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A Convergent Route to the Spirohexenolide Macrocycle

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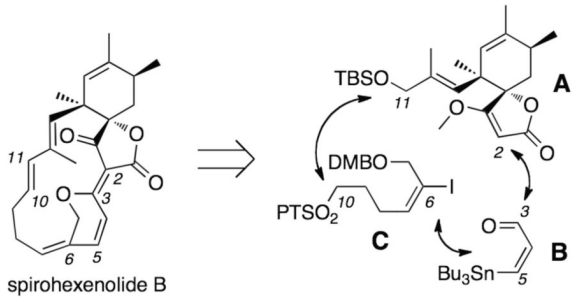
Abstract



Using key functional dissections, the synthesis of spirohexenolides is examined through a three component strategy that features a 1,2–addition to couple tetronate and aldehyde components forming the C2–C3 bond, and a Stille coupling to install the third sulfone–containing component. The macrocycle is completed by an intramolecular Julia–Kocienski reaction to form the C10–C11 *trans*–disubstituted olefin. Application of this strategy is described in progress towards the synthesis of (±)–spirohexenolide B.

The spirohexenolides A (**1a**) and B (**1b**)1 comprise a family of structurally unique spirotetronate natural products2 isolated from strains of *Streptomyces platensis* (Scheme 1).3 Preliminary cytotoxic screening studies indicated that the spirohexenolides displayed a unique activity in the NCI–60 cell line analysis, while maintaining a low toxicity in mice.1 This data combined with a unique uptake and localization within tumor cells suggested a novel mode of action, which was recently shown to target the human macrophage migration inhibitory factor (hMIF).4 Exploratory studies on the natural material identified only one position, the C8 carbinol, which could be readily modified and retain activity.4 Efforts were focused on developing synthetic entry to the class in order to perform more complete structure–activity relationship (SAR) studies for preclinical evaluation.

Given the comparable activity1,4 of spirohexenolide A (**1a**), B (**1b**) and the corresponding acetate **1c** (Scheme 1), our studies focused on preparation of the putative biosynthetic deoxy–precursor **1b**.

A modular strategy was implemented based on dissection of the molecule into three components: spirotetronate **5**, aldehyde **6**, and sulfone **7** (Scheme 1). A four–staged process

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Supporting Information Available: Experimental procedures and copies of NMR spectra from compounds **2**–**5**, **7**, **8**–**13**, **15**–**19**, cif files for the X-ray structures of **12** and **23**, as well as a further description of the oxidation of **19** and related model studies are available free of charge via the Internet at http://pubs.acs.org.

was envisoned for their assembly that began by the addition of the lithium salt of **5** to aldehyde **6**.5 The resulting adduct **4** had the required vinyl stannane handle for a Stille coupling with iodide component **7**. With all three components in place, a Julia–Kocienski olefination would then complete the carbocyclic framework enabling completion of the synthesis through dehydrative pyran formation, as illustrated in the conversion of **2** to **1b** (Scheme 1).

Our studies began by preparation of the northern component, spirotetronate **5** (Scheme 2). Diastereoselective construction of the cyclohexene system was accomplished by the Lewis acid catalyzed Diels–Alder reaction of triene **9**, prepared from readily available ester **8**,6 with α–acetoxyacrolein7 as the dienophile. The reaction favored the desired regioisomer, as precedented by a previously reported reaction using a similar triene substrate with α-bromoacrolein as the dienophile under Lewis acid catalysis.8a The adduct formed with high *endo* selectivity, as expected from previous studies on similar substrates.8 Adduct (±)–**10** could be separated chromatographically from the other non-aldehydic byproducts, which constituted the majority of the remainder of the reaction mixture, when a benzoate protecting group was used on the primary alcohol. Using this procedure pure (±)–**10** could be obtained in a 74% overall yield from **8**.

