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TETRAHEDRON

METAL-MEDIATED TWO-ATOM CARBOCYCLE ENLARGEMENT IN AQUEOUS MEDIUM[1]

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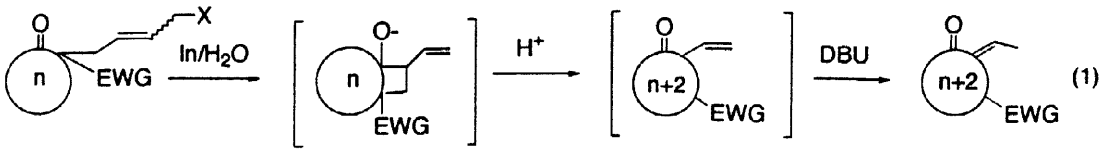
Summary: *The indium and tin-mediated carbonyl allylations of 1,3-dicarbonyl compounds have been studied in aqueous medium. The study led to the development of a novel two-atom carbocycle-enlargement in water. Five-, six-, seven-, eight-, and twelve-membered rings are enlarged by two carbon atoms into seven-, eight-, nine-, ten-, and fourteen-membered ring derivatives respectively. Tetralone derivatives are similarly expanded to 6-8 fused ring systems; and indanone derivatives are expanded to 5-7 fused ring systems. The use of both indium and zinc as the metal mediators provided the ring expansion products successfully. The use of water as a solvent was found to be essential for the ring expansion reaction.*

INTRODUCTION

The importance of medium size (8, 9, 10) rings in organic chemistry is exemplified by their being the structural core of a large number of biologically important natural products. These compounds include byssochlamic acid,[2] isabelin,[3] dactylol,[4] precapnelladiene,[5] pleuromutilin,[6] albolic acid,[7] steganone,[8] taxol,[9] and others. The study of varied ring systems closely parallels their availability. Thus, the continuing evolution of cyclization methods plays a critical role in extending our understanding and in developing the utility of functionalized medium and large size rings. Among the many methods for medium and large ring synthesis, ring expansion occupies a unique position, inasmuch as the usual disfavored entropy effect associated with medium and large size ring formations can be prevented.[10] An important recent advance in ring expansion studies is the use of free radicals.[11] The advantages of free radicals in synthesis include ease of execution, compatibility with a wide range of functional groups, as well as the capability of specific generation at designated sites.[12] However, as shown by Dowd, free radical ring expansion is not successful with two-atom expansion, where reductive dehalogenation usually occurs.[11] For two-atom ring expansions, the photochemical method of [2+2] cyclization-decyclization, commonly known as the de Mayo reaction, is the most successful.[13] The [2+2] cycloaddition of an acetylenic ester to the enamine of a cyclic ketone and subsequent opening of the annulated cyclobutene moiety formed is another useful method for two-carbon ring expansion.[14] Other n+2 ring expansions include through the 1,3-migration of allylic alcohols or ethers,[15] through aldol-type condensations,[16] and via Paquette's cycloether-carbocycle enlargement.[17] Recently, we described the preliminary investigation of a novel-carbocycle enlargement reaction based on a Barbier-Grignard type reaction in water (Eq. 1).[18] Here we report the detailed studies on this carbocyle expansion method.



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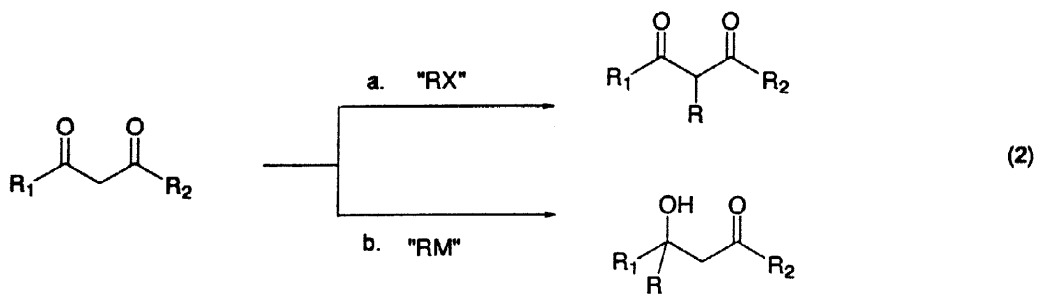
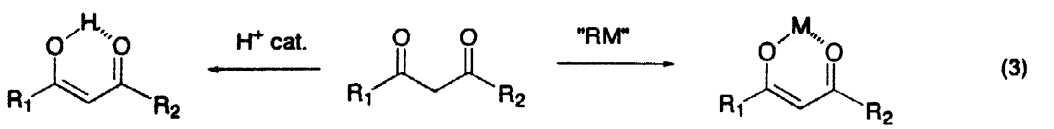
RESULTS AND DISCUSSION

The electrophilic alkylation of 1,3-dicarbonyl compounds and related compounds whereby stabilized carbanions react with an alkyl halide to give the corresponding alkylation products (eq 2, path a) constitutes one of the most useful methods for carbon-carbon bond formation.[19] Dicarbonyl compounds have also been used as nucleophiles in transition-metal catalyzed alkylation reactions[20], in Michael addition reactions[21] and in condensation reactions.[22] In contrast to the facility with which they undergo electrophilic alkylation, addition of an organometallic reagent to the carbonyl group of 1,3-dicarbonyl compounds to form a nucleophilic alkylation product (eq 2, path b) is relatively difficult. It is a dilemma that while the acidity of the hydrogen on the carbon in between the two carbonyl groups makes 1,3-dicarbonyl compounds excellent nucleophiles, that same acidity makes the corresponding nucleophilic carbonyl alkylation extremely difficult. When an organometallic reagent is allowed to react with these compounds, instead of addition to the carbonyl group, the organometallic reagent will be protonated instantly due to the large pKa difference[23] between the hydrogen in an alkane and the hydrogen in a 1,3-dicarbonyl compound, generating a stable cyclic enolate complex (eq 3). The 1,3-dicarbonyl compounds are equally prone to acid catalyzed enolization. The enolized structures generated under both acid and base conditions are inert towards nucleophilic attack. To overcome such an intrinsic difficulty, the acidity and basicity of the incoming organometallic reagent has to be carefully balanced (for example, using a ceric reagent) to avoid the competing, facile enolization process.[24] The reaction process, however, is still intriguing.



(2)



(3)

A convenient carbonyl allylation of 1,3-dicarbonyl compounds was found to be very effective via a Barbier-type reaction using water as the solvent.[25] Stirring ethyl 2-oxo-cyclopentanecarboxylate and allyl bromide with indium powder[26] in a mixture of methanol/water (1:4) for 10 hr at room temperature resulted in the formation of the corresponding β-hydroxyl ester in 76% yield as a mixture of diastereomers (entry 1). A range of 1,3-dicarbonyl compounds were subsequently investigated (Eq. 4) (Table I). Under slightly acidic conditions, an equally efficient allylation product was obtained when indium was replaced by tin (entry 2).[27] The reactivity difference between indium and tin can be attributed to the relatively low first ionization potential of indium with respect to tin.[28] Ethyl 2-oxo-cyclohexanecarboxylate reacts similarly to give the corresponding products in a higher diastereoselectivity (10:1) (entries 9 and 10). The best yields were obtained when the allylation was carried out on 2-acetylbutyrolactone. However, in this case, a 1:1 mixture of diastereomers was produced. An acyclic 1,3-dicarbonyl compound (ethyl acetoacetate) reacted as well as the cyclic compounds. Allylation of a 1,3-diketone mainly gave the bis-allylation product. The reaction was equally successful when

carried out in water alone (entries 7 and 8). Replacing allyl bromide with allyl chloride does not adversely affect the reaction yield significantly (entries 5 and 6).

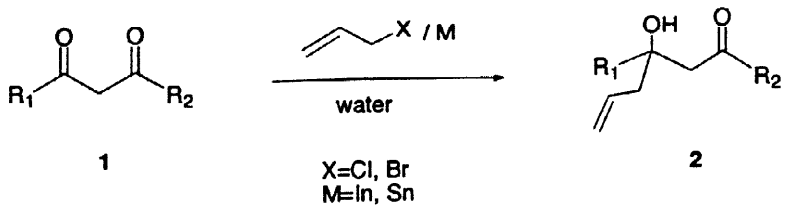
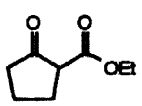
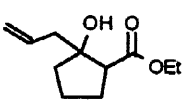
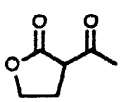
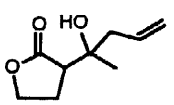
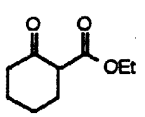
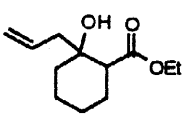
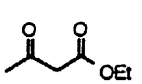
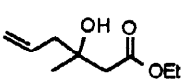
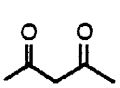
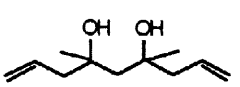


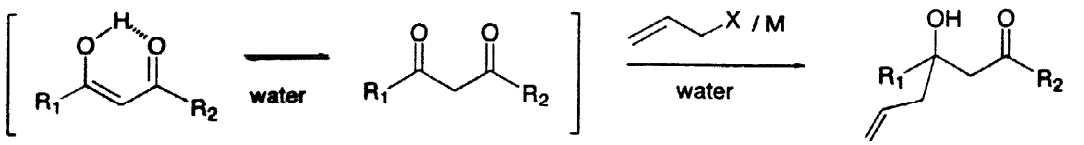
Table 1. Allylation of 1,3-Dicarbonyl Compounds in Aqueous Medium

Entry	Substrate(1)	X-	Metal/Solvent/Time(h)	Product(2)	Yield(%)[a]
1		Br	In/A/10		76[b]
2		Br	Sn/B/20		57[b]
	1a			**2a**	
3		Br	In/B/10		quant.[c]
4		Br	Sn/B/20		94[c]
5	**1b**	Cl	In/B/10	**2b**	quant.[c]
6		Cl	Sn/B/20		90[c]
7		Br	In/H_2O/10		quant.[c]
8		Br	Sn/H_2O/48		94[c]
9		Br	In/A/10		75[d]
10		Br	Sn/B/20		47[d]
	1c			**2c**	
11		Br	In/B/10		98
12		Br	Sn/B/20		76
	1d			**2d**	
13		Br	In/B/10		75[e]
14		Br	Sn/B/20		70[e]
	1e			**2e**	

All reactions were carried out at room temperature with the reactants in a molecular ratio of carbonyl compound/allyl halide/metal (1/3/3), unless otherwise mentioned. A: methanol/water (1:4); B: methanol/ 0.1N HCl (1:4); a. isolated yields; b. as a mixture of diastereomers(5:1); c. as a mixture of diastereomers(1:1); d. as a mixture of diastereomers(10:1); e. about 20% of the monoallylation product was also isolated.

