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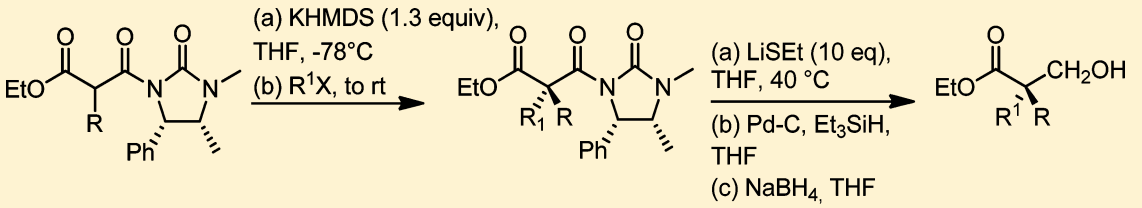
Stereoselective Formation of Quaternary Stereogenic Centers via Alkylation of α-Substituted Malonate-Imidazolidinones

Thobela Bixa, Roger Hunter,* Ana Andrijevic, Wade Petersen, Hong Su, and Francis Dhoro

Department of Chemistry, University of Cape Town, Rondebosch 7701, South Africa

Supporting Information



ABSTRACT: A new stereoselective alkylation methodology is presented for formation of chiral, nonracemic quaternary centers via a chiral auxiliary protocol involving α-alkylated malonate imidazolidinones. Based on two X-ray structures of quaternized products, the diastereoselectivity observed may be rationalized via a transition-state involving an s-*trans*$_{C-N}$ conformation of the C−N bond of the auxiliary, with the metal cation (K^+) chelated into the malonate six-membered hole as a *Z*-enolate. A deprotection protocol involving ethanethiolate exchange of the imide to the corresponding thioester, followed by a standard Fukuyama reduction and a borohydride reduction, furnishes α,α′-quaternized β-hydroxypropionates in high ee overall.

INTRODUCTION

The construction of acyclic stereogenic quaternary centers in nonracemic form[1] is seen to be a challenging problem that has seen an explosion of interest from the organic synthesis community over the last 10 years or so in terms of the relevance of this structural motif to both natural product synthesis as well as medicinal chemistry programs. Methodologies reported for this purpose have covered the complete gamut of asymmetric synthesis strategies ranging from the classical diastereoselective auxiliary-controlled type to modern approaches centered in enantioselective catalysis, and in which four key reaction types stand out as (i) allylic substitution,[2] (ii) conjugate addition,[3] (iii) nucleophilic allylation,[4] and (iv) alkylation in which aldol and Mannich reactions will not be reviewed here. The alkylation option covers a plethora of options of nucleophiles based on single-[5] and double-stabilizing functionalities,[6] and is the most historical as it has blossomed out of traditional carbonyl chemistry. While a solution to the asymmetric formation of acyclic tertiary stereogenic centers in nonracemic form using an auxiliary-control methodology has been provided by the seminal work of Evans and others,[7] by comparison, the equivalent asymmetric production of acyclic quaternary centers poses the challenge of controlling the enolate geometry of the disubstituted (terminus) enolate intermediate.[5a,b,f,j] Recently, an elegant methodology has been reported[8] that addresses this issue via a stereoselective carbometalation-oxidation protocol. In this article, we report on the use of a highly diastereoselective auxiliary-controlled quaternization methodology that addresses the issue of stereodefined disubstituted enolate generation.

RESULTS AND DISCUSSION

The choice to pursue malonate as the template was influenced not only by its well-behaved alkylation credentials together with the possibility of chelation within the enolate for fixing enolate geometry but also by the presence of C-1 ester groups for further elaboration postalkylation and carbonyl chemodifferentiation.[6e] To date, to the best of our knowledge, only one asymmetric diastereoselective alkylation of an α-substituted malonate has been reported, and that involved using a menthol ester auxiliary on a half-acid ester (2 equiv of LDA were needed for alkylation),[9a] in which the range of alkyl groups was limited and dr's were relatively modest. Enantioselective malonate alkylation via PTC catalysis has recently been reported,[6e] while asymmetric malonate fluorination has been achieved via both diastereoselective[9b] and enantioselective[9c] protocols. Similarly, acetoacetate has been used as a template for diastereoselective Michael additions in modest de using triphenylphosphine as catalyst.[10] Another attractive feature for choosing malonate was the ease of generation of the α-alkylated malonate imidazolidinones, which were readily available from malonate half-acid ester[11] **2**, as depicted in Scheme 1. Initial screening with Evans' auxiliary in the diastereoselective quaternization step revealed that warming the solution to 0 °C in order to achieve a high conversion in the alkylation resulted in a significant degree of elimination of the auxiliary, particularly with R groups larger than ethyl, whereas switching to the well-known auxiliary (4*S*,5*R*)-1,5-dimethyl-4-phenylimidazolidin-2-one **3**[12] (referred to as the "down/down" enantiomer in the text) based on (1*S*,2*R*)-ephedrine avoided this problem, allowing alkylations to

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Scheme 1. Synthesis of the Auxiliary-Malonates 4a−f Using the Down/Down Auxiliary

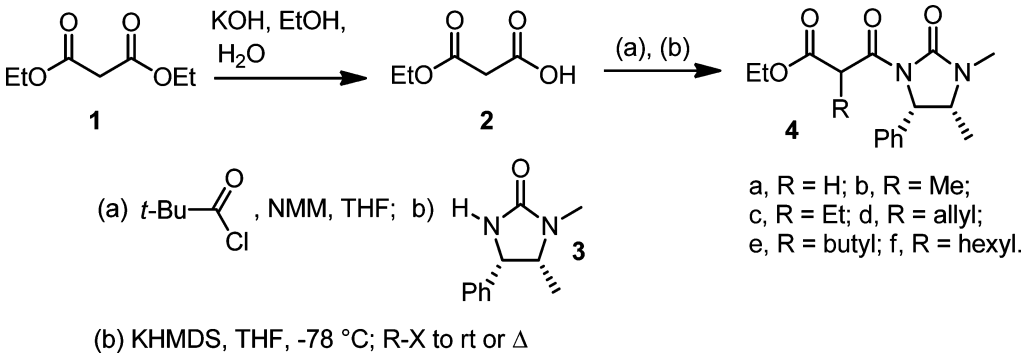
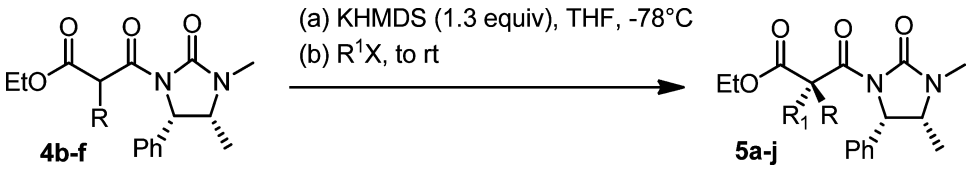


Table 1. Diastereoselectivity of Quaternization of 4



entry	Cpd	R	R^1	yield[a]	dr[b] (data)
1	**5a**	Me	allyl[c]		60:40
2	**5a**	allyl	Me	83	95:5
3	**5b**	Et	Me	95	95:5
4	**5c**	Et	allyl[d]	92	96:4
5	**5d**	Et	Bn	89	96:4
6	**5e**	*n*-Bu	Me	88	95:5
7	**5f**	*n*-Bu	allyl[d]	85	96:4
8	**5g**	*n*-Bu	Bn	84	93:7
9	**5h**	*n*-Hex	Me	90	99:1
10	**5i**	*n*-Hex	allyl[d]	87	>99:1
11	**5j**	*n*-Hex	Bn	82	>99:1

