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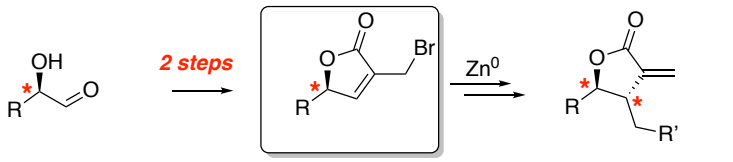
Graphical Abstract



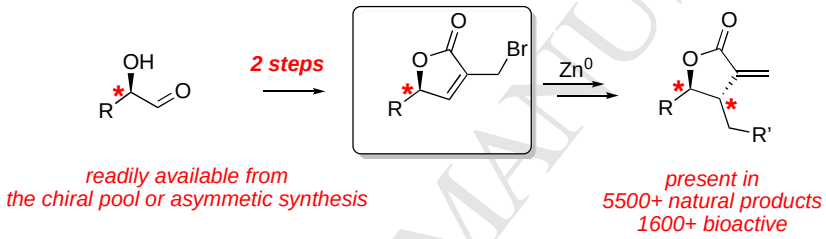
readily available from
the chiral pool or asymmetic synthesis

present in
5500+ natural products
1600+ bioactive

Rapid and scalable synthesis of chiral bromolactones as precursors to α-*exo*-methylene-γ-butyrolactone-containing sesquiterpene lactones

Roman Lagoutte, Miryam Pastor, Mathéo Berthet, Nicolas Winssinger*
School of Chemistry and Biochemistry, NCCR Chemical Biology, University of Geneva, 30 quai Ernest Ansermet, CH-1205 Geneva, Switzerland
E-mail: nicolas.winssinger@unige.ch

Abstract
The sesquiterpene lactones cover a diverse and pharmacologically important diversity space. In particular, the electrophilic α-*exo*-methylene-γ-butyrolactone moiety that is preponderant in this natural product family has been shown to readily engage in covalent inhibition via conjugate addition of cysteine residues in target proteins. However, the synthetic accessibility of sesquiterpenes or related probes to investigate their mode of action remains laborious. Herein, we present a rapid and scalable route to chiral bromolactones as enabling precursors in the synthesis of sesquiterpene lactones.



Keywords
Sesquiterpene lactones, covalent inhibitors, α-*exo*-methylene-γ-butyrolactones, bromolactones, enantioselective synthesis, Barbier coupling

1. Introduction
"Tell him to move to Biology!" This was Prof Robert B. Woodward's advice, during a visit at the University of Louvain in the mid-seventies, to Prof Léon Ghosez while discussing the promotion of a colleague.[1] In Woodward's vision, the organic chemist's creativity and ability to synthesize almost any molecules was central to the design of synthetic probes necessary to elucidate biological mechanisms. This anecdote farsighted synthetic chemistry's contribution to chemical biology. While chemical biology has grown through cross-fertilization with other disciplines, synthetic organic chemistry remains central to the pursuit of novel chemical entities as tools capable of modulating cellular processes and probes reporting on diverse cellular activity. Covalent inhibitors hold a special place in chemical biology, as the instigator of chemoproteomics, facilitating target identification and assessing target engagement by virtue of the fact that they remain covalently associated with the protein.[2-3] While there was a historical reluctance to advance covalent inhibitors in drug discovery efforts,[4] a resurging interest in this inhibition modality has resulted in several therapeutics being recently approved.[5-8]

Nature has long harnessed covalent inhibition and the biosynthesis of secondary metabolites has evolved to deliver mildly reactive functionalities in the major classes of secondary metabolites. An eminent example is the biosynthesis of sesquiterpene

lactones, a large and structurally diverse family of natural products with a high tendency for harbouring electrophilic functional groups known to engage cysteine residues in their biological target.[9] Of particular relevance, the α-*exo*-methylene-γ-butyrolactone moiety has been shown to be the warhead in a number of natural products (figure 1),[10] including parthenolide,[11] helenalin,[12-14] deoxyelephantopin,[15] ainsliadimer A,[16] EM-23[17] or IJ-5,[18] to only name a few. To further emphasize the importance of this class of compounds, a Reaxys search for only natural products containing this structural motif returns over 5500 entries, over 1600 of which have associated yet ill-studied biological activity.[19]

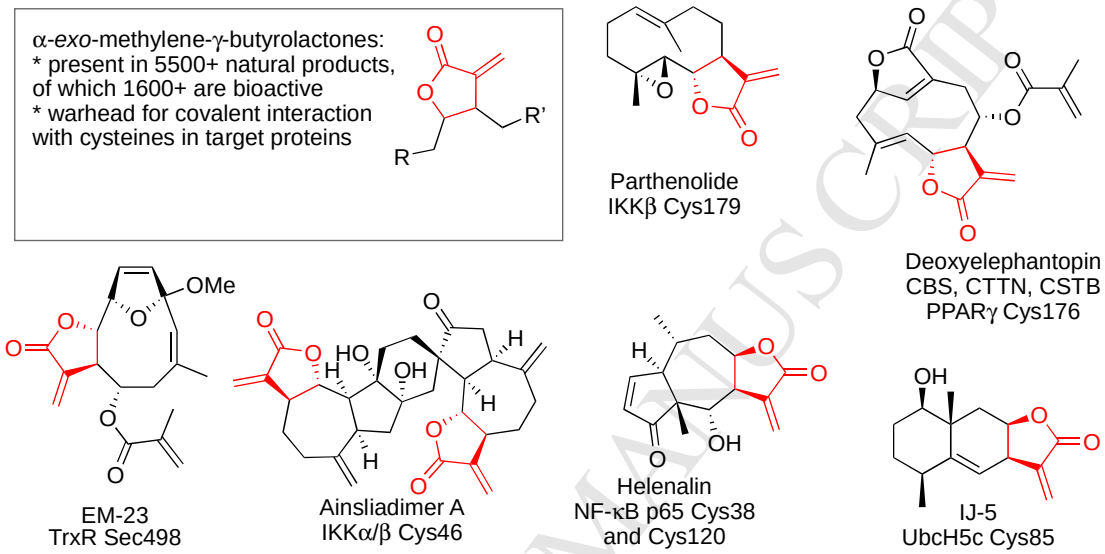
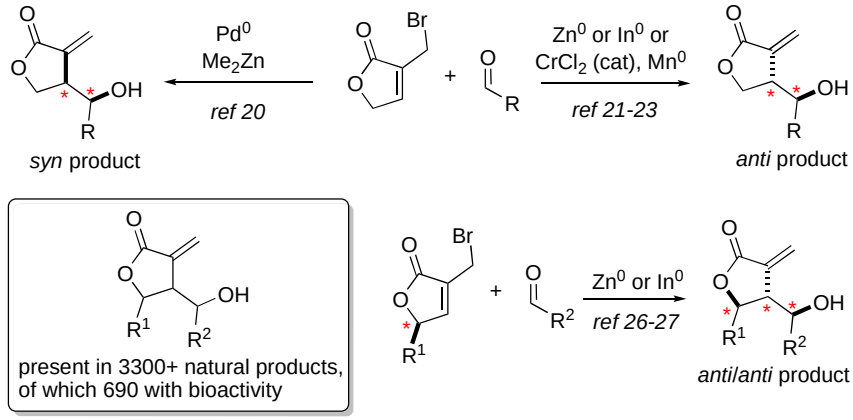


Figure 1. Selected examples of sesquiterpene lactones acting as covalent inhibitors to their biological targets

In order to access the α-*exo*-methylene-γ-butyrolactone present in these diverse natural products, Barbier allylation of aldehydes using bromolactones (Scheme 1) has proven efficient and versatile. Again, over 3300 natural products contain the resulting motif, nearly 700 of which have associated biological activity. Operationally simple, it can be used in a convergent manner for the late-stage introduction of the α-*exo*-methylene electrophile. Moreover, studies with the simplest bromolactone showed that remarkably high *syn*[20] or *anti*[21-23] diastereoselectivity can be achieved at the two newly formed stereocentres. For example, the Xu group has successfully used the zinc-mediated Barbier allylation for the total synthesis of 8-epigrosheimin.[24] Likewise, the Harki group accessed simplified analogues of helenalin to probe its ability to cross-link cysteines 38 and 120 in the p65 portion of NF-κB.[25] In the context of our study of deoxyelephantopin and its covalent interactome, we too used the zinc-mediated Barbier allylation of chiral bromolactones with a γ-substituent, which led to coupling products with three contiguous stereocentres with high *anti*/*anti* diastereoselectivity induced by the first γ-stereocentre.[26-27] With an enantioselective total synthesis in mind and despite the considerable research efforts towards the enantioselective γ-functionalization of γ-butenolides,[28-38] we were surprised to find that the straightforward enantioselective preparation of γ-substituted bromolactones remained an unmet challenge.[39] We herein present a scalable and versatile synthesis of high-value enantiopure bromolactones from inexpensive starting materials and reagents.

