

Intramolecular Radical Allylation with Allylic Sulfones— A Synthesis of (±)-Botryodiplodin

Robert Nougier*, Stéphane Gastaldi, Didier Stien, Michèle Bertrand
and Philippe Renaud[#]

LCMO, UMR 6517, Faculté des Sciences St Jérôme, Boîte 562,

Av. Normandie Niemen, 13397, Marseille, Cedex 20, France

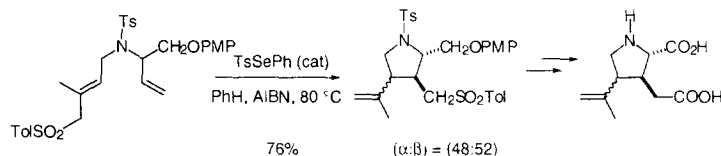
[#] Université de Fribourg, Institut de Chimie Organique, Pérolles, CH-1700 Fribourg, Switzerland

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Abstract: Isopropenyl-5-membered-ring acetal or lactone are potential precursors of (±)-botryodiplodin (**1**). Several pathways, involving 5-*exo-trig* ring closure onto allylic sulfones, have been investigated. The iodine atom transfer methodology allowed the preparation of the desired skeleton through intramolecular addition of an α -alkoxycarbonyl radical to the double bond of the appropriate allylic ethyl sulfone. Subsequent deprotonation and kinetic reprotonation led to the key precursor **14** with a high stereoselectivity.
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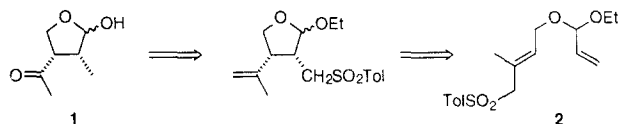
Due to the ready fragmentation of β -sulfonylated alkyl radicals, allyl sulfones have become very popular as radical allylating reagents.^{1,2} In a previous article, we have reported a formal synthesis of kainic acids based on the radical rearrangement of an allylic sulfone.³ This process allows in one step the construction of the desired skeleton, that is, a 2,3,4-trisubstituted pyrrolidine bearing an isopropenyl group in position 4 (Scheme 1).

Scheme 1



Since the isopropenyl group can be readily transformed into an acetyl group *via* ozonolysis, we thought that the same methodology might be suited to the synthesis of botryodiplodin (**1**) (Scheme 2), well known for its antibiotic and antileukemic activities.^{4,5}

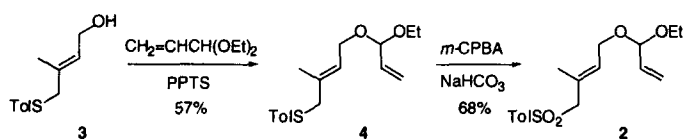
Scheme 2



Sulfone **2** was prepared in two steps, according to scheme 3, starting from **3**, which is easily available from acetoxychlorination of isoprene.⁶ The reaction of **3** with acrolein diethylacetal led to **4** which was then oxidized by *meta*-chloroperbenzoic acid.

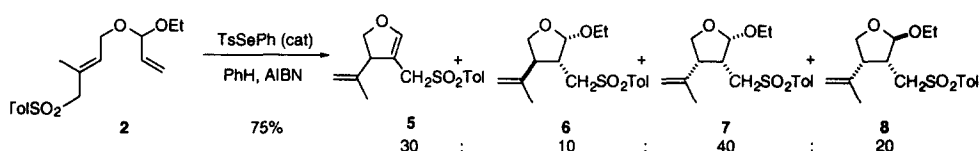
E-mail: robert.nougier@lcmo.u-3mrs.fr

Scheme 3



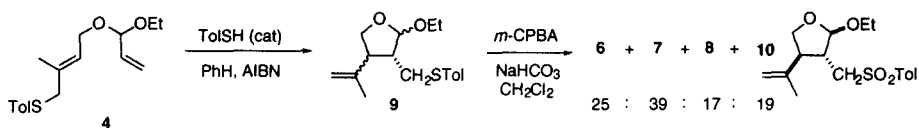
The rearrangement of **2** was performed in refluxing benzene in the presence of a catalytic amount of TolSO₂SePh (20 mol%) and AIBN as the initiator. This led to a mixture of four products **5-8** in a 30:10:40:20 ratio determined by GPC and analytical HPLC on the crude mixture (Scheme 4). The structures of **6-8** were unambiguously assigned from NOESY experiments after isolation of pure samples by preparative HPLC.