[a]After chromatography on the "down/down" series. [b]By chiral HPLC using a Chiralcel OD column on the "up/up" series. [c]From allyl bromide; allyl iodide gave the same diastereoselectivity. [d]From allyl iodide.

proceed at ambient temperature to achieve full conversion and without auxiliary elimination.[13] Regarding the timing of introduction of the α-substituent R to generate the α-substituted auxiliary-malonates **4**, it was found to be more practical to prepare a large quantity of auxiliary-malonate **4a** (R = H) and introduce the α-substituents individually via alkylation rather than converting α-substituted diethyl malonates individually. In this sequence, the starting material **4a** could be most conveniently prepared in around 90% yield by activating half-acid ester **2** with pivaloyl chloride in THF with *N*-methylmorpholine as base, followed by reaction with the 2-imidazolidinone auxiliary **3**. **4a** was a crystalline solid that could be crystallized to high purity. Other methodologies that could be used included DCC (with BtOH in which the yield was around 80%, but the isolation was complicated by the formation of the urea byproduct), using the acid chloride (prepared with $SOCl_2$, but with losses due to volatility), and using PPh_3/BtCl[14] (troublesome to separate the product from BtH), the latter two reactions returning lower yields of around 65%. Thereafter, various R groups could be introduced using alkylation of **4a** with KHMDS as base, and the relevant alkyl bromide or iodide (see the Experimental Section) to form auxiliary-malonates **4b−f** in high yield (>85%) after chromatography (Scheme 1). Compounds **4b−f** were prepared using both enantiomers of the auxiliary **3** (referred to as "down/down" or "up/up" accordingly), which were both taken through quaternization.

Monosubstituted products **4b−f** were produced in a nonstereoselective manner as a 50:50 mixture of diastereomers according to both NMR and chiral HPLC analysis, and this result was considered to be significant regarding diastereoselectivity, and will be commented on later in the discussion concerning the origin of stereoselectivity in the quaternized products. In this regard, reaction of **4a** with less than a stoichiometric amount of base (0.4 equiv to the malonate), reacting with benzyl bromide and quenching the reaction at −20 °C (with full conversion of the enolate), still resulted in an approximately 50:50 ratio of benzylated diastereomers, strongly suggesting that the dr of ∼50:50 observed in the monoalkylation of **4a** reflects formation of the kinetic product. Products **4b,c** with small products **4b,c** with small R groups were crystalline solids that could be crystallized to a single diastereomer, while the products with longer-chain substituents (**4d−f**) were oils that were characterized as a diastereoisomeric mixture by NMR spectroscopy, HRMS, and chiral HPLC. Moving on to the all-important quaternization step, we were surprised to find that the use of LDA as base (1.3 equiv) at −78 °C in dry THF, followed by addition of the electrophile and allowing the solution to warm up to room temperature, gave back mainly starting material with minimal conversion to the

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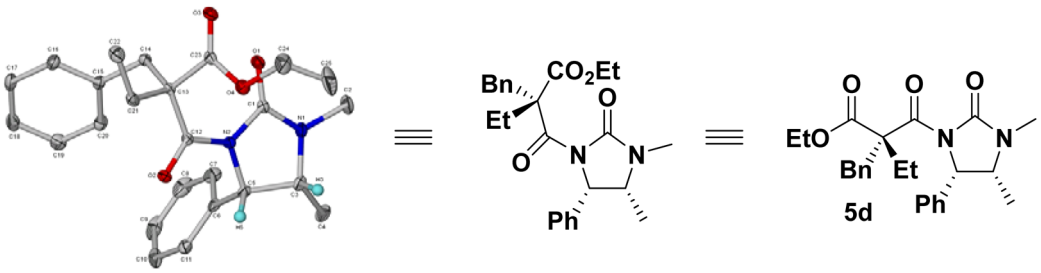

Figure 1. X-ray structure of **5d**.

alkylated product (<10%). Switching to LiHMDS gave the same result. Eventually, it was discovered that full conversion could only be attained using KHMDS as base, with NaHMDS giving only a moderate conversion (~50%) under the conditions described. Furthermore, in keeping with other quaternizations, good results could only be achieved with reactive S_N2-type electrophiles (MeI, allylBr/I, BnBr) in which full conversion could be achieved in each case without a cosolvent by allowing the reaction to warm and stir for a number of hours at room temperature. For R > Me, allylations were carried out with allyl iodide. Table 1 summarizes the results for the "down/down" series varying the two alkyl substituents to afford products **5a–j**.

The diastereoselectivity (reported as a dr) in the quaternized products **5** was measured by chiral HPLC on the "up/up" series (see the Supporting Information), which revealed a healthy separation between the two diastereomers. These results were corroborated by ^{1}H NMR spectroscopy, which was less accurate for calculating the dr but nevertheless supported the formation of one diastereomer predominantly. The results in Table 1 reveal that, apart from R as Me, which gave no diastereoselectivity at all in allylation (entry 1), all other combinations where R was C-2 or larger and R^1 was anything in size from C-1 upward gave a dr equal to or in excess of 95:5 (93:7 for **5g**), with larger groups giving effectively complete diastereoselectivity. Yields were good to excellent in each case. A single-crystal X-ray structure determination for each of the products **5d** and **5f** derived from the "down/down" auxiliary (shown in the Supporting Information) revealed absolute configurations at the new quaternary stereogenic centers to be *S* in each case. Figure 1 shows the structure for **5d**, which is redrawn in the customary all-*cis*-carbonyl conformation.

A major clue as to the origin of the diastereoselectivity was given by the X-ray structures (see the Supporting Information), which showed a preference for the auxiliary to adopt an s-*trans*$_{C-N}$ conformation, as shown in Figure 2 for **5d**. Invoking this in the transition state in conjunction with the customary electrophile attack *anti*- to the phenyl and methyl groups on the auxiliary leads one to conclude that reaction proceeds via a *Z*-enolate from the *si*-face. Such an enolate geometry would be promoted by potassium chelation into the six-membered malonate hole rather than the alternative involving the imidazolidinone moiety as is well-known for Evans' enolates with oxazolidinone as the auxiliary and the cation as lithium.[7] The proposed transition state is depicted in Figure 2.

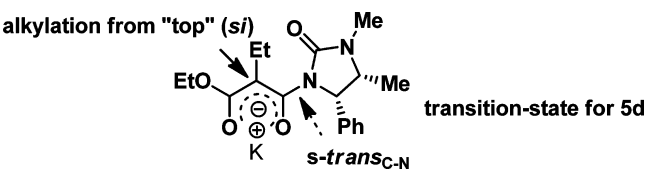

Figure 2. Proposed transition state of quaternization.

Importantly, such a transition state allows the R group to position into a relatively uncrowded area facing the imidazolidinone carbonyl oxygen. Support for this comes from the classical literature on boron enolate aldol reactions involving oxazolidinone auxiliaries.[7,15] Here, an s-*cis*$_{C-N}$ conformation is also preferred when the boron (metal) is chelated to the aldehyde carbonyl. Furthermore, the fact that the reaction only worked with potassium as the cation suggests the importance of having the latter close to the site of electrophile attack, and this aspect effectively offers a solution to the enolate geometry control problem pertaining to terminally disubstituted enolates, except, in this case, one of the groups is an ester. In addition, the unselective result (see entry 1 in Table 1) involving a dr of 60:40 from the allylation with the much smaller Me group (as R) presumably arises as a result of both s-*cis* and s-*trans*$_{C-N}$ conformers being populated (reaction occurs from around 0 °C onward), which leads to opposite facial selectivities in the alkylation. Similarly, this interpretation can be extended to R = H in the monoalkylation of **4a** to afford derivatives **4b–f** (Scheme 1), in which there was also effectively no diastereoselectivity observed. High diastereoselectivities in quaternization are possible with Me so long as it is introduced as R^1 (to afford cpds **5a**, **5b**, **5e**, **5h**), effectively offering a workable solution to achieving a high diastereoselectivity for any combination of R and R^1 provided R^1 is an S_N2-reactive electrophile.

