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# *anti*-Aldol reactions of chiral alcohol-substituted vinylogous urethanes and the synthesis of (−)-prelactone B

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ABSTRACT

This paper describes a convenient and efficient method for synthesizing chiral alcohol-substituted vinylogous urethanes, in which the double bond has *E* configuration was determined by single crystal X-ray analysis. In addition, we investigated the *anti*-aldol reactions of these chiral vinylogous urethane anions. The use of (1*S*,2*R*,4*R*)-1-(hydroxydiphenylmethyl)-7,7-dimethylbicyclo[2,2,1]-heptan-2-ol as a chiral auxiliary, provided the best enantioselectivities, and the resulting vinylogous urethane lactone could be used for the synthesis of (−)-prelactone B. A plausible mechanism for the generation of major enantiomeric isomer was discussed.

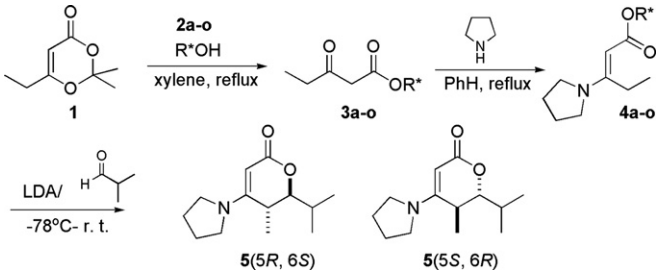


## 1. Introduction

The aldol reaction of vinylogous urethane (VU) anions with aldehyde has become a powerful synthetic tool, because the resulting 4,5-dihydro-1-pyrones are versatile precursors for the synthesis of numerous natural products.[1] It has been shown that both *syn* and *anti* chiral vinylogous urethane lactones (VULs) can be obtained through the reaction of chiral pyrrolidine substituted vinylogous urethane enolates with aldehydes. The chiralities of the resulting VULs are presumably dictated by the chiral environment of the vinylogous urethane enolate aggregations, which originated in the chiral arm of pyrrolidine. Although chiral pyrrolidine substituted vinylogous urethanes have been successfully applied to obtain homochiral *syn* aldol products and applied in several total syntheses,[2] the application of chiral pyrrolidine substituted vinylogous urethane to obtain homochiral *anti*-aldol products has been less successful.[3] In previous studies, we have demonstrated that chiral butenolides can be obtained through a [2,3]-Wittig rearrangement process of chiral alcohol-substituted vinylogous urethane (CASVU).[4] In this study, we report on the use of these chiral alcohol-substituted vinylogous urethanes in chiral *anti*-aldol reactions.

## 2. Results and discussion

Chiral ketoesters **3a**–**o** were first synthesized through the condensation of chiral alcohol **2a**–**o**[5] with 1 equiv of 2,2-dimethyl-6-ethyl-4*H*-1,3-dioxin-4-one **1** in good yields[6] (Scheme 1).




**Scheme 1.** Synthesis of VUL **5**.

Chiral vinylogous urethane **4a**–**o** was then subsequently obtained in 84–95% yields through the condensation of pyrrolidine with ketoesters **3a**–**o**, respectively. The pyrrolidine substituted vinylogous urethane has an *E* configuration for the double bond geometry.[7] To unequivocally determine *E*/*Z* configuration of the double bond in **4a**–**o**, single crystal of **4g** and **4o** were carefully collected then, respectively, subjected to X-ray crystallography analysis. X-ray analysis revealed that both **4g** and **4o** have *E* configuration double bond[8] (Figs. 1 and 2).

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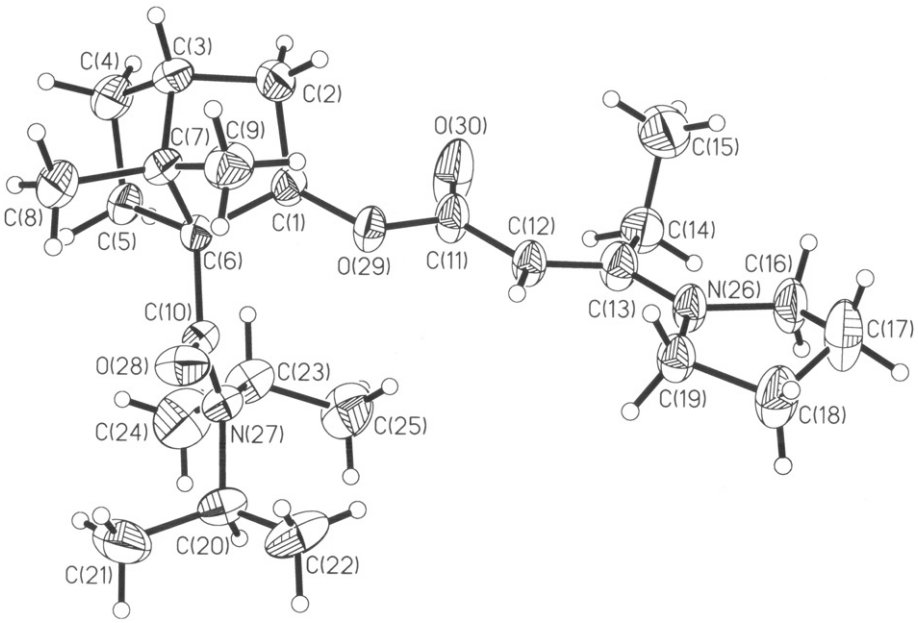



**Fig. 1.** ORTEP view of the X-ray crystallographic structure of **4g** (thermal ellipsoids shown at 30% probability).

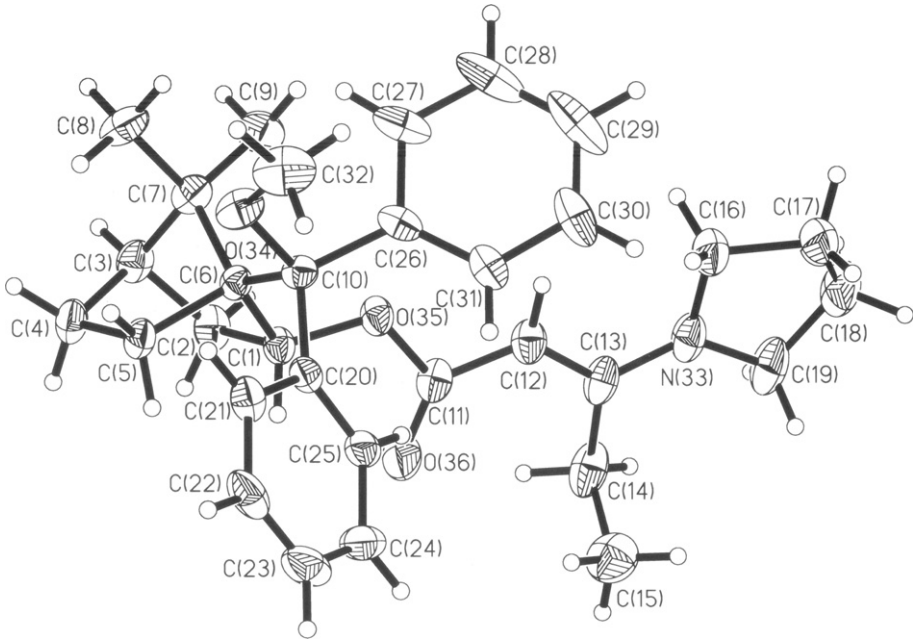



**Fig. 2.** ORTEP view of the X-ray crystallographic structure of **4o** (thermal ellipsoids shown at 30% probability).

The typical procedure for the *anti*-aldol reaction of chiral alcohol-substituted vinylogous urethanes was conducted using 2.5 (entries 1–6) or 3.5 (entries 7 and 8) equivalents of LDA as a base. Kinetic deprotonation of **4a**–**o** at −78 °C for 30 min was followed by warming to room temperature for 20 min. After being re-cooled to −78 °C and stirred for 30 min, 2.5 equiv of isobutyraldehyde (1 N in THF, 2.5 mL) was added to the reaction mixture. Warming to room temperature over a 2 h period provided vinylogous urethane lactone **5** in moderate to good yields as indicated in Table 1. In these reactions, **4h** was difficult to deprotonate; therefore, we were unable to obtain compound **5** (Table 1).

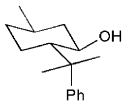
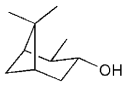
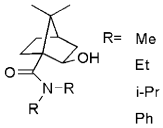
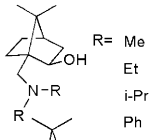
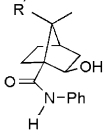
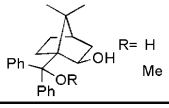
Chiral HPLC analysis (Chiralcel® OJ) of **5** from each respective reaction of **4a**–**o** revealed diastereoselectivities and enantioselectivities as indicated in Table 1. Compound **5** showed excellent diastereoselectivities (90–99%). While simple chiral secondary alcohol-substituted VU (entries 1–4) yielded 35–40% enantioselectivities, ketopinic acid derived VU provided more promising results (entries 5, 6, and 8). The aldol reaction of **4n** provided compound **5** with 92% ee.[9] It should be noted that while VU **4n** generates **5** with a negative optical rotation sign, VUs **4c** and **4o** reacted to obtain **5** with a positive rotation sign.

The VU **4n** was investigated further by having it react with various aldehydes, the reaction provided compound **6a**–**d** in high diastereoselectivities (>96% de) and 75–89% enantioselectivities, as shown in Table 2.

To study the absolute stereochemistry of the major *anti*-aldol product, prelactone B was selected to serve as a synthetic standard as well as a short-term synthetic target.[10]

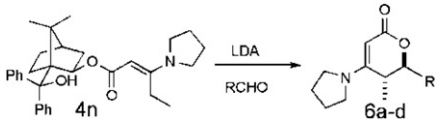
Prelactone B is the sub-structure of bafilomycin $A_1$ with broad range of biological activities[11,12] (Scheme 2).

