



Radical Oxidative Cyclization of Spiroacetals to Bis-spiroacetals: An Overview

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Abstract: The use of iodobenzene diacetate and iodine under photolytic conditions provides an efficient method for the oxidative cyclization of spiroacetals bearing a hydroxyalkyl side chain to bis-spiroacetals. An overview is provided of the use of this reaction for the synthesis of several bis-spiroacetal containing natural products such as the polyether antibiotics salinomycin and CP44,161 and the shellfish toxins, the spirolides.

Keywords: Spiroacetals, bis-spiroacetals, oxidative radical cyclization

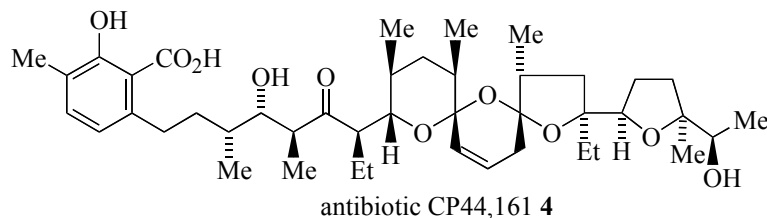
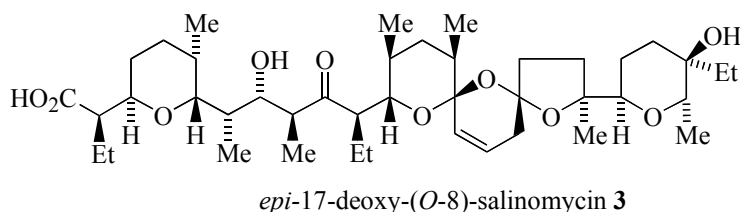
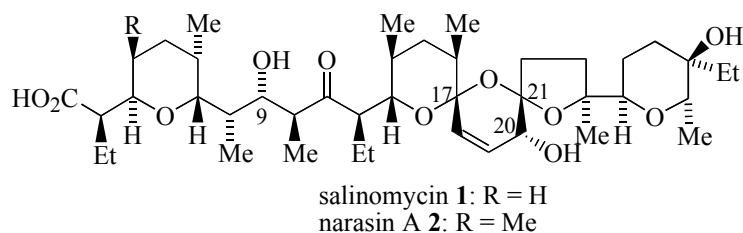
Introduction

Tricyclic bis-spiroacetal ring systems are present as sub-units in a diverse range of natural products and have attracted attention from synthetic chemists due to their stereochemical complexity and variety in their biological activity. Several reviews on the chemistry of more common bicyclic spiroacetals have been published [1] and reviews on the chemistry of bis-spiroacetals have also been forthcoming [2]. Many of the synthetic methods adopted for the construction of spiroacetals rely on the control of stereochemistry at the anomeric centre being dictated by the relative thermodynamic stability of the different isomers formed using an acid-catalysed spiroacetalisation step. The major

isomer produced in this case is that which has the maximum number of anomeric effects with minimum steric interactions. When these two factors work in opposite directions lower stereoselectivity is observed. In tricyclic bis-spiroacetal systems the balance between these factors needs careful consideration when predicting the outcome of the spiroacetalisation step as the small differences in energy and interconversion barriers often lead to the formation of a range of isomeric structures. We herein describe the subtle interplay of steric and electronic effects in the construction of several bis-spiroacetal ring systems in the context of our own work using a kinetically controlled oxidative radical cyclization rather than a thermodynamically controlled acid-catalysed cyclization to construct the representative bis-spiroacetals. This radical cyclization approach also provides a convenient method to access the thermodynamically less stable isomers.

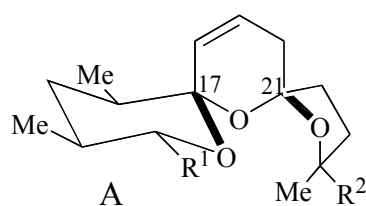
Results and Discussion

Remote intramolecular free radical functionalization [3] provides an elegant method for the construction of bis-spiroacetal ring systems from spiroacetal precursors. Our first example of this approach [4] was the assembly of the unsaturated 6,6,5-bis-spiroacetal ring system present in the polyether antibiotics salinomycin (**1**, [5]), narasin A (**2**, [6]), *epi*-deoxysalinomycin (**3**, [7]) and antibiotic CP44,161 (**4**, [8]).

