Synthesis of β- and β,β-substituted Morita–Baylis–Hillman adducts using a two-step protocol

David I. Magee, Same Ratshonka, Jessica McConaghy, and Maggie Hood

Abstract: The synthesis of a large number of β- and β,β-substituted keto esters was successful by the use of the Knoevenagel condensation reaction. The stereoselectivity of these reactions was improved by alteration of various substituent groups. Although there were few examples of complete Z selectivity, the use of *tert*-butyl acetoacetate with either aromatic or aliphatic aldehydes afforded Z selectivity. The selective reductions of these substituted keto esters was successfully achieved by using a combination of $NaBH_4$ and $CeCl_3 \cdot 7H_2O$ or $Yb(OTf)_3$, which allowed a facile synthesis of a large number of stereochemically pure substituted Morita–Baylis–Hillman adducts, including β,β-substituted adducts.

Key words: Morita–Baylis–Hillman, Knoevenagel, reduction, β,β-substituted.

Résumé : On a effectué avec succès la synthèse d'un grand nombre d'esters β- et β,β-substitués en faisant appel à la condensation de Knoevenagel. On a amélioré la stéréosélectivité de ces réactions en procédant à l'altération de divers substituants. Même s'il n'y a que peu d'exemples de sélectivité Z complète, l'utilisation de l'acétoacétate de *tert*-butyle avec des aldéhydes aromatiques ou aliphatiques conduit à la formation de produits avec une sélectivité Z. On a effectué avec succès les réductions sélectives de ces cétoesters substitués en utilisant une combinaison de $NaBH_4$ et de $CeCl_3 \cdot 7H_2O$ ou de $Yb(OTf)_3$; ceci a permis de réaliser une synthèse facile d'un grand nombre d'adduits de Morita-Baylis-Hillman substitués et stéréochimiquement purs, y compris des adduits β,β-substitués.

Mots-clés : Morita–Baylis–Hillman, Knoevenagel, réduction, β,β-substitué.

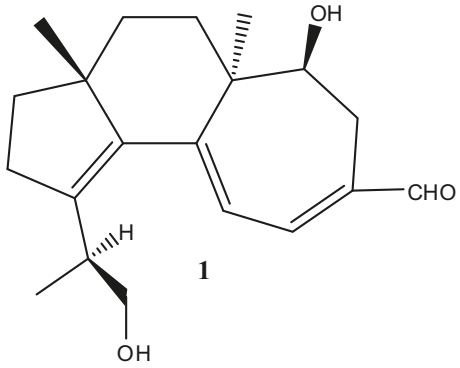
[Traduit par la Rédaction]

Introduction

There is significant interest in the field of natural product synthesis for the purpose of developing methodology for the synthesis of compounds with medicinal properties. Sarcodonin A (**1**) is a natural product found in the fungus *Sarcodon scabrosus*, which has been found to possess antibacterial and anti-inflammatory properties.[1] The cyanthane diterpenes are characterized by a fused 5,6,7-tricyclic array (Fig. 1), with most containing a C-3 isopropyl group that is not functionalized. Sarcodonin A is an exception, as it has an alcohol functionality at C-19, which generates a chiral centre at C-18. This increased level of oxidation makes the synthesis of sarcodonin A significantly more difficult than other members of the cyanthane family, since it requires controlling the configuration of a stereogenic centre on a pendant side chain relative to which it is attached. Since this particular type of stereochemical arrangement has been proven to be particularly troublesome to handle synthetically, this compound provides an interesting target to address this challenge.

Recently, the MaGee group[2] demonstrated that enantioselective deprotonation can be used to help address this problem. To implement this strategy for the synthesis of sarcodonin A, a potential symmetry in the molecule had to be delineated. Upon close examination it was envisioned that the left-hand portion of sarcodonin A could be constructed from the [3.2.1]-bicyclic diketone **4** (Scheme 1), thus, compounds like **2** became the lynchpin for our proposed synthesis.

Fig. 1. Sarcodonin A.



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There appeared to be several approaches for the construction of this type of structure; these included: (1) addition of an allyl cation, or equivalent, to a conjugated diene;[3] (2) [3 + 3] carbocyclization of a nitroallylic ester and an enamine;[4] and (3) an α,α′-annulation strategy[5] involving reaction between a cyclic enamine and a biselectrophile (i.e., a compound that could serve as both an alkylation and Michael addition agent) (Fig. 2). For our purposes, however, each

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Scheme 1. Retrosynthetic analysis of sarcodonin A.

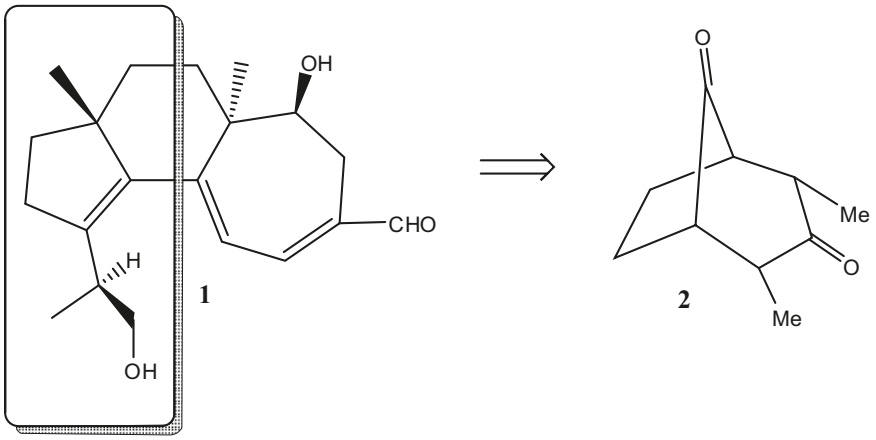
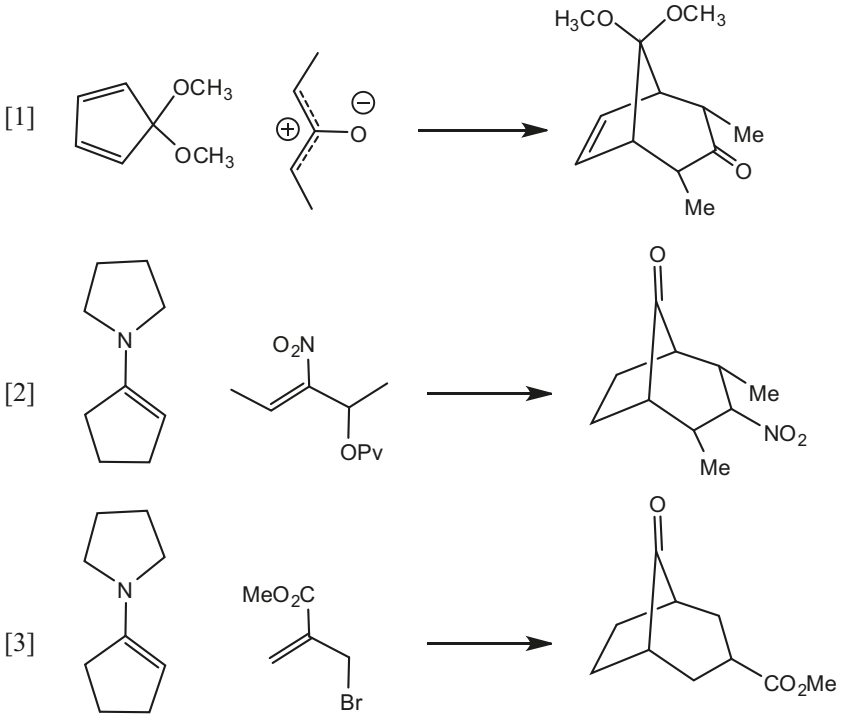


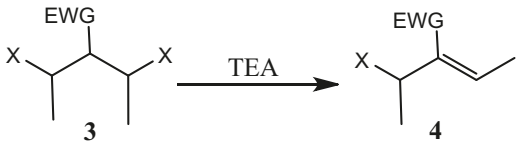
Fig. 2. Various approaches to construct [3.2.1]-bicyclic ketones.



approach had limitations. For instance, oxyallyl cation addition to 1,1-diethoxycyclopentadiene proceeds in very poor yield, which is unacceptable as the first step in a total synthesis. The [3 + 3]-carbocyclization route using nitroallylic esters proceeds in acceptable yields and is easily scaled up, however, all attempts to perform a Nef reaction failed.[6] Finally, the α,α′-annulation strategy efficiently generates compounds such as [3.2.1]-bicyclic ketones, however, it is underfunctionalized, and the ability to synthesize and use more highly substituted derivatives to participate in the annulation reaction has not been demonstrated.

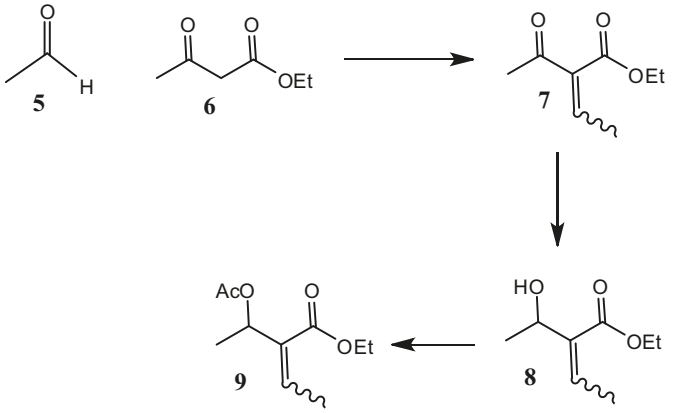
To solve the issue of underfunctionalization, compounds like **4** (Scheme 2) were required, and it was felt that these can potentially be accessed from Morita–Baylis–Hillman (MBH) adducts.[7] Unfortunately, β-branched MBH adducts are difficult to obtain using classical conditions, therefore, several chemical solutions have been reported.[8–15] Although each has their own advantages, they all have the limitation in requiring reactive organometallic and (or) toxic reagents and not being very amenable to scale up.