**Table 1**
Summary of results of the synthesis of compounds **3a–o**, **4a–o** and stereoselectivities of the *anti*-aldol reaction studies

| Entry | R*OH | | % Yield[a] | | | % ee[b] | % de |
|---|---|---|---|---|---|---|---|
| | **2** | | **3** | **4** | **5** | | |
| 1 |  | **a** | 86 | 89 | 83 | 40 | 98 |
| 2 |  | **b** | 86 | 88 | 81 | 39 | 99 |
| 3 |  | **c** | 89 | 88 | 76 | −40 | 99 |
| 4 |  | **d** | 90 | 92 | 76 | 35 | 99 |
| 5 |  | **e** | 68 | 90 | 89 | 70 | 99 |
| | | **f** | 68 | 89 | 89 | 58 | 99 |
| | | **g** | 70 | 84 | 74 | 20 | 99 |
| | | **h** | 62 | 92 | N.R. | | |
| 6 |  | **i** | 70 | 95 | 80 | 55 | 99 |
| | | **j** | 75 | 92 | 74 | 58 | 99 |
| | | **k** | 80 | 95 | 68 | 43 | 99 |
| | | **l** | 64 | 91 | 77 | 66 | 99 |
| 7 |  | **m** | 70 | 95 | 55 | 37 | 90 |
| 8 |  | **n** | 75 | 93 | 85 | 92 | 98 |
| | | **o** | 76 | 92 | 77 | −58 | 93 |

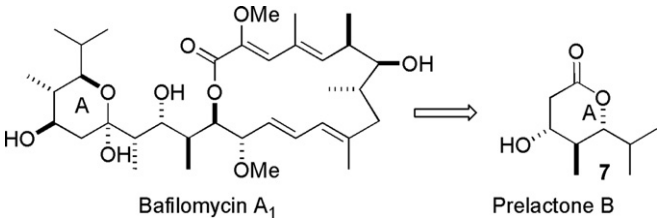
[a] Isolated yield.
[b] The ee values and de values were determined using HPLC analysis on a Chiralcel OJ column [detected at 290 nm; eluent, *n*-hexane/ethanol, 94/6 (v/v)].

**Table 2**
Aldol reaction of **4n** with various aldehydes



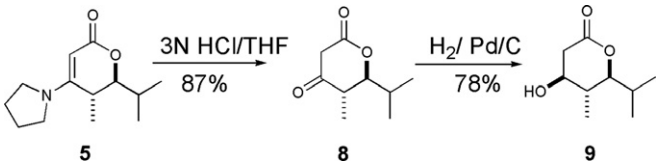

| Entry | Aldehyde | | % Yield[a] | % de | % ee[b] |
|---|---|---|---|---|---|
| 1 |  | **a** | 55 | 96 | 84 |
| 2 |  | **b** | 65 | 98 | 89 |
| 3 |  | **c** | 83 | 98 | 81 |
| 4 |  | **d** | 65 | 99 | 75 |

[a] Isolated yield.
[b] The ee values and de values were determined by HPLC analysis on a Chiralcel OJ column [detected at 290 nm; eluent, *n*-hexane/ethanol, 94/6 (v/v)].



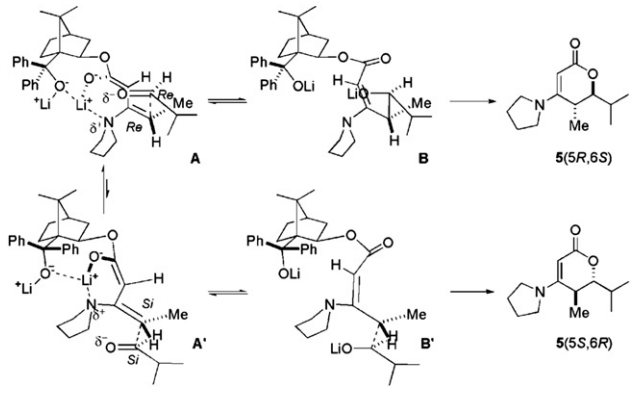

**Scheme 2.** Prelactone B fragment in the bafilomycin $A_1$.

Compound **5** generated from the aldol reaction of **4n** was subjected to acid hydrolysis with aqueous HCl to obtain an 87% yield of β-ketolactone **8**. Hydrogenation of **8** under $H_2$ atmosphere using palladium on carbon afforded β-hydroxyl δ-lactone **9** in 78% yield. Compound **9** showed the same NMR spectra as prelactone B, but with the opposite rotation sign $[\alpha]_D^{26}$ −53.3 (*c* 1.66, MeOH); rotation for prelactone B [lit. $[\alpha]_D^{26}$ +62.1 (*c* 1.72, MeOH)][11b] indicated that the absolute stereochemistry of the major *anti* product **5** generated from the aldol reaction to be (5*R*,6*S*). Therefore, *ent*-prelactone B **9** was synthesized starting from **5** in 68% overall yield (Scheme 3).




**Scheme 3.** Synthesis of (−)-prelactone B.

To account for the enantioselectivity of **5**, resulting from the aldol reaction of **4n** with aldehyde, a plausible mechanism was drawn as shown in Scheme 4. Schlessinger et al. has proposed that




**Scheme 4.** Plausible mechanism for the generation of **5**(5*R*,6*S*) from enolate of **4n**.

vinylogous urethane enolate anion reacted with aldehyde through a dipole stabilized transition state in which developing aldolate oxygen anion can be stabilized by the nitrogen partial positive charge and aldehyde approached enolate *antiperplanar* to the lithium nitrogen bond of the enolate aggregation.[2b,13] When enolate of **4n** reacted with aldehyde, enolate can form transition state **A** to have lithium aggregation at the α-face (*anti* to *gem*-dimethyl group) or transition state **A′** to have lithium aggregation at the β-face (*syn* to *gem*-dimethyl group), since *gem*-dimethyl group and neighboring phenyl group can disrupt enolate aggregation in

transition state **A′**, the reaction will most likely take place from the more populated transition state **A** in a *Re*–*Re* fashion to generate aldolate **B**, which then cyclized to give vinylogous urethane lactone **5** (5*R*,6*S*) as the major product.

## 3. Conclusion

In summary, we have prepared a series of chiral alcohol-substituted vinylogous urethanes, the double bond geometry was determined by single crystal X-ray analysis. Enantioselectivities of the resulting products from the *anti*-aldol reaction of these chiral vinylogous urethanes were studied and later applied to the synthesis of (−)-prelactone B. Finally, a plausible mechanism was proposed to account for the generation of the major enantiomer. Further studies on synthetic applications as well as mechanistic studies of the reaction are in progress in our laboratory.

## 4. Experimental section

### 4.1. General remarks

NMR spectra were taken with a Varian Mercury-200 nuclear magnetic resonance spectrometer (200 MHz for $^1$H NMR, 50 MHz for $^{13}$C NMR) in $CDCl_3$. Chemical shifts were reported in parts per million (ppm) relative to internal standard $CDCl_3$ (7.24 ppm) and coupling constant was reported in hertz (Hz). Optical rotation was 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; absolute values were corrected for the rotation of cell with solvent. 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 Instrument center of The National Science Consul at National Chung Hsing University. Mass spectra were 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. Progress of the reactions was monitored by analytical thin layer chromatography on Analtech 250 nm hard layer silica gel 60 F-250 plates sliced into 1 cm×5 cm sections. Visualization was effected 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% aqueous NaOH, and water (permanganate)]. Flash chromatography was performed on silica gel 230–400 mesh, eluted with appropriate solvents.

### 4.2. General procedure for the synthesis of ketoesters 3a–o

*4.2.1. (1R,2R,4R)-1,7,7-Trimethylbicyclo[2.2.1] hept-2-yl 3-oxopentanoate (**3a**).* 2,2-Dimethyl-6-ethyl-4*H*-1,3-dioxin-4-one **1** (1.25 g, 8 mmol) and the solvent, xylene (40 mL), were added to isoborneol (1.23 g, 8 mmol) in 250 mL round-bottom flask. The mixture was heated to reflux for 6 h and concentrated in vacuo to remove the solvent. Crude material was purified by flash chromatography (EtOAc/*n*-hexane, 1/4) yielding 1.73 g of ketoesters **3a** in 86% yield. Colorless oil. $R_f$=0.45 (*n*-hexane/EtOAc, 4/1); $[\alpha]_D^{32}$ −1.2 (*c* 5, $CH_2Cl_2$); IR ($CHCl_3$) 2952, 2882, 1728, 1637, 1562, 1456, 1376, 1306, 1231, 1043 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 4.67 (dd, *J*=7.2, 5.6 Hz, 1H, C*H*OC=O), 3.39 (s, 2H, C$H_2$C=O), 2.54 (q, *J*=7.3 Hz, 2H, C$H_2$CH$_3$), 1.82–1.21 (m, 7H), 1.06 (t, *J*=7.3 Hz, 3H, CH$_2$C$H_3$), 0.92 (s, 3H, CC$H_3$), 0.83 (s, 3H, CC$H_3$), 0.81 (s, 3H, CC$H_3$); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 203.0, 166.6, 81.9, 48.9, 48.5, 46.7, 44.8, 38.5, 36.2, 33.5, 26.8, 19.9, 19.6, 11.2, 7.3; HRMS-EI calcd for $C_{15}H_{24}O_3$ 252.1725, found 252.1731.

*4.2.2. (1R,2S,4R)-1,7,7-Trimethylbicyclo[2.2.1] hept-2-yl 3-oxopentanoate (**3b**).* This was synthesized according to the general procedure, on an 8 mmol scale in 76% yield. Colorless oil. $R_f$ 0.44 (*n*-hexane/EtOAc, 4/1); $[\alpha]_D^{32}$ −26.1 (*c* 3, $CH_2Cl_2$); IR ($CHCl_3$) 2963, 2883, 1737, 1715, 1643, 1563, 1456, 1312, 1234 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 4.92 (ddd, *J*=9.9, 3.4, 2.1 Hz, 1H, C*H*OC=O), 3.43(s, 2H, C$H_2$C=O), 2.55 (q, *J*=7.4 Hz, 2H, C$H_2$CH$_3$), 2.49–1.15 (m, 7H), 1.07 (t, *J*=7.4 Hz, 3H, CH$_2$C$H_3$), 0.88 (s, 3H, CC$H_3$), 0.85 (s, 3H, CC$H_3$), 0.82 (s, 3H, CC$H_3$); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 203.1, 167.4, 80.9, 49.1, 48.8, 47.7, 44.7, 36.4, 36.1, 27.8, 26.9, 19.5, 18.6, 13.3, 7.4; HRMS-EI calcd for $C_{15}H_{24}O_3$ 252.1725, found 252.1718.

