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Approaches to the synthesis of arisugacin A

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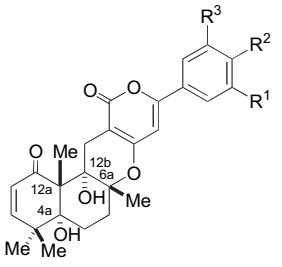
Abstract—Approaches to the synthesis of the important acetylcholinesterase inhibitor, arisugacin A, are described. Two different routes to the key AB ring system are described: the first utilizes an intramolecular Diels–Alder reaction on a furan substrate and the second a 6π-electrocyclization of a substituted triene followed by cycloaddition with singlet oxygen. The successful synthesis of a fully functionalized AB ring system of arisugacin A, the tetraol **52** from hydroxy-β-ionone **22** in 16 steps and 9.3% overall yield is described. Several useful synthetic transformations to this molecule and its analogues are reported, e.g., the formation of the furan Diels–Alder cycloadduct **14** and its conversion into the oxa-bridged structures **17** and **21**, the preparation of the dienes **25** and **26** and the conversion of the later into the endoperoxide **30** and its diol **36**, the preparation of the endoperoxide **40** and the oxa-bridged system **42**, and finally the use of the enelactone **43** and its ultimately successful conversion into **52**. In addition, several novel rearrangements are described, producing the unusual compounds **62**, **65**, and **67**. Finally, the successful coupling of the pyrone unit to the AB ring system is described to give compounds **70** and **71**. The novel reduction of these compounds to the cyclic ether **74** is described.

1. Introduction

Arisugacin A (**1a**), a compound isolated in 1997 from a strain of *Penicillium* sp. FO-4259, is a potent and specific inhibitor of acetylcholinesterase (AChE), which may be clinically useful for the treatment of Alzheimer's disease (AD), the most common form of dementia.[1] The inhibitory activity of arisugacin A reduces the rate of hydrolysis of acetylcholine (ACh), a neurotransmitter in the cholinergic neuron system, thereby increasing the amount of ACh in the brain.[2] Moreover, this compound shows a higher selectivity for AChE in the nervous system than for butyrylcholinesterase (BuChE), which should reduce the unfavorable side effects associated with non-specific inhibitors such as tacrine.[3]

As shown in Figure 1, arisugacin A consists structurally of a tetracyclic ring core possessing four contiguous stereocenters and an aryl group connected to an α-pyrone moiety with the angular methyl and hydroxyl groups at the AB and BC ring junctures having the trans–anti–trans relationship. With respect to its three-dimensional structure, a docking simulation of arisugacin A with AChE showed that this relatively flat compound when stretched out as a long sheet appeared to reside in the extended narrow active site of AChE.[1b] Because of its structural complexity, its therapeutic significance, and limited supply from natural sources, synthetic chemists have been attracted to this compound. Recently, both the Õmura and Hsung groups have independently reported total syntheses of arisugacin A using a formal [3+3] cycloaddition strategy to construct the dihydro-pyranopyrone ring system.[4]

In our retrosynthetic analysis of arisugacin A (Scheme 1), we envisioned a coupling of the pyrone unit with the advanced AB ring system at a late synthetic stage. The highly oxygenated decalin system **3** would derive from



	R^1	R^2	R^3
Arisugacin A (**1a**)	H	OMe	OMe
Arisugacin B (**1b**)	H	OMe	H
Territrem A (**1c**)	$-OCH_2O-$		OMe
Territrem B (**1d**)	OMe	OMe	OMe
Territrem B (**1e**)	OMe	OH	OMe

Figure 1. Arisugacin A and its family.

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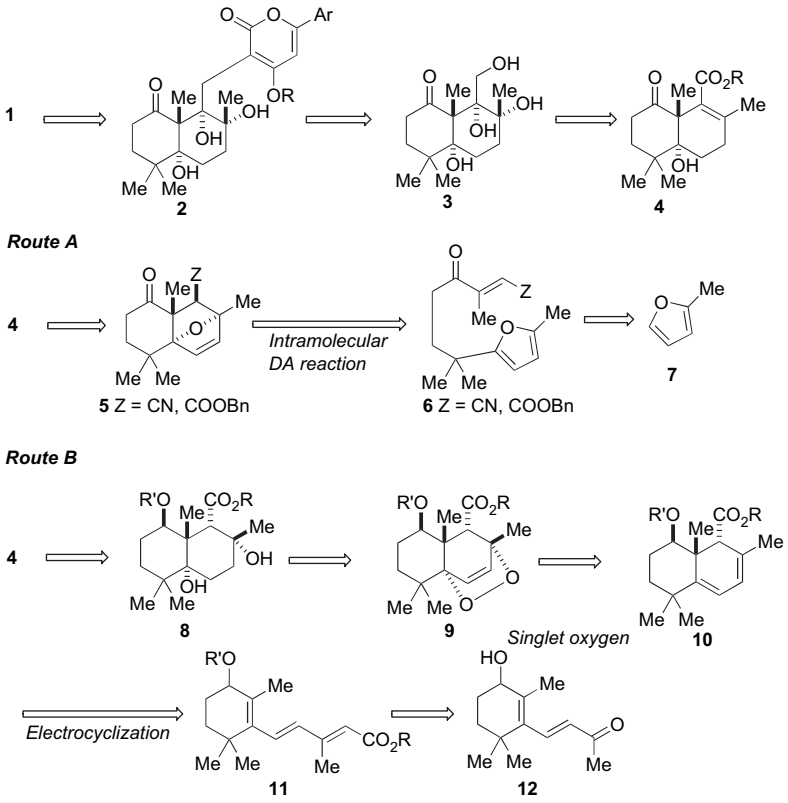


Scheme 1. Retrosynthetic analysis.

dihydroxylation of the advanced intermediate **4**, which would be formed via two different approaches. First, we could construct the oxa-bridged compound **5** using an intramolecular Diels–Alder reaction of furan (IMDAF), which has already been studied in our group (Route A).[5,6] In this case, one would expect the stereochemistry of the fused ring juncture in the AB ring system to be trans since (1) the *exo* cycloadduct (keto group in the *exo* position) would be favored over the *endo* cycloadduct and (2) the trans ring juncture is much more stable in these systems. The key feature of the second approach (Route B) is the construction of the bicyclic core by a 6π-electrocyclization[7] of the triene **11** followed by cycloaddition with singlet oxygen.[8] We assumed that the stereochemical outcome in the reaction of the diene **10** with singlet oxygen would be controlled by the steric interaction between the angular methyl group and the incoming oxygen, which would also lead to the trans fused decalin system. Herein, we describe the synthesis of the highly oxygenated AB ring system of arisugacin A and our approach toward the total synthesis of the natural product.

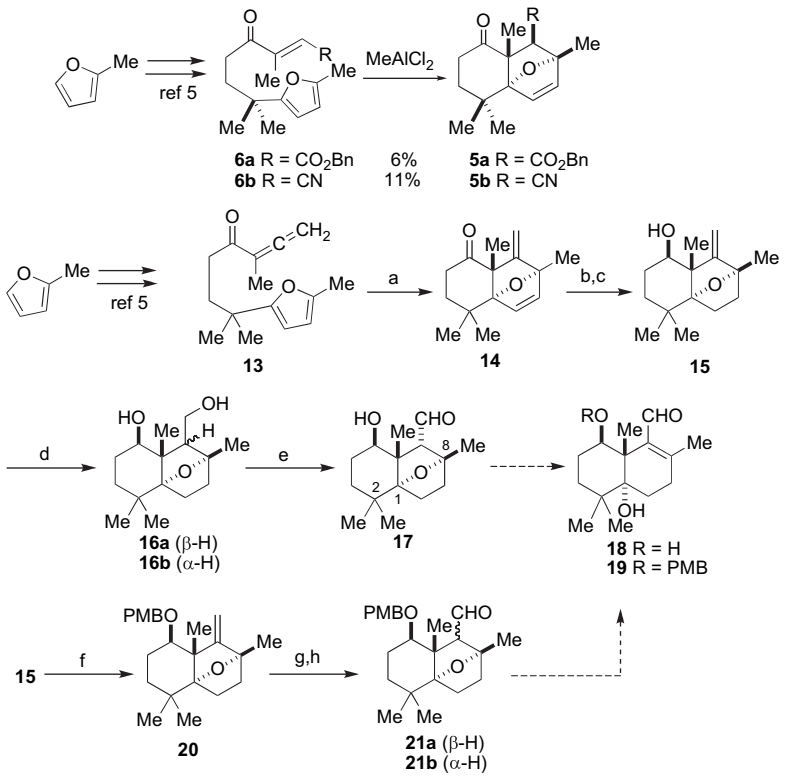
2. Results and discussion

2.1. Synthesis of AB ring system using an IMDAF reaction

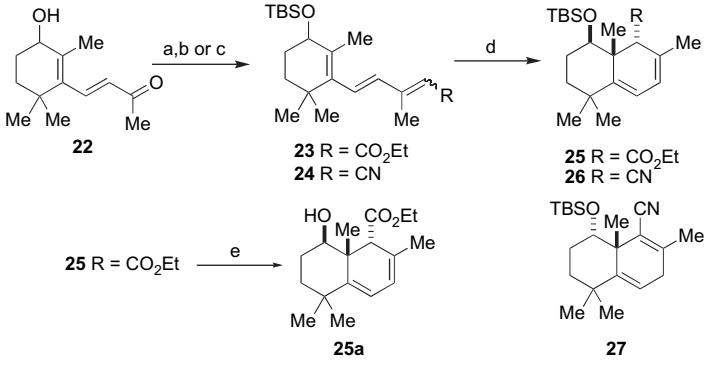
In recent work in our laboratory,[5] we demonstrated the construction of oxygen-bridged bicyclic ring systems using the IMDAF reaction. IMDAF reactions of the precursors to the AB ring system having alkene dienophiles, e.g., the ester **6a** and the nitrile **6b**, gave the expected cycloadducts **5ab** in low yields, presumably due to a facile retro Diels–Alder reaction.[5] However, the analogous allenic ketone **13** afforded the desired cycloadduct **14** as a single diastereomer in 91% yield in the presence of dimethylaluminum chloride (Scheme 2). Diimide reduction[9] of the endocyclic double bond of **14** gave the ketone, which was selectively converted to the β-alcohol in 64% yield using lithium in ammonia. We conducted the sequence of hydroboration and oxidation as described below to afford the free or PMB protected hydroxy aldehydes **17** and **21ab** although their yields were not optimized. Unfortunately, all attempts to open the oxygen-bridged ring of compounds **17** and **21ab** to the corresponding trans fused decalin system using bases such as DBU, NaOH or LDA were unsuccessful. In fact, we could observe only epimerization of the proton α to the aldehyde. Presumably, the oxa-tricyclic starting materials **17** and **21ab** are more stable than the hydroxy enal products **18** and **19** under these basic conditions because the 1,3-diaxial interaction between the angular and C2 methyl groups is somewhat reduced when C1 and C8 are linked by the oxygen bridge. However, although we were unable to synthesize the desired compounds **18** or **19** via this route, we used the oxa-bridged compounds **17** and **21a** as the coupling material in subsequent reactions. This will be discussed in a later section.

2.2. Synthesis of AB ring system via electrocyclization/singlet oxygen cycloaddition

The second approach toward the AB ring system began by investigating the key electrocyclization. Thus, we first synthesized the two triene precursors having different electron-withdrawing groups, i.e., the ester and nitrile (Scheme 3). Hydroxy β-ionone **22**, easily prepared in two steps from α-ionone,[10] was protected as the *tert*-butyldimethylsilyl



Scheme 2. Reagents and conditions: (a) Me_2AlCl, CH_2Cl_2, −20 °C, 91%; (b) $KO_2CN{=}NCO_2K$, AcOH, CH_2Cl_2, −78 °C to 23 °C; (c) Li/NH_3, Et_2O, MeOH, −33 °C, 64% (+12% starting material); (d) $BH_3{\cdot}DMS$, H_2O_2, NaOH, 77% (**16a/16b**=2.2:1); (e) Dess–Martin periodinane, CH_2Cl_2, 72% (from **16a**); (f) $PMBOC(NH)CCl_3$, TfOH, Et_2O, 89%; (g) $BH_3{\cdot}DMS$, H_2O_2, NaOH, 25%; (h) Dess–Martin periodinane, CH_2Cl_2, 85% (**21a/21b**=2.1:1).

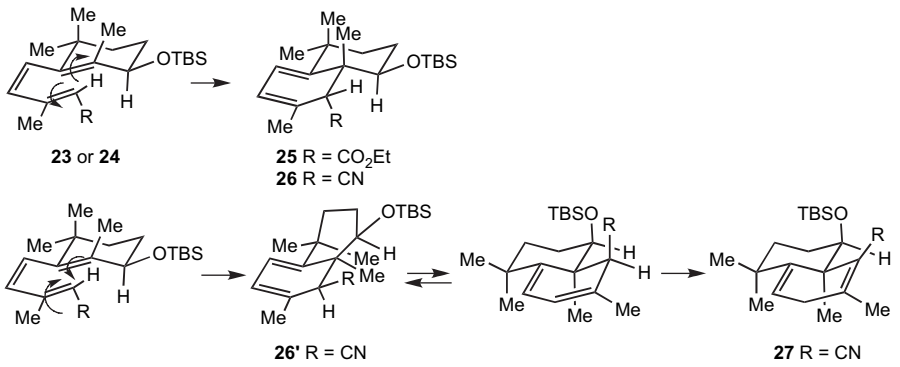


Scheme 3. Reagents and conditions: (a) TBSCl, imid, DMF, 96%; (b) $(EtO)_2P(O)CH_2CO_2Et$, NaH, Et_2O, 90% (*E*/*Z*=7.2:1); (c) $(MeO)_2P(O)CH_2CN$, BuLi, THF, −78 °C, 87% (*E*/*Z*=2.0:1); (d) see Table 1; (e) HF, CH_3CN, 86%.

(TBS) ether **22a**.[11] Horner–Wadsworth–Emmons reaction of this silyl ether afforded the corresponding trienes **23**[12] and **24**[13] in 90% and 87%, respectively, favoring the *E* stereoisomers. Presumably, the small size of the nitrile group in compound **24** resulted in the low stereoselectivity of this reaction as compared to the ester (2:1 vs 7.2:1). As shown in Table 1, we explored the electrocyclization of the trienes **23** and **24** by modifying the reported reaction procedure.[7a] The triene **23** was first isomerized to the *Z*-isomer by way of sodium lamp irradiation in the presence of benzanthrone and subsequently cyclized thermally to give the diene **25** in 56% yield as a single diastereomer. We improved the yield to 64% when the *Z*-isomer was isolated by flash column chromatography before cyclization. It should be noted that microwave reaction of the substrate **23** significantly reduced the reaction time, but the yield of the desired product did not increase. The structure of the cyclized product **25** was confirmed by its conversion into the known alcohol **25a** (and eventually into the lactone **38**, see Scheme 7) and comparison of the spectroscopic data of those two compounds with that reported previously in the literature for the

Table 1. Triene electrocyclization studies

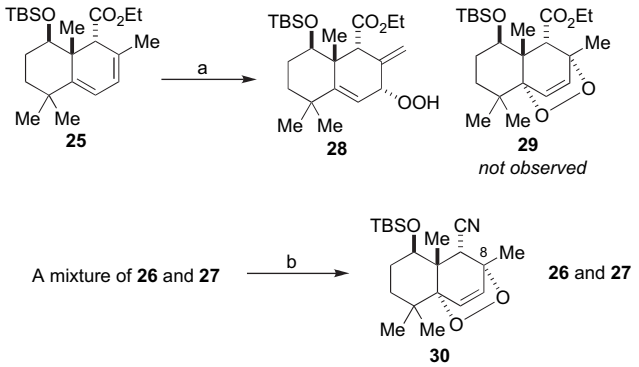
Entry	Compd	Conditions	Results
1	**23**	(i) *hν*, benzanthrone, THF, 5 h; (ii) DMF, 154 °C, 3 d	**25**, 64%
2	**23**	(i) *hν*, benzanthrone, THF, 5 h; (ii) μw, DMF, 250 °C, 5 min	**25**, 44%
3	**23**	μw, DMF, 250 °C, 5 min	Complex mixtures
4	**24**	(i) *hν*, benzanthrone, THF, 5 h; (ii) DMF, 154 °C, 3 d	**26+27**, 62% (3:2)



Scheme 4.

alcohol[7d] and lactone.[7c,d] We explain this stereospecificity based on the assumption that the 6π-electrocyclization takes place preferentially via one of the two possible transition states, namely from the face opposite to the silyloxy group, to avoid an unfavorable steric interaction (Scheme 4). On the other hand, the electrocyclization of the nitrile substrate **24** gave an inseparable mixture of the desired diene **26** and the isomerized compound **27** in which one double bond was conjugated with the nitrile group. Presumably, the steric effect of the small nitrile group allowed the reaction to occur via both transition states to produce both possible compounds **26** and **26′**. This latter compound **26′** then isomerized to the more stable unsaturated nitrile **27** in which the steric interaction between the nitrile group and OTBS group is eliminated.

We next examined the cycloaddition[14] of the cyclized dienes **25** and **26** with singlet oxygen (Scheme 5). We performed photoperoxidation of a solution of the diene **25** in deuterated chloroform using methylene blue as a sensitizer under irradiation with a tungsten lamp (GE, 300 W), while keeping the temperature around 0 °C. Unfortunately, the ^{1}H NMR analysis of the product indicated that it was not the expected endoperoxide **29**, but the hydroperoxide **28**, which was apparently generated via the ene reaction of the less hindered alkene of the diene with singlet oxygen. It is likely that the axial ethyl ester group sterically prevented the proximal approach of singlet oxygen from the bottom face of the compound. However, when we applied the same reaction to a mixture of the isomeric diene nitriles **26** and **27**, we obtained the desired endoperoxide **30** along with a mixture of

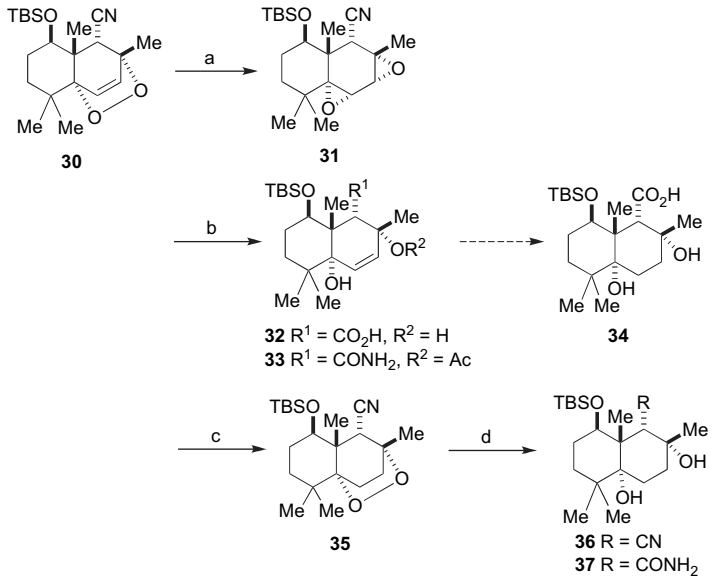


Scheme 5. Reagents and conditions: (a) *hν*, O_2, methylene blue, $CHCl_3$, 0 °C, 3.5 h, 51%; (b) *hν*, O_2, methylene blue, $CHCl_3$, 0 °C, 20 h, 28% (59% of a recovered mixture of **26** and **27**).

the starting material **26** and the intact isomer **27**. An X-ray crystallographic analysis of the endoperoxide **30** (see Supplementary data for ORTEP drawing of **30**) indicated that the OTBS group is located in the equatorial position and that the angular methyl group and the bridgehead oxygen have a trans relationship. Therefore, we were convinced that the singlet oxygen reaction of the diene nitrile **26** occurred from the face *syn* to the nitrile substituent to circumvent the steric interaction between the C-8 methyl group and the incoming singlet oxygen.

