JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Total Syntheses of Multiple Cladiellin Natural Products by Use of a Completely General Strategy

J. Stephen Clark,*[,†] Raphaëlle Berger,[†] Stewart T. Hayes,[‡] Hans Martin Senn,[†] Louis J. Farrugia,[†] Lynne H. Thomas,[†] Angus J. Morrison,[§] and Luca Gobbi[∥]

[†]WestCHEM, School of Chemistry, Joseph Black Building, University of Glasgow, University Avenue, Glasgow G12 8QQ, United Kingdom

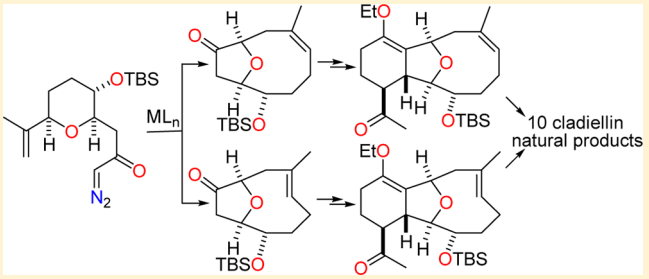
[‡]School of Chemistry, University of Nottingham, University Park, Nottingham NG7 2RD, United Kingdom

[§]MSD Newhouse Research Site, Lanarkshire ML1 5SH, United Kingdom

[∥]Discovery Chemistry (PRCB), F. Hoffmann-La Roche Ltd. Pharmaceuticals Division, CH-4070 Basel, Switzerland

Supporting Information

ABSTRACT: The enantioselective total syntheses of 10 cladiellin natural products have been completed, starting from the known allylic alcohol (+)-**14**, which can be prepared in large quantities. The bridged tricyclic core of the cladiellins has been constructed via three ring-forming reactions: (i) an intramolecular reductive cyclization between an aldehyde and an unsaturated ester, mediated by samarium(II) iodide, to form a tetrahydropyranol; (ii) reaction of a metal carbenoid, generated from a diazo ketone, with an ether to produce an ylide-like intermediate that rearranges to produce *E*- or *Z*-oxabicyclo[6.2.1]-5-undecen-9-one; and (iii) a Diels–Alder cycloaddition reaction to construct the third ring found in the core structure of the cladiellins. The key ring-forming reaction, in which a diazo ketone is converted into a bridged bicyclic ether, can be tuned to give either of the isomeric oxabicyclo[6.2.1]-5-undecen-9-ones as the major product by switching from a copper to a rhodium catalyst and selecting the appropriate reaction conditions. The tricyclic products obtained from the three-step sequence involving the Diels–Alder cycloaddition reaction can be employed as advanced intermediates to prepare a wide range of cladiellin natural products.



INTRODUCTION

In 1968, Kennard et al.[1] reported the isolation of a novel diterpene from samples of the gorgonian *Eunicella stricta* collected in the Mediterranean near Banyuls-sur-Mer; the same compound was later isolated from samples of *Eunicella labiata* collected off the coast of southern Spain.[2] The compound was named eunicellin and was identified as the first member of what transpired to be a large family of ether-bridged tricyclic diterpenes (Figure 1).[3,4] To date, more than 100 cladiellin (also termed eunicellin) natural products have been isolated from marine invertebrates found in diverse locations, and many of them display significant biological activities.[3,4]

The cladiellins comprise the largest subset of a group of diterpenes that includes the sarcodictyins, briarellins, and asbestinins (Figure 2).[3] Faulkner and co-workers[5] proposed that the cladiellins, briarellins, and asbestinins are connected biosynthetically and are produced by transannular bond formation between C-2 and C-11 and subsequent introduction of the ether bridge. Formation of a seven-membered cyclic ether or lactone by bond construction between the C-3 hydroxyl group and one of the methyl groups in the isopropyl side chain leads to the briarellin skeleton, and subsequent migration of a methyl group produces the asbestinins. The sarcodictyins were isolated after Faulkner's hypothesis but conform to this general biosynthetic scheme.[6]

All cladiellins possess an oxatricyclo[6.6.1.0^{2,7}]pentadecane ring system bearing one-carbon substituents at C-3, C-7, and C-11 (cladiellin numbering) and an isopropyl group or oxidized isopropyl group at C-14.[3,4] In a few cases, an additional ether bridge spans the nine-membered ring. The cladiellins also possess varying levels of unsaturation and oxygenation; unsaturation is usually located at C-6–C-7/C-7–C-16 and at C-11–C-12/C-11–C-17, and oxygenation occurs at C-3 and frequently at positions C-6, C-7, and C-11–C-13 (see examples in Figure 1). Although the cladiellins share the same ether-bridged skeleton, structural errors and stereochemical mis-assignments have occurred in some cases where structure has been deduced on the basis of NMR data alone. Friedrich and Paquette[7] have attempted to correct errors associated with polyhydroxylated cladiellins by reanalyzing the NMR data reported for these compounds and comparing it to data obtained from cladiellins whose structures have been confirmed by synthesis or by use of X-ray diffraction data. However, the

Received: November 27, 2012

   dx.doi.org/10.1021/jo302542h | *J. Org. Chem.* XXXX, XXX, XXX–XXX

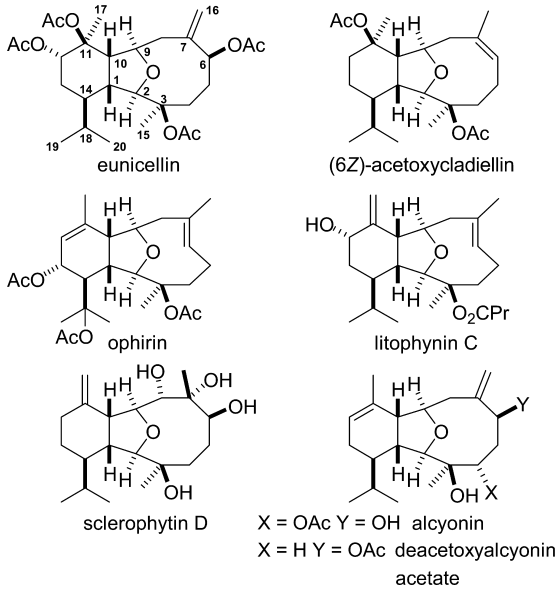


Figure 1. Representative cladiellin natural products illustrating structural diversity.

stuctures of many cladiellins have yet to be confirmed by synthesis, and it is likely that some errors remain.

The work presented in this article concerns the total synthesis of the cladiellin natural products shown in Figure 3. Over the past 15 years or so, the cladiellins have become popular synthetic targets because of their challenging core structures, the dense functionality found in many of them, and the significant challenges they present with regard to stereocontrol.[8]

The first total synthesis of a cladiellin natural product was reported by MacMillan and Overman in 1995.[9a] They completed a total synthesis of (−)-6-acetoxycladiella-7(16),11-dien-3-ol [also named (−)-deacetoxyalcyonin acetate] in 19 steps, starting from (*S*)-dihydrocarvone. In this synthesis a Prins-pinacol condensation−rearrangement sequence was used to construct a reduced isobenzofuran system, and formation of the medium ring was accomplished by an intramolecular Nozaki−Hiyama−Kishi reaction. The same combination of reactions was used to prepare the compound

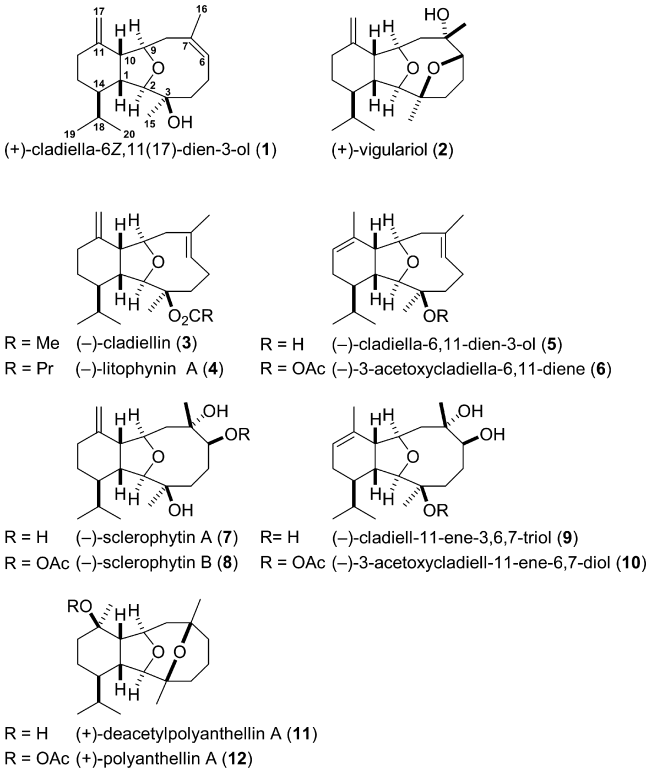


Figure 3. Cladiellin natural product targets.

that had been proposed to be sclerophytin A, thereby demonstrating that the natural product did not have the structure suggested originally (Figure 4).[9b,10] In contemporaneous studies, Paquette and co-workers[11] prepared the compound that had been proposed to be sclerophytin A,

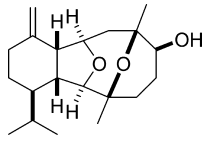


Figure 4. Structure originally proposed for sclerophytin A.

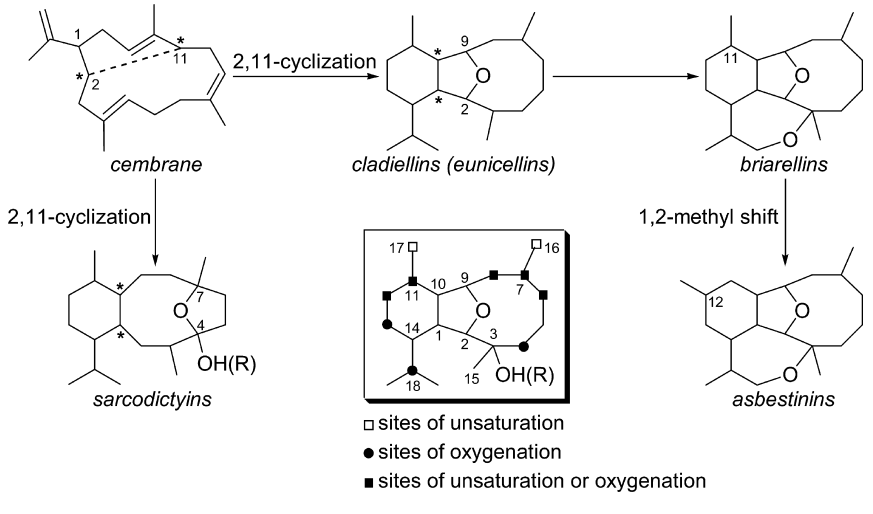


Figure 2. Faulkner's proposed biosynthesis of oxygen-bridged 2,11-cyclized diterpene natural products.

dx.doi.org/10.1021/jo302542h | *J. Org. Chem.* XXXX, XXX, XXX−XXX

using a ring-expanding Claisen rearrangement reaction to construct the medium-sized ring. Subsequently, the Overman and Paquette groups[12] assigned new structures to sclerophytins A and B (compounds **7** and **8** in Figure 3) and completed total syntheses of both natural products.

Following the pioneering work of the Overman and Paquette groups, several other groups made significant synthetic contributions to this area. Molander et al.[13] synthesized (−)-6-acetoxycladiella-7(16),11-dien-3-ol (Figure 1) in 18 steps, starting from the natural product (*R*)-(−)-*α*-phellandrene. In their synthetic route, sequential [4 + 3] cycloaddition and Nozaki−Hiyama−Kishi reactions were used to construct a tetracyclic intermediate that underwent ring scission to reveal the medium-ring ether and deliver the tricyclic core. Crimmins et al.[14] then developed a highly successful strategy for the synthesis of many of the cladiellins in which ring-closing metathesis (RCM) is used to construct the nine-membered cyclic ether and the other rings are constructed stereoselectively using an intramolecular Diels−Alder reaction. The Crimmins group has used this strategy to prepare (−)-ophirin B,[14a,c] (−)-astrogorgin,[14c] (+)-vigulariol (**2**),[14f] and (−)-sclerophytin A (**7**)[14f] as well as 11-acetoxy-4-deoxyasbestinin,[14b,d] asbestinin-12,[14d] and the compound originally purported to be briarellin J.[14e]

The vast majority of cladiellin natural products possess an *E*-alkene at C-6 to C-7 or an anti 1,2-diol that would result from syn dihydroxylation of this alkene. Most strategies used for the construction of the cladiellins are not amenable to the introduction of the strained *E*-alkene into the medium-sized ring. However, in 2006, Kim and co-workers[15] reported that intramolecular amide alkylation with an *E* allylic chloride as the electrophile could be used to construct an *E*-oxonene that could be elaborated to give the complete cladiellin system possessing an *E*-alkene at C-6−C-7. This approach was used to complete total syntheses of (−)-6-acetoxycladiella-7(16),11-dien-3-ol (deacetoxyalcyonin acetate), (−)-cladiella-6,11-dien-3-ol (**5**), (−)-cladiell-11-ene-3,6,7-triol (**9**), and (+)-polyanthellin A (**12**) (Figures 1 and 3).[15]

Over the past four years, several other research groups have reported total syntheses of members of the cladiellin family of natural products. Hoppe and co-workers[16] reported a concise total synthesis of (+)-vigulariol from (*R*)-(−)-cryptone in which their asymmetric homoaldol methodology was used to generate a reduced isobenzofuran and RCM was employed to construct the third ring. Although this synthesis is undoubtedly the shortest reported for any cladiellin natural product, the yield was modest for a route of such brevity, due to the formation of mixtures of isomers and relatively low yields during the homoaldol and RCM reactions. Nevertheless, this synthesis is a testemony to the power of Hoppe's asymmetric homoaldol methodology.