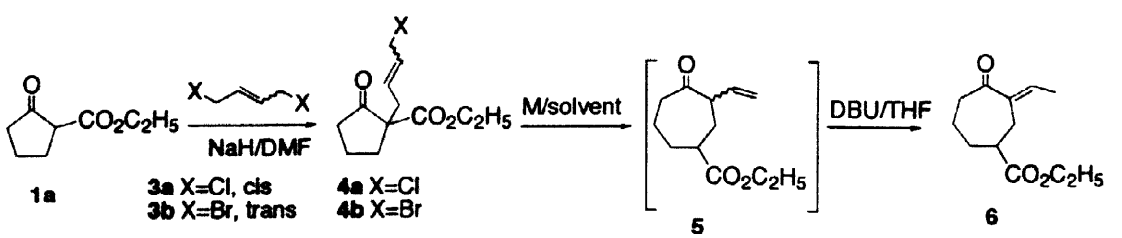
Scheme 1 outlines the rationale of the allylation reaction. Despite the fact that there is an equilibrium between the enolate form and the dicarbonyl form, allylation of 1,3-dicarbonyl compounds mediated by the aqueous Barbier-type reaction only occurs on the carbonyl form. Alcohols and olefins are inert under the reaction conditions. Reaction of the ketone form eventually drives the equilibrium to the desired direction.

Scheme 1. Rationale for Carbonyl Alkylation of 1,3-Carbonyl Compounds in Water



The success of the carbonyl allylation of 1,3-dicarbonyl compounds quickly led us to investigate the projected ring expansion. The initial two-carbon ring expansion study was carried out on the cyclopentanone carboxylate **4a** (Scheme 2). The choice of a β-keto ester for the initial study is based on several reasons: (1) these compounds are readily available; (2) the alkylation of β-keto esters is simple; (3) the presence of the carboxylate group facilates the ring opening of the intermediate. Allylation of ethyl 1-oxocyclopentane-2-carboxylate (**1a**) with cis-1,4-dichloro-2-butene (**3a**) or trans-2,4-dibromo-2-butene (**3b**) was readily accessible in DMF in the presence of NaH, providing the expansion precursors **4a** and **4b**. Then, after the cyclopentanone derivative **4a** was stirred for 10 hr with indium metal powder in water and at room temperature, TLC showed the disappearance of the starting material. After work-up, the ^{1}H NMR measurement of the crude mixture indicated the presence of two sets of terminal olefins, corresponding to two diastereomers (**5**). Upon treatment with DBU, both sets of terminal olefin signals disappeared and resulted in a single compound **6**. Flash chromatography on silica gel provided an overall 50% of the pure product over two steps. The presence of a quartet peak at 6.8 (integrated to 1 H) and a doublet peak at 1.8 (integrated to 3 H's) in the ^{1}H NMR spectrum of the new compound established the location and geometry of the olefin as indicated.

Scheme 2.



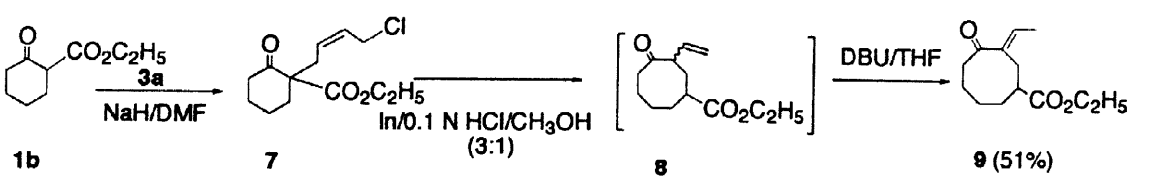
Subsequently, a range of conditions that may affect the reaction have been examined. The studies are listed in Table 2. When the initial cyclization was carried out in DMF, at 130°C, a complicated mixture was generated without any recognizable product; whereas at room temperature, no reaction was observed. Switching the expansion medium to regular organic solvents, such as methanol or THF, did not lead to the proceeding of the reaction either, with the starting material being recovered completely. Replacing the chloro

compound with a bromo derivative **4b** resulted in a moderate increase in the yield of the ring expansion product. The potential use of other metal mediators for the ring expansion was also examined. When the bromo compound was stirred with zinc powder in saturated aqueous NH_4Cl, only the reductive-debromination product was obtained. Whereas the use of 3% aqueous NH_4Cl as solvent led to the expansion product. On the other hand, the uses of other metals were less effective. Reaction of bismuth with the bromo compound **4b** only provided reductive-debromination products, whereas the use of tin as the mediator resulted in a complicated mixture. Thus, it seems that indium is preferable and is used as the standard protocol for subsequent studies. Through a similar sequence of transformations, a cyclohexanone derivative **7** was expanded to an octanone ring **9** (Scheme 3).

Table 2. Expansion of Five-Membered Ring

Substrate (4)	Method	Time(h)/Temp.(°C)	6 Overall Yield (%)
4a	In/0.1NHCl/CH_3OH (3:1)	10/r.t.	50
4a	In/DMF	3/130	complicated
4a	In/DMF	24/r.t.	0
4a	In/MeOH	24/r.t.	0
4b	In/0.1NHCl/CH_3OH (3:1)	3/r.t.	70
4b	Zn/sat. aq. NH_4Cl	5/r.t.	0
4b	Zn/3% aq. NH_4Cl	5/r.t.	60
4b	Bi/H_2O/THF pH=1-2	12/r.t.	0
4b	Sn/0.1NHCl/CH_3OH (1:1)	8/r.t.	Complicated

Scheme 3.



1b **7** **8** **9** (51%)

Scheme 4.

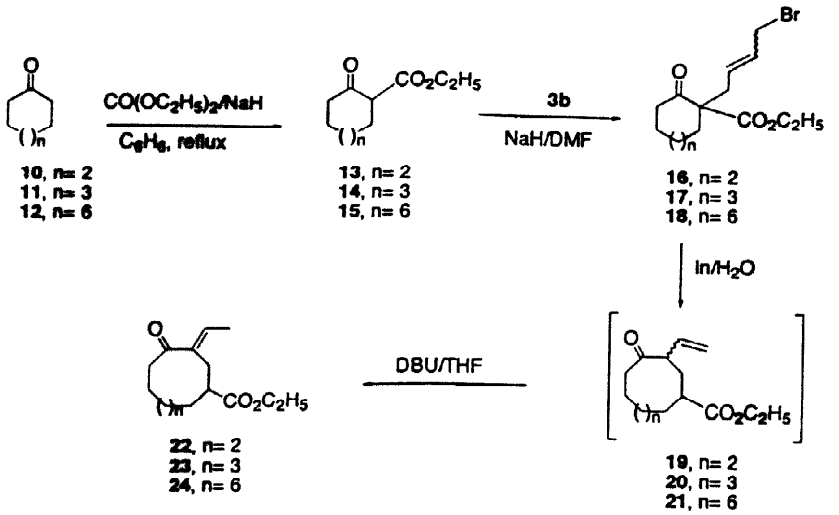
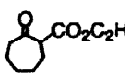
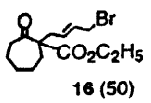
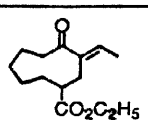
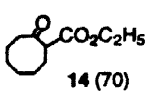
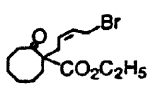
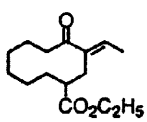
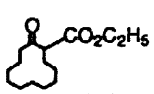
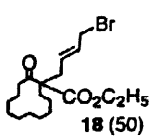
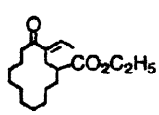


