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#### Dibromomethane as one-carbon source in organic synthesis: a versatile methodology to prepare the cyclic and acyclic α-methylene or α-keto acid derivatives from the corresponding terminal alkenes

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Dedicated to Professor Teh-Chang Chou of National Chung Cheng University on the occasion of his 60th birthday

**Abstract**—Ozonolysis of mono-substituted alkenes **A-1** followed by reacting with a preheated mixture of  $CH_2Br_2-Et_2NH$  affords  $\alpha$ -substituted acroleins **A-2** in good yields. Under very mild reaction conditions, these  $\alpha$ -substituted acroleins **A-2** can be easily converted to  $\alpha$ -methylene esters **A-4**, which could be further converted to the corresponding  $\alpha$ -keto esters **A-5**. This methodology can be also applied to the preparation of  $\alpha$ -methylene lactones **B-4**,  $\alpha$ -methylene lactams, and  $\alpha$ -keto lactones **B-5** with various ring sizes. © 2004 Elsevier Ltd. All rights reserved.

#### 1. Introduction

In the previous studies, the ozonide 2 or aldehyde 3 was treated with a preheated mixture of CH<sub>2</sub>Br<sub>2</sub> and Et<sub>2</sub>NH to give the acrolein 4 in modest to good yields (Eqs. 1 and 2)<sup>1</sup> whilst the aryl alkyl ketone 5 reacted with a mixture of CH<sub>2</sub>Br<sub>2</sub> and Et<sub>2</sub>NH under microwave condition to give the corresponding  $\alpha$ -methylene ketone **6** (Eq. 3).<sup>2</sup> The  $\beta$ -carbon of the conjugated carbonyl compound was derived from CH<sub>2</sub>Br<sub>2</sub>. In comparison with similar transformation reported in the literature,  $^{3-5}$  the characteristic features of our methodology are described as follows. Both CH<sub>2</sub>Br<sub>2</sub> and Et<sub>2</sub>NH are cheap. Their salts can be easily prepared in situ and used in the same flask to carry out the  $\alpha$ -methylenation. The reaction was carried out in nonaqueous media under mild reaction condition. In addition, both ozonide and aldehyde can be converted to the desired product. Therefore, a preheated mixture of CH<sub>2</sub>Br<sub>2</sub> and Et<sub>2</sub>NH is a convenient and economic reagent as one-carbon synthetic equivalent in organic synthesis.

$$\begin{array}{c} \mathsf{R} \\ 1 \end{array} \xrightarrow[]{0,3,} \\ \mathsf{CH}_2\mathsf{Cl}_2 \end{array} \left[ \begin{array}{c} \mathsf{R} \\ \mathsf{Q} \end{array} \right] \xrightarrow[]{0,0} \\ \mathsf{Q} \end{array} \right] \xrightarrow[]{0,0} \\ (\mathsf{CH}_2\mathsf{Br}_2, \,\mathsf{Et}_2\mathsf{NH}] \\ \mathsf{H} \\ \mathsf{H} \\ \mathsf{Q} \end{array} \right] \xrightarrow[]{0,0} \\ \mathsf{H} \\ \mathsf{H} \\ \mathsf{H} \\ \mathsf{Q} \\ \mathsf{H} \\ \mathsf{Q} \\ \mathsf{Q$$

$$R \xrightarrow{H} (CH_2Br_2, Et_2NH) \xrightarrow{H} H$$

$$4 \xrightarrow{O} (2)$$

$$\begin{array}{c} R & \overbrace{O}^{Ar} & \underline{[CH_2Br_2, Et_2NH]}_{Microwave} & R & \overbrace{O}^{Ar} & (3) \end{array}$$

 $\alpha$ -Methylene- $\gamma$ -butyrolactone is an important moiety in several biological active compounds. Therefore, the development of their preparative methodologies has been attractive to many synthetic organic chemists.<sup>6-19</sup> However, there are only few reports to describe the preparation of  $\alpha$ -methylene- $\beta$ -propiolactones<sup>20,21</sup> and  $\alpha$ -methylene- $\delta$ -valerolactones.<sup>22,23</sup> To the best of our knowledge, there is no general strategy which can be useful to prepare 4- to 7-memebred ring  $\alpha$ -methylene lactones.<sup>24</sup>  $\alpha$ -Keto acid derivatives play important roles not only in organic synthesis but also in biologically active natural products.<sup>25,26</sup> The preparation of the  $\alpha$ -keto acid was categorized as the following. Oxidation of  $\alpha$ -hydroxy esters or their equivalents,<sup>27a-c</sup> oxidative cleavage of the double bond of  $\alpha$ , $\beta$ -unsaturated carbonyl compounds,<sup>27d,e</sup>  $\alpha$ -oxidation of carbonyl groups,<sup>27f</sup> and metal-catalyzed double carbonylation<sup>27g</sup> are typical methods to prepare  $\alpha$ -keto acid derivatives.<sup>27</sup> Likewise,  $\alpha$ -keto amides are mostly obtained from amidation of  $\alpha$ -hydroxy esters or acids, followed by oxidation. Of the above methods, most lack generality or suffer from lengthy procedures. The use of toxic KCN and drastic hydrolytic conditions limit the application of some

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Figure 1. Retrosynthesis of the acyclic and cyclic  $\alpha$ -methylene or  $\alpha$ -keto carboxylates.

methods for the preparation of  $\alpha$ -keto acid derivatives with labile functional groups.<sup>27a-c</sup>

In our previous report, we described a methodology to prepare the  $\alpha$ -methylene acid or  $\alpha$ -keto acid derivatives from the corresponding terminal alkenes. The  $\alpha$ -methylene group is a masked form of carbonyl group. The  $\alpha$ -substituted acroleins were proved to be the suitable precursors to the formation of  $\alpha$ -keto acid derivatives.<sup>28</sup> Its retrosynthetic analysis was described in Figure 1. The  $\alpha$ , $\beta$ unsaturated carboxylic acid A-3 would be prepared from the mild oxidation of the  $\alpha$ ,  $\beta$ -unsaturated aldehyde A-2, which would be derived easily from terminal alkene A-1 by our reaction condition as shown in Eq. 1. The methyl acrylate A-4 would be a reasonable precursor to the  $\alpha$ -keto acid ester A-5. By using similar methodology, the hydroxyalkene B-1 would be a reasonable starting material for the preparation of  $\alpha$ -methylene lactone B-4 and  $\alpha$ -keto lactone **B-5**. The ring size of the lactone is dependent on the chain length of the spacer between the hydroxy and alkene moieties of compound B (Fig. 1). In this report, we shall describe our effort in the synthesis of acyclic and cyclic  $\alpha$ -methylene acid derivatives and their  $\alpha$ -keto acid derivatives in detail.

#### 2. Results and discussion

# 2.1. Preparation of acyclic $\alpha$ -methylene acids and their $\alpha$ -keto acid derivatives from the corresponding terminal alkenes

The ozonolysis of 1-decene (1a) followed by addition of a preheated mixture of  $CH_2Br_2$  and  $Et_2NH$  afforded acrolein 4a in 62% yield. The oxidation of acroleins to methyl

acrylates by MnO<sub>2</sub> in the presence of KCN in methanol has been reported in high yield.<sup>29</sup> In order to avoid using toxic KCN, we tried to use other reagents. The oxidation of  $\alpha$ -substituted acrolein 4a by Jones reagent gave an inseparable mixture of the acrylic acid 7a in addition to an over-oxidized product. We found that a modified procedure using sodium chlorite in the presence of a chlorine scavenger (i.e, 2-methyl-2-butene) resulted in the acrylic acid 7a formation in 98% yield.<sup>30</sup> The acrylic acid 7a was treated with 1 equiv. of diazomethane to give the methyl acrylate 8a in excellent yield. The presence of excess diazomethane might result in the further 1,3-dipolar cycloaddition to give  $\Delta^1$ -pyrazoline.<sup>31</sup> In general, the isolation of the acrylic acid 7a is not necessary before its reaction with diazomethane. The ozonolysis of methyl acrylate 8a followed by the reduction with Ph<sub>3</sub>P afforded  $\alpha$ -keto ester **9a** in 69% yield (Scheme 1).

As the reaction conditions involved in Scheme 1 were very mild, it was likely that the sequence might tolerate the presence of the labile groups. Both the keto-olefins  $1b^{32}$  and  $1c^{32}$  can be converted to the  $\alpha$ -substituted acroleins 4b and 4c, respectively, in good yields where the keto groups remain intact. Moreover, the acrolein 4c, with the quaternary center adjacent to the  $\alpha$ -methylene group, was formed in 61% yield. These acroleins could be converted to  $\alpha$ -keto esters **9b** and **9c** in good yields. Hydroxy-olefin **1d**, acetoxy-olefin 1e, and iodo-olefin 1f were also transformed into the corresponding a-keto ester derivatives in good yields via similar sequences (Scheme 1). The only exception was that the reducing agent in the ozonolysis of hydroxyacrylate 8d was Me<sub>2</sub>S rather than Ph<sub>3</sub>P. It is because the polarity of  $\alpha$ -keto ester **9d** is close to Ph<sub>3</sub>PO on silica gel thin layer chromatography. When  $\alpha$ -keto ester 9d was exposed to the silica gel for a long period of time while



Scheme 1. Reagents and conditions: (i) (a)  $O_3$ ,  $CH_2Cl_2$ , -78 °C; (b) preheated mixture of  $Et_2NH$  and  $CH_2Br_2$  (mol equiv.=5:15); (ii) 2.3 mol equiv. NaClO<sub>2</sub>, *t*-BuOH, 2 mol equiv. NaH<sub>2</sub>PO<sub>4</sub>·2H<sub>2</sub>O, 3 mol equiv. MeCH=CMe<sub>2</sub>; (iii) CH<sub>2</sub>N<sub>2</sub>; (iv) (a)  $O_3$ ,  $CH_2Cl_2$ , -78 °C; (b) 0.7 mol equiv. Ph<sub>3</sub>P; (v) (a)  $O_3$ ,  $CH_2Cl_2$ , -78 °C; (b) 1.1 mol equiv. Me<sub>2</sub>S.

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Scheme 2. Reagents and conditions: (i) 5 mol equiv. SOCl<sub>2</sub>; (ii) NH<sub>4</sub>OH; (iii) pyrrolidine; (iv) 1.1 mol equiv. L-valine methyl ester, 2 mol equiv. Et<sub>3</sub>N; (v) O<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C; 0.7 mol equiv. Ph<sub>3</sub>P.

eluting with the lower polarity solvent system, it would result in the dimerization of the  $\alpha$ -keto ester 9d. This obstacle can be overcome by using Me<sub>2</sub>S as reducing agent, where the DMSO byproduct is easily removed by extraction.

Acrylic acid **7a** was converted to the acryloyl chloride 8a'with thionyl chloride in excellent yield. There is no double bond isomerization problem under this acidic condition. The crude acid chloride 8a' reacted with ammonium hydroxide to give an excellent yield of acrylamide 10g, which was subjected to the ozonolysis to yield the corresponding  $\alpha$ -keto amide 11g in 90% yield. The acryloyl chloride 8a' also reacted with pyrrolidine or  $(\pm)$ -valine methyl ester to afford the corresponding acryloyl amides 10h and 10i in excellent yields. Under similar conditions, these  $\alpha$ -substituted acryloyl amides were also converted to the corresponding  $\alpha$ -keto amide 11g-11h in excellent yields. The ozonolysis of acrylic acid 7a followed by reduction with Ph<sub>3</sub>P afforded the  $\alpha$ -keto acid **9a**<sup>'</sup> in 73% yield (Scheme 2). In general, the yield for the formation of  $\alpha$ -keto amides is better than that of  $\alpha$ -keto esters. Our methodology is suitable to prepare the acyclic  $\alpha$ -methylene acid derivatives and their  $\alpha$ -keto acid derivatives with labile functional groups.

# 2.2. Preparation of mono-substituted $\alpha$ -methylene lactones with different ring sizes

The secondary alcohols **13a-13d**, prepared from the addition of alkenylmagnesium bromides with cyclohexane-

carbaldehyde (12), were treated with acetic anhydride to give the acetates 14a-14d in excellent yields (Scheme 3). The ozonolysis of acetoxy-alkene 14a followed by treatment with a preheated mixture of CH<sub>2</sub>Br<sub>2</sub> and Et<sub>2</sub>NH in the same flask gave 3-cyclohexylacrolein instead of the desired  $\alpha$ -substituted acrolein. Presumably, the elimination of the acetic acid from β-acetoxy aldehyde intermediate is a preferred process. We tried to change the protecting group with less leaving tendency in order to avoid this elimination problem. Under the catalysis of acetonyltriphenylphosphonium bromide (ATPB),<sup>33</sup> the secondary alcohol 13a reacted with 3,4-dihydro-2H-pyran (DHP) to give tetrahydropyranyl ether (OTHP) 18a in excellent yield. Fortunately, we were able to obtain the acrolein product 19a in 58% yield by using our standard  $\alpha$ -methylenation protocol. The  $\alpha$ -substituted acrolein **19a** was oxidized by sodium chlorite to give the corresponding acrylic acid, which was subsequently deprotected with ATPB in MeOH<sup>33</sup> to give the corresponding hydroxy-acid 21a. Compound 21a was treated with o-nitrophenylsulfonyl chloride<sup>34</sup> in the presence of Na<sub>2</sub>CO<sub>3</sub> to give  $\beta$ -cyclohexyl- $\alpha$ -methylene- $\beta$ propiolactone (17a) in excellent yield.

The ozonolysis of acetoxy-alkene **14b** followed by our standard  $\alpha$ -methylenation protocol afforded the desired  $\alpha$ -methylene aldehyde **15b**, which was subsequently treated with NaClO<sub>2</sub> followed by reaction with CH<sub>2</sub>N<sub>2</sub> to give methyl acrylate **16b** in excellent yield. The lactonization of the acetoxy-ester **16b** was achieved by treatment with hydrogen chloride, which was generated in situ from the



Scheme 3. Reagents and conditions: (i)  $CH_2 = CH(CH_2)nMgBr$ , THF, -78 °C; (ii) cat. DMAP, pyridine, Ac<sub>2</sub>O,  $CH_2CI_2$ ; (iii) (a) O<sub>3</sub>,  $CH_2CI_2$ , -78 °C; (b) preheated mixture of  $Et_2NH$  and  $CH_2Br_2$  (mol ratio 5:15); (iv) 2.3 mol equiv. NaClO<sub>2</sub>, *t*-BuOH, 2 mol equiv. NaH<sub>2</sub>PO<sub>4</sub>-2H<sub>2</sub>O, 3 mol equiv. MeCH=CMe<sub>2</sub>; (v) CH<sub>2</sub>N<sub>2</sub>; (vi) cat. AcCl, MeOH; (vii) DHP, cat. ATPB, CH<sub>2</sub>CI<sub>2</sub>; (viii) cat. ATPB, MeOH; (ix) *o*-NO<sub>2</sub>PhSO<sub>2</sub>Cl, Na<sub>2</sub>CO<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>.

reaction of a catalytic amount of acetyl chloride in the presence of methanol, to give the  $\gamma$ -cyclohexyl- $\alpha$ -methylene- $\gamma$ -butyrolactone (**17b**) in 86% yield. Following the same reaction sequences, the acetoxy-alkene **14c** was also converted to the  $\delta$ -cyclohexyl- $\alpha$ -methylene- $\delta$ -valerolactone (**17c**) in good yield (Scheme 3).

The acetoxy-acrylate 16d was prepared in a similar manner in good yield from the acetoxy-alkene 14d in order to synthesize 7-membered ring  $\alpha$ -methylene lactone. Unfortunately, the acetoxy-acrylate 16d cannot undergo lactonization by treatment with acid methanol (Scheme 3). We isolated the corresponding acyclic hydroxy-ester from the methanolysis of the acetoxy group. However, we did not obtain the lactonization product 17d when compound 16d was treated with NaOMe in methanol. The disappearance of the double bond indicates that the 1,4-addition of the methyl acrylate 16d may occur under this condition. In order to solve this problem, we tried to use different coupling reagent to achieve the lactonization. Under the catalysis of ATPB, the secondary alcohol 13d was protected as OTHP 18d in excellent yield. The ozonolysis of alkene 18d followed by our standard  $\alpha$ -methylenation protocol afforded the desired  $\alpha$ -methylene aldehyde **19d**, which was subsequently treated with NaClO<sub>2</sub> to give the corresponding acrylic acid 20d. The lactonization of the hydroxy-acid 20d was achieved by treatment with o-nitrophenylsulfonyl chloride in the presence of Na<sub>2</sub>CO<sub>3</sub> to give the  $\varepsilon$ -cyclohexyl- $\alpha$ -methylene-ε-caprolactone (17d) in 86% yield (Scheme 3). Herein, o-nitrophenylsulfonyl chloride was demonstrated to be an excellent reagent to promote the 4- and 7-membered ring  $\alpha$ -methylene lactones formation from their hydroxy-acid precursors. The hydrogen chloride in methanol is suitable to accomplish the 5- and 6-membered ring  $\alpha$ -methylenelactones formation from their acetoxyester precursors.

# 2.3. Preparation of geminal di-substituted $\alpha$ -methylene lactones with different ring size

The tertiary alcohols 24a-24d, prepared from the addition of alkenylmagnesium bromides to acetophenone (22) and cyclohexanone (23) respectively, were treated with acetic anhydride to give the acetates 25a-25d in excellent yield (Scheme 4). The ozonolysis of alkene 25a followed by our standard  $\alpha$ -methylenation protocol gave the desired  $\alpha$ methylene aldehyde 26a. The  $\alpha$ -substituted acrolein 26a was oxidized by sodium chlorite to give the corresponding acrylic acid, which was subsequently treated with CH<sub>2</sub>N<sub>2</sub> to give methyl acrylate 27a in excellent yield. The lactonization of the acetoxy-ester 27a was achieved by treatment with a trace amount of HCl in methanol to give  $\alpha$ methylene- $\gamma$ -butyrolactone **28a** in 75% yield. The  $\alpha$ methylene- $\gamma$ -butyrolactone **28c** was also prepared in the similar manner from the corresponding alkene 24c. The chemical yields in each step are good to excellent (Scheme 4). Mechanistically, the acetoxy group of compound 27a will undergo methanolysis to give the corresponding hydroxy compound as an intermediate, which then undergoes 5-membered ring formation.

Since the 5-membered ring  $\alpha$ -methylene lactones (**28a** and **28c**) were successfully formed under acidic condition, we tried to prepare their 6-membered ring analogues (**28b** and **28d**) from their acyclic precursors (**27b** and **27d**) under similar conditions. However, we obtained the elimination products rather than the ring formation products in each case. It is well known that 6-membered ring. Before the lactonization, the tertiary hydroxy compounds derived from **27b** and **27d** prefer to form the relatively stable tertiary carbocation intermediates, which may further undergo  $\alpha$ -proton elimination. In order to solve this



Scheme 4. Reagents and conditions: (i)  $CH_2$ =CH( $CH_2$ )nMgBr, THF, -78 °C; (ii)  $Ac_2O$ , cat. DMAP,  $CH_2Cl_2$ ; (iii) (a)  $O_3$ ,  $CH_2Cl_2$ , -78 °C; (b) preheated mixture of Et<sub>2</sub>NH and  $CH_2Br_2$  (mol equiv.=5:15); (iv) 2.3 mol equiv. NaClO<sub>2</sub>, *t*-BuOH, 2 mol equiv. NaH<sub>2</sub>PO<sub>4</sub>-2H<sub>2</sub>O, 3 mol equiv. MeCH=CMe<sub>2</sub>; (v) CH<sub>2</sub>N<sub>2</sub>; (vi) cat. AcCl, MeOH; (vii) K<sub>2</sub>CO<sub>3</sub>, MeOH; (viii) *o*-NO<sub>2</sub>PhSO<sub>2</sub>Cl, Na<sub>2</sub>CO<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>.

problem, we considered to use *o*-nitrophenylsulfonyl chloride as the promoter. The acetoxy-acrolein **26b** was oxidized by sodium chlorite to give the acetoxy-acrylic acid **29b**, in which the acetoxy group was converted to give the hydroxy-acrylic acid **30b** in good yield. The lactonization of the hydoxy-acid **30b** was successfully achieved by treatment with *o*-nitrophenylsulfonyl chloride in the presence of Na<sub>2</sub>CO<sub>3</sub> to give  $\alpha$ -methylene- $\delta$ -valerolactone **28b** in 71% yield. The 6-membered ring  $\alpha$ -methylenespirolactone **28d** was also prepared under similar condition from the hydroxy-acid **30d** (Scheme 4).

### 2.4. Preparation of bicyclic $\alpha$ -methylene lactones with different ring size

The cyclic *trans*-alcohols **32a-32b**, prepared from the addition of alkenylmagnesium bromides with 1,2-epoxycyclohexane (31) in the presence of CuI, were treated with acetic anhydride to give the acetates 33a-33b in excellent yields (Scheme 5). The ozonolysis of alkene 33a followed by our standard  $\alpha$ -methylenation protocol gave the desired  $\alpha$ -methylene aldehyde **34a**. The  $\alpha$ -substituted acrolein **34a** was oxidized by sodium chlorite followed by treatment with  $CH_2N_2$  to give the methyl acrylate **35a** in excellent yield. The lactonization of the acetoxy-ester 35a was achieved by treatment with a catalytic amount of HCl in methanol to give the *trans*-fused bicyclic  $\alpha$ -methylenelactone 36a in 89% yield. The 6-membered ring analogues 36b were also prepared in a similar manner from the corresponding terminal alkene precursor 33b. The chemical yields in each step are good to excellent (Scheme 5).

In order to prepare the *cis*-fused bicyclic lactones, the inversion of the hydroxy stereogenic centers of compounds **32a** and **32b** was achieved by Mitsunobu reaction<sup>35</sup> to give the corresponding *cis*-benzoxy-alkene **33c** and **33d** in good yields. Since the benzoate group of compound **35c** is more reluctant to methanolysis under acidic condition, we tried to use the basic condition to achieve the lactonization. When compound **35c** was treated with NaOMe in MeOH, we obtained the *cis*-fused bicyclic  $\alpha$ -methylene- $\gamma$ -lactone **36c** in 76% yield. The 6-membered ring *cis*-fused bicyclic analogue **36d** was also prepared in a similar manner (Scheme 5).

