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Asymmetric Total Synthesis of Caribenol A via an Intramolecular Diels–Alder Reaction

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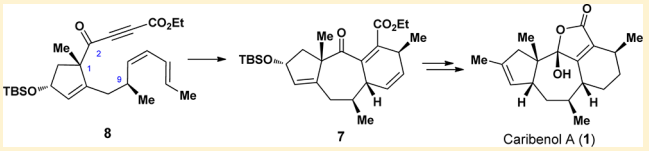
Supporting Information

ABSTRACT: A total synthesis of the caribenol A (**1**), a novel natural product with an intriguing tetracyclic framework, has been achieved. The synthesis features an intramolecular Diels–Alder (IMDA) reaction for the facile construction of the tricyclic [5−7−6] skeleton of caribenol A (**1**) and a biomimetic oxidation reaction for the formation of the 2-hydroxyfuran-2(5*H*)-one motif of caribenol A (**1**) as key steps. This synthetic approach also reveals that the sp^2 carbon at C(2) in substrate **8** is a critical factor for the formation of the tricyclic [5−7−6] skeleton in **7**.



INTRODUCTION

During the course of the past four decades, there has been a steady increase in the number reports describing the isolation of tricyclic diterpenoids from a variety of different natural resources.[1] Caribenol A (**1**), which is characterized by the presence of three unique all-*cis* methyl groups at the C(1), C(5) and C(9) positions and a 2-hydroxyfuran-2(5*H*)-one motif within a tetracyclic ring system, was isolated in 2007 by Rodriguez et al.[2] from the West Indian gorgonian octocoral *Pseudopterogorgia elisabethae* and represents a novel type of norditerpene with a unique structure and prominent biological activities. Of particular interest is its inhibitory activity toward *Mycobacterium tuberculosis* ($H_{37}Rv$) because this bacteria causes tuberculosis, which is a disease that causes over three million deaths worldwide each year.[3]

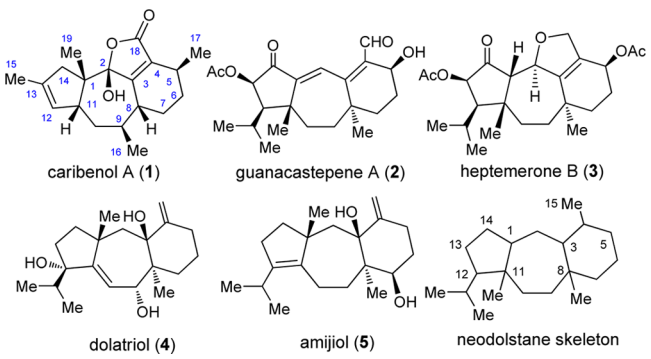


Figure 1. Naturally occurring biologically active terpenoids.

The molecular structure of caribenol A (**1**, Figure 1) was established by a combination of single-crystal X-ray analysis and comprehensive 2D NMR measurements.[2] From a structural perspective, caribenol A (**1**) can be considered as a new class of C19 rearranged terpene with an unprecedented tetracyclic ring core embodying six stereocenters (two of which are quaternary), an array of functional groups, including all-*cis* substituents at the C (1, Me), C (2, OH), C (5, Me) and C (9, Me) positions, and a potentially labile 2-hydroxyfuran-2(5*H*)-one motif, which represents a considerable total synthesis challenge. Indeed, significant research efforts have been directed toward exploring feasible strategies for the chemical synthesis of this scarce yet pharmacologically significant natural substance.[4]

Guanacastepene A (**2**), heptemerone B (**3**), dolatriol (**4**) and amijiol (**5**) are biologically active natural products that belong to neodolastane-type family of diterpenoids. Guanacastepene A was isolated from an unidentified endophytic fungus colonizing a *Daphnopsis americana* tree in the Guanacaste conservation area of Costa Rica. It showed interesting activities against drug-resistant strains of *Staphylococcus aureus* and *Enterococcus faecalis*.[5] Heptemerone B was isolated from the "ink cap" mushroom *Coprinus heptemerus*.[6] This molecule strongly inhibited the fungal germination of the plant pathogen *Magnaporthe grisea*, which is well-known as the cause of rice blast disease and is therefore a major problem in rice-cultivating countries. Dolatriol was isolated from the sea hare *Stylocheilus longicauda* and found to be cytotoxic and to markedly inhibit the growth of P-388 leukemia.[7] Amijiol was isolated from the

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toxic brown seaweed *Dictyota linearis* in 1982 and found to be cytotoxic.[8]

Structurally, caribenol A (**1**) and the neodolastanes (**2**–**5**) share a characteristic [5–7–6] tricyclic substructure and an array of stereogenic centers, including more than two chiral quaternary carbons. In light of their attractive structures and interesting bioactivities, it is perhaps not surprising that these molecules have attracted considerable levels of interest from the synthetic chemists with regards to their total syntheses.[9]

A previous investigation from our laboratories revealed that an intramolecular Diels–Alder (IMDA) reaction[10] could be used as an efficient method for the construction of the [5–7–6] tricyclic carbon skeleton. We have subsequently applied this reaction to the construction of the scaffolds of guanacastepene O,[11] as well as dolatriol (**4**) and amijiol (**5**).[12] The first total synthesis of caribenol A (**1**) was disclosed by our group in 2010.[13] The current study concerns the asymmetric construction of the [5–7–6] tricyclic core of caribenol A (**1**) using the IMDA reaction as the key step in the process. Herein, we report a full account of our synthetic effort to reduce our proposed IMDA reaction into practice, which represents a substantial extension of our early communication. The demonstrated chemistry could be amendable to the synthesis of the derivatives of caribenol A (**1**).

RESULTS AND DISCUSSION

Synthetic Plan. In 2006, when we investigated the use of the IMDA reaction for the formation of the [5–7–6] tricyclic core of guanacastepenes,[11b] we noticed that substrates **A** and **B** (Figure 2), which contained a doubly activated acetylene tethered to a *trans*- or *cis*-substituted penta-1,3-diene, respectively, yielded the same product **C**.

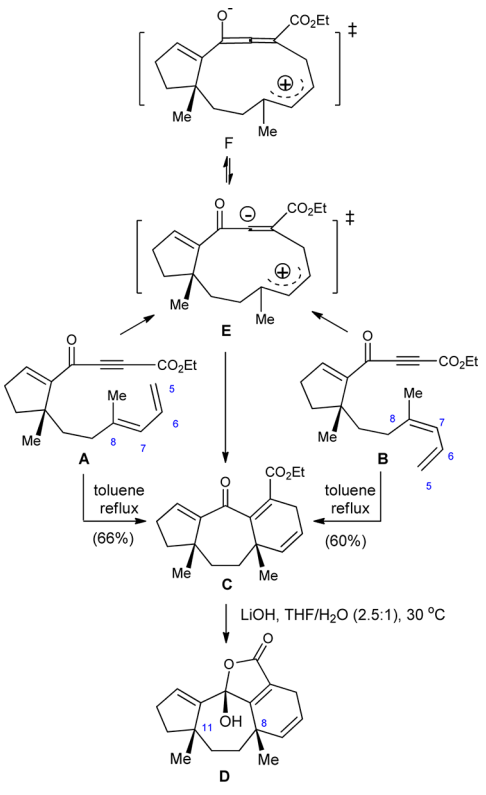

Figure 2. Intramolecular Diels–Alder reactions of **A** and **B**.

We speculated that the IMDA reaction may have proceeded in a stepwise manner via the initial formation of a bond between the termini of the diene and the dienophile[14] to give intermediates **E** and **F**, which would have been stabilized through the conjugation of the ketone group, as well as synergistic effects. Interestingly, it was also established that **C** could be converted to **D**, and the structure **D** has been confirmed by its X-ray crystallographic analysis.[11b] Thus, this chemistry effectively realized the formation of the pivotal 2-hydroxyfuran-2(5*H*)-one motif in caribenol A (**1**), via a sequential *in situ* ester-hydrolysis/intramolecular lactolization process.[11b] It is noteworthy that this observation actually shines a light on our total synthesis of caribenol A (**1**).

Retrosynthetically, caribenol A (**1**) could be traced back to the corresponding fully functionalized precursor **6** through the disconnection of the C13–C15 bond. In the forward direction, this sp3–sp2 bond connection could be realized via the Pd-catalyzed Negishi coupling reaction of Me_2Zn with the vinyl triflate or vinyl iodide derived from the ketone **6**. It was also envisaged that the 2-hydroxyfuran- 2(5*H*)-one motif in **6** could be generated from the keto ester **7** via a base-mediated ester hydrolysis, followed by an intramolecular lactolization, as demonstrated in the conversion of **C** to **D** in Figure 2.

It was expected that keto ester **7** would be derived from **8** via the IMDA reaction and that the stereochemistries at the C5 and C8 positions would be controlled by the chiral centers at the C1 and C9 positions. The carbonyl group at the C2 position (sp^2 carbon) was found to be critical to the success of the IMDA reaction. In our previous experience,[11] the application of a substrate bearing a sp^3-type carbon at this position failed to give the desired annulated product. Similar results have also been reported by Kwon[15] and MacMillan[16] in their synthetic studies toward the total synthesis of guanacastepenes. Furthermore, as well as reducing the LUMO energy of the dienophile, this carbonyl group could also promote the overlap between the diene and the dienophile (see the 3D structure of **8** in Figure 3).

For the synthesis of substrate **8**, we wanted to adopt our previously applied chemistry involving the coupling of enone **9**

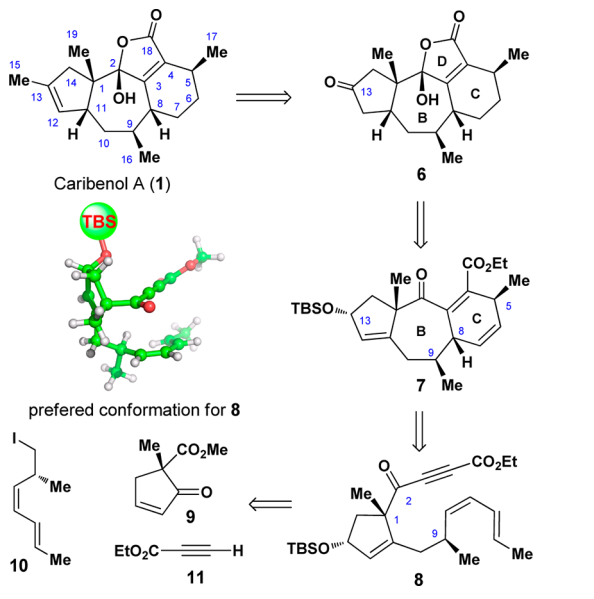

Figure 3. Retrosynthetic analysis of caribenol A (**1**).

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with iodide **10** and the subsequent acetylenation of the coupling product with **11**.[11b]

Synthesis of Precursor 8. On the basis of the planned strategy for the total synthesis of caribenol A (**1**) shown in Figure 3, the two pilot substrates **8** and **12** were proposed as the precursors of the IMDA reaction for the syntheses of the products **7** and **13** (Figure 4). We were especially interested in

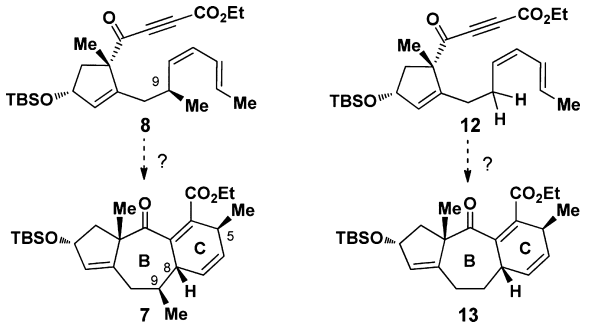
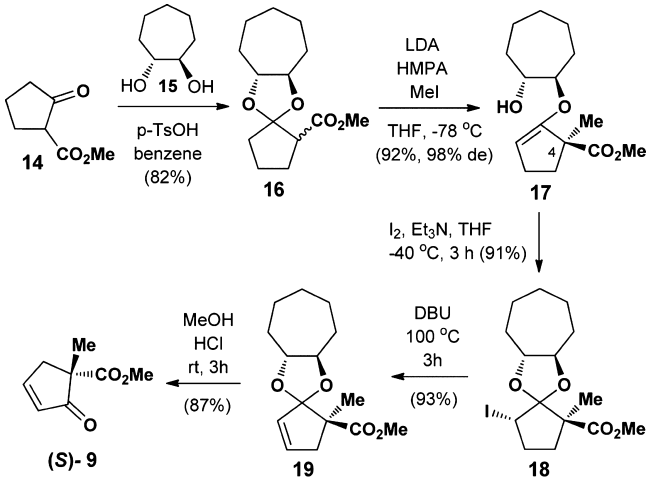


Figure 4. Proposed IMDA reactions.