*4.2.3. (1R,2S,5R)-5-Methyl-2-(2-phenypropane-2-yl)cyclohexyl 3-oxopentanoate (**3c**).* This was synthesized according to the general procedure, on an 8 mmol scale. Yield: 89%. Colorless oil. $R_f$ 0.56 (*n*-hexane/EtOAc, 4/1); $[\alpha]_D^{32}$ −11.6 (*c* 4, $CH_2Cl_2$); IR ($CHCl_3$) 3051, 2978, 1742, 1722, 1633, 1520, 1327, 1223, 1150 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 7.56–7.11 (m, 5H, Ar*H*), 4.83 (ddd, *J*=4.4, 4.4, 4.5 Hz, 1H, C*H*OC=O) 2.79 (d, *J*=15.7 Hz, 1H, *AB*q, C*H*HC=O), 2.63 (d, *J*=15.7 Hz, 1H, *AB*q, CH*H*C=O), 2.37 (q, *J*=7.2 Hz, 2H, C$H_2$CH$_3$), 2.28–1.61 (m, 8H), 1.31 (s, 3H, CC$H_3$), 1.26 (s, 3H, CC$H_3$), 1.01 (t, *J*=7.2 Hz, 3H, CH$_2$C$H_3$), 1.21 (d, 3H, *J*=7.4 Hz, CHC$H_3$); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 203.5, 166.6, 151.9, 127.9(2C), 125.4 (2C), 124.9, 75.1, 50.2, 48.7, 41.4, 39.5, 36.1, 34.5, 31.3, 29.7, 29.3, 29.1, 26.3, 23.5, 21.7, 7.4; HRMS-EI calcd for $C_{21}H_{30}O_3$ 330.2195, found 330.2201.

*4.2.4. (1R,2R,3R,5S)-2,6,6-Trimethylbicyclo[3.1.1] heptan-1-yl 3-oxopentanoate (**3d**).* This was synthesized according to the general procedure, on an 8 mmol scale in 90% yield. Colorless oil. $R_f$ 0.52 (*n*-hexane/EtOAc, 4/1); $[\alpha]_D^{32}$ −35.1 (*c* 5, $CH_2Cl_2$); IR ($CHCl_3$) 2930, 1733, 1718, 1637, 1306, 1231, 1156, 979 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 5.11 (m, 1H, C*H*OC=O), 3.44 (s, 2H, C$H_2$C=O), 2.57 (q, *J*=7.3 Hz, 2H, C$H_2$CH$_3$), 2.43–1.56 (m, 7H), 1.23 (s, 3H, CC$H_3$), 1.11 (d, *J*=7.1 Hz, 3H, CHC$H_3$), 1.10 (t, *J*=7.3 Hz, 3H, CH$_2$C$H_3$), 0.96 (s, 3H, CC$H_3$); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 203.3, 167.1, 75.2, 49.3, 47.3, 43.5, 41.5, 38.1, 36.1, 35.6, 33.3, 27.3, 23.6, 20.4, 7.4; HRMS-EI calcd for $C_{15}H_{24}O_3$ 252.1725, found 252.1718.

*4.2.5. (1S,2R,4R)-7,7-Dimethylbicyclo[2.2.1] heptane-1-carboxylic acid dimethylamide-2-yl 3-oxopentanoate (**3e**).* This was synthesized according to the general procedure, on an 8 mmol scale in 68% yield. Pale-yellow oil. $R_f$ 0.43 (*n*-hexane/EtOAc, 2/1); $[\alpha]_D^{26}$ −83.6 (*c* 1.0, $CH_2Cl_2$); IR ($CHCl_3$) 2973, 2945, 1733, 1715, 1627, 1273, 1259, 918 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 5.22 (dd, *J*=7.5, 4.4 Hz, 1H, C*H*OC=O), 3.40 (s, 2H, C$H_2$C=O), 2.98 (br, 6H, N(C$H_3$)$_2$), 2.50 (q, *J*=7.4 Hz, 2H, C$H_2$CH$_3$), 2.07–1.01 (m, 7H), 1.30 (s, 3H, CC$H_3$), 1.17 (s, 3H, CC$H_3$), 1.06 (t, *J*=7.4 Hz, 3H, CH$_2$C$H_3$); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 202.9, 171.3, 166.5, 79.2, 58.6, 51.1, 48.8, 44.8, 39.5, 37(2C), 36.6, 29.4, 26.9, 21.8, 21.3, 7.5; HRMS-EI calcd for $C_{17}H_{27}NO_4$ 309.1940, found 309.1938; MS-EI 309 ($M^+$, 8), 193 (84), 99 (60), 72 (100), 57 (76).

*4.2.6. (1S,2R,4R)-7,7-Dimethylbicyclo[2.2.1] heptane-1-carboxylic acid diethylamide-2-yl 3-oxopentanoate (**3f**).* This was synthesized according to the general procedure, on an 8 mmol scale in 68% yield. Pale-yellow oil. $R_f$ 0.45 (*n*-hexane/EtOAc, 2/1); $[\alpha]_D^{26}$ −34.2 (*c* 1.6, $CH_2Cl_2$); IR ($CHCl_3$) 2978, 1739, 1717, 1620, 910 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 5.17 (dd, *J*=6.2, 5.1 Hz 1H, C*H*OC=O), 3.58–3.43 (br, 2H, NC$H_2$CH$_3$), 3.34 (s, 2H, C$H_2$C=O), 3.16–3.05 (br, 2H, NC$H_2$CH$_3$), 2.48 (q, *J*=7.3 Hz, 2H, C$H_2$CH$_3$), 2.20–1.20 (m, 7H), 1.29 (s, 3H, CC$H_3$), 1.11 (s, 3H, CC$H_3$), 1.06–0.99 (m, 9H, N(CH$_2$C$H_3$)$_2$, CH$_2$C$H_3$); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 202.3, 169.5, 165.9, 78.9, 58.4,

50.8, 48.2, 44.3, 40.2 (2C), 39.2, 36.1, 29.6, 26.4, 21.2, 21.1, 13.7, 12.1, 7.0; HRMS-EI calcd for $C_{19}H_{31}NO_4$ 337.2254, found 337.2261; MS-EI 337 ($M^+$, 11), 221 (90), 149 (47), 99 (100).

*4.2.7. (1S,2R,4R)-7,7-Dimethylbicyclo [2.2.1] heptane-1-carboxylic acid diisopropylamide-2-yl 3-oxopentanoate (**3g**).* This was synthesized according to the general procedure, on an 8 mmol scale in 70% yield. Pale-yellow oil. $R_f$ 0.47 (*n*-hexane/EtOAc, 2/1); $[\alpha]_D^{26}$ −24.7 (*c* 1.2, $CH_2Cl_2$); IR ($CHCl_3$) 2968, 2930, 1739, 1718, 1627, 1273, 1259, 761, 713 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 5.06 (dd, *J*=3.5, 3.6 Hz, 1H, C*H*OC=O), 4.17 (hep, *J*=6.8 Hz, 1H, NC*H*), 3.42 (d, *J*=15.1 Hz, 1H, *A*Bq, C*H*HC=O), 3.30 (d, *J*=15.1 Hz, 1H, A*B*q, CH*H*C=O), 3.25 (hep, *J*=6.8 Hz, 1H, NC*H*), 2.52 (m, 2H, $CH_2CH_3$), 2.25–1.5 (br, 7H), 1.36 (d, *J*=6.8 Hz, 6H, NCH($CH_3$)$_2$), 1.28 (s, 3H), 1.10 (s, 3H), 1.05 (d, *J*=7.1 Hz, 6H, NCH($CH_3$)$_2$), 1.03 (t, *J*=7.3 Hz, 3H, $CH_2CH_3$); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 202.8, 169.5, 166.4, 80.1, 59.2, 51.4, 48.5, 47.2, 46.3, 44.6, 40.0, 36.8, 29.7, 29.6, 26.8, 21.8, 21.5, 21.1, 20.5 (2C), 20.5; HRMS-EI calcd for $C_{21}H_{35}NO_4$ 365.2566, found 365.2559; MS-EI 365 ($M^+$, 27), 249 (81), 206 (42), 99 (100).

*4.2.8. (1S,2R,4R)-7,7-Dimethylbicyclo[2.2.1] heptane-1-carboxylic acid diphenylamide-1-yl 3-oxopentanoate (**3h**).* This was synthesized according to the general procedure, on an 8 mmol scale in 62% yield. Pale-yellow oil. $R_f$ 0.50 (*n*-hexane/EtOAc, 2/1); $[\alpha]_D^{26}$ −70.0 (*c* 1.0, $CH_2Cl_2$); IR ($CHCl_3$) 3010, 2977, 2931, 1738, 1718, 1622, 1255, 754 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 7.34–7.05 (m, 10H, Ar*H*), 4.37 (dd, *J*=7.4, 4.2 Hz, 1H, C*H*OC=O), 3.54 (s, 2H, $CH_2C$=O), 2.58 (q, *J*=7.1 Hz, 2H, $CH_2CH_3$), 1.92–0.8 (m, 7H), 1.25 (s, 3H, CC$H_3$), 1.07 (s, 3H, CC$H_3$), 1.04 (t, *J*=7.1 Hz, 3H, $CH_2CH_3$); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 203.3, 171.5, 166.2, 143.0 (2C), 128.9 (8C), 128.3 (2C), 81.0, 59.3, 51.5, 48.8, 44.7, 39.7, 31.1, 26.5, 21.3, 21.2, 7.2; HRMS-EI calcd for $C_{27}H_{31}NO_4$ 433.2253, found 433.2261.