Despite the low yield of the endoperoxide **30**, we continued the synthesis because we were able to obtain a reasonable amount of material by repeating the singlet oxygen reaction several times using the recovered starting material. We next attempted to both reduce the endocyclic alkene and cleave the endoperoxide O–O bond in one step using palladium-catalyzed hydrogenation. While most attempts gave various side products, it was noteworthy that the endoperoxide **30** was converted to the diepoxide **31** via palladium-catalyzed isomerization, an interesting reaction, which has already been reported in the literature (Scheme 6).[15] Alternatively, a series of stepwise reductions were tried. The initial cleavage of the peroxide bond by treatment of compound **30** with zinc/acetic acid produced the alkenes **32** and **33**, in which the nitrile group was simultaneously hydrolyzed to give the carboxylic acid or the acetyloxy amide. However, all further efforts toward reduction of the endocyclic alkene moiety in the acid **32** failed. Instead, we successfully reduced both the double bond and the peroxide bond in **30** by changing the sequence of reduction steps. First, diimide reduction of the endoperoxide **30** afforded the reduced endoperoxide **35** in good yield after five iterative reactions (overall 98%). To increase the amount of the reduced product **35**, it was crucial to select the proper combination of solvents, i.e., a 2:1 ratio of methanol and tetrahydrofuran. Finally, the peroxide bond was cleaved by zinc/acetic acid to give an 84% yield of a 1:2.7 mixture of the dihydroxy nitrile **36** along with the hydrolyzed amide **37**.

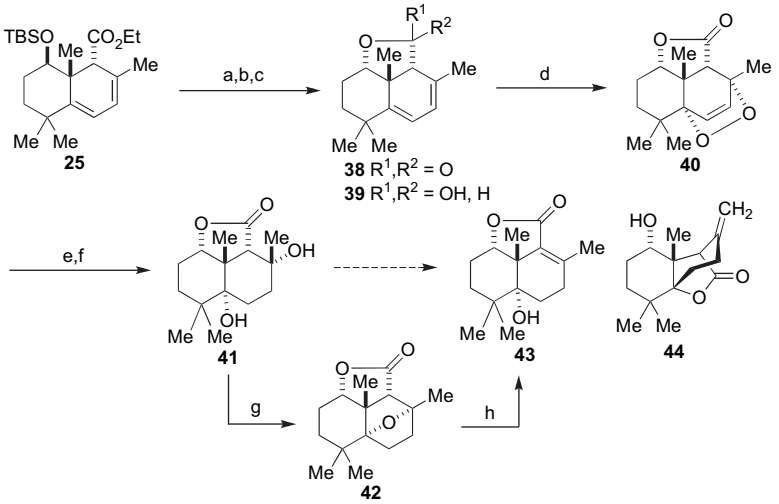
At this point, even though we obtained the desired compounds **36** and **37** as planned, the synthetic difficulty as well as the low efficiency prompted us to search for a new route to overcome these problems. Corey had reported that the cycloaddition of singlet oxygen to the lactone **38** produced the endoperoxide **40** in excellent yield in the total synthesis of forskolin (Scheme 7).[14] Thus, we transformed the ester **25** to the corresponding lactone **38** by modifying the



Scheme 6. Reagents and conditions: (a) H_2, Pd/C, MeOH, 1 d, 46% (19% SM); (b) Zn, AcOH, 1.5 h, **32** (70%), **33** (9%); (c) $KO_2CN{=}NCO_2K$, AcOH, MeOH/THF (2:1), −78 °C to 23 °C, 18 h, 98% (1:20=**30**/**35** after five times); (d) Zn, AcOH, 84% (**36**/**37**=1:2.7).

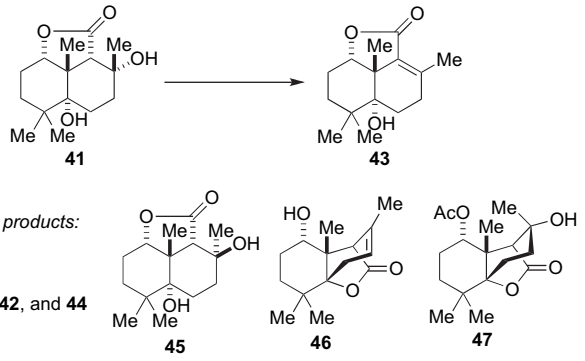
previously reported work of Cha,[7c] which involved removing the TBS group to give the alcohol **25a**, Swern oxidation to the ketone **25b**, and $NaBH_4$ reduction. The last reduction step afforded a 2.5:1 mixture of the lactone **38** and the lactol **39**, which were easily separated by column chromatography. Since the hydride addition to the ketone occurs preferentially from the β-face, this implies that the 1,3-steric interaction of the axial ester is more dominant than the 1,2- or 1,4-steric interaction of the axial methyl groups. The cycloaddition of singlet oxygen to the lactone **38** afforded the desired endoperoxide **40** as a single isomer in 99% yield. Following the same procedures we had applied previously, we carried out the two consecutive reductions of the endoperoxide **40** with diimide followed by zinc/acetic acid to produce the dihydroxy lactone **41** in 96% yield without any difficulty.

Next, we needed to regioselectively eliminate the β-hydroxy group of the dihydroxy lactone **41** while retaining the other hydroxyl group at the ring juncture. As illustrated in Table 2, the elimination reactions of the dihydroxy lactone **41** did not proceed under basic conditions, with only starting material being recovered.[16] Treatment of the lactone **41** with thionyl chloride gave the epimeric tertiary alcohol **45** (38%) along with a mixture of the two rearranged lactones **44** and **46** in 25% yield. The formation of **45** is perhaps due to a retro-aldol aldol process with **45** being more stable than **41** due to the lack of one 1,3-diaxial methyl–methyl interaction. Acetylation produced the rearranged lactone **47** in 61% yield without any dehydration. However, it was noted that the oxa-bridged compound **42** was generated under either mesylation (entry 6, 21%) or acidic conditions (entry 9, 64%). Encouraged by this result, we investigated a practical



Scheme 7. Reagents and conditions: (a) HF, CH_3CN, 86%; (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 97%; (c) $NaBH_4$, 95% (**38**/**39**=2.5:1); (d) *hν*, O_2, methylene blue, $CHCl_3$, 0 °C, 5.5 h, 99%; (e) $KO_2CN{=}NCO_2K$, AcOH, CH_2Cl_2, −78 °C to 23 °C; (f) Zn, AcOH, 96% (two steps); (g) see Table 2; (h) LDA, THF, −78 °C, 96% (**43**/**44**=4.6:1).

Table 2. Elimination reaction of **41**



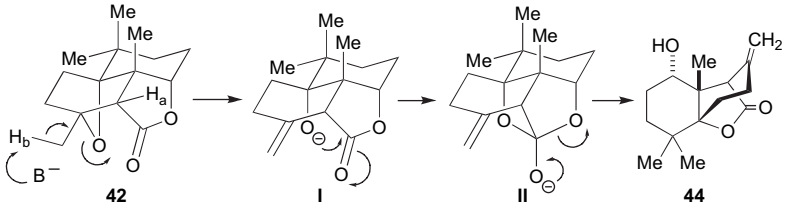
Entry	Conditions	Results
1	KOH, dioxane, 85 °C, 20 h	No reaction
2	LiOH, MeOH, 23 °C, 2 d	No reaction
3	KOH, MeOH, 23 °C, 12 h	No reaction
4	$SOCl_2$, pyr, 0 °C, 1 h	**45** (38%), **44**+**46** (25%)
5	Ac_2O, DMAP, Et_3N, THF, 23 °C, 20 h	**47** (61%)
6	MsCl, DMAP, pyr, CH_2Cl_2, 23 °C, 7 d	**42** (21%)
7	H_2SO_4, CH_2Cl_2, 23 °C, 16 h	**38** (81%)
8	$BF_3{\cdot}Et_2O$, CH_2Cl_2, −78 to 23 °C, 3 h	No reaction
9	TsOH, MS 4 Å, PhH, 90 °C, 20 h	**42** (64%), **38** (24%)
10	HF/pyr, KI, 23 °C, 15 min	**42** (80%), **38** (trace)

procedure to transform the dihydroxy lactone **41** to the oxabicyclic compound **42**. We thought it might be possible to take advantage of the release of the ring strain of the oxa-bridged ring system as the driving force in a subsequent elimination step later in the synthesis. It has been reported that 1,4-cyclohexanediol could be dehydrated to produce the corresponding oxabicyclic compound under mild acidic conditions.[17] Following this literature protocol, we treated the dihydroxy lactone **41** with HF/pyridine in the presence of potassium iodide for a short period of time and obtained the desired oxa-bridged compound **42** cleanly in 80% yield. Finally, we opened the bridged oxygen of this lactone **42** with lithium diisopropylamide at low temperature. In this case, the rearranged lactone **44** was also produced as a side product. As shown in Scheme 8, we believe that the mechanism for the formation of **44** involves the initial proton abstraction from one of the methyl protons (H_b), which generated the tertiary alkoxide anion **I** by β-elimination. The addition of the resulting alkoxide to the nearby lactone group formed the tetrahedral intermediate **II**, which was rearranged to afford the less strained lactone **44**.

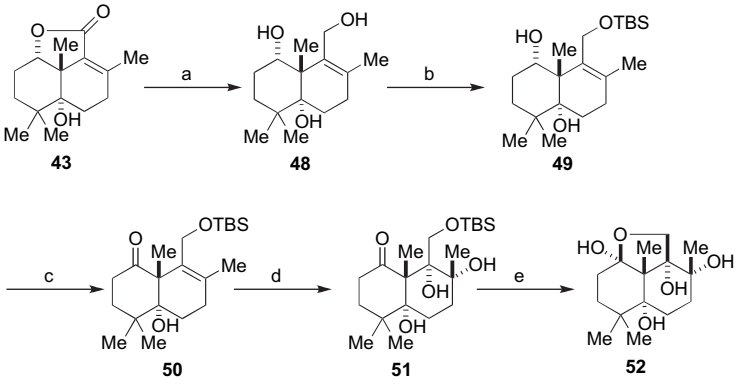
Our final goal was the conversion of the key intermediate **43** to the tetraol **52** having the four contiguous stereogenic centers and all of the functional groups of the AB ring system (Scheme 9). Thus, we first reduced the hydroxy lactone to the triol **48**, which was protected as the TBS ether **49**. Although oxidation of the sterically hindered secondary alcohol in **49** by Dess–Martin periodinane failed, the alcohol was converted to the ketone **50** in 95% yield by Ley's method (TPAP/NMO). Dihydroxylation of the endocyclic alkene **50** with stoichiometric osmium tetroxide in pyridine occurred from the less hindered α-face to furnish the triol **51** in 83% yield. Careful removal of the silyl protecting group using TBAF afforded the desired tetraol **52**, which existed as the hemiketal form **52**. Thus, the synthesis of the highly oxygenated AB ring system of arisugacin A was successfully completed. It converts hydroxy-β-ionone **22** into **52** in 16 steps and 9.3% overall yield.

2.3. The synthesis of 6-aryl-4-hydroxy-2-pyrones

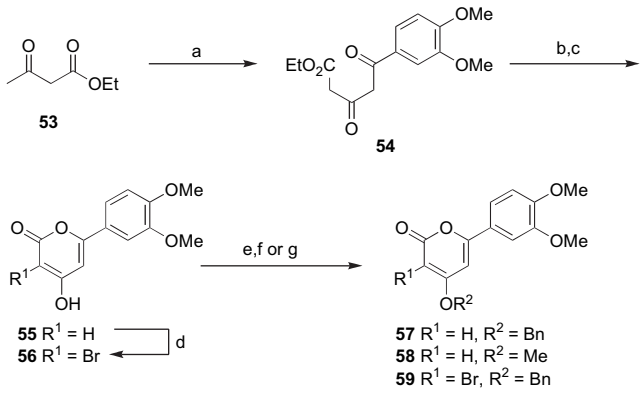
The preparation of the 6-aryl-pyrone was carried out using the procedure reported by Hua[18a] (Scheme 10). Ethyl acetoacetate **53** was treated with lithium diisopropylamide (LDA)



Scheme 8.



Scheme 9. Reagents and conditions: (a) DIBAL, THF, −78 °C to 23 °C, 6 h, 83%; (b) TBSCl, Et_3N, DMAP, CH_2Cl_2, 84%; (c) TPAP, NMO, CH_2Cl_2, 95%; (d) OsO_4, pyr, 83%; (e) TBAF, THF, 89%.



Scheme 10. Reagents and conditions: (a) LDA, THF, TMEDA, methyl 3,4-dimethoxybenzoate, 55%; (b) KOH, MeOH/H_2O; (c) TFAA, 72% (two steps); (d) Br_2, AcOH, 95%; (e) BnBr, K_2CO_3, CH_3CN, 90 °C, 48%; (f) Me_2SO_4, K_2CO_3, 83%; (g) BnBr, K_2CO_3, CH_3CN, 90 °C, 78% (from **56**).

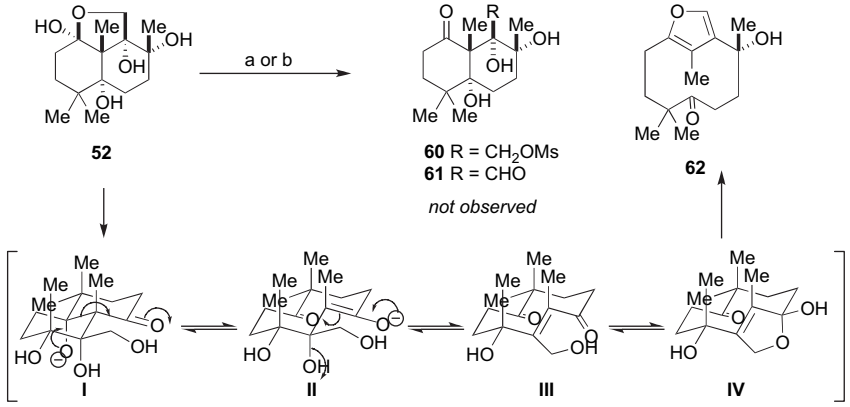
followed by the addition of methyl 3,4-dimethoxybenzoate to afford the diketoester **54** in 55% yield. Since the Claisen condensation of the diketoester **54** required high temperature at low pressure in the literature,[18] milder reaction conditions were required to synthesize the pyrone **55** on a large scale. Thus, the hydrolysis of the diketoester **54** afforded the corresponding acid, which was cyclized using trifluoroacetic anhydride to give the desired pyrone **55** in good yield.[19] Although this hydroxy pyrone **55** can be used directly for coupling reactions, we also prepared several other useful pyrone derivatives. We brominated the 4-hydroxy-2-pyrone **55** in acetic acid to furnish the 3-bromo-2-pyrone **56** in 95% yield. Both the pyrone **55** and the 3-bromo-2-pyrone **56** were protected by benzyl and methyl groups to give the ethers **57**–**59**. However, all attempts to introduce silyl protecting groups on the C4 hydroxyl group of the pyrones **55** and **56** failed due either to the low reactivity of hydroxy pyrones or the instability of the products.

2.4. First coupling attempt—unexpected rearrangement

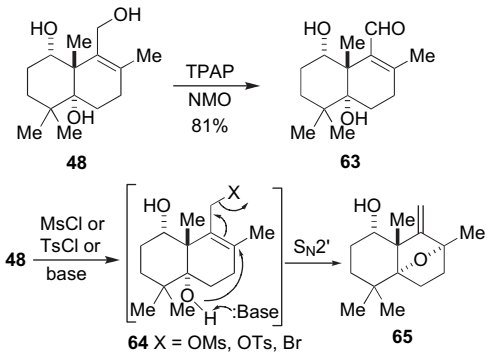
Our initial plan for the connection of a fully functionalized AB ring system **52** with the pyrones **57**–**59** involved transition metal promoted coupling reactions. Thus, it was necessary to transform the advanced intermediate **52** into an electrophilic partner, e.g., either a mesylate or an aldehyde. However, mesylation of the tetraol **52** did not give the corresponding mesylate **60**, but only the bicyclic furan **62** in 95% yield (Scheme 11). Alternatively, when we tried to oxidize the compound **52** to the corresponding aldehyde **61**, we again isolated the same unexpected furan **62**. The structure of **62** was confirmed on the basis of spectroscopic evidence such as the proton NMR spectrum (especially the olefinic singlet at δ 7.08), four olefinic carbons in the carbon NMR spectrum and the carbonyl stretch in the IR spectrum. In addition, we realized that this undesired compound **62** was easily formed when a small amount of acid was present in the deuterated chloroform used in the NMR sample. We explain the formation of this furan **62** as shown in Scheme 11. The severe steric interaction among the three axial methyl groups would promote a retro aldol reaction[20] in the presence of base, namely the alkoxide **I** would open the bicyclic ring to afford the ketone enolate **II**. β-Elimination to give the hydroxymethylenone **III** followed by cyclization would give the hydroxy dihydrofuran **IV**, which would rapidly aromatize via dehydration to generate the highly strained bicyclic furan **62**. The formation of **62** under acidic condition could be explained by a similar acid-promoted mechanism.[21] Consequently, the conversion of the highly functionalized tetraol **52** to the advanced intermediate **60** or **61** was unsuccessful. Thinking that the tertiary hydroxyl group at the ring juncture of **52** had caused the problems observed during acidic or basic treatment, we decided to select less functionalized and more stable AB ring systems as substrates.

