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Synthesis of Plakortone B and Analogs

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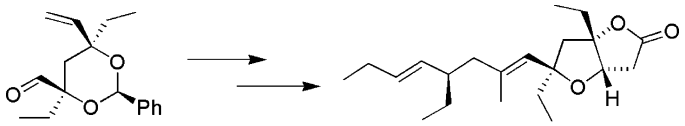
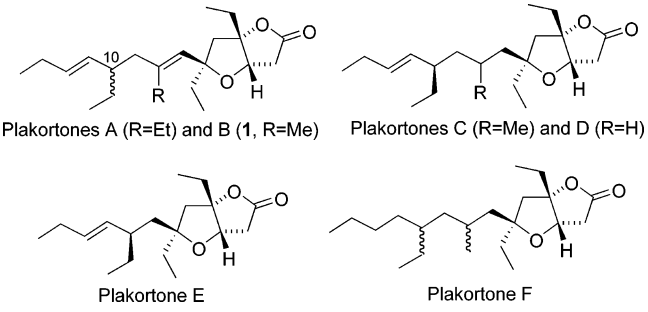
ABSTRACT



Plakortone B

Use of a palladium-mediated alkoxycarbonylation/lactonization process provides a variable route to analogs of the plakortones. Four different analogs, including natural plakortone B, have been synthesized via this route.

The plakortones are a family of natural product furanolactones isolated from the Caribbean sponges *Plakortis halichondrioides* (plakortones A−D)[1] and *Plakortis simplex* (plakortones B−F; Figure 1).[2] Plakortones A−D show activity as activators of the cardiac sarcoplasmic reticulum Ca^{2+} ATPase (SERCA).[1] Molecules with this activity are of interest as agents to increase calcium pumping in order to correct cardiac muscle relaxation abnormalities.[3] Diverse structures such as gingerol and heparin show similar activity; however, neither has been shown to be clinically effective.[4] From the limited published activity data on the plakortones, a hypothesis was presented that the central core furanolactone is necessary for function, and the hydrophobic "tail" might be altered to provide maximum efficacy.[1] A synthetic route that allows for rapid construction of plakortone analogs with variable side chains is therefore desirable. The configurations of the plakortone side chains were not confirmed in the initial isolation. Recent syntheses of D and E established the configuration at C_{10} shown in Figure 1.[5] However, the C_{10} configuration in plakortones A−C and F is still undetermined.



Plakortones A (R=Et) and B (**1**, R=Me)

Plakortones C (R=Me) and D (R=H)

Plakortone E

Plakortone F

Figure 1. The plakortone family.

A key operation in the retrosynthetic analysis of plakortone B (**1**, Scheme 1) is creation of the furanolactone core by intramolecular alkoxypalladation−lactonization as developed previously in this laboratory[6] and also applied by Kitching.[5a] Access to diol **2** (along with other analogs) could be achieved by a metal-catalyzed sp^2-sp^3 coupling reaction between **3**

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(4) (a) Kobayashi, M.; Shoji, N.; Ohizumi, Y. *Biochim. Biophys. Acta* **1987**, *903*, 96. (b) Xu, Z. C.; Kirchberger, M. A. *J. Biol. Chem.* **1989**, *264*, 16644.

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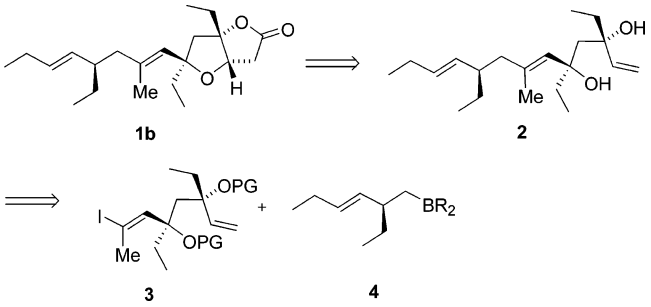
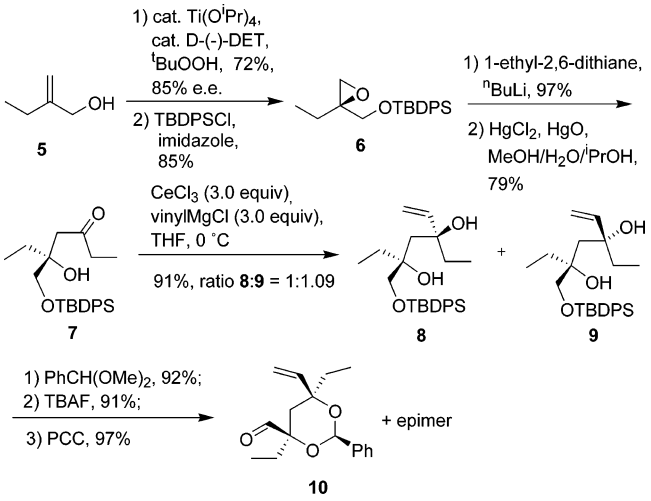
Scheme 1. Retrosynthetic Analysis of Plakortone B