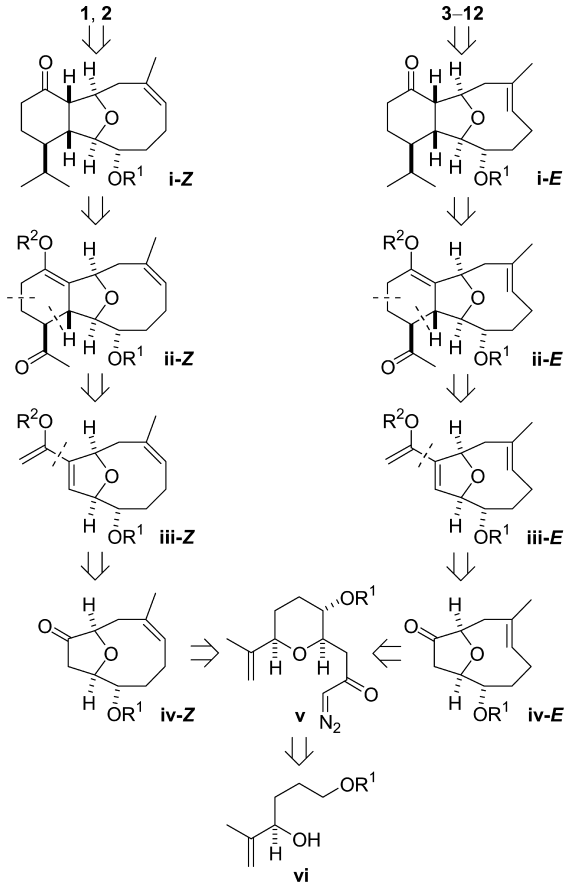
In 2009, Campbell and Johnson[17] reported a concise total synthesis of (+)-polyanthellin A from methallyl alcohol. In common with the Overman and Hoppe strategies, a reduced isobenzofuran was synthesized first and RCM was then employed to close the medium-sized ring. In this case, however, a Lewis-acid-mediated [3 + 2] cycloaddition of a cyclopropane to an aldehyde was used to construct the reduced isobenzofuran system. The following year, Morken and co-workers[18,19] reported a synthesis of (−)-sclerophytin A from geranial that also proceeded via a reduced isobenzofuran, prepared by Oshima−Utimoto reaction of an allylic alcohol and a subsequent radical cyclization reaction, and relied on RCM to construct the third ring.

In published total syntheses where RCM has been used to construct a medium-sized ring containing a trisubstituted *Z*-alkene, yields of 40−50% have been obtained. The majority of cladiellins possess a highly strained *E*-alkene or an anti 1,2-diol that would result from syn dihydroxylation of an *E*-alkene, rather than a *Z*-alkene, at C-6−C-7. However, with the exception of that devised by Kim and co-workers,[15] published strategies do not allow introduction of a strained *E*-alkene into the nine-membered ring. Our objective was to develop a completely general approach to the synthesis of cladiellins that would not rely on RCM to construct the medium-sized ring and that could be used to prepare compounds containing either an *E*- or *Z*-alkene at C-6−C-7 and also the polyhydroxylated sclerophytin-type natural products. We now report the successful realization of this strategy and its application to the total synthesis of 10 cladiellin natural products (Figure 3).[20]

RESULTS AND DISCUSSION

Total syntheses were based on the retrosynthetic analysis shown in Scheme 1. In the case of (+)-cladiella-6*Z*,11(17)-dien-3-ol (**Z-1**) and (+)-vigulariol (**2**), removal of the methylene group at C-17 and the methyl substituent (C-15) at C-3 leads to the ketone **i-Z**. For the *E*-configured natural products **3**−**6**, those containing an anti 1,2-diol at C-6 and C-7 (natural products **7**−**10**), and compounds containing a C-3−C7 ether bridge (compounds **11** and **12**), analogous disconnections of

Scheme 1. Retrosynthetic Analysis for Cladiellin Natural Products



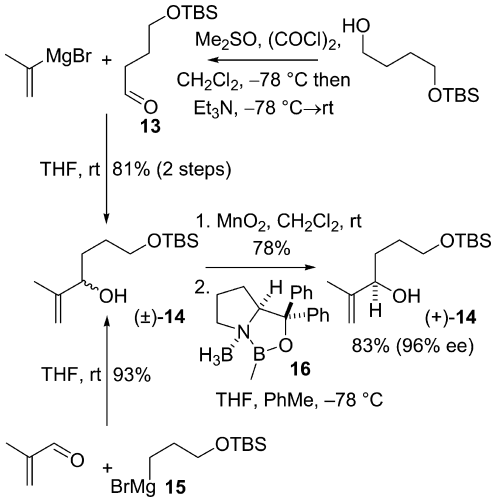
dx.doi.org/10.1021/jo302542h | J. Org. Chem. XXXX, XXX, XXX−XXX

one-carbon fragments from C-3 and C-15 give the isomeric intermediate **i-*E***. Conversion of the isopropyl group into a methyl ketone and the C-11 carbonyl group into an enol ether (C-11−C-10) in each case gives the tricylic systems **ii-*Z*** and **ii-*E***. Diels−Alder disconnection then reveals the isomeric bicyclic dienes **iii-*Z*** and **iii-*E***. The diene **iii-*Z*** is disconnected to give the bicyclic ketone **iv-*Z***, and the diene **iii-*E*** is disconnected to give the bicyclic ketone **iv-*E***. In principle, the isomeric ketones **iv-*Z*** and **iv-*E*** could be prepared by rearrangement of an oxonium ylide or ylide equivalent produced by reaction of the ether with a metal carbenoid generated from the diazo ketone **v**.[21−24] The diazo ketone **v** can be disconnected further to give the simple allylic alcohol **vi** as the starting material.

The synthetic strategy implied by the analysis in Scheme 1 has several attractive features. First, the ketones **iv-*Z*** and **iv-*E*** are isomers produced from a common intermediate (**v**) relatively late in the synthesis. Second, the routes from ketones **iv-*Z*** and **iv-*E*** to the late-stage tricyclic intermediates **i-*Z*** and **i-*E*** run in parallel, with common methodology employed in both series. Finally, the late-stage intermediates **i-*Z*** and **i-*E*** possess the functionality required to access virtually any member of the cladiellin family of natural products.

The first objective was preparation of the cyclization precursor corresponding to the diazo ketone **v** shown in Scheme 1. The starting material selected for the synthesis is the allylic alcohol (+)-**14** and this compound was prepared with high enantiomeric excess (ee) by two approaches (Schemes 2

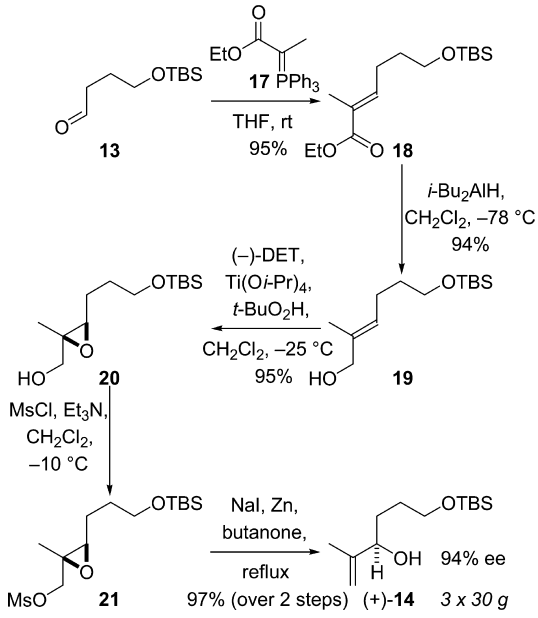
Scheme 2. Enantioselective Synthesis of Alcohol (+)-14 by Enantioselective Ketone Reduction



and 3). In the first approach (Scheme 2), addition of 2-propenylmagnesium bromide to the aldehyde **13** or reaction of the Grignard reagent **15** with methacrolein was used to prepare the alcohol (±)-**14**. Oxidation and asymmetric reduction of the resulting enone, by use of the oxazaborolidine **16** and following the well-established CBS protocol, afforded the alcohol (+)-**14** in 83% yield and with 96% ee.[25]

For large-scale work a more cost-effective method for the production of the allylic alcohol (+)-**14** was required, and this was accomplished via a route devised by Williams et al.[26] (Scheme 3). The synthesis commenced with Wittig olefination of the aldehyde **13** with the stabilized ylide **17** to afford the α,β-unsaturated ester **18**. Ester reduction afforded the allylic alcohol **19**, and subsequent Sharpless asymmetric epoxidation provided

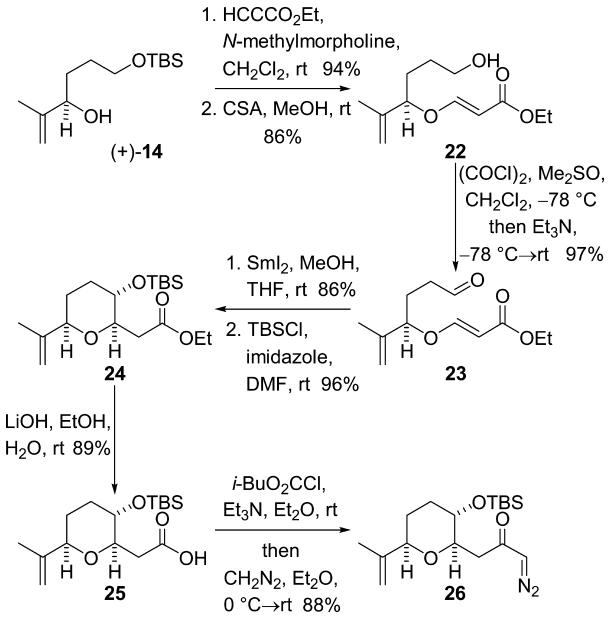
Scheme 3. Enantioselective Synthesis of Allylic Alcohol (+)-14 on a Large Scale



the epoxyalcohol **20** in high yield and with high ee (confirmed by HPLC analysis of a later intermediate in the synthesis, vide infra).[27] The epoxy alcohol **20** was then converted into the allylic alcohol (+)-**14** in 97% yield by mesylation of the free hydroxyl group and treatment of the resulting mesylate **21** with sodium iodide and zinc powder in butanone at reflux.[26] The sequence provided the allylic alcohol (+)-**14** with 94% ee and in sufficient quantities (>30 g per batch) to complete the syntheses of 10 cladiellin natural products.

