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Regioselective Methylation of the Secondary Carbinol Center of *prim, sec*-Diols

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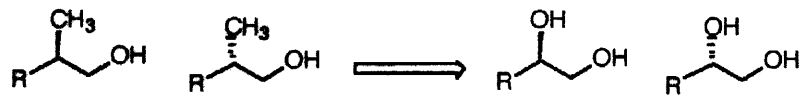
Abstract **Reaction of 2-oxo-4-phenyl-1,3,2-dioxathiolane and 2-oxo-4-(*tert*-butyldiphenylsilylmethyl)-1,3,2-dioxathiolane with trimethylaluminium selectively took place at the secondary carbinol center to give 2-phenyl-1-propanol and 3-(*tert*-butyldiphenylsilyl)-2-methylpropanol. When the *endo*- or *exo*-isomer of (*S*)-2-oxo-4-phenyl-1,3,2-dioxathiolane reacted with trimethylaluminium, (*R*)-2-phenyl-1-propanol was obtained in 75% ee or 90% ee, respectively.**

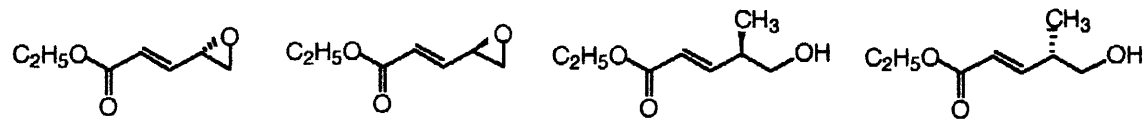
The chiral carbon atom bearing a methyl group or a hydroxyl group is widespread in natural products such as polypropionate derived compounds.[1] For the construction of the carbon framework of these compounds, a primary alcohol having a stereogenic center at the C2 position [(*R*)-**1** and (*S*)-**1**] would be a fundamental building block (Scheme 1). As a possible approach for the construction of this class of compounds, regioselective and stereospecific methylation of the secondary carbinol center of *prim, sec*-1,2-diols would be conceivable (Scheme 1).



Scheme 1

In order to materialize this transformation, the hydroxyl group(s) must be activated and thus, rendered amenable to subsequent substitution. Since epoxides can be readily prepared from *vic*-diols, they could be considered to be activated diols and have been widely utilized in organic synthesis. The reactions of 1,2-epoxyalkanes with $(CH_3)_3Al$ have been reported to afford the corresponding 2-methylalkanols with low to moderate stereoselectivity depending on the substituent pattern of the epoxide ring.[2]

Miyashita and his co-workers have recently demonstrated an interesting transformation of *prim, sec*-1,2-diols into the primary alcohols having a chiral carbon atom bearing a methyl group at the C2 position *via* epoxides.[3] Thus, the reaction of epoxide (*S*)-**2** or (*R*)-**2** with $(CH_3)_3Al$ in the presence of water exclusively took place at the more hindered position with inversion of the configuration to afford, respectively, primary alcohol (*R*)-**3** and (*S*)-**3** (Scheme 2).



Scheme 2

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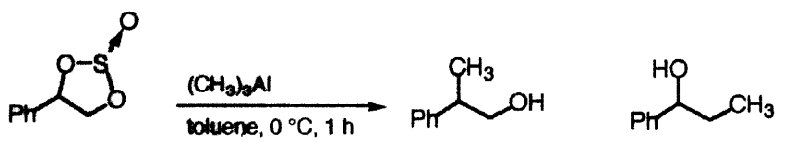
Cyclic sulfites and cyclic sulfates are also considered as activated diols.[4] Fleischer et al. reported that the reaction of 2-oxo-(4,4,5-triphenyl)-1,3,2-dioxathiolane with alcohols in the presence of triethylamine selectively gave the corresponding 1,2,2-triphenyl-2-alkoxyethanol.[5] In contrast, the reaction of 4-substituted-2-oxo-1,3,2-dioxathiolanes with Grignard reagents or alkyllithiums took place at the sulfur atom rather than the carbon atom.[6] In this communication, we wish to report the preparation of the primary alcohols having a methyl group at the C2 position by regioselective methylation of the secondary carbinol center of *prim*, *sec*-diols *via* 1,3,2-dioxathiolane.