Oxidation of aldehyde **10** proved difficult; buffered $KMnO_4$ 9 and $NaClO_2$ 10 both failed to provide good conversion to the carboxylic acid. However, it was found that I_2 in basic methanol11 offered acceptable conversion to the methyl ester. While effective, the highly alkaline nature of this reaction resulted in the removal of the acetate and partial cleavage of the benzoate group, which necessitated further processing to converge at diol **11**. The structure of **11** was further confirmed by collection of an X–ray crystal structure of a derivatized *p*–bromobenzoate **12** (inset, Scheme 2).

With the structure of ester **11** confirmed, we turned to reinstall an acetate at the tertiary hydroxyl group in order to construct the tetronate ring by a Dieckmann cyclization. Lewis acid catalysis with $Sc(OTf)_3$ provided excellent conversion to the corresponding bis–acetylated product,12 which was then converted to the primary TBS ether **13**. Switching to TBS protection at C11 was key to achieving a satisfactory yield of the spirotetronate product **5**. The desired Dieckmann cyclization was effected by the treatment of **13** with LiHMDS in a mixture of HMPA and THF,13,14 followed by methylation of the incipient tetronic acid salt with dimethylsulfate (Scheme 2). While not fully optimized, this route offered a 22% overall yield of **5** in 9 steps from **8**.

Our studies then turned to construction of the component **7**. By applying methods of Bates, 15 gram quantities of alkyne **14** were prepared from oxetane and then converted to the corresponding 1–phenyl–1*H*–tetrazol–5–yl (PT)16 sulfone **15** in two steps under conventional conditions (Scheme 3). At scales greater than 0.1 mol, the oxidation conditions and workup directly effected deprotection of the THP group, affording carbinol **15**.

We then turned to complete fragment **7** by installation of the vinyl iodide. While it was expected that the primary carbinol would direct the hydrostannation,17 the regioselectivity of this process was low, which after iodination afforded **16** in only 18% after purification. Given the rapid access to this grams of precursor **15** (an overall yield of 84% in 2 steps from **14**), we did not focus on optimization. Rather, we turned our efforts to evaluate the component assembly. This necessitated protection of **16** as the 3,4-dimethoxybenzylether **7** using lepidine **17** in a comparable manner to that developed by Dudley for the formation of PMB ethers.18

The assembly process began with the coupling of components **5** and **6**. Using established protocols,19 lithium salt of tetronate **5** was prepared and added to aldehyde **6** to afford

stannane **4** as an inseparable 1 : 1 mixture of diastereomers (Scheme 4). The resulting product was then coupled under modified Stille conditions20 to vinyl iodide **7** to afford adduct **3**. Protecting group manipulations, followed by oxidation with TPAP,21 delivered aldehyde **18**, as a 1 : 1: mixture of inseparable diastereomers. Macrocyclization was achieved by the intramolecular Julia–Kocienski olefination22 of one of the diastereomers of **18** to afford *E*–olefin **2** (Scheme 1), which was desilylated to provide alcohol **19**. Evidence for the *trans*–configuration at C10–C11 bond was indicated by a $^{3}J_{H10–H11}$ = 15.5 Hz in **2** and 16.0 Hz in **19**.23

Initial attempts to purify the macrocycle **18** were hindered by coelution of oligomeric byproducts, presumably from the diastereomer of **18** that did not cyclize. We eventually isolated pure **19**22 by improved chromatographic conditions.

With the full carbocyclic framework intact, conversion to spirohexenolide B (**1b**) seemed to be just at hand through a three–step sequence (left, Scheme 5). As outlined, the plan called for oxidation at C3 followed by removing the DMB protecting group at C21, and a dehydrative deprotection of tetronate **2**.

Unfortunately, the oxidation of allylic alcohol **19** was problematic, with only Dess–Martin periodinane or IBX providing a single ketone product (see Supporting Information). However, inspection of the resulting ^{1}H–NMR spectrum showed that the disubstituted olefin in the enone chemical shift region was *trans*, with a $^{3}J_{H-H}$ = 16.0 Hz, indicating that the product was not ketone **20**.

