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Synthetic Studies on Dicyclopenta[a,d]cyclooctane Terpenoids: Construction of the Core Structure of Fusicoccins and Ophiobolins on the Route Involving a Wagner-Meerwein Rearrangement

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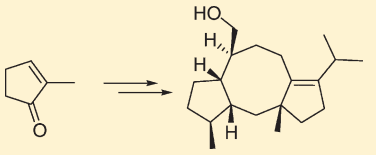
Supporting Information

ABSTRACT: The total diastereoselective synthesis of dicyclopenta[a,d]cyclooctane core skeleton of tricyclic terpenoids, fusicoccins, and ophiobolins is reported. The synthesis commences from 2-methylcyclopent-2-en-1-one and leads first to the easily accessible intermediary cyclopenta[8]annulene **18**. The subsequent steps include two key transformations: shifting the angular methyl group from the angular to the neighboring position employing a carbocationic rearrangement (**26** → **28**) and construction of a quaternary stereogenic center via alkylation of α-methylcyclooctanone intermediate (**38** → **48**). In the context of the latter transformation, a series of model experiments on alkylation of 2-methylcyclooctan-1-one were conducted. The stereochemical assignments were verified by X-ray analyses of the key structures **39** and **50**.

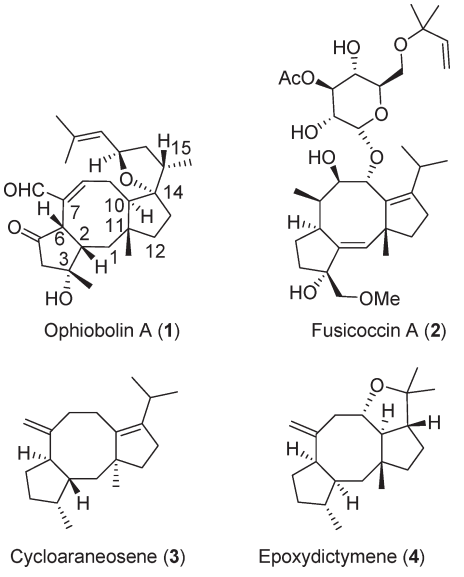


INTRODUCTION

Terpenoids with dicyclopenta[a,d]cyclooctane (5-8-5) carbon skeleton are fairly broadly distributed in Nature. Sesterterpenoid, ophiobolin A (**1**), and its congeners were first isolated from a plant pathogenic fungus, *Ophiobolus miyabeanus*, and reported in 1965.[1−3] Somewhat later a diterpenoid of the same tricyclic core, fusicoccin A (**2**), was obtained from a culture of fungus, *Fusicoccum amygdali*, responsible for a wilting disease of peach and almond trees in Southern Europe.[4,5] Since then several other 5-8-5 di- and sester-terpenoids were isolated from various fungi,[6−14] insect wax,[15,16] brown alga,[17] liverworts,[18−22] and plants.[23−27] Compounds **1** and **2** are characterized by the presence of multiple oxygen-containing functional groups. However, hydrocarbon terpenes such as cycloaraneosene[28] (**3**) or those bearing a scarce oxygen functions, as epoxydictymene[17] (**4**) were also obtained from natural sources (see Scheme 1).

Several of 5-8-5 terpenoids exhibit phytotoxic activity, e.g. **1** and **2**, as well as those isolated from *Drechslera maydis*, the casual agent of Southern corn leaf blight or *Drechslera sorogica*, the casual agent of leaf spot on Johnson grass.[7,8] A nematocidal activity of potential use in the treatment of human parasitic diseases has been revealed for ophiobolanes generated by *Aspergillus ustus* and *Cochliobolus heterostropus*[10,11] whereas sesterterpenoids from the marine fungus, *Emericelle variecolor*, showed cytotoxic activity.[13] The fusicoccane terpenoids exhibit a range of biological activities resulting from their interactions with 14−3−3 proteins.[29] Fusicoserpenol, from Madagascar medicinal plant *Hypotestes serepenus*, shows a significant antifungal activity,[27] whereas periconicins, produced by an endophytic fungus *Periconia* sp., an antibacterial activity.[14] An attention has been recently focused on cotylenins, metabolites of the fungus *Cladosporium* sp., endowed with a potent cell-differentiation and antitumor activities.[30−32]

Scheme 1. Structures of Representative Ophiobolanes and Fusicoccanes



The exuberant molecular architecture and a broad range of biological activities of fusicoccanes and ophiobolanes stimulated an interest in developing a generalized methodology for the construction of 5-8-5 ring system[33−60] as well as interest in a total synthetic approach to important representatives of these natural products: albolic acid,[61−63] cycloaraneosene,[64−67] ceroplastol,[63] (+)-ceroplastol I,[68] ceroplastol II,[61−63] (-)-cotylenol,[69,70]

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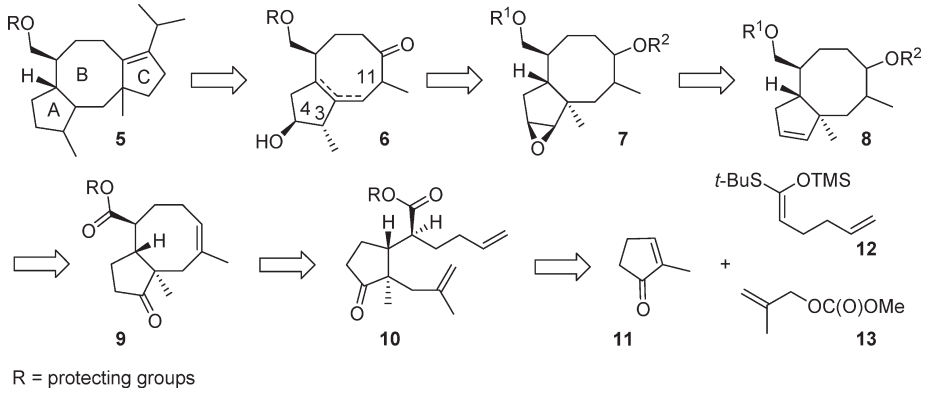
Scheme 2. Retrosynthetic Analysis of the Core Structure 5



(+)-epoxydictymene,[71−75] plagiospirolides A and B,[76,77] (+)-fusicoauritone,[78] fusicogigantones,[79,80] (+)-ophiobolin C.[81,82] Syntheses of some related interesting structures have also been published.[83−88] The specific methodology for the construction of medium-sized rings has been extensively reviewed.[89−93]

We now report a synthesis of a core tricyclic structure of fusicoccanes and ophiobolanes following the synthetic route starting from 2-methylcyclopent-2-en-1-one. The synthesis is based upon the carbocationic rearrangement that shifts a methyl group from an angular to an adjacent position in the cyclopentacyclooctane core, and an annulation of 2-methylcyclooctan-1-one derivatives.[94,95]

RESULTS AND DISCUSSION

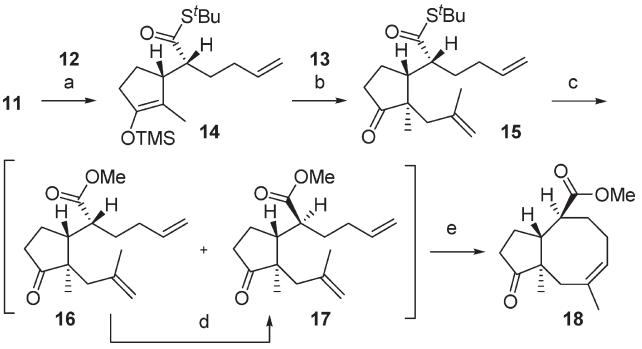
In the retrosynthetic analysis we have elected to approach the 5-8-5 ring structure **5** (Scheme 2) through annulation of α-methyl ketone intermediate **6**. Surprisingly, there are no reports in the literature on annulation of 2-methylcyclooctanones although it has been reported that 2-methylcyclooctanone may be transformed into a "thermodynamic" enolate with bromomagnesium diisopropylamide (BMDA).[96−98] Should that specific feature of methyl cyclooctanone be easily accessible, the attachment of suitable carbon atom unit to C-11 in **6** and closing of ring C would be reduced to a set of routine operations.

The intermediate **6** would be prepared from **7** through a carbocationic rearrangement triggered by an opening of the epoxide ring. The rearrangement was thought to provide a reliable means for a stereoselective insertion of a methyl group at C-3 and for providing a functional group at C-4 that could serve as a handle for further transformations. A plethora of examples of an angular methyl group shift in carbocationic rearrangements of terpenoids and steroids has been reported in the literature.[99−103] However, no direct analogy involving an eight-membered ring system could be found.

The epoxide **7** would be prepared from ketone **9** via ene **8**. The intermediate **9** would be available through the ring closing metathesis reaction of 1,8-diene **10**. Straightforward preparation of **10** from 2-methylcyclopent-2-en-1-one (**11**), ketene acetal **12** (generated from *S*-*tert*-butyl hex-5-enethioate) and methyl isopropenyl carbonate **13** have recently been reported.[104]

Considering the stereochemical aspects of the synthesis, we assume the intermediate **9** would be accessible in a fully stereocontrolled fashion. It was anticipated that the epoxidation of **8** and the following rearrangement would secure the required diastereoselectivity of formation of **6**. The stereochemistry of generation of the subsequent stereogenic centers within the eight-membered ring remains largely to be explored.

Scheme 3. The Synthesis of the Key Bicyclic Intermediate 18



[a] Key: (a) TMSOTf, cat., CH_2Cl_2, −78 °C and then pyridinemethanol (ref 104); (b) $Pd(OAc)_2$-1,4-bis(diphenylphosphine)butane, cat, THF, 86% yield in two steps; (c) MeOK-MeOH, reflux, chromatography; (d) total yield with recycling, 60%; (e) Grubbs' second generation cat. (3 mol %), CH_2Cl_2, reflux, 96−98%.

The procedure for the preparation of intermediate **9** from **11**, **12**, and **13** has been reported earlier from our laboratory.[104] It involves a tandem Mukaiyama−Michael addition−Tsuji alkylation to afford *tert*-butylthioester **15** and methanolysis of this intermediate as illustrated in Scheme 3. The methanolysis was accompanied by epimerization at the stereogenic center in the α-position to the carbonyl group to give a mixture of methyl esters, **16** and **17** in a ratio of ca. 1:1. For the purpose of the present work, recycling of the epimer **16** and a large-scale metathesis procedure of **17** using the Grubbs' second generation catalyst[105] were developed. These modifications allowed preparation of **18** in a 60% overall yield from **15** (see: Experimental Section).

The oxo group in **18** (Scheme 4) was protected as ethylene ketal in the usual way and the derivative **19** was reduced with lithium aluminum hydride to afford **20** (94% yield in two steps). The double bond in **20** was subjected to a hydroboration−oxidation procedure[106] to afford isomerically pure diol (83% yield). The structure **21** was assigned to this product on the grounds of

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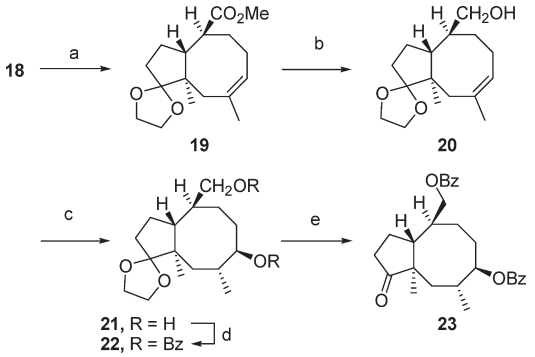
Scheme 4. Transformation of 18 into 23



[a] Key: (a) $(CH_2OH)_2$, *p*-TSA, benzene, reflux, 96%; (b) $LiAlH_4$, THF, reflux, 98%; (c) 1. $BH_3 \cdot THF$, 2. H_2O_2, NaOH, 83% or 1. TBSCl, imidazole; 2. $BH_3 \cdot THF$ and then H_2O_2, NaOH, 3. $Bu_4NF \cdot 3H_2O$, 64% in three steps, (d) BzCl, DMAP, py, 0 °C → rt, 98%; (e) *p*-TSA, aq. dioxane, 40 °C, 98%.

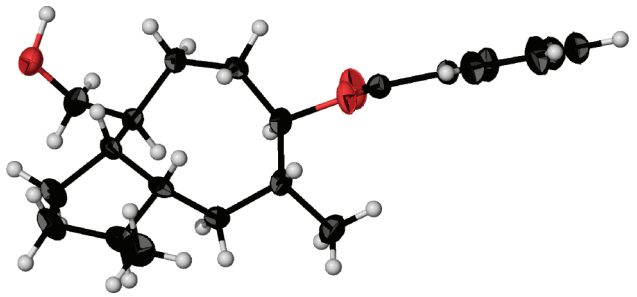
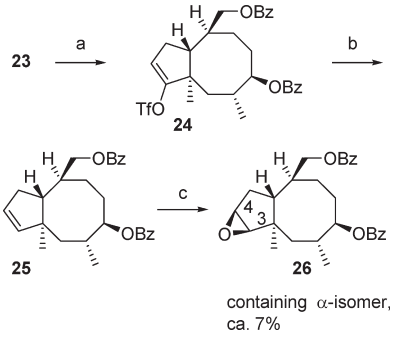


Figure 1. ORTEP diagram of the X-ray structure of **39**.

