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Total synthesis of (–)-dihydroprotolichesterenic acid via diastereoselective conjugate addition to chiral fumarates

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Abstract

A diastereoselective conjugate addition of a variety of monoorganocuprates, Li[RCuI], to chiral fumarates to provide functionalized succinates has been developed. The utility of this reaction is demonstrated in a concise total synthesis of (–)-dihydroprotolichesterenic acid that required only four steps and proceeded in an overall 31% yield.

Keywords

Conjugate addition; Total Synthesis; Chiral Auxiliary; Butyrolactone; Succinate

Functionalized succinic acid derivatives and compounds that may be derived therefrom are structural motifs that are commonly found in biologically active molecules of natural and non-natural origin. Some notable examples include the matrix metalloproteinase inhibitor BB-1101 (**1**),¹ the antifungal and antibacterial agent dihydroprotolichesterenic acid (**2**),² the glaucoma drug pilocarpine (**3**),³ and the anti-inflammatory and antiviral agent antrocin D (**4**) (Figure 1).⁴

Because of the obvious importance of the functionalized, four-carbon building blocks found in these and other compounds, there has been considerable interest in developing efficient methods for enantioselective and stereoselective synthesis of substituted succinates.⁵ Toward this end, three general diastereoselective approaches using chiral auxiliaries have been reported. These include alkylations of enolates,⁶ oxidative cross couplings of enolates,⁷ and radical mediated conjugate additions to unsaturated carbonyl compounds (Scheme 1).⁸ However, these methods typically suffer from low stereoselectivity or production of toxic stoichiometric byproducts. Furthermore, none of the current strategies to access the succinate core enable access to any desired diastereomer from a single starting material.

Diastereoselective conjugate additions that are directed by chiral oxazolidinones have been extensively explored since their initial report in 1993.⁹ In a useful advance in the area, Bergdahl reported that the diastereofacial selectivity of copper-mediated conjugate additions to chiral *N*-crotonyl oxazolidinones can be reversed by varying Lewis acid additives and

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Supplementary Material

Experimental procedures and spectral data for all new compounds can be found with the online version at <http://dx.doi.org/>

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solvents, thus enabling a single starting material **5** to be converted into the two diastereomeric products **6** and **7**. (Scheme 2).¹⁰ Prior to this discovery, the only tactic that could be used to direct an organometallic reagent to the other face of the carbon-carbon double bond of a crotonate derivative was to employ an enantiomorphous chiral auxiliary on the starting material.

In the context of work directed toward the stemofoline alkaloids, we had occasion to expand the utility of the Bergdahl chemistry to γ -alkoxy crotonates,¹¹ and we then queried whether it might also be extended to fumarate derivatives such as **10**. If the regio- and stereoselective additions of organometallic reagents to fumarates could be controlled, it would be possible to access a variety of useful succinate derivatives. However, we could not be certain of the regiochemical outcome of cuprate additions to **10** because two carbon atoms are β to an activating carbonyl group. Curran and Sibi had each shown that radical additions proceeded β to the imide moiety of such compounds,⁸ and Evans had found that Mukaiyama-Michael reactions with chiral fumarates also occurred at the carbon atom β to the imide moiety.¹² However, there was no guiding precedent for the reactions of such substrates with organocuprate-derived reagents.

In order to probe the feasibility of inducing addition to chiral fumarates at the carbon atom distal to the chiral auxiliary, we prepared the chiral fumarate **10** in 78% yield from commercially available monomethyl fumarate **8** and oxazolidinone **9** in the presence of pivaloyl chloride, lithium chloride, and triethylamine (Scheme 3).¹³

We quickly found that implementing Bergdahl's conditions for the TMSI-mediated conjugate addition of monoorganocuprate reagents, Li[RCuI], to **10** required little optimization. Indeed, reaction of **10** with the monomethylcuprate Li[MeCuI] derived from methylolithium and (CuI)₄(DMS)₃ in the presence of TMSI proceeded with a high degree of regio- and diastereoselectivity to furnish the mono substituted succinate **11a** (R = Me) in 89% yield and 19:1 dr (Entry 1, Table 1). None of the regioisomeric addition product was detected in the NMR spectrum of the reaction mixture. The absolute stereochemistry of **11a** was established by its subsequent conversion into **2** (*vide infra*).

The observed regioselectivity in the reaction of **10** with a monomethylcuprate reagent is consistent with other conjugate additions that proceed via different mechanistic pathways.^{8,12} The enhanced reactivity at the carbon atom β to the imide moiety of **10** can be attributed to its greater electropositive character that is reflected by the relative chemical shifts of the two olefinic carbon atoms in the ¹³C NMR spectrum of **10**.¹⁴ Namely, the chemical shift of the carbon atom β to the imide moiety (δ = 133.4 ppm) is 1.5 ppm further downfield than the carbon atom α to the imide (δ = 131.9 ppm). The presence of TMSI, which is proposed to interact selectively with the oxygen atom of the imide carbonyl group,¹⁰ in the reaction mixture would be expected to further increase the electropositive character of this carbon atom.

