With TBABr (entry 6) the yield was very low, but a further increase in diastereoselectivity was obtained. In this case the diastereoselectivity was similar to that obtained with PhSeBr. Good diastereoselectivity was also found using two equivalents of PhSeCl and one equivalent of $TBAClO_4$, TBACl or TBABr (entries

Keywords: selenium; cyclization.

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PII: S0040-4039(02)00093-X

Table 1. Yields and selectivities for the 6-*endo* cyclization

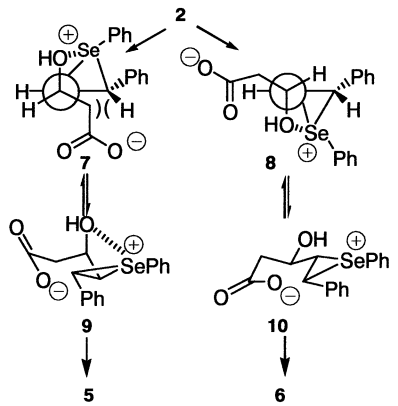
Entry	PhSeCl (equiv.)	$TBAClO_4$ (equiv.)	TBACl (equiv.)	TBABr (equiv.)	Yield (%)[a]	**5**/**6**
1	1	–	–	–	40[b]	57/43
2	2	–	–	–	69[b]	76/24
3	3	–	–	–	97[b]	89/11
4	1	1	–	–	25[c]	78/22
5	1	–	1	–	10[c]	75/25
6	1	–	–	1	8[c]	90/10
7[d]	1	1	–	–	59[c]	89/11
8[e]	1	–	1	–	13[c]	76/24
9[f]	1	–	1	–	7[c]	77/23
10	2	1	–	–	60[c]	88/12
11	2	–	1	–	43[c]	88/12
12	2	–	–	1	42[c]	90/10
	PhSeBr					
13	1	–	–	–	48[b]	89/11
14	2	–	–	–	94[b]	93/7
15	3	–	–	–	90[b]	92/8
16	1	1	–	–	48[c]	94/6
17	1	–	1	–	10[c]	87/13
18	1	–	–	1	7[c]	89/11
19[d]	1	1	–	–	49[c]	95/5

[a] Reaction time 1 h; in all the reactions reported the remaining products were starting material and $(PhSe)_2$.
[b] Isolated yield.
[c] Determined by ^1H NMR.
[d] PhSeX and TBAX added to a solution of compound **2**.
[e] Reaction time: 30 min.
[f] Reaction time: 15 min.

10–12). In particular, using PhSeCl (2 equiv.) and TBACl (1 equiv.) we found the same diastereoselectivity obtained using 3 equiv. of PhSeCl (entries 3 and 11). Again high diastereoselectivities were found with PhSeBr and TBAX (entries 16–18). The reactions performed with TBAX were usually realized by adding the PhSeX solution to a mixture of compound **2** and TBAX. When we added to the solution of compound **2** a solution of PhSeCl and $TBAClO_4$ we found, respectively, better yield and diastereoselectivity (entries 4 and 7). No change was observed when we used PhSeBr pre-mixed with $TBAClO_4$ (entries 16 and 19). Finally, the reaction with PhSeCl and TBACl was stopped at different times, but yield and stereoselectivity did not change (entries 5, 8 and 9). These data indicate that the reaction carried out with PhSeCl with or without TBAX showed selectivities ranging from 57 to 90%. Reactions carried out with PhSeBr with or without TBAX showed higher selectivities (87–95%). When the reaction was realized with only one equivalent of PhSeX with or without TBAX, the yield was poor. When the reaction was carried out with two or three equivalents of PhSeX both yield and stereoselectivity were high.

The major diastereoisomer could come via transition state **3** that displays the intramolecular hydrogen bond and also a stabilizing Se···O interaction, absents in the transition state **4** leading to the minor diastereoisomer. Similar intramolecular hydrogen bonds have been claimed in the 6-*exo* iodolactonozation.[7] Moreover, it has been reported that selenium can interact with nearby heteroatoms.[8–12] These two factors could lead to a lower energy transition state, then explaining the preference for the δ-lactone having the OH group axially disposed. These factors, however, are not sufficient to explain the observed diastereoselectivity with the increasing amount of X^- counter ion. It is known that the counter ion of the selenium electrophile plays an important but still not well understood role in the addition reactions.[13] Both seleniranium ions, generated by the attack of the $PhSe^+$ species on both sides of the C=C double bond, have the stabilizing interaction between the positive selenium atom and the allylic oxygen atom. It should be noted that in seleniranium ion **7** the unfavourable nonbonding interaction between the CH_2COO^- group and the hydrogen atom should lead to a higher energy for this seleniranium ion compared with the seleniranium **8** where this interaction is absent (Scheme 2). Seleniranium **7**, depicted in Scheme 2, shows that it is possible to maintain the Se–O interaction during the cyclization process (see **9**), whereas in seleniranium **8**, when the COO^- group reaches C_6, the Se–O interaction is lost (see **10**).

Seleniranium **8** is more stable and the activation energy for its cyclization is higher, while seleniranium ion **7** is less stable with a lower transition state energy for the cyclization process. Then, seleniranium ion **8** lives sufficiently to undergo the intermolecular attack of the Cl^- or Br^- or ClO_4^- species at the positively charged selenium atom. As a matter of fact, in increasing the amount of X^- we increased the selectivity since seleniranium **8** is preferentially destroyed to again give starting material and PhSeX.[14] The increasing amount of



Scheme 2.

