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Concise and stereocontrolled synthesis of the southern γ-butyrolactone subunit of polycavernoside A

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Abstract

The southern γ-butyrolactone subunit **8** of polycavernoside A was readily assembled by a novel and connective methodology involving an initial ene-reaction followed by an intramolecular oxidative cyclisation. © 2000 Published by Elsevier Science Ltd.

Keywords: ene reactions; oxidation; silicon; lactones; polycavernoside A.

In the preceding communication, we have disclosed some of our results on the establishment of an efficient and connective novel methodology for the rapid and stereocontrolled assembly of silyl-substituted γ-butyrolactones **3**, based upon a tandem ene-reaction/oxidative cyclisation of aldehydes **1** with allylsilane **2**.[1] Subsequent functionalisation of **3** afforded a simple preparation of variously substituted *exo*-methylene-γ-butyrolactones **4** (Fig. 1).

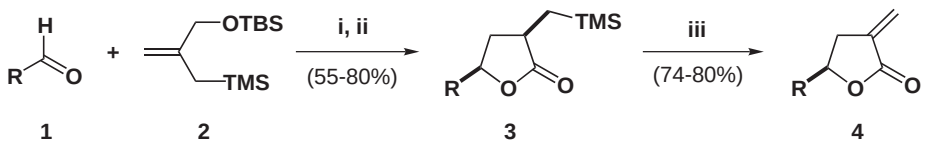

Figure 1. i = Et_2AlCl; ii = TBAF/THF then TPAP/NMO; iii = LDA/TMSCl then NBS then TBAF

In this article, we wish to report an expedient synthesis of the southern γ-butyrolactone subunit of polycavernoside A **5**,[2] a marine toxin isolated by Yasumoto et al. in 1992 and responsible for fatal human intoxication on the island of Guam,[3] using as a key-step our novel ene/oxidative cyclisation methodology. Our retrosynthetic analysis is described in Fig. 2.

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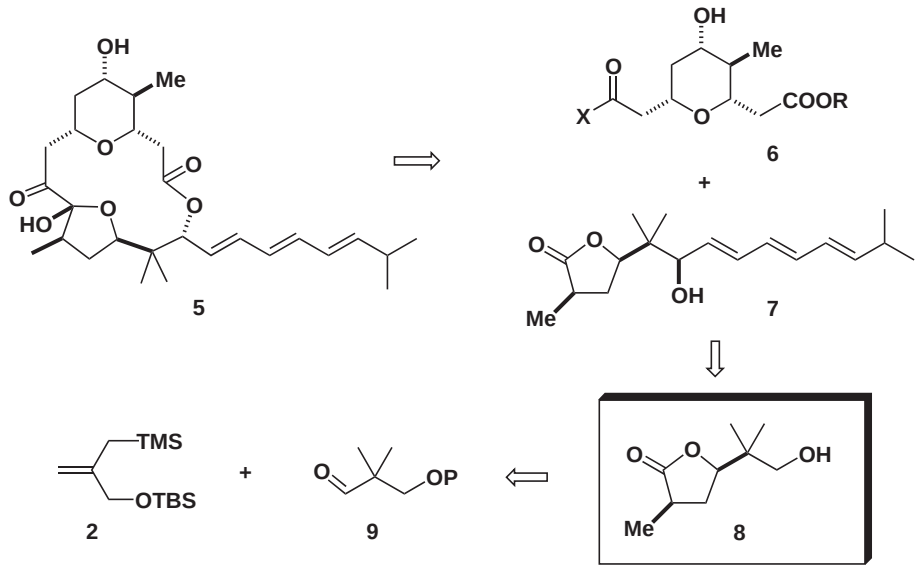

Figure 2.

Cleavage of the macrocyclic lactone and α-ketol functions of **5** generated two fragments **6** and **7** of approximately the same molecular size. Removal of the polyene portion of subunit **7** afforded butyrolactone **8**, which was further disconnected, by application of the ene-oxidative cyclisation retron, to the allylsilane **2** and the key aldehyde **9**. Our synthesis of **8** is illustrated in Fig. 3.