and one of a variety of side chain derivatives (exemplified here by the borane **4**).[7] Variation in the structure of **4** would provide an array of plakortone analogs.

The synthesis of core precursor **10** began with the Sharpless asymmetric epoxidation[8] of alcohol **5** followed by silylation to give epoxide **6** in good yield and 85% ee (Scheme 2). Epoxide ring opening with the anion from

Scheme 2. Synthesis of the Core Structure of Plakortone B

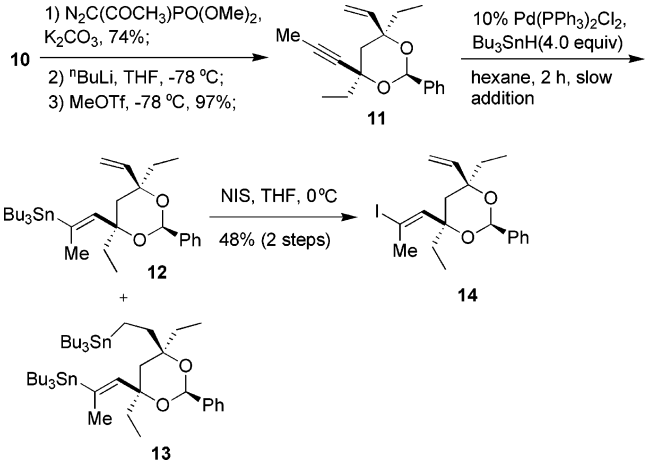


1-ethyl-2,6,-dithiane,[9] followed by oxidative deprotection,[9b] provided hydroxyketone **7**. The diastereoselective vinylation of **7** proved difficult, as the hydroxyl moiety gave essentially no selectivity using a variety of carbon nucleophiles and enolization reduced the efficiency of the reaction with certain carbanions. However, treatment with in situ generated vinylcerium chloride[10] provided the two diastereomers **8** and **9** in high overall yield. Complete separation was effected by preparative HPLC.

Protection of quaternary diol **9** was not trivial. The protection must occur under mild conditions for compatibility with the tertiary allylic alcohol, and the group must be easily removed later in the synthesis. The benzylidene acetal, formed by treatment of **9** with catalytic acid and benzaldehyde dimethyl acetal, satisfies both criteria. The protection gave a mixture of epimers at the acetal position in excellent overall yield. The isomers were easily separable and both are useful, but the major isomer was carried forward in the development of the synthesis. Deprotection and oxidation with pyridinium chlorochromate gave aldehyde **10**.[11] The configuration was confirmed by 1D NOE difference experiments (see Supporting Information)

Conversion of **10** to the corresponding acetylene using the acetyldiazophosphonate protocol[12] was followed by methylation to provide **11** in excellent yield (Scheme 3). Taking

Scheme 3. Synthesis of the Trisubstituted Olefin



advantage of hexane as solvent[13] for Pd-catalyzed hydrostannylations to minimize competitive stannane dimerization, **11** was converted to **12** regiospecifically, but unexpectedly, distannane **13** was formed as a byproduct.

Although hydrostannylation of alkenes is common under radical conditions,[14] the palladium-catalyzed variant is rare and usually occurs only with highly activated olefins.[15] Other

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(9) (a) Seebach, D.; Corey, E. J. *J. Org. Chem.* **1975**, *40*, 231. (b) Grobel, B. T.; Seebach, D. *Synthesis* **1977**, 357.

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(12) (a) Muller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521. (b) Gilbert, J. C.; Weerasooriya, U. *J. Org. Chem.* **1982**, *47*, 1837.

