Pergamon

SCIENCE DIRECT®

Tetrahedron: *Asymmetry* 14 (2003) 3005–3018

TETRAHEDRON: *ASYMMETRY*

Synthesis of (±)- and (−)-botryodiplodin using stereoselective radical cyclizations of acyclic esters and acetals

Robert Nouguier,[a,*] Stéphane Gastaldi,[a] Didier Stien,[a] Michèle Bertrand,[a] Félix Villar,[b] Olivier Andrey[b] and Philippe Renaud[b,*,†]

[a]*Laboratoire de Chimie Moléculaire Organique, UMR 6517, Boite 562, Faculté des Sciences St Jérôme, Université d'Aix-Marseille III, Av. Escadrille Normandie-Niemen, 13397 Marseille Cedex 20, France*
[b]*Université de Fribourg, Département de Chimie, Pérolles, CH-1700 Fribourg, Switzerland*

Received 30 May 2003; accepted 19 June 2003

Abstract—Three different routes for the stereoselective synthesis of botryodiplodin have been investigated. The intramolecular allylation of acetals proved to be unsatisfactory due to unstable intermediates and poor stereocontrol. Zard intramolecular radical allylation of a 2-iodopropionate derivative allows the development of an expeditious synthesis of racemic botryodiplodin. The relative configuration within the final product was corrected by a deprotonation–reprotonation step. The cyclization of allenyl bromoacetals was investigated next and proved to be satisfactory for the synthesis of racemic and enantiomerically pure botryodiplodin. Good stereocontrol was achieved by cyclizing a *gem*-dibromide followed by the stereoselective reduction of the thus formed cyclic monobromide.

1. Introduction

(−)-Botryodiplodin (−)-**1** is a simple lactol natural product which has been isolated from *Botryodiplodia theobromae*,[1,2] *Penicillium roqueforti*,[3] *Penicillium stipitatum*[4,5] and other fungi.[6] This mycotoxin exhibits antibiotic and antileukemic activity.[1,4,7,8] Its relative and absolute configuration has been established by total synthesis.[9–19] However, despite a strong interest for its preparation, only two syntheses of enantiomerically pure botryodiplodin have been reported.[13,15,16] Both approaches use chiral building blocks derived from natural products (D-ribose and methylenomycin A). Herein we report our efforts toward the stereoselective synthesis of (±)-botryodiplodin using radical cyclizations.[20,21] The absolute configuration of a key acetal intermediate is controlled by a chiral auxiliary, allowing the preparation of naturally occurring (−)-botryodiplodin.

* Corresponding authors. Tel.: +33-4-91288232; fax: +33-4-9167-0944 (R.N.); Tel.: +41-31-631-4359; fax: +41-31-631-3426 (P.R.); e-mail: robert.nouguier@univ.u-3mrs.fr; philippe.renaud@ioc.unibe.ch
† Present address: Universität Bern, Departement für Chemie und Biochemie, Freiestrasse 3, CH-3000 Bern 9, Switzerland.

0957-4166/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2003.06.004

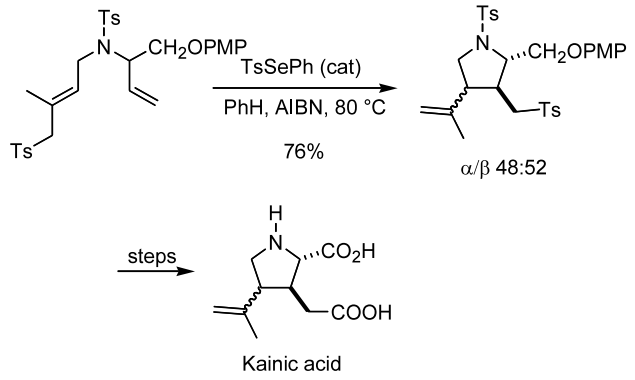
2. Results and discussion

2.1. Approach 1. Allylic sulfones: cyclization of acetal derivatives

Due to the ready fragmentation of β-sulfonylated alkyl radicals, allyl sulfones have become very popular radical allylating reagents.[22–32] Previously we have reported a formal synthesis of kainic acids based on the radical rearrangement of an allylic sulfone.[33] This intramolecular allylation allows the construction of the basic skeleton of kainic acid, a 2,3,4-trisubstituted pyrrolidine bearing an isopropylidene in position 4, in a one step process (Scheme 1).

Since the isopropylidene group can readily be transformed into an acetyl group via ozonolysis, we thought that the same methodology could be applied for the synthesis of (±)-botryodiplodin **1** (Scheme 2).

Sulfone **2** was prepared in two steps starting from **3**, which is easily available from acetoxychlorination of isoprene (Scheme 3).[34,35] The reaction of **3** with acrolein diethylacetal led to **4** which was then oxidized with *meta*-chloroperbenzoic acid.



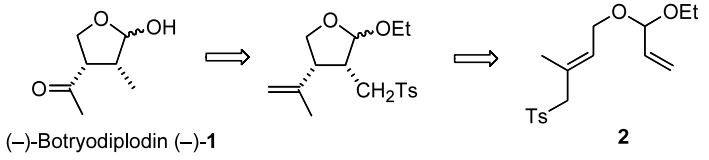
Scheme 1.

The rearrangement of **2** was performed in refluxing benzene in the presence of a catalytic amount of $TolSO_2SePh$ (20 mol%) and AIBN as the initiator. This led to **5** (mixture of 3 diastereomers) and the elimination product **6** in a 70:30 ratio (Scheme 4). The relative configurations within the three diastereomers of **5** was unambiguously assigned from NOESY experiments after isolation of pure samples by semi-preparative HPLC.

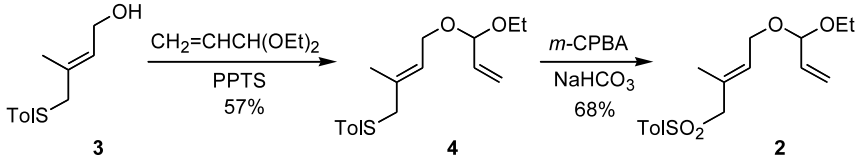
Due to the instability of the acetal moiety in the reaction media, which becomes acidic through the formation of *para*-toluenesulfinic acid, the formation of **6** could not be avoided, even when the rearrangement was performed in the presence of pyridine.

Though **6** might be converted readily into **5**, we thought we could avoid the elimination of EtOH by rearranging sulfide **4** in the presence of a catalytic amount of *para*-thiocresol (Scheme 5). However, the resulting products **7** formed in a 10:20:25:45 ratio were too unstable to be isolated by chromatography on silica gel. The direct reduction of the crude mixture with Bu_3SnH failed to give **7′**. Therefore, the cyclization products **7** were converted by oxidation with *meta*-chloroperbenzoic acid into a 25:39:17:19 mixture of the four diasteromers of **5**. GC analysis of the crude product showed that **6** was not present and that a new cyclized product, presumably (*r*-2,*t*-3,*c*-4)-**5**, was produced. No attempt to isolate a pure sample of this fourth isomer was made.

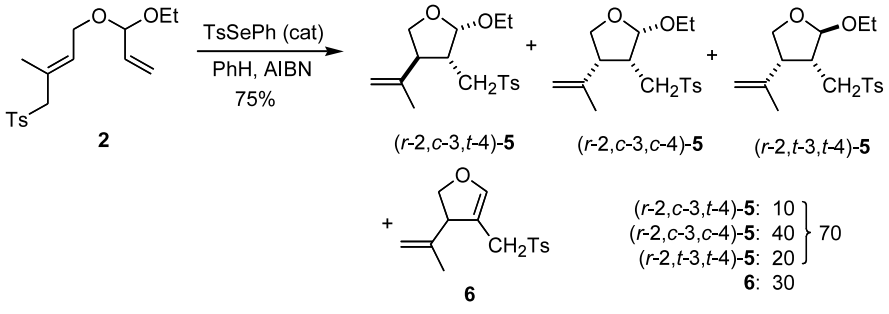
The diastereoselectivity of these 5-*exo* ring closures is low compared to the related cyclizations of 1,2-disubstituted 3-oxa- and 3-aza-5-hexenyl radicals. These two systems afford five-membered heterocycles with substituents at C(2) and C(3) in a *trans* arrangement (see Scheme 1 for such an example).[33,36] The stereoselectivity can be rationalized by the influence of an anomeric effect that favors transition states bearing a pseudo-axial ethoxy group. The major isomer (*r*-2,*c*-3,*c*-4)-**5**



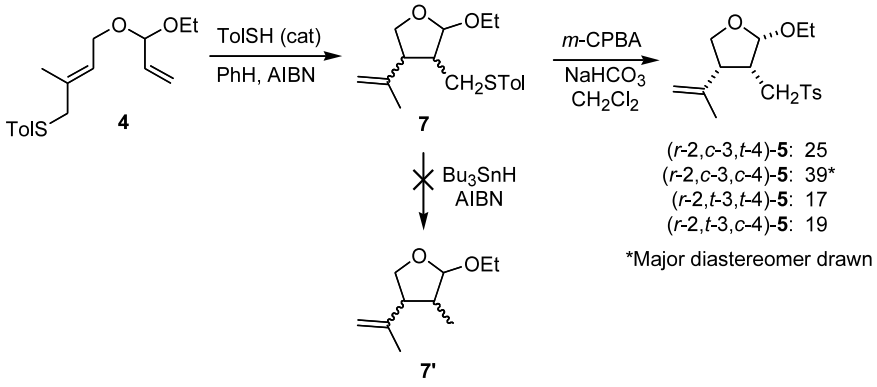
Scheme 2.



Scheme 3.

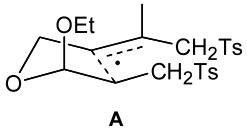


Scheme 4.



Scheme 5.

would originate from the transition structure **A** (Fig. 1). Based on our recent study of the Ueno–Stork reaction, the low stereoselectivity is not surprising.[37,38] Indeed, large alkyl groups at C(4), such as a 2,2-disubtituted ethenyl substituents, give only moderate *cis* stereoselectivity relative to the alkoxy group at C(2). Moreover, the stereogenic center at C(3) is not controlled when simple alkyl substituents are present.



A

Figure 1.

2.2. Approach 2. Allylic sulfones: Intramolecular allylation of 2-bromopropionate derivatives

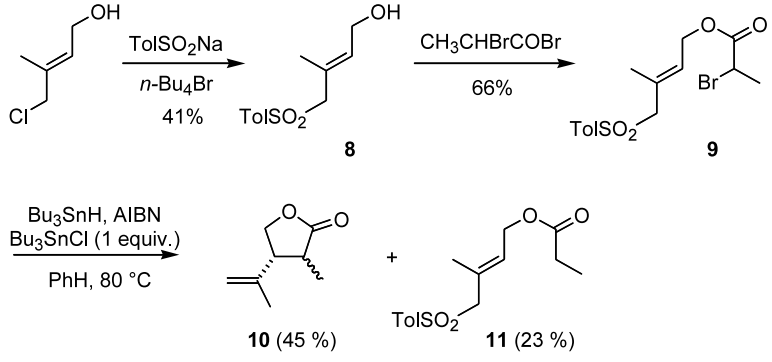
Both the low selectivity and the instability of the acetals, led us to investigate a closely related pathway involving α-alkoxycarbonyl radicals. For such systems, it is well established that the 5-*exo* ring closure is a slow process due to the preferred unfavourable *Z* conformation of esters.[39,40] This is well demonstrated by the cyclization of bromide **9**, which was prepared according to Scheme 6.

Even when the reaction was carried out by slow addition of tributyltin hydride at 80°C using a syringe pump, the reduction product **11** was the major product. In order to modify the *Z*/*E* conformational equilibrium of the ester moiety by complexation of the carbonyl with a Lewis acid, we performed the reduction of **9** in the presence of 1 equiv. of Bu_3SnCl.[41,42] Under these conditions, lactone **10**, formed as a 57:43 mixture of *trans* and *cis* isomers, became the major product. However, the non-cyclized product **11** was still isolated in 23% yield (Scheme 6).

