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Radical Reactions |*Hot Paper*|

Synthesis of Polysubstituted γ-Butenolides via a Radical Pathway: Cyclization of α-Bromo Aluminium Acetals and Comparison with the Cyclization of α-Bromoesters at High Temperature

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Abstract: Polysubstituted butenolides were obtained in good to high yields from α-bromoesters derived from propargyl alcohols by a one-pot reaction involving the radical cyclization of α-bromo aluminium acetals, followed by the oxidation of the resulting cyclic aluminium acetals in an Oppenauer-type process and migration of the exocyclic C=C bond into the α,β-position. Comparison with the direct cyclization of α-bromoesters at high temperature and under high dilution conditions is described. Deuterium-labelling experiments allowed us to uncover "invisible" 1,5-hydrogen atom transfers (1,5-HATs) that occur during these cyclization processes, together with the consequences of the latter in the epimerization of stereogenic centres. Compared to the classical approach, the cyclization of aluminium acetals proved to be highly chemoselective and its efficiency was illustrated by the short total syntheses of optically enriched γ-butenolides isolated from *Plagiomnium undulatum* and from *Kyrtuhrix maculans*.

Introduction

γ-Butenolides represent an important class of compounds as part of many natural compounds, which display a wide range of biological activities (Figure 1). Moreover, they can be regarded as functionalized chiral building blocks for the elaboration of more complex structures, for these cyclic compounds can be easily converted into diastereomerically pure material.[1] Among the synthetic methods available to build or decorate the butenolide skeleton,[2] the ring-closing metathesis approach has proved to be particularly efficient.[3] This strategy, however, is limited to the preparation of butenolides for which the C=C bond is di- or trisubstituted, as the synthesis of the more sterically demanding tetrasubstituted butenolides proved inefficient.[4] For this purpose, the ruthenium-catalysed cyclocarbonylation[5] and the carbocupration-carboxylation[6] of allenyl alcohols, as well as the transition-metal catalysed cyclization of 2,3-dienyl carboxylic acid derivatives[2e,f,7] have proved to be much more valuable.

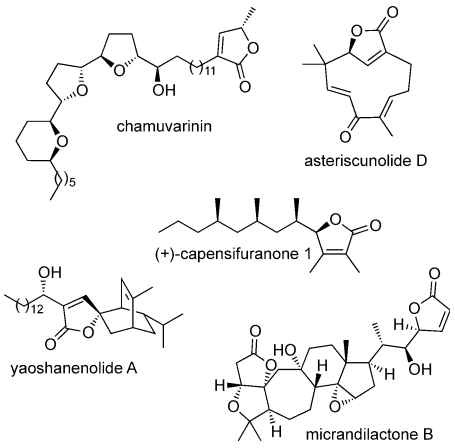

Figure 1. Selected examples of natural compounds containing a γ-butenolide skeleton.

Another approach that could be envisaged to form the butenolide moiety is the radical cyclization of α-bromoesters derived from simple propargylic alcohols. Although the strategy seems appealing, this type of radical cyclization involving electrophilic radical derived from α-bromoesters is known to be hampered by the slow equilibrium between the reactive, minor, *s-cis* conformer and major *s-trans* conformer. As a result the cyclization of this type of bromoesters in the presence of a hydrogen-atom donor usually leads to dehalogenated, non-cyclized products.[8] This explains why high dilution (ca. 10^{-2} M), slow addition techniques, and high temperature (typically refluxing benzene or toluene) are required in order for

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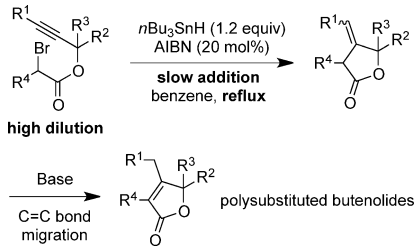
the electrophilic radical intermediate to have a sufficient lifetime to undergo cyclization prior to intermolecular hydrogen-atom abstraction from the chain-carrier reagent (typically a tin hydride derivative).[9] Pattenden and co-workers reported examples of such radical cyclizations, which, combined with a base-mediated migration of the exocyclic C=C bond into the α,β-position, gave access to the γ-butenolide subunit (Scheme 1).[9a]

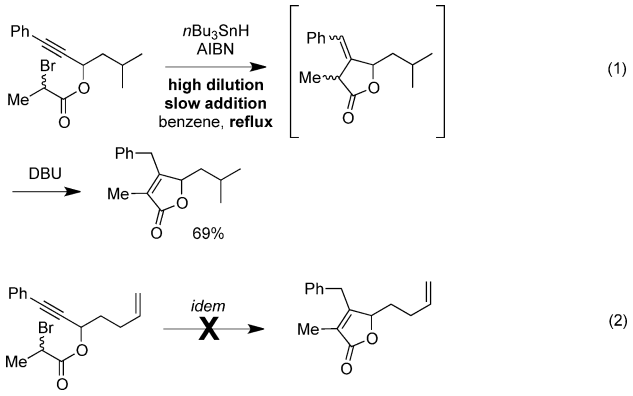


Scheme 1. Pattenden's approach to the butenolide unit.

