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A Convenient Access to γ-Lactones from *O*-Allyl-α-Bromoesters using a One-Pot Ionic–Radical–Ionic Sequence

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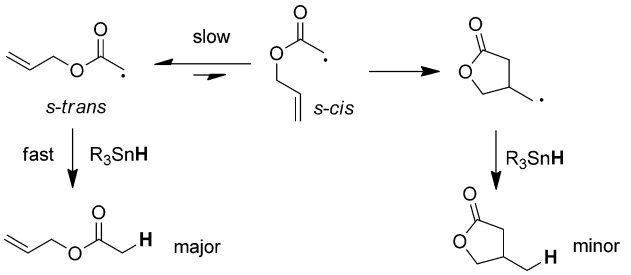
In memory of Prof. Athelstan L. J. Beckwith, a pioneer in the field of free radical chemistry

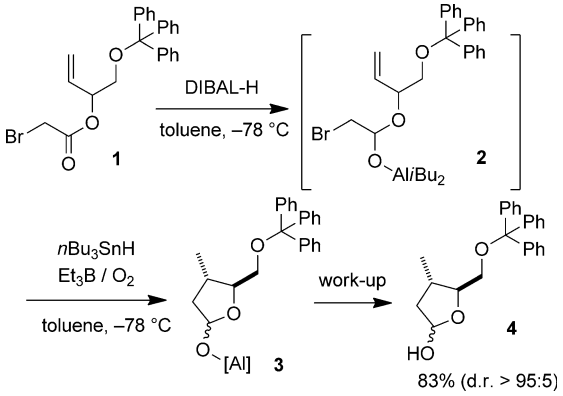
γ-Lactones are of great interest in industry due to the odorant properties of these small, volatile molecules, which makes them attractive candidates for applications as flavorings in food and fragrances in perfumes.[1] Among the different strategies to access γ-lactones, the radical cyclization of *O*-allyl-α-haloesters[2] under reducing conditions seems, at first, to be especially appealing. However, it is now well established that this approach is not, in most cases, an efficient process. The failure of the process is due to conformational constraints, which result in a slow equilibrium that lies in favor of the *s-trans* rotamer (Scheme 1).[3] This rotamer is



Scheme 1. Cyclization of α-haloesters under reducing conditions.

unable to cyclize and instead undergoes hydrogen abstraction from the radical-chain carrier, leading to the uncyclized dehalogenated product (Scheme 1). Some isolated examples of successful cyclization of α-haloesters under reducing conditions have been reported,[4] but both high temperature and high dilution are required to facilitate the equilibrium between *s-cis* and *s-trans* conformers and to decrease the rate for the intermolecular hydrogen atom abstraction from the chain carrier, respectively.

A solution to the problem encountered for the cyclization of α-haloesters under reductive conditions was reported in the 1980s independently by the groups of Ueno[5] and Stork.[6] The Ueno–Stork approach[7] consists of the use of the related α-haloacetals, which were found to cyclize very efficiently, even at low temperatures, to give the corresponding cyclic acetals. The resulting cyclic acetals have proven to be useful precursors for the corresponding lactones, although this transformation requires at least one additional step. Moreover, both the hydrolysis and the direct oxidation of the acetal moiety require the use of either a Brønsted or a Lewis acid, which poses a limitation to this approach in the case of substrates with highly acid-sensitive functionalities.[8] Recently, we reported that α-bromo aluminum acetals, prepared from the corresponding α-bromo esters by reduction with DIBAL-H, can be cyclized at low temperature under reducing conditions, delivering γ-lactols[9] and methylene-γ-lactols[10] in good to high yields. The method proved efficient with a range of substrates, including acid-sensitive precursors such as **1** (Scheme 2).



Scheme 2. Radical cyclization of aluminum acetals under reducing conditions.

