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Graphical Abstract

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Diastereoselective addition of monoorganocuprates to a chiral fumarate: reaction development and synthesis of (–)-di-hydroprotolichesterinic acid

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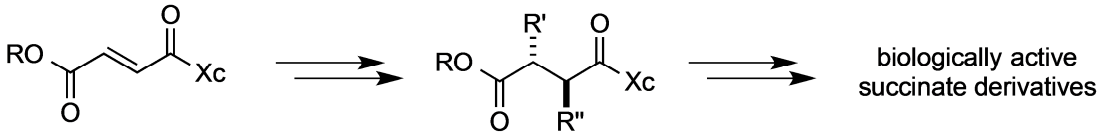

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ABSTRACT

Recent studies of diastereoselective conjugate additions of monoorganocuprates, Li[RCuI], to chiral γ-alkoxycrotonates and fumarates are disclosed. This methodology was applied to the shortest total synthesis of (–)-dihydroprotolichesterinic acid to date, but several attempts to prepare other succinate-derived natural products, such as pilocarpine and antrodin E, were unsuccessful.

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1. Introduction

A number of biologically active molecules possess a core substructure based on a functionalized succinic acid motif (Figure 1). Representative members of this general family include the paraconic acid family of natural products, such as dihydroprotolichesterinic acid (**1**), roccellaric acid (**2**), and nephromopsinic acid (**3**) among others.[1] These compounds exhibit a broad spectrum of activities, especially antibacterial and antifungal properties. Additionally, the FDA approved glaucoma drug pilocarpine (**4**),[2] the anti-inflammatory and antiviral compound antrodin E (**5**),[3] the matrix metalloproteinase (MMP) inhibitor BB-1101 (**6**),[4] and the anti-HIV agent arctigenin (**7**) are all based around a functionalized succinate core.[5]

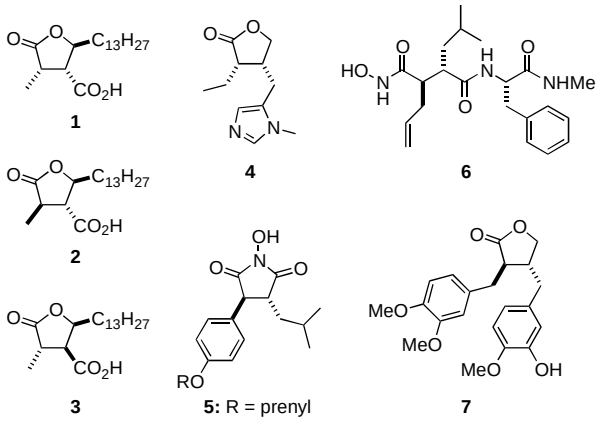
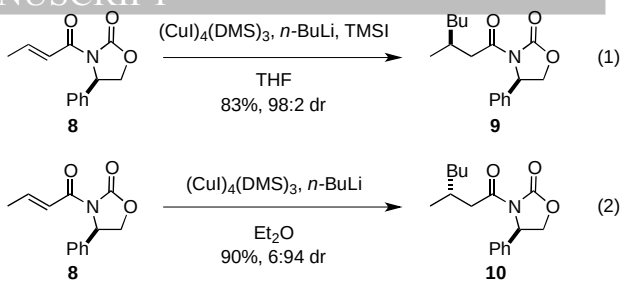


Figure 1. Selection of biologically active succinic acid derivatives.

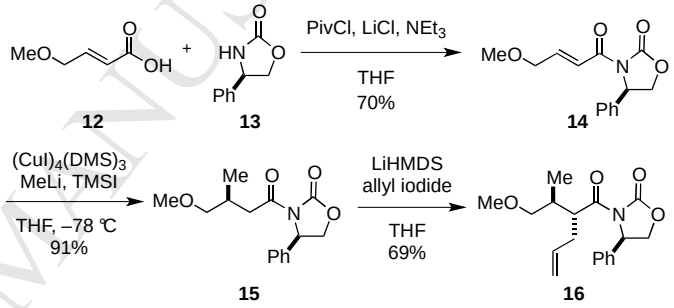
Owing to the wide variety of biologically active molecules containing a functionalized succinic acid moiety, it is not surprising that numerous approaches to synthesize chiral succinates have been developed.[6] Several catalytic, enantioselective methods involving the use of chiral Lewis acids,[7,8] transition metals,[9,10] and organocatalysts have been reported.[11] However, the vast majority of methods that enable access to enantiomeric succinate derivatives utilize a chiral auxiliary in aldol,[12] alkylation,[13] conjugate addition,[14] and oxidative enolate coupling reactions.[15] Notably, there is a report wherein a chiral auxiliary provides selective access to more than one possible diastereomer in enantiomerically-pure form,[16] but this process appears limited to aldol reactions with aryl aldehydes and enals. We thus realized there was an opportunity to develop a more general approach to the enantioselective and diastereoselective synthesis of 2,3-disubstituted succinic acid derivatives. We report herein our efforts to achieve this goal.

2. Background

Since the first report in 1993,[17] chiral oxazolidinones have been used extensively as chiral auxiliaries to induce diastereoselective conjugate addition reactions to crotonates. In an important advance in the field, Bergdahl and co-workers reported in 2004 that the diastereoselectivity of copper mediated conjugate addition reactions to chiral crotonates could be altered by simply varying Lewis acid additives, solvent, or the nature of the nucleophilic organometallic reagent.[18] This useful methodology allows for the chiral crotonate **8** to be differentiated into either diastereomer **9** or **10** in good yield and excellent diastereoselectivity by simply changing the reaction conditions (Equations 1 and 2). Before this pivotal report, the only way to achieve the opposite diastereofacial selectivity in the addition was to employ the enantiomeric starting material.



In the context of work directed toward alkaloids of the stemofoline family,[19,20] we sought to exploit a version of the Bergdahl protocol using iodotrimethylsilane (TMSI) for the stereoselective generation of an early stage intermediate. Specifically, the chiral crotonate **14** was prepared in 70% yield from **12** and **13** and then subjected to the reaction conditions developed by Bergdahl to provide **15** as a single diastereoisomer in 91% yield. The imide **15** was subjected to standard allylation conditions to deliver **16** in 69% yield. Intermediate **16** was then advanced in a set of model studies that ultimately led to syntheses of didehydrostemofoline and isodidehydrostemofoline.[20b,c]

