Tetrahedron Letters 50 (2009) 5126–5129

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Stereoselective S_N2' alkylation reaction sequence of the γ,δ-epoxy α,β-unsaturated ester system via γ,δ-chlorohydrin intermediates by the use of a $R_3Al–CuCN$ reagent

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ARTICLE INFO

Article history:
Received 2 June 2009
Revised 20 June 2009
Accepted 23 June 2009
Available online 26 June 2009

Keywords:
Epoxy unsaturated ester
S_N2' alkylation reaction
Chlorohydrin
$R_3Al–CuCN$ reagent
Quaternary asymmetric carbon atom

ABSTRACT

A novel stereoselective S_N2' alkylation reaction sequence of the γ,δ-epoxy α,β-unsaturated ester system has been developed which involves a regioselective substitution reaction with chloride ions at the γ-position and a subsequent S_N2' alkylation reaction of the resulting γ-chloro-δ-hydroxy derivatives with a $R_3Al–CuCN$ reagent. The new methodology was demonstrated to be applicable to a variety of substrates and to provide various δ-hydroxy-α-alkyl-β,γ-unsaturated esters including those bearing a quaternary asymmetric carbon atom at the α-position in a highly stereoselective manner and high yields.

Stereoselective construction of the polypropionate-derived chains, that are found in many macrolide and ansamycin antibiotics, has been of great importance in the community of medicinal chemistry and 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 methodology for this purpose. In this context, we have already developed two new synthetic methodologies that involved the highly γ-selective S_N2 alkylation reaction of γ,δ-epoxy-α,β-unsaturated esters with $Me_3Al–H_2O$[2] and $R_3Al–R'_3SiOTf$[3] reagents, resulting in the formation of δ-hydroxy-γ-methyl- and δ-hydroxy-γ-alkyl-α,β-unsaturated esters, respectively, in a stereospecific manner.

On the contrary, it has been known that stereoselective introduction of a methyl group at the α-position of the γ,δ-epoxy-α,β-unsaturated ester system via an S_N2' reaction is quite difficult. To overcome this synthetic problem, we have successfully developed the first stereoselective S_N2' methylation reaction of γ,δ-epoxy-α,β-unsaturated esters with a $Me_2Zn–CuCN$ reagent.[4] For example, the reaction of an epoxy ester **1** with a $Me_2Zn–CuCN$ reagent in DMF gave rise to the *anti*-S_N2' product **2**-*anti* with remarkable high regio- and stereoselectivity (Scheme 1).[4]

On the other hand, to synthesize the corresponding *syn*-S_N2' product **2**-*syn* from the *trans*-epoxy ester **1**, an epoxide-opening reaction that occurs in a *syn*-S_N2' manner is required. However, such transformation in one-step is extremely difficult, because the copper-mediated or the copper-catalyzed S_N2' reaction generally occurs by an *anti*-attack of a nucleophile with respect to a leaving group.[5] In order to realize this particular *syn*-S_N2' alkylation reaction of the γ,δ-epoxy-α,β-unsaturated ester system, we newly designed the two-step reaction sequence involving a regioselective substitution reaction of **1** with chloride ions at the γ-position and a subsequent S_N2' alkylation reaction of the resulting *anti*-chlorohydrin **3** with a $R_3Al–CuCN$ reagent, as shown in Scheme 1. In this context, Dieter and Guo recently reported tandem regio- and stereoselective bis-allylic substitution reactions of *anti*-5-acetoxy-4-halo-α,β-unsaturated esters, prepared from *trans*-γ,δ-epoxy-α,β-enoates, with alkyl magnesium cuprates, in which the first substitution reaction with alkyl magnesium cuprate occurred at the α-position in an S_N2' manner followed by the second S_N2' reaction of the resulting allylic acetate at the β-position.[6] On the other hand, Tamamura has reported the two-step *syn*-S_N2' alkylation reaction of γ,δ-aziridinyl-α,β-enoates which involved the first regioselective S_N2 reaction with methanesulfonic acid followed by an *anti*-S_N2' alkylation of the resulting δ-amino-γ-mesyloxy-α,β-enoates with an organocopper reagent.[7]

