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Asymmetric [2,3]-Wittig rearrangement of the dienolates of chiral secondary alcohol-substituted β-pyrrolidinyl-γ-allyloxyl-α,β-unsaturated esters: total synthesis of (+)-eldanolide

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ABSTRACT

The asymmetric [2,3]-Wittig rearrangement of the dienolates of various chiral β-pyrrolidinyl-γ-allyloxyl-α,β-unsaturated esters was investigated using different chiral secondary alcohol substitutions. When (1*S*,2*R*,4*R*)-2-hydroxy-7,7-dimethylbicyclo[2,2,1]heptane-1-carboxylic acid diisopropylamide was used as chiral auxiliary, it provided the best enantioselectivity in the rearrangement. When various γ-allyloxy substitutions underwent temperature and additive studies, 1,1-dimethylpropenoxy substitution was found to give the best enantioselectivity. The methodology was applied to the total synthesis of (+)-eldanolide.

1. Introduction

Recently, we have reported studies of the [2,3]-Wittig rearrangement involving the use of dienolates of achiral β-pyrrolidinyl-γ-allyloxyl-α,β-unsaturated esters.[1] Since the resulting cyclized products could be transformed into α,β-unsaturated γ-monosubstituted γ-lactones,[2,3] which are potentially important starting materials for the synthesis of a variety of natural products, studies on the asymmetric [2,3]-Wittig rearrangement involving the chiral version of the unsaturated ester would be of interest.[4] Herein, we report our investigation on the asymmetric [2,3]-Wittig rearrangement related to the use of various chiral secondary alcohol-substituted β-pyrrolidinyl-γ-allyloxyl-α,β-unsaturated esters.

2. Results and discussion

Our studies commenced with the synthesis of various chiral secondary alcohol-substituted simple β-pyrrolidinyl-γ-allyloxyl-α,β-unsaturated esters, as shown in Scheme 1. Reactions of 2-(allyloxy)acetyl chloride **1** with Meldrum's acid provide **2** in 95% yield, and the subsequent treatment of **2** with various chiral secondary alcohols **3a**–**3e** in refluxing toluene generated chiral ketoesters **4a–4e** in 75–86% yields, respectively.[5] Finally, condensation of **4a–4e** with pyrrolidine successfully provided **5a–5e** in 92–97% yields, respectively (Scheme 1).

With the unsaturated esters **5a–5e** in hand, compounds **5a–5e** were first subjected to rearrangement studies in order to test their behaviors and efficacies in the [2,3]-Wittig rearrangement. When reactions were carried out by deprotonation with lithium diisopropylamine (2 equiv) at −78 °C and then slowly warmed up to room temperature within a 5-h period, rearrangement of the dienolate of **5d** provided β-pyrrolidinyl-γ-allyl-α,β-unsaturated γ-lactone **7** in 48% enantiomeric excess, with the best enantioselectivity among the rearrangements of dienolates of **5a–e** (Scheme 2).

The unsaturated lactone **7** was presumably obtained through a three-step sequence; the first step, involved the LDA deprotonation; the second step, a [2,3]-Wittig rearrangement, which was an enantioselection-determining step; and finally, the cyclization of resulting lithium alkoxides (*S*)-**8** and (*R*)-**8**, which were en route to unsaturated lactones (*S*)-**7** and (*R*)-**7** (Scheme 3). Since the chemical yield and enantioselectivity of the resulting unsaturated lactones were highly susceptible to the reaction conditions, especially temperature changes, the enantioselectivity of the rearrangement of **5d** was further optimized through detailed temperature and additive studies, as shown in Table 1.[6] When **5d** was reacted at constant temperature throughout the reaction without the addition of LiBr (entries 1, 2, 5, and 8), enantioselectivities were found to decrease when increasing the temperature. Although lower temperature conditions increased the enantioselectivities of the rearrangements, temperatures at or below −40 °C were found to not be efficient for the rearrangement and the subsequent cyclizations (entry 1). When LiBr was added for the rest of studies, the enantioselectivities dramatically increased, presumably due to the perturbation of lithium aggregation,[7] subsequently biasing the formation of one enantiomer over the other. The temperature of

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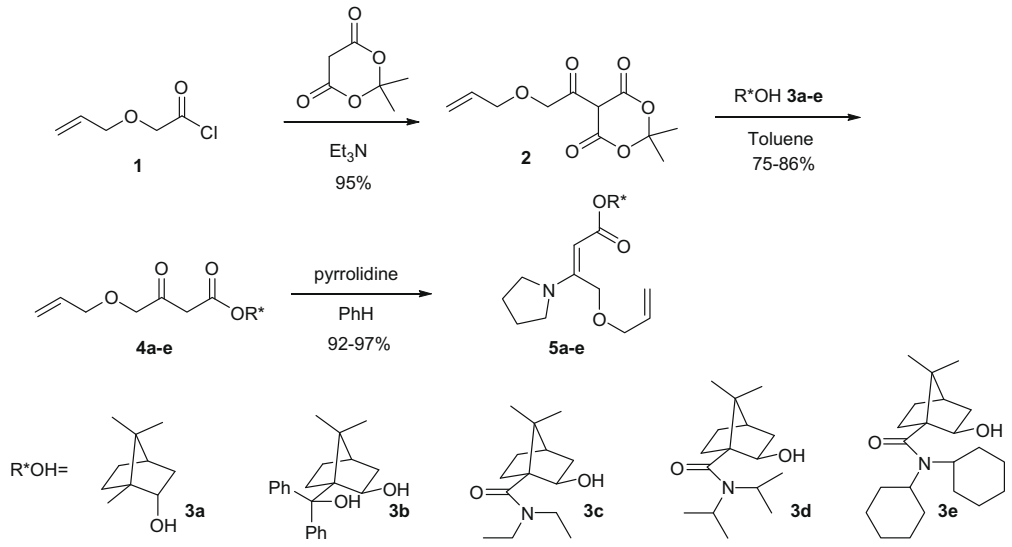
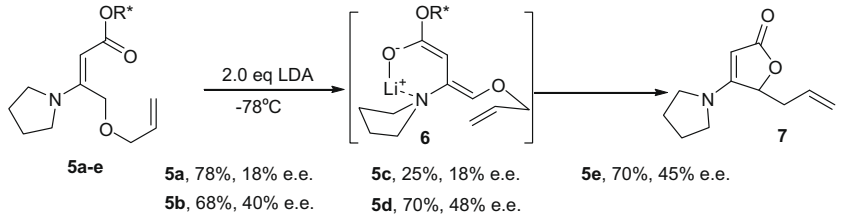
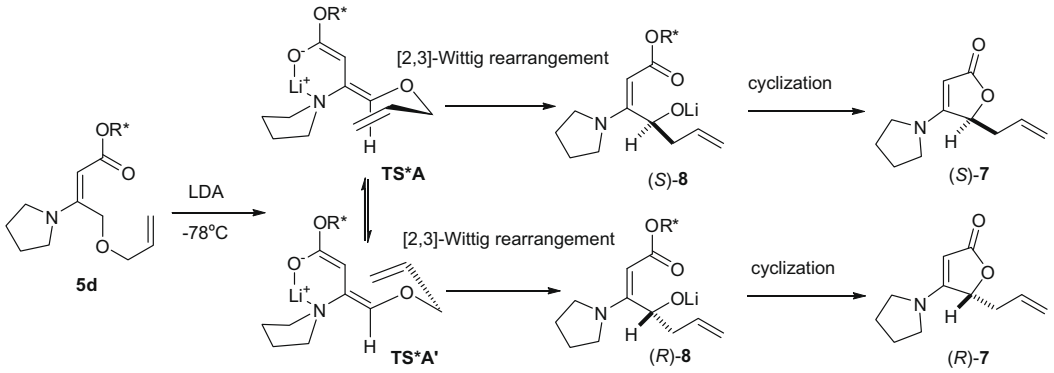


Scheme 1.



Scheme 2.



Scheme 3.

−30 °C was effective for the rearrangement and cyclization (entry 3), which provided a reasonable 86% enantiomeric excess. When reactions were performed at higher temperatures, similar to cases without LiBr, the enantioselectivities of the rearrangement deteriorated with increasing temperature (entries 6, 7, 9, and 10).

