CHAPTER 4

Enantioselective Allylic Alkylations of Vinylogous β-Ketoester Derivatives: Total Synthesis of (+)-Carissone[†]

4.1 INTRODUCTION

Cyclic, unsaturated ketones possessing γ-substitution (e.g., **261**) are highly useful intermediates for applications in complex molecule synthesis (Figure 4.1.1).[1] Such γ-substituted enone moieties are typically accessed via transformations of masked, cyclic 1,3-dicarbonyl compounds made popular by Stork and Danheiser.[2] These so-called vinylogous esters (e.g., **259**) enable the regioselective functionalization of the ring, and are amenable to the preparation of numerous compounds possessing an array of substitution. A principle challenge to accessing members of this substrate class is the stereoselective construction of a quaternary stereocenter at the γ-position of the enone.[3] Although methods for the asymmetric introduction of this moiety exist,[4] we envisioned

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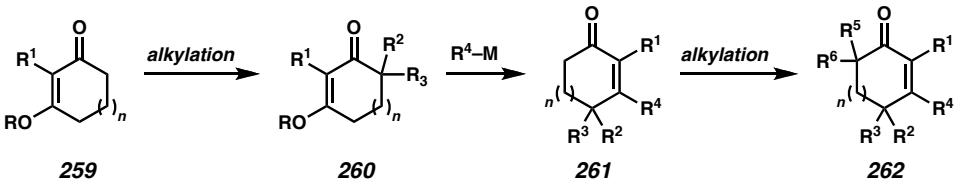
[†] Studies toward the synthesis of (+)-carissone were performed primarily by Samantha R. Levine as a Marcella R. Bonsall Summer Undergraduate Research Fellow and partially sponsored by the Dalton Fund. Portions of this work were also conducted in collaboration with Krastina V. Petrova and Justin T. Mohr. These works have been published. See: (a) Levine, S. R.; Krout, M. R.; Stoltz, B. M. *Org. Lett.* **2009**, *11*, 289–292. (b) Petrova, K. V.; Mohr, J. T.; Stoltz, B. M. *Org. Lett.* **2009**, *11*, 293–295.

an enantioselective approach that harnesses the palladium-catalyzed alkylation methodology that has recently been developed in our laboratory.[5] Herein, we detail our investigations of this important class of substrates and uncover a complex interplay between reaction selectivity and substrate structure and electronics.

Figure 4.1.1. Representative transformations of vinylogous esters.



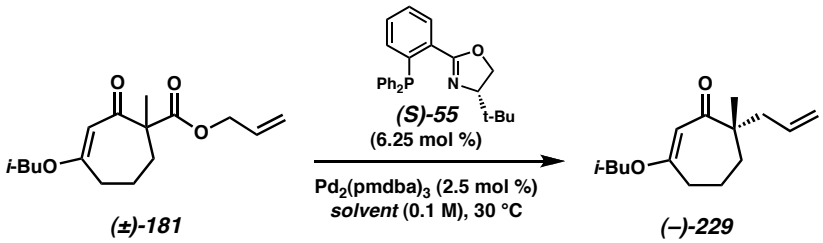
4.2 ENANTIOSELECTIVE DECARBOXYLATIVE ALKYLATIONS OF VINYLOGOUS β-KETOESTER DERIVATIVES

Our explorations of the asymmetric alkylation of vinylogous esters focused on the application of racemic β-ketoester derivatives. These substrates offer a practical advantage over enol carbonate and silyl enol ether substrates due to their ease of preparation and purification, as well as increased stability as enolate precursors.[6] The design of methods directed toward the preparation and functionalization of seven-membered rings en route to the synthesis of natural products is an ongoing area of research in our laboratory,[7] and thus our asymmetric alkylation studies initiated with the seven-membered ring vinylogous ester substrate class.

4.2.1 EFFECT OF SOLVENT

The optimization of the decarboxylative alkylation of vinylogous ester derivatives centered on vinylogous β-ketoester (±)-**181** (Table 4.2.1). Exposure of this substrate to our typical reaction conditions employing a palladium(0) catalyst and (*S*)-*t*-Bu-PHOX ((*S*)-**55**) in THF at 30 °C smoothly generated α-quaternary ketone **229** in 94% yield and 84% ee (entry 1). While this substrate class exhibited good reactivity, the selectivity provided by ligand **55** was lower than anticipated. Previous studies in our laboratory have established a minor role of solvent for selectivity of the asymmetric alkylation reactions,[5a] although in certain circumstances solvent can have a notable effect on selectivity.[5c] Accordingly, a survey of common reaction solvents revealed similar yields of ketone **229** with a distinct enhancement in selectivity. The use of ethereal solvents provided a modest increase in enantioselectivity, with conditions in Et_2O producing **229** in 86% ee (entries 2–5). Substitution with aromatic solvents benzene and toluene enabled a more substantial improvement in selectivity, with up to 88% ee in toluene (entries 6 and 7). Our results indicate that alkylations of substrates such as **181** are readily influenced by solvent, and thus it is a necessary variable for future vinylogous β-ketoester studies.

*Table 4.2.1. Solvent screen for the Pd-catalyzed alkylation of vinylogous β-ketoester (±)-**181***



entry[a]	solvent	yield (%)[b]	ee (%)[c]
1	THF	94	84
2	1,4-dioxane	86	84
3	2-methyl THF	75	85
4	TBME	88	85
5	Et_2O	93	86
6	benzene	84	86
7	toluene	91	88

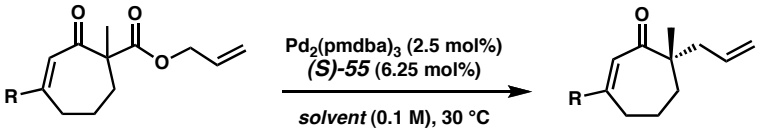
[a] pmdba = bis(4-methoxybenzylidene)acetone. [b] Isolated yield. [c] Enantiomeric excess determined by chiral HPLC.

4.2.2 EFFECT OF SUBSTRATE SUBSTITUTION

In addition to the optimization of solvent for the alkylation selectivity, we also examined the identity of the vinylogous moiety. The vinylogous ester substrate class contrasts most other substrates that we have examined in that they allow structural variations while maintaining similar functional reactivity for subsequent transformations. For example, the vinylogous ester **259** depicted in Figure 4.1.1 could possess OR where R = Me, Et, and *i*-Bu, and all three substrates would be unique, yet could function in a similar manner for each subsequent transformation, ultimately providing the same product at the end of the reaction sequence (i.e., **261**). This significant feature greatly expands the substrate potential for the transformation and allows the examination of the role of electronics toward reactivity and selectivity.

In our studies of vinylogous β-ketoester derivatives, we observed that substitution of the R group with ether derivative **263** furnished quaternary ketone **264** in similar selectivity (cf. entries 1–3, Table 4.2.2). Modification of the ether group to an acyl functionality facilitated the construction of ketones **266** and **268** with enhanced selectivity (88 and 90% ee, respectively), with benzoate **268** providing the best results (entries 4–6). The use of a thiophenyl-derived vinylogous ester **269** produced a similar result, affording vinylogous thioester **270** in 89% ee (entry 7). This limited data set demonstrates that reducing the electron density of the vinylogous moiety results in a marked improvement in selectivity and facilitates an increase in the reaction rate.[8] We can rationalize the electronic role of substitution and reaction rate as a decrease in the energy required for the cleavage of a C–C bond in the decarboxylation event.[9] However, the influence on selectivity is complex. As we descend down each entry in Table 4.2.2, the resulting enolate p*Ka* is distinctly reduced, suggesting that the electronics of the palladium–enolate complex impact the reaction such that an electron-deficient complex enhances selectivity,[10] although the exact correlation is difficult to discern.[11] Nonetheless, the versatile nature of this substrate class holds the potential for interesting applications.

Table 4.2.2. Variation of the vinylogous functional group for improved stereoselectivity



entry	R	substrate	product	solvent	yield (%)[a]	ee (%)[b]
1	*i*-BuO	***181***	***229***	THF	94	84
2	*i*-BuO	***181***	***229***	Et_2O	93	86
3	CH_3OCH_2O	***263***	***264***	THF	79	85
4	*t*-$BuCO_2$	***265***	***266***	THF	68	87
5	*t*-$BuCO_2$	***265***	***266***	Et_2O	84	88
6	$PhCO_2$	***267***	***268***	THF	85	90
7[c]	PhS	***269***	***270***	Et_2O	86	89

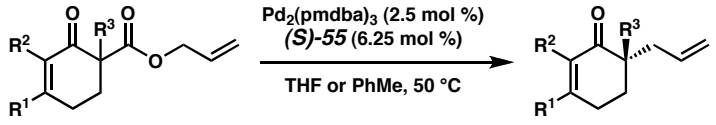
[a] Isolated yield. [b] Enantiomeric excess determined by chiral HPLC. [c] Using $Pd(dmdba)_2$ at 25 °C.

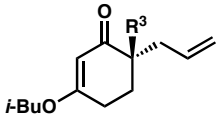
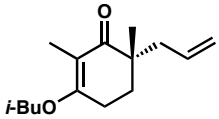
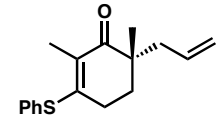
4.2.3 EXTENSIONS TO SIX-MEMBERED RINGS

The established viability of seven-membered vinylogous β-ketoester substrates for our asymmetric alkylation method encouraged the extension to six-membered derivatives. Application of the six-membered analog **271** with our standard conditions required an increase in reaction temperature to 50 °C to achieve complete conversion to ketone **272**, although with a noticeable decrease in selectivity to 83% ee (entry 1, Table 4.2.3). Solvent identity displays a key role for six-membered substrates, as the use of toluene for the production of **272** increased the selectivity to 86% ee (entry 2). Moreover, substitution at the α-position of the β-ketoester to an ethyl group afforded ketone **274** in 86% ee (entry 3).[12] Examination of substrates that possess substitution α to the vinylogous moiety afforded strikingly different results. Substrate reactivity for the production of vinylogous ester **275** was exceedingly slow at 50 °C, and an increase to 80 °C facilitated complete conversion to **276** with a modest 75% ee (entries 4 and 5).

However, the utilization of a vinylogous thioester **277** enabled complete conversion at 50 °C to α-quaternary vinylogous thioester **278** in a remarkable 92% ee, with an absence of solvent influence (entries 6 and 7).

Table 4.2.3. Six-membered vinylogous β-ketoester substrates



entry	product	R^3	substrate	product	solvent	yield (%)	ee (%)
1		Me	***271***	***272***	THF	80	83
2		Me	***271***	***272***	toluene	79	86
3[a]		Et	***273***	***274***	THF	82	86
4[b]			***275***	***276***	toluene	19	79
5[c]			***275***	***276***	toluene	86	75
6			***277***	***278***	toluene	86	92
7			***277***	***278***	THF	88	92

[a] Reaction performed using 5 mol % $Pd(dmdba)_2$. [b] β-ketoester starting material was isolated in 69% yield. [c] At 80 °C.

In general, substrates that possess a six-membered ring require additional energy to break the C–C bond in the decarboxylation event of the β-ketoester compared to seven-membered rings, resulting in increased reaction temperatures and times (see the subsection 4.3.3.1).[13] A comparison of substrates **271** and **275** underscores the difference in reactivity and selectivity resulting from the addition of a methyl group to the α-position (cf. entries 2 and 4). Moreover, adjusting the electronics of the vinylogous moiety exhibits a large impact on selectivity (cf. entries 4 and 6). Taken together, these

seemingly trivial substrate changes have a significant impact on reactivity and selectivity, making it difficult to delineate reaction trends.

4.2.4 FUTURE STUDIES OF VINYLOGOUS β-KETOESTER SUBSTRATES

Our preliminary asymmetric alkylation studies of vinylogous β-ketoester substrates have displayed a range of selectivities and reactivities, indicating a complex role of substrate structure and electronics of the vinylogous moiety. Future efforts for this class of substrates will expand on substrate substitution for both seven and six-membered rings to examine the generality of the transformation. In addition to the increase in number of substrates, a thorough investigation encompassing solvent variation and substrate electronics could enable the development of predictive tools for general use. Furthermore, the utility of enol carbonate vinylogous ester derivatives and ligands possessing variable electronic properties are viable options for challenging substrates.[10] The elaboration of the various vinylogous products obtained from the asymmetric alkylation reaction into useful intermediates is of importance for the utility of this class of molecules. Importantly, the reactivities and selectivities observed for the vinylogous ester derivatives provide access to a variety of enantioenriched α-quaternary enones using Stork–Danheiser chemistry and provide a firm precedent for future studies.

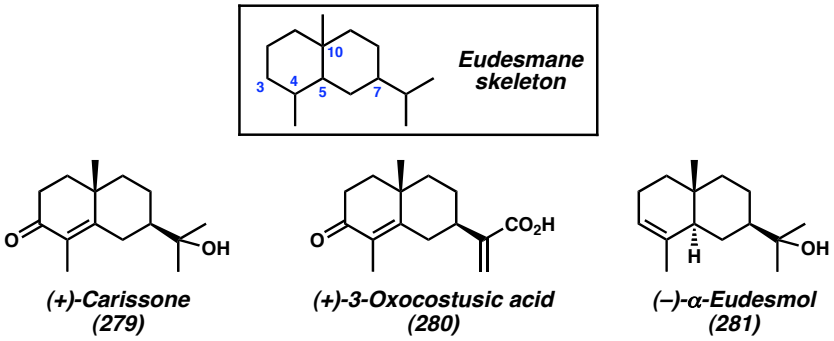
4.3 CATALYTIC ENANTIOSELECTIVE APPROACH TO THE EUDESMANE SESQUITERPENOIDS

The production of highly enantioenriched materials from the enantioselective alkylation of vinylogous β-ketoester derivatives enables their use for various applications. Specifically, we sought to harness this transformation as the key enantioselective reaction in a multistep synthesis. Here we detail our efforts to utilize the asymmetric alkylation of vinylogous β-ketoester derivatives toward a general approach to the eudesmane sesquiterpenoids.

4.3.1 BACKGROUND OF THE EUDESMANE SESQUITERPENOIDS

The flowering plants of the family Asteraceae (Compositae) have many historical uses, including rubber, medicines, edible oils and vegetables, and pesticides.[14] Among these floras are a large number of species abundant in structurally diverse sesquiterpenoids, particularly ones that contain the eudesmane skeleton (Figure 4.3.1). Over 1000 eudesmanes have been identified from these sources with their structures diverging based on oxygenation and oxidation patterns within the carbon framework.

Figure 4.3.1. Representative eudesmane sesquiterpenoids.