2.5. Attempted addition of nucleophilic pyrones to the AB ring system

We then considered other AB ring systems as substrates for the coupling reaction with the various pyrones to overcome the problems associated with tetraol **52**. Consequently, we turned our attention to the strained lactone **47** with the idea that anionic pyrone nucleophiles would add easily to the carbonyl group of such a strained lactone to afford the coupled ketone. Furthermore, we decided to try to utilize some derivatives of the triol **48**, since the lack of the ketone function would be an effective solution to preventing the retro aldol reaction since the required β-hydroxy ketone would not be present. First, the primary alcohol of the triol **48** was selectively oxidized to give the aldehyde **63** in 81% yield (Scheme 12). However, when we attempted to prepare derivatives of **48** containing good leaving groups such as tosylate, mesylate or bromide, e.g., **64**, only the



Scheme 11. Reagents and conditions: (a) MsCl, DMAP, pyr, 3 h, 23 °C, 95%; (b) TPAP, NMO, CH_2Cl_2, 23 °C, 74%.



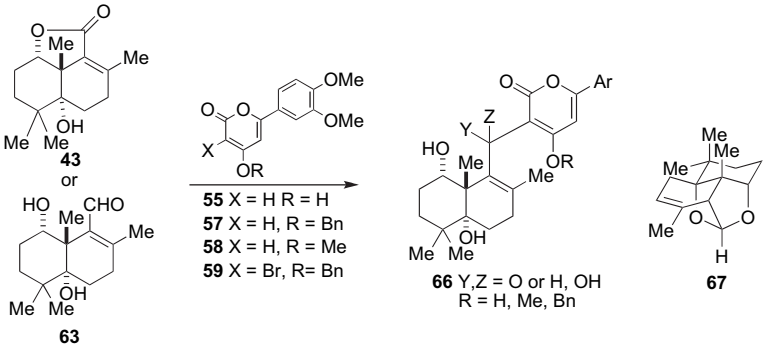
Scheme 12.

oxatricyclic compound **65** was produced as a single product. Presumably, the first intermediate **64** is formed and cyclizes to **65** via an S_N2'-type displacement of the allylic leaving group with the internal tertiary alkoxide. This process indicates the ease of formation of this oxa-bridged system, presumably a result of the steric interaction of the A ring methyl groups. As a result, we were able to investigate the coupling reactions of nucleophilic pyrones with only the lactone **43** and the aldehyde **63**. As illustrated in Table 3, the lithiated pyrone anions, generated via either treatment of the pyrones **55**, **57**, or **58** with LDA or butyllithium or metal–halogen exchange of the bromo pyrone **59**, did not react with the lactone **43** or the aldehyde **63**. A Reformatsky-type reaction[22] of the bromide **59** using a large excess of zinc also did not provide the desired product **66**. Instead, we obtained previously isolated compounds such as the lactone **45** or the oxa-bridged lactone **42** as major products. It appears that the pyrone anion is not nucleophilic enough to attack the hydroxy lactone, but only acts as a base to generate the tertiary alkoxide, which subsequently attacks the lactone carbonyl to give the rearranged lactone **45**, or which undergoes an intramolecular Michael reaction to produce the oxatricyclic lactone **42**. We also tried chromium mediated reactions[23] because it is well known that organochromium species can tolerate many different functional groups.[24] However, the reactions gave only the novel very strained acetal **67** as the major product. The structure of this unusual compound was tentatively assigned by a careful analysis of the ^{1}H NMR, ^{13}C NMR, and IR spectra. In particular, the proton at 5.21 ppm and the carbon at 103.5 ppm indicated that the compound **67** must be acetal. Therefore, we concluded that protection of the hydroxyl group at the ring juncture is necessary to prevent the formation of the side products.

2.6. Indium catalyzed coupling reactions

Since it is clear that a free hydroxyl group at the ring juncture of an AB ring precursor caused some problems during the coupling reactions, we speculated that the oxa-bridged compound **42** would be a good substrate since it is a protected form of the tertiary alcohol, which could be unmasked later in the synthesis. On the other hand, Lee reported an efficient synthesis of a 2*H*-pyran by the indium(II) catalyzed reaction of 4-hydroxycoumarins with α,β-unsaturated aldehydes.[25] In this synthesis, the initial condensation between the aldehyde and a 4-hydroxycoumarin provided an oxatriene intermediate, which was subsequently cyclized to afford a pyran. In order to apply this protocol to our system, the oxa-bridged compound **42** had to be converted to a compound containing an aldehyde functionality. Thus, we reduced the oxatricyclic lactone **42** to the lactol **68** by lithium aluminum hydride at 0 °C in excellent yield (Scheme 13). Then, coupling reaction of the lactol **68** with the hydroxy pyrone **55** in the presence of indium trichloride successfully furnished the desired coupled product **70** as a single diastereomer. The structure of

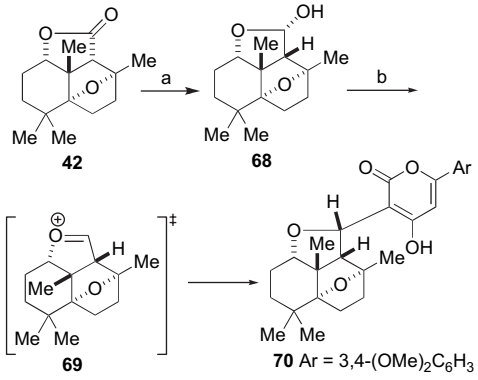
Table 3. Study of pyrone coupling



Entry	Compd	Conditions	Results
1	**43**	3.0 equiv LDA, 1.5 equiv **55**, THF, −78 to 23 °C, 5 h	**45** (67%)
2	**43**	3.0 equiv *n*-BuLi, 3.0 equiv **57**, THF, −78 to 0 °C, 1 h	**42** (63%)
3	**43**	3.0 equiv *t*-BuLi, 1.5 equiv **59**, THF, −78 to 0 °C, 1.5 h	No reaction
4	**43**	3.0 equiv *n*-BuLi, 3.0 equiv **59**, THF, −78 to 0 °C, 1.5 h	**42**[a]
5	**43**	10 equiv Zn, 3.0 equiv **59**, benzene/THF, 85 °C, 18 h	No reaction
6	**63**	6.0 equiv *t*-BuLi, 3.0 equiv **59**, THF/HMPA, −78 to 0 °C, 1 h	Complex mixtures
7	**63**	3.0 equiv *t*-BuLi, 1.5 equiv **59**, THF, −78 to 0 °C, 1 h	Complex mixtures
8	**63**	3.0 equiv *n*-BuLi, 3.0 equiv **59**, THF, −78 to 0 °C, 1 h	Complex mixtures
9	**63**	5.0 equiv $CrCl_2$, 1.0 equiv $NiCl_2$, 3.0 equiv **59**, DMF, −60 to 23 °C, 24 h	No reaction
10	**63**	3.0 equiv $CrCl_2$, 2.0 equiv **59**, THF, 23 °C, 18 h	**67** (39%)
11	**63**	3.0 equiv LDA, 3.0 equiv **58**, THF/HMPA, −78 to 23 °C, 14 h	No reaction

[a] The yield was not determined.

the compound **70** was determined by a comparison of the spectroscopic data with that of the same compound published by Hsung et al.[26] Unlike the mechanism reported in the literature, we believe that the formation of the coupled compound **70** involves the generation of the oxocarbonium intermediate **69** followed by the addition of the pyrone nucleophile **55** from the less hindered β-face.

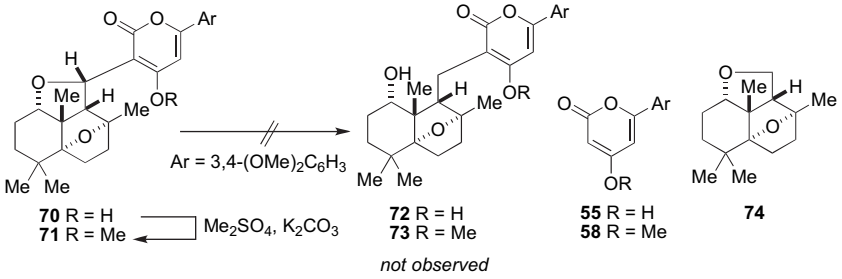


Scheme 13. Reagents and conditions: (a) $LiAlH_4$, THF, 0 °C, 100%; (b) **55**, $InCl_3$, CH_3CN, THF, 80 °C, 73%.

For further transformation of the compound **70** toward arisugacin A, we needed to cleave the strained carbon–oxygen bond of compound **70** to provide the corresponding reduced compound **72**. As shown in Table 4, however, only the carbon–carbon bond next to the pyrone moiety was cleaved to give the ether **74** and the simple pyrone **55** when compound **70** was treated with triethylsilane in the presence of several acids.[27] We postulate that the acids must preferentially coordinate with the carbonyl group of the pyrone moiety to generate the stabilized protonated pyrone intermediate and thus make the pyrone a better leaving group than the strained ether. Thus, we protected the hydroxyl group of the pyrone moiety as the methyl ether **71** and carried out reduction of compound **71** under the same conditions. Unfortunately, it produced the same compound **74** and the 4-methoxy pyrone **58** with none of the desired alcohol **73**.

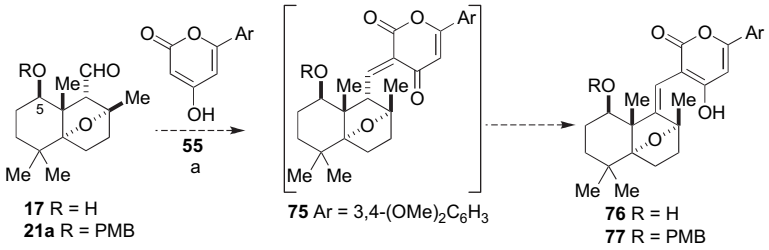
In contrast to the lactol **68**, in which the C5 oxygen is in the axial position, we assumed that the β-hydroxy aldehyde **17** with the opposite stereochemistry at C5 would react with the hydroxy pyrone **55** in the presence of the indium catalyst to afford the coupled product **75** without any bond formation between the two groups since they would now be in a trans orientation. In addition, the PMB protected alcohol **21a** could be a more stable precursor in order to prevent the formation of the ethereal carbon–oxygen bond. Thus, we tested this idea using the two aldehydes **17** and **21a**, which were synthesized via the first IMDAF approach. The coupling reaction of the aldehyde **17** with the hydroxy pyrone **55** was attempted under the same conditions as above, but the reaction did not proceed at all (Scheme 14). The PMB protected aldehyde **21a** was also subjected to the coupling reaction with the pyrone **55** in the presence of indium(III) chloride, but only the starting material **21a** was recovered. Unlike the case of the lactol **68**, it seems that the activation of the aldehyde **17** or **21a** by indium catalyst did not occur perhaps due to the steric congestion around the aldehyde moiety. Thus the formation of an oxocarbonium intermediate such as **69** seems to be required for this coupling to proceed well.

Table 4. Study of reduction of coupled pyrone substrate



Entry	Substrates	Conditions	Results
1	**70**	Et_3SiH, TFA, CH_2Cl_2, 23 °C, 6 h	No reaction
2	**70**	Et_3SiH, TFA, DCE, 60 °C, 44 h	**70**+**55**+**74**[a]
3	**70**	Et_3SiH, CF_3SO_3H, CH_2Cl_2, 23 °C, 2.5 h	Decomposed
4	**70**	Et_3SiH, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 23 °C, 24 h	**55**+**74** (68%)
5	**71**	Et_3SiH, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 23 °C, 18 h	**58**+**74** (quant)

[a] The yield was not determined.



Scheme 14. Reagents and conditions: (a) **55**, $InCl_3$, CH_3CN, THF, 80 °C.

3. Conclusion

We have studied the synthesis of the AB ring system of arisugacin A using two synthetic methodologies. The first approach was based on an intramolecular Diels–Alder reaction of furan (IMDAF) and gave the synthetically useful intermediates **17** and **21a** even though we did not open the oxa-bridged ring to give the hydroxy enals. We then synthesized the highly oxygenated AB ring system using two crucial methods, namely electrocyclization and singlet oxygen reaction, in 16 steps in 9.3% overall yield starting from hydroxy β-ionone. Finally, coupled products, such as the cyclic ether **70**, were obtained via an indium catalyzed reaction; however arisugacin A could not be prepared from this compound. Synthetic studies of other coupling reactions between various AB ring systems and pyrone units are currently underway and will be reported in due course.

4. Experimental section

4.1. General

4.1.1. (±)-(1*R*,6*R*,8*R*)-2,2,6,8-Tetramethyl-7-methylene-11-oxatricyclo[6.2.1.0^{1,6}]-9-undecen-5-one (14). To a solution of the allenic ketone **13**[5] (455 mg, 1.96 mmol) in dichloromethane (20 mL) cooled to −78 °C was added a solution of dimethylaluminum chloride (2.15 mL, 2.15 mmol, 1.0 M in hexane). After stirring for 30 min, the reaction mixture was allowed to warm to −20 °C and stirred for an additional 3 h. The mixture was quenched with saturated sodium bicarbonate (30 mL), extracted with dichloromethane (3×25 mL), washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (10:1 hexane/ethyl acetate) to give the oxatricyclic compound **14** (416 mg, 91%) as a solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.30 (d, J=5.6 Hz, 1H), 6.19 (d, J=5.6 Hz, 1H), 5.07 (s, 1H), 4.99 (s, 1H), 2.72 (ddd, J=15.9, 13.6, 6.1 Hz, 1H), 2.42 (ddd, J=15.9, 4.7, 3.1 Hz, 1H), 2.08 (ddd, J=13.6, 13.6, 4.7 Hz, 1H), 1.59 (ddd, J=13.6, 6.1, 3.1 Hz, 1H), 1.54 (s, 3H), 1.35 (s, 3H), 1.25 (s, 3H), 1.09 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 210.2, 154.4, 140.0, 133.7, 105.3, 96.8, 86.6, 59.2, 35.1, 34.4, 32.5, 27.1, 25.4, 23.5, 15.6. IR (neat): 3081, 2967, 2931, 2869, 1712, 1476, 1452, 1384, 1370, 1319, 1250, 1201, 1164, 1124, 1083, 1066, 1011, 943, 886, 758 cm^{-1}. HRMS (EI) m/z found for M$^+$ 232.1459 calcd for $C_{15}H_{20}O_2$ 232.1463.

4.1.2. (±)-(1*R*,6*R*,8*R*)-2,2,6,8-Tetramethyl-7-methylene-11-oxatricyclo[6.2.1.0^{1,6}]-5-undecanone (14a). To a suspension of **14** (0.491 g, 2.11 mmol) and dipotassium azodicarboxylate[28] (1.642 g, 8.45 mmol) in dichloromethane (20 mL) cooled to −78 °C was slowly added a solution of acetic acid (0.97 mL, 16.0 mmol) in dichloromethane (2 mL). The reaction mixture was stirred at −78 °C for 2 h and then slowly warmed to 23 °C. Stirring was continued until the suspension became white and then the solvent was removed under reduced pressure. The residue was diluted with ether (30 mL) and the residual potassium acetate was filtered off through a pad of Celite. The solvent was completely removed under reduced pressure to yield the crude product, which was purified by column chromatography on silica gel (10:1 hexane/ethyl acetate) to provide the reduced compound **14a** (430 mg, 87%) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 4.98 (s, 1H), 4.84 (s, 1H), 2.64 (ddd, J=15.3, 13.2, 6.0 Hz, 1H), 2.40 (ddd, J=15.2, 4.9, 3.7 Hz, 1H), 2.12 (ddd, J=13.4, 13.4, 3.5 Hz, 1H), 1.81–1.78 (m, 2H), 1.62–1.56 (m, 3H), 1.43 (s, 3H), 1.36 (s, 3H), 1.15 (s, 3H), 1.12 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 210.5, 158.6, 103.6, 93.5, 84.6, 62.1, 38.2, 35.9, 35.0, 33.7, 25.9, 25.7, 23.7, 22.9, 18.3. IR (neat): 3082, 2973, 2871, 1716, 1665, 1475, 1450, 1420, 1383, 1324, 1248, 1223, 1180, 1102, 1063, 1031, 1014, 922, 888, 828, 780 cm^{-1}. HRMS (EI) m/z found for M$^+$ 234.1629, calcd for $C_{15}H_{22}O_2$ 234.1620.

4.1.3. (±)-(1*R*,5*R*,6*S*,8*R*)-2,2,6,8-Tetramethyl-7-methylene-11-oxatricyclo[6.2.1.0^{1,6}]undecan-5-ol (15). To a preformed solution of lithium (30 mg, 4.32 mmol) in ammonia (3 mL) was added a solution of the ketone **14a** (50 mg, 0.21 mmol) and methanol (8 mL, 0.20 mmol) in diethyl ether (1 mL), and the resulting mixture was allowed to stir for 5 h at −33 °C. The mixture was poured into aqueous ammonium chloride solution (10 mL) and diluted with diethyl ether (10 mL). After extraction with diethyl ether (3×10 mL), the combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (4:1 to 1:1 hexane/diethyl ether) to yield the alcohol **15** (32 mg, 64%) along with the starting material **14a** (6 mg, 12%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 4.76 (s, 1H), 4.69 (s, 1H), 3.61 (dd, J=9.1, 6.6 Hz, 1H), 1.80–1.69 (m, 4H), 1.66–1.61 (m, 2H), 1.58–1.49 (m, 2H), 1.48 (s, 3H), 1.38 (ddd, J=13.3, 3.4, 3.4 Hz, 1H), 1.16 (s, 3H), 1.02 (s, 3H), 0.97 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 165.0, 98.9, 92.6, 85.3, 73.0, 53.3, 38.6, 36.5, 33.8, 27.0, 26.2, 26.1, 24.1, 18.6, 14.6. HRMS (EI) m/z found for M$^+$ 236.1775, calcd for $C_{15}H_{24}O_2$ 236.1776.

