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A new and effective route to (±)-botryodiplodin and (±)-*epi*-botryodiplodin acetates using a halogen atom transfer Ueno–Stork cyclization

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Abstract—(±)-Botryodiplodin and (±)-*epi*-botryodiplodin acetates were prepared in good yields following a practical four step route. The method, for the construction of the strategic tetrahydrofuran ring, hinged on an unprecedented halogen atom transfer Ueno–Stork cyclization of an *O*-allyl α,α-dihalohemiacetal acetate, catalyzed by the redox complex CuCl/*N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine.

Addition of a carbon–halogen bond across a carbon–carbon unsaturated bond using a transition metal catalyzed atom transfer radical reaction[1,2] is a significant tool for the construction of rings (atom transfer radical cyclization, ATRC)[3] or polymers (atom transfer radical polymerization, ATRP).[4] The method has some important advantages over other radical techniques, including (i) low cost of the catalyst; (ii) ease of work-up; and above all, (iii) high productivity and (iv) preservation of all the carbon–halogen bonds on converting the reactant into product. The manoeuvre is typically accomplished in the presence of redox catalysts, mainly complexes between CuCl and bi- or poly-dentate nitrogen ligands.[2,3] The ring closure of an archetypal substrate, tethering a sufficiently reactive C–X function (the carbon site needs to be bound to EWG groups) and an olefin group, is initiated by abstraction of the halogen atom by the reduced form of the catalyst, which then passes into the oxidized form. The resulting electrophilic radical attacks the olefinic end giving rise to a nucleophilic radical, which gets back the halogen from the catalyst in its oxidized form yielding the product. The final step results in the regeneration of the catalyst, which can initiate a new reaction cycle.

Although there are many reports on the synthetic use of transition metal catalyzed ATRC,[1–3] one area that has been neglected is the radical cyclization of haloacetals (for sake of completeness, examples of atom transfer cyclizations of iodoacetals have been reported,[5] but all involving a free radical chain mechanism), better known as the Ueno–Stork reaction.[5] To the best of our knowledge, there have only been two reports in this area, both relatively recently, and both reports discuss the use of chloral as a precursor.[6,7] In line with our interest in applying Cu(I) catalyzed ATRC to α-perchlorocarbonyl compounds,[8–11] we have investigated the elaboration of dichloro aldehydes **A**[12] into dichlorinated γ-lactones **E** using a Ueno–Stork cyclization in the key step. Preliminary tests showed that cyclization of the acetylated hemiacetal **C** forms the halogenated tetrahydrofuran **D** (in comparison, *O*-allyl 2,2-dichlorohemiacetal acetates are much less reactive than the related 2,2,2-trichloro compounds owing to the higher energies of their LUMO's[1,13]). Use of CuCl/*N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (PMDETA) (10 mol %) in acetonitrile

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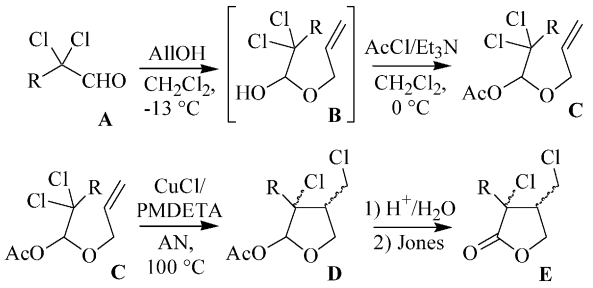


Scheme 1. Synthetic path from 2,2-dichloroaldehydes to dichlorinated γ-lactones, using a transition metal catalyzed atom transfer Ueno–Stork cyclization as key step.

(AN) at 100 °C, within a Schlenk tube, was shown to be a more effective redox complex (as observed by other authors[14]) than alternative CuCl/*N*,*N*,*N*′,*N*′-tetramethylethylenediamine or CuCl/bipyridine catalysts, which gave incomplete conversions (around 80%) under the same reaction conditions (see Scheme 1).

