Synthesis of Oxacycles by Tandem Radical Addition−Cyclization Reactions

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Dedicated to Professor Klaus Grohmann

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β-Alkoxyalkylidenemalonates undergo tandem radical addition–cyclization reactions to provide oxacycles of different ring sizes in good chemical efficiency. A variety of nucleophilic radicals participate in the addition–cyclization reactions, and the reaction requires the use of lanthanide triflates as Lewis acids. Compound **9** gave the 5-*exo* cyclization product **13** in 80 % yield and greater than 50:1 diastereoselectivity favoring the *trans* isomer. Radical addition–cyclization reactions using substrate **26**, in which the 5-*exo* pathway was blocked, gave exclusively the 6-*endo* products **27**–**32** in good yields (68–88 %) and moderate to good selectivity (1.2:1 to 14:1). Generally, 7-*endo* cyclization dominated over the 6-*exo* mode. Addition of various nucleophilic radicals to substrate **33** using ytterbium triflate as a Lewis acid gave the 7-*endo* products **34**–**39** in moderate to good yield (49–75 %). Substrate **41**, in which the 6-*exo* pathway was blocked, gave the 7-*endo* products **42**–**47** cleanly. The diastereoselectivities in these cyclizations were dependent on the size of the radical; bulky radicals gave lower selectivities. Radical addition–cyclization using **48** gave the 8-*endo* products **49**–**53** in good yield (58–86 %).

Introduction

Development of new methodologies using radical intermediates continues to attract interest from synthetic chemists.[1] Radical chemistry offers complementary (or at times even superior) reaction characteristics to ionic methods for carbon−carbon bond formation. Radical methods are especially well suited for the construction of rings and for setting up reaction sequences, so that multiple carbon−carbon bonds can be formed in a single operation.

Oxacycles constitute an important structural unit in many biologically active natural products. Numerous radical methodologies have been reported that offer routes towards oxacycles, especially substituted furans,[2] however, most have achieved only modest success in obtaining products with consistently high levels of diastereoselectivity, in cases when two or more chiral centers are formed in a single operation. In contrast to the large number of reports on the synthesis of five-membered rings, the formation of larger rings by radical methods has received less attention. One prominent method for the formation of oxacycles by radical chemistry involves intramolecular cyclization of a carbon radical onto an acceptor, by which an oxygen atom can be incorporated into the substrate (Figure 1, Method A). The selectivities in these reactions are generally good.[3] Alternatively, the cyclization of an oxygen-centered radical onto an acceptor, leading to oxacycles, has also been reported (Figure 1, method B).[4,5]

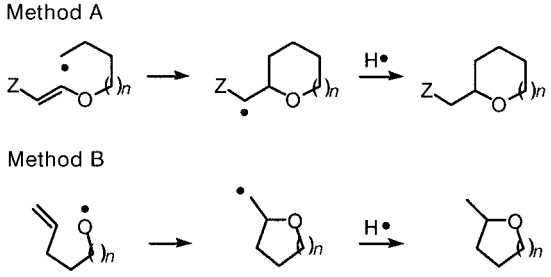

Figure 1. Synthesis of oxacycles by intramolecular cyclization

We have been interested in developing a general method for the synthesis of oxacycles of different ring sizes. When we started our work, there were no examples demonstrating intermolecular nucleophilic radical additions to β-oxygenated acrylate acceptors.[6] Intramolecular cyclizations have been reported, however, in which radicals added efficiently to the slightly deactivated β-alkoxyacrylate acceptors. Despite the high temperatures (80 °C) that were required in most cases, relatively high selectivities were observed in these systems. Notably, radical cyclizations forming 2,5- and 2,6-substituted furan and pyran rings proceeded with high levels of *cis* selectivity.[3]

Our methodology is outlined in Scheme 1 and involves the intermolecular addition of a carbon radical to a doubly

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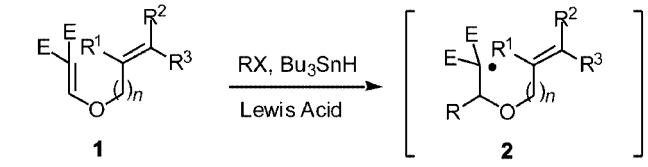
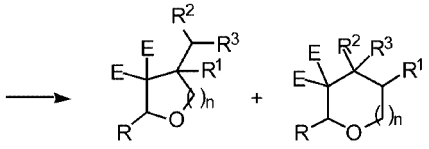
activated acceptor containing an ether linkage, followed by an intramolecular trapping of the ensuing radical with a second acceptor.[7] In this strategy, a doubly activated malonate-type β-oxygenated acceptor **1** provides sufficient activation at the β-position to facilitate chemoselective intermolecular nucleophilic radical addition, even at low temperatures. The highly electrophilic intermediate, the malonyl radical **2**, is able to promote cyclization onto simple unactivated alkenes, providing access to oxacycles of different ring sizes.[8] The addition of the nucleophilic radical to the electron poor substrate is enhanced by the use of Lewis acids.[9] Furthermore, Lewis acid coordination to the substrate boosts the electrophilicity of the intermediate malonyl radical.[10]



1 **2**

E = Ester
R = Alkyl, α-alkoxyalkyl
R^1, R^2, R^3 = H or Me
n = 1, 2, 3



3 *exo* **4** *endo*

Scheme 1

Critical issues that need to be addressed in this approach are:

(1) the feasibility of the methodology, especially for the formation of seven- and eight-membered oxacycles,

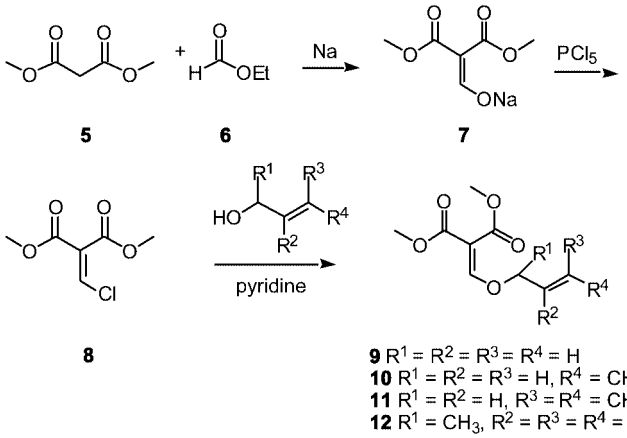
(2) *exo*/*endo* selectivity in the formation of oxacycles (**3** vs. **4**),

(3) the diastereoselectivity of the reaction, and

(4) the effect of the Lewis acid on cyclization efficiency and diastereoselectivity. Answers to these questions and models accounting for the diastereoselectivity of the products are provided in this full account.[11]

Results and Discussion

Our experiments began with the investigation of the addition−cyclization reactions leading to the five-membered ring tetrahydrofurans. Several β-alkoxyalkylidenemalonates (**9**−**12**) were synthesized in good overall yields following literature procedures (Scheme 2).[12] Thus, treatment of dimethyl malonate with sodium metal and ethyl formate gave a sodium alkoxide salt **7**.[13] Reaction of **7** with phosphorus pentachloride provided the known vinyl chloride **8**, which, when treated with the appropriate allyl alcohol and pyridine, furnished the substrates **9**−**12** in good yields (75−85 %), ready for cyclization.



5 **6** **7**

8

9 $R^1 = R^2 = R^3 = R^4 = H$
10 $R^1 = R^2 = R^3 = H$, $R^4 = CH_3$
11 $R^1 = R^2 = H$, $R^3 = R^4 = CH_3$
12 $R^1 = CH_3$, $R^2 = R^3 = R^4 = H$

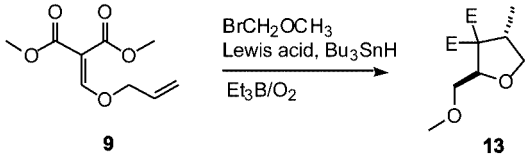
Scheme 2

5-*exo* Cyclizations

The initial experiments were designed to ascertain the optimal reaction conditions for the intermolecular addition−cyclization reaction. The radical additions were conducted according to our previously reported procedure,[14] involving

1) Tin hydride as reducing agent/chain carrier,
2) Et_3B/O_2 as a low-temperature radical initiator, and
3) A Lewis acid (Table 1).[9]

Table 1. Effect of Lewis acid and temperature on radical addition−cyclizations



9 **13**

Entry	Lewis acid	*T*, °C	Yield, %[a][b]	Ratio *trans*:*cis*[c]
1	none	−78	39	> 50:1
2	$Yb(OTf)_3$	−78	72	> 50:1
3	$Y(OTf)_3$	−78	87	16:1
4	$Zn(OTf)_2$	−78	86	39:1
5	$Mg(ClO_4)_2$	−78	72	13:1
6	$Yb(OTf)_3$	r.t.	reduction	−
7[d]	$Yb(OTf)_3$	−78	85	17:1
8[e]	$Yb(OTf)_3$	−78	82	11:1

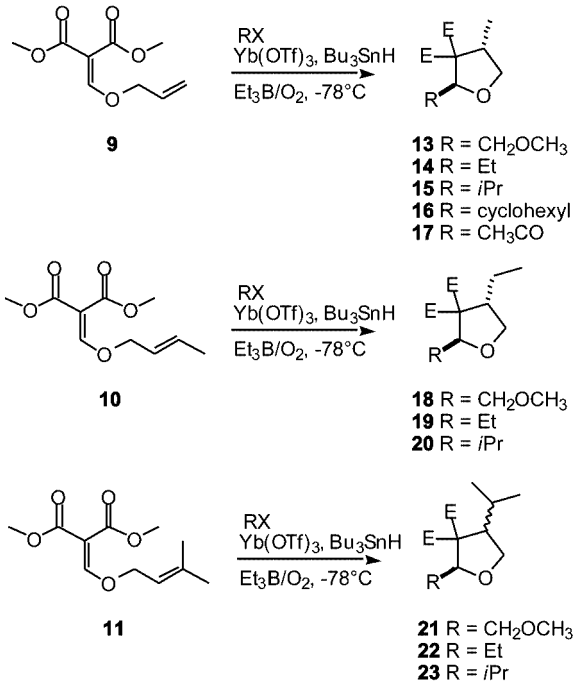
[a] Preparative reactions were conducted using 10 equiv. bromomethyl methyl ether, 5 equiv. of Bu_3SnH, 1 equiv. of Lewis acid and 5 equiv. of triethylborane. [b] Isolated yields for column-purified materials. [c] Product ratios were determined by ^1H NMR integration (500 MHz). [d] 2 Equiv. of Bu_3SnH was used. [e] 5 Equiv. of tris(trimethylsilyl)silane was used as the H-atom donor.