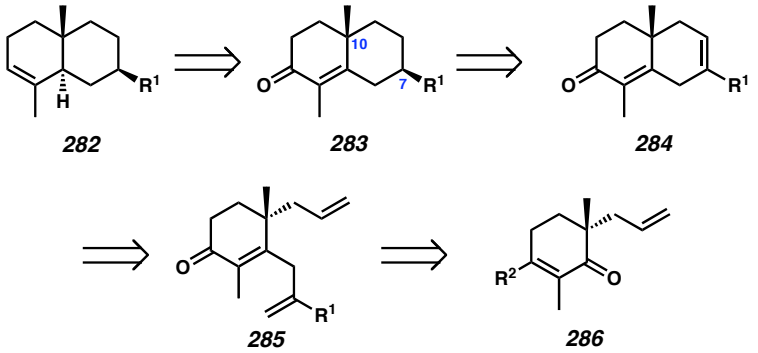
(+)-Carissone (279) ***(+)-3-Oxocostusic acid (280)*** ***(–)-α-Eudesmol (281)***

This ever-growing[15] class of important secondary metabolites possesses a wide range of biological properties including plant growth inhibition, insect antifeedant, antibacterial, antifungal, and antitumor activities. Representative eudesmanes comprise antibacterial agents (+)-carissone (**279**)[16] and (+)-3-oxocostusic acid (**280**),[17] as well as P/Q-type calcium channel blocker (–)-α-eudesmol (**281**)[18] (Figure 4.3.1). These examples typify common structural motifs within this class of sesquiterpenoids, primarily the C(10) all-carbon quaternary stereocenter and stereogenic C(7) substituent. The structural similarities and interesting biology associated with this class of molecules has stimulated several synthetic efforts, most of which employ semisynthetic or chiral pool strategies.[19,20,21] To date, no catalytic asymmetric approach toward these eudesmanes has been developed. Herein, we report an approach[22] that incorporates our recent method for the catalytic asymmetric formation of enantioenriched all-carbon quaternary stereocenters into a general synthetic strategy for this class of sesquiterpenoids.

4.3.2 RETROSYNTHETIC ANALYSIS OF THE EUDESMANE CARBOCYCLIC CORE

In devising a strategy to access the eudesmanes, we simplified our target structure to enone **283**, which has been utilized in the preparation of structures such as **282**[19e] and embodies many features present in various family members (cf. **283** and **279**, **280**) (Scheme 4.3.1). We envisioned that the stereochemistry of the C(7) substituent could arise by means of the diastereoselective hydrogenation of a substituted cyclohexene (i.e., **284**), the stereochemical outcome of which would be controlled by the C(10) quaternary stereocenter. This cyclohexene could be obtained from a ring-closing metathesis of triolefin **285**, which would be derived from an appropriately substituted α-quaternary ketone (i.e., **286**). Thus, we sought to develop an efficient and selective preparation of the C(10) quaternary stereocenter[3] as the key control element in our synthetic approach toward the eudesmanes.

Scheme 4.3.1. Retrosynthetic analysis of the eudesmanes



4.3.3 TOTAL SYNTHESIS OF (+)-CARISSONE

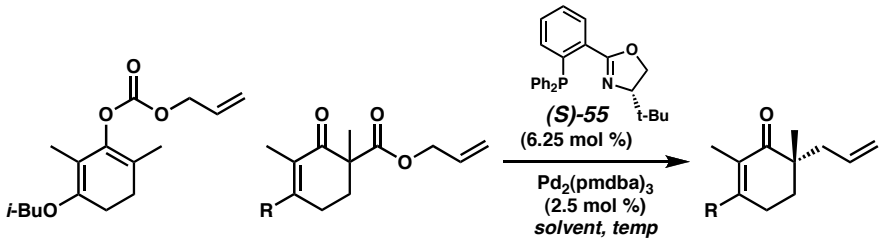
4.3.3.1 Pd-CATALYZED ENANTIOSELECTIVE ALKYLATION OF VINYLOGOUS ESTER DERIVATIVES

The enantioselective alkylation of ketone enolates is an area of intense investigation in our laboratory.[5] This method has resulted in the preparation of a wide range of carbonyl compounds with adjacent quaternary stereocenters with high levels of selectivity and excellent yields, some of which have proved valuable in synthetic endeavors.[7e,10b,23] The application of α-quaternary ketones such as **286** for the devised strategy would require a carbonyl transposition (i.e., **286** → **285**), and we therefore chose to exploit the unique properties of vinylogous esters (i.e., **286** where R^2 = OR) pioneered by Stork and Danheiser[2] for this purpose.

Our initial studies for the asymmetric generation of quaternary stereocenters utilizing vinylogous ester derivatives focused on enol carbonates due to preliminary investigations[4a,10b] that have demonstrated successes for similar substrates. Exposure of allyl enol carbonate **287** to typical reaction conditions consisting of a palladium(0) catalyst and ligand (*S*)-**55**[24] in toluene generated vinylogous ester (+)-**276**, albeit in variable yield and selectivity (Table 4.3.1, entry 1). Unfortunately, the instability of **287** impeded further studies, as these results were highly dependent on the composition of this enol carbonate.[25] Given the range of substrate possibilities for this transformation,[5d] we next focused on racemic β-ketoester (±)-**275**. Surprisingly, this substrate proved only modestly reactive at 50 °C, producing ketone **276** in 19% yield and 79% ee (entry 2).[26] Increasing the reaction temperature to 80 °C enabled complete conversion to ketone **276**, although with slightly reduced selectivity (entry 3). As the lack of reactivity seemed to

be a major complication with this substrate, we considered vinylogous thioesters (i.e., (±)-**277**) for their reported activation properties.[4a] Indeed, racemic β-ketoester (±)-**277** did prove more reactive and produced ketone (+)-**278** at 50 °C in good yield and 92% ee (entry 4). A screen of solvents revealed that benzene (entry 5) and ethereal solvents (entries 6 and 7) provided similar selectivities to toluene.

Table 4.3.1. Asymmetric allylation of vinylogous ester derivatives



287 ***R = Oi-Bu, (±)-275*** ***R = SPh, (±)-277*** ***R = Oi-Bu, (+)-276*** ***R = SPh, (+)-278***

entry	substrate	solvent	T (°C)	product	yield[a] (%)	ee[b] (%)
1	***287***	toluene	25	***276***	22–61	84–88
2	***275***	toluene	50	***276***	19[c]	79
3	***275***	toluene	80	***276***	86	75
4	***277***	toluene	50	***278***	86	92
5	***277***	benzene	50	***278***	61[d]	92
6	***277***	THF	50	***278***	88	92
7	***277***	1,4-dioxane	50	***278***	90	91

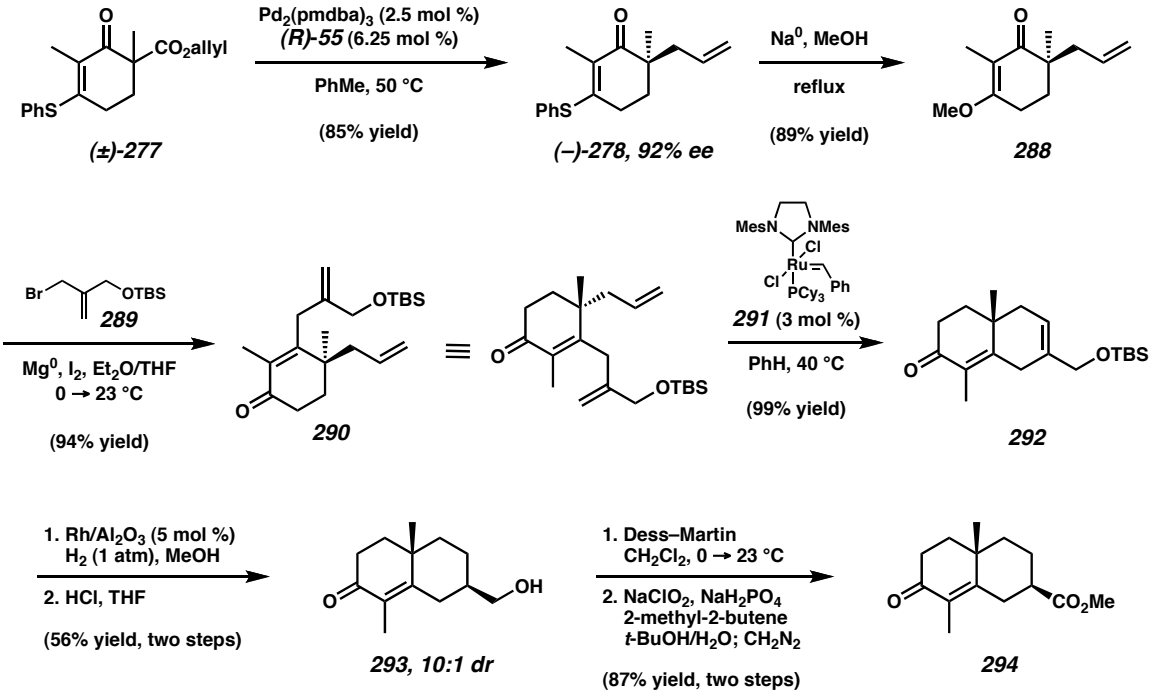
[a] Isolated yields. [b] Enantiomeric excess determined by chiral HPLC or SFC. [c] β-Ketoester (±)-***275*** was recovered in 69% yield. [d] β-Ketoester (±)-***277*** was recovered in 26% yield.

4.3.3.2 PREPARATION OF THE BICYCLIC CORE

With optimal conditions for the preparation of **278**, we sought to demonstrate the feasibility of using this ketone for the total synthesis of (+)-carissone (**279**). Accordingly, racemic β-ketoester (±)-**277** was transformed to (–)-**278** in 85% yield[27] and 92% ee using ligand (*R*)-**55** to correlate with the natural antipode of **279** (Scheme 4.3.2). Subsequent

conversion of vinylogous thioester **278** into vinylogous ester **288** was achieved with sodium methoxide in refluxing methanol. Exposure of the resulting vinylogous ester to the substituted allylmagnesium bromide generated from **289**[28] provided enone **290** in 94% yield. We were encouraged by the success of allylmagnesium bromide additions to vinylogous ester **288** and investigated similar reactions of various organometallic reagents with vinylogous thioester **278**; however, several conditions afforded intractable mixtures with no desired products.[29] Nonetheless, ring-closing metathesis of enone **290** using Grubbs' catalyst **291**[30] efficiently prepared the desired substrate (i.e., **292**) for the diastereoselective hydrogenation. Gratifyingly, the heterogeneous hydrogenation of **292** utilizing Rh/Al_2O_3 catalyst[31] in methanol and subsequent TBS cleavage provided alcohol **293** in good overall yield with excellent diastereoselectivity.[32] This notable transformation generates alcohol **293** with the C(10) and C(7) stereocenters in the desired syn configuration required for **279**. Conversion of alcohol **293** to ester **294** was achieved by a two-step process involving Dess–Martin oxidation,[33] followed by chlorite oxidation[34] with diazomethane workup.

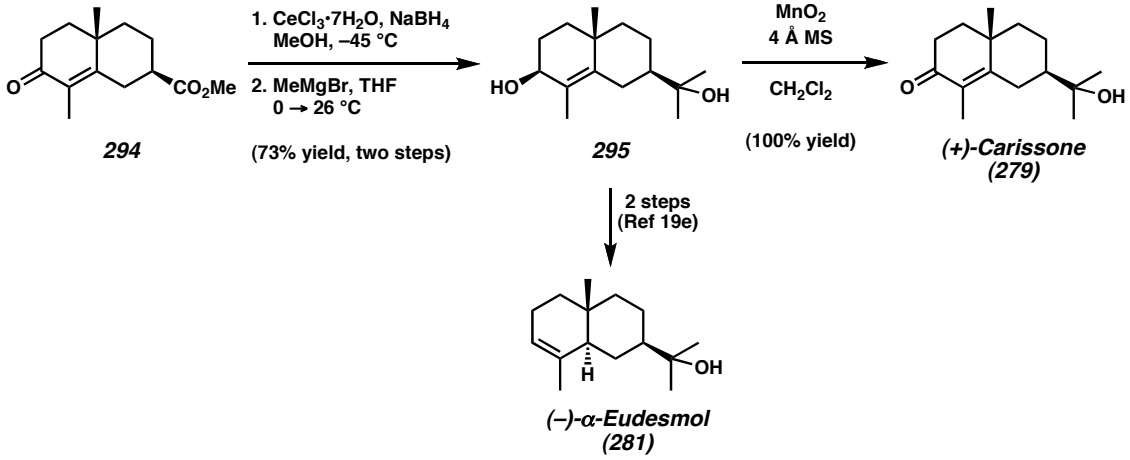
Scheme 4.3.2. Enantioselective synthesis of the eudesmane bicyclic core



4.3.3.3 COMPLETION OF (+)-CARISSONE AND A FORMAL SYNTHESIS OF (–)-α-EUDESMOL

The availability of ester **294** in the desired configuration enabled preparation of (+)-carissone (**279**) in short order. Diastereoselective reduction of the enone carbonyl under Luche conditions,[35] followed by treatment of the resulting alcohol with methylmagnesium bromide[21f] provided diol **295**[19a] in 73% yield (Scheme 4.3.3). The preparation of this diol intersects Aoyama's synthesis (–)-α-eudesmol (**281**)[19e] and represents a formal total synthesis. Furthermore, facile allylic oxidation with manganese dioxide gave (+)-carissone (**279**) having spectroscopic data (^{1}H NMR, ^{13}C NMR, IR, HRMS, optical rotation) identical to those reported for natural **279**.

*Scheme 4.3.3. End game for (+)-carissone (**279**) and the formal synthesis of (–)-α-eudesmol (**281**)*



4.4 CONCLUSION

In summary, we have described the palladium-catalyzed asymmetric alkylation of various vinylogous β-ketoester substrates to provide access to enantioenriched α-quaternary ketones in high yields. Our studies revealed a significant influence of solvent, substrate structure, and electronics on the reactivity and selectivity of the transformation. Importantly, the incorporation of electron-withdrawing groups on the vinylogous moiety increases reaction rates and enhances selectivities over tradition vinylogous esters. We have demonstrated the utility of the resulting α-quaternary products in a general synthetic approach for the total synthesis of the eudesmane sesquiterpenoids. Fundamental to this strategy is the use of the resulting C(10) quaternary stereocenter to control the C(7) stereochemistry via a diastereoselective hydrogenation, providing a highly selective and efficient route to the antibacterial agent (+)-carissone (**279**). Studies to understand the interplay between substrate reactivity and selectivity for the asymmetric alkylation of vinylogous ester derivatives, as well as the

use of the resulting enantioenriched products in the synthesis of other bioactive natural substances, are currently underway.