Removal of the auxiliary to complete the methodology as a means of synthesizing quaternary centers in high enantioenriched form proved to be challenging and was carried out in the "up/up" series. The standard methods involving metal hydroperoxide or hydroxide to promote acyl-oxygen fission showed no chemoselectivity between the two carboxyl functions. Similarly, reaction with $LiBH_4$, which was thought would result in preferential complexation of the lithium cation into the auxiliary hole, also gave mixtures of carbonyl-group reduction products. Fortunately, it was eventually established that chemoselective auxiliary removal could be achieved using a Fukuyama reduction protocol[16] with minimal dithioester formation by heating with LiSEt (10 equiv) in THF at 45 °C. Presumably the high lipophilicity and crowded nature of the substrate repels the reagent, making for the slightly more stringent conditions than normal. In such a way, four selected quaternized products (**5d**, **5e**, **5i**, and **5j**) could each be transformed into thioesters **6a–d** in 77–89% yield after chromatography, and with auxiliary recovery (>80%) (Table 2).

Thereafter, reduction with Et_3SiH on Pd–C in THF furnished the aldehydes **7a–d** (not shown), which appeared to be somewhat unstable toward isolation and so were isolated

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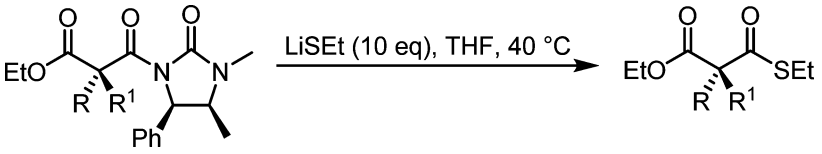
Table 2. Auxiliary Exchange by LiSEt

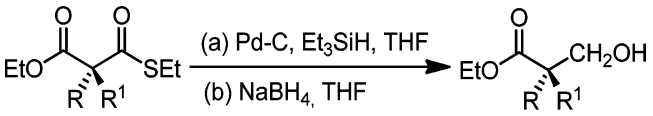


compound[a]	product	R-group	R^1-group	reaction time (h)	yield (%)
5d	**6a**	Et	Bn	5	82
5e	**6b**	*n*-Bu	Me	2	77
5i	**6c**	*n*-Hex	allyl	4	89
5j	**6d**	*n*-Hex	Bn	7	70

[a]Carried out on the "up/up" series.

as their primary alcohols **8a**−**d** following a standard borohydride reduction (Table 3). Yields overall for these last two steps on a small scale (0.1−0.2 mmol scale) were about 60%, while final ee's were ∼95% according to chiral HPLC. In the case of **6c**, reduction of the allyl group double bond occurred as mentioned in Fukuyama's original article (monosubstituted olefins), to afford **8c** containing hexyl and propyl as the two R groups, which was isolated and characterized as its benzoate derivative (**9**) in order to obtain an ee measurement.

Table 3. Fukuyama Protocol To Afford *α,α′*-Dialkylated, *β*-Hydroxy Esters 8



6a-d **8a-d**

compound	product	R-group	R^1-group	yields (%)[a]	ee (%) (data)
6a	**8a**	Et	Bn	65	94
6b	**8b**	*n*-Bu	Me	55	[b]
6c	**8c**[c]	*n*-Hex	Pr[d]	54[e]	94
6d	**8d**	*n*-Hex	Bn	60	>99

[a]Over the two steps. [b]No UV chromophore. [c]**8c** isolated as its benzoate (**9**). [d]Reduction of the allyl group double bond occurred. [e]Over three steps.

CONCLUSION

In conclusion, we have discovered a means of controlling the geometry of a chiral terminally disubstituted enolate derived from an *α*-substituted malonate-imidazolidinone, based on a preference for the potassium cation to chelate to the malonate part of the anion. High diastereoselectivities in alkylation to afford quaternary centers were achieved in which a transition state is proposed involving the auxiliary adopting an s-*trans*$_{C-N}$ conformation, as suggested by X-ray analysis of two quaternized products. The auxiliary removal of such adducts with lithium ethanethiolate can be achieved chemoselectively to afford the corresponding thioesters, which undergo Fukuyama reduction to afford quaternized chirons in high ee overall of relevance to natural product synthesis and medicinal chemistry scaffolds.

EXPERIMENTAL SECTION

General Information. All reaction solvents were freshly distilled under nitrogen, in which THF was distilled from sodium wire with benzophenone, MeCN distilled from calcium hydride, and DCM distilled from phosphorus pentoxide. Reagents were obtained from commercial sources and used as obtained unless stated. All reactions were carried out in oven-dried glassware with a magnetic stirrer, and performed under a nitrogen atmosphere unless otherwise stated. Reaction temperatures were achieved with heat/silicone oil (for >25 °C), ice/NH_4Cl salt (for 0 °C), and acetone/liquid nitrogen (<−20 °C). Aqueous solutions were prepared using deionized water. All reactions were monitored by TLC using aluminum-backed silica gel 60 F254 plates, while column chromatography was carried out using Kieselgel 60 silica gel. Active compounds were observed under a UV lamp (ultraviolet), while non-UV-active compounds were sprayed with a 2.5% solution of *p*-anisaldehyde in a mixture of sulfuric acid and ethanol (1:10 v/v), iodine vapor, or ceric ammonium sulfate solution and then heated. Nuclear magnetic resonance (NMR) spectra were recorded at 399.95 or 300.08 MHz for ^1H, and 100.6 MHz for ^{13}C. Chemical shifts (δ) and *J*-coupling values are reported in units of ppm and Hz, respectively. Chemical shifts for ^1H and ^{13}C were recorded relative to residual chloroform, at 7.26 and 77.16 ppm, respectively. High-resolution mass spectra (HRMS) were recorded in electrospray positive mode with a quadrupole time-of-flight analyzer system. Infrared (IR) spectroscopy absorptions were measured in units of cm^{-1}. Optical rotations were measured at 20 °C and are reported as $[\alpha]_D^{20}$ (*c* g/mL, solvent). The determination of melting points was carried out using a hot-stage microscope (HSM) and are uncorrected. HPLC analyses were carried out with a Chiralcel OD column.

General Procedure for the Synthesis of *α*-Substituted Auxiliary-Malonates 4b−f. To a solution of diethyl malonate (50 mmol) in EtOH (10 mL) at 0 °C was added dropwise a solution of aq. KOH in H_2O (60 mmol, 2.5 M), and the contents were allowed to slowly warm up to rt. After 1 h, the EtOH was removed under reduced pressure, and the concentrate was diluted with water (10 mL) and extracted with DCM (3 × 20 mL) to remove unreacted diester. The aqueous layer was then acidified with conc. HCl to pH = 2 and then re-extracted with DCM (3 × 30 mL); the organic extracts combined, dried over $MgSO_4$, filtered under vacuum, and concentrated *in vacuo* to obtain the half-acid ester **2** (5.9 g, 90%) as a colorless oil.