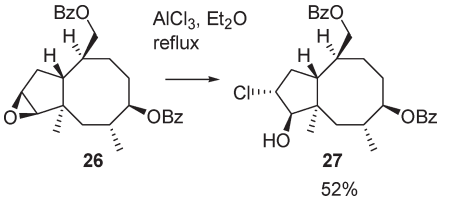
Scheme 5. Synthesis of Dibenzoyloxy Epoxide 26



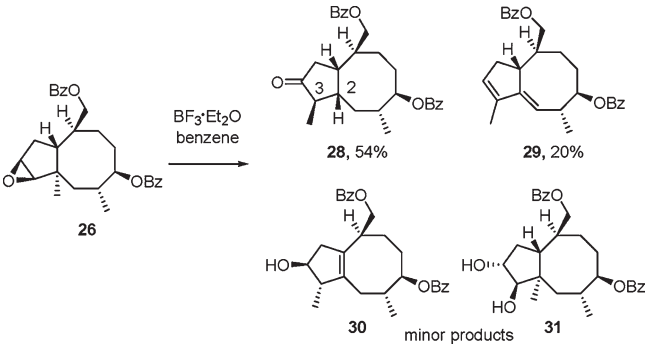
[a] Key: (a) Tf_2O, 2,6-di-*tert*-butyl-3-methylpyridine, DCE, 73 °C, 95%; (b) Bu_3SnH, $Pd(PPh_3)_4$, LiCl, THF, rt, 83%; (c) *m*-CPBA, CH_2Cl_2, 98%.

the reagent approach from the less hindered face of the eight-membered ring (opposite to the methyl group) and has been later confirmed by an X-ray analysis of a more advanced intermediate in the synthesis, **39** (see Scheme 9 and Figure 1). The same product **21** was obtained when the hydroxy group in **20** was protected as a TBS-derivative, and then hydroboration−oxidation was executed, followed by the removal of the protective group (72% overall yield). The diol **21** was transformed into dibenzoate **22** and then into dibenzoyloxy ketone **23.**

Scheme 6. An Attempted Rearrangement of Epoxide 26 with $AlCl_3$



Scheme 7. BF_3-Induced Rearrangement of Epoxide 26



Treatment of **23** (Scheme 5) with triflic anhydride (1.3 equiv) and 2,6-di-*tert*-butyl-3-methylpyridine[107,108] (1.5 equiv) in anhydrous dichloroethane at 68−73 °C for 1.5 h gave (after chromatography) enol triflate **24** along with some unchanged **23** (95% yield based on the consumed material). The triflate **24** was subjected to the $Pd(PPh_3)_4$-catalyzed coupling with tributylstannane in the presence of lithium chloride, following the Scott and Stille procedure[97,109] to afford **25** in 83% yield.

The ene **25** was oxidized with *m*-CPBA in dichloromethane at room temperature to give mixture of **26** and its more congested 3α,4α-epimer (98% yield, the epimer ratio of ca. 12:1, by ^1H NMR), which was found inseparable by chromatography. This material was used for further experiments.

Epoxide **26** (Scheme 6) turned out to be resistant to the action of mild Lewis acids, as $ZnCl_2$ or $Ti(Oi\text{-}Pr)_4$ in diethyl ether. At reflux, anhydrous $AlCl_3$ in diethyl ether afforded a mixture of products in which one component predominated. This product was isolated by chromatography and its structure was tentatively assigned by HRMS, ^1H, and ^{13}C NMR as the chlorohydrin **27** (52% yield, the alternative regioselectivity of the epoxide ring-opening could not be excluded).

Treatment of **26** (Scheme 7) with $BF_3 \cdot Et_2O$ in benzene, at room temperature, afforded a mixture of at least four products. Flash chromatography of the crude postreaction mixture allowed to isolate two products in 54 and 20% yields (both oily) and a mixture of more polar minor products that were collected for a further purification.

The major product showed (HR MS) the same elemental composition as the substrate. Its IR spectra, unexpectedly, indicated the presence of a carbonyl group in a five-membered ring (ν 1739 cm^{-1}). The ^1H NMR indicated the lack of an angular methyl group and the presence of the $CHCH_3$ moiety (δ 1.17 ppm, d, J = 7.5 Hz). The ^{13}C NMR spectra showed interalia signal at δ 219.9 ppm typical for a ketone carbonyl group. These spectral data were roughly supportive of the

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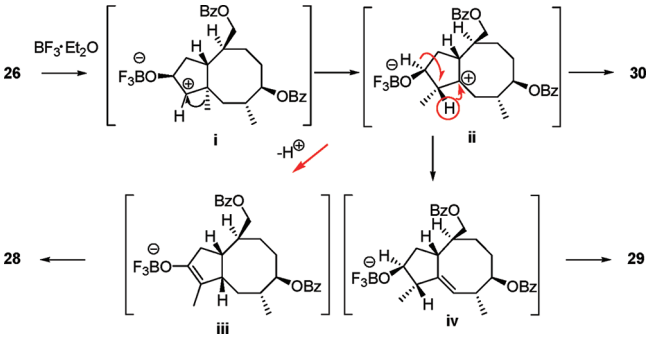
Scheme 8. Proposed Mechanism for Rearrangement of Epoxide 26



structure **28**. The stereochemical details of this product could be clarified only by the X-ray analysis of the already mentioned crystalline derivative **39** (Scheme 9). As it follows from the ORTEP diagram showed in Figure 1, the protons at the ring junction positions (C-2) and the methyl group at C-3 are in a cis-relationship.

The ^{1}H NMR spectrum of the second major product (20% yield) showed the presence of two vinylic protons and a methyl group located at a double bond (δ 1.77 ppm, br s, 3H). Structure **29** was assigned for this product on the grounds of the HR MS, ^{1}H, and ^{13}C NMR.

From a mixture of minor side products, collected from several experiments, two additional compounds were isolated using semipreparative HPLC. For the faster eluting compound, the structure **30** was assigned from HR MS, ^{1}H, and ^{13}C NMR spectra. The second product was identified as the diol **31.** The latter was apparently generated by the opening of an epoxide ring in substrate **26** with a residual water.

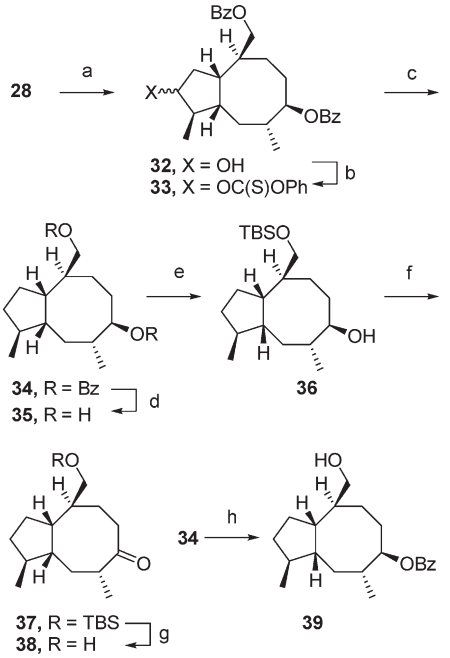
In practical terms, the rearrangement was carried out using 50−100 mg portions of **26**. The combined product of several runs was purified by chromatography to afford **28** in a 48−54% yield. An increase of the "per run" amount of substrate **26** was invariably resulting in the decreased yield of **28**.

The mechanistic route to the major product involves epoxide ring-opening to generate intermediate **i** (Scheme 8), followed by migration of the angular methyl group to form **ii**. A 1,2-hydride ion shift and loss of a proton from **ii** afford enol **iii** and after protonation ketone **28**. The carbocation **ii** loses a proton to give **30**. Alternatively, the intermediate **iv** is formed, which gives a rise to the diene **29**. It should be noted that the methyl group in the position α to the oxo group in **28** is located in the sterically less-congested environment (the β-face).

The major rearrangement product **28** was endowed with the carbon skeleton of the targeted natural products, although the initially foreseen rearrangement pathway materialized only as a minor constituent of the mixture (**30**). The selective formation of two new stereogenic centers in **28** was an important feature of the process. In the event, it was chosen to remove the oxygen function in the five-membered ring of **28** and proceed with an annulation of the eight-membered ring.

The oxo group in **28** was reduced with sodium borohydride in a mixture of THF and methanol. The homogeneous alcohol **32** (Scheme 9) isolated in a 90% yield was converted to its *O*-phenyl thiocarbonyl derivative **33** and the latter was treated with tri-*n*-butyltin hydride in the presence of catalytic amount of AIBN, in refluxing benzene, in accordance with the Barton−McCombie

Scheme 9. Transformation of 28 into 37 and 38 and Preparation of a Crystalline Derivative (39) for X-ray Analysis



[a] Key: (a) $NaBH_4$, MeOH-THF, 90%; (b) PhOC(S)Cl, py, CH_2Cl_2, 85%; (c) *n*-Bu_3SnH, AIBN (cat.), benzene, reflux, 83%; (d) KOH, MeOH, rt, 16 h, 98%; (e) TBSCl, imidazole, MeCN, 0 °C → rt, 90%; (f) Dess-Martin periodinane, CH_2Cl_2, 92%; (g) $Bu_4NF \cdot 3H_2O$, THF, 98%; (h) MeONa, MeOH, rt, 85%.

procedure.[110] The deoxygenation product **34** was obtained in 71% yield (from **32**).

Simple and high-yield transformations were developed to transform dibenzoate **34** into the required cyclooctanone derivatives, that is, compounds **37** and **38**. Thus, alkaline hydrolysis provided diol **35** that was regioselectively silylated at the primary hydroxyl group. The derivative **36** was oxidized with the Dess−Martin periodinane into ketone **37**. Finally, the protective group in the latter compound was removed to provide the corresponding free alcohol **38**. In search for a crystalline derivative, suitable for X-ray analysis, the monobenzoate **39** was prepared as shown in Scheme 9. The ORTEP diagram of the structure **39** is presented in Figure 1. The key features of this structure have already been discussed.

With α-methyl ketones **37** and **38** in hand, the stage was set for a quaternary stereogenic center construction. Kraft and Holton[96] have shown that treatment of 2-methylcyclooctanone with BMDA leads to the thermodynamic enolate that can be trapped as a trimethylsilyl derivative. BMDA has also been used[97,98] to transform the 2-methylcyclohexanone into its thermodynamic enolate and then into respective triflate or trimethylsilyl enol ether in moderate yield. Disappointingly, our preliminary attempts to transform either **37** or **38** into the corresponding silyl enol ethers failed. To resolve the problem model experiments appeared necessary.

The compound 2-methylcyclooctanone (**40**) on treatment with BMDA and the TMSCl under the reported conditions[96,97] afforded the thermodynamic enolate (**41**, Scheme 10). No isomeric enolate could be detected (^{1}H NMR, GC). However, the product contained a considerable amount of the unreacted

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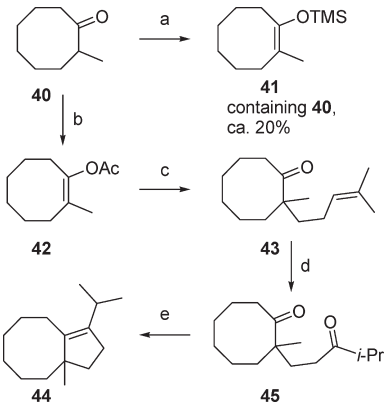
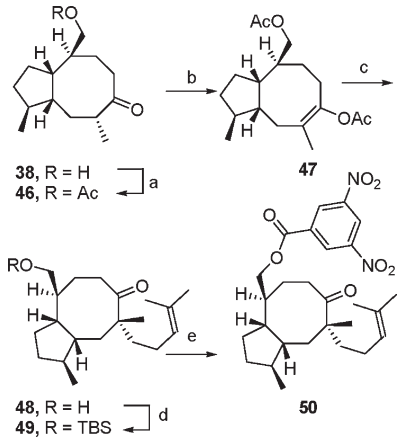
Scheme 10. Model Experiments on Annulation of 2-Methylcyclooctan-1-one (40)



[a] Key: (a) *i*-Pr_2NMgBr (BMDA), TMSCl, Et_3N, HMPA, Et_2O; (b) Ac_2O, $HClO_4$, CCl_4, rt, 92%; (c) 1. MeLi, DME, 0 °C, 2. 5-iodo-2-methylpent-2-ene, HMPA, 72%; (d) 1. BH_3·THF, 0 °C 2. H_2O_2, NaOH, 3. Dess-Martin periodinane, 91% in three steps; (e) $TiCl_3$, Zn−Cu alloy, DME, reflux, 95% yield, 86% pure by GC.

Scheme 11. Alkylation of Cyclooctanone via the Enolacetate Derivative



[a] Key: (a) Ac_2O, py, rt, 95%; (b) Ac_2O, $HClO_4$, 5 mol %, CCl_4, 0 °C → rt, 92%; (c) 1. MeLi, DME, 0 °C, 2. 5-iodo-2-methylpent-2-ene, HMPA, rt, 46%; (d) TBSCl, imidazole, MeCN, 89%. (e) (from **48**) 3,5-dinitrobenzoyl chloride, py, 0 °C → rt, 92%.

starting ketone. Upon the use of 1.25 equiv of the base, 3 equiv of TMSCl, 3.5 equiv of Et_3N, and 0.4 equiv HMPA, the ratio of the ketone **40** to the enol derivative **41** was found as 34:66 (by GC). A further increase of base amount to 6 equiv along with a proportional increase of the remaining reaction components led to a mixture of **40** and **41** in a ratio of 19:81. No further increase of the enolate content could be achieved by either increasing an amount of the base or by varying other reaction conditions.