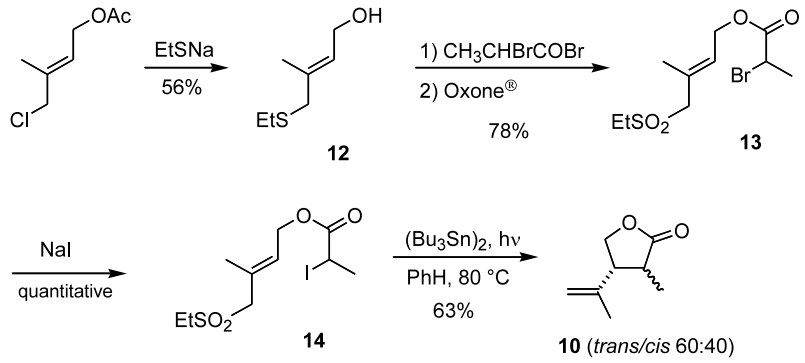
The iodine atom transfer methodology was shown to be one of the best procedures to suppress the direct reduction competing with lactone ring closure.[39,40,43] In our case, this procedure could only be applied if the sulfonyl radical ejected during the β-fragmentation step would produce, through α-scission, an alkyl radical that is able to react with the starting material via atom transfer. Zard allylation protocol involving allyl ethyl sulfones was ideally suited to that purpose.[28–30]

Iodide **14** was prepared according to Scheme 7 and was irradiated with a sun lamp in the presence of a catalytic amount of hexabutylditin. The cyclization became efficient at 80°C and lactone **10** was isolated in 63% yield as a *trans*/*cis* 60:40 mixture of isomers.

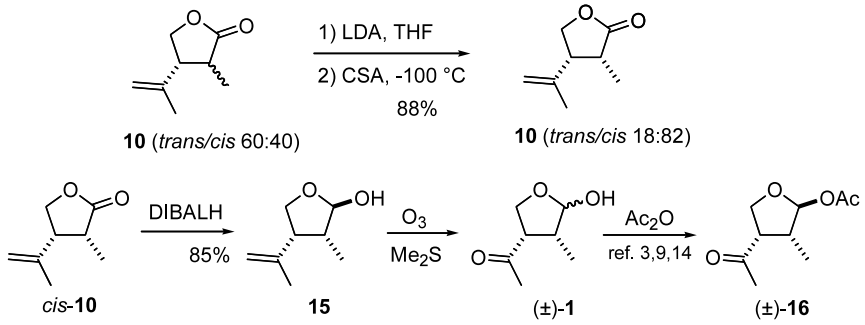
The relative configuration of the major isomer was incorrect to prepare botryodiplodin **1**. Therefore, it was



Scheme 6.



Scheme 7.



Scheme 8.

necessary to invert the configuration at C(3) by deprotonation and kinetic reprotonation of the enolate with camphorsulfonic acid (CSA) according to Scheme 8. After separation by HPLC (the *trans* isomer could be recycled), the *cis* isomer was transformed into (±)-botryodiplodin (±)-**1** according to literature procedure.[19] The lactol (±)-**1** was obtained as a mixture of epimers, its structure was unambiguously assigned after acetylation and comparison of ^{1}H and ^{13}C NMR spectra of acetate (±)-**16** with literature data of the acetate derived from natural botryodiplodin.[3,9,14]

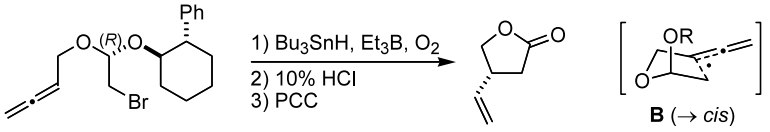
This 2-bromopropionate cyclization strategy described here is suitable for the preparation of racemic botryodipodin. However, it cannot be easily extended to enantiomerically enriched botryodiplodin.

2.3. Approach 3. Cyclization of bromoacetals

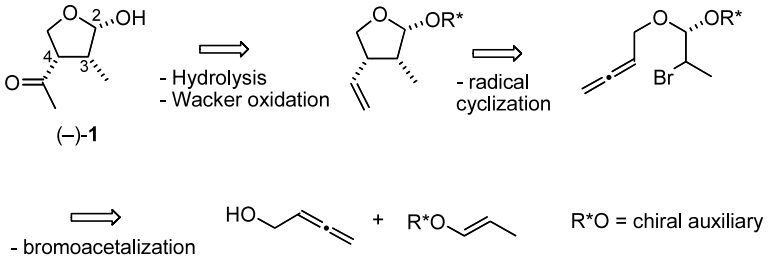
We have recently reported a detailed study of the stereochemistry of the radical cyclization of haloacetals (Ueno–Stork reaction[44–49]).[37,38] The stereochemical outcome of such reactions can be efficiently controlled by the stereogenic acetal center.[50] For instance, we have shown that an excellent level of stereocontrol can be achieved at position 4 when the formed tetrahydrofuran is not substituted at position 3. This observation opens a possibility for controlling the absolute stereochemistry by using a chiral auxiliary approach. A facile preparation of enantiomerically pure 4-vinyl-γ-butyrolactone from an enantiomerically and diastereomerically pure allenyl acetal has been achieved to demonstrate the feasibility of this process (Scheme 9).[37,51] The choice of the allenyl radical trap was dictated by the necessity to have a small (or linear) substituent to achieve high level of *cis* stereocontrol relative to the alkoxy group at C(2).

This reaction opens a very straightforward approach for the synthesis of botryodiplodin depicted in Scheme 10. The key reactions being the radical cyclization of an allenyl acetal leading to a 4-vinylsubstituted tetrahydrofuran and a Wacker oxidation to convert the vinyl moiety into an acetyl group. By using a chiral auxiliary, this method is expected to deliver optically active botryodiplodin.

Based on our stereochemical model for the Ueno–Stork reaction, the stereoselective preparation of 3,4-disubstituted tetrahydrofurans was expected to be problematic:

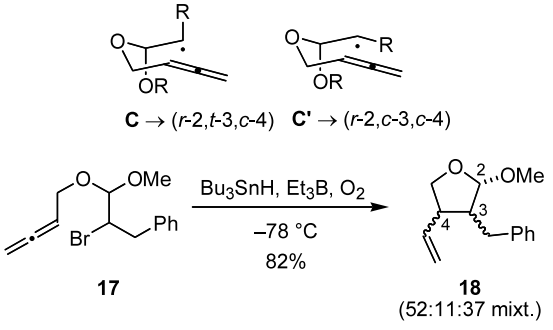


Scheme 9.



Scheme 10.

the C(4) center should be nicely controlled by the acetal center (model **B**). However, the C(3) center should not be easy to control because of the opposing effects of the two vicinal substituents. Indeed, according to the classical Beckwith–Schiesser–Houk model,[52,53] the alkoxy group should favor the *trans* product (model **C**) and the C(4) substituent should favor the *cis* product (model **C′**). This expected low stereochemical control is supported by previous cyclizations of systems bearing alkyl substituents at position 3.[37] This was further confirmed with **17**, a non-volatile model system for the synthesis of botryodiplodin. Treatment of **17** under standard cyclization conditions (Bu_3SnH, Et_3B, O_2 at −78°C) gave **18** in good yield but as mixture of three isomers (Scheme 11).

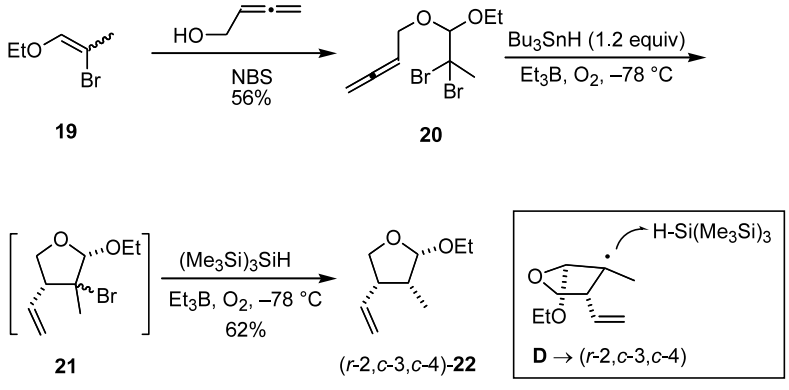


Scheme 11.

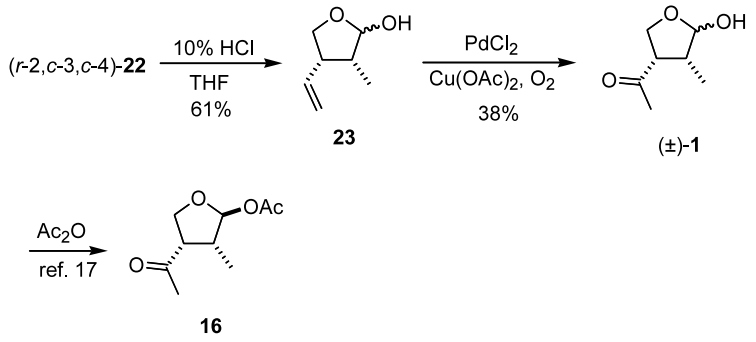
In order to solve this stereoselectivity problem, the *gem*-dibromide **20** was prepared from enol ether **19** and 2,3-butadien-1-ol by treatment with *N*-bromosuccinimide (Scheme 12). Radical cyclization with 1 equiv. of tin hydride furnished the intermediate bromotretrahydrofuran **21** (mixture of two isomers). Without isolation of bromide **21**, a second equiv. of tin hydride was added to the reaction mixture and the desired reduced acetal (*r*-2,*c*-3,*c*-4)-**22** was isolated as a 2:1 mixture with (*r*-2,*t*-3,*c*-4)-**22**. A better stereocontrol was obtained when a bulkier reducing agent such as tris(trimethylsilyl)silane[54,55] was used for the second reduction step. In this way, the desired product (*r*-2,*c*-3,*c*-4)-**22** was obtained in 62% yield in a one-pot procedure starting from **20**. Traces of organotin derivatives were removed by treatment of the reaction mixture with an aqueous NaOH solution.[56] Careful analysis of the crude product revealed that (*r*-2,*t*-3,*c*-4)-**22** was also present (*c*-3/*t*-3 4:1) together with 2% of non-identified isomers. The preferential formation of (*r*-2,*c*-3,*c*-4)-**22** is easily explained by reduction of the cyclic radical from the less hindered face *anti* to the two vicinal substituents (model **D**).[57]

The synthesis of racemic botryodiplodin (±)-**1** was achieved by hydrolysis of the acetal **22** (10% HCl) followed by Wacker oxidation ($PdCl_2/Cu(OAc)_2/O_2$)[58] of the lactol **23** (Scheme 13). Under these mild conditions, the unstable botryodiplodin was obtained as a mixture of anomers. Physical and spectral data are in accordance with literature data.[3,14] For further characterization, the lactol was transformed to the known (±)-botryodiplodin acetate **16**.[3,9]

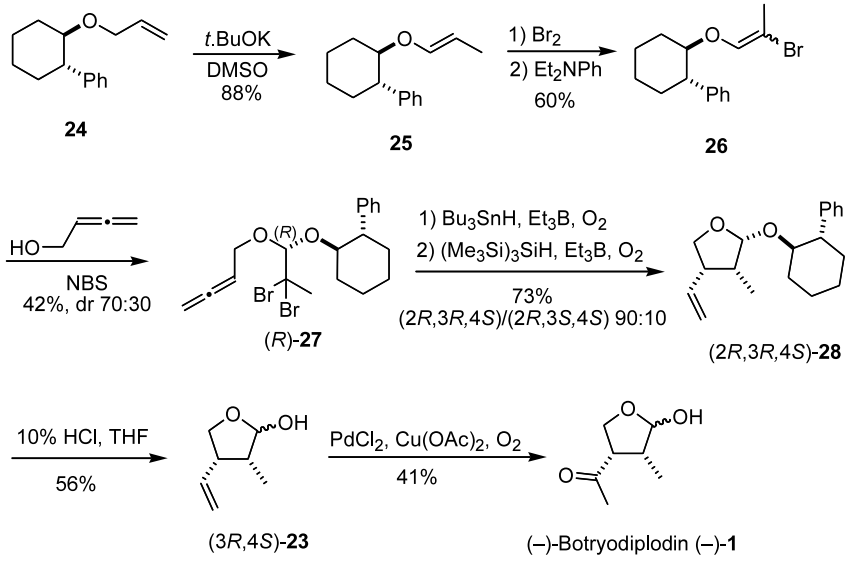
The preparation of enantiomerically pure (−)-botryodiplodin (−)-**1** was examined next (Scheme 14). For this purpose, we decided to start with easily available



Scheme 12.



