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New cycloaddition/fragmentation strategies for preparing 5-7-5 and 5-7-6 fused tricyclic ring systems

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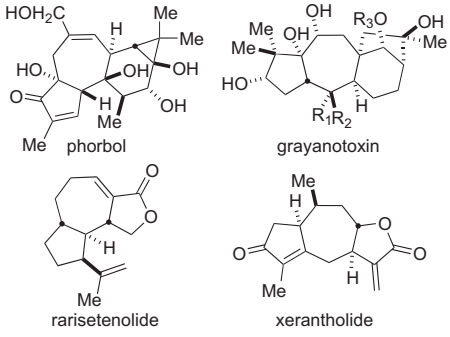
ABSTRACT

Tethering additional functionality to cyclobutadienyl iron tricarbonyl complexes provides new opportunities for the rapid construction of medium-ring-containing polycyclic compounds. Specifically, an intramolecular cycloaddition between cyclobutadiene and a tethered olefin, followed by an intramolecular cyclopropanation of the resulting cyclobutene-containing adduct generates highly strained pentacyclic intermediates. These compounds can then be relaxed thermally to generate 5-7-5 and 5-7-6 fused tricyclic ring systems that are shared with numerous natural products.

1. Introduction

Medium-ring-containing, polycyclic natural products, such as phorbol, grayanotoxin, rarisetenolide, and xerantholide provide ample motivation for improved strategies toward 5-7-5 or 5-7-6 tricyclic ring systems. The construction of these tricyclic ring systems has been accomplished by various approaches.[1] Of the myriad ring forming strategies that are possible, only a handful has been used in total synthesis.



Some of the recent approaches are summarized in Scheme 1. The first example relies on annulation of a third ring onto a fused bicyclic ring precursor.[2] For example, a Knoevenagel condensation served as a key step to annulate the six-membered ring on a bicyclic hydroazulene precursor **1**→**2** in the study toward the synthesis of guanacastepene C.[3] The second strategy highlighted is an intramolecular ring closure between the two outer rings to generate the central seven-membered ring. A variety of general methods for synthesis of seven-membered ring are applied in this category. For example, the Overman group reported a convergent and enantioselective total synthesis of (+)-guanacastepene N featuring a regioselective 7-*endo* Heck cyclization as the key step to afford the tricyclic skeleton (**3**→**4**).[4] In a related disconnection, the West group used an oxonium ylide [1,2]-shift in their approach to the tigliane-daphnane skeleton (**5**→**6**).[5] Both high yield and selectivity were achieved in this transformation.

A third strategy is based on an intramolecular cycloaddition between two groups attached to a preexisting ring to generate two additional rings. In the total synthesis of C8-*epi*-guanacastepene O, the Yang team applied the intramolecular Diels–Alder reaction between an alkyne and diene to form the desired tricyclic systems with cis-annulated methyl groups in 60% yield.[6] Wender's successful syntheses of phorbol and related natural products also featured this general strategy.[1b,7] The fourth approach represents a particularly rapid means of generating complex ring systems from acyclic precursors. Transition-metal catalyzed cyclization plays a significant role in this category. The Ojima's group, for example, developed a rhodium catalyzed, silane-mediated [2+2+2+1] cycloaddition of enediynes in moderate to excellent yields to provide tricycle **10**.[8]

We have been interested in developing new methods of constructing medium-ring-containing compounds. In particular,

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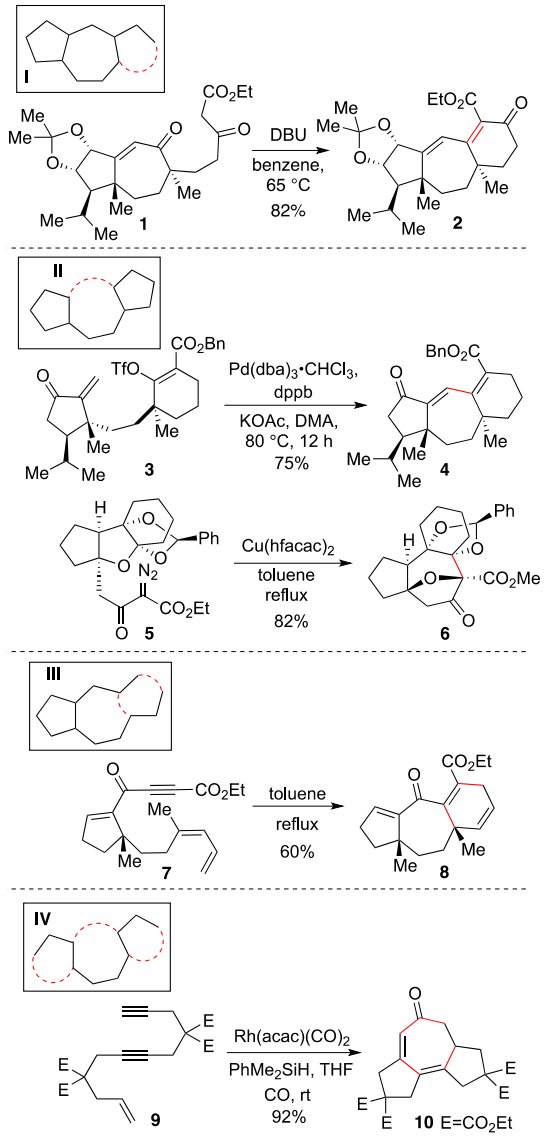
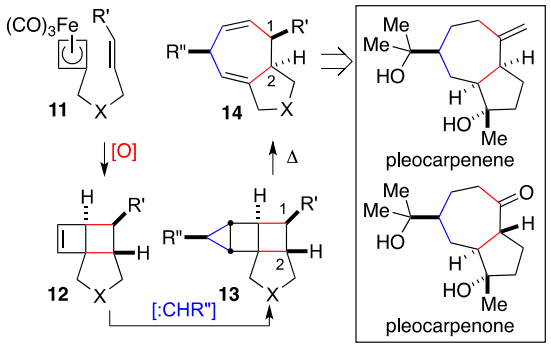


Scheme 1. Construction of 5-7-5(6) ring systems.

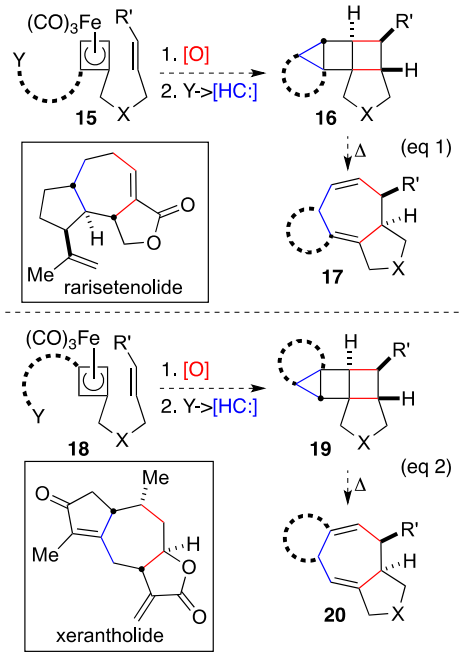
intramolecular cycloadditions of iron tricarbonyl cyclobutadienyl complexes have been shown to generate highly functionalized, strained cyclobutene adducts that can be used to access medium ring skeletons through subsequent fragmentations.[9] For example, as shown in Scheme 2, we have used this cycloaddition, followed by an intermolecular cyclopropanation and thermal fragmentation to



Scheme 2. 5-7 Ring systems through a cyclobutadiene cycloaddition/cyclopropanation/thermal fragmentation sequence.

prepare 5-7 ring systems. Interestingly, the stereochemistry at the C2 position becomes inverted during the thermal rearrangement step of this sequence. This synthetic strategy has been used in the total syntheses of (+)- and (−)-pleocarpenene and pleocarpenone.[10]

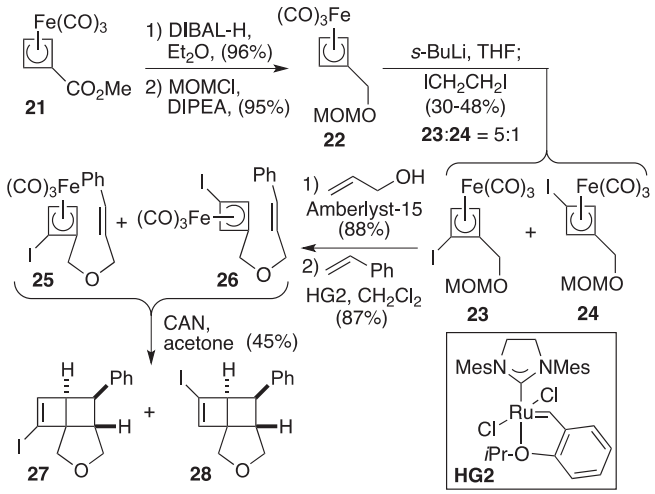
Given the prevalence of tricyclic ring systems among terpenoid natural products, we thought that an efficient approach toward these targets could be achieved by incorporating an *intramolecular* cyclopropanation[11] of the cyclobutene intermediate **12** in this reaction sequence. While generating the strained precursor to the central seven-membered ring, the intramolecular cyclopropanation would also establish an additional ring of the polycyclic target. Furthermore, as illustrated in Scheme 3, depending on the attachment point of the tethered carbenoid precursor (Y in **15** and **18**), two unique tricyclic ring systems **17** and **20** should be accessible through this approach (Eqs. 1 and 2). Described herein are our preliminary studies exploring the feasibility of this strategy for generating these medium-ring-containing tricyclic systems.



Scheme 3. Generation of tricyclic ring systems using an intramolecular cyclopropanation.