4.1.4. (±)-(1*R*,5*R*,6*S*,7*R*,8*R*)-7-(Hydroxymethyl)-2,2,6,8-tetramethyl-11-oxatricyclo[6.2.1.0^{1,6}]-5-undecanol (16a) and (±)-(1*R*,5*R*,6*S*,7*S*,8*R*)-7-(hydroxymethyl)-2,2,6,8-tetramethyl-11-oxatricyclo[6.2.1.0^{1,6}]-5-undecanol (16b). To a solution of the alkene **15** (23 mg, 0.097 mmol) in dichloromethane (1 mL) cooled to 0 °C was added borane/dimethyl sulfide complex (28 μL, 0.30 mmol). The reaction mixture was allowed to warm to 23 °C and stirred for 3 h. The solution was again cooled to 0 °C and treated with 15% sodium hydroxide (0.2 mL) and 30% hydrogen peroxide (0.2 mL). The reaction mixture was allowed to warm to 23 °C and stirred for another 24 h. Ammonium chloride (5 mL) and ethyl acetate (5 mL) were added to the reaction mixture. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3×5 mL). The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (1:1 hexane/ethyl acetate) to give the alcohol **16a** (13 mg, 53%) and its epimer **16b** (6 mg, 24%). Compound **16a**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 4.12 (dd, J=11.0, 4.7 Hz, 1H), 3.87 (dd, J=11.9, 11.6 Hz, 1H), 3.68 (dd, J=11.6, 4.2 Hz, 1H), 3.07 (br s, 2H), 1.93 (ddd, J=13.2, 9.2, 6.3 Hz, 1H), 1.79–1.69 (m, 4H), 1.65–1.59 (m, 2H), 1.40–1.27 (m, 2H), 1.25 (s, 3H), 1.22 (s, 3H), 0.97 (s, 3H), 0.93 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz)

δ: 92.5, 82.9, 71.6, 61.7, 59.2, 53.0, 41.2, 35.8, 34.1, 27.9, 26.8, 26.5, 24.0, 18.2, 17.9. HRMS (EI) *m/z* found for M^+ 254.1897, calcd for $C_{15}H_{26}O_3$ 254.1892. Compound **16b**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 3.60 (dd, *J*=11.6, 4.3 Hz, 1H), 3.57 (dd, *J*=10.2, 10.2 Hz, 1H), 3.53 (dd, *J*=10.2, 4.2 Hz, 1H), 2.02 (br s, 2H), 1.81 (ddd, *J*=17.8, 9.4, 4.7 Hz, 1H), 1.81–1.78 (m, 1H), 1.74 (ddd, *J*=13.6, 13.6, 3.5 Hz, 1H), 1.67 (ddd, *J*=12.8, 12.8, 4.8 Hz, 1H), 1.67–1.62 (m, 1H), 1.58 (ddd, *J*=12.6, 3.9, 3.9 Hz, 1H), 1.45 (ddd, *J*=12.3, 9.2, 4.8 Hz, 1H), 1.42 (s, 3H), 1.38 (ddd, *J*=13.3, 3.4, 3.4 Hz, 1H), 1.29 (ddd, *J*=9.5, 4.7, 2.2 Hz, 1H), 1.10 (s, 3H), 1.00 (s, 3H), 0.95 (s, 3H).

4.1.5. (±)-(1*R*,5*R*,6*S*,7*S*,8*R*)-5-Hydroxy-2,2,6,8-tetramethyl-11-oxatricyclo[6.2.1.0^{1,6}]undecane-7-carboxaldehyde (17). To a solution of the alcohol **16a** (6.9 mg, 0.027 mmol) in dichloromethane (3 mL) under argon was added the Dess–Martin periodinane (13 mg, 0.030 mmol). The suspension was stirred at 23 °C for 1 h, and then a solution of sodium thiosulfate in saturated sodium bicarbonate (5 mL) was added. The mixture was stirred vigorously until the organic layer was clear. The organic layer was separated. The aqueous layer was extracted with diethyl ether (3×10 mL). Both layers were washed with saturated sodium bicarbonate and brine. The combined organic layer was then dried over magnesium sulfate and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (4:1 to 2:1 hexane/ethyl acetate) to give the hydroxy aldehyde **17** (5 mg, 72%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 9.72 (d, *J*=6.2 Hz, 1H), 4.33 (dd, *J*=11.6, 4.2 Hz, 1H), 2.07 (d, *J*=6.2 Hz, 1H), 1.90 (ddd, *J*=13.2, 9.2, 6.2 Hz, 1H), 1.83–1.77 (m, 2H), 1.73 (ddd, *J*=11.7, 2.3, 2.3 Hz, 1H), 1.68–1.62 (m, 1H), 1.61 (ddd, *J*=12.6, 7.8, 3.8 Hz, 1H), 1.54 (br s, 1H), 1.44 (ddd, *J*=12.2, 12.2, 6.2 Hz, 1H), 1.40 (ddd, *J*=13.1, 3.3, 3.3 Hz, 1H), 1.40 (s, 3H), 1.21 (s, 3H), 1.03 (s, 3H), 0.94 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 204.5, 93.2, 84.3, 70.1, 69.1, 56.9, 41.0, 36.4, 34.0, 27.5, 26.8, 26.5, 24.2, 18.3, 16.8. IR (neat): 3450, 2979, 2938, 2871, 1708, 1477, 1460, 1383, 1103, 1046, 1008, 994 cm^{-1}.

4.1.6. (±)-(1*R*,5*R*,6*S*,8*R*)-5-((4-Methoxyphenyl)-methoxy)-2,2,6,8-tetramethyl-7-methylene-11-oxatricyclo[6.2.1.0^{1,6}]undecane (20). To a solution of the alcohol **15** (200 mg, 0.85 mmol) in diethyl ether (8 mL) were added *p*-methoxybenzyl trichloroacetimidate (478 mg, 1.69 mmol) and trifluoromethanesulfonic acid (2 μL, 0.02 mmol) at 23 °C. The reaction mixture was stirred for 15 min and then quenched with aqueous sodium bicarbonate (10 mL). The mixture was extracted with diethyl ether (3×15 mL), and the combined organic layer was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (15:1 hexane/diethyl ether) to yield the PMB ether **20** (267 mg, 89%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.25 (d, *J*=8.8 Hz, 2H), 6.85 (d, *J*=8.8 Hz, 2H), 4.87 (s, 1H), 4.71 (s, 1H), 4.49 (d, *J*=11.1 Hz, 1H), 4.31 (d, *J*=11.1 Hz, 1H), 3.80 (s, 3H), 3.37 (dd, *J*=11.8, 3.7 Hz, 1H), 1.82–1.68 (m, 4H), 1.57–1.49 (m, 3H), 1.48 (s, 3H), 1.37 (ddd, *J*=13.2, 13.2, 3.1 Hz, 1H), 1.23 (s, 3H), 1.02 (s, 3H), 0.97 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 163.8, 158.8, 131.4, 129.0, 113.4, 100.1, 92.7, 85.2, 81.1, 72.0, 55.1, 52.6, 38.3, 36.5, 33.8, 26.8, 26.2, 24.1, 23.5, 18.9, 16.2. IR (neat): 3075, 2984, 2933, 2868, 2835, 1613, 1514, 1463, 1382, 1302, 1248, 1172, 1086, 1039, 887, 822 cm^{-1}.

4.1.7. (±)-(1*R*,5*R*,6*S*,7*S*,8*R*)-5-[(4-Methoxyphenyl)methoxy]-2,2,6,8-tetramethyl-11-oxatricyclo[6.2.1.0^{1,6}]undecane-7-carboxaldehyde (21a) and (±)-(1*R*,5*R*,6*S*,7*R*,8*R*)-5-[(4-methoxyphenyl)methoxy]-2,2,6,8-tetramethyl-11-oxatricyclo[6.2.1.0^{1,6}]undecane-7-carboxaldehyde (21b). Following the same procedure as that used for the synthesis of **16ab**, the reaction of the alkene **20** (200 mg, 0.56 mmol) and borane/dimethyl sulfide complex (0.11 mL, 1.16 mmol) gave a mixture of the corresponding alcohols (52 mg, 25%) after purification by column chromatography on silica gel (6:1 hexane/ethyl acetate).

Following the same procedure as that used for the synthesis of **17**, the reaction of the mixture of the alcohols (52 mg, 0.14 mmol) and Dess–Martin periodinane (71 mg, 0.17 mmol) gave the aldehyde **21a** (30 mg, 58%) and the aldehyde **21b** (14 mg, 27%) after purification by column chromatography on silica gel (10:1 hexane/ethyl acetate). Compound **21a**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 9.48 (d, *J*=6.1 Hz, 1H), 7.20 (d, *J*=8.6 Hz, 2H), 6.85 (d, *J*=8.6 Hz, 2H), 4.49 (d, *J*=11.0 Hz, 1H), 4.17 (d, *J*=11.0 Hz, 1H), 3.96 (dd, *J*=11.8, 3.6 Hz, 1H), 3.79 (s, 3H), 2.10 (d, *J*=6.1 Hz, 1H), 1.96 (ddd, *J*=12.8, 7.0, 3.5 Hz, 1H), 1.90 (ddd, *J*=13.2, 9.2, 6.0 Hz, 1H), 1.78 (ddd, *J*=12.6, 12.6, 3.5 Hz, 1H), 1.74 (ddd, *J*=13.6, 13.6, 3.5 Hz, 1H), 1.66–1.61 (m, 1H), 1.58–1.53 (m, 1H), 1.48–1.42 (m, 2H), 1.39 (s, 3H), 1.25 (s, 3H), 1.04 (s, 3H), 0.96 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 203.7, 158.8, 130.3, 128.9, 113.5, 93.2, 84.2, 77.3, 69.0, 68.7, 57.2, 55.1, 41.0, 36.3, 34.2, 26.6, 26.5, 24.4, 21.4, 18.3, 18.2. Compound **21b**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 9.69 (d, *J*=2.9 Hz, 1H), 7.23 (d, *J*=8.5 Hz, 2H), 6.87 (d, *J*=8.5 Hz, 2H), 4.63 (d, *J*=11.6 Hz, 1H), 4.30 (d, *J*=11.6 Hz, 1H), 3.79 (s, 3H), 3.36 (dd, *J*=11.9, 3.7 Hz, 1H), 2.12 (dd, *J*=2.9, 2.5 Hz, 1H), 1.97 (ddd, *J*=12.9, 9.2, 4.0 Hz, 1H), 1.86 (ddd, *J*=13.0, 9.2, 5.5 Hz, 1H), 1.82 (ddd, *J*=12.8, 7.0, 3.5 Hz, 1H), 1.73 (ddd, *J*=12.7, 12.7, 4.0 Hz, 1H), 1.68 (ddd, *J*=13.6, 13.6, 3.1 Hz, 1H), 1.54 (dddd, *J*=13.0, 13.0, 13.0, 3.0 Hz, 1H), 1.42 (ddd, *J*=13.3, 3.2, 3.2 Hz, 1H), 1.38 (dddd, *J*=12.4, 12.4, 5.5, 2.4 Hz, 1H), 1.31 (s, 3H), 1.26 (s, 3H), 1.00 (s, 3H), 0.96 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 204.2, 159.1, 130.8, 129.2, 113.7, 93.7, 84.9, 84.8, 70.5, 68.9, 55.2, 52.2, 36.5, 34.4, 32.6, 27.2, 26.5, 24.7, 21.9, 21.7, 14.0.

4.1.8. (±)-(*E*)-4-[1-(3-[(1,1-Dimethylethyl)dimethylsilyloxy]-2,6,6-trimethyl-1-cyclohexenyl)]-3-buten-2-one (22a).[11] To a solution of the hydroxy ketone **22** (3.403 g, 16.3 mmol) in dimethylformamide (16 mL) at 0 °C were added imidazole (1.668 g, 24.5 mmol) and *tert*-butyldimethylsilyl chloride (3.694 g, 24.5 mmol). The reaction mixture was stirred for 1.5 h and quenched with aq ammonium chloride (40 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (3×50 mL). The combined organic layers were washed with water and brine, dried over magnesium sulfate, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (15:1 pentane/ethyl acetate) to give the silyl ether **22a**[11] (5.162 g, 98%) as an oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.19 (d, *J*=16.4 Hz, 1H), 6.11 (d, *J*=16.4 Hz, 1H), 4.01 (dd, *J*=5.5, 5.5 Hz, 1H), 2.28 (s, 3H),

1.84–1.77 (m, 1H), 1.74 (s, 3H), 1.68–1.62 (m, 2H), 1.42–1.37 (m, 1H), 1.06 (s, 3H), 1.01 (s, 3H), 0.89 (s, 9H), 0.08 (s, 3H), 0.08 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 198.4, 143.2, 137.9, 135.7, 132.8, 70.9, 35.4, 34.5, 28.9, 28.4, 28.3, 27.2, 25.8, 18.4, 18.1, −4.2, −4.7. IR (neat): 2955, 2857, 1695, 1675, 1463, 1360, 1253, 1085, 1050, 837 cm^{-1}.

4.1.9. (±)-(2*E*,4*E*)Ethyl-5-[1-(3-[(1,1-dimethylethyl)dimethylsilyloxy]-2,6,6-trimethyl-1-cyclohexenyl)]-3-methyl-2,4-pentadienoate (23a).[12] To a suspension of sodium hydride (3.18 g, 73.0 mmol, 55% in mineral oil) in diethyl ether (50 mL) cooled to 0 °C was slowly added a solution of triethyl phosphonoacetate (12.6 mL, 63.3 mmol) in diethyl ether (10 mL). After the reaction mixture was stirred for 1 h at 0 °C, a solution of the enone **22a** (15.13 g, 46.9 mmol) in diethyl ether (10 mL) was added. The reaction was allowed to warm to 23 °C and stirred for 18 h. The mixture was quenched with aq ammonium chloride, extracted with diethyl ether, washed with brine, dried over magnesium sulfate, and concentrated. The crude product was purified by column chromatography on silica gel (20:1 to 15:1 hexane/ethyl acetate) to give a 7.2:1 mixture of the ethyl dienoates **23a**[12] and **23b** (16.66 g, 90%) as an oil. Compound **23a**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.51 (d, J=16.1 Hz, 1H), 6.11 (d, J=16.1 Hz, 1H), 5.75 (br s, 1H), 4.17 (q, J=7.1 Hz, 2H), 4.02 (dd, J=5.5, 5.5 Hz, 1H), 2.32 (s, 3H), 1.85–1.75 (m, 1H), 1.72 (s, 3H), 1.69–1.61 (m, 2H), 1.42–1.37 (m, 1H), 1.29 (t, J=7.1 Hz, 3H), 1.02 (s, 3H), 0.98 (s, 3H), 0.91 (s, 9H), 0.09 (s, 3H), 0.09 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 167.2, 152.4, 139.5, 137.0, 133.3, 132.6, 118.6, 71.1, 59.6, 35.3, 34.7, 29.2, 28.4 (2C), 25.9, 18.4, 18.2, 14.3, 13.6, −4.2, −4.6. IR (neat): 2956, 2932, 2857, 1714, 1609, 1471, 1463, 1362, 1352, 1252, 1234, 1153, 1083, 1048, 836, 773 cm^{-1}.

4.1.10. (±)-(2*E*,4*E*)-5-[1-(3-[(1,1-Dimethylethyl)dimethylsilyloxy]-2,6,6-trimethyl-1-cyclohexenyl)]-3-methyl-2,4-pentadienenitrile (24a).[13] To a solution of diethyl cyanomethylphosphonate (0.75 mL, 4.64 mmol) in tetrahydrofuran (30 mL) cooled to −78 °C was added *n*-butyllithium (1.92 mL, 2.5 M in pentane). After the mixture stirred for 20 min, a solution of the enone **22** (1.002 g, 3.11 mmol) in tetrahydrofuran (10 mL) was added and the resulting solution was allowed to warm to 23 °C. The reaction mixture was stirred for 16 h and quenched with aqueous ammonium chloride (40 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (3×50 mL). The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated. The crude product was purified by column chromatography on silica gel (20:1 to 15:1 hexane/ethyl acetate) to yield a 2.0:1 mixture of the trienenitriles **24a**[13] and **24b** (0.935 g, 87%) as an oil. Compound **24a**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.51 (d, J=16.1 Hz, 1H), 6.15 (d, J=16.1 Hz, 1H), 5.17 (br s, 1H), 4.00 (dd, J=5.4, 5.4 Hz, 1H), 2.19 (d, J=1.1 Hz, 3H), 1.81–1.76 (m, 1H), 1.71 (s, 3H), 1.67–1.61 (m, 2H), 1.41–1.36 (m, 1H), 1.02 (s, 3H), 0.98 (s, 3H), 0.90 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 156.9, 138.8, 135.4, 133.64, 133.57, 96.9, 70.9, 35.2, 34.6, 29.0, 28.4, 28.3, 25.8, 18.4, 18.1, 16.4, −4.3, −4.7 (one low field carbon not observed). IR (neat): 2956, 2857, 2211, 1618, 1586, 1471, 1463, 1389, 1361, 1351, 1252, 1083, 1049, 1005 cm^{-1}.

4.1.11. (±)-(1*R*,8*R*,8a*R*)Ethyl-8-[(1,1-dimethylethyl)dimethylsilyloxy]-2,5,5,8a-tetramethyl-1,5,6,7,8,8a-hexahydronaphthalene-1-carboxylate (25). Procedure A: The triene **23** (351 mg, 0.89 mmol) and benzanthrone (309 mg, 1.34 mmol) were dissolved in tetrahydrofuran (30 mL). The solution was stirred for 5 h under the irradiation of a medium-pressure mercury lamp (Hanovia model 73A36, 550 W). The solvent was removed under reduced pressure and the benzanthrone was filtered off through Celite with the aid of hexane. The solvent was again removed under reduced pressure to give the isomerized products, which were dissolved in dimethylformamide (2.5 mL). The reaction solution was stirred for 3 d at 154–160 °C. After the mixture was cooled to 23 °C, the solvent was removed under reduced pressure to give the crude product, which was purified by column chromatography on silica gel (25:1 to 20:1 hexane/diethyl ether) to yield the cyclized product **25** (197 mg, 56%) as an oil.

Procedure B: Procedure A was used, but the crude material (the isomerized intermediate) was purified by column chromatography on silica gel.

Procedure C: Following procedure A, the crude isomerized products were prepared. They were stirred for 5 min at 250 °C under microwave heating. The solvent was removed under reduced pressure and the crude material was purified by column chromatography on silica gel.

Procedure D: A solution of the triene **23** in dimethylformamide was stirred for 10 min at 250 °C under microwave heating. The solvent was removed under reduced pressure and the crude material was purified by column chromatography on silica gel.

Compound **25**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 5.69 (s, 2H), 4.17–4.11 (m, 1H), 4.01–3.96 (m, 2H), 2.83 (s, 1H), 1.84 (s, 3H), 1.75 (dddd, J=13.3, 13.0, 11.4, 3.7 Hz, 1H), 1.61 (dddd, J=13.0, 4.4, 4.0, 3.5 Hz, 1H), 1.49 (ddd, J=13.6, 13.3, 3.5 Hz, 1H), 1.41 (ddd, J=13.6, 4.0, 3.7 Hz, 1H), 1.22 (t, J=7.2 Hz, 3H), 1.13 (s, 3H), 1.11 (s, 6H), 0.89 (s, 9H), 0.04 (s, 3H), 0.00 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 171.5, 150.0, 128.7, 121.7, 116.8, 74.2, 59.6, 54.6, 43.4, 37.2, 34.5, 32.2, 31.1, 27.9, 25.9, 22.6, 18.0, 17.9, 14.2, −3.6, −5.3.