4.5 EXPERIMENTAL SECTION

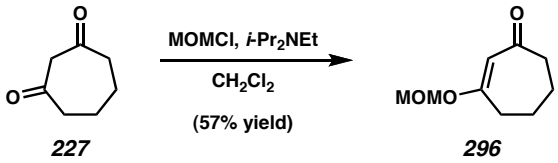
4.5.1 MATERIALS AND METHODS

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon. All the starting materials were purchased from commercial sources and used as received, unless otherwise stated. Liquids and solutions were transferred via syringe or positive-pressure cannulation. Brine solutions refer to saturated aqueous sodium chloride solutions. TMEDA was distilled from sodium under nitrogen prior to use. Benzenethiol was distilled under nitrogen prior to use. For data regarding the conversion of (±)-**181** to (–)-**229**, see Chapter 3 of this thesis. Previously reported methods were used to prepare (*S*)-*t*-BuPHOX ((*S*)-**55**) and (*R*)-*t*-BuPHOX ((*R*)-**55**),[36] as well as $Pd_2(pmdba)_3$.[37] Grubbs' catalyst **291** was a generous gift from Materia, Inc. Rhodium was purchased from Strem as a 1 wt % loading on alumina powder in reduced form. Diazomethane (**199**) was freshly prepared from Diazald as a solution in Et_2O. Manganese dioxide was purchased from Aldrich in activated form, ~85%, <5 μm, and used as received. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, anisaldehyde, or $KMnO_4$ staining. SiliCycle SiliaFlash P60 Academic Silica Gel (particle size 40–63 μm; pore diameter 60 Å) was used for flash chromatography. Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing Chiralpak AD and OD-H columns

(4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. with 1 mL/min flow rate and visualization at 254 nm. Analytical chiral supercritical fluid chromatography was performed with a Berger Analytix SFC (Thar Technologies) utilizing a Chiralpak AD-H column (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. with 2 mL/min flow rate at 30 °C and visualization at 244 nm. Optical rotations were measured with a Jasco P-1010 polarimeter at 589 nm in spectrophotometric grade solvents. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz and 75 MHz respectively) or a Varian Inova 500 (at 500 MHz and 126 MHz, respectively), and are reported relative to Me_4Si (δ 0.0 ppm).[38] Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicity and qualifier abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, comp = complex, br = broad, app = apparent. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). Melting points are uncorrected. High-resolution mass spectra were obtained from the Caltech Mass Spectral Facility

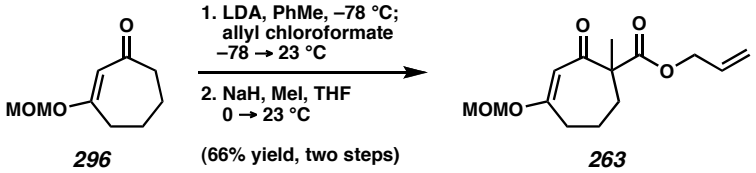
4.5.2 PREPARATIVE PROCEDURES

4.5.2.1 ASYMMETRIC ALKYLATION OF VINYLOGOUS β-KETOESTER DERIVATIVES



227 *296*

Vinylogous ester 296. To a solution of dione **227** (574.6 mg, 4.55 mmol, 1.0 equiv) in CH_2Cl_2 (22.8 ml, 0.2 M) was added MOM-Cl (381 μL, 5.01 mmol, 1.1 equiv) followed by *i*-Pr_2NEt (873 μL, 5.01 mmol, 1.1 equiv). After 12 h the reaction was diluted with CH_2Cl_2 (25 mL), washed with 1 N HCl, sat aq $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude material was purfied by flash chromatography on SiO_2 (4:1 → 2:1 hexanes/EtOAc) to give **296** (441.9 mg, 2.596 mmol, 57% yield) as a pale yellow oil. R_f = 0.16 (2:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.50 (s, 1H), 4.97 (s, 2H), 3.43 (s, 3H), 2.59–2.55 (comp m, 4H), 1.90–1.74 (comp m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.4, 173.8, 108.0, 94.2, 57.0, 42.0, 32.9, 23.8, 21.4; IR (Neat Film NaCl) 2942, 1645, 1611, 1454, 1376, 1215, 1153, 1071, 972, 924 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_9H_{15}O_3$ $[M + H]^+$: 171.1021, found 171.1055.

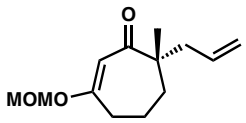


296 (66% yield, two steps) *263*

Vinylogous β-ketoester 263. To a solution of *i*-Pr_2NH (764 μL, 5.45 mmol, 2.1 equiv) in PhMe (18 mL) cooled to –78 °C was added a solution of *n*-BuLi (2.09 mL of a 2.55 M solution in hexane, 5.32 mmol, 2.05 equiv). The flask was placed in a 0 °C cooling bath for 10 min, cooled back down to –78 °C, and to this was added a solution of vinylogous ester **296** (441.9 mg, 2.60 mmol, 1.0 equiv) in PhMe (2 mL, wash with extra 2 mL). After 30 min, allyl chloroformate (290 μL, 2.73 mmol, 1.05 equiv) was added dropwise and the bath was removed. The reaction was quenched with 1 N $KHSO_4$ (15 mL) after stirring at room temperature for 30 min, the layers were separated, and the aq was extracted with CH_2Cl_2 (3 x 15 mL). The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo.

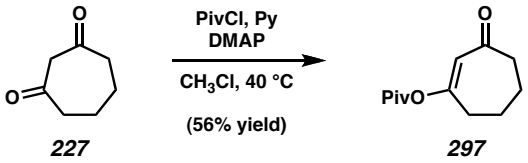
The resulting crude oil was dissolved in THF (5.2 mL, 0.5 M) and cooled to 0 °C in an ice bath. To this was added NaH (124.6 mg, 3.12 mmol, 1.2 equiv) in one portion, and after 30 min, MeI (485 μL, 7.79 mmol, 3.0 equiv) was added and the cooling bath was removed. After 4 h, the reaction was quenched with 50% sat. aq NH_4Cl (15 mL) and diluted with Et_2O (15 mL), the layers were separated, and the aq was extracted with Et_2O (3 x 15 mL). The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude was purified by flash chromatography on SiO_2 (6:1 → 3:1 → 2:1 hexanes/EtOAc) to afford vinylogous β-ketoester **263** (459.6 mg, 1.71 mmol, 66% yield over two steps) as a colorless oil. R_f = 0.22 (4:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.87 (dddd, *J* = 17.2, 10.4, 5.6, 5.6 Hz, 1H), 5.57 (d, *J* = 1.1 Hz, 1H), 5.29 (app dq, *J* = 17.2, 1.6 Hz, 1H), 5.21 (app dq, *J* = 10.4, 1.3 Hz, 1H), 4.99 (d, *J* = 6.1 Hz, 1H), 4.96 (d, *J* = 6.1 Hz, 1H), 4.66–4.52 (comp m, 2H), 3.43 (s, 3H), 2.61 (dddd, *J* = 18.1, 9.8, 4.1, 1.2 Hz, 1H), 2.48–2.38 (comp m, 2H), 2.06–1.92 (m, 1H), 1.87–

1.64 (comp m, 2H), 1.43 (s, 3H); IR (Neat Film NaCl) 2938, 1734, 1649, 1617, 1454, 1423, 1379, 1234, 1147, 1114, 1069, 966, 926, 861 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{14}H_{21}O_5$ $[M + H]^+$: 269.1389, found 269.1381.



264

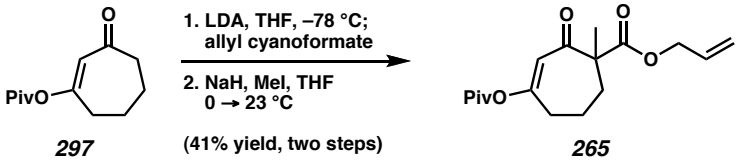
Vinylogous ester 264. A typical asymmetric alkylation reaction was run on 28.6 mg (0.100 mmol) of **263** at 30 °C in THF (0.1 M) for 9 h using (*S*)-**55** and $Pd_2(pmdba)_3$. The crude material was purified by flash chromatography on SiO_2 (6:1 hexanes/EtOAc, PhMe load) to provide **264** (17.8 mg, 0.0794 mmol, 79% yield) as a pale yellow oil. $R_f = 0.31$ (1:1 hexanes/EtOAc); IR (Neat Film NaCl) 2934, 1620, 1454, 1389, 1216, 1148, 1067, 992, 957, 924, 879 cm^{-1}. HPLC conditions: 0.5% EtOH in hexanes, OD-H column, t_R (min): major = 12.69, minor = 13.59.



227 ***297***

Vinylogous pivalate 297. To a solution of diketone **227** (229.7 mg, 1.82 mmol, 1.0 equiv) dissolved in $CHCl_3$ (9.1 mL, 0.2 M) was added pyridine (147 μL, 1.82 mmol, 1.0 equiv), PivCl (247 μL, 2.00 mmol, 1.1 equiv), and DMAP (44.5 mg, 0.364 mmol, 0.2 equiv), and the resulting solution was placed in a 40 °C oil bath. After 24 h, the reaction was diluted with CH_2Cl_2 (10 mL), washed with 1 N HCl (10 mL), then sat. aq $NaHCO_3$ (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude oil was

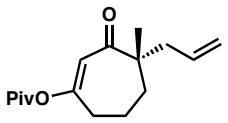
purified by flash chromatography on SiO_2 (9:1 → 6:1 hexanes/EtOAc, PhMe load) to give **297** (213.2 mg, 1.01 mmol, 56% yield) as a colorless oil. R_f = 0.23 (6:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.80–5.79 (m, 1H), 2.64 (dd, *J* = 7.0, 5.4 Hz, 2H), 2.58 (dd, *J* = 6.7, 5.5 Hz, 2H), 1.97–1.81 (comp m, 4H), 1.24 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.7, 176.3, 167.5, 122.1, 43.2, 39.1, 33.4, 27.0, 24.4, 21.7; IR (Neat Film NaCl) 2974, 2938, 2873, 1749, 1667, 1650, 1481, 1458, 1369, 1275, 1114 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{12}H_{18}O_3$ $[M]^+$: 210.1256, found 210.1253.



297 ***265***

Vinylogous β-ketoester 265. To a solution of *i*-Pr_2NH (333 μL, 2.38 mmol, 1.2 equiv) in THF (8 mL) at 0 °C was added a solution of *n*-BuLi (890 μL of a 2.45 M solution in hexane, 2.18 mmol, 1.1 equiv). After 30 min, the solution was cooled to –78 °C and a solution of vinylogous pivalate **297** (416.5 mg, 1.98 mmol, 1.0 equiv) in THF (2 mL) was added dropwise via cannula transfer. After 1 h at –78 °C, allyl cyanoformate (237 μL, 2.18 mmol, 1.1 equiv) was added. After 30 min the reaction was quenched with 50% sat. aq NH_4Cl (10 mL) and warmed to room temperature. The layers were separated and the aq layer was extracted with Et_2O (3 x 15 mL), the combined organics were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography on SiO_2 (9:1 → 3:1 hexanes/Et_2O) to provide the desired acylated intermediate (274.0 mg, 0.93 mmol, 47% yield).

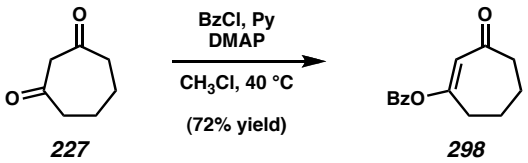
The resulting intermediate was dissolved in THF (4.7 mL, 0.2 M) and cooled to 0 °C, at which point NaH (44.7 mg, 1.12 mmol, 1.2 equiv) was added in one portion. After 20 min, MeI (173 μL, 2.79 mmol, 3.0 equiv) was added and the cooling bath was removed. The reaction was quenched with 50% sat. aq NH_4Cl after 10 h, diluted with Et_2O (10 mL), the layers were separated and the aq layer was extracted with Et_2O (3 x 10 mL). The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated to a crude oil. Purification by flash chromatography on SiO_2 (9:1 → 6:1 hexanes/Et_2O) provided vinylogous β-ketoester **265** (253.2, 0.821 mmol, 41% yield over two steps) as a colorless oil. R_f = 0.34 (3:1 hexanes/Et_2O); ^1H NMR (300 MHz, $CDCl_3$) δ 5.87 (dddd, *J* = 17.2, 10.4, 5.7, 5.7 Hz, 1H), 5.83 (d, *J* = 1.0 Hz, 1H), 5.29 (app dq, *J* = 17.2, 1.5 Hz, 1H), 5.21 (app dq, *J* = 10.4, 1.3 Hz, 1H), 4.62 (app dt, *J* = 5.6, 1.4 Hz, 2H), 2.61 (dddd, *J* = 18.6, 8.7, 4.3, 1.4 Hz, 1H), 2.50–2.39 (comp m, 2H), 2.07–1.94 (m, 1H), 1.91–1.81 (m, 1H), 1.76 (ddd, *J* = 11.0, 7.6, 2.9 Hz, 1H), 1.43 (s, 3H), 1.24 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.9, 176.1, 173.2, 164.6, 131.8, 121.0, 118.5, 66.1, 66.0, 60.0, 39.2, 34.0, 33.7, 27.0, 23.5, 21.6, 15.4; IR (Neat Film NaCl) 2977, 2934, 1746, 1685, 1650, 1454, 1379, 1274, 1233, 1180, 1103, 1027, 980, 909 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{17}H_{25}O_5$ $[M + H]^+$: 309.1702, found 309.1619.



266

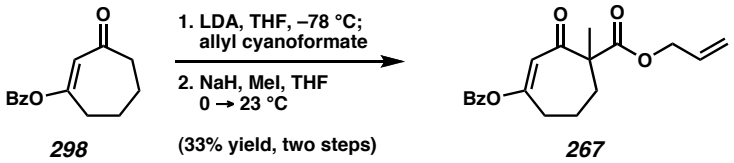
Vinylogous pivalate 266. A typical asymmetric alkylation reaction was run on 42.0 mg (0.136 mmol) of **265** at 30 °C in Et_2O (0.1 M) for 2 h using (*S*)-**55** and $Pd_2(pmdba)_3$. The crude material was purified by preparative TLC on SiO_2 (3:1

hexanes/Et_2O) to provide **266** (30.2 mg, 0.114 mmol, 84% yield) as a pale yellow oil. R_f = 0.34 (1:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.72–5.71 (m, 1H), 5.70 (dddd, *J* = 16.6, 10.5, 7.4, 7.4 Hz, 1H), 5.08–5.06 (m, 1H), 5.05–5.06 (m, 1H), 5.05–5.00 (m, 1H), 2.49 (dd, *J* = 6.3, 5.3 Hz, 2H), 2.30 (app qd, *J* = 13.7, 7.4 Hz, 2H), 1.92–1.61 (comp m, 4H), 1.25 (s, 9H), 1.15 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.2, 176.4, 162.7, 133.8, 120.6, 118.4, 52.5, 44.6, 39.2, 34.9, 34.8, 27.1, 24.3, 20.0; IR (Neat Film NaCl) 2976, 2936, 2873, 1749, 1656, 1480, 1461, 1379, 1276, 1105, 914 cm^{-1}. HPLC conditions: 0.25% *i*-PrOH in hexanes, OD-H column, t_R (min): major = 10.24, minor = 11.73.



