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Gold-Catalyzed Enantio- and Diastereoselective Syntheses of Left Fragments of Azadirachtin/Meliacarpin-Type Limonoids

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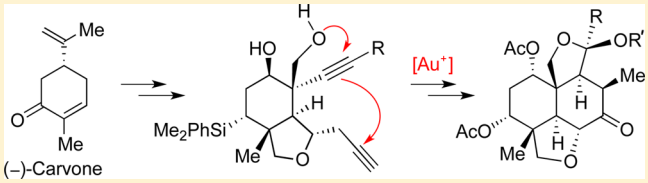
Supporting Information

ABSTRACT: Meliacarpin-type limonoids are an important class of organic insecticides. Their syntheses are challenging due to their chemical complexity. Here, we report the highly enantio- and diastereoselective synthesis of the left fragments of azadirachtin I and 1-cinnamoylmelianolone, being two important family members of meliacarpin-type limonoids, via pairwise palladium- and gold-catalyzed cascade reactions. Gold-catalyzed reactions of 1,7-diynes were performed as model studies, and the efficient construction of tetracyclic late-stage intermediates was achieved on the basis of this key transformation. Our unique route gave both of the left fragments in 23 steps from the commercially available chiral starting material (−)-carvone. This study significantly advances research on the synthesis of the meliacarpin-type limonoids.



INTRODUCTION

The azadirachtin/meliacarpinin-type natural products occupy a special position in biologically active small molecules, among which azadirachtin A (**1**, Figure 1) is known as one of the most powerful anti-insect compounds with low toxicity to mammalian cells.[1] The structure−activity relationships of azadirachtin A have been explored by the isolation, derivatization, and degradation of the naturally occurring form, but the scope of its chemical transformations is limited by the sensitivity of this molecule to acids, bases, and oxidants.[2] The chemical biology studies of azadirachtin A, including its mechanism of action, would be significantly facilitated by use of de novo synthesized analogues.

Since the isolation of azadirachtin A in 1968, its structure has attracted attentions from the organic synthesis communities. The "relay total synthesis", accomplished by Ley and co-workers, was a milestone in the study of azadirachtin A, which is one of the most challenging targets for total synthesis, and a high bar for synthetic chemists.[2] The key to their success was the strategic disconnection of the C8−C14 bond, leading to the left fragment **2** (Figure 1) and the right fragment that represent tremendous synthetic challenges. In the de novo synthesis of left fragment **2**, Ley's group used an intramolecular Diels−Alder reaction to close the A ring (**3** → **4**, Figure 1); subsequent transformations, including an intramolecular aldol reaction and a Michael addition, afforded the desired tetracyclic structure with a densely functionalized decalin core.[3] Among various left-fragment studies,[4−7] Murai's group also used an intramolecular Diels−Alder reaction as a key transformation to construct both the A and B rings in a single step.[4] The intramolecular Diels−Alder reaction used by Watanabe's group provided the A ring and the THF motif simultaneously.[5] Another synthetic study that achieved formation of the tetracyclic skeleton of the left fragment was reported by Nicolaou's group. They obtained **10** from the readily available chiral starting material **9** (Figure 1) through a sequence of steps to install the tetrahydrofuran and γ-lactone motifs.[6]

Based on the previous studies, we aimed to establish a practical approach to synthesize the azadirachtin family natural products and analogues, which will pave the way for further biological investigations. Various azadirachtin congeners have excellent antifeedant activities; for example, azadirachtin I (**11**, Figure 2) and 1-cinnamoylmelianolone (**13**) have strong actions against *Spodoptera litura* and *Heliothis virescens*, respectively, with potencies similar to that of azadirachtin A.[8,9]

However, the anti-insect and other potential biological activities of these compounds have not been well studied, mainly because of their limited availability.[10] Practical chemical syntheses are therefore needed. Convergent strategies, which

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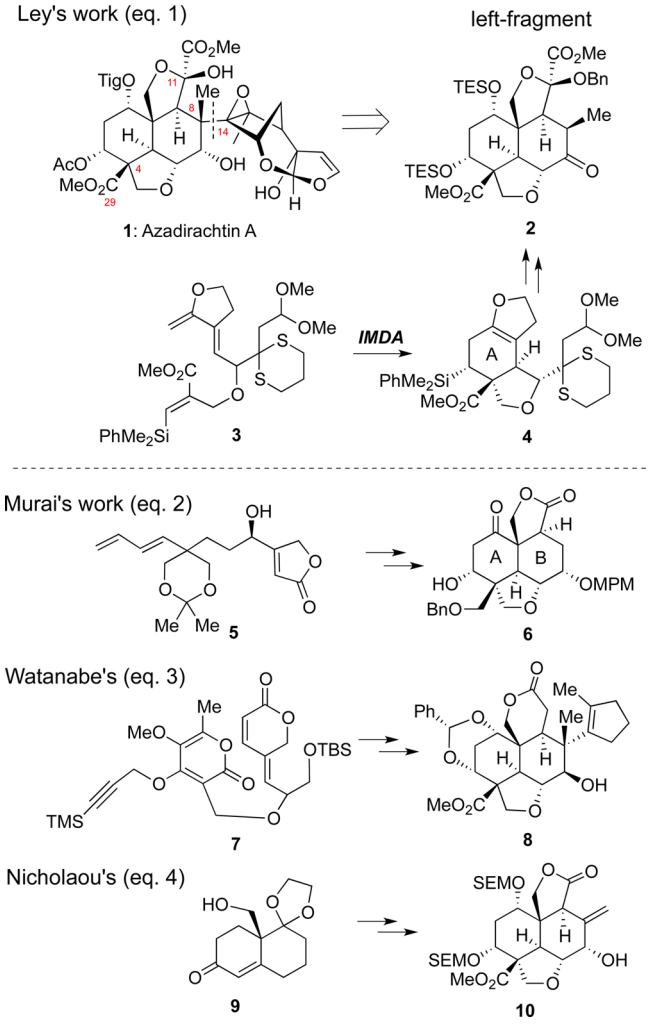

Figure 1. Left fragments of meliacarpin-type limonoids.

need a concise and scalable route for the preparation of densely functionalized left fragments in enantiopure form, are promising approaches. We hypothesize that azadirachtin I (**11**, Figure 2) and its C11 (azadirachtin A numbering throughout) diastereomer, 11-*epi*-azadirachtin I (**12**),[8] could be prepared from one left fragment, tetracycle **15**. For another meliacarpin-type limonoid, 1-cinnamoylmelianolone (**13**), retrosynthetic analysis gives intermediate **14**, in which the C11 ketone is masked as a ketal. Intermediate **14** could be divided into two fragments by disconnecting the C8−C14 bond to give the left-wing fragment **16**. The major differences between **15**/**16** and Ley's left-wing fragment **2** are the substituents on C4 and C11.

Given the similarities between drimane-type sesquiterpenoids (**A** in Figure 2) and the synthetic targets **2** (Figure 1), **15**, and **16** (Figure 2), we thought that a streamlined strategy for drimane synthesis, which was based on a gold-catalyzed cascade reaction of 1,7-diyne, could be further developed as an efficient route to the desired decalin intermediates.[11] Here, we described the evolution of our synthetic strategies to the left fragments of meliacarpin-type limonoids, including the attempted synthesis of **2**, and the successful syntheses of **15**[12] and **16**. Although gold-catalyzed transformations in natural product synthesis have already been reported,[13] our goal of streamlining the preparation of complex targets **2**, **15**, and **16** was still a significant challenge and required considerable experimentation, although there are numerous precedents for gold-catalyzed cascade cyclizations of diynes.[14]

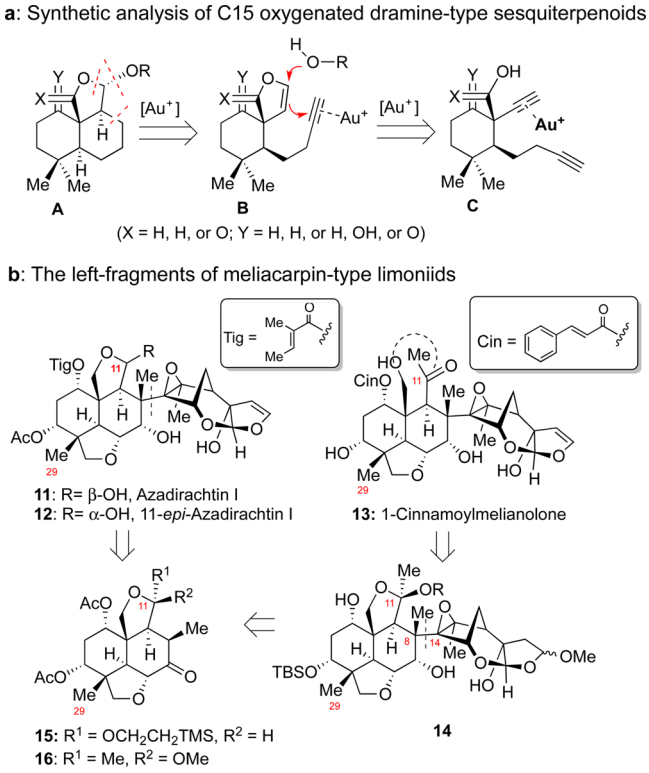

Figure 2. (a) Synthetic analysis of C15 oxygenated dramine-type sesquiterpenoids. (b) Left fragments of meliacarpin-type limonoids.

RESULTS AND DISCUSSION

Gold-Catalyzed Cascade Reactions of 1,7-Diynes with Different Substituents. Our early efforts toward the syntheses of the left fragments of meliacarpin-type limonoids used substrates **17a**−**e** bearing different substituents on one alkyne[11] to explore the substrate scope in the gold-catalyzed cascade transformations (Table 1). Accordingly, compound (±)-**17a** could be converted to (±)-**18a** in 90% yield with *p*-nitrobenzyl alcohol as an external nucleophile (entry 1). Under the same reaction conditions, (±)-**17b** decomposed (entry 2). We reasoned that a trace amount of water could trigger hydrolysis of the congested tetracyclic ketal (±)-**18**, and the resultant product might undergo decomposition under the reaction conditions. We therefore carried out the gold-catalyzed cascade reaction of (±)-**17b**, which proceeded smoothly in the presence of 50 wt % 4 Å molecular sieves; as expected, product **18b** was obtained in 60% isolated yield (entry 3). On the other hand, (±)-**18b** was obtained in 46% yield in the presence of $MgSO_4$ (entry 4). We further tested other substituted 1,7-diynes (±)-**17c**, (±)-**17d**, and (±)-**17e**. Although (±)-**18c** and (±)-**18d** were obtained in moderate yields (entries 5 and 7), in the case of (±)-**17e**, which owned carboxylate substituent, significant decomposition was observed during complete conversion of the starting material, and (±)-**18e** was isolated in low yields (entries 9 and 10).

We also tested 1,7-diynes with a ketal structure to probe the functional group compatibility of the gold-catalyzed cascade transformation (Figure 3). For substrate (±)-**19a**, cascade cyclization product (±)-**20a**, whose structure was confirmed by single-crystal X-ray analysis, was obtained in moderate yield. In

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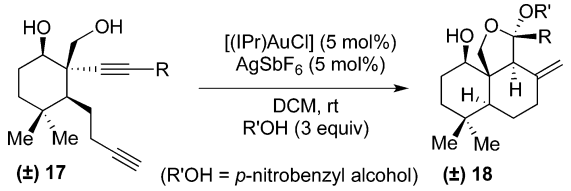
Table 1. Gold-Catalyzed Cascade Reactions of Various 1,7-Diynes[a]



(±) **17** (R'OH = *p*-nitrobenzyl alcohol) (±) **18**

entry	R	additive	time	product	yield (%)
1	H (**17a**)		30	**18a**	90
2	Me (**17b**)		10	**18b**	dec
3		4 Å M.S.	10	**18b**	60
4		$MgSO_4$	10	**18b**	46
5	CH_2OMe (**17c**)	4 Å M.S.	15	**18c**	62
6		$MgSO_4$	15	**18c**	32
7	Ph (**17d**)	4 Å M. S.	25	**18d**	50
8		$MgSO_4$	25	**18d**	37
9	CO_2Me (**17e**)	4 Å M. S.	60	**18e**	30
10		$MgSO_4$	30	**18e**	25

[a]Conditions: diyne (0.1−0.15 mmol), *p*-nitrobenzyl alcohol (3.0 equiv), [(IPr)AuCl]/$AgSbF_6$ (5 mol %), additive (50 wt %), DCM (0.05 M), rt. Diynes and products are racemic. IPr: 1,3-Bis(2,6-diisopropylphenyl)imidazole-2-ylidene. 4 Å M.S.: 4 Å molecular sieves.

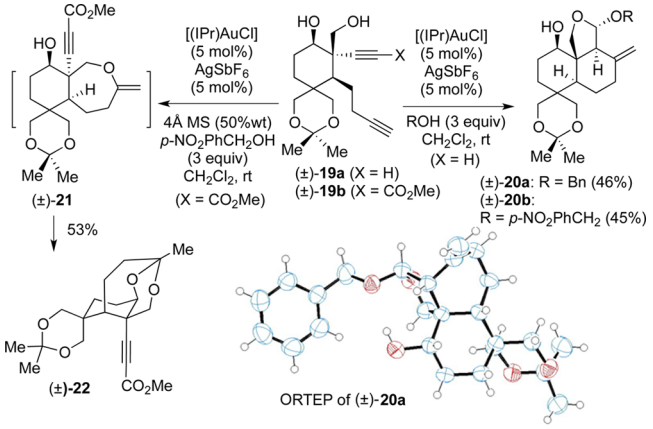


Figure 3. Gold-catalyzed cascade reactions of 1,7-diynes **19a** and **19b**.

the presence of *p*-nitrobenzyl alcohol, (±)-**20b** formed smoothly, which suggested that (±)-**19a** was a viable substrate but inferior to the counterpart (±)-**17a** without the ketal functionality. On the other hand, when substrate (±)-**19b** bearing a carboxylate ester at the terminal of acetylene was subjected to gold-catalyzed annulation without a drying agent, decomposition was observed. When 4 Å molecular sieves were added, ketal (±)-**22** was isolated as the major product in 53% yield, presumably through intermediate (±)-**21**. This suggests that 7-*exo*-*dig* cyclization was favored over the desired 5-*endo*-*dig* cyclization, which indicates that gold-catalyzed cascade reactions of 1,7-diynes with an internal alkyne could not be used as substrates for the construction of the left fragments of meliacarpin-type limonoids.

Synthetic Efforts toward Azadirachtin Left Fragment 2. Retrosynthetic analysis showed that the α-methyl carbonyl structure of the azadirachtin left fragments could be introduced by allylic oxidation of **23** followed by olefin hydrogenation (Figure 4). The C1- and C3-protected hydroxyl groups of **23** could be furnished from ketone **24**, following the reported

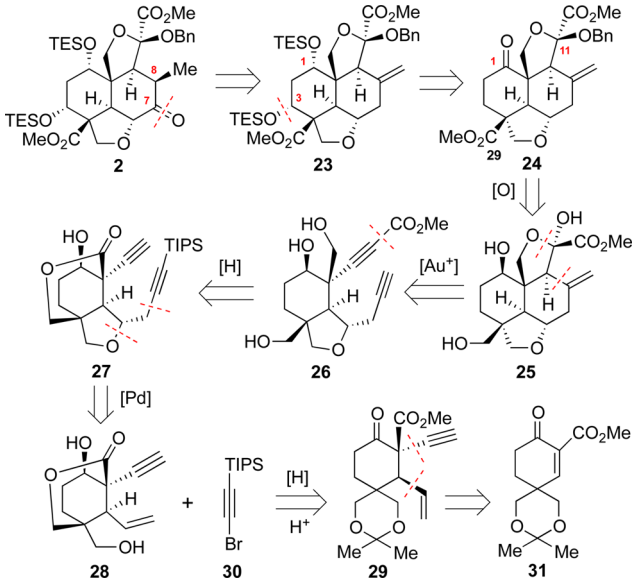


Figure 4. Retrosynthetic analysis of the left fragments of meliacarpin-type limonoids.

transformations of similar systems.[15] The C11 ketal functionality could be derived from the semiketal **25** with inversion of the C11 stereogenic center. Meanwhile, the C1 ketone and the methoxylcarbonyl group at C4 of **24** could be obtained by oxidation of the alcohols. We envisaged compound **25** as a late-stage intermediate, which could be obtained through our gold-catalyzed cascade reaction from diyne **26**, a key precursor with five continuous stereogenic centers. The highly substituted bicycle **26** could be accessed from the monoprotected diyne **27** through reduction of the δ-lactone and alkyne functionalization. The palladium-catalyzed oxyalkynylation of olefins developed by Waser and co-workers[16] is a powerful method for constructing the tetrahydrofuran motif and simultaneously introducing an alkyne fragment; this would convert bicyclic lactone **28** to tricyclic compound **27** in a single transformation. By tightening up the two hydroxymethylene groups with a ketal protecting group, the bridged bicycle **28** could be formed from substituted cyclohexanone **29** by 1,4-addition of the vinyl group to the enone **31** followed by stereoselective installation of acetylene.

In the forward direction, we started from the readily prepared cyclohexenone (±)-**31**.

Compound (±)-**31** was subjected to 1,4-addition of a vinyl Grignard reagent and then treated with the hypervalent iodonium reagent **32** to give (±)-**29** in 82% yield (Scheme 1). We thought that the twist-boat conformation would be favored because of the highly substituted nature of cyclohexanone (±)-**29** and that the nucleophile would preferentially attack the ketone from one face; this was verified by $NaBH_4$ reduction to produce **33** in diastereomerically pure form (dr >19:1). Deprotection of the diol in (±)-**33** under acidic conditions led to spontaneous lactonization, which gave (±)-**28** in excellent yield via presumable intermediate (±)-**34**. However, subjection of (±)-**28** to the palladium-catalyzed oxyalkynylation reaction[16] led to decomposition. Given the incompatibility of the β-hydroxyl lactone with the strong basic conditions (^{t}BuONa), the secondary alcohol in **33** was first protected with TBS to give (±)-**36**. Acidic deprotection condition afforded lactonization product (±)-**37**, which still decomposed in Pd-catalyzed oxyalkynylation. In the end, to

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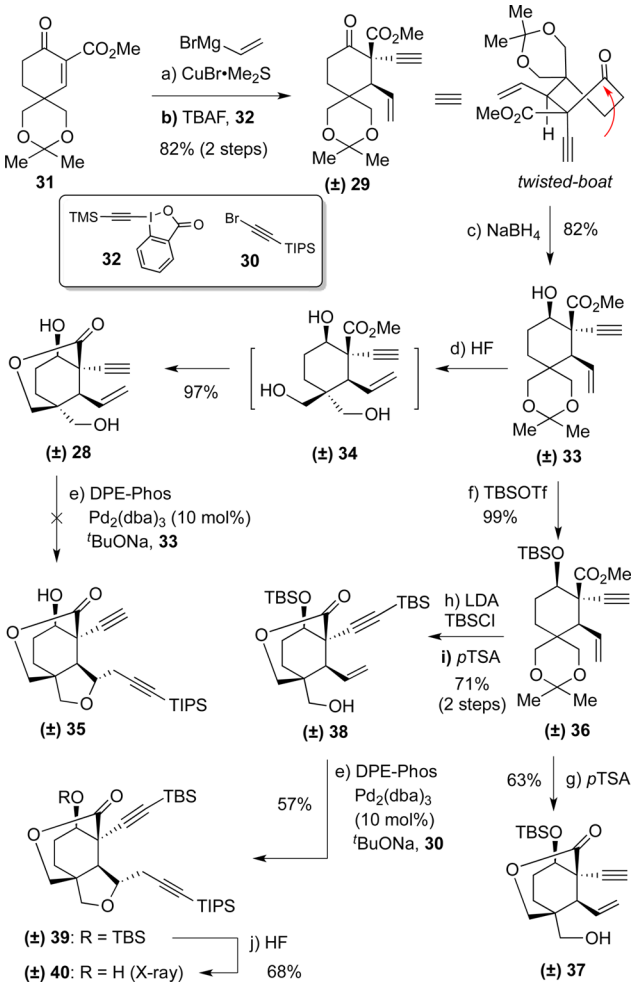
Scheme 1. Preparation of 1,7-Diyne 40[a]



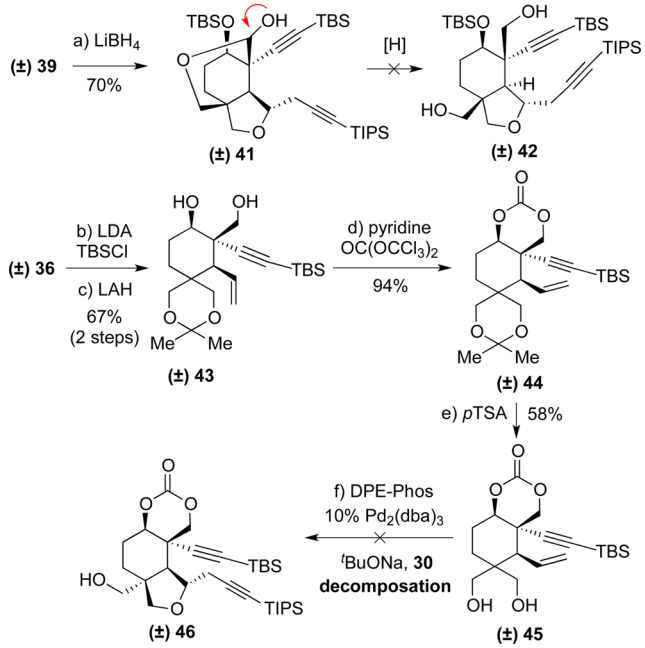
[a]Reaction conditions: (a) vinyl Grignard reagent (2.0 equiv), CuBr·Me_2S (0.3 equiv), THF, −78 °C; (b) **32** (1.3 equiv), TBAF (1.3 equiv), THF, −78 °C; (c) $NaBH_4$ (0.4 equiv), MeOH, −50 °C; (d) HF (2.0 equiv), acetonitrile, rt; (e) $Pd_2(dba)_3$ (0.1 equiv), DPE-Phos (0.2 equiv), NaO^{t}Bu (1.4 equiv), **30** (1.4 equiv), toluene, 65 °C; (f) TEA (3.5 equiv), TBSOTf (2.5 equiv), DCM, −10 °C; (g) *p*-TSA monohydrate (cat), acetonitrile, rt; (h) TBSCl (3.0 equiv), LDA (2.0 equiv), THF, −78 °C to rt; (i) *p*-TSA monohydrate (1.5 equiv), acetonitrile, −10 °C; (j) 40% HF aqueous solution (3.0 equiv), acetonitrile, 40 °C. *p*-TSA: *p*-toluenesulfonic acid. $Pd_2(dba)_3$: tris(dibenzylideneacetone)dipalladium. DPE-Phos: bis(2-diphenylphosphinophenyl)ether.

inhibit side transformations, the TBS group was used to block the terminal alkyne of (±)-**36**, and bridged lactone (±)-**38** was obtained in 71% overall yield over two steps. Palladium-catalyzed oxyalkynylation of (±)-**38** provided compound (±)-**39** with the desired stereochemistry as the major product, probably because *syn*-pentane interactions of the vinyl group and the two axial carbons in the transition state were minimized. Treatment of (±)-**39** with HF aqueous solution in acetonitrile removed the TBS protecting group on the secondary alcohol to afford (±)-**40**, the structure of which was confirmed by single-crystal X-ray analysis. We were able to prepare this tricyclic intermediate with five contiguous stereogenic centers in 22% overall yield over seven steps from cyclohexanone (±)-**31** by exploiting the latent symmetry of 1,7-diyne (±)-**39**.

With (±)-**39** in hand, we attempted to reduce its lactone moiety into diol (±)-**42** through reduction. In the event, when the *δ*-lactone in (±)-**39** was reduced with $LiBH_4$, product (±)-**41** bearing a semiketal was obtained as a major product, presumably because of the steric hindrance of (±)-**41**, which prevents its further reduction to diol (±)-**42**. Because of the intractable problem, an alternative route for construction of the 1,7-diyne substrate for the gold-catalyzed cascade reaction was investigated. Ester (±)-**36** was converted to diol (±)-**43** in two steps. Formation of the cyclic carbonate and hydrolysis of the ketal were effected by treatment with triphosgene and *p*-toluenesulfonic acid (*p*-TSA), respectively. When (±)-**45** was subjected to the reaction conditions for palladium-catalyzed olefin oxyalkynylation, decomposition of the starting materials was observed and no desired tricyclic product (±)-**46** was isolated. According to the results, we were unable to test the gold-catalyzed cascade reaction using this model.

Enantio- and Diastereoselective Syntheses of the Left Fragment 15 of Azadirachtin I and 11-*epi*-Azadiractin I. Having encountered difficulty in achieving the chemistry illustrated in Scheme 2, we moved on to prepare the

Scheme 2. Attempts To Synthesize Precursors for the Gold-Catalyzed Cyclization[a]



[a]Reaction conditions: (a) $LiBH_4$ (14.0 equiv), THF, rt; (b) TBSCl (3.0 equiv), LDA (2.0 equiv), THF, −78 °C to rt; (c) $LiAlH_4$ (2.0 equiv), THF, rt; (d) pyridine (3.0 equiv), triphosgene (2.0 equiv), DCM, −10 °C; (e) *p*-TSA monohydrate (1.5 equiv), acetonitrile, −10 °C to rt; (f) $Pd_2(dba)_3$ (10 mol%), DPE-Phos (0.2 equiv), NaO^{t}Bu (1.4 equiv), **30** (1.4 equiv), toluene, 65 °C.

azadirachtin I left fragment **15**, which bears a simple methyl group at C4 (Figure 5). Similar to our retrosynthetic analysis of **2**, tetracycle **15** could be formed from the advanced intermediate **47**, which could be afforded by our gold-catalyzed cascade reaction of 1,7-diyne **48**. Further destruction of **48** would lead to bicycle **49**, which could be synthesized from **50**. Use of the palladium-catalyzed olefin oxyalkynylation would enable the preparation of **50** from **51**. Cyclohexanone **51** could in turn be obtained from conjugated addition followed by aldol

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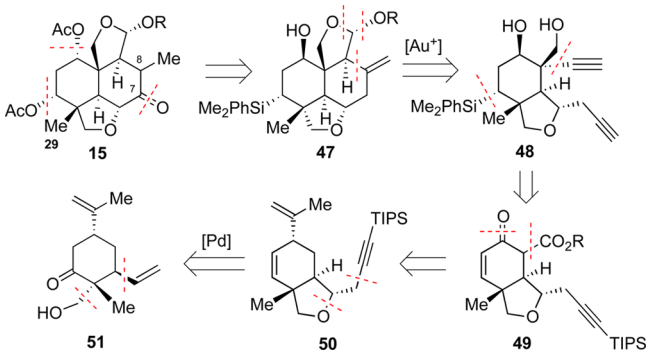


Figure 5. Retrosynthetic analysis of azadirachtin 1 left fragment **15**.

