Stereochemical investigation on the construction of poly-functionalized bicyclo[3.3.1]nonenones by successive Michael reactions of 2-cyclohexenones†

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A method for the practical construction of poly-functionalized bicyclo[3.3.1]nonenones by successive Michael reactions of cyclohexenones **1** with acrylates **2** using K_2CO_3 and TBAB (n-$Bu_4N^+Br^-$) was developed. The construction could be carried out in both stepwise and one-pot reactions with similar tendencies in regioselectivity. The α-regioselectivity in the intramolecular Michael reaction agreed with that stereoelectronically expected in intermolecular reactions based upon consideration of the HOMO orbital profile of the enolate I, the precursor to ring-closure, although the reaction site was trisubstituted and prone to steric hindrance in most of the examples presented. For the acetoxymethylacrylates substituted at either the α or γ position, steric hindrance of the substituents (R_2 and R_3) served as a controlling factor to induce high regiocontrol. Facial selection in the protonation of enolate II, formed upon ring-closure, was also affected by these substituents. In both the intramolecular Michael reaction and the protonation of enolate II, the ammonium counter cation played an important role.

Introduction

Many natural products bearing the bicyclo[3.3.1]nonane skeleton, such as garsubellin A,[1] huperzine A,[2] plukenetione A,[3] lycopodine[4] and so forth, have been shown to exhibit promising biologically activity and also have unique complex structures. Therefore, they have attracted attention as targets for organic synthesis. The key step towards the synthetic goals would be the construction of the bicyclo[3.3.1]nonane core and many types of synthetic methods for this purpose have been reported.[5,6] Bicyclo[3.3.1]nonanes have also found use as synthetic intermediates for other ring systems.[7] In relation to research on bicyclic natural product synthesis carried out in our group,[8] we also have been interested in this ring system.

To preparation of a densely functionalized bicyclo[3.3.1]nonane core, such as that seen in garsubellin A, we envisioned that the [3 + 3] annulation reaction between α-acetoxymethylacrylates (which could function as double Michael acceptors) and cyclohexenones with substituents α to the carbonyl group would meet our objective. As presented in a preliminary report, we have found that this could be realized in either a two-step or one-pot procedure using K_2CO_3 in conjunction with tetrabutylammonium bromide (TBAB) as a phase transfer catalyst to furnish the desired bicyclic compounds with high regioselectivity.[9] Quite a while ago, two groups independently and ingeniously utilized bromomethyl acrylates as double Michael acceptors in conjunction with enamines derived from cyclohexanones as double Michael donors; Lawton in preparing bicyclo[3.3.1]nonanes[10] and Stetter in providing adamantane derivatives in a cascade of reactions, including two initial Michael reactions.[11] Despite the high potential of this group of double Michael acceptors for the construction of various ring systems, as far as we are aware, they have been overlooked over the years, and have not been exploited for bicyclic systems by others. We have found that cyclohexenones could be applied directly, not necessitating enamines, and that a regioselectivity issue which is unique to our system and has not been exploited in this type of [3 + 3] reaction previously, could be controlled for the amphiphilic Michael donors. In this paper, in addition to providing details of these previous results, we report on the extended scope of the reaction by utilizing additionally-functionalized double Michael acceptors *en route* to more advanced and complex synthetic intermediates, and on the stereocontrol in the annulation step (the second step) for the newly examined substrates. Also provided is a rationale on the regio- and stereo-selectivity based upon theoretical calculations.

Results and discussion

The stepwise Michael reactions of 2 or 6-mono- or 2,6-disubstituted-cyclohexenones **1** with acrylate **2a**[12] were examined first.[9a] Annulation precursor **3a** was obtained by the intermolecular Michael reaction of **1a** with acrylates **2a**, by the use of LDA where deprotonation α to the keto-carbonyl group of the thermodynamically less acidic site was required (Scheme 1). Upon treating the annulation precursor **3a** with K_2CO_3 and TBAB, the intramolecular Michael reaction proceeded to give α-*endo*-**4a**, which was a kinetically protonated product, (90%) and α-*exo*-**4a** (3%).[13,14] The relative stereochemistry of α-*endo*-**4a** was confirmed by X-ray structural analysis (Fig. 1).[15]‡

Furthermore, treatment of the annulation precursor **3a** in the presence of acrylate **2a** (2.0 eq) with K_2CO_3 and TBAB gave the annulation product **5** in 51% yield (Scheme 2).[13] Thus, not only

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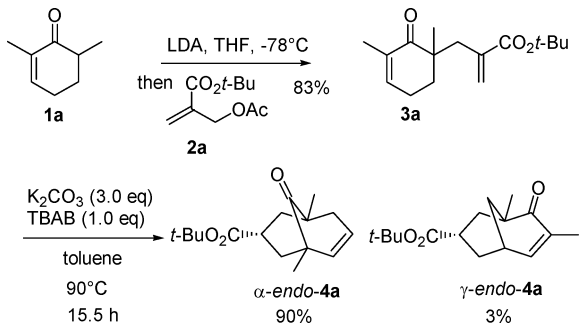
‡ CCDC reference numbers 600955–600957. For crystallographic data in CIF format see DOI: 10.1039/b615702e



Scheme 1

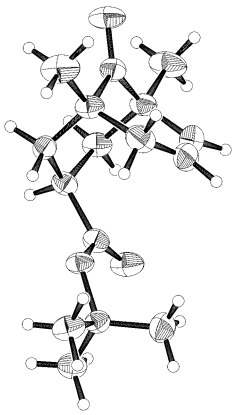
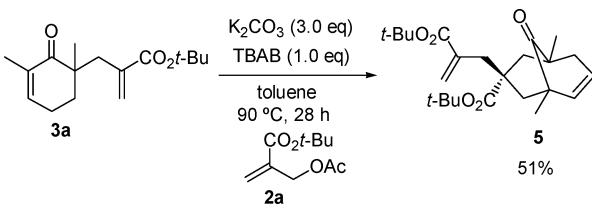


Fig. 1 ORTEP drawing of α-*endo*-**4a** showing the thermal ellipsoids at the 30% probability level.



Scheme 2 Intramolecular Michael reaction of **3a** in the presence of acrylate **2a**.

protonation, but also alkylation of the intermediate enolate was preferred from the *exo*-side.

The stepwise Michael reactions of 2-cyclohexenone **1a** with acrylates **2b** and **c**,[16a,b] bearing a stereocenter that would serve as a stereogenic center for the second Michael reaction, were also investigated, in order to construct more densely-functionalized bicyclic compounds (Table 1).[13] Regardless of the fact that the Michael donor was greatly hindered and led to the formation of the quaternary center β from the enolate double bond, the stereoelectronically favored *E*-**3b** was formed as the exclusive isomer in the intermolecular Michael reaction of cyclohexenone **1a** with acrylate **2b** (Table 1, entry 1).[17,18] The major product from the intramolecular reaction of *E*-**3b** was the α,α′ annulation product with an *exo* methyl group and an *endo t*-Bu ester group, and it was accompanied by a small amount of the γ-7-*endo*,8-*exo* product. The stereochemistry of α-7-*endo*,8-*exo*-**4b** was confirmed by X-ray structural analysis (Fig. 2).[15]‡ Despite the formation of regioisomers, the stereoselectivity regarding the newly generated stereocenters was completely controlled. In the intermolecular

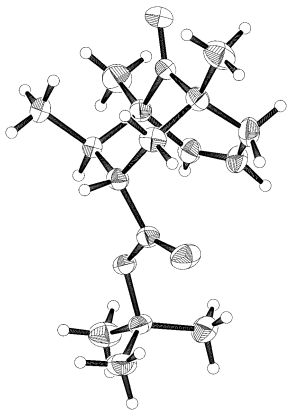


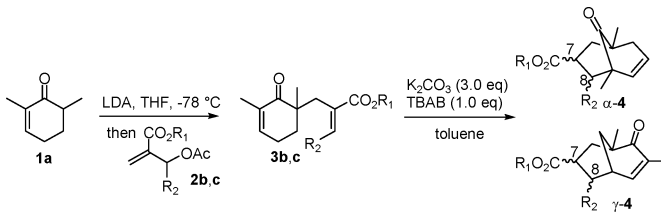
Fig. 2 ORTEP drawing of α-7-*endo*,8-*exo*-**4b** showing the thermal ellipsoids at the 30% probability level.

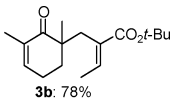
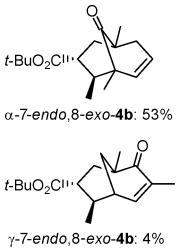
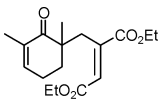
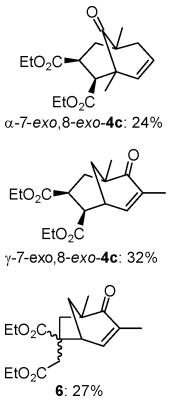
Michael reaction of acrylate **2c**, *Z*-**3c** was obtained as a minor product along with *E*-**3c** (Table 1, entry 2). The isomers could be separated by preparative TLC and only *E*-**3c** was used for the intramolecular Michael reaction. Treatment of annulation precursor *E*-**3c** with K_2CO_3 and TBAB gave the bicyclo[3.3.1]nonenones α- and γ-**4c** along with the bicyclo[3.2.1]octane **6**, generated by bond formation between the γ-carbon of the enolate and the C2′-carbon of the tether. The stereochemistry of the annulation products α- and γ-**4c** was characteristically and specifically "*exo*,*exo*" in contrast to results involving the *t*-Bu ester.

Table 2 summarizes the results of the stepwise Michael reactions of cyclohexenones **1a**–**c** with 1-substituted acrylates **2d** and **e**,[16c,d] which have a stereogenic carbon center for the first Michael reaction.[13,18] The annulation precursors **3d**–**g** were obtained as mixtures of diastereomers by the intermolecular Michael reactions of cyclohexenones **1a**–**c** with acrylates **2d** and **e**, respectively (dr = 1.2–4.5 : 1.0), and were used for the sequential intramolecular Michael reaction without separation. The intramolecular Michael reaction of **3d**, generated from cyclohexenone **1a** with acrylate **2d**, gave α-6-*exo*,7-*endo*-**4d** as the major product, along with a small amount of γ-6-*exo*,7-*endo*-**4d**, both of which have the methyl group on the convex face of the compounds and are products of *exo*-face protonation (Table 2, entry 1). Judging from the relative stereochemistry of the first junction in the products, the major product can be looked upon as that exclusively from the major *R**,*R** isomer of **3d**, whereas the minor product can be viewed as that from the minor *R**,*S** isomer of **3d**. Thus, it is suggested that the annulation reaction of each isomer of **3d** was completely stereospecific, with one diastereomer giving the α-annulation product and the other giving the γ-product. Under likewise conditions, annulation precursors **3e**–**g** gave mixtures of products with α- and γ-6-*exo*,7-*exo*-**4e**–**g** as the main products (Table 2, entries 2–4).[19]

In order to investigate the stereochemical outcome of the annulation process in more detail, the diastereomeric mixture of **3f** was separated with high-performance liquid chromatography and the two diastereomers were subjected separately to the annulation conditions (Scheme 3). The annulation product α-6-*exo*,7-*exo*-**4f** was obtained as the exclusive product in the reaction of one of the diastereomers, and this indicated that the relative stereochemistry of the reactant was "*anti*" in regards with the first juncture.[20] Thus, as for the reaction of *anti*-**3f**, annulation can be regarded as

Table 1 Stepwise Michael reactions of 2-cyclohexenone **1a** with acrylates **2b**,**c**



Entry	Acrylate	3[a]	Conditions	Products[a,b]
1		 **3b**: 78% only *E*	90 °C, 67 h	 α-7-*endo*,8-*exo*-**4b**: 53% γ-7-*endo*,8-*exo*-**4b**: 4%
2		 **3c**: 62% (*E* : *Z* = 10 : 1)[c]	110 °C, 27 h	 α-7-*exo*,8-*exo*-**4c**: 24% γ-7-exo,8-*exo*-**4c**: 32% **6**: 27%

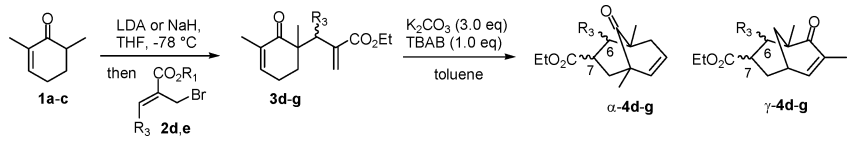
[a] Isolated yield. [b] The numbering is based on the bicyclo[3.3.1]non-2-ene core. [c] A mixture of *E*-and *Z*-**3c** was obtained in the intermolecular Michael reaction of **1a** and **2c** (*E* : *Z* = 10 : 1). The mixture was separated into *E*-and *Z*-**3c** by preparative TLC. Only *E*-**3c** was used for the intramolecular Michael reaction.