In this Letter, we report a highly stereoselective *syn*-S_N2' alkylation reaction sequence of the γ,δ-epoxy α,β-unsaturated ester system which involves the charcoal-promoted substitution

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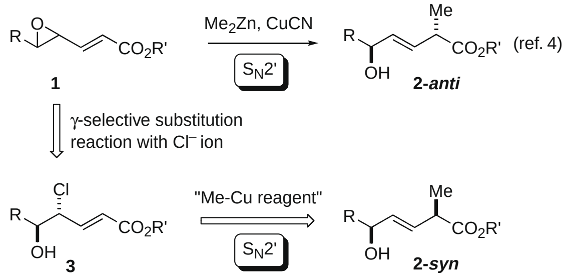
doi:10.1016/j.tetlet.2009.06.106

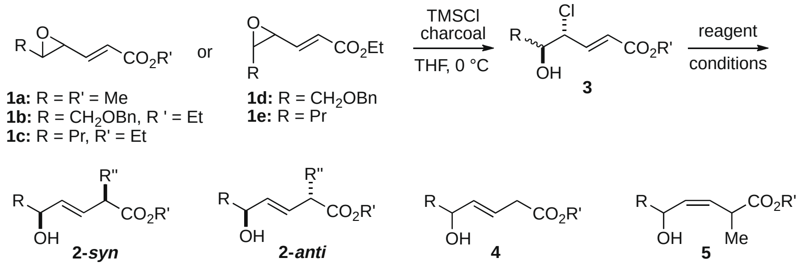


Scheme 1. S_N2' methylation reactions of γ,δ-epoxy α,β-unsaturated ester **1**.

reaction with TMSCl at the γ-position and a subsequent S_N2' alkylation reaction of the resulting γ-chloro-δ-hydroxy derivatives with a R_3Al–CuCN reagent with remarkably high stereoselectivity.

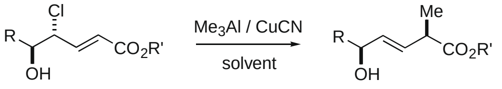
Initially, we chose methyl *trans*-4,5-epoxy-2-hexenoate (**1a**) readily obtainable from methyl sorbate as a model substrate and examined the above two-step reaction sequence. Thus, the reaction of **1a** with TMSCl in the presence of charcoal in THF at 0 °C afforded *anti*-γ-chloro-δ-hydroxy-α,β-unsaturated ester **3a** (dr = 91:9) in 96% yield (Scheme 2).[8] Although other additives such as MS4A, silica gel, and one equivalent of water were examined to effect γ-selective chlorination, charcoal was the promoter of choice. Since commercially available charcoal adsorbs water on the surface, HCl generated from TMSCl and water would probably act as an acid catalyst and promote the chloride substitution reaction on the solid surface.

Next, we examined the key S_N2' methylation reaction of **3a** under various conditions and the results are summarized in Table 1. The reaction of **3a** with Me_2CuLi in THF produced the desired *syn*-methylation product **2a**-*syn* in 71% yield (entry 1), although a considerable amount of the reduction product **4a** (12% yield) was accompanied. On the other hand, the reaction of **3a** with a Me_2Zn–CuCN reagent[4] in DMF afforded a 5:1 mixture of **2a**-*syn* and **5a** in 92% combined yield (entry 2), whereas the reaction with lithium trimethyl zincate did not produce **2a**-*syn* at all (entry 3). To our great pleasure, the reaction of **3a** with an organocopper reagent prepared from Me_3Al and CuCN[9] in THF gave the desired product **2a**-*syn* in complete regio- and stereoselectivity in 95% yield (entry 4). While the reaction of chlorohydrin **3b**-*anti* bearing a benzyloxy group on the side chain, which was prepared from **1b** in 99% yield (dr >99:1), with Me_3Al–CuCN in THF proceeded similarly, the yield of **2b**-*syn* was variable and lacked reproducibility (entry 5). Therefore, we next examined the solvent effect of the reaction with the Me_3Al–CuCN reagent (entries 6–9). As a result, while the reactions in CH_2Cl_2 and in Et_2O were not effective at all, use of a more polar solvent, for example, DMF, exhibited higher reactivity. In particular, MeCN was found to enhance the reaction