Both the high-dilution (ca. 10^{-2} M) and the slow-addition technique required to achieve this radical cyclization make this approach unattractive, especially on large scale. Moreover, under these reaction conditions the highly reactive alkenyl radical intermediates resulting from the 5-*exo-dig* cyclization process are very likely to lead to side-reactions prior to hydrogen-atom abstraction from the chain-carrier reagent, the concentration of which in the medium is voluntarily maintained sufficiently low in order not to interfere with the cyclization process. For all these reasons, we were intrigued by the report by Pattenden and co-workers and decided to reinvestigate this reaction in detail. This study allowed us to shed light on "invisible" hydrogen-atom transfers, which might result in complications after the cyclization process. We propose herein an alternative route to circumvent these chemoselectivity issues by the means of a radical cyclization at low temperature of aluminium acetal intermediates. The mildness of this novel approach is illustrated by the total synthesis of two enantioenriched, naturally occurring butenolides.

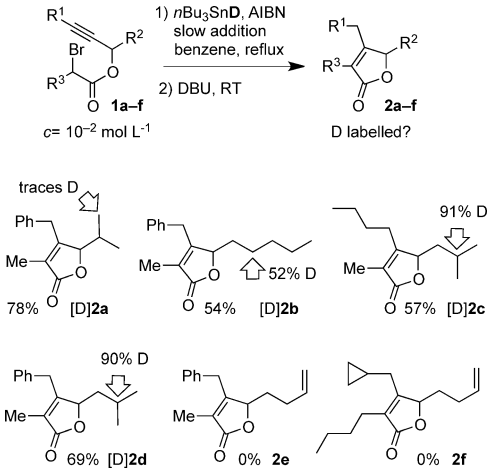
Results and Discussion

We started our investigations by repeating some of the examples described in the original paper by Pattenden and co-workers. Under the reaction conditions reported in their seminal contribution, we were able to achieve the radical cyclization of some α-bromoesters, with limited reduction of the electrophilic radical intermediate (ca. 10–15%), in good agreement with the observations by these authors. Following in situ treatment with a base, several tetrasubstituted butenolides were indeed isolated in good yields and high purity by flash-chromatography over silica gel/KF (9:1)[10] [Scheme 2, Eq. (1)]. However, as we suspected, the success of this reaction proved to strongly depend upon the nature of the bromoester used as precursor and, with some substrates not even traces of butenolide were observed [Scheme 2, Eq. (2)].



Scheme 2. Preparation of butenolides through a radical cyclization under Pattenden's condition.[9a]

We believed that the failure of the reaction with substrates such as the one used in Scheme 2 [Eq. (2)] was not due to the radical-cyclization process itself, as the size and the nature of the side-chain were not expected to have a dramatic influence on the rate of the cyclization step. The absence of formation of the desired butenolides in some cases was more likely the result of the outcome of the highly reactive alkenyl radical intermediate. We decided then to conduct a systematic study, using a tin deuteride derivative as the chain-carrier reagent, with the hope that it would allow us to determine the fate of the alkenyl radical intermediate in these reactions. The results are shown in Scheme 3.



Scheme 3. Deuterium-labelling experiment.

The results obtained in the presence of tributyltin deuteride clearly indicate that 1,5-hydrogen atom transfer (1,5-HAT)[11,12] could take place under the reaction conditions described by Pattenden and co-workers. In some cases, these translocation processes did not interfere with the formation of the desired products, as illustrated by the preparation of compounds **2a–d**, which were isolated in moderate to good yields, with or without incorporation of the deuterium atom on the side-

chain. As expected, the translocation process is accelerated by an increase in the stabilization of the carbon-centred radical (Figure 2) resulting from the 1,5-hydrogen shift (see deuterium incorporation in **2a**, **2b**, vs. **2c** and **2d**), and this effect counter-balances effectively the statistical effect (number of hydrogen atoms that can be abstracted from primary, secondary and tertiary positions).[13]

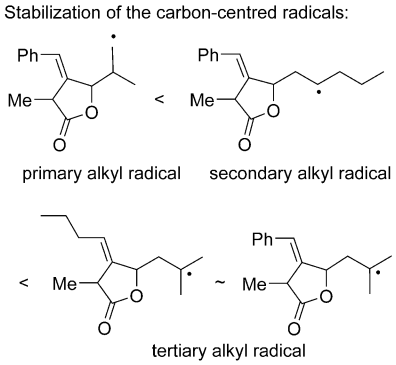
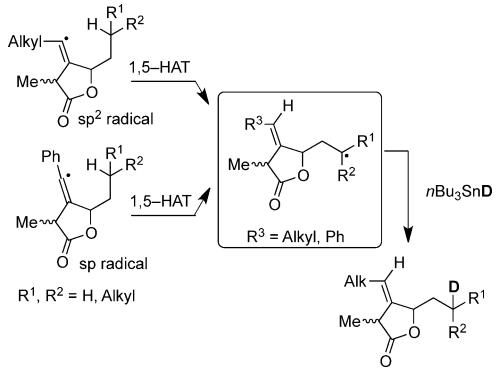