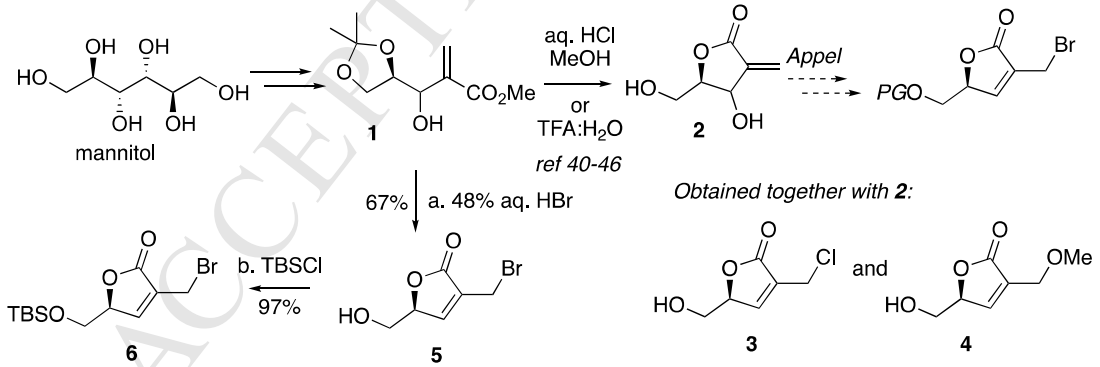


Scheme 1. Barbier allylation of aldehydes with bromolactones: stereochemical considerations and impact

2. Results and discussion

2.2 Preparation of bromolactones

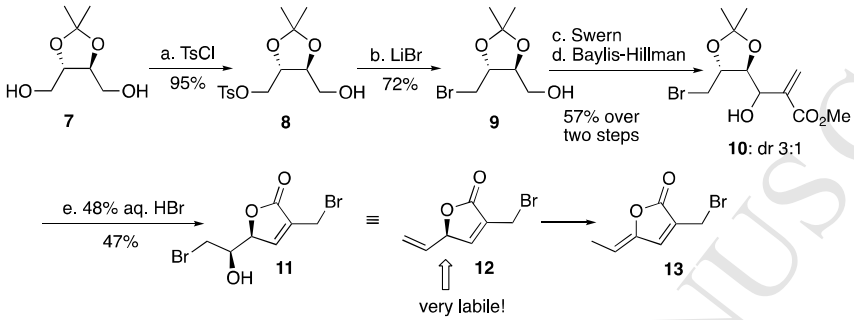
As a starting point in our investigation, we envisioned that the product of the acid-mediated hydrolysis and concomitant lactonisation of enantiopure **1**, readily accessible from mannitol,[40-46] could be converted into a bromolactone under standard Appel conditions *via* **2** (scheme 2). We opted for the aqueous HCl/methanol protocol and the expected product **2** was obtained. However, much to our surprise, we could also identify two side-products **3** and **4**, resulting from further reaction of **2** with chloride and methanol as nucleophiles, respectively. We reasoned that treatment with concentrated aqueous HBr would provide the necessary highly nucleophilic bromide to directly convert **1** into **5**. Thus, when **1** was treated with 48% HBr at room temperature, **5** was obtained as a single product in high yield. The primary alcohol in highly polar **5** can readily be masked as TBS ether **6** for ease of manipulation or subsequent reactions.



Scheme 2. Preparation of bromolactones **5** and **6**. Conditions: a. 48% aq. HBr, rt, 67%; b. TBSCl, imidazole, CH_2Cl_2, rt, 97%.

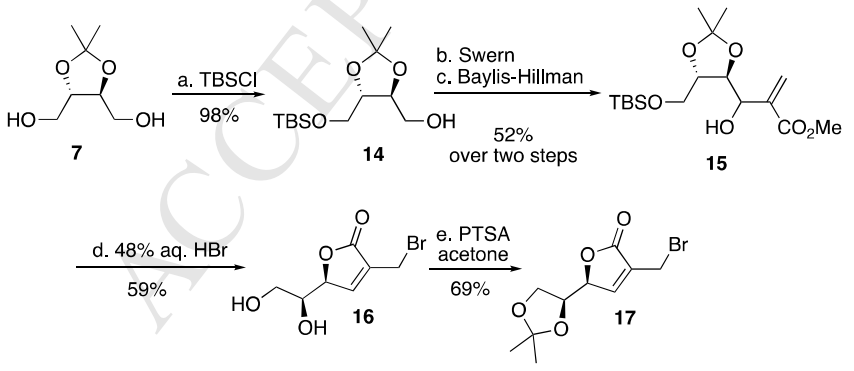
With this simple approach to enantiopure bromolactones in hand, we set out to explore the scope of this reaction. During our studies on deoxyelephantopin, we used bromolactone **12** as Barbier coupling partner (scheme 3). However, owing to its skip-diene position the γ-proton is very labile leading **12** to undergo prototropic rearrangement to **13**, making its direct preparation using 48% HBr impossible. We therefore capitalised on the ability of bromohydrins to eliminate in the presence of zinc to provide an olefin, and therefore anticipated that its surrogate **12** would deliver

the desired olefin under the zinc-mediated Barbier allylation conditions. Diol **7**,[47] readily available from L-tartaric acid[48] was monotosylated, and tosylate **8** converted into bromide **9** under modified Finkelstein conditions, using anhydrous LiBr in refluxing acetone/dimethylformamide.[49] Swern oxidation and Baylis-Hillman reaction provided secondary alcohol **10** as an inconsequential mixture of diastereomers. It should be noted that the intermediate aldehyde is very prone to the formation of a stable hydrate, and consequently aqueous work-up is to be avoided: the Swern oxidation allows removal of all by-products by simple filtration on silica gel leading to yields superior to any other oxidation methods we examined. Treatment with 48% HBr provided bromolactone **11**, which indeed underwent bromohydrin elimination in the presence of zinc (*vide infra*).



Scheme 3. Preparation of bromolactone **11**. Conditions: a. NaH, TsCl, THF, 0 °C, 95%; b. LiBr, acetone/DMF, reflux, 72%; c. $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C; d. methyl acrylate, DABCO, rt, 57% over two steps; e. 48% aq. HBr, rt, 47%.