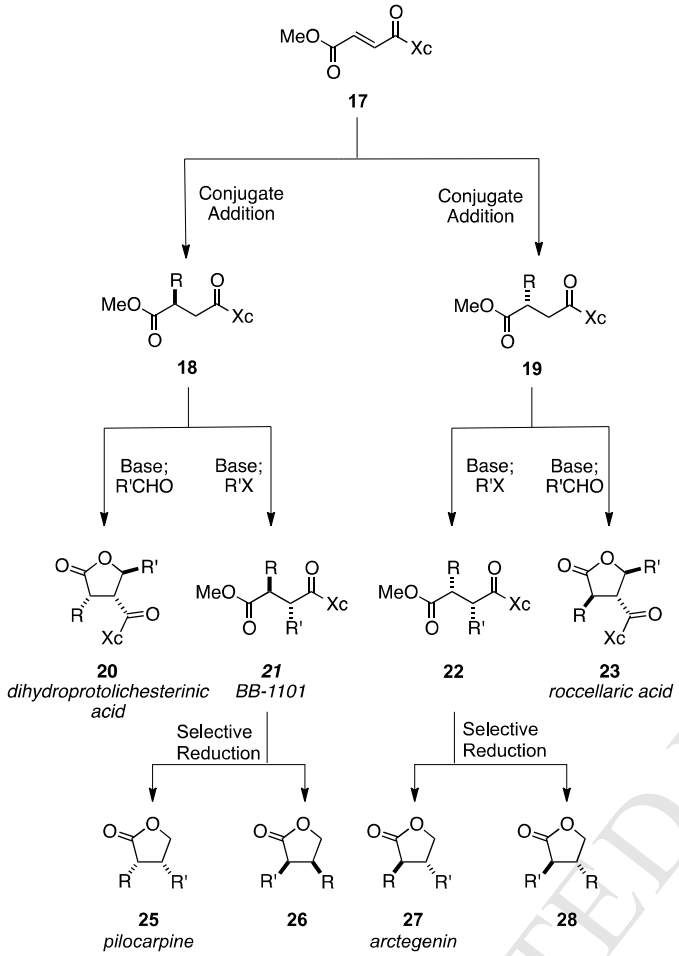


Scheme 1. Extension of the conjugate addition methodology to a γ-alkoxy crotonate.

Inspired by this successful extension of the Bergdahl methodology, we queried whether the substrate scope might be extended to a chiral fumarate derivative **17** (X_c = **13**) (Scheme 2). If the regio- and stereochemical outcome of this reaction could be controlled, both succinate derivatives **18** and **19** could be selectively accessed from the single chiral starting material **17**. Realization of this objective would be of considerable utility given the ubiquity of the succinic acid and butyrolactone motifs in both natural products and drugs (*vida supra)*. Indeed, both Curran and Sibi have demonstrated that radical conjugate additions occur at the carbon atom β to the imide moiety,[21] and Evans reported that Mukaiyama-Michael reactions also occur β to the imide moiety.[22] However, there was no precedent for the reactions of organocuprate-derived reagents with such substrates, so it was clearly necessary to establish the regiochemical course of such additions.

Notably, if these additions were to occur with a high degree of regio- and stereocontrol, a diverse range of succinate derivatives could be readily accessed by the overall plan outlined in Scheme 2. For example, the enolates derived from monosubstituted succinates **18** and **19** would be expected to undergo aldol reactions with aldehydes to furnish trisubstituted lactones **20** and **23**, thereby providing facile access to dihydroprotolichesterinic acid (**1**) and roccellaric acid (**2**) after cleavage of the chiral auxiliary X_c. Moreover, the enolates generated from **18** and **19** could be alkylated to provide the disubstituted succinates **21** or **22**, respectively, and these intermediates could be further transformed to give MMP inhibitors such as BB-1101 (**6**). Finally, selective reduction of the disubstituted succinates **21** and **22** at either the ester or the imide moieties was envisioned to

provide four different disubstituted lactones **25**, **26**, **27**, and **28**. By the appropriate choice of substituents (R and R'), compounds **25** and **27** represent pilocarpine (**4**) or arctigenin (**7**). The potential to prepare a number of natural products in as few as four steps provided ample motivation to examine the feasibility and scope of copper mediated conjugate addition reactions to chiral fumarate derivatives.



Scheme 2. Potential strategy to access diverse succinic acid derivatives from a single chiral starting material.

3. Results and Discussion

3.1 Reaction Development and Substrate Scope

In order to set the stage for our studies, monomethyl fumarate **29** was treated with pivaloyl chloride and triethylamine, followed by **13** and lithium chloride to provide fumarate **30** in 78% yield (Equation 3).[23] The stage was then set to test the copper mediated conjugate addition to fumarate **30**. When fumarate **30** was treated with lithium monomethyl cuprate (Li[MeCuI]) in the presence of TMSI under the conditions reported by Bergdahl,[18] the expected succinate **31a** (R = Me) was isolated in 89% yield with excellent stereoselectivity (Table 1, entry a). The scope of the method was evaluated using monoalkylcuprates derived from ethyl- and *n*-butyllithium, and these reactions also led to the formation of the corresponding succinates **31b** and **31c** with excellent stereoselectivity (Table 1, entries b,c). We also discovered that the process could be extended to monophenylcuprate as illustrated by the preparation of the phenyl substituted succinate **31d** with high stereoselectivity (Table 1, entry d). In preliminary experiments, we were unable to extend the method to the monorganocuprates generated from *tert*-butyllithium, vinyllithium, or acetylides (Table 1, entries e-g), but we did not experiment with conditions extensively.

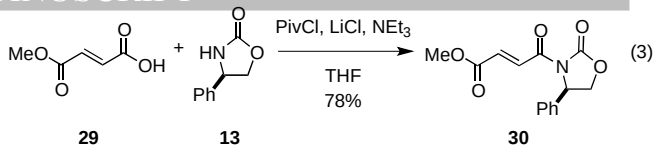
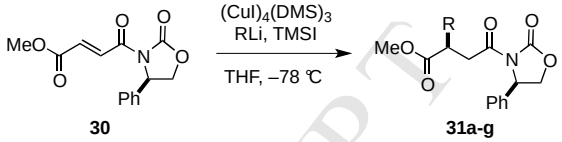


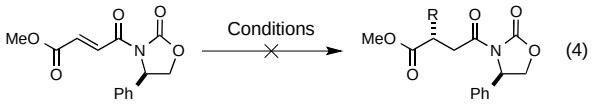
Table 1. Diastereoselective conjugate additions



Entry[a]	Alkyllithium	Yield (%)[b]	dr[c]
a	MeLi	89	19:1
b	EtLi	72	19:1
c	*n*-BuLi	83	19:1
d	PhLi	82	19:1
e	*t*-BuLi	NR	–
f	vinyl lithium	NR	–
g	lithium phenylacetylide	NR	–

[a]Reactions performed with $(CuI)_4(DMS)_3$ (1.4 eq.), RLi (1.35 eq.), TMSI (1.35 eq.) [b]Yield based on isolated product after silica gel chromatography. [c]dr based on HPLC using a Chiralcel OD-H column.

Because the TMSI promoted conjugate additions summarized in Table 1 proceeded smoothly with high selectivity, we then set to the task of testing the feasibility of reversing the diastereoselectivity of these reactions by modifying the conditions as reported.[18] However, contrary to our expectations, treating **30** with cuprates derived from methylmagnesium bromide, methyllithium, or *n*-butyllithium under a variety of conditions returned largely unreacted starting material; none of the desired 1,4-adduct **32** (R = Me or *n*-Bu) was isolated (Equation 4). Some variables that were examined included the use of different solvents and Lewis acid additives; even Gilman reagents failed to react with **30**.