After the completion of studies using simple allyloxyl substitution, substituted propenoxyl groups such as 2-methyl, 1,1-dimethyl, and 3,3-dimethyl were used to study their rearrangement. Although 2-methyl-substituted **12** was straightforwardly synthesized, similar to the synthesis of **5d** as shown in Scheme 4, the synthesis of 1,1-dimethyl and 3,3-dimethyl substitution proved to be more difficult, partially due to the early introduction of these sensitive alkene groups. Therefore a synthetic strategy involving the introduction of these alkenes at a later stage was designed to overcome this problem. Ketoester **13** was first synthesized in 94% yield by refluxing **3d** with Meldrum's acid, and then by treating **13** with bromine to afford bromoketoester **14** in a satisfactory 88% yield. The reaction of sodium alkoxide of **15a**–**b** with **14** generated **16a**–**b** in 75–79% yields. Finally, **17a**–**b** were obtained with the condensation of pyrrolidine under refluxing benzene conditions in 96–98% yields (Scheme 5).

gem-Dimethyl-substituted **17a** was used to study the rearrangement, as shown in Scheme 6 and Table 2. While studies indicated that the rearrangement cannot occur efficiently at −30 °C (entries 1 and 2), it reacted smoothly to provide unsaturated lactone **18** in good enantioselectivities,[8] when reactions were performed at −20 °C or −15 °C (entries 4–10). Similar to previous studies, the addition of LiBr also improved the enantioselectivity, though less dramatically than in the case of **5d**, increasing from

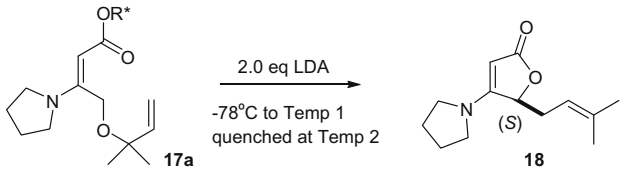
Table 1
Rearrangement studies of **5d**

Entry	LiBr (equiv)	Temp 1[a]	Temp 2[b]	ee[c] (%)	Yield[d] (%)
1	0.0	−40	−40	45	26
2	0.0	−30	−30	48	90
3	1.0		−30	86	92
4	1.0		−15	85	92
5	0.0	−20	−20	31	91
6	1.0		−20	74	93
7	1.0		−15	74	92
8	0.0	−15	−15	30	92
9	1.0		−15	57	94
10	1.0		−10	57	95

[a] Reaction temperature after LDA deprotonation (3 h).
[b] Quenched temperature.
[c] Enantiomeric excesses of **7** were determined by HPLC column using a chiral stationary phase (Chiralpak AD-H, *n*-hexane/methanol 17:1).
[d] Isolated yields.

77% to 93% enantiomeric excess (entry 3 vs entry 4). According to these studies, the rearrangement of **17a** seems to be more stereoselective, even without LiBr addition, and also more tolerable over a broader temperature range. This is presumably due to the existence of a bulky *gem*-dimethyl group, which constrained the rotational degree of freedom, therefore rendering steric bias in favor of one diastereomeric transition state over the other.

When vinyl methyl-substituted compounds such as **12** and **17b** were used in the reaction studies as shown in Scheme 7, the rearrangement of **12** at temperatures above −20 °C generated **19** in



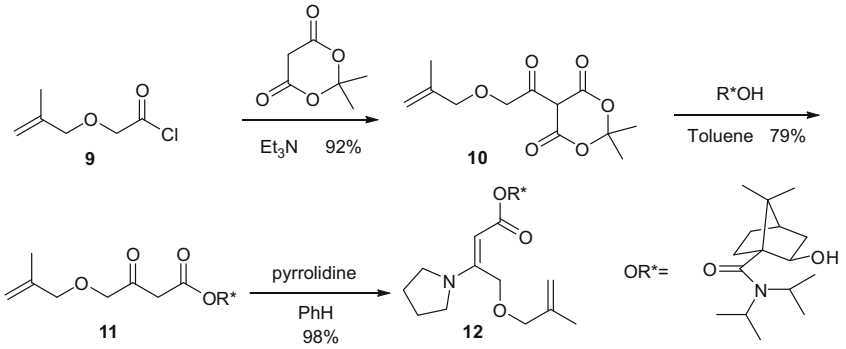
Scheme 6.

Table 2
Rearrangement studies of **17a**

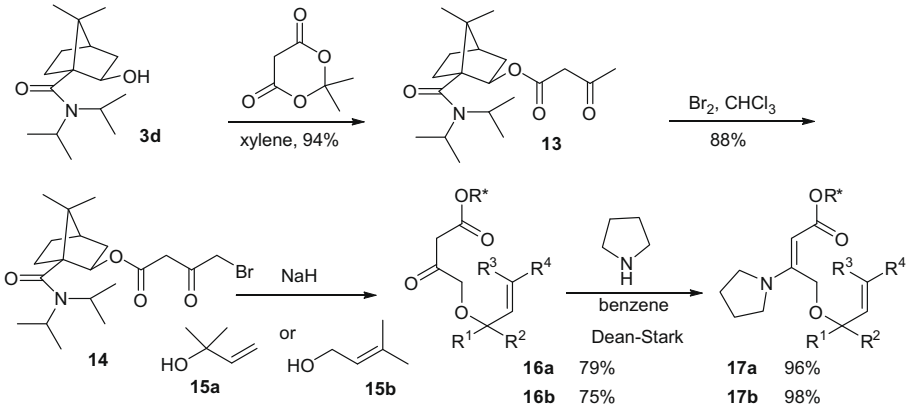
Entry	LiBr (equiv)	Temp 1[a]	Temp 2[b]	ee[c] (%)	Yield[d] (%)
1	1.0	−30	−30	N.D.[e]	Trace
2	1.0	−30	−25	N.D.	Trace
3	0.0	−20	−20	77	86
4	1.0	−20	−20	93	88
5	1.0	−20	−10	95	93
6	1.0	−20	−5	93	90
7	1.0	−15	−15	90	88
8	1.0	−15	−10	87	93
9	1.0	−15	−5	90	90
10	1.0	−15	0	88	92

[a] Reaction temperature after LDA deprotonation (3 h).
[b] Quenched temperature.
[c] Enantiomeric excesses of **18** were determined by HPLC column using a chiral stationary phase (Chiralpak AD-H, *n*-hexane/methanol 17:1).
[d] Isolated yields.
[e] Not determined.

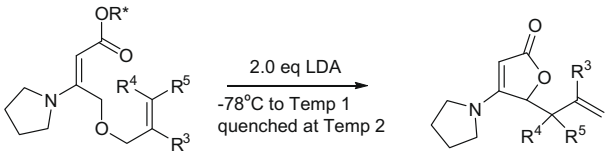
70–73% yields with moderate enantioselectivities (53–60% ee, Table 3). In contrast, the rearrangement of **17b** did not provide



Scheme 4.



Scheme 5.



12 $R^4=R^5=H$, $R^3=Me$ **19**

17b $R^4=R^5=Me$, $R^3=H$ **20**

Scheme 7.

Table 3
Rearrangement studies of **12**

Entry	LiBr (equiv)	Temp 1[a]	Temp 2[b]	ee[c] (%)	Yield[d](%)
1	1.0	−30	−25	N.D.[e]	Trace
2	1.0	−30	−20	N.D.	Trace
3	1.0	−20	−20	60	70
4	1.0	−20	−15	65	73
5	1.0	−20	−10	55	72
6	1.0	−20	−5	53	70
7	1.0	−15	−15	44	77
8	1.0	−15	−10	44	72
9	1.0	−15	0	43	77

[a] Reaction temperature after LDA deprotonation (3 h).
[b] Quenched temperature.
[c] Enantiomeric excesses of **19** were determined by HPLC column using a chiral stationary phase (Chiralpak AD-H, *n*-hexane/methanol 17:1).
[d] Isolated yields.
[e] Not determined.

meaningful enantioselectivity, presumably hampered by the existence of a bulky vinyl *gem*-dimethyl group at the reacting center, which prevented the rearrangement from occurring in an orderly fashion (Table 4).

Table 4
Rearrangement studies of **17b**

Entry	LiBr (equiv)	Temp 1[a]	Temp 2[b]	ee[c] (%)	Yield[d] (%)
1	1.0	−30	−20	25	40
2	1.0	−20	−5	−11	40
3	1.0	−15	−5	−13	68

[a] Reaction temperature after LDA deprotonation (3 h).
[b] Quenched temperature.
[c] Enantiomeric excesses of **20** were determined by HPLC column using a chiral stationary phase (Chiralpak AD-H, *n*-hexane/methanol 17:1).
[d] Isolated yields.

Since the rearrangement of **17a** was able to achieve reasonable enantioselectivity, the resulting unsaturated lactone **18** can be transformed into butenolide and serve as a valuable starting building block for various natural product syntheses. Eldanolide **21**, the pheromone of the male African sugar stem borer, with a very similar structure, can be easily synthesized to demonstrate our methodology.[9,10] Since (+)-eldanolide possesses a prenyl group with the (*R*)-absolute stereochemistry, (1*R*,2*S*,4*S*)-2-hydroxy-7,7-dimethylbicyclo[2,2,1]heptane-1-carboxylic acid diisopropylamide **22** was chosen as a chiral auxiliary to start the synthesis. Unsaturated ester **26** was synthesized following the previously designed protocol, as shown in Scheme 8.

When **26** was deprotonated with LDA at −78 °C, and then warmed to −20 °C for 3 h, γ-prenyl-substituted unsaturated lactone **27** was obtained in 90% yield with 93% enantiomeric excess. Subsequent treatment of **27** with lithium in liquid ammonia, followed by the Cope elimination using metachloroperbenzoic acid provided γ-prenyl-substituted butenolide **28** {$[\alpha]_D^{26} = -125.2$ (*c* 1.15, MeOH) [lit.[9b] $[\alpha]_D^{20} = -130$ (*c* 0.80, MeOH)]}, in two steps in 72% yield (93% ee). Final introduction of the methyl group, as in Vigneron's final approach,[9b] upon treatment of **28** with dimethyl cuprate in the presence of trimethylsilyl chloride gave (+)-eldanolide **21** in 85% yield and 93% enantioselectivity. Synthetic (+)-**21** possessed spectroscopic data {e.g., 300 MHz ^{1}H and 75 MHz ^{13}C; $[\alpha]_D^{26} = +46.5$ (*c* 1.02, MeOH) [lit.[9b] $[\alpha]_D^{20} = +51.5$ (*c* 1.15, MeOH)]} identical to the natural pheromone.