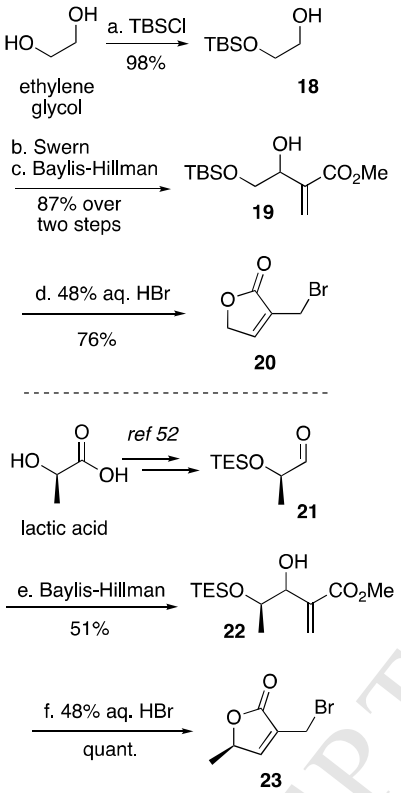
To further extend the scope of this reaction, diol **7** was desymmetrised by mono-silylation as its mono-TBS ether **14** (scheme 4). Swern oxidation and Baylis-Hillman reaction provided secondary alcohol **15**, as an inconsequential mixture of diastereomers. Treatment with 48% HBr provided diol **16**, resulting from TBS ether cleavage under these conditions. The diol in highly polar **16** could in turn be readily converted to its isopropylidene acetal **17** under standard conditions, as a valuable handle for further functionalization.



Scheme 4. Preparation of bromolactones **16** and **17**. Conditions: a. NaH, TBSCl, THF, 0 °C, 98%; b. $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C; c. methyl acrylate, DABCO, rt, 52% over two steps; d. 48% aq. HBr, rt, 59%; e. PTSA, acetone, rt, 69%.

Rather than an issue, the TBS ether cleavage with 48% HBr felt advantageous as it could unmask the alcohol involved in the lactonisation process (scheme 5). As a proof of concept and using ethylene glycol as starting material, mono-silylation, Swern oxidation and Baylis-Hillman reaction provided **19**, which uneventfully and in high

yield provided bromolactone **20** upon treatment with 48% HBr. While numerous syntheses of **20** exist,[50-51] this approach demonstrates that TBS is a suitable protecting group during the preparation of substrates in which the alcohol is involved in the lactonisation process during the HBr-mediated reaction, thereby paving the way to the successful design and synthesis of further bromolactones. The acid-labile TES group may however also be used: and indeed, Baylis-Hillman reaction on aldehyde **21**, readily available from lactic acid,[52] followed by treatment with 48% HBr provided bromolactone **23**. Importantly, bromolactone **23** was obtained essentially enantiopure demonstrating the lack of epimerisation in the Baylis-Hillman reaction and concurring the absence of diastereomers obtained in the HBr-mediated cyclisation leading to **11** and **16**.

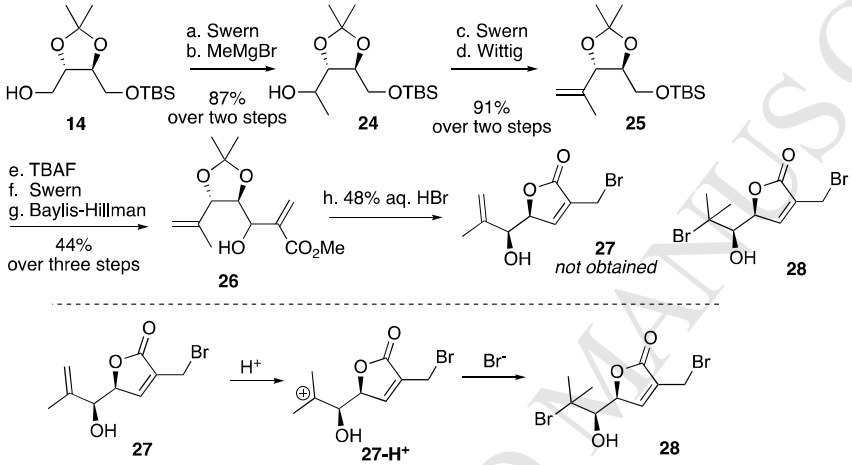


Scheme 5. Preparation of bromolactones **20** and **23**. a. NaH, TBSCl, THF, 0 °C, 98%; b. $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C; c. methyl acrylate, DABCO, rt, 87% over two steps; d. 48% aq. HBr, rt, 76%; e. methyl acrylate, DABCO, rt, 51%; f. 48% aq. HBr, rt, quantitative.

The mono-TBS ether in **14** can serve the other purpose of allowing functionalization of the other primary alcohol and ultimately of the bromolactone. In light of their biosyntheis, sesquiterpene lactones usually have a methyl-substituted olefin adjacent to the butyrolactone (scheme 6). We envisioned that a *gem*-disubstituted terminal olefin substituent could provide a bromolactone with a useful functionalised allylic alcohol for further modification. In addition, this would provide a further testing ground for the title transformation as these olefins readily form tertiary cations in the presence of strong acids. Swern oxidation and treatment with methylmagnesium bromide provided secondary alcohol **24**, as an inconsequential mixture of diastereomers. Oxidation of the alcohol followed by olefination provided *gem*-disubstituted terminal olefin **25**. TBAF-mediated desilylation, Swern oxidation and Baylis-Hillman reaction provided secondary alcohol **26**. However long this reaction

sequence may look, it is noteworthy that, owing the essentially quantitative nature of the reactions involved, simple precipitation and filtrations through silica are enough to provide clean crude products to be used in the following steps without further purification. Accordingly, substrate **26** could be obtained in a few days in 23% yield over 9 steps and a single final purification by column chromatography.

Treatment of **26** with 48% HBr did indeed promote the formation of the bromolactone moiety, but as anticipated none of the desired *gem*-disubstituted olefin **27** was present: instead, a major undesired product was observed, which we identified as Markovnikov olefin hydrobromation product bromohydrin **28**. The formation of this by-product may be explained by the protonation of the *gem*-disubstituted olefin under the very acidic reaction conditions, followed by trapping of the resulting cation by a bromide nucleophile.

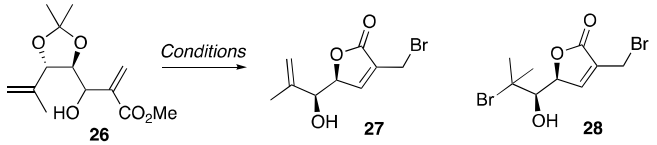


Scheme 6. Attempted synthesis of bromolactone **27**. Conditions: a. $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C; b. MeMgBr, Et_2O, 0 °C, 87% over two steps; c. $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C; d. $Ph_3P^+CH_3Br^-$, ^{n}BuLi, THF, -78 °C, 91% over two steps; e. TBAF, THF, 0 °C, 85%; f. $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C; g. methyl acrylate, DABCO, rt, 52% over two steps; h. 48% aq. HBr, rt, *see text*.

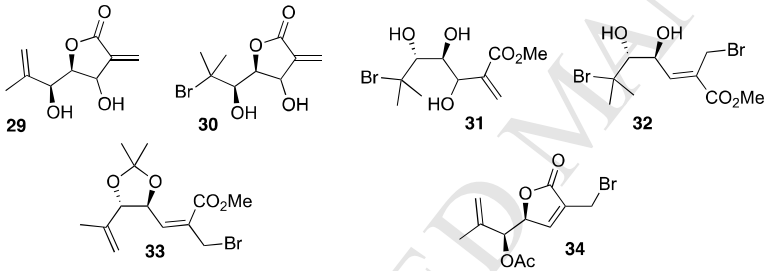
Not disheartened, we took this result as a chance to examine the actual factors behind the success of this transformation under relatively harsh conditions. As protonation of the olefin to the tertiary cation was problematic, we first evaluated the importance of using concentrated 48% HBr (around 8.9 M aqueous HBr) by using HBr at various dilutions. With 1 M aqueous HBr, substrate **26** underwent slow deacetalation and lactonisation and the olefin remained intact (**29**, table 1, entry 1); however, the desired allylic rearrangement did not take place. Mild heating at 50 °C only resulted in appearance of some olefin hydrobromation product (**30**, entry 2). While the distribution was unchanged with 2 M HBr (entry 3), upon treatment with 3 M or 4.5 M HBr at room temperature, significant hydrobromation took place while no allylic rearrangement took place (**29**, entries 4 and 5). This may be explained by the fact that in 48% HBr, the bromide anion is highly nucleophilic, whereas in diluted aqueous HBr, the bromide ion is solvated and therefore much less nucleophilic. Nevertheless, treatment of **25** with LiBr-, NaBr- or KBr-saturated 1 M aqueous HBr had no effect on the outcome of the reaction: neither hydrobromation nor allylic rearrangement took place (entries 6 to 8). Unsolvated bromide seems therefore to be required for the transformation to succeed in forming the bromolactone moiety. Using biphasic

