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An Intramolecular Diels−Alder Strategy for the Asbestinins: Enantioselective Total Syntheses of 11-Acetoxy-4-deoxyasbestinin D and Asbestinin-12

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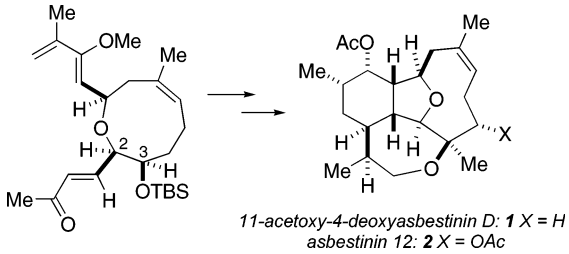


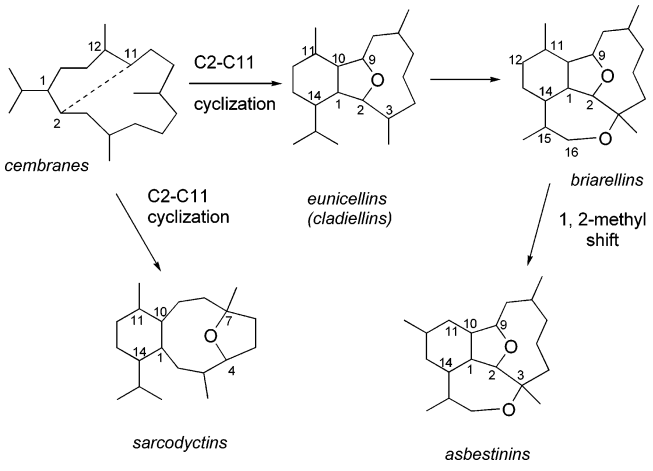
*11-acetoxy-4-deoxyasbestinin D: **1** X = H*
*asbestinin 12: **2** X = OAc*

The enantioselective total syntheses of 11-acetoxy-4-deoxyasbestinin D and asbestinin-12 have been completed. A glycolate aldol reaction provided a diene useful for ring-closing metathesis to form an oxonene, which was ultimately employed as a template to execute a highly stereoselective intramolecular Diels−Alder cycloaddition, forming the hydroisobenzofuran moiety. The absolute configuration of the asbestinin subclass was confirmed via these synthetic efforts.

Introduction

The C2−C11-cyclized cembranoids are secondary metabolites of gorgonian octocoral, which include the eunicellins (also known as the cladiellins), briarellins, asbestinins, and sarcodyctins. Cyclization of the cembranoid diterpene skeleton has been postulated as the biosynthetic origin of these four subclasses of marine diterpenes (Scheme 1).[1] The presence of an oxygen bridge from C4 to C7 differentiates the sarcodyctins from the three other classes which possess a C2−C9 oxygen bridge. The briarellins and asbestinins, unlike the cladiellins, feature an oxepane ring, which results from an oxygen bridge from C3 to C16, forming a tetracyclic core. The asbestinins arise from a suprafacial 1,2-methyl shift from C11 to C12 of the briarellins, rendering this subclass the furthest evolved from the original cembranoid structure in the proposed biosynthesis.

SCHEME 1. Proposed Biosynthetic Pathway of the C2−C11-Cyclized Cembranoids



(1) For reviews, see: (a) Rodríguez, A. D. *Tetrahedron* **1995**, *51*, 4571. (b) Bernardelli, P.; Paquette, L. A. *Heterocycles* **1998**, *49*, 531. (c) Sung, P.-J.; Chen, M.-C. *Heterocycles* **2002**, *57*, 1705.

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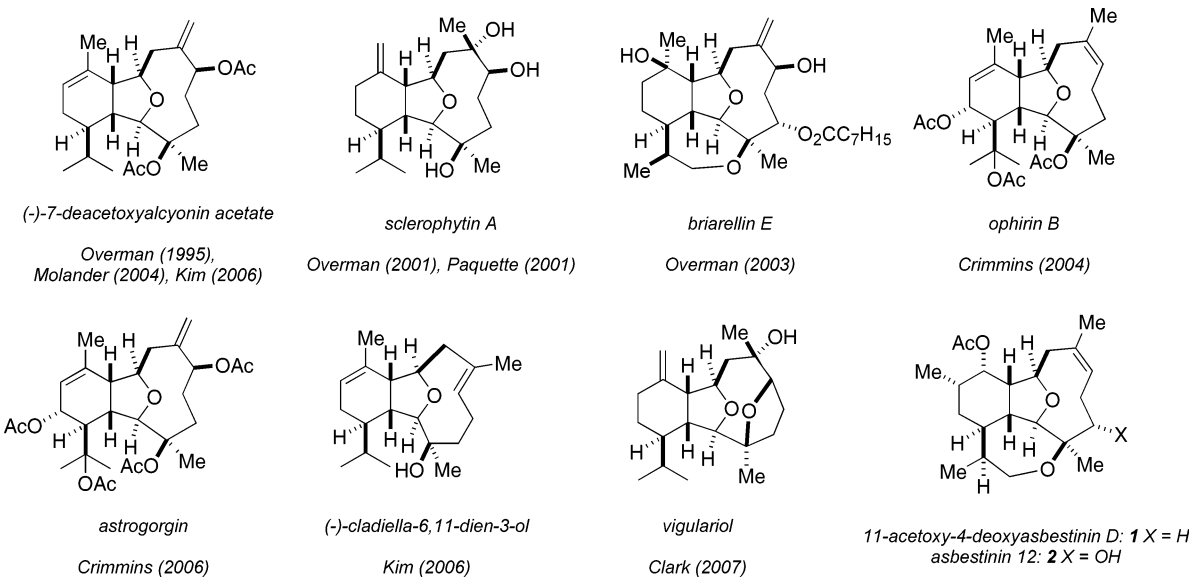

FIGURE 1. C2−C11 cyclized cembranoid natural products prepared via total synthesis.

Intense efforts from the synthetic community over the past decade have been directed toward the C2−C11-cyclized cembranoids, and several total syntheses have resulted. Overman reported the first total synthesis of a cladiellin, (−)-7-deacetoxyalcyonin acetate, in 1995 (Figure 1) based on a novel Prins−pinacol rearrangement to construct the hydroisobenzofuran unit.[2] Several years later, the Molander group divulged a strategically different approach to this same molecule.[3] The Paquette and Overman groups detailed concurrent efforts toward sclerophytin A, resulting in a structural reassignment and ultimately the total synthesis of the corrected structure.[4] The Overman group also reported the first and only total syntheses of members of the briarellin subclass in 2003, briarellins E and F.[5] Each of the above approaches relied upon initial formation of the hydroisobenzofuran unit, followed by formation of the oxonene portion of the molecules at a late stage of the synthesis.

We have recently developed a general approach for the construction of seven-,[6] eight-,[7] and nine-membered rings[8] by exploiting acyclic conformational constraints to facilitate ring-closing metathesis for the formation of medium ring ethers. This strategy has been expanded to a novel approach to the eunicellin diterpenes which relies upon initial construction of the oxonene ring via a ring-closing metathesis, followed by construction of the hydroisobenzofuran moiety via a highly selective intramolecular Diels−Alder cycloaddition. The total syntheses of two cladiellin natural products, ophirin B and astrogorgin, have been accomplished using this approach.[9] Very recently, Kim and coworkers have utilized a very similar intramolecular Diels−Alder strategy to prepare several cladiellins, which contain or are derived from an *E*-oxonene.[10] In 2007, Clark reported a synthesis of vigulariol featuring formation of the cyclohexene unit through an intermolecular Diels−Alder cycloaddition.[11]

Until recently, the asbestinins were the only subclass of C2−C11 cyclized cembranoid natural products which had not been prepared by chemical synthesis.[12] 11-Acetoxy-4-deoxyasbestinin D (**1**)[13] and asbestinin-12 (**2**)[14] feature a captivating molecular topography, including 9 and 10 contiguous stereocenters, respectively, as well as a fully substituted tetrahydrofuran. Our interest in the asbestinin subclass was further strengthened by the intriguing biological properties displayed by some members of this family.[1] 11-Acetoxy-4-deoxyasbestinin D (**1**) demonstrates cytotoxicity against CHO-K1 cells (ED_{50} = 4.82 μg/mL) as well as strong antimicrobial activity against *Klebsiella pneumoniae*.[13] Additionally, while it seemed likely that the absolute configuration of the asbestinins followed the cladiellins and briarellins, some question regarding the absolute configuration of the asbestinins existed in the literature, in part because no member of the asbestinin subclass had been prepared by total synthesis.[1] We report herein a full account of the approach developed for the asbestinin subclass, and the application of this strategy to the total syntheses of 11-acetoxy-4-deoxyas-

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(3) Molander, G. A.; St. Jean, D. J., Jr.; Haas, J. *J. Am. Chem. Soc.* **2004**, *126*, 1642.
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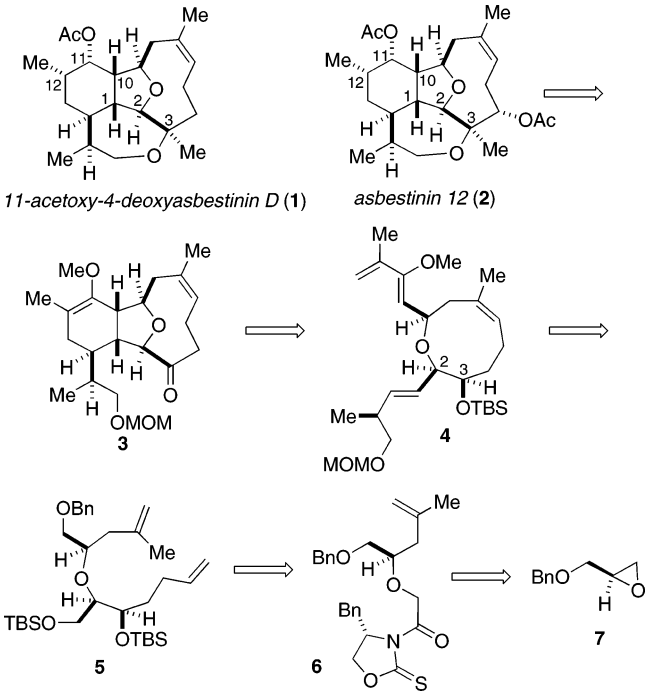
SCHEME 2. Retrosynthetic Analysis



bestinin D (**1**) and asbestinin-12 (**2**), serving to confirm the absolute configuration of this family of natural products.

Strategically, ketone **3** was targeted as a point of divergence for the syntheses of 11-acetoxy-4-deoxyasbestinin D (**1**) and asbestinin-12 (**2**) (Scheme 2). The desire to apply the previously developed Diels−Alder strategy used for the eunicellins to complete the first total synthesis of a member of the asbestinin subclass of natural products resulted in selection of tetraene **4** as the Diels−Alder substrate. Tetraene **4** would be prepared from diene **5** by ring-closing metathesis followed by further functionalization. While construction of the diene metathesis substrate for the ophirin B and astrogorgin syntheses was accomplished through the use of an asymmetric glycolate alkylation as the key step,[7a,9,15] the strategy for the synthesis of diene **5** hinged upon the development and application of an asymmetric glycolate aldol reaction to establish the ether linkage stereochemistry of the oxonene precursor.[16] The required thioimide **6** for the aldol reaction would be prepared from (*R*)-benzyl glycidyl ether (**7**).

Tetraene **4** was an attractive Diels−Alder substrate in that it would incorporate the required stereochemistry of the C15 methyl group prior to the Diels−Alder reaction. While the 2,3-substitution on the diene was viewed as a potential problem with regard to the ability of the diene to adopt the required s-cis conformation, and the electronic character of the dienophile was less than optimal, the facility of the Diels−Alder reaction in the ophirin synthesis[9] provided optimism for the success of the Diels−Alder reaction of tetraene **4**. Thus, we set out to prepare tetraene **4** and investigate its performance in the designed cycloaddition.