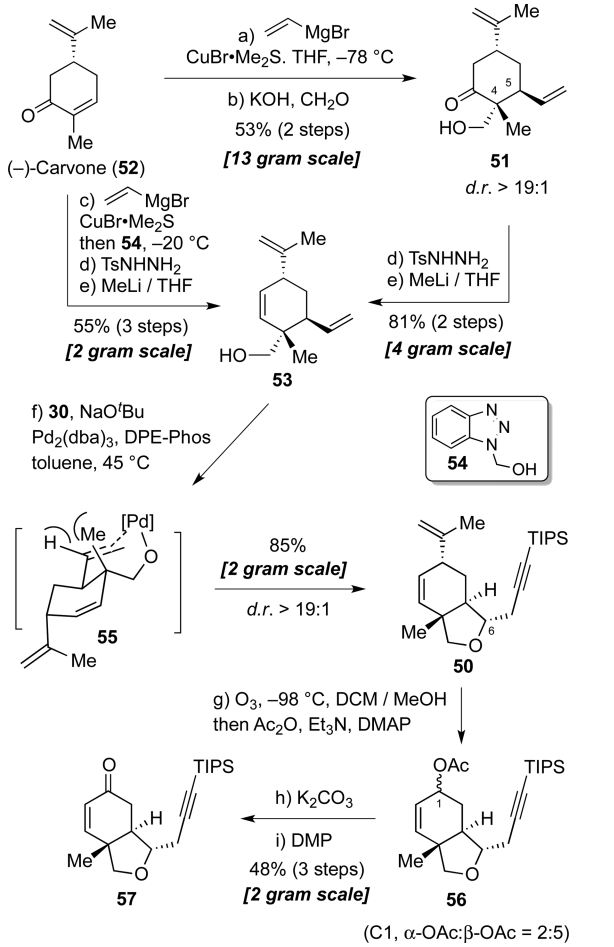
reaction of enantiopure (−)-carvone, a widely used chiral starting material.

In the forward direction, the stereogenic center at C5 was secured by diastereoselective copper(I)-catalyzed 1,4-addition of a vinyl Grignard reagent to the (−)-carvone (**52**) (Scheme 3). The resulting cyclohexanone condensed with formaldehyde in the presence of KOH to afford **51** as a single diastereomer in 53% isolated yield over two steps.[17] Subsequently, **51** was converted to the *p*-toluenesulfonyl hydrazone derivative, which underwent a Shapiro reaction to provide highly substituted cyclohexene **53** in 81% yield over two steps. Alternatively, the enolate formed from the 1,4-addition of **52** was trapped by reagent **54**,[18] followed by converting the ketone to the olefin via the Shapiro reaction to afford product **53** as a single diastereomer in 55% yield over three steps.

Importantly, both routes to enantiopure **53** proceeded smoothly on the multigram scale, setting the stage for the palladium-catalyzed olefin oxyalkynylation. The [6,5]-bicycle **50** was obtained from **53** in 85% yield on a gram scale under the optimized reaction conditions. This cascade transformation was remarkable not only in terms of the high chemo- and regioselectivities but also because of the excellent diastereoselectivity of the new stereogenic center (C6). This result can be attributed to the *syn*-pentane interaction between the methyl and vinyl group in the transition state **55** being minimized. Ozonolysis followed by acetylation and the Criegee rearrangement, a protocol developed by Schreiber and co-workers,[19] converted the propenyl group in **50** to an acetate group, giving **56** as a pair of inseparable diastereomers (dr = 2:5).[20] The epimerization of C1 can be rationalized by invoking an allyl cation intermediate during the Criegee rearrangement. Hydrolysis of acetate **56** followed by alcohol oxidation yielded compound **57** as a single diastereomer. This three-step sequence converted **50** to **57** on a gram scale in 48% overall yield.

With **57** in hand, we first acetylated at C10 using Mander's reagent **58a** (Scheme 4) in the presence of NaHMDS to prepare **49a**, which was confirmed by single-crystal X-ray analysis. Attachment of a phenyldimethylsilyl group at C3, which serves as a masked form of the hydroxyl group, was achieved by 1,4-addition of enone **49a** using $PhMe_2SiLi$/Et_2Zn.[21] Treatment of the resulting *β*-keto ester with iodonium reagent **32** afforded **59a**. It is worth noting that the phenyldimethylsilyl and alkyne groups were both introduced diastereoselectively, presumably under the influence of the axial methyl group at C4. *β*-Keto ester **59a** was reduced to diol **60** as a pair of inseparable diastereomers (C1, *α*-OH/*β*-OH = 2:5) in 84% yield. At this stage, methods were sought to increase the

Scheme 3. Scalable Preparation of Enantiopure 57[a]



[a]Reaction conditions: (a) vinyl Grignard reagent (1.5 equiv), CuBr·Me_2S (0.3 equiv), THF, −78 °C; (b) KOH (10% in MeOH), formalin (3.0 equiv), rt; (c) vinyl Grignard reagent (3.0 equiv), CuBr·Me_2S (0.3 equiv), THF, − 78 °C, then **54** (1.4 equiv), − 20 °C; (d) $TsNHNH_2$ (1.0 equiv), MeOH, 50 °C; (e) MeLi (4.0 equiv), THF, rt; (f) $Pd_2(dba)_3$ (0.1 equiv), DPE-Phos (0.2 equiv), NaO^{t}Bu (1.5 equiv), **30** (1.2 equiv), toluene, 45 °C; (g) O_3, − 98 °C, MeOH, DCM, then Ac_2O (12.0 equiv), DMAP (0.1 equiv), Et_3N (12.0 equiv), reflux; (h) K_2CO_3 (3.1 equiv), MeOH, 0 °C; (i) DMP (1.2 equiv), DCM, rt. DMP: Dess−Martin periodinane.

diastereopurity of **60** to minimize potential complications in the gold-catalyzed cascade cyclization and following transformations because each of the diastereoisomers might have the potential to generate a pair of products. Diol **60** was obtained via the same transformations in similar yields but in the form of a 1:9 diastereomeric mixture at C1 by simply switching the methyl ester to an ethyl ester (**57** → **49b** → **59b** → **60**). The precursor for our key step, 1,7-diyne **48**, was obtained in excellent yield by desilylation of the TIPS-acetylene group in **60**.

The stage was set for the gold-catalyzed cascade reaction (Scheme 5). Substrate **48** was first submitted to the optimum conditions identified during the total synthesis of drimane sesquiterpenoids (5% [(IPr)AuCl]/$AgSbF_6$, DCM, rt), in which an alcohol (3.0 equiv) was used as the external nucleophile. We chose 2-(trimethylsilyl)ethanol because the deprotection would be facile. The tetracyclic product **47** was isolated in 15% yield as a single diastereomer, and **62** was

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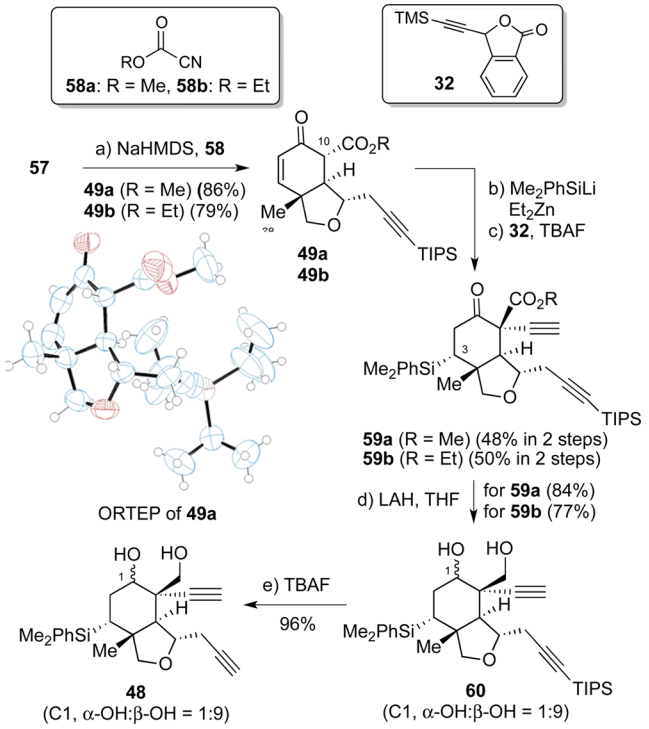
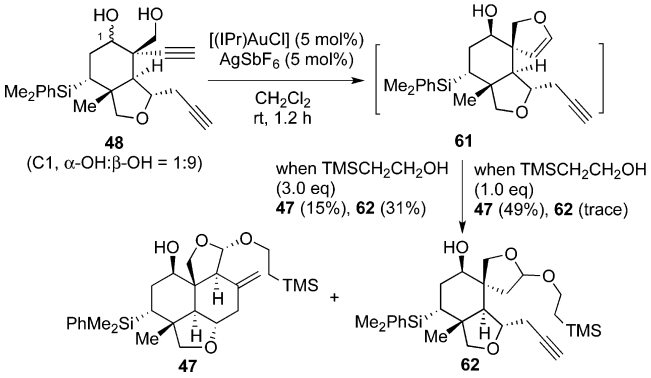
Scheme 4. Synthesis of 1,7-Diyne 48[a]



[a]Reaction conditions (R = Me): (a) for synthesis of **49a** (R = Me), **57** (1.0 equiv), THF, −78 °C, NaHMDS (2.2 equiv), then **58a** (1.3 equiv); for synthesis of **49b** (R = Et), **57** (1.0 equiv), THF, −78 °C, NaHMDS (2.2 equiv), then **58b** (1.3 equiv); (b) for synthesis of **59a**, $PhMe_2SiLi$ (2.2 equiv), Et_2Zn (2.2 equiv), THF, −78 °C; (c) **32** (0.9 equiv), TBAF (2 equiv), THF, 0 °C; for synthesis of **59b**, $PhMe_2SiLi$ (2.2 equiv), Et_2Zn (2.2 equiv), THF, −78 °C; (c) **32** (0.9 equiv), TBAF (2 equiv), THF, 0 °C; (d) $LiAlH_4$ (2.0 equiv), THF, rt; (e) TBAF (2.0 equiv), THF, 50 °C. NaHMDS: sodium hexamethyldisilazane.

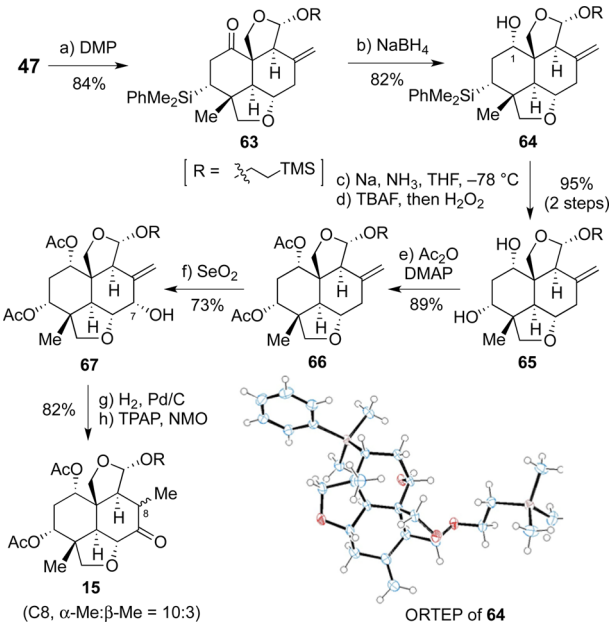
Scheme 5. Gold-Catalyzed Cascade Reaction Leading to Tetracyclic Late-Stage Intermediate 47



identified as a major side product, We reasoned this phenomenon was caused by direct addition of the alcohol to the vinyl ether functionality in intermediate **61**. To minimize this intermolecular reaction, which competes with the desired gold-catalyzed intramolecular cyclization, we reduced the amount of alcohol to 1.1 equiv. The yield of the desired product **47** was increased to 49%, and only a trace amount of **62** was detected.

We then concentrated on the late-stage elaboration of **47** to achieve **15**, the left fragment of azadirachtin I, and 11-*epi*-azadirachtin I (Scheme 6). Inversion of the C1 alcohol was

Scheme 6. Synthesis of Azadirachtin I Left Fragment 15[a]



[a]Reaction conditions: (a) DMP (1.5 equiv), $NaHCO_3$ (2.0 equiv), DCM, rt; (b) $NaBH_4$ (0.6 equiv), MeOH, THF, −10 °C; (c) Na (5.0 equiv), NH_3, THF, −78 °C; (d) TBAF (2.2 equiv), THF, rt, then H_2O_2 (10.0 equiv), $KHCO_3$ (1.5 equiv), MeOH, rt;(e) Ac_2O (8.0 equiv), DMAP (12.0 equiv), DCE, reflux; (f) SeO_2 (5.0 equiv), ^tBuOOH (5.0 equiv), DCM, rt; (g) H_2 (1 atm), Pd/C, EtOAc, rt; (h) TPAP (0.1 equiv), NMO (2.0 equiv), 4 Å molecular sieves (100 wt %), DCM, rt. TPAP: tetrapropylammonium perruthenate.

achieved by redox manipulation. DMP oxidation gave ketone **63** in 84% yield. The desired product **64** was afforded in 82% yield by $NaBH_4$, which was presumably controlled by the bulky silyl group. The easily separated diastereomer **47** was obtained in 7% yield as a minor product of ketone reduction. Birch reduction followed by treatment with TBAF/H_2O_2 completed oxidation of the carbon−silicon bond in excellent yield over two steps.[22] Diol **65** was then acetylated to produce diacetate **66**, which subsequently underwent allylic oxidation with SeO_2 to introduce a hydroxyl group at C7 (**67**). The C7 stereochemistry of **67**, which was a single diastereomer, was deduced by coupling constant analysis and molecular modeling.[12] Hydrogenation of the olefin and oxidation of the C7 alcohol in **67** gave **15** as a pair of diastereomers (C8, *α*-Me/*β*-Me = 10:3) in 82% yield over two steps. The stereochemistry of *α*-Me **15** was confirmed by extensive two-dimensional NMR experiments (see the Supporting Information for details).

Enantio- and Diastereoselective Syntheses of 1-Cinnamoylmelianolone Left Fragment 16. Encouraged by the successful synthesis of **15**, we then prepared tetracycle **16**, the left fragment of 1-cinnamoylmelianolone (**13**). We tackled this problem by exploring two different approaches (Figure 6). Approach A relied on derivatizing the tetracyclic compound **47**, a key intermediate in our synthesis of **15**, which would involve the formation of a C11−C12 bond within the crowded and densely functionalized decalin architecture. In approach B, intermediate **68**, which contained the complete

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J. Org. Chem. 2016, 81, 751−771

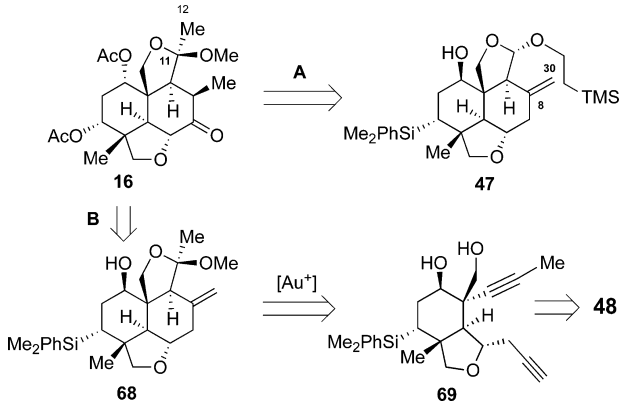
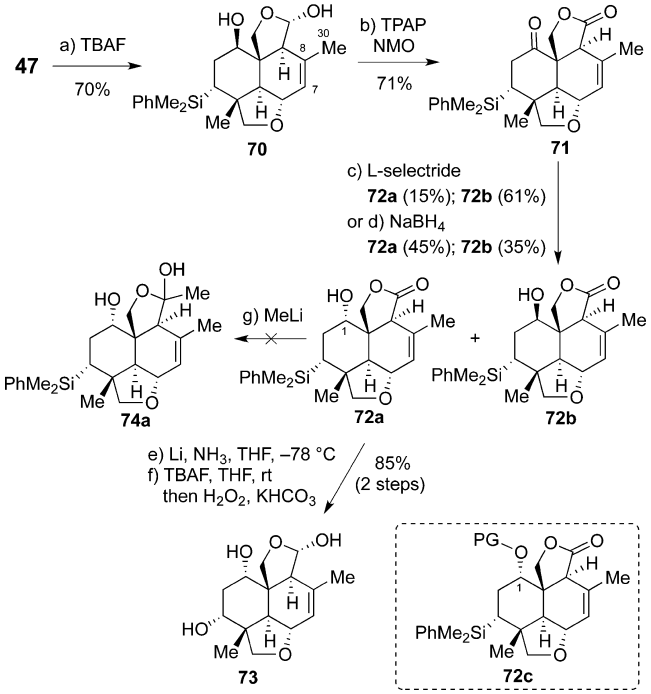


Figure 6. Retrosynthetic analysis of 1-cinnamoylmelianolone left fragment **16**.

carbon skeleton of **16**, could be obtained via the gold-catalyzed cascade reaction of 1,7-diyne **69** using an internal alkyne.

We first devised a concise sequence of reactions to introduce the missing methyl group (Scheme 7). Treatment of **47** with

Scheme 7. Exploration of Strategy A[a]



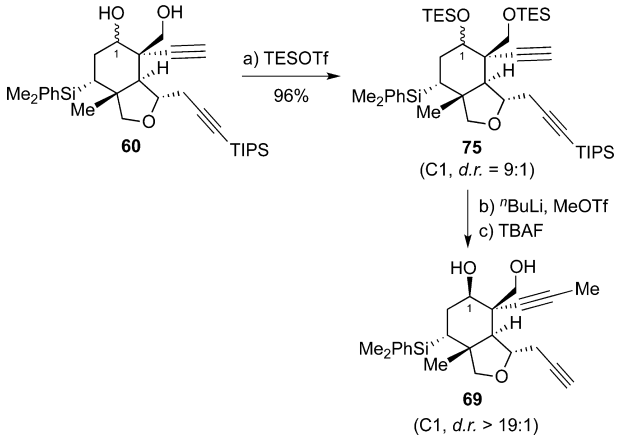
[a]Reaction conditions: (a) TBAF (2.0 equiv), THF, reflux; (b) TPAP (0.14 equiv), NMO (3.0 equiv), 4 Å molecular sieves (100 wt %), DCM, rt; (c) L-Selectride (1.4 equiv), THF, 0 °C; (d) $NaBH_4$ (2.0 equiv), MeOH, 0 °C; (e) Li (40.0 equiv), NH_3, THF, −78 °C; (f) TBAF (2.0 equiv), THF, rt, then H_2O_2 (10.0 equiv), $KHCO_3$ (1.5 equiv), MeOH, rt; (g) MeLi (2.5 equiv), Et_2O, rt.

TBAF in refluxing THF afforded **70** in 70% yield as the only isolated product. In this reaction, the C8−C30 double bond isomerized to give a C7−C8 olefin, and the 2-(trimethylsilyl)-ethyl group was removed.[23] Hemiacetal **70**, which was acid sensitive, decomposed in the presence of DMP, but the Ley−Griffith oxidation synchronously oxidized both the secondary alcohol and hemiacetal functionalities in **70** to provide **71** in 71% yield.[24] Reduction of the C1 ketone by L-Selectride or $NaBH_4$ gave a pair of diastereomers, **72a** and **72b**, in comparable yields. Although the dimethylphenylsilyl group in **72a** was successfully converted to a hydroxyl group in two steps, the lactone was also reduced during the Birch reduction, which resulted in hemiacetal **73** as the final product. To avoid unnecessary redox manipulations, we focused on nucleophilic addition of lactone **72a** to install the desired C12 methyl group. However, treatment of either **72a** or **72b** with excess MeLi only led to recovery of the starting materials.

We reasoned that the C1 hydroxyl group was deprotonated first, and the resulting anion would prevent addition of MeLi to the lactone. Installation of the C12 methyl group through MeLi addition therefore entailed protection of the C1 hydroxyl group of **72a** (cf. **72c**). Our aim was to develop an efficient route that would provide a range of analogues for a detailed structure−activity relationship study; therefore, approach A was deprioritized because of the drawbacks of additional protecting group management steps, coupled with the suboptimal ketone reduction of **71** in terms of diastereoselectivity.

Execution of strategy B began with protection of both primary and secondary alcohols in **60** with triethylsilyl trifluoromethanesulfonate (TESOTf) in one step to afford **75** in excellent yield (Scheme 8). Methylation of the terminal

Scheme 8. Synthesis of 1,7-Diyne 69[a]



[a]Reaction conditions: (a) TESOTf (2.5 equiv), Et_3N (3.0 equiv), DCM, −78 °C; (b) ^{n}BuLi (2.0 equiv), MeOTf (2.5 equiv), HMPA, THF, rt; (c) TBAF (4.0 equiv), THF, 50 °C. TES, triethylsilyl.

alkyne was effected by deprotonation and treatment with MeOTf,[25] and then global deprotection of the silyl protecting groups provided **69** in diastereomerically pure form (dr >19:1). The diastereomerically enriched product was an unintended bonus and simplified compound characterization.

We then turned our attention to the key cascade cyclization step (Scheme 9). The gold-catalyzed reaction of 1,7-diyne **69** afforded a pair of diastereoisomers, **76** and **77**, in similar yields. The addition of $MgSO_4$ (50 wt %) gave the best results. Either pure **76** or **77** was converted to a mixture of **76** and **77** in the presence of excess 2-(trimethylsilyl)ethanol under acidic conditions at room temperature, which meant that a ketal isomerization existed. A mixture of **76** and **77** was converted to **68** as a single diastereomer in almost quantitative yield when MeOH was used.

However, when the gold-catalyzed cascade reaction was performed in the presence of MeOH (3.0 equiv), the tetracyclic

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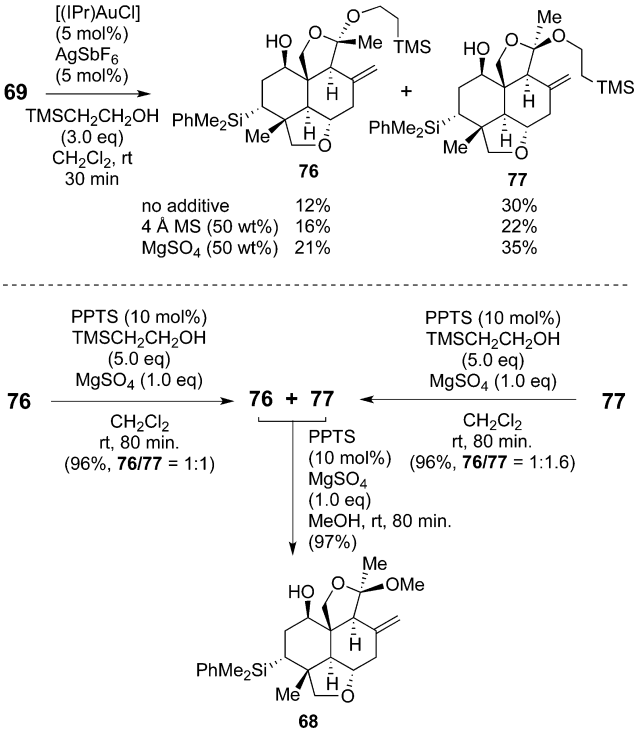
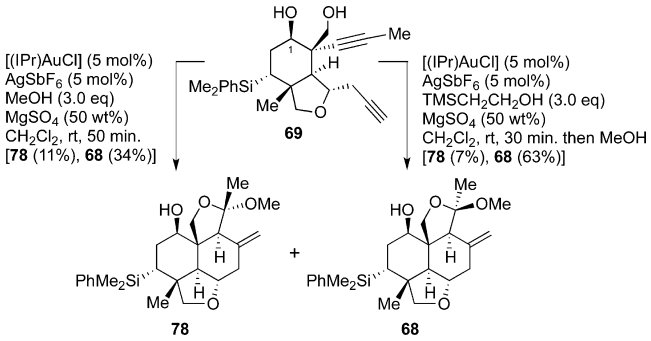
Scheme 9. Gold-Catalyzed Cascade Reactions Leading to Tetracyclic Skeletons



compounds **78** and **68** were obtained in 11% and 34% yields, respectively (Scheme 10).

Scheme 10. Preparation of Key Intermediate 68

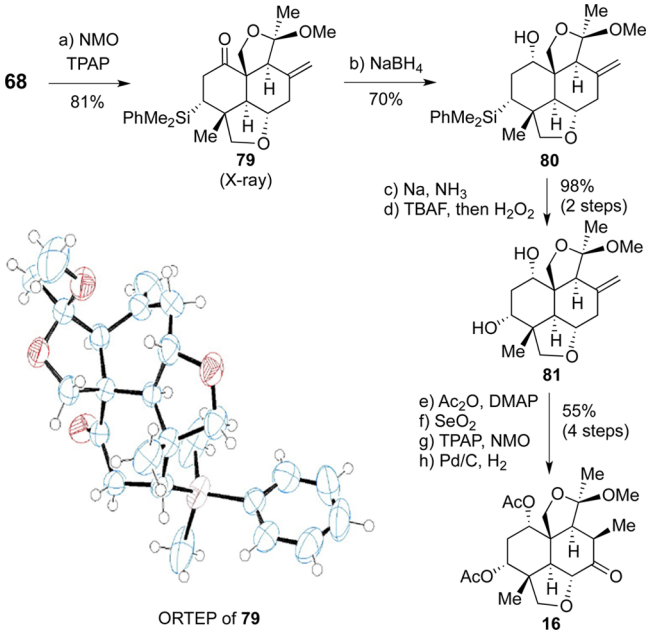


Our observations suggested that one-pot preparation of **68** from 1,7-diyne **69** could be achieved by addition of excess MeOH after the gold-catalyzed cascade cyclization. This one-pot protocol gave **68** in over 60% isolated yield, presumably because **68** was more stable than **76** and **77**, and compound **78** was still obtained as a minor product under such conditions.