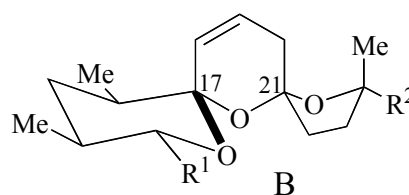


The four possible stereoisomers of the 1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene ring system present in the salinomycin family of polyether antibiotics are depicted in Figure 1. Diastereomer A represents the stereochemistry adopted by salinomycin (**1**) and CP44,161 (**4**) and has three stabilizing anomeric effects but exhibits unfavourable 1,3-dipole-dipole interactions. 21-*epi*-salinomycin B has only one anomeric effect and is the thermodynamically least stable diastereomer. The 17-*epi*-diastereomer C exhibits three anomeric effects and although it exhibits unfavourable 1,3-diaxial interactions between the C17 oxygen atom and the C21 methylene it lacks the unfavourable 1,3-dipole-dipole interactions exhibited by diastereomer A and 17-*epi*-21-*epi*-diastereomer D. This qualitative analysis leads to the assumption that 17-*epi*-diastereomer C exhibits the most thermodynamically stable configuration. It transpires that in the cyclic structure that salinomycin (**1**) adopts, the repulsive 1,3-dipolar interactions in diastereomer A are compensated for by a hydrogen bond between the C9 and C20 hydroxy groups. Bis-spiroacetals whose structures preclude this remote hydrogen bond do not adopt the salinomycin configuration A.

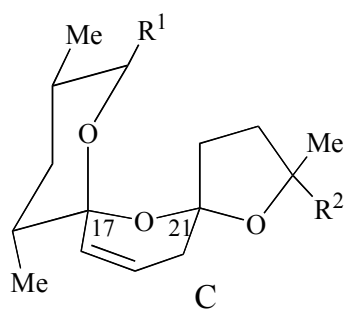
Figure 1



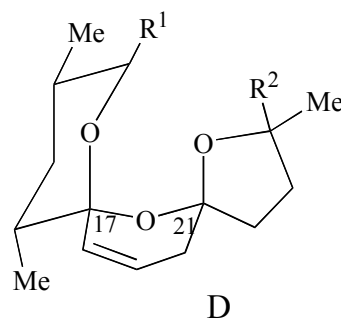
salinomycin, CP 44,161
3 anomeric effects
dipole-dipole unfavourable



21-*epi*-salinomycin, 21-*epi*-CP 44,161
1 anomeric effect



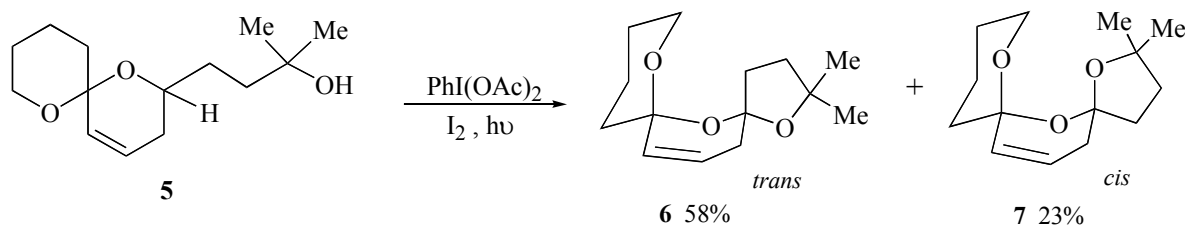
17-*epi*-salinomycin, 17-*epi*-CP44,161
3 anomeric effects



17-*epi*-21-*epi*-salinomycin, 17-*epi*-21-*epi*-CP 44,161
3 anomeric effects
dipole-dipole unfavourable

During initial model studies directed towards the synthesis of salinomycin (**1**) it was observed that irradiation of spiroacetal alcohol **5** in the presence of iodobenzene diacetate and iodine yielded a 2.5:1 separable mixture of the major *trans* bis-spiroacetal **6** together with the minor *cis* isomer **7** in 81% yield (Scheme 1). The *trans* isomer is stabilized by only three out of the four possible anomeric effects but is the thermodynamically isomer due to the absence of unfavourable 1,3-dipole interactions between carbon-oxygen bonds on the central ring [9].