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Results and Discussion

The synthesis of glycolate **6** began with the addition of 2-propenylmagnesium bromide to (*R*)-benzyl glycidyl ether (**7**) to provide a secondary alcohol **8**,[17] which was O-alkylated with sodium bromoacetate (Scheme 3). Standard formation of glycolate **6** was accomplished by coupling of the resultant glycolic acid **9** with (*S*)-4-benzyloxazolidinethione using *N*,*N*′-dicyclohexylcarbodiimide. Alternatively, the oxazolidinone variant **10** of glycolate **6** was formed by acylation of the mixed anhydride of the glycolic acid with lithiated (*S*)-4-benzyloxazolidinone to provide glycolate **10**. Concurrent with these efforts, an improved procedure for asymmetric glycolate aldol reactions was being developed in our laboratory.[16d] As part of this program, a variety of conditions were explored to determine the optimal protocol for effecting the addition of pent-4-enal[18] to each of these glycolyl imides. Ultimately, it was determined that the ideal conditions for each of these reactions involved initial formation of the chlorotitanium enolate of the glycolate, followed by addition of *N*-methylpyrrolidinone 10 min prior to addition of the aldehyde. As has been observed previously in our laboratory, imide **10** provided a slightly higher yield (78%) but lower diastereoselectivity (10:1 dr) than the corresponding thioimide **6** (70%, >19:1 dr).[7c] For our purposes, we chose to proceed using thioimide adduct **11** since the minor diastereomer was not observed by ^{1}H NMR, facilitating purification of the desired product.

With the desired diene **11** in hand, the key ring-closing metathesis reaction was examined. Upon subjecting thioimide **11** to the Grubbs second-generation catalyst in refluxing CH_2Cl_2,[19] only dimer **13** was obtained (Scheme 3). Similarly, diol **14**, obtained by reduction of thioimide **11**, provided dimer **15** as the major product under the same conditions. However, protection of the secondary alcohol as the *tert*-butyldimethylsilyl ether and reduction of the chiral auxiliary provided diene **16**, which underwent smooth formation of oxonene **17** in the presence of the Grubbs catalyst $[Cl_2(Cy_3P)(IMes)Ru{=}CHPh]$. Similarly, reduction of the thioimide **11** and protection of the diol as the corresponding bis-*tert*-butyldimethylsilyl ether provided diene **5**, which yielded the desired oxonene **18** in 99% yield using ring-closing metathesis conditions. Importantly, it was discovered that increasing the concentration of diene **5** in CH_2Cl_2 from 2 to 10 mM provided a much more scalable and a higher yielding reaction without competitive dimerization.

With the crucial oxonene in hand, formation of the diene and dienophile necessary for the Diels−Alder reaction was examined. Oxidation of alcohol **17** provided an aldehyde **19**, which was hoped to be useful in an olefination reaction to install the dienophile with the stereocenter at C15 already in place (Scheme 4).[20] A number of reactions were attempted for this olefination, including a Schlosser−Wittig reaction,[21] a Julia−Kocienscki olefination,[22] as well as a cross-metathesis reaction using the

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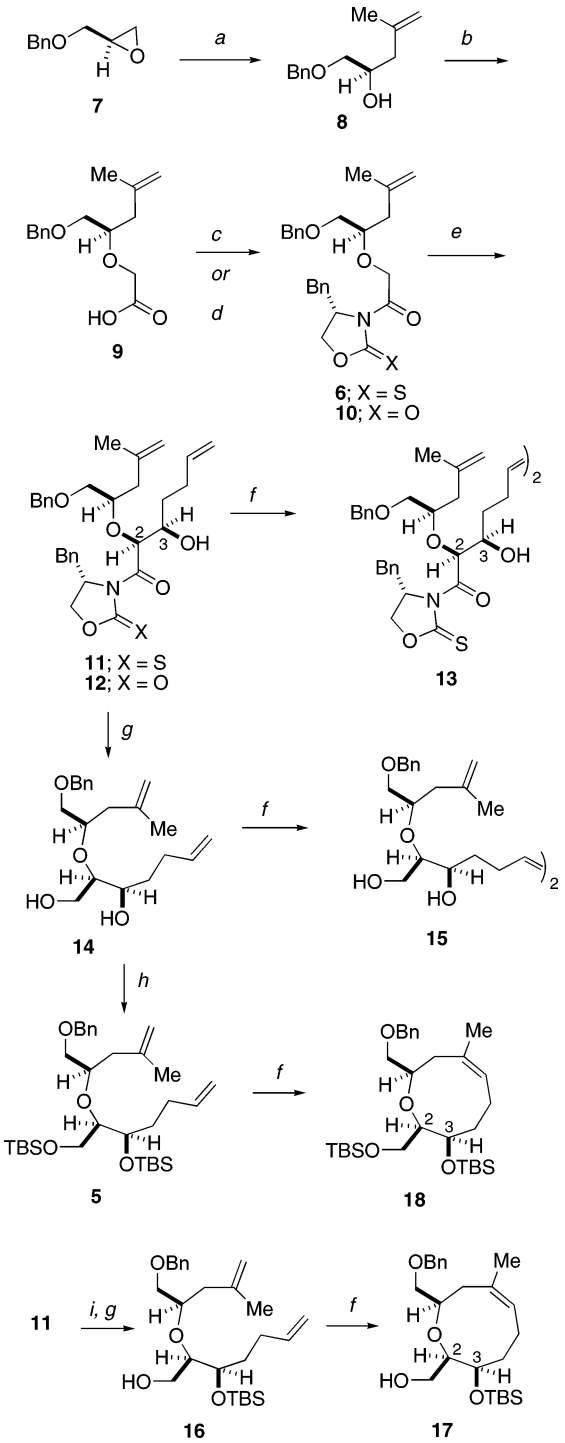
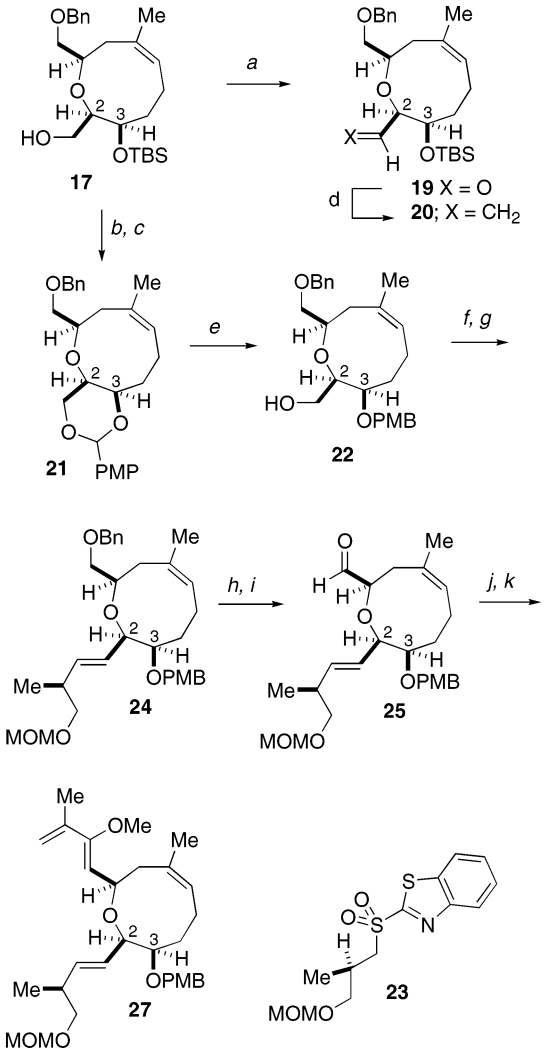
SCHEME 3. Synthesis of the Oxonene[a]



[a] Conditions: (a) $CH_2{=}C(CH_3)MgBr$, CuI, THF, −40 °C, 99%; (b) NaH, $BrCH_2CO_2H$, THF, DMF, 95%; (c) (*S*)-benzyl-1,3-oxazolidine-2-thione, DCC, DMAP, CH_2Cl_2, 86%; (d) Me_3CCOCl, Et_3N, THF, −78 to 0 °C; (*S*)-lithio-4-benzyloxazolidin-2-one, 95% (e) $TiCl_4$, *i*-Pr_2NEt, NMP, pent-4-enal, CH_2Cl_2, −78 °C, X = S: 70%, >19:1 dr, X = O: 78%, 10:1 dr; (f) $Cl_2(Cy_3P)(IMes)Ru{=}CHPh$, CH_2Cl_2, 40 °C; (g) $LiBH_4$, MeOH, Et_2O, 0 °C, 95%; (h) TBSCl, imid., DMAP, DMF, 50 °C, 87%; (i) TBSOTf, 2,6-lutidine, CH_2Cl_2, 96%.

alkene **20** derived from aldehyde **19** through a methylene Wittig reaction.[23] However, none of these reactions effectively installed the dienophile. At this point, it was speculated that the steric effect of the C3 *tert*-butyldimethylsilyl ether was precluding

SCHEME 4. Attempted Unactivated Intramolecular Diels−Alder Cycloaddition[a]



[a] Conditions: (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 to 0 °C, 92%; (b) *n*-Bu_4NF, THF, 85%; (c) *p*-anisaldehyde dimethyl acetal, PPTS, DMF, 84%; (d) Ph_3PCH_3Br, *t*-BuOK, THF, 0 °C, 81%; (e) *i*-Bu_2AlH, CH_2Cl_2, 0 °C, 89%; (f) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 to 0 °C; 91%; (g) sulfone **23**, KHMDS, THF, −78 to +25 °C, 69%; (h) LDBB, THF, −78 °C, 78%; (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 to 0 °C, 91%; (j) $Ph_3P{=}C(OMe)C(O)Me$ (**26**), C_6H_6, 80 °C, 79%; (k) Ph_3PCH_3Br, KO-*t*-Bu, THF, 0 °C, 86%.

reaction at C1. The TBS ether was replaced by a *p*-methoxybenzyl ether by removal of the silyl ether from alcohol **17**, followed by formation of the *p*-methoxybenzylidene acetal **21**. Regioselective reduction of the acetal provided alcohol **22**, which was oxidized to the aldehyde under Swern conditions.[20] A Julia−Kocienscki olefination on the aldehyde using sulfone **23** provided the desired dienophile **24**.[22] Attention was then turned to the installation of the diene. A reductive cleavage of the benzyl ether in the presence of the *p*-methoxybenzyl ether was accomplished using lithium di-*tert*-butyldiphenylide, and the resultant alcohol was oxidized[20] to aldehyde **25**. Two sequential Wittig olefinations provided the desired tetraene **27**.[24]

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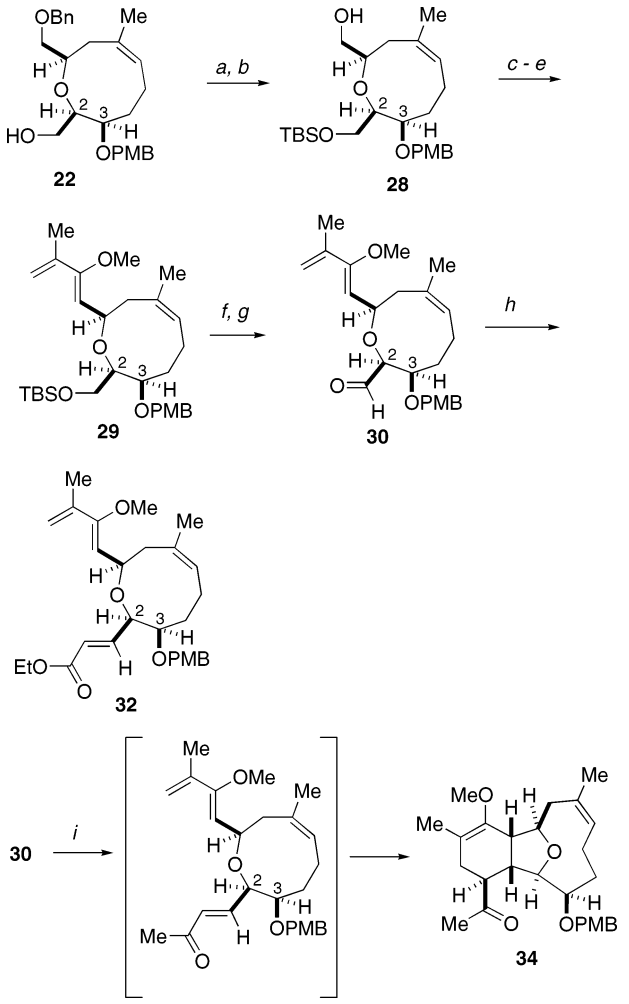
SCHEME 5. Intramolecular Diels−Alder Cycloaddition[a]



[a] Conditions: (a) TBSCl, imid., DMAP, CH_2Cl_2, 96%; (b) LDBB, THF, −78 °C, 79%; (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 to 0 °C, 90%; (d) $Ph_3P{=}C(OMe)C(O)Me$ (**26**), $PhCH_3$, 110 °C, 86%; (e) Ph_3PCH_3Br, KO-*t*-Bu, THF, 0 °C, 73%; (f) *n*-Bu_4NF, THF, 89%; (g) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 to 0 °C, 86%; (h) $Ph_3P{=}CHCO_2Et$ (**31**), $PhCH_3$, 80 °C, 91%; (i) $Ph_3P{=}CHC(O)Me$ (**33**), $PhCH_3$, 110 °C, 71%.

