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Chemoselective access to substituted butenolides via a radical cyclization pathway: mechanistic study, limits and application

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Abstract: We developed a new approach to γ-lactols and methylene-γ-lactols based upon the radical cyclization of aluminium acetals obtained by reduction of α-bromoesters with DIBAL-H. The cyclic aluminium acetals resulting from the cyclization process could engage in situ in further functionalization, as illustrated by the Oppenauer-type oxidation to give the corresponding lactones and γ-butenolides. The preparation of butenolides using this strategy compared favourably with the direct, tin-mediated cyclization of α-bromoesters, for which side reactions such as epimerization via [1,5]-HAT processes have been observed.

Keywords: C–C bond formation; cyclizations; ESOC-19; mechanism; natural product synthesis; radical reactions.

Introduction

γ-Butenolides are part of many natural compounds (Fig. 1), which display a wide range of biological activities, including cardiotonic, antibiotic, and anti-inflammatory activities [1–5]. They can also be regarded as useful chiral building blocks for the elaboration of more complex structures. Numerous strategies have been developed to access this important class of compounds, among which the ring-closing metathesis approach was found to be very efficient [6–12], as long as the endocyclic C=C bond of the butenolides is only di- or trisubstituted. On the contrary, the synthesis of tetrasubstituted butenolides using this straightforward strategy proved to be rather inefficient [13].

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Preparation of butenolides based on radical chemistry

Previous work and reinvestigation of a “classical” radical cyclization

Although radical chemistry has demonstrated over the years its efficiency for the formation of related small ring systems (in particular 5-membered rings), the free-radical approaches to the butenolide moiety have been scarcely explored. One of the reasons why this strategy has been overlooked is the fact that the 5-exo-trig and 5-exo-dig cyclizations of electrophilic radicals generated from α-bromoesters were found to be relatively slow compared to the intermolecular hydrogen atom abstraction from the chain-carrier reagent (typically a tin hydride derivative). This unusual behaviour is not due to the cyclization step itself but rather to the slow equilibrium between the reactive, minor, s-cis conformer and major s-trans conformer [14]. For the radical cyclization to compete favourably with the trapping of the electrophilic radical prior to cyclization, high dilution (ca. $10^{-2}$ M), slow addition techniques, and high temperature (typically refluxing benzene or toluene) are generally required [15–17]. These conditions were applied by the Pattenden group to prepare a variety of butenolides from α-bromoesters derived from propargylic alcohols. The radical process was followed by subsequent base-mediated migration of the exocyclic C=C bond to give the γ-butenolide subunit (Scheme 1, Equation a) [15]. Beside the practical aspect that makes this approach requiring high dilution not really attractive for practitioners, the dilution conditions also imply that the highly reactive alkenyl radical resulting from the 5-exo-dig process should have sufficient lifetime to lead to side-reactions prior to hydrogen atom abstraction from the chain-carrier reagent. In a tin-free approach, Wayner and co-workers used ketyl radicals derived by hydrogen atom abstraction from isopropanol to promote the radical cyclization of the same class of α-bromoesters [18]. Under their reaction conditions, the alkenyl radical abstracts a hydrogen atom from the solvent to give the methylene-lactone and a ketyl radical that sustains the radical chain. Isomerization of the exocyclic C=C bond into the conjugated position was observed under the reaction conditions, delivering the desired butenolides, as well as the formation of a brominated compound resulting from a radical cascade involving a 1,5-hydrogen atom abstraction (1,5–HAT), followed by halogen atom transfer from the precursor. This hydrogen atom transfer is in this case an undesired side-reaction, which is the result of the intramolecular trapping of the alkenyl radical intermediate to generate a new carbon-centred radical (Scheme 1, Equation b). The tin-free approach did not proved to be general as the best yields were obtained with precursors having a gem-dimethyl substitution (or equivalent) that accelerates the radical cyclization process.

