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Pentadienyl sulfoxide in triene synthesis. Efficient assembly of the Northern fragment of polycavernoside A

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ABSTRACT

Various polyunsaturated fragments, akin to the polycavernoside A Northern fragment, can be synthesized efficiently using as key steps a double Mislow–Braverman–Evans rearrangement of bis-allylic sulfoxides and a novel Julia-type 1,6-reductive elimination.

Polyunsaturated subunits are common structural features present in a large number of biologically active natural products, many of which display an all-trans configuration of the C=C double bonds. Among these compounds, polycavernoside A **1** (Fig. 1), a marine toxin isolated from the red algae *Polycavernosa tsudai* and *Gracilaria edulis*[1] which possesses a triene unit, has attracted our attention. This compound and some of its congeners have been implicated as the causative toxins of several fatal human poisonings.

The complex architecture of **1**, coupled with its biological activity, has attracted considerable attention, and several total syntheses of polycavernoside A **1** have been reported.[2]

Our retrosynthetic analysis of polycavernoside A **1** is depicted in Figure 1. Classical disconnections of the C1–O and C9–C10 bonds lead to three fragments. The Southern part of the target molecule embodies a tetrasubstituted tetrahydropyran core **7** and a disaccharide residue **6**. Our group has previously disclosed an expedient synthesis of **7**[3] and the disaccharide residue has already been prepared efficiently by Murai and co-workers.[4] In this Letter, we describe an innovative approach towards the Northern fragment **2** of polycavernoside A **1**. In our strategy, the triene function present in alcohol **2** would originate from pentadienyl sulfoxide **3**, aldehyde **4** and isobutyraldehyde **5**. γ-Butyrolactone **4** has already been assembled using a tandem ene-reaction, intramolecular oxidative cyclization protocol.[5] The salient features of the methodology reported in this Letter revolve around the use of the allylic sulfoxide **3** as a 1,5-dianion equivalent.

The rearrangement of allylic sulfoxides **8** to allylic sulfenates **9** was discovered and developed in the sixties by Mislow and coworkers,[6] Braverman and Stabinsky[7] and Evans et al.[8] The so-called Mislow–Braverman–Evans rearrangement is a reversible [2,3]-sigmatropic shift and the equilibrium is usually strongly biased towards the allylic sulfoxide **8** (Fig. 2).

In the early 1980s, Corey described the interesting behaviour of 1-phenylsulfinylmethyl-1,3-butadiene **3** which underwent a double sigmatropic rearrangement; the sulfoxide moving rapidly at

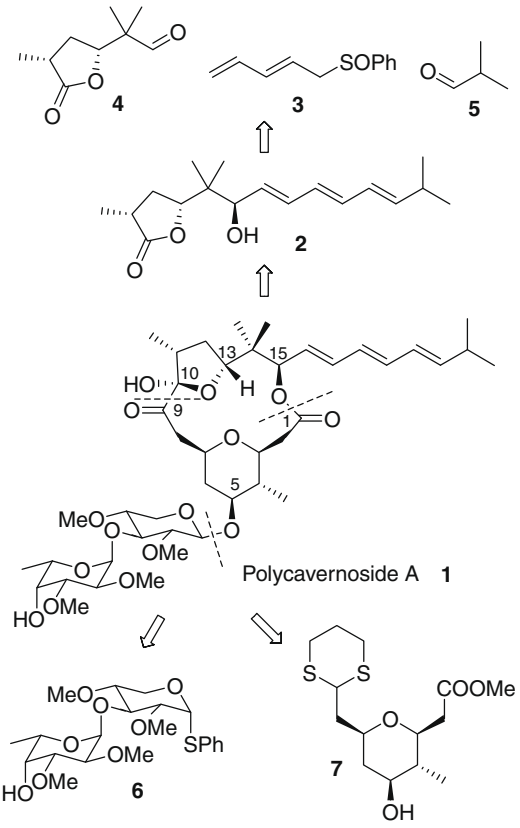

Figure 1. Proposed retrosynthesis of polycavernoside A **1**.

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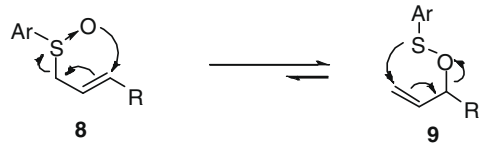

Figure 2. Mislow–Braverman–Evans rearrangement of allylic sulfoxides.