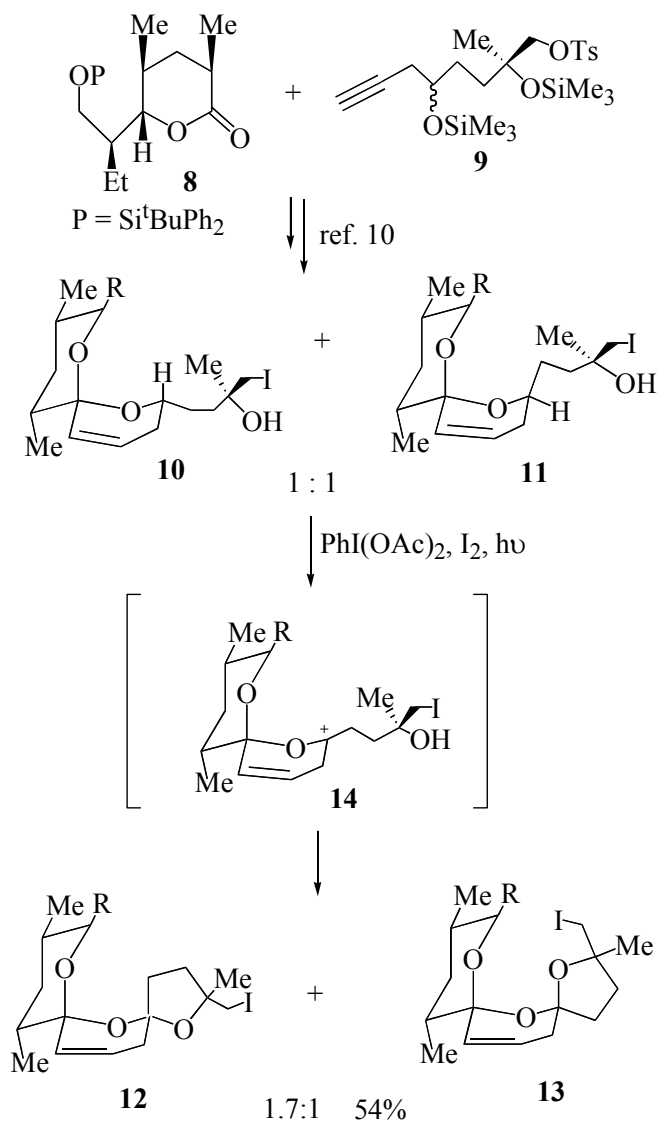
Scheme 1



In light of the fact that the major isomer obtained in this model oxidative cyclization was the *trans* isomer **6** which has the same stereochemistry as that present in *epi*-deoxysalinomycin (**3**) we embarked on the synthesis of this polyether antibiotic using this methodology. Union of lactone **8** with acetylene **9** provided the key cyclization precursors **10** and **11** bearing an iodomethyl group for further elaboration of the resultant bis-spiroacetals **12** and **13** (Scheme 2). The key oxidative cyclization was then achieved upon irradiation of either iodohydrin **10** or iodohydrin **11** in a solution of cyclohexane, containing iodine and iodobenzene diacetate affording the *trans* bis-spiroacetal **12** and the *cis* bis-spiroacetal **13** in a ratio of 1.7:1 [10]. This outcome may be explained by the proposed mechanism wherein both diastereomeric precursors **10** and **11** form the same carbocation intermediate **14** (derived from the corresponding free radical), that is subsequently trapped predominantly from the least hindered α -face, to give the *trans* bis-spiroacetal **12** as the major product.