With the core skeleton in hand, we synthesized **16** (Scheme 11) through a sequence of transformations similar to those used in synthesis of the azadirachtin I left-wing fragment.

Ketone **79** was prepared by Ley–Griffith oxidation of **68**; its structure was confirmed by single-crystal X-ray analysis.[26] The correct stereogenic center at C1 was obtained by $NaBH_4$ reduction, which afforded alcohol **80** in 70% yield. The dimethylphenylsilyl group was converted in two steps to the hydroxyl group to produce diol **81** in excellent yield. After acetylation, allylic oxidation, and olefin hydrogenation, tetracycle **16** was isolated as a single diastereomer in 55% yield over four steps; the stereochemistry was confirmed using NOESY experiments (see the Supporting Information for details).

Scheme 11. Synthesis of 1-Cinnamoylmelianolone Left Fragment 16[a]



[a]Reaction conditions: (a) TPAP (0.1 equiv), NMO (2.0 equiv), 4 Å molecular sieves (100 wt %), DCM, rt; (b) $NaBH_4$ (1.5 equiv), MeOH, DCM, rt; (c) Na (10.0 equiv), NH_3, THF, −78 °C; (d) TBAF (2.2 equiv), THF, rt, then H_2O_2 (10.0 equiv), $KHCO_3$ (1.5 equiv), MeOH, rt; (e) Ac_2O (5.0 equiv), DMAP (7.0 equiv), DCE, reflux; (f) SeO_2 (5.0 equiv), ^tBuOOH (10.0 equiv), DCM, rt; (g) TPAP (0.1 equiv), NMO (2.0 equiv), 4 Å molecular sieves (100 wt %), DCM, rt; (h) H_2 (1 atm), Pd/C, MeOH, THF, rt.

CONCLUSION

In summary, based on the powerful gold-catalyzed cascade reaction, we developed a concise strategy for synthesizing the left-wing fragments of azadirachtin-type limonoids with minimum use of protecting groups. We first explored the gold-catalyzed tandem reactions of 1,7-diynes with an internal alkyne. Furthermore, we investigated the synthetic route to the azadirachtin left-wing fragments and completed the enantioselective syntheses of azadirachtin I and 1-cinnamoylmelianolone left-wing fragments, **15** and **16**, in 21 and 23 linear steps, respectively. The other notable feature of our approach is the palladium-catalyzed intramolecular olefin oxyalkynylation, which enabled the rapid generation of molecular complexity with high diastereoselectivity. The work reported here not only highlights state-of-the-art stereoselective synthesis, with a single stereogenic center of the (−)-carvone dictating nine contiguous stereogenic centers, including two quaternary ones, but is also a milestone in our program aimed at understanding and developing azadirachtin-type limonoids as environmentally friendly insecticides. We have also recently achieved an enantio- and diastereoselective synthesis of the fully functionalized furopyran moiety (the right-wing fragment) of azadirachtins,[27] which in conjunction with the work reported here paves the way for the de novo syntheses of natural products **11**–**13**. Further investigations and results will be reported in due course.

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EXPERIMENTAL SECTION

Synthesis of Triethyl(((1*S*,2*S*,6*R*)-1-ethynyl-3,3-dimethyl-6-((triethylsilyl)oxy)-2-(4- (trimethylsilyl)but-3-yn-1-yl)-cyclohexyl)methoxy)silane (S2). To a solution of compound **S1**[11] (1.07 g, 3.5 mmol) in dry DCM (30 mL) were added the Et_3N (1.8 mL, 14 mmol) and TESOTf (2.26 mL, 10.5 mmol) at −78 °C in sequence. The reaction mixture was stirred for 50 min and quenched with saturated NH_4Cl solution (20 mL). The aqueous layer was extracted with ethyl acetate (2 × 15 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated under vacuum. The residue was purified by flash chromatography on silica gel (hexanes) to give **S2** (1.7 g) as a colorless oil in 91% yield: R_f = 0.80 (silica gel, hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.02 (d, J = 10.4 Hz, 1H), 3.95 (d, J = 10.4 Hz, 1H), 3.70 (dd, J = 10.6, 4.4 Hz, 1H), 2.55−2.42 (m, 2H), 2.33−2.22 (m, 1H), 2.04 (s, 1H), 1.65−1.52 (m, 3H), 1.48−1.42 (m, 1H), 1.30−1.20 (m, 2H), 1.02−0.96 (m, 18H), 0.95 (s, 3H), 0.95 (s, 3H), 0.66−0.58 (m, 12H), 0.14 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 108.8, 90.8, 83.5, 77.7, 69.6, 63.9, 52.7, 47.3, 34.2, 32.8, 28.5, 28.0, 22.9, 6.9, 6.8, 5.2, 4.5, 0.2; IR (neat, cm^{-1}) 2960, 2357, 770, 1639, 1274, 1109, 763, 750; HRMS-ESI calcd for $C_{30}H_{59}O_2Si_3$ [M + H$^+$] 535.3817, found 535.3820.

Synthesis of (((1*S*,2*S*,6*R*)-3,3-Dimethyl-1-(prop-1-yn-1-yl)-6-((triethylsilyl)oxy)-2-(4- (trimethylsilyl)but-3-yn-1-yl)-cyclohexyl)methoxy)triethylsilane (S3). To a solution of compound **S2** (0.535 g, 1 mmol) in dry THF (15 mL) were added HMPA (0.35 mL, 2 mmol) and ^{n}BuLi solution (2.4 M in hexane, 0.83 mL, 2 mmol) at −78 °C. The mixture was stirred for 0.5 h, after which time MeI (0.2 mL, 3 mmol) was added. The mixture was stirred at 0 °C for 2.5 h and quenched with the saturated NH_4Cl solution (10 mL). The aqueous layer was extracted with ethyl acetate (2 × 15 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated under vacuum. The residue was purified by flash chromatography on silica gel (hexanes) to **S3** (0.44 g) as a yellow oil in 80% yield: R_f = 0.80 (silica gel, hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.99 (d, J = 10.4 Hz, 1H), 3.88 (d, J = 10.4 Hz, 1H), 3.63 (dd, J = 10.8, 3.9 Hz, 1H), 2.53−2.43 (m, 2H), 2.32−2.25 (m, 1H), 1.76 (s, 3H), 1.64−1.51 (m, 3H), 1.43 (d, J = 13.4 Hz, 1H), 1.24 (dd, J = 11.4, 6.8 Hz, 2H), 0.97 (dt, J = 21.7, 10.7 Hz, 24H), 0.60 (dq, J = 15.8, 7.9 Hz, 12H), 0.15 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 109.2, 86.2, 83.5, 78.2, 76.5, 64.2, 53.2, 47.2, 34.2, 33.0, 28.7, 28.0, 22.8, 7.0, 6.9, 5.2, 4.6, 3.7, 0.3; IR (neat, cm^{-1}): 3520, 2955, 2913, 2876, 1248, 1109, 1099, 1005, 841, 822, 748, 727; HRMS-ESI-TOF calcd for $C_{31}H_{61}O_2Si_3$ [M + H$^+$] 549.3974, found 549.3975.

Synthesis of (1*R*,2*S*,3*S*)-3-(But-3-yn-1-yl)-2-(hydroxymethyl)-4,4-dimethyl-2-(prop-1-yn-1-yl)cyclohexan-1-ol (17b). To a solution of compound **S3** (0.434 g, 0.78 mmol) in dry THF (25 mL) was added the TBAF solution (1.0 M in THF, 3.94 mL, 3.94 mmol) at room temperature. The mixture was stirred at room temperature for 1 h and quenched with the saturated NH_4Cl solution (15 mL). The aqueous layer was extracted with ethyl acetate (3 × 15 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated under vacuum. The residue was purified by flash chromatography on silica gel (EtOAc/hexane = 1/1) to give product **17b** (0.155 g) as a white solid in 81% overall yield: R_f = 0.45 (silica gel, EtOAc/hexanes = 1/3); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.05 (d, J = 11.1 Hz, 1H), 3.70 (dd, J = 11.7, 3.3 Hz, 1H), 3.49 (d, J = 11.1 Hz, 1H), 3.28 (br s, 1H), 2.77 (br s, 1H), 2.51−2.40 (m, 1H), 2.37−2.25 (m, 1H), 1.98−1.95 (m, 1H), 1.86 (s, 3H), 1.85−1.74 (m, 2H), 1.65 (dd, J = 19.7, 7.6 Hz, 1H), 1.60−1.53 (m, 1H), 1.43 (d, J = 13.6 Hz, 1H), 1.34−1.26 (m, 2H), 0.89 (s, 3H), 0.76 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 84.7, 81.5, 80.2, 79.3, 68.3, 61.5, 52.9, 48.8, 39.4, 34.0, 32.4, 27.4, 26.8, 22.1, 21.3, 3.7; IR (neat, cm^{-1}) 3429, 2955, 748, 631, 565; HRMS-ESI-TOF calcd for $C_{16}H_{24}NaO_2$ [M + Na$^+$] 271.1669, found 271.1664.

Synthesis of (((1*S*,2*S*,6*R*)-3,3-Dimethyl-1-(phenylethynyl)-6-((triethylsilyl)oxy)-2-(4- (trimethylsilyl)but-3-yn-1-yl)-cyclohexyl)methoxy)triethylsilane (S4). To a solution of compound **S2** (0.535 g, 1 mmol) in dry MeCN (10 mL) were added PhI (0.3 mL, 2 mmol), Et_3N (0.4 mL, 3 mmol), and $PdCl_2(PPh_3)_2$ (70 mg, 0.1 mmol) at room temperature. The mixture was stirred at room temperature for 10 min, and then CuI (10 mg, 0.05 mmol) was added. The mixture was stirred at 90 °C for 2 h and quenched with the saturated NH_4Cl solution (10 mL). The aqueous layer was extracted with ethyl acetate (2 × 10 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated under vacuum. The residue was purified by flash chromatography on silica gel (hexanes) to give product **S4** (0.43 g) as a yellow oil in 71% overall yield: R_f = 0.58 (silica gel, EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (dd, J = 7.7, 1.8 Hz, 2H), 7.32−7.25 (m, 3H), 4.11 (d, J = 10.4 Hz, 1H), 4.05 (d, J = 10.4 Hz, 1H), 3.79 (dd, J = 10.7, 4.5 Hz, 1H), 2.67−2.55 (m, 1H), 2.55−2.44 (m, 1H), 2.41−2.30 (m, 1H), 1.68−1.61 (m, 2H), 1.52−1.46 (m, 1H), 1.38 (t, J = 4.2 Hz, 1H), 1.33−1.27 (m, 2H), 1.03−0.98 (m, 18H), 0.96 (s, 6H), 0.68−0.60 (m, 12H), 0.15 (s, 9H); ^{13}C (125 MHz, $CDCl_3$) 131.6, 128.2, 127.3, 124.8, 109.0, 97.3, 83.9, 82.0, 77.8, 64.1, 53.3, 48.1, 34.4, 32.9, 28.8, 28.1, 23.0, 7.1, 7.0, 5.3, 4.6, 1.1, 0.3; IR (neat, cm^{-1}) 2911, 2876, 2174, 1458, 1248, 1107, 1009, 841, 745; HRMS-ESI-TOF calcd for $C_{36}H_{63}O_2Si_3$ [M + H$^+$] 611.4130, found 611.4130.

Synthesis of (1*R*,2*S*,3*S*)-3-(But-3-yn-1-yl)-2-(hydroxymethyl)-4,4-dimethyl-2-(phenylethynyl)cyclohexan-1-ol (17d). To a solution of compound **S4** (0.61 mg, 1 mmol) in dry THF (10 mL) was added the TBAF solution (1.0 M in THF, 5 mL, 5 mmol) at 0 °C. The mixture was stirred at room temperature for 1 h and quenched with the saturated NH_4Cl solution (10 mL). The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated under vacuum. The residue was purified by flash chromatography on silica gel (EtOAc/hexane = 1/4) to give product **17d** (0.2 g) as a yellow oil in 64% overall yield: R_f = 0.75 (silica gel, EtOAc/hexanes = 1/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50−7.44 (m, 2H), 7.34−7.29 (m, 3H), 4.20 (dd, J = 11.3, 5.6 Hz, 1H), 3.89 (d, J = 11.5 Hz, 1H), 3.66 (dd, J = 11.1, 5.4 Hz, 1H), 3.11 (br s, 1H), 2.68 (br s, 1H), 2.60−2.52 (m, 1H), 2.46−2.37 (m, 1H), 2.02−1.92 (m, 2H), 1.89−1.83 (m, 1H), 1.79−1.66 (m, 2H), 1.54−1.46 (m, 2H), 1.40−1.32 (m, 1H), 0.95 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 132.0, 128.4, 128.3, 84.5, 79.2, 68.6, 61.7, 52.8, 49.6, 39.4, 34.2, 32.5, 27.6, 26.9, 22.2, 21.4; IR (neat, cm^{-1}) 3267, 2955, 2865, 1437, 1367, 1275, 1261, 1071, 754, 690, 669; HRMS-ESI-TOF calcd for $C_{21}H_{27}O_2$ [M + H$^+$] 311.2006, found 311.2010.

Synthesis of Methyl 3-((1*S*,2*S*,6*R*)-3,3-Dimethyl-6-((triethylsilyl)oxy)-1-(((triethylsilyl)oxy)methyl)-2-(4-(trimethylsilyl)but-3-yn-1-yl)cyclohexyl)propiolate (S5). To a solution of compound **S2** (0.535 g, 1 mmol) in dry THF (15 mL) was added the ^{n}BuLi solution (2.4 M in hexane, 0.83 mL, 2 mmol) at −78 °C. The mixture was stirred for 0.5 h, after which time $ClCO_2Me$ (0.23 mL, 3 mmol) was added. The mixture was stirred at −78 °C for 1 h and quenched with the saturated NH_4Cl solution (10 mL). The aqueous layer was extracted with ethyl acetate (2 × 10 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated under vacuum. The residue was purified by flash chromatography on silica gel (hexanes) to **S5** (0.45 g) as a yellow oil in 76% yield: R_f = 0.85 (silica gel, EtOAc/hexane = 1/4); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.01 (q, J = 10.3 Hz, 2H), 3.77−3.69 (m, 4H), 2.53−2.45 (m, 1H), 2.40−2.26 (m, 2H), 1.64−1.56 (m, 2H), 1.50−1.44 (m, 1H), 1.41−1.37 (m, 1H), 1.27 (t, J = 11.3 Hz, 2H), 1.03−0.95 (m, 18H), 0.95 (d, J = 3.3 Hz, 6H), 0.62 (dd, J = 15.8, 7.9 Hz, 12H), 0.14 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.4, 108.4, 95.8, 84.1, 63.1, 52.3, 51.8, 48.2, 34.3, 32.7, 28.6, 27.9, 22.4, 7.0, 6.9, 5.1, 4.5, 0.3; IR (neat, cm^{-1}) 3435, 2955, 2878, 2230, 2174, 1719, 1458, 1250, 1107, 1011, 843, 820, 741, 729; HRMS-ESI-TOF calcd for $C_{32}H_{61}O_4Si_3$ [M + H$^+$] 593.3872, found 593.3872.

Synthesis of 3-((1*S*,2*S*,6*R*)-3,3-Dimethyl-6-((triethylsilyl)oxy)-1-(((triethylsilyl)oxy)methyl)-2-(4-(trimethylsilyl)but-3-yn-1-yl)-cyclohexyl)prop-2-yn-1-ol (S6). To a solution of compound **S5** (0.593 g, 1 mmol) in dry THF (15 mL) was added the $LiAlH_4$ solution (1.0 M in THF, 2 mL, 2 mmol) at 0 °C. The mixture was stirred at room temperature for 1 h and quenched with saturated Seignette salt solution (10 mL). The aqueous layer was extracted with ethyl acetate (3 × 15 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated under vacuum. The residue was purified by flash chromatography on silica gel (EtOAc/hexane = 1/20) to **S6**

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J. Org. Chem. 2016, 81, 751−771

(0.405 g) as a yellow oil in 72% yield: R_f = 0.35 (silica gel, EtOAc/hexane = 1/10); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.22 (s, 2H), 4.00 (d, J = 10.4 Hz, 1H), 3.92 (d, J = 10.4 Hz, 1H), 3.68 (dd, J = 10.9, 4.1 Hz, 1H), 2.47−2.38 (m, 3H), 1.75−1.65 (m, 1H), 1.64−1.50 (m, 3H), 1.49−1.40 (m, 1H), 1.40−1.34 (m, 1H), 1.30−1.22 (m, 1H), 1.01−0.96 (m, 18H), 0.94 (d, J = 9.9 Hz, 6H), 0.65−0.57 (m, 12H), 0.15 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 109.1, 93.3, 84.4, 79.7, 77.9, 63.5, 52.5, 51.7, 47.5, 34.2, 32.9, 28.6, 27.7, 22.6, 7.0, 6.9, 5.2, 4.5, 0.3; IR (neat, cm^{-1}) 3418, 2955, 2876, 2172, 1111, 1007, 841, 820, 727; HRMS-ESI-TOF calcd for $C_{31}H_{61}O_3Si_3$ [M + H$^+$] 565.3923, found 565.3924.

Synthesis of Triethyl(((1*S*,2*S*,6*R*)-1-(3-methoxyprop-1-yn-1-yl)-3,3-dimethyl-6-((triethylsilyl)oxy)-2-(4-(trimethylsilyl)but-3-yn-1-yl)cyclohexyl)methoxy)silane (S7). To a solution of compound **S6** (0.33 g, 0.58 mmol) in dry THF (10 mL) was added NaH (28 mg, 1.17 mmol) at room temperature. The mixture was stirred for 0.5 h, after which time MeI (0.18 mL, 2.92 mmol) was added. The mixture was stirred at 50 °C for 2 h and quenched with the saturated NH_4Cl solution (20 mL). The aqueous layer was extracted with ethyl acetate (2 × 15 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated under vacuum. The residue was purified by flash chromatography on silica gel (EtOAc/hexane = 1/30) to **S7** (0.286 g) as a yellow oil in 87% yield: R_f = 0.60 (silica gel, EtOAc/hexane = 1/10); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.08 (s, 2H), 4.01 (d, J = 10.4 Hz, 1H), 3.93 (d, J = 10.4 Hz, 1H), 3.67 (dd, J = 10.3, 4.6 Hz, 1H), 3.38 (s, 3H), 2.53−2.35 (m, 2H), 2.32−2.20 (m, 1H), 1.65−1.49 (m, 3H), 1.43 (d, J = 13.6 Hz, 1H), 1.30−1.16 (m, 2H), 0.96 (dd, J = 15.1, 7.1 Hz, 18H), 0.93 (s, 6H), 0.60 (dd, J = 15.4, 7.7 Hz, 12H), 0.11 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 108.7, 93.6, 83.5, 77.7, 76.9, 67.6, 64.0, 60.3, 57.3, 53.0, 47.6, 34.2, 32.8, 28.6, 28.1, 23.0, 7.0, 6.9, 5.1, 4.6, 4.5, 4.4, 0.2; IR (neat, cm^{-1}) 3418, 2955, 2876, 2174, 1636, 1458, 1248, 1101, 1007, 883, 841, 741; HRMS-ESI-TOF calcd for $C_{32}H_{63}O_3Si_3$ [M + H$^+$] 579.4080, found579.4081.

Synthesis of Triethyl(((1*S*,2*S*,6*R*)-1-(3-methoxyprop-1-yn-1-yl)-3,3-dimethyl-6((triethylsilyl)oxy)-2(4-(trimethylsilyl)but-3-yn-1-yl)cyclohexyl)methoxy)silane (17c). To a solution of compound **S7** (286 mg, 0.5 mmol) in dry THF (10 mL) was added the TBAF solution (1.0 M in THF, 2.5 mL, 2.5 mmol) at 0 °C. The mixture was stirred at room temperature for 1 h and quenched with the saturated NH_4Cl solution (15 mL). The aqueous layer was extracted with ethyl acetate (2 × 15 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated under vacuum. The residue was purified by flash chromatography on silica gel (EtOAc/hexane = 1/1) to give product **17c** (0.108 g) as a white solid in 87% overall yield: R_f = 0.20 (silica gel, EtOAc/hexanes = 1/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.15 (s, 2H), 4.11 (d, J = 10.9 Hz, 1H), 3.77 (dd, J = 11.4, 3.0 Hz, 1H), 3.59−3.49 (m, 2H), 3.39 (s, 3H), 3.06 (br s, 1H), 2.50−2.41 (m, 1H), 2.37−2.27 (m, 1H), 1.96 (t, J = 2.2 Hz, 1H), 1.89−1.81 (m, 1H), 1.81−1.75 (m, 1H), 1.72−1.65 (m, 1H), 1.64−1.54 (m, 1H), 1.45 (dt, J = 13.6, 3.2 Hz, 1H), 1.36 (t, J = 4.1 Hz, 1H), 1.33−1.23 (m, 1H), 0.90 (s, 3H), 0.77 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 89.5, 84.5, 79.9, 79.1, 68.5, 61.5, 60.2, 57.7, 52.6, 49.0, 39.3, 34.0, 32.5, 27.5, 26.8, 22.2, 21.3; IR (neat, cm^{-1}) 3306, 2936, 2872, 1454, 1368, 1188, 1093, 1051, 1010, 900, 750, 632; HRMS-ESI-TOF calcd for $C_{17}H_{26}NaO_3$ [M + Na$^+$] 301.1774, found 301.1775.

Synthesis of Methyl 3-((1*S*,2*S*,6*R*)-2-(But-3-yn-1-yl)-6-hydroxy-1-(hydroxymethyl)-3,3- dimethylcyclohexyl)propiolate (17e). To a solution of compound **S5** (0.296 g, 0.5 mmol) in MeOH (10 mL) was added K_2CO_3 (0.345 g, 2.5 mmol) at room temperature. The mixture was stirred for 0.5 h at 40 °C and quenched with the saturated NH_4Cl solution (10 mL). The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated under vacuum to provide the crude product.

To the solution of the crude product in THF (10 mL) was added 2 M HCl solution (2 M in H_2O, 1 mL) at room temperature. The mixture was stirred for 1 h and quenched with the saturated $NaHCO_3$ solution (10 mL). The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The organic layer was washed with brine (5 mL), dried over Na_2SO_4, filtered, and evaporated under vacuum. The residue was purified by flash chromatography on silica gel (EtOAc/hexane = 1/4) to provide **17e** (0.13 g) as a white solid in 90% overall yield in two steps: R_f = 0.42 (silica gel, EtOAc/hexane = 1/2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.17 (d, J = 11.2 Hz, 1H), 3.98 (br s, J = 10.2 Hz, 1H), 3.87 (dd, J = 11.6, 4.3 Hz, 1H), 3.75 (s, 3H), 3.58 (d, J = 11.4 Hz, 1H), 3.50 (br s, J = 16.4, 9.1 Hz, 1H), 2.53−2.42 (m, 1H), 2.39−2.28 (m, 1H), 1.97 (t, J = 2.5 Hz, 1H), 1.87−1.76 (m, 2H), 1.76−1.67 (m, 1H), 1.67−1.58 (m, 1H), 1.51−1.40 (m, 2H), 1.30 (td, J = 13.8, 3.9 Hz, 1H), 0.91 (s, 3H), 0.77 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.3, 92.6, 84.1, 78.3, 75.5, 68.8, 61.2, 52.8, 51.8, 49.3, 39.1, 34.0, 32.3, 27.4, 26.8, 22.1, 21.0; IR (neat, cm^{-1}) 3412, 3296, 2955, 2230, 1435, 1258, 1128, 1078, 1055, 752, 635; HRMS-ESI-TOF calcd for $C_{17}H_{24}NaO_4$ [M + Na$^+$]: 315.1567, found 315.1568.

General Procedure for the Gold-Catalyzed Cascade Cyclization of Diynes. The diyne was dissolved in dry DCM (0.05 M), after which additive (50 wt %), *p*-NO_2BnOH (3.0 equiv), (IPr)AuCl (5 mol %), and $AgSbF_6$ (5 mol %) were added to the solution at room temperature sequentially. The reaction mixture was stirred for 10−60 min and subsequently purified by flash chromatography on silica gel.

Synthesis of (3*S*,3a*S*,6a*S*,10*R*,10a*S*)-7,7-Dimethyl-4-methylene-3-((4-nitrobenzyl)oxy)decahydro-*1H*-naphtho[1,8*a*−*c*]-furan-10-ol ((±)-18a). Diyne (±)-**17a**: 23.4 mg, 0.1 mmol; reaction time 30 min; flash chromatography on silica gel: EtOAc/hexane = 1/6; product mass: 35 mg; yield: 90%; R_f = 0.80 (silica gel, EtOAc/hexanes = 1/2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (d, J = 8.7 Hz, 2H), 7.50 (d, J = 8.6 Hz, 2H), 4.86 (s, 1H), 4.86−4.80 (m, 3H), 4.59 (d, J = 12.8 Hz, 1H), 4.20 (s, 1H), 4.14 (d, J = 9.1 Hz, 1H), 4.07 (d, J = 9.1 Hz, 1H), 3.52 (dd, J = 10.8, 4.2 Hz, 1H), 2.86 (s, 1H), 2.30−2.18 (m, 2H), 1.81−1.71 (m, 2H), 1.70−1.62 (m, 1H), 1.41−1.27 (m, 4H), 0.86 (s, 3H), 0.74 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.8, 145.4, 144.6, 128.4, 123.9, 112.5, 107.9, 77.2, 67.8, 67.6, 63.7, 52.3, 44.2, 39.3, 33.3, 31.0, 27.8, 27.3, 20.6, 20.2; IR (neat, cm^{-1}) 3075, 2930, 2853, 1607, 1521, 1456, 1345, 1094, 1046, 976, 849, 738; HRMS-ESI calcd for $C_{22}H_{29}NO_5Na$ [M + Na$^+$] 410.1938, found 410.1947.

