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Exploration of Ring Rearrangement Metathesis Reaction: A General and Flexible Approach for the Rapid Construction [5,*n*]-Fused Bicyclic Systems en Route to Linear Triquinanes

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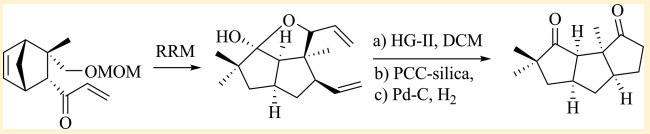
Supporting Information

ABSTRACT: Structurally diverse [5,*n*] bicyclic systems with *cis* ring junction stereochemistry were accessed readily through RRM (ring rearrangement metathesis) reaction of properly functionalized [2.2.1]norbornene skeletons. Several bicyclic enones, ketones, alcohols, and ethers acted as the substrates and yielded the respective linearly fused [5,*n*] bicyclic systems stereoselectively after the RRM reaction. Such [5,5]bicyclic enone scaffolds were then synthetically manipulated to core structural analogue of naturally occurring liner triquinane hirsutene having *cis-syn-cis* stereochemistry.



INTRODUCTION

Polyquinane is a generic name given to carbocyclic frameworks composed of fused five-membered rings, and it constitutes an important class of sesquiterpenoids. Since their discovery, polyquinane natural products have generated a worldwide interest among organic chemists due to their unique and fascinating molecular architecture and promising biological activities.[1] Among polyquinanes the natural products having triquinane framework are more abundant and nearly 80 such natural products are known in literature and they are frequently encountered among plants, marine and microbial sources.[2] Triquinane natural products containing all three types of C-11 tricyclopentanoid skeleton **1** (linearly fused five membered rings), **2** (angularly fused five membered rings), and **3** (five membered rings fused in propellane fashion) as the core ring systems are reported in literature (Figure 1).[3] The class of linearly fused tricyclopentanoids is further divided depending upon the mode of fusion of the third cyclopentane ring. The two isomers **4** and **5** are termed as *cis-anti-cis* and *cis-syn-cis*, respectively. It has been shown that **4** is only marginally more stable than the hindered folded form **5**. Among the two stereoisomeric C_{11} linear triquinanes, *cis-anti-cis* isomer **4** has received relatively greater attention because it constitutes the basic carbocyclic framework of a large number of naturally occurring triquinane sesquiterpenoids such as hirsutic acid (**6**), hirsutene (**7**), capnellene (**8**), and ceratopicanol (**9**) (Figure 1). The significant interest of the scientific community in the chemistry of polycyclopentanoids is partly due to its novel and intricate carbocyclic network of natural triquinanes and also because of diverse biological properties exhibited by some members. For example, hirsutic acid (**6**) exhibits antibiotic properties, whereas capnellene (**8**) and its congeners inhibit growth of microorganisms along with prevention of larval settlement.

Triquinanes are always regarded as "important" synthetic targets, which is evident from numerous elegant syntheses documented in literature. Hirsutene (**7**) has been one of the most popular targets among triquinanes because of its unique cyclic framework. Numerous synthetic strategies have been developed or adopted for the rapid assembly of the linearly fused five-membered rings present in hirsutene.[4−6]

Some of the exploited strategies are highlighted in the Figure 2, such as Curran's radical cyclization strategy,[4d] Wender's arene−olefin meta photocycloaddition,[4e] Paquette's annulation,[4c] Hudlicky's [4 + 1] diene−carbene annulation, and [3 + 2] dienolate−enone annulation,[4f] Mehta's retro olefin metathesis strategy,[4g] Rawal's photocycloaddition−fragmentation,[4h] and Little's intramolecular 1,3-diyl cycloaddition.[4i] It is impossibleto mention all of the reported syntheses, but it is evident that hirsutene is a classic example of a heritage molecule that illustrates the power of strategic disconnection (strategy driven synthesis) for rapid assembly for such linear triquinanes (Figure 2).

PRESENT WORK

In the quest for a relatively unexplored synthetic strategy for such linear triquinanes, we envisioned that RRM (ring rearrangement metathesis) reaction might serve as a key reaction for the construction of core cyclic framework of hirsutene and its structural congeners. The sequential combination of RCM (ring-closing metathesis) and ROM (ring-opening metathesis) resulting in the domino process is classified as ring-rearrangement metathesis (RRM).[7] In these domino reactions, a strained carbocyclic compound with a suitable alkene appendage is converted into a new bicyclic framework through an intramolecular ROM−RCM sequence (Figure 3). Stereocenters remain unchanged during the metathesis reaction, so the most important feature of RRM is

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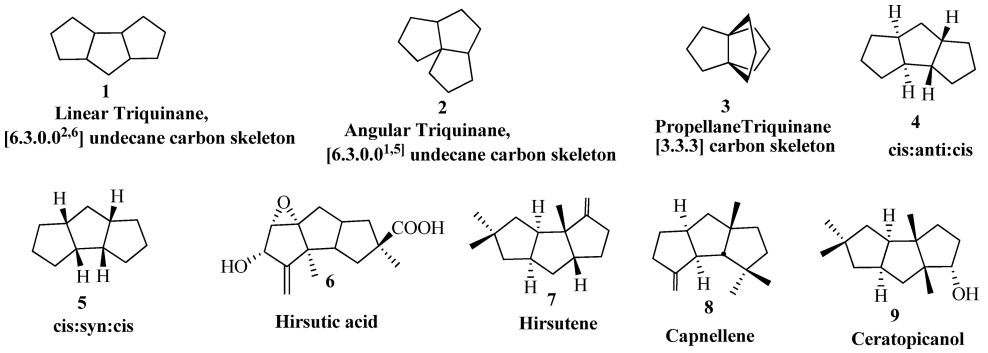

Figure 1. Naturally occurring triquinanes.

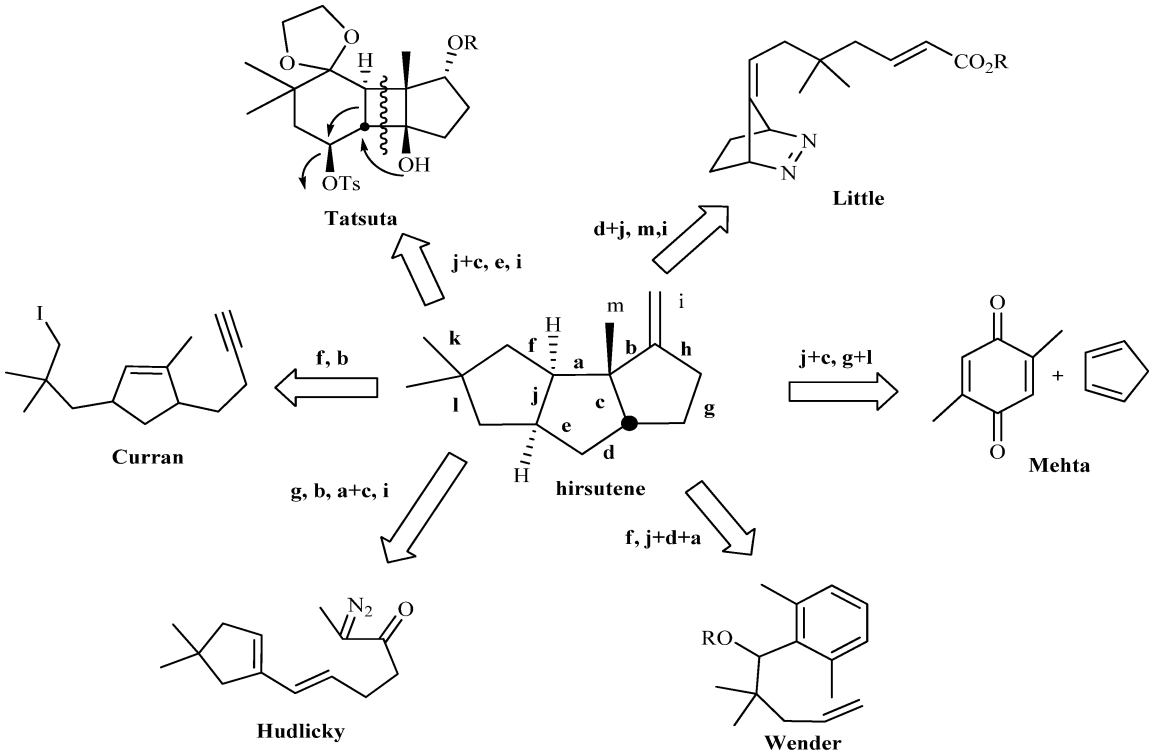

Figure 2. Previous important synthetic approaches for linear triquinane hirsutene.

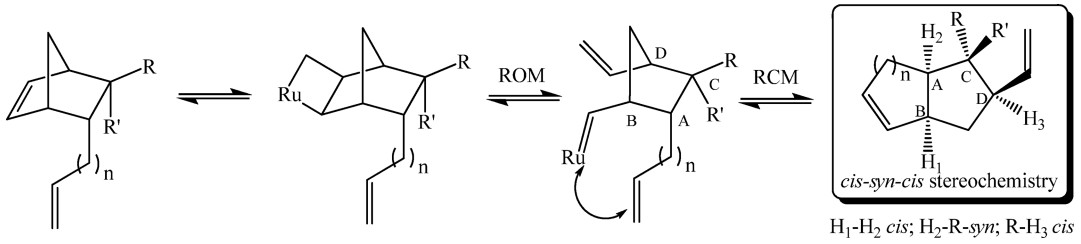

Figure 3. Schematic view of RRM cascade.

the capacity to transfer the stereochemical information from the starting material into the product in its original form. Bridged bicyclic systems (especially norbornene skeletons) are very suitable for such kinds of domino metathesis reactions. Owing to the highly strained ring system, these substrates are highly reactive, so the release of energy is the driving force for the reaction. The introduction of an external olefin, usually ethylene, is necessary to avoid oligomerization, a common side reaction in RRM (Figure 3). A few research groups have already made seminal contributions by adopting RRM strategies for the total synthesis of natural products such as indolizidine 251F, *trans*-kumausyne, and aburatubolactam A.[7d]

The main objective of this paper is to report a flexible synthetic pathway for the construction of the triquinane framework present in many sesquiterpenes through successful exploration of the RRM reaction. A general retrosynthetic scheme was outlined below. Diketone **11** would serve as a potential key precursor for hirsutene and related molecule such

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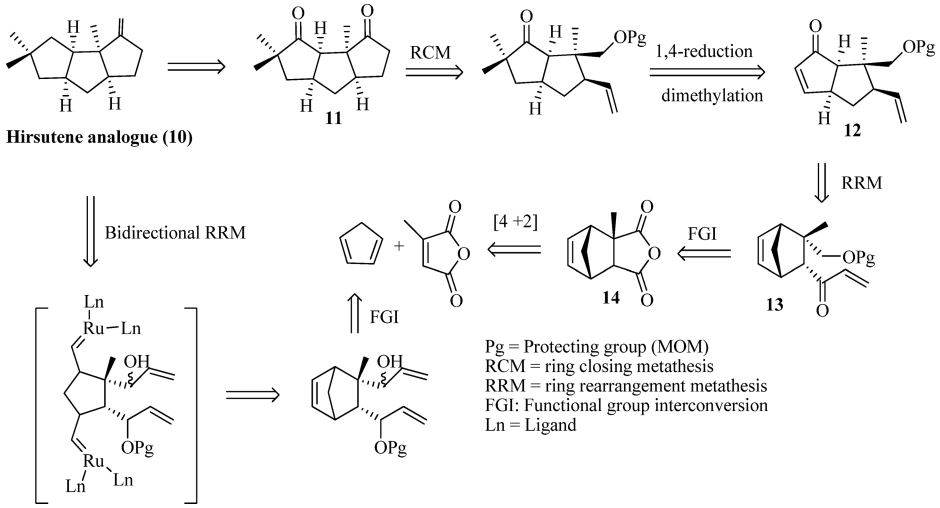
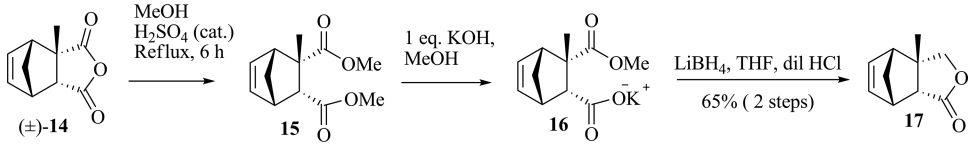
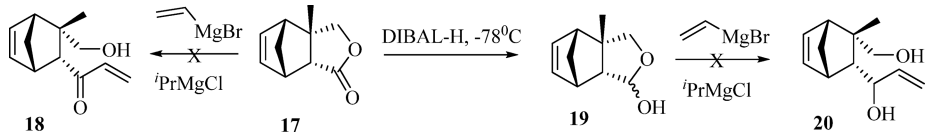
Scheme 1. Proposed Retrosynthetic Analysis of Linear Triquinane Analogues through Exploration of RRM/RCM Reaction Sequence



Scheme 2. Synthesis of the RRM Precursor



Scheme 3. Attempted Synthesis of the RRM Precursor 13



as ceratopicanol. The tricyclic diketone (**11**) can be assembled through a ring-closing metathesis (RCM) reaction by functional group adjustment (FGA) of bicyclic compound **12**. The ketone **12** was planned to be accessed by the crucial RRM reaction sequence of enone **13**, which in turn can be synthesized from the cyclic anhydride **14** as shown in Scheme 1. Compound **14** would be synthesized from the product of a Diels–Alder reaction between cyclopentadiene and citraconic anhydride. Close inspection reveals that if the proposed RRM works successfully as anticipated, we will be able to synthesize the analogue of the naturally occurring triquinanes (hirsutene and ceratopicanol). The diketone **11** will have *cis-syn-cis* geometry after the RRM/RCM reaction, whereas in the natural triquinane the geometry present is *cis-anti-cis* (Figure 2 and Scheme 1). Nevertheless, although the natural product cannot be achieved as hoped, it will be an excellent opportunity to explore the RRM reaction as a useful strategy for the construction of linear triquinane frameworks as such strategies will be highly atom economical in nature and create new alternative pathways for the construction of linear triquinanes with relative ease. An adventurous bidirectional RRM strategy was also proposed as shown in Scheme 1.

RESULTS AND DISCUSSION

As depicted from the retrosynthetic strategy (Scheme 1), our initial target was to synthesize RRM precursor **13**. Diels–Alder reaction between cyclopentadiene and citraconic anhydride afforded the desired cycloadduct **14** in 92% yield (endo product was obtained exclusively). Compound **14** on treatment with MeOH and a catalytic amount of concd H_2SO_4 under refluxing conditions furnished the diester **15**. The regioselective hydrolysis of unhindered ester moiety in compound **15** using 1 equiv of KOH in methanol at room temperature gave the intermediate **16**, which upon reduction with $LiBH_4$ followed by acidification furnished the lactone compound **17** in 65% yield (Scheme 2).[8]

However, compound **17** failed to react to provide diol **18** in the presence of vinylmagnesium bromide. Even in the presence of certain additives such as cerium(III) chloride or ^{i}PrMgCl[9] also the reaction failed to furnish the desired product. The lactone **17** was then reduced to the corresponding lactol **19** using DIBAL-H and was immediately subjected to similar reaction conditions, which also turned out to be unsuccessful to afford the desired diol **18** (Scheme 3).

Having failed in our previous attempts to synthesize the required RRM precursor, we then decided to change our synthetic strategy. Next, compound **14** was subjected to $LiAlH_4$ reduction to afford diol **21** in 92% yield. Regioselective MOM protection[10] of the sterically more congested primary hydroxyl group was achieved in two steps: first, the formation of orthoester (prepared in situ from 1,4-diol and trimethyl orthoformate) followed by regioselective cleavage of unsymmetrical orthoester with DIBAL-H furnished **22a** in 85% of yield and 7:1 diastereomeric ratio. Second, oxidation of the

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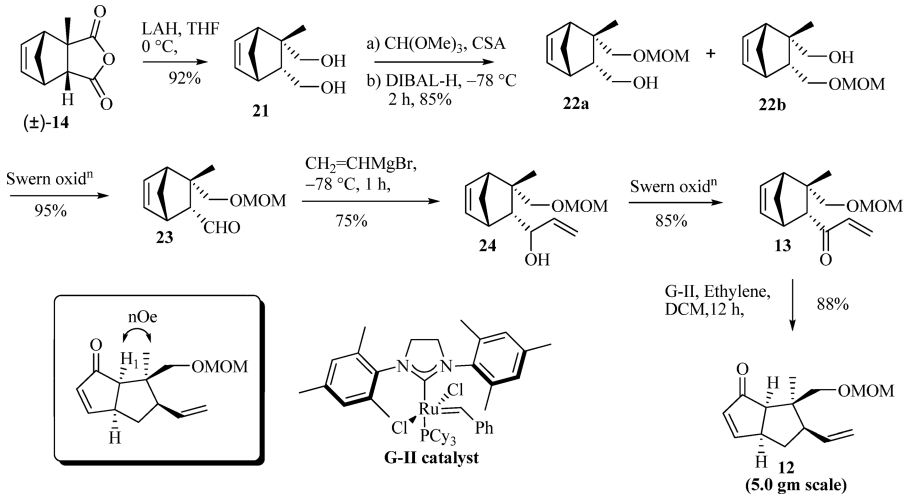
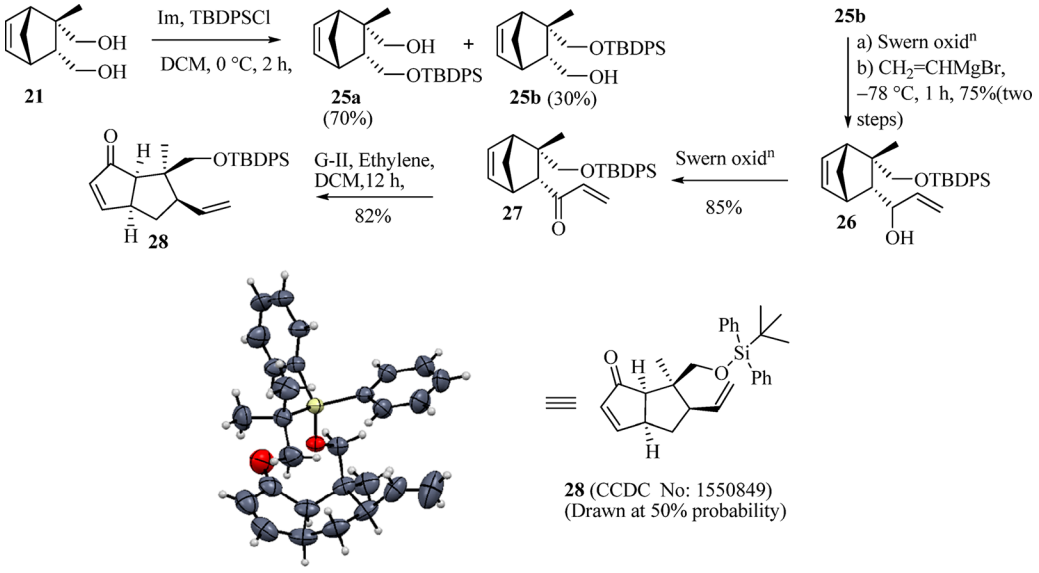
Scheme 4. Synthesis of Linearly Fused Bicyclic Enone through Exploration of RRM Reaction



Scheme 5. Synthesis of Bicyclic Enone 28 through Exploration of RRM Reaction



alcohol functionality in **22a** under Swern conditions[11] afforded the aldehyde **23** in 95% yield. Addition of CH_2=CHMgBr on aldehyde **23** at −78 °C afforded the secondary alcohol **24** in 75% yield as single diastereomer (the stereochemistry at the newly created stereocenter was not assigned) which on oxidation under Swern condition afforded the unsaturated ketone **13** in 85% yield (Scheme 4).