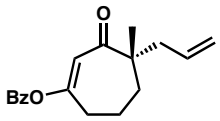
227 *298*

Vinylogous benzoate 298. Prepared in the exact manner as vinylogous pivalate **297** using 220.5 mg (1.75 mmol) of diketone **227**. The crude material was purified by flash chromatography on SiO_2 (6:1 → 4:1 hexanes/EtOAc, PhMe load) to provide **298** (291.8 mg, 1.27 mmol, 72% yield) as a pale yellow oil. R_f = 0.26 (4:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08–8.05 (comp m, 2H), 7.66–7.60 (m, 1H), 7.51–7.46 (comp m, 2H), 5.99 (s, 1H), 2.77–2.69 (comp m, 4H), 2.05–1.87 (comp m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.7, 167.4, 164.3, 134.0, 130.2, 129.8, 128.8, 122.6, 43.3, 33.5, 24.5, 21.8; IR (Neat Film NaCl) 3064, 2941, 2870, 1733, 1663, 1652, 1601, 1452, 1315, 1262, 1202, 1176, 1112, 1090, 1052, 1024, 878, 855, 708, 524 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{14}H_{14}O_3$ $[M]^+$: 230.0943, found 230.0940.



298 (33% yield, two steps) ***267***

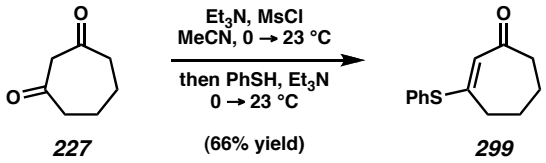
Vinylogous β-ketoester 267. Prepared in the exact manner as vinylogous β-ketoester **265**. Purified by flash chromatography on SiO_2 (9:1 → 6:1 hexanes/EtOAc) to afford **267** (229.6 mg, 0.699 mmol, 33% yield over two steps) as a pale yellow oil. R_f = 0.37 (4:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06–8.03 (comp m, 2H), 7.64–7.58 (m, 1H), 7.49–7.44 (comp m, 4H), 6.01 (d, *J* = 6.0 Hz, 1H), 5.90 (dddd, *J* = 17.0, 10.6, 5.7, 5.7 Hz, 1H), 5.31 (app dq, *J* = 17.2, 1.4 Hz, 1H), 5.22 (ddd, *J* = 10.4, 2.3, 1.2 Hz, 1H), 4.65 (app dt, *J* = 5.7, 1.3 Hz, 2H), 2.77 (dddd, *J* = 18.6, 8.9, 4.1, 1.4 Hz, 1H), 2.65–2.47 (comp m, 2H), 2.13–2.01 (m, 1H), 1.97–1.76 (m, 1H), 1.81 (ddd, *J* = 14.3, 7.6, 3.5 Hz, 1H), 1.47 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.8, 173.2, 164.3, 164.1, 133.9, 131.8, 130.2, 129.0, 128.7, 121.4, 118.6, 66.1, 60.0, 34.1, 33.9, 23.4, 21.8; HRMS (FAB+) *m/z* calc'd for $C_{19}H_{21}O_5$ $[M + H]^+$: 329.1389, found 329.1378.



268

Vinylogous benzoate 268. A typical asymmetric alkylation reaction was run on 39.5 mg (0.120 mmol) of **267** at 30 °C in THF (0.1 M) for 8 h (overnight) using (*S*)-**55** and $Pd_2(pmdba)_3$. The crude material was purified by preparative TLC on SiO_2 (4:1 hexanes/EtOAc) to provide **268** (2.1 mg, 0.102 mmol, 85% yield) as a colorless oil. R_f = 0.47 (4:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08–8.04 (comp m, 2H), 7.64–7.59 (m, 1H), 7.51–7.45 (comp m, 2H), 5.90 (app t, *J* = 1.1 Hz, 1H), 5.74 (dddd, *J* =

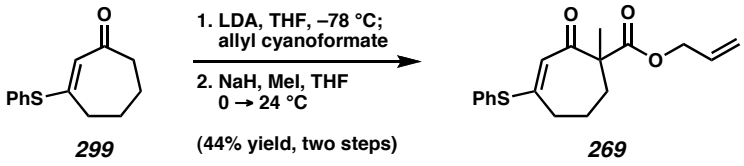
16.3, 10.8, 7.4, 7.4, 1H), 5.10–5.09 (m, 1H), 5.07–5.03 (m, 1H), 2.68–2.63 (comp m, 2H), 2.34 (app qt, J = 13.8, 1.1 Hz, 2H), 1.99–1.67 (comp m, 4H), 1.19 (s, 3H). HPLC conditions: 2% *i*-PrOH in hexanes, OD-H column, t_R (min): major = 10.86, minor = 12.39.



227 ***299***

Vinylogous thioester 299. To a solution of dione **227** (1.3727 g, 10.88 mmol, 1.0 equiv) in MeCN (12.1 mL, 0.9 M) cooled to 0 °C was added Et_3N (1.70 mL, 12.2 mmol, 1.12 equiv) and MsCl (884 μL, 11.4 mmol, 1.05 equiv). The reaction was slowly warmed to 23 °C over 1 h, then cooled to 0 °C and Et_3N (1.70 mL, 12.2 mmol, 1.12 equiv) followed by freshly distilled PhSH (1.15 mL, 11.21 mmol, 1.03 equiv) were added. The reaction was slowly warmed to 23 °C overnight. When starting material was consumed, the reaction was quenched with sat. aq Na_2CO_3 (30 mL), extracted with Et_2O (3 x 50 mL), the organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to a yellow oil. The crude oil was purified by flash chromatography on SiO_2 (3:1 → 1:1 hexanes/Et_2O) to afford **299** as a pale yellow solid (1.5617 g, 7.154 mmol, 66% yield). R_f = 0.31 (1:1 hexanes/Et_2O); mp = 73–75 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48–7.46 (comp m, 2H), 7.43–7.40 (comp m, 3H), 5.48 (s, 1H), 2.65 (dd, J = 6.1, 6.1 Hz, 2H), 2.55 (dd, J = 6.3, 6.3 Hz, 2H), 1.93–1.88 (comp m, 2H), 1.84–1.79 (comp m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.6, 163.5, 163.4, 135.6, 130.2, 130.0, 129.7, 124.3, 41.4, 33.0, 24.9, 21.0; IR (Neat Film NaCl) 3058, 2939, 2866, 1648. 1586,

1475, 1440, 1267, 1190, 1016, 750, 691 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{13}H_{14}OS$ $[M]^+$: 218.0765, found 218.0758.

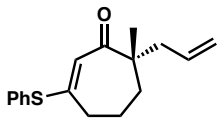


299 ***269***

Vinylogous β-ketoester 269. To a solution of *i*-Pr_2NH (590 μL, 4.21 mmol, 1.3 equiv) in THF (14 mL) at 0 °C was added a solution of *n*-BuLi (1.56 mL of a 2.5 M solution in hexane, 3.89 mmol, 1.2 equiv). After 30 min, the solution was cooled to –78 °C and a solution of vinylogous thioester **299** (707.5 mg, 3.24 mmol, 1.0 equiv) in THF (2.2 mL) was added dropwise via cannula transfer. After 1 h at –78 °C, allyl cyanoformate (389 μL, 3.56 mmol, 1.1 equiv) was added. After 2 h the reaction was quenched with 50% sat. aq NH_4Cl (5 mL) and warmed to room temperature. The layers were separated and the aq layer was extracted with Et_2O (3 x 10 mL), the combined organics were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo.

The resulting crude oil was dissolved in THF (4.7 mL) and cooled to 0 °C, at which point NaH (149 mg, 3.73 mmol, 1.15 equiv) was added in two portions. After 20 min, MeI (605 μL, 9.72 mmol, 3 equiv) was added and the cooling bath was removed. The reaction was quenched with 50% sat. aq NH_4Cl after 11 h, diluted with Et_2O (10 mL), the layers were separated and the aq layer was extracted with Et_2O (3 x 10 mL). The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated to a crude yellow oil. Purification by flash chromatography on SiO_2 (6:1 → 3:1 hexanes/Et_2O) provided vinylogous β-ketoester **269** (0.3426 g, 1.08 mmol, 34% yield

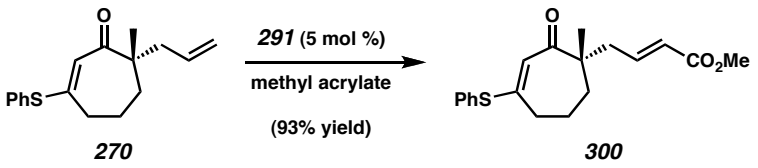
over two steps) as a pale yellow oil. R_f = 0.25 (3:1 hexanes/Et_2O); ^1H NMR (500 MHz, $CDCl_3$) δ 7.46–7.38 (comp m, 5H), 5.86 (dddd, *J* = 10.5, 5.6, 5.6, 0.7 Hz, 1H), 5.56 (d, *J* = 1.5 Hz, 1H), 5.29 (dddd, *J* = 17.1, 1.5, 1.5, 1.5 Hz, 1H), 5.23 (dddd, *J* = 10.5, 1.2, 1.2, 1.2 Hz, 1H), 4.60 (dddd, *J* = 19.5, 5.9, 1.5, 1.5 Hz, 2H), 2.67 (dddd, *J* = 17.6, 10.3, 3.7, 1.7 Hz, 1H), 2.50–2.43 (comp m, 2H), 2.08–1.98 (m, 1H), 1.86–1.77 (m, 1H), 1.68 (ddd, *J* = 14.2, 6.4, 5.4 Hz, 1H), 1.38 (s, 3H)); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.6, 173.6, 159.5, 135.6, 131.8, 130.1, 129.9, 123.8, 118.7, 66.0, 58.8, 34.2, 33.7, 23.9, 23.8; IR (Neat Film NaCl) 3060, 2982, 2935, 1735, 1650, 1593, 1440, 1230, 1178, 1113, 980, 750, 692 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{18}H_{20}O_3S$ $[M]^+$: 316.1133, found 316.1119.



270

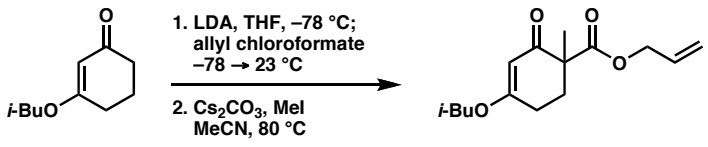
Vinylogous thioester 270. A typical asymmetric alkylation reaction was run on 78.2 mg (0.287 mmol) of **269** at 25 °C in Et_2O (0.1 M) for 5 h using (*S*)-**55** and $Pd(dmdba)_2$. The crude material was purified by flash chromatography on SiO_2 (15:1 → 9:1 hexanes/Et_2O, PhMe load) to provide **270** (67.1 mg, 0.246 mmol, 86% yield) as a pale yellow oil. R_f = 0.46 (3:1 hexanes/Et_2O); ^1H NMR (500 MHz, $CDCl_3$) δ 7.49–7.46 (comp m, 2H), 7.42–7.38 (comp m, 3H), 5.66 (dddd, *J* = 16.8, 10.1, 7.3, 7.3 Hz, 1H), 5.54 (s, 1H), 5.04–4.98 (comp m, 2H), 2.59–2.48 (m, 2H), 2.29 (dd, *J* = 13.7 7.3 Hz, 1H), 2.20 (dd, *J* = 13.7, 7.6 Hz, 1H), 1.93–1.77 (comp m, 2H), 1.64–1.58 (m, 1H), 1.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.0, 155.7, 135.5, 134.2, 130.4, 129.8, 129.8, 124.0, 118.1, 51.3, 44.6, 36.3, 35.2, 24.3, 22.5; IR (Neat Film NaCl) 3074, 2931, 2865, 1650, 1597, 1474, 1440, 1197, 916, 749, 691 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{17}H_{20}SO$

$[M]^+$: 272.1235, found 272.1243; $[\alpha]_D^{24.8}$ –86.35° (*c* 0.905, CH_2Cl_2, 89% ee). HPLC conditions: see derivative **300**.



270 *300*

Acrylate 300. To a solution of vinylogous thioester **270** (19.4 mg, 0.0712 mmol, 1.0 equiv) was added methyl acrylate (128 μL, 0.142 mmol, 20 equiv), followed by Grubbs' catalyst **291** (3.1 mg, 0.0036 mmol, 0.05 equiv) and CH_2Cl_2 (100 μL). The vial was flushed with argon, capped, and immersed in a 40 °C oil bath overnight. After 10 h, the reaction was concentrated under reduced pressure and purified by preparative TLC on SiO_2 (3:1 hexanes/Et_2O) to give acrylate **300** (21.9 mg, 0.0663 mmol, 93% yield) as a pale yellow oil. R_f = 0.19 (3:1 hexanes/Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50–7.40 (comp m, 5H), 6.84 (ddd, *J* = 15.7, 8.0, 8.0 Hz, 1H), 5.81 (ddd, *J* = 15.4, 1.3, 1.3 Hz, 1H), 5.51 (s, 1H), 3.72 (s, 3H), 2.56 (dd, *J* = 7.0, 5.0 Hz, 2H), 2.46 (ddd, *J* = 13.8, 7.4, 1.3 Hz, 1H), 2.33 (ddd, *J* = 13.8, 7.4, 1.3 Hz, 1H), 1.90–1.75 (comp m, 3H), 1.69–1.61 (m, 1H), 1.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.7, 166.7, 157.0, 145.3, 135.6, 130.1, 130.0, 129.9, 124.0, 123.3, 51.6, 51.3, 42.8, 36.3, 35.3, 24.8, 22.5; IR (Neat Film NaCl) 3057, 2934, 1723, 1654, 1597, 1439, 1272, 1197, 1113, 986, 751, 692 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{19}H_{22}O_3S$ $[M]^+$: 330.1290, found 330.1293; $[\alpha]_D^{25.1}$ –58.79° (*c* 0.355, CH_2Cl_2, 89% ee). HPLC conditions: 3% EtOH in hexanes, AD column, t_R (min): major = 22.3, minor = 18.7.

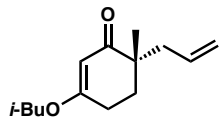


301 (86% yield, two steps) ***271***

Vinylogous β-ketoester 271. To a solution of *i*-Pr_2NH (854 μL, 6.09 mmol, 2.05 equiv) in PhMe (20 mL) cooled to –78 °C was added a solution of *n*-BuLi (2.32 mL of a 2.56 M solution in hexane, 5.94 mmol, 2.0 equiv). The flask was placed in a 0 °C cooling bath for 10 min, cooled back down to –78 °C, and to this was added a solution of vinylogous ester **301**[39] (500 mg, 2.97 mmol, 1.0 equiv) in PhMe (3 mL, wash with extra 1 mL). After 30 min, allyl chloroformate (332 μL, 3.12 mmol, 1.05 equiv) was added dropwise and the bath was removed. The reaction was quenched with 1 N $KHSO_4$ (15 mL) after stirring at room temperature for 30 min, the layers were separated, and the aq was extracted with Et_2O (2 x 10 mL). The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo.