The synthesis of the key α-diazo ketone **26** was undertaken as shown in Scheme 4. The allylic alcohol (+)-**14** was converted into the *E*-vinylogous carbonate (94% yield, 94% ee by chiral HPLC analysis).[28] Cleavage of the silyl ether provided the

Scheme 4. Synthesis of Diazo Ketone 26, the Key Cyclization Precursor

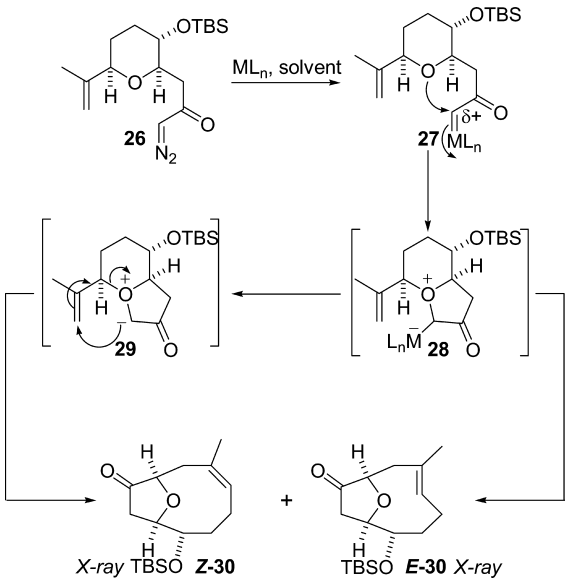


dx.doi.org/10.1021/jo302542h | J. Org. Chem. XXXX, XXX, XXX−XXX

primary alcohol **22**, and subsequent Swern oxidation delivered the aldehyde **23**. Stereoselective reductive cyclization was then performed in high yield by use of SmI_2 and employing a procedure described by Nakata and co-workers.[29] The resulting tetrahydropyranol was then silylated to give the TBS ether **24** in 96% yield. The ethyl ester was then saponified to produce the carboxylic acid **25**, and the α-diazo ketone **26** was obtained by formation of a reactive mixed anhydride and treatment of this with a 10-fold excess of diazomethane.[30]

It was anticipated that the key ring-forming reaction could be performed by treatment of the diazo ketone **26** with a suitable metal complex (ML_n) to produce an electrophilic metal carbenoid **27** (Scheme 5). Reaction of the carbenoid with the

Scheme 5. Metal-Mediated Formation of the 11-Oxabicyclo[6.2.1]-5-undecen-9-one System



ether and rearrangement of the resulting metal-bound ylide **28** or the free oxonium ylide **29** would then afford the isomeric ketones ***Z*-30** and ***E*-30** (Scheme 5).[20,23c,g,h]

Results from studies concerning the rearrangement of oxonium ylides or ylide-like intermediates generated from metal carbenoids, performed by us and others,[21−24] suggested that copper acetylacetonate complexes would serve as efficient catalysts for carbenoid generation, and so the reactions mediated by these complexes were investigated (Table 1). Treatment of the diazo ketone **26** with $Cu(acac)_2$ in dichloromethane at reflux gave a low yield of the products ***Z*-30** and ***E*-30** but with reasonable selectivity (3.5:1 *Z*:*E*) (entry 1, Table 1). A significant increase in the overall yield was obtained by use of the more electron-deficient complex $Cu(tfacac)_2$, but the *Z*:*E* isomer ratio altered little (entry 2, Table 1). In contrast, a significant improvement in both the yield (95%) and level of stereocontrol (5.0:1 *Z*:*E*) was observed when $Cu(hfacac)_2$ was employed as the catalyst and the reaction time was reduced substantially (entry 3, Table 1). A brief study of the influence of reaction temperature on the outcome of the $Cu(hfacac)_2$-mediated reaction was then conducted (entries 3−5, Table 1). Reducing the temperature to room temperature or 0 °C resulted in an increase in reaction time but also gave a marginal increase in *Z*:*E* selectivity without reducing the yield.

Table 1. Copper-Catalyzed Reactions of Diazo Ketone 26 to Give Bridged Bicyclic Ethers *Z*-30 and *E*-30 (Scheme 5)

entry	catalyst[a]	solvent	temp	time	yield **30**[b] (%)	ratio *Z*:*E* **30**[c]
1	$Cu(acac)_2$	CH_2Cl_2	reflux	3 h	30	3.5:1
2	$Cu(tfacac)_2$	CH_2Cl_2	reflux	3 h	70	3.6:1
3	$Cu(hfacac)_2$	CH_2Cl_2	reflux	15 min	95	5.0:1
4	**$Cu(hfacac)_2$**	**CH_2Cl_2**	**rt**	**3 h**	**94**	**5.9:1**
5	$Cu(hfacac)_2$	CH_2Cl_2	0 °C	7 h	96	5.5:1
6	**$Cu(hfacac)_2$**	**THF**	**reflux**	**45 min**	**74**	**6.9:1**
7	$Cu(hfacac)_2$	C_6H_6	reflux	30 min	94	4.8:1
8	$Cu(hfacac)_2$	DCE	reflux	15 min	85	3.9:1
9	$Cu(hfacac)_2$	Et_2O	reflux	15 min	93	3.1:1
10	$Cu(hfacac)_2$	MeCN	reflux	2 h	78	1.3:1
11	$Cu(hfacac)_2$	hexane/ CH_2Cl_2	reflux	15 min	92	4.0:1

[a]Commercially available complex (2 mol %) was used. [b]Combined isolated yield of *Z* and *E* isomers. [c]Isomer ratios were determined by ^1H NMR analysis of products prior to purification.

Previous work had shown that choice of solvent can have a significant influence on both the yield and level of diastereocontrol obtained from reactions of metal carbenoids with allylic ethers.[23,24] In order to explore the effect of solvent on the yield and stereochemical outcome, the $Cu(hfacac)_2$-catalyzed reaction was performed in a variety of solvents at reflux (entries 6−11, Table 1). The reaction performed in tetrahydrofuran (THF; entry 6, Table 1) resulted in highest selectivity for the *Z* isomer (6.9:1 *Z*:*E*), albeit with a reduced product yield. When the reaction was carried out in acetonitrile at reflux (entry 10, Table 1), the proportion of the *E* isomer increased substantially (1.3:1 *Z*:*E*). The use of benzene, dichloroethane (DCE), diethyl ether, or a mixture of hexane and dichloromethane afforded the products **30** in excellent yield but the *Z*:*E* isomer ratios were somewhat lower than those obtained when the reactions were performed in dichloromethane or THF at reflux (entries 7−9 and 11, Table 1). Interestingly, although the results presented in Table 1 show that solvent has a significant influence on the yield and isomer ratio, a simple direct correlation to solvent polarity is not evident.

Selective synthesis of the bicyclic ketone ***E*-30** was required in order to be able to synthesize the medium-ring core bearing an *E*-alkene. Although it was possible to tune the copper-catalyzed reaction by changing the solvent, it was not possible to achieve complete reversal of stereoselectivity, and so rhodium complexes were screened as catalysts. Copper complexes are usually superior catalysts for the generation and rearrangement of oxonium ylides or ylide-like intermediates from allylic ethers, but we have observed dramatic changes in both the yield and stereochemical outcome when allylic ethers react with rhodium carbenoids to give medium-ring carbocycles.[23e,f] Thus, the use of rhodium complexes as catalysts allowed both the steric and electronic properties of the ligand(s) attached to the metal center to be varied in an attempt to tune the reaction to give predominantly the bridged bicyclic ether ***E*-30**.

Preliminary results showed that reaction of the diazo ketone **26** with $Rh_2(OAc)_4$ in dichloromethane delivered a mixture (1.2:1 *E*:*Z*) of the bicyclic ethers **30** in 52% yield (entry 1, Table 2). Five other rhodium(II) carboxylate complexes were screened as catalysts in dichloromethane at reflux (entries 2−5

dx.doi.org/10.1021/jo302542h | J. Org. Chem. XXXX, XXX, XXX−XXX

Table 2. Rhodium-Catalyzed Reactions of Diazo Ketone 26 to Give Bridged Bicyclic Ethers *Z*-30 and *E*-30 (Scheme 5)

entry	catalyst[a]	solvent	temp	time	yield 30[b] (%)	ratio *Z*:*E* 30[c]
1	$Rh_2(OAc)_4$	CH_2Cl_2	reflux	1 h	52	1.2:1
2	$Rh_2(tfa)_4$	CH_2Cl_2	reflux	25 min	90	1.7:1
3	$Rh_2(tfacam)_4$	CH_2Cl_2	reflux	15 min	63	1:1.2
4	$Rh_2(cap)_4$	CH_2Cl_2	reflux	15 min	*d*	*d*
5	$Rh_2(pfb)_4$	CH_2Cl_2	reflux	15 min	71	1:2.7
6	$Rh_2(pfb)_4$	CH_2Cl_2	rt	30 min	36	1.5:1
7	$Rh_2(pfb)_4$	THF	reflux	15 min	74	1:1.7
8	$Rh_2(pfb)_4$	THF	rt	30 min	19	1:1.1
9	$Rh_2(pfb)_4$	DCE	reflux	15 min	66	1:1.4
10	$Rh_2(tpa)_4$	CH_2Cl_2	reflux	15 min	63	1:4.3
11	$Rh_2(tpa)_4$	CH_2Cl_2	rt	1 h	49	1:1.8
12	$Rh_2(tpa)_4$	THF	reflux	15 min	45	1:2.7
13	$Rh_2(tpa)_4$	THF	rt	18 h	32	1.4:1
14	**$Rh_2(tpa)_4$**	**DCE**	**reflux**	**15 min**	**56**	**1:6.3**

[a]2 mol % rhodium complex was used. [b]Combined isolated yield of *Z* and *E* isomers. [c]Isomer ratios were determined by ^{1}H NMR analysis of products prior to purification. [d]Neither of the desired bicyclic ketones was produced and a complex mixture of other products was obtained.

and 10, Table 2).[31] The complex $Rh_2(tfa)_4$ gave the bicyclic ketones **30** in excellent yield (1.7:1 *Z*:*E*) (entry 2, Table 2), while $Rh_2(tfacam)_4$[31a] afforded the bicyclic ketones **30** (1:1.2 *Z*:*E*) in 63% yield (entry 3, Table 2). When the reaction was performed with $Rh_2(cap)_4$,[31b] the bicyclic ketones **30** were not obtained (entry 4, Table 2). More promising results were obtained when either $Rh_2(pfb)_4$[31c,d] or $Rh_2(tpa)_4$[31e] was employed as the catalyst in dichloromethane at reflux (entries 5 and 10, Table 2). These catalysts delivered a reasonable yield of the bridged bicyclic ethers **30** with a significant preference for the *E* isomer.

The promising initial results obtained when either $Rh_2(pfb)_4$ or $Rh_2(tpa)_4$ was employed as the catalyst encouraged their further investigation, and so reactions were performed in dichloromethane, THF, or dichloroethane at room temperature or at reflux (entries 5−14, Table 2). In the case of both $Rh_2(pfb)_4$ and $Rh_2(tpa)_4$, the yields and levels of *E*-selectivity were generally lower when the reactions were performed at room temperature. The best result was obtained when the reaction was performed with $Rh_2(tpa)_4$ in DCE at reflux. In this case, the bridged bicyclic ethers **30** were obtained in 56% yield with 1:6.3 preference for the required *E* isomer (entry 14, Table 2).

The isomeric products ***Z*-30** and ***E*-30** are separable by column chromatography on silver nitrate-impregnated silica gel and are crystalline solids. It was possible to confirm their structures by X-ray analysis (racemic material was used), and the X-ray diffraction data for compound (±)-***E*-30** shows that the alkene is twisted out of planarity by an angle of approximately 20°, indicating that ***E*-30** is significantly higher in energy than ***Z*-30**. This was confirmed by exposure of (±)-***E*-30** to a solution of 2,2′-azobis(isobutyronitrile) (AIBN) and ethanethiol in benzene at reflux, which resulted in complete isomerization to give the thermodynamically more stable compound (±)-***Z*-30**.[32]

The fact that the changes in catalyst produce dramatic variations in the stereochemical outcome suggests that the reaction might proceed through a metal-bound ylide rather than a free ylide. In order to prove that the observed diastereoselectivities did not arise because of product isomerization, control reactions were performed in which each of the bicyclic ketones **30** was heated at reflux in dichloromethane in presence of either $Cu(hfacac)_2$ or $Rh_2(tpa)_4$ for 2 h. In both cases, alkene isomerization was not observed, a finding which means that the observed *E*:*Z* ratios reflect the kinetic ratios produced by the rearrangement reaction. Given that the rearrangement reaction is irreversible and there is no evidence for alkene isomerization after rearrangement, the distribution of isomers must arise either because rearrangement takes place from diastereomeric ylides with differing configurations at the oxonium center or because C−C bond formation proceeds directly from metal-bound intermediates that are not free ylides.