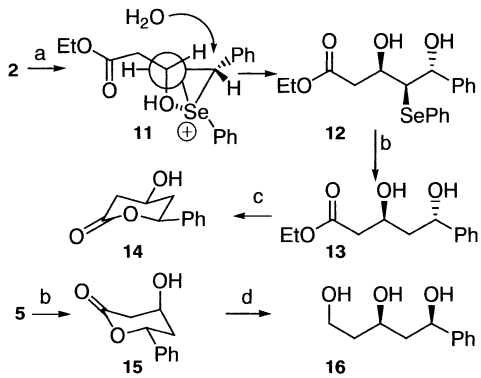
PhSeX gave, as expected, higher yield; the increasing amount of X^- gave lower yield since it destroys the intermediate seleniranium ions.[15] Moreover, the selenium cation being a soft electrophile reacts better with Br^- than with Cl^- or ClO_4^-. The best conditions, from a synthetic point of view, were with two equivalents of PhSeBr.

In order to synthesize the 4,6-diequatorial δ-lactone, β-hydroxy ester **1** was allowed to react with PhSeCl[16] in acetonitrile/water for a few minutes.[17] We were delighted to find a very interesting result. The 1,3-*anti* diol **12** was obtained in 80% yield and in excellent diastereomeric ratio (95/5). The reaction proceeds through the more stable seleniranium ion **11**, which undergoes the attack by a molecule of water to give **12**. When the reaction was quenched after 30 min the yield was lower (65%) with almost the same selectivity. The lower yield can be ascribed to the acid conditions realized during the reaction. Indeed, it is well known that hydroxy selenides react under these conditions.[4,5] The stereochemistry was not confirmed at this stage, but when δ-lactone **14** was obtained. Also, the diastereomeric ratio was better confirmed by the ^1H NMR spectrum of **13** obtained after removal of the PhSe group (95% yield). Finally, cyclization of **13** in refluxing toluene gave the δ-lactone **14** in 70% yield (Scheme 3).

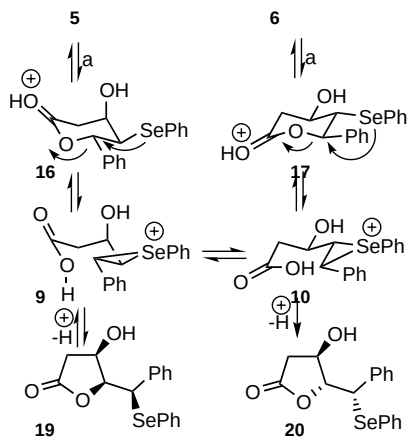
The diastereomeric structure **15** was obtained after removal of the PhSe group in compound **5**. Reduction of compound **15** gave the triol **16**. The mixture of δ-lactones **5** and **6** were isolated by washing the crude reaction with light petroleum in order to remove diphenyldiselenide. When the reaction mixture was purified by chromatography we obtained a mixture of δ-lactones **5** and **6** and γ-lactone **20**. Then the mixture of δ-lactones **5** and **6** was stirred in dichloromethane with silica gel and eluted to give a quantitative yield (98%) of 4,5-*trans*-γ-lactone **20** with excellent diasteromeric ratio (**20**/**19** >95:5) (Scheme 4). The acid conditions realized with silica gel caused the protonation of δ-lactones and the intramolecular Se attack at C_6 to afford ring opening. This rearrangement can be ascribed to the fact that these reactions proceed via a loose S_N2 transition state. The equatorial position of the PhSe group in δ-lactones and the exocyclic position of the PhSe group in γ-lactones allows alignment of selenium, carbon and oxygen atoms at the required 180°.

The intermediate seleniranium ions **9** and **10** then cyclized to give the thermodynamically more stable γ-lactone **20** with excellent stereoselectivity. The cyclization realized under kinetic conditions afforded exclusively the δ-lactones because the phenyl group can support the partial positive charge at C_6 allowing the rupture of C_6–Se bond, whereas the allylic OH group disfavours the attack at C_5.[1]

In conclusion, two complementary approaches have been realized for the stereoselective synthesis of 4,6-disubstituted δ-lactones. The first approach is based on intramolecular selenolactonization. The second approach is based on the intermolecular hydroxyselenenylation followed by cyclization. In the former case, electronic effects, such as Se···O interaction and intramolecular hydrogen bond, as well as the nature and concentration of X^- species are important factors for the stereoselective outcome of these reactions. To the best of our knowledge the effect of the concentration and the nature of X^- ions on the stereoselectivity of cyclizations induced by PhSeX is shown for the first time. In the latter case the first example of direct



Scheme 3. *Reagents and conditions*: (a) PhSeCl, CH_3CN/H_2O, rt, 80%; (b) Bu_3SnH, AIBN, C_6H_6, reflux, 95%; (c) cat. PPTS, toluene, reflux, 70%; (d) $LiAlH_4$, Et_2O, rt, 80%.



Scheme 4. *Reagents and conditions*: (a) SiO_2, CH_2Cl_2, rt, 98%.

formation of 1,3-*anti* diol synthesis with high diastereoselectivity is reported. The 1,3-*syn* diol can be prepared by reduction of the corresponding δ-lactone. At present this approach is under development in our laboratory in order to understand the scope and limitations of both the stereoselective synthesis of lactones and 1,3-*anti* and *syn* diols.

Acknowledgements

Financial support from the University of Palermo (funds for selected research topics) and Italian MURST within the National Research Project 'Non-aromatic heterocycles in stereocontrolled processes' is gratefully acknowledged.

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