Scheme 13.



Scheme 14.

(1*R*,2*S*)-2-phenylcyclohexanol as a chiral auxiliary.[59] Allylation of the alcohol gave the allyl ether **24** in quantitative yield. The double bond was isomerized under basic conditions to afford the *cis*-1-propenyl ether **25**. Bromination of the double bond followed by elimination reaction gave the β-bromopropenyl ether **26** in 60% yield. Treatment of **26** with NBS in the presence of 2,3-butadien-1-ol led to the *gem*-dibromoacetal **27** in 42% yield as a 70:30 mixture of diastereoisomers which were separated by flash chromatography. Cyclization of the major isomer (*R*)-**27** was carried out in one pot by adding first 1.2 equiv. of Bu_3SnH followed by 1.2 equiv. of $(Me_3Si)_3SiH$ to give the reduced cyclic acetal **28** in 73% yield and good diastereoselectivity (3*R*/3*S* 90:10) (Scheme 14). Separation of the diastereomers by flash chromatography gave the pure (2*R*,3*R*,4*S*)-**24**.

The synthesis of (–)-botryodiplodin was achieved by hydrolysis of the cyclic acetal (2*R*,3*R*,4*S*)-**28** to optically active **23**. At this stage, the chiral auxiliary (1*R*,2*S*)-2-phenylcyclohexanol was recovered in 61% yield. Finally, Wacker oxidation of the resulting lactol **23** led to (–)-botryodiplodin (–)-**1** as a mixture of anomers in 41% yield. The enantiomeric purity (>99% ee) was determined by GC analysis on a chiral column.

3. Conclusions

In conclusion, we have examined several different routes for the stereoselective synthesis of botryodiplodin. Zard intramolecular radical allylation of a 2-iodopropionate derivative allows to synthesize racemic botryodiplodin. However, the relative configuration of the final product has to be corrected by a deprotonation–reprotonation step. The related intramolecular allylation of acetals was not satisfactory due to the instability of the intermediates under our reaction conditions and poor stereocontrol. Finally, the cyclization of allenyl bromoacetals proved to be satisfactory for the synthesis of racemic botryodiplodin. A good stereocontrol was achieved by cyclizing a *gem*-dibromide followed by the stereoselective reduction of the formed cyclic monobromide. The use of (1*R*,2*S*)-2-phenylcyclohexanol as chiral auxiliary allows enantiomerically pure (–)-botryodiplodin to be prepared. These results demonstrate that the *gem*-dibromoacetal method is suitable for asymmetric synthesis of polysubstituted γ-lactones, a motive frequently encountered in biologically active natural products.

4. Experimental

4.1. General

THF was freshly distilled from K under N_2; CH_2Cl_2 from CaH_2 under N_2. Et_3B soln (1 M) in hexane was freshly prepared from commercially available Et_3B (95%, Aldrich). Other reagents were obtained from commercial sources and used as received. Flash column chromatography (FC) and filtration: Baker silica gel (0.063–0.200 mm); AcOEt, Et_2O and hexane as eluents. Thin-layer chromatography (TLC): Merck silica gel 60 F_{254} analytical plates; detection either with UV or by spraying with a soln of vanilin and subsequent heating. Semi-preparative high-pressure liquid chromatography (HPLC): Waters 610 fitted with two columns in series (25×100 mm) Prep Nova-Pak® HR silica 6 μm 60 Å. Gas chromatography (GC): Shimadzu GC-14A fitted with a capillary column J&W (DB-1, 30 m, ∅ 0.32 mm, N_2 1 bar). FT-IR: Mattson Unicam 5000. NMR: Varian Gemini 200 ($^1H = 200$ MHz, $^{13}C = 50.3$ MHz), Bruker AM 360 ($^1H = 360$ MHz), Bruker avance DRX 500 ($^1H = 500.13$ MHz, $^{13}C = 125.8$ MHz); chemical shift in ppm relative to tetramethylsilane (=0 ppm) or $CHCl_3$ (=7.26 ppm) for ^1H and $CDCl_3$ (=77.0 ppm) for ^{13}C. MS: Vacuum Generators Micromass VG 70/70E and DS 11-250; CI (CH_4), EI (70 eV); m/z (%). High resolution mass spectra (HRMS) were recorded on a FTICR mass spectrometer Bruker 4.7 BioApex II. Elementary analysis: Ilse Beetz, Microanalytisches Laboratorium, D-8640 Kronach (Germany).

4.2. Approach 1

4.2.1. 1-[(*E*)-4-(1-Ethoxyallyloxy)-2-methylbut-2-enylsulfanyl]-4-methylbenzene 4. A solution of **3** (1.0 g, 5.8 mmol), acrolein diethylacetal (3.15 g, 24.2 mmol) and PPTS (376 mg, 1.5 mmol) in CH_2Cl_2 (20 mL) was heated at reflux for 2 h. Meanwhile CH_2Cl_2 was distilled to remove EtOH, and fresh CH_2Cl_2 was gradually added to maintain the volume of the solution constant. After the solution was cooled to room temperature, 1 g of $NaHCO_3$ was added. The resulting slurry was concentrated and purified by FC (pentane/EtOAc 100:0 to 93:7) to give **4** (800 mg, 57%). ^1H NMR (200 MHz, $CDCl_3$): 7.25 (d, 2H, $J=8.6$ Hz, 2 arom. H), 7.06 (d, 2H, $J=8.6$ Hz, 2 arom. H), 5.80 (ddd, 1H, $J=15.4$, 10.5, 4.9 Hz, C*H*=CH_2), 5.4–5.2 (m, 3H, 3 vinyl. H), 4.75 (d, 1H, $J=4.9$ Hz, OC*H*(OEt)CH=CH_2), 4.02 (d, 2H, $J=6.9$ Hz, OCH_2CH=), 3.6–3.3 (m, 4H, OCH_2CH$_3$+CH_2STol), 2.30 (s, 3H, CH_3Ar), 1.75 (s, 3H, CH_3C=), 1.19 (t, 3H, $J=7.1$ Hz, CH_3CH$_2$O). ^{13}C NMR (50 MHz, $CDCl_3$): 136.4 (s), 135.2 (d), 134.9 (s), 132.1 (d), 131.1 (d), 129.3 (d), 124.6 (d), 118.2 (t), 100.4 (d), 61.4 (t), 60.8 (t), 44.4 (t), 20.9 (q), 15.4 (q), 15.1 (q). Anal. calcd for $C_{17}H_{24}O_2S$: C, 69.82; H, 8.27. Found: C, 69.78; H, 8.21.

4.2.2. 1-[(*E*)-4-(1-Ethoxyallyloxy)-2-methylbut-2-ene-1-sulfonyl]-4-methylbenzene 2. A slurry of **4** (120 mg, 0.41 mmol) and $NaHCO_3$ (154 mg, 1.85 mmol) in CH_2Cl_2 (4 mL) was cooled in an ice bath. Wet 70% *m*-CPBA (222 mg, 1 mmol) was slowly added to the slurry over 20 min, and the mixture was stirred for 3 h. The mixture was basified with 30% NH_4OH and extracted with CH_2Cl_2. The organic layer was successively washed with diluted NH_4OH, brine, dried over Na_2SO_4, concentrated, and purified by FC (pentane/EtOAc 90:10 to 80:20) to give **2** (90 mg, 68%). ^1H NMR (200 MHz, $CDCl_3$): 7.72 (d, 2H, $J=8.3$ Hz, 2 arom. H), 7.37 (d, 2H, $J=8.3$ Hz, 2 arom. H), 5.78 (ddd, 1H, $J=15.1$, 10.3, 4.6 Hz, C*H*=CH_2), 5.4–5.2 (m, 3H, 3 vinyl. H), 4.80 (d, 1H, $J=4.6$ Hz, OC*H*(OEt)CH=CH_2), 4.1–3.9 (m, 2H, OCH_2CH=), 3.74 (s, 2H, CH_2SO_2), 3.6–3.3 (m, 2H, OCH_2CH$_3$), 2.44 (s, 3H, CH_3Ar), 1.81 (s, 3H, CH_3C=), 1.20 (t, 3H, $J=6.8$ Hz, CH_3CH$_2$O). ^{13}C NMR (50 MHz, $CDCl_3$): 144.6 (s), 135.4 (s), 134.9 (d), 132.0 (d), 129.6 (d), 128.4 (d), 127.1 (s), 118.4 (t), 100.7 (d), 65.9 (t), 61.2 (t), 60.9 (t), 21.6 (q), 17.2 (q), 15.1 (q). Anal. calcd for $C_{17}H_{24}O_4S$: C, 62.94; H, 7.46. Found: C, 62.91; H, 7.36.

4.2.3. Cyclization of 2: 2-Ethoxy-4-isopropenyl-3-(toluene-4-sulfonylmethyl)tetrahydrofuran 5 and 3-isopropenyl-4-(toluene-4-sulfonylmethyl)-2,3-dihydrofuran 6. A solution of **2** (90 mg, 0.28 mmol) in degassed benzene (10 mL) was stirred at reflux for 10 h. Every 1 h, $TolSO_2SePh$ and AIBN were added by portions (total amount: 19 mg (0.06 mmol) and 3 mg (0.02 mmol), respectively). The solution was concentrated and the oily residue was purified by semi-preparative HPLC on silica gel (trimethylpentane/AcOEt 95:5, 30 mL/min) to give by order of elution: (*r*-2,*c*-3,*t*-4)-**5** (17 mg), **6** (11 mg), (*r*-2,*c*-3,*c*-4)-**5** (20 mg), (*r*-2,*t*-3,*t*-4)-+**5** (18 mg), global yield 75%.

(*r*-2,*c*-3,*t*-4)-**5**. ^1H NMR (400 MHz, $CDCl_3$): 7.80 (d, 2H, $J=8.2$ Hz, 2 arom. H), 7.35 (d, 2H, $J=8.2$ Hz, 2 arom. H), 4.88 (d, 1H, $J=4.5$ Hz, OC*H*(OEt)CH), 4.82 (br s, 1H, =CH_2), 4.73 (s, 1H, =CH_2), 3.95 (pseudo t, 1H, $J=8.6$ Hz, OCH*H*CH), 3.62 (dq, 1H, $J=9.6$, 7.2 Hz, OC*H*HCH$_3$), 3.58 (pseudo t, 1H, $J=8.4$ Hz, OC*H*-HCH), 3.57 (dd, 1H, $J=14.3$, 11.0 Hz, C*H*HTs), 3.19 (dq, 1H, $J=9.6$, 7.2 Hz, OCH*H*CH$_3$), 3.0 (dd, 1H, $J=14.3$, 1.8 Hz, CH*H*Ts), 2.73 (pseudo dt, 1H, $J=$ 11.0, 8.6 Hz, C*H*CH$_2$O), 2.43 (s, 3H, CH_3Ar), 2.40 (superimposed tdd, 1H, $J=11.0$, 4.5, 1.8 Hz, C*H*CH$_2$Ts), 1.51 (s, 3H, CH_3C=CH_2), 1.1 (t, 3H, $J=7.2$ Hz, CH_3CH$_2$O). ^{13}C NMR (50 MHz, $CDCl_3$): 144.7 (s), 141.3 (s), 136.6 (s), 129.8 (d), 128.1 (d), 114.5 (t), 102.2 (d), 69.2 (t), 63.2 (t), 54.0 (t), 49.3 (d), 41.5 (d), 21.6 (q), 18.4 (q), 15.2 (q).