In further experiments on generating a thermodynamic enolate we resorted to the classic House procedure.[111] Ketone **40** was treated with acetic anhydride in the presence of catalytic amount of perchloric acid in carbon tetrachloride. The product **42** isolated in a 92% yield (after chromatography) was found

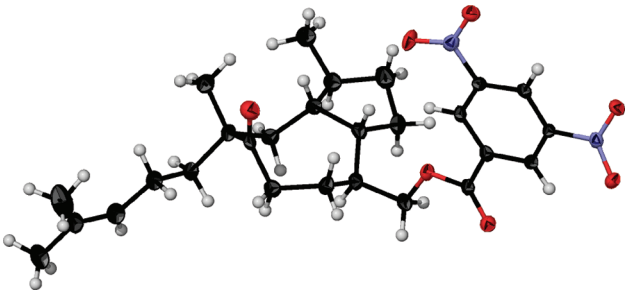


Figure 2. ORTEP diagram of the X-ray structure of 3,5-dinitrobenzoate **50**.

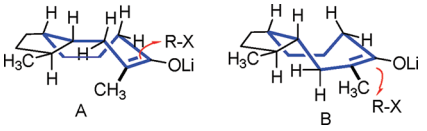


Figure 3. Stereochemistry of alkylation of enolate generated from **47** (partial structure).

stable enough to be stored in a refrigerator for a few weeks without a notable decomposition.

Next, the enol acetate **42** was converted into lithium enolate with methyllithium in dimethoxyethane[111] and the enolate was allowed to react with 5-iodo-2-methylpent-2-ene.[112−114] The alkylation product **43** was obtained in a 72% yield. The latter was transformed into the dione **45** using the hydroboration−oxidation procedure. To conclude the model experiments, the diketone **45** was subjected to the McMurry coupling[115] to afford the 5−8 bicycle **44** in an excellent yield.

With the experience gained on model experiments, we returned to the main course of synthesis. The hydroxy ketone **38** was transformed into acetoxy ketone **46** under mild conditions (Scheme 11). The latter product was then treated with acetic anhydride and perchloric acid in carbon tetrachloride to afford enol acetate **47** in 88% yield from **46**. Interestingly, attempted direct conversion of **38** into **47** resulted in a mixture of products, presumably resulting from transannular interactions. The enol acetate **47** was treated with methyllithium in DME (4 mol equiv) at 0 °C to generate intermediate dianion that was quenched with 5-iodo-2-methylpent-2-ene (5 equiv) and HMPA. The product was purified by chromatography to afford the hydroxy ketone **48** in 46% yield. The structure of **48** was elucidated by converting it to a crystalline 3,5-dinitrobenzoate **50** and a single crystal X-ray analysis (the ORTEP diagram is presented in Figure 2). It was evident that alkylation of lithium enolate generated from **47** occurred on the "internal" convex side of the bicyclic system (the α-face of the molecule). For the further transformations, the hydroxy group in **48** was protected as the *O*-tert-butyldimethylsilyl derivative **49**.

Analysis of molecular models of lithium enolate generated from **47** indicated that conformational flexibility in the region of C-2−C-1−C-11 is restrained by both the fused five-membered ring and by the double bond. The following two conformations could be distinguished: **A** (Figure 3, the substituent at C-7 is omitted for the sake of clarity), the β-hydrogen atom at C-1 is oriented pseudoaxially, in parallel to the angular proton, and **B**, the β-hydrogen atom at C-1 is oriented pseudoequatorially. The reagent approach from the β-side (outer convex) appears to be

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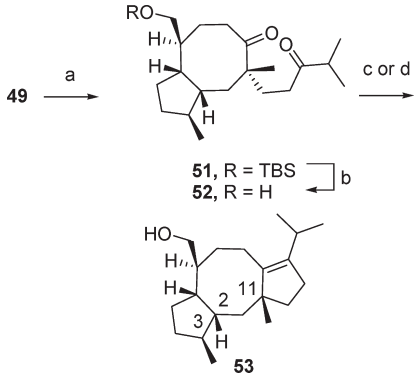
Scheme 12. Completion of the 5-8-5 Ring System Construction



[a] Key: (a) 1. $BH_3 \cdot THF$, 0 °C → rt, 2. H_2O_2, NaOH, 3. Dess-Martin periodinane, 87% in three steps; (b) $Bu_4NF \cdot 3H_2O$, THF, 84%; (c) 1. $TiCl_3$, Zn/Cu, DME, reflux, 2. $Bu_4NF \cdot 3H_2O$, THF, 27%; (d) $TiCl_3$, Zn/Cu, DME, reflux, 16%.

preferred for the conformer A while the opposite preference may be deducted for the conformer B. The observed selectivity of alkylation was not apparent from the molecular model.

To complete the construction of the tricyclic structure, the *O*-tert-butyldimethylsilyl derivative **49** was transformed into 1,5-diketone **51** (Scheme 12). The latter was subjected to the titanium chloride induced coupling followed by desilylation to afford **53** (27% yield). Alternatively, the hydroxy group protection was removed first and the resulted hydroxy diketone **52** was cyclized to provide **53** in 16% yield. The low yield of the product obtained on each of those routes reflects likely the difficulty in recovering of organic material from the heterogeneous postreaction mixture at a small scale.

In conclusion, the synthesis of a tricyclic 5-8-5 ring structure, that is, compound **53**, related to fusicoccins and ophiobolins, has been accomplished starting from 2-methylcyclopent-2-en-1-one. Two of five stereogenic centers in **53** were generated in the Mukaiyama−Michael addition and the epimerization steps. On the route from the key cyclopenta-cyclooctane derivative **18** to the final product **53**, three stereogenic centers were created or modified. The stereocenter at the ring junction (C-2) was generated in the rearrangement involving a rebound hydrogen ion shift. The stereogenic center, located at five-membered ring (at C-3) was defined by the direction of protonation of enolate generated in the rearrangement process, likely under a thermodynamic control. The stereocenter located at the eight-membered ring (at C-11) reflects the stereoselectivity of alkylation of enolate prepared from methyl ketone **37**.

EXPERIMENTAL SECTION

Melting points were determined on a hot-stage apparatus and are uncorrected. NMR spectra were recorded in $CDCl_3$ solutions (if not otherwise indicated) for ^1H at 200 MHz/^{13}C at 50 MHz, ^1H at 400 MHz/^{13}C at 100 MHz, and ^1H at 500 MHz/^{13}C at 125 MHz. Chemical shifts are quoted on the δ scale taking the solvent signal as the internal standard ($CHCl_3$, ^1H NMR 7.26 ppm; $CDCl_3$, ^{13}C NMR 77.00 ppm). High-resolution mass spectra (HRMS) were taken applying electron ionization (EI) at 70 eV or liquid secondary ion mass spectroscopy (LSIMS), or electrospray ionization (ESI). HPLC analyses were performed with an analytical column (25/0.46 cm), Nucleosil 50/5 μm, and a variable UV SPD−6A detector at 254 nm with a flow rate of 1 mL/min. Preparative HPLC chromatography was performed on the same apparatus using two columns connected in series (Nucleosil 50/7 μm, 25/2.0 cm, 56 g of gel), UV detector at 254 nm, flow rate 15 mL/min. Column chromatography was performed on Merck silica gel 60, 230−400 mesh (deactivated with 2% Et_3N in hexanes, where indicated) and TLC on aluminum sheets, Merck 60F 254. Anhydrous solvents were obtained by distillation from benzophenone ketyl (THF), $LiAlH_4$ (diethyl ether), or calcium hydride (dichloromethane). Triethylamine and diisopropylamine was distilled over calcium hydride. Air-sensitive reactions were performed in flame-dried glassware under argon. Organic extracts were dried over anhydrous Na_2SO_4 (if other not indicated) and solvents were evaporated using a rotary evaporator. Tris(dibenzylideneacetone)dipalladium, palladium(II) acetate, 1,2-bis-(diphenylphosphino)-ethane, and 1,4-bis-(diphenylphosphino)-butane as well as Grubbs first and second generation catalysts were purchased from Aldrich. $BF_3 \cdot Et_2O$ was redistilled directly before use; other reagents were used as they were purchased. Elemental analyses were preformed in our analytical laboratory.

Methyl (2*S)-2[(1*R**,2*R**)-2-methyl-2-(2-methylprop-2-enyl)-3-oxocyclopentyl]hex-5-enoate (17) and Methyl (2*R**)-2[(1*R**,2*R**)-2-methyl-2-(2-methylprop-2-enyl)-3-oxocyclopentyl]hex-5-enoate (16) (a Procedure Including the Recycling of 16)[104].** To a solution of MeOK in MeOH (prepared from potassium, 5.0 g, 128.2 mmol and MeOH, 40 mL), thioester[104] **15** (7.026 g, 20.9 mmol) in MeOH (20 mL) was added and the mixture was heated under reflux for 2.5 h. After cooling to rt, water (200 mL) was added and the mixture was extracted with toluene (3 × 50 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was evaporated. The residue was chromatographed on silica (200 g, 3% EtOAc/hexanes) to give consecutively **17** (2.64 g, 45%) and **16** (2.46 g, 40%). Routinely, a broad fraction of **17**, containing **16** ca. 10% by ^1H NMR, was collected and used further in the metathesis reaction. Pure **16** was recycled to the epimerization procedure: to a solution of MeOK (prepared from potassium, 7.71 g, 197.7 mmol and MeOH, 65 mL), **16** (7.86 g, 28.3 mmol) in MeOH (10 mL) was added and the mixture was heated under reflux. After 16 h, the mixture was cooled to rt, diluted with water (300 mL) and extracted with toluene (3 × 100 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was evaporated. The residue was chromatographed on silica (350 g, 3% EtOAc/hexanes) to give **17** (3.14 g, 40%, the total yield 60%) and **16** (2.98 g, 38%).

Methyl (3a*R,4*S**,9a*R**)-8,9a-dimethyl-1-oxo-2,3,3a,4,5,6,9,9a-octahydro-1*H*-cyclopenta[8]annulene-4-carboxylate (18) (a Procedure Using 17 Contaminated with 16).** To a solution of **17** (2.16 g, 7.75 mmol, containing **16**, ca. 10%) in ahydrous DCM (775 mL), Grubbs II cat.[105] (33.0 mg, 0.5 mol %) was added in one portion and the mixture was heated under reflux for 24 h (until the substrate was consumed, TLC 10% EtOAc/hexanes). The second portion of the same catalyst was then added (33.0 mg, 0.5 mol %) and heating was continued for subsequent 16 h. After cooling, the solvent was evaporated and the residue was chromatographed on silica (52 g, 5% EtOAc/hexanes) to give **18** (slightly yellow oil, 1.72 g, 89%), identical with a sample described previously.[104]

Essentially same results were obtained using Grubbs−Hoveyda catalyst[116,117] in the same molar ratio.

Methyl (3a*R,4*S**,9a*R**)-8,9a-dimethyl-2,3,3a,4,5,6,9,9a-octahydrospiro[cyclopenta[8]annulene-1,2′-[1,3]dioxolane]-4-carboxylate (19).** A mixture of **18** (3.502 g, 14.01 mmol), ethylene glycol (8.3 mL, 147.20 mmol), *p*-TSA (83.4 mg, 0.44 mmol), and benzene (100 mL) was heated under reflux for 16 h in a flask equipped with a Dean−Stark adapter for water separation. After cooling, the solution was washed with sat. aq $NaHCO_3$ (2 × 15 mL) and dried. The solvent was evaporated and the residue was chromatographed on silica gel (120 g, 5% EtOAc/hexanes) to give **19** (3.959 g, 96%). ^1H NMR

(200 MHz): 5.44−5.28 (m, 1H), 3.90 (s, 4H), 3.61 (s, 3H), 2.68−2.52 (m, 2H), 2.46−2.10 (m, 2H), 2.10−1.75 (m, 2H) overlapping 1.76 (br s, 3H), 1.75−1.50 (m, 6H), 0.90 (s, 3H). ^{13}C NMR (200 MHz): 176.4, 136.3, 124.5, 119.6, 65.4, 64.0, 51.0, 49.3, 44.3, 41.6, 35.0, 31.5, 31.3, 27.4, 24.0, 23.6, 15.5. HRMS (EI) calcd for $C_{17}H_{26}O_4$, 294.1831; found, 294.1824.