Unfortunately, upon subjecting tetraene **27** to a variety of conventional thermal and microwave conditions, none of the desired intramolecular Diels−Alder cycloadduct was observed. At least two possible sources were postulated for the observed low reactivity. First, the 2,3-disubstituted diene hinders the rotation of the C11−C12 carbon−carbon bond due to the eclipsing interaction present in the necessary s-cis conformation of the diene. Second, the dienophile is significantly reduced in reactivity (compared to the dienophile in the cladiellin series Diels−Alder reactions)[9] because of the absence of an electron-withdrawing group.

A more activated dienophile, still possessing the 2,3-disubstituted diene, was constructed to determine whether the low reactivity was due to the diene or the dienophile. To this end, alcohol **22** was protected as its *tert*-butyldimethylsilyl ether, and the benzyl ether was reductively removed to give alcohol **28** (Scheme 5). Oxidation of the primary alcohol to the aldehyde under Swern conditions[20] followed by two sequential Wittig reactions, the first with a stabilized ylide [$Ph_3P{=}C(OMe)C(O)$-Me] (**26**)[24] and the second with methylentriphenylphosphorane, provided triene **29**. Following deprotection of the silyl ether,

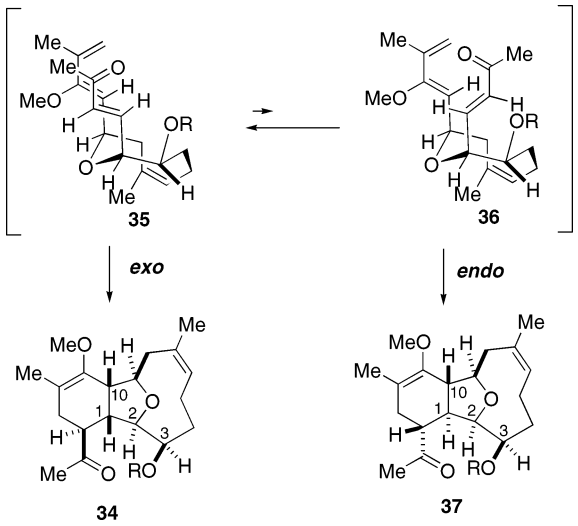


FIGURE 2. Proposed Diels−Alder reaction selectivity models.

the resultant alcohol was oxidized using Swern conditions to yield aldehyde **30**.[20] Aldehyde **30** was treated with two separate stabilized ylides to provide the corresponding enoate and enone. After 1 h in refluxing benzene in the presence of [(ethoxycarbonyl)methylene]triphenylphosphorane (**31**),[25] enoate **32** was isolated. However, using (acetylmethylene)triphenylphosphorane (**33**),[26] intramolecular Diels−Alder cycloaddition ensued under the conditions of the Wittig reaction to provide the desired tricycle **34** (76%, 4:1 dr) favoring the exo-diastereomer. Encouraged by this result, we set out to improve the diastereoselectivity of this transformation and streamline the synthesis of the Diels−Alder precursor. Based upon the studies of the Diels−Alder reaction in ophirin B,[9] as well as data reported by Holmes and co-workers,[27] it was speculated that the C3 configuration as well as the size of the C3 protecting group would significantly influence the diastereoselectivity observed in the cycloaddition. These results were rationalized using the selectivity models **35** and **36** (Figure 2). As the size of R increases, the steric interaction between the C14 vinyl proton and R increases, resulting in an increase in energy of the endo transition state therefore increasing the proportion of the exo Diels−Alder adduct **34**. Seeking to improve the diastereoselectivity of the cycloaddition, as well as shorten the overall synthesis, the installation of a bulky trialkylsilyl group at C3 of the Diels−Alder precursor seemed the most direct path forward.

Utilizing oxonene **18** (prepared in seven steps from (*R*)-benzyl glycidyl ether), a dissolving metal reduction provided the primary alcohol **38** (Scheme 6). Swern oxidation[20] and two successive Wittig olefinations as described for diene **29** above[24] efficiently provided triene **39**. At this point, a variety of conditions were examined for the selective deprotection of the primary silyl ether in the presence of the acid-sensitive enol ether. An assortment of different buffered hydrogen fluoride conditions provided the primary alcohol with concomitant hydrolysis of the enol ether to provide enone **40**.[28] Neither

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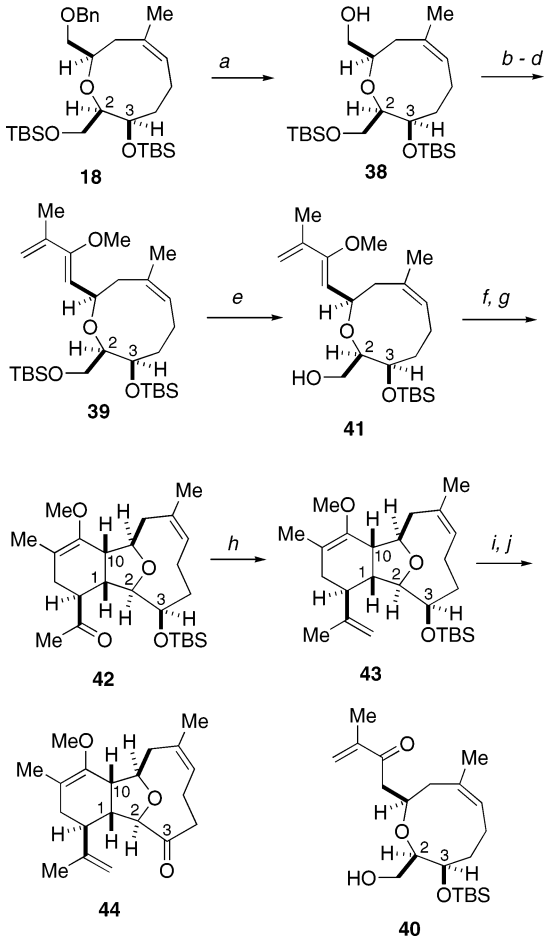
SCHEME 6. Synthesis of the Common Ketone Intermediate[a]



[a] Conditions: (a) Na, NH_3, THF, −78 °C, 86%; (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 to 0 °C, 94%; (c) $Ph_3P{=}C(OMe)C(O)Me$ (**26**), $PhCH_3$, 110 °C, 84%; (d) Ph_3PCH_3Br, KO-*t*-Bu, THF, 0 °C, 87%; (e) NH_4F, MeOH, 79%; (f) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 to 0 °C, 93%; (g) $Ph_3P{=}CHC(O)Me$ (**31**), $PhCH_3$, 110 °C, 80%; (h) Ph_3PCH_3Br, KO-*t*-Bu, THF, 85%; (i) *n*-Bu_4NF, THF, 95%; (j) Dess−Martin periodinane, pyridine, CH_2Cl_2, 98%.

alkaline conditions nor tetrabutylammonium fluoride were selective in removing the primary silyl ether, even at low temperature. Eventually, it was found that treatment of triene **39** with ammonium fluoride in methanol provided the desired alcohol **41** in 79% yield (91% brsm).[29] Swern oxidation[20] of the alcohol and treatment of the resultant aldehyde with (acetylmethylene)triphenylphosphorane (**33**)[26] triggered a rapid in situ intramolecular Diels−Alder cycloaddition to provide the desired tricycle **42** in good yield, as a single observable diastereomer, further supporting the proposed selectivity models (vide supra).

With an effective route to tricycle **42** in hand, a sequence for establishing the C15 stereocenter needed to be determined. A substrate-controlled diastereoselective hydroboration/oxidation of the corresponding 1,1-disubstituted olefin was envisioned to accomplish this goal. To this end, methylenation of ketone **42** provided the triene **43** (Scheme 6). Functionalization of the oxonene ring was next accomplished via a deprotection and oxidation at C3 to provide ketone **44**,[30] the divergence point in the syntheses of 11-acetoxy-4-deoxyasbestinin D and asbestinin-12. A suitable crystal for X-ray crystallographic analysis of ketone **44** was obtained (see the Supporting Information). We were encouraged to find that the configuration of the five stereocenters established to this point matched the desired configurations for the asbestinins. Previous two-dimensional NMR data (COSY, NOESY) analysis had led us to speculate that the oxonene of the tricyclic portion of the cladiellins and asbestinins existed in a concave conformation. This was also apparent in the solid-state conformation of ketone **44**. Encouraged by the prospect of operating stereoselectively on this concave ketone **44**, alkylation with methylmagnesium chloride provided the tertiary alcohol **45** as a single diastereomer (Scheme 7). Hydrolysis of the enol ether provided the α-methyl ketone **46**. It was determined by two-dimensional NMR analysis that the undesired configuration at C12 was the major product of this reaction. Fortunately, facile epimerization of the C12 configuration was accomplished using sodium methoxide, and the two diastereomers **46** and **47** were trivially separated via flash column chromatography. While the thermodynamic ratio of **46**:**47** was only 1:1.2, ketone **46** could be easily recycled and an 85% yield of ketone **47** was obtained after two recycles. Treatment of the ketone **47** with L-Selectride provided a single diastereomer of the secondary alcohol, and selective esterification of the secondary alcohol provided acetate **48**.