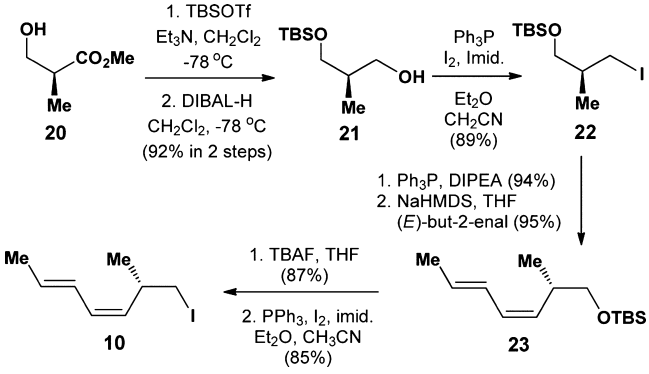
the stereochemical outcomes of these transformations, which could reveal the intrinsic relationships between the stereogenic centers at the C(5), C(8) and C(9) positions.

A convergent and flexible strategy was designed for the synthesis of **8** and **12**. Schemes 1, 2, and 3 summarize the

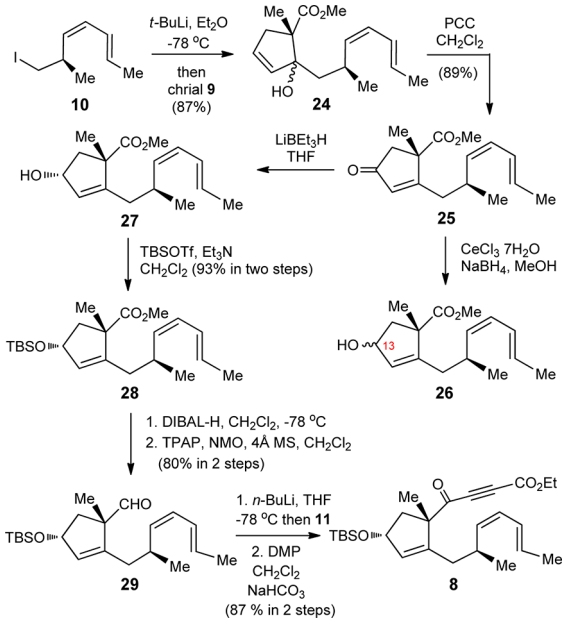
Scheme 1. Asymmetric Synthesis of (*S*)-Enone 9



Scheme 2. Synthesis of Chiral Diene 10



Scheme 3. Synthesis of Compound 8



chemistry that was used to synthesize **8**. Our investigation toward the synthesis of **8** commenced with the preparation of enone **9**,[17] where the chiral cyclic diol **15** was used as a source of chirality. Synthetically, **14** was treated with the chiral diol **15** in the presence of *p*-TsOH in benzene to give ketal **16**[17] in 82% yield. The quaternary carbon center at the C(4) position with the requisite relative disposition with respect to the chiral diol was then set by the stereoselective methylation of ketal **16** from the α-face to give the methylated product **17** in 92% yield (de >98%). The subsequent iodoketalization of the enol ether **17** with iodine (2.0 equiv) in the presence of Et_3N (1.0 equiv) proceeded in a stereoselective manner to afford **18** in 91% yield as a single diastereoisomer. Treatment of the iodoketal **18** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) for 3 h at 100 °C afforded ketal **19** in 93% yield. Subsequent treatment of the ketal **19** with HCl (10%) in MeOH afforded the chiral enone ester **9** in 87% yield, together with the recovered (*R*,*R*)-cycloheptane-1,2-diol **15** in 80% yield.

For the synthesis of the chiral iodide **10**, (*S*)-methyl 3-hydroxy-2-methylpropanoate (**20**) was first protected as its silyl ether before being reduced with diisobutylaluminium hydride (DIBAL-H) to the primary alcohol **21** in a 92% yield over the two steps. The primary alcohol in **21** was then converted to the corresponding iodide **22** in 89% yield following the treatment of the alcohol with I_2 in the presence of imidazole in a mixture of Et_2O and acetonitrile. The iodide **22** was then reacted with Ph_3P in the presence of *N*,*N*-diisopropylethylamine (DIPEA) to give the corresponding Wittig reagent, which was reacted with (*E*)-but-2-enal to afford diene **23** in a 89% yield over the two steps. Subsequent removal of the silyl ether in diene **23** provided the primary alcohol, which was converted to iodide **10** in a 74% yield over the two steps.

With both the enone **9** and the iodide **10** in hand, we then proceeded to investigate the synthesis of the precursor **8** to evaluate its behavior in the IMDA reaction (Scheme 3).

Thus, the halogen−lithium exchange reaction of **10** gave the corresponding organolithium species, which reacted with the chiral enone **9** to afford the allylic alcohol **24** in 87% yield as a pair of diastereoisomers. This allylic alcohol then underwent a

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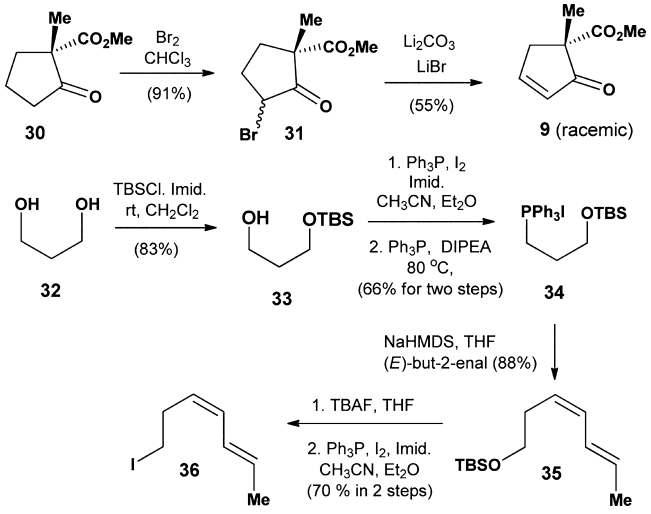
pyridinium chlorochromate (PCC)-mediated oxidative rearrangement[18] to give enone **25** in 89% yield. We initially tried to achieve the regio- and stereoselective reduction of enone **25** under Luche's reduction; however, compound **26** was formed as a pair of diastereoisomers. Following the application of considerable investigative efforts, a method was developed for the chemo- and stereoselective reduction of enone **25** using $LiBEt_3H$ as the reducing agent. This method afforded alcohol **27**, which was then exposed to a mixture of TBSOTf and Et_3N in CH_2Cl_2 to give the corresponding silyl ether **28** in 93% yield.

To construct the doubly activated acetylene **8**, compound **28** was subjected to a DIBAL-H reduction to the corresponding alcohol before being oxidized with DMP in the presence of $NaHCO_3$ in CH_2Cl_2 to give aldehyde **29** in an 80% yield over the two steps. The nucleophilic addition of (3-ethoxy-3-oxoprop-1-yn-1-yl) lithium to aldehyde **29**, followed by DMP-mediated oxidation of the resulting alcohol, afforded the keto ester **8** in an 87% yield over the two steps.

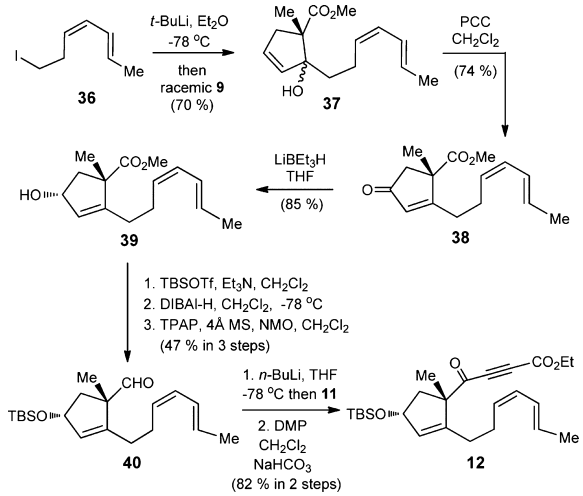
Synthesis of Precursor 12. Having established a synthetically viable asymmetric route to access keto ester **8**, our attention turned toward the synthesis of the other substrate **12** as its racemic form, because the conclusions generated from this study would be similar to those derived from its optically active counterpart. The details of the synthesis of the counterpart are listed in Schemes 4 and 5.

Scheme 4. Synthesis of Iodide 36



Our synthetic efforts began with the construction of bromide **31** in 91% yield via the bromination of the known keto ester **30** with bromine. Bromide **31** was then treated with a mixture of Li_2CO_3 and LiBr to afford enone **9** in 55% yield. For the synthesis of iodide **36**, diol **32** was selectively protected as its mono-TBS ether, and the remaining free hydroxy group in **33** was converted to its iodide, before being reacted with Ph_3P in the presence of DIPEA to give the Wittig salt **34** in a 66% yield over the two steps. The subsequent Wittig reaction proceeded smoothly following the treatment of **34** with sodium hexamethyldisilazide (NaHMDS) to give the corresponding ylide, which was reacted with (*E*)-but-2-enal to give (*Z*,*E*)-diene **35**[19] in 88% yield with a *Z* selectivity ratio greater than 5:1. The treatment of **35** with tetrabutylammonium fluoride (TBAF) in THF afforded the unprotected alcohol, which was converted to the corresponding iodide **36** in a 70% yield over the two steps.

Scheme 5. Synthesis of Precursor 12



The synthesis of compound **12** was conducted according to the same approach used for the synthesis of precursor **8**. The details of this synthesis are listed in Scheme 5.

Briefly, the halogen−-lithium exchange reaction of iodide **36** with *t*-BuLi gave the corresponding organolithium species, which was reacted with the racemic enone **9** generated above to give the allylic alcohol **37** in 70% yield as a pair of diastereoisomers at the newly generated carbon center. This mixture was then subjected to a PCC-mediated oxidative rearrangement to give enone **38** as a pair of enantiomers in 74% yield. The reduction of **38** with $LiBEt_3H$ proceeded in a regio- and stereoselective manner to afford the allylic alcohol **39** in 85% yield. The secondary hydroxyl group in **39** was protected as the silyl ether, before being subjected to a sequential reduction/oxidation process to give aldehyde **40** in a 47% yield over the three steps. The nucleophilic addition of (3-ethoxy-3-oxoprop-1-yn-1-yl)lithium to the aldehyde **40**, followed by oxidation of the resultant alcohol with DMP, provided the keto ester **12** in an 82% yield over the two steps.

IMDA Reaction of Substrates 8 and 12. With compounds **8** and **12** in hand, our attention turned to evaluating their performances in the IMDA reaction. Initially, the IMDA reactions of **8** and **12** were conducted in the presence of several different Lewis acids, such as $MgBr_2$, $ZnCl_2$, TMSOTf, $AlCl_3$, $MeAlCl_2$, and $BF_3{\cdot}Et_2O$, but none of these conditions afforded the desired products **7** and **13** (Figure 4), respectively. The reaction was then evaluated at different temperature ranging from ambient temperature to 120 °C. Unfortunately, however, no reaction was observed at temperatures below 100 °C, whereas the use of higher temperatures led to the formation of complex product mixtures. These failures were attributed to the instability of the 1,3-butadiene moieties in both substrates, which could not tolerate to harsh reaction conditions employed.

Despite these initial disappointing results, we persevered with our investigation and subsequently established that a catalytic amount of 2,6-di-*tert*-butyl-4-methylphenol (BHT) was capable of effecting the desired IMDA reaction, leading to **7** as a single diastereoisomer in 92% yield (Scheme 6).