{(3a*R,4*S**,9a*R**)-8,9a-Dimethyl-2,3,3a,4,5,6,9,9a-octahydrospiro[cyclopenta [8]annulene-1,2′-[1,3]dioxolan]-4-yl}-methanol (20).** Ester **19** (3.952 g, 13.44 mmol) in THF (20 mL) was added dropwise to a suspension $LiAlH_4$ (306.5 mg, 8.06 mmol) in THF (50 mL) and the mixture was heated under reflux for 30 min. After cooling, the reagent excess was destroyed by careful addition of sat. aq Na_2SO_4 (ca. 8 mL) and then Et_2O (100 mL) was added. The solid was filtered off and the filtrate was washed with brine (2 × 30 mL) and dried ($MgSO_4$). The solvent was evaporated and the residue was chromatographed on silica gel (30% EtOAc/hexanes) to give **20** (3.504 g, 98%). ^{1}H NMR (200 MHz): 5.46−5.30 (m, 1H), 3.90 (s, 4H), 3.75−3.45 (m, 2H), 2.64−2.48 (m, 1H), 2.55 (d, *J* = 13.6 Hz, 1H), 2.42−1.90 (m, 3H), 1.90−1.20 (m, 7H) overlapping 1.75 (br s, 3H), 0.88 (s, 3H). ^{13}C NMR (50 MHz): 135.4, 125.0, 119.8, 65.9, 65.2, 63.8, 49.1, 44.8, 36.1, 35.7, 31.9, 30.9, 27.4, 24.3, 21.8, 15.9. HRMS (EI) calcd for $C_{16}H_{26}O_3$, 266.1875; found, 266.1882.

(3a*R,4*S**,7*R**,8*R**,9a*R**)-4-(Hydroxymethyl)-8,9a-dimethyldecahydrospiro[cyclopenta[8]annulene-1,2′-[1,3]dioksolan]-7-ol (21).** (a) BH_3·THF (1 M in THF, 21.1 mL, 21.10 mmol) was added to a solution of **20** (2.688 g, 10.10 mmol) in THF (30 mL) and stirred at 0 °C. The mixture was allowed to warm to rt and after 6 h cooled again to 0 °C. Ten percent aq NaOH (27.6 mL, 66.75 mmol) and H_2O_2 (30%, 10.0 mL, 88.2 mmol) were then added and stirring was continued for 16 h. The mixture was diluted with water (60 mL) and sat. aq NH_4Cl (60 mL) and extracted with EtOAc (5 × 30 mL). The combined organic extracts were washed with sat. aq NH_4Cl (50 mL) and dried. The solvent was evaporated and the residue was chromatographed on silica gel (5% MeOH/DCM) to give 21 (2.384 g, 83%).

(b) A solution of **20** (824.0 mg, 3.1 mmol) in anhyd MeCN (5 mL) was added to a solution of TBSCl (793.0 mg, 5.26 mmol) and imidazole (394.0 mg, 5.78 mmol) in anhyd MeCN (10 mL) and stirred at 0 °C. The mixture was stirred at 0 °C for 2 h and then at rt 16 h, diluted with water (30 mL) and extracted with DCM (4 × 10 mL). The combined extracts were dried over $MgSO_4$ and the solvent was evaporated. The residue chromatographed on silica gel (10% EtOAc/hexanes) gave (3a*R**,4*S**,9a*R**)-4-[*tert*-Butyldimethylsilyloxy)methyl]-8,9a-dimethyl-2,3,3a,4,5,6,9,9a-octahydrospiro[cyclopenta[8]annulen-1,2′-[1,3]dioxolane] silyl ether (1.177 g, 96%). ^{1}H NMR (200 MHz): 5.48−5.29 (m, 1H), 3.91 (s, 4H), 3.51 (dd, *J* = 5.0, 0.8 Hz, 2H), 2.62−2.46 (m, 1H), 2.40−2.12 (m, 1H), 2.11−1.86 (m, 2H), 1.84−1.36 (m, 8H) overlapping 1.75 (s, 3H), 0.89 (s, 3H), 0.87 (s, 9H), 0.00 (s, 6H). ^{13}C NMR (50 MHz): 135.2, 125.3, 120.0, 65.8, 65.2, 63.9, 49.1, 44.9, 35.9, 35.7, 31.9, 31.1, 27.5, 25.9, 24.5, 21.6, 18.2, 16.0, −5.4, −5.5. HRMS (EI) calcd for $C_{22}H_{40}O_3Si$, 380.2747; found, 380.2752.

BH_3·THF (1 M in THF, 3.3 mL, 3.30 mmol) was added to a solution of the later product (419.0 mg, 1.10 mmol) in THF (10 mL), stirred at 0 °C. Stirring at rt was continued for 6 h and then the mixture was cooled again to 0 °C, and 10% aq NaOH (0.57 mL, 1.43 mmol, 1.3 equiv) and H_2O_2 (30%, 0.16 mL, 1.4 equiv) were added. The mixture was allowed to warm to rt and set aside for 16 h. Water (30 mL) and sat. aq NH_4Cl (30 mL) were then added and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with sat. aq NH_4Cl (50 mL) and dried. The solvent was evaporated and the residue was chromatographed on silica gel (30% EtOAc/hexanes) to give (3a*R**,4*S**,7*R**,8*R**,9a*R**)-4-[(*tert*-butyldimethylsilyloxy)methyl]-8,9a-dimethyldecahydrospiro[cyclopenta[8]annulene-1,2′-[1,3]dioxolan]-7-ol (316.0 mg, 72%) ^{1}H NMR (200 Hz): 4.02−3.76 (m, 4H), 3.58 (dd, *J* = 9.8, 4.0 Hz, 1H), 3.35 (dd, *J* = 9.9, 9.8 Hz, 1H), 3.14−2.96 (m, 1H), 2.18−1.88 (m, 3H), 1.88−1.60 (m, 5H), 1.60−1.30 (m, 5H), 1.30−1.05 (m, 1H), 0.98 (d, *J* = 6.6 Hz, 3H), 0.88 (s, 9H), 0.83 (s, 3H), 0.02 (s, 6H). ^{13}C NMR (50 MHz): 120.7, 79.7, 65.1, 63.5, 63.5, 47.3, 42.0, 40.7, 38.4, 36.9, 32.0, 31.0, 26.0, 24.4, 21.9, 20.3, 19.2, 18.3, −5.4, −5.4. Anal. calcd for $C_{22}H_{42}O_4Si$: C, 66.28; H, 10.62. Found: C, 66.27; H, 10.53. A mixture of this silyl ether (302.2 mg, 0.76 mmol), $Bu_4NF·3H_2O$ (310.9 mg, 0.99 mmol, 1.3 equiv) and THF (15 mL) was stirred at rt for 16 h, and then it was diluted with water (40 mL) and extracted DCM (3 × 15 mL). The combined organic extracts were dried and the solvent was evaporated. The residue was chromatographed on silica gel (5% MeOH/DCM) to give **21** (215.5 mg, 92%). ^{1}H NMR (400 MHz, $CDCl_3$ + D_2O): 4.02−3.80 (m, 4H), 3.61 (dd, *J* = 10.6, 3.7 Hz, 1H), 3.41 (dd, *J* = 10.6, 1.0 Hz, 1H), 3.14−3.05 (dt, *J* = 10.5, 3.6 Hz, 1H), 2.15−2.02 (m, 1H), 2.00−1.74 (m, 4H), 1.74−1.60 (m, 4H), 1.58−1.34 (m, 4H), 1.30−1.14 (m, 1H), 1.09−0.87 (m, 1H) overlapping 0.97 (d, *J* = 6.7 Hz, 3H), 0.84 (s, 3H). ^{13}C NMR (100 MHz): 120.7, 79.3, 65.1, 63.5, 63.2, 47.2, 42.0, 40.6, 38.5, 36.6, 31.9, 30.8, 24.4, 21.8, 20.6, 19.2. HRMS (ESI) calcd for $C_{16}H_{28}O_4Na$, 307.1880; found, 307.1891.

{(3a*R,4*S**,7*R**,8*R**,9a*R**)-7-(Benzoyloxy)-8,9a-dimethyldecahydrospiro(cyclopenta[8]annulene)-1,2′-[1,3]dioxolan]-4-yl}methyl Benzoate (22).** Benzoil chloride (2.1 mL, 17.53 mmol) was added dropwise to a stirred at 0 °C solution of **21** (2.268 g, 7.97 mmol) in pyridine (20 mL) containing DMAP (48.7 mg, 0.40 mmol). The mixture was stirred at rt for 16 h and then the bulk of the solvent was evaporated. The residue was diluted with water (150 mL) and extracted with DCM (4 × 30 mL). The combined extracts were washed with 5% aq HCl (2 × 30 mL), dried ($MgSO_4$), and the solvent was evaporated. The residue was chromatographed on silica gel (10−15% EtOAc/hexanes) to give **22** as a viscous oil (3.850 g, 98%). ^{1}H NMR (400 MHz): 8.05−7.92 (m, 4H), 7.57−7.50 (m, 2H), 7.46−7.40 (m, 4H), 4.66 (m, 1H), 4.39 (dd, *J* = 11.2, 4.0 Hz, 1H), 4.14 (dt, *J* = 11.2, 9.9 Hz, 1H), 4.03−3.87 (m, 4H), 2.44−2.27 (m, 2H), 2.10−1.90 (m, 4H), 1.82−1.48 (m, 6H), 1.34 (dd, *J* = 16.0, 8.3 Hz, 1H), 0.94 (d, *J* = 6.2 Hz, 3H), 0.93 (s, 3H). ^{13}C NMR (50 MHz): 166.4, 165.8, 132.8, 132.6, 130.8, 130.2, 129.4, 128.3, 128.2, 120.5, 81.6, 66.2, 65.5, 64.0, 47.3, 40.5, 39.0, 38.9, 34.7, 32.0, 27.3, 24.5, 21.7, 21.3, 19.2. Anal. calcd for $C_{30}H_{36}O_6$ (492.62): C, 73.15; H, 7.37. Found: C, 73.11 H; 7.55.

(3a*R,4*S**,7*R**,8*R**,9a*R**)-7-[(Benzoyloxy)-8,9a-dimethyl-1-oxodecahydro-1*H*-cyclopenta[8]annulen-4-yl]methyl Benzoate (23).** *p*-TSA (78.1 mg, 0.78 mmol) was added to a solution of ketal **22** (3.842 g, 7.81 mmol) in dioxane (90 mL) and water (30 mL). The mixture was stirred at 40 °C for 6 h and then diluted with water (150 mL) and extracted with DCM (3 × 40 mL). The combined extracts were dried ($MgSO_4$) and the solvent was evaporated. The residue was chromatographed on silica gel (120 g, 15% EtOAc/hexanes) to give ketone **23** (3.499 g, 98%). ^{1}H NMR (200 MHz): 8.20−7.78 (m, 4H), 7.70−7.32 (m, 6H), 4.69 (dt, *J* = 10.1, 3.8 Hz, 1H), 4.48 (dd, *J* = 11.2, 4.0 Hz, 1H), 4.26 (dt, *J* = 11.2, 8.1 Hz, 1H), 2.68−2.42 (m, 1H), 2.40−1.40 (m, 12H), 1.01 (d, *J* = 6.6 Hz, 3H), 0.90 (s, 3H). ^{13}C NMR (50 MHz): 220.1, 166.4, 165.7, 133.0, 132.8, 103.5, 130.1, 129.4, 129.4, 128.4, 128.2, 81.2, 66.0, 51.6, 40.3, 40.0, 36.7, 35.8, 34.0, 27.1, 22.7, 21.9, 21.7, 18.2. HRMS (ESI) calcd for $C_{28}H_{32}O_5Na$, 471.2142; found, 471.2139.

(3a*R,5*R**,6*R**,9*S**,9a*R**)-9-(Benzoyloxymethyl)-6-benzoyloxy-3a,5-dimethyl-3a,4,5,6,7,8,9,9a-octahydro-1*H*-cyclopenta-[8]annulen-3-yl Trifluoromethanesulfonate (24).** A mixture of **23** (7.790 g, 17.38 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (5.353 g, 26.07 mmol), Tf_2O (3.7 mL, 22.61 mmol) and anhyd DCE (250 mL) was heated at 73 °C. The progress of reaction was followed by TLC and the heating was discontinued when along with the substrate and the triflate an unidentified side product appeared, after ca. 1.5 h. The mixture was cooled and concentrated and pentane (200 mL) was added. The solid was filtered off and the solvent was evaporated. The residue was chromatographed on silica gel (5% EtOAc/hexanes) to give enol triflate **24** (8.582 g, 95% based on consumed substrate) and unchanged **23** (805.1 mg). For **24**, ^{1}H NMR (400 MHz): 8.07−7.98 (m, 4H),

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7.60−7.53 (m, 2H), 7.48−7.40 (m, 4H), 5.69 (br s, 1H), 4.70 (dt, *J* = 10.6, 4.4 Hz, 1H), 4.35 (dd, *J* = 11.2, 4.8 Hz, 1H), 4.19 (dd, *J* = 11.2, 8.8 Hz, 1H), 2.54−2.38 (m, 2H), 2.32−2.18 (m, 2H), 2.14−1.97 (m, 3H), 1.92 (d, *J* = 16.3 Hz, 1H), 1.82−1.68 (m, 2H), 1.54 (dd, *J* = 16.3, 8.8 Hz, 1H), 1.08 (s, 3H), 1.01 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz): 166.4, 165.8, 154.6, 133.1, 132.9, 130.5, 130.0, 129.5, 128.4, 128.3, 113.6, 81.4, 65.8, 47.6, 41.7, 39.5, 35.5, 32.6, 29.5, 26.9, 21.9, 21.5, 20.1. ^{19}F (376 MHz): −74.3. HRMS (ESI) calcd for $C_{29}H_{31}F_3O_7SNa$, 603.1635; found, 603.1660.