The stage was set for our proposed substrate-controlled stereoselective hydroboration of the 1,1-disubstituted olefin. Much precedent exists in the literature involving similar highly stereoselective reactions in less conformationally restricted substrates.[31] Treatment of diene **48** with 9-BBN chemoselectively and regioselectively provided the primary alcohol upon oxidation, however, the diastereoselectivity (∼1:1 dr) observed for the reaction was poor (Scheme 7). Seeking to improve this selectivity, we hoped to install a C3 protecting group in an attempt to impede borane addition from the undesired face of the alkene. Installation of a trimethylsilyl ether at C3 and regioselective hydroboration of the 1,1-disubstituted alkene provided the desired alcohol as the major product, but still with low diastereoselectivity (1.7:1 dr). Increasing the steric bulk at C3 further, the triethylsilyl analogue **49** was prepared and treated with 9-BBN to provide the alcohol (80%, 2.2:1 dr). A *tert*-butyldimethylsilyl ether provided identical diastereoselectivity to the triethylsilyl variant. A triisopropylsilyl ether could not be installed at C3 presumably due to the sterically crowded environment of the tertiary alcohol that is likely oriented inside the concave face of the tricycle. Not satisfied with the stereoselectivity obtained using 9-BBN, we turned our attention to a chiral hydroborating reagent. While 1,1-disubstituted olefins are generally poor substrates for reagent-controlled stereoselective hydroboration reactions, upon treatment with (+)-diisopinocampheylborane, followed by oxidative workup, a single diastereomer of the primary alcohol **50** was obtained.[32] To our knowledge, this stands as only the second example of the use of (+)-diisopinocampheylborane for a highly diaste-

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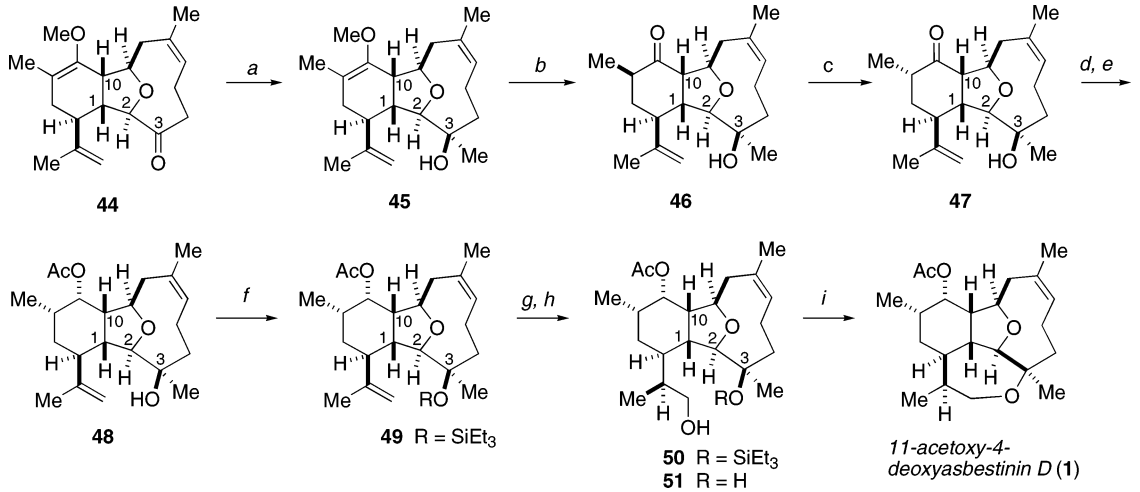
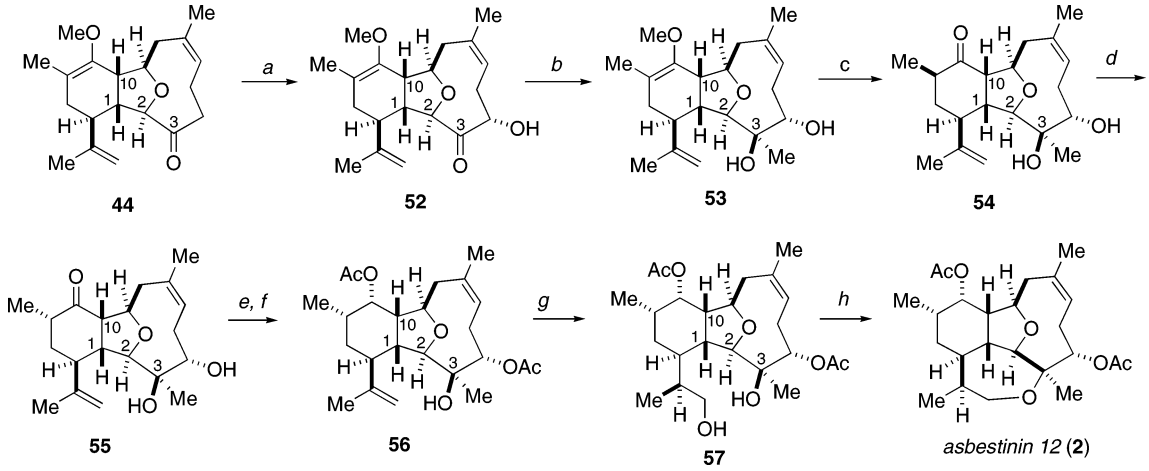
SCHEME 7. Completion of 11-Acetoxy-4-deoxyasbestinin D[a]



[a] Conditions: (a) MeMgCl, THF, 0 °C, 98%; (b) HCl, $CHCl_3$, 96%, **46**:**47** = 10:1 dr; (c) NaH, MeOH, 99%, **46**:**47** = 1:1.2 dr; (d) L-Selectride, THF, −78 °C, 94%; (e) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 99%; (f) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 80%; (g) (+)-Ipc_2BH, THF; NaOH, H_2O_2; (h) *n*-Bu_4NF, THF, 64% (two steps); (i) Tf_2O, 2,6-lutidine, $CHCl_3$, 0−25 °C, 66%.

SCHEME 8. Completion of Asbestinin-12[a]



[a] Conditions: (a) Davis oxaziridine, KHMDS, THF, −78 °C, 84%; (b) MeMgCl, THF, 0 °C, 83%; (c) HCl, $CHCl_3$, 99%, 11:1 dr; (d) NaH, MeOH, 99%, 1:1.4 dr; (e) L-Selectride, THF, −78 °C, 94%; (f) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 85%; (g) (+)-Ipc_2BH, THF; $NaBO_3$, 74%; (h) Tf_2O, 2,6-lutidine, $CHCl_3$, 0−25 °C, 69%.

reoselective hydroboration of a 1,1-disubstituted olefin.[33] Due to difficulties encountered in separating the primary alcohol from the isopinocampheol byproduct, the C3 protecting group was removed using *n*-Bu_4NF to provide the diol **51** in 64% over two steps. Utilizing conditions employed by Overman in the syntheses of briarellins E and F,[5] the primary triflate was formed and an in situ etherification ensued to provide 11-acetoxy-4-deoxyasbestinin D (**1**) along with recovered diene **48** as a result of elimination of the primary triflate. Spectroscopic data for synthetic **1** matched the reported data for the natural product in all regards.[13] The optical rotation for the synthetic and natural materials were identical when measured under the same conditions.

For asbestinin-12 (**2**),[14] we again hoped to exploit the inherent concavity of ketone **44** to perform a diastereoselective transformation. This time, an α-hydroxylation of the potassium enolate of ketone **44** using Davis oxaziridine provided the alcohol **52** as a single diastereomer (Scheme 8).[34] Treatment of the ketone with methylmagnesium chloride as before provided the diol **53**. Hydrolysis again provided the undesired C12 configuration of ketone **54** as the major product. Epimerization under alkaline conditions gave the desired C12 methyl configuration **55**. A single diastereomeric triol was obtained upon reduction of ketone **55** with L-Selectride, whereupon selective protection of the secondary alcohols was accomplished in the presence of the tertiary alcohol providing diacetate **56**. At this point, we hoped to examine the role of the C3 protecting group in the diastereoselectivity of the hydroboration. Earlier, the triethylsilyl ether was ultimately employed as the hydroboration substrate for monitoring purposes, but this was not necessary for diacetate **56**. Treatment of diene **56** with (+)-diisopinocampheylborane and oxidation provided the desired diol **57** as a

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single diastereomer in good yield,[32] confirming that the reagent controls the selectivity. Oxidation with the milder sodium perborate conditions proved useful in this case to prevent hydrolysis of the labile C4 acetate. Using triflic anhydride and 2,6-lutidine,[5] asbestinin-12 (**2**) was obtained in good yield. All data reported for the natural material again corresponded well with the data for synthetic asbestinin 12 (**2**).[14]

Conclusion

In summary, highly stereoselective syntheses of 11-acetoxy-4-deoxyasbestinin D (**1**) and asbestinin-12 (**2**) have been completed in 26 and 25 steps, respectively. The strategy for completing these two molecules hinged upon the formation of an oxonene ring using an asymmetric gylcolate aldol reaction. This oxonene was used as a manifold for an intramolecular Diels−Alder cycloaddition to form the hydroisobenzofuran moiety. A chiral hydroborating reagent proved useful in establishing the stereocenter at C15. These syntheses stand as the first molecules of the asbestinin subclass to be prepared by chemical methods and serve to confirm the absolute configuration of the asbestinins.

Experimental Section

(1*R*′,2*S*′,3*R*,4*R*′)-2-(1-Benzyloxymethyl-3-methylbut-3-enyloxy)-1-(4-benzyl-2-thioxooxazolidin-3-yl)-3-hydroxyhept-6-en-1-one (11). Preparation of hex-5-ene-1,2-diol: Into a flask equipped with a mechanical stirrer, an addition funnel, and a low temperature thermometer were added allylmagnesium chloride (2.0 M in THF, 800.0 mL, 1.600 mol) and 800 mL of THF. The solution was cooled to −20 °C. Glycidol (35.40 mL, 533.3 mmol) in 800 mL of THF was added dropwise via addition funnel keeping the temperature at −20 °C. The mixture was stirred 1 h at −20 °C and then quenched by the addition of saturated aqueous NH_4Cl. The organic layer was washed with brine, and the combined aqueous extracts were washed twice with 50% EtOAc/hexanes. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash column chromatography (10% then 50% EtOAc/hexanes) provided 57.16 g (93%) of the diol as a colorless oil. Preparation of pent-4-enal: Into a flask equipped with a mechanical stirrer was added hex-5-ene-1,2-diol (65.31 g, 562.2 mmol), 800 mL of CH_2Cl_2, and 800 mL of water. Sodium periodate (240.52 g, 1.1245 mol) was added to the biphasic solution which was stirred for 1 h. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$. The organic layer was washed twice with 10% $Na_2S_2O_3$ in water, then dried over Na_2SO_4. The volume was reduced to 100 mL in vacuo at 0 °C. Purification via distillation (bp 96 °C, 760 mmHg) gave 29.33 g (63%) of the aldehyde as a colorless liquid.[18]

Into a flask equipped with an addition funnel were added glycolate **6** (28.63 g, 65.13 mmol) and 435 mL of CH_2Cl_2. The solution was cooled to −78 °C, and titanium tetrachloride (7.50 mL, 68.4 mmol) was added dropwise via addition funnel. The solution was stirred 10 min at −78 °C, and *N*,*N*-diisopropylethylamine (26.92 mL, 162.8 mmol) was added dropwise to give a purple solution that was stirred at −78 °C for 2.5 h. *N*-Methylpyrrolidinone (6.57 mL, 68.3 mmol) was added to the solution via addition funnel and stirred for 10 min. Pent-4-enal was added dropwise via addition funnel and stirred at −78 °C for 2 h. The solution was warmed to −40 °C for 1 h, quenched by the addition of half-saturated aqueous NH_4Cl, and warmed to room temperature. The aqueous layer was extracted twice with CH_2Cl_2, and then the combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash column chromatography (20% then 50% EtOAc/Hexanes) provided 23.61 g (70%) of the alcohol as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.67−1.78 (m, 2H), 1.80 (s, 3H), 2.01 (dd, J = 13.2, 11.1 Hz, 1H), 2.15 (ddd, J = 14.9, 7.1, 7.1 Hz, 1H), 2.20−2.36 (m, 3H), 2.41 (dd, J = 14.0, 7.9 Hz, 1H), 3.20 (dd, J = 13.3, 2.8 Hz, 1H), 3.51 (dd, J = 10.3, 2.7 Hz, 1H), 3.68 (dd, J = 10.3, 7.6 Hz, 1H), 3.92−4.01 (m, 2H), 4.14 (dd, J = 9.4, 2.1 Hz, 1H), 4.19 (ddd, J = 9.3, 9.3, 9.3 Hz, 1H), 4.47 (d, J = 12.3 Hz, 1H), 4.53 (d, J = 12.3 Hz, 1H), 4.77 (m, 1H), 4.84 (s, 1H), 4.86 (s, 1H), 4.98 (d, J = 10.2 Hz, 1H), 5.05 (dd, J = 17.2, 1.5 Hz, 1H), 5.83 (dddd, J = 17.0, 10.3, 3.6, 3.6 Hz, 1H), 6.34 (d, J = 2.0 Hz, 1H), 7.08−7.35 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.6, 29.9, 33.2, 36.7, 40.7, 60.9, 70.6, 72.5, 73.1, 74.2, 78.7, 80.8, 114.0, 114.9, 127.22, 127.24, 127.5, 128.4, 128.9, 129.3, 135.6, 138.0, 138.1, 141.6, 172.2, 185.2; IR (film) 3458 (br), 2924, 1712 (str), 1446, 1361, 1324, 1206, 1128 cm^{-1}; $[\alpha]^{23}_D$ = +25 (c = 0.43, CH_2Cl_2); HRMS (electrospray ionization) calcd for $C_{30}H_{38}NO_5S$ [M + 1]$^+$ 524.2471, found 524.2473.

