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Total synthesis of prostratin, a bioactive tigliane diterpenoid: access to multi-stereocenter cyclohexanes from a phenol

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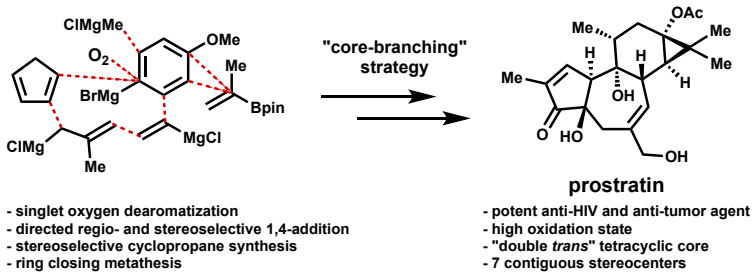


ABSTRACT: Tiglianes such as prostratin and related diterpenoids are biologically significant natural molecules and long-standing targets for organic synthesis community. Due to the complex polycyclic scaffolds, high oxygenation level and dense functional groups and stereocenters, their de novo chemical syntheses still face formidable challenges despite extensive efforts in the last 40 years. This account details the development of a modular and concise synthesis of prostratin, a potent anti-HIV and anticancer agent. The key approach in this synthesis involved a sequence of oxidative dearomatization and sequential stereoselective installation of peripheral groups to rapidly building the contiguously substituted cyclohexane C-ring. Inspired by Wender's work, an acid- and solvent-controlled stereodivergent formation of cyclopropane D-ring was developed. Mechanistic investigations by computational methods revealed that the competition between intra- and intermolecular hydrogen bonding led to different conformations, thus favoring different protonation processes. The designed as well as unexpected chemistry along this campaign reflected the uniqueness of the natural structures and should be amenable to future chemical synthesis of related complex polycyclic molecules.

INTRODUCTION

Terpene natural products have long provided effective drugs or leads, such as paclitaxel (Taxol®) and artemisinin, for human being in combating various diseases. Tiglianes and daphnanes are two families of diterpenes with closely related biosynthetic origin, and mainly isolated from extracts of *Euphorbiaceae* and *Thymelaeaceae* which have been widely used in traditional Chinese medicine. To date, over 300 molecular entities within these families have been identified. Many members exhibited remarkable biological functions including anti-viral, anti-cancer, analgesic, neurotrophic and tumor promotional activities.[1,2] For instance, phorbol (**2**) and phorbol-13-myrisitate-12-acetate (PMA, **3**) are ultra-potent tumor promoters by activation of protein kinase C (PKC). Resiniferatoxin (RTX, **5**), the hottest chemical ever known, is a potent non-opioid analgesic and currently in phase I clinical trials to treat severe pain for patients with advanced cancer.[3]

Prostratin (**1**, Figure 1) was originally isolated from *Pimelea prostrata* and structurally elucidated by Hecker and co-workers in 1976.[4] In 1992, Cox and co-workers ascertained **1** as the active ingredient in *Homalanthus nutans*, locally known as mamala tree which had been used as tribal medicine for viral diseases in Samoa.[5] Prostratin is a potent anti-HIV agent. On one hand, it was reported that prostratin protected CD4+ T cells by the down-regulation of HIV receptor CD4 and co-receptors. On the other hand, it stimulates viral replication in latently infected cells by interaction with Protein Kinase C (PKC).[6] The latter function renders prostratin as a promising lead in developing an adjuvant therapy to eradicate HIV-AIDS infection.[7] In addition, prostratin was reported to effectively suppress pancreatic cancer cells,[8] myeloid leukemia cells[9] and breast cancer cells.[10]

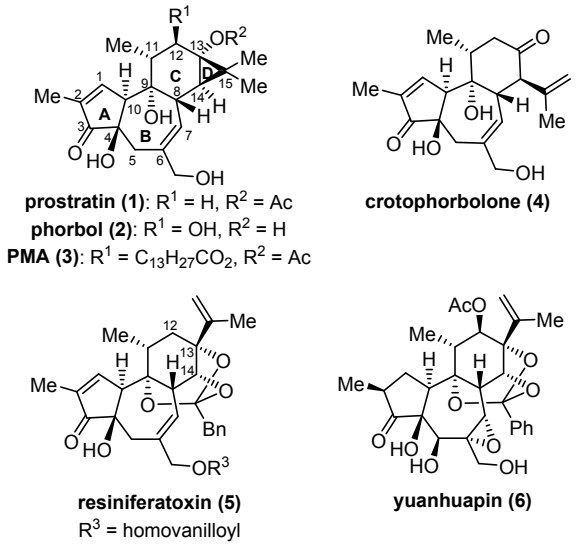


Figure 1. representative members of tigliane and daphnane family diterpenoids

Structurally, tigliane and daphnane diterpenoids share a [5/7/6] A/B/C tricyclic carbon core with usually contiguous multi-stereocenters and high oxygenation pattern (Figure 1). Due to the C4,C10 and C8,C9 double *trans* configuration in tigliane and daphnane skeleton and the congested substitution, these molecules show rigid three-dimensional representation. Tiglianes further distinguish themselves by a highly substituted cyclopropane ring D, while daphananes usually possess a caged orthoester moiety.

The combination of biological activities and structural complexity have rendered tigliane and daphnane diterpenoids continuously to be attractive yet highly challenging targets for the synthetic community. Besides an elegant

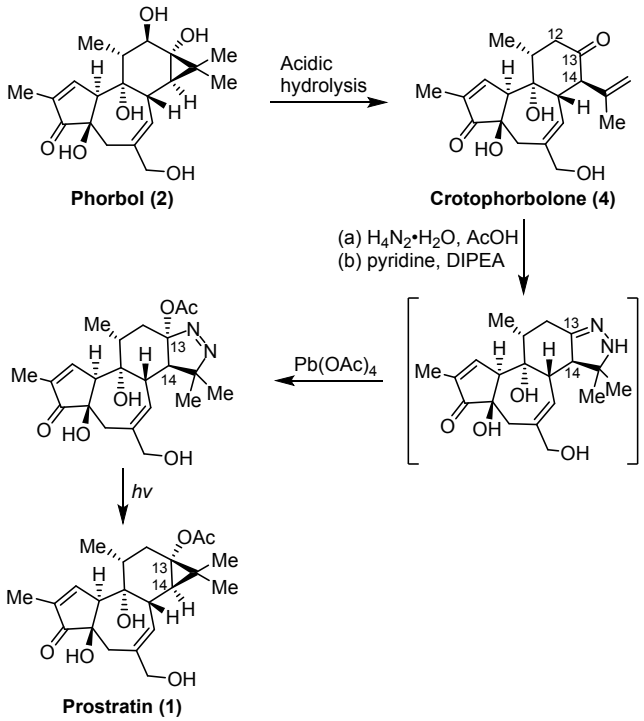


Figure 2. Semi-synthesis of prostratin from phorbol by Wender

semi-synthesis of prostratin (**1**) from crotophorbolone (**4**) by the Wender group (Figure 2),[11] since early 1980s, many *de novo* synthetic approaches have been reported.[12] The first total synthesis of phorbol (**2**)[13] was achieved by Wender and co-workers featuring an selective intramolecular oxidopyriylium/alkene [5+2] cycloaddition approach to rapidly build the B/C rings.[14,15] With this approach, the same group successfully developed an improved synthesis of **2**, the first total synthesis of RTX (**5**)[16] and highly complex non-natural analogues of yuanhuapin (**6**)[17]. Using fully-functionalized C-ring as the bridgehead radical precursors, Inoue and co-workers developed delicate chemo- and stereoselective methods to assemble the tricyclic core, thus accomplished total synthesis of crotophorbolone[18] and very recently RTX[19]. Despite the achievements, the challenge to harmonize skeleton assembly and functional group installation necessitated long synthetic sequence (>30 steps). In 2016, by judicious selection of (+)-3-carene as the C,D-ring precursor and using a dazzling array of reactions including Pauson-Khand reaction, C-H oxidation and ring reorganization, Baran and co-workers were able to achieve an asymmetric synthesis of phorbol in only 19 steps.[20]

Remarkably, the previous syntheses all adopted a "C ring first" strategy where multiple substituents and/or stereochemical pattern within the cyclohexane ring were introduced in early stage. However, the distinctive structural difference between tiglianes and daphananes resides in the C ring and previous reports had suggested that subtle variations on the C ring often led to dramatic changes in biological activities. Consequently, aiming at a general strategy for both tiglianes and daphananes, and future full modifications of them, we sought to take a different strategy. We planned to build the C ring from a simple, two-dimensional phenol moiety by controlled stepwise yet rapid manipulation of necessary oxidation states, substituents and stereocenters. Recently, we have demonstrated the feasibility of such strategy by a successful total synthesis of prostratin.[21] In this article, we wish to disclose the full details of our efforts that led to the short and flexible synthetic strategy.

RESULTS AND DISCUSSION

Strategic Design and Retrosynthetic Analysis

Tigliane and daphnane diterpenoids share a characteristic [5/7/6] tricyclic carbon core structure. We envisaged a tigliane diterpenoid could be reached by cyclopropanation of a common intermediate **7**, from which orthoester formation should also lead to a daphnane diterpenoid. Intermediate **7** might be accessed by oxidative dearomatization and subsequent stereoselective functionalizations from **10**. Due to its polyfunctional nature, cyclohexadienone quinol **9** could serve as the key intermediate for rapid and controllable modification of C-ring. If successful, such a programmed "core-branching" synthetic sequence should maximize the potential in peripheral derivatization, allowing to build various densely functionalized three-dimensional C-ring from a planar

phenol. Oxidative dearomatization[22] has been an effective approach for transforming phenolic compounds into complex three-dimensional structures. In this plan, ring-closing metathesis (RCM) were to be used for forging the seven-member ring, and an epoxide opening reaction

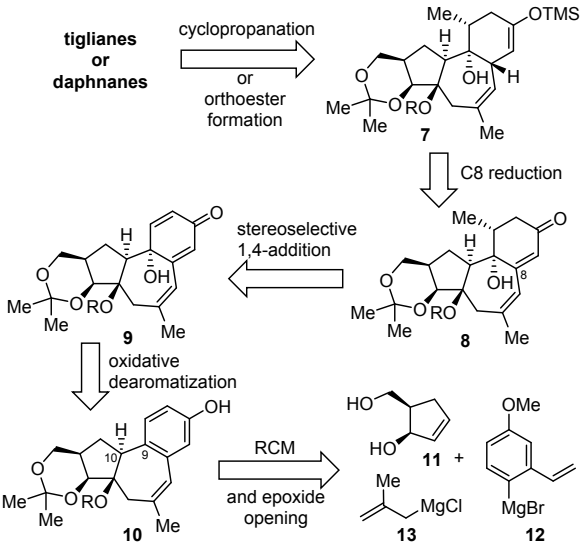


Figure 3. Retrosynthetic analysis of tigliane and daphnane natural product

for the C9-C10 bond. Therefore, **10** could be modularly assembled from three simple building blocks (**11, 12, 13**) (Figure 3).

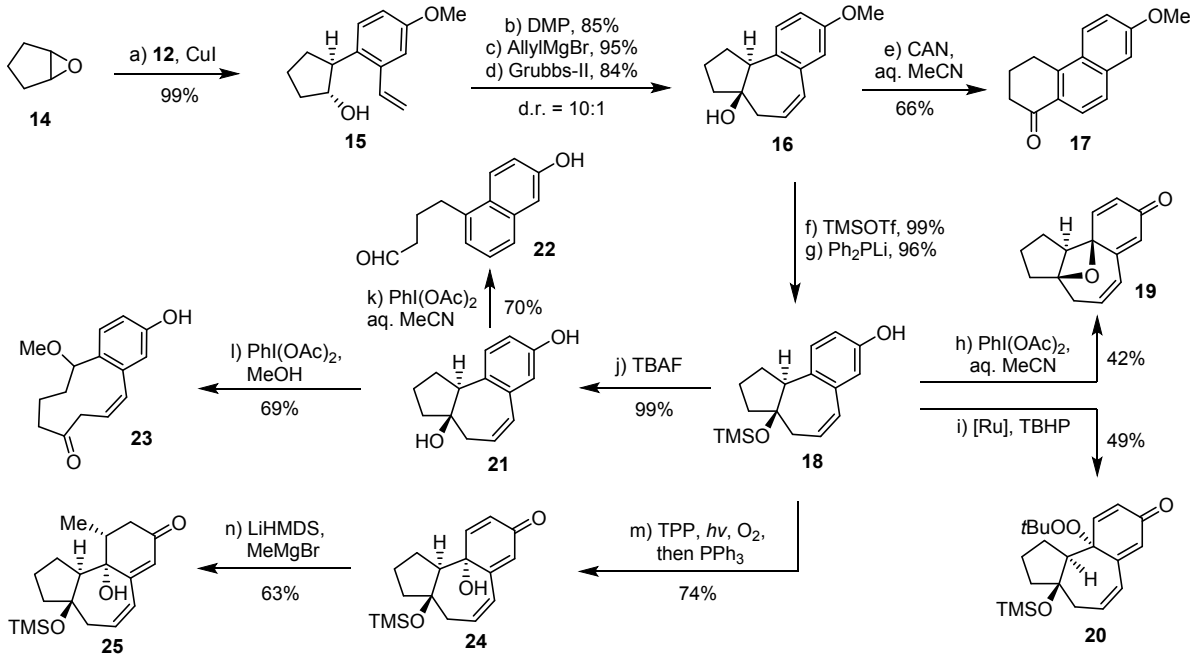
Model Studies

In order to test the above strategy and quickly establish the [5/7/6] tricyclic core with five key contiguous stereocenters (C4, C8-C10, C11), we took a commercially available epoxide **14** for our model study (Scheme 1). Treatment of cyclopentene oxide **14** with Gringnard reagent **12** in the presence of cuprous iodide provided epoxide opening product *tans*-**15** in excellent yield (99%). Exposure of alcohol **15** to Dess-Martin periodinane followed by addition with allyl magnesium bromide delivered a diene together with its inseparable C4-epimer in good yield (81% over two steps, 10:1 dr). Employing Grubbs second-generation catalyst at a low catalyst loading (0.1 mol%), RCM reaction successfully delivered the desired tricyclic compound **16** in 84% yield.

At this stage, we explored various conditions for the planned oxidative dearomatization reaction. Direct treatment of **16** with ceric ammonium nitrate (CAN) in aqueous acetonitrile mainly afforded ketone **17** (66%), probably via allylic oxidation and Wagner-Meerwein-type rearrangement. We then sought to first demethylate the aryl methyl ether. However, attempts in removing the methyl group by strong Lewis acids (i.e., BBr_3, TMSI etc.) all led to decomposition or starting material. In addition, using sodium ethylthiolate at elevated temperature resulted in unstable yields due to accompanying competitive dehydration and other side reactions (see SI for more details). After silylation of the tertiary alcohol, we found that *in situ* generated lithium diphenylphosphide[23] was best for this demethylation, giving phenol **18** in 96% yield.

Numerous methods had been reported for oxidative dearomatization of phenols. Among them, hypervalent iodine reagents emerged as the convenient option and had been widely used. In our case, however, treatment of **18** with $PhI(OAc)_2$ led to formation of oxetane **19** as the major

Scheme 1. ABC Model System and Attempted Oxidative Dearomatization[a]



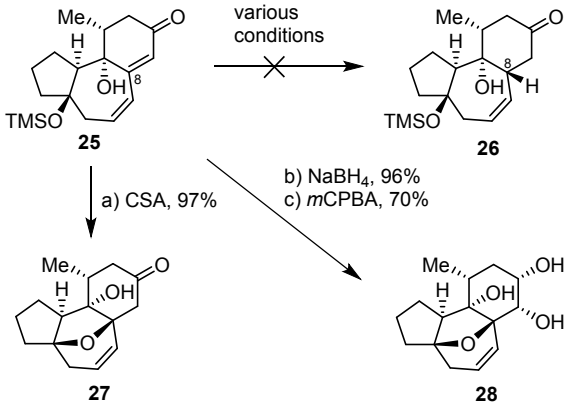
[a]Reagents and conditions: (a) **12**, CuI (10 mol%), THF, 0 °C to rt, 99%; (b) DMP, $NaHCO_3$, CH_2Cl_2, 0 °C to rt, 85%; (c) AllylMgBr, Et_2O, -78 °C, 95%; (d) Grubbs second-generation catalyst (0.1 mol%), toluene, 80 °C, 84%, 10:1 dr; (e) CAN, $MeCN/H_2O$ (3:1), rt, 66%; (f) TMSOTf, Et_3N, CH_2Cl_2, 0 °C to rt, 99%; (g) n-BuLi, Ph_2PH, THF, 0 °C to 60 °C, 96%; (h) $PhI(OAc)_2$, $NaHCO_3$, $MeCN/H_2O$ (3:1), 0 °C to rt, 42%; (i) $Ru(PPh_3)_3Cl_2$ (3 mol%), TBHP, PhH, rt, 49%; (j) TBAF, THF, 0 °C, 99%; (k) $PhI(OAc)_2$, $MeCN/H_2O$ (3:1), rt, 70%; (l) $PhI(OAc)_2$, MeOH, rt, 69%; (m) TPP (5 mol%), hv, O_2, $CHCl_3$, 0 °C, then PPh_3, 0 °C, 74%; (n) LiHMDS, 0 °C, then added HMPA,

MeMgBr, THF, -78 °C, 63%. THF = tetrahydrofuran, DMP = Dess-Martin periodinane, dr = diastereomeric ratio, CAN = ceric ammonium nitrate, TMSOTf = trimethylsilyl triflate, TBHP = tert-butyl hydroperoxide, TBAF = tetrabutylammonium fluoride, TPP = tetraphenylporphyrin, LiHMDS = lithium hexamethyldisilazide, HMPA = hexamethylphosphoramide.

product via an intramolecular reaction. Also, treatment of desilylated phenol **21** with $PhI(OAc)_2$ in aqueous acetonitrile produced naphthol **22** with ring rearrangement and C-C bond cleavage. When the solvent was methanol, crystalline **23** with a 10-membered ring was isolated in 69% yield, probably via C-C bond cleavage and benzylic cation intermediate. Interestingly, ruthenium-catalysed dearomatization with TBHP could form the dearomatization product **20** in 49% yield. However, cleavage of corresponding O-O bond in various conditions ($TiCl_4$, PPh_3, Mg/MeOH, $P(OPh)_3$, Pd/C) were all unsuccessful.

Fortunately, the required oxidative dearomatization proceeded smoothly at ambient temperature with singlet oxygen[24] using tetraphenylporphyrin (TPP) as the photosensitizer and 400 W sodium lamp as the light source. After consumption of starting material, the unstable peroxy quinol intermediate was reduced by triphenylphosphine to the desired cyclohexadienone **24**. To our delight, **24** was isolated in good yield (74%) and as a single diastereoisomer.

Scheme 2. Attempts to construction of C8 stereochemistry[a]



[a]Reagents and conditions. (a) CSA, CH_2Cl_2, -78 °C to rt, 97%; (b) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, -78 °C, 96%; (c) *m*CPBA, $NaHCO_3$, CH_2Cl_2; silica gel, 70%. *m*CPBA = meta-chloroperoxybenzoic acid.

With a concise and scalable route to cyclohexadienone **24**, we proceeded to explore the possibility of stereocontrolled transformations on the C-ring. An alkoxide directed conjugate addition procedure reported by Liotta and co-workers was adopted.[25] Thus, deprotonation of cyclohexadienone **24** with lithium hexamethyldisilazide (LiHMDS) followed by the addition of methyl magnesium bromide in the presence of HMPA delivered C11-methyl adduct **25** in 63% yield as a single diastereoisomer. We next attempted to set C8 stereochemistry (scheme 2). Attempts to generate **26** from **25** by employing a variety of conditions, including conjugate addition (Stryker's reagent, Rh/Et_3SiH, L-selectride, $NiCl_2/NaBH_4$, etc), selective olefin reduction (Pd/C, Crabtree's catalyst), or dissolving metal reduction, to our dismay, did not give any desired product. Presumably, this failure was due to unfavorable attachment of a hydrogen atom from the concave face and a shielding effect of TMS moiety (Figure 4). Furthermore, removing TMS group of **25** under acidic or fluoride conditions all led to full conversion to

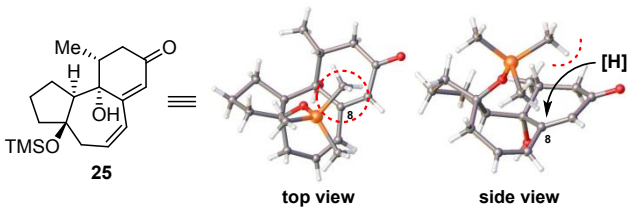


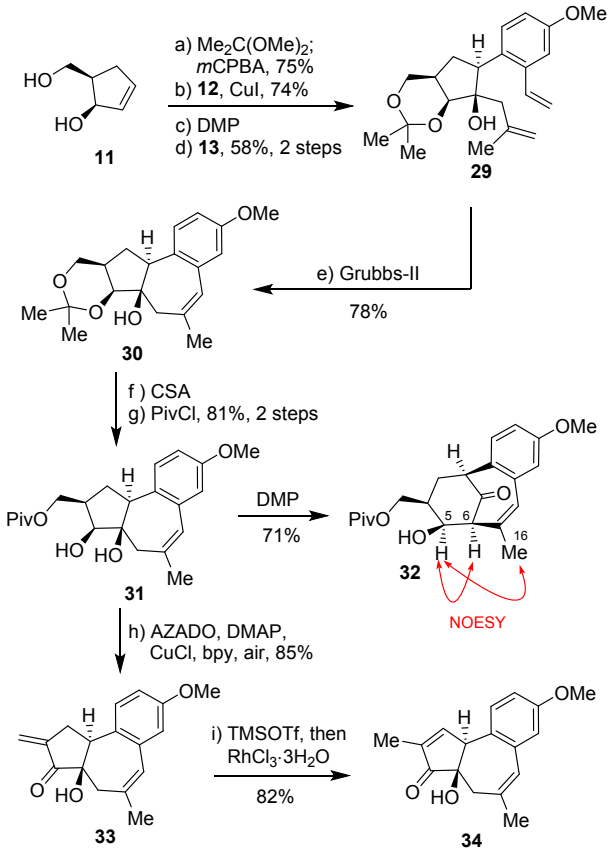
Figure 4. Crystal structure of **25** from top view and side view

bridged tetracycle **27** (97%). When ketone **25** was subjected to Luche reduction conditions ($NaBH_4$, $CeCl_3$), quantitative and stereoselective formation of 1,4-*cis*-diol was observed. Treatment of the resulting diol with *m*-chloroperoxybenzoic acid (*m*CPBA) directly provided triol **28** in 70% yield as a single isomer. In this case, the oxa-bridged ring was again formed by facile intramolecular epoxide opening.

The above work demonstrated the potential of our strategy in building the tricyclic framework with a highly simplified A-ring. Furthermore, we conducted studies for incorporation and manipulation of a functionalized A-ring more relevant to the natural products (scheme 3). We started from protection of the known racemic diol **11** (synthesized from cyclopentadiene through 3 steps, see experimental section for more details) with acetonide group and a one-pot stereoselective epoxidation (75%). Following the route similar to Scheme 1, a copper-catalysed epoxide opening of **SI-13** with **12** (74% yield), DMP oxidation, followed by allylation with **13** furnished diene **29** (58% yield, over two steps), whose relative configuration was confirmed by X-ray crystallography. Ring-closing metathesis smoothly forged the 7-membered ring of **30** (78% yield). Next, removal of acetonide group with camphorsulfonic acid in refluxing aqueous methanol produced the corresponding triol which was selectively pivalated at the primaryl alcohol to form **31** in 81% yield over two steps. Furthermore, using Iwabuchi's method,[26] i.e. 2-azaadamantane-N-oxyl (AZADO) and CuCl catalyzed aerobic oxidation, pivalate **31** was cleanly transformed to *exo*-enone **33** in 85% yield with concomitant elimination of pivalic acid. Notably, attempts using other methods such as Swern, PCC, IBX, Corey-Kim, Ley, Pfitzner-Moffatt, Oppenauer, or Fetizon's reagent all failed[27]. In most cases, 1,2-diol cleavage was observed as the major side reaction (see SI for more details). For example, Dess–Martin periodinane led to formation of bridged ketone **32** in 71% yield. Considering that bridged ketones are commonly found in synthetically challenging natural products (e.g. hyperforin), this discovery may provide a novel method for their preparation. In addition, Parikh-Doering oxidation[27j] of **31** gave **33** in low yield (40%), while Anelli's conditions (TEMPO, NaClO, KBr, $NaHCO_3$) gave **33** in irreproducible yields (30~74%). Going forward, an *exo* to *endo* isomerization of the enone was realized in 82% yield by using catalytic amount of rhodium(III) chloride[28] after *in*

situ protection of the hydroxyl group with TMSOTf. The silyl group was essential to prevent side reactions. Interestingly, during this isomerization, TMS group was also removed.

Scheme 3. Synthesis of A-ring Model Compound[a]



[a]Reagents and conditions. (a) $Me_2C(OMe)_2$, PPTs (10 mol%), CH_2Cl_2, 0 °C to rt, then $NaHCO_3$, *m*CPBA, 0 °C to rt, 75%; (b) **12**, CuI (10 mol%), THF, 0 °C to rt, 74%; (c) DMP, $NaHCO_3$, CH_2Cl_2, rt; (d) **13**, THF, 0 °C to rt, 58%, 2 steps; (e) Grubbs second generation catalyst (10 mol%), toluene, 110 °C, 78%; (f) CSA, $MeOH/H_2O$ (5:1), 90 °C; (g) PivCl, pyridine, DMAP, CH_2Cl_2, 0 °C to rt, 81%, 2 steps; (h) AZADO (10 mol%), DMAP, CuCl (20 mol%), bpy (20 mol%), MeCN, rt, 85%; (i) TMSOTf, Et_3N, CH_2Cl_2, 0 °C to rt, then $RhCl_3·3H_2O$ (10 mol%), $EtOH/H_2O$ (10:1), 100 °C, 82%. PPTs = pyridinium *p*-toluenesulfonate, CSA = (±)-camphor-10-sulfonic acid, PivCl = pivaloyl chloride, DMAP = 4-dimethylaminopyridine, AZADO = 2-azaadamantane-N-oxyl, bpy = 2,2'-bipyridine.

Retrosynthetic Analysis of Prostratin (1)

On the basis of the above investigations, a retrosynthetic analysis of prostratin (**1**) was designed. As delineated in Figure 5, our synthetic approach relied on the late-stage RCM to forging B-ring from diene **35** with fully functionalized A, C, D rings. The D ring should be formed by cyclopropanation of enone **36**. In order to solve the problem of C8 chemistry that we could not set in the model study (see Scheme 2), a double directed addition approach was considered for installing C11-methyl and C8-vinyl substituents from **37**. Cyclohexadienone **37**, an oxidative dearomatization product from phenol **38** should be rapidly accessed from diol **11** and reagent **39**.

Thus, started from diol **11** (scheme 4), synthesis of phenol **38** involved one-pot acetal protection and epoxidation, copper-catalyzed epoxide opening of with **39**, protection of the resulting secondary alcohol with TBS group, and removal of the methyl with Ph_2PLi. These steps were smoothly done

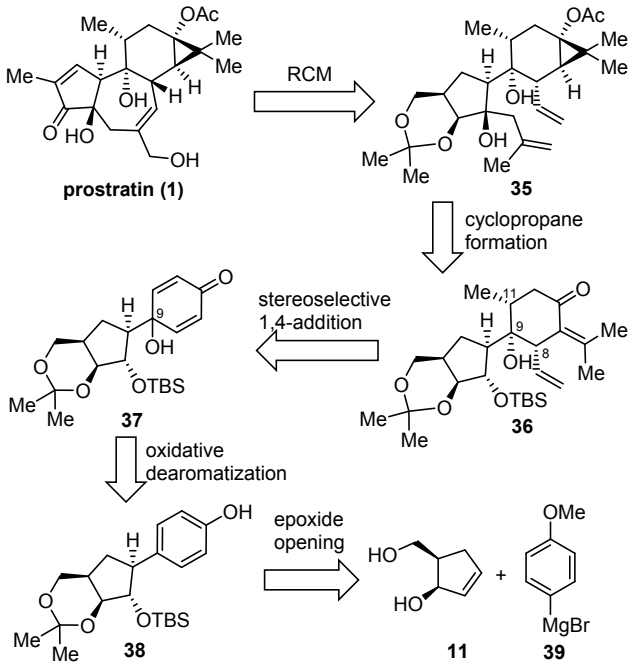
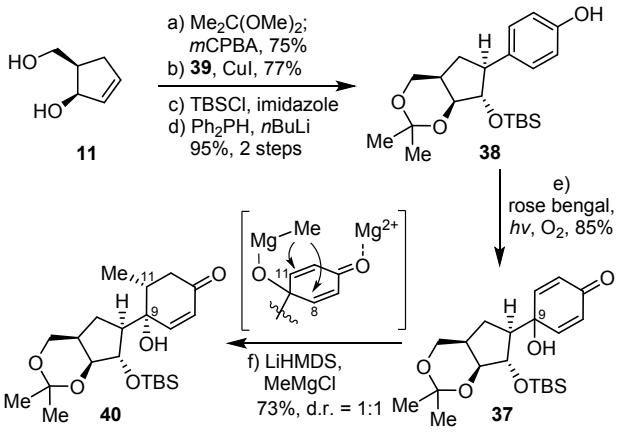


Figure 5. Retrosynthetic analysis of prostratin

in >20g scale and good yields. According to our previous oxidative dearomatization conditions using TPP as the sensitizer and chloroform as the solvent, only low conversion of **38** was observed. After extensive experiments, it was found that by changing the sensitizer to rose bengal and solvent to mixed methanol/chloroform (1:1), the desired C9-hydroxylated cyclohexadienone **37** was observed in 85% yield. Interestingly, intermediate peroxy quinol was not detectable, presumably because protic solvent accelerated rupture of the initially formed O-O bond. Theoretically, addition of a Grignard reagent to **37** could form six regio- or diastereoisomers. In practice, treatment of **37** with LiHMDS and then

Scheme 4. Synthesis of ketone 40[a]

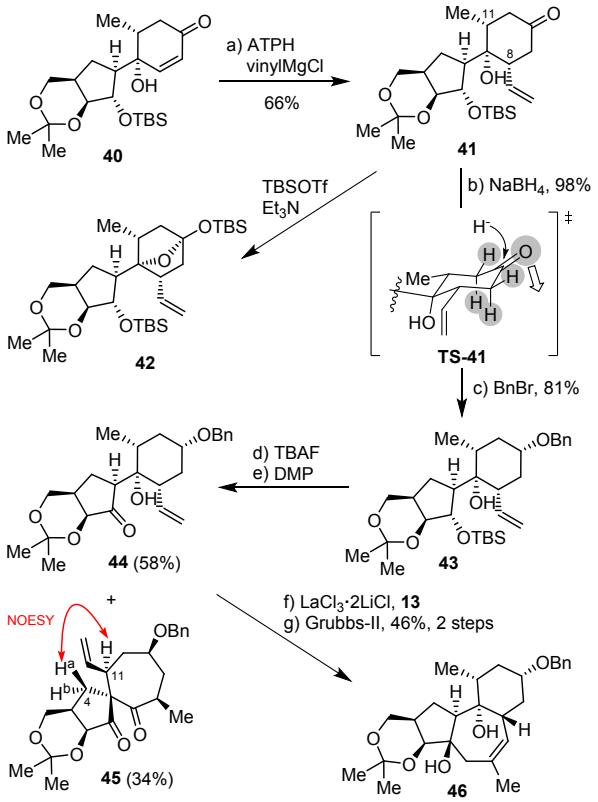


[a]Reagents and conditions. (a) $Me_2C(OMe)_2$, PPTs (10 mol%), CH_2Cl_2, 0 °C to rt, then $NaHCO_3$, *m*CPBA, 0 °C to rt, 75%; (b) **39**, CuI (10 mol%), THF, 0 °C to rt, 77%; (c) TBSCl, imidazole, CH_2Cl_2, 0 °C to rt; (d) *n*-BuLi, Ph_2PH, THF, 0 °C to 80 °C, 95%, 2 steps; (e) Rose bengal (5 mol%), *hv*, O_2, MeOH/$CHCl_3$ (1:1), 85%; (f) LiHMDS, -60 °C, then added DMPU, MeMgCl, -78 °C to -30 °C, 73%, 1:1 dr. TBSCl = *tert*-butyldimethylsilyl chloride, DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone.