The formation of cyclic aluminum acetals such as **3** offers the opportunity to investigate an in situ Meerwein–Ponndorff–Verley reduction of ketones and aldehydes.[11] To the best of our knowledge, the reactivity of such aluminum acetals as a reducing agent has not been studied thus far.[12] As far as the aluminum acetal is concerned, the overall process

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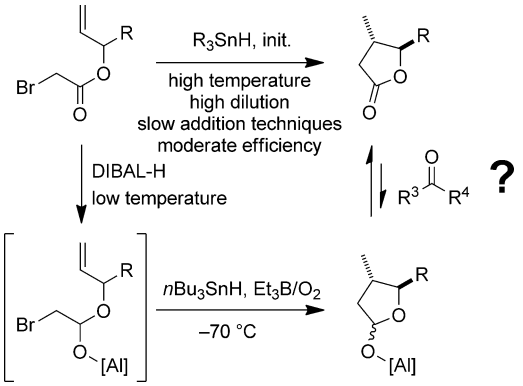
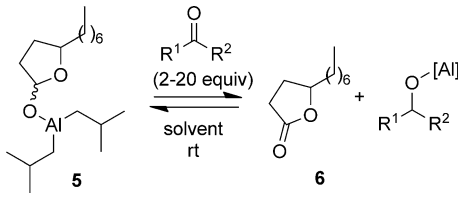


Scheme 3. Efficient preparation of γ-lactones from α-bromo esters using a one-pot process.

would result in the oxidation of the acetal center, a Tishchenko-type intermediate, via the reverse process (Oppenauer oxidation).[13] Should this approach be successful, it would provide a direct and efficient access to γ-lactones from readily accessible α-haloesters (Scheme 3).

We investigated the feasibility of this reaction using cyclic aluminum acetal **5** as starting material for the Oppenauer oxidation. It was obtained from the corresponding lactone **6** by reduction with 1.2 equivalents of DIBAL-H at low temperature. The reduction step was monitored by thin layer chromatography (TLC) and gas chromatography (GC) using bicyclohexyl as an internal standard. Following complete conversion into the cyclic aluminum acetal, a ketone or aldehyde was added and the reaction was allowed to warm to room temperature. Several ketones and aldehydes were tested in this Oppenauer-type oxidation (Scheme 4).



Scheme 4. Oppenauer-type oxidation of aluminum acetals.

Different solvents that were found to be compatible with the radical cyclization of aluminum acetals[14] were also investigated. The reactions were carried out at a concentration of 0.12 M to work at a similar concentration to that used for the radical cyclization of aluminum acetals. The hydride acceptors were added at −70 °C and the reaction mixture was then allowed to warm to room temperature. The results are summarized in Table 1.

The Oppenauer-type oxidation of cyclic aluminum acetal **5** was first attempted with acetone as an acceptor for the hydride transfer. The oxidation took place at room temperature in dichloromethane using only two equivalents of acetone, giving γ-lactone **6** in moderate yield (Table 1, entry 1). Similar results were obtained in hexane (44%), while a slightly higher yield (62%) was obtained in toluene (Table 1, entries 3 and 5). The use of a larger excess of acetone (20 equivalents) in dichloromethane or toluene allowed the yields to be further increased to about 70% (Table 1, entries 2 and 6). In *n*-hexane, the use of 20 equivalents of acetone led to γ-lactone **6** in 59% yield (Table 1, entry 4). Aldehydes proved much more reactive in this Oppenauer-type oxidation, with the reaction being almost complete within 4 hours. Both aliphatic and aromatic aldehydes can be used with similar efficiency. For instance, the addition of two equivalents of isobutyraldehyde to aluminum acetal **5** led to γ-lactone **6** in high yields for the reactions carried out in dichloromethane or in toluene (Table 1, entries 7 and 8). Similarly, the use of two equivalents of benzaldehyde also gave a high yield of γ-lactone **6** (Table 1, entries 9 and 10).

Table 1. Oppenauer-type oxidation of aluminum acetals.

Entry	R^1	R^2	Equiv	Solvent	Time [h]	Yield [%][a]
1	Me	Me	2	CH_2Cl_2	20 h	45
2	Me	Me	20	CH_2Cl_2	20 h	71
3	Me	Me	2	*n*-hexane	20 h	44
4	Me	Me	20	*n*-hexane	20 h	59
5	Me	Me	2	toluene	20 h	62
6	Me	Me	20	toluene	20 h	70
7	*i*Pr	H	2	CH_2Cl_2	4 h	85
8	*i*Pr	H	2	toluene	4 h	91
9	Ph	H	2	CH_2Cl_2	4 h	88
10	Ph	H	2	toluene	4 h	94

[a] GC yields determined using bicyclohexyl as an internal standard.