(*r*-2,*c*-3,*c*-4)-**5**. ^1H NMR (400 MHz, $CDCl_3$): 7.77 (d, 2H, $J=8.1$ Hz, 2 arom. H), 7.32 (d, 2H, $J=8.1$ Hz, 2 arom. H), 4.88 (s, 1H, =CH_2), 4.78 (d, 1H, $J=5.1$ Hz, OC*H*(OEt)CH), 4.76 (s, 1H, =CH_2), 3.94 (pseudo t, 1H, $J=8.7$ Hz, OC*H*HCH), 3.74 (dd, 1H, $J=8.9$, 6.6 Hz, OCH*H*CH), 3.59 (dq, 1H, $J=9.4$, 7.1 Hz, OC*H*HCH$_3$), 3.45 (dd, 1H, $J=14.5$, 10.0 Hz, C*H*HTs), 3.12 (dq, 1H, $J=9.4$, 7.2 Hz, OCH*H*CH$_3$), 3.05 (dd, 1H, $J=14.5$, 2.8 Hz, CH*H*Ts), 3.02 (superimposed ddd, 1H, $J=11.0$, 8.7, 6.6 Hz, C*H*CH$_2$O), 2.75 (dddd, 1H, $J=11.0$, 10.0, 5.1, 2.8 Hz, C*H*CH$_2$Ts), 2.40 (s, 3H, CH_3Ar), 1.66 (s, 3H, CH_3C=CH$_2$), 1.06 (t, 3H, $J=7.1$ Hz, CH_3CH$_2$O). 13C (50 MHz, $CDCl_3$): 144.6 (s), 142.7 (s), 136.7 (s),

129.8 (d), 128.1 (d), 116.8 (t), 102.0 (d), 69.0 (t), 62.8 (t), 53.1 (t), 47.3 (d), 40.7 (d), 21.6 (q), 20.6 (q), 15.0 (q).

(*r*-2,*t*-3,*t*-4)-**5**. ^{1}H NMR (400 MHz, $CDCl_3$): 7.80 (d, 2H, $J=8.0$ Hz, 2 arom. H), 7.35 (d, 2H, $J=8.0$ Hz, 2 arom. H), 4.92 (s, 1H, OC*H*(OEt)CH), 4.49 (s, 1H, =CH_2), 4.55 (s, 1H, =CH_2), 3.95 (pseudo t, 1H, $J=8.0$ Hz, OC*H*HCH), 3.72 (pseudo t, 1H, $J=9.0$ Hz, OCH-*H*CH), 3.62 (dq, 1H, $J=9.6$, 7.1 Hz, OC*H*HCH_3), 3.35 (dq, 1H, $J=9.6$, 7.1 Hz, OCH*H*CH_3), 3.21 (pseudo q, 1H, $J=8.0$ Hz, OCH_2C*H*), 2.92–2.79 (ABX pattern, 2H, $J_{AB}=14.6$ Hz, $J_{AX}=10.6$ Hz, $J_{BX}=2.4$ Hz, CH_2Ts), 2.65 (ddd, 1H, $J=10.6$, 7.2, 2.4 Hz, C*H*CH_2Ts), 2.40 (s, 3H, CH_3Ar), 1.55 (s, 3H, CH_3C=), 1.15 (t, 3H, $J=7.1$ Hz, CH_3CH_2O). 13C (100 MHz, $CDCl_3$): 145.0 (s), 141.0 (s), 136.5 (s), 130.18 (d), 128.5 (d), 113.4 (t), 106.6 (d), 68.3 (t), 63.3 (t), 53.6 (t), 46.4 (d), 42.2 (d), 23.2 (q), 21.8 (q), 15.3 (q).

6. ^{1}H NMR (200 MHz, $CDCl_3$): 7.75 (d, 2H, $J=8.3$ Hz, 2 arom. H), 7.35 (d, 2H, $J=8.3$ Hz, 2 arom. H), 6.2 (s, 1H, OC*H*=), 4.82 (br s, 1H, =CH*H*), 4.72 (br s, 1H, =C*H*H), 4.41 (dd, 1H, =CH, $J=10.5$, 9.3 Hz, OC*H*-HCH), 4.19 (dd, 1H, $J=10.5$, 5.9 Hz, OCH*H*CH), 3.78 (br d, 1H, $J=14.4$ Hz, C*H*HTs), 3.72 (br d, 1H, $J=14.4$ Hz, CH*H*Ts), 3.60 (superimposed m, 1H, C*H*CH_2O), 2.45 (s, 3H, CH_3Ar), 1.60 (br s, 3H, CH_3C=CH_2). ^{13}C NMR (50 MHz, $CDCl_3$): 148.3 (d), 144.6 (s), 142.9 (s), 135.5 (s), 129.6 (d), 128.4 (d), 113.8 (t), 104.1 (s), 74.8 (t), 52.8 (t), 51.0 (d), 21.5 (q), 18.1 (q).

4.2.4. Cyclization of 4: 2-Ethoxy-4-isopropenyl-3-(toluene-4-sulfonylmethyl)tetrahydrofuran 5. To a solution of **4** (200 mg, 0.68 mmol) in refluxing degassed benzene (14 mL) was added over 5 h with a syringe pump a solution of thiocresol (17 mg, 0.14 mmol) and AIBN (23 mg, 0.14 mmol) in benzene (1 mL). After the end of the addition, the mixture was refluxed for 1 h and then concentrated. CH_2Cl_2 (6 mL) was added to the residue followed by *m*-CPBA (293 mg, 1.7 mmol) and $NaHCO_3$ (571 mg, 6.8 mmol) at 0°C. Once the oxidation completed (TLC monitoring), the crude reaction was washed with H_2O and dried over Na_2SO_4. After concentration, the crude product was purified by filtration through a short pad of silica gel yielding a mixture of the four diastereoisomers of **5** (106 mg, 0.33 mmol, 49%) in a 15:39:17:19 ratio.

4.3. Approach 2

4.3.1. (*E*)-3-Methyl-4-(toluene-4-sulfonyl)but-2-en-1-ol 8. A slurry of 4-chloro-3-methylbut-2-en-1-ol (400 mg, 2.46 mmol), sodium *p*-toluenesulfinate (1.93 g, 5.4 mmol) and TBAB (200 mg) in a mixture of acetone (4 mL), benzene (4 mL) and H_2O (5 mL) was stirred at 60°C for 15 h. The mixture was cooled, diluted with water (10 mL) and extracted with Et_2O (3×10 mL). The combined organic layers were dried over Na_2SO_4, concentrated and the residue was purified by FC (pentane/EtOAc 80:20 to 60:40) to give **8** (240 mg, 41%). ^{1}H NMR (200 MHz, $CDCl_3$): 7.74 (d, 2H, $J=8.3$ Hz, 2 arom. H), 7.25 (d, 2H, $J=8.3$ Hz, 2 arom. H), 5.25 (t, 1H, $J=6.4$ Hz, =C*H*CH_2OH), 4.08 (d, 2H, $J=6.4$ Hz, =CHCH_2OH), 3.72 (s, 2H, CH_2SO_2), 2.43 (s, 3H, CH_3Ar), 2.33 (s broad, 1H, O*H*), 1.78 (s, 3H, CH_3C=). 13C (50 MHz, $CDCl_3$): 144.8 (s), 135.5 (s), 134.7 (s), 129.6 (d), 128.3 (d), 126.0 (d), 65.9 (t), 58.9 (t), 21.6 (q), 17.1 (q).

4.3.2. 2-Bromopropionic acid (*E*)-3-methyl-4-(toluene-4-sulfonyl)but-2-enyl ester 9. To a solution of **8** (440 mg, 1.83 mmol) and Et_3N (0.56 mL) in CH_2Cl_2 (15 mL), cooled at −40°C, 2-bromopropionyl bromide (412 mg, 1.9 mmol) was added. The solution was stirred for 2 h at −20°C, warmed to 0°C, and acidified with 1N HCl. The organic layer was washed successively with 1N HCl, saturated $NaHCO_3$ and brine, dried over Na_2SO_4, concentrated, and purified by FC (pentane/EtOAc 80:20 to 70:30) to give **9** (450 mg, 66%). ^{1}H NMR (200 MHz, $CDCl_3$): 7.75 (d, 2H, $J=8.3$ Hz, 2 arom. H), 7.35 (d, 2H, $J=8.3$ Hz, 2 arom. H), 5.28 (br t, 1H, $J=6.8$ Hz, =C*H*CH_2O), 4.60 (m, 2H, CH_2O), 4.33 (q, 1H, $J=6.9$ Hz, C*H*BrCH_3), 3.75 (s, 2H, CH_2Ts), 2.45 (s, 3H, CH_3Ar), 1.85 (br s, 3H, CH_3C=), 1.79 (d, $J=6.0$ Hz, 3H, CH_3CHBr). 13C (50 MHz, $CDCl_3$): 169.5 (s), 144.5 (s), 135.0 (s), 130.1 (s), 129.5 (d), 128.2 (d), 127.9 (d), 65.4 (t), 61.6 (t), 39.6 (d), 21.4 (q), 21.3 (q), 17.2 (q). Anal. calcd for $C_{15}H_{19}O_4SBr$: C, 48.01; H, 5.10. Found: C, 47.83; H, 4.92.

4.3.3. Cyclization of 9: 4-Isopropenyl-3-methyldihydrofuran-2-one 10 and propionic acid (*E*)-3-methyl-4-(toluene-4-sulfonyl)but-2-enyl ester 11. A solution of **9** (150 mg, 0.4 mmol) and Bu_3SnCl (0.180 mL, 0.4 mmol) in degassed benzene (9 mL) was heated at reflux for 12 h while a solution of Bu_3SnH (0.14 mL, 1.3 equiv.) and AIBN (7 mg, 0.1 equiv.) in benzene (1 mL) was added over a period of 11 h. After cooling the solution was concentrated, the residue was dissolved in *t*-BuOH (4 ml) and heated at reflux with $NaBH_3CN$ (34 mg, 0.54 mmol) for 1 h. The reaction mixture was concentrated and the residue dissolved in CH_2Cl_2 was washed with H_2O, dried over Na_2SO_4, concentrated, analyzed by GPC, and purified by chromatography on silica gel (pentane/EtOAc 100:0 to 70:30) to give 10 (25 mg, 45%) as a 40:60 mixture of *cis*/*trans* isomers (cf. part 4.3.7. for the separation and for spectral data of each isomer), and 11 (28 mg, 23%).

11: ^{1}H NMR (200 MHz, $CDCl_3$): 7.55 (d, 2H, $J=8.3$ Hz, 2 arom. H), 7.35 (d, 2H, $J=8.3$ Hz, 2 arom. H), 5.25 (t, 1H, $J=6.8$ Hz, =C*H*CH_2O), 4.55 (d, 2H, $J=6.8$ Hz, CH_2O), 3.75 (s, 2H, CH_2Ts), 2.45 (s, 3H, CH_3Ar), 2.30 (q, 2H, $J=7.0$ Hz, CH_2CH$_3$), 1.80 (s, 3H, CH_3C=), 1.10 (t, 3H, $J=7.0$ Hz, CH$_2$CH_3).

4.3.4. (*E*)-4-Ethylsulfanylbut-2-en-1-ol 12. To a solution 4-chloro-3-methylbut-2-en-1-ol acetate (3.0 g, 18.4 mmol) in THF (30 mL) was slowly added a solution of EtSNa (2.10 g, 36.8 mmol) in EtOH (30 mL). After the solution was stirred for 4 h, the reaction mixture was concentrated, and dissolved in Et_2O. The organic layer was washed with water, and the aqueous layer was extracted with Et_2O (3×30 mL). The combined organic layers were dried over Na_2SO_4, concentrated and

purified by chromatography on silica gel (pentane/EtOAc 97:3 to 90:10) to give **12** (1.5 mg, 56%). ^{1}H NMR (200 MHz, $CDCl_3$): 5.40 (t, 1H, $J=6.6$ Hz, =C*H*CH$_2$O), 4.05 (d, 2H, $J=6.6$ Hz, CH$_2$O), 3.0 (s, 2H, CH$_2$S), 2.75 (br s, 1H, O*H*), 2.30 (q, 2H, $J=7.6$ Hz, CH$_3$CH$_2$S), 1.65 (s, 3H, CH$_3$C=), 1.10 (t, 3H, $J=7.6$ Hz, CH$_3$CH$_2$S). ^{13}C NMR (50 MHz, $CDCl_3$): 134.2 (s), 126.2 (d), 58.7 (t), 40.3 (t), 24.6 (t), 14.9 (q), 14.2 (q).