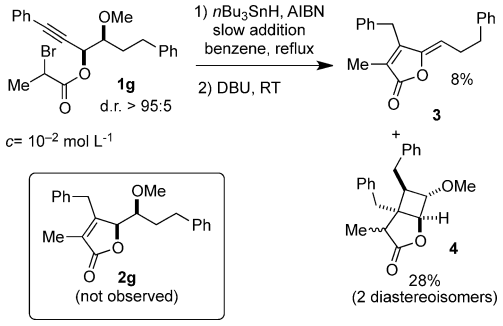
Figure 2. Effect of the stabilization of the resulting carbon-centred radical on the translocation process.

Interestingly, both sp-hybridized and sp^2-hybridized alkenyl radicals underwent 1,5-HAT with similar efficiency (Scheme 4), as indicated by the relative percentage of deuterium incorporation in **2c** and **2d**. Contrary to what is commonly observed in translocation processes leading to 1-hexenyl radical, for which the carbon-centred radical is located in a suitable position to undergo 5-*exo-trig* cyclization and then deliver 5-membered rings,[11c] the radicals formed in the translocation process in this study are 1-pentenyl radicals and they do not cyclize very rapidly neither in a 5-*endo-trig* mode,[14,15] nor in a 4-*exo-trig* mode. Accordingly, these newly formed carbon-centred radicals abstract instead the deuterium atom from the tributyltin deuteride to give, after treatment with a base, the desired butenolides. In this case, the translocation process remains "invisible" for the reactions carried out with nBu$_3$SnH. In some other cases, however, 4-*exo-trig* cyclization was observed (vide infra).



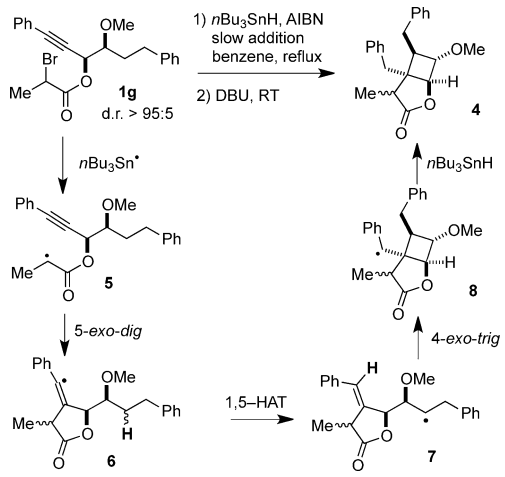
Scheme 4. Translocation process with sp- and sp^2-hybridized alkenyl radicals.

It is worth noting that while only trace amounts of deuterium atom were incorporated at the 5-position (isopropyl side-chain) in **2a**, the butenolide was isolated with only about 30% of deuterium atom incorporation at the benzylic position. Similarly, compound **2b** was obtained with only 52% of deuterium incorporation, exclusively at the 5-position (*n*-pentyl side-chain). So far two possibilities can be envisaged to explain the incorporation of hydrogen atom at the benzylic position: either the alkenyl radical abstracts a hydrogen atom from a unknown source of hydrogen atom (from the alkyl chains of the tin hydride or from the products resulting from the thermal decomposition of AIBN), or more likely the base used in this study (DBU) is capable of abstracting a proton (or deuterium) from the benzylic position. If the protons at the benzylic position were exchangeable in the presence of a base, then it would explain why less than 100% of deuterium atom incorporation was measured for all the substrates that did not undergo quantitative 1,5-HATs. This was later confirmed by the use of a milder base to promote the C=C bond migration (vide infra). Butenolides **2e** and **2f** could not be observed under the aforementioned reaction conditions and the cyclization led in these cases to complex mixtures. It is likely that the alkenyl radical resulting from the radical cyclization of **1e** underwent either 1,5-HAT or 6-*exo-trig* cyclization, or both. In the case of compound **1f**, the resulting alkenyl radical either evolved by 1,5-HAT (on both possible sites), 6-*exo-trig* cyclization, or more likely by ring-opening of the cyclopropylalkenyl radical intermediate. Unfortunately, the complex reaction mixture did not allow us to isolate any of these compounds. In some cases, such as the cyclization of compound **1g**, the carbon-centred radical underwent 4-*exo-trig* cyclization to give bicyclic compounds such as **4** (Scheme 5).



Scheme 5. Formation of bicyclic compounds by a translocation process.

