Synthesis of γ- and δ-Lactones from Alkynols

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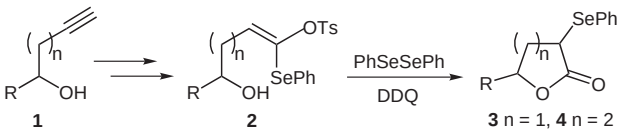
Abstract: The reaction of alkynyl phenyl selenides with *p*-toluenesulfonic acid gives rise to a proton-induced ring-closure reaction affording γ- and δ-lactones.

Key words: alkynes, lactone-cyclization reactions, organoselenium reagents, regiospecificity

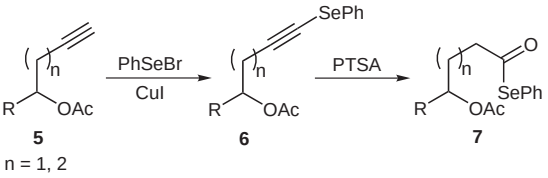
Substituted γ- and δ-lactones are the basic structural units of many complex and biologically active natural products and they are also of great interest as synthetic intermediates in organic synthesis.[1] Several synthetic methods for the synthesis of lactones have been developed[2] during the last few years and some of these involve alkynols as starting products. Thus, MaGee[3] has shown that γ- or δ-lactones can be formed by intramolecular trapping of ketenes, themselves available from the corresponding hydroxy alkynyl ethers by a retro-ene reaction. Schreiber and co-workers[4] developed a protocol for the conversion of hydroxy alkynyl ethers into the corresponding δ-lactones by treatment with mercuric(II) chloride and *p*-toluenesulfonic acid. γ-Lactones were also obtained from 4-trimethylsilyl-3-alkyn-1-ols via Wacker-type oxidation reactions as reported by Compain.[5] More recently, Jacobsen[6] proposed a direct method for the conversion of terminal epoxides into γ-lactones in a single step by the formation of a cyclic keteneaminal intermediate and subsequent hydrolysis and protodesilylation.

In a previous work[7] we reported that alkynols **1** can be transformed into the corresponding (*Z*)-α-(phenylseleno)vinyl *p*-toluenesulfonates **2**. These latter compounds undergo to a selenium-promoted regiospecific ring-closure reaction affording α-phenylseleno γ- or δ-lactones **3** or **4**, respectively (Scheme 1).

Moreover, we have also reported[8] that the reaction of alkynyl phenyl selenides **6**, prepared from the acetyl derivatives **5** of compounds **1**, with an excess of *p*-toluenesulfonic acid monohydrate (PTSA), in dichloromethane, gave the phenyl selenocarboxylates **7** (Scheme 2).

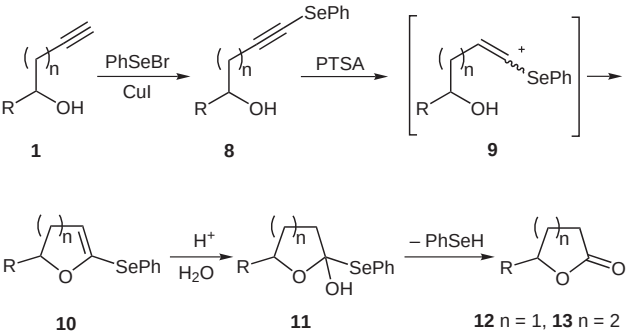


Scheme 1



Scheme 2

In the present paper we now describe a simple procedure to convert alkynols **1** into γ- or δ-lactones **12** or **13** by an acid-promoted regiospecific cyclization reaction of alkynyl phenyl selenide derivatives **8** (Scheme 3). The alkynyl phenyl selenides **8** were easily prepared from the corresponding alkynyl alcohols[9] **1** according to the method reported in literature.[10]



Scheme 3

Thus, it can be suggested that the reaction of **8** with an excess of *p*-toluenesulfonic acid monohydrate, in dichloromethane at 60 °C, proceeds through a regiospecific proton addition to **8** with the formation of the selenium-stabilized vinylic cation intermediate **9**. This cation is then intramolecularly trapped by the hydroxy group to afford the cyclization product **10**, which readily adds a molecule of water to give **11**. Under the reaction conditions employed, **11** eliminates a molecule of phenylselenol to give γ-lactone **12** or δ-lactone **13**. The yellow color of the final reaction mixture is due to the presence of diphenyl diselenide, which is formed by the oxidation of the phenylselenol. The products obtained by this procedure and the reaction yields[11] are reported in Table 1.