We were intrigued by the report by Pattenden and co-workers and decided to reinvestigate this reaction in detail in order to define clearly its scope and the fate of the alkenyl radical under these reaction conditions. We started our investigations by repeating some of the examples described in the original paper by Pattenden...
and co-workers but using tributyltin deuteride as the chain-carrier reagent. The study clearly proved that 1,5-hydrogen atom transfer (1,5-HAT) could take place when a poor hydrogen atom donor is present or when the concentration in hydrogen atom donor is too low for the intermolecular trapping to compete with the intramolecular rearrangement (Scheme 2). The success of this reaction proved to strongly depend upon the nature of the bromoester and some precursors did not give more than traces of butenolide. In most cases, the translocation process did not seem, at first, to interfere with the formation of the desired products. As expected, the 1,5–HAT process is accelerated by the increase in the stabilization of the carbon-centred radical resulting from the translocation process. The process does not seem to depend upon the geometry of the alkenyl radical, as both sp-hybridized and sp²-hybridized alkenyl radicals underwent 1,5-HAT and gave very similar results. The carbon-centred radicals formed during the 1,5–HAT process do not cyclize very rapidly neither in a 5-endo-trig mode [19–24], nor in a 4-exo-trig mode, although this mode of cyclization has been sometimes observed during our investigations [25]. This is in sharp contrast with the translocation processes leading to 1-hexenyl radical, for which the 5-exo-trig cyclization process is very rapid, thus delivering 5-membered rings in high yields [26]. Here, the translocation process remains “invisible” for most of the reactions are generally carried out with nBu₃SnH.
During this study, DBU proved to be capable of abstracting a proton (or deuterium) from the benzylic position, which explains why <100% of deuterium atom incorporation was measured for all the substrates that did not undergo quantitative 1,5-HATs. This was confirmed by the use of a milder base, such as iPr$_2$NEt, to promote the C=C bond migration. α-Bromoesters presenting a stereogenic centre on the side-chain have been prepared and tested in the radical cyclization. For some of them, the radical cyclization was followed by 1,5–HAT and led, after C=C bond migration with the help of a mild base (iPr$_2$NEt), to the corresponding butenolide. These butenolides were then isolated with almost complete epimerization of the stereogenic centre located on the side-chain. In the examples depicted in Scheme 3 (Equation a and b), the propargylic alcohol required for the preparation of the bromoester precursor was easily obtained in an optically pure manner from L-isoleucine. In this case the one-pot sequence delivered the butenolide in 57% yield after migration of the C=C bond in the presence of iPr$_2$NEt, as a nearly 1:1 mixture of diastereoisomers (Scheme 3, Equation a). The epimerization which is the result of a 1,5–HAT occurred then almost exclusively at a remote position on the side-chain and not at the highly base-sensitive butenolide moiety. Both syn and anti isomers underwent the radical cyclization-translocation process, as indicated by the complete racemization observed during the cyclization at high temperature of a mixture of optically pure, syn- and anti-precursor (Scheme 3, Equation b). Chiral HPLC analysis indicated the formation of syn- and anti-butenolides as a racemic mixture. In some other cases, the fate of the carbon-centred radical resulting from the cyclization-translocation process remained unclear and only complex mixtures were obtained (Scheme 3, Equations c and d).

This study allowed us to shed light on “invisible” hydrogen-atom transfers, which might result in complications after the cyclization process. In some cases, a complete epimerization of a stereogenic centre located at a position that was not suspected at first glance to be sensitive was observed. In some other cases, the radical resulting from the translocation process was found to undergo 4-exo-trig cyclization to give bicyclic systems [25]. All these observation are the results of reaction kinetics that allow for the translocation process to compete favourably with the intermolecular processes, and as such, there is no reason for these complications.

**Scheme 3**: Epimerization of “unreactive” stereogenic centres via a radical process.
to be limited to tin hydride as the chain-carrier reagent. Any other reaction conditions that would make the slow 5-exo-dig cyclization process of α-bromoesters possible (that is, reaction conditions that would prevent the trapping of the electrophilic radical prior to cyclization), would necessarily involve a slow hydrogen atom transfer, and as a result a lifetime for the alkenyl radical long enough to undergo rearrangements.