Scheme 2. S_N2' alkylation reaction sequence of γ,δ-epoxy α,β-unsaturated esters **1a–e**.

Table 1
Reactions of chlorohydrins **3** with various methylating agents[a]



3a R = R' = Me
3b R = CH_2OBn, R' = Et
2a-*syn* R = R' = Me
2b-*syn* R = CH_2OBn, R' = Et

Entry	Chlorohydrin	Me-Metal (equiv) CuX (equiv)	Solvent	**2**-*syn*[b] (%)
1	**3a**-*anti*[c]	Me_2CuLi (2)	THF	**2a**-*syn* 71[d]
2	**3a**-*anti*[c]	Me_2Zn (2), CuCN (2)	DMF	**2a**-*syn* 92[e]
3	**3a**-*anti*[c]	Me_3ZnLi (1.1)[f]	THF	**2a**-*syn* 0[g]
4	**3a**-*anti*[c]	Me_3Al (2.2), CuCN (1.1)	THF	**2a**-*syn* 95
5	**3b**-*anti*	Me_3Al (2.2), CuCN (1.1)	THF	**2b**-*syn* 20~70
6	**3b**-*anti*	Me_3Al (2.2), CuCN (1.1)	CH_2Cl_2	Complex mixture
7	**3b**-*anti*	Me_3Al (2.2), CuCN (1.1)	Et_2O	**2b**-*syn* 0[h]
8	**3b**-*anti*	Me_3Al (2.2), CuCN (1.1)	DMF	**2b**-*syn* 70[i]
9	**3b**-*anti*	Me_3Al (2.2), CuCN (1.1)	MeCN	**2b**-*syn* 88

[a] The reaction was carried out at 0 °C for 1 h unless otherwise noted.
[b] Determined by ^1H NMR using pyrazine as an internal standard.
[c] dr = 91:9.
[d] Allylic alcohol **4** was accompanied in 12% yield.
[e] A mixture of stereoisomers (**2**/**5** = 5:1) was produced.
[f] The reaction was carried out at −78 °C for 1 h.
[g] A mixture of allylic alcohol **4** (10%) and the starting material (24%) was obtained.
[h] The starting material was recovered unchanged.
[i] An inseparable mixture of by-products was formed along with the starting material.

Table 2
The S_N2' alkylation reaction of various γ,δ-epoxy α,β-unsaturated esters with a R_3Al–CuCN reagent via chlorohydrins **3**[a]

Entry	Epoxide	Yield of **3**[b] (%)	R_3Al	Product	Yield of **2**[b] (%)	**2**-*syn*:**2**-*anti*[c]
1	**1b**	99	Me_3Al	**2b**-*syn*	88	96:4
2	**1c**	99	Me_3Al	**2c**-*syn*	99	96:4
3	**1d**	97[d]	Me_3Al	**2d**-*anti*	79	4:96
4	**1e**	84[d,e]	Me_3Al	**2e**-*anti*	68	1:>99
5	**1a**	96[f]	Et_3Al	**2f**-*syn*	90[g]	>99:1
6	**1a**	96[f]	*i*-Bu_3Al	**2g**-*syn*	86[g,h]	>99:1

[a] The reaction was carried out with R_3Al (2.2 equiv) and CuCN (1.1 equiv) in MeCN at 0 °C for 18 h unless otherwise noted.