4.1.12. (±)-(1*R*,8*R*,8a*R*)-8-[(1,1-Dimethylethyl)dimethylsilyloxy]-2,5,5,8a-tetramethyl-1,5,6,7,8,8a-hexahydronaphthalene-1-carbonitrile (26) and (±)-(8*S*,8a*S*)-8-[(1,1-dimethylethyl)dimethylsilyloxy]-2,5,5,8a-tetramethyl-3,5,6,7,8,8a-hexahydronaphthalene-1-carbonitrile (27). Following procedure A as used for the synthesis of **25**, the reaction of the triene **24** (935 mg, 2.71 mmol) and benzanthrone (934 mg, 4.06 mmol) gave a 3:2 mixture of the cyclized products **26** and **27** (579 mg, 62%) as an oil. Compound **26**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 5.89 (d, J=5.8 Hz, 1H), 5.82 (dq, J=5.8, 1.5 Hz, 1H), 4.10 (dd, J=11.2, 4.6 Hz, 1H), 2.94 (s, 1H), 1.91 (d, J=1.5 Hz, 3H), 1.82–1.75 (m, 1H), 1.69 (dddd, J=13.0, 4.6, 4.0, 4.0 Hz, 1H), 1.61–1.58 (m, 1H), 1.50–1.47 (m, 1H), 1.15 (s, 3H), 1.10 (s, 3H), 1.03 (s, 3H), 0.91 (s, 9H), 0.17 (s, 3H), 0.13 (s, 3H). Compound **27**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 5.59 (t, J=3.7 Hz, 1H), 4.01 (br d, J=2.1 Hz, 1H), 2.72 (m, 2H), 2.04

(d, J=14.3, 14.3, 4.0, 1.8 Hz, 1H), 1.98 (s, 3H), 1.78–1.73 (m, 1H), 1.50–1.45 (m, 1H), 1.32 (s, 3H), 1.20 (ddd, J=12.8, 3.4, 3.4 Hz, 1H), 1.16 (s, 3H), 1.12 (s, 3H), 0.79 (s, 9H), 0.13 (s, 3H), 0.05 (s, 3H).

4.1.13. (±)-(1*R*,3*R*,8*R*,8a*R*)Ethyl-8-[(1,1-dimethylethyl)-dimethylsilyloxy]-3-hydroperoxy-5,5,8a-trimethyl-2-methylene-1,2,3,5,6,7,8,8a-octahydronaphthalene-1-carboxylate (28). To a solution of the dienes **25** (31 mg, 0.079 mmol) in chloroform (3.5 mL) was added methylene blue (0.3 mg). The reaction mixture was cooled to 0 °C. Oxygen gas was bubbled into the reaction mixture, which was stirred for 3 h at 0 °C under the irradiation of a high-pressure sodium lamp (GE Lucalox LU-400/BU, 400 W). The solvent was removed under reduced pressure. The resulting residue was purified by column chromatography on silica gel (8:1 to 4:1 hexane/ethyl acetate) to give the hydroperoxide **28** (17 mg, 51%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.84 (s, 1H), 5.50 (d, J=4.3 Hz, 1H), 5.39 (s, 2H), 4.61 (d, J=4.3 Hz, 1H), 4.38 (dd, J=11.3, 4.8 Hz, 1H), 4.09 (q, J=7.2 Hz, 1H), 4.08 (q, J=7.2 Hz, 1H), 3.24 (s, 1H), 1.79 (dddd, J=13.3, 13.0, 11.3, 3.4 Hz, 1H), 1.63 (dddd, J=13.0, 4.8, 3.7, 3.6 Hz, 1H), 1.57 (ddd, J=13.5, 13.3, 3.6 Hz, 1H), 1.45 (ddd, J=13.5, 3.7, 3.4 Hz, 1H), 1.24 (t, J=7.2 Hz, 1H), 1.15 (s, 3H), 1.11 (s, 3H), 1.06 (s, 3H), 0.89 (s, 9H), 0.03 (s, 3H), −0.03 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 171.1, 159.5, 139.5, 120.5, 114.3, 81.2, 72.6, 60.4, 54.9, 44.5, 37.1, 35.5, 31.3, 31.2, 27.6, 25.8, 23.0, 18.0, 14.1, −3.8, −5.3. IR (neat): 3463, 2964, 2932, 2858, 1782, 1730, 1678, 1463, 1395, 1253, 1107, 838 cm^{-1}. HRMS (MALDI) m/z found for $(M+Na)^+$ 447.2549, calcd for $C_{23}H_{40}O_5NaSi$ 447.2537.

4.1.14. (±)-(1*R*,5*R*,6*R*,7*R*,8*R*)-5-[(1,1-Dimethylethyl)-dimethylsilyloxy]-2,2,6,8-tetramethyl-9,10-dioxatricyclo[6.2.2.0^{1,6}]dodec-11-ene-7-carbonitrile (30). Following the same procedure as that used in the synthesis of **28**, the reaction of a mixture of the dienes **26** and **27** (365 mg, 1.05 mmol) in chloroform (6 mL) in the presence of methylene blue (5 mg) and oxygen at 0 °C for 20 h gave the endoperoxide **30** (110 mg, 28%) along with a mixture of **26** and **27** (217 mg, 59%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.58 (d, J=8.6 Hz, 1H), 6.41 (d, J=8.6 Hz, 1H), 4.55 (dd, J=11.2, 4.5 Hz, 1H), 2.27 (s, 1H), 1.85–1.78 (m, 2H), 1.71–1.66 (m, 1H), 1.58 (s, 3H), 1.30–1.25 (m, 1H), 1.16 (s, 3H), 1.05 (s, 3H), 0.97 (s, 3H), 0.92 (s, 9H), 0.23 (s, 3H), 0.15 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 134.0 (2C), 118.3, 84.3, 73.7, 73.2, 47.3, 46.1, 35.4, 33.5, 28.3, 27.0, 26.3, 25.0, 23.6, 20.2, 18.4, −2.7, −4.6. IR (neat): 2952, 2931, 2894, 2857, 2240, 1657, 1632, 1463, 1380, 1254, 1125, 1097, 1069 cm^{-1}. HRMS (MALDI) m/z found for $(M+Na)^+$ 400.2269, calcd for $C_{21}H_{35}NO_3NaSi$ 400.2278.

4.1.15. Side products in Scheme 6.

4.1.15.1. (±)-(1*R*,2*S*,3*R*,4*S*,4a*R*,8*R*,8a*S*)-(2,3:4,4a)Bis-epoxy-8-[(1,1-dimethylethyl)dimethylsilyloxy]-2,5,5,8a-tetramethyl-decahydronaphthalene-1-carbonitrile (31). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 4.04 (dd, J=7.8, 7.8 Hz, 1H), 3.32 (d, J=2.6 Hz, 1H), 3.23 (d, J=2.6 Hz, 1H), 2.82 (s, 1H), 1.77–1.72 (m, 2H), 1.61–1.55 (m, 1H), 1.46 (s, 3H), 1.44 (ddd, J=14.0, 3.4, 3.4 Hz, 1H), 1.19 (s, 3H), 1.12 (s, 3H), 0.89 (s, 9H), 0.75 (s, 3H), 0.18 (s, 3H), 0.12 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 116.8, 74.0, 67.1, 55.1, 50.5, 49.2, 45.3, 41.1, 35.5, 33.9, 27.5, 26.4, 25.8, 25.5, 24.4, 18.2, 18.0, −3.9, −4.9. HRMS (EI) m/z found for $(M+H)^+$ 378.2467, calcd for $C_{21}H_{36}NO_3Si$ 378.2464.

4.1.15.2. (±)-(1*S*,2*R*,4a*R*,8*R*,8a*S*)-8-[(1,1-Dimethylethyl)-dimethylsilyloxy]-2,4a-dihydroxy-2,5,5,8a-tetramethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalene-1-carboxylic acid (32) and (±)-(1*S*,2*R*,4a*R*,8*R*,8a*S*)-8-[(1,1-dimethylethyl)-dimethylsilyloxy]-2-acetyloxy-4a-hydroxy-2,5,5,8a-tetramethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalene-1-carboxamide (33). A solution of the endoperoxide **30** (20 mg, 0.053 mmol) in acetic acid (0.2 mL) was cooled in an ice bath until the acetic acid just began to crystallize. The ice bath was removed and zinc dust (18 mg, 0.28 mmol) was added all at once with vigorous stirring. After 1.5 h, the excess zinc dust was filtered off through a pad of Celite and the resulting solution was treated with water (5 mL), extracted with dichloromethane (3×5 mL), washed with aq sodium bicarbonate and brine, and dried over magnesium sulfate. The solvent was removed under reduced pressure and the resulting residue was purified by column chromatography on silica gel (2:1 to 1:3 hexane/ethyl acetate) to give the dihydroxy acid **32** (14 mg, 70%) and the acetate **33** (2 mg, 9%). Compound **32**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 5.94 (d, J=9.8 Hz, 1H), 5.77 (dd, J=9.8, 1.8 Hz, 1H), 3.67 (dd, J=10.9, 4.5 Hz, 1H), 2.65 (d, J=1.8 Hz, 1H), 1.79–1.72 (m, 2H), 1.56–1.53 (m, 1H), 1.42 (s, 3H), 1.32–1.29 (m, 1H), 1.15 (s, 3H), 1.01 (s, 3H), 0.96 (s, 3H), 0.88 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H). Compound **33**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.18 (br s, 1H), 5.87 (d, J=5.7 Hz, 1H), 5.71 (dd, J=5.7, 1.5 Hz, 1H), 4.92 (br s, 1H), 3.90 (dd, J=11.3, 4.7 Hz, 1H), 2.84 (br s, 1H), 1.83 (s, 3H), 1.76 (dddd, J=13.4, 12.7, 11.3, 3.5 Hz, 1H), 1.65 (dddd, J=12.7, 4.7, 4.0, 3.8 Hz, 1H), 1.56 (s, 3H), 1.46–1.35 (m, 2H), 1.15 (s, 3H), 1.14 (s, 3H), 0.91 (s, 9H), 0.13 (s, 3H), 0.07 (s, 3H).

4.1.15.3. (±)-(1*R*,5*R*,6*S*,7*R*,8*R*)-5-[(1,1-Dimethylethyl)dimethylsilyloxy]-2,2,6,8-tetramethyl-9,10-dioxatricyclo[6.2.2.0^{1,6}]dodecane-7-carbonitrile (35). To a suspension of the endoperoxide **30** (360 mg, 0.95 mmol) and dipotassium azodicarboxylate (926 mg, 4.77 mmol) in methanol (10 mL) and tetrahydrofuran (5 mL) cooled to −78 °C was slowly added acetic acid (0.56 mL, 9.78 mmol). The reaction mixture was stirred at −78 °C for 2 h and then slowly warmed to 23 °C. Stirring was continued until the suspension became white and then the solvent was removed under reduced pressure. The residue was diluted with water (30 mL) and diethyl ether (30 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (2×30 mL). The combined organic layers were washed with brine and dried over magnesium sulfate. The solvent was removed under reduced pressure to yield a mixture of **30** and **35**. The procedure was repeated five times to give a 1:20 mixture of **30** and **35** (356 mg, 98%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 4.51 (dd, J=11.5, 4.4 Hz, 1H), 2.52 (s, 1H), 2.13 (ddd, J=14.2, 11.0, 8.3 Hz, 1H), 2.04–1.93 (m, 2H), 1.72–1.66 (m, 3H), 1.59–1.56 (m, 1H), 1.36 (s, 3H), 1.24 (s, 3H), 1.21 (ddd, J=13.1, 13.1, 3.6 Hz, 1H), 1.02 (s, 3H), 0.98 (s, 3H), 0.91 (s, 9H), 0.22 (s, 3H), 0.13 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 118.8, 83.1, 74.8, 74.7, 49.9, 45.1, 36.9, 35.1, 28.6, 27.7, 26.6, 26.2, 25.9, 23.2, 21.5, 21.3, 18.3, −3.0, −4.6.

4.1.15.4. (±)-(1*R*,2*R*,4a*R*,8*R*,8a*S*)-8-[(1,1-Dimethylethyl)dimethylsilyloxy]-2,4a-dihydroxy-2,5,5,8a-tetramethyldecahydronaphthalene-1-carbonitrile (36). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 4.49 (dd, J=8.7, 7.0 Hz, 1H), 2.98 (br s, 1H), 2.77 (s, 1H), 2.33 (br s, 1H), 2.11–2.04 (m, 1H), 1.89–1.82 (m, 2H), 1.73–1.64 (m, 4H), 1.44 (s, 3H), 1.20 (ddd, J=13.6, 3.5, 3.5 Hz, 1H), 1.14 (s, 3H), 1.00 (s, 3H), 0.89 (s, 3H), 0.88 (s, 9H), 0.18 (s, 3H), 0.11 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 120.4, 77.9, 73.7, 69.3, 52.3, 46.9, 38.0, 34.4, 33.3, 30.3, 28.0, 26.5, 26.3, 25.9, 24.0, 21.6, 18.1, −3.5, −4.8. IR (neat): 3446, 2954, 2856, 2240, 1471, 1389, 1252, 1090, 1061, 1029, 836, 776 cm^{-1}. HRMS (MALDI) m/z found for $(M+Na)^+$ 404.2594, calcd for $C_{21}H_{39}NO_3NaSi$ 404.2591.

4.1.15.5. (±)-(1*S*,2*R*,4a*R*,8*R*,8a*S*)-8-[(1,1-Dimethylethyl)dimethylsilyloxy]-2,4a-dihydroxy-2,5,5,8a-tetramethyldecahydronaphthalene-1-carboxamide (37). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.36 (br s, 2H), 3.57 (dd, J=10.3, 4.7 Hz, 1H), 2.59 (s, 1H), 1.98 (br s, 1H), 1.87–1.80 (m, 3H), 1.74–1.67 (m, 2H), 1.64–1.58 (m, 1H), 1.52–1.48 (m, 1H), 1.42 (s, 3H), 1.24–1.22 (m, 1H), 1.19 (s, 3H), 0.97 (s, 3H), 0.89 (s, 3H), 0.86 (s, 9H), 0.06 (s, 3H), 0.02 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 173.9, 94.1, 74.1, 68.3, 61.1, 50.2, 35.6, 35.2, 34.9, 28.0, 26.7, 26.2, 25.7, 24.9, 22.8, 17.9, 15.6, −3.9, −5.0. IR (neat): 3271, 2953, 2857, 1682, 1556, 1472, 1392, 1254, 1107, 1053, 995 cm^{-1}. HRMS (MALDI) m/z found for $(M+Na-H_2O)^+$ 404.2595, calcd for $C_{21}H_{39}NO_3NaSi$ 404.2591.

4.1.16. (±)-(1*R*,8*R*,8a*R*)Ethyl-8-hydroxy-2,5,5,8a-tetramethyl-1,5,6,7,8,8a-hexahydronaphthalene-1-carboxylate (25a).[6c] To a solution of the silyl ether **25** (1.409 g, 3.60 mmol) in acetonitrile (35 mL) was added dropwise concentrated hydrofluoric acid (1.5 mL, 49%). The reaction mixture was stirred for 18 h and quenched with aqueous sodium bicarbonate (30 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (3×50 mL). The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (3:1 hexane/ethyl acetate) to give the alcohol **25a**[6c] (859 mg, 86%) as an oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 5.74 (s, 2H), 4.19–4.13 (m, 1H), 4.08–4.01 (m, 1H), 3.66 (dd, J=4.5, 11.3 Hz, 1H), 2.90 (s, 1H), 2.01 (br s, 1H), 1.75 (dddd, J=13.0, 12.7, 11.3, 4.2 Hz, 1H), 1.75 (s, 3H), 1.69 (dddd, J=13.0, 4.5, 4.2, 4.1 Hz, 1H), 1.47 (ddd, J=13.6, 4.2, 4.1 Hz, 1H), 1.39 (ddd, J=13.6, 12.7, 4.2 Hz, 1H), 1.21 (t, J=7.1 Hz, 3H), 1.14 (s, 3H), 1.10 (s, 3H), 1.09 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 172.2, 147.8, 128.3, 121.6, 117.8, 74.1, 60.4, 56.1, 44.3, 37.6, 34.6, 32.5, 31.3, 26.5, 22.6, 18.3, 14.2. IR (neat): 3493, 3044, 2960, 2938, 2869, 1717, 1464, 1364, 1239, 1178, 1158, 1132, 1040, 827 cm^{-1}.

4.1.17. (±)-(1*R*,8a*R*)Ethyl-2,5,5,8a-tetramethyl-8-oxo-1,5,6,7,8,8a-hexahydronaphthalene-1-carboxylate (25b).[6c] To a solution of oxalyl chloride (0.54 mL, 6.19 mmol) in dichloromethane (40 mL) cooled to −78 °C was added dimethyl sulfoxide (0.88 mL, 12.4 mmol). After 15 min, a solution of the alcohol **25a** (859 mg, 3.09 mmol) in dichloromethane (5 mL) was added to the reaction mixture. After 30 min, triethylamine (2.15 mL, 15.4 mmol) was added and then the dry ice bath was removed. After the reaction mixture was stirred for another 1 h, it was quenched with aqueous ammonium chloride (40 mL), extracted with diethyl ether (3×40 mL), washed with brine, and dried over magnesium sulfate. The solvent was removed under reduced pressure. The resulting residue was purified by column chromatography on silica gel (8:1 hexane/ethyl acetate) to give the ketone **25b**[6c] (829 mg, 97%) as an oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.68 (dq, J=5.7, 1.3 Hz, 1H), 5.65 (d, J=5.7 Hz, 1H), 4.01 (q, J=7.1 Hz, 2H), 3.22 (s, 1H), 2.57–2.54 (m, 2H), 1.92 (d, J=1.3 Hz, 3H), 1.87–1.76 (m, 2H), 1.23 (s, 3H), 1.22 (s, 3H), 1.20 (s, 3H), 1.17 (t, J=7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 214.7, 171.0, 147.4, 129.0, 121.0, 116.4, 60.3, 54.4, 49.1, 35.4, 34.6, 34.4, 30.1, 29.9, 23.6, 23.0, 14.0. IR (neat): 3036, 2969, 2934, 2869, 1728, 1709, 1448, 1366, 1327, 1210, 1181, 1145, 1030, 841, 829 cm^{-1}.