The formation of bicyclic compound **4** is the result of a radical cascade involving the cyclization of electrophilic radical **5** to give alkenyl radical **6** (Scheme 6). The latter undergoes 1,5-HAT to generate carbon-centred radical **7**, which either abstracts a hydrogen atom from the tributyltin hydride or cyclizes onto the activated carbon=carbon double bond in a 4-*exo-trig* mode to give benzylic radical **8**. Hydrogen atom abstraction from the chain carrier reagent leads to bicyclic lactone **4**. We assume that the presence of substituents at vicinal positions in **1g** allows for an increase in the rate of the 4-*exo-trig* cycliza-

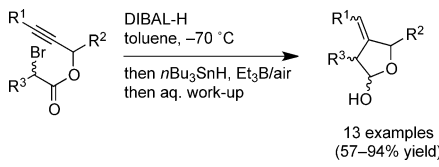


Scheme 6. Proposed mechanism for the formation of bicyclic lactone **4**.

tion process. A similar case of rate enhancement thanks to a vicinal effect has been reported for 1,5-HAT.[13a] This would explain why this type of rearrangement was not observed with related precursors **1b–d**.

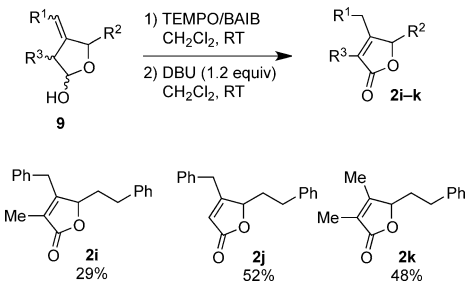
Alkylidene butenolide **3** presumably results from butenolide **2g** (not observed under these reaction conditions) by the elimination of the methoxy group. This observation confirms that the base used in this sequence (DBU) is basic enough to deprotonate, at least partially, these γ-butenolides (vide infra).

These results prompted us to investigate a new route to butenolides based upon our previous work on the radical cyclization of aluminium acetals. The latter are generated from the corresponding α-bromoesters by reduction at low temperature with diisobutylaluminium hydride (DIBAL-H) and they proved to be suitable substrates for a radical cyclization at low temperature. This reaction was found to be particularly efficient to prepare γ-lactols[16] and methylene-γ-lactols[17] (Scheme 7).



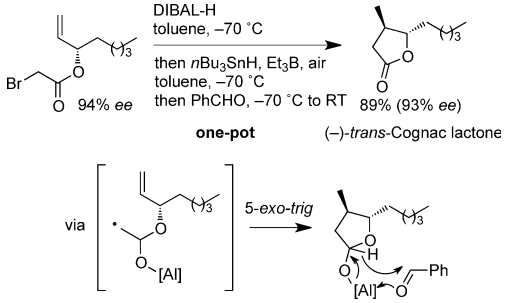
Scheme 7. Preparation of methylene-γ-lactols by the radical cyclization of α-bromoaluminium acetals at low temperature.

We first searched for reaction conditions to oxidize the methylene-γ-lactols into the corresponding methylene-γ-lactones. Among the different oxidizing reagent tested, only TEMPO/BAIB ([bis(acetoxy)iodo]benzene)[18] gave the desired compounds without migration of the C=C bond (91–99% yields, NMR monitoring). In our hands, these compounds could not be purified by flash chromatography as the migration occurred on silica gel. The crude reaction mixtures were then treated with a base to give the desired butenolides **2i–k** in low to moderate yields over the two steps (29–52%) (Scheme 8).



Scheme 8. TEMPO/BAIB oxidation of methylene-γ-lactols and DBU-mediated migration of the C=C bond to give butenolides.

Not satisfied by these results, we investigated the possibility to directly access the desired butenolides from α-bromoesters, without isolation of the sensitive methylene-γ-lactols. The sequence is based on the reactivity of the cyclic aluminium acetals formed as products of the radical cyclization. These aluminium species were found to react with nucleophiles, but they could also transfer a hydride onto the carbonyl group of a ketone or an aldehyde.[19] The Oppenauer-type oxidation of the cyclic aluminium acetals proved to be very efficient for the preparation of γ-lactones from α-bromoesters. Only a two- to threefold excess of a cheap, commercially available aldehyde was required to perform the oxidation in situ and obtain γ-lactones in high yields, as previously illustrated by the synthesis of (−)-*trans*-cognac lactone (Scheme 9).[20]

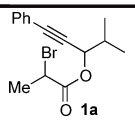
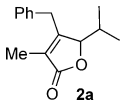
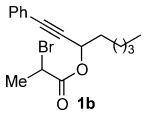
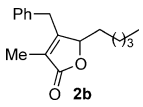
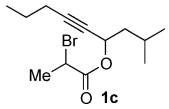
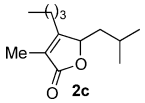
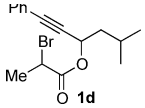
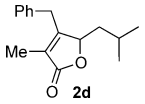
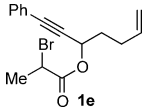
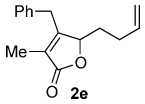
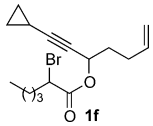
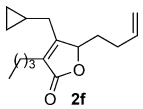
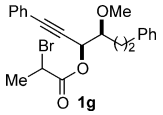
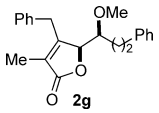
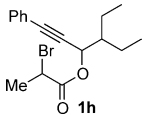
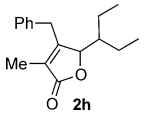
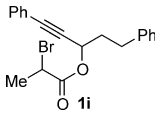
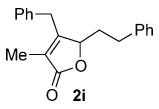


Scheme 9. Sequence reduction/cyclisation/oxidation leading to γ-lactones.