The resulting crude oil was dissolved in MeCN (12 mL, 0.25 M), and to this was added Cs_2CO_3 (1.160 g, 3.56 mmol, 1.2 equiv) and MeI (555 μL, 8.90 mmol, 3.0 equiv). The reaction was placed in an 80 °C oil bath and stirred vigorously, and after 17 h the contents were warmed to room temperature. The reaction was diluted with EtOAc (25 mL), dried over $MgSO_4$, filtered, and concentrated to a crude oil. Purification by flash chromatography on SiO_2 (6:1 → 2:1 → 1:2 hexanes/Et_2O) to afford vinylogous β-ketoester **271** (679.8 mg, 2.55 mmol, 86% yield over two steps) as a colorless oil. R_f = 0.53 (2:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.94–5.81 (m, 1H), 5.36 (s, 3H), 5.29 (app dq, *J* = 17.2, 1.6, 1H), 5.20 (app dq, *J* = 10.5, 1.3 Hz, 1H), 4.61 (ddd, *J* = 5.5, 2.9, 1.5 Hz, 2H), 3.60 (d, *J* = 6.5 Hz, 2H), 2.65–2.35 (comp m, 4H), 2.01 (septuplet,

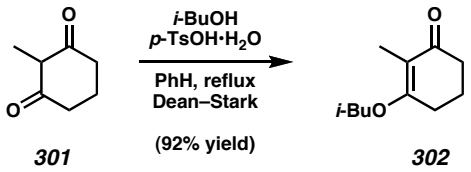
J = 6.8 Hz, 1H), 1.88 (ddd, J = 13.0, 8.0, 4.8 Hz, 1H), 1.42 (s, 3H), 0.97 (d, J = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.7, 176.9, 172.7, 131.9, 118.2, 101.8, 75.0, 65.7, 52.5, 31.8, 27.8, 26.5, 20.7, 19.2; HRMS (FAB+) *m/z* calc'd for $C_{15}H_{23}O_4$ $[M + H]^+$: 267.1596, found 267.1594.



272

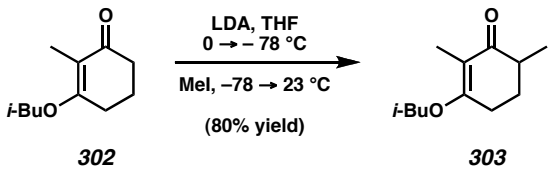
Vinylogous ester 272. A typical asymmetric alkylation reaction was run on 26.6 mg (0.100 mmol) of **271** at 50 °C in PhMe (0.1 M) for 33 h using (*S*)-**55** and $Pd(dmdba)_2$. The crude material was purified by flash chromatography on SiO_2 (9:1 → 6:1 hexanes/EtOAc) to provide **272** (17.5 mg, 078.7 μmol, 79% yield) as a colorless oil. R_f = 0.37 (6:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.81–5.68 (m, 1H), 5.25 (s, 1H), 5.08 (s, 1H), 5.05–5.02 (m, 1H), 3.58 (d, J = 3.5 Hz, 2H), 2.42 (t, J = 6.4 Hz, 2H), 2.36 (dd, J = 13.6, 7.7 Hz, 1H), 2.18 (dd, J = 13.6, 7.7 Hz, 1H), 2.02 (septuplet, J = 6.7 Hz, 1H), 1.92 (app dt, J = 13.4, 6.2 Hz, 1H), 1.70 (app dt, J = 13.5, 6.2 Hz, 1H), 1.08 (s, 3H), 0.97 (d, J = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.7, 176.2, 134.5, 118.0, 101.4, 74.8, 43.3, 41.7, 31.9, 27.9, 26.1, 22.3, 19.2; IR (Neat Film NaCl) 2962, 2932, 2875, 1654, 1611, 1384, 1368, 1239, 1194, 1178, 996, 912, 840 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{14}H_{23}O_2$ $[M + H]^+$: 223.1698, found 223.1706. HPLC conditions: 5% *i*-PrOH, OD-H column, t_R (min): major = 5.75, minor = 6.40.

4.5.2.2 ENANTIOSELECTIVE TOTAL SYNTHESIS OF (+)-CARISSONE



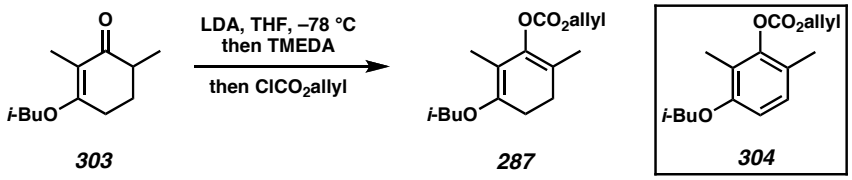
301 *302*

Vinylogous ester 302.[40] Diketone **301** (3.000 g, 23.78 mmol, 1.0 equiv) was partially dissolved in PhH (42.5 mL, 0.56 M), and *i*-BuOH (12.75 mL, 137.9 mmol, 5.8 equiv) and *p*-TsOH•H_2O (226 mg, 1.19 mmol, 0.05 equiv) were added with vigorous stirring. A Dean–Stark adapter and a water-cooled condenser were attached to the flask and the contents were warmed to reflux in a 104 °C oil bath. Upon consumption of **301** by TLC analysis (ca. 3.5 h), the reaction was cooled to ambient temperature, diluted with Et_2O (50 mL), and poured into saturated aq $NaHCO_3$ (20 mL). The layers were separated and the aq layer was extracted with Et_2O (3 x 15 mL). The organics were combined, washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to afford a pale brown oil. To this oil was added PhMe (ca. 10 mL) followed by further concentration in vacuo. Purification by bulb-to-bulb distillation yielded vinylogous ester **302** (3.988 g, 21.88 mmol, 92% yield) as a clear, colorless oil. R_f = 0.48 (2:1 EtOAc/hexanes); bp = 135–140 °C at 0.8 torr; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.76 (d, J = 6.5 Hz, 2H), 2.54 (ddd, J = 6.1, 1.5, 1.5 Hz, 2H), 2.34 (t, J = 7.1 Hz, 2H), 2.08–1.90 (comp m, 3H), 1.72 (app t, J = 1.5 Hz, 3H), 0.99 (d, J = 6.7 Hz, 6H). All other spectral data are consistent with reported values.



302 ***303***

Methyl vinylogous ester 303.[40] To a solution of *i*-Pr_2NH (1.12 mL, 7.99 mmol, 1.9 equiv) in THF (26 mL, 0.15 M) at 0 ˚C was added dropwise a solution of *n*-BuLi (2.55 M in hexanes, 3.06 mL, 7.80 mmol, 1.85 equiv). After 15 min, a solution of vinylogous ester **302** (765.2 mg, 4.198 mmol, 1.0 equiv) in THF (2.0 mL) was added dropwise via cannula transfer. The resulting solution was cooled to –78 ˚C and stirred for 45 min, to which a solution of MeI (485 μL, 7.80 mmol, 1.85 equiv) in THF (5.0 mL) was added over 30 min via positive-pressure cannula transfer. The cooling bath was allowed to expire over ca. 4 h and the reaction was quenched with brine (15 mL), the phases were separated, and the aq layer was extracted with hexanes (3 x 25 mL). The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to a yellow oil. Purification by flash chromatography (4:1 → 2:1 hexanes/Et_2O) afforded methyl vinylogous ester **303** (659 mg, 3.36 mmol, 80% yield) as a pale yellow oil. R_f = 0.48 (2:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.73 (ddd, *J* = 15.6, 9.2, 6.5 Hz, 2H), 2.61 (ddd, *J* = 17.3, 5.3, 1.2 Hz, 1H), 2.55–2.44 (m, 1H), 2.35–2.19 (m, 1H), 2.06 (app dq, *J* = 8.3, 4.8 Hz, 1H), 1.98 (app septet, *J* = 6.6 Hz, 1H), 1.71 (dd, *J* = 1.6, 1.6 Hz, 3H), 1.73–1.60 (m, 1H), 1.14 (d, *J* = 6.9 Hz, 3H), 0.99 (d, *J* = 6.7 Hz, 6H). All other spectral data are consistent with reported values.

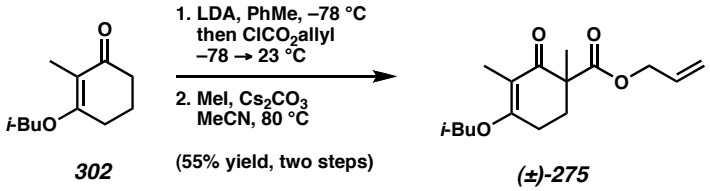


303 ***287*** ***304***

Enol carbonate 287. To a solution of *i*-Pr_2NH (1.56 mL, 11.15 mmol, 1.2 equiv) in THF (85 mL, 0.11 M) at 0 ˚C was added a solution of *n*-BuLi (2.55 M in hexanes, 4.0 mL, 10.22 mmol, 1.1 equiv) dropwise. The reaction mixture was allowed to stir for 30 min and then cooled to –78 ˚C. A solution of ketone **303** (1.824 g, 9.29 mmol, 1.0 equiv) in THF (10 mL) was added dropwise via cannula and stirred for 1 h. TMEDA (1.67 mL, 11.15 mmol, 1.2 equiv) was then added via syringe and the resulting solution stirred for 75 min. To this solution was added allyl chloroformate (1.08 mL, 10.13 mmol, 1.09 equiv) via syringe and the reaction mixture was stirred at –78 ˚C for an additional hour. The reaction was quenched with saturated aq $NaHCO_3$ (40 mL) and H_2O (40 mL), and the flask was transferred to a 23 ˚C water bath and allowed to equilibrate. The phases were separated and the aqueous was extracted with Et_2O (2 x 200 mL). The combined organics were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to afford enol carbonate **287** as a yellow oil (2.472 g); ^{1}H NMR analysis shows **287** is the major product with other impurities present. R_f = *unstable to* SiO_2; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.97 (dddd, J = 16.4, 10.8, 5.8, 5.8 Hz, 1H), 5.42 (app d, J = 17.2 Hz, 1H), 5.33 (app d, J = 10.4 Hz, 1H), 4.72 (dd, J = 5.7, 0.8 Hz, 2H), 3.86 (d, J = 6.7 Hz, 2H), 2.85 (app t, J = 7.9 Hz, 2H), 2.52 (app t, J = 7.9 Hz, 2H), 2.19 (s, 3H), 1.92 (app septuplet, J = 6.7 Hz, 1H), 1.82 (s, 3H), 0.93 (d, J = 6.7 Hz, 6H); IR (Neat Film NaCl) 2963, 1760, 1736, 1699, 1361, 1248, 1170, 990 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{13}H_{19}O_4$ $[M - C_3H_5]^+$: 239.1283, found 239.1273.

This material was unstable to various purification attempts (distillation or flash chromatography using silica gel or Florisil) and storage. Aromatic carbonate **304** was identified as a colorless oil from this complex mixture. R_f = 0.51 (4:1 hexanes/EtOAc);

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.97 (d, *J* = 8.4 Hz, 1H), 6.65 (d, *J* = 8.4 Hz, 1H), 6.00 (dddd, *J* = 17.1, 10.5, 5.7, 5.7 Hz, 1H), 5.43 (dddd, *J* = 17.2, 1.4, 1.4, 1.4 Hz, 1H), 5.33 (dddd, *J* = 10.5, 1.2, 1.2, 1.2 Hz, 1H), 4.75 (app dt, *J* = 5.8, 1.3 Hz, 2H), 3.70 (d, *J* = 6.4 Hz, 2H), 2.14 (s, 3H), 2.09 (s, 3H), 2.09 (app septuplet, *J* = 6.6 Hz, 1H), 1.03 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.3, 153.0, 148.7, 131.4, 127.7, 121.8, 119.5, 119.4, 109.1, 74.9, 69.2, 28.6, 19.5, 15.7, 9.2; IR (Neat Film NaCl) 2960, 2874, 1762, 1620, 1494, 1470, 1365, 1244, 1202, 1172, 1115, 1048, 799 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{16}H_{22}O_4$ $[M]^+$: 278.1518, found 278.1517.

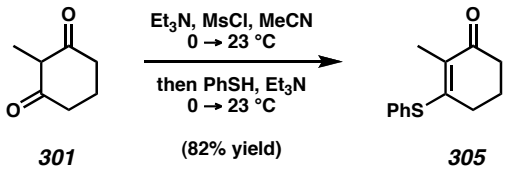


302 ***(±)-275***

β-Ketoester (±)-275. To a –78 °C solution of *i*-Pr_2NH (425 μL, 3.03 mmol, 1.9 equiv) in PhMe (10 mL) was added dropwise *n*-BuLi (2.55 M in hexanes, 1.16 mL, 2.96 mmol, 1.85 equiv). The reaction vessel was placed in an ice/water bath and allowed to stir for 10 min, and then cooled to –78 °C. A solution of vinylogous ester **302** (291 mg, 1.60 mmol, 1.0 equiv) in PhMe (1.4 mL) was added dropwise via cannula to the reaction vessel, and the resulting solution was allowed to stir for 30 min. Allyl chloroformate (173 μL, 1.63 mmol, 1.02 equiv) was added dropwise, and the reaction vessel was allowed to warm to 23 °C over 1 h. After stirring for 4 h, the reaction was slowly quenched with aq $KHSO_4$ (1 N, 4 mL) and the resulting biphasic mixture was allowed to stir for 10 min. The phases were separated, and the aq phase was extracted with Et_2O (2 x 10 mL). The combined organic extracts were washed with brine (10 mL),

dried over $MgSO_4$, filtered, and concentrated in vacuo. The isolated crude yellow oil was used in the next step without further purification.