4.3.5. 2-Bromopropionic acid (*E*)-4-ethanesulfonyl-3-methylbut-2-enyl ester 13. To a solution of **12** (500 mg, 3.44 mmol) in CH_2Cl_2 (3 mL) was added pyridine (306 μl, 3.8 mmol). The solution was cooled in an ice bath, treated with 2-bromopropionyl bromide (817 mg, 3.8 mmol) and stirred for 1 h. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed twice with H_2O. The organic layer was dried over Na_2SO_4 and concentrated. The residue was dissolved in MeOH (10 mL) and cooled at 0°C. A cooled solution of Oxone® (6.26 g, 3 equiv.) in H_2O (15 mL) was added. The reaction mixture was stirred for 2 h and $CHCl_3$ (30 mL) was added. After extraction with $CHCl_3$ (3×15 mL), the combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by FC (pentane/EtOAc 80:20 to 70:30) to give **13** (660 mg, 62%; the yield was improved up to 78% when starting from 3.3 g of **12**). ^{1}H NMR (200 MHz, $CDCl_3$): 5.60 (t, 1H, $J=6.8$ Hz, =C*H*CH$_2$O), 4.70 (m, 2H, CH$_2$O), 4.35 (q, 1H, $J=6.8$ Hz, C*H*BrCH$_3$), 3.65 (s, 2H, CH$_2$SO$_2$), 2.95 (q, 2H, $J=7.5$ Hz, CH$_3$CH$_2$SO$_2$), 1.85 (s, 3H, CH$_3$C=), 1.72 (d, 3H, $J=6.8$ Hz, CHBrCH$_3$), 1.27 (t, 3H, $J=7.5$ Hz, CH$_3$CH$_2$SO$_2$). ^{13}C NMR (50 MHz, $CDCl_3$): 169.4 (s), 130.5 (s), 127.3 (d), 61.4 (t), 60.9 (t), 45.4 (t), 39.7 (d), 21.1 (q), 16.8 (q), 6.0 (q). Anal. calcd for $C_{10}H_{17}O_4SBr$: C, 38.35; H, 5.47. Found: C, 38.25; H, 5.43.

4.3.6. 2-Iodopropionic acid (*E*)-4-ethanesulfonyl-3-methylbut-2-enyl ester 14. To a solution of **13** (157 mg, 0.5 mmol) in acetone (0.5 mL) was added NaI (105 mg, 0.7 mmol). The solution was stirred in the dark for 1 h, Et_2O (2 mL) was added, and the slurry was filtered through a pad of silica gel, the pad was washed with Et_2O. The filtrate was concentrated at low temperature in the dark to give **14** (180 mg, quantitative) pure enough to be used in the following step without further purification. ^{1}H NMR (200 MHz, $CDCl_3$): 5.63 (t, 1H, $J=6.8$ Hz, =C*H*CH$_2$O), 4.66 (m, 2H, CH$_2$O), 4.40 (q, 1H, $J=7.1$ Hz, C*H*ICH$_3$), 3.60 (s, 2H, CH$_2$SO$_2$), 2.95 (q, 2H, $J=7.6$ Hz, CH$_3$CH$_2$SO$_2$), 1.95 (s, 3H, CH$_3$C=), 1.85 (d, 3H, $J=7.1$ Hz, CHICH$_3$), 1.33 (t, 3H, $J=7.6$ Hz, CH$_3$CH$_2$SO$_2$). ^{13}C NMR (50 MHz, $CDCl_3$): 171.7 (s), 130.9 (s), 127.8 (d), 61.7 (×2 t), 45.8 (t), 23.2 (q), 17.4 (q), 12.7 (d), 6.5 (q).

4.3.7. Cyclization of 14: 4-Isopropenyl-3-methyldihydrofuran-2-one 10. A solution of **14** (5.3 g 14.71 mmol) and hexabutylditin (2.2 mL, 4.41 mmol) in degassed benzene (74 mL) was irradiated for 5 h with a 300 W sun lamp, while heating at reflux. The benzene was slowly evaporated and the residue was bulb to bulb distilled (150°C, 20 mbar). The cyclized product **10** was obtained as a *cis*/*trans* 40:60 mixture. The residue, that still contained cyclization products, was dissolved in EtOH and 50% aqueous NaOH was added. The solution was heated at reflux for 1 h, cooled and concentrated. The residue was dissolved in H_2O and extracted with Et_2O (3×10 mL) to remove the tin derivatives. The aqueous layer was acidified with 1N HCl and extracted with Et_2O (5×10 mL). The combined organic extracts were dried over Na_2SO_4, concentrated, and purified by FC (pentane/EtOAc 100:0 to 95:5) to give an additional crop of **10** as a *cis*/*trans* 20:80 mixture (very volatile; global yield: 1.29 g, 63%). Pure samples of both stereoisomers of **10** were obtained by semi-preparative HPLC on silica gel (trimethylpentane/EtOAc 96:4, 20 mL/min).

trans-**10**: ^{1}H NMR (200 MHz, $CDCl_3$): 4.91 (br s, 1H, CH$_2$=C), 4.85 (s, 1H, CH$_2$=C), 4.33 (dd, 1H, $J=9.0$, 8.1 Hz, C*H*HO), 3.90 (dd, 1H, $J=10.3$. 9.0 Hz, CH*H*O), 2.75 (pseudo td, 1H, $J=10.7$, 8.1 Hz, C*H*CH$_2$O), 2.50 (dq, 1H, $J=11.2$, 7.0 Hz, C*H*CH$_3$), 1.70 (s, 3H, CH$_3$C=), 1.20 (d, $J=7.0$ Hz, 3H, CH$_3$CH). (50 MHz, $CDCl_3$): 179.1 (s), 140.5 (s), 113.8 (t), 69.4 (t), 51.1 (d), 38.0 (d), 19.6 (q), 13.6 (q).

cis-**10**: ^{1}H NMR (200 MHz, $CDCl_3$): 4.80 (br s, 1H, CH$_2$=C), 4.65 (s, 1H, CH$_2$=C), 4.24 (dd, 1H, $J=9.5$, 6.1 Hz, C*H*HO), 4.12 (dd, 1H, $J=9.5$, 3.9 Hz, CH*H*O), 3.05 (ddd, 1H, $J=8.1$, 6.1, 3.9 Hz, C*H*CH$_2$O), 2.64 (dq, 1H, $J=8.1$, 7.3 Hz, C*H*CH$_3$), 1.55 (br s. 3H, CH$_3$C=), 0.98 (d, $J=7.3$ Hz, 3H, CH$_3$CH). ^{13}C NMR (50 MHz, $CDCl_3$): 179.2 (s), 141.4 (s), 113.8 (t), 69.6 (t), 46.2 (d), 36.9 (d), 20.6 (q), 9.9 (q).

10 (mixture of diastereomers): Anal. calcd for $C_8H_{12}O_2$: C. 68.55; H, 8.63. Found: C, 68.52; H, 8.60.

4.3.8. Isomerization of 10. To a solution of LDA (1.646 g of *i*-Pr$_2$NH and 11.8 mL of 1.25 M *n*-BuLi in hexane) in THF (50 mL) cooled at −20°C was added a *cis*/*trans* 40:60 mixture of **10** (1.14 g, 8.1 mmol). The solution was stirred at −20°C for 20 min and then warmed up to 0°C. This solution was added to a solution of camphorsulfonic acid (CSA, 5.66 g, 3 equiv.) in CH_2Cl_2 (50 mL) at −100°C. The reaction mixture was stirred and warmed from −100°C to room temperature, and then saturated $NaHCO_3$ (10 mL) was added with vigorous stirring. After extraction with CH_2Cl_2, the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The crude residue was a *cis*/*trans* 82:18 mixture of isomers, as determined by ^{1}H NMR (based on the signals of vinylic protons at 4.85 and 4.65 ppm, *trans*-**10** and *cis*-**10**, respectively), GC and HPLC (*iso*-octane/EtOAc 96:4, 2 mL/min, retention time 3.9 and 6.1 min for *trans*-**10** and *cis*-**10**, respectively). It was purified as previously decribed to give **10** (1.0 g, 88%). The mixture was separated by semi-preparative chromatography on silica gel (trimethylpentane/EtOAc 96:4, 20 mL/min) which provided pure *cis*-**10** (0.75 g).

4.3.9. Acetic acid 4-acetyl-3-methyltetrahydrofuran-2-yl ester 16. A solution of *cis*-**10** (70 mg, 0.5 mmol) in CH_2Cl_2 (6 mL) was cooled at −78°C. DIBALH (1 M in

hexane, 1.25 mL, 1.25 mmol) was added and the mixture was stirred for 15 min. The reaction mixture was treated with MeOH (0.5 mL) and a solution of Rochelle salt (15 mL, 12.5 equiv.) and saturated NH_4Cl (15 mL) were added. The mixture was extracted with CH_2Cl_2, the organic extracts were dried over Na_2SO_4, concentrated, and purified by FC (pentane/EtOAc 95:5 to 70:30) to give **15** (60 mg, 85%) as a single epimer at C2. ^{1}H NMR (200 MHz, $CDCl_3$): 5.18 (s, 1H, *H*2), 4.89 (pseudo sext, 1H, $J=1.2$ Hz, =CH_2), 4.60 (br s, 1H, =CH_2), 4.12 (pseudo t, 1H, $J=7.9$ Hz, C*H*HO), 3.96 (pseudo t, 1H, $J=8.9$ Hz, CH*H*O), 3.15 (pseudo q, 1H, $J=7.9$ Hz, C*H*CH_2O), 2.31 (pseudo quint, 1H, $J=7.3$ Hz, C*H*CH_3), 1.75 (br s, 3H, CH_3C=), 0.80 (d, 3H, $J=7.1$ Hz, CH_3CH), (OH not observed). ^{13}C NMR (50 MHz, $CDCl_3$): 141.9 (s), 111.4 (t), 104.5 (d), 68.9 (t), 46.2 (d), 42.2 (d), 23.3 (q), 11.4 (q). Anal. calcd for $C_8H_{14}O_2$: C. 67.57; H, 9.92. Found: C, 67.55; H, 9.91.

The ozonolyzis of **15** was conducted according to literature.[19] The ^{1}H spectrum of botryodiplodin **1** in $CDCl_3$ resulted from an equilibrium between the different isomeric forms. Acetylation according to literature procedure produced the known acetate **16**.[14] ^{1}H NMR data were very similar to those described in the literature.[2,9] Only one epimer at C(2) was detected. ^{1}H NMR (200 MHz, $CDCl_3$): 5.95 (s, 1H, OC*H*O), 4.35 (pseudo t, 1H, $J=8.5$ Hz, C*H*HO), 4.1 (pseudo t, 1H, $J=9.0$ Hz, CH*H*O), 3.7–3.5 (m, 1H, C*H*CH_2O), 2.69 (pseudo quint, 1H, $J=8.0$ Hz, C*H*CH_3), 2.22 (s, 3H, CH_3C=O), 2.07 (s, 3H, CH_3C=O), 0.9 (d, 3H, $J=7.3$ Hz, CH_3CH).

4.4. Approach 3

4.4.1. 1-[2-Bromo-3-(2,3-butadienyloxy)-3-methoxypropyl]benzene 17. To a soln of 1-methoxy-3-phenylpropene (1.23 g, 8.3 mmol) and 2,3-butadien-1-ol (0.58 g, 8.3 mmol) in CH_2Cl_2 was added at −30°C NBS (1.48 g, 8.3 mmol) in portions. The mixture was stirred at −20°C for 3 h, diluted with hexane, filtered and washed successively with KOH (5%), H_2O and sat. NaCl. The organic phase was dried and concentrated under reduced pressure to give the bromoacetal **17** (1.5 g, 61%) as a yellow oil.