Here, this one-pot sequence was combined with the base-mediated migration of the C=C bond and applied to the cyclization of α-bromoesters **1a–i**. Gratifyingly, butenolides **2a–i** presenting a tetrasubstituted C=C bond were obtained in good to high yields in most cases. The results are reported in Table 1.

Bromoesters **1a–1d** were efficiently converted into the corresponding aluminium acetals by treatment with DIBAL-H in toluene at −70 °C. The conversion was monitored by thin-layer chromatography (TLC) and, after completion *n*Bu_3SnH, Et_3B and air were added slowly. The reaction mixture was stirred at low temperature until complete disappearance of the propargylic alcohol (resulting from the decomposition of the aluminium acetals on TLC). The formation of methylene-γ-lactols could be observed by TLC. Addition of a threefold excess of a cheap, commercially available aldehyde into the reaction

Table 1. Preparation of γ-butenolides with a tetrasubstituted C=C bond by radical cyclization of aluminium acetals, followed by oxidation and C=C bond migration.

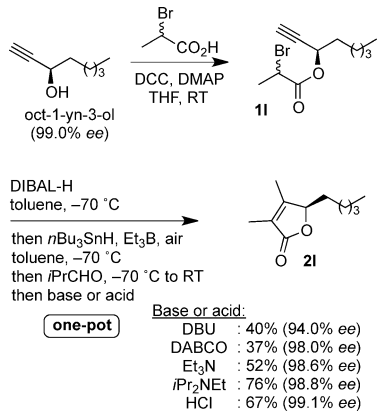
Entry	Substrate	Butenolides[a]	Yield [%][b]
1	 **1a**	 **2a**	75
2	 **1b**	 **2b**	88
3	 **1c**	 **2c**	77
4	 **1d**	 **2d**	73
5	 **1e**	 **2e**	82
6	 **1f**	 **2f**	63
7	 **1g**	 **2g**	33[c,d]
8	 **1h**	 **2h**	88
9	 **1i**	 **2i**	74

[a] All reactions were carried out in toluene on 2 mmol scale using 1.2–1.5 equiv DIBAL-H at −70 °C (unless otherwise stated), 1.2–1.5 equiv nBu$_3$SnH and 0.3–0.5 equiv Et$_3$B (1 M in hexanes); oxidation was carried out with 3.0 equiv of iPrCHO; C=C migration was achieved with 2.0 equiv DBU. [b] After purification by chromatography on silica gel (silice/KF 9:1). [c] 3 equiv of DIBAL-H was used. [d] 40% of propargylic alcohol recovered.

mixture (e.g., PhCHO or iPrCHO) at low temperature, followed by warming to room temperature, resulted in the non-reversible hydride transfer from the cyclic aluminium acetal to the aldehyde. Once the oxidation of the aluminium acetal into the corresponding methylene-γ-lactone was complete (TLC or GC monitoring), a base (typically DBU) was added to achieve the migration of the exocyclic C=C bond to the α,β-position.

This one-pot, four-step sequence led to tetrasubstituted butenolides **2a–2d** in good to high yields (73–88%, Table 1, entries 1–4). This approach compares favourably with the direct cyclization at high temperature described in Scheme 3. Moreover, the use of nBu$_3$SnD in the one-pot, four-step sequence, allowed us to prove the mildness of these reaction conditions, as no 1,5-HAT took place in this case. More interestingly, butenolides **2e** and **2f** could be obtained in good yields (82 and 63% yields, respectively), while the cyclization at high temperature gave only complex mixtures, with no traces of these two compounds (vide supra; Table 1, entries 5 and 6). As previously observed for the synthesis of methylene-γ-lactols,[17] butenolide **2f** was obtained without ring-opening of the cyclopropyl unit.[21] Surprisingly, the reduction of bromoester **1g** required an excess of DIBAL-H (3 equiv) and the one-pot sequence gave butenolide **2g** only in a modest 33% yield (Table 1, entry 7), together with the propargylic alcohol resulting from the thermal decomposition of the aluminium acetal intermediate (ca. 40% yield). Under these reaction conditions, and contrary to what was observed at high temperature under Pattenden's conditions (vide supra), no rearrangements were observed. As the presence of an alkoxy substituent in the bromoester precursors did not seem to interfere neither in the reduction step, nor in the cyclization process in previous studies,[16,17,20] we wondered whether the problems encountered here were simply due to steric hindrance. We decided to test this hypothesis with compound **1h**, which possess a structure similar to **1a** but with bulkier substituents. The one-pot sequence, however, proceeded without any problems and butenolide **2h** was obtained in high yield (Table 1, entry 8). It seems then that it is the combination of an alkoxy group *and* a secondary carbon atom directly linked to the propargylic position that makes the reduction more difficult and decreases the stability of the aluminium acetal intermediate. Finally, butenolide **2i** was obtained in good yield from bromoester **1i** (Table 1, entry 9).