[(3a*S,5*R**,6*R**,9*S**,9a*R**)-6-(Benzoyloxy)-3a,5-dimethyl-3a,4,5,6,7,8,9,9a-octahydro-1*H*-cyclopenta[8]annulen-9-yl]-methyl Benzoate (25).** Enol triflate **24** (8.576 g, 14.74 mmol) in THF (21 mL) was added to a solution of $Pd(PPh_3)_4$ (851.4 mg, 0.74 mmol) and LiCl (2.752 g, 65.01 mmol) in THF (200 mL) and stirred at rt under argon. To this mixture, *n*-Bu_3SnH (11.1 mL, 41.27 mmol) was added by means of a syringe pump over 10 min. After 5 h, the solvent was evaporated and the residue was chromatographed on silica gel (20% EtOAc/hexanes) to give **25** (5.302 g, 83%). ^{1}H NMR (400 MHz): 8.06−8.00 (m, 4H), 7.58−7.52 (m, 2H), 7.46−7.40 (m, 4H), 5.74−5.70 (m, 1H), 5.52−5.49 (m, 1H), 4.72 (dt, *J* = 10.3, 4.4 Hz, 1H), 4.35 (dd, *J* = 11.2, 4.2 Hz, 1H), 4.19 (dd, *J* = 11.2, 8.8 Hz, 1H), 2.42−2.17 (m, 4H), 2.16−1.92 (m, 3H), 1.86−1.58 (m, 4H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.92 (s, 3H). ^{13}C NMR (200 MHz): 166.5, 165.8, 144.7 132.9, 132.7, 130.7, 130.2, 129.4, 128.8, 128.3, 128.2, 81.9, 66.5, 48.0, 44.7, 42.9, 35.9, 34.9, 32.9, 27.8, 26.9, 26.8, 22.1, 21.8, 21.7, 17.5, 13.6. HRMS (ESI) calcd for $C_{28}H_{32}O_4Na$, 455.2193; found, 455.2197.

[(1a*R,1b*R**,3*R**,4*R**,7*S**,7a*R**,8a*S**)-4-(Benzoyloxy)-1b,3-dimethyldecahydro-1a*H*-cycloocta[3,4]cyclopenta[1,2-*b*]-oxiren-7-yl]methyl Benzoate (26).** *m*-CPBA (77%, 3.014 g, 13.35 mmol) was added to a solution of ene **25** (5.290 g, mmol) in DCM (200 mL) stirred at rt. After 2.5 h, the solution was washed with 10% aq $Na_2S_2O_3$ (2 × 50 mL) and 5% aq $NaHCO_3$ (2 × 50 mL) and dried. The solvent was evaporated and the residue was chromatographed on silica gel (10% EtOAc/hexanes) to give **26** contaminated with its diastereomer (5.212 mg, 98% in a ratio 12:1 by ^{1}H NMR). For **26**, ^{1}H NMR (400 MHz): 8.05−7.98 (m, 4H), 7.58−7.51 (m, 2H), 7.46−7.40 (m, 4H), 4.65 (dt, *J* = 10.6, 4.1 Hz, 0.93H), 4.33 (dd, *J* = 11.0, 4.0 Hz, 1H), 4.09 (dd, *J* = 11.0, 8.9 Hz, 1H), 3.33 (d, *J* = 2.9 Hz, 0.93H), 3.06 (d, *J* = 2.9 Hz, 0.93H), 2.38−2.14 (m, 2H), 2.08−1.86 (m, 5H), 1.82−1.50 (m, 5H), 1.04 (d, *J* = 6.7 Hz, 3H), 0.85 (s, 3H). ^{13}C NMR (100 MHz): 166.4, 165.9, 133.0, 132.8, 130.6, 130.1, 129.5, 129.5, 128.4, 128.3, 81.6, 66.6, 66.1, 52.0, 43.2, 41.5, 35.6, 33.2, 33.1, 30.7, 26.8, 22.2, 21.7, 19.5. HRMS (ESI) calcd for $C_{28}H_{32}O_5Na$, 471.2142; found, 471.2170. The signals of the diastereomer (from the mixture), ^{1}H NMR (400 MHz): 4.93 (dt, *J* = 9.5, 3.2 Hz, 0.07H), 3.40 (d, *J* = 2.8 Hz, 0.07H), 3.03 (d, *J* = 2.8 Hz, 0.07H).

{(1*S,2*S**,3a*R**,4*S**,7*R**,8*R**,9a*R**)-2-Chloro-7-(benzoyloxy)-1-hydroxy-8,9a-dimethyldecahydro-1*H*-cyclopenta[8]annulen-4-yl}methyl Benzoate (27).** $AlCl_3$ (3.2 mg, 0.024 mmol) was added to a solution of epoxide **26** (9.9 mg, 0.022 mmol) in anhyd Et_2O (1 mL) and stirred under argon. The mixture was heated under reflux for 2 h, cooled, washed with water (2 × 3 mL) and brine (2 × 3 mL), and dried ($MgSO_4$). The solvent was evaporated and the residue was chromatographed on silica gel (0.5 g, 10% EtOAc/hexanes) to give **27** (5.6 mg, 52%). ^{1}H NMR (400 MHz): 8.05−7.99 (m, 4H), 7.60−7.51 (m, 2H), 7.48−7.39 (m, 4H), 4.67 (dt, *J* = 10.4, 3.9 Hz, 1H), 4.33 (dd, *J* = 11.0, 4.4 Hz, 1H), 4.17 (dd, *J* = 11.0, 9.1 Hz, 1H), 4.02 (dt, *J* = 8.0, 1.5 Hz, 1H), 3.82 (d, *J* = 1.5 Hz, 1H), 2.77−2.66 (m, 1H), 2.42−2.24 (m, 2H), 2.18−1.88 (m, 5H), 1.86−1.66 (m, 3H), 1.63−1.51 (m, 1H), 1.05 (s, 3H), 1.01 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (100 MHz): 166.4, 165.9, 133.0, 132.8, 130.7, 130.1, 129.5, 129.5, 128.4, 128.3, 92.2, 81.2, 66.6, 63.0, 46.9, 43.0, 39.7, 39.7, 37.7, 34.6, 27.3, 22.1, 21.4, 21.2. HRMS calcd for $C_{28}H_{33}ClO_5Na$, 507.1909; found, 507.1888.

Rearrangement of Epoxide 26. $BF_3 \cdot Et_2O$ (27.6 μL, 0.218 mmol) was added to a solution of the above-described epoxide **26** (65 mg, 0.145 mmol) in anhyd benzene (5 mL), stirred at 0 °C and then the cooling bath was removed and the mixture was left for 2 h. Saturated aq $NaHCO_3$ (1 mL) was added and stirring was continued until the mixture become colorless (ca. 10 min). The mixture was then diluted with DCM (10 mL) and washed with sat. aq $NaHCO_3$ (5 mL) and dried ($MgSO_4$). The solvent was evaporated and the residue was chromatographed on silica gel (15−20% EtOAc/hexanes) to give consecutively ketone **28** (31.2−35.1 mg, 48−54%), diene **29** (13.0 mg, 20%), and a mixture of minor products. The procedure was carried repeatedly to collect ca. 2.5 g of **28**. HPLC chromatography of minor side products collected from several experiments gave **30** and **31** (Nucleosil 50/5 μm 250 × 4 mm column, 1 mL/min., 10% *i*-PrOH/hexanes).

{(1S,3aS*,4 S*,7R*,8R*,9aS*)-7-(Benzoyloxy)-1,8-dimethyl-2-oxo-decahydro-1H-cyclopenta[8]annulen-4-yl}methyl Benzoate (**28**).* IR 1739 cm^{-1} (C═O), 1715 cm^{-1} ($COOC_6H_5$). ^{1}H NMR (400 MHz): 8.08−7.99 (m, 4H), 7.60−7.54 (m, 2H), 7.49−7.42 (m, 4H), 4.85−4.78 (m, 1H), 4.32 (dd, *J* = 11.1, 3.7 Hz, 1H), 4.25 (dd, *J* = 11.1, 5.3 Hz, 1H), 2.60−2.34 (m, 4H), 2.30−1.90 (m, 7H), 1.84−1.73 (m, 2H), 1.17 (d, *J* = 7.5 Hz, 3H), 1.05 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (100 MHz): 219.9, 166.5, 165.9, 133.1, 132.9, 130.6, 130.0, 129.6, 129.5, 128.5, 128.4, 79.4, 69.0, 53.4, 45.9, 41.7, 39.4, 38.5, 37.6, 36.9, 31.8, 28.7, 20.9, 16.3. HRMS (ESI) calcd for $C_{28}H_{32}O_5Na$, 471.2142; found, 471.2172.

{(5R,6R*,9S*,9aR*)-6-(Benzoyloxy)-3,5-dimethyl-5,6,7,8,9,9a-hexahydro-1H-cyclopenta[8]annulen-9-yl}methyl Benzoate (**29**).* ^{1}H NMR (400 MHz): 8.08−8.01 (m, 4H), 7.58−7.25 (m, 2H), 7.47−7.41 (m, 4H), 5.76 (br s, 1H), 5.14 (br d, *J* = 8.9 Hz, 1H), 4.95−4.89 (m, 1H), 4.48 (dd, *J* = 11.1, 2.9 Hz, 1H), 4.26 (dd, *J* = 11.1, 8.2 Hz, 1H), 2.92−2.77 (m, 2H), 2.73−2.63 (m, 1H), 2.06−1.65 (m, 6H) overlapping 1.77 (br s, 3H), 1.14 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz) 166.6, 166.2, 150.5, 139.5, 132.9, 132.8, 131.6, 130.8, 130.3, 129.5, 128.4, 128.3, 120.2, 79.0, 68.5, 44.2, 41.9, 37.3, 29.7, 29.2, 18.4, 12.9. HRMS (ESI) calcd for $C_{28}H_{30}O_4Na$, 453.2036; found, 453.2052.

[(1S,2S*,4S*,7R*,8R*)-7-(Benzoyloxy)-2-hydroxy-1,8-dimethyl-2,3,4,5,6,7, 8,9-octahydro-1H-cyclopenta[8]annulen-4-yl]methyl Benzoate (**30**).* ^{1}H NMR (500 MHz): 8.02−7.93 (m, 4H), 7.55−7.43 (m, 2H), 7.42−7.34 (m, 4H), 5.28−5.24 (m, 1H), 4.87 (ddd, *J* = 10.9, 3.5, 3.5 Hz, 1H), 4.87 (dd, *J* = 11.1, 3.1 Hz, 1H), 4.11 (dd, *J* = 11.1, 7.5 Hz, 1H), 3.90 (br s, 1H), 2.82−2.70 (m, 2H), 2.43−2.34 (m, 1H), 2.10−1.80 (m, 5H), 1.15−0.90 (m, 3H) overlapping 1.04 (d, *J* = 7.3 Hz, 3H) and 1.04 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (100 MHz): 166.5, 165.9, 139.9, 132.9, 132.8, 132.1, 130.7, 130.2, 129.6, 129.5, 128.4, 128.4, 81.0, 78.6, 67.1, 50.8, 39.2, 38.4, 35.7, 32.9, 31.5, 26.7, 20.5, 16.5. HRMS (ESI) calcd for $C_{28}H_{32}O_5Na$, 471.2142; found, 471.2126.

[(1R,2R*,3aR*,4S*,7R*,8R*,9aR*)-7-(Benzoyloxy)-1,2-dihydroxy-8,9a-dimethyldecahydro-1H-cyclopenta[8]annulen-4-yl]methyl Benzoate (**31**).* ^{1}H NMR (400 MHz): 8.04−7.97 (m, 4H), 7.57−7.50 (m, 2H), 7.45−7.37 (m, 4H), 4.72−4.66 (m, 1H), 4.35 (dd, *J* = 11.0, 4.2 Hz, 1H), 4.18−4.04 (m, 2H), 3.55 (d, *J* = 0.7 Hz, 1H), 3.11 (br s, 2H), 2.52−2.42 (m, 1H), 2.37−2.22 (m, 2H), 2.14−1.88 (m, 3H), 1.84−1.46 (m, 4H), 1.42−1.18 (m, 1H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.99 (s, 3H). ^{13}C NMR (50 MHz): 166.6, 166.0, 133.0, 132.7, 130.6, 130.0, 129.5, 129.4, 128.4, 128.3, 91.0, 81.5, 79.5, 66.7, 45.9, 43.1, 38.5, 37.8, 37.6, 34.5, 27.1, 21.7, 21.2, 21.2. HRMS (ESI) calcd for $C_{28}H_{34}O_6Na$, 489.2248; found, 489.2223.

[(1*S,2ξ,3a*S**,4*S**,7*R**,8*R**,9a*S**)-7-(Benzoyloxy)-2-hydroxy-1,8-dimethyldecahydro-1*H*-cyclopenta[8]annulen-4-yl]-methyl Benzoate (32).** $NaBH_4$ (43.3 mg, 1.12 mmol) was added to a solution of **28** (2.460 g, 4.56 mmol) in MeOH and THF (2:1, 60 mL) and stirred at rt. After 1 h, acetone (5 mL) was added, and the mixture was diluted with water (80 mL) and extracted with DCM (3 × 20 mL). The combined extracts were dried ($MgSO_4$) and the solvent was evaporated. The residue was chromatographed on silica gel (30% EtOAc/hexanes) to give **32** (1.851 g, 74%). ^{1}H NMR (200 MHz): 8.10−7.96 (m, 4H), 7.68−7.38 (m, 6H), 4.70−4.55 (m, 1H), 4.36 (dd, *J* = 10.9, 3.0 Hz,

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1H), 4.22 (dd, J = 10.9, 4.6 Hz, 1H), 3.68−3.45 (m, 1H), 2.30−1.20 (m, 14H), 1.12 (d, J = 6.3 Hz, 3H), 1.07 (d, J = 6.2 Hz, 3H). ^{13}C NMR (50 MHz): 166.5, 165.9, 132.8, 132.7, 130.7, 130.2, 129.5, 129.4, 128.3, 128.3, 80.8, 77.2, 69.0, 52.8, 47.4, 41.1, 39.7, 38.9, 37.9, 35.4, 32.3, 31.7, 20.8, 17.2. HRMS (ESI) calcd for $C_{28}H_{34}O_5Na$, 473.2299; found, 473.2315.