Synthesis of (3*S*,3a*S*,6a*S*,10*R*,10a*S*)-3,7,7-Trimethyl-4-methylene-3-((4-nitrobenzyl)oxy)decahydro-1*H*-naphtho[1,8*a*−*c*]-furan-10-ol ((±)-18b). Diyne (±)-**17b**: 37 mg, 0.15 mmol; (**A**) additive: 4 Å M.S. (18.5 mg); reaction time 10 min; flash chromatography on silica gel: EtOAc/hexane = 1/6; product mass 36 mg; yield 60%; R_f = 0.80 (silica gel, EtOAc/hexanes = 1/2); (**B**) additive: $MgSO_4$ (18.5 mg); reaction time 10 min; product mass 28 mg; yield: 46%; ^{1}H NMR (500 MHz, C_6D_6) δ 7.83 (d, J = 8.7 Hz, 2H), 6.96 (d, J = 8.7 Hz, 2H), 4.80 (s, 2H), 4.71 (s, 1H), 4.34 (d, J = 12.5 Hz, 1H), 4.22 (d, J = 12.5 Hz, 1H), 4.07 (q, J = 9.2 Hz, 2H), 3.51 (dd, J = 11.6, 4.2 Hz, 1H), 2.83 (s, 1H), 2.28−2.17 (m, 1H), 2.06−1.98 (m, 1H), 1.91−1.77 (m, 1H), 1.57−1.49 (m, 1H), 1.43 (dd, J = 11.4, 4.0 Hz, 1H), 1.37−1.32 (m, 1H), 1.24 (s, 3H), 1.17 (dd, J = 12.8, 5.4 Hz, 1H), 1.12 (t, J = 3.5 Hz, 1H), 1.08 (dd, J = 13.6, 3.4 Hz, 1H), 0.67 (s, 3H), 0.56 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 147.8, 145.1, 144.7, 128.4, 123.6, 114.8, 109.0, 76.6, 66.9, 66.7, 62.0, 53.8, 44.9, 39.3, 33.2, 31.3, 28.4, 28.0, 20.7, 19.8, 19.5; IR (neat, cm^{-1}) 3418, 2961, 2916, 2849, 1755, 1524, 1348, 1261, 1101, 1016, 800, 750; HRMS-ESI-TOF calcd for $C_{23}H_{31}NNaO_5$ [M + Na$^+$] 424.2094, found 424.2094.

Synthesis of (3*R*,3a*S*,6a*S*,10*R*,10a*S*)-3-(Methoxymethyl)-7,7-dimethyl-4-methylene-3-((4-nitrobenzyl)oxy)decahydro-1*H*-naphtho[1,8*a*−*c*]furan-10-ol ((±)-18c). Diyne (±)-**17c**: 37 mg, 0.15 mmol; (**A**) additive: 4 Å M.S. (18.5 mg); reaction time 10 min; flash chromatography on silica gel: EtOAc/hexane = 1/6; product mass 40 mg; yield: 62%; R_f = 0.80 (silica gel, EtOAc/hexanes = 1/2); (**B**) additive: $MgSO_4$ (18.5 mg); reaction time 10 min; product mass 21 mg; yield 32%; ^{1}H NMR (500 MHz, C_6D_6) δ 7.84 (d, J = 8.5 Hz, 2H), 7.13 (d, J = 8.4 Hz, 2H), 4.96 (s, 1H), 4.85 (d, J = 10.1 Hz, 2H), 4.55 (d, J = 12.1 Hz, 1H), 4.46 (d, J = 12.1 Hz, 1H), 4.16 (d, J = 9.1 Hz, 1H), 4.05 (d, J = 9.1 Hz, 1H), 3.50 (d, J = 10.9 Hz, 1H), 3.48−3.43 (m, 1H), 3.18 (d, J = 10.7 Hz, 1H), 3.01 (s, 1H), 2.98 (s, 3H), 2.25 (td, J = 13.2, 6.2 Hz, 1H), 2.04 (t, J = 11.2 Hz, 1H), 1.86−1.78 (m, 1H), 1.53 (tt, J = 11.6, 5.9 Hz, 1H), 1.45−1.38 (m, 1H), 1.39−1.29 (m, 1H), 1.16 (dd, J = 12.6, 5.6 Hz, 1H), 1.13−1.07 (m, 1H), 1.04 (dt, J = 11.4, 5.6 Hz, 1H), 0.66 (s, 3H), 0.54 (s, 3H); ^{13}C NMR

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J. Org. Chem. 2016, 81, 751−771

(125 MHz, C_6D_6) δ 148.0, 144.7, 143.7, 128.9, 123.6, 115.5, 108.2, 76.9, 71.4, 67.5, 65.5, 63.1, 58.8, 53.8, 44.6, 39.4, 33.4, 31.2, 28.5, 28.3, 20.7, 20.0; IR (neat, cm^{-1}) 3422, 2926, 2853, 1522, 1346, 1275, 1261, 1065, 750; HRMS-ESI-TOF calcd for $C_{24}H_{33}NNaO_6$ [M + Na^+] 454.2200, found 454.2198.

Synthesis of (3*R*,3a*S*,6a*S*,10*R*,10a*S*)-7,7-Dimethyl-4-methylene-3-((4-nitrobenzyl)oxy)-3-phenyldecahydro-1*H*-naphtho[1,8*a*−*c*]furan-10-ol ((±)-18d). Diyne (±)-**17d**: 47 mg, 0.15 mmol; (**A**) additive: 4 Å M.S. (23.5 mg); reaction time 25 min; flash chromatography on silica gel: EtOAc/hexane = 1/6; product mass 34.7 mg; yield 50%; R_f = 0.90 (silica gel, EtOAc/hexanes = 1/2); (**B**) additive: $MgSO_4$ (23.5 mg); reaction time 25 min; product mass 25.5 mg; yield 37%; ^{1}H NMR (500 MHz, C_6D_6) δ 7.77 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 11.3 Hz, 4H), 7.08 (t, J = 7.3 Hz, 1H), 6.88 (d, J = 8.4 Hz, 2H), 4.80 (s, 1H), 4.57 (s, 1H), 4.49 (s, 1H), 4.32−4.27 (m, 3H), 3.84 (d, J = 12.0 Hz, 1H), 3.60 (dd, J = 11.5, 4.2 Hz, 1H), 3.20 (s, 1H), 2.04−1.95 (m, 1H), 1.92−1.85 (m, 1H), 1.70−1.63 (m, 1H), 1.51−1.34 (m, 4H), 1.23−1.10 (m, 3H), 0.68 (s, 3H), 0.63 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 147.9, 144.6, 144.2, 138.4, 128.8, 128.6, 123.6, 115.9, 111.1, 76.7, 67.7, 67.1, 63.4, 54.4, 45.4, 39.4, 33.4, 31.5, 28.6, 27.9, 20.9, 19.5; IR (neat, cm^{-1}) 3431, 2928, 1522, 1346, 1261, 1109, 1036, 750; HRMS-ESI-TOF calcd for $C_{28}H_{33}NNaO_5$ [M + Na^+] 486.2251, found 486.2250.

Synthesis of Methyl (3*R*,3a*S*,6a*S*,10*R*,10a*S*)-10-Hydroxy-7,7-dimethyl-4-methylene-3- ((4-nitrobenzyl)oxy)decahydro-1*H*-naphtho[1,8*a*−*c*]furan-3-carboxylate ((±)-18e). Diyne (±)-**17e**: 44 mg, 0.15 mmol; (**A**) additive: 4 Å M. S. (22 mg); reaction time 60 min; flash chromatography on silica gel: EtOAc/hexane = 1/6; product mass 20 mg; yield 30%; R_f = 0.61 (silica gel, EtOAc/hexanes = 1/2); (**B**) additive $MgSO_4$ (22 mg); reaction time 30 min; product mass 16.5 mg; yield: 25%; ^{1}H NMR (500 MHz, C_6D_6) δ 7.79 (d, J = 8.6 Hz, 2H), 7.04 (d, J = 8.6 Hz, 2H), 4.80 (s, 1H), 4.75 (s, 1H), 4.50 (d, J = 11.8 Hz, 1H), 4.24 (q, J = 9.1 Hz, 2H), 4.12 (d, J = 11.8 Hz, 1H), 3.39 (dd, J = 11.6, 4.2 Hz, 1H), 3.33 (s, 3H), 3.06 (s, 1H), 2.73−2.62 (m, 1H), 2.03−1.94 (m, 1H), 1.81−1.73 (m, 1H), 1.48−1.41 (m, 2H), 1.37−1.30 (m, 2H), 1.13−1.06 (m, 2H), 1.00 (dd, J = 13.8, 3.1 Hz, 1H), 0.61 (s, 3H), 0.49 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 167.8, 148.2, 143.9, 143.1, 129.1, 123.7, 115.6, 109.8, 76.8, 68.8, 66.9, 65.5, 53.4, 51.8, 44.6, 39.3, 33.4, 31.0, 28.2, 27.4, 20.5, 19.9; IR (neat, cm^{-1}) 3420, 2930, 2864, 1524, 1346, 1059, 970; HRMS-ESI-TOF calcd for $C_{24}H_{31}NNaO_7$ [M + Na^+] 468.1993, found 468.1996.

Synthesis of (3*S*,3a*S*,6a*S*,10*R*,10a*S*)-2′,2′-Dimethyl-4-methylene-3-((4-nitrobenzyl)oxy)octahydro-1*H*,8*H*-spiro[naphtho[1,8*a*−*c*]furan-7,5′-[1,3]dioxan]-10-ol ((±)-20b). To a solution of (±)-**19a** (62 mg, 0.2 mmol) in DCM (4 mL) were added (IPr)AuCl (6.2 mg, 0.01 mmol), 4-nitrobenzyl alcohol (92 mg, 0.6 mmol), and $AgSbF_6$ (3.4 mg, 0.01 mmol) ambient temperature sequentially. After 0.5 h of stirring, MnO_2 (0.52 g, 6 mmol) was added, and the reacting mixture was stirred overnight. The reaction system was purified by flash chromatography on silica gel (EtOAc/hexanes = 1/6) to provide (±)-**20b** (41 mg) as a colorless oil in 45% yield (R_f = 0.45, EtOAc/hexanes = 1/2): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (d, J = 8.7 Hz, 2H), 7.49 (d, J = 8.7 Hz, 2H), 4.88 (s, 2H), 4.86−4.79 (m, 2H), 4.58 (d, J = 12.8 Hz, 1H), 4.12 (d, J = 9.2 Hz, 1H), 3.94 (s, 1H), 3.89 (d, J = 11.5 Hz, 1H), 3.82 (dd, J = 19.3, 10.4 Hz, 2H), 3.53 (dd, J = 11.7, 4.2 Hz, 1H), 3.44 (d, J = 11.5 Hz, 1H), 3.19 (d, J = 11.6 Hz, 1H), 2.88 (s, 1H), 2.33 (m, 2H), 2.28−2.20 (m, 1H), 1.94 (m, 2H), 1.82 (dd, J = 13.9, 3.9 Hz, 1H), 1.38 (s, 3H), 1.35 (s, 3H), 1.34−1.30 (m, 2H), 1.04−0.96 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.8, 144.5, 144.2, 128.4, 123.9, 113.6, 107.7, 98.6, 76.3, 69.6, 67.8, 67.5, 62.8, 61.4, 52.3, 42.4, 37.0, 30.6, 27.3, 27.0, 26.6, 21.0, 19.6; HRMS-ESI-TOF calcd for $C_{25}H_{33}NNaO_7$ [M + Na^+] 482.2149, found 482.2165; IR (neat, cm^{-1}) 2940, 2367, 1522, 1261, 1098, 750.

Synthesis of (3*S*,3a*S*,6a*S*,10*R*,10a*S*)-3-(Benzyloxy)-2′,2′-dimethyl-4-methyleneoctahydro-1*H*,8*H*-spiro[naphtho[1,8*a*−*c*]-furan-7,5′-[1,3]dioxan]-10-ol ((±)-20a). To a solution of (±)-**19a** (31 mg, 0.1 mmol) in DCM (2 mL), (IPr)AuCl (3.1 mg, 0.005 mmol), benzylic alcohol (31 μL, 0.3 mmol), $AgSbF_6$ (1.7 mg, 0.005 mmol) was added at ambient temperature sequentially. After 0.5 h stirring, MnO_2 (0.26 g, 3 mmol) was added and the reacting mixture was stirred for overnight. The reaction system was purified by flash chromatography on silica gel (EtOAc/hexanes =1/6) to provide (±)-**20a** (19 mg) as a white solid in 46% yield (R_f = 0.7, EtOAc/hexanes = 1/2): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.27 (m, 5H), 4.88 (s, 1H), 4.85−4.83 (m, 1H), 4.83−4.81 (m, 1H), 4.74 (d, J = 11.6 Hz, 1H), 4.46 (d, J = 11.6 Hz, 1H), 4.14 (d, J = 9.1 Hz, 1H), 3.90 (d, J = 11.5 Hz, 1H), 3.84 (d, J = 11.5 Hz, 1H), 3.78 (d, J = 9.1 Hz, 1H), 3.52 (dd, J = 11.6, 4.3 Hz, 1H), 3.45 (d, J = 11.5 Hz, 1H), 3.20−3.16 (m, 1H), 2.84 (s, 1H), 2.39−2.29 (m, 2H), 2.26−2.18 (m, 1H), 1.97−1.89 (m, 2H), 1.86−1.79 (m, 1H), 1.38 (s, 3H), 1.37−1.22 (m, 5H), 1.04−0.95 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.6, 137.0, 128.7, 128.1, 128.0, 113.2, 107.1, 98.6, 76.3, 69.6, 68.7, 67.5, 63.0, 61.4, 52.3, 42.3, 37.0, 30.6, 27.4, 27.0, 26.7, 21.0, 19.7; HRMS-ESI-TOF calcd for $C_{25}H_{35}O_5$ [M + H^+] 415.2479, found 415.2482; IR (neat, cm^{-1}) 2926, 2855, 1728, 1275, 1072, 1024, 750. Melting range of crystal: 99.6 to 101.3 °C.

Synthesis of Methyl 3-(2,2,3′-Trimethylhexahydro-1′*H*-spiro[[1,3]dioxane-5,6′-[3,9]epoxybenzo[*c*]oxepin]-9a′(7′*H*)-yl)propiolate ((±)-22). To a solution of (±)-**19b** (36 mg, 0.1 mmol) in DCM (2 mL), 4 Å molecular sieves (18 mg), (IPr)AuCl (3.1 mg, 0.005 mmol), 4-nitrobenzyl alcohol (46 mg, 0.3 mmol), and $AgSbF_6$ (1.7 mg, 0.005 mmol) was added at ambient temperature sequentially. After 0.5 h of stirring, the reacting system was purified by flash chromatography on silica gel (EtOAc/hexanes = 1/6) to provide product (±)-**22** (19 mg) as a colorless oil in 53% yield (R_f = 0.81, EtOAc/hexanes = 1/2): ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.30 (d, J = 10.1 Hz, 1H), 4.10 (s, 1H), 4.07−3.98 (m, 2H), 3.91 (d, J = 10.1 Hz, 1H), 3.77−3.69 (m, 4H), 3.48 (d, J = 11.6 Hz, 1H), 2.46−2.41 (m, 1H), 2.04−1.99 (m, 1H), 1.98−1.81 (m, 4H), 1.76−1.66 (m, 2H), 1.55−1.47 (m, 1H), 1.42 (s, 6H), 1.36 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.6, 98.9, 98.1, 89.6, 76.1, 71.6, 70.5, 68.9, 68.4, 52.8, 42.4, 40.7, 35.5, 34.6, 30.2, 24.7, 24.6, 23.2, 23.1, 20.3; HRMS-ESI-TOF calcd for $C_{20}H_{29}O_6$ [M + H^+] 365.1959, found 365.1964; IR (neat, cm^{-1}) 2990, 2926, 2857, 2232, 1717, 1261, 1194, 1094, 750.

Synthesis of Methyl (7*S*,8*R*)-8-Ethynyl-3,3-dimethyl-9-oxo-7-vinyl-2,4-dioxaspiro[5.5]undecane-8-carboxylate ((±)-29). To a suspension of compound CuBr·Me_2S (0.17 g, 0.825 mmol) in dry THF (25 mL), vinyl grignard reagent (0.7 M in THF, 7.9 mL, 5.5 mmol) was added slowly at −78 °C. After the mixture was stirred at the same temperature for 20 min, the solution of enone (±)-**31** (0.7 g, 2.75 mmol) in THF (10 mL) was introduced into the reaction mixture dropwise. After completion of the addition, the mixture was stirred at −78 °C and quenched by saturated NH_4Cl solution (20 mL). The aqueous layer was extracted with ethyl acetate (2 × 15 mL). The organic layer was combined and dried over Na_2SO_4 and evaporated under vacuum, and the residue was purified by flash chromatography on silica gel (EtOAc/hexanes = 1/10) to provide crude product (R_f = 0.81, EtOAc/hexanes = 1/2).

To a solution of crude product in THF (25 mL) were added iodonium X (1.23 g, 3.58 mmol) and TBAF solution (1.0 M, 3.6 mL, 3.6 mmol) at −78 °C. The mixture was stirred at −78 °C for 5 h and quenched with saturated NH_4Cl solution (15 mL). The aqueous layer was extracted with ethyl acetate (2 × 15 mL). The organic layer was combined and dried over Na_2SO_4 and evaporated under vacuum, and the residue was purified by flash chromatography on silica gel (EtOAc/hexanes = 1/4) to provide (±)-**29** (0.69 g) as a pale yellow oil in 82% yield in two steps (R_f = 0.19, EtOAc/hexanes = 1/6): ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.22−6.13 (m, 1H), 5.34 (dd, J = 10.0, 1.4 Hz, 1H), 5.19 (dd, J = 16.8, 1.0 Hz, 1H), 4.04 (d, J = 12.1 Hz, 1H), 3.99 (d, J = 11.8 Hz, 1H), 3.78−3.73 (m, 4H), 3.36 (dd, J = 11.8, 2.4 Hz, 1H), 2.80−2.71 (m, 1H), 2.64−2.57 (m, 1H), 2.55 (s, 1H), 2.50−2.43 (m, 1H), 2.37 (d, J = 10.4 Hz, 1H), 1.92−1.85 (m, 1H), 1.42 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.5, 167.7, 132.0, 121.3, 98.4, 79.2, 76.4, 67.7, 64.0, 59.9, 56.6, 53.5, 35.5, 35.0, 29.3, 28.3, 19.4; HRMS-ESI-TOF calcd for $C_{17}H_{22}O_5Na$ [M + Na^+] 329.1359, found 329.1362; IR (neat, cm^{-1}) 3283, 2992, 2955, 2886, 1732, 1456, 1437, 1373, 1250, 1225, 1200, 1113, 1072, 1034, 930, 837.

Synthesis of Methyl (7*S*,8*R*,9*R*)-8-Ethynyl-9-hydroxy-3,3-dimethyl-7-vinyl-2,4-dioxaspiro[5.5]undecane-8-carboxylate ((±)-33). To a solution of (±)-**29** (1.52 g, 5 mmol) in MeOH (40 mL) was added $NaBH_4$ (76 mg, 2 mmol) at −50 °C. The mixture was

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J. Org. Chem. 2016, 81, 751−771

stirred at −50 °C for 0.5 h and quenched with saturated NH_4Cl solution (25 mL). The aqueous layer was extracted with DCM (2 × 20 mL), and the organic layer was combined and evaporated under vacuum. The residue was purified by flash chromatography on silica gel (EtOAc/hexanes = 1/6) to provide (±)-**33** (1.25 g) as colorless oil in 82% yield (R_f = 0.43, EtOAc/hexanes = 1/4): ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.15−6.06 (m, 1H), 5.06 (s, 1H), 5.03 (dd, J = 5.8, 2.1 Hz, 1H), 4.31−4.25 (m, 2H), 4.18 (s, 1H), 4.12 (d, J = 12.1 Hz, 1H), 3.72 (s, 3H), 3.55 (d, J = 11.9 Hz, 1H), 3.29 (dd, J = 11.9, 1.6 Hz, 1H), 2.81 (d, J = 10.9 Hz, 1H), 2.37 (s, 1H), 2.15−2.06 (m, 1H), 1.88−1.82 (m, 2H), 1.79−1.71 (m, 1H), 1.42 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7, 135.3, 118.8, 97.8, 83.4, 73.8, 71.2, 69.3, 67.4, 52.9, 50.9, 49.9, 35.4, 26.2, 24.4, 21.5, 21.1; HRMS-ESI-TOF calcd for $C_{17}H_{24}O_5Na$ [M + Na^+] 331.1516, found 331.1517; IR (neat, cm^{-1}) 3528, 2994, 1773, 1260, 750.

Synthesis of (1*R*,5*S*,8*R*,9*S*)-1-Ethynyl-8-hydroxy-5-(hydroxymethyl)-9-vinyl-3-oxabicyclo[3.3.1]nonan-2-one ((±)-28). To a solution of (±)-**33** (0.28 g, 0.91 mmol) in MeCN (8 mL) was added 40% HF aqueous solution (82 μL, 1.83 mmol). The mixture was stirred at ambient temperature for 0.5 h and quenched with saturated $NaHCO_3$ solution (3 mL). The aqueous layer was extracted with EtOAc (2 × 5 mL), and the organic layer was combined and evaporated under vacuum. The residue was collected and purified with flash chromatography on silica gel (DCM/MeOH = 10/1) to provide (±)-**28** (0.21 g) as white solid in 97% yield (R_f = 0.43, DCM/MeOH = 10/1): ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.66−5.54 (m, 1H), 5.38−5.23 (m, 2H), 4.32 (d, J = 12.1 Hz, 1H), 4.21 (d, J = 12.1 Hz, 1H), 3.90−3.83 (m, 1H), 3.37 (dd, J = 23.8, 10.8 Hz, 2H), 3.04 (br s, 1H), 2.66 (br s, 1 H), 2.51−2.43 (m, 2H), 2.18−2.09 (m, 1H), 1.99−1.91 (m, 1H), 1.72−1.52 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.7, 132.2, 121.6, 81.8, 75.7, 75.4, 75.1, 67.0, 53.0, 50.5, 36.6, 32.2, 27.7; HRMS-ESI-TOF calcd for $C_{13}H_{16}O_4Na$ [M + Na^+] 259.0941, found 259.0941; IR (neat, cm^{-1}) 3399, 2926, 1719, 1256, 1155, 1063, 937, 783

Synthesis of Methyl (7*S*,8*R*,9*R*)-9-((*tert*-Butyldimethylsilyl)-oxy)-8-ethynyl-3,3-dimethyl-7-vinyl-2,4-dioxaspiro[5.5]-undecane-8-carboxylate ((±)-36). To a solution of (±)-**33** (0.805g, 2.6 mmol) in DCM (30 mL) were added Et_3N (1.2 mL, 9.1 mmol) and TBSOTf (1.5 mL, 6.5 mmol) sequentially at −78 °C. The mixture was stirred at −10 °C for 1.2 h and quenched with saturated NH_4Cl solution (25 mL). The aqueous layer was extracted with DCM (2 × 20 mL), and the organic layer was combined and dried over Na_2SO4. The volatiles were evaporated under vacuum, and the residue was collected and purified with flash chromatography on silica gel (EtOAc/hexanes = 1/20) to provide (±)-**36** (1.1 g) as a colorless oil in 99% yield (R_f = 0.55, EtOAc/hexanes = 1/6): ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89 (br s, 1H), 5.23−5.02 (m, 2H), 4.25 (br s, 1H), 3.97 (d, J = 11.5 Hz, 1H), 3.79−3.51 (m, 5H), 2.54 (br s, 1H), 2.30 (s, 1H), 2.18−1.49 (m, 5H), 1.39 (s, 3H), 1.37 (s, 3H), 0.86 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5, 134.6, 119.4, 97.7, 85.6, 74.2, 72. 7, 68.5, 67.3, 52.8, 52.2, 35.4, 27.7, 26.4, 25.9, 24.2, 19.9, 18.1, −4.5, −4.9; HRMS-ESI-TOF calcd for $C_{23}H_{38}NaO_5Si$ [M+Na^+]: 445.2381, found 445.2387; IR (neat, cm^{-1}) 3443, 3308, 2951, 2930, 2857, 1746, 1256, 1234, 1202, 1117, 1099, 1061, 835, 777.

Synthesis of (1*R*,5*S*,8*R*,9*S*)-8-((*tert*-Butyldimethylsilyl)oxy)-1-ethynyl-5-(hydroxylmethyl)-9-vinyl-3-oxabicyclo[3.3.1]nonan-2-one ((±)-37). To a solution of (±)-**36** (42 mg, 0.1 mmol) in MeCN (2 mL) was added TsOH·H_2O (cat.) at ambient temperature. The mixture was stirred for 2.5 h, and the reacting mixture was purified by flash chromatography on silica gel (EtOAc/hexanes = 1/2) to provide (±)-**37** (22 mg) in 63% yield (R_f = 0.52, EtOAc/hexanes = 1/1): ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.72−5.62 (m, 1H), 5.36 (dd, J = 10.2, 1.2 Hz, 1H), 5.31 (d, J = 16.8 Hz, 1H), 4.32 (dd, J = 12.1, 2.2 Hz, 1H), 4.25−4.19 (m, 1H), 3.93 (dd, J = 11.0, 5.1 Hz, 1H), 3.42 (dd, J = 5.0, 3.7 Hz, 2H), 2.49 (d, J = 10.1 Hz, 1H), 2.31 (s, 1H), 2.06−2.00 (m, 1H), 1.93−1.86 (m, 1H), 1.84−1.74 (m, 1H), 1.73−1.68 (m, 1H), 1.66 (d, J = 5.4 Hz, 1H), 0.90 (s, 9H), 0.16 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4, 133.1, 121.2, 83.1, 76.4, 74.8, 73.9, 67.5, 53.0, 51.8, 36.7, 32.8, 30.2, 25.9, 18.2, −4.2, −4.5; HRMS-ESI-TOF calcd for $C_{19}H_{30}O_4NaSi$ [M + Na^+] 373.1806, found 373.1806; IR (neat, cm^{-1}) 3497, 2926, 2855, 1719, 1638, 1256, 1150, 1115, 837, 775.

Synthesis of (1*R*,5*S*,8*R*,9*S*)-1-((*tert*-Butyldimethylsilyl)-ethynyl)-8-((*tert*-butyldimethylsilyl)oxy)-5-(hydroxymethyl)-9-vinyl-3-oxabicyclo[3.3.1]nonan-2-one ((±)-38). To a solution of (±)-**36** (0.645 g, 1.53 mmol) in dry THF (20 mL) was added TBSCl (0.7 g, 4.59 mmol) at −78 °C followed by the addition of LDA (2.0 M, 1.5 mL, 3 mmol) dropwise. The reacting mixture was stirred at ambient temperature for 3.5 h and quenched with saturated NH_4Cl solution (15 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL). The organic layer was combined, dried over Na_2SO_4, and evaporated under vacuum. The residue was purified with flash chromatography on silica gel to give product (±)-**S9** (0.7 g) in 85% yield (R_f = 0.79, EtOAc/hexanes = 1/10).