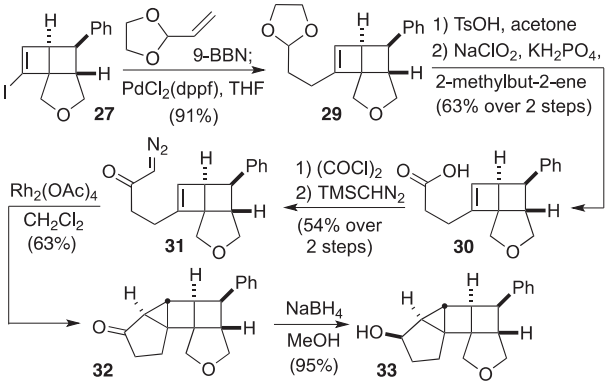
2. Results and discussion

The first challenge to be addressed in advancing this strategy was the introduction of the additional functionality on the cyclobutadienyl iron tricarbonyl complex. A solution is summarized in Scheme 4. DIBAL-H reduction of the iron methyl ester complex **21**, followed by formation of the MOM-ether **22** allowed for the directed *ortho* lithiation, which generates a mixture of 1,2- and 1,3-disubstituted iron complexes **23** and **24** in a 5:1 ratio. At this stage, the separation of these regioisomers through silica gel column chromatography was not readily feasible. Therefore, the two regioisomers, **23** and **24** were carried through the subsequent transformations together. Under acidic conditions, the MOM group was replaced by an allyl group. Treatment of the resulting ether with styrene in the presence of Hoveyda–Grubbs second catalyst (HG2) provided efficiently compounds **25** and **26**, which were then oxidized with CAN to form cyclobutenes **27** and **28**. These two regioisomeric cycloadducts were separable and each subjected independently to the following studies.



Scheme 4. Syntheses of functionalized cyclobutene compounds.

The reaction sequences to convert cyclobutenes **27** and **28** into the polycyclic thermolysis precursors are shown in Scheme 5. A B-alkyl Suzuki–Miyaura cross-coupling[12] on **27** was used to provide intermediate **29**, using a borane species prepared from acrolein ethylene acetal. *p*-Toluenesulfonic acid-mediated acetal deprotection and Pinnick oxidation then delivered carboxylic acid **30**. The diazo motif in **31** was introduced through the intermediacy of an acid chloride. An effective cyclopropanation was achieved by a $Rh_2(OAc)_4$ catalyzed diazo-decomposition of compound **31** to afford the highly strained cyclopropane **32** as a white solid in a stereospecific manner. Support for the stereochemical assignment was obtained through NMR and X-ray crystallographic studies (Fig. 1). Sodium borohydride was used to reduce compound **32** to alcohol **33** as the sole diastereomer. In a similar fashion, cyclopropane **38** was generated from cyclobutene adduct **28** (Scheme 6).



Scheme 5. Synthesis of polycyclic substrate **33**.

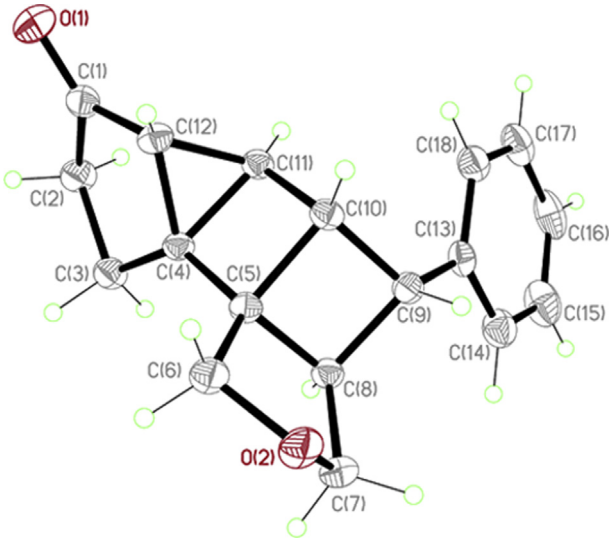
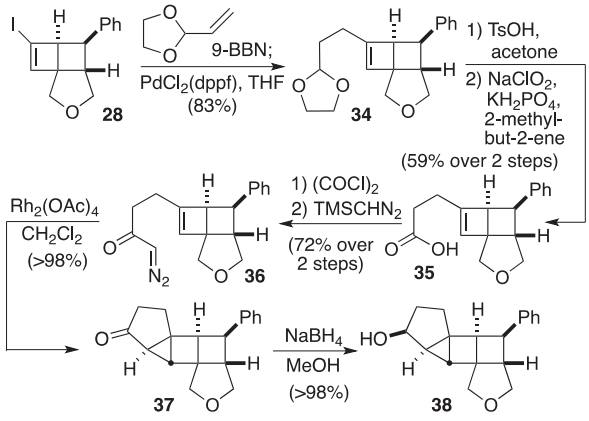
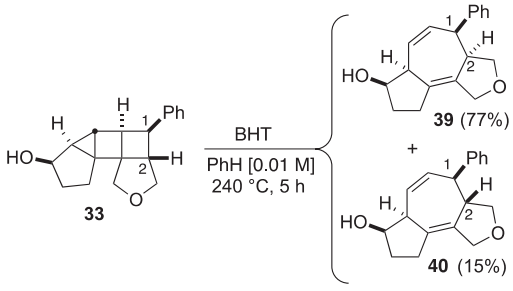


Fig. 1. Crystal structure of cyclopropane **32**.



Scheme 6. Synthesis of polycyclic substrate **38**.

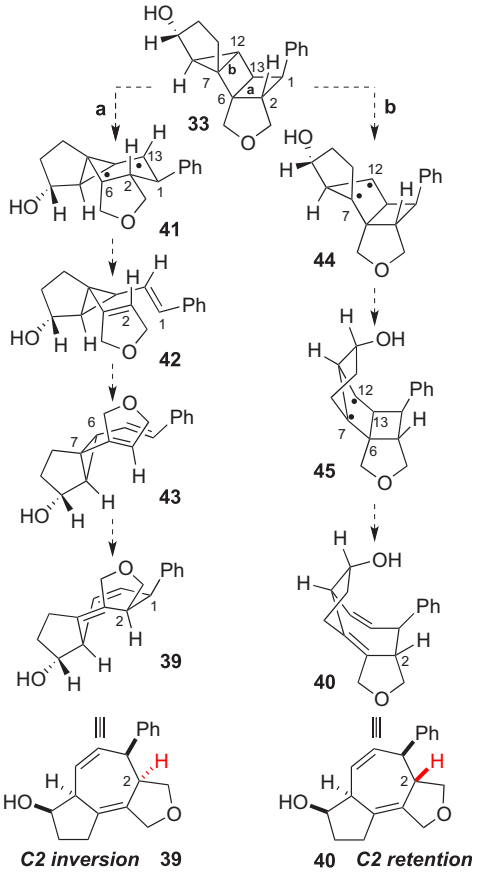


Scheme 7. Thermal rearrangement of cycloadduct **33**.

With a reliable route to the alternative ring systems in hand, we examined their thermal ring openings. When compound **33** was subjected to 240 °C for 5 h in benzene, two diastereomers (**39** and **40**), epimeric at C2 were generated in a 5:1 ratio and a combined yield of 92% (Scheme 7).

A mechanism that accounts for the formation of these two diastereomeric products is suggested in Scheme 8. The strained thermal precursor **33** is thought to rearrange through two competing pathways (**a** and **b**) to deliver the corresponding diastereomeric products **39** and **40**. In pathway **a**, a divinyl cyclopropane intermediate **42** can be generated through either a concerted or a stepwise diradical pathway. To facilitate the subsequent Cope rearrangement, a bond rotation along C6–C7 can occur to adopt boat conformation **43**. Reestablishing the C1–C2 bond through a Cope rearrangement at the expense of the C6–C7 cyclopropane bond then accounts for the stereo-inversion at C2 in product **39**. Moreover, homolytic bond cleavage of C7–C12 in **33** is likely in this highly strained system (bond/path **b**). The resulting diradical **44** could isomerize from the '*anti*' to '*syn*' conformation **45**. Fragmentation of the C6–C13 bond would then lead to product **40** where the C2 stereocenter is retained.

As summarized in Table 1, the nature of the C1 substituent appears to influence the relative rates of these two thermal rearrangement pathways. Entries 1 and 2 indicated that replacing the phenyl group with a methyl ester changes the ratio of the



Scheme 8. Mechanism of thermal rearrangements.

diastereomeric products slightly from 4:1 to 2.4:1. The molecular framework also has an impact on the stereochemical outcome; both stereo-inverted and stereo-retained products were obtained for substrates **33**, **46**, **49**, **52**, and **58** (entries 1–4 & 7), while substrates **38** and **56** afforded exclusively stereo-inverted tricyclic ring systems (entries 5 & 6).[13] Substrates bearing all-carbon skeletons (entries 3 & 7) rearranged as smoothly as the oxygen containing systems. Efforts were also made to extend this tricyclic ring forming strategy to 5-7-6 ring architecture (entry 4). The six-membered ring unit was incorporated in the cyclobutadiene cycloaddition step by lengthening the tether between the olefin and the iron tricarbonyl cyclobutadiene ring by one methylene group.

The stereochemical identities of these fragmentation products were determined through NMR studies. Specifically, the relative stereochemistry of C1 and C2 in the rearranged products **59** and **60** was determined by examining the NOESY interactions relative to the carbinol proton H_e. Fig. 2 summarizes the results of these experiments. These findings indicated the inversion at C2 and retention at C1 of diastereomer **59**, while the retention of stereochemistry at both C1 and C2 of diastereomer **60**.

3. Conclusion

We have successfully developed a novel method to synthesis 5-7-5(6) tricyclic ring systems through an intramolecular cyclopropanation/thermal fragmentation strategy. The stereochemical course of the fragmentation appears to be substrate dependent. Nevertheless, a library of various tricyclic ring systems can be generated fairly rapidly in good to moderate yields from a simple precursor.