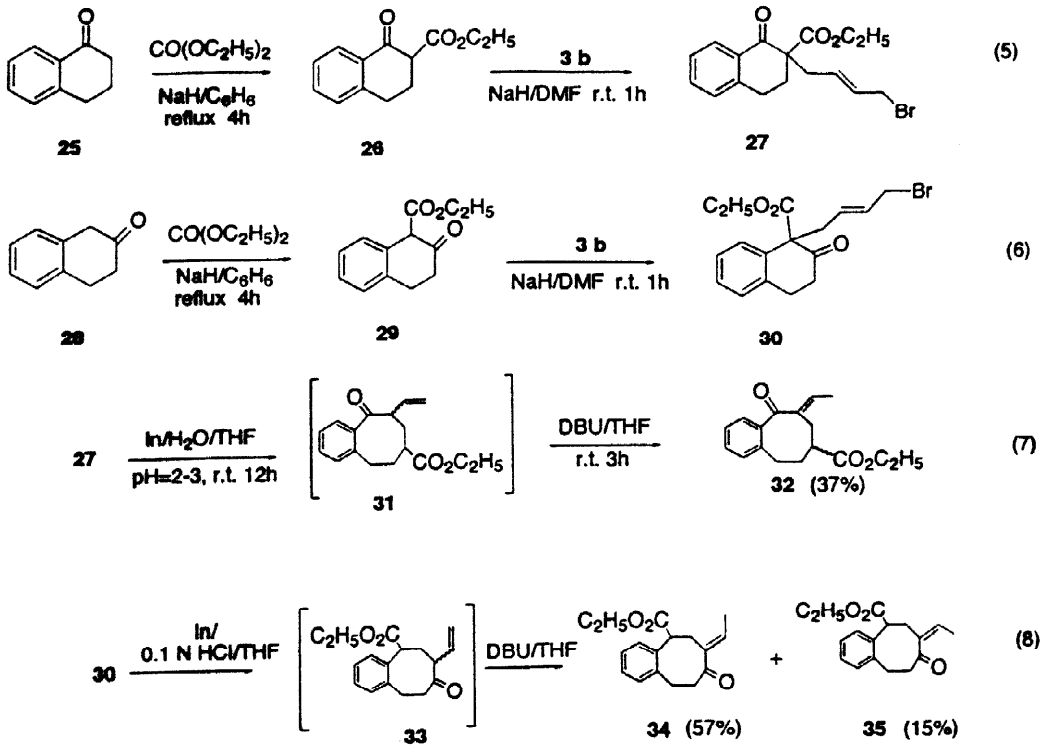
Table 3. Expansion of Seven-, Eight- and Twelve- Membered Rings

Cycloketone	Carboxylate (Yield %)	Allylation (Yield %)	Ring Expansion Condition	Expansion Product (yield %)
 10	 13 (80)	 16 (50)	In/H2O/THF (2:1)/r.t./10h	 22 (72)
 11	 14 (70)	 17 (50)	In/H2O/THF (2:1)/r.t./12h	 23 (50)
 12	 15 (59)	 18 (50)	In/H2O/THF (5:1)/r.t./12h	 24 (49)

Likewise, seven-, , eight- and twelve-membered ring compounds (**16**, **17**, and **18**) were expanded similarly with indium in water to give nine-, ten- and fourteen-membered-ring products (**19**, **20**, and **21**) respectively (Scheme 4) (Table 3). In all these cases, only the vinyl type products were initially observed. Subsequent DBU treatment isomerized the olefin to a conjugated system (**22**, **23**, and **24**). In all cases, the substrates were not water-soluble. However, under fast-stirring conditions, together with the use of some cosolvent (THF), the phase separation did not prevent the proceeding of the reaction. The starting β-keto ester for each expansion was obtained by carboxylation of the corresponding cycloalkanone by the standard procedure.

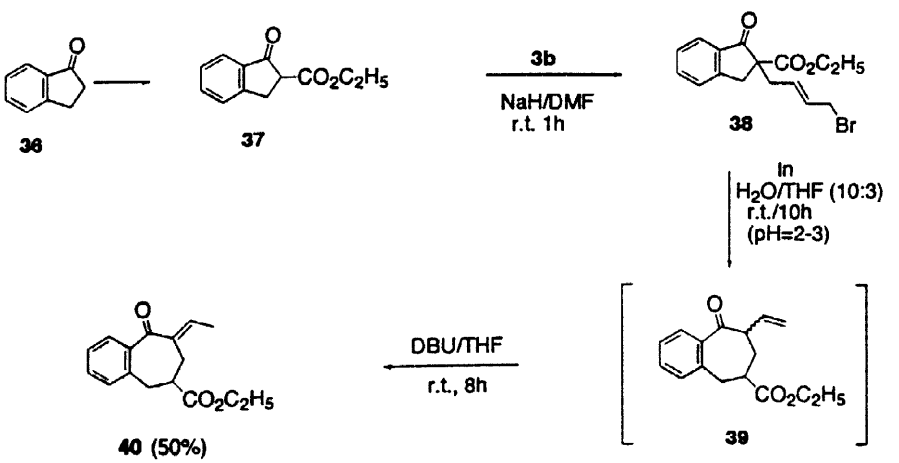
The expansion of tetralone derivatives led to a 6-8 fused ring system. The expansion of both α- and β-tetralones was examined. The required expansion precusors **27** and **30** for both studies were similarly prepared from **25** and **28** through the carboxylation reaction followed by allylation with compound **3b** (Eq. 5, Eq. 6). When the α-tetralone derivative **27** was subjected to the indium reaction under our standard conditions, only reductive-debomination products were observed. However, the use of a medium with a slightly increased pH (2-3) prevented the reduction from taking place, giving the ring expansion product **32** successfully (Eq. 7). On the other hand, the expansion of the β-teralone derivative **30** was not affected by the

acidity of the medium, giving the 6-8 fused ring expected products (34, 35) under the standard ring expansion conditions (Eq. 8).

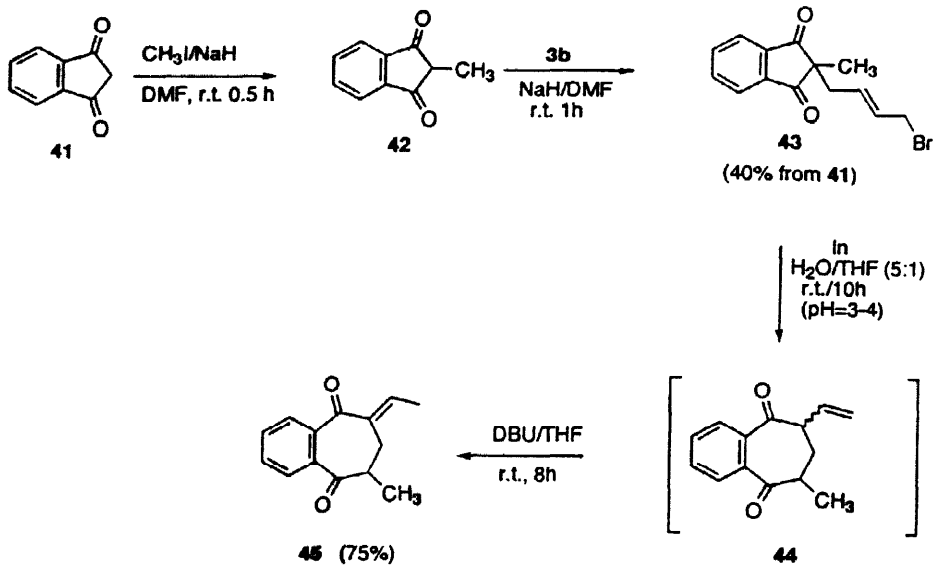


The expansion of indanone derivatives was equally successful. The reaction of ethyl 2-(trans-4-bromo-2-buten-1-yl)-1-oxo-2-indanecarboxylate (38), prepared from 1-indanone (36) through carboxylation followed by alkylation, with indium in a mixture of water/THF generated the 6-7 fused ring system 39, which was isomerized to 40(Scheme 5). Similarly, the reaction of an indandione derivative 43, synthesized from 1,3-indandione (41) through methylation and alkylation, with indium followed by DBU treatment, generated the corresponding expansion product 45 in 75% isolated yield (Scheme 6).

Scheme 5.

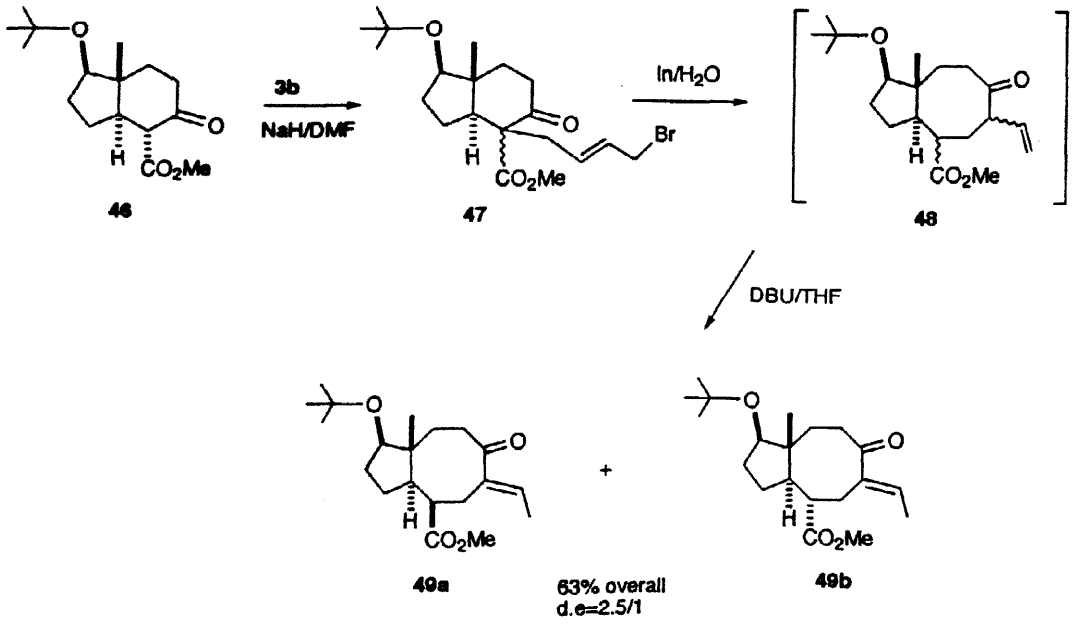


Scheme 6.