*4.2.9. (1R,2R,4R)-1-Dimethyl aminomethyl-7,7-dimethylbicyclo[2.2.1] hept-2-yl 3-oxopentanoate (**3i**).* This was synthesized according to the general procedure, on an 8 mmol scale in 70% yield. Pale-yellow oil. $R_f$ 0.41 (*n*-hexane/EtOAc, 2/1); $[\alpha]_D^{26}$ −34.6 (*c* 1.0, $CH_2Cl_2$); IR ($CHCl_3$) 2977, 2892, 1728, 1716, 1637, 1562, 1376, 1231, 1043 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 4.9 (m, 1H, C*H*OC=O), 3.46 (s, 2H, $CH_2C$=O), 2.62 (q, *J*=7.3 Hz, 2H, $CH_2CH_3$), 2.62–2.18 (br, 8H, N($CH_3$)$_2$, NC$H_2$), 2.14–1.75 (m, 7H), 1.26 (s, 3H, CC$H_3$), 1.08 (t, *J*=7.3 Hz, 3H, $CH_2CH_3$), 0.90 (s, 3H, CC$H_3$); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 203.3, 166.3, 79.9, 56.7, 51.6, 49, 48.2, 47.4 (2C), 44.8, 39.4, 36.4, 30.8, 26.9, 20.5, 19.9, 7.3.; HRMS-EI calcd for $C_{17}H_{29}NO_3$ 295.2147, found 295.2149; MS-EI 295 ($M^+$, 10), 180(60), 58(100), 45(17).

*4.2.10. (1R,2R,4R)-1-Diethylamino-methyl-7,7-dimethylbicyclo[2.2.1] hept-2-yl 3-oxopentanoate (**3j**).* This was synthesized according to the general procedure, on an 8 mmol scale in 75% yield. Pale-yellow oil. $R_f$ 0.40 (*n*-hexane/EtOAc, 2/1); $[\alpha]_D^{26}$ −32.1 (*c* 1.0, $CH_2Cl_2$); IR ($CHCl_3$) 2975, 2878, 1728, 1710, 1637, 1545, 1376, 1233 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 4.79 (dd, *J*=6.9, 3.1 Hz, 1H, C*H*OC=O), 3.39 (s, 2H, $CH_2C$=O), 3.11 (q, *J*=7.1 Hz, 2H, $CH_2CH_3$), 2.62–2.18 (m, 8H, N($CH_2CH_3$)$_2$, NC$H_2$, $CH_2CH_3$), 2.14–1.75 (m, 7H), 1.08 (t, *J*=7.1 Hz, 3H, $CH_2CH_3$), 0.95 (t, *J*=7.0 Hz, 6H, N($CH_2CH_3$)$_2$), 0.93 (s, 3H, CC$H_3$), 0.87 (s, 3H, CC$H_3$); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 203.1, 166.4, 80.7, 52.1, 50.6, 49.1, 47.8 (2C), 47.7, 45.2, 39.5, 36.4, 30.7, 26.9, 20.6, 20.0, 11.5 (2C), 7.4; HRMS-EI calcd for $C_{19}H_{33}NO_3$ 323.2460, found 323.2467; MS-EI 323 ($M^+$, 15), 308(71), 208(38),86(100), 57(76).

*4.2.11. (1R,2R,4R)-1-Diisopropylaminomethyl-7,7-dimethylbicyclo [2.2.1] hept-2-yl 3-oxopentanate (**3k**).* This was synthesized according to the general procedure, on an 8 mmol scale in 80% yield. Pale-yellow oil. $R_f$ 0.40 (*n*-hexane/EtOAc, 2/1); $[\alpha]_D^{26}$ −21.8 (*c* 1.0, $CH_2Cl_2$); IR ($CHCl_3$) 2972, 2876, 1730, 1712, 1640, 1545, 1376, 1230 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 4.77 (dd, *J*=7.3, 3.4 Hz, 1H, C*H*OC=O), 3.40 (s, 2H, $CH_2C$=O), 2.86 (hep, *J*=6.7 Hz, 2H, N($CH$)$_2$), 2.66 (d, *J*=14.0 Hz, 1H, *A*Bq, NC*H*H), 2.56 (q, *J*=7.2 Hz, 2H, $CH_2CH_3$), 2.27 (d, *J*=14.0, 1H, A*B*q, NCH*H*), 2.20–1.5 (m, 7H), 1.07 (t, *J*=7.2 Hz, 3H, $CH_2CH_3$), 0.98 (s, 3H, CC$H_3$), 0.93 (d, *J*=6.7 Hz Hz, 12H, N(CH($CH_3$)$_2$)$_2$), 0.89 (s, 3H, CC$H_3$); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 202.7, 166.2, 80.8, 64.8, 51.5, 48.7, 47.9, 47.2 (2C), 45.0, 39.5, 36.2, 30.2, 26.5, 22.0 (2C), 20.6, 19.7, 18.9(2C), 7.2; HRMS-EI calcd for $C_{21}H_{37}NO_3$ 351.2773, found 351.2777; MS-EI 351($M^+$, 12), 336(100), 238(27), 114(78), 85(24), 57(43).

*4.2.12. (1R,2R,4R)-1-Diphenylaminomethyl-7,7-dimethylbicyclo [2.2.1] hept-2-yl 3-oxopentanoate (**3l**).* This was synthesized according to the general procedure, on an 8 mmol scale in 64% yield. Pale-yellow oil. $R_f$ 0.43 (*n*-hexane/EtOAc, 2/1); $[\alpha]_D^{26}$ −85.1 (*c* 1, $CH_2Cl_2$); IR ($CHCl_3$) 2977, 2875, 1725, 1712, 1637, 1545, 1376, 1352 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 7.25 (d, *J*=6.8 Hz, 4H, Ar*H*), 7.22 (dd, *J*=7.8, 6.8 Hz, 6H, Ar*H*), 4.51 (dd, *J*=7.5, 3.4 Hz, 1H, C*H*OC=O), 4.05 (d, *J*=15.0 Hz, 1H, *A*Bq, NC*H*H), 3.85 (d, *J*=15.0 Hz, 1H, A*B*q, NCH*H*), 3.10 (s, 2H, $CH_2C$=O), 2.42 (q, *J*=5.6 Hz, 2H, $CH_2CH_3$), 1.72–0.8 (m, 10H), 1.25 (s, 3H, CC$H_3$), 1.02 (s, 3H, CC$H_3$); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 203.7, 166.3, 149.3 (2C), 129.5 (4C), 121.7(6C), 80.1, 53.4, 49.2, 48.9, 48.5, 45.5, 39.8, 36.6, 30.6, 27.1, 21.1, 20.3, 7.7; HRMS-EI calcd for $C_{27}H_{33}NO_3$ 419.2460, found 419.2469.

*4.2.13. (1S,2R,4R)-7,7-Dimethylbicyclo [2.2.1] heptane-1-carboxylic acid phenylamide-2-yl 3-oxopentanoate (**3m**).* This was synthesized according to the general procedure, on an 8 mmol scale in 70% yield. Pale-yellow oil. $R_f$ 0.32 (*n*-hexane/EtOAc, 2/1); $[\alpha]_D^{31}$ −34.8 (*c* 0.4, $CH_2Cl_2$); IR ($CHCl_3$) 3411, 2931, 1718, 1675, 1595, 1526, 1440, 1317 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 7.51 (d, *J*=8.1 Hz, 2H, Ar*H*), 7.49 (s, 1H, N*H*), 7.31(dd, *J*=8.1, 7.5 Hz, 2H, Ar*H*), 7.09 (t, *J*=7.5 Hz, 1H, Ar*H*), 5.15 (dd, *J*=5.9, 5.5 Hz, 1H, C*H*OC=O), 3.42 (s, 2H, $CH_2C$=O), 2.45 (q, *J*=7.3 Hz, 2H, $CH_2CH_3$), 2.35–1.03(m, 7H), 1.31 (s, 3H, CC$H_3$), 1.12 (s, 3H, CC$H_3$), 0.96 (t, *J*=7.3 Hz, 3H, $CH_2CH_3$); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 202.99, 169.74, 166.50, 137.73, 128.82(2C), 124.12, 120.11(2C), 80.17, 59.01, 49.05, 48.95, 45.85, 39.24, 36.42, 31.21, 26.62, 21.14, 20.75, 7.26; HRMS-EI calcd for $C_{21}H_{27}NO_4$ 357.1940, found 357.1945.

*4.2.14. (1S,2R,4R)-1-(Hydroxydiphenylmethyl)-7,7-dimethylbicyclo [2.2.1] heptan-2-yl 3-oxopentanoate (**3n**).* This was synthesized according to the general procedure, on an 8 mmol scale in 75% yield. Pale-yellow oil. $R_f$ 0.32 (*n*-hexane/EtOAc, 7/1); $[\alpha]_D^{26}$ +56.9 (*c* 0.6, $CH_2Cl_2$); IR ($CHCl_3$) 3583, 3054, 2984, 2941, 1744, 1718, 1271, 1256, 761, 710 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 7.78–7.58 (m, 4H, Ar*H*), 7.30–7.12 (m, 6H, Ar*H*), 5.24 (dd, *J*=7.7, 3.8 Hz, 1H, C*H*OC=O), 3.07 (d, *J*=16.0 Hz, 1H, *A*Bq, C*H*HC=O), 3.02 (d, *J*=16.0 Hz, 1H, A*B*q, CH*H*C=O), 2.35–2.21 (q, *J*=7.5 Hz, 2H, $CH_2CH_3$), 2.00–1.08 (m, 7H), 1.47 (s, 3H, CC$H_3$), 1.00 (t, *J*=7.2 Hz, 3H, $CH_2CH_3$), 0.64 (s, 3H, CC$H_3$); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 202.4, 164.3, 149.1, 143.1, 128.2(2C), 127.6, 126.4(2C), 126.1, 125.8, 125.7 (2C), 82.1, 80.8, 58.6, 51.1, 47.7, 47.4, 38.1, 36.1, 30.9, 26.6, 24.2, 22.3, 7.1; HRMS-EI calcd for $C_{27}H_{32}O_4$ 420.2301, found 420.2296; MS-EI 420 ($M^+$, 4), 183 (94), 105 (100), 77 (48).

