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Asymmetric synthesis of stereodefined α-alkyl-γ-benzyloxymethyl-β-trimethylsilyl-γ-butyrolactones that serve as an efficient precursor for constructing carbon skeletons having a tertiary or quaternary stereogenic center

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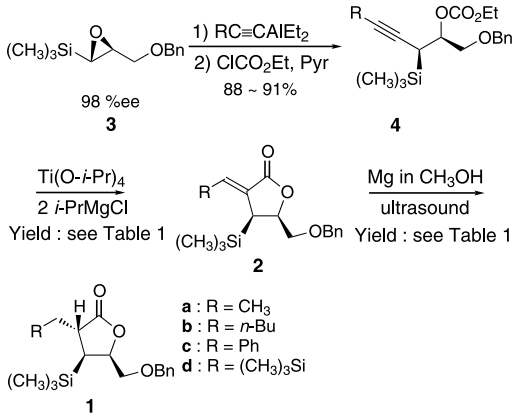
Abstract—The optically active lactone **1** can be transformed to a chiral building block or intermediate for constructing carbon skeletons containing either a tertiary or quaternary stereogenic center by taking advantage of the steric bulk as well as the reactivity of a trimethylsilyl group at the β-position of **1**.

There are many natural and artificial biologically important compounds that have a tertiary or quaternary stereogenic carbon center in their structure as the main unit or a subunit, and thus, development of asymmetric synthetic methodology that allows preparation of these skeletons is important. Herein we report an easy method for synthesizing optically active γ-benzyloxymethyl-β-trimethylsilyl-γ-butyrolactones **1** having a variety of alkyl groups at the stereodefined α-position,



Scheme 1.

and show that they can serve as an efficient precursor for preparing a chiral building block or intermediate for constructing carbon skeletons containing either a tertiary[1] or quaternary[2] stereogenic center.

Our synthetic approach to **1**, which is summarized in Scheme 1, involves the synthesis of α-alkylidene lactones **2** from readily available, optically active 3-trimethylsilylglycidol benzyl ether (**3**) using, as a key reaction, Ti(II)-mediated intramolecular nucleophilic acyl substitution reaction (INAS reaction),[3] and their stereoselective reduction.

The epoxide **3** with 98% ee was prepared in 74% overall yield by the Katsuki–Sharpless asymmetric epoxidation of (*E*)-3-trimethylsilyl-2-propen-1-ol and the following benzylation.[4] The reaction of **3** with $RC{\equiv}CAlEt_2$ (2 equiv.) where R is Me, *n*-Bu, Ph and $Si(CH_3)_3$ in hexane afforded the corresponding epoxide ring-opening products exclusively in 93–96% yield.[5] After conversion of the hydroxy group of the products to ethyl carbonate (≈95% yield), the resulting carbonates **4** were reacted with a divalent titanium reagent Ti(O-*i*-Pr)$_4$/2*i*-PrMgCl[6] to provide, after hydrolysis, the INAS products **2** in high yield. The yield of **2** from **4** and their $[\alpha]_D$ values are summarized in Table 1. Conversion of **2** to **1** was carried out efficiently by reduction with a Mg/CH_3OH reagent under ultrasound irradiation,[7,8] which proceeded with almost 100% stereoselectivity except for **2d**. In the case of **2d**, **1d** and its diastereomer were produced in a ratio of 85:15; however, successive

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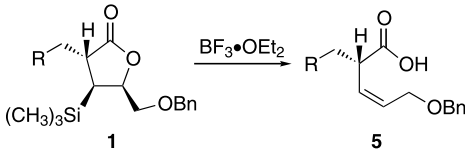
Table 1. Ti(II)-mediated INAS reaction[a] of **4** to **2** and its reduction[b] to **1**