In order to assess the potential application of the ring expansion method in natural product synthesis, the expansion of 5-6 fused compound **46** was invesitgated (Scheme 7). Allylation of **46** with **3b** generated the expansion precursor **47**. Reaction of bicyclic compound **47** with indium metal in water generated two sets of diastereomers (**48**), which were transformed to a 2.5/1 mixture of diastereomers (**49a** and **490b**) upon DBU treatment in 63% isolated overall yield over two steps. X-ray crystal analysis shows the major diastereomer corresponding to structure **49a** in which all three substituents (t-butoxyl, methyl and carboxylate) are cis-related (Fig. 1).[29] In conclusion, a novel two-atom carbocycle expansion method has been developed based on an aqueous Barber-type reaction. Application of the carbocycle-enlargement method to the synthesis of a variety of medium-ring bioactive compounds is presently being undertaken.

Scheme 7.



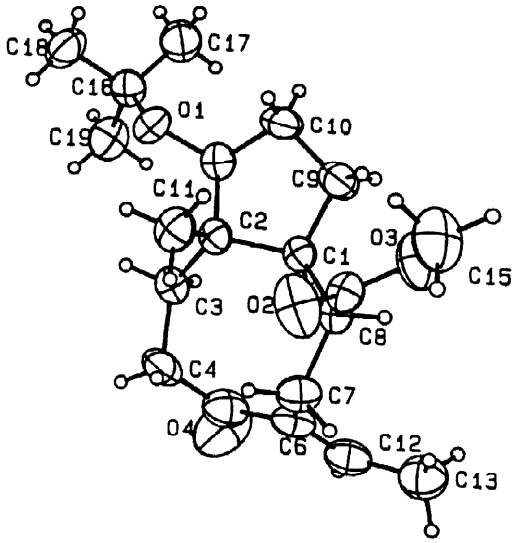


Figure 1. Perspective View of 18a. Thermal ellipsoids are drawn at the 50% probability level except for hydrogen atoms which are arbitrarily small for clarity.

ACKNOWLEDGMENT

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EXPERIMENTAL

Commercially available compounds were used without further purification. Indium powder was purchased from Aldrich Chemical Company and was used as received. All organic solvents were freshly distilled prior to use. Air-sensitive reactions were generally conducted under a positive pressure of dry N_2 within glassware which had been flame-dried under a stream of dry N_2. Anhydrous solvents and reaction mixtures were transferred by oven-dried syringe or cannula. Flash chromatography employed E. Merck silica gel (Kiesegel 60, 230-400 mesh). ^1H NMR and ^{13}C NMR spectra were recorded from G.E. Omega 400 (400 MHz) instrument, with TMS as an internal standard. Infra-Red spectra were performed on FT-IR (Mattson Cygnus 100). Mass spectra were obtained at the Center of Instrumental Facility of Tulane University and at the Medical School of McGill University. Crystal analysis was performed on an Enraf Nonius CAD-4 X-ray diffractometer. Elemental analyses were performed at the Center of Instrumental Facility of Tulane University and at Atlanta Microlab.

Sample procedure for the carbonyl allylation of 1,3-dicarbonyl compounds, ethyl 2-(2-propenyl)-2-hydroxycyclopentanecarboxylate (2a):

To a mixture of ethyl 2-oxo-cyclopentanecarboxylate (**1a**) (156 mg, 1 mmol) and allyl bromide (363 mg, 3 mmol) in 5 mL of methanol/water (1/4) was added indium powder (345 mg, 3 mmol) in one portion. The reaction mixture was stoppered and stirred vigorously at room temperature for 10 hr. The reaction was then stopped by the addition of 1 N HCl and extracted with ether (4x10 mL). The combined organic phase was washed with brine, dried over magnesium sulfate, and concentrated. The corresponding allylation product **2a** was isolated by flash column chromatography on silica gel (eluent: hexane/ethyl acetate = 10:1) (total 150 mg, 76%). Isomer A: IR(film): 3497, 3075, 2977, 1722, 1640, 1445, 1376, 1300, 1179, 1035, 916 cm^{-1}. ^1H NMR(400MHz, $CDCl_3$, ppm): δ 5.86(m, 1H), 5.07(m, 2H), 4.15(q, J =7.2 Hz, 2H), 3.45(Br, 1H), 2.53(t, J =10.8 Hz, 1H), 2.24(m, 2H), 2.06-1.56(m, 6H), 1.25(t, J =7.2 Hz, 3H). ^{13}C NMR(100MHz, $CDCl_3$, ppm): δ 175.62, 134.15, 118.08, 81.81, 60.61, 51.08, 44.67, 38.12, 28.33, 21.73, 14.17. HRMS(EI): Calc'd for $C_{11}H_{18}O_3$-C_3H_5, 157.0865; Found, 157.0874. Isomer B, IR(film): 3503, 2980, 1728, 1660, 1447, 1370, 1300, 1193, 111, 1026 cm^{-1}. ^1H NMR(400MHz, $CDCl_3$, ppm): δ 5.89(m, 1H), 5.14(m, 2H), 4.14(q, J =7.2 Hz, 2H), 3.13(Br, 1H), 2.77(t, J =7.5 Hz, 1H), 2.24(m, 2H), 1.93-1.65(m, 6H), 1.26(t, J =7.2 Hz, 3H). ^{13}C NMR(100MHz, $CDCl_3$, ppm): δ 174.24, 133.55, 119.30, 82.49, 60.42, 55.35, 41.58, 37.68, 26.94, 21.50, 14.26. HRMS(EI): Calc'd for $C_{11}H_{18}O_3$-C_3H_5, 157.0865; Found, 157.0867.

Ethyl 2-(2-propenyl)-2-hydroxycyclohexanecarboxylate (2b):

By the same procedure as described above, the reaction of ethyl 2-oxo-cyclohexanecarboxylate (170 mg, 1 mmol), allyl bromide (363 mg, 3 mmol), and indium powder (345 mg, 3 mmol) in 5 mL of methanol/water (1:4) for 10 hr followed by column chromatography on silica gel (eluent: hexane/ethyl acetate = 10:1) generated compound **2b** (total 159 mg, 75%). Isomer A, IR(film): 3516, 2937, 1709, 1620, 1185, 987 cm^{-1}. ^1H NMR(400MHz, $CDCl_3$, ppm): δ 5.8(m, 1H), 5.0(m, 2H), 4.12(q, J =7 Hz, 2H), 3.76(br, 1H), 2.3(dd, J=3.5, 15.6 Hz, 1H), 2.2(m, 2H), 1.82-1.46(m, 8H), 1.23(t, J =7 Hz, 3H). ^{13}C NMR(100MHz, $CDCl_3$, ppm): δ 176.88, 133.68, 118.02, 70.90, 60.53, 49.22, 47.02, 35.06, 26.00, 24.87, 2074, 14.13. HRMS(EI): Calc'd for $C_{12}H_{20}O_3$-C_3H_5, 171.1021; Found, 171.1022. Isomer B, IR(film): 3516, 2938, 2864, 1709, 1620, 1184, 985cm^{-1}. ^1H NMR(400MHz, $CDCl_3$, ppm): δ 5.89(m, 1H), 5.10(m, 2H), 4.16(q, J =7.2 Hz, 2H), 3.39(br, 1H), 2.48(dd, J =4.2, 11.43 Hz, 1H), 2.30(m, 2H), 1.98-1.54(m, 8H), 1.29(t, J =7.2 Hz, 3H). ^{13}C NMR(100MHz, $CDCl_3$, ppm): δ 174.27, 133.31, 118.28, 72.57, 60.68, 52.41, 39.08, 36.05, 25.35, 24.40, 22.13, 14.21. Anal. Calc'd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.70; H, 9.61.

Ethyl 2-(2-propenyl)-2-hydroxycyclohexanecarboxylate (2c):

By the same procedure as described above, the reaction of 2-acetylbutyrolactone (128 mg, 1 mmol), allyl bromide (363 mg, 3 mmol), and indium powder (345 mg, 3 mmol) in 5 mL of methanol/water (1:4) for 10 hr followed by column chromatography on silica gel (eluent: hexane/ethyl acetate = 10:1) generated compound **2c** (total 170 mg, ca. 100%). Isomer A, IR(film): 3499, 3077, 2978, 2917, 1755, 1640, 1456, 1375, 1283, 1173, 1022, 958, 922cm^{-1}. ^1H NMR(400MHz, $CDCl_3$, ppm): δ 5.95(m, 1H), 5.13(m, 2H), 4.36(m, 1H), 4.17(m, 1H), 3.70(br, 1H), 2.76(m, 1H), 2.25(m, 4H), 1.2(s, 3H). ^{13}C NMR(100MHz, $CDCl_3$, ppm): δ 179.35, 133.48, 118.52, 72.57, 66.42, 47.25, 44.90, 25.16, 23.59. HRMS(EI): Calc'd for $C_9H_{14}O_3$-C_3H_5, 129.0552; Found, 129.0540. Isomer B, IR(film): 3491, 3077, 2978, 2915, 1757, 1640, 1456, 1379, 1281, 1171, 1028, 926 cm^{-1}. ^1H NMR(400MHz, $CDCl_3$, ppm): δ 5.89(m, 1H), 5.15(m, 2H), 4.36(m, 1H), 4.18(m, 1H), 3.45(s, 1H), 2.72(dd, J =5.4, 11 Hz, 1H), 2.32(m, 4H), 1.31(s, 3H). ^{13}C NMR(100MHz, $CDCl_3$, ppm): δ 178.14, 133.00, 119.23, 72.26, 66.32, 48.59, 43.46, 29.69, 24.77. HRMS(EI): Calc'd for $C_9H_{14}O_3$-C_3H_5, 129.0552; Found, 129.0545.