The radical derived from bromomethyl methyl ether was used for the optimization experiments. Addition of the methoxymethyl radical to **9** proceeded to a small extent in

the absence of a Lewis acid (Table 1, Entry 1), providing the cyclized product **13**. The reaction occurred regioselectively at the β-position of the malonate acceptor **9**, and was followed by clean 5-*exo* cyclization to furnish **13**.[15] A brief study was then undertaken to evaluate the effect of different Lewis acids on the yield and diastereoselectivity of the radical addition−cyclizations. Good yields of the purified product were obtained in the presence of several Lewis acids (Table 1, Entries 2−5). The use of $Yb(OTf)_3$ as a Lewis acid offered the best combination of yield and diastereoselectivity, providing essentially a single compound. The relative stereochemistry of the cyclized product was determined as *trans* by several 1D NOE experiments. The addition−cyclization was not feasible at room temperature, and instead a product from the reduction of the α,β-unsaturated olefin was isolated (Table 1, Entry 6).

In an effort to probe whether the cyclization is reversible, the nature and the amount of the H-atom donor was varied. Reaction with only two equivalents of tin hydride gave significantly lower levels of selectivity for **13** (85 % chemical yield). The selectivity fell from greater than 50:1 when five equivalents of tin hydride were used (Table 1, Entry 2) to 17:1 when two equivalents were used (Table 1, Entry 7). The use of the poorer H-atom donor tris(trimethylsilyl)silane also resulted in a similarly decreased selectivity (5 equiv. led to an 82 % yield of **13** with an 11:1 ratio of diastereoisomers, Table 1, Entry 8). Lowering the concentration of the H-atom donor apparently results in a reduction in kinetic control, leading to an erosion in diastereoselectivity.[16,17] This process does not, however, result in the formation of the 6-*endo* product, consistent with the higher rate of reaction for the 5-*exo* pathway versus the 6-*endo* pathway.[15,18]

Table 2. Effect of radical precursor and alkene substituent on radical addition−cyclizations



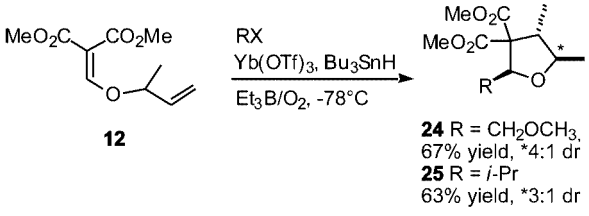
Entry	Substrate	RX	Product	Yield, %[a][b]	Ratio *trans*:*cis*[c]
1	**9**	CH_3OCH_2Br	**13**	72	> 50:1
2	**9**	EtI	**14**	55	> 50:1
3	**9**	*i*PrI	**15**	70	> 50:1
4	**9**	cyclohexyl iodide	**16**	79	> 50:1
5	**9**	$CH_3C(O)Br$	**17**	78	6:1
6	**10**	CH_3OCH_2Br	**18**	75	4:1[d]
7	**10**	EtI	**19**	50	5:1
8	**10**	*i*PrI	**20**	70	5:1
9	**11**	CH_3OCH_2Br	**21**	75	1.1:1
10	**11**	EtI	**22**	52	1.2:1
11	**11**	*i*PrI	**23**	65	2.5:1

[a] Preparative reactions were conducted using 10 equiv. of radical precursor, 5 equiv. of Bu_3SnH, 1 equiv. of Lewis acid and 5 equiv. of triethylborane. [b] Isolated yields for column purified materials. [c] Product ratios were determined by ^1H NMR integration (500 MHz). [d] This selectivity was incorrectly reported as 50:1 in the initial communication (see ref.[11]).

Knowing both the optimal Lewis acid and reaction conditions, we evaluated the effect of different radicals on the diastereoselectivity of the addition−cyclization reactions (Table 2). Addition of primary radicals (methoxymethyl and ethyl) followed by cyclization proceeded smoothly to give **13** and **14** in good yield and with good selectivity (Table 2, Entries 1 and 2). Similarly, addition and cyclization with secondary radicals were also successful, yielding the products **15** and **16** as single isomers (Table 2, Entries 3 and 4). In contrast, reaction with the acetyl radical (generated from acetyl bromide), displayed significantly lower levels of selectivity (Table 2, Entry 5). It is likely that epimerization of the chiral center α to the carbonyl group occurs readily under the reaction conditions, as well as during silica gel chromatography (the initial enantiomeric ratio of 6:1 decreases to 4:1 after column chromatography on silica gel).

Reactions with substrates containing substituents on the acceptor olefin also proceeded in high yields. Substrate **10**, containing a disubstituted (*E*)-olefin, cyclized efficiently upon radical addition to afford product **18** as a 4:1 mixture of diastereomers in 75 % yield (Table 2, Entry 6). Reactions with the ethyl and isopropyl radicals were also successful, furnishing the products **19** and **20** as a mixture of isomers (5:1) (Table 2, Entries 7 and 8). In contrast to the highly selective cyclizations with **9** and the moderately selective reactions with **10**, the reaction of substrate **11**, containing a trisubstituted olefin, did not show any preference for a *cis* or *trans* cyclization. Nearly equal amounts of the isomeric tetrahydrofurans were obtained irrespective of the radical precursor used (Table 2, Entries 9−11).

In an effort to probe the impact of an additional chiral center adjacent to the oxygen on addition−cyclization, the addition of the methoxymethyl radical to **12** was investigated (Scheme 3). Starting with racemic **12**, radical addition took place cleanly, followed by cyclization leading to the tetrasubstituted furan **24**, with a 4:1 preference for the diastereomer shown. Stereochemical assignments are based on 1D NOE experiments. Reaction with the isopropyl radical was similar to that with the methoxymethyl radical, yielding product **25** as a 3:1 mixture of isomers.



Scheme 3

The diastereoselectivities for the cyclizations of compound **9** are high. The *trans* stereochemistry for the cyclization products **13**−**20** was established by NOE analysis. The product stereochemistry is consistent with the predictions of Beckwith and Houk for 5-*exo* radical cyclizations, in which an equatorial substitution arrangement is preferred in the transition state (Model A, Figure 2).

Introduction of a methyl substituent on the alkene acceptor **10** leads to diminished selectivity. Once again the stereochemistry of the major diastereomer is consistent with the Beckwith−Houk model, with the reaction proceeding via a transition state in which the substituents are equatorially arranged (Model B, R^1 = H). In the alternative boat transition state (Model C, R^1 = H) there is an allylic interaction between the methyl group and the chain. In contrast to the highly selective reactions with substrate **9**, reactions with substrate **11**, with dimethyl substitution at the alkene terminus, are not selective. In the chairlike transition state, there is a severe allylic strain between the (*Z*)-methyl group and the allylic axial hydrogen (Model B, R^1 = CH_3, Figure 2). The alternative boatlike transition state is also destabilized by gauche interactions between the methyl and ester substituents (Model C, Figure 2). Thus, both the chair and the boatlike transition states are equally probable, leading to a 1:1 ratio of products. In the reaction of **12**, the initial radical addition is diastereoselective. The intermediate radical then cyclizes via a chair-like transition state to provide the product as a mixture of diastereomers (Models D and E, Figure2). We do not have a ready explanation for the diastereoselectivity in the initial radical addition.

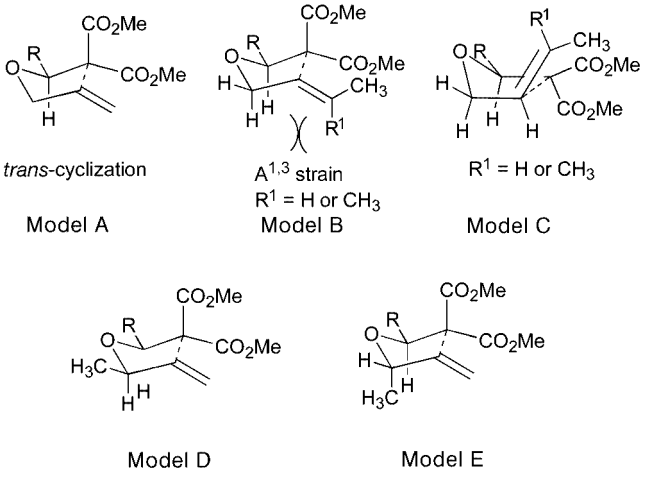


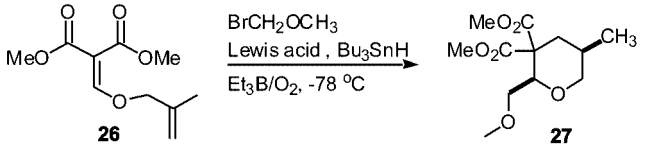
Figure 2. Proposed transition states for 5-*exo* cyclization

5-*exo* versus 6-*endo* Cyclizations

Having established that the addition−cyclization strategy is feasible for the construction of five-membered ethers, we turned our attention to the formation of six-membered rings. Our initial goal was to evaluate the competition between 5-*exo* and 6-*endo* mode of cyclization.[19] It is well established in the literature that the reaction rate is greatly retarded when the substitution on the acceptor alkene is increased at the site undergoing radical addition.[20] Thus, using a substrate in which the 5-*exo* pathway was blocked by a methyl group (**26**) (prepared from **8** and 2-methyl-2-propen-1-ol), we evaluated the selectivity for the addition−cyclization reaction. Initial experiments involved the determination of the optimal Lewis acid for the addition−cyclization experiment using the methoxymethyl radical and evaluation of the *endo*/*exo* selectivity (Table 3).