***O*-{(1*S**,2ξ,3a*S**,4*S**,7*R**,8*R**,9a*S**)-7-(Benzoyloxy)-4-(benzoyloxymethyl)-1,8-dimethyldecahydro-1*H*-cyclopenta[8]annulen-2-yl} *O*-phenyl Thiocarbonate (33).** *O*-Phenyl chlorothioxoformate (0.85 mL, 6.18 mmol) was added to a stirred solution of **32** (1.850 g, 4.12 mmol) in DCM (40 mL) containing pyridine (1.1 mL, 12.28 mmol). The mixture was stirred at rt for 2 h and then washed with 5% HCl (40 mL). The aqueous extracts were combined and extracted with DCM (3 × 15 mL). The combined organic solutions were dried ($MgSO_4$) and the solvent was evaporated. The residue was chromatographed on silica gel (60 g, 10% EtOAc/hexanes) to give **33** (2.051 g, 85%). ^{1}H NMR (400 MHz): 8.07−8.02 (m, 3H), 7.59−7.53 (m, 2H), 7.48−7.37 (m, 5H), 7.31−7.21 (m, 3H), 7.12−7.07 (m, 2H), 5.15−5.07 (m, 1H), 4.66 (dd, J = 10.3, 7.5 Hz, 1H), 4.40 (dd, J = 11.1, 2.6 Hz, 1H), 4.21 (dd, J = 11.1, 4.7 Hz, 1H), 2.59−2.49 (m, 1H), 2.20−1.25 (m, 12H), 1.19 (d, J = 6.9 Hz, 3H), 1.05 (d, J = 6.5 Hz, 3H). ^{13}C NMR (100 MHz): 194.9, 166.6, 166.0, 153.3, 132.9, 132.8, 130.7, 130.2, 129.6, 129.6, 129.5, 128.4, 128.4, 126.5, 121.9, 88.7, 80.3, 68.9, 49.6, 46.8, 40.8, 39.7, 37.6, 36.2, 35.4, 32.3, 31.1, 20.7, 17.8. HRMS (ESI) calcd for $C_{35}H_{38}O_6SNa$, 609.2281; found, 609.2287.

[(1*S,3a*S**,4*S**,7*S**,8*R**,9a*R**)-7-(Benzoyloxy)-1,8-dimethyldecahydro-1*H*-cyclopenta[8]annulen-4-yl]methyl Benzoate (34).** A mixture of **33** (2.040 g, 3.48 mmol) and AIBN (97.3 mg, 0.68 mmol) in benzene (15 mL) was added dropwise over 30 min by means of syringe pump to a solution of (n-Bu)$_3$SnH (2.05 mL, 7.61 mmol) in anhyd benzene (100 mL) heated under reflux under argon. After 30 min, a new portion of AIBN (97.3 mg, 0.680 mmol) was added and heating was continued for 30 min. The mixture was cooled and the solvent was evaporated. The residue was chromatographed on silica gel (60 g, 10% EtOAc/hexanes) to give **34** (1.290 g, 83%). ^{1}H NMR (200 MHz): 8.12−8.00 (m, 4H), 7.60−7.40 (m, 6H), 4.65 (dd, J = 10.4, 3.8 Hz, 1H), 4.39 (dd, J = 10.8, 3.0 Hz, 1H), 4.24 (dd, J = 10.8, 5.0 Hz, 1H), 2.40−1.18 (m, 13H), 1.15−0.92 (m, 2H) overlapping 1.06 (d, J = 7.1 Hz, 3H) and 1.03 (d, J = 6.7 Hz, 3H). ^{13}C NMR (50 MHz): 166.6, 165.9, 132.7, 132.7, 130.8, 130.4, 129.5, 129.4, 128.3, 128.3, 80.9, 69.4, 49.0, 46.4, 44.0, 41.1, 38.1, 36.2, 33.2, 32.5, 31.7, 31.4, 20.9, 20.4. HRMS (EI) calcd for $C_{28}H_{34}O_4Na$, 457.2349; found, 457.2345.

(3*S,3a*R**,5*R**,6*S**,9*S**,9a*S**)-9-(Hydroxymethyl)-3,5-dimethyldecahydro-1*H*-cyclopenta[*8*]annulen-6-yl Benzoate (39).** MeONa (0.46 M in MeOH, 1.9 mL, 0.868 mmol) was added to a solution of **34** (188.4 mg, 0.434 mmol) in MeOH (14 mL) stirred at rt under argon. After 16 h, next portion of MeONa (1.9 mL) was added and stirring was continued for 24 h. The mixture was then diluted with water (100 mL) and extracted Et_2O (3 × 15 mL). The combined extracts were washed with brine NaCl (2 × 15 mL) and dried ($MgSO_4$). The solvent was evaporated and the residue was chromatographed on silica gel (6 g, 25% EtOAc/hexanes) to give **39** (121.2 mg, 85%). mp 87−89 °C. ^{1}H MNR (400 MHz): 8.07−8.02 (m, 2H), 7.58−7.52 (m, 2H), 7.47−7.43 (m, 1H), 4.58 (dd, J = 10.3, 7.2 Hz, 1H), 3.71 (dd, J = 10.6, 3.1 Hz, 1H), 3.59 (dd, J = 10.6, 5.3 Hz, 1H), 2.13−1.94 (m, 2H), 1.92−1.18 (m, 14H), 1.05 (d, J = 6.6 Hz, 3H), 1.01 (d, J = 6.4 Hz, 3H). ^{13}C NMR (50 MHz): 165.9, 132.6, 130.8, 129.3, 128.2, 81.0, 67.2, 48.8, 46.3, 43.6, 41.0, 38.7, 38.3, 33.1, 32.6, 31.1, 31.0, 20.8, 20.5. HRMS calcd for $C_{21}H_{30}O_3Na$, 353.2087; found, 353.2072.

X-ray analysis of **39**: ORTEP diagram is shown in Figure 1; crystal data are presented in the Supporting Information.

(3*S,3a*R**,5*R**,6*S**,9*S**,9a*S**)-9-(Hydroxymethyl)-3,5-dimethyldecahydro-1*H*-cyclopenta[8]annulen-6-ol (35).** A mixture of **34** (1.043 g, 2.395 mmol), KOH (5 g, 89.29 mmol) and MeOH (20 mL) was stirred under argon at rt for 16 h and then concentrated. The residue was diluted with water (50 mL) and extracted Et_2O (3 × 20 mL). The combined extracts were washed with brine (20 mL) and dried. The solvent was evaporated and the residue was chromatographed on silica gel (30 g, 10% MeOH/DCM) to give **35** (531.0 mg, 98%). ^{1}H NMR (400 MHz, DMSO-d$_6$): 4.33 (d, J = 5.1 Hz, 1H), 4.26 (dd, J = 5.1, 5.1 Hz, 1H), 3.25−3.15 (m, 1H), 2.94−2.86 (m, 1H), 1.90−1.55 (m, 7H), 1.48−1.08 (m, 7H), 1.02−0.82 (m, 2H) overlapping 0.96 (d, J = 6.8 Hz, 3H) and 0.93 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d$_6$): 75.8, 65.3, 48.5, 45.6, 43.5, 43.3, 38.5, 38.4, 35.2, 33.6, 31.4, 30.4, 21.5, 20.5. HRMS (EI) calcd for $C_{14}H_{26}O_2$, 226.1933; found, 226.1930.

(3*S,3a*R**,5*R**,6*S**,9*S**,9a*R**)-9-[(*tert*-Butyldimethylsilyl)oxy]methyl-3,5-dimethyldecahydro-1*H*-cyclopenta[8]annulen-6-ol (36).** Imidazole (158.6 mg, 2.330 mmol) and *tert*-BuMe$_2$SiCl (351.2 mg, 2.330 mmol) were added to a solution of **35** (439.3 mg, 1.942 mmol) in MeCN (20 mL) stirred at 0 °C. The mixture was left at rt for 16 h and then it was diluted with water (20 mL) and extracted DCM (3 × 15 mL). The combined extracts were dried and evaporated. The residue was chromatographed on silica gel (5% EtOAc/hexanes) to give **36** (594.7 mg, 90%). ^{1}H NMR (400 MHz): 3.59 (dd, J = 9.7, 3.3 Hz, 1H), 3.39 (dd, J = 9.7, 6.6 Hz, 1H), 3.19−3.12 (m, 1H), 2.00−1.90 (m, 1H), 1.88−1.78 (m, 1H), 1.76−1.62 (m, 5H), 1.55−1.32 (m, 7H), 1.25−1.12 (m, 2H), 1.03 (d, J = 6.1 Hz, 3H), 1.00 (d, J = 6.6 Hz, 3H), 0.89 (s, 9H), 0.03 (s, 6H). ^{13}C NMR (50 MHz): 67.3, 49.0, 46.1, 44.0, 43.5, 38.8, 38.7, 35.0, 33.1, 31.7, 30.8, 26.0, 21.1, 20.5, 18.3, −5.4, −0.5.5. HRMS (ESI) calcd for $C_{20}H_{40}O_2SiNa$, 363.2690; found, 363.2680.

(3*S,3a*R**,5*R**,9*S**,9a*R**)-9-[(*tert*-Butyldimethylsilyl)oxy]-methyl-3,5-dimethyldecahydro-1*H*-cyclopenta[8]annulen-6-one (37).** Dess−Martin periodinane (889.4 mg, 2.098 mmol) was added to a solution of **36** (594.7 mg, 1.748 mmol) in DCM (20 mL) and stirred under argon at rt. After 15 min, water (20 mL) and 5% aq NaOH (2 mL) were added and the mixture was stirred for 10 min. The aq layer was separated and extracted with DCM (3 × 15 mL). The combined organic solutions were dried ($MgSO_4$) and the solvent was evaporated. The residue was chromatographed on silica gel (20 g, 20% EtOAc/hexanes) to give **37** (543.9 mg, 92%). ^{1}H NMR (400 MHz): 3.52 (dd, J = 9.9, 3.5 Hz, 1H), 3.40 (dd, J = 9.9, 6.4 Hz, 1H), 2.54−2.40 (m, 3H), 2.07−1.98 (m, 1H), 1.85−1.61 (m, 5H), 1.59−1.40 (m, 4H), 1.34−1.24 (m, 2H), 1.04 (d, J = 6.8 Hz, 3H), 1.01 (d, J = 6.8 Hz, 3H), 0.87 (s, 9H), 0.01 (s, 6H). ^{13}C NMR (100 MHz): 218.5, 66.5, 50.2, 49.8, 43.7, 43.2, 39.4, 38.5, 36.5, 32.5, 31.1, 29.8, 25.9, 20.5, 18.3, 17.4, −5.5, −0.5.5. HRMS (ESI) calcd for $C_{20}H_{38}O_2SiNa$, 361.2533; found, 361.2518.

(3*S,3a*R**,5*R**,9*S**,9a*S**)-9-(Hydroxymethyl)-3,5-dimethyldecahydro-6*H*-cyclopenta[8]annulen-6-one (38).** A mixture of **37** (542.8 mg, 1.61 mmol), $Bu_4NF·3H_2O$ (783.8 mg, 2.48. mmol) and THF (15 mL) was stirred at rt for 16 h and then it was diluted with 5% HCl (10 mL) and extracted DCM (3 × 10 mL). The combined extracts were dried and the solvent was evaporated. The residue was chromatographed on silica gel (15 g, 35% EtOAc/hexanes) to give **38** (352.5 mg, 98%). IR (DCM): 3622 cm^{-1}, 1701 cm^{-1}. ^{1}H NMR (500 MHz): 3.62 (dd, J = 10.6, 3.5 Hz, 1H), 3.45 (dd, J = 10.6, 6.5 Hz, 1H), 2.58−2.41 (m, 3H), 2.13−2.03 (m, 1H), 1.86−1.62 (m, 4H), 1.60−1.18 (m, 7H), 1.10−0.85 (m, 1H) overlapping 1.04 (d, J = 6.7 Hz, 3H) and 1.02 (d, J = 6.7 Hz, 3H). ^{13}C NMR (125 MHz): 218.3, 66.5, 50.1, 49.8, 43.8, 43.4, 39.5, 38.5, 36.7, 32.4, 30.7, 30.0, 20.5, 17.2. HRMS (ESI) calcd for $C_{14}H_{24}O_2Na$, 247.1667; found, 247.1678.

