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Stereoselective Formation of Tetrahydrofuran Rings via [3 + 2] Annulation: Total Synthesis of Plakortone L

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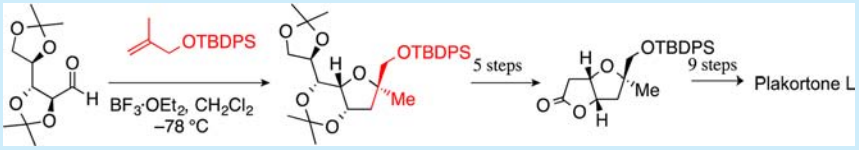
Supporting Information



ABSTRACT: The [3 + 2] annulation of 2,3-*O*-isopropylidene-*aldehydo*-aldose with methallyl ether leads to the stereoselective formation of a substituted tetrahydrofuran system, which is converted to a bicyclic lactone derivative via consecutive deprotection, oxidative cleavage of the terminal diol, oxidation of the resulting lactol, and Barton−McCombie deoxygenation. The efficiency of this process was demonstrated by the first total synthesis of Plakortone L.

Plakortones L, N, and P represent a novel class of furanolactone compounds isolated from the Australian sponge, *Plakinastrella clathrata*, in 2011 by Garson et al.[1] and are classified as the Plakortone family due to their structural similarity. The structures are characterized by an aromatic unit connected to a bicyclic lactone ring system by a methylene chain. Their biological activities have not been assessed because of the small amounts of isolated products available for screening. To date, several studies concerning the total syntheses of Plakortones B−F, a series of biologically active ethyl-branched furanolactones isolated from Caribbean sponges, have been reported;[2−4] however, no synthetic studies on Plakortones L, N, and P have been reported. Herein, we describe the first total synthesis of Plakortone L (**1**, Figure 1), with the stereoselective formation of the substituted tetrahydrofuran moiety.

Previously, we reported a novel method for the construction of tetrahydrofuran derivatives based on the [3 + 2] annulation reactions of electron-rich olefins, such as allylsilanes,[5] vinyl ethers,[6] or vinyl sulfides,[7] with the 2,3-*O*-isopropylidene derivatives of *aldehydo*-aldoses. Recently, we found that methallyl ether was also applicable in this annulation reaction as a nucleophile.[8] This synthetic protocol enabled the stereocontrolled installation of two stereogenic centers on the tetrahydrofuran ring in a single step (Scheme 1). The reaction proceeds via the attack of the nucleophile on the carbonyl group from the less-hindered face (*Si*-face in this case), thus generating a carbocation intermediate. The carbocation is

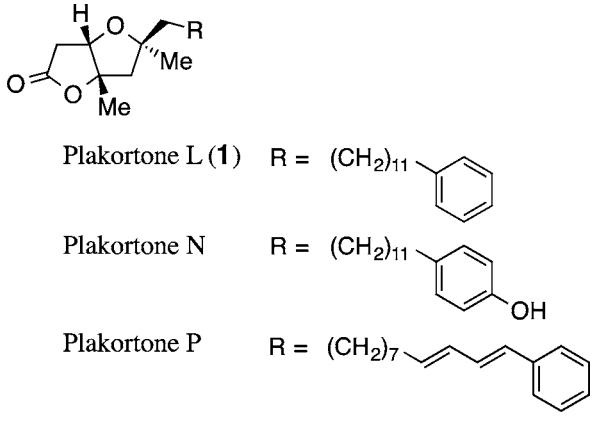
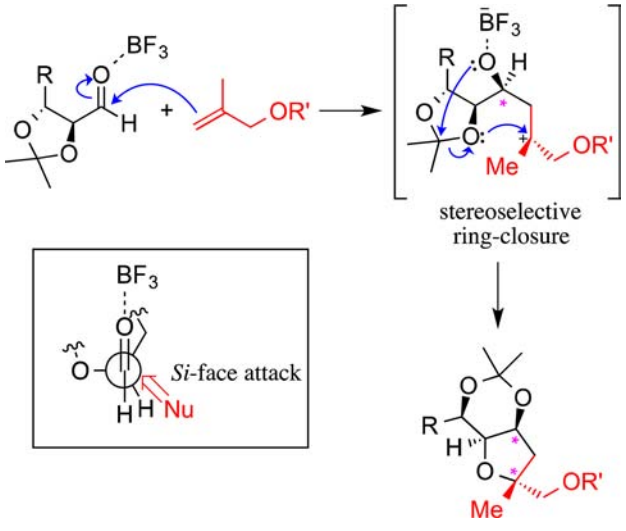


Figure 1. Structures of Plakortone L, N, and P.