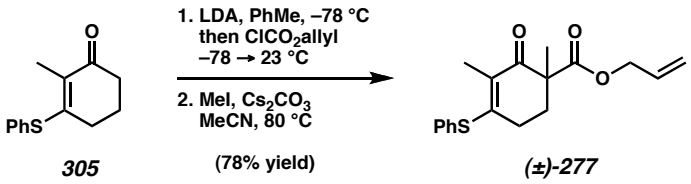
The resulting crude yellow oil was dissolved in MeCN (5.9 mL, 0.27 M), and Cs_2CO_3 (603 mg, 1.85 mmol, 1.16 equiv), and MeI (276 μL, 4.44 mmol, 2.8 equiv) were added. A water-cooled condenser was attached to the flask and the resulting suspension was warmed to reflux in an 80 °C oil bath with vigorous stirring. After 10 h, the reaction was cooled to room temperature and diluted with EtOAc (25 mL). The organics were dried with $MgSO_4$, filtered, and the solvent was evaporated in vacuo. Purification by flash chromatography (15:1 → 9:1 → 4:1 hexanes/EtOAc) afforded β-ketoester (±)-**275** as pale yellow oil (246 mg, 55% yield over two steps). R_f = 0.27 (2:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.82 (dddd, *J* = 17.2, 10.7, 5.4, 5.4 Hz, 1H), 5.22 (dddd, *J* = 17.2, 1.6, 1.6, 1.6 Hz, 1H), 5.15 (dddd, *J* = 10.5, 1.2, 1.2, 1.2 Hz, 1H), 4.56 (dddd, *J* = 13.5, 5.4, 1.5, 1.5 Hz, 2H), 3.72 (ddd, *J* = 9.2, 6.6, 3.2 Hz, 2H), 2.69–2.62 (m, 1H), 2.53–2.44 (comp m, 2H), 1.95 (app septuplet, *J* = 6.6 Hz, 1H), 1.85–1.80 (m, 1H), 1.70 (dd, *J* = 1.5, 1.5 Hz, 3H), 1.36 (s, 3H), 0.95 (dd, *J* = 6.7, 0.8 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 195.8, 172.6, 170.3, 131.9, 117.8, 113.8, 73.9, 65.5, 51.6, 31.2, 28.8, 23.0, 20.8, 19.1, 19.0, 8.0; IR (Neat Film NaCl) 2961, 2935, 2875, 1733, 1649, 1618, 1460, 1382, 1354, 1237, 1176, 1103, 983 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{16}H_{25}O_4$ $[M + H]^+$: 281.1753, found 281.1740.



301 ***305***

Vinylogous Thioester 305.[4a] To a solution of diketone **301** (2.500 g, 19.82 mmol,

1.0 equiv) in MeCN (22.0 mL, 0.9 M) was added Et_3N (3.1 mL, 22.2 mmol, 1.12 equiv) and the solution was allowed to stir for 5 min, then cooled to 0 °C. Methanesulfonyl chloride (1.63 mL, 21.0 mmol, 1.06 equiv) was added, and the reaction was warmed to 23 °C over 2 h. Stirring was continued for 5 h, at which point the reaction was cooled to 0 °C. Triethylamine (3.1 mL, 22.2 mmol, 1.12 equiv) was added, followed by benzenethiol (2.1 mL, 20.4 mmol, 1.03 equiv). The reaction was allowed to warm to 23 °C over 2 h and stirring was continued for 9 h. Saturated aq Na_2CO_3 (35 mL) was added, the phases were separated, and the aq phase was extracted with Et_2O (3 x 60 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and the solvent was evaporated in vacuo. Purification by flash chromatography (4:1 → 2:1 hexanes/Et_2O) afforded vinylogous thioester **305** as a white crystalline solid (3.565 g, 16.33 mmol, 82% yield). R_f = 0.34 (1:1 hexanes/Et_2O); mp = 85 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51–7.49 (m, 2H), 7.44–7.37 (comp m, 3H), 2.38 (t, J = 6.5 Hz, 2H), 2.18 (tq, J = 6.5, 2.0 Hz, 2H), 1.97 (t, J = 2.0 Hz, 3H), 1.87 (app pentuplet, J = 6.0 Hz, 2H). All other spectral data are consistent with reported values.



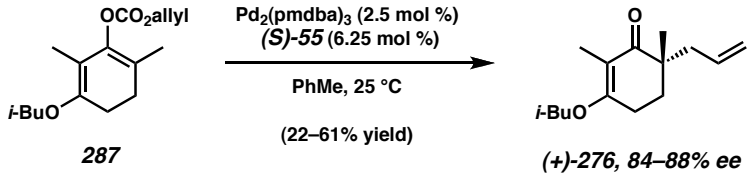
305 *(±)-277*

β-Ketoester (±)-277. To a –78 °C solution of *i*-Pr_2NH (2.63 mL, 18.78 mmol, 2.00 equiv) in PhMe (70 mL) was added dropwise *n*-BuLi (2.53 M in hexanes, 7.24 mL, 2.00 equiv). The reaction vessel was warmed to 0 °C, allowed to stir for 10 min, and cooled to –78 °C. A solution of vinylogous thioester **305** (2.00 g, 9.16 mmol, 1.00 equiv) in PhMe

(15 mL) was added dropwise via cannula to the reaction vessel, and the resulting solution was allowed to stir for 30 min. Allyl chloroformate (1.02 mL, 9.62 mmol, 1.05 equiv) was added dropwise and the reaction vessel was allowed to warm to 23 °C over 1 h. Stirring was continued for 4 h, at which point aq $KHSO_4$ (1 N, 70 ml) was slowly added and the resulting solution was allowed to stir for 10 min. The phases were separated, and the aq phase was extracted with Et_2O (3 x 30 mL). The combined organic extracts were washed with brine (1 x 30 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The isolated crude yellow oil was used in the next step without further purification.

To a solution of the crude yellow oil (3.32 g) in CH_3CN (40 mL) in a flask with an attached reflux condenser was added cesium carbonate (4.48 g, 13.74 mmol, 1.50 equiv) and MeI (1.71 mL, 27.48 mmol, 3.00 equiv). The resulting suspension was refluxed at 80 °C for 5 h, at which point additional MeI (1.00 mL, 16.06 mmol, 1.75 equiv) was added. The reaction was refluxed at 80 °C for 2 h, cooled to room temperature, filtered through Celite (EtOAc eluent), dried over Na_2SO_4, filtered, and the solvent was evaporated in vacuo. Purification by flash chromatography (18% EtOAc in hexanes) afforded β-ketoester (±)-**277** as a colorless oil that solidifies to a white solid over time or in a –20 °C freezer (2.26 g, 7.14 mmol, 78% yield over two steps). R_f = 0.35 (30% EtOAc in hexanes); mp 34 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51–7.35 (comp m, 5H), 5.87 (app ddt, *J* = 10.5, 17.1, 5.4 Hz, 1H), 5.27 (app ddt, *J* = 17.1, 1.7, 1.8 Hz, 1H), 5.22 (app ddt, *J* = 9.9, 1.7, 1.2 Hz, 1H), 4.65 (dddd, *J* = 1.5, 1.8, 5.7, 13.5 Hz, 1H), 4.55 (dddd, *J* = 1.5, 1.8, 5.7, 13.5 Hz, 1H), 2.41–2.32 (m, 1H), 2.30–2.21 (m, 1H), 2.16–2.06 (1H), 2.00 (t, *J* = 1.8 Hz, 3H), 1.78 (ddd, *J* = 4.5, 8.1, 13.2 Hz, 1H), 1.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.0, 172.6, 156.7, 135.6, 131.9, 129.7, 129.5, 128.9, 118.1, 65.7,

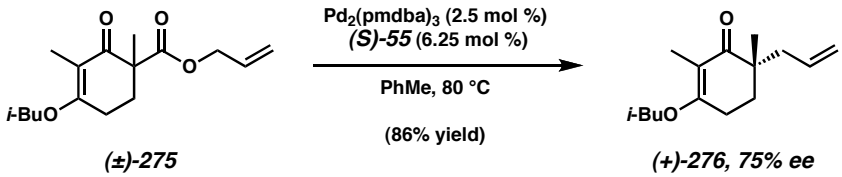
52.3, 33.1, 27.4, 20.7, 12.9; IR (Neat Film NaCl) 2936, 1733, 1656, 1580, 1314, 1254, 1238, 1174, 985, 752, 693 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{18}H_{20}O_3S$ $[M + H]^+$: 317.1211, found 317.1211.



287 ***(+)-276, 84–88% ee***

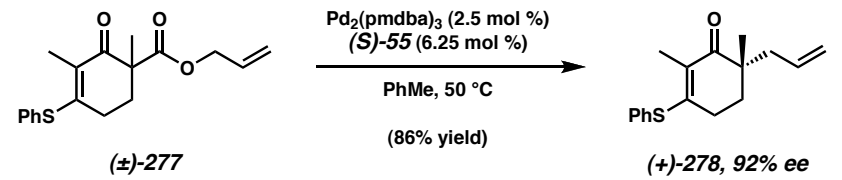
Ketone (+)-276 from enol carbonate 287. A 1-dram vial containing a stir bar was charged with $Pd_2(pmdba)_3$ (4.9 mg, 0.0045 mmol, 0.025 equiv) and (*S*)-**55** (4.4 mg, 0.0112 mmol, 0.0625 equiv), sealed with a septum, and the atmosphere was purged by three evacuate/purge cycles. To this was added PhMe (0.9 mL) and the ligation reaction was stirred for 30 min in a 25 °C oil bath, upon which time a solution of enol carbonate **287** (50.2 mg, 0.179 mmol, 1.0 equiv) in PhMe (0.9 mL, 0.1 M total) was added via cannula. After 21.5 h the reaction was diluted with Et_2O (2 mL), filtered through a SiO_2 plug, and concentrated in vacuo. The filtrate was purified by flash chromatography on SiO_2 (15:1 → 4:1 hexanes/EtOAc) to afford ketone **276** as a pale yellow oil (22–61% yield, 84–88% ee). R_f = 0.49 (4:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.73 (dddd, *J* = 16.6, 10.6, 7.4, 7.4 Hz, 1H), 5.06–5.04 (m, 1H), 5.04–5.01 (m, 1H), 3.74 (dd, *J* = 9.7, 6.7 Hz, 2H), 2.59–2.47 (comp m, 2H), 2.33 (dd, *J* = 13.7, 7.2 Hz, 1H), 2.16 (dddd, *J* = 13.7, 7.6, 1.0, 1.0 Hz, 1H), 1.98 (app septuplet, *J* = 6.6 Hz, 1H), 1.90 (ddd, *J* = 13.3, 7.2, 5.7 Hz, 1H), 1.72–1.67 (m, 1H), 1.70 (dd, *J* = 1.6, 1.6 Hz, 3H), 1.06 (s, 3H), 0.99 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.7, 169.5, 134.8, 117.8, 113.3, 73.8, 42.5, 41.9, 31.5, 29.0, 22.5, 22.4, 19.2, 8.0; IR (Neat Film NaCl) 3076, 2962, 2931, 1622,

1463, 1381, 1355, 1229, 1113, 1002, 915 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{15}H_{24}O_2$ $[M]^+$: 236.1776, found 236.1771; $[\alpha]_D^{21.2}$ +13.2° (*c* 0.20, CH_2Cl_2, 88% ee). SFC conditions: 5% *i*-PrOH, AD column, t_R (min): major = 5.18, minor = 6.02.



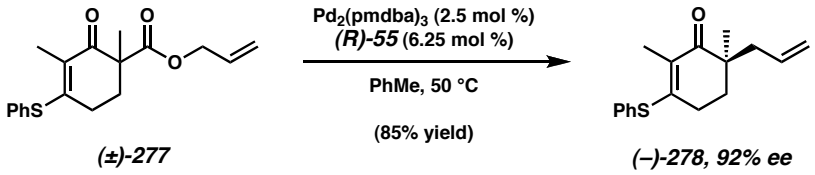
(±)-275 *(+)-276, 75% ee*

Ketone (+)-276 from β-ketoester (±)-275. A 2-dram vial containing a stir bar was charged with $Pd_2(pmdba)_3$ (10.6 mg, 0.00968 mmol, 0.025 equiv) and (*S*)-**55** (9.4 mg, 0.0242 mmol, 0.0625 equiv). This was connected to a 1-dram vial containing a stir bar and β-ketoester (±)-**275** (108.6 mg, 0.387 mmol, 1.0 equiv) via a cannula, and PhMe (3.9 mL, 0.1 M) was added to the vial containing the Pd/L and immediately immersed in liquid N_2. The vials were rigorously degassed by three freeze-pump-thaw cycles and warmed to 23 °C. After ligation for 30 min (purple → orange color change), the catalyst solution was transferred to the substrate via cannula and immersed in an 80 °C oil bath, at which point the reaction immediately turned yellow in color. After 23 h the reaction was cooled to ambient temperature, diluted with Et_2O (4 mL), and filtered through a small SiO_2 plug. The filtrate was concentrated and purified by flash chromatography as above to afford ketone **276** as a colorless oil (78.5 mg, 0.332 mmol, 86% yield, 75% ee).



(±)-277 *(+)-278, 92% ee*

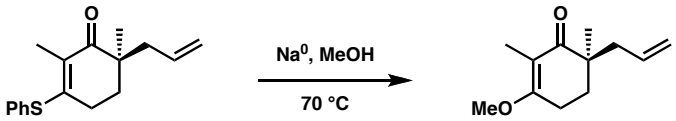
Ketone (+)-278 from β-ketoester (±)-277. The reaction was performed exactly as described for enol carbonate **287** using β-ketoester (±)-**277** (41.8 mg, 0.132 mmol, 1.0 equiv). After complexation of the metal for 30 min at 25 °C, a solution of the substrate was added and the reaction was warmed to 50 °C in an oil bath. After 23 h, the reaction was cooled to room temperature, diluted with Et_2O, and filtered through a SiO_2 plug. The filtrate was concentrated and purified by flash chromatography (15:1 → 9:1 hexanes/EtOAc) to afford ketone **278** as a colorless oil (31.0 mg, 0.114 mmol, 86% yield, 92% ee). R_f = 0.35 (9:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52–7.48 (m, 2H), 7.43–7.35 (comp m, 3H), 5.68 (dddd, *J* = 16.6, 10.4, 7.6, 7.6 Hz, 1H), 5.03 (dddd, *J* = 9.9, 2.4, 0.9, 0.6 Hz, 1H), 5.01 (dddd, *J* = 17.4, 2.4, 1.5, 1.2 Hz, 1H), 2.32 (app ddt, *J* = 13.8, 7.2, 1.2 Hz), 2.19–2.10 (comp m, 3H), 1.96 (app t, *J* = 1.8 Hz, 3H), 1.81 (ddd, 13.5, 6.4, 6.4 Hz, 1H), 1.66–1.56 (m, 1H), 1.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.5, 155.6, 135.6, 134.4 130.3, 129.6, 129.5, 128.8, 118.2, 43.1, 41.7, 33.1, 26.9, 22.3, 12.9; IR (Neat Film NaCl) 3074, 2964, 2929, 1652, 1582, 1440, 1339, 1287, 1228 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{17}H_{20}OS$ $[M + H]^+$: 273.1313, found 273.1317; $[\alpha]_D^{19.0}$ +56.7° (*c* 1.36, CH_2Cl_2, 92% ee). HPLC conditions: 4% EtOH in hexanes, AD column, t_R (min): major = 7.24, minor = 9.48.