[b] Combined isolated yield by silica gel column chromatography.

[c] Determined by ^{13}C NMR (quantitative integration).

[d] DMF was used as solvent.

[e] dr = 80:20.

[f] dr = 91:9.

[g] THF was used as solvent.

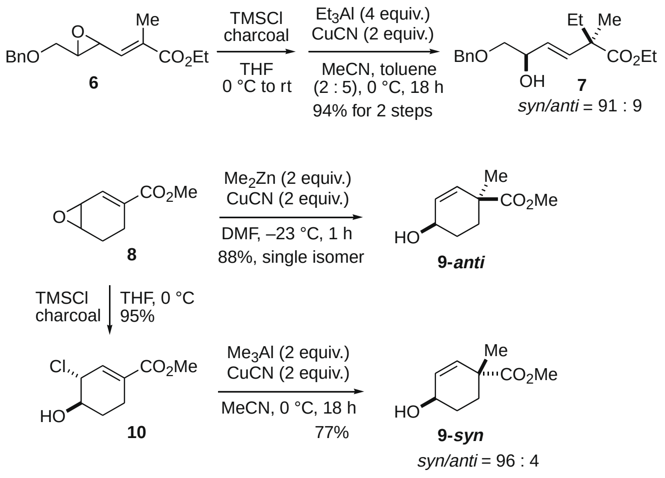
[h] γ-Alkylation product was formed in 4% yield.

rate remarkably and to give the best result in this reaction (entry 9).

The excellent results of the preliminary experiments led us to investigate the scope of the present S_N2' alkylation reaction sequence (Table 2).[10,11] Thus, the S_N2' methylation reaction sequence of *trans*-γ,δ-epoxy unsaturated esters (**1b**, **c**) bearing a benzyloxy or a propyl side chain efficiently occurred giving rise to the desired products **2b**-*syn* and **2c**-*syn*, respectively, in high stereoselectivity (*syn*/*anti* = 96:4) and high yields (entries 1 and 2). The methodology was also applicable to *cis*-epoxy congeners **1d** and **1e** (entries 3 and 4), although DMF was the choice of solvent in the substitution reaction with chloride ions[12] and the S_N2' reaction of the chlorohydrin derived from **1e** resulted in a slightly lower yield.

It is noteworthy that the S_N2' alkylation reactions of **1a** with more bulky trialkylaluminum reagents such as triethylaluminum and triisobutylaluminum smoothly occurred in the presence of CuCN to furnish the ethyl and isobutyl substitution products, respectively, in complete stereoselectivity and high yields (entries 5 and 6).

In order to demonstrate the potential of the new synthetic methodology, we designed stereoselective construction of a quaternary carbon center by the use of the present method (Scheme 3). Thus, the substitution reaction of epoxy methacrylate **6** with TMSCl followed by treatment of the resulting chlorohydrin with a Et_3Al-CuCN reagent produced tertiary ester **7** bearing an α-quaternary asymmetric carbon atom (*syn*/*anti* = 91:9) in 94% yield.[13,14] Interestingly, addition of toluene as co-solvent accelerated the rate of the S_N2' reaction significantly, maybe due to enhancement of the Lewis acidity of the organocopper species and promotion of elimination of chloride ions. It should be noted that *anti*- and *syn*-S_N2' alkylation products bearing an α-quaternary asymmetric carbon atom are available from the same starting material by the use of the requisite organocopper species. For example, the two-step S_N2' reaction of methyl 4,5-epoxy-2-cyclohexene carboxylate **8**[15] produced **9**-*syn* (*syn*/*anti* = 96:4), while the reaction of **8** with a Me_2Zn–CuCN reagent in DMF furnished **9**-*anti*[16] as the sole product in 88% yield. These two methodologies provide very useful technologies for the synthesis of tertiary carboxylic acid esters bearing an α-quaternary carbon center in a stereoselective manner.



