STUDIES RELATING TO THE SYNTHESIS OF LAURENENYNES: CONSTRUCTION OF THE ALKYLIDENE SIDE CHAIN *VIA* [2,3]-WITTIG-STILL REARRANGEMENT AT THE ANOMERIC CENTER OF A FURANOSIDE DERIVATIVE#

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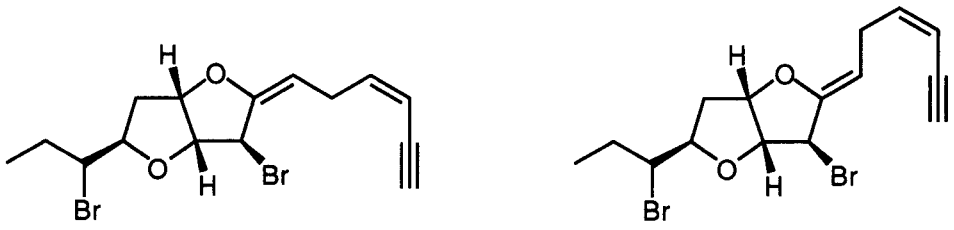
Abstract–The construction of the C_6 alkylidene side chain of laurenenynes has been investigated using the [2,3]-Wittig-Still rearrangement at the anomeric position of an appropriate glycofuranoside derivative, followed by further chemical transformations.

Red algae produce a variety of secondary metabolites, many of which are halogenated C_{15} cyclic ethers of various ring sizes.[2,3] Recently, we reported the total synthesis of *trans*-(–)-kumausyne, a bromine-containing trisubstituted tetrahydrofuran isolated from the red algae *Laurencia nipponica*.[4] As part of our continuing study on the synthesis of related marine natural products, we have chosen to explore a synthetic route to laurenenynes A and B (Figure 1), isolated from an undescribed species of *Laurencia* collected on the Pacific coast of central Japan.[5]



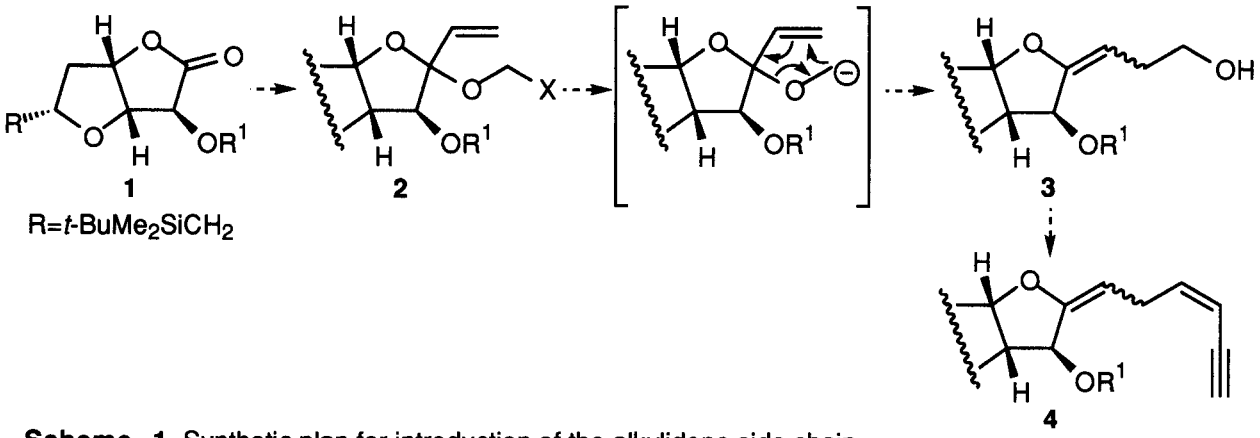
Laurenenyne A Laurenenyne B

Figure 1

In the earlier description on the synthesis of kumausyne,[4] we reported the preparation of an antipode of bicyclic lactone (**1**) as a synthetic intermediate from L-arabinose. Likewise, starting from D-arabinose, lactone (**1**) itself, which has a closely related structure to the laurenenyne's framework, could be obtained in the same manner. Therefore, our goal from the outset is to develop a method for introducing the C_6 alkylidene side chain at the carbonyl carbon of lactone (**1**). Our plan is outlined in Scheme 1. The key step is the [2,3]-Wittig rearrangement on the anomeric center of 1-vinylglycofuranoside (**2**). Tomooka *et al.* reported a pyranose version of the anomeric [2,3]-Wittig rearrangement using a propargyl 1-vinyl-α-glucopyranoside derivative.[6] More recently, another group successfully applied Tomooka's strategy to the synthesis of a *C*-glycoside using methoxycarbonylmethyl 1-vinyl-α-glucopyranoside.[7] However,