(±)-277 *(–)-278, 92% ee*

Scale up of ketone (–)-278 from β-ketoester (±)-277. In a glove box, a flask containing a stir bar was charged with $Pd_2(pmdba)_3$ (493.1 mg, 045 mmol, 0.025 equiv)

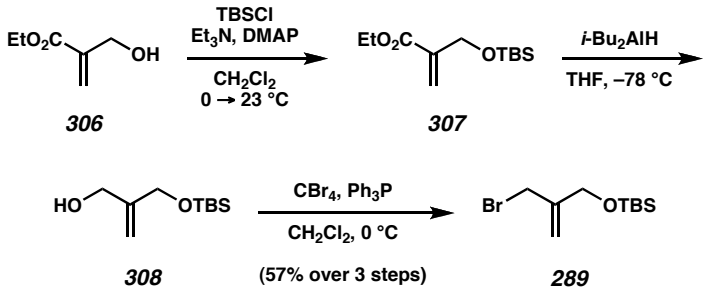
and ligand (*R*)-**55** (435.9 mg, 1.125 mmol, 0.0625 equiv). The solids were dissolved in PhMe (150 mL) and stirred for 45 min (purple → orange color change). To this was added a solution of β-ketoester (±)-**277** (5.6956 g, 18.00 mmol, 1.0 equiv) in PhMe (30 mL, 0.1 M total). The flask was transferred out of the glove box, placed under an argon atmosphere and warmed in a 50 °C oil bath (orange → yellow color change). After 66 h, the reaction was cooled to room temperature and concentrated in vacuo. Purification by flash chromatography (as above, dry load onto SiO_2) afforded ketone (–)-**278** as a pale yellow oil (4.184 g, 15.36 mmol, 85% yield, 92% ee) and recovered β-ketoester (±)-**277** (500.5 mg, 1.582 mmol, 9% yield). $[\alpha]_D^{25.4}$ –57.4° (*c* 1.00, CH_2Cl_2, 92% ee).



(–)-278, 92% ee *(–)-288*

Methoxy vinylogous ester (–)-288. To a 3-neck flask equipped with water-cooled reflux condenser charged with dry MeOH (33.7 mL, 0.26 M) at 0 °C was added hexanes-washed Na^0 (1.047 g, 45.5 mmol, 5.2 equiv), after which the bath was removed. The contents were stirred at 23 °C until all Na^0 was dissolved. A solution of ketone **278** (2.3991 g, 8.81 mmol, 1.0 equiv) in MeOH (10 mL) was added dropwise via cannula to the generated NaOMe and the resulting solution was heated in an oil bath at 70 °C. Upon consumption of **278** by TLC analysis (4:1 hexanes/EtOAc), the reaction mixture was cooled to ambient temperature and transferred to a separate flask with Et_2O and concentrated in vacuo to a thick yellow slurry. This was dissolved in saturated aq $NaHCO_3$ (150 mL), stirred for ca. 20 min, and extracted with Et_2O (3 x 100 mL). The

organics were dried over Na_2SO_4, filtered, and concentrated in vacuo to a yellow oil. Purification by flash chromatography (15:1 → 6:1 hexanes/EtOAc) afforded ketone (–)-**288** as a colorless oil that solidifies in a –20 °C freezer to an off-white semisolid (1.5241 g, 7.845 mmol, 89% yield). R_f = 0.40 (4:1 hexanes-EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.74 (dddd, *J* = 16.8, 10.5, 7.5, 7.5 Hz, 1H), 5.07–5.05 (m, 1H), 5.05–5.02 (m, 1H), 3.80 (s, 3H), 2.62–2.49 (comp m, 2H), 2.33 (dd, *J* = 13.7, 7.2 Hz, 1H), 2.17 (dddd, *J* = 13.8, 7.6, 1.0, 1.0 Hz, 1H), 1.92 (ddd, *J* = 13.4, 7.2, 5.8 Hz, 1H), 1.72 (ddd, *J* = 13.4, 6.7, 5.6 Hz, 1H), 1.68 (dd, *J* = 1.6, 1.6 Hz, 3H), 1.06 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.6, 169.6, 134.8, 117.9, 113.2, 55.0, 42.5, 41.9, 31.4, 22.4, 21.8, 7.9; IR (Neat Film NaCl) 2929, 1620, 1461, 1375, 1356, 1234, 1154, 1116, 999, 916 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{12}H_{18}O_2$ $[M]^+$: 194.1307, found 194.1310; $[\alpha]_D^{22.9}$ –10.6° (*c* 1.26, CH_2Cl_2, 92% ee).



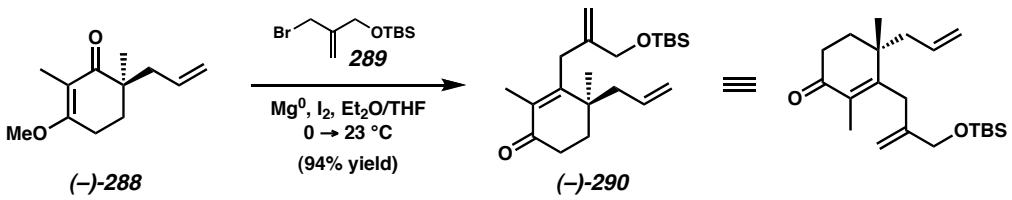
TBS-acrylate 307.[41] To a solution of α-hydroxymethylacrylate **306**[42] (4.7012 g, 36.19 mmol, 1.0 equiv) and TBSCl (6.00 g, 39.8 mmol, 1.1 equiv) in CH_2Cl_2 (72 mL, 0.5 M) at 0 °C was added Et_3N (15.1 mL, 108.6 mmol, 3.0 equiv) and DMAP (442 mg, 3.62 mmol, 0.1 equiv). The reaction was allowed to stir for 30 min, at which point the cooling bath was removed and the contents warmed to 23 °C and stirred overnight. The reaction mixture was filtered into a separatory funnel and washed with 1N HCl (70 mL),

saturated aq $NaHCO_3$ (100 mL), and brine (100 mL). The organics were dried over $MgSO_4$, filtered, and concentrated in vacuo to afford TBS-acrylate **307** as a colorless oil (8.806 g). The material was used in the next step without purification. R_f = 0.63 (6:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.25 (dd, *J* = 2.0, 2.0 Hz, 1H), 5.90 (dd, *J* = 2.0, 2.0 Hz, 1H), 4.37 (dd, *J* = 2.1, 2.1 Hz, 2H), 4.21 (q, *J* = 7.1 Hz, 2H), 1.30 (t, *J* = 7.1 Hz, 3H), 0.92 (s, 9H), 0.08 (s, 6H).

Allylic alcohol 308.[41] To a solution of crude TBS-acrylate **307** (8.806 g, 36.03 mmol, 1.0 equiv) in THF (144 mL, 0.25 M) cooled to –78 ˚C was added dropwise *i*-Bu_2AlH (neat, 14.1 mL, 79.3 mmol, 2.2 equiv) over 15 min. The resulting solution was stirred at –78 ˚C until complete consumption by TLC analysis (4:1 hexanes/EtOAc), at which point the excess *i*-Bu_2AlH was quenched with dry EtOAc (4 mL). The resulting solution was stirred for 10 min at –78 °C, then warmed to 0 °C and aged for 30 min. A solution of Rochelle's salt (75 mL, 1 M) was then added slowly with vigorous stirring. The cooling bath was removed and the contents were vigorously stirred until two homogeneous layers appeared (several hours). The phases were separated and the aq layer was extracted with Et_2O (3 x 75 mL), the combined organics were washed with brine (2 x 100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to afford **308** as a cloudy colorless oil (7.29 g). The crude material was used in the next reaction without purification. R_f = 0.19 (4:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.10 (s, 1H), 5.08 (s, 1H), 4.24 (s, 2H), 4.17 (d, *J* = 5.5 Hz, 2H), 1.95 (t, *J* = 6.0 Hz, 1H), 0.91 (s, 9H), 0.09 (s, 6H).

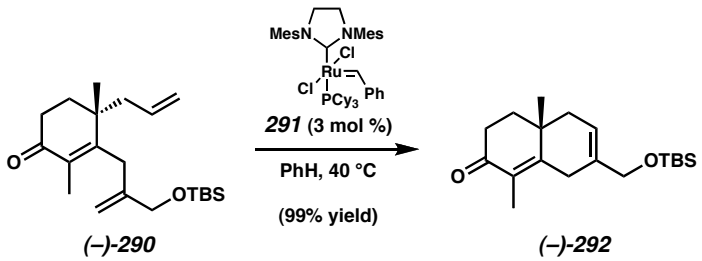
Allylic bromide 289.[28] To a solution of crude allylic alcohol **308** (7.29 g, 36.04 mmol, 1.0 equiv) in CH_2Cl_2 (120 mL, 0.3 M) cooled to 0 ˚C was added CBr_4 (17.942,

54.1 mmol, 1.5 equiv) and PPh_3 (11.331 g, 43.2 mmol, 1.2 equiv). The reaction mixture was stirred at 0 ˚C until consumption by TLC analysis (4:1 hexanes/EtOAc; required ca. 30 min). The reaction was then quenched slowly with saturated aq $NaHCO_3$ (40 mL) and warmed to ambient temperature while stirring. The phases were separated and the aq layer was extracted with EtOAc (3 x 50 mL). The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford a yellow oil containing a Ph_3PO precipitate. This material was dry loaded on SiO_2 and purified by flash chromatography (24:1 → 15:1 → 3:1 hexanes/Et_2O). Fractions containing the desired product were repurified by flash chromatography on SiO_2 (49:1 → 24:1 hexanes/acetone) to afford allylic bromide **289** as a pale yellow oil (5.4251 g, 20.45 mmol, 57% yield over 3 steps). R_f = 0.48 (24:1 hexanes/Et_2O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.26–5.25 (m, 1H), 5.23 (ddd, *J* = 1.4, 1.4, 1.4 Hz, 1H), 4.27 (dd, *J* = 1.4, 1.4 Hz, 2H), 4.01 (s, 2H), 0.92 (s, 9H), 0.10 (s, 6H). All other spectral data are consistent with reported values.



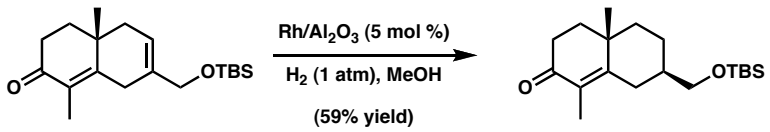
Triolefin (–)-290. To a flask containing Mg^0 turnings (125.4 mg, 5.16 mmol, 3.0 equiv) was added Et_2O (30 mL) and a chip of I_2. The contents were stirred for 25 min at 23 ˚C and then cooled to 0 ˚C. A solution of allylic bromide **289** (1.141 g, 4.30 mmol, 2.5 equiv) in Et_2O (5 mL) was transferred via cannula to the Mg/Et_2O and stirred for 30 min at 0 °C, then warmed to 23 °C over 30 min. A solution of ketone **288** (333.5 mg,

1.72 mmol, 1.0 equiv) in THF (5 mL) was transferred dropwise to the allylmagnesium bromide via cannula, followed by washings to total 35 mL of THF. Upon consumption of ketone **288** by TLC analysis (4:1 hexanes/EtOAc), the reaction was quenched slowly with aq ammonium chloride (50 mL) and stirred until complete dissolution of Mg^0. The phases were separated and the aq phase was extracted with EtOAc (3 x 50 mL). The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated to a pale yellow oil. Purification by flash chromatography (9:1 → 4:1 hexanes/Et_2O, dry load onto SiO_2) afforded the desired triolefin **290** as a colorless oil (563.4 mg, 1.616 mmol, 94% yield). R_f = 0.62 (4:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, C_6D_6) δ 5.54 (dddd, *J* = 17.6, 10.3, 7.3, 7.3 Hz, 1H), 5.06 (dd, *J* = 3.2, 1.7 Hz, 1H), 4.97 (ddd, *J* = 10.3, 2.2, 1.2 Hz, 1H), 4.92 (dddd, *J* = 16.9, 2.4, 1.2, 1.2 Hz, 1H), 4.56 (d, *J* = 1.2 Hz, 2H), 3.95 (s, 2H), 2.75 (dd, *J* = 17.1, 17.1 Hz, 2H), 2.36 (dddd, *J* = 17.1, 17.1, 10.3, 5.1 Hz, 1H), 2.33 (dddd, *J* = 17.1, 17.1, 7.1, 5.4 Hz, 1H), 2.01 (dddd, *J* = 13.9, 13.9, 13.9, 7.6 Hz, 2H), 1.89 (s, 3H), 1.60 (ddd, 13.4, 6.8, 5.1 Hz, 1H), 1.41 (ddd, 13.4, 10.0, 5.1 Hz, 1H), 0.98 (s, 9H), 0.87 (s, 3H), 0.06 (s, 6H); ^{13}C NMR (126 MHz, C_6D_6) δ 196.6, 158.9, 144.4, 134.5, 134.3, 118.0, 110.3, 67.1, 43.2, 39.2, 34.2, 33.9, 33.2, 26.1, 23.9, 18.5, 12.5, –5.2; IR (Neat Film NaCl) 3078, 2930, 2857, 1668, 1610, 1463, 1337, 1081, 1005, 912, 836, 776 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{21}H_{36}O_2Si$ $[M]^+$: 348.2485, found 348.2499; $[\alpha]_D^{21.0}$ –37.3° (*c* 1.11, CH_2Cl_2, 92% ee).



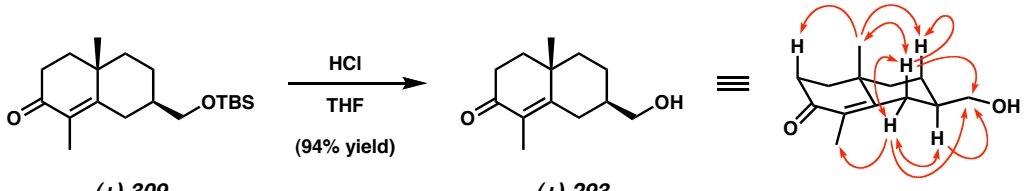
(–)-290 *(–)-292*

Cyclohexene (–)-292. Triolefin **290** (280.1 mg, 0.804 mmol, 1.0 equiv) was dissolved in PhH (16 mL, 0.05 M) and sparged with N_2 for 15 min. Grubbs' catalyst **291** (20.5 mg, 0.0241 mmol, 0.03 equiv) was added to the solution and the flask was placed in a 40 ˚C oil bath. Upon consumption by TLC analysis (3:1 hexanes/Et_2O), the reaction was cooled to ambient temperature and ethyl vinyl ether (8 mL) was added to the solution. After stirring for ca. 30 min the solution was concentrated in vacuo. Purification via flash chromatography (9:1 → 4:1 hexanes/Et_2O) afforded cyclohexane **292** as a colorless oil (256.3 mg, 0.800 mmol, 99% yield). R_f = 0.30 (3:1 hexanes/Et_2O); ^{1}H NMR (500 MHz, C_6D_6) δ 5.58 (dddd, *J* = 5.4, 1.5, 1.5, 1.5 Hz, 1H), 3.93 (d, *J* = 1.2 Hz, 1H), 2.86 (d, *J* = 22.0 Hz, 1H), 2.60 (d, *J* = 21.7 Hz, 1H), 2.32–2.29 (comp m, 2H), 1.87 (d, *J* = 1.2 Hz, 3H), 1.83 (dd, *J* = 16.9, 2.0 Hz, 1H), 1.61 (dd, *J* = 16.9, 6.1 Hz, 1H), 1.45–1.35 (comp m, 2H), 0.99 (s, 9H), 0.85 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (126 MHz, C_6D_6) δ 196.4, 157.4, 135.1, 129.5, 119.5, 66.7, 39.6, 36.4, 35.1, 34.3, 29.7, 26.1, 24.0, 18.6, 11.2, –5.1, –5.2; IR (Neat Film NaCl) 2929, 2857, 1668, 1615, 1463, 1305, 1257, 1158, 1086, 1048, 837, 776 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{19}H_{31}O_2Si$ $[M + H - H_2]^+$: 319.2093, found 319.2096; $[\alpha]_D^{21.2}$ –9.4° (*c* 0.60, CH_2Cl_2, 92% ee).