In the process of further evaluating the structure of **22**, we removed the DMB protecting group with DDQ. Samples of the resulting carbinol **23** were crystallized (mp = 170–172 °C). The X–ray crystallographic structure was determined (Scheme 5), indicating that transposition of the allylic alcohol from C3 to C5 had occurred during the oxidation of **19**, which then oxidized to afford dienone **22** and not the desired isomer **20**. To confirm that the rearrangement had occurred at the oxidation step and not during some previous operation, we conducted gCOSY, gHSQC and gHMBC analyses of compound **19**, all of which support the proposed structure. This NMR evidence, combined with the crystal structure of dienone **23**, indicates that the macrolide core of **1b** was complete.

To date, we have demonstrated methods to prepare the intact, racemic, skeleton of the spirohexenolides. Efforts are now underway to establish methods to install the pyran motif at an earlier stage within the synthesis as well as to develop routes that could deliver intermediates **20** or **21** *en route* to a total synthesis of **1b**.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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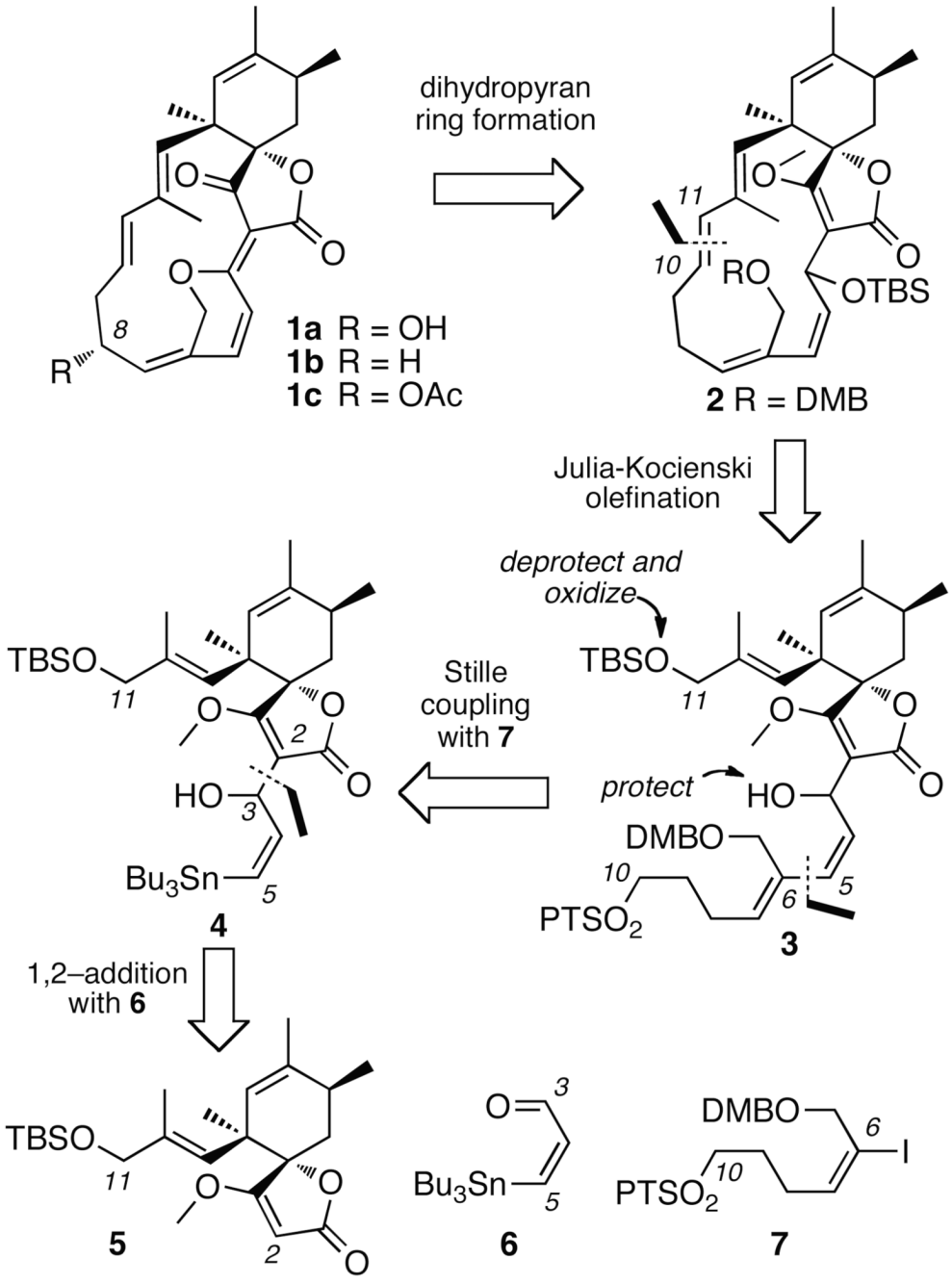
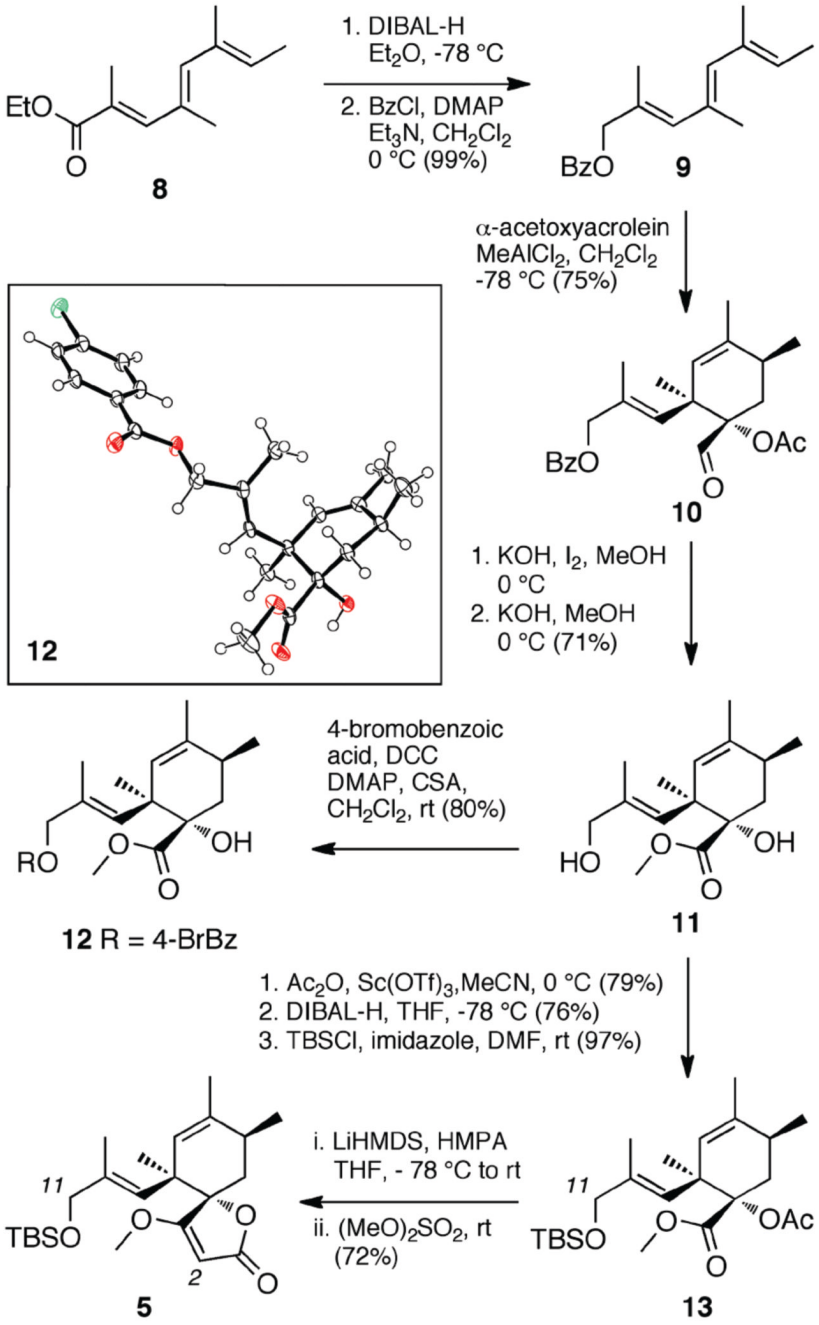
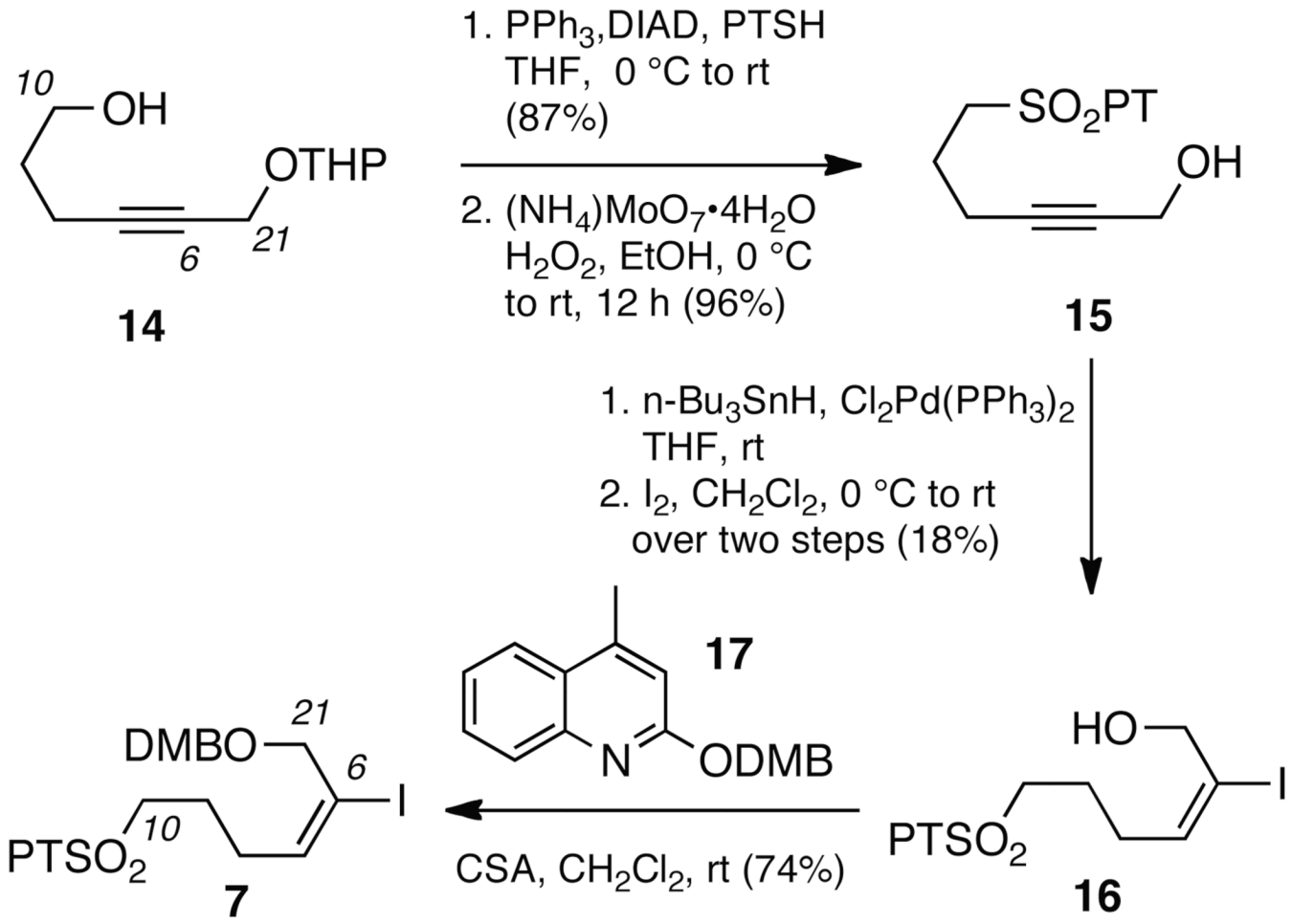
23. Assignment of the relative stereochemistry at C3 in **2** or **19** was not attempted, but may be possible through NOESY studies or modification of the C3 -OH of **19** to form a crystalline derivative.



