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Diastereo- and Enantioselective Synthesis of Allylsilane. A Useful C-Ring Fragment of Taxol.

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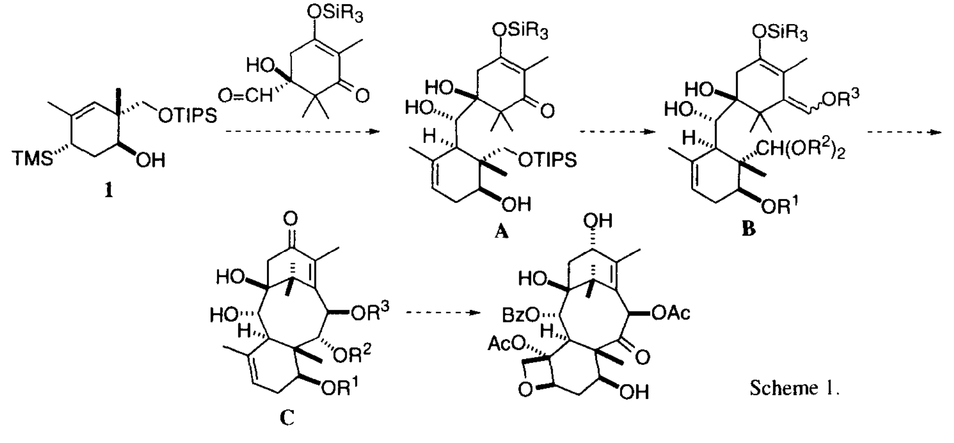
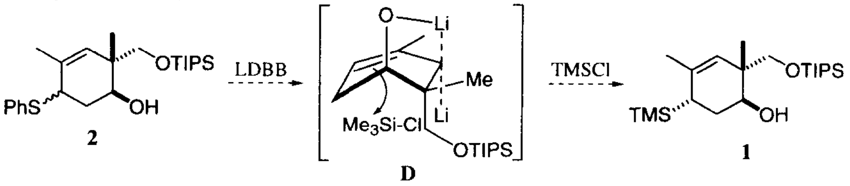
Abstract: Enantioselective synthesis of a taxol C-ring fragment containing an allylsilane moiety is described. Diastereoselective [4 + 2] cycloaddition of the pyrone with (*R*)-*t*-butylbenzyl vinyl ether followed by appropriate transformations gave a mixture of two regioisomeric cyclohexenyl sulfides, which was converted to the title compound with almost complete diastereo- and enantioselectivities by treating with Li and 4,4'-di-*t*-butylbiphenyl followed by quenching with chlorotrimethylsilane.

In connection with our program for taxane synthesis,[1] we have designed the allylsilane **1** as a versatile C-ring fragment of taxol. Considering the well-established reaction style of allylsilanes,[2] use of this substrate may enable stereo- and regiospecific coupling with the A-ring fragment aldehyde[3] to form **A**. After appropriate manipulation, the resulting **B** would undergo B-ring cyclization[4] to afford a useful precursor **C** for taxol (Scheme 1).



Scheme 1.

Such highly functionalized allylsilanes were not hitherto so readily available, but we recently described a stereo- and regio-defined synthetic method of allylsilanes containing an oxygen functionality.[5] In the present

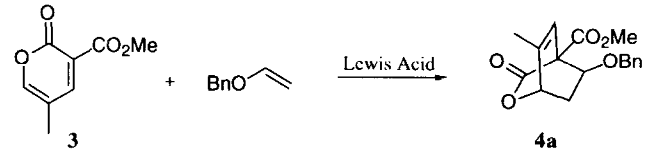


(Eq 1)

LDBB = lithium 4,4'-di-*t*-butylbiphenylide study, we envisioned, starting from the cyclohexenyl sulfide **2**, generation of allylanionic species **D** with a rigid conformation fixed by the OLi group and its conversion to the desired **1** (eq. 1).

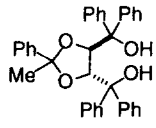
At first, for preparation of **2** containing two chiral centers, an enantioselective [4 + 2] cycloaddition of the pyrone **3**⁶⁾ with benzyl vinyl ether was attempted under the influence of chiral Lewis acids. Typical examples are shown in eq 2. In contrast to the high ee attained with 5-unsubstituted pyrones,⁷⁾ the 5-methyl group of **3** seems to prevent a rigid transition state in the cycloaddition process, and the ee was 32% at best by using (+)-TADDOL-$TiCl_2(O^iPr)_2$.

Attempts for Enantioselective Cycloaddition



(Eq 2)

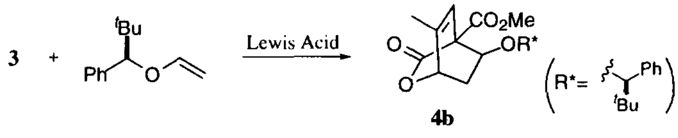
Lewis Acid	Reaction Conditions	Yield (ee)
(+)-BINOL-$TiCl_2(O^iPr)_2$	toluene, -45°C, 16 h	40% (10% ee)
(+)-TADDOL-$TiCl_2(O^iPr)_2$	toluene/MS4A, -50 °C, 12 h	52% (32% ee)
(+)-Eu(hfc)$_3$	$ClCH_2CH_2Cl$, rt, 15 h	60% (10% ee)



(+)-TADDOL

Diastereoselective cycloaddition⁸⁾ was next examined by using chiral (*R*)-*t*-butylbenzyl vinyl ether.⁹⁾ The results are shown in eq 3. Although the levels of diastereoselection attained in these procedures were not so high as desired, a synthetically acceptable result was obtained by performing the reaction in the presence of Me_2AlCl, and the resulting two diastereomers could be separated cleanly by column chromatography.