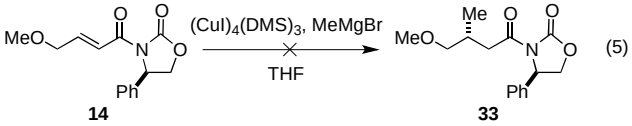


Conditions

$(CuI)_3(DMS)_4$, $MeMgBr$, Et_2O
$(CuI)_3(DMS)_4$, $MeMgBr$, THF
$(CuI)_3(DMS)_4$, $MeLi$, THF
$(CuI)_3(DMS)_4$, $MeLi$, CH_2Cl_2
$(CuI)_3(DMS)_4$, $MeLi$, $MgBr_2$, THF
$(CuI)_3(DMS)_4$, $MeLi$, $ZnCl_2$
Me_2CuLi, THF
$(CuI)_3(DMS)_4$, *n*-$BuLi$, THF
$(CuI)_3(DMS)_4$, *n*-$BuLi$, Et_2O
$(CuI)_3(DMS)_4$, *n*-$BuLi$, $TMSCl$, THF

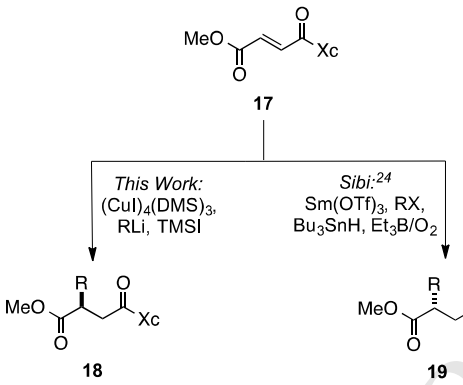
Reasoning that the ester moiety might have some deleterious effect on the reactivity of the conjugated double bond of **30**,

returned our attention to the chiral γ-methoxy crotonate **14**. Although a similar transformation has been reported,[24] we found **14** to be unreactive to conditions reported by Bergdahl (Equation 5). Based upon these few experiments, it seems that TMSI may be required to promote 1,4-additions to chiral alkoxy crotonates and fumarates, although further work is needed in order to clarify the origin of the surprising lack of reactivity of such substrates toward conjugate addition.



14 **33**

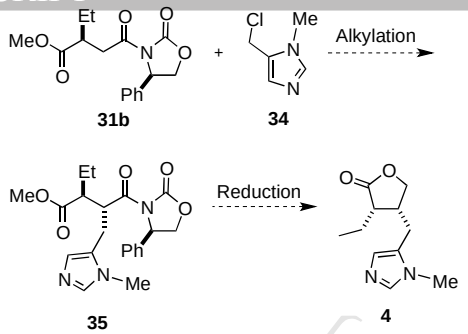
We were unable to reverse the diastereoselectivity of conjugate additions of organometallic reagents to either **14** or **30** by simply changing the reaction conditions; however, these important experiments did establish the feasibility of effecting highly stereoselective additions of monoorganocuprates to a chiral fumarate. Because this method thus complements the radical conjugate addition reactions developed by Sibi,[25] it is now possible to enable selective access to the substituted succinates **18** and **19** from the single chiral fumarate **17** (X_c = Evans's oxazolidinone) (Scheme 3). Notwithstanding the setback of not achieving our original goal, a number of biologically active targets are accessible using this new methodology, so we turned to the task of proof-of-principle studies.



Scheme 3. Divergent access to chiral fumarates.

3.2 Towards the Synthesis of Pilocarpine (4)

Pilocarpine (**4**) is an FDA approved treatment for glaucoma and was first isolated from the South American tree *Pilocarpus jaborandi* in 1875. Since the isolation of **4**, there have been ten total syntheses and three formal syntheses.[26] In accord with the general strategy depicted in Scheme 1, we examined the possibility of developing a short synthesis of **4**. Having already prepared the chiral succinate **31b** (See Table 1, entry b), we envisioned that a stereoselective alkylation of **31b** with the known imidazole **34**[26k,l,27] would furnish the disubstituted succinate **35**, selective reduction of which would furnish pilocarpine (**4**) in only four steps from commercially available materials (Scheme 4). Unfortunately, although halide **34** is known to undergo alkylation with softer nucleophiles such as anilines and malonates,[26k,l] we were unable to alkylate the enolate of **31b** with **34** under a number of conditions.

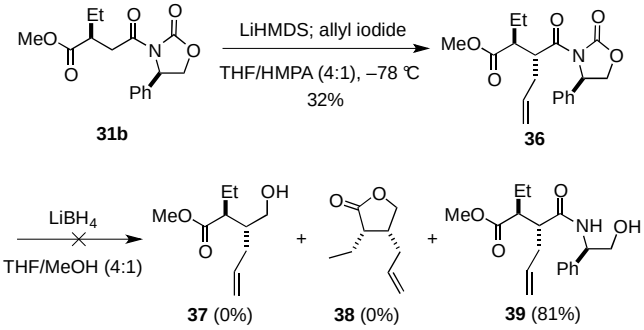


31b **34** **35** **4**

Scheme 4. A synthetic approach to pilocarpine (**4**).

The recalcitrant nature of enolates related to those derived from **31b** was previously noted by Evans, who found that only more reactive alkylating agents such as methyl iodide, allylbromide and benzyl bromide gave good yields of alkylated products.[28] Indeed, after somewhat extensive experimentation with solvents, bases, and alkylating agents, we were able to prepare **36**, albeit in only 32% yield (Scheme 5). Notwithstanding the low yield in this alkylation, we turned to the selective reduction and lactonization of **36** to give **38**, which upon oxidative cleavage of the olefin would deliver an aldehyde that is an intermediate in a previous synthesis of pilocarpine.[26f]

Unfortunately, in contrast to literature precedent,[29] reduction of **36** with $LiBH_4$ in THF/MeOH gave the ring-opened product **39** in 81% yield rather than the expected alcohol **37** or lactone **38** **(Scheme 5)**. Although a number of other conditions have been reported to selectively reduce succinates related to **36**,[26d,30] standard conditions involving $Zn(BH_4)_2$ in THF and $NaBH_4$ in $MeOH/H_2O$ either led to no reduction or over reduction. Although we were able to convert **30** into **36,** our inability to selectively reduce **36** to give **37** or **38** precluded our efforts to develop a short synthesis of pilocarpine (**4**), so we turned our focus to alternate succinate-derived natural products.