Reaction in the absence of any Lewis acid was not efficient, resulting in the formation of the ethyl addition−cyclization product by a 6-*endo* pathway; the ethyl radical was derived from triethylborane. A minor amount of **27** was also obtained (Table 3, Entry 1). As expected, none of the 5-*exo* product was observed, and the cyclization proceeded exclusively by the 6-*endo* pathway. Addition of $Yb(OTf)_3$ as a Lewis acid gave greatly improved yields for the 6-*endo* product (Table 3, Entry 2), but with low diastereoselectivity. Other Lewis acids were equally effective in the addition−cyclization reactions (Table 3, Entries 3−5), providing the six-membered ring product with a range of selectivities. Although the diastereoselectivity for the 6-*endo* product was not high, none of the 5-*exo* product was formed, irrespective of the Lewis acid used. From these experiments, $Yb(OTf)_3$ was identified as the best Lewis acid, because not only was it easy to use, but it also provided the product in optimal yield and diastereoselectivity.

Table 3. Optimization of reaction conditions for the 6-*endo* cyclization

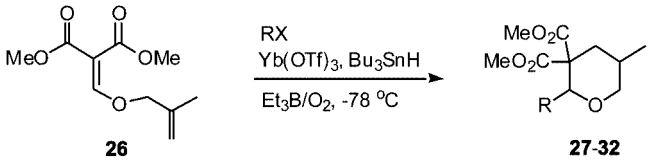


Entry	Lewis acid	*T*, °C	Yield, %[a][b]	*dr*[c]
1	none	−78	10 [d]	–
2	$Yb(OTf)_3$	−78	85	1.5:1
3	$Y(OTf)_3$	−78	70	2:1
4	$Zn(OTf)_2$	−78	78	3:1
5	$Mg(ClO_4)_2$	−78	80	3:1
6	$Yb(OTf)_3$	r.t.	– [e]	

[a] Preparative reactions were conducted using 10 equiv. bromomethyl methyl ether, 5 equiv. of Bu_3SnH, 1 equiv. of Lewis acid and 5 equiv. of triethylborane. [b] Isolated yields for column purified materials. [c] Product ratios were determined by ^1H NMR integration (500 MHz). [d] 22 % of ethyl radical addition product was isolated. [e] Only the product of addition of the ethyl radical was observed.

The addition of different radical precursors to substrate **26** also proceeded with good yields and moderate diastereoselectivity (Table 4, Entries 1−6).[21] As the steric bulk of the radical increased, higher diastereoselectivities were obtained (compare Entries 3 and 6). Reaction with the adamantyl radical gave the highest diastereoselectivity of 14:1. The relative stereochemistry was found to be *cis* and was determined by several 1D NOE experiments.[22] In contrast to the formation of the five-membered ethers discussed above where the diastereoselectivity is established during the cyclization, the stereochemistry in the formation of **27** is installed after the cyclization has occurred. Two potential models can be put forward to explain the observed *cis* selectivity for the products. In the first model (Model F, Figure3), the radical resulting from cyclization undergoes selective H-atom transfer from an axial direction in a chairlike transition state. In the second model, H-atom transfer occurs from an axial direction in a boatlike transition state (Model G, Figure 3).

Table 4. Addition of different radicals in the 6-*endo* cyclization reaction



Entry	R	Product	Yield, %[a][b]	*dr*[c]
1	$-CH_2OCH_3$	**27**	85	1.5:1
2	ethyl	**28**	70	1.2:1
3	isopropyl	**29**	68	2.5:1
5	cyclohexyl	**30**	78	6:1
4	$CH_3C(O)$	**31**	72	2:1
6	adamantyl	**32**	88	14:1

[a] Preparative reactions were conducted using 10 equiv. of radical precursor, 5 equiv. of Bu_3SnH, 1 equiv. of Lewis acid and 5 equiv. of triethylborane. [b] Isolated yields for column purified materials. [c] Product ratios were determined by ^1H NMR integration (500 MHz).

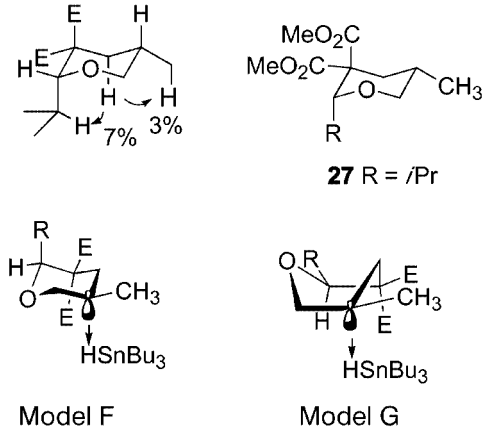


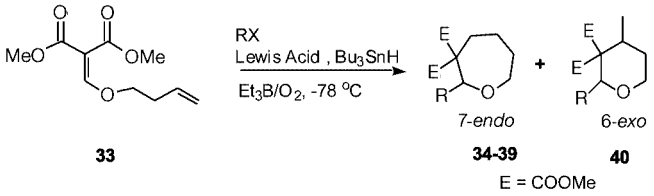
Figure 3. Proposed transition states for 6-*endo* cyclization

The second model (Model G) is more consistent with the observed selectivity increase, because the size of the equatorial R group increases, reaching the highest ratio with the bulky adamantyl group.[23] Axial attack is also consistent with the observations of Giese and co-workers on atom transfer to cyclohexyl radicals.[24]

6-*exo* versus 7-*endo* Cyclizations

Formation of medium-sized rings has been and still remains a major challenge in synthetic chemistry.[25] Our subsequent series of experiments investigated the competition between 6-*exo* and 7-*endo* modes of cyclization. Although a large number of examples of cyclizations in the 6-*exo* mode are known, literature precedents also suggest forma-

Table 5. Addition of different radicals in the 6-*exo* vs. 7-*endo* cyclization



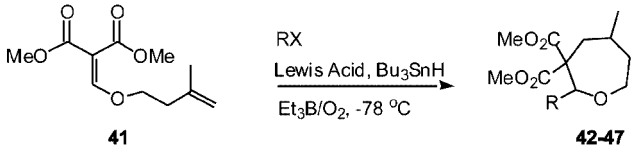
Entry	Lewis Acid[a]	R	Product	Yield, %[b] [c]	7-*endo*:6-*exo*[d]
1	$Yb(OTf)_3$	$-CH_2OCH_3$	**34**	75	9:1
2	$Y(OTf)_3$	$-CH_2OCH_3$	**34**	50	2:1
3	$Sm(OTf)_3$	$-CH_2OCH_3$	**34**	86	5:1
4	$Mg(ClO_4)_2$	$-CH_2OCH_3$	**34**	73	> 50:1[e]
5	$Yb(OTf)_3$	ethyl	**35**	49	19:1
6	$Yb(OTf)_3$	isopropyl	**36**	57	6:1
7	$Yb(OTf)_3$	cyclohexyl	**37**	66	> 50:1
8	$Yb(OTf)_3$	$CH_3C(O)$	**38**	69	> 50:1
9	$Yb(OTf)_3$	adamantyl	**39**	71	> 50:1[e]

[a] Reactions in the absence of a Lewis acid gave a mixture of the 7-*endo* and uncyclized products in 31 % yield when $BrCH_2OCH_3$ was used as the radical precursor. [b] Preparative reactions were conducted using 10 equiv. of radical precursor, 5 equiv. of Bu_3SnH, 1 equiv. of Lewis acid and 5 equiv. of triethylborane. [c] Isolated yields for column-purified materials. [d] Product ratios were determined by ^1H NMR integration (500 MHz). [e] Uncyclized product was also isolated.

tion of the 7-*endo* product, depending on reactivity of the radical partners and/or steric constraints.[26] The effect of the Lewis acid on the mode of cyclization was initially assessed using the methoxymethyl radical and substrate **33** (Table 5). Of the four different Lewis acids examined, $Yb(OTf)_3$ showed the best characteristics (Table 5, Entries 1−4). Generally, 7-*endo* cyclization dominated over the 6-*exo* mode.[27] Reaction with magnesium perchlorate gave some uncyclized product. Addition of various nucleophilic radicals to substrate **33** using $Yb(OTf)_3$ as a Lewis acid was also examined (Table 5, Entries 5−9). In all of these experiments, the 7-*endo* product was formed as the sole or the major product. Addition of the bulky adamantyl radical led to the formation of some uncyclized material (Table 5, Entry 9). The relative stereochemistry of the 6-*exo* products was not determined because they were only formed in minor amounts.

Having established that 7-*endo* radical cyclizations were feasible, we investigated the addition of radicals to substrate **41**. In this substrate, reaction by the 6-*exo* mode is retarded by a methyl group on the alkene. Initially, addition of the methoxymethyl radical using different Lewis acids was attempted (Table 6). Radical addition−cyclization resulted in the exclusive formation of the 7-*endo* product. The diastereoselectivity was somewhat dependent on the Lewis acid used (Table 6, Entries 1−3); $Yb(OTf)_3$ provided optimal results (Entry 1).[28] The relative stereochemistry was determined to be *trans*, and this was established by 1D NOE experiments (enhancements are shown in Figure 4). Addition of different nucleophilic radicals was then examined (Table 6, Entries 4−8), using $Yb(OTf)_3$ as a Lewis acid. The yields were moderate to good for the addition−cyclization reactions, but the diastereoselectivities were dependent on the size of the radicals. It is interesting to note that the stereoselectivities were higher for 7-*endo* cyclizations in reactions with the smaller ethyl, isopropyl, and cyclohexyl radicals than with the bulky adamantyl radical (compare Entries 4, 5 and 6 with Entry 8). This is in contrast to the trend observed in the 6-*endo* cyclizations, where bulkier radicals gave higher diastereoselectivities (see Table 4). As was observed before, reaction with the acetyl radical was moderately selective. Once again epimerization was a factor in lowering selectivity. The stereoselectivity in the formation