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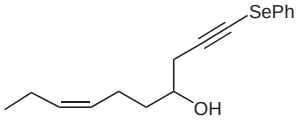
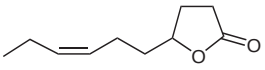
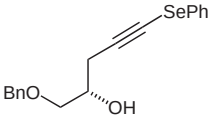
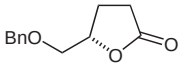
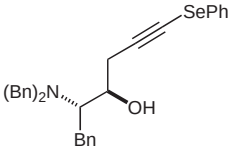
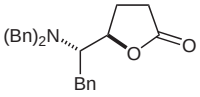
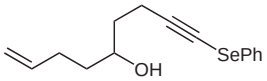
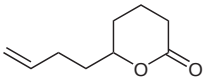
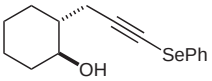
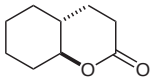
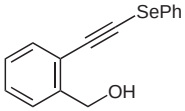
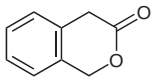
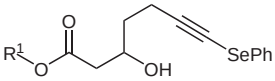
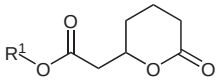
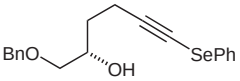
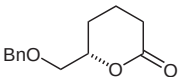
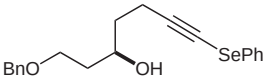
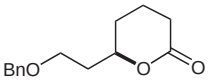
Table 1 Synthesis of γ- and δ-Lactones **12** and **13** from the Reaction of **8** with Monohydrated *p*-Toluenesulfonic Acid in CH_2Cl_2 at 60 °C

Entry	Substrate		Lactone		Yield (%)[a]
1		**8a**		**12a**	60
2		**8b**		**12b**	71
3		**8c**		**12c**	67[b]
4		**8d**		**13a**	68
5		**8e**		**13b**	75[c]
6		**8f**		**13c**	65[b]
7		**8g**		**13d**	58[d]
8		**8h**		**13e**	61[b]
9		**8i**		**13f**	59[b]

[a] Isolated yield after column chromatography.
[b] Yields based on the starting alkynol. The corresponding alkynyl phenyl selenide was not isolated.
[c] Racemic product.
[d] A 1:1 mixture of the two diastereoisomers; R^1 = (–)-*endo*-borneyl.

Substrates **8a–c** gave the expected γ-lactones **12a–c** in good yields. The reactions were not influenced by the presence of the other functional groups. Optically active lactones **12b** and **12c** were obtained from the corresponding chiral non-racemic alkynyl alcohols. Compound **12b** has been used by several authors for the synthesis of various natural products,[12] whereas γ-lactone **12c** is a valuable and versatile intermediate for the synthesis of hydroxymethylene dipeptide isosters, which are pharmaceutically important compounds that possess the basic structure of HIV protease[13a] and γ-secretase inhibitors.[13b]

The cyclofunctionalization of alkynols mediated by organoselenium intermediates proceeds easily also for substrates **8d–i** affording the expected δ-lactones **13a–f** in fairly good yields. Lactone **13d** is constituted by 1:1 mixture of two diastereoisomers which could not be separated. From the chiral non-racemic alkynyl phenyl selenides **8h** and **8i** the optically active δ-lactones **13e** and **13f**, respectively, were obtained. Lactone **13e** is a protected derivative of (*S*)-5-hydroxymethyl-δ-valerolactone, which is a valuable synthetic intermediate for the synthesis of LTB_5[14a] and is potentially useful for the preparation of a range of insect pheromones.[14b] On the other hand, the *S* enantiomer of **13f** was employed for the synthesis of the ionophore antibiotic Routiennocin.[15]

In conclusion, in this paper we described a new cyclofunctionalization reaction, involving organoselenium intermediates, which can be conveniently employed for the synthesis of γ- and δ-lactones. The procedure reported herein favorably compares with similar methods described in the literature particularly in the case of the synthesis of δ-lactones. Very likely, our procedure can also be applied to the synthesis of medium-sized lactones.

Applications of the presently described method to the synthesis of other biologically active compounds are presently under way.