Table 1
Thermal fragmentations

entry	substrate	thermolysis products (yield)[a]	
(1)	**33**	**39** (77%)	**40** (15%)
(2)	**46**	**47** (50%)	**48** (21%)
(3)	**49**	**50** (76%)	**51** (9%)
(4)	**52**	**53** (47%)	**54** (40%)
(5)	**38**	**55** (49%)	N/A[b]
(6)	**56**	**57** (70%)	N/A[b]
(7)	**58**	**59** (63%)	**60** (33%)

[a]Product ratio was determined by ^{1}H NMR. [b]Only one diastereomer was observed for this substrate. [c]Not readily separable by column chromatography.

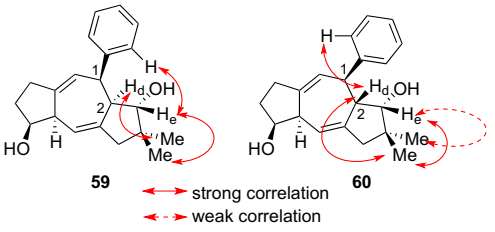


Fig. 2. Stereochemistry determination by 2-D NOESY experiment.

4. Experimental section

4.1. General

Proton nuclear magnetic resonance spectra (H NMR) chemical shifts are reported in parts per million downfield from tetramethylsilane with the solvent resonance as the reference ($CDCl_3$: δ 7.26 ppm; C_6D_6: δ 7.16 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, br=broad, m=multiplet), and coupling constants (Hz). Carbon nuclear magnetic resonance spectra (C NMR) were recorded with complete proton decoupling. Chemical shifts

are reported in ppm downfield from tetramethylsilane with the solvent resonance as the reference ($CDCl_3$: δ 77.23 ppm; C_6D_6: δ 128.39 ppm). Infrared (IR) spectra are reported in wave numbers (cm^{-1}). Bands are characterized as broad (br), strong (s), medium (m), or weak (w). High resolution mass spectral analyses (HRMS) were performed at Boston College. Melting points (mp) are reported uncorrected.

Starting materials and reagents were purchased from commercial suppliers and used without further purification except the following: Dry CH_2Cl_2, DMF, hexane, toluene, diethyl ether, THF, and benzene were used from a solvent purification system.[14] Hexanes and Et_2O used in chromatography were distilled before use. Molecular sieves were dried in a 250 °C oven overnight before use. (Cyclobutadienyl)iron tricarbonyl was prepared as reported in the literature and displayed satisfactory spectral data. All oxygen- or moisture-sensitive reactions were carried out under N_2 atmosphere in oven-dried (140 °C, >4 h) or flame-dried glassware. Air- or moisture-sensitive liquids were transferred by syringe or cannula and were introduced into the reaction flasks through rubber septa or through a stopcock under N_2 positive pressure. Degassing refers to a flow of dry N_2(g) bubbling through reaction solvent for 15 min. Unless otherwise stated, reactions were stirred with a Teflon covered stir bar. Concentration refers to the removal of solvent using a rotary evaporator followed by use of a vacuum pump at approximately 1 Torr. Silica gel column chromatography refers to flash chromatography[15] and was performed using 60 Å (230–400 mesh ASTM) silica gel. Thin layer chromatography was performed on glass back 60 Å (250 μm thickness) silica gel plates.

*4.1.1. Iron tricarbonyl cyclobutadiene-1-methyl-MOM-ether (**22**).* In a round bottom flask (50 mL) with a stir bar and septum were placed iron tricarbonyl cyclobutadiene-1-methanol (2.26 g, 10.2 mmol) and $(i\text{-Pr})_2NEt$ (10.2 mL, 1.0 M). The flask was cooled to 0 °C and MOMCl (1.0 mL, 13.2 mmol) was added dropwise under N_2 atmosphere. The reaction was allowed to warm to room temperature and stirred overnight. TLC analysis (R_f: 0.85 in 2:1 hexanes/Et_2O) indicated full conversion before saturated aqueous NH_4Cl solution (30 mL) was added to quench the reaction. The mixture was transferred into a separatory funnel (125 mL) and the aqueous layer was extracted with CH_2Cl_2 (3×30 mL). The combined organic layer was washed with brine (20 mL) and dried over $MgSO_4$. Concentration afforded a dark yellow oil that was purified immediately by silica gel column chromatography (10:1 hexanes/Et_2O) to collect compound **22** (2.58 g, 9.69 mmol, 95% yield) as a yellow oil. H NMR (400 MHz, $CDCl_3$): δ 4.26 (2H, s), 4.12 (2H, s), 4.06 (1H, s), 3.85 (2H, s), 3.34 (3H, s). C NMR (100 MHz, $CDCl_3$): δ 214.3, 95.9, 80.5, 64.7, 63.0, 62.7, 55.4. IR (KBr thin film): 2952 (w), 2886 (w), 2046 (s), 1966 (s), 1152 (w), 1101 (w), 1037 (m), 613 (m), 588 (s). DART-HRMS (m/z): calcd for $[M-MOM]^+$: 204.9588; Found: 204.9589.

*4.1.2. 1,2- and 1,3-Iodocyclobutadienyl iron tricarbonyl complexes (**23** & **24**).* To a solution of mom-ether **22** (2.58 g, 9.68 mmol) in THF (48.0 mL, 0.20 M) under N_2 atmosphere at −78 °C was added freshly titrated *s*-BuLi (9.68 mmol, 1.26 M in cyclohexane) dropwise. The resulting dark solution was allowed to stir at this temperature for another 15 min before adding 1,2-diiodoethane (3.01 g, 10.7 mmol). Then the mixture was allowed to warm to room temperature and allowed to stir for 1 h before saturated aqueous NH_4Cl solution (50 mL) was added to quench the reaction. The mixture was then poured into a separatory funnel (250 mL). The aqueous layer was extracted with Et_2O (3×50 mL). The combined organic layer was washed with brine (50 mL) and dried over $MgSO_4$. The resulting solution was concentrated and purified immediately by silica gel column chromatography (100:1 hexanes/Et_2O with a gradient to 20:1 hexanes/Et_2O) to afford a mixture of compounds **23** and **24** (1.80 g, 4.64 mmol, 48% yield, 5:1 *ortho*/*para*) as a yellow oil. Compound **23**:[16] H NMR (500 MHz, $CDCl_3$): δ 4.68 (2H, d, J=2.5 Hz), 4.58 (1H, s), 4.41 (1H, s), 3.90 (1H, d, J=12.5 Hz), 3.82 (1H, d, J=13.0 Hz), 3.41 (3H, s). C NMR (125 MHz, $CDCl_3$): δ 213.1, 96.3, 96.2, 83.2, 67.3, 63.2, 62.1, 55.7. IR (KBr thin film, CH_2Cl_2 solution): 3060 (w), 3027 (w), 2934 (w), 2048 (s), 1972 (s), 1150 (w), 1099 (w), 1041 (w), 613 (w), 583 (m) cm^{-1}. DART-HRMS (m/z): calcd for $[M-MOM]^+$: 330.8555; Found: 330.8565.

*4.1.3. Ethers (**25** & **26**).* In a round bottom flask (25 mL) with condenser, stir bar and septum was placed a mixture of alcohols **23** & **24** (295.7 mg, 0.755 mmol), Amberlyst-15 (88.7 mg), and allyl alcohol (4.0 mL, 0.20 M). The reaction mixture was heated to 90 °C until judged complete (4 h) by TLC analysis (R_f: 0.50 in 1:2 Et_2O/hexanes). After cooling to room temperature, the reaction mixture was concentrated and purified by silica gel column chromatography (10:1 hexanes/Et_2O) to afford the allylic ethers of the iodocyclobutadienyl complexes (**25a** and **26a**) (267.7 mg, 0.664 mmol, 88% yield) as dark yellow oil. Compound **25a**: H NMR (500 MHz, $CDCl_3$): δ 5.91 (1H, m), 5.33 (1H, dd, J=17.0, 2.0 Hz), 5.21 (1H, dd, J=11.0, 2.0 Hz), 4.57 (1H, s), 4.40 (1H, s), 4.06 (2H, m), 3.77 (2H, s). C NMR (125 MHz, $CDCl_3$): δ 213.5, 134.5, 117.8, 83.7, 72.0, 67.2, 64.7, 63.2, 27.0. IR (KBr thin film, CH_2Cl_2 solution): 2955 (w), 2856 (w), 2359 (w), 2341 (w), 2050 (s), 1977 (s), 1116 (w), 1075 (w), 930 (w), 613 (m), 584 (m), 508 (w) cm^{-1}. DART-HRMS (m/z): calcd for $[M-MOM]^+$: 330.8555; Found: 330.8563. Compounds **25a** & **26a**: H NMR (500 MHz, $CDCl_3$): δ 5.89 (m), 5.21–5.35 (m), 4.57 (compound **25a**, 1H, s), 4.45 (compound **26a**, 2H, s), 4.40 (compound **25a**, 1H, s), 4.06 (compound **25a**, 2H, m), 4.01 (compound **26a**, 2H, td, J=6.0, 1.5 Hz), 3.80 (compound **26a**, 2H, s), 3.77 (compound **25a**, 2H, s).