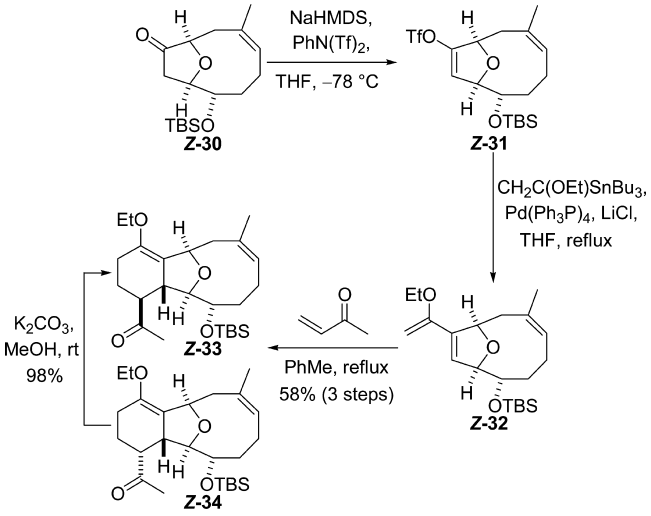
With these experimental findings in mind, we embarked on a computational study to explore the reactivities of the putative diastereomeric free oxonium ylides (see Supporting Information). The key question was whether rearrangement of the free ylide **29** would be expected to give either the *Z*- or *E*-configured product **30** preferentially. To shed light onto this problem, we investigated the conformational landscape and the [2,3]-sigmatropic rearrangement reaction of a slightly simplified model ylide, an analogue of ylide **29** in Scheme 5, using density functional theory (see Supporting Information). This computational study of the energetics of rearrangement of the free oxonium ylide suggested that the reaction should proceed with low *E*/*Z* selectivity. The fact that rearrangement in the presence of the catalyst does proceed diastereoselectively, and that selectivity can be controlled by choice of the catalyst and reaction conditions, suggests that a free ylide is not involved in the reaction.

Synthesis of (+)-Cladiella-6*Z*,11(17)-dien-3-ol (*Z*-1) and (+)-Vigulariol (2). The first natural product target selected for total synthesis was (+)-vigulariol (**2**) (Figure 3).[20a] This compound was isolated from samples of the sea pen *Vigularia juncea* collected near the Penghu Islands off the west coast of Taiwan and was found to possess in vitro cytotoxic activity against cultured A 549 (human lung adenocarcinoma) cells with an IC_{50} of 18.33 μg/mL.[33] Prior to its isolation from natural sources, vigulariol had been obtained inadvertently by Paquette and co-workers[12c] during their total synthesis of sclerophytin A. However, full characterization had not been reported prior to its isolation as a natural product.[33]

We anticipated preparing (+)-vigulariol (**2**) from the alcohol ***Z*-1**, which subsequently transpired to be a natural product in its own right.[34] To synthesize ***Z*-1** from the bridged bicyclic ether ***Z*-30** following the general strategy outlined in Scheme 1, the third ring would be constructed by a Diels−Alder reaction (Scheme 6). The ketone ***Z*-30** was first converted into the enol triflate ***Z*-31** and then subjected to Stille coupling with tributyl(1-ethoxyvinyl)tin to give the ethoxy diene ***Z*-32** required for the subsequent cycloaddition reaction.[35] The Diels−Alder reaction of the diene ***Z*-32** with methyl vinyl ketone proceeded regioselectively and exhibited high diastereofacial selectivity with respect to the diene ***Z*-32**. A mixture of the isomeric tricyclic ketones ***Z*-33** and ***Z*-34** (2:1 ratio), corresponding to the expected exo and endo adducts, was obtained in 58% yield over three steps. The required isomer ***Z*-33** proved to be the more thermodynamically stable ketone, and epimerization of the mixture of Diels−Alder adducts afforded the ketone ***Z*-33** exclusively and in high yield (Scheme 6).

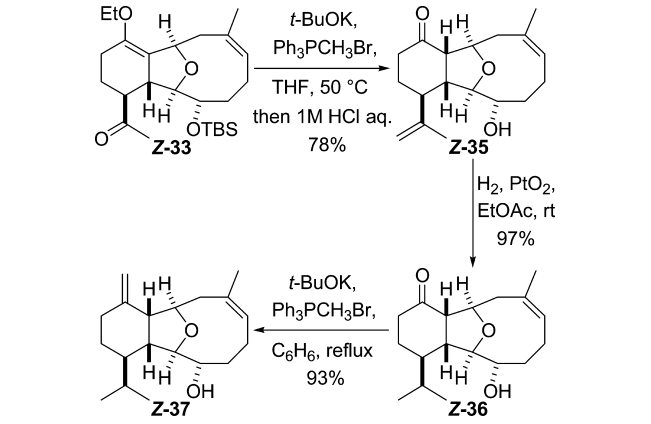
dx.doi.org/10.1021/jo302542h | *J. Org. Chem.* XXXX, XXX, XXX−XXX

Scheme 6. Conversion of *Z*-30 into the Tricyclic Cladiellin Core by Diels–Alder Reaction



Standard Wittig methylenation of the ketone and quenching of the reaction with aqueous acid afforded the hydroxyketone *Z*-**35**, resulting from enol ether hydrolysis and concomitant loss of the TBS group (Scheme 7). Selective hydrogenation of the

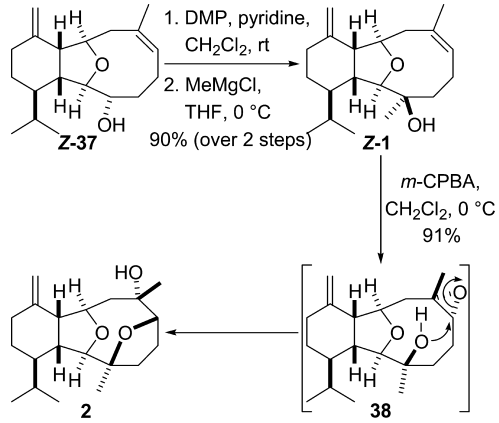
Scheme 7. Functionalization of the Tricyclic Core



side-chain alkene of the diene *Z*-**35** under carefully controlled conditions delivered the ketone *Z*-**36** in excellent yield. Methylenation of the ketone *Z*-**36** with a large excess of methylene triphenylphosphonium ylide in benzene at reflux then provided the alcohol *Z*-**37** in excellent yield.[36]

Introduction of a methyl substituent at the C-3 position was required to complete the total syntheses of the natural products **1** and **2**. Installation of the final one-carbon fragment (C-15) was accomplished by oxidation of the alcohol *Z*-**37** by the use of the Dess–Martin protocol[37] and reaction of the resulting ketone with methylmagnesium chloride in THF at 0 °C (Scheme 8). This reaction provided the tertiary alcohol *Z*-**1** in excellent yield and with a very high degree of diastereocontrol. The alcohol *Z*-**1** had been synthesized by Paquette and co-workers[12c] during studies concerning the total syntheses of scelerophytins A and B, and the spectroscopic data for our sample were found to be in close agreement with data reported by them. However, the magnitude of the optical rotation differed: $[\alpha]_D^{22}$+69.7 (*c* 0.60, $CHCl_3$) was recorded, compared to $[\alpha]_D^{22}$ +95.3 (*c* 0.40, $CHCl_3$) reported by Paquette and co-

Scheme 8. Completion of the Total Synthesis of (+)-Vigulariol (2)



workers.[12c] In addition, Paquette and co-workers reported that they isolated the alcohol *Z*-**1** as an oil, whereas the material synthesized by us is a solid with melting point 91–93 °C. Following the completion of our synthesis of (+)-cladiella-6*Z*,11(17)-dien-3-ol (*Z*-**1**), the compound was isolated along with several other cladiellin natural products from the soft coral *Cladiella pachyclados* collected in the Red Sea.[34] The NMR data for the natural material and synthetic (+)-cladiella-6*Z*,11(17)-dien-3-ol (*Z*-**1**) matched very well.[38] Very recently, Crimmins et al.[14e] disclosed a total synthesis of this compound; the NMR data, optical rotation {$[\alpha]_D^{25}$ +82.2 (*c* 0.27, $CHCl_3$)} and melting point (91–92 °C) reported by them are in close agreement with data for our sample of (+)-cladiella-6*Z*,11(17)-dien-3-ol (*Z*-**1**).

The final steps in the synthesis of (+)-vigulariol (**2**) involved chemoselective and stereoselective alkene epoxidation, followed by intramolecular nucleophilic epoxide opening by the tertiary hydroxyl group to form the ether bridge. Initially, we expected to perform this sequence of reactions in a stepwise manner, but treatment of the diene *Z*-**1** with *m*-chloroperoxybenzoic acid (*m*-CPBA) in dichloromethane at 0 °C afforded (+)-vigulariol (**2**) directly.[39] (+)-Vigulariol (**2**) was obtained instead of the epoxide **38** even when a neutral oxidant such as dimethyldioxirane was used to epoxidize the diene *Z*-**1**. This observation suggests that the epoxide is predisposed to undergo attack by the C-3 hydroxyl group because conformational effects place this substituent in close proximity to C-6 and in a position that favors nucleophilic opening of the epoxide via an S_N2 trajectory (Scheme 8). This observation has been confirmed by Hoppe and co-workers[16] and by Crimmins et al.[14e] during their total syntheses of (+)-vigulariol.

The total synthesis of (+)-cladiella-6*Z*,11(17)-dien-3-ol (*Z*-**1**) from the known and readily available allylic alcohol (+)-**14** was accomplished in 16 steps and 15.1% yield. The synthesis of (+)-vigulariol (**2**) is one step longer and the natural product was obtained in 13.8% overall yield from (+)-**14**.

Synthesis of (–)-Cladiella-6,11-dien-3-ol (5), (–)-3-Acetoxycladiella-6,11-diene (6), (–)-Cladiell-11-ene-3,6,7-triol (9), and (–)-3-Acetoxycladiell-11-ene-6,7-diol (10). The vast majority of cladiellin natural products possess either a highly strained 6*E*-alkene in the medium-sized ring or an anti 1,2-diol at C-6 and C-7 that would result from syn dihydroxylation of an *E*-alkene. However, researchers have generally targeted cladiellins that contain a *Z*-alkene in the medium ring or those that lack an alkene at this position. To

dx.doi.org/10.1021/jo302542h | J. Org. Chem. XXXX, XXX, XXX–XXX

date, only Kim and co-workers[15] have devised a general route for the preparation of cladiellin natural products possessing the common but more synthetically challenging 6*E* configuration. In most previous syntheses of natural products containing an anti 1,2-diol at positions C-6 and C-7, this functionality has been introduced by syn dihydroxylation of the 6*Z*-alkene, followed by inversion of configuration at the C-6 stereocenter.[12] Thus, it is evident that any completely general strategy for the synthesis of the cladiellin natural products must be flexible enough to allow construction of the strained 6*E*-alkene as well as the 6*Z*-alkene. To test the generality of our strategy in this regard, the natural products (−)-cladiella-6,11-dien-3-ol (**5**),[40] (−)-3-acetoxycladiella-6,11-diene (**6**),[41] (−)-cladiell-11-ene-3,6,7-triol (**9**),[42] and (−)-3-acetoxycladiell-11-ene-6,7-diol (**10**)[42] were selected as targets.

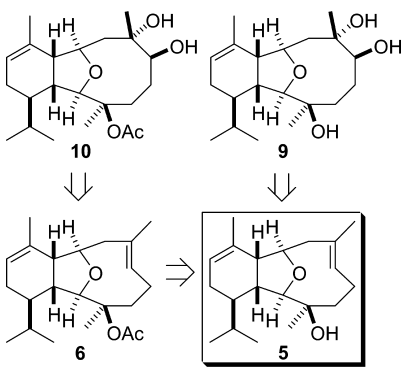
The structure of (−)-cladiella-6,11-dien-3-ol (**5**) was first reported by Hochlowski and Faulkner in 1980[40] following its isolation from an unknown soft coral collected at Majuro Atoll in the Marshall Islands. (−)-3-Acetoxycladiella-6,11-diene (**6**), the acetate derivative of the alcohol **5**, was later isolated by Shin and co-workers[41] from a gorgonian of the genus *Muricella* that had been collected near Jaeju Island, South Korea. Both the alcohol **5** and the acetate **6** were found to be active in brine-shrimp lethality assays, with the former compound having very high activity (LD_{50} 0.3 ppm). The acetate **6** also exhibited moderate in vitro cytotoxicity against several human tumor cell lines.

The natural products (−)-cladiell-11-ene-3,6,7-triol (**9**) and (−)-3-acetoxycladiell-11-ene-6,7-diol (**10**) are dihydroxylated (C-6, C-7) analogues of the cladiellins **5** and **6**.[42,43] The triol **9** and the diol **10** were isolated from a sample of a *Cladiella* species of soft coral collected at Ishigaki Island, Okinawa.[42] The compounds were fully characterized by Uchio et al.,[42,43] and the structure of the crystalline triol **9** was confirmed by X-ray diffraction analysis.