It was assumed that the role of BHT in the reaction related to its ability to inhibit the polymerization of the diene, which was probably initiated by trace amounts of peroxides or oxygen.[20] Thus, using this manoeuver, as well as establishing

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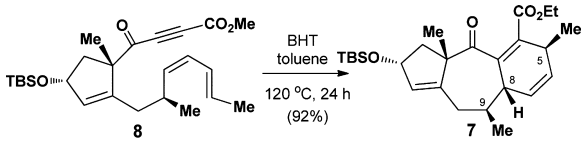
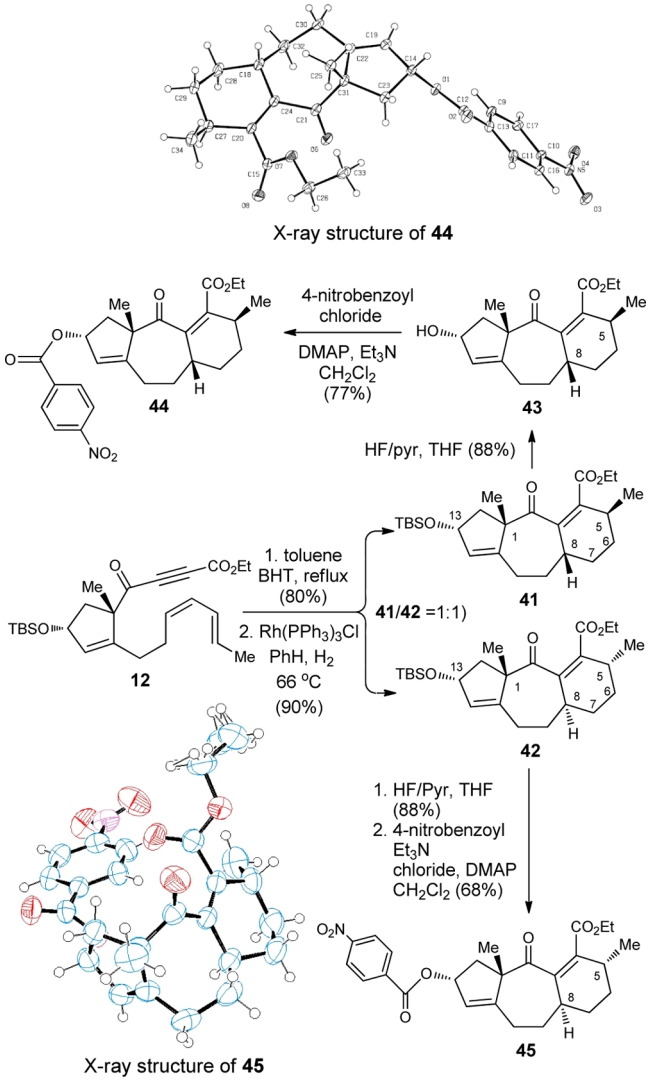
Scheme 6. Synthesis of the [5-7-6] Tricylic Product 7



the formation of the [5−7−6] tricylic core, the relative stereochemistries of the chiral centers at the C(5), C(8) and C(9) positions were secured. The stereochemistry of **7** was later confirmed by an X-ray single-crystal diffraction study of its derivative.

We then proceeded to evaluate the IMDA reaction of **12** (Scheme 7). Thus, under the identical conditions to those

Scheme 7. IMDA Reaction of Substrate 12



listed in Scheme 6, substrate **12** proceeded smoothly through the IMDA reaction to afford an inseparable mixture (1:1), which was then subjected to a regioselective hydrogenation with the Wilkinson catalyst under balloon pressure of H_2 in benzene to afford **41** and **42** in a combined yield of 72%; the ratio for **41** and **42** was 1:1.

To confirm their stereochemical integrities, **41** and **42** were converted to the corresponding *p*-nitrobenzoate products **44** and **45**, respectively, via a sequential desilylation/benzoylation process. In the event, **41** was treated with HF/Pyr, and the resultant alcohol **43** was reacted with 4-nitrobenzoyl chloride in the presence of Et_3N and a catalytic amount of 4-dimethylaminopyridine (DMAP) to give the ester **44** in 77% yield. Subsequent crystallographic analysis of **44** indicated that the relative stereochemistry in **43** was set up in a manner similar to that of the natural product.

In a similar manner, the alcohol derived from **42** was treated with 4-nitrobenzoyl chloride in the presence of Et_3N and a catalytic amount of DMAP to give the desired product **45** in 68% yield. The stereochemistry of this compound was also confirmed by X-ray crystallographic analysis.

Computational experiments were conducted to account for the formation of equal amounts of the products **41a** and **42a** from substrate **12**. As illustrated in Figure 5, the calculated

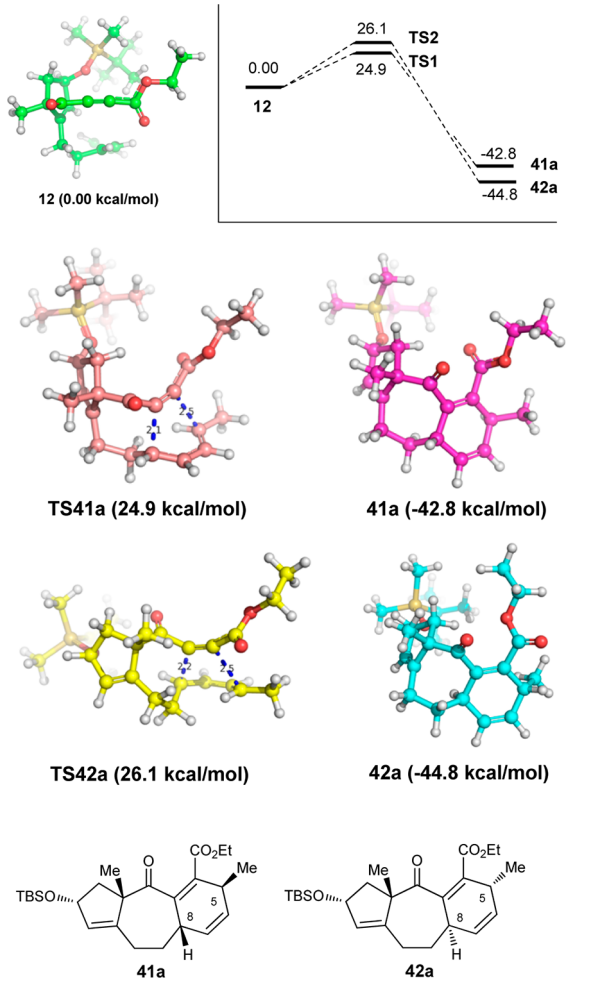


Figure 5. Computational experiments for the formation of equal amount of products **41a** and **42a** via the IMDA reaction of **12**.

values[21] for the transition state energies of products **41a** and **42a** were 24.9 and 26.1 kcal/mol, respectively (see Supporting Information for detail), indicating that the IMDA reaction of substrate **12** was proceeding through two competitive pathways to afford equal amounts of the products **41a** and **42a**.

Having confirmed the feasibility of the IMDA reaction for the construction of the [5−7−6] tricyclic core of caribenol A (**1**) based on the IMDA reaction of **8** to give **7**, we initiated our total synthesis of caribenol A according to our planned strategy

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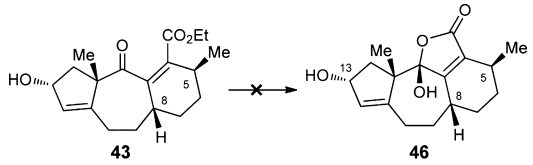
illustrated in Figure 3. To achieve the proposed chemistry, substrate **43** was selected as a model to test the proposed chemistry. In the event, substrate **43** treated with base under various basic conditions (such as the water solution of THF in the presence of LiOH, NaOH, and KOH, or the water solution of dioxane in the presence of LiOH, NaOH, and KOH) for the formation of 2-hydroxyfuran-2(5*H*)-one motif; however, no desired product **46** could be observed (Scheme 8).

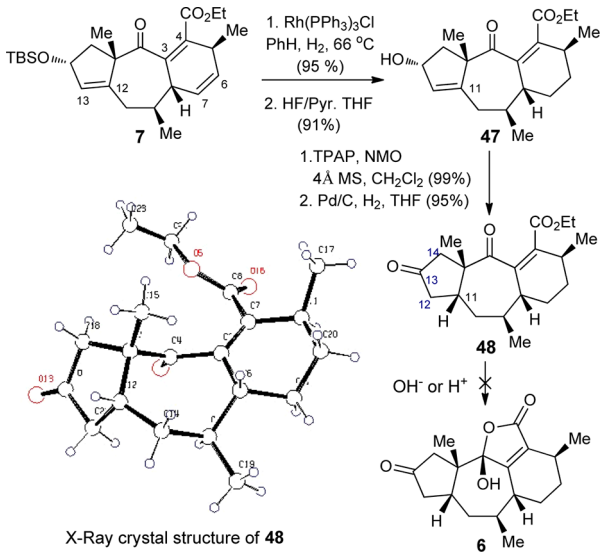
Scheme 8. Attempted Formation of the 2-Hydroxyfuran-2(5*H*)-one Motif in 46



On the basis of this result, it was necessary to find an alternative pathway to complete our total synthesis. It was envisaged that the double bonds at the C(6)−C(7) and C(12)−C(13) positions in **7** could be selectively saturated under Pd-catalyzed hydrogenation conditions in the presence of the double bond at the C(3)−C(4) position, based on the level of the steric hindrance surrounding this bond.

To achieve the selective hydrogenation, **7** was subjected to a variety of catalysts, including Pd/C, $Pd/BaSO_4$, and $Pd/CaCO_3$, for the proposed chemistry; however, desired product was not obtained. We then designed a stepwise approach to achieve the goal. In the event, **7** was hydrogenated in the presence of $Rh(PPh_3)_3Cl$[22] to regioselectively removed its C(6)−C(7) double bond and provided the desired product **47** in 86% yield following the removal of its silyl group with HF/Pyr (Scheme 9).

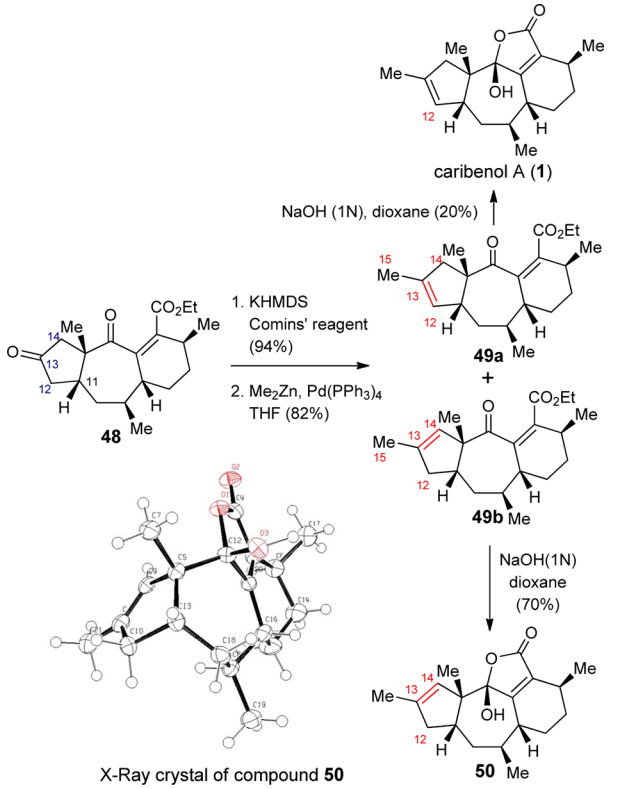
Scheme 9. Synthesis of Intermediate 48



We next searched for a method capable of facilitating the regio- and stereoselective saturation of the C(12)−C(13) double bond in **47**. It was envisaged that this transformation could be realized via a stepwise synthetic transformation involving the initial oxidation of the secondary alcohol in **47** to the corresponding enone, followed by the reduction of the double bond. To this end, the allylic alcohol in **47** was converted to the corresponding enone via a Ley oxidation,[23] and the resulting enone was then subjected to the Pd/C-catalyzed hydrogenation to give **48** as a single isomer in 94% yield. The structure of ketone **48** was confirmed by X-ray crystallographic analysis. However, when we attempted to construct the 2-hydroxyfuran-2(5*H*)-one motif in compound **6**, no desired product could be observed under either basic or acidic conditions.