Table 6. Addition of different radicals in the 7-*endo* cyclization



Entry	Lewis acid[a]	R	Product	Yield, %[b] [c]	*dr*[d]
1	$Yb(OTf)_3$	$-CH_2OCH_3$	**42**	76	10:1
2	$Sm(OTf)_3$	$-CH_2OCH_3$	**42**	80	4:1
3	$Mg(ClO_4)_2$	$-CH_2OCH_3$	**42**	73	3:1
4	$Yb(OTf)_3$	ethyl	**43**	56	13:1
5	$Yb(OTf)_3$	isopropyl	**44**	73	13:1
6	$Yb(OTf)_3$	cyclohexyl	**45**	67	10:1
7	$Yb(OTf)_3$	$CH_3C(O)$	**46**	70	6:1
8	$Yb(OTf)_3$	adamantyl	**47**	51	5:1

[a] Reactions in the absence of a Lewis acid gave < 5 % yield of the cyclized product when $BrCH_2OCH_3$ was used as the radical precursor. [b] Preparative reactions were conducted using 10 equiv. of radical precursor, 5 equiv. of Bu_3SnH, 1 equiv. of Lewis acid and 5 equiv. of triethylborane. [c] Isolated yields for column purified materials. [d] Product ratios were determined by ^1H NMR integration (500 MHz).

of **42**−**47** is established in a H-atom transfer step. Two models could account for the observed product stereochemistry (Models H and I). Of these, Model H (in which the methyl group has a minimal steric interaction and atom transfer occurs from an axial direction) rationalizes the observed selectivity. The alternative chairlike transition state (Model I), which also leads to the major product, is less likely because of eclipsing interactions. In Model H, the minor diastereomer could arise from H-atom transfer in an equatorial direction. This contradicts the experimental observation of lower selectivity when the size of the R group is increased. An alternative model for the formation of the minor isomer is Model J. This conformer may be slightly favored with large R groups, due to an increase in the buttressing effect between the diester and the R group.

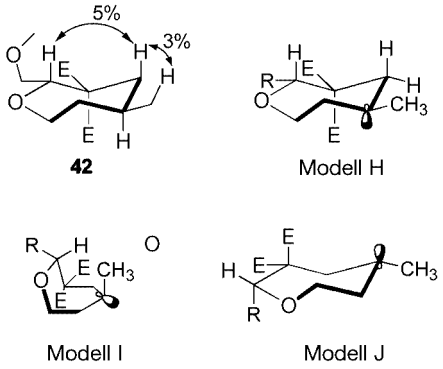


Figure 4. Proposed transition states for 7-*endo* cyclization

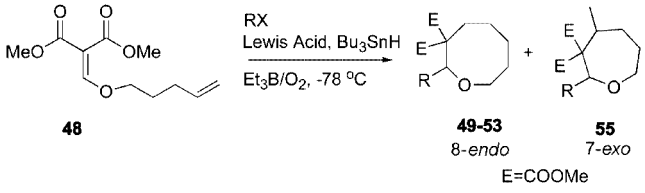
7-*exo* vs. 8-*endo* Cyclizations

The existing literature clearly demonstrates the predominance of the 8-*endo* mode of cyclizations over the 7-*exo* mode.[29] Lee and co-workers have shown that the transition states for 8-*endo* cyclization are more favorable than those for the 7-*exo* pathway.[30] We have briefly examined the regioselectivity for 7-*exo* and 8-*endo* cyclizations using substrate **48** and these results are shown in Table 7. The regioselectivities in these experiments were initially evaluated using the methoxymethyl radical as the reactant and three different Lewis acids (Table 7, Entries 1−3). The mode of cyclization was independent of the Lewis acid used, providing the 8-*endo* isomer as the major product. Reaction using $Yb(OTf)_3$ as the Lewis acid gave **49** in high yield (Entry 1) whereas $Mg(ClO_4)_2$ gave a moderate yield of **49** along with minor amounts of the uncyclized compound (Table 7, Entry 3). Addition of different radicals to **48** using ytterbium triflate as the Lewis acid gave moderate yields of the cyclized compounds (Table 7, Entries 4−7). The 8-*endo* selectivity was modest to good in these reactions, depending on the reactant. Reactions with the methoxymethyl (Table 7, Entry 1) or isopropyl (Table 7, Entry 5) radicals gave the 8-*endo* compounds as the major products. Variable amounts of the 7-*exo* and uncyclized products were also observed in these reactions. The acetyl radical behaved as a pseudoelectrophilic radical and addition to the unactivated double bond also took place (Table 7, Entry 7). The more bulky adamantyl radical gave the addition product without cyclization (Table 7, Entry 8).

Conclusions

In conclusion, we have demonstrated a simple and efficient method for the preparation of oxacycles with various ring sizes. Additionally, we have shown that in the presence of a Lewis acid, radicals readily add to β-alkoxy acrylate acceptors containing a doubly activating malonate moiety

Table 7. Addition of different radicals in the 7-*exo* vs. 8-*endo* cyclization



Entry	Lewis Acid[a]	R	Product	Yield, %[b] [c]	8-*endo*:7-*exo*[d]
1	$Yb(OTf)_3$	$-CH_2OCH_3$	**49**	86	> 50:1
2	$Sm(OTf)_3$	$-CH_2OCH_3$	**49**	57	> 50:1[e]
3	$Mg(ClO_4)_2$	$-CH_2OCH_3$	**49**	58	9:1[e]
4	$Yb(OTf)_3$	ethyl	**50**	56	6:1 [e]
5	$Yb(OTf)_3$	isopropyl	**51**	63	13:1
6	$Yb(OTf)_3$	cyclohexyl	**52**	62	> 50:1[e]
7	$Yb(OTf)_3$	$CH_3C(O)$	**53**	58	1.5:1
8	$Yb(OTf)_3$	adamantyl	**54**	67	–[f]

[a] Reactions in the absence of a Lewis acid gave < 20 % of the 8-*endo* product when $BrCH_2OCH_3$was used as the radical precursor. [b] Preparative reactions were conducted using 10 equiv. of radical precursor, 5 equiv. of Bu_3SnH, 1 equiv. of Lewis acid and 5 equiv. of triethylborane. [c] Isolated yields for column purified materials. [d] Product ratios were determined by ^1H NMR integration (500 MHz). [e] Minor amounts (< 5 %) of the uncyclized product were also formed. [f] Only the uncyclized compound was obtained.

even at −78 °C. The addition−cyclization experiments reported in this work clearly illustrate the utility of free radical intermediates in the construction of multiple C−C bonds in a single operation. In this work we have also shown that substituted furans can be synthesized with excellent levels of stereocontrol and have shed light on the regioselectivity/diastereoselectivity in the formation of larger oxacycles. Experiments are underway to explore enantiocontrol in these novel tandem reactions.

Experimental Section

General: Dichloromethane was distilled from calcium hydride and tetrahydrofuran was distilled from benzophenone ketyl prior to use. Thin-layer chromatographic analyses were performed on silica gel Whatman-60F glass plates and the components were visualized by-illumination with UV light or by staining with phosphomolybdic acid. Flash chromatography was performed using E. Merck silica gel 60 (230−400 mesh). Melting points were determined using the Fisher−Johns melting point apparatus. All glassware was oven dried, assembled hot, and cooled under a stream of dry nitrogen before use. ^{1}H NMR were recorded with a Varian Unity/Inova-500 NB (500 MHz) spectrometer. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane, using residual $CHCl_3$ (δ =7.27 ppm) as an internal standard. Data are reported as follows: chemical shift, multiplicity, coupling constant(s) and integration. ^{13}C NMR were recorded with a Varian Unity/Inova-500 NB (125 MHz) spectrometer using broadband proton decoupling. Chemical shifts are reported in parts per million downfield from tetramethylsilane, using the central resonance of $CDCl_3$ (δ = 77.0 ppm) as an internal standard. Elemental analyses were performed in house on a Perkin−Elmer Series II CHNS/O Analyzer 2400. High-resolution mass spectra (HRMS) [EI+] were recorded by the Mass Spectrometry Laboratory, University of South Carolina, Columbia, SC and Ohio State University, Columbus, OH.

General Procedure for the Preparation of Enoyloxymethylenemalonates: Dimethyl chloromethylenemalonate (10 mmol) and pyridine (1 mL) were added to the corresponding alcohol (12 mmol) and the resulting solution was stirred at room temperature for 15 minutes. After removal of the excess alcohol by evaporation under reduced pressure, the residue was acidified with 5 % aqueous HCl (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined CH_2Cl_2 extracts were dried with Na_2SO_4 and concentrated in vacuo leaving a colorless oil which was purified by column chromatography (using 10 % ethyl acetate in hexane as eluent), furnishing the desired compound in 75−85 % yield.

Dimethyl [(Allyloxy)methylene]malonate (9): R_f = 0.5 (ethyl acetate/hexane, 40:60). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.74 (s, 3 H), 3.89 (s, 3 H), 4.61 (d, J = 7.1 Hz, 2 H), 5.34 (d, J = 10 Hz, 1 H), 5.40 (d, J = 15 Hz, 1 H), 5.89−5.97 (m, 1 H), 7.62 (s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 52.2, 52.3, 76.6, 106.1, 120.2, 131.8, 164.2, 164.5, 165.4 ppm. HRMS: *m*/*z* calcd. for M^+ 200.0685, found M^+ 200.0677.

Dimethyl [(But-2-enyloxy)methylene]malonate (10): R_f = 0.5 (ethyl acetate/hexane, 40:60). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.77 (d, J = 6.5 Hz, 3 H), 3.76 (s, 3 H), 3.82 (s, 3 H), 4.56 (d, J = 6.5 Hz, 2 H), 5.58−5.67 (m, 1 H), 5.83−5.91 (m, 1 H), 7.68 (s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.1, 52.2, 52.4, 769, 105.7, 124.9, 133.8, 164.4, 164.7, 165.6 ppm. HRMS: *m*/*z* calcd. for M^+ 214.0841, found M^+ 214.0837.

Dimethyl [(3-Methylbut-2-enyloxy)methylene]malonate (11): R_f = 0.5 (ethyl acetate/hexane, 40:60). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.71 (s, 3 H), 1.77 (s, 3 H), 3.72 (s, 3 H), 3.77 (s, 3 H), 4.60 (d, J = 7.0 Hz, 2 H),5.35−5.39 (m, 1 H), 5.58−5.67 (m, 1 H), 7.66(s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.5, 26.1, 52.1, 52.2, 72.7, 105.5, 118.3, 141.6, 164.6, 164.7, 165.7 ppm. HRMS: *m*/*z* calcd. for M^+ 229.1076, found M^+ 229.1071.