with methylmagnesium chloride in the presence of DMPU, 1,4-*cis*-addition product **40** was isolated together with the other 1,4-*cis*-diastereomer **SI-16** in approximately 1:1 ratio. The isomers were readily separated by column chromatography on silica gel. Similar to the previous model synthesis (**24** to **25**), the 1,4- over 1,2- selectivity and the *cis*- over *trans*- selectivity could be understood by invoking an alkoxide-guided methyl addition process.[25]

With gram scale preparation of **40**, we next explored the second directed 1,4-addition at C8. With similar protocol as above, addition of **40** with vinyl magnesium bromide afforded the desired ketone **41** in 43% yield; competitive 1,2-adduct was also formed in 32% yield (**SI-17**). Other methods, such as organo-copper or zinc reagents, could also provide **41**, but in lower yields. We reasoned that a bulky Lewis acid might block C13-carbonyl group to prevent 1,2-addition and at the same time accelerate 1,4-addition by reducing LUMO of the enone. Indeed, treatment of **40** with Yamamoto's aluminum tris(2,6-diphenylphenoxide) (ATPH)[29] before addition of vinylmagnesium chloride led to conjugate addition product **41** up to 66% along with 22% **SI-17**. A single crystal of **41** suitable for X-ray diffraction confirmed its relative configuration that clearly indicated the desired 8,11-cis configuration. Attempts to prepare silyl

Scheme 5. Synthesis of tricyclic 46[a]

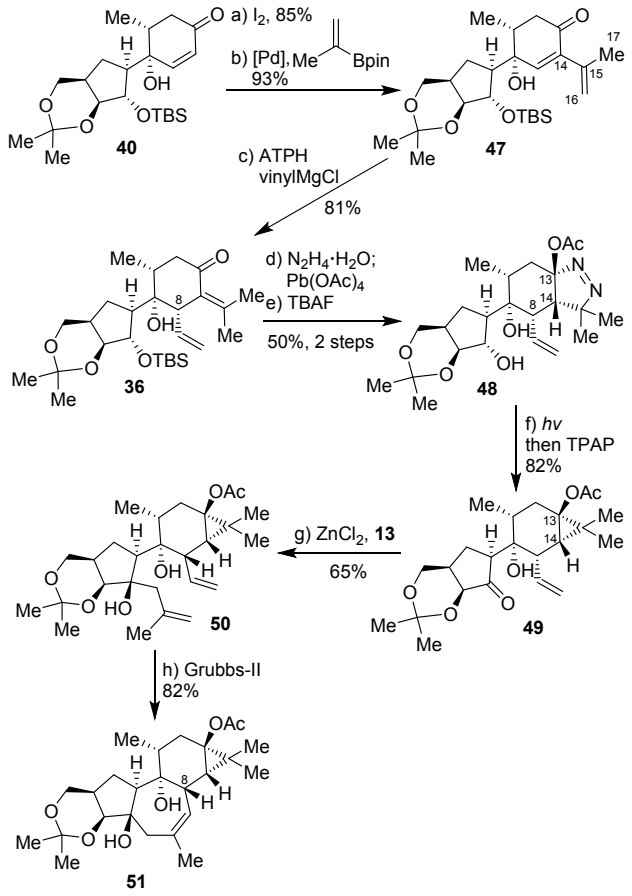


[a]Reagents and conditions. (a) Me_3Al, 2,6-diphenylphenol, vinylMgCl, THF, -78 °C to rt, 66%; (b) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH/CH_2Cl_2 (1:1), -78 °C, 98%; (c) NaH, BnBr, TBAI, 0 °C to rt, 81%; (d) TBAF, THF, rt; (e) DMP, $NaHCO_3$, *t*-BuOH, rt, 58% **44**, 34% **45**, two steps; (f) $LaCl_3{\cdot}2LiCl$, **13**, THF, -78 °C to 0 °C; (g) Grubbs second-generation catalyst, toluene (50 mol%), 110 °C, 46%, 2 steps. TBAI = tetrabutylammonium iodide.

enol ether from **40** under various conditions (ATPH, vinylMgCl, then TBSCl or TBSOTf) did not give the desired product. On the other hand, usual deprotonation and silylation reaction of **41** with TBSOTf/ Et_3N, or TBSCl/LiHMDS) all led to silylated acetal **42** as the major product.

In order to explore the construction of B-ring (Scheme 5), ketone **41** was stereoselectively reduced to furnish the corresponding alcohol (98%), which was subsequently protected as its benzyl ether **43** (81%). Based on the crystal structure of **41** (see SI), a chair-like conformation might be involved in the transition state of this reduction process (**TS-41**). Attacking of a small hydride from the axial direction would lead to movement of the oxygen atom toward the equatorial position (marked by the bold arrow), avoiding otherwise overlapping with the two equatorial α-protons. Treatment of **43** with TBAF, then oxidizing diol by Dess-Martin periodinane provided ketone **44** as the desired

Scheme 6. Synthesis of tetracyclic 51 with wrong D-ring[a]



[a]Reagents and conditions. (a) I_2, pyridine, CH_2Cl_2, 50 °C, 85%; (b) $Pd(PPh_3)_2Cl_2$ (5 mol%), $AsPh_3$ (10 mol%), 2-propenylBPin, Ag_2O, THF/H_2O (8:1), 93%; (c) Me_3Al, 2,6-diphenylphenol, vinylMgCl, THF, -78 °C to rt, 81%; (d) $N_2H_4{\cdot}H_2O$, EtOH, 90 °C, then $Pb(OAc)_4$, CH_2Cl_2; (e) TBAF, THF, 0 °C, 50%, 2 steps; (f) *hv*, EtOAc, rt; then TPAP (20 mol%), NMO, 4ÅMS, 0 °C to rt, 82%; (g) $ZnCl_2$, 13, THF, -78 °C, 65%; (h) Grubbs second-generation catalyst (50 mol%), toluene, 110 °C, 82%. 2-propenylBPin = 2-propenyl boronic acid pinacol ester, TPAP = tetrapropylammonium perruthenate, NMO = *N*-methylmorpholine *N*-oxide, 4ÅMS = 4Å molecular sieves.

product (58%) together with a side product which was identified as spiro-diketone **45** (34%). Formation of **45** could be viewed as an unusual oxidative regio- and stereoselective semi-pinacol rearrangement. Next, introduction of 2-methylallyl group to C4 was accomplished through addition of 2-methylallyl magnesium chloride **13** mediated by $LaCl_3{\cdot}2LiCl$, affording the corresponding diene as single diastereomer. Simple mixing the Grignard reagent with **44** led to complex mixture and retro-aldol reaction was observed as a side reaction. Subsequently, ring closing metathesis of diene catalyzed by Grubbs' second generation catalyst in toluene gave the desired tricyclic compound **46** in 46% yield over two steps. These results provided a viable route to the [5-7-6] skeleton with several desired key stereocenters.

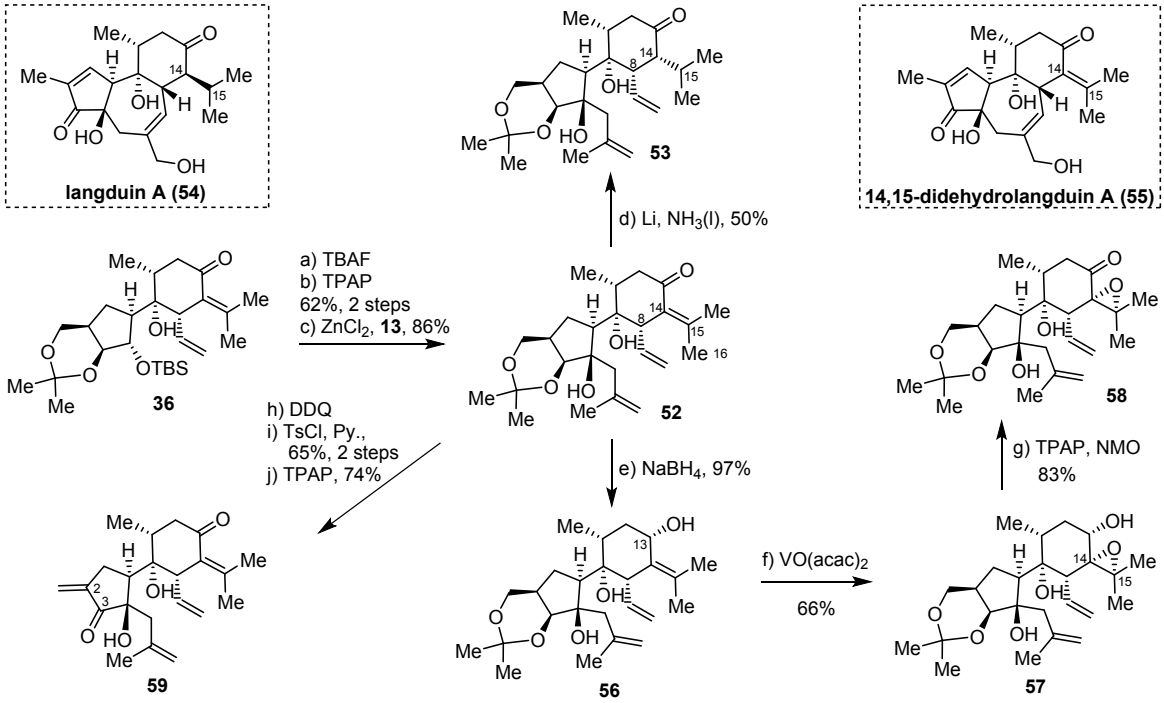
Scheme 7. Failed B-ring-then-D-ring detours

In order to further construct the cyclopropane D ring onto the skeleton, we first wanted to attach isopropenyl group with C15 to C17 via an iodination/cross-coupling sequence (scheme 6). Thus, Johnson iodination was used by heating **40** with iodine and pyridine in refluxing methylene dichloride to furnish α-iodoenone in 85% yield. Palladium-catalyzed cross-coupling between the α-iodoenone and 2-isopropenyl boronic acid pinacol ester produced the desired **47** in excellent yield (93%). Next, we found that setting a vinyl group at C8 which was cis relationship with C9 hydroxyl was challenging. Numerous attempts in substrate-directed 1,4-conjugate addition, such as organocopper reagents, or rhodium, nickel catalyzed additions, failed to give the desired product. In most cases, the starting material was recovered. When vinyl Grignard reagent and TMSCl were used in the presence of HMPA, 35% of 1,4-addition product **36** was isolated, in which the terminal double bond in isopropenyl was isomerized to internal. We reasoned that the low reactivity was due to the particularly high steric hindrance around C8. Finally, we found that the bulky Lewis acid ATPH discussed above could efficiently enhance reactivity at C8 and **36** could be isolated in 81% yield as a single diastereomer.

Inspired by Wenders' previous work in semi-synthesis of prostratin,[11] we persued a photochemical cyclopropanation method for D ring. Notably, in Wender's work, crotophorbolone (**4**), as a nonconjugated enone, was used as the reactant where C14 stereocenter was preset. In our case, however, **36** was a conjugated enone and selective formation of C14 stereocenter was the key to correctly build the D ring.

In event, an ethanolic solution of enone **36** was heated with an excess of hydrazine hydrate furnished unstable pyrazoline intermediate, which was immediately oxidized in the same reaction flask with lead (IV) tetraacetate to generate a cyclic diazene. After treatment with tetrabutylammonium fluoride (TBAF), the product **48** was isolated in 50% yield. However, the configurations of the newly formed C13,C14 stereocenters were initially not clear based on NMR spectra. Furthermore, photolytic extrusion of nitrogen (300W UV lamp, 254 nm) of **48** followed by oxidation gave **49** in 82% yield as single isomer.

Exposure of **49** to methallyl zinc reagent (generated via $ZnCl_2$ and **13**) at -78°C in THF for 30 minutes was found to effectively yielded diene **50** in good isolated yield (65%). It



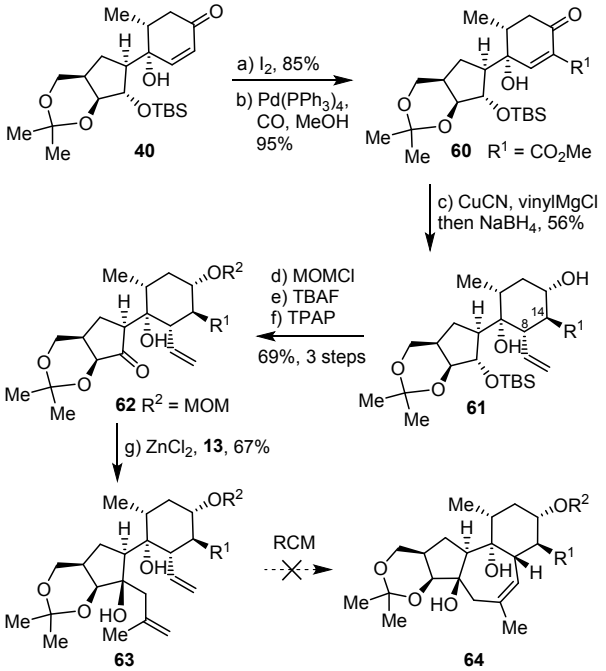
[a]Reagents and conditions. (a) TBAF, THF, 0 °C to rt; (b) TPAP (10 mol%), NMO, 4ÅMS, 0 °C to rt, 62%, 2 steps; (c) $ZnCl_2$, **13**, THF, -78 °C, 86%; (d) Li, NH_3(l), THF, -78 °C, 50%; (e) $NaBH_4$, MeOH/CH_2Cl_2 (1:1), 0 °C, 97%; (f) $VO(acac)_2$ (5 mol%), TBHP, CH_2Cl_2, 0 °C to rt, 66%; (g) TPAP (10 mol%), NMO, 4ÅMS, 0 °C to rt, 83%; (h) DDQ (20 mol%), MeCN/THF/H_2O (1:4:1), rt; (i) TsCl, pyridine, DMAP, CH_2Cl_2, 0 °C to rt, 65%, 2 steps; (j) TPAP (10 mol%), NMO, 4ÅMS, 0 °C to rt, 74%. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

should be mentioned that using direct addition of Grignard reagent **13** or $LaCl_3$·2LiCl/**13** resulted in mostly retro-aldol side reaction. Next, formation of B ring from **50** in the conditions of RCM was achieved and the desired product was isolated in 82% yield. However, the catalyst loading had to be increased up to 50 mol%. At this stage, we compared the ^{1}H NMR spectrum of **51** with the one from reported prostratin **1**. To our surprise, the chemical shift of allylic C8-H in **50** was at 4.05 ppm while it was at 3.38 ppm for **1**.[11,30] The large difference led us to consider that the relative configuration of C8 and C14 was *cis* rather than the *trans* stereochemistry in natural tiglianes. Finally, X-ray analysis of **48** showed that C14 was indeed of the undesired configuration.

Failed B-ring-then-D-ring detours

In order to correctly install the C14 thus the D ring stereochemistry, an attractive alternative approach would involve reversing the sequence of B-ring and D-ring formation. We decided to first construct rigid ABC tricyclic structure and then form the cyclic diazene as a precusor to D ring. This idea was also encouraged by the success of Wender's semi-synthesis. Thus, treatment of enone **36** with TBAF, followed by oxidation in Ley's conditions (TPAP, NMO) furnished the corresponding diketone intermediate in 62% yield over the two steps (scheme 7). The methallylation with the above-mentioned zinc reagent-based method again successfully afforded the desired product **52** in 86% yield. X-ray crystallographic analysis of a single crystal of **52** revealed its full structure. Interestingly, this time, retro-aldol reaction was not observed.

Scheme 8. synthesis of 62[a]



[a]Reagents and conditions. (a) I_2, pyridine, CH_2Cl_2, 50 °C, 85%; (b) $Pd(PPh_3)_4$ (5 mol%), CO (1 atm), Et_3N, MeOH/THF (1:1), 95%; (c) CuCN, vinylMgCl, THF, -78 °C to rt; then $NaBH_4$, $CeCl_3$·7H_2O, MeOH/CH_2Cl_2 (1:1), -78 °C to rt, 56%; (d) MOMCl, DIPEA, CH_2Cl_2, 0 °C to rt; (e) TBAF, THF, 0 °C to rt; (f) TPAP (10 mol%), NMO, 4ÅMS, 0 °C to rt, 69%, 3 steps; (g) $ZnCl_2$, **13**, THF, -78 °C, 67%.

With efficient access of **52**, we proceeded for B-ring formation. Success in ring closing metathesis of **52** might pave a way to langduin A (**54**),[31] 14,15-didehydrolangduin A (**55**)[32] as well as **1**. However, in sharp contrast to the substrates discussed above, attempts with various catalysts and conditions for RCM of compound **52** led to essentially no reaction (see supporting imformation). We hypothesized that the rigid and bulky dimethylmethylene group at C14 might block the approaching of the catalyst, and reducing the C14-C15 double bond might solve the problem. We found that dissolving metal reduction with lithium in liquid ammonia could provide ketone **53** in 50% yield. However, the single crystal analysis of **53** clearly showed 8,14-*cis* configuration that did not match with the structure in natural langduin A. Alternatively, a three-step sequence was used to epoxidize the C14-C15 double bond. Thus, reduction of C13-carbonyl group in **52**, followed by hydroxy-directed vanadium-catalysed epoxidation delivered epoxide **57** in good yield and diastereoselectivity. **57** was then oxidized to ketone **58** in 83% yield. The relative configuration of **57** was confirmed by X-ray crystallography. Disappointedly, all of the three compounds (**56**, **57**, **58**) were found to be not viable in RCM conditions.

We also tried to release possible steric hindrance of A ring by a sequence of manipulations. Thus, removal of the acetonide group by catalytic amount of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[33] in mixed solvent (acetonitrile/THF/H_2O, 1:4:1) followed by selective tosylation of primary alcohol (TsCl, pyridine, 65% for two steps) and subsequent cascade oxidation/elimination (TPAP, NMO) provided diketone **59** in 74% yield. However, diketone **59** again was inert to the RCM conditions.

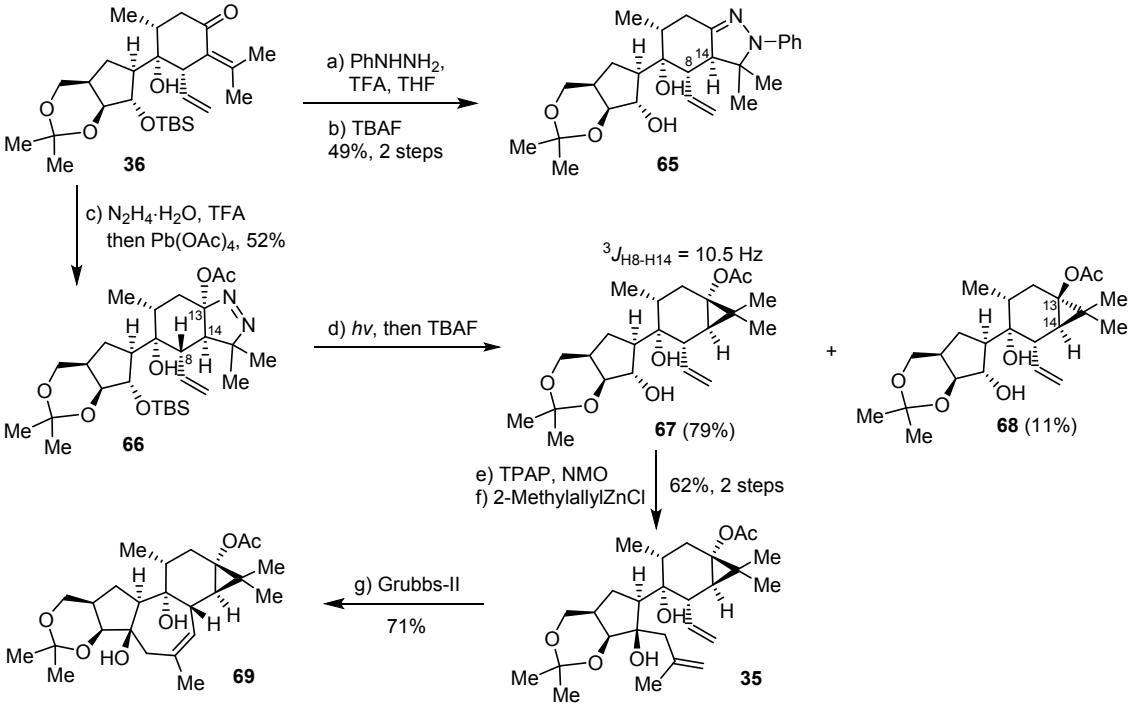
The failure in ring closing metathesis discussed above prompted us to reconsider a suitable substituent at C14 (scheme 8). Palladium-catalyzed carbonylation of iodide which was iodinated from **40** in methanol generated ester **60** in excellent yield (94%). Treatment of **60** with vinyl copper reagent (generated from CuCN and vinylMgCl) followed by reduction using Luche's method afforded secondary alcohol **61** in 56% yield. Coupling constant of H8 and H14 ($^3J_{H8\text{-}H14}$ = 11.2 Hz) indicated 8,14-*trans* configuration of **61**. Protection of alcohol **61** with MOM group, deprotection of the TBS group followed by Ley oxidation unveiled ketone **62** in 69% yield for the three steps. Zinc-mediated methallylation of **62** gave diene **63** in modest yield (67%). Unfortunately, compound **63** was also immune to various RCM conditions.

Successful D ring formation and synthesis of the tetracyclic scaffold

The initial attempt in building D ring led only to wrong configuration at C14 (Scheme 6). We reasoned that C14 stereocenter should be formed through protonation of an enamine-like intermediate during reaction between the enone substrate and hydrazine. If so, proton source could play an important role in this step. Because the pyrazoline compound

derived from condensation of enone **36** and hydrazine hydrate was unstable to

Scheme 9. Revised cyclopropane and trans heptane[a]



[a]Reagents and conditions. (a) $PhNHNH_2$, TFA, THF, 90 °C; (b) TBAF, THF, 0 °C, 49%, 2 steps; (c) $N_2H_4{\cdot}H_2O$, TFA, THF, 90 °C; then $Pb(OAc)_4$, CH_2Cl_2, 0 °C, 52%; (d) *hv*, EtOAc, rt; then TBAF, THF, 0 °C, 79% **67**, 11% **68**; (e) TPAP (20 mol%), NMO, 4ÅMS, 0 °C to rt; (f) $ZnCl_2$, **13**, THF, -78 °C, 62%, 2 steps; (g) Grubbs second-generation catalyst (40 mol%), toluene, 110 °C, 71%. TFA = trifluoroacetic acid.

acid and oxygen, we decided to firstly investigate the condensation of **36** with phenylhydrazine (scheme 9). After extensive experiments using different solvents and proton sources, we found that trifluoroacetic acid (TFA) could smoothly promote the condensation in refluxing THF. After deprotection of TBS group, the N-phenyl pyrazoline adduct **65** was isolated in 49% overall yield. The key ^3J coupling constant between H8 and H14 was found to be 11.4 Hz. Furthermore, X-ray diffraction analysis of **65** clearly indicated 8,14-*trans* configuration.

This result encouraged us to test the reaction between enone **36** and hydrazine hydrate in the presence of TFA in THF. Indeed, this operation furnished the unstable pyrazoline (observed with NMR) which was oxidized in one-pot to generate diazene **66** in 52% yield. Photolysis of **66** resulted the desired cyclopropane intermediate which, upon treatment with TBAF, was transformed to **67** in good yield (79%). Small amount (11%) of accompanying stereoisomer with an unexpected *trans*-bicyclo[4.1.0]heptane **68** was also isolated. The unusual highly strained structure of **68** was unambiguously established to be 13,14-*trans* configuration by X-ray diffraction of a crystal. To the best of our knowledge, this represents the first *trans*-bicyclo[4.1.0]heptane bicyclic framework observed by X-ray crystallographic analysis.

Next, C4 hydroxyl group was oxidized to an unstable ketone using Ley oxidation, which was subjected to methallyl zinc reagent to generated the desired diene **35** in 62% overall as a single diastereoisomer, along with a small amount of retro-aldol byproducts. It should be noted that the transformation was not only highly stereoselective but also rapid (1.1 eq. zinc reagent, -78 °C, <5 min). At this stage, we tried different conditions for the pivotal ring-closing metathesis reaction and found that using 40 mol% of the Grubbs second generation catalyst, the desired product **69** could be formed in 71% yield along with 20% recovered starting material. Consequently, the tetracyclic scaffold of tigliane diterpenoids was successfully established.

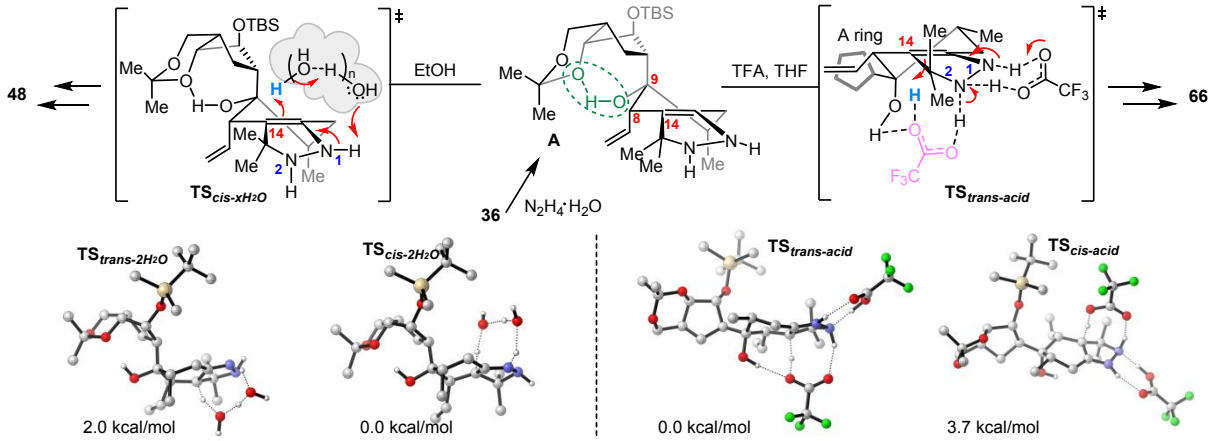
Computational studies on the mechanism of solvent- and acid-controlled stereodivergent protonation

During building the cyclopropane D ring, the completely inversed stereoselectivity in formation of C14 stereocenter by using different reaction conditions was intriguing (Scheme 10). Therefore, DFT calculation was performed to understand the origin of such selectivity.[35] The calculated results indicated the possible reaction mechanism that correlated with the experimental results.

In the X-ray structure of **36**, intramolecular hydrogen bond between the tertiary hydroxyl group at C9 and the ethereal oxygen locked the half-chair conformation of C-ring, which contained three axial substituents. Under the neutral reaction conditions, such intramolecular interaction should remain

unchanged in intermediate **A** . In this case, $(H_2O)_x$ bridge was able to work as proton shuttle to transfer the hydrogen from N1 to C14. Herein, $\mathbf{TS}_{cis\text{-}xH_2O}$ referred to a transition state which involved x water molecules and where the H atom was added to C14 in an *anti*-position relative to hydroxyl, alkenyl and methyl on the same 6-membered cycle. Via $\mathbf{TS}_{cis\text{-}xH_2O}$, an intermediate

Scheme 10. The caculated results on the stereodivergent protonation[a]



[a]The Gibbs free energy of the preferred tansition states were set as 0.0 kcal/mol, and the relative energy of the other transition states were given for comparation. In the structures of transition states, hydrogen atoms on carbon atoms were omitted for clarity.

with 8,14-*cis* configuration (**Int_{cis}**) was obtained, which would lead to **48** via the following treatment. The calculated results showed the number of water molecules in $(H_2O)_x$ bridge greatly influenced the value of activation energy relative to the starting materials. However, in the three groups (*x = 2, 3 or 4*) of transition states, the transfer of H to C14 via **$TS_{cis\text{-}xH_2O}$** was always favored, rendering the formation of **Int_{cis}**. Structurally, as depicted in Scheme 11, the axial attack of hydrogen would lead to a chair-form transition state **$TS_{cis\text{-}2H_2O}$**, which should be more favorable than the half-chair-form **$TS_{trans\text{-}2H_2O}$** according to the Fürst-Plattner rule.

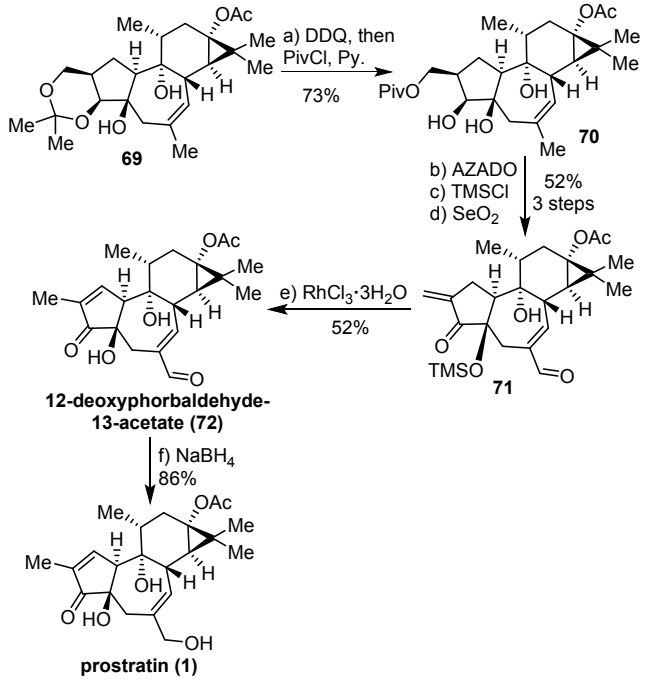
When CF_3COOH was added to the reaction system, we envisioned that the rigid structure of **A**, which was constructed by the intramolecular hydrogen bond, might be interrupted. Correspondingly, another two transition states **$TS_{cis\text{-}acid}$** and **$TS_{trans\text{-}acid}$** were located (Scheme 10). In this case, pairwise hydrogen bond interaction between **A** and CF_3COOH was formed. Then, hydrogen migration was completed with the assistance of another CF_3COOH molecule. From the point view of activation energy, when the hydrogen atom was added at the same face with the pendent hydroxyl group ($TS_{trans\text{-}acid}$), the transition state was highly favored by 3.7 kcal/mol. There might be two possible causes of this phenomenon. Firstly, in **$TS_{trans\text{-}acid}$**, the H-

bond interaction between the pendent hydroxyl group and CF_3COOH should stabilize the structure of **$TS_{trans\text{-}acid}$** and lower the activation energy relatively. Secondly, when the intramolecular hydrogen bond was broken, the bulky substituents on C8, C11 and C9 were all relaxed to be equatorial, then the axial attack of H atom from the bottom face would afford a more stable isomer with equatorial bulky substituent on C14.