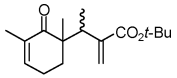
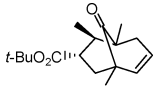
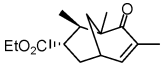
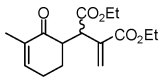
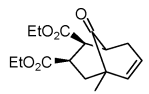
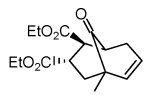
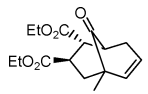
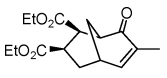
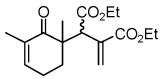
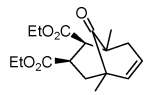
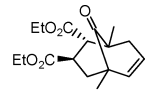
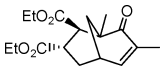
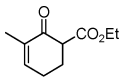
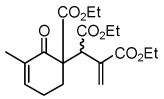
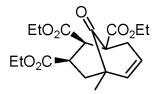
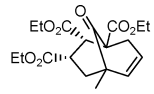
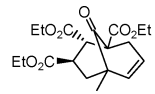
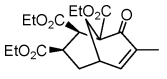
stereospecific and protonation as stereoselective. The reaction of the other diastereomer, logically *syn*-**3f**, was not as clean giving rise to two γ and three α annulation products, among which the major product was γ-6-*exo*,7-*exo*-**4f**. The reaction of *syn*-**3f** was not as selective as that of *anti*-**3f**. Thus, as a whole, for the reaction of **2e** as the double Michael acceptor, the *anti*-series of diastereomers underwent stereospecific reaction to give the α-annulation product, whereas the *syn*-series gave rise to both the α and γ-products.

Since the stepwise Michael reactions of cyclohexenones **1** with acrylates **2** proceeded sufficiently, one-pot Michael reactions were subsequently examined (Table 3).[13] The reaction of **1a** with **2a** in the two operation method[9a] gave annulation products with a higher ratio of the thermodynamically more stable α-*exo*-**4a** compared with the stepwise protocol (Table 3, entry 1). In the case of entry 2, the ratios were similar to those of the stepwise reactions. The one-pot Michael reactions of cyclohexenones **1c** and **d** bearing the active methylene could be performed by the one-operation method (Table 3, entries 3 and 4). The one-pot Michael reaction of **1d** afforded γ-*endo*-**4h** as the major product (Table 3, entry 4). The relative stereochemistry of γ-*endo*-**4h** was confirmed by X-ray structural analysis (Fig. 3).[15]‡

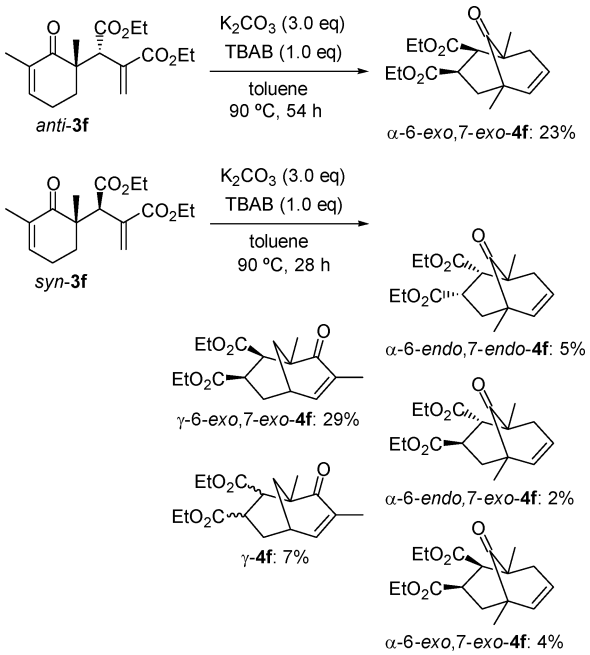
In order to examine the effect of the counter cation in the intramolecular Michael reaction, *t*-BuOK was used as the base instead of the combination of TBAB and K_2CO_3 (Scheme 4). Treatment of the annulation precursor **3a** with *t*-BuOK (3.0 eq) (toluene, rt, 7 h then 90 °C, 24 h) gave γ-*exo*-**4a** in 40% yield. On the other hand, the reaction of **3a** with *t*-BuOK (3.0 eq) in the presence of 18-crown-6 (3.0 eq) (toluene, rt, 2 h) gave carboxylic acids **7**, generated from hydrolysis of the annulation products α-*exo*-**4a** and γ-*exo*-**4a** (α-*exo*-**7**: 8%, γ-*exo*-**7**: 16%). Since the regioselectivity changed dramatically with the obvious intervention of the potassium ion, favoring the γ product, it was suggested that under phase transfer conditions, not the free potassium ion but the ammonium ion was what interacted with the enolate. Since the region of charge in the ammonium is sterically shielded by the alkyl groups, its interaction with the enolate oxygen

Table 2 Stepwise Michael reactions of 2-cyclohexenones **1a**–**c** with acrylates **2d** and **e**



Entry	1	Acrylate	Conditions	3[a]	Conditions	Products[a,b]			
1	 **1a**	 **2d**	LDA, −78 °C	 **3d**: 52% (3.6 : 1.0)[c]	90 °C, 88 h	 α-6-*exo*,7-*endo*-**4d**: 65%			 γ-6-*exo*,7-*endo*-**4d**: 10%
2	 **1b**	 **2e**	LDA, −78 °C	 **3e**: 55% (2.1 : 1.0)[c]	110 °C, 9.5 h	 α-6-*exo*,7-*exo*-**4e**: 20%	 α-6-*exo*,7-*endo*-**4e**: 3%	 α-6-*endo*,7-*exo*-**4e**: 6%	 γ-6-exo,7-*exo*-**4e**: 12%
3	 **1a**	 **2e**	LDA, −78 °C	 **3f**: 71% (1.2 : 1.0)[c]	90 °C, 72 h	 α-6-*exo*,7-*exo*-**4f**: 35%		 α-6-*endo*,7-*exo*-**4f**: 4%	 γ-6-*exo*,7-*exo*-**4f**: 42%
4	 **1c**	 **2e**	NaH, 0 °C	 **3g**: 90% (4.5 : 1.0)[c]	110 °C, 9.5 h	 α-6-*exo*,7-*exo*-**4g**: 36%	 α-6-*endo*,7-*endo*-**4g**: 10%	 α-6-*endo*,7-*exo*-**4g**: 8%	 γ-6-*exo*,7-*exo*-**4g**: 9%

[a] Isolated yield. [b] The numbering is based on the bicyclo[3.3.1]non-2-ene core. [c] The diastereomer ratio was determined by ^{1}H NMR.



Scheme 3 Intramolecular Michael reaction of *anti*- and *syn*-**3f**.

atom must be weaker than that of metals in metal enolates, and this difference in interaction could be the reason for the observed difference in regioselectivity, according to the base used.

To elucidate the factors controlling the observed selectivity, *ab initio* calculations on the intramolecular Michael reactions were performed at the HF/6–31G* level with compounds **3′** as models of the annulation precursors.[21] Since the counter cation experiments suggested the presence of loose interaction of the ammonium ion with the enolate oxygen, and not by metals, we decided to ignore the counter cation as an approximation to simplify the theoretical calculations. Both chair-like and boat-like transition states leading to both α and γ products were calculated. The relative energies of the transition states for **3a′**–**c′** and **h′** are summarized in Table 4.[22] For transition states leading to both the α- and γ-products, the chair forms were more stable than the boat forms, and the chair form (leading to the α-product) was the most

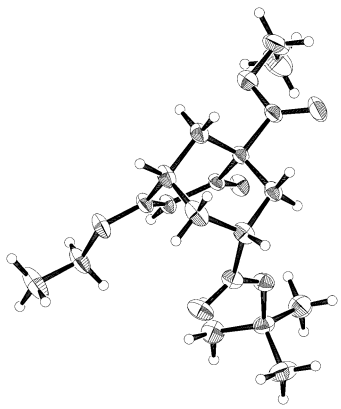
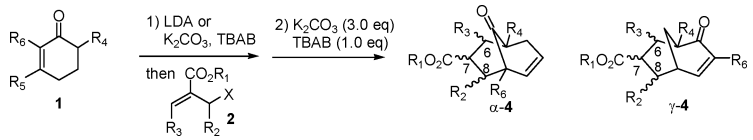
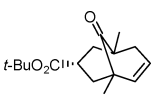
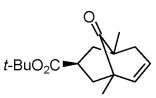
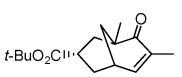
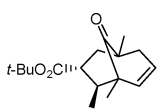
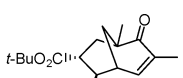
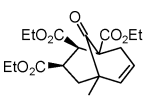
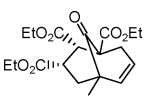
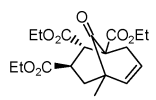
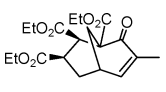
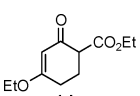
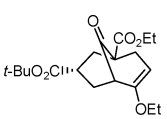
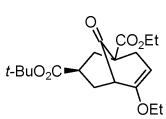
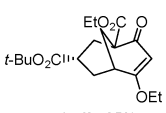


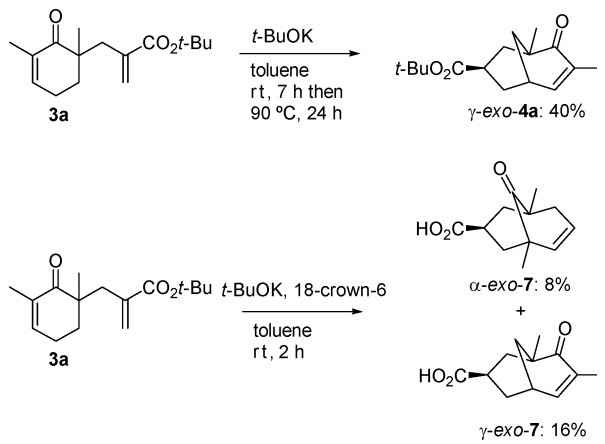
Fig. 3 ORTEP drawing of γ-*endo*-**4h** showing the thermal ellipsoids at the 30% probability level.

Table 3 One-pot Michael reactions of 2-cyclohexenones **1a**, **c** and **d** with acrylates **2a**, **b** and **e**



Entry	**1**	Acrylate	Conditions	Products[a]			
1	 **1a**	 **2a**	(i) LDA, −78 °C, THF, 6 h; (ii) 90 °C, 18 h	 α-*endo*-**4a**: 34%	 α-*exo*-**4a**: 32%		 γ-*endo*-**4a**: 4%
2[b]	 **1a**	 **2b**	(i) LDA, −78 °C, THF, 3 h; (ii) 110 °C, 18 h	 α-7-*endo*,8-*exo*-**4b**: 54%			 γ-7-*endo*,8-*exo*-**4b**: 16%
3[b,c]	 **1c**	 **2e**	K_2CO_3, TBAB, toluene, rt, 24 h; then 110 °C, 8 h	 α-6-*exo*,7-*exo*-**4g**: 14%	 α-6-*endo*,7-*endo*-**4g**: 4%	 α-6-*endo*,7-*exo*-**4g**: 18%	 γ-6-*exo*,7-*exo*-**4g**: 4%
4[c]	 **1d**	 **2a**	K_2CO_3, TBAB, toluene, 40 °C, 18 h; then 80 °C, 25 h	 α-*endo*-**4h**: 25%		 α-*exo*-**4h**: 6%	 γ-*endo*-**4h**: 35%

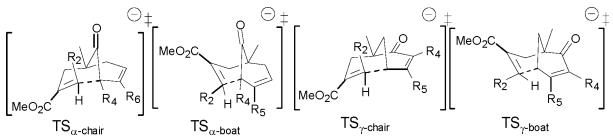
[a] Isolated yield. [b] The numbering is based on the bicyclo[3.3.1]non-2-ene core. [c] K_2CO_3 (3.0 eq) and TBAB (1.0 eq) were used.