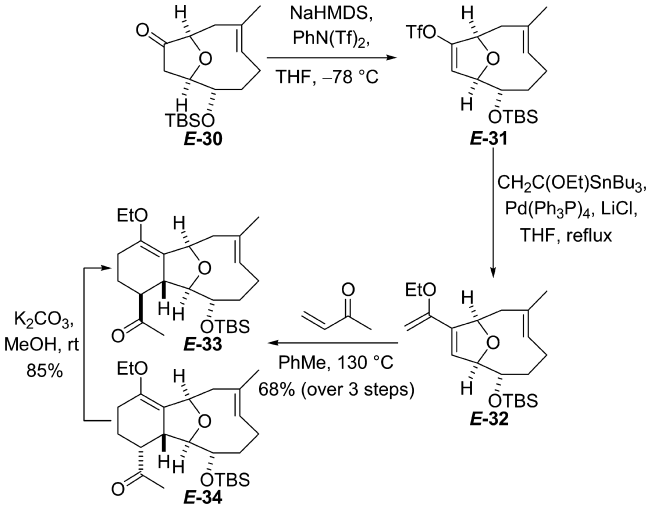
At the outset of our synthetic studies, we recognized that the cladiellin targets **6**, **9**, and **10** should be accessible from (−)-cladiella-6,11-dien-3-ol (**5**) in just one or two additional steps by acetylation and/or stereoselective dihydroxylation (Scheme 9). Consequently, the stereoselective synthesis of alcohol **5** was the primary objective.

The discovery that the bicyclic ketone ***E*-30** could be obtained as the major cyclization product from the rhodium-catalyzed reaction of diazo ketone **26** meant that the total synthesis of the cladiellin natural products possessing an *E*-alkene (e.g., compounds **3**−**6**, Figure 1) or an anti 1,2-diol in the medium-sized ring (e.g., compounds **7**−**10**, Figure 1) was a realistic proposition. The immediate synthetic objective was construction of the complete tricyclic core found in the *E*-configured cladiellins. A three-step sequence analogous to that developed for the synthesis of the tricyclic core of (+)-vigulariol (**2**) was utilized that delivered the tricyclic ketones ***E*-33** and ***E*-34** (1.6:1 ratio) in 68% yield over three steps (Scheme 10);

Scheme 9



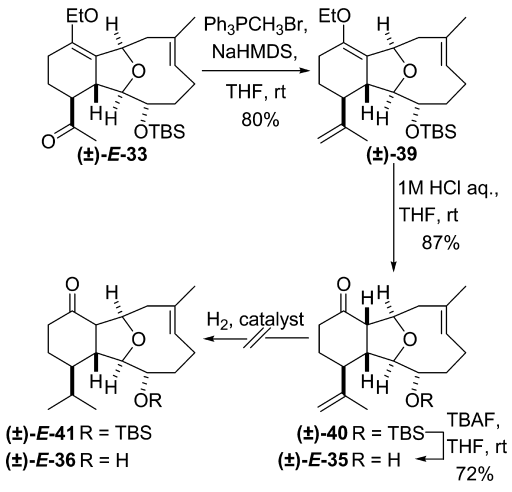
Scheme 10. Conversion of *E*-30 into the Complete Tricyclic Cladiellin Core via Diels−Alder Cycloaddition Reaction



subsequent epimerization of the mixture afforded ***E*-33** in 85% yield. In order to obtain good yields from the Stille coupling reaction, it was essential to use tributyl(1-ethoxyvinyl)tin that had been freshly prepared and distilled immediately prior to reaction with the enol triflate ***E*-31**.[44]

The next objective was transformation of the methyl ketone into the isopropyl group found in the majority of the cladiellins, and it was expected that this could be achieved by sequential ketone methylenation and selective hydrogenation by analogy with the procedure used during the total synthesis of (+)-vigulariol (**2**).[20a] Preliminary studies were performed on racemic material, and Wittig olefination of ketone (±)-***E*-33** delivered the triene (±)-**39** (Scheme 11). Subsequent acid-mediated hydrolysis of the enol ether in (±)-**39** delivered the

Scheme 11. Attempted Installation of the Isopropyl Group by Selective Hydrogenation



dx.doi.org/10.1021/jo302542h | J. Org. Chem. XXXX, XXX, XXX−XXX

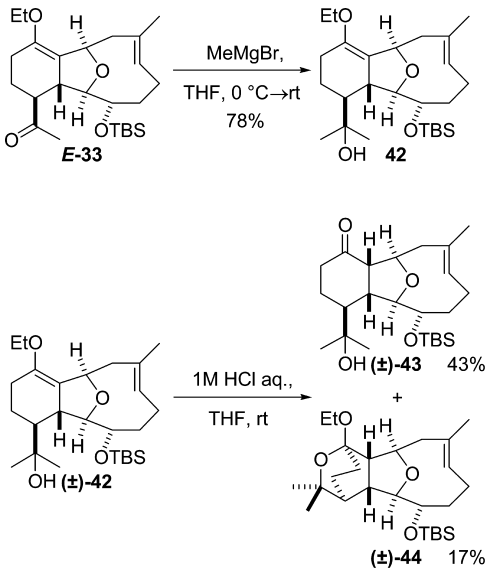
ketone (±)-**40** as a crystalline solid, which was subjected to X-ray crystallographic analysis. The X-ray data showed that selective hydrogenation would be a challenging proposition because the endocyclic *E*-alkene of the ketone (±)-**40** is twisted out of planarity by an angle of >20° and thus should be highly reactive.

Selective hydrogenation of the diene ***Z*-35** had been accomplished by use of platinum oxide and hydrogen at atmospheric pressure during the total synthesis of vigulariol (Scheme 7),[20a] but attempted hydrogenation of the diene (±)-**40** employing these conditions failed to deliver the ketone (±)-***E*-41** and gave a complex mixture of products instead (Scheme 11). When hydrogenation was performed at atmospheric or higher pressure with catalysts such as Wilkinson's catalyst, titanocene dichloride,[45] or Raney nickel, mixtures of isomerized starting material, fully saturated compounds, and decomposition products were obtained. A possible complicating factor might have been the presence of the sterically demanding TBS protecting group in (±)-**40**, which could have been shielding the terminal alkene, thereby hindering the approach of the catalyst. However, removal of the TBS group to give the free alcohol (±)-***E*-35** and subsequent hydrogenation failed to deliver the required compound (±)-***E*-36**.

It was clear that the isopropyl group could not be introduced by selective alkene hydrogenation, and so alternative approaches to the formation of this group were explored. First, selective hydroboration of the terminal alkene of diene (±)-**40** with 9-borabicyclo[3.3.1]nonane (9-BBN) followed by acidic treatment was explored.[46] However, this reaction failed to deliver the required product. Sequential reduction of the ketone (±)-***E*-33**, conversion of the resulting secondary alcohol into a suitable leaving group (tosylate, mesylate, or triflate), and displacement with various organometallic reagents also failed to give the required product.

A new approach to the construction of the isopropyl group was required. Addition of methylmagnesium bromide to the methyl ketone ***E*-33** afforded the tertiary alcohol **42**, which we hoped to deoxygenate (Scheme 12). In preliminary studies,

Scheme 12. Installation of Isopropyl Group by Deoxygenative Removal of an Acetate Group

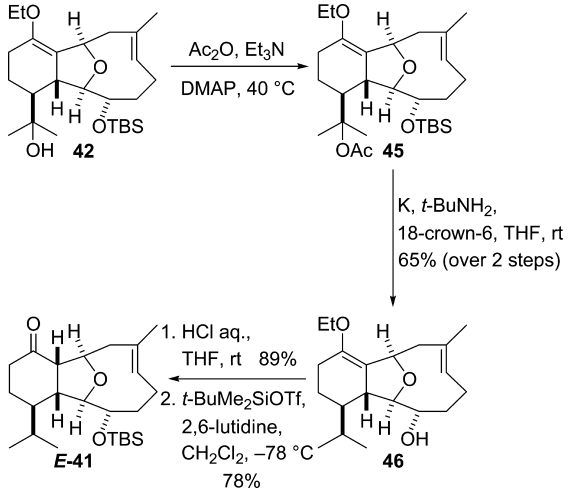


acid-mediated hydrolysis of the enol ether (±)-**42** produced a mixture of the required ketone (±)-**43** and the bridged acetal (±)-**44**. An analogous reaction had been observed by Crimmins et al.[14c] during their synthesis of ophirin B, and so formation of the bridged acetal (±)-**44** was unsurprising. Consequently, the decision was made not to reveal the ketone at C-11 until the extraneous oxygen substituent had been excised from the side chain.

It was anticipated that deoxygenation of the tertiary alcohol could be performed by use of the combination of a Lewis acid and a trialkylsilane or by employing the Barton–McCombie procedure.[47] However, attempts to perform direct reduction of the tertiary alcohol (±)-**43** with boron trifluoride etherate and triethylsilane led to isomerization and desilylation of the starting material. Preparation of the xanthate derivative of the tertiary alcohol, required to perform the Barton–McCombie deoxygenation reaction, was also unsuccessful.[47]

Kim and co-workers[15] had faced the challenge of converting a tertiary alcohol into an isopropyl group in an analogous compound during their total synthesis of cladiella-6,11-dien-3-ol (**5**). They had solved the problem by converting the tertiary alcohol into the corresponding acetate and subjecting it to reduction conditions developed by Barton and co-workers,[48] and so this sequence was investigated. The alcohol **42** was selected as the starting material in order to avoid generating the side product **44** (Scheme 12). Acetylation of this alcohol under standard conditions delivered the tertiary acetate **45** required for the reduction reaction (Scheme 13). A solution of acetate

Scheme 13. Elaboration of the Tricyclic Core to Produce the Key Advanced Intermediate *E*-41



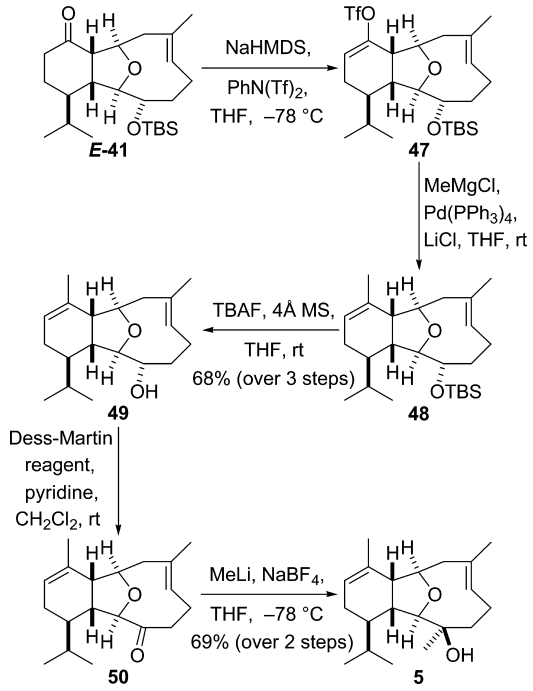
45 in THF was then added to the deep blue solution produced by solvation of potassium metal by 18-crown-6 in a mixture of *t*-butylamine and THF.[49,50] After reappearance of the royal-blue coloration, the remaining potassium was consumed by addition of ethanol, and the alcohol **46** was then isolated in 65% yield over two steps. Various workup procedures were explored in an attempt to prevent loss of the TBS protecting group during the reduction reaction, but the alcohol **46** was obtained as the major or sole product in all cases.

Following the successful synthesis of alcohol **46** possessing the requisite isopropyl substituent, the next objective was formation of the trisubtituted alkene present in the six-membered ring of cladiella-6,11-dien-3-ol (**5**). Hydrolysis of the

dx.doi.org/10.1021/jo302542h | *J. Org. Chem.* XXXX, XXX, XXX–XXX

enol ether **46** under acidic conditions afforded the corresponding ketone (Scheme 13). Reprotection of the secondary alcohol as TBS ether was achieved to give the silyl ether ***E*-41**. Kinetic deprotonation of the ketone and trapping of the enolate as the triflate was performed by treatment of ketone **41** with sodium bis(trimethylsilyl)amide (NaHMDS) in the presence of $PhNTf_2$ at −78 °C (Scheme 14). The resulting enol triflate

Scheme 14. Completion of Synthesis of the (−)-Cladiella-6,11-dien-3-ol (5)

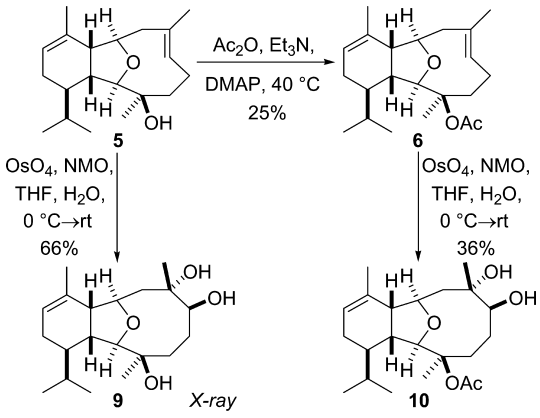


47 was subjected to a Kumada-type coupling reaction with methylmagnesium chloride to afford diene **48** possessing the requisite trisubstituted alkene.[51] The diene **48** could not be separated from phosphine impurities generated from the palladium catalyst, and so the crude product was treated with tetra-*n*-butylammonium fluoride (TBAF) to give the secondary alcohol **49**, which could be purified more easily.