systems with dichloromethane or benzene as co-solvent (entries 9 and 10) was successful in delivering the bromolactone portion but did not prevent hydrobromation; while this may be disappointing, this result is important as dichloromethane can practically be used as "transfer" solvent for substrates free of HBr-sensitive functional groups (as above). In order to prevent the parasitic olefin protonation event, a qualitative consideration of pK_bs was necessary. With HBr having a pK_a of roughly -9 and olefins a pK_b of around -4, we looked at organic solvents which could serve as buffers. While methanol (pK_b -2, entry 11) prevented lactonisation but not hydrobromation, acetone (pK_b -7, entry 12) successfully prevented hydrobromation but also deacetalation. While not unexpected, this supports the role of water contained in 48% HBr for the overall transformation as the same result was observed with 33% HBr in acetic acid (entry 13). Gratifyingly, ethyl acetate (pK_b -6.5, entry 14) led to exclusive formation of the desired bromolactone **27**, as did acetonitrile (pK_b -10, entry 15).

Table 1. Optimisation of the conditions for the preparation of bromolactone **27**



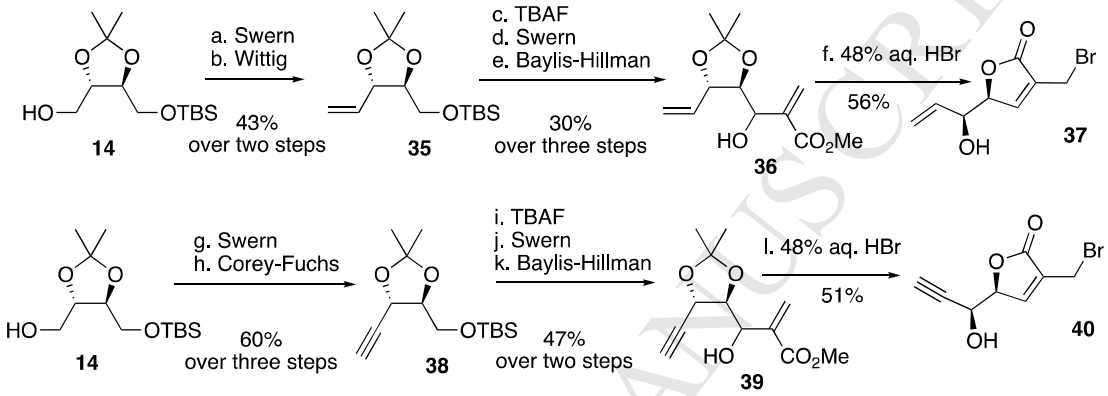
Proposed side-products observed by ^{1}H-NMR of the crude product:



Entry	Conditions[a]	Products observed (conversion)[b]
1	Aq. 1 M HBr, rt, o/n	**26** (31%) + **29** (69%)
2	Aq. 1 M HBr, 50 °C, o/n	**26** (6%) + **29** (35%) + **46** (59%)
3	Aq. 2 M HBr, rt, o/n	**26** (18%) + **29** (82%)
4	Aq. 3 M HBr, rt, o/n	**29** (56%) + **30** (44%)
5	Aq. 4.5 M HBr, rt, o/n	**29** (37%) + **30** (63%)
6	Aq. 1M HBr saturated with LiBr rt, o/n	**26** (21%) + **29** (79%)
7	Aq. 1M HBr saturated with NaBr rt, o/n	**26** (32%) + **29** (68%)
8	Aq. 1M HBr saturated with KBr rt, o/n	**26** (30%) + **29** (70%)
9	Biphasic: CH_2Cl_2/48% HBr, rt, o/n	**28** (100%)
10	Biphasic: benzene/48% HBr, rt, o/n	**28** (100%)
11	MeOH/48% HBr, rt, o/n	**31** (27%) + **32** (73%)
12	Acetone/48% HBr, rt, o/n	**26** (86%) + **33** (14%)
13	33% HBr in acetic acid, rt, o/n	**26** (76%) + **33** (24%)
14	EtOAc/48% HBr, rt, o/n[c]	**27** (100%, 68%[d, e])
15	MeCN/48% HBr, rt, o/n[c]	**27** (100%, 52%[d])

[a] Carried out on 0.1 mmol scale, overnight as the allylic rearrangement is the slowest step; [b] Determined by ^{1}H-NMR analysis of the crude product; [c] None of acetylated compound **34** was observed; [d] Isolated yields; [e] 55% isolated yield on gram-scale.

In complete analogy and using these buffered conditions, we were able to access olefin-substituted bromolactone **37** as well as alkyne-substituted bromolactone **40**, as potentially valuable fragments for the synthesis of unnatural analogues of sesquiterpene lactones (scheme 7).[53] Briefly, as above, Swern oxidation and Wittig olefination of **14** provided primary olefin **35**. TBAF-mediated desilylation, Swern oxidation and Baylis-Hillman reaction provided secondary alcohol **36**. Finally, treatment with 48% HBr with ethyl acetate as co-solvent provided bromolactone **37**. Alternatively, Swern oxidation and a Corey-Fuchs reaction sequence on **14** provided terminal alkyne **38**. TBAF-mediated desilylation, Swern oxidation and Baylis-Hillman reaction provided secondary alcohol **39**. Finally, treatment with 48% HBr with ethyl acetate as co-solvent provided alkyne-substituted bromolactone **40**.

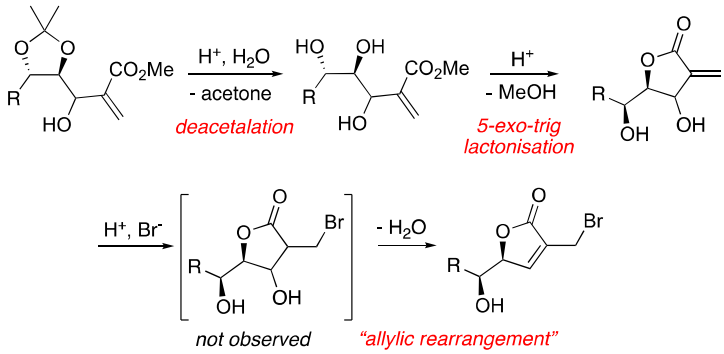


Scheme 7. Synthesis of bromolactones **37** and **40**. Conditions: a. $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C; b. $Ph_3P^+CH_3Br^-$, ^nBuLi, THF, -78 °C, 43% over two steps; c. TBAF, THF, 0 °C, 37%; d. $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C; e. methyl acrylate, DABCO, rt, 82% over two steps; f. 48% aq. HBr, EtOAc rt, 56%; g. $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C; h. CBr_4, Ph_3P, CH_2Cl_2, 0 °C, 65% over two steps; ^nBuLi, THF, -78 °C, 92%; i. TBAF, THF, 0 °C, 95%; j. $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C; k. methyl acrylate, DABCO, rt, 49% over two steps; l. 48% aq. HBr, EtOAc rt, 51%.