To a solution of (±)-**S9** (0.26 g, 0.48 mmol) in MeCN (5 mL) was added TsOH·H_2O (0.14 g, 0.73 mmol) at −10 °C. The reacting mixture was stirred at the same temperature for 1.5 h and quenched with saturated $NaHCO_3$ solution (5 mL). The aqueous layer was extracted with EtOAc (2 × 5 mL). The organic layer was combined and dried over Na_2SO_4. The volatiles were evaporated under vacuum, and the residue was purified with flash chromatography on silica gel (EtOAc/hexanes = 1/3) to give (±)-**38** (0.19 g) as a white solid in 84% yield (EtOAc/hexanes = 1/2): ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.71−5.61 (m, 1H), 5.33−5.23 (m, 2H), 4.29 (dd, J = 12.0, 2.1 Hz, 1H), 4.18 (dd, J = 12.0, 1.0 Hz, 1H), 3.91 (dd, J = 10.9, 5.1 Hz, 1H), 3.47−3.35 (m, 2H), 2.47 (d, J = 10.2 Hz, 1H), 2.05−1.97 (m, 1H), 1.90−1.83 (m, 1H), 1.80−1.63 (m, 3H), 0.90 (s, 18H), 0.17 (s, 3H), 0.07 (d, J = 7.0 Hz, 6H), 0.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.3, 133.6, 120.9, 105.6, 88.1, 76.2, 74.7, 67.6, 53.7, 52.2, 36.7, 32.8, 30.2, 26.2, 25.9, 18.2, 16.7, −4.2, −4.4, −4.6; HRMS-ESI-TOF calcd for $C_{25}H_{44}NaO_4Si_2$ [M + Na^+] 487.2670, found 487.2668; IR (neat, cm^{-1}) 3522, 2951, 2928, 2857, 1722, 1634, 1256, 1150, 1111, 837, 773.

Synthesis of (3a*S*,6*R*,7*R*,7a*S*)-7-((*tert*-Butyldimethylsilyl)-ethynyl)-6-((*tert*-butyldimethylsilyl)oxy)-1-(3-(triisopropylsilyl)prop-2-yn-1-yl)hexahydro-3*H*-3a,7-(methanooxymethano)isobenzofuran-8-one ((±)-39). To a solution of $Pd_2(dba)_3$ (6 mg, 0.0065 mmol), DPE-Phos (7 mg, 0.013 mmol), and Na^{t}Obu (9 mg, 0.091 mmol) in toluene (1 mL) was added a solution of (±)-**38** (30 mg, 0.065 mmol) and bromo reagent (24 mg, 0.091 mmol) in toluene (1 mL) at ambient temperature. The reacting mixture was heated to 65 °C and stirred for 3.5 h. The reaction was quenched with saturated NH_4Cl solution (2 mL). The aqueous layer was extracted by EtOAc (3 × 2 mL). The organic layer was combined and dried over Na_2SO_4. The volatiles were extracted under vacuum, and the residue was purified with flash chromatography on silica gel (EtOAc/hexanes = 1/5) to provide (±)-**39** (24 mg) as a pale yellow solid in 57% yield (R_f = 0.20, EtOAc/hexanes = 1/5): ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.46 (d, J = 11.9 Hz, 1H), 4.29 (d, J = 12.0 Hz, 1H), 4.10 (d, J = 9.8 Hz, 1H), 3.96 (dd, J = 10.3, 5.1 Hz, 1H), 3.58−3.49 (m, 2H), 3.01−2.85 (m, 2H), 2.68 (d, J = 9.9 Hz, 1H), 2.11−2.04 (m, 1H), 1.92−1.79 (m, 2H), 1.59−1.49 (m, 1H), 1.13−1.01 (m, 21H), 0.94 (s, 9H), 0.89 (s, 9H), 0.16 (s, 3H), 0.12 (s, 3H), 0.11 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.0, 104.5, 103.9, 88.2, 83.6, 77.5, 77.1, 75.2, 74.2, 51.9, 49.4, 41.1, 31.2, 30.5, 26.2, 26.1, 25.8, 18.7, 18.1, 16.6, 11.3, −4.4, −4.6, −4.6, −4.7; HRMS-ESI-TOF calcd for $C_{36}H_{64}NaO_4Si_3$ [M + Na^+] 667.4005, found 667.4034; IR (neat, cm^{-1}) 3433, 2943, 2862, 1751, 1250, 1136, 1115, 839, 775, 669.

Synthesis of (3a*S*,6*R*,7*R*,7a*S*)-7-((*tert*-Butyldimethylsilyl)-ethynyl)-6-hydroxy-1-(3 (triisopropylsilyl)prop-2-yn-1-yl)-hexahydro-3*H*-3a,7-(methanooxymethano)isobenzofuran-8-one ((±)-40). To a solution of (±)-**39** (80 mg, 0.124 mmol) in MeCN (2 mL) was added 40% HF aqueous solution (20 L, 0.372 mmol) at ambient temperature. The reacting mixture was warmed to 40 °C, stirred for 2.5 h, and quenched with saturated $NaHCO_3$ solution (2 mL). The aqueous layer was extracted with EtOAc (2 × 2 mL). The organic layer was combined and dried over Na_2SO_4. The volatiles were evaporated under vacuum, and the residue was purified with flash chromatography on silica gel (EtOAc/hexanes = 1/3) to

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give (±)-**40** (45 mg) as a pale yellow solid in 68% yield (R_f = 0.38, EtOAc/hexanes = 1/2): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.54 (dd, J = 12.1, 2.0 Hz, 1H), 4.36 (d, J = 11.5 Hz, 1H), 4.14 (dt, J = 10.0, 3.2 Hz, 1H), 3.95 (dd, J = 11.3, 4.7 Hz, 1H), 3.64−3.56 (m, 2H), 3.01−2.86 (m, 2H), 2.77−2.69 (m, 1H), 2.35−2.20 (m, 1H), 2.01−1.93 (m, 1H), 1.85−1.73 (m, 1H), 1.71−1.58 (m, 1H), 1.15−1.06 (m, 21H), 0.98 (s, 9H), 0.17 (s, 3H), 0.16 (s, 3H; ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 103.9, 101.3, 90.6, 83.8, 77.8, 75.4, 74.3, 51.2, 49.3, 41.3, 31.1, 27.8, 26.2, 25.8, 18.8, 16. 6, 11.34, −4.7; HRMS-ESI-TOF calcd for $C_{30}H_{50}NaO_4Si_2$ [M + Na^+] 553.3140, found 553.3141; IR (neat, cm^{-1}) 3478, 2930, 2864, 2172, 1258, 1080, 1022, 810, 777.

Synthesis of (3a*S*,6*R*,7*R*,7a*S*,8*S*)-7-((*tert*-Butyldimethylsilyl)-ethynyl)-6-((*tert*-butyldimethylsilyl)oxy)-1-(3-(triisopropylsilyl)prop-2-yn-1-yl)hexahydro-3*H*-3a,7-(methanooxymethano)isobenzofuran-8-ol ((±)-41). To a solution of (±)-**39** (17 mg, 0.026 mmol) in dry THF (1 mL) was added a solution of $LiBH_4$ (2.0 M in THF, 26 μL, 0.372 mmol) at ambient temperature. The reacting mixture was stirred at the same temperature for 2 h and quenched with saturated NH_4Cl solution (1 mL). The aqueous layer was extracted with EtOAc (2 × 2 mL). The organic layer was combined and dried over Na_2SO_4. The volatiles were evaporated under vacuum, and the residue was purified with flash chromatography on silica gel (EtOAc/hexanes = 1/8) to provide (±)-**41** (12 mg) as a colorless oil in 70% yield (R_f = 0.51, EtOAc/hexanes = 1/4): ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.21 (d, J = 10.6 Hz, 1H), 5.03 (d, J = 10.5 Hz, 1H), 4.31−4.26 (m, 1H), 4.11−4.06 (m, 1H), 3.91 (dd, J = 12.1, 2.4 Hz, 1H), 3.84 (d, J = 13.1 Hz, 1H), 3.47 (d, J = 8.4 Hz, 1H), 3.42 (d, J = 8.4 Hz, 1H), 2.94−2.86 (m, 2H), 2.75−2.65 (m, 1H), 2.39 (d, J = 9.6 Hz, 1H), 2.04−1.96 (m, 1H), 1.91 (dd, J = 13.1, 6.1 Hz, 1H), 1.54−1.45 (m, 1H), 1.09 (dd, J = 12.5, 5.1 Hz, 21H), 0.94 (d, J = 4.0 Hz, 18H), 0.20 (s, 3H), 0.14 (s, 3H), 0.12 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 106.8, 105.1, 98.3, 87.4, 83.5, 80.8, 74.9, 74.0, 70.3, 52.5, 40.7, 40.7, 32.0, 31.9, 26.7, 26.3, 26.0, 18.9, 18.9, 18.1, 16.6, 11.5, −4.3, −4.4, −4.5, −4.8; HRMS-ESI-TOF calcd for $C_{36}H_{66}O_4NaSi_3$ [M + Na^+] 669.4161, found 669.4164; IR (neat, cm^{-1}) 2929, 2862, 2171, 1464, 1251, 1122, 1085, 838, 775, 674.

Synthesis of (7*S*,8*S*,9*R*)-8-((*tert*-Butyldimethylsilyl)ethynyl)-8-(hydroxymethyl)-3,3-dimethyl-7-vinyl-2,4-dioxaspiro[5.5]-undecan-9-ol ((±)-43). To a solution of (±)-**S9** (0.54 g, 1 mmol) in dry THF (12 mL) was added $LiAlH_4$ (76 mg, 2 mmol) was added at ambient temperature. The reacting mixture was stirred for 2 h, quenched with saturated potassium sodium tartrate solution (10 mL), and stirred for another 3 h. The aqueous layer was extracted with EtOAc (2 × 10 mL). The organic layer was combined and dried over Na_2SO_4. The volatiles were evaporated under vacuum, and the residue was purified with flash chromatography on silica gel (EtOAc/hexanes = 1/2) to provide (±)-**43** (0.31 g) as a white solid in 79% yield (R_f = 0.43, EtOAc/hexanes = 1/2): ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.06−5.95 (m, 1H), 5.06 (d, J = 3.3 Hz, 1H), 5.03 (s, 1H), 4.36 (d, J = 12.1 Hz, 1H), 4.11 (s, 1H), 3.92 (d, J = 12.1 Hz, 1H), 3.73 (t, J = 10.2 Hz, 1H), 3.56 (d, J = 11.9 Hz, 1H), 3.42 (dd, J = 11.0, 4.2 Hz, 1H), 3.26 (d, J = 11.8 Hz, 1H), 2.34−2.26 (m, 2H), 2.17−2.09 (m, 1H), 2.07−2.02 (m, 1H), 2.01−1.95 (m, 1H), 1.80−1.67 (m, 2H), 1.40 (s, 3H), 1.38 (s, 3H), 0.94 (s, 9H), 0.11 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.4, 117.9, 110.6, 97.7, 88.5, 70.5, 69.6, 67.6, 67.0, 51.3, 44.8, 35.1, 27.4, 26.2, 26.2, 21.6, 20.3, 16.6, −4.5, −4.6; HRMS-ESI-TOF calcd for $C_{22}H_{38}O_4NaSi$ [M + Na^+] 417.2432, found 417.2430; IR (neat, cm^{-1}) 3445, 2951, 2930, 2857, 1452, 1371, 1258, 1200, 1061, 837, 764, 750.

Synthesis of (4a*S*,5*S*)-4a-((*tert*-Butyldimethylsilyl)ethynyl)-2′,2′-dimethyl-5-vinyltetrahydro-4*H*,5*H*-spiro[benzo[*d*][1,3]-dioxine-6,5′-[1,3]dioxan]-2-one ((±)-44). To a solution of (±)-**43** (0.1 g, 0.253 mmol) in dry DCM (12 mL) were added pyridine (61 μL, 0.76 mmol) and BTC (0.15 g, 0.507 mmol) at −10 °C. The reacting mixture was stirred for 35 min and quenched with saturated $NaHCO_3$ solution (10 mL). The aqueous layer was extracted with DCM (2 × 8 mL). The organic layer was combined and dried over Na_2SO_4. The volatiles were evaporated under vacuum, and the residue was purified with flash chromatography on silica gel (EtOAc/hexanes = 1/4) to provide (±)-**44** (0.1 g) as a white solid in 94% yield (R_f = 0.54, EtOAc/hexanes = 1/2): ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.72−5.61 (m, 1H), 5.31−5.20 (m, 2H), 4.60 (s, 1H), 4.34 (dd, J = 11.4 Hz, 2H), 4.28−4.23 (m, 1H), 3.93 (d, J = 12.2 Hz, 1H), 3.54 (d, J = 11.9 Hz, 1H), 3.27 (dd, J = 11.9, 1.6 Hz, 1H), 2.42 (d, J = 11.1 Hz, 1H), 2.20−2.11 (m, 1H), 2.05−1.95 (m, 2H), 1.67 (m, 1H), 1.37 (s, 3H), 1.36 (s, 3H), 0.90 (s, 9H), 0.11−0.06 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.2, 132.3, 121.3, 104.9, 97.8, 90.5, 78.7, 74.5, 68.8, 67.0, 51.9, 34.8, 34.7, 26.9, 26.0, 23.3, 20.5, 20.4, 16.5, −4.9; HRMS-ESI-TOF Calcd for $C_{23}H_{36}O_5NaSi$ [M + Na^+] 443.2224, found 443.2223; IR (neat, cm^{-1}) 3443, 2930, 2857, 1769, 1260, 1204, 1115, 839, 750.

Synthesis of (4a*S*,5*S*)-4a-((*tert*-Butyldimethylsilyl)ethynyl)-6,6-bis(hydroxymethyl)-5-vinylhexahydro-4*H*-benzo[*d*][1,3]-dioxin-2-one ((±)-45). To a solution of (±)-**44** (96 mg, 0.23 mmol) in MeCN (2 mL) was added TsOH (59 mg, 0.34 mmol) at −10 °C. The reacting mixture was heated to ambient temperature, stirred for 2 h, and quenched with saturated $NaHCO_3$ solution (2 mL). The aqueous layer was extracted with EtOAc (2 × 2 mL). The organic layer was combined and dried over Na_2SO_4. The volatiles were evaporated, and the residue was purified by flash chromatography on silica gel (EtOAc/hexanes = 1/1) to provide (±)-**45** (50 mg) as a white solid in 58% yield (R_f = 0.40, EtOAc/hexanes = 1/1): ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.88−5.78 (m, 1H), 5.36 (d, J = 16.6 Hz, 1H), 5.31−5.26 (m, 1H), 4.62 (s, 1H), 4.45−4.36 (m, 2H), 4.21 (d, J = 11.5 Hz, 1H), 3.95 (d, J = 11.6 Hz, 1H), 3.49 (dd, J = 26.5, 11.4 Hz, 2H), 2.80 (d, J = 11.2 Hz, 1H), 2.36 (s, 2H), 2.16−2.09 (m, 1H), 2.02−1.95 (m, 1H), 1.61 (td, J = 13.8, 3.9 Hz, 1H), 1.40−1.34 (m, 1H), 0.92 (s, 9H), 0.15−0.10 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.4, 133.8, 120.8, 105.2, 89.9, 78.8, 74.6, 69.7, 66.5, 48.5, 41.1, 34.8, 26.1, 23.5, 19.9, 16.5, −4.8, −4.8; HRMS-ESI Calcd for $C_{20}H_{32}O_5NaSi$ [M + Na^+] 403.1911, found 403.1913; IR (neat, cm^{-1}) 3431, 2953, 2857, 1734, 1250, 1202, 1126, 1061.

Synthesis of (3*S*,5*R*)-2-Methyl-5-(prop-1-en-2-yl)-3-vinylcyclohexanone (S8). To a solution of CuBr·Me_2S (5.5 g, 27 mmol) in dry THF (200 mL) was added a solution of vinyl Grignard reagent (1.0 M in THF, 135 mL, 135 mmol) at −78 °C, and the reaction mixture was then stirred at the same temperature for 10 min. To this solution was added a solution of **52**, (−)-carvone (13.5 g, 90 mmol) in dry THF (50 mL) at −78 °C, and the mixture was continuously stirred for an additional 1 h and then quenched with a saturated solution of NH_4Cl (100 mL). The mixture was extracted with ethyl acetate (2 × 100 mL), and the combined organic extracts were dried over Na_2SO_4. The extracts were filtered off and then evaporated under vacuum. The residue was purified by flash chromatography on silica gel (EtOAc/hexanes = 1/40) to give compound **S8** (15.05 g) as a yellow oil in 94% yield: R_f = 0.65 (EtOAc/hexanes) = 1/20; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.60 (dt, J = 16.8, 9.9 Hz, 1H), 5.14−5.04 (m, 2H), 4.75 (d, J = 19.5 Hz, 2H), 2.89−2.77 (m, 1H), 2.66−2.58 (m, 2H), 2.46 (dd, J = 13.1, 3.4 Hz, 1H), 2.32 (t, J = 13.0 Hz, 1H), 2.03−1.88 (m, 2H), 1.73 (s, 3H), 0.96 (d, J = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.3, 147.6, 136.9, 117.6, 110.0, 47.5, 47.0, 46.7, 41.6, 37.2, 20.6, 12.5; IR (neat, cm^{-1}) 3078, 2973, 2933, 2874, 1713, 1674, 1643, 1450, 1429, 1209, 1153, 1093; HRMS-APCI calcd for $C_{12}H_{19}O$ [M + H^+] 179.1430, found 179.1432.

Synthesis of (2*R*,3*S*,5*R*)-2-(Hydroxymethyl)-2-methyl-5-(prop-1-en-2-yl)-3-vinylcyclohexanone (51). To a solution of **S8** (15.05 g, 84.4 mmol) in KOH solution (10% in MeOH, 85 mL) was added a solution of formalin (37%, 19 mL, 253 mmol) in a dropwise manner at 0 °C, and the mixture was then stirred at the same temperature for 15 min. The reaction was quenched by addition of a solution of NH_4Cl (6.7 g) in water (100 mL). After removal of methanol under vacuum, the mixture was then extracted with CH_2Cl_2 (5 × 100 mL), and the combined extracts were dried over Na_2SO_4. The extracts were filtered off, and the solvent was removed under vacuum. The residue was purified by a flash chromatography on silica gel (EtOAc/hexanes = 1/8) to give compound **51** (9.87 g) as a yellow oil in 56% yield: R_f = 0.36 (EtOAc/hexanes = 1/6); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.82−5.53 (m, 1H), 5.09 (d, J = 3.7 Hz, 1H), 5.06 (s, 1H), 4.85 (s, 1H), 4.68 (s, 1H), 3.63 (dd, J = 11.4, 6.3 Hz, 1H), 3.47 (dd, J = 11.3, 7.2 Hz, 1H), 2.75−2.60 (m, 3H), 2.60−2.50 (m, 2H), 2.09−1.93 (m, 1H), 1.91−1.81 (m, 1H), 1.71 (s, 3H), 0.99 (s, 3H);

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^{13}C NMR (125 MHz, $CDCl_3$) δ 217.1, 146.4, 136.9, 117.3, 112.3, 77.4, 77.1, 76.9, 66.2, 52.7, 42.2, 41.4, 40.5, 29.5, 21.9, 15.8; IR (neat, cm^{-1}) 3440, 2975, 2940, 2875, 2364, 2331, 1714, 1705, 1699, 1456, 1377, 1045, 999, 895; HRMS-ESI-TOF calcd for $C_{13}H_{20}NaO_2$ [M + Na$^+$] 231.1356, found 231.1354.

Synthesis of ((1*R*,4*R*,6*S*)-1-Methyl-4-(prop-1-en-2-yl)-6-vinylcyclohex-2-en-1-yl)methanol (53). To a solution of compound **51** (4 g, 19 mmol) in MeOH (100 mL) was added $TsNHNH_2$ (3.35g, 18 mmol) at room temperature, and the reaction mixture was stirred heated at 50 °C for 12 h. The methanol was removed under vacuum to give the crude hydrzone; R_f = 0.52 (EtOAc/hexanes = 1/2).

To a solution of the crude product made above in dry THF (190 mL) was added a solution of MeLi (1.6 M in Et_2O, 47.5 mL, 76 mmol) at −78 °C. The mixture was warmed to room temperature and then stirred for 2 h. The reaction was quenched by addition of a saturated solution of NH_4Cl (50 mL), the mixture was extracted with ethyl acetate (2 × 50 mL), and the extracts were dried over Na_2SO_4. The solvent was evaporated under vacuum. The residue was purified by a flash chromatography on silica gel (EtOAc/hexanes = 1/8) to give compound **53** (2.96 g) as a yellow oil in 81% overall yield for two steps: R_f = 0.54 (EtOAc/hexanes = 1/6); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.84−5.74 (m, 1H), 5.70 (dd, J = 10.0, 4.3 Hz, 1H), 5.52 (d, J = 10.1 Hz, 1H), 5.03 (dd, J = 13.3, 12.1 Hz, 2H), 4.83 (s, 1H), 4.70 (s, 1H), 3.38 (d, J = 3.2 Hz, 2H), 2.72 (s, 1H), 2.46−2.37 (m, 1H), 1.76 (s, 3H), 1.75−1.72 (m, 1H), 1.61 (d, J = 13.4 Hz, 1H), 0.83 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.6, 134.0, 134.4, 130.4, 115.5, 111.8, 69.9, 41.1, 40.4, 39.0, 28.6, 22.1, 18.9; IR (neat, cm^{-1}) 3416, 3075, 2963, 2933, 2872, 2350, 1643, 1453, 1373, 1039, 911, 895; HRMS-APCI calcd for $C_{13}H_{21}O$ [M + H$^+$] 193.1587, found 193.1585.

To a solution of CuBr·Me_2S (615 mg, 3 mmol) in dry THF(50 mL) was added a solution of vinyl Grignard reagent (1.0 M in THF, 30 mL, 30 mmol) at −78 °C, and the reaction mixture was then stirred at the same temperature for 10 min. To this reaction mixture was slowly added a solution of **52**, (−)-carvone (1.5 g, 10 mmol) in dry THF (20 mL) at −78 °C, and the reaction mixture then stirred at the same temperature for 0.5 h. To the above mixture was added a solution of **54** (2.09 g, 14 mmol) in THF (20 mL), and the resultant mixture was then stirred at −20 °C for 2 h. The reaction was quenched by addition of a saturated solution of NH_4Cl (50 mL), and the mixture was extracted with ethyl acetate (2 × 50 mL). The combined organic extracts were dried over Na_2SO_4. The extracts were filtered off, and the filtrate was concentrated under vacuum, and the residue was purified by a flash chromatography on silica gel (EtOAc/hexanes = 1/8) to give diastereomers **51** (1.66 g, α-Me/β-Me = 3:10). The diastereoselectivity was confirmed by ^{1}H NMR spectrum of mixture.

To a solution of diastereomers **51** (1.66 g, α-Me/β-Me = 3:10) in MeOH (80 mL) was added $TsNHNH_2$ (1.41 g, 7.6 mmol) at room temperature, and the resultant mixture was stirred at 50 °C for 12 h. The methanol was evaporated under vacuum to obtain the crude hydrazone product.

To a solution of crude hydrazone made above in dry THF (80 mL) was added a solution of MeLi (1.6 M in Et_2O, 17.5 mL, 28 mmol) at −78 °C, and the reaction mixture was warmed to room temperature, followed by stirring for additional 2 h. The reaction was quenched with a saturated solution of NH_4Cl (20 mL), and the mixture was extracted with ethyl acetate (2 × 20 mL). The combined organic extracts were first dried over Na_2SO_4. The extracts were filtered off, and then concentrated under vacuum, and the residue was purified by a flash chromatography on silica gel (EtOAc/hexanes = 1/8) to give compound **53** (1.06 g) as a yellow oil in 55% overall yield for 3 steps.

Synthesis of Triisopropyl(3-((1*S*,3a*R*,6*R*,7a*R*)-3a-Methyl-6-(prop-1-en-2-yl)-1,3,3a,6,7,7a-hexahydroisobenzofuran-1-yl)-prop-1-yn-1-yl)silane (50). To a solution of $Pd_2(dba)_3$ (915.7 mg, 1 mmol), DPE-Phos (1.077 g, 2 mmol), and NaO^{t}Bu (1.44g, 15 mmol) in dry toluene (80 mL) was added a solution of compound **53** (1.92 g, 10 mmol) and alkynyl bromide (3 g, 11.5 mmol) in toluene (20 mL) at room temperature, and the mixture was then stirred at 45 °C for 3 h. The reaction was quenched by addition of a saturated solution of NH_4Cl (40 mL), and the mixture was extracted with ethyl acetate (2 × 20 mL). The combined organic extracts were dried over Na_2SO_4. The extracts were filtered off, and the filtrate was evaporated under vacuum, and the residue was purified by a flash chromatography on silica gel (EtOAc/hexanes = 1/50) to give compound **50** (3.15 g) as a colorless oil in 85% yield: R_f = 0.36 (EtOAc/hexanes = 1/20); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.99 (d, J = 9.8 Hz, 1H), 5.46 (dd, J = 9.8, 3.2 Hz, 1H), 4.76 (s, 1H), 4.71 (s, 1H), 3.75−3.68 (m, 1H), 3.63 (d, J = 6.9 Hz, 1H), 3.52 (d, J = 6.9 Hz, 1H), 2.94−2.89 (m, 1H), 2.64−2.52 (m, 2H), 2.03−1.94 (m, 1H), 1.87−1.80 (m, 2H), 1.78 (s, 3H), 1.11−0.99 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.4, 132.8, 130.0, 111.2, 104.7, 82.4, 77.5, 76.5, 47.3, 43.0, 42.2, 25.5, 23.9, 21.7, 20.6, 18.7, 11.4; IR (neat, cm^{-1}) 2957, 2941, 2864, 2171, 1645, 1462, 1371, 1018, 993, 883, 677; HRMS-ESI-TOF calcd for $C_{24}H_{41}OSi$ [M + H$^+$] 373.2921, found 373.2921.