At the outset, the reaction of 2-oxo-4-phenyl-1,3,2-dioxathiolane (**4**) with $(CH_3)_3Al$ was examined. In a reaction of **4** (*endo* : *exo* = 1 : 1.3) with 2 molar amounts of $(CH_3)_3Al$ in toluene at 0 °C for 1 h, 2-phenyl-1-propanol (**5**) was, as expected, isolated in 62% yield with 16% recovery of the starting material **4** (Scheme 3, Table 1, entry 3; see also entry 4). When the reaction was carried out with the use of 3 molar amounts of $(CH_3)_3Al$, the yield of **5** was increased to 94% (Table 1, entry 6; see also entry 7), while **5** was hardly formed in the reaction when an equimolar amount of $(CH_3)_3Al$ was used (Table 1, entry 1). Dichloromethane could also be used as the solvent of the present reaction (Table 1, entries 9 and 10), while no reaction took place in diethyl ether, diisopropyl ether and DMF (Table 1, entries 11, 12, and 13). In all the reactions examined, no detectable amount of 1-phenyl-1-propanol (**6**) was formed.



4 **5** **6**

Scheme 3

Table 1. Reaction of **4** with $(CH_3)_3Al$ at 0 °C for 1 h

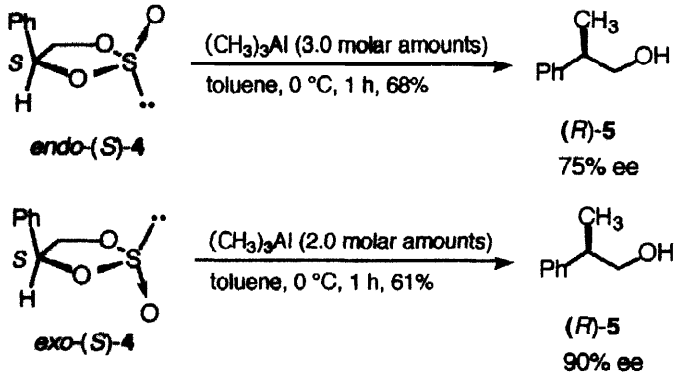
Entry	$(CH_3)_3Al$ /ma[a] (*endo* : *exo*)[b]	Solvent	Yield of **5**/%[c,d]	Recovery of **4**/%[c,d] (*endo* : *exo*)[b]
1	1.0 (1 : 0.9)	toluene	7	80
2	1.5 (1 : 0.9)	toluene	21	77 (1 : 1.3)
3	2.0 (1 : 1.3)	toluene	62	16 (1 : 15)
4[e]	2.0 (1 : 0.9)	toluene	40	21 (*exo*)
5	2.4 (1 : 0.9)[f]	toluene	74	20 (1 : 3.0)
6	3.0 (1 : 0.9)	toluene	94	nd
7[e]	3.0 (1 : 1.3)	toluene	84	nd
8	5.0 (1 : 1.3)[g]	toluene	82	nd
9	3.0 (1 : 0.9)	CH_2Cl_2	70	28 (1 : 4.27)
10	5.0 (1 : 1.3)	CH_2Cl_2	77	nd
11	3.0 (1 : 0.9)	Et_2O	nd	>99 (1 : 1.24)
12	3.0 (1 : 0.9)	*i*-Pr_2O	nd	>99 (1 : 1.24)
13	5.0 (1 : 1.3)[h]	DMF	nd	83

a) ma = Molar amount. b) Ratio was determined by NMR. c) Isolated yield. d) nd = Could not be detected. e) The reactions in entries 4 and 7 were carried out under the same conditions as entry 3 and entry 6, respectively. f) The reaction was carried out for 5.5 h. g) The reaction was carried out for 0.3 h. h) The reaction was carried out for 0.5 h.

As can be seen from Table 1, the proportion of the *exo*-isomer was invariably increased in the recovered **4**. Although no investigation concerning the isomerization of the *endo*- and *exo*-forms has been made, the results

suggest that the *endo*-isomer reacted more readily with $(CH_3)_3Al$ under the conditions examined. At the present stage of investigation, however, the exceptional result obtained in the reaction of **4** with $(CH_3)_3Al$ in a ratio of 1 : 2 could not be explained (Table 1; entries 3 and 4).

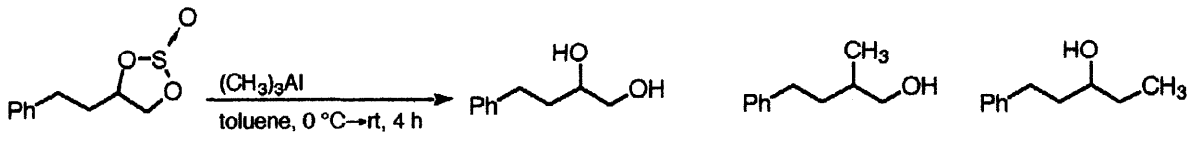
In order to confirm the stereochemistry of the reaction, the *endo*-isomer of (*S*)-2-oxo-4-phenyl-1,3,2-dioxathiolane [(*S*)-**4**] reacted with $(CH_3)_3Al$ in toluene at 0 °C for 1 h resulted in the formation of (*R*)-2-phenyl-1-propanol [(*R*)-**5**] in 75% ee (68% yield). The reaction of the *exo*-isomer of (*S*)-**4** gave (*R*)-**5** in 90% ee (61% yield) (Scheme 4).



