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Synthesis of β-Hydroxy-γ-trimethylsilyl-γ-butyrolactone as Key Chiral Building Block for Preparation of Four-Carbon Chain Units Having Tertiary Stereogenic Carbon

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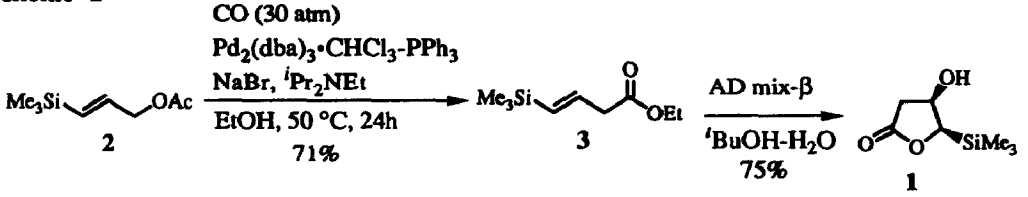
Abstract : *A new chiral building block β-hydroxy-γ-trimethylsilyl-γ-butyrolactone (1) was prepared from γ-trimethylsilylallyl acetate (2) via two steps in excellent overall yield. The lactone 1 is useful precursor to four-carbon chain blocks having tertiary stereogenic center such as 6, 10 and 11.*

In connection with the increasing demand for preparation of chiral compounds in optically active form, the development of new versatile chiral building blocks has attracted much interest in recent years.[1] Herein we report the synthesis of a new chiral building block β-hydroxy-γ-trimethylsilyl-γ-butyrolactone (1) which opens up an interesting entry into valuable four-carbon chain blocks having tertiary stereogenic carbon.

The chiral lactone **1** was prepared from readily available γ-trimethylsilylallyl acetate (2) via two steps in excellent overall yield as shown in Scheme 1. The acetate **2** was

Scheme 1



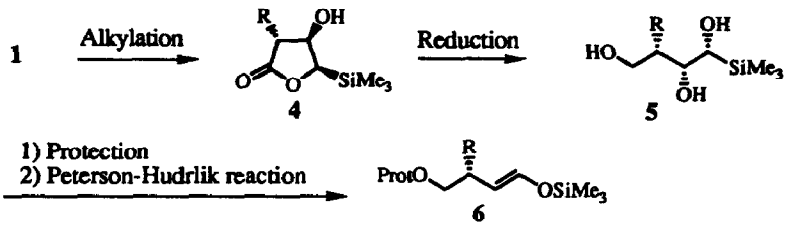
2 **3** **1**

converted into ethyl 4-trimethylsilyl-3(*E*)-butenoate (**3**) exclusively in 71% yield by palladium catalyzed carbon monoxide insertion reaction.[2] The Sharpless asymmetric dihydroxylation of **3**[3,4] by using AD-mix-β reagent afforded **1** in 75% yield, the enantiomeric excess of which was found to be 86% by Mosher ester analysis of the

protodesilylated product of **1**. The enantiomeric excess of **1** could be upgraded to >99% by one recrystallization from hexane-ethyl acetate (75% recovered),[5] and used for next reactions. Although we used AD-mix-β as a chiral reagent, use of AD-mix-α reagent should provide the antipode of **1**.

We envisioned that the lactone **1** could be converted into the four-carbon chain blocks having tertiary stereogenic carbon such as **6** via alkylation[6], reduction to triol and then the Peterson-Hudrlik reaction[7] as shown in Scheme 2. Reported the following is the realization of this idea.

Scheme 2



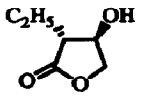
The dianion of **1** was generated in THF at -78°C by the addition of lithium diisopropylamide (LDA) (2.2 equiv) followed by stirring for 30 min at this temperature. An alkyl halide was added to this solution at -78°C, and the mixture was stirred at -78°C~ -60°C for several hours and quenched with saturated NH_4Cl solution at -78°C to give the alkylated product **4**. Table 1 summarizes the results of the alkylation with various alkyl halides.

Table 1

Entry	Reaction conditions: RX	Solvent	Reaction time (h)	4 Isolated yield (%)
1	MeI	THF	1.5	**a** 86
2	EtI	THF	6	**b** 35[b]
3	EtI	THF, HMPA[a]	1	**b** 77
4	^{n}BuI	THF, HMPA[a]	1.5	**c** 65[b]
5		THF	2	**d** 84[c]
6		THF	2.5	**e** 60
7		THF	2.5	**f** 76

[a] With 10% HMPA, [b] ^{1}H NMR yield, [c] Containing allenyl product (5%).

The product **4** appeared as a single isomer, as determined by TLC and by both ^1H (300 MHz) and ^{13}C NMR (75 MHz).[6] The configuration of the alkylated product **4** assigned as shown in Scheme 2 was confirmed by converting **4b** to **7** by protodesilylation ($^nBu_4NF$, THF, 0 °C), and also **4a** to known compound **11a** (*vide infra*). The enantiomer of **7** was previously synthesized by alkylation of the dianion of (*S*)-(-)-β-hydroxy-γ-butyrolactone (**8**).[6d] Noteworthy here is the fact that the yields of the alkylation of the dianion of **1** were far better than those of **8** presumably due to the higher solubility of the former thanks to the presence of the trimethylsilyl group.