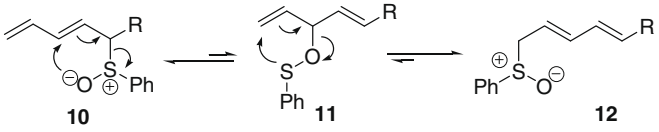

Figure 3. Displacement of the equilibrium of substituted pentadienyl sulfoxide.

room temperature along the polyenic chain.[9] As a result, if a substituent is present on one side of the molecule, the equilibrium will be displaced to the terminal sulfoxide **12** in order to generate the more substituted olefin and to minimize steric repulsions (Fig. 3). Despite the synthetic potential resulting from this observation, only a few applications of this compound could be found in the literature.[10]

The particular ability of the sulfoxide to 'walk' along the dienyl system of **3** provides us with a unique entry into the rapid and connective assembly of conjugated trienes. We envisioned that disubstituted trienes such as **13** would originate from the

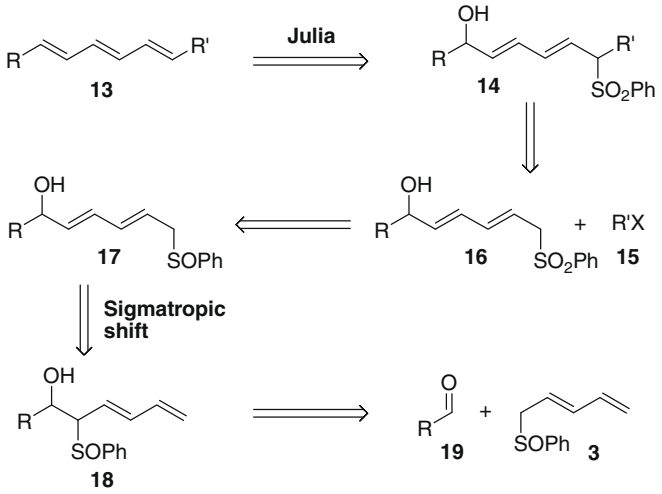

Figure 4. Retrosynthetic analysis of a conjugated triene.

corresponding 1,6-hydroxysulfones **14** by a Julia-type 1,6-reductive elimination. These sulfones would in turn be generated by alkylation at the allylic position of **16**, itself produced by oxidation of sulfoxide **17**. Alcohol **17** would be readily available by addition of the conjugated anion derived from **3** onto aldehyde **19**, followed by the double sigmatropic rearrangement of the

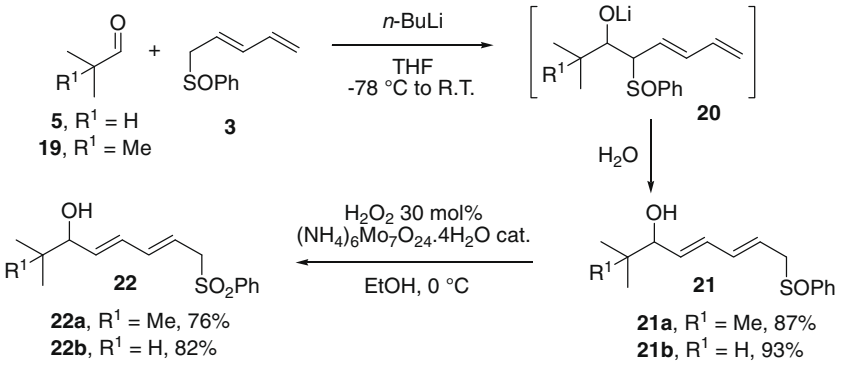

Figure 5. Alkylation-rearrangement-oxidation of allylic sulfoxide **3**.