Scheme 2. An α,β-unsaturated compound suitably substituted for use in an α,α′-annulation sequence for sarcodonin A synthesis.



Given these limitations, an alternative route for the synthesis of the targeted annulation agent was sought. It was felt that the Knoevenagel reaction[16] between an aldehyde and ethyl acetoacetate would give rise to an α,β-unsaturated keto ester like **7**, and that upon reduction with an appropriate reducing agent would provide the MBH adduct **8** (Scheme 3). Although there was precedent for this approach,[17] in our

Scheme 3. Synthesis of Morita–Baylis–Hillman (MBH) adducts using the Knoevenagel condensation/reduction two-step protocol.



hands we routinely obtained low yields (>30%). If more substituted examples were used (e.g., Ph substituted on the alkene rather than methyl) then a much slower reduction occurred and did not have complete conservation of stereochemistry. Given these difficulties, we decided to investigate the breadth and scope of this reaction focusing on different substitution patterns, electron-withdrawing groups, and reduction conditions. Herein we report our study on the preparation of MBH adducts by this two-step protocol and show that it is rapid and generally applicable to the formation of β- and β,β-disubstituted MBH compounds.

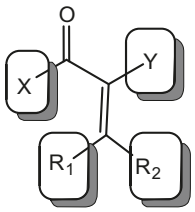
Results and discussion

The first step was the synthesis of the intermediate keto esters via a Knoevenagel condensation reaction. Literature reports have demonstrated this method to be appropriate for reactions between aromatic and aliphatic aldehydes, as well as different 1,3-dicarbonyl compounds[16] such as acetoacetates. The breadth of this reaction was attractive, since it would allow for the construction of a wide variety of adducts and thus permit the exploration of the scope of this two-step process.

In deciding what compounds should be generated, consideration was given to each quadrant of the alkene (Fig. 3). For instance, if Y were an ester then it could be easily varied from *tert*-butyl to methyl or benzyl to probe the sterics. It was also envisaged that electron-withdrawing groups (EWGs, Y) other than esters could be explored, such as a SO_2Ph, a ketone, or a cyano group. The ketone (X) could also be varied from a methyl to a branched or long-chain aliphatic ketone or to an aromatic ketone. Altering this quadrant allowed one to explore the effect of sterics on both the E:Z ratios obtained in the Knoevenagel condensations, as well as the ease of hydride reduction. Moving to the other quadrants of the double bond, R_1 and (or) R_2 could be replaced with branched or long-chain aliphatic or aromatic units. Finally, if both R_1 and R_2 were replaced with carbons then this would provide access to β,β-substituted adducts that could then be transformed into β,β-substituted MBH adducts; these are little known or studied compounds.

It is important to note that all of these alterations were important for obtaining a variety of substituted symmetrical and unsymmetrical compounds that have the potential to be very useful α,α′-annulation agents (biselectrophiles) for not only

Fig. 3. Different quadrants of the Knoevenagel condensation product.



the formation of substituted [3.2.1]-bicyclic diketones, but also a variety of other natural products. With this in mind, 18 different Knoevenagel products were synthesized following general procedures (Tables 1 and 2).

It was decided to first investigate what effect, if any, aromatic and aliphatic aldehydes had on the E and Z stereoselectivity when condensed with 1,3-dicarbonyl compounds. Thus, condensation of different acetoacetates with various aliphatic aldehydes (Table 1, entries 1–6) showed that regardless of whether a methyl, isopropyl, pentyl, or cyclohexyl group was on the terminus of the double bond, all condensations afforded roughly the same mixture of isomers (1.5–2.3:1) with Z being favoured over the E isomer in most cases. The exception to this was entry 6 where a *tert*-butyl group was able to confer complete stereochemical control, albeit in low chemical yield.

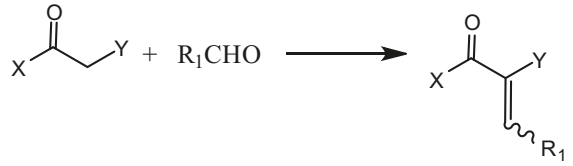
Other notable results obtained are entries 7–9 (Table 1), where the ester functionality was varied from methyl to *tert*-butyl to benzyl. It was found that increasing the bulk of the EWG group also increased the selectivity of the reaction in favour of the Z isomer. This was surprising, since it was expected that E stereoselectivity would be preferred as one increased the size of the ester group.[18] However, Tanikaga et al.[19] demonstrated that the stereoselectivity of the Knoevenagel product is affected by slight differences in steric requirements between the two EWGs and when the differences between X, Y, and R_2 (Fig. 3) are rather small then selectivity in favour of the Z isomer is preferred.

The effect of EWGs other than esters was also investigated. In entry 11 (Table 1), a sulfone was used for comparison and, as reported by Tanikaga et al.,[20] an overwhelming preference for the E-isomer was observed. However, as expected,[21] use of a cyano group (Table 1, entry 14) in place of an ester preferentially gave the Z-isomer.

Continuing with this survey of different combinations, various alkyl groups were substituted on the ketone (Table 1, entries 10, 12, and 13) to assess if improved selectivity could be obtained and if the reduction would tolerate increased steric hindrance near the ketone. Not surprisingly, as the steric hindrance around the ketone increased there was an improvement in the stereochemical purity. This increase in stereoselectivity came at a price as the yield of Knoevenagel product decreased substantially as the acetoacetate became bulkier.

With a large number of aldehydes screened, a decision was made to look at the possibility of doing the condensation with a number of ketones ranging from straight-chain aliphatic (symmetric and unsymmetric), to cyclic aliphatic, to heterocyclic. These were condensed with ethyl acetoacetate to form β,β-substituted Knoevenagel products (Table 2).

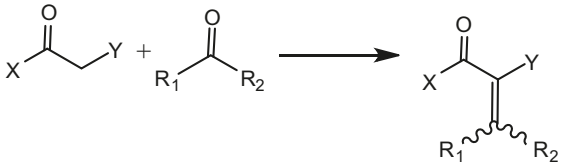
Table 1. Synthesis of β-substituted unsaturated keto esters by the Knoevenagel condensation reaction.



Entry	X	Y	R′	Time (h)	Product	Yield (%)	Isomer ratio (E:Z)	Method
1	Me	CO_2t-Bu	Me	12	10	83	1:2.3	A
2	Me	CO_2t-Bu	*i*-Pr	12	11	70	1:2.3	A
3	Me	CO_2t-Bu	$(CH_2)_4CH_3$	10	12	80	2:3	A
4	Me	CO_2Me	C_6H_{11}	4	13	84	2:3	A
5	Me	CO_2Me	$(CH_2)_4CH_3$	4	14	20	1:2	B
6	Me	CO_2Et	*t*-Bu	12	15	14	Z	B
7	Me	CO_2Me	Ph	3	16	80	1:1	B
8	Me	CO_2Bn	Ph	3	17	77	2:3	B
9	Me	CO_2t-Bu	Ph	10	18	50	Z	B
10	Ph	CO_2Et	Ph	3	19	70	Z	B
11	Ph	SO_2Ph	Ph	12	20	78	E	B
12	*i*-Pr	CO_2Me	Ph	3	21	60	1.8:1	B
13	*t*-Bu	CO_2Me	Ph	10	22	18	Z	B
14	Ph	CN	C_6H_{11}	48	23	50	Z	C

Note: Reagents: (A) CH_3COCH_2–Y; RCHO; piperidine; EtOH; 0 °C; (B) X–$COCH_2$–Y; RCHO; piperidine; AcOH; benzene; reflux; (C) $PhCOCH_2CN$; RCHO; proline; EtOH; room temperature (RT).

Table 2. Synthesis of β,β-substituted unsaturated keto esters by the Knoevenagel condensation reaction using the Lewis acids $ZnCl_2$ or $TiCl_4$.



Entry	X	Y	R′, R″	Time (h)	Product	Yield (%)
1	Me	OEt	Me, Me	72	24	42
2	Me	OEt	$(CH_2)_5$	16	25	28
3	Me	OEt	$(CH_2)_4$	16	26	38
4	Me	OEt	$C(C_2H_4)_2NCO_2CH_3$	16	27	32
5	Me	OEt	Me, C_7H_{15}	16	28	27

With a number of Knoevenagel condensation products in hand, the stage was set to look at the critical 1,2-hydride reduction. Upon examination of the literature there appeared to be several approaches. The first method to be studied was reduction using Luche conditions.[22] The advantage of this method was that selective 1,2-reduction could be obtained under conditions that did not affect other functional groups such as carboxylic acids, esters, amides, or nitro groups.[19] Furthermore, the reaction could be conducted at room temperature without the special exclusion of air or moisture. Even though there was a lot of precedent literature that consistently showed that Luche conditions were the appropriate choice for the selective 1,2-reduction of α-enones, it was not clear how it was going to perform on keto esters like **7**, as there were few reports of its use for the reduction of β′-oxocarbonyl compounds.[23] Regardless, following the procedure outlined by Luche, compounds **16** and **17** were treated with 1 mol equiv of sodium borohydride and cerium trichloride in methanol at 0 °C and room temperature (to assess the influence of temperature on the yield) to provide allylic alcohols **29** and **30** in 34%–80% overall yield (Table 3). From these results it was clear that effecting the reduction at room temperature gave the best results.