To a solution of **2** (5.61 g, 42.5 mmol, 1.62 equiv) and *N*-methylmorpholine (4.25 g, 42.0 mmol, 1.60 equiv) in dry THF at −15 °C under an Ar atmosphere was added dropwise a solution of freshly distilled pivaloyl chloride in dry THF (36.8 mmol, 1.4 equiv, 0.5 M), and the reaction was allowed to stir at this temperature for 30 min. Thereafter, (4*S*,5*R*)-1,5-dimethyl-4-phenylimidazolidin-2-one (5.00 g, 26.3 mmol) **3** was added over a period of 5 min and the contents slowly warmed to rt and left to stir overnight at 30 °C. After 12 h, the organic solvent was removed *in vacuo*, and EtOAc (150 mL) was added to the crude residue to dissolve the organic product, which was subsequently washed with 1 M HCl (3 × 75 mL), followed by sat. $NaHCO_3$ (3 × 75 mL). The organic extract was then dried with $MgSO_4$, and the product was purified by column chromatography after removal of the organic solvent to afford ethyl 3-((4*R*,5*S*)-3,4-dimethyl-2-oxo-5-phenylimidazolidin-1-yl)-3-oxopropanoate (**4a**), (7.36 g, 92% yield) as a colorless solid, which was recrystallized from EtOAc/hexane. mp 84 °C; $[\alpha]_D^{20}$ = −6.2, (*c* = 1.0, DCM); IR ν_{max} (cm^{-1}) 3008, 2860, 1736, 1687; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 (m, 3H),

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7.18 (m, 2H), 5.32 (d, J = 8.7 Hz, 1H), 4.18 (q, J = 7.2 Hz, 2H), 4.02 (s, 1H), 3.97 (s, 1H), 3.93 (dq, J = 8.7, 6.6 Hz, 1H), 2.81 (s, 3H), 1.26 (t, J = 7.2 Hz, 3H), 0.80 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 167.7, 165.1, 155.6, 136.1, 128.6, 128.3, 127.2, 61.3, 59.5, 54.2, 43.5, 28.3, 15.1, 14.2; Anal. Calc. for $C_{16}H_{20}N_2O_4$ (%): C, 63.14; H, 6.61; N, 9.20. Found (%): C, 63.19; H, 6.57; N, 9.24.

To a solution of **4a** (0.40 g, 1.31 mmol) in THF (3.5 mL) at −78 °C was added KHMDS (3.15 mL, 0.5M, 1.58 mmol, 1.2 equiv), and the contents were allowed to stir at this temperature for 30 min. Thereafter, the alkylating agent (3.0 equiv) was added at −78 °C and the contents were allowed to slowly warm up to rt and left to stir at the appropriate temperature. After 14 h, the reaction was quenched with sat. $NH_4Cl/Na_2S_2O_3$ (25 mL) and extracted with DCM (3 × 25 mL), the organic solvents were combined, dried over $MgSO_4$, and filtered under pressure, and the organic solvent was removed under reduced pressure. The residue was purified by column chromatography (30% EtOAc in hexane) to afford a mixture of diastereomers of products **4b−f**.

*Ethyl 3-((4R,5S)-3,4-Dimethyl-2-oxo-5-phenylimidazolidin-1-yl)-2-methyl-3-oxopropanoate (**4b**).* Scale: 1.31 mmol (0.400 g), with MeI (0.25 mL, 3.93 mmol) at room temperature. Yield: 0.375 g, 90% as an off-white solid and as a mixture of diastereomers. Recrystallization from EtOAc/hexane to a constant mp afforded one single diastereomer: mp 152−153 °C; $[\alpha]_D^{20}$ = −31.9, (c = 1.0, DCM); IR ν_{max} (cm^{-1}) 3010, 2863, 1732, 1689; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (m, 3H), 7.22 (m, 2H), 5.30 (d, J = 8.7 Hz, 1H), 4.65 (q, J = 7.5 Hz, 1H), 4.25−4.05 (m, 2H), 3.90 (dq, J = 8.7, 6.6 Hz, 1H), 2.81 (s, 3H), 1.39 (d, J = 7.5 Hz, 3H), 1.21 (t, J = 7.6 Hz, 3H), 0.80 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.1, 169.0, 155.7, 136.2, 128.5, 128.2, 127.3, 61.2, 59.8, 54.3, 45.9, 28.4, 15.2, 14.2, 13.5; Anal. Cal. for $C_{17}H_{22}N_2O_4$ (%): C, 64.13; H, 6.97; N, 8.80. Found (%): C, 64.02; H, 7.04; N, 8.89.

*Ethyl 2-((4R,5S)-3,4-Dimethyl-2-oxo-5-phenylimidazolidine-1-carbonyl)butanoate (**4c**).* Scale: 1.31 mmol (0.400 g) with ethyl iodide (0.32 mL, 3.93 mmol) at 65 °C for 12 h. Yield: 0.388 g, 89% as a 51:49 colorless solid and a mixture of diastereomers. Recrystallization from EtOAc/hexane to a constant mp afforded one single diastereomer: mp 126−129 °C; $[\alpha]_D^{20}$ = −4.5, (c = 1.0, DCM); IR ν_{max} (cm^{-1}) 3010, 2863, 1732, 1689; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (m, 3H), 7.21 (m, 2H), 5.31 (d, J = 8.8 Hz, 1H), 4.59 (dd, J = 5.6, 2.8 Hz 1H), 4.25−4.08 (m, 2H), 3.91 (dq, J = 8.8, 6.8 Hz, 1H), 2.82 (s, 3H), 2.04−1.86 (m, 2H), 1.20 (t, J = 7.2 Hz, 3H), 0.97 (t, J = 8.0 Hz, 3H), 0.80 (d, J = 6.8 Hz, 3H); ^{13}C (100.6 MHz, $CDCl_3$) δ 170.3, 168.1, 155.7, 136.2, 128.5, 128.2, 127.3, 61.0, 59.8, 54.2, 52.7, 28.3, 22.1, 15.2, 14.2, 12.2; Anal. Calcd for $C_{18}H_{24}N_2O_4$ (%): C, 65.04; H, 7.28; N, 8.43. Found (%): C, 64.85; H, 7.06; N, 8.36.

*Ethyl 2-((4R,5S)-3,4-Dimethyl-2-oxo-5-phenylimidazolidine-1-carbonyl)pent-4-enoate (**4d**).* Scale: 1.31 mmol (0.400 g) with allyl bromide (0.34 mL, 3.93 mmol) at 20 °C. Yield: 0.393 g, 87% as an oil and a 52:48 mixture of diastereomers. IR ν_{max} (cm^{-1}) 3010, 2959, 2863, 1732, 1689; HRMS (ES) m/z: $[M + H]^+$ Calcd for $C_{19}H_{25}N_2O_4$ 345.1813; Found 345.1814.

Major Diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 3H), 7.20 (m, 1H), 7.17 (m, 1H), 5.81−5.45 (m, 1H), 5.35 (d, J = 8.8 Hz, 1H), 5.12−5.02 (m, 1H), 5.01−4.92 (m, 1H), 4.91 (dd, J = 4.2, 2.6 Hz, 1H), 4.25−4.11 (m, 2H), 3.98−3.85 (m, 1H), 2.83 (s, 3H), 2.50−2.21 (m, 2H), 1.25 (t, J = 7.2 Hz, 3H), 0.80 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.6, 169.7, 155.1, 136.1, 135.0, 128.5, 128.2, 127.2, 117.1, 61.3, 58.8, 54.1, 50.9, 32.8, 28.3, 15.2, 14.3.