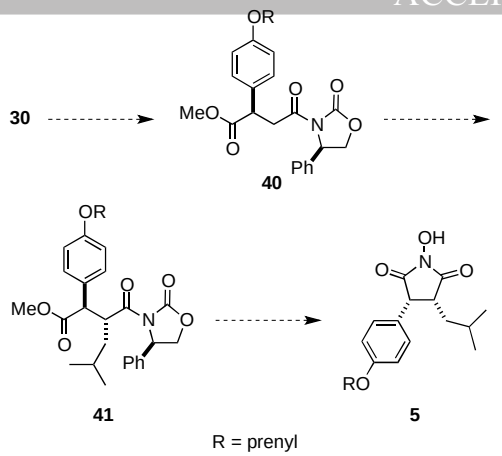


31b **36** **37** (0%) **38** (0%) **39** (81%)

Scheme 5. Attempted concise synthesis of pilocarpine (**4**)**.**

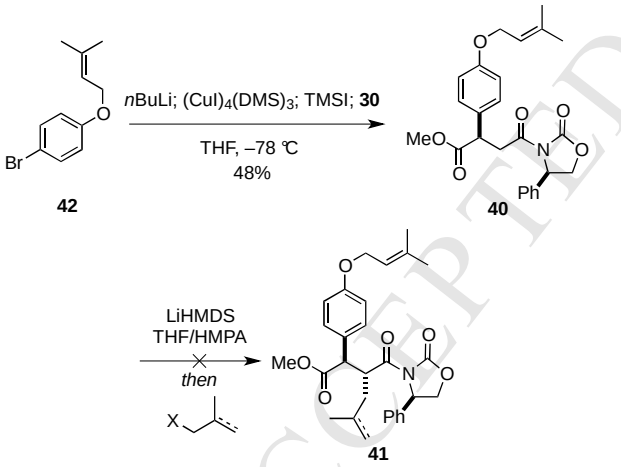
3.3 Towards the Synthesis of Antrodin E (5)

Antrodin E (**5**), which is also known as camphorataimide D, has been shown to possess both anti-inflammatory and anti-viral properties.[3] Since its isolation in 2002, there has only been one synthesis of racemic **5**, and the synthesis required 10 steps.[31] We envisaged an alternate strategy that could deliver **5** as a single enantiomer in only four steps (Scheme 6). The plan required that a substituted monoarylcuprate add to **30** to give **40**. Alkylation of the enolate derived from **40**, which we recognized might be problematic from our experience with **31b**, followed by reaction with hydroxylamine would then furnish antrodin E (**5**).



Scheme 6. A synthetic approach to antrodin E (**5**).

In the event, aryl bromide **42** was subjected to lithium-bromide exchange, and the intermediate aryllithium reagent was converted into its monoaryl cuprate by treatment with $(CuI)_4(DMS)_3$, which reacted with fumarate **30 to** give the aryl succinate **40** in 48% yield (Scheme 7); varying the reaction temperature had no beneficial effect on the yield. Control experiments in which the aryllithium reagent was quenched showed that lithium-halogen exchange was complete. Based upon the observed reactivity of the enolate of **31b**, it was not unexpected that treating the enolate of **40** with several isobutyl alkylating agents as well as 2-methallylbromide returned the starting material **40**. Because alkylations of enolates of substituted succinates are challenging, it occurred to us to examine aldol reactions of such enolates as the products of these reactions also map onto a number of interesting natural products.



Scheme 7. Attempted synthesis of succinate **41**.

*3.4 Total Synthesis of (–)-dihydroprotolichesterinic acid (**1**)*

Dihydroprotolichesterinic acid (**1**) together with roccellaric acid (**2**) and nephromopsinic acid (**3**) are representative members of the paraconic acid family of natural products.[1] Dihydroprotolichesterinic acid exhibits anti-fungal and anti-bacterial properties and has been synthesized six times.[9,32] Other related paraconic acids have also been synthesized.[33] Our synthesis commenced with the readily available succinate **31a** (Table 1, entry a), but we quickly discovered that even aldol reactions of such compounds can be problematic (Table 2). For example, using conditions that had been reported by Sibi for a related compound,[25] the directed aldol reaction of the boron enolate of **31a** with myristyl aldehyde (**42**) gave the desired adduct **43** in only 24% yield (Table 2, entry a). We then embarked on a screen of Lewis acids ($TiCl_4$, Bu_2BOTf) and bases (DIPEA, DBU, LiHMDS, di-*tert*-butylpyridine) and eventually found the combination of di-*n*-butylboron triflate and Hünig's base was optimal (Table 2, entry b). The concentrations and stoichiometries of the reagents were then incrementally increased until we found the optimal number of equivalents and concentration that delivered lactone **43** in 54% (95% brsm) as a single diastereomer based upon the ^1H NMR spectrum of the crude reaction mixture (Table 2, entries c-g). It is unclear why the reaction never proceeded to completion as considerable amounts of starting **31a** were invariably obtained. When the lactone **43** was subjected to standard hydrolysis conditions,[25] dihydroprotolichesterinic acid (**1**) was isolated in 85% yield. The ^1H and ^{13}C NMR spectra, melting point, and optical rotation of synthetic **1** thus obtained are consistent with those reported in the literature.[32] We also corroborated the structure of **1** by x-ray crystallography.[34] The total synthesis of dihydroprotolichesterinic acid (**1**) was thus achieved in four steps from commercially available material with a 31% overall yield (56% based upon recovered starting material).

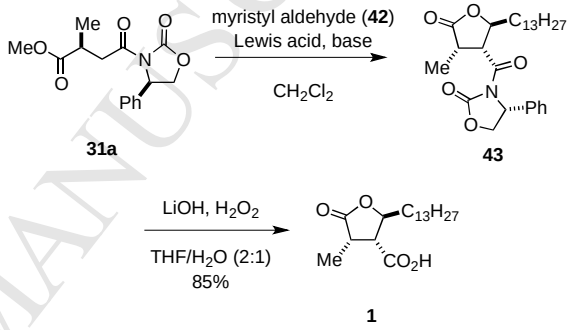


Table 2. Optimization of the aldol reaction of **31a** and **42**.

Entry	Bu_2BOTf (eq.)	Base (eq.)	Conc. (M)	Yield[a]
a	1.2	TEA (1.3)	0.1	24%
b	1.2	DIPEA (1.3)	0.1	38%
c	1.2	DIPEA (1.3)	0.3	36%
d	1.2	DIPEA (1.3)	0.5	36%
e	1.5	DIPEA (1.7)	0.5	38%
f	1.2	DIPEA (1.3)	0.9	38%
g	1.5	DIPEA (1.7)	0.9	54%

[a]Yields based on isolated product after silica gel chromatography.

4. Summary

In summary, we developed the first conjugate additions of monoalkyl- and monoarylcuprates to a chiral fumarate to provide substituted succinates in good yields and excellent diastereoselectivities. We discovered that TMSI appears to be a critical additive in these reactions, because 1,4-additions were not observed in its absence. Even though we were unable to gain divergent access to diastereomeric 2,3-disubstituted succinic acid derivatives via copper mediated conjugate additions, our work complements the radical addition method developed by Sibi, thereby enabling realization of this goal. Our original plans to elaborate these adducts into succinate-derived natural products

via subsequent enolate alkylations or selective reduction of the *N*-acyloxazolidinone moiety were unavailing. On the other hand, aldol reactions of chiral enolates generated from these adducts were successful, and we completed the shortest total synthesis of (–)-dihydroprotolichesterinic acid (**1**) to date. This synthesis required only four steps from commercially available starting materials and proceeded in 31% overall yield (56% based on recovered staring material.

