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A regio- and stereoselective α-methylation of γ,δ-epoxy-α,β-unsaturated esters with a Me_2Zn–CuCN reagent†

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A highly regio- and stereoselective α-methylation reaction of γ, δ-epoxy-α, β-unsaturated esters was achieved by using a Me_2Zn–CuCN reagent.

Stereoselective construction of polypropionate-derived chains, that are found in many macrolide antibiotics, has been of great importance in synthetic organic chemistry.[1] While aldol-type reactions are widely used in this area, substitution reactions of epoxides with a methyl anion equivalent also provide a powerful method for this purpose. In this connection, we have reported that a γ,δ-epoxy-α,β-unsaturated ester undergoes an S_N2-type substitution reaction with the Me_3Al–H_2O system to afford a γ-methylated δ-hydroxy-α,β-unsaturated ester stereospecifically.[2]

On the contrary, it has been known that introduction of a methyl group at the α-carbon via an S_N2'-type reaction is quite difficult.[3] Thus, treatment of a γ,δ-epoxy-α,β-unsaturated ester with MeCuCNLi led to a 2:1 mixture of the regioisomers, and $Me_2CuCNLi_2\cdot BF_3$, which effected highly stereoselective S_N2' methylation of γ-mesyloxy-δ-siloxy-α,β-unsaturated esters,[4] also failed to give a result (Scheme 1).

In the course of synthetic studies of natural products having a substituted tetrahydropyran moiety, we became intrigued by this type of transformation. We envisioned that the combined use of Me_2Zn and a copper salt may afford an S_N2' product, a useful precursor of an α-methyl δ-lactone, with high regio- and stereoselectivity.[5]

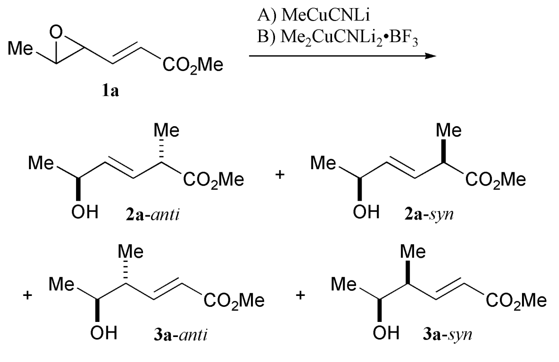
The reactions of the ester **1a** with Me_2Zn and a copper salt are summarized in Table 1. Although the reaction using CuI or CuOTf merely resulted in recovery of the starting material (entries 1 and 2), CuCN gave the desired product **2a**-*anti* in high regio- and stereoselectivity (entry 3). The solvent effect of the reaction with the Me_2Zn-CuCN reagent was then examined (entries 4-6). While the reaction in ether was very sluggish, use of a more polar solvent, *e.g.* MeCN, exhibited higher reactivity. In particular, DMF was found to enhance the reaction rate dramatically, which allowed us to perform the reaction with a catalytic amount of CuCN at −23 °C (entry 7). It should be noted that the regioselectivity of the present method is much higher than that of the conventional method using organocuprates.[3]

The excellent results of the preliminary experiments led us to investigate the scope of the present S_N2' methylation reaction (Scheme 2 and Table 2). Since direct assignment of the

Table 1 Reactions of ester **1a** with Me_2Zn and CuX[a]

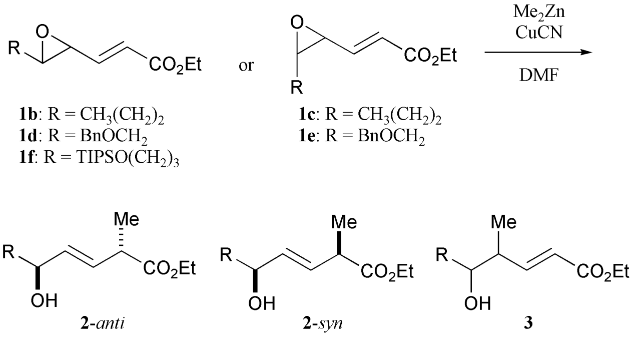
Entry	CuX (equiv.)	Solvent	Yield[b] (%)	**2a** (*anti*:*syn*)[c]	**3a** (*anti*:*syn*)[c]
1	CuI (2)	THF	n.r.[d]	—	—
2	CuOTf (2)	THF	n.r.[d]	—	—
3	CuCN (2)	THF	85	91 (98:2)	9 (86:14)
4	CuCN (2)	Et_2O	9	n.d.	n.d.
5	CuCN (2)	MeCN	64	89 (97:3)	11 (92:8)
6	CuCN (2)	DMF[e]	86[f]	90 (99:1)	10 (n.d)
7	CuCN (0.2)	DMF[e]	74[f]	94 (99:1)	6 (n.d)

[a] The reaction was performed at 0 °C for 2 h unless otherwise noted. [b] Determined by ^1H NMR spectroscopy unless otherwise noted. [c] The diastereoselectivities were determined by GLC analyses. [d] The starting material was recovered unchanged. [e] The reaction was performed at −23 °C. [f] Combined isolated yield.



yield / **2a** (*anti* : *syn*) : **3a** (*anti* : *syn*)
A : 71% / 68 (99 : 1) : 32 (97 : 3)
B : 65% / 68 (79 : 21) : 32 (94 : 6)

Scheme 1 Reactions of the ester **1a** with methylcopper reagents previously reported.