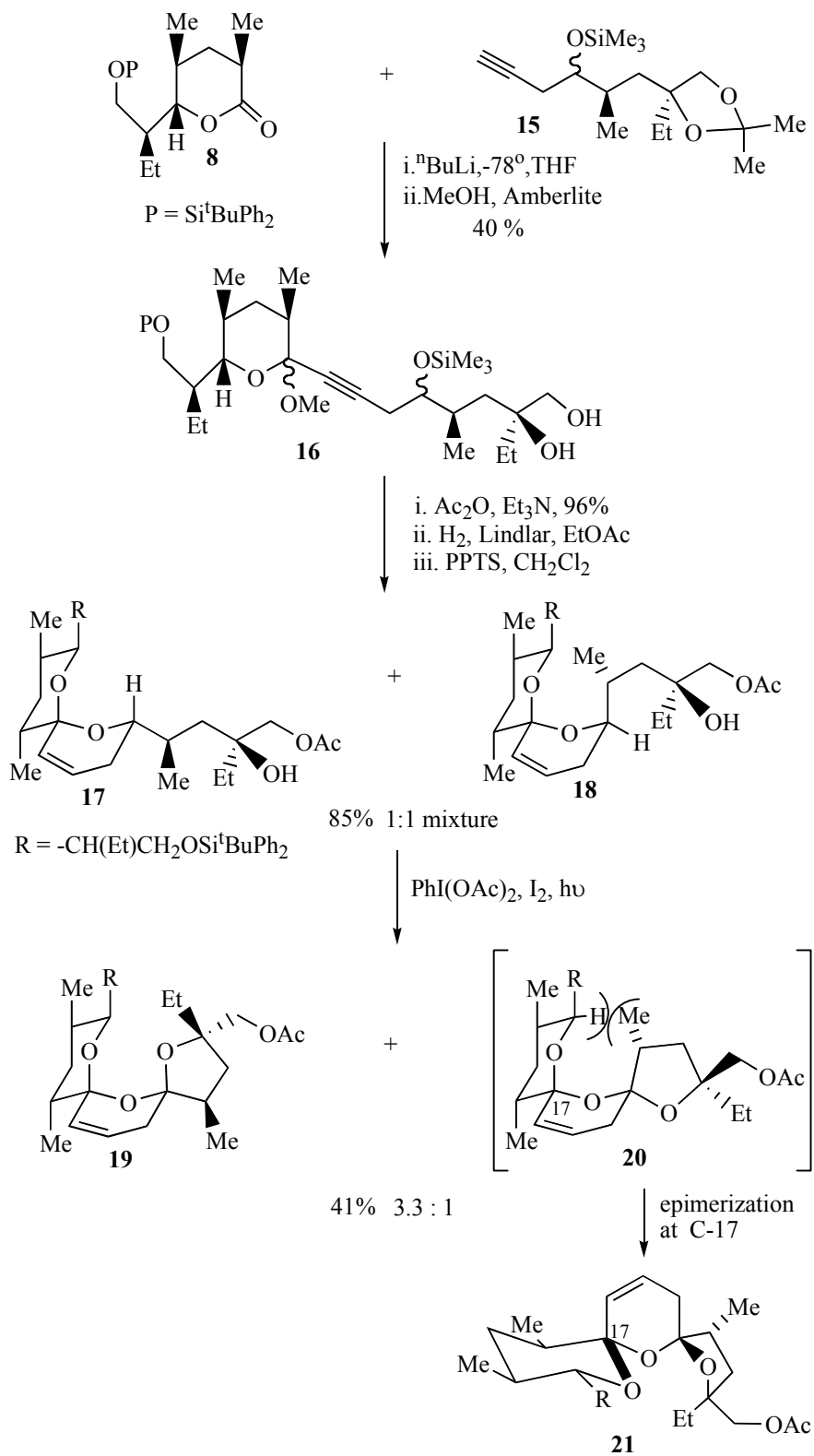
Pleasingly the major isomer obtained from the above radical induced oxidative cyclization had the same *trans* stereochemistry as that present in *epi*-17-deoxysalinomycin (**3**). We therefore set about appending the terminal tetrahydropyran E ring to this key bis-spiroacetal intermediate **12**. After considerable effort we were forced to abandon this work due to the incompatibility of the sensitive bis-spiroacetal moiety with a key ring expansion reaction planned for introduction of the tetrahydropyran E ring [11]. We therefore turned our attention to the synthesis of the related antibiotic CP44,161 **4** that contained a terminal tetrahydrofuran ring whose synthesis did not require recourse to this ring expansion step.

Scheme 2



Assembly of the bis-spiroacetal core of antibiotic CP44,161 (**4**) was effected using methodology previously applied to the synthesis of the bis-spiroacetal moiety of *epi*-17-deoxy-(*O*-8)-salinomycin (**3**), starting from acetylene **15** and lactone **8** as used previously (Scheme 3). Addition of the lithium acetylide derived from acetylene **15** to lactone **8** followed by treatment of the intermediate lactol with methanol and Amberlite IR 118 resin effected hydrolysis of the acetonide group and formation of more stable methyl acetals as a mixture of diastereomers that were not separated.

