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# (2*S*, 3*S*)-2,3-Epoxy-3-trimethylsilylpropanal as a New Conjunctive Reagent

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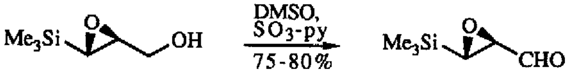
*Summary: The title epoxy aldehyde (>98% ee) has been prepared. Its reactions with nucleophiles afforded the corresponding adducts with a diastereoselectivity up to 86:14. Synthetic versatility of the chiral epoxy silane moiety makes this aldehyde a useful conjunctive reagent.*

Addition of nucleophiles to carbonyl compounds having other functional group(s) is a potential method in the synthesis of complex molecules, in which the functional group can play a dual role (i) to control the relative stereochemistry between itself and the incoming nucleophile and (ii) to enable further synthetic elaboration starting from this functionality.1) Here we disclose a new entry to such compounds, that is, the title aldehyde2) which has an optically active epoxy silane moiety.

We have reported a preparation of highly optically active (2*S*, 3*S*)-2,3-epoxy-3-trimethylsilyl-1-propanol (1) by a catalytic version of the Sharpless asymmetric epoxidation (with L-(+)-diisopropyl tartrate) from 3-trimethylsilylallyl alcohol.3) Oxidation of this alcohol should afford the title compound, but it was not trivial due to the presence of a sensitive epoxy silane moiety. The Swern oxidation (DMSO-$(COCl)_2$/$NEt_3$)4) was of a low reproducibility to give a varying amount of a by-product which was frequently the only product recovered.5) However, after considerable experimentation, we found a Swern version using DMSO-$SO_3\cdot py$/$NEt_3$6) afforded a satisfactory result: the desired aldehyde **2** could be obtained constantly in good yields after workup and simple distillation (eq 1).7) The ee of the aldehyde was verified to be >98% by its reduction ($NaBH_4$) to the parent alcohol **1** whose ee was again determined to be >98%.



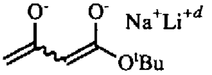
**1** >98%ee　　**2** >98%ee

(1)

With the aldehyde **2** in hand, we proceeded to survey its reactivity with organometallic reagents. Since the nucleophilic additions to aldehydes having *trans*-α,β-epoxy group are known to show low diastereoselectivities8) except for a certain case where a technique of bouble asymmetric synthesis was applied,9) we revisited to see the *syn*-/*anti*-selectivity on this particular aldehyde **2** (eq 2). Chemoselectivity between aldehyde and epoxy silane, the latter of which is also reactive towards nucleophiles,[10)] is another problem. The results are summarized in Table 1.[11)]

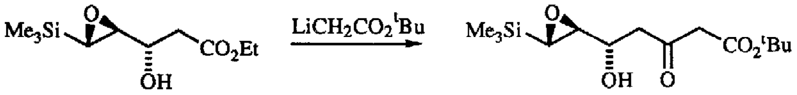
**Table 1.** Reaction of **2** with organometallics

( 2 )

| Entry | "R-Metal" | Conditions | 3 | *syn*/*anti*[a] | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | BuLi | $Et_2O$, -78°C | **a** | 29 : 71 | 75 |
| 2 | " | THF, -78°C | **a** | 39 : 61 | - - |
| 3 | BuMgBr | $Et_2O$, -78°C | **a** | 26 : 74 | - - |
| 4 | " | THF, -78°C | **a** | 36 : 64 | 72 |
| 5 | $CH_2=CHCH_2MgCl$ | $Et_2O$, -78°C | **b** | 46 : 54 | 66 |
| 6 | PhMgBr | THF, -78°C | **c** | 65 : 35 | 69 |
| 7 | $BuLi/Ti(O^iPr)_4$ (1:1.1) | hexane, r.t. | **a** | 30 : 70 | low |
| 8 | $Et_2Zn/Ti(O^iPr)_4$ (1:1.1) | hexane, -20°C | **d**[c] | 14 : 86 | 81 |
| 9 | $BrZnCH_2CO_2Et$[d] | $CH_2(OMe)_2$, 0°C | **e** | 20 : 80 | 87 |
| 10 |  | THF, -78°C | **f**[e] | 40 : 60 | 43 |
| 11 | " + $ZnCl_2$ (1:1) | THF, -78°C | **f** | 39 : 61 | - - |
| 12 | " + $ZnCl_2$ (1:2) | THF, -78°C | **f** | 26 : 74 | 67 |
| 13 | $Me_3SiCN$/KCN-18-c-6 | toluene, -30°C | **g**[f] | 80:20 or 20:80 | 89[g] |