Scheme 2 Reactions of the ester with CuCN–Me_2Zn reagent.

Table 2 Reactions of various γ,δ-epoxy-α,β-unsaturated esters with Me_2Zn–CuCN reagent in DMF[a]

Entry	Epoxide	Method	Product	Yield[b] (%)	**2**:**3**[c]	**2**-*anti*:**2**-*syn*[d]
1	**1b**	A	**2b**-*anti*	81	95:5	>95:<5
2	**1c**	A	**2c**-*syn*	75	98:2	<5:>95
3	**1d**	B	**2d**-*anti*	91	98:2	>98:<2
4	**1e**	B	**2e**-*syn*	98	93:7	<2:>98
5	**1f**	B	**2f**-*anti*	99	92:8	98:2

[a] Method A: 0.2 equiv. of CuCN was used. Method B: 2 equiv. of CuCN was used. The reaction was performed at −23 °C unless otherwise noted. [b] Combined isolated yield. [c] Determined by ^1H NMR spectroscopy. [d] Determined by ^{13}C NMR spectroscopy.

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† Electronic supplementary information (ESI) available: IR and NMR spectra of compounds **2b–g**. See http://www.rsc.org/suppdata/cc/b2/b205957f/

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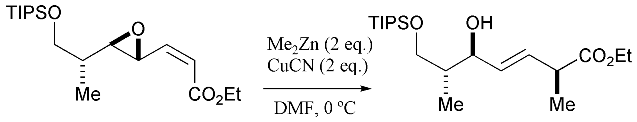
configuration was difficult, the products were converted into the corresponding δ-lactones (*vide infra*).

With a view to examining the stereospecificity of the transformation, two pairs of *trans*- and *cis*-epoxides were subjected to the methylation reaction (entries 1–4). As was expected, *trans*-epoxides **1b** and **1d** afforded the S_N2'-*anti*-products, while the corresponding *syn*-isomers were obtained from *cis*-epoxides **1c** and **1e** with high regioselectivity. The substrates (**1d**, **1e**, **1f**) bearing an oxygen functional group on the side chain also gave satisfactory results, though use of a stoichiometric amount of CuCN was required in these cases.[6] Epoxide **1g** having a *cis*-olefin moiety also underwent a stereoselective S_N2'-methylation reaction to give **2g**-*syn* in excellent yield and stereoselectivity (Scheme 3).

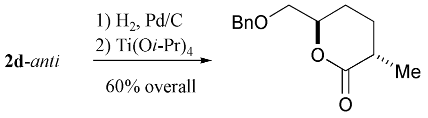


1g

96% **2g**-*syn*

Scheme 3 The reaction of an epoxy-*cis*-unsaturated ester.

Hydrogenation of the products followed by lactonization mediated by $Ti(OPr^i)_4$ effected conversion into the corresponding δ-lactones as shown in Scheme 4. It is noteworthy that stereoselective synthesis of this type of 2,5-disubstituted δ-lactone is not easy, *e.g.*, methylation of a 5-substituted δ-lactone by treatment with LDA followed by MeI led to a 1 : 1 mixture of diastereomers.



Scheme 4 Transformation of the α-methylated product to a δ-lactone.

In conclusion, a highly regio- and stereoselective α-methylation reaction of γ,δ-epoxy-α,β-unsaturated esters has been developed by using the Me_2Zn–CuCN reagent. It is noteworthy that the substrates in optically active form can be easily prepared from the corresponding dienoates by Shi's asymmetric epoxidation reaction.[7] Since the S_N2'-products are readily converted into the corresponding δ-lactones, the present method should be useful for asymmetric total synthesis of natural products having a substituted δ-lactone or a tetrahydropyran moiety.

Notes and references

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6 Typical procedure for the present reaction with a stoichiometric amount of CuCN: to a mixture of methyl 4,5-epoxy-2-hexenoate (1.0 g, 7.0 mmol), CuCN (1.3 g, 14.1 mmol) and DMF (18 mL) was added Me_2Zn (2.0 M solution in toluene: 7.0 mL, 14.1 mmol) at −23 °C on which the color turned from pale green to yellow. The reaction mixture was stirred for 1 h, quenched by water and stirred for an additional 1 h. After filtration through a pad of Celite, the filtrate was extracted with ether. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by silica gel chromatography (hexane–ether; 1 : 1) afforded the α-methylated product (α:γ = 90 : 10) as a pale yellow oil (0.95 g, 86% yield). The reaction with a catalytic amount of CuCN was also performed in a similar manner as noted above.

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