Potentially, this is an extremely powerful transformation and to demonstrate this, we have investigated the synthesis of (±)-botryodiplodin acetate **1a** (Fig. 1). (−)-Botryodiplodin is a natural toxin (with a DL50 of 16.8 mg/Kg)[15] produced by a number of fungal microorganisms.[16,17] Following its isolation by Sen Gupta in late 1966,[18] this compound, which exibits antibacterial activity[17,18] and cytostatic action against neoplastic cells,[19–22] has been the subject of many synthetic efforts. Previous synthetic strategies involve fermentation processes,[15,18,21,23] and low yield transformations of stereopure substances with no assembly of C–C bonds.[24,25] In addition, there are a number of total syntheses, which can be roughly classified into three general subtypes, namely (i) pericyclic,[26–29] (ii) ionic[30] (under this heading we group two syntheses[31,32] where ionic reactions were used to introduce C(3) and/or C(4) substituents onto a cyclic starting material) and (iii) radical,[33,34] depending on the method used to construct the C(3)–C(4) bond.

All previous synthetic strategies have led to the formation of the lactol of **1a**, often together with large amounts of the C-3 diastereomer (called *epi*-botryodiplodin **1b**) in unsatisfactory yield [usually around 10% or less, apart from the syntheses of Wilson (42%)[28] and Dulcere (35%)[34]]. A more efficient synthesis of the 2-methoxy derivative[34] of botryodiplodin is possible, although this derivative is devoid of biological activity[35] and it is not easy to deprotect. Interestingly, since botryodiplodin is rather unstable under acid conditions it is not possible to purify it using chromatography on silica gel.[31,34] To prevent its early degradation, acetylation of the hemiacetal group to give **1a** has been reported, although this operation is not particularly efficient (around 60–80% yield).[26,27,29,32] The acetylation could be a powerful element of convergence, since pyrolysis of mixtures of acetates of botryodiplodin and its *epi*-form produce a single enol ether, which on reaction with 1 equiv of acetic acid affords only β-botryodiplodin acetate.[29]

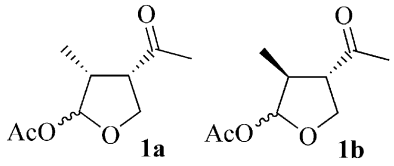
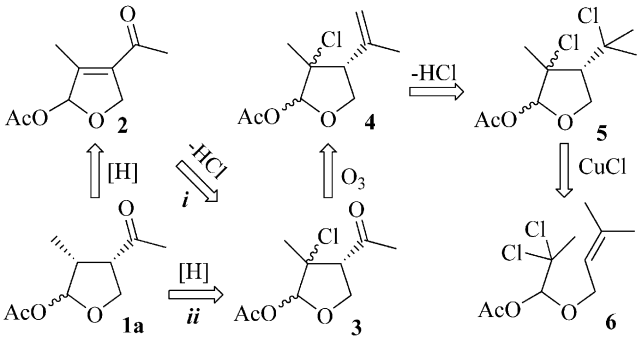


Figure 1. Structures of (±)-botryodiplodin (**1a**) and (±)-*epi*-botryodiplodin (**1b**) acetates.

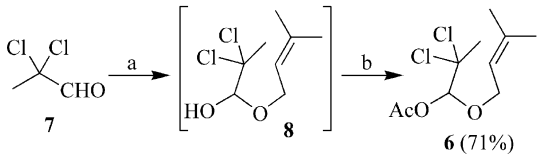
Owing to the important biological properties of botryodiplodin, including its ability to cause DNA-protein cross-links,[36] and considering that it contains the same electrophilic γ-ketoaldehyde functionality present in the levuglandins,[37] the design of more robust, versatile and facile synthetic approach to **1a** is of current interest. In this letter, we wish to report that (±)-botryodiplodin **1a** and (±)-*epi*-botryodiplodin **1b** acetates were prepared in a satisfactory overall yield of 69% (in a 63:37 ratio) following a straightforward and robust four step route starting from the readily available *O*-allyl-α,α-dihalohemiacetal acetate **6**. The method for the construction of the substituted tetrahydrofuran ring hinges on an unprecedented halogen atom transfer Ueno–Stork cyclization (HATUSC), catalyzed by the redox complex CuCl-PMDETA.

Scheme 2 shows a retrosynthetic analysis of (±)-botryodiplodin. It starts with precursor **2** where the Δ^3 unsaturation is introduced in the ring so that catalytic hydrogenation gives the desired stereochemistry at the C-3 and C-4 sites of **1a**. The C=C bond in **2** could be formed by regioselective elimination of tertiary chloride **3**. Different stereoisomers of **3** should undergo elimination to give **2** and so a diastereoselective route to **3** is not required.