4.1.18. (±)-(2a*R*,8a*S*,8b*R*)-3,6,6,8b-Tetramethyl-2a,6,7,8,8a,8b-hexahydro-2*H*-naphtho(1,8-*bc*)furan-2-one (38)[6c] and (±)-(2*S*,2a*R*,8a*S*,8b*R*)-3,6,6,8b-tetramethyl-2a,6,7,8-hexahydro-2*H*-naphtho(1,8-*bc*)furan-2-ol (39).[6c] To a solution of the ketone **25b** (510 mg, 1.85 mmol) in ethanol (20 mL) cooled to 0 °C was added sodium borohydride (349 mg, 9.23 mmol) in portions. The reaction mixture was stirred for 16 h and the solvent was mostly removed under reduced pressure. The residue was diluted with diethyl ether (20 mL) and then aqueous ammonium chloride was added. The organic layer was separated and the aqueous layer was extracted with diethyl ether (3×25 mL). The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated. The resulting residue was purified by column chromatography on silica gel (5:1 to 2:1 hexane/ethyl acetate) to give the lactone **38**[6c] (290 mg, 68%) and the lactol **39**[6c] (113 mg, 27%). Compound **38**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 5.86 (d, J=5.8 Hz, 1H), 5.82 (dq, J=5.7, 1.1 Hz, 1H), 4.41 (dd, J=2.7, 2.7 Hz, 1H), 2.64 (s, 1H), 2.09–2.03 (m, 2H), 1.98 (d, J=1.1 Hz, 3H), 1.52 (ddd, J=13.6, 13.3, 5.2 Hz, 1H), 1.30 (ddd, J=13.6, 3.5, 3.5 Hz, 1H), 1.21 (s, 3H), 1.13 (s, 3H), 1.10 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 176.4, 141.8, 127.6, 120.8, 119.8, 85.0, 56.3, 43.1, 34.5, 33.0, 30.4, 27.9, 22.6, 22.1, 21.4. IR (neat): 3054, 2963, 2934, 1771, 1453, 1382, 1367, 1251, 1162, 973, 964 cm^{-1}. Compound **39**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 5.72–5.69 (m, 2H), 5.08 (d, J=6.3 Hz, 1H), 4.24 (dd, J=2.6, 2.6 Hz, 1H), 3.63 (br s, 1H), 2.04 (d, J=6.3 Hz, 1H), 1.91–1.80 (m, 2H), 1.87 (d, J=1.0 Hz, 3H), 1.54 (ddd, J=13.3, 13.3, 4.3 Hz, 1H), 1.26–1.20 (m, 1H), 1.09 (s, 3H), 1.08 (s, 3H), 1.06 (s, 3H).

4.1.19. (±)-(3*R*,3a*S*,5a*S*,8a*R*,8b*S*)-3a,5a,6,7,8,8b-Hexahydro-3,8,8,8b-tetramethyl-4*H*-3,8a-etheno-3*H*-furo[4,3,2-*de*]-1,2-benzodioxin-4-one (40).[11] Following the procedure that was used in the synthesis of **28**, the reaction of the diene **38** (290 mg, 1.25 mmol), methylene blue (5 mg, 0.01 mmol), and oxygen at 0 °C for 6 h gave the endoperoxide **40**[11] (326 mg, 99%) as a solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.63 (d, J=8.6 Hz, 1H), 6.39 (d, J=8.6 Hz, 1H), 4.32 (dd, J=6.2, 6.2 Hz, 1H), 2.13 (s, 1H), 2.09–2.02 (m, 2H), 1.68 (ddd, J=13.6, 8.8, 4.2 Hz, 1H), 1.62 (s, 3H), 1.27 (ddd, J=13.6, 8.7, 4.2 Hz, 1H), 1.17 (s, 3H), 1.14 (s,

3H), 0.96 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 174.2, 136.7, 131.9, 83.8, 81.7, 74.3, 54.0, 46.6, 34.4, 30.4, 27.6, 26.3, 26.0, 22.8, 18.4. IR (neat): 3054, 2936, 2875, 1770, 1466, 1370, 1269, 1206, 1179, 1036, 1005, 951, 903 cm^{-1}.

4.1.20. (±)-(2a*S*,3*R*,5a*R*,8a*S*,8b*R*)-3,5a-Dihydroxy-3,6,6,8b-tetramethyldecahydronaphtho-[1,8-*bc*]furan-2-one (41). Following the procedure that was used in the synthesis of **35**, the reaction of the endoperoxide **40** (317 mg, 1.20 mmol), dipotassium azodicarboxylate (1.165 g, 6.00 mmol), and acetic acid in dichloromethane with only one repetition gave the crude **40a**, which was used directly in the next step. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 4.28 (dd, J=4.3, 3.0 Hz, 1H), 2.34 (s, 1H), 2.14 (ddd, J=13.2, 9.1, 8.9 Hz, 1H), 2.04 (dddd, J=15.4, 7.2, 4.1, 4.1 Hz, 1H), 1.94–1.97 (m, 3H), 1.81 (ddd, J=13.3, 4.2, 4.0 Hz, 1H), 1.74 (ddd, J=13.6, 10.4, 8.8 Hz, 1H), 1.46 (s, 3H), 1.35 (s, 3H), 1.02 (ddd, J=13.6, 4.2, 3.9 Hz, 1H), 1.003 (s, 3H), 0.997 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 175.0, 82.5, 82.4, 75.7, 56.5, 42.7, 35.5, 30.3, 29.2, 25.9, 25.2, 24.0, 21.1 (2C), 20.1. IR (neat): 2937, 1770, 1455, 1370, 1266, 1180, 1027, 997 cm^{-1}. To a suspension of the crude **40a** and zinc dust (756 mg, 11.6 mmol) in dichloromethane (25 mL) at 0 °C was added acetic acid (0.17 mL, 2.97 mmol). After 2.5 h, excess zinc was filtered off through a pad of Celite. The resulting solution was washed with sodium bicarbonate and water, dried over magnesium sulfate, and concentrated. The recrystallization (hexane/dichloromethane) gave the dihydroxy lactone **41** (310 mg, 96% two steps) as a solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 4.67 (br s, 1H), 4.33 (br s, 1H), 4.27 (dd, J=5.3, 3.3 Hz, 1H), 2.33 (s, 1H), 2.16–2.11 (m, 1H), 2.05–1.93 (m, 4H), 1.74–1.65 (m, 2H), 1.47 (s, 3H), 1.27 (s, 3H), 1.08 (ddd, J=13.3, 4.3, 3.6 Hz, 1H), 0.98 (s, 3H), 0.95 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 178.5, 83.5, 75.3, 68.5, 59.8, 45.6, 35.4, 33.6, 32.2, 30.4, 26.1, 25.6, 24.8, 23.9, 21.5. HRMS (MALDI) m/z found for (M+Na)$^+$ 291.1561, calcd for $C_{15}H_{24}O_4Na$ 291.1567.

4.1.21. (±)-(2*R*,2a*S*,4a*S*,7a*R*,7b*S*)Hexahydro-2,7,7,7b-tetramethyl-3*H*-3,7a-ethano-3*H*-furo[4,3,2-*cd*]-1-benzofuran-3-one (42). The dihydroxy lactone **41** (250 mg, 0.92 mmol) was added to a stirred solution of HF·pyridine (2.5 mL) containing potassium iodide (309 mg, 1.86 mmol) in a polyethylene bottle. The reaction mixture was stirred at 23 °C for 15 min, quenched by pouring onto ice water, and extracted with diethyl ether (3×25 mL). The ether extract was washed with aqueous sodium thiosulfate, dried over magnesium sulfate, and poured through a short column of alumina. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (4:1 hexane/ethyl acetate) to give the oxabridged compound **42** (187 mg, 80%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 4.29–4.27 (m, 1H), 2.33 (s, 1H), 2.02–1.98 (m, 1H), 1.99–1.87 (m, 2H), 1.84–1.76 (m, 2H), 1.72–1.63 (m, 2H), 1.53 (s, 3H), 1.36 (s, 3H), 1.27–1.10 (m, 1H), 1.06 (s, 3H), 0.98 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 175.9, 92.3, 85.1, 84.0, 63.8, 47.3, 36.4, 33.2, 30.6, 27.6, 26.0, 24.4, 24.1, 22.8, 18.5. IR (neat): 2936, 1760, 1478, 1456, 1385, 1366, 1269, 1214, 1188, 1093, 1021, 967 cm^{-1}. HRMS (MALDI) m/z found for (M+Na)$^+$ 273.1470, calcd for $C_{15}H_{22}O_3Na$ 273.1461.

4.1.22. Side products in Table 2.

4.1.22.1. (±)-(1*R*,5*S*,6*S*,7*R*)-5-Hydroxy-2,2,6-trimethyl-8-methylene-11-oxatricyclo[5.3.2.0^{1,6}]dodecan-12-one (44). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 4.89 (br d, J=1.6 Hz, 1H), 4.86 (br d, J=1.6 Hz, 1H), 3.69 (dd, J=2.7, 2.7 Hz, 1H), 3.04 (s, 1H), 2.67 (m, 1H), 2.38–2.34 (m, 2H), 2.14 (ddd, J=14.5, 14.4, 3.2 Hz, 1H), 2.03–1.99 (m, 1H), 1.97 (dddd, J=14.5, 14.4, 3.1, 2.9 Hz, 1H), 1.91–1.75 (m, 1H), 1.68 (ddd, J=14.5, 5.6, 3.2 Hz, 1H), 1.12 (ddd, J=13.8, 3.3, 3.3 Hz, 1H), 1.09 (s, 3H), 1.00 (s, 3H), 0.96 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 177.4, 140.0, 112.4, 92.2, 73.2, 59.4, 48.3, 35.3, 29.8, 27.1, 26.4, 25.7, 25.5, 24.0, 20.1. IR (neat): 3434, 2969, 2945, 1755, 1652, 1459, 1384, 1365, 1287, 1253, 1180, 1030, 944 cm^{-1}. HRMS (MALDI) m/z found for (M+Na)$^+$ 273.1461, calcd for $C_{15}H_{22}O_3Na$ 273.1461.

4.1.22.2. (±)-(2a*S*,3*S*,5a*R*,8a*S*,8b*S*)-3,5a-Dihydroxy-3,6,6,8b-tetramethyldecahydronaphtho[1,8-*bc*]furan-2-one (45). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 4.25 (dd, J=5.5, 5.5 Hz, 1H), 2.54 (s, 1H), 2.44 (dddd, J=9.7, 9.5, 7.2, 7.1 Hz, 1H), 2.34 (dd, J=15.4, 9.7 Hz, 1H), 2.21–2.15 (m, 2H), 2.06–1.99 (m, 2H), 1.93 (ddd, J=14.1, 14.0, 4.0 Hz, 1H), 1.72 (s, 3H), 1.58 (br s, 1H), 1.33 (s, 3H), 1.26 (br s, 1H), 1.23 (ddd, J=14.1, 7.6, 4.4 Hz, 1H), 1.10 (s, 3H), 1.07 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 172.8, 89.6, 81.7, 77.3, 60.5, 44.4, 36.9, 32.7, 30.7, 30.0, 26.3, 24.9, 24.6, 23.2, 21.9.

4.1.22.3. (±)-(1*R*,5*S*,6*S*,7*R*)-5-Hydroxy-2,2,6,8-tetramethyl-11-oxatricyclo[5.3.2.0^{1,6}]dodec-8-en-12-one (46). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 5.43 (m, 1H), 3.75 (m, 1H), 2.68 (br s, 1H), 2.38–2.37 (m, 2H), 2.12–2.09 (m, 1H), 2.04–1.96 (m, 2H), 1.85 (s, 3H), 1.67 (dddd, J=11.6, 2.9, 2.9, 2.9 Hz, 1H), 1.13 (ddd, J=14.1, 3.4, 3.4 Hz, 1H), 1.09 (s, 3H), 1.04 (s, 3H), 1.03 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 176.0, 131.8, 120.5, 90.3, 72.5, 54.7, 45.2, 35.1, 30.7, 29.6, 26.4, 25.5, 24.3, 22.9, 18.3. IR (neat): 3437, 2932, 1748, 1459, 1383, 1261, 1204, 1175, 1056, 1012, 960 cm^{-1}. HRMS (MALDI) m/z found for (M+Na)$^+$ 273.1461, calcd for $C_{15}H_{22}O_3Na$ 273.1461.

4.1.22.4. (±)-(1*R*,5*S*,6*S*,7*R*,8*R*)-5-Acetyloxy-8-hydroxy-2,2,6,8-tetramethyl-11-oxatricyclo[5.3.2.0^{1,6}]dodecan-12-one (47). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 4.84 (dd, J=2.9, 2.9 Hz, 1H), 2.88 (br s, 1H), 2.13 (m, 1H), 2.06 (s, 3H), 2.05–1.95 (m, 3H), 1.82 (ddd, J=14.6, 12.3, 6.0 Hz, 1H), 1.70–1.59 (m, 3H), 1.46 (s, 3H), 1.34 (s, 3H), 1.15 (ddd, J=12.3, 5.2, 2.8 Hz, 1H), 1.10 (s, 3H), 0.96 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 177.6, 170.6, 91.3, 73.5, 69.4, 59.8, 47.0, 36.4, 34.9, 30.3, 27.9, 26.4, 24.5, 22.8, 22.2, 21.1, 20.9. IR (neat): 3366, 2949, 2877, 1748, 1457, 1243, 1177, 1134, 1021, 1004 cm^{-1}. HRMS (MALDI) m/z found for (M+Na)$^+$ 333.1673, calcd for $C_{17}H_{26}O_5Na$ 333.1672.

4.1.23. (±)-(5a*R*,8a*S*,8b*S*)-5a-Hydroxy-3,6,6,8b-tetramethyl-4,5,5a,6,7,8,8a,8b-octahydronaphtho[1,8-*bc*]furan-2-one (43). To a solution of diisopropylamine (0.17 mL, 1.21 mmol) in tetrahydrofuran (10 mL) cooled to −78 °C was added *n*-butyllithium (0.50 mL, 2.5 M in hexane). After the mixture stirred for 30 min, a solution of the oxabridged compound **42** (207 mg, 0.83 mmol) was added to the LDA solution at −78 °C. After the reaction mixture was stirred for 1 h, it was quenched with aqueous ammonium chloride and warmed up to 23 °C. The organic

layer was separated and the aqueous layer was extracted with diethyl ether (3×25 mL). The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (1:1 hexane/ethyl acetate) to yield the hydroxy lactone **43** (164 mg, 79%) and the rearranged lactone **44** (36 mg, 17%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 4.26 (dd, J=10.9, 7.3 Hz, 1H), 2.53 (dddd, J=20.1, 10.0, 1.2, 1.2 Hz, 1H), 2.33–2.26 (m, 2H), 2.23 (s, 3H), 2.04 (ddd, J=14.6, 10.0, 5.3 Hz, 1H), 1.93–1.88 (m, 1H), 1.64–1.59 (m, 2H), 1.35 (ddd, J=14.6, 1.1, 1.1 Hz, 1H), 1.32 (br s, 1H), 1.21 (s, 3H), 1.08 (s, 3H), 1.06 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 169.0, 150.7, 127.7, 84.8, 77.2, 44.9, 35.7, 34.7, 29.6, 28.8, 27.5 (2C), 26.4, 24.4, 18.3. IR (neat): 3489, 2977, 2936, 2871, 1714, 1663, 1467, 1448, 1368, 1350, 1312, 1271, 1206, 1150, 1055, 1020, 993 cm^{-1}. HRMS (MALDI) m/z found for $(M+Na)^+$ 273.1460, calcd for $C_{15}H_{22}O_3Na$ 273.1461.

4.1.24. (±)-(1*S*,4a*R*,8a*S*)-8-Hydroxymethyl-4,4,7,8a-tetramethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalene-1,4a-diol (48). To a solution of the hydroxy ketone **43** (98 mg, 0.39 mmol) in tetrahydrofuran (3 mL) cooled to −78 °C was slowly added diisobutylaluminum hydride (DIBAL, 1.96 mL, 1.0 M in tetrahydrofuran). The reaction mixture was slowly warmed up to 0 °C for 6 h and then quenched with aqueous potassium sodium tartrate. The resulting solution was vigorously stirred until it became clear. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3×15 mL). The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated. The residue was purified by column chromatography on silica gel (2:1 hexane/ethyl acetate) to give the triol **48** (83 mg, 83%) as a solid. The spectroscopic data of **48** were identical with those reported in the literature.[4b] ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 4.67 (br s, 3H), 4.33 (d, J=12.2 Hz, 1H), 4.06 (m, 1H), 3.97 (d, J=12.2 Hz, 1H), 2.18 (ddd, J=18.7, 9.3, 9.3 Hz, 1H), 2.06–1.92 (m, 3H), 1.77–1.63 (m, 3H), 1.76 (s, 3H), 1.10–1.07 (m, 1H), 1.01 (s, 3H), 0.99 (s, 3H), 0.97 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 134.6, 134.5, 77.9, 73.2, 57.2, 46.0, 38.1, 30.2, 28.7, 27.7, 25.5, 25.0, 24.5, 23.3, 19.2. IR (neat): 3385, 2946, 1476, 1457, 1384, 1305, 1138, 1086, 1012, 993, 919 cm^{-1}.

4.1.25. (±)-(1*S*,4a*R*,8a*S*)-8-[(1,1-Dimethylethyl)dimethylsilyloxymethyl]-4,4,7,8a-tetramethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalene-1,4a-diol (49). To the solution of the triol **48** (52 mg, 0.20 mmol) in dichloromethane (1 mL) were added triethylamine (0.11 mL, 0.79 mmol), 4-(dimethylamino)pyridine (2 mg, 0.016 mmol) and *tert*-butyldimethylsilyl chloride (68 mg, 0.45 mmol) at 23 °C. The solution was stirred for 20 h and quenched with saturated aq ammonium chloride. The mixture was extracted with dichloromethane (3×10 mL), washed with saturated sodium chloride (15 mL), dried over magnesium sulfate, and concentrated under vacuum. The residue was purified by flash column chromatography (10:1 hexane/ethyl acetate) to give the dihydroxy TBS ether **49** as a white solid (63 mg, 84%). Mp 98–99 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 5.61 (m, 1H), 5.23 (m, 1H), 4.37 (d, J=11.2 Hz, 1H), 4.07 (d, J=11.2 Hz, 1H), 4.01 (m, 1H), 2.33 (ddd, J=18.0, 9.6, 9.6 Hz, 1H), 2.07 (ddd, J=14.1, 14.1, 4.1 Hz, 1H), 1.97 (m, 1H), 1.89 (dd, J=18.0, 6.3 Hz, 1H), 1.75 (dm, J=14.0 Hz, 1H), 1.72–1.64 (m, 2H), 1.69 (s, 3H), 1.05 (br ddd, J=13.7, 3.4, 3.4 Hz, 1H), 1.01 (s, 3H), 0.99 (s, 6H), 0.89 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 136.4, 132.3, 76.3, 73.2, 58.6, 45.8, 38.3, 30.4, 29.9, 28.0, 25.7, 25.1, 24.55, 24.51, 23.3, 19.3, 18.1, −5.5, −5.7. IR (neat): 3420, 2956, 2931, 2890, 2859, 1471, 1461, 1420, 1388, 1253, 1018, 996, 983, 837, 778 cm^{-1}. HRMS (MALDI) m/z found for $(M+Na)^+$ 391.2647, calcd for $C_{21}H_{40}O_3SiNa$ 391.2639.