In a round bottom flask (25 mL) with condenser, stir bar and septum were placed allylic ethers of the iodocyclobutadienyl complexes (**25a** & **26a**) (291.9 mg, 0.725 mmol), freshly purified styrene (322 μL, passed through a neutral Al_2O_3 plug to remove inhibitor), Hoveyda–Grubbs second-generation catalyst (22.8 mg, 5 mol %), and CH_2Cl_2 (4.0 mL, 0.20 M). The reaction mixture was heated to reflux for overnight. After allowing to cool, 30 wt % silica gel was added to the flask and stirred vigorously at room temperature for 30 min. Filtration and concentration provided a dark orange oil, which was then purified by silica gel column chromatography (100:1 hexanes/Et_2O with a gradient to 10:1 hexanes/Et_2O) to afford orange oil compounds **25** and **26** (291.3 mg, 0.631 mmol, 87% yield) as a mixture of cis and trans isomers. Compound **25**: H NMR (500 MHz, $CDCl_3$): δ 7.40 (2H, d, J=7.5 Hz), 7.32 (2H, m), 7.25 (1H, m), 6.66 (1H, d, J=20.0 Hz), 6.31 (1H, m), 4.59 (1H, s), 4.41 (1H, s), 4.23 (2H, m), 3.83 (2H, s). IR (KBr thin film, CH_2Cl_2 solution): 2953 (w), 2854 (w), 2049 (s), 1977 (s), 1116 (w), 1073 (w), 967 (w), 737 (w), 613 (m), 585 (m), 507 (w) cm^{-1}. DART-HRMS (m/z): calcd for $[M-MOM]^+$: 330.8555; Found: 330.8559. Compounds **25** & **26**: H NMR (500 MHz, $CDCl_3$): δ 7.40 (d, J=7.0 Hz), 7.32 (t, J=7.5 Hz), 7.26 (m), 6.66 (m), 6.31 (m), 4.59 (compound **25**, 1H, s), 4.47 (compound **26**, 2H, s), 4.41 (compound **25**, 1H, s), 4.23 (compound **25**, 2H, m), 4.18 (compound **26**, 2H, d, J=6.0 Hz), 3.85 (s).

*4.1.4. Cyclobutadiene cycloaddition adducts (**27** & **28**).* To a solution of compounds **25** & **26** (291.3 mg, 0.631 mmol) in acetone (316.0 mL, 0.0020 M) was added cerium ammonium nitrate (CAN) (1.039 g, 1.90 mmol). The reaction was allowed to stir at room temperature for 15 min while a vigorous evolution of gas was observed. Then saturated aqueous $NaHCO_3$ solution (5 mL) was added to quench the reaction. Stirring was continued for 20 min to allow precipitation of the cerium salts, which was removed by subsequent vacuum filtration. The filtrate was dried over $MgSO_4$. Filtration and concentration provide an oil that was then purified by silica gel column chromatography (20:1 hexanes/Et_2O with a gradient to 10:1 hexanes/Et_2O) to afford cycloadduct **27** (90.8 mg, 0.278 mmol, 53% yield) as pale sticky yellow oil and cycloadduct **28**

as a white solid (15.3 mg, 0.047 mmol, 45% yield). Cycloadduct **27**: H NMR (500 MHz, $CDCl_3$): δ 7.31 (2H, t, J=7.5 Hz), 7.21 (1H, t, J=7.5 Hz), 7.10 (2H, d, J=7.5 Hz), 4.11 (1H, dd, J=9.5, 1.5 Hz), 3.93 (1H, d, J=10.0 Hz), 3.89 (1H, dd, J=10.0, 7.0 Hz), 3.73 (1H, d, J=8.0 Hz), 3.46 (1H, d, J=10.5 Hz), 3.40 (1H, dd, J=7.5, 5.5 Hz), 2.75 (1H, m). C NMR (125 MHz, $CDCl_3$): δ 145.7, 141.9, 128.6, 127.4, 126.6, 93.1, 73.5, 69.1, 65.1, 53.0, 47.0, 43.5. IR (KBr thin film, CH_2Cl_2 solution): 3026 (w), 2956 (s), 2840 (m), 2359 (w), 1529 (m), 1267 (w), 1091 (w), 1057 (m), 888 (s), 817 (m), 774 (w), 710 (w) cm^{-1}. DART-HRMS (m/z): calcd for $[M+H]^+$: 325.0089; Found: 325.0100. Cycloadduct **28**: (mp: 45–47 °C). H NMR (500 MHz, $CDCl_3$): δ 7.32 (3H, m), 7.24 (2H, d, J=7.0 Hz), 6.90 (1H, d, J=1.5 Hz), 4.09 (1H, dd, J=10.0, 1.5 Hz), 3.91 (1H, d, J=10.0 Hz), 3.85 (1H, dd, J=10.0, 6.5 Hz), 3.64 (2H, dd, J=10.0, 8.0 Hz), 3.56 (1H, dd, J=7.5, 5.5 Hz), 2.99 (1H, m). C NMR (125 MHz, $CDCl_3$): δ 146.2, 138.9, 128.3, 128.2, 126.7, 92.6, 73.6, 69.6, 62.7, 56.7, 44.8, 43.2. IR (KBr thin film, CH_2Cl_2 solution): 3067 (m), 3039 (s), 3018 (m), 2959 (w), 2897 (s), 2835 (w), 1530 (w), 1160 (w), 1060 (w), 853 (w), 710 (m), 594 (br) cm^{-1}. DART-HRMS (m/z): calcd for $[M+H]^+$: 325.0089; Found: 325.0087.

*4.1.5. Cyclobutene (**29**).* To a solution of 9-BBN (1.00 g, 8.24 mmol) in THF (16.0 mL) at 0 °C was added acrolein ethylene under N_2 atmosphere. The reaction was allowed to stir at room temperature for 4 h before DMF (0.83 mL, 1.6 M), H_2O (2.2 mL, 0.60 M), Cs_2CO_3 (1.17 g, 3.59 mmol), Ph_3As (80.0 mg, 0.266 mmol), compound **27** (430.7 mg, 1.33 mmol), and $PdCl_2$(dppf) (68.1 mg, 7 mol %) were sequentially added. The reaction was heated to 80 °C for 15 h. After cooling, the mixture was poured into a separatory funnel with 5% LiCl aqueous solution (20 mL). The aqueous layer was extracted with Et_2O (3×20 mL). The combined organic layer was washed with brine (20 mL) and dried over $MgSO_4$. The resulting solution was concentrated and immediately purified by silica gel column chromatography (10:1 hexanes/Et_2O with a gradient to 1:1 hexanes/Et_2O) to afford cyclobutene **29** (361.3 mg, 1.21 mmol, 91% yield) as colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 (2H, t, J=7.5 Hz), 7.16 (1H, t, J=7.5 Hz), 7.10 (2H, d, J=7.0 Hz), 5.72 (1H, d, J=1.5 Hz), 4.89 (1H, t, J=5.0 Hz), 4.09 (1H, d, J=9.5 Hz), 3.96 (2H, m), 3.89 (1H, d, J=10.0 Hz), 3.85 (3H, m), 3.68 (1H, d, J=10.0 Hz), 3.42 (1H, dd, J=8.0, 6.0 Hz), 3.26 (1H, d, J=8.0 Hz), 2.77 (1H, t, J=6.0 Hz), 2.25 (2H, m), 1.86 (2H, m). C NMR (125 MHz, $CDCl_3$): δ 150.3, 143.2, 128.7, 128.3, 127.4, 126.0, 104.1, 73.9, 69.3, 65.2, 58.5, 46.8, 46.2, 44.9, 31.0, 23.2. IR (KBr thin film, CH_2Cl_2 solution): 3080 (m), 3060 (s), 2957 (m), 2942 (s), 1600 (w), 1402 (w), 1383 (w), 1138 (m), 1029 (br), 895 (w), 758 (s), 701 (s), 537 (m), 448 (w) cm^{-1}. DART-HRMS (m/z): calcd for $[M+H]^+$: 299.1647; Found: 299.1637.

*4.1.6. Carboxylic acid (**30**).* To a solution of compound **29** (456.0 mg, 1.53 mmol) in acetone (7.0 mL, 0.20 M) and water (4.0 mL, 0.40 M) was added *p*-toluenesulfonic acid monohydrate (319.8 mg, 1.68 mmol). The reaction was heated to reflux until judged complete (4 h) by TLC analysis (R_f: 0.35, 1:1 hexanes/Et_2O). Then, saturated aqueous $NaHCO_3$ solution (10 mL) was added to quench the reaction. The aqueous layer was extracted with Et_2O (3×15 mL). The combined organic layer was washed with brine (20 mL) and dried over $MgSO_4$. The resulting solution was concentrated to provide the aldehyde intermediate without further purification.

The aldehyde intermediate was dissolved in *tert*-butanol (6.1 mL, 0.25 M) and H_2O (3.0 mL, 0.50 M) in a round bottom flask (25 mL) with a stir bar at 0 °C. 2-Methyl-2-butene (several milliliters pipetted) was added followed by KH_2PO_4 (832.0 mg, 6.11 mmol) and $NaClO_4$ (552.6 mg, 6.11 mmol). The reaction was allowed to stir at room temperature overnight until judged complete by TLC analysis (R_f: 0.55, 1:8 hexanes/Et_2O). The mixture was transferred to a separatory funnel and extracted with ethyl acetate (3×15 mL). The combined organic layer was washed with brine (15 mL) and dried over $MgSO_4$. The resulting solution was concentrated and purified immediately by silica gel column chromatography (85:15 hexanes/EtOAc with a gradient to 35:65 hexanes/EtOAc) to afford compound **30** (234.1 mg, 0.866 mmol, 63% yield over two steps) as colorless oil. H NMR (500 MHz, $CDCl_3$): δ 7.27 (2H, t, J=7.5 Hz), 7.17 (1H, t, J=7.5 Hz), 7.09 (2H, d, J=7.5 Hz), 5.76 (1H, t, J=1.5 Hz), 4.09 (1H, d, J=9.5 Hz), 3.91 (1H, d, J=10.0 Hz), 3.84 (1H, dd, J=9.5, 6.5 Hz), 3.69 (1H, d, J=10.0 Hz), 3.44 (1H, dd, J=8.5, 6.0 Hz), 3.28 (1H, d, J=8.0 Hz), 2.79 (1H, t, J=5.5 Hz), 2.58 (2H, t, J=7.5 Hz), 2.47 (2H, m). C NMR (125 MHz, $CDCl_3$): δ 178.7, 149.1, 142.9, 129.4, 128.3, 127.4, 126.0, 73.8, 69.1, 58.3, 46.7, 46.3, 44.8, 31.3, 23.7. IR (KBr thin film, CH_2Cl_2 solution): 3060 (s), 3027 (s), 3002 (s), 1732 (m), 1709 (m), 1447 (w), 1203 (br), 1063 (w), 887 (w), 712 (w), 590 (br) cm^{-1}. DART-HRMS (m/z): calcd for $[M+H]^+$: 271.1334; Found: 271.1344.