3. Conclusion

In conclusion, we have demonstrated that chiral secondary alcohol-substituted β-pyrrolidinyl-γ-allyloxyl-α,β-unsaturated esters can successfully undergo asymmetric [2,3]-Wittig rearrangement to provide γ-monosubstituted α,β-unsaturated lactone in good enantioselectivity. (+)-Eldanolide was successfully synthesized to demonstrate this methodology. Applications of this study for the synthesis of other natural products are currently in progress in our laboratory.

4. Experimental

Melting points were determined on a Fisher-Jones melting point apparatus and are uncorrected. Optical rotations were measured at ambient temperature on a Jasco P-1010 polarimeter using a NaD (586 nm) lamp quartz cell with a path length of 0.1 dm; abs values were corrected for the rotation of cell with solvent.

^{1}H NMR was recorded at 300 MHz on a Varian Mercury-300 nuclear magnetic resonance spectrometer. Chemical shift is reported in ppm (δ) from tetramethylsilane with the solvent resonance of $CDCl_3$ (7.24 ppm) as the internal standard. Data are reported as follows: chemical shift (multiplicity {s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet}, integration, coupling constant (Hz), and assignment.) (*J*) refers to the observed coupling constant(s) in hertz. The chemical shift difference in hertz between the signals for protons A and B of an AB quartet is Du. As described in Silverstein, Bassler, and Morririll's text, a four-line two-spin pattern was analyzed as shown in the figure below and by using the equation; (a–c) = $[(Du)^2 + JAB^2]^{0.5}$. Letting (a–c) = x and rearranging the equation solves for Du = $[(x)^2 - JAB^2]^{0.5}$. For those examples where multiples were recognized as the A and B protons of ABmx pattern, the chemical shift is reported as the midpoint of the multiplet.

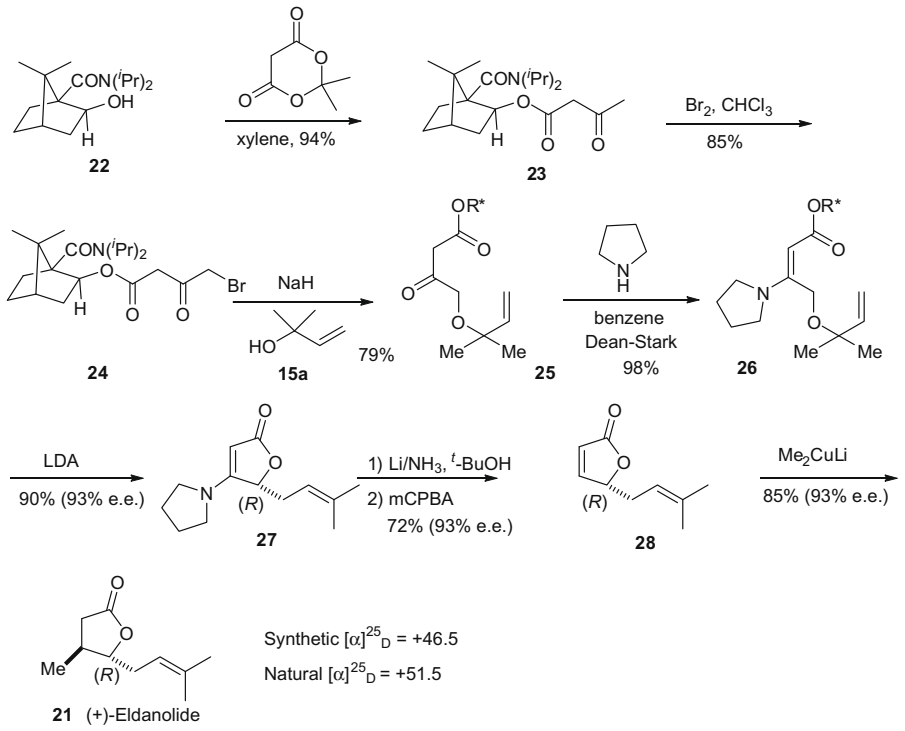
Chemical shift of ^{13}C NMR spectra was also recorded on the Varian Mercurry-200 NMR instrument (50 MHz) using the solvent resonance of $CDCl_3$ (δ 77.0 ppm) as the internal standard.

Infrared spectra were recorded on a Perkin–Elmer 1600 series Fourier transform infrared spectrometer. Infrared frequencies are reported in reciprocal centimeters (cm^{-1}).

Analytical HPLC analyses were performed with a Jasco PU-980 and LDC spectrometer Jasco UV-975 detector using 5um silica columns supplied by Hypersil® with 250 × 4.6 mm column. The UV spectra were recorded with a Jasco V-530 UV/VIS spectrophotometer. Chiral compounds were analyzed using Chiralcel OJ or OD columns supplied by Chiral Technologies Inc.® Gmax and gs mean maximum and shoulder, respectively.

Mass spectra were recorded on a VG-7035 mass spectrometer at an ionizing voltage of either 70 or 20 eV; alternatively, samples were analyzed by the Instrumental center of National Science Consul at National Chung Hsing University. Mass spectra are reported as *m*/*z* values for the parent peak M+ and/or the major fragments. The values in parentheses refer to the relative peak intensities. Microanalyses were carried out by Instrumental center of National Science Consul at National Chung Hsing University.

Reaction progress was monitored by analytical thin-layer chromatography on Analtech 250 nm hard layer Silica Gel 60 F-250 plates cut into 1 cm × 5 cm sections. Visualization was effected



Scheme 8.

by ultraviolet light (254 nm), followed by dipping the plate into the appropriate stain and then charring on a hot plate. [15% (w/v) solvent of phosphoromolybdic acid and 95% ethanol (PMA); or 1.8% (w/v) solution of anisaldehyde, 2.5% concentrated sulfuric acid, 0.07% acetic acid, and 95% ethanol (Anisaldehyde); or 0.6% (w/v) solution of potassium permanganate, 6.1% potassium carbonate, 1.5% of 5% aq NaOH, and water (permanganate)].

Flash chromatography was performed on silica gel 230–400 mesh, eluted with appropriate solvents.

Reactions requiring heating were immersed in thermostat-controlled silicon-oil baths. The low temperature baths were dry ice/acetone (−78 °C), dry ice/CCl_4 (−20 °C), and ice water (0 °C). Reactions, which were maintained at low temperature for extended periods of time, were kept in Neslab thermostat-controlled Cryobath with stirrer. Reactions other than those in which water was present as a solvent, reagent or by-product were normally performed under a slight positive pressure of nitrogen in vessels, which had been flame-dried under a slow nitrogen flow and sealed with rubber septa. The nitrogen gas was dried by passing it through a drying tube filled with Drierite®. Additions of liquid to the vessels were made via a syringe or a cannula through septa. Solid was added through open septa. All reactions were stirred with Teflon-coated magnetic stir bars. Removal of solvents was normally accomplished using a Jasco rotary evaporator connected to a vacuum pump. The flask was heated, if necessary, by a warm water bath. Samples were lyophilized on a labconco Freeze dryer at a pressure of approximately 0.03 mm Hg.

4.1. Reagents and solvents

The following solvents were distilled directly before use, under a slightly positive pressure of nitrogen. Diethyl ether and tetrahydrofuran were distilled from sodium benzophenone ketyl, and pyridine was distilled from calcium hydride. Methanol was distilled from magnesium methoxide and methylene chloride was distilled from calcium hydride. Chloroform, isopropyl alcohol, hexane, and cyclohexane for infrared spectra, HPLC analyses, and optical rotations were labeled as spectroscopic grade by the manufacturer.

Reagents were purchased from the Aldrich Chemical Company, Fluka, and Lancaster Synthesis.

4.2. General procedure for the synthesis of ketoesters

4.2.1. Synthesis of 4-allyloxy-3-oxo-butyric acid (1*S*,2*R*)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl ester 4a

(1*S*)-*endo*-(−)-Borneol (1.1 g, 7.4 mmol) and **2** (1.8 g, 7.4 mmol) in 25 mL round-bottomed flask with xylene (12 mL) were heated at reflux under Dean–Stark apparatus. After being refluxed for 3 h, the xylene was removed under vacuo, and then the crude material was purified by flash chromatography (*n*-hexane/ethyl acetate, 10:1) to afford 1.7 g of **4a** in 78% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.93–5.80 (m, 1H), 5.27 (dd, J = 15.5, 1.7 Hz, 1H), 5.20 (dd, J = 10.4, 1.7 Hz, 1H), 4.92 (ddd, J = 10.0, 3.5, 2.2 Hz, 1H), 4.09 (s, 2H), 4.03 (d, J = 5.6 Hz, 2H), 3.52 (s, 2H), 2.39–0.81 (m, 7H), 0.88 (s, 3H), 0.85 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 201.6, 167.1, 133.5, 117.9, 81.1, 74.7, 72.3, 48.8, 47.8, 46.2, 44.8, 36.4, 27.9, 27.0, 19.6, 18.7, 13.3; HRMS-EI calcd for $C_{17}H_{26}O_4$, 294.1831 found 294.1833; MS-EI 294 (M^+, 2), 137 (100), 95 (88), 81 (70); $[\alpha]_D^{26} = -26.4$ (c 0.39, CH_2Cl_2).