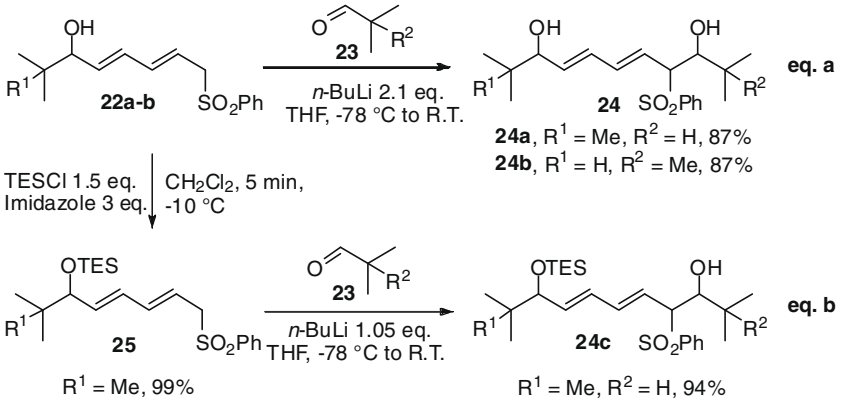

Figure 6. Alkylation of pentadienyl sulfones.

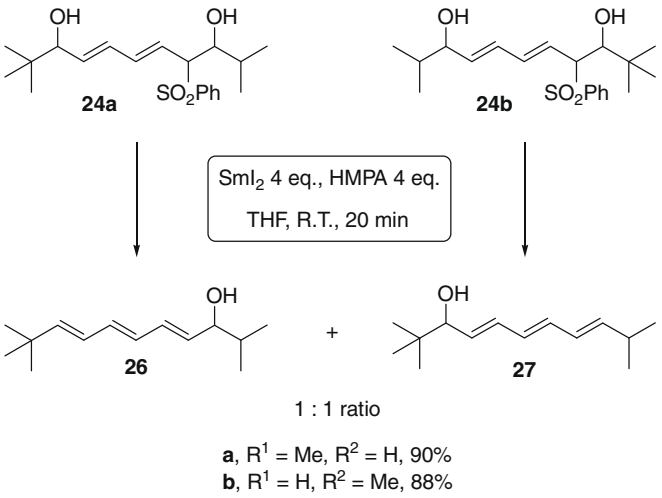

Figure 7. The 1,2- and 1,6-reductive eliminations of **24a–b**.

initially produced sulfoxide **18** to form the terminal derivative **17** (Fig. 4).

In the event, lithiation of **3**, followed by the addition of aldehydes **5** or **19**, proceeded smoothly.[9,10] After double sigmatropic rearrangement of the in situ generated alkoxides **20**, the sulfoxides **21** were oxidized chemoselectively to the corresponding sulfones **22** (Fig. 5). The geometry of the dienyl unit was found to be exclusively (*E*, *E*).

The dienyl sulfones **22** were then easily alkylated at the α-position, either through the use of the dianion (Fig. 6, equation a), or after protection of the secondary alcohol function as a TES ether (Fig. 6, equation b).

In order to create the desired triene functionality, a regio- and stereoselective reductive elimination was required. In view of the potential sensitivity of the triene functionality towards strong reducing agents, it was decided to test the use of SmI_2 initially under conditions akin to those employed in the Julia–Lythgoe olefination (Fig. 7).[11]

Gratifyingly, the reaction of alcohols **24a** and **24b** with 4 equiv of SmI_2, at room temperature, smoothly generated the desired trienes in excellent yields. Unfortunately, although the reaction was stereoselective in favour of the all-trans triene, a 1:1 mixture of **26**:**27** was obtained, indicating a complete lack of selectivity between the 1,2- and 1,6-reductive elimination pathways (Fig. 7).

Interestingly, the silyl ether **24c** displayed the same behaviour as the free alcohols **24a–b**. Indeed, the silylated alcohol had no influence on the competition between the 1,2- and 1,6-reductive eliminations and a 1:1 mixture of **26**:**28** was observed (Fig. 8).

In stark contrast, addition of the benzoates **29a–b**, prepared by selective protection of the distal hydroxy function of **24a–b** using BzCl/TMEDA[12] (Fig. 9), to a THF solution of SmI_2, at −78 °C, resulted in the exclusive formation of the desired trienes **26a–b**.