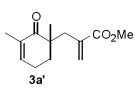
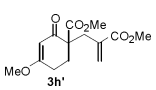
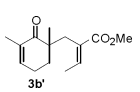
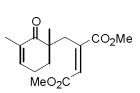


Scheme 4 Effect of the counter cation in the intramolecular Michael reaction.

stable of the four. The $TS_{\alpha\text{-chair}}$ transition state was *ca.* 4 kcal mol^{-1} more stable than the $TS_{\gamma\text{-chair}}$ transition state,[23] except for **3c**′ and **3h**′ where the differences were much smaller. These calculations nicely correspond with the experimental data from a relative point of view. As a general trend, the experimental ratio of the γ product was higher than expected from calculation, thus it can be said that our approximations in not considering the ammonium ion in the calculations slightly underestimated the stability of the transition state leading to the γ product. In light of this good correlation between experiment and calculation, it could be assumed that, in the reaction involving *t*-BuOK, the potassium ion stabilizes the $TS_{\gamma\text{-chair}}$ transition state by electrostatic interaction with the ester moiety of the acceptor. Similar interaction is not possible for the sterically favored $TS_{\alpha\text{-chair}}$ transition state, since the two oxygen functions are in an *anti* relationship, although it could be in force for $TS_{\alpha\text{-boat}}$.

Table 4 Relative energies of the transition state in the intramolecular Michael reactions of **3a**′–**c**′ and **h**′ at the HF/6–31G* level



Entry		Relative energy/kcal mol^{-1}			
		$TS_{\alpha\text{-chair}}$	$TS_{\alpha\text{-boat}}$	$TS_{\gamma\text{chair}}$	$TS_{\gamma\text{-boat}}$
1	 3a′	0	+8.80	+4.77	+9.72
2	 3h′	0	+7.54	+0.06	+6.20
3	 3b′	0	+8.91	+4.06	+8.98
4	 3c′	0	+9.63	+1.76	+10.19

Tables 5 and 6 indicate relative transition state energies in the intramolecular Michael reaction for *anti*- and *syn*-**3d**′–**g**′ at the HF/6–31G* level, respectively.[22] For the intramolecular Michael reaction of *anti*-**3d**′–**g**′, the $TS_{\alpha\text{-chair}}$ transition state was more stable than the transition state, leading to the γ-product by 5.9–10.3 kcal mol^{-1} (Table 5), which is larger than the differences in Table 4. Experimentally, these diastereomers could be regarded as species giving rise to only the α-product. Thus, it can be considered that the $TS_{\gamma\text{-chair}}$ transition states in the intramolecular Michael reaction of *anti*-**3d**′–**g**′ were destabilized by the R_3 substituents. The relative difference in energy between the α and γ-series for *syn*-**3d**′–**g**′ was rather small and in good accordance with the higher proportion of the γ-product compared with the *anti*-series (Table 6). In the *syn*-series, whichever the product (α or γ), the chair-like transition state was much more stable.

The HOMOs and HOMO potential maps of the enolates generated from **3a**′ and **h**′ are illustrated in Fig. 4.[24] The HOMO potential maps showed higher electron density at the C2-carbon than at the C4-carbon, as would be expected from precedence in similar conjugated systems. The 3-OMe substituent did not affect the relative electron density. Thus, although we are dealing with an intramolecular reaction and α-annulation gives rise to the sterically hindered quaternary carbon in most of the examples, the primary factor controlling regioselectivity here could be said to be the profile of the HOMO.

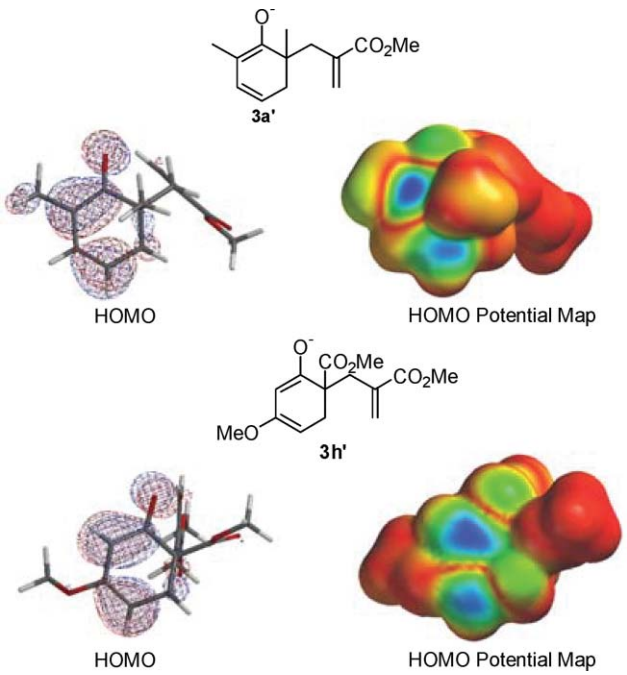
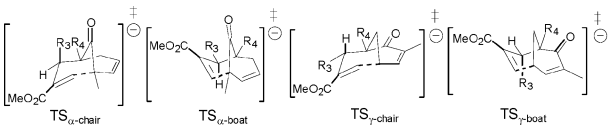


Fig. 4 HOMOs and HOMO potential maps of the enolates of **3a**′ and **h**′ by B3LYP/6–31G* calculations.

The significant difference in regioselectivity observed between diastereomers of the *anti* series and the *syn* series can be attributed to steric effects in the transition state (Fig. 5). For the *anti* series, there is an $A^{1,2}$ strain between the 2′-carboxylate of the tether and the 1′-R_3 group in the $TS_{\gamma\text{-chair}}$ transition state. This strain should

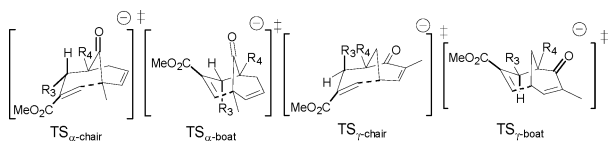
Table 5 Relative energies of the transition state in the intramolecular Michael reactions of *anti*-**3d′**–**g′** at the HF/6–31G* level



Entry	*anti*-**3′**	Relative energy/kcal mol^{-1} TS$_{\alpha\text{-chair}}$	TS$_{\alpha\text{-boat}}$	TS$_{\gamma\text{-chair}}$	TS$_{\gamma\text{boat}}$
1	*anti*-**3d′**	0 (−765.695)[a]	+9.97	+5.91 (−765.686)[a]	+7.75
2	*anti*-**3e′**	0 (−914.326)[a]	+9.41	+10.53 (−914.309)[a]	+7.29
3	*anti*-**3f′**	0 (−953.295)[a]	+10.07	+9.42 (−953.280)[a]	+7.29
4	*anti*-**3g′** (R_4 = CO_2Me)	0 (−1140.889)[a]	+10.00	+7.19 (−1140.876)[a]	+8.54

[a] The absolute energy (au) calculaated at the HF/6–31G* level in parentheses.

Table 6 Relative energies of the transition state in the intramolecular Michael reactions of *syn*-**3d′**–**g′** at the HF/6–31G* level



Entry	*syn*-**3′**	TS$_{\alpha\text{-chair}}$	Relative energy/kcal mol^{-1} TS$_{\alpha\text{-boat}}$	TS$_{\gamma\text{-chairt}}$	TS$_{\gamma\text{-boat}}$
1	*syn*-**3d′**	0 (−765.692)[a]	+8.27	+1.48 (−765.689)[a]	+8.83
2	*syn*-**3e′**	0 (−914.626)[a]	+11.03	+3.93 (−914.321)[a]	+9.23
3	*syn*-**3f′**	0 (−953.295)[a]	+9.57	+1.85 (−953.292)[a]	+14.13
4	*syn*-**3g′** (R_4 = CO_2Me)	0 (−1140.896)[a]	+13.71	+2.53 (−1140.892)[a]	+19.28

[a] The absolute energy (au) calculated at the HF/6–31G* level in parentheses.

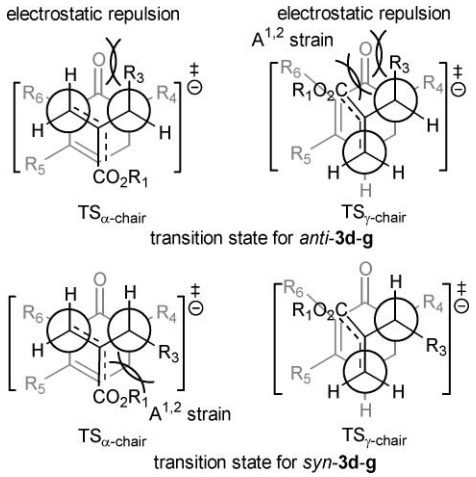
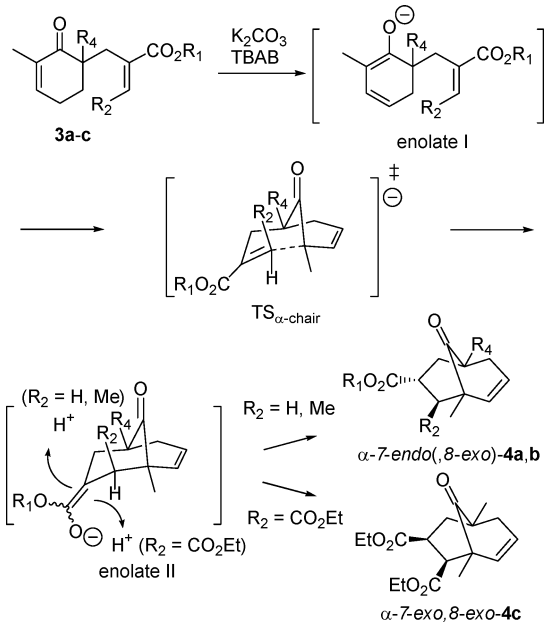


Fig. 5 Newman projection of the transition state in the intramolecular Michael reaction of *anti*- and *syn*-**3d**–**g**.



Scheme 5 Stereoselectivity in the intramolecular Michael reactions of **3a**–**c**.

disfavour the $TS_{\gamma\text{-chair}}$ transition state, and increase the energy difference between the $TS_{\alpha\text{-chair}}$ and $TS_{\gamma\text{-chair}}$ transition states, with the difference calculated between the two chair-type transition states for the corresponding 1′-unsubstituted substrates (Table 5). In some cases, this steric hindrance seemed to be so significant, that the $TS_{\gamma\text{-chair}}$ transition state was calculated to be higher in energy (Table 5, entries 2 and 3). Conversely, for the *syn* series, the absolute energy of the $TS_{\gamma\text{-chair}}$ transition state was uniformly lower than that of the corresponding *anti* $TS_{\gamma\text{-chair}}$ transition state, most likely due to release of the $A^{1,2}$ strain. As for the *syn* $TS_{\alpha\text{-chair}}$ transition state, the $A^{1,2}$ strain becomes operative and serves as an destabilizing factor. However, there is also stabilization gained by relief of the repulsive electrostatic interaction present in the *anti* $TS_{\alpha\text{-chair}}$ transition state between the R_3 or R_4 ester and the keto-carbonyl groups. Thus, the relative stability between the *anti* and *syn* $TS_{\alpha\text{-chair}}$ transition states seems to depend upon which of these offsetting factors contributes more. Nonetheless, the overall effect is a narrowing down in the energy gap between the $TS_{\alpha\text{-chair}}$ and the $TS_{\gamma\text{-chair}}$ transition states (Table 6).

Schemes 5 and 6 summarize the major pathways for the reactions of **3a**–**h**. The observed selectivity in the protonation of enolate II for **3a**, **b** and **d** can be rationalized to be due to reaction from the less crowded convex side, *i.e.*, the *exo* side, giving the *endo* products as the exclusive or the major products (R_2 or R_3 = H, Me). As for the opposite propensity observed when R_2 or R_3 is CO_2Et (**3c** and **e**–**g**), the reason is less obvious and we can only make a guess. It could be that since these Et esters are less prone to steric hindrance than their *t*-Bu counterparts, electrostatic interaction between the R_2 or R_3 ester and the ammonium ion, which can be assumed to preside near the enolate oxygen on the convex side of the molecule in enolate II, is at play, thereby making the convex face more hindered than the concave face. This would direct protonation to occur upon the *endo* face.