Of note in this preliminary investigation was the fact that, even though the reaction was started with a 1:1 mixture of isomers, the final stereoisomeric ratio of the products was found to be 2:3. There were several possibilities to account for this. Firstly, if the reduction of one isomer was faster than the other and the rate of isomerization of the starting materials was approximately the same as the reduction, then this would lead to a preponderance of one isomer. A second possibility was that there was some isomerization that took place after the reduction had occurred, presumably this would lead to a predominance of the thermodynamic product. Finally, it is possible that the reduction of one isomer was much more efficient than the other.

Table 3. Reduction of Knoevenagel condensation products **16** and **17** to allylic alcohols **29** and **30** using Luche conditions.

Starting material (E:Z isomer ratio)	Temp. (°C)	Time (h)	Product	Yield (%)	Isomer ratio (E:Z)
16 (1:1)	0	2	**29**	50	2:3
16 (1:1)	25	2	**29**	80	2:3
17 (2:3)	0	2	**30**	34	2:3
17 (2:3)	25	2	**30**	77	2:3

With the optimal conditions for the Luche reduction obtained, other reducing agents were investigated to see if greater success could be realized; these included lithium tri-*tert*-butoxyaluminium hydride (LATB-H),[24] borane methyl sulfide complex (BMS),[25] and $Yb(OTf)_3$[26] (Table 4). Of these, only $Yb(OTf)_3$ consistently reduced the ketone; however, the yields were substantially inferior to the yields under Luche conditions.

Based on the optimized conditions, all of the compounds in Tables 1 and 2 were reduced using the Luche method, and the results are summarized in Table 5. It was observed that as the substituent on the terminus of the alkene increased in size, the yield of the reduction product improved (Table 5, entries 1–7). This was presumably due to a diminution of competing side reactions such as Michael addition, self-condensation, or 1,4-reduction. This was especially true for the methyl-substituted compound (Table 5, entries 1 and 2) where it was observed that good yields could only be realized if the reduction was allowed to run for only a few seconds. It was also observed that in most cases it was possible to obtain pure isomers when starting with either pure E or Z starting material. The exception to this was the phenyl ketone **16**, for which the same isomer ratio of products was obtained after reduction regardless of the isomer ratio of the starting ketones.

Another notable result was the reduction of the cyano compound (Table 5, entry 18). It was found that the desired reduction product (Z-isomer) along with the fully reduced product, in which the double bond was also reduced, was obtained in approximately a 1:1 ratio. Although the desired product was present, the two compounds were found to be inseparable by column chromatography; thus, pure MBH adduct could not be achieved by this method.

Having succeeded with the reduction of the β-substituted Knoevenagel condensation products, the reduction of the β,β-substituted 1,3-dicarbonyl compounds was examined (Table 5). All the ketones (**24**–**28**) reduced very efficiently and in a short period of time (15 min) to produce the β,β-substituted MBH adducts in good to excellent yields. Of particular note is entry 23 (Table 5) where compound **52** was obtained in 71%; this result shows that additional functional groups may be present without adversely affecting the reduction.

α,α′-Annulation strategy for construction of the [3.2.1]-bicyclic ketone

With a suitable method available to generate amounts of alcohol **31** in hand, investigation into transforming it to the targeted annulation agent **57** was undertaken (Scheme 4). Fortunately, when alcohol **31** was treated with triphenylphosphine and *N*-bromosuccinimide (NBS)[27] at –30 °C, allylic bromide **55** was obtained in 48% yield as a 1:1 mixture of E- and Z-isomers. Alternatively, **31** could be efficiently acylated with acetyl chloride, pivaloyl chloride, and methyl chloroformate in 71%, 65%, and 73% yields, respectively.[4,17] Treatment of each of these biselectrophiles with 1-pyrrolidino-1-cyclopentene (**56**) with and without triethylamine in refluxing ethanol or acetonitrile provided variable success, with the desired cycloadducts, **57a** and **57b**, being most efficiently produced in 43% yield as a 1:1 mixture of isomers using bromide **55**.

Table 4. Reduction of selected Knoevenagel products with tri-*tert*-butoxyaluminium hydride (LATB-H), borane methyl sulfide complex (BMS), and $Yb(OTf)_3$.

Reducing agents	Starting material (E:Z isomer ratio)	Time (h)	Product	Yield (%)	Isomer ratio (E:Z)
LATB-H	**16** (1:1)	2	**29**	nr	—
	19 (0:1)	2	**43**	nr	—
BMS	**16** (1:1)	3	**29**	40	2:3
	17 (2:3)	3	**30**	27	2:3
	18 (0:1)	3	**42**	10	Z
	19 (0:1)	3	**43**	nr	—
	21 (2:1)	3	**45/46**	10	2:3
$Yb(OTf)_3$	**16** (1:1)	2	**29**	20	2:3
	17 (2:3)	2	**30**	10	2:3
	18 (0:1)	2	**42**	40	Z
	19 (0:1)	2	**43**	nr	—-

Note: nr, no reaction.

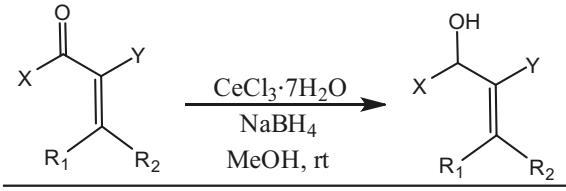
The isolated products were determined to be an approximately 50:50 mixture of symmetric and asymmetric esters based on an analysis of the ^1H and ^{13}C NMR spectra. The stereochemistries of the esters were assigned on the basis of correlations observed in the NOESY spectrum of the mixture. For the symmetric ester, the methine hydrogens on the carbons bearing the methyl groups were assigned as equatorial based on NOESY correlations observed between these hydrogens and the axial methylene hydrogens. The ester was assigned as axial based on NOESY correlations observed between the axial methyl hydrogens and the methine hydrogen on the carbon bearing the ester group (Fig. 4, **57a**).

A similar analysis for the asymmetric ester determined the ester group to be axial. For the side of the molecule with the methyl group axial, NOESY correlations similar to those for the symmetric ester were observed, with an additional NOESY correlation observed between the methyl hydrogens and the axial methine hydrogen on the carbon bearing the equatorial methyl group. In addition, NOESY correlations were observed between the equatorial methyl hydrogens and one of the axial methylene hydrogens (Fig. 4, **57b**).

Conclusion

In conclusion, a large number of β- and β,β-substituted α,β-unsaturated keto esters were synthesized using the Knoevenagel condensation. For the synthesis of the β-keto esters, it was demonstrated that the stereoselectivity of the reaction was improved by alteration of various substituents on the ketone, ester group, and various aldehydes. From our results, a Z-selective Knoevenagel condensation can be achieved by the use of *tert*-butyl acetoacetate with either aromatic or aliphatic

Table 5. Reduction of the Knoevenagel condensation products using Luche conditions.



Entry	X	Y	R_1, R_2	Time	Product	Yield (%)	Isomer ratio (E:Z)
1	Me	CO_2t-Bu	Me, H	0.5 min	**31**	66	E
2	Me	CO_2t-Bu	H, Me	1 min	**32**	68	Z
3	Me	CO_2t-Bu	*i*-Pr, H	3 min	**33**	79	E
4	Me	CO_2t-Bu	H, *i*-Pr	3 min	**34**	66	Z
5	Me	CO_2t-Bu	$(CH_2)_4CH_3$, H	5 min	**35**	75	E
6	Me	CO_2t-Bu	H, $(CH_2)_4CH_3$	5 min	**36**	72	Z
7	Me	CO_2Et	*t*-Bu, H	3 min	**37**	92	Z
8	Me	CO_2Me	$(CH_2)_4CH_3$, H	2 h	**38**	40	E
9	Me	CO_2Me	H, $(CH_2)_4CH_3$	2 h	***ſ*39**	49	Z
10	Me	CO_2Me	C_6H_{11}, H	5 min	**40**	52	E
11	Me	CO_2Me	H, C_6H_{11}	5 min	**41**	56	Z
12	Me	CO_2t-Bu	Ph, H	2 h	**42**	60	Z
13	Ph	CO_2Et	Ph, H	2 h	**43**	77	Z
14	Ph	SO_2Ph	Ph, H	15 min	**44**	40	E
15	*i*-Pr	CO_2Me	Ph, H	2 h	**45**	65	E
16	*i*-Pr	CO_2Me	H, Ph	2 h	**46**	71	Z
17	*t*-Bu	CO_2Me	Ph, H	2 h	**47**	nr	—
18	Ph	CN	C_6H_{11}, H	5 min	**48**	52	Z
19	Me	CO_2Et	Me, Me	15 min	**49**	91	—
21	Me	CO_2Et	$(CH_2)_5$	15 min	**50**	91	—
22	Me	CO_2Et	$(CH_2)_4$	15 min	**51**	90	—
23	Me	CO_2Et	$(C_2H_4)_2NCO_2CH_3$	15 min	**52**	71	—
24	Me	CO_2Et	CH_3, nC_7H_{15}	15 min	**53**	82	Z
25	Me	CO_2Et	nC_7H_{15}, CH_3	15 min	**54**	82	E

Note: nr, no reaction.

Scheme 4. Synthesis of a [3.2.1]-bicyclic ketone using a Morita–Baylis–Hillman (MBH) adduct as a biselectrophile.