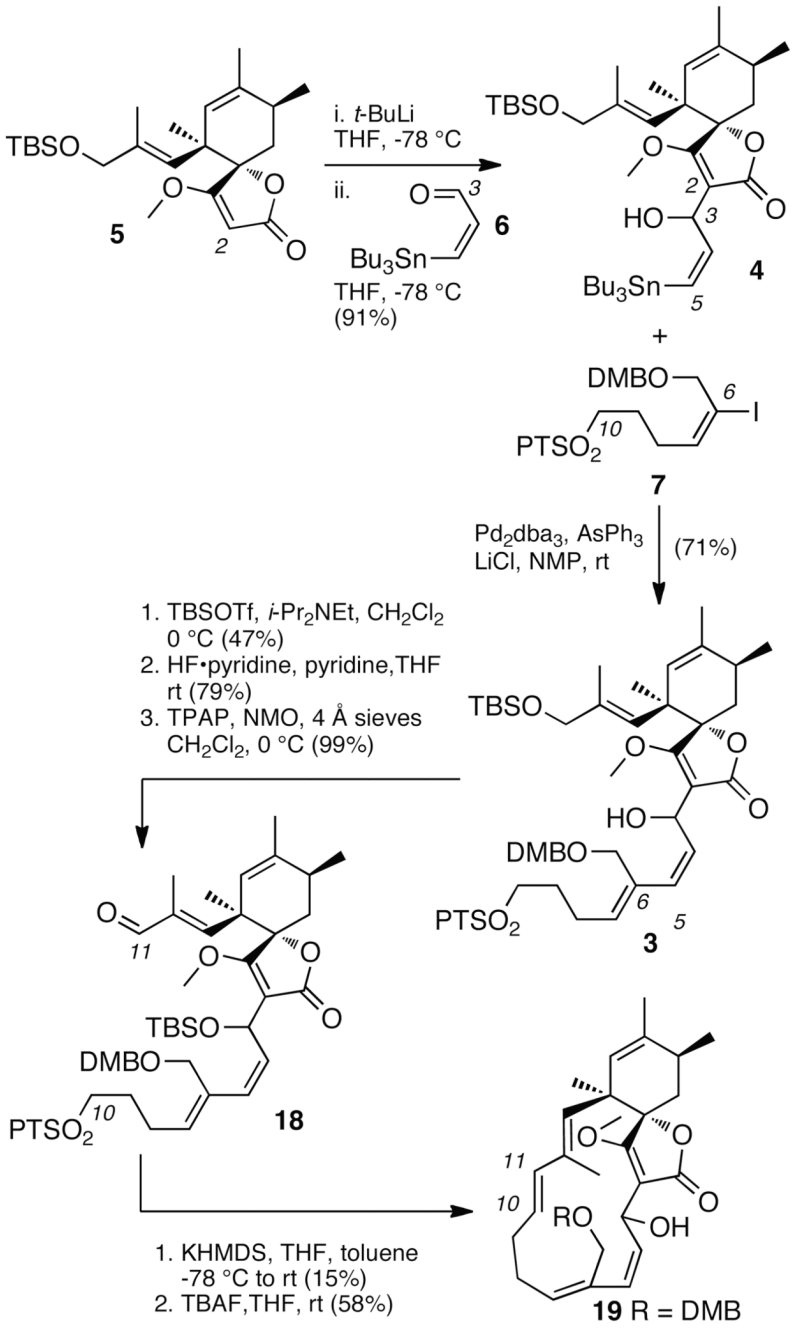
Scheme 1.
Retrosynthetic analysis of spirohexenolide B (**1b**)