Scheme 3. Stereoselective construction of asymmetric quaternary carbon atoms.

In conclusion, we have developed a highly regio- and stereoselective *syn*-α-methylation reaction sequence of the γ,δ-epoxy-α,β-unsaturated ester system which involved a substitution reaction with chloride ions at the γ-position and a subsequent S_N2' alkylation reaction of the resulting chlorohydrins with a R_3Al–CuCN reagent. It is noteworthy that three types of methylation products with a different substitution pattern are obtainable from the same α,β-epoxy unsaturated ester by the reaction with Me_3Al–H_2O[2] leading to an S_N2-methylation product at the γ-position, with a Me_2Zn–CuCN reagent[4] giving rise to an *anti*-S_N2' methylation product at the α-position, and with TMSCl followed by a Me_3Al–CuCN reagent leading to a *syn*-S_N2' methylation product, respectively. Since the optically active α,β-epoxy unsaturated esters are readily available by the Katsuki-Sharpless asymmetric epoxidation[17] of allylic alcohols and the Shi asymmetric epoxidation[18] of dienoates, the new methodologies provide very useful technologies in the synthesis of natural products, particularly, those including the polypropionate-derived structures. Application of these methods to natural product synthesis is now on going in our laboratory.

Acknowledgments

The authors thank Dr. Eri Fukushi and Mr. Kenji Watanabe (GC–MS & NMR Laboratory, Graduate School of Agriculture, Hokkaido University) for their mass spectrometric analyses. Financial support from the Ministry of Education, Culture, Sports, Science and Technology, Japan (a Grant-in-Aid for Scientific Research (B) (No. 16350049)) is gratefully acknowledged.

Supplementary data

Supplementary data (characterization data) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.06.106.

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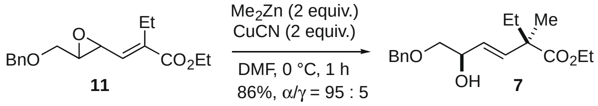
10. *Typical procedure for the substitution reaction of a γ,δ-epoxy-α,β-unsaturated ester with TMSCl in the presence of charcoal*: To a mixture of methyl *trans*-4,5-epoxy-2-hexenoate (**1a**) (2.0 g, 14.1 mmol), charcoal (1.41 g), and THF (70 mL) was added TMSCl (3.57 mL, 28.1 mmol) at 0 °C and the mixture was stirred at the same temperature for 1.5 h. After the reaction mixture was filtered through a pad of Florisil, MeOH and a 1 M aqueous solution of HCl were added to the filtrate in order and the mixture was stirred for 15 min. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc = 7:2) gave chlorohydrin **3a**-*anti* (γ/δ = 91:9) as a pale yellow oil (2.50 g, 99% yield).
11. *Typical procedure for the S_N2' reaction of a chlorohydrin with a Me_3Al–CuCN reagent:* To a mixture of chlorohydrin **3a**-*anti* (1.0 g, 5.6 mmol), CuCN (551.5 mg, 6.2 mmol), and MeCN (28 mL) was added a solution of Me_3Al (2.0 M solution in hexane, 6.2 mL, 12.3 mmol) at 0 °C and the mixture was stirred at same temperature for 18 h. Then, water was added and the reaction mixture was filtered through a pad of Celite. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc = 3:1) afforded the α-methylated product **2a**-*syn* (single isomer) as a pale yellow oil (781 mg, 89% yield).
12. For example, the substitution reaction of **1e** in THF afforded chlorohydrin **3e** as a mixture of regioisomers (dr = 66:34) in 63% yield.
13. An excess amount of a Me_3Al–CuCN reagent was required for completion of the reaction.
14. The tertiary ester **7** was also synthesized by the reaction of the α-ethyl-substituted epoxy unsaturated ester **11** with a Me_2Zn–CuCN reagent.



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