Scheme 4



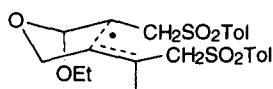
The formation of **5** might be due to the production of *para*-toluenesulfinic acid as a by-product of the reaction. Though **5** would in principle be converted readily into **6-8**, we thought we could avoid the elimination of EtOH by rearranging sulfide **4** in the presence of a catalytic amount of *para*-thiocresol (Scheme 5). However the resulting products **9** formed in a 10:20:25:45 ratio could not be isolated by chromatography on silica gel. Since the direct reduction of the crude mixture of sulfides **9** by Bu₃SnH or Raney Nickel failed, the cyclization products were converted, *via* oxidation with *meta*-chloroperoxybenzoic acid, into a mixture of **6-8** together with the product **10** corresponding to the fourth isomer, in a 25:39:17:19 ratio.

Scheme 5



The diastereoselectivity of these 5-*exo* ring closures is surprisingly low compared to the related cyclizations of 1,2-disubstituted 3-oxa⁷ and 3-aza-5-hexenyl radicals³ which give rise to five-membered heterocycles where the relative configuration of the stereogenic centers respectively α - and β to the heteroatom is 100% *trans*.

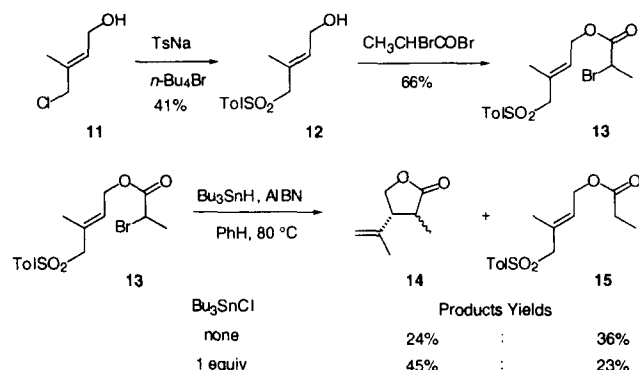
Figure 1



This apparently abnormal selectivity can be rationalized by the influence of anomeric stabilization which is responsible for the ethoxy group occupying preferentially a pseudo-axial position in the transition state; the major isomer (**7**) would originate from the transition structure drawn in figure 1. This peculiar feature, typical of the cyclizations of α -acetalic radicals has already been pointed out by several authors.⁸

Both the low selectivity and the instability of the products, inherent to their acetalic nature, led us to investigate a closely related pathway involving α -alkoxycarbonyl radicals. The major drawback of 5-*exo* ring closure in this case is that the cyclization is slowed down because of the rotation barrier around the O=C-O bond of the ester function.⁹ This is well demonstrated by the cyclization of bromide **13** which was prepared according to scheme 6.

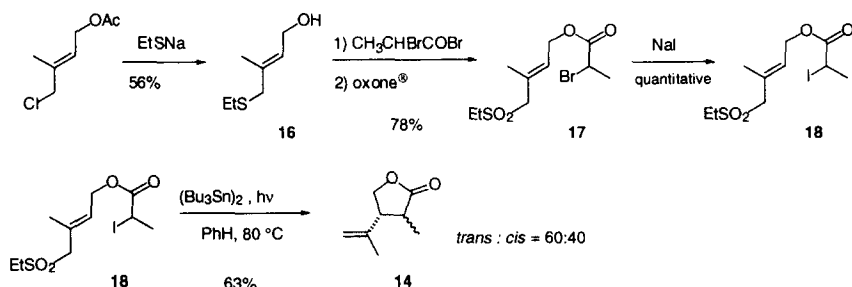
Scheme 6



Even at 80°C , the reaction, carried out by monitoring a slow addition of tributyltin hydride with a syringe pump, led to **15** as the major product. An attempt to modify the conformational equilibrium of the ester group through the complexation of the carbonyl with a Lewis acid, led us to perform the reduction of **13** in the presence of 1 equivalent of Bu_3SnCl .^{10,11} Under these conditions, lactone **14**, formed as a 57:43 mixture of *trans* and *cis* isomers, became effectively the major product, but **14** was still isolated in rather large amount.