This particular sequence deserves some comment. Indeed, the chemoselective protection of the remote hydroxy group can be performed with high selectivity because of the presence of a particularly strong hydrogen bond between the proximal alcohol

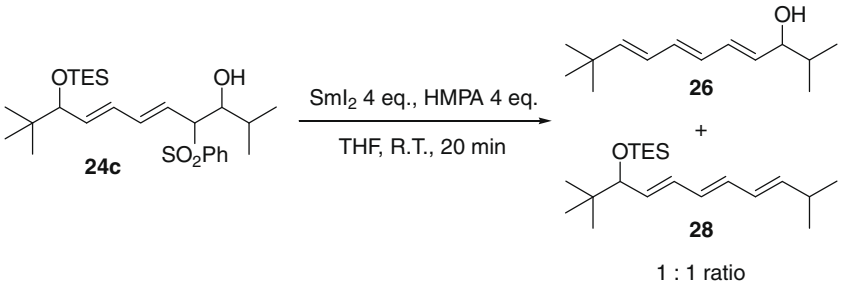

Figure 8. The 1,2- and 1,6-reductive eliminations of **24c**.

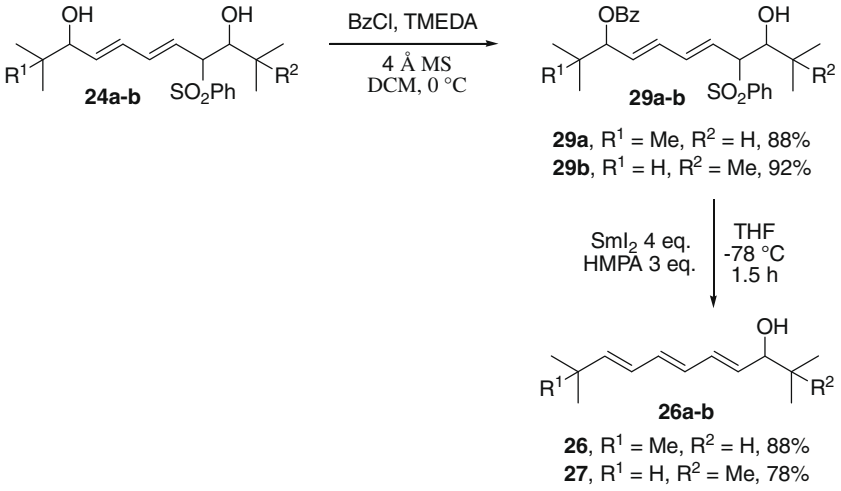

Figure 9. Regio- and stereoselective 1,6-reductive elimination of **29a–b**.

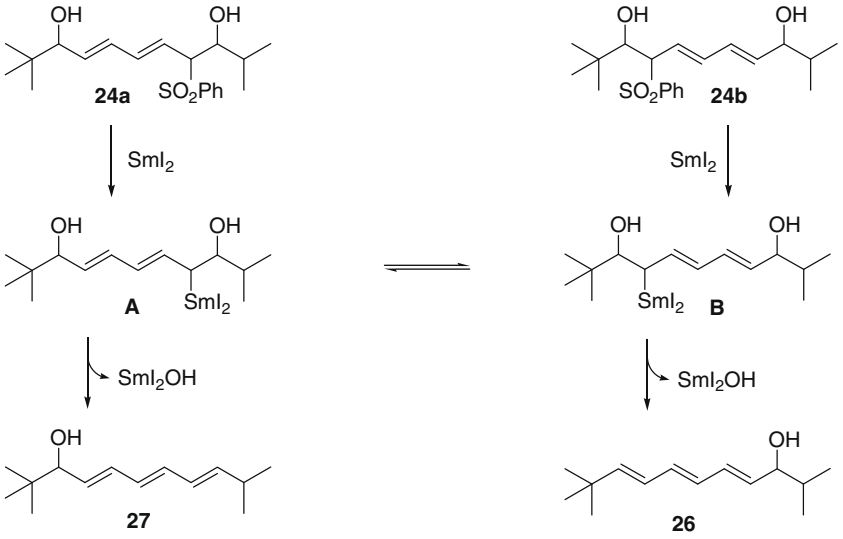

Figure 10. Proposed mechanism for the reductive elimination of alcohols **24a–b**.