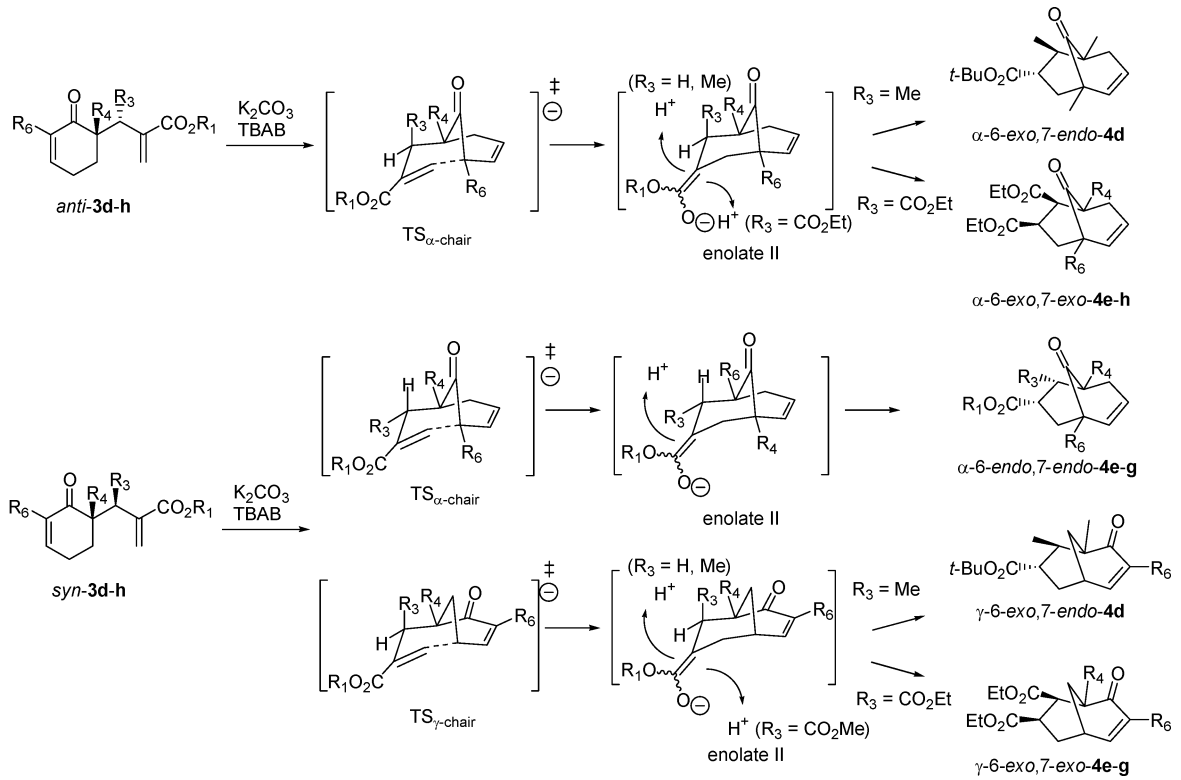
Conclusions

In summary, we have developed a practical method for the construction of poly-functionalized bicyclo[3.3.1]nonenones by successive Michael reactions of cyclohexenones **1** with acrylates **2** which function as double Michael acceptors. The construction could be carried out in both a stepwise and a one-pot reaction with similar tendencies in regioselectivity. The generally high α-regioselectivity in the intramolecular Michael reaction was in good correlation with the profile of the HOMO orbital of enolate I, as usually observed for similar conjugated enolates in intermolecular reactions. However, the regioselectivity was somewhat dependent on the substitution pattern of the reactants (R_2 or R_3). Consequent protonation was also selective, but the preferred face differed with the substitution pattern. In both the intramolecular Michael reaction and the protonation of enolate II, the ammonium counter cation played an important role. Synthetic studies towards natural products using the developed methodology are now in progress.

Experimental

All reactions involving air- and moisture-sensitive reagent were carried out under N_2. Tetrahydrofuran (THF) was distilled after refluxing over Na–benzophenone before use. Merck silica gel $60F_{254}$ TLC aluminum sheets was used for routine monitoring of reaction. Column chromatography was performed on Merck silica gel 60 (70–230 mesh, ASTM). Merck silica gel $60F_{254}$ was used for preparative thin-layer chromatography.

Melting points were taken on a Yanagimoto melting-point apparatus. NMR spectra were recorded on JEOL JNM-LA500 instruments. Internal references for ^1H NMR spectra were Me_4Si (TMS; 0.0 ppm) for $CDCl_3$, CD_3OD (3.30 ppm), C_5D_5N (7.55 ppm), and $C_6D_5CD_3$ (2.09 ppm). Chemical shifts for ^{13}C NMR spectra were referenced to $CDCl_3$ (77.0 ppm), CD_3OD (49.0 ppm), C_5D_5N (135.5 ppm), and $C_6D_5CD_3$ (20.4 ppm). MS were recorded on a JEOL JMS-SX102A instrument under electron ionization (EI) conditions (70 eV). Elemental analyses were carried out on a Perkin-Elmer 2400II analyzer.



Scheme 6 Stereoselectivity in the intramolecular Michael reactions of *anti*- and *syn*-**3d**–**h**.

Typical procedure for preparation of the annulation precursor using LDA

To a stirred solution of LDA, prepared from *i*-Pr_2NH (0.30 mL, 2.32 mmol) and *n*-BuLi (1.56 M in THF, 1.20 mL, 1.93 mmol), was added a solution of cyclohexenone **1a** (201.1 mg, 1.62 mmol) in THF (0.5 mL) at −78 °C. After 0.5 h, a solution of acrylate **2a** (322.4 mg, 1.61 mmol) in THF (0.5 mL) was added and the mixture was stirred at −78 °C for 6.5 h. The mixture was quenched with sat. NH_4Cl and extracted with Et_2O. The combined organic layer was washed with water, brine, dried over Na_2SO_4, and evaporated. The resulting residue was purified by column chromatography (silica gel, hexane–EtOAc 10 : 1) to give **3a** (355.3 mg, 83%).

Typical procedure for the intramolecular Michael reaction

To a solution of **3a** (203.3 mg, 0.77 mmol) in toluene (1.0 mL) were added K_2CO_3 (319.3 mg, 2.31 mmol) and TBAB (248.3 mg, 0.77 mmol). The mixture was stirred at 90 °C for 15.5 h. After complete consumption of **3a** by GC monitoring, the mixture was cooled to rt and quenched with sat. NH_4Cl. The resulting mixture was extracted with ether. The combined organic layer was washed with H_2O, brine, dried over $MgSO_4$, filtered and evaporated. The resulting residue was purified by preparative TLC (silica gel, hexane–EtOAc 10 : 1) to give annulation products α-*endo*-**4a** (183.0 mg, 90%) and γ-*endo*-**4a** (6.7 mg, 3%).

Typical procedure for the one-pot Michael reactions by two operations

To a solution of LDA, prepared from *i*-Pr_2NH (0.080 mL, 0.58 mmol) and *n*-BuLi (1.56 M in THF, 0.31 mL, 0.48 mmol), was added a solution of cyclohexenone **1a** (50.2 mg, 0.40 mmol) in THF (0.5 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 30 min. Then, a solution of acrylate **2a** (81.2 mg, 0.48 mmol) in THF (0.5 mL) was added to the mixture at −78 °C. After the reaction mixture was allowed to warm to rt over 6 h, to the reaction mixture was added K_2CO_3 (167.7 mg, 1.21 mmol) and TBAB (130.9 mg, 0.41 mmol). The mixture was stirred at 90 °C for 18 h. After complete consumption of **3a**, by GC monitoring, the mixture was cooled to rt and quenched with sat. NH_4Cl. The resulting mixture was extracted with Et_2O. The combined organic layer was washed with H_2O and brine, dried over $MgSO_4$, filtered and evaporated. The resulting residue was purified by preparative TLC (silica gel, hexane–EtOAc 10 : 1) to give α-*endo*-**4a** (36.1 mg, 34%), α-*exo*-**4a** (33.5 mg, 32%), and γ-*endo*-**4a** (4.0 mg, 4%).

Typical procedure for the one-pot Michael reactions by one operation

To a solution of cyclohexenone **1d** (100.7 mg, 0.48 mmol) in THF (1.5 mL) were added acrylate **2a** (94.5 mg, 0.48 mmol), K_2CO_3 (203.6 mg, 1.47 mmol) and TBAB (152.6 mg, 0.47 mmol). The resulting mixture was warmed to 45 °C and stirred for 18 h. After complete consumption of **1d** by GC monitoring, the reaction mixture was heated to 80 °C and stirred. After 25 h, the mixture was quenched with sat. NH_4Cl and extracted with Et_2O. The combined organic layer was washed with H_2O and brine, dried over $MgSO_4$, filtered and evaporated. The resulting residue was purified by preparative TLC (silica gel, EtOAc–hexane 1 : 10) to give α-*endo*-**4h** (35.5 mg, 25%), α-*exo*-**4h** (8.5 mg, 6%), and γ-*endo*-**4h** (49.1 mg, 35%).

6-Ethoxycarbonyl-2-methyl-2-cyclohexenone (1c). Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.76–6.72 (m, 1 H), 4.24 (dq, $J = 10.7$, 7.0 Hz, 1 H), 4.19 (dq, $J = 10.7$, 7.0 Hz, 1 H), 3.37–3.41 (m, 1 H), 2.48–2.32 (m, 3 H), 2.22–2.16 (m, 1 H), 1.80 (dt, $J =$ 1.8, 1.5 Hz, 3 H), 1.28 (t, $J = 7.0$ Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.5, 170.3, 145.3, 135.2, 61.0, 53.6, 26.1, 24.4, 15.9, 14.1; anal. calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.71; H, 7.61.

3-Acetoxy-2-methylenebutylic acid *tert*-butyl ester (2a). Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.26 (q, $J = 1.2$ Hz, 1 H), 5.74 (q, $J = 1.2$ Hz, 1 H), 4.77 (t, $J = 1.2$ Hz, 2 H), 2.10 (s, 3 H), 1.50 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 164.4, 136.9, 126.1, 81.3, 62.6, 28.0 (×3), 20.8; anal. calcd for $C_{10}H_{16}O_4$: C, 59,98; H, 8.05. Found: C, 59.81; H, 7.90.

3-Acetoxy-2-methylenebutylic acid *tert*-butyl ester (2b)[16a]. Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.19 (t, $J = 1.2$ Hz, 1 H), 5.71 (t, $J = 1.2$ Hz, 1 H), 5.68 (qt, $J = 6.7$, 1.2 Hz, 1 H), 2.07 (s, 3 H), 1.50 (s, 9 H), 1.39 (d, $J = 6.7$ Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7, 164.5, 142.6, 123.4, 81.2, 68.2, 28.0 (×3), 21.1, 20.0; EI-HRMS: m/z calcd for $C_{11}H_{18}O_4$ [M$^+$]: 214.1205. Found: 214.1202. Anal. calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.63; H, 8.56.

3-Acetoxy-3-ethoxycarbonyl-2-methylenepropionic acid ethyl ester (2c)[16b]. Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.49 (s, 1 H), 5.98 (s, 1 H), 5.98 (s, 1 H), 4.26 (q, $J = 7.0$ Hz, 2 H), 4.22 (q, $J = 7.0$ Hz, 2 H), 2.17 (s, 3 H), 1.31 (t, $J = 7.0$ Hz, 3 H), 1.26 (t, $J = 7.0$ Hz, 3 H).

6-(2′-*tert*-Butoxycarbonyl-2′-propenyl)-2,6-dimethyl-2-cyclohexenone (3a). Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.64–6.61 (m, 1 H), 6.12 (d, $J = 1.8$ Hz, 1 H), 5.44 (dt, $J = 1.8$, 0.9 Hz, 1 H), 2.70 (dd, $J = 13.4$, 0.9 Hz, 1 H), 2.47 (dd, $J = 13.4$, 0.9 Hz, 1 H), 2.46–2.38 (m, 1 H), 2.32–2.24 (m, 1 H), 1.87–1.77 (m, 2 H), 1.76 (q, $J = 1.8$ Hz, 3 H), 1.48 (s, 9 H), 1.04 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.1, 166.9, 143.1, 138.6, 134.2, 127.3, 80.4, 44.9, 37.2, 33.9, 27.9 (×3), 22.7, 22.0, 16.5; HR-EIMS: m/z calcd for $C_{16}H_{24}O_3$ [M$^+$]: 264.1725. Found: 264.1736; anal. calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.66; H, 9.08.