[(1*S,3a*S**,4*S**,8*R**,9a*R**)-1,8-Dimethyl-7-oxodecahydro-1*H*-cyclopenta[8]annulen-4-yl]methyl Acetate (46).** Ac_2O (205 μL, 2.159 mmol) was added to a solution of **38** (322.6 mg, 1.430 mmol) in pyridine (10 mL). The mixture was stirred at rt for 3 h and then it was diluted with water (20 mL) and extracted DCM (3 × 10 mL). The combined extracts were washed with 5% HCl (2 × 5 mL), dried ($MgSO_4$), and the solvent was evaporated. The residue chromatographed

on silica gel (10 g, 15% EtOAc/hexanes) to give **46** (364.0 mg, 95%). ^{1}H NMR (400 MHz): 4.04 (dd, J = 11.0, 3.3 Hz, 1H), 3.82 (dd, J = 11.0, 6.6 Hz, 1H), 2.54−2.39 (m, 3H), 2.05−1.94 (m, 1H) overlapping 2.02 (s, 3H), 1.88−1.42 (m, 10H), 1.33−1.21 (m, 1H), 1.03 (d, J = 6.8 Hz, 3H), 1.01 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz): 217.8, 171.2, 68.2, 50.2, 49.8, 43.9, 43.2, 38.0, 36.3, 32.3, 32.3, 31.3, 30.0, 20.9, 20.3, 17.2. HRMS (ESI) calcd for $C_{16}H_{26}O_3Na$, 289.1774; found, 289.1769.

[(1*S,3a*S**,4*S**,9a*R**)-7-(Acetyloxy)-1,8-dimethyl-2,3,3a,4,5,6,9,9a-octahydro-1*H*-cyclopenta[8]annulen-4-yl]methyl Acetate (47).** Ac_2O (255 μL, 2.325 mmol) and $HClO_4$ (70%, 3.4 μL, 0.152 mmol) were consecutively added to a solution of **46** (364.0 mg, 1.163 mmol) in CCl_4 (38 mL) and stirred at 0 °C. The cooling bath was removed and the mixture was left at rt for 16 h. Et_2O (20 mL) was then added and the solution was washed with sat. aq $NaHCO_3$ (2 × 10 mL) and brine (10 mL), and dried ($NaSO_4$). The solvent was evaporated and the residue was chromatographed on silica gel (10 g, 7% EtOAc/hexanes) to give **47** (387.7 mg, 92%). ^{1}H NMR (400 MHz): 4.09 (dd, J = 10.9, 3.6 Hz, 1H), 3.92 (dd, J = 10.9, 6.5 Hz, 1H), 2.74−2.65 (m, 1H), 2.22−1.72 (m, 8H) overlapping 2.13 (s, 3H) and 2.05 (s, 3H), 1.72−1.1.31 (m, 4H) overlapping 1.54 (s, 3H), 1.12−0.99 (m, 1H), 1.03 (d, J = 6.6 Hz, 3H). ^{13}C NMR (100 MHz): 171.4, 169.6, 141.9, 123.4, 68.6, 48.3, 44.8, 41.6, 37.5, 36.2, 33.2, 33.1, 29.7, 29.5, 21.0, 20.8, 20.7, 17.5. HRMS (EI) calcd for $C_{18}H_{28}O_4$, 308.1988; found, 308.1998.

(3*S,3a*R**,5*R**,9*S**,9a*S**)-9-(Hydroxymethyl)-3,5-dimethyl-5-(4-methylpent-3-enyl)decahydro-6*H*-cyclopenta[8]annulen-6-one (48).** MeLi (1.6 M in Et_2O, 1.8 mL, 2.88 mmol) was evaporated and the residue was dissolved in DME (5 mL). To this solution, stirred under argon at 0 °C, enol acetate **47** (218.8 mg, 0.711 mmol) in DME (3 mL) was added. The mixture was stirred at 0 °C for 1 h and then 5-iodo-2-methylpent-2-ene (686.5 mg, 3.268 mmol) and HMPA (5 mL) were consecutively added. The mixture was stirred at rt for 3 h and then it was diluted with Et_2O (40 mL) and washed with brine (20 mL) and water (10 mL). The combined aq extracts were washed with Et_2O (3 × 20 mL). The combined organic solutions were washed with brine (2 × 20 mL) and dried. The solvent was evaporated and the residue was chromatographed on silica gel (25−30% EtOAc/hexanes) to give **48** (100.0 mg, 46%). ^{1}H NMR (400 MHz): 5.05−4.97 (m, 1H), 3.64 (dd, J = 10.5, 2.8 Hz, 1H), 3.37 (dd, J = 10.5, 6.8 Hz, 1H), 2.84−2.73 (m, 1H), 2.20−2.09 (m, 2H), 2.02−1.88 (m, 2H), 1.82−1.22 (m, 11H) overlapping 1.65 (s, 3H) and 1.54 (s, 3H), 1.16−0.98 (m, 2H) overlapping 1.05 (s, 3H), 0.96−0.87 (m, 1H) overlapping 0.93 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz): 219.1, 132.1, 123.8, 66.6, 51.8, 45.9, 43.4, 42.0, 41.1, 40.8, 39.5, 37.1, 31.8, 31.6, 29.3, 25.6, 23.3, 20.2, 18.4, 17.6. HRMS (ESI) calcd for $C_{20}H_{34}O_2Na$, 329.2460; found, 329.2460.

{(1*S,3a*S**,4*S**,8*R**,9a*R**)-1,8-Dimethyl-8-(4-methylpent-3-enyl)-7-oxodecahydro-1*H*-cyclopenta[8]annulen-4-yl}methyl 3,5-dinitrobenzoate (50).** 3,5-Dinitrobenzoyl chloride (43.3 mg, 0.185 mmol) was added to a solution of **48** (46.1 mg, 0.150 mmol) in pyridine (3 mL) and stirred at 0 °C. The mixture was left at rt for 16 h and then it was diluted with water (30 mL) and extracted Et_2O (3 × 10 mL). The combined extracts were washed with 5% HCl (3 × 5 mL) and brine (10 mL) and then dried ($MgSO_4$). The solvent was evaporated and the residue was chromatographed on silica gel (0.5 g, 20% EtOAc/hexanes) to give **50** as yellow crystals (79.3 mg, 92%). mp 112−114 °C. ^{1}H NMR (500 MHz): 9.21 (dd, J = 2.2, 2.2 Hz, 1H), 9.21 (d, J = 2.2 Hz, 2H), 5.03−4.97 (m, 1H), 4.48 (dd, J = 10.9, 3.8 Hz, 1H), 4.19 (dd, J = 10.9, 7.6 Hz, 1H), 2.86 (ddd, J = 14.6, 12.0, 2.7 Hz, 1H), 2.17 (ddd, J = 14.6, 7.7, 2.6 Hz, 1H), 2.11−2.03 (m, 1H), 2.00−1.56 (m, 8H) overlapping 1.67 (s, 3H), 1.54 (s, 3H), 1.50−1.34 (m, 5H), 1.26−1.12 (m, 1H), 1.07 (s, 3H), 0.97 (d, J = 6.8 Hz, 3H). ^{13}C NMR (125 MHz): 218.2, 162.6, 148.7, 133.9, 132.1, 129.3, 123.7, 122.4, 70.7, 51.7, 46.0, 43.5, 40.8, 40.6, 39.3, 38.7, 36.5, 32.3, 31.5, 29.4, 25.6, 23.2, 19.9, 18.2, 17.5. Anal. calcd for $C_{27}H_{36}O_7N_2$ (500.60): C, 64.78; H, 7.25; N, 5.60. Found: C 64.90; H 7.13; N 5.57.

X-ray analysis of **50**: ORTEP diagram is shown in Figure 2; crystal data are presented in the Supporting Information.

(3*S,3a*R**,5*R**,9*S**,9a*R**)-9-{[(*tert*-Butyldimethylsilyl)oxy]-methyl}-3,5-dimethyl-5-(4-methylpent-3-enyl)decahydro-6*H*-cyclopenta[8]annulen-6-one (49).** *tert*-$BuMe_2SiCl$ (85.5 mg, 0.567 mmol) was added to a solution of **48** (102.6 mg, 0.334 mmol) and imidazole (38.7 mg, 0.596 mmol, 1.7 eqiuv.) in MeCN (8 mL) and stirred at 0 °C. The mixture set aside at rt for 16 h and then diluted with water (20 mL) and extracted DCM (3 × 10 mL). The combined extracts were dried and the solvent was evaporated. The residue was chromatographed on silica gel (3 g, 2.5% EtOAc/hexanes) to give **49** (125.1 mg, 89%) ^{1}H NMR (400 MHz): 5.05−4.98 (m, 1H), 3.56 (dd, J = 9.7, 2.9 Hz, 1H), 3.29 (dd, J = 9.7, 7.3 Hz, 1H), 2.80−2.70 (m, 1H), 2.13 (d, J = 9.4, 1H), 1.94 (dd, J = 14.9, 9.5 Hz, 1H), 1.80−1.22 (m, 13H) overlapping 1.65 (s, 3H) and 1.54 (s, 3H), 1.14−0.90 (m, 2H) overlapping 1.04 (s, 3H), 0.92 (d, J = 6.8 Hz, 3H) and 0.87 (s, 9H), 0.02 and 0.01 (s, 6H). ^{13}C NMR (100 MHz): 219.3, 132.0, 123.9, 66.6, 51.8, 45.9, 43.4, 42.1, 41.1, 40.8, 39.5, 37.2, 32.0, 31.7, 29.1, 25.9, 25.6, 23.3, 20.2, 18.4, 18.3, 17.6, −5.4, −5.5. HRMS (ESI) calcd for $C_{26}H_{48}O_2SiNa$, 443.3316; found, 443.3334.

(3*S,3a*R**,5*R**,9*S**,9a*R**)-9-{[(*tert*-Butyldimethylsilyl)oxy]-methyl}-3,5-dimethyl-5-(4-methyl-3-oxopentyl)decahydro-6*H*-cyclopenta[8]annulen-6-one (51).** BH_3·THF (475 μL, 0.485 mmol, 1 M in THF) was added to a solution of ene **49** (99.6 mg, 0.237 mmol) in THF (4 mL) and stirred under argon at 0 °C. The mixture was left at rt for 6 h and then 10% aq NaOH (430 μL, 1.080 mmol) and H_2O_2 (30%, 430 μL, 3.749 mmol) were consecutively added. After subsequent 16 h, the mixture was diluted with sat. aq NH_4Cl (10 mL) and extracted Et_2O (3 × 10 mL). The combined extracts were washed with brine (2 × 10 mL), dried, and the solvent was evaporated. The residue was dissolved in DCM (10 mL) and Dess−Martin periodinane (261.1 mg, 0.615 mmol) was added. The mixture was stirred for 15 min and then water (10 mL) and 5% aq NaOH (1 mL) were added. After 10 min, the aqueous layer was separated and extracted with DCM (3 × 10 mL). The combined organic solutions were dried ($MgSO_4$) and the solvent was evaporated. The residue was chromatographed on silica gel (3 g, 5% EtOAc/hexanes) to give **51** (89.9 mg, 87%). ^{1}H NMR (400 MHz): 3.54 (dd, J = 9.7, 2.8 Hz, 1H), 3.29 (dd, J = 9.7, 6.8 Hz, 1H), 2.76−2.66 (m, 1H), 2.53 (sept, J = 7.0, 1H), 2.40 (ddd, J = 17.2, 10.5, 5.2 Hz, 1H), 2.19−2.06 (m, 3H), 1.97 (dd, J = 9.2, 8.8 Hz, 1H), 1.88 (ddd, J = 14.8, 10.5, 5.2 Hz, 1H), 1.79−1.49 (m, 5H), 1.45−1.15 (m, 6H), 1.05 (d, J = 7.0, 3H), 1.03 (d, J = 7.0, 3H), 0.99 (s, 3H), 0.92 (d, J = 6.8 Hz, 3H), 0.86 and 0.85 (s, 9H), 0.01 and 0.00 (s, 6H). ^{13}C NMR (100 MHz): 219.2, 214.0, 66.5, 51.1, 46.0, 43.4, 41.8, 41.1, 41.0, 39.6, 37.2, 35.3, 33.5, 31.9, 31.7, 29.1, 25.9, 20.2, 18.4, 18.3, 18.2, 18.2, −5.4, −5.5. HRMS (ESI) calcd for $C_{26}H_{48}O_3SiNa$, 459.3242; found, 459.3265.

(3*S,3a*R**,5*R**,9*S**,9a*R**)-3,5-Dimethyl-9-(hydroxymethyl)-5-(4-methyl-3-oxopentyl)decahydro-6*H*-cyclopenta[8]-annulen-6-one (52).** $Bu_4NF·3H_2O$ (67.0 mg, 0.212 mmol) was added to a solution of **51** (46.4 mg, 0.106 mmol) in THF (5 mL) and stirred at rt. After 16 h, the mixture was diluted with 5% HCl (10 mL) and extracted with DCM (3 × 10 mL). The combined extracts were dried and the solvent was evaporated. The residue was chromatographed on silica gel (1 g, 35% EtOAc/hexanes) to give **52** (28.6 mg, 84%). mp 85−88 °C. ^{1}H NMR (400 MHz): 3.63 (dd, J = 10.6, 3.1 Hz, 1H), 3.38 (dd, J = 10.6, 6.8 Hz, 1H), 2.80−2.70 (m, 1H), 2.54 (sept, J = 7.0, 1H), 2.46−2.38 (m, 1H), 2.22−2.06 (m, 3H), 1.96 (dd, J = 14.5, 9.2, Hz, 1H), 1.88 (ddd, J = 14.5, 10.6, 5.1 Hz, 1H), 1.82−1.20 (m, 10H), 1.15−0.92 (m, 2H) overlapping 1.06 (d, J = 7.0, 3H), 1.04 (d, J = 7.0, 3H), 1.00 (s, 3H) and 0.93 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz): 218.9, 214.0, 66.5, 51.1, 46.0, 43.4, 41.7, 41.1, 41.0, 39.6, 37.0, 35.5, 31.8, 31.6, 29.3, 20.2, 18.4, 18.3, 18.2. HRMS (EI) calcd for $C_{20}H_{34}O_3$, 322.2508; found, 322.2505.