Minor Diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 3H), 7.20 (m, 1H), 7.17 (m, 1H), 5.81−5.45 (m, 1H), 5.30 (d, J = 8.8 Hz, 1H), 5.12−5.02 (m, 1H), 5.01−4.92 (m, 1H), 4.80 (dd, J = 5.4, 3.6 Hz, 1H), 4.25−4.11 (m, 2H), 3.98−3.85 (m, 1H), 2.82 (s, 3H), 2.50−2.21 (m, 2H), 1.21 (t, J = 7.2 Hz, 3H), 0.80 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.6, 170.7, 155.1, 136.7, 135.4, 128.6, 128.3, 127.3, 117.1, 61.3, 58.8, 54.2, 51.1, 32.8, 28.3, 15.2, 14.3.

*Ethyl 2-((4R,5S)-3,4-Dimethyl-2-oxo-5-phenylimidazolidine-1-carbonyl)hexanoate (**4e**).* Scale: 0.400 g (1.31 mmol) with 1-bromobutane (0.42 mL, 3.93 mmol) and TBAI (0.241 g, 0.655 mmol, 0.5 equiv) at 65 °C. Yield: 0.411 g, 87% as a colorless oil and a 51:49 mixture of diastereomers. IR ν_{max} (cm^{-1}) 3010, 2861, 1732, 1689; HRMS (ES) m/z: $[M + H]^+$ Calcd for $C_{20}H_{29}N_2O_4$ 361.2125; Found 361. 2127.

Major Diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (m, 3H), 7.23 (m, 1H), 7.12 (m, 1H), 5.31 (d, J = 8.6 Hz, 1H), 4.63 (dd, J = 5.3, 3.4 Hz, 1H), 4.24−4.19−4.09 (m, 2H), 3.96−3.88 (m, 1H), 2.82 (s, 3H), 2.00−1.75 (m, 2H), 1.35−1.28 (m, 2H), 1.25−1.18 (m, 2H), 1.20 (t, J = 7.2 Hz, 3H), 0.82 (t, J = 7.2 Hz, 3H), 0.80 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.4, 168.4, 155.7, 136.2, 128.4, 128.2, 127.2, 61.1, 59.7, 54.0, 51.1, 29.2, 28.3, 27.6, 22.6, 15.1, 14.3, 14.2.

Minor Diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (m, 3H), 7.23 (m, 1H), 7.12 (m, 1H), 5.36 (d, J = 8.6 Hz, 1H), 4.61 (dd, J = 6.4, 1.2 Hz, 1H), 4.24−4.09 (m, 2H), 3.96−3.88 (m, 1H), 2.81 (s, 3H), 2.00−1.75 (m, 2H), 1.35−1.28 (m, 2H), 1.25−1.18 (m, 2H), 1.26 (t, J = 7.2 Hz, 3H), 0.87 (t, J = 7.2 Hz, 3H), 0.79 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.5, 168.8, 155.7, 136.7, 128.6, 128.3, 127.3, 61.1, 59.8, 54.2, 51.3, 29.3, 28.7, 27.9, 22.7, 15.1, 14.3, 14.2.

*Ethyl 2-((4R,5S)-3,4-Dimethyl-2-oxo-5-phenylimidazolidine-1-carbonyl)octanoate (**4f**).* Scale: 0.400 g (1.31 mmol) with 1-bromohexane (0.55 mL, 3.93 mmol) and TBAI (0.241 g, 0.655 mmol, 0.5 equiv) at 65 °C. Yield: 0.458 g, 90% as a colorless oil and a 51:49 mixture of diastereomers.

IR ν_{max} (cm^{-1}) 3010, 2860, 1732, 1689; HRMS (ES) m/z: $[M + H]^+$ Calcd for $C_{22}H_{33}N_2O_4$ 389.2443; Found 389.2440.

Major Diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 3H), 7.20 (m, 1H), 7.17 (m, 1H), 5.31 (d, J = 8.8 Hz, 1H), 4.63 (dd, J = 4.6, 3.6 Hz, 1H), 4.24−4.24−4.08 (m, 2H), 3.97−3.88 (m, 1H), 2.82 (s, 3H), 1.95−1.86 (m, 2H), 1.35−1.17 (m, 8H), 1.20 (t, J = 7.2 Hz, 3H), 0.84 (t, J = 7.2 Hz, 3H), 0.80 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.4, 168.4, 155.7, 136.2, 128.4, 128.2, 127.2, 61.1, 59.7, 54.2, 51.3, 29.3, 29.2, 28.9, 28.3, 27.6, 22.6, 15.1, 14.2, 14.2.

Minor Diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 3H), 7.17 (m, 2H), 5.36 (d, J = 8.4 Hz, 1H), 4.79 (dd, J = 6.0, 2.4 Hz, 1H), 4.24−4.08 (m, 2H), 3.97−3.88 (m 1H), 2.82 (s, 3H), 1.95−1.86 (m, 2H), 1.35−1.17 (m, 8H), 1.25 (t, J = 7.2 Hz, 3H), 0.85 (t, J = 7.2 Hz, 3H), 0.79 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.5, 168.8, 155.7, 136.7, 128.6, 128.3, 127.3, 61.1, 59.8, 54.2, 51.3, 29.3, 29.2, 28.9, 28.7, 27.9, 22.7, 15.2, 14.2, 14.2.

General Procedure for the Synthesis of α,α′-Disubstituted Auxiliary-Malonates 5a−j. To a solution of the appropriate derivative of **4** (0.6 mmol) in THF (2 mL) at −78 °C was added a solution of KHMDS (1.56 mL, 0.78 mmol, 1.3 equiv, 0.5 M), and the reaction contents were allowed to stir at this temperature for 30 min. Thereafter, the appropriate alkylating agent (1.8 mmol, 3 equiv) was slowly added, and the reaction contents were allowed to slowly warm up to rt and left to stir overnight for 20 h. The reaction was quenched with sat. NH_4Cl (15 mL) and extracted with DCM (3 × 15 mL), the organic extracts were dried over $MgSO_4$ and filtered under vacuum, and the organic solvent was removed *in vacuo*. The crude residue was chromatographed using EtOAc/hexane mixtures to afford the derivative **5**, which was analyzed by chiral HPLC and ^{1}H NMR spectroscopy for diastereoselectivity.

*Ethyl (R)-2-((4R,5S)-3,4-Dimethyl-2-oxo-5-phenylimidazolidine-1-carbonyl)-2-methylpent-4-enoate (**5a**).* Scale: 0.200 g (0.581 mmol) of **4d** with MeI (0.11 mL, 1.77 mmol). Yield: 0.173 g, 83% as a colorless oil and a 95:5 mixture of diastereomers.$[\alpha]_D^{20}$ = −33.3, (c = 1.0, DCM); IR ν_{max} 3010, 2991, 2858, 1735, 1675; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (m, 3H), 7.17 (m, 2H), 5.80−5.71 (m, 1H), 5.29 (d, J = 8.4 Hz, 1H), 5.04−4.98 (m, 1H), 4.97−4.89 (m, 1H), 4.25−4.13 (m, 2H), 3.90 (dq, J = 8.4, 6.4 Hz, 1H), 2.79 (s, 3H), 2.78−2.63 (m, 2H), 1.45 (s, 3H), 1.27 (t, J = 7.2 Hz, 3H), 0.79 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.1, 170.2, 155.9, 136.7, 133.8, 128.6, 128.2, 127.0, 118.2, 60.8, 60.5, 54.5, 54.5, 40.5, 28.3, 21.4, 15.1, 14.3; HRMS (ES) m/z: $[M + H]^+$ Calcd for $C_{20}H_{27}N_2O_4$ 359.1971; Found 359.1971.