6-(2′-*tert*-Butoxycarbonyl-2′-*Z*-butenyl)-2,6-dimethyl-2-cyclohexenone (3b). Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.82 (q, $J = 7.3$ Hz, 1 H), 6.65–6.61 (m, 1 H), 2.85 (d, $J = 13.7$ Hz, 1 H), 2.54–2.45 (m, 1 H), 2.43 (d, $J = 13.7$ Hz, 1 H), 2.29–2.20 (m, 1 H), 1.90–1.79 (m, 2 H), 1.76 (q, $J = 1.7$ Hz, 3 H), 1.74 (d, $J = 7.3$ Hz, 3 H), 1.46 (s, 9 H), 1.01 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.3, 167.9, 143.0, 138.4, 134.2, 131.5, 80.0, 45.7, 35.3, 31.8, 28.1 (×3), 22.8, 21.9, 16.6, 15.2; HR-EIMS: m/z calcd for $C_{17}H_{26}O_3$ [M$^+$] 278.1882. Found: 278.1893; anal. calcd for $C_{17}H_{26}O_3$: C, 73.34; H, 9.41. Found: C, 73.06; H, 9.50.

6-(2′*E*-2′-Ethoxylcarbonyl-3′-ethoxylcarbonyl-2′-propenyl)-2,6-dimethyl-2-cyclohexenone (*E*-3c). Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.74 (s, 1 H), 6.65–6.61 (m, 1 H), 4.26–4.14 (m, 4 H), 3.30 (d, $J = 12.5$ Hz, 1 H), 3.17 (d, $J =$ 12.5 Hz, 1 H), 2.54–2.44 (m, 1 H), 2.30–2.20 (m, 1 H), 1.94 (dt, $J = 13.4$, 5.2 Hz, 1 H), 1.87 (ddd, $J = 13.4$, 8.5, 5.5 Hz, 1 H), 1.74 (q, $J = 1.8$ Hz, 3 H), 1.31 (t, $J = 7.3$ Hz, 3 H), 1.30 (t, $J = 7.3$ Hz, 3 H), 1.03 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.4, 167.4, 165.7, 145.3, 142.8, 134.2, 128.0, 61.5, 60.5, 45.5, 36.0, 32.6, 22.7, 21.5, 16.5, 14.1, 14.0; HR-EIMS: m/z calcd for $C_{17}H_{24}O_5$ [M$^+$]: 308.1624. Found: 308.1630; anal. calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.84. Found: C, 66.13; H, 8.10.

6-(2′*Z*-2′-Ethoxylcarbonyl-3′-ethoxylcarbonyl-2′-propenyl)-2,6-dimethyl-2-cyclohexenone (*Z*-3c). Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.66–6.62 (m, 1 H), 5.83 (t, $J = 1.0$ Hz, 1 H), 4.24 (dq, $J = 10.7$, 7.0 Hz, 1 H), 4.19 (dq, $J = 10.7$, 7.0 Hz, 1 H), 4.16 (q, $J = 7.0$ Hz, 2 H), 2.95 (dd, $J = 13.7$, 1.2 Hz, 1 H), 2.42–2.30 (m, 2 H), 2.37 (dd, $J = 13.7$, 0.9 Hz, 1 H), 2.08 (ddd, $J = 13.4$, 9.4, 5.5 Hz, 1 H), 1.76 (q, $J = 1.6$ Hz, 3 H), 1.71 (dt, $J =$ 13.4, 4.9 Hz, 1 H), 1.31 (t, $J = 7.0$ Hz, 3 H), 1.26 (t, $J = 7.0$ Hz, 3 H), 1.12 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.9, 168.6, 164.5, 146.5, 143.5, 133.9, 123.9, 61.3, 60.7, 45.0, 42.0, 32.8, 22.7, 22.5, 16.4, 14.0, 13.8; HR-EIMS: m/z calcd for $C_{17}H_{24}O_5$ [M$^+$]: 308.1624. Found: 308.1631; anal. calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.84. Found: C, 66.49; H, 7.84.

6-(2′-*tert*-Butoxycarbonyl-1′-methyl-2′-propenyl)-2,6-dimethyl-2-cyclohexenone (3d). A mixture of diastereomers: dr 3.6 : 1.0; yellow oil; major-**3d**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.65–6.62 (m, 1 H), 6.25 (d, $J = 1.2$ Hz, 1 H), 5.45 (bs, 1 H), 3.55 (d, $J =$ 7.3 Hz, 1 H), 2.45–2.36 (m, 1 H), 2.28–2.19 (m, 1 H), 2.03–1.95 (m, 1 H), 1.79–1.70 (m, 4 H), 1.54 (s, 9 H), 1.06 (d, $J = 7.3$ Hz, 3 H), 0.93 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.3, 166.8, 142.4, 134.8, 125.0, 124.6, 80.3, 47.0, 34.6, 31.4, 28.0 (×3), 22.3, 18.6, 16.6, 15.3; minor-**3d**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.62–6.59 (m, 1 H), 6.13 (d, $J = 1.2$ Hz, 1 H), 5.50 (bs, 1 H), 3.33 (d, $J = 7.3$ Hz, 1 H), 2.73–2.55 (m, 1 H), 2.17–2.10 (m, 1 H), 2.03–1.95 (m, 1 H), 1.79–1.70 (m, 4 H), 1.50 (s, 9 H), 1.00 (d, $J = 7.3$ Hz, 3 H), 0.98 (s, 3 H); HR-EIMS m/z calcd for $C_{17}H_{26}O_3$ [M$^+$]: 278.1882. Found: 278.1876; anal. calcd for $C_{17}H_{26}O_3$: C, 73.34; H, 9.41. Found: C, 73.46; H, 9.63.

6-(1′,2′-Diethoxycarbonyl-2′-propenyl)-2-methyl-2-cyclohexenone (3e). a mixture of diastereomers: dr 2.1 : 1; yellow oil; major-**3e**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.72–6.68 (m, 1 H), 6.41 (s, 1 H), 5.69 (s, 1 H), 4.32 (d, $J = 6.1$ Hz, 1 H), 4.26–4.11 (m, 4 H), 2.83 (ddd, $J = 12.8$, 6.1, 4.6 Hz, 1 H), 2.45–2.27 (m, 2 H), 2.20–2.10 (m, 1 H), 1.99–1.91 (m, 1 H), 1.77 (s, 3 H), 1.31 (t, $J = 7.0$ Hz, 3 H), 1.23 (t, $J = 7.0$ Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.0, 172.0, 166.1, 144.5, 137.2, 135.4, 127.2, 61.1, 60.7, 48.8, 45.5, 26.4, 25.4, 16.0, 14.1, 14.0; minor-**3e**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.69–6.66 (m, 1 H), 6.41 (s, 1 H), 5.89 (s, 1 H), 4.26–4.11 (m, 4 H), 3.95 (d, $J = 9.1$ Hz, 1 H), 3.09 (ddd, $J = 14.3$, 9.1, 4.3 Hz, 1 H), 2.45–2.27 (m, 2 H), 1.99–1.91 (m, 1 H), 1.76 (s, 3 H), 1.72–1.61 (m, 1 H), 1.30 (t, $J = 7.0$ Hz, 3 H), 1.26 (t, $J = 7.0$ Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.9, 172.8, 166.1, 144.4, 137.2, 135.2, 128.1, 61.1, 60.9, 49.8, 45.6, 26.1, 25.7, 15.9, 14.1, 14.0; HR-EIMS: m/z calcd for $C_{17}H_{22}O_5$ [M$^+$]: 294.1467. Found: 294.1475; anal. calcd for $C_{17}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 65.06; H, 7.53.

6-(1′,2′-Diethoxycarbonyl-2′-propenyl)-2,6-dimethyl-2-cyclohexenone (3f). A mixture of diastereomers: dr 1 : 1.2; yellow oil; major-**3f**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.64–6.60 (m, 1 H), 6.49 (s, 1 H), 6.10 (s, 1 H), 4.23 (q, $J = 7.1$ Hz, 2 H), 4.15 (dq, $J = 10.8$, 7.1 Hz, 1 H), 4.12 (s, 1 H), 4.10 (dq, $J = 10.8$, 7.1 Hz, 1 H), 2.40–2.30 (m, 2 H), 1.96 (ddd, $J = 13.5$, 8.5, 6.4 Hz, 1 H),

1.77 (q, $J = 1.6$ Hz, 3 H), 1.71 (dt, $J = 13.5$, 4.8 Hz, 1 H), 1.31 (t, $J = 7.1$ Hz, 3 H), 1.30 (s, 3 H), 1.25 (t, $J = 7.1$ Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.8, 171.5, 166.8, 143.1, 135.2, 133.7, 129.6, 61.1, 60.4, 48.4, 47.7, 32.5, 22.4, 17.6, 16.3, 14.0, 13.9; minor-**3f**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.67–6.63 (m, 1 H), 6.48 (s, 1 H), 5.74 (s, 1 H), 4.37 (s, 1 H), 4.20 (q, $J = 7.1$ Hz, 2 H), 4.08 (q, $J = 7.1$ Hz, 2 H), 2.55 (ddd, $J = 13.3$, 10.1, 6.1 Hz, 1 H), 2.40–2.25 (m, 2 H), 1.79 (q, $J = 1.6$ Hz, 3 H), 1.56 (dt, $J = 13.3$, 3.9 Hz, 1 H), 1.30 (t, $J = 7.1$ Hz, 3 H), 1.19 (t, $J = 7.1$ Hz, 3 H), 1.05 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.9, 171.9, 166.2, 142.8, 135.6, 133.9, 129.9, 61.0, 60.4, 51.1, 46.1, 29.8, 22.3, 20.4, 16.4, 13.9, 13.8; HR-EIMS: m/z calcd for $C_{17}H_{24}O_5$ [M$^+$]: 308.1624. Found: 308.1630; anal. calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.84. Found: C, 66.08; H, 7.72.

6-(1′,2′-Diethoxycarbonyl-2′-propenyl)-6-ethoxycarbonyl-2-methyl-2-cyclohexenone (3g). A mixture of diastereomers: dr 4.5 : 1; yellow oil; major-**3g**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.63–6.60 (m, 1 H), 6.48 (s, 1 H), 5.73 (s, 1 H), 4.69 (s, 1 H), 4.25–4.05 (m, 6 H), 2.66 (ddd, $J = 13.1$, 11.3, 5.5 Hz, 1 H), 2.46–2.35 (m, 1 H), 2.35–2.25 (m, 1 H), 2.30–2.25 (m, 1 H), 1.82–1.80 (m, 3 H), 1.30 (t, $J = 7.0$ Hz, 3 H), 1.22 (t, $J = 7.0$ Hz, 3 H), 1.21 (t, $J = 7.0$ Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.7, 171.1, 169.6, 166.0, 144.0, 135.3, 135.1, 129.7, 61.6, 61.3, 60.9, 59.1, 47.6, 27.1, 23.5, 16.4, 14.1, 13.9, 13.8; minor-**3g**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.63–6.60 (m, 1 H), 6.52 (s, 1 H), 5.97 (s, 1 H), 4.39 (s, 1 H), 4.25–4.05 (m, 6 H), 2.46–2.35 (m, 1 H), 2.35–2.23 (m, 2 H), 2.22–2.14 (m, 1 H), 1.82–1.80 (m, 3 H), 1.31 (t, $J = 7.0$ Hz, 3 H), 1.24 (t, $J = 7.0$ Hz, 3 H), 1.21 (t, $J = 7.0$ Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.5, 171.3, 170.2, 166.7, 143.7, 135.2, 134.7, 129.0, 61.5, 61.2, 61.0, 59.1, 48.9, 30.5, 23.6, 16.4, 14.1, 13.9, 13.8; HR-EIMS: m/z calcd for $C_{19}H_{26}O_7$ [M$^+$]: 366.1679. Found: 366.1662; anal. calcd for $C_{19}H_{26}O_7$: C, 62.28; H, 7.15. Found: C, 61.98; H, 7.45.

7-*endo*-*tert*-Butoxycarbonyl-1,5-dimethylbicyclo[3.3.1]non-2-en-9-one (α-*endo*-4a). yellow solid; mp 75 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.55 (ddd, $J = 9.7$, 4.3, 2.4 Hz, 1 H), 5.30 (ddd, $J = 9.7$, 2.7, 1.2 Hz, 1 H), 2.81 (ddd, $J = 18.3$, 4.3, 0.9 Hz, 1 H), 2.73 (ddd, $J = 14.3$, 3.4, 1.8 Hz, 1 H), 2.59 (ddd, $J = 14.0$, 3.7, 1.8 Hz, 1 H), 2.43 (ddt, $J = 7.3$, 6.4, 1.8 Hz, 1 H), 2.31–2.25 (m, 1 H), 1.80 (dd, $J = 14.0$, 6.4 Hz, 1 H), 1.72 (ddd, $J = 14.3$, 7.3, 1.8 Hz, 1 H), 1.47 (s, 9 H), 1.09 (s, 3 H), 1.07 (s, 3 H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 216.5, 172.9, 133.4, 128.3, 80.5, 46.5, 45.5, 43.7, 42.5, 41.4, 38.1, 27.9 (×3), 24.0, 21.6; HR-EIMS: m/z calcd for $C_{16}H_{24}O_3$ [M$^+$]: 264.1725. Found: 264.1734; anal. calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.79; H, 9.23.