We then decided to install the C-15 methyl group first and then generate the 2-hydroxyfuran- 2(5*H*)-one motif. To this end, ketone **48** was initially reacted with Comins' reagent[24] followed by a Pd-catalyzed Negishi coupling reaction[25] with $ZnMe_2$ to afford products **49a** and **49b** as a pair of regioisomers in a ratio of 1:2 (Scheme 10). Unfortunately, compound **49a**,

Scheme 10. Synthesis of Intermediate 50



which contained the desired regiochemistry, was found to be the minor product. Although the regiochemical outcome of this transformation was disappointing, we were particularly interested in the stereochemical outcomes of these products for the base-mediated formation of their 2-hydroxyfuran-2(5*H*)-one motifs, which could provide useful information for the development of the next generation of total synthesis.

With this in mind, **49a** was treated with a mixture of LiOH in THF/H_2O under the same conditions as those used for the conversion of **C** to **D** in Figure 2; however, the starting material was recovered, and no desired product was formed. On the other hand, when NaOH was employed as a base in dioxane as the solvent, caribenol A (**1**) was obtained in 20% yield, and the reaction was accompanied by significant decomposition of both the product and the starting material **49a** (Scheme 10).

In contrast, substrate **49b** was transformed into the corresponding annulated product **50** in 70% yield. The

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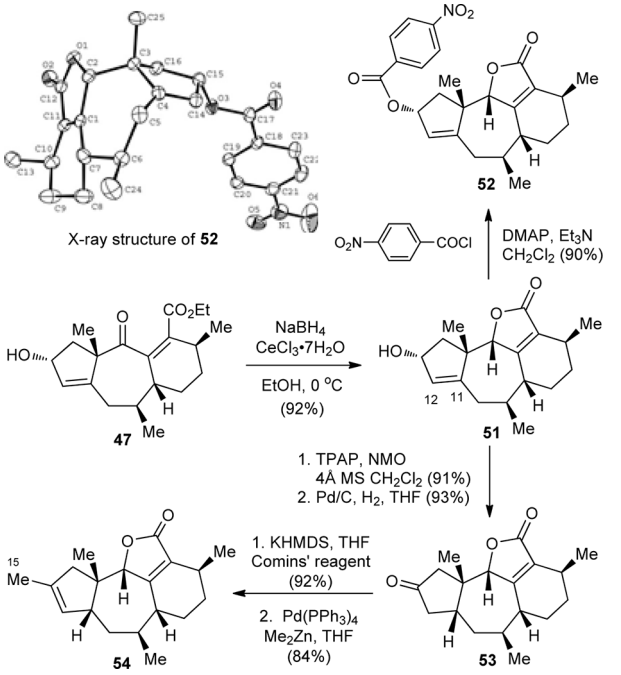
structure of **50** was confirmed by X-ray crystallographic analysis. Although a total synthesis of caribenol A could be achieved using the chemistry described above, the issues associated with the formation of the enolate of **48**, as well as the low yield obtained for the formation of the 2-hydroxyfuran-2(5*H*)-one motif in caribenol A (**1**), were considered to be particularly limiting to this approach, and the decision was taken to search for a better pathway for this total synthesis.

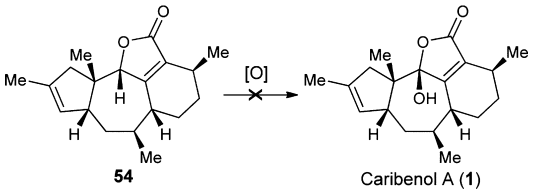
It was envisaged that the desired regioselective enolization could be realized if **53** (Scheme 11) was employed as the substrate for the reaction, because its natural product-like conformation could facilitate the formation of the enol triflate with the desired regiochemistry from compound **53**. To test this hypothesis, the ketone group in **47** was stereoselectively reduced with $NaBH_4$ in the presence of $CeCl_3$ to give the corresponding hydroxyl group, which underwent an intramolecular lactonization *in situ* to afford lactone **51** with the required furan-2(5*H*)-one moiety in 92% yield. To confirm its structure, lactone **51** was converted to the corresponding *p*-nitrobenzoate **52**, and its structure was confirmed by X-ray crystallographic analysis. To prepare lactone **54**, the hydroxyl group in **51** was oxidized to the corresponding ketone using a TPAP/NMO oxidation, before being hydrogenated to saturate its C(11)−C(12) double bond to afford **53** in 85% yield. Pleasingly, the treatment of compound **53** with KHMDS in THF followed by Comins' reagent provided its corresponding enol triflate in 92% yield as a single isomer, indicating the influence of the substrate formation on the enolization of the ketone. Thus, under the conditions of the Negishi coupling reaction, the enol triflate made above was successfully coupled with Me_2Zn to afford the desired product **54** in 84% yield.

We then proceeded to investigate the final stage of the total synthesis of the target molecule, and to assess the lability of the proton at the C(2) position, we attempted to carry out its direct oxidation. Although a variety of different oxidative methods[26] (such as LDA/O_2, LiOAc/H_2O/O_2, (^{t}BuO)$_2$/acetone) were screened for this particular transformation, the target molecule caribenol A was not formed (Scheme 12).

Scheme 11. Regioselective Synthesis of 54



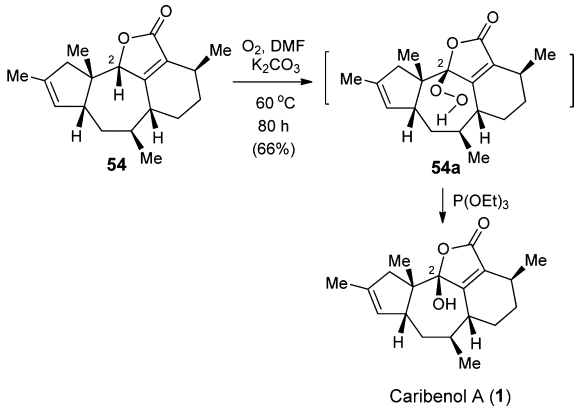
Scheme 12. Oxidation of 54



The failure of this reaction was attributed to the steric congestion provided by the adjacent quaternary carbon in **54**, which prevented the oxidizing agents from accessing the C(2) position.

Completion of the Total Synthesis. To achieve the total synthesis of caribenol A (**1**), we investigated the application of a strategy originally developed by Corey and Ensley,[27] which involved the sequential formation-reduction of the 2-hydroperoxy-furan-2(5*H*)-one of **54a** via the treatment of compound **54** with O_2 in the presence of P(OEt)$_3$ under basic conditions (Scheme 13). Pleasingly, this synthetic transformation successfully allowed for the formation of the 2-hydroperoxyfuran-2(5*H*)-one motif, and caribenol A (**1**) was consequently obtained in a 66% yield.

Scheme 13. Completion of the Total Synthesis



The synthesized caribenol A (**1**) was shown to be identical to the natural product caribenol A on the basis of a comparison of its ^{1}H and ^{13}C NMR data with those of the natural material.[2] The optical rotation of the synthesized material was also consistent with that of the reported natural product ($[\alpha]^{20}_D$ = +47 (*c* 0.4, $CHCl_3$); lit. $[\alpha]^{20}_D$ = +40.0° (*c* 1.0, $CHCl_3$)).[2]

CONCLUSION

The asymmetric total synthesis of caribenol A (**1**) has been completed within 17 steps using an IMDA reaction to construct the 5−7−6 tricyclic core of caribenol A and a biomimetic oxidation to incorporate the hydroxyl group into its unique butenoide moiety as the key steps. The developed chemistry could be applicable for the syntheses of the caribenol-type of natural product-like compounds, which could be utilized for exploring their structure−activity relationship against *Mycobacterium tuberculosis* (H37Rv).

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EXPERIMENTAL SECTION

General Methods. Unless noted, all commercial reagents and solvents were used without further purification. All reactions were carried out under a nitrogen atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. All the chemicals were purchased commercially and used without further purification. Anhydrous THF and diethyl ether were distilled from sodium benzophenone, and dichloromethane was distilled from calcium hydride. Yields refer to chromatographically, unless otherwise stated.

Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad.

3-((*tert*-Butyldimethylsilyl)oxy)propan-1-ol (33). To a solution of propane-1,3-diol **32** (30.4 g, 400 mmol) in anhydrous THF (400 mL) were sequentially added Et_3N (66.6 mL, 480 mmol) and TBSCl (60.3 g, 400 mmol) at 0 °C, and the mixture was first warmed to room temperature and then stirred at the same temperature for 2 h. The reaction was quenched by addition of a saturated solution of NH_4Cl (200 mL) and then extracted with Et_2O (3 × 200 mL). The combined organic phase was dried with anhydrous sodium sulfate. The solvent was removed under vacuum, and the residue was purified by a flash column chromatography on silica gel (hexane/ethyl acetate = 10/1) to give **33** (62.0 g) in 83% yield as a colorless oil. R_f = 0.7 (hexane/EtOAc = 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79−3.83 (m, 2H), 3.75−3.77 (m, 2H), 2.76 (s, 1H), 1.65−1.81 (m, 2H), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, CDCl3) δ 62.7, 62.2, 34.2, 25.8, 18.1, −5.6. HRMS (ESI) calcd for $C_9H_{22}O_2SiNa$ $[M + Na]^+$ 213.1287, found 213.1280.

Synthesis of *tert*-Butyl((3*Z*,5*E*)-hepta-3,5-dien-1-yloxy)-dimethylsilane (35). To a solution of **33** (80.0 g, 421 mmol) and PPh_3 (121.3 g, 463 mmol) in CH_3CN (160 mL) and Et_2O (256 mL) were added I_2 (112.3 g, 442 mmol) and imidazole (37.0 g, 547 mmol) sequentially at 0 °C, and the mixture was stirred at the same temperature for 10 min. The mixture was then warmed to 25 °C and stirred for 1 h. The reaction was worked up by removal of solvent under vacuum, and the brown residue was washed with pentane (300 mL × 5). The extracts were filtered through a silica gel pad and washed with pentane. The filtrate was concentrated under vacuum to give an iodide as colorless oil (110 g, 87% yield). This material was utilized in the next step without further purification. R_f = 0.7 (hexane/EtOAc = 10/1).

To a 1000 mL flask were added the iodide made above, DIPEA (71.0 mL, 400 mmol) and PPh_3 (157.2 g, 600 mmol), and the mixture was then heated at 80 °C for 24 h under nitrogen atmosphere. After cooling to room temperature, the reaction mixture was washed with Et_2O (3 × 300 mL), and the yellowish solid Wittig salt was recovered in yield 76% (170.0 g as white powder).

To a solution of the Wittig salt (40.0 g, 71.2 mmol) made above in THF (250 mL) was added NaHMDS (39.2 mL, 78.3 mmol) in a dropwise manner, and the mixture was warmed to 0 °C and stirred for 30 min After cooling back to −78 °C, crontonaldehyde (7.0 mL, 85.4 mmol) was added to the above reaction mixture, and the formed mixture was stirred at the same temperature for 30 min. The mixture was then warmed to room temperature and stirred for an additional 3 h. The reaction was quenched with aqueous saturated NH_4Cl (300 mL), and the mixture was then extracted with Et_2O (3 × 200 mL). The combined organic phase was dried with anhydrous sodium sulfate. The solvent was removed *in vacuum*, and the residue was purified by a flash column chromatography on silica gel (hexane/ethyl acetate, 100/1) to give **35** (14.1 g, 88% yield). R_f = 0.9 (hexane/EtOAc = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.24−6.44 (m, 1H), 6.02 (t, J = 10.9 Hz, 1H), 5.66−5.79 (m, 1H), 5.30 (dt, J = 10.5, 7.6 Hz, 1H), 3.63 (t, J = 7.0 Hz, 2H), 2.40 (d, J = 6.9 Hz, 2H), 1.77 (dd, J = 6.7, 0.6 Hz, 3H), 0.90 (s, 9H), 0.06 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 130.3, 129.5, 127.1, 125.2, 62.9, 31.5, 25.9, 18.3, 18.3, −5.3.

Synthesis of (2*E*,4*Z*)-7-Iodohepta-2,4-diene (36). To a solution of compound **35** (16.0 g, 70.8 mmol) in THF (200 mL) was added TBAF (22.3 g, 85.2 mmol) at 0 °C, and the mixture was the stirred at room temperature for 3 h. The reaction was quenched by addition of aqueous saturated NH_4Cl (150 mL), the mixture was extracted with Et_2O (3 × 150 mL), and the combined organic phase was dried with anhydrous sodium sulfate. The solvent was removed under vacuum, and the residue was purified by a flash column chromatography on silica gel (hexane/ethyl acetate, 10/1) to give **35a** (7.0 g, 89% yield) as a colorless oil. R_f = 0.4 (hexane/EtOAc = 10/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.37 − 6.28 (m, 1H), 6.08 (t, J = 11.0 Hz, 1H), 5.71 (dq, J = 13.7, 6.7 Hz, 1H), 5.27 (dd, J = 18.3, 7.8 Hz, 1H), 3.72 − 3.57 (m, 2H), 2.42 (q, J = 6.8 Hz, 2H), 1.89 (s, 1H), 1.76 (d, J = 6.7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 131.5, 130.4, 126.6, 124.5, 62.2, 31.1, 18.2.