(2*S*,3*R*,9*R*)-9-Benzyloxymethyl-3-(*tert*-butyldimethylsilanyloxy)-2-(*tert*-butyldimethylsilanyloxymethyl)-7-methyl-2,3,4,5,8,9-hexahydrooxonine (18). Into a flask equipped with a reflux condenser were added diene **5** (16.56 g, 29.24 mmol) and 2.9 L of CH_2Cl_2. The solution was brought to reflux for 30 min, followed by the addition of Grubbs' catalyst (1.25 g, 1.47 mmol) and stirring for 3 h at reflux. The solution was cooled to room temperature and concentrated in vacuo. Purification by flash column chromatography (1% EtOAc/hexanes) provided 15.53 g (99%) of the oxonene as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.02 (s, 3H), 0.03 (s, 9H), 0.88 (s, 9H), 0.89 (s, 9H), 1.42 (dddd, J = 3.9, 3.9, 13.5, 13.5 Hz, 1H), 1.73 (m, 1H), 1.79 (s, 3H), 1.86 (m, 1H), 1.98 (d, J = 14.02 Hz, 1H), 2.44 (dd, J = 14.2, 7.9 Hz, 1H), 2.81 (dddd, J = 13.2, 13.2, 13.2, 4.4 Hz, 1H), 3.29−3.35 (m, 2H), 3.38 (m, 1H), 3.54 (dd, J = 13.6, 8.9 Hz, 1H), 3.67 (dd, J = 11.0, 8.5 Hz, 1H), 3.92 (dd, J = 11.1, 2.4 Hz, 1H), 3.96 (m, 1H), 4.56 (s, 2H), 5.34 (dd, J = 11.4, 5.3 Hz, 1H), 7.27−7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.2, −5.1, −4.8, 18.1, 18.3, 25.3, 25.8, 25.9, 26.0, 26.1, 32.2, 36.1, 61.8, 67.7, 73.0, 73.4, 77.9, 84.3, 126.1, 127.5, 127.6, 128.3, 134.7, 138.4; IR (film) 2928, 1471, 1254, 1089 cm^{-1}; $[\alpha]^{24}_D$ = +33.6 (c = 1.16, CH_2Cl_2); HRMS (electrosray ionization) calcd for $C_{30}H_{54}O_4Si_2Na$ [M + Na]$^+$ 557.3459, found 557.3455.

(3*S*,7*S*,8*R*,14*R*,15*R*,16*R*)-1-[14-(*tert*-Butyldimethylsilanyloxy)-6-methoxy-5,10-dimethyl-15-oxatricyclo[6.6.1.0^{2,7}]pentadeca-5,-10-dien-3-yl]ethanone (42). Into a flask equipped with a reflux condenser was added the aldehyde (664 mg, 1.68 mmol), 17 mL of toluene, and 1-(triphenyl-l5-phosphanylidene)propan-2-one (31) (1.61 g, 5.05 mmol). The solution was brought to reflux overnight and then cooled to room temperature. The mixture was concentrated in vacuo and then purified by flash column chromatography (5% then 10% EtOAc/hexanes) provided 583 g (80%) of the ketone as a colorless oil: ^{1}H NMR (400 MHz, C_6D_6, 60 °C) δ 0.007 (s, 3H), 0.011 (s, 3H), 0.89 (s, 9H), 1.56−1.65 (m, 1H), 1.62 (s, 3H), 1.84 (s, 3H), 1.86 (s, 3H), 1.87−2.02 (m, 3H), 2.12 (m, 1H), 2.29 (dd, J = 17.2, 6.5 Hz, 1H), 2.67 (m, 1H), 2.70 (d, J = 14.4 Hz, 1H), 2.89 (ddd, J = 6.9, 3.6, 3.6 Hz, 1H), 3.10 (m, 1H), 3.22 (m, 1H), 3.26 (s, 3H), 4.02 (dd, J = 8.4, 3.7 Hz, 1H), 4.20 (ddd, J = 10.4, 4.5, 4.5 Hz, 1H), 4.45 (ddd, J = 4.9, 2.5, 2.5 Hz, 1H), 5.49 (m, 1H); ^{13}C NMR (100 MHz, C_6D_6, 60 °C) δ −4.8, −4.7, 16.2, 18.2, 23.0, 26.1, 27.6, 28.2, 28.5, 33.1, 39.0, 40.1, 41.2, 46.7, 56.7, 73.3, 80.4, 84.3, 113.3, 130.0, 131.2, 149.1, 207.4; IR (film) 2927, 1712 (str), 1445, 1360, 1251, 1088 cm^{-1}; $[\alpha]^{22}_D$ = +40.8 (c = 1.10, CH_2Cl_2); HRMS (electrospray ionization) calcd for $C_{25}H_{43}O_4Si$ [M + 1]$^+$ 435.2931, found 435.2935.

(1*R*,2*S*,6*S*,7*R*,8*R*,9*R*)-6-Isopropenyl-3-methoxy-4,9,13-trimethyl-15-oxatricyclo[6.6.1.0^{2,7}]-pentadeca-3,12-dien-9-ol (45). A flask was charged with methylmagnesium chloride (3.0 M in THF, 3.47 mL, 10.4 mmol) and 70 mL of THF. The solution was cooled to 0 °C, and the ketone **44** (659 mg, 2.08 mmol) was added in 35 mL of THF dropwise. The solution was stirred 30 min and then quenched with saturated aqueous NH_4Cl, warmed to room temperature, and diluted with Et_2O. The layers were separated, and

the aqueous portion was washed twice with Et_2O. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification via flash column chromatography (10% EtOAc/ hexanes) provided 678 mg (98%) of the alcohol as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (s, 3H), 1.66 (s, 3H), 1.69 (s, 3H), 1.69−1.79 (m, 1H), 1.85−1.96 (m, 2H), 1.90 (s, 3H), 2.00 (m, 1H), 2.17 (m, 2H), 2.28 (ddd, J = 11.2, 11.2, 4.5 Hz, 1H), 2.43 (dd, J = 11.7, 6.9 Hz, 1H), 2.75 (dd, J = 7.1, 7.1 Hz, 1H), 2.95 (d, J = 14.7 Hz, 1H), 3.07−3.24 (m, 2H), 3.52 (s, 3H), 3.87 (s, 1H), 4.18 (ddd, J = 8.6, 3.3, 3.3 Hz, 1H), 4.82 (s, 1H), 4.83 (m, 1H), 5.84 (dd, J = 10.9, 6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.8, 19.0, 27.1, 28.3, 28.9, 35.2, 36.7, 38.8, 41.8, 42.9, 45.0, 58.6, 75.3, 83.4, 89.4, 113.0, 116.7, 128.7, 136.5, 147.0, 149.1; IR (film) 3511 (br), 2914, 1447, 1119, 1058 cm^{-1}; $[\alpha]^{24}_D$ = +74 (c = 0.42, CH_2Cl_2); HRMS (electrospray ionization) calcd for $C_{21}H_{32}O_3Na$ [M + Na]$^+$ 355.2249, found 355.2251.

(1*R*,2*S*,4*R*,6*S*,7*R*,8*R*,9*R*)-9-Hydroxy-6-isopropenyl-4,9,13-trimethyl-15-oxatricyclo[6.6.1.0^{2,7}]pentadec-12-en-3-one (46). A flask was charged with alcohol **45** (678 mg, 0.255 mmol), 20 mL of $CHCl_3$, and 2.5 mL of water. Hydrochloric acid (12 M, 2.50 mL, 30.0 mmol) was added to the biphasic solution and stirred for 2 h. The reaction was quenched by the slow addition of saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous portion was washed twice with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash column chromatography (10% then 25% EtOAc/hexanes) gave 562 mg (87%) of the ketone as a white solid and 58 mg (9%) of the (4*S*)-product (**47**) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (s, 3H), 1.07 (d, J = 6.6 Hz, 3H), 1.59 (dd, J = 25.8, 13.0 Hz, 1H), 1.69 (s, 3H), 1.71−1.78 (m, 1H), 1.85−2.03 (m, 4H), 1.93 (s, 3H), 2.48 (ddd, J = 12.3, 12.3, 2.8 Hz, 1H), 2.59 (dddd, J = 11.7, 11.7, 6.5, 6.5 Hz, 1H), 2.69 (dd, J = 12.0, 7.0 Hz, 1H), 2.91−2.97 (m, 2H), 3.07 (m, 1H), 3.13 (ddd, J = 11.9, 11.9, 6.4 Hz, 1H), 3.94 (s, 1H), 4.36 (ddd, J = 9.9, 3.1, 3.1 Hz, 1H), 4.86 (m, 2H), 5.83 (dd, J = 11.5, 5.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 18.5, 27.2, 28.4, 28.7, 35.2, 38.5, 39.0, 41.8, 46.0, 48.7, 54.1, 74.8, 80.5, 91.3, 113.4, 128.3, 136.6, 146.2, 211.7; IR (film) 3514 (br), 2928, 1702 (str), 1453, 1377, 1184, 1076 cm^{-1}; $[\alpha]^{24}_D$ = +40 (c = 0.18, CH_2Cl_2); HRMS (electrospray ionization) calcd for $C_{20}H_{30}O_3Na$ [M + Na]$^+$ 341.2093, found 341.2094.

(1*R*,2*S*,4*S*,6*S*,7*R*,8*R*,9*R*)-9-Hydroxy-6-isopropenyl-4,9,13-trimethyl-15-oxatricyclo[6.6.1.02,7]pentadec-12-en-3-one (47). Into a flask containing the previous ketone **46** (551 mg, 1.73 mmol) and 17 mL of methanol was added catalytic sodium hydride. After the mixture was stirred 15 min, the reaction was quenched by the slow addition of saturated aqueous NH_4Cl and diluted with Et_2O. The layers were separated, and the aqueous portion was washed twice with Et_2O. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash column chromatography (10% then 25% EtOAc/hexanes) gave 246 mg (45%) of the ketone as a colorless oil and 303 mg (55%) of the (4*R*)-product (**46**) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (d, J = 6.8 Hz, 3H), 1.14 (s, 3H), 1.59−1.71 (m, 2H), 1.77 (s, 3H), 1.80−1.87 (m, 1H), 1.88 (s, 3H), 1.92−1.99 (m, 1H), 2.01 (dd, J = 14.8, 3.7 Hz, 1H), 2.11 (ddd, J = 13.9, 8.6, 7.1 Hz, 1H), 2.34 (s, 1H), 2.47 (ddd, J = 8.6, 8.6, 5.5 Hz, 1H), 2.58 (ddq, J = 21.7, 7.0, 7.0 Hz, 1H), 2.83 (ddd, J = 7.8, 7.8, 7.8 Hz, 1H), 2.84−2.93 (m, 2H), 3.02 (ddd, J = 8.1, 8.1, 4.6 Hz, 1H), 3.72 (d, J = 4.6 Hz, 1H), 4.58 (ddd, J = 6.3, 3.3, 3.3 Hz, 1H), 4.89 (d, J = 0.7 Hz, 1H), 4.92 (d, J = 1.3 Hz, 1H), 5.71 (dd, J = 11.3, 5.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.5, 20.0, 25.3, 28.5, 28.9, 34.7, 36.5, 38.4, 40.7, 40.9, 45.9, 53.3, 74.7, 77.7, 89.1, 112.7, 129.2, 134.2, 146.9, 212.9; IR (film) 3443 (br), 2928, 1710 (str), 1642, 1446, 1376, 1081 cm^{-1}; $[\alpha]^{24}_D$ = +92 (c = 0.19, CH_2Cl_2); HRMS (electrospray ionization) calcd for $C_{20}H_{30}O_3Na$ [M + Na]$^+$ 341.2093, found 341.2098.