Crucial tandem ring-opening/ring-closing metathesis (RRM)[12] of enone **13** under ethylene atmosphere furnished bicyclic enone **12** in 88% yield using 3.5 mol % of G-II catalyst on a multigram scale. A remarkable increase in the yield of the reaction was observed when the reaction was carried out in ethylene-saturated dichloromethane in high dilution using G-II as catalyst. G-I catalyst provided only 30% desired product with a good amount of oligomerized materials. The geometry (ring fusion stereochemistry) of the newly formed compound was investigated using 1D and 2D NMR techniques. NOESY experiments show the cross peak between the methyl group and the angular proton marked as H_1. 1D NOE experiments also suggested that the methyl group and H_1 are in close proximity (1.18% enhancement of the angular hydrogen on irradiating the methyl group, 1.82% enhancement of the methyl group irradiating the angular hydrogen H_1).

As the domino metathesis (ROM followed by RCM) reaction worked excellently, we thought to explore the reaction further. For this reason we performed same series of reactions on analogous bicyclic enone compound **27**. Compound **27** was synthesized as depicted in Scheme 5, and the diol **21** was monoprotected as its TBDPS ether in the presence of imidazole and TBDPS-Cl to furnish compounds **25a** (70%) and **25b** (30%). Compound **25b** on Swern oxidation and vinyl Grignard addition afforded compound **26**, which on further Swern oxidation afforded the required enone **27**. The anticipated RRM reaction of **27** proceeded well and afforded compound **28** in 82% yield. The relative stereochemistry of compound **28** was confirmed through single-crystal X-ray analysis, and the ORTEP view is also presented in Scheme 5.

As the initial two RRM reactions proceeded well, we wanted to explore the substrate scope of this reaction for the generation of a new bicyclic framework. The aldehyde **23** was then synthetically manipulated to several structurally analogous enones **29**−**40**, which serve as potential RRM precursors (the

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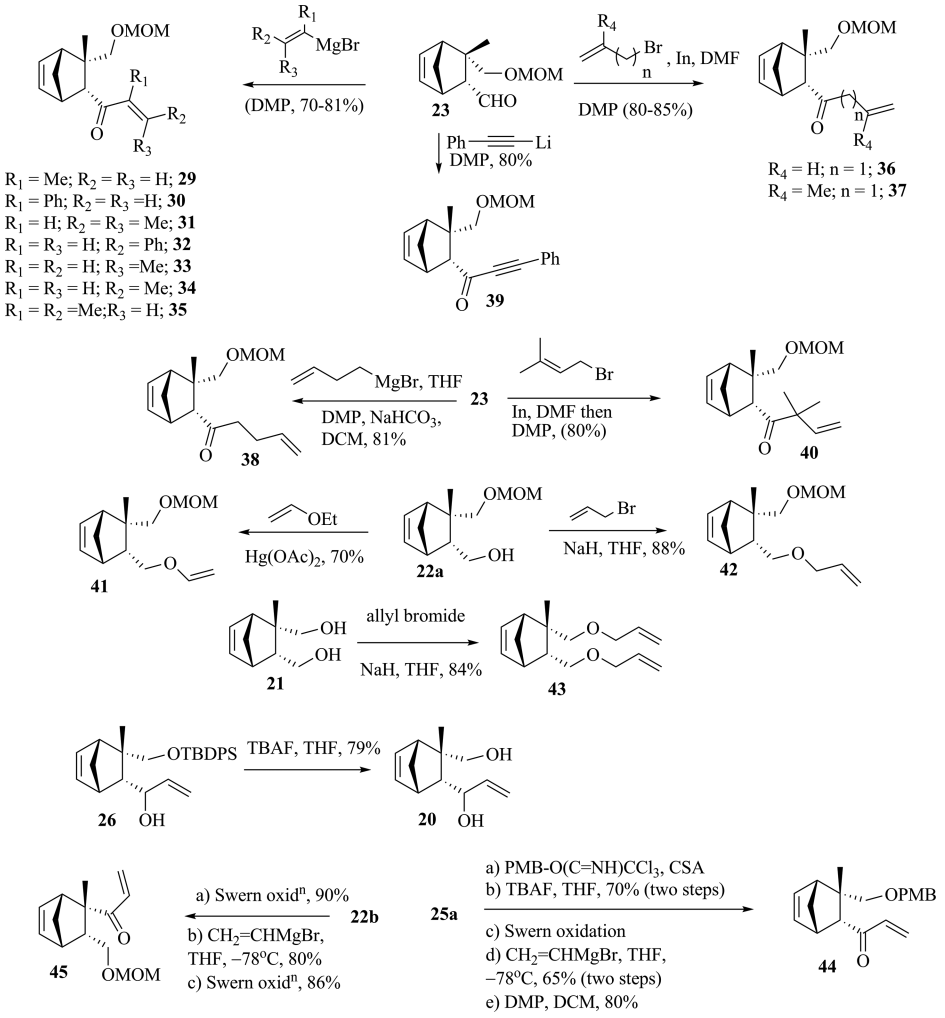
Scheme 6. Synthesis of the RRM Precursors



detail synthetic procedure and characterization are provided in the Supporting Information). Substrates **29**−**35** were synthesized as described in Scheme 6. A suitable Grignard reagent (prepared in situ from the corresponding vinylic bromide and Mg turnings) was usually reacted with aldehyde **23** followed by DMP oxidation[13] to furnish the RRM precursors. Similarly, aldehyde **23** was reacted with substituted allyl bromides in a metallic indium (In)-based Barbier-type allylation reaction followed by DMP oxidation to furnish precursors **36** and **37**. The alkynone **39** was prepared from aldehyde **23** and phenyl acetylide followed by DMP oxidation as shown in Scheme 6. Another RRM precursor ketone **40** was synthesized by reacting aldehyde **23** with prenyl bromide and indium powder and then oxidizing the resulting alcohol under DMP conditions. Several *O*-vinyl ether and *O*-allyl ethers were also envisioned as potential RRM precursors and easily synthesized as depicted in Scheme 6. Alcohol **22a** was first converted to its corresponding *O*-vinyl ether by treatment with vinyl ethyl ether in the presence of $Hg(OAc)_2$[14] to furnish another RRM precursor **41** in 70% yield. RRM precursor **42** was obtained upon O-allylation of alcohol **22a** in the presence of NaH and allyl bromide, and when diol **21** was treated with NaH and excess allyl bromide, bis-O-allylated RRM precursor **43** was obtained. Removal of the silyl ether functionality (−OTBDPS) with TBAF in compound **26** afforded bicyclic diol **20**, which also can act as another RRM precursor. Manipulating the protecting group in compound **25a** as shown in Scheme 6 furnished bicyclic enone **44** containing a −PMB (4-methoxy benzyl) group, which also served as another RRM precursor. Another RRM precursor compound **45** was also prepared from **22b** as shown below (Scheme 6).

Next, the RRM reaction of **29**−**40** was attempted under similar conditions as described previously in Scheme 4. The product structure and isolated yield are summarized in Table 1. Compounds **29** and **35** afforded the corresponding bicyclic [5,5] enone **46** in good yield with exclusive *cis-syn-cis* geometry as anticipated, but unfortunately, compound **30** did not afford the bicyclic [5,5] enone as expected. Probably the bulky −Ph group causes enough steric crowding during the final RCM pathway (the Ru-based metathesis catalyst may not bind properly with the substrate) so that product formation was not observed. Enones **31**−**34**, on RRM reaction with G-II catalyst, afforded the known bicyclic enone **12** in good yield (Table 1). Compound **36** on RRM reaction furnished [6,5] bicyclic enones **47** in 75% yield, and no isomerization of the double bond was observed. Unfortunately, compound **37** on RRM reaction did not afford the desired substituted [6,5]-fused bicyclic enone (starting material was recovered), whereas compound **38** under similar RRM conditions afforded [7,5]-fused bicyclic enone **48** in 76% yield.

The keto alkyne compound **39** on RRM reaction was expected to furnish the bicyclic triene (with one conjugated

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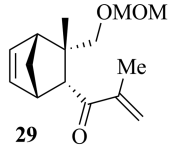
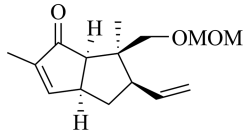
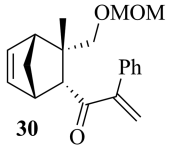
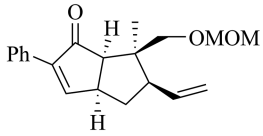
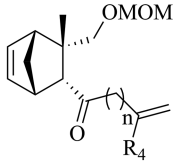
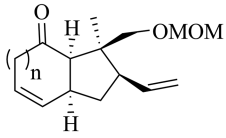
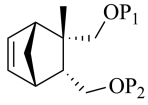
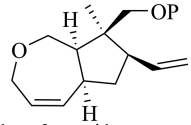
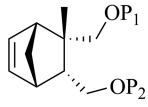
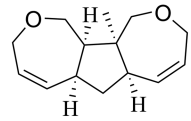
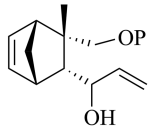
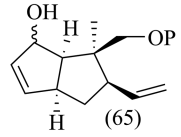
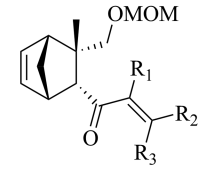
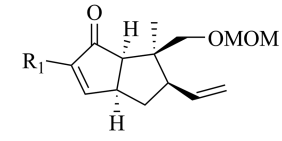
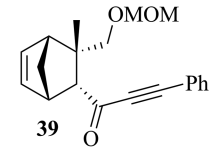
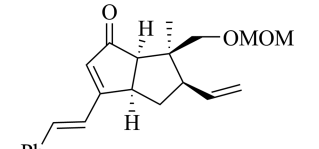
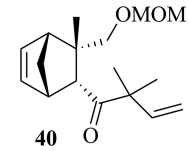
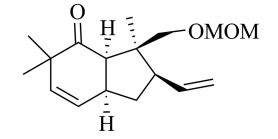
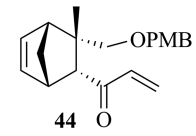
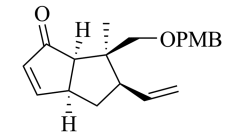
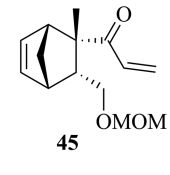
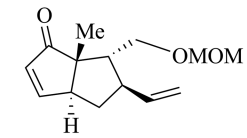
Table 1. Structures and Isolated Yields of Cyclic Products Obtained after RRM Reaction[a]

RRM precursors	Bicyclic scaffolds after RRM
 **29**	 **46** (83%)
 **30**	 Not formed 40% SM recovered
 R_4 = H; n = 1; **36** R_4 = Me; n = 1; **37** R_4 = H, n = 2; **38**	 n = 1; **47** (75% from **36**) No product from **37** n = 2, **48** (76% from **38**)
 P_1 = MOM; P_2 = vinyl; **41** P_1 = MOM; P_2 = allyl; **42**	 No product from **41**, P = MOM, **49** (76% from **42**) P = allyl, **50** (30% from **43** after 2 h)
 P_1 = P_2 = allyl; **43**	 **51** (70% from **43** after 1 d)
 P = MOM; **24** P = TBDPS; **26** P = H; **20**	 P = MOM, **52** (65%) P = TBDPS, **53** (68%) P = H, **54** (55%)

RRM precursors	Bicyclic scaffolds after RRM
 R_1 = H; R_2 = R_3 = Me; **31** R_1 = H; R_2 = Ph; R_3 = H; **32** R_1 = H = R_2; R_3 = Me; **33** R_1 = R_3 = H; R_2 = Me; **34** R_1 = R_2 = Me; R_3 = H; **35**	 **12** → (65%) → (72%) → (70%) → (70%) → **46** (76%)
 **39**	 Not formed (SM recovered)
 **40**	 Not formed (SM recovered)
 **44**	 **55** (70%)
 **45**	 **56** (70%)

[a]NB: Yields refer to isolated yield obtained after purification. Two separate conditions were tried as mentioned for unsuccessful reactions (refluxing in DCM or toluene).

double bond), but unfortunately, the expected product was not obtained. The ketone **40** under these RRM conditions did not provide the desired bicyclic product; instead, after a few hours, TLC analysis indicated that although the starting material was consumed intractable mixtures of unidentified products were obtained. Vinyl ether **41** was next subjected to RRM reaction with G-II catalyst, but to our dismay, the desired product could not be obtained. TLC of the reaction mixtures indicated that the starting material had disappeared, but no clear formation of any detectable and well-visualizable spots on TLC was found. The hydrolysis of the vinyl ether may be possible, but as the RRM reaction was carried out in completely inert atmosphere that possibility can be ruled out. Allyl ether **42** was next subjected to the RRM reaction with G-II catalyst to afford tetrahydrooxepine derivative (**49**) in 76% yield as the major product. The structure of **49** was confirmed by ^{1}H−^{1}H NOESY analysis. The bisallyl ether compound **43** on RRM reaction with G-II catalyst afforded the tetrahydrooxepine derivative **50** in 30% yield within 2 h as the major product at room temperature but eventually after refluxing in DCM for 1 d afforded the tricyclic product **51** in 70% yield as the major product. The mono- and bis-tetrahydrooxepine scaffold (**49**−**51**) seems to be relatively new in the scientific literature and was synthesized for the first time by RRM reaction as shown here. Next, the

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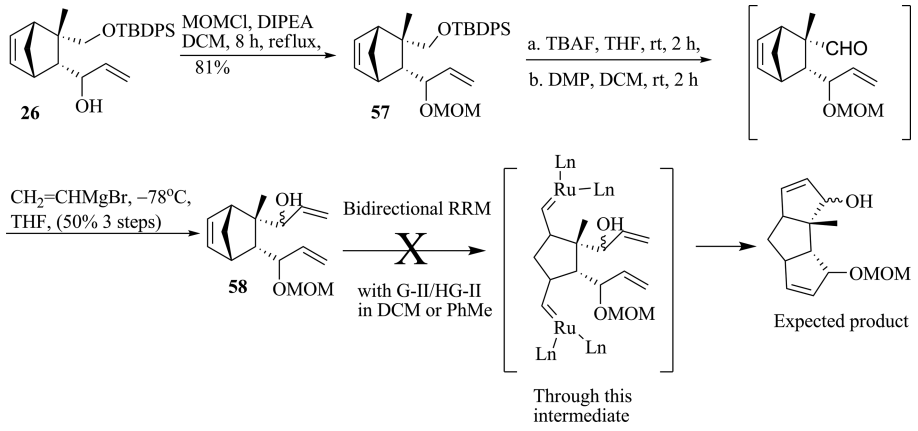
J. Org. Chem. 2018, 83, 2087−2103

Scheme 7. Attempted Bidirectional RRM Approach To Construct the Triquinane Framework



compounds **24** and **26** with a free secondary alcohol moiety were subjected to RRM reaction with G-II catalyst, and the corresponding [5,5] fused bicyclic products (**52** and **53**) were obtained in reasonably good yields. The enone analogous to compound **13** (**44**) having a PMB group also underwent RRM reaction to furnish the bicyclic ketone **55** in good yield. It was evident that the RRM reaction is compatible with several protecting groups such as MOM, TBDPS, and PMB. Finally, the diol **20** was subjected to RRM reaction under similar conditions, and the corresponding product was **54** isolated in 55% yield. The enone **45**, after RRM reaction furnished the bicyclic compound **56** with a methyl substitution at the ring junction (70% yield), seemed to be a unique substrate in the whole series as it installs a −Me group in the ring fusion (generation of an all-carbon quaternary center). In general, we can claim that suitably substituted bridged bicyclic compounds can serve as a potential precursor for the RRM reaction and afforded the respective [5,*n*] linearly fused bicyclic compounds with *cis-syn-cis* geometry.

To explore the feasibility of such an RRM tactic en route to the construction of linear triquinanes, we speculate that strategically unique bidirectional RRM will be very helpful and handy as shown previously in Scheme 1. Such bidirectional RRM reaction seems to be a more direct and flexible approach for preparing linear tricyclopentanoid systems as documented earlier.[15] For that purpose, alcohol **26** was taken, and the free hydroxyl group was protected as its MOM ether and led to compound **57** with 81% yield. Desilylation with TBAF followed by Dess−Martin oxidation on compound **57** afforded the aldehyde, which was immediately treated with vinylmagnesium bromide at −78 °C to furnish the bis-alkenol **58** with 50% (three steps) overall yield as shown in Scheme 7. Bidirectional RRM reaction was then attempted with Ru-based metathesis catalyst in DCM or toluene as solvent, but the anticipated RRM reaction was not successful in our hands.

To complete the synthesis of the hirsutene analogue as depicted in Scheme 1, we next proceeded to the chemoselective reduction of the enone unsaturation in compound **12**. Thus, when compound **12** was treated with Stryker's reagent ($[(PPh_3)CuH]_6$)[16] in benzene solvent it furnished the desired product **59** in excellent yield (90%). Since Stryker's reagent is expensive, other alternative and economical strategies were employed to have a sufficient amount of **59** for the completion of the synthesis. L-Selectride reduction[17] of enone **12** generated a mixture of compounds arising from both the 1,4 as well as 1,2 reduction in 1:1 ratio. Cu-mediated conjugate reduction using MeLi/CuI/DiBAL-H[18] mainly gave the 1,2 reduction, while CuI/DIBAL-H[19] did not result any reduction. Fortunately, a reagent system consisting of CuI/$LiAlH_4$/HMPA[20] at −78 °C promoted the conjugate reduction within 10 min and furnished solely compound **59** in 86% overall yield (Scheme 8; Table 2).