4.2.2. Synthesis of 4-allyloxy-3-oxo-butyric acid (1*R*,2*R*)-1-(hydroxy-diphenyl-methyl)-7,7-dimethyl-bicyclo[2.2.1]hept-2-yl ester 4b

According to the general procedure in 75% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, J = 7.9 Hz, 2 H), 7.54 (d, J = 7.9 Hz, 2H), 7.24–7.01 (m, 6H), 5.83 (m, 1H), 5.28–5.16 (m, 2H), 5.14 (m, 1H), 3.94 (d, J = 5.7 Hz, 2H), 3.87 (s, 2H), 3.60 (s, 2H), 2.29–0.98 (m, 7H), 1.14 (s, 3H), 0.57 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 201.3, 164.3, 149.2, 143.3, 133.3, 128.5 (2C), 128.0 (2C), 126.8 (2C), 126.5, 126.1, 126.0 (2C), 118.4, 82.7, 74.6, 72.4, 59.1, 51.4, 47.7, 45.2, 38.3, 31.3, 29.7, 26.9, 24.4, 22.5; HRMS-EI calcd for $C_{29}H_{34}O_5$, 462.2406 found 462.2411; MS-EI 462 (M^+, 1), 183 (100), 123 (20), 105 (56); $[\alpha]_D^{26} = +63.6$ (c 1.4, CH_2Cl_2).

4.2.3. Synthesis of 4-allyloxy-3-oxo-butyric acid (1*R*,2*R*)-1-diethylcarbamoyl-7,7-dimethyl-bicyclo[2.2.1]hept-2-yl ester 4c

According to the general procedure in 82% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.90–5.77 (m, 1H), 5.25 (dd, J = 17.3, 1.5 Hz, 1H), 5.19 (dd, J = 10.3, 1.5 Hz, 1H), 5.15 (m, 1H), 4.01 (s, 2H), 3.99 (d, J = 5.6 Hz, 2H), 3.59–3.52 (m, 2H), 3.44 (d, J = 1.0 Hz, 1H, *A*Bq), 3.43 (d, J = 1.0 Hz, 1H, A*B*q), 3.06 (br, 2H), 2.06–0.61 (m, 7H), 1.29 (s, 3H), 1.11 (s, 3H), 1.04 (t, J = 6.5 Hz, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 201.3, 169.8, 166.1, 133.4, 117.9, 79.5, 74.7, 72.2, 58.7, 51.2, 44.7, 40.5 (2C), 39.5, 29.2, 26.8, 22.5, 21.5, 21.4, 13.9 (2C); HRMS-EI calcd for $C_{21}H_{33}NO_5$, 379.2359 found 379.2354; MS-EI 379 (M^+, 3), 222 (94), 139 (72), 72 (100), 58 (80); $[\alpha]_D^{26} = -20.3$ (c 0.37, CH_2Cl_2).

4.2.4. Synthesis of 4-allyloxy-3-oxo-butyric acid (1*R*,2*R*)-1-diisopropylcarbamoyl-7,7-dimethyl-bicyclo-[2.2.1]hept-2-yl ester 4d

According to the general procedure in 80% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.84 (m, 1H), 5.34–5.18 (m, 2H), 5.05 (dd, J = 7.1, 3.9 Hz, 1H), 4.16 (sep, J = 6.6 Hz, 1H), 4.05 (s, 2H), 4.01 (d, J = 5.5 Hz, 2H), 3.49 (s, 2H), 3.25 (sep, J = 6.7 Hz, 1H), 2.10–0.86 (m, 7H), 1.37 (d, J = 6.6 Hz, 6H), 1.30 (s, 3H), 1.14 (s, 3H), 1.10 (d, J = 6.7 Hz, 3H), 1.05 (d, J = 6.7 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 201.6, 169.5, 166.4, 133.4, 118.2, 80.4, 74.8, 72.3, 59.3, 51.5, 47.2, 46.3, 45.5, 44.7, 40.0, 29.8, 29.7, 26.8, 21.8, 21.6, 21.1, 20.6, 20.5; HRMS-EI calcd for $C_{23}H_{37}NO_5$, 407.2672 found 407.2678; MS-EI 407 (M^+, 4), 149 (60), 141 (88), 121 (58), 86 (100); $[\alpha]_D^{26} = -35.0$ (c 0.5, CH_2Cl_2).

4.2.5. Synthesis of 4-allyloxy-3-oxo-butyric acid (1*R*,2*R*)-1-dicyclohexylcarbamoyl-7,7-dimethyl-bicyclo[2.2.1]hept-2-yl ester 4e

According to the general procedure in 86% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.95–5.77 (m, 1H), 5.29 (dd, J = 17.0, 1.8 Hz, 1H), 5.24 (dd, J = 10.2, 1.8 Hz, 1H), 5.08 (dd, J = 7.2, 3.5 Hz, 1H), 4.08 (s, 2H), 4.03 (d, J = 5.4 Hz, 2H), 3.67 (br, 2H), 3.50 (s, 2H), 2.82–2.70 (m, 4H), 2.60–2.50 (m, 4H), 2.10–0.81 (m, 7H), 2.03–2.02 (m, 12H), 1.30 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 201.4, 169.6, 166.2, 133.4, 118.0, 80.5, 74.7, 72.2, 60.3, 59.5, 56.9, 56.3, 51.4, 45.5, 44.7, 39.9, 31.6, 31.4, 29.9, 29.8, 26.8, 26.7 (2C), 25.8 (2C), 25.2 (2C), 21.8, 21.5; HRMS-EI calcd for $C_{29}H_{45}NO_5$, 487.3298 found 487.3301; MS-EI 487 (M^+, 10), 329 (60), 247 (100), 181 (54), 138 (57); $[\alpha]_D^{26} = -19.8$ (c 0.3, CH_2Cl_2).

4.2.6. Synthesis of 4-(1-methyl-allyloxy)-3-oxo-butyric acid (1*R*,2*R*)-1-diisopropylcarbamoyl-7,7-dimethyl-bicyclo[2.2.1]hept-2-yl ester 11

According to the general procedure in 79% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.04 (dd, J = 7.5, 3.7 Hz, 1H), 4.91 (dd, J = 7.0, 0.9 Hz, 2H), 4.17 (sep, J = 6.7 Hz, 1H), 4.03 (d, J = 14.0 Hz, 1H, *A*Bq), 3.98 (d, J = 14.0 Hz, 1H, A*B*q), 3.89 (s, 2H), 3.48 (s, 2H), 3.24 (sep, J = 6.7 Hz, 1H), 2.06–0.97 (m, 7H), 1.69 (s, 3H), 1.36 (d, J = 6.7 Hz, 3H), 1.35 (d, J = 6.7 Hz, 3H), 1.28 (s, 3H), 1.12 (s, 3H), 1.08 (d, J = 6.7 Hz, 3H), 1.04 (d, J = 6.7 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 201.6, 169.4, 166.3, 140.8, 113.2, 80.4, 75.2, 74.6, 59.2, 51.4, 47.2, 46.3, 45.5, 44.7, 40.0, 29.7, 26.8, 21.8, 21.5, 21.1, 20.6, 20.5, 20.4, 19.3.

HRMS-EI calcd for $C_{24}H_{39}NO_5$, 421.2828 found 421.2822; MS-EI 421 (M^+, 4), 167 (49), 139 (97), 55 (100); $[\alpha]_D^{26} = -37.9$ (c 0.21, CH_2Cl_2).

4.2.7. Synthesis of 3-oxo-butyric acid (1*R*,2*R*)-1-diisopropylcarbamoyl-7,7-dimethyl-bicyclo[2.2.1]hept-2-yl ester 13

According to the general procedure in 94% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.09 (dd, J = 7.6, 3.5 Hz, 1H), 4.18 (sep, J = 6.6 Hz, 1H), 3.43 (d, J = 15.5 Hz, 1H, *A*Bq), 3.37 (d, J = 15.5 Hz, 1H, A*B*q), 3.27 (sep, J = 6.7 Hz, 1H), 2.25 (s, 3H), 2.09–0.99 (m, 7H), 1.39 (d, J = 6.7 Hz, 3H), 1.38 (d, J = 6.7 Hz, 3H), 1.32 (s, 3H), 1.15 (s, 3H), 1.12 (d, J = 6.6 Hz, 3H), 1.07 (d, J = 6.6 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 200.1, 169.5, 166.2, 80.3, 59.4, 51.5, 49.8, 47.3, 46.4, 44.8, 44.7, 40.1, 30.6, 29.8, 26.8, 21.8, 21.6, 21.1, 20.6, 20.5; HRMS-EI calcd for $C_{20}H_{33}NO_4$, 351.2410 found 351.2403; MS-EI 351 (M^+, 3), 206 (37), 167 (49), 149 (39), 139 (100), 121 (39), 85 (71); $[\alpha]_D^{26} = -16.9$ (c 0.19, CH_2Cl_2).