Endgame of total synthesis of prostratin

With the tetracyclic advanced intermediate **69** in hand, the remaining key transformations should include functional group manipulations at A ring and C20 allylic oxidation (scheme 11). Based on previous model studies, removal of the acetonide group by catalytic amount of DDQ in a solvent mixture (acetonitrile/THF/H_2O, 8:2:1) followed by one-pot selective pivalation of the primary hydroxyl group furnished **70** in 73% yield. The full structure and relative configuration were confirmed by X-ray diffraction analysis. Selective aerobic oxidation of pivalate **70** using Iwabuchi's AZADO conditions cleanly provided the desired ketone with concurrent elimination of the pivalate group. After protection of C4 alcohol with TMS group, the corresponding product was isolated in 64% overall yield. Allylic oxidation of the B ring C20 methyl group to aldehyde with SeO_2 delivered **71** in 81% yield. Next, isomerization of *exo*-enone **71** to the *endo*-enone using rhodium(III) chloride hydrate as the catalyst was accompanied by solvolytic removal of TMS group, thus giving 12-deoxyphorbaldehyde-13-acetate (**72**) in 52% yield. Finally, reduction of C20 aldehyde group with $NaBH_4$ to the alcohol was achieved in 86% yield, concluding a total synthesis of prostratin (**1**). The NMR spectra and physical properties of synthetic **72** and **1** were identical to those reported for the natural products.[11,30,34]

Scheme 11. Completion of the synthesis of prostratin



[a]Reagents and conditions. (a) 20 mol% DDQ, MeCN/THF/H_2O (8:2:1), rt; then PivCl, pyridine, DMAP, CH_2Cl_2, 0 °C to rt, 73%; (b) 20 mol% AZADO, DMAP, 30 mol% CuCl, 30

mol% 2,2'-bpy, MeCN, 0 °C to rt; (c) TMSCl, imidazole, CH_2Cl_2, 40 °C, 64%, 2 steps; (d) SeO_2, PhH, 80 °C, 81%; (e) 30 mol% $RhCl_3 \cdot 3H_2O$, EtOH, 100 °C, 52%; (f) $NaBH_4$, MeOH, -50 °C, 86%.

CONCLUSIONS

In conclusion, a modular route to [5/7/6] tricyclic core of tigliane and daphnane diterpenoids has been developed. The key approach involved an oxidative dearomatization of planar and readily accessible phenol moiety and the following concise and highly controlled functionalizations, in order to build the complex and biologically critical six-membered C ring. Following this strategy, a total synthesis of prostratin has been accomplished in 23 steps from commercially available cyclopentadiene. The synthetic route also features several highly stereoselective reactions including a bulky Lewis acid promoted stereoselective conjugate addition, a solvent- and acid-controlled stereoselective cyclopropane formation and a late-stage RCM for B ring formation. DFT investigations of the mechanism in D ring formation revealed that a switch of intramolecular hydrogen bond mode led to stereodivergent protonation. This modular synthetic approach should be amenable to syntheses of other challenging natural and unnatural members within the tigliane and daphnane families.

EXPERIMENTAL SECTION

General Information. Unless otherwise noted, all reactions were carried out in a flame-dried, septum-sealed flask under an atmosphere of argon. Analytical thin-layer chromatography was performed on glass plates coated with 0.25 mm 230–400 mesh silica gel containing a fluorescent indicator. Visualization was accomplished by exposure to a UV lamp, and/or treatment with a solution of p-anisaldehyde or 10% ethanolic phosphomolybdic acid (PMA) followed by brief heating with a heating gun. Most of the products were compatible with standard silica gel chromatography. Column chromatography was performed on silica gel 60N (spherical and neutral, 200–300 mesh) using standard methods.

NMR spectra were measured on a Bruker Avance-400 spectrometer and chemical shifts (δ) are reported in parts per million (ppm). ^{1}H NMR spectra were recorded at 400 MHz in NMR solvents ($CDCl_3$) and referenced internally to corresponding solvent resonance, and ^{13}C NMR spectra were recorded at 100 MHz, Chemical shift were reported in ppm on the δ scale relative to $CHCl_3$ (δ = 7.26 for ^{1}H NMR, δ = 77.00 for ^{13}C NMR). All ^{13}C NMR data were obtained with the use of broadband decoupling ($^{13}C\{^1H\}$) and reported as proton-decoupled data. Coupling constants are reported in Hz with multiplicities denoted as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Infrared spectra were collected on a Thermo Fisher Nicolet 6700 FT-IR spectrometer using ATR (Attenuated Total Reflectance) method. Absorption maxima (ν max) are reported in wavenumbers (cm^{-1}). High resolution mass Spectra (HRMS) were obtained on a Bruker Apex IV FTMS spectrometer or an Agilent 6224 LC/MS TOF spectrometer. Single crystal X-ray diffraction analysis were carried out by Dr. Yousong Ding on Bruker apex duo equipment at Center for Applied Chemistry Research, Frontier Institute of Science and Technology, Xi'an Jiaotong University. Melting points were determined on a Hannon MP300 apparatus and are not corrected.

Commercial reagents were purchased from J&K, Energy, Sigma-Aldrich, Alfa Aesar, Acros Organics, Strem Chemicals or TCI and used as received unless otherwise stated. THF, toluene and benzene were purified by distillation over sodium/benzophenone and stored under N_2, MeCN were purchased from Acros Organics and used directly without further purification.

The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublet, ddd = doublet of a doublet of a doublet, dt = doublet of a triplet, td = triplet of a doublet, m = multiplet, br = broad.

Preparation of (1R,2*S*)-2-(4-methoxy-2-vinylphenyl)cyclopentan-1-ol (15). A three-necked flask fitted with a reflux condenser, a nitrogen inlet and an addition funnel was charged with Mg (3.34 g, 138.97 mmol, 1.50 equiv), several granules of crystalline iodine were added, 4-methoxy-2-vinylbromobenzene (29.60 g, 138.97 mmol, 1.50 equiv), was added dropwise over ca. 30 min, and the flask was heated for several minutes with a heat gun to initiate the reaction. The addition causes the solution to gently reflux, and once all of the 4-methoxy-2-vinylbromobenzene had been added, the reaction mixture was heated with a heating mantle to continue the reflux for an additional 30 min. To the freshly prepared solution of the (4-methoxy-2-vinylphenyl) magnesium bromide **12** was added copper iodide (1.80 g, 9.45 mmol, 0.10 equiv) at 0 °C, stirred for 30 min. To this reaction mixture was then added cyclopentene oxide **14** (7.80 g, 92.72 mmol, 1.00 equiv) dissolved in THF (100 mL) dropwise over a period of 30 min at 0 °C. The reaction mixture was stirred to room temperature for 3 h, The reaction was cooled to 0 °C and quenched with sat. aq. ammonium chloride. Ethyl acetate (5 x 50 mL) was added, and the upper organic layer was separated. The organic layer was dried with anhydrous sodium sulfate, the crude was purified by flash chromatography (petroleum ether/ ethyl acetate 20:1 → 10:1 → 5:1) to give the secondary alcohol **15** (20 g, 91.67 mmol, 99%) as pale yellow oil. *Rf* 0.43 (silica gel, 9:1 petroleum ether/ ethyl acetate, UV, blue, PMA); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (dd, *J* = 17.3, 10.9 Hz, 2H), 7.01 (d, *J* = 2.7 Hz, 1H), 6.84 (dd, *J* = 8.6, 2.7 Hz, 1H), 5.61 (dd, *J* = 17.3, 1.2 Hz, 1H), 5.32 (dd, *J* = 10.9, 1.2 Hz, 1H), 4.22 (dd, *J* = 13.6, 6.8 Hz, 1H), 3.81 (s, 3H), 3.21 (dd, *J* = 16.8, 7.9 Hz, 1H), 2.24-2.02 (m, 2H), 1.95-1.57 (m, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 158.0, 138.9, 135.4, 132.9, 126.9, 116.4, 114.0, 111.5, 80.1, 55.4, 49.2, 33.9, 32.0, 21.9; HRMS (ESI^+) *m/z* calcd for $C_{14}H_{22}NO_2$ $(M+NH_4)^+$: 236.1643, found: 236.1645; IR (neat) *ν* 3377, 2953, 1503, 1569, 1493, 1287, 1241, 1029, 987, 856, 815 cm^{-1}.

Preparation of (*S*)-2-(4-methoxy-2-vinylphenyl)cyclopentan-1-one (SI-1). To a stirred solution of secondary alcohol **15** (3.00 g, 13.74 mmol, 1 equiv) in CH_2Cl_2 (40 mL) at 0 °C was added Dess-Martin periodinane (8.74 g, 20.62 mmol, 1.50 equiv), and the reaction mixture was stirred at room temperature for 3 h. The resulting mixture was then quenched with sat. aq. $NaHCO_3$ (10 mL), the biphasic mixture was extracted with CH_2Cl_2 (3 x 50 mL), the combined organic extracts were washed with brine (50 mL), The organic layer was dried with anhydrous sodium sulfate, the crude was purified by flash chromatography (petroleum ether/ ethyl acetate 15:1) to give the ketone **SI-1** (2.53 g, 11.71 mmol, 85%) as pale yellow oil. *Rf* 0.36 (silica gel, 9:1 petroleum ether/ ethyl acetate, UV, blue, PMA); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, *J* = 2.7 Hz, 1H), 6.95 (d, *J* = 8.5 Hz, 1H), 6.90-6.78 (m, 2H), 5.61 (dd, *J* = 17.2, 1.1 Hz, 1H), 5.32 (dd, *J* = 10.9, 1.1 Hz, 1H), 3.80 (s, 3H),

3.54 (dd, *J* = 11.4, 8.6 Hz, 1H), 2.55-2.40 (m, 2H), 2.38-2.26 (m, 1H), 2.20-2.10 (m, 1H), 2.07-1.87 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, CDCl3) δ 219.0, 158.6, 139.1, 135.0, 128.9, 128.9, 117.1, 114.0, 111.9, 55.4, 52.4, 38.7, 32.5, 21.0; HRMS (ESI$^+$) *m/z* calcd for $C_{14}H_{17}O_2$ $(M+H)^+$: 217.1215, found: 217.1223; IR (neat) *ν* 2950, 2835, 1496, 1290, 1271, 1247, 1036, 856, 812 cm^{-1}.

Preparation of (1R,2S)-1-allyl-2-(4-methoxy-2-vinylphenyl)cyclopentan-1-ol (SI-2). To a stirred solution of ketone **SI-1** (2.00 g, 9.26 mmol, 1.00 equiv) in Et_2O (20.0 mL) at -78 °C was added allylmagnesium bromide (14.0 mL, 1.0 M in Et_2O, 1.50 equiv) dropwise over ca. 30 min under nitrogen, and the reaction mixture was stirred at -78 °C for 3 h. The resulting mixture was then quenched with sat. aq. ammonium chloride. Ethyl acetate (3 x 10 mL) was added, and the upper organic layer was separated. The organic layer was dried with anhydrous sodium sulfate, the crude was purified by flash chromatography (petroleum ether/ ethyl acetate 20:1) to give alcohol **SI-2** (2.27 g, 8.79 mmol, 95%, d.r. = 10:1, inseparable mixture) as pale yellow oil. *Rf* 0.55 (silica gel, 9:1 petroleum ether/ ethyl acetate, UV, blue, PMA); ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.6 Hz, 1H), 7.14-6.99 (m, 2H), 6.86 (dd, *J* = 8.6, 2.8 Hz, 1H), 5.79 (ddt, *J* = 17.5, 10.4, 7.3 Hz, 1H), 5.60 (dd, *J* = 17.2, 2.4 Hz, 1H), 5.32 (dd, *J* = 10.9, 2.4 Hz, 1H), 5.07-4.98 (m, 2H), 3.83 (s, 3H), 3.19 (dd, *J* = 10.9, 7.8 Hz, 1H), 2.28-1.57 (m, 10H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 158.3, 139.8, 136.0, 134.6, 129.7 (two peaks), 118.2, 116.8, 113.4, 112.0, 82.0, 55.4, 48.9, 45.2, 38.4, 31.8, 21.8; HRMS (ESI$^+$) *m/z* calcd for $C_{17}H_{26}NO_2$ $(M+NH_4)^+$: 276.1952, found: 276.1958; IR (neat) *ν* 3558, 2954, 1492, 1287, 1242, 1030, 990, 910, 874, 856, 815 cm^{-1}.

Preparation of (3aR,10bS)-8-methoxy-2,3,4,10b-tetrahydrobenzo[e]azulen-3a(1H)-ol (16) and (3aS,10bS)-8-methoxy-2,3,4,10b-tetrahydrobenzo[e]azulen-3a(1H)-ol (SI-3). To a stirred solution of **SI-2** (2.60 g, 10.06 mmol, 1.00 equiv) in toluene (100 mL) was added Grubbs 2nd generation catalyst (8.5 mg, 0.001 equiv) under nitrogen, and the resultant mixture was stirred at 80 °C (oil bath) for 3 h. The mixture was concentrated to dryness and the residue was purified by flash chromatography (petroleum ether/ ethyl acetate 15:1) to give **16** (1.95 g, 8.47 mmol, 84%) as yellow solid (m.p. 71.4-74.4 °C), and its diastereoisomer **SI-3** (186.5 mg, 0.81 mmol, 8%) as yellow oil. **16**: *Rf* 0.48 (silica gel, 9:1 petroleum ether/ ethyl acetate, UV, blue, PMA); ^1H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, *J* = 8.4 Hz, 1H), 6.86-6.74 (m, 2H), 6.46 (d, *J* = 12.7 Hz, 1H), 5.78 (dt, *J* = 12.7, 4.1 Hz, 1H), 3.81 (s, 3H), 3.00-2.89 (m, 1H), 2.74 (dd, *J* = 19.4, 4.7 Hz, 1H), 2.62 (d, *J* = 19.4 Hz, 1H), 2.20-1.87 (m, 6H), 1.66-1.52 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 158.5, 136.1, 130.1, 129.7, 129.7, 129.1, 117.1, 113.3, 78.6, 55.6, 53.3, 46.9, 43.0, 30.6, 24.4; HRMS (ESI$^+$) *m/z* calcd for $C_{15}H_{22}NO_2$ $(M+NH_4)^+$: 248.1638, found: 248.1645; IR (neat) *ν* 3400, 2952, 1602, 1505, 1250, 1162, 1036, 871, 820, 803, 773, 682 cm^{-1}. **SI-3**: *Rf* 0.23 (silica gel, 9:1 petroleum ether/ ethyl acetate, UV, blue, PMA); ^1H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, *J* = 8.4 Hz, 1H), 6.73 (dd, *J* = 8.4, 2.6 Hz, 1H), 6.68 (d, *J* = 2.6 Hz, 1H), 6.61 (d, *J* = 10.5 Hz, 1H), 5.97 (dt, *J* = 10.5, 7.0 Hz, 1H), 3.79 (s, 3H), 3.01 (dd, *J* = 10.1, 8.1 Hz, 1H), 2.28 (dd, *J* = 12.6, 7.8 Hz, 1H), 2.19 (dd, *J* = 12.6, 6.2 Hz, 1H), 2.02-1.93 (m, 3H), 1.83-1.70 (m, 3H), 1.65-1.55 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 158.0, 137.6, 134.0, 132.5, 131.7, 128.6, 114.7, 112.6, 93.86, 59.9, 55.4, 39.4, 39.0, 36.3, 23.9; HRMS (ESI$^+$) *m/z* calcd for $C_{15}H_{18}O_2Na$ $(M+Na)^+$: 253.1204, found: 253.1189; IR (neat) *ν* 3392, 2949, 1603, 1494, 1265, 1242, 1040, 873, 858, 782, 762 cm^{-1}.

Preparation of 7-methoxy-3,4-dihydrophenanthren-1(2H)-one (17) and 4-(6-methoxynaphthalen-1-yl)butanal (SI-4). To a stirred solution of **16** (23 mg, 0.10 mmol, 1.00 equiv) in MeCN/H_2O (v:v，3:1，2 mL) at room temperature was added slowly ceric ammonium nitrate (164 mg, 0.30 mmol, 3.00 equiv) and the reaction mixture was stirred at room temperature for 30 mins. The reaction mixture was concentrated to dryness and purified directly by preparative flash chromatography (9:1 petroleum ether/ ethyl acetate, twice) to yield the aldehyde **SI-4** as pale yellow oil (6 mg, 26 μmol, 26%), the ketone **17** as yellow solid (15 mg, 66 μmol, 66%). **17**: *Rf* 0.62 (silica gel, 9:1 petroleum ether/ ethyl acetate, UV, blue, PMA); ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.7 Hz, 1H), 8.04 (d, *J* = 9.2 Hz, 1H), 7.64 (d, *J* = 8.7 Hz, 1H), 7.22 (dd, *J* = 9.2, 2.6 Hz, 1H), 7.15 (d, *J* = 2.6 Hz, 1H), 3.95 (s, 3H), 3.35 (t, *J* = 6.1 Hz, 2H), 2.80 – 2.65 (m, 2H), 2.28 (dt, *J* = 12.8, 6.3 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$); δ 198.3, 159.5, 143.0, 137.6, 128.4, 126.5, 126.4, 125.8, 123.6, 119.0, 107.0, 55.4, 38.3, 25.7, 22.8. **SI-4**: *Rf* 0.71 (silica gel, 9:1 petroleum ether/ ethyl acetate, UV, blue, PMA); ^1H NMR (400 MHz, $CDCl_3$) δ 9.70 (s, 1H), 7.88 (d, *J* = 9.1 Hz, 1H), 7.55 (d, *J* = 8.2 Hz, 1H), 7.28 (dd, *J* = 8.1, 7.1 Hz, 1H), 7.16 – 7.02 (m, 3H), 3.85 (s, 3H), 3.07 – 2.93 (m, 2H), 2.45 (td, *J* = 7.2, 1.4 Hz, 2H), 2.05 – 1.91 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 202.2, 157.3, 137.4, 135.2, 127.2, 126.1, 125.8, 125.3, 124.1, 118.5, 106.7, 55.3, 43.4, 32.2, 23.1; HRMS (ESI$^+$) *m/z* calcd for $C_{15}H_{17}O_2$ $(M+H)^+$: 229.1229, found: 229.1222; IR (neat) *ν* 2934, 1625, 1255, 1219, 1034, 844, 822, 737 cm^{-1}.

Preparation of (((3aR,10bS)-8-methoxy-2,3,4,10b-tetrahydrobenzo[e]azulen-3a(1H)-yl)oxy)trimethylsilane (SI-5). To a stirred solution of **16** (1.20 g, 5.21 mmol, 1.00 equiv) and Et_3N (1.40 mL, 10.10 mmol, 2.00 equiv) in CH_2Cl_2 (20 mL) at 0 °C were added TMSOTf (1.40 mL, 7.82 mmol, 1.50 equiv) dropwise over ca. 10 min, and the reaction mixture was stirred at room temperature for 3 h. The resulting mixture was then quenched with sat. aq. sodium bicarbonate. CH_2Cl_2 was added (3 x 10 mL), the organic layer was dried with anhydrous sodium sulfate, the crude product was purified by flash chromatography (petroleum ether) to give **SI-5** (1.56 g, 5.16 mmol, 99%) as pale yellow oil. *Rf* 0.34 (silica gel, petroleum ether, UV, blue, PMA); ^1H NMR (400 MHz, $CDCl_3$) δ 7.06 (d, *J* = 8.3 Hz, 1H), 6.77-6.67 (m, 2H), 6.42 (d, *J* = 12.5 Hz, 1H), 5.70 (dt, *J* = 12.5, 4.1 Hz, 1H), 3.80 (s, 3H), 2.81 (dd, *J* = 11.8, 6.6 Hz, 1H), 2.70 (dd, *J* = 19.2, 4.5 Hz, 1H), 2.53 (dd, *J* = 19.2, 2.8 Hz, 1H), 2.19-2.00 (m, 3H), 2.00-1.83 (m, 3H), 1.62-1.43 (m, 1H), -0.17 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 157.4, 137.1, 132.3, 130.8, 128.8, 127.2, 115.9, 111.5, 81.9, 55.4, 54.2, 46.7, 44.6, 30.1, 24.4, 2.0; HRMS (ESI$^+$) *m/z* calcd for $C_{18}H_{26}O_2SiNa$ $(M+Na)^+$: 325.1599, found: 325.1581; IR (neat) *ν* 2952, 1504, 1270, 1247, 1045, 835, 751, 692 cm^{-1}.

Preparation of (3aR,10bS)-3a-((trimethylsilyl)oxy)-1,2,3,3a,4,10b-hexahydrobenzo[e]azulen-8-ol (18). To a stirred solution of diphenylphosphine (8.60 mL, 49.60 mmol, 3.00 equiv) in THF (80 mL) at 0 °C was added cold *n*-butyllithium solution (22.5 mL, 2.2 M in hexane, 49.60 mmol, 3.00 equiv) by syringe over ca. 20 min under nitrogen. The red solution was allowed to warm to room temperature over about 30 min before **SI-5** (5.00 g, 16.53 mmol, 1.00 equiv) in THF (5 mL) was added. The mixture was stirred at 60 °C (oil bath) for 3 h. Then the resulting mixture was quenched with sat. aq. ammonium chloride. Ethyl acetate (5 x 10 mL) was added, and the upper organic layer was separated. The organic layer was dried with anhydrous sodium sulfate. The crude was purified by flash chromatography (petroleum ether/ ethyl acetate 20:1) to give **18** as white solid (m.p. 91.6-92.8 °C) (4.6 g, 15.91 mmol, 96%). *Rf* 0.60 (silica gel, 9:1 petroleum ether/ ethyl acetate, UV, blue, PMA); ^1H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, *J* = 7.8 Hz, 1H), 6.73-6.60 (m, 2H), 6.38 (d, *J* = 12.6 Hz, 1H), 5.70 (dt, *J* = 12.6, 4.1 Hz, 1H), 4.99 (s, 1H), 2.80 (dd, *J* = 11.5, 6.7 Hz, 1H), 2.76-2.65 (m, 1H), 2.52 (dd, *J* = 19.3, 2.7 Hz, 1H), 2.16-1.85 (m, 6H), 1.58-1.47 (m, 1H), -0.15 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 153.1, 137.3, 132.3, 130.5, 129.0, 127.4, 117.0, 113.2, 81.8, 54.2, 46.7, 44.6, 30.1, 27.1, 24.4, 2.0; HRMS (ESI$^+$) *m/z* calcd for

$C_{17}H_{24}O_2SiNa$ $(M+Na)^+$: 311.1443, found: 311.1427; IR (neat) ν 3277, 2955, 2868, 1502, 1247, 1098, 1045, 860, 834, 752, 698 cm^{-1}.

Preparation of (3aR,10aR,10bR)-1,2,3,10b-tetrahydro-3a,10a-epoxybenzo[e]azulen-8(4H)-one (19). To a stirred solution of phenol **18** (11.5 mg, 0.04 mmol, 1.00 equiv) and $NaHCO_3$ (6.7 mg, 0.08 mmol, 2.00 equiv) in $MeCN/H_2O$ (3:1 v/v, 0.5 mL) was added $PhI(OAc)_2$ (13.0 mg, 1.00 mmol, 1.10 equiv) at 0 °C, the reaction mixture was stirred at room temperature for 1 h, then the mixture was concentrated to dryness and the crude product was carefully purified by column chromatography (petroleum ether/ ethyl acetate 5:1) to give **19** (3.6 mg, 0.017 mmol, 42%) as pale yellow oil. *Rf* 0.20 (silica gel, 9:1 petroleum ether/ ethyl acetate, UV, blue, PMA); ^1H NMR (400 MHz, $CDCl_3$) δ 7.03 (d, *J* = 10.2 Hz, 1H), 6.24-6.18 (m, 2H), 6.08 (dt, *J* = 11.9, 3.7 Hz, 1H), 5.99 (s, 1H), 2.96 (d, *J* = 20.1 Hz, 1H), 2.80 (d, *J* = 8.5 Hz, 1H), 2.54 (dd, *J* = 20.1, 3.7 Hz, 1H), 2.37-2.21 (m, 1H), 2.14-1.92 (m, 3H), 1.82-1.65 (m, 1H), 1.53-1.39 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 186.5, 158.2, 144.8, 134.9, 130.0, 127.3, 125.4, 92.7, 76.4, 49.8, 39.3, 37.8, 28.1, 26.0; HRMS (ESI^+) *m/z* calcd for $C_{14}H_{15}O_2$ $(M+H)^+$: 215.1061, found: 215.1067; IR (neat) ν 2926, 1652, 1601, 1216, 1089, 958, 907, 751 cm^{-1}.

Preparation of (3aR,10aS,10bS)-10a-(tert-butylperoxy)-3a-((trimethylsilyl)oxy)-2,3,3a,4,10a,10b-hexahydrobenzo[e]azulen-8(1H)-one (20). To a stirred solution of phenol **18** (288.5 mg, 1.00 mmol, 1.00 equiv) and $RuCl_2(PPh_3)_3$ (29.0 mg, 0.03 mmol, 0.03 equiv) in dry benzene (5.0 mL) at room temperature as added a solution of TBHP (0.38 mL, 2.6 M in dry benzene, 12.0 mmol, 10.0 equiv) dropwise under nitrogen. The mixture was stirred at room temperature for 3 h, then the mixture was concentrated to dryness and the crude product was purified by flash chromatography (petroleum ether/ ethyl acetate 20:1) to give **20** (225.0 mg, 0.60 mmol, 49%) as pale yellow oil. *Rf* 0.33 (silica gel, 15:1 petroleum ether/ ethyl acetate, UV, blue, PMA); ^1H NMR (400 MHz, $CDCl_3$) δ 6.79 (d, *J* = 10.2 Hz, 1H), 6.21 (d, *J* = 12.1 Hz, 1H), 6.17 (d, *J* = 10.2 Hz, 1H), 6.00 (s, 1H), 5.72 (dd, *J* = 12.1, 6.2 Hz, 1H), 2.71 (dd, *J* = 18.7, 6.2 Hz, 1H), 2.38 (d, *J* = 18.7 Hz, 1H), 1.97 (dd, *J* = 11.7, 6.7 Hz, 1H), 1.80-1.65 (m, 4H), 1.62-1.56 (m, 2H), 1.12 (s, 9H), -0.02 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 187.3, 157.9, 150.3, 131.0, 129.6, 127.8, 127.5, 81.8, 81.4, 79.4, 57.6, 41.4, 39.8, 27.2, 26.7, 20.7, 1.6; HRMS (ESI^+) *m/z* calcd for $C_{21}H_{32}O_4SiNa$ $(M+Na)^+$: 399.1967, found: 399.1953; IR (neat) ν 2974, 2876, 1663, 1249, 953, 891, 837, 748 cm^{-1}.

Preparation of (3aR,10bS)-2,3,4,10b-tetrahydrobenzo[e]azulene-3a,8(1H)-diol (21). To a stirred solution of **18** (288 mg, 1.00 mmol, 1.00 equiv) in THF (10 mL) was added TBAF (3 mL, 1 M in THF, 3.00 mmol, 3.00 equiv) at 0 °C. When TLC detected starting material consumption (~1 h), the mixture was quenched by sat. aq. ammonium chloride, extracted by ethyl acetate (3 x 10 mL). The organic layer was dried with anhydrous sodium sulfate. The crude was purified by flash chromatography (petroleum ether/ ethyl acetate 5:1→2:1) to give **21** as yellow solid (m.p. 169-171 °C) (214 mg, 99 mmol, 99%). *Rf* 0.19 (silica gel, 5:1 petroleum ether/ ethyl acetate, UV, blue, PMA); ^1H NMR (400 MHz, DMSO-d6) δ 9.04 (s, 1H), 6.92 (d, *J* = 8.0 Hz, 1H), 6.57 (d, *J* = 9.1 Hz, 1H), 6.56 (s, 1H), 6.27 (d, *J* = 12.7 Hz, 1H), 5.64 (dt, *J* = 12.5, 3.9 Hz, 1H), 3.58 (s, 1H), 2.69 (dd, *J* = 11.5, 6.9 Hz, 1H), 2.57 – 2.43 (m, 2H), 2.10 – 1.69 (m, 5H), 1.58 – 1.34 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d6) δ 155.4, 136.9, 130.3, 129.8, 129.6, 128.1, 117.8, 113.8, 77.9, 52.6, 46.5, 44.6, 30.4, 23.7; HRMS (ESI^+) *m/z* calcd for $C_{14}H_{17}O_2$ $(M+H)^+$: 217.1229, found: 217.1230; IR (neat) ν 3254, 2924, 2853, 1504, 1455, 1259, 1185, 1158, 1024, 865, 680 cm^{-1}.

Preparation of 4-(6-hydroxynaphthalen-1-yl)butanal (22). 21 (22 mg, 0.10 mmol, 1.00 equiv) was dissolved in $MeCN/H_2O$ (v:v, 3:1, 1.3 mL). $PhI(OAc)_2$ (35 mg, 0.11 mmol, 1.10 equiv) was added, and then stirred at room temperature for 10 min, color of solution changed from yellow to dark red. The residue was concentrated in vacuo and purified directly by preparative flash chromatography (2:1 petroleum ether/ ethyl acetate, twice) to yield **22** as yellow oil (15 mg, 0.07 mmol, 70%). *Rf* 0.37 (silica gel, 2:1 petroleum ether/ ethyl acetate, UV, blue, PMA); ^1H NMR (400 MHz, $CDCl_3$) δ 9.78 (s, 1H), 7.96 (d, *J* = 9.0 Hz, 1H), 7.55 (d, *J* = 8.3 Hz, 1H), 7.38 – 7.29 (m, 1H), 7.21 – 7.06 (m, 3H), 3.16 – 2.95 (m, 2H), 2.53 (t, *J* = 7.1 Hz, 2H), 2.16 – 1.95 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 202.5, 153.2, 137.4, 135.3, 127.2, 126.3, 125.7, 125.5, 124.1, 117.7, 110.4, 43.5, 32.2, 23.0; HRMS (ESI^+) *m/z* calcd for $C_{14}H_{15}O_2$ $(M+H)^+$: 215.1072, found: 215.1066; IR (neat) ν 3417, 2925, 2854, 1652, 1046, 806, 757 cm^{-1}.

Preparation of (Z)-3-hydroxy-12-methoxy-9,10,11,12-tetrahydrobenzo[10]annulen-8(7H)-one (23). To a stirred solution of phenol **21** (45 mg, 0.2 mmol, 1.00 equiv) in MeOH (2 mL) at 0 °C was added slowly $PhI(OAc)_2$ (74 mg, 0.23 mmol, 1.10 equiv). The mixture was allowed to warm to room temperature over 2 h. Then the reaction mixture was concentrated to dryness and purified directly by preparative flash chromatography (2:1 petroleum ether/ ethyl acetate) to afford **23** (34 mg, 0.14 mmol, 69%) as yellow solid (m.p. 137-139 °C). *Rf* 0.58 (silica gel, 2:1 petroleum ether/ ethyl acetate, UV, blue, PMA); ^1H NMR (400 MHz, DMSO-d6) δ 9.51 (s, 1H), 7.17 (d, *J* = 8.4 Hz, 1H), 6.77 (d, *J* = 8.4 Hz, 1H), 6.57 (d, *J* = 10.9 Hz, 1H), 6.45 (s, 1H), 6.14 – 5.91 (m, 1H), 4.27 – 4.05 (m, 1H), 3.32 – 3.17 (m, 1H), 2.82 (s, 3H), 2.66 (d, *J* = 11.8 Hz, 1H), 2.47 – 2.30 (m, 1H), 2.19 (s, 1H), 1.89 (s, 2H), 1.61 (s, 1H), 1.44 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d6) δ 212.0, 157.0, 139.1, 130.8, 129.2, 128.3, 128.1, 116.0, 114.5, 76.9, 55.3, 44.5, 35.7, 21.7; HRMS (ESI^+) *m/z* calcd for $C_{15}H_{19}O_3$ $(M+H)^+$: 247.1334, found: 247.1330; IR (neat) ν 3238, 2937, 2915, 1601, 1435, 1239, 1215, 1087, 879, 823 cm^{-1}.