The alcohol **49** is the C-3 epimer of a compound prepared by Kim and co-workers[15] as a late-stage intermediate during their total synthesis of (−)-cladiella-6,11-dien-3-ol (**5**). The synthesis of **5** was completed in two further steps: oxidation of the secondary alcohol to give the ketone **50** and subsequent nucleophilic addition to install the final methyl group (Scheme 14). There were concerns regarding the stability of the ketone **50** and so this compound was subjected to the final nucleophilic addition reaction without purification. Standard Grignard addition of methylmagnesium chloride to the ketone **50** produced (−)-cladiella-6,11-dien-3-ol (**5**) in 58% over the two steps, and the yield could be improved to 69% over two steps by employing the protocol (reaction with methyllithium in the presence of $NaBF_4$ at −78 °C) developed by Paquette.[11a,12c] (−)-Cladiella-6,11-dien-3-ol (**5**) was obtained with high diastereoselectivity, and the spectroscopic and other data for this compound were identical to those reported for the natural product.[40]

Kim and co-workers[15] had reported that the natural product (−)-cladiell-11-ene-3,6,7-triol (**9**) could be obtained by dihydroxylation of (−)-cladiella-6,11-dien-3-ol (**5**). Dihydroxylation was found to be highly diastereoselective, and the triol **9** was obtained as a single diastereomer in 66% yield by treatment of the diene **5** with osmium tetroxide (2 mol %) in the presence of *N*-methylmorpholine *N*-oxide (NMO) as stoichiometric reoxidant (Scheme 15). The spectroscopic and other data for

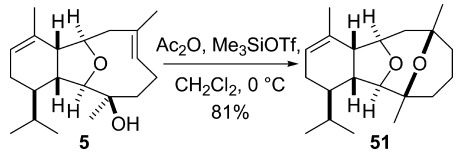
Scheme 15. Synthesis of (−)-3-Acetoxycladiella-6,11-diene (6), (−)-Cladiell-11-ene-3,6,7-triol (9), and (−)-3-Acetoxycladiell-11-ene-6,7-diol (10) from (−)-Cladiella-6,11-dien-3-ol (5)



synthetic (−)-cladiell-11-ene-3,6,7-triol (**9**) were identical to those reported for the natural product.[42,52] The triol **9** was isolated as a colorless crystalline solid, allowing further structural confirmation by single-crystal X-ray crystallography.

Two further natural products (**6** and **10**) were prepared from (−)-cladiella-6,11-dien-3-ol (**5**) (Scheme 15). (−)-Acetoxycladiella-6,11-diene (**6**) had not been synthesized previously, and acetylation of the tertiary alcohol **5** to give this compound proved to be surprisingly difficult. After considerable experimentation, the acetate **6** could be obtained by treatment of the alcohol **5** with triethylamine and DMAP, with acetic anhydride as solvent at 40 °C. Despite the modest yield, sufficient material was prepared to show that spectroscopic and other data matched those reported for the natural material.[41] Interestingly, attempted acetylation of the alcohol **5** by treatment with acetic anhydride and trimethylsilyl trifluoromethanesulfonate (TMSOTf) produced the tetracyclic compound **51** (Scheme 16).[53] Hochlowski and Faulkner[40] had reported

Scheme 16



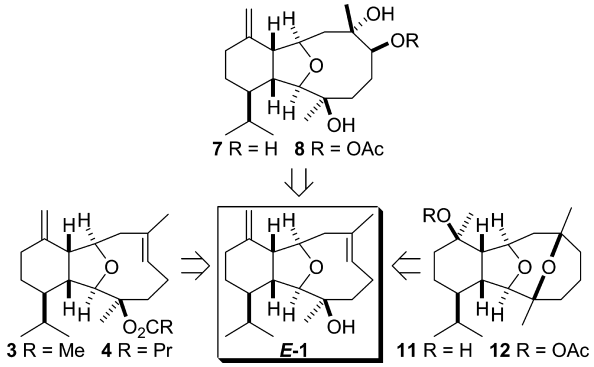
formation of this compound by treatment of the natural product **5** with boron trifluoride etherate during their isolation work. Kim and co-workers[15] had also observed this reaction during their total synthesis of polyanthellin A. The difficulties encountered when trying to acetylate the alcohol **5** and the relative ease of cyclization to give the ether **51** suggest that the alcohol **5** adopts a conformation in which the hydroxyl group is positioned toward the interior of medium-sized ring and in close proximity to the alkene.

dx.doi.org/10.1021/jo302542h | J. Org. Chem. XXXX, XXX, XXX−XXX

The synthesis of 3-acetoxycladiellin-11-ene-6,7-diol (**10**), a compound that had not been synthesized previously, was undertaken with the small quantity of (−)-3-acetoxycladiella-6,11-diene (**6**) that had been prepared (Scheme 15). Selective dihydroxylation was performed by treatment of the acetate **6** with substoichiometric quantities of osmium tetroxide in the presence of NMO at 0 °C to give 3-acetoxycladiellin-11-ene-6,7-diol (**10**) in 36% yield. Due to the limited availability of the starting material, the dihydroxylation reaction was not optimized. This was the first synthesis of 3-acetoxycladiellin-11-ene-6,7-diol (**10**), and a sufficient amount of synthetic material was obtained to demonstrate that the spectroscopic and other data for synthetic material were identical to those reported for the natural product.[42,54]

Synthesis of (−)-Sclerophytin A (7), (−)-Sclerophytin B (8), (+)-Deacetylpolyanthellin A (11), and (+)-Polyanthellin A (12). Following completion of the enantioselective total syntheses of four members of the cladiellin family of natural products featuring an endocyclic alkene in the six-membered ring, attention turned to the synthesis of cladiellin natural products possessing an exocyclic alkene (C-11−C-17) in the six-membered ring (Scheme 17). The total syntheses of

Scheme 17



cladiellin (**3**) and litophytin A (**4**) have not been reported, making them very attractive targets for synthesis. It seemed likely that these compounds could be prepared from the alcohol ***E*-1** and that this late-stage intermediate could also serve as a precursor to (−)-sclerophytin A (**7**), (−)-sclerophytin B (**8**), (+)-deacetylpolyanthellin A (**11**), and (+)-polyanthellin A (**12**) (Scheme 17).

Cladiellin (**3**) is a particularly significant natural product because it was the second oxygen-bridged 2,11-cyclized diterpene to be isolated and it lends its name to the entire family of marine natural products. Cladiellin (**3**) was first extracted from samples of a *Cladiella* species that had been collected on the Great Barrier Reef and its structure was reported by Wells and co-workers in 1977.[55] Shin and co-workers[41] later isolated it from samples of a *Muricella* species that also contained the natural products **5** and **6**.

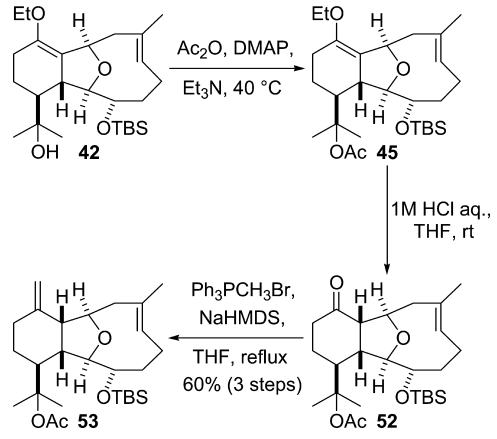
Litophynin A (**4**) was isolated from a *Litophyton* species collected in Sukumo Bay, Japan, and its structure was reported in 1987.[56] This natural product was reported to display insecticidal activity against the silkworm *Bombyx mori* L. (ED_{50} 12 ppm).

In 1988, Sharma and Alam[57] reported the isolation of sclerophytins A and B (**7** and **8**) from samples of the soft coral *Sclerophytum capitalis* collected in Micronesia. Sclerophytin A was reported to possess cytotoxic activity against L1210 cells at a concentration of 0.001 $\mu g \cdot mL^{-1}$. On the basis of extensive NMR analysis, Sharma and Alam[57] originally proposed structures for sclerophytins A and B that had an additional ether linkage bridging between C-3 and C-7. However, these structures were subsequently shown to be incorrect following pioneering synthetic studies performed by the groups of Overman and Paquette;[10−12] these researchers later demonstrated that sclerophytins A and B have the structures shown in Figure 3 (**7** and **8**) by synthesizing both of them.

Polyanthellin A (**12**) was isolated from the gorgonian *Briareum polyanthes* collected off the coast of Puerto Rico by Rodríguez and co-workers,[58] and its structure was reported in 2003. In the course of their characterization studies, Rodríguez and co-workers[58] prepared deacetylpolyanthellin A (**11**) by deacetylation of polyanthellin A (**12**) using lithium aluminum hydride. Following careful analysis of NMR data, Rodríguez and co-workers[58] concluded that compounds **11** and **12** were spectroscopically identical (but with $[\alpha]_D$ values that are opposite, implying an antipodal relationship) to natural products that had been isolated from samples of a *Briareum* species by Bowden et al.[59] However, these earlier workers had misassigned the compounds as having tertiary hydroxyl groups at C-3 and C-7 instead of the additional ether bridge spanning these positions.[59] Rodríguez and co-workers[58] showed that deacetylpolyanthellin A (**11**) and polyanthellin A (**12**) have activity against the malaria parasite *Plasmodium falciparum* with IC_{50} values of 16 $\mu g \cdot mL^{-1}$.

The synthesis of the new targets started from the alcohol **42**, a compound that features as a late-stage intermediate in our syntheses of the cladiellin natural products **5**, **6**, **9**, and **10** (Scheme 18). Acetylation of the tertiary alcohol followed by

Scheme 18. Elaboration of the Tricyclic Core



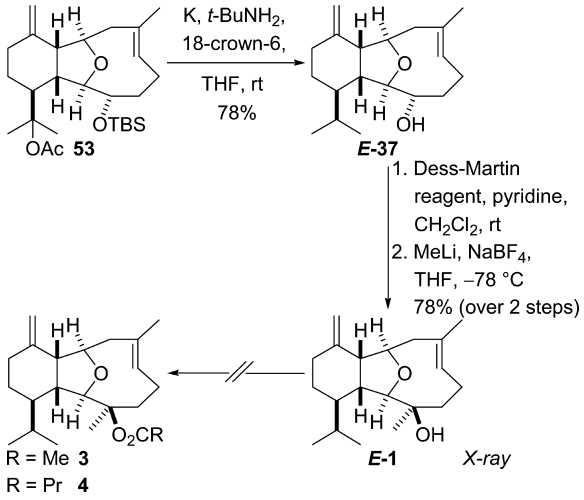
acid-catalyzed enol ether hydrolysis afforded the ketone **52**, and subsequent Wittig methylenation produced the diene **53** in 60% yield over the three-step sequence (Scheme 18).

Reductive removal of the acetate to give the isopropyl substituent was performed by Barton's procedure[48] (Scheme 19). The TBS group was also removed during the reaction to give the alcohol ***E*-37** in 78% yield. At this stage, introduction of the C-3 methyl substituent was required to give the tertiary alcohol ***E*-1**. This transformation was achieved by oxidation of secondary alcohol with Dess−Martin periodinane[37] and exposure of the resulting ketone to MeLi and $NaBF_4$ in THF at −78 °C.[11a,12c]

In principle, the alcohol ***E*-1** could serve as an advanced intermediate for the synthesis of many cladiellin natural

dx.doi.org/10.1021/jo302542h | J. Org. Chem. XXXX, XXX, XXX−XXX

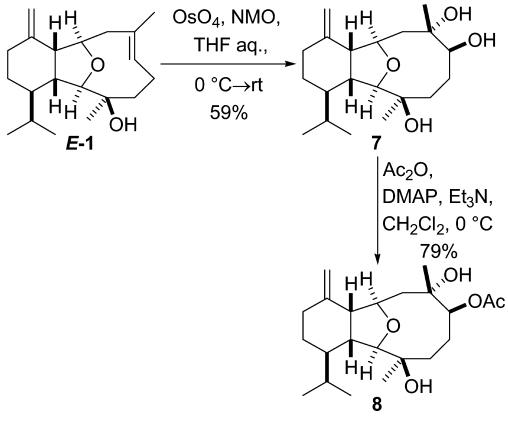
Scheme 19. Deoxygenative Removal of Acetate Group to Give the Key Late-Stage Intermediate *E*-1



products. Esterification of the tertiary alcohol ***E*-1** to give the natural products cladiellin (**3**) and litophynin A (**4**) was explored first (Scheme 19). Acetylation of (−)-cladiella-6,11-dien-3-ol (**5**), a very similar compound to the alcohol ***E*-1**, had been performed already, and so acetylation of the alcohol ***E*-1** was expected to deliver cladiellin (**3**). However, reaction of the alcohol ***E*-1** with acetic anhydride in the presence of triethylamine and DMAP at either room temperature or 40 °C produced a complex mixture of byproducts instead of the required ester. Deprotonation of the tertiary alcohol prior to addition of acetic anhydride, or the replacement of acetic anhydride with acetyl chloride as the acetylating agent, also failed to deliver cladiellin (**3**). The failure of these reactions suggests that there are subtle conformational differences between the medium-ring portions of the alcohols **5** and ***E*-1**, with the tertiary hydroxyl group of the substrate ***E*-1** being shielded even more effectively than that in the isomeric compound **5**.