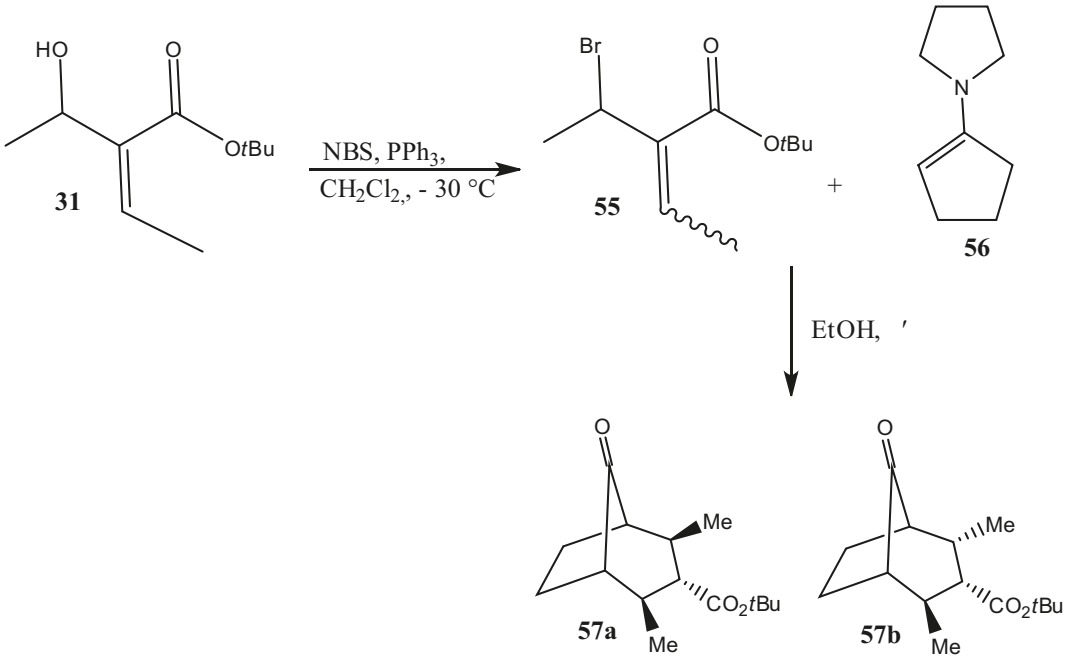
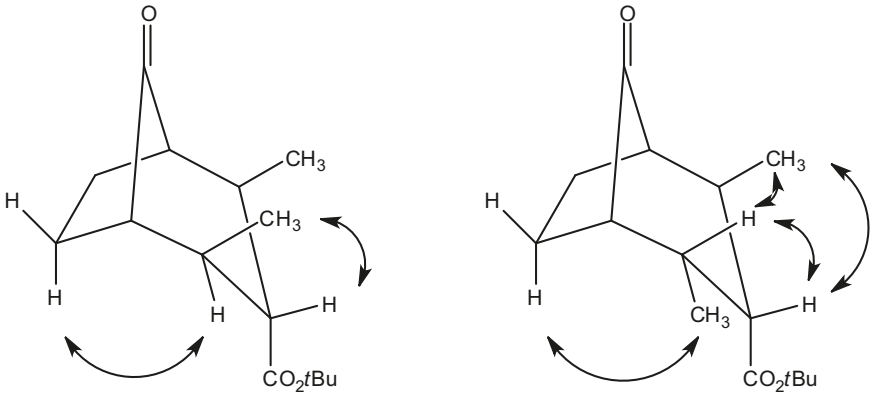


Fig. 4. Partial NOESY correlations observed for the (A) symmetric ester and (B) asymmetric ester.



57a **57b**

aldehydes. An added advantage of the *tert*-butyl ester derivatives was that it allowed for easy chromatographic separation of the stereoisomers. Although there were a few examples of complete Z selectivity, for the most part ratios of approximately 70:30 were routinely obtained. A number of β,β-substituted Knoevenagel condensation products were also obtained by the use of various symmetrical and unsymmetrical ketones with $TiCl_4$ or zinc chloride. In the case of an unsymmetrical ketone a 1:1 mixture of isomers was obtained.

These β- and β,β-substituted keto ester compounds were subjected to a variety of different reducing conditions to generate substituted MBH products, many of them previously unknown and inaccessible via traditional MBH methods. It was found that the reduction of these β-oxoesters was most successful using Luche conditions with good to excellent yields (40%–92%) being obtained within a few minutes at room temperature. In most cases, it was determined that there was no scrambling of the stereochemistry when either pure E- or Z-isomers were reduced. Since it is well-documented that Knoevenagel products are readily isomerized by simple heating,[28] this is important because, coupled with the ability to separate them by chromatography, it offers the potential of cycling both β-oxoester compounds to either MBH product in a stereochemically pure fashion.

Studies aimed at using these substituted MBH adducts for a variety of different synthetic endeavors are currently underway and results will be communicated in due course.

General experimental procedures

All reactions were carried out in flame-dried round bottom flasks (RBF) or in oven-dried glassware (pyrex) (140 °C, 1 h) unless stated otherwise. Temperatures indicated refer to an external bath. All reactions were magnetically stirred, unless stated otherwise. Standard techniques were used for solvent purifications. Anhydrous reaction solvents were available via the use of Grubbs-type columns. Air- and moisture-sensitive reagents were handled via standard techniques. Reagents were purchased from common suppliers and used as received unless stated otherwise. SiO_2 flash chromatography was performed using Silicycle silica gel (30–60 μm particle size). Nuclear magnetic resonance (NMR) spectroscopy was performed on a Varian INOVA 300 MHz or on a Varian UNITY 400 MHz (referred to proton resonance frequency). ^{1}H NMR spectroscopic data are presented in parts per million (δ) relative to tetramethylsilane as an internal standard. All proton–proton NMR coupling constants (*J*) are expressed in Hertz (Hz). ^{13}C NMR data are presented in parts per million (δ) relative to $CDCl_3$ (77.16 ppm) as an internal standard unless otherwise stated. Infrared spectra (IR) were recorded on a NEXUS 470 FTIR. Main peaks are reported as wavenumbers in cm^{-1}. High-resolution mass spectra (HRMS) were recorded using a Waters Xevo Q-Tof mass spectrometer. Samples were dissolved into a mixture of acetonitrile / deionized water / formic acid (50%:50%:0.1% composition), filtered on a 0.2 μm membrane filter, and then immediately introduced into the instrument by infusion at a rate of 10 μL/min. The ionization mode was electrospray positive (ESI+), which predominantly produced protonated cations ($[M + H]^+$ species). High-resolution spectra were acquired using a sodium formate solution as a lock mass reference solution and used as a mass correction when acquiring the sample spectra. ESI$^+$ conditions were optimized with a capillary voltage between 2 kV, a sample cone of 30, an extraction cone of 3.0, a source temperature of 120 °C, a desolvation temperature of 200 °C, a desolvation gas flow of 500 L/h, and a cone gas flow of 10 L/h. The MS data were acquired over a range of 20–1000 *m/z* with a scan duration of 1 s. Melting points were measured on a Gallenkamp melting point apparatus and all melting points are uncorrected.

General procedure for the synthesis of α,β-unsaturated dicarbonyl compounds 10–13

To a cooled (0 °C) mixture of aldehyde (50 mmol) and acetoacetate (15 mmol) was added a mixture of piperidine (0.03 mL) and EtOH (0.025 mL). The mixture was stirred at 0 °C for 12 h, and the reaction was quenched with cold aqueous 20% tartaric acid. The products were extracted with ethyl acetate, and the extracts were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2, hexane–AcOEt 10:1).

Preparation of tert-*butyl (*E*)- and (Z)-2-acetyl-but-2-enoate (10)*

Following the general procedure, esters **10a** and **10b** were formed in 83% yield (2.2 g) as a 1.2:3 mixture of E- and Z-isomers.[16]

Preparation of **tert-*butyl* (E)-** *and* **(Z)-2-acetyl-4-methylpent-2-enoate (11)**

Following the general procedure, esters **11a** and **11b** were formed in 70% yield (2.23 g) as a 1.2:3 mixture of E- and Z-isomers.[16]

Preparation of **tert-*butyl* (E)-** *and* **(Z)-2-acetyloct-2-enoate (12)**

Following the general procedure, esters **12a** and **12b** were formed in 80% yield as a 2:3 mixture of E- and Z-isomers. (Z)-Isomer **12a**: IR (neat, cm^{-1}): 2985, 1724, 1657, 1625, 1577, 1497, 1448, 1394, 1234, 1213, 1043, 949, 890, 757, 695. ^1H NMR ($CDCl_3$, 300 MHz) δ: 0.93 (t, 3H, J = 7.0 Hz), 1.21–1.51 (m, 8H), 1.52 (s, 9H), 2.31 (s, 3H), 6.82 (t, 1H, J = 9.5 Hz). ^{13}C NMR ($CDCl_3$, 300 MHz) δ: 22.0, 29.8, 52.0, 70.0, 126.0, 128.7, 129.6, 130.5, 133.3, 135.8, 139.9, 168.6. HRMS (M^+ + H) calcd for $C_{14}H_{25}O_3$: 241.1801; found: 241.1803. (*E*)-Isomer **12b**: IR (neat, cm^{-1}): 2985, 1724, 1657, 1625, 1577, 1497, 1448, 1394, 1234, 1213, 1043, 949, 890, 757, 695. ^1H NMR ($CDCl_3$, 300 MHz) δ: 0.89 (t, 3H, J = 6.8 Hz), 1.21–1.40 (m, 8H), 1.50 (s, 9H), 2.33 (s, 3H), 6.80 (t, 1H, J = 7.8 Hz). ^{13}C NMR ($CDCl_3$, 400 MHz) δ: 13.9, 22.3, 28.0, 29.1, 31.0, 31.4, 81.8, 137.2, 147.6, 163.7, 201.6. HRMS (M^+ + H) calcd for $C_{14}H_{25}O_3$: 241.1804; found: 241.1804.