2.2. Mechanism

These observations allow us to propose a general course for this HBr-mediated complex transformation (scheme 8). Under the acid aqueous conditions, deacetalation readily takes place, leading to a very polar intermediate, which rapidly undergoes kinetic 5-*exo*-*trig* lactonisation to the polar α-*exo*-methylene-β-hydroxy-γ-butyrolactone. The resulting electrophilic α-*exo*-methylene-γ-butyrolactone undergoes hydrobromation. This hydrobromation step is akin to the conjugate addition of bromide as nucleophile and a very well-established transformation of α,β-unsaturated carbonyl compounds using concentrated HBr either as 48% HBr in water or 33% in acetic acid. Finally, under the very acidic conditions, the resulting β-hydroxy-γ-butyrolactone intermediate undergoes dehydration to the desired *endo*-butenolide. It is important to note that throughout the transformation, no epimerisation can take place at the stereocentre to become the γ-position of the γ-butyrolactone, which guarantees a full transfer of chirality from the substrate. Furthermore, once the *endo*-butenolide is formed, if a deprotonation/tautomerisation event were to take place at the γ-position towards a thermodynamically favourable dienolate/dienol, irreversible elimination of the bromide takes place: this is very important for the

design of the bromolactone and its substrate, as an sp^2 substituent in the γ-position, such as vinyl, carbonyl or aryl groups, readily leads to such degradation and no bromolactone is obtained under the present reaction conditions.

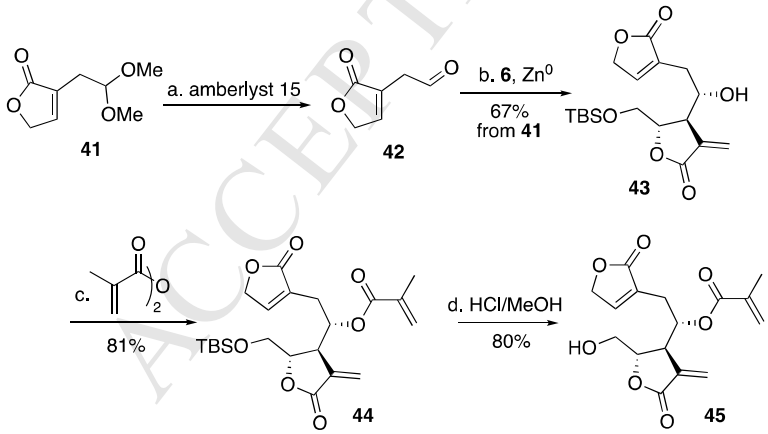


Scheme 8. Proposed course for the HBr-mediated transformation.

2.3. Synthetic applications to open-chain analogues of sesquiterpene lactones

Open-chain analogues have proven to be very efficient probes for the study of their biologically active α-*exo*-methylene-γ-butyrolactone containing sesquiterpene lactone counterparts.[25-26] Thus, with a range of bromolactones in hand, we set out to probe their synthetic utility by applying a small yet relevant subset in the synthesis of open-chain analogues of deoxyelephantopin and 15-deoxygoyazensolide.

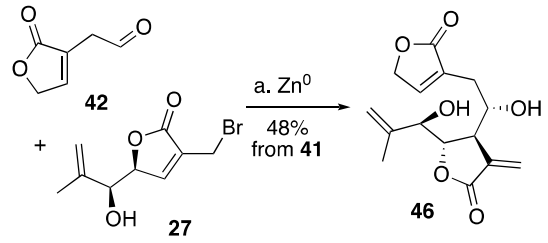
Thus, using bromolactone **6**, a simplified analogue of deoxyelephantopin recapitulating all the polar interactions of the parent natural product (scheme 9). Briefly, zinc-mediated Barbier coupling of **6** with aldehyde **42** provided secondary alcohol **43** with high *anti*/*anti* diastereoselectivity, which was methacryloylated under standard conditions. The TBS ether in **44** could in turn be readily and quantitatively removed in the presence of lactones and esters by treatment with dilute HCl in methanol, making it a valuable handle for further functionalization.



Scheme 9. Synthetic application of bromolactone **6**. Conditions: a. amberlyst 15, THF/H_2O, rt, *then* filtration over celite onto **6**; b. Zn^0, THF, aq. NH_4Cl, 67%; c. methacrylic anhydride, DMAP, Et_3N, CH_2Cl_2, 0 °C, 81%; d. 2 M HCl, MeOH, rt, 80%.

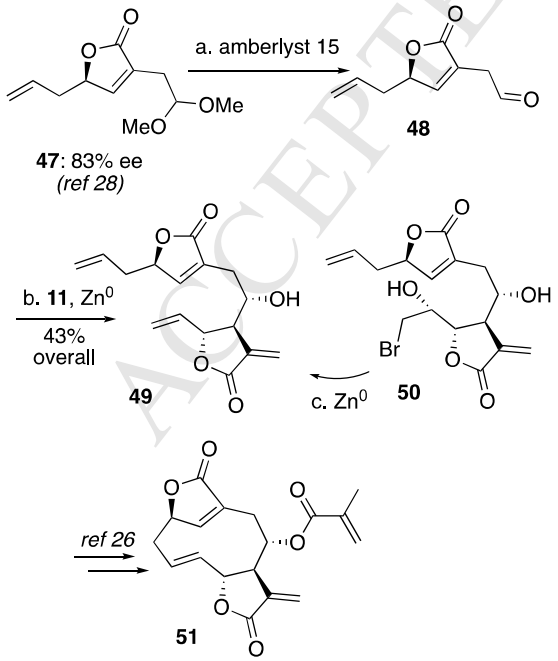
As already mentioned, the primary alcohol in bromolactone **5** was masked as its TBS ether bromolactone **6**, out of sheer practical convenience as bromolactone **5** was highly polar and the resulting Barbier product even more so. However, alcohol-

substituted bromolactones can directly be used for Barbier coupling with aldehydes. Thus, coupling of bromolactone **27** and aldehyde **42** successfully provided secondary alcohol **46** (scheme 10).



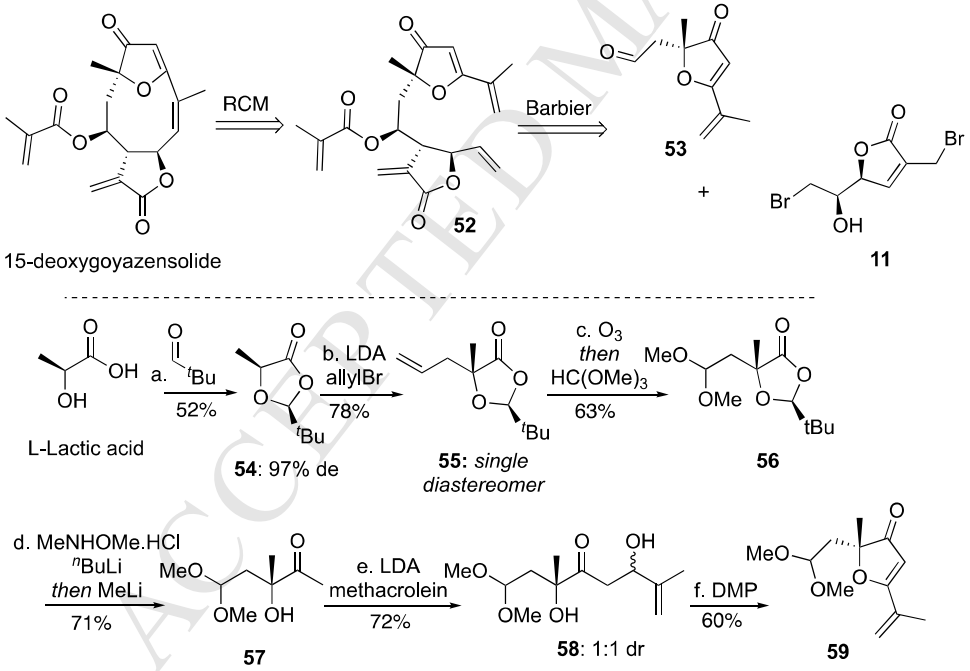
Scheme 10. Bromolactone **27** as coupling partner. Conditions: a. Zn^0, THF, aq. NH_4Cl, 48%.