General Procedure for the Carboxylation Reaction:[30]

A two-necked, round-bottomed flask equipped with a magnetic stirrer was fitted with a 50 ml pressure-equalizing constant-rate dropping funnel and a condenser, the top of which was connected to a mercury trap to prevent the entrance of air during the reaction and for the detection of gas evolution. The dropping funnel was removed and 60% sodium hydride dispersion in mineral oil was added. The mineral oil was removed by washing the dispersion four times with dry benzene under N_2 atmosphere. Benzene was removed with a pipette after the sodium hydride was allowed to settle. After most of the mineral oil had been removed, 60 ml of benzene was added to the sodium hydride, followed by diethyl carbonate, this mixture was heated to reflux, and a solution of cycloheptanone in benzene was added dropwise from the dropping funnel over a period of 3-4 h. After the addition was completed, this mixture was refluxed until the evolution of hydrogen ceases (15-20 min). When the reaction mixture has cooled to room temperature, acetic acid was added dropwise , forming pasty solid. Then ice-cold water was added and the mixture was stirred until all the solid material has been dissolved. The organic layer was separated, and the aqueous layer was extracted three times with benzene. The combined benzene extracts were washed three times with cold water. The organic layer was dried over $MgSO_4$ and filtered. The solvent was evaporated in vacuo. The residual materiel was chromatography on silica gel (eluent hexane:ethyl acetate).

General Procedure for the alkylation of 1,3-Dicarbonyl Compounds:

To a suspension of NaH(60% suspension in mineral oil) in dry DMF (or THF), a solution of the 1,3-dicarbonyl compound in DMF was added under nitrogen. After completion of the addition, the mixture was stirred at room temperature for 10 min, followed by the addition of a solution cis-1,4-dichloro-2-butene or trans-1,4-dibromo-2-butene in DMF. After stirred for 1h at room temperature, the reaction was quenched by saturated NH_4Cl solution. The mixture was extracted with ether for four times. The combined organic layer was washed three times with water, dried over $MgSO_4$, filtered and concentrated in vacuo to give crude material. Flash column chromatography of the crude product on silica gel (eluent: hexane-ethyl acetate) gave the corresponding product.

General Procedure for the Ring Expansion:

To a mixture of the ring expansion precursor in the appropriate solvent was added the metal mediator (In, Zn, Sn or Bi). The reaction mixture was vigorously stirred at room temperature for the specified period of time, quenched with 1N HCl, and extracted with ether. The combined organic phase was dried over anhydrous magnesium sulfate, filtered and concentrated to give a crude mixture of ring expansion products. The crude material was then dissolved in THF, and mixed with DBU (1 equivalent). The mixture was stirred at room temperature and followed by TLC. After completion, the solvent was removed in vacuo. Flash column chromatography on silica gel provided the isomerization product.

Ethyl 1-(cis-4-chloro-2-buten-1-yl)-2-oxo-1-cyclopentanecarboxylate (4a):

Following the general alkylation procedure, the reaction of ethyl 2-oxocyclopentanecarboxylate (312 mg, 2 mmol) with NaH (80 mg, 60% dispersion in mineral oil, 2 mmol) and cis-1,4-dichloro-2-butene (375 mg, 3 mmol) in DMF followed by column chromatography on silica gel (eluent: hexane/ethyl acetate = 15 : 1) provided **4a** (310 mg, 63%). IR(film): 3030, 2976, 1749, 1726, 1653, 1448, 1404, 1251, 1026, 860, 756 cm^{-1}. ^1H NMR(400MHz, $CDCl_3$, ppm): δ 5.76(m, 1H), 5.52(m, 1H0, 4.15(q, J =7.2 Hz, 2H), 4.09(m, 2H0, 1.91-2.74(m, 8H), 1.24(t, J =7.2 Hz, 3H). ^{13}C NMR(100MHz, $CDCl_3$, ppm): δ 214.50, 170.75, 128.83, 128.79, 61.68, 59.69, 38.98, 38.02, 32.46, 30.77, 19.61, 14.08. HRMS: Calc'd for $C_{12}H_{18}O_3Cl$ (M+1), 245.0944; Found, 245.0944.

Ethyl 1-(trans-4-bromo-2-buten-1-yl)-2-oxo-1-cyclopentanecarboxylate (4b):

Following the general alkylation procedure, the reaction of ethyl 2-oxocyclopentanecarboxylate (3 g, 19.2 mmol) with NaH (922 mg, 60% dispersion in mineral oil, 23 mmol) and trans-1,4-dibromo-2-butene (4.5 g, 21 mmol) in THF followed by column chromatography on silica gel (eluent: hexane/ethyl acetate = 15 :

1) provided **4b** (3.9 g, yield 70%). IR(film): 3041, 2982, 2935, 2903, 1753, 1728, 1734, 1450cm^{-1}. ^{1}H NMR(400MHz, $CDCl_3$, ppm): δ 5.72-5.59(m, 2H), 4.08(q, *J* =7.2 Hz, 2H), 3.83(d, *J* =6.8 Hz, 2H), 2.58(dd, *J* =14.0, 7.2 Hz, 1H), 2.39-2.14(m, 4H), 1.97-1.82(m, 3H), 1.17(t, *J* =7.2 Hz, 3H). ^{13}C NMR(100MHz, $CDCl_3$, ppm): δ 214.19, 170.60, 130.62, 130.35, 61.44, 59.75, 37.88, 35.76, 32.38, 32.21, 19.45, 14.04. HRMS: Calc'd for $C_{12}H_{18}O_3Br$ (M+1), 289.0440; Found, 289.0439.

3-(E)-Ethylidene-4-oxo-cycloheptanecarboxylic Acid Ethyl Ester (6):

Following the general procedure for ring expansion, ethyl 1-(cis-4-chloro-2-buten-1-yl)-2-oxo-1-cyclopentanecarboxylate (245 mg, 1 mmol) was reacted with indium powder (230 mg, 2 mmol) in 10 ml of aqueous 0.1N HCl/methanol (3:1). The crude material was treated with DBU (304 mg, 2 mmol) in 10 ml THF. Work-up followed by column chromatography on silica gel (eluent: hexane/ethyl acetate 20:1) provided **6** (106 mg, 50%). IR(film): 1757, 1726, 1685, 1650, 1618, 1454, 1255, 1192, 1026cm^{-1}. ^{1}H NMR(400MHz, $CDCl_3$, ppm): δ 6.77(q, *J* =7.2 Hz, 1H), 4.15(m, 2H), 1.50-2.94 (m, 9H), 1.79(d, *J* =7.2 Hz, 3H), 1.26(t, *J* =7.2 Hz, 3H). ^{13}C NMR(100MHz, $CDCl_3$, ppm): δ 203.16, 175.02, 138.31, 136.36, 60.63, 45.71, 42.55, 33.44, 28.90, 23.17, 14.19, 13.88. HRMS: Calc'd for $C_{12}H_{18}O_3$, 210.1256; Found, 210.1246.

Ethyl 1-(cis-4-chloro-2-buten-1-yl)-2-oxo-1-cyclohexanecarboxylate (7):

Following the general alkylation procedure, the reaction of ethyl 2-oxo-1-cyclohexanecarboxylate (340 mg, 2 mmol) with NaH (80 mg, 60% dispersion in mineral oil, 2 mmol) and cis-1,4-dichloro-2-butene (375 mg, 3 mmol) in DMF followed by column chromatography on silica gel (eluent: hexane/ethyl acetate = 20 : 1) provided **7** (333 mg, yield 65%). IR(film): 2930, 2860, 1745, 1716, 1618, 1448, 1402, 1259, 1082cm^{-1}. ^{1}H NMR(400MHz, $CDCl_3$, ppm): δ 5.61(m, 1H), 5.49(m, 1H), 4.10(q, *J* =7.2 Hz, 2H), 3.98(d, *J* =7.6 Hz, 2H), 2.54(dd, *J* =7.2, 14.4 Hz, 1H), 2.37(m, 4H), 1.93(m, 1H), 1.60(m, 3H), 1.37(m, 1H), 1.16(t, *J* =7.2 Hz, 3H). ^{13}C NMR(100MHz, $CDCl_3$, ppm): δ 207.23, 171.22, 128.87, 128.10, 61.45, 60.48, 41.00, 38.95, 35.86, 32.12, 27.39, 22.43, 14.04. Anal. Calc'd. for $C_{13}H_{19}ClO_3$: C, 60.21; H, 7.51. Found: C, 60.35; H, 7.40.

3-(E)-Ethylidene-4-oxo-cyclooctanecarboxylic Acid Ethyl Ester (9):

Following the general procedure for ring expansion, ethyl 1-(cis-4-chloro-2-buten-1-yl)-2-oxo-1-cycloheptanecarboxylate (317 mg, 1 mmol) was reacted with indium powder (230 mg, 2 mmol) in 10 ml of aqueous 0.1N HCl/methanol (3:1). The crude material was treated with DBU (304 mg, 2 mmol) in 10 ml THF. Work-up followed by column chromatography on silica gel (eluent: hexane/ethyl acetate 20:1) provided **9** (113 mg, 50%). IR(film): 1730, 1683, 1618, 1446, 1375, 1182, 1039, 862, 721cm^{-1}. ^{1}H NMR(400MHz, $CDCl_3$, ppm): 6.78(q, *J* =7.2 Hz, 1H), 4.14(m, 2H), 2.85(m, 3H), 2.44(m, 2H), 1.50-1.90(m, 6H), 1.80(d, *J* =7.2 Hz, 3H), 1.26(t, *J* =7.2 Hz, 3H). ^{13}C NMR(100MHz, $CDCl_3$, ppm): δ 205.29, 174.92, 137.95, 136.95, 60.58, 44.58, 39.51, 29.35, 27.89, 26.34, 23.56, 14.22, 14.13. HRMS: Calc'd for $C_{13}H_{20}O_3$, 224.1413; Found, 224.1400.