Synthesis of (3*S*,3a*R*,7a*R*)-7a-Methyl-3-(3-(triisopropylsilyl)-prop-2-yn-1-yl)-1,3a,4,7a-tetrahydroisobenzofuran-5(3*H*)-one (57). A solution of compound **50** (2.23 g, 6 mmol) in dry CH_2Cl_2/MeOH (60 mL/1.94 mL) was continuously bubbled with ozone at −98 °C until the starting material was fully consumed by monitoring with TLC, and the reaction mixture was then warmed to room temperature and stirred for additional 0.5 h. Then reaction mixture was then cooled to 0 °C. To this solution were added Et_3N (10 mL, 72 mmol), DMAP (73 mg, 0.6 mmol), and Ac_2O (6.8 mL, 72 mmol), and the reaction mixture was stirred at 40 °C for 3 h. The reaction was quenched by addition of Me_2S (6 mL) and water (6 mL), and the mixture was extracted with CH_2Cl_2 (2 × 20 mL). The extracts were dried over Na_2SO_4. The extract was filtered off, and the filtrate was evaporated under vacuum. The residue was purified by a flash chromatography on silica gel (EtOAc/hexanes = 1/8) to give a couple of diastereomers **56** (dr = 2.5:1); R_f = 0.36 and 0.35 (EtOAc/hexanes = 1/6). The diastereomeric ratio (between 20:1 and 1:1) was deduced by ^{1}H NMR, and it was variable from batch to batch.

To a solution of diastereomers **56** in MeOH (30 mL) was added K_2CO_3 (3.26 g, 18.3 mmol) at 0 °C, and the mixture was stirred at the same temperature for 1.5 h. The reaction was quenched by addition of a solution of NH_4Cl (3.26 g) in water (20 mL), and the methanol in the mixture was removed under vacuum. The mixture was extracted with CH_2Cl_2 (2 × 10 mL), and the combined extracts were dried over Na_2SO_4. The extract was filtered off, and the filtrate was evaporated under vacuum to give crude products.

To a solution of above crude product in CH_2Cl_2 (35 mL) was added DMP (2.97 g, 7 mmol) at room temperature, and the mixture was stirred at the same temperature for 2 h. The reaction was quenched by addition of a saturated solution of $Na_2S_2O_3$ (10 mL), the resultant mixture was extracted with ethyl acetate (2 × 10 mL), and the combined extracts were dried over Na_2SO_4. The solution was filtered off, and the filtrate was evaporated under vacuum. The residue was purified by a flash chromatography on silica gel (EtOAc/hexanes = 1/5) to give compound **57** (1.0 g) as a colorless oil in 48% overall yield in three steps: R_f = 0.40 (EtOAc/hexanes = 1/4); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.07 (d, J = 9.8 Hz, 1H), 5.92 (d, J = 9.8 Hz, 1H), 3.95−3.82 (m, 1H), 3.73 (d, J = 7.2 Hz, 1H), 3.66 (d, J = 7.2 Hz, 1H), 2.71 (dd, J = 17.0, 3.8 Hz, 1H), 2.61 (d, J = 5.0 Hz, 2H), 2.56−2.48 (m, 1H), 2.46−2.34 (m, 1H), 1.18 (s, 3H), 1.07−0.95 (m, 23H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.4, 152.5, 129.9, 103.5, 83.6, 75.4, 49.0, 43.7, 36.2, 25.1, 19.3, 18.6, 11.3; IR (neat, cm^{-1}) 2941, 2864, 2172, 1862, 1674, 1464, 1456, 1381, 1373, 1244, 1016, 881; HRMS-ESI-TOF calcd for $C_{21}H_{34}NaO_2Si$ [M + Na$^+$] 369.2220, found 369.2229; $[\alpha]^{26}_{589}$ −41.2 (c = 0.48, $CHCl_3$).

Synthesis of Methyl (3*S*,3a*R*,4*R*,7a*R*)-7a-Methyl-5-oxo-3-(3-(triisopropylsilyl)prop-2- yn-1-yl)-1,3,3a,4,5,7a-hexahydroisobenzofuran-4-carboxylate (49a). To a solution of compound **57** (0.694 g, 2 mmol) in dry THF (20 mL) was added NaHMDS solution (2.0 M in THF, 2.2 mL, 4.4 mmol) at −78 °C. The reaction mixture was stirred for 1 h, and then methyl cyanoformate (0.2 mL, 2.6 mmol) was added. The reaction mixture was stirred for 40 min and quenched with saturated water (15 mL). The aqueous layer was extracted with ethyl acetate (2 × 10 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated under vacuum. The residue was purified by flash chromatography on silica gel (EtOAc/hexanes = 1/7) to give compound **49a** (0.7 g) as a white solid in 86% yield: R_f = 0.35

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(EtOAc/hexanes = 1/4); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (d, J = 9.8 Hz, 1H), 5.95 (d, J = 9.8 Hz, 1H), 3.95−3.90 (m, 1H), 3.71 (s, 2H), 3.69 (s, 3H), 3.40 (d, J = 13.7 Hz, 1H), 3.06 (dd, J = 13.6, 10.4 Hz, 1H), 2.71 (dd, J = 17.6, 3.8 Hz, 1H), 2.16 (dd, J = 17.6, 3.0 Hz, 1H), 1.18 (s, 3H), 0.98 (t, J = 5.7 Hz, 23H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.4, 169.2, 153.1, 128.7, 103.6, 82.9, 76.2, 75.1, 53.9, 52.2, 48.5, 43.8, 24.6, 20.2, 18.5, 18.5, 11.2; IR (neat, cm^{-1}) 2942, 2864, 2173, 1744, 1681, 1275, 1261, 1017, 883, 764, 750; HRMS-ESI-TOF calcd for $C_{23}H_{36}O_4NaSi$ [M + Na$^+$] 427.2275, found 427.2276. Melting range of crystal: 86.4−86.9 °C.

Synthesis of Methyl (3*S*,3a*R*,4*R*,7*R*,7a*R*)-7-(Dimethyl(phenyl)silyl)-4-ethynyl-7α- methyl-5-oxo-3-(3-(triisopropylsilyl)prop-2-yn-1-yl)octahydroisobenzofuran-4-carboxylate (59a). To a suspension of lithium (236 mg, 34 mmol) in dry THF (20 mL) under argon atmosphere was added $PhMe_2SiCl$ (1.65 mL, 10 mmol) at 0 °C. The reaction mixture was stirred for 12 h.

To a solution of $ZnEt_2$ (1.0 M in toluene, 6.6 mL, 6.6 mmol) in dry THF (5 mL) was added the well-prepared $PhMe_2SiLi$ reagent (14 mL) at 0 °C. The reaction mixture was stirred for 10 min and then cooled to −78 °C. A solution of compound **49a** (1.22 g, 3 mmol) in THF (5 mL) was added to the reaction mixture, and then the mixture was stirred for 45 min and quenched by saturated NH_4Cl solution (10 mL) and 2 M HCl solution (5 mL). The aqueous layer was extracted with ethyl acetate (2 × 15 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated under vacuum. The residue was purified by flash chromatography on silica gel (EtOAc/hexanes = 1/10) to give product **S9a**; R_f = 0.42 (EtOAc/hexanes = 1/6).

To a solution of the above product **S9a** in dry THF (25 mL) were added iodonium **32** (0.98 g, 2.84 mmol) and the TBAF solution (1.0 M in THF, 5.9 mL, 5.9 mmol) at −78 °C in sequence. The reaction mixture was warmed to 0 °C and then stirred for 3.5 h followed by quenching with saturated NH_4Cl solution (30 mL). The aqueous layer was extracted with ethyl acetate (2 × 20 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated under vacuum. The residue was purified by flash chromatography on silica gel (Et_2O/toluene = 1/60) to give compound **59a** (0.82 g) as yellow oil in 48% overall yield in two steps: R_f = 0.42 (EtOAc/hexanes = 1/6); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47−7.44 (m, 2H), 7.38−7.34 (m, 3H), 4.42−4.36 (m, 1H), 3.78 (s, 3H), 3.73 (d, J = 8.3 Hz, 1H), 3.32 (d, J = 7.9 Hz, 1H), 3.03 (dd, J = 15.4, 8.9 Hz, 1H), 2.96 (dd, J = 17.4, 3.4 Hz, 1H), 2.70 (dd, J = 15.4, 3.5 Hz, 1H), 2.62 (dd, J = 17.4, 5.0 Hz, 1H), 2.53 (d, J = 9.7 Hz, 2H), 1.57 (dd, J = 8.8, 3.6 Hz, 1H), 1.27 (s, 3H), 1.08 (t, J = 4.9 Hz, 21H), 0.42 (s, 3H), 0.37 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.0, 168.0, 137.6, 133.7, 129.6, 128.3, 105.6, 82.6, 78.6, 77.9, 76.0, 74.8, 56.2, 55.2, 53.3, 44.1, 36.9, 31.5, 25.7, 22.6, 18.8, 11.5, −1.7, −1.8; IR (neat, cm^{-1}) 3312, 2924, 2864, 1736, 1728, 1452, 1254, 1232, 1030, 835, 818, 737, 675; HRMS-ESI-TOF calcd for $C_{33}H_{48}NaO_4Si$ [M + Na$^+$] 587.2983, found 587.2979.

Synthesis of (3*S*,3a*R*,4*S*,5*R*,7*R*,7a*R*)-7-(Dimethyl(phenyl)silyl)-4-ethynyl-4-(hydroxymethyl)-7α-methyl-3-(3-(triisopropylsilyl)prop-2-yn-1-yl)octahydroisobenzofuran-5-ol (60). To a solution of compound **59a** (1 g, 1.77 mmol) in dry THF (18 mL) was added $LiAlH_4$ (0.134 g, 3.54 mmol) at −98 °C. The reaction mixture was stirred for 0.5 h and warmed to room temperature, and then the reaction mixture was stirred for another 1 h and quenched with saturated Seignette salt solution (15 mL). The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated under vacuum. The residue was purified by flash chromatography on silica gel (EtOAc/hexanes = 2/3) to give inseparable diastereomers **60** (0.8 g, α-OH/β-OH = 1:2.5) in 84% yield: R_f = 0.30 (EtOAc/hexanes = 1/2). The diastereomeric ratio was deduced by the ^{1}H NMR spectrum.

Synthesis of (3*S*,3a*R*,4*R*,7a*R*)-Ethyl 7a-Methyl-5-oxo-3-(3-(triisopropylsilyl)prop-2- yn-1-yl)-1,3,3a,4,5,7a-hexahydroisobenzofuran-4-carboxylate (49b). To a solution of compound **57** (0.35 g, 1 mmol) in dry THF (10 mL) was added a solution of NaHMDS (2.0 M in THF, 1.1 mL, 2.2 mmol) at −78 °C, and the mixture was then stirred at the same temperature for 1 h. To this solution was added ethyl cyanoformate (0.13 mL, 1.3 mmol), and the reaction mixture was stirred at the same temperature for 20 min. The reaction was quenched by addition of water (10 mL), the resultant mixture was extracted with ethyl acetate (2 × 10 mL), and the combined extracts were dried over Na_2SO_4. The extracts were filtered off and evaporated under vacuum. The residue was purified by a flash chromatography on silica gel (EtOAc/hexanes = 1/6) to give product **49b** and unreacted **57**.

To a solution of above mixture of **57** and **49b** made above in dry THF (10 mL) was added a solution of NaHMDS (2.0 M in THF, 0.5 mL, 1 mmol) at −78 °C, and the mixture was then stirred at the same temperature for 1 h. To this solution was added ethyl cynoformate (0.65 mL, 0.65 mmol), and the resultant mixture was stirred at the same temperature for 20 min. The reaction was quenched by addition of water (10 mL), the mixture was extracted with ethyl acetate (2 × 10 mL), and the combined organic extracts were dried over Na_2SO_4. The extracts were filtered off and evaporated under vacuum. The residue was purified by a flash chromatography on silica gel (EtOAc/hexanes = 1/6) to give compound **49b** (0.33 g) as colorless oil in 79% yield: R_f = 0.40 (EtOAc/hexanes = 1/4); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (d, J = 9.8 Hz, 1H), 6.01 (d, J = 9.8 Hz, 1H), 4.32−4.14 (m, 2H), 4.04−3.94 (m, 1H), 3.78 (q, 2H), 3.44 (d, J = 13.7 Hz, 1H), 3.20−3.01 (m, 1H), 2.78 (dd, J = 17.5, 3.7 Hz, 1H), 2.24 (dd, J = 17.6, 3.0 Hz, 1H), 1.31 (t, J = 7.1 Hz, 3H), 1.24 (s, 3H), 1.09−1.02 (m, 23H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.7, 168.9, 153.0, 129.0, 104.0, 83.2, 76.5, 75.3, 61.6, 54.3, 48.8, 44.0, 25.0, 20.5, 18.7, 14.1, 11.4; IR (neat, cm^{-1}) 2941, 2865, 2174, 1740, 1682, 1464, 1385, 1259, 1020, 914, 883, 748; HRMS-ESI-TOF calcd for $C_{24}H_{38}NaO_4Si$ [M + Na$^+$] 441.2432, found 441.2429.

Synthesis of (3*S*,3a*R*,4*R*,7*R*,7a*R*)-Ethyl 7-(Dimethyl(phenyl)-silyl)-4-ethynyl-7a-methyl-5-oxo-3-(3-(triisopropylsilyl)prop-2-yn-1-yl)octahydroisobenzofuran-4-carboxylate (59b). To a suspension of lithium (0.87 g, 125.8 mmol) in dry THF (74 mL) was added $PhMe_2SiCl$ (6.1 mL, 37 mmol) under argon atmosphere at 0 °C, and the mixture was then stirred at the same temperature for 12 h.

To a solution of $ZnEt_2$ (1.5 M in toluene, 16.7 mL, 25 mmol) in dry THF (39 mL) was added the reagent $PhMe_2SiLi$ made above (54 mL) at 0 °C, and the mixture was first stirred at the same temperature for 10 min. To this solution was added a solution of compound **49b** (4.78 g, 11.4 mmol) in THF (20 mL) at −78 °C in a dropwise manner, and the mixture was then stirred at the same temperature for 45 min. The reaction was quenched by addition of a saturated solution of NH_4Cl (40 mL), the mixture was extracted with ethyl acetate (2 × 40 mL), and the combined organic extracts were dried over Na_2SO_4. The extracts were filtered off and evaporated under vacuum. The residue was purified by a flash chromatography on silica gel (EtOAc/hexanes = 1/8) to give product **S9b**; R_f = 0.53 (EtOAc/hexanes = 1/6).

To a solution of product **S9b** made above in dry THF (110 mL) was added a solution of iodonium **32** (4.32 g, 12.54 mmol), followed by addition of TBAF solution (1.0 M in THF, 28.5 mL, 28.5 mmol) at −78 °C. The mixture was then warmed to 0 °C and stirred for an additional 3.5 h. The reaction was quenched by addition of a saturated solution of NH_4Cl (20 mL), the mixture was extracted with ethyl acetate (2 × 20 mL), and the combined organic extracts were dried over Na_2SO_4. The extracts were filtered off and evaporated under vacuum. The residue was purified by a flash chromatography on silica gel (Et_2O/toluene = 1/60) to give compound **59b** (4.68 g) as yellow oil in 50% overall yield in two steps: R_f = 0.32 (Et_2O/toluene = 1/20); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49−7.42 (m, 2H), 7.38−7.33 (m, 3H), 4.26−4.21 (m, 1H), 3.72 (d, J = 8.0 Hz, 1H), 3.33 (d, J = 7.9 Hz, 1H), 3.09−3.02 (m, 1H), 2.97 (dd, J = 17.3, 3.3 Hz, 1H), 2.69 (dd, J = 15.4, 3.2 Hz, 1H), 2.60 (dd, J = 17.4, 5.2 Hz, 1H), 2.53 (s, 1H), 2.49 (d, J = 10.0 Hz, 1H), 1.58−1.55 (m, 1H), 1.31−1.27 (m, 3H), 1.09−1.05 (m, 11H), 0.41 (s, 1H), 0.37 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.1, 167.5, 137.5, 133.7, 129.5, 128.2, 108.6, 105.6, 82.4, 77.8, 76.0, 74.9, 62.8, 56.4, 55.1, 44.2, 37.0, 31.5, 25.7, 22.5, 18.8, 18.7, 13.8, 11.5, −1.7, −1.7; IR (neat, cm^{-1}) 3312, 1941, 2864, 2171, 1734, 1732, 1726, 1462, 1454, 1427, 1254, 1230; HRMS-ESI-TOF calcd for $C_{34}H_{50}NaO_4Si_2$ [M + Na$^+$] 601.3140, found 601.3140; $[\alpha]^{26}_{589}$ −67.1 (c = 0.033, $CHCl_3$).

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Synthesis of (3*S*,3a*R*,4*S*,7*R*,7a*R*)-7-(Dimethyl(phenyl)silyl)-4-ethynyl-4-(hydroxylmethyl)-7α-methyl-3-(3-(triisopropylsilyl)-prop-2-yn-1-yl)octahydroisobenzofuran-5-ol (60). To a solution of compound **59b** (1.75 g, 3.03 mmol) in dry THF (30 mL) was added $LiAlH_4$ (0.11 g, 3.03 mmol) at −98 °C, the mixture was first stirred at the same temperature for 0.5 h and then warmed to room temperature, and then the mixture was then stirred for an additional 1 h. The reaction was quenched with a saturated solution of Seignette salt (25 mL) slowly, and the resultant mixture was stirred until a clear solution was obtained. The mixture was extracted with ethyl acetate (3 × 25 mL), and the combined extracts were dried with Na_2SO_4. The extracts were filtered off and evaporated under vacuum. The residue was purified by a flash chromatography on silica gel (EtOAc/hexanes = 2/3) to give inseparable diastereomers **60** (1.26 g, α-OH/β-OH = 1:9) in 77% yield: R_f = 0.30 (EtOAc/hexanes = 1/2). The diastereomeric ratio was deduced from the ^{1}H NMR spectrum.

β-OH **60**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50−7.46 (m, 2H), 7.37−7.33 (m, 3H), 4.14−4.07 (m, 2H), 3.98−3.93 (m, 1H), 3.70 (d, J = 11.3 Hz, 1H), 3.63 (d, J = 7.6 Hz, 1H), 312 (d, J = 7.6 Hz, 1H), 2.99 (dd, J = 17.3, 3.6 Hz, 1H), 2.73 (dd, J = 17.3, 4.4 Hz, 1H), 2.37 (s, 1H), 2.18 (d, J = 10.7 Hz, 1H), 2.03−1.98 (m, 1H), 1.94−1.89 (m, 1H), 1.39 (dd, J = 5.8, 4.6 Hz, 1H), 1.23 (s, 3H), 1.09 (d, J = 2.9 Hz, 21H), 0.46 (s, 3H), 0.40 (d, J = 5.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.7, 133.6, 129.3, 128.1, 105.8, 86.4, 82.5, 79.5, 77.2, 73.8, 73.1, 61.5, 52.4, 44.0, 43.8, 29.3, 28.6, 26.1, 25.5, 18.8, 11.5.

Diastereomers **60** (α-OH/β-OH = 1:9): IR (neat, cm^{-1}) 3416, 3308, 2943, 2890, 2864, 2170, 1738, 1464, 1427, 1283 1111, 1055; HRMS-ESI-TOF calcd for $C_{32}H_{50}O_3NaSi_2$ [M + Na$^+$] 561.3191, found 561.3191.

Synthesis of (3*S*,3a*R*,4*S*,7*R*,7a*R*)-7-(Dimethyl(phenyl)silyl)-4-ethynyl-4-(hydroxylmethyl)-7a-methyl-3-(prop-2-yn-1-yl)-octahydroisobenzofuran-5-ol (48). To a solution of mixture **60** (α-OH/β-OH = 1:9, 1.25 g, 2.32 mmol) in THF (20 mL) was added a solution of TBAF (1.0 M in THF, 4.6 mL, 4.6 mmol) at room temperature, and the reaction mixture was stirred at 50 °C overnight. The reaction was quenched by addition of a saturated solution of NH_4Cl (20 mL), and the mixture was then extracted with ethyl acetate (2 × 20 mL). The combined organic extracts were dried over Na_2SO_4. The extracts were filtered off and evaporated under vacuum. The residue was purified by a flash chromatography on silica gel (EtOAc/hexanes = 1/1) to give inseparable diasteroisomers **48** (0.85 g, α-OH/β-OH = 1:9) as yellow solids in 96% yield: R_f = 0.31 (EtOAc/hexanes = 1/1). The diastereomeric ratio was determined from the ^{1}H NMR spectrum.

β-OH **48**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50−7.46 (m, 2H), 7.37−7.33 (m, 3H), 4.14 (d, J = 11.5 Hz, 1H), 4.08−4.03 (m, 2H), 3.71−3.66 (m, 2H), 3.17 (d, J = 7.6 Hz, 1H), 2.88 (d, J = 17.1 Hz, 1H), 2.65 (dd, J = 17.1, 2.4 Hz, 1H), 2.39 (s, 1H), 2.07−2.00 (m, 2H), 1.95−1.90 (m, 1H), 1.39−1.36 (m, 1H), 1.24 (s, 3H), 0.47 (s, 3H), 0.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.6, 133.6, 129.3, 128.1, 86.1, 81.6, 79.7, 73.6, 73.1, 70.5, 61.3, 52.3, 44.2, 43.9, 29.9, 28.8, 25.2, 25.0, −0.9.

Diastereomers **48** (α-OH/β-OH = 1:9): IR (neat, cm^{-1}) 3416, 3304, 3069, 3048, 2927, 2885, 1427, 1418, 1254, 1170, 1055, 1028; HRMS-ESI-TOF calcd for $C_{23}H_{31}O_3Si$ [M + Na$^+$] 383.2037, found 383.2036.

Synthesis of (2a*S*,2a1*R*,4a*S*,5*R*,7a*S*,8*R*,10*R*,10a*R*)-10-(Dimethyl(phenyl)silyl)-10α-methyl-4-methylene-5-(2-(trimethylsilyl)ethoxy)dodecahydronaphtho[1,8-*bc*:4,4*a*−*c*′]-difuran-8-ol (47). To a solution of diasteroisomers **48** (α-OH/β-OH = 1:9, 35 mg, 0.091 mmol) in dry DCM (1.8 mL) were sequentially added 2-(trimethylsilyl)ethanol (14 μL, 0.1 mmol), (IPr)AuCl (2.8 mg, 0.0046 mmol), and $AgSbF_6$ (1.6 mg, 0.0046 mmol) at room temperature. The reaction mixture was then stirred at the same temperature for 1.2 h. The reaction mixture was purified by flash chromatography on silica gel (EtOAc/hexane = 1/8) to give compound **47** (20 mg) in 49% yield (base on β-OH **9**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55−7.49 (m, 2H), 7.38−7.34 (m, 3H), 5.24 (s, 1H), 5.05 (s, 1H), 5.02 (s, 1H), 4.10 (d, J = 8.6 Hz, 1H), 3.93−3.84 (m, 2H), 3.77 (dd, J = 11.3, 4.1 Hz, 1H), 3.63 (d, J = 8.6 Hz, 1H), 3.59−3.49 (m, 2H), 3.39 (d, J = 8.1 Hz, 1H), 2.83 (dd, J = 12.5, 4.3 Hz, 1H), 2.46 (s, 1H), 2.07−2.02 (m, 1H), 2.01−1.94 (m, 1H), 1.89 (t, J = 11.5 Hz, 1H), 1.60 (d, J = 11.3 Hz, 1H), 1.38 (d, J = 6.1 Hz, 1H), 1.06−0.94 (m, 5H), 0.47 (s, 3H), 0.03 (s, 9H).; ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.0, 139.1, 133.8, 129.3, 128.1, 114.7, 104.5, 80.47, 75.8, 72.7, 66.3, 65.4, 58.2, 54.1, 51.1, 44.0, 42.9, 32.2, 31.3, 22.3, 18.2, −0.4, −0.8, −1.4; IR (neat, cm^{-1}) 3395, 2952, 2889, 1426, 1251, 1083, 1014, 859, 835, 814, 774, 701; HRMS-ESI-TOF calcd for $C_{28}H_{44}O_4NaSi_2$ [M + Na$^+$] 523.2670, found 523.2668; $[\alpha]^{26}_{589}$ +43.1 (c = 0.13, $CHCl_3$).

Synthesis of (2a*S*,2a1*R*,4a*S*,5*R*,7a*S*,8*R*,10*R*,-10a*R*)-10-(Dimethyl(phenyl)silyl)-10α-methyl-4-methylene-5-(2-(trimethylsilyl)ethoxy)dodecahydronaphtho[1,8-*bc*:4,4*a*−*c*′]-difuran-8-ol (47). To a solution of diasteroisomers **48** (α-OH:β-OH = 1:9, 25 mg, 0.065 mmol) in dry DCM (1.3 mL) were sequentially added 2-(trimethylsilyl)ethanol (28 μL, 0.2 mmol), (IPr)AuCl (2 mg, 0.0033 mmol), and $AgSbF_6$ (1.1 mg, 0.0033 mmol) at room temperature. The reaction mixture was then stirred at the same temperature for 1.2 h. The reaction mixture was purified by a flash chromatography on silica gel (EtOAc/hexane = 1/8) to give compound **47** (4.5 mg) in 15% yield (based on β-OH **48**) and compound **62** (9 mg) in 62% yield (based on β-OH **48**).

Compound **47**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55−7.49 (m, 2H), 7.38−7.34 (m, 3H), 5.24 (s, 1H), 5.05 (s, 1H), 5.02 (s, 1H), 4.10 (d, J = 8.6 Hz, 1H), 3.93−3.84 (m, 2H), 3.77 (dd, J = 11.3, 4.1 Hz, 1H), 3.63 (d, J = 8.6 Hz, 1H), 3.59−3.49 (m, 2H), 3.39 (d, J = 8.1 Hz, 1H), 2.83 (dd, J = 12.5, 4.3 Hz, 1H), 2.46 (s, 1H), 2.07−2.02 (m, 1H), 2.01−1.94 (m, 1H), 1.89 (t, J = 11.5 Hz, 1H), 1.60 (d, J = 11.3 Hz, 1H), 1.38 (d, J = 6.1 Hz, 1H), 1.06−0.94 (m, 5H), 0.47 (s, 3H), 0.03 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.0, 139.1, 133.8, 129.3, 128.1, 114.7, 104.5, 80.47, 75.8, 72.7, 66.3, 65.4, 58.2, 54.1, 51.1, 44.0, 42.9, 32.2, 31.3, 22.3, 18.2, −0.4, −0.8, −1.4; IR (neat, cm^{-1}) 3395, 2952, 2889, 1426, 1251, 1083, 1014, 859, 835, 814, 774, 701; HRMS-ESI-TOF calcd for $C_{28}H_{44}O_4NaSi_2$ [M + Na$^+$] 523.2670, found 523.2668; $[\alpha]^{26}_{589}$ + 43.1 (c = 0.13, $CHCl_3$).