7-*endo*-*tert*-Butoxycarbonyl-1,3-dimethylbicyclo[3.3.1]non-3-en-2-one (γ-*endo*-4a). Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.60–6.56 (m, 1 H), 2.59–2.54 (m, 1 H), 2.57–2.53 (m, 1 H), 2.40–2.35 (m, 1 H), 2.37–2.32 (m, 1 H), 2.14–2.09 (m, 1 H), 1.80 (ddd, $J = 14.0$, 7.3, 4.0 Hz, 1 H), 1.66 (bs, 3 H), 1.57–1.53 (m, 1 H), 1.40 (dd, $J = 14.0$, 7.6 Hz, 1 H), 1.37 (s, 9 H), 1.09 (s, 3 H).

7-*endo*-*tert*-Butoxycarbonyl-1,5,8-*exo*-trimethylbicyclo[3.3.1]-non-2-en-9-one (α-7-*endo*,8-*exo*-4b). Yellow solid; mp 77 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.50 (ddd, $J = 9.4$, 4.3, 2.4 Hz, 1 H), 5.31 (ddd, $J = 9.4$, 2.7, 0.9 Hz, 1 H), 2.84 (qt, $J = 7.3$, 1.5 Hz, 1 H), 2.78 (ddd, $J = 17.7$, 4.3, 0.9 Hz, 1 H), 2.66 (dt, $J = 14.6$, 1.5 Hz, 1 H), 2.27 (dddd, $J = 17.7$, 2.7, 2.4, 1.8 Hz, 1 H), 2.21 (dt, $J = 7.6$, 1.5 Hz, 1 H), 1.86 (ddd, $J = 14.6$, 7.6, 1.8 Hz, 1 H), 1.48 (s, 9 H), 1.06 (s, 3 H), 1.06 (s, 3 H), 0.93 (d, $J = 7.3$ Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.4, 172.9, 134.9, 127.6, 80.5, 50.2, 46.2, 45.3, 44.3, 43.7, 38.2, 28.0 (×3), 23.9, 19.4, 16.3; HR-EIMS: m/z calcd for $C_{17}H_{26}O_3$ [M$^+$]: 278.1882. Found: 278.1881; anal. calcd for $C_{17}H_{26}O_3$: C, 73.34; H, 9.41. Found: C, 73.10; H, 9.37.

7-*endo*-*tert*-Butoxycarbonyl-1,2,6-*exo*-trimethylbicyclo[3.3.1]non-3-en-2-one (γ-7-*endo*,8-*exo*-4b). Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.63–6.60 (m, 1 H), 2.64–2.57 (m, 1 H), 2.28–2.23 (m, 2 H), 2.22–2.17 (m, 1 H), 1.90–1.85 (m, 1 H), 1.80 (ddd, $J = 12.8$, 2.7, 2.1 Hz, 1 H), 1.65 (bs, 3 H), 1.54 (dd, $J = 14.0$, 7.3 Hz, 1 H), 1.37 (s, 9 H), 1.24 (d, $J = 7.3$ Hz, 3 H), 1.09 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.3, 173.3, 147.7, 136.1, 80.2, 43.9, 41.2, 37.1, 35.4, 31.6, 28.9, 28.1 (×3), 25.5, 20.1, 16.4; HR-EIMS: m/z calcd for $C_{17}H_{26}O_3$ [M$^+$]: 278.1882. Found: 278.1891; anal. calcd for $C_{17}H_{26}O_3$: C, 73.34; H, 9.41. Found: C, 73.57; H, 9.45.

7-*exo*,8-*exo*-Diethoxycarbonyl-1,5-dimethylbicyclo[3.3.1]non-2-en-9-one (α-7-*exo*,8-*exo*-4c). Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.88 (ddd, $J = 9.4$, 4.0, 3.1 Hz, 1 H), 5.34 (ddd, $J = 9.4$, 2.4, 1.2 Hz, 1 H), 4.18–4.06 (m, 2 H), 4.18–4.06 (m, 2 H), 3.51 (dt, $J = 13.7$, 5.2 Hz, 1 H), 3.01 (dd, $J = 5.2$, 1.8 Hz, 1 H), 2.59 (ddd, $J = 18.6$, 4.0, 1.2 Hz, 1 H), 2.52 (td, $J = 13.7$, 1.8 Hz, 1 H), 2.45 (dddd, $J = 18.6$, 3.1, 2.4, 1.8 Hz, 1 H), 2.03 (ddd, $J = 13.7$, 5.2, 1.8 Hz, 1 H), 1.24 (t, $J = 7.0$ Hz, 3 H), 1.24 (t, $J = 7.0$ Hz, 3 H), 1.14 (s, 3 H), 1.12 (s, 3 H).

6-*exo*,7*exo*-Diethoxycarbonyl-1,3-dimethylbicyclo[3.3.1]non-3-en-2-one (γ-7-*exo*,8-*exo*-4c). Yellow oil; ^{1}H NMR (500 MHz, C_6D_5N) δ 6.70–6.64 (m, 1 H), 4.22–4.08 (m, 4 H), 3.30–3.27 (m, 1 H), 3.08–3.04 (m, 1 H), 2.83 (dt, $J = 13.4$, 5.2 Hz, 1 H), 2.20 (t, $J = 13.4$ Hz, 1 H), 2.14 (ddd, $J = 13.4$, 5.2, 1.8 Hz, 1 H), 1.92–1.86 (m, 1 H), 1.82 (bs, 3 H), 1.64 (ddd, $J = 13.1$, 2.1, 2.1 Hz, 1 H), 1.15 (t, $J = 7.0$ Hz, 3 H), 1.14 (s, 3 H), 1.11 (t, $J = 7.0$ Hz, 3 H); ^{13}C NMR (125 MHz, C_6D_5N) δ 202.7, 173.5, 172.7, 145.8, 138.8, 61.0, 60.6, 42.6, 41.8, 37.4, 36.7, 35.0, 34.4, 25.1, 16.0, 14.2, 14.2; HR-EIMS: m/z calcd for $C_{17}H_{24}O_5$ [M$^+$]: 308.1624. Found: 308.1633.

7-*endo*-*tert*-Butoxycarbonyl-1,5,6-*exo*-trimethylbicyclo[3.3.1]non-2-en-9-one (α-6-*exo*,7-*endo*-4d). Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.52 (ddd, $J = 9.4$, 4.0, 2.7 Hz, 1 H), 5.30 (ddd, $J = 9.4$, 2.7, 0.9 Hz, 1 H), 2.99 (ddd, $J = 18.3$, 4.0, 0.9 Hz, 1 H), 2.92 (qt, $J = 7.3$, 2.1 Hz, 1 H), 2.48 (dt, $J = 14.0$, 2.1 Hz, 1 H), 2.27 (dt, $J = 18.3$, 2.7 Hz, 1 H), 2.22 (dt, $J = 6.4$, 2.1 Hz, 1 H), 1.87 (dd, $J = 14.0$, 6.4 Hz, 1 H), 1.47 (s, 9 H), 1.08 (s, 3 H), 1.05 (s, 3 H), 0.92 (d, $J = 7.3$ Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.0, 172.9, 133.6, 128.2, 80.5, 48.7, 46.3, 45.9, 45.2, 44.1, 37.8, 27.9 (×3), 21.7, 21.6, 18.7; HR-EIMS: m/z calcd for $C_{17}H_{26}O_3$ [M$^+$]: 278.1882. Found: 278.1871; anal. calcd for $C_{17}H_{26}O_3$: C, 73.34; H, 9.41. Found: C, 73.64; H, 9.19.

7-*endo*-*tert*-Butoxycarbonyl-1,3,8-*exo*-trimethylbicyclo[3.3.1]non-3-en-2-one (γ-6-*exo*,7-*endo*-4d). Yellow solid; mp 59 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.60–6.57 (m, 1 H), 2.52–2.47 (m, 1 H), 2.45 (q, $J = 7.3$ Hz, 1 H), 2.29–2.23 (m, 2 H), 1.92 (ddd, $J = 14.0$, 6.7, 4.0 Hz, 1 H), 1.80–1.78 (m, 2 H), 1.66 (bs, 3 H), 1.37 (s, 9 H), 1.08 (d, $J = 7.3$ Hz, 3 H), 1.02 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.3, 173.2, 146.7, 136.6, 80.0, 45.3, 43.9,

36.1, 33.7, 31.0, 28.1 (×3), 23.5, 23.4, 16.6, 15.9; HR-EIMS: *m/z* calcd for $C_{17}H_{26}O_3$ [M$^+$]: 278.1882. Found: 278.1887; anal. calcd for $C_{17}H_{26}O_3$: C, 73.34; H, 9.41. Found: C, 73.14; H, 9.58.

6-*exo*,7*exo*-Diethoxycarbonyl-1-methylbicyclo[3.3.1]non-2-en-9-one (α-6-*exo*,7-*exo*-4e). Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.88–5.83 (m, 1 H), 5.42–5.38 (m, 1 H), 4.19–4.07 (m, 4 H), 3.35–3.31 (m, 1 H), 3.29 (dt, J = 13.0, 4.9 Hz, 1 H), 2.92–2.89 (m, 1 H), 2.93–2.85 (m, 1 H), 2.60–2.52 (m, 1 H), 2.41 (t, J = 13.0 Hz, 1 H), 2.07 (ddd, J = 13.0, 4.9, 2.1 Hz, 1 H), 1.24 (t, J = 7.0 Hz, 3 H), 1.23 (t, J = 7.0 Hz, 3 H), 1.13 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.8, 172.9, 171.9, 134.3, 127.7, 61.0, 60.9, 52.6, 46.6, 45.9, 38.8, 37.9, 37.1, 21.1, 14.1, 14.0; HR-EIMS: *m/z* calcd for $C_{16}H_{22}O_5$ [M$^+$]: 294.1467. Found: 294.1471.

6-*exo*,7-*endo*-Diethoxycarbonyl-1-methylbicyclo[3.3.1]non-2-en-9-one (α-6-*exo*,7-*endo*-4e). Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.56 (ddd, J = 9.5, 4.0, 2.5 Hz, 1 H), 5.30 (ddd, J = 9.5, 2.5, 0.8 Hz, 1 H), 4.21–4.12 (m, 4 H), 3.90 (dd, J = 4.0, 2.2 Hz, 1 H), 3.04–3.00 (m, 2 H), 2.84–2.79 (m, 1 H), 2.72 (ddt, J = 18.3, 6.7, 2.5 Hz, 1 H), 2.58 (dt, J = 14.1, 2.2 Hz, 1 H), 2.09 (dd, J = 14.1, 6.6 Hz, 1 H), 1.30 (t, J = 7.0 Hz, 3 H), 1.26 (t, J = 7.0 Hz, 3 H), 1.09 (s, 3 H).

6-*endo*,7-*exo*-Diethoxycarbonyl-1-methylbicyclo[3.3.1]non-2-en-9-one (α-6-*endo*,7-*exo*-4e). Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.87 (ddd, J = 9.4, 4.0, 3.4 Hz, 1 H), 5.39 (ddd, J = 9.4, 2.4, 1.2 Hz, 1 H), 4.21–4.11 (m, 4 H), 3.36 (td, J = 13.0, 4.9 Hz, 1 H), 3.19 (dd, J = 13.0, 4.3 Hz, 1 H), 3.03 (dd, J = 7.0, 4.3 Hz, 1 H), 2.62–2.53 (m, 1 H), 2.43 (dd, J = 18.9, 4.0 Hz, 1 H), 2.10 (dd, J = 13.0, 4.9 Hz, 1 H), 1.65 (t, J = 13.0 Hz, 1 H), 1.25 (t, J = 7.0 Hz, 3 H), 1.24 (t, J = 7.0 Hz, 3 H), 1.12 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.4, 174.1, 171.5, 132.9, 128.9, 61.1, 60.9, 50.7, 46.0, 45.7, 42.2, 38.6, 32.3, 20.7, 14.1 (×2); HR-EIMS: *m/z* calcd for $C_{16}H_{22}O_5$ [M$^+$]: 294.1467. Found: 294.1459.