*4.1.7. Diazoketone (**31**).* To a solution of compound **30** (234.1 mg, 0.866 mmol) in dry benzene (4.4 mL, 0.20 M) were added DMF (0.67 μL, 1 mol %) and oxalyl chloride (223.1 μL, 2.30 mmol) at 0 °C under N_2 atmosphere. The reaction was allowed to slowly warm to room temperature and stirring until no gas-evolution anymore (2 h). The solvent and unreacted oxalyl chloride were removed under vacuum. Then THF (4.4 mL, 0.20 M) and CH_3CN (4.4 mL, 0.20 M) were added at 0 °C under N_2 atmosphere. TMS-diazomethane (0.866 mL, 2.0 M in cyclohexane) was added slowly with an air-tight syringe. A bright yellow color developed during the addition. The reaction was allowed to stir at room temperature until judged complete (2 h) by TLC analysis (R_f=0.3, 1:1 hexanes/EtOAc). The reaction mixture was concentrated and purified by silica gel column chromatography (5% Et_3N in hexanes washed silica gel, 90:10 hexanes/EtOAc with a gradient to 75:25 hexanes/EtOAc) to afford compound **31** (137.6 mg, 0.468 mmol, 54% yield over two steps) as a bright yellow oil. H NMR (500 MHz, $CDCl_3$): δ 7.27 (2H, t, J=7.5 Hz), 7.17 (1H, t, J=7.5 Hz), 7.09 (2H, dd, J=10.0, 8.0 Hz), 5.71 (1H, s), 5.22 (1H, br), 4.09 (1H, d, J=9.5 Hz), 3.89 (1H, d, J=10.0 Hz), 3.84 (1H, dd, J=9.5, 6.5 Hz), 3.68 (1H, d, J=10.0 Hz), 3.43 (1H, dd, J=8.0, 5.5 Hz), 3.27 (1H, d, J=8.0 Hz), 2.78 (1H, t, J=5.5 Hz), 2.46 (4H, m). C NMR (125 MHz, $CDCl_3$): δ 193.8, 149.6, 143.1, 129.1, 128.3, 127.4, 126.0, 73.9, 69.2, 58.5, 46.7, 46.2, 44.8, 23.7. IR (KBr thin film, CH_2Cl_2 solution): 3060 (s), 3028 (s), 2931 (s), 2850 (w), 2360 (w), 2341 (w), 2103 (m), 1645 (w), 1371 (w), 746 (w), 697 (w) cm^{-1}. DART-HRMS (m/z): calcd for $[M+H]^+$: 295.1447; Found: 295.1448.

*4.1.8. Cyclopropane (**32**).* To a solution of compound **31** (10 mg, 0.034 mmol) in CH_2Cl_2 (1.7 mL, 0.020 M) was added rhodium acetate (0.3 mg, 0.7 μmol, 2 mol %). The reaction was allowed to stir at room temperature until judged complete (1 h) by TLC analysis (R_f=0.4, 1:1 hexanes/EtOAc). Then the reaction mixture was concentrated and purified by silica gel column chromatography (90:10 hexanes/EtOAc with a gradient to 50:50 hexanes/EtOAc) to afford compound **32** (84% yield) as a white solid (mp: 117–125 °C). H NMR (500 MHz, $CDCl_3$): δ 7.19–7.40 (5H, m), 4.05 (1H, d, J=9.5 Hz), 3.86 (1H, dd, J=9.5, 6.5 Hz), 3.73 (1H, d, J=10.0 Hz), 3.71 (1H, t, J=6.0 Hz), 3.47 (1H, d, J=10.0 Hz), 3.24 (1H, t, J=6.0 Hz), 2.69 (1H, d, J=2.0 Hz), 2.27–2.32 (1H, m), 2.10 (1H, m), 2.01–2.04 (1H, m), 1.92 (1H, s), 1.74 (1H, s). C NMR (125 MHz, $CDCl_3$): δ 212.3, 140.9, 128.6, 127.1, 126.4, 74.0, 69.1, 52.8, 44.7, 43.5, 43.4, 40.0, 37.9, 35.0, 24.0, 20.8. IR (KBr thin film, CH_2Cl_2 solution): 3059 (m), 2955 (m), 2844 (br), 2360 (m), 2341 (m), 1730 (s), 1281 (w), 1172 (m), 1053 (w), 902 (w) cm^{-1}. DART-HRMS (m/z): calcd for $[M+H]^+$: 267.1385; Found: 267.1390.

*4.1.9. Thermolysis precursor (**33**).* To a solution of compound **32** (11.0 mg, 0.0413 mmol) in MeOH (0.60 mL, 0.065 M) at 0 °C was added $NaBH_4$ (3.2 mg, 0.0826 mmol) slowly. The reaction was allowed to stir at this temperature until judged complete (5 min) by

TLC analysis (R_f: 0.1, 1:1 hexanes/EtOAc). The reaction crude was diluted by CH_2Cl_2 and carefully quenched with saturated aqueous NH_4Cl solution at 0 °C. The aqueous layer was extracted with CH_2Cl_2 (3×5 mL). The combined organic layer was washed with brine (5 mL) and dried over $MgSO_4$. The resulting solution was concentrated and purified immediately by silica gel column chromatography (75:25 hexanes/EtOAc with a gradient to 50:50 hexanes/EtOAc) to afford compound **33** (10.6 mg, 0.0392 mmol) as a colorless oil. H NMR (400 MHz, $CDCl_3$): δ 7.34 (2H, dt, J=1.6, 7.6 Hz), 7.19–7.23 (3H, m), 4.55 (1H, m), 4.00 (1H, d, J=9.6 Hz), 3.80 (1H, dd, J=9.6, 5.6 Hz), 3.72 (1H, d, J=10.0 Hz), 3.62 (1H, t, J=6.8 Hz), 3.39 (1H, d, J=9.6 Hz), 3.14 (1H, t, J=6.4 Hz), 2.52 (1H, d, J=7.6 Hz), 1.99 (1H, dd, J=7.2, 12.4 Hz), 1.91 (1H, td, J=12.4, 7.6 Hz), 1.74 (1H, m), 1.69 (1H, s), 1.45 (1H, d, J=4.8 Hz), 1.01 (1H, m). C NMR (125 MHz, $CDCl_3$): δ 141.7, 128.4, 127.3, 126.1, 74.2, 74.1, 69.4, 52.9, 43.9, 43.8, 43.3, 34.8, 32.5, 30.5, 22.3, 16.2. IR (KBr thin film, CH_2Cl_2 solution): 3385 (w), 3037 (m), 3026 (m), 2924 (s), 2905 (m), 2360 (s), 2341 (s), 1491 (w), 1054 (w), 779 (s), 743 (s), 682 (m), 540 (m) cm^{-1}. DART-HRMS (m/z): calcd for $[M+H]^+$: 269.1542; Found: 269.1530.

*4.1.10. Compound (**34**).* The procedure was followed as described for compound **29** to afford compound **34** as a colorless oil in 83% yield. H NMR (500 MHz, $CDCl_3$): δ 7.25 (2H, t, J=7.5 Hz), 7.17 (3H, m), 6.05 (1H, s), 4.67 (1H, t, J=4.5 Hz), 4.05 (1H, d, J=9.0 Hz), 3.84 (4H, m), 3.77 (2H, m), 3.64 (1H, d, J=10.0 Hz), 3.41 (1H, dd, J=8.0, 5.0 Hz), 3.30 (1H, d, J=8.0 Hz), 2.86 (1H, t, J=5.5 Hz), 1.61 (4H, m). C NMR (125 MHz, $CDCl_3$): δ 151.8, 142.4, 128.2, 127.9, 127.3, 126.2, 104.2, 74.0, 70.5, 65.0, 65.0, 54.5, 50.6, 45.6, 43.1, 31.1, 25.2. IR (KBr thin film, CH_2Cl_2 solution): 2939 (s), 2849 (s), 1409 (w), 1136 (s), 1067 (s), 1036 (s), 943 (w), 897 (m), 712 (s), 866 (br), 551 (w) cm^{-1}. DART-HRMS (m/z): calcd for $[M+H]^+$: 299.1647; Found: 299.1636.

*4.1.11. Compound (**35**).* The procedure was followed as described for compound **30** to afford compound **35** as colorless oil in 59% yield over two steps. H NMR (500 MHz, $CDCl_3$): δ 7.27 (2H, t, J=7.0 Hz), 7.18 (3H, m), 6.09 (1H, d, J=1.5 Hz), 4.07 (1H, d, J=9.5 Hz), 3.86 (2H, td, J=9.5, 3.0 Hz), 3.64 (1H, d, J=9.5 Hz), 3.43 (1H, dd, J=7.5, 5.5 Hz), 3.32 (1H, d, J=8.5 Hz), 2.88 (1H, t, J=5.5 Hz), 2.24 (2H, m), 1.90 (1H, m), 1.75 (1H, m). C NMR (125 MHz, $CDCl_3$): δ 178.6, 150.4, 142.2, 128.6, 128.3, 127.3, 126.4, 73.9, 70.4, 54.6, 50.8, 45.4, 43.0, 31.2, 25.6. IR (KBr thin film, CH_2Cl_2 solution): 3425 (w), 3183 (w), 2946 (m), 1732 (m), 1710 (m), 1504 (w), 1463 (m), 1167 (w), 762 (s), 697 (w), 580 (w), 546 (w) cm^{-1}. DART-HRMS (m/z): calcd for $[M+H]^+$: 271.1334; Found: 271.1345.