Scheme 1. Stereoselective Formation of Tetrahydrofuran Ring



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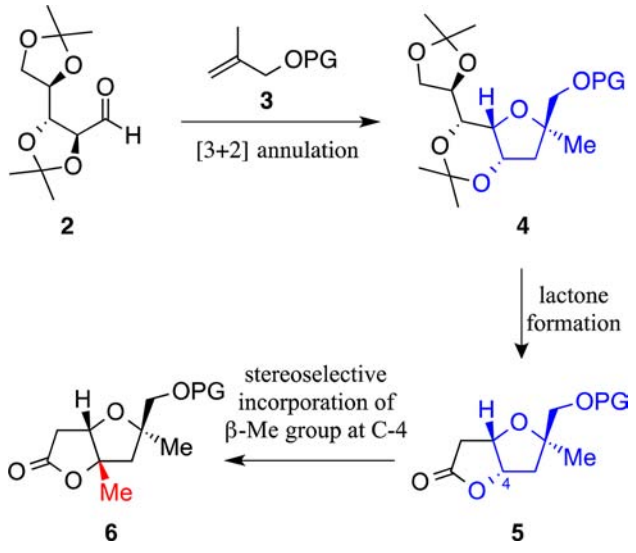
trapped with the spatially neighboring oxygen atom on the sterically favored face to afford the corresponding tetrahydrofuran ring in a stereoselective manner. As a part of the study to apply the annulation reaction to the total synthesis of tetrahydrofuran-containing natural products, we now demonstrate the total synthesis of Plakortone L (**1**).

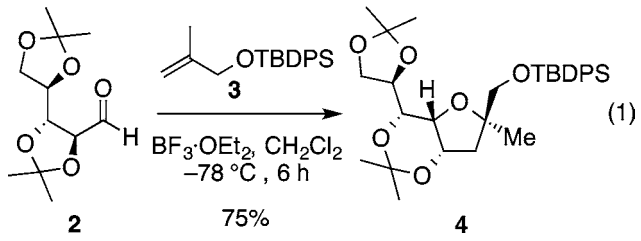
Our approach for the synthesis of the core structure of Plakortones is shown in Scheme 2. We planned the

Scheme 2. Synthetic Strategy for the Common Core Structure of Plakortones

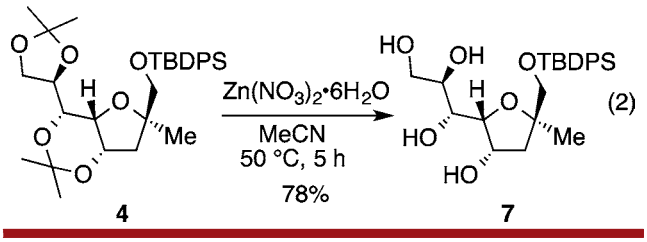


construction of the tetrahydrofuran part by the [3 + 2] annulation of aldehyde **2** with protected methallyl alcohol **3**. Based on our previous synthetic route to *trans*-kumausyne,[5] furanolactone **5** was envisaged from furan **4** in a five-step reaction sequence including the deisopropylidenation, oxidative cleavage of the terminal diol, oxidation of the resulting lactol, and Barton−McCombie deoxygenation of the remaining hydroxyl group. The stereoselective incorporation of the *β*-Me group at the C-4 position was expected by following a strategy such as iodolactonization to afford furanolactone **6**, which is the common core structure for the synthesis of Plakortones L, N, and P. After removal of the protecting group from furanolactone **6**, oxidation of the primary alcohol would provide the corresponding aldehyde. The total synthesis of Plakortone L (**1**) would be accomplished by the extension of the side chain via Wittig olefination of the aldehyde derivative, followed by hydrogenation of the olefin moiety.

Our approach began with the [3 + 2] annulation of readily accessible starting materials, isopropylidene-protected D-arabinose **2**[9] and methallyl *tert*-butyldiphenylsilyl ether (**3**),[10] in the presence of $BF_3{\cdot}OEt_2$ at −78 °C in CH_2Cl_2 to afford tetrahydrofuran **4** in 75% isolated yield as a single stereoisomer (eq 1).