Encouraged by these results we decided to study the preparation of optically enriched compounds in order to make sure that our reaction conditions would allow for the preparation of optically active compounds. Indeed, it is well-known that γ-substituted butenolides can undergo epimerization under basic conditions,[22] in particular in the presence of relatively strong bases such as DBU.[23] We decided to investigate the possibility to achieve the C=C bond migration without loss of optical activity and we first turned our attention to the synthesis of enantioenriched butenolides from natural sources. Butenolides **2l** was isolated from *Plagiomnium undulatum* in 2001[24] and its absolute configuration was determined by Brückner, König and co-workers who proposed the first total synthesis of the natural compound.[25] The original synthesis required seven steps from heptanal and we believed our methodology might offer an alternative and shorter route to this natural compound. The precursor for the radical cyclization, α-bromoester **1l**, was obtained in high yield from commercially available (+)-oct-1-yn-3-ol (99.0% *ee*) and (±)-2-bromopropionic acid (Scheme 10). Gratifyingly, butenolide **2l** was obtained in good yields and with high levels of enantiomeric excesses from α-bromoester **1l** under our standard reaction conditions, using a variety of bases to achieve the migration of the exocyclic C=C bond. Among the different bases tested to perform the migration of the C=C bond into the α,β-position, iPr$_2$NEt gave the best results, both in terms of yield and enantiomeric excess. The use of aqueous HCl to promote the migration of



Scheme 10. Expeditive synthesis of tetrasubstituted butenolide from *P. undulatum*.

the C=C bond also led to **2l** in excellent enantiomeric excess, albeit in slightly lower yield. This represents the shortest synthesis to date of this natural compound.

The high chemoselectivity of our approach was further demonstrated by the synthesis of another representative of the butenolide family. Maculalactone A (Figure 3) is the most abundant secondary metabolite produced by the marine cyanobacterium *Kyrtuhrix maculans*. This compound was isolated in 1996 by Brown and co-workers and it presents an unusual tribenzyl butenolide skeleton,[26] which is common to the other maculalactones B and M (Figure 3).[27]

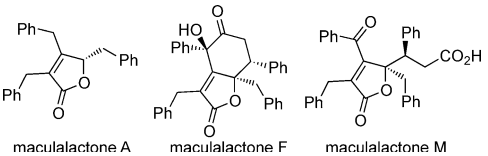
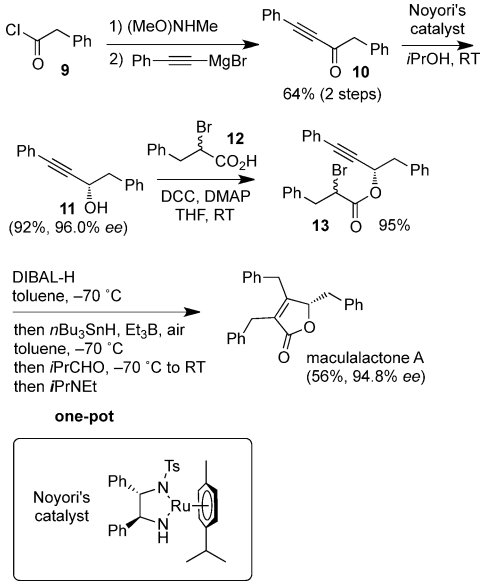


Figure 3. Maculalactone A and some other members of the family.