Preparation of methyl **(E)-** *and* **(Z)-2-(cyclohexylmethylene)-3-oxobutanoate (13)**

Following the general procedure, esters **13a** and **13b** were formed in 84% yield as a 2:3 mixture of E- and Z-isomers.[23]

General procedure for the synthesis of α,β-unsaturated dicarbonyl compounds 14–22 using the Knoevenagel condensation reaction

1,3-Dicarbonyl compound (10 mmol), benzene (50 mL), aldehyde (10 mmol), glacial acetic acid (1 mmol), and piperidine (1 mmol) were placed in an oven-dried RBF equipped with a Dean–Stark apparatus. The mixture was heated to reflux and maintained there until TLC showed the complete consumption of starting material. Upon cooling to room temperature, the solution was diluted with diethyl ether (50 mL) and water (25 mL). The organic layer was separated and washed with water (25 mL), 1 mol/L HCl solution (2 × 25 mL), and then sodium hydrogen carbonate solution until neutrality was reached. The organic layer was dried (Na_2SO_4), filtered, and the solvent evaporated in vacuo. The crude product was purified by flash chromatography (hexane – diethyl ether).

Preparation of methyl **(E)-** *and* **(Z)-2-acetyloct-2-enoate (14)**

Following the general procedure, esters **14a** and **14b** were formed in 70% yield as a 1:2 mixture of E- and Z-isomers.[16]

Preparation of ethyl **(Z)-2-acetyl-4,4-dimethylpent-2-enoate (15)**

Following the general procedure, ester **15** was formed in 24% yield as a single Z-isomer.[29]

Preparation of methyl **(E)-** *and* **(Z)-2-benzylidene-3-oxobutanoate (16)**

Following the general procedure, esters **16a** and **16b** were formed in 80% yield as a 1:1 mixture of E- and Z-isomers.[16]

Preparation of benzyl **(E)-** *and* **(Z)-2-benzylidene-3-oxobutanoate (17)**

Following the general procedure, esters **17a** and **17b** were formed in 77% yield as a 2:3 mixture of E- and Z-isomers.[30]

Preparation of **tert-*butyl* 2-benzylidene-3-oxobutanoate (18)**

Following the general procedure, ester **18** was formed in 50% yield as a single Z-isomer.[31]

Preparation of ethyl **(Z)-2-benzoyl-3-phenylacrylate (19)**

Following the general procedure, ester **19** was formed in 70% yield as a single Z-isomer.[16,32]

Preparation of **(E)-1,3-diphenyl-2-(phenylsulfonyl)prop-2-en-1-one (20)**

Following the general procedure, ester **20** was formed as a brown solid that was recrystalized from ethanol to give 2.7 g (78% yield) of the E-isomer.[7] mp 135–136.5 °C (lit.[7] 136 °C).

Preparation of methyl **(E)-** *and* **(Z)-2-isobutyryl-3-phenylacrylate (21)**

Following the general procedure, ester **21** was formed in 60% yield as an 1.8:1 mixture of E- and Z-isomers.[16,33]

Preparation of methyl **2-benzylidene-4,4-dimethyl-3-oxopentanoate (22)**

Following the general procedure, ester **22** was formed in 18% yield as a Z-isomer.[34]

Preparation of (Z)-3-cyclohexyl-2 (benzo)acrylonitrile (23)

In a RBF under argon was added benzoylacetonitrile (1.45 g 10.0 mmol) and ethanol (30 mL). To this, L-proline (0.23 g, 2.0 mmol) and cyclohexane carboxaldehyde (1.21 mL, 10.0 mmol) were added. The mixture was allowed to stir at room temperature for 48 h. It was then concentrated in vacuo and purified via SiO_2 chromatography (15:1 hexane – ethyl acetate) to give 1.19 g (50% yield) of **23** as a clear yellow oil.[35]

Preparation of ethyl α-isopropylidine acetoacetate (24)

Ethyl acetoacetate (13.0 g, 0.100 mol), acetone (8.7 g, 0.15 mol), acetic anhydride (12.8 mL), and fused zinc chloride (1.9 g) were heated under reflux for 72 h. After cooling, diethyl ether (25 mL) was added and the resulting solution was washed with water (4 × 25 mL). The combined water washings were extracted with Et_2O (50 mL), and the combined organic extracts were dried with $MgSO_4$, filtered, and the solvent evaporated under reduced pressure. The oily residue was purified via SiO_2 chromatography (10:1 hexane – AcOEt) to give 7.42 g (42%) of **17** as a yellow oil.[36]

General procedure for the synthesis of α,β-unsaturated dicarbonyl compounds 25–28 using $TiCl_4$

CH_2Cl_2 (20 mL) and THF (20 mL) were placed in a RBF cooled to 0 °C. To this $TiCl_4$ (2.2 mL, 20 mmol) was carefully added dropwise, followed by ketone (10 mmol) and ethyl acetoacetate (1.08 mL, 10 mmol) in THF (5 mL). After complete addition, pyridine (3.2 mL, 40 mmol) was added and the solution was allowed to slowly warm to room temperature and stir for 16 h. The reaction mixture was diluted with H_2O and ethyl acetate (1:1, 100 mL) and the aqueous

phase was separated. The organic phase was washed with H_2O (3 × 50 mL), $NaHCO_3$, and brine and then dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The oily residue was purified via SiO_2 chromatography (7:1 hexane – ethyl acetate).

Preparation of ethyl α-cyclohexylidine acetoacetate (25)

Following the general procedure, ester **18** was formed in 38% yield (0.75 g) as a pale yellow oil.[37]

Preparation of ethyl α-cyclopentylidine acetoacetate (26)

Following the general procedure, ester **19** was formed in 28% yield (0.55 g) as a pale yellow oil.[38]

Preparation of methyl 4-(1-(ethoxycarbonyl)-2-oxopropylidine)piperdine-1-carboxylate (27)

Following the general procedure, ester **20** was formed in 32% yield (0.8 g) as a pale yellow oil.[39]

Preparation of ethyl (*E*)- and (*Z*)-2-acetyl-3-methyldec-2-enoate (28)

Following the general procedure, esters **28a** and **28b** were formed in 27% yield (0.64 g) as colourless oils in a 1.25:1 mixture of E- and Z-isomers. *Z*-Isomer **28a**: IR (neat, cm^{-1}): 2954, 2929, 2857, 1725, 1700, 1624, 1466, 1354, 1225, 1119, 1053. ^1H NMR ($CDCl_3$, 300 MHz) δ: 0.88 (t, 3H, J = 7.1 Hz), 1.22–1.38 (m, 8H), 1.30 (t, 3H, J = 7.0 Hz), 1.42–1.55 (m, 2H), 1.95 (s, 3H), 2.28 (s, 3H), 2.34–2.42 (m, 2H), 4.24 (q, 2H, J = 7.2 Hz). ^{13}C NMR ($CDCl_3$, 300 MHz) δ: 14.3, 21.3, 22.8, 28.2, 29.2, 29.9, 30.8, 31.8, 31.9, 36.8, 60.9, 132.1, 157.4, 166.3, 200.3. HRMS (M^+ + H) calcd for $C_{15}H_{27}O_3$: 255.1961; found: 255.1960. *E*-Isomer **28b**: IR (neat, cm^{-1}): 2928, 2857, 1725, 1722, 1625, 1466, 1355, 1273, 1225, 1118, 1056. ^1H NMR ($CDCl_3$, 300 MHz) δ: 0.87 (t, 3H, J = 7.0 Hz), 1.18–1.35 (m, 8H), 1.29 (t, 3H, J = 7.2 Hz), 1.42–1.60 (m, 2H), 2.08 (s, 3H), 2.14–2.21 (m, 2H), 2.28 (s, 3H), 4.22 (q, 2H, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$, 300 MHz) δ: 14.26, 14.3, 20.8, 22.8, 28.3, 29.2, 29.9, 31.2, 31.9, 37.1, 60.9, 132.2, 157.4, 165.9, 201.0. HRMS (M^+ + H) calcd for $C_{15}H_{27}O_3$: 255.1961; found: 255.1960.

General procedure for the reduction of Knoevenagel adducts using Luche conditions

Adducts **10**–**28** (1 mmol) and $CeC1_3{\cdot}7H_2O$ (1 mmol) were dissolved in methanol (2.5 mL) and $NaBH_4$ (38 mg, 1 mmol) was added in one portion with stirring. A vigorous gas evolution occurred and then stirring was continued for the specified time before the pH was adjusted to neutrality with dilute aqueous HCl. The mixture was extracted with diethyl ether (3 × 15 mL), the combined organic extracts were dried over $MgSO_4$, and the solvent evaporated under reduced pressure. The crude product was analyzed for quantitative isomer determination by ^1H NMR. It was then purified by column chromatography and identified by the usual spectroscopic methods.

Preparation of methyl (E)- and (Z)-2-benzylidene-3-hydroxybutanoate (29)

Following the general procedure (15 min), alcohols **29a** and **29b** were formed in 80% yield as a 2:3 mixture of E- and Z-isomers.[40]

Preparation of benzyl (E)- and (Z)-2-benzylidene-3-hydroxybutanoate (30)

Following the general procedure (15 min), alcohols **30a** and **30b** were formed in 77% yield as a 2:3 mixture of E- and Z-isomers. Z-Isomer **30a**: IR (neat, cm^{-1}): 3421, 3031, 2974, 1718, 1497, 1455, 1385, 1212, 1142, 1014, 921, 751, 697. ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.44 (d, 3H, J = 6.5 Hz), 2.35 (d, 1H, J = 6.2 Hz), 4.64 (q, 1H, J = 6.3 Hz), 5.16 (s, 2H) 6.85 (s, 1H), 7.23–7.60 (m, 10H). ^{13}C NMR ($CDCl_3$, 400 MHz) δ: 22.4, 66.8, 69.9, 128.1, 128.2, 128.4, 128.5, 132.7, 135.0, 135.4, 137.5, 168.8. HRMS (M^+ + H) calcd for $C_{18}H_{19}O_3$: 283.1334; found: 283.1334. E-Isomer **30b**: IR (neat, cm^{-1}): 3421, 3031, 2974, 1718, 1497, 1455, 1385, 1212, 1142, 1082, 1014, 921, 751, 697. ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.48 (d, 3H, J = 6.5 Hz), 2.20 (s, 1H, J = 6.3 Hz), 4.84 (q, 1H, J = 5.9 Hz), 5.16 (s, 2H), 7.21–7.43 (m, 10H), 7.85 (s, 1H). ^{13}C NMR ($CDCl_3$, 400 MHz) δ: 23.3, 65.0, 66.8, 128.3, 128.5, 128.6, 128.7, 128.9, 129.2, 134.5, 135.6, 140.0, 167.5. HRMS (M^+ + H) calcd for $C_{18}H_{19}O_3$: 283.1334; found: 283.1334.