1,5–HAT is not the only side reaction that can be observed under reaction conditions implying a low concentration of hydrogen atom donor (here nBu3SnH), and cyclization of the alkenyl radical onto an acceptor present on the substrate is another possibility that has to be considered. During our attempts at preparing the natural tribenzyl butenolide skeleton of maculalactone A (Fig. 1), the most abundant secondary metabolite produced by the marine cyanobacterium Kyrtuhrrix maculans, we first investigated the radical cyclization of a bromoester precursor under reaction conditions used by Pattenden and co-workers (cyclization in refluxing benzene (c = 10−2 M) with a slow addition of solutions of nBu3SnH and AIBN over 16 h) [15]. Under these reaction conditions, the reaction led to a complex mixture of products, with only traces of maculalactone A. The main products that were isolated from this mixture were a fused tricyclic lactone and the reduced, uncyclized ester, isolated in 28 and 20% yields, respectively (Scheme 4). In this case, the alkenyl radical intermediate could not be trapped rapidly enough by intermolecular hydrogen atom abstraction from the tin hydride, and the intramolecular addition onto one of the aromatic rings present on both side chains occurred. The mechanism for the aromatization is yet unclear. Other products resulting from intermolecular addition onto the solvent (benzene) might also have been formed under these reaction conditions, but this remains a speculation since we were not able to characterize any other by-products from the complex mixture.

**Radical cyclisation of α-bromoaluminium acetals**

An alternative, indirect route to γ-lactones was developed in the 1980s and relied on the cyclization of α-haloacetals. The reaction was developed independently by the groups of Ueno [27, 28] and Stork [29–33] and is now known as the Ueno–Stork reaction [34]. The cyclic acetals resulting from a 5-exo-trig cyclization process could easily be converted into γ-lactones using Jones [27] or Grieco’s conditions [35]. These reaction conditions, however, proved difficult to apply to substrates presenting acid-sensitive functionalities. This is particularly true for hydroxyl protecting groups, which could be cleaved under these conditions [36, 37]. The related 5-exo-dig cyclisation of α-bromoacetals involving the intramolecular addition onto Carbon-Carbon triple bond also proved to be very powerful, however, in this case the hydrolysis usually leads to substituted furans instead of the corresponding desired methylene-γ-lactols [38–41].

**Mild access to γ-lactols and methylene-γ-lactols**

The introduction of trialkylboranes as a source of alkyl radicals represents a significant advance in the field of radical chemistry as it allows initiation of radical chain processes at a very low temperature [42]. Besides
the beneficial effect to the selectivities of radical reactions (including chemoselectivity), the possibility to carry out reactions at −78 °C also offers the opportunity to extend the scope of precursors to include thermally unstable intermediates. We have first developed a general, one-pot approach to \( \gamma \)-lactols and methylene-\( \gamma \)-lactols based upon the formation of an \( \alpha \)-bromo aluminium acetal, followed by its cyclization under reductive radical conditions at low temperature [43, 44].

Aluminum acetals are well-known intermediates that can be easily obtained from the corresponding esters by reduction with di-iso-butyaluminum hydride (DIBAL-H). These proved to be stable enough at low temperature to be trapped with highly reactive electrophiles, such as TMS-imidazole or silyl triflates [45, 46], acetic anhydride [47–49] or acid fluorides [50].

\( \alpha \)-Bromoesters derived from allylic and propargylic alcohols were found to participate efficiently in a one-pot reaction involving 1) the formation of an \( \alpha \)-bromo aluminium acetal at low temperature, and 2) the radical \( \text{nBu}_3\text{SnH} \)-mediated radical cyclization at low temperature. A simple, neutral aqueous work-up delivered the corresponding \( \gamma \)-lactols and methylene-\( \gamma \)-lactols in good to high yields (Scheme 5) [43, 44]. Only the more hindered substrates (those with two alkyl substituents at the alpha position) were found to give less stable aluminium acetals, and thus lower yields (ca. 50 \%) for the preparation of the cyclized compounds. Acid-sensitive protecting groups, such as the labile trityl group (Tr) were usually not cleaved under these very mild reaction conditions. The proposed mechanism for this cyclization is very similar to the accepted mechanism for the parent Ueno-Stork reaction. Only the structure of the precursor for the radical cyclization differs from the simple structure of classical \( \alpha \)-bromo acetals, but without any obvious consequences on the stereochemical outcome of the cyclization.