Compound **62**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51−7.45 (m, 2H), 7.38−7.33 (m, 3H), 5.08 (d, J = 5.2 Hz, 1H), 4.04 (dt, J = 10.0, 3.5 Hz, 1H), 3.90 (d, J = 9.4 Hz, 1H), 3.75 (d, J = 9.4 Hz, 1H), 3.71−3.62 (m, 2H), 3.60−3.54 (m, 1H), 3.40−3.31 (m, 1H), 3.18 (d, J = 7.6 Hz, 1H), 2.96−2.87 (m, 1H), 2.83−2.76 (m, 1H), 2.32 (d, J = 10.2 Hz, 1H), 2.23 (dd, J = 14.0, 5.4 Hz, 1H), 2.05 (t, J = 2.6 Hz, 1H), 2.00−1.91 (m, 3H), 1.34−1.30 (m, 1H), 1.10 (s, 3H), 0.94−0.82 (m, 2H), 0.47 (s, 3H), 0.40 (s, 3H), 0.00 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1, 133.6, 129.2, 128.1, 102.1, 82.0, 79.0, 76.9, 74.5, 71.0, 64.9, 64.0, 51.5, 47.9, 46.0, 41.9, 31.0, 30.9, 25.1, 23.6, 18.2, −0.3, −0.5, −1.4; HRMS-ESI-TOF calcd for $C_{28}H_{44}O_4NaSi_2$ [M + Na$^+$] 523.2670, found 523.2670; IR (neat, cm^{-1}) 3450, 2952, 1650, 1427, 1249, 1032, 835, 775, 703.

Synthesis of (2a*S*,2a1*R*,4a*S*,5*R*,7a*S*,10*R*,10a*R*)-10-(Dimethyl-(phenyl)silyl)-10α-methyl-4-methylene-5-(2-(trimethylsilyl)-ethoxy)decahydronaphtho[1,8-*bc*:4,4*a*−*c*′]difuran-8(2a*H*)-one (63). To a solution of compound **47** (0.25 g, 0.5 mmol) in dry DCM (5 mL) were added $NaHCO_3$ (84 mg, 1 mmol) and DMP (0.32 g, 0.75 mmol) at room temperature, and the mixture was stirred at the same temperature for 0.5 h. The reaction was quenched by addition of a saturated solution of $NaHCO_3$ (4 mL), and the mixture was then extracted with CH_2Cl_2 (2 × 4 mL). The combined organic extracts were dried over Na_2SO_4. The extracts were filtered off and evaporated under vacuum. The residue was purified by a flash chromatography on silica gel (EtOAc/hexane = 1/7) to give compound **63** (0.21 g) as a colorless oil in 84% yield: R_f = 0.53 (silica gel, EtOAc/hexanes = 1/4); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46−7.41 (m, 2H), 7.35−7.30 (m, 3H), 4.89 (s, 1H), 4.85 (s, 1H), 4.83 (s, 1H), 4.28 (d, J = 9.1 Hz, 1H), 4.07−3.98 (m, 1H), 3.79 (d, J = 8.0 Hz, 1H), 3.74 (d, J = 9.1 Hz, 1H), 3.72−3.66 (m, 1H), 3.50−3.44 (m, 1H), 3.42 (d, J = 8.1 Hz, 1H), 3.39 (s, 1H), 2.80 (dd, J = 14.9, 8.3 Hz, 1H), 2.73 (dd, J = 15.4, 8.0 Hz, 1H), 2.53 (d, J = 14.9 Hz, 1H), 2.10 (dd, J = 15.5, 5.3 Hz, 1H), 1.81 (d, J = 11.8 Hz, 1H), 1.63 (d, J = 8.1 Hz, 1H), 1.40 (s, 3H), 0.98−0.86 (m, 2H), 0.33 (s, 3H), 0.29 (s, 3H), −0.00 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.8, 142.5, 137.6, 133.7, 129.4, 128.1, 117.3, 107.1,

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J. Org. Chem. 2016, 81, 751−771

80.2, 71.3, 67.5, 65.1, 58.3, 54.2, 54.0, 42.1, 38.8, 37.9, 34.4, 22.1, 18.0, −1.3, −1.6, −2.0; IR (neat, cm^{-1}) 2953, 2892, 1715, 1427, 1250, 1109, 1033, 835, 775, 703; HRMS-ESI-TOF calcd for $C_{28}H_{42}O_4NaSi_2$ [M + Na^+] 521.2514, found 521.2513.

Synthesis of (2a*S*,2a1*R*,4a*S*,5*R*,7a*S*,8*S*,10*R*,10a*R*)-10-(Dimethyl(phenyl)silyl)-10α-methyl-4-methylene-5-(2-(trimethylsilyl)ethoxy)dodecahydronaphtho[1,8-*bc*:4,4*a*−*c*′]-difuran-8-ol (64). To a solution of compound **63** (135 mg, 0.37 mmol) in MeOH/THF (2.5/0.5 mL) was added $NaBH_4$ (10 mg, 0.27 mmol) at −10 °C, and the mixture was stirred at the same temperature for 0.5 h. The reaction was quenched by addition of a saturated solution of NH_4Cl (3 mL), and the mixture was extracted with EtOAc (3 × 3 mL). The combined extracts were dried over Na_2SO_4. The extracts were filtered off and evaporated under vacuum. The residue was purified by a flash chromatography on silica gel (EtOAc/hexane = 1/10) to give compound **64** (110 mg) as a white solid in 82% yield, R_f = 0.69 (silica gel, EtOAc/hexanes = 1/4) and compound **47** (10 mg) in 7% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (dd, J = 6.4, 3.0 Hz, 2H), 7.38−7.32 (m, 3H), 5.24 (s, 1H), 5.06 (s, 1H), 4.96 (s, 1H), 4.05 (t, J = 2.9 Hz, 1H), 3.90 (d, J = 8.2 Hz, 1H), 3.86−3.79 (m, 1H), 3.49 (dddd, J = 17.2, 11.2, 10.4, 5.2 Hz, 2H), 3.37 (d, J = 8.2 Hz, 1H), 2.86 (dd, J = 11.5, 4.3 Hz, 1H), 2.75 (s, 1H), 2.19−2.12 (m, 1H), 2.11−1.99 (m, 3H), 1.35 (dd, J = 6.7, 1.4 Hz, 1H), 1.02−0.88 (m, 5H), 0.53 (s, 3H), 0.39 (s, 3H), 0.04 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.0, 140.8, 133.9, 128.6, 127.7, 113.5, 102.5, 80.8, 73.9, 70.2, 69.8, 64.8, 52.4, 50.0, 48.8, 44.4, 41.9, 30.3, 28.5, 21.8, 18.7, −1.0, −1.3, −1.6; IR (neat, cm^{-1}) 2953, 2926, 1260, 1250, 1090, 1017, 860, 835, 814, 702; HRMS-ESI-TOF calcd for $C_{28}H_{44}O_4NaSi_2$ [M + Na^+] 523.2670, found 523.2668. Melting range of crystal: 113.3−113.6 °C.

Synthesis of (2a*S*,2a1*S*,4a*S*,5*R*,7a*S*,8*S*,10*R*,10a*R*)-10a-Methyl-4-methylene-5-(2-(trimethylsilyl)ethoxy)-dodecahydronaphtho[1,8-*bc*:4,4*a*−*c*′]difuran-8,10-diol (65). To liquid ammonia (1.2 mL) was added a solution of compound **64** (55 mg, 0.11 mmol) in dry THF (1.2 mL) at −78 °C, followed by addition of Na (12.7 mg, 0.55 mmol), and the resultant mixture was then stirred at the same temperature for 1 min. The reaction was quenched by addition of a saturated solution of NH_4Cl (2 mL), and the mixture was extracted with EtOAc (3 × 2 mL). The combined organic extracts were dried over Na_2SO_4. The extracts were filtered off and concentrated under vacuum to afford the crude product.

To a solution of the above crude product in THF (1 mL) was added a solution of TBAF (1.0 M in THF, 0.24 mL, 0.24 mmol) at room temperature, and the reaction mixture was stirred at the same temperature for 1 h. To this solution were sequentially added MeOH (0.5 mL), $KHCO_3$ (16.5 mg 0.165 mmol), and 30% H_2O_2 solution (0.125 mL, 1.1 mmol) at room temperature, and the resultant mixture was stirred at the same temperature for 5 h. The reaction was quenched by addition of a saturated solution of $Na_2S_2O_3$ (2 mL), the resultant mixture was extracted with EtOAc (3 × 2 mL), and the combined organic extracts were dried over Na_2SO_4. The extracts were filtered off and concentrated under vacuum. The residue was purified by a flash chromatography on silica gel (EtOAc/hexane = 2/3) to give compound **65** (40 mg) as a white solid in 95% overall yield in two steps: R_f = 0.38 (silica gel, EtOAc/hexanes = 1/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.23 (s, 1H), 5.09 (s, 1H), 4.97 (s, 1H), 4.25 (s, 1H), 4.11 (d, J = 7.4 Hz, 1H), 3.84−3.77 (m, 2H), 3.67−3.57 (m, 3H), 3.54 (d, J = 7.4 Hz, 1H), 3.49−3.43 (m, 1H), 2.94−2.74 (m, 4H), 2.36 (d, J = 11.6 Hz, 1H), 2.19−2.12 (m, 2H), 2.08−2.01 (m, 1H), 0.98−0.82 (m, 5H), 0.02 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.7, 113.9, 102.5, 76.4, 73.7, 71.3, 71.2, 69.3, 64.9, 52.6, 50.1, 44.2, 44.2, 43.3, 32.6, 18.9, 18.7, −1.3; IR (neat, cm^{-1}) 3400, 2950, 2892, 1457, 1248, 1080, 1015, 860, 835; HRMS-ESI-TOF calcd for $C_{20}H_{34}O_5NaSi$ [M + Na^+] 405.2068, found 405.2068.

Synthesis of (2a*S*,2a1*S*,4a*S*,5*R*,7a*S*,8*S*,10*R*,10a*R*)-10α-Methyl-4-methylene-5-(2-(trimethylsilyl)ethoxy)-dodecahydronaphtho[1,8-*bc*:4,4*a*−*c*′]difuran-8,10-diyl Diacetate (66). To a solution of compound **65** (38 mg, 0.1 mmol) in dry DCE (2.5 mL) were added Ac_2O (38 μL, 0.4 mmol) and DMAP (73 mg, 0.6 mmol) at room temperature, and the mixture was stirred at 90 °C for 12 h. To ensure the conversion, a second batch of Ac_2O (38 μL, 0.4 mmol) and DMAP (73 mg, 0.6 mmol) was added to the reaction mixture, which was stirred at at 90 °C for an additional 6 h. The reaction was quenched by addition of a saturated solution of NH_4Cl (2.5 mL), the mixture was extracted with CH_2Cl_2 (2 × 2.5 mL), and the combined extracts were dried over Na_2SO_4. The extracts were filtered off and concentrated under vacuum, and the residue was purified by a flash chromatography on silica gel (EtOAc/hexane = 1/2) to give compound **66** (41 mg) as a colorless oil in 89% yield: R_f = 0.82 (silica gel, EtOAc/hexanes = 1/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.24−5.18 (m, 2H), 5.10 (s, 1H), 5.01 (s, 1H), 4.93 (t, J = 2.8 Hz, 1H), 3.78−3.72 (m, 1H), 3.71−3.61 (m, 4H), 3.56 (d, J = 7.9 Hz, 1H), 3.38−3.30 (m, 1H), 2.93−2.86 (m, 2H), 2.40 (d, J = 11.7 Hz, 1H), 2.36−2.30 (m, 1H), 2.21 (t, J = 11.1 Hz, 1H), 2.10−2.01 (m, 7H), 0.97 (s, 3H), 0.91−0.80 (m, 2H), −0.01 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 169.6, 141.4, 114.4, 103.0, 76.3, 73.6, 71.6, 71.4, 69.1, 64.8, 52.1, 48.5, 45.8, 43.7, 42.7, 28.8, 21.3, 21.1, 19.1, 17.9, −1.3; IR (neat, cm^{-1}) 2950, 2893, 2357, 2330, 1738, 1250, 1053, 1017, 835, 750; HRMS-ESI-TOF calcd for $C_{24}H_{38}O_7NaSi$ [M + Na^+] 489.2279, found 489.2278.

Synthesis of (2a*R*,2a1*S*,3*S*,4a*S*,5*R*,7a*S*,8*S*,10*R*,10a*R*)-3-Hydroxy-10a-methyl-4-methylene-5-(2-(trimethylsilyl)ethoxy)-dodecahydronaphtho[1,8-*bc*:4,4*a*−*c*′]difuran-8,10-diyl Diacetate (67). To a solution of compound **66** (40 mg, 0.086 mmol) in dry CH_2Cl_2 (1.7 mL) were added SeO_2 (48 mg, 0.43 mmol) and ^{t}BuOOH solution (5.5 M in decane, 78 μL, 0.43 mmol) at room temperature, and the mixture was stirred at the same temperature for 7 h. The solvent was removed under vacuum, and the residue was purified by a flash chromatography on silica gel (EtOAc/hexane = 2/3) to give compound **67** (30 mg) as a colorless oil in 73% yield: R_f = 0.40 (silica gel, EtOAc/hexanes = 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.36 (s, 1H), 5.26−5.20 (m, 2H), 5.15 (s, 1H), 4.95 (s, 1H), 4.62 (d, J = 2.5 Hz, 1H), 3.80−3.60 (m, 6H), 3.38−3.30 (m, 1H), 3.25 (s, 1H), 3.15 (d, J = 12.3 Hz, 1H), 2.36 (d, J = 16.7 Hz, 1H), 2.11−2.03 (m, 7H), 0.97 (s, 3H), 0.89−0.84 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2, 169.8, 143.3, 117.2, 103.0, 77.4, 77.1, 77.0, 76.9, 76.2, 74.9, 71.4, 68.8, 64.9, 48.4, 48.2, 42.3, 36.2, 28.8, 21.3, 21.1, 18.7, 17.9, −1.3; IR (neat, cm^{-1}) 3445, 2953, 2929, 2894, 1738, 1732, 1377, 1248, 1053, 860, 837; HRMS-ESI-TOF calcd for $C_{24}H_{38}O_8NaSi$ [M + Na^+] 505.2227, found 505.2228.

Synthesis of (2a*R*,2a1*S*,4a*S*,5*R*,7a*S*,8*S*,10*R*,10a*R*)-4,10a-Dimethyl-3-oxo-5-(2-(trimethylsilyl)ethoxy)-dodecahydronaphtho[1,8-*bc*:4,4*a*−*c*′]difuran-8,10-diyl Diacetate (15). To a solution of compound **67** (17 mg, 0.035 mmol) in EtOAc (0.7 mL) was added Pd/C (10% on carbon, 3 mg), and the mixture was then degassed with H_2 five times. The mixture was then stirred at room temperature for 1.5 h. The reaction was worked up by filtration of the mixture through a Celite pad, followed by washing the pad with EtOAc. The filtrate was concentrated under vacuum to give the crude hydrogenated products.

To a solution of the crude product made above in dry CH_2Cl_2 (0.7 mL) was sequentially added 4 Å molecular sieves (17 mg), TPAP (1.5 mg, 0.0043 mmol), and NMO (8.3 mg, 0.07 mmol) at room temperature, and then the mixture was stirred at the same temperature for 1 h. The reaction mixture was purified by flash chromatography on silica gel (EtOAc/hexane = 1/2) to give compound **15** as a pair of diastereomers (14 mg, α-Me/β-Me = 10:3) in 82% overall yield in two steps: R_f = 0.61 and 0.51 (silica gel, EtOAc/hexanes = 1:1). The ratio was confirmed by ^{1}H NMR spectrum.

Two diastereomers could be separated by flash chromatography, and the relative stereochemistry of the major isomer **15** (α-Me) was determined by 2D-NMR spectra. α-Me **15**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.24 (t, J = 2.8 Hz, 1H), 4.96 (t, J = 2.8 Hz, 1H), 4.82 (s, 1H), 4.42 (d, J = 14.1 Hz, 1H), 4.22 (d, J = 9.4 Hz, 1H), 3.86 (d, J = 9.5 Hz, 1H), 3.78−3.71 (m, 1H), 3.66 (s, 2H), 3.38−3.30 (m, 1H), 2.74 (d, J = 14.0 Hz, 1H), 2.45 (d, J = 11.2 Hz, 1H), 2.40−2.30 (m, 2H), 2.10−2.01 (m, 7H), 1.23 (d, J = 6.4 Hz, 3H), 1.07 (s, 3H), 0.90−0.83 (m, 2H), −0.00 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.5, 170.1, 169.5, 105.6, 77.3, 71.8, 70.6, 69.3, 65.0, 59.4, 47.9, 47.5, 43.7, 43.0, 28.5, 21.3, 21.1, 18.0, 17.8, 13.0, −1.3; IR (neat, cm^{-1}) 2925, 2855, 1738, 1732, 1377, 1250, 1058, 1024, 999, 860, 837, 802; HRMS-

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J. Org. Chem. 2016, 81, 751−771

ESI-TOF calcd for $C_{24}H_{38}O_8NaSi$ [M + Na^+] 505.2228, found 505.2228; $[\alpha]^{26}_{589}$ +96.1 (c = 0.25, $CHCl_3$).

Synthesis of (2a*S*,2a1*R*,4a*S*,5*S*,7a*S*,8*R*,10*R*,10a*R*)-10-(Dimethyl(phenyl)silyl)-4,10a-dimethyl-2a,2a1,4a,5,8,9,10,10a-octahydro-1*H*,7*H*-naphtho[1,8-*bc*:4,4*a*−*c*′]difuran-5,8-diol (70). To a solution of compound **47** (0.16 g, 0.32 mmol) in dry THF (3.5 mL) was added the TBAF solution (1.0 M in THF, 0.64 mL, 0.64 mmol) at room temperature. The mixture was refluxed for 3.5 h and quenched with the saturated NH_4Cl solution (3 mL). The aqueous layer was extracted with ethyl acetate (3 × 3 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated under vacuum. The residue was purified by flash chromatography on silica gel (EtOAc/hexane = 1/1) to give compound **70** (90 mg) as a white solid in 70% overall yield: R_f = 0.41 (silica gel, EtOAc/hexanes = 1/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50−7.45 (m, 2H), 7.37−7.33 (m, 3H), 5.93 (s, 1H), 5.14 (s, 1H), 4.14 (d, J = 11.3 Hz, 1H), 4.10 (d, J = 9.2 Hz, 1H), 3.88−3.79 (m, 3H), 3.45 (d, J = 8.1 Hz, 1H), 2.53 (s, 1H), 1.95−1.89 (m, 1H), 1.88−1.81 (m, 1H), 1.76 (s, 3H), 1.72 (d, J = 11.1 Hz, 1H), 1.42 (d, J = 4.4 Hz, 1H), 1.13 (s, 3H), 0.43 (s, 3H), 0.36 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.8, 133.5, 133.0, 129.3, 128.5, 128.1, 98.3, 81.3, 75.4, 71.4, 65.3, 62.6, 52.6, 47.7, 41.9, 32.5, 31.8, 22.9, 22.6, −0.5, −0.5; IR (neat, cm^{-1}) 3440, 2954, 2893, 1252, 1083, 986, 815, 733, 703, 469; HRMS-ESI-TOF calcd for $C_{23}H_{32}O_4NaSi$ [M + Na^+] 423.1962, found 423.1965.

Synthesis of (2a*S*,2a1*R*,4a*S*,7a*S*,10*R*,10a*R*)-10-(Dimethyl(phenyl)silyl)-4,10a-dimethyl-2a,2a1,4a,9,10,10a-hexahydro-1*H*,7*H*-naphtho[1,8-*bc*:4,4*a*−*c*′]difuran-5,8-dione (71). To a solution of compound **70** (40 mg, 0.1 mmol) in dry DCM (2 mL) were added 4 Å molecular sieves (40 mg), NMO (35 mg, 0.3 mmol), and TPAP (5 mg, 0.014 mmol) at room temperature. The mixture was stirred for 1 h and quenched by filtration through a Celite pad that was washed with DCM. The solvent was evaporated under vacuum, and the residue was purified by flash chromatography on silica gel (EtOAc/hexane = 1/2) to give compound **71** (28 mg) as a white solid in 71% yield: R_f = 0.81 (silica gel, EtOAc/hexanes = 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46−7.40 (m, 2H), 7.40−7.32 (m, 3H), 5.89 (s, 1H), 4.34 (d, J = 10.0 Hz, 1H), 4.29−4.22 (m, 2H), 4.00 (d, J = 8.3 Hz, 1H), 3.63 (d, J = 8.3 Hz, 1H), 3.23 (s, 1H), 3.09 (dd, J = 16.0, 8.5 Hz, 1H), 2.61 (dd, J = 16.0, 1.9 Hz, 1H), 1.93 (d, J = 11.3 Hz, 1H), 1.85 (s, 3H), 1.69 (dd, J = 8.5, 1.9 Hz, 1H), 1.33 (s, 3H), 0.38 (s, 3H), 0.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.1, 173.0, 136.7, 133.9, 130.4, 129.7, 128.3, 80.6, 70.5, 67.8, 53.5, 51.9, 46.9, 40.9, 36.7, 34.5, 22.4, 21.3, −1.5, −2.0; IR (neat, cm^{-1}) 2963, 1776, 1713, 1253, 1160, 1036, 817, 703; HRMS-ESI-TOF calcd for $C_{23}H_{28}O_4NaSi$ [M + Na^+] 419.1649, found 419.1643.

Synthesis of Compounds (2a*S*,2a1*R*,4a*S*,7a*S*,8*S*,10*R*,10a*R*)-10-(Dimethyl(phenyl)silyl)-8-hydroxy-4,10a-dimethyl-2a,4a,8,9,10,10a-hexahydro-1*H*,7*H*-naphtho-[1,8-*bc*:4,4*a*−*c*′]-difuran-5(2a1*H*)-one (72a) and (2a*S*,2a1*R*,4a*S*,7a*S*,8*R*,10-*R*,10a*R*)-10-(Dimethyl(phenyl)silyl)-8-hydroxy-4,10a-dimethyl-2a,4a,8,9,10,10a-hexahydro-1*H*,7*H*-naphtho[1,8-*bc*:4,4*a*−*c*′]-difuran-5(2a1*H*)-one (72b). To a solution of compound **71** (26 mg, 0.066 mmol) in THF (1.5 mL) was added L-Selectride (1.0 M in THF, 92 μL, 0.092 mmol) at 0 °C. The mixture was stirred for 30 min and quenched with saturated NH_4Cl solution (2 mL). The aqueous layer was extracted with ethyl acetate (2 × 2 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated under vacuum. The residue was purified by flash chromatography on silica gel (EtOAc/hexane = 1/3) to give product **72a** (4 mg, R_f = 0.50 (silica gel, EtOAc/hexanes = 1/2)) as a white solid in 15% yield and **72b** (16 mg, R_f = 0.39 (silica gel, EtOAc/hexanes = 1/2)) as a white solid in 61% yield. Compound **72a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51−7.46 (m, 2H), 7.38−7.34 (m, 3H), 6.07 (s, 1H), 4.21 (t, J = 11.4 Hz, 2H), 4.04 (d, J = 8.2 Hz, 1H), 3.98 (d, J = 9.9 Hz, 1H), 3.81 (s, 1H), 3.57 (d, J = 8.2 Hz, 1H), 3.47 (s, 1H), 2.16−2.10 (m, 1H), 2.08 (d, J = 11.5 Hz, 1H), 1.97 (s, 3H), 1.88−1.82 (m, 1H), 1.40 (dd, J = 6.6, 1.6 Hz, 1H), 1.10 (s, 3H), 0.43 (s, 3H), 0.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.1, 140.1, 133.7, 130.9, 129.1, 128.4, 128.1, 81.7, 71.5, 70.1, 68.5, 48.3, 46.3, 45.0, 41.1, 30.4, 29.5, 22.6, 21.6, −0.8, −1.4; IR (neat, cm^{-1}) 2953, 2918, 1767, 1428, 1380, 1249, 1163, 1033, 995, 813, 736, 702, 491; HRMS-ESI-TOF calcd for $C_{23}H_{30}O_4NaSi$ [M + Na^+] 421.1806, found 421.1799. Compound **72b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49−7.45 (m, 2H), 7.40−7.35 (m, 3H), 6.03 (s, 1H), 4.43 (d, J = 9.6 Hz, 1H), 4.21 (d, J = 11.4 Hz, 1H), 4.14 (d, J = 9.5 Hz, 1H), 3.91 (d, J = 8.1 Hz, 1H), 3.74 (dd, J = 11.8, 3.9 Hz, 1H), 3.52 (d, J = 8.2 Hz, 1H), 2.90 (s, 1H), 2.08−2.01 (m, 1H), 1.93 (s, 3H), 1.87−1.82 (m, 1H), 1.70 (d, J = 11.3 Hz, 1H), 1.45 (d, J = 6.0 Hz, 1H), 1.13 (s, 3H), 0.43 (s, 3H), 0.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5, 138.4, 133.6, 130.9, 129.5, 128.8, 128.3, 81.4, 76.3, 70.9, 66.3, 52.8, 52.4, 44.9, 41.5, 32.9, 31.9, 22.9, 21.5, −0.5, −0.6; IR (neat, cm^{-1}) 2925, 2854, 1770, 1380, 1259, 1108, 1037, 813, 701, 471; HRMS-ESI-TOF calcd for $C_{23}H_{30}O_4NaSi$ [M + Na^+] 421.1806, found 421.1809.

Synthesis of (2a*S*,2a1*S*,4a*S*,5*S*,7a*S*,8*S*,10*R*,10a*R*)-4,10a-Dimethyl-2a,2a1,4a,5,8,9,10,10a-octahydro-1*H*,7*H*-naphtho[1,8-*bc*:4,4*a*−*c*′]difuran-5,8,10-triol (73). To the liquid ammonia (0.8 mL) was added a solution of compound **72a** (5 mg, 0.0125 mmol) in dry THF (1 mL) at −78 °C. Then Li (3.5 mg, 0.5 mmol) was added, and the reaction mixture was stirred for 5 min at −78 °C. The reaction was quenched with a saturated NH_4Cl solution (1.5 mL). The aqueous layer was extracted with EtOAc (3 × 1.5 mL). The combined organic layer was dried over Na_2SO_4 and filtered. The solvent was removed under vacuum to afford the crude product.