Preparation of tert*-butyl (E)-2-(1-hydroxyethyl)-but-2-enoate (31)*

Following the general procedure (15 s), E-alcohol **31** was formed in 66% yield as a colourless oil. IR (neat, cm^{-1}): 3508, 2977, 2932, 1683, 1645, 1456, 1368, 1322, 1291, 1149, 1060, 988, 897, 761. ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.39 (d, 3H, J = 6.7 Hz), 1.51 (s, 9H), 1.80 (d, 3H, J = 7.4 Hz), 3.80 (b, 1H), 4.70 (q, 1H, J = 6.7 Hz), 6.69 (q, 1H, J = 7.4 Hz). ^{13}C NMR ($CDCl_3$, 300 MHz) δ: 13.7, 23.4, 28.4, 64.9, 81.5, 136.2, 136.8, 166.9. HRMS (M^+ + H) calcd for $C_{10}H_{19}O_3$: 187.1334: found: 187.1332.

Preparation of tert*-butyl (Z)-2-(1-hydroxyethyl)-but-2-enoate (32)*

Following the general procedure (15 s), Z-alcohol **32** was formed in 68% yield as a colourless oil. IR (neat, cm^{-1}): 3462, 2977, 1684, 1645, 1456, 1368, 1291, 1148, 1104. ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.34 (d, 3H, J = 6.5 Hz), 1.53 (s, 9H), 1.95 (d, 3H, J = 7.2 Hz), 4.40 (q, 1H, J = 6.5 Hz), 6.15 (q, 1H, J = 7.2 Hz). ^{13}C NMR ($CDCl_3$, 300 MHz) δ: 15.5, 22.5, 28.5, 70.3, 81.8, 134.7, 137.4, 167.4. HRMS (M^+ + H) calcd for $C_{10}H_{19}O_3$: 187.1334; found: 187.1332.

Preparation of tert*-butyl (E)-2-(1-hydroxyethyl)-4-methylpent-2-enoate (33)*

Following the general procedure (1 min), E-alcohol **33** was formed in 79% yield as a colourless oil. IR (neat, cm^{-1}): 3514, 2969, 2932, 2871, 1684, 1641, 1457, 1368, 1324, 1276, 1153, 1120, 1065, 900, 773. ^1H NMR ($CDCl_3$, 300 MHz) δ: 0.98 (d, 3H, J = 6.7 Hz), 1.03 (d, 3H, J = 6.7 Hz), 1.38 (d, 3H, J = 6.7 Hz), 1.50 (s, 9H), 2.60–2.75 (m, 1H), 3.71 (d, 1H, J = 10.9 Hz), 4.61–4.72 (m, 1H), 6.35 (d, 1H, J = 10.3 Hz). ^{13}C NMR ($CDCl_3$, 300 MHz) δ: 22.4, 22.5, 24.0, 27.3, 28.4, 65.3, 81.5, 133.1, 148.5, 167.3. HRMS (M^+ + H) calcd for $C_{12}H_{23}O_3$: 215.1647; found: 215.1647.

Preparation of* tert-*butyl (Z)-2-(1-hydroxyethyl)-4-methylpent-2-enoate (34)

Following the general procedure (1 min), Z-alcohol **34** was formed in 66% yield as a colourless oil. IR (neat, cm^{-1}): 3514, 2969, 2932, 2871, 1684, 1641, 1457, 1368, 1324, 1276, 1153, 1120, 1065, 900, 773. ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.03 (d, 3H, J = 6.7 Hz), 1.38 (d, 3H, J = 6.7 Hz), 1.50 (s, 9H), 2.70 (d, 1H, J = 6.2 Hz), 3.00–3.06 (m, 1H), 4.61–4.72 (m, 1H), 6.35 (d, 1H, J = 10.3 Hz). ^{13}C NMR ($CDCl_3$, 300 MHz) δ: 22.65, 22.78, 22.79, 28.39, 28.44, 65.3, 81.8, 134.4, 146.0, 167.6. HRMS (M^+ + H) calcd for $C_{12}H_{23}O_3$: 215.1647; found: 215.1647.

Preparation of* tert-*butyl (E)-2-(1-hydroxyethyl)oct-2-enoate (35)

Following the general procedure (5 min), E-alcohol **35** was formed in 75% yield as a colourless oil. IR (neat, cm^{-1}): 3471, 2960, 2930, 2857, 1686, 1454, 1368, 1277, 1148, 1066, 850. ^1H NMR ($CDCl_3$, 300 MHz) δ: 0.91 (t, 3H, J = 7.0 Hz), 1.30–1.51 (m, 8H) 1.62 (s, 9H), 2.80 (bs, 1H) 2.28 (s, 3H), 4.41 (q, 1H, J = 6.5 Hz), 6.61 (t, 3H, J = 6.7 Hz). ^{13}C NMR ($CDCl_3$, 300 MHz) δ: 13.9, 22.5, 28.1, 28.3, 32.0, 82.2, 137.7, 146.9, 148.0, 163.1, 166.1, 195.0. HRMS (M^+ + H) calcd for $C_{14}H_{27}O_3$: 243.1961; found: 243.1961.

Preparation of* tert-*butyl (Z)-2-(1-hydroxyethyl)oct-2-enoate (36)

Following the general procedure (5 min), Z-alcohol **36** was formed in 72% yield as a colourless oil. IR (neat, cm^{-1}): 3430, 2960, 2930, 2859, 1713, 1458, 1368, 1250, 1153, 846. ^1H NMR ($CDCl_3$, 300 MHz) δ: 0.91 (t, 3H, J = 6.5 Hz), 1.20–1.51 (m, 8H) 1.52 (s, 9H), 2.28 (s, 3H), 2.80 (d, 1H, J = 6.3 Hz), 4.41 (q, 1H, J = 7.0 Hz) 6.10 (t, 1H, J = 6.7 Hz). ^{13}C NMR ($CDCl_3$, 300 MHz) δ: 13.9, 22.4, 26.9, 28.3, 32.0, 82.2, 138.2, 146.9, 148.0, 163.1, 165.1, 195.0. HRMS (M^+ + H) calcd for $C_{14}H_{27}O_3$: 243.1961; found: 243.1961.

Preparation of ethyl (Z)-2-(1-hydroxyethyl)-4,4-dimethylpent-2-enoate (37)

Following the general procedure (1 min), Z-alcohol **37** was formed in 66% yield as a colourless oil. IR (neat, cm^{-1}): 3441, 2959, 2872, 1725, 1661, 1464, 1380, 1271, 1235, 1194, 1140, 1071, 1028. ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.15 (s, 9H), 1.35 (t, 2H, J = 7.2 Hz), 2.28 (s, 3H), 4.23 (q, 3H, J = 6.7 Hz), 5.65 (s, 1H). ^{13}C NMR ($CDCl_3$, 300 MHz) δ: 14.3, 22.5, 29.6, 33.3, 60.0, 61.0, 134.7, 141.3, 169.1. HRMS (M^+ + H) calcd for $C_{11}H_{21}O_3$: 201.1491; found: 201.1491.

Preparation of methyl (E)-2-(1-hydroxyethyl)oct-2-enoate (38)

Following the general procedure (15 min), E-alcohol **38** was formed in 40% yield as a colourless oil. IR (neat, cm^{-1}): 3447, 2959, 1718, 1496, 1436, 1367, 1226, 1139, 1012, 753, 697. ^1H NMR ($CDCl_3$, 300 MHz) δ: 0.85 (t, 3H, J = 6.9 Hz), 1.52–1.60 (m, 6H, J = 6.7 Hz), 1.39 (d, 3H, J = 6.5 Hz), 2.40 (q, 1H, J = 7.3 Hz), 2.59 (bs, 1H) 3.80 (s, 3H), 4.52 (t, 2H, J = 6.4 Hz), 6.79 (t, 1H, J = 7.4 Hz). ^{13}C NMR ($CDCl_3$, 300 MHz) δ: 13.0, 22.0, 33.0, 51.8, 80.5, 128.2, 129.0, 134.4, 135.4, 141.5, 167.0. HRMS (M^+ + H) calcd for $C_{11}H_{21}O_3$: 201.1491; found: 201.1491.

Preparation of methyl (Z)-2-(1-hydroxyethyl)oct-2-enoate (39)

Following the general procedure (15 min), Z-alcohol **39** was formed in 49% yield as a colourless oil. IR (neat, cm^{-1}): 3447, 2959, 1718, 1496, 1436, 1367, 1226, 1139, 1012, 753, 697. ^1H NMR ($CDCl_3$, 300 MHz) δ: 0.85 (t, 3H, J = 7.0 Hz), 1.51–1.60 (m, 6H), 1.39 (d, 3H, J = 6.5 Hz), 2.40 (q, 1H, J = 7.4 Hz), 2.59 (bs, 1H), 3.80 (s, 3H), 4.52 (t, 2H, J = 6.4 Hz), 6.19 (t, 1H, J = 7.7 Hz). ^{13}C NMR ($CDCl_3$, 300 MHz) δ: 13.0, 20.2, 33.5, 52.0, 74.8, 128.6, 129.0, 134.0, 135.2, 141.5, 167.4. HRMS (M^+ + H) calcd for $C_{11}H_{21}O_3$: 201.1491; found: 201.1491.