*4.2.15. (1S,2R,4R)-1-(Methoxyphenylmethyl)-7,7-dimethylbicyclo [2.2.1] hept-2-yl 3-oxopentanoate (**3o**).* This was synthesized according to the general procedure, on an 8 mmol scale in 76% yield. Pale-yellow oil. $R_f$ 0.44 (*n*-hexane/EtOAc, 10/1); $[\alpha]_D^{29}$ −4.2 (*c* 1.0, $CH_2Cl_2$); IR ($CHCl_3$) 3050, 2941, 1737, 1713, 1449 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 7.77–7.55 (m, 4H, Ar*H*), 7.39–7.24 (m, 6H, Ar*H*), 4.80 (dd, *J*=8.0, 3.4 Hz, 1H, C*H*OC=O), 3.04 (d, *J*=14.0 Hz, 1H, *A*Bq, C*H*HC=O), 3.02 (d, *J*=14.0 Hz, 1H, A*B*q, CH*H*C=O), 2.79 (s, 3H, O$CH_3$), 2.41–2.22 (m, 2H, $CH_2CH_3$), 1.90–0.87 (m, 7H), 1.13 (s, 3H, CC$H_3$) 1.01 (t, *J*=7.3 Hz, 3H, $CH_2CH_3$), 0.63 (s, 3H, CC$H_3$); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 202.8, 165.8, 140.1, 138.7, 131.4(2C), 129.4(2C), 127.3(2C), 126.8,

126.7, 126.5(2C), 87.4, 81.6, 60.8, 52.4, 49.9, 48.8, 48.7, 38.9, 35.9, 31.3, 25.3, 23.1, 22.5, 7.3; HRMS-EI calcd for $C_{28}H_{34}O_4$ 434.2457, found 434.2453; MS-EI 434 ($M^+$, 1), 318 (27), 197 (100), 77 (14).

### 4.3. Synthesis of compounds 4a–o

*4.3.1. (1R,2R,4R)-1,7,7-Trimethyl bicyclo[2.2.1] hept-2-yl (E)-3-(pyrrolidin-1-yl)pent-2-enoate (**4a**).* The solvent benzene (20 mL) was added to 3-oxo-pentanoic acid (1,7,7-trimethyl-bicyclo [2,2,1] hept-*exo*-2-yl) ester **3a** (1.26 g, 5 mmol) in a 50 mL round-bottom flask, followed by the addition of pyrrolidine (0.5 mL, 6.0 mmol) and a catalytic quantity of *tert*-butanol (0.5 mL). The mixture was heated to reflux under Dean–Stark apparatus to remove water. After 10 h, the reaction mixture was concentrated in vacuo to remove solvent to obtain 1.36 g of product in 89% yield. The material was used directly in the following reaction without further purification. Pale-yellow oil. $[\alpha]_D^{32}$ −0.8 (*c* 5, $CH_2Cl_2$); IR ($CHCl_3$) 3011, 2957, 2882, 1712, 1670, 1562, 1450, 1140, 1055, 1028 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 4.64 (dd, *J*=6.0, 5.4 Hz, 1H, C*H*OC=O), 4.34 (s, 1H, C=C*H*), 3.28 (br, 4H, N($CH_2$)$_2$), 2.88 (m, 2H, CH=CC$H_2$CH$_3$), 1.89 (m, 4H, N($CH_2CH_2$)$_2$), 1.80–1.25 (m, 7H), 1.13 (t, *J*=7.4 Hz, 3H, CH=CCH$_2$C$H_3$), 0.99 (s, 3H, CC$H_3$), 0.83 (s, 3H, CC$H_3$), 0.80 (s, 3H, CC$H_3$); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 167.9, 164.0, 82.8, 77.8, 48.2, 47.1 (2C), 46.4, 44.8, 38.8, 33.6, 26.9, 24.8 (2C), 22.9, 19.9, 19.7, 12.4, 11.1; HRMS-EI calcd for $C_{19}H_{31}NO_2$ 305.2355, found 305.2349.

*4.3.2. (1R,2S,4R)-1,7,7-Trimethylbicyclo[2.2.1] hept-2-yl (E)-3-(pyrrolidin-1-yl)pent-2-enoate (**4b**).* This was synthesized according to the general procedure, on a 5 mmol scale in 88% yield. Pale-yellow oil. $[\alpha]_D^{32}$ −25.5 (*c* 5.5, $CH_2Cl_2$); IR ($CHCl_3$) 3010, 2952, 2872, 1664, 1568, 1456, 1344, 1140, 1033 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 4.87 (ddd, *J*=9.9, 3.4, 1.8 Hz, 1H, C*H*OC=O), 4.42 (s, 1H, C=C*H*), 3.30 (br, 4H, N($CH_2$)$_2$), 2.90 (m, 2H, CH=CC$H_2$CH$_3$), 2.30–0.90 (m, 7H), 1.90 (m, 4H, N($CH_2CH_2$)$_2$), 1.14 (t, *J*=7.5 Hz, 3H, CH=CCH$_2$C$H_3$), 0.89 (s, 3H, CC$H_3$), 0.84 (s, 3H, CC$H_3$), 0.82 (s, 3H, CC$H_3$); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 169.1, 164.4, 83.1, 77.0, 48.6, 47.5(2C), 45.0, 37.0, 28.1, 27.2, 25.1 (2C), 23.3, 19.7, 18.8, 13.5, 13.4, 12.7; HRMS-EI calcd for $C_{19}H_{31}NO_2$ 305.2355, found 305.2365.

*4.3.3. (1R,2S,5R)-5-Methyl-2-(2-phenypropane-2-yl)cyclohexyl (E)-3-(pyrrolidin-1-yl)pent-2-enoate (**4c**).* This was synthesized according to the general procedure, on a 5 mmol scale in 88% yield. Pale-yellow oil. $[\alpha]_D^{32}$ +19.2 (*c* 4.0, $CH_2Cl_2$); IR ($CHCl_3$) 3014, 2957, 2925, 2871, 1664, 1567, 1460, 1140, 1092, 1033 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 7.24 (d, *J*=8.2 Hz, 1H, Ar*H*), 7.36–7.07 (m, 4H, Ar*H*), 4.76 (ddd, *J*=4.2, 4.2, 4.1 Hz, 1H, C*H*OC=O), 3.90 (s, 1H, C=C*H*), 3.62–3.02 (br, 4H, N($CH_2$)$_2$), 2.91 (q, *J*=7.3 Hz, 2H, CH=CC$H_2$CH$_3$), 2.18–1.88 (br, 4H, N($CH_2CH_2$)$_2$), 1.57–0.82 (m, 10H), 1.26 (s, 6H, 2CC$H_3$), 1.16 (t, *J*=7.3 Hz, 3H, CH=CCH$_2$C$H_3$); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 167.5, 164.5, 151.8, 128.9, 127.7, 125.7, 125.6, 124.6, 83.2, 71.8, 50.8, 45.4(2C), 42.4, 40.0, 34.7, 31.3, 29.6, 27.8, 27.1, 24.1 (2C), 23.2, 21.7, 12.7; HRMS-EI calcd for $C_{25}H_{37}NO_2$ 383.2824, found 383.2830.

*4.3.4. (1R,2R,3R,5S)-2,6,6-Trimethylbicyclo[3.1.1] heptan-1-yl (E)-3-(pyrrolidin-1-yl)pent-2-enoate (**4d**).* This was synthesized according to the general procedure, on a 5 mmol scale in 92% yield. Pale-yellow oil. $[\alpha]_D^{32}$ −32.4 (*c* 5.0, $CH_2Cl_2$); IR ($CHCl_3$) 3011, 2973, 2952, 2928, 1711, 1667, 1562, 1456, 1343, 1140, 1036 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 5.05 (m, 1H, C*H*OC=O), 4.41 (s, 1H, C=C*H*), 3.47–3.05 (br, 4H, N($CH_2$)$_2$), 2.92 (q, *J*=7.5 Hz, 2H, CH=CC$H_2$CH$_3$), 2.66–1.62 (m, 7H), 1.95–1.87 (br, 4H, N($CH_2CH_2$)$_2$), 1.21 (s, 3H, CC$H_3$), 1.13 (d, 3H, *J*=9.8 Hz, CHC$H_3$), 1.09 (t, *J*=7.5 Hz, 3H, CH=CCH$_2$C$H_3$), 0.96 (s, 3H, CC$H_3$); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 168.6, 164.6, 83.0, 71.2, 47.7, 47.6(2C), 43.8, 41.5, 38.3, 36.4, 33.6, 27.5, 25.1 (2C), 23.6, 23.3, 20.6, 12.7; HRMS-EI calcd for $C_{19}H_{31}NO_2$ 305.2355, found 305.2354.

*4.3.5. (1S,2R,4R)-7,7-Dimethylbicyclo[2.2.1] heptane-1-carboxylic acid dimethylamide-2-yl (E)-3-(pyrrolidin-1-yl)pent-2-enoate (**4e**).* This was synthesized according to the general procedure, on a 5 mmol scale in 90% yield. Pale-yellow oil. $[\alpha]_D^{26}$ −5.3 (*c* 1.0, $CH_2Cl_2$); IR ($CHCl_3$) 3012, 2977, 1711, 1623, 1459, 1381, 732 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 5.15 (dd, *J*=7.5, 4.0 Hz, 1H, C*H*OC=O), 4.32 (s, 1H, C=C*H*), 3.50–3.10 (br, 4H, N($CH_2$)$_2$), 2.96 (s, 6H, N($CH_3$)$_2$), 3.00–2.77 (m, 2H, CH=CC$H_2$CH$_3$), 2.02–1.10 (m, 7H), 1.92 (br, 4H, N($CH_2CH_2$)$_2$), 1.35 (s, 3H, CC$H_3$), 1.18 (s, 3H, CC$H_3$), 1.14 (t, *J*=7.3 Hz, 3H, CH=CCH$_2$C$H_3$); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 172.6, 167.8, 165.0, 82.5, 76.5, 58.7, 50.8, 47.0 (br, 2C), 45.1, 40.2, 37.0 (2C), 29.8, 27.1, 25.1 (br, 2C), 23.4, 22.1, 21.5, 12.7; HRMS-EI calcd for $C_{21}H_{34}N_2O_3$ 362.5063, found 362.5070; MS-EI 362($M^+$, 12), 152(100), 151(89), 72(29).