Toward elucidating the scope of this process, the reactions of the chiral fumarate **10** with monoorganocuprates derived from several other alkylolithium reagents were examined (Table 1). In each case, the additions proceeded with high regio- and diastereoselectivity to give **11b-d**. The absolute stereochemistry of **11b-d** was assigned based on analogy with **11a**. Although monoorganocuprates derived from organolithium species and (CuI)₄(DMS)₃ added smoothly to **10** in the presence of TMSI, efforts to switch the diastereoselectivity of this reaction according to the Bergdahl protocol have thus far been unsuccessful. We have examined a number of alternate reaction conditions. For example, use of alkylcuprates derived from Grignard reagents, MgBr[RCuI], as described by Bergdahl did not give detectable amounts of any conjugate addition product.¹⁰ Reactions in which various

chelating Lewis acids such as MgBr_2 , ZnCl_2 , and MnCl_2 were used with monoorganocuprates, $\text{Li}[\text{RCuI}]$, gave only small amounts of products arising from 1,4-addition. Hence, the ability to control the diastereofacial selectivity in cuprate additions to chiral fumarate derivatives by the simple expedient of changing conditions as was done for **5** remains an unsolved problem.

Having established the underlying feasibility of inducing highly regio- and diastereoselective additions to **10**, we sought to exemplify the utility of the process by applying it to a synthetic problem. We thus identified (–)-dihydroprotolichesterinic acid (**2**), a member of the paraconic acid family of natural products,¹⁵ as a suitable target. (–)-Dihydroprotolichesterinic acid has been synthesized three times in racemic form^{16a–c} and twice in enantiomerically pure form.^{15d–e} However, we envisioned that a more concise enantioselective synthesis of **2** could be achieved using our methodology.

With the key intermediate **11a** in hand, all that remained to complete a synthesis of **2** was a diastereoselective aldol reaction, which we envisioned would proceed with concomitant lactone formation, and removal of the chiral auxiliary. Although an aldol reaction of a substrate similar to **11a** had been reported,¹⁷ use of those conditions for **11a** gave **12** in only 24% yield. After some experimentation, we discovered that enolization of **11a** at a higher concentration (0.9 M) with *n*- Bu_2BOTf (1.5 equiv) in the presence of Hünig's base (1.7 equiv), followed by the addition of myristyl aldehyde (1.2 equiv) and reacting for 15 h at 0 °C furnished the lactone **12** in 53% yield (95% based upon recovered starting material) and >95:5 dr (based on ^1H NMR of the crude reaction mixture) (Scheme 4). This aldol reaction was surprisingly sluggish, and despite repeated efforts, we were unable to identify conditions that would provide complete conversion. Hydrolysis of the oxazolidinone ring in **12** under standard conditions delivered (–)-dihydroprotolichesterinic acid (**2**) in 85% yield, thereby completing a four step, enantioselective synthesis of **2** that proceeded in 31% overall yield (56% based upon recovered starting material). The structure of synthetic **2** was confirmed by x-ray crystallography,¹⁸ and it also gave ^1H and ^{13}C NMR spectra and optical rotation data consistent with those published.^{16a}

In summary, we report the first diastereoselective conjugate addition of alkyl and aryl monoorganocuprates, $\text{Li}[\text{RCuI}]$, to chiral fumarates, thereby providing a rapid and stereoselective entry to substituted succinate derivatives. The practical utility of the method was demonstrated by its application to the concise, enantioselective synthesis of (–)-dihydroprotolichesterinic acid (**2**).

Supplementary Material

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Figure 1.
Biologically active molecules accessible through succinate derivatives.

1. Alkylation

2. Oxidative Enolate Coupling

3. Radical Mediated Conjugate Addition

Scheme 1.
Diastereoselective Routes to Access Succinates

Scheme 2.
Bergdahl's Switchable Conjugate Addition.¹⁰

Scheme 3.
Preparation of Chiral Fumarate **10**

Scheme 4.
Synthesis of (–)-Dihydroprotolichesterenic Acid

Table 1

Diastereoselective Conjugate Addition

Entry	Alkyl lithium	Yield ^b	dr ^c
a	MeLi	89%	19:1
b	EtLi	72%	19:1
c	<i>n</i> -BuLi	83%	19:1
d	PhLi	82%	19:1

^a¹³C NMR spectrum chemical shifts (ppm) for **10**.

^b Isolated yields after purification by flash column chromatography.

^c Based on HPLC analysis using a Chiralcel OD-H column.