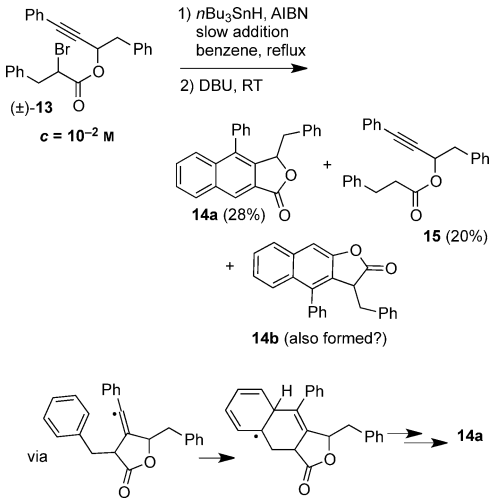
Interestingly, the authors noticed that the natural compound was biosynthesized in a partially racemized form (90–95% *ee* only).[4,28,29] Maculalactone A and its derivatives present promising activity as antifouling agents,[4,28] a property that is used by the long-lived, extremely slow-growing cyanobacterium *K. maculans* to protect itself indirectly from herbivores. Our synthesis started with commercially available acyl chloride **9**. The latter was converted into the corresponding Weinreb amide in 89% yield (Scheme 11). Addition of the Grignard reagent of phenylacetylene onto the Weinreb amide gave enone **10** in 72% yield. Several other routes have been explored to prepare directly enone **10** from acyl chloride **9**, including the use of 1-TMS-phenylacetylene in the presence of $AlCl_3$ or the use of copper acetylide, but the best result in terms of yield and purity was obtained in the two-step sequence via the Weinreb amide. The configuration of the chiral centre of propargylic alcohol **11** was set using asymmetric reduction of ynone **10** using Noyori's ruthenium-based catalyst (see the Supporting Information for details). This reduction led to propargylic alcohol **11** in 92% yield and with good level of enantiomeric excess (96.0% *ee*).[30] The coupling between propargylic alcohol **11** and racemic bromoacid **12** to give α-bromoester **13** was achieved in high yield (95%) using classical conditions (DCC, DMAP cat.). Bromoester **13** then engaged in the key step, which consisted first in the reduction with DIBAL-H to give the corresponding aluminium acetal. This thermally labile intermediate underwent radical cyclization at low temperature (below −70 °C) in the presence of nBu_3SnH, using Et_3B/air as an initiator. The resulting cyclic aluminium acetal was then oxidized in the presence of *i*PrCHO into the corresponding arylidene-γ-lactone. The mixture of stereoisomers was then converted into maculalactone A by addition of iPr_2NEt (Scheme 11). Under these reaction conditions maculalactone A could be obtained with a high level of enantiomeric excess (94.8% *ee*), close to the one determined for the natural compound. In this case, the migration of the C=C bond into the α,β-position proved to be extremely slow and it required extended reaction time to reach good yields. The use of DBU also led to maculalactone A, in much shorter reaction time than with iPr_2NEt, but with complete racemization, in sharp contrast with what was previously observed for the preparation of the tetrasubstituted butenolide from *P. undulatum* (vide supra). The use of aqueous HCl failed to promote the C=C bond migration with this substrate. Although we decided not to explore this route, an even more straightforward approach to propargylic alcohol **11** would require enantioselective addition of alkynylmetals onto phenylacetaldehyde. This would shorten the enantioselective synthesis of maculalactone A down to only three steps.

This route was next compared with the direct radical cyclization of bromoester **13**, under reaction conditions used by Pattenden and co-workers. A solution of bromoester (±)-**13** in benzene ($c = 10^{-2}$ M) was heated at reflux and the solutions of



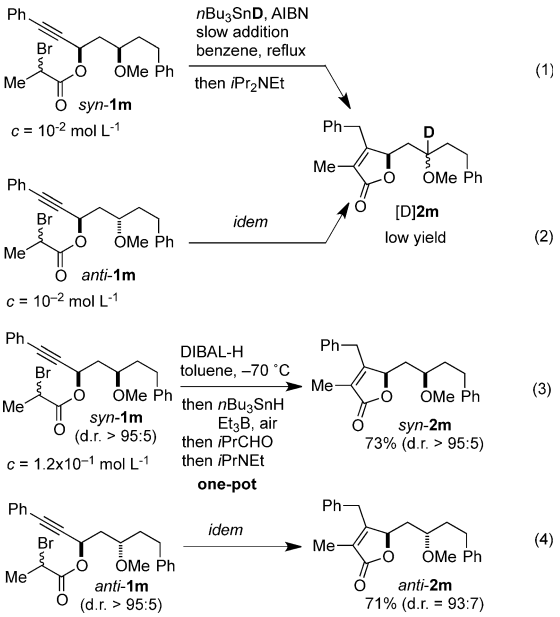
Scheme 11. Total synthesis of maculalactone A using a radical cyclization at low temperature.

nBu$_3$SnH and AIBN in benzene were then added slowly over 16 h. Interestingly, under these reaction conditions no traces of maculalactone A could be detected either by TLC or by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. The main products that could be characterized from the complex reaction mixture were lactone **14a** and ester **15**, isolated in 28 and 20% yields, respectively (Scheme 12). The presence of **14a** indicates that the alkenyl radical intermediate was not trapped rapidly enough by the tin hydride under these reaction conditions. As a result side reactions such as the intramolecular addition onto the aromatic rings present on the side-chains took place. Although we were not able to assess with certitude the structures of the other by-products, it seems plausible that cyclization did not take place exclusively at only one of the two aromatic rings located at the side-chains. Accordingly, although not isolated, lactone **14b** might also be present in the reaction mixture, as well as other products resulting from intermolecular addition onto the solvent (benzene).[31]



Scheme 12. Attempt at preparing maculalactone A under "classical" reaction conditions (Pattenden's conditions).