Preparation of (3aR,10aS,10bS)-10a-hydroxy-3a-((trimethylsilyl)oxy)-2,3,3a,4,10a,10b-hexahydrobenzo[e]azulen-8(1H)-one (24). Phenol **18** (2.00 g, 6.93 mmol, 1.00 equiv) was dissolved in chloroform (32 mL) and tetraphenylporphine (TPP) (213.0 mg, 0.35 mmol, 0.05 equiv) was added. The reaction was kept under oxygen atmosphere by bubbling with an oxygen balloon. The solution was irradiated using 400W sodium lamp at 0 °C for 12 h. Then to the resulting solution was added triphenylphosphine (1.84 g, 7.01 mmol, 1.00 equiv) at 0 °C. After 1 h the reaction mixture was concentrated to dryness and purified directly by flash chromatography (petroleum ether/ ethyl acetate 5:1) to give the desired compound **24** as pale pink solid (m.p. 102.5-103.2 °C) (1.56 g, 5.12 mmol, 74%). *Rf* 0.28 (silica gel, 2:1 petroleum ether/ ethyl acetate, UV, blue, PMA); ^1H NMR (400 MHz, $CDCl_3$) δ 6.89 (d, *J* = 10.1 Hz, 1H), 6.24 (dd, *J* = 12.0, 3.2 Hz, 1H), 6.08 (dd, *J* = 10.1, 1.9 Hz, 1H), 5.92 (s, 1H), 5.88 (ddd, *J* = 12.0, 6.2, 2.8 Hz, 1H), 2.78 (dd, *J* = 19.0, 6.2 Hz, 1H), 2.50 (dt, *J* = 19.0, 2.8 Hz, 1H), 2.27 (dd, *J* = 12.4, 7.0 Hz, 1H), 2.10 (s, 1H), 1.90-1.79 (m, 1H), 1.74 -1.63 (m, 3H), 1.61-1.49 (m, 2H), -0.02 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 186.8, 159.5, 150.5, 133.3, 128.7, 125.6, 125.3, 81.7, 72.0, 61.4, 41.9, 40.1, 27.5, 21.1, 1.6; HRMS (ESI^+) *m/z* calcd for $C_{17}H_{24}O_3SiNa$ $(M+Na)^+$: 327.1392, found: 327.1378; IR (neat) ν 3343, 2955, 1652, 1604, 1247, 952, 929, 837, 772, 757 cm^{-1}.

Preparation of (3aR,10R,10aS,10bS)-10a-hydroxy-10-methyl-3a-((trimethylsilyl)oxy)-2,3,3a,4,9,10,10a,10b-octahydrobenzo[e]azulen-8(1H)-one (25). To a stirred solution of hydroxyl ketone **24** (30.0 mg, 0.099 mmol, 1.00 equiv) in THF (2.0 mL) was added lithium hexamethyl

disilazide (0.10 mL, 1.0 M in THF, 0.10 mmol, 1.00 equiv) dropwise at 0 °C under nitrogen. After being stirred for 10 min, the reaction mixture was added HMPA (0.17 mL, 10 equiv), followed by methylmagnesium bromide (0.030 mL, 0.10 mmol, 3.0 M in THF, 1.00 equiv). The mixture was stirred at -78 °C for 1 h. Then the resulting mixture was quenched with sat. aq. ammonium chloride, extracted by ethyl acetate (3 x 5 mL), and the upper organic layer was separated. The organic layer was dried with anhydrous sodium sulfate. The crude product was purified by flash chromatography (petroleum ether/ ethyl acetate 5:1) to give **25** as pale pink solid (m.p. 95.1-96.9 °C) (20 mg, 0.062 mmol, 63%). *Rf* 0.53 (silica gel, 2:1 petroleum ether/ ethyl acetate, UV, blue, PMA); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.15 (dd, *J* = 11.9, 3.0 Hz, 1H), 5.82 (ddd, *J* = 11.9, 6.1, 2.8 Hz, 1H), 5.73 (s, 1H), 2.75-2.57 (m, 3H), 2.51 (dt, *J* = 18.9, 3.0 Hz, 1H), 2.30 (dd, *J* = 16.2, 5.4 Hz, 1H), 2.14 (dd, *J* = 12.7, 6.6 Hz, 1H), 2.05 (s, 1H), 2.01-1.94 (m, 2H), 1.79-1.66 (m, 3H), , 1.55-1.45 (m, 1H), 1.08 (d, *J* = 6.8 Hz, 3H), -0.01 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 199.4, 159.7, 133.1, 129.0, 125.9, 82.5, 75.8, 64.0, 43.0, 42.1, 40.5, 37.5, 28.2, 21.6, 16.9, 1.6; HRMS (ESI$^+$) *m/z* calcd for $C_{18}H_{29}O_3Si(M+H)^+$: 321.1876, found: 321.1880; IR (neat) *ν* 2974, 1637, 1246, 1089, 976, 933, 836, 749 cm^{-1}.

Preparation of (3aR,6aS,10R,10aS,10bS)-10a-hydroxy-10-methyl-2,3,9,10,10a,10b-hexahydro-1H,4H-3a,6a-epoxybenzo[e]azulen-8(7H)-one (27). Camphorsulfonic acid (14.5 mg, 0.062 mmol, 1.00 equiv) was added into the solution of **25** (20 mg, 0.063 mmol, 1.00 equiv) in MeOH (1 mL) at room temperature, then stirred 1 h, the color of reaction mixture changed from colorless to dark green. The crude product was concentrated to dryness and purified directly by preparative flash chromatography (5:1 petroleum ether/ ethyl acetate) to afford **27** as white solid (m.p. 112-114 °C) (15 mg, 0.06 mmol, 97%). *Rf* 0.30 (silica gel, 2:1 petroleum ether/ ethyl acetate, blue, PMA); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.98 (ddd, *J* = 9.6, 4.3, 2.3 Hz, 1H), 5.88 – 5.73 (m, 1H), 2.68 – 2.53 (m, 3H), 2.53 – 2.14 (m, 4H), 2.07 – 1.72 (m, 6H), 1.65 – 1.48 (m, 2H), 1.10 (d, *J* = 6.3 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 209.2, 133.0, 128.7, 90.1, 87.8, 85.7, 61.6, 46.3, 44.4, 37.7, 37.2, 34.4, 28.8, 27.0, 17.2; HRMS (ESI$^+$) *m/z* calcd for $C_{15}H_{21}O_3$ (M+H)$^+$: 249.1491, found: 249.1491; IR (neat) *ν* 3449, 2964, 2915, 1715, 1206, 1118, 1107, 944, 879, 696 cm^{-1}.

Preparation of (3aR,8S,10R,10aS,10bS)-10-methyl-3a-((trimethylsilyl)oxy)-2,3,3a,4,8,9,10,10b-octahydrobenzo[e]azulene-8,10a(1H)-diol (SI-8). To a solution of the ketone **25** (64.0 mg, 0.20 mmol, 1.00 equiv) in MeOH (2.0 mL), $CeCl_3{\cdot}7H_2O$ (74.5 mg, 0.20 mmol, 1.00 equiv) and $NaBH_4$ (7.6 mg, 0.20 mmol, 1.0 equiv) were sequentially added at -78 °C. The reaction mixture was stirred for 2 h and quenched by H_2O, extracted by ethyl acetate (3 x 5 mL), the upper organic layer was separated and the organic layer was dried with anhydrous sodium sulfate. The crude product was purified by flash chromatography (petroleum ether/ ethyl acetate 2:1) to give the diol **SI-8** (62.5 mg, 0.19 mmol, 96%) as a white solid (m.p. 153.1-155.2 °C), and its diastereoisomer (2.6 mg, 0.008 mmol, 4%) as colorless oil, d.r. = 24:1. *Rf* 0.23 (silica gel, 2:1 petroleum ether/ ethyl acetate, UV, blue, PMA); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.02 (d, *J* = 11.8 Hz, 1H), 5.57 (s, 1H), 5.47 (ddd, *J* = 11.8, 5.9, 2.9 Hz, 1H), 4.20 (d, *J* = 4.2 Hz, 1H), 2.59 (dd, *J* = 18.4, 5.9 Hz, 1H), 2.37 (d, *J* = 18.4 Hz, 1H), 2.03 (dd, *J* = 12.9, 6.1 Hz, 1H), 1.93 (ddd, *J* = 12.5, 6.5, 3.3 Hz, 1H), 1.82-1.86 (m, 1H), 1.81-1.60 (m, 7H), 1.48-1.36 (m, 1H), 1.35-1.26 (m, 1H), 1.07 (d, *J* = 6.6 Hz, 3H), 0.01 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 142.0, 133.3, 131.1, 126.8, 82.2, 75.0, 67.8, 61.4, 42.1, 41.8, 38.0, 34.8, 29.3, 21.5, 17.6, 1.8; HRMS (ESI$^+$) *m/z* calcd for $C_{18}H_{30}O_3SiNa$ (M+Na)$^+$: 345.1854, found: 345.1856; IR (neat) *ν* 3554, 2965, 1245, 1083, 952, 934, 833, 751 cm^{-1}.

Preparation of (3aR,6aR,7R,8R,10R,10aS,10bS)-10-methyl-1,2,3,7,8,9,10,10b-octahydro-4H,10aH-3a,6a-epoxybenzo[e]azulene-7,8,10a-triol (28). To a solution of the corresponding diol **SI-8** (160.0 mg, 0.50 mmol, 1.00 equiv) in CH_2Cl_2 (5.0 mL), $NaHCO_3$ (84.0 mg, 1.00 mmol, 2.00 equiv), *m*CPBA (purity 85%, 122.0 mg, 0.60 mmol, 1.20 equiv) were sequentially added at 0 °C. The reaction mixture was stirred at room temperature for 1 h, then the mixture was concentrated to dryness and the crude product was purified by flash chromatography (petroleum ether/ ethyl acetate 1:1→1:2) to give triol **28** (92.0 mg, 0.35 mmol, 70%) as a white solid (m.p. 145.7-147.9 °C). *Rf* 0.17 (silica gel, 1:2 petroleum ether/ ethyl acetate, UV, blue, PMA); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.45 (d, *J* = 9.9 Hz, 1H), 5.98 (dd, *J* = 9.9, 2.7 Hz, 1H), 4.03-3.96 (m, 1H), 3.83 (s, 1H), 2.59 (d, *J* = 17.6 Hz, 1H), 2.34-2.28 (m, 1H), 2.02-1.94 (m, 2H), 1.89-1.47 (m, 10H), 1.04 (d, *J* = 6.6 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 131.7, 127.4, 91.1, 86.0, 85.8, 72.3, 68.1, 60.5, 38.5, 37.8, 33.2, 32.0, 28.3, 27.8, 17.2; HRMS (ESI$^+$) *m/z* calcd for $C_{15}H_{26}NO_4$ (M+NH_4)$^+$: 284.1861, found: 284.1856; IR (neat) *ν* 3509, 3381, 2963, 2872, 952, 911, 852, 835 cm^{-1}.

Preparation of (3S,3aR,6aR)-3-hydroxy-3,3a,4,6a-tetrahydro-2H-cyclopenta[b]furan-2-one (SI-9) and (3R,3aR,6aR)-3-hydroxy-3,3a,4,6a-tetrahydro-2H-cyclopenta[b]furan-2-one (SI-10). Freshly distilled cyclopentadiene (194 g, 240 mL, 2.94 mol, 1.46 equiv) was added into the solution of aq. glyoxylic acid (225 mL, 50% in H_2O, 2.01 mol, 1.00 equiv) in H_2O (400 mL) at 0 °C, the resultant bilayer mixture was stirred vigorously at room temperature for 4 d. The aqueous layer was washed with heptane (3 x 300 mL) and neutralized by $NaHCO_3$ (Caution: large amounts of CO_2), then extracted with ethyl acetate (10 x 500 mL). The organic layer was dried over anhydrous sodium sulfate. The crude product was concentrated to dryness to give lactone **SI-9** and **SI-10** (183 g, 1.31 mol, 65%) as inseparable mixture (d.r.~2:1) which was sufficiently pure for the next step (detected by ^{1}H NMR). **Major isomer**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.32 – 6.14 (m, 1H), 5.89 (dd, *J* = 5.1, 2.4 Hz, 1H), 5.31 (dt, *J* = 6.1, 1.9 Hz, 1H), 4.74 (d, *J* = 9.3 Hz, 1H), 3.19 (tt, *J* = 9.3, 6.1 Hz, 1H), 2.72 – 2.65 (m, 1H), 2.49 – 2.34 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 177.7, 141.1, 127.5, 86.5, 69.1, 40.5, 30.8. **Minor isomer**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.10 – 6.01 (m, 1H), 5.86 (dd, *J* = 5.5, 2.0 Hz, 1H), 5.55 – 5.44 (m, 1H), 4.14 (d, *J* = 7.2 Hz, 1H), 3.09 – 2.95 (m, 1H), 2.78 – 2.73 (m, 1H), 2.56 – 2.52 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 178.2, 136.8, 129.2, 87.4, 74.3, 44.1, 36.6.

Preparation of (S)-1-((1S,2R)-2-hydroxycyclopent-3-en-1-yl)ethane-1,2-diol (SI-11) and (R)-1-((1S,2R)-2-hydroxycyclopent-3-en-1-yl)ethane-1,2-diol (SI-12). To the solution of lactone **SI-9**/**SI-10** (50 g, 357 mmol, 1.00 equiv) in dry THF (1 L) was carefully added $LiAlH_4$ (15 g, 395 mmol, 1.10 equiv) at 0 °C (Caution: exothermic, large amounts of H_2 evolved). After addition, the resultant gray suspension was carefully warmed up to 90 °C (oil bath) for 18 h (10:1, DCM/MeOH, Rf = 0.15, blue, PMA). The mixture was cooled to 0 °C and quenched slowly by H_2O. The mixture was filtered through a pad of celite (200 g), washed with THF (6 x 500 mL). The crude product was concentrated to dryness to give as dark yellow oil triol **SI-11**/**SI-12** (51 g, 353 mmol, 99%) as inseparable mixture (d.r.~2:1). **SI-11**: ^{1}H NMR (400 MHz, D_2O) δ 6.13 – 6.09 (m, 1H), 5.97 – 5.92 (m, 1H), 4.75 (d, *J* = 5.0 Hz, 1H), 3.88 – 3.82 (m, 1H), 3.79 – 3.76 (m, 1H), 3.57 (dd, *J* = 12.1, 6.4 Hz, 1H), 2.33 – 2.08 (m, 3H); ^{13}C{^{1}H} NMR (100 MHz, D_2O) δ 136.4, 131.7, 75.4, 71.5, 64.9, 44.4, 32.6. **SI-12**: ^{1}H NMR (400 MHz, D_2O) δ 6.18 – 6.13 (m, 1H), 5.92 – 5.87 (m, 1H), 4.63 (d, *J* = 6.2 Hz, 1H), 3.94 –3.88 (m, 1H), 3.84 – 3.80 (m, 1H), 3.64 – 3.59 (m, 1H), 2.41 (d, *J* = 7.9 Hz, 2H), 2.18 – 2.14 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, D_2O) δ 136.4, 131.8, 75.5, 72.3, 64.9, 44.0, 33.4.

Preparation of (1R,5R)-5-(hydroxymethyl)cyclopent-2-en-1-ol (11). To a solution of triol **SI-11**/**SI-12** (50 g, 347 mmol, 1.00 equiv) in EtOH/H_2O (v:v, 1:1, 1 L) was slowly added sodium periodate (84 g, 392 mmol, 1.13 equiv) at 0 °C, the resultant mixture was stirred vigorously at room temperature. When TLC detected starting material consumption (~2 h, 10:1, DCM/MeOH, Rf = 0.75, blue, PMA), the mixture was filtered. The filtrate was slowly added $NaBH_4$ (27 g, 711 mmol, 2.00 equiv) at 0 °C (Caution: exothermic). The dark solution was stirred overnight. Then KHF_2 (54 g, 691 mmol, 2.00 equiv) was added, dark solution changed to clear yellow (20:1, DCM/MeOH, Rf = 0.25, dark blue, PMA). The resultant mixture was filtered, washed with EtOH. The crude product was purified by flash chromatography (20:1, DCM/MeOH) to give diol **11** as yellow oil (27.7 g, 243 mmol, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.07 – 5.99 (m, 1H), 5.85– 5.82 (m, 1H), 4.94 (d, *J* = 7.0 Hz, 1H), 3.86 (dd, *J* = 11.0, 4.5 Hz, 1H), 3.79 (dd, *J* = 11.0, 8.2 Hz, 1H), 2.50 (ddd, *J* = 12.9, 7.2, 4.7 Hz, 1H), 2.44 – 2.33 (m, 1H), 2.30 – 2.16 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 135.2, 132.4, 77.7, 62.7, 42.5, 33.6. Diol **11** was prepared according to reference 36.

Preparation of (1aS,1bS,5aR,6aS)-3,3-dimethylhexahydrooxireno[2',3':4,5]cyclopenta[1,2-d][1,3]dioxine (SI-13). To a stirred solution of diol **11** (11.4 g, 100 mmol, 1.00 equiv) in CH_2Cl_2 (80 mL) and $Me_2C(OMe)_2$ (20 mL), at 0 °C was added PPTs (2.5 g, 9.95 mmol, 0.10 equiv), the reaction mixture was stirred at room temperature for 18 h. After TLC detected starting material consumption, $NaHCO_3$ (42 g, 500 mmol, 5.00 equiv), *m*CPBA (purity 85%, 40.6 g, 200 mmol, 2.00 equiv) were sequentially added at 0 °C. Then the reaction mixture was stirred at room temperature for 15 h. The resulting mixture was quenched with sat. aq. $Na_2S_2O_3$/CH_2Cl_2 (v/v, 1:2, 500 mL). The organic layer was dried with anhydrous sodium sulfate. The crude product was purified by flash chromatography (petroleum ether/ ethyl acetate 20:1) to give **SI-13** as pale yellow oil (12.84 g, 75 mmol, 75%). *Rf* 0.51 (silica gel, 10:1 petroleum ether/ ethyl acetate, pale blue, PMA); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.39 (d, *J* = 4.5 Hz, 1H), 4.13 (dd, *J* = 12.2, 4.5 Hz, 1H), 3.63 (dd, *J* = 12.2, 1.4 Hz, 1H), 3.52 (s, 1H), 3.45 (d, *J* = 2.4 Hz, 1H), 2.07 – 1.91 (m, 2H), 1.65 (ddt, *J* = 10.7, 4.6, 3.0 Hz, 1H), 1.45 (s, 3H), 1.35 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 97.2, 77.3, 77.0, 76.7, 69.9, 59.7, 57.5, 56.4, 30.8, 28.9, 28.8, 19.2; HRMS (ESI$^+$) *m/z* calcd for $C_9H_{14}O_3Na$ (M+Na)$^+$: 193.0841, found: 193.0867; IR (neat) *ν* 2992, 2938, 2883, 1374, 1256, 1196, 1113, 844, 765 cm^{-1}.

Preparation of (4aR,6S,7S,7aS)-6-(4-methoxy-2-vinylphenyl)-2,2-dimethylhexahydrocyclopenta[d][1,3]dioxin-7-ol (SI-14). To the freshly prepared solution of the (4-methoxy-2-vinylphenyl) magnesium bromide **12** (from 4-methoxy-2-vinylbromobenzene (3.75 g, 17.63 mmol, 1.50 equiv) and Mg (423 mg, 17.63 mmol, 1.50 equiv)) in THF (20 mL) was added copper iodide (224 mg, 1.18 mmol, 0.10 equiv.) at 0 °C, stirred for 30 min. To this reaction mixture was added dropwise a solution of cyclopentene oxide **SI-13** (2.00 g, 11.75 mmol, 1.00 equiv) in THF (20 mL) over a period of 30 min at 0 °C. The reaction mixture was stirred at room temperature for 3 h. Then the reaction was re-cooled to 0 °C and quenched with sat. aq. ammonium chloride, extracted by ethyl acetate (5 x 20 mL). The organic layer was dried with anhydrous sodium sulfate. The crude was purified by flash chromatography (petroleum ether/ ethyl acetate 5:1) to give the secondary alcohol **SI-14** (2.65 g, 8.7 mmol, 74%) as pale yellow oil. *Rf* 0.50 (silica gel, 2:1 petroleum ether/ ethyl acetate, UV, dark green, *p*-anisaldehyde); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.6 Hz, 1H), 7.13 (dd, *J* = 17.2, 10.9 Hz, 1H), 6.97 (s, 1H), 6.84 (d, *J* = 8.5 Hz, 1H), 5.59 (d, *J* = 17.2 Hz, 1H), 5.30 (d, *J* = 10.9 Hz, 1H), 4.24 – 4.07 (m, 2H), 4.02 (dd, *J* = 11.6, 4.3 Hz, 1H), 3.80 (s, 3H), 3.63 (dd, *J* = 11.7, 3.7 Hz, 1H), 3.35 – 3.16 (m, 1H), 2.53 (d, *J* = 2.6 Hz, 1H), 2.20 (dd, *J* = 10.4, 5.3 Hz, 1H), 2.12 – 1.86 (m, 2H), 1.42 (s, 3H), 1.39 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 157.9, 138.3, 135.2, 132.4, 128.0, 116.3, 114.0, 111.1, 98.3, 85.4, 78.3, 60.8, 55.2, 47.7, 36.9, 35.0, 28.4, 20.4; HRMS (ESI$^+$) *m/z* calcd for $C_{18}H_{25}O_4$ (M+H)$^+$: 305.1753, found: 305.1748; IR (neat) *ν* 3397, 2989, 2908, 1494, 1196, 1028, 986, 845 cm^{-1}.

Preparation of (4aR,6S,7R,7aS)-6-(4-methoxy-2-vinylphenyl)-2,2-dimethyl-7-(2-methylallyl)hexahydrocyclopenta[d][1,3]dioxin-7-ol (29). To the solution of secondary alcohol **SI-14** (304 mg, 1.00 mmol, 1.00 equiv) in DCM (10 mL) was sequentially added $NaHCO_3$ (168 mg, 2.00 mmol, 2.00 equiv), Dess-Martin periodinane (636 mg, 1.50 mmol, 1.50 equiv), then stirred 2 h at room temperature. The resulting mixture was then quenched with sat. aq. $NaHCO_3$ (10 mL), the biphasic mixture was extracted with DCM (3 x 20 mL). The organic layer was dried with anhydrous sodium sulfate. The resulting yellow oil was used for the next step without further purification. 2-Methylmagnesium chloride (3 mL, 0.5 M in THF, 1.5 mmol, 1.50 equiv) was added into the solution of above crude ketone in THF (10 mL) at 0 °C, then stirred 6 h at room temperature. The resultant mixture was quenched with sat. aq. ammonium chloride, extracted by ethyl acetate (3 x 20 mL), and upper organic layer was separated. The crude product was purified by flash chromatography (petroleum ether/ ethyl acetate 5:1) to give **29** as white foam (m.p. 111-113 °C) (580 mg, 0.58 mmol, 58%, 2 steps). *Rf* 0.69 (silica gel, 2:1 petroleum ether/ ethyl acetate, UV, purple, *p*-anisaldehyde); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.7 Hz, 1H), 7.07 (dd, *J* = 17.1, 10.9 Hz, 1H), 6.96 (s, 1H), 6.85 (d, *J* = 8.7 Hz, 1H), 5.56 (d, *J* = 17.2 Hz, 1H), 5.28 (d, *J* = 10.9 Hz, 1H), 4.81 (s, 1H), 4.68 (s, 1H), 4.12 (d, *J* = 4.6 Hz, 1H), 4.02 – 3.92 (m, 1H), 3.87 – 3.77 (m, 3H), 3.65 (dd, *J* = 11.3, 4.6 Hz, 1H), 3.21 (t, *J* = 8.5 Hz, 1H), 2.98 (s, 1H), 2.30 (d, *J* = 13.7 Hz, 1H), 2.25 – 2.10 (m, 3H), 1.99 – 1.89 (m, 1H), 1.74 (s, 3H), 1.44 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.0, 143.0, 139.4, 136.0, 130.6, 130.0, 116.4, 114.4, 113.3, 111.4, 99.0, 81.5, 74.7, 62.0, 55.2, 47.6, 47.1, 36.0, 34.0, 27.8, 24.3, 22.0; HRMS (ESI$^+$) *m/z* calcd for $C_{22}H_{30}O_4Na$ (M+Na)$^+$: 381.2042, found: 381.2043; IR (neat) *ν* 3479, 2964, 2936, 2875, 1492, 1247, 1028, 897, 819 cm^{-1}.

Preparation of (7aR,7bS,11aR,12aS)-3-methoxy-6,9,9-trimethyl-11,11a,12,12a-tetrahydro-7H-benzo[4,5]azuleno[1,2-d][1,3]dioxin-7a(7bH)-ol (30). Under argon, to a stirred solution of **29** (36 mg, 0.10 mmol, 1.00 equiv) in toluene (5 mL) was added Grubbs 2nd generation catalyst (8.5 mg, 0.01 mmol, 0.10 equiv), and the resultant mixture was stirred at 110 °C (oil bath) for 12 h. The mixture was concentrated to dryness and the residue was purified by flash chromatography (petroleum ether/ ethyl acetate 5:1) to give **30** as pale yellow oil (26 mg, 0.078 mmol, 78%). *Rf* 0.29 (silica gel, 2:1 petroleum ether/ ethyl acetate, UV, brown, *p*-anisaldehyde); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (d, *J* = 8.3 Hz, 1H), 6.85 – 6.65 (m, 2H), 6.38 (s, 1H), 4.22 (dd, *J* = 12.1, 3.8 Hz, 1H), 3.97 (d, *J* = 4.6 Hz, 1H), 3.90 – 3.82 (m, 1H), 3.79 (s, 3H), 3.34 (s, 1H), 2.99 (dd, *J* = 13.2, 5.0 Hz, 1H), 2.64 – 2.36 (m, 3H), 1.97 (s, 3H), 1.93 (dd, *J* = 11.9, 5.6 Hz, 2H), 1.51 (s, 3H), 1.41 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 157.7, 136.9, 135.8, 129.7, 126.9, 126.3, 116.0, 111.4, 98.6, 77.4, 76.5, 60.8, 55.2, 51.4, 50.3, 36.3, 30.1, 28.8, 27.8, 19.8; HRMS (ESI$^+$) *m/z* calcd for $C_{20}H_{27}O_4$ (M+H)$^+$: 331.1909, found: 331.1910; IR (neat) *ν* 3517, 2906, 2877, 1375, 1266, 1156, 904, 771 cm^{-1}.

Preparation of ((2R,3S,3aR,10bS)-3,3a-dihydroxy-8-methoxy-5-methyl-1,2,3,3a,4,10b-hexahydrobenzo[e]azulen-2-yl)methyl pivalate (31). To a stirred solution of **30** (250 mg, 0.76 mmol, 1.00 equiv) in

MeOH/H_2O (v:v, 5:1, 12 mL) was added camphorsulfonic acid (176 mg, 0.76 mmol, 1.00 equiv) at 25 °C, and the resultant mixture was stirred at 90 °C (oil bath) for 12 h. The mixture was concentrated to dryness and re-dissolved in DCM (15 mL). Pyridine (0.3 mL, 3.8 mmol, 5.00 equiv), DMAP (93 mg, 0.76 mmol, 1.00 equiv.), PivCl (0.28 mL, 2.3 mmol, 3.00 equiv) were sequentially added into reaction solution at 0 °C. The mixture was allowed to stir at 25 °C for 12 h. The reaction was quenched by sat. $NaHCO_3$ (3 mL) and extracted with DCM (3 x 20 mL). The organic layer was concentrated *in vacuo* and purified by preparative thin layer chromatography (petroleum ether/ ethyl acetate 5:1) to give **31** (233 mg, 0.61 mmol, 81%, 2 steps) as white solid (m.p. 141-143 °C). *Rf* 0.45 (silica gel, 2:1 petroleum ether/ ethyl acetate, UV, brown, *p*-anisaldehyde); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (d, *J* = 8.0 Hz, 1H), 6.76 (d, *J* = 7.6 Hz, 2H), 6.37 (s, 1H), 4.46 (dd, *J* = 10.8, 7.7 Hz, 1H), 4.25 (dd, *J* = 10.8, 6.6 Hz, 1H), 3.91 – 3.84 (m, 1H), 3.80 (s, 3H), 3.36 (d, *J* = 3.6 Hz, 1H), 3.03 (t, *J* = 9.3 Hz, 1H), 2.62 – 2.41 (m, 2H), 2.26 (dt, *J* = 13.9, 7.1 Hz, 1H), 2.02 (dd, *J* = 13.6, 6.5 Hz, 2H), 1.97 (s, 3H), 1.23 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.0, 143.0, 139.4, 136.0, 130.6, 130.0, 116.4, 114.3, 113.3, 111.4, 99.0, 81.5, 74.7, 62.0, 55.2, 47.6, 47.1, 35.9, 34.0, 27.8, 24.2, 22.0; HRMS (ESI$^+$) *m/z* calcd for $C_{22}H_{30}O_5Na$ (M+Na)$^+$: 397.1991, found: 397.2008; IR (neat) *ν* 3443, 3347, 2931, 2887, 1729, 1247, 1161, 1101, 1037, 905, 810 cm^{-1}.

Preparation of ((5S,7R,8S,9S)-8-hydroxy-2-methoxy-10-methyl-12-oxo-6,7,8,9-tetrahydro-5H-5,9-methanobenzo[9]annulen-7-yl)methyl pivalate (32). To a stirred solution of diol **31** (10 mg, 0.027 mmol, 1.00 equiv) in DCM (1 mL) was added $NaHCO_3$ (9 mg, 0.11 mmol, 4.00 equiv) and Dess-Martin periodinane (23 mg, 0.054 mmol, 2.00 equiv) at 0 °C. After 8 h stirring at room temperature, the residue was concentrated *in vacuo* and purified by preparative thin layer chromatography (petroleum ether/ ethyl acetate 2:1) to give colorless film **32** as sole product (7 mg, 0.019 mmol, 71%). *Rf* 0.45 (silica gel, 2:1 petroleum ether/ ethyl acetate, UV, pink, *p*-anisaldehyde); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (d, *J* = 8.3 Hz, 1H), 6.73 (dd, *J* = 8.3, 2.6 Hz, 1H), 6.68 (d, *J* = 2.5 Hz, 1H), 6.28 (s, 1H), 4.28 (dd, *J* = 11.2, 4.9 Hz, 1H), 4.19 – 4.09 (m, 1H), 4.06 (d, *J* = 8.8 Hz, 1H), 3.77 (s, 3H), 3.68 – 3.52 (m, 1H), 3.06 (s, 1H), 2.11 (s, 3H), 2.09 – 1.98 (m, 1H), 1.92 (td, *J* = 13.5, 10.1 Hz, 1H), 1.73 (tt, *J* = 8.4, 4.8 Hz, 1H), 1.18 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 208.7, 178.5, 158.8, 133.7, 132.4, 130.5, 128.1, 127.2, 118.0, 113.1, 74.2, 65.7, 65.5, 55.4, 55.3, 40.3, 38.9, 29.6, 27.2, 24.9; HRMS (ESI$^+$) *m/z* calcd for $C_{22}H_{28}O_5Na$ (M+Na)$^+$: 395.1834, found: 395.1839; IR (neat) *ν* 3454, 2924, 2854, 1709, 1604, 1462, 1271, 1157, 1033, 818 cm^{-1}.