Attempts for Diastereoselective Cycloaddition

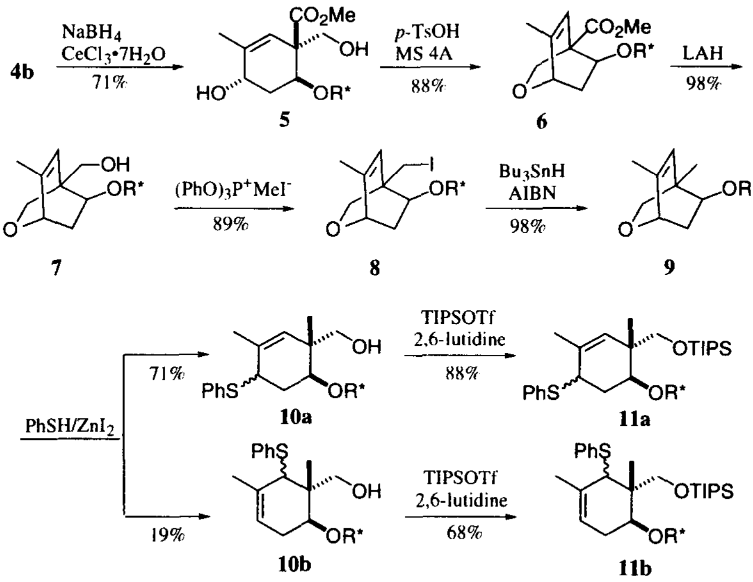


(Eq 3)

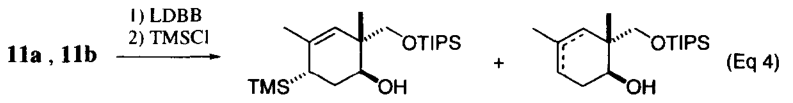
Lewis Acid	Reaction Conditions	Yield (DS Ratio)
$TiCl_2(O^iPr)_2$	CH_2Cl_2, -78 °C/1h, -45°C/16 h	61% (84:16)
$SnCl_4$	CH_2Cl_2, -78 °C/2.5h, -45°C/5 h	28% (90:10)
Me_2AlCl	CH_2Cl_2, -78 °C/61h	75% (86:14)
None	CH_3NO_2, 100 °C/3h	45% (73:27)

The optically active substance **4b** (95% ee)¹⁰⁾ was converted to the allylsulfide as follows. Thus, the lactone moiety of **4b** was selectively reduced to the diol **5** in 71% yield with $NaBH_4$ and $CeCl_3{\cdot}7H_2O$, and **5** underwent cyclization under acidic conditions to give **6** in 88% yield. Conversion of the ester of **6** to a methyl group was performed via three steps (85% overall yield) and the resulting allylic ether **9** was treated with benzenethiol in the presence of a catalytic amount of $ZnCl_2$, yielding a mixture of regio- and diastereomeric isomers **10a** and **10b**. After separation of these regioisomers with column chromatography, protection of the remaining hydroxy group of each isomer with TIPS gave the substrate **11a** and **11b**.

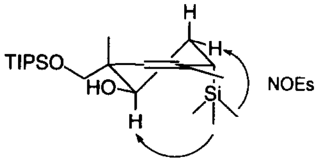
Scheme 2. Preparation of Allyl Sulfides.



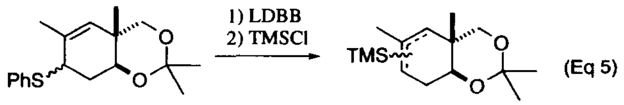
Irrespective of the diastereomeric mixture, conversion of both **11a** and **11b** to the desired allylsilane was performed efficiently: treatment of each isomer with LDBB at -45 °C for 10 min followed by silylation with TMSCl at -78 °C gave the corresponding allylsilane **1**[11] with complete regio- and diastereoselectivities in good yields together with a small amount of protonated one (ca. 10%).



1: 56% from **11a**
69% from **11b**



In contrast to the specific transformation of **11**, the acetonide **12** failed to undergo selective conversion, but resulted in the formation of a complex mixture including protonated ones. These results have strongly supported that the OLi moiety generated from the benzyl ether plays an important role in fixing the conformation of **D**, which reacts with the silylating reagent on the less hindered site to yield **1**.



12

ca. 70%

Thus, the present LDBB/TMSCl methodology has proven useful even for specific generation of OLi fixed allylic lithium which led us to an enantioselective synthesis of taxol C ring fragment with almost complete diastereo- and enantioselectivities.

We are currently studying application to taxol synthesis of this optically active C-ring fragment.

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9) The vinyl ether was prepared by using optically active *t*-butylbenzyl alcohol prepared by asymmetric reduction of the parent ketone: see, Brown, H. C.; Cho, B. T.; Park, W. S. *J. Org. Chem.* **1988**, *53*, 1231-1238. Optical purity of the alcohol was confirmed to be 95% ee by ^{1}H-NMR analysis of the corresponding (+)-MTPA ester.
10) The absolute configuration of this compound was determined by X-ray crystallographic analysis.
11) Stereochemical feature of this compound was determined by NOE experiments described in the text.

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