Dimethyl [(1-Methylallyloxy)methylene]malonate (12): R_f = 0.5 (ethyl acetate/hexane, 40:60). Oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.46 (d, J = 6.5 Hz, 3 H), 3.76 (s, 3 H), 3.82 (s, 3 H), 4.56−4.62 (m, 1 H), 5.29 (d, J = 10.0 Hz, 1 H), 5.38 (d, J = 15.3 Hz, 1 H), 5.83−5.90 (m, 1 H), 7.66 (s, 1 H) ppm. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 21.8, 54.1, 54.3, 83.9, 105.8, 118.5, 137.3, 163.2, 164.7, 165.7 ppm. HRMS: *m*/*z* calcd. for M^+ 214.0841, found M^+ 214.0829.

Dimethyl [(2-Methylallyloxy)methylene]malonate (26): Oil. R_f = 0.5 (ethyl acetate/hexane, 40:60). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.74 (s, 3 H), 3.74 (s, 3 H), 3.81 (s, 3 H), 4.49 (s, 2 H), 5.04 (d, J = 9.2 Hz, 2 H), 7.59 (s, 1 H) ppm. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 19.2, 52.1, 52.4, 79.6, 106.2, 115.2, 139.6, 164.3, 164.6, 165.4 ppm. HRMS: *m*/*z* calcd. for M^+ 214.0841, found M^+ 214.0837.

Dimethyl (But-3-enyloxy)methylene]malonate (33): R_f = 0.5 (ethyl acetate/hexane, 40:60). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.45−2.50 (m, 2 H), 3.74 (s, 3 H), 3.79 (s, 3 H), 4.16 (t, J = 6.9 Hz, 2 H), 5.11−5.17 (m, 2 H), 5.73−5.79 (m, 2 H), 7.62 (s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 34.2, 52.1, 52.2, 76.1, 105.7, 118.6, 132.6, 164.5, 164.7, 165.5 ppm. HRMS: *m*/*z* calcd. for M^+ 214.0841, found M^+ 214.0840.

Dimethyl [(3-Methylbut-3-enyloxy)methylene]malonate (41): R_f = 0.5 (ethyl acetate/hexane, 40:60). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.75 (s, 3 H), 2.42 (t, J = 6.9 Hz, 2 H), 3.73 (s, 3 H), 3.77 (s, 3 H), 4.21 (t, J = 6.9 Hz, 2 H), 4.74 (s, 1 H), 4.84 (s, 1 H), 7.63 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 22.9, 37.9, 52.1, 52.2, 75.5, 105.6, 113.7, 140.8, 164.6, 164.8, 165.6 ppm. HRMS: *m*/*z* calcd. for M^+ 228.0998, found M^+ 228.1001.

Dimethyl [(Pent-4-enyloxy)methylene]malonate (48): R_f = 0.5 (ethyl acetate/hexane, 40:60). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.80−1.86 (m, 2 H), 2.13−2.18 (m, 2 H), 3.74 (s, 3 H), 3.80 (s, 3 H), 4.14 (t, J = 6.5 Hz, 2 H), 5.01−5.08 (m, 2 H), 5.73−5.82 (m, 1 H), 7.63 (s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 28.9, 29.6, 52.1, 52.3, 76.3, 105.7, 116.2, 137.0, 164.6, 165.0, 165.6 ppm. HRMS: *m*/*z* calcd. for M^+ 229.1076, found M^+ 229.1072.

General Procedure for the Preparation of 5-, 6-, 7-, and 8-Membered Oxacycles: Freshly-distilled THF (2.0 mL) and CH_2Cl_2 (4.0 mL) were added to a one-necked round bottomed flask containing $Yb(OTf)_3$ (124 mg, 0.2 mmol) and the malonate (0.2 mmol) under N_2.This mixture was then cooled in a dry ice/acetone bath. To this solution was added the radical precursor (2 mmol), Bu_3SnH (0.275 mL, 1 mmol), and Et_3B solution (1.0 mL of a 1.0 M solution in hexane, 1 mmol). At once, O_2 (5.0 mL) was added. After complete consumption of the starting material (TLC, ~ 3 h), the reaction was diluted with diethyl ether (20 mL). Silica gel (~ 2.5 g) was added and the mixture was concentrated. The resulting powder was washed with hexanes (100 mL) and the product was eluted by washing with diethyl ether (60 mL). Evaporation of the diethyl ether fraction yielded the crude product as a colorless oil or solid. Silica gel chromatography furnished the desired compound in good yield.

Dimethyl 2-Methoxymethyl-4-methyldihydrofuran-3,3-dicarboxylate (13): R_f = 0.4 (ethyl acetate/hexane, 40:60); oil. ^{1}H NMR

(500 MHz, $CDCl_3$): δ = 0.99 (d, *J* = 7 Hz, 3 H), 3.02−3.14 (m, 1 H), 3.32 (s, 3 H), 3.42−3.51 (m, 2 H), 3.67 (dd, *J* = 11, 2.5 Hz, 1 H), 3.75 (s, 3 H), 3.77 (s, 3 H), 4.23 (dd, *J* = 8.5, 7.5 Hz, 1 H), 4.62 (q, *J* = 2.5 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.2, 40.4, 52.6, 52.7, 59.5, 65.1, 72.6, 74.2, 81.6, 169.8, 170.0 ppm. HRMS: *m*/*z* calcd. for M^+ 247.1182, found M^+ 247.1185.

Dimethyl 2-Ethyl-4-methyldihydrofuran-3,3-dicarboxylate (14): R_f = 0.6 (ethyl acetate/hexane, 40:60); oil. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.94 (d, *J* = 7.3 Hz, 3 H), 0.99 (t, *J* = 7.3 Hz, 3 H), 1.18−1.27 (m, 1 H), 1.57−1.63 (m, 1 H), 2.97−3.06 (m, 1 H), 3.39 (dd, *J* = 8.2, 6.7 Hz, 1 H), 3.72 (s, 3 H), 3.74 (s, 3 H), 4.19 (t, *J* = 7.6 Hz, 1 H), 4.26 (dd, *J* = 10.2, 2.6 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.4, 15.1, 25.2, 39.8, 52.3, 52.4, 67.0, 74.0, 83.6, 169.8, 170.1 ppm. HRMS: *m*/*z* calcd. for MNa^+ 253.1046, found MNa^+ 253.1061.

Dimethyl 2-Isopropyl-4-methyldihydrofuran-3,3-dicarboxylate (15): R_f = 0.6 (ethyl acetate/hexane, 40:60); oil. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.91(d, *J* = 7 Hz, 3 H), 0.97 (d, *J* = 7 Hz, 3 H), 1.01 (d, *J* = 6.5 Hz, 3 H), 1.72−1.79 (m, 1 H), 3.03−3.11 (m, 1 H), 3.41 (t, *J* = 8 Hz, 1 H), 3.75 (s, 3 H), 3.76 (s, 3 H), 4.19−4.24 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.2, 15.7, 18.4, 27.9, 38.2, 49.7, 49.9, 63.9, 71.2, 84.7, 167.6, 167.8 ppm. HRMS: *m*/*z* calcd. for M^+ 244.1311, found M^+ 244.1312.

Dimethyl 2-Cyclohexyl-4-methyldihydrofuran-3,3-dicarboxylate (16): R_f = 0.6 (ethyl acetate/hexane, 40:60); oil. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.96 (d, *J* = 7 Hz, 3 H), 1.09−1.22 (m, 5 H), 1.36−1.43 (br. s, 1 H), 1.61−1.78 (m, 5 H), 3.04−3.12 (m, 1 H), 3.40 (t, *J* = 7.5 Hz, 1 H), 3.76 (s, 3 H), 3.77 (s, 3 H), 4.19−4.24 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.1, 26.3, 26.5, 26.6, 28.7, 31.1, 40.6, 40.9, 52.4, 52.6, 66.5, 73.9, 86.7, 170.2, 170.6 ppm. HRMS: *m*/*z* calcd. for M^+ 284.1624, found M^+ 284.1626.

Dimethyl 2-Acetyl-4-methyldihydrofuran-3,3-dicarboxylate (17): R_f = 0.4 (ethyl acetate/hexane, 40:60); oil. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.02 (d, *J* = 7.2 Hz, 3 H), 2.2 (s, 3 H), 3.05−3.17 (m, 1 H), 3.55 (dd, *J* = 8.5, 7.2 Hz, 1 H), 3.66 (s, 3 H), 3.77 (s, 3 H), 4.26 (dd, *J* = 8.5, 7.2 Hz, 1 H), 4.93 (s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.6, 27.7, 43.3, 52.7, 53.4, 66.9, 67.0, 74.5, 88.4, 168.9, 206.2 ppm. HRMS: *m*/*z* calcd. for M^+ 244.0947, found M^+ 244.0941.

Dimethyl 4-Ethyl-2-(methoxymethyl)dihydrofuran-3,3-dicarboxylate (18): R_f = 0.4 (ethyl acetate/hexane, 40:60); oil. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.94 (t, *J* = 7.5 Hz, 3 H), 1.04−1.14 (m, 1 H), 1.59−1.68 (m, 1 H), 2.88−2.96 (m, 1 H), 3.33 (s, 3 H), 3.44 (q, *J* = 5 Hz, 1 H), 3.57 (t, *J* = 8.5 Hz, 1 H), 3.64 (dd, *J* = 10.5, 3 Hz, 1 H), 3.76 (s, 3 H), 3.77 (s, 3 H), 4.26 (dd, *J* = 8.5, 7.5 Hz, 1 H), 4.61−4.65 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.8, 22.4, 47.4, 52.6, 52.7, 59.5, 64.9, 72.2, 72.7, 82.1, 169.8, 170.2 ppm. HRMS: *m*/*z* calcd. for M^+ 261.1338, found M^+ 261.1329.