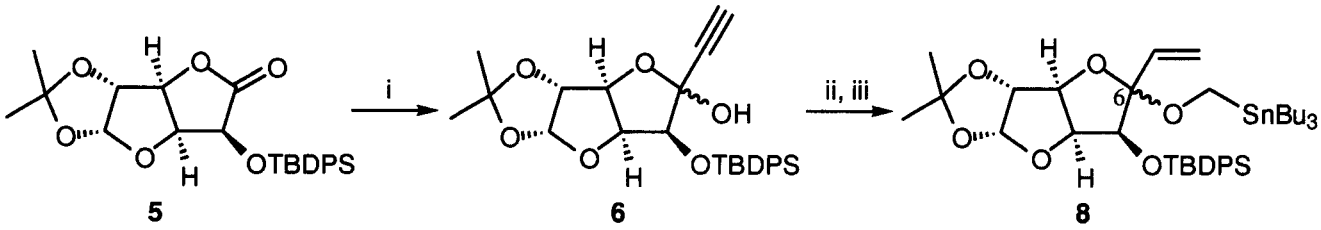
#Dedicated to Professor Teruaki Mukaiyama on the occasion of his 73rd birthday.

applicability of the [2,3]-Wittig rearrangement to a furanoside substrate has not been disclosed. To determine the feasibility of our approach, we explored the [2,3]-Wittig-Still rearrangement[8] employing the readily accessible glucono-6,3-lactone as a suitable model substrate. Herein, we describe the preliminary investigation of the synthetic route to the alkylidene side chain model found in the laurenenynes.



Scheme 1. Synthetic plan for introduction of the alkylidene side chain.

5-*O*-*tert*-Butyldiphenylsilyl-1,2-*O*-isopropylidene-α-D-glucono-6,3-lactone (**5**) was prepared by isopropylidenation[9] and the usual silylation (TBDPSCl, imidazole/DMF). To efficiently prepare the substrate for the [2,3]-rearrangement, direct introduction of a vinyl group into lactone (**5**) using vinylmagnesium bromide was initially attempted. However, in this reaction, ring opening of the vinyl adduct easily occurred to form the vinyl ketone *in situ* and further addition of another vinyl Grignard reagent to the carbonyl moiety proceeded rapidly, producing a divinylcarbinol derivative. In contrast, the addition of ethynyllithium to the carbonyl group of **5** smoothly proceeded to afford the desirable adduct (**6**), which could be isolated without difficulty[10] (Scheme 2). The resulting hemiacetal (**6**) was converted into a tributylstannylmethyl glycoside by condensation with the corresponding alcohol (**7**)[11] in the presence of boron trifluoride-ether complex. Reduction of the ethynyl moiety to an olefin using the Lindlar catalyst furnished the desired substrate (**8**) as a nearly 1:1 mixture of anomers at *C*6.



reagents: i. HC≡CLi, THF, –78 °C; 63% ii. Bu_3SnCH_2OH (**7**), $BF_3{\cdot}OEt_2$, CH_2Cl_2, –10 °C; 48% iii. H_2, Lindlar cat. ($Pd\text{-}CaCO_3\text{-}PbO$), EtOH, rt; 80%

Scheme 2. Preparation of substrate for the [2,3]-Wittig-Still rearrangement

Treatment of this anomeric mixture of **8** with butyllithium in THF at –78 °C led to the [2,3]-rearranged product as a single isomer (Eq. 1).[12] The *Z* geometry of the newly formed olefinic bond was established by an NOE experiment. This stereochemical assignment is also consistent with transition-state models as shown in Figure 2. Both substrates (6*R*)-**8** and (6*S*)-**8** would provide the same rearranged product ((*Z*)-**9**) through the more favorable transition states **C** and **D**. To confirm this hypothesis, the Wittig-Still rearrangement was separately carried out using each anomer. As a result, both substrates ((6*R*)-**8** and (6*S*)-**8**) afforded the same product ((*Z*)-**9**) with complete stereoselectivity (Eq. 2).