Ethyl 2-oxocyclododecanecarboxylate (15):

A 250 ml two-necked, round-bottomed flask equipped with a magnetic stirrer was fitted with a 50 ml pressure-equalizing constant-rate dropping funnel and a condenser. To the flask, sodium hydride (4.5 g, 112 mmol, 60% dispersion in mineral oil) was added. The mineral oil was removed by washing the dispersion four times with 20 ml portions of dry benzene under N_2 atmosphere. The benzene was removed with a pipette after the sodium hydride was allowed to settle. After most of the mineral oil had been removed, 60 ml of benzene was added to the sodium hydride, followed by diethyl carbonate (6.5 g, 55 mmol), this mixture was heated to reflux, and a solution of cyclododecanone (5.4 g, 30 mmol) in 10 ml of benzene was added dropwise over a period of 3-4 hours. After the addition was completed, this mixture was allowed to reflux until the evolution of hydrogen ceases(15-20 minutes). When the reaction mixture has cooled to room temperature, 10 ml of glacial

acetic acid was added dropwise, and a heavy, pasty solid separated. Then ice-cold water (about 100 ml) was added dropwise and the stirring was continued until all the solid material has dissolved. The benzene layer was separated; and the aqueous layer is extracted three times with 50 ml portions of benzene. The combined benzene extracts were washed three times with 50 ml portions of cold water. The organic layer was dried over $MgSO_4$ for 5 hr. $MgSO_4$ was removed by filtration; and the solvent is evaporated under vacuum. Flash chromatography of the crude material on silica gel (eluent: Hexanes/ethyl acetate=20:1) gave 4.5g compound **15** (yield 59%). The product existed in an equilibrating mixture of the ketone and enol tautomers. ^{1}HNMR(400MHz, $CDCl_3$, ppm): δ **ketone** 4.06(q, J =6.80 Hz, 2H), 3.54(dd, J =3.6, 11.6 Hz, 1H), 2.75-1.13(m, 23 H); **enol** δ 12.85(s, 1H), 4.13(q, 2H, J =7.2 Hz), 2.75-1.13(m, 23H). IR(KBr): 3406, 2935, 2870, 1747, 1707, 1641, 1628cm^{-1}. Anal. Calc'd. for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 70.69; H, 10.35.

Ethyl 1-(trans-4-bromo-2-buten-1-yl)-2-oxocycloheptane carboxylate (16):

Following the general alkylation procedure, the reaction of ethyl 2-oxocycloheptane carboxylate (3.78 g, 20.5 mmol) with NaH (880 mg, 60% dispersion in mineral oil, 22 mmol) and trans-1,4-dibromo-2-butene (4.69 g, 21.9 mmol) in DMF followed by column chromatography on silica gel (eluent: hexane/ethyl acetate = 15: 1) provided **16** (3.25 g, yield 50 %). IR(film): 3063, 2935, 2864, 1739, 1707, 1655cm-^{1}. ^{1}H NMR(400MHz, $CDCl_3$, ppm): δ 5.55-5.65(m, 2H), 4.05(q, J =7.2 Hz, 2H), 3.76(d, J =6.4 Hz, 2H), 2.65-1.20(m. 12H), 1.12(t, J =7.2 Hz, 3H)ppm. ^{13}C NMR(100MHz, $CDCl_3$, ppm): δ 208.66, 171.57, 131.04, 130.01, 62.68, 61.16, 41.99,37.80, 32.52, 32.33, 29.71, 25.42, 24.55, 14.06ppm. HRMS: Calc'd for $C_{14}H_{21}O_3Br$-Br, 237.1491; Found, 237.1492.

Ethyl 1-(cis-4-bromo-2-buten-1-yl)-2-oxocyclooctanecarboxylate (17):

Following the general alkylation procedure, the reaction of ethyl 2-oxocyclooctanecarboxylate (3.2 g, 16 mmol) with NaH (800 mg, 60% dispersion in mineral oil, 20 mmol) and trans-1,4-dibromo-2-butene (3.4 g, 16 mmol) in DMF followed by column chromatography on silica gel (eluent: hexane/ethyl acetate =20 : 1) provided **17** (2.7 g, yield 50 %). IR(film): 3063, 2930, 2864, 2856, 1747, 1714, 1655cm-^{1}. ^{1}H NMR(400MHz, $CDCl_3$, ppm): δ 5.68-5.58(m, 2H), 4.07(q, J =7.2 Hz, 2H), 3.81(d, J =6.4 Hz, 2H), 2.77-1.23(m, 13H), 1.14(t, J =7.2 Hz, 3H), 0.93-0.83(m, 1H). ^{13}C NMR(100MHz, $CDCl_3$, ppm): δ 211.83, 171.01, 131.12, 129.75, 62.39, 61.34, 38.56, 33.82, 32.60, 29.12, 28.54, 25.42, 24.11, 22.90, 14.08. HRMS: Calc'd for $C_{15}H_{23}BrO_3$-OEt, 285.0480; Found, 285.0475.

Ethyl 1-(trans-4-bromo-2-buten-1-yl)-2-oxocyclododecanecarboxylate (18):

Following the general alkylation procedure, the reaction of ethyl 2-oxocyclododecanecarboxylate (2.54 g, 10 mmol) with NaH (440 mg, 60% dispersion in mineral oil, 11 mmol) and trans-1,4-dibromo-2-butene (2.35 g, 11 mmol) in DMF followed by column chromatography on silica gel (eluent: hexane/ethyl acetate = 15 : 1) provided **18** (1.9 g, yield 50%). IR(film) 3036, 2935, 2870, 1747, 1714, 1655cm-^{1}. ^{1}H NMR(400MHz, $CDCl_3$, ppm): δ 5.78-5.71(m, 1H), 5.59-5.51(m, 1H), 4.180(q, J =7.2Hz, 2H), 3.89(d, J =7.6Hz, 1H), 2.96-1.24(m, 25H). ^{13}C NMR(100MHz, $CDCl_3$, ppm): δ 206.62, 172.11, 130.33, 130.07, 63.46, 61.39, 34.09, 33.19, 32.55, 28.82, 26.47, 26.33, 23.46, 22.62, 22.01, 21.81, 21.49, 18.87, 14.16. HRMS: Calc'd for $C_{19}H_{31}O_3Br$, 386.1460; Found, 386.1450.

Ethyl 3-(E-ethylidene)-4-oxocyclononanecarboxylate (22):

Following the general procedure for ring expansion, ethyl 1-(trans-4-bromo-2-buten-1-yl)-2-oxocycloheptane carboxylate (471.9 mg, 1.498 mmol) was reacted with indium powder (250 mg, 2.2 mmol) in 15 ml of water/THF (2:1). The crude material was treated with DBU. Work-up followed by column chromatography on silica gel (eluent: hexane/ethyl acetate 20:1) provided **22** (255 mg, 72%). IR(film): 3111, 2937, 2876, 1730, 1674 cm^{-1}. ^{1}H NMR(400MHz, $CDCl_3$, ppm): δ 6.2(q, J =7.2 Hz, 1H), 4.0(q, J =7.6

Hz, 2H), 2.7-2.4(m, 5H), 1.9-1.8(m, 1H), 1.7(d, J =7.2 Hz, 3H), 1.7-1.30(m, 7H), 1.2(t, J =7.6 Hz, 3H). ^{13}C NMR(100MHz, $CDCl_3$, ppm): δ 210.08, 175.62, 141.80, 132.13, 60.40, 41.63, 40.98, 27.78, 25.27, 24.65, 24.43, 24.17, 14.19, 13.83. HRMS: Calc'd for $C_{14}H_{22}O_3$, 238.1569; Found, 238.1566.

Ethyl 3-(E-ethylidene)-4-oxo-cyclodecane carboxylate (23):

Following the general ring expansion procedure, reaction of ethyl 1-(cis-4-bromo-2-buten-1-yl)-2-oxocyclooctanecarboxylate (350 mg, 1.06 mmol) with indium (350 mg, 3.07 mmol) in 15 ml water/THF (2:1). The crude material was treated with DBU. Work-up followed by column chromatography on silica gel (eluent: hexane/ethyl acetate=15:1) provided **23** (130 mg, yield 50%). IR(film): 3040, 2935, 2872, 1730, 1666 cm^{-1}. ^1H NMR(400MHz, $CDCl_3$, ppm): δ 6.37(q, 1H, J= 6.80 Hz), 4.11(q, 2H, J= 7.2 Hz), 2.8-2.5(m, 5H), 1.96-1.88(m, 1H), 1.87(d, 3H, J= 6.80 Hz), 1.82-1.15(m, 12H). ^{13}C NMR(100MHz, $CDCl_3$, ppm): δ 207.22, 176.39, 142.08, 134.47, 60.37, 40.06, 39.72, 29.88, 27.81, 26.27, 24.40, 24.01, 23.09, 14.24, 14.21. HRMS: Calc'd for $C_{15}H_{24}O_3$, 252.1726; Found, 252.1724.

Ethyl 3-(E-ethylidene)-4-oxocyclotetradecanecarboxylate (24):

Following the general ring expansion procedure, reaction of ethyl 1-(trans-4-bromo-2-buten-1-yl)-2-oxocyclododecanecarboxylate (387.2 mg, 1 mmol) with indium (344 mg, 3 mmol) in 6 ml water/THF (5:1). The crude material was treated with DBU. Work-up followed by column chromatography on silica gel (eluent: hexane/ethyl acetate=15:1) provided **24** (150 mg, yield 49%). IR(film): 3072, 2931, 2860, 1730, 1666 cm^{-1}. ^1H NMR(400MHz, $CDCl_3$, ppm): δ 6.89(q, 1H, J= 6.8 Hz), 4.15(q, 2H, J= 7.2 Hz), 2.99-2.92(m, 1H), 2.72-2.39(m, 4H), 2.20-1.72(m, 4H), 1.6-0.9(m, 20H). ^{13}C NMR(100MHz, $CDCl_3$, ppm): δ 201.33, 176.31, 140.85, 139.81, 60.19, 42.12, 34.90, 27.91, 26.86, 26.16, 25.37, 25.03, 24.97, 24.93, 24.37(2C), 23.45, 15.10, 14.34.. HRMS: Calc'd for $C_{19}H_{32}O_3$ (M^+) 308.2351; Found, 308.2350.