With these promising results in hands, we then turned our attention to the preparation of a series of γ-lactones from α-halo esters using a one-pot sequence. The latter involves the formation of an aluminum acetal by reduction with DIBAL-H, followed by the radical cyclization under reducing conditions and the Oppenauer oxidation of the resulting cyclic aluminum acetal. The results are presented in Table 2.

α-Bromoesters **7a–g** were prepared from the corresponding allyl alcohols using standard procedures for esterification. The reduction of **7a–g** was achieved in toluene below −70 °C using 1.2 equivalents of DIBAL-H. After complete conversion (TLC monitoring), the resulting aluminum acetals were cyclized in the presence of nBu_3SnH (1.2–1.4 equiv) using Et_3B/O_2 as a radical initiator. The radical cyclization was usually complete within 5 hours (TLC and GC monitoring). Once the radical cyclization had been achieved, the aldehyde (*i*PrCHO or PhCHO, 2–3 equiv) was added and the reaction mixture was allowed to warm to room temperature (25 °C). Following this one-pot protocol, **7a** was converted into γ-lactone **8a** in high yield and with a high level of diastereoselectivity (Table 2, entry 1). Oxidation leading to **8b** proved to be somewhat slower, probably as a result of the increased steric hindrance close to the reactive aluminum acetal center. As expected from our previous work, a low level of diastereoselectivity was observed in this case (Table 2, entry 2). Similarly, α-bromoesters **7c** and

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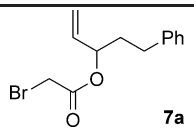
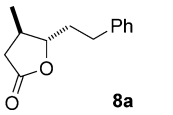
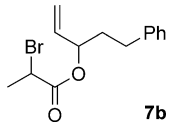
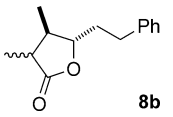
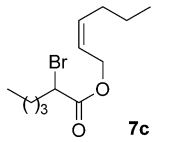
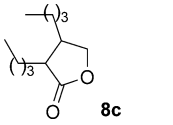
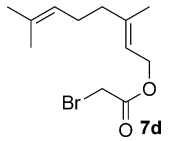
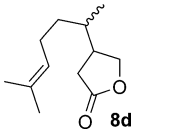
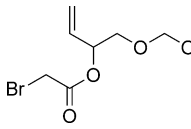
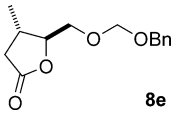
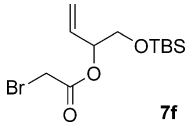
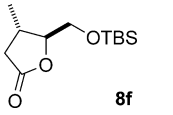
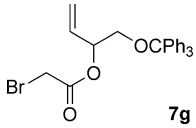
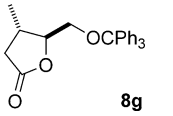
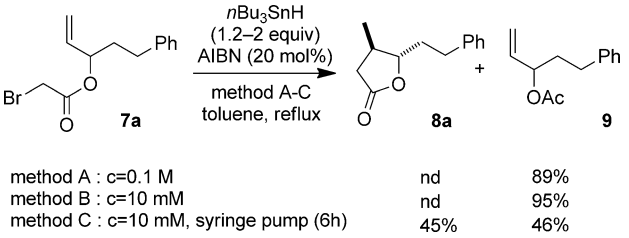
Table 2. Synthesis of γ-lactones using the reduction–cyclization sequence, followed by in-situ Oppenauer oxidation.