In order to demonstrate the applicability of our methodology to prepare the benzo-fused bicyclic  $\alpha$ -methylene lactones with different ring size, 2-allylphenol (37) was used as the

starting material. The phenolic group of compound 37 was protected as OTHP 38 in good yield. The ozonolysis of alkene 38 followed by our standard  $\alpha$ -methylenation protocol in the same flask gave the desired  $\alpha$ -methylene aldehyde **39**. The  $\alpha$ -substituted acrolein **39** was oxidized by sodium chlorite, followed by treatment with CH<sub>2</sub>N<sub>2</sub> to give methyl acrylate 40 in excellent yield. When compound 40 was treated with a catalytic amount of acetyl chloride in the presence of methanol, the reaction was quite messy and we did not obtain the desired lactone 42.  $\alpha$ -Methylene lactone 42 is known to be unstable and it is sensitive to the nucleophilic solvent.<sup>36</sup> Therefore, the OTHP group of compound 40 was deprotected to give the corresponding hydroxy-acrylate 41. Compound 41 was treated with trifluoroacetic acid in toluene at 90 °C for 2 h<sup>37</sup> to give the desired product 42. The crude product was confirmed by the <sup>1</sup>H NMR. Since it is too unstable to be purified by silica gel column chromatography, the crude product 42 was then treated with cyclopentadiene to give the Diels-Alder adduct 43 as a mixture of two diastereomers in a ratio of 4 to 1 in 51% overall yield from compound 41. We found that the major adduct was a less polar isomer.

For the purpose to prepare the 6-membered ring benzofused bicyclic  $\alpha$ -methylene lactone from compound 38, elongation of the side chain is required. The hydroboration of the alkene 38 followed by treatment with hydrogen peroxide gave the corresponding primary alcohol 44 in 65% yield. The alcohol 44 was oxidized by PCC to give the corresponding aldehyde 45. By using our standard  $\alpha$ -methylenation protocol, the aldehyde 45 was converted to the desired  $\alpha$ -methylene aldehyde **46** in 62% yield. The  $\alpha$ -substituted acrolein 46 was oxidized by sodium chlorite followed by treatment with CH<sub>2</sub>N<sub>2</sub> to give methyl acrylate 47 in excellent yield. The OTHP-acrylate 47 was treated with a catalytic amount of acetyl chloride in the presence of methanol to give benzo-fused  $\alpha$ -methylene- $\gamma$ -valerolactone 48 in good yield (Scheme 6). No double bond isomerization occurred during this acid-catalyzed lactonization.

# 2.5. Preparation of mono-substituted $\alpha$ -methylene lactams with different ring size

In order to demonstrate the applicability of our methodology to prepare the  $\alpha$ -methylene lactams with different ring size, the secondary alcohol **12c** and **12d** were converted to the corresponding azides **49c** and **49d** by Mitsunobu reaction condition<sup>38</sup> in good yields. We found that these azides were





Scheme 6. Reagents and conditions: (i) cat. ATPB, dihydropyran; (ii) (a)  $O_3$ ,  $CH_2Cl_2$ , -78 °C; (b) preheated mixture of Et<sub>2</sub>NH and CH<sub>2</sub>Br<sub>2</sub> (mol equiv.=5:15); (iii) 2.3 mol equiv. NaClO<sub>2</sub>, *t*-BuOH, 2 mol equiv. NaH<sub>2</sub>PO<sub>4</sub>-2H<sub>2</sub>O, 3 mol equiv. MeCH=CMe<sub>2</sub>; (iv) CH<sub>2</sub>N<sub>2</sub>; (v) cat. ATPB, MeOH; (vi) (a) CF<sub>3</sub>CO<sub>2</sub>H, toluene, 90 °C; (b) cyclopentadiene; (vii) (a) 9-BBN; (b) H<sub>2</sub>O<sub>2</sub>, NaOH; ; (viii) PCC, CH<sub>2</sub>Cl<sub>2</sub>. (ix) (a) O<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C; (b) preheated mixture of Et<sub>2</sub>NH and CH<sub>2</sub>Br<sub>2</sub> (mol equiv.=4:15); (x) cat. AcCl, MeOH.

decomposed slowly by the silica gel. However, they can still be purified by flash silica gel column chromatograpy. It is worthy to mention that both of these compounds are photosensitive and decomposed rapidly at room temperature in the pure state. Therefore, they must be freshly prepared and used directly for further reaction. The ozonolysis of azido-alkene **49c** followed by our standard  $\alpha$ -methylenation protocol gave the desired  $\alpha$ -methylene aldehyde **50c**. The azido group is compatible with the ozone treatment. The freshly prepared azido-acrolein **50c** was oxidized by sodium chlorite to give the corresponding acrylic acid, which was subsequently treated with CH<sub>2</sub>N<sub>2</sub> to give azido-acrylate **51c** in good yield. Compound **51c** was treated with triphenylphosphine followed by the addition of water to give the  $\alpha$ -methylene- $\gamma$ -butyrolactam **52c** in 80% yield (Scheme 7).

Although the azido compounds **49c**, **50c** and **51c** are not quite stable, they are still applicable to further functional group transformations. To our surprise, the azido-acrolein **50d** is more unstable than **50c**. It was decomposed quickly by silica gel during the separation and too unstable to the further transformations. In order to solve this problem, the azido group of compound **49d** was reduced with Ph<sub>3</sub>P followed by treatment with water to give the corresponding amino compound, which was then treated with methyl chloroformate to give carbamate **53d** in high yield. The ozonolysis of carbamato-alkene **53d** followed by our standard  $\alpha$ -methylenation protocol in the same flask gave

the desired  $\alpha$ -methylene aldehyde **54d**. According to the above-mentioned reaction sequences, the carbamatoacrolein **55d** was converted to the carbamato-acrylate **55d** in excellent yield. The lactamization of compound **55d** was achieved by the treatment of trimethylaluminium in toluene to give  $\alpha$ -methylene- $\delta$ -valerolactam **56d** in 72% yield (Scheme 7).<sup>39</sup>

# 2.6. Preparation of $\alpha$ -keto lactones with different ring size from the corresponding $\alpha$ -methylene lactones

We have been successful employing our methodology to prepare 4- to 7-membered ring  $\alpha$ -methylenelactones. We tried to cleave their  $\alpha$ -methylene groups by ozone in order to prepare the corresponding  $\alpha$ -keto lactones. The ozonolysis of 5-membered ring  $\alpha$ -methylene- $\gamma$ -lactone 17b in  $CH_2Cl_2$  at -78 °C followed by the reduction with  $Ph_3P$  gave the corresponding  $\alpha$ -keto- $\gamma$ -butyrolactone 17b' as an intermediate which tautomerized completely to its enol form 17b''. In CDCl<sub>3</sub>, no keto form isomer 17b' was detected by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy. The characteristic peaks of the  ${}^{13}C$  NMR spectrum for compound 17b'' are the ones at  $\delta$  170.3 ppm for the carbonyl carbon,  $\delta$ 142.2 ppm for the  $\alpha$ -carbon, and  $\delta$  117.6 ppm for the  $\beta$ -carbon. No absorption appears above  $\delta$  170.3 ppm in the <sup>13</sup>C NMR spectrum as well as none appears between  $\delta$ 2-4 ppm in the <sup>1</sup>H NMR spectrum indicate that there is no keto isomer present in the solution (Eq. 4).



Scheme 7. Reagents and conditions: (i) DEAD,  $Ph_3P$ ,  $(PhO)_2PON_3$ ; (ii) (a)  $O_3$ ,  $CH_2Cl_2$ , -78 °C; (b) preheated mixture of  $Et_2NH$  and  $CH_2Br_2$  (mol equiv.=5:15); (iii) 2.3 mol equiv. NaClO<sub>2</sub>, *t*-BuOH, 2mol equiv. NaH<sub>2</sub>PO<sub>4</sub>-2H<sub>2</sub>O, 3 mol equiv. MeCH=CMe<sub>2</sub>; (iv) CH<sub>2</sub>N<sub>2</sub>; (v) Ph<sub>3</sub>P; H<sub>2</sub>O; (vi) ClCO<sub>2</sub>Me, K<sub>2</sub>CO<sub>3</sub>; (vii) Me<sub>3</sub>Al, toluene.

(4)



The ozonolysis of the  $\gamma, \gamma$ -disubstituted- $\alpha$ -methylene- $\gamma$ lactone 28a followed by reduction with Ph<sub>3</sub>P gave the  $\alpha$ -keto- $\gamma$ -butyrolactone **28a'** as an intermediate which equilibrated with its enol form 28a''. The  $\beta$ -olefinic proton absorption of compound 28a'' appears at  $\delta$  6.52 ppm as a singlet in CDCl<sub>3</sub>. The methylene group adjacent to the keto group of compound 28a' appears as AB-type splitting pattern at  $\delta$  3.18–3.20 ppm. The ratio of the enol form (28a'') and keto form (28a') is 100:19 as estimated by integrations (Eq. 4). Under similar reaction condition, the  $\gamma,\gamma$ -disubstituted- $\alpha$ -methylenespirolactone **28c** was converted to the  $\alpha$ -keto- $\gamma$ -butyrolactone **28c**' as an intermediate which equilibrated with its enol form 28c''. The  $\beta$ -olefinic proton absorption of compound 28c'' appears at  $\delta$  6.31 ppm as a singlet in CDCl<sub>3</sub>. The methylene group adjacent to the keto group of compound 28c' appears as a singlet at  $\delta$ 2.75 ppm. The isomeric ratio of the enol form (28c'') and keto form (28c') is 100:20 as estimated by integrations (Eq. 4).





R=Cyclohexyl, Y=H **17c** X=Methyl, Y=Phenyl **28b** 



According to the above-mentioned ozonolysis condition, the 6-membered ring  $\alpha$ -methylene lactones (17c and 28b) gave complicated mixtures. The ozonolysis of the  $\alpha$ -methylene- $\delta$ -valerolactones (17c and 28b) in dichloromethane at -78 °C followed by treatment with Et<sub>3</sub>N<sup>40</sup> also gave a complicated mixture. Interestingly, when compound 17c was treated with ozone in the presence of methanol, we isolated the 5-membered ring lactol (17c'') as a mixture of two diastereomers, which were derived from the skeletal rearrangement of the corresponding  $\alpha$ -keto- $\delta$ -caprolactones (17c') intermediate. The characteristic peaks of the <sup>13</sup>C NMR spectrum for compound 17c'' are the absorptions at  $\delta$ 171.8 ppm for the carbonyl carbon and  $\delta$  102.0 and 101.5 ppm for quarternary carbon bearing the hydroxy group. No absorption appears above  $\delta$  171.8 ppm in <sup>13</sup>C NMR spectrum indicates that there is no keto group present



The ozonolysis of both the *cis*- and *trans*-bicyclic  $\alpha$ -methylene- $\gamma$ -lactones (**36a** and **36c**) followed by reduction with Ph<sub>3</sub>P gave the enol product **36c**'' only (Eq. 5). The characteristic peaks of the <sup>13</sup>C NMR spectrum for compound **36c**'' are the absorptions at  $\delta$  170.9 ppm for

in product 17c'' (Eq. 7). A broad and strong OH absorption at 3447 cm<sup>-1</sup> in the infrared spectrum also supports the structure of compound 17c''. Similar result was obtained from the ozonolysis of compound **28b** in the presence of methanol (Eq. 6).

(6)



The ozonolysis of 7-membered ring  $\alpha$ -methylene lactone **17d** in CH<sub>2</sub>Cl<sub>2</sub> at -78 °C followed by the reduction with Ph<sub>3</sub>P gave the corresponding  $\alpha$ -keto- $\gamma$ -lactone **17d**', which does not equilibrate to its enol form **17d**'' in CDCl<sub>3</sub> as judged from its <sup>13</sup>C NMR spectrum (Eq. 7). The characteristic peaks of the <sup>13</sup>C NMR spectrum for compound **17d**' are the absorptions at  $\delta$  200.1 ppm for the keto carbonyl carbon and at  $\delta$  166.2 ppm for the lactone carbonyl carbon. No absorption appeares between 100–160 ppm in <sup>13</sup>C NMR spectrum indicates that there is no enol isomer present in the solution (Eq. 7).

#### 3. Conclusions

In summary, we have developed a general methodology to prepare the acyclic  $\alpha$ -substituted acrylic acids and their derivatives from the corresponding terminal alkenes. The further cleavage of their  $\alpha$ -methylene groups by the ozonolysis gave the corresponding  $\alpha$ -keto acid derivatives in good yields. The reaction conditions in each step are quite mild that substrates with labile functional groups can be used. This methodology can also be applied to prepare 4- to 7-membered ring  $\alpha$ -methylene lactones in good yields. For the 5- and 7-membered ring  $\alpha$ -methylenelactones, the further cleavage of their  $\alpha$ -methylene groups by the ozonolysis in  $CH_2Cl_2$  gave the corresponding  $\alpha$ -keto lactones in good yields. Their tautomeric ratio is ring-size and substituent-dependent. For the 6-membered ring  $\alpha$ -methylene lactones, the further cleavage of their  $\alpha$ -methylene groups by the ozonolysis in the presence of methanol gave the skeletal rearranged 5-membered ring lactols in good yields.

#### 4. Experimental

All reactions were carried out under nitrogen. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Melting points were determined by using a Thomas–Hoover melting point apparatus and were uncorrected. The <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Bruker ACP 300 and Bruker Avance DPX400 spectrometer, and chemical shifts were given in ppm downfield from tetramethylsilane (TMS). IR spectra were taken with a Perkin–Elmer 682 spectrophotometer and only noteworthy absorptions were listed. Mass spectra were measured on a Micromass Trio-2000

GC/MS spectrometer (National Chiao–Tung University) by electronic impact at 70 eV (unless otherwise indicated). High Resolution Mass Spectroscopy (HRMS) was measured on a Finnigan/Thermo Quest MAT (National Chung Hsing University) or VG-11-250J (Academia Sinica) Mass Spectrometer.  $\alpha$ -Substituted acroleins **4a-4f** were prepared from terminal alkenes **1a-1f** according to our report.<sup>1b</sup>

# 4.1. General procedure to prepare the secondary alcohol from Grignard reagent with carbonyl compound

Allyl bromide (1/10 of 5.81 g, 48 mmol) is added, without stirring, to a mixture of magnesium turings (1.21 g, 50 mmol) in 10 mL of anhydrous THF. After the reaction started, the remaining allyl bromide in 10 mL of THF is added dropwise with stirring so that the THF barely refluxes. The mixture is then refluxed for 2 h, cooled to room temperature, and added 20 mL of THF to dilute the Grignard reagent. To a solution of cyclohexanecarbaldehyde (12) (4.71 g, 42 mmol) in 40 mL of THF was added the Grignard reagent dropwise at -78 °C and stirred at this temperature for 1 h. The reaction is quenched with aqueous ammonium chloride solution and extracted with ethyl acetate. The organic layer was dried over MgSO<sub>4</sub>, concentrated, and chromatographed on silica gel column to give the secondary alcohol 13a (5.95 g, 38.6 mmol) in 92% yield.

**4.1.1. 1-Cyclohexylbut-3-en-1-ol** (**13a**).<sup>41</sup> 92% Yield; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  5.79–5.87 (m, 1H,  $-CH=CH_2$ ), 5.11–5.16 (m, 2H,  $-CH=CH_2$ ), 3.37–3.41 (m, 1H, CH–OH), 2.30–2.40 (m, 1H,  $-CH_2-CH=CH_2$ ), 2.05–2.15 (m, 1H,  $-CH_2-CH=CH_2$ ), 1.01–1.77 (m, 11H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  135.4, 117.7, 74.7, 43.0, 38.8, 29.1, 28.0, 26.5, 26.2, 26.1; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 3390 (OH), 3074, 2976, 2924, 2852, 1639, 1449, 985, 911; MS *m*/*z* (rel intensity): 144 (M<sup>+</sup>–18, 4), 113 (M<sup>+</sup>–41, 2), 95 (100), 67 (18); HRMS Calcd for C<sub>10</sub>H<sub>18</sub>O–CH<sub>2</sub>-CH=CH<sub>2</sub> 113.0967, found:113.0961.

**4.1.2. 1-Cyclohexylpent-4-en-1-ol** (**13b**).<sup>42</sup> 82% Yield, TLC  $R_{\rm f}$ =0.32 (hexane/EtOAc=10:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  5.80–5.87 (m, 1H, –CH=CH<sub>2</sub>), 4.94–5.06 (m, 2H, –CH=CH<sub>2</sub>), 3.34–3.38 (m, 1H, CH–OH), 2.25– 2.32 (m, 1H, –CH<sub>2</sub>–CH=CH<sub>2</sub>), 2.11–2.18 (m, 1H, –CH<sub>2</sub>–CH=CH<sub>2</sub>), 1.01–1.77 (m, 13H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  138.8, 114.6, 75.7, 43.7, 33.3, 30.3, 29.2, 27.8, 26.5, 26.3, 26.2; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 3398 (OH), 3077, 1450, 1085, 985, 910; MS *m*/*z* (rel intensity): 168 (M<sup>+</sup>, 2), 111 (52), 109 (32), 83 (100), 55 (82); HRMS Calcd for C<sub>11</sub>H<sub>20</sub>O 168.1514, found: 168.1516.

**4.1.3. 1-Cyclohexylhex-5-en-1-ol (13c).**<sup>42</sup> 85% Yield, TLC  $R_f$ =0.34 (hexane/EtOAc=10:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  5.76–5.83 (m, 1H, –C*H*=CH<sub>2</sub>), 4.91–5.01 (m, 2H, –CH=CH<sub>2</sub>), 3.32–3.34 (m, 1H, C*H*–O), 2.05–2.07 (m, 2H, –C*H*=CH=CH<sub>2</sub>), 1.06–1.76 (m, 15H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  138.8, 114.5, 76.0, 43.6, 33.7, 33.5, 29.2, 27.7, 26.5, 26.3, 26.2, 25.2; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 3323 (OH), 3076, 2978, 2924, 1450, 1086, 909; MS *m/z* (rel intensity): 182 (M<sup>+</sup>, 7), 95 (33), 81 (36), 55 (39), 41 (52); HRMS Calcd for C<sub>12</sub>H<sub>22</sub>O 182.1671, found: 182.1665.

4844

**4.1.4. 1-Cyclohexylhept-6-en-1-ol (13d).** 80% Yield, TLC  $R_{\rm f}$ =0.35 (hexane/EtOAc=10:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  5.76–5.82 (m, 1H, –C*H*=CH<sub>2</sub>), 4.89–5.00 (m, 2H, –CH=CH<sub>2</sub>), 3.31 (br, 1H, C*H*–OH), 2.03–2.05 (m, 2H, –CH<sub>2</sub>–CH=CH<sub>2</sub>), 0.86–1.76 (m, 17H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  138.9, 114.2, 76.0, 43.5, 33.9, 33.7, 29.2, 29.0, 27.7, 26.5, 26.3, 26.2, 25.4; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 3420 (OH), 3076, 2926, 1451, 1086; MS *m*/*z* (rel intensity): 196 (M<sup>+</sup>, 2), 113 (23), 95 (100), 69 (16), 55 (13); HRMS Calcd for C<sub>13</sub>H<sub>24</sub>O 196.1827, found: 196.1835.

**4.1.5. 2-Phenylhex-5-en-2-ol** (**24a**).<sup>43</sup> 90% Yield, TLC  $R_{\rm f}$ =0.35 (hexane/EtOAc=10:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  7.24–7.46 (m, 5H), 5.76–5.85 (m, 1H, –CH=CH<sub>2</sub>), 4.93–5.01 (m, 2H, –CH=CH<sub>2</sub>), 1.89–2.11 (m, 4H), 1.58 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  147.6, 138.7, 128.1, 126.5, 124.7, 114.5, 74.6, 43.0, 30.2, 28.4; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 3420 (OH), 3025, 2926, 1638, 1456, 997, 912; MS *m*/*z* (rel intensity): 176 (M<sup>+</sup>, 7), 121 (100), 105 (22), 77 (12), 43 (43); HRMS Calcd for C<sub>12</sub>H<sub>16</sub>O 176.1201, found: 176.1200.

**4.1.6. 2-Phenylhept-6-en-2-ol** (**24b**).<sup>44</sup> 81% Yield, TLC  $R_f$ =0.38 (hexane/EtOAc=10:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  7.41–7.43 (m, 2H), 7.30–7.34 (m, 2H), 7.20–7.24 (m, 1H), 5.69–5.76 (m, 1H, –CH=CH<sub>2</sub>), 4.89–4.97 (m, 2H, –CH=CH<sub>2</sub>), 1.96–2.02 (m, 2H, –CH<sub>2</sub>–CH=CH<sub>2</sub>), 1.77–1.82 (m, 2H), 1.54 (s, 3H), 1.35–1.38 (m, 1H), 1.23–1.35 (m, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  147.9, 138.6, 128.1, 126.5, 124.7, 114.6, 74.6, 43.6, 33.9, 30.1, 23.2; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 3407 (OH), 3063, 2929, 1753, 1678, 1493, 997, 911; MS *m/z* (rel intensity): 190 (M<sup>+</sup>, 3), 175 (8), 121 (100), 105 (13), 43 (37); HRMS Calcd for C<sub>13</sub>H<sub>18</sub>O 190.1358, found: 190.1351.

**4.1.7. 1-But-3-enylcyclohexanol** (**24c**).<sup>45</sup> 86% Yield, TLC  $R_{\rm f}$ =0.4 (hexane/EtOAc=10:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  5.80–5.90 (m, 1H, –CH=CH<sub>2</sub>), 4.93–5.05 (m, 2H, CH=CH<sub>2</sub>), 2.13–2.15 (m, 2H, CH<sub>2</sub>-CH=CH<sub>2</sub>), 1.27–1.70 (m, 12H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  139.3, 114.2, 71.3, 41.4, 37.4, 27.4, 25.8, 22.2; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 3375 (OH), 3077, 2923, 2852, 1640, 1450, 985, 912; MS *m*/*z* (rel intensity): 136 (M<sup>+</sup>–18), 99 (65), 98 (100), 81 (50), 55 (63); HRMS Calcd for C<sub>10</sub>H<sub>18</sub>O–H<sub>2</sub>O 136.1252, found: 136.1249.

**4.1.8. 1-Pent-4-enylcyclohexanol (24d).**<sup>45</sup> 80% Yield, TLC  $R_{\rm f}$ =0.42 (hexane/EtOAc=10:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  5.78–5.85 (m, 1H, –CH=CH<sub>2</sub>), 4.93–5.03 (m, 2H, CH=CH<sub>2</sub>), 2.05–2.06 (m, 2H, CH<sub>2</sub>–CH=CH<sub>2</sub>), 1.43–1.58 (m, 14H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  138.8, 114.4, 71.3, 41.8, 37.3, 34.2, 25.8, 22.2, 22.1; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 3330 (OH), 3077, 2928, 2856, 1640, 1449, 997, 910; MS *m*/*z* (rel intensity): 150 (M<sup>+</sup>–18, 33), 99 (62), 98 (100), 81 (41), 55 (36); HRMS Calcd for C<sub>11</sub>H<sub>20</sub>O–H<sub>2</sub>O 150.1409, found: 150.1402.

#### **4.2.** General procedure to prepare the secondary alcohol from Grignard reagent with epoxide

Allylmagnesium bromide obtained from allyl bromide (847 mg, 7.0 mmol) and magnesium powder (243 mg, 10.0 mmol) in THF. The Grignard reagent was added to a

well-stirred suspension of copper(I) iodide (171 mg, 0.9 mmol) in 10 mL of THF at -5 °C. After the copper iodide dissolved (*ca.* 30 min) the solution is cooled to -20 °C, and cyclohexene oxide (588 mg, 6 mmol) is added dropwise. The reaction is warmed slowly to room temperature and stirred at room temperature for 10 h. The reaction mixture is poured into 10 mL of iced cold, saturated NH<sub>4</sub>Cl solution. The aqueous phase is extracted with saturated NaCl solution, dried over MgSO<sub>4</sub>, concentrated and chromatographed on silica gel column to give the alcohol **32a** as colorless oil (789 mg, 5.64 mmol) in 94% yield.