(1*R*,2*S*,3*S*,4*S*,6*S*,7*R*,8*R*,9*R*)-6-Isopropenyl-4,9,13-trimethyl-15-oxatricyclo[6.6.1.0^{2,7}]pentadec-12-ene-3,9-diol. Into a flask charged with the ketone **47** (523 mg, 1.64 mmol) was added 16 mL of THF. The solution was cooled to −78 °C, and L-Selectride (1.0 M in THF, 1.97 mL, 1.97 mmol) was added dropwise. The reaction was stirred for 10 min and then quenched by the addition of sodium hydroxide (3 M, 1.0 mL, 3.0 mmol) and hydrogen peroxide (30%, 2.0 mL, 18 mmol). The mixture was stirred for 3 h at room temperature and then diluted with Et_2O. The layers were separated, and the aqueous portions were washed twice with Et_2O. The combined organic extracts were dried over Na_2SO_4, and concentrated in vacuo. Purification by flash column chromatography (25% EtOAc/hexanes) gave 493 mg (94%) of the alcohol as a white solid: ^{1}H NMR (400 MHz, C_6D_6, 60 °C) δ 0.95 (d, J = 7.0 Hz, 3H), 1.19 (m, 1H), 1.28 (s, 3H), 1.33 (m, 2H), 1.56 (m, 1H), 1.64−1.73 (m, 2H), 1.70 (s, 3H), 1.75 (s, 3H), 1.77−1.94 (m, 2H), 1.89 (m, 1H), 2.19 (ddd, J = 7.8, 4.2, 4.2 Hz, 1H), 2.69−2.92 (m, 4H), 3.42 (s, 1H), 3.91 (d, J = 7.5 Hz, 1H), 4.24 (dd, J = 6.7, 3.8 Hz, 1H), 4.86 (s, 1H), 4.88 (d, J = 1.3 Hz, 1H), 5.52 (dd, J = 11.0, 6.1 Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6, 60 °C) δ 17.2, 22.0, 24.6, 28.4, 28.8, 29.7, 31.8, 38.5, 38.6, 39.8, 42.6, 45.9, 72.2, 74.7, 80.0, 89.5, 110.6, 130.0, 132.3, 149.8; IR (film) 3329 (br), 2921, 1439, 1373, 1088 cm^{-1}; $[\alpha]^{25}_D$ = +5.7 (c = 0.46, CH_2Cl_2); HRMS (electrospray ionization) calcd for $C_{20}H_{32}O_3Na$ [M + Na]$^+$ 343.2249, found 343.2248.

(1*R*,2*S*,3*S*,4*S*,6*S*,7*R*,8*R*,9*R*)-Acetic Acid 9-Hydroxy-6-isopropenyl-4,9,13-trimethyl-15-oxatricyclo[6.6.1.0^{2,7}]pentadec-12-en-3-yl Ester (48). Into a flask containing the secondary alcohol (406 mg, 1.27 mmol) in 26 mL of CH_2Cl_2 were added triethylamine (707 μL, 5.07 mmol) and 4-dimethylaminopyridine (16.0 mg, 0.127 mmol). Acetic anhydride (240 μL, 2.53 mmol) was added to the solution, and the resulting solution was stirred overnight. The reaction was quenched using saturated aqueous NH_4Cl, and the layers were separated. The aqueous portions were washed twice with CH_2Cl_2, dried over Na_2SO_4, and concentrated in vacuo. Purification via flash column chromatography (25% EtOAc/hexanes) gave 453 mg (99%) of the ester as a colorless oil: ^{1}H NMR (400 MHz, C_6D_6, 60 °C) δ 0.87 (d, J = 7.0 Hz, 3H), 1.25 (s, 3H), 1.37 (ddd, J = 13.7, 6.2, 4.1 Hz, 1H), 1.50−1.69 (m, 4H), 1.66 (s, 3H), 1.67 (s, 3H), 1.74 (dd, J = 14.6, 3.9 Hz, 1H), 1.77−1.92 (m, 2H), 1.81 (s, 3H), 2.32 (ddd, J = 4.9, 4.9, 4.9 Hz, 1H), 2.66−2.78 (m, 3H), 2.89 (m, 1H), 3.88 (d, J = 6.6 Hz, 1H), 4.25 (dd, J = 7.0, 3.8 Hz, 1H), 4.83 (s, 1H), 4.85 (d, J = 1.3 Hz, 1H), 5.22 (dd, J = 5.1, 3.7 Hz, 1H), 5.51 (dd, J = 11.1, 6.0 Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6, 60 °C) δ 16.8, 20.7, 21.5, 24.9, 28.4, 29.7, 30.1, 30.2, 38.1, 38.8, 39.7, 43.0, 44.2, 73.8, 74.7, 79.7, 89.3, 111.1, 130.0, 132.6, 149.2, 170.0; IR (film) 3465(br), 2924, 1737 (str), 1450, 1374, 1237, 1039 cm^{-1}; $[\alpha]^{25}_D$ = +42.2 (c = 1.32, CH_2Cl_2); HRMS (electrospray ionization) calcd for $C_{22}H_{35}O_4$ [M + 1]$^+$ 363.2536, found 363.2542.

(1*R*,2*S*,3*S*,4*S*,6*S*,7*R*,8*R*,9*R*)-Acetic Acid 6-Isopropenyl-4,9,13-trimethyl-9-triethylsilanyloxy-15-oxatricyclo[6.6.1.0^{2,7}]pentadec-12-en-3-yl Ester (49). A flask was charged with ester **48** (64.0 mg, 0.176 mmol) in 2 mL of CH_2Cl_2 and cooled to 0 °C. 2,6-Lutidine (62 μL, 0.53 mmol) and triethylsilyl trifluoromethanesulfonate (60 μL, 0.27 mmol) were added sequentially and the mixture stirred for 1 h at 0 °C. The reaction was quenched by the addition of saturated aqueous NH_4Cl and warmed to room temperature, and the layers were separated. The aqueous portions were washed twice with CH_2Cl_2, dried over Na_2SO_4, and concentrated in vacuo. Purification via flash column chromatography (5% EtOAc/hexanes) gave 67 mg (80%) of the alkene as a colorless oil: ^{1}H NMR (400 MHz, C_6D_6, 60 °C) δ 0.62 (q, J = 7.8 Hz, 6H), 0.83 (d, J = 5.8 Hz, 3H), 1.00 (t, J = 7.9 Hz, 9H), 1.38 (ddd, J = 13.9, 3.1, 3.1 Hz, 1H), 1.55−1.65 (m, 2H), 1.57 (s, 3H), 1.71 (s, 3H), 1.73−1.89 (m, 4H), 1.79 (s, 3H), 1.86 (s, 3H), 2.20 (dd, J = 7.1, 4.6 Hz, 1H), 2.63 (d, J = 13.9 Hz, 1H), 2.68 (m, 1H), 2.96 (dd, J = 8.8, 8.8 Hz, 1H), 3.03 (d, J = 5.3 Hz, 1H), 3.97 (d, J = 10.4 Hz, 1H), 4.08 (d, J = 1.63 Hz, 1H), 4.88 (s, 1H), 4.94 (m, 1H), 5.19 (m, 1H), 5.44 (dd, J = 10.6, 5.6 Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6, 60 °C) δ 7.3, 7.5, 18.2, 20.7, 23.1, 23.5, 26.7, 28.5,

28.9, 29.5, 38.5, 39.2, 39.5, 41.4, 44.8, 74.1, 78.4, 79.4, 88.3, 110.1, 130.5, 130.9, 149.4, 170.5; IR (film) 2957, 1739 (str), 1462, 1373, 1235, 1116, 1048 cm^{-1}; $[\alpha]^{23}_D = -33$ ($c = 0.43$, CH_2Cl_2); HRMS (electrospray ionization) calcd for $C_{28}H_{48}O_4SiNa$ $[M + Na]^+$ 499.3220, found 499.3223.

(1*R*,1*S*′,2*S*,3*S*,4*S*,6*S*,7*R*,8*R*,9*R*)-Acetic Acid 9-Hydroxy-6-(2-hydroxy-1-methylethyl)-4,9,13-trimethyl-15-oxatricyclo[6.6.1.0^{2,7}]-pentadec-12-en-3-yl Ester (51). A flask was charged with alkene **49** (10.4 mg, 21.8 μmol) in 500 μL of THF. (+)-Diisopinocampheylborane (24.0 mg, 83.2 μmol) was added to the solution, and the resulting solution was allowed to stir 30 min. The reaction was quenched by the addition of sodium hydroxide (3 M, 130 μL, 0.390 mmol) and then hydrogen peroxide (30%, 260 μL, 2.29 mmol). The biphasic solution was stirred for 3 h and then diluted with brine and Et_2O. The layers were separated, and the aqueous portion was washed twice with Et_2O, dried over Na_2SO_4, and concentrated in vacuo. For purification purposes, the product and isopinocampheol were carried on to the next reaction as a mixture. In a separate experiment, purification via flash column chromatography (10% EtOAc/hexanes) gave the alcohol as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.59 (q, $J = 7.8$ Hz, 6H), 0.81 (d, $J = 6.5$ Hz, 3H), 0.94 (t, $J = 7.9$ Hz, 9 H), 1.01 (d, $J = 6.7$ Hz, 3H), 1.22 (d, $J = 15.3$ Hz, 1H), 1.47 (s, 3H), 1.59−1.94 (m, 9H), 1.77 (s, 3H), 2.08−2.18 (m, 2H), 2.10 (s, 3H), 2.52 (ddd, $J = 12.2$, 12.2, 8.3 Hz, 1H), 2.66 (m, 2H), 3.41 (dd, $J = 10.9$, 5.3 Hz, 1H), 3.63 (m, 1H), 3.78 (d, $J = 10.7$ Hz, 1H), 3.93 (s, 1H), 5.14 (m, 1H), 5.48 (dd, $J = 11.2$, 5.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 6.8, 6.9, 7.0, 15.8, 18.3, 21.2, 22.9, 26.7, 28.3, 28.5, 29.8, 32.9, 38.1, 38.7, 38.9, 44.4, 66.5, 73.9, 78.2, 78.8, 87.3, 130.0, 130.7, 171.4; IR (film) 3446 (br), 2957, 1737 (str), 1457, 1374, 1237, 1137, 1117, 1043 cm^{-1}; $[\alpha]^{26}_D = +2.3$ ($c = 0.68$, CH_2Cl_2); HRMS (electrospray ionization) calcd for $C_{28}H_{50}O_5SiNa$ $[M + Na]^+$ 517.3326, found 517.3328.

Into a flask containing the alcohol **50** in 500 μL of THF was added tetrabutylammonium fluoride (1.0 M in THF, 63 μL, 63 μmol). The solution was stirred for 1 h, quenched by the addition of saturated aqueous NH_4Cl, and diluted with Et_2O. The layers were separated, and the aqueous portion was washed three times with Et_2O, dried over Na_2SO_4, and concentrated in vacuo. Purification via flash column chromatography (30% EtOAc/hexanes) gave 5.1 mg (64% over two steps) of the diol as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.82 (d, $J = 6.0$ Hz, 3H), 0.86−0.99 (m, 1H), 0.88 (d, $J = 6.9$ Hz, 3H), 1.17 (d, $J = 9.8$ Hz, 1H), 1.42 (s, 3H), 1.64 (dd, $J = 13.9$, 8.4 Hz, 1H), 1.75−1.85 (m, 6H), 1.79 (s, 3H), 1.93 (m, 1H), 2.09−2.13 (m, 1H), 2.10 (s, 3H), 2.34 (br s, 1H), 2.49 (dd, $J = 8.7$, 8.7 Hz, 1H), 2.60 (dd, $J = 21.1$, 11.0 Hz, 1H), 2.69 (d, $J = 14.4$ Hz, 1H), 3.46 (dd, $J = 11.6$, 5.5 Hz, 1H), 3.53 (dd, $J = 11.5$, 11.5 Hz, 1H), 3.78 (d, $J = 10.2$ Hz, 1H), 4.04 (s, 1H), 5.18 (d, $J = 3.7$ Hz, 1H), 5.52 (dd, $J = 10.7$, 5.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 1.0, 14.1, 18.4, 21.2, 23.0, 28.4, 29.4, 29.7, 29.8, 30.9, 37.9, 38.1, 42.2, 45.7, 65.4, 74.0, 75.1, 79.9, 89.1, 130.1, 171.4; IR (film) 3355 (br), 2925, 1736 (str), 1455, 1381, 1237, 1017 cm^{-1}; $[\alpha]^{26}_D = +33$ ($c = 0.39$, CH_2Cl_2); HRMS (electrospray ionization) calcd for $C_{22}H_{36}O_5K$ $[M + K]^+$ 419.3546, found 419.3545.