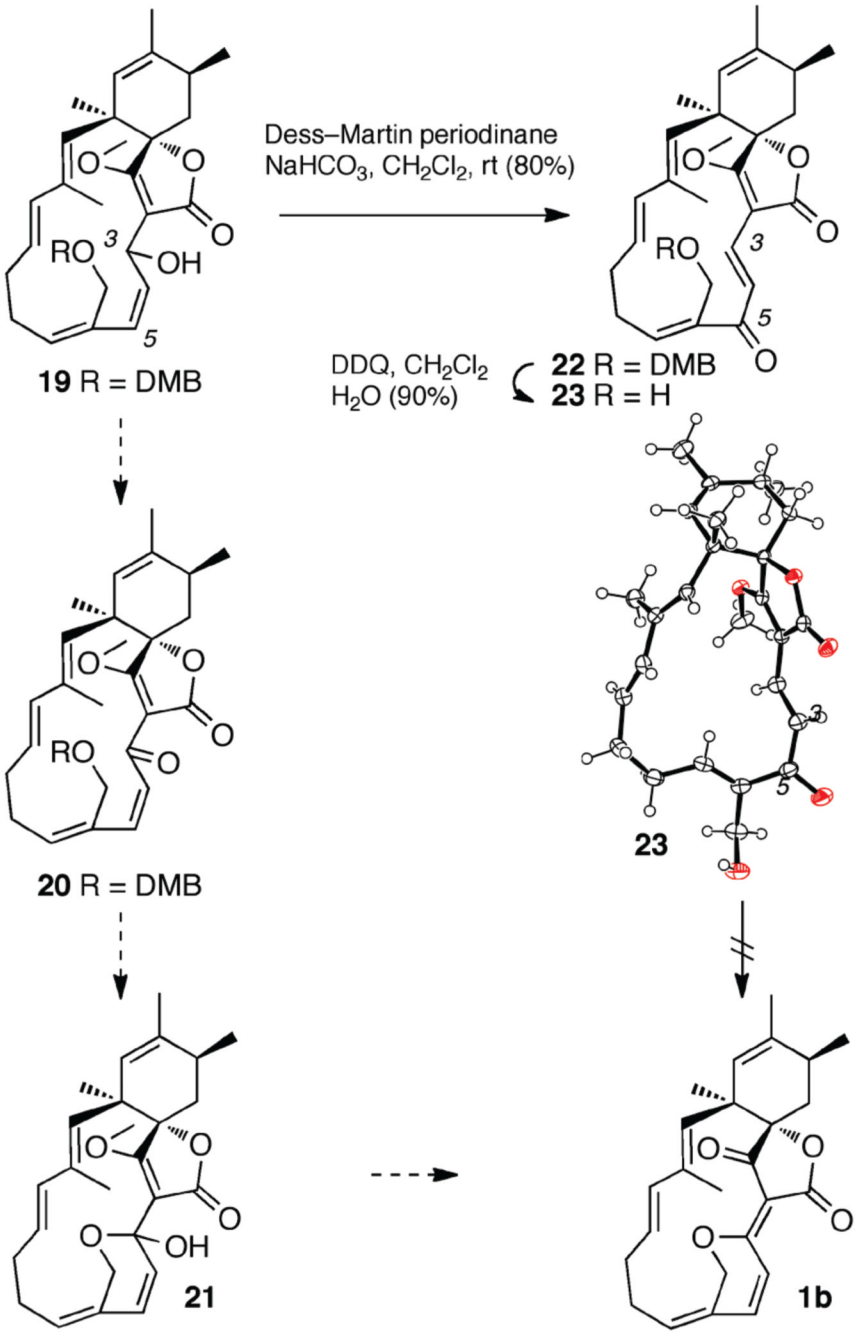
Scheme 2.
Synthesis of the tetronate component **5**



Scheme 3.
Synthesis of the vinyl iodide component **7**.



Scheme 4.
Component assembly.



Scheme 5.
Attempted conversion to spirohexenolide B (**1b**)