**4.2.1.** *trans*-2-Allylcyclohexanol (32a).<sup>46</sup> 94% Yield, TLC  $R_{\rm f}$ =0.30 (hexane/EtOAc=3:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  5.78–5.84 (m, 1H, –C*H*=CH<sub>2</sub>), 4.96–5.04 (m, 2H, –CH=CH<sub>2</sub>), 3.19–3.23 (m, 1H, C*H*–OH), 2.41–2.44 (m, 1H, –C*H*<sub>2</sub>–CH=CH<sub>2</sub>), 2.05–2.08 (m, 1H, –C*H*<sub>2</sub>–CH=CH<sub>2</sub>), 0.91–1.94 (m, 9H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  137.4, 115.8, 74.4, 44.8, 37.2, 35.5, 30.2, 25.4, 24.8; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 3445 (OH), 3025, 2925, 1637, 1495, 1027; MS *m*/*z* (rel intensity): 122 (M<sup>+</sup>–18, 62), 98 (59), 93 (56), 81 (100), 79 (58); HRMS Calcd for C<sub>9</sub>H<sub>16</sub>O–H<sub>2</sub>O 122.1096, found: 122.1086.

**4.2.2.** *trans*-**2**-**But**-**3**-**enylcyclohexanol** (**32b**). 90% Yield, TLC  $R_{\rm f}$ =0.33 (hexane/EtOAc=3:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  5.79–5.86 (m, 1H, –C*H*=CH<sub>2</sub>), 4.92–5.04 (m, 2H, –CH=CH<sub>2</sub>), 3.36–3.41 (m, 1H, C*H*–OH), 2.18–2.22 (m, 1H, –C*H*<sub>2</sub>–CH=CH<sub>2</sub>), 2.11–2.15 (m, 1H, –C*H*<sub>2</sub>–CH=CH<sub>2</sub>), 1.18–1.85 (m, 11H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  138.7, 114.5, 75.3, 46.3, 35.2, 30.1, 29.1, 28.5, 25.6, 25.5; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 3398 (OH), 3014, 1455, 1055; MS *m*/*z* (rel intensity): 136 (M<sup>+</sup>–18, 30), 97 (M<sup>+</sup>–57, 30), 81 (100), 67 (48), 43 (40), 41 (63); HRMS Calcd for C<sub>10</sub>H<sub>18</sub>O 154.1358, found: 154.1361.

#### **4.3.** General procedure to prepare the acetate from the corresponding alcohol

To a solution of secondary alcohol **13a** (1.0 g, 6.5 mmol), pyridine (0.63 mL, 7.8 mmol) and a catalytic amount of DMAP (N,N-dimethylaminopyridine, 9.52 mg, 0.78 mmol) in 25 mL of CH<sub>2</sub>Cl<sub>2</sub> was added acetic anhydride (0.74 mL, 7.8 mmol). The reaction mixture was stirred at room temperature for 10 h. The reaction mixture was concentrated, chromatographed on silica gel column to give the corresponding acetate **14a** (1.27 g, 6.5 mmol) in 95% yield.

**4.3.1. 1-Cyclohexylbut-3-enyl acetate** (**14a**).<sup>47</sup> 95% Yield; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  5.71–5.77 (m, 1H, –*CH*=CH<sub>2</sub>), 5.02–5.08 (m, 2H, –*CH*=CH<sub>2</sub>), 4.76–4.80 (m, 1H, *CH*–OAc), 2.20–2.40 (m, 2H, –*CH*<sub>2</sub>–*CH*=CH<sub>2</sub>), 2.03 (s, 3H, –*COCH*<sub>3</sub>), 0.99–1.75 (m, 11H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  170.7, 134.2, 117.2, 76.7, 40.7, 35.9, 29.0, 28.1, 26.3, 26.0, 25.9, 21.0; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 3077, 2928, 2854, 1738, 1644, 1540, 1449, 1371, 914, 834; MS *m*/*z* (rel intensity): 155 (M<sup>+</sup>–41, 15), 136 (M<sup>+</sup>–60, 8), 95 (100), 83 (34), 69 (26), 55 (40); HRMS Calcd for C<sub>12</sub>H<sub>20</sub>O<sub>2</sub>–CH<sub>2</sub>CH=CH<sub>2</sub> 155.1072, found:. 155.1070.

**4.3.2.** 1-Cyclohexylpent-4-enyl acetate (14b). 93% Yield, TLC  $R_{\rm f}$ =0.7 (hexane/EtOAc=10:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>,

400 MHz)  $\delta$  5.75–5.82 (m, 1H, –*CH*=*C*H<sub>2</sub>), 4.93–5.01 (m, 2H, –*C*H=*C*H<sub>2</sub>), 4.73–4.78 (m, 1H, *CH*–OAc), 2.00–2.04 (m, 2H, –*C*H<sub>2</sub>–*C*H=*C*H<sub>2</sub>), 2.01 (s, 3H, –*COCH<sub>3</sub>*), 0.98–1.74 (m, 13H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  170.4, 138.1, 114.7, 77.4, 41.3, 30.5, 29.8, 28.9, 28.1, 26.4, 26.1, 26.0, 21.1; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 3077, 2927, 2854, 1737, 1449, 1371, 940, 912; MS *m*/*z* (rel intensity): 210 (M<sup>+</sup>, 3), 95 (12), 43 (100), 41 (24), 32 (42); HRMS Calcd for C<sub>13</sub>H<sub>22</sub>O<sub>2</sub> 210.1620, found: 210.1621.

**4.3.3. 1-Cyclohexylhex-5-enyl acetate** (14c). 90% Yield, TLC  $R_{\rm f}$ =0.7 (hexane/EtOAc=10:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  5.70–5.76 (m, 1H, –CH=CH<sub>2</sub>), 4.89–4.97 (m, 2H, –CH=CH<sub>2</sub>), 4.70–4.71 (m, 1H, CH–OAc), 1.98–2.02 (m, 2H, –CH<sub>2</sub>–CH=CH<sub>2</sub>), 2.00 (s, 3H, –COCH<sub>3</sub>), 0.97–1.67 (m, 15H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  170.7, 138.3, 114.6, 77.6, 41.2, 33.5, 30.5, 28.9, 28.0, 26.3, 26.04, 26.00, 24.6, 20.9; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 3075, 2928, 2854, 1736, 1449, 1371, 965, 909; MS *m*/*z* (rel intensity): 181 (M<sup>+</sup>–43, 3), 95 (18), 81 (21), 43 (100), 32 (51); HRMS Calcd for C<sub>14</sub>H<sub>24</sub>O<sub>2</sub> 224.1776, found: 224.1767.

**4.3.4. 1-Cyclohexylhept-6-enyl acetate** (**14d**). 91% Yield; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  5.76–5.82 (m, 1H, –*CH*=CH<sub>2</sub>), 4.92–5.01 (m, 2H, –*CH*=*CH*<sub>2</sub>), 4.72–4.75 (m, 1H, *CH*–OAc), 2.03–2.05 (m, 2H, –*CH*<sub>2</sub>–*CH*=*CH*<sub>2</sub>), 2.04 (s, 3H, –*COCH*<sub>3</sub>), 0.98–1.67 (m, 17H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  170.9, 138.8, 114.3, 77.9, 41.2, 33.6, 31.0, 29.0, 28.8, 28.1, 26.4, 26.12, 26.05, 24.9, 21.1; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 3076, 2928, 2854, 1735, 1639, 1540, 1450, 1370, 1242, 1019, 993, 970; MS *m*/*z* (rel intensity): 238 (M<sup>+</sup>, 4), 167 (M<sup>+</sup>–60, 8), 149 (24), 111 (54), 95 (68), 83 (100), 71 (48), 69 (51), 57 (76), 55 (98); HRMS Calcd for C<sub>15</sub>H<sub>26</sub>O<sub>2</sub> 238.1933, found:.238.1937.

**4.3.5. 2-Phenylhex-5-enyl acetate (25a).** 93% Yield, TLC  $R_{\rm f}$ =0.50 (hexane/EtOAc=10:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  7.22–7.35 (m, 5H), 5.70–5.79 (m, 1H, –CH=CH<sub>2</sub>), 4.91–5.00 (m, 2H, –CH=CH<sub>2</sub>), 1.94–2.16 (m, 4H), 2.05 (s, 3H, –COCH<sub>3</sub>), 1.86 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  169.5, 144.7, 138.0, 128.1, 127.0, 124.4, 114.5, 83.7, 41.5, 28.1, 24.9, 22.1; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 3024, 2934, 1736, 1639, 1496, 1367, 1014, 734; MS *m*/*z* (rel intensity): 158 (M<sup>+</sup>–60, 18), 143 (19), 121 (100), 105 (21), 43 (20); HRMS Calcd for C<sub>14</sub>H<sub>18</sub>O<sub>2</sub> 218.1307, found: 218.1311.

**4.3.6. 2-Phenylhept-6-enyl acetate (25b).** 91% Yield, TLC  $R_{\rm f}$ =0.51 (hexane/EtOAc=10:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  7.20–7.33 (m, 5H), 5.68–5.75 (m, 1H, –*CH*=CH<sub>2</sub>), 4.90–4.98 (m, 2H, –*CH*=*CH*<sub>2</sub>), 1.95–2.05 (m, 4H), 2.04 (s, 3H, –*COCH*<sub>3</sub>), 1.82 (s, 3H), 1.27–1.31 (m, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  169.5, 144.9, 138.3, 128.1, 126.7, 124.4, 114.6, 83.9, 41.9, 33.6, 24.8, 22.9, 22.1; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 3027, 2937, 1734, 1640, 1496, 1364, 1016, 735; MS *m*/*z* (rel intensity): 232 (M<sup>+</sup>, 2), 163 (23), 131 (13), 121 (100), 43 (27); HRMS Calcd for C<sub>15</sub>H<sub>20</sub>O<sub>2</sub> 232.1463, found: 232.1470.

**4.3.7. 1-But-3-enylcyclohexyl acetate (25c).**<sup>48</sup> 94% Yield, TLC  $R_{\rm f}$ =0.60 (hexane/EtOAc=10:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  5.75–5.82 (m, 1H, –CH=CH<sub>2</sub>), 4.91–5.02 (m, 2H, –CH=CH<sub>2</sub>), 2.17–2.21 (m, 2H, CH<sub>2</sub>–CH=CH<sub>2</sub>),

2.02 (s, 3H,  $-COCH_3$ ), 1.94–2.01 (m, 2H), 1.24–1.51 (m, 10H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  170.3, 138.6, 114.3, 83.6, 36.6, 34.5, 27.5, 25.5, 22.2, 21.8; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 3077, 2933, 2860, 1731, 1450, 1367, 963, 910; MS *m/z* (rel intensity): 141 (M<sup>+</sup>–55, 10), 136 (M<sup>+</sup>–60, 60), 98 (80), 80 (62), 55 (91), 43 (100); HRMS Calcd for C<sub>12</sub>H<sub>20</sub>O<sub>2</sub> 196.1463, found: 196.1472.

**4.3.8. 1-Pent-4-enylcyclohexyl acetate** (**25d**). 92% Yield, TLC  $R_{\rm f}$ =0.60 (hexane/EtOAc=10:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  5.69–5.77 (m, 1H, –CH=CH<sub>2</sub>), 4.88–4.96 (m, 2H, –CH=CH<sub>2</sub>), 2.11–2.14 (m, 2H, –CH<sub>2</sub>–CH=CH<sub>2</sub>), 1.95 (s, 3H, –COCH<sub>3</sub>), 1.96–1.99 (m, 2H), 1.80–1.84 (m, 2H), 1.18–1.47 (m, 10H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$ 170.2, 138.5, 114.4, 83.7, 36.9, 34.4, 33.8, 25.5, 22.3, 22.0, 21.7; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 3077, 2932, 2861, 1732, 1449, 1366, 966, 910; MS *m*/*z* (rel intensity): 150 (M<sup>+</sup>–60, 18), 109 (40), 99 (100), 81 (48), 67 (43); HRMS Calcd for C<sub>13</sub>H<sub>22</sub>O<sub>2</sub> 210.1620, found: 210.1622.

**4.3.9.** *trans*-**2**-Allylcyclohexyl acetate (**33a**). 96% Yield, TLC  $R_{\rm f}$ =0.7 (hexane/EtOAc=3:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  5.66–5.70 (m, 1H, –CH=CH<sub>2</sub>), 4.90–4.95 (m, 2H, –CH=CH<sub>2</sub>), 4.44–4.48 (m, 1H, CHOAc), 2.17– 2.20 (m, 2H), 0.98–1.98 (m, 9H), 1.97 (s, 3H, –COCH<sub>3</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  170.4, 136.3, 115.9, 76.3, 41.6, 36.8, 31.7, 30.1, 25.0, 24.4, 21.1; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 3014, 2953, 2868, 1736, 1371, 944, 913; MS *m/z* (rel intensity): 140 (M<sup>+</sup>–42, 20), 122 (100), 107 (33), 93 (52).

**4.3.10.** *trans*-**2**-**But**-**3**-enylcyclohexyl acetate (33b). 97% Yield, TLC  $R_{\rm f}$ =0.7 (hexane/EtOAc=3:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  5.74–5.97 (m, 1H, –C*H*=CH<sub>2</sub>), 4.92–5.00 (m, 2H, –CH=C*H*<sub>2</sub>), 4.81–4.86 (m, 1H, CHOAc), 2.02–2.05 (m, 3H), 1.28–1.65 (m, 10H), 2.03 (s, 3H, –COC*H*<sub>3</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  170.9, 138.0, 114.7, 76.7, 43.8, 32.7, 29.7, 28.9, 28.5, 25.4, 25.2, 21.1; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 3071, 2950, 1738, 1450, 1373, 944, 912; MS *m/z* (rel intensity): 154 (M<sup>+</sup>–42, 2), 95 (31), 81 (23), 43 (100), 41 (28).

# 4.4. General procedure to prepare the benzoate from the corresponding alcohol by Mitsunobu reaction

To a stirred suspension of Ph<sub>3</sub>P (2.24 g, 8.57 mmol) and benzoic acid (1.05 g, 8.57 mmol) in toluene (25 mL) cooled to -30 °C was added a solution of secondary alcohol **32a** (1000 mg, 7.14 mmol) in toluene (5 mL). A solution of DEAD (diethyl azodicarboxylate, 1.492 g, 8.57 mmol) in toluene (10 mL) was added dropwise over 15 min to the vigorously stirred mixture while the temperature was maintained at -30 °C. When the addition was complete the mixture was allowed to warm gradually to 0 °C over 1 h where upon saturated aqueous sodium bicarbonate 30 (mL) was added. The aqueous phase was separated and extracted with ethyl acetate. The organic extracts were combined, dried, concentrated and chromatographed on silica gel column to give the benzoate **33c** (1.39 g, 5.71 mmol) in 80% yield.

**4.4.1.** *cis*-2-Allylcyclohexyl benzoate (33c).<sup>49</sup> 80% Yield; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  8.07–8.09 (m, 2H), 7.41– 7.55 (m, 3H), 5.73–5.80 (m, 1H, –CH=CH<sub>2</sub>), 5.27 (br s, 1H, CHOCOPh), 4.92–4.98 (m, 2H,  $-CH=CH_2$ ), 1.26– 2.15 (m, 11H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  165.7, 136.5, 132.6, 130.9, 129.4, 128.2, 116.1, 72.4, 40.4, 36.9, 30.1, 27.4, 25.1, 20.9; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 3031, 2930, 2857, 1715, 1490, 1358, 1069; MS *m*/*z* (rel intensity): 244 (M<sup>+</sup>, 3), 202 (8), 122 (53), 105 (100), 77 (27); HRMS Calcd for C<sub>16</sub>H<sub>20</sub>O<sub>2</sub> 244.1463, found: 244.1469.

**4.4.2.** *cis*-**2**-**But**-**3**-enylcyclohexyl benzoate (**33d**). 68% Yield, TLC  $R_f$ =0.78 (hexane/EtOAc=3:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  8.05–8.07 (m, 2H), 7.42–7.57 (m, 3H), 5.79–5.85 (m, 1H, –CH=CH<sub>2</sub>), 5.13–5.18 (m, 1H, CHOCOPh), 4.94–5.04 (m, 2H, –CH=CH<sub>2</sub>), 2.13–2.15 (m, 2H), 1.27–1.28 (m, 11H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  166.3, 138.0, 132.6, 130.7, 129.5, 128.3, 114.8, 77.5, 43.9, 32.9, 29.7, 29.0, 28.5, 25.5, 25.3; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 3032, 2949, 2867, 1715, 1451, 1069; MS *m*/*z* (rel intensity): 258 (M<sup>+</sup>, 1), 121 (41), 105 (100), 77 (62), 67 (28); HRMS Calcd for C<sub>17</sub>H<sub>22</sub>O<sub>2</sub> 258.1620, found: 258.1629.

#### **4.5.** General procedure to prepare the tetrahydropyranyl ether from the corresponding alcohol

To a solution of alcohol **13a** (1.00 g, 6.5 mmol) and 3,4dihydro-2*H*-pyran (0.65 mL, 7.2 mmol) in 20 mL of dichloromethane was added ATPB (0.26 g, 0.65 mmol) and the solution was stirred at room temperature. The reaction was complete in 30 min. The solution was concentrated and chromatographed on silica gel column to give the desired **18a** (1.47 g, 6.17 mmol) in 95% yield as a mixture of two diastereomers.

**4.5.1. 2-(1-Cyclohexylbut-3-enyloxy)tetrahydropyran** (18a). 95% Yield, a mixture of two diastereomers; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  5.74–5.88 (m, 1H, –*CH*=CH<sub>2</sub>), 4.97–5.04 (m, 2H, –*CH*=CH<sub>2</sub>), 4.66 and 4.64 (br, 1H, O–*CH*–O), 3.80–3.97 (m, 1H, *CH*–OTHP), 3.41–3.45 (m, 2H, *CH*<sub>2</sub>–O–*C*H), 2.31–2.33 (m, 2H, –*CH*<sub>2</sub>–CH=CH<sub>2</sub>), 1.01–1.69 (m, 17H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  135.8, 135.1, 116.4, 115.9, 99.4, 96.8, 81.9, 79.3, 62.5, 62.4, 41.3, 40.6, 36.7, 34.6, 30.92, 30.91, 29.0, 28.8, 28.7, 26.6, 26.3, 26.27, 26.25, 26.22, 25.5, 19.8; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 3076, 2926, 2861, 1439, 1132, 1024; MS *m*/*z* (rel intensity): 136 (M<sup>+</sup>–HOTHP, 37), 111 (38), 83 (72), 55 (63), 41 (100); HRMS Calcd for C<sub>15</sub>H<sub>26</sub>O<sub>2</sub>–C<sub>5</sub>H<sub>10</sub>O<sub>2</sub> 136.1252, found: 136.1247.

**4.5.2. 2-(1-Cyclohexylhep-6-enyloxy)tetrahydropyran** (18d). 89% Yield, TLC  $R_f$ =0.82 (hexane/EtOAc=10:1), a mixture of two diastereomers; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  5.77–5.82 (m, 1H, CH=CH<sub>2</sub>), 4.90–5.00 (m, 2H, CH=CH<sub>2</sub>), 4.63 and 4.59 (br, 1H, O–CH–O), 3.89–3.90 (m, 1H, CH–OTHP), 3.35–3.47 (m, 2H, CH<sub>2</sub>–O–CH), 2.03–2.05 (m, 2H, CH<sub>2</sub>–CH=CH<sub>2</sub>), 1.01–1.81 (m, 23H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  139.1, 138.9, 114.2, 114.1, 98.9, 97.5, 82.0, 80.6, 62.8, 62.6, 41.4, 40.7, 33.8, 33.7, 31.6, 31.2, 31.1, 29.6, 29.2, 28.9, 28.5, 26.7, 26.5, 26.48, 26.42, 25.6, 25.5, 24.5, 20.1, 19.9; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 3076, 2925, 1453, 1114, 1077; MS *m/z* (rel intensity): 281 (M<sup>+</sup>+1, 4), 197 (M<sup>+</sup>–83, 8), 97 (18), 85 (100), 55 (10), 41 (8); HRMS Calcd for C<sub>18</sub>H<sub>32</sub>O<sub>2</sub> 280.2402, found: 280.2401.

**4.5.3. 2-(2-Allylphenoxy)tetrahydropyran** (**38**). 92% Yield, TLC  $R_f$ =0.83 (hexane/EtOAc 10=1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  7.09–7.25 (m, 3H, Ph), 6.92–6.95 (m, 1H, Ph), 5.95–6.05 (m, 1H), 5.42 (br t, *J*=3.2 Hz, 1H), 5.02–5.10 (m, 2H), 3.87–3.90 (m, 1H), 3.59–3.62 (m, 1H), 3.42–3.44 (m, 2H), 1.61–1.89 (m, 6H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  154.7, 137.2, 129.8, 129.1, 127.3, 121.3, 115.2, 114.2, 96.1, 61.8, 34.7, 30.5, 25.3, 18.8; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 2942, 2875, 1490, 1455, 1355, 1236, 1201, 1125, 1037, 970; MS *m*/*z* (rel intensity): 218 (M<sup>+</sup>, 5), 134 (80), 133 (12), 119 (15), 115 (12), 91 (16), 85 (100), 57 (28); HRMS Calcd for C<sub>14</sub>H<sub>18</sub>O<sub>2</sub> 218.1307, found: 218.1302.

4.5.4. 3-[2-(Tetrahydropyran-2-yloxy)phenyl]propan-1ol (44). To a solution of 9-BBN in hexane (0.4 M in hexane, 2.6 mL, 1.04 mmol) was added a solution of alkene 38 (200 mg, 0.92 mmol) in anhydrous benzene (2 mL) dropwise over 20 min while the temperature was maintained under refluxing condition. After stirring under refluxing condition for 2 h, the resulting solution was cooled to 50 °C. To the resulting solution was added a mixture of 6N NaOH (1 mL) and hydrogen peroxide (30 wt% solution in water, 2 mL) dropwise over 5 min and stirred at 50 °C for 1 h. The reaction mixture was cooled to room temperature and saturated aqueous  $K_2CO_3$  (10 mL) was added. The aqueous phase was separated and extracted with ether. The organic extracts were combined, dried, concentrated and chromatographed on silica gel column to give the alcohol 44 (141 mg, 0.60 mmol) in 65% yield. TLC  $R_f=0.23$  (hexane/ EtOAc=10:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 7.09-7.17 (m, 3H, Ph), 6.92-6.94 (m, 1H, Ph), 5.41-5.43 (m, 1H), 3.80-3.90 (m, 1H), 3.60-3.64 (m, 3H), 2.74-2.78 (m, 2H), 1.63-1.92 (m, 9H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  154.8, 130.6, 130.0, 127.0, 121.5, 114.3, 96.4, 62.1, 61.9, 33.0, 30.5, 26.2, 25.1, 19.0; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 3366, 2923, 2851, 1594, 1455, 1355, 1235, 1118, 1053, 978, 751; MS m/z (rel intensity): 236 (M<sup>+</sup>, 2), 152 (60), 134 (58), 107 (38), 85 (100), 67 (28), 57 (30); HRMS Calcd for C<sub>14</sub>H<sub>20</sub>O<sub>3</sub> 236.1412, found: 236.1410.