*4.3.6. (1S,2R,4R)-7,7-Dimethylbicyclo[2.2.1] heptane-1-carboxylic acid diethylamide-2-yl (E)-3-(pyrrolidin-1-yl)pent-2-enoate (**4f**).* This was synthesized according to the general procedure, on a 5 mmol scale in 89% yield. Colorless solid. Mp 106–108 °C; $[\alpha]_D^{33}$ −6.2 (*c* 0.8, $CH_2Cl_2$); IR ($CHCl_3$) 3010, 2977, 1723, 1621, 1456, 1380, 724 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 5.11 (dd, *J*=7.1, 4.4 Hz, 1H, C*H*OC=O), 4.29 (s, 1H, C=C*H*), 3.57 (m, 4H, N($CH_2CH_3$)$_2$), 3.20 (br, 4H, N($CH_2$)$_2$), 2.92 (m, 1H, CH=CC*H*HCH$_3$), 2.80 (m, 1H, CH=CCH*H*CH$_3$), 1.88 (br, 4H, N($CH_2CH_2$)$_2$), 2.10–1.20 (m, 7H), 1.36 (s, 3H, CC$H_3$), 1.14 (s, 3H, CC$H_3$), 1.10–1.00(m, 9H, N($CH_2CH_3$)$_2$, CH=CCH$_2$C$H_3$); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 170.9, 167.6, 164.7, 82.4, 76.3, 58.8, 50.8, 47.3 (2C), 44.9, 44.2, 39.6 (2C), 30.3, 26.9, 25.0 (2C), 23.1, 21.8, 21.6, 13.8 (2C), 12.5; HRMS-EI calcd for $C_{23}H_{38}N_2O_3$ 390.2884, found 390.2877; MS-EI 390 ($M^+$, 2), 221 (56), 152 (9), 149 (100).

*4.3.7. (1S,2R,4R)-7,7-Dimethyl-bicyclo [2.2.1] heptane-1-carboxylic acid diisopropylamide-2-yl (E)-3-(pyrrolidin-1-yl)pent-2-enoate (**4g**).* This was synthesized according to the general procedure, on a 5 mmol scale in 84% yield. Colorless solid. Mp 116–118 °C; $[\alpha]_D^{27}$ −24.4 (*c* 0.6, $CH_2Cl_2$); IR ($CHCl_3$) 3038, 2974, 2930, 1626, 1562, 1434, 1135, 680 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 4.98 (dd, *J*=7.1, 3.9 Hz, 1H, C*H*OC=O), 4.32 (s, 1H, C=C*H*), 4.24 (hep, *J*=6.8 Hz 1H, NC*H*), 3.42 (br, 4H, N($CH_2$)$_2$), 3.24 (hep, *J*=6.8 Hz 1H, NC*H*), 2.92 (m, 1H, CH=CC*H*HCH$_3$), 2.66 (m, 1H, CH=CCH*H*CH$_3$), 1.89 (br, 4H, N($CH_2CH_2$)$_2$), 2.10–1.20 (m, 7H), 1.37 (d, *J*=6.8 Hz, 6H, NCH(C$H_3$)$_2$), 1.34 (s, 3H, CC$H_3$), 1.14 (s, 3H, CC$H_3$), 1.20–1.01 (m, 9H, NCH(C$H_3$)$_2$, CH=CCH$_2$C$H_3$); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 170.5, 167.8, 164.7, 82.4, 77.2, 59.4, 51.0, 46.9, 45.9, 44.9, 40.5, 30.0, 26.9, 24.9, 23.2, 21.9, 21.7, 21.0, 20.6, 20.4, 20.2, 12.6; HRMS-EI calcd for $C_{25}H_{42}N_2O_3$ 418.3195, found 418.3200; MS-EI 418 ($M^+$, 12), 318 (6), 169 (13), 152 (100).

*4.3.8. (1S,2R,4R)-7,7-Dimethylbicyclo[2.2.1] heptane-1-carboxylic acid diphenylamide-1-yl (E)-3-(pyrrolidin-1-yl)pent-2-enoate (**4h**).* This was synthesized according to the general procedure, on a 5 mmol scale in 92% yield. Colorless solid. Mp 125–127 °C; $[\alpha]_D^{26}$ −37.5 (*c* 1.0, $CH_2Cl_2$); IR ($CHCl_3$) 3010, 2977, 1723, 1621, 1456, 1380, 1261, 723 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 7.34–7.05 (m, 10H, Ar*H*), 4.55 (s, 1H, C=C*H*), 4.03(dd, *J*=7.2, 4.4 Hz, 1H, C*H*OC=O), 3.5–3.1 (br, 4H, N($CH_2$)$_2$), 3.15 (m, 1H, CH=CC*H*HCH$_3$), 2.81 (m, 1H, CH=CCH*H*CH$_3$), 2.03–1.80 (br, 4H, N($CH_2CH_2$)$_2$), 1.92–0.8 (m, 10H), 1.40 (s, 3H, CC$H_3$), 1.21(s, 3H, CC$H_3$); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 173.2, 167.6, 165.0, 129.1 (8C), 138.0 (2C), 128.5 (2C), 82.8, 78.1, 59.9, 51.5, 49.1 (br, 2C), 40.7, 32.4, 27.3 (br, 2C), 23.6, 22.1, 21.7, 13.0; HRMS-EI calcd for $C_{31}H_{38}N_2O_3$ 486.2882, found 486.2885.

*4.3.9. (1R,2R,4R)-1-Dimethyl aminomethyl-7,7-dimethylbicyclo[2.2.1] hept-2-yl (E)-3-(pyrrolidin-1-yl)pent-2-enoate (**4i**).* This was synthesized according to the general procedure, on a 5 mmol scale in 95% yield. Pale-yellow oil. $[\alpha]_D^{26}$ −44.8 (*c* 1.0, $CH_2Cl_2$); IR ($CHCl_3$) 3011,

2952, 2872, 1710, 1650, 1562, 1456, 1325, 1225, 1144 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 4.78 (dd, $J$=7.7, 3.4 Hz, 1H, C*H*OC=O), 4.37 (s, 1H, C=C*H*), 3.5–3.1 (br, 4H, N($CH_2$)$_2$), 3.1–2.6 (m, 2H, CH=CC$H_2$CH$_3$), 2.5 (d, $J$=12.9 Hz, 1H, *A*Bq, NC*H*H), 2.20 (s, 6H, N($CH_3$)$_2$), 2.17 (d, $J$=12.9 Hz, 1H, A*B*q, NCH*H*), 2.17–1.6 (m, 7H), 1.96–1.86 (br, 4H, N($CH_2CH_2$)$_2$), 1.14 (t, $J$=7.5 Hz, 3H, CH=CCH$_2$C$H_3$), 1.01 (s, 3H, CC$H_3$), 0.86 (s, 3H, CC$H_3$); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 167.8, 164.6, 82.9, 76.5, 56.8, 51.6, 47.9, 47.7 (2C), 47.3 (br, 2C), 45.2, 40.1, 30.2, 27.2, 25.0 (br, 2C), 23.2, 20.8, 20.3, 12.8; HRMS-EI calcd for $C_{21}H_{36}N_2O_2$ 348.2777, found 348.2775; MS-EI 348 ($M^+$, 26), 179 (29), 152 (100), 110 (40), 58 (25).

*4.3.10. (1R,2R,4R)-1-Diethylamino-methyl-7,7-dimethylbicyclo[2.2.1] hept-2-yl (E)-3-(pyrrolidin-1-yl)pent-2-enoate (**4j**).* This was synthesized according to the general procedure, on a 5 mmol scale in 92% yield. Pale-yellow oil. $[\alpha]_D^{26}$ −49.9 ($c$ 1.0, $CH_2Cl_2$); IR ($CHCl_3$) 3010, 2965, 2873, 1714, 1652, 1558, 1456, 1325, 1228, 1078 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 4.69 (dd, $J$=7.8 3.4 Hz, 1H, C*H*OC=O), 4.35 (s, 1H, C=C*H*), 3.40–3.10 (br, 4H, N($CH_2$)$_2$), 3.10–2.0 (m, 6H, N($CH_2CH_3$)$_2$, CH=CC$H_2$CH$_3$), 2.70 (d, $J$=13.8 Hz, 1H, *A*Bq, NC*H*H), 2.27 (d, $J$=13.8, 1H, A*B*q, NCH*H*), 2.0–1.70 (br, 4H, N($CH_2CH_2$)$_2$), 1.95–0.8 (m, 7H), 1.14 (t, $J$=7.5 Hz, 6H, N($CH_2CH_3$)$_2$), 1.01 (s, 3H, CC$H_3$), 0.95 (t, $J$=7.1 Hz, 3H, CH=CCH$_2$C$H_3$), 0.80 (s, 3H, CC$H_3$); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 167.8, 164.3, 83.1, 76.9, 51.7, 49.9, 47.8 (2C), 47.7 (br, 2C), 45.4, 40.1, 30.5, 27.0, 25.4 (br, 2C), 24.9, 23.1, 20.8, 20.3, 12.7, 11.4 (2C); HRMS-EI calcd for $C_{23}H_{40}N_2O_2$ 376.3090, found 376.3082; MS-EI 376 ($M^+$, 33), 208 (44), 152 (100),151 (70), 86 (84).

*4.3.11. (1R,2R,4R)-1-Diisopropylamino methyl-7,7-dimethyl-bicyclo [2.2.1] hept-2-yl (E)-3-(pyrrolidin-1-yl)pent-2-enoate (**4k**).* This was synthesized according to the general procedure, on a 5 mmol scale in 95% yield. Pale-yellow oil. $[\alpha]_D^{26}$ −77.3 ($c$ 1.0, $CH_2Cl_2$); IR ($CHCl_3$) 3011, 2967, 2872, 1711, 1650, 1562, 1451, 1320, 1230, 1154 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 4.66 (dd, $J$=7.9, 3.2 Hz, 1H, C*H*OC=O), 4.37 (s, 1H, C=C*H*), 3.40–3.20 (br, 4H, N($CH_2$)$_2$), 3.20–2.70 (m, 4H, N($CH$)$_2$, CH=CC$H_2$CH$_3$), 2.87 (d, $J$=13.9 Hz, 1H, *A*Bq, NC*H*H), 2.24 (d, $J$=13.9 Hz, 1H, A*B*q, NCH*H*), 2.01–1.80 (b, 4H, N($CH_2CH_2$)$_2$), 1.95–1.10 (m, 7H), 1.13 (t, $J$=7.5 Hz, 3H, CH=CCH$_2$C$H_3$), 0.99 (d, $J$=5.3 Hz, 6H, CH($CH_3$)$_2$), 0.95 (s, 3H, CC$H_3$) 0.91 (d, $J$=5.3 Hz, 6H, CH($CH_3$)$_2$), 0.90 (s, 3H, CC$H_3$); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 168.2, 164.3, 83.3, 77.5, 51.5, 48.1, 47.3(2C), 47.2(br, 2C), 45.5, 40.5, 39.5, 30.4, 26.9, 25.1 (br, 2C), 23.1, 22.6 (2C), 20.9, 20.3, 18.9(2C), 12.7; HRMS-EI calcd for $C_{25}H_{44}N_2O_2$ 404.3403, found 404.3401; MS-EI 404($M^+$, 14), 361(70), 152(100), 114(85).