*Ethyl (R)-2-((4R,5S)-3,4-Dimethyl-2-oxo-5-phenylimidazolidine-1-carbonyl)-2-methylbutanoate (**5b**).* Scale: 0.200 g (0.602 mmol) of

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4c with MeI (0.11 mL, 1.77 mmol). Yield: 0.198 g, 95%, as a colorless oil and as a 95:5 mixture of diastereomers.

$[\alpha]_D^{20}$ = −32.6, (*c* = 0.65, DCM); IR ν_{max} 3012, 2863, 1737, 1676; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (m, 3H), 7.16 (m, 2H), 5.28 (d, *J* = 8.4 Hz, 1H), 4.25−4.11 (m, 2H), 3.89 (dq, *J* = 8.4, 6.4 Hz, 1H), 2.76 (s, 3H), 2.02−1.90 (m, 2H), 1.42 (s, 3H), 1.25 (t, *J* = 7.2 Hz, 3H), 0.82 (t, *J* = 7.2 Hz, 3H), 0.76 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.9, 170.8, 155.4, 136.9, 128.6, 128.2, 127.1, 60.6, 60.5, 55.5, 54.4, 29.0, 28.3, 21.0, 15.1, 14.3, 9.1; HRMS (ES) *m*/*z*: [M + H]$^+$ Calcd for $C_{19}H_{27}N_2O_4$ 347.1967; Found 347.1971.

*Ethyl (S)-2-((4R,5S)-3,4-Dimethyl-2-oxo-5-phenylimidazolidine-1-carbonyl)-2-ethylpent-4-enoate (**5c**).* Scale: 0.200 g (0.602 mmol) of **4c** with allyl iodide (0.17 mL, 1.86 mmol). Yield: 0.203 g, 92%, as a colorless oil and a 96:4 mixture of diastereomers.0

$[\alpha]_D^{20}$ = −23.6, (*c* = 1.0, DCM); IR ν_{max} (cm^{-1}) 3010, 2987, 2860, 1737, 1675; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 3H), 7.19 (m, 2H), 5.49−5.37 (m, 1H), 5.32 (d, *J* = 8.4 Hz, 1H), 5.00−4.94 (m, 1H), 4.91−4.85 (m, 1H), 4.25−4.11 (m, 2H), 3.91 (dq, *J* = 8.4, 6.4 Hz, 1H), 2.93−2.85 (m, 1H), 2.78 (s, 3H), 2.74−2.68 (m, 1H), 2.00 (q, *J* = 7.6 Hz, 2H), 1.26 (t, *J* = 7.2 Hz, 3H), 0.81 (t, *J* = 7.6 Hz, 3H), 0.79 (d, *J* = 7.6 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.5, 169.8, 155.3, 136.7, 133.3, 128.5, 128.2, 127.3, 118.0, 60.6, 60.5, 58.8, 54.4, 37.5, 28.3, 26.0, 15.1, 14.4, 8.7; HRMS (ES) *m*/*z*: [M + H]$^+$ Calcd for $C_{21}H_{29}N_2O_4$ 373.2126; Found 373.2127.

*Ethyl (S)-2-Benzyl-2-((4R,5S)-3,4-dimethyl-2-oxo-5-phenylimidazolidine-1-carbonyl)butanoate (**5d**).* Scale: 0.200 g, (0.602 mmol) of **4c** with benzyl bromide (0.21 mL, 1.77 mmol). Yield: 0.219 g, 89%, as a colorless solid and as a 96:4 mixture of diastereomers. mp 107−110 °C; $[\alpha]_D^{20}$ = −42.0, (*c* = 0.8, DCM); IR ν_{max} (cm^{-1}) 3010, 3009, 2863, 1739, 1635; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (m, 3H), 7.25 (m, 2H), 7.07 (m, 1H), 6.98 (m, 2H), 6.84 (m, 2H), 5.37 (d, *J* = 8.5 Hz, 1H), 4.04 (q, *J* = 9.6 Hz, 2H), 3.95 (dq, *J* = 8.5, 6.6 Hz, 1H), 3.37 (bs, 2H), 2.81 (s, 3H), 1.98−1.89 (m, 2H), 1.12 (t, *J* = 9.6 Hz, 3H), 0.87 (t, *J* = 7.5 Hz, 3H), 0.86 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.5, 169.9, 155.6, 137.1, 136.7, 130.7, 128.6, 128.2, 128.0, 127.8, 126.4, 61.0, 60.5, 55.4, 54.7, 39.5, 28.4, 26.7, 15.1, 14.1, 9.1; Anal. Calcd for $C_{25}H_{30}N_2O_4$ (%): C, 71.07; H, 7.16; N, 6.63. Found (%): C, 70.81; H, 6.99; N, 6.67.

*Ethyl (R)-2-((4R,5S)-3,4-Dimethyl-2-oxo-5-phenylimidazolidine-1-carbonyl)-2-methylhexanoate (**5e**).* Scale: 0.200g (0.555 mmol) of **4e** with methyl iodide (0.10 mL, 1.61 mmol). Yield: 0.283 g, 88%, as a colorless oil and a 95:5 mixture of diastereomers. $[\alpha]_D^{20}$ = −40.5, (*c* = 1.0, DCM); IR ν_{max} (cm^{-1}) 3010, 2859, 1739, 1677; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 3H), 7.17 (m, 2H), 5.30 (d, *J* = 8.4 Hz, 1H), 4.20 (m, 2H), 3.91 (dq, *J* = 8.4, 6.4 Hz, 1H), 2.78 (s, 3H), 1.92 (m, 2H), 1.45 (s, 3H), 1.37−1.80 (m, 3H), 1.27 (t, *J* = 6.8 Hz, 3H), 1.10−1.00 (m, 1H), 0.86 (t, *J* = 7.2 Hz, 3H), 0.78 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.1, 170.9, 155.3, 136.8, 128.6, 128.2, 127.0, 60.7, 60.5, 55.0, 54.4, 35.8, 28.3, 26.7, 23.2, 21.6, 15.1, 14.3, 14.1; HRMS (ES) *m*/*z*: [M + H]$^+$ Calcd for $C_{21}H_{31}N_2O_4$ 375.2286; Found 375.2284.

*Ethyl (S)-2-Allyl-2-((4R,5S)-3,4-dimethyl-2-oxo-5-phenylimidazolidine-1-carbonyl)hexanoate (**5f**).* Scale: 0.200 g (0.555 mmol) of **4e** with allyl iodide (0.15 mL, 1.64 mmol). Yield: 0.189 g, 85%, as a colorless solid and a 96:4 mixture of diastereomers. mp 88−90 °C; $[\alpha]_D^{20}$ = −30.2, (*c* = 0.8, DCM); IR ν_{max} (cm^{-1}) 3009, 2989, 2861, 1738, 1674; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 3H), 7.20 (m, 2H), 5.49−5.40 (m, 1H), 5.31 (d, *J* = 8.4 Hz, 1H), 5.00−4.95 (m, 1H), 4.90−4.87 (m, 1H), 4.25−4.09 (m, 2H), 3.91 (dq, *J* = 8.4, 6.4 Hz, 1H), 2.90−2.89 (m, 1H), 2.79 (s, 3H), 2.75−2.69 (m, 1H), 2.00−1.92 (m, 2H), 1.35−1.19 (m, 3H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.08−0.98 (m, 1H), 0.86 (t, *J* = 7.2 Hz, 3H), 0.79 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.6, 170.0, 155.3, 136.7, 133.4, 128.5, 128.2, 127.3, 118.0, 60.6, 60.5, 58.4, 54.4, 38.1, 32.8, 28.3, 26.3, 23.1, 15.1, 14.4, 14.1; Anal. Calcd for $C_{23}H_{32}N_2O_4$ (%): C, 68.97; H, 8.05; N, 6.99. Found (%): C, 68.53; H, 7.89; N, 7.00.