4.5.5. 3-[2-(Tetrahydropyran-2-yloxy)phenyl]propionaldehyde (45). To a mixture of alcohol 44 (200 mg, 0.85 mmol), 4 Å molecular sieve (200 mg), and sodium acetate (83.7 mg, 1.02 mmol) in 5 mL of CH<sub>2</sub>Cl<sub>2</sub> was added PCC (pyridinium chloroformate, 220 mg, 1.02 mmol) at room temperature. After stirring at room temperature for 2 h, the reaction mixture was concentrated. The crude residue was added 10 mL of ether. The solution was filtered and the chromium salt was washed three times with 5 mL of ether. The combined filtrates were evaporated and the residue was chromatograped on silica gel column to give the aldehyde 45 (141 mg, 0.60 mmol) in 71% yield. TLC  $R_{\rm f}=0.55$  (hexane/EtOAc=10:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 9.82 (s, 1H, CHO), 7.09–7.19 (m, 3H, Ph), 6.89-6.93 (m, 1H, Ph), 5.42-5.44 (m, 1H), 4.81-4.92 (m, 1H), 4.55–4.65 (m, 1H), 2.96–3.00 (m, 2H), 2.75–2.78 (m, 2H), 1.26–1.88 (m, 6H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$ 202.0, 154.7, 129.8, 129.0, 127.5, 121.3, 114.1, 96.1, 62.0, 44.0, 30.4, 25.1, 23.5, 18.9; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 3030, 2942, 2875, 1719, 1490, 1237, 1123, 1036, 966, 754; MS m/z (rel intensity): 234 (M<sup>+</sup>, 4), 166 (12), 152 (18), 150 (24), 134 (24), 85 (100), 67 (16), 57 (16); HRMS Calcd for C<sub>14</sub>H<sub>18</sub>O<sub>3</sub> 234.1256, found: 234.1248.

4848

#### 4.6. General procedure to prepare the azide from the corresponding alcohol by modified Mitsunobu reaction

To a mixture of alcohol **12c** (1.0 g, 5.90 mmol) and  $Ph_3P$  (1.87 g, 7.14 mmol) in 18 mL of THF was subsequently added DEAD (1.24 g, 7.14 mmol) and diphenylphosphonic azide (1.96 g, 7.14 mmol) in the dark at room temperature. After stirring at room temperature for 6 h, the reaction mixture was concentrated and chromatographed on silica gel column to give azido compound **49c** (0.97 g, 5.01 mmol) in 85% yield.

**4.6.1.** (1-Azidopent-4-enyl)cyclohexane (49c). 85% Yield, TLC  $R_f$ =0.86 (hexane/EtOAc=5:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  5.74–5.85 (m, 1H, –CH=CH<sub>2</sub>), 4.99–5.09 (m, 2H, –CH=CH<sub>2</sub>), 3.08–3.11 (m, 1H, CHN<sub>3</sub>), 2.13–2.24 (m, 2H, –CH<sub>2</sub>–C=CH<sub>2</sub>), 1.07–1.78 (m, 13H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  137.6, 115.3, 68.0, 42.4, 30.8, 30.6, 29.9, 28.6, 26.3, 26.2, 26.1; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 2996, 2094, 1640, 1448, 1088, 910; MS *m*/*z* (rel intensity): 193 (M<sup>+</sup>, 3), 192 (20), 138 (30), 95 (25), 83 (47), 67 (31), 55 (100), 41 (67); HRMS Calcd for C<sub>11</sub>H<sub>19</sub>N<sub>3</sub> 193.1579, found: 193.1577.

**4.6.2.** (1-Azidohex-5-enyl)cyclohexane (49d). 78% Yield, TLC  $R_{\rm f}$ =0.97 (hexane/EtOAc=10:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  5.77–5.84 (m, 1H, –C*H*=CH<sub>2</sub>), 4.96–5.05 (m, 2H, –CH=C*H*<sub>2</sub>), 3.00–3.10 (m, 1H), 2.08–2.10 (m, 2H), 1.12–1.79 (m, 15H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  138.3, 114.9, 68.6, 42.3, 33.5, 30.8, 30.0, 28.6, 26.3, 26.2, 26.1, 25.7; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 3076, 2928, 2854, 2095, 1640, 1449, 1259, 991, 911, 741; MS *m*/*z* (rel intensity): 207 (M<sup>+</sup>, 4), 179 (20), 136 (28), 124 (22), 97 (100), 96 (84), 82 (52), 69 (46), 57 (24), 55 (84); HRMS Calcd for C<sub>12</sub>H<sub>21</sub>N<sub>3</sub> 207.1735, found: 207.1742.

4.6.3. (1-Cyclohexylhex-5-enyl)carbamic acid methyl ester (53d). To a solution of the azide 49d (4.0 g, 19.33 mmol) in THF (18 mL) was added a solution of Ph<sub>3</sub>P (5.57 g, 21.3 mmol) in 2 mL of THF (2 mL) at 40 °C for 30 min. The resulted solution was added H<sub>2</sub>O (0.4 mL, 22 mmol) and stirred at room temperature for 10 h. The resulted solution was treated with  $K_2CO_3$  (3.3 g, 24.4 mmol) in 20 mL of water and stirred for 20 min whereupon methyl chloroformate (2.5 g, 24.4 mmol) was added. After stirring for 1 h, the aqueous phase was separated and extracted with ethyl acetate. The organic extracts were combined, dried, concentrated and chromatographed on silica gel column to give the benzoate 53d (2.31 g, 9.67 mmol) in 50% yield. TLC  $R_{\rm f}$ =0.73 (hexane/ EtOAc=1:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 5.75-5.81 (m, 1H), 4.93-5.03 (m, 2H), 4.38-4.41 (m, 1H), 3.65 (s, 3H), 3.46-3.49 (m, 1H), 2.03-2.07 (m, 2H), 1.50-1.76 (m, 4H), 0.96-1.23 (m, 11H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 157.0, 138.6, 114.6, 55.6, 51.9, 42.3, 33.6, 31.7, 29.6, 28.1, 26.4, 26.24, 26.22, 25.4; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 3321, 2925, 2851, 1698, 1540, 1456, 1255, 649; MS m/z (rel intensity): 239  $(M^+, 5), 170(31), 156(100), 114(28), 88(45), 81(49), 76$ (56), 55 (15); HRMS Calcd for  $C_{14}H_{25}NO_2$  239.1885, found: 239.1875.

# 4.7. General procedure to prepare the $\alpha$ -substituted acrolein from terminal alkene

A two-necked flask fitted with a glass tube to admit ozone, a

CaCl<sub>2</sub> drying tube and a magnetic stirring bar is charged with terminal alkene 14b (400 mg, 1.9 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL). The flask is cooled to -78 °C and ozone is bubbled through the solution. When the solution turns blue, ozone addition is stopped. Nitrogen is passed through the solution until the blue color is discharged. A mixture of Et<sub>2</sub>NH (2.94 mL, 28.5 mmol) and CH<sub>2</sub>Br<sub>2</sub> (0.67 mL, 9.5 mmol) was heated to 55 °C for 1.5 h to give a yellow solution and then cooled to room temperature. To a solution of ozonide in CH<sub>2</sub>Cl<sub>2</sub> generated above was added a preheated mixture of Et<sub>2</sub>NH and CH<sub>2</sub>Br<sub>2</sub> at -78 °C. After the addition, the cooling bath was removed and the reaction mixture was stirred at room temperature. The reaction was complete in 1.5 h and the reaction mixture was concentrated. To the crude mixture, ether was added and most of the ammonium salts were precipitated out. After filtration, the filtrate was concentrated, chromatographed on the silica gel column to give the desired product 15b (297.9 mg, 1.33 mmol) in 70% yield.

**4.7.1. 1-Cyclohexyl-3-formylbut-3-enyl acetate** (15b). 70% Yield, TLC  $R_f=0.6$  (hexane/EtOAc=10:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  9.43 (s, 1H, CHO), 6.22 (s, 1H,  $-C=CH_2$ ), 5.97 (s, 1H,  $-C=CH_2$ ), 4.77–4.81 (m, 1H, CHOAc), 2.55–2.59 (m, 1H,  $-CH_2-C=CH_2$ ), 2.27–2.30 (m, 1H,  $-CH_2-C=CH_2$ ), 1.90 (s, 3H,  $-COCH_3$ ), 0.98– 1.69 (m, 11H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  193.7, 170.4, 146.6, 135.2, 75.5, 41.5, 29.8, 28.8, 27.9, 26.1, 25.8, 25.8, 20.8; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 3089, 2853, 1732, 1695, 1452, 988; MS *m*/*z* (rel intensity): 164 (M<sup>+</sup>–60, 3), 95 (26), 88 (30), 55 (38), 43 (100); HRMS Calcd for C<sub>13</sub>H<sub>20</sub>O<sub>3</sub>– CH<sub>3</sub>CO<sub>2</sub>H 164.1201, found: 164.1205.

**4.7.2. 1-Cyclohexyl-4-formylhex-4-enyl acetate** (**15c**). 65% Yield, TLC  $R_{\rm f}$ =0.62 (hexane/EtOAc=10:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  9.46 (br s, 1H, CHO), 6.22 (s, 1H, -C=CH<sub>2</sub>), 5.95 (s, 1H, -C=CH<sub>2</sub>), 4.67–4.69 (m, 1H, CHOAc), 2.00–2.15 (m, 2H, -CH<sub>2</sub>–C=CH<sub>2</sub>), 1.99 (s, 3H, -COCH<sub>3</sub>), 0.91–1.68 (m, 13H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  194.3, 170.8, 149.5, 134.2, 77.0, 41.0, 29.1, 28.8, 28.0, 26.2, 25.9, 25.8, 23.9, 20.9; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 3088, 2853, 1731, 1696, 1450, 1085; MS *m/z* (rel intensity): 195 (M<sup>+</sup>-43, 10), 178 (25), 113 (73), 95 (50), 55 (37); HRMS Calcd for C<sub>14</sub>H<sub>22</sub>O<sub>3</sub>–CH<sub>3</sub>CO 195.1385, found: 195.1384.

**4.7.3. 1-Cyclohexyl-5-formylhex-5-enyl acetate (15d).** 73% Yield; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  9.53 (s, 1H), 6.24 (s, 1H, C=*CH*<sub>2</sub>), 5.99 (s, 1H, C=*CH*<sub>2</sub>), 4.72–4.77 (m, 1H, *CHOCO*), 2.23–2.25 (m, 2H), 2.04 (s, 3H, –COC*H*<sub>3</sub>), 1.47–1.75 (m, 9H), 1.00–1.18 (m, 6H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  194.4, 170.9, 149.9, 134.0, 77.5, 41.2, 30.7, 28.9, 28.1, 27.6, 26.3, 26.04, 25.97, 23.7, 21.0; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 2929, 2854, 1731, 1696, 1507, 1449, 1371, 1243, 1020, 963, 733; MS *m*/*z* (rel intensity): 192 (M<sup>+</sup>–60, 24), 109 (44), 95 (40), 81 (100), 67 (36), 55 (56); HRMS Calcd for C<sub>15</sub>H<sub>24</sub>O<sub>3</sub>–HOAc 192.1514, found: 192.1516.

**4.7.4. 2-[Cyclohexyl(tetrahydropyran-2-yloxy)methyl]**propenal (19a). 58% Yield, TLC  $R_f$ =0.65 (hexane/ EtOAc=10:1); A mixture of two diastereomers; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  9.55 (s, 0.6H, CHO), 9.50 (s, 0.4H, CHO), 6.44 (s, 0.4H, -C=CH<sub>2</sub>), 6.27 (s, 0.6H, -C=CH<sub>2</sub>), 6.13 (s, 0.6H,  $-C=CH_2$ ), 6.08 (s, 0.4H,  $-C=CH_2$ ), 4.21– 4.43 (m, 2H, O–CH–O), 3.82–3.87 (m, 1H), 3.41–3.44 (m, 1H,  $CH_2$ –O–CH), 1.44–1.83 (m, 17H), 0.87–1.21 (m, 7H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  193.5, 193.2, 150.6, 149.2, 134.9, 100.9, 95.3, 78.1, 74.9, 63.0, 62.1, 42.2, 42.0, 30.6, 30.5, 29.6, 29.5, 29.2, 28.1, 27.7, 26.34, 26.32, 26.14, 26.07, 25.97, 25.92, 25.35, 25.24, 19.8, 19.3; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 2997, 2853, 1689, 1450, 1024, 971; MS *m*/*z* (rel intensity): 151 (M<sup>+</sup>–OTHP, 6), 84 (46), 67 (20), 55 (58), 41 (100); HRMS Calcd for C<sub>15</sub>H<sub>24</sub>O<sub>3</sub>–C<sub>5</sub>H<sub>9</sub>O<sub>2</sub> 151.1123, found: 151.1114.

4.7.5. 2-[4-Cyclohexyl-4-(tetrahydropyran-2-yloxy)butyl]propenal (19d). 76% Yield, TLC  $R_f=0.69$  (hexane/ EtOAc=10:1); A mixture of the diastereomers, ratio=1:1; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  9.50 (s, 1H, CHO), 6.23 (s, 0.5H, C= $CH_2$ ), 6.21 (s, 0.5H, C= $CH_2$ ), 5.96 (s, 1H, C=CH<sub>2</sub>), 4.57-4.58 (m, 1H, O-CH-O), 4.52-4.59 (m, 1H, O-CH-O), 3.84-3.86 (m, 1H, CH<sub>2</sub>-O-CH), 3.34-3.44 (m, 2H, CH-OTHP), 2.19-2.20 (m, 2H, CH<sub>2</sub>-C=CH<sub>2</sub>), 1.43-1.71 (m, 16H), 0.94-1.21 (m, 5H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 194.6, 194.5, 150.3, 150.2, 133.83, 133.81, 99.1, 97.6, 81.7, 80.4, 62.9, 62.6, 41.4, 40.8, 31.2, 31.1, 29.0, 28.7, 28.5, 28.4, 27.9, 27.7, 26.6, 26.39, 26.37, 26.35, 26.32, 25.5, 25.4, 23.6, 20.2, 19.8; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 3085, 2923, 1693, 1451, 1029; MS m/z (rel intensity): 276 (M<sup>+</sup>-18, 8), 211 (10), 175 (21), 85 (100), 41 (22); HRMS Calcd for C<sub>18</sub>H<sub>30</sub>O<sub>3</sub> 294.2195, found: 294.2196.

**4.7.6. 3-Formyl-1-methyl-1-phenylbut-3-enyl acetate** (**26a**). 73% Yield, TLC  $R_{\rm f}$ =0.45 (hexane/EtOAc=10:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  9.39 (s, 1H, CHO), 7.21–7.32 (m, 5H, Ph–H), 6.06 (s, 1H, –C=CH<sub>2</sub>), 6.04 (s, 1H, C=CH<sub>2</sub>), 2.95 (s, 2H, –CH<sub>2</sub>–C=CH<sub>2</sub>), 2.03 (s, 3H, –COCH<sub>3</sub>), 1.79 (s, 3H, CH<sub>3</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  193.5, 169.1, 144.8, 143.7, 137.7, 128.0, 127.0, 124.5, 82.8, 39.0, 24.3, 22.9; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 3026, 2937, 1736, 1687, 1496, 1016, 735; MS *m*/*z* (rel intensity): 173 (M<sup>+</sup>–59, 8), 172 (40), 143 (81), 128 (72), 121 (100).

**4.7.7. 4-Formyl-1-methyl-1-phenylpent-4-enyl acetate** (**26b**). 81% Yield, TLC  $R_{\rm f}$ =0.47 (hexane/EtOAc=10:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  9.44 (s, 1H, CHO), 7.20–7.31 (m, 5H), 6.14 (s, 1H, -C=CH<sub>2</sub>), 5.90 (s, 1H, -C=CH<sub>2</sub>), 2.12–2.17 (m, 4H), 2.05 (s, 3H,  $-COCH_3$ ), 1.86 (s, 3H,  $-CH_3$ ); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  194.0, 169.2, 149.3, 144.2, 133.6, 128.0, 126.7, 124.2, 83.1, 39.9, 24.6, 22.0, 21.8; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 3027, 2845, 1731, 1629, 1496, 1016, 735; MS *m*/*z* (rel intensity): 246 (M<sup>+</sup>, 4), 186 (18), 163 (22), 121 (71), 43 (100).

**4.7.8. 1-(2-Formylallyl)cyclohexyl acetate (26c).** 62% Yield, TLC  $R_f$ =0.45 (hexane/EtOAc=10:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  9.50 (s, 1H, CHO), 6.25 (s, 1H, -C=CH<sub>2</sub>), 6.10 (s, 1H, -C=CH<sub>2</sub>), 2.87 (s, 2H,  $-CH_2$ -C=CH<sub>2</sub>), 2.06–2.09 (m, 2H), 1.97 (s, 3H,  $-COCH_3$ ), 1.19–1.51 (m, 8H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  194.4, 170.6, 145.8, 137.6, 82.9, 34.5, 34.2, 25.2, 22.3, 21.6; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 2997, 2933, 2860, 1730, 1696, 1449, 1368, 964, 920; MS *m*/*z* (rel intensity): 164 (M<sup>+</sup>-46, 24), 99 (100), 94 (38), 84 (42), 43 (83); HRMS Calcd for C<sub>12</sub>H<sub>18</sub>O<sub>3</sub> 210.1256, found: 210.1253.

**4.7.9. 1-(3-Formylbut-3-enyl)cyclohexyl** acetate (26d). 85% Yield, TLC  $R_f$ =0.5 (hexane/EtOAc=10:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  9.45 (s, 1H, CHO), 6.19 (s, 1H, -C=CH<sub>2</sub>), 5.92 (s, 1H, -C=CH<sub>2</sub>), 2.12–2.16 (m, 4H), 1.94 (s, 3H,  $-COCH_3$ ), 1.92–1.96 (m, 2H), 1.18–1.46 (m, 8H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  194.3, 170.1, 149.9, 133.7, 83.2, 35.2, 34.3, 25.4, 22.0, 21.6, 21.2; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 3086, 2934, 2860, 1731, 1690, 1450, 1367, 1041; MS *m*/*z* (rel intensity): 165 (M<sup>+</sup>–59, 44), 164 (100), 146 (50), 99 (76), 43 (88); HRMS Calcd for C<sub>13</sub>H<sub>20</sub>O<sub>3</sub> 224.1412, found: 224.1405.

**4.7.10.** *trans*-**2**-(**1**-Formylvinyl)cyclohexyl acetate (34a). 76% Yield, TLC  $R_f$ =0.45 (hexane/EtOAc=10:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  9.44 (s, 1H, CHO), 6.21 (s, 1H, -C=CH<sub>2</sub>), 5.95 (s, 1H, -C=CH<sub>2</sub>), 4.79–4.84 (m, 1H, CHOAc), 2.67–2.72 (m, 1H, -CH-C=CH<sub>2</sub>), 1.19–2.00 (m, 8H), 1.87 (s, 3H,  $-COCH_3$ ); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  193.9, 170.3, 151.3, 133.7, 74.3, 40.5, 31.93, 31.86, 25.3, 24.4, 20.9; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 3090, 2996, 1733, 1633, 1455, 1373, 1024; MS *m*/*z*(rel intensity): 196 (M<sup>+</sup>, 3), 169 (41), 136 (38), 124 (56), 109 (100), 81 (78), 67 (54); HRMS Calcd for C<sub>11</sub>H<sub>16</sub>O<sub>3</sub> 196.1099, found: 196.1094.

**4.7.11.** *trans*-2-(2-Formylallyl)cyclohexyl acetate (34b). 69% Yield, TLC  $R_f$ =0.47 (hexane/EtOAc=10:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  9.44 (s, 1H, CHO), 6.23 (s, 1H, -C=CH<sub>2</sub>), 5.97 (s, 1H, -C=CH<sub>2</sub>), 4.84–4.90 (m, 1H, CHOAc), 2.58–2.61 (m, 1H,  $-CH_2$ –C=CH<sub>2</sub>), 2.17–2.31 (m, 1H,  $-CH_2$ –C=CH<sub>2</sub>), 1.95–2.05 (m, 1H), 1.91 (s, 3H,  $-COCH_3$ ), 1.23–1.96 (m, 8H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  193.7, 170.5, 146.3, 135.3, 75.3, 43.7, 31.9, 28.9, 28.5, 25.4, 25.2, 20.9; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 3091, 2952, 1732, 1692, 1452, 1372, 946; MS *m/z* (rel intensity): 167 (M<sup>+</sup>–43, 32), 166 (29), 81 (28), 43 (100), 41 (27); HRMS Calcd for C<sub>12</sub>H<sub>18</sub>O<sub>3</sub>–CH<sub>3</sub>CO 167.1072, found: 167.1081.

**4.7.12.** *cis*-2-(1-Formylvinyl)cyclohexyl benzoate (34c). 71% Yield, TLC  $R_f$ =0.6 (hexane/EtOAc=3:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  9.47 (s, 1H, CHO), 8.00–8.02 (m, 2H, Ph–H), 7.54–7.57 (m, 1H), 7.27–7.46 (m, 2H), 6.22 (s, 1H, –C=CH<sub>2</sub>), 5.94 (s, 1H, –C=CH<sub>2</sub>), 5.38 (br s, 1H, CHOCOPh), 2.90–2.94 (br d, *J*=12.8 Hz, 1H, –CH–C=CH<sub>2</sub>), 1.56–2.05 (m, 8H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  194.4, 165.9, 151.4, 135.0, 133.2, 131.1, 129.8, 128.8, 70.9, 38.6, 30.9, 26.0, 25.2, 20.8; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 3032, 2859, 1715, 1707, 1450, 1069; MS *m/z* (rel intensity): 258 (M<sup>+</sup>, 12), 240 (18), 136 (10), 105 (100), 77 (16); HRMS Calcd for C<sub>16</sub>H<sub>18</sub>O<sub>3</sub> 258.1256, found: 258.1259.