[a] *Syn*/*anti* ratio determined by $^1H$ nmr analysis of a crude product. Assignments of *syn*-/*anti*-structures are described in text. [b] Combined, isolated yield. [c] R=Et. [d] Prepared according to ref 12. [e] $R=CH_2COCH_2CO_2{}^tBu$. [f] R=CN and the product is the silyl ether (ref 13). [g] Yield of a crude sample essentially pure by $^1H$ nmr.

Alkyllithium and Grignard reagents showed moderate selectivities (1:1--1:3) (entries 1-6) which are consistent with our previous result.[8i)] In general, organozinc reagents showed higher *anti*-preferred selectivities (entries 8, 9, and 12).[14)] $Et_2Zn$-$Ti(O$-*i*-$Pr)_4$ is noteworthy to show the highest value of 14:86 (entry 8) which is also *the highest diastereoselectivity* recorded for reactions of *trans*-α,β-epoxy aldehydes with achiral reagents.[8,15)] This selectivity would come from the zinc-titanium reagent itself rather than the *trans*-silyl group remote from the reaction center. The stereochemistries of the products **3a-d** were determined by their $^1H$ nmr spectra which had been reported previously.[11)] The structure of (major-)**3e** was correlated with that of (major-)**3f** (eq 3)[16)] which was shown to be the depicted one (*anti*) based on a derivatization.[17)]

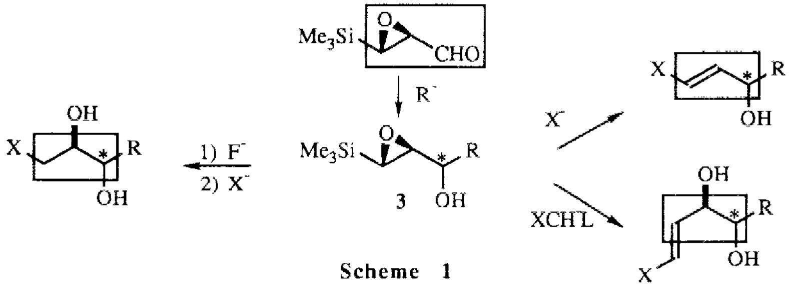


major-**3e** major-**3f**

( 3 )

The formation of the cyanohydrin (entry 13) also proceeded with a good diastereoselectivity eventhough its mechanism must be quite different from that of organozinc additions. It deserves a comment that, at our hands, some reagents such as BuZnI/CuI/$BF_3$·$OEt_2$,[18] TiCl(O-*i*-Pr)$_3$-BuLi or BuMgBr,[19] and $Me_3SiCN/ZnI_2$[13] could not be used, resulting in destruction of **2** due probably to the fragile epoxy silane moiety under these reaction conditions.

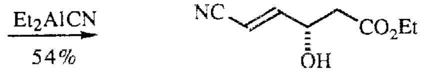
The adducts **3** should be useful intermediates as such or after stereochemical tune, if necessary.[20] Thus the second extention of a carbon chain and/or introduction of a functional group can be achieved based on the versatile epoxy silane moiety, broadening the utility of **2** as a conjunctive reagent. A few representative reactions are illustrated in Scheme 1.[3,10,21,22]



**Scheme 1**

For example, a reaction of **3e** with $Et_2AlCN$ (1.3 equiv) afforded the α,β-unsaturated nitrile **4** without being affected by its hydroxy and ester groups (eq 4). The compound **5** prepared from pure *anti*-**3f** in 2 steps reacted with $Ph_2CuLi$ to give **6** in good yield, demonstrating an introduction of the optically active side chain of HMG-CoA reductase inhibitors to an aromatic ring (eq 5).[17]