Scheme 3



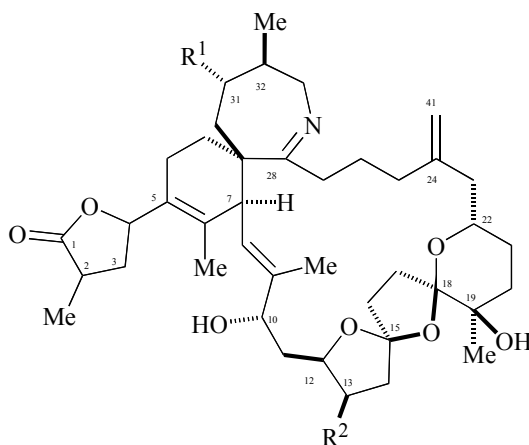
Protection of the primary hydroxyl group as an acetate allowed ready purification of the acetates by flash chromatography. Partial hydrogenation of the alkyne **16** to a *cis*-olefin followed by acid catalyzed cyclization resulted in a 1:1 mixture of spiroacetals **17** and **18** that were inseparable by flash chromatography. This initial spirocyclisation is carried out under thermodynamically controlled conditions such that the most stable configuration is afforded at the newly formed spiro centre owing to maximum stabilization by the anomeric effect. The two isomeric spiroacetals **17** and **18** therefore only differ in the position that the side chain adopts.

Spiroacetals **17** and **18** were treated with iodobenzene diacetate and iodine to afford a 3.3:1 mixture of tricyclic bis-spiroacetals **19** and **20**. The preference for *cis* bis-spiroacetal **19** in this cyclisation reaction can be attributed to the presence of the additional methyl group in the tetrahydrofuran ring, which causes unfavourable steric interactions upon formation of the minor *trans* bis-spiroacetal **20**. *Trans* bis-spiroacetal **20** therefore undergoes rapid epimerisation at the allylic spirocentre to *cis* bis-spiroacetal **21**. The presence of the additional methyl group exhibited a marked effect on the stereochemical outcome of the oxidative cyclisation in that the oxidative cyclisation of the related spiroacetals **10** and **11** which lack this additional methyl group provided the *trans* isomer as the major product (Scheme 2).

The major bis-spiroacetal **19** isolated from this oxidative cyclisation has the 17-*epi*-21-*epi*-salinomycin stereochemistry (Figure 1) whereas the minor *cis* isomer **21** has the correct bis-spiroacetal stereochemistry for salinomycin (**1**) and CP44,161 (**4**). Given that it is well established that long range hydrogen bonding in the final molecule can dramatically alter the position of the bis-spiroacetal equilibrium, it was envisaged that thermodynamically controlled cyclization after the whole carbon skeleton of the natural product has been assembled, will allow convergence of the bis-spiroacetal stereochemistry to that depicted in *cis* isomer **21**.

The successful use of an intramolecular radical cyclization strategy to construct the five membered ring of the 6,6,5-bis-spiroacetal moiety of the polyether antibiotics *epi*-17-deoxy-*O*-8-salinomycin (**3**) and CP44,161 (**4**) prompted us to extend this methodology to the synthesis of the novel 6,5,5-bis-spiroacetal present in the shellfish toxins, spiroside B (**22**) and D (**23**).

Spirolides B (**22**) and D (**23**) are members of a novel family of marine macrolides isolated from mussels (*Mytilus edulis*) and scallops (*Placopecten magellanicus*) during routine monitoring for diarrhetic shellfish toxins in Nova Scotia, Canada in 1995 [12]. They induce characteristic symptoms in the mouse bioassay possibly through muscarinic acetylcholine receptor antagonism and are weak activators of L-type transmembrane Ca²⁺ channels. The relative and absolute stereochemistry has not been established to date, but a tentative assignment based on NMR studies has been reported [13]. In common with the pinnatoxins [14], the spiroptides possess a seven-membered spiro-linked cyclic imine together with the novel 1,7,9-trioxadispiro[4.1.5.2]tetradecane bis-spiroacetal ring system.