Scheme 8. Chemoselective Reduction of Enone Unsaturation

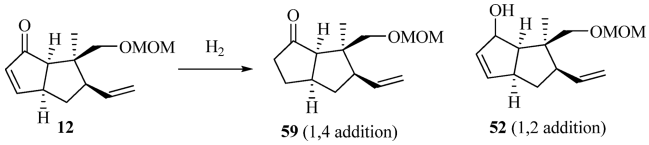


Table 2. Optimization of Chemoselective Conjugate Reduction of Bicyclic Enone 12

entry	$[H_2]$	*T* (°C)	time	isolated yield (%)
1	$[Ph_3P{\cdot}CuH]_6$, benzene	−78 °C	6 h	90%
2	L-Selectride	−78 °C to rt	12 h	20% (1,2:1,4 = 1:1)
3	CuI/DIBAL-H	−78 °C to rt	6 h	0
4	CuI/DIBAL-H/MeLi	−78 °C to rt	6 h	mainly 1,2 addition (80%)
5	CuI, $LiAlH_4$, HMPA	−78 °C	10 min	86%

Ketone **59** was then regioselectively *gem*-dimethylated[21] using LiHMDS as base and MeI as the alkylating agent to furnish compound **60** in 78% yield (based on recovered starting material (brsm); Scheme 9). With compound **60** in hand, we next reduced the carbonyl functionality with LAH in THF solvent to afford compound **61** in 80% yield. The stereochemistry of the newly created alcohol stereocenter adjacent to the *gem*-dimethyl functionality is not crucial as later on it needs to be removed (serving as redundant functionality). We assign the relative stereochemistry of the newly generated stereocenter by assuming preferable attack of the "H" from the more accessible concave face of the starting material through a chelation-controlled transition state. Compound **61** was then refluxed with PPTS in *tert*-butyl alcohol[22] solvent to furnish the bicyclic diol **62** in 70% yield after removal of the MOM ether. Chemoselective oxidation of the primary alcohol functionality of compound **62** was accomplished with BIAB and TEMPO[23] to afford aldehyde **63** in 76% yield (Scheme 9). Compound **63** on vinylmagnesium bromide addition at −78 °C afforded

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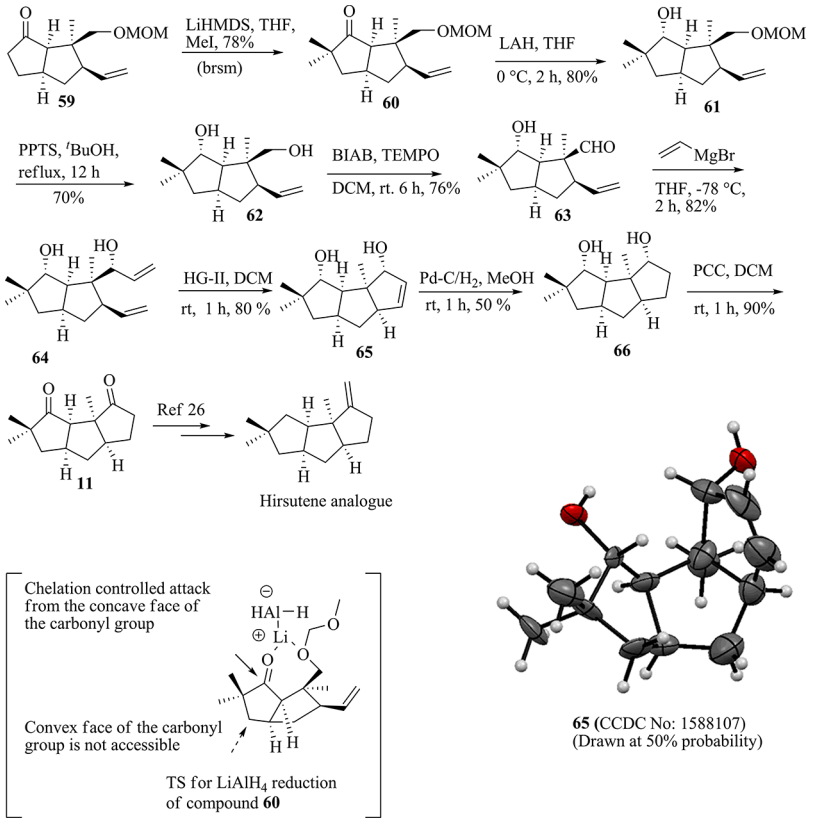
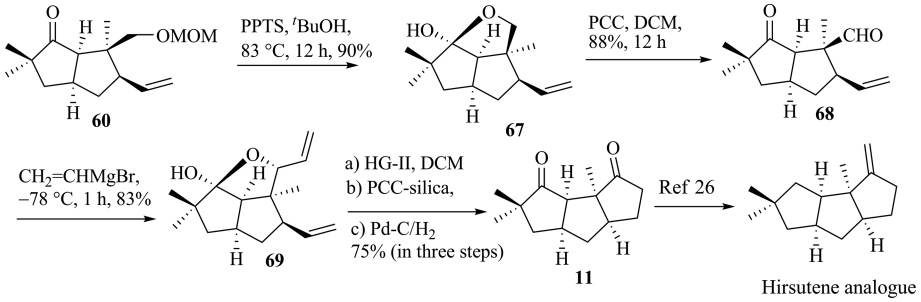
J. Org. Chem. 2018, 83, 2087−2103

Scheme 9. Attempt To Construct the Tricyclic Core of Linear Triquinane



Scheme 10. Construction of the Tricyclic Core of Linear Triquinane



compound **64** as a single stereoisomer. Ring-closing metathesis (RCM) reaction of compound **64** was carried out with HG-II catalyst[24] (5 mol %) in DCM solvent for 2 h at room temperature. The attempted RCM reaction proceeded smoothly, the tricyclic compound **65** was obtained in 80% yield, and fortunately, compound **65** is a solid crystalline compound whose structure was confirmed through single-crystal X-ray analysis. The relative stereochemistry of the tricyclic core was further confirmed as *cis-syn-cis*, and the middle cyclopentane ring seems to be planar where the LH (left-hand) and RH (right-hand) cyclopentane rings form the wall, and eventually, the whole structure is bowl shaped. Compound **65** on hydrogenation with Pd−C afforded compound **66** in disappointingly lower yield (50% only; Scheme 9). All of our attempts to increase the yield of this hydrogenation step met with limited success. We thought if we could convert diol **66** to the diketone **11** (the stereoisomer of **11** was known in the literature and synthesis of naturally occurring hirsutene was accomplished from that), we might achieve the formal synthesis of hirsutene stereoisomer. For that purpose, the diol **66** was next subjected to oxidation with PCC in DCM solvent, to furnish compound **11** in 90% yield. The overall yield of diketone **11** was 9.8% from bicyclic enone **59**.

In the quest for a relatively shorter and high-yielding route for compound **11**, initially deprotection of MOM group was attempted by treating compound **60** in the presence of PPTS in *tert*-butyl alcohol to furnish the lactol **67** in 90% yield. It was noteworthy to mention that the free alcohol was never isolated; the moment MOM group was cleaved concomitant cyclization instantly took place to furnish the lactol product. PCC oxidation[25] of lactol **67** in dry DCM afforded the keto aldehyde **68** in excellent yield (88%). Chemoselective addition of vinylmagnesium bromide on aldehyde **68** at −78 °C afforded the vinylic lactol **69** in 83% yield (Scheme 10). Attempted RCM reaction of lactol **69** in the presence of several Ru-based metathesis catalysts was next attempted. Catalysts such as G-I, G-II, and HG-I failed to provide the desired RCM product. To our delight, the anticipated RCM reaction proceeded smoothly

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when lactol **69** was reacted in the presence of HG-II catalyst (2 mol %), and the ring-closed lactol was obtained. The crude lactol was next subjected to oxidative transformation with PCC-silica gel followed by hydrogenation with Pd−C to furnish the tricyclic diketone **11** in 75% yield (three steps; overall yield of **11** is 38% from **59**).

The diketone **11** obtained after the RRM/RCM reaction has *cis-syn-cis* geometry, whereas in the natural triquinane the geometry present was *cis-anti-cis* (Figures 1 and 2). Nevertheless, although the natural product could not be achieved as expected, we thought it would be an excellent opportunity to explore the RRM reaction as a useful strategy for the construction of linear triquinane frameworks. The synthesis of hirsutene from stereoisomer of **11** was reported elsewhere;[26] hence, we have reason to believe that our reported procedure may constitute a formal synthesis of hirsutene analogue.

CONCLUSION

In conclusion, a general and flexible strategy involving the RRM reaction as a key transformation was successfully explored to access the [5,*n*]-fused bicyclic enone scaffold with *cis-syn-cis* stereochemistry in high yield and atom economy. The synthesized bicyclic enone framework was found to be present in many triquinane natural products. The bicyclic enones were then synthetically manipulated to tricyclic core of naturally occurring linearly fused triquinane (hirsutene) analogues through ring-closing metathesis (RCM) reaction and oxidative transformation of a vinylic lactol. The developed route should act as an efficient and reliable strategy for construction of such molecules in a stereodefined way.

EXPERIMENTAL DETAILS

General Procedures. All oxygen and/or moisture-sensitive reactions were carried out under N_2 atmosphere in glassware that had been flame-dried under vacuum (ca. 0.5 Torr) and purged with N_2 prior to use. Unless otherwise stated, materials were obtained from commercial suppliers and used without further purification. THF and diethyl ether were distilled from sodium benzophenone ketyl. Dichloromethane (DCM) and hexane were distilled from calcium hydride. Reactions were stirred magnetically using Teflon-coated magnetic stirring bars. Teflon-coated magnetic stirring bars and syringe needles were dried in an oven at 120 °C for at least 12 h prior to use and then cooled in a desiccator cabinet over Drierite. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel plates with UV light, ethanolic anisaldehyde, and phosphomolybdic acid/heat as developing agents. Silica gel 100−200 mesh was used for column chromatography. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated. NMR spectra were recorded on 600, 400, and 200 MHz spectrometers at 25 °C in $CDCl_3$ using TMS as the internal standard. Chemical shifts are shown in δ. ^{13}C NMR spectra were recorded with a complete proton-decoupling environment. The chemical shift value is listed as δ_H and δ_C for ^1H and ^{13}C, respectively. Coupling constants (J) are reported in hertz (Hz), and the resonance multiplicity abbreviations used are s, singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quartet; m, multiplet; comp, overlapping multiplets of magnetically nonequivalent protons. Mass spectrometric analysis was performed in the CRF, IIT-Kharagpur (TOF analyzer).

*(±)-3a-Methyl-3a,4,7,7a-tetrahydro-4,7-methanoisobenzofuran-1,3-dione (**14**).* A flask equipped with a Vigreux column and a distillation system was charged with dicyclopentadiene and heated to 210 °C. Cyclopentadiene was recovered and collected in an ice-cold flask. The cyclopentadiene (6.6 g, 99.85 mmol) was then added to a solution of 3-methyl furan-2,5-dione (2.0 g, 20 mmol) in diethyl ether (30 mL) at 0 °C. The reaction mixture was then stirred overnight at room temperature. After evaporation of the diethyl ether under reduced pressure, the residue was washed with hexane, and recrystallization from methanol furnished the desired compound **14** (3.27 g, 18.4 mmol, 92%) as a colorless solid: R_f = 0.5 (EtOAc/hexane = 1:10); δ_H (400 MHz, $CDCl_3$) δ 6.38 (dd, J = 5.8, 3.0 Hz, 1H), 6.29 (dd, J = 5.9, 2.9 Hz, 1H), 3.53−3.36 (m, 1H), 3.12 (d, J = 4.6 Hz, 1H), 3.08−2.98 (m, 1H), 1.87−1.76 (m, 2H), 1.62 (s, 3H); δ_C (101 MHz, $CDCl_3$) δ 174.9, 170.9, 137.3, 135.3, 53.8, 53.5, 52.1, 50.7, 46.7, 21.4; HRMS (ESI) m/z for $C_{10}H_{10}O_3Na$ $[M + Na]^+$ calcd 201.0600, found 201.0612.

*(±)-Dimethyl 2-Methylbicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate (**15**).* A solution of compound **14** (1.78 g, 10.0 mmol) in MeOH (10 mL) and H_2SO_4 (1.4 mL) mixture was refluxed for 6 h under N_2 atmosphere. The reaction mixture was then concentrated in vacuo. The residue was next diluted with water and extracted with ethyl acetate. The combined organic layer was washed with an aqueous solution of $NaHCO_3$ and brine and dried over Na_2SO_4. Evaporation of the organic layer in vacuo furnished pure diester **15** (1.7 g, 7.6 mmol): R_f = 0.5 (EtOAc/hexane = 1:20); δ_H (200 MHz, $CDCl_3$) δ_H: 6.40 (dd, J = 5.6, 3.0 Hz, 1H), 6.15 (dd, J = 5.6, 3.0 Hz, 1H), 3.66 (s, 3H), 3.59 (s, 3H), 3.03 (s, 1H), 2.82 (s, 1H), 2.76 (d, J = 3.0 Hz, 1H), 1.61 (s, 3H); 1.57−1.50 (m, 2H); δ_C (50 MHz, $CDCl_3$) 175.0, 174.1, 136.5, 135.4, 56.2, 56.1, 52.6, 51.8, 51.5, 46.3, 46.2, 27.0; HRMS (ESI) m/z for $C_{12}H_{16}O_4Na$ $[M + Na]^+$ calcd 247.0946, found 247.0948.

*(±)-3a-Methyl-3a,4,7,7a-tetrahydro-4,7-methanoisobenzofuran-1(3H)-one (**17**).* To a solution of diester **15** (1.93 g, 8.62 mmol) in MeOH (15 mL) was added a solution of KOH (484 mg, 8.62 mmol) in methanol (10 mL) in a dropwise fashion with constant stirring at room temperature. The reaction mixture was stirred for 1 h and then concentrated in vacuo. The residue obtained was washed with $CHCl_3$ (10 mL × 2) to afford the crude potassium salt **16**.

To the suspension of the salt **16** (1.81 g, 7.32 mmol) in THF (140 mL) was added $LiBH_4$ (637 mg, 29.3 mmol) at 0 °C. The reaction mixture was then stirred at room temperature for 6 h. The reaction was then quenched by addition of water, and the reaction mixture was concentrated in vacuo. The aqueous layer was acidified with minimum amount of dilute HCl and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo to afford pure **17** (916 mg, 65%): R_f = 0.5 (EtOAc/hexane = 1:20); δ_H (400 MHz, $CDCl_3$) 6.34 (dd, J = 5.6, 2.8 Hz, 1H), 6.28 (dd, J = 5.6, 2.8 Hz, 1H), 3.88 (abq, J = 7.0 Hz, 2H), 3.29 (s, 1H), 2.76 (d, J = 4.8 Hz, 1H), 2.72 (s, 1H), 1.74−1.68 (m, 2H), 1.42 (s, 3H); δ_C (100 MHz, $CDCl_3$) 178.8, 137.1, 136.5, 77.0, 55.6, 52.6, 50.5, 47.1, 46.4, 26.6; HRMS (ESI) m/z for $C_{10}H_{12}O_2Na$ $[M + Na]^+$ calcd 187.0734, found 187.0734.

*(±)-2-Methylbicyclo[2.2.1]hept-5-ene-2,3-diyl)dimethanol (**21**).* $LiAlH_4$ (0.79 g, 20.8 mmol) was suspended in anhydrous THF (40 mL), and the suspension was cooled to 0 °C. A solution of cycloadduct **14** (2.90 g, 16.2 mmol) in dry THF (20 mL) was added dropwise. The reaction mixture was then heated to reflux for 2 h, and after cooling to 0 °C, it was quenched with Na_2SO_4 solution carefully. It was then filtered on a Celite pad, and the solid cake was washed twice with hot Et_2O. The combined organic layers were dried with Na_2SO_4, concentrated under reduced pressure, and purified by column chromatography (EtOAc/hexane = 1:1) to furnish the diol (2.51 g, 14.9 mol) in 92% yield: R_f = 0.2 (EtOAc/hexane = 1:1); δ_H (400 MHz, $CDCl_3$) δ_H (400 MHz, $CDCl_3$) δ 6.11 (dt, J = 5.8, 3.3 Hz, 1H), 6.02 (dt, J = 5.5, 3.4 Hz, 1H), 3.63−3.53 (m, 2H), 3.38−3.25 (m, 2H), 2.69 (s, 1H), 2.32 (s, 1H), 2.05 (dq, J = 7.2, 4.6 Hz, 1H), 1.70 (d, J = 8.2 Hz, 1H) 1.36 (dt, J = 8.3, 1.9 Hz, 1H), 1.30 (s, 3H); δ_C (101 MHz, $CDCl_3$) 136.3, 133.9, 67.6, 64.5, 53.3, 52.8, 47.4, 46.8, 46.6, 26.8; HRMS (ESI) m/z for $C_{10}H_{16}O_2Na$ $[M + Na]^+$ calcd 191.1200, found 191.1205.

3-((Methoxymethoxy)methyl)-3-methylbicyclo[2.2.1]hept-5-en-2-yl)methanol. A mixture of trimethylorthoformate (1.76 g, 11.9 mmol), diol **21** (1 g, 5.95 mmol), and a catalytic amount of D-10-camphorsulfonic acid (27 mg, 0.119 mmol) in dry DCM (20 mL) was stirred at room temperature for 24 h. After completion of the reaction as monitored by TLC analysis, the solution was cooled to −78 °C. DIBAL-H (30 mL, 30 mmol) was then added dropwise into the resulting mixture and stirred at −78 °C for 2 h. The reaction

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mixture was then quenched with dry methanol and stirred for further 1.5 h. The product was then extracted with DCM. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to furnish the crude product. The crude product was then purified by column chromatography (EtOAc/hexane = 1:5) to furnish the products as diastereomeric mixtures (0.98 g, 7:1 ratio) in 85% yield.

*Major product **22a**:* R_f = 0.30 (EtOAc/hexane = 1:5); δ_H (600 MHz, $CDCl_3$) 6.14 (dd, J = 5.4, 3.0 Hz, 1H), 6.08 (dd, J = 5.4, 3.0 Hz, 1H), 4.64 (d, J = 6.6 Hz, 1H), 4.61 (d, J = 6.6 Hz, 1H), 3.52−3.48 (m, 2H), 3.40 (s, 3H), 3.35−3.27 (m, 2H), 2.77 (s, 1H), 2.41 (s, 1H), 2.11−2.06 (m, 1H), 1.73 (d, J = 8.4 Hz, 1H), 1.40 (dt, J = 8.4, 1.8 Hz, 1H), 1.34 (s, 3H); δ_C (51 MHz, $CDCl_3$) 136.5, 134.1, 96.7, 73.4, 63.9, 55.5, 53.1, 53.0, 47.2, 46.7, 45.0, 27.2; HRMS (ESI) m/z for $C_{12}H_{20}O_3Na$ $[M + Na]^+$ calcd 235.1309, found 235.1307.

*3-((Methoxymethoxy)methyl)-2-methylbicyclo[2.2.1]hept-5-en-2-yl)methanol (minor product) (**22b**):* R_f = 0.32 (EtOAc/hexane = 1:5); δ_H (400 MHz, $CDCl_3$) 6.19 (dd, J = 5.9, 3.0 Hz, 1H), 6.05 (dd, J = 5.9, 3.0 Hz, 1H), 4.60 (s, 2H), 3.52−3.41 (m, 2H), 3.37 (s, 3H), 3.32 (d, J = 10.3 Hz, 1H), 3.29−3.22 (m, 1H), 2.84 (dd, J = 9.9, 2.7 Hz, 1H), 2.76 (s, 1H), 2.41 (s, 1H), 2.10−2.05 (m, 1H), 1.71 (d, J = 8.5 Hz, 1H), 1.44−1.36 (m, 1H), 1.32 (s, 3H); δ_C (101 MHz, $CDCl_3$) 137.0, 133.8, 96.4, 77.4, 77.1, 76.7, 69.6, 67.3, 55.6, 53.0, 49.8, 47.2, 46.6, 46.5, 26.4; HRMS (ESI) m/z for $C_{12}H_{20}O_3Na$ $[M + Na]^+$ calcd 235.1309, found 235.1305.