*4.1.12. Compound (**36**).* The procedure was followed as described for compound **31** to afford compound **36** as bright yellow oil in 72% yield over two steps. H NMR (500 MHz, $CDCl_3$): δ 7.27 (2H, m), 7.18 (3H, m), 6.06 (1H, d, J=1.5 Hz), 4.98 (1H, s), 4.06 (1H, d, J=9.5 Hz), 3.85 (2H, dd, J=9.5, 5.5 Hz), 3.64 (1H, d, J=10.0 Hz), 3.43 (1H, dd, J=8.0, 5.0 Hz), 3.30 (1H, d, J=8.0 Hz), 2.87 (1H, t, J=5.5 Hz), 2.16 (2H, br), 1.90 (1H, m), 1.75 (1H, m). C NMR (125 MHz, $CDCl_3$): δ 194.0, 150.4, 142.2, 128.5, 128.5, 128.1, 127.2, 126.2, 73.8, 70.2, 54.4, 50.6, 45.2, 42.8, 37.9, 25.8. IR (KBr thin film, CH_2Cl_2 solution): 3084 (w), 2956 (m), 2846 (m), 2359 (m), 2341 (m), 2103 (s), 1643 (s), 1373 (s), 1350 (s), 1150 (m), 712 (w), 552 (w) cm^{-1}. DART-HRMS (m/z): calcd for $[M+H]^+$: 295.1447; Found: 295.1443.

*4.1.13. Compound (**37**).* The procedure was followed as described for compound **32** to afford compound **37** as a white solid in quant. yield. H NMR (500 MHz, $CDCl_3$): δ 7.34 (2H, t, J=7.5 Hz), 7.28 (2H, d, J=7.5 Hz), 7.23 (1H, t, J=7.5 Hz), 3.97 (1H, d, J=9.5 Hz), 3.87 (1H, dd, J=9.5, 6.5 Hz), 3.79 (1H, t, J=7.0 Hz), 3.73 (1H, d, J=10.5 Hz), 3.30 (1H, d, J=10.0 Hz), 3.22 (1H, t, J=6.5 Hz), 2.97 (1H, dd, J=8.0, 3.0 Hz), 2.34 (1H, d, J=3.0 Hz), 1.91 (2H, m), 1.73 (1H, td, J=13.5, 9.0 Hz), 1.63 (1H, s), 1.22 (1H, dd, J=13.0, 7.5 Hz). C NMR (125 MHz, $CDCl_3$): δ 212.4, 141.8, 128.6, 126.7, 126.4, 74.0, 70.0, 52.5, 45.1, 44.2, 43.6, 38.9, 38.8, 35.3, 30.0, 23.1. IR (KBr thin film, CH_2Cl_2 solution): 3060 (m), 3028 (s), 3007 (s), 2851 (m), 2359 (w), 1728 (m), 1451 (w), 1384 (w), 1178 (w), 746 (w), 577 (w) cm^{-1}. DART-HRMS (m/z): calcd for $[M+H]^+$: 267.1385; Found: 267.1379.

*4.1.14. Compound (**38**).* The procedure was followed as described for compound **33** to afford compound **38** as colorless oil in 99% yield. H NMR (500 MHz, $CDCl_3$): δ 7.32 (2H, t, J=7.5 Hz), 7.25 (2H, d, J=7.5 Hz), 7.21 (1H, t, J=7.0 Hz), 4.44 (1H, q, J=7.0 Hz), 3.94 (1H, d, J=9.5 Hz), 3.84 (1H, dd, J=9.5, 6.5 Hz), 3.76 (1H, d, J=10.0 Hz), 3.71 (1H, t, J=7.0 Hz), 3.28 (1H, d, J=9.5 Hz), 3.13 (1H, t, J=6.5 Hz), 2.85 (1H, dd, J=8.0, 3.0 Hz), 2.07 (1H, d, J=2.5 Hz), 1.70 (1H, m), 1.33 (1H, d, J=5.5 Hz), 1.29 (1H, m), 0.89 (2H, m). C NMR (125 MHz, $CDCl_3$): δ 142.6, 128.3, 126.9, 126.0, 74.1, 73.0, 70.6, 51.2, 45.4, 44.9, 44.4, 33.6, 33.2, 31.1, 24.3, 22.4. IR (KBr thin film, CH_2Cl_2 solution): 3363 (w), 3057 (m), 3028 (s), 2952 (m), 2850 (w), 1492 (w), 1453 (w), 1384 (w), 1067 (w), 755 (s), 696 (s), 540 (s) cm^{-1}. DART-HRMS (m/z): calcd for $[M+H]^+$: 269.1542; Found: 269.1535.

*4.1.15. Thermolysis products (**39** & **40**).* In a pressure vessel with a stir bar was added a solution of compound **33** (32.2 mg, 0.120 mmol) and BHT (39.6 mg, 0.179 mmol) in dry benzene (12.0 mL, 0.010 M). The reaction mixture was degassed for 5 min before sealing the pressure vessel. Then, the flask was emerged into a wax bath, heating from room temperature to 240 °C. The reaction was heated at this temperature for 5 h. After allowing to cool, the reaction mixture was concentrated and purified immediately by silica gel column chromatography (R_f: 0.5 in 1:4 hexanes/Et_2O, 100:10 hexanes/EtOAc with a gradient to 80:20 hexanes/EtOAc) to afford compounds **39** (20.7 mg, 0.0769 mmol, 77% yield) and **40** (4.1 mg, 0.0153 mmol, 15% yield) as colorless oils. Compound **39**: H NMR (500 MHz, C_6D_6): δ 7.30 (2H, dd, J=8.0, 1.5 Hz), 7.19 (2H, m), 7.09 (1H, m), 5.77 (1H, m), 5.33 (1H, dd, J=10.0, 2.0 Hz), 4.03 (1H, d, J=10.5 Hz), 3.93 (1H, t, J=3.0 Hz), 3.89 (1H, t, J=8.5 Hz), 3.74 (1H, m), 3.65 (1H, m), 3.28 (1H, br), 3.19 (1H, m), 3.17 (1H, br), 2.41 (1H, m), 1.86 (1H, dd, J=16.5, 9.0 Hz), 1.71 (1H, dd, J=13.0, 8.0 Hz), 1.30 (1H, m). ^{13}C NMR (125 MHz, C_6D_6): δ 141.0, 135.1, 134.7, 132.7, 131.0, 128.7, 127.4, 126.3, 77.1, 72.2, 71.6, 51.9, 48.0, 46.5, 33.2, 29.3. IR (KBr thin film, CH_2Cl_2 solution): 3059 (w), 3029 (m), 2934 (s), 2909 (m), 2359 (w), 2342 (w), 1449 (w), 757 (s), 701 (m), 541 (w) cm^{-1}. DART-HRMS (m/z): calcd for $[M+H]^+$: 269.1542; Found: 269.1530. Compound **40**: H NMR (500 MHz, $CDCl_3$): δ 7.31 (2H, t, J=8.0 Hz), 7.23 (3H, m), 5.99 (2H, d, J=1.0 Hz), 4.34–4.40 (2H, m), 4.33 (1H, d, J=13.0 Hz), 3.64 (1H, d, J=11.0 Hz), 3.49 (1H, br), 3.46 (1H, t, J=7.0 Hz), 3.14 (1H, dd, J=11.0, 8.0 Hz), 3.08 (1H, br), 2.36 (2H, br), 1.90 (2H, m). C NMR (125 MHz, $CDCl_3$): δ 143.8, 138.2, 134.3, 129.8, 128.8, 128.0, 127.3, 126.7, 75.8, 73.4, 71.7, 48.3, 46.4, 45.7, 32.9, 27.9. IR (KBr thin film, CH_2Cl_2 solution): 3398 (br), 3035 (w), 3019 (w), 2959 (s), 2920 (s), 2853 (s), 2362 (w), 1724 (w), 1384 (m), 1280 (w), 1066 (m), 762 (s), 572 (m) cm^{-1}. DART-HRMS (m/z): calcd for $[M+H]^+$: 269.1542; Found: 269.1551.

*4.1.16. Compound (**46**).* The procedure was followed as described for compound **33** to afford compound **46** as colorless oil in 81% yield. H NMR (500 MHz, $CDCl_3$): δ 4.56 (1H, dd, J=13.5, 8.5 Hz), 3.89 (1H, d, J=9.5 Hz), 3.71 (3H, s), 3.69 (1H, dd, J=10.0, 6.5 Hz), 3.61 (1H, d, J=10.0 Hz), 3.30 (1H, d, J=10.0 Hz), 3.17 (1H, t, J=6.5 Hz), 3.12 (1H, dd, J=7.5, 6.0 Hz), 2.37 (1H, d, J=8.0 Hz), 1.99 (1H, dd, J=12.5, 7.5 Hz), 1.92 (1H, dt, J=13.0, 7.5 Hz), 1.81 (2H, s), 1.68 (1H, m), 1.39 (1H, d, J=5.0 Hz), 1.09 (1H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.5, 73.9, 73.6, 69.2, 53.8, 51.8, 42.8, 41.4, 40.7, 34.6, 32.3, 30.4, 22.2, 17.0.

IR (KBr thin film, CH_2Cl_2 solution): 3081 (w), 3060 (w), 3028 (m), 2926 (s), 1732 (w), 1600 (w), 1493 (w), 1449 (w), 1059 (w), 1028 (m), 755 (m), 698 (m), 539 (m) cm^{-1}. DART-HRMS (*m*/*z*): calcd for $[M+H]^+$: 251.1283; Found: 251.1288.