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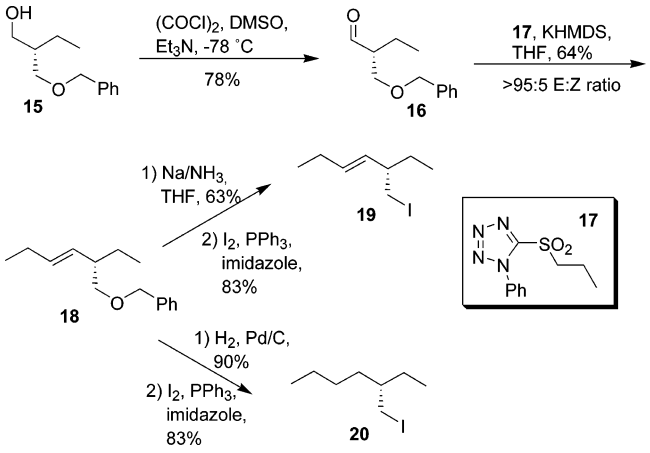
more active catalysts such as $Pd(OAc)_2/PCy_3$ increased the amount of byproduct formed. Slow addition of tri(*n*-butyl)-tin hydride reduced byproduct formation to a manageable level, and vinyl iodide **14** was isolated in 48% yield over two steps.

In order to create side chain analogs of the plakortones, an adaptable synthetic route is required. To illustrate the viability of our strategy, two different side chains were created. Swern oxidation of (*S*)-2-benzyloxymethyl-butanol **15**[16] furnished aldehyde **16**, which was converted into (*E*)-1,2-disubstituted olefin **18** in moderate yield and excellent stereoselectivity by the use of **17** in the modified Julia reaction.[17] From this olefin, two different side chains were easily accessed by varying the conditions used to remove the benzyl protecting group. Pd-catalyzed hydrogenation effected debenzylation along with saturation of the olefin, giving (*S*)-2-ethylhexanol, whereas a dissolving metal reduction removed the benzyl group without affecting the olefin,[18] providing *E*-(*S*)-2-ethylhexen-3-ol. The alcohols were converted to iodides **19** and **20** in good yield with PPh_3/I_2/imidazole. The attachment of the side chains to the core

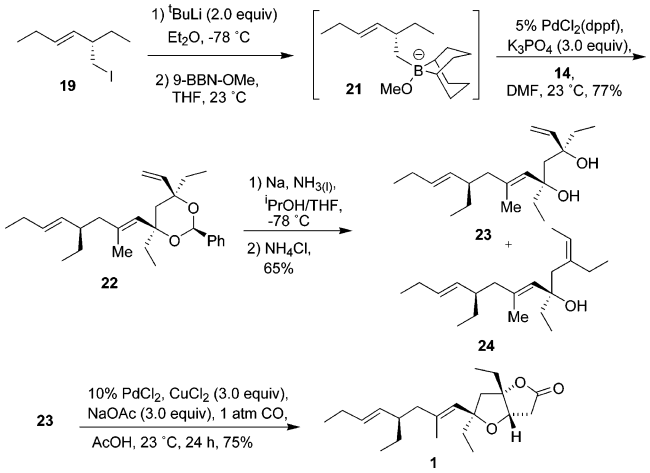
Scheme 4. Synthesis of Two Side Chain Analogs



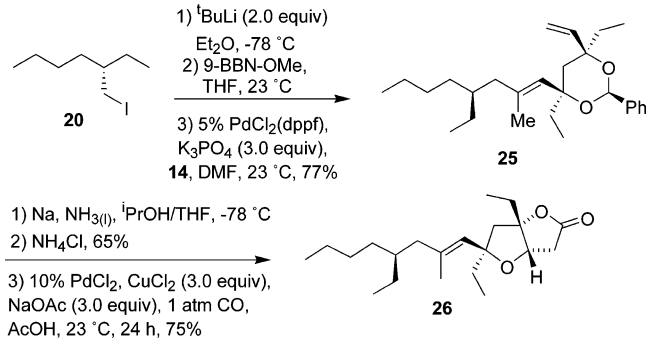
structure **14** requires an sp^3-sp^2 coupling process. Using a modified Suzuki coupling,[7a,c] iodide **19** was converted to the corresponding homoallyllithium, which was then treated with *B*-methoxybora-bicyclo[3.3.1]nonane to form boronate **21** in situ. Addition of vinyl iodide **14** in the presence of $PdCl_2$(dppf) and K_3PO_4 as base effected coupling to give **22** stereospecifically and in good yield. Mild acidic conditions for deprotection of **22** gave no reaction, and more vigorous conditions caused decomposition of the tertiary allylic alcohol product **23**. Hydrogenolysis proved to be incompatible with the olefins. When **22** was treated with a solution of Na/NH_3 in the absence of proton source, clean removal of the acetal was observed, although the major product was not diol **23** but olefin **24**. If the cleavage is performed under Birch reduction conditions in the presence of isopropanol, the yield of diol **23** was increased to 65%.