*(±)-3-((Methoxymethoxy)methyl)-3-methylbicyclo[2.2.1]hept-5-ene-2-carbaldehyde (**23**).* Oxalyl chloride (1.35 mL, 15.0 mmol) was taken in DCM (45 mL), and the reaction vessel was kept at −78 °C. Dimethyl sulfoxide (DMSO, 2.6 mL, 30.0 mmol) was then added, and the reaction mixture was stirred at the same temperature for 25 min. Alcohol **22a** (2.12 g, 10.0 mmol) in DCM was then added, and the mixture was stirred for a further 45 min at the same temperature. After that, triethylamine (Et_3N, 8.3 mL, 60 mmol) was added, and the reaction mixture was gradually warmed to room temperature during 1 h. Water was added to the reaction solution, and it was extracted with DCM and washed with brine. The organic solvent was then dried over Na_2SO_4, concentrated in vacuo, and purified by column chromatography (EtOAc/hexane = 1:10) to furnish the desired aldehyde **23** (2.0 g, 9.5 mmol) in 95% yield: R_f = 0.7 (EtOAc/hexane = 1:10); δ_H (400 MHz, $CDCl_3$) δ 9.38 (d, J = 4.3 Hz, 1H), 6.32 (dd, J = 5.8, 2.9 Hz, 1H), 6.27 (dd, J = 5.8, 3.0 Hz, 1H), 4.52 (s, 2H), 3.32 (s, 3H), 3.30 (s, 2H), 3.02 (s, 1H), 2.60 (s, 1H), 2.54 (d, J = 3.8 Hz, 1H), 1.71 (d, J = 8.9 Hz, 1H), 1.53 (d, J = 8.9 Hz, 1H), 1.41 (s, 3H); δ_C (51 MHz, $CDCl_3$)205.0, 137.1, 134.2, 96.6, 72.7, 62.3, 55.3, 51.4, 49.8, 47.4, 46.3, 40.9, 27.0; HRMS (ESI) m/z for $C_{12}H_{18}O_3Na$ $[M + Na]^+$ calcd 233.1320, found 233.1325.

*(±)-3-((Methoxymethoxy)methyl)-3-methylbicyclo[2.2.1]hept-5-en-2-yl)prop-2-en-1-ol (**24**).* A freshly generated solution of vinylmagnesium bromide (10.0 mmol) was added to aldehyde **23** (1.5 g, 7.14 mmol) taken in 21.0 mL of anhydrous THF at −78 °C. The reaction mixture was then kept at the room temperature for 1 h; after that, saturated NH_4Cl solution was added to it. The solution was then extracted with EtOAc, and the organic layer was washed with water and brine. The organic layer was dried (Na_2SO_4) and evaporated under reduced pressure. Purification of the crude residue by column chromatography (EtOAc/hexane = 1:10) afforded the alcohol **24** (1.26 g) in 75% yield: R_f = 0.5 (EtOAc/hexane = 1:7); δ_H (400 MHz, $CDCl_3$) δ 6.14 (dd, J = 5.8, 2.9 Hz, 1H), 6.08 (dd, J = 5.9, 2.8 Hz, 1H), 5.92−5.83 (m, 1H), 5.28−5.09 (m, 2H), 4.69−4.57 (m, 2H), 3.74−3.63 (m, 1H), 3.58 (d, J = 9.7 Hz, 1H), 3.40 (s, 1H), 3.38 (s, 3H), 2.76−2.68 (m, 1H), 2.39 (d, J = 2.6 Hz, 1H), 1.86 (dd, J = 10.2, 3.2 Hz, 1H), 1.67 (dt, J = 8.5, 1.5 Hz, 1H), 1.37 (t, J = 1.8 Hz, 1H), 1.34 (s, 3H); δ_C (101 MHz, $CDCl_3$) 139.9, 136.4, 134.1, 115.1, 96.7, 74.3, 73.4, 57.6, 55.7, 53.7, 47.0, 46.8, 45.6, 27.4; HRMS (ESI) m/z for $C_{14}H_{22}O_3Na$ $[M + Na]^+$ calcd 261.1467, found 261.1461.

*(±)-3-((Methoxymethoxy)methyl)-3-methylbicyclo[2.2.1]hept-5-en-2-yl)prop-2-en-1-one (**13**).* Swern oxidation of the alcohol **24** (1.6 g, 6.7 mmol) afforded the ketone **13** (1.34 g, 5.71 mmol) in 85% yield as described for preparation of compound **23**: R_f = 0.5 (EtOAc/hexane = 1:10); δ_H (600 MHz, $CDCl_3$)6.43−6.39 (m, 2H), 6.16−6.13 (m, 2H), 5.66 (d, J = 10.2 Hz, 1H), 4.43 (s, 2H), 3.30 (s, 3H), 3.15−3.10 (m, 3H), 2.96 (s, 1H), 2.57 (s, 1H), 1.66 (d, J = 9.0 Hz, 1H), 1.49 (s, 3H), 1.46 (d, J = 9.0 Hz, 1H); δ_C (51 MHz, $CDCl_3$)200.8, 137.7, 135.9, 134.4, 126.2, 96.6, 73.0, 59.5, 55.1, 51.9, 49.7, 47.0, 46.9, 26.5; HRMS (ESI) m/z for $C_{14}H_{20}O_3Na$ $[M + Na]^+$ calcd 259.1310, found 259.1315.

General Procedure for RRM Reaction. Enone **13** (5.0 g, 42.3 mmol, 0.01M) was dissolved in 500 mL of anhydrous and degassed DCM and stirred at room temperature. Ethylene gas (prepared freshly by dropwise addition of phosphoricacid to ethanol) was bubbled through the solution for 15 min followed by addition of G- II catalyst (300 mg, 0.35 mmol, 3.5 mol %). The reaction flask was then again flushed with ethylene gas, and the reaction was allowed to stir for 12 h at room temperature under an ethylene balloon. The reaction solution was then concentrated under reduced pressure and the product was purified by column chromatography.

*(±)-6-((Methoxymethoxy)methyl)-6-methyl-5-vinyl-4,5,6,6a tetrahydropentalen-1(3aH)-one (**12**).* After the RRM reaction as stated earlier the product was purified by column chromatography (EtOAc/hexane = 1:5) to afford the compound **12** (879 mg, 3.72 mmol) in 88% yield: R_f = 0.5 (EtOAc/hexane = 1:5); δ_H (600 MHz, $CDCl_3$) 7.52 (dd, J = 5.4, 2.4 Hz, 1H), 5.97 (dd, J = 5.4, 1.8 Hz, 1H), 5.85−5.79 (m, 1H), 5.06−5.04 (m, 2H), 4.41 (d, J = 6.0 Hz, 1H), 4.38 (d, J = 6.0 Hz, 1H), 3.49 (d, J = 9.6 Hz, 1H), 3.48−3.46 (m, 1H), 3.42 (d, J = 9.6 Hz, 1H), 3.30 (s, 3H), 2.61 (d, J = 7.2 Hz, 1H), 2.58−2.55 (m, 1H), 2.03−1.98 (m, 1H), 1.89−1.84 (m, 1H), 1.15 (s, 3H); δ_C (150 MHz, $CDCl_3$) 210.7, 164.3, 137.4, 132.8, 116.2, 96.9, 70.6, 59.4, 58.5, 52.5, 47.0, 46.8, 34.9, 25.3; HRMS (ESI) m/z for $C_{14}H_{20}O_3Na$ $[M + Na]^+$ calcd 259.1310, found 259.1323.

*(±)-3-((tert-Butyldiphenylsilyloxy)methyl)-2-methylbicyclo[2.2.1]-hept-5-en-2-yl)methanol (**25a**).* To a solution of compound **21** (1.0 g, 6 mmol) in DCM (30 mL) were added sequentially imidazole (449 mg, 6.6 mmol) and *tert*-butyldiphenylsilyl chloride (TBDPS-Cl, 1.79 mL, 6.6 mmol) at 0 °C, and the reaction mixture was left at room temperature for 4 h. Water was then added to the reaction solution, which was then extracted with DCM. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The crude product was then purified by column chromatography (EtOAc/hexane = 1:50) to afford the mono TBDPS protected ethers in 7:3 (**25a**/**25b**) ratio.

*3-((tert-Butyldiphenylsilyloxy)methyl)-2-methylbicyclo[2.2.1]-hept-5-en-2-yl)methanol (**25a**):* R_f = 0.5 (EtOAc/hexane = 1:5); δ_H (400 MHz, $CDCl_3$) 7.70−7.64 (m, 4H), 7.48−7.40 (m, 6H), 6.14 (dd, J = 5.8, 3.0 Hz, 1H), 5.87 (dd, J = 5.7, 2.9 Hz, 1H), 3.66−3.60 (m, 3H), 3.46 (t, J = 10.8 Hz, 1H), 3.30 (t, J = 10.8 Hz, 1H), 2.52 (s, 1H), 2.39 (s, 1H), 2.05−2.00 (m, 1H), 1.67 (d, J = 8.6 Hz, 1H), 1.41 (s, 3H), 1.33 (d, J = 8.6 Hz, 1H), 1.05 (s, 9H); δ_C (101 MHz, $CDCl_3$) 135.6, 135.5, 133.5, 129.9, 129.8, 127.8, 77.4, 77.0, 76.7, 67.8, 66.2, 53.2, 52.6, 47.4, 46.9, 46.6, 26.9, 26.7, 19.0; HRMS (ESI) m/z for $C_{26}H_{34}O_2SiNa$ $[M + Na]^+$ calcd 429.2226, found 429.2210.

*(±)-3-((tert-Butyldiphenylsilyloxy)methyl)-3-methylbicyclo[2.2.1]-hept-5-en-2-yl)methanol (**25b**):* R_f = 0.5 (EtOAc/hexane = 1:5); δ_H (400 MHz, $CDCl_3$) 7.69−7.62 (m, 4H), 7.47−7.37 (m, 6H), 6.02 (dd, J = 5.8, 2.9 Hz, 1H), 5.95 (dd, J = 5.8, 2.9 Hz, 1H), 3.59 (d, J = 10.3 Hz, 1H), 3.51 (dd, J = 11.5, 5.1 Hz, 1H), 3.43 (dd, J = 11.5, 9.9 Hz, 1H), 3.30 (d, J = 10.3 Hz, 1H), 2.74 (s, 1H), 2.23 (d, J = 2.5 Hz, 1H), 2.15−2.10 (m, 1H), 1.66 (dt, J = 8.6, 1.5 Hz, 1H), 1.36−1.28 (m, 4H), 1.05 (s, 9H); δ_C (101 MHz, $CDCl_3$) 136.3, 135.9, 135.6, 134.2, 129.8, 127.8, 77.3, 77.0, 76.7, 68.9, 64.4, 53.3, 53.1, 47.4, 46.9, 46.8, 27.3, 27.0, 19.3; HRMS (ESI) m/z for $C_{26}H_{34}O_2SiNa$ $[M + Na]^+$ calcd 429.2226, found 429.2235.

*(±)-1-(3-((tert-Butyldiphenylsilyloxy)methyl)-3-methylbicyclo-[2.2.1]hept-5-en-2-yl)prop-2-en-1-ol (**26**).* Swern oxidation of the alcohol **25b** (2.43 g, 6 mmol) was performed as described earlier for the preparation of compound **23**, afforded the aldehyde as colorless oil which was then used for the next step without further purification.

A freshly generated solution of vinylmagnesium bromide (7.2 mL, 7.2 mmol) was added to the aldehyde taken in 25 mL of anhydrous THF at −78 °C. The reaction mixture was then kept at room temperature for 1 h, and then saturated NH_4Cl solution was added.

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J. Org. Chem. 2018, 83, 2087−2103

The solution was then extracted with EtOAc, and the organic layer was washed with water and brine. The organic layer was dried (Na_2SO_4) and evaporated under reduced pressure. Purification of the crude residue by column chromatography and the alcohol **26** (1.94 g, 4.5 mmol) was obtained with 75% over all yield (1.94 g): R_f = 0.5 (EtOAc/hexane = 1:10); δ_H (400 MHz, $CDCl_3$) 7.74−7.66 (m, 4H), 7.48−7.38 (m, 6H), 6.04 (dd, J = 5.6, 2.9 Hz, 1H), 5.96−5.89 (m, 2H), 5.29−5.16 (m, 2H), 4.67 (s, 1H), 3.80−3.74 (m, 2H), 3.38 (d, J = 10.5 Hz, 1H), 2.70 (s, 1H), 2.20 (s, 1H), 1.94−1.90 (m, 1H), 1.64−1.62 (m, 1H), 1.31 (s, 4H), 1.09 (s, 9H); δ_C (101 MHz, $CDCl_3$) 140.1, 136.2, 136.0, 135.7, 134.1, 130.0, 129.9, 127.8, 127.8, 115.4, 74.9, 68.9, 57.9, 53.7, 47.3, 47.1, 46.9, 27.4, 27.0, 19.3; HRMS (ESI) m/z for $C_{28}H_{36}O_2SiNa$ $[M + Na]^+$ calcd 455.2383, found 455.2370.

*(±)-1-(3-((tert-Butyldiphenylsilyloxy)methyl)-3-methylbicyclo-[2.2.1]hept-5-en-2-yl)prop-2-en-1-one (**27**).* Swern oxidation of the alcohol **26** (600 mg, 1.4 mmol) afforded the ketone **27** (510 mg, 1.19 mmol) in 85% yield: R_f = 0.5 (EtOAc/hexane = 1:10) δ_H (400 MHz, $CDCl_3$) 7.61−7.58 (m, 4H), 7.41−7.34 (m, 6H), 6.33−6.25 (m, 2H), 6.08−6.03 (m, 2H), 5.56 (d, J = 10.5, Hz, 1H), 3.33 (d, J = 9.6 Hz, 1H), 3.19 (d, J = 9.6 Hz, 1H), 3.05 (d, J = 2.8 Hz, 1H), 2.93 (s, 1H), 2.63 (s, 1H), 1.62 (d, J = 8.6 Hz, 1H), 1.47 (s, 3H), 1.44 (d, J = 8.6 Hz, 1H), 1.04 (s, 9H); δ_C (101 MHz, $CDCl_3$) 200.8, 137.6, 135.8, 135.7, 134.8, 133.8 129.5, 127.5, 126.4, 68.5, 59.9, 51.8, 51.0, 46.9, 46.6, 27.0, 26.5, 19.4; HRMS (ESI) m/z for $C_{28}H_{34}O_2SiNa$ $[M + Na]^+$ calcd 453.2226, found 453.2221.

*(±)-6-((tert-Butyldiphenylsilyloxy)methyl)-6-methyl-5-vinyl-4,5,6,6a-tetrahydropentalen-1(3aH)-one (**28**).* After the RRM reaction on compound **27** (510 mg, 1.19 mmol) as described previously, the product was purified by column chromatography (EtOAc/hexane = 1:10) to afford the bicyclic enone **28** (435 mg, 1.01 mmol) in 82% yield: mp 188−190 °C: R_f = 0.5 (EtOAc/hexane = 1:5); δ_H (400 MHz, $CDCl_3$) δ 7.71−7.58 (m, 4H), 7.57 (dd, J = 5.7, 2.8 Hz, 1H), 7.47−7.33 (m, 6H), 6.03 (dd, J = 5.6, 1.9 Hz, 1H), 5.43−5.34 (m, 1H), 4.84 (dd, J = 17.0, 2.3 Hz, 1H), 4.66 (dd, J = 10.2, 2.3 Hz, 1H), 3.82 (d, J = 10.6 Hz, 1H), 3.45 (dtt, J = 8.9, 6.7, 2.3 Hz, 1H), 3.38 (d, J = 10.5 Hz, 1H), 2.58 (d, J = 6.9 Hz, 1H), 2.51−2.41 (m, 1H), 2.00 (ddd, J = 12.3, 9.0, 6.8 Hz, 1H), 1.91 (td, J = 12.0, 11.6, 8.7 Hz, 1H), 1.05 (s, 3H), 1.03 (s, 9H); δ_C (101 MHz, $CDCl_3$) 210.4, 164.7, 137.8, 136.2, 133.7, 133.3, 129.5, 127.5, 115.7, 65.5, 58.7, 58.7, 48.9, 46.8, 34.4, 27.2, 25.5, 19.1; HRMS (ESI) m/z for $C_{28}H_{34}O_2SiNa$ $[M + Na]^+$ calcd 453.2226, found 453.2228.

General Procedure for Vinyl Grignard Reaction. To a stirred suspension of Mg turnings (1.5 equiv) in dry THF was added a small amount of 1,2 dibromoethane and the suspension refluxed until effervescence ended. Properly substituted vinylic bromide in THF solvent (2 equiv) was then added slowly, and the solution was stirred for 30 min. After 30 min, the reaction mixture was cooled to −78 °C, and the aldehyde (1 equiv) was then added dropwise. The reaction mixture was then allowed to attain room temperature over 2 h. The reaction solution was then quenched with saturated solution of ammonium chloride and extracted with ethyl acetate. The organic extract was washed with brine and dried over Na_2SO_4. The organic solution was concentrated under reduced pressure, and the product was purified by column chromatography.

General Procedure for DMP Oxidation Reaction. To a solution of the secondary alcohol (1 equiv) in DCM were added $NaHCO_3$ (5 equiv) and DMP sequentially. The reaction mixture was then stirred at room temperature for 2 h; after that time, TLC analysis indicated that complete conversion was achieved. The reaction solution was then quenched with saturated $Na_2S_2O_3$, and extracted with DCM. The organic solution was then successively washed with saturated $NaHCO_3$ and brine. The organic solution was then dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the crude carbonyl compound. The crude product was then immediately purified by column chromatography.

*(±)-1-(3-((Methoxymethoxy)methyl)-3-methylbicyclo[2.2.1]hept-5-en-2-yl)-2-methylprop-2-en-1-one (**29**):* R_f = 0.5 (EtOAc/hexane = 1:10); δ_H (600 MHz, $CDCl_3$) 6.41 (dd, J = 5.4, 3.0 Hz, 1H), 6.11 (dd, J = 5.4, 3.0 Hz, 1H), 5.91 (s, 1H), 5.72 (s, 1H), 4.42 (Abq, J = 6.0 Hz, 2H), 3.46 (d, J = 3.0 Hz, 1H), 3.29 (s, 3H), 3.09 (d, J = 9.0 Hz, 1H), 3.00 (d, J = 9.0 Hz, 1H), 2.90 (s, 1H), 2.56 (s, 1H), 1.83 (s, 3H); 1.66 (d, J = 8.4 Hz, 1H), 1.46 (s, 3H), 1.45 (d, J = 8.4 Hz, 1H); δ_C (151 MHz, $CDCl_3$) 203.1, 146.6, 136.3, 133.9, 123.6, 96.6, 72.7, 55.1, 52.1, 49.7, 47.6, 47.1, 25.8, 18.0; HRMS (ESI) m/z calcd. for $C_{15}H_{22}O_3Na$ $[M + Na]^+$ 273.1466, found 273.1459.

*(±)-1-(3-((Methoxymethoxy)methyl)-3-methylbicyclo[2.2.1]hept-5-en-2-yl)-2-phenylprop-2-en-1-one (**30**):* R_f = 0.5 (EtOAc/hexane = 1:10); δ_H (400 MHz, $CDCl_3$) 7.38−7.28 (m, 5H), 6.36 (dd, J = 5.6, 2.9 Hz, 1H), 6.15 (t, J = 4.2 Hz, 1H), 6.04 (s, 1H), 5.82 (s, 1H), 4.40 (s, 2H), 3.41 (d, J = 2.9 Hz, 1H), 3.27 (s, 3H), 3.20 (s, 2H), 2.97 (s, 1H), 2.54 (s, 1H), 1.63 (d, J = 8.9 Hz, 1H), 1.43 (d, J = 8.8 Hz, 1H), 1.36 (s, 3H); δ_C (151 MHz, $CDCl_3$) 203.0, 151.3, 137.7, 135.8, 134.6, 128.3, 128.2, 128.0, 123.6, 96.6, 77.2, 77.2, 77.0, 76.8, 72.8, 56.9, 55.2, 52.3, 50.4, 48.0, 47.1, 25.9; HRMS (ESI) m/z for $C_{20}H_{24}O_3Na$ $[M + Na]^+$ calcd 335.1623, found 335.1609

*(±)-1-(3-((Methoxymethoxy)methyl)-3-methylbicyclo[2.2.1]hept-5-en-2-yl)-3-methylbut-2-en-1-one (**31**):* R_f = 0.5 (EtOAc/hexane = 1:10); δ_H (400 MHz, $CDCl_3$) 6.40 (dd, J = 5.6, 3.0 Hz, 1H), 6.14−6.03 (m, 2H), 4.46 (dd, J = 8.4, 7.6, 2H), 3.31 (s, 3H), 3.18−3.08 (m, 2H), 2.95−2.89 (m, 1H), 2.83 (d, J = 2.9 Hz, 1H), 2.56 (d, J = 2.8 Hz, 1H), 2.08 (d, J = 1.3 Hz, 3H), 1.87 (d, J = 1.3 Hz, 3H), 1.58 (d, J = 5.9 Hz, 1H), 1.47 (s, 3H), 1.42 (d, 1.3 Hz, 1H); δ_C (101 MHz, $CDCl_3$) 201.3, 154.1, 136.1, 134.5, 125.3, 96.7, 73.4, 63.6, 55.2, 51.8, 49.1, 46.8, 46.7, 27.8, 26.7, 20.7; HRMS (ESI) m/z for $C_{16}H_{24}O_3Na$ $[M + Na]^+$ calcd 287.1623, found 287.1627.