**4.7.13.** *cis*-2-(2-Formylallyl)cyclohexyl benzoate (34d). 64% Yield, TLC  $R_f$ =0.63 (hexane/EtOAc=3:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  9.51 (s, 1H, CHO), 7.99–8.02 (m, 2H), 7.53–7.56 (m, 1H), 7.41–7.45 (m, 2H), 6.29 (s, 1H, –C=CH<sub>2</sub>), 5.98 (s, 1H, –C=CH<sub>2</sub>), 5.22–5.26 (m, 1H, CHOCOPh), 2.55–2.76 (m, 2H, –CH<sub>2</sub>–C=CH<sub>2</sub>), 1.27–2.20 (m, 8H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  194.3, 166.5, 146.7, 136.1, 133.2, 130.9, 129.9, 128.7, 76.5, 44.6, 32.5, 29.5, 28.9, 26.0, 25.8; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 3033, 2869, 1714, 1629, 1451, 1070; MS *m/z* (rel intensity): 273 (M<sup>+</sup>+1, 12), 243 (M<sup>+</sup>–29, 12), 203 (5), 150 (7), 105 (100), 77 (21); HRMS Calcd for  $C_{17}H_{20}O_3$  272.1412, found: 272.1406.

**4.7.14. 2-[2-(Tetrahydropyran-2-yloxy)phenyl]propenal** (**39).** 52% Yield, TLC  $R_f$ =0.5 (hexane/EtOAc=5:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  9.76 (s, 1H), 7.18–7.34 (m, 3H), 6.99–7.03 (m, 1H), 6.34 (s, 1H, C=CH<sub>2</sub>), 6.28 (s, 1H, C=CH<sub>2</sub>), 5.42 (br t, 1H), 3.83–3.89 (m, 1H), 3.59–3.63 (m, 1H), 1.56–1.82 (m, 6H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  192.2, 154.4, 147.4, 132.9, 130.3, 130.1, 124.8, 121.5, 114.7, 96.5, 61.8, 30.2, 25.2, 18.4; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 2943, 2870, 1701, 1597, 1488, 1454, 1236, 1201, 1111, 1036, 961, 919; MS *m/z* (rel intensity): 232 (M<sup>+</sup>, 1), 148 (55), 147 (8), 85 (100), 91 (15), 77 (4), 57 (16); HRMS Calcd for C<sub>14</sub>H<sub>16</sub>O<sub>3</sub> 232.1099, found: 232.1102.

**4.7.15. 2-[2-(Tetrahydropyran-2-yloxy)benzyl]propenal** (**46**). 62% Yield, TLC  $R_f$ =0.69 (hexane/EtOAc=5:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  9.65 (s, 1H, CHO), 7.14–7.21 (m, 3H, Ph), 6.95–6.97 (m, 1H, Ph), 6.04 (br s, 2H), 5.42 (br s, 1H), 3.82–3.85 (m, 1H), 3.62 (s, 3H), 1.29–1.86 (m, 6H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  194.0, 154.9, 149.3, 134.5, 130.9, 127.9, 127.0, 121.3, 114.3, 96.2, 61.9, 30.4, 28.5, 25.2, 18.7; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 2942, 2869, 2851, 1693, 1490, 1455, 1238, 1202, 1121, 1036, 967, 922, 872, 754; MS *m*/*z* (rel intensity): 246 (M<sup>+</sup>, 1), 162 (56), 85 (100); HRMS Calcd for C<sub>15</sub>H<sub>18</sub>O<sub>3</sub> 246.1256, found:. 246.1262.

**4.7.16. 2-(2-Azido-2-cyclohexylethyl)propenal (50c).** 62% Yield, TLC  $R_f$ =0.7 (hexane/EtOAc=10:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  9.55 (s, 1H, CHO), 6.42 (s, 1H, -C=CH<sub>2</sub>), 6.15 (s, 1H, -C=CH<sub>2</sub>), 3.26-3.29 (m, 1H, CHN<sub>3</sub>), 2.59-2.64 (m, 1H, -CH<sub>2</sub>-C=CH<sub>2</sub>), 2.24-2.30 (m, 1H, -CH<sub>2</sub>-C=CH<sub>2</sub>), 1.09-1.78 (m, 11H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  194.1, 146.7, 136.8, 66.2, 42.7, 30.6, 29.8, 28.4, 26.2, 26.1, 25.9; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 2928, 2853, 2095, 1698, 1449, 1089; MS *m*/*z* (rel intensity): 207 (M<sup>+</sup>, 5), 178 (21), 162 (18), 110 (22), 86 (37), 84 (54), 55 (43), 49 (100); HRMS Calcd for C<sub>11</sub>H<sub>17</sub>N<sub>3</sub>O 207.1372, found: 207.1374.

**4.7.17.** (1-Cyclohexyl-4-formylpent-4-enyl)carbamic acid methyl ester (54d). 65% Yield, TLC  $R_{\rm f}$ =0.77 (hexane/EtOAc=1:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  9.50 (s, 1H, CHO), 6.28 (br s, 1H, -CH=CH<sub>2</sub>), 5.99 (br s, 1H, -C=CH<sub>2</sub>), 4.51-4.55 (m, 1H, NH), 3.64 (s, 3H, OCH<sub>3</sub>), 3.43-3.46 (m, 1H, NCH), 2.18-2.52 (m, 3H), 1.01-1.72 (m, 12H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  194.5, 157.0, 149.6, 134.6, 55.2, 51.9, 42.2, 30.4, 29.5, 28.1, 26.3, 26.1, 25.9; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 3323 (NH), 2925, 1698, 1540, 1456; MS *m*/*z* (rel intensity): 253 (M<sup>+</sup>, 1), 252 (M<sup>+</sup>-1, 2), 170 (40), 116 (100), 109 (38); HRMS Calcd for C<sub>14</sub>H<sub>23</sub>NO<sub>3</sub> 253.1678, found: 253.1676.

# 4.8. General procedure to prepare the $\alpha$ -substituted acrylic acid from the corresponding $\alpha$ -substituted acrolein

To a solution of aldehyde **4a** (2.57 g, 16.64 mmol) in 60 mL of *t*-butyl alcohol and 5.3 mL of 2-methyl-2-butene (3.50 g, 49.93 mmol) was added a solution of sodium chlorite (3.46 g, 38.28 mmol) and sodium dihydrogenphosphate (5.19 g, 33.29 mmol) in 22 mL of water dropwise over a

10 min period. The pale yellow reaction mixture was stirred at room temperature for 2.5 h. The reaction mixture was concentrated, the residue then dissolved in 30 mL of water and this extracted with 100 mL of hexane. The aqueous layer was acidified to pH 3 with 2 N HCl and extracted with two 50 mL portions of ether. The combined ether layers were washed with 50 mL of water, dried with Na<sub>2</sub>SO<sub>4</sub>, concentrated and chromatographed on silica gel column to give product **7a** (2.77 g, 16.31 mmol) in 98% yield.

**4.8.1. 2-Heptylacrylic acid** (**7a**). 98% Yield; colorless oil; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  10.11 (br, 1H, CO<sub>2</sub>H), 6.27 (s, 1H, C=CH<sub>2</sub>), 5.63 (s, 1H, C=CH<sub>2</sub>), 2.29 (t, J=7.3 Hz, 2H, -CH<sub>2</sub>(C=CH<sub>2</sub>)-), 1.37-1.51 (m, 2H), 1.17-1.37 (m, 8H), 0.88 (t, J=7.1 Hz, 3H, -CH<sub>3</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  173.0, 140.4, 126.7, 31.8, 31.5, 29.2, 29.1, 28.4, 22.6, 14.0; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 2500-3250 (OH), 1690 (C=O), 1625, 1437, 1160, 948; MS *m*/*z* (rel intensity): 170 (M<sup>+</sup>, 6), 152 (10), 113 (13), 97 (42), 87 (100), 69 (35); HRMS Calcd for C<sub>10</sub>H<sub>18</sub>O<sub>2</sub> (M<sup>+</sup>) 170.1307, found 170.1313.

**4.8.2. 2-(3-Oxocyclohexyl)acrylic acid** (**7b**). 83% Yield; white solid, mp 80–81 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  6.42 (s, 1H, C=CH<sub>2</sub>), 5.70 (s, 1H, C=CH<sub>2</sub>), 2.97 (t, *J*=10.9 Hz, 1H), 2.20–2.60 (m, 4H), 1.98–2.15 (m, 2H), 1.55–1.85 (m, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  210.8, 171.4, 142.5, 126.5, 46.4, 41.1, 39.4, 30.4, 24.8; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 2500–3550 (OH), 1689 (C=O), 1622, 1416, 1284, 1152; MS *m*/*z* (rel intensity): 168 (M<sup>+</sup>, 8), 150 (10), 125 (8), 109 (4), 95 (4), 62 (46), 45 (100).

**4.8.3. 2-(1,1-Dimethyl-3-oxobutyl)acrylic acid (7c).** 72% Yield; red brown oil; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  6.31 (s, 1H, C=CH<sub>2</sub>), 5.73 (s, 1H, C=CH<sub>2</sub>), 2.91 (s, 2H, -CH<sub>2</sub>C=O), 2.08 (s, 3H, CH<sub>3</sub>CO), 1.27 (s, 6H, C(CH<sub>3</sub>)<sub>2</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  208.3, 172.3, 146.2, 125.9, 53.0, 36.7, 31.6, 28.2; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 2500–3550 (OH), 1714 (C=O), 1611, 1358, 1305, 1258, 1138, 1104; MS *m*/*z* (rel intensity): 170 (M<sup>+</sup>, 6), 152 (18), 137 (22), 124 (16), 109 (22), 95 (40), 81 (20), 67 (38), 43 (100); HRMS Calcd for C<sub>9</sub>H<sub>14</sub>O<sub>3</sub> 170.0943, found 170.0949.

**4.8.4. 2-(8-Hydroxyoctyl)acrylic acid** (**7d).** 85% Yield; white solid, mp 32 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  6.25 (s, 1H, C=CH<sub>2</sub>), 5.61 (s, 1H, C=CH<sub>2</sub>), 3.63 (t, J=6.6 Hz, 2H, -CH<sub>2</sub>OH), 2.29 (t, J=7.4 Hz, 2H, -CH<sub>2</sub>(C=CH<sub>2</sub>)-), 1.25-1.55 (m, 12H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  171.8, 140.4, 126.2, 62.7, 32.4, 31.4, 29.2, 29.0, 28.3, 25.6; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 3418 (OH), 1717 (C=O), 1629, 1436, 1195, 1162, 1052, 943; MS *m*/*z* (rel intensity): 183 (M<sup>+</sup>-OH, 4), 137 (15), 108 (10), 92 (72), 91 (100), 81 (9), 69 (10), 55 (12).

**4.8.5. 2-(8-Acetoxyoctyl)acrylic acid (7e).** 98% Yield; pale yellow oil; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  6.27 (s, 1H, C=CH<sub>2</sub>), 5.63 (s, 1H, C=CH<sub>2</sub>), 4.06 (t, *J*=6.8 Hz, 2H, -CH<sub>2</sub>(C=CH<sub>2</sub>)-), 2.29 (t, *J*=7.3 Hz, 2H), 2.04 (s, 3H, OCOCH<sub>3</sub>), 1.30-1.65 (m, 12H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  172.5, 171.3, 126.7, 64.6, 31.4, 29.2, 29.1, 28.6, 28.3, 25.9, 21.0; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 1690 (C=O), 1625, 1437, 1160, 1160, 948; MS *m/z* (rel intensity): 242

(M<sup>+</sup>, 2), 224 (2), 209 (5), 137 (15), 91 (100), 81 (15), 69 (11), 55 (13), 43 (20); HRMS Calcd for  $C_{13}H_{20}O_3$  224.1412, found 224.1398.

**4.8.6. 2-(8-Iodooctyl)acrylic acid** (**7f).** 98% Yield; yellow solid, mp 32 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  6.29 (s, 1H, C=CH<sub>2</sub>), 5.64 (s, 1H, C=CH<sub>2</sub>), 3.18 (t, *J*=7.1 Hz, 2H, -CH<sub>2</sub>I), 2.29 (t, *J*=7.3 Hz, 2H, -CH<sub>2</sub>(C=CH<sub>2</sub>)-), 1.82 (quin, *J*=6.9 Hz, 2H), 1.32-1.51 (m, 10H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  172.8, 140.2, 126.9, 33.5, 31.4, 30.5, 29.1, 29.0, 28.4, 28.3, 7.1; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 2500-3450 (OH), 1687 (C=O), 1624; MS *m/z* (rel intensity): 310 (M<sup>+</sup>, 3), 283 (6), 183 (15), 137 (48), 91 (100), 81 (48), 69 (25), 55 (45), 41 (38); HRMS Calcd for C<sub>11</sub>H<sub>19</sub>IO<sub>2</sub> (M<sup>+</sup>) 310.0430, found 310.0414.

4.8.7. 3-Cyclohexyl-2-methylene-3-(tetrahydropyran-2yloxy)propionic acid (20a). 93% Yield, TLC  $R_f=0.4$ (hexane/EtOAc=1:1); A mixture of the diastereomers; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 6.46 (s, 0.6H, C=CH<sub>2</sub>), 6.42 (s, 0.4H, C=CH<sub>2</sub>), 5.91 (s, 0.4H, C=CH<sub>2</sub>), 5.79 (s, 0.6H, C=CH<sub>2</sub>), 4.63-4.64 (m, 0.4H, O-CH-O), 4.55-4.56 (m, 0.6H, O-CH-O), 4.37-4.39 (m, 0.6H, CH-OTHP), 4.17-4.19 (m, 0.4H, CH-OTHP), 3.80-3.95 (m, 0.6H, CH<sub>2</sub>-O-CH), 3.65-3.75 (m, 0.4H, CH2-O-CH), 3.50-3.53 (m, 0.6H, CH2-O-CH), 3.45-3.55 (m, 0.4H, CH2-O-CH), 0.95-2.00 (m, 17H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$ 170.96, 170.92, 140.7, 139.4, 128.6, 127.9, 100.7, 94.9, 80.8, 77.1, 62.7, 62.0, 42.5, 42.2, 30.6, 30.4, 29.7, 29.4, 28.3, 27.9, 26.4, 26.4, 26.2, 26.1, 26.0, 25.9, 25.4, 25.3, 19.5, 19.1; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 2500-3500 (OH), 1715, 1450, 1028, 734; MS m/z (rel intensity): 268 (M<sup>+</sup>, 3), 185 (66), 167 (90), 85 (100), 55 (14); HRMS Calcd for C<sub>15</sub>H<sub>24</sub>O<sub>4</sub> 268.1675, found: 268.1685.

**4.8.8. 6-Cyclohexyl-2-methylene-6-(tetrahydropyran-2-yloxy)hexanoic acid (20d).** 91% Yield, TLC  $R_{\rm f}$ =0.40 (hexane/EtOAc=1:1). A mixture of the diastereomers, ratio=1:1; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  6.28 (s, 1H, C=CH<sub>2</sub>), 5.64–5.65 (m, 1H, C=CH<sub>2</sub>), 4.59–4.65 (m, 1H, O–CH–O), 3.90–3.91 (m, 1H, CH<sub>2</sub>–O–CH), 3.39–3.50 (m, 2H, CH<sub>2</sub>–O–CH), 2.29–2.31 (m, 2H, CH<sub>2</sub>–C=CH<sub>2</sub>), 1.48–1.75 (m, 16H), 0.88–1.25 (m, 5H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  172.3, 172.2, 140.2, 140.1, 126.8, 126.7, 99.0, 97.7, 81.7, 80.6, 62.9, 62.7, 41.5, 40.87, 40.86, 31.7, 31.5, 31.2, 31.1, 29.4, 29.1, 28.7, 28.6, 28.4, 26.7, 26.4, 25.5, 24.2, 23.8, 20.1, 19.9; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 2500–3500 (OH), 2853, 1697, 1626, 1453, 1132, 952; MS *m/z* (rel intensity): 209 (M<sup>+</sup>–101, 7), 163 (8), 143 (11), 85 (100), 67 (8); HRMS Calcd for C<sub>18</sub>H<sub>30</sub>O<sub>4</sub> 310.2144, found: 310.2150.

#### **4.9.** General procedure to prepare the methyl acrylate from the corresponding acrylic acid

To a solution of  $\alpha$ -substituted acrylic acid **7a** (287.2 mg, 1.69 mmol) in 3 mL of CH<sub>2</sub>Cl<sub>2</sub> was added a solution of CH<sub>2</sub>N<sub>2</sub> in ethyl ether at room temperature. The progress of the reaction should be monitored carefully by TLC. Excess of the CH<sub>2</sub>N<sub>2</sub> will cause the further 1,3-dipolar cyclo-addition on the double bond. When the reaction was complete, the reaction mixture was concentrated and the residue was chromatographed on silica gel column to give methyl acrylate **8a** (304 mg, 1.66 mmol) in 98% yield.

**4.9.1. Methyl 2-heptylacrylate (8a).** 98% Yield; colorless oil; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  6.12 (s, 1H, C=*CH*<sub>2</sub>), 5.51 (s, 1H, C=*CH*<sub>2</sub>), 3.75 (s, 3H, OCH<sub>3</sub>), 2.29 (t, *J*=7.3 Hz, 2H,  $-CH_2$ (C=*C*H<sub>2</sub>)–), 1.40–1.68 (m, 2H), 1.21–1.40 (m, 8H), 0.88 (t, *J*=6.9 Hz, 3H,  $-CH_3$ ); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  167.8, 140.9, 124.3, 51.6, 31.9, 31.8, 29.1, 29.0, 28.4, 22.6, 14.0; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 1718 (C=O), 1629, 1435, 1192, 1148, 940; MS *m/z* (rel intensity): 184 (M<sup>+</sup>, 8), 153 (12), 127 (20), 101 (100), 88 (58), 81 (18), 69 (30); HRMS Calcd for C<sub>11</sub>H<sub>20</sub>O<sub>2</sub> 184.1463, found 184.1461.

**4.9.2. Methyl 2-(3-oxocyclohexyl)acrylate (8b).** 96% Yield; pale yellow oil; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  6.24 (s, 1H, C=CH<sub>2</sub>), 5.57 (s, 1H, C=CH<sub>2</sub>), 3.77 (s, 3H, OCH<sub>3</sub>), 2.88–3.05 (m, 1H), 2.25–2.50 (m, 4H), 2.00–2.15 (m, 2H), 1.53–1.80 (m, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  210.5, 166.9, 143.2, 124.0, 51.9, 46.5, 41.1, 39.7, 30.4, 24.8; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 1705 (C=O), 1626, 1436, 1285, 1144; MS *m*/*z* (rel intensity): 182 (M<sup>+</sup>, 42), 150 (100), 139 (32), 122 (52), 108 (22), 95 (36), 79 (44), 67 (34), 53 (38), 41 (50); HRMS Calcd for C<sub>10</sub>H<sub>14</sub>O<sub>3</sub> 182.0943, found 182.0933.

**4.9.3. Methyl 2-(1,1-dimethyl-3-oxobutyl)acrylate (8c).** 86% Yield; yellow oil; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  6.10 (s, 1H, C=*CH*<sub>2</sub>), 5.62 (s, 1H, C=*CH*<sub>2</sub>), 3.73 (s, 3H, OCH<sub>3</sub>), 2.89 (s, 2H, -*CH*<sub>2</sub>C=O), 2.05 (s, 3H, *CH*<sub>3</sub>CO), 1.25 (s, 6H, C(CH<sub>3</sub>)<sub>2</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  207.9, 167.8, 147.0, 123.4, 53.1, 51.5, 36.9, 31.6, 28.1; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 1709 (C=O), 1614, 1434, 1357, 1316, 1258, 945; MS *m*/*z* (rel intensity): 184 (M<sup>+</sup>, 2), 152 (4), 127 (5), 95 (4), 81 (3), 67 (3), 62 (48), 45 (100); HRMS Calcd for C<sub>10</sub>H<sub>16</sub>O<sub>3</sub> 184.1099, found 184.1100.

**4.9.4. Methyl 2-(8-hydroxyoctyl)acrylate (8d).** 91% Yield; pale yellow oil; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  6.12 (s, 1H, C=CH<sub>2</sub>), 5.51 (s, 1H, C=CH<sub>2</sub>), 4.03 (s, 3H, OCH<sub>3</sub>), 3.63 (t, *J*=6.6 Hz, 2H, -CH<sub>2</sub>OH), 2.29 (t, *J*=7.3 Hz, 2H, -CH<sub>2</sub>(C=CH<sub>2</sub>)-), 1.20-1.60 (m, 13H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  167.9, 140.8, 124.4, 63.0, 51.7, 32.7, 31.8, 29.3, 29.1, 28.3, 25.7; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 3418 (OH), 1717 (C=O), 1436, 1262, 1195, 1162, 1052, 943; MS *m*/*z* (rel intensity): 214 (M<sup>+</sup>, 1), 182 (18), 154 (14), 125 (10), 101 (100), 81 (55), 67 (55), 55 (88), 41 (53).

**4.9.5.** Methyl 2-(8-acetoxyoctyl)acrylate (8e). 87% Yield; pale yellow oil; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  6.12 (br s, 2H, OH and =CH<sub>2</sub>), 5.51 (s, 1H, C=CH<sub>2</sub>), 4.05 (t, *J*=4.7 Hz, 2H, AcOCH<sub>2</sub>), 3.75 (s, 3H, CO<sub>2</sub>CH<sub>3</sub>), 2.29 (t, *J*=7.0 Hz, -CH<sub>2</sub>(C=CH<sub>2</sub>)-), 2.03 (s, 3H, OCOCH<sub>3</sub>), 1.25-1.65 (m, 12H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  171.1, 167.8, 140.8, 124.4, 64.5, 51.6, 31.8, 29.2, 29.1, 29.0, 28.5, 28.3, 25.8, 20.9; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 1721 (C=O), 1628, 1437, 1234, 1037, 940, 815; MS *m*/*z* (rel intensity): 256 (M<sup>+</sup>, 1), 224 (38), 182 (35), 164 (28), 136 (28), 125 (18), 101 (52), 95 (32), 81 (55), 67 (56), 55 (80), 43 (100); HRMS Calcd for C<sub>14</sub>H<sub>24</sub>O<sub>4</sub> 256.1674, found 256.1659.

**4.9.6.** Methyl 2-(8-iodooctyl)acrylate (8f). 87% Yield; pale yellow oil; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  6.12 (s, 1H, C=CH<sub>2</sub>), 5.52 (s, 1H, C=CH<sub>2</sub>), 3.75 (s, 3H, OCH<sub>3</sub>), 3.18 (t, J=7.1 Hz, 2H, -CH<sub>2</sub>I), 2.29 (t, J=7.2 Hz, 2H,

−*CH*<sub>2</sub>(C=CH<sub>2</sub>)−), 1.82 (quin, *J*=6.9 Hz, 2H), 1.31−1.48 (m, 10H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz) δ 167.8, 140.8, 124.4, 51.7, 33.5, 31.8, 30.4, 29.1, 29.0, 28.4, 28.3, 7.1; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 1716 (C=O), 1628, 1435, 1194, 1155, 945; MS *m*/*z* (rel intensity): 324 (M<sup>+</sup>, 8), 293 (12), 197 (43), 165 (32), 137 (100), 109 (18), 95 (65), 81 (82), 67 (48), 55 (65), 41 (45); HRMS Calcd for C<sub>12</sub>H<sub>21</sub>IO<sub>2</sub> 324.0586, found 324.0584.