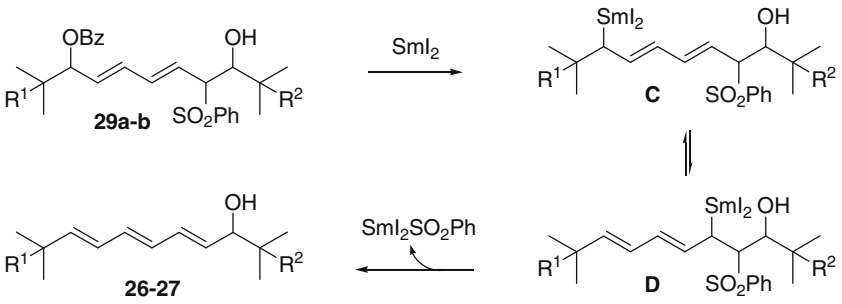

Figure 11. Proposed mechanism for the reductive elimination of benzoates **29a–b**.

function and one of the oxygens of the sulfone residue. This interaction strongly decreases the reactivity of the β-hydroxy substituent. The selective 1,6-reductive elimination of the benzoyl sulfone originates from the chemoselective activation of the benzoate moiety by SmI_2.[13]

In the case of substrates **24a–b**, samarium diiodide reduces the phenylsulfonyl group, leading to carbon–sulfur bond cleavage and generation of the putative organosamarium species **A** and **B**, respectively. Direct elimination of SmI_2OH would result in the regioselective formation of trienes **26** and **27**. However, a competitive 1,5-migration of SmI_2 generates an equilibrium between **A** and **B**, leading to a complete lack of selectivity in the elimination step (Fig. 10).

In contrast to this non-selective reductive elimination process, reaction of SmI_2 with esters **29a–b** chemoselectively results in the generation of the benzoate radical anion, followed by cleavage of the C–O bond and formation of the samarium species **C** (Fig. 11). After 1,5-migration, elimination of SmI_2SO_2Ph from intermediate **D** affords the desired trienes **26** or **27**, exclusively.

With an efficient methodology for the rapid and connective assembly of trienes in hand, we next turned our attention to the synthesis of the Northern fragment of polycavernoside A **1** (Fig. 12). In this particular case, we envisioned as the key step the coupling between sulfone **22b** and aldehyde **4**. Double deprotonation of **22b**, followed by addition of lactone-aldehyde **4**[4] afforded the corresponding diol-sulfone which was chemoselectively acylated with benzoyl bromide in the presence of triethylamine and DMAP. Only the distal alcohol reacted and hydroxysulfone **30** was obtained in high yield and selectivity. Reductive elimination using SmI_2 furnished the target molecule **2**, possessing an all-trans geometry of the C=C double bonds.

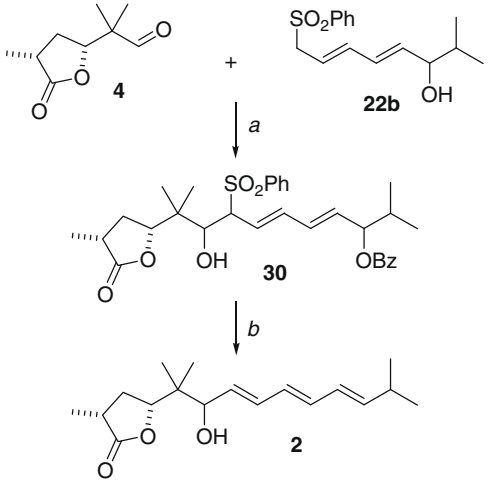

Figure 12. Synthesis of the Northern fragment **2** of polycavernoside A. Reagents and conditions: (a) (i) *n*-BuLi 2.05 equiv, **4**, THF, −78 °C to rt, 94%; (ii) BzBr, NEt_3, DMAP, DCM, −78 °C, 89%; (b) SmI_2 4 equiv, HMPA 4 equiv, THF, rt, 4 h, 94%.

Although alcohol **2** was obtained as a 1:1 mixture of epimers, both isomers can be used in the next step of the synthesis. Indeed, the 'good diastereoisomer' can be coupled under classical esterification conditions while the wrong one could, in principle, be united to the bottom half using Mitsunobu's conditions.

In summary, an efficient synthesis of the Northern fragment **2** of polycavernoside **A 1** has been developed using a novel methodology based upon the sigmatropic rearrangement of dienyl sulfoxides. An unprecedented 1,6-reductive elimination has been performed selectively in the presence of a 1,2-hydroxysulfone. This approach gave access to the desired triene **2** with an excellent overall yield of 60%. These results clearly demonstrate the viability of our methodology. Efforts are now currently dedicated to broadening the scope of this connective synthesis of polyenes and applying it as a key step in the assembly of various natural products.

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