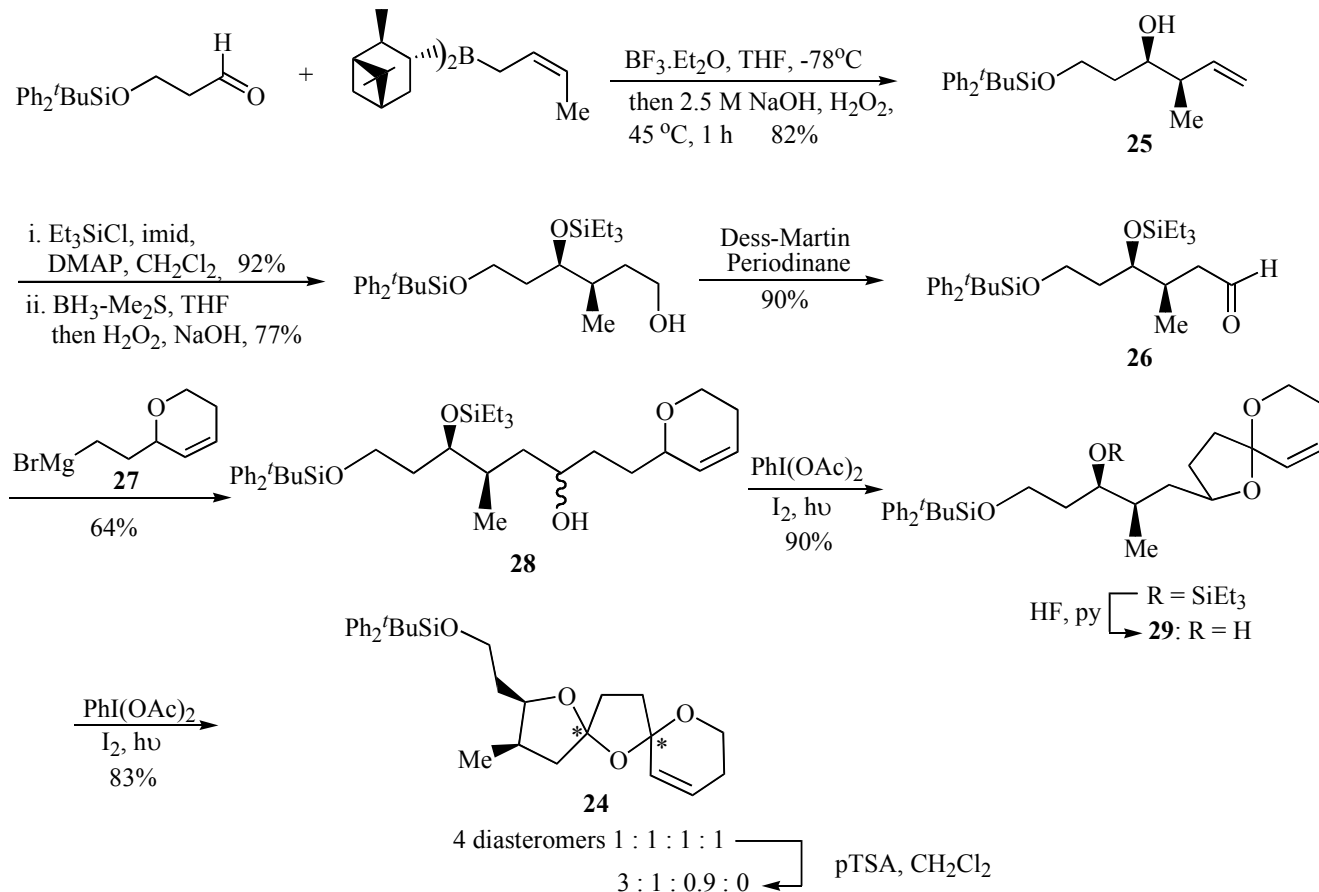


Spirolide B **22**: R¹=H, R²=Me

Spirolide D **23**: R¹=Me, R²=Me

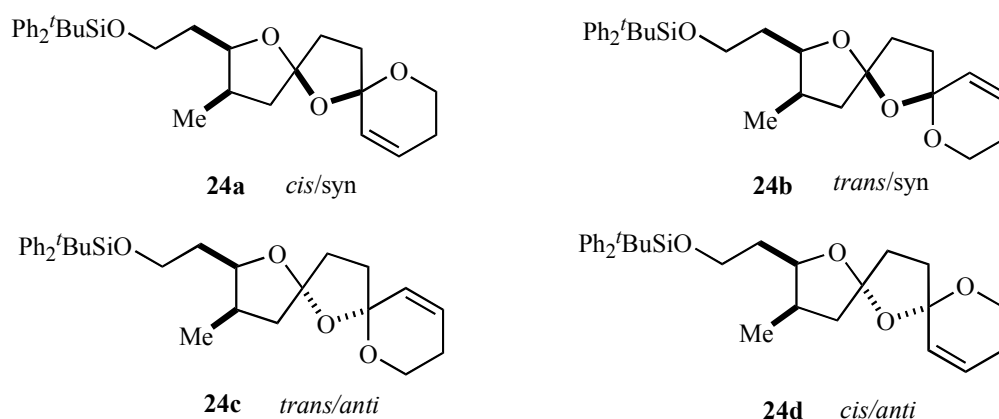
The 6,5,5-bis-spiroacetal unit of the spirolides B (**22**) and D (**23**) is challenging due to the presence of two five-membered rings, for which the anomeric effect is considerably reduced as compared with six-membered rings. It was envisaged that the two spiroacetal centres in the key bis-spiroacetal fragment **24** provide an excellent synthetic target for using an iterative oxidative radical cyclisation strategy to construct the two five-membered rings in a stepwise fashion (Scheme 4).