*(±)-(E)-1-(3-((Methoxymethoxy)methyl)-3-methylbicyclo[2.2.1]-hept-5-en-2-yl)-3-phenylprop-2-en-1-one (**32**):* R_f = 0.5 (EtOAc/hexane = 1:10); δ_H (600 MHz, $CDCl_3$) 7.60−7.53 (m, 2H), 7.48 (d, J = 16.0 Hz, 1H), 7.41 (dd, J = 5.0, 2.0 Hz, 3H), 6.78 (d, J = 16.0 Hz, 1H), 6.44 (dd, J = 5.7, 3.0 Hz, 1H), 6.16 (dd, J = 5.7, 3.1 Hz, 1H), 4.43 (s, 2H), 3.29 (s, 3H), 3.23−3.13 (m, 3H), 3.02 (dt, J = 3.5, 1.6 Hz, 1H), 2.60 (t, J = 2.3 Hz, 1H), 1.71 (dt, J = 8.8, 1.6 Hz, 1H), 1.56 (s, 3H), 1.53−1.47 (m, 1H); δ_C (151 MHz, $CDCl_3$) 200.4, 140.9, 136.1, 134.8, 134.5, 130.2, 128.9, 128.3, 127.5, 96.7, 73.2, 61.1, 55.2, 52.0, 49.9, 47.2, 47.0, 26.8; HRMS (ESI) m/z for $C_{20}H_{24}O_3Na$ $[M + Na]^+$ calcd 335.1623, found 335.1627.

*(±)-(Z)-1-(3-((Methoxymethoxy)methyl)-3-methylbicyclo[2.2.1]-hept-5-en-2-yl)but-2-en-1-one (**33**):* R_f = 0.5 (EtOAc/hexane = 1:10); δ_H (600 MHz, $CDCl_3$) 6.78 (dt, J = 15.3, 7.0 Hz, 1H), 6.39 (dd, J = 5.7, 3.0 Hz, 1H), 6.21−6.10 (m, 2H), 4.46 (d, J = 3.3 Hz, 2H), 3.32 (s, 2H), 3.16−3.08 (m, 2H), 3.02 (d, J = 3.0 Hz, 1H), 2.94 (s, 1H), 2.58 (s, 1H), 1.89 (dd, J = 7.0, 1.7 Hz, 3H), 1.66−1.57 (m, 4H), 1.52−1.40 (m, 5H); δ_C (151 MHz, $CDCl_3$) 200.3, 141.0, 136.1, 134.4, 133.0, 96.7, 73.2, 60.2, 55.2, 51.9, 49.3, 47.0, 46.8, 26.6, 18.1; HRMS (ESI) m/z for $C_{15}H_{22}O_3Na$ $[M + Na]^+$ calcd 273.1466, found 273.1462.

*(±)-(E)-1-(3-((Methoxymethoxy)methyl)-3-methylbicyclo[2.2.1]-hept-5-en-2-yl)but-2-en-1-one (**34**):* R_f = 0.5 (EtOAc/hexane = 1:10); δ_H (600 MHz, $CDCl_3$) 6.42 (dd, J = 5.7, 3.0 Hz, 1H), 6.19 (dd, J = 11.4, 1.8 Hz, 1H), 6.15−6.09 (m, 2H), 4.48 (s, 2H), 3.33 (s, 3H), 3.21−3.12 (m, 2H), 2.99−2.95 (m, 1H), 2.89 (d, J = 2.9 Hz, 1H), 2.58 (s, 1H), 2.08 (dd, J = 7.1, 1.6 Hz, 3H), 1.60 (d, J = 9.4 Hz, 1H), 1.48 (s, 3H), 1.45 (d, J = 9.4 1H); δ_C (151 MHz, $CDCl_3$)202.3, 141.9, 136.0, 134.6, 129.2, 96.7, 73.2, 63.5, 55.2, 51.8, 49.3, 46.7, 46.9, 26.7, 15.8; HRMS (ESI) m/z for $C_{15}H_{22}O_3Na$ $[M + Na]^+$ calcd 273.1466, found 273.1461.

*(±)-1-(3-((Methoxymethoxy)methyl)-3-methylbicyclo[2.2.1]hept-5-en-2-yl)-2-methylbut-2-en-1-one (**35**):* R_f = 0.5 (EtOAc/hexane = 1:10); δ_H (400 MHz, $CDCl_3$) 6.29 (dd, J = 5.7, 3.0 Hz, 1H), 6.17 (dd, J = 5.6, 3.1 Hz, 1H), 5.63 (dd, J = 7.4, 1.8 Hz, 1H), 4.42 (s, 2H), 3.29 (s, 3H), 3.26−3.16 (m, 2H), 3.10 (d, J = 2.9 Hz, 1H), 2.98−2.92 (m, 1H), 2.53 (s, 1H), 1.93 (s, 3H), 1.88−1.83 (m, 1H), 1.72−1.76 (m, 4H), 1.65 (d, J = 8.6 Hz, 1H), 1.46−1.37 (m, 6H); δ_C (101 MHz, $CDCl_3$) 207.5, 138.7, 135.6, 134.9, 130.4, 96.8, 72.9, 58.7, 55.3, 52.5, 50.9, 47.9, 47.3, 26.8, 21.0, 15.5; HRMS (ESI) m/z for $C_{16}H_{24}O_3Na$ $[M + Na]^+$ calcd 287.1623, found 287.1625.

General Procedure for Barbier-Type Allylation. To a suspension of metallic In powder (1.2 equiv) in dry DMF were added NaI (4 equiv) and substituted allyl bromide (3 equiv), and the solution was kept at room temperature for 30 min. After that time, aldehyde (1 equiv) was added, and the reaction mixture was stirred at

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J. Org. Chem. 2018, 83, 2087−2103

the same temperature overnight. After completion of the reaction, the reaction mixture was filtered through a Celite pad and washed with ethyl acetate. The combined filtrate was extracted with ethyl acetate. The combined organic layer was washed with brine and it was then dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was then subjected to flash chromatography to afford the secondary alcohol.

*(±)-1-((3-((Methoxymethoxy)methyl)-3-methylbicyclo[2.2.1]hept-5-en-2-yl)but-3-en-1-one (**36**):* R_f = 0.5 (EtOAc/hexane = 1:10); δ_H (600 MHz, $CDCl_3$) 6.32 (dd, J = 5.4, 2.4 Hz, 1H), 6.10 (dd, J = 5.4, 2.4 Hz, 1H), 5.92−5.85 (m, 1H), 5.15 (dd, J = 10.2, 1.2 Hz, 1H), 5.10 (dd, J = 10.2, 1.2 Hz, 1H), 4.44 (d, J = 6.6 Hz, 1H), 4.39 (d, J = 6.6 Hz, 1H), 3.30 (s, 3H), 3.29−3.27 (m, 1H), 3.26−3.21 (m, 2H), 3.09 (d, J = 9.0 Hz, 1H), 2.89 (s, 2H), 2.46 (s, 1H), 1.64 (d, J = 9.0 Hz, 1H), 1.44 (s, 3H), 1.41 (d, J = 9.0 Hz, 1H); δ_C (151 MHz, $CDCl_3$) 209.5, 135.6, 134.2, 131.3, 118.2, 96.6, 72.9, 60.1, 55.2, 52.2, 50.6, 50.5, 50.3, 47.5, 47.4, 47.3, 26.6; HRMS (ESI) m/z for $C_{15}H_{22}O_3Na$ $[M + Na]^+$ calcd 273.1466, found 273.1459

*(±)1-(3-((Methoxymethoxy)methyl)-3-methylbicyclo[2.2.1]hept-5-en-2-yl)-3-methylbut-3-en-1-one (**37**):* R_f = 0.5 (EtOAc/hexane = 1:10); δ_H (400 MHz, $CDCl_3$) 6.34−6.27 (m, 1H), 6.14−6.07 (m, 1H), 4.92 (s, 1H), 4.78 (s, 1H), 4.43 (q, J = 6.5 Hz, 2H), 3.31 (d, J = 4.7 Hz, 3H), 3.22 (d, J = 10.5 Hz, 2H), 3.11 (d, J = 7.4 Hz, 2H), 2.99−2.93 (m, 1H), 2.86 (s, 1H), 2.47 (s, 1H), 1.73 (s, 3H), 1.63 (d, J = 8.7 Hz, 1H), 1.4−1.39 (m, 4H); δ_C (101 MHz, $CDCl_3$) 209.5, 140.0 135.7, 134.5, 114.7, 96.8, 73.0, 59.7, 55.3, 54.9, 52.4, 50.4, 47.8, 47.4, 26.7, 22.9; HRMS (ESI) m/z for $C_{16}H_{24}O_3Na$ $[M + Na]^+$ calcd 287.1623, found 287.1627.

*(±)-1-(3-((Methoxymethoxy)methyl)-3-methylbicyclo[2.2.1]hept-5-en-2-yl)-2,2-dimethylbut-3-en-1-one (**40**):* R_f = 0.5 (EtOAc/hexane = 1:10); δ_H (400 MHz, $CDCl_3$) 6.14 (s, 2H), 5.95 (dd, J = 17.6, 10.4 Hz, 1H), 5.20−5.16 (m, 2H), 4.40 (d, J = 6.4 Hz, 1H), 4.35 (d, J = 6.4 Hz, 1H), 3.28 (s, 3H), 3.22 (d, J = 9.2 Hz, 1H), 3.10−3.05 (m, 2H), 2.73 (s, 1H), 2.42 (s, 1H), 1.66−1.63 (m, 2H), 1.36 (s, 3H), 1.18 (s, 3H), 1.17 (s, 3H); δ_C (100 MHz, $CDCl_3$) 213.2, 142.8, 135.3, 134.8, 114.3, 96.7, 72.7, 55.3, 54.0, 52.8, 52.1, 51.8, 50.1, 47.9, 26.1, 23.3, 23.1; HRMS (ESI) m/z calcd. for $C_{17}H_{26}O_3Na$ $[M + Na]^+$, 301.1779, found 301.1779; HRMS (ESI) m/z for $C_{17}H_{26}O_3Na$ $[M + Na]^+$ calcd 301.1781, found 301.1792.

*(±)-1-(3-((Methoxymethoxy)methyl)-3-methylbicyclo[2.2.1]hept-5-en-2-yl)pent-4-en-1-one (**38**).* For the synthesis of compound **38**, a similar procedure was followed as depicted previously with freshly generated homoallyl Grignard reagent followed by DMP oxidation to furnish the desired compound in 81% overall yield: R_f = 0.5 (EtOAc/hexane = 1:10); δ_H (400 MHz, $CDCl_3$) 6.30 (dd, J = 5.6, 3.2 Hz, 1H), 6.10 (dd, J = 5.6, 3.2 Hz, 1H), 5.76−5.83 (m, 1H), 5.03−4.94 (m, 2H), 4.41 (Abq, J = 6.4 Hz, 2H), 3.27 (s, 3H), 3.18 (d, J = 8.8 Hz, 1H), 3.16 (d, J = 8.8 Hz, 1H), 2.88−2.82 (m, 2H), 2.62−2.50 (m, 3H), 2.46 (s, 1H), 2.32−2.26 (m, 1H), 2.20−2.16 (m, 1H), 1.65−1.60 (m, 1H), 1.42 (s, 3H); δ_C (101 MHz, $CDCl_3$) 211.1, 137.7, 135.7, 134.5, 115.0, 96.7, 73.0, 60.9, 55.3, 52.2, 50.3, 47.4, 44.8, 29.8, 27.9, 26.8; HRMS (ESI) m/z for $C_{16}H_{24}O_3Na$ $[M + Na]^+$ calcd 287.1623, found 287.1620.

*(±)-1-(3-((Methoxymethoxy)methyl)-3-methylbicyclo[2.2.1]hept-5-en-2-yl)-3-phenylprop-2-yn-1-one (**39**).* To a solution of phenyl acetylene (0.33 mL, 3 mmol) in dry THF, ^{n}BuLi was added slowly at −78 °C. The reaction mixture was then kept at same temperature for 1 h and then aldehyde **23** (420 mg, 2 mmol) was added slowly to the reaction solution. The reaction mixture was allowed to attain room temperature over 1.5 h and stirred at room temperature for another 1 h and then quenched with saturated NH_4Cl solution. The organic part was separated out and aqueous part was washed with ethyl acetate. The combined organic layer was dried over Na_2SO_4 and concentrated under reducer pressure. The crude material was then subjected to flash chromatography to provide the secondary alcohol which on DMP oxidation according to the stated procedure furnished compound **39** with 80% overall yield: R_f = 0.5 (EtOAc/hexane = 1:10); δ_H (400 MHz, $CDCl_3$) 7.60−7.53 (m, 2H), 7.46 (t, J = 7.4 Hz, 1H), 7.39 (t, J = 7.6 Hz, 2H), 6.38 (dd, J = 5.6, 2.8 Hz, 1H), 6.21 (dd, J = 5.5, 3.0 Hz, 1H), 4.52 (s, 2H), 3.47 (d, J = 9.1 Hz, 1H), 3.35 (s, 3H), 3.22 (d, J = 9.0 Hz, 1H), 3.12 (s, 1H), 3.08 (s, 1H), 2.64 (s, 1H), 1.66 (d, J = 8.9 Hz, 1H), 1.54 (s, 3H), 1.50 (d, J = 8.7 Hz, 1H); δ_C (101 MHz, $CDCl_3$) 188.2, 136.2, 135.3, 133.1, 133.0, 130.7, 128.8, 120.4, 96.9, 90.2, 89.4, 77.5, 77.2, 76.9, 73.3, 65.0, 55.4, 51.7, 50.1, 46.8, 46.8, 27.1; HRMS (ESI) m/z for $C_{20}H_{22}O_3Na$ $[M + Na]^+$ calcd 333.1468, found 333.1455.

*(±)-5-((Methoxymethoxy)methyl)-5-methyl-6-(vinyloxymethyl)-bicyclo[2.2.1]hept-2-ene (**41**).* To a solution of alcohol **22a** (318 mg, 1.5 mmol) in ethyl vinyl ether (3.5 mL) was added $Hg(OAc)_2$ (96 mg, 0.3 mmol) at 0 °C, and the reaction mixture was stirred at room temperature overnight. The reaction mixture was then concentrated under reduced pressure to afford a crude oil which was purified by flash chromatography (EtOAc/hexane = 1:30) on neutralized silica gel (with 1% Et_3N) to afford **41** (250 mg, 1.05 mmol, 70%) as a colorless oil: R_f = 0.5 (EtOAc/hexane = 1:15); δ_H (600 MHz, $CDCl_3$) 6.45 (dd, J = 14.3, 6.8 Hz, 1H), 6.26 (dd, J = 5.9, 3.1 Hz, 1H), 6.13 (dd, J = 5.9, 3.0 Hz, 1H), 4.62−4.53 (m, 2H), 4.13 (dd, J = 14.4, 1.9 Hz, 1H), 3.97 (dd, J = 6.8, 1.8 Hz, 1H), 3.61 (dd, J = 9.8, 6.4 Hz, 1H), 3.38 (s, 3H), 3.30 (t, J = 9.5 Hz, 1H), 3.25−3.14 (m, 2H), 2.92 (s, 1H), 2.60 (d, J = 2.5 Hz, 1H), 2.13 (ddd, J = 9.5, 6.4, 3.2 Hz, 1H), 1.66 (d, 8.4 Hz, 1H), 1.52−1.44 (d, 8.4 Hz, 1H), 1.33 (s, 3H); δ_C (151 MHz, $CDCl_3$) 151.9, 138.1, 134.0, 96.8, 86.2, 77.2, 77.0, 76.8, 72.8, 68.3, 55.2, 51.6, 49.5, 46.8, 45.7, 44.6, 26.6; HRMS (ESI) m/z for $C_{14}H_{22}O_3Na$ $[M + Na]^+$ calcd 261.1467, found 261.1460.

*(±)-6-(Allyloxymethyl)-5-((methoxymethoxy)methyl)-5-methylbicyclo[2.2.1]hept-2-ene (**42**).* To a solution of the alcohol **22a** (70 mg, 0.33 mmol) in THF (6.0 mL) was added 60% NaH (16 mg, 0.396 mmol) at 0 °C, and the solution was stirred for 30 min at the same temperature. Allyl bromide (0.037 mL, 0.429 mmol) was then added at 0 °C to the reaction solution and it was stirred for further 2 h. The reaction solution was then quenched with water and extracted successively with ethyl acetate. The organic layer was then washed with brine and dried over Na_2SO_4. The crude product was next purified by flash column chromatography to obtain compound **42** (73 mg, 0.29 mmol) in 88% yield: R_f = 0.5 (EtOAc/hexane = 1:20); δ_H (600 MHz, $CDCl_3$) 6.24 (dd, J = 5.8, 3.0 Hz, 1H), 6.13 (dd, J = 5.7, 2.9 Hz, 1H), 5.94−5.89 (m, 1H), 5.27 (dq, J = 17.2, 1.7 Hz, 1H), 5.18 (dq, J = 10.3, 1.5 Hz, 1H), 4.61−4.55 (m, 2H), 3.96−3.92 (m,, 2H), 3.38 (s, 3H), 3.31 (dd, J = 9.1, 6.3 Hz, 1H), 3.25−3.13 (m, 2H), 3.05 (t, J = 9.2 Hz, 1H), 2.92 (t, J = 2.4 Hz, 1H), 2.63−2.57 (m, 1H), 2.08−2.05 (m, 1H), 1.64 (d, J = 9.0, 1H), 1.46 (d, J = 8.4, 1H), 1.31 (s, 3H); δ_C (151 MHz, $CDCl_3$) 137.9, 135.1, 134.2, 116.6, 96.8, 72.8, 71.9, 70.5, 55.2, 51.5, 50.3, 46.7, 45.8, 44.5, 26.7; HRMS (ESI) m/z for $C_{15}H_{24}O_3Na$ $[M + Na]^+$ calcd 275.1623, found 275.1622.