### **4.10.** General procedure to prepare the acrylic amide from the corresponding acrylic acid

To a solution of  $\alpha$ -substituted acrylic acid **7a** (522.9 mg, 3.07 mmol) in 10 mL of CH<sub>2</sub>Cl<sub>2</sub> was added thionyl chloride (1.10 g, 9.21 mmol). The reaction mixture was refluxed for 3 h and then concentrated in vacuo. The residue was redissolved in 10 mL of CH<sub>2</sub>Cl<sub>2</sub> and the resulted solution was treated with 28% aqueous NH<sub>3</sub> solution at 0 °C and stirred for 30 min. The reaction mixture was added 20 mL of water and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layer was washed with 50 mL of water, dried with Na<sub>2</sub>SO<sub>4</sub> and concentrated. The crude mixture was chromatographed on silica gel column to give acrylic amide **10g** (462 mg, 2.73 mmol) in 89% yield.

**4.10.1. 2-Heptylacrylamide (10g).** 89% Yield; white solid, mp 70–71 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  5.82 (br, 1H, NH<sub>2</sub>), 5.68 (s, 1H, C=CH<sub>2</sub>), 5.33 (s, 1H, C=CH<sub>2</sub>), 2.30 (t, J=9.5 Hz, 2H,  $-CH_2$ (C=CH<sub>2</sub>)–), 1.40–1.51 (m, 2H), 1.20–1.34 (m, 8H), 0.88 (t, J=6.5 Hz, 3H,  $-CH_3$ ); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  170.9, 144.7, 118.5, 32.2, 31.8, 29.2, 29.1, 28.1, 22.6, 14.0; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 3528 (N– H), 3409 (N–H), 1673 (C=O), 1623, 1580, 1375; MS *m/z* (rel intensity): 169 (M<sup>+</sup>, 3), 112 (12), 98 (6), 86 (10), 62 (46), 45 (100).

**4.10.2. 2-Heptyl-1-(pyrrolidin-1-yl)prop-2-en-1-one** (**10h**). 83% Yield; pale yellow oil; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  5.19 (s, 1H, C=CH<sub>2</sub>), 5.11 (s, 1H, C=CH<sub>2</sub>), 2.30 (t, *J*=7.3 Hz, 2H,  $-CH_2(C=CH_2)$ -), 1.85–1.93 (m, 4H, 2x–NCH<sub>2</sub>), 1.40–1.50 (m, 2H), 1.21–1.35 (m, 8H), 0.88 (t, *J*=6.8 Hz, 3H,  $-CH_3$ ); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  170.6, 146.6, 114.2, 48.6, 45.3, 33.7, 31.7, 29.2, 29.0, 27.6, 26.1, 24.3, 22.5, 13.9; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 1614 (C=O), 1438, 912; MS *m*/*z* (rel intensity): 223 (M<sup>+</sup>, 42), 208 (12), 194 (10), 180 (13), 166 (50), 152 (42), 138 (100), 126 (36), 98 (28), 70 (42); HRMS Calcd for C<sub>14</sub>H<sub>25</sub>NO 223.1936, found 223.1932.

**4.10.3.** *N*-(2-*n*-Heptylacryloyl))valine methyl ester (10i). 89% Yield; pale yellow oil; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  6.27 (br d, *J*=8.6 Hz, 1H, NH), 5.66 (s, 1H, C=CH<sub>2</sub>), 5.31 (s, 1H, C=CH<sub>2</sub>), 4.64 (d, *J*=11.7 Hz, 0.5H), 4.62 (d, *J*=11.7 Hz, 0.5 H), 3.76 (s, 3H, OCH<sub>3</sub>), 2.18–2.40 (m, 3H), 1.40–1.51 (m, 2 H), 1.20–1.40 (m, 8H), 0.85–0.98 (m, 9H, 3xCH<sub>3</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  172.6, 168.7, 145.5, 117.7, 56.9, 52.1, 32.3, 31.7, 31.4, 29.1, 29.0, 28.0, 22.6, 19.0, 17.8, 14.0; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 3332 (N–H), 1744 (C=O), 1659 (C=O), 1620, 1509, 1203; MS *m*/*z* (rel intensity): 283 (M<sup>+</sup>, 10), 252 (6), 224 (100), 170 (46), 153 (65), 69 (18), 55 (39), 41 (40); HRMS Calcd for C<sub>16</sub>H<sub>29</sub>NO<sub>3</sub> 283.2147, found 283.2134.

### **4.11.** General procedure to prepare the methyl acrylate from the corresponding acrolein in one flask

To a mixture of aldehyde **15b** (324 mg, 1.0 mmol), *t*-butyl alcohol (3.6 mL) and 2-methyl-2-butene (210 mg, 3.0 mmol) was added a solution of sodium chlorite (208 mg, 2.30 mmol) and sodium dihydrogenphosphate (312 mg, 2.0 mmol) in 1.3 mL of water dropwise over a 10 min period. The pale yellow reaction mixture was stirred at room temperature for 2.5 h. The reaction mixture was concentrated, redissolved in 3 mL of water and extracted with 10 mL of hexane. The aqueous layer was acidified to pH 3 with 2 N HCl and extracted with two 15 mL portions of ether. The combined ether layers were washed with 10 mL of water, dried with Na<sub>2</sub>SO<sub>4</sub> and concentrated to give the crude product of the acrylic acid. To a solution of the crude acrylic acid in 3 mL of CH<sub>2</sub>Cl<sub>2</sub> was added a solution of CH<sub>2</sub>N<sub>2</sub> in ethyl ether at room temperature. When the reaction was complete, the reaction mixture was concentrated and the residue was chromatographed on silica gel column to give methyl acrylate 16b (241 mg, 0.95 mmol) in 95% yield.

**4.11.1. 4**-Acetoxy-4-cyclohexyl-2-methylenebutyric acid methyl ester (16b). 95% Yield, <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  6.11 (br s, 1H, C=CH<sub>2</sub>), 5.51 (br s, 1H, C=CH<sub>2</sub>), 4.85-4.90 (m, 1H, CHOCO), 3.71 (s, 3H, OCH<sub>3</sub>), 2.65-2.69 (m, 1H, CH<sub>2</sub>-C=CH<sub>2</sub>), 2.27-2.33 (m, 1H, CH<sub>2</sub>-C=CH<sub>2</sub>), 1.93 (s, 3H, -COCH<sub>3</sub>), 1.00-1.71 (m, 11H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  170.5, 167.1, 137.2, 126.7, 75.8, 51.8, 41.5, 34.4, 28.9, 28.0, 26.3, 25.91, 25.87, 20.8; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 2928, 2857, 1730, 1650, 1237; MS *m*/*z* (rel intensity): 223 (M<sup>+</sup>-31, 4), 141 (43), 95 (100), 83 (41), 58 (43); HRMS Calcd for C<sub>14</sub>H<sub>22</sub>O<sub>4</sub>-OCH<sub>3</sub> 223.1334, found: 223.1324.

**4.11.2. 5-Acetoxy-5-cyclohexyl-2-methylenepentanoic** acid methyl ester (16c). 93% Yield, TLC  $R_{\rm f}$ =0.65 (hexane/EtOAc=10:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  6.09 (s, 1H, C=CH<sub>2</sub>), 5.49 (s, 1H, C=CH<sub>2</sub>), 4.68–4.73 (m, 1H, CHOCO), 3.70 (s, 3H, OCH<sub>3</sub>), 2.24–2.27 (m, 2H, CH<sub>2</sub>–C=CH<sub>2</sub>), 2.00 (s, 3H, –COCH<sub>3</sub>), 1.60–1.71 (m, 9H), 0.93–1.17 (m, 4H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  170.8, 167.3, 139.9, 124.9, 77.2, 51.6, 41.1, 29.9, 28.8, 28.1, 28.0, 26.3, 26.0, 25.9, 21.0; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 2919, 2850, 1735, 1636, 1264; MS *m*/*z* (rel intensity): 225 (M<sup>+</sup>–43), 208 (10), 177 (6), 149 (M<sup>+</sup>–119, 25), 143 (28), 111 (32), 43 (100), 32 (95); HRMS Calcd for C<sub>15</sub>H<sub>24</sub>O<sub>4</sub> 268.1675, found: 268.1682.

**4.11.3. 2-(4-Acetoxy-4-cyclohexylbutyl)**acrylic acid methyl ester (16d). 96% Yield, <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  6.14 (s, 1H, C=CH<sub>2</sub>), 5.52 (s, 1H, C=CH<sub>2</sub>), 4.73–4.77 (m, 1H, CHOCO), 3.75 (s, 3H), 2.25–2.30 (m, 2H), 2.05 (s, 3H, -COCH<sub>3</sub>), 1.44–1.75 (m, 10H), 0.97–1.16 (m, 5H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  170.8, 167.5, 140.3, 124.8, 77.5, 51.6, 41.2, 31.6, 30.6, 28.9, 28.1, 26.3, 26.04, 25.98, 24.2, 21.0; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 2929, 2854, 1730, 1632, 1447, 1371, 1243, 1020, 966, 751; MS *m*/*z* (rel intensity): 222 (M<sup>+</sup>-60, 24), 157 (84), 140 (72), 125 (100), 95 (48), 81 (56), 67 (42), 55 (68); HRMS Calcd for C<sub>16</sub>H<sub>26</sub>O<sub>4</sub>-HOAc 222.1620, found: 222.1623.

**4.11.4. 4-Acetoxy-2-methylene-4-phenylpentanoic acid methyl ester (27a).** 95% Yield, TLC  $R_f$ =0.48 (hexane/EtOAc=10:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  7.21–7.30 (m, 5H), 6.16 (s, 1H, C=CH<sub>2</sub>), 5.39 (s, 1H, C=CH<sub>2</sub>), 3.57 (s, 3H, OCH<sub>3</sub>), 3.00 (s, 2H, CH<sub>2</sub>-C=CH<sub>2</sub>), 2.02 (s, 3H, -COCH<sub>3</sub>), 1.85 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  169.2, 167.7, 143.6, 135.9, 128.6, 127.9, 126.9, 124.7, 83.0, 51.6, 43.7, 24.0, 22.0; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 2949, 2845, 1735, 1631, 1496, 1017, 768; MS *m*/*z* (rel intensity): 261 (M<sup>+</sup>-1, 2), 220 (14), 163 (22), 121 (100), 43 (20); HRMS Calcd for C<sub>15</sub>H<sub>18</sub>O<sub>4</sub> 262.1205, found: 262.1198.

**4.11.5. 5-Acetoxy-2-methylene-5-phenylhexanoic acid** methyl ester (27b). 96% Yield, TLC  $R_f$ =0.52 (hexane/ EtOAc=10:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  7.21–7.32 (m, 5H), 6.09 (s, 1H, C=CH<sub>2</sub>), 5.47 (s, 1H, C=CH<sub>2</sub>), 3.69 (s, 3H, OCH<sub>3</sub>), 2.14–2.21 (m, 4H), 2.06 (s, 3H, -COCH<sub>3</sub>), 1.87 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  169.3, 167.2, 144.4, 139.9, 128.0, 126.7, 124.6, 124.3, 83.4, 51.5, 40.8, 26.3, 24.8, 21.9; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 2949, 2845, 1731, 1629, 1063, 735; MS *m*/*z* (rel intensity): 276 (M<sup>+</sup>, 5), 187 (13), 121 (100), 77 (12), 43 (62); HRMS Calcd for C<sub>16</sub>H<sub>20</sub>O<sub>4</sub> 276.1362, found: 276.1362.

**4.11.6. 3**-(**1**-Acetoxy-1-cyclohexyl)-2-methylenepropionic acid methyl ester (27c). 96% Yield, TLC  $R_{\rm f}$ =0.47 (hexane/EtOAc=10:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  6.19 (s, 1H, -C=CH<sub>2</sub>), 5.50 (s, 1H, -C=CH<sub>2</sub>), 3.70 (s, 3H, OCH<sub>3</sub>), 2.93 (s, 2H,  $-CH_2$ -C=CH<sub>2</sub>), 2.11–2.14 (m, 2H), 1.95 (s, 3H,  $-COCH_3$ ), 1.22–1.47 (m, 8H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  170.4, 168.0, 136.3, 128.2, 83.1, 51.8, 38.4, 34.3, 31.5, 25.2, 22.5, 22.2, 21.6; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 2999, 2933, 2861, 1726, 1627, 1451, 1100; MS *m*/*z* (rel intensity): 181 (M<sup>+</sup>–59, 33), 141 (M<sup>+</sup>–99, 33), 99 (64), 98 (75), 81 (25), 43 (100); HRMS Calcd for C<sub>13</sub>H<sub>20</sub>O<sub>4</sub> 240.1362, found: 240.1367.

**4.11.7. 4-(1-Acetoxy-1-cyclohexyl)-2-methylenebutyric** acid methyl ester (27d). 90% Yield, TLC  $R_f$ =0.47 (hexane/EtOAc=10:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  6.08 (s, 1H, C=CH<sub>2</sub>), 5.50 (s, 1H, C=CH<sub>2</sub>), 3.70 (s, 3H, OMe), 2.01–2.25 (m, 4H), 1.97–2.01 (m, 2H), 1.96 (s, 3H, -COCH<sub>3</sub>), 1.34–1.47 (m, 8H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  170.2, 167.5, 140.2, 124.7, 83.4, 51.7, 36.0, 34.4, 25.5, 22.1, 21.7; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 2935, 2861, 1730, 1632, 1450, 1367, 1107; MS *m*/*z* (rel intensity): 194 (M<sup>+</sup>-60, 20), 135 (40), 134 (51), 99 (100), 95 (47); HRMS Calcd for C<sub>13</sub>H<sub>20</sub>O<sub>4</sub>–CH<sub>3</sub>CO<sub>2</sub>H 194.1307, found: 194.1301.

**4.11.8.** *trans*-2-(2-Acetoxy-1-cyclohexyl)acrylic acid methyl ester (35a). 98% Yield, TLC  $R_{\rm f}$ =0.48 (hexane/EtOAc=10:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  6.06 (s, 1H, C=CH<sub>2</sub>), 5.45 (s, 1H, C=CH<sub>2</sub>), 4.72–4.78 (m, 1H, CHOCO), 3.65 (s, 3H, OCH<sub>3</sub>), 2.59–2.65 (m, 1H, CH–C=CH<sub>2</sub>), 1.59–2.02 (m, 4H), 1.83 (s, 3H, -COCH<sub>3</sub>), 1.17–1.32 (m, 4H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  170.2, 167.3, 141.8, 123.9, 74.7, 51.5, 44.2, 32.1, 31.9, 25.3, 24.4, 20.8; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 2938, 2860, 1731, 1629, 1438, 925; MS *m*/*z* (rel intensity): 166 (M<sup>+</sup>–60, 73), 151 (47), 134 (45), 79 (48), 43 (100); HRMS Calcd for C<sub>12</sub>H<sub>18</sub>O<sub>4</sub> 226.1205, found: 226.1196.

**4.11.9.** *trans*-3-(2-Acetoxy-1-cyclohexyl)-2-methylenepropionic acid methyl ester (35b). 91% Yield, TLC  $R_{\rm f}$ =0.53 (hexane/EtOAc=10:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  6.12 (s, 1H, C=CH<sub>2</sub>), 5.53 (s, 1H, C=CH<sub>2</sub>), 4.95-4.96 (m, 1H, CHOCO), 3.73 (s, 3H, OCH<sub>3</sub>), 2.68-2.69 (m, 1H, CH<sub>2</sub>-C=CH<sub>2</sub>), 2.31-2.34 (m, 1H, CH<sub>2</sub>-C=CH<sub>2</sub>), 1.94-2.01 (m, 1H), 1.94 (s, 3H, -COCH<sub>3</sub>), 1.63-1.68 (m, 8H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  170.6, 167.1, 136.9, 126.8, 75.6, 51.8, 43.8, 36.5, 28.9, 28.5, 25.5, 25.3, 20.9; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 2952, 2869, 1731, 1632, 1439, 945; MS *m*/*z* (rel intensity): 240 (M<sup>+</sup>, 33), 141 (12), 82 (15), 43 (100), 41 (25).

**4.11.10.** *cis*-2-(1-Methoxycarbonylvinyl)cyclohexyl benzoate (35c). 94% Yield, TLC  $R_f$ =0.62 (hexane/ EtOAc=3:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  7.99–8.02 (m, 2H), 7.51–7.55 (m, 1H), 7.40–7.44 (m, 1H), 6.17 (s, 1H, C=CH<sub>2</sub>), 5.54 (s, 1H, C=CH<sub>2</sub>), 5.47 (br s, 1H, CHOCO), 3.75 (s, 3H, OCH<sub>3</sub>), 2.88–2.91 (m, 1H, CH– C=CH<sub>2</sub>), 1.59–2.07 (m, 8H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  167.2, 165.6, 141.4, 132.7, 130.9, 129.4, 128.3, 125.2, 70.8, 51.9, 41.5, 30.5, 25.8, 25.3, 20.4; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 2936, 2860, 1715, 1629, 1025, 735; MS *m*/*z* (rel intensity): 288 (M<sup>+</sup>, 11), 256 (20), 166 (13), 105 (100), 77 (16); HRMS Calcd for C<sub>17</sub>H<sub>20</sub>O<sub>4</sub> 288.1362, found: 288.1368.

**4.11.11.** *cis*-2-(2-Methoxycarbonylallyl)cyclohexyl benzoate (35d). 95% Yield, TLC  $R_f$ =0.65 (hexane/ EtOAc=3:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  7.98–8.01 (m, 2H), 7.50–7.52 (m, 1H), 7.39–7.43 (m, 2H), 6.10 (s, 1H, C=CH<sub>2</sub>), 5.56 (s, 1H, C=CH<sub>2</sub>), 5.26–5.27 (m, 1H, CHOCO), 3.69 (s, 3H, OCH<sub>3</sub>), 2.82–2.86 (m, 1H, CH<sub>2</sub>– C=CH<sub>2</sub>), 2.51–2.57 (m, 1H, CH<sub>2</sub>–C=CH<sub>2</sub>), 2.18–2.20 (m, 1H), 1.53–1.79 (m, 7H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  167.2, 166.0, 136.7, 132.6, 130.5, 129.4, 128.2, 127.2, 76.3, 51.8, 43.8, 36.4, 29.0, 28.5, 25.6, 25.4; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 2952, 2869, 1714, 1632, 1025; MS *m*/*z* (rel intensity): 303 (M<sup>+</sup>+1, 3), 202 (M<sup>+</sup>–100, 3), 180 (12), 120 (3), 105 (100), 77 (13); HRMS Calcd for C<sub>18</sub>H<sub>22</sub>O<sub>4</sub> 302.1518, found: 302.1521.

**4.11.12. 2-[2-(Tetrahydropyran-2-yloxy)phenyl]acrylic** acid methyl ester (**40**). 88% Yield, TLC  $R_{\rm f}$ =0.44 (hexane/EtOAc=10:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$ 7.22–7.30 (m, 2H), 7.14–7.16 (m, 1H), 6.99–7.01 (m, 1H), 6.26 (s, 1H, C=CH<sub>2</sub>), 5.73 (s, 1H, C=CH<sub>2</sub>), 5.43 (br t, 1H), 3.81–3.85 (m, 1H), 3.76 (s, 3H, OCH<sub>3</sub>), 3.58–3.61 (m, 1H), 1.55–1.80 (m, 6H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$ 167.9, 154.3, 140.2, 129.9, 129.7, 127.5, 126.1, 121.4, 114.3, 96.2, 61.4, 51.9, 30.2, 25.1, 18.1; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 2947, 2874, 1726, 1487, 1455, 1323, 1274, 1233, 1202, 1123, 1035, 962, 920; MS *m/z* (rel intensity): 262 (M<sup>+</sup>, 1), 178 (56), 146 (50), 118 (16), 85 (100), 67 (13), 57 (16); HRMS Calcd for C<sub>15</sub>H<sub>18</sub>O<sub>4</sub> 262.1205, found: 262.1206.

**4.11.13. 2-[2-(Tetrahydropyran-2-yloxy)benzyl]acrylic** acid methyl ester (47). 82% Yield, TLC  $R_{\rm f}$ =0.71 (hexane/EtOAc=5:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$ 7.13–7.18 (m, 3H), 6.92–6.94 (m, 1H), 6.19 (br s, 1H, C=CH<sub>2</sub>), 5.43 (br t, J=3.0 Hz, 1H), 5.35 (br s, 1H, C=CH<sub>2</sub>), 3.60–3.84 (m, 2H), 3.76 (s, 3H, OCH<sub>3</sub>), 1.60– 1.84 (m, 6H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  167.6, 155.0, 139.5, 130.6, 127.7, 127.5, 125.6, 121.2, 114.2, 96.1, 61.8, 51.7, 32.2, 30.4, 25.2, 18.7; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 2946, 2875, 2844, 1717, 1490, 1455, 1238, 1137, 1037, 968, 754; MS *m*/*z* (rel intensity): 276 (M<sup>+</sup>, 4), 192 (64), 160 (52), 131 (30), 85 (100), 67 (16), 57 (18); HRMS Calcd for C<sub>16</sub>H<sub>20</sub>O<sub>4</sub> 276.1362, found: 276.1358.

**4.11.14. 4-Azido-4-cyclohexyl-2-methylenebutyric acid methyl ester (51c).** 62% Yield, TLC  $R_{\rm f}$ =0.73 (hexane/EtOAc=10:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  6.25 (s, 1H, -C=*CH*<sub>2</sub>), 5.68 (s, 1H, -C=*CH*<sub>2</sub>), 3.74 (s, 3H, OCH<sub>3</sub>), 3.30 (m, 1H, *CHN*<sub>3</sub>), 2.61–2.63 (m, 1H,  $-CH_2$ –*C*=*CH*<sub>2</sub>), 2.30–2.33 (m, 1H,  $-CH_2$ –*C*=*CH*<sub>2</sub>), 1.65–1.76 (m, 6H), 1.11–1.20 (m, 5H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  167.0, 137.0, 128.0, 66.7, 51.8, 42.4, 34.6, 29.7, 28.2, 26.2, 26.0, 25.9; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 2999, 2853, 2103, 1731, 1631, 1450; MS *m/z* (rel intensity): 206 (M<sup>+</sup>–31, 33), 100 (31), 83 (42), 55 (100), 41 (98), 39 (43); HRMS Calcd for C<sub>12</sub>H<sub>19</sub>N<sub>3</sub>O<sub>2</sub>–OCH<sub>3</sub> 206.1293, found: 206.1294.