To a solution of alcohol **35a** (7.0 g, 62.5 mmol) in CH_3CN (100 mL) and Et_2O (160 mL) were sequentially added PPh_3 (19.7 g, 75.2 mmol), I_2 (20.6 g, 81.3 mmol) and imidazole (6.4 g, 93.8 mmol) at 0 °C, and the mixture was then warmed to room temperature and stirred at the same temperature for 2 h. The solvent was removed under vacuum, and the residue was then extracted with pentane. The extracts were filtered through a silica gel pad, and the filtrate was concentrated to give iodide **36** (11.0 g) yield 79% as colorless oil. R_f = 0.9 (hexane/EtOAc = 10/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.27 (dd, J = 13.7, 12.3 Hz, 1H), 6.07 (t, J = 11.0 Hz, 1H), 5.80 − 5.70 (m, 1H), 5.22 (dd, J = 18.1, 7.5 Hz, 1H), 3.15 (t, J = 7.4 Hz, 2H), 2.75 (q, J = 7.4 Hz, 2H), 1.78 (d, J = 6.7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 131.0, 130.8, 126.9, 126.5, 31.9, 18.3, 4.9.

Synthesis of Compound 38. To a solution of iodide **36** (2.0 g, 9.01 mmol) in anhydrous Et_2O (60 mL) was added *t*-BuLi (1.3 M, 10.1 mL) at −78 °C, and the resultant mixture was stirred at the same temperature for 30 min. To this solution was added the racemic enone **9** (0.925 g, 6.01 mmol) in Et_2O (30 mL) slowly at −78 °C, and the mixture was further stirred at the same temperature for 3 h. The reaction was quenched by addition of a saturated solution of NH_4Cl (60 mL), and mixture was extracted with Et_2O (3 × 50 mL). The combined organic phase was dried with anhydrous sodium sulfate. The solvent was removed under vacuum, and the residue was purified by a flash column chromatography on silica gel(hexane/ethyl acetate, 10/1) to give **37** (1.05 g) as a pair of diastereoisomers in 70% yield as colorless oil. R_f = 0.4 (hexane/EtOAc = 5/1). HRMS (ESI) calcd for $C_{15}H_{22}NaO_3$ $[M + Na]^+$ 273.1467, found 273.1454.

To a solution of compound **37** (1.0 g, 4 mmol) in CH_2Cl_2 (100 mL) was added PCC (2.15 g, 10 mmol) at room temperature, and the mixture was stirred at the same temperature for 3 h. The reaction was quenched by addition of hexane (200 mL), and mixture was filtered off a silica gel pad. The filtrate was concentrated and the residue was purified by a flash column chromatography (hexane/ethyl acetate, 10/1) on silica gel to give **38** (0.74 g, 74% yield) as a colorless oil. R_f = 0.4 (hexane/EtOAc = 5/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.18−6.23 (m, 1H), 5.98 (s, 1H), 5.90−5.97 (m, 1H), 5.63−5.72 (m, 1H), 5.13−5.20 (m, 1H), 3.65 (s, 3H), 2.86 (d, J = 18.3 Hz, 1H), 2.35−2.44 (m, 3H), 2.26−2.32 (m, 1H), 2.23 (d, J = 18.3 Hz, 1H), 1.73 (d, J = 6.8 Hz, 3H), 1.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.0, 181.6, 173.9, 130.5, 129.9, 129.4, 126.5, 126.3, 53.1, 52.5, 48.0, 29.0, 24.9, 22.4, 18.3. HRMS (ESI) calcd for $C_{15}H_{22}O_3$ $[M + H]^+$ 249.1491, found 249.1493. IR ν_{max} 3468, 2954, 1734, 1615, 1450, 1266, 1196, 985 cm^{-1}.

Synthesis of Compound 39. To a solution of compound **38** (940 mg, 3.8 mmol) in anhydrous THF (50 mL) was added $LiHBEt_3$ (1.0 M, 7.58 mL, 7.58 mmol) at −78 °C, and the mixture was stirred at same temperature for 30 min. The reaction was quenched by addiiton of a saturated solution of NH_4Cl (50 mL) and then extracted with Et_2O (3 × 50 mL). The combined organic phase was dried with anhydrous sodium sulfate. The solvent was removed under vacuum, and the residue was purified through column chromatography (hexane/ethyl acetate = 10/1) to give **39** (800 mg, 85% yield) as a colorless oil. R_f = 0.3 (hexane/EtOAc = 5/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ6.23−6.40 (m, 1H), 5.95 (t, J = 10.9 Hz, 1H), 5.74 (d, J = 1.6 Hz, 1H), 5.65−5.71 (m, 1H), 5.20−5.28 (m, 1H), 4.64 (s, 1H), 3.71 (s, 3H), 2.81 (s, 1H), 2.31−2.38 (m, 2H), 2.27 (d, J = 14.2 Hz, 1H), 2.06−2.15 (m, 1H), 1.92−2.04 (m, 2H), 1.77 (d, J = 6.6 Hz, 3H), 1.30 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.5, 150.7,

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129.8, 129.7, 129.2, 128.1, 126.8, 74.9, 55.9, 52.5, 47.4, 27.3, 25.7, 21.9, 18.2. HRMS (ESI) calcd for $C_{15}H_{22}O_3Na$ $[M + Na]^+$ 273.1467, found 273.1454. IR ν_{max} 3431, 2954, 1734, 1431, 1263, 1111, 802 cm.$^{-1}$.

Synthesis of Compound 39a. To a solution of allylic alchol **39** (360 mg, 1.44 mmol) in CH_2Cl_2 (100 mL) was added Et_3N (0.4 mL, 2.88 mmol) at −78 °C, followed by addition of TBSOTf (0.5 mL, 2.16 mmol) at −78 °C in a dropwise manner. After being stirred at −78 °C for 2 h, the reaction was quenched by addition of a saturated solution of sodium chloride (50 mL), followed by extraction with Et_2O (3 × 50 mL). The combined organic phase was dried over anhydrous sodium sulfate. The solvent was removed under vacuum, and the residue was purified through a flash column chromatography on silica gel (hexane/ethyl acetate = 50/1) to give **39a** (390 mg, 74% yield) as a colorless oil. R_f = 0.9 (hexane/EtOAc = 5/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.28−6.35 (m, 1H), 5.93 (t, J = 10.9 Hz, 1H), 5.63−5.70 (m, 1H), 5.48 (d, J = 1.7 Hz, 1H),5.18−5.31 (m, 1H), 4.79−4.89 (m, 1H), 3.66 (s, 3H), 2.28−2.45 (m, 2H), 2.23−2.28 (m, 1H), 2.09−2.14 (m, 1H), 2.03−2.09 (m, 1H), 1.93−2.03 (m, 1H), 1.76 (d, J = 6.7 Hz, 3H), 1.25 (s, 3H), 0.88 (s, 9H), 0.06 (d, J = 3.2 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.1, 149.2, 129.4, 128.9, 128.6, 128.6, 126.9, 75.5, 55.5, 51.8, 47.7, 27.4, 25.9, 25.7, 23.1, 18.2, −4.6, −4.6. HRMS (ESI) calcd for $C_{21}H_{36}O_3SiNa$ $[M + Na]^+$ 387.2331, found 387.2319. IR ν_{max} 2960, 1737, 1257, 1089, 833, 755 cm^{-1}.

Synthesis of Compound 39b. To a solution of compound **39a** (440 mg, 1.21 mmol) in anhydrous CH_2Cl_2 (80 mL) was added DIBAL (1.0 M, 3.63 mL, 3.63 mmol) at −78 °C. After being stirred for 2 h at same temperature, the reaction was quenched by addition of a saturated solution of potassium tartrate hydrate (150 mL), and the mixture was then stirred at room temperature until clear solution was obtained. The mixture was extracted with Et_2O (3 × 50 mL), the combined organic layer was dried over anhydrous Na_2SO_4, the solvent was then removed under vacuum, and the residue was purified by a flash chromatography on silica gel (hexane/ethyl acetate = 10/1) to give **39b** (345 mg, 85% yield) as a colorless oil. R_f = 0.65(hexane/EtOAc = 5/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.28−6.36 (m, 1H), 5.93 (t, J = 10.9 Hz, 1H), 5.62−5.67 (m, 1H), 5.48 (d, J = 1.6 Hz, 1H), 5.24−5.29 (m, 1H), 4.62 (d, J = 5.5 Hz, 1H), 3.48−3.52 (m, 1H), 3.39 (t, J = 9.5 Hz, 1H), 3.32−3.34 (m, 1H), 2.38 (q, J = 7.4 Hz, 2H), 1.97−2.07 (m, 2H), 1.92−1.96 (m, 2H), 1.75 (d, J = 5.8 Hz, 3H), 0.97 (s, 3H), 0.87 (s, 9H), 0.07 (d, J = 3.4 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.4, 129.3, 128.8, 128.8, 126.9, 126.3, 73.9, 67.5, 51.4, 47.5, 26.1, 25.7, 25.6, 22.2, 18.2, 17.9, −4.6, −4.9. HRMS (ESI) calcd for $C_{20}H_{37}O_2Si$ $[M + H]^+$ 337.2563, found 337.2562. IR ν_{max} 3444, 2930, 1726, 1261, 1038, 796 cm^{-1}.

Synthesis of Compound 40. To a solution of primary alcohol **39b** (0.80 g, 2.29 mmol) in dry CH_2Cl_2 (60 mL) were added 4 Å MS (400 mg), NMO (653 mg, 5.58 mmol) and TPAP (47 mg, 0.114 mmol) sequentially at room temperature, and the mixture was stirred at the same temperature for 1 h. The reaction was worked up by filtration of the reaction mixture through a silica gel pad, and the filtrate was concentrated under vacuum. The residue was further purified by a flash column chromatography on silica gel (hexane/ethyl acetate = 100/1) to give **40** (580 mg, 73% yield) as a colorless oil. R_f = 0.9 (hexane/EtOAc = 5/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.52 (s, 1H), 6.29 (dd, J = 13.8, 12.2 Hz, 1H), 5.94 (t, J = 10.9 Hz, 1H), 5.71 (d, J = 1.7 Hz, 1H), 5.70 − 5.63 (m, 1H), 5.21 (dt, J = 10.6, 7.4 Hz, 1H), 4.86 (d, J = 6.4 Hz, 1H), 2.33 (dd, J = 15.8, 8.5 Hz, 2H), 2.05 (dt, J = 4.6, 2.3 Hz, 1H), 2.02 − 1.93 (m, 2H), 1.90 (t, J = 7.8 Hz, 1H), 1.77 (d, J = 6.7 Hz, 3H), 1.13 (s, 3H), 0.88 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.7, 147.7, 131.3, 129.7, 129.1, 128.0, 126.7, 75.2, 61.2, 44.8, 27.2, 25.8, 25.5, 18.2, 18.0, 17.7, −4.5, −4.7. HRMS (ESI) calcd for $C_{20}H_{34}O_2SiNa$ $[M + Na]^+$ 357.2226, found 357.2206. IR ν_{max} 2960, 2936, 1725, 1354, 1249, 836, 775 cm^{-1}.

Synthesis of Compound 12. To a solution of ethyl propiolate **11** (0.255 mL, 2.52 mmol) in dry THF (30 mL) was added *n*-BuLi (2.4*M*, 1.05 mL, 2.52 mmol) at −78 °C, and the mixture was then stirred at the same temperature for for 30 min. To this solution was slowly added a solution of aldehyde **40** (280 mg, 0.84 mmol) in THF (10 mL) at the same temperature, and the formed mixture was stirred at the same temperature for an additional 30 min. The reaction was quenched by addition of a saturated solution of NH_4Cl (60 mL), and the mixture was extracted with Et_2O (3 × 50 mL). The combined organic phase was dried over anhydrous sodium sulfate. The solvent was concentrated under vacuum, and the residue was purified by a flash column chromatography on silica gel (hexane/ethyl acetate = 10/1) to give a pair of isomers of propargyl alcohols as a colorless oil, which could be used directly for next step.