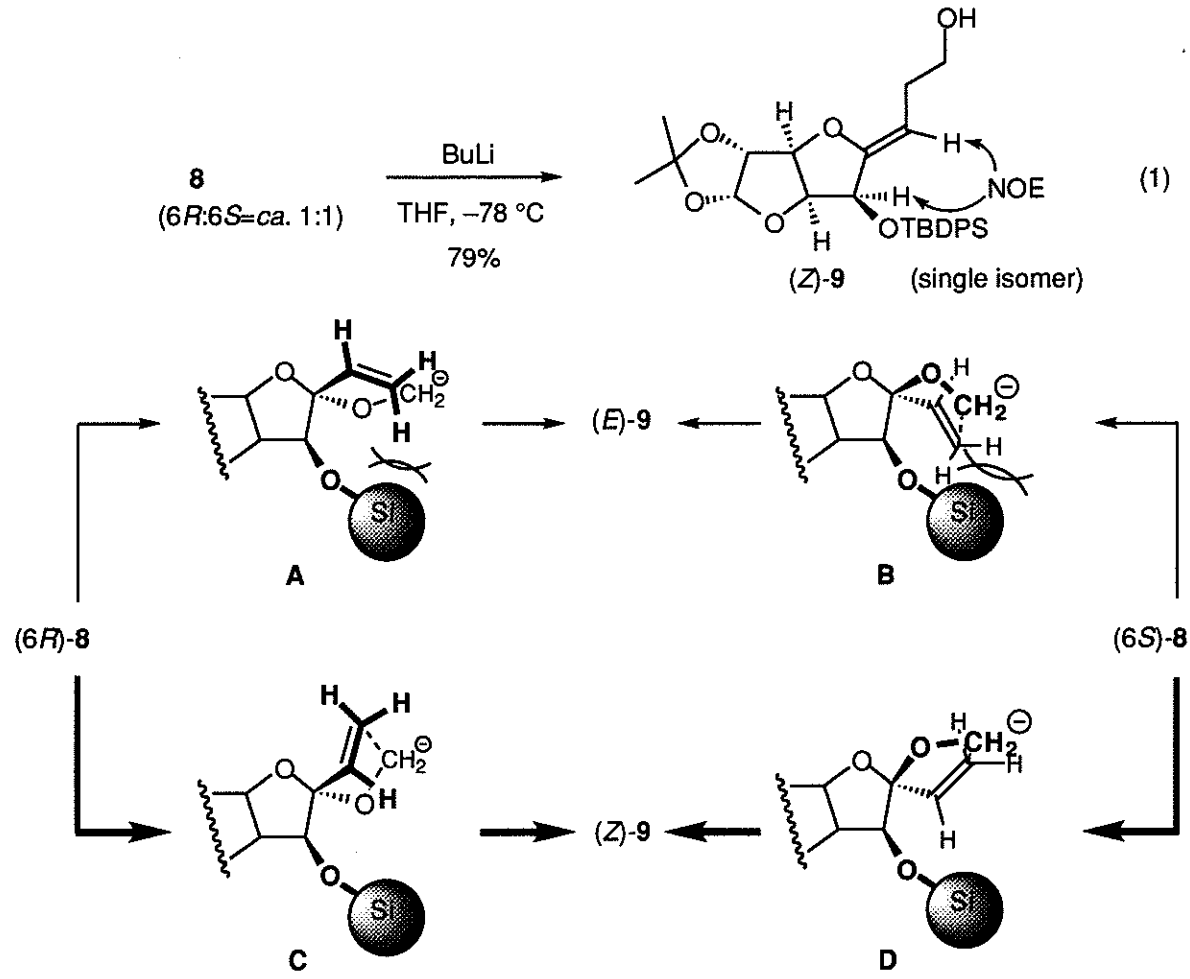
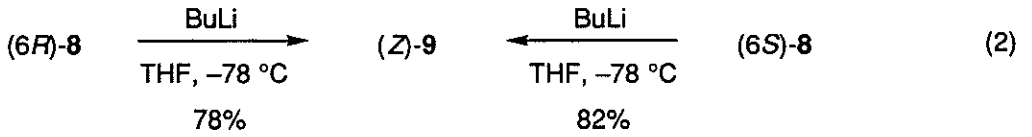
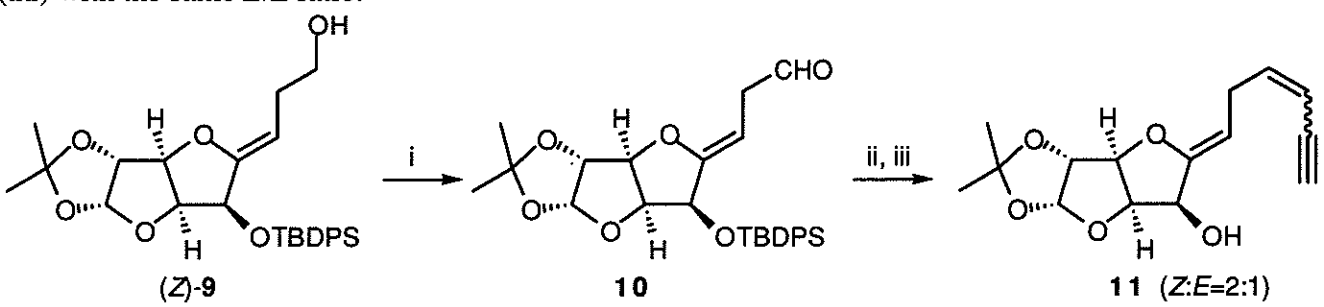