4.2.8. Synthesis of 4-bromo-3-oxo-butyric acid (1*R*,2*R*)-1-diisopropylcarbamoyl-7, 7-dimethyl-bicyclo[2.2.1] hept-2-yl ester 14

To **13** (6.2 g, 17.6 mmol) in 100 mL round-bottomed three-necked flask with $CHCl_3$ (50 mL) at 0 °C was added dropwise a solution of bromine (0.9 mL, 17.6 mmol) in $CHCl_3$ (10 mL) through an addition funnel. After stirring for 30 min at 0 °C, the reaction was allowed to warm to room temperature and then stirred for additional 16 h. Next, H_2O (100 mL) was added to quench the reaction, after which the organic layer was separated and washed by saturated aqueous sodium bicarbonate until the pH reached neutral 7.0. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and then concentrated in vacuo to give a crude material. The crude material was purified by flash chromatography (*n*-hexane/ethyl acetate, 10:1) to afford 6.7 g of product **14** in 88% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.10 (dd, J = 7.6, 3.5 Hz, 1H), 4.17 (sep, J = 6.6 Hz, 1H), 4.03 (d, J = 12.8 Hz, 1H, *A*Bq), 3.99 (d, J = 12.8 Hz, 1H, A*B*q), 3.69 (d, J = 16.0 Hz, 1H, *A*Bq), 3.63 (d, J = 16.0 Hz, 1H, A*B*q), 3.27 (sep, J = 6.7 Hz, 1H), 2.09–0.99 (m, 7H), 1.39 (d, J = 6.7 Hz, 3H), 1.38 (d, J = 6.7 Hz, 3H), 1.31 (s, 3H), 1.14 (s, 3H), 1.12 (d, J = 6.6 Hz, 3H), 1.06 (d, J = 6.6 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 194.4, 169.5, 165.6, 80.7, 59.4, 51.6, 47.4, 46.5, 45.6, 44.7, 40.0, 34.1, 29.7, 26.8, 21.8, 21.7, 21.1, 20.7, 20.5, 20.4; HRMS-EI calcd for $C_{20}H_{32}BrNO_4$, 429.1515 found 428.0959; MS-EI 428 (M^+, 1), 167 (34), 139 (100), 121 (38), 84 (33); $[\alpha]_D^{26} = -20.9$ (c 0.2, CH_2Cl_2).

4.2.9. Synthesis of 4-(1,1-dimethyl-allyloxy)-3-oxo-butyric acid (1*R*,2*R*)-1-diisopropylcarbamoyl-7,7-dimethyl-bicyclo[2.2.1] hept-2-yl ester 16a

To NaH (0.19 g, 60%, 4.7 mmol, pre-washed with *n*-hexane) in a 50 mL round-bottomed three-necked flask with THF (20 mL) at 0 °C was added dropwise a solution of compound **14** (1.0 g, 2.33 mmol) in THF (3 mL). The reaction mixture was stirred for 30 min at 0 °C, after which a solution of 2-methyl-3-buten-2-ol **15a** (0.3 mL, 2.33 mmol) in THF (2 mL) was added dropwise into the reaction, and then allowed to warm to room temperature slowly, and stirred for additional 6 h at room temperature. The reaction was quenched by the slow addition of water (20 mL), the reaction mixture was acidified with aqueous HCl (1 M) to pH 4.0, and then extracted with EtOAc (10 mL × 2). The combined organic layer was washed with brine, then dried over anhydrous sodium sulfate, and concentrated to give crude material. The crude material was purified by flash chromatography (*n*-hexane/ethyl acetate, 10:1) to afford 0.80 g of product **16a** in 79% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.71 (dd, J = 17.3, 11.0 Hz, 1H), 5.10 (dd, J = 17.3, 1.6 Hz, 1H), 5.09 (dd, J = 11.0, 1.6 Hz, 1H), 5.06 (dd, J = 7.3, 4.0 Hz, 1H), 4.19 (sep, J = 6.6 Hz, 1H), 3.91 (s, 2H), 3.57 (d, J = 16.3 Hz, 1H, *A*Bq), 3.47 (d, J = 16.3 Hz, 1H, A*B*q), 3.27 (sep, J = 6.7 Hz, 1H), 2.09–0.99 (m, 7H), 1.39 (d, J = 6.7 Hz, 3H), 1.38 (d, J = 6.7 Hz, 3H), 1.31 (s, 3H), 1.28 (s, 6H), 1.15 (s, 3H), 1.11 (d, J = 6.6 Hz, 3H), 1.07 (d, J = 6.6 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 202.6, 169.4, 166.6, 142.2, 115.2, 80.2, 76.4, 68.8, 59.2, 51.4, 47.2, 46.2, 45.6, 44.7, 40.0, 29.7, 26.8, 25.5, 25.3, 21.9, 21.5, 21.1, 20.6, 20.5, 20.4; HRMS-EI calcd for $C_{25}H_{41}NO_5$, 435.2985 found 435.2990; MS-EI 435 (M^+, 1), 206 (78), 149 (100), 86 (67), 84 (46); $[\alpha]_D^{26} = -29.0$ (c 0.47, CH_2Cl_2).

4.2.10. Synthesis of 4-(3-methyl-but-2-enyloxy)-3-oxo-butyric acid (1*R*,2*R*)-1-diisopropylcarbamoyl-7,7-dimethyl-bicyclo [2.2.1] hept-2-yl ester 16b

Following the same procedure as in the preparation of compound **16a** in 75% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.27 (t, J = 8.5 Hz, 1H), 5.04 (dd, J = 7.2, 3.5 Hz, 1H), 4.16 (sep, J = 6.6 Hz, 1H), 4.00 (s, 2H), 3.98 (d, J = 8.5 Hz, 2H), 3.47 (s, 2H), 3.24 (sep, J = 6.7 Hz, 1H), 2.07–0.99 (m, 7H), 1.72 (s, 3H), 1.63 (s, 3H), 1.37 (d, J = 6.7 Hz, 3H), 1.36 (d, J = 6.7 Hz, 3H), 1.29 (s, 3H), 1.13 (s, 3H), 1.09 (d, J = 6.6 Hz, 3H), 1.04 (d, J = 6.6 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 201.9, 169.4, 166.4, 138.4, 119.9, 80.3, 74.6, 67.7, 51.5, 47.2, 46.3, 45.6, 44.7, 40.0, 29.8, 26.8, 25.7, 21.9, 21.5, 21.1, 20.6, 20.5, 20.4, 20.3, 18.0; HRMS-EI calcd for $C_{25}H_{41}NO_5$, 435.2985 found 435.2981; MS-EI 435 (M^+, 1), 206 (78), 149 (100), 86 (56); $[\alpha]_D^{26} = -26.5$ (c 0.6, CH_2Cl_2).

4.2.11. Synthesis of 3-oxo-butyric acid (1*S*,2*S*)-1-diisopropylcarbamoyl-7,7-dimethyl-bicyclo[2.2.1]hept-2-yl ester 23

According to the general procedure in 94% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.09 (dd, J = 7.6, 3.5 Hz, 1H), 4.18 (sep, J = 6.6 Hz, 1H), 3.43 (d, J = 15.5 Hz, 1H, *A*Bq), 3.37 (d, J = 15.5 Hz, 1H, A*B*q), 3.27 (sep, J = 6.7 Hz, 1H), 2.25 (s, 3H), 2.09–0.99 (m, 7H), 1.39 (d, J = 6.7 Hz, 3H), 1.38 (d, J = 6.7 Hz, 3H), 1.32 (s, 3H), 1.15 (s, 3H), 1.12 (d, J = 6.6 Hz, 3H), 1.07 (d, J = 6.6 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 200.1, 169.5, 166.2, 80.3, 59.4, 51.5, 49.8, 47.3, 46.4, 44.8, 44.7, 40.1, 30.6, 29.8, 26.8, 21.8, 21.6, 21.1, 20.6, 20.5; $[\alpha]_D^{26} = +16.8$ (c 0.38, CH_2Cl_2).

4.2.12. Synthesis of 4-bromo-3-oxo-butyric acid (1*S*,2*S*)-1-diisopropylcarbamoyl-7,7-dimethyl-bicyclo[2.2.1] hept-2-yl ester 24

Following the same procedure as in the preparation of compound **14** in 85% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.10 (dd, J = 7.6, 3.5 Hz, 1H), 4.17 (sep, J = 6.6 Hz, 1H), 4.03 (d, J = 12.8 Hz, 1H, *A*Bq), 3.99 (d, J = 12.8 Hz, 1H, A*B*q), 3.69 (d, J = 16.0 Hz, 1H, *A*Bq), 3.63 (d, J = 16.0 Hz, 1H, A*B*q), 3.27 (sep, J = 6.7 Hz, 1H), 2.09–0.99 (m, 7H), 1.39 (d, J = 6.7 Hz, 3H), 1.38 (d, J = 6.7 Hz, 3H), 1.31 (s, 3H), 1.14 (s, 3H), 1.12 (d, J = 6.6 Hz, 3H), 1.06 (d, J = 6.6 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 194.4, 169.5, 165.6, 80.7, 59.4, 51.6, 47.4, 46.5, 45.6, 44.7, 40.0, 34.1, 29.7, 26.8, 21.8, 21.7, 21.1, 20.7, 20.5, 20.4; $[\alpha]_D^{26} = +20.7$ (c 0.32, CH_2Cl_2).

4.2.13. Synthesis of 4-(1,1-dimethyl-allyloxy)-3-oxo-butyric acid (1*S*,2*S*)-1-diisopropylcarbamoyl-7,7-dimethyl-bicyclo [2.2.1]hept-2-yl ester 25

Synthesis starting from **24**, following the same procedure as in the preparation of compound **16a** in 79% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.75 (dd, J = 17.4, 11 Hz, 1H),5.18 (d, J = 17.4 Hz, 1H), 5.13 (d, J = 11 Hz, 1H), 5.06 (dd, J = 7.3, 4.0 Hz, 1H), 4.19 (sep, J = 6.6 Hz, 1H), 3.91 (s, 2H), 3.57 (d, J = 16.3 Hz, 1H, *A*Bq), 3.47 (d, J = 16.3 Hz, 1H, A*B*q), 3.27 (sep, J = 6.7 Hz, 1H), 2.09–0.99 (m, 7H), 1.39 (d, J = 6.7 Hz, 3H), 1.38 (d, J = 6.7 Hz, 3H), 1.31 (s, 3H), 1.28 (s, 6H), 1.15 (s, 3H), 1.11 (d, J = 6.6 Hz, 3H), 1.07 (d, J = 6.6 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 202.6, 169.4, 166.6, 142.2, 115.2, 80.2, 76.4, 68.8, 59.2, 51.4, 47.2, 46.2, 45.6, 44.7, 40.0, 29.7, 26.8, 25.5, 25.3, 21.9, 21.5, 21.1, 20.6, 20.5, 20.4; HRMS-EI calcd for $C_{25}H_{41}NO_5$, 435.2985 found 435.2990; MS-EI 435 (M^+, 1), 206 (78), 149 (100), 86 (67), 84 (46); $[\alpha]_D^{26} = +29.0$ (c 0.52, CH_2Cl_2).