Preparation of methyl (E)-2-cyclohexzylidene-3-hydroxybutanoate (40)

Following the general procedure (5 min), E-alcohol **40** was formed in 52% yield as a colourless oil. IR (neat, cm^{-1}): 3447, 2959, 1718, 1496, 1436, 1367, 1226, 1139, 1012, 753, 697. ^1H NMR ($CDCl_3$, 300 MHz) δ: 0.80–1.38 (m, 10H), 1.40 (d, 3H, J = 6.7 Hz), 1.41–1.80 (m, 1H), 2.50 (bs, 1H) 3.80 (s, 3H), 4.71 (t, 1H, J = 9.9 Hz), 6.53 (d, 1H, J = 9.2 Hz). ^{13}C NMR ($CDCl_3$, 400 MHz) δ: 24.3, 25.6, 25.8, 26.0, 32.5, 37.4, 52.0, 65.5, 132.3, 148.6, 168.4. HRMS (M^+ + H) calcd for $C_{12}H_{21}O_3$: 213.1491; found: 213.1491.

Preparation of methyl (Z)-2-cyclohexzylidene-3-hydroxybutanoate (41)

Following the general procedure (5 min), Z-alcohol **41** was formed in 56% yield as a colourless oil. IR (neat, cm^{-1}): 3447, 2959, 1718, 1496, 1436, 1367, 1226, 1139, 1012, 753, 697. ^1H NMR ($CDCl_3$, 300 MHz) δ: 0.80–1.38 (m, 10H, J = 6.5 Hz), 1.39 (d, 3H, J = 6.5 Hz), 1.40–1.80 (m, 1H), 2.50 (bs, 1H) 3.80 (s, 3H), 4.71 (t, 1H, J = 9.7 Hz), 5.93 (d, 1H, J = 9.7 Hz). ^{13}C NMR ($CDCl_3$, 400 MHz) δ: 22.6, 25.5, 26.0, 26.1, 32.5, 37.9, 51.3, 69.5, 133.0, 146.4, 168.1. HRMS (M^+ + H) calcd for $C_{12}H_{21}O_3$: 213.1491; found: 213.1491.

Preparation of* tert-*butyl (Z)-2-benzylidene-3-hydroxybutanoate (42)

Following the general procedure (15 min), Z-alcohol **42** was formed in 50% yield.[41]

Preparation of ethyl (Z)-2-(hydroxyl(phenyl)methyl)-3-phenylacrylate (43)

Following the general procedure (15 min), (*Z*)-alcohol **43** was formed in 64% yield.[28]

Preparation of (E)-1,3-diphenyl-2-(phenylsulfonyl)prop-2-en-1-ol (44)

Following the general procedure (15 min), with the exception that a 4 mol equiv excess of sodium borohydride and cerium trichloride were used, alcohol **44** was formed in 40% yield as a colourless solid based on reacted starting material. mp 145–147 °C. IR (neat, cm^{-1}): 3478, 1619, 1493, 1446, 1298, 12589, 1142, 1089, 1049, 1029, 773, 698, 611. ^1H NMR ($CDCl_3$, 300 MHz) δ: 4.03 (bs, 1H), 6.09 (s, 1H), 7.02–7.14 (m, 4H), 7.25–7.32 (m, 3H), 7.38–7.54 (m, 8H),

8.14 (s, 1H). ^{13}C NMR ($CDCl_3$, 300 MHz) δ: 69.6, 126.0, 127.5, 127.6, 128.3, 129.0, 129.1, 129.6, 130.3, 132.7, 132.9, 139.2, 141.3, 143.0, 143.5. HRMS (M^+ + H) calcd for $C_{21}H_{19}O_3S$: 351.1055; found: 351.1055.

*Preparation of methyl (**E**)-2-benzylidene-3-hydroxy-4-methylpentanoate (45)*

Following the general procedure (15 min), E-alcohol **45** was formed in 65% yield as a colourless oil. IR (neat, cm^{-1}): 3447, 2959, 1718, 1496, 1436, 1367, 1226, 1139, 1012, 753, 697. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.69 (d, 3H, J = 6.7 Hz), 1.04 (d, 3H, J = 6.7 Hz), 2.03 (m, 1H), 3.22 (d, 1H, J = 2.7 Hz), 3.85 (s, 3H), 4.22 (t, 1H, J = 9.9 Hz), 7.26–7.43 (m, 5H), 7.80 (s, 1H). ^{13}C NMR ($CDCl_3$, 300 MHz) δ: 18.0, 19.5, 33.0, 51.8, 80.5, 128.2, 129.0, 134.4, 135.4, 141.5, 167.4. HRMS (M^+ + H) calcd for $C_{14}H_{19}O_3$: 235.1334; found: 235.1334.

*Preparation of methyl (**Z**)-2-benzylidene-3-hydroxy-4-methylpentanoate (46)*

Following the general procedure (15 min), Z-alcohol **46** was formed in 71% yield as a colourless oil. IR (neat, cm^{-1}): 3447, 2959, 1718, 1496, 1436, 1367, 1226, 1139, 1012, 753, 697. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.86 (d, 3H, J = 6.7 Hz), 1.02 (d, 3H, J = 6.7 Hz), 1.92 (m, 1H, J = 2.7 Hz), 2.10 (s, 1H), 3.63 (s, 3H), 4.06 (d, 1H, J = 9.9 Hz), 6.83 (s, 1H), 7.23–7.40 (m, 5H). ^{13}C NMR ($CDCl_3$, 300 MHz) δ: 19.6, 33.5, 52.0, 74.8, 128.6, 128.67, 129.0, 133.2, 134.0, 141.5, 167.4. HRMS (M^+ + H) calcd for $C_{14}H_{19}O_3$: 235.1334; found: 235.1334.

*Preparation of (**Z**)-3-cyclohexyl-2-(hydroxy(phenyl)methyl) acrylonitrile (48)*

Following the general procedure (5 min), alcohol **48** and its saturated analogue were formed in 52% yield as a yellow oil that was inseparable by SiO_2 chromatography. IR (neat, cm^{-1}): 3444, 3063, 3031, 2926, 2853, 2221, 1450, 1047, 701. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.67–1.76 (m, 10H), 2.17 (d, 1H, J = 4.0 Hz), 2.51–2.62 (m, 1H), 5.27 (d, 1H, J = 4.0 Hz), 6.37 (d, 1H, J = 10.0 Hz), 7.25–7.41 (m, 5H). ^{13}C NMR ($CDCl_3$, 400 MHz) δ: 25.4, 25.8, 32.1, 40.7, 74.6, 126.4, 126.5, 126.7, 128.9, 128.95, 129.0, 153.2. HRMS (M^+ + H) calcd for $C_{16}H_{20}NO$: 242.1546; found: 242.1545.

Preparation of methyl 2-(1-hydroxyethyl)-3-methylbut-2-enoate (49)

Following the general procedure (15 min), alcohol **49** was formed in 91% yield as pale yellow oil. IR (neat, cm^{-1}): 3450, 2970, 2931, 2856, 1715, 1448, 1372, 1300, 1253, 1210, 1146, 1108, 916, 733. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.34 (t, 3H, J = 7.1 Hz), 1.35 (d, 3H, J = 6.6 Hz), 1.83 (s, 3H), 1.9 (s, 3H), 2.80 (d, 1H, J = 1.4), 4.28 (q, 2H, J = 7.0 Hz), 4.74 (p, 1H, J = 6.9 Hz). ^{13}C NMR ($CDCl_3$, 300 MHz) δ: 14.4, 20.8, 22.5, 23.2, 60.5, 66.1, 131.9, 140.0, 169.3. HRMS (M^+ + H) calcd for $C_8H_{15}O_3$: 159.1021; found: 159.1021.

Preparation of ethyl 2-cyclohexylidene-3-hydroxybutanoate (50)

Following the general procedure (15 min), alcohol **50** was formed in 69% yield as a pale yellow oil. IR (neat, cm^{-1}): 3456, 2980, 2931, 2856, 1718, 1656, 1448, 1367, 1300, 1263, 1210, 1146, 1108, 1025, 916, 733. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.32 (d, 3H, J = 7.2 Hz), 1.36 (t, 3H, J = 6.8 Hz), 1.53–1.71 (m, 6H), 2.20–2.35 (m, 4H), 2.49 (d, 1H, J = 7.3 Hz), 4.26 (q, 2H, J = 7.2 Hz), 4.80 (p, 1H, J = 6.7 Hz). ^{13}C NMR ($CDCl_3$, 300 MHz) δ: 14.4, 23.0, 26.5, 28.0, 28.1, 30.4, 33.4, 60.6, 65.9, 129.6, 145.1, 169.8. HRMS (M^+ + H) calcd for $C_{12}H_{21}O_3$: 213.1491; found: 213.1491.

Preparation of ethyl 2-cyclopentylidene-3-hydroxybutanoate (51)

Following the general procedure (15 min), alcohol **51** was formed in 94% yield as a pale yellow oil. IR (neat, cm^{-1}): 3447, 2976, 2931, 2856, 1717, 1448, 1367, 1300, 1263, 1210, 1146, 1108, 916, 733. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.32 (t, 3H, J = 7.2 Hz), 1.39 (d, 3H, J = 6.7 Hz), 1.60–1.78 (m, 4H), 2.28–2.40 (m, 2H), 2.66–2.72 (m, 2H), 3.64 (d, 1H, J = 10.4 Hz), 4.24 (q, 2H, J = 7.0 Hz), 4.6 (p, 1H, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$, 300 MHz δ): 14.2, 25.9, 26.1, 30.3, 34.8, 34.82, 60.8, 128.1, 166.4, 169.2, 199.2. HRMS (M^+ + H) calcd for $C_{11}H_{19}O_3$: 199.1334; found: 199.1334.