4.1.26. (±)-(4a*R*,8a*R*)-4a-Hydroxy-8-[(1,1-dimethylethyl)dimethylsilyloxymethyl]-4,4,7,8a-tetramethyl-3,4,4a,5,6,8a-hexahydro-2*H*-naphthalen-1-one (50). The dihydroxy TBS ether **49** (35 mg, 0.10 mmol) was dissolved in dichloromethane (0.8 mL) including *N*-methylmorpholine *N*-oxide (NMO, 17 mg, 0.15 mmol) and 4 Å molecular sieves (15 mg). Tetrapropylammonium perruthenate (TPAP, 2 mg, 0.006 mmol) was added to the reaction mixture and it was stirred for 2.5 h at 23 °C. The solvent was removed in vacuo and then flash column chromatography on silica gel (8:1 hexane/ethyl acetate) was performed to afford the hydroxy ketone **50** as a white solid (33 mg, 95%). Mp 108–109 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 4.44 (d, J=12.4 Hz, 1H), 3.99 (d, J=12.4 Hz, 1H), 2.94 (ddd, J=14.9, 14.9, 8.9 Hz, 1H), 2.23–2.10 (m, 4H), 2.04 (dd, J=17.9, 7.2 Hz, 1H), 1.88 (ddd, J=13.4, 13.4, 6.8 Hz, 1H), 1.71 (s, 3H), 1.70–1.60 (m, 2H), 1.54 (s, 3H), 1.20 (s, 3H), 1.01 (s, 3H), 0.86 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 214.7, 133.9, 133.7, 80.8, 61.4, 60.7, 38.8, 37.8, 35.8, 28.4, 26.8, 25.9, 24.9, 23.4, 23.3, 20.1, 18.2, −5.5, −5.6. IR (neat): 3674, 3527, 3393, 3053, 2958, 2706, 2306, 1704, 1661, 1471, 1254, 973, 847, 773, 679 cm^{-1}. HRMS (MALDI) m/z found for $(M+Na)^+$ 389.2481, calcd for $C_{21}H_{38}O_3SiNa$ 389.2482.

4.1.27. (±)-(4a*R*,7*R*,8*S*,8a*S*)-8-[(1,1-Dimethylethyl)dimethylsilyloxymethyl]-4a,7,8-trihydroxy-4,4,7,8a-tetramethyloctahydronaphthalen-1-one (51). Osmium tetroxide (33 mg, 0.082 mmol) was added to the solution of the hydroxy ketone **50** (34 mg, 0.13 mmol) in pyridine (0.5 mL) at 23 °C. The solution was stirred for 18 h and quenched with saturated sodium bisulfite (1.5 mL). The mixture was stirred for an additional 2.5 h and extracted with ethyl acetate (5×10 mL). The combined organic layers were washed with saturated sodium chloride, dried over magnesium sulfate, and concentrated under vacuum. The resulting residue was purified by column chromatography on silica gel (4:1 hexane/ethyl acetate) to give the triol **51** (30 mg, 83%) as a white solid. Mp 134–137 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 4.30 (s, 1H), 4.18 (s, 1H), 3.77 (d, J=11.0 Hz, 1H), 3.70 (d, J=11.0 Hz, 1H), 2.90 (ddd, J=16.3, 9.7, 9.0 Hz, 1H), 2.74 (m, 1H), 2.32 (ddd, J=16.3, 4.5, 4.5 Hz, 1H), 2.10 (ddd, J=13.8, 13.8, 4.7 Hz, 1H), 1.89 (ddm, J=14.5, 14.5 Hz, 1H), 1.79 (m, 2H), 1.67 (ddd, J=14.5, 4.3, 2.3 Hz, 1H), 1.57 (s, 3H), 1.36 (ddd, J=13.8, 4.3, 2.3 Hz, 1H), 1.18 (s, 3H), 1.11 (s, 3H), 1.08 (s, 3H), 0.89 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 219.6, 78.5, 77.3, 74.3, 67.3, 60.4, 37.3, 37.1, 35.4, 31.2, 28.0, 27.9, 25.8, 25.5, 24.5, 21.1, 18.2, −5.8, −6.0. IR (neat): 3470, 3383, 2956, 2930, 2858, 1686, 1472, 1408, 1372, 1326, 1256, 1072, 1054, 840, 781 cm^{-1}. HRMS (MALDI) m/z found for $(M+Na)^+$ 423.2539, calcd for $C_{21}H_{40}O_5SiNa$ 423.2537.

4.1.28. (±)-(2a*R*,3*R*,5a*R*,8a*R*,8b*S*)-3,6,6,8b-Tetramethyldecahydronaphtho[1,8-*bc*]furan-2a,3,5a,8a-tetraol (52). A solution of tetrabutylammonium fluoride (0.22 mL, 1.0 M in THF) was added to the solution of the triol **51** (30 mg, 0.07 mmol) in THF (0.5 mL) at 23 °C. The reaction mixture was stirred for 30 min and diluted with ethyl acetate (10 mL). The solution was washed with saturated aq ammonium chloride (5 mL) and the organic layer was set aside. The aqueous layer was extracted with dichloromethane (2×5 mL). The combined organic layers were dried over magnesium sulfate, concentrated under vacuum, and the residue was purified by column chromatography on silica gel (1:1 hexane/ethyl acetate) to afford the tetraol **52** (19 mg, 89%) as a white solid. Mp 127–129 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 4.37 (m, 1H), 4.20 (dd, J=9.2, 1.3 Hz, 1H), 4.16 (m, 1H), 3.94 (d, J=9.2 Hz, 1H), 3.48 (d, J=2.8 Hz, 1H), 2.27 (ddd, J=13.2, 13.2, 4.8 Hz, 1H), 2.03–1.87 (m, 4H), 1.64–1.57 (m, 2H), 1.48–1.44 (m, 2H), 1.32 (s, 3H), 1.21 (s, 3H), 1.09 (s, 3H), 0.97 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 108.7, 84.7, 77.1, 76.6, 72.2, 53.6, 38.0, 33.9, 32.9, 29.5, 27.5, 25.7, 27.3, 22.3, 15.4. IR (KBr): 3451, 3368, 2981, 2963, 1455, 1372, 1221, 1044, 996, 650 cm^{-1}.

4.1.29. Ethyl-5-(3,4-dimethoxyphenyl)-3,5-dioxopentanoate (54).[18a] To a solution of diisopropylamine (LDA, 8.90 mL, 63.5 mmol) in tetrahydrofuran (THF, 100 mL) cooled to −20 °C was added *n*-butyllithium (49.1 mL, 1.1 M in hexane). The solution was stirred for 45 min. In a separate flask, freshly distilled ethyl acetoacetate **53** (3.33 g, 25.6 mmol) and THF (50 mL) were added and the resulting solution was cooled to −78 °C. To this solution was added the solution of LDA via cannula followed by the addition of tetramethylethylenediamine (TMEDA, 3.84 mL, 25.4 mmol), and the solution was stirred at 0 °C for 3 h. To this dianion solution was added a solution of methyl 3,4-dimethoxybenzoate (5.01 g, 25.5 mmol) in THF (15 mL) and then the reaction mixture was warmed to 23 °C. After stirring for 48 h, the reaction mixture was treated with acetic acid and stirred for an additional 10 min. HCl (1 N, 200 mL) was added to the reaction mixture, which was extracted with diethyl ether (3×200 mL). The organic layer was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (3:1 to 1:1 hexane/ethyl acetate) to give the diketo acid **54** (4.10 g, 55%) as an oil. The spectroscopic data of **54** were consistent with those reported in the literature.[18a] ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.44–7.41 (m, 1H), 7.36–7.35 (m, 1H), 6.83–6.80 (m, 1H), 6.18–6.17 (m, 1H), 4.17–4.11 (m, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 3.38–3.37 (m, 2H), 1.24–1.17 (m, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 186.1, 183.8, 167.5, 152.8, 148.8, 126.8, 121.2, 110.3, 109.3, 95.7, 61.2, 55.8, 55.7, 44.9, 13.9.

4.1.30. 5-(3,4-Dimethoxyphenyl)-3,5-dioxopentanoic acid (54a).[18a] To a solution of potassium hydroxide (188 mg, 3.35 mmol) in ethanol (7.5 mL) and water (1.5 mL) was added the diketoester **54** (197 mg, 0.67 mmol) at 23 °C. After the mixture was stirred for 15 h, about 80% of the solvent was removed by heating under reduced pressure. The residue was diluted with ethyl acetate and quenched with 1 N HCl (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3×15 mL). The combined organic layer was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure to give the crude acid **54a**[18a] (173 mg, 97%), which was used directly in the next step without further purification. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 9.95 (br s, 1H), 7.51 (d, J=8.4 Hz, 1H), 7.42 (s, 1H), 6.90 (d, J=8.4 Hz, 1H), 3.94 (s, 3H), 3.93 (s, 3H), 3.91 (s, 2H), 3.52 (s, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 183.3, 153.3, 149.0, 126.4, 121.6, 110.5, 109.6, 104.6, 96.1, 56.3, 56.04, 55.98, 44.4.

4.1.31. 6-(3,4-Dimethoxyphenyl)-4-hydroxy-2-pyrone (55).[18] To a suspension of the crude acid **54a** (173 mg, 0.65 mmol) in diethyl ether (3 mL) was added trifluoroacetic anhydride (0.14 mL, 0.99 mmol) at 23 °C. After stirring for 1.5 h, the reaction mixture was filtered to collect the crude yellow solids, which were washed with diethyl ether and dried under vacuum to give the pyrone **55** (120 mg, 72%, two steps from **54**). The spectroscopic data of **55** were consistent with those reported in the literature.[15] ^{1}H NMR (DMSO, 500 MHz) δ: 11.75 (br s, 1H), 7.40 (dd, J=8.5, 1.9 Hz, 1H), 7.31 (d, J=1.9 Hz, 1H), 7.04 (d, J=8.5 Hz, 1H), 6.68 (d, J=1.7 Hz, 1H), 5.30 (d, J=1.7 Hz, 1H), 3.80 (s, 3H), 3.78 (s, 3H). ^{13}C NMR (DMSO, 125 MHz) δ: 171.2, 163.5, 160.6, 151.5, 149.2, 123.8, 119.2, 112.0, 108.8, 97.4, 89.0, 55.98, 55.96.

4.1.32. 6-(3,4-Dimethoxyphenyl)-4-phenylmethoxy-2-pyrone (57). To a suspension of the pyrone **55** (100 mg, 0.40 mmol) in acetonitrile (5 mL) were added anhydrous potassium carbonate (167 mg, 1.21 mmol) and benzyl bromide (0.14 mL, 1.18 mmol) at 23 °C. The reaction mixture was refluxed at 85 °C for 6 h and quenched with ammonium chloride. The mixture was extracted with dichloromethane (3×15 mL), washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (3:2 hexane/ethyl acetate) to give the benzyloxy pyrone **57** (65 mg, 48%) as a yellow solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.41–7.36 (m, 6H), 7.27 (d, J=1.9 Hz, 1H), 6.87 (d, J=8.5 Hz, 1H), 6.38 (d, J=2.0 Hz, 1H), 5.56 (d, J=2.0 Hz, 1H), 5.03 (s, 2H), 3.90 (s, 3H), 3.89 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 170.3, 164.2, 160.2, 151.3, 149.0, 134.3, 128.72, 128.70, 127.8, 123.7, 119.0, 110.9, 108.2, 96.7, 88.6, 70.7, 55.93, 55.88.

4.1.33. 6-(3,4-Dimethoxyphenyl)-4-methoxy-2-pyrone (58).[29] A suspension of the pyrone **55** (100 mg, 0.40 mmol), dimethyl sulfate (0.19 mL, 2.00 mmol), and potassium carbonate (278 mg, 2.01 mmol) in acetone (4 mL) was stirred at 23 °C for 1 h. Water (2 mL) was added, and the resulting solution was stirred at 23 °C for 24 h. After addition of aqueous ammonium chloride, the mixture was extracted with ethyl acetate (3×10 mL). The organic layers were washed with water and brine, dried over magnesium sulfate, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (1:1 hexane/ethyl acetate) to give the known 4-methoxy pyrone **58**[29] (88 mg, 83%) as a pale yellow solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.39 (dd, J=8.5, 2.0 Hz, 1H), 7.30 (d, J=2.0 Hz, 1H), 6.90 (d, J=8.5 Hz, 1H), 6.33 (d, J=2.0 Hz, 1H), 5.50 (d, J=2.0 Hz, 1H), 3.94 (s, 3H), 3.92 (s, 3H), 3.85 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 171.5, 164.4, 160.2, 151.4, 149.1, 123.8, 119.1, 111.0, 108.4, 96.7, 87.7, 56.1, 55.99, 55.96.

4.1.34. 3-Bromo-6-(3,4-dimethoxyphenyl)-4-phenylmethoxy-2-pyrone (59). To a solution of the pyrone **55** (100 mg, 0.40 mmol) in acetic acid (0.4 mL) was added dropwise bromine (23 μL, 0.45 mmol) at 23 °C. After stirring for 1 h, the reaction mixture was diluted with ice water (2 mL) and the precipitated solid was filtered, washed with water, and dried under vacuum. The crude bromo pyrone **56** (125 mg, 95%) was used directly in the next step without further purification. ^{1}H NMR (DMSO, 500 MHz) δ: 7.35 (dd, J=8.5, 2.0 Hz, 1H), 7.23 (d, J=2.0 Hz, 1H), 7.06 (d, J=8.5 Hz, 1H), 6.66 (s, 1H), 3.80 (s, 3H), 3.79 (s, 3H). ^{13}C NMR (DMSO, 125 MHz) δ: 167.2, 160.1, 158.7, 151.8, 149.3, 123.0, 119.3, 112.2, 108.7, 96.6, 85.9, 56.0, 55.9. To a suspension of the bromo pyrone **56** (15 mg, 0.046 mmol) in acetonitrile (1 mL) were added anhydrous potassium carbonate (19 mg, 0.14 mmol) and benzyl bromide (15 μL, 0.13 mmol) at 23 °C. The reaction mixture was refluxed at 90 °C for 24 h and quenched with ammonium chloride. The mixture was extracted with dichloromethane (3×8 mL), washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (2:1 to 1:1 hexane/ethyl acetate) to give the benzyloxy pyrone **59** (15 mg, 78%) as a yellow solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.46–7.38 (m, 5H), 7.34 (dd, J=8.4, 2.0 Hz, 1H), 7.25 (d, J=2.0 Hz, 1H), 6.90 (d, J=8.4 Hz, 1H), 6.53 (s, 1H), 5.36 (s, 2H), 3.93 (s, 3H), 3.92 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 166.4, 160.4, 160.3, 152.0, 149.3, 134.7, 129.0, 128.8, 126.9, 123.3, 119.4, 111.1, 108.6, 92.2, 89.7, 71.8, 56.2, 56.1.

4.1.35. (±)-(*R*)-2-Hydroxy-2,6,6,12-tetramethyl-10-oxabicyclo[7.2.1]dodeca-1(11),9(12)-dien-5-one (62). To the solution of the tetraol **52** (12 mg, 0.04 mmol) in pyridine (0.2 mL) cooled to 0 °C were added 4-(dimethylamino)pyridine (DMAP, 0.5 mg, 0.004 mmol) and methanesulfonyl chloride (5 μL, 0.06 mmol). After the solution had stirred for 2.5 h, it was diluted with dichloromethane (0.5 mL) and poured into aqueous ammonium chloride (1 mL). The mixture was extracted with dichloromethane (3×5 mL) and ethyl acetate (5 mL). The combined organic layers were dried over magnesium sulfate and concentrated. Flash column chromatography (2:1 hexane/ethyl acetate) afforded the furan **62** (10 mg, 95%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.08 (s, 1H), 2.95 (m, 1H), 2.64 (ddd, J=13.0, 13.0, 4.2 Hz, 1H), 2.53 (ddd, J=13.2, 13.2, 4.1 Hz, 1H), 2.29 (s, 3H), 2.18 (dd, J=12.2, 12.2 Hz, 1H), 1.62–1.57 (m, 3H), 1.59 (s, 3H), 1.43 (ddd, J=13.1, 4.1, 1.8 Hz, 1H), 1.26 (s, 3H), 0.89 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 205.7, 153.8, 138.9, 127.5, 118.7, 73.5, 45.8, 45.4, 41.9, 32.0, 31.1, 28.9, 22.3, 21.6, 15.2. IR (neat): 3462, 2960, 2926, 1678, 1612, 1542, 1458, 1411, 1363, 1327, 1240, 1106, 1040, 893, 731 cm^{-1}. HRMS (EI) m/z found for M^+ 250.1560, calcd for $C_{15}H_{22}O_3$ 250.1569.

4.1.36. (±)-(4a*R*,8*S*,8a*S*)-4a,8-Dihydroxy-2,5,5,8a-tetramethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalene-1-carboxaldehyde (63).[4b] To a solution of the triol **48** (15 mg, 0.059 mmol) and *N*-methylmorpholine *N*-oxide (NMO, 8 mg, 0.068 mmol) in dichloromethane (0.5 mL) was added tetrapropylammonium perruthenate (TPAP, 1 mg, 0.003 mmol) at 23 °C. After the reaction mixture was stirred for 30 min, the solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (1:1 hexane/ethyl acetate) to give the aldehyde **63** (12 mg, 81%) as an oil. The proton NMR data seem to indicate that this compound exists as the lactol **63a**. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.39 (s, 1H), 5.38 (m, 1H), 5.09 (m, 1H), 3.96 (br s, 1H), 2.44 (m, 1H), 2.26–1.43 (m, 6H), 1.73 (br s, 3H), 1.13 (s, 3H), 1.05 (m, 1H), 0.96 (s, 6H).