Because of the overlap of the diagnostic Me protons in the ^{1}H NMR spectrum of compound **4**, the stereochemistry of the newly formed chiral centers on the tetrahydrofuran ring was established after removal of the isopropylidene groups. The treatment of **4** with $Zn(NO_3)_2{\cdot}6H_2O$[11] in MeCN at 50 °C for 5 h afforded tetraol **7** in 78% yield (eq 2). In the NOESY experiments of compound **7** (Figure 2), both H-3 and H-5b protons showed a strong NOE correlation to H-4, while H-5a showed an NOE to Me-24 (see Supporting Information for



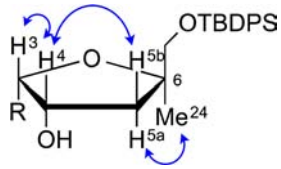
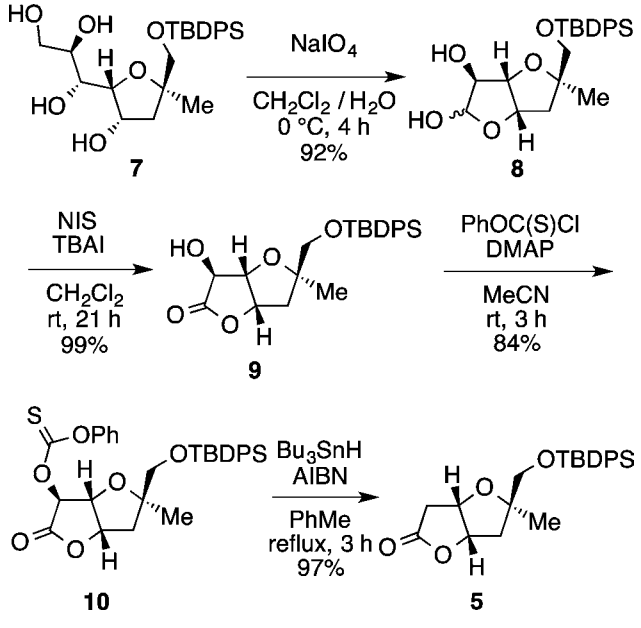


Figure 2. NOESY correlation of compound 7.

detail). These NOE data were consistent with the relative configurations of C-4 and C-6 in Plakortones.

According to our previous report on the synthesis of *trans*-kumausyne,[5] tetraol **7** was converted to furanolactone **5** (Scheme 3). The oxidative cleavage of terminal diol using

Scheme 3. Synthesis of Furanolactone 5



$NaIO_4$ in CH_2Cl_2/H_2O at 0 °C for 4 h afforded lactol **8** in 92% yield; oxidation of **8** with NIS/Bu_4NI[12] afforded lactone **9** in a quantitative yield. Subsequent Barton−McCombie deoxygenation[13] of lactone **9** afforded furanolactone **5** in a satisfactory overall yield.

Next, we envisaged that the *β*-Me group at the C-4 position could be incorporated via stereospecific formation of *cis*-fused