*Ethyl (S)-2-Benzyl-2-((4R,5S)-3,4-dimethyl-2-oxo-5-phenylimidazolidine-1-carbonyl)hexanoate (**5g**).* Scale: 0.200 g (0.555 mmol) of **4e** with benzyl bromide (0.20 mL, 1.68 mmol). Yield: 0.163 g, 84%, as a colorless oil and a 93:7 mixture of diastereomers.$[\alpha]_D^{20}$ = −10.7, (*c* = 2.3, DCM); IR ν_{max} (cm^{-1}) 3011, 3009, 2861, 1737, 1674; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (m, 3H), 7.26 (m, 2H), 7.07 (m, 1H), 6.99 (m, 2H), 6.82 (m, 2H), 5.36 (d, *J* = 8.4 Hz, 1H), 4.04 (q, *J* = 7.2 Hz, 2H), 3.95 (dq, *J* = 8.4, 6.8 Hz, 1H), 3.38 (bs, 2H), 2.81 (s, 3H), 1.87−1.77 (m, 2H), 1.42−1.30 (m, 1H), 1.29−1.20 (m, 2H), 1.12 (t, *J* = 7.2 Hz, 3H), 1.10−1.05 (m, 1H), 0.87 (t, *J* = 6.8 Hz, 3H), 0.85 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.6, 170.1, 155.5, 137.0, 136.6, 130.6, 128.5, 128.2, 127.8, 127.8, 126.4, 60.8, 60.5, 59.9, 54.5, 39.7, 33.1, 28.4, 26.7, 23.1, 15.1, 14.1, 14.1; HRMS (ES) *m*/*z*: [M + H]$^+$ Calcd for $C_{27}H_{35}N_2O_4$ 451. 2593; Found 451.2590.

*Ethyl (R)-2-((4R,5S)-3,4-Dimethyl-2-oxo-5-phenylimidazolidine-1-carbonyl)-2-methyloctanoate (**5h**).* Scale: 0.200 g (0.515 mmol) of **4f** with methyl iodide (0.10 mL, 1.61 mmol). Yield: 0.187 g, 90%, as a colorless oil and a 99:1 mixture of diastereomers.$[\alpha]_D^{20}$ = −47.0, (*c* = 1.0, DCM); IR ν_{max} (cm^{-1}) 3011, 2865, 1735, 1675; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 3H), 7.17 (m, 2H), 5.29 (d, *J* = 8.4 Hz, 1H), 4.26−4.12 (m, 2H), 3.90 (dq, *J* = 8.4, 6.4 Hz, 1H), 2.78 (s, 3H), 1.98−1.85 (m, 2H), 1.45 (s, 3H), 1.38−1.31 (m, 1H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.26−1.22 (m, 6H), 1.13−0.98 (m, 1H), 0.85 (t, *J* = 6.8 Hz, 3H), 0.78 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.1, 170.9, 155.3, 136.8, 128.6, 128.2, 127.0, 60.7, 60.5, 55.1, 54.4, 36.0, 31.7, 29.7, 28.3, 24.4, 22.7, 21.6, 15.1, 14.3, 14.2; HRMS (ES) *m*/*z*: [M + H]$^+$ Calcd for $C_{23}H_{35}N_2O_4$ 403.2590; Found 403.2587.

*Ethyl (S)-2-Allyl-2-((4R,5S)-3,4-dimethyl-2-oxo-5-phenylimidazolidine-1-carbonyl)octanoate (**5i**).* Scale: 0.200 g (0.515 mmol) of **4f** with allyl iodide (0.14 mL, 1.53 mmol). Yield: 0.192 g, 87%, as a colorless oil and a >99:1 mixture of diastereomers.$[\alpha]_D^{20}$ = −27.2, (*c* = 1.0, DCM); IR ν_{max} (cm^{-1}) 3010, 2988, 2860, 1735, 1674; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 3H), 7.18 (m, 2H), 5.50−5.41 (m, 1H), 5.31 (d, *J* = 8.4 Hz, 1H), 5.00−4.96 (m, 1H), 4.91−4.87 (m, 1H), 4.24−4.11 (m, 2H), 3.91 (dq, *J* = 8.4, 6.4 Hz, 1H), 2.96−2.88 (m, 1H), 2.79 (s, 3H), 2.76−2.69 (m, 1H), 1.97−1.88 (m, 2H), 1.28−1.22 (m, 7H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.19−1.00 (m, 1H), 0.85 (t, *J* = 6.8 Hz, 3H), 0.80 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.6, 170.0, 155.3, 136.7, 133.4, 128.5, 128.2, 127.3, 118.0, 60.6, 60.5, 58.4, 54.4, 38.1, 33.0, 31.7, 29.6, 28.3, 24.0, 22.7, 15.1, 14.4, 14.2; HRMS (ES) *m*/*z*: [M + H]$^+$ Calcd for $C_{25}H_{37}N_2O_4$ 429.2762; Found 429.2753.

*Ethyl (S)-2-Benzyl-2-((4R,5S)-3,4-dimethyl-2-oxo-5-phenylimidazolidine-1-carbonyl)octanoate (**5j**).* Scale: 0.200 g (0.515 mmol) of **4f** with benzyl bromide (0.18 mL, 1.52 mmol). Yield: 0.202 g, 82%, as a colorless oil and a >99:1 mixture of diastereomers. $[\alpha]_D^{20}$ = −10.8, (*c* = 1.0, DCM); IR ν_{max} (cm^{-1}) 3013, 3010, 2863, 1739, 1677; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (m, 3H), 7.26 (m, 2H), 7.07 (m, 1H), 6.99 (m, 2H), 6.82 (m, 2H), 5.36 (d, *J* = 8.4 Hz, 1H), 4.04 (q, *J* = 7.2 Hz, 2H), 3.94 (dq, *J* = 8.4, 6.6 Hz, 1H), 3.38 (bs, 2H), 2.81 (s, 3H), 1.90−1.80 (m, 2H), 1.42−1.35 (m, 1H), 1.30−1.20 (m, 6H), 1.11 (t, *J* = 7.2 Hz, 3H), 1.16−1.08 (m, 1H), 0.86 (d, *J* = 6.6 Hz, 3H), 0.85 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.6, 170.0, 155.5, 137.0, 136.6, 130.6, 128.5, 128.2, 127.8, 127.8, 126.4, 60.8, 60.5, 60.0, 54.5, 39.7, 33.2, 31.8, 29.6, 28.4, 24.4, 22.7, 15.1, 14.2, 14.1; HRMS (ES) *m*/*z*: [M + H]$^+$ Calcd for $C_{29}H_{39}N_2O_4$ 479.2916; Found 479.2910.

General Procedure for Converting Quaternized Products 5 to Hydroxyesters 8. To a solution of ethanethiol (0.19 mL, 2.63 mmol, 10.5 equiv) in THF (2.0 mL) at −78 °C was slowly added *n*-BuLi (1.00 mL, 2.50 mmol, 10 eq, 2.5 M). After 30 min, a solution of **5** (100 mg, 0.25 mmol) in the "up/up" series in THF (1.5 mL) was slowly added to the reaction mixture at −78 °C, and the contents were allowed to gradually warm up to rt over 1 h. Thereafter, the reaction mixture was warmed to 40 °C and stirred at this temperature until TLC indicated the complete conversion of starting material (see Table 2 for durations). Thereafter, the contents were cooled to rt and quenched with sat. $NaHCO_3$ (15 mL) and extracted with DCM (3 × 20 mL), and the organic extracts were combined and dried over $MgSO_4$. Following the removal of organic solvent under reduced pressure, the crude residue was purified by column chromatography using (5% EtOAc in hexane) to afford thioester **6**.