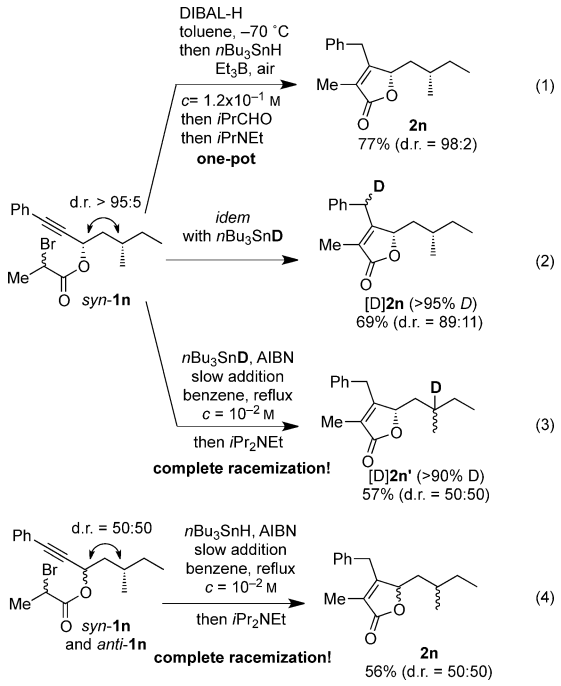
The chemoselectivity of our methodology compared to the classical approach at high temperature was illustrated further with the attempted cyclization of compounds *syn*-**1m** and *anti*-**1m** (Scheme 13). The reactions carried out at high temperature from *syn*-**1m** and *anti*-**1m** were expected to result in the epimerization of the target butenolides due to undesired 1,5-HAT.[32] The translocation process was demonstrated by using tributyltin deuteride. In the case of *syn*-**1m** and *anti*-**1m**, however, the expected butenolides [D]**2m** were only observed as minor components of a complex crude reaction mixture. Nevertheless the disappearance of the characteristic signal for the proton C*H*(OMe) indicates that deuterium has been incorporated at this position [Scheme 13, Eqs. (1) and (2)]. On the contrary, the radical cyclization of aluminium acetals at low temperature proved to be extremely chemoselective and allowed for a mild cyclization reaction to take place. Under the optimized



Scheme 13. 1,5-HATs resulting in epimerization during radical cyclization at high temperature.

reaction conditions, the cyclization of aluminium acetals at low temperature led to *syn*-**2m** and *anti*-**2m** in good yields from *syn*-**1l** and *anti*-**1m**, respectively, with only minor loss (if any) of the stereochemical information [Scheme 13, Eqs. (2) and (3)].

Finally, we turned our attention to precursor **1n**, easily prepared in an optically pure manner from L-isoleucine (Scheme 14, see the Supporting Information for details). The cyclization of **1n** was carried out at low temperature, via its aluminium acetal, under our optimized reaction conditions to give **2n** in good yield and as a single diastereoisomer [Scheme 14, Eq. (1)]. When nBu$_3$SnH was replaced with nBu$_3$SnD, the cyclization at low temperature, followed by oxidation on the presence of isobutyraldehyde and iPr$_2$NEt-promoted C=C bond migration, butenolide [D]**2n** was obtained with deuterium incorporation exclusively at the benzylic position [Scheme 14, Eq. (2)]. The direct radical cyclization of **1n** under the reaction conditions described by Pattenden and coworkers led to [D]**2n**′ as a nearly 1:1 mixture of diastereoisomers. As clearly indicated by deuterium-labelling experiments, epimerization occurred almost exclusively at a remote position on the side-chain and not at the butenolide moiety [Scheme 14, Eq. (3)]. The high level of deuterium incorporation on the side-chain proves that nearly quantitative 1,5-HAT occurred after 5-*exo*-*dig* cyclization. This radical cascade led to a complete epimerization of a stereogenic centre located at a position that was not suspected at first glance to be sensitive. The relative configuration in **1n** (*syn* or *anti*) has no influence on the 1,5-HAT process, as shown by the racemization observed during the cyclization of a mixture of *syn*- and *anti*-**1n** at high temperature, which led to a racemic mixture of butenolides *syn*- and *anti*-**2n** [see chiral HPLC analysis in the Supporting Information; Scheme 14, Eq. (2)].



Scheme 14. Epimerization of remote position by 1,5-HATs during radical cyclization at high temperature.

Conclusions

We have reported herein a general access to the sterically demanding tetrasubstituted γ-butenolides from easily accessible α-bromoesters as precursors. The target butenolides were obtained in good to high yields using a one-pot sequence involving the formation of a thermally labile aluminium acetal intermediate, followed by a radical cyclization and oxidation of the resulting cyclic aluminium acetals by the use of a cheap, commercially available aldehyde. The migration of the C=C bond was then achieved under basic or acidic conditions. This approach allows for the preparation of optically active butenolides as illustrated by the efficient synthesis of two natural compounds. The mechanistic study also shed light on "invisible" 1,5-hydrogen-atom transfers that occur during the radical cyclization under previously reported reaction conditions for the direct cyclization of α-bromoesters (high temperature and high dilution). As illustrated with several examples of the present study, these 1,5-HATs are no longer "invisible" when epimerization of stereocentres occurs, or when rearrangements leading to by-products are possible.

Experimental Section

See the Supporting Information for details.

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Keywords: butenolides · deuterium-labeling experiments · hydrogen transfer · maculalactone A · radical reactions

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