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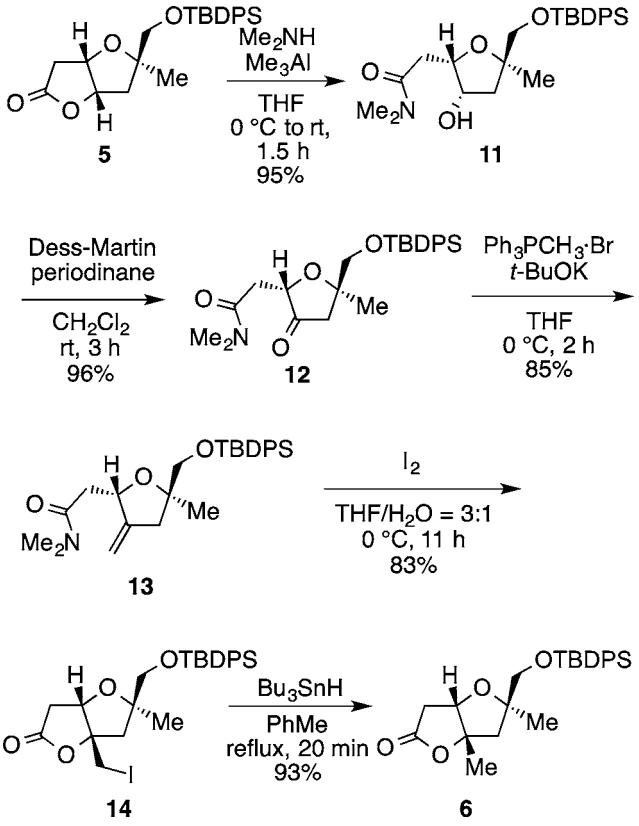
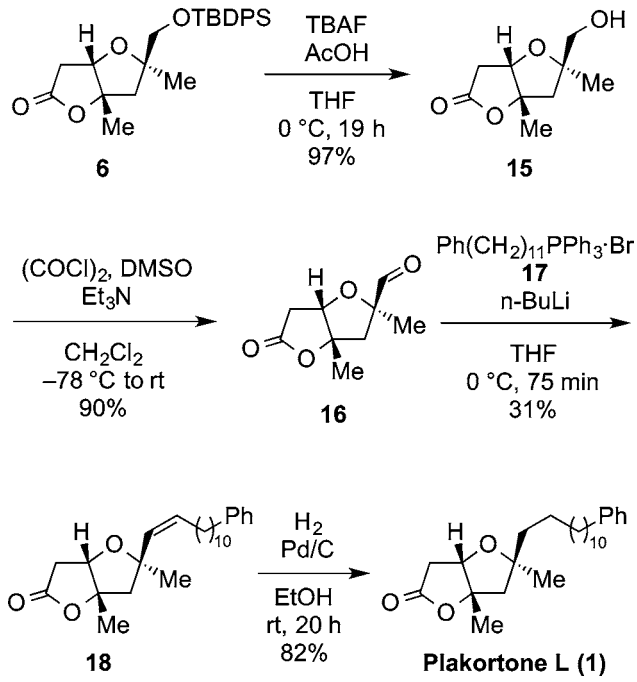
bicyclic lactone by iodolactonization of an *exo*-methylene intermediate (Scheme 4). The treatment of **5** with Me_2NH/Me_3Al[14] afforded hydroxy amide **11**, which was oxidized with Dess-Martin periodinane to afford ketone **12**. Wittig methylenation of **12** afforded the desired *exo*-methylene amide, **13**, in a good overall yield. The key iodolactonization step[14,15] was carried out with iodine in THF/H_2O (v/v = 3:1) at 0 °C for 11 h, affording *cis*-fused bicyclic lactone **14** in a stereospecific manner. The deiodination of compound **14** with Bu_3SnH afforded furanolactone **6**, the common core structure of Plakortones L, N, and P. The *syn*-relationship between H-3 and the newly introduced iodomethyl group in compound **14** or the Me group in compound **6** was confirmed by the observation of NOESY correlations between the corresponding protons.

Scheme 4. Synthesis of Furanolactone 6 via Stereospecific Iodolactonization from 5



With the core furanolactone **6** in hand, our efforts were directed toward the extension of the side chain (Scheme 5). After removal of the protecting group, Swern oxidation of the resulting primary alcohol afforded aldehyde **16**, which was subjected to Wittig olefination using the ylide prepared in situ by phosphonium salt **17**[16] and BuLi to afford the desired product **18**. However, the yield of the Wittig reaction was low (31%). Attempts to improve the yield of this reaction by longer reaction times or using several equivalents of the Wittig reagent were unsuccessful, presumably due to the steric crowding imposed by the substituents around the formyl group. The hydrogenation of **18** using H_2/Pd–C completed the total synthesis of Plakortone L (**1**). The spectroscopic data of synthetic compound **1** and optical rotation $\{[\alpha]_D^{28} = -20.4$ (*c* 0.27, $CHCl_3$)} (ref $\{[\alpha]_D = -20.1$ (*c* 0.0019, $CHCl_3$)} were all in excellent agreement with those previously reported.[1]

Scheme 5. Extension of the Side Chain: Synthesis of Plakortone L (1)



In conclusion, we have demonstrated the convenience of applying the [3 + 2] annulation of 2,3-*O*-isopropylidene-*aldehydo*-aldose with methallyl ether to directly access a substituted tetrahydrofuran system in a highly stereoselective manner. The utility of this approach was described through its application to the synthesis of the common structural motif of Plakortones. We accomplished the first total synthesis of Plakortone L, and the synthesis of the other members of Plakortones, N and P, is currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and product characterization data with ^1H and ^{13}C NMR spectra for all new compounds and Plakortone L (**1**), and NOESY spectrum for compound **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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