Bromolactone **11** was designed as an enantiopure surrogate to labile bromolactone **12**; we however needed to determine whether it could undergo bromohydrin elimination under the Barbier conditions (scheme 11). To this end, we reacted **11** with the enantioenriched aldehyde partner we used in our synthesis of analogues of deoxyelephantopin, and we were delighted to observe partial elimination under our standard Barbier coupling conditions. The Barbier coupling is a fast and rather exothermic reaction; in contrast, bromohydrin elimination is rather slow and may not undergo complete elimination in the timeframe of the coupling. We thus reasoned that heat would benefit the more difficult bromohydrin elimination. Accordingly, the desired olefin **49** was cleanly obtained after re-submission of the mixture of **49** and **50** to the reaction conditions at 50 °C. Alternatively, carrying out the Barbier coupling at room temperature follow by heating at 50 °C directly provided **49** as intermediate in our asymmetric synthesis of nordeoxyelephantopin the transformation in a one pot two steps manner is essential to avoid premature degradation of the organozinc species and ensure diastereoselectivity of the Barbier coupling.



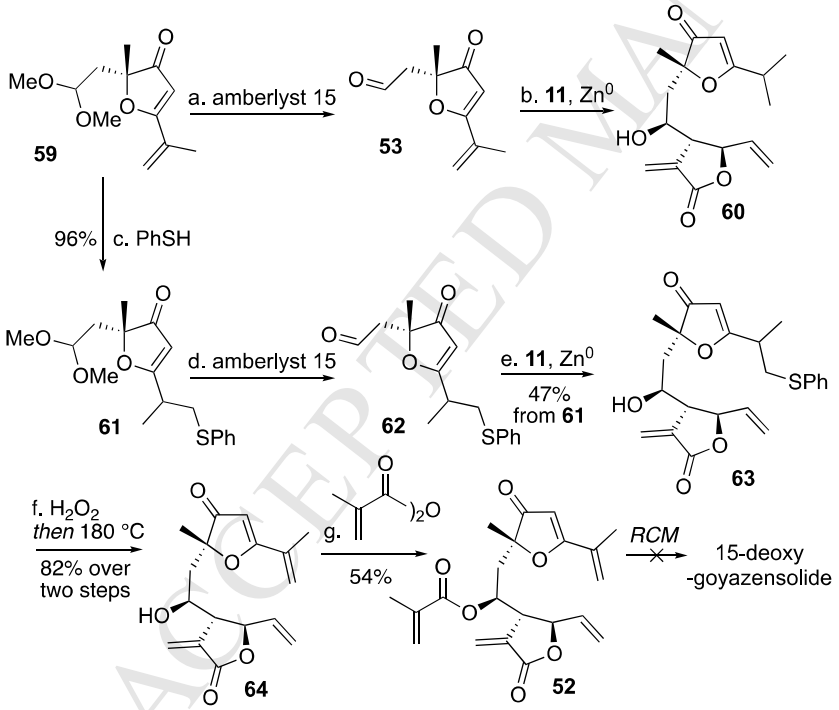
Scheme 11. Bromolactone **11** as enantiopure surrogate for bromolactone **12**. Conditions: a. amberlyst 15, THF/H_2O, rt, *then* filtration over celite onto **11**; b. Zn^0, THF, aq. NH_4Cl, rt then 50 °C, 43% from **47**; c. Zn^0, THF, aq. NH_4Cl, 50 °C.

We further demonstrated the late-stage use of this valuable surrogate in a formal synthesis of 15-deoxygoyazensolide.[54] To this end, we envisioned a late-stage ring-closing metathesis (scheme 12) in complete analogy with Hale's work on Eremantholide A.[55] The substrate to the ring-closing metathesis would arise from a Barbier coupling between surrogate **11** and enantiopure aldehyde **53**, hitherto unknown and for which we developed a synthesis in analogy with Smith's work on 3(2*H*)-furanones.[56] L-Lactic acid was protected as its acetal **54**, obtained with excellent enantio- and diastereopurity after recrystallization at -78 °C. Based on Seebach's work on self-regenerating stereocenters,[57] allylation provided olefin **55** as a single diastereomer, which was ozonolysed and the resulting aldehyde protected as its dimethyl acetal **56**. *In situ* Weinreb amide formation and treatment with methyllithium provide methyl ketone **57**. Treatment with two equivalents of LDA and methacrolein provided β-hydroxy ketone **58**. In his original 1981 report, Smith III first oxidised his β-hydroxy ketones to the β-diketones with Collins' reagent and subsequently cyclised with mild aqueous acid, stating that "the oxidation were carried out under acidic conditions, it might be possible in "one pot" to effect direct cyclization to the desired 3(2*H*)-furanone". Only published in 1983, the Dess-Martin periodinane oxidation of alcohols into their carbonyl counterpart[58] felt adapted owing to the release of acetic acid as a by-product. And indeed, DMP oxidation of **58** provided 3(2*H*)-furanone **59** in a single step and good yield. IBX in refluxing ethyl acetate[59] proved to be superior in terms of cleanliness, yield and ease of workup but it also led to partial cleavage of the acetal.



Scheme 12. Retrosynthetic analysis towards 15-deoxygoyazensolide and preparation of fragment **59**. Conditions: a. ^{t}BuCHO, pentane, PTSA, H_2SO_4, Dean-Stark, 45 °C, followed by three recrystallizations at -78 °C, 57%, 97% de; b. LDA, THF, allyl bromide, -78 °C, 78%; c. O_3, CH_2Cl_2, -78 °C, *then* Me_2S *then* $HC(OMe)_3$, PPTS, rt, 63%; d. MeNHOMe.HCl, ^{n}BuLi, THF, -78 °C, then MeLi, 71%; e. LDA, methacrolein, THF, -78 °C, 72%; f. DMP, CH_2Cl_2, rt, 60%.

The dimethyl acetal in **59** was readily cleaved under acidic conditions and crude aldehyde **53** was directly used in the Barbier coupling with bromolactone **11** (Scheme 13). While coupling and bromohydrin olefination took place, the dienone suffered conjugate reduction to its isopropyl derivative **60**, which was confirmed by submitting **59** to the Barbier conditions and resulted in complete reduction of the γ,δ-olefin at room temperature within the timeframe of the Barbier coupling (not shown). The dienone in **59** was thus masked by conjugate addition of thiophenol at the δ position. Diastereomers **61** were deacetalated as above and Barbier coupling provided secondary alcohol **63** with high diastereoselectivity. Oxidation of the sulfide with hydrogen peroxide in HFIP, followed by sulfoxide elimination under microwave irradiation provided dienone **64**. Finally, methacryloylation provided **52**, which unfortunately never agreed to undergoing ring-closing metathesis under Hale's conditions or any other of the various conditions we explored, only resulting in linear dimerization products or the recovery of unreacted starting material. In addition to the poor reactivity of the type III olefin, i.e. *gem*-disubstituted and highly electron-poor, already found in Hale's substrate, the extra rotor may have placed our substrate outside of the narrow reactivity window successfully exploited by Hale. Nevertheless, this venture further demonstrated the utility of bromolactone **11** for the introduction of γ-vinyl-substituted α-*exo*-methylene-γ-butyrolactones for the synthesis of sesquiterpene lactone derivatives.



Scheme 13. Attempted synthesis of 15-deoxygoyazensolide. Conditions: a. amberlyst 15, CH_2Cl_2, rt; b. Zn^0, THF, aq. NH_4Cl, rt *then* 50 °C, 23% from **59**; c. PhSH, Et_3N, DCM, rt, 96%; d. amberlyst 15, CH_2Cl_2, rt; e. Zn^0, THF, aq. NH_4Cl, rt *then* 50 °C, 47% from **61**; f. 37% H_2O_2, HFIP, rt *then* pyridine, PhMe, 180 °C (microwave), 82% over two steps; g. methacrylic anhydride, DMAP, Et_3N, CH_2Cl_2, 0 °C, 54%.