[(1*S,3a*S**,4*S**,9a*R**,10a*R**)-1,9a-Dimethyl-7-isopropyl-1,2,3,3a,4,5,6,8,9,9a, 10,10a-dodecahydrodicyclopenta[*a*,*d*]-[8]annulen-4-yl]methanol (53).** (a) Zn/Cu (352,1 mg, 5.468 mmol) was added to suspension of $TiCl_3$ (352.1 mg, 2.280 mmol) in anhyd DME (29 mL) and stirred under argon. The mixture was heated under reflux for 6 h and then dione **52** (28.6 mg, 0.089 mmol) in anhyd DME (9.5 mL) was added dropwise by means of syringe pump over 12 h. The mixture was heated under reflux for additional 6 h, cooled, and filtered through a pad of silica gel (in hexane) and the solvent was evaporated. The residue was chromatographed on silica gel (7.5% EtOAc/hexanes) to give alcohol **53** (4.1 mg, 16%).

(b) Zn/Cu (386.8 mg, 6.001 mmol) was added to suspension of $TiCl_3$ (364.0 mg, 2.360 mmol) in anhyd DME (30 mL) and stirred under argon. The mixture was heated under reflux for 6 h and then dione **51** (40.0 mg, 0.092 mmol) in anhyd DME (10 mL) was added dropwise by means of syringe pump over 12 h. The mixture was heated under reflux for additional 6 h, cooled, and filtered through a pad of silica gel (in hexane). The filtrate was evaporated and the residue was dissolved in THF (2 mL). $Bu_4NF \cdot 3H_2O$ (580.5 mg, 1.84 mmol) was added and the mixture was stirred for 16 h; then it was diluted with 5% HCl (10 mL) and extracted with DCM (3 × 10 mL). The combined extracts were dried and the solvent was evaporated. The residue was chromatographed on silica gel (7.5% EtOAc/hexanes) to give **53** (7.2 mg, 27%). IR (film) 3352 cm^{-1} (OH). ^1H NMR (400 MHz): 3.62 (dd, *J* = 10.6, 3.5 Hz, 1H), 3.52 (dd, *J* = 10.6, 6.0 Hz, 1H), 2.61 (sept, *J* = 6.8 Hz, 1H), 2.34−2.26 (m, 1H), 2.19−2.14 (m, 2H), 1.94 (dt, *J* = 13.6, 5.5 Hz, 1H), 1.89−1.81 (m, 1H), 1.77−1.33 (m, 10H), 1.27−0.89 (m, 4H) overlapping 0.99 (d, *J* = 6.8 Hz, 3H) and 0.96 (d, *J* = 6.8 Hz, 3H),and 0.95 (s, 3H), and 0.91 (d, *J* = 7.0 Hz). ^{13}C NMR (100 MHz): 141.1, 139.0, 67.9, 48.8, 47.6, 46.0, 44.5, 43.9, 39.9, 37.6, 33.3, 32.9, 30.7, 26.9, 26.7, 24.9, 21.7, 21.6, 21.0, 20.6. HRMS (ESI) calcd for $C_{20}H_{34}ONa$, 313.2502; found, 313.2500.

(*E*)-Trimethyl(2-methylcyclooct-1-enyloxy)silane (41). MeMgBr (3 M in Et_2O, 6.8 mL, 20.4 mmol) was added to a solution of diisopropylamine (2.8 mL, 20.0 mmol) in Et_2O (50 mL) and stirred at rt. The mixture was stirred 24 h and then a solution of 2-methylcyclooctanone (**40**) (560 mg, 4.0 mmol) in Et_2O (12 mL) was added followed after 15 min with TMSCl (3.0 mL, 24.0 mmol, 6.0 equiv), Et_3N (3.6 mL, 26.0 mmol, 6.5 equiv), and HMPA (0.35 mL, 2.0 mmol, 0.5 eqiuv). After consecutive 24 h, the solution was washed with sat. NH_4Cl (2 × 20 mL), dried, and the solvent was evaporated. The residue was passed through pad of silica gel (5 g, 10% EtOAc/hexanes) and the solvent was evaporated to give a colorless oil. GC analysis of the product before and after filtration through silica gel indicated no changes; in the both cases ketone **40** and silyl enol ether **41** were present in a ratio of 19:81.

In analogous experiments, the following results were obtained:

i-Pr_2NMgBr, Et_2O	TMSCl, Et_3N, HMPA	40:41 ratio (by GC)
1.25 equiv, 12 h	3 equiv, 3.25 equiv, 12 h	34:66
1.25 equiv, 12 h[a]	3 equiv, 3.25 equiv, 12 h	32:68
1.25 equiv, 24 h	3 equiv, 3.25 equiv, 24 h	21:79
5 equiv, 12 h	6 equiv, 6.5 equiv, 12 h	24:76
5 equiv, 24 h	6 equiv, 6.5 equiv, 24 h	19:81

[a] Bromomagnesium diisopropylamide was prepared by mixing *i*-Pr_2NH and MeMgBr in a ratio of 1.5:1 (in the other experiments 1.02:1).

2-Methylcyclooct-1-en-1-yl Acetate (42).[111] To a solution of ketone **40** (3.604 g, 25.7 mmol) in CCl_4 (15 mL), Ac_2O (4.9 mL, mmol) and 70% $HClO_4$ (110 μL, 1.29 mmol, 5 mol %) were added at 0 °C and stirred for 16 h at rt. Then reaction mixture was diluted with Et_2O (100 mL), washed with with sat. solution of $NaHCO_3$ (3 × 30 mL), brine (1 × 30 mL), dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel (150 g, 5% EtOAc/hexane) to give **42** as a colorless oil (4.349 g, 92% yield). ^1H NMR (200 MHz): 2.36−2.22 (m, 2H), 2.21−2.04 (m, 3H) overlapping 2.13 (s, 3H), 1.68−1.40 (m, 7H) overlapping 1.53 (s, 3H). ^{13}C NMR (50 MHz): 169.4, 143.5, 117.8, 31.4, 30.1, 28.8, 28.4, 26.6, 25.7, 20.8, 15.6, which is in agreement with these reported.[118]

5-Iodo-2-methylpent-2-ene Was Obtained by the Modified Reported Procedure[112]**.** Cyclopropyl methyl ketone (6.2 mL, 100 mmol) in anhyd Et_2O (10 mL) was added dropwise over 30 min to a refluxing solution of MeMgI in Et_2O (3.33 M, 30 mL, 100 mmol). The mixture was heated at reflux temperature for an additional 30 min, cooled, and poured into a 50% H_2SO_4 (45 mL) cooled to 0 °C. The mixture was allowed to warm to rt and stirring was continued for 30 min; then the organic layer was separated. The aqueous layer was extracted with Et_2O (2 × 10 mL). The combined organic extract was washed with brine (2 × 10 mL) and dried. The solvent was evaporated and the residue was distilled at 82−84 °C/20 mmHg to give the title product (10.272 g, 49%, >99% pure by GC). ^1H NMR (200 MHz): 5.15−5.00 (m, 1H), 3.10 (t, *J* = 7.4 Hz, 2H), 2.57 (dt, J=7.4, 7.4 Hz, 2H), 1.69 (br s, 3H), 1.61 (br s, 3H), which is in agreement with those reported.[113]

2-Methyl-2-(4-methylpent-3-enyl)cyclooctanone (43). Commercial MeLi in Et_2O (1.6 M, 1.37 mL, 2.19 mmol) was evaporated in a stream of dry argon and the residue was dissolved in dry DME (3 mL). To this solution, stirred at 0 °C, enol acetate 42 (194.5 mg, 1.07 mmol) was added dropwise and stirring was continued at rt for 1 h. The mixture was then cooled to 0 °C and 5-iodo-2-methylpent-2-ene (471.3 mg, 2.24 mmol) and HMPA (3 mL) were consecutively added. The mixture was stirred at 0 °C for 30 min and at rt for 1 h and then brine (5 mL) and water (5 mL) were added. The organic layer was separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic extract was dried ($MgSO_4$) and the solvent was evaporated. The residue was chromatographed on silica gel (10 g, 7% EtOAc/hexane) to give **43** (170.8 mg, 72%). ^1H NMR (200 MHz) 5.11−4.97 (m, 1H), 2.79−2.62 (m, 2H), 2.00−1.20 (m, 14H) overlapping 1.65 and 1.55 (2 × s, 6H), 1.03 (s, 3H). ^{13}C NMR (50 MHz): 220.8, 131.8, 124.0, 50.0, 38.8, 36.6, 34.4 30.3, 25.9, 25.6, 24.9, 24.3, 22.7, 18.5, 17.5. MS (EI, *m*/*z*) 222 (M^+, 1): 140 (100), 97 (31), 84 (27), 69 (54), 55 (27), 41 (59). HRMS (EI) calcd for $C_{15}H_{26}O$, 222.1984; found, 222.1987.

2-Methyl-2-(4-methyl-3-oxopentyl)cyclooctan-1-one (45). $BH_3 \cdot THF$ (1 M in THF, 2.2 mL, 2.20 mmol) was added dropwise to a solution of **43** (246.8 mg, 1.11 mmol) in THF (2 mL) and stirred at 0 °C. The mixture was stirred at rt for 6 h and then cooled to 0 °C again and 10% aq NaOH (2 mL) and H_2O_2 (30%, 2 mL) were consecutively added. The mixture was left at rt for 16 h, and then aq NH_4Cl (10 mL) was added and the product was extracted with Et_2O (3 × 10 mL). The combined extract was dried and the solvent was evaporated. The residue (consisting of the respective diol) was dissolved in DCM (5 mL) and Dess−Martin periodinane (1.077 g, 2.53 mmol) was added portionwise at 0 °C. The mixture was left at rt for 20 h and then it was diluted with 5% aq NaOH (30 mL) and extracted with Et_2O (3 × 10 mL). The combined organic extract was washed with brine (20 mL), dried, and the solvent was evaporated. The residue was chromatographed on silica gel (12 g, 7% EtOAc/hexane) to give **45** (241.7 mg, 91%). ^1H NMR (200 MHz): 2.71 (dt, *J* = 11.2, 3.6 Hz, 1H), 2.54 (t, *J* = 7.0 Hz, 1H), 2.33 (dd, *J* = 10.4, 6.0 Hz, 1H), 2.24 (dd, *J* = 10.4, 5.6 Hz, 1H), 2.21−2.00 (m, 2H), 1.87−1.20 (m, 11H), 1.06 (d, *J* = 2.0 Hz, 3H]), 1.02 (d, *J* = 2.0 Hz, 3H), 0.97 (s, 3H). ^{13}C NMR (50 MHz): 220.5, 214.1, 49.4, 40.9, 36.7, 35.0, 34.9, 32.0, 30.4, 25.9, 24.8, 24.2, 18.2, 18.2. MS (EI, *m*/*z*) 238 (M^+, 9): 99 (35), 81 (31), 71 ($C_3H_7^+$, 100), 69 (40), 55 (38), 43 (60), 41 (42). HRMS (EI) calcd for $C_{15}H_{26}O_2$, 238.1933; found, 238.1938.

3-Isopropyl-9a-methyl-2,4,5,6,7,8,9,9a-octahydro-1*H*-cyclopenta[8]annulene (44). A mixture of $TiCl_3$ (111.1 mg, 0.72 mmol), Cu-activated Zn powder (freshly prepared, 118.0 mg, 1.81 mmol) and DME (10 mL) was heated at reflux temperature for 2 h. To this suspension, at reflux temperature a solution of dione **45** (21.5 mg, 0.09 mmol) in DME (4 mL) was added by means of a syringe pomp over 12 h. The mixture was heated under reflux for an additional 5 h, cooled, diluted with hexane

(10 mL), and filtered through a plug of silica gel (5 mL). The filtrate was evaporated and the residue was chromatographed on silica gel (10 g, hexanes) to give **44** (17.6 mg, 95%, 86% pure by GC). ^{13}C NMR: 167.1 and 160.0 (C═C). GC MS major pick: 19.16 min, *m*/*e* 206. MS (EI, *m*/*z*) 206 (M^+, 17): 205, 149 (11), 123 (10), 109 (11), 97 (6), 95 (5), 81 (5). HRMS (EI) calcd for $C_{15}H_{26}$, 206.2035; found, 206.2037.

■ ASSOCIATED CONTENT

Supporting Information. ^{1}H/^{13}C NMR spectra of compounds **16**−**39**, **43**, **45**, **48**−**53**, ^{19}F NMR spectrum of compound **24**, IR spectrum of **28**, GC analysis of **44**, and crystal data of compounds **39** and **50**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

†Author responsible for the X-ray structure of compound **39**.

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