5. Experimental

5.1. General

Tetrahydrofuran and diethyl ether were dried by filtration through two columns of activated, neutral alumina according to the procedure described by Grubbs.[35] Methanol, acetonitrile and dimethylformamide were dried by filtration through two columns of activated molecular sieves, and toluene was dried by filtration through one column of activated, neutral alumina followed by one column of Q5 reactant. Methylene chloride, diisopropylamine, triethylamine, and diisopropylethylamine were distilled from calcium hydride immediately prior to use. All solvents were determined to have less than 50 ppm H_2O by Karl Fischer coulometric moisture analysis. Iodotrimethylsilane (TMSI) was distilled over copper powder and calcium hydride in the dark immediately before use. All reagents were reagent grade and used without purification unless otherwise noted. All reactions involving air or moisture sensitive reagents or intermediates were performed under an inert atmosphere of nitrogen or argon in glassware that was flame dried. Reaction temperatures refer to the temperature of the cooling/heating bath. Volatile solvents were removed under reduced pressure using a Büchi rotary evaporator at 25–30 °C. Thin layer chromatography performed using run on pre-coated plates of silica gel with a 0.25 mm thickness containing 60F-254 indicator (Merck). Chromatography was performed using forced flow (flash chromatography) and the indicated solvent system on 230-400 mesh silica gel (E. Merck reagent silica gel 60) according to the method of Still,[36] unless otherwise noted.

Infrared (IR) spectra were obtained either neat on sodium chloride or as solutions in the solvent indicated and reported as wavenumbers (cm^{-1}). Proton nuclear magnetic resonance (^1H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectra were obtained at the indicated field as solutions in $CDCl_3$ unless otherwise indicated. Chemical shifts are referenced to the deuterated solvent and are reported in parts per million (ppm, δ) downfield from tetramethylsilane (TMS, δ = 0.00 ppm). Coupling constants (*J*) are reported in Hz and the splitting abbreviations used are: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; comp, overlapping multiplets of magnetically nonequivalent protons; br, broad; app, apparent.

5.2. Experimental Procedures

(4*R*)-3-[(2*E*)-4-Methoxybut-2-enoyl]-4-phenyl-1,3-oxazolidin-2-one (**14**).

Pivaloyl chloride (0.572 g, 4.74 mmol) was added dropwise to a solution of acid **12** (0.500 g, 4.31 mmol) in THF (15 mL) at –20 °C. After 1 h, 4-(*R*)-phenyloxazolidinone (**13**) (2.06 g, 12.6 mmol) and LiCl (0.201 g, 4.74 mmol) were added in one portion, and the reaction was warmed to room temperature and stirred overnight. The reaction was diluted with H_2O (5 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (2 x 5 mL), brine (1 x 5 mL), dried (Na_2SO_3), and concentrated under reduced pressure. The residue was purified via flash column chromatography eluting with hexanes/EtOAc (1:1) to give 0.983 g (87%) of **14** as a white solid: mp = 70-71 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.49 (ddd, *J* = 15.4, 2.0, 2.0 Hz, 1 H), 7.35 (comp, 5 H), 7.07 (ddd, *J* = 15.6, 4.4, 4.4 Hz, 1 H), 5.51 (dd, *J* = 8.7, 4.1 Hz, 1 H), 4.73 (dd, *J* = 8.7, 8.7 Hz, 1 H), 4.30 (dd, *J* = 8.7, 3.8 Hz, 1 H), 4.14 (dd, *J* = 4.6, 2.0 Hz, 2 H), 3.42 (s, 3 H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 164.4, 153.8, 146.8, 139.3, 129.3, 128.8, 126.2, 120.4, 71.6, 70.2, 58.9, 57.9; MS (CI) m/z 261 [$C_{14}H_{15}NO_4$ (M) requires 261].

(4*R*)-3-[(3*S*)-4-Methoxy-3-methylbutanoyl]-4-phenyl-1,3-oxazolidin-2-one (**15**).

A solution of methyllithium (0.91 M in hexanes, 15.7 mL, 14.2 mmol) was added dropwise to a slurry of $(CuI)_3(DMS)_4$ (prepared according to House)[37] (3.51 g, 14.8 mmol) in THF (63 mL) at –78 °C. The mixture was stirred at –78 °C for 20 min, whereupon iodotrimethylsilane (2.80 g, 14.2 mmol) was added dropwise. The resulting mixture was stirred for 10 min at –78 °C, and a solution of **14** (2.98 g, 11.4 mmol) in THF (17 mL) was then added dropwise. After 5 h, Et_3N (5.77 g, 57.0 mmol) was added dropwise, and stirring was continued for 1 h at –78 °C. The reaction was quenched with conc. NH_4OH (5 mL), sat. aq. NH_4Cl (5 mL) was added, and the reaction was warmed to room temperature. The layers were separated, and the aqueous layer was extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with brine (25 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified via flash column chromatography eluting with hexanes/EtOAc (4:1) to give 2.87 g (91%) of **15** as a pale yellow crystalline solid: mp = 53-54 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.30 (comp, 4 H), 5.40 (dd, *J* = 8.5, 3.4 Hz, 1 H), 4.65 (dd, *J* = 12.0, 12.0 Hz, 1 H), 4.25 (dd, *J* = 8.9, 3.8 Hz, 1 H), 3.21 (s, 3 H), 3.08 (dd, *J* = 16.8, 5.8 Hz, 1 H), 2.72 (dd, *J* = 16.4, 7.9 Hz, 1 H), 2.30 (m, 1 H), 0.88 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 172.2, 153.9, 129.3, 128.9, 126.2, 77.5, 70.1, 58.9, 57.8, 39.7, 30.1, 17.1.

(4*R*)-3-[(2*R*)-2-[(2*S*)-1-Methoxypropan-2-yl]pent-4-enoyl]-4-phenyl-1,3- oxazolidin-2-one (**16**)

A solution of *n*-BuLi (2.76 M in hexanes, 4.1 mL, 11 mmol) was added dropwise to a solution of hexamethyldisilazane (1.94 g, 12.0 mmol) in THF (12 mL) at –78 °C, and the reaction was stirred for 20 min at –78 °C and then at 0 °C for 20 min. After being cooled again to –78 °C, a solution of **15** (2.9 g, 10.4 mmol) in THF (21 mL) was added dropwise. The reaction was stirred at –78 °C for 1 h and then between –45 °C and –35 °C for 20 min before returning to –78 °C. Allyl iodide (5.21 g, 31.0 mmol) was added dropwise, and the reaction was stirred at –78 °C for 2 h then transferred to a –45 °C bath. After maintaining the reaction temperature at –45 °C for 30 min, the reaction was allowed to gradually warm to –10 °C over 1 h. The reaction was then stirred at –10 °C for 3 h and then quenched by adding saturated aqueous NH_4Cl (15 mL). EtOAc (30 mL) was added, and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 25 mL), and the combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude reaction mixture was purified via flash column chromatography eluting with hexanes/EtOAc (4:1) to give 2.28 g (69%) of **16** as a colorless oil: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.30 (comp, 4 H), 5.56 (m, 1 H), 5.42 (dd, *J* = 8.9, 3.8 Hz, 1 H), 4.81 (dd, *J* = 16.4, 1.7 Hz, 1 H), 4.80 (d, *J* = 10.9 Hz), 4.63 (dd, *J* = 8.9, 8.9 Hz, 1 H), 4.23 (dd, *J* = 8.9, 3.4 Hz, 1 H), 4.09 (ddd, *J* = 9.4, 6.5, 4.8 Hz, 1 H), 3.34 (dd, *J* = 4.8, 2.7 Hz, 2 H), 3.29 (s, 3 H), 2.34 (ddd, *J* = 14.0, 14.0, 7.9 Hz, 1 H), 2.25 (ddd, *J* = 12.6, 12.6, 6.5 Hz, 1 H), 2.06 (m, 1 H), 1.01 (d, *J* = 6.8 Hz, 3 H): ^{13}C NMR ($CDCl_3$, 300 MHz) δ 174.9, 153.9, 139.5, 135.2, 129.2, 128.8, 126.3, 117.3, 75.9, 69.8, 59.1, 58.1, 44.7, 36.0, 34.4, 15.2; LRMS (CI) m/z 318 [$C_{18}H_{23}NO4_4$ (M + 1)

requires 318].