Dimethyl 2,4-Diethyldihydrofuran-3,3-dicarboxylate (19): R_f = 0.6 (ethyl acetate/hexane, 40:60); oil. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 7.3 Hz, 3 H), 1.01 (t, *J* = 7.3 Hz, 3 H), 1.08−1.17 (m, 1 H), 1.24−1.31 (m, 1 H), 1.50−1.62 (m, 2 H), 2.83−2.89 (m, 1 H), 3.52 (t, *J* = 8.3 Hz, 1 H), 3.73 (s, 3 H), 3.74 (s, 3 H), 4.21 (t, *J* = 8.3 Hz, 3 H), 4.28 (dd, *J* = 10.3, 2.7 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.3, 12.6, 22.9, 25.3, 46.8, 49.1, 52.4, 52.5, 71.8, 84.1, 168.8, 170.1 ppm. HRMS: *m*/*z* calcd. for MNa^+ 267.1202, found MNa^+ 267.1226.

Dimethyl 4-Ethyl-2-isopropyldihydrofuran-3,3-dicarboxylate (20): R_f = 0.6 (ethyl acetate/hexane, 40:60); oil. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.86−0.91 (m, 6 H), 0.97 (d, *J* = 6.7 Hz, 3 H), 1.05−1.12 (m, 1 H), 1.46−1.54 (m, 1 H), 1.69−1.79 (m, 1 H), 2.83−2.91 (m, 1 H), 3.48 (t, *J* = 8.1 Hz, 1 H), 3.73 (s, 3 H), 3.74 (s, 3 H), 4.18−4.22 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.7, 18.1, 21.2, 23.0, 30.6, 47.8, 52.3, 52.5, 66.5, 71.9, 87.9, 170.4, 170.5 ppm. HRMS: *m*/*z* calcd. for MNa^+ 281.1359, found MNa^+ 281.1348.

Dimethyl 4-Isopropyl-2-(methoxymethyl)dihydrofuran-3,3-dicarboxylate (21): R_f = 0.4 (ethyl acetate/hexane, 40:60); oil. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.86 (d, *J* = 7 Hz, 3 H), 0.99 (d, *J* = 7 Hz, 3 H), 1.58−1.66 (m, 1 H), 2.88−2.93 (m, 1 H), 3.32 (s, 3 H), 3.53 (dd, *J* = 10.5, 4 Hz, 1 H), 3.64 (t, *J* = 9 Hz, 1 H), 3.74 (s, 3 H), 3.78 (s, 3 H), 4.14−4.20 (m, 2 H), 4.64−4.68 (dd, *J* = 4.5, 4 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.4, 22.9, 28.3, 51.9, 52.7, 53.6, 59.5, 64.6, 70.5, 72.7, 82.9, 169.9, 170.4 ppm. HRMS: *m*/*z* calcd. for M^+ 275.1495, found M^+ 275.1492.

Dimethyl 2-Ethyl-4-isopropyldihydrofuran-3,3-dicarboxylate (22): R_f = 0.6 (ethyl acetate/hexane, 40:60); oil. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.85 (t, *J* = 6.9 Hz, 3 H), 0.96- 1.02 (m, 6 H), 1.22−1.31 (m, 1 H), 1.42−1.47 (m, 1 H), 2.83−2.89 (m, 1 H), 3.59−3.64 (m, 1 H), 3.73 (s, 3 H), 3.76 (s, 3 H), 4.07−4.12 (m, 2 H), 4.38 (dd, *J* = 10.5, 2.8 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.1, 20.2, 22.8, 28.4, 29.6, 51.6, 52.4, 52.5, 54.0, 69.8, 85.3, 170.3, 170.7 ppm. HRMS: *m*/*z* calcd. for MNa^+ 281.1359, found MNa^+ 281.1344.

Dimethyl 2,4-Diisopropyldihydrofuran-3,3-dicarboxylate (23): R_f = 0.6 (ethyl acetate/hexane, 40:60); oil. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.85 (t, *J* = 6.7 Hz, 6 H), 0.96 (d, *J* = 6.5 Hz, 6 H), 1.48−1.54 (m, 1 H), 1.66−1.74 (m, 1 H), 2.85 (q, *J* = 7.7 Hz, 1 H), 3.56−3.63 (m, 1 H), 3.74 (s, 3 H), 3.76 (s, 3 H), 4.08−4.13(m, 1 H), 4.32 (d, *J* = 4.6 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.5, 20.6, 21.6, 22.9, 28.7, 30.8, 52.5, 52.7, 58.0, 70.4, 71.4, 89.3, 170.5, 170.8 ppm. HRMS: *m*/*z* calcd. for MNa^+ 295.1515, found MNa^+ 295.1529.

Dimethyl 2-Methoxymethyl-4,5-dimethyldihydrofuran-3,3-dicarboxylate (24): R_f = 0.4 (ethyl acetate/hexane, 40:60); oil. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.95 (d, *J* = 7 Hz, 3 H), 1.32 (d, *J* = 6 Hz, 3 H), 2.56−2.64 (m, 1 H), 3.32 (s, 3 H), 3.43 (q, *J* = 4.5 Hz, 1 H), 3.58−3.63 (m, 2 H), 3.75 (s, 3 H), 3.76 (s, 3 H), 4.58−4.62 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.1, 18.8, 46.9, 52.6, 52.7, 59.5, 65.9, 72.7, 80.3, 81.2, 169.9, 170.5 ppm. HRMS: *m*/*z* calcd. for M^+ 261.1338, found M^+ 261.1339.

Dimethyl 2-Isopropyl-4,5-dimethyldihydrofuran-3,3-dicarboxylate (25): R_f = 0.6 (ethyl acetate/hexane, 40:60); oil. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.84−0.90 (m, 6 H), 0.97 (d, *J* = 6.7 Hz, 3 H), 1.28 (d, *J* = 6 Hz, 3 H), 1.71−1.80 (m, 1 H), 2.49−2.58 (m, 1 H), 3.47−3.54 (m, 1 H), 3.72 (s, 3 H), 3.74 (s, 3 H), 4.23 (d, *J* = 5.3 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.3, 17.8, 18.5, 21.2, 30.3, 47.4, 51.5, 52.3, 67.5, 79.7, 86.9, 170.6, 170.9 ppm. HRMS: *m*/*z* calcd. for MNa^+ 281.1359, found MNa^+ 281.1343.

Dimethyl 2-Methoxymethyl-5-methyldihydropyran-3,3-dicarboxylate (27): (Diastereomeric mixture) Major/Minor, 1.5:1; R_f = 0.4 (ethyl acetate/hexane, 40:60); oil. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.82 (d, *J* = 6.7 Hz, 3 H, minor), 0.85 (d, *J* = 6.7 Hz, 3 H, major), 1.20−1.26 (m, 1 H, major), 1.50 (t, *J* = 12.6 Hz, 1 H, minor), 1.61−1.71 (m, 1 H, major), 1.89 (dd, *J* = 13.9, 11.4 Hz, 1 H, major), 2.33 (dd, *J* = 13.9, 3.9 Hz, 1 H, major), 2.47 (qd, *J* = 13.3, 2.0 Hz, 1 H, minor), 3.10 (t, *J* = 11.4 Hz, 1 H, minor), 3.17 (t, *J* =

10.4 Hz, 1 H, major), 3.29 (s, 3 H, major), 3.36 (s, 3 H, minor), 3.44 (dd, J = 10.4, 6.0 Hz, 1 H, major), 3.60 (ddd, J = 11.4, 4.5, 1.7 Hz, 1 H, major), 3.67 (s, 3 H, major), 3.71 (s, 3 H, minor), 3.75 (s, 3 H, minor), 3.77 (s, 3 H, major), 3.82 (dd, J = 6.9, 2.8 Hz, 1 H, minor), 3.95 (ddd, J = 11.2, 4.7, 1.8 Hz, 1 H, minor), 4.10 (q, J = 7.2 Hz, 1 H, minor), 4.29 (t, J = 6 Hz, 1 H, major) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.8, 17.2, 27.5, 27.8, 33.2, 40.1, 52.6, 52.8, 52.9, 53.2, 56.2, 56.7, 59.2, 59.3, 68.5, 70.4, 73.4, 74.1, 75.3, 80.9, 169.5, 170.5, 171.0 ppm. HRMS: m/z calcd. for M^+ 261.1338, found M^+ 261.1330.

Dimethyl 2-Ethyl-5-methyldihydropyran-3,3-dicarboxylate (28): R_f = 0.6 (ethyl acetate/hexane, 40:60); oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.83 (d, J = 6.5 Hz, 3 H), 0.94 (t, J = 7.4 Hz, 3 H), 1.52−1.62 (m, 1 H), 1.74−1.86 (m, 2 H), 2.26−2.32 (m, 1 H), 3.01−3.08 (m, 1 H), 3.49 (ddd, J = 11.5, 4.7, 1.6 Hz, 1 H), 3.67 (s, 3 H), 3.77 (s, 3 H), 3.96−4.01 (m, 1 H), 4.39 (d, J = 11.7, 3.2, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.2, 17.2, 19.5, 27.9, 32.5, 52.9, 53.2, 58.1, 65.6, 74.8, 170.0, 170.8 ppm. $C_{12}H_{20}O_5$: calcd. C 59.00, H 8.25; found C 59.20, H 7.96.

Dimethyl 2-Isopropyl-5-methyldihydropyran-3,3-dicarboxylate (29): R_f = 0.6 (ethyl acetate/hexane, 40:60); oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.74 (d, J = 6.4 Hz, 3 H), 0.84 (d, J = 6.7 Hz, 3 H), 0.98 (d, J = 6.4 Hz, 3 H), 1.58−1.68 (m, 1 H), 1.85 (dd, J = 13.9, 11.7 Hz, 1 H), 2.12−2.21 (m, 1 H), 2.27−2.33 (m, 1 H), 3.10 (t, J = 10.9 Hz, 1 H), 3.50 (ddd, J = 11.4, 5.0, 1.8 Hz, 1 H); 3.65 (s, 3 H), 3.75 (s, 3 H), 4.05 (d, J = 10.1 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.3, 20.0, 20.5, 26.5, 28.0, 33.3, 52.4, 53.1, 57.6, 67.3, 80.2, 170.6, 171.8 ppm. HRMS: m/z calcd. for M^+ 259.1545, found M^+ 259.1534.