Ethyl 3,4-dihydro-2-(trans-4-bromo-2-buten-1-yl)-1-oxo-2-napthoate (27):

Following the general alkylation procedure, the reaction of ethyl 2,3,4-trihydro-1-oxo-2-naphthoate (2 g, 9.2 mmol) with NaH (450 mg, 60% dispersion in mineral oil, 11.25 mmol) and trans-1,4-dibromo-2-butene (2.14 g, 10 mmol) in DMF followed by column chromatography on silica gel (eluent: hexane/ethyl acetate = 15 : 1) provided **27** (1.65 g, yield 51%). IR(film) 3068, 3024, 2987, 2937, 2876, 2856, 1774, 1732, 1695, 1637, 1602 cm-1. ^1H NMR(400MHz, $CDCl_3$, ppm): δ 7.97(d, J =7.6Hz, 1H), 7.40(t, J =7.6Hz, 1H), 7.24(t, J =7.6Hz, 1H), 7.16(d, J =7.6Hz, 1H), 5.83-5.63(m, 2H), 4.07(q, J =7.2Hz, 2H), 3.94(d, J =7.6Hz, 1H), 3.84(d, J =6.8Hz, 1H), 3.06-2.43(m, 6H), 1.04(t, J =7.2Hz, 3H). ^{13}C NMR(100MHz, $CDCl_3$, ppm): δ 194.65, 171.05, 142.99, 133.48, 131.85, 130.83, 130.46, 128.78, 127.77, 126.69, 61.31, 57.31, 36.75, 32.62, 30.71, 25.76, 14.04. HRMS: Calc'd for $C_{17}H_{20}O_3Br$ (M+1): 351.0596; Found, 351.0597.

Ethyl 1,3,4-trihydro-2-oxo-1-naphthoate (29):

Following the same procedure as for compound **15**, the title compound was prepared from β-tetralone (5 g, 34.2 mmol), diethyl carbonate (10 g, 85.6 mmol), and NaH (4 g, 60% dispersion in mineral oil, 100 mmol) in benzene (200 mL). The compound was isolated by flash column on silica gel (eluent: hexane/ethyl acetate = 15: 1) (3.7 g, 50%), as an equilibrating mixture of ketone and enol isomers and was used directly for the next reaction. IR(KBr): 3400, 3074, 1726, 1639, 1608, 1575 cm-1. HRMS: Calc'd for $C_{13}H_{15}O_3$ (M+1): 219.1021; Found, 219.1021.

Ethyl 3,4-dihydro-1-(trans-4-bromo-2-buten-1-yl)-2-oxo-1-naphthoate (30):

Following the general alkylation procedure, the reaction of ethyl 1,2,3-trihydro-2-oxo-1-naphthoate (**29**) (1 g, 4.6 mmol) with NaH (200 mg, 60% dispersion in mineral oil, 4.6 mmol) and trans-1,4-dibromo-2-butene (1 g, 4.7 mmol) in DMF followed by column chromatography on silica gel (eluent: hexane/ethyl acetate = 15 : 1) provided **30** (650mg, yield 40 %). IR(film) 3068, 3022, 2982, 2943, 2856, 1747, 1714, 1660,

1496cm-1. ^{1}H NMR(400MHz, $CDCl_3$, ppm): δ 7.26-7.19(m, 4H), 5.59-5.52(m, 1H), 5.35-5.27(m, 1H), 4.11-4.01(m, 2H), 3.70(d, J =7.2 Hz, 2H), 3.13-2.28(m, 5H), 2.60-2.53(m, 1H), 1.09(t, J =7.2 Hz, 3H). ^{13}C NMR(100MHz, $CDCl_3$, ppm): δ 207.86, 170.49, 136.49, 135.44, 130.73, 129.68, 128.57, 127.61, 127.29, 126.87, 62.58, 61.81, 39.11, 32.23, 31.57, 27.70, 13.80. HRMS: Calc'd for $C_{17}H_{20}O_3Br$ (M+1) 351.0596; Found, 351.0597.

Ethyl 7,8,9,10-tetrahydro-6-(E-ethylidene)-bezocyclooctene-5-one-8-carboxylate (32):

Following the general ring expansion procedure, reaction of ethyl 3,4-dihydro-2-(trans-4-bromo-2-buten-1-yl)-1-oxo-2-naphthoate (200 mg, 0.569 mmol) with indium (340 mmg, 2.98 mmol) in 15 ml water/THF (2:1) with the pH of the medium being adjusted at 2-3 with 0.1 N aq. HCl. The crude material was treated with DBU. Work-up followed by column chromatography on silica gel (eluent: hexane/ethyl acetate=15:1) provided **32** (57 mg, yield 37%). IR(film): 3068, 2989, 2943, 2877, 1774, 1739, 1674, 1655, 1608, 1562, 1464cm-1. ^{1}H NMR(400MHz, $CDCl_3$, ppm): δ 7.46-7.39(m, 2H), 7.29-7.26(m, 1H), 7.18(d, J =7.2 Hz, 1H), 7.04(q, J = 7.2 Hz, 1H), 4.13(q, J = 6.8 Hz, 2H), 2.89-2.65(m, 4H), 2.38-2.25(m, 2H), 1.94(d, J =7.2 Hz, 3H), 1.92-1.80(m, 1H), 1.24(t, J =6.8 Hz, 3H). ^{13}C NMR(100MHz, $CDCl_3$, ppm): δ 197.59, 175.02, 140.85, 140.28, 138.44, 138.39, 131.67, 130.15, 128.63, 126.80, 60.66, 46.39, 31.96, 30.69, 28.30, 14.61, 14.21. HRMS(FAB): Calc'd for $C_{17}H_{21}O_3$(M+1), 273.1491; Found, 273.1490.

Ethyl 5, 6,9,10-tetrahydro-7-(Z-ethylidene)-benzocyclooctene-8-one-5-carboxylate (34) and Ethyl 5, 6,9,10-tetrahydro-7-(E-ethylidene)-benzocyclooctene-8-one-5-carboxylate (35):

Following the general procedure for ring expansion, ethyl 3,4-dihydro-1-(trans-4-bromo-2-buten-1-yl)-2-oxo-1-naphthoate (150 mg, 0.427 mmol) was reacted with indium powder (300 mg, 1.403 mmol) in 8 ml of water/THF (10:3). The crude material was treated with DBU. Work-up followed by column chromatography on silica gel (eluent: hexane/ethyl acetate=15:1) provided **34** (14 mg, yield 12%) and **35** (67 mg, 57%). Compound **34**: IR(film): 3063, 3036, 2982, 2943, 2870, 1739, 1707, 1682, 1655, 1622, 1568cm-1 . ^{1}H NMR(400MHz, $CDCl_3$, ppm): δ 7.23-7.11(m, 4H), 5.24(q, J =7.2 Hz, 1H), 4.19-4.14(m, 2H), 3.79(dd, J =12.4, 4.4 Hz, 1H), 3.01-2.74(m, 5H), 2.40(t, J =12.4 Hz, 1H), 1.47(d, J =7.2 Hz, 3H), 1.21(t, J =7.2 Hz, 3H). ^{13}C NMR(100MHz, $CDCl_3$, ppm): δ 212.40, 173.13, 140.32, 139.01, 137.42, 129.91, 127.72, 127.70, 126.27, 125.38, 61.01, 48.39, 45.83, 38.63, 30.88, 29.42. HRMS: Calc'd for $C_{17}H_{21}O_3$(M+1), 273.1491; Found, 273.1490. Compound **35**: IR(Film): 3068, 3022, 2982, 2943, 2877, 1734, 1687, 1660, 1622, 1562, 1543, 1496cm-1. ^{1}H NMR(400MHz, $CDCl_3$, ppm): δ 7.18-7.08(m, 4H), 6.0(q, J =6.8 Hz, 1H), 4.24-4.10(m, 2H), 3.83(dd, J =11.6, 6.4 Hz, 1H), 3.31-3.26(m, 1H), 3.06-2.73(m, 5H), 1.53(d, J =6.8 Hz, 3H), 1.21(t, J =7.2 Hz, 3H). ^{13}C NMR(100MHz, $CDCl_3$, ppm): δ 206.10, 173.16, 139.03, 138.66, 136.413, 132.06, 130.36, 128.52, 127.87, 127.30, 61.13, 47.73, 44.98, 30.14, 29.21, 14.125, 13.32. HRMS: Calc'd for $C_{17}H_{21}O_3$(M+1), 273.1491; Found, 273.1500.

Ethyl 2-(trans-4-bromo-2-buten-1-yl)-1-oxo-2-indanecarboxylate(38):

Following the general alkylation procedure, the reaction of ethyl 1-oxo-2-indanecaboxylate (1.86 g, 9.1 mmol) with NaH (40 mg, 60% dispersion in mineral oil, 10.0 mmol) and trans-1,4-dibromo-2-butene (3.114 g, 14.56 mmol) in DMF followed by column chromatography on silica gel (eluent: hexane/ethyl acetate = 15 : 1) provided **38** (1.227 g, yield 40%). IR(film): 3068, 3036, 2982, 2877, 1739, 1714, 1655, 1608, 1581, 1469cm-1. ^{1}H NMR(400MHz, $CDCl_3$, ppm): δ 7.76(d, J =7.6 Hz, 1H), 7.63(t, J =7.6 Hz, 1H), 7.48(d, J =7.6 Hz, 1H), 7.39(t, J =7.6 Hz, 1H), 5.83-5.76(m, 1H), 5.67-5.59(m, 1H), 4.15(q, J =7.2 Hz, 2H), 3.86-3.76(m, 2H), 3.64(d, J =17.2 Hz, 1H), 3.09(d, J =17.2 Hz, 1H), 2.90(dd, J =14.4, 7.6 Hz, 1H), 2.56(dd, J =14.4, 7.6 Hz, 1H), 1.20(t, J =7.2 Hz, 3H). ^{13}C NMR(100MHz, $CDCl_3$, ppm): δ 201.845, 170.456, 152.965, 135.539, 134.876, 130.912, 130.103, 127.838, 126.495, 124.731, 61.743, 59.963, 37.084, 36.033, 32.263, 14.060. HRMS: Calc'd for $C_{16}H_{18}O_3Br$ (M+1), 337.0439; Found, 337.0439.