(*R*,*E*)-Methyl 4-oxo-4-(2-oxo-4-phenyloxazolidin-3-yl)but-2-enoate (30).

A solution of methyl fumarate (**29**) (2.66 g, 20.4 mmol) and pivaloyl chloride (2.70 g, 2.76 mL, 22.5 mmol) in THF (40 mL) was cooled to –20 °C. Triethylamine (4.13 g, 5.68 mL, 40.8 mmol) was added dropwise, and the mixture was stirred 1.5 h at –20 °C. The cooling bath was removed, and the solution was allowed to warm to room temperature. Solid LiCl (0.953 g, 22.5 mmol) and (R)-phenyl-oxazolidone **13** (5.00 g, 30.6 mmol) were added portionwise, and the reaction was stirred 12 h. H_2O (10 mL) and ethyl acetate (50 mL) were added. The layers were separated, and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The combined organic layers were washed with 1 M HCl (1 x 25 mL), saturated Na_2CO_3 (2 x 50 mL), saturated brine (1 x 50 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by flash chromatography, eluting with hexanes/ethyl acetate (3:1) to provide 4.38 g (78%) of the chiral methyl fumarate **30** as a white solid: mp 92-94 °C; ^{1}H NMR (400 MHz) δ 8.17 (d, *J* = 15.7 Hz, 1 H), 7.43 (comp, 5 H), 6.87 (d, *J* = 15.7, 1 H), 5.50 (dd, *J* = 4.0, 8.9 Hz, 1 H), 4.76 (t, *J* = 8.9 Hz, 1 H), 4.36 (dd, *J* = 4.0, 8.9 Hz, 1 H), 3.81 (s, 3 H); ^{13}C NMR (100 MHz) δ 165.1, 163.1, 153.2, 138.2, 133.8, 132.2, 129.1, 128.8, 125.9, 70.2, 57.7, 52.2; IR (neat) 1780, 1727, 1690, 1387, 1341, 1306, 1279, 1196 cm^{-1}; mass spectrum (CI) *m/z* 275.0869 [$C_{14}H_{13}NO_5$ (M+1) requires 275.0794].

(*S*)-Methyl 2-methyl-4-oxo-4-((*R*)-2-oxo-4-phenyloxazolidin-3-yl) butanoate (31a).

A suspension of $(CuI)_4(DMS)_3$ (0.405 g, 1.71 mmol) in THF (8.6 mL) was prepared and cooled to –78 °C, whereupon MeLi (1.31 M in hexanes, 1.2 mL, 1.59 mmol) was added dropwise. The resulting orange solution was stirred for 40 min at –78 °C. Iodotrimethylsilane (0.33 g, 0.25 mL, 1.65 mmol) was added dropwise, and stirring was continued for 30 min. A solution of chiral fumarate **30** (0.337 g, 1.22 mmol) in THF (1.75 mL) was added dropwise, and the reaction was stirred for 6 h at –78 °C. Triethylamine (0.620 g, 0.836 mL, 6.12 mmol) was added, and the reaction was stirred 1 h. Saturated NH_4Cl (10 mL) was added, and the cooling bath was removed. Upon reaching room temperature, the septum was removed, and the solution was stirred until a homogeneous blue solution was obtained. The reaction mixture was poured into H_2O (10 mL) and ethyl acetate (10 mL), and the layers were separated. The aqueous phase was extracted with ethyl acetate (3 x 15 mL). The combined organic layers were washed with brine (1 x 30 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified via flash chromatography, eluting with hexanes/ethyl acetate (5:1) to provide 0.521 g (86%) of **31a** as a white solid: mp 77-78 °C; ^{1}H NMR (400 MHz) δ 7.40-7.27 (comp, 5 H), 5.42 (dd, *J* = 3.9, 8.7 Hz, 1 H), 4.70 (t, *J* = 8.7 Hz, 1 H), 4.27 (dd, *J* = 3.9, 8.7 Hz, 1 H), 3.55 (s, 3 H), 3.44 (dd, *J* = 7.5, 17.8 Hz, 1 H), 3.04-2.90 (comp, 2 H), 1.21 (d, *J* = 7.5 Hz, 3 H); ^{13}C NMR (100 MHz) δ 175.5, 170. 8, 153.6, 138.6, 128.9, 128.4, 125.5, 70.0, 57.3, 51.6, 38.9, 34.9, 16.8; IR (neat) 1781,1733, 1707, 1386 cm^{-1}; mass spectrum (CI) *m/z* 291.1107 [$C_{15}H_{17}NO_5$ (M+1) requires 291.1107].

(*S*)-Methyl 2-ethyl-4-oxo-4-((*R*)-2-oxo-4-phenyloxazolidin-3-yl)butanoate (31b).

Compound **31b** was prepared on 1 mmol scale via the same method as **31a**, employing EtLi in place of MeLi. Isolated 0.210 g (72 %) of **31b** as a white solid: mp 80-81 °C; ^{1}H NMR (300 MHz) δ 7.26-7.41 (comp, 5 H), 5.42 (dd, *J* = 3.8, 8.7 Hz, 1 H), 4.70 (t, *J* = 8.9 Hz, 1 H), 4.26 (dd, *J* = 4.1, 8.9 Hz, 1 H), 3.42 (dd, *J* = 9.7, 18.2 Hz, 1 H), 3.04 (dd, *J* = 4.6, 18.2 Hz, 1 H), 2.77-2.86 (m, 1 H), 1.55-1.72 (comp, 2 H), 0.92 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (75 Hz) δ 174.9, 171.2, 153.7, 138.6, 129.1, 128.5, 125.7, 70.1, 57.4, 51.5, 41.9, 37.1, 24.9, 11.4; IR (neat) 1782, 1733, 1707 1386, 1197 cm^{-1}; mass spectrum (CI) *m/z* 306.1340 [$C_{16}H_{20}NO_5$ (M + 1) requires 306.1340].

(*S*)-methyl 2-(2-oxo-2-((*R*)-2-oxo-4-phenyloxazolidin-3-yl)ethyl)hexanoate (31c).