4.3. General procedure for the synthesis of vinylogous urethanes

4.3.1. Synthesis of 4-Allyloxy-3-pyrrolidin-1-yl-but-2-enoic acid (1*S*,2*R*)-1,7,7-trimethyl-bicyclo[2.2.1]hept 2-yl ester 5a

To a solution of **4a** (1.0 g, 3.4 mmol) in a 10 mL round-bottomed flask with benzene (10 mL) as solvent were added pyrrolidine (0.34 mL, 4.1 mmol) and *tert*-butyl alcohol (0.2 mL). The reaction mixture was heated to reflux at 100 °C for 40 min using Dean-Stark apparatus to remove water. After removal of benzene under vacuo, 1.2 g of **5a** was obtained in 98% yield and then used in the next reaction without further purifications. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.99–5.86 (m, 1H), 5.28 (dd, J = 17.3, 1.6 Hz, 1H), 5.22 (dd, J = 10.4, 1.6 Hz, 1H), 4.89 (d, J = 11.3 Hz, 1H, *A*Bq), 4.81 (d, J = 11.3 Hz, 1H, A*B*q), 4.86 (m, 1H), 4.55 (s, 1H), 4.06 (d, J = 5.7 Hz, 2H), 3.30 (br, 4H), 2.37–0.94 (m, 7H), 1.90 (br, 4H), 0.89 (s, 3H), 0.84 (s, 3H), 0.81 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.0, 156.3, 134.7, 117.0, 86.5, 77.5, 71.3, 64.2, 48.6, 47.8, 47.6 (2C), 45.0, 37.0, 28.0, 27.2, 25.1 (2C), 19.7, 18.8, 13.5; HRMS-EI calcd for $C_{21}H_{33}NO_3$, 347.2460 found 347.2468; MS-EI 347 (M^+, 12), 194 (100), 139 (71), 95 (58), 81 (56); $[\alpha]_D^{26} = -34.7$ (c 0.4, CH_2Cl_2).

4.3.2. Synthesis of 4-allyloxy-3-pyrrolidin-1-yl-but-2-enoic acid (1*R*,2*R*)-1-(hydroxy-diphenyl-methyl)-7,7-dimethyl-bicyclo[2.2.1] hept-2-yl ester 5b

According to the general procedure in 92% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, J = 7.9 Hz, 2H), 7.64 (d, J = 7.9 Hz, 2H), 7.26–7.02 (m, 6H), 5.93–5.80 (m, 1H), 5.22 (dd, J = 17.3, 1.6 Hz, 1H), 5.14 (dd, J = 10.4, 1.6 Hz, 1H), 5.08 (dd, J = 7.8, 3.8 Hz, 1H), 4.76 (d, J = 11.7 Hz, 1H, *A*Bq), 4.56 (s, 1H), 4.50 (d, J = 11.7 Hz, 1H, A*B*q), 3.84 (d, J = 5.7 Hz, 2H), 3.78–3.22 (br, 4H), 2.39–0.85 (m, 7H), 1.86 (br, 4H), 1.53 (s, 3H), 0.55 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.8, 157.2, 149.2, 144.0, 134.7, 128.4 (2C), 127.6 (2C), 126.8 (2C), 126.4, 126.0, 116.9, 85.0, 81.4, 79.5, 70.8, 63.8, 59.0, 51.1, 47.8 (2C), 39.2, 39.0, 30.8, 29.7, 27.2, 25.1, 24.6 (2C), 22.7, 16.6; HRMS-EI calcd for $C_{33}H_{41}NO_4$, 515.3036 found 515.3030; MS-EI 515 (M^+, 12), 247 (100), 181 (27); $[\alpha]_D^{26} = -48.2$ (c 0.14, CH_2Cl_2).

4.3.3. Synthesis of 4-allyloxy-3-pyrrolidin-1-yl-but-2-enoic acid (1*R*,2*R*)1-diethylcarbamoyl-7,7-dimethyl-bicyclo[2.2.1]hept-2-yl ester 5c

According to the general procedure in 96% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.95–5.82 (m, 1H), 5.22 (dd, J = 17.2, 1.6 Hz, 1H), 5.12 (dd, J = 10.3, 1.6 Hz, 1H), 5.07 (dd, J = 7.6, 4.0 Hz, 1H), 4.86 (d, J = 11.4 Hz, 1H, *A*Bq), 4.70 (d, J = 11.4 Hz, 1H, A*B*q), 4.40 (s, 1H), 4.01 (d, J = 5.7 Hz, 2H), 3.61–3.49 (m, 2H), 3.01 (br, 2H), 2.01–0.96 (m, 7H), 1.85 (br, 4H), 1.33 (s, 3H), 1.11 (s, 3H), 1.01 (t, J = 6.9 Hz, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.9, 167.6, 156.7, 134.6, 117.0, 85.9, 76.8, 71.2, 64.1, 58.8, 50.9, 47.9 (2C), 45.0, 40.2, 40.1 (2C), 30.3, 27.0, 24.9 (2C), 21.8, 21.7, 14.0 (2C); HRMS-EI calcd for $C_{25}H_{40}N_2O_4$, 432.2988 found 432.2984; MS-EI 432 (M^+, 20), 222 (76), 194 (66), 139 (96), 58 (100); $[\alpha]_D^{26} = -48.0$ (c 0.8, CH_2Cl_2).

4.3.4. Synthesis of 4-allyloxy-3-pyrrolidin-1-yl-but-2-enoic acid (1*R*,2*R*)-1-diisopropylcarbamoyl-7,7-di-methyl-bicyclo[2.2.1]hept-2-yl ester 5d

According to the general procedure in 97% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.95–5.82 (m, 1H), 5.23 (dd, J = 17.3, 1.6 Hz, 1H), 5.12 (dd, J = 10.4, 1.6 Hz, 1H), 5.00 (d, J = 11.3 Hz, 1H, *A*Bq), 4.97 (dd, J = 7.8, 3.7 Hz, 1H), 4.61 (d, J = 11.3 Hz, 1H, A*B*q), 4.44 (s, 1H), 4.22 (sep, J = 6.7 Hz, 1H), 4.02 (dt, J = 5.7, 1.5 Hz, 2H), 3.53 (br, 2H), 3.51 (sep, J = 6.7 Hz, 1H), 3.09 (br, 2H), 2.37–1.09 (m, 7H), 1.87 (br, 4H), 1.36 (d, J = 6.7 Hz, 6H), 1.32 (s, 3H), 1.13 (s, 3H), 1.05 (d, J = 6.7 Hz, 3H), 1.00 (d, J = 6.7 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.4, 167.8, 156.7, 134.6, 117.0, 85.9, 77.6, 71.2, 64.1, 59.4, 51.2, 47.8 (2C), 47.0, 46.0, 45.0, 40.5, 30.0, 27.0, 25.4 (1C), 24.6 (1C), 22.0, 21.7, 21.1, 20.7, 20.5, 20.3; HRMS-EI calcd for $C_{27}H_{44}N_2O_4$, 460.3301 found 460.3296; MS-EI 460 (M^+, 20), 194 (91), 152 (80), 139 (100), 55 (40),; $[\alpha]_D^{26} = -15.9$ (c 0.1, CH_2Cl_2).

4.3.5. Synthesis of 4-allyloxy-3-pyrrolidin-1-yl-but-2-enoic acid (1*R*,2*R*)-1-dicyclohexylcarbamoyl-7,7-dimethyl-bicyclo[2.2.1]hept-2-yl ester 5e

According to the general procedure in 98% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.02–5.83 (m, 1H), 5.27 (dd, J = 17.3, 1.7 Hz, 1H), 5.24 (dd, J = 10.3, 1.7 Hz, 1H), 5.10–5.04 (m, 1H), 5.07 (d, J = 11.4 Hz, 1H, *A*Bq), 4.58 (d, J = 11.4 Hz, 1H, A*B*q), 4.47 (s, 1H), 4.05 (d, J = 5.8 Hz, 2H), 3.76 (br, 2H), 3.50 (br, 4H), 3.16 (br, 4H), 2.81–2.52 (m, 8H), 2.17–0.84 (m, 7H), 1.96–1.12 (m, 12H), 1.34 (s, 3H), 1.15 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.8, 167.7, 156.6, 134.7, 128.3, 117.1, 86.1, 71.2, 64.1, 59.8, 56.8, 56.1, 51.2, 48.0 (2C), 45.1, 40.5, 31.8, 31.4, 31.3, 31.0, 29.9, 27.0, 26.8 (2C), 25.9 (2C), 25.3 (4C), 22.1, 21.8; HRMS-EI calcd for $C_{33}H_{52}N_2O_4$, 540.3927 found 540.3921; MS-EI 540 (M^+, 6), 250 (49), 167 (60), 139 (100), 83 (65); $[\alpha]_D^{26} = -40.9$ (c 0.15, CH_2Cl_2).