Preparation of (3aR,10bS)-3a-hydroxy-8-methoxy-5-methyl-2-methylene-1,3a,4,10b-tetrahydrobenzo[e]azulen-3(2H)-one (33). To a solution of **31** (50 mg, 0.13 mmol, 1.00 equiv) in MeCN (10 mL) was sequentially added DMAP (16 mg, 0.13 mmol, 1.00 equiv), CuCl (2.6 mg, 27 μmol, 0.20 equiv), 2,2'-dipyridyl (4.2 mg, 27 μmol, 0.20 equiv) and AZADO (2.0 mg, 13 μmol, 0.10 equiv) at 25 °C. The solution was stirred at room temperature for 4 h under air. After the reaction color changed from brown to green, the reaction was concentrated *in vacuo* and purified by preparative thin layer chromatography (petroleum ether/ ethyl acetate 5:1) to give **33** (31 mg, 0.11 mmol, 85%) as yellow oil. *Rf* 0.70 (silica gel, 2:1 petroleum ether/ ethyl acetate, UV, yellow, *p*-anisaldehyde); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (d, *J* = 8.5 Hz, 1H), 6.80 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.74 (d, *J* = 2.6 Hz, 1H), 6.34 (s, 1H), 6.22 (s, 1H), 5.61 (s, 1H), 3.81 (s, 3H), 3.38 – 3.26 (m, 1H), 3.19 – 3.00 (m, 2H), 2.79 (d, *J* = 19.5 Hz, 1H), 2.48 (d, *J* = 19.5 Hz, 1H), 1.98 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 203.6, 158.7, 142.5, 136.7, 135.3, 128.7, 126.7, 125.9, 120.3, 117.1, 112.3, 75.6, 55.2, 46.1, 43.3, 31.2, 27.7; HRMS (ESI$^+$) *m/z* calcd for $C_{17}H_{19}O_3$ (M+H)$^+$: 271.1334, found: 271.1332; IR (neat) *ν* 3407, 2955, 2922, 2853, 1722, 1454, 1253, 1049, 897, 880, 772 cm^{-1}.

Preparation of (3aR,10bS)-3a-hydroxy-8-methoxy-2,5-dimethyl-4,10b-dihydrobenzo[e]azulen-3(3aH)-one (34). To a solution of **33** (20 mg, 0.074 mmol, 1.00 equiv) and Et_3N (31 μL, 0.22 mmol, 3.00 equiv) in DCM (3 mL) was slowly added TMSOTf (33 μL, 0.15 mmol, 2.00 equiv) at 0 °C. After 3 h stirring at room temperature, the residue was concentrated *in vacuo*. The resulting oil was dissolved in EtOH/H_2O (v:v, 10:1, 3 mL), followed by addition of $RhCl_3{\cdot}3H_2O$ (20 mg, 5.80 μmol, 0.10 equiv) under argon. The reaction mixture was warmed up to 100 °C (oil bath) for 2 h. The residue was concentrated *in vacuo* and purified by preparative thin layer chromatography (petroleum ether/ ethyl acetate 5:1) to give **34** as yellow foam (16 mg, 0.06 mmol, 82%). *Rf* 0.38 (silica gel, 2:1 petroleum ether/ ethyl acetate, UV, yellow, *p*-anisaldehyde); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (s, 1H), 7.07 (d, *J* = 9.1 Hz, 1H), 6.81 (dd, *J* = 4.4, 1.9 Hz, 2H), 6.41 (s, 1H), 4.01 (d, *J* = 2.0 Hz, 1H), 3.82 (s, 3H), 2.73 (d, *J* = 19.3 Hz, 1H), 2.48 (d, *J* = 19.4 Hz, 1H), 2.02 (s, 3H), 1.94 (dd, *J* = 2.6, 1.5 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 206.0, 158.7, 153.4, 140.5, 137.3, 136.7, 126.7, 126.0, 125.5, 116.6, 112.5, 73.8, 55.3, 51.5, 42.3, 27.9, 10.7; HRMS (ESI$^+$) *m/z* calcd for $C_{17}H_{19}O_3$ (M+H)$^+$: 271.1334, found: 271.1329; IR (neat) *ν* 3416, 2956, 2925, 2853, 1750, 1506, 1250, 1102, 841, 734 cm^{-1}.

Preparation of (4aR,6S,7S,7aS)-6-(4-methoxyphenyl)-2,2-dimethylhexahydrocyclopenta[d][1,3]dioxin-7-ol (SI-15). To a solution of the 4-Methoxyphenylmagnesium bromide **39** (200 mL, 1.0 M in THF, 200 mmol, 2.00 equiv) was added copper (I) iodide (1.9 g, 10.0 mmol, 0.10 equiv) at 0 °C, stirred for 30 min. To this reaction mixture was then added a solution of cyclopentene oxide **SI-13** (17.0 g, 100 mmol, 1.00 equiv) in THF (200 mL) dropwise over a period of 30 min at 0 °C. The reaction mixture was stirred to room temperature for 12 h, The reaction was cooled to 0 °C and quenched with sat. aq. ammonium chloride. Ethyl acetate (5 x 100 mL) was added, and the upper organic layer was separated. The organic layer was dried with anhydrous sodium sulfate, the crude residue was purified by flash chromatography (petroleum ether/ ethyl acetate 20:1→10:1→5:1) to give the secondary alcohol **SI-15** (21.4 g, 77 mmol, 77%) as yellow oil. *Rf* 0.20 (silica gel, 2:1 petroleum ether/ ethyl acetate, UV, dark blue, PMA); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 4.16 (dd, *J* = 5.8, 1.9 Hz, 1H), 4.04 (m, 2H), 3.79 (s, 3H), 3.67 (dd, *J* = 11.6, 4.8 Hz, 1H), 2.90 (dd, *J* = 16.7, 9.3 Hz, 1H), 2.25 (m, 1H), 2.14 – 1.98 (m, 3H), 1.45 (s, 3H), 1.41 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.3, 134.7, 128.5, 113.9, 98.5, 85.8, 78.3, 61.1, 55.3, 51.9, 36.9, 34.7, 28.2, 20.8; HRMS (ESI$^+$) *m/z* calcd for $C_{16}H_{22}O_4Na$ (M+Na)$^+$: 301.1416, found: 301.1401; IR (neat) *ν* 3392, 2989, 2926, 1512, 1246, 1033, 842, 828 cm^{-1}.

Preparation of 4-((4aR,6S,7S,7aS)-7-((tert-butyldimethylsilyl)oxy)-2,2-dimethylhexahydrocyclopenta[d][1,3]dioxin-6-yl)phenol (38). To a stirred solution of **SI-15** (27.8 g, 100 mmol, 1.00 equiv) and imidazole (20.4 g, 300 mmol, 3.00 equiv) in CH_2Cl_2 (300 mL) at 0 °C were added TBSCl (18.1 g, 120 mmol, 1.20 equiv) and the reaction mixture was stirred at room temperature for 12 h. The resulting mixture was then quenched with sat. aq. sodium bicarbonate. CH_2Cl_2 (3 x 100 mL) was added, the organic layer was dried with anhydrous sodium sulfate, and filtrated, concentrated to afford the crude residue, which was used in the next reaction without further purification. To a stirred solution of diphenylphosphine (52 mL, 300 mmol, 3.00 equiv) in THF (400 mL) at 0 °C was added *n*-butyllithium solution (120 mL, 2.5 M in hexane, 300 mmol, 3.00 equiv) by syringe over ca. 30 min under argon. The red

solution was allowed to warm to room temperature over about 30 min before above crude residue in THF (100 mL) was added. The mixture was stirred at 80 °C (oil bath) for 12 h. Then the resulting mixture was quenched with sat. aq. ammonium chloride at 0 °C. Ethyl acetate (500 mL) was added, and the upper organic layer was separated. The organic layer was dried with anhydrous sodium sulfate. The crude was purified by flash chromatography (petroleum ether/ ethyl acetate 30:1→20:1→10:1) to give phenol **38** as white solid (m.p. 95-97 °C) (35.9 g, 95 mmol, 95%, over 2 steps). *Rf* 0.17 (silica gel, 10:1 petroleum ether/ ethyl acetate, UV, dark blue, *p*-anisaldehyde); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (d, *J* = 8.5 Hz, 2H), 6.76 (d, *J* = 8.5 Hz, 2H), 5.33 (s, 1H), 4.11 – 4.01 (m, 2H), 3.89 (dd, *J* = 6.5, 1.7 Hz, 1H), 3.67 (dd, *J* = 11.7, 4.7 Hz, 1H), 2.87 (dt, *J* = 11.9, 7.0 Hz, 1H), 2.24 (td, *J* = 11.7, 5.9 Hz, 1H), 2.11 – 1.91 (m, 2H), 1.44 (s, 3H), 1.42 (s, 3H), 0.80 (s, 9H), -0.14 (s, 3H), -0.17 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 154.1, 135.3, 128.9, 115.1, 98.5, 87.0, 78.8, 61.3, 52.9, 37.2, 34.3, 28.1, 25.7, 20.6, 18.0, -4.9, -5.0; HRMS (ESI$^+$) *m/z* calcd for $C_{21}H_{34}O_4SiNa$ (M+Na)$^+$: 401.2124, found: 401.2114; IR (neat) *ν* 3253, 2954, 2927, 2859, 1515, 1369, 1252, 1144, 1103, 1027, 838, 774 cm^{-1}.

Preparation of 4-((4aR,6R,7S,7aS)-7-((tert-butyldimethylsilyl)oxy)-2,2-dimethylhexahydrocyclopenta[d][1,3]dioxin-6-yl)-4-hydroxycyclohexa-2,5-dien-1-one (37). Phenol **38** (1.00 g, 2.64 mmol, 1.00 equiv) was dissolved in chloroform/methnol (v/v, 1:1, 30 mL) and rose bengal (purity 90%, 149 mg, 0.13 mmol, 0.05 equiv) was added. The reaction was kept under oxygen atmosphere by bubbling with an oxygen balloon. The solution was irradiated using 400W sodium lamp at room temperature for 24 h. The reaction mixture was concentrated to dryness and purified directly by flash chromatography (petroleum ether/ ethyl acetate 10:1→5:1) to give the desired cyclohexadienone **37** as pale orange solid (m.p. 79-80 °C) (886 mg, 2.24 mmol, 85%). *Rf* 0.22 (silica gel, 5:1 petroleum ether/ ethyl acetate, UV, dark brown, *p*-anisaldehyde); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 – 6.88 (m, 2H), 6.19 – 6.13 (m, 2H), 4.09 (dd, *J* = 12.0, 3.4 Hz, 2H), 3.98 (d, *J* = 3.6 Hz, 1H), 3.77 (s, 1H), 3.65 (dd, *J* = 12.0, 2.1 Hz, 1H), 2.22 – 2.02 (m, 3H), 1.90 – 1.79 (m, 1H), 1.45 (s, 3H), 1.37 (s, 3H), 0.86 (s, 9H), 0.09 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 185.3, 152.0, 151.0, 128.2, 127.6, 98.4, 79.3, 77.5, 70.0, 60.3, 57.3, 35.8, 28.7, 26.6, 25.6, 19.4, 17.7, -4.5, -4.7; HRMS (ESI$^+$) *m/z* calcd for $C_{21}H_{34}O_5SiNa$ (M+Na)$^+$: 417.2073, found: 417.2056; IR (neat) *ν* 3369, 2926, 2855, 1664, 1379, 1096, 1072, 833, 773 cm^{-1}.

Preparation of (4R,5R)-4-((4aR,6R,7S,7aS)-7-((tert-butyldimethylsilyl)oxy)-2,2-dimethylhexahydrocyclopenta[d][1,3]dioxin-6-yl)-4-hydroxy-5-methylcyclohex-2-en-1-one (40) and (4S,5S)-4-((4aR,6R,7S,7aS)-7-((tert-butyldimethylsilyl)oxy)-2,2-dimethylhexahydrocyclopenta[d][1,3]dioxin-6-yl)-4-hydroxy-5-methylcyclohex-2-en-1-one (SI-16). To a stirred solution of **37** (1.00 g, 2.53 mmol, 1.00 equiv) in THF (25 mL) was added lithium hexamethyl disilazide (2.53 mL, 1.0 M in THF, 2.53 mmol, 1.00 equiv) dropwise at -60 °C under argon. After being stirred for 10 min, the reaction mixture was added DMPU (1.53 mL, 12.65 mmol, 5.00 equiv), followed by methylmagnesium chloride (2.53 mL, 6.40 mmol, 3.0 M in THF, 3.00 equiv). The mixture was stirred at -78 °C for 1 h and warmed to -30 °C for 6h. Then the resulting mixture was quenched with sat. aq. ammonium chloride, extracted by ethyl acetate (3 x 20 mL), and the upper organic layer was separated. The organic layer was dried with anhydrous sodium sulfate. The crude product was purified by flash chromatography (petroleum ether/ ethyl acetate 20:1→10:1) to give **40** as white solid (m.p. 123-125 °C) (394 mg, 0.96 mmol, 38%), and the more polar diastereomer **SI-16** as yellow solid (m.p. 89-91 °C) (380 mg, 0.94 mmol, 37%, 75% combined two diastereomers, d.r.~1:1). **40**: *Rf* 0.68 (silica gel, 5:1 petroleum ether/ ethyl acetate, UV, dark blue, *p*-anisaldehyde); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (d, *J* = 10.2 Hz, 1H), 5.95 (d, *J* = 10.2 Hz, 1H), 4.17 – 4.06 (m, 2H), 3.99 (s, 1H), 3.66 (d, *J* = 11.9 Hz, 1H), 3.24 (s, 1H), 2.53 (m, 2H), 2.46 – 2.29 (m, 2H), 2.12 (m, 1H), 1.99 (dd, *J* = 22.3, 11.7 Hz, 1H), 1.79 (m, 1H), 1.45 (s, 3H), 1.38 (s, 3H), 1.10 (d, *J* = 6.6 Hz, 3H), 0.87 (s, 9H), 0.10 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 198.8, 153.1, 128.8, 98.3, 79.4, 77.6, 72.9, 60.3, 54.8, 42.4, 37.7, 36.2, 28.9, 26.8, 25.6, 19.3, 17.7, 14.8, -4.4, -4.9; HRMS (ESI$^+$) *m/z* calcd for $C_{22}H_{38}O_5SiNa$ (M+Na)$^+$: 433.2386, found: 433.2400; IR (neat) *ν* 3430, 2954, 2926, 1664, 1381, 1250, 1195, 1065, 834, 777 cm^{-1}. **SI-16**: *Rf* 0.43 (silica gel, 5:1 petroleum ether/ ethyl acetate, UV, dark blue, *p*-anisaldehyde); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (d, *J* = 10.3 Hz, 1H), 5.93 (d, *J* = 10.3 Hz, 1H), 4.18 (dd, *J* = 12.1, 2.8 Hz, 1H), 3.98 (dd, *J* = 15.8, 12.8 Hz, 3H), 3.74 (d, *J* = 12.1 Hz, 1H), 2.66 – 2.45 (m, 2H), 2.38 – 2.22 (m, 3H), 2.18 – 2.08 (m, 1H), 1.95 (dt, *J* = 12.6, 8.8 Hz, 1H), 1.48 (s, 3H), 1.40 (s, 3H), 1.08 (d, *J* = 6.7 Hz, 3H), 0.83 (s, 9H), 0.05 (s, 3H), 0.01 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 198.4, 155.5, 127.9, 98.4, 79.1, 77.8, 72.9, 60.3, 56.5, 42.7, 37.6, 35.4, 29.0, 26.3, 25.6, 18.8, 17.7, 14.7, -4.5; HRMS (ESI$^+$) *m/z* calcd for $C_{22}H_{38}O_5SiNa$ (M+Na)$^+$: 433.2386, found: 433.2369; IR (neat) *ν* 3391, 2927, 2894, 1664, 1373, 1195, 1070, 832, 778 cm^{-1}.

Preparation of (3R,4R,5R)-4-((4aR,6R,7S,7aS)-7-((tert-butyldimethylsilyl)oxy)-2,2-dimethylhexahydrocyclopenta[d][1,3]dioxin-6-yl)-4-hydroxy-3-methyl-5-vinylcyclohexan-1-one (41) and (1R,2R,4S,6R)-1-((4aR,6R,7S,7aS)-7-((tert-butyldimethylsilyl)oxy)-2,2-dimethylhexahydrocyclopenta[d][1,3]dioxin-6-yl)-2-methyl-4-(prop-1-en-2-yl)-6-vinylcyclohexane-1,4-diol (SI-17). Me_3Al (2.0 M in toluene, 0.85 mL, 1.7 mmol, 2.00 equiv) was added in a portion to a solution of 2,6-diphenyl phenol (1.27 g, 5.1 mmol, 6.00 equiv) in toluene (25 mL) at 25°C. The resultant ATPH yellow-orange solution was stirred at 25 °C for 30 min. Under Argon, to a solution of **40** (349 mg, 0.85 mmol, 1.00 equiv.) in toluene (10 mL) was added ATPH solution prepared above at -78 °C dropwise over 30 min under argon. The resultant dark yellow solution was added vinylmagnesium chloride solution (4.3 mL, 4.25 mmol, 1.0 M in THF, 5.00 equiv) at -78 °C over 30 min, the bright yellow mixture was warmed to room temperature over 12h. When TLC detected starting material consumption, the solution was quenched with sat. aq. ammonium chloride at 0 °C, filtered. Ethyl acetate (3 x 20 mL) was added, and the upper organic layer was separated. The organic layer was dried with anhydrous sodium sulfate, the crude was purified by flash chromatography (petroleum ether/ ethyl acetate 7:1) to give 1,4-adduct **41** as yellow solid (m.p. 96-98 °C) (245 mg, 0.56 mmol, 66%), 1,2-adduct **SI-17** as yellow solid (m.p. 93-95 °C) (88 mg, 0.19 mmol, 22%). **41**: *Rf* 0.26 (silica gel, 5:1 petroleum ether/ ethyl acetate, blue, *p*-anisaldehyde); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.08 (ddd, *J* = 17.2, 10.3, 9.0 Hz, 1H), 5.18 – 4.99 (m, 2H), 4.64 (dd, *J* = 9.3, 3.2 Hz, 1H), 3.90 (dd, *J* = 7.2, 3.2 Hz, 1H), 3.84 (dd, *J* = 11.4, 5.7 Hz, 1H), 3.62 (s, 1H), 3.46 (dd, *J* = 11.4, 7.2 Hz, 1H), 2.87 – 2.72 (m, 1H), 2.69 – 2.50 (m, 2H), 2.30 (ddd, *J* = 12.9, 9.2, 6.7 Hz, 1H), 2.21 – 2.00 (m, 3H), 1.99 – 1.84 (m, 1H), 1.61 – 1.44 (m, 2H), 1.35 (s, 3H), 1.30 (s, 3H), 0.98 (d, *J* = 6.6 Hz, 3H), 0.92 (s, 9H), 0.17 (s, 3H), 0.12 (s, 3H); ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 210.9, 138.8, 115.5, 98.5, 80.9, 77.2, 73.4, 61.5, 49.6, 49.3, 45.1, 44.7, 40.2, 35.5, 27.5, 25.8, 25.7, 22.1, 17.7, 15.8, -3.9, -5.4; HRMS (ESI$^+$) *m/z* calcd for $C_{24}H_{42}O_5SiNa$ (M+Na)$^+$: 461.2699, found: 461.2682; IR (neat) *ν* 3457, 2952, 2929, 1716, 1381, 1370, 1250, 1196, 1101, 834, 778 cm^{-1}. **SI-17**: *Rf* 0.22 (silica gel, 5:1 petroleum ether/ ethyl acetate, blue, *p*-anisaldehyde); ^{1}H NMR

(400 MHz, $CDCl_3$) δ 5.98 (d, *J* = 10.2 Hz, 1H), 5.87 (dd, *J* = 17.4, 10.5 Hz, 1H), 5.68 (d, *J* = 10.2 Hz, 1H), 5.24 – 5.03 (m, 2H), 4.19 (d, *J* = 5.0 Hz, 1H), 4.00 (dd, *J* = 11.8, 4.4 Hz, 1H), 3.95 (d, *J* = 5.0 Hz, 1H), 3.56 (dd, *J* = 11.8, 3.7 Hz, 1H), 2.35 – 2.20 (m, 2H), 2.08 (dd, *J* = 10.4, 5.9 Hz, 1H), 1.83 (d, *J* = 9.6 Hz, 1H), 1.68 – 1.44 (m, 4H), 1.40 (s, 3H), 1.34 (s, 3H), 0.96 (d, *J* = 6.6 Hz, 3H), 0.88 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 141.9, 134.7, 131.6, 114.1, 98.0, 80.0, 78.1, 72.6, 72.3, 60.8, 52.9, 40.9, 36.1, 33.3, 28.5, 28.2, 25.8, 20.1, 17.8, 14.5, -4.4, -4.9; HRMS (ESI^+) *m/z* calcd for $C_{24}H_{42}O_5SiNa$ $(M+Na)^+$: 461.2699, found: 461.2719; IR (neat) *ν* 3454, 2928, 2856, 1380, 1081, 995, 833, 776 cm^{-1}.

Preparation of tert-butyl(((1R,3R,4R,5R)-4-((4aR,6R,7S,7aS)-7-((tert-butyldimethylsilyl)oxy)-2,2-dimethylhexahydrocyclopenta[d][1,3]dioxin-6-yl)-3-methyl-5-vinyl-7-oxabicyclo[2.2.1]heptan-1-yl)oxy)dimethylsilane (42). To a solution of ketone **41** (14 mg, 0.032 mmol, 1.00 equiv.) in DCM (0.5 mL) was added Et_3N (0.023 mL, 0.16 mmol, 5.00 equiv.) at 0 °C, after stirring for 15 min, TBSOTf (0.022 mL, 0.096 mmol, 3.00 equiv.) was added to the reaction mixture at 0 °C, then warmed up to room temperature and stirred overnight. Then the resulting mixture was quenched with sat. $NaHCO_3$, extracted by DCM. The crude product was purified by flash chromatography (petroleum ether/ ethyl acetate 50:1 with 1% Et_3N) to give product **42** (10 mg, 0.018 mmol, 57%) as colorless oil. *Rf* 0.39 (silica gel, 30:1 petroleum ether/ ethyl acetate, blue, PMA); ^1H NMR (400 MHz, $CDCl_3$) δ 6.14 – 6.05 (m, 1H), 4.97 – 4.91 (m, 2H), 4.29 (d, *J* = 6.9 Hz, 1H), 4.06 (dd, *J* = 11.9, 4.5 Hz, 1H), 3.98 (d, *J* = 4.9 Hz, 1H), 3.62 (dd, *J* = 11.9, 2.5 Hz, 1H), 2.59 – 2.49 (m, 1H), 2.48 – 2.37 (m, 1H), 2.17 – 1.84 (m, 5H), 1.62 – 1.59 (m, 1H), 1.54 – 1.50 (m, 1H), 1.38 (s, 3H), 1.31 (s, 3H), 1.20 – 1.11 (m, 1H), 1.03 (d, *J* = 6.8 Hz, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.14 (s, 6H), 0.11 (s, 3H), 0.09 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 140.8, 113.5, 106.7, 97.7, 83.9, 80.3, 80.2, 60.9, 51.2, 48.8, 46.1, 43.5, 42.3, 35.7, 29.3, 28.6, 26.0, 25.7, 19.9, 19.5, 18.0, 17.9, -3.0, -4.6, -4.8.

Preparation of (1R,2R,4S,6R)-1-((4aR,6R,7S,7aS)-7-((tert-butyldimethylsilyl)oxy)-2,2-dimethylhexahydrocyclopenta[d][1,3]dioxin-6-yl)-2-methyl-6-vinylcyclohexane-1,4-diol (SI-18). To a solution of the ketone **41** (2.00 g, 4.57 mmol, 1.00 equiv) in MeOH/DCM (v:v, 1:1, 40 mL), $CeCl_3{\cdot}7H_2O$ (1.7 g, 4.57 mmol, 1.00 equiv) and $NaBH_4$ (347 mg, 9.14 mmol, 2.00 equiv) were sequentially added at -78 °C. The reaction mixture was stirred for 2 h and quenched by H_2O, extracted by ethyl acetate (3 x 50 mL), the upper organic layer was separated and the organic layer was dried with anhydrous sodium sulfate. The crude product was purified by flash chromatography (petroleum ether/ ethyl acetate 5:1) to give the alcohol **SI-18** as white foam (1.97 g, 4.48 mmol, 98%). *Rf* 0.42 (silica gel, 2:1 petroleum ether/ ethyl acetate, dark brown, *p*-anisaldehyde); ^1H NMR (400 MHz, $CDCl_3$) δ 6.10 (dt, *J* = 17.5, 9.8 Hz, 1H), 5.12 – 4.94 (m, 2H), 4.61 (dd, *J* = 9.7, 3.3 Hz, 1H), 3.84 (ddd, *J* = 17.1, 9.3, 4.5 Hz, 2H), 3.61 (ddd, *J* = 15.3, 10.7, 4.5 Hz, 1H), 3.45 (dd, *J* = 11.3, 7.4 Hz, 1H), 2.28 – 2.17 (m, 2H), 2.11 (qd, *J* = 14.5, 7.3 Hz, 1H), 1.74 (dd, *J* = 23.8, 12.1 Hz, 1H), 1.68 – 1.40 (m, 8H), 1.34 (s, 3H), 1.30 (s, 3H), 0.94 (d, *J* = 6.0 Hz, 3H), 0.91 (s, 9H), 0.16 (s, 3H), 0.10 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 140.5, 114.7, 98.4, 81.0, 77.5, 73.3, 69.5, 61.7, 49.6, 47.4, 39.5, 39.4, 37.8, 35.4, 27.5, 26.3, 25.8, 22.2, 17.7, 15.6, -4.0, -5.4; HRMS (ESI^+) *m/z* calcd for $C_{24}H_{45}O_5Si$ $(M+H)^+$: 441.3036, found:441.3030; IR (neat) *ν* 3573, 3491, 2948, 2857, 1059, 835, 778 cm^{-1}.

Preparation of (1R,2R,4S,6R)-4-(benzyloxy)-1-((4aR,6R,7S,7aS)-7-((tert-butyldimethylsilyl)oxy)-2,2-dimethylhexahydrocyclopenta[d][1,3]dioxin-6-yl)-2-methyl-6-vinylcyclohexan-1-ol (43). To a stirred solution of alcohol **SI-18** (3.08 g, 7 mmol, 1.00 equiv) in THF (100 mL) was added slowly NaH (2.8 g, 60%, 70 mmol, 10.00 equiv) at room temperature. After stirring 30 min, tetrabutylammonium iodide (2.58 g, 7 mmol, 1.00 equiv) and benzyl bromide (6 mL, 35 mmol, 5.00 equiv) were sequentially added to the above solution at 0 °C. The reaction mixture was stirred overnight at room temperature and quenched by sat. aq. ammonium chloride, extracted by ethyl acetate (3 x 100 mL). Organic layer was dried with anhydrous sodium sulfate. The crude product was purified by flash chromatography (petroleum ether/ ethyl acetate 100:0→10:1) to give **43** as white solid (3 g, 5.67 mmol, 81%). *Rf* 0.32 (silica gel, 9:1 petroleum ether/ ethyl acetate, blue, PMA); ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.20 (m, 5H) , 6.13 (dt, *J* = 17.5, 9.8 Hz, 1H), 5.12 – 4.96 (m, 2H), 4.65 – 4.49 (m, 3H), 3.85 (ddd, *J* = 17.1, 9.3, 4.5 Hz, 2H), 3.46 (dd, *J* = 11.3, 7.1 Hz, 1H), 3.42 – 3.34 (m, 1H), 3.08 (s, 1H), 2.32 – 2.01 (m, 3H), 1.82 (d, *J* = 11.7 Hz, 1H), 1.76 – 1.58 (m, 3H), 1.48 (dd, *J* = 14.6, 7.4 Hz, 2H), 1.34 (s, 3H), 1.30 (s, 3H), 0.95 (d, *J* = 6.5 Hz, 3H), 0.91 (s, 9H), 0.15 (s, 3H), 0.11 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 140.8, 139.3, 128.3, 127.4, 127.2, 114.6, 98.4, 81.0, 77.7, 75.9, 73.5, 69.4, 61.7, 49.9, 47.3, 37.8, 36.2, 35.8, 35.4, 27.5, 26.4, 25.8, 22.1, 17.7, 15.7, -4.0, -5.4; HRMS (ESI^+) *m/z* calcd for $C_{31}H_{51}O_5Si$ $(M+H)^+$: 531.3506, found: 531.3505; IR (neat) *ν* 3475, 2933, 2859, 1250, 1101, 1068, 833, 778 cm^{-1}.

Preparation of (4aR,6S,7aS)-6-((1R,2R,4S,6R)-4-(benzyloxy)-1-hydroxy-2-methyl-6-vinylcyclohexyl)-2,2-dimethyltetrahydrocyclopenta[d][1,3]dioxin-7(4H)-one (44) and (1S,3R,4a'R,5R,7R,7a'S)-5-(benzyloxy)-2',2',3-trimethyl-7-vinyldihydro-4'H-spiro[cycloheptane-1,6'-cyclopenta[d][1,3]dioxine]-2,7'(5'H)-dione (45). To a stirred solution of **43** (1.27 g, 2.40 mmol, 1.00 equiv) in THF (50 mL) was added TBAF (3.6 mL, 1 M in THF, 3.60 mmol, 1.50 equiv) at room temperature. After stirring overnight, TLC detected starting material consumption. The solution was quenched with sat. aq. ammonium chloride at 0 °C, extracted by ethyl acetate (3 x 50 mL). The crude product was purified by flash chromatography (petroleum ether/ ethyl acetate 2:1→1:1) to afford colorless oil (1 g). To the solution of above secondary alcohol (1 g, 2.40 mmol, 1.00 equiv) in DCM (40 mL) was sequentially added *tert*-butanol (0.88 mL, 9.60 mmol, 4.00 equiv), $NaHCO_3$ (1.6 g, 19.20 mmol, 8.00 equiv), Dess-Martin periodinane (4.1 g, 9.60 mmol, 4.00 equiv), then stirred overnight at room temperature. The reaction mixture was concentrated to dryness and purified directly by flash chromatography (petroleum ether/ ethyl acetate 5:1) to give **44** as white foam (580 mg, 1.39 mmol, 58%) and **45** as white solid (m.p. 107-109 °C) (364 mg, 0.82 mmol, 34%). **44**: *Rf* 0.51 (silica gel, 2:1 petroleum ether/ ethyl acetate, pink, *p*-anisaldehyde); ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.22 (m, 5H), 5.83 (ddd, *J* = 17.2, 10.2, 8.7 Hz, 1H), 5.13 – 4.95 (m, 2H), 4.64 – 4.48 (m, 2H), 4.22 (dd, *J* = 12.3, 3.9 Hz, 1H), 4.06 (d, *J* = 5.4 Hz, 1H), 3.70 (dd, *J* = 12.2, 1.2 Hz, 1H), 3.49 – 3.33 (m, 1H), 2.63 (dd, *J* = 13.3, 7.3 Hz, 1H), 2.43 – 2.25 (m, 2H), 1.94 – 1.72 (m, 4H), 1.66 (dd, *J* = 23.4, 12.2 Hz, 1H), 1.55 – 1.49 (m, 1H), 1.46 (s, 3H), 1.37 (s, 3H), 0.99 (d, *J* = 6.5 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 139.1, 137.8, 128.3, 127.5, 127.3, 117.1, 98.4, 75.8, 75.8, 71.6, 69.6, 59.9, 54.4, 47.2, 37.6, 35.5, 33.6, 32.6, 28.5, 25.9, 19.0, 16.0; HRMS (ESI^+) *m/z* calcd for $C_{25}H_{35}O_5$ $(M+H)^+$: 415.2485, found: 415.2475; IR (neat) *ν* 2936, 2858, 1752, 1686, 1375, 1087, 970, 936, 714 cm^{-1}. **45**: *Rf* 0.29 (silica gel, 2:1 petroleum ether/ ethyl acetate, pink, *p*-anisaldehyde); ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.26 (m, 5H), 5.66 (dt, *J* = 16.8, 9.7 Hz, 1H), 5.15 – 5.00 (m, 2H), 4.58 (d, *J* = 11.9 Hz, 1H), 4.49 (d, *J* = 11.9 Hz, 1H), 4.17 (dd, *J* = 12.3, 3.9 Hz, 1H), 4.07 (d, *J* = 4.7 Hz, 1H), 3.65 – 3.57 (m, 1H), 3.57 – 3.44 (m, 1H), 2.91 (dd, *J* = 10.8, 6.4 Hz, 1H), 2.63 (t, *J* = 12.8 Hz, 1H), 2.43 (t, *J* = 9.7 Hz, 1H), 2.39 – 2.23 (m, 1H), 2.07 (dd, *J* = 14.4, 3.2 Hz, 2H), 2.02 – 1.92 (m, 1H), 1.78 (dd, *J* = 13.0, 6.4 Hz, 1H), 1.48 (d, *J* = 3.7 Hz, 1H), 1.43

(s, 3H), 1.33 (s, 3H), 1.10 (d, *J* = 6.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 215.3, 211.5, 138.5, 138.2, 128.4, 127.5, 127.5, 116.8, 98.1, 78.7, 72.2, 70.2, 68.6, 59.4, 44.0, 41.6, 38.3, 37.0, 32.7, 30.6, 28.6, 19.1, 17.6; HRMS (ESI$^+$) *m/z* calcd for $C_{25}H_{33}O_5$ $(M+H)^+$: 413.2328, found: 413.2339; IR (neat) *ν* 3374, 2986, 2935, 1634, 1370, 1223, 1101, 1038, 967, 895, 729, 696 cm^{-1}.