Entry	Substrate[a]	Product	Yield[b]	d.r.[c]
1	 **7a**	 **8a**	91 %[e]	>95:5
2	 **7b**	 **8b**	88 %[d,e]	50:50
3	 **7c**	 **8c**	83 %[d,e]	55:45
4	 **7d**	 **8d**	90 %[d,e]	50:50
5	 **7e**	 **8e**	80 %[f]	>95:5
6	 **7f**	 **8f**	85 %[f]	>95:5
7	 **7g**	 **8g**	62 %[d]	>95:5

[a] All reactions were carried out with α-bromo esters (2 mmol) in toluene (see the Supporting Information for details), using DIBAL-H (1.2 equiv) at −70 °C, then nBu$_3$SnH (1.2–1.4 equiv), and Et$_3$B (0.3–1.1 equiv), unless otherwise stated. [b] Yields of isolated products. [c] Diastereomeric ratio (d.r.) determined by GC or ^{1}H NMR spectroscopic analysis. [d] γ-Lactones were isolated as mixture of diastereoisomers. [e] Oxidation carried out with PhCHO (3 equiv). [f] Oxidation carried out with *i*PrCHO (3 equiv).

7d, presenting a substituent at the α-position of the ester functionality, could be cyclized into **8c** and **8d**, respectively, in good to high yields (Table 2, entries 3 and 4). γ-Lactone **8d** was obtained as a mixture of two diastereoisomers, with no diastereomeric control of the newly formed stereogenic center (Table 2, entry 4). Interestingly, this one-pot process allowed the cyclization of **7e–g** into the corresponding γ-lactones **8e–g** presenting a hydroxy group protected with an acid-sensitive protecting group, which included benzyloxymethyl (BOM), *tert*-butyldimethylsilyl (TBS), or even triphenylmethyl (Tr), thus demonstrating the mildness of the method (Table 2, entries 5–7).

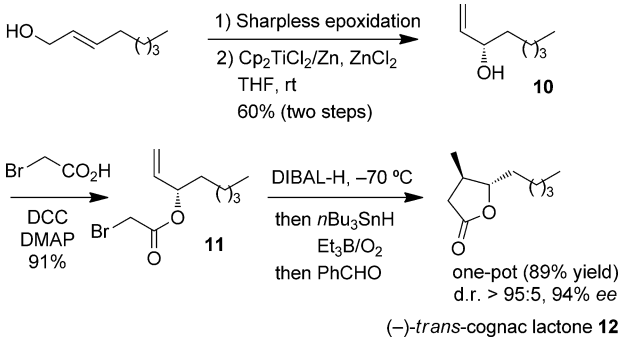
For the sake of comparison, we attempted the radical cyclization of **7a** under "classical" conditions. The reactions were carried out in refluxing toluene to accelerate the equilibrium between the *s-trans* and *s-cis* conformers. While the one-pot approach involving the cyclization of **7a** via an aluminum acetal intermediate led to **8a** in approximately 90 % yield, the reduced compound **9** was obtained as the sole product when nBu$_3$SnH/AIBN was introduced at once to a 0.1 M refluxing solution of **7a** in toluene (Scheme 5, method A). Still, the reduced compound **9** was obtained exclusively for the reaction carried out at an initial concentration in tin hydride of 10 mM (Scheme 5, method B). Finally, even at high dilution (10 mM) and using a slow addition of the tin hydride (over 6 h), compound **9** was the major product (Scheme 5, method C), with the expected lactone **8a** being isolated in only 45 % yield.[15]



Scheme 5. Cyclization of α-bromoester **7a** under classical tin-hydride conditions.

To illustrate the efficiency of the one-pot approach, the sequence was applied to the total synthesis of (−)-*trans*-cognac lactone (Scheme 6). Felluga and co-workers recently reported the synthesis of *trans*-cognac lactone using non-reducing conditions, that is, the atom-transfer method. The radical cyclization was achieved in moderate yield (60 %) using a CuCl/bipyridine-promoted cyclization of a trichloroacetate derivative at 145 °C in acetonitrile. Dehalogenation of the resulting chlorinated γ-lactone was achieved with nBu$_3$SnH and gave cognac lactone in high yield (88 %) but with only relatively moderate levels of diastereoselectivity (74 % *de*).[16]

The required optically enriched allylic alcohol **10** was readily obtained from commercially available (*E*)-1-octen-3-ol, using a two-steps sequence involving a Sharpless asymmetric epoxidation,[17] followed by ring opening of the epoxide with Ti^{III}.[18] The α-bromo ester precursor **11** was prepared using standard conditions for esterification, and then



Scheme 6. A straightforward approach to (−)-*trans*-cognac lactone.