To a solution of DMP (1.07g, 2.52 mmol) and $NaHCO_3$ (0.56 g, 6.72 mmol) in CH_2Cl_2 (50 mL) was added a solution of the propargyl alcohol made above in CH_2Cl_2 (10 mL) slowly, and the mixture was then stirred at room temperature for 2 h. The reaction was worked up by addition of hexane (200 mL) with vigorous stirring. The formed mixture was filtered through a silica gel pad, and the filtrate was concentrated under vacuum. The residue was further purified by a flash chromatography on silica gel (hexane/ethyl acetate = 50/1) to give **12** (298 mg, 82% in two steps) as a colorless oil. It is worthwhile to mention that this product is very sensitive to organic base. R_f = 0.9 (hexane/EtOAc = 5/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.30−6.38 (m, 1H), 5.95 (t, J = 10.9 Hz, 1H), 5.66−5.79 (m, 1H), 5.63 (d, J = 1.7 Hz, 1H), 5.23−5.29 (m, 1H), 4.76−5.00 (m, 1H), 4.27 (q, J = 7.2 Hz, 2H),δ 2.36−2.45 (m, 2H), 2.33 (dd, J = 13.7, 4.4 Hz, 1H)., 2.11 (dd, J = 13.7, 7.0 Hz, 1H), 2.03−2.07 (m, 1H), 1.94−2.00 (m, 1H), 1.78 (d, J = 6.5 Hz, 3H), 1.32 (t, J = 7.1 Hz, 3H), 1.25 (s, 3H), 0.88 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.4, 152.2, 147.5, 131.4, 129.7, 129.2, 128.2, 126.9, 80.8, 79.9, 75.6, 62.7, 62.5, 46.7, 31.4, 27.5, 25.9, 25.8, 20.9, 18.2, 18.1, 13.9, −4.5, −4.6. HRMS (ESI) calcd for $C_{25}H_{38}NaO_4Si$ $[M + Na]^+$ 453.2437, found 453.2432. IR ν_{max} 2936, 1725, 1682, 1242, 836, 775 cm^{-1}.

Synthesis of Compound 7. To a solution of compound **8** (200 mg) in toluene (50 mL) was added BHT (20 mg), and the mixture was degassed with nitrogen for 3 times and then stirred under refluxing condition for 24 h. After cooling to room temperature, the solvent was removed under vacuum, and the residue was purified by a flash column chromatography on silica gel (hexane/ethyl acetate = 40/1) to give **7** (184 mg, 92% yield) as a colorless oil. R_f = 0.4 (hexane/EtOAc = 20/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.77−5.80 (m, 1 H), 5.59−5.63 (m, 1 H), 5.50 (s, 1 H), 4.91−4.94 (m, 1 H), 4.11−4.18 (m, 2 H) 3.19−3.21 (m, 1 H), 2.52−2.58 (m, 1 H), 2.31 (dd, J = 13.5 Hz, 2.5 Hz, 1 H), 2.03 (dd, J = 12.0 Hz, 6.0 Hz, 1 H), 1.82 (dd, J = 12.0 Hz, 7.5 Hz, 1 H), 1.68−1.73 (m, 1 H), 1.55−1.57 (m, 1 H), 1.27 (t, J = 7.5 Hz, 3 H), 1.18 (s, 3 H), 1.12 (d, J = 7.0 Hz, 3 H), 1.08 (d, J = 7.0 Hz, 3 H), 0.89 (s, 9 H), 0.05 (d, J = 7.0 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.5, 167.1, 148.5, 148.3, 132.1, 130.8, 130.0, 125.1, 76.4, 60.9, 60.5, 47.8, 45.5, 44.3, 36.3, 30.3, 21.3, 20.7, 20.3, 18.2, 14.0. HRMS (ESI) calcd for $C_{26}H_{40}O_4SiNa$ $[M + Na]^+$ 467.2594, found 467.2587.

Syntheses of Compunds 42b and 43. To a solution of **12** (25 mg) in toluene (20 mL) was added BHT (5 mg), and the mixture was degassed with nitrogen for 3 times and then stirred under refluxing for 24 h. After being cooled to room temperature, the solvent was removed under vacuum, and the residue was further purified a flash chromatography on silica gel (hexane/ethyl acetate = 20/1) to give compounds **41a** and **42a** (20 mg, 80% yield) as a pair of inseparable isomers.

To a solution of the mixture of **41a** and **42a** (20 mg, 0.047 mmol) in benzene (5 mL) was added $Rh(PPh_3)_3Cl$ (8.6 mg, 0.0094 mmol), and the mixture was degassed with hydrogen for 3 times and then stirred at 70 °C for 3 h. After being cooled to room temperature, the solvent was removed under vacuum, and the residue was purified by a flash chromatography on silica gel (hexane/ethyl acetate = 50/1) to give **41** and **42** (18 mg, 90% yield) as a pair of inseparable isomers.

To a solution of isomers **41** and **42** (20 mg, 0.46 mmol) in anhydrous THF (5 mL) was added HF/Py (0.04 mL, 0.46 mmol), and the mixture was then stirred at room temperature for 3 h. The reaction was quenched by addition of a saturated solution of $NaHCO_3$ (aq) (5 mL), and the mixture was extracted with ethyl acetate (3 × 5 mL). The combined organic phase was dried over anhydrous sodium sulfate. The solvent was removed under vacuum, and the residue was purified

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by a flash chromatography on silica gel (hexane/ethyl acetate = 10/1) to give **42b** (6.5 mg. 44% yield) and **43** (6.5 mg, 44% yield).

Compound **42b**: R_f = 0.5 (hexane/EtOAc = 2/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.65 (s, 1H), 4.70−4.73 (m, 1H), 4.12−4.21 (m, 2H), 2.70−2.77 (m, 1H), 2.44−2.52 (m, 2H), 2.27−2.41 (m, 3H), 2.13 (dd, J = 14.1 Hz, 7.0 Hz, 1H), 1.90−1.99 (m, 1H), 1.72−1.78 (m, 2H), 1.62−1.70 (m, 3H), 1.30−1.47 (m, 3H), 1.22−1.28 (m, 6H), 1.06 (J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.2, 168.8, 149.3, 149.2, 137.8, 132.4, 74.8, 61.0, 60.9, 46.9, 36.2, 31.1, 30.29, 29.8, 29.3, 26.3, 21.7, 20.0, 14.0. HRMS (ESI) calcd fo $C_{19}H_{26}NaO_4$ $[M + Na]^+$ 341.1729, found 341.1721. IR ν_{max} 2966, 1260, 1092, 1025, 802 cm^{-1}.

Compound **43**: R_f = 0.5 (hexane/EtOAc = 2/1); R_f = 0.5 (hexane/EtOAc = 2/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.56 (s, 1H), 4.55 (s, 1H), 4.07−4.18 (m, 2H), 2.98 (s, 1H), 2.65−2.73 (m, 1H), 2.53−2.59 (m, 1H), 2.50 (s, 1H), 2.38 (d, J = 14.2 Hz, 1H), 2.20 (t, J = 13.2 Hz, 1H), 2.00−2.05 (m, 1H), 1.97 (dd, J = 14.2 Hz, 7.2 Hz, 1H), 1.75−1.83 (m, 2H), 1.48 (s, 3H), 1.37 (d, J = 13.0 Hz, 2H), 1.29 (s, 1H), 1.25 (t, J = 7.2 Hz, 3H), 1.03 (d, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.4, 169.2, 150.5, 147.2, 139.1, 130.8, 73.9, 62.3, 60.9, 46.2, 38.1, 34.7, 31.8, 31.0, 30.9, 29.1, 21.5, 19.7, 13.9. HRMS (ESI) calcd for $C_{19}H_{26}O_4Na$ $[M + Na]^+$ 341.1729, found 341.1724. IR ν_{max} 2963, 2920, 1259, 1096, 1026, 801 cm^{-1}.

Synthesis of Compound 44. To a solution of compound **43** (15 mg, 0.047 mmol), Et_3N (13 μL, 0.094 mmol) and DMAP (3 mg, 0.024 mmol) in dry CH_2Cl_2 (4 mL) was added 4-nitrobenzoyl chloride (13 mg, 0.071 mmol), and the mixture was stirred at room temperature for 30 min. The solvent was removed under vacuum, and the residue was purified by a flash chromatography (hexane/ethyl acetate = 5/1) to give **44** (17 mg, 77% yield) as a light yellow solid. R_f = 0.6 (hexane/EtOAc = 2/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ8.20−8.34 (m, 4H), 5.87−5.89 (m, 1H), 5.60 (s, 1H), 4.08−4.14 (m, 2H), 2.90 (dd, J = 14.3 Hz, 3.7 Hz, 1H), 2.62−2.78 (m, 2H), 2.46 (s, 1H), 2.21−2.31 (m, 1H), 2.16 (dd, J = 14.3 Hz, 7.7 Hz, 1H), 1.93−2.07 (m, 1H), 1.75−1.86 (m, 2H), 1.50 (s, 3H), 1.28−1.47 (m, 3H), 1.22 (t, J = 7.2 Hz, 3H), 1.04 (d, J = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.8, 168.2, 164.6, 153.3, 150.5, 147.9, 138.5, 135.9, 130.8, 125.0, 123.5, 79.2, 61.5, 60.9, 41.3, 34.7, 31.8, 30.6, 29.7, 27.6, 26.7, 24.9, 24.7, 20.4, 14.0. HRMS (ESI) calcd for $C_{26}H_{29}O_7NNa$ $[M + Na]^+$ 490.1842, found 490.1837.

Synthesis of Compound 45. To a solution of alcohol **42b** (15 mg, 0.047 mmol), DMAP (3 mg) and Et_3N (12 μL, 0.084 mmol) in dry CH_2Cl_2 (4 mL) was added 4-nitrobenzoyl chloride (13 mg, 0.071 mmol), and the mixture was stirred at room temperature for 30 min. The solvent was removed under vacuum, and the residue was purified by a flash chromatography on silica gel (hexane/ethyl acetate = 5/1) to give **45** (15 mg, 68% yield) as a light yellow solid. R_f = 0.6 (hexane/EtOAc = 2/1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15−8.31 (m, 4H), 5.89 (d, J = 3.8 Hz, 1H), 5.81 (s, 1H), 4.15 (qd, J = 7.1, 1.7 Hz, 2H), 2.69−2.77 (m, 1H), 2.65 (dd, J = 14.7 Hz, 3.5 Hz, 1H), 2.48−2.59 (m, 1H), 2.39−2.45 (m, 1H), 2.34 (dd, J = 14.7 Hz, 7.3 Hz, 2H), 1.92−2.03 (m, 1H), 1.66−1.73 (m, 2H), 1.48−1.57 (m, 1H), 1.40 (d, J = 12.7 Hz, 1H), 1.33 (s, 3H), 1.23−1.29 (m, 1H), 1.21 (t, J = 7.1 Hz, 3H), 0.98 (d, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.2, 169.6, 164.6, 153.1, 150.6, 145.8, 141.6, 136.0, 130.8, 127.6, 123.4, 79.5, 60.9, 59.9, 43.7, 36.1, 32.4, 31.2, 30.5, 29.3, 26.9, 23.0, 19.9, 13.9. HRMS (ESI) calcd for $C_{26}H_{29}O_7NNa$ $[M + Na]^+$ 490.1842, found 490.1835.