**4.11.15. 2-(3-Cyclohexyl-3-methoxycarbonylaminopropyl)acrylic acid methyl ester (55d).** 82% Yield, TLC  $R_{\rm f}$ =0.82 (hexane/EtOAc=1:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  6.14 (s, 1H, C=CH<sub>2</sub>), 5.58 (s, 1H, C=CH<sub>2</sub>), 4.47 (br d, J=9.6 Hz, 1H), 3.80 (s, 3H), 3.70 (s, 3H), 3.49–3.66 (m, 1H), 2.20–2.45 (m, 2H), 1.13–1.75 (m, 13H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  167.9, 157.4, 140.5, 125.7, 55.8, 52.4, 52.2, 42.7, 31.8, 29.9, 29.3, 28.6, 26.8, 26.62, 26.60; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 3326 (N–H), 2926, 2852, 1717, 1634, 1539, 1448, 1244, 1158, 1081, 948; MS *m*/*z* (rel intensity): 283 (M<sup>+</sup>, 4), 200 (100), 170 (16), 168 (48), 136 (12), 124 (30), 88 (16), 55 (12); HRMS Calcd for C<sub>15</sub>H<sub>25</sub>NO<sub>4</sub> 283.1784, found: 283.1778.

# **4.12.** General procedure of the deprotection of OTHP to the corresponding alcohol catalyzed by ATPB

To a solution of OTHP-protected compound **20a** (143 mg, 0.5 mmol) in a mixture of  $CH_2Cl_2/MeOH$  (5 mL, 1:1 by volume) was added ATPB (20 mg, 0.05 mmol) and the solution was stirred at room temperature for 1 h. The solution was concentrated and chromatographed on silica gel column to give the desired **21a** (85 mg, 0.47 mmol) in 93% yield.

**4.12.1. 3-Cyclohexyl-3-hydroxy-2-methylenepropionic** acid (21a). 93% Yield; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$ 6.41 (s, 1H, C=CH<sub>2</sub>), 5.83 (s, 1H, C=CH<sub>2</sub>), 4.11 (d, *J*=7.1 Hz, 1H, CH–OH), 1.93–1.97 (m, 1H), 1.56–1.75 (m, 6H), 0.96–1.24 (m, 4H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  171.2, 140.3, 128.6, 77.2, 42.3, 29.9, 28.2, 26.3, 26.0, 25.9; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 2500–3500 (OH), 2927, 1695, 1627, 1450, 1132, 949; MS *m*/*z* (rel intensity): 166 (M<sup>+</sup>–18, 3), 102 (100), 83 (43), 55 (52), 41 (52); HRMS Calcd for C<sub>10</sub>H<sub>16</sub>O<sub>3</sub>–H<sub>2</sub>O 166.0994, found: 166.0996.

**4.12.2. 6**-Cyclohexyl-6-hydroxy-2-methylenehexanoic acid (21d). 95% Yield; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$ 6.25 (s, 1H, C=CH<sub>2</sub>), 5.62 (s, 1H, C=CH<sub>2</sub>), 3.36–3.39 (m, 1H, CH–OH), 2.29–2.33 (m, 2H, CH<sub>2</sub>–C=CH<sub>2</sub>), 0.99– 1.76 (m, 15H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  171.8, 140.2, 126.5, 76.0, 43.6, 33.4, 31.4, 29.2, 27.8, 26.5, 26.3, 26.2, 24.7; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 2500–3500 (OH), 2925, 1714, 1627, 1438, 1154, 944; MS *m*/*z* (rel intensity): 226 (M<sup>+</sup>, 8), 165 (100), 139 (3), 105 (13), 77 (11); HRMS Calcd for  $C_{13}H_{22}O_3$  226.1569, found: 226.1575.

**4.12.3. 2-(2-Hydroxyphenyl)acrylic acid methyl ester** (**41**).<sup>50</sup> 77% Yield, TLC  $R_f$ =0.26 (hexane/EtOAc=5:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  7.40 (br s, 1H, OH), 7.12–7.26 (m, 2H), 6.91–6.95 (m, 1H), 6.44 (br s, 1H, C=CH<sub>2</sub>), 5.90 (br s, 1H, C=CH<sub>2</sub>), 3.86 (s, 3H, OCH<sub>3</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  169.5, 153.5, 139.4, 130.6, 130.2, 129.8, 124.7, 120.6, 117.3, 52.8; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 3393, 2952, 1698, 1622, 1455, 1437, 1326, 1287, 1222, 1112; MS *m/z* (rel intensity): 179 (M<sup>+</sup>+1, 4), 178 (M<sup>+</sup>, 44), 146 (100), 119 (26), 91 (40), 90 (38), 89 (20), 65 (16); HRMS Calcd for C<sub>10</sub>H<sub>10</sub>O<sub>3</sub> 178.0630, found: 178.0632.

### **4.13.** General procedure to prepare the hydroxy-acid from the corresponding acetoxy-aldehyde

According to general procedure described above, acrolein **26b** (246 mg, 1.0 mmol) was converted to the corresponding acrylic acid **29b**. The crude product of compound **29b** was mixed with  $K_2CO_3$  (207 mg, 1.5 mmol) in 5 mL of MeOH and stirred at room temperature for 6 h. The reaction mixture was concentrated and the crude mixtures were dissolved in ethyl acetate. The organic phase was extracted with water, 1 N HCl and brine, respectively. The organic phase was dried over MgSO<sub>4</sub>, concentrated and chromatographed on silica gel column to give hydroxy-acid **30b** (172 mg, 0.78 mmol) in 78% yield.

**4.13.1. 5-Hydroxy-2-methylene-5-phenylhexanoic acid** (**30b**). 78% Yield, <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  7.21–7.45 (m, 5H), 6.22 (s, 1H, C=C*H*<sub>2</sub>), 5.58 (s, 1H, C=C*H*<sub>2</sub>), 2.29–2.32 (m, 1H), 2.15–2.18 (m, 1H), 1.96–2.04 (m, 2H), 1.58 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  172.2, 147.3, 140.1, 128.2, 127.0, 126.7, 124.8, 74.6, 42.8, 30.3, 26.4; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 2500–3500 (OH), 2923, 1702, 1625, 1446, 1151; MS *m*/*z* (rel intensity): 220 (M<sup>+</sup>, 1), 187 (16), 121 (100), 105 (14), 77 (10); HRMS Calcd for C<sub>13</sub>H<sub>16</sub>O<sub>3</sub> 220.1099, found: 220.1092.

**4.13.2. 4-(1-Hydroxy-1-cyclohexyl)-2-methylenebutyric** acid (**30d**). 82% Yield, <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$ 6.24 (s, 1H, C=CH<sub>2</sub>), 5.65 (s, 1H, C=CH<sub>2</sub>), 2.37–2.41 (m, 2H, CH<sub>2</sub>–C=CH<sub>2</sub>), 1.10–1.65 (m, 12H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  171.9, 140.7, 126.6, 71.6, 40.9, 37.3, 25.8, 25.3, 22.2; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 2500–3500 (OH), 2925, 1715, 1627, 1438, 1154; MS *m*/*z* (rel intensity): 198 (M<sup>+</sup>, 2), 137 (70), 99 (100), 81 (38), 55 (22); HRMS Calcd for C<sub>11</sub>H<sub>18</sub>O<sub>3</sub> 198.1256, found: 198.1259.

### **4.14.** General procedure to prepare the lactone from the acetoxy-acrylate under acidic condition

To a mixture of acetoxy-acrylate **16b** (150 mg, 0.59 mmol) in 3 mL of MeOH was added catalytic amount of acetyl chloride and stirred at room temperature for 7 h. The reaction mixture was concentrated and chromatographed on silica gel column to give the lactone **17b** (91 mg, 0.51 mmol) in 86% yield.

**4.14.1. 5-Cyclohexyl-3-methylenedihydrofuran-2-one** (17b).<sup>51</sup> 86% Yield; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  6.18

(br t, J=2.8 Hz, 1H, C= $CH_2$ ), 5.59 (br t, J=2.8 Hz, 1H, C= $CH_2$ ), 4.21–4.27 (m, 1H, CHOCO), 2.91–2.97 (m, 1H, CH<sub>2</sub>–C= $CH_2$ ), 2.67–2.69 (m, 1H, CH<sub>2</sub>–C= $CH_2$ ), 1.01– 1.92 (m, 11H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  170.4, 134.9, 121.5, 81.4, 43.0, 31.2, 28.1, 27.7, 26.2, 25.6, 25.4; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 2927, 2854, 1763, 1450, 1121, 1027; MS *m*/*z* (rel intensity): 180 (M<sup>+</sup>, 10), 151 (44), 134 (72), 97 (100), 69 (80); HRMS Calcd for C<sub>11</sub>H<sub>16</sub>O<sub>2</sub> 180.1150, found: 180.1158.

**4.14.2. 6-Cyclohexyl-3-methylenetetrahydropyran-2-one** (**17c**). 79% Yield, TLC  $R_f$ =0.48 (hexane/EtOAc=10:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  6.39 (s, 1H, C=CH<sub>2</sub>), 5.53 (s, 1H, C=CH<sub>2</sub>), 4.07-4.11 (m, 1H, CHOCO), 2.67-2.68 (m, 1H, CH<sub>2</sub>-C=CH<sub>2</sub>), 2.52-2.53 (m, 1H, CH<sub>2</sub>-C=CH<sub>2</sub>), 1.66-1.93 (m, 9H), 1.13-1.23 (m, 6H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  166.0, 134.2, 127.5, 84.9, 42.2, 28.1, 27.3, 26.3, 26.0, 25.9, 25.2; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 2926, 2854, 1714, 1624, 1174, 1087, 974; MS *m*/*z* (rel intensity): 194 (M<sup>+</sup>, 5), 112 (75), 110 (100), 83 (76), 41 (84); HRMS Calcd for C<sub>12</sub>H<sub>18</sub>O<sub>2</sub> 194.1307, found: 194.1304.

**4.14.3. 5-Methyl-3-methylene-5-phenyldihydrofuran-2**one (**28a**).<sup>52</sup> 75% Yield, TLC  $R_{\rm f}$ =0.43 (hexane/ EtOAc=10:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  7.26–7.38 (m, 5H), 6.26 (br s, 1H, C=CH<sub>2</sub>), 5.63 (br s, 1H, C=CH<sub>2</sub>), 3.15–3.16 (m, 2H, CH<sub>2</sub>–C=CH<sub>2</sub>), 1.73 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  169.6, 144.6, 135.1, 128.6, 127.7, 124.1, 122.5, 83.8, 42.6, 30.0; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 2928, 1761, 1667, 1447, 1115, 737; MS *m*/*z* (rel intensity): 188 (M<sup>+</sup>, 22), 173 (100), 105 (76), 77 (41), 68 (68); HRMS Calcd for C<sub>12</sub>H<sub>12</sub>O<sub>2</sub> 188.0837, found: 188.0828.

**4.14.4. 3-Methylene-1-oxa-spiro**[**4.5**]**decan-2-one** (**28**c).<sup>53</sup> 79% Yield, TLC  $R_{\rm f}$ =0.40 (hexane/EtOAc=10:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  6.21 (t, J=2.8 Hz, 1H, C=CH<sub>2</sub>), 5.59 (t, J=2.8 Hz, 1H, C=CH<sub>2</sub>), 2.70 (t, J=2.8 Hz, 2H, CH<sub>2</sub>– C=CH<sub>2</sub>), 1.39–1.80 (m, 10H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  169.9, 135.6, 122.1, 83.4, 39.5, 37.4, 24.7, 22.4; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 2998, 2933, 2859, 1759, 1665, 1448, 1191; MS *m*/*z* (rel intensity): 166 (M<sup>+</sup>, 33), 124 (15), 123 (100), 110 (52), 68 (40); HRMS Calcd for C<sub>10</sub>H<sub>14</sub>O<sub>2</sub> 166.0994, found: 166.0993.

**4.14.5.** *trans*-**3**-**Methylenehexahydrobenzofuran-2-one** (**36a**).<sup>54</sup> 89% Yield, TLC  $R_{\rm f}$ =0.43 (hexane/EtOAc=10:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  6.04 (d, *J*=3.2 Hz, 1H, C=*CH*<sub>2</sub>), 5.36 (d, *J*=3.2 Hz, 1H, C=*CH*<sub>2</sub>), 3.67–3.72 (m, 1H, CHOCO), 1.24–2.39 (m, 9H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  170.5, 139.6, 117.0, 83.0, 48.8, 30.4, 25.7, 24.8, 24.0; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 2939, 2864, 1769, 1675, 1456, 1117, 935; MS *m*/*z* (rel intensity): 152 (M<sup>+</sup>, 2), 124 (100), 95 (83), 79 (81), 67 (51); HRMS Calcd for C<sub>9</sub>H<sub>12</sub>O<sub>2</sub> 152.0837, found: 152.0843.

**4.14.6.** *trans*-**3**-Methyleneoctahydrochromen-2-one (**36b**).<sup>54</sup> 87% Yield, TLC  $R_{\rm f}$ =0.45 (hexane/EtOAc=10:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  6.35 (s, 1H, C=CH<sub>2</sub>), 5.50 (s, 1H, C=CH<sub>2</sub>), 4.07-4.13 (m, 1H, CHOCO), 2.64-2.65 (m, 1H, CH<sub>2</sub>-C=CH<sub>2</sub>), 2.51-2.52 (m, 1H, CH<sub>2</sub>-C=CH<sub>2</sub>), 1.25-2.04 (m, 9H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  166.4, 134.6, 127.9, 84.8, 45.1, 29.1, 28.9, 27.7, 25.8, 25.7; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 2951, 2869, 1759, 1666, 1436, 1125, 941;

MS m/z (rel intensity): 166 (M<sup>+</sup>, 7), 97 (100), 96 (43), 40 (70), 39 (92); HRMS Calcd for C<sub>10</sub>H<sub>14</sub>O<sub>2</sub> 166.0994, found: 166.1003.

**4.14.7. 3-Methylenechroman-2-one** (**48**).<sup>55</sup> 67% Yield, TLC  $R_{\rm f}$ =0.64 (hexane/EtOAc=5:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  7.06–7.28 (m, 4H), 6.43 (s, 1H, –C=CH<sub>2</sub>), 5.78 (s, 1H, –C=CH<sub>2</sub>) 3.81 (s, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  163.2, 150.9, 131.8, 128.4, 128.2, 127.7, 124.5, 121.2, 117.0, 32.0; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 2927, 2855, 1713, 1456, 1224, 1150; MS *m/z* (rel intensity): 160 (M<sup>+</sup>, 100), 131 (48), 105 (8), 91 (8), 77 (16), 69 (18); HRMS Calcd for C<sub>10</sub>H<sub>8</sub>O<sub>2</sub> 160.0524, found: 160.0521.

#### **4.15.** General procedure to prepare the lactone from benzoxy-acrylates promoted by NaOMe/MeOH

To a mixture of benzoate-acrylate 35c (150 mg, 0.52 mmol) in 4 mL of MeOH was added NaOMe (31 mg, 0.57 mmol) and stirred at room temperature for 4 h. The reaction mixture was concentrated and chromatographed on silica gel column to give the lactone 36c (60 mg, 0.40 mmol) in 76% yield.

**4.15.1.** *cis*-**3**-**Methylenehexahydrobenzofuran-2-one** (**36c**).<sup>54</sup> 76% Yield, TLC  $R_{\rm f}$ =0.41 (hexane/EtOAc=3:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  6.19 (d, *J*=2.4 Hz, 1H, C=*CH*<sub>2</sub>), 5.50 (d, *J*=2.4 Hz, 1H, C=*CH*<sub>2</sub>), 4.51–4.56 (m, 1H, CHOCO), 3.00–3.03 (m, 1H, CH–C=CH<sub>2</sub>), 1.25–1.87 (m, 8H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  170.9, 139.9, 119.7, 76.9, 39.6, 28.9, 26.3, 21.1, 20.5; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 2938, 1771, 1224, 1131, 935.

**4.15.2.** *cis*-**3**-Methyleneoctahydrochromen-2-one (**36d**).<sup>54</sup> 70% Yield, TLC  $R_{\rm f}$ =0.40 (hexane/EtOAc=3:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  6.21 (t, *J*=2.8 Hz, 1H, C=*CH*<sub>2</sub>), 5.60 (t, *J*=2.8 Hz, 1H, C=*CH*<sub>2</sub>), 4.35–4.38 (m, 1H, *CHOCO*), 2.99–3.05 (m, 1H, *CH*–C=*CH*<sub>2</sub>), 2.64–2.65 (m, 1H, *CH*– C=*CH*<sub>2</sub>), 1.27–2.08 (m, 9H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  170.5, 135.0, 121.7, 81.1, 45.1, 32.5, 28.6, 27.9, 25.4, 25.3; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 2942, 2868, 1719, 1622, 1186, 944; MS *m*/*z* (rel intensity): 166 (M<sup>+</sup>, 6), 137 (10), 98 (12), 97 (100), 69 (24); HRMS Calcd for C<sub>10</sub>H<sub>14</sub>O<sub>2</sub> 166.0994, found: 166.0986.

**4.15.3.** General procedure to prepare lactone from the hydroxy-acid promoted by *o*-nitrobenzenesulfonyl chloride. Anhydrous Na<sub>2</sub>CO<sub>3</sub> (456.0 mg, 4.34 mmol) was added to a solution of **21a** (79.2 mg, 0.43 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2.5 mL). After 15 min, *o*-nitrobenzenesulfonyl chloride (144.1 mg, 0.65 mmol) was added and the mixture left to stir at room temperature for 2 h. The mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (7.5 mL) and water (2.5 mL) and stirred for 15 min. The organic layer was separated and the aqueous layer extracted with CH<sub>2</sub>Cl<sub>2</sub> (3×15 mL). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated. Purification by silica gel column chromatography (hexane/EtOAc=98:2) provided **17a** as a colorless oil (58.3 mg, 81%).

**4.15.4. 4-Cyclohexyl-3-methylene-1-oxetan-2-one** (17a). 81% Yield, TLC  $R_{\rm f}$ =0.42 (hexane/EtOAc=10:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  5.91 (t, *J*=1.7 Hz, 1H, C=CH<sub>2</sub>), 5.42

(t, J=1.7 Hz, 1H, C=CH<sub>2</sub>), 4.69 (dt, J=7.1, 1.7 Hz, 1H, CHOCO), 1.10–1.87 (m, 11H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  163.7, 145.2, 115.1, 83.2, 40.9, 28.0, 27.4, 26.0, 25.4, 25.3; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 2928, 2854, 1827, 1452, 1206, 939; MS *m*/z (rel intensity): 149 (M<sup>+</sup>-17, 20), 111 (51), 83 (70), 55 (96), 43 (100); HRMS Calcd for C<sub>10</sub>H<sub>14</sub>O<sub>2</sub> 166.0994, found: 166.0990.

**4.15.5.** 7-Cyclohexyl-3-methyleneoxepan-2-one (17d). 87% Yield, TLC  $R_f$ =0.47 (hexane/EtOAc=10:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  5.64 (s, 1H, C=CH<sub>2</sub>), 5.36 (s, 1H, C=CH<sub>2</sub>), 3.90–3.95 (m, 1H, CHOCO), 2.32–2.44 (m, 2H, CH<sub>2</sub>–C=CH<sub>2</sub>), 1.04–1.84 (m, 15H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  172.6, 143.5, 122.2, 84.1, 42.9, 31.4, 30.6, 28.6, 27.9, 26.3, 26.1, 26.0, 25.9; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 2926, 2854, 1729, 1449, 1168, 928, 878; MS *m*/*z* (rel intensity): 208 (M<sup>+</sup>, 2), 180 (20), 125 (73), 97 (100), 83 (57); HRMS Calcd for C<sub>13</sub>H<sub>20</sub>O<sub>2</sub> 208.1463, found: 208.1472.

**4.15.6. 6-Methyl-3-methylene-6-phenyltetrahydropyran-2-one (28b).** 71% Yield, TLC  $R_f$ =0.45 (hexane/EtOAc=10:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  7.26–7.36 (m, 5H), 6.45 (s, 1H, C=CH<sub>2</sub>), 5.48 (s, 1H, C=CH<sub>2</sub>), 2.53–2.57 (m, 1H), 2.32–2.38 (m, 2H), 2.12–2.17 (m, 1H), 1.69 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  165.7, 143.9, 132.9, 128.7, 128.4, 127.3, 124.4, 84.9, 34.2, 30.9, 24.5; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 2979, 2932, 1714, 1622, 1446, 1140, 929; MS *m*/*z* (rel intensity): 202 (M<sup>+</sup>, 9), 187 (9), 121 (100), 105 (11), 43 (64); HRMS Calcd for C<sub>13</sub>H<sub>14</sub>O<sub>2</sub> 202.0994, found: 202.0997.

**4.15.7. 2-Methylene-1-oxaspiro**[**5.5**]**undecan-2-one** (**28d**). 80% Yield, TLC  $R_{\rm f}$ =0.35 (hexane/EtOAc=10:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  6.44 (s, 1H, C=CH<sub>2</sub>), 5.54 (s, 1H, C=CH<sub>2</sub>), 2.62–2.66 (m, 2H, CH<sub>2</sub>–C=CH<sub>2</sub>), 1.73– 1.86 (m, 6H), 1.32–1.58 (m, 6H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  165.6, 133.4, 127.7, 82.2, 36.5, 31.9, 25.2, 23.5, 21.5; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 2929, 2861, 1714, 1622, 1447, 1132; MS *m*/*z* (rel intensity): 180 (M<sup>+</sup>, 64), 137 (100), 124 (46), 82 (22), 55 (24); HRMS Calcd for C<sub>11</sub>H<sub>16</sub>O<sub>2</sub> 180.1150, found: 180.1151.

**4.15.8. 3-Methylene-***3H***-benzofuran-2-one (42).**<sup>37</sup> A solution of hydroxy-ester **41** (49.9 mg, 0.28 mmol) in dry toluene (1.4 mL) was treated with trifluoroacetic acid (5 drops). The lactone **42** was formed after the mixture was refluxed for 2 h. The lactone **42** was known to be stable for a few days in solution. However, it polymerizes quickly on the silica gel during the separation. Therefore, the reaction mixture was cooled down to room temperature and then added cyclopentadiene (0.2 mL, 2.8 mmol) and stirred at ambient temperature for 1.5 h. The resulting solution was concentrated under vacuum and two diastereomers (55% yield) can be separated by column chromatography.

Compound **43**-minor: pale yellow solid, mp 51–52 °C; 11% yield, TLC  $R_{\rm f}$ =0.82 (hexane/EtOAc=5:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  7.26–7.32 (m, 2H), 7.09–7.15 (m, 2H), 6.50–6.52 (m, 1H), 6.18–6.20 (m, 1H), 3.22 (s, 1H, bridgehead-H), 2.91 (s, 1H, bridgehead-H), 2.11–2.15 (m, 1H), 2.04–2.06 (m, 1H), 1.82–1.86 (m, 1H), 1.62–1.65 (m, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  179.4, 152.8, 139.6,

133.2, 133.1, 128.4, 123.9, 123.1, 110.5, 55.6, 50.9, 48.0, 43.4, 41.8; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 3063, 2973, 2877, 1794, 1617, 1475, 1460, 1234, 1125, 1073, 1037; MS *m*/*z* (rel intensity): 212 (M<sup>+</sup>, 56), 146 (88), 118 (68), 90 (58), 66 (100); HRMS Calcd for C<sub>14</sub>H<sub>12</sub>O<sub>2</sub> 212.0837, found: 212.0834.