Compound **11c** was prepared on 1 mmol via the same method as **31a**, employing *n*-BuLi in place of MeLi. Isolated 0.275 g (83%) of **31c** as a clear oil. ^{1}H NMR (300 MHz) δ 7.43-7.29 (m, 5 H), 5.44 (dd, *J* = 8.8, 4.3 Hz, 1 H), 4.72 (t, *J* = 8.8 Hz, 1 H), 4.31-4.26 (m, 1 H), 3.54 (s, 3 H), 3.43 (dd, *J* = 18.0, 9.6 Hz, 1 H), 3.06 (dd, *J* = 18.0, 4.3 Hz, 1 H), 2.92-2.82 (m, 1 H), 1.67-1.48 (m, 3 H), 1.30-1.28 (m, 3 H), 0.89-0.87 (m, 3 H); ^{13}C NMR (75 MHz): δ 175.4, 171.5, 154.0, 138.9, 129.1, 126.0, 77.7, 70.4, 57.8, 51.9, 40.8, 37.8, 31.8, 29.4, 22.7, 14.1; IR (neat) 2957, 2861, 1785, 1733, 1704, 1386 cm^{-1}; mass spectrum (CI) *m/z* 334.1656 [$C_{16}H_{20}NO_5$ (M + 1) requires 336.1654].

(*R*)-methyl 4-oxo-4-((*R*)-2-oxo-4-phenyloxazolidin-3-yl)-2-phenylbutanoate (31d).

Compound **31d** was prepared on 1 mmol via the same method as **31a**, employing PhLi in place of MeLi. The reaction was run on 1 mmol scale and 0.290 g (82%) of compound **31d** was isolated as a clear oil. ^{1}H NMR (300 MHz) δ 7.46-7.29 (m, 9 H), 7.27-7.26 (m, 1 H), 5.58 (dd, *J* = 11.2, 4.4 Hz, 1 H), 5.37 (dd, *J* = 8.8, 3.5 Hz, 1 H), 4.58 (t, *J* = 8.8 Hz, 1 H), 4.21 (dd, *J* = 8.8, 3.4 Hz, 1H), 3.53 (s, 3 H), 3.27 (dd, *J* = 17.3, 11.2 Hz, 1 H), 2.62 (dd, *J* = 17.3, 4.4 Hz, 1 H); ^{13}C NMR (125 MHz) δ 172.5, 171.5, 153.0, 138.9, 136.9, 129.9, 129.1, 128.8, 128.6, 128.5, 128.3, 128.1, 127.8, 125.7, 70.0, 58.1, 51.7, 44.8, 38.6, 29.7; IR (neat) 2922, 2852, 1781, 1735, 1699, 1383, 1192 cm^{1}; mass spectrum (CI) *m/z* 354.1336 [$C_{20}H_{20}NO_5$ (M + 1) requires 354.1341].

Methyl (2*S*,3*R*)-2-ethyl-3-((*R*)-2-oxo-4-phenyloxazolidine-3-carbonyl)hex-5-enoate (36)

n-Butyllithium (2.5 M solution in hexanes, 0.7 mL, 1.8 mmol,) was added to a solution of hexamethyldisilazane (0.31 g, 1.9 mmol) in THF (1.9 M) at –78 °C. The solution was stirred for 15 min at –78 °C, 30 min at 0 °C, and then again at –78 °C. Hexamethylphosphoramide (0.47 g, 2.6 mmol) was added to the solution, and succinate **31b** (0.360 g, 0.85 mmol) in THF (1.6 mL) was added dropwise. The solution was stirred for 1 h at –78 °C, whereupon allyl iodide (0.44 g, 2.6 mmol) was added. The reaction was stirred for 6 h at which time 1 M HCl (2.5 mL) was added and the reaction allowed to warm to room temperature. The mixture was extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with brine (1 x 20 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The resulting crude reaction mixture purified via column chromatography eluting with hexanes/ethyl acetate (8:1 → 6:1) to provide 0.10 g (34%) of **36** as a clear colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35-7.26 (m, 5H), 5.48 (dddd, *J* = 17.0, 10.2, 7.6, 6.7 Hz, 1 H), 5.42 (dd, *J* = 8.7, 3.7 Hz, 1 H), 4.77 (ddt, *J* = 10.2, 1.8, 0.9 Hz, 1 H), 4.72 (dq, *J* = 17.0, 1.5 Hz, 1 H), 4.67 (t, *J* = 8.9 Hz, 1 H), 4.30 (td, *J* = 8.5, 4.7 Hz, 1 H), 4.26 (dd, *J* = 8.9, 3.8 H, 1 H), 2.65 (ddd, *J* = 10.7, 8.5, 3.8 Hz, 1 H), 2.32-2.27 (m, 1 H), 2.23-2.19 (m, 1 H), 1.67-1.60 (m, 1 H), 1.55-1.48 (m, 1 H), 0.85 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (150 MHz; $CDCl_3$): δ 174.4, 173.4, 153.3, 138.9, 133.7, 129.0 (2C), 128.7, 126.2 (2C), 117.7, 69.6, 57.9, 51.6, 49.0, 44.1, 34.9, 23.5, 11.9; IR (film, NaCl) 2968, 1779, 1733, 1701, 1384, 1195, 1168 cm^{-1}; HRMS (ESI)

m/z 368.1498 [$C_{19}H_{25}NO_5Na^+$ (M + Na)$^+$ requires 668.1474].

Methyl (2*S*,3*R*)-3-(((*R*)-2-hydroxy-1-phenylethyl)carbamoyl)-2-methylhex-5-enoate (39)

Imide **36** (0.070 g, 0.203 mmol) was dissolved in a mixture of THF (1 mL) and MeOH (0.04 mL) and cooled to –78 °C. Lithium borohydride (2 M in THF, 1 mL, 2.0 mmol) was added, and the reaction was transferred to a 0 °C bath and stirred for 1 h. The reaction was quenched with sat. aq. Rochelle's salt (3 mL), the ice bath was removed, and the reaction was stirred 1 h at room temperature. EtOAc (5 mL) was added, and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 5 mL). The combined organic extracts were washed with brine (1 x 10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified via column chromatography eluting with hexanes/EtOAc (4:1 → 3:2) to provide 0.064 g (81%) of **39** as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.27 (m, 5 H), 6.44 (d, *J* = 7.2, 1 H), 5.64 (ddt, *J* = 17.1, 10.1, 7.1, 1 H), 5.08 (dt, *J* = 7.1, 5.0, 1 H), 5.04-4.94 (m, 2H), 3.87 (d, *J* = 5.0, 2 H), 3.70 (s, 3 H), 2.64 (td, *J* = 9.5, 4.3, 1 H), 2.49 (td, *J* = 9.5, 4.3, 1 H), 2.4-2.33 (m, 1 H), 2.14-2.07 (m, 1 H), 1.70-1.54 (m, 2 H), 0.89 (t, *J* = 7.4, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.7, 173.2, 138.7, 134.8, 128.8 (2C), 127.9, 126.8 (2 C), 117.57, 117.51, 66.5, 55.9, 51.7, 49.58, 49.44, 35.5, 23.8, 11.9; IR (film) 3298, 2935, 2877, 1733, 1645, 1541, 1733, 1645, 1541, 1272, 1166, 700 cm^{-1}; HMRS (ESI) m/z 342.1670 [$C_{18}H_{25}NO_4Na^+$ (M + Na)$^+$ requires 342.1676].