7-*exo*,8-*exo*-Diethoxycarbonyl-3-methylbicyclo[3.3.1]non-3-en-2-one (γ-6-*exo*,7-*exo*-4e). Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.83–6.78 (m, 1 H), 4.16 (q, J = 7.0 Hz, 2 H), 4.12 (q, J = 7.0 Hz, 2 H), 3.28–3.24 (m, 1 H), 3.01–2.97 (m, 1 H), 2.77–2.71 (m, 1 H), 2.56 (dt, J = 12.8, 4.9 Hz, 1 H), 2.29 (td, J = 12.8, 4.3 Hz, 1 H), 2.11–2.05 (m, 1 H), 1.96–1.90 (m, 1 H), 1.83 (s, 3 H), 1.77 (ddd, J = 12.8, 4.9, 2.3 Hz, 1 H), 1.26 (t, J = 7.0 Hz, 3 H), 1.20 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.9, 173.4, 172.1, 148.3, 137.5, 60.9, 60.6, 44.7, 43.4, 36.0, 30.3, 29.8, 24.5, 15.6, 14.1, 14.0; HR-EIMS: *m/z* calcd for $C_{16}H_{22}O_5$ [M$^+$]: 294.1467. Found: 294.1455.

6-*exo*,7-*exo*-Diethoxycarbonyl-1,5-dimethylbicyclo[3.3.1]non-2-en-9-one (α-6-*exo*,7-*exo*-4f). Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.79 (dt, J = 9.4, 3.4, 3.4 Hz, 1 H), 5.42 (ddd, J = 9.4, 2.4, 1.5 Hz, 1 H), 4.18–4.04 (m, 4 H), 3.44 (dt, J = 13.0, 4.9 Hz, 1 H), 3.09 (dd, J = 4.9, 1.8 Hz, 1 H), 2.66 (ddd, J = 18.9, 3.4, 1.5 Hz, 1 H), 2.52 (t, J = 13.0 Hz, 1 H), 2.45 (ddd, J = 18.9, 3.4, 2.4 Hz, 1 H), 1.92 (ddd, J = 13.0, 4.9, 1.8 Hz, 1 H), 1.25 (t, J = 7.0 Hz, 3 H), 1.23 (t, J = 7.0 Hz, 3 H), 1.18 (s, 3 H), 1.09 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.6, 172.8, 171.7, 134.9, 127.7, 60.9, 60.6, 58.4, 46.2, 46.0, 45.9, 39.4, 38.5, 21.7, 21.3, 14.1, 14.0; HR-EIMS: *m/z* calcd for $C_{17}H_{24}O_5$ [M$^+$]: 308.1624. Found: 308.1639; anal. calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.84. Found: C, 66.01; H, 7.92.

6-*endo*,7-*exo*-Diethoxycarbonyl-1,5-dimethylbicyclo[3.3.1]non-2-en-9-one (α-6-*endo*,7-*exo*-4f). Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.85 (ddd, J = 9.4, 4.0, 3.1 Hz, 1 H), 5.39 (ddd, J = 9.4, 2.4, 1.2 Hz, 1 H), 4.22–4.07 (m, 4 H), 3.56 (td, J = 12.7, 4.6 Hz, 1 H), 3.03 (ddd, J = 18.9, 4.0, 1.2 Hz, 1 H), 2.77 (d, J = 12.7 Hz, 1 H), 2.14 (dd, J = 12.7, 4.6 Hz, 1 H), 2.08 (ddd, J = 18.9, 3.1, 2.4 Hz, 1 H), 1.67 (t, J = 12.7 Hz, 1 H), 1.28 (t, J = 7.0 Hz, 3 H), 1.23 (t, J = 7.0 Hz, 3 H), 1.14 (s, 3 H), 1.13 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.3, 173.8, 171.5, 132.6, 128.9, 61.0, 60.8, 56.0, 46.4, 46.1, 42.5, 40.1, 38.8, 22.2, 21.4, 14.2, 14.1; HR-EIMS: *m/z* calcd for $C_{17}H_{24}O_5$ [M$^+$]: 308.1624. Found: 308.1635; anal. calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.84. Found: C, 66.01; H, 7.92.

7-*exo*,8-*exo*-Diethoxycarbonyl-1,3-dimethylbicyclo[3.3.1]non-3-en-2-one (γ-6-*exo*,7-*exo*-4f). Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.82–6.78 (m, 1 H), 4.21–4.04 (m, 4 H), 2.88 (d, J = 5.2 Hz, 1 H), 2.79–2.74 (m, 1 H), 2.65 (dt, J = 13.0, 5.2 Hz, 1 H), 2.49 (td, J = 13.0, 4.6 Hz, 1 H), 2.21–2.15 (m, 1 H), 1.87–1.83 (m, 1 H), 1.84–1.80 (m, 1 H), 1.81 (s, 3 H), 1.28 (t, J = 7.0 Hz, 3 H), 1.20 (t, J = 7.0 Hz, 3 H), 1.10 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.0, 173.4, 172.2, 148.2, 137.4, 60.7, 60.2, 47.3, 44.2, 37.8, 35.4, 30.5, 23.8, 23.0, 15.8, 14.1, 14.0; HR-EIMS: *m/z* calcd for $C_{17}H_{24}O_5$ [M$^+$]: 308.1624. Found: 308.1634; anal. calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.84. Found: C, 66.38; H, 7.86.

1-Methyl-5,6-*exo*,7-*exo*-triethoxycarbonylbicyclo[3.3.1]non-2-en-9-one (α-6-*exo*,7-*exo*-4g). Yellow oil; ^{1}H NMR (500 MHz, $C_6D_5CD_3$) δ 5.25 (dt, J = 9.4, 3.4 Hz, 1 H), 4.98 (ddd, J = 9.4, 2.4, 1.5 Hz, 1 H), 4.10–3.88 (m, 6 H), 3.40 (dd, J = 4.5, 1.8 Hz, 1 H), 3.24 (dt, J = 13.1, 4.5 Hz, 1 H), 3.20 (ddd, J = 19.2, 3.4, 2.4 Hz, 1 H), 2.54 (t, J = 13.1 Hz, 1 H), 2.02 (ddd, J = 19.2, 3.4, 1.5 Hz, 1 H), 1.57 (ddd, J = 13.1, 4.5, 1.8 Hz, 1 H), 1.11 (s, 3 H), 1.08 (t, J = 7.0 Hz, 3 H), 1.05 (t, J = 7.0 Hz, 3 H), 0.98 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $C_6D_5CD_3$) δ 203.8, 171.6, 170.5, 170.5, 135.2, 127.1, 61.6, 60.8, 60.7, 59.1, 55.2, 45.6, 40.4, 39.5, 37.9, 21.6, 14.2, 14.1, 14.0; HR-EIMS: *m/z* calcd for $C_{19}H_{26}O_7$ [M$^+$]: 366.1679. Found: 366.1676; anal. calcd for $C_{19}H_{26}O_7$: C, 62.28; H, 7.15. Found: C, 62.15; H, 7.19.

1-Methyl-5,6-*endo*,7-*endo*-triethoxycarbonylbicyclo[3.3.1]non-2-en-9-one (α-6-*endo*,7-*endo*-4g). Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.62 (ddd, J = 9.4, 4.6, 2.4 Hz, 1 H), 5.48 (dd, J = 9.4, 2.4 Hz, 1 H), 4.28–4.12 (m, 4 H), 4.10 (q, J = 7.0 Hz, 2 H), 3.91 (d, J = 8.2 Hz, 1 H), 3.18 (dt, J = 18.3, 2.4 Hz, 1 H), 3.03 (dd, J = 18.3, 4.6 Hz, 1 H), 2.84 (td, J = 8.2, 7.3 Hz, 1 H), 2.28 (dd, J = 13.4, 8.2 Hz, 1 H), 2.10 (dd, J = 13.4, 7.3 Hz, 1 H), 1.29 (t, J = 7.0 Hz, 3 H), 1.27 (t, J = 7.0 Hz, 3 H), 1.22 (t, J = 7.0 Hz, 3 H), 1.14 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.2, 173.6, 171.9, 170.2, 136.2, 124.6, 61.6, 61.1 (×2), 59.4, 51.0, 45.1, 40.0, 39.6, 39.5, 21.6, 14.1, 14.0, 13.9; HR-EIMS: *m/z* calcd for $C_{19}H_{26}O_7$ [M$^+$]: 366.1679. Found: 366.1694; anal. calcd for $C_{19}H_{26}O_7$: C, 62.28; H, 7.15. Found: C, 62.07; H, 7.31.

1-Methyl-5,6-*endo*,7-*exo*-triethoxycarbonylbicyclo[3.3.1]non-2-en-9-one (α-6-*endo*,7-*exo*-4g). Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.87 (ddd, J = 9.4, 4.3, 2.7 Hz, 1 H), 5.35 (ddd, J = 9.4, 2.7, 1.2 Hz, 1 H), 4.31 (dq, J = 10.7, 7.0 Hz, 1 H), 4.27 (dq, J = 10.7, 7.0 Hz, 1 H), 4.17 (q, J = 7.0 Hz, 2 H), 4.14 (dq, J = 10.7, 7.0 Hz, 1 H), 4.09 (dq, J = 10.7, 7.0 Hz, 1 H), 4.03 (dd, J = 13.1, 1.2 Hz, 1 H), 3.43 (td, J = 13.1, 4.6 Hz, 1 H), 3.39–3.32 (m, 1 H), 2.53 (ddd, J = 19.5, 4.3, 1.2 Hz, 1 H), 2.09 (dd, J = 13.1, 4.6 Hz,

1 H), 1.79 (t, J = 13.1 Hz, 1 H), 1.34 (t, J = 7.0 Hz, 3 H), 1.27 (t, J = 7.0 Hz, 3 H), 1.20 (t, J = 7.0 Hz, 3 H), 1.14 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.9, 173.9, 170.6, 170.1, 132.0, 128.0, 61.7, 61.5, 61.1, 59.0, 51.8, 46.4, 40.6, 39.3, 35.4, 20.7, 14.1, 14.0, 13.9; HR-EIMS: m/z calcd for $C_{19}H_{26}O_7$ [M$^+$]: 366.1679. Found: 366.1668; anal. calcd for $C_{19}H_{26}O_7$: C, 62.28; H, 7.15. Found: C, 62.01; H, 7.43.

3-Methyl-1,7-*exo*,8-*exo*-triethoxycarbonylbicyclo[3.3.1]non-3-en-2-one (γ-6-*exo*,7-*exo*-4g). Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.86–6.83 (m, 1 H), 4.27–4.04 (m, 6 H), 3.50 (d, J = 5.4 Hz, 1 H), 2.87–2.83 (m, 1 H), 2.76 (ddd, J = 13.2, 3.5, 1.8 Hz, 1 H), 2.73 (ddd, J = 13.2, 5.4, 3.5 Hz, 1 H), 2.58–2.53 (m, 1 H), 2.03 (td, J = 13.2, 4.0 Hz, 1 H), 1.84 (bs, 3 H), 1.70–1.64 (m, 1 H), 1.26 (t, J = 7.0 Hz, 3 H), 1.25 (t, J = 7.0 Hz, 3 H), 1.23 (t, J = 7.0 Hz, 3 H).

7-*endo*-*tert*-Butoxycarbonyl-2-ethoxy-5-ethoxycarbonylbicyclo[3.3.1]non-2-en-9-one (α-*endo*-4h). Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.56 (dd, J = 4.6, 2.7 Hz, 1 H), 4.27–4.20 (m, 2 H), 3.74–3.68 (m, 2 H), 3.11 (dd, J = 16.8, 2.7 Hz, 1 H), 2.84 (tt, J = 5.3, 2.4 Hz, 1 H), 2.82–2.76 (m, 1 H), 2.72–2.57 (m, 4 H), 2.17 (dt, J = 13.7, 5.3 Hz, 1 H), 1.46 (s, 9 H), 1.31 (t, J = 7.0 Hz, 3 H), 1.30 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 207.6, 172.2, 171.7, 151.6, 93.2, 80.7, 62.8, 61.4, 56.9, 49.1, 37.1, 36.8, 32.8, 32.2, 28.0 (×3), 14.5, 14.1; HR-EIMS: m/z calcd for $C_{19}H_{28}O_6$ [M$^+$]: 352.1886. Found: 352.1879; anal calcd for $C_{19}H_{28}O_6$: C, 64.75; H, 8.01. Found: C, 64.61; H, 8.05.