11-Acetoxy-4-deoxyasbestinin D (1). A flask charged with diol **51** (8.9 mg, 24 μmol) in 1.1 mL of THF was cooled to 0 °C. 2,6-Lutidine (13.6 μL, 0.117 mmol) followed by trifluoromethanesulfonic anhydride (5.8 μL, 34 μmol) were added to the solution, and the resulting solution was allowed to stir for 45 min at 0 °C. The solution was warmed to room temperature for 4 h and then quenched via the addition of saturated aqueous NH_4Cl. The mixture was diluted with Et_2O, and the layers were separated. The aqueous portion was washed three times with Et_2O, dried over Na_2SO_4, and concentrated in vacuo. Purification via flash column chromatography (10% EtOAc/Hexanes) gave 5.5 mg (66%) of 11-acetoxy-4-deoxyasbestinin D as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (d, $J = 7.1$ Hz, 3H), 0.92 (d, $J = 7.2$ Hz, 3H), 1.01 (m, 1H), 1.35 (s, 3H), 1.52 (ddd, $J = 13.5$, 13.5, 9.7 Hz, 1H), 1.61 (m, 1H), 1.75 (s, 3H), 1.75 (m, 2H), 1.84−2.08 (m, 5H), 2.10 (s, 3H), 2.34 (ddd, $J = 10.4$, 10.4, 10.4 Hz, 1H), 2.50 (br d, $J = 14.8$ Hz, 1H), 2.55 (ddd, $J = 14.5$, 10.3, 4.8 Hz, 1H), 3.48 (dd, $J = 13.2$, 3.2 Hz, 1H), 3.86 (d, $J = 15.2$ Hz, 1H), 3.87 (d, $J = 8.7$ Hz, 1H), 4.10 (ddd, $J = 5.5$, 2.9, 2.9 Hz, 1H), 5.31 (dd, $J = 5.1$, 2.8 Hz, 1H), 5.47 (dd, $J = 8.1$, 8.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.0, 17.9, 21.3, 23.4, 26.1, 28.9, 31.3, 31.5, 37.3, 37.5, 38.0, 38.5, 40.5, 45.8, 67.9, 73.5, 76.4, 81.0, 92.2, 128.7, 130.8, 171.3; IR (film) 2926, 1737 (str), 1459, 1377, 1231, 1088 cm^{-1}; $[\alpha]^{26}_D = -15$ ($c = 0.17$, $CHCl_3$); HRMS (electrospray ionization) calcd for $C_{22}H_{35}O_4$ $[M + 1]^+$ 363.2536, found 363.2539.

An authentic sample of 11-acetoxy-4-deoxyasbestinin D was provided by Dr. Abimael D. Rodríguez (University of Puerto Rico, Río Piedras)[3] and purified in the same manner as described above, and an optical rotation was obtained under identical conditions: $[\alpha]^{25}_D = -15$ ($c = 0.10$, $CHCl_3$). The ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of the authentic sample also mirrored the synthetic material.

(1*R*,2*S*,6*S*,7*R*,8*R*,10*S*)-10-Hydroxy-6-isopropenyl-3-methoxy-4,13-dimethyl-15-oxatricyclo[6.6.1.0^{2,7}]pentadeca-3,12-dien-9-one (52). A flask containing the ketone **44** (280 mg, 0.885 mmol) in 20 mL of THF was cooled to −78 °C. Potassium hexamethyldisilazide (0.5 M in toluene) was added dropwise, and the solution was allowed to stir for 1 h at −78 °C. Davis oxaziridine (278 mg, 1.062 mmol) was added in 10 mL of THF to the enolate, and the solution was allowed to stir for 45 min at −78 °C. The reaction was quenched by the addition of saturated aqueous NH_4Cl. The mixture was diluted with Et_2O, and the layers were separated. The aqueous portions were washed three times with Et_2O, dried over Na_2SO_4, and concentrated in vacuo. Purification via flash column chromatography (10% EtOAc/hexanes) gave 245 mg (84%) of the alcohol as a white solid: ^{1}H NMR (400 MHz, C_6D_6, 60 °C) δ 1.54 (s, 3H), 1.56 (s, 3H), 1.67 (s, 3H), 1.80 (dd, $J = 16.5$, 4.9 Hz, 1H), 1.95 (m, 1H), 2.03 (dd, $J = 14.0$, 8.3 Hz, 1H), 2.20−2.31 (m, 2H), 2.44 (m, 1H), 2.61 (dd, $J = 6.3$, 6.3 Hz, 1H), 2.76 (m, 1H), 3.03 (dd, $J = 11.4$, 7.6 Hz, 1H), 3.14 (br d, $J = 9.6$ Hz, 1H), 3.23 (s, 3H), 4.22 (ddd, $J = 10.1$, 10.1, 3.7 Hz, 1H), 4.30 (m, 1H), 4.59 (s, 1H), 4.74 (s, 1H), 4.78 (s, 1H), 5.30 (dd, $J = 7.5$, 7.5 Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6, 60 °C) δ 16.0, 19.5, 24.8, 34.9, 35.3, 39.9, 42.0, 42.8, 43.7, 57.8, 79.2, 83.6, 84.1, 112.7, 116.7, 121.8, 138.7, 147.1, 149.0, 214.4; IR (film) 3419 (br), 2912, 1715 (str), 1447, 1051 cm^{-1}; $[\alpha]^{24}_D = +55.3$ ($c = 6.50$, CH_2Cl_2); HRMS (electrospray ionization) calcd for $C_{20}H_{28}O_4$ $[M + Na]^+$ 355.1886, found 355.1891.

(1*R*,2*S*,6*S*,7*R*,8*R*,9*R*,10*S*)-6-Isopropenyl-3-methoxy-4,9,13-trimethyl-15-oxatricyclo[6.6.1.0^{2,7}]pentadeca-3,12-diene-9,10-diol (53). A flask was charged with methylmagnesium chloride (3.0 M in THF, 6.42 mL, 19.3 mmol) and 24 mL of THF. The solution was cooled to 0 °C, and the ketone **52** (320 mg, 0.963 mmol) was added in 8 mL of THF dropwise. The solution was stirred 30 min, quenched with saturated aqueous NH_4Cl, warmed to room temperature, and diluted with Et_2O. The layers were separated, and the aqueous portion was washed twice with Et_2O. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification via flash column chromatography (20% EtOAc/hexanes) provided 278 mg (83%) of the alcohol as a white solid: ^{1}H NMR (400 MHz, C_6D_6, 60 °C) δ 1.28 (s, 3H), 1.59 (s, 3H), 1.65 (s, 3H), 1.78 (s, 3H), 1.91 (dd, $J = 16.8$, 5.1 Hz, 1H), 1.99−2.09 (m, 2H), 2.13 (dd, $J = 14.6$, 4.4 Hz, 1H), 2.20−2.31 (m, 2H), 2.40 (ddd, $J = 9.7$, 9.7, 5.2 Hz, 1H), 2.56 (ddd, $J = 10.3$, 7.4, 2.7 Hz, 1H), 2.76−2.85 (m, 2H), 3.12 (m, 1H), 3.29 (s, 3H), 3.51 (dd, $J = 7.5$, 4.3 Hz, 1H), 4.13 (d, $J = 2.6$ Hz, 1H), 4.27 (ddd, $J = 7.4$, 4.4, 2.9 Hz, 1H), 4.83 (s, 2H), 5.68 (dd, $J = 10.7$, 6.7 Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6, 60 °C) δ 16.0, 19.6, 24.3, 27.7, 35.1, 36.1, 38.0, 42.9, 43.4, 44.1, 58.0, 76.5, 77.4, 82.5, 87.5, 112.5, 115.8, 126.0, 135.9, 147.8, 149.7; IR (film) 3437 (br), 2910, 1445, 1376, 1118, 1092, 1050 cm^{-1}; $[\alpha]^{24}_D = +82$ ($c = 0.34$, CH_2Cl_2); HRMS (electrospray ionization) calcd for $C_{21}H_{32}O_4Na$ $[M + Na]^+$ 371.2199, found 371.2202

(1*R*,2*S*,4*R*,6*S*,7*R*,8*R*,9*R*,10*S*)-9,10-Dihydroxy-6-isopropenyl-4,9,13-trimethyl-15-oxatricyclo[6.6.1.0^{2,7}]pentadec-12-en-3-one (54). A flask was charged with diol **53** (220 mg, 0.631 mmol), 10 mL of $CHCl_3$, and 450 μL of water. Hydrochloric acid (12 M, 450 μL, 5.4 mmol) was added to the biphasic solution, and the resulting solution was stirred for 2 h. The reaction was quenched by the slow addition of saturated aqueous $NaHCO_3$ and diluted with CH_2Cl_2. The layers were separated, and the aqueous portion was washed twice with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash column chromatography (20% EtOAc/hexanes) gave 192 mg (91%) of the ketone as a white solid and 16 mg (8%) of the (4*S*)-product (**55**) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$, 60 °C) δ 1.06 (d, J = 6.6 Hz, 3H), 1.08 (s, 3H), 1.58 (ddd, J = 13.0, 13.0, 13.0 Hz, 1H), 1.69 (s, 3H), 1.89 (s, 3H), 1.88−1.99 (m, 2H), 2.08 (m, 1H), 2.33 (br s, 1H), 2.46 (ddd, J = 15.0, 12.3, 2.8 Hz, 1H), 2.48−2.60 (m, 2H), 2.63 (dd, J = 11.7, 7.6 Hz, 1H), 2.83−3.06 (m, 3H), 3.53 (br dd, J = 6.9, 6.9 Hz, 1H), 4.09 (s, 1H), 4.36 (ddd, J = 9.5, 3.2, 3.2 Hz, 1H), 4.86 (s, 2H), 5.76 (dd, J = 10.6, 6.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 60 °C) δ 14.5, 18.6, 24.4, 27.9, 35.9, 36.9, 39.3, 42.1, 46.8, 47.9, 54.4, 76.3, 77.0, 80.5, 89.2, 113.4, 125.0, 137.0, 146.3, 210.9; IR (film) 3523 (br), 2925, 1705 (str), 1450, 1184, 1071 cm^{-1}; $[\alpha]^{22}_D$ = +35 (c = 0.37, CH_2Cl_2); HRMS (electrospray ionization) calcd for $C_{20}H_{30}O_4Na$ $[M + Na]^+$ 357.2042, found 357.2043.