Gratifyingly, methylene-, alkylidene-, and arylidene-\( \gamma \)-lactols could be efficiently converted into the corresponding 1,4-diols under mild reaction conditions (typically by using sodium borohydride in THF/MeOH), or into 1,4-dienes under Wittig–Horner conditions with a stabilized phosphorous ylide [44].

**One-pot access to \( \gamma \)-lactones and butenolides via a stepwise radical cyclisation of aluminium acetal–Oppenauer type oxidation**

We first investigated the possibility to modify the one-pot reaction involving aluminium acetals in order to access directly the desired \( \gamma \)-lactones and butenolides from \( \alpha \)-bromoesters, without isolation of the \( \gamma \)-lactols or the sensitive methylene-\( \gamma \)-lactols. Although the reactivity of aluminium acetals with nucleophiles and
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Some electrophiles was long known [51], the use of aluminium acetals as stoichiometric reducing agent has been overlooked. The transfer of a hydride from the cyclic aluminium acetal resulting from the radical cyclization process would allow for a mild oxidation into the corresponding lactone functionality. The Oppenauer-type oxidation of the cyclic aluminium acetals proved to be very efficient for the preparation of \( \gamma \)-lactones from \( \alpha \)-bromoesters [52]. The cyclization of \( \alpha \)-bromoesters derived from allylic alcohols were carried out, as previously, and the resulting aluminium acetals were treated with 2–3 fold excess of a cheap, commercially available aldehyde. Following this one-pot protocol, the \( \gamma \)-lactones were obtained in good to high yields. The radical cyclization was usually complete within 5 h (TLC and GC monitoring) and once the radical cyclization had been achieved, the aldehyde (\( \text{iPrCHO} \) or \( \text{PhCHO}, 2–3 \text{equiv} \)) was then added. The reaction mixture was allowed to warm to room temperature (25 °C) and stirred at this temperature until completion. The choice of the aldehyde can be crucial in order to facilitate the purification and separate the desired lactone from the unreacted aldehyde and the corresponding alcohol that is formed during the process. Here again, the one-pot process proved to be compatible with the presence of acid-sensitive protecting groups, such as benzyloxymethyl (BOM), tert-butyldimethylsilyl (TBS), or even triphenylmethyl (Tr), thus demonstrating the mildness of the method (Scheme 6).

**Synthesis of (–)-trans-Cognac-lactone**

The efficiency of this one-pot approach to \( \gamma \)-lactones was illustrated by a short total synthesis of (–)-trans-cognac lactone (Scheme 7). The strategy was inspired by a previous synthesis by Yadav and co-workers who

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**Scheme 6:** Preparation of \( \gamma \)-lactones based upon the cyclization of \( \alpha \)-bromo aluminium acetals.

**Scheme 7:** Synthesis of (–)-trans-Cognac lactone.
reported an approach based upon the Ueno-Stork reaction for the formation of the 5-membered ring [53]. The enantio-enriched allylic alcohol required for the preparation of the radical precursor was readily obtained in two steps from commercially available (E)-1-octen-3-ol. A Sharpless asymmetric epoxidation [54], gave the enantio-enriched epoxide (94% ee) and the latter was cleaved in the presence of TiIII to give the desired alcohol [55, 56]. The α-bromo ester precursor was prepared in high yield using standard conditions for esterification. The three-step, one-pot sequence gave (−)-trans-cognac lactone in 89% yield and with high levels of diastereoselectivity (d.r. > 95:5) and enantiomeric purity (94% ee) [52].

Preparation of butenolides

This one-pot sequence was then applied to the cyclization of α-bromoesters derived from propargylic alcohols and combined with the base mediated migration of the C=C bond. Following this strategy, butenolides presenting a tetrasubstituted C=C bond were obtained in good to high yields in most cases [25]. As previously observed, the choice of the base proved to be crucial to ensure high enantiomeric excesses as the butenolides could be easily deprotonated to give the aromatic anion. A base such as DBU usually gave good results in terms of yields but this base is not recommended for the preparation of optically active material (vide infra).

This indirect route to butenolides compares favourably with the direct cyclization of α-bromoesters at high temperature and under high dilution conditions. Because the radical cyclization could be then carried out at low temperature and at a significantly higher concentration in tin hydride (typically 1.2 × 10^-1 M, without the need for slow addition techniques), no complications due to the high reactivity of the alkenyl radical intermediate were observed. The use of nBuSnD allowed us to prove the absence of 1,5-HAT under these reaction conditions. Some butenolides that could not be obtained via the direct route at high temperature, were obtained in good to high yields with this approach (Scheme 8).