Synthesis of Compound 47. To a solution of compound 7 (163 mg, 0.35 mmol) in benzene (10 mL) was added $Rh(PPh_3)_3Cl$ (34.2 mg, 0.037 mmol), and the mixture was degassed with hydrogen for 3 times. The reaction mixture was then stirred at 70 °C for 3 h. The solvent was removed under vacuum, and the residue was purified by a flash column chromatography on silica gel (hexane/ethyl acetate = 5/1) to give **47a** (155 mg, 95%) as a colorless oil. R_f = 0.4 (hexane/EtOAc=20/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.44 (s, 1 H), 4.89 (dd, J = 7.0 Hz, 6.0 Hz, 1 H), 4.14 (m, 2 H), 2.75−2.78 (m, 1 H), 2.34 (dd, J = 13.0 Hz, 2.0 Hz, 1 H), 1.87−2.01 (m, 3 H), 1.58−1.77 (m, 5 H), 1.18−1.24 (m, 1 H), 1.23 (t, J = 7.5 Hz, 3 H), 1.18 (s, 3 H), 1.01 (d, J = 7.0 Hz, 3 H), 0.98 (d, J = 6.5 Hz, 3 H), 0.86 (s, 9 H), 0.03 (d, J = 5.5 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.3, 167.3, 152.0, 148.6, 133.1, 131.8, 76.3, 60.8, 60.3, 47.4, 45.2, 39.4, 36.8, 28.8, 25.9, 25.8, 21.6, 20.7, 19.7, 18.2, 14.0, −4.3, −4.4. HRMS (ESI) calcd for $C_{26}H_{42}O_4SiNa$ $[M + Na]^+$ 469.2750, found 469.2751.

To a solution of compound **47a** (163 mg, 0.35 mmol) in THF (10 mL) was added HF/Py (0.27 mL, 3.7 mmol), and the mixture was stirred at room temperature for 3 h. The reaction was quenched by addition of a saturated solution of $NaHCO_3$ (20 mL) and extracted with Et_2O (3 × 20 mL). The combined organic phase was dried with anhydrous sodium sulfate. The solvent was removed *in vacuo*, and the residue was purified by a flash column chromatography on silica gel (hexane/ethyl acetate = 5/1) to give **47** (105 mg, 91% yield) as a colorless oil. R_f = 0.4 (hexane/EtOAc = 5/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.59 (s, 1 H), 4.60 (m, 1 H), 4.09−4.18 (m, 2 H), 2.85 (d, J = 10.0 Hz, 1 H), 2.65−2.70 (m, 1 H), 2.45 (dd, J = 12.5 Hz, 2.5 Hz, 1 H), 2.31 (dd, J = 12.5 Hz, 2.5 Hz, 1 H), 2.17−2.18 (m, 1 H), 1.94−2.05 (m, 3 H), 1.83−1.91 (m, 1 H), 1.14 (s, 3 H), 1.48−1.50 (m, 2 H), 1.25 (t, J = 7.0 Hz, 3 H), 1.05 (d, J = 7.0 Hz, 3 H), 1.01 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.4, 169.1, 149.7, 149.6, 137.3, 131.5, 74.2, 61.5, 61.1, 46.6, 43.6, 38.7, 30.9, 29.1, 25.0, 22.2, 21.1, 20.1, 14.0. HRMS (ESI) calcd for $C_{20}H_{28}O_4Na$ $[M + Na]^+$ 355.1885, found 355.1879.

Synthesis of Compound 48. To a solution of alcohol **47** (100 mg, 0.30 mmol) in dry CH_2Cl_2 (10 mL) were added molecular sieves (400 mg), NMO (88 mg, 0.75 mmol) and TPAP (10 mg, 0.03 mmol), and the resultant mixture was stirred at room temperature for 2 h. Then the mixture was filtered through a silica gel pad, and the filtrate was concentrated under vacuum. The residue was purified by a flash chromatography on silica gel (hexane/ethyl acetate=5/1) to give **47b** (99 mg, in 99% yield) as a colorless oil. R_f = 0.5 (hexane/EtOAc = 2/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86 (s, 1H), 4.08 (q, J = 7.2 Hz, 2H), 3.04 (d, J = 18.4 Hz, 1H), 2.75 (dd, J = 13.6, 2.3 Hz, 1H), 2.60−2.70 (m, 1H), 2.23−2.30 (m, 1H), 2.12−2.16 (m, 2H), 1.71−1.85 (m, 3H), 1.60−1.66 (m, 1H), 1.52 (s, 3H), 1.26−1.33 (m, 1H), 1.19 (t, J = 7.1 Hz, 3H), 1.06 (d, J = 6.7 Hz, 3H), 1.01 (d, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, CDCl3) δ 207.1, 207.0, 180.9, 167.9, 149.6, 135.9, 130.6, 61.1, 58.6, 47.7, 44.4, 39.6, 38.6, 30.0, 27.6, 23.5, 22.9, 21.3, 19.9, 13.9. HRMS (ESI) calcd for $C_{20}H_{27}O_4$ $[M + H]^+$ 331.1909, found 331.1909. IR ν_{max} 2966, 1746, 1263, 1046, 802 cm^{-1}.

To a solution of **47b** (100 mg, 0.3 mmol) in anhydrous THF (20 mL) was added Pd/C (10 wt %, 31.5 mg, 0.03 mmol), and the resultant mixture was degassed with hydrogen for 3 times. The mixture was stirred under hydrogen for 2 h. The mixture was filtered off through a silica gel pad, and the filtrate was concentrated under vacuum. The residue was purified by a flash chromatography (hexane/ethyl acetate = 5/1) to give **48** (95 mg, 95% yield) as a colorless oil. R_f = 0.4 (hexane/EtOAc = 5/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.10−4.20 (m, 2H), 2.82 (t, J = 14.4 Hz, 1H), 2.65−2.68 (m, 1H), 2.36−2.44 (m, 1H), 2.28−2.36 (m, 1H), 2.19−2.25 (m, 1H), 2.12 (dd, J = 18.3 Hz, 9.2 Hz, 1H), 1.95−2.05 (m, 3H), 1.77−1.85 (m, 1H), 1.68−1.75 (m, 1H), 1.56−1.61 (m, 1H), 1.50 (s, 3H), 1.26 (t, J = 7.1 Hz, 2H), 1.21−1.25 (m, 3H), 1.03 (d, J = 6.9 Hz, 3H), 0.98 (d, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.3, 209.3, 168.8, 147.9, 138.0, 60.8, 54.7, 49.2, 43.1, 42.5, 42.4, 39.5, 31.9, 31.4, 30.8, 27.0, 22.4, 21.1, 19.9, 14.0. HRMS (ESI) calcd for $C_{20}H_{28}O_4Na$ $[M + Na]^+$ 355.1885, found 355.1883. IR ν_{max} 2960, 2923, 1746, 1260, 1095, 1043, 802 cm^{-1}.

Syntheses of Compounds 49a and 49b. To a solution of ketone **48** (205 mg, 0.62 mmol) in THF was added KHMDS (1.0 M, 1.24 mmol) at −78 °C, and the misture was stirred at the same temperature for 30 min. To this solution was added a solution of Comins' reagent (0.484 g, 1.24 mmol) in THF (10 mL) at −78 °C in a dropwise fashion, and the mixture was stirred at the same temperature for additional 2 h. The reaction was quenched by addition of a saturated solution of NH_4Cl (25 mL), and the mixture was extracted with ether (3 × 20 mL). The combined organic extracts were washed with brine, and dried with Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by a flash chromatography on silica gel (hexane/ethyl acetate = 10/1) to give a mixture of **48a** and **48b** (268 mg, 94%).

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To a degassed compound **48a** and **48b** (310 mg, 0.67 mmol) and $Pd(PPh_3)_4$ (77 mg, 0.067 mmol) in dry THF (30 mL) was added dimethyl zinc (1.0 M in hexane, 0.80 mL) at room temperature in a dropwise manner, and the mixture was stirred at same temperature for 1 h. The reaction was quenched by addition of a saturated solution of NH_4Cl (20 mL), and the mixture was extracted with Et_2O (3 × 50 mL). The combined organic extracts were dried over anhydrous sodium sulfate. The solvent was removed under vacuum, and the residue was purified by a flash chromatography on silica gel (hexane/ethyl acetate = 20/1) to give **49a** and **49b** (180 mg, 82% yield) in a ratio of 1:2).

Compound **49a**: R_f = 0.8 (hexane/EtOAc = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.95 (s, 1H), 4.12−4.25 (m, 2H), 3.12 (d, J = 16.2 Hz, 1H), 2.51−2.69 (m, 2H), 2.30 (d, J = 22.5 Hz, 1H), 1.86−1.98 (m, 1H), 1.78−1.85 (m, 2H), 1.70 (d, J = 14.8 Hz, 3H), 1.36−1.56 (m, 4H), 1.30−1.34 (m, 4H), 1.20−1.29 (m, 3H), 1.05 (d, J = 7.0 Hz, 3H), 1.00 (d, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.2, 169.9, 158.2, 137.8, 125.4, 119.9, 60.7, 57.1, 51.1, 46.4, 41.1, 38.5, 33.8, 31.5, 28.6, 26.1, 25.1, 21.0, 19.1, 16.4, 14.0. HRMS (ESI) calcd for $C_{21}H_{30}O_3Na$ $[M + Na]^+$ 353.2093, found 353.2086. IR ν_{max} 2927, 1725, 1451, 1248, 1059 cm^{-1}.

Compound **49b**: R_f = 0.8 (hexane/EtOAc = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.82 (s, 1H), 4.01−4.17 (m, 2H), 2.67 (d, J = 5.2 Hz, 1H), 2.17−2.30 (m, 3H), 1.90−2.04 (m, 1H), 1.68−1.77 (m, 4H), 1.60−1.67 (m, 3H), 1.29−1.47 (m, 3H), 1.24 (t, J = 7.1 Hz, 3H), 1.20 (s, 3H), 0.97 (d, J = 1.6 Hz, 3H), 0.96 (d, J = 2.5 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.7, 167.9, 148.2, 141.9, 133.7, 129.1, 64.6, 60.6, 46.2, 42.9, 40.5, 35.6, 32.5, 29.0, 25.7, 22.4, 21.9, 21.4, 19.1, 16.7, 13.8. HRMS (ESI) calcd for $C_{21}H_{31}O_3$ $[M + H]^+$ 331.2273, found 331.2268. IR ν_{max} 2966, 2929, 1718, 1694, 1257, 1095, 1028, 807 cm^{-1}.

Synthesis of Compound 50. To a solution of compound **49b** (50 mg, 0.15 mmol) in dioxane (16 mL) was added NaOH (1.0 N, 8 mL), and the resultant mixture was stirred at 70 °C for overnight. After cooling to room temperature, the reaction was quenched by addition of a saturated solution of NH_4Cl solution (20 mL) and then extracted with Et_2O (3 × 30 mL). The combined organic extracts were dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by preparative thin layer chromatography (hexane/ethyl acetate = 5/1) to give **50** (32 mg, 70%) as white solid. R_f = 0.4 (hexane/EtOAc = 5/1); ^{1}H NMR (400 MHz, C6D6) δ 4.98 (s, 1H), 2.79 (s, 1H), 2.52−2.58 (m, 1H), 2.16−2.28 (m, 2H), 2.05−2.13 (m, 1H), 1.65−1.81 (m, 2H), 1.61 (d, J = 17.0 Hz, 1H), 1.46−1.54 (m, 2H), 1.41−1.44 (m, 3H), 1.38 (t, J = 6.4 Hz, 6H), 1.16−1.26 (m, 2H), 0.83−1.01 (m, 2H), 0.77 (t, J = 6.1 Hz, 3H); ^{13}C NMR (100 MHz, C6D6) δ 169.5, 163.9, 139.4, 132.2, 130.1, 108.7, 57.0, 44.3, 43.2, 42.9, 41.0, 31.7, 30.6, 28.2, 27.6, 24.1, 22.8, 18.3, 15.8. HRMS (ESI) calcd. for $C_{19}H_{26}O_3Na$ $[M + Na]^+$ 325.1780, found 325.1773. IR ν_{max} 2966, 1731, 1459, 1260, 1098, 1074, 1016, 799 cm^{-1}.

Caribenol A (1). To a solution of compound **49a** (7.0 mg, 0.021 mmol) in dioxane (2 mL) was added a solution of NaOH (1.0 N, 2 mL), and the resultant mixture was stirred at 70 °C for overnight. After cooling to room temperature, the reaction was quenched by addition of a saturated solution of NH_4Cl (20 mL) and then extracted with Et_2O (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by a preparative thin layer chromatography (hexane/ethyl acetate = 5/1) to give caribenol A (**1**) (1.3 mg, 20%) as white solid. Rf = 0.4 (hexane/EtOAc = 5/1); $[\alpha]^{20}_D$ = +47 (c 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ4.89 (s, 1H), 3.10 (s, 1H), 2.44 (s, 1H), 2.19−2.30 (m, 1H), 2.07−2.16 (m, 1H), 2.02 (d, J = 16.7 Hz, 1H), 1.73−1.84 (m, 2H), 1.62−1.73 (m, 1H), 1.51 (s, 3H), 1.47 (s, 3H), 1.40 (d, J = 6.9 Hz, 3H), 1.22−1.29 (m, 2H), 0.99−1.12 (m, 1H), 0.81−0.98 (m, 2H), 0.75 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 169.7, 163.5, 137.5, 132.7, 127.1, 109.6, 53.7, 49.3, 46.9, 43.0, 39.3, 31.8, 30.8, 28.4, 27.8, 25.4, 22.0, 18.5, 16.3. HRMS (ESI) calcd for $C_{19}H_{27}O_3$ $[M + H]^+$ 303.1960, found 303.1959.