Entry	4	2		1	
		Yield (%)[c]	$[\alpha]_D$ (*c*, $CHCl_3$)	Yield (%)[d]	$[\alpha]_D$ (*c*, $CHCl_3$)
1	**a**; R = CH_3	60	−107 (2.51)	94	−33.7 (0.90)
2	**b**; R = *n*-Bu	70	−143 (1.10)	84	−45.6 (0.81)
3	**c**: R = Ph	65	−117 (2.42)	83	−16.7 (1.13)
4	**d**; R = $(CH_3)_3Si$	70	−114 (1.22)	63[e]	−60.1 (1.11)

[a] The reaction was carried out in Et_2O at −55 to −45°C for 3 h, with reactants ratio of **4**:Ti(O-*i*-Pr)$_4$:*i*-PrMgCl = 1.0:1.5:3.0.
[b] **2**:Mg turnings = 1:10, rt, under ultrasound irradiation.
[c] Isolated yield by column chromatography after treatment of the crude reaction mixture with *p*-TsOH, which resulted in lactonization of the corresponding α,β-unsaturated ester co-produced as a minor product.
[d] Isolated yield based on **2**.
[e] Overall yield via two-step reaction of reduction with Mg/CH_3OH and isomerization with $[(CH_3)_3Si]_2NK$/*t*-BuOH (see text).

treatment of the diastereomeric mixture with $[(CH_3)_3Si]_2NK$ (−78°C to 0°C, in THF) and *t*-BuOH (−78°C to 0°C) resulted in complete isomerization of the minor isomer, eventually providing pure **1d** in 63% overall yield. The structure of **1a–d** shown in Scheme 1 was determined by their NOE experiments. The yield of **1** from **2** and their $[\alpha]_D$ values are also summarized in Table 1.

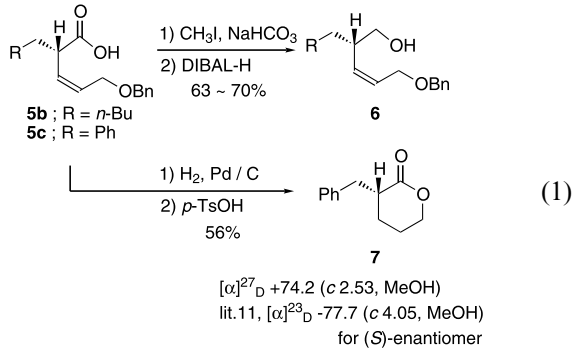
Treatment of the lactones **1a–d** with $BF_3{\cdot}OEt_2$ (3 equiv.) resulted in smooth Peterson olefination reaction[9,10] to afford the corresponding **5a–d** in excellent yield as shown in Scheme 2. The enantiomeric excess (ee) of **5b** and **5c** thus obtained was determined to be 98 and 97% ee, respectively, by ^1H NMR analysis of the MTPA esters after converting to the corresponding alcohol **6** as shown in Eq. (1). Meanwhile, the absolute configuration of **5c** was established by converting to known (*R*)-2-benzylvalerolactone (**7**)[11] as also shown in Eq. (1).



1 **5**

5	Isolated yield (%)	$[\alpha]_D$ (*c*, $CHCl_3$)
a ; R = Me	83	+116 (0.71)
b ; R = *n*-Bu	87	+75.1 (1.23)
c ; R = Ph	84	+60.8 (1.23)
d ; R = $(CH_3)_3Si$	94	+94.8 (0.83)

Scheme 2.

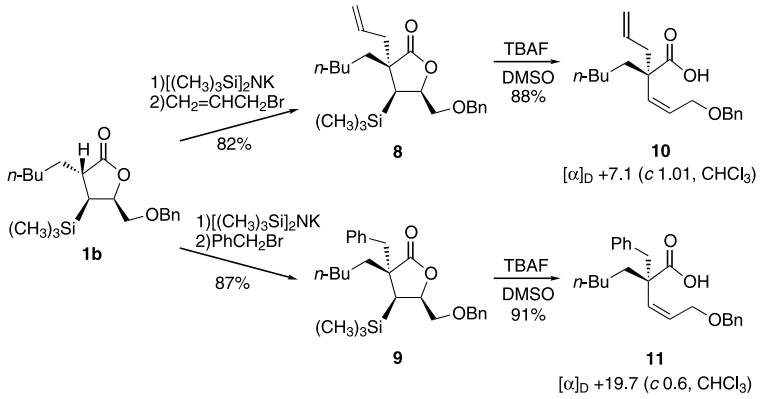


(1)