Dimethyl 2-Cyclohexyl-5-methyldihydropyran-3,3-dicarboxylate (30): R_f = 0.6 (ethyl acetate/hexane, 40:60); white solid; m.p. 59−62 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.86 (d, J = 6.7 Hz, 3 H), 0.87−0.94 (m, 1 H), 0.96−1.05 (m, 1 H), 1.10−1.24 (m, 3 H), 1.28 (br. d, J = 12.8 Hz, 1 H), 1.59−1.69 (m, 3 H), 1.72−1.78 (m, 1 H), 1.82−1.94 (m, 3 H), 2.31 (dd, J = 13.7, 3.8 Hz, 1 H), 3.20 (t, J = 10.2 Hz, 1 H), 3.50 (ddd, J = 11.4, 5.0, 1.7 Hz, 1 H), 3.65 (s, 3 H), 3.74 (s, 3 H), 4.10 (d, 9.6 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.4, 26.2, 26.5, 28.0, 29.6, 30.0, 33.6, 36.5, 52.5, 53.2, 57.4, 68.0, 79.2, 170.0, 170.8 ppm. $C_{16}H_{26}O_5$: calcd. C 64.41, H 8.78; found C 63.95, H 8.77.

Dimethyl 2-Acetyl-5-methyldihydropyran-3,3-dicarboxylate (31): (Diastereomeric mixture) major/minor (2:1); R_f = 0.4 (ethyl acetate/hexane, 40:60); white solid; m.p. 69−71 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.84 (d, J = 6.4 Hz, 3 H, major), 0.82 (d, J = 6.4 Hz, 3 H, minor), 1.72 (t, J = 11.8 Hz, 2 H), 2.26 (s, 3 H, major), 2.28 (s, 3 H, minor), 2.44−2.53 (m, 2 H), 2.96 (t, J = 10.9 Hz, 1 H, minor), 3.13 (t, J = 10.9 Hz, 1 H, major), 3.67 (s, 3 H, minor), 3.75 (s, 6 H), 3.78 s, 3 H, minor), 3.97(s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.4, 17.0, 26.6, 27.0, 27.6, 27.8, 33.6, 39.4, 52.9, 53.0, 53.2, 53.5, 55.4, 59.6, 71.2, 75.0, 81.8, 84.6, 169.0, 169.5, 170.0, 171.0, 208.0, 208.4 ppm. $C_{12}H_{18}O_6$: calcd. C 55.81, H 7.02; found C 55.53, H 7.01.

Dimethyl 5-Methyl-2-(tricyclo[3.3.1.1^{0,0}]dec-1-yl)dihydropyran-3,3-dicarboxylate (32): R_f = 0.6 (ethyl acetate/hexane, 40:60); white solid; m.p. 64−67 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.86 (d, J = 6.5 Hz, 3 H), 1.58−1.68 (m, 10 H), 1.82 (br. d, J = 11.4 Hz, 3 H), 1.94 (br. s, 3 H), 2.16−2.6 (m, 2 H), 3.44 (t, J = 10.9 Hz, 1 H), 3.58 (ddd, J = 11.2, 5.5, 1.2 Hz, 1 H), 3.66 (s, 3 H), 3.73 (s, 3 H), 3.92 (s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.6, 27.4, 28.9, 34.8, 37.1, 39.4, 40.4, 52.4, 53.1, 57.6, 70.0, 81.6, 171.0, 172.0 ppm. HRMS: m/z calcd. for M^+ 350.2093, found M^+ 350.2091.

Dimethyl 2-(Methoxymethyl)oxepane-3,3-dicarboxylate (34): R_f = 0.4 (ethyl acetate/hexane, 40:60); oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.48−1.56 (m, 1 H), 1.66−1.82 (m, 3 H), 2.07 (ddd, J = 14.1, 9.7, 1.2 Hz, 1 H), 2.38 (ddd, J = 13.7, 8.6, 0.6 Hz, 1 H), 3.36 (s, 3 H), 3.50−3.54 (m, 1 H), 3.55−3.60 (m, 2 H), 3.70 (s, 3 H), 3.71 (s, 3 H), 4.02−4.09 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.6, 31.2, 35.4, 52.6, 52.9, 59.4, 62.2, 73.2, 74.8, 81.8, 171.5, 172.2 ppm. HRMS: m/z calcd. for M^+ 260.1260, found M^+ 260.1261.

Dimethyl 2-Ethyloxepane-3,3-dicarboxylate (35): R_f = 0.6 (ethyl acetate/hexane, 40:60); oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.98 (t, J = 7.2 Hz, 3 H), 1.44−1.52 (m, 2 H), 1.56−1.64 (m, 1 H), 1.66−1.84 (m, 3 H), 2.11−2.17 (m, 1 H), 2.39 (ddd, J = 14.3, 9.4, 1.3 Hz, 1 H), 3.42−3.49 (m, 1 H), 3.70 (s, 3 H), 3.72 (s, 3 H), 3.73−3.77 (m, 1 H), 4.06−4.12 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.5, 22.8, 26.8, 31.7, 35.2, 52.2, 52.8, 64.2, 74.0, 84.6, 170.8, 171.5 ppm. HRMS: m/z calcd. for M^+ 244.1311, found M^+ 244.1308.

Dimethyl 2-Isopropyloxepane-3,3-dicarboxylate (36): R_f = 0.6 (ethyl acetate/hexane, 40:60); oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.81 (d, J = 6.6 Hz, 3 H), 0.97 (d, J = 6.6 Hz, 3 H), 1.34−1.43 (m, 1 H), 1.62−1.68 (m, 1 H), 1.69−1.82 (m, 2 H), 1.92−1.99 (m, 1 H), 2.18 (dd, J = 14.3, 8.7 Hz, 1 H), 2.40−2.46 (m, 1 H), 3.40 (dt, J = 11.6, 3.9 Hz, 1 H), 3.71 (s, 3 H), 3.72 (s, 3 H), 3.88 (d, J = 4.2 Hz, 1 H), 4.15−4.20 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.2, 22.1, 22.8, 31.6, 32.1, 35.2, 52.6, 52.8, 63.4, 75.3, 87.6, 171.5, 172.9 ppm. HRMS: m/z calcd. for M^+ 258.1467, found M^+ 258.1459.

Dimethyl 2-Cyclohexyloxepane-3,3-dicarboxylate (37): R_f = 0.6 (ethyl acetate/hexane, 40:60); oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.04−1.23 (bm, 5 H), 1.54−1.8 (bm, 10 H), 2.13 (dd, J = 14.3, 8.7 Hz, 1 H), 2.42 (ddd, J = 14.4, 10.4, 0.8 Hz, 1 H), 3.32−3.40 (m, 1 H), 3.69 (s, 3 H), 3.70 (s, 3 H), 3.82 (d, J = 4.5 Hz, 1 H), 4.10−4.16 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.6, 26.5, 26.7, 27.0, 27.9, 31.9, 32.1, 35.4, 42.0, 52.5, 52.6, 63.0, 75.1, 87.3, 171.5, 172.8 ppm. HRMS: m/z calcd. for M^+ 298.1780, found M^+ 298.1777.

Dimethyl 2-Acetyloxepane-3,3-dicarboxylate (38): R_f = 0.4 (ethyl acetate/hexane, 40:60); oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.63−1.70 (m, 1 H), 1.74−1.85 (m, 2 H), 1.88−1.95 (m, 1 H), 1.97−2.03 (m, 1 H), 2.29 (s, 3 H), 2.41 (ddd, J = 14.4, 7.7, 1.5 Hz, 1 H), 3.69−3.72 (m, 1 H), 3.73 (s, 3 H), 3.74 (s, 3 H), 4.02−4.08 (m, 1 H), 4.17 (s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.2, 27.1, 30.4, 36.3, 52.8, 53.2, 63.4, 71.3, 87.2, 170.0, 171.8, 209.8 ppm. HRMS: m/z calcd. for M^+ 259.1182, found M^+ 259.1177.

Dimethyl 2-(Tricyclo[3.3.1.1^{0,0}]dec-1-yl)oxepane-3,3-dicarboxylate (39): R_f = 0.6 (ethyl acetate/hexane, 40:60); oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.39−1.51 (m, 1 H), 1.54−1.65 (m, 15 H), 1.86−1.91 (br. s, 3 H), 2.02−2.09 (m, 1 H), 2.61 (dd, J = 14.3, 10.4 Hz, 1 H), 3.30 (dt, J = 12.2, 3.7 Hz, 1 H), 3.71 (s, 3 H), 3.73 (s, 3 H), 3.78 (s, 1 H), 4.22−4.27 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.0, 28.6, 32.2, 37.2, 37.7, 37.9, 38.2, 39.5, 52.3, 52.6, 60.9, 91.2, 172.1, 172.8 ppm. HRMS: m/z calcd. for M^+ 350.2093, found M^+ 350.2089.

Dimethyl 2-Methoxymethyl-5-methyloxepane-3,3-dicarboxylate (42): R_f = 0.4 (ethyl acetate/hexane, 40:60); oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.98 (d, J = 6.9 Hz, 3 H), 1.52 (dd, J = 13.7, 10.9 Hz, 1 H), 1.64−1.69 (m, 2 H), 2.03−2.11 (m, 1 H), 2.34

(dd, J = 13.6, 1.2 Hz, 1 H), 3.33 (s, 3 H), 3.55 (dd, J = 10.6, 2.5 Hz, 1 H), 3.67 (s, 3 H), 3.73 (s, 3 H), 3.74−3.78 (m, 3 H), 3.96 (dd, J = 7.4, 2.5 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.2, 28.6, 37.4, 45.8, 52.4, 52.8, 59.3, 61.8, 68.5, 75.4, 79.8, 170.1, 171.7 ppm. HRMS: *m*/*z* calcd. for M^+ 275.1495, found M^+ 275.1497.