Preparation of (1R,3S,4aR,7aR,7bS,11aR,12aS,12bR)-3-(benzyloxy)-1,6,9,9-tetramethyl-1,2,3,4,4a,7,11,11a,12,12a-decahydro-12bH-benzo[4,5]azuleno[1,2-d][1,3]dioxine-7a,12b(7bH)-diol (46). To a solution of **44** (8 mg, 0.019 mmol, 1.00 equiv) in THF (2 mL) was added freshly prepared 2-methylallyllanthanum chloride (58 µL, 0.5 M in THF, 0.029 mmol, 1.50 equiv) at -78 °C, stirred 1 h at the same temperature, then warmed to 0 °C, quenched with sat. aq. ammonium chloride. The reaction mixture was concentrated to dryness and purified directly by flash chromatography (petroleum ether/ ethyl acetate 10:1) to give yellow oil (9 mg) which was used to next step. Under argon, the solution of above secondary alcohol (9 mg, 0.019 mmol, 1.00 equiv) in toluene (2 mL) was added Grubbs 2nd generation catalyst (8 mg, 9.5 µmol, 0.50 equiv). The solution was warmed up to 110 °C (oil bath) for 12 h. The reaction mixture was concentrated to dryness and purified directly by flash chromatography (petroleum ether/ ethyl acetate 5:1) to give **46** as dark brown oil (3.9 mg, 8.8 µmol, 46%, 2 steps). *Rf* 0.35 (silica gel, 5:1 petroleum ether/ ethyl acetate, pink, *p*-anisaldehyde); ^1H NMR (400 MHz, $CDCl_3$); δ 7.46 – 7.20 (m, 5H), 5.03 (s, 1H), 4.56 (s, 2H), 3.82 – 3.66 (m, 2H), 3.56 – 3.44 (m, 1H), 3.37 (tt, *J* = 11.0, 3.9 Hz, 1H), 3.12 (s, 1H), 3.05 (d, *J* = 13.0 Hz, 1H), 2.48 (d, *J* = 17.6 Hz, 1H), 2.33 – 2.09 (m, 3H), 2.07 – 1.95 (m, 1H), 1.86 (dd, *J* = 13.5, 5.1 Hz, 1H), 1.83 – 1.68 (m, 5H), 1.63 (dd, *J* = 11.9, 4.6 Hz, 1H), 1.54 – 1.43 (m, 1H), 1.40 (s, 3H), 1.36 (s, 3H), 1.33 – 1.29 (m, 1H), 1.03 (d, *J* = 6.4 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 139.1, 134.9, 128.3, 127.9, 127.5, 127.4, 99.3, 78.3, 75.8, 75.5, 74.9, 69.6, 62.6, 56.4, 43.9, 40.6, 37.2, 36.9, 36.7, 35.5, 29.4, 27.2, 26.5, 24.6, 17.3; HRMS (ESI$^+$) *m/z* calcd for $C_{27}H_{38}O_5Na$ $(M+Na)^+$: 465.2617, found: 465.2616; IR (neat) *ν* 3539, 2956, 2919, 2849, 1455, 1377, 1261, 1095, 807, 697 cm^{-1}.

Preparation of (4S,5R)-4-((4aR,6R,7S,7aS)-7-((tert-butyldimethylsilyl)oxy)-2,2-dimethylhexahydrocyclopenta[d][1,3]dioxin-6-yl)-4-hydroxy-2-iodo-5-methylcyclohex-2-en-1-one (SI-20). To a stirred solution of hydroxyl ketone **40** (2.00 g, 4.87 mmol, 1.00 equiv) and pyridine (3.92 mL, 48.7 mmol, 10.00 equiv) in CH_2Cl_2 (50 mL) at room temperature was added I_2 (6.18 g, 24.3 mmol, 5.00 equiv). The dark solution was stirred at 50 °C (oil bath) for 18 h. The resulting mixture was quenched with sat. aq. $Na_2S_2O_3/CH_2Cl_2$ (v/v, 1:2, 200 mL). The organic layer was dried with anhydrous sodium sulfate. The crude product was purified by flash chromatography (petroleum ether/ ethyl acetate 10:1) to give iodide **SI-20** as yellow solid (m.p. 155-159 °C) (2.22 g, 4.14 mmol, 85%). *Rf* 0.60 (silica gel, 5:1 petroleum ether/ ethyl acetate, UV, purple, *p*-anisaldehyde); ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (s, 1H), 4.12 (dd, *J* = 12.2, 3.2 Hz, 2H), 3.99 (d, *J* = 3.6 Hz, 1H), 3.67 (dd, *J* = 12.2, 1.7 Hz, 1H), 3.19 (s, 1H), 2.67 (qd, *J* = 17.0, 5.8 Hz, 2H), 2.49 (td, *J* = 9.7, 2.7 Hz, 1H), 2.40 – 2.32 (m, 1H), 2.17 – 2.06 (m, 1H), 2.03 – 1.90 (m, 1H), 1.86 – 1.78 (m, 1H), 1.46 (s, 3H), 1.43 (s, 3H), 1.09 (d, *J* = 6.9 Hz, 3H), 0.87 (s, 9H), 0.10 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 191.6, 161.6, 104.6, 98.4, 79.4, 77.6, 76.1, 60.2, 54.7, 40.7, 37.9, 36.2, 29.2, 27.1, 25.6, 19.2, 17.7, 14.6, -4.4, -4.9; HRMS (ESI$^+$) *m/z* calcd for $C_{22}H_{37}IO_5SiNa$ $(M+Na)^+$: 559.1353, found: 559.1349; IR (neat) *ν* 3469, 2954, 2927, 2855, 1677, 1093, 1072, 968, 833, 775 cm^{-1}.

Preparation of (4R,5R)-4-((4aR,6R,7S,7aS)-7-((tert-butyldimethylsilyl)oxy)-2,2-dimethylhexahydrocyclopenta[d][1,3]dioxin-6-yl)-4-hydroxy-5-methyl-2-(prop-1-en-2-yl)cyclohex-2-en-1-one (47). To a stirred solution of **SI-20** (260 mg, 0.48 mmol, 1.00 equiv) in THF (8 mL) was added $Pd(PPh_3)_2Cl_2$ (17 mg, 0.024 mmol, 0.05 equiv), $AsPPh_3$ (15 mg, 0.048 mmol, 0.10 equiv), Ag_2O (111 mg, 0.768 mmol, 1.6 equiv) at room temperature under argon. After 30 min, the dark mixture was added 2-isopropenyl boronic acid pinacol ester (0.18 mL, 0.96 mmol, 2.00 equiv) and H_2O (1 mL). The resultant solution was stirred at 80 °C (oil bath) for 12 h. The mixture was concentrated to dryness and the residue was purified by flash chromatography (petroleum ether/ ethyl acetate 10:1) to give **47** as yellow solid (m.p. 126-128 °C) (203 mg, 0.45 mmol, 93%). *Rf* 0.51 (silica gel, 5:1 petroleum ether/ ethyl acetate, UV, dark brown, *p*-anisaldehyde); ^1H NMR (400 MHz, $CDCl_3$) δ 6.67 (d, *J* = 0.8 Hz, 1H), 5.16 (d, *J* = 1.0 Hz, 1H), 5.06 (s, 1H), 4.20 – 4.08 (m, 2H), 4.00 (d, *J* = 3.2 Hz, 1H), 3.68 (d, *J* = 11.9 Hz, 1H), 3.30 (s, 1H), 2.64 – 2.40 (m, 3H), 2.34 (dd, *J* = 12.3, 6.6 Hz, 1H), 2.16 – 1.97 (m, 2H), 1.91 (s, 3H), 1.84 – 1.76 (m, 1H), 1.46 (s, 3H), 1.39 (s, 3H), 1.11 (d, *J* = 6.6 Hz, 3H), 0.87 (s, 9H), 0.10 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 197.5, 148.1, 140.7, 140.6, 116.5, 98.3, 79.3, 77.6, 73.2, 60.3, 55.0, 43.4, 37.7, 36.2, 28.9, 26.9, 25.6, 22.4, 19.2, 17.7, 14.8, -4.4, -4.9; HRMS (ESI$^+$) *m/z* calcd for $C_{25}H_{43}O_5$ Si $(M+H)^+$: 451.2880, found: 451.2862; IR (neat) *ν* 3495, 2955, 2930, 2910, 1665, 1197, 1107, 1081, 836, 777 cm^{-1}.

Preparation of (3S,4R,5R)-4-((4aR,6R,7S,7aS)-7-((tert-butyldimethylsilyl)oxy)-2,2-dimethylhexahydrocyclopenta[d][1,3]dioxin-6-yl)-4-hydroxy-5-methyl-2-(propan-2-ylidene)-3-vinylcyclohexan-1-one (36) and (2R,3S,4R,5R)-4-((4aR,6R,7S,7aS)-7-((tert-butyldimethylsilyl)oxy)-2,2-dimethylhexahydrocyclopenta[d][1,3]dioxin-6-yl)-4-hydroxy-5-methyl-2-(prop-1-en-2-yl)-3-vinylcyclohexan-1-one (SI-21). Me_3Al (2.0 M in toluene, 0.44 mL, 0.88 mmol, 2.00 equiv) was added in a portion to a solution of 2,6-diphenyl phenol (655 mg, 2.64 mmol, 6.00 equiv) in toluene (10 mL) at 25 °C. The resultant ATPH yellow-orange solution was stirred at 25 °C for 30 min. To a stirred solution of **47** (200 mg, 0.44 mmol, 1.00 equiv) in toluene (5 mL) was added ATPH solution prepared above at -78 °C dropwise over 30 min under argon. The resultant dark yellow solution was added vinylmagnesium chloride solution (2.2 mL, 2.2 mmol, 1.0 M in THF, 5.00 equiv) at -78 °C for 1 h, the bright yellow mixture was warmed to room temperature over 12h. The resulting mixture was then quenched with sat. aq. ammonium chloride, filtered. Ethyl acetate (3 x 20 mL) was added, and the upper organic layer was separated. The organic layer was dried with anhydrous sodium sulfate, the crude was purified by flash chromatography (petroleum ether/ ethyl acetate 20:1→10:1) to give enone **36** (171 mg, 0.36 mmol, 81%) as white solid (m.p. 100-103 °C), **SI-21** as yellow solid (m.p. 114-115 °C) (8.4 mg, 0.018 mmol, 4%). **36**: *Rf* 0.47 (silica gel, 10:1 petroleum ether/ ethyl acetate, UV, purple, *p*-anisaldehyde); ^1H NMR (400 MHz, $CDCl_3$) δ 6.28 (ddd, *J* = 17.5, 10.4, 4.9 Hz, 1H), 5.03 (dt, *J* = 10.4, 1.9 Hz, 1H), 4.89 (dt, *J* = 17.5, 1.9 Hz, 1H), 4.14 (dd, *J* = 12.0, 3.0 Hz, 1H), 4.09 (d, *J* = 2.6 Hz, 1H), 3.96 (d, *J* = 3.2 Hz, 1H), 3.69 (d, *J* = 12.0 Hz, 1H), 3.59 – 3.50 (m, 1H), 2.99 (s, 1H), 2.42 (qd, *J* = 15.8, 7.0 Hz, 2H), 2.35 – 2.28 (m, 1H), 2.21 (dd, *J* = 14.2, 7.2 Hz, 1H), 2.16 – 2.10 (m, 1H), 2.09 (s, 3H), 2.07 – 2.00 (m, 1H), 1.78 (s, 3H), 1.72 – 1.61 (m, 2H), 1.45 (s, 3H), 1.40 (s, 3H), 1.09 (d, *J* = 7.1 Hz, 3H), 0.85 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 203.5, 145.7, 137.4, 131.7, 114.6, 98.2, 79.4, 77.7, 74.6, 60.4, 57.1, 50.5, 46.3, 37.7, 35.8, 29.2, 26.7, 25.7, 23.1, 22.0, 19.0, 17.7, 17.1, -4.3, -4.9; HRMS (ESI$^+$) *m/z* calcd for $C_{27}H_{47}O_5$ Si $(M+H)^+$: 479.3193, found: 479.3189; IR (neat) *ν* 3491, 2950, 2926, 2855, 1682, 1382, 1253, 1069, 830, 773 cm^{-1}. **SI-21**: *Rf*

0.12 (silica gel, 10:1 petroleum ether/ ethyl acetate, UV, purple, *p*-anisaldehyde); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85 (dt, *J* = 17.5, 10.1 Hz, 1H), 5.10 (dd, *J* = 17.5, 8.6 Hz, 2H), 4.91 (s, 1H), 4.81 (dd, *J* = 9.6, 2.9 Hz, 1H), 4.68 (s, 1H), 3.87 (ddd, *J* = 17.2, 9.3, 4.4 Hz, 1H), 3.67 (s, 1H), 3.47 (dd, *J* = 11.4, 7.0 Hz, 1H), 3.41 (d, *J* = 11.9 Hz, 1H), 2.68 (t, *J* = 13.7 Hz, 1H), 2.64 – 2.54 (m, 1H), 2.31 (ddd, *J* = 12.7, 9.6, 7.2 Hz, 1H), 2.19 – 2.08 (m, 1H), 1.94 (ddd, *J* = 13.2, 6.6, 4.3 Hz, 1H), 1.63 (s, 3H), 1.61 – 1.51 (m, 1H), 1.34 (s, 3H), 1.29 (s, 3H), 0.98 (d, *J* = 6.5 Hz, 3H), 0.92 (s, 9H), 0.17 (s, 3H), 0.12 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 209.5, 141.2, 137.0, 117.0, 116.0, 98.4, 80.7, 77.4, 73.8, 61.4, 58.7, 52.3, 49.7, 45.3, 40.1, 35.4, 27.4, 26.0, 25.8, 21.9, 19.4, 17.7, 16.0, -4.0, -5.4; HRMS (ESI$^+$) *m/z* calcd for $C_{27}H_{46}O_5SiNa$ (M+Na)$^+$: 501.3012, found: 501.3015; IR (neat) *ν* 3514, 2928, 2855, 1713, 1369, 1250, 1059, 835, 779 cm^{-1}.

Preparation of (3aS,4S,5R,6R,7aR)-5-hydroxy-5-((4aR,6R,7S,7aS)-7-hydroxy-2,2-dimethylhexahydrocyclopenta[d][1,3]dioxin-6-yl)-3,3,6-trimethyl-4-vinyl-3,3a,4,5,6,7-hexahydro-7aH-indazol-7a-yl acetate (48). To a stirred solution of **36** (560 mg, 1.17 mmol, 1.00 equiv) in EtOH (10 mL) was added hydrazine hydrate (344 µL, 85% in H_2O, 5.85 mmol, 5.00 equiv) at 0 °C dropwise over 10 min. The resultant pale yellow solution was heated at 90 °C (oil bath) for 12 h. Upon complete consumption of starting material (by TLC), the solvent was removed *in vacuo*, and the flask was backfilled with argon. A solution of $Pb(OAc)_4$ (2.59 g, 5.85 mmol, 5.00 equiv.) in CH_2Cl_2 (10 mL) was added to the above residue in CH_2Cl_2 (10 mL) at 0 °C dropwise by syringe over 30 min, and allowed to stir for 3 h. The reaction was quenched by addition of sat. aq. sodium bicarbonate (5 mL) at 0 °C, filtered and extracted with CH_2Cl_2 (5 x 10 mL). The reaction mixture was concentrated under reduced pressure. To a solution of the resulting residue in THF (10 mL) was added TBAF (5.85 mL, 1.0 M in THF, 5.85 mmol, 5.00 equiv) and the reaction mixture was stirred at 0 °C for 2 h. The resulting mixture was then quenched with sat. aq. ammonium chloride (10 mL). Ethyl acetate (5 x 10 mL) was added, and the upper organic layer was separated. The organic layer was dried with anhydrous sodium sulfate, the crude product was purified by flash chromatography (petroleum ether/ ethyl acetate 5:1→2:1) to give **48** (255 mg, 0.58 mmol, 50%, 2 steps) as colorless solid (m.p. 161-163 °C). *Rf* 0.32 (silica gel, 1:1 petroleum ether/ ethyl acetate, brown, *p*-anisaldehyde); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.34 – 6.16 (m, 1H), 5.24 – 5.15 (m, 2H), 4.58 (d, *J* = 8.5 Hz, 1H), 4.08 – 3.90 (m, 2H), 3.56 (dd, *J* = 11.8, 4.5 Hz, 1H), 2.96 (s, 1H), 2.74 (t, *J* = 9.1 Hz, 1H), 2.50 (d, *J* = 8.6 Hz, 1H), 2.30 – 2.17 (m, 1H), 2.12 (s, 3H), 2.09 – 1.98 (m, 2H), 1.87 (ddd, *J* = 12.8, 6.6, 2.5 Hz, 1H), 1.72 (dt, *J* = 9.7, 9.3 Hz, 1H), 1.66 – 1.56 (m, 1H), 1.49 (s, 3H), 1.48 (s, 3H), 1.39 (s, 3H), 1.30 (s, 3H), 0.99 (d, *J* = 6.7 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 169.3, 136.4, 118.1, 116.0, 98.3, 89.4, 79.6, 78.7, 72.7, 61.0, 51.7, 49.0, 45.2, 35.7, 35.3, 33.8, 30.4, 28.1, 28.0, 23.7, 22.0, 20.8, 15.1; HRMS (ESI$^+$) *m/z* calcd for $C_{23}H_{37}N_2O_6$ (M+H)$^+$: 437.2652, found: 437.2703; IR (neat) *ν* 3382, 2953, 2924, 1712, 1369, 1271, 1243, 1215, 1112, 1056, 968, 916 cm^{-1}.

Preparation of (1R,3R,4R,5S,6S)-4-((4aR,6S,7aS)-2,2-dimethyl-7-oxohexahydrocyclopenta[d][1,3]dioxin-6-yl)-4-hydroxy-3,7,7-trimethyl-5-vinylbicyclo[4.1.0]heptan-1-yl acetate (49). To a stirred solution of secondary alcohol **48** (100 mg, 0.23 mmol, 1.00 equiv) in ethyl acetate (6 mL), was irradiated using 300W mercury lamp at 25 °C. After 12 h, the reaction mixture was concentrated under reduced pressure. To a solution of the resulting residue in CH_2Cl_2 (10 mL) was added 4Å MS (100 mg), 4-Methylmorpholine N-oxide monohydrate (93 mg, 0.69 mmol, 3.00 equiv) and TPAP (16 mg, 0.046 mmol, 0.20 equiv) at 0 °C, and the reaction mixture was stirred at room temperature for 8 h. Then the mixture was concentrated to dryness and the crude product was purified by flash chromatography (petroleum ether/ ethyl acetate 5:1) to give ketone **49** (77 mg, 0.19 mmol, 82%) as colorless solid (m.p. 149-151 °C). *Rf* 0.32 (silica gel, 2:1 petroleum ether/ ethyl acetate, purple, *p*-anisaldehyde); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81 (ddd, *J* = 17.1, 10.2, 8.9 Hz, 1H), 5.09 (dd, *J* = 17.1, 1.3 Hz, 1H), 4.99 (dd, *J* = 10.2, 1.9 Hz, 1H), 4.24 (dd, *J* = 12.2, 3.6 Hz, 1H), 4.04 (d, *J* = 4.4 Hz, 1H), 3.82 (s, 1H), 3.72 (d, *J* = 12.2 Hz, 1H), 3.07 (t, *J* = 8.6 Hz, 1H), 2.60 (dd, *J* = 12.8, 8.1 Hz, 1H), 2.54 – 2.35 (m, 1H), 2.09 – 1.89 (m, 5H), 1.87 – 1.77 (m, 2H), 1.61 (dd, *J* = 15.7, 3.9 Hz, 1H), 1.46 (s, 3H), 1.40 (s, 3H), 1.36 (s, 3H), 1.04 (s, 3H), 0.98 – 0.89 (m, 4H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 216.4, 171.5, 136.3, 117.5, 98.2, 75.5, 72.0, 65.84, 59.6, 56.0, 43.0, 35.2, 33.1, 32.2, 30.6, 29.0, 26.5, 25.6, 23.9, 21.1, 18.6, 18.0, 14.8; HRMS (ESI$^+$) *m/z* calcd for $C_{23}H_{34}O_6Na$ (M+Na)$^+$: 429.2253, found: 429.2257; IR (neat) *ν* 3478, 2923, 2875, 1730, 1723, 1372, 1237, 1081, 1034, 972, 919, 827 cm^{-1}.

Preparation of (1R,3R,4R,5S,6S)-4-hydroxy-4-((4aR,6S,7R,7aS)-7-hydroxy-2,2-dimethyl-7-(2-methylallyl)hexahydrocyclopenta[d][1,3]dioxin-6-yl)-3,7,7-trimethyl-5-vinylbicyclo[4.1.0]heptan-1-yl acetate (50). To a stirred solution of **49** (41 mg, 0.1 mmol, 1.00 equiv) in THF (3 mL) was added freshly prepared 2-methylallylzinc chloride (0.24 mL, 0.5 M in THF, 0.12 mmol, 1.20 equiv) at -78 °C. After 30 minutes, the reaction was quenched by addition of sat. aq. ammonium chloride at 0 °C. Ethyl acetate (3 x 5 mL) was added, and the upper organic layer was separated. The organic layer was dried with anhydrous sodium sulfate. The crude was purified by flash chromatography (petroleum ether/ ethyl acetate 10:1) to give **50** (30 mg, 0.065 mmol, 65%) as colorless foam. *Rf* 0.33 (silica gel, 10:1 petroleum ether/ ethyl acetate, purple, *p*-anisaldehyde); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.07 (dt, *J* = 17.4, 10.1 Hz, 1H), 5.21 (dd, *J* = 17.4, 2.0 Hz, 1H), 5.06 (dd, *J* = 10.1, 2.1 Hz, 1H), 4.87 (dd, *J* = 2.1, 1.4 Hz, 1H), 4.69 (s, 1H), 4.15 (dd, *J* = 12.1, 3.2 Hz, 1H), 4.01 (d, *J* = 3.3 Hz, 1H), 3.89 (d, *J* = 1.4 Hz, 1H), 3.67 (d, *J* = 12.0 Hz, 1H), 3.30 (d, *J* = 1.5 Hz, 1H), 3.22 (t, *J* = 9.4 Hz, 1H), 2.52 (d, *J* = 14.3 Hz, 1H), 2.45 (dd, *J* = 12.4, 8.0 Hz, 1H), 2.23 (q, *J* = 12.1 Hz, 1H), 2.12 – 1.92 (m, 5H), 1.79 (s, 3H), 1.77 – 1.61 (m, 3H), 1.58 – 1.48 (m, 1H), 1.45 (s, 3H), 1.44 (s, 3H), 1.33 (s, 3H), 1.01 (s, 3H), 0.99 (d, *J* = 6.6 Hz, 3H), 0.96 (d, *J* = 9.2 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 171.4, 143.1, 140.1, 114.7, 114.4, 98.7, 82.8, 75.5, 73.7, 66.4, 60.5, 53.2, 50.1, 41.7, 36.1, 34.5, 34.1, 31.2, 29.8, 29.0, 25.8, 24.8, 23.7, 21.1, 18.9, 18.7, 16.2; HRMS (ESI$^+$) *m/z* calcd for $C_{27}H_{42}O_6Na$ (M+Na)$^+$: 485.2879, found: 485.2880; IR (neat) *ν* 3499, 2923, 1736, 1456, 1373, 1236, 1099, 969, 907, 889 cm^{-1}.

Preparation of (1R,2aR,3aS,3bS,6aR,6bS,10aR,11aS,11bR)-6a,11b-dihydroxy-1,3,3,5,8,8-hexamethyl-1,3,3a,3b,6,6a,6b,10,10a,11,11a,11b-dodecahydrocyclopropa[3',4']benzo[1',2':4,5]azuleno[1,2-d][1,3]dioxin-2a(2H)-yl acetate (51). To a stirred solution of **50** (50 mg, 0.11 mmol, 1.00 equiv) in toluene (3 mL) was added Grubbs 2nd generation catalyst (46 mg, 0.054 mmol, 0.50 equiv) under Ar, and the resultant mixture was stirred at 110 °C (oil bath) for 12 h. The mixture was concentrated to dryness and the residue was purified by flash chromatography (petroleum ether/ ethyl acetate 5:1) to give **51** (39 mg, 0.09 mmol, 82%) as yellow oil. *Rf* 0.18 (silica gel, 10:1 petroleum ether/ ethyl acetate, purple, *p*-anisaldehyde); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.24 (s, 1H), 4.06 (d, *J* = 8.3 Hz, 1H), 3.72 (d, *J* = 9.0 Hz, 1H), 3.67 (dd, *J* = 10.8, 6.6 Hz, 1H), 3.48 (t, *J* = 11.2 Hz, 1H), 3.08 (s, 1H), 2.73 (s, 1H), 2.50 (d, *J* = 17.9 Hz, 1H), 2.39 – 2.16 (m, 2H), 2.01 (s, 3H), 1.83 (s, 3H), 1.81 – 1.74 (m, 3H), 1.70 – 1.60 (m, 3H), 1.38 (s, 3H), 1.35 (s, 3H), 1.18 (s, 3H), 1.09 (s, 4H), 0.96 (d, *J* = 6.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 171.4, 135.5, 127.7, 99.4, 78.9, 74.6, 73.4, 65.9, 63.0, 57.4, 42.4,

36.4, 35.8, 34.6, 31.7, 30.6, 27.6, 26.9, 26.7, 25.8, 24.8, 23.8, 21.1, 17.2, 15.8; HRMS (ESI+) *m/z* calcd for $C_{25}H_{38}O_6Na$ $(M+Na)^+$: 457.2566, found: 457.2557; IR (neat) *ν* 3439, 2962, 1722, 1371, 1259, 1098, 1016, 869, 798 cm^{-1}.

Preparation of (4aR,6S,7aS)-6-((1R,2S,6R)-1-hydroxy-6-methyl-4-oxo-3-(propan-2-ylidene)-2-vinylcyclohexyl)-2,2-dimethyltetrahydrocyclopenta[d][1,3]dioxin-7(4H)-one (SI-22). TBAF (0.31 mL, 1.0 M in THF, 0.31 mmol, 1.50 equiv) was slowly added into a solution of **36** (100 mg, 0.21 mmol, 1.00 equiv) was dissolved in THF (5 mL) at 0 °C. After addition, the reaction was allowed to stir for 3 h at 25 °C. The resulting mixture was then quenched with sat. aq. ammonium chloride (1 mL), extracted with EtOAc. The organic layer was dried with anhydrous sodium sulfate and concentrated *in vacuo* to afford yellow oil which was sufficiently pure for the next step. The above product dissolved in DCM (10 mL), followed by sequential addition of powdered 4Å MS (100 mg), NMO (86 mg, 0.63 mmol, 3.00 equiv), TPAP (7.4 mg, 0.021 mmol, 0.10 equiv) at 0 °C, and the reaction mixture was stirred at room temperature for 8 h. Then the mixture was concentrated to dryness and the crude product was purified by flash chromatography (petroleum ether/ ethyl acetate 5:1) to give ketone **SI-22** (47 mg, 0.13 mmol, 62%, 2 steps) as yellow solid (m.p. 103-105 °C). *Rf* 0.53 (silica gel, 1:1 petroleum ether/ ethyl acetate, UV, purple, *p*-anisaldehyde); ^1H NMR (400 MHz, $CDCl_3$) δ 5.70 (ddd, *J* = 17.1, 10.2, 8.4 Hz, 1H), 5.01 (dd, *J* = 10.2, 1.1 Hz, 1H), 4.94 (d, *J* = 17.1 Hz, 1H), 4.35 – 4.25 (m, 1H), 4.15 (d, *J* = 4.4 Hz, 1H), 3.76 (d, *J* = 1.1 Hz, 1H), 3.75 – 3.70 (m, 1H), 2.72 (dd, *J* = 12.4, 8.2 Hz, 1H), 2.57 (dd, *J* = 18.1, 12.8 Hz, 1H), 2.39 – 2.26 (m, 1H), 2.16 (dd, *J* = 18.1, 4.2 Hz, 1H), 2.05 – 1.90 (m, 6H), 1.85 (s, 3H), 1.53 (s, 3H), 1.43 (s, 3H), 1.01 (d, *J* = 6.8 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 215.7, 204.7, 144.0, 136.0, 133.0, 116.8, 98.5, 77.3, 75.6, 71.9, 59.8, 56.8, 49.9, 42.9, 35.2, 32.2, 29.0, 26.3, 23.1, 22.2, 18.8, 14.5; HRMS (ESI+) *m/z* calcd for $C_{21}H_{30}O_5Na$ $(M+Na)^+$: 385.1990, found: 385.1991; IR (neat) *ν* 3493, 2923, 1735, 1685, 1377, 1225, 1159, 1081, 980, 922, 822, 759 cm^{-1}.

Preparation of (3S,4R,5R)-4-hydroxy-4-((4aR,6S,7R,7aS)-7-hydroxy-2,2-dimethyl-7-(2-methylallyl)hexahydrocyclopenta[d][1,3]dioxin-6-yl)-5-methyl-2-(propan-2-ylidene)-3-vinylcyclohexan-1-one (52). To a stirred solution of **SI-22** (100 mg, 0.28 mmol, 1.00 equiv) in THF (3 mL) was added freshly prepared 2-methylallylzinc chloride (0.66 mL, 0.5 M in THF, 0.33 mmol, 1.20 equiv) at -78 °C. After 30 minutes, the reaction was quenched by addition of sat. aq. ammonium chloride (0.5 mL) at 0 °C. Ethyl acetate (3 x 5 mL) was added, and the upper organic layer was separated. The organic layer was dried with anhydrous sodium sulfate. The crude was purified by flash chromatography (petroleum ether/ ethyl acetate 10:1) to give **52** (86 mg, 0.24 mmol, 86%) as colorless foam (m.p. 156-159 °C). *Rf* 0.54 (silica gel, 5:1 petroleum ether/ ethyl acetate, UV, purple, *p*-anisaldehyde); ^1H NMR (400 MHz, $CDCl_3$) δ 6.27 – 6.07 (m, 1H), 5.05 (d, *J* = 10.3 Hz, 1H), 4.91 (d, *J* = 15.3 Hz, 2H), 4.67 (s, 1H), 4.15 (dd, *J* = 12.1, 3.3 Hz, 1H), 4.05 (d, *J* = 3.3 Hz, 1H), 3.69 – 3.63 (m, 3H), 3.52 (s, 1H), 2.55 (dd, *J* = 15.3, 10.1 Hz, 1H), 2.49 – 2.34 (m, 2H), 2.34 – 2.18 (m, 2H), 2.18 – 2.07 (m, 5H), 1.84 (s, 3H), 1.82 (s, 3H), 1.78 – 1.68 (m, 1H), 1.53 – 1.43 (m, 7H), 1.07 (d, *J* = 6.9 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 203.7, 146.3, 142.5, 136.9, 131.6, 115.1, 114.8, 98.8, 83.8, 76.4, 74.8, 60.5, 53.5, 51.4, 49.9, 45.6, 36.4, 33.5, 29.4, 27.5, 24.8, 23.2, 22.7, 19.0, 16.7; HRMS (ESI+) *m/z* calcd for $C_{25}H_{38}O_5Na$ $(M+Na)^+$: 441.2617, found: 441.2620; IR (neat) *ν* 3534, 3491, 2989, 2929, 2853, 1679, 1380, 1251, 1190, 1083, 968, 900, 850 cm^{-1}.