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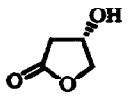

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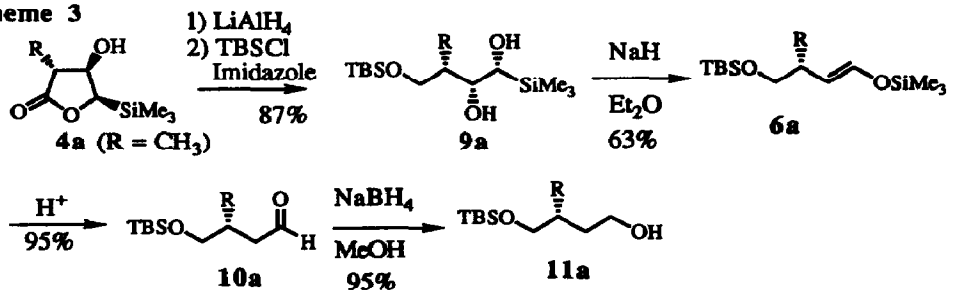
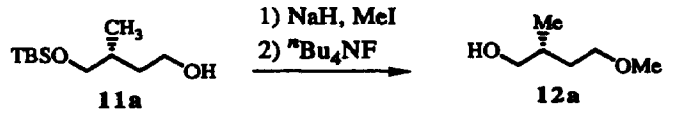
The conversion of **4** to **6** was carried out as follows (Scheme 3). The reduction of **4a** with $LiAlH_4$ in THF afforded the corresponding triol quantitatively which was reacted with $^tBuMe_2SiCl$ (1.05 equiv) in the presence of imidazole in DMF resulting in specific monosilylation to afford **9a** in 87% yield. Treatment of **9a** with NaH in Et_2O[7] provided

Scheme 3



6a in 63% yield.[8] The compound **6a** can be hydrolyzed to **10a** in 95 % yield by treatment with a catalytic amount of 1M HCl in THF-H_2O (5:1). The reduction of **10a** with $NaBH_4$ in CH_3OH afforded the alcohol **11a** [$([\alpha]_D^{28}$ = +7.8° (c 0.96, $CHCl_3$), lit.[9] $[\alpha]_D^{22}$ = +8.0° (c 1.07, $CHCl_3$)]. We confirmed that the racemization did not occur during these transformations by the MTPA method after converting **11a** to the alcohol **12a** (eq 2).



(2)

In conclusion, we have synthesized a new versatile chiral building block **1** with >99% ee from readily available **2** in 40% overall yield via two-step reactions and one

recrystallization. The compound **1** opens up a potentially general route to four-carbon chain units having tertiary stereogenic center, such as **6**, **10** and **11**.

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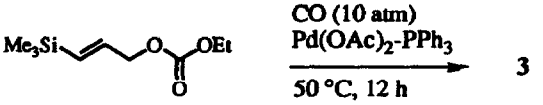
2) Murahashi, S.; Imada, Y.; Taniguchi, Y.; Higashiura, S. *J. Org. Chem.* **1993**, *58*, 1538. The compound **3** was also obtained from ethyl γ-trimethylsilylallyl carbonate under the reaction conditions shown below in 50% yield with *E*/*Z* = 20/1 (Tsuji, J.; Sato, K.; Okumoto, H. *J. Org. Chem.* **1984**, *49*, 1341).



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4) AD reaction of vinylsilanes, see: (a) Okamoto, S.; Tani, K.; Sato, F.; Sharpless, K. B.; Zargarian, D. *Tetrahedron Lett.* **1993**, *34*, 2509. (b) Soderquist, J. A.; Rane, A. M.; López, C. J. *Tetrahedron Lett.* **1993**, *34*, 1893.

5) The data of optically pure **1**.
^{1}H NMR (300MHz, $CDCl_3$) δ 0.19 (s, 9H), 2.20 (br s, 1H), 2.47 (d, J = 17.8 Hz, 1H), 2.78 (dd, J = 5.6, 17.8 Hz, 1H), 4.12 (d, J = 4.1 Hz, 1H), 4.68 - 4.73 (m, 1H).
^{13}C NMR (75 MHz, $CDCl_3$) δ -3.01, 39.82, 69.92, 82.50, 179.05.
mp = 89.5 - 90.5 °C
$[\alpha]_D^{28}$ = -14.1° (c 0.73, $CHCl_3$)

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8) The data of **6a**
^{1}H NMR (300MHz, $CDCl_3$) δ 0.03 (s, 6H), 0.18 (s, 9H), 0.89 (s, 9H), 0.96 (d, J = 6.8 Hz, 3H), 2.15 - 2.24 (m, 1H), 3.33 (dd, J = 7.2, 9.7 Hz, 1H), 3.43 (dd, J = 6.1, 9.7 Hz, 1H), 4.87 (dd, J = 8.4, 12.1 Hz, 1H), 6.23 (d, J = 12.0 Hz, 1H)
^{13}C NMR (75 MHz, $CDCl_3$) δ -5.30, -0.46, 17.64, 18.45, 25.95, 35.42, 68.72, 114.71, 139.60.
$[\alpha]_D^{28}$ = -1.0° (c 1.00, $CHCl_3$)

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