Dimethyl 2-Ethyl-5-methyloxepane-3,3-dicarboxylate (43): R_f = 0.6 (ethyl acetate/hexane, 40:60); oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.96 (t, J = 7.3 Hz, 3 H), 1.00 (d, J = 6.7 Hz, 3 H), 1.48−1.54 (m, 2 H), 1.65−1.75 (m, 3 H), 1.98−2.12 (m, 1 H), 2.34−2.38 (m, 1 H), 3.64 (dd, J = 10.6, 1.7 Hz, 1 H), 3.68 (s, 3 H), 3.70−3.74 (m, 1 H), 3.76 (s, 3 H), 3.77−3.82 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.6, 24.1, 26.4, 28.9, 37.4, 46.1, 52.4, 52.8, 63.2, 68.1, 81.8, 170.8, 172.6 ppm. HRMS: *m*/*z* calcd. for M^+ 258.1467, found M^+ 258.1458.

Dimethyl 2-Isopropyl-5-methyloxepane-3,3-dicarboxylate (44): R_f = 0.6 (ethyl acetate/hexane, 40:60); oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.83 (d, J = 6.9 Hz, 3 H), 0.95 (d, J = 6.7 Hz, 3 H), 0.97 (d, J = 6.9 Hz, 3 H), 1.56−1.60 (m, 1 H), 1.61−1.65 (m, 1 H), 1.67−1.74 (m, 1 H), 2.04−2.11 (m, 1 H), 2.26−2.36 (m, 2 H), 3.42 (d, J = 7.5 Hz, 1 H), 3.58−3.64 (m, 1 H), 3.65 (s, 3 H), 3.75 (s, 3 H), 3.77−3.84 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.2, 20.8, 23.9, 28.7, 33.2, 37.6, 47.1, 52.0, 52.5, 62.5, 69.2, 86.2, 170.6, 172.4 ppm. HRMS: *m*/*z* calcd. for M^+ 272.1624, found M^+ 272.1618.

Dimethyl 2-Cyclohexyl-5-methyloxepane-3,3-dicarboxylate (45): R_f = 0.6 (ethyl acetate/hexane, 40:60); oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.96 (d, J = 6.9 Hz, 3 H), 1.07−1.24 (m, 4 H), 1.50−1.76 (m, 8 H), 1.89−2.01 (m, 2 H), 2.04−2.11 (m, 1 H), 2.33 (dd, J = 13.9, 1.2 Hz, 1 H), 3.47 (d, 7.4 Hz, 1 H), 3.57−3.62 (m, 1 H), 3.66 (s, 3 H), 3.75 (s, 3 H), 3.77−3.82 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.1, 26.4, 26.6, 27.0, 28.7, 30.3, 31.1, 37.6, 43.3, 47.2, 52.2, 52.4, 62.3, 69.2, 85.5, 170.4, 171.4 ppm. HRMS: *m*/*z* calcd. for M^+ 312.1937, found M^+ 312.1938.

Dimethyl 2-Acetyl-5-methyloxepane-3,3-dicarboxylate (46): R_f = 0.4 (ethyl acetate/hexane, 40:60); oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.00 (d, J = 6.7 Hz, 3 H), 1.59−1.66 (m, 1 H), 1.67−1.75 (m, 1 H), 1.80−1.90 (m, 2 H), 2.27 (s, 3 H), 2.41 (d, J = 13.9 Hz, 1 H), 3.74 (s, 3 H), 3.75 (s, 3 H), 3.77−3.81 (m, 1 H), 3.91−3.99 (m, 1 H), 4.12 (s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.2, 26.9, 28.2, 37.4, 44.3, 52.8, 53.0, 63.4, 68.8, 86.0, 170.0, 171.0, 209.2 ppm. HRMS: *m*/*z* calcd. for M^+ 272.1260, found M^+ 272.1255.

Dimethyl 5-Methyl-2-(tricyclo[3.3.1.1^{0,0}]dec-1-yl)oxepane-3,3-dicarboxylate (47): R_f = 0.6 (ethyl acetate/hexane, 40:60); oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.96 (d, J = 6.9 Hz, 3 H), 1.56−1.68 (m, 12 H), 1.70−1.80 (m, 4 H), 1.92−1.96 (br. s, 3 H), 2.36 (br. d, J = 14.1 Hz, 1 H), 3.37 (s, 1 H), 3.55−3.62 (m, 1 H), 3.68 (s, 3 H), 3.72 (s, 3 H), 3.83−3.90 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.8, 28.9, 29.1, 37.2, 37.4, 39.2, 40.3, 48.6, 52.1, 52.4, 61.9, 69.8, 89.3, 170.2, 171.2 ppm. HRMS: *m*/*z* calcd. for M^+ 364.2250, found M^+ 364.2244.

Dimethyl 2-(Methoxymethyl)oxocane-3,3-dicarboxylate (49): R_f = 0.4 (ethyl acetate/hexane, 40:60); oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.21−1.29 (m, 1 H), 1.52−1.66 (m, 3 H), 1.69−1.82 (m, 2 H), 2.02 (dq, J = 7.4, 1.8 Hz, 1 H), 2.45 (dt, J = 11.6, 1.8 Hz, 1 H), 3.34 (s, 3 H), 3.54−3.58 (m, 2 H), 3.67 (dd, J = 10.2, 2.7 Hz, 1 H), 3.69 (s, 3 H), 3.72 (s, 3 H), 3.87−3.92 (m, 1 H), 4.14 (dd, J = 7.2, 2.5 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.1, 26.7, 27.9, 31.5, 52.4, 52.7, 59.4, 61.0, 72.3, 75.4, 76.2, 171.2, 172.4 ppm. HRMS: *m*/*z* calcd. for MNa^+ 297.1308, found MNa^+ 297.1307.

Dimethyl 2-Ethyloxocane-3,3-dicarboxylate (50): R_f = 0.6 (ethyl acetate/hexane, 40:60); oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.02 (t, J = 7.2 Hz, 3 H), 1.22−1.30 (m, 2 H), 1.52−1.59 (m, 1 H), 1.62−1.72 (m, 5 H), 1.97−2.03 (m, 1 H), 2.46−2.54 (m, 1 H), 3.51−3.56 (m, 1 H), 3.69 (s, 3 H), 3.73 (s, 3 H), 3.84 (dd, J = 10.4, 1.8 Hz, 1 H), 4.02−4.08 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.3, 11.9, 24.2, 26.4, 27.4, 28.3, 28.6, 29.8, 30.6, 31.8, 52.2, 52.6, 63.6, 64.5, 74.1, 75.2, 80.1, 84.0, 127.1, 132.9, 170.9, 171.1, 171.5, 172.0 ppm. HRMS: *m*/*z* calcd. for M^+ 258.1461, found M^+ 258.1467.

Dimethyl 2-Isopropyloxocane-3,3-dicarboxylate (51): R_f = 0.6 (ethyl acetate/hexane, 40:60); oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.82 (d, J = 6.7 Hz, 3 H), 0.99 (d, J = 6.7 Hz, 3 H), 1.15−1.23 (m, 1 H), 1.60−1.70 (m, 5 H), 1.86−1.90 (m, 1 H), 1.94−1.99 (m, 1 H), 2.49−2.55 (m, 1 H), 3.49−3.54 (m, 1 H), 3.69 (s, 3 H), 3.73 (s, 3 H), 3.89 (d, J = 4.7 Hz, 1 H), 4.00−4.05 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.7, 22.8, 24.3, 26.5, 28.6, 31.8, 32.6, 52.4, 52.5, 63.1, 74.3, 82.4, 171.9, 172.4 ppm. HRMS: *m*/*z* calcd. for M^+ 272.1624, found M^+ 272.1622.

Dimethyl 2-Cyclohexyloxocane-3,3-dicarboxylate (52): R_f = 0.6 (ethyl acetate/hexane, 40:60); white solid, m.p. 61−65 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.05−1.20 (m, 6 H), 1.47−1.52 (m, 1 H), 1.58−1.65 (m, 6 H), 1.67−1.75 (m, 4 H), 1.92−1.98 (m, 1 H), 2.49−2.56 (m, 1 H), 3.47−3.52 (m, 1 H), 3.70 (s, 3 H), 3.73 (s, 3 H), 3.85 (d, J = 4.8 Hz, 1 H), 3.96−4.02 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.5, 26.6, 26.7, 27.1, 28.5, 28.6, 31.8, 31.9, 33.1, 42.9, 52.3, 52.4, 62.8, 73.9, 81.9, 171.8, 172.2 ppm. HRMS: *m*/*z* calcd. for M^+ 312.1937, found M^+ 312.1939.

Dimethyl 2-Acetyloxocane-3,3-dicarboxylate (53): R_f = 0.4 (ethyl acetate/hexane, 40:60); white solid, m.p. 82−86 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.50−1.61 (m, 4 H), 1.72−1.79 (m, 1 H), 1.93−1.97 (m, 2 H), 2.25 (s, 3 H), 2.31−2.37 (m, 1 H), 3.56−3.64 (m, 1 H), 3.68 (s, 3 H), 3.70 (s, 3 H), 3.97 (dt, J = 11.7, 3.0 Hz, 1 H), 4.18 (s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.1, 24.2, 26.7, 27.0, 32.6, 52.8, 53.1, 62.9, 72.4, 84.8, 171.2, 172.1, 210.9 ppm. HRMS: *m*/*z* calcd. for M^+ 272.1260, found M^+ 272.1252.

Dimethyl 2-{(Pent-4-enyloxytricyclo[3.3.1.1^{0,0}]dec-1-yl)methyl}-malonate (54): R_f = 0.6 (ethyl acetate/hexane, 40:60); oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.40−1.45 (m, 3 H), 1.56−1.62 (m, 8 H), 1.65−1.71 (m, 3 H), 1.95 (br. s, 3 H), 2.04−2.08 (m, 2 H), 3.44−3.47 (m, 1 H), 3.60 (d, J = 7.2 Hz, 2 H), 3.69 (s, 3 H), 3.71 (s, 3 H), 3.72−3.75 (m, 1 H), 4.89−5.01 (m, 2 H), 5.74−5.82 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 28.3, 29.6, 30.6, 37.2, 37.9, 38.6, 52.6, 52.8, 52.9, 73.8, 85.2, 113.9, 138.4, 168.2, 170.1 ppm. HRMS: *m*/*z* calcd. for M^+ 364.2250, found M^+ 364.2243.

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