Preparation of (2R,3S,4R,5R)-4-hydroxy-4-((4aR,6S,7R,7aS)-7-hydroxy-2,2-dimethyl-7-(2-methylallyl)hexahydrocyclopenta[d][1,3]dioxin-6-yl)-2-isopropyl-5-methyl-3-vinylcyclohexan-1-one (53). To a Schlenk flask equipped with liquid ammonia (~5 mL) was added lithium wire (4.6 mg, 0.66 mmol, 5.00 equiv) at -78 °C under Ar. After 15 minutes, a solution of **52** (55 mg, 0.13 mmol, 1.00 equiv) in THF (1.5 mL) was dropped into the dark blue ammonia solution at -78 °C. The reaction was allowed to stir for 2 h at the same temperature, and then warmed up to 0 °C. The reaction was quenched with solid NH_4Cl, followed by addition sat. aq. NH_4Cl. After warming to room temperature, the aqueous layer was extracted with EtOAc, and the combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude oil was purified by flash chromatography (petroleum ether/ ethyl acetate 20:1→10:1) to give **53** (27 mg, 0.065 mmol, 50%) as colorless solid (m.p. 158-160 °C). *Rf* 0.66 (silica gel, 5:1 petroleum ether/ ethyl acetate, purple, *p*-anisaldehyde); ^1H NMR (400 MHz, $CDCl_3$) δ 5.40 (dt, *J* = 16.8, 10.4 Hz, 1H), 5.18 – 5.10 (m, 1H), 5.04 (d, *J* = 16.8 Hz, 1H), 4.89 (s, 1H), 4.72 (s, 1H), 4.25 – 4.08 (m, 2H), 3.72 (d, *J* = 12.1 Hz, 1H), 3.58 (s, 1H), 3.50 (s, 1H), 3.22 (dd, *J* = 10.7, 4.5 Hz, 1H), 2.56 (d, *J* = 14.3 Hz, 1H), 2.53 – 2.21 (m, 6H), 2.15 (d, *J* = 14.3 Hz, 1H), 1.89 – 1.73 (m, 4H), 1.68 (dd, *J* = 11.4, 6.9 Hz, 1H), 1.49 (s, 3H), 1.45 (s, 3H), 1.01 (d, *J* = 6.7 Hz, 3H), 0.96 (d, *J* = 6.4 Hz, 3H), 0.92 (d, *J* = 6.7 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 212.6, 143.1, 135.1, 118.8, 114.9, 98.8, 83.5, 75.6, 73.9, 60.4, 56.8, 53.3, 50.4, 50.1, 44.2, 36.2, 34.4, 29.4, 28.1, 24.8, 22.6, 19.7, 19.0, 15.3; HRMS (ESI+) *m/z* calcd for $C_{25}H_{40}O_5Na$ $(M+Na)^+$: 443.2773, found: 443.2775; IR (neat) *ν* 3523, 3489, 2961, 2877, 1705, 1379, 1261, 1086, 864, 798 cm^{-1}.

Preparation of (1R,2S,4S,6R)-1-((4aR,6S,7R,7aS)-7-hydroxy-2,2-dimethyl-7-(2-methylallyl)hexahydrocyclopenta[d][1,3]dioxin-6-yl)-6-methyl-3-(propan-2-ylidene)-2-vinylcyclohexane-1,4-diol (56). $NaBH_4$ (18 mg, 0.48 mmol, 2.00 equiv) was added into a solution of **52** (100 mg, 0.24 mmol, 1.00 equiv) in MeOH/DCM (v:v, 1:1, 10 mL) at 0 °C. After stirring 6 h at the same temperature, the reaction was quenched by H_2O (0.5 mL), concentrated to dryness. The crude product was purified by flash chromatography (petroleum ether/ ethyl acetate 5:1) to give **56** (97 mg, 0.46 mmol, 97%) as yellow solid (m.p. 134-136 °C). *Rf* 0.65 (silica gel, 2:1 petroleum ether/ ethyl acetate, purple, *p*-anisaldehyde); ^1H NMR (400 MHz, $CDCl_3$) δ 6.34 – 6.15 (m, 1H), 5.00 – 4.90 (m, 1H), 4.87 (s, 1H), 4.69 (s, 1H), 4.62 (dd, *J* = 12.2, 7.5 Hz, 1H), 4.23 – 4.07 (m, 2H), 3.78 (s, 1H), 3.70 (d, *J* = 8.6 Hz, 1H), 3.65 (d, *J* = 12.2 Hz, 1H), 3.46 (s, 1H), 2.60 (d, *J* = 14.3 Hz, 1H), 2.22 – 1.98 (m, 3H), 1.91 – 1.76 (m, 11H), 1.75 – 1.62 (m, 3H), 1.54 (dd, *J* = 13.1, 7.3 Hz, 1H), 1.48 (s, 3H), 1.45 (s, 3H), 1.39 (dd, *J* = 12.8, 6.8 Hz, 1H), 1.04 (d, *J* = 6.9 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 143.3, 139.8, 134.0, 132.2, 114.5, 114.0, 98.8, 83.2, 76.8, 73.8, 67.5, 60.7, 54.3, 50.4, 50.3, 36.1, 34.9, 34.4, 29.2, 28.2, 24.8, 21.0, 20.9, 19.2, 16.1; HRMS (ESI+) *m/z* calcd for $C_{25}H_{40}O_5Na$ $(M+Na)^+$: 443.2773, found: 443.2775; IR (neat) *ν* 3511, 3440, 2973, 2928, 2874, 1371, 1196, 1155, 984, 968, 894, 863, 819 cm^{-1}.

Preparation of (3R,4S,6R,7S,8R)-7-((4aR,6S,7R,7aS)-7-hydroxy-2,2-dimethyl-7-(2-methylallyl)hexahydrocyclopenta[d][1,3]dioxin-6-yl)-2,2,6-trimethyl-8-vinyl-1-oxaspiro[2.5]octane-4,7-diol (57). To a stirred solution of **56** (82 mg, 0.19 mmol, 1.00 equiv) and $VO(acac)_2$ (2.5 mg, 9.5 μmol, 0.05 equiv) in DCM (3 mL) was added TBHP (32 μL, 6 M in decane, 0.19 mmol, 1.00 equiv) at 0 °C, and then slowly warmed up to 25 °C for 1 h. The mixture was quenched by sat. aq. NaS_2O_3, extracted with EtOAc. The organic layer was dried with anhydrous sodium sulfate, the crude was purified by flash chromatography (petroleum ether/ ethyl acetate 5:1→2:1→1:1) to give **57** (56 mg, 0.12 mmol,

66%) as colorless solid (m.p. 149-151 °C). *Rf* 0.42 (silica gel, 2:1 petroleum ether/ ethyl acetate, purple, *p*-anisaldehyde); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.33 (dt, *J* = 17.2, 10.1 Hz, 1H), 5.24 (dd, *J* = 10.1, 2.1 Hz, 1H), 5.13 (dd, *J* = 17.2, 1.9 Hz, 1H), 4.96 – 4.87 (m, 1H), 4.72 (s, 1H), 4.30 (s, 1H), 4.14 (dd, *J* = 12.1, 3.2 Hz, 1H), 3.98 (d, *J* = 3.2 Hz, 1H), 3.84 (d, *J* = 8.9 Hz, 1H), 3.70 (t, *J* = 7.7 Hz, 1H), 3.62 (d, *J* = 12.1 Hz, 1H), 3.37 (d, *J* = 0.8 Hz, 1H), 2.86 (d, *J* = 9.6 Hz, 1H), 2.41 (dd, *J* = 12.2, 8.7 Hz, 2H), 2.24 – 1.99 (m, 3H), 1.83 (s, 3H), 1.80 – 1.51 (m, 5H), 1.46 (s, 3H), 1.44 (s, 3H), 1.43 (s, 3H), 1.40 – 1.36 (m, 1H), 1.35 (s, 3H), 1.03 (d, *J* = 6.3 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 142.7, 136.6, 118.2, 115.3, 98.9, 83.6, 78.2, 74.2, 69.0, 68.3, 63.5, 60.4, 53.1, 50.3, 46.2, 37.6, 34.2, 34.1, 30.0, 28.1, 24.8, 22.5, 20.7, 18.9, 16.5; HRMS (ESI$^+$) *m/z* calcd for $C_{25}H_{40}O_6Na$ (M+Na)$^+$: 459.2723, found: 459.2715; IR (neat) *ν* 3473, 2974, 2935, 2907, 1373, 1085, 966, 927, 862, cm^{-1}.

Preparation of (3S,6R,7S,8R)-7-hydroxy-7-((4aR,6S,7R,7aS)-7-hydroxy-2,2-dimethyl-7-(2-methylallyl)hexahydrocyclopenta[d][1,3]dioxin-6-yl)-2,2,6-trimethyl-8-vinyl-1-oxaspiro[2.5]octan-4-one (58). **57** (12 mg, 0.027 mmol, 1.00 equiv) dissolved in DCM (1 mL), followed by sequential addition of powdered 4Å MS (15 mg), NMO (3.7 mg, 0.027 mmol, 3.00 equiv), TPAP (1 mg, 2.7 μmol, 0.10 equiv) at 0 °C, and the reaction mixture was stirred at room temperature for 8 h. Then the mixture was concentrated to dryness and the crude product was purified by flash chromatography (petroleum ether/ ethyl acetate 5:1) to give ketone **58** (10 mg, 0.022 mmol, 83%) as colorless solid (m.p. 210-212 °C). *Rf* 0.42 (silica gel, 2:1 petroleum ether/ ethyl acetate, purple, *p*-anisaldehyde); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89 (dt, *J* = 17.0, 10.1 Hz, 1H), 5.31 – 5.07 (m, 2H), 4.91 (s, 1H), 4.70 (s, 1H), 4.17 (dd, *J* = 12.1, 3.3 Hz, 1H), 4.01 (d, *J* = 3.0 Hz, 2H), 3.62 (d, *J* = 12.2 Hz, 1H), 3.18 (d, *J* = 9.8 Hz, 1H), 3.04 (s, 1H), 2.73 (dd, *J* = 20.2, 13.8 Hz, 1H), 2.57 – 2.44 (m, 1H), 2.38 (d, *J* = 14.1 Hz, 1H), 2.24 – 2.06 (m, 4H), 1.92 – 1.83 (m, 1H), 1.82 (s, 3H), 1.75 – 1.66 (m, 1H), 1.63 (s, 3H), 1.49 (s, 3H), 1.48 (s, 3H), 1.19 (s, 3H), 1.08 (d, *J* = 6.4 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 208.4, 142.5, 135.0, 118.7, 115.4, 99.0, 84.4, 77.7, 77.3, 77.01, 76.7, 74.1, 72.1, 66.1, 60.6, 53.0, 50.4, 47.8, 42.9, 35.2, 33.8, 30.0, 27.6, 24.7, 21.4, 20.3, 18.93, 14.9; HRMS (ESI$^+$) *m/z* calcd for $C_{25}H_{38}O_6Na$ (M+Na)$^+$: 457.2566, found: 457.2570; IR (neat) *ν* 3510, 3489, 2978, 2909, 2879, 1726, 1377, 1196, 1159, 1082, 970, 931, 870 cm^{-1}.

Preparation of (3S,4R,5R)-4-hydroxy-4-((1S,2R)-2-hydroxy-2-(2-methylallyl)-4-methylene-3-oxocyclopentyl)-5-methyl-2-(propan-2-ylidene)-3-vinylcyclohexan-1-one (59). **52** (89 mg, 0.21 mmol, 1.00 equiv) was dissolved in THF/MeCN/H_2O (v/v/v, 1 mL/ 4mL/ 1mL), followed by addition of DDQ (4.8 mg, 0.021 mmol, 0.20 equiv) at 25 °C. The dark red solution was allowed to stir at the same temperature for 18 h, concentrated to dryness, and then re-dissolved in DCM (5 mL). To the yellow solution was sequentially added DMAP (26 mg, 0.21 mmol, 1.00 equiv), pyridine (83 μL, 1.05 mmol, 5.00 equiv), TsCl (80 mg, 0.42 mmol, 2.00 equiv) at 0 °C. After stirring at room temperature for 8 h, the mixture was concentrated to dryness and the crude product was purified by flash chromatography (petroleum ether/ ethyl acetate 10:1→5:1) to give yellow oil (73 mg, 0.14 mmol, 65%, 2 steps). To a solution of the above compound (73 mg, 0.14 mmol, 1.00 equiv) in DCM (5 mL) was sequentially added powdered 4Å MS (100 mg), NMO (56 mg, 0.41 mmol, 3.00 equiv), TPAP (4.8 mg, 0.014 mmol, 0.10 equiv) at 0 °C, and the reaction mixture was stirred at room temperature for 8 h. Then the mixture was concentrated to dryness and the crude product was purified by flash chromatography (petroleum ether/ ethyl acetate 5:1) to give **59** (36 mg, 0.1 mmol, 74%) as yellow solid (m.p. 94-96 °C). *Rf* 0.57 (silica gel, 5:1 petroleum ether/ ethyl acetate, UV, purple, *p*-anisaldehyde); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.24 (t, *J* = 2.2 Hz, 1H), 5.79 (ddd, *J* = 17.3, 10.2, 8.2 Hz, 1H), 5.52 (t, *J* = 2.2 Hz, 1H), 4.98 (d, *J* = 10.7 Hz, 2H), 4.80 – 4.72 (m, 2H), 4.06 (s, 1H), 3.29 (s, 1H), 3.27 (d, *J* = 8.1 Hz, 1H), 2.75 – 2.65 (m, 2H), 2.65 – 2.53 (m, 2H), 2.37 (d, *J* = 13.9 Hz, 1H), 2.24 (d, *J* = 13.9 Hz, 1H), 2.17 (dt, *J* = 7.3, 4.4 Hz, 2H), 2.02 (s, 3H), 1.74 (s, 3H), 1.63 (s, 3H), 1.02 (d, *J* = 6.6 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 206.7, 203.7, 145.8, 140.8, 140.2, 136.6, 132.2, 121.4, 116.5, 115.6, 83.3, 76.5, 49.5, 47.8, 46.7, 44.0, 35.7, 26.7, 23.9, 23.3, 22.2, 15.0; HRMS (ESI$^+$) *m/z* calcd for $C_{22}H_{30}O_4Na$ (M+Na)$^+$: 381.2042, found: 381.2040; IR (neat) *ν* 3454, 2953, 2923, 2852, 1751, 1682, 1606, 1376, 1184, 1065, 984, 911, 731 cm^{-1}.

Preparation of methyl (3R,4R)-3-((4aR,6R,7S,7aS)-7-((tert-butyldimethylsilyl)oxy)-2,2-dimethylhexahydrocyclopenta[d][1,3]dioxin-6-yl)-3-hydroxy-4-methyl-6-oxocyclohex-1-ene-1-carboxylate (60). To a solution of **SI-20** (110 mg, 0.2 mmol, 1.00 equiv) in MeOH/THF (v:v, 1:1, 4 mL) was sequentially added Et_3N (138 μL, 1.0 mmol, 5.00 equiv), $Pd(PPh_3)_4$ (12 mg, 0.01 mmol, 0.05 equiv) at room temperature. Then the mixture was transferred into autoclave, backfilled CO for 3 times. Then the reaction was heated at 55 °C (oil bath) under CO (1 atm.) for 12 h. After cooling to room temperature, the reaction mixture was filtered through a pad of celite, concentrated in vacuo, and purified by flash chromatography (petroleum ether/ ethyl acetate 5:1) to afford **60** (89 mg, 0.19 mmol, 95%) as yellow oil. *Rf* 0.19 (silica gel, 5:1 petroleum ether/ ethyl acetate, purple, *p*-anisaldehyde); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 1.1 Hz, 1H), 4.19 – 4.05 (m, 2H), 4.00 (d, *J* = 3.6 Hz, 1H), 3.79 (s, 3H), 3.67 (dd, *J* = 12.0, 1.6 Hz, 1H), 3.43 (s, 1H), 2.62 (dd, *J* = 17.1, 4.7 Hz, 1H), 2.57 – 2.44 (m, 2H), 2.37 (dd, *J* = 12.5, 6.2 Hz, 1H), 2.18 – 2.08 (m, 1H), 2.08 – 1.93 (m, 1H), 1.82 (dt, *J* = 12.5, 8.1 Hz, 1H), 1.46 (s, 3H), 1.39 (s, 3H), 1.11 (d, *J* = 6.9 Hz, 3H), 0.87 (s, 9H), 0.10 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 193.7, 164.6, 158.0, 131.5, 98.4, 79.3, 77.4, 73.2, 60.2, 54.7, 52.2, 43.1, 37.5, 36.3, 28.9, 26.7, 25.6, 19.2, 17.7, 14.7, -4.4, -4.9; HRMS (ESI$^+$) *m/z* calcd for $C_{24}H_{41}O_7Si$ (M+H)$^+$: 469.2622, found: 469.2618; IR (neat) *ν* 3490, 2927, 2876, 2854, 1742, 1682, 1282, 1095, 832, 775 cm^{-1}.

Preparation of methyl (1S,2S,3R,4R,6S)-3-((4aR,6R,7S,7aS)-7-((tert-butyldimethylsilyl)oxy)-2,2-dimethylhexahydrocyclopenta[d][1,3]dioxin-6-yl)-3,6-dihydroxy-4-methyl-2-vinylcyclohexane-1-carboxylate (61). Vinylmagnesium chloride (0.5 mL, 2 M in THF, 1.00 mmol, 2.00 equiv) was added into a suspension of CuCN (45 mg, 0.50 mmol, 1.00 equiv) in THF (5 mL) at 0 °C and stirred for 10 min. To the solution of **60** (234 mg, 0.50 mmol, 1.00 equiv) in THF (5 mL) was slowly added above prepared cooper reagent at -78 °C, and warmed up to room temperature with stirring for 12 h. The mixture was quenched with sat. aq. ammonium chloride (0.5 mL), extracted with EtOAc (3 x 5 mL). The organic layer was dried with anhydrous sodium sulfate, concentrated in vacuo, and re-dissolved in DCM/MeOH (v:v, 1:1, 10 mL). The yellow solution was added $CeCl_3{\cdot}7H_2O$ (186 mg, 0.50 mmol, 1.00 equiv), cooled to -78 °C, followed by portion-wise addition of $NaBH_4$ (95 mg, 2.50 mmol, 5.00 equiv), and warmed up to room temperature for 6 h. The mixture was quenched by adding H_2O (0.5 mL), then concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/ ethyl acetate 5:1→2:1) to give **61** (140 mg, 0.56 mmol, 56%) as yellow oil. *Rf* 0.21 (silica gel, 2:1 petroleum ether/ ethyl acetate, purple, *p*-anisaldehyde); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.06 – 5.86 (m, 1H), 5.11 – 4.96 (m, 2H), 4.64 (dd, *J* = 9.9, 3.4 Hz, 1H), 3.85 (d, *J* = 3.5 Hz, 3H), 3.62 (s, 3H), 3.49 (s, 1H), 3.46 – 3.36 (m, 1H), 2.80 – 2.67 (m, 1H), 2.45 – 2.33 (m, 1H), 2.26 – 2.07 (m, 2H), 2.04 (s, 1H), 1.77 – 1.35 (m, 8H), 1.32 (s,

3H), 1.27 (s, 3H), 0.93 (d, *J* = 6.3 Hz, 3H), 0.90 (s, 9H), 0.15 (s, 3H), 0.10 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 174.7, 137.1, 117.0, 98.5, 80.9, 77.3, 73.2, 70.9, 61.6, 54.5, 51.3, 50.6, 48.9, 38.2, 37.5, 35.4, 27.3, 25.9, 25.8, 22.4, 17.7, 15.5, -4.0, -5.5; HRMS (ESI$^+$) *m/z* calcd for $C_{26}H_{47}O_7Si$ $(M+H)^+$: 499.3091, found: 499.3092; IR (neat) *ν* 3469, 2929, 2857, 1741, 1371, 1068, 833, 775 cm^{-1}.

Preparation of methyl (1S,2S,3R,4R,6S)-3-((4aR,6S,7aS)-2,2-dimethyl-7-oxohexahydrocyclopenta[d][1,3]dioxin-6-yl)-3-hydroxy-6-(methoxymethoxy)-4-methyl-2-vinylcyclohexane-1-carboxylate (62). MOMCl (0.23 mL, 3.00 mmol, 2.00 equiv) was added into a stirred solution of **61** (760 mg, 1.52 mmol, 1.00 equiv) and DIPEA (0.75 mL, 4.56 mmol, 3.00 equiv) in DCM (20 mL) at 0 °C. After addition, the reaction was allowed to room temperature for 12 h. The mixture was quenched with sat. aq. $NaHCO_3$ (2 mL), extracted with DCM (3 x 10 mL). The organic layer was dried with anhydrous sodium sulfate and concentrated in vacuo to yield crude yellow oil which was used directly to the next step. To the above residue solution in THF (30 mL) was added TBAF (4.6 mL, 1 M in THF, 4.56 mmol, 3.00 equiv) at 0 °C. After stirring at room temperature for 3 h, the reaction was quenched with sat. aq. NH_4Cl (2 mL), extracted with EtOAc (3 x 15 mL). The organic layer was concentrated in vacuo and purified by flash chromatography (petroleum ether/ ethyl acetate 5:1→2:1) to give yellow oil (586 mg). The above product dissolved in DCM (10 mL), followed by sequential addition of powdered 4Å MS (600 mg), NMO (558 mg, 4.1 mmol, 3.00 equiv), TPAP (48 mg, 0.14 mmol, 0.10 equiv) at 0 °C, and the reaction mixture was stirred at room temperature for 8 h. Then the mixture was concentrated to dryness and the crude product was purified by flash chromatography (petroleum ether/ ethyl acetate 5:1) to give ketone **62** (448 mg, 1.05 mmol, 69%, 3 steps) as yellow oil. *Rf* 0.34 (silica gel, 5:1 petroleum ether/ ethyl acetate, purple, *p*-anisaldehyde); ^1H NMR (400 MHz, $CDCl_3$) δ 5.59 (dt, *J* = 17.4, 10.1 Hz, 1H), 5.12 – 4.99 (m, 2H), 4.68 (d, *J* = 7.0 Hz, 1H), 4.56 (d, *J* = 7.0 Hz, 1H), 4.20 (dd, *J* = 12.2, 4.1 Hz, 1H), 4.04 (d, *J* = 5.2 Hz, 1H), 3.80 (td, *J* = 10.8, 4.6 Hz, 1H), 3.72 – 3.64 (m, 1H), 3.59 (s, 3H), 3.31 (s, 3H), 2.93 (t, *J* = 11.1 Hz, 1H), 2.62 – 2.44 (m, 2H), 1.94 – 1.77 (m, 3H), 1.69 (d, *J* = 11.6 Hz, 1H), 1.43 (s, 3H), 1.33 (s, 3H), 0.98 (d, *J* = 6.4 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 174.5, 133.9, 119.9, 98.5, 95.0, 76.1, 75.7, 71.3, 59.9, 55.3, 54.1, 51.4, 51.3, 37.2, 34.2, 32.7, 28.2, 25.6, 19.1, 15.9; HRMS (ESI$^+$) *m/z* calcd for $C_{22}H_{34}O_8Na$ $(M+Na)^+$: 449.2151, found: 449.2155; IR (neat) *ν* 3456, 2949, 1728, 1142, 1028, 919, 733 cm^{-1}.

Preparation of methyl (1S,2S,3R,4R,6S)-3-hydroxy-3-((4aR,6S,7R,7aS)-7-hydroxy-2,2-dimethyl-7-(2-methylallyl)hexahydrocyclopenta[d][1,3]dioxin-6-yl)-6-(methoxymethoxy)-4-methyl-2-vinylcyclohexane-1-carboxylate (63). To a stirred solution of **62** (43 mg, 0.10 mmol, 1.00 equiv) in THF (5 mL) was added freshly prepared 2-methylallylzinc chloride (300 μL, 0.5 M in THF, 0.15 mmol, 1.50 equiv) at -78 °C under Ar. After 5 minutes, the reaction was quenched with sat. aq. NH_4Cl (0.5 mL) at 0 °C, extracted with EtOAc (3 x 5 mL). The organic layer was dried with anhydrous Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/ ethyl acetate 10:1) to yield **63** (32 mg, 0.067 mmol, 67%) as colorless oil. *Rf* 0.65 (silica gel, 10:1 petroleum ether/ ethyl acetate, purple, *p*-anisaldehyde); ^1H NMR (400 MHz, $CDCl_3$) δ 5.90 (dt, *J* = 17.5, 10.2 Hz, 1H), 5.21 – 5.09 (m, 2H), 4.84 (s, 1H), 4.79 (s, 1H), 4.69 (d, *J* = 6.9 Hz, 2H), 4.55 (d, *J* = 6.9 Hz, 1H), 4.17 – 4.10 (m, 2H), 3.77 (td, *J* = 10.8, 4.2 Hz, 1H), 3.72 – 3.66 (m, 1H), 3.60 (s, 3H), 3.50 (d, *J* = 1.6 Hz, 1H), 3.31 (s, 3H), 2.86 – 2.76 (m, 2H), 2.55 – 2.36 (m, 2H), 2.23 – 2.12 (m, 1H), 1.94 (d, *J* = 14.2 Hz, 1H), 1.90 – 1.81 (m, 2H), 1.77 (s, 3H), 1.59 – 1.48 (m, 3H), 1.42 (s, 3H), 1.35 (s, 3H), 1.08 (d, *J* = 6.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 174.7, 143.3, 136.7, 117.5, 114.2, 98.6, 94.9, 81.9, 76.0, 74.9, 72.6, 60.3, 55.3, 52.9, 52.2, 51.4, 51.2, 49.5, 38.6, 35.4, 35.3, 29.2, 28.5, 24.6, 18.9, 17.1; HRMS (ESI$^+$) *m/z* calcd for $C_{26}H_{43}O_8$ $(M+H)^+$: 483.2958, found: 483.2955; IR (neat) *ν* 3462, 3070, 2945, 1733, 1373, 1250, 1102, 1042, 973 cm^{-1}.

Preparation of (3aR,4S,5R,6R)-5-((4aR,6R,7S,7aS)-7-hydroxy-2,2-dimethylhexahydrocyclopenta[d][1,3]dioxin-6-yl)-3,3,6-trimethyl-2-phenyl-4-vinyl-3,3a,4,5,6,7-hexahydro-2H-indazol-5-ol (65). Phenylhydrazine (62 μL, 0.63 mmol, 1.00 equiv) was added into a stirred solution of **36** (300 mg, 0.63 mmol, 1.00 equiv) and TFA (47 μL, 0.63 mmol, 1.00 equiv) in THF (5 mL) at room temperature. The reaction was heated to 90 °C (oil bath) for 16 h, then concentrated in vacuo. The crude residue was purified by flash chromatography (petroleum ether/ ethyl acetate 5:1) to give yellow oil. The yellow oil was dissolved in THF (5 mL), followed by addition of TBAF (1.26 mL, 1 M in THF, 1.26 mmol, 1.00 equiv) at 0 °C. After stirring at 0 °C for 2 h, the reaction was quenched with sat. aq. ammonium chloride (0.5 mL) at 0 °C. Ethyl acetate (3 x 5 mL) was added, and the upper organic layer was separated. The organic layer was dried with anhydrous sodium sulfate. The crude was purified by flash chromatography (petroleum ether/ ethyl acetate 5:1) to give **65** (140 mg, 0.31 mmol, 49%, 2 steps) as yellow solid (m.p. 232-234 °C). *Rf* 0.29 (silica gel, 1:1 petroleum ether/ ethyl acetate, dark purple, *p*-anisaldehyde); ^1H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.18 (m, 4H), 6.99 (t, *J* = 6.7 Hz, 1H), 6.07 – 5.88 (m, 1H), 5.28 (d, *J* = 10.4 Hz, 1H), 5.20 (d, *J* = 17.6 Hz, 1H), 4.80 (d, *J* = 8.5 Hz, 1H), 4.08 – 3.92 (m, 2H), 3.57 (dd, *J* = 11.9, 4.3 Hz, 1H), 3.01 (d, *J* = 11.4 Hz, 1H), 2.96 (s, 1H), 2.55 – 2.44 (m, 3H), 2.40 – 2.26 (m, 1H), 2.04 (td, *J* = 10.7, 5.4 Hz, 1H), 1.82 (ddt, *J* = 18.6, 12.8, 9.2 Hz, 2H), 1.65 – 1.58 (m, 1H), 1.58 (s, 3H), 1.40 (s, 3H), 1.31 (s, 3H), 1.05 (d, *J* = 6.5 Hz, 3H), 0.81 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 152.8, 145.9, 137.6, 128.4, 122.3, 120.9, 118.8, 98.2, 79.5, 78.9, 75.1, 70.1, 61.0, 55.1, 51.4, 48.7, 38.9, 35.5, 31.2, 29.5, 28.1, 27.3, 20.7, 17.1, 16.4; HRMS (ESI$^+$) *m/z* calcd for $C_{27}H_{39}N_2O_4$ $(M+H)^+$: 455.2910, found: 455.2905; IR (neat) *ν* 3156, 2979, 2933, 2855, 1491, 1364, 1032, 918, 764, 700 cm^{-1}.