Preparation of methyl 4-(1-(ethoxycarbonyl)-2-hydroxypropylidene)piperidine-1-carboxylate (52)

Following the general procedure, alcohol **52** was formed in 71% yield as a pale yellow oil. IR (neat, cm^{-1}): 3455, 2980, 2873, 1684, 1456, 1412, 1371, 1213, 1132, 1095, 1071, 1024, 862, 769. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.32 (t, 3H, J = 7.0 Hz), 1.37 (d, 3H, J = 6.7 Hz), 2.54–2.46 (m, 5H), 3.46–3.58 (m, 4H), 3.70 (s, 3H), 4.26 (q, 2H, J = 7.2 Hz), 4.75 (p, 1H, J = 6.5 Hz). ^{13}C NMR ($CDCl_3$, 300 MHz) δ: 14.5, 23.1, 29.6, 32.0, 44.1, 44.4, 52.9, 61.0, 65.4, 132.2, 140.8, 156.0, 168.9. HRMS (M^+ + H) calcd for $C_{13}H_{22}NO_5$: 272.1498; found: 272.1498.

*Preparation of ethyl (**Z**)-2-(1-hydroxyethyl)-3-methyldec-2-enoate (53)*

Following the general procedure (15 min), Z-alcohol **53** was formed in 82% yield as a pale yellow oil. IR (neat, cm^{-1}): 3509, 3419, 2929, 2857, 1720, 1624, 1465, 1366, 1272, 1164, 1117, 1056, 967, 779, 722. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.88 (t, 3H, J = 7.2 Hz), 1.24–1.48 (m, 10H), 1.33 (t, 3H, J = 7.2 Hz), 1.35 (d, 3H, J = 6.7 Hz), 1.80 (s, 3H), 2.14–2.22 (m, 2H), 2.67 (d, 1H, J = 8.4 Hz), 4.25 (q, 2H, J = 7.2 Hz), 4.71 (p, 1H, J = 7.4 Hz). ^{13}C NMR ($CDCl_3$, 300 MHz) δ: 14.3, 14.5, 18.6, 22.6, 22.8, 28.4, 29.4, 29.8, 32.0, 37.1, 60.6, 66.3, 76.5, 132.0, 143.7, 169.4. HRMS (M^+ + H) calcd for $C_{15}H_{29}O_3$: 257.2117; found: 257.2118.

*Preparation of ethyl (**E**)-2-(1-hydroxyethyl)-3-methyldec-2-enoate (54)*

Following the general procedure (15 min), E-alcohol **54** were formed in 82% yield as a pale yellow oil. IR (neat, cm^{-1}): 3515, 3419, 2929, 2857, 1720, 1700, 1624, 1465, 1354, 1224, 1172, 1118, 1052, 970, 859, 781, 668, 646, 563. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.88 (t, 3H, J = 6.8 Hz), 1.32 (t, 3H, J = 7.0 Hz), 1.35 (d, 3H, J = 6.5 Hz), 1.88 (s, 3H), 2.04–2.22 (m, 2H), 2.81 (d, 1H, J = 8.0 Hz), 4.27 (q, 2H, J = 7.2 Hz), 4.72 (p, 1H, J = 6.3 Hz). ^{13}C NMR ($CDCl_3$, 300 MHz) δ: 14.3, 14.5, 21.4, 22.8, 28.4, 29.3, 29.9, 31.9,

35.0, 60.7, 65.9, 131.6, 144.8, 169.6. HRMS ($M^+ + H$) calcd for $C_{15}H_{29}O_3$: 257.2117; found: 257.2117.

General procedure for the reduction of Knoevenagel adducts using BMS

In a 50 mL three-neck flask equipped with a magnetic stirring bar and a reflux condenser, THF (3 mL) and β-keto ester (0.5 mmol) were added. To this well-stirred solution under an argon atmosphere was added BMS (0.50 mmol). After stirring for 75 min, excess hydride was quenched by the addition of methanol (0.5 mL), and the solution was diluted with water (25 mL) and extracted with diethyl ether (6 × 10 mL). The combined organic extracts was dried over $MgSO_4$ and, after filtration and evaporation of solvent, the crude product was purified by silica gel chromatography.

Preparation of methyl 2-benzylidene-3-hydroxybutanoate (29)

Two isomers were obtained: E and Z (2:3); 40% yield.

Preparation of* tert*-butyl 2-benzylidene-3-hydroxybutanoate (42)

1,2- and 1,4-addition products and two isomers (E and Z) were obtained in 10% yield.

Preparation of ethyl (Z)-2-(hydroxyl(phenyl)methyl)-3-phenylacrylate (43)

No reduction.

Preparation of methyl (E)- and (Z)-2-isobutyryl-3-phenylacrylate (45)

Two isomers were obtained (E and Z in a ratio of 2:3) in 10% yield, but they were not separable.

General procedure for the reduction of Knoevenagel adducts with sodium borohydride and $Yb(OTf)_3$

The keto ester (0.05 g, 1 mmol), MeOH (3 mL), and $Yb(OTf)_3$ (1.1 equiv) were added to a RBF and stirred at room temperature for 30 min. The solution was cooled to –78 °C and then $NaBH_4$ (1.1 equiv) was added slowly. The resulting mixture was stirred for 30 min at this temperature and then quenched by the addition of saturated aqueous ammonium chloride (10 mL). The reaction mixture was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic extract was dried over anhydrous $MgSO_4$. After filtering, the solvent was evaporated under reduced pressure and the product purified by flash column chromatography.

Preparation of methyl 2-benzylidene-3-hydroxybutanoate (29)

Two isomers were obtained: E and Z (2:3); 20% yield.

Preparation of* tert*-butyl 2-benzylidene-3-hydroxybutanoate (42)

The Z-isomer was obtained in 40% yield.

Preparation of ethyl (Z)-2-(hydroxyl(phenyl)methyl)-3-phenylacrylate (43)

No reduction.

Preparation of *tert*-butyl 2-(1-bromo-ethyl)-but-2-enoate (55)

To a RBF, under argon, was added alcohol **31** (3.29 g, 20.8 mmol) and CH_2Cl_2 (30 mL). The solution was cooled to –30 °C and triphenylphosphine (5.8 g, 22.1 mmol) was added, followed by NBS (3.9 g, 21.9 mmol). When the reaction was deemed complete using TLC, ~4 h at –30 °C, the solution was diluted with CH_2Cl_2, washed with $NaHCO_3$ (2×), brine, and then dried over $MgSO_4$. It was then filtered and solvent was removed in vacuo. The product was then purified via column chromatography using hexane – ethyl acetate (10:1) as eluent to yield bromide **55** as a yellow oil (2.2 g, 48%) that was immediately used in the next reaction. IR (neat, cm^{-1}): 2981, 2927, 1720, 1640, 1445, 1387, 1262, 1153, 1095, 1033, 913, 763, 734. ^1H NMR ($CDCl_3$, 300 MHz) δ: 6.92 (q, 0.33 H, J = 7.4 Hz) and 6.35 (qd, 0.66 H, J = 0.9, 7.2 Hz), 5.23 (q, 0.33H, J = 7.1 Hz), 5.11 (qt, 0.66 H, J = 0.9, 7.1 Hz), 4.29 (m, 2H), 2.05–1.85 (m, 6H), 1.32 (m, 3H). ^{13}C NMR ($CDCl_3$, 300 MHz) δ: 166.2, 140.3, 136.4, 60.8, 37.9, 24.3, 15.7, 14.2.

Preparation of 2,4-dimethyl-8-oxo-bicyclo[3.2.1]octane-3-carboxylic acid *tert*-butyl ester (57)

To a RBF, under argon, was added enamine **56** (1.36 g, 9.95 mmol), CH_3CN (15 mL), and triethylamine (1.2 g, 11.9 mmol). To this solution was then added bromoalkene **55** (2.2 g, 9.95 mmol) in CH_3CN (10 mL). After complete addition, the solution was heated at reflux for 20 h, cooled, and then water (15 mL) was added and heating at reflux was continued for 1.5 h. After cooling to room temperature, the solution was extracted with CH_2Cl_2 (4×). The combined organic phases were washed with brine, dried over $MgSO_4$, and filtered. The solvent was removed in vacuo to yield a brown oil that was purified via column chromatography using hexane – ethyl acetate (4:1) as eluent to yield ketone **57** as a yellow oil (0.79 g, 36%). IR (neat, cm^{-1}): 2975. ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.76 (m, 0.5H), 2.63 (dp, J = 2.9, 7.4 Hz, 0.5H), 2.45 (m, 1H), 2.26 (dd, J = 2.6, 7.7 Hz, 0.5H), 2.16–1.94 (m, 3H), 1.92–1.78 (m, 2.5H), 1.71 (t, J = 8.4 Hz, 1H), 1.48 (s, 4.5H), 1.47 (s, 4.5H), 1.17 (d, J = 7.3 Hz, 1.5H), 1.08 (d, J = 7.1 Hz, 4.5H). ^{13}C NMR ($CDCl_3$, 300 MHz) δ: 220.1, 219.6, 174.7, 173.4, 81.0, 80.8, 52.2, 49.9, 49.5, 48.8, 48.4, 45.8, 43.0, 39.0, 28.23, 28.2, 25.1, 22.6, 22.0, 21.5, 17.7, 17.4. HRMS ($M^+ + H$) calcd for $C_{15}H_{25}O_3$: 253.1804; found: 253.1805.

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