A reaction flask with Pd/C (5.4 mg, 0.051 mmol, 0.30 equiv) was purged with argon for 10 min, and dry THF (1.0 mL) was added. To this suspension was slowly added a solution of thioester **6** (0.170

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mmol) in THF (1.5 mL), followed by triethylsilane (0.081 mL, 0.51 mmol, 3.0 equiv), and the contents were allowed to stir at rt. After 2 h, the contents were diluted with EtOAc (10 mL), filtered through Celite under reduced pressure, and washed with EtOAc (2 × 20 mL), and the organic extracts were concentrated *in vacuo*. Aldehyde **7** was pure enough by ^{1}H NMR spectroscopy to be used without further purification in the next step. $NaBH_4$ (32 mg, 0.85 mmol, 5.0 equiv) was suspended in dry THF (1.0 mL) at 0 °C under nitrogen. To this solution was slowly added the crude mixture of **7** (0.170 mmol) in THF (1.5 mL) at the same temperature. After 2 h, the reaction mixture was slowly quenched with HCl (1.0 M, 10 mL) and extracted with DCM (3 × 15 mL), and the organic extracts were dried over $MgSO_4$, which were filtered under reduced pressure and concentrated *in vacuo*. The crude residue was purified by column chromatography (20% EtOAc in hexane) to afford the alcohol **8**.

*Ethyl (2R)-2-Benzyl-2-(hydroxymethyl)butanoate (**8a**).* Scale: 0.100 g (0.237 mmol) of **5d**; yield of **6a**, 0.060 g, 82% as a pale-yellow oil. Scale: 0.050 g (0.170 mmol) of **6a**; yield of **8a** over two steps, 0.026 g, 65% as a clear oil and in 94% ee. $[\alpha]_D^{20} = -21.9$, (c = 0.9, DCM); IR ν_{max} (cm^{-1}) 3339, 3012, 2855, 1730; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (m, 5H), 4.24−4.12 (m, 2H), 3.71 (m, 1H), 3.51 (m, 1H), 3.08 (d, J = 13.4 Hz, 1H), 2.86 (d, J = 13.4 Hz, 1H), 2.15 (bs, 1H), 1.75−1.65 (m, 1H), 1.51−1.42 (m, 1H), 1.27 (t, J = 7.2 Hz, 3H), 0.91 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.3, 137.2, 130.5, 128.3, 126.7, 63.6, 60.7, 52.6, 39.0, 26.5, 14.3, 8.9; HRMS (ES) m/z: [M + H]$^+$ Calcd for $C_{14}H_{21}O_3$ 237.1485; Found 237.1483.

*Ethyl (2S)-2-(Hydroxymethyl)-2-methylhexanoate (**8b**).* Scale: 0.100 g (0.267 mmol) of **5e**; yield of **6b**, 0.053 g, 77% as a clear liquid. Scale: 0.050 g (0.202 mmol) of **6b**; yield of **8b** over two steps, 0.021 g, 55% as a clear oil. $[\alpha]_D^{20} = -2.6$, (c = 1.3, DCM); IR ν_{max} (cm^{-1}) 3337, 2853, 1732; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.17 (q, J = 7.2 Hz, 2H), 3.71 (d, J = 11.2 Hz, 1H), 3.47 (d, J = 11.2 Hz, 1H), 2.16 (bs, 1H), 1.65−1.51 (m, 2H), 1.27 (t, J = 7.2 Hz, 3H), 1.29−1.18 (m, 4H), 1.17 (s, 3H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.4, 68.5, 60.7, 47.8, 35.8, 26.5, 23.3, 19.8, 14.4, 14.0; HRMS (ES) m/z: [M + H]$^+$ Calcd for $C_{10}H_{21}O_3$ 189.1496; Found 189.1491.

*Ethyl (2R)-2-Benzyl-2-(hydroxymethyl)octanoate (**8d**).* Scale: 0.100 g (0.209 mmol) of **5j**; yield of **6d**, 0.051 g, 70% as a yellow liquid. Scale: 0.040 g (0.114 mmol) of **6d**; yield of **8d** over two steps, 0.020 g, 60% as a clear oil in >99% ee. $[\alpha]_D^{20} = -1.4$, (c = 0.85, DCM); IR ν_{max} (cm^{-1}) 3341, 3009, 2856, 1733; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29−7.17 (m, 5H), 4.24−4.11 (m, 2H), 3.71 (d, J = 11.5 Hz, 1H), 3.50 (d, J = 11.5 Hz, 1H), 3.09 (d, J = 13.4 Hz, 1H), 2.86 (d, J = 13.4 Hz, 1H), 2.12 (bs, 1H), 1.67−1.59 (m, 2H), 1.47−1.39 (m, 1H), 1.25 (t, J = 6.8 Hz, 3H), 1.29−1.24 (m, 7H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.5, 137.2, 130.5, 128.3, 126.7, 64.0, 60.7, 52.3, 39.4, 33.8, 31.8, 30.0, 24.5, 22.7, 14.3, 14.2; HRMS (ES) m/z: [M + H]$^+$ Calcd for $C_{18}H_{29}O_3$ 293.2111; Found 293.2108.

*Ethyl (2S)-2-Benzoyloxymethyl-2-propyloctanoate (**9**).* Scale: 0.100 g (0.233 mmol) of **5i**; yield of **6c**, 0.062 g, 89% as a yellow liquid. Scale: 0.037 g (0.123 mmol) of **6c** gave crude alcohol **8c**, to which in DCM (1.0 mL) at 0 °C was added benzoyl chloride (29.0 μL, 0.246 mmol, 2.0 equiv), and the contents were allowed to warm to rt. After 2 h, the contents were quenched with sat. $NaHCO_3$ (10 mL) and extracted with EtOAc (3 × 15 mL), the organic extracts were dried over $MgSO_4$ and filtered under vacuum, and the organic solvent was removed *in vacuo*. The crude residue was chromatographed using EtOAc/hexane mixtures to afford benzoate **9** (yield 0.023 g, 54% over three steps from **6c**) as a colorless oil in 94% ee. $[\alpha]_D^{20} = -8.0$, (c = 0.65, DCM); IR ν_{max} (cm^{-1}) 3013, 2855, 1733, 1720; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (m, 2H), 7.56 (m, 1H), 7.44 (m, 2H), 4.44 (s, 2H), 4.17 (q, J = 7.1 Hz, 2H), 1.71−1.65 (m, 4H), 1.27 (m, 10H), 1.24 (t, J = 7.1 Hz, 3H), 0.91 (t, J = 7.3 Hz, 3H), 0.85 (t, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.0, 166.4, 133.1, 130.4, 129.7, 128.6 65.8, 60.7, 49.7, 36.0, 33.7, 31.7, 29.8, 24.0, 22.7, 17.5, 14.7, 14.4, 14.1; HRMS (ES) m/z: [M + H]$^+$ Calcd for $C_{21}H_{33}O_4$ 349.2373; Found 349.2377.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra and HPLC traces of all compounds, and X-ray data for **5d** and **5f** are presented. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Fax: +27 21 650 5195. E-mail: Roger.Hunter@uct.ac.za (R.H.).

Notes

The authors declare no competing financial interest.

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