This small selection of examples was essentially aimed at demonstrating the viability of using these bromolactones as coupling partners together with aldehydes in the Barbier allylation, resulting in a motif present in thousands of natural products. The secondary alcohol obtained in the course of the Barbier allylation should however

readily undergo a Barton-McCombie deoxygenation.[60] Furthermore, it should be noted that sesquiterpene lactones exist at various stages of oxidation beyond the α-*exo*-methylene: accordingly, a wealth of further modifications of this motif are available in the literature, including epoxidation,[61] dihydroxylation,[62] conjugate reduction,[26, 63] conjugate addition of C-nucleophiles,[64] ring-closing metathesis[65] or cross-metathesis,[66] to only name a few, to further extend the scope of natural products potentially reachable from these bromolactones.

Conclusion

In summary, we have developed an efficient and versatile route allowing rapid access to enantiopure bromolactones. This route takes advantage of a sequence of operationally simple and scalable reactions, owing to the nature of the reagents and the high yielding transformations involved. Furthermore, this synthesis benefits from very cheap and readily available starting materials from the chiral pool, such as tartaric acid available in both enantiomeric forms. In fact, any chiral α-hydroxy aldehyde, whereby the alcohol is masked as its TBS ether or with any acid-labile protecting group, may be substrate and precursor to bromolactones, provided that the resulting bromolactone can sustain the buffered yet strongly acidic reaction conditions. Finally, we anticipate that having access to a broad range of bromolactones as valuable precursors to α-*exo*-methylene-γ-butyrolactones will further stimulate the study of the vast pharmacologically important yet ill-studied diversity space of the sesquiterpene lactones and their unnatural analogues, thereby facilitating the understanding of their mode of action and ultimately their potential use in the clinics as the drugs of tomorrow.

Experimental Section

Compound 5 – To a solution of **1** (1.61 g, 7.5 mmol, 1 equiv) in CH_2Cl_2 (7.5 mL) at room temperature was added 48% aqueous HBr (75 mL) and stirring was continued overnight. The reaction mixture was poured in water and extracted with EtOAc. The combined organic layers were carefully washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered through a pad of silica and concentrated *in vacuo*. Purification by column chromatography (silica, cyclohexane/EtOAc 5:1 to 1:2) provided bromolactone **5** as a pale yellow solid (1.03 g, 5.0 mmol, 67 %). $\mathbf{R_f}$ **=** 0.32 (cyclohexane/EtOAc 1:2). **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ 7.43 (q, *J*=1.4 Hz, 1H, H-3), 5.10 (ddq, *J*=5.3, 3.4, 1.6 Hz, 1H, H-4), 4.10 (t, *J*=1.4 Hz, 2H, H-1), 4.00 (dd, *J*=12.3, 3.8 Hz, 1H, H-5a), 3.80 (dd, *J*=12.3, 5.0 Hz, 1H, H-5b), 2.21 (s, 1H, O*H*) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, 25 °C): δ 171.2 (C-6), 149.8 (C-3), 132.5 (C-2), 82.1 (C-4), 62.2 (C-5), 20.8 (C-1) ppm.

Compound 6 – To a solution of TBSCl (830 mg, 5.5 mmol, 1.1 equiv) in dry CH_2Cl_2 (7.5 mL) was added imidazole (509 mg, 7.5 mmol, 1.5 equiv). The resulting mixture was stirred at room temperature for 30 min. To the resulting cloudy solution was added **5** (1.03 g, 5.0 mmol, 1 equiv). Stirring was continued until disappearance of the starting as monitored by TLC. Filtration over a pad of silica, washing with pentane/ether 2:1), concentration in vacuo and purification by column chromatography (silica, pentane/ether 10:1 to 2:1) provided silyl ether **6** as a pale yellow solid (1.56 g, 4.85 mmol, 97%). $\mathbf{R_f}$ **=** 0.45 (cyclohexane/EtOAc 5:1). **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ 7.43 (q, *J*=1.4 Hz, 1H, H-3), 5.00 (dddd, *J*=5.9, 4.7, 3.1, 1.6 Hz, 1H, H-4), 4.10 (t, *J*=1.4 Hz, 2H, H-1),

3.92 (dd, *J*=10.9, 4.4 Hz, 1H, H-5a), 3.82 (dd, *J*=10.9, 5.1 Hz, 1H, H-5b), 0.87 (s, 9H, C(C*H*$_3$)$_3$), 0.07 (s, 3H, Si(*C*H$_3$)$_2$), 0.06 (s, 3H, Si(*C*H$_3$)$_2$) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, 25 °C): δ 170.8 (C-6), 150.4 (C-3), 132.2 (C-2), 81.3 (C-4), 62.8 (C-5), 25.7 (C(*C*H$_3$)$_3$), 20.8 (C-1), 18.2 (*C*(CH$_3$)$_3$), -5.5 (Si(*C*H$_3$)$_2$) ppm.

Compound 11 – To a solution of **10** (2.2 g, 7.0 mmol, 1 equiv) in CH_2Cl_2 (14 mL) at room temperature was added 48% aqueous HBr (14 mL) and stirring was continued overnight. The reaction mixture was poured in water and extracted with EtOAc. The combined organic layers were carefully washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered through a pad of silica and concentrated *in vacuo*. Purification by column chromatography provided bromolactone **11** as a pale yellow solid (1 g, 3.3 mmol, 47%). **R_f =** 0.37 (cyclohexane/EtOAc 5:1). **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ 7.45 (q, *J*=1.5 Hz, 1H, H-3), 5.26 (dq, *J*=3.2, 1.5 Hz, 1H, H-4), 4.12 (ddd, J =6.7, 5.3, 3.2 Hz, H-5), 4.11 (t, *J*=1.5 Hz, 2H, H-1), 3.58 (dd, *J*=10.6, 5.3 Hz, 1H, H-6a), 3.46 (ddd, *J*=10.6, 6.7, 0.8 Hz, 1H, H-6b) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, 25 °C): δ 170.2 (C-7), 148.9 (C-3), 132.8 (C-2), 81.1 (C-4), 70.9 (C-5), 33.1 (C-6), 20.5 (C-1) ppm.

Compound 16 – To a solution of **15** (1.8 g, 5 mmol, 1 equiv) in CH_2Cl_2 (10 mL) at room temperature was added 48% aqueous HBr (10 mL) and stirring was continued overnight. The reaction mixture was poured in water and extracted with EtOAc. The combined organic layers were carefully washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered through a pad of silica and concentrated *in vacuo*. Purification by column chromatography (silica, CH_2Cl_2/MeOH, 1:0 to 10:1) provided bromolactone **16** as a pale yellow solid (699 mg, 2.95 mmol, 59 %). **R_f =** 0.15 (EtOAc). **^{1}H-NMR** (400 MHz, MeOD, 25 °C): δ 7.65 (t, *J*=1.3 Hz, 1H, H-3), 5.18 (dt, *J*=3.3, 1.5 Hz, 1H, H-4), 4.18 (q, *J*=1.4 Hz, 2H, H-1), 3.83 (td, *J*=6.2, 3.4 Hz, 1H, H-5), 3.66 (dd, *J*=11.2, 6.3 Hz, 1H, H-6a), 3.62 (ddd, *J*=11.2, 6.5 Hz, 1H, H-6b) ppm. **^{13}C-NMR** (100 MHz, MeOD, 25 °C): δ 173.4 (C-7), 152.9 (C-3), 132.7 (C-2), 83.5 (C-4), 72.6 (C-5), 63.9 (C-6), 21.4 (C-1) ppm.