*(±)-5,6-Bis(allyloxymethyl)-5-methylbicyclo[2.2.1]hept-2-ene (**43**):* R_f = 0.5 (EtOAc/hexane = 1:25); δ_H (600 MHz, $CDCl_3$) 6.23 (dd, J = 5.8, 3.1 Hz, 1H), 6.11 (dd, J = 5.8, 3.0 Hz, 1H), 5.95−5.84 (m, 2H), 5.33−5.23 (m, 2H), 5.16 (t, J = 10.8, 2H), 3.94−3.89 (m, 4H), 3.34 (dd, J = 9.3, 6.3 Hz, 2H), 3.13−3.01 (m, 3H), 2.90 (s, 1H), 2.58 (s, 1H), 2.06−2.01 (m, 1H), 1.63 (d, J = 7.8 1H), 1.44 (d, J = 8.4, 1H), 1.31 (s, 3H); δ_C (151 MHz, $CDCl_3$) 138.0, 135.4, 135.1, 134.0, 116.6, 116.2, 75.0, 72.1, 71.9, 70.7, 51.6, 50.2, 46.7, 45.8, 44.8, 26.8; HRMS (ESI)m/z for $C_{16}H_{24}O_2Na$ $[M + Na]^+$ calcd 271.1674, found 271.1671.

*(±)-1-(3-(Hydroxymethyl)-3-methylbicyclo[2.2.1]hept-5-en-2-yl)-prop-2-en-1-ol (**20**).* Compound **26** (430 mg, 1.0 mmol) was taken in dry THF 4 (mL) and treated with TBAF (1M) (1.1 mL, 1.1 mmol) at 0 °C and left for 5 h at room temperature. The reaction was quenched with addition of saturated NH_4Cl and extracted with ethyl acetate. The organic layer was washed with brine and dried over Na_2SO_4. The organic layer was evaporated under reduced pressure. The crude product was purified by column chromatography to afford compound **20** in (150 mg, 79%) yield: R_f = 0.5 (EtOAc/hexane = 1:2). δ_H (400 MHz, $CDCl_3$) δ 6.14 (dd, J = 5.8, 3.0 Hz, 1H), 6.05 (dd, J = 5.8, 2.9 Hz, 1H), 5.93−5.85 (m, 1H), 5.29−5.12 (m, 2H), 3.78 (dd, J = 10.6, 7.5 Hz, 1H), 3.66 (d, J = 11.3 Hz, 1H), 3.36 (d, J = 11.2 Hz, 1H), 2.68 (s, 1H), 2.34 (t, J = 2.3 Hz, 1H), 1.84 (dd, J = 10.5, 3.2 Hz, 1H), 1.68 (dt, J = 8.7, 1.5 Hz, 1H), 1.33 (d, J = 8.4 Hz, 1H), 1.34 (s, 3H); δ_C (101 MHz, $CDCl_3$) 140.1, 136.6, 133.7, 115.9, 75.6, 67.7, 56.7, 53.9,

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J. Org. Chem. 2018, 83, 2087−2103

47.2, 46.9, 46.9, 26.7; HRMS (ESI) m/z for $C_{12}H_{18}O_2Na$ $[M + Na]^+$ calcd 217.1205, found 217.1209.

*(±)-1-(−3-((4-Methoxybenzyloxy)methyl)-3-methylbicyclo[2.2.1]-hept-5-en-2-yl)prop-2-en-1-one (**44**).* The enone **44** was prepared from **25a** in five steps by following a series of known reactions in 39% yield (step 1: PMB protection; step 2: TBDPS removal with TBAF; step 3: Swern oxidation; step 4: vinyl Grignard addition; step 5: DMP oxidation); δ_H (400 MHz, $CDCl_3$) δ 7.23−7.11 (m, 2H), 6.91−6.77 (m, 2H), 6.46−6.30 (m, 2H), 6.16−6.01 (m, 2H), 5.59 (dt, J = 10.6, 1.5 Hz, 1H), 4.29−4.09 (m, 2H), 3.78 (d, J = 1.6 Hz, 3H), 3.14−2.94 (m, 3H), 2.92 (s, 1H), 2.58−2.49 (m, 1H), 1.70−1.57 (m, 1H), 1.46 (d, J = 1.5 Hz, 3H), 1.45−1.40 (m, 1H); δ_C (101 MHz, $CDCl_3$) 201.1, 158.9, 138.0, 135.8, 134.5, 130.9, 128.9, 125.9, 113.5, 74.9, 72.4, 59.5, 55.2, 52.0, 50.4, 47.0, 26.6; HRMS (ESI) m/z for $C_{20}H_{24}O_3Na$ $[M + Na]^+$ calcd 335.1623, found 335.1625.

*(±)-1-(3-((Methoxymethoxy)methyl)-2-methylbicyclo[2.2.1]hept-5-en-2-yl)prop-2-en-1-one (**45**).* For the preparation of compound **45** from compound **22b**, same procedure was followed which was used for the preparation of compound **13** from compound **22a**: R_f = 0.5 (EtOAc/hexane = 1:10); δ_H (600 MHz, $CDCl_3$) 6.73 (dd, J = 16.9, 10.3 Hz, 1H), 6.33 (dd, J = 5.8, 2.9 Hz, 1H), 6.25 (dd, J = 16.9, 2.0 Hz, 1H), 6.13 (dd, J = 5.8, 2.9 Hz, 1H), 5.61 (dd, J = 10.3, 2.0 Hz, 1H), 4.66−4.58 (m, 2H), 3.95 (dd, J = 10.0, 5.2 Hz, 1H), 3.38 (s, 3H), 3.11 (t, J = 10.3 Hz, 1H), 3.04 (dq, J = 3.5, 1.8 Hz, 1H), 2.85 (q, J = 2.0 Hz, 1H), 2.30−2.33 (m, 1H), 1.67 (dt, J = 8.7, 1.6 Hz, 1H), 1.52 (dt, J = 8.9, 1.9 Hz, 1H), 1.44 (s, 3H); δ_C (151 MHz, $CDCl_3$) 201.1, 138.0, 135.2, 133.5, 127.6, 96.6, 69.7, 58.0, 55.2, 53.7, 51.6, 45.9, 45.4, 26.8; HRMS (ESI) m/z for $C_{14}H_{20}O_3Na$ $[M + Na]^+$ calcd 259.1310, found 259.1314.

*((±))-6-((Methoxymethoxy)methyl)-2,6-dimethyl-5-vinyl-4,5,6,6a-tetrahydropentalen-1(3aH)-one (**46**):* R_f = 0.5 (EtOAc/hexane = 1:5); δ_H (600 MHz, $CDCl_3$) 7.13 (s, 1H), 5.81−5.75 (m, 1H), 5.02 (d, J = 12.0 Hz, 2H), 4.37 (q, J = 6.0 Hz, 2H), 3.45 (d, J = 9.6 Hz, 1H), 3.41 (d, J = 9.6 Hz, 1H), 3.35−3.30 (m, 1H), 3.30 (s, 3H), 2.62 (d, J = 6.6 Hz, 1H), 2.57−2.52 (m, 1H), 2.00−1.95 (m, 1H), 1.80−1.75 (m, 1H), 1.72 (s, 3H), 1.14 (s, 3H); δ_C (151 MHz, $CDCl_3$) 210.3, 157.8, 140.1, 137.6, 116.0, 96.8, 70.7, 59.2, 58.9, 55.4, 47.1, 44.0, 35.1, 25.4, 10.1; HRMS (ESI) m/z for $C_{15}H_{22}O_3Na$ $[M + Na]^+$ calcd 273.1466, found 273.1459.

*(±)-3-((Methoxymethoxy)methyl)-3-methyl-2-vinyl-3,3a,5,7a-tetrahydro-1H-inden-4(2H)-one (**47**):* R_f = 0.5 (EtOAc/hexane = 1:5); δ_H (400 MHz, $CDCl_3$) 5.78−5.72 (m, 2H), 5.63−5.60 (m, 1H), 5.09−5.04 (m, 2H), 4.42 (d, J = 6.8 Hz, 1H), 4.38 (d, J = 6.8 Hz, 1H), 3.41 (d, J = 9.6 Hz, 1H), 3.30 (s, 3H), 3.22 (d, J = 9.6 Hz, 1H), 3.10−3.05 (m, 1H), 2.90−2.80 (m, 2H), 2.51 (d, J = 10.4 Hz, 1H), 2.27−2.19 (m, 2H), 1.76−1.73 (m, 1H), 1.04 (s, 3H); δ_C (101 MHz, $CDCl_3$) 211.0, 137.1, 131.3, 120.6, 116.8, 96.9, 70.3, 58.3, 55.7, 54.6, 51.9, 39.1, 38.2, 37.5, 24.0; HRMS (ESI) m/z for $C_{15}H_{22}O_3Na$ $[M + Na]^+$ calcd 273.1466, found 273.1459.

*(±)-3-((Methoxymethoxy)methyl)-3-methyl-2-vinyl-1,3,3a,5,6,8a-hexahydroazulen-4(2H)-one (**48**):* R_f = 0.5 (EtOAc/hexane = 1:5); δ_H (400 MHz, $CDCl_3$) 5.99−5.90 (m, 1H), 5.63−5.61 (m, 1H), 5.52−5.50 (m, 1H), 5.01−4.94 (m, 2H), 4.46 (s, 2H), 3.75 (d, J = 9.2 Hz, 1H), 3.45−3.43 (m, 1H), 3.26 (s, 3H), 3.11−3.03 (m, 2H), 2.79−2.73 (m, 1H), 2.58−2.50 (m, 2H), 2.45−2.39 (m, 2H), 2.27−2.10 (m, 4H), 1.25 (s, 3H); δ_C (101 MHz, $CDCl_3$) 210.6, 139.2, 134.1, 128.0, 115.2, 97.0, 70.7, 61.5, 55.5, 53.0, 48.1, 45.3, 39.6, 27.8, 23.3; HRMS (ESI) m/z for $C_{16}H_{24}O_3Na$ $[M + Na]^+$ calcd 287.1623, found 287.1620.

*(±)-8-((Methoxymethoxy)methyl)-8-methyl-7-vinyl-3,5a,6,7,8,8a-hexahydro-1H-cyclopenta[c]oxepine (**49**):* R_f = 0.5 (EtOAc/hexane = 1:10); δ_H (600 MHz, $CDCl_3$) 5.84−5.78 (m, 1H), 5.48 (dq, J = 12.1, 2.5 Hz, 1H), 5.28 (dq, J = 11.9, 2.9 Hz, 1H), 5.07−5.00 (m, 2H), 4.54 (q, J = 6.5 Hz, 2H), 4.40 (dq, J = 16.9, 2.8 Hz, 1H), 4.15 (dq, J = 16.8, 2.9 Hz, 1H), 3.95 (dd, J = 11.9, 5.4 Hz, 1H), 3.80 (t, J = 11.8 Hz, 1H), 3.42−3.32 (m, 4H), 3.28−3.18 (m, 2H), 2.44 (td, J = 11.3, 5.4 Hz, 1H), 2.25 (dt, J = 12.1, 7.6 Hz, 1H), 2.18−2.12 (m, 1H), 1.68−1.57 (m, 2H), 1.02 (s, 3H); δ_C (151 MHz, $CDCl_3$) 138.3, 138.0, 132.9, 124.7, 115.6, 97.0, 71.4, 70.5, 68.4, 55.5, 55.4, 54.9, 46.8, 45.7, 38.5, 37.7, 23.1; HRMS (ESI) m/z for $C_{15}H_{24}O_3Na$ $[M + Na]^+$ calcd 275.1623, found 275.1628.

*(±)-8-(Allyloxymethyl)-8-methyl-7-vinyl-3,5a,6,7,8,8a-hexahydro-1H-cyclopenta[c]oxepine (**50**):* R_f = 0.5 (EtOAc/hexane = 1:11); δ_H (600 MHz, $CDCl_3$) 5.90−5.79 (m, 2H), 5.48 (d, J = 12.0 Hz 1H), 5.31−5.24 (m, 2H), 5.14 (d, J = 10.8 Hz, 1H), 5.06−4.99 (m, 2H), 4.39 (dt, J = 17.0, 2.7 Hz, 1H), 4.19−4.12 (m, 1H), 3.94 (dd, J = 12.8, 5.2 Hz, 2H), 3.86 (d, J = 5.0 Hz, 2H), 3.80 (t, J = 11.6 Hz, 1H), 3.21 (d, J = 9.6 Hz, 2H), 3.09 (d, J = 9.5 Hz, 1H), 2.42 (tt, J = 15.1, 7.4 Hz, 1H), 2.27−2.07 (m, 2H), 1.67 (q, J = 11.8 Hz, 1H), 1.01 (s, 3H); δ_C (151 MHz, $CDCl_3$) 138.3, 135.0, 132.8, 124.6, 116.0, 115.5, 72.8, 72.0, 71.3, 68.6, 55.3, 55.0, 47.3, 38.8, 38.1, 23.3; HRMS (ESI) m/z for $C_{16}H_{24}O_2Na$ $[M + Na]^+$ calcd 271.1674, found 271.1677.

*COMPOUND **51**:* R_f = 0.5 (EtOAc/hexane = 1:5); δ_H (600 MHz, $CDCl_3$) 5.70−5.66 (m, 1H), 5.52−5.49 (m, 2H), 5.33 (dq, J = 12.2, 2.7 Hz, 1H), 4.32 (dq, J = 17.1, 2.8 Hz, 1H), 4.25−4.11 (m, 3H), 3.90 (dd, J = 12.0, 4.7 Hz, 1H), 3.67 (dt, J = 12.0, 5.0 Hz, 2H), 3.55 (dd, J = 12.5, 0.8 Hz, 1H), 3.12−3.01 (m, 1H), 2.38−2.21 (m, 2H), 1.56 (td, J = 12.3, 10.6 Hz, 1H), 1.12 (s, 3H); δ_C (101 MHz, $CDCl_3$) 131.6, 130.0, 127.9, 125.5, 74.3, 71.4, 70.9, 68.4, 55.2, 50.7, 48.5, 41.6, 38.9, 25.3; HRMS (ESI) m/z for $C_{14}H_{20}O_2Na$ $[M + Na]^+$ calcd 243.1361, found 243.1346.

*(±)-6-((Methoxymethoxy)methyl)-6-methyl-5-vinyl-1,3a,4,5,6,6a-hexahydropentalen-1-ol (**52**):* R_f = 0.5 (EtOAc/hexane = 1:4); δ_H (400 MHz, $CDCl_3$) 5.95−5.93 (m, 1H), 5.74−5.60 (m, 2H), 5.04−4.98 (m, 1H), 4.97−4.87 (m, 2H), 4.65−4.54 (m, 2H), 3.58 (d, J = 9.8 Hz, 1H), 3.46−3.31 (m, 5H), 2.41−2.28 (m, 2H), 2.16−2.09 (m, 2H), 1.41 (dt, J = 12.9, 6.3 Hz, 1H), 1.18 (s, 3H); δ_C (101 MHz, $CDCl_3$) 139.0, 138.9, 131.7, 115.1, 97.1, 78.8, 72.2, 63.6, 55.9, 55.4, 48.5, 46.5, 34.9, 26.3; HRMS (ESI) m/z for $C_{14}H_{22}O_3Na$ $[M + Na]^+$ calcd 261.1467, found 261.1460.

*(±)-6-((tert-Butyldiphenylsilyloxy)methyl)-6-methyl-5-vinyl-1,3a,4,5,6,6a-hexahydropentalen-1-ol (**53**):* R_f = 0.5 (EtOAc/hexane = 1:4); δ_H (400 MHz, $CDCl_3$) 7.70−7.66 (m, 4H), 7.47−7.38 (m, 6H), 5.95−5.93 (m, 1H), 5.73−5.54 (m, 2H), 5.09 (d, J = 2.9 Hz, 1H), 4.90−4.77 (m, 2H), 3.71 (d, J = 10.4 Hz, 1H), 3.51 (d, J = 10.4 Hz, 1H), 3.43−3.40 (m, 1H), 2.40−2.28 (m, 2H), 2.15−2.08 (m, 1H), 1.45−1.34 (m, 1H), 1.12 (s, 3H), 1.08 (s, 9H); δC (101 MHz, $CDCl_3$)139.4, 139.0, 135.7, 133.5, 131.8, 129.7, 127.7, 114.8, 78.4, 67.0, 63.5, 55.4, 48.2, 48.1, 34.6, 27.1, 25.9, 19.4; HRMS (ESI) m/z for $C_{28}H_{36}O_2SiNa$ $[M + Na]^+$ calcd 455.2383, found 455.2388.

*(±)-6-(Hydroxymethyl)-6-methyl-5-vinyl-1,3a,4,5,6,6a-hexahydropentalen-1-ol (**54**):* R_f = 0.5 (EtOAc/hexane = 1:1.5) δ_H (400 MHz, $CDCl_3$) δ 5.95 (dt, J = 5.5, 1.9 Hz, 1H), 5.80−5.64 (m, 2H), 5.02−4.86 (m, 4H), 3.70 (d, J = 11.4 Hz, 1H), 3.46 (d, J = 11.5 Hz, 1H), 3.38−3.35 (m, 1H), 2.45−2.27 (m, 2H), 2.23−2.08 (m, 1H), 1.49−1.35 (m, 1H), 1.16 (s, 3H); δ_C (101 MHz, $CDCl_3$) 139.3, 139.3, 131.7, 115.0, 78.6, 66.8, 63.3, 55.5, 48.2, 47.9, 35.0, 25.9; HRMS (ESI) m/z for $C_{12}H_{18}O_2Na$ $[M + Na]^+$ calcd 217.1206, found 217.1200.

*(±)-6-((4-Methoxybenzyloxy)methyl)-6-methyl-5-vinyl-4,5,6,6a-tetrahydropentalen-1(3aH)-one (**55**):* R_f = 0.5 (EtOAc/hexane = 1:5); δ_H (600 MHz, $CDCl_3$) 7.43 (dd, J = 5.6, 2.8 Hz, 1H), 7.21−7.04 (m, 2H), 6.92−6.80 (m, 2H), 5.91 (dd, J = 5.8, 1.6 Hz, 1H), 5.70−5.83 (m, 1H), 5.13−4.92 (m, 2H), 4.23 (d, J = 11.4 Hz, 1H), 4.13 (d, J = 11.4 Hz, 1H), 3.80 (s, 3H), 3.45 (dd, J = 25.0, 9.3 Hz, 2H), 3.30 (d, J = 9.3 Hz, 1H), 2.56 (dd, J = 21.5, 9.2 Hz, 2H), 1.92−1.89 (m, 2H), 1.11 (s, 3H); δ_C (151 MHz, $CDCl_3$) 210.9, 163.8, 158.8, 137.7, 132.8, 130.7, 129.0, 116.1, 113.4, 72.7, 72.6, 60.0, 58.7, 55.2, 47.3, 47.0, 35.3, 25.4; HRMS (ESI) m/z for $C_{20}H_{24}O_3Na$ $[M + Na]^+$ calcd 335.1623, found 335.1629.

*(±)-6-((Methoxymethoxy)methyl)-6a-methyl-5-vinyl-4,5,6,6a-tetrahydropentalen-1(3aH)-one (**56**):* R_f = 0.5 (EtOAc/hexane = 1:5); δ_H (400 MHz, $CDCl_3$) 7.58 (dd, J = 5.6, 2.9 Hz, 1H), 6.00 (dd, J = 5.6, 1.8 Hz, 1H), 5.60−5.69 (m, 1H), 5.02−4.90 (m, 2H), 4.59−4.47 (m, 2H), 3.78 (dd, J = 10.2, 4.1 Hz, 1H), 3.51 (dd, J = 10.2, 7.9 Hz, 1H), 3.33 (s, 3H), 3.03−2.91 (m, 2H), 2.20−2.07 (m, 2H), 1.76 (dt, J = 13.1, 4.5 Hz, 1H), 1.29 (s, 3H); δ_C (101 MHz, $CDCl_3$) 213.4, 166.2, 138.5, 132.3, 116.1, 96.8, 65.5, 55.7, 55.4, 55.0, 52.8, 48.2, 34.6, 24.5; HRMS (ESI) m/z for $C_{14}H_{20}O_3Na$ $[M + Na]^+$ calcd 259.1310, found 259.1321.