*4.3.12. (1R,2R,4R)-1-Diphenylamino-methyl-7,7-dimethyl-bicyclo [2.2.1] hept-2-yl (E)-3-(pyrrolidin-1-yl)pent-2-enoate (**4l**).* This was synthesized according to the general procedure, on a 5 mmol scale in 91% yield. Pale-yellow oil. $[\alpha]_D^{26}$ −299.3 ($c$ 1.0, $CH_2Cl_2$); IR ($CHCl_3$) 3017, 2978, 2882, 1710, 1645, 1557, 1456, 1335, 1235 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 7.22 (d, $J$=7.7 Hz, 4H, Ar*H*), 7.20 (t, $J$=7.7, 7.4 Hz, 4H, Ar*H*), 6.86 (t, $J$=7.4 Hz, 2H, Ar*H*), 4.35 (dd, $J$=7.9, 3.6 Hz, 1H, C*H*OC=O), 4.28 (s, 1H, C=C*H*), 4.17 (d, $J$=15.4 Hz, 1H, *A*Bq, NC*H*H), 3.85 (d, $J$=15.4 Hz, 1H, A*B*q, NCH*H*), 3.4–3.2 (br, 4H, N($CH_2$)$_2$), 3.05 (m, 1H, CH=CC*H*HCH$_3$), 2.72 (m, 1H, CH=CCH*H*CH$_3$), 2.01–1.90 (m, 4H, N($CH_2CH_2$)$_2$), 1.95–1.10 (m, 7H), 1.25 (s, 6H, 2CC$H_3$), 1.10 (t, $J$=7.2 Hz, 3H, CH=CCH$_2$C$H_3$); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 167.6, 164.4, 149.5 (2C), 129.1(4C), 121.8 (4C), 121.1 (2C), 83.5, 76.0, 53.4, 53.0, 49.2 (br, 2C), 48.3, 45.6, 40.5, 30.4, 27.2, 25.7, 25.3 (br, 2C), 23.4, 21.2, 20.5, 12.8; HRMS-EI calcd for $C_{31}H_{40}N_2O_2$ 473.3090, found 472.3083; MS-EI 472 ($M^+$, 36), 303 (81), 234 (71), 182 (89), 152 (100).

*4.3.13. (1S,2R,4R)-7,7-Dimethylbicyclo [2.2.1] heptane-1-carboxylic acid phenylamide-2-yl (E)-3-(pyrrolidin-1-yl)pent-2-enoate (**4m**).* This was synthesized according to the general procedure, on a 5 mmol scale in 95% yield. Pale-yellow oil. $[\alpha]_D^{31}$ −90.7 ($c$ 4.0, $CH_2Cl_2$); IR ($CHCl_3$) 3347, 3052, 2984, 2877, 1672, 1592, 1440, 1264, 1129, 891 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 8.56 (br, 1H, N*H*), 7.49 (d, $J$=8.2 Hz, 2H, Ar*H*), 7.2 (dd, $J$=8.8, 6.8 Hz, 2H, Ar*H*), 7.00 (t, $J$=6.8 Hz, 1H, Ar*H*), 5.06 (dd, $J$=6.2, 5.1 Hz, 1H, C*H*OC=O), 4.32 (s, 1H, C=C*H*), 3.41 (br, 2H, NC$H_2$), 3.11 (br, 2H, NC$H_2$), 2.83 (m, 2H, CH=CC$H_2$CH$_3$), 2.46–2.23 (m, 2H), 1.88 (br, 4H, N($CH_2$)$_2$), 1.80–1.73 (m, 5H), 1.26 (s, 3H, CC$H_3$), 1.08 (m, 6H, CH=CCH$_2$C$H_3$, CC$H_3$); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 170.74, 167.25, 166.28, 138.58, 128.68 (2C), 123.41, 119.82 (2C), 81.56, 76.12, 59.06, 50.08, 48.28, 47.19, 45.82, 40.16, 31.47, 27.26, 25.31, 24.82, 23.55, 21.52, 20.76, 12.42; HRMS-EI calcd for $C_{25}H_{34}N_2O_3$ 410.2569, found 410.2564.

*4.3.14. (1S,2R,4R)-1-(Hydroxydiphenylmethyl)-7,7-dimethylbicyclo [2.2.1] heptan-2-yl (E)-3-(pyrrolidin-1-yl)pent-2-enoate (**4n**).* This was synthesized according to the general procedure, on a 5 mmol scale. Pale-yellow solid. Mp 84–85 °C; $[\alpha]_D^{35}$ −43.8 ($c$ 4.0, $CH_2Cl_2$); IR ($CHCl_3$) 3514, 2974, 2947, 2883, 1675, 1627, 1563, 1445, 1130, 1029, 718 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 7.79–7.64 (m, 4H, Ar*H*), 7.26–7.03 (m, 6H, Ar*H*), 5.06 (dd, $J$=7.4, 4.5 Hz, 1H, C*H*OC=O), 4.74 (s, 1H, O*H*), 4.06 (s, 1H, C=C*H*), 3.50–3.04 (br, 4H, N($CH_2$)$_2$), 3.00–2.79 (m, 1H, CH=CC*H*HCH$_3$), 2.60–2.45 (m, 1H, CH=CCH*H*CH$_3$), 2.41–1.00 (m, 7H), 2.10–1.80 (br, 4H, N($CH_2CH_2$)$_2$), 1.60 (s, 3H, CC$H_3$), 0.94 (t, $J$=7.4 Hz, 3H, CH=CCH$_2$C$H_3$), 0.54 (s, 3H, CC$H_3$); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 165.7, 165.4, 149.1, 144.1, 128.4 (2C), 127.6(2C), 126.7(2C), 126.4(2C), 125.9(2C), 81.5, 81.4, 79.1, 58.9, 51.0, 47.8, 47.3(2C), 39.0, 30.8, 27.2, 25.0(2C), 24.6, 23.2, 22.7, 12.3; HRMS-EI calcd for $C_{31}H_{39}NO_3$ 473.2930, found 473.2922; MS-EI 473 ($M^+$, 10), 169 (26), 152 (100), 77 (27).

*4.3.15. (1S,2R,4R)-1-(Methoxyphenylmethyl)-7,7-dimethylbicyclo [2.2.1] heptan-2-yl (E)-3-(pyrrolidin-1-yl)pent-2-enoate (**4o**).* This was synthesized according to the general procedure, on a 5 mmol scale in 92% yield. Pale-yellow solid. Mp 147–148 °C; $[\alpha]_D^{32}$ −27.8 ($c$ 4.0, $CH_2Cl_2$); IR ($CHCl_3$) 2968, 2882, 1675, 1567, 1562, 1451, 1344, 1140, 1060 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 7.92–7.56 (m, 4H, Ar*H*), 7.40–7.16 (m, 6H, Ar*H*), 4.56 (dd, $J$=7.4, 3.6 Hz, 1H, C*H*OC=O), 3.89 (s, 1H, C=C*H*), 3.50–3.10 (br, 4H, N($CH_2$)$_2$), 3.02–2.62 (m, 2H, CH=CC$H_2$CH$_3$), 2.82 (s, 3H, OC$H_3$), 1.94 (br, 4H, N($CH_2CH_2$)$_2$), 1.82–0.85 (m, 7H), 1.20 (s, 3H, CC$H_3$), 1.07 (t, $J$=7.4 Hz, 3H, CH=CCH$_2$C$H_3$) 0.74 (s, 3H, CC$H_3$); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 167.0, 164.4, 140.4, 139.8, 131.9(2C), 129.7(2C), 128.3, 127.1(2C), 126.4, 126.2(3C), 88.1, 83.0, 78.3, 61.0, 52.6, 50.5, 48.6, 47.4(2C), 39.8, 31.4, 25.6, 25.2, 23.6, 23.2, 23.0, 12.7; HRMS-EI calcd for $C_{32}H_{41}NO_3$ 487.3086, found 487.3079; MS-EI 487 ($M^+$, 4), 318 (16), 197 (58), 152 (100).

### 4.4. Synthesis of VULs 5, 6a–d

*4.4.1. 5,6-Dihydro-6-isopropyl-5-methyl-4-(pyrrolidin-1-yl)pyran-2-one (**5**).* To a THF solution (1 mL) of **4n** (474 mg, 1 mmol) was added a THF solution of LDA (1 N, 3.5 mL) at −78 °C. The temperature of the reaction mixture was allowed to rise to 20 °C for a period of 40 min. After being re-cooled to −78 °C and stirred for 30 min, a solution of isobutyraldehyde (1 N in THF, 4 mL) was added to the reaction mixture. This mixture was then allowed to warm to room temperature slowly over a period of 2 h. The reaction was quenched by the addition of aqueous ammonium chloride (1 N, 5 mL), extracted with $CH_2Cl_2$ (5 mL×2), and dried over anhydrous sodium sulfate, followed by concentration to afford the crude material. The crude was purified by flash chromatography (*n*-hexane/acetone, 2/1) to give *anti* VUL **5** (190 mg, 0.85 mmol) in 85% yield. Colorless solid, mp 111–112 °C; $R_f$ 0.42 (*n*-hexane/acetone, 2/1); $[\alpha]_D^{26}$ −25.6 ($c$ 1.0, $CH_2Cl_2$); IR ($CHCl_3$) 2978, 1653, 1584, 1576, 1357, 1207 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 4.46(s, 1H, C*H*=C), 3.67 (d, $J$=9.6 Hz, 1H, OC*H*), 3.45–3.17 (br, 4H, N($CH_2$)$_2$), 2.60 (q, $J$=7.0 Hz, 1H, C*H*CH$_3$),

2.10–1.91 (m, 5H, N($CH_2CH_2$)$_2$, $CH(CH_3)_2$), 1.30 (d, $J$=7.0 Hz, 3H, CHC$H_3$), 1.03 (d, $J$=6.6 Hz, 3H, CHC$H_3$), 0.83 (d, $J$=6.7 Hz, 3H, CHC$H_3$); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 166.4, 161.4, 86.3, 81.5, 47.4, 46.9, 31.9, 30.0, 25.2, 24.5, 19.7, 19.6, 18.5; HRMS-EI calcd for $C_{13}H_{21}NO_2$ 223.1572, found 223.1577.