Compound 17 – To a stirred solution of bromolactone **16** (420 mg, 1.77 mmol, 1 equiv) in acetone (17.7 mL) at room temperature was added PTSA monohydrate (30 mg, 0.18 mmol, 0.1 equiv) and the resulting mixture was stirred at the same temperature until disappearance of the starting material as monitored by TLC. The reaction mixture was diluted with Et_2O, washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4, filtered over silica and concentrated in vacuo. Purification by column chromatography (silica, cyclohexane/EtOAc 201:1 to 2:1) provided bromolactone **17** as a pale yellow solid (340 mg, 1.22 mmol, 69%). **R_f =** 0.44 (cyclohexane/EtOAc 2:1). **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ 7.39 (q, *J*=1.4 Hz, 1H, H-3), 5.03 (dq, *J*=3.3, 1.6 Hz, 1H, H-4), 4.41 (ddd, *J*=6.7, 5.4, 3.8 Hz, 1H, H-5), 4.12 (t, *J*=1.4 Hz, 2H, H-1), 4.09 (dd, *J*=8.9, 6.7 Hz, 1H, H-6a), 3.83 (dd, *J*=8.9, 5.5 Hz, 1H, H-6b), 1.43 (d, *J*=0.7 Hz, 3H, H-9a), 1.35 (s, 3H, H-9b) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, 25 °C): δ 170.3 (C-7), 148.7 (C-3), 132.9 (C-2), 110.6 (C-8), 80.0 (C-4), 74.3 (C-5), 64.7 (C-6), 26.0 (C-9), 25.0 (C-9), 20.6 (C-1) ppm.

Compound 20 – To a solution of **19** (1.3 g, 5 mmol, 1 equiv) in CH_2Cl_2 (10 mL) at room temperature was added 48% aqueous HBr (10 mL) and stirring was continued overnight. The reaction mixture was poured in water and extracted

with EtOAc. The combined organic layers were carefully washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered through a pad of silica and concentrated *in vacuo*. Purification by column chromatography provided bromolactone **20** as a pale yellow oil (672 mg, 3.8 mmol, 76 %). $\mathbf{R_f}$ **=** 0.48 (cyclohexane/EtOAc 2:1). **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ 7.53 (quint, J=1.7 Hz, 1H, H-3), 4.85 (q, J=1.7 Hz, 2H, H-4), 4.09 (q, J=1.7 Hz, 2H, H-1) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, 25 °C): δ 171.5 (C-5), 149.1 (C-3), 131.0 (C-2), 70.2 (C-4), 20.8 (C-1) ppm.

Compound 23 – To a solution of **22** (26 mg, 0.094 mmol, 1.0 equiv) in CH_2Cl_2 (0.15 mL) at room temperature was added 48% aqueous HBr (0.15 mL) and stirring was continued for 18h. At 0°C, a saturated solution of $NaHCO_3$ was slowly added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by column chromatography (silica, pentane/Et_2O 5:1 to 0:1) provided bromolactone **23** as a colourless oil (17.9 mg, 0.094 mmol, quant.). $\mathbf{R_f}$ **=** 0.28 (pentane/Et_2O 1:1). **^{1}H NMR** (500 MHz, $CDCl_3$, 25°C): δ 7.39 (d, J=1.4 Hz, 1H, H-3), 5.09 (dddd, J=8.4, 6.9, 5.3, 1.6 Hz, 1H, H-4), 4.09 (t, J=1.4 Hz, 2H, H-1), 1.46 (d, J=6.8 Hz, 3H, H-5) ppm. **^{13}C NMR** (167 MHz, $CDCl_3$, 25°C): δ 170.8 (C-6), 153.4 (C-3), 131.0 (C-2), 77.6 (C-4), 21.0 (C-1), 18.7 (C-5) ppm.

Compound 27 – To a solution of **26** (1.76 g, 6.9 mmol, 1 equiv) in EtOAc (6.9 mL) at room temperature was added 48% aqueous HBr (6.9 mL) and stirring was continued overnight. The reaction mixture was poured in water and extracted with EtOAc. The combined organic layers were carefully washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered through a pad of silica and concentrated *in vacuo*. Purification by column chromatography (silica gel, cyclohexane/EtOAc 10:1 to 1:1) provided bromolactone **27** as a pale yellow solid (940 mg, 3.8 mmol, 55 %). $\mathbf{R_f}$ **=** 0.39 (cyclohexane/EtOAc 1:1). **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ 7.33 (q, J=1.4 Hz, 1H, H-3), 5.09 (t, J=1.4 Hz, 1H, H-8), 5.07 (d, J=1.4 Hz, 1H, H-8), 5.05 (d, J=1.6 Hz, 1H, H-4), 4.13 (dd, J=13.6, 6.6 Hz, 1H, H-5), 4.10 (t, J=1.5 Hz, 2H, H-1), 1.84 (d, J=1.3 Hz, 3H, H-7) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, 25 °C): δ 170.5 (C-9), 149.5 (C-3), 142.1 (C-6), 132.4 (C-2), 115.1 (C-8), 82.9 (C-4), 76.3 (C-5), 20.7 (C-1), 18.6 (C-7) ppm.

Compound 37 – To a solution of **36** (466 mg, 1.93 mmol, 1 equiv) in EtOAc (3.8 mL) at room temperature was added 48% aqueous HBr (3.8 mL) and stirring was continued overnight. The reaction mixture was poured in water and extracted with EtOAc. The combined organic layers were carefully washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered through a pad of silica and concentrated *in vacuo*. Purification by column chromatography (silica gel, cyclohexane/EtOAc 10:1 to 1:1) provided bromolactone **37** as an off-white solid (242 mg, 1.1 mmol, 56 %). $\mathbf{R_f}$ **=** 0.36 (cyclohexane/EtOAc 1:1). **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ 7.40 (q, J=1.4 Hz, 1H, H-3), 5.85 (ddd, J=17.0, 10.4, 6.4 Hz, 1H, H-6), 5.43 (dt, J=17.1, 1.2 Hz, 1H, H-7), 5.35 (dt, J=10.5, 1.2 Hz, 1H, H-7), 4.97 (dq, J=5.7, 1.6 Hz, 1H, H-4), 4.30 (ddt, J=6.8, 5.7, 1.2 Hz, 1H, H-5), 4.09 (t, J=1.4 Hz, 2H, H-1) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, 25 °C): δ 170.7 (C-8),

149.4 (C-3), 134.3 (C-6), 130.7 (C-2), 119.5 (C-7), 83.5 (C-4), 73.3 (C-5), 20.7 (C-1) ppm.

Compound 40 – To a solution of **39** (720 mg, 3 mmol, 1 equiv) in EtOAc (6 mL) at room temperature was added 48% aqueous HBr (6 mL) and stirring was continued overnight. The reaction mixture was poured in water and extracted with EtOAc. The combined organic layers were carefully washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered through a pad of silica and concentrated *in vacuo*. Purification by column chromatography (silica gel, cyclohexane/EtOAc 10:1 to 1:1) provided bromolactone **40** as a pale yellow solid (352 mg, 1.53 mmol, 51 %). $\mathbf{R_f}$ **=** 0.34 (cyclohexane/EtOAc 1:1). **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ 7.49 (q, *J*=1.5 Hz, 1H, H-3), 5.07 (dt, *J*=6.1, 1.6 Hz, 1H, H-4), 4.57 (dd, *J*=5.5, 3.3 Hz, 1H, H-5), 4.12 (q, *J*=2.4, 1.9 Hz, 2H, H-1), 2.61 (d, *J*=2.2 Hz, 1H, H-7), 2.46 (d, *J*=5.1 Hz, 1H, O*H*) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, 25 °C): δ 170.0 (C-8), 148.3 (C-3), 133.5 (C-2), 82.1 (C-4), 78.8 (C-6), 76.7 (C-7), 63.3 (C-5), 20.4 (C-1) ppm.

Supporting information
Supplementary data related to this article can be found at

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Declaration of Interests
The authors declare no conflict of interest.

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