The ketone group in **3** could be formed by ozonolysis of precursor **4**, which contains an isopropenyl substituent at C-4. The *exo* double bond in **4** can be replaced by a second C–Cl function located in a 1,3-relationship with the *endo* C–Cl bond to give dichloride **5**. The relative position of the two halogen atoms in **5** is strategic and gives the opportunity to apply a retro HATUSC, through which the C(3)–C(4) bond is disconnected to afford the starting *O*-allyl-α,α-dihalohemiacetal acetate **6**. Unlike the reported procedures for forming haloacetals (used in standard Ueno–Stork reactions),[5] starting



Scheme 2. Retrosynthetic path of **1a**.

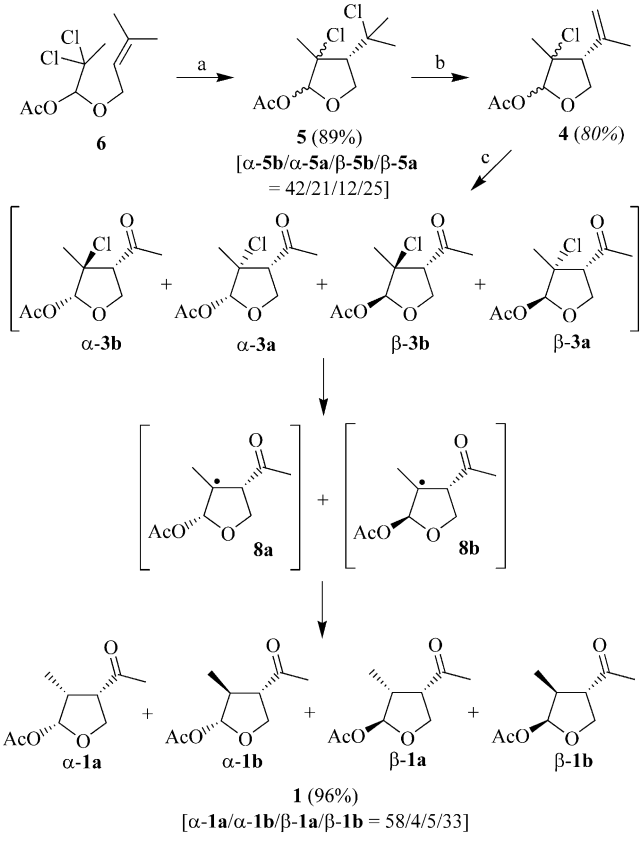


Scheme 3. (a) 3-Methyl-2-buten-1-ol, CH_2Cl_2, −13 °C, 1 h. (b) AcCl, Et_3N, CH_2Cl_2, 0 °C, 20 h.

material **6** was obtained by taking advantage of the susceptibility of α,α-dichloro aldehydes to undergo nucleophilic attack by oxygen nucleophiles to form relatively stable hemiacetals.[38] Thus, adding the appropriate allylic alcohol to α,α-dichloropropanal (**7**) in CH_2Cl_2 at −13 °C and acetylating the intermediate hemiacetal **8** (with acetyl chloride) gave the expected haloacetal **6** (Scheme 3) in good yield (71%).

The ensuing cyclization of **6** was efficiently accomplished in AN at 100 °C (yield 89%), within a Schlenk tube, using the redox complex CuCl-PMDETA (10 mol %). The cyclization reaction showed, as expected,[5] a modest diastereoselectivity, to give all four possible isomers of dihalogenated tetrahydrofuran **5**:[†] α-**5a**, β-**5a**, α-**5b** and β-**5b** were formed in the ratio 21/25/42/12 (Scheme 4). In contrast to the configurational lability of the stereogenic centre at C-3 for the 3-alkyl-3-chloro-4-chloroalkyl-γ-lactams under the conditions of the ATRC reaction,[8] the analogous position in **5** appears instead stable, thus excluding the possibility of reversible radical generation at this site by the redox catalyst. Dehydrohalogenation of the inseparable mixture of diastereomers of **5**, to convert the (1-Cl-1-methyl)-ethyl substituent into an isopropenyl group, was carried out, within a Schlenk tube, at 130 °C using AgOAc (1.1 equiv) in *t*-butanol. Notwithstanding the presence of two tertiary chlorides, we were pleased to observe that only monoelimination was observed and this was regioselective to give the less substituted terminal alkene **4**, which was isolated as an inseparable 22/25/41/12 mixture of α-**4a**/β-**4a**/α-**4b**/β-**4b** isomers.