Mixture of diastereoisomers. IR (KBr): 3030, 2933, 2835, 1955, 1604, 1454, 1354, 1120, 1060, 850 cm^{-1}. ^{1}H NMR (360 MHz, $CDCl_3$): 7.35–7.21 (m, 5 arom. H), 5.33–5.24 (m, 1H, C*H*=C=CH_2), 4.84–4.81 (m, 2H, CH=C=CH_2), 4.57 (d, 1H, $J=4.6$ Hz, MeOC*H*CHBr, 1 diast.), 4.54 (d, 1H, $J=5.2$ Hz, MeOC*H*CHBr, 2 diast.), 4.20–4.14 (m, 3H, OCH_2CH=C, MeOCHC*H*Br), 3.49 (s, 3H, CH_3O, 1 diast.), 3.47 (s, 3H, CH_3O, 2 diast.), 3.41 (dd, 1H, $J=3.4$, 14.7 Hz, CHBrC*H*HPh), 3.02 (dd, 1H, $J=10.1$, 14.7 Hz, CHBrCH*H*Ph). ^{13}C NMR (50 MHz, $CDCl_3$). Diastereoisomer 1: 209.5 (s), 138.1 (s), 129.3 (d), 128.3 (d), 126.7 (d), 104.1 (d), 87.4 (d), 76.1 (t), 66.0 (t), 56.0 (d), 55.4 (q), 38.9 (t). Diastereoisomer 2: 103.6 (d), 87.3 (d), 66.2 (t), 39.4 (t). CI-MS (CH_4) *m*/*z* (%): 229 ($M^+[Br^{81}]$–69, 39), 227 ($M^+[Br^{79}]$–69, 38), 197 (76), 195 (79), 151 (49), 149 (57), 147 (54), 133 (86), 119 (39), 91 (100), 85 (27), 61 (31). Anal. Calcd. for $C_{14}H_{17}O_2Br$ (297.19): C, 56.58; H, 5.77. Found: C, 56.52; H, 5.72.

4.4.2. 3-Benzyl-2-methoxy-4-vinyltetrahydrofuran 18. To a soln of **17** (1.0 g, 3.4 mmol) and Bu_3SnH (1.2 g, 4.1 mmol) in toluene (84 mL) was added a 1 M soln of Et_3B in hexane (4.7 mL, 4.7 mmol) at −78°C followed by air (3 mL). The soln was kept at −78°C for 3 h. A 1 M NaOH soln (45 mL) was added and the heterogeneous mixture was stirred for 2 h at rt. The organic layer was washed with H_2O, dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by FC (hexane/Et_2O 40:1) to afford the cyclic acetal **18** (0.61 g, 82%) as a 52:11:37 mixture of three diastereoisomers.

IR (KBr): 3078, 3028, 2912, 2831, 1494, 1454, 1041 cm^{-1}. ^{1}H NMR (360 MHz, $CDCl_3$). Major diastereoisomer: 7.30–7.15 (m, 5 Arom. H), 6.04 (dt, 1H, $J=10.1$, 17.1 Hz, C*H*=CH_2), 4.97–4.90 (m, 2H, CH=CH_2), 4.66 (d, 1H, $J=4.3$ Hz, MeOC*H*CHBn), 4.12 (dd, 1H, $J=7.6$, 8.5 Hz, OC*H*HCH=CH_2), 3.74 (dd, 1H, $J=3.4$, 8.5 Hz, OCH*H*CH=CH_2), 3.34 (s, 3H, OCH_3), 2.89–2.39 (m, 4H). Second diastereoisomer: 5.69 (ddd, 1H, $J=8.5$, 9.5, 17.4 Hz, C*H*=CH_2), 4.73 (d, 1H, $J=2.8$ Hz, MeOC*H*CHBn), 4.00 (t, 1H, $J=8.5$ Hz, OC*H*-HCH=CH_2), 3.66 (t, 1H, $J=8.9$ Hz, OCH*H*CH=CH_2). CI-MS (CH_4) *m*/*z* (%): 219 (M^++1, 7), 187 (100), 169 (67), 157 (86), 129 (23), 117 (29), 91 (66). Anal Calcd. for $C_{14}H_{18}O_2$ (218.30): C, 77.03; H, 8.31. Found: C, 77.07; H, 8.31.

4.4.3. 4-(2,2-Dibromo-1-ethoxypropoxy)-1,2-butadiene 20. To a soln of (*Z*/*E*)-β-bromopropenyl ethyl ether **19** (1.65 g, 10 mmol) and 2,3-butadien-1-ol (0.70 g, 10 mmol) in CH_2Cl_2 (15 mL) cooled at −20°C was added NBS (1.78 g, 10 mmol) in portions. The mixture was stirred at the same temperature for 2 h. Then hexane was added to precipitate the succinimide. After filtration, the organic phase was washed succesively with KOH (5%), H_2O and NaCl. Dried with $MgSO_4$ and the solvent removed under reduced pressure. Purification by FC (hexane/Et_2O 20:1) gave the dibromoacetal **20** (1.75 g, 56%) as a colorless oil.

IR (KBr): 2980, 2930, 2881, 1955, 1442, 1373, 1105, 1068, 910, 871 cm^{-1}. ^{1}H NMR (360 MHz, $CDCl_3$): 5.31 (q, 1H, $J=7$ Hz, OCH_2C*H*=C=CH_2), 4.83 (td, 2H, $J=2.1$, 6.4 Hz, OCH_2CH=C=CH_2), 4.64 (s, 1H, OC*H*CBr_2Me), 4.40–4.37 (m, 2H, OCH_2CH=C=CH_2), 3.95–3.80 (m, 2H, OCH_2CH_3), 2.42 (s, 3H, CBr_2CH_3), 1.29 (t, 3H, $J=7.2$ Hz, OCH_2CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): 209.6 (s), 105.9 (d), 87.2 (d), 76.1 (t), 67.9 (t), 67.5 (t), 67.3 (s), 34.0 (q), 15.2 (q). CI-MS (CH_4) *m*/*z* (%): 247 (53), 245 (100), 243 (56), 183 (11), 181 (12), 153 (23), 101 (95), 99 (21).

4.4.4. (*r*-2,*c*-3,*c*-4)-2-Ethoxy-3-methyl-4-vinyltetrahydrofuran 22. A soln of **20** (1.43 g, 4.56 mmol) and Bu_3SnH (1.57 g, 5.4 mmol) in toluene (100 mL) was cooled at −78°C and a 1 M soln of Et_3B in hexane (6.4 mL, 6.4 mmol) was added followed by air (4.0 mL). The resulting soln was kept at −78°C for 3 h. Then $(TMS)_3SiH$ (1.34 g, 5.4 mmol) was added followed by air (4 mL). The resulting soln was kept at −78°C for 3 h. A 1 M NaOH soln (60 mL) was added and the

heterogeneous mixture was stirred for 2 h at rt. The organic layer was washed with H_2O, dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by FC (pentane/Et_2O 60:1) to afford (*r*-2,*c*-3,*c*-4)-**22** (0.44 g, 62%) as a colorless oil.

IR (KBr): 3076, 2976, 2881, 1639, 1428, 1078, 1043, 912 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): 5.96 (dt, 1H, $J=10.1$, 17.1 Hz, C*H*=CH_2), 4.98–4.92 (m, 2H, CH=CH_2), 4.91 (d, 1H, $J=4.7$ Hz, OC*H*CHMe), 4.06 (t, 1H, $J=7.6$ Hz, OC*H*HCHCH=CH_2), 3.77–3.68 (m, 2H, OCH*H*CHCH=CH_2, OC*H*HCH_3), 3.41 (dq, 1H, $J=7.1$, 9.8 Hz, OCH*H*CH_3), 2.77 (ddd, 1H, $J=4.3$, 9.3, 7.0 Hz, C*H*CH=CH_2), 2.38–2.10 (m, 1H, C*H*CH_3), 1.18 (t, 3H, $J=7.1$ Hz, OCH_2CH_3), 0.91 (d, 3H, $J=7.2$ Hz, CHCH_3). ^{13}C NMR (50 MHz, $CDCl_3$): 139.6 (d), 115.4 (t), 104.9 (d), 72.1 (t), 62.7 (t), 46.1 (d), 41.2 (d), 15.3 (q), 9.7 (q). CI-MS (CH_4): 157 (M^++1, 17, 155 (30), 139 (30), 127 (35), 126 (42), 111 (100), 87 (13). HRMS (CI-isobutane) calculated for $C_9H_{17}O_2$ ([M^++1]): 157.12230. Found: 157.12239.

4.4.5. 3-Methyl-4-vinyltetrahydro-2-furanol 23. A soln of (*r*-2,*c*-3,*c*-4)-**22** (163 mg, 1.04 mmol) in THF (2 mL) and 10% HCl (1 mL) was kept at rt for 30 min. After extraction with Et_2O, the organic phases were washed with sat. $NaHCO_3$ and H_2O, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by FC (pentane/Et_2O 1:1) to afford **23** (81 mg, 61%) as a mixture of two anomers.

^1H NMR (360 MHz, $CDCl_3$): Major diasteroisomer: 5.75 (ddd, 1H, $J=8.5$, 10.7, 16.8 Hz, C*H*=CH_2), 5.17–5.09 (m, 2H, CH=CH_2), 5.10 (d, 1H, $J=0.9$ Hz, HOC*H*CHMe), 4.14 (t, 1H, $J=8.2$ Hz, OC*H*-HCHCH=CH_2), 3.75 (t, 1H, $J=8.2$ Hz, OCH-*H*CHCH=CH_2), 3.15–3.04 (m, 1H, C*H*CH=CH_2), 2.73–2.68 (m, 1H, OH), 2.29–2.00 (m, 1H, C*H*CH_3), 0.94 (d, 3H, $J=7.3$ Hz, CHCH_3). Minor diasteroisomer: 5.96 (ddd, 1H, $J=9.2$, 10.4, 16.8 Hz, C*H*=CH_2), 5.34 (t, 1H, $J=4.6$ Hz, HOC*H*CHMe), 5.06–5.00 (m, 2H, CH=CH_2), 4.04 (dd, 1H, $J=7.0$, 8.6 Hz, OC*H*-HCHCH=CH_2), 3.90 (dd, 1H, $J=4.0$, 8.5 Hz, OCH-*H*CHCH=CH_2), 2.86–2.78 (m, 1H, C*H*CH=CH_2), 2.73–2.68 (m, 1H, OH), 2.59–2.53 (m, 1H, C*H*CH_3), 0.99 (d, 3H, CHCH_3).

4.4.6. (±)-Botryodiplodin (±)-1. A suspension of lactol (40 mg, 0.31 mmol), $PdCl_2$ (6 mg, 0.031 mmol) and $Cu(OAc)_2{\cdot}2H_2O$ (133 mg, 0.61 mmol) in *N*,*N*-dimethylacetamide/H_2O (7:1) (0.6 mL) was placed under oxygen and stirred at rt for 4 days. The mixture was diluted with Et_2O, filtered through Celite employing Et_2O to wash the filter cake, poured into water (3 mL) and extracted with Et_2O. The organic phases were dryed and evaporated under reduced pressure. The crude product was purified by FC (pentane/Et_2O 1:1) to furnish (±)-botryodiplodin **1** (27 mg, 38%).