Methyl-(2*S*,3*R*)-2-ethyl-3-(((*R*)-2-hydroxy-1-phenylethyl)carbamoyl)hex-5-enoate (40)

n-BuLi (2.54 M in hexanes, 0.37 mL, 0.90 mmol) was added dropwise to a solution of aryl bromide **42** (0.22 g, 0.91 mmol) in THF (2.0 mL) at –78 °C, and the solution was stirred 15 min. The resulting solution was added via cannula to a suspension of $(CuI)_4(DMS)_3$ (0.22 g, 0.95 mmol) in THF (2.8 mL) at –78 °C, and the resulting black solution was stirred 20 min. Iodotrimethylsilane was added dropwise to the reaction and stirring continued for 5 min. A solution of fumarate **30** (0.20 g, 0.73 mmol) in THF (1.0 mL) was then added dropwise, and the reaction was stirred 6 h at –78 °C. Triethylamine (1.8 g, 17.9 mmol) was added, and stirring was continued for 1 h, whereupon sat. aq. NH_4Cl (10 mL) was added. The reaction was warmed to room temperature, the septum was removed, and the solution was stirred until it was a homogenous, blue solution. The reaction was diluted with H_2O (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic phases were washed with brine (1 x 30 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product subjected to column chromatography eluting with hexanes/ethyl acetate (3:1) to afford 0.179 (56%) of **23** as a white solid: mp 120–122 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.27-7.40 (comp, 5 H), 7.19 (d, *J* = 8.7, 2 H), 6.84 (d, *J* = 8.8, 2 H), 5.46-5.49 (m, 1 H), 5.40 (dd, *J* = 3.9, 8.8 Hz, 1 H), 4.66 (t, *J* = 8.8 Hz, 1 H), 4.48 (d, *J* = 6.8 Hz, 2 H), 4.25 (dd, *J* = 3.9, 8.8 Hz, 1 H), 4.06 (dd, *J* = 5.2, 9.7 Hz, 1 H), 3.84 (dd, *J* = 9.7, 18.2 Hz, 1 H), 3.51 (s, 3 H), 3.29 (dd, *J* = 5.2, 18.2 Hz, 1 H), 1.79 (s, 3 H), 1.73 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.4, 170.8, 158.4, 153.7, 138.6, 138.4, 129.5, 129.2, 128.9, 128.6, 125.7, 119.6, 114.9, 70.2, 64.8, 57.5, 52.2, 45.7, 39.5, 25.8, 18.2; IR (film, NaBr) 2917, 1781, 1733, 1704, 1611, 1511 cm^{-1}; HRMS (ESI) m/z 460.1733 [$C_{25}H_{27}NO_6Na^+$ (M + Na) requires 460. 1731].

(*R*)-3-((2*S*,3*R*,4*S*)-4-Methyl-5-oxo-2-tridecyltetrahydrofuran-3-carbonyl)-4-phenyloxazolidin-2-one (43).

A solution of **31a** (0.250 g, 0.858 mmol) in CH_2Cl_2 (1 mL) was cooled to 0 °C, whereupon dibutylboron triflate (0.354 g, 1.29 mmol) was added dropwise. Hünig's base (0.184 g, 1.29 mmol), which had been freshly distilled from calcium hydride was then added, and the solution was stirred for 30 min at room temperature and then cooled to –78 °C. A solution of freshly distilled tetradecanal (0.220 g, 1.03 mmol) in methylene chloride (0.2 mL) was added dropwise, and the solution was stirred for 20 min at –78 °C and then at 0 °C for 15 h. A solution of MeOH/H_2O_2 (30% in H_2O) (2:1, 1 mL) was added, and the mixture was stirred 1 h. The layers were separated, and the aqueous layer was extracted with methylene chloride (3 x 2 mL). The combined organic layers were washed with brine (1 x 5 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure yielding a clear oil. Purification by recrystallization from methyl *tert*-butyl ether yielded 0.217 g (54%) of **43** as a white solid: mp 107-108 °C; ^{1}H NMR (600 MHz) δ 7.41-7.34 (comp, 5 H), 5.43 (dd, *J* = 3.5, 8.9 Hz, 1 H,), 4.79-4.74 (comp, 2 H), 4.43 (dd, *J* = 3.5, 8.9 Hz, 1 H), 4.21 (dd, *J* = 7.5, 9.2 Hz, 1 H), 3.21 (dq, *J* = 7.5, 9.2 Hz, 1 H), 1.69-1.58 (comp, 2 H), 1.39-1.26 (comp, 22 H), 0.88 (t, *J* = 6.9 Hz, 3 H), 0.80 (d, *J* = 7.5 Hz, 3 H); ^{13}C NMR (150 MHz) δ 177.2, 169.3, 153.2, 138.3, 129.3, 129.3, 126.6, 79.1, 70.2, 57.8, 49.3, 37.7, 34.7, 29.7, 29.7, 29.7, 29.6, 29.6, 29.6, 29.5, 29.4, 29.4, 29.4, 29.3, 29.1, 25.5, 24.7, 22.7, 14.1, 11.6; IR (neat) 2917, 2848, 1787, 1758, 1696, 1382, 1204 cm^{-1} ; mass spectrum (CI) *m/z* 472.3063 [$C_{28}H_{42}NO_5$ (M+1) requires 472.30].

(2*S*,3*R*,4*S*)-4-methyl-5-oxo-2-tridecyltetrahydrofuran-3-carboxylic acid (dihydroprotolichesterinic acid) (1).

To a solution of **43** (0.243 g, 0.515 mmol) in THF/H_2O (4:1, 4.2 mL) at 0 °C, was added H_2O_2 (30% in H_2O, 2.1 mmol, 0.25 mL) and LiOH•H_2O (0.032 g, 0.773 mmol). The flask was removed from the ice bath and stirred at room temperature for 5 h. The reaction was quenched with 10% aqueous $Na_2S_2O_3$ (2 mL). The THF was removed under reduced pressure. The pH was adjusted to pH = 12 with 3 M NaOH and extracted with EtOAc (3 x 3 mL). The pH of the aqueous layer was then adjusted to pH = 1 with 1 M HCl, and the mixture was extracted with EtOAc (3 x 3 mL). The combined organic layers were washed with brine (1 x 10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to yield 0.142 g (85%) of **1** as a white solid: mp 105-106 °C (lit. 106 °C);[32a] $[\alpha]_D^{22}$ = –51.1° (c = 1.75, $CHCl_3$) [lit. $[\alpha]_D^{20}$ = –49.5° (c = 1.75, $CHCl_3$)];[32a] ^{1}H NMR (600 MHz) δ 4.65 (comp, 1 H), 3.10-3.08 (comp, 1 H), 2.97 (dq, *J* = 8.8, 7.5 Hz, 1 H), 1.70-1.61 (comp, 2 H), 1.41-1.28 (comp, 25 H), 0.88 (t, *J* = 6.9 Hz, 3 H)**;** ^{13}C NMR (150 MHz) δ 177.9, 174.8, 80.0, 50.2, 36.7, 34.5, 31.9, 29.7, 29.7, 29.7, 29.6, 29.6, 29.5, 29.4 29.3, 25.4, 22.7, 14.1, 11.5; IR (neat) 2955, 2919, 2852, 1765, 1726, 1698 cm^{-1}; mass spectrum (ESI) *m/z* 349.2350 [$C_{19}H_{34}O_4$ (M+Na) requires 349.2349].

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