**43**-major: pale yellow solid, mp 83–84 °C; 44% yield, TLC  $R_{\rm f}$ =0.87 (hexane/EtOAc=5:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  7.22–7.27 (m, 1H), 7.01–7.09 (m, 3H), 6.61–6.64 (m, 1H), 6.19–6.21 (m, 1H), 3.19 (s, 1H, bridgehead-H), 3.07 (s, 1H, bridgehead-H), 2.44–2.49 (m, 2H), 1.50–1.56 (m, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  181.2, 153.1, 141.0, 134.0, 132.0, 128.3, 124.6, 123.5, 110.2, 54.4, 50.6, 47.2, 43.6, 42.4; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 3053, 2974, 2875, 1795, 1615, 1478, 1461, 1236, 1123, 1075, 1038; MS *m*/*z* (rel intensity): 212 (M<sup>+</sup>, 40), 146 (76), 118 (48), 90 (26), 66 (100); HRMS Calcd for C<sub>14</sub>H<sub>12</sub>O<sub>2</sub> 212.0837, found: 212.0838.

4.15.9. 5-Cyclohexyl-3-methylenepyrrolidin-2-one (52c).<sup>39</sup> The solution of the azide 51c (30.8 mg, 0.13 mmol) and Ph<sub>3</sub>P (39.3 mg, 0.15 mmol) in THF (1 mL) was stirred at room temperature for 30 min. To the resulting solution was added H<sub>2</sub>O (0.1 mL) and stirred at room temperature for 6 h. The reaction mixture was concentrated, chromatographed on silica gel column to give the lactam 52c (18.6 mg, 0.10 mmol) in 80% yield. TLC  $R_f=0.5$  (hexane/EtOAc=10:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  7.03 (br, 1H, NH), 5.94 (t, J=2.7 Hz, 1H, CH=CH<sub>2</sub>), 5.30 (s, 1H, CH=CH<sub>2</sub>), 3.38-3.40 (m, 1H, CHNCO), 2.83-2.85 (m, 1H, CH<sub>2</sub>CH=CH<sub>2</sub>), 2.51-2.56 (m, 1H, -CH<sub>2</sub>CH=CH<sub>2</sub>), 0.90-1.77 (m, 11H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 170.7, 139.6, 115.4, 56.2, 43.6, 30.9, 28.7, 28.5, 26.3, 25.8, 25.7, 25.8; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 3216 (NH), 2928, 2855, 1697, 1661, 1450, 1264, 928; MS m/z (rel intensity) 178 (M<sup>+</sup>-1, 2), 96 (100), 55 (7), 53 (15), 41 (20); HRMS Calcd for C<sub>11</sub>H<sub>17</sub>NO 179.1310, found: 179.1313.

4.15.10. 6-Cyclohexyl-3-methylene-2-oxo-piperidine-1carboxylic acid methyl ester (56d). A mixture of the acrylate 55d (101.9 mg, 0.36 mmol) in toluene (3.2 mL) was added Me<sub>3</sub>Al (2.0 M in toluene, 0.35 mL, 0.71 mmol) at 0 °C dropwise over 5 min and stirred at 0 °C for 2 h. The reaction mixture was quenched by the addition of brine at 0 °C. The aqueous phase was separated and extracted with ethyl acetate. The organic extracts were combined, dried, concentrated and chromatographed on silica gel column to give compound 56d (65 mg, 0.26 mmol) in 72% yield. TLC  $R_{\rm f}$ =0.64 (hexane/EtOAc=1:1); <sup>1</sup>H NMR (CDCl<sub>2</sub>, 400 MHz) δ 5.11 (s, 1H, C=CH<sub>2</sub>), 4.77 (s, 1H, C=CH<sub>2</sub>), 3.66 (s, 3H, -OCH<sub>3</sub>), 3.52-3.55 (m, 1H), 2.13-2.17 (m, 2H), 1.14–1.76 (m, 13H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 176.3, 157.7, 155.9, 107.5, 55.9, 52.4, 42.9, 30.0, 29.7, 29.6, 28.6, 26.8, 26.64, 26.63; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 2927, 2852, 1703, 1634, 1539, 1449, 1361, 1258, 1191, 1148, 1081, 962, 893; MS m/z (rel intensity): 252 (M<sup>+</sup>+1, 2), 251 (M<sup>+</sup>, 1), 200 (28), 182 (40), 170 (56), 107 (100), 88 (48), 76 (48); HRMS Calcd for C<sub>14</sub>H<sub>21</sub>NO<sub>3</sub> 251.1521, found: 251.1531.

### 4.16. General procedure to prepare the $\alpha$ -keto ester from the methyl acrylate by ozonolysis

In a 25 mL of two-necked flask, equipped with a magnetic

stirrer, a drying tube and a gas dispersing tube (with porous fritted tip), were placed 10 mL of  $CH_2Cl_2$  and  $\alpha$ -substituted acrylate **8a** (250.7 mg, 1.36 mmol). A stream of ozone was bubbled through the solution at -78 °C. Ozone treatment was terminated when the mixture assumed a blue color. A stream of nitrogen removed excess ozone. To the resulted solution was added Ph<sub>3</sub>P (356.7 mg, 1.36 mmol) and the reaction was warmed slowly to room temperature and stirred for 4 h. The reaction mixture was concentrated and the residue was chromatographed on silica gel column to give 176 mg of  $\alpha$ -keto ester **9a** in 69% yield.

**4.16.1. 2-Oxononanoic acid methyl ester (9a).** 69% Yield; pale yellow oil; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  3.86 (s, 3H, OCH<sub>3</sub>), 2.83 (t, *J*=7.1 Hz, 2H, -CH<sub>2</sub>(C=O)), 1.61–1.66 (m, 2H), 1.20–1.35 (m, 8H), 0.88 (t, *J*=6.8 Hz, 3H, -CH<sub>3</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  194.3, 161.6, 52.8, 39.3, 31.5, 28.8, 22.9, 22.5, 14.0; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 1728 (C=O), 1435, 1273, 1067; MS *m*/*z* (rel intensity): 186 (M<sup>+</sup>, 3), 128 (12), 127 (100), 109 (10), 97 (3); HRMS Calcd for C<sub>10</sub>H<sub>18</sub>O<sub>3</sub> 186.1256, found 186.1255.

**4.16.2. 2-Oxo-2-(3-oxocyclohexyl)acetic acid methyl ester (9b).** 64% Yield; pale yellow oil; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  3.89 (s, 3H, OCH<sub>3</sub>), 2.00–2.60 (m, 6H), 1.50–1.85 (m, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  208.4, 193.9, 161.1, 53.1, 46.1, 41.2, 40.8, 26.6, 24.5; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 1732, 1706 (C=O), 1446, 1251, 1106, 1061, 1033; MS *m/z* (rel intensity): 184 (M<sup>+</sup>, 8), 156 (6), 125 (50), 97 (100), 69 (76), 55 (38), 41 (88).

**4.16.3. 3,3-Dimethyl-2,5-dioxohexanoic acid (9c).** 71% Yield; yellow oil; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  3.81 (s, 3H, OCH<sub>3</sub>), 3.12 (s, 2H, -CH<sub>2</sub>C=O), 2.13 (s, 3H, CH<sub>3</sub>CO), 1.26 (s, 6H, C(CH<sub>3</sub>)<sub>2</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  207.4, 196.9, 161.9, 54.0, 52.3, 43.7, 29.9, 24.8; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 2500–3550 (OH), 1689 (C=O), 1622, 1416, 1284, 1152; MS *m*/*z* (rel intensity): 187 (M<sup>+</sup>+1, 2), 127 (42), 99 (22), 83 (3), 69 (3), 59 (4), 43 (100).

**4.16.4. 10-Hydroxy-2-oxodecanoic acid methyl ester** (**9d**). 62% Yield; pale yellow oil; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  3.86 (s, 3H, OCH<sub>3</sub>), 3.62 (t, *J*=6.6 Hz, 2H, -CH<sub>2</sub>OH), 2.83 (t, *J*=7.3 Hz, 2H, -CH<sub>2</sub>(C=CH<sub>2</sub>)-), 1.25-1.70 (m, 13H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  194.3, 161.6, 62.8, 52.8, 39.2, 32.6, 29.1, 28.8, 25.6, 22.8; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 3441 (OH), 1735 (C=O), 1436, 1263, 1067; MS *m*/*z* (rel intensity): 216 (M<sup>+</sup>, 2), 157 (32), 139 (35), 121 (17), 97 (23), 81 (13), 69 (100), 55 (82), 41 (39); HRMS Calcd for C<sub>11</sub>H<sub>20</sub>O<sub>4</sub> 216.1362, found 216.1356.

**4.16.5. 10**-Acetoxy-2-oxodecanoic acid methyl ester (9e). 69% Yield; pale yellow oil; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$ 4.05 (t, *J*=6.9 Hz, 2H, CH<sub>2</sub>OAc), 3.86 (s, 3H, OCH<sub>3</sub>), 2.83 (t, *J*=7.3 Hz, 2H, CH<sub>2</sub>(C=CH<sub>2</sub>)-), 2.04 (s, 3H, OCCH<sub>3</sub>), 1.25-1.65 (m, 12H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  194.3, 171.2, 161.6, 64.5, 52.8, 39.2, 29.1, 29.0, 28.8, 28.5, 25.8, 22.9, 21.0; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 1731 (C=O), 1437, 1237, 1064; MS *m*/*z* (rel intensity): 258 (M<sup>+</sup>, 1), 199 (42), 157 (92), 139 (52), 95 (12), 69 (100), 55 (70), 43 (88); HRMS Calcd for C<sub>13</sub>H<sub>22</sub>O<sub>5</sub> 258.1467, found 258.1461. **4.16.6. 10-Iodo-2-oxodecanoic acid methyl ester (9f).** 67% Yield; pale yellow oil; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  3.86 (s, 3H, OCH<sub>3</sub>), 3.18 (t, *J*=6.8 Hz, 2H, -CH<sub>2</sub>I), 2.83 (t, *J*=7.2 Hz, 2H, -CH<sub>2</sub>C=O), 1.82 (quin, *J*=7.1 Hz, 2H), 1.52–1.65 (m, 2H), 1.31–1.40 (m, 8H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  194.2, 161.6, 52.8, 39.2, 33.4, 30.3, 29.0, 28.8, 28.2, 22.8, 7.03; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 1725 (C=O), 1433, 1268, 1061; MS *m/z* (rel intensity): 326 (M<sup>+</sup>, 2), 267 (100), 197 (8), 181 (10), 169 (11), 155 (13), 139 (16), 91 (30), 69 (58), 55 (60), 41 (39); HRMS Calcd for C<sub>11</sub>H<sub>19</sub>IO<sub>3</sub> 326.0379, found 326.0374.

**4.16.7. 2-Oxononanamide** (**11g**). 90% Yield; white solid, mp 91–92 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  6.85 (br s, 1H, NH<sub>2</sub>), 5.80 (br s, 1H, NH<sub>2</sub>), 2.90 (t, *J*=9.7 Hz, 2H, –*CH*<sub>2</sub>(C=O)), 1.55–1.65 (m, 2H), 1.15–1.45 (m, 8H), 0.88 (t, *J*=6.8 Hz, 3H, –*C*H<sub>3</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  198.8, 162.1, 36.5, 31.6, 29.0, 23.2, 22.6, 14.0; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 3404 (N–H), 3216 (N–H), 1716 (C=O), 1671 (CONH<sub>2</sub>), 1403, 1103; MS *m*/*z* (rel intensity): 171 (M<sup>+</sup>, 3), 149 (8), 127 (31), 109 (5), 62 (46), 57 (50), 45 (100); HRMS Calcd for C<sub>9</sub>H<sub>17</sub>NO<sub>2</sub> 171.1259, found 171.1266.

**4.16.8. 1-Pyrrolidin-1-yl-nonane-1,2-dione** (**11h**). 85% Yield; pale yellow oil; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  3.60 (t, *J*=6.5 Hz, 2H, NCH<sub>2</sub>), 3.51 (t, *J*=6.8 Hz, 2H, NCH<sub>2</sub>), 2.83 (t, *J*=7.4 Hz, 2H, -CH<sub>2</sub>C=O), 1.77-1.96 (m, 4H), 1.56-1.63 (m, 2H), 1.25-1.40 (m, 8H), 0.88 (t, *J*=6.8 Hz, 3H, -CH<sub>3</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  201.1, 163.2, 47.2, 46.2, 39.2, 31.6, 29.1, 29.0, 26.3, 23.6, 23.0, 22.5, 14.0; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 1711 (C=O), 1634 (C=O), 1400, 1086; MS *m/z* (rel intensity): 225 (M<sup>+</sup>, 8), 98 (88), 75 (100).

**4.16.9.** *N*-(**2**-Oxononanoyl)valine methyl ester (11i). 85% Yield; pale yellow oil; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  7.37 (br d, *J*=8.6 Hz, 1H, NH), 4.48 (d, *J*=9.4 Hz, 0.5H), 4.47 (d, *J*=9.4 Hz, 0.5H), 3.75 (s, 3H, OCH<sub>3</sub>), 2.90 (t, *J*=7.6 Hz, 2H), 2.22 (sext, *J*=5.2 Hz, 1H), 1.52–1.65 (m, 3H), 1.20–1.35 (m, 7H), 0.85–0.97 (m, 9H, 3xCH<sub>3</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  198.6, 171.3, 160.0, 57.3, 52.3, 36.8, 31.6, 31.3, 29.0, 23.2, 22.6, 18.9, 17.7, 14.0; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 3400 (N–H), 1741 (C=O), 1681 (C=O), 1510, 1461, 920; MS *m*/*z* (rel intensity): 285 (M<sup>+</sup>, 8), 254 (2), 224 (9), 158 (15), 130 (100), 98 (15), 72 (22), 57 (42), 41 (20); HRMS Calcd for C<sub>15</sub>H<sub>27</sub>NO<sub>4</sub> 285.1940, found 285.1947.

### 4.17. General procedure to prepare the $\alpha$ -keto lactone from $\alpha$ -methylene lactone by ozonolysis in CH<sub>2</sub>Cl<sub>2</sub>

A two-necked flask fitted with a glass tube to admit ozone, a  $CaCl_2$  drying tube and a magnetic stirring bar is charged with  $\alpha$ -methylene lactone **17b** (90.0 mg, 0.50 mmol) in  $CH_2Cl_2$  (5 mL). The flask is cooled to -78 °C and ozone is bubbled through the solution. When the solution turns blue, ozone addition is stopped. Nitrogen is passed through the solution until the blue color is discharged. To the resulted solution was added Ph<sub>3</sub>P (104.9 mg, 0.40 mmol) and warmed slowly to room temperature. The reaction mixture was concentrated and the residue was chromatographed on silica gel column to give  $\alpha$ -keto lactone **17b**' (72.8 mg, 0.40 mmol) in 80% yield.

**4.17.1. 5-Cyclohexyl-3-hydroxy-5H-furan-2-one** (**17b**'). 80% Yield, TLC  $R_{\rm f}$ =0.4 (hexane/EtOAc=10:1); enol form only; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  6.21 (d, *J*=2.0 Hz, 1H, CH=COH), 5.87 (br s, 1H, OH), 4.74 (dd, *J*=5.6 and 2.0 Hz, 1H, CHOCO), 1.64–1.80 (m, 5H), 1.14–1.27 (m, 6H,); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  170.3, 142.2, 117.6, 83.7, 41.8, 28.2, 28.1, 26.1, 25.7, 25.6; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 3391 (OH), 2928, 1757, 1264, 1037; MS *m*/*z* (rel intensity): 182 (M<sup>+</sup>, 2), 137 (12), 100 (100), 83 (18), 55 (33); HRMS Calcd for C<sub>10</sub>H<sub>14</sub>O<sub>3</sub> 182.0943, found: 182.0940.

**4.17.2. 7-Cyclohexyl-oxepane-2,3-dione** (**17d**<sup>7</sup>). 80% Yield, TLC  $R_{\rm f}$ =0.43 (hexane/EtOAc=3:1); keto form only; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  3.95–3.99 (m, 1H,  $CH_2$ –CO), 2.60–2.62 (m, 1H), 2.48–2.51 (m, 1H), 1.03– 1.99 (m, 15H,); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  200.1, 166.2, 82.8, 42.4, 38.2, 29.8, 28.5, 28.2, 26.1, 25.8, 25.7, 20.1; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 2925, 2854, 1747, 1714, 1652, 1451, 1118, 736; MS *m*/*z* (rel intensity): 210 (M<sup>+</sup>, 33), 122 (40), 109 (100), 81 (78), 67 (86); HRMS Calcd for C<sub>12</sub>H<sub>18</sub>O<sub>3</sub> 210.1256, found: 210.1266.

**4.17.3. 5-Methyl-5-phenyldihydrofuran-2,3-dione** (**28***a*') **and 3-Hydroxy-5-methyl-5-phenyl-5***H***-furan-2-one (<b>28***a*'').<sup>56</sup> 73% Yield, TLC  $R_{\rm f}$ =0.37 (hexane/EtOAc=10:1); a mixture of keto and enol forms (1: 5). Keto form **28***a*': <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  7.25–7.40 (m, 5H), 3.19–3.20 (m, 1H, CH<sub>2</sub>–CO), 1.90 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  193.2, 159.4, 142.7, 129.0, 128.7, 125.1, 83.5, 48.1, 31.9. Enol form (**28***a*''): <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  7.25–7.40 (m, 5H), 6.52 (s, 1H, CH=COH), 1.89 (s, 3H), 1.82 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  169.7, 142.7, 140.3, 128.5, 128.3, 124.8, 123.9, 85.7, 22.7; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 2500–3500 (OH), 2931, 1746, 1264, 915; MS *m*/*z* (rel intensity): 190 (30), 189 (52), 144 (100), 134 (83), 104 (41); HRMS Calcd for C<sub>11</sub>H<sub>10</sub>O<sub>3</sub> 190.0630, found: 190.0627.

**4.17.4. 1-Oxaspiro**[**4.5**]decane-2,3-dione (**28**c<sup>'</sup>) and **3-hydroxy-1-oxaspiro**[**4.5**]dec-3-en-2-one (**28**c<sup>''</sup>).<sup>57</sup> 80% Yield, TLC  $R_{\rm f}$ =0.35 (hexane/EtOAc=10:1), a mixture of keto and enol forms (2: 5). Keto form **28**c<sup>'</sup>: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  2.75 (s, 2H, CH<sub>2</sub>-CO), 1.26–1.89 (m, 10H,); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  194.1, 159.9, 83.3, 45.7, 29.6, 24.3, 22.0 (2°). Enol form **28**c<sup>''</sup>: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  6.31 (s, 1H, CH=COH), 1.26–1.89 (m, 10H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  169.9, 141.3, 124.1, 85.4, 35.8, 24.7, 22.6; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 3433 (OH), 2932, 1742, 1264, 1193, 972; MS *m*/*z* (rel intensity): 168 (M<sup>+</sup>, 30), 123 (100), 122 (32), 112 (47), 67 (24); HRMS Calcd for C<sub>9</sub>H<sub>12</sub>O<sub>3</sub> 168.0786, found: 168.0784.

**4.17.5. 3-Hydroxy-5,6,7,7a-tetrahydro-4H-benzofuran-2-one** (**36c**<sup>*''*</sup>). 81% Yield, TLC  $R_{\rm f}$ =0.37 (hexane/ EtOAc=3:1); enol form only; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  4.60 (dd, *J*=11.2, 6.0 Hz, 1H, CHOCO), 2.93–2.98 (m, 1H), 2.40–2.53 (m, 1H), 1.88–2.03 (m, 3H), 1.21–1.38 (m, 4H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  170.9, 134.9, 134.0, 78.4, 33.9, 25.4, 23.7, 22.7; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 3253 (OH), 2939, 1752, 1218, 1061; MS *m/z* (rel intensity): 154 (M<sup>+</sup>, 22), 109 (100), 97 (22), 81 (20), 69 (20); HRMS Calcd for C<sub>8</sub>H<sub>10</sub>O<sub>3</sub> 154.0630, found: 154.0635.

# 4.18. General procedure to prepare the $\alpha$ -keto lactone from $\alpha$ -methylene lactone by ozonolysis in methanol/CH<sub>2</sub>Cl<sub>2</sub>

A two-necked flask fitted with a glass tube to admit ozone, a  $CaCl_2$  drying tube and a magnetic stirring bar is charged with  $\alpha$ -methylene-lactone **17c** (95 mg, 0.49 mmol) in  $CH_2Cl_2$  (3 mL) and methanol (2 mL). The flask is cooled to -78 °C and ozone is bubbled through the solution. When the solution turns blue, ozone addition is stopped. Nitrogen is passed through the solution until the blue color is discharges. To the resulted solution was added Ph<sub>3</sub>P (131 mg, 0.50 mmol) and warmed slowly to room temperature. The reaction mixture was concentrated and the residue was chromatographed on silica gel column to give  $\alpha$ -keto lactone **17c**' (79.3 mg, 0.35 mmol) in 71% yield.

**4.18.1. 5-Cyclohexyl-2-hydroxytetrahydrofuran-2-carboxylic acid methyl ester** (**17**c''). 71% Yield; a mixture of two diastereomers; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  3.83–3.88 (m, 1H), 3.82 (s, 3H), 0.99–1.26 (m, 15H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  171.8, 171.7, 102.0, 101.5, 87.1, 85.1, 52.9, 43.4, 42.2, 35.5, 35.2, 29.9, 29.4, 28.7, 28.5, 27.9, 26.4, 25.9, 25.8, 25.7; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 3447 (OH), 2924, 2852, 1747, 1449, 1272, 1198, 1156, 1056, 890; MS *m*/*z* (rel intensity): 227 (M<sup>+</sup>–1, 2), 151 (95), 145 (68), 133 (42), 127 (45), 109 (45), 85 (100), 67 (43), 55 (46); HRMS Calcd for C<sub>12</sub>H<sub>20</sub>O<sub>4</sub>–CO<sub>2</sub>CH<sub>3</sub> 169.1229, found: 169.1233.

**4.18.2.** 2-Hydroxy-5-methyl-5-phenyltetrahydrofuran-2carboxylic acid methyl ester (**28b**<sup>*''*</sup>). 75% Yield; a mixture of two diastereomers; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  7.23– 7.49 (m, 5H), 3.99 (br s, 1H, OH), 3.87 and 3.83 (s, 3H), 2.14–2.58 (m, 4H), 1.72 and 1.70 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  172.5, 172.6, 147.5, 147.0, 128.1, 128.0, 126.7, 126.6, 124.9, 124.6, 102.4, 88.0, 87.8, 53.2, 53.0, 39.2, 38.9, 35.1, 34.9, 30.9, 29.2; IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 3472 (OH), 2924, 2852, 1744, 1494, 1445, 1265, 1066, 892; MS *m*/*z* (rel intensity): 221 (M<sup>+</sup>–15, 60), 177 (100), 161 (60), 131 (64), 117 (44), 105 (42), 91 (28), 77 (25); HRMS Calcd for C<sub>13</sub>H<sub>16</sub>O<sub>4</sub>–CH<sub>3</sub> 221.0814, found: 221.0810.

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