Synthesis of Compound 51. To a solution of **47** (95 mg, 0.29 mmol) and $CeCl_3{\cdot}7H_2O$ (160 mg, 0.43 mmol) in ethanol (10 mL) was added $NaBH_4$ (110 mg, 2.9 mmol) in one portion at 0 °C, and the mixture was then stirred at the same temperature for 30 min. The reaction was quenched by addition of a saturated NH_4Cl solution (20 mL) and then extracted with Et_2O (3 × 50 mL). The combined organic extracts were dried over anhydrous sodium sulfate. The solvent was removed under vacuum, and the residue was purified by a flash column chromatography on silica gel (hexane/ethyl acetate = 2/1) to give **51** (76 mg) in 92% yield as a colorless oil. R_f = 0.3 (hexane/EtOAc = 2/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.41 (d, J = 0.7 Hz, 1H), 4.76−4.78 (m, 1H), 4.69 (s, 1 H), 2.52−2.54 (m, 1H), 2.07−2.30 (m, 1H), 2.03−2.07 (m, 2H), 1.77−1.90 (m, 3H), 1.59−1.63 (m, 3H), 1.92−1.51 (m, 1H), 1.33−1.38 (m, 1H), 1.28 (s, 3H), 1.19 (d, J = 7.1 Hz, 3H), 1.11 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7, 163.8, 152.2, 132.3, 129.8, 87.9, 74.1, 51.2, 44.6, 43.5, 42.0, 35.5, 28.7, 27.0, 26.4, 24.8, 21.6, 17.7. HRMS (ESI) calcd for $C_{18}H_{24}O_3Na$ $[M + Na]^+$ 311.1623, found 311.1624.

Synthesis of Compound 52. To a solution of compound **51** (18 mg, 0.063 mmol) and DMAP (2 mg) and Et_3N (17 μL, 0.123 mmol) in dry CH_2Cl_2 (4 mL) was added 4-nitrobenzoyl chloride (17 mg, 0.094 mmol), and the mixture was stirred at room temperature for 30 min. The solvent was removed under vacuum, and the residue was purified by a flash chromatography on silica gel (hexane/ethyl acetate = 5/1) to give **12** (24.5 mg, 90% yield) as white solids. R_f = 0.3 (hexane/EtOAc = 5/1); R_f = 0.6 (hexane/EtOAc = 2/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15−8.34 (m, 4H), 5.83 (t, J = 6.2 Hz, 1H), 5.55 (s, 1H), 4.76 (s, 1H), 2.43−2.62 (m, 2H), 2.19 (dd, J = 13.3, 6.6 Hz, 1H), 2.08−2.14 (m, 1H), 1.90−2.02 (m, 1H), 1.80−1.87 (m, 3H), 1.65−1.70 (m, 1H), 1.50−1.55 (m, 1H), 1.39 (s, 3H), 1.23−1.29 (m, 1H), 1.19 (d, J = 7.1 Hz, 3H), 1.12 (d, J = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 164.7, 163.8, 155.0, 150.4, 135.7, 132.1, 130.9, 125.2, 123.4, 87.6, 78.6, 50.9, 42.9, 41.3, 40.7, 35.6, 28.0, 27.6, 26.2, 24.2, 21.4, 17.8. HRMS (ESI) calcd for $C_{25}H_{27}NO_6Na$ $[M + H]^+$ 460.1736, found 460.1731. IR ν_{max} 2960, 2931, 1747, 1705, 1522, 1270, 1103, 722 cm^{-1}.

Synthesis of Compound 53. To a solution of compound **51** (34 mg, 0.12 mmol) and 4 Å MS (50 mg) in dry CH_2Cl_2 (10 mL) were added NMO (21 mg, 0.18 mmol) and TPAP (2.4 mg, 0.007 mmol) at 20 °C, and the mixture was stirred at the same temperature for 1.5 h. The reaction was worked up by addition of silica gel (100 mg), and the formed slurry was dried under vacuum. The residue was purified by a flash chromatography on silica gel (hexane/ethyl acetate = 2/1) to give an enone **51a** (31 mg, 91% yield) as a colorless oil. R_f = 0.4 (hexane/EtOAc = 2/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.76 (s, 1H), 4.85−4.86 (m, 1H), 2.73 (dd, J = 12.6 Hz, 1.2 Hz, 1H), 2.47−2.48 (m, 1H), 2.27 (d, J = 4.5 Hz, 1H), 2.09−2.24 (m, 2H), 1.90−1.93 (m, 1H), 1.71−1.79 (m, 1H), 1.53−1.55 (m, 2H), 1.49 (s, 3H), 1.29−1.37 (m, 1H), 1.20−1.27 (m, 1H), 1.20 (d, J = 6.5 Hz, 3H), 1.18 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.9, 184.1, 171.9, 162.8, 133.0, 129.2, 85.3, 49.8, 45.6, 43.6, 43.0, 36.9, 29.2, 28.7, 26.6, 25.2, 21.9, 17.4. HRMS (ESI) calcd for $C_{18}H_{23}O_3$ $[M + H]^+$ 287.1647, found 287.1693.

To a solution of the enone **51a** (42 mg, 0.15 mmol) in dry THF (4 mL) was added Pd/C (10 wt %, 15 mg, 0.015 mmol), and the resultant mixture was degassed with hydrogen for 3 times and then stirred at room temperature for 2 h. The reaction mixture was filtered off through a silica gel pad, and the filtrate was concentrated under vacuum. The residue was purified by a flash chromatography on silica gel (hexane/ethyl acetate = 5/1) to give **53** (39 mg, 93% yield) as a colorless oil. R_f = 0.2 (hexane/EtOAc = 5/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.97 (s, 1H), 2.77−2.83 (m, 1H), 2.40−2.47 (m, 2 H), 1.96−2.10 (m, 4H), 1.85−1.89 (m, 2H), 1.54 (dd, J = 15.3 Hz, 3.6 Hz, 1H), 1.39 (s, 3 H), 1.25 (d, J = 6.9 Hz, 3H), 1.18−1.28 (m, 4H), 1.18 (d, J = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 217.2, 171.8, 163.0, 132.6, 86.6, 45.9, 45.6, 44.9, 44.3, 41.2, 40.6, 32.3, 31.0, 29.4, 28.8, 27.8, 22.6, 18.2. HRMS (ESI) calcd for $C_{18}H_{24}O_3Na$ $[M + Na]^+$ 311.1623, found 311.1623.

Synthesis of Compound 54. To a solution of compound **53** (15 mg, 0.052 mmol) in dry THF (5 mL) was added KHMDS (115 μL, 0.057 mmol) at −78 °C, and the mixture was stirred at the same temperature for 30 min. To this solution was added Comins' reagent (*N*-(5-chloro-2-pyridyl)triflimide) (23 mg, 0.057 mmol) in dry THF

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(2 mL) −78 °C, and the mixture was then stirred at the same temperature for additional 3 h. The reaction was quenched by addition of a saturated solution of NH_4Cl (5 mL), and the mixture was extracted with Et_2O (3 × 10 mL). The combined extracts were dried over sodium sulfate. The solvent was removed under vacuum, and the residue was purified by a flash chromatography on silica gel (hexane/ethyl acetate = 10/1) to give its corresponding triflate **53a** (20 mg, 92% yield) as colorless oil. R_f = 0.4 (hexane/EtOAc = 5/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.42 (s, 1 H), 4.80 (s, 1 H), 2.68 (t, J = 3.4 Hz, 1H), 2.48−2.50 (m, 1H), 2.21−2.26 (m, 1H), 2.10−2.13 (m, 1H), 2.01−2.04 (m, 3H), 1.75−1.77 (m, 1H), 1.56−1.61 (m, 2H), 1.43 (s, 3H), 1.28 (d, J = 6.9 Hz, 3H), 1.18−1.24 (m, 2H), 1.00 (d, J = 1.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 163.3, 147.0, 132.6, 119.5, 86.0, 49.7, 45.3, 44.5, 38.8, 38.0, 32.3, 30.8, 29.8, 28.8, 27.8, 22.0, 18.1. HRMS (ESI) calcd for $C_{19}H_{24}O_5F_3S$ $[M + H]^+$ 421.1297, found 421.1294.

To a degassed solution of the enol triflate (12 mg, 0.028 mmol) and $Pd(PPh_3)_4$ (3.3 mg, 0.0028 mmol) in dry THF (4 mL) was added dimethyl zinc in toluene (1.2 M, 71 μL, 0.085 mmol) in a dropwise manner at room temperature and the mixture was stirred at the same temperature for 1 h. The reaction was quenched by addition of a saturated solution of NH_4Cl (5 mL), and the mixture was extracted with Et_2O (3 × 10 mL). The combined extracts were dried over sodium sulfate. The solvent was removed under vacuum and the residue was purified by a flash chromatography on silica gel (hexane/ethyl acetate =20/1) to give **54** (6.7 mg, 84% yield). R_f = 0.6 (hexane/EtOAc = 40/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.01−5.02 (m, 1 H), 4.81−4.82 (m, 1H), 2.46−2.51 (m, 2H), 2.06−2.09 (m, 1H), 1.94−2.00 (m, 2H),1.86−1.93 (m, 1H), 1.60−1.69 (m, 5H), 1,49 (dd, J = 15.0 Hz, 3.2 Hz, 1H), 1.36−1.42 (m, 1H), 1.30 (s, 3H), 1.26 (d, J = 9.3 Hz, 3H), 1.10−1.20 (m, 2H), 0.94 (d, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.6, 164.7, 138.4, 131.5, 126.0, 87.6, 54.0, 46.0, 45.5, 44.3, 39.1, 32.5, 30.6, 30.1, 28.9, 27.7, 22.3, 18.3, 16.6. HRMS (ESI) calcd for $C_{19}H_{27}O_2$ $[M + H]^+$ 287.2011, found 287.2006.

Total Synthesis of Caribenol A (1). To a solution of compound **54** (5 mg) in dry DMF (1.0 mL) was added K_2CO_3 (20 mg), and the mixture was degassed with oxygen. To this solution was added triethyl phosphite (8 μL), and the mixture was stirred at 60 °C for 80 h. After cooling to room temperature, the reaction was quenched by addition of water (3 mL), and the mixture was extracted with Et_2O (3 × 10 mL). Combined extracts were dried over sodium sulfate. The solvent was removed *in vacuum*, and the residue was purified by preparative thin layer chromatography (hexane/ethyl acetate = 10/1) to give caribenol A (**1**) (3.3 mg) in 66% yield, together with the recovered starting material (1.4 mg). The reaction temperature is critical to the desired reaction, and higher temperature will lead to the decomposition of caribenol A. R_f = 0.4 (hexane/EtOAc = 5/1); $[\alpha]^{20}_D$ = +47 (*c* 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.89 (s, 1H), 3.10 (s, 1H), 2.44 (s, 1H), 2.19−2.30 (m, 1H), 2.07−2.16 (m, 1H), 2.02 (d, J = 16.7 Hz, 1H), 1.73−1.84 (m, 2H), 1.62−1.73 (m, 1H), 1.50−1.60 (m, 1H), 1.51 (s, 3H), 1.47 (s, 3H), 1.40 (d, J = 6.9 Hz, 3H), 1.22−1.29 (m, 1H), 0.99−1.12 (m, 1H), 0.81−0.98 (m, 2H), 0.75 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 169.7, 163.5, 137.5, 132.7, 127.1, 109.6, 53.7, 49.3, 46.9, 43.0, 39.3, 31.8, 30.8, 28.4, 27.8, 25.4, 22.0, 18.5, 16.3. HRMS (ESI) calcd for $C_{19}H_{27}O_3$ $[M + H]^+$ 303.1960, found 303.1959.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H NMR and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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