*4.4.2. 5,6-Dihydro-6-propyl-5-methyl-4-(pyrrolidin-1-yl)pyran-2-one (**6a**).* This was synthesized according to the general procedure, on a 1 mmol scale. Yield: 55%. Colorless solid. Mp 83–84 °C; $R_f$ 0.38 ($n$-hexane/acetone, 2/1); $[\alpha]_D^{32}$ −57.4 ($c$ 0.4, $CH_2Cl_2$); IR ($CHCl_3$) 3053, 2963, 2935, 2871, 1668, 1579, 1376, 1225, 793 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 4.47 (s, 1H, C$H$=C), 4.15 (dd, $J$=8.9, 4.8 Hz, 1H, OC$H$), 3.50–3.10 (br, 4H, N($CH_2$)$_2$), 2.38 (q, $J$=7.1 Hz, 1H, C$H$CH$_3$), 2.05–1.80 (br, 6H, N($CH_2CH_2$)$_2$, $CH_2CH_2CH_3$), 1.60–1.22 (m, 2H, $CH_2CH_2CH_3$), 1.31 (d, $J$=7.1 Hz, 3H, CHC$H_3$), 0.90 (t, $J$=6.8 Hz, 3H, $CH_2CH_2CH_3$); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 166.4, 161.5, 81.4, 80.4, 47.5, 46.9, 35.5, 34.8, 25.3, 24.6, 19.3, 18.4, 13.8; HRMS-EI calcd for $C_{13}H_{21}NO_2$ 223.1572, found 223.1567; MS-EI 223 ($M^+$, 47), 208 (14), 180 (100), 70 (47).

*4.4.3. 5,6-Dihydro-6-tert-butyl-5-methyl-4-(pyrrolidin-1-yl)pyran-2-one (**6b**).* This was synthesized according to the general procedure, on a 1 mmol scale. Yield: 65%. Colorless solid, mp 118–119 °C; $R_f$ 0.44 ($n$-hexane/acetone, 2/1); $[\alpha]_D^{30}$ −40.8 ($c$ 0.4, $CH_2Cl_2$); IR ($CHCl_3$) 3055, 2963, 2872, 1665, 1579, 1435, 1381, 1226 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 4.47 (s, 1H, C$H$=C), 3.85 (s, 1H, OC$H$), 3.47–3.18 (br, 4H, N($CH_2$)$_2$), 2.62 (q, $J$=7.1 Hz, 1H, C$H$CH$_3$), 2.05–1.92 (br, 4H, N($CH_2CH_2$)$_2$), 1.32 (d, $J$=7.1 Hz, 3H, CHC$H_3$) 0.93 (s, 9H, C($CH_3$)$_3$); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 166.8, 161.6, 88.7, 82.0, 47.0, 36.6, 29.6, 29.4, 26.9 (3C), 25.2, 24.6, 21.0; HRMS-EI calcd for $C_{14}H_{23}NO_2$ 237.1729, found 237.1733; MS-EI 237 ($M^+$, 14), 222 (8), 180 (100), 70 (18).

*4.4.4. 5,6-Dihydro-5-methyl-6-((E)-2-prop-1-enyl)-4-(pyrrolidin-1-yl)pyran-2-one (**6c**).* This was synthesized according to the general procedure, on a 1 mmol scale. Yield: 83%. Colorless solid, mp 115–116 °C; $R_f$ 0.29 ($n$-hexane/acetone, 2/1); $[\alpha]_D^{29}$ −55.2 ($c$ 2.2, $CH_2Cl_2$); IR ($CHCl_3$) 3053, 2987, 1612, 1579, 1425, 1271, 1257, 759, 713 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 5.80–5.56 (m, 2H, C$H$=C$H$), 4.57 (d, $J$=5.7 Hz, 1H, OC$H$), 4.49 (s, 1H, C$H$=C), 3.50–3.13 (br, 4H, N($CH_2$)$_2$), 2.46 (q, $J$=7.1 Hz, 1H, C$H$CH$_3$), 2.05–1.85 (br, 4H, N($CH_2CH_2$)$_2$), 1.65 (d, $J$=5.6 Hz, 3H, CH=CHC$H_3$) 1.32 (d, $J$=7.1 Hz, 3H, CHC$H_3$); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 166.5, 161.2, 129.5, 128.8, 82.0, 80.8, 47.5, 47.0, 35.7, 25.4, 24.6, 17.9, 17.7; HRMS-EI calcd for $C_{13}H_{19}NO_2$ 221.1416, found 221.1420; MS-EI 221 ($M^+$, 10), 206 (8), 162 (100), 70 (19).

*4.4.5. 5,6-Dihydro-5-methyl-6-phenyl-4-(pyrrolidin-1-yl)pyran-2-one (**6d**).* This was synthesized according to the general procedure, on a 1 mmol scale. Yield: 65%. Colorless solid, mp 148–149 °C; $R_f$ 0.28 ($n$-hexane/acetone, 2/1); $[\alpha]_D^{32}$ −81.7 ($c$ 1.0, $CH_2Cl_2$); IR ($CHCl_3$) 2995, 1657, 1580, 1437, 1372 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 7.43–7.23 (m, 5H, Ar$H$), 5.33 (s, 1H, OC$H$), 4.51 (s, 1H C$H$=C), 3.51–3.06 (br, 4H, N($CH_2$)$_2$), 2.96 (q, $J$=7.0 Hz, 1H, C$H$CH$_3$), 1.92 (br, 4H, N($CH_2CH_2$)$_2$), 1.51 (d, $J$=7.0 Hz, 3H, CHC$H_3$); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 166.5, 160.7, 139.9, 128.3(2C), 127.4, 125.4(2C), 82.4, 80.6, 47.4, 47.0, 35.9, 25.2, 24.5, 18.7; HRMS-EI calcd for $C_{16}H_{19}NO_2$ 257.1416, found 257.1416; MS-EI 257 ($M^+$, 100), 242 (37), 198 (41), 70 (20).

### 4.5. Synthesis of (−)-prelactone B

*4.5.1. (5R,6S)-Dihydro-6-isopropyl-5-methyl-3H-pyran-2,4-dione (**8**).* 3 N aqueous hydrochloric acid (0.75 mL, 2.25 mmol) was added to compound **5** (80 mg, 0.36 mmol) in THF (1 mL) at room temperature. After stirring for 22 h, the reaction mixture was diluted with water (2 mL) and extracted with ethyl acetate (2 mL×2). Combined organic layers were dried over anhydrous sodium sulfate and concentrated to produce the crude material. The crude material was purified by flash chromatography ($n$-hexane/EtOAc, 2/1) to give pure lactone **8** (53 mg) in 87% yield. Colorless oil. $R_f$ 0.53 ($n$-hexane/acetone, 2/1); $[\alpha]_D^{26}$ −18.5 ($c$ 0.5, $CH_2Cl_2$); IR ($CHCl_3$) 3043, 2968, 2930, 2877, 1723, 1637, 1466, 1386 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 4.18 (dd, $J$=10.6, 2.5 Hz, 1H, OC$H$), 3.56 (d, $J$=19.3 Hz, 1H, $A$Bq, C$H$HC=O), 3.41 (d, $J$=19.3 Hz, 1H, A$B$q, CH$H$C=O), 2.53–2.43 (m, 1H, C$H$($CH_3$)$_2$), 2.10–1.95 (m, 1H, C$H$CH$_3$), 1.15 (d, $J$=7.1 Hz, 6H, CH(C$H_3$)$_2$) 0.99 (d, $J$=6.9 Hz, 3H, CHC$H_3$); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 203.1, 167.6, 83.8, 45.5, 45.0, 28.6, 19.5, 13.5, 10.1; HRMS-EI calcd for $C_9H_{14}O_3$ 170.0943, found 170.0950; MS-EI 170 ($M^+$, 12), 127 (51), 98 (45), 85 (100).

*4.5.2. (4S,5R,6S)-Tetrahydro-4-hydroxy-6-isopropyl-5-methylpyran-2-one (**9**).* Lactone **8** (46 mg, 0.27 mmol) with 5% palladium on carbon (0.2 g) in 95% ethanol (5 mL) was hydrogenated under hydrogen atmosphere (1 atm) for 20 h. The reaction mixture was filtered and concentrated to produce the crude material. The material was purified by flash chromatography ($n$-hexane/EtOAc, 2/1) to obtain β-hydroxy lactone **9** (36 mg, 78%). $R_f$ 0.68 ($n$-hexane/acetone, 2/1); $[\alpha]_D^{26}$ −53.3 ($c$ 1.66, MeOH); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 3.76 (m, 2H, OC$H$, C$H$OH), 2.93 (dd, $J$=17.0, 5.8 Hz, 1H, C$H$HC=O), 2.50–2.30 (br, 1H, O$H$) 2.47 (dd, $J$=17.0, 8.0 Hz, 1H, CH$H$C=O), 1.99 (m, 1H, C$H$CH$_3$), 1.75 (m, 1H, C$H$($CH_3$)$_2$), 1.10 (d, $J$=6.9 Hz, 3H, CHC$H_3$), 1.07 (d, $J$=6.6 Hz, 3H, CHC$H_3$), 0.92 (d, $J$=6.8 Hz, 3H, CHC$H_3$).

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## Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.12.009. These data includes MOL files and InChiKeys of the most important compounds described in this article.

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