^1H NMR (360 MHz, $CDCl_3$): 5.18 (s, 1H, HOC*H*CHMe), 4.28 (t, 1H, $J=8.9$ Hz, H5), 4.09–3.99 (m, H5 and H5′), 3.67 (q, 1H, $J=7.0$ Hz, H5′), 3.42 (dt, 1H, $J=2.8$, 7.6 Hz, H4), 2.91 (bs, 1H, OH), 2.61 (quint, 1H, $J=7.3$ Hz, H3), 2.51–2.40 (m, 1H, H3′), 2.29 (s, 3H, CH_3CO), 2.20 (s, 3H, CH'_3CO), 1.06 (d, 3H, $J=7.3$ Hz, CHCH_3), 0.86 (d, 3H, $J=7.0$ Hz, CHCH'_3). ^{13}C NMR (50 MHz, $CDCl_3$): 206.4 (s), 104.1 (d), 100.3 (d′), 69.8 (t′), 66.4 (t), 53.0 (d), 52.8 (d′), 42.5 (d), 41.2 (d′), 32.3 (q′), 30.3 (q), 12.3 (q), 9.5 (q′). CI-MS (CH_4) *m*/*z* (%): 145 (M^++1, 6), 127 (M^++1−H_2O, 100), 97 (5), 83 (17). HRMS (ESI) for $C_7H_{12}O_3Na$: calculated 167.06786; found 167.06780.

4.4.7. (1*R*,2*S*)-2-Phenylcyclohexyl 2-propenyl ether 24. A round-bottomed flask was charged with NaH (300 mg, 12.5 mmol). After removing the mineral oil by washing with pentane (3×5 mL) it was suspended in THF (28 mL). A soln of (1*R*,2*S*)-phenylcyclohexanol (2.0 g, 11.4 mmol) in THF (10 mL) was added at 0°C. The grey mixture was stirred at rt until hydrogen evolution was finished (ca. 30 min). Allyl bromide (1.52 g, 12.54 mmol) was added at rt and the mixture was heated at reflux for 3 h. Finally, aq. NH_4Cl was added slowly to the reaction mixture to neutralize the base. After extraction with Et_2O, the organic phase was washed with NaCl, dried and the solvent evaporated under reduced pressure to afford **24** as a yellow oil (2.35 g, 95%).

^1H NMR (360 MHz, $CDCl_3$): 7.31–7.16 (m, 5 arom. H), 5.57 (ddt, 1H, $J=5.5$, 9.5, 18.0 Hz, C*H*=CH_2), 4.97–4.95 (m, 1H, CH=C*H*H), 4.94–4.91 (m, 1H, CH=CH*H*), 3.78 (ddt, 1H, $J=1.2$, 5.5, 13.0 Hz, OC*H*-HCH=CH_2), 3.58 (ddt, 1H, $J=1.5$, 5.5, 12.8 Hz, OCH-*H*CH=CH_2), 3.34 (dt, 1H, $J=4.6$, 10.4 Hz, OC*H*CHPh), 2.54 (ddd, 1H, $J=3.7$, 10.1, 13.7 Hz, OCHC*H*Ph), 2.21–2.13 (m, 1H), 1.90–1.82 (m, 2H), 1.76–1.70 (m, 1H), 1.58–1.46 (m, 1H), 1.40–1.35 (m, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): 144.8 (s), 135.5 (d), 128.0 (d), 127.8 (d), 126.0 (d), 115.9 (t), 81.6 (d), 70.2 (t), 51.3 (d), 33.9 (t), 32.6 (t), 26.1 (t), 25.1 (t).

4.4.8. (1*R*,2*S*)-2-Phenylcyclohexyl (*Z*)-1-propenyl ether 25. A soln of **24** (5.68 g, 26.3 mmol) was added to a soln of *t*-BuOK (1.02 g, 9.1 mmol) in dry DMSO (10 mL) at rt. The black reaction mixture was heated at 40°C for 5 days. The reaction was neutralized by addition of a saturated aq. soln of NaCl. After extraction with Et_2O, the organic phase was washed with H_2O, dried over $MgSO_4$ and the solvent evaporated to furnish the **25** (4.98 g, 88%) as a yellow oil.

IR (KBr): 3030, 2931, 2858, 1666, 1448, 1259, 1089 cm^{-1}. ^1H NMR (360 MHz, $CDCl_3$): 7.31–7.14 (m, 5 arom. H), 5.73 (dq, 1H, $J=1.8$, 6.1 Hz, OC*H*=CH), 4.12 (quint, 1H, $J=6.7$ Hz, OCH=C*H*), 3.58 (dt, 1H, $J=4.0$, 10.1 Hz, OC*H*CHPh), 2.64 (ddd, 1H, $J=3.7$, 10.1, 13.7 Hz, OCHC*H*Ph), 2.43–2.38 (m, 1H), 2.22–2.12 (m, 2H), 1.94–1.83 (m, 2H), 1.78–1.72 (m, 1H), 1.62–1.33 (m, 2H), 1.33 (dd, 3H, $J=1.5$, 6.7 Hz, CH=CHCH_3). ^{13}C NMR (50 MHz, $CDCl_3$): 144.5 (d), 144.0 (s), 128.2 (d), 127.8 (d), 126.1 (d), 100.7 (d), 83.8 (d), 50.5 (d), 33.6 (t), 32.9 (t), 25. 9(t), 25.0 (t), 9.1 (q). CI-MS (CH_4) *m*/*z* (%): 217 (M^++1, 19), 216 (M+. 33), 160 (30), 159 (100), 157 (17), 91 (32).

4.4.9. 2-Bromo-1-propenyl (1*R*,2*S*)-2-phenylcyclohexyl ether 26. Bromine (2.96 g, 18.52 mmol) was added dropwise to a soln of **25** (4.0 g, 18.5 mmol) in CH_2Cl_2 (10 mL) cooled at −20°C until the orange color remain. Then, solid $Na_2S_2O_3$ was added. The resulting mixture was filtered and dried. After evaporation, the dibromoether was isolated as a red dark oil (5.86 g, 15.6 mmol) that was directly slowly added to a refluxing soln of *N*,*N*-diethylaniline (3.25 g, 21.8 mmol) in benzene (10 mL). After 45 min heating under reflux, the black mixture was cooled down to rt and diluted with Et_2O. A soln of HCl 2N (4 mL) was added and the aqueous phase was extracted several times with Et_2O. Finally the organic phases were washed with H_2O. The crude product was purified by FC (hexane/Et_2O 40:1) over silica gel previously treated with Et_3N (2.5%). The bromopropenyl ether **26** was isolated (2.76 g, 60%) as a mixture of isomers. IR (KBr): 3028, 2933, 2858, 1678, 1448, 1186, 1024 cm^{-1}. ^1H NMR (360 MHz, $CDCl_3$): 7.30–7.15 (m, 5 arom. H), 5.89 (q, 1H, $J=1.2$ Hz, OC*H*=CHBrMe), 3.68 (dt, 1H, $J=4.6$, 10.4 Hz, OC*H*CHPh), 2.69 (ddd, 1H, $J=3.7$, 10.1, 13.7 Hz, OCHC*H*Ph), 2.26–2.10 (m, 1H), 1.93–1.85 (m, 2H), 1.86 (d, 3H, $J=1.5$, CH_3), 1.79–1.73 (m, 1H), 1.61–1.58 (m, 2H), 1.42–1.30 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): 143.2 (s), 141.5 (d), 128.1 (d), 127.9 (d), 126.4 (d), 97.5 (s), 85.2 (d), 50.3 (d), 33.1 (t), 33.0 (t), 25.6 (t), 24.9 (t), 22.2 (q). EI-MS *m*/*z* (%): 296 (M^++1, 21), 294 (20), 159 (86), 158 (36), 1290 (30), 117 (67), 115 (74), 92 (59), 91 (100).

4.4.10. 2,3-Butadienyl (1*R*)-2,2-dibromo-1-{[(1*R*,2*S*)-2-phenyl cyclohexyl]oxy}prop-1-yl ether (*R*)-27. To a soln of **26** (1.47 g, 5.0 mmol) and 2,3-butadien-1-ol (0.35 g, 5.0 mmol) in CH_2Cl_2 (5 mL) cooled at −20°C was added in portions NBS (0.89 g, 5.0 mmol). The resulting mixture was stirred at the same temperature for 2 h. Hexane was added to precipitate succinimide. After filtration, the filtrate was washed successively with KOH (5%), H_2O and NaCl, dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by FC (hexane/Et_2O 40:1) furnished **27** as 7:3 mixture of diasteroisomers. The two diasteroisomers were separated by FC (hexane/Et_2O 85:1) and (*R*)-**27** (0.94 g, 42%) was isolated.

(*R*)-**27** (major isomer): $[\alpha]_D^{25}=-2.3$ (*c* 1, CH_2Cl_2). ^1H NMR (360 MHz, $CDCl_3$): 7.30–7.16 (m, 5 arom. H), 5.35 (quint, 1H, $J=6.7$ Hz, OCH_2CH=C=CH_2), 4.87–4.84 (m, 2H, OCH_2CH=C=CH_2), 4.36 (ddt, 1H, $J=1.8$, 7.0, 11.3 Hz, OC*H*HCH=C=CH_2), 4.29 (ddt, 1H, $J=1.5$, 7.3, 11.6 Hz, OCH*H*CH=C=CH_2), 4.16 (s, 1H, OC*H*CBr_2Me), 3.77 (dt, 1H, $J=4.3$, 10.1 Hz, OC*H*CHPh), 2.63 (ddd, 1H, $J=3.7$, 10.1, 13.7 Hz, OCHC*H*Ph), 2.29–2.22 (m, 1H), 1.93–1.86 (m, 1H), 1.86 (s, 3H, CH_3), 1.78–1.72 (m, 1H), 1.62–1.30 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$): 209.4 (d), 144.1 (s), 128.2 (d), 126.5 (d), 106.0 (d), 87.7 (d), 82.1 (d), 76.1 (t), 69.5 (t), 68.1 (s), 51.1 (d), 34.3 (q), 34.1 (t), 33.8 (t), 25.7 (t), 25.1 (t).

(*S*)-**27** (minor isomer): ^1H NMR (360 MHz, $CDCl_3$): 7.29–7.23 (m, 5 arom. H), 5.11 (quint, 1H, $J=7.0$ Hz, C*H*=C=CH_2), 4.79 (dt, 2H, $J=2.1$, 6.4 Hz, CH=C=CH_2), 4.74 (s, 1H, OC*H*CBr_2Me), 3.90 (dt, 2H, $J=2.1$, 7.0 Hz, OCH_2CH=C=CH_2), 3.82 (dt, 1H, $J=$ 4.3, 10.4 Hz, OC*H*CHPh), 2.65 (dt, 1H, $J=3.9$, 10.4 Hz, OCHC*H*Ph), 2.31–2.26 (m, 1H), 2.16 (s, 3H, CH_3), 1.96–1.91 (m, 2H), 1.79–1.76 (m, 1H), 1.63–1.56 (m, 2H), 1.41–1.32 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): 209.2 (s), 143.9 (s), 128.1 (d), 127.9 (d), 126.1 (d), 102.4 (d), 87.8 (d), 78.7 (d), 75.9 (t), 68.0 (t), 67.9 (s), 50.4 (d), 33.6 (q), 33.5 (t), 31.3 (t), 25.8 (t), 24.8 (t).

Mixture of diasteroisomers: IR (KBr): 3028, 2931, 2856, 1955, 1448, 1105, 1066, 848 cm^{-1}. FAB-MS: 375 (M^+−69, 20), 296 (60), 294 (63), 231 (35), 211 (68), 159 (100), 129 (95).