Figure 2. Transition state models of [2,3]-Wittig rearrangement.



Elaboration of the alkylidene side chain was achieved by a sequence including the Peterson olefination, which is known to predominantly give (*Z*)-enyne products.[13] Transformation of homoallylic alcohol ((*Z*)-**9**) into aldehyde (**10**) with *o*-iodoxybenzoic acid, followed by the Peterson reaction with *tert*-butyllithium and 1,3-bis(trimethylsilyl)propyne furnished the enyne product as an inseparable isomeric mixture with modest stereoselectivity (*Z*:*E*=2:1). Finally, treatment with tetrabutylammonium fluoride provided alcohol (**11**) with the same *E*/*Z* ratio.



reagents: i. *o*-iodoxybenzoic acid, DMSO; 64% ii. $TMSC{\equiv}CCH_2TMS$, *t*-BuLi, THF ; 38% iii. Bu_4NF, THF; 88%

Scheme 3. Construction of the enyne side chain.

In conclusion, we have disclosed that the [2,3]-Wittig-Still rearrangement at the anomeric center of the furanoside derivative provided (*Z*)-rearranged product with complete stereoselectivity, regardless of the starting anomeric configuration. The resulting homoallylic alcohol could be transformed into the C_6 alkylidene side chain found in laurenenynes. Towards the goal of the total synthesis of laurenenyne B, application of this approach to lactone (**1**) as well as other biologically interesting compounds such as prostacyclins is currently under way.

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12. 400 MHz ^{1}H NMR (in $CDCl_3$) 1.11 (s, 9H), 1.30 (s, 3H), 1.37 (s, 3H), 2.33-2.35 (m, 2H), 3.61-3.63 (m, 2H), 4.18 (dd, *J*=2.9, 3.4 Hz, 1H), 4.41 (d, *J*=2.9 Hz, 1H), 4.54 (dd, *J*=2.0, 3.4 Hz, 1H), 4.59 (dt, *J*=2.0, 7.3 Hz, 1H), 4.62 (d, *J*=3.9 Hz, 1H), 5.99 (d, *J*=3.9 Hz, 1H), 7.38-7.46 (m, 6H), 7.71-7.82 (m, 4H); (in C_6D_6) 1.06 (s, 3H), 1.28 (s, 3H), 1.19 (s, 9H), 2.35-2.64 (m, 2H), 3.66 (s, 2H), 4.00 (d, *J*=3.9 Hz, 1H), 4.11 (t, *J*=3.4 Hz, 1H), 4.32 (d, *J*=3.9 Hz, 1H), 4.47 (d, *J*=3.4 Hz, 1H), 4.87 (t, *J*=7.3 Hz, 1H), 5.85 (d, *J*=3.4 Hz, 1H), 7.16-7.28 (m, 6H), 7.84-7.86 (m, 2H). 100 MHz ^{13}C NMR (in $CDCl_3$) 19.2, 26.8, 27.1, 28.5, 62.4, 73.4, 80.5, 83.8, 84.5, 94.3, 106.9, 112.6, 127.7, 127.9, 130.1, 132.6, 133.1, 135.7, 136.0, 155.7.
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