Ozonolysis of **4** was conducted in *t*-butanol, a participating solvent,[39] working at a temperature high enough to prevent solvent solidification. The reaction, monitored by gas-chromatography, showed a very clean transformation. However, when we tried to recover the ensuing ketone **3**, it was disappointing to see that after evaporation of the solvent, the crude product rapidly changed from a colourless into a black liquid releasing (at the same time) a plentiful amount of HCl (warning!!). The main component of the mixture, albeit present in modest quantity (ca. 40%), was 3-acetyl-4-methylfuran. Evidently ketone **3** is prone to a facile and autocatalytic dehydrohalogenation to give the expected conjugated intermediate **2**, but unfortunately, this substance is unstable and is prone to 1,4-hydro-acyloxy-elimination to form an aromatic ring. We tried a



Scheme 4. (a) CuCl/PMDETA, CH_3CN, 100 °C, 4 h. (b) AgOAc, *tert*-butanol, 130 °C, 6 h. (c) O_3, *tert*-butanol, 27 °C. (d) Bu_3SnH, AIBN, toluene, 80 °C, 8 h.

number of different work-up procedures with a view to isolating **3** or **2**, but this was unsuccessful.

Unable to secure the key ketone **2**, we were compelled to look for a synthetic detour. As an alternative, radical hydro-de-chlorination of the crude mixture of the four diastereoisomers of **3** was investigated using Bu_3SnH/AIBN. Since the two radical intermediates, **8a** and **8b**, which originate from **3**, can be considered planar, it was of interest to see if Bu_3SnH was able to preferentially approach the less congested side of both radicals, to give a stereoselective synthesis of **1**.[33]

Radical reduction of **3** with Bu_3SnH (1 equiv)/AIBN (0.03 equiv) was carried out in toluene at 80 °C within a Schlenk tube, adding the radical initiator, previously dissolved in toluene, in small aliquots every 1.5 h. Despite the relatively high temperature, the reduction was highly stereoselective. After 8 h, the reaction mixture was allowed to cool and, without preliminary concentration, passed through a flash silica gel column using petroleum ether as the eluant. This permitted **1** (which has very low R_f values in toluene or petroleum ether) to be easily separated from the organotin by-products. The expected 2-acetoxy-tetrahydrofurans **1a**–**b** were obtained in 96% yield as an α/β anomeric mixture of (±)-botryodiplodin **1a** and (±)-*epi*-botryodiplodin **1b** acetates, in a ratio of 58/5/4/33, respectively. Interestingly,

[†] The anomeric centres were named according to rule 2-Carb-6.2 of the IUPAC '*Nomenclatures of Carbohydrates*' (recommendations 1996).

the most sterically congested and major product, α-**1a**, has only occasionally been reported by other authors in trace amounts. The overall yield for **1a** starting from **6** is 44% (25% for **1b**), while from 2,2-dichloropropanal **7** the overall yield is a respectable 31% (18% for **1b**).

In summary, (±)-botryodiplodin acetate **1a**, a stable derivative of the natural mycotoxin, together with its *epi*-isomer **1b**, was prepared in a satisfactory global yield (compared with the previous published methods) following a straightforward 4 step route, which is suitable for multigram synthesis. The synthesis further demonstrates the synthetic value of α,α-perchloroaldehydes.[12] Key features of the approach include an unprecedented transition metal catalyzed halogen atom transfer Ueno–Stork cyclization of an *O*-allyl-α,α-dihalohemiacetal acetate (the catalyst being the redox complex CuCl/*N*,*N*,*N*′,*N*′,*N*″-pentamethyldiethylenetriamine) and a stereoselective radical reduction mediated by Bu_3SnH.

Acknowledgements

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Supplementary data

Experimental procedures, characterization data and ^1H NMR spectra for compounds **1**, **4**, **5** and **6**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.08.121.

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