*4.1.17. Compounds (**47** & **48**).* The procedure was followed as described for compounds **39** & **40** to afford a mixture of compound **47** (50% yield) and compound **48** (21% yield) as colorless oil. Compound **47**: H NMR (500 MHz, C_6D_6): δ 5.62 (2H, m), 4.32 (1H, dd, *J*=13.0, 1.0 Hz), 4.13 (1H, t, *J*=3.5 Hz), 4.02 (1H, dd, *J*=12.5, 1.5 Hz), 3.83 (1H, dd, *J*=9.0, 5.0 Hz), 3.75 (1H, t, *J*=9.5 Hz), 3.26 (3H, s), 3.04 (1H, br), 2.93 (1H, td, *J*=5.0, 2.0 Hz), 2.84 (1H, quintet, 1.5 Hz), 2.30 (1H, m), 1.91 (1H, dd, *J*=13.0, 8.5 Hz), 1.85 (1H, ddd, *J*=16.5, 9.5, 1.5 Hz), 1.39 (2H, m). C NMR (100 MHz, C_6D_6): δ 173.2, 133.1, 132.2, 131.6, 76.7, 73.6, 71.9, 53.8, 52.3, 47.7, 44.8, 33.8, 28.8. IR (KBr thin film, CH_2Cl_2 solution): 3397 (br), 3070 (w), 3042 (s), 2950 (m), 2922 (m), 2870 (m), 2840 (w), 2359 (s), 2342 (s), 1721 (s), 1435 (m), 1266 (m), 1198 (s), 1171 (s), 1066 (m), 1016 (w), 748 (w), 701 (s), 531 (w) cm^{-1}. DART-HRMS (*m*/*z*): calcd for $[M+H]^+$: 251.1283; Found: 251.1275. Compound **48**: H NMR (400 MHz, C_6D_6): 6.11 (1H, qd, *J*=10.8, 2.8 Hz), 5.91 (1H, ddd, *J*=10.8, 3.2, 2.4 Hz), 4.24 (1H, t, *J*=7.6 Hz), 4.21 (1H, dm, *J*=15.2 Hz), 4.13 (1H, dm, *J*=12.8 Hz), 3.81 (1H, t, *J*=3.6 Hz), 3.47 (1H, dd, *J*=11.2, 8.0 Hz), 3.39 (1H, ddq, *J*=1.2, 2.8, 5.6 Hz), 3.26 (3H, s), 3.01 (1H, br), 2.81 (1H, br), 1.96 (1H, m), 1.76 (1H, dd, *J*=9.6, 17.6 Hz), 1.46 (1H, dd, *J*=8.4, 13.2 Hz), 1.27 (2H, m). C NMR (100 MHz, C_6D_6): δ 173.8, 133.7, 130.8, 130.7, 130.6, 75.6, 73.0, 71.5, 51.7, 48.2, 46.0, 42.8, 33.4, 28.3. IR (KBr thin film, CH_2Cl_2 solution): 3369 (br), 3060 (s), 3027 (s), 2910 (s), 2850 (m), 2360 (m), 2341 (m), 1737 (m), 1492 (w), 1449 (m), 1331 (w), 1260 (w), 1196 (w), 1160 (m), 1079 (w), 1041 (w), 753 (m), 697 (m), 544 (w) cm^{-1}. DART-HRMS (*m*/*z*): calcd for $[M+H]^+$: 251.1283; Found: 251.1284.

*4.1.18. Compound (**49**).* The procedure was followed as described for compound **33** to afford compound **49** as colorless oil in quant. yield. H NMR (500 MHz, $CDCl_3$): δ 7.32 (2H, t, *J*=8.0 Hz), 7.21 (3H, m), 4.52 (1H, m), 4.05 (1H, t, *J*=6.5 Hz), 3.96 (1H, d, *J*=7.5 Hz), 3.13 (1H, dd, *J*=8.0, 6.0 Hz), 2.50 (1H, d, *J*=7.5 Hz), 1.87 (2H, dd, *J*=10.5, 7.5 Hz), 1.65 (1H, s), 1.56 (3H, m), 1.54 (1H, d, *J*=14.0 Hz), 1.42 (1H, d, *J*=14.0 Hz), 1.38 (1H, d, *J*=5.5 Hz), 1.10 (3H, s), 0.99 (3H, s), 0.85 (1H, d, *J*=6.5 Hz). C NMR (125 MHz, $CDCl_3$): δ 142.9, 128.3, 127.6, 125.7, 80.6, 74.3, 50.2, 47.9, 45.1, 44.7, 41.8, 38.8, 35.4, 32.0, 30.7, 28.8, 22.0, 21.7, 17.4. IR (KBr thin film, CH_2Cl_2 solution): 3424 (br), 3356 (s), 2955 (s), 2875 (m), 1449 (w), 1048 (s), 762 (m), 690 (w), 558 (m) cm^{-1}. DART-HRMS (*m*/*z*): calcd for $[M+H]^+$: 311.2011; Found: 311.2004.

*4.1.19. Compound (**50**).* The procedure was followed as described for compounds **39** & **40** to afford compound **50** as colorless oil in 76% yield. H NMR (500 MHz, C_6D_6): δ 7.30 (2H, m), 7.21 (2H, m), 7.11 (1H, m), 6.02 (1H, qd, *J*=10.5, 2.5 Hz), 5.95 (1H, td, *J*=10.5, 3.0 Hz), 4.08 (1H, dd, *J*=11.0, 5.0 Hz), 3.97 (1H, t, *J*=3.5 Hz), 3.26 (1H, br), 3.09 (1H, m), 2.96 (1H, s), 2.36 (1H, m), 2.25 (1H, d, *J*=16.5 Hz), 2.11 (1H, dd, *J*=17.5, 9.0 Hz), 1.98 (1H, d, *J*=16.5 Hz), 1.62 (1H, dd, *J*=13.5, 8.5 Hz), 0.89 (3H, s), 0.73 (3H, s). C NMR (125 MHz, C_6D_6): δ 146.1, 138.8, 135.8, 133.0129.3, 128.7, 128.6, 128.2, 126.9, 82.5, 76.3, 51.0, 48.7, 45.7, 45.6, 39.5, 33.5, 29.6, 28.5, 24.0. IR (KBr thin film, CH_2Cl_2 solution): 3425 (br), 3060 (s), 3028 (s), 2935 (s), 1452 (w), 1077 (w), 760 (w), 701 (w) cm^{-1}. DART-HRMS (*m*/*z*): calcd for $[M+H]^+$: 311.2011; Found: 311.2012.

*4.1.20. Compound (**52**).* The procedure was followed as described for compound **33** to afford compound **52** as colorless oil in 91% yield. H NMR (500 MHz, $CDCl_3$): δ 7.33 (2H, m), 7.20 (3H, m), 4.50 (1H, m), 3.90 (1H, m), 3.64–3.71 (3H, m), 3.47 (1H, m), 2.96 (1H, m), 2.67 (1H, d, *J*=10.0 Hz), 2.27 (1H, m), 1.96 (1H, dd, *J*=10.0, 7.5 Hz), 1.81–1.91 (2H, m), 1.60–1.68 (1H, m), 1.60 (1H, s), 1.41 (1H, d, *J*=5.5 Hz), 0.93 (1H, m). C NMR (125 MHz, $CDCl_3$): δ 142.0, 128.4, 127.4, 126.0, 74.0, 67.6, 64.1, 46.2, 43.5, 41.6, 38.9, 34.0, 31.0, 30.9, 30.4, 20.9, 16.7. IR (KBr thin film, CH_2Cl_2 solution): 3352 (w), 3030 (w), 2922 (s), 2359 (w), 1092 (m), 760 (s), 750 (s), 704 (s), 546 (w) cm^{-1}. DART-HRMS (*m*/*z*): calcd for $[M+H]^+$: 283.1698; Found: 283.1700.

*4.1.21. Compounds (**53** & **54**).* The procedure was followed as described for compounds **39** & **40** to afford a mixture of compound **53** (47% yield) and **54** (40% yield) as colorless oil. [Note: diastereomers **53** & **54** were not readily separable by column chromatography until their disubstituted olefin in the cycloheptadiene ring was reduced by hydrogenation.] To a solution of the mixture (17.7 mg, 0.0628 mmol) in ethanol (1.3 mL, 0.050 M) was added Pd/C (6.3 mg). Then the flask was purged with hydrogen gas (3×). The reaction was allowed to stir at room temperature under H_2 atmosphere for 1 h before filtered through a silica plug and washed with EtOAc. After concentration, the reaction crude was then purified by silica gel column chromatography (10:1 hexanes/EtOAc with a gradient to 2:1 hexanes/EtOAc) to afford compound **53a** and **54a** as clear colorless oil in quant. yield. Compound **53a** H NMR (500 MHz, C_6D_6): δ 7.09–7.22 (5H, m), 4.42 (1H, d, *J*=12.0 Hz), 3.84 (1H, t, *J*=3.5 Hz), 3.78 (1H, m), 3.71 (1H, d, *J*=11.5 Hz), 3.33 (1H, td, *J*=12.5, 3.5 Hz), 3.15 (1H, td, *J*=11.0, 3.0 Hz), 2.60 (1H, m), 2.45 (2H, d, *J*=11.0 Hz), 2.01–2.12 (2H, m), 1.80 (1H, m), 1.58–1.69 (3H, m), 1.53–1.57 (1H, m), 1.27–1.39 (3H, m). C NMR (125 MHz, $CDCl_3$): δ 146.3, 139.9, 132.3, 129.3, 129.0, 127.0, 77.0, 72.0, 68.9, 48.9, 45.9, 45.2, 34.4, 30.8, 30.3, 29.2, 26.6. IR (KBr thin film, CH_2Cl_2 solution): 3428 (br), 3060 (m), 3028 (m), 2949 (s), 2899 (s), 2843 (s), 1725 (w), 1460 (m), 1378 (m), 1250 (m), 1093 (m), 775 (w), 566 (w) cm^{-1}. DART-HRMS (*m*/*z*): calcd for $[M+H]^+$: 285.1855; Found: 285.1848. Compounds **53a** and **54a**: H NMR (500 MHz, C_6D_6): δ 7.19 (m), 7.10 (m), 7.00 (d, *J*=7.5 Hz), 4.59 (**54a**, 1H, *J*=7.5 Hz), 4.41 (**53a**, 1H, d, *J*=12.0 Hz), 3.84 (**53a**, 1H, t, *J*=3.5 Hz), 3.83 (**54a**, 1H, s), 3.78 (m), 3,71 (**53a**, 1H, d, *J*=11.5 Hz), 3.66 (**54a**, 1H, d, *J*=13.0 Hz), 3.33 (**53a**, 1H, td, *J*=12.5, 3.5 Hz), 3.24 (**54a**, 1H, m), 3.15 (**53a**, 1H, td, *J*=11.0, 3.0 Hz), 2.91 (**54a**, 1H, t, *J*=11.5 Hz), 2.60 (m), 2.44 (m), 2.32 (**54a**, 1H, dd, *J*=16.0, 8.0 Hz), 2.07 (m), 1.92 (**54a**, m), 1.81 (m), 1.42–1.69 (m), 1.23–1.39 (m), 1.12 (**54a**, m), 0.85–1.00 (**54a**, m).