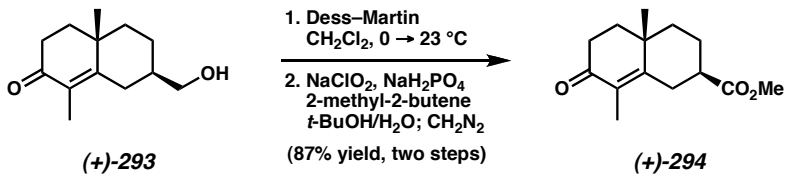
(–)-292 *(+)-309, 10:1 dr*

Enone (+)-309. Cyclohexene **292** (25.0 mg, 78.0 μmol, 1.0 equiv) was dissolved in MeOH (3.1 mL, 25 mM) and Rh/Al_2O_3 catalyst (40.1 mg, 3.90 μmol, 0.05 equiv) was added with vigorous stirring. The vial was placed under an atmosphere of hydrogen via a balloon and stirred at 26 °C. Upon consumption by TLC (3:1 hexanes/Et_2O, developed thrice), the solids were filtered over Celite washing with EtOAc and concentrated in vacuo. Purification via flash chromatography (9:1 hexanes/Et_2O) afforded the desired enone **309** as a colorless oil (14.8 mg, 45.9 μmol, 59% yield, 10:1 dr). R_f = 0.36 (3:1 hexanes/Et_2O, developed twice); ^{1}H NMR (500 MHz, C_6D_6, major diastereomer) δ 3.33 (ddd, *J* = 14.0, 9.8, 5.1 Hz, 2H), 2.63 (ddd, *J* = 14.7, 1.7, 1.7 Hz, 1H), 2.38–2.26 (comp m, 2H), 1.96 (s, 3H), 1.68 (dd, *J* = 13.7, 13.7 Hz, 1H), 1.44 (ddd, *J* = 13.4, 13.4, 3.7 Hz, 1H), 1.42-1.39 (m, 1H), 1.31–1.23 (comp m, 2H), 1.08 (ddd, *J* = 14.2, 14.2, 3.6 Hz, 1H), 0.99 (s, 9H), 0.84 (s, 3H), 0.06 (s, 6H); ^{13}C NMR (126 MHz, C_6D_6) δ 197.0, 160.0, 129.2, 68.1, 41.6, 41.5, 37.7, 36.0, 34.1, 30.9, 26.1, 24.7, 22.2, 18.5, 11.2, –5.2 (2C); IR (Neat Film NaCl) 2928, 2857, 1668, 1612, 1472, 1256, 1098, 838, 776 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{19}H_{35}O_2Si$ [M + H]$^+$: 323.2406, found 323.2402; $[\alpha]_D^{21.4}$ +73.0° (*c* 0.53, CH_2Cl_2, 92% ee).



(+)-309 *(+)-293* *NOE*

Alcohol (+)-293. Enone **309** (40.3 mg, 0.125 mmol, 1.0 equiv) was dissolved in THF (2.5 mL, 50 mM) and aq 1 N HCl (1.0 mL) was added with vigorous stirring. Upon consumption by TLC (2:1 hexanes/EtOAc), brine was added, the layers were separated, and the aq layer was extracted with Et_2O (3 x 4 mL). The combined organics were washed with saturated aq $NaHCO_3$, this aq was back extracted with Et_2O (2 x 5 mL), the organics were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification via flash chromatography (2:1 → 1:1 hexanes/EtOAc) afforded alcohol **293** as a colorless oil (24.5 mg, 0.118 mmol, 94% yield, 10:1 dr). R_f = 0.37 (1:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, C_6D_6, major diastereomer) δ 3.12 (d, *J* = 5.5 Hz, 2H), 2.52 (ddd, *J* = 14.6, 1.9, 1.9 Hz, 1H), 2.37–2.24 (comp m, 2H), 1.92 (dd, *J* = 1.3, 1.3 Hz, 3H), 1.52 (ddd, *J* = 13.1, 13.1, 3.1 Hz, 1H), 1.43 (ddd, *J* = 13.4, 13.4, 5.3 Hz, 1H), 1.36–1.33 (m, 1H), 1.29–1.21 (comp m, 3H), 1.17–1.09 (m, 1H), 1.03 (ddd, *J* = 12.9, 12.9, 3.3 Hz, 1H), 0.79 (s, 3H), 0.74 (br s, 1H); ^{13}C NMR (126 MHz, C_6D_6) δ 197.2, 160.1, 129.1, 67.7, 41.5, 41.4, 37.7, 35.9, 34.1, 30.8, 24.6, 22.2, 11.3; IR (Neat Film NaCl) 3418 (br), 2924, 1660, 1652, 1608, 1453, 1352, 1150, 1083, 1013 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{13}H_{20}O_2$ $[M]^+$: 208.1463, found 208.1463; $[\alpha]_D^{23}$ +120.9° (*c* 0.35, CH_2Cl_2, 92% ee).



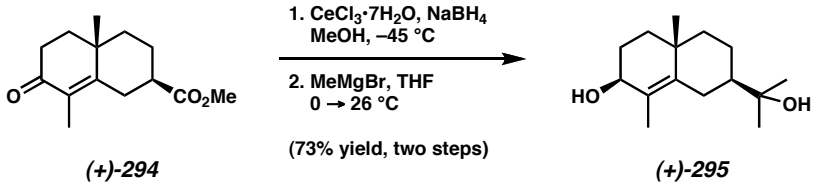
(+)-293 *(+)-294*

Ester (+)-294. To a solution of alcohol **293** (24.5 mg, 0.118 mmol, 1.0 equiv) in CH_2Cl_2 (2.4 mL, 50 mM) at 0 °C was added Dess–Martin periodinane (69.8 mg, 0.165 mmol, 1.4 equiv), and after 5 min the bath was removed and the reaction was

stirred at room temperature. Upon completion by TLC analysis (2:1 hexanes/EtOAc), the reaction was diluted with 1:1 hexanes/Et_2O (4 mL) and filtered through a small silica gel plug. Heptanes (5 mL) were added and the filtrate was concentrated in vacuo to a white solid. Purification by filtration through a silica gel plug (3:1 → 1:1 hexanes/Et_2O) afforded a colorless oil (22.3 mg) that was used in the next step.

The resulting material was dissolved in *t*-BuOH (1.7 mL), to which 2-methyl-2-butene (85 μL, 0.80 mmol, 7.4 equiv) was added with stirring. To this was added a solution of $NaH_2PO_4 \bullet H_2O$ (103 mg, 0.746 mmol, 6.9 equiv) and $NaClO_2$ (89.9 mg, 0.995 mmol, 9.2 equiv) in water (850 μL) over ca. 5 min. Upon consumption by TLC analysis (1:1 hexanes/EtOAc), the *t*-BuOH was removed on a rotovap, water (2 mL) was added to this slurry, and 1 N HCl was added dropwise until pH < 3. The resulting aq layer was extracted with Et_2O (4 x 4 mL), a stir bar was added and the extract was cooled in an ice/water bath. A fresh solution of CH_2N_2 in Et_2O (5 mL) was added and the bath was allowed to expire. After the solution was colorless it was dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification via flash chromatography (3:1 → 2:1 hexanes/Et_2O) afforded ester **294** as a colorless oil that solidifies to a white solid over time or in a –20 °C freezer (24.4 mg, 0.103 mmol, 87% yield over two steps). The diastereomers are separable by flash chromatography with 3:1 hexanes/Et_2O. R_f = 0.59 (1:1 hexanes/EtOAc); mp = 46–48 °C; ^{1}H NMR (500 MHz, C_6D_6, major diastereomer) δ 3.38 (s, 3H), 2.83–2.76 (m, 1H), 2.30–2.09 (comp m, 4H), 1.82 (m, 3H), 1.66–1.62 (comp m, 2H), 1.32 (ddd, *J* = 13.6, 13.6, 4.9 Hz, 1H), 1.17 (ddd, *J* = 13.2, 3.9, 3.9 Hz, 1H), 1.12 (ddd, *J* = 13.5, 2.8, 2.8 Hz, 1H), 0.91–0.85 (m, 1H), 0.72 (s, 3H); ^{13}C NMR (126 MHz, C_6D_6) δ 196.8, 174.7, 157.7, 129.9, 51.3, 43.5, 40.9, 37.4, 35.4, 34.0, 29.9,

24.7, 21.9, 11.2; IR (Neat Film NaCl) 2949, 1733, 1668, 1613, 1435, 1350, 1301, 1256, 1190, 1173, 1024, 914 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{14}H_{21}O_3$ $[M + H]^+$: 237.1491, found 237.1493; $[\alpha]_D^{20.4}$ +64.0° (*c* 0.56, CH_2Cl_2, 92% ee).

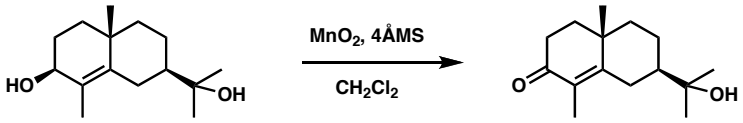


(+)-294 *(+)-295*

Diol (+)-295.[19a,e] To a solution of ester **294** (10.1 mg, 42.7 μmol, 1.0 equiv) in MeOH (1.7 mL, 25 mM) was added $CeCl_3 \bullet 7H_2O$ (47.8 mg, 128 μmol, 3.0 equiv), followed by cooling to ca. –45 °C in a MeCN/CO_2(s) bath. Solid $NaBH_4$ (3.2 mg, 85.5 μmol, 2.0 equiv) was added, and upon consumption by TLC analysis (1:1 hexanes/EtOAc), acetone (5 drops) was added, followed by brine (1 mL) and EtOAc (1 mL). The suspension was warmed to room temperature, the aq layer was extracted with EtOAc (2 x 4 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to a colorless film (9.1 mg). This material was used directly in the following reaction.

To a solution of the crude material in THF (1.5 mL, 25 mM) at 0 °C was added a solution of MeMgBr (71 μL, 2.7 M in THF, 191 μmol, 5 equiv) and the bath was removed after 5 min. Upon consumption by TLC analysis (1:1 hexanes/EtOAc), the reaction was cooled in an ice/water bath, and MeOH (200 μL), brine (1 mL), saturated aq NH_4Cl (1mL), and EtOAc (2 mL) were added. The aq layer was extracted with EtOAc (2 x 4 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification via flash chromatography (2:1 hexanes/EtOAc) afforded diol **295** as a colorless film that solidifies over time to an off-white solid (7.4 mg, 31.0 μmol, 73% yield over two steps, >20:1 dr).

R_f = 0.30 (1:1 hexanes/EtOAc); mp = 123–126 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.03 (app t, *J* = 6.6 Hz, 1H), 2.60 (app dt, *J* = 13.5, 2.8 Hz, 1H), 1.94–1.88 (m, 1H), 1.73 (s, 3H), 1.71–1.23 (comp m, 11H), 1.21 (s, 6H), 1.08 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.7, 126.9, 72.9, 71.7, 50.7, 41.7, 36.2, 35.3, 29.0, 27.4, 27.0, 26.9, 24.8, 23.2, 15.2; IR (Neat Film NaCl) 3366 (br), 2934, 2863, 1455, 1374, 1277, 1138, 1076, 1014, 922, 734 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{15}H_{26}O_2$ $[M]^+$: 238.1933, found 238.1921; $[\alpha]_D^{21.6}$ +21.6° (*c* 0.34, MeOH, 92% ee).



(+)-295 *(+)-279*

(+)-Carissone (279).[19e] To a solution of diol **295** (3.1 mg, 13.0 μmol, 1.0 equiv) in CH_2Cl_2 (520 μL, 25 mM) was added oven-dried 4 Å MS (15 mg), followed by MnO_2 (13.3 mg, 130 μmol, 10 equiv). Upon consumption by TLC (1:1 hexanes/EtOAc), the reaction was diluted with Et_2O (2 mL) and filtered through a small plug of silica gel, washing with Et_2O. This was concentrated in vacuo to afford (+)-carrisone (**279**) as a colorless film (3.1 mg, 131 μmol, 100% yield). R_f = 0.34 (1:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.86 (app dt, *J* = 14.4, 2.6 Hz, 1H), 2.51 (ddd, *J* = 16.9, 13.3, 6.4 Hz, 1H), 2.39 (app dt, *J* = 16.8, 3.8 Hz, 1H), 1.90 (app t, *J* = 13.9 Hz, 1H), 1.82–1.69 (comp m, 4H), 1.78 (s, 3H), 1.55–1.36 (comp m, 3H), 1.26 (s, 3H), 1.25 (s, 3H), 1.20 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.1, 162.6, 128.8, 72.4, 49.6, 41.9, 37.3, 35.8, 33.7, 28.7, 27.5, 26.7, 22.5, 22.4, 10.9; IR (Neat Film NaCl) 3448 (br), 2970, 2935, 1652, 1608, 1452, 1353, 1300, 1212, 1189, 1149, 1014, 918, 817 cm^{-1}; HRMS (FAB+) *m/z*

calc'd for $C_{15}H_{25}O_2$ $[M + H]^+$: 237.1855, found 237.1844; $[\alpha]_D^{23.1}$ +119.6° (*c* 0.31, $CHCl_3$, 92% ee); lit. $[\alpha]_D^{22}$ +138.7° (*c* 0.163, $CHCl_3$).

4.6 NOTES AND REFERENCES

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(8) Qualitatively, the reaction rates for the electron deficient acyl substrates are faster than the traditional vinylogous esters. For example, substrates **181** and **263** require 10–16 h to reach complete conversion, whereas substrates **265**, **267**, and **269** reach full conversion in 2–4 h.

(9) We have recently obtained spectroscopic and crystallographic evidence indicating that a Pd–β-keto carboxylate complex is the resting state of the catalytic cycle for

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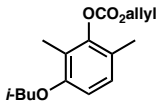

304

(26) The reactivity of vinylogous β-ketoester (±)-**275** contrasts significantly with that of related derivative (±)-**271**. See the subsection 4.2.3.

(27) β-ketoester (±)-**275** was recovered in 9% yield.

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