(1*R*,2*S*,4*S*,6*S*,7*R*,8*R*,9*R*,10*S*)-9,10-Dihydroxy-6-isopropenyl-4,9,13-trimethyl-15-oxatricyclo[6.6.1.0^{2,7}]pentadec-12-en-3-one (55). Into a flask containing the previous ketone **54** (242 mg, 0.724 mmol) and 24 mL of methanol was added catalytic sodium hydride. After being stirred for 15 min, the reaction was quenched by the slow addition of saturated aqueous NH_4Cl and diluted with Et_2O. The layers were separated, and the aqueous portion was washed twice with Et_2O. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash column chromatography (20% EtOAc/hexanes) gave 103 mg (42%) of the ketone as a colorless oil and 139 mg (58%) of the (4*R*)-product as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$, 60 °C) δ 1.02 (d, J = 6.8 Hz, 3H), 1.21 (s, 3H), 1.62 (ddd, J = 14.2, 9.2, 5.5, Hz, 1H), 1.73 (s, 3H), 1.77 (s, 3H), 1.94−2.09 (m, 3H), 2.35−2.55 (m, 4H), 2.72−2.81 (m, 2H), 2.95 (ddd, J = 13.3, 11.4, 7.5 Hz, 1H), 3.04 (ddd, J = 7.6, 7.6, 7.6 Hz, 1H), 3.53 (dd, J = 7.4, 3.0 Hz, 1H), 3.77 (d, J = 5.7 Hz, 1H), 4.60 (m, 1H), 4.84 (s, 1H), 4.90 (s, 1H), 5.65 (dd, J = 10.7, 6.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 60 °C) δ 15.0, 20.2, 22.7, 27.9, 34.7, 34.8, 37.2, 40.2, 41.2, 45.0, 53.5, 76.1, 76.2, 77.2, 87.3, 112.1, 125.8, 134.5, 147.0, 211.9; IR (film) 3459 (br), 2930, 1710 (str), 1448, 1377, 1048 cm^{-1}; $[\alpha]^{21}_D$ = +54 (c = 1.9, CH_2Cl_2); HRMS (electrospray ionization) calcd for $C_{20}H_{30}O_4Na$ $[M + Na]^+$ 357.2042, found 357.2041.

(1*R*,2*S*,3*S*,4*S*,6*S*,7*R*,8*R*,9*R*,10*S*)-6-Isopropenyl-4,9,13-trimethyl-15-oxatricyclo[6.6.1.0^{2,7}]pentadec-12-ene-3,9,10-triol. Into a flask charged with the ketone **55** (158 mg, 0.472 mmol) was added 5 mL of THF. The solution was cooled to −78 °C, and L-Selectride (1.0 M in THF, 567 μL, 0.567 mmol) was added dropwise. The reaction was stirred for 10 min and then quenched by the addition of sodium hydroxide (3 M, 288 μL, 0.864 mmol) and hydrogen peroxide (30%, 566 μL, 5.184 mmol). The mixture was stirred for 3 h at room temperature and then diluted with CH_2Cl_2. The layers were separated, and the aqueous portions were washed twice with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash column chromatography (50% EtOAc/hexanes) gave 148 mg (94%) of the alcohol as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$, 60 °C) δ 0.99 (d, J = 6.1 Hz, 3H) 1.29 (s, 3H), 1.38 (m, 1H), 1.73 (s, 3H), 1.83 (s, 3H), 1.98 (dd, J = 14.6, 3.9 Hz, 1H), 2.06 (m, 1H), 2.13−2.28 (m, 3H), 2.61 (s, 2H), 2.78 (d, J = 14.4 Hz, 1H), 3.00 (ddd, J = 11.6, 8.2, 8.2, Hz, 1H), 3.65 (m, 1H), 3.78 (s, 1H), 3.92 (d, J = 7.0 Hz, 1H), 4.37 (d, J = 2.5 Hz, 1H), 4.75 (s, 1H), 4.84 (s, 1H), 5.64 (dd, J = 9.8, 7.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 60 °C) δ 16.9, 21.6, 22.9, 28.2, 28.4, 31.4, 34.4, 38.3, 39.5, 41.3, 45.5, 72.2, 75.9, 76.9, 79.8, 88.0, 110.7, 125.8, 134.2, 149.1; IR (film) 3382 (br), 2912, 1440, 1366, 1052 cm^{-1}; $[\alpha]^{21}_D$ = +2.8 (c = 3.2, CH_2Cl_2); HRMS (electrospray ionization) calcd for $C_{20}H_{32}O_4Na$ $[M + K]^+$ 375.3284, found 375.3289.

(1*R*,2*S*,3*S*,4*S*,6*S*,7*R*,8*R*,9*R*,10*S*)-Acetic Acid 9-Hydroxy-6-isopropenyl-4,9,13-trimethyl-15-oxatricyclo[6.6.1.0^{2,7}]pentadec-12-en-3,10-yl Diester (56). Into a flask containing the triol (122 mg, 0.363 mmol) in 10 mL of CH_2Cl_2 were added triethylamine (253 μL, 1.81 mmol) and 4-dimethylaminopyridine (4.4 mg, 0.036 mmol). Acetic anhydride (103 μL, 1.09 mmol) was added to the solution, and the resulting solution was stirred for 5 h. The reaction was quenched using saturated aqueous NH_4Cl, and the layers were separated. The aqueous portions were washed twice with CH_2Cl_2, dried over Na_2SO_4, and concentrated in vacuo. Purification via flash column chromatography (20% EtOAc/hexanes) gave 130 mg (85%) of the ester as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$, 60 °C) δ 0.90 (d, J = 7.0 Hz, 3H), 1.24 (s, 3H), 1.47 (m, 1H), 1.63 (ddd, J = 13.5, 8.8, 4.1 Hz, 1H), 1.71 (s, 3H), 1.79 (s, 3H), 1.90 (dd, J = 14.8, 3.6 Hz, 1H), 1.91−2.08 (m, 2H), 2.04 (s, 3H), 2.07 (s, 3H), 2.25−2.34 (m, 2H), 2.61−2.68 (m, 2H), 2.77 (d, J = 14.9 Hz, 1H), 3.12 (ddd, J = 12.9, 11.5, 8.2 Hz, 1H), 3.90 (d, J = 6.4 Hz, 1H), 4.19 (d, J = 2.6 Hz, 1H), 4.75 (m 1H), 4.76 (s, 1H), 4.84 (s, 1H), 5.16 (dd, J = 4.1, 4.1 Hz, 1H), 5.70 (dd, J = 11.2, 6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 60 °C) δ 16.5, 20.9, 21.1, 21.3, 23.5, 28.3, 29.6, 29.8, 32.9, 37.9, 39.2, 42.1, 43.8, 73.7, 75.5, 78.7, 79.6, 87.6, 111.1, 125.2, 134.9, 148.3, 170.51, 170.54; IR (film) 3362 (br), 2933, 1734 (str), 1448, 1374, 1238 (str), 1038 cm^{-1}; $[\alpha]^{22}_D$ = +18 (c = 3.1, $CHCl_3$); HRMS (electrospray ionization) calcd for $C_{24}H_{36}O_6Na$ $[M + Na]^+$ 443.2410, found 443.2408.

(1*R*,1*S*′,2*S*,3*S*,4*S*,6*S*,7*R*,8*R*,9*R*,10*S*)-Acetic Acid 9-Hydroxy-6-(2-hydroxy-1-methylethyl)-4,9,13-trimethyl-15-oxatricyclo-[6.6.1.0^{2,7}]pentadec-12-en-3,10-yl Diester (57). A flask was charged with alkene **56** (16.1 mg, 38.3 μmol) in 1 mL of THF. (+)-Diisopinocampheylborane (33.1 mg, 115 μmol) was added to the solution, and the resulting solution was allowed to stir 30 min. The reaction was quenched by the addition of 1 mL of water and sodium perborate tetrahydrate (53.0 mg, 345 μmol), allowed to stir for 3 h, and then diluted with brine and Et_2O. The layers were separated, and the aqueous portion was washed twice with Et_2O, dried over Na_2SO_4, and concentrated in vacuo. Purification via flash column chromatography (10% then 30% EtOAc/hexanes) gave 12.3 mg (74%) of the diol as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.82 (d, J = 6.0 Hz, 3H), 8.87 (d, J = 6.9 Hz, 3H), 1.02 (m, 1H), 1.17 (m, 1H), 1.38 (s, 3H), 1.70−1.92 (m, 5H), 1.81 (s, 3H), 2.06 (m, 1H), 2.10 (s, 3H), 2.11 (s, 3H), 2.90 (br s, 1H), 2.46 (dd, J = 10.3, 8.1 Hz, 1H), 2.69 (d, J = 14.8 Hz, 1H), 3.15 (ddd, J = 13.5, 11.5, 7.7 Hz, 1H), 3.53−3.62 (m, 3H), 3.87 (d, J = 10.7 Hz, 1H), 4.04 (s, 1H), 4.89 (d, J = 7.6 Hz, 1H), 5.18 (d, J = 3.3 Hz, 1H), 5.65 (dd, J = 10.3, 4.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 18.4, 21.2, 21.5, 21.8, 23.3, 24.7, 28.3, 29.4, 30.9, 32.5, 36.6, 38.0, 41.0, 45.7, 65.0, 73.8, 75.7, 77.8, 79.9, 88.7, 125.2, 133.9, 171.4, 171.6; IR (film) 3392 (br), 2926, 1735 (str), 1375, 1244 (str), 1024 cm^{-1}; $[\alpha]^{21}_D$ = −11 (c = 0.40, CH_2Cl_2); HRMS (electrospray ionization) calcd for $C_{24}H_{38}O_7Na$ $[M + Na]^+$ 461.2516, found 461.2519.

Asbestinin-12 (2). A flask charged with diol **57** (13.7 mg, 31.2 μmol) in 1.6 mL of $CHCl_3$ was cooled to 0 °C. 2,6-Lutidine (18.2 μL, 0.156 mmol) followed by trifluoromethanesulfonic anhydride (5.80 μL, 34.4 μmol) were added to the solution, and the resulting solution was allowed to stir 30 min at 0 °C. The solution was warmed to room temperature for 4 h and then quenched via the addition of saturated aqueous NH_4Cl. The mixture was diluted with $CHCl_2$, and the layers were separated. The aqueous portion was washed three times with CH_2Cl_2, dried over Na_2SO_4, and concentrated in vacuo. Purification via flash column chromatography (15% EtOAc/hexanes) gave 9.0 mg (69%) of asbestinin-12 as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (d, J = 7.1 Hz, 3H), 0.92 (d, J = 7.2 Hz, 3H), 1.00 (ddd, J = 13.4, 3.3, 1.7 Hz, 1H), 1.42 (s, 3H), 1.51 (ddd, J = 3.8, 3.8, 3.8 Hz, 1H), 1.62 (m, 2H), 1.79 (s,

3H), 1.85 (dd, $J = 14.6$, 4.5 Hz, 1H), 1.98 (ddd, $J = 10.8$, 3.1, 3.1 Hz, 1H), 2.02 (m, 1H), 2.10 (s, 3H), 2.12 (s, 3H), 2.26 (ddd, $J = 11.0$, 11.0, 11.0 Hz, 1H), 2.68 (d, $J = 15.1$ Hz, 1H), 3.19 (ddd, $J = 13.8$, 11.1, 7.4 Hz, 1H), 3.49 (dd, $J = 13.3$, 3.8 Hz, 1H), 3.85 (d, $J = 13.1$ Hz, 1H), 3.93 (d, $J = 9.1$ Hz, 1H), 4.10 (ddd, $J = 3.4$, 3.4, 3.4 Hz, 1H), 4.87 (d, $J = 7.4$ Hz, 1H), 5.28 (dd, $J = 4.9$, 2.9 Hz, 1H), 5.74 (dd, $J = 10.8$, 6.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.8, 18.2, 19.3, 21.3, 21.6, 29.6, 31.3, 31.4, 33.4, 36.9, 37.6, 38.3, 40.8, 44.9, 67.8, 73.6, 76.7, 79.2, 81.7, 91.3, 126.7, 131.6, 170.8, 171.3; IR (film) 2926, 1737 (str), 1459, 1377, 1231, 1088 cm^{-1}; $[\alpha]^{21}_D = -22$ ($c = 0.29$, $CHCl_3$); HRMS (electrospray ionization) calcd for $C_{24}H_{36}O_6$ $[M + Na]^+$ 443.2410, found 443.2411.

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Supporting Information Available: Experimental procedures as well as ^{1}H and ^{13}C NMR spectra for all new compounds, 11-acetoxy-4-deoxyasbestinin D, and asbestinin-12. This material is available free of charge via the Internet at http://pubs.acs.org.

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