7-*exo*-*tert*-Butoxycarbonyl-2-ethoxy-5-ethoxycarbonylbicyclo[3.3.1]non-2-en-9-one (α-*exo*-4h). Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.81 (t, J = 3.7 Hz, 1 H), 4.27–4.20 (m, 2 H), 3.78–3.72 (m, 2 H), 3.30 (dd, J = 17.4, 1.2 Hz, 1 H), 3.01 (tt, J = 12.8, 4.3 Hz, 1 H), 2.91 (t, J = 3.4 Hz, 1 H), 2.52 (td, J = 12.8, 1.2 Hz, 1 H), 2.44 (dd, J = 17.4, 4.0 Hz, 1 H), 2.33 (ddt, J = 12.8, 4.3, 3.4 Hz, 1 H), 2.21 (dt, J = 12.8, 4.3, 3.4 Hz, 1 H), 2.02 (td, J = 12.8, 3.4 Hz, 1 H), 1.45 (s, 9 H), 1.32–1.27 (m, 6 H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 206.4, 173.1, 171.3, 150.5, 94.2, 81.0, 63.0, 61.6, 56.9, 50.1, 40.6, 37.0, 34.0, 33.4, 28.0 (×3), 14.4, 14.1; HR-EIMS: m/z calcd for $C_{19}H_{28}O_3$ [M$^+$]: 352.1886. Found: 352.1888.

7-*endo*-*tert*-Butoxycarbonyl-4-ethoxy-1-methylbicyclo[3.3.1]non-3-en-2-one (γ-*endo*-4h). Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.22 (s, 1 H), 4.24–4.15 (m, 2 H), 3.90 (dq, J = 9.4, 7.0 Hz, 1 H), 3.80 (dq, J = 9.4, 7.0 Hz, 1 H), 2.84 (dd, J = 14.6, 1.5 Hz, 1 H), 2.70–2.65 (m, 2 H), 2.65–2.59 (m, 2 H), 1.92 (dd, J = 14.6, 7.6 Hz, 1 H), 1.72 (dd, J = 12.5, 2.4 Hz, 1 H), 1.70–1.64 (m, 1 H), 1.40 (t, J = 7.0 Hz, 3 H), 1.38 (s, 9 H), 1.24 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.0, 179.3, 172.8, 172.5, 103.6, 80.9, 64.6, 60.8, 52.3, 36.5, 36.1, 34.2, 29.2, 27.5 (×3), 25.8, 14.2, 14.0; HR-EIMS: m/z calcd for $C_{19}H_{28}O_6$ [M$^+$]: 352.1886. Found: 352.1884; anal calcd for $C_{19}H_{28}O_6$: C, 64.75; H, 8.01. Found: C, 64.58; H, 7.95.

7-*endo*-*tert*-Butoxycarbonyl-7-*exo*-(2′-*tert*-butoxycarbonyl-2′-propenyl)-2-ethoxy-1,5-dimethylbicyclo[3.3.1]non-2-en-9-one (5). Yellow oil; ^{1}H NMR (500 MHz, C_6D_5N) δ 6.16 (bs, 1 H), 5.53 (ddd, J = 9.4, 4.3, 2.4 Hz, 1 H), 5.47 (bs, 1H), 5.37–5.33 (m, 1 H), 2.88 (dd, J = 18.0, 4.3 Hz, 1 H), 2.78 (dd, J = 13.9, 3.7 Hz, 1 H), 2.71 (dd, J = 13.9, 3.7 Hz, 1 H), 2.59 (d, J = 13.1 Hz, 1 H), 2.55 (d, J = 13.1 Hz, 1 H), 2.23–2.16 (m, 1 H), 1.68 (d, J = 13.9 Hz, 1 H), 1.66 (d, J = 13.9 Hz, 1 H), 1.48 (s, 9 H), 1.47 (s, 9 H), 1.16 (s, 3 H), 1.12 (s, 3 H); ^{13}C NMR (125 MHz, C_6D_5N) δ 215.9, 173.7, 166.8, 138.5, 134.2, 128.7, 128.1, 81.0, 80.7, 48.8, 48.3, 47.1, 46.3, 45.4, 43.9, 43.7, 28.1 (×3), 27.9 (×3), 24.9, 22.2; HR-EIMS: m/z calcd for $C_{24}H_{36}O_5$ [M$^+$]: 404.2563. Found: 404.2577; anal. calcd for $C_{24}H_{36}O_5$: C, 71.26; H, 8.97. Found: C, 71.09; H, 8.88.

6-Ethoxycarbonyl-6-ethoxycarbonylmethyl-1,3-dimethylbicyclo[3.2.1]oct-3-en-2-one (6). Major : minor *ca.* 3 : 2; major-**6**: yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.79–6.76 (m, 1 H), 4.15–4.06 (m, 4 H), 3.14 (d, J = 15.5 Hz, 1 H), 2.80 (dd, J = 7.0, 4.3 Hz, 1 H), 2.66 (d, J = 15.5 Hz, 1 H), 2.57 (d, J = 14.6 Hz, 1 H), 1.96–1.92 (m, 1 H), 1.86 (ddd, J = 11.9, 4.3, 1.8 Hz, 1 H), 1.72 (d, J = 1.5 Hz, 3 H), 1.58 (d, J = 14.6 Hz, 1 H), 1.26 (s, 3 H), 1.23 (t, J = 7.0 Hz, 3 H), 1.22 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.1, 173.6, 170.7, 146.2, 135.8, 60.9, 60.8, 56.5, 53.7, 47.1, 45.7, 45.3, 41.4, 20.7, 15.1, 14.1, 14.1; HR-EIMS: m/z calcd for $C_{17}H_{24}O_5$ [M$^+$]: 308.1624. Found: 308.1612; anal. calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.84. Found: C, 66.49; H, 7.76; minor-**6**: yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.92–6.88 (m, 1 H), 4.25–4.14 (m, 2 H), 4.10 (q, J = 7.0 Hz, 2 H), 3.08 (dd, J = 7.3, 4.0 Hz, 1 H), 2.82 (d, J = 16.1 Hz, 1 H), 2.59 (d, J = 14.6 Hz, 1 H), 2.53 (d, J = 16.1 Hz, 1 H), 1.95 (ddd, J = 11.6, 4.0, 1.5 Hz, 1 H), 1.85 (d, J = 11.6 Hz, 1 H), 1.80 (d, J = 1.5 Hz, 3 H), 1.46 (dd, J = 14.6, 1.5 Hz, 1 H), 1.28 (t, J = 7.0 Hz, 3 H), 1.27 (s, 3 H), 1.23 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.1, 175.6, 171.1, 147.0, 136.0, 61.4, 60.7, 56.0, 52.7 (×2), 45.7, 42.5, 42.0, 19.9, 15.3, 14.1, 14.1; HR-EIMS: m/z calcd for $C_{17}H_{24}O_5$ [M$^+$]: 308.1624. Found: 308.1610.

1,5-Dimethyl-7-*endo*-hydroxycarbonylbicyclo[3.3.1]non-2-en-9-one (α-*endo*-7). Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.66 (dt, J = 9.5, 3.9 Hz, 1 H), 5.21 (ddd, J = 9.5, 2.4, 1.5 Hz, 1 H), 3.15 (tt, J = 12.8, 4.4 Hz, 1 H), 2.37 (ddd, J = 18.7, 3.9, 1.3 Hz, 1H), 2.18 (ddd, J = 18.7, 3.9, 2.4 Hz, 1 H), 2.10–1.99 (m, 2 H), 1.79 (dt, J = 12.8, 1.3 Hz, 1 H), 1.76 (t, J = 12.8 Hz, 1 H), 1.11 (s, 3 H), 1.04 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.0, 176.6, 133.1, 128.6, 46.5, 46.2, 45.0, 44.3, 43.5, 37.7, 23.8, 21.6; EI-HRMS: m/z calcd for $C_{12}H_{16}O_3$ [M$^+$]: 208.1099. Found: 208.1101.

1,3-Dimethyl-7-*endo*-hydroxycarbonylbicyclo[3.3.1]non-3-en-2-one (γ-*exo*-7). Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.74–6.71 (m, 1 H), 2.76–2.71 (m, 1 H), 2.56 (tt, J = 13.0, 4.4 Hz, 1 H), 2.12–2.06 (m, 1 H), 1.93–1.87 (m, 2 H), 1.81 (s, 3 H), 1.69 (td, J = 13.0, 3.9 Hz, 1 H), 1.56 (ddd, J = 12.7, 2.5, 1.9 Hz, 1 H), 1.42 (t, J = 13.0 Hz, 1 H), 1.12 (s, 3 H).

X-Ray structure determination‡

A crystal suitable for X-ray structure determination was mount on a Mac science DIP2030 imaging plate equipped with graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). Unit-cell parameters were determined by autoindexing several images in each data set separately with the DENZO program.[25] For each data set, rotation images were collected in 3° increments with a total rotation of 180° about φ (60 frames). Data were processed by using the SCALEPACK program.[2] The structure were solved by a direct method and refined by full-matrix least-squares methods with the TeXsan (Rigaku) program.[26]

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13 The relative stereochemistry of the annulation products **4** was determined by coupling constants and/or ^{1}H dif-NOE experiments. The coupling constants are summarized in the ESI† (Table S1). Figure S1 indicates the ^{1}H dif-NOE experiments.

14 According to HF/6–31G* calculations, α-*exo*-**4a**′ was 1.6 kcal mol^{-1} more stable than α-*endo*-**4a**′. The details of the HF/6–31G* calculations are described in the ESI† (Table S2).

15 Crystal data: For α-*endo*-**4a**: triclinic system, space group $P\bar{1}$ (#2), a = 8.5780(9) Å, b = 9.4770(9) Å, c = 9.818(1) Å, V = 763.6(1) Å^3, Z = 2, ρ_{calc} = 1.150 g cm^{-3}, F(000) = 288, R = 0.212 (R_w = 0.432) for 1994 reflections out of 2520 collected (172 parameters) with $I > 3$ (I). Goodness of fit = 1.94. For α-7-*endo*,8-*exo*-**4b**: monoclinic system, space group $P2_1/a$ (#14), a = 12.3010(4) Å, b = 11.0530(3) Å, c = 13.2020(4) Å, V = 1655.76(9) Å^3, Z = 4, ρ_{calc} = 1.117 g cm^{-3}, F(000) = 608, R = 0.122 (R_w = 0.292) for 2684 reflections out of 3449 collected (181 parameters) with $I > 3$ (I). Goodness of fit = 1.47. For γ-*endo*-**4h**: triclinic system, space group $P\bar{1}$ (#2), a = 9.8930(3) Å, b = 11.1740(2) Å, c = 19.1870(7) Å, V = 1920.77(10) Å^3, Z = 4, ρ_{calc} = 1.219 g cm^{-3}, F(000) = 760, R = 0.225 (R_w = 0.449) for 6944 reflections out of 7906 collected (451 parameters) with $I > 3$ (I). Goodness of fit = 2.13.

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18 The numbering is based on the bicylo[3.3.1]non-2-ene core.

19 When a diastereomer mixture of **4g** (α-6-*exo*,7-*exo*-**4g**: α-6-*endo*,7-*endo*-**4g**: α-6-*endo*,7-*exo*-**4g**: γ-**4g** = 1:1.7:1.3:2.2) was treated with DBU in toluene at 80 °C for 13 h, the relative ratio of α-6-*endo*,7-*exo*-**4g** increased (α-6-*exo*,7-*exo*-**4g**: α-6-*exo*,7-*exo*-**4g**: γ-**4g** = 1 : 4.2 : 0.7). This suggested that α-6-*endo*,7-*exo*-products were thermodynamically favored (see also the ESI (Table S2))‡.

20 The relative stereochemical relationship between the two newly formed stereocenters was arbitrarily designated *anti–syn* according to the structures depicted in Scheme 3.

21 The calculations were performed with PC Spartan Pro, Wavefunction, Inc., Irvine, CA 92715.

22 All the results of the HF/6–31G* calculations on the intramolecular Michael reaction are provided in the ESI (Table S2)‡.
23 Calculations on the non-substituted model compound ($R_1 = Me$, $R_2 = R_3 = R_5 = R_6 = H$) also exhibited the same tendency (see the ESI (Table S2)‡.
24 HOMO orbitals and HOMO potential maps of enolates generated from other cyclization precursors are summarized in the ESI (Fig. S2)‡.
25 *DENZO and SCALEPACK: Processing of X-ray Diffraction Data Collected in Oscillation Mode*; Z. Otwinowsky and W. Minor, *Methods Enzymol.*, 1997, 276. The program is available from Mac Science Co.
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