*tert-Butyl 3-(1-(Methoxymethoxy)allyl)-2-methylbicyclo[2.2.1]-hept-5-en-2-yl)methoxy)diphenylsilane (**57**):* To a solution of

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J. Org. Chem. 2018, 83, 2087−2103

compound **26** (1.3 g, 3 mmol) in dry DCM (9 mL), DIPEA (0.6 mL, 3.3 mmol) and MOM-Cl(0.35 mL, 4.5 mL) was added sequentially at 0 °C. The mixture was left at room temperature for 1 day. The reaction was quenched with water and extracted with DCM. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. Purification of the crude residue by column chromatography gives compound **57** (1.15 g) with 81% yield: R_f = 0.5 (EtOAc/hexane = 1:50). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71−7.69 (m, 4H), 7.52−7.33 (m, 7H), 6.28 (dd, J = 5.9, 3.1 Hz, 1H), 5.97 (dd, J = 5.9, 3.0 Hz, 1H), 5.62−5.43 (m, 1H), 4.41 (dd, J = 6.6, 1.9 Hz, 1H), 4.21 (dd, J = 6.5, 2.4 Hz, 1H), 3.77 (d, J = 9.4 Hz, 1H), 3.45 (d, J = 9.6 Hz, 1H), 3.30 (dd, J = 10.9, 8.5 Hz, 1H), 2.90−2.87 (m, 1H), 2.86 (s, 3H), 2.66 (s, 1H), 1.89 (dd, J = 10.8, 3.3 Hz, 1H), 1.63 (q, J = 4.4 Hz, 1H), 1.44 (d, J = 3.6 Hz, 4H), 1.11 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.7, 138.3, 135.8, 135.7, 135.6, 134.2, 134.2, 133.0, 129.5, 129.4, 127.6, 127.5, 127.5, 117.8, 93.9, 79.4, 77.4, 77.1, 76.7, 68.8, 56.2, 55.3, 51.6, 46.7, 46.1, 27.8, 27.0, 27.0, 19.5; HRMS (ESI) m/z for $C_{30}H_{40}O_3SiNa$ $[M + Na]^+$ calcd 499.2645, found 499.2635.

*3-(1-(Methoxymethoxy)allyl)-2-methylbicyclo[2.2.1]hept-5-en-2-yl)prop-2-en-1ol (**58**).* Compound **57** (1.14 g, 2.4 mmol) was dissolved dry THF (8 mL), treated with TBAF (2.7 mL in, 1 M) at 0 °C, and left at room temperature for 2 h. The reaction solution was quenched with saturated NH_4Cl and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The crude product was used for next step. The primary alcohol was dissolved in dry DCM, $NaHCO_3$ was added, and then Dess−Martin periodinane was added at 0 °C. After 1 h, the reaction was quenched with $Na_2S_2O_3$ and extracted with DCM. The organic layer was washed with $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The crude aldehyde was then used for the next step.

The crude aldehyde was dissolved in dry THF, immediately treated with freshly prepared vinyl magnesium bromide solution (2.7 mL, 1 M) at −78 °C, and left at room temperature for 2 h. The reaction mixture was quenched with saturated NH_4Cl and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The crude product was purified by column chromatography to afford compound **58** (320 mg) with 50% overall yield: R_f = 0.5 (EtOAc/hexane = 1:50). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.22 (dd, J = 5.9, 2.9 Hz, 1H), 6.03 (dd, J = 6.0, 2.8 Hz, 1H), 5.96 (ddd, J = 16.8, 10.5, 6.1 Hz, 1H), 5.65 (dt, J = 17.2, 9.5 Hz, 1H), 5.40−5.14 (m, 4H), 4.76−4.65 (m, 2H), 4.54 (d, J = 6.3 Hz, 1H), 4.00 (d, J = 6.1 Hz, 1H), 3.83 (t, J = 9.8 Hz, 1H), 3.39 (s, 3H), 2.68 (s, 1H), 2.42 (s, 1H), 1.98 (dd, J = 10.6, 3.2 Hz, 1H), 1.64 (d, J = 8.7 Hz, 1H), 1.31 (d, J = 8.7 Hz 1H), 1.23 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.7, 137.1, 137.1, 133.8, 119.5, 116.1, 93.8, 80.7, 77.4, 77.0, 76.7, 74.0, 56.9, 56.1, 53.7, 50.5, 46.7, 46.2, 22.6; HRMS (ESI) m/z for $C_{16}H_{24}O_3Na$ $[M + Na]^+$ calcd 287.1623, found 287.1600.

*(±)-6-((Methoxymethoxy)methyl)-6-methyl-5-vinylhexahydropentalen-1(2H)-one (**59**). Procedure Using Stryker's Reagent.* $[(Ph_3P)CuH]_6$ (1.61 g, 0.82 mmol) was weighed under inert atmosphere and added to the solution of eneone **12** (484 mg, 2.05 mmol) in 20 mL of deoxygenated benzene at −78 °C under positive argon atmosphere. Then the resultant red solution was allowed to stir at room temperature until starting material had been consumed as shown by TLC analysis. The reaction solution was then diluted with EtOAc (50 mL) and washed with saturated NH_4Cl (20 mL), saturated $NaHCO_3$ (10 mL), and saturated NaCl (10 mL). The organic phase was dried over Na_2SO_4 and concentrated under vacuum to afford the ketone. The crude product was then purified by column chromatography (EtOAc/hexane = 1:9) to furnish ketone **59** (439 mg, 1.84 mmol, 90%) as a colorless oil.

Procedure Using CuI/LiAlH$_4$/HMPA Reagent. Dry CuI was dissolved in HMPA at 50 °C, and the solution was cooled to room temperature. Then the solution of CuI (1.32 g, 6.98 mmol) in HMPA (24 mL) was added dropwise at −78 °C to a vigorously stirred suspension of $LiAlH_4$ (265 mg, 6.98 mmol) in anhydrous THF (62 mL). The generated orange color suspension was gradually turned to brown. The stirring was continued for additional 1 h, and then enone **12** (823 mg, 3.49 mmol) in anhydrous THF (10 mL) was added dropwise to the mixture at −78 °C. Within 10 min, the enone was completely consumed as indicated by TLC analysis. The reaction mixture was then quenched with an aq saturated solution of NH_4Cl (5 mL) at −78 °C and the resulting mixture was warmed to room temperature. The reaction mixture was then filtered through a pad of silica gel, which was washed with EtOAc (100 mL). The combined filtrates were washed with water (50 mL) and brine (20 mL), dried with anhydrous Na_2SO_4, and filtered. The solvents were evaporated under reduced pressure to give the crude product, which was purified by column chromatography (EtOAc/hexane = 1:9) to furnish ketone **59** (714 mg, 3.0 mmol, 86%) as a colorless oil. In both the cases, the spectral characterization values are similar as given below: R_f = 0.6 (EtOAc/hexane = 1:5); δ_H (600 MHz, $CDCl_3$)5.90−5.84 (m, 1H), 5.08−5.05 (m, 2H), 4.45 (d, J = 6.6 Hz, 1H), 4.36 (d, J = 6.6 Hz, 1H), 3.41 (s, 2H), 3.34 (s, 3H), 2.91−2.88 (m, 1H), 2.58−2.52 (m, 1H), 2.36 (d, J = 10.2 Hz, 1H), 2.34−2.30 (m, 1H), 2.23−2.17 (m, 1H), 2.07−2.02 (m, 1H), 1.98−1.90 (m, 2H), 1.88−1.84 (m, 1H), 1.07 (s, 3H); δ_C (51 MHz, $CDCl_3$) 221.6, 137.6, 116.0, 96.7, 70.7, 59.9, 57.9, 55.6, 49.6, 40.2, 39.2, 38.6, 25.9, 25.7; HRMS (ESI) m/z for $C_{14}H_{22}O_3Na$ $[M + Na]^+$ calcd 261.1465, found 261.1465.

*(±)-6-((Methoxymethoxy)methyl)-2,2,6-trimethyl-5 vinylhexahydropentalen-1(2H)-one (**60**).* A magnetically stirred solution of the ketone **59** (476 mg, 2.0 mmol) in THF (8 mL) maintained at 0 °C was treated dropwise with LiHMDS (2.0 mL, 1 M solution in THF) over 5 min. The resulting mixture was stirred at 0 °C for 0.75 h then warmed to 18 °C over 1.25 h. The reaction mixture was recooled to 0 °C, and then MeI (0.2 mL, 3.0 mmol) was added dropwise. The reaction mixture was then allowed to stir for 0.75 h and warmed to 18 °C over a period of 1.25 h. The reaction mixture was then recooled to 0 °C and treated with a further aliquot of LiHMDS (2.0 mL of 1 M solution in THF) then MeI (0.2 mL, 3.0 mmol) using the warming and cooling cycle as mentioned above. This process was repeated twice more and then the reaction mixture was treated with NH_4Cl (10 mL) and $Na_2S_2O_3$ (10 mL). The separated aqueous phase was extracted with ethyl acetate (2 × 30 mL), filtered, and concentrated under reduced pressure to give dark yellow oil. The crude product was purified by column chromatography (EtOAc/hexane = 1:20) to afford ketone **60** (404 mg, 1.52 mmol, 78%) as a colorless oil: R_f = 0.4 (EtOAc/hexane = 1:10); δ_H (600 MHz, $CDCl_3$) 5.84−5.81 (m, 1H), 5.08−5.03 (m, 2H), 4.45 (d, J = 6.0 Hz, 1H), 4.37 (d, J = 6.0 Hz, 1H), 3.43 (d, J = 9.6 Hz, 1H), 3.33 (s, 3H), 3.29 (d, J = 9.6 Hz, 1H), 2.90−2.86 (m, 1H), 2.76 (d, J = 12.0 Hz, 1H), 2.40−2.37 (m, 1H), 2.09−2.06 (m, 1H), 2.05−1.99 (m, 1H), 1.78−1.71 (m, 1H), 1.70−1.68 (m, 1H), 1.12 (s, 3H), 1.06 (s, 3H), 1.02 (s, 3H); δ_C (51 MHz, $CDCl_3$) 223.0, 137.5, 116.0, 96.7, 69.2, 58.5, 58.1, 55.6, 50.3, 48.2, 45.6, 39.5, 35.4, 26.4, 25.0, 22.9; HRMS (ESI) m/z for $C_{16}H_{26}O_3Na$ $[M + Na]^+$ calcd 289.1779, found 289.1768.

*(±)-6-((Methoxymethoxy)methyl)-2,2,6-trimethyl-5-vinyloctahydropentalen-1-ol (**61**).* A magnetically stirred solution of LAH (39 mg, 1.0 mmol) in THF (3 mL) maintained at 0 °C was treated dropwise over 4 h, with a solution of ketone **60** (266 mg, 1.0 mmol) in THF (2 mL). After a further 2 h at 0 °C, the reaction mixture was quenched with addition of Na_2SO_4 (3 mL of a saturated solution). The resulting gray white precipitate was removed by filtration and washed with ethyl acetate. The combined filtrate was concentrated under reduced pressure to give colorless oil. Subjection of this material to flash chromatography (EtOAc/hexane = 1:5) afforded compound **61** (214 mg, 0.8 mmol, 80%) as a colorless oil: R_f = 0.2 (EtOAc/hexane = 1:5); δ_H (600 MHz, $CDCl_3$) 5.83−5.79 (m, 1H), 5.00−4.96 (m, 2H), 4.67 (d, J = 6.0 Hz, 1H), 4.62 (d, J = 6.0 Hz, 1H), 3.75−3.73 (m, 2H), 3.41 (s, 3H), 3.40 (d, J = 9.6 Hz, 1H), 3.35 (d, J = 9.6 Hz, 1H), 3.09 (s, 1H), 2.63−2.60 (m, 1H), 2.36−2.30 (m, 1H), 2.20 (t, J = 9.6 Hz, 1H), 2.04−2.00 (m, 1H), 1.77 (dd, J = 12.0, 9.0 Hz, 1H), 1.35−1.32 (m, 1H), 1.20−1.18 (m, 1H), 1.17 (s, 3H), 1.07 (s, 3H), 0.94 (s, 3H); δ_C (50 MHz, $CDCl_3$) 138.2, 115.1, 97.0, 81.1, 72.7, 59.9, 57.4, 55.7, 45.7, 45.4, 44.4, 38.4, 38.1, 27.2, 20.0; HRMS (ESI) m/z for $C_{16}H_{28}O_3Na$ $[M + Na]^+$ calcd 291.1935, found 291.1936.

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*(±)-6-(Hydroxymethyl)-2,2,6-trimethyl-5-vinyloctahydropentalen-1-ol (**62**).* Compound **61** (130 mg, 0.5 mmol) and PPTS (878 mg, 3.5 mmol) in *tert*-butyl alcohol (10 mL) was heated at 83 °C for 12 h. Then the reaction solution was cooled to room temperature and poured into water. The resulting mixture was extracted with EtOAc (3 × 20 mL). The combined organic layer were washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure. The crude material was next subjected to flash chromatography (EtOAc/hexane = 1:4) to afford the diol **62** (78 mg, 0.35 mmol, 70%) as a colorless oil: R_f = 0.5 (EtOAc/hexane = 1:3); δ_H (600 MHz, $CDCl_3$) 5.84−5.82 (m, 1H), 5.01−4.87 (m, 2H), 3.89 (d, *J* = 11.3 Hz, 1H), 3.81 (d, *J* = 9.9 Hz, 1H), 3.39 (d, *J* = 11.2 Hz, 1H), 2.67−2.55 (m, 1H), 2.34 (dt, *J* = 9.5, 7.2 Hz, 1H), 2.21 (t, *J* = 10.3 Hz, 1H), 2.13−2.09 (m, 1H), 1.95−1.86 (m, 1H), 1.82 (dd, *J* = 13.1, 9.1 Hz, 1H), 1.32 (dt, *J* = 13.4, 6.9 Hz, 1H), 1.22−1.19 (m, 1H), 1.17 (s, 3H), 1.05 (s, 3H), 0.91 (s, 3H); δ_C (151 MHz, $CDCl_3$) 139.1, 114.8, 81.8, 67.2, 59.1, 56.7, 47.5, 45.6, 44.1, 38.6, 37.5, 27.1, 27.1, 20.0; HRMS (ESI) *m*/*z* for $C_{14}H_{24}O_2Na$ $[M + Na]^+$ calcd 247.1674, found 247.1666..

*(±)-6-Hydroxy-1,5,5-trimethyl-2-vinyloctahydropentalene-1-carbaldehyde (**63**).* To the solution of the diol **62** (50 mg, 0.22 mmol) in dry DCM (1.5 mL), BAIB (86 mg, 0.27 mmol), and TEMPO (9 mg, 0.0.055 mmol) was added sequentially at 0 °C and left at room temperature for 5 h. After that time the reaction mixture was quenched with saturated solution of sodium thiosulfate. The organic layer was then extracted with DCM. The organic layer was then dried over Na_2SO_4 and evaporated under reduced pressure, and the product was purified through flash chromatography (EtOAc/hexane = 1:7) to afford the aldehyde **63** (37 mg, 76%): R_f = 0.5 (EtOAc/hexane = 1:8); δ_H (400 MHz, $CDCl_3$) 9.74 (s, 1H), 5.87−5.79 (m, 1H), 5.14−4.98 (m, 2H), 3.66 (d, *J* = 9.1 Hz, 1H), 2.78−2.71 (m, 1H), 2.59 (q, *J* = 8.3 Hz, 1H), 2.36 (dd, *J* = 11.5, 9.0 Hz, 1H), 2.16 (dt, *J* = 14.6, 7.5 Hz, 2H), 1.81 (dd, *J* = 12.9, 8.6 Hz, 1H), 1.62 (dt, *J* = 13.4, 9.0 Hz, 1H), 1.24 (s, 3H), 1.00 (s, 3H), 0.91 (s, 3H).

*(±)-6-(1-Hydroxyallyl)-2,2,6-trimethyl-5-vinyloctahydropentalen-1-ol (**64**).* Freshly generated solution of vinyl magnesium bromide (0.76 mL, 0.76 mmol) was added to a solution of aldehyde **63** (25 mg, 0.11 mmol) in anhydrous THF at −78 °C. The reaction mixture was then kept at the room temperature for 1 h, after that saturated NH_4Cl solution was added to it. The solution was then extracted with EtOAc, and the organic layer was washed with water and brine. The organic layer was dried (Na_2SO_4) and evaporated under reduced pressure. This material was next subjected to flash chromatography (EtOAc/hexane = 1:5) to afford the inseparable mixture of diol **64** (23 mg, 0.09 mmol, 82%) as a colorless oil: R_f = 0.5 (EtOAc/hexane = 1:8) δ_H (600 MHz, $CDCl_3$) 6.14−6.05 (m, 1H), 6.03−5.97 (m, 1H), 5.37 (dd, *J* = 17.3, 1.9 Hz, 1H), 5.22 (dt, *J* = 10.7, 1.8 Hz, 1H), 5.01−4.95 (m, 2H), 4.60 (dd, *J* = 4.0, 2.0 Hz, 1H), 4.01 (d, *J* = 9.3 Hz, 1H), 2.76 (q, *J* = 9.6 Hz, 1H), 2.38−2.24 (m, 3H), 1.88 (dd, *J* = 13.1, 9.3 Hz, 1H), 1.40 (dd, *J* = 13.0, 1.7 Hz, 1H), 1.26 (dd, *J* = 13.2, 9.9 Hz, 1H), 1.09 (s, 3H), 0.98 (s, 3H), 0.93 (s, 3H); δ_C (151 MHz, $CDCl_3$) 140.4, 136.7, 115.4, 115.1, 81.6, 73.3, 60.3, 55.4, 51.0, 46.9, 43.7, 37.8, 37.1, 27.0, 22.8, 19.6; HRMS (ESI) *m*/*z* for $C_{16}H_{26}O_2Na$ $[M + Na]^+$ calcd 273.1831, found 273.1826.

*Compound **65**.* The solution of the diol compound **64** (23 mg, 0.09 mmol) in dry dichloromethane (5.0 mL) was degassed for 30 min properly and to that solution HG-II catalyst (4 mg, 0.006 mmol) was added at room temperature. The reaction solution was then stirred for an hour at that temperature and after that the reaction solution was quenched by purging air to destroy any residual amount of catalyst. The solvent was evaporated, the crude mass was directly loaded to the column loaded with silica, the product was eluted (EtOAc/hexane = 1:3), and a crystalline solid **65** (18 mg, 0.08 mmol, 90%) was isolated: mp 112−115 °C: R_f = 0.5 (EtOAc/hexane = 1:3); δ_H (600 MHz, $CDCl_3$) 5.88 (dd, *J* = 5.8, 2.1 Hz, 1H), 5.79 (dt, *J* = 5.4, 2.3 Hz, 1H), 4.93 (d, *J* = 2.0 Hz, 1H), 3.62 (d, *J* = 9.0 Hz, 1H), 2.89−2.86 (m, 1H), 2.77−2.68 (m, 1H), 2.14−2.03 (m, 2H), 1.67 (dd, *J* = 12.8, 8.6 Hz, 1H), 1.32−1.24 (m, 1H), 1.19 (s, 3H), 1.06−0.99 (m, 1H), 0.97 (s, 3H), 0.88 (s, 3H); δ_C (151 MHz, $CDCl_3$) 140.1, 132.1, 83.3, 79.5, 60.9, 59.3, 54.8, 45.7, 44.2, 39.9, 35.9, 27.1, 23.5, 20.1; HRMS (ESI) *m*/*z* for $C_{14}H_{22}O_2Na$ $[M + Na]^+$ calcd 245.1518, found 245.1511.