For the key step, treatment of **23** with catalytic $PdCl_2$ and $CuCl_2$ reoxidant in glacial acetic acid buffered with NaOAc under an atmosphere of carbon monoxide[19] furnished plakortone B (**1b**) in 75% yield. Only one product was observed, and the trisubstituted olefin was not affected by the cyclization conditions. The synthesized plakortone B (**1**) showed good agreement with the published ^1H and ^{13}C NMR spectra of natural plakortone B.[1] On the basis of this good agreement and the work of Kitching in the syntheses of plakortones D and E,[5] it is reasonable to assign the natural stereochemistry at C_{10} of plakortone B as that shown in Scheme 5.

Scheme 5. Completion of the Synthesis of Plakortone B



Scheme 6. Synthesis of 11,12-Dihydroplakortone B **26**



This methodology was then extended to the synthesis of three other plakortone analogs. Coupling of side chain **20** to vinyl iodide **14** as before, followed by reductive deprotection and cyclization, provided 11,12-dihydro-plakortone B in 25% yield overall from vinyl iodide **14** (Scheme 6). Because of

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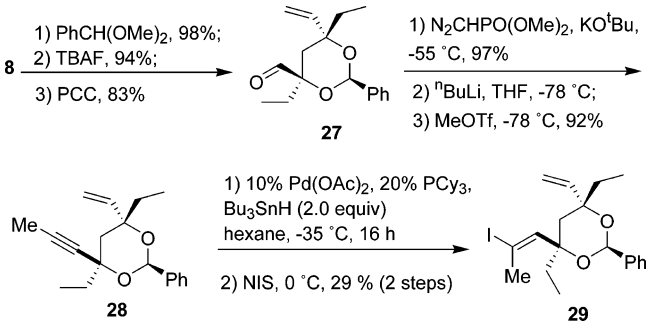
the low selectivity during vinylation of ketone **7**, large amounts of diol **8** were available and could be converted to epimers of the plakortone family (Scheme 7). Core vinyl

Scheme 7. Synthesis of Core Epimer **29**

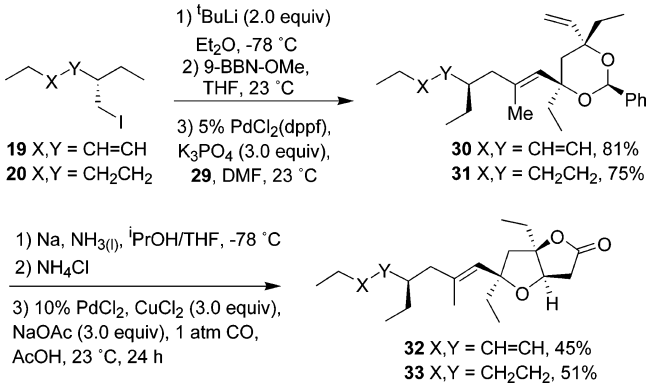


iodide **29** was synthesized using a route parallel to that shown in Schemes 2 and 3. Only one benzylidene acetal epimer (leading to **27**) was formed for this diastereomer of the diol, as opposed to the two observed in the protection of diol **9**.

Conversion to the methylacetylene **28** proceeded smoothly. In this case, the rate of hydrostannylation was much faster, but again competing hydrostannylation of the vinyl group in **28** was observed. When the reaction was performed at −35 °C, the optimum yield of the desired monostannane was achieved. Treatment of the mixture of mono- and distannylation products with *N*-iodosuccinimide gave, after purification, vinyl iodide **29** as one isomer in 29% yield over two steps.

The core vinyl iodide **29** was converted to the desired plakortone analogs by coupling with side chain iodides **19** and **20** as before, followed by reductive deprotection and cyclization to provide 3,4-epiplakortone B (**32**) and 3,4-epi-11,12-dihydroplakortone B (**33**) in 36% and 38% yield, respectively, from vinyl iodide **29** (Scheme 8).

Scheme 8. Syntheses of 3,4-Epiplakortone B **32** and 3,4-Epi-11,12-dihydroplakortone B **33**



In summary, we have established a viable synthetic route to various analogs of the plakortone family, employing an efficient palladium-catalyzed alkoxycarbonylation/ lactonization process on complex intermediates.

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Supporting Information Available: Experimental procedures and product characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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