Scheme 4



Formation of oxaspiro rings by hydrogen abstraction promoted by hypervalent iodine led to the spirocyclization precursors **28** and **29** as an effective strategy for the synthesis of the key 6,5,5-bis-spiroacetal **24** present in compounds **22** and **23**. Aldehyde **26** provided the substituents required for the substituted tetrahydrofuran ring of the 6,5,5-bis-spiroacetal ring system and these were introduced in a stereocontrolled manner by crotyl metallation of a protected 3-hydroxypropanal that afforded the desired homoallylic alcohol **25** in 82% yield and >97% d.e. The *R,R* configuration was selected both by analogy with pinnatoxin A [14] and the relative stereochemistry of the spirocyclic products proposed by Falk *et al* [13]. The resultant homoallylic alcohol **25** was then converted into aldehyde **26** in good yield using standard transformations. The synthesis of aldehyde **26** is also flexible enabling access to bis-spiroacetals of varying relative and absolute stereochemistry by the appropriate choice of chiral crotyl borane used to prepare the homoallylic alcohol intermediate **25**. Coupling of aldehyde **26** with the Grignard reagent **27** proved problematic. Standard Grignard reaction conditions failed to yield the desired product and only mediocre yields were obtained using an organolithium species derived from the analogous iodide. Alcohol **28** was finally prepared reproducibly in 64% yield using Barbier conditions in diethyl ether, together with the undesired Wurtz coupling product of **27**. Cyclisation of **28** using iodobenzene diacetate and iodine with irradiation afforded spiroacetal **29** in 90% yield after removal of the triethylsilyl ether by portionwise addition of HF·pyridine over several hours. Finally, bicyclic spiroacetal **29** underwent smooth radical oxidative cyclisation to a 1:1:1:1 mixture of the four possible diastereomers of bis-spiroacetal **24** upon treatment with iodobenzene diacetate and iodine with irradiation. Prolonged stirring of the initial 1:1:1:1 product mixture with a catalytic quantity of *p*-toluenesulfonic acid in dichloromethane gave a 3:1:1:0.9 mixture (**24a**:**24b**:**24c**, Figure 2) of three of the four possible isomers and these were then separable by careful chromatography [15].

Figure 2



Note: The *cis/trans* notation refers to the arrangement of oxygens across the central ring and *syn/anti* to the arrangement of the central oxygen and the alkyl substituent, respectively.

The stereochemistry assigned to the bis-spiroacetal isomers **24a-c** was assigned on the basis of 2D NMR and *ab initio* molecular modeling [15] and it was satisfying that the major bis-spiroacetal isomer **24a** had the same stereochemistry as that assigned by NMR spectroscopy to the bis-spiroacetal ring system of spiroalides B (**22**) and D (**23**) [13]. Notably the initial oxidative radical cyclizations did not provide any stereocontrol in the initially formed isomeric mixture of 1,7,9-trioxadispiro[4.1.5.2]-tetradecanes supporting the concept that control of stereochemistry in systems containing two five-membered rings is more problematic than similar bis-spiroacetals containing six-membered rings.

Conclusions

A summary of the use of radical initiated oxidative cyclization using iodobenzene diacetate and iodine as a key step to prepare several biologically active natural products containing a bis-spiroacetal unit has been presented. The stereochemistry of the bis-spiroacetal products obtained is dependent on the nature of the cyclization precursor and introduction of substituents (as small as a methyl group) onto the initial bicyclic spiroacetal ring can have a significant effect on the stereochemistry of the cyclization products produced.

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