introduced to the one-pot sequence to give (−)-*trans*-cognac lactone **12** in 89% yield and with high levels of diastereoselectivity (d.r. > 95:5) and enantiomeric purity (94% *ee*).[19]

In conclusion, we have developed a straightforward access to γ-lactones from easily accessible precursors. This one-pot sequence allowed the desired γ-lactones to be obtained in good to high yields. This approach appears quite general and efficient, and competes favorably with the direct cyclization of α-halo esters under tin-hydride conditions, which require both high dilutions and/or slow addition techniques, as well as high temperatures, for only moderate efficiency. This very simple approach tolerates substitution at the different positions of the starting α-bromo ester derivatives with a high flexibility. Both aliphatic and aromatic aldehydes proved highly reactive as oxidants for this unprecedented preparative Oppenauer-type oxidation of an *O*-aluminum acetal center. The result is a large variety of aldehydes to choose from in order to facilitate the purification of the desired products. The efficiency of the methodology was illustrated by a straightforward synthesis of optically enriched (−)-*trans*-cognac lactone (four steps from commercially available allyl alcohol, 94% *ee*).

Experimental Section

Diisobutylaluminum hydride (DIBAL-H, 2 mL, 1.2 M in toluene, 2.4 mmol) was added dropwise to a solution of α-bromoester **7a** (0.566 g, 2.0 mmol) and bicyclohexyl (0.333 g, 2.0 mmol, used as an internal standard for GC monitoring) in toluene (16 mL) under argon atmosphere at −78 °C. After complete disappearance of the starting material (TLC monitoring), Et_3B (0.6 mL, 1 M in hexanes, 0.6 mmol) and $n$$Bu_3SnH$ (0.65 mL, 2.4 mmol) were simultaneously added dropwise at −78 °C. Subsequently, air (0.3 mL) was introduced via a syringe above the solution, and the mixture was kept at −70 °C. After 2 h, Et_3B (0.4 mL, 1 M in hexanes, 0.4 mmol), $n$$Bu_3SnH$ (0.16 mL, 0.6 mmol), and air (1 mL) were added to the solution, and the reaction mixture was stirred at −70 °C until complete disappearance of the allyl alcohol (TLC monitoring, vanillin revelation, and GC monitoring with a sample quenched with 0.5 M HCl, extracted with Et_2O, washed with aqueous $NaHCO_3$, and filtered over silica-KF). Benzaldehyde (0.61 mL, 6 mmol) was added at once and the cooling bath was removed. The reaction mixture was stirred at room temperature (25 °C) for ca. 4 h (GC monitoring) and then quenched with 0.5 M HCl (17 mL). Next, Et_2O was added and the organic phase was collected. The aqueous phase was extracted four times with Et_2O. The resulting organic phase was washed with an aqueous $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (first with petroleum ether/Et_2O 80:20, then with CH_2Cl_2 to remove benzyl alcohol). γ-Lactol **8a** (372 mg, 91%) was obtained as a colorless oil.

Acknowledgements

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Keywords: aluminum acetals · cognac lactone · Oppenauer oxidation · radical cyclization · γ-lactone

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Domino Reactions

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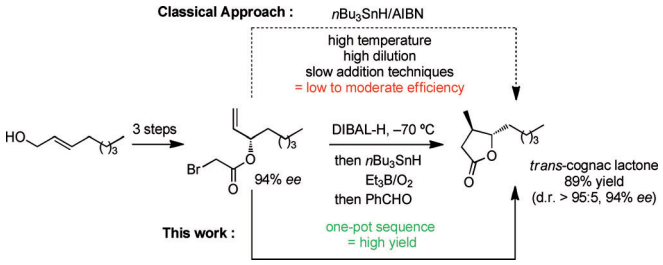
A Convenient Access to γ-Lactones from *O*-Allyl-α-Bromoesters using a One-Pot Ionic–Radical–Ionic Sequence



Cognac in the jar! An efficient one-pot sequence for the preparation of γ-lactones is described. Following reduction of α-bromo ester precursors with DIBAL-H and radical cyclization of the resulting *O*-aluminum acetals, a preparative in-situ Oppenauer-type oxidation of the cyclic *O*-aluminum acetal using simple aldehydes or ketones gives access to γ-lactones in high yields.