The iodine atom transfer methodology was shown to be one of the best procedure to avoid the direct reduction competitive to lactone ring closure.⁹ In our case such a procedure could only apply if the sulfonyl radical ejected during the β -fragmentation step would produce, through α -scission, an alkyl radical able to react with the starting material *via* atom transfer. Zard allylation protocol involving allyl ethyl sulfones was ideally suited to that purpose.^{2b}

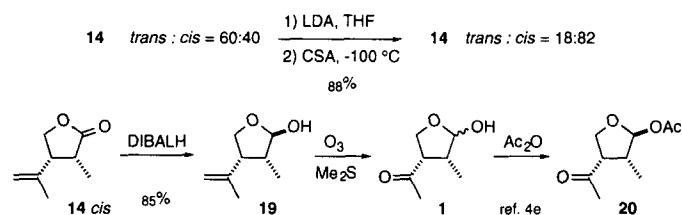
Scheme 7



Iodide **18** was prepared according to scheme 7 and was irradiated with a sunlamp in the presence of a catalytic amount of hexabutylditin. Again, the cyclization became efficient at 80°C , and lactone **14** was isolated, as the unique product, in 63% yield as a 60:40 mixture of *trans* and *cis* isomers.¹²

Since the relative configuration of the major isomer did not correspond to that of botryodiplodin (**1**), the configuration at C(3) was inverted through deprotonation and kinetic reprotonation of the enolate with camphorsulfonic acid (Scheme 8). After separation by semi-preparative HPLC (the *trans* isomer could be recycled), the *cis* isomer was transformed into (\pm)-botryodiplodin according to the literature.^{4c} The lactol **1** was obtained as a mixture of epimers, its structure was unambiguously assigned after acetylation and comparison of ^1H - and ^{13}C -NMR spectra of acetate **20** with literature data of the acetate derived from natural botryodiplodin.^{4c}

Scheme 8



References and Notes

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- [11] For a related effect of Bu_3SnCl , see: Sibi, M. P.; Ji, J. G. *J. Am. Chem. Soc.* **1996**, 118, 3063-64.
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14 trans: ¹H NMR (CDCl₃, 200 MHz) δ 4.91 (br s, 1H); 4.85 (s, 1H); 4.33 (dd, *J* = 9.0, 8.1, 1H); 3.90 (dd, *J* = 10.3, 9.0, 1H); 2.75 (pseudo td, *J* = 10.7, 8.1, 1H); 2.50 (dq, *J* = 11.2, 7.0, 1H); 1.70 (s, 3H); 1.20 (d, *J* = 7.0, 3H); ¹³C NMR (CDCl₃, 50 MHz) δ 179.1, 140.5, 113.8, 69.4, 51.1, 38.0, 19.6, 13.6. **14 cis**: ¹H NMR (CDCl₃, 200 MHz) δ 4.80 (br s, 1H); 4.65 (s, 1H); 4.24 (dd, *J* = 9.5, 6.1, 1H); 4.12 (dd, *J* = 9.5, 3.9, 1H); 3.05 (pseudo ddd, *J* = 8.1, 6.1, 3.9, 1H); 2.64 (dq, *J* = 8.1, 7.3, 1H); 1.55 (br s, 3H); 0.98 (d, *J* = 7.3, 3H); ¹³C NMR (CDCl₃, 50 MHz) δ 179.2, 141.4, 113.8, 69.6, 46.2, 36.9, 20.6, 9.9. Anal. Calcd. for C₈H₁₂O₂: C, 68.55; H, 8.63. Found: C, 68.52; H, 8.60.