Synthesis of naturally-occurring butenolides

The methodology was successfully applied to the preparation of optically enriched compounds (butenolides from natural sources or unnatural ones), such as a butenolide from Plagiomnium undulatum [57], whose previous synthesis was reported in in 2005 by Brückner, König and co-workers [58], maculalactone A, which could not be obtained under the Pattenden’s conditions (vide supra), or other butenolides presenting a stereogenic centre on the side-chain at a position that was found to be epimerized at high temperature. The precursor for the radical cyclization leading to the tetrasubstituted butenolide from Plagiomnium undulatum was...
prepared in one step from commercially available (+)-oct-1-yn-3-ol (99.0 % ee) and 2-bromopropionic acid. In this case the cyclized compound was obtained in good yield and with a high level of enantiomeric excess under our standard reaction conditions, using \( \text{iPr}_2\text{NEt} \) as the base. This represents the shortest synthesis to date of this natural compound (Scheme 9).

Our synthesis of maculalactone A [59] started with a commercially available acyl chloride (Scheme 10). The precursor for the radical cyclization was assembled in four steps. These include the addition of the Grignard reagent of phenylacetylene onto a Weinreb amide and the asymmetric reduction of the resulting ynone using Noyori’s ruthenium-based catalyst [60]. This reduction led to propargylic alcohol with a good level of enantiomeric excess (96.0 % ee). The \( \alpha \)-bromoester then engaged in the key step, delivering maculalactone A [13, 61–64] in 56 % yield and with a level of enantiomeric excess (94.8 % ee) close to the one determined for the natural compound [61]. In this case, the migration of the \( \text{C} = \text{C} \) bond into the \( \alpha, \beta \)-position proved to be extremely slow and it required extended reaction time to reach good yields. Interestingly, the use of DBU resulted in much shorter reaction time but complete racemization of the final compound.

Chemoselectivity issues

The methodology proved to be much more chemoselective than the classical approach at high temperature as illustrated with the examples depicted in Scheme 11, which either could not be formed at high temperature (for substrates shown in Scheme 11, Equations a and b), or led to the butenolides with epimerization of the stereogenic centre present on the side chain (as for the substrate shown in Scheme 11, Equation c). The radical cyclization of aluminium acetales at low temperature allowed for a mild cyclization reaction to take place, without any side-reaction after the initial cyclization. As expected, the use of \( \text{nBu}_2\text{SnD} \) indicated that the trapping of the alkenyl radical occurred exclusively in an intermolecular fashion, with no 1,5–HAT taking place at so low temperature (Scheme 11, Equation d) [25].
Conclusion

We have reported herein a general approach to $\gamma$-lactols and methylene-$\gamma$-lactols from easily accessible $\alpha$-bromoesters. Reduction of the latter to form thermally labile aluminium acetal intermediate allows for the subsequent radical reaction to occur efficiently at low temperature. The resulting cyclic aluminium acetals can either be hydrolyzed to give $\gamma$-lactols or oxidized by the use of a cheap, commercially available aldehyde. Similar reaction conditions applied to $\alpha$-bromoesters derived from propargylic alcohols, followed by the migration of the carbon-carbon double bond under basic or acidic conditions, gave $\gamma$-butenolides. The target compounds were obtained in good to high yields using these one-pot sequences. This methodology is a valuable alternative to both the Ueno-Stork reaction and the direct cyclization of $\alpha$-bromoesters. On the one hand, acid sensitive compounds, such as methylene-$\gamma$-lactols, become accessible under these mild reaction conditions. On the other hand, the 1,5-hydrogen atom transfers leading to epimerization of stereocentres or to the formation of by-products during the direct cyclization of $\alpha$-bromoesters (as highlighted by our mechanistic study), are now totally suppressed under our reaction conditions. Therefore this approach allows for the preparation of a wider range of functionalized, optically active $\gamma$-butenolides, as illustrated by the efficient synthesis of several natural compounds.

References