*Compound **66**.* To the solution of the tricyclic diol compound **65** (15 mg, 0.067 mmol) in dry methanol was added Pd−C (5.0 mg, 0.046 mmol) at room temperature. The solution was then kept in the presence of H_2 atmosphere and stirred for 2.5 h. The reaction mixture was filtered out and washed with ethyl acetate. The filtrate was then evaporated under reduced pressure, and the product was purified by flash chromatography (EtOH/hexane = 1:4) to furnish a white solid compound **66** (7.5 mg, 0.033 mmol, 50%): R_f = 0.5 (EtOAc/hexane = 1:4); δ_H (600 MHz, $CDCl_3$) 4.43 (dd, *J* = 10.0, 7.0 Hz, 1H), 3.93 (d, *J* = 10.3 Hz, 1H), 2.59−2.53 (m, 1H), 2.18−2.11 (m, 3H), 2.03 (dt, *J* = 12.6, 7.6 Hz, 1H), 1.89−1.84 (m, 2H), 1.79−1.72 (m, 1H), 1.36−1.32 (m, 1H), 1.16 (dd, *J* = 13.2, 7.2 Hz, 1H), 1.10 (s, 3H), 1.06 (s, 3H), 0.98 (q, *J* = 11.9 Hz, 1H), 0.93 (s, 3H); δ_C (151 MHz, $CDCl_3$) 81.6, 75.8, 59.0, 54.2, 52.2, 44.9, 44.4, 40.4, 33.3, 27.3, 25.0, 22.7, 20.4; HRMS (ESI) *m*/*z* for $C_{14}H_{24}O_2Na$ $[M + Na]^+$ calcd 247.1674, found 247.1681.

*Compound **11**.* Diol **66** (7.5 mg, 0.033 mmol) was taken in dry DCM (3.0 mL), a finely grinded mixture of silicagel and PCC (4 equiv of PCC was mixed with equal weight of silicagel and grinded to a fine powder) was added at 0 °C and left at room temperature for 24 h. The reaction mixture was then filtered, and the residue was washed with ethyl acetate to furnish the crude product. The crude product was then purified through flash chromatography to afford pure diketone **11** as white solid (6.6 mg, 0.03 mmol). The spectral characteristic data for **11** are given in the following section.

*(±)-2a,6,6-Trimethyl-3-vinyloctahydro-2H-pentaleno[1,6-bc]-furan-6a-ol (**67**).* A mixture of compound **60** (130 mg, 0.5 mmol) and PPTS (878 mg, 3.5 mmol) in *tert*-butyl alcohol (10 mL) was heated at 83 °C for 12 h. Then the mixture was cooled to room temperature and poured into water. The resulting mixture was then extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The crude material was next subjected to flash chromatography to afford the lactol **67** (100 mg, 0.45 mmol, 90%) as a colorless oil: R_f = 0.2 (EtOAc/hexane = 1:10); δ_H (600 MHz, $CDCl_3$) 5.83−5.68 (m, 1H), 5.07−4.99 (m, 2H), 3.93 (d, *J* = 9.2 Hz, 1H), 3.70 (d, *J* = 9.2 Hz, 1H), 2.67 (d, *J* = 10.8 H, 1H), 2.61−2.52 (m, 1H), 2.46−2.41 (m, 1H), 1.83−1.82 (m, 1H), 1.43−1.37 (m, 2H), 1.30 (s, 3H), 1.01 (s, 3H), 0.97 (s, 3H); δ_C (51 MHz, $CDCl_3$) 137.8, 116.9, 115.8, 75.9, 64.4, 56.2, 52.6, 46.9, 46.8, 39.7, 36.2, 26.0, 24.7, 20.4; HRMS (ESI) *m*/*z* for $C_{14}H_{22}O_2Na$ $[M + Na]^+$ calcd 245.1546, found 245.1548.

*(±)-1,5,5-Trimethyl-6-oxo-2-vinyloctahydropentalene-1-carbaldehyde (**68**).* The lactol **67** (100 mg, 0.45 mmol) was dissolved in CH_2Cl_2 (5 mL) and PCC (582 mg, 2.7 mmol, 6 equiv) was added to the reaction solution. The reaction mixture instantly turned black, and it was stirred for an additional 12 h at room temperature. The heterogeneous mixture was then filtered through Celite, and removal of the solvent in vacuo gave crude product which was purified by flash chromatography to afford the aldehyde **68** (87 mg, 0.40 mmol, 88%) as a colorless oil: R_f = 0.5 (EtOAc/hexane = 1:10); δ_H (600 MHz, $CDCl_3$) 9.37 (s, 1H), 5.79−5.73 (m, 1H), 5.18−5.12 (m, 2H), 2.86−2.84 (m, 1H), 2.72 (d, *J* = 11.4 Hz, 1H), 2.54−2.52 (m, 1H), 2.22−2.18 (m, 1H), 2.08−2.05 (m, 1H), 1.79−1.75 (m, 1H), 1.56 (s, 3H), 1.45−1.41 (m, 1H), 1.26 (s, 3H), 1.03 (s, 3H); δ_C (51 MHz, $CDCl_3$) 223.3, 206.0, 134.7, 117.8, 61.9, 59.6, 58.1, 51.1, 45.8, 38.0, 34.6, 25.9, 23.0, 20.2; HRMS (ESI) *m*/*z* for $C_{14}H_{20}O_2Na$, $[M + Na]^+$ calcd 243.1360, found 243.1361.

*(±)-2a,6,6-Trimethyl-2,3-divinyloctahydro-2H-pentaleno[1,6-bc]-furan-6a-ol (**69**).* Freshly generated solution of vinyl magnesium bromide (0.76 mL, 0.76 mmol) was added to a solution of aldehyde **68** (80 mg, 0.36 mmol) taken in 2 mL of anhydrous THF at −78 °C. The reaction mixture was then kept at room temperature for 1 h followed by addition of saturated NH_4Cl solution. The reaction solution was extracted with EtOAc, and the organic layer was washed with water and brine. The organic layer was dried (Na_2SO_4) and evaporated under reduced pressure. This material was next subjected to flash chromatography to afford the lactol **69** (71 mg, 0.3 mmol, 83%) as a colorless oil: R_f = 0.6 (EtOAc/hexane = 1:10); δ_H (600 MHz, $CDCl_3$) 5.90−5.86 (m, 1H), 5.80−5.75 (m, 1H), 5.19−5.12 (m, 1H), 5.06−5.03 (m, 2H), 4.39 (d, *J* = 7.2 Hz, 1H), 2.73 (d, *J* = 11.4 Hz, 1H),

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2.68−2.63 (m, 1H), 2.51−2.49 (m, 1H), 2.16−2.11 (m, 1H), 1.83 (dd, J = 12.6, 9.0 Hz, 1H), 1.51−1.46 (m, 1H), 1.40 (dd, J = 8.4, 12.6 Hz, 1H), 1.18 (s, 3H), 1.01 (s, 3H), 0.99 (s, 3H); δ_C (51.0 MHz, $CDCl_3$) 138.2, 137.3, 116.0, 115.9, 115.8, 86.3, 66.4, 57.4, 54.9, 48.0, 47.8, 38.2, 36.3, 25.4, 21.5, 20.6; HRMS (ESI) m/z for $C_{16}H_{24}O_2Na$, $[M + Na]^+$ calcd 271.1673, found 271.1674.

Compound 11: RCM Reaction. The solution of the vinylic lactol **69** (60 mg, 0.24 mmol) in dry dichloromethane (2.0 mL) was degassed for 30 min by argon-purging. HG-II catalyst (8 mg, 0.01 mmol) was then added to the reaction solution at room temperature. The reaction solution was then stirred for 12 h at that temperature and after that the reaction solution was quenched with purging of air to destroy any residual amount of catalyst. The solvent was then evaporated under reduced pressure, and the crude product was directly subjected for the next step.

PCC Oxidation and Hydrogenation. The ring-closed product obtained in the previous step was taken in dry DCM (2.0 mL), a finely grinded mixture of silicagel and PCC (6 equiv of PCC was mixed with equal weight of silicagel and grinded to a fine powder) was added at 0 °C and left at room temperature for 24 h. The reaction mixture was then filtered, and the residue was washed with ethyl acetate. The combined filtrate was evaporated under reduced pressure and the crude material was used for the next step. To the crude tricyclic diketo compound in dry methanol was added Pd−C (40.0 mg, 0.375 mmol) at room temperature. The solution was then kept in the presence of H_2 atmosphere and stirred for 2.5 h. The reaction mixture was then filtered out and washed with ethyl acetate. The filtrate was then evaporated under reduced pressure. The product was purified by flash chromatography to afford diketone **11** (34 mg, 75% in three steps) as a white solid: mp 46−48 °C: R_f = 0.5 (EtOAc/hexane = 1:20); δ_H (600 MHz, $CDCl_3$) 2.89−2.79 (m, 1H), 2.75 (d, J = 10.2 Hz, 1H), 2.50−2.39 (m, 3H), 2.36−2.31 (m, 1H), 2.07−2.02 (m, 2H), 1.69−1.65 (m, 1H), 1.38 (dd, J = 13.1, 9.3 Hz, 1H), 1.34−1.29 (m, 1H), 1.25 (s, 3H), 1.14 (s, 3H), 1.03 (s, 3H); δ_C (101 MHz, $CDCl_3$) 221.6, 221.4, 61.3, 60.7, 51.7, 48.8, 46.0, 38.0, 37.1, 35.1, 26.2, 23.4, 23.2, 21.4; HRMS (ESI) m/z for $C_{14}H_{20}O_2Na$ $[M + Na]^+$ calcd 243.1361, found 243.1348.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b03021.

Experimental details and $^1H/^{13}C$/DEPT-135 NMR for all compounds; 2D-NOESY NMR spectra of some compounds (PDF)

X-ray data for compound **28** (CIF)

X-ray data for compound **65** (CIF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Devon, T. K., Scott, A. I. *Handbook of Naturally Occurring Compounds*; Academic Press: New York, 1972; Vol. *II*, p 180. (b) Nakanishi, K., Goto, T.; Ito, S.; Natori, S.; Nozoe, S. *Natural Products Chemistry*; Kodansha Ltd.: Tokyo, 1983; Vol. *III*, Chapter 2, pp 51−56.

(2) (a) Bohlmann, F.; Jakupovic, J. *Phytochemistry* **1980**, *19*, 259−265. (b) Sheikh, Y. M.; Singy, G.; Kaisin, M.; Eggert, H.; Djerassi, C.; Tursch, B.; Daloze, D.; Braekman, J. C. *Tetrahedron* **1976**, *32*, 1171−1178. (c) Martin, D. G.; Slomp, G.; Mizsak, S.; Duchamp, D. J.; Chidester, C. G. *Tetrahedron Lett.* **1970**, *11*, 4901−4904.

(3) (a) Paquette, L. A. *Topics in Current Chemistry*; Springer-Verlag, 1984; Vol. *119*, pp 1−146. (b) Paquette, L. A. *Topics in Current Chemistry* **1979**, *79*, 41−165.

(4) For recent reviews on the synthesis of linear triquinane natural products, see: (a) Mehta, G.; Srikrishna, A. *Chem. Rev.* **1997**, *97*, 671−719. (b) Singh, V.; Thomas, B. *Tetrahedron* **1998**, *54*, 3647−3692. (c) Paquette, L. A. *Curr. Org. Chem.* **2002**, *6*, 1045−1056. (d) Curran, P. V.; Rakiewicz, D. M. *J. Am. Chem. Soc.* **1985**, *107*, 1448−1449. (e) Wender, P. A.; Howbert, J. J. *Tetrahedron Lett.* **1982**, *23*, 3983. (f) Hudlicky, T.; Kutchan, T. M.; Wilson, S. R.; Mao, D. T. *J. Am. Chem. Soc.* **1980**, *102*, 6351−6353. (g) Mehta, G.; Murthy, N.; Reddy, D. S.; Reddy, A. V. *J. Am. Chem. Soc.* **1986**, *108*, 3443−3452. (h) Rawal, V. H.; Fabre, A.; Iwasa, S. *Tetrahedron Lett.* **1995**, *36*, 6851−6854. (i) Little, R. D.; Muller, G. W. *J. Am. Chem. Soc.* **1981**, *103*, 2744−2749.

(5) For methods on the total synthesis of hirsutene until 2004, see: Hudlicky, T.; Reed, J. W. *The Way of Synthesis*; Wiley-VCH: Weinheim2007.

(6) For recent reports on the total synthesis of hirsutene (since 2004), see: (a) Banwell, M. G.; Edwards, A. J.; Harfoot, G. J.; Jolliffe, K. A. *Tetrahedron* **2004**, *60*, 535−547. (b) Singh, V.; Vedantham, P.; Sahu, P. K. *Tetrahedron* **2004**, *60*, 8161−8169. (c) Jiao, L.; Yuan, C.; Yu, Z.-X. *J. Am. Chem. Soc.* **2008**, *130*, 4421−4430. (d) Chandler, C. L.; List, B. *J. Am. Chem. Soc.* **2008**, *130*, 6737−6739. (e) Fan, X.; Tang, M.-X.; Zhuo, L.-G.; Tu, Y. Q.; Yu, Z.-X. *Tetrahedron Lett.* **2009**, *50*, 155−157. (f) Shen, S.-J.; Li, W.-D. Z. *J. Org. Chem.* **2013**, *78*, 7112−7120.

(7) (a) Zielinski, G. K.; Grela, K. *Chem. - Eur. J.* **2016**, *22*, 9440−9454. (b) Vincent, G.; Karila, D.; Khalil, G.; Sancibrao, P.; Gori, D.; Kouklovsky, C. *Chem. - Eur. J.* **2013**, *19*, 9358−9365. (c) Porta, M.; Blechert, S. In *Metathesis in Natural Product Synthesis*; Cossy, J., Arseniyadis, S., Meyer, C., Eds.; Wiley-VCH: Weinheim, 2010; pp 313−342. (d) Schmidt, B.; Krehl, S. In *Domino and Other Olefin Metathesis Sequences, in Olefin Metathesis Theory and Practice*; Grela, K., Ed.; John Wiley & Sons, Inc., Hoboken, 2014; pp 187−232. (e) Kotha, S.; Aswar, V. S. *Org. Lett.* **2016**, *18*, 1808−1811. (f) Kotha, S.; Ravikumar, O.; Sreevani, G. *Tetrahedron* **2016**, *72*, 6611−6615. (g) Kotha, S.; Gunta, R. *J. Org. Chem.* **2017**, *82*, 8527−8535. (h) Weatherhead, G. S.; Cortez, G. A.; Schrock, R. R.; Hoveyda, A. H. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 5805−5809.

(8) Gogoi, S.; Argade, N. P. *Tetrahedron* **2004**, *60*, 9093−9097.

(9) Citron, C. A.; Wickel, S. M.; Schulz, B.; Draeger, S.; Dickschat, J. S. *Eur. J. Org. Chem.* **2012**, 6636−6646.

(10) Takasu, M.; Naruse, Y.; Yamamoto, H. *Tetrahedron Lett.* **1988**, *29*, 1947−1950.

(11) Mancuso, A. J.; Brownfain, D. S.; Swern, D. *J. Org. Chem.* **1979**, *44*, 4148−4150.

(12) (a) Wrobleski, A.; Sahasrabudhe, K.; Aube, J. *J. Am. Chem. Soc.* **2004**, *126*, 5475−5481. (b) Malik, C. K.; Ghosh, S. *Org. Lett.* **2007**, *9*, 2537−2540. (c) Matcha, K.; Maity, S.; Malik, C. K.; Ghosh, S. *Tetrahedron Lett.* **2010**, *51*, 2754−2757. (d) Bose, S.; Ghosh, M.; Ghosh, S. *J. Org. Chem.* **2012**, *77*, 6345−6350.

(13) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155−4156.

(14) (a) Palani, N.; Balasubramanian, K. K. *J. Org. Chem.* **1998**, *63*, 5318−5323. (b) Arbour, M.; Godbout, C.; Spino, C. *J. Org. Chem.* **2009**, *74*, 3806−3814.

(15) (a) Pfeiffer, M. W. B.; Phillips, A. J. *J. Am. Chem. Soc.* **2005**, *127*, 5334−5335. (b) Pfeiffer, M. W. B.; Phillips, A. W. J. *Tetrahedron Lett.* **2008**, *49*, 6860−6861. (c) Clark, J. S.; Hamelin, O. *Angew. Chem., Int. Ed.* **2000**, *39*, 372−374. (d) Clark, J. S.; Kimber, M. C.; Robertson, A.; McErlean, C. S.; Wilson, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 6157−

DOI: 10.1021/acs.joc.7b03021
J. Org. Chem. 2018, 83, 2087−2103

6162. (e) Standen, P. E.; Kimber, M. C. *Tetrahedron Lett.* **2013**, *54*, 4098−4101.
(16) (a) Chandler, C. L.; Phillips, A. J. A. *Org. Lett.* **2005**, *7*, 3493−3495. (b) Mahoney, W. S.; Brestensky, D. M.; Stryker, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 291−293.
(17) Zhang, S.; Zhen, J.; Reith, M. E. A.; Dutta, A. K. *Bioorg. Med. Chem.* **2006**, *14*, 3953−3966.
(18) (a) Crimmins, M. T.; Martin, T. J.; Martinot, T. A. *Org. Lett.* **2010**, *12*, 3890−3893. (b) Alvarez-Ibarra, C.; Arias, S.; Bañón, G.; Fernández, M. J.; Rodríguez, M.; Sinisterra, V. J. *J. Chem. Soc., Chem. Commun.* **1987**, 1509−1511.
(19) Ogasawara, K.; ElAzab, A. S.; Taniguchi, T. *Heterocycles* **2002**, *56*, 39−43.
(20) (a) Ren, J.; Wang, J.; Tong, R. *Org. Lett.* **2015**, *17*, 744−747. (b) Sridhar, Y.; Srihari, P. *Eur. J. Org. Chem.* **2013**, *2013*, 578−587. (c) Tsuda, T.; Fujii, T.; Kawasaki, K.; Saegusa, T. *J. Chem. Soc., Chem. Commun.* **1980**, 1013−1014.
(21) Banwell, M. G.; Edwards, A. J.; Harfoot, G. J.; Jolliffe, K. A. *Tetrahedron* **2004**, *60*, 535−547.
(22) (a) Ghosh, A. K.; Wang, Y. *J. Am. Chem. Soc.* **2000**, *122*, 11027−11028. (b) Monti, H.; Leandri, G.; Klos-Ringquet, M.; Corriol, C. *Synth. Commun.* **1983**, *13*, 1021−1026.
(23) Anelli, P. L.; Montanari, F.; Quici, S. 1990, *Organic Syntheses*; Wiley, 1990; Collect. Vol. *8*, p 367.
(24) (a) Gessler, S.; Randl, S.; Blechert, S. *Tetrahedron Lett.* **2000**, *41*, 9973−9976. (b) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168−8179.
(25) Hsung, R. P.; Cole, K. P.; Zehnder, L. R.; Wang, J.; Wei, L.-L.; Yang, X.-F.; Coverdale, H. A. *Tetrahedron* **2003**, *59*, 311−324.
(26) Mehta, G.; Reddy, A. V. *J. Chem. Soc., Chem. Commun.* **1981**, 756−757.

DOI: 10.1021/acs.joc.7b03021
J. Org. Chem. 2018, 83, 2087−2103