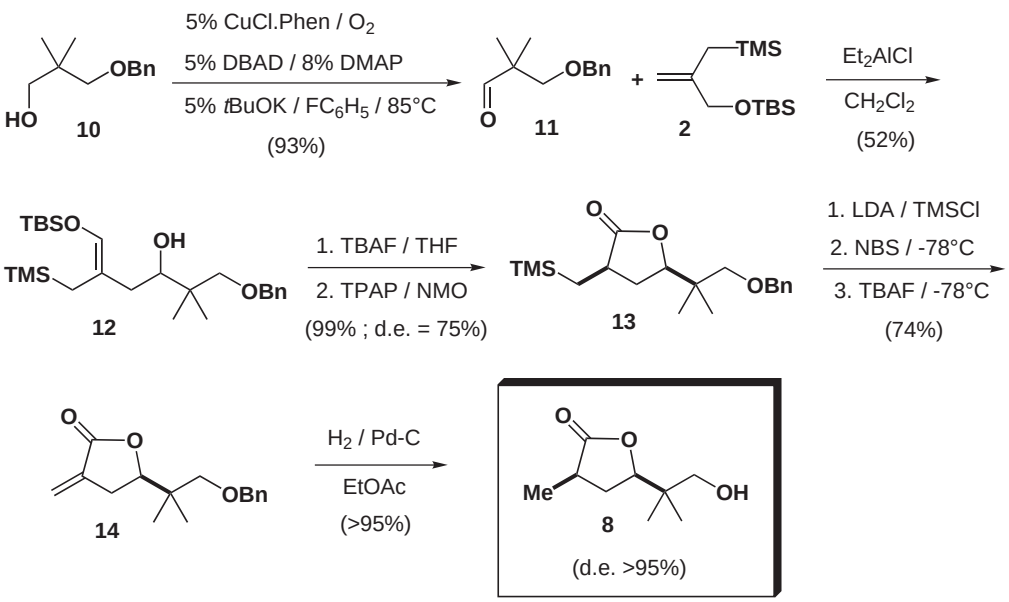

Figure 3.

Oxidation of the monoprotected alcohol **10**, using a modification of our recently reported copper-catalysed aerobic oxidation protocol,[4] delivered the desired aldehyde **11** in 97% isolated yield. Subsequent ene reaction between aldehyde **11** and allylsilane **2**, catalysed by Et_2AlCl, generated the required enolsilane **12**, which was submitted to a chemoselective oxidative–desilylation procedure, affording in excellent yield the desired α-(trimethylsilylmethyl)-lactone **13** (d.e.: 75%). Transformation of **13** into the corresponding α-methylenelactone **14**, via the one-pot protocol described in Fig. 3, proceeded smoothly and afforded product **14** in 74% yield. Finally, catalytic hydrogenation using Pd/C in EtOAc,[5] reduced the *exo*-methylene C–C double bond and simultaneously removed the benzyl protecting group, directly producing the *syn*-disubstituted lactone **8** in quantitative yield and as a single diastereoisomer, possessing the correct stereochemistry and functionality for further transformation into the southern portion of polycavernoside A.[6]

The extremely high selectivity observed during the catalytic hydrogenation of the *exo*-methylene double bond of **14** appeared rather surprising in light of previous results obtained in the reduction of 5-substituted *exo*-methylene γ-butyrolactones.[7] Closer examination of the products formed during the early stages of the hydrogenation revealed that a rapid, metal-catalysed, isomerisation of the exocyclic double bond of **14** into the endocyclic position took place, generating butenolides **15** and **16**. A subsequent, and more sluggish, reduction of this trisubstituted alkene eventually afforded the final product **8**. It thus transpires that the high facial selectivity observed in the formation of **8** results from a 1,2-diastereocontrol, the bulky side chain at C_5 directing the approach of the reductant from the α-face of butenolides **15** and **16** (Fig. 4).

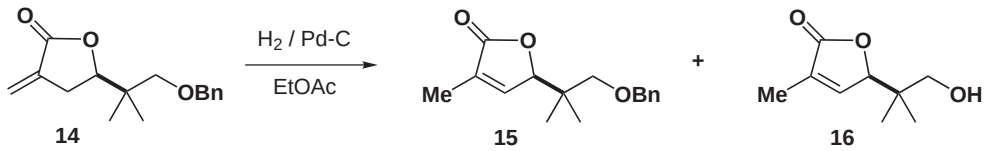

Figure 4.

In summary, we have reported a concise and efficient synthesis (five steps, 35% overall yields) of the southern lactone subunit **8** of polycavernoside A, using as a key-step our recently disclosed ene/oxidative cyclisation methodology. Current efforts are now being directed towards delineating the full scope of this connective methodology, defining an enantioselective version and completing the total synthesis of polycavernoside A **5**. The results of these investigations will be reported in due course.

Acknowledgements

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