Ethyl 7,8,9-trihydro-6-(E-ethylidne)-benzocycloheptene-5-one-8-carboxylate (40):

Following the general procedure for ring expansion, ethyl 2-(trans-4-bromo-2-buten-1-yl)-1-oxo-2-indanecarboxylate (201 mmg, 0.596 mmol) was reacted with indium powder (203.8 mg, 1.79 mmol) in 8 ml of water/THF (1:1) with the pH be adjusted to 2-3 with 0.1N aqueous HCl. The crude material was treated with DBU. Work-up followed by column chromatography on silica gel (eluent: hexane/ethyl acetate=15:1) provided **40** (76.6 mg, yield 50%). IR(film): 3068, 2989, 2943, 2883, 1774, 1739, 1687, 1655, 1622, 1562, 1469cm-1. ^{1}H NMR(400MHz, $CDCl_3$, ppm): δ 7.72(d, *J* =7.2 Hz, 1H), 7.43(t, *J* =7.2 Hz, 1H), 7.34(t, *J* =7.2 Hz, 1H), 7.19(d, *J* =7.2 Hz, 1H), 7.06(q, *J* =7.2 Hz, 1H), 4.21-4.12(m, 2H), 3.13-3.09(m, 1H), 2.99-2.93(m, 2H), 2.69(dd, *J* =14.4, 6.4 Hz, 1H), 2.60(dd, *J* =14.4, 6.4 Hz, 1H), 1.89(d, *J* =7.2 Hz, 3H), 1.28(t, *J* =6.8 Hz, 3H). ^{13}C NMR(100MHz, $CDCl_3$, ppm): δ 196.49, 173.93, 138.50, 137.92, 137.03, 136.61, 132.22, 129.94, 129.00, 127.45, 60.89, 42.07, 33.23, 26.29, 14.27, 14.19. HRMS(FAB): Calc'd for $C_{16}H_{19}O_3$(M+1), 259.1335; Found, 259.1345.

2-methyl-2-(trans-4-bromo-2-buten-1-yl)-1,3-indandione (43):

To a suspension of NaH (288 mg, 60% dispersion in mineral oil, 7.2 mmol) and 1,3-indandione (1.0 g, 6.8 mmol) in 10 ml DMF was added dropwise a solution of methyl iodide (965 mg, 6.8 mmol) in 3 ml of DMF. The mixture was stirred for 30 min followed by the addition of another portion of NaH (288 mg, 7.2 mmol). Then, trans-1,4-dibromo-2-butene (1.54 g, 7.2 mmol) in 10 ml DMF was added to the reaction mixture dropwise, stirred for another 30 min under nitrogen. The reaction was quenched with 0.1 N aq. HCl. The reaction mixture was extracted with ether (4x40 ml). The ether layer was washed with water, dried over $MgSO_4$, filtered and vaporized in vacuo. Flash chromatography on silica gel (eluent: hexanes:ethyl acetate=15:1) gave ethyl 2-methyl-2-(trans-4-bromo-2-buten-1-yl)-1,3-indandione(0.797g, yield 40%). IR(film): 3074, 3041, 2924, 1877, 1753, 1714, 1655, 1601, 1562, 1456cm-1. ^{1}H NMR(400MHz, $CDCl_3$, ppm): δ 7.95-7.93(m, 2H), 7.84-7.82(m, 2H), 5.71-5.64(m, 1H), 5.51-5.43(m, 1H), 3.67(d, *J* =7.2 Hz, 2H), 2.49(d, *J* =7.2 Hz, 2H), 1.24(s, 3H). ^{13}C NMR(100MHz, $CDCl_3$, ppm): δ 203.62, 141.04, 135.98, 130.99, 129.05, 123.47, 53.88, 37.36, 31.89, 19.13. HRMS: Calc'd for $C_{14}H_{14}O_2Br$ (M+1), 293.0177; Found, 293.0178.

7,8-Dihydro-8-methyl-6-(E-ethylidene)-benzocycloheptene-5,9-dione(45):

Following the general procedure for ring expansion, 2-methyl-2-(trans-4-bromo-2-buten-1-yl)-1,3-indandione (80 mg, 0.273 mmol) was reacted with indium powder (100 mg, 0.877 mmol) in 6 ml of water/THF (5:1) with the pH be adjusted to 3-4 with 0.1N aqueous HCl. The crude material was treated with DBU. Work-up followed by column chromatography on silica gel (eluent: hexane/ethyl acetate 15:1) provided **45** (43.4 mg, yield 75%). IR(film): 3074, 3036, 2976, 2935, 2877, 1774, 1739, 1701, 1687, 1655, 1562cm-1. ^{1}H NMR(400MHz, $CDCl_3$, ppm): δ 7.88-7.84(m, 1H), 7.63-7.59(m, 2H), 7.49-7.47(m, 1H), 7.02(q, *J* =7.2 Hz, 1H), 2.93-2.89(m, 1H), 2.83(dd, *J* =14.4, 4.8 Hz, 1H), 2.49(dd, *J* =14.4, 9.2 Hz, 1H), 1.91(d, *J* =7.2 Hz, 3H), 1.28(d, *J* =6.4 Hz, 3H). ^{13}C NMR(100MHz, $CDCl_3$, ppm): δ 208.35, 193.87, 139.15, 138.02, 136.17, 135.43, 132.61, 131.74, 129.21, 128.16, 47.23, 29.42, 17.64, 14.48. HRMS: Calc'd for $C_{14}H_{15}O_2$(M+1): 215.1072; Found, 215.1072.

Methyl 1β-tert-Butoxy-4-(E-4-bromo-2-butenyl)-4,5,6,7,8,9-hexahydro-9aβ-methyl-5-oxo-4-cyclopentacyclohexenecarboxylate (47):

Following the general alkylation procedure, the reaction of **46** (500 mg, 1.77 mmol) with NaH (71 mg, 60% dispersion in mineral oil, 1.77 mmol) and trans-1,4-dibromo-2-butene (379 mg, 1.77 mmol) in DMF followed by flash chromatography on silica gel (eluent: hexanes:ethyl acetate=20:1 to 2:1) gave **47** (345 mg, yield 47%) as a mixture of two diastereomers. Major isomer: IR(film): 3041, 2970, 2883, 1774, 1707cm^{-1}. ^{1}H NMR(400MHz, $CDCl_3$, ppm): δ 5.8 (m, 2H), 3.9(m, 2H), 3.67(s, 3H), 3.32(t, *J* =8.3 Hz, 1H), 2.95(dt, *J* =6.3, 14.7 Hz, 1H), 2.5(dd, *J* =7.3, 13.3 Hz, 1H), 1.3-2.4 (m, 9H), 1.1(s, 9H), 0.93(s, 3H). ^{13}C

NMR(100MHz, $CDCl_3$, ppm): δ 208.54, 172.62, 131.27, 130.04, 79.41, 72.66, 61.71, 52.20, 52.02, 42.36, 37.26, 36.76, 36.34, 32.86, 31.07, 28.66, 20.52, 10.84. HRMS: Calc'd for $C_{20}H_{31}BrO_4$-Br, 335.2209; Found, 335.2203.

Methyl 1β-tert-Butoxy-6-(E)-ethylidene-3aα, 4α,5,6,7,8,9,9a-octahydro-10aβ-methyl-7-oxo-4β-cyclopentacyclooctenecarboxylate (49):

Following the general procedure for ring expansion, compound **47** (60 mg, 0.15 mmol) was reacted with indium powder (52 mg, 0.45 mmol) in 2 ml of aqueous 0.1N HCl/methanol (3:1). The crude material was treated with DBU (46 mg, 0.3 mmol) in 1 ml THF. Work-up followed by column chromatography on silica gel (eluent: hexane/ethyl acetate 20:1) provided **49** (32 mg, 63%) as a mixture of diastereomers (2.5 : 1). The major isomer was recrystalized in hexane/ethyl acetate to give a crystal for x-ray analysis. Major isomer: IR(film): 1732, 1678, 1617, 1437, 1361, 1192, 1161, 1116, 1072cm^{-1}. ^1H NMR(400MHz, $CDCl_3$, ppm): δ 6.8(q, J=7.3 Hz, 1H), 3.7(s, 3H), 3.3(m, 1H), 3.0(m, 2H), 2.55(m, 1H), 2.3(m, 1H), 2.0(m, 2H), 1.8(d, J=7.3 Hz, 3H), 1.6(s, 3H), 1.4-1.8(m, 3H), 1.1(s, 9H), 0.93(s, 3H). ^{13}C NMR(100MHz, $CDCl_3$, ppm): δ 205.50, 175.08, 137.25, 80.77, 72.84, 51.63, 46.58, 45.87, 42.34, 40.66, 36.86, 30.90, 28.74, 27.59, 25.79, 14.59, 14.17. HRMS: Calc'd for $C_{20}H_{32}O_4$-C_4H_8, 280.1674; Found, 280.1676.

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