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(9) All new compounds were fully characterized by MS, ^{1}H NMR and ^{13}C NMR spectroscopy and by combustion analysis. Compounds **1b**,**c**,[8] **1e**[16] and **1h**,**i**[8] were prepared as described in the literature from the corresponding epoxides whereas compound **1f** was obtained by reduction of the corresponding aldehyde with $NaBH_4$. Alkynol **1a** was obtained by reaction of a propargyl organometallic reagent with the proper carbonyl compound.[5] Compound **1d** was prepared by reduction of the corresponding ketone[17] with $NaBH_4$. Hydroxy ester **1g** was obtained by reduction of the corresponding oxoester, which was synthesized by alkylation of the dianion[18] of (–)-*endo*-borneyl 3-oxobutanoate.[19] Physical, spectral and analytical data of selected compounds are reported below.
(2*S*,3*R*)-2-(Dibenzylamino)-1-phenylhex-5-yn-3-ol (1c).
Oil, 72% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.38–7.06 (m, 15 H), 4.05–3.90 (m, 1 H), 3.80–3.50 (m, 4 H), 3.16–2.58 (m, 3 H), 2.58 (ddd, 1 H, *J* = 16.7, 3.7, 2.7 Hz), 2.23 (ddd, 1 H, *J* = 16.7, 8.3, 2.7 Hz), 2.08 (d, 1 H, *J* = 4.7 Hz), 1.94 (t, 1 H, *J* = 2.7 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 140.9, 139.5 (2 C), 129.5 (2 C), 128.8 (3 C), 128.3 (4 C), 128.2 (3 C), 126.9 (2 C), 125.9, 81.3, 70.9, 70.6, 62.8, 54.7, 54.2, 32.1, 25.7. Anal. Calcd for $C_{26}H_{27}NO$: C, 84.51; H, 7.37; N, 3.79. Found: C, 84.18; H, 7.67; N, 3.62.
(3*R*)-1-(Benzyloxy)hept-6-yn-3-ol (1i).
Oil, 73% yield. $[\alpha]_D^{23}$ +24.6 (*c* 1.75, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.45–7.20 (m, 5 H), 4.51 (s, 2 H), 3.94 (quint, 1 H, *J* = 5.7 Hz), 3.79–3.57 (m, 2 H), 3.07 (br s, 1 H), 2.32 (dt, 2 H, *J* = 5.0, 2.6 Hz), 1.95 (t, 1 H, *J* = 2.6 Hz), 1.82–1.58 (m, 4 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 137.7, 128.4 (2 C), 127.7 (2 C), 127.6, 84.2, 73.2 (2 C), 69.8, 68.9, 68.4, 36.2, 35.7. MS: *m/z* (relative intensity) = 218 (18), 159 (11), 109 (64), 91 (100), 83 (10), 65 (12). Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.29; H, 8.65.

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(11) **Ring-Closure Reaction. General Procedure.**
To a solution of the alkynyl phenyl selenide **8** (1 mmol) in CH_2Cl_2 (15 mL) powdered *p*-toluenesulfonic acid monohydrate (4 mmol) was added at r.t. and the reaction mixture was stirred at 60 °C. The progress of the reaction was monitored by TLC. Reaction times ranged from 1–9 h. Solid K_2CO_3 and CH_2Cl_2 were added and the mixture was filtered. The filtrate was dried and evaporated. After chromatography on silica gel column, compounds **12** and **13** were obtained in a pure form. Compounds **12a** and **13c** are commercial products whereas lactones **12c**,[20] **13a**[21] and **13b**[22] have physical and spectral data identical to those reported in the literature. Physical and spectral data of **12b**, **13e** and **13f** are reported below.
(5*S*)-5-[(Benzyloxy)methyl]dihydrofuran-2(3*H*)-one (12b).[23,]
Oil, 71% yield. $[\alpha]_D^{24}$ +21.0 (*c* 1.45, EtOH) {Lit.[23] $[\alpha]_D^{15}$ +18.1 (*c* 2.7, EtOH)}. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 177.2, 137.6, 128.4 (2 C), 127.7, 127.5 (2 C), 78.9, 73.4, 71.5, 28.3, 24.0. MS: *m/z* (%) = 206 (2), 105 (22), 91 (100), 85 (78), 65 (19).
(6*S*)-6-[(Benzyloxy)methyl]tetrahydro-2*H*-pyran-2-one[24] (13e).
Oil, 61% yield. $[\alpha]_D^{22}$ +9.1 (*c* 2.88, $CHCl_3$). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 171.1, 137.7, 128.4 (2 C), 127.7, 127.6 (2 C), 79.0, 73.5, 71.8, 29.6, 24.5, 18.2. MS: *m/z* (%) = 129 (1) [M – 91], 114 (58), 99 (35), 91 (100), 71 (45), 55 (23).
(6*R*)-6-[2-(Benzyloxy)ethyl]tetrahydro-2*H*-pyran-2-one[25] (13f).
Oil, 59% yield. $[\alpha]_D^{28}$ +55.0 (*c* 2.01, $CHCl_3$). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 171.8, 138.1, 128.3 (2 C), 127.9 (2 C), 127.6, 77.5, 73.1, 65.7, 36.0, 29.6, 27.9, 18.3. MS: *m/z* (%) = 234 (16), 206 (8), 107 (44), 91 (100), 79 (14), 68 (30), 55 (12).

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