Scheme 4

These results suggest that the complexation of the S→O group with $(CH_3)_3Al$ is essential for the success of the reaction. The lower selectivity observed in *endo*-(*S*)-**4** than that in *exo*-(*S*)-**4** would be rationalized by the formation of a transition state with extensive bond-breaking (SN1-type transition state) to release the compression energy exerted between the phenyl group and the complexed S→O group.[7]

When 2-oxo-4-(2-phenylethyl)-1,3,2-dioxathiolane (**7**) was treated with an equimolar amount of $(CH_3)_3Al$ in toluene at 0 °C to room temperature for 4 h, 92% of **7** was recovered (Scheme 5; Table 2, entry 1), while with 5 molar amounts of $(CH_3)_3Al$, 4-phenyl-1,2-butanediol (**8**) was obtained in 92% yield without any detectable formation of either 2-methyl-4-phenylbutanol (**9**) or 1-phenylpentan-3-ol (**10**) (Table 2, entry 3).



7 (*endo* : *exo* = 1 : 1.6) **8** **9** **10**

Scheme 5

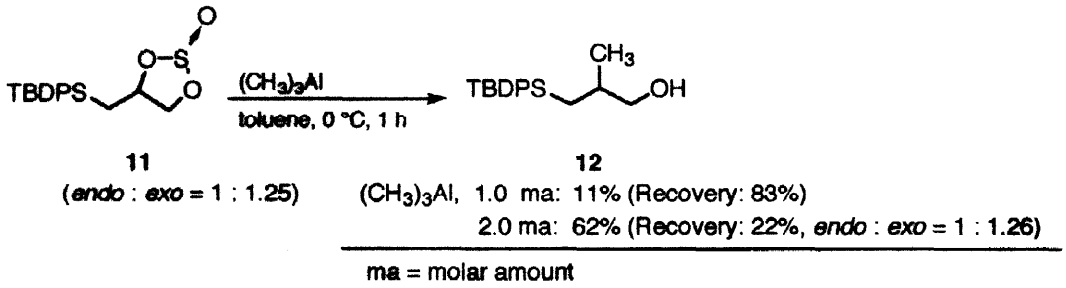
Table 2. Reaction of **7** (*endo* : *exo* = 1 : 1.6) with $(CH_3)_3Al$ in toluene at 0 °C→rt for 4 h

Entry	$(CH_3)_3Al$/ma[a]	Lewis acid	Yield of **8**/%[b, c]	Recovery of **7**/%[b, c]
1	1.0	none	nd [89]	92 [89]
2	3.0	none	24 [26]	76 [73]
3	5.0	none	92 [86]	nd [9]
4	5.0	BF_3·OEt_2	nd [nd]	79 [99]
5	5.0	$La(OTf)_3$	13	83

a) ma = Molar amount. b) nd = Could not be detected. c) [ ] = The results obtained in a separate experiment under the same conditions.

These results suggest that $(CH_3)_3Al$ exclusively attacked the sulfur atom instead of the carbon atom. It is interesting to note that the ring cleavage was retarded by the addition of $BF_3{\cdot}OEt_2$ or $La(OTf)_3$ (Table 2, entries 4 and 5).[8] Based on these results, it could be assumed that, when the effective stabilizing factor for the carbocationic character is absent in the intermediate formed in the transition state, $(CH_3)_3Al$ attacks the sulfur atom rather than the carbinol centers.

In view of these considerations, the reaction of 2-oxo-4-(*tert*-butyldiphenylsilylmethyl)-1,3,2-dioxathiolane (**11**) with $(CH_3)_3Al$ could be anticipated to occur at the secondary carbinol center, because silyl groups stabilize carbenium ions generated at the β position. As expected, the reaction of **11** (*endo* : *exo* = 1 : 1.25) with 2 molar amounts of $(CH_3)_3Al$ in toluene at 0 °C for 1 h gave 3-(*tert*-butyldiphenylsilyl)-2-methylpropanol (**12**) in 62% yield with 22% recovery of **11** (Scheme 6). When **11** was treated with an equimolar amount of $(CH_3)_3Al$, **12** was obtained in 11% yield and 83% of **11** was recovered.



Scheme 6

In summary, regioselective methylation of the secondary carbinol center of *prim*, *sec*-1,2-diols has been accomplished *via* 2-oxo-1,3,2-dioxathiolanes which are accessible in a single step from the 1,2-diols.

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References and Notes

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