To a solution of the above crude product in THF (0.8 mL) was added TBAF solution (1.0 M in THF, 25 μL, 0.025 mmol) at room temperature. The mixture was stirred for 1 h, after which time MeOH (0.4 mL), $KHCO_3$ (1.9 mg, 0.019 mmol), and 30% H_2O_2 solution (14 μL, 0.125 mmol) were added. The mixture was stirred overnight and quenched with the saturated $Na_2S_2O_3$ solution (1.5 mL). The aqueous layer was extracted with ethyl acetate (3 × 1.5 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated under vacuum. The residue was purified by flash chromatography on silica gel (DCM/MeOH = 30/1) to give compound **73** (3 mg) as a white solid in 85% overall yield in two steps: R_f = 0.30 (silica gel, DCM/MeOH = 30/1); ^{1}H NMR (500 MHz, CD_3OD) δ 5.93 (s, 1H), 5.02 (s, 1H), 4.24 (d, J = 11.3 Hz, 1H), 4.06 (d, J = 6.6 Hz, 1H), 3.98 (s, 1H), 3.89−3.81 (m, 2H), 3.72 (d, J = 8.7 Hz, 1H), 3.58 (d, J = 5.7 Hz, 1H), 2.96 (s, 1H), 2.30 (d, J = 11.4 Hz, 1H), 2.07 (s, 2H), 1.94 (s, 1H), 1.81 (s, 3H), 1.01 (s, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 136.3, 126.4, 101.6, 77.2, 72.0, 71.9, 71.3, 68.3, 55.5, 43.7, 42.1, 32.4, 21.3, 18.4; IR (neat, cm^{-1}) 3346, 2925, 2854, 1655, 1457, 1270, 1122, 1081, 772; HRMS-ESI-TOF calcd for $C_{15}H_{22}O_5Na$ [M + Na^+] 305.1359, found 305.1360.

Synthesis of (((3*S*,3a*R*,4*S*,5*R*,7*R*,7a*R*)-7-(Dimethyl(phenyl)-silyl)-4-ethynyl-7α-methyl-4-(((triethylsilyl)oxy)methyl)-3-(3-(triisopropylsilyl)prop-2-yn-1-yl)octahydroisobenzofuran-5-yl)oxy)triethylsilane (75). To a solution of mixture **60** (α-OH:β-OH = 1:9, 0.62 g, 1.15 mmol) in dry DCM (12 mL) were added the Et_3N (0.48 mL, 3.45 mmol) and TESOTf (0.65 mL, 2.875 mmol) at −78 °C in sequence. The reaction mixture was stirred for 1 h and quenched with water (10 mL). The aqueous layer was extracted with DCM (2 × 10 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated under vacuum. The residue was purified by flash chromatography on silica gel (EtOAc/hexanes = 1/60) to give inseparable diastereomers **75** (0.84 g, α-OTES/β-OTES = 1:9) as colorless oils in 96% yield, R_f = 0.85, EtOAc/hexanes = 1/20). The diastereomeric ratio was deduced from its ^{1}H NMR spectrum. β-OTES **75**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51−7.47 (m, 2H), 7.37−7.32 (m, 3H), 4.57−4.46 (m, 1H), 4.06 (d, J = 10.5 Hz, 1H), 3.97 (dd, J = 10.9, 3.8 Hz, 1H), 3.89 (d, J = 10.5 Hz, 1H), 3.65 (d, J = 7.5 Hz, 1H), 3.16 (d, J = 7.6 Hz, 1H), 3.03 (dd, J = 17.2, 3.4 Hz, 1H), 2.76 (dd, J = 17.2, 5.1 Hz, 1H), 2.10 (d, J = 3.4 Hz, 1H), 2.03 (d, J = 10.5 Hz, 1H), 1.93−1.85 (m, 1H), 1.74−1.67 (m, 1H), 1.39−1.32 (m, 1H), 1.35 (s, 3H), 1.11 (d, J = 3.2 Hz, 21H), 0.98−0.91 (m, 18H), 0.64−0.52 (m, 12H), 0.45 (s, 3H), 0.41 (d, J = 4.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.2, 133.6, 129.1, 128.0, 107.2, 89.4, 81.3, 79.6, 77.0, 75.4, 70.4, 63.6, 52.8, 44.6, 43.9, 30.2, 29.8, 25.8, 24.5, 18.9, 11.6, 7.0, 6.9, 5.1, 4.5, 4.4, −0.3, −0.7. Diastereomers **75**: IR (neat, cm^{-1}) 3310, 2955, 2876, 2172, 1464, 1456, 1427, 1416, 1252, 1240, 1104, 1037; HRMS-ESI-TOF calcd for $C_{44}H_{78}NaO_3Si_4^+$ [M + Na^+] 789.4920, found 789.4919.

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J. Org. Chem. 2016, 81, 751−771

Synthesis of (3*S*,3a*R*,4*S*,5*R*,7*R*,7a*R*)-7-(Dimethyl(phenyl)-silyl)-4-(hydroxymethyl)-7α- methyl-4-(prop-1-yn-1-yl)-3-(prop-2-yn-1-yl)octahydroisobenzofuran-5-ol (69). To a solution of diastereomers **75** (α-OTES:β-OTES = 1:9, 153 mg, 0.2 mmol) in dry THF (3 mL) was added the ^{n}BuLi solution (2.4 M in hexane, 166 μL, 0.4 mmol) at −78 °C. The mixture was stirred for 1 h, after which time MeOTf (55 μL, 0.5 mmol) and HMPA (0.3 mL) were added. The mixture was stirred at for 26 h and quenched with the saturated NH_4Cl solution (3 mL). The aqueous layer was extracted with ethyl acetate (2 × 3 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated under vacuum. The residue was purified by flash chromatography on silica gel (EtOAc/hexane = 1/60) to give the product in 89% yield: R_f = 0.85 (silica gel, EtOAc/hexanes = 1/20).

To a solution of the above product in dry THF (3 mL) was added the TBAF (209 mg, 0.8 mmol) at room temperature. The mixture was stirred overnight at 50 °C and quenched with the saturated NH_4Cl solution (3 mL). The aqueous layer was extracted with ethyl acetate (3 × 3 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated under vacuum. The residue was purified by flash chromatography on silica gel (EtOAc/hexane = 1/1) to give product **69** (60 mg) as a white solid in 84% overall yield in two steps: R_f = 0.31 (silica gel, EtOAc/hexanes = 1/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52−7.44 (m, 2H), 7.39−7.32 (m, 3H), 4.12−4.07 (m, 1H), 4.05−3.96 (m, 2H), 3.71−3.61 (m, 2H), 3.16 (d, *J* = 7.7 Hz, 1H), 2.97 (d, *J* = 3.4 Hz, 1H), 2.87 (dt, *J* = 17.1, 3.0 Hz, 1H), 2.66−2.58 (m, 1H), 2.35 (d, *J* = 6.0 Hz, 1H), 2.19 (d, *J* = 10.6 Hz, 1H), 2.06−1.98 (m, 2H), 1.96−1.90 (m, 1H), 1.88 (s, 3H), 1.39−1.35 (m, 1H), 1.22 (s, 3H), 0.47 (s, 3H), 0.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.8, 133.6, 129.2, 128.1, 81.7, 81.2, 80.7, 79.8, 77.8, 73.8, 70.2, 61.5, 52.9, 44.3, 44.3, 30.2, 28.9, 25.2, 25.0, 3.7, −0.8; IR (neat, cm^{-1}) 3417, 3306, 2924, 2854, 1259, 1108, 1069, 1049, 1028, 833, 764, 750; HRMS-ESI-TOF calcd for $C_{24}H_{32}O_3NaSi$ [M + Na$^+$] 419.2014, found 419.2013.

Synthesis of Compounds (2a*S*,2a1*R*,4a*S*,5*R*,7a*S*,8*R*,10*R*,-10a*R*)-10-(Dimethyl(phenyl)silyl)-5,10a-dimethyl-4-methylene-5-(2-(trimethylsilyl)ethoxy)decahydro-1*H*,7*H*-naphtho-[1,8-*bc*:4,4*a*−*c*′]difuran-8-ol (76) and (2a*S*,2a1*R*,4a*S*,5*S*,7a*S*,8*R*,-10*R*,10a*R*)-10-(Dimethyl(phenyl)silyl)-5,10a-dimethyl-4-methylene-5-(2-(trimethylsilyl)ethoxy)decahydro-1*H*,7*H*-naphtho-[1,8-*bc*:4,4*a*−*c*′]difuran-8-ol (77). To a solution of compound **69** (30 mg, 0.076 mmol) in dry DCM (1.5 mL) were added 2-(trimethylsilyl)ethanol (32.5 μL, 0.227 mmol), (IPr)AuCl (2.3 mg, 0.0038 mmol), and $AgSbF_6$ (1.3 mg, 0.0038 mmol) at room temperature sequentially. The reaction mixture was then stirred for 0.5 h and then purified by flash chromatography on silica gel (EtOAc/hexane = 1/10−1/4) to give compound **76** (9 mg) as a white solid in 12% yield and compound **77** (15 mg) as a white solid in 30% yield: R_f = 0.72 and 0.55 (silica gel, EtOAc/hexanes = 1/4).

Compound **76**: ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.53−7.49 (m, 2H), 7.38−7.34 (m, 3H), 4.95 (s, 1H), 4.84 (s, 1H), 4.03−3.91 (m, 3H), 3.83−3.71 (m, 3H), 3.60−3.53 (m, 1H), 3.50−3.44 (m, 1H), 3.33 (d, *J* = 7.8 Hz, 1H), 2.72−2.65 (m, 1H), 2.63 (s, 1H), 2.30 (dd, *J* = 16.2, 3.7 Hz, 1H), 1.92−1.86 (m, 1H), 1.73−1.65 (m, 1H), 1.53 (d, *J* = 12.1 Hz, 1H), 1.41 (dd, *J* = 5.7, 1.7 Hz, 1H), 1.25 (s, 3H), 1.20 (s, 3H), 0.91−0.87 (m, 2H), 0.42 (s, 3H), 0.35 (s, 3H), 0.04 (s, 9H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 143.3, 139.4, 133.7, 129.1, 128.0, 118.9, 106.8, 80.7, 73.9, 71.2, 66.1, 63.8, 57.3, 51.6, 49.7, 42.4, 36.7, 32.2, 31.2, 22.1, 18.2, 18.2, −0.7, −0.7, −1.7; IR (neat, cm^{-1}) 3460, 2950, 2926, 1425, 1384, 1250, 1031, 1000, 860, 832, 815, 702; HRMS-ESI-TOF calcd for $C_{29}H_{46}O_4NaSi_2$ [M + Na$^+$] 537.2827, found 537.2823.

Compound **77**: ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.56−7.48 (m, 2H), 7.40−7.33 (m, 3H), 4.86 (s, 1H), 4.84 (d, *J* = 2.2 Hz, 1H), 4.17−4.10 (m, 1H), 3.88 (d, *J* = 9.2 Hz, 1H), 3.78−3.73 (m, 2H), 3.56−3.45 (m, 2H), 3.39−3.31 (m, 2H), 3.08 (s, 1H), 2.56 (s, 1H), 2.07 (dd, *J* = 15.5, 6.1 Hz, 1H), 1.96−1.90 (m, 2H), 1.80 (d, *J* = 4.5 Hz, 1H), 1.46 (d, *J* = 12.1 Hz, 1H), 1.41−1.36 (m, 3H), 1.07 (s, 3H), 0.93−0.84 (m, 3H), 0.41 (s, 3H), 0.35 (s, 3H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 143.7, 139.4, 133.7, 129.1, 128.0, 116.3, 108.2, 80.6, 75.3, 71.8, 64.9, 63.5, 57.1, 53.4, 49.7, 42.2, 39.7, 32.7, 32.1, 21.7, 19.8, 18.7, −0.7, −0.9, −1.7; IR (neat, cm^{-1}) 3450, 2949, 2923, 1428, 1378, 1250, 1111, 1026, 834, 814, 774, 700; HRMS-ESI-TOF calcd for $C_{29}H_{46}O_4NaSi_2$ [M + Na$^+$] 537.2827, found 537.2823.

Synthesis of (2a*S*,2a1*R*,4a*S*,5*R*,7a*S*,8*R*,10*R*,10a*R*)-10-(Dimethyl(phenyl)silyl)-5-methoxy-5,10a-dimethyl-4-methylenedecahydro-1*H*,7*H*-naphtho[1,8-*bc*:4,4*a*−*c*′]difuran-8-ol (68). To a solution of compounds **69** (44 mg, 0.111 mmol) in dry DCM (2.2 mL) were added $MgSO_4$ (22 mg), 2-(trimethylsilyl)ethanol (47 μL, 0.333 mmol), (IPr)AuCl (3.4 mg, 0.0055 mmol), and $AgSbF_6$ (1.9 mg, 0.0055 mmol) at room temperature sequentially. The reaction mixture was stirred for 30 min, and then MeOH (2.2 mL) was added. The reaction mixture was stirred for 1 h and quenched with the saturated $NaHCO_3$ solution (2.5 mL). The aqueous layer was extracted with DCM (3 × 2.5 mL) and dried over Na_2SO_4. The solution was filtered and evaporated under vacuum. The residue was purified by flash chromatography on silica gel (EtOAc/hexane = 1/3) to give compound **78** (4 mg) in 8% yield and compound **68** (31 mg) in 65% yield: ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.53−7.48 (m, 2H), 7.40−7.33 (m, 3H), 4.87 (d, *J* = 0.8 Hz, 1H), 4.84 (d, *J* = 2.2 Hz, 1H), 4.08−4.01 (m, 1H), 3.89 (d, *J* = 9.2 Hz, 1H), 3.75 (d, *J* = 8.0 Hz, 1H), 3.70 (d, *J* = 9.2 Hz, 1H), 3.56−3.50 (m, 1H), 3.34 (d, *J* = 8.0 Hz, 1H), 3.11 (s, 3H), 3.04−2.97 (m, 1H), 2.59 (s, 1H), 2.07 (dd, *J* = 15.5, 6.2 Hz, 1H), 1.95−1.90 (m, 2H), 1.87−1.81 (m, 1H), 1.70−1.64 (m, 1H), 1.45 (d, *J* = 12.1 Hz, 1H), 1.41−1.37 (m, 1H), 1.35 (s, 3H), 1.06 (s, 3H), 0.41 (s, 3H), 0.35 (s, 3H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 143.5, 139.3, 133.7, 129.1, 128.0, 116.4, 108.4, 80.6, 75.2, 71.7, 64.8, 63.1, 53.5, 49.7, 47.2, 42.2, 39.5, 32.7, 32.2, 21.7, 19.0, −0.8, −0.9; IR (neat, cm^{-1}) 3441, 2950, 2884, 1631, 1427, 1378, 1252, 1112, 1026, 892, 833, 816, 701, 471; HRMS-ESI-TOF calcd for $C_{25}H_{36}O_4NaSi$ [M + Na$^+$] 451.2275, found 451.2273.

Synthesis of (2a*S*,2a1*R*,4a*S*,5*R*,7a*S*,10*R*,-10a*R*)-10-(Dimethyl-(phenyl)silyl)-5-methoxy-5,10a-dimethyl-4-methylenedecahydro-7*H*,8*H*-naphtho[1,8-*bc*:4,4*a*−*c*′]difuran-8-one (79). To a solution of compound **68** (26 mg, 0.061 mmol) in dry DCM (1 mL) were added 4 Å molecular sieves (26 mg), NMO (14 mg, 0.122 mmol), and TPAP (2 mg, 0.0061 mmol) at room temperature. The mixture was stirred for 0.5 h and purified by flash chromatography on silica gel (EtOAc/hexane = 1/4) to give compound **79** (21 mg) as a white solid in 81% yield: R_f = 0.83 (silica gel, EtOAc/hexanes = 1/1); ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.47−7.42 (m, 2H), 7.37−7.31 (m, 3H), 4.85 (s, 1H), 4.79 (d, *J* = 0.8 Hz, 1H), 4.16−4.09 (m, 1H), 4.05 (d, *J* = 9.5 Hz, 1H), 3.81−3.77 (m, 2H), 3.45 (d, *J* = 8.0 Hz, 1H), 3.29 (s, 1H), 3.13−3.04 (m, 4H), 2.97−2.90 (m, 1H), 2.48 (dd, *J* = 15.6, 1.5 Hz, 1H), 1.94 (dd, *J* = 15.6, 6.4 Hz, 1H), 1.75 (d, *J* = 11.8 Hz, 1H), 1.67 (dd, *J* = 8.9, 1.4 Hz, 1H), 1.61 (s, 1H), 1.37 (s, 3H), 1.30 (s, 3H), 0.34 (s, 3H), 0.31 (s, 3H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 208.8, 142.2, 138.0, 133.8, 129.4, 128.2, 117.2, 109.1, 80.0, 71.2, 68.0, 57.5, 57.1, 55.0, 47.4, 42.0, 39.0, 36.9, 34.5, 21.6, 18.7, −1.8, −2.0; IR (neat, cm^{-1}) 2956, 2937, 1705, 1378, 1261, 1111, 1049, 1023, 817; HRMS-ESI-TOF calcd for $C_{25}H_{34}O_4NaSi$ [M + Na$^+$] 449.2119, found 449.2117. Melting range of crystal: 104.9−105.8 °C.

Synthesis of (2a*S*,2a1*R*,4a*S*,5*R*,7a*S*,8*S*,10*R*,10a*R*)-10-(Dimethyl(phenyl)silyl)-5- methoxy-5,10a-dimethyl-4-methylenedecahydro-1*H*,7*H*-naphtho[1,8-*bc*:4,4*a*−*c*′]difuran-8-ol (80). To a solution of compound **79** (20 mg, 0.047 mmol) in MeOH/THF (0.8/0.2 mL) was added $NaBH_4$ (2.7 mg, 0.07 mmol) at −10 °C. The mixture was stirred for 15 min at −10 °C and 15 min at room temperature, after which time it was quenched with the saturated NH_4Cl solution (2 mL). The aqueous layer was extracted with ethyl acetate (3 × 2 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated under vacuum. The residue was purified by flash chromatography on silica gel (EtOAc/hexane = 1/4) to give compound **80** (14 mg) as a white solid in 70% yield: R_f = 0.48 (silica gel, EtOAc/hexanes = 1/4); ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.56−7.50 (m, 2H), 7.38−7.32 (m, 3H), 4.93−4.87 (m, 2H), 4.09−4.01 (m, 1H), 3.88 (d, *J* = 8.0 Hz, 1H), 3.81 (d, *J* = 9.2 Hz, 1H), 3.68 (dd, *J* = 6.0, 2.9 Hz, 1H), 3.46 (d, *J* = 9.2 Hz, 1H), 3.37 (d, *J* = 8.0 Hz, 1H), 3.12 (s, 3H), 3.09−3.00 (m, 1H), 2.69 (s, 1H), 2.19 (dd, *J* = 15.7, 6.4 Hz, 1H), 2.14−2.06 (m, 1H), 1.97 (d, *J* = 12.2 Hz, 1H), 1.86−1.80 (m, 1H), 1.73 (d, *J* = 3.7 Hz, 1H), 1.41−1.34 (m, 4H), 1.05 (s, 3H), 0.43 (s, 3H), 0.38 (s, 3H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 145.0,

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J. Org. Chem. 2016, 81, 751−771

140.8, 133.9, 128.7, 127.8, 115.2, 108.6, 81.0, 72.9, 72.0, 69.1, 61.8, 48.9, 47.4, 47.1, 42.1, 39.6, 30.7, 29.7, 21.5, 19.2, −1.1, −1.2; IR (neat, cm^{-1}) 3420, 2942, 2895, 1377, 1250, 1105, 1078, 1041, 1026, 890, 815, 702, 423; HRMS-ESI-TOF calcd for $C_{25}H_{36}O_4NaSi$ [M + Na^+] 451.2275, found 451.2274.

Synthesis of (2a*S*,2a1*S*,4a*S*,5*R*,7a*S*,8*S*,10*R*,10a*R*)-5-Methoxy-5,10a-dimethyl-4-methylenedecahydro-1*H*,7*H*-naphtho[1,8-*bc*:4,4a−*c*′]difuran-8,10-diol (81). To the liquid ammonia (1 mL) was added Na (13 mg, 0.56 mmol) at −78 °C. The reaction mixture was stirred for 5 min. Then a solution of compound **80** (24 mg, 0.056 mmol) in dry THF (1 mL) was added dropwise. After being stirred for 2 min, the reaction mixture was quenched with a saturated NH_4Cl solution (2 mL). The aqueous layer was extracted with ethyl acetate (3 × 2 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated under vacuum to afford the crude product.

To a solution of the above crude product in THF (0.8 mL) was added TBAF solution (1.0 M in THF, 0.123 mL, 0.123 mmol) at room temperature. The mixture was stirred for 1 h, after which time MeOH (0.4 mL), $KHCO_3$ (8.4 mg, 0.084 mmol), and 30% H_2O_2 solution (63 μL, 0.56 mmol) were added. The mixture was stirred for 5 h and quenched with the saturated $Na_2S_2O_3$ solution (2 mL). The aqueous layer was extracted with ethyl acetate (3 × 2 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated under vacuum. The residue was purified by flash chromatography on silica gel (EtOAc/hexane = 3/2) to give compound **81** (17 mg) as a white solid in 98% overall yield for two steps: R_f = 0.19 (silica gel, EtOAc/hexanes = 1/1); ^{1}H NMR (500 MHz, CD_2Cl_2) δ 4.95−4.90 (m, 2H), 4.18−4.10 (m, 1H), 3.97 (d, *J* = 7.3 Hz, 1H), 3.94−3.89 (m, 1H), 3.80 (d, *J* = 9.2 Hz, 1H), 3.78−3.73 (m, 1H), 3.50 (d, *J* = 7.3 Hz, 1H), 3.40 (d, *J* = 9.2 Hz, 1H), 3.18−3.04 (m, 6H), 2.80 (s, 1H), 2.28 (dd, *J* = 15.9, 5.8 Hz, 1H), 2.22 (d, *J* = 12.3 Hz, 1H), 2.11−2.00 (m, 2H), 1.38 (s, 3H), 0.94 (d, *J* = 0.5 Hz, 3H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 144.9, 115.5, 108.6, 76.0, 73.9, 72.1, 71.9, 68.3, 61.4, 49.0, 47.1, 44.2, 42.1, 39.2, 33.5, 19.0, 18.4; IR (neat, cm^{-1}) 3390, 2925, 2830, 1456, 1377, 1144, 1106, 1078, 1044, 1025, 883; HRMS-ESI-TOF calcd for $C_{17}H_{26}O_5Na$ [M + Na^+] 333.1673, found 333.1672.

Synthesis of (2a*R*,2a1*S*,4*R*,4a*S*,5*R*,7a*S*,8*S*,10*R*,10a*R*)-5-Methoxy-4,5,10a-trimethyl-3-oxodecahydro-1*H*,7*H*-naphtho[1,8-*bc*:4,4a−*c*′]difuran-8,10-diyl Diacetate (16). To a solution of compound **81** (7.6 mg, 0.025 mmol) in dry DCE (1 mL) were added Ac_2O (12 μL, 0.125 mmol) and DMAP (22 mg, 0.175 mmol) at room temperature. The mixture was stirred at 90 °C for 12 h and quenched with the saturated NH_4Cl solution (1.5 mL). The aqueous layer was extracted with DCM (2 × 1.5 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated under vacuum. The residue was purified by flash chromatography on silica gel (EtOAc/hexane = 1/2) to give crude compound.

To a solution of above crude compound in dry DCM (0.7 mL) were added SeO_2 (14 mg, 0.125 mmol) and ^{t}BuOOH solution (5.5 M in decane, 45 μL, 0.25 mmol) at room temperature. The mixture was stirred for 4.5 h and quenched by filtration through a Celite pad, which was washed with EtOAc/hexane = 1/2. The solvent was evaporated off.

To a solution of the above crude product in dry DCM (0.7 mL) were added 4 Å molecular sieves (10 mg), NMO (5.8 mg, 0.05 mmol), and TPAP (1 mg, 0.0025 mmol) at room temperature. The mixture was stirred for 1 h and quenched by filtration through a Celite pad that was washed with EtOAc/hexane = 2/1. The solvent was evaporated to dryness.

To a solution of the above crude product in MeOH/THF (0.3 mL/0.3 mL) was added Pd/C (10% on carbon, 2.5 mg) in one portion, and then the solution was degassed H_2 five times. The mixture was stirred for 45 min at room temperature and quenched by filtration through a Celite pad, which was washed with EtOAc. The solvent was evaporated under vacuum, and the residue was purified by flash chromatography on silica gel (EtOAc/hexane = 1/1) to give compound **16** (5.5 mg) as a white solid in 55% overall yield in four steps: R_f = 0.21 (silica gel, EtOAc/hexanes = 1/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.98−4.94 (m, 2H), 4.14 (d, *J* = 14.3 Hz, 1H), 3.80 (d, *J* = 9.6 Hz, 1H), 3.66 (d, *J* = 3.0 Hz, 2H), 3.55 (d, *J* = 9.6 Hz, 1H), 3.11 (s, 3H), 2.84 (d, *J* = 14.3 Hz, 1H), 2.37 (d, *J* = 16.7 Hz, 1H), 2.23 (d, *J* = 6.2 Hz, 1H), 2.12−2.01 (m, 9H), 1.45 (s, 3H), 1.26 (d, *J* = 6.8 Hz, 4H), 1.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.3, 170.2, 170.0, 107.0, 77.9, 75.3, 74.0, 71.3, 67.2, 57.3, 47.7, 46.9, 43.2, 42.7, 41.7, 29.6, 21.49, 21.2, 21.0, 18.5; IR (neat, cm^{-1}) 2920, 2850, 1732, 1377, 1254, 1043, 888, 763, 750; HRMS-ESI-TOF calcd for $C_{21}H_{30}O_8Na$ [M + Na^+] 433.1833, found 433.1832; $[\alpha]^{26}_{589}$ −44.7 (*c* = 0.25, $CHCl_3$).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02560.

X-ray data for compound **20a** (CIF)
X-ray data for compound **40** (CIF)
X-ray data for compound **49a** (CIF)
X-ray data for compound **64** (CIF)
X-ray data for compound **79** (CIF)
Detailed experimental procedures, compound characterization data, and complete ref 2e (PDF)

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Notes

The authors declare no competing financial interest.

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