The alcohol ***E*-1** had been identified as a potential advanced intermediate for the synthesis of sclerophytins A and B, and work now focused on synthesizing these polyhydroxylated natural products (Scheme 20). Chemoselective and diastereoselective dihydroxylation of the trisubstituted *E*-alkene of alcohol ***E*-1** delivered (−)-sclerophytin A (**7**) in 59% yield. As

Scheme 20. Completion of the Syntheses of (−)-Sclerophytin A (7) and (−)-Sclerophytin B (8)

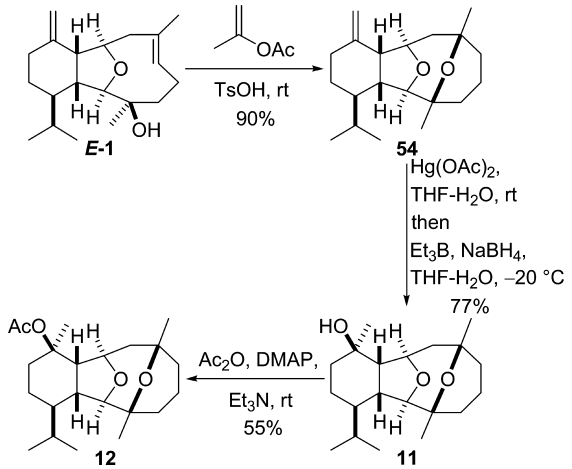


previously reported by Paquette and co-workers,[12b,c] selective acetylation of the secondary alcohol was possible, and this reaction delivered (−)-sclerophytin B (**8**) in 79% yield (Scheme 20). Spectroscopic and other data for synthetic (−)-sclerophytin A (**7**) and (−)-sclerophytin B (**8**) were identical to those reported for the compounds isolated from natural sources.[57]

Although it was not possible to esterify the tertiary alcohol ***E*-1**, an interesting transformation was encountered during screening of potential acetylation conditions. Attempted acid-catalyzed acetylation of tertiary alcohol ***E*-1** with isopropenyl acetate in the presence of *p*-toluenesulfonic acid (*p*-TSA)[60] afforded the tetracyclic compound **54** instead of the acetate **3**. The tetracyclic compound **54** had been reported by Paquette and co-workers[12c] during their synthesis of the compound that had been proposed to be sclerophytin A (Figure 4), and our spectroscopic data matched those reported for this compound. Formation of the additional cyclic ether can be explained by the fact that the hydroxyl group is located in close proximity to the alkene, and upon treatment with a Brønsted acid, the oxygen attacks the tertiary carbocation formed by protonation of the strained *E*-alkene, resulting in relief of strain in the medium-sized ring.

The formation of compound **54** presented an opportunity to synthesize the cladiellin natural products (+)-deacetylpolyanthellin A (**11**) and (+)-polyanthellin A (**12**). These natural products had been synthesized from the alkene **51**, a regioisomer of **54**, by Kim and co-workers[15] using an oxymercuration−demercuration sequence, and so these conditions were applied to our system (Scheme 21). Treatment of

Scheme 21. Completion of Syntheses of (+)-Deacetylpolyanthellin A (11) and (+)-Polyanthellin A (12)



the alkene **54** with mercury(II) acetate in aqueous THF followed by demercuration[61] afforded (+)-deacetylpolyanthellin A (**11**) in 77% yield, as a 10:1 mixture of diastereomers, favoring that shown; subsequent acetylation delivered (+)-polyanthellin A (**12**) in 55% yield (Scheme 21). Both enantiomers of deacetylpolyanthellin A and polyanthellin A have been isolated from natural sources and the present route provided the dextrorotary compound consistent with reports of Kim and co-workers,[15] Campbell and Johnson,[17] and Bowden et al.[59] Spectroscopic and other data for both synthetic (+)-deace-

dx.doi.org/10.1021/jo302542h | J. Org. Chem. XXXX, XXX, XXX−XXX

tylpolyanthellin A (**11**) and (+)-polyanthellin A (**12**) were identical to those reported for the natural products.

CONCLUSIONS

The enantioselective total syntheses of 10 cladiellin natural products have been completed starting from the readily available and known allylic alcohol (+)-**14**. Three important ring-forming reactions have been used to construct the tricyclic core of the cladiellins: (i) a SmI_2-mediated reductive cyclization to form the tetrahydropyran **24**; (ii) a metal-catalyzed reaction of diazo ketone **26** to generate an ylide-like intermediate that rearranges to produce the bridged bicyclic ethers *Z*-**30** and *E*-**30**; and (iii) a Diels–Alder cycloaddition reaction to construct the third ring found in the core structure of the cladiellins. The key ring-forming reaction, in which diazo ketone **26** is converted into a bridged bicyclic ether, can be tuned to give either of the isomeric ketones *Z*-**30** or *E*-**30** as the major product by judicious choice of catalyst and reaction conditions. A three-step sequence is then used to convert the ketones *Z*-**30** and *E*-**30** into the tricyclic ketones *Z*-**33** or *E*-**33**, which can be used as advanced intermediates to prepare virtually any member of the cladiellin family of natural products.

The versatility of our route has been demonstrated by completion of the enantioselective syntheses of 10 natural products from the alcohol (+)-**14**: (+)-cladiella-6*Z*,11(17)-dien-3-ol (*Z*-**1**) in 16 steps, (+)-vigulariol (**2**) in 17 steps, (−)-cladiella-6,11-dien-3-ol (**5**) in 20 steps, (−)-3-acetoxycladiella-6,11-diene (**6**) in 21 steps, (−)-sclerophytin A (**7**) in 18 steps, (−)-sclerophytin B (**8**) in 19 steps, (−)-cladiell-11-ene-3,6,7-triol (**9**) in 21 steps, 3-acetoxycladiellin-11-ene-6,7-diol (**10**) in 22 steps, (+)-deacetylpolyanthellin A (**11**) in 19 steps, and (+)-polyanthellin A (**12**) in 20 steps.

EXPERIMENTAL SECTION

General Experimental. Air- and moisture-sensitive reactions were performed under an atmosphere of nitrogen or argon in oven or flame-dried apparatus. Organic solvents were dried by use of a Pure Solv solvent purification system or dried and distilled by standard methods: tetrahydrofuran (THF) by distillation from sodium benzophenone ketyl, dichloromethane by distillation from calcium hydride. Reagents were obtained from commercial suppliers and used as supplied, unless otherwise stated. Reactions were monitored by thin-layer chromatography on plastic-backed 0.25 mm silica gel plates or Merck silica gel 60 covered alumina plates F254. Plates were viewed under UV light or were visualized by use of either potassium permanganate solution or acidic ethanolic anisaldehyde solution. Column chromatography was performed under pressure on silica gel (Fluorochem LC60A, 35–70 μm, or Merck 7734 grade) with HPLC-grade solvents as eluent. Petroleum ether used for column chromatography was the 40–60 °C fraction. Unless stated otherwise, high-resolution mass spectra were obtained on a mass spectrometer equipped with a double-focusing magnetic sector mass analyzer.

(*E*)-6-(*tert*-Butyldimethylsilanyloxy)-2-methylhex-2-enoic Acid Ethyl Ester (18).[26,27] To a stirred solution of oxalyl chloride (33.0 g, 373 mmol) in anhydrous dichloromethane (640 mL) cooled at −78 °C was added slowly a solution of anhydrous dimethyl sulfoxide (DMSO; 40.0 mL, 562 mmol) in anhydrous dichloromethane (200 mL), and the resulting solution was stirred for 30 min. 4-(*tert*-Butyldimethylsilyl)oxy-1-butanol (31.0 g, 152 mmol)[62] in anhydrous dichloromethane (460 mL) was then added dropwise. The resulting solution was stirred at the same temperature for a further 2 h and then quenched with triethylamine (76.8 g, 760 mmol) at −78 °C. The reaction mixture was allowed to warm to room temperature (rt), stirred for 30 min, and then diluted with dichloromethane (500 mL) and water (300 mL). The aqueous phase was separated and extracted with dichloromethane (3 × 150 mL). The organic extracts were combined and washed with brine (300 mL) and then dried ($MgSO_4$) and concentrated in vacuo to afford the crude aldehyde, which was used for the next step without purification.

To a stirred solution of the unpurified aldehyde in anhydrous THF (1.5 L) was added ethyl 2-(triphenylphosphoranylidene)propanoate (82.5 g, 227 mmol) in one portion. The resulting solution was stirred at rt for 48 h and the reaction was then quenched by addition of ethyl acetate (500 mL) and water (500 mL). The aqueous phase was separated and extracted with ethyl acetate (3 × 300 mL). The organic extracts were combined, washed with brine (300 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash column chromatography of the residue on silica gel (petroleum ether/ethyl acetate 20:1) afforded the alkene **18** (40.8 g, 95% over two steps) as a colorless oil. R_f = 0.77 (petroleum ether/ethyl acetate 2:1); ν_{max} ($CHCl_3$) 2955, 2930, 2887, 2858, 1711, 833, 814 775, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.77 (1H, tq, J = 7.5, 1.4 Hz), 4.18 (2H, q, J = 7.1 Hz), 3.62 (2H, t, J = 6.2 Hz), 2.26–2.21 (2H, m), 1.82 (3H, br d, J = 1.4 Hz), 1.65 (2H, tt, J = 7.6, 6.2 Hz), 1.30 (3H, t, J = 7.1 Hz), 0.89 (9H, s), 0.04 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 142.0, 128.2, 62.5, 60.5, 31.8, 26.1, 25.2, 18.4, 14.4, 12.5, −5.2; high-resolution mass spectrometry (HRMS) [chemical ionization (CI), isobutane] m/z calcd for $C_{15}H_{31}O_3Si$ $[M + H]^+$ 287.2045, found 287.2041; low-resolution mass spectrometry (LRMS) (CI, isobutane) m/z (% intensity) 287.3 (100), 241.3 (18), 229.3 (11). Anal. Calcd for $C_{15}H_{30}O_3Si$: C, 62.89; H, 10.55. Found: C, 62.89; H, 10.48.

(*E*)-6-(*tert*-Butyldimethylsilanyloxy)-2-methylhex-2-en-1-ol (19).[26,27] To a stirred solution of the ester **18** (39.8 g, 139 mmol) in anhydrous dichloromethane (1.40 L) at −78 °C was added diisobutylaluminium hydride (DIBAL-H; 350 mL of a 1.0 M solution in hexane, 350 mmol) dropwise over 1.5 h. The resulting solution was stirred for 30 min, then quenched with a saturated aqueous solution of sodium potassium tartrate (500 mL) and allowed to warm to rt. The reaction mixture was then diluted with ethyl acetate (800 mL) and stirred vigorously until the appearance of two phases. The aqueous phase was separated and extracted with ethyl acetate (3 × 500 mL). The organic extracts were combined, washed with brine (500 mL), dried ($MgSO_4$), and concentrated in vacuo to yield a colorless oil. Flash column chromatography on silica gel (petroleum ether/ethyl acetate 7:1) afforded the allylic alcohol **19** (31.8 g, 94%) as a colorless oil. R_f = 0.48 (petroleum ether/ethyl acetate, 2:1); ν_{max} ($CHCl_3$) 3339, 2955, 2930, 2888, 2859, 1097, 1007, 835, 814, 775, 716 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.41 (1H, tq, J = 7.2, 1.2 Hz), 3.99 (2H, d, J = 6.0 Hz), 3.61 (2H, t, J = 6.4 Hz), 2.09 (2H, q, J = 7.4 Hz), 1.66 (3H, s), 1.58 (2H, tt, J = 7.4, 6.4 Hz), 1.32–1.24 (1H, m), 0.89 (9H, s), 0.05 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.2, 126.1, 69.2, 62.7, 32.8, 26.1, 24.1, 18.5, 13.8, −5.1; HRMS (CI, isobutane) calcd for $C_{13}H_{27}OSi$ $[M - OH]^+$ 227.1833, found 227.1832; LRMS (CI, isobutane) m/z (% intensity); 245.5 (15), 227.5 (100), 95.2 (80). Anal. Calcd for $C_{13}H_{28}O_2Si$: C, 63.88; H, 11.55. Found: C, 63.75; H, 11.64.