4.3.6. Synthesis of 4-(1-methyl-allyloxy)-3-pyrrolidin-1-yl-but-2-enoic acid (1*R*,2*R*)-1-diisopropylcarbamo-yl-7,7-dimethyl-bicyclo[2.2.1]hept-2-yl ester 12

According to the general procedure in 98% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.02 (d, J = 11.6 Hz, 1H, *A*Bq), 4.99 (dd, J = 8.1, 3.7 Hz, 1H), 4.95 (dd, J = 2.05, 0.9 Hz, 2H), 4.62 (d, J = 11.6 Hz, 1H, A*B*q), 4.46 (s, 1H), 4.24 (sep, J = 6.6 Hz, 1H), 3.94 (s, 2H), 3.60 (br, 2H), 3.22 (sep, J = 6.7 Hz, 1H), 3.13 (br, 2H), 2.04–0.94 (m, 7H), 1.58 (br, 4H), 1.71 (s, 3H), 1.39 (d, J = 6.7 Hz, 3H), 1.38 (d, J = 6.7 Hz, 3H), 1.34 (s, 3H), 1.15 (s, 3H), 1.07 (d, J = 6.6 Hz, 3H), 1.02 (d, J = 6.6 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.5, 167.9, 156.8, 142.2, 112.0, 85.9, 77.6, 74.2, 64.1, 59.5, 51.2, 47.9 (2C), 47.1, 46.1, 45.0, 40.5, 30.0, 27.0, 25.4, 24.7, 22.1, 21.8, 21.2, 20.8, 20.5, 20.4, 19.6; HRMS-EI calcd for $C_{28}H_{46}N_2O_4$, 474.3458 found 474.3453; MS-EI 474 (M^+, 17), 250 (81), 154 (90), 152 (100), 138 (70); $[\alpha]_D^{26} = -44.8$ (c 0.2, CH_2Cl_2).

4.3.7. Synthesis of 4-(1,1-dimethyl-allyloxy)-3-pyrrolidin-1-yl-but-2-enoic acid (1*R*,2*R*)-1-diisopropylcarbamoyl-7,7-dimethyl-bicyclo [2.2.1]hept-2-yl ester 17a

According to the general procedure in 96% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.89 (dd, J = 17.6, 10.7 Hz, 1H), 5.16 (dd, J = 17.6, 1.2 Hz, 1H), 5.12 (dd, J = 10.7, 1.2 Hz, 1H), 4.98 (dd, J = 7.8, 3.2 Hz, 1H), 4.90 (d, J = 10.4 Hz, 1H, *A*Bq), 4.49 (d, J = 10.4 Hz, 1H, A*B*q), 4.39 (s, 1H), 4.24 (sep, J = 6.6 Hz, 1H), 3.52 (br, 2H), 3.22 (sep, J = 6.7 Hz, 1H), 3.09 (br, 2H), 2.02–0.99 (m, 7H), 1.88 (br, 4H), 1.38 (d, J = 6.7 Hz, 3H), 1.36 (d, J = 6.7 Hz, 3H), 1.31 (s, 3H), 1.32 (s, 6H), 1.14 (s, 3H), 1.06 (d, J = 6.6 Hz, 3H), 1.02 (d, J = 6.6 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.5, 167.6, 158.1, 143.3, 114.1, 84.9, 77.4, 75.8, 59.5, 57.6, 51.2, 48.1 (2C), 47.1, 46.0, 45.0, 40.4, 30.0, 27.0, 25.8, 25.5, 24.7 (2C), 22.1, 21.8, 21.2, 20.8, 20.5, 20.4; HRMS-EI calcd for $C_{29}H_{48}N_2O_4$, 488.3614 found 488.3617; MS-EI 488 (M^+, 30), 250 (56), 154 (100), 153 (88), 137 (84), 86 (47); $[\alpha]_D^{26} = -23.7$ (c 0.2, CH_2Cl_2).

4.3.8. Synthesis of 4-(3-methyl-but-2-enyloxy)-3-pyrrolidin-1-yl-but-2-enoic acid (1*R*,2*R*)-1-diisopropylcarbamoyl-7,7-dimethyl-bicyclo[2.2.1]hept-2-yl ester 17b

According to the general procedure in 98% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.39 (t, J = 7.0 Hz, 1H), 5.05 (d, J = 11.3 Hz, 1H, *A*Bq), 5.04 (dd, J = 7.6, 3.8 Hz, 1H), 4.65 (d, J = 11.3 Hz, 1H, A*B*q), 4.50 (s, 2H), 4.28 (sep, J = 6.6 Hz, 1H), 4.05 (d, J = 7.0 Hz, 2H), 3.58 (br, 2H), 3.27 (sep, J = 6.7 Hz, 1H), 3.15 (br, 2H), 2.08–0.98 (m, 7H), 1.92 (br, 4H), 1.76 (s, 3H), 1.69 (s, 3H), 1.43 (d, J = 6.7 Hz, 3H), 1.42 (d, J = 6.7 Hz, 3H), 1.38 (s, 3H), 1.19 (s, 3H), 1.11 (d, J = 6.6 Hz, 3H), 1.07 (d, J = 6.6 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.5, 167.9, 157.0, 137.5, 120.9, 85.9, 77.7, 66.6, 64.1, 59.5, 51.2, 47.7 (2C), 47.1, 46.1, 45.1, 40.6, 30.1, 27.1, 25.8, 24.5 (2C), 22.1, 21.8, 21.2, 20.8, 20.5, 20.4, 17.9; HRMS-EI calcd for $C_{29}H_{48}N_2O_4$, 488.3614 found 488.3610; $[\alpha]_D^{26} = -32.1$ (c 0.18, CH_2Cl_2).

4.3.9. Synthesis of 4-(1,1-dimethyl-allyloxy)-3-pyrrolidin-1-yl-but-2-enoic acid (1*S*,2*S*)-1-diisopropylcar-bamoyl-7,7-dimethyl-bicyclo [2.2.1]hept-2-yl ester 26

According to the general procedure in 98% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.89 (dd, J = 17.6, 10.7 Hz, 1H), 5.16 (dd, J = 17.6, 1.2 Hz, 1H), 5.12 (dd, J = 10.7, 1.2 Hz, 1H), 4.98 (dd, J = 7.8, 3.2 Hz, 1H), 4.90 (d, J = 10.4 Hz, 1H, *A*Bq), 4.49 (d, J = 10.4 Hz, 1H, A*B*q), 4.41 (d, J = 10.0 Hz, 1H, *A*Bq), 4.39 (s, 1H), 4.24 (sep, J = 6.6 Hz, 1H), 3.52 (br, 2H), 3.22 (sep, J = 6.7 Hz, 1H), 3.09 (br, 2H), 2.02–0.99 (m, 7H), 1.88 (br, 4H), 1.38 (d, J = 6.7 Hz, 3H), 1.36 (d, J = 6.7 Hz, 3H), 1.31 (s, 3H), 1.32 (s, 6H), 1.14 (s, 3H), 1.06 (d, J = 6.6 Hz, 3H), 1.02 (d, J = 6.6 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.5, 167.6, 158.1, 143.3, 114.1, 84.9, 77.4, 75.8, 59.5, 57.6, 51.2, 48.1 (2C), 47.1, 46.0, 45.0, 40.4, 30.0, 27.0, 25.8, 25.5, 24.7 (2C), 22.1, 21.8, 21.2, 20.8, 20.5, 20.4; HRMS-EI calcd for $C_{29}H_{48}N_2O_4$, 488.3614 found 488.3615; $[\alpha]_D^{26} = +23.8$ (c 0.21, CH_2Cl_2).

4.4. General procedure for the [2,3]-Wittig rearrangement of vinylogous urethanes 5a–e

4.4.1. Synthesis of 5-allyl-4-pyrrolidin-1-yl-5*H*-furan-2-one 7

To compound **5d** (50.0 mg, 0.1 mmol) with THF (1 mL) at −78 °C in a 30 mL round-bottomed flask was added a solution of LDA (0.25 mL, 0.25 mmol, 1 N in THF/*n*-hexane), which was then allowed to warm to room temperature over a period of 6 h. The reaction was quenched by the addition of aqueous ammonium chloride solution (1 M, 2 mL), the reaction mixture was extracted with EtOAc (5 mL × 2), dried over anhydrous sodium sulfate, and then concentrated to give crude material. The crude material was purified by flash chromatography (*n*-hexane/acetone, 4:1) to afford 14.7 mg of product **7** in 70% yield with 48% ee. [HPLC Chiralpak AD-H, *n*-hexane/methanol 17:1; 0.5 mL/min; t_R = 67.8 min (minor), t_R = 80.6 min (major)]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.91–5.70 (m, 1H), 5.19 (dd, J = 9.0, 1.2 Hz, 1H), 5.15 (dd, J = 15.2, 1.2 Hz, 1H), 4.91 (dd, J = 6.8, 3.0 Hz, 1H), 4.52 (s, 1H), 3.33 (br, 4H), 2.71 (dd, J = 6.8, 3.0 Hz, 1H), 2.43 (dd, J = 15.2, 9.0 Hz, 2H), 2.08–1.90 (br, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 174.1, 168.2, 131.0, 118.4, 81.2, 78.0, 49.5, 48.2, 35.8, 25.7, 24.3; HRMS-EI calcd for $C_{11}H_{15}NO_2$, 193.1103 found 193.1100.