*4.1.22. Compound (**55**).* The procedure was followed as described for compounds **39** & **40** to afford compound **55** as colorless oil in 49% yield. H NMR (500 MHz, $CDCl_3$): δ 7.20–7.29 (5H, m), 5.91 (1H, s), 5.68 (1H, d, *J*=2.5 Hz), 4.40 (1H, s), 4.07 (1H, d, *J*=12.5 Hz), 4.01 (1H, t, *J*=8.0 Hz), 3.65–3.68 (2H, m), 3.58 (1H, s), 3.54 (1H, s), 3.49 (1H, d, *J*=3.0 Hz), 3.63 (1H, m), 2.51 (1H, m), 1.83 (2H, m). C NMR (125 MHz, $CDCl_3$): δ 144.9, 141.0, 140.5, 130.2, 128.2, 127.0, 125.5, 118.2, 76.5, 72.0, 71.9, 49.0, 45.7, 45.4, 32.6, 31.4. IR (KBr thin film, CH_2Cl_2 solution): 3430 (br), 3059 (s), 3037 (s), 2957 (m), 2852 (m), 2358 (w), 2338 (w), 1600 (w), 1490 (w), 1450 (m), 1383 (m), 1062 (m), 751 (s), 699 (w), 540 (m) cm^{-1}. DART-HRMS (*m*/*z*): calcd for $[M+H]^+$: 269.1542; Found: 269.1547.

*4.1.23. Compound (**56**).* The procedure was followed as described for compound **33** to afford compound **56** as colorless oil in 89% yield. H NMR (500 MHz, $CDCl_3$): δ 4.52 (1H, br), 3.84 (1H, d, *J*=9.5 Hz), 3.71 (1H, m), 3.70 (3H, s), 3.66 (1H, d, *J*=10.0 Hz), 3.19 (1H, d, *J*=10.5 Hz), 3.12 (1H, quintet, *J*=5.0 Hz), 2.70 (1H, dd, *J*=7.5, 2.5 Hz), 2.12 (1H, d, *J*=2.5 Hz), 1.93 (2H, m), 1.77 (1H, dd, *J*=12.0, 7.0 Hz), 1.69 (1H, td, *J*=11.5, 7.0 Hz), 1.45 (1H, d, *J*=3.0 Hz), 1.34 (1H, d, *J*=5.5 Hz), 1.11 (1H, m). C NMR (125 MHz, $CDCl_3$): δ 174.2, 73.5, 73.0, 70.3, 52.3, 51.8, 43.2, 42.9, 42.6, 33.4, 32.6, 31.0, 23.1, 21.9. IR (KBr thin film, CH_2Cl_2 solution): 3441 (w), 3060 (s), 3040 (s), 2921 (s), 2359 (w), 1732 (m), 1449 (w), 1265 (w), 1174 (w), 1070 (w), 758

(w), 595 (w) cm^{-1}. DART-HRMS (*m*/*z*): calcd for $[M+H]^+$: 251.1283; Found: 251.1283.

*4.1.24. Thermolysis product (**57**).* The procedure was followed as described for compounds **39** & **40** to afford compound **57** as colorless oil in 70% yield. H NMR (500 MHz, C_6D_6): δ 5.63 (1H, s), 5.45 (1H, dd, *J*=6.0, 2.0 Hz), 4.50 (1H, d, *J*=12.0 Hz), 4.19 (1H, d, *J*=12.0 Hz), 3.99 (1H, t, *J*=3.5 Hz), 3.81 (2H, d, *J*=7.0 Hz), 3.30 (3H, s), 2.97–3.01 (3H, m), 2.41 (1H, m), 2.17 (1H, dd, *J*=15.5, 10.5 Hz), 1.63–1.68 (1H, m), 1.36–1.44 (1H, m). C NMR (125 MHz, $CDCl_3$): δ 172.9, 145.6, 144.4, 119.7, 118.4, 75.9, 73.0, 72.8, 51.9, 50.0, 46.4, 43.9, 32.8, 32.2. IR (KBr thin film, CH_2Cl_2 solution): 3422 (br), 3059 (s), 3026 (m), 2902 (w), 2359 (s), 2341 (s), 1735 (m), 1491 (w), 1450 (m), 1196 (m), 1168 (m), 1062 (w), 757 (s), 698 (s), 540 (m) cm^{-1}. DART-HRMS (*m*/*z*): calcd for $[M+H]^+$: 251.1283; Found: 251.1287.

*4.1.25. Compound (**58**).* The procedure was followed as described for compound **33** to afford compound **58** as colorless oil in 86% yield. H NMR (500 MHz, $CDCl_3$): δ 7.26 (3H, m), 7.15 (2H, t, *J*=7.0 Hz), 4.38 (1H, q, *J*=7.0 Hz), 4.11 (1H, t, *J*=7.0 Hz), 3.99 (1H, d, *J*=8.5 Hz), 3.12 (1H, t, *J*=6.5 Hz), 2.80 (1H, dd, *J*=7.5, 2.5 Hz), 1.90 (1H, d, *J*=2.5 Hz). C NMR (125 MHz, $CDCl_3$): δ 143.7, 128.1, 127.2, 125.6, 80.5, 73.1, 49.1, 48.9, 46.9, 45.1, 42.9, 36.0, 34.0, 33.1, 31.2, 29.1, 26.9, 24.5, 21.8. IR (KBr thin film, CH_2Cl_2 solution): 3439 (m), 3356 (br), 3024 (s), 2952 (m), 2893 (w), 1601 (w), 1452 (m), 1055 (m), 760 (s), 697 (s), 557 (w), 538 (w) cm^{-1}. DART-HRMS (*m*/*z*): calcd for $[M+H]^+$: 311.2011; Found: 311.1997.

*4.1.26. Compounds (**59** & **60**).* The procedure was followed as described for compounds **39** & **40** to afford a mixture of compounds **59** (63% yield) and **60** (33% yield) as colorless oils. Compound **59**: H NMR (500 MHz, C_6D_6): δ 7.46 (2H, d, *J*=8.5 Hz), 7.16 (2H, m), 7.07 (1H, m), 5.70 (1H, br), 5.65 (1H, br), 3.96 (1H, t, *J*=4.0 Hz), 3.71 (1H, t, *J*=2.0 Hz), 3.36 (1H, d, *J*=8.5 Hz), 3.10 (1H, br), 2.99 (1H, br), 2.51 (1H, m), 2.28 (1H, m), 1.84 (1H, d, *J*=14.0 Hz), 1.55 (2H, m), 1.41 (1H, m), 0.85 (3H, s), 0.72 (3H, s). C NMR (125 MHz, C_6D_6): δ 144.2, 143.3, 140.7, 131.1, 128.7, 128.6, 128.2, 127.2, 125.9, 121.8, 82.3, 76.7, 52.1, 49.5, 47.7, 45.8, 40.8, 32.8, 32.0, 26.3, 20.2. IR (KBr thin film, CH_2Cl_2 solution): 3421 (w), 3334 (w), 2957 (m), 2926 (m), 2899 (w), 2359 (s), 2341 (s), 1698 (w), 1541 (w), 1464 (w), 778 (s), 767 (s), 739 (m), 529 (m) cm^{-1}. DART-HRMS (*m*/*z*): calcd for $[M+H]^+$: 311.2011; Found: 311.2011. Compound **60**: H NMR (500 MHz, C_6D_6): δ 7.21 (3H, m), 7.10 (2H, m), 5.81 (1H, dd, *J*=4.5, 2.0 Hz), 5.35 (1H, t, *J*=1.5 Hz), 4.04 (1H, t, *J*=3.5 Hz), 3.89 (1H, dt, *J*=7.5, 2.5 Hz), 3.14 (2H, m), 2.99 (1H, s), 2.72 (1H, m), 2.63 (1H, d, *J*=15.0 Hz), 2.23 (1H, dd, *J*=16.0, 12.5 Hz), 2.13 (1H, d, *J*=16.0 Hz), 1.78 (1H, dd, *J*=13.0, 8.0 Hz), 1.37 (1H, m), 0.87 (3H, s), 0.71 (3H, s). C NMR (125 MHz, C_6D_6): δ 148.1, 145.9, 142.7, 129.7, 129.0, 128.6, 128.1, 126.6, 118.2, 82.4, 76.8, 52.2, 50.4, 46.7, 45.0, 39.2, 32.1, 30.6, 27.7, 23.2. IR (KBr thin film, CH_2Cl_2 solution): 3502 (w), 3425 (w), 3348 (w), 3059 (m), 3026 (s), 2936 (s), 2853 (w), 2406 (w), 1449 (w), 1384 (w), 1068 (w), 761 (s), 696 (s), 544 (m) cm^{-1}. DART-HRMS (*m*/*z*): calcd for $[M+H]^+$: 311.2011; Found: 311.2017.

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Supplementary data

Additional experimental procedures, compound data, and ^1H NMR and ^{13}C NMR spectra are available. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.05.129.

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