Preparation of (3aR,4S,5R,6R,7aS)-5-((4aR,6R,7S,7aS)-7-((tert-butyldimethylsilyl)oxy)-2,2-dimethylhexahydrocyclopenta[d][1,3]dioxin-6-yl)-5-hydroxy-3,3,6-trimethyl-4-vinyl-3,3a,4,5,6,7-hexahydro-7aH-indazol-7a-yl acetate (66) and (4S,5R,6R)-5-((4aR,6R,7S,7aS)-7-((tert-butyldimethylsilyl)oxy)-2,2-dimethylhexahydrocyclopenta[d][1,3]dioxin-6-yl)-3,3,6-trimethyl-4-vinyl-4,5,6,7-tetrahydro-3H-indazol-5-ol (SI-23). To a stirred solution of **36** (200 mg, 0.42 mmol, 1.00 equiv) and TFA (0.93 mL, 1.26 mmol, 3.00 equiv) in THF (10 mL) was added hydrazine hydrate (72 μL, 85% in H_2O, 1.26 mmol, 3.00 equiv) at 0 °C dropwise over 10 min. The resultant pale yellow solution was heated at 90 °C (oil bath) for 12 h. Upon complete consumption of starting material (by TLC), the solvent was removed in vacuo, and the flask was backfilled with argon. A solution of $Pb(OAc)_4$ (931 mg, 2.10 mmol, 5.00 equiv) in CH_2Cl_2 (10 mL) was added to the above residue in CH_2Cl_2 (10 mL) at 0 °C dropwise by syringe over 30 min, and allowed to stir for 3 h. The reaction was quenched by addition of sat. aq. sodium bicarbonate (3 mL) at 0 °C, filtered and extracted with CH_2Cl_2 (5 x 10 mL). The combined organic layers were dried with anhydrous sodium sulfate, the crude product was purified by flash chromatography (petroleum ether/ ethyl acetate 10:1→5:1) to give diazene **66** (120 mg, 0.22 mmol, 52%) as white foam, **SI-23** as yellow foam (56 mg, 0.11 mmol, 27%). **66**: *Rf* 0.36 (silica gel, 2:1 petroleum ether/ ethyl acetate, brown, *p*-anisaldehyde); ^1H NMR (400 MHz, $CDCl_3$) δ 6.00 – 5.85 (m, 1H),

5.31 – 5.11 (m, 2H), 4.38 (d, *J* = 8.1 Hz, 1H), 3.98 – 3.85 (m, 2H), 3.51 (dd, *J* = 11.6, 4.9 Hz, 1H), 2.81 (s, 1H), 2.43 (d, *J* = 10.5 Hz, 1H), 2.21 (d, *J* = 14.2 Hz, 1H), 2.16 – 2.10 (m, 1H), 2.09 – 2.06 (m, 1H), 2.05 (s, 3H), 2.01 – 1.95 (m, 1H), 1.94 – 1.85 (m, 2H), 1.56 (dd, *J* = 11.7, 5.4 Hz, 1H), 1.51 (s, 3H), 1.35 (s, 3H), 1.30 (s, 3H), 1.29 – 1.27 (m, 1H) 1.26 (s, 3H), 1.21 (d, *J* = 7.1 Hz, 3H), 0.87 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.3, 138.4, 118.1, 117.8, 98.1, 92.1, 80.6, 78.0, 75.1, 61.1, 54.2, 45.7, 42.5, 35.6, 35.4, 35.1, 27.8, 27.4, 25.7, 22.2, 21.8, 20.8, 17.6, 16.6, -4.1, -5.4; HRMS (ESI$^+$) *m/z* calcd for $C_{29}H_{50}N_2O_6SiNa$ (M+Na)$^+$: 573.3336, found: 573.3331; IR (neat) *ν* 3565, 2933, 2857, 1739, 1367, 1244, 1053, 835, 777 cm^{-1}. **SI-23**: *Rf* 0.30 (silica gel, 2:1 petroleum ether/ ethyl acetate, UV, pink, *p*-anisaldehyde); ^1H NMR (400 MHz, $CDCl_3$) δ 5.72 (dt, *J* = 16.4, 10.0 Hz, 1H), 5.36 – 5.16 (m, 2H), 4.18 (d, *J* = 2.2 Hz, 1H), 4.10 (dd, *J* = 12.0, 3.5 Hz, 1H), 3.94 (d, *J* = 3.8 Hz, 1H), 3.66 (dd, *J* = 12.0, 1.8 Hz, 1H), 3.16 (d, *J* = 9.6 Hz, 1H), 3.00 (ddd, *J* = 17.5, 6.1, 2.5 Hz, 1H), 2.85 (s, 1H), 2.73 (dd, *J* = 17.5, 1.7 Hz, 1H), 2.32 – 2.23 (m, 1H), 2.22 – 2.07 (m, 2H), 2.01 – 1.92 (m, 1H), 1.63 – 1.54 (m, 1H), 1.42 (s, 3H), 1.37 (s, 3H), 1.33 (s, 3H), 1.30 (s, 3H), 1.11 (d, *J* = 7.1 Hz, 3H), 0.87 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 150.4, 149.2, 135.3, 120.0, 98.1, 92.1, 79.4, 77.8, 75.2, 60.4, 54.0, 47.3, 36.0, 35.6, 29.1, 28.4, 26.9, 25.7, 21.4, 20.5, 19.1, 17.7, 16.3, -4.3, -4.9; HRMS (ESI$^+$) *m/z* calcd for $C_{27}H_{47}N_2O_4Si$ (M+H)$^+$: 491.3305, found: 491.3297; IR (neat) *ν* 3501, 2930, 2859, 1379, 1194, 1089, 1075, 966, 833, 778 cm^{-1}.

Preparation of (1S,3R,4R,5S,6R)-4-hydroxy-4-((4aR,6R,7S,7aS)-7-hydroxy-2,2-dimethylhexahydrocyclopenta[d][1,3]dioxin-6-yl)-3,7,7-trimethyl-5-vinylbicyclo[4.1.0]heptan-1-yl acetate (67) and (1R,3R,4R,5S,6R)-4-hydroxy-4-((4aR,6R,7S,7aS)-7-hydroxy-2,2-dimethylhexahydrocyclopenta[d][1,3]dioxin-6-yl)-3,7,7-trimethyl-5-vinylbicyclo[4.1.0]heptan-1-yl acetate (68). To a stirred solution of diazene **66** (100 mg, 0.18 mmol, 1.00 equiv) in ethyl acetate (20 mL), was irradiated using 300W mercury lamp at 25 °C. After 12 h, the reaction mixture was concentrated under reduced pressure. To a solution of the resulting residue in THF (20 mL) was added TBAF (0.36 mL, 1.0 M in THF, 0.36 mmol, 2.00 equiv) and the reaction mixture was stirred at 0 °C for 2 h. The resulting mixture was then quenched with sat. aq. ammonium chloride. Ethyl acetate (5 x 10 mL) was added, and the upper organic layer was separated. The organic layer was dried with anhydrous sodium sulfate, the crude product was purified by flash chromatography (petroleum ether/ ethyl acetate 2:1) to give alcohol **67** (58 mg, 0.14 mmol, 79%) as colorless foam and trans isomer **68** (8 mg, 0.019 mmol, 11%) as white solid (m.p. 130-133 °C). **67**: *Rf* 0.78 (silica gel, 1:1 petroleum ether/ ethyl acetate, dark blue, *p*-anisaldehyde); ^1H NMR (400 MHz, $CDCl_3$) δ 6.29 (dt, *J* = 17.2, 9.9 Hz, 1H), 5.23 (s, 1H), 5.11 – 4.98 (m, 2H), 4.62 (dd, *J* = 8.8, 2.0 Hz, 1H), 4.04 (dd, *J* = 6.4, 2.0 Hz, 1H), 3.92 (dd, *J* = 11.6, 5.4 Hz, 1H), 3.52 (dd, *J* = 11.6, 5.4 Hz, 1H), 3.31 (s, 1H), 2.28 – 2.16 (m, 1H), 2.13 – 1.98 (m, 3H), 2.04 (s, 3H), 1.72 – 1.56 (m, 2H), 1.44 – 1.40 (m, 1H), 1.38 (s, 3H), 1.35 – 1.31 (m, 1H), 1.30 (s, 3H), 1.15 (s, 3H), 1.08 (s, 3H), 0.89 (d, *J* = 6.2 Hz, 3H), 0.62 (d, *J* = 3.9 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 173.3, 140.0, 115.1, 98.2, 79.3, 77.5, 73.6, 62.9, 61.4, 50.7, 44.8, 36.5, 35.9, 32.5, 30.6, 27.9, 27.3, 23.6, 22.3, 21.2, 21.1, 16.5, 15.3; HRMS (ESI$^+$) *m/z* calcd for $C_{23}H_{36}O_6Na$ (M+Na)$^+$: 431.2410, found: 431.2401; IR (neat) *ν* 3396, 2935, 2243, 1719, 1369, 1248, 1049, 994, 913, 849, 730 cm^{-1}. **68**: *Rf* 0.66 (silica gel, 1:1 petroleum ether/ ethyl acetate, dark blue, *p*-anisaldehyde); ^1H NMR (400 MHz, $CDCl_3$) δ 6.44 (ddd, *J* = 16.7, 10.5, 6.0 Hz, 1H), 5.32 – 5.18 (m, 2H), 4.28 (d, *J* = 7.5 Hz, 1H), 4.10 (dd, *J* = 11.6, 4.4 Hz, 2H), 3.67 (dd, *J* = 12.0, 2.5 Hz, 1H), 3.23 (dd, *J* = 12.0, 6.0 Hz, 1H), 2.39 – 2.24 (m, 3H), 2.17 – 1.95 (m, 6H), 1.74 – 1.52 (m, 3H), 1.44 (s, 3H), 1.37 (s, 3H), 1.30 (s, 3H), 1.05 (d, *J* = 6.9 Hz, 6H), 0.24 (d, *J* = 12.1 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.8, 138.1, 117.5, 98.1, 80.1, 79.0, 77.9, 64.1, 60.9, 54.5, 44.9, 41.8, 39.8, 36.4, 36.1, 32.7, 29.0, 28.7, 25.2, 21.2, 19.9, 17.3, 15.9; HRMS (ESI$^+$) *m/z* calcd for $C_{23}H_{37}O_6$ (M+H)$^+$: 409.2590, found: 409.2588; IR (neat) *ν* 3534, 3384, 2957, 2935, 2871, 1733, 1373, 1221, 1194, 967, 912, 836 cm^{-1}.

Preparation of (1S,3R,4R,5S,6R)-4-hydroxy-4-((4aR,6S,7R,7aS)-7-hydroxy-2,2-dimethyl-7-(2-methylallyl)hexahydrocyclopenta[d][1,3]dioxin-6-yl)-3,7,7-trimethyl-5-vinylbicyclo[4.1.0]heptan-1-yl acetate (35). To a stirred solution of secondary alcohol **67** (204 mg, 0.50 mmol, 1.00 equiv), 4Å MS (200 mg), 4-Methylmorpholine N-oxide monohydrate (203 mg, 1.50 mmol, 3.00 equiv) in CH_2Cl_2 (40 mL) at 0 °C was added TPAP (35 mg, 0.10 mmol, 0.20 equiv), and the reaction mixture was stirred at room temperature for 5 h. The resulting mixture filtered through a short pad of Florisil®, elution with CH_2Cl_2 (20 mL) and concentrated in vacuo. The resulting oil was dissolved in THF (10 mL), at -78 °C was added a solution of 2-Methylallylzinc chloride (0.55 mmol, 1.10 equiv, prepared from 0.55 mL zinc chloride (1.0 M in THF) and 1.10 mL 2-Methylallylmagnesium chloride (0.5 M in THF)), and the reaction mixture was stirred at -78 °C for 5 min. Then warmed to 0 °C, the resulting mixture was quenched with sat. aq. ammonium chloride. Ethyl acetate (3 x 10 mL) was added, and the upper organic layer was separated. The organic layer was dried with anhydrous sodium sulfate, the crude was purified by flash chromatography (petroleum ether/ ethyl acetate 10:1) to give diene **35** (143 mg, 0.31 mmol, 62%, over 2 steps) as colorless oil. *Rf* 0.32 (silica gel, 5:1 petroleum ether/ ethyl acetate, purple, *p*-anisaldehyde); ^1H NMR (400 MHz, $CDCl_3$) δ 6.29 (ddd, *J* = 17.1, 10.4, 9.2 Hz, 1H), 5.12 (dd, *J* = 10.4, 8.7 Hz, 2H), 4.83 (s, 1H), 4.66 (s, 1H), 4.22 – 4.04 (m, 3H), 3.65 (d, *J* = 12.0 Hz, 1H), 3.40 (s, 1H), 2.75 (d, *J* = 14.3 Hz, 1H), 2.44 – 2.34 (m, 1H), 2.30 – 2.18 (m, 2H), 2.12 (dd, *J* = 8.7, 5.1 Hz, 1H), 2.01 (s, 3H), 1.97 (d, *J* = 14.3 Hz, 1H), 1.79 (s, 3H), 1.77 – 1.68 (m, 2H), 1.64 – 1.57 (m, 1H), 1.48 – 1.44 (m, 1H), 1.42 (s, 3H), 1.38 (s, 3H), 1.11 (s, 3H), 1.09 (s, 3H), 1.06 (d, *J* = 6.2 Hz, 3H), 0.74 (d, *J* = 5.1 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 172.0, 143.7, 141.0, 115.2, 114.2, 98.6, 82.0, 75.4, 73.3, 64.3, 60.6, 53.1, 49.6, 44.5, 36.7, 34.9, 31.5, 30.7, 29.2, 28.5, 24.8, 23.8, 23.0, 21.1, 19.1, 18.3, 15.8; HRMS (ESI$^+$) *m/z* calcd for $C_{27}H_{42}O_6Na$ (M+Na)$^+$: 485.2879, found: 485.2873; IR (neat) *ν* 3443, 2926, 1723, 1371, 1232, 1197, 1135, 969, 871 cm^{-1}.

Preparation of (1R,2aS,3aR,3bS,6aR,6bS,10aR,11aS,11bR)-6a,11b-dihydroxy-1,3,3,5,8,8-hexamethyl-1,3,3a,3b,6,6a,6b,10,10a,11,11a,11b-dodecahydrocyclopropa[3',4']benzo[1',2':4,5]azuleno[1,2-d][1,3]dioxin-2a(2H)-yl acetate (69). To a stirred solution of **35** (50 mg, 0.11 mmol, 1.00 equiv) in toluene (5 mL) was added Grubbs 2nd generation catalyst (37.4 mg, 0.043 mmol, 0.4 equiv) under argon, and the resultant mixture was stirred at 110 °C (oil bath) for 12 h. The mixture was concentrated to dryness and the residue was purified by flash chromatography (petroleum ether/ ethyl acetate 5:1) to give **69** (34 mg, 0.078 mmol, 71%) as pale yellow solid (m.p. 138-141 °C), and recovered starting material 35 (10 mg, 0.022 mmol, 20%). *Rf* 0.15 (silica gel, 5:1 petroleum ether/ ethyl acetate, brown, *p*-anisaldehyde); ^1H NMR (400 MHz, $CDCl_3$) δ 5.43 – 5.31 (m, 1H), 3.96 (dd, *J* = 11.6, 4.5 Hz, 1H), 3.70 (d, *J* = 6.1 Hz, 1H), 3.61 (dd, *J* = 11.6, 5.1 Hz, 1H), 3.42 (s, 1H), 2.50 (t, *J* = 6.1 Hz, 1H), 2.45 (d, *J* = 17.0 Hz, 1H), 2.13 (d, *J* = 17.0 Hz, 1H), 2.10 – 2.05 (m, 1H), 2.03 (s, 3H), 2.02 – 1.88 (m, 3H), 1.89 – 1.79 (m, 2H), 1.73 (s, 3H), 1.58 (dd, *J* = 15.7, 5.3 Hz, 1H), 1.43 (s, 3H), 1.39 (s, 3H),

1.12 (s, 3H), 1.09 (s, 3H), 1.00 (d, *J* = 6.9 Hz, 3H), 0.91 (d, *J* = 7.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 172.2, 134.8, 127.8, 98.8, 77.6, 77.4, 75.8, 65.0, 61.7, 54.3, 48.0, 39.6, 35.7, 34.9, 31.3, 31.2, 28.8, 28.2, 25.6, 23.8, 22.7, 21.7, 21.3, 19.0, 15.9; HRMS (ESI$^+$) *m/z* calcd for $C_{25}H_{38}O_6Na$ (M+Na)$^+$: 457.2566, found: 457.2562; IR (neat) *ν* 3513, 2973, 2943, 2869, 1742, 1368, 1226, 1120, 1056, 1011, 875 cm^{-1}.

Preparation of ((1aR,1bS,4aR,5S,6R,7aS,7bR,8R,9aS)-9a-acetoxy-4a,5,7b-trihydroxy-1,1,3,8-tetramethyl-1a,1b,4,4a,5,6,7,7a,7b,8,9,9a-dodecahydro-1H-cyclopropa[3,4]benzo[1,2-e]azulen-6-yl)methyl pivalate (70) and ((1aR,4aR,5S,6R,7aS,8R,9aS)-9a-acetoxy-4a,5-dihydroxy-1,1,3,8-tetramethyl-1a,4,4a,5,6,7,7a,8,9,9a-decahydro-1H-cyclopropa[3,4]benzo[1,2-e]azulen-6-yl)methyl pivalate (SI-24). To a stirred solution of **69** (32 mg, 0.074 mmol, 1.00 equiv) in THF/MeCN/H_2O (v/v/v, 2 mL/ 8mL/ 1mL) was added DDQ (3.4 mg, 0.015 mmol, 0.20 equiv). The dark solution was stirred at room temperature for 18 h. Upon complete consumption of starting material (by TLC), the solvent was removed in vacuo, then the residue was redissolved in CH_2Cl_2 (5 mL), at 0 °C was added DMAP (9 mg, 0.074 mmol, 1.00 equiv), pyridine (29 µL, 0.37 mmol, 5.00 equiv), pivaloyl chloride (28 µL, 0.22 mmol, 3.00 equiv) in sequence. The yellow solution was stirred at room temperature for 8 h. Then the mixture was concentrated to dryness and the crude product was purified by flash chromatography (petroleum ether/ ethyl acetate 10:1→5:1) to give **70** (26 mg, 0.054 mmol, 73%) as a yellow solid (m.p. 163-165 °C) and **SI-24** (2.7 mg, 5.9 µmol, 8%) as a yellow solid (m.p. 101-105 °C). **70**: *Rf* 0.38 (silica gel, 2:1 petroleum ether/ ethyl acetate, blue, *p*-anisaldehyde); ^1H NMR (400 MHz, $CDCl_3$) δ 5.36 (d, *J* = 4.1 Hz, 1H), 4.32 (dd, *J* = 11.2, 7.9 Hz, 1H), 4.01 (dd, *J* = 11.2, 5.3 Hz, 1H), 3.61 (t, *J* = 6.6 Hz, 1H), 3.21 (d, *J* = 5.9 Hz, 1H), 3.08 (s, 1H), 2.48 – 2.43 (m, 1H), 2.39 (d, *J* = 16.6 Hz, 1H), 2.28 (d, *J* = 16.6 Hz, 1H), 2.20 – 2.10 (m, 1H), 2.03 (s, 3H), 2.00 – 1.81 (m, 4H), 1.76 (s, 3H), 1.70 – 1.65 (m, 1H), 1.56 (dd, *J* = 14.0, 5.0 Hz, 1H), 1.19 (s, 9H), 1.13 (s, 3H), 1.07 (s, 3H), 0.98 (d, *J* = 6.5 Hz, 3H), 0.83 (d, *J* = 6.6 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 179.2, 172.3, 135.0, 128.6, 77.9, 77.5, 74.9, 64.6, 53.3, 45.3, 39.6, 39.4, 38.8, 35.0, 31.8, 30.8, 28.8, 27.2, 25.9, 23.4, 22.9, 21.3, 18.7, 15.7; HRMS (ESI$^+$) *m/z* calcd for $C_{27}H_{42}O_7Na$ (M+Na)$^+$: 501.2828, found: 501.2826; IR (neat) *ν* 3352, 2959, 2924, 1717, 1374, 1246, 1154, 1050, 997, 888 cm^{-1}. **SI-24**: *Rf* 0.58 (silica gel, 2:1 petroleum ether/ ethyl acetate, UV, dark blue, *p*-anisaldehyde); ^1H NMR (400 MHz, $CDCl_3$) δ 5.71 (s, 1H), 4.38 (dd, *J* = 10.8, 7.5 Hz, 1H), 4.16 (dd, *J* = 10.8, 6.6 Hz, 1H), 3.80 (t, *J* = 5.0 Hz, 1H), 3.21 (d, *J* = 4.7 Hz, 1H), 2.63 – 2.55 (m, 1H), 2.48 – 2.25 (m, 4H), 2.22 – 2.07 (m, 2H), 2.04 (s, 3H), 1.92 – 1.66 (m, 6H), 1.34 (s, 1H), 1.20 (s, 9H), 1.15 (s, 3H), 1.10 (d, *J* = 6.8 Hz, 3H), 0.97 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 178.7, 171.2, 139.0, 136.2, 126.0, 125.3, 77.2, 77.0, 64.3, 63.8, 51.2, 48.7, 42.2, 38.8, 33.7, 33.2, 31.4, 29.3, 29.3, 27.4, 27.2, 21.5, 21.0, 20.7, 16.5; HRMS (ESI$^+$) *m/z* calcd for $C_{27}H_{40}O_6Na$ (M+Na)$^+$: 483.2723, found: 483.2720; IR (neat) *ν* 3496, 2956, 2925, 2870, 1722, 1361, 1280, 1233, 1158, 981, 890 cm^{-1}.

Preparation of (1aR,1bS,4aR,7aS,7bR,8R,9aS)-7b-hydroxy-1,1,3,8-tetramethyl-6-methylene-5-oxo-4a-((trimethylsilyl)oxy)-1,1a,1b,4,4a,5,6,7,7a,7b,8,9-dodecahydro-9aH-cyclopropa[3,4]benzo[1,2-e]azulen-9a-yl acetate (SI-25). To a stirred solution of **70** (22 mg, 0.046 mmol, 1.00 equiv), DMAP (5.6 mg, 0.046 mmol, 1.00 equiv) in MeCN (10 mL) was added Cuprous chloride (1.4 mg, 0.014 mmol, 0.3 equiv), 2,2'-dipyridyl (2.2 mg, 0.014 mmol, 0.30 equiv), 2-azaadamantane-N-oxyl (1.4 mg, 9.2 µmol, 0.2 equiv) at 0 °C. The dark solution was stirred at room temperature for 18 h under air. The resulting green mixture filtered through a short pad of Florisil®, elution with CH_2Cl_2 (10 mL) and concentrated in vacuo. The residue was used in the next reaction without further purification. Imidazole (63 mg, 0.92 mmol, 20 equiv), TMSCl (40 µL, 0.46 mmol, 10 equiv), were successively added to a solution of the above crude in CH_2Cl_2 (5 mL) at room temperature. The reaction mixture was warmed to 40 °C (oil bath) and stirred for 5 h. Then the mixture was concentrated to dryness and the crude product was purified by flash chromatography (petroleum ether/ ethyl acetate 20:1→10:1) to give **SI-25** (10.8 mg, 0.029 mmol, 64%, over 2 steps) as a colorless oil. *Rf* 0.52 (silica gel, 5:1 petroleum ether/ ethyl acetate, UV, purple, *p*-anisaldehyde); ^1H NMR (400 MHz, $CDCl_3$) δ 6.06 (s, 1H), 5.42 (s, 2H), 2.96 – 2.65 (m, 3H), 2.40 (d, *J* = 15.8 Hz, 1H), 2.22 – 2.15 (m, 1H), 2.05 (s, 3H), 2.04 – 1.86 (m, 3H), 1.68 (s, 3H), 1.67 – 1.59 (m, 1H), 1.15 (s, 3H), 1.10 (s, 3H), 1.05 (d, *J* = 6.9 Hz, 3H), 0.95 (d, *J* = 7.0 Hz, 1H), 0.03 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 203.0, 172.4, 142.9, 136.4, 128.6, 119.1, 78.3, 73.7, 64.5, 53.0, 41.8, 40.6, 35.6, 31.7, 30.7, 28.6, 24.3, 23.6, 22.8, 21.2, 18.9, 15.6, 1.4; HRMS (ESI$^+$) *m/z* calcd for $C_{25}H_{38}O_5SiNa$ (M+Na)$^+$: 469.2386, found: 469.2380; IR (neat) *ν* 3431, 2956, 1728, 1642, 1375, 1250, 1106, 1085, 991, 842, 736 cm^{-1}

Preparation of (1aR,1bS,4aR,7aS,7bR,8R,9aS)-3-formyl-7b-hydroxy-1,1,8-trimethyl-6-methylene-5-oxo-4a-((trimethylsilyl)oxy)-1,1a,1b,4,4a,5,6,7,7a,7b,8,9-dodecahydro-9aH-cyclopropa[3,4]benzo[1,2-e]azulen-9a-yl acetate (71). To a stirred solution of ketone **SI-25** (7.2 mg, 0.016 mmol, 1.00 equiv) in benzene (6 mL) was added selenium dioxide (8.9 mg, 0.08 mmol, 5.00 equiv). The yellow solution was stirred at 80 °C (oil bath) for 30 min. Then the mixture was concentrated to dryness and the crude product was purified by flash chromatography (petroleum ether/ ethyl acetate 5:1→2:1) to give aldehyde **71** (6.1 mg, 0.013 mmol, 81%) as a colorless foam. *Rf* 0.12 (silica gel, 5:1 petroleum ether/ ethyl acetate, UV, purple, *p*-anisaldehyde); ^1H NMR (400 MHz, $CDCl_3$) δ 9.42 (s, 1H), 6.74 (dd, *J* = 6.5, 2.1 Hz, 1H), 6.08 (s, 1H), 5.43 (s, 1H), 3.58 (d, *J* = 17.1 Hz, 1H), 2.83 – 2.66 (m, 2H), 2.48 (t, *J* = 6.5 Hz, 1H), 2.36 – 2.16 (m, 2H), 2.09 (s, 3H), 1.95 (dd, *J* = 15.9, 7.9 Hz, 1H), 1.85 (dd, *J* = 12.0, 7.7 Hz, 1H), 1.69 (dd, *J* = 15.9, 5.6 Hz, 1H), 1.20 (s, 3H), 1.17 (d, *J* = 7.2 Hz, 1H), 1.10 (s, 3H), 1.07 (d, *J* = 6.9 Hz, 3H), 0.05 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 201.8, 192.1, 172.4, 157.9, 142.3, 141.8, 119.8, 77.8, 74.7, 63.9, 52.6, 42.6, 35.2, 31.5, 31.1, 30.5, 28.8, 23.8, 22.7, 21.3, 18.8, 15.5, 1.3; HRMS (ESI$^+$) *m/z* calcd for $C_{25}H_{36}O_6SiNa$ (M+Na)$^+$: 483.2179, found: 483.2189; IR (neat) *ν* 3400, 2957, 2921, 2850, 1730, 1684, 1370, 1249, 1072, 976, 845 cm^{-1}.

Preparation of 12-deoxyphorbaldehyde-13-acetate (72). A flame-dried 10 mL vial was charged with **71** (12 mg, 0.026 mmol, 1.00 equiv) and $RhCl_3{\cdot}3H_2O$ (2.1 mg, 7.8 µmol, 0.30 equiv), EtOH (3 mL) at room temperature. The reaction mixture was heated to 100 °C (oil bath) and stirred for 30 min. After being cooled to room temperature, the reaction mixture was filtrated through a short pad of Celite with CH_2Cl_2, the mixture was concentrated to dryness and the crude product was purified by preparative thin layer chromatography (2:1 CH_2Cl_2/ Et_2O) to yield 12-deoxyphorbaldehyde-13-acetate **72** (5.3 mg, 0.014 mmol, 52%) as a colorless foam. *Rf* 0.42 (silica gel, 2:1 CH_2Cl_2/ Et_2O, UV, dark blue, *p*-anisaldehyde); ^1H NMR (600 MHz, $CDCl_3$) δ 9.43 (s, 1H), 7.55 (s, 1H), 6.71 (dd, *J* = 5.6, 1.8 Hz, 1H), 5.65 (s, 1H), 3.37 (t, *J* = 5.3 Hz, 1H), 3.08 (s, 1H), 2.88 (d, *J* = 19.5 Hz, 1H), 2.44 (d, *J* = 19.5 Hz, 1H), 2.15 – 2.07 (m, 1H), 2.07 (s, 3H), 2.06 – 1.99 (m, 1H), 1.78 (d, *J* = 1.4 Hz, 3H), 1.60 (dd, *J* = 14.7, 11.2 Hz, 1H), 1.24 (s, 3H), 1.08 (s, 3H), 1.02 (d, *J* = 5.3 Hz, 1H), 0.90 (d, *J* = 6.5 Hz, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 208.2, 193.7, 173.4, 160.4, 158.1, 142.8, 133.4, 76.7, 72.8, 63.2, 55.7, 41.4, 36.5, 34.5, 31.9, 31.6, 23.1, 22.9, 21.2, 18.5, 15.2, 10.1; HRMS (ESI$^+$) *m/z* calcd for $C_{22}H_{28}O_6Na$

(M+Na)$^+$: 411.1784, found: 411.1778; IR (neat) ν 3396, 2927, 2874, 1712, 1630, 1379, 1262, 1193, 1014, 911, 736 cm^{-1}.

Preparation of prostratin (1). A flame-dried 10 mL vial was charged with **72** (3.7 mg, 9.5 µmol, 1.00 equiv) and MeOH (2 mL). The reaction flask was cooled to –50 °C, $NaBH_4$ (0.4 mg, 10.5 µmol, 1.10 equiv) was added slowly. Upon complete consumption of starting material (ca 15 min), the reaction mixture was quenched by the addition of 100 µL H_2O. Then the mixture was concentrated to dryness and the crude product was purified by preparative thin layer chromatography (1:1 CH_2Cl_2/ Et_2O, twice) to yield prostratin **1** (3.2 mg, 8.2 µmol, 86%) as a colorless film. *Rf* 0.13 (silica gel, 1:1 CH_2Cl_2/ Et_2O, twice, UV, dark blue, *p*-anisaldehyde); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.58 (s, 1H), 5.68 (d, *J* = 5.1 Hz, 1H), 5.38 (s, 1H), 4.03 (d, *J* = 12.8 Hz, 1H), 3.98 (d, *J* = 12.8 Hz, 1H), 3.26 (s, 1H), 2.99 (t, *J* = 5.1 Hz, 1H), 2.53 (d, *J* = 19.0 Hz, 1H), 2.48 (d, *J* = 19.0 Hz, 1H), 2.31 (s, 1H), 2.14 – 2.02 (m, 1H), 2.07 (m, 3H), 2.03 – 1.92 (m, 1H), 1.83 – 1.71 (m, 3H), 1.57 (dd, *J* = 14.7, 11.3 Hz, 1H), 1.19 (s, 3H), 1.06 (s, 3H), 0.88 (d, *J* = 6.5 Hz, 3H), 0.85 (d, *J* = 5.3 Hz, 1H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 209.1, 173.2, 161.2, 139.9, 132.8, 130.2, 76.0, 73.7, 68.2, 63.6, 55.7, 39.1, 38.6, 36.2, 32.4, 31.7, 23.3, 22.7, 21.2, 18.5, 15.3, 10.1; ^{1}H NMR (600 MHz, C_6D_6) δ 7.48 (s, 1H), 5.69 (d, *J* = 5.3 Hz, 1H), 3.74 (d, *J* = 12.8 Hz, 1H), 3.69 (d, *J* = 12.8 Hz, 1H), 3.47 (s, 1H), 3.12 (t, *J* = 4.4 Hz, 1H), 2.46 (d, *J* = 19.0 Hz, 1H), 2.38 (d, *J* = 19.0 Hz, 1H), 2.11 – 2.07 (m, 1H), 2.02 (dd, *J* = 14.5, 6.9 Hz, 1H), 1.72 (dd, *J* = 14.5, 11.4 Hz, 1H), 1.60 – 1.59 (m, 3H), 1.55 (s, 3H), 1.10 (s, 3H), 1.01 (s, 3H), 0.98 (d, *J* = 6.4 Hz, 3H), 0.88 (d, *J* = 5.3 Hz, 1H); ^{13}C{^{1}H} NMR (150 MHz, C_6D_6) δ 208.7, 172.9, 160.9, 140.7, 133.1, 130.0, 76.3, 74.1, 68.2, 64.0, 56.4, 39.7, 39.0, 36.8, 33.1, 32.5, 23.5, 22.9, 20.8, 19.1, 15.6, 10.2; HRMS (ESI$^+$) *m/z* calcd for $C_{22}H_{30}O_6Na$ (M+Na)$^+$: 413.1940, found: 413.1934; IR (neat) ν 3379, 2985, 2923, 2874, 1705, 1628, 1378, 1329, 1262, 1016, 911, 735 cm^{-1}.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: xxx.

List of SI-compounds

Tables for optimization of key reactions

DFT calculation details

^{1}H NMR and ^{13}C NMR spectra for all new compounds (PDF)

The X-ray crystallographic data of compds. **23, 27, 29, 41, 47, 52, 53, 57, 65, 68, 70, SI-9, SI-11, SI-21** (CIF)

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Notes

A pending patent has been applied for by Xi'an Jiaotong University on the synthetic route of prostratin.

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