4.5. General procedure for [2,3]-Wittig rearrangement of 5d with LiBr addition

To **5d** (50 mg, 0.11 mmol) in a 5 mL round-bottomed flask with THF (1 mL) was added a solution of LiBr (0.1 mL, 1.0 M THF) at room temperature. After the reaction mixture was cooled to −78 °C, LDA (1.0 M, 0.25 mL, 0.25 mmol) was added and allowed to warm to −30 °C and stirred for an additional 3 h. After being warmed to −15 °C, the reaction was quenched by the addition of aqueous ammonium chloride (1 M, 3 mL), and then the reaction mixture was extracted with ethyl acetate (5 mL × 3). The combined organic layer was washed with brine then dried over anhydrous sodium sulfate, and concentrated to give crude material. The crude material was purified by flash chromatography (*n*-hexane/acetone, 2:1) to afford 24.5 mg of product **16** in 92% yield with 85% ee [HPLC Chiralpak AD-H, *n*-hexane/methanol 17:1; 0.5 mL/min; t_R = 71.7 min (minor), t_R = 86.8 min (major)].

4.5.1. Synthesis of 5-(3-methyl-but-2-enyl)-4-pyrrolidin-1-yl-5*H*-furan-2-one 18

To **17a** (50 mg, 0.1 mmol) in a 5 mL round-bottomed flask with THF (1 mL) was added a solution of LiBr (0.1 mL, 1.0 M THF) at room temperature. After the reaction mixture was cooled to −78 °C, LDA (1.0 M, 0.25 mL, 0.25 mmol) was added and then allowed to warm to −20 °C, and stirred for an additional 3 h. After warming to −10 °C, the reaction was quenched by the addition of

aqueous ammonium chloride (1 N, 3 mL), and then the reaction mixture was extracted with ethyl acetate (5 mL × 3). The combined organic layer was washed with brine, then dried over anhydrous sodium sulfate, and concentrated to give a crude material. The crude material was purified by flash chromatography (*n*-hexane/acetone, 2:1) to afford 24.5 mg of product **18** in 93% yield with 95% ee [HPLC Chiralpak AD-H, *n*-hexane/methanol 17:1; 0.5 mL/min; t_R = 45.1 min (minor), t_R = 58.6 min (major)]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.18–5.11 (m, 1H), 4.86 (ddd, J = 3.2 Hz, 1H), 4.51 (s, 1H), 3.34 (br, 4H), 2.76–2.66 (br, 2H), 2.01 (br, 4H), 1.70 (s, 3H), 1.62 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 174.2, 168.5, 135.3, 116.8, 81.82, 77.9, 49.5, 48.2, 30.6, 25.8, 25.5, 24.4, 17.8; HRMS-EI calcd for $C_{13}H_{19}NO_2$, 221.1416 found 221.1415; $[\alpha]_D^{26} = +24.1$ (*c* 0.33, CH_2Cl_2).

4.5.2. Synthesis of 5-(2-methyl-allyl)-4-pyrrolidin-1-yl-5*H*-furan-2-one 19

According to the similiar procedure as in the preparation of **18** in 73% yield with 65% ee [HPLC Chiralpak AD-H, *n*-hexane/methanol 17:1; 0.5 mL/min; t_R = 52.7 min (minor), t_R = 64.4 min (major)]. ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.94 (dd, J = 8.3, 2.5 Hz, 1H), 4.88 (d, J = 1.3 Hz, 1H), 4.84 (d, J = 1.3 Hz, 1H), 4.51 (s, 1H), 3.32 (br, 4H), 2.67 (dd, J = 14.7, 2.5 Hz, 1H), 2.26 (dd, J = 14.7, 8.3 Hz, 1H), 2.32–1.92 (br, 4H), 1.81 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 174.3, 168.9, 140.2, 114.2, 82.2, 77.6, 49.4 (br, 2C), 40.7, 25.4 (br, 2C), 22.7; HRMS-EI: ($C_{12}H_{17}NO_2$) Calcd, 207.1259; found, 207.1254.

4.5.3. Synthesis of 5-(1,1-dimethyl-allyl)-4-pyrrolidin-1-yl-5*H*-furan-2-one 20

According to the similiar procedure as in the preparation of **18** in 40% yield with 25% ee [HPLC Chiralpak AD-H, *n*-hexane/methanol 17:1; 0.25 mL/min; t_R = 86.1 min (minor), t_R = 92.2 min (major)]. ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.90 (dd, J = 17.4, 10.6 Hz, 1H), 5.11 (d, J = 17.4 Hz, 1H), 5.08 (d, J = 10.6 Hz, 1H), 4.67 (s, 1H), 4.62 (s, 1H), 3.24–3.22 (br, 4H), 2.00–1.65 (br, 4H), 1.21 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 174.2, 169.3, 143.7, 113.6, 85.1, 84.6, 51.3 (2C), 42.7, 25.2 (2C), 20.6 (2C); HRMS-EI: ($C_{13}H_{19}NO_2$) Calcd, 221.1416; found, 221.1411.

4.6. Synthesis of (+)-eldanolide

4.6.1. Synthesis of 5(*R*)-(3-methyl-but-2-enyl)-4-pyrrolidin-1-yl-5*H*-furan-2-one 27

According to the procedure in the preparation of **18** in 90% yield with 93% ee [HPLC Chiralpak AD-H, *n*-hexane/methanol 17:1; 0.5 mL/min; t_R = 45.1 min (major), t_R = 57.8 min (minor)]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.12 (dd, J = 7.4, 7.2 Hz, 1H), 4.84 (dd, J = 13.7, 3.2 Hz, 1H), 4.49 (s, 1H), 3.35 (br, 4H), 2.72–2.68 (m, 1H), 2.34–2.32 (m, 1H), 2.04–1.93 (m, 4H), 1.68 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 174.5, 168.6, 135.5, 116.8, 82.0, 49.6, 48.2, 30.7, 26.0, 25.7, 17.9; $[\alpha]_D^{26} = -25.8$ (*c* 0.42, CH_2Cl_2).

4.6.2. Synthesis of 5(*R*)-(3-methyl-but-2-enyl)-5*H*-furan-2-one 28

To lithium (31 mg, 4.5 mmol) in 30 mL liquid ammonia at −78 °C, was added a solution of **27** (100 mg, 0.45 mmol) and *tert*-butyl alcohol in 2 mL THF. The reaction mixture was stirred for 3 h and then the reaction was quenched by the addition of isoprene (0.5 mL). The ammonia was allowed to evaporate off after which the reaction mixture was diluted with saturated aqueous ammonium chloride (10 mL) and extracted with ethyl acetate (5 mL × 3). The organic layers were combined, dried over anhydrous sodium sulfate, and the solvent was removed in vacuo to give 86 mg of crude material. To the crude material dissolved in CH_2Cl_2 (5 mL) at 0 °C was added m-CPBA (114 mg, 0.46 mmol), and the reaction was followed by TLC until it reached completion. The reaction was quenched by saturated sodium bicarbonate (5 mL) and then the reaction mixture was extracted with CH_2Cl_2 (5 mL × 3). Combined organic layers were washed with brine then dried over anhydrous sodium sulfate, and concentrated in vacuo to give crude material. The crude material was purified by flash chromatography (*n*-hexane/ethyl acetate, 6:1) to afford 49.5 mg of product **28**, two steps in 72% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (dd, J = 5.9, 1.6 Hz, 1H), 6.06 (dd, J = 5.9, 1.9 Hz, 1H), 5.03 (dq, J = 5.9, 14 Hz, 1H), 4.97 (t, J = 6.3, 1H), 2.40 (m, 2H), 1.66 (s, 3H), 1.56 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.9, 156.1, 136.4, 121.4, 116.1, 82.9, 31.6, 25.5, 17.7; $[\alpha]_D^{26} = -125.2$ (*c* 1.15, MeOH).

4.6.3. Synthesis of (4*S*, 5*R*)-(+)-eldanolide 21

To CuI (186 mg, 0.98 mmol) in ether (10 mL) in a 25 mL three-necked round-bottomed flask at −20 °C under an Ar atmosphere was added a solution of MeLi (1.5 N, 1.3 mL, 1.95 mmol), then allowed to warm to 0 °C. To the reaction mixture pre-cooled to −78 °C was added TMSCl (186 mg, 0.98 mmol) and then compound **20** (49.5 mg, 0.33 mmol) in ether (5 mL). After being stirred for 4 h at −78 °C, the reaction mixture was warmed to −30 °C, then the reaction was quenched with saturated aqueous ammonium chloride (10 mL), and the reaction mixture was allowed to warm to room temperature and extracted with CH_2Cl_2 (5 mL×3). The combined organic layer was washed with brine, then dried over anhydrous sodium sulfate, and concentrated in vacuo to give crude material. The crude material was purified by flash chromatography (*n*-hexane/ethyl acetate, 6:1) to afford 46.5 mg of product **21**, two steps in 85% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.18 (tq, J = 5.9, 14.0 Hz, 1H), 4.03 (dt, J = 6.1, 5.9 Hz, 1H), 2.61 (dd, J = 9.0, 5.9 Hz, 2H), 2.35–2.40 (m, 1H), 2.15–2.35 (m, 1H), 2.15 (dd, J = 16.2, 8.8 Hz, 1H), 1.66 (s, 3H), 1.57 (s, 3H), 1.06 (d, J = 6.4 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 176.5, 135.3, 117.8, 87.0, 37.0, 35.0, 32.1, 25.8, 17.9, 17.6; $[\alpha]_D^{26} = +46.5$ (*c* 1.02, MeOH).

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