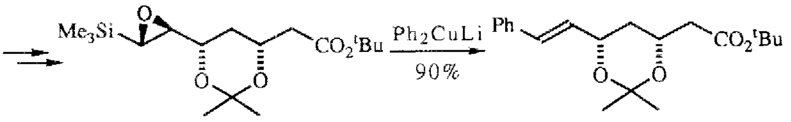
**3 e**



**4**

( 4 )

*anti*-**3 f**



**5** **6**

( 5 )

In summary, reactions of the new, optically active aldehyde **2** prepared here demonstrate its synthetic utility as a conjunctive reagent. Further synthetic applications of **2** are now under active investigation.

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2) This aldehyde is a new compound which has not appeared in *Chem. Abstra.*

3) Kobayashi, Y.; Ito, T.; Yamakawa, I.; Urabe, H.; Sato, F. *Synlett* **1991**, 811.

4) Review: Tidwell, T. T. *Synthesis* **1990**, 857.

5) The by-product is 3-chloro-3-trimethylsilyl-1,2-propanediol resulting from the addition of $Cl^-$ to **1**. Its formation could be avoided by the use of DMSO-$SO_3$·py. PCC did not afford the desired aldehyde in good yield, either.

6) Nicolaou, K. C.; Duggan, M. E.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 6676.

7) Preparation of **2**: To a stirred mixture of the epoxy alcohol **1** (2.0 g, 13.7 mmol), DMSO (19.53 mL, 275 mmol), and $NEt_3$ (19.6 mL, 142 mmol) in $CH_2Cl_2$ (18.4 mL) was added $SO_3$·py complex (13.1 g, 82.2 mmol) in two portions at 0°C. After the resulting homogeneous solution had been stirred for 30 min at the same temperature with TLC monitoring, it was diluted with 1:1-ether/pentane (90 mL). The organic layer was washed successively with water, 1 N-HCl, and $NaHCO_3$ solution. After drying ($Na_2SO_4$) and removal of the solvent on a rotary evaporator, the residual oil was purified by Kugelrohr distillation (b.p. 50--60°C (bath temp)/7 mmHg) to give the pure title aldehyde (1.59 g, 80%). $^1H$ nmr ($CDCl_3$, TMS) $\delta$ ppm 0.10 (s, 9 H), 2.49 (d, $J$ = 3.4 Hz, 1 H), 3.14 (d/d, $J$ = 3.4, 6.6 Hz, 1 H), 8.79 (d, $J$ = 6.6 Hz, 1 H). $[\alpha]_D^{18}$ +89.4° (*c* 1.18, $CHCl_3$).

8) In general, nucleophilic additions to *trans*-substituted epoxy aldehydes are much less diastreoselective than those to *cis*- or *gem*-substituted ones.

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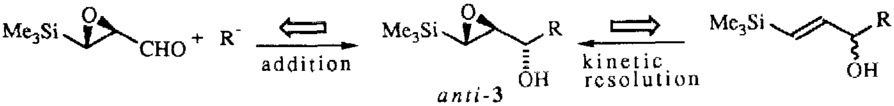
11) This method is an alternative one for the preparation of highly optically active (*anti*)-**3** which we have routinely prepared by a kinetic resolution in the Sharpless epoxidation: Kitano, Y.; Matsumoto, T.; Sato, F. *Tetrahedron* **1988**, *44*, 4073.



*anti*-**3**

The *syn*- and *anti*-isomers were often separable on silica gel.

12) $BrZnCH_2CO_2Et$: Rathke, M. W. *Org. React.* **1975**, *22*, 438. $[CH_2{=}C(O^-)CH{=}C(O^-)O^tBu]Na^+Li^+$: Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082.

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14) For a rationale of the *anti* preference: see ref 8b.

15) Addition of nucleophiles to **2** under chiral conditions (cf. ref 9) will be described in our full account.

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