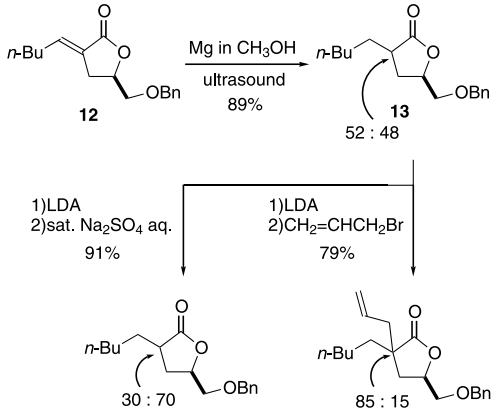
The compound **5** might find utility as a chiral building block or intermediate for constructing carbon skeletons containing a tertiary stereogenic center by taking advantage of the versatile reactivity of the carboxyl and (*Z*)-3-benzyloxy-1-propenyl groups embedded in it.

The compound **1** might serve as the precursor for construction of a carbon skeleton containing a quaternary stereogenic center through stereoselective alkylation of the lactone enolate derived from **1**, and the following Peterson olefination reaction. We investigated this possibility starting with **1b**. Although the methylation of the enolate generated from **1b** and $[(CH_3)_3Si]_2NK$ with MeI proceeded with low diastereoselectivity of 68:32, the allylation with $CH_2{=}CHCH_2Br$ and benzylation with $PhCH_2Br$ proceeded with excellent diastereoselectivity to afford exclusively the corresponding **8** and **9** as shown in Scheme 3, the structure of which was, respectively, confirmed by NOE experiments.[12,13] The compounds **8** and **9** thus obtained could be readily converted to **10** and **11**, respectively, by the reaction with *n*-Bu_4NF.[14] The easy synthesis of the compound of the type **10** is especially noteworthy, since it might serve as a useful chiral intermediate for constructing carbon skeletons having a quaternary carbon center, because it has three different functional groups at the stereogenic center, i.e. allyl, carboxyl and (*Z*)-3-benzyloxy-1-propenyl groups which might independently allow further elaboration.

In the conversion of **2** to **1** and then to **5**, **10** (via **8**), or **11** (via **9**) described above, the trimethylsilyl group present in **2** plays indispensable dual roles which are the control of the stereochemistry for constructing the tertiary or quaternary carbon center, and the generation of the double bond by Peterson olefination reaction. With respect to the former role, we found that the reduction of **12**, which lacks a trimethylsilyl group at the β-position, to **13** proceeded with 52:48 diastereoselectivity as shown in Scheme 4. Similarly, the kinetic protonation or alkylation of the lactone enolate generated from **13** proceeded with 30:70 or 85:15 diastereoselectivity, respectively.



Scheme 3.



Scheme 4.

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8. Hydrogenation of the alkene moiety of **2** in the presence of a palladium or rhodium catalyst did not give **1** at all. The reaction resulted in double bond migration into the ring and/or the debenzylation of the benzyl ether.
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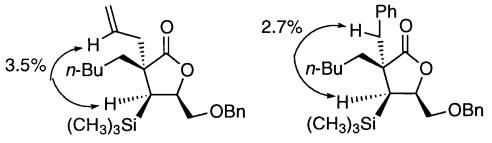
12. Alkylation of the lactone enolate with an alkyl halide such as *n*-butyl iodide did not proceed.
13. The stereochemistry of the compound **8** and **9** was determined by NOE-difference experiments.



Values in % refer to NOE

14. The reaction of the compound **8** and **9** with $BF_3{\cdot}OEt_2$ did not give the corresponding Peterson olefination product.