4.1.37. (±)-(1*R*,5S,6*R*,8*R*)-2,2,6,8-Tetramethyl-7-methylene-11-oxatricyclo[6.2.1.0^{1,6}]-5-undecanol (65). To a solution of the known triol **48** (5 mg, 0.020 mmol) in dichloromethane (0.3 mL) was added triethylamine (8 μL, 0.057 mmol), 4-(dimethylamino)pyridine (0.3 mg, 0.002 mmol), and *p*-toluenesulfonyl chloride (6 mg, 0.031 mmol). The reaction mixture was stirred for 2 h and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (5:1 hexane/ethyl acetate) to give alcohol **65** (2 mg, 43%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 4.94 (s, 1H), 4.73 (s, 1H), 3.70 (br s, 1H), 3.45 (m, 1H), 1.99 (ddd, J=14.1, 14.1, 3.5 Hz, 1H), 1.89 (dddd, J=14.4, 14.4, 3.0, 3.0 Hz, 1H), 1.79 (ddd, J=12.6, 11.0, 5.2 Hz, 1H), 1.71 (ddd, J=14.3, 6.5, 3.0 Hz, 1H), 1.68 (ddd, J=12.7, 9.2, 5.4 Hz, 1H), 1.62–1.54 (m, 2H), 1.49 (s, 3H), 1.20 (s, 3H), 1.20–1.18 (m, 1H), 1.06 (s, 3H), 0.99 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 162.8, 100.2, 93.1, 85.9, 75.6, 51.8, 38.2, 33.5, 30.7, 26.8, 26.3, 25.5, 24.4, 22.2, 17.7. IR (neat): 3503, 3072, 2935, 2866, 1668, 1475, 1410, 1382, 1292, 1201, 1161, 1085, 1057, 1018, 975, 953, 921 cm^{-1}. HRMS (EI) m/z found for M^+ 236.1782, calcd for $C_{15}H_{24}O_2$ 236.1776.

4.1.38. (±)-(1*R*,2*R*,4*S*,8*S*,12*S*)-7,7,11,12-Tetramethyl-3,13-dioxatetracyclo[6.3.1.1^{2,8}.0^{4,12}]tridec-10-ene (67). To a mixture of the aldehyde **63** (11 mg, 0.044 mmol) and chromium(II) chloride (16 mg, 0.13 mmol) in THF (0.5 mL) was added a solution of the bromo pyrone **59** (36 mg, 0.086 mmol) in THF (0.5 mL) at 23 °C. The reaction mixture was stirred for 18 h and then quenched with cold water (5 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (3×5 mL). The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (4:1 hexane/ethyl acetate) to afford the acetal **67** (4 mg, 39%) as a side product. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 5.38 (m, 1H), 5.21 (s, 1H), 3.96 (m, 1H), 2.21 (ddd, J=18.1, 2.2, 2.2 Hz, 1H), 2.12 (ddd, J=13.5, 13.5, 4.5 Hz, 1H), 2.10–2.05 (m, 1H), 2.06 (s, 1H), 1.82 (ddd, J=14.5, 6.5, 4.0 Hz, 1H), 1.76–1.70 (m, 1H), 1.74 (d, J=0.9 Hz, 3H), 1.13 (s, 3H), 1.40 (ddd, J=13.5, 4.3, 2.5 Hz, 1H), 0.96 (s, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 130.0, 120.2, 103.5, 84.5, 80.3, 59.4, 44.3, 34.8, 31.0, 29.8, 26.4, 23.3, 22.2, 22.1, 13.5. IR (neat): 2962, 2923, 2876, 1451, 1381, 1270, 1175, 1066, 1041, 1026, 987, 927, 850 cm^{-1}.

4.1.39. (±)-(2*R*,2a*S*,3S,4a*S*,7a*R*,7b*S*)-3-[Hexahydro-2,7,7,7b-tetramethyl-3*H*-2,7a-ethano-3*H*-furo[4,3,2-*dc*]-1-benzo-3-furanyl]-6-(3,4-dimethoxyphenyl)-4-hydroxy-2-pyrone (70). To a solution of the lactone **42** (20 mg, 0.080 mmol) in THF (0.5 mL) cooled to 0 °C was added lithium aluminum hydride (12 mg, 0.32 mmol). After the

reaction mixture was stirred for 1 h, it was quenched with one drop of water and one drop of 15% sodium hydroxide solution. Magnesium sulfate was added and the mixture was stirred for additional 10 min. Filtration and concentration gave the crude product, which was dried in vacuum to give the lactol **68** (20 mg, 100%). The product **68** was used in the next step without further purification. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 5.44 (s, 1H), 4.19 (dd, J=3.0, 3.0 Hz, 1H), 2.45 (br s, 1H), 1.95–1.91 (m, 1H), 1.93 (s, 1H), 1.86–1.83 (m, 2H), 1.80–1.63 (m, 3H), 1.55 (ddd, J=12.0, 12.0, 3.3 Hz, 1H), 1.44 (s, 3H), 1.36 (s, 3H), 1.05 (ddd, J=13.5, 3.5, 3.5 Hz, 1H), 1.04 (s, 3H), 0.95 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 99.2, 90.9, 82.5, 82.1, 70.0, 50.5, 36.9, 33.6, 30.7, 27.5, 26.4, 23.7, 23.4, 22.1, 19.3. IR (neat): 3228, 2947, 2870, 1460, 1379, 1345, 1138, 1088, 1070, 995, 953, 919 cm^{-1}. To a solution of the lactol **68** (18 mg, 0.071 mmol) and the pyrone **55** (18 mg, 0.072 mmol) in acetonitrile (0.8 mL) and THF (0.2 mL) was added indium(III) chloride (8 mg, 0.036 mmol) at 23 °C. The reaction mixture was stirred for 4 h at 85 °C and then cooled to 23 °C. The solvent was removed under reduced pressure to give the crude product, which was purified by column chromatography on silica gel (1:1 hexane/ethyl acetate) to yield the coupled product **70** (25 mg, 73%). The spectroscopic data of **70** were consistent with those reported in the literature.[23] ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 11.06 (s, 1H), 7.37 (dd, J=8.5, 2.1 Hz, 1H), 7.29 (d, J=2.1 Hz, 1H), 6.91 (d, J=8.5 Hz, 1H), 6.29 (br s, 1H), 5.37 (d, J=2.4 Hz, 1H), 3.99 (dd, J=2.9, 2.9 Hz, 1H), 3.92 (s, 6H), 2.60 (d, J=2.4 Hz, 1H), 2.04–1.98 (m, 1H), 1.90–1.87 (m, 2H), 1.80–1.71 (m, 3H), 1.66–1.61 (m, 1H), 1.61 (s, 3H), 1.28 (s, 3H), 1.08 (s, 3H), 0.97 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 167.1, 162.9, 159.4, 151.3, 149.1, 123.9, 118.8, 111.0, 108.1, 99.7, 97.3, 90.4, 85.6, 84.6, 80.6, 67.9, 56.01, 56.00, 51.0, 36.3, 33.7, 30.6, 27.9, 26.5, 24.7, 23.9, 22.5, 19.6.

4.1.40. (±)-(2*R*,2a*S*,3S,4a*S*,7a*R*,7b*S*)-3-[Hexahydro-2,7,7,7b-tetramethyl-3*H*-2,7a-ethano-3*H*-furo[4,3,2-*dc*]-1-benzo-3-furanyl]-6-(3,4-dimethoxyphenyl)-4-methoxy-2-pyrone (71). Following the same procedure as that used for the synthesis of **58**, the reaction of the coupled product **70** (3 mg, 0.006 mmol), dimethyl sulfate (5 μL, 0.053 mmol), and potassium carbonate (7 mg, 0.051 mmol) gave the 4-methoxy-2-pyrone **71** (2 mg, 65%) after purification by column chromatography on silica gel (10:1 dichloromethane/methanol). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.39 (dd, J=8.5, 2.1 Hz, 1H), 7.34 (d, J=2.1 Hz, 1H), 6.91 (d, J=8.5 Hz, 1H), 6.51 (s, 1H), 5.40 (d, J=4.5 Hz, 1H), 4.39 (dd, J=3.4, 3.4 Hz, 1H), 3.97 (s, 3H), 3.943 (s, 3H), 3.938 (s, 3H), 2.90 (d, J=4.5 Hz, 1H), 1.99 (ddd, J=13.3, 13.3, 3.5 Hz, 1H), 1.86–1.80 (m, 2H), 1.73–1.62 (m, 3H), 1.58–1.52 (m, 1H), 1.50 (s, 3H), 1.38 (s, 3H), 1.08 (s, 3H), 1.01 (ddd, J=13.5, 3.9, 3.9 Hz, 1H), 0.97 (s, 3H).

4.1.41. (±)-(2*R*,2a*S*,4a*S*,7a*R*,7b*S*)Hexahydro-2,7,7,7b-tetramethyl-3*H*-2,7a-ethano-3*H*-furo[4,3,2-*dc*]-1-benzofuran (74). A solution of the coupled compound **70** (3 mg, 0.006 mmol) in dichloromethane (0.1 mL) was treated with triethylsilane (3 μL, 0.019 mmol) and boron trifluoride diethyl etherate (1 μL, 0.008 mmol) at 23 °C. The reaction mixture was stirred for 24 h and then quenched with one drop of triethylamine. The solvent was removed under reduced pressure to give the crude residue, which was purified by column chromatography on silica gel (1:1 hexane/ethyl acetate) to afford the reduced oxatetracyclic compound **74** (1 mg, 68%) and the pyrone **55** (1 mg, 65%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 4.08 (dd, J=10.0, 1.0 Hz, 1H), 3.57 (dd, J=10.0, 7.1 Hz, 1H), 3.56 (dd, J=3.0, 3.0 Hz, 1H), 1.96 (ddd, J=13.8, 13.8, 3.8 Hz, 1H), 1.90 (ddd, J=14.9, 6.5, 2.8 Hz, 1H), 1.84–1.76 (m, 3H), 1.71 (ddd, J=12.2, 12.0, 6.2 Hz, 1H), 1.61 (ddd, J=12.0, 8.8, 6.1 Hz, 1H), 1.55 (ddd, J=14.9, 14.5, 3.5 Hz, 1H), 1.38 (s, 3H), 1.29 (s, 3H), 1.05 (ddd, J=13.1, 3.8, 3.5 Hz, 1H), 1.04 (s, 3H), 0.95 (s, 3H).

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Supplementary data

A general experimental section, the proton and carbon NMR spectra, and some infrared spectra for all new compounds and the ORTEP drawing and the CIF file for the X-ray crystal structure of compound **30**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.02.085.

References and notes

1. (a) Õmura, S.; Kuno, F.; Otoguro, K.; Sunazuka, T.; Shiomi, K.; Masuma, R.; Iwai, Y. *J. Antibiot.* **1995**, *48*, 745–746; (b) Otoguro, K.; Kuno, F.; Õmura, S. *Pharmacol. Ther.* **1997**, *76*, 45–54; (c) Handa, M.; Sunazuka, T.; Nagai, K.; Kimura, R.; Otoguro, K.; Harigaya, Y.; Õmura, S. *J. Antibiot.* **2001**, *54*, 386–391.
2. Yoshida, M.; Hasegawa, M.; Noda, Y.; Nabeshima, T. *Dementia* **1995**, *9*, 233–245.
3. (a) Summers, W. K.; Majovski, L. V.; Marsh, G. M.; Tachiki, K.; King, A. *N. Engl. J. Med.* **1986**, *315*, 1241–1245; (b) Relman, A. S. *N. Engl. J. Med.* **1991**, *324*, 349–352.
4. (a) Sunazuka, T.; Handa, M.; Nagai, K.; Shirahata, T.; Harigaya, Y.; Otoguro, K.; Kuwajima, I.; Õmura, S. *Org. Lett.* **2002**, *4*, 367–369; (b) Hsung, R. P.; Cole, K. P.; Zehnder, L. R.; Wang, J.; Wei, L.; Yang, X.; Coverdale, H. A. *Tetrahedron* **2003**, *59*, 311–324; (c) For earlier work, see: Zehnder, L. R.; Hsung, R. P.; Wang, J.; Golding, G. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 3876–3879; (d) For a review, see: Sunazuka, T.; Omura, S. *Chem. Rev.* **2005**, *105*, 4559–4580.
5. Jung, M. E.; Min, S.-J. *J. Am. Chem. Soc.* **2005**, *127*, 10834–10835.
6. For uses of the IMDAF, see: (a) Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795–819; (b) Kappe, C. O.; Murphree, S. S.; Padwa, A. *Tetrahedron* **1997**, *53*, 14179–14233; (c) Mukaiyama, T.; Takebayashi, T. *Chem. Lett.* **1980**, 1013–1016; (d) Bailey, M. S.; Brisdon, B. J.; Brown, D. W.; Stark, K. M. *Tetrahedron Lett.* **1983**, *24*, 3037–3040; (e) Yu, S.; Beese, G.; Keay, B. A. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2729–2731; (f) For some problems, see: Dean, F. M. *Adv. Heterocycl. Chem.* **1982**, *30*, 167–238; (g) Dean, F. M. *Adv. Heterocycl. Chem.* **1982**, *31*,

237–344; (h) Keay, B. A.; Rajapaksa, D.; Rodrigo, R. *Can. J. Chem.* **1984**, *62*, 1093–1098.
7. (a) Fráter, G. *Helv. Chim. Acta* **1974**, *57*, 2446–2454; (b) Fráter, G.; Muller, U. *Helv. Chim. Acta* **1988**, *71*, 808–811; (c) Venkataraman, H.; Cha, J. K. *J. Org. Chem.* **1989**, *54*, 2505–2506; (d) Leclaire, M.; Lallemand, J. Y. *Tetrahedron Lett.* **1989**, *30*, 6331–6334.
8. For review of 1,3-diene photooxidiation, see: (a) Balci, M. *Chem. Rev.* **1981**, *81*, 91–108; (b) Clennan, E. L. *Tetrahedron* **1991**, *47*, 1343–1382.
9. Zhang, X.; Khan, S. I.; Foote, C. S. *J. Org. Chem.* **1995**, *60*, 4102–4107.
10. Rosenberger, M.; McDougal, P.; Bahr, J. *J. Org. Chem.* **1982**, *47*, 2130–2184.
11. Leclaire, M.; Jean, P.; Lopez, R.; Ricard, L.; Plessix, H.; Lallemand, J. Y. *Tetrahedron* **1995**, *51*, 6983–6998.
12. (a) Ref. 7d; (b) Haag, A.; Eugster, C. H. *Helv. Chim. Acta* **1982**, *65*, 1795–1803.
13. Katsuta, Y.; Ito, M.; Yoshihara, K.; Nakanishi, K.; Kikkawa, T.; Fujiwara, T. *J. Org. Chem.* **1994**, *59*, 6917–6921.
14. Corey, E. J.; Jardine, P. D.; Rohloff, J. C. *J. Am. Chem. Soc.* **1988**, *110*, 3672–3673.
15. Suzuki, M.; Ohtake, H.; Kameya, Y.; Hamanaka, N.; Noyori, R. *J. Org. Chem.* **1989**, *54*, 5292–5302.
16. (a) Colombo, M.; Zinczuk, J.; Bacigaluppo, J. A.; Somoza, C.; Rúveda, E. A. *J. Org. Chem.* **1990**, *55*, 5631–5639; (b) Hashimoto, S.; Sakata, S.; Sonegawa, M.; Ikekami, S. *J. Am. Chem. Soc.* **1988**, *110*, 3670–3672.
17. Dong, D. C.; Edward, J. T. *Can. J. Chem.* **1980**, *58*, 1324–1326.
18. (a) Hua, D. H.; Chen, Y.; Sin, H.-S.; Maroto, M. J.; Robinson, P. D.; Newell, S. W.; Perchellet, E. M.; Ladesich, J. B.; Freeman, J. A.; Perchellet, J.-P.; Chiang, P. K. *J. Org. Chem.* **1997**, *62*, 6888–6896; (b) Douglas, C.; Sklenicka, H. M.; Shen, H. C.; Mathisa, D. S.; Degen, S. J.; Golding, G. M.; Morgan, C. D.; Shih, R. A.; Mueller, K. L.; Scurer, L. M.; Johnson, E. W.; Hsung, R. P. *Tetrahedron* **1999**, *55*, 13683–13696.
19. Cha, J. K.; Harris, T. M.; Ray, J. A.; Venkataraman, H. *Tetrahedron Lett.* **1989**, *30*, 3505–3508.
20. Wang, J.; Cole, K. P.; Wei, L.; Zehnder, L. R.; Hsung, R. P. *Tetrahedron Lett.* **2002**, *43*, 3337–3340.
21. Jung, M. E.; Min, S.-J. *Tetrahedron Lett.* **2004**, *45*, 6753–6755.
22. (a) Fürstner, A. *Synthesis* **1989**, 571–590; (b) Jung, M. E.; Starkey, L. S. *Tetrahedron* **1997**, *53*, 8815–8824.
23. (a) Takai, K.; Kimura, K.; Kuroda, T.; Hiyama, T.; Nozaki, T. *Tetrahedron Lett.* **1983**, *24*, 5281–5284; (b) Chen, X.-T.; Bhattacharya, S. K.; Zhou, B.; Gutteridge, C. E.; Pettus, T. R. R.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 6563–6579.
24. Fürstner, A. *Chem. Rev.* **1999**, *99*, 991–1045.
25. Lee, Y. R.; Kim, D. H.; Shim, J.-J.; Kim, S. K.; Park, J. H.; Cha, J. S.; Lee, C.-S. *Bull. Korean Chem. Soc.* **2002**, *23*, 998–1001.
26. Shen, H. C.; Wang, J.; Cole, K. P.; McLaughlin, M. J.; Morgan, C. D.; Douglas, C. J.; Hsung, R. P.; Coverdale, H. A.; Gerasyuto, A. I.; Hahn, J. M.; Heather, J. L.; Sklenicka, M.; Wei, L.-L.; Zehnder, L. R.; Zificsak, C. A. *J. Org. Chem.* **2003**, *68*, 1729–1735.
27. (a) Fry, J. L.; Orfanopoulos, M.; Adlington, M. G.; Dittman, W. R., Jr.; Silverman, S. B. *J. Org. Chem.* **1978**, *43*, 374–375; (b) West, C. T.; Donnelly, S. J.; Kooistra, D. A.; Doyle, M. P. *J. Org. Chem.* **1973**, *33*, 2675–2681; (c) Olah, G. A.; Arvanaghi, M.; Ohannesian, L. *Synthesis* **1986**, 770–772.
28. Groves, J. T.; Ma, K. W. *J. Am. Chem. Soc.* **1977**, *99*, 4076–4082.
29. Tominaga, Y.; Ushirogochi, A.; Matsuda, Y. *J. Heterocycl. Chem.* **1987**, *24*, 1557–1567.