[(2*R*,3*R*)-3-[3-(*tert*-Butyldimethylsilanyloxy)propyl]-2-methyloxiranyl]methanol (20).[26,27] To a suspension of 4 Å powdered molecular sieves (6 g) in anhydrous dichloromethane (1.0 L) at −20 °C were added freshly distilled titanium tetraisopropoxide (1.74 g, 6.13 mmol), freshly distilled (−)-diethyl tartrate (1.89 g, 9.20 mmol), and *tert*-butylhydroperoxide (32.6 mL of a 5.62 M solution in dichloromethane, 184 mmol). The reaction mixture was stirred for 20 min at −20 °C, and then a solution of the allylic alcohol **19** (30.0 g, 123 mmol) in anhydrous dichloromethane (200 mL) was added slowly, with the temperature maintained at −20 °C. The mixture was stirred for a further 1 h and the reaction was quenched by addition of water (100 mL) and a solution of 30 wt % sodium hydroxide in brine (100 mL). The reaction mixture was stirred for a further 30 min and then allowed to warm to rt. The molecular sieves were removed by filtration, and the aqueous phase was separated and extracted with dichloromethane (3 × 300 mL). The organic extracts were combined, washed with brine (300 mL), dried ($MgSO_4$), and concentrated in vacuo to yield a colorless oil. Flash column chromatography of the residue on silica gel (petroleum ether/ethyl acetate, gradient elution 5:1 → 2:1) afforded the epoxy alcohol **20** (30.3 g, 95%) as a colorless

dx.doi.org/10.1021/jo302542h | J. Org. Chem. XXXX, XXX, XXX–XXX

oil. R_f = 0.40 (petroleum ether/ethyl acetate 1:1); $[\alpha]_D^{23}$ +14.9 (*c* 1.00, $CHCl_3$) {lit.[27] $[\alpha]_D^{21}$ +10.7 (*c* 2.21, $CHCl_3$)}; ν_{max} ($CHCl_3$) 3433, 2955, 2929, 2886, 2858, 834, 813, 773 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.70−3.55 (4H, m), 3.07 (1H, dd, *J* = 6.0, 5.9 Hz), 1.74−1.60 (5H, m), 1.28 (3H, s), 0.89 (9H, s), 0.05 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 65.5, 62.7, 61.0, 60.1, 29.8, 26.1, 24.9, 18.4, 14.3, −5.2; HRMS (CI, isobutane) calcd for $C_{13}H_{29}O_3Si$ $[M + H]^+$ 261.1887, found 261.1888; LRMS (CI, isobutane) *m*/*z* (% intensity) 261.5 (30), 243.5 (42), 203.4 (100), 129.3 (90). Anal. Calcd for $C_{13}H_{28}O_3Si$: C, 59.95; H, 10.84. Found: C, 59.98; H, 10.88.

6-*tert*-Butyldimethylsilyloxy-2-methyl-1-hexen-3-ol [(±)-14]. To a stirred slurry of magnesium turnings (2.8 g, 86 mmol) and iodine (trace) in anhydrous THF (12 mL) was added a solution of (3-bromopropoxy)(*tert*-butyl)dimethylsilane (20 g, 78 mmol) in anhydrous THF (130 mL) dropwise. After complete addition, the resulting brown solution was stirred for a further 1 h before a solution of freshly distilled methacrolein (2.7 g, 39 mmol) in anhydrous THF (8 mL) was added dropwise over 30 min. The resulting mixture was stirred for a further period of 1 h and then quenched by addition of a saturated aqueous solution of NH_4Cl (160 mL) and diethyl ether (120 mL). The aqueous phase was separated and extracted with diethyl ether (3 × 80 mL). The organic extracts were combined, washed with brine (160 mL), dried ($MgSO_4$), and concentrated in vacuo to yield a colorless oil. Flash column chromatography on silica gel (petroleum ether/ethyl acetate 5:1) afforded the alcohol **(±)-14** as a colorless oil (8.8 g, 93%).

(*R*)-6-*tert*-Butyldimethylsilyloxy-2-methyl-1-hexen-3-ol [(+)-14] (Epoxide Opening).[26] To a stirred solution of epoxy alcohol **20** (30.3 g, 117 mmol) and triethylamine (17.7 g, 175 mmol) in anhydrous dichloromethane (580 mL) at −10 °C was slowly added methanesulfonyl chloride (16.0 g, 140 mmol). The solution was stirred for 10 min, then quenched by addition of water (100 mL) and diluted with dichloromethane (250 mL). The organic phase was washed with brine (100 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to yield a colorless oil. The crude epoxy mesylate **21** was carried on to the next step without further purification.

To a stirred solution of the crude mesylate **21** in butan-2-one (580 mL) was added sodium iodide (87.4 g, 583 mmol), and the reaction mixture was heated at reflux for 1 h, giving a brown slurry. Zinc powder (11.4 g, 175 mmol) was then added and the reaction was stirred at reflux for a further 1 h, giving a gray solution. The reaction mixture was then allowed to cool to rt and diluted with ethyl acetate (500 mL) and a saturated aqueous solution of NH_4Cl (300 mL). The aqueous phase was separated and extracted with ethyl acetate (3 × 300 mL). The organic extracts were combined, washed with brine (300 mL), dried ($MgSO_4$), and concentrated in vacuo to yield a brown oil. Flash column chromatography on silica gel (petroleum ether/diethyl ether, gradient elution 30:1 → 20:1 → 15:1) afforded the alcohol **(+)-14** as a colorless oil (27.6 g, 97% over two steps). R_f = 0.42 (petroleum ether/ethyl acetate 5:1); ν_{max} ($CHCl_3$) 3378, 2954, 2929, 2885, 2857, 898, 835, 774 cm^{-1}; $[\alpha]_D^{23}$ +8.7 (*c* 1.01, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 4.96 (1H, br s), 4.83 (1H, br s), 4.08−4.04 (1H, m), 3.66 (2H, t, *J* = 5.7 Hz), 2.53 (1H, d, *J* = 3.8 Hz), 1.72 (3H, s), 1.71−1.56 (4H, m), 0.90 (9H, s), 0.06 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.7, 110.9, 75.6, 63.5, 32.5, 29.0, 26.1, 18.5, 18.0, −5.2; HRMS (CI, isobutane) *m*/*z* calcd for $C_{13}H_{29}O_2Si$ $[M + H]^+$ 245.1937, found 245.1932; LRMS (CI, isobutane) *m*/*z* (% intensity) 245.5 (80), 227.4 (100), 137.3 (60), 113.3 (80). Anal. Calcd for $C_{13}H_{28}O_2Si$: C, 63.88; H, 11.55. Found: C, 63.73; H, 11.65.

6-(*tert*-Butyldimethylsilanyloxy)-2-methylhex-1-en-3-one. To a stirred solution of alcohol **(±)-14** (9.7 g, 40 mmol) in anhydrous dichloromethane (200 mL) at rt was added manganese dioxide (87 g, 1.0 mol) in five portions. The resulting solution was stirred for 1 h; then additional manganese dioxide (17 g, 20 mmol) was added in one portion and the reaction mixture was stirred for a further 1 h. The mixture was filtered through Celite, washed with dichloromethane (400 mL) and boiling ethyl acetate (150 mL), and then concentrated to give yield a yellow oil. Purification of the residue by flash column chromatography on silica gel (petroleum ether/diethyl ether, gradient elution 1:0 → 25:1) afforded the enone as a colorless oil (7.54 g, 78%). R_f = 0.49 (petroleum ether/ethyl acetate 5:1); ν_{max} ($CHCl_3$) 2954, 2929, 2885, 2858, 1674, 1630, 1462, 1454, 1362, 1334, 1290, 1260, 1095, 1006, 965, 876, 839 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.95 (1H, br s), 5.73 (1H, br s), 3.61 (2H, t, *J* = 6.1 Hz), 2.75 (2H, t, *J* = 7.3 Hz), 1.85 (3H, br s), 1.86−1.76 (2H, m), 0.86 (9H, s), 0.01 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.9, 144.6, 124.4, 62.2, 33.7, 27.5, 26.1, 18.3, 17.7, −5.3; HRMS (ESI) *m*/*z* calcd for $C_{13}H_{26}O_2SiNa$ $[M + Na]^+$ 265.1594, found 265.1593.

(*R*)-6-*tert*-Butyldimethylsilyloxy-2-methyl-1-hexen-3-ol [(+)-14] (Asymmetric Reduction).[26] To a stirred solution of the oxazaborolidine complex **16** (0.17 M solution in a 4:1 mixture of THF and toluene, 19.7 mmol) at −78 °C was added a solution of the enone (11.9 g, 49.3 mmol) in anhydrous THF (120 mL) over 2 h. The reaction was stirred for 1 h and then quenched by dropwise addition of methanol (20 mL) and warmed to rt. The mixture was diluted with water (400 mL) and diethyl ether (400 mL) and the aqueous phase was separated and extracted with diethyl ether (2 × 250 mL). The organic extracts were combined, washed with brine (250 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash column chromatography on silica gel (petroleum ether/diethyl ether, gradient elution 9:1 → 2:1) afforded the alcohol **(+)-14** as a colorless oil (10.0 g, 83%). $[\alpha]_D^{21}$ +9.11 (*c* = 1.25, $CHCl_3$). The enantiomeric excess was determined by reverse-phase HPLC analysis (acetonitrile/water 55:45; 0.5 mL·min^{-1}) of the corresponding benzoyl ester. The enantiomeric benzoates had retention times of 48.05 min (1.84%) and 50.33 min (98.16%). A racemic sample of the benzoates had components with retention times of 48.05 min (49.52%) and 50.33 min (50.48%).

Ethyl (*E*)-3-[6-(*tert*-Butyldimethylsilyloxy)-2-methyl-1-hexen-3-yl]oxypropenoate. To a stirred solution of alcohol **(+)-14** (668 mg, 2.73 mmol) in anhydrous dichloromethane (7 mL) at rt were added ethyl propiolate (537 mg, 5.47 mmol) and *N*-methylmorpholine (553 mg, 5.47 mmol). The resulting brown solution was stirred for 18 h and then concentrated in vacuo to yield a dark brown oil. Flash column chromatography on silica gel (petroleum ether/ethyl acetate 30:1) afforded the title compound as a colorless oil (881 mg, 94%). The enantiomeric purity of this compound was determined to be 94% by normal-phase chiral HPLC analysis [AD-H column; temp 20 °C; 0.2% 2-propanol in hexane; flow rate 0.5 mL·min^{-1}). R_f = 0.71 (petroleum ether/ethyl acetate 2:1); $[\alpha]_D^{23}$ −8.4 (*c* = 1.00, $CHCl_3$); ν_{max} ($CHCl_3$) 2955, 2929, 2897, 2859, 1713, 1643, 1624, 909, 835, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47 (1H, d, *J* = 12.4 Hz), 5.25 (1H, d, *J* = 12.4 Hz), 4.97 (1H, dd, *J* = 1.4, 1.4 Hz), 4.95 (1H, br s), 4.26 (1H, br t, *J* = 6.7 Hz), 4.13 (1H, q, *J* = 7.1 Hz), 4.12 (1H, q, *J* = 7.1 Hz), 3.66−3.57 (2H, m), 1.81−1.67 (2H, m), 1.66 (3H, s), 1.61−1.47 (2H, m), 1.25 (3H, t, *J* = 7.1 Hz), 0.88 (9H, s), 0.04 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 161.6, 142.9, 114.7, 98.0, 86.6, 62.6, 59.8, 29.6, 28.6, 26.1, 18.4, 17.0, 14.5, −5.2; HRMS (CI, isobutane) *m*/*z* calcd for $C_{18}H_{35}O_4Si$ $[M + H]^+$ 343.2305, found 343.2302; LRMS (CI, isobutane) *m*/*z* (% intensity) 343.5 (7), 227.4 (18), 137.2 (100). Anal. Calcd for $C_{18}H_{34}O_4Si$: C, 63.11; H, 10.00. Found: C, 63.14; H, 10.04.

(*R*)-Ethyl (*E*)-3-(6-Hydroxy-2-methyl-1-hexen-3-yl)-oxypropenoate (22). To a stirred solution of the silyl ether (1.0 g, 2.9 mmol) in MeOH (30 mL) at rt was added camphorsulfonic acid (CSA) (67 mg, 0.29 mmol). The resulting solution was stirred for 30 min at rt, and $NaHCO_3$ was added to neutralize the CSA. The remaining solid was filtered and the solution was concentrated in vacuo to yield a yellow oil. The crude product was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate, gradient elution 5:1 → 