4.4.11. (2*R*,3*R*,4*S*)-3-Methyl-2-{[(1*R*,2*S*)-2-phenylcyclohexyl]oxy}-4-vinyl tetrahydrofuran 28. A soln of (*R*)-**27** (0.42 g, 1 mmol) and Bu_3SnH (0.35 g, 1.2 mmol) in toluene (25 mL) was cooled at −78°C and a 1 M soln of Et_3B in hexane (1.4 mL. 1.4 mmol) was added followed by air (1.0 mL). The resulting soln was kept at −78°C for 3 h, then $(TMS)_3SiH$ (0.30 g, 1.2 mmol) was added followed by air (1 mL). The reaction mixture was kept at −78°C for 3 h and a 1 M NaOH soln (15 mL) was added and the heterogeneus mixture was stirred for 2 h at rt. The organic layer was washed with H_2O, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product (90% ds) was purified by FC (pentane/Et_2O 40:1) to afford the (2*R*,3*R*,4*S*)-**28** (0.21 g, 73%) as a colorless oil. $[\alpha]_D^{25}=+8.2$ (*c* 1, CH_2Cl_2). IR (KBr): 3030, 2955, 2928, 2856, 1521, 1365, 1244, 1074, 1035 cm^{-1}. ^1H NMR (360 MHz, $CDCl_3$): 7.28–7.13 (m, 5 arom. H), 5.87 (dt, 1H, $J=10.1$, 17.1 Hz, C*H*=CH_2), 4.90 (dd, 1H, $J=2.1$, 10.1 Hz, CH=C*H*H), 4.84 (ddd, 1H, $J=0.6$, 2.1, 17.1 Hz, CH=CH*H*), 4.30 (d, 1H, $J=4.6$ Hz, OC*H*CHMe), 3.96 (dd, 1H, $J=7.6$ Hz, OC*H*HCHCH=CH_2), 3.63 (dd, 1H, $J=4.3$, 8.5 Hz, OCH*H*CHCH=CH_2), 3.51 (dt, 1H, $J=4.3$, 10.1 Hz, OC*H*CHPh), 2.59 (dq, 1H, $J=4.3$, 9.5, 17.4 Hz, C*H*CH=CH_2), 2.48 (ddd, 1H, $J=3.7$, 10.1, 13.4 Hz, OCHC*H*Ph), 2.19–2.12 (m, 1H), 1.89–1.68 (m, 4H), 1.62–1.23 (m, 4H), 0.44 (d, 3H, $J=7.3$ Hz, $CHCH_3$). ^{13}C NMR (50 MHz, $CDCl_3$): 144.7 (s), 140.0 (d), 128.1 (d), 127.9 (d), 125.9 (d), 115.0 (t), 106.0 (d), 81.3 (d), 71.9 (t), 51.6 (d), 45.9 (d), 41.3 (d), 35.0 (t), 33.3 (t), 25.9 (t), 25.2 (t), 9.4 (q). CI-MS (CH_4) *m*/*z* (%): 288 (M^++1, 11), 287 (50), 217 (20), 159 (100), 111 (86), 91 (19). Anal. Calcd. for $C_{19}H_{26}O_2$ (288.42): C, 79.68; H, 9.15. Found: C, 79.20; H, 9.41.

4.4.12. (3*R*,4*S*)-3-Methyl-4-vinyltetrahydrofuran-2-ol (3*R*,4*S*)-23. A soln of (2*R*,3*R*,4*S*)-**28** (80 mg, 0.28 mmol) in THF (1.3 mL) and 10% HCl (1 mL) was kept at rt for 30 min. After extraction with Et_2O, the organic phases were washed with sat. $NaHCO_3$ and H_2O, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by FC (pentane/Et_2O 1:1) to afford (3*R*,4*S*)-**23** (20 mg, 56%) and (1*R*,2*S*)-phenylcyclohexanol (30 mg, 61%). Spectral data identical with racemic compound (vide supra).

4.4.13. (−)-Botryodiplodin (−)-1. A suspension of lactol (15 mg, 0.12 mmol), $PdCl_2$ (2 mg, 0.012 mmol) and $Cu(OAc)_2{\cdot}2H_2O$ (52 mg, 0.24 mmol) in *N*,*N*-dimethylacetamide/H_2O 7:1 (0.3 mL) was placed under oxygen and stirred at rt for 4 days. The mixture was diluted with Et_2O, filtered through Celite with Et_2O to wash the filter cake, poured into water (1.5 mL) and extracted with Et_2O. The organic phases were dried and concentrated under reduced pressure. The crude product was purified by FC (pentane/Et_2O 1:1) to furnish (−)-botryodiplodin (7 mg, 41%). The optical purity (>98% ee) was determined by GC (β-cyclodextrin, 35% diacetoxy, 120°C): (−)-**1**: $t_R = 10.09$ min, (+)-**1**: $t_R = 10.40$ min. Spectral data identical with literature data.[2] $[\alpha]_D^{25} = -68$ (*c* 0.35, MeOH) {lit.:[6] $[\alpha]_D^{25} = -70$ (*c* 0.124, MeOH)}.

Acknowledgements

This work was supported by the Swiss National Science Foundation (project 20-67'106.01) and by the Swiss Federal Office for Science and Education (OFES-BBW, Action COST D12)

References

1. Sen Gupta, R.; Chandran, R. R.; Divekar, P. V. *Indian J. Exptl. Biol.* **1966**, *4*, 152.
2. Arsenault, G. P.; Althaus, J. R.; Divekar, P. V. *J. Chem. Soc. D, Chem. Commun.* **1969**, 1414.
3. Moreau, S.; Lablache-Combier, A.; Biguet, J.; Foulon, C.; Delfosse, M. *J. Org. Chem.* **1982**, *47*, 2358.
4. Fuska, J.; Kuhr, I.; Nemec, P.; Fuskova, A. *J. Antibiot.* **1974**, *27*, 123.
5. Fuska, J.; Proksa, B.; Uhrin, D. *Folia Microbiol. (Prague, Czech Republic)* **1988**, *33*, 238.
6. Nakagawa, F.; Kodama, K.; Furuya, K.; Naito, A. *Agric. Biol. Chem.* **1979**, *43*, 1597.
7. Renauld, F.; Moreau, S.; Lablache-Combier, A. *Tetrahedron* **1984**, *40*, 1823.
8. Renauld, F.; Moreau, S.; Lablache-Combier, A.; Tiffon, B. *Tetrahedron* **1985**, *41*, 955.
9. McCurry, P. M., Jr.; Abe, K. *Tetrahedron Lett.* **1973**, *14*, 4103.
10. McCurry, P. M., Jr.; Abe, K. *J. Am. Chem. Soc.* **1973**, *95*, 5824.
11. Mukaiyama, T.; Wada, M.; Hanna, J. *Chem. Lett.* **1974**, 1181.
12. Wilson, S. R.; Myers, R. S. *J. Org. Chem.* **1975**, *40*, 3309.
13. Sakai, K.; Amemiya, S.; Inoue, K.; Kojima, K. *Tetrahedron Lett.* **1979**, *20*, 2365.
14. Kurth, M. J.; Yu, C. M. *J. Org. Chem.* **1985**, *50*, 1840.
15. Rehnberg, N.; Frejd, T.; Magnusson, G. *Tetrahedron Lett.* **1987**, *28*, 3589.
16. Rehnberg, N.; Magnusson, G. *Acta Chem. Scand.* **1990**, *44*, 377.
17. Dulcère, J.-P.; Mihoubi, M. N.; Rodriguez, J. *Nat. Prod. Lett.* **1992**, *1*, 209.
18. Dulcère, J.-P.; Mihoubi, M. N.; Rodriguez, J. *J. Org. Chem.* **1993**, *58*, 5709.
19. Daub, G. W.; Edwards, J. P.; Okada, C. R.; Allen, J. W.; Maxey, C. T.; Wells, M. S.; Goldstein, A. S.; Dibley, M. J.; Wang, C. J.; Ostercamp, D. P.; Chung, S.; Cunningham, P. S.; Berliner, M. A. *J. Org. Chem.* **1997**, *62*, 1976.
20. For a preliminary communication of this work, see: Nouguier, R.; Gastaldi, S.; Stien, D.; Bertrand, M.; Renaud, P. *Tetrahedron Lett.* **1999**, *40*, 3371.
21. For a preliminary communication of this work, see: Villar, F.; Andrey, O.; Renaud, P. *Tetrahedron Lett.* **1999**, *40*, 3375.
22. Chatgilialoglu, C.; Ferreri, C.; Ballestri, M.; Curran, D. P. *Tetrahedron Lett.* **1996**, *37*, 6387.
23. Chatgilialoglu, C.; Alberti, A.; Ballestri, M.; Macciantelli, D.; Curran, D. P. *Tetrahedron Lett.* **1996**, *37*, 6391.
24. Ryu, I. Y.; Kreimerman, S.; Niguma, T.; Minaka, S.; Komatsu, M.; Luo, Z. Y.; Curran, D. P. *Tetrahedron Lett.* **2001**, *42*, 947.
25. Xiang, J.; Evarts, J.; Rivkin, A.; Curran, D. P.; Fuchs, P. L. *Tetrahedron Lett.* **1998**, *39*, 4163.
26. Kim, S.; Lim, C. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 3265.
27. Schaffner, A.; Renaud, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 2658.
28. For a review, see: Bertrand, F.; Le Guyader, F.; Liguori, L.; Ouvry, G.; Quiclet-Sire, B.; Seguin, S.; Zard, S. Z. *C. R. Acad. Sci. Ser. II C* **2001**, 547.
29. Zard, S. Z. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 672.
30. Quiclet-Sire, B.; Zard, S. Z. *J. Am. Chem. Soc.* **1996**, *118*, 1209.
31. Bertrand, M. P. *Org. Prep. Proc. Int.* **1994**, *26*, 257.
32. Simpkins, N. S. *Sulphones in Organic Synthesis*; Pergamon Press: Oxford, 1993 and references cited therein.
33. Bertrand, M. P.; Gastaldi, S.; Nouguier, R. *Tetrahedron Lett.* **1996**, *37*, 1229.
34. Bertrand, M. P.; Gastaldi, S.; Nouguier, R. *Tetrahedron* **1998**, *54*, 12829.
35. Oroshnik, W.; Mallory, R. A. *J. Am. Chem. Soc.* **1950**, *72*, 4608.
36. Bertrand, M. P.; De Riggi, I.; Gastaldi, S.; Nouguier, R.; Jaime, C.; Virgili, A. *J. Org. Chem.* **1995**, *60*, 6040.
37. Villar, F.; Equey, O.; Kolly-Kovac, T.; Renaud, P. *Chem. Eur. J.* **2003**, *9*, 1566.
38. Corminboeuf, O.; Renaud, P.; Schiesser, C. H. *Chem. Eur. J.* **2003**, *9*, 1578.
39. Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140.
40. Curran, D. P.; Tamine, J. *J. Org. Chem.* **1991**, *56*, 2746.
41. Renaud, P.; Gerster, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2562.
42. For a related effect of Bu_3SnCl on a cyclization reaction, see: Sibi, M. P.; Ji, J. G. *J. Am. Chem. Soc.* **1996**, *118*, 3063–3064.
43. Byers, J. In *Radicals in Organic Synthesis*; Renaud, P.; Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 1, p. 72.
44. Ueno, Y.; Chino, K.; Watanabe, M.; Moriya, O.; Okawara, M. *J. Am. Chem. Soc.* **1982**, *104*, 5564.
45. Ueno, Y.; Moriya, O.; Chino, K.; Watanabe, M.; Kawara, M. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1351.
46. Stork, G.; Mook, R., Jr.; Biller, S. A.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1983**, *105*, 3741.
47. Stork, G.; Sher, P. M.; Chen, H.-L. *J. Am. Chem. Soc.* **1986**, *108*, 6384.

48. Stork, G. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 149.
49. (a) Stork, G. *Bull. Soc. Chim. Fr.* **1990**, *127*, 675; (b) Stork, G.; Franklin, P. J. *Aust. J. Chem.* **1992**, *45*, 275.
50. For a discussion of the role of the anomeric effect in radical cyclization, see: Beckwith, A. L. J.; Page, D. M. *J. Org. Chem.* **1998**, *63*, 5144.
51. Villar, F.; Renaud, P. *Tetrahedron Lett.* **1998**, *39*, 8655.
52. Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925.
53. Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959.
54. Chatgilialoglu, C. In *Radicals in Organic Synthesis*; Renaud, P.; Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 1, p. 28.
55. Chatgilialoglu, C. *Acc. Chem. Res.* **1992**, *25*, 188.
56. Renaud, P.; Lacôte, E.; Quaranta, L. *Tetrahedron Lett.* **1998**, *39*, 2123.
57. Renaud, P. In *Radicals in Organic Synthesis*; Renaud, P.; Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 1, p. 400.
58. Smith, A. B.; Cho, Y. S.; Friestad, G. K. *Tetrahedron Lett.* **1998**, *39*, 8765.
59. Gonzales, J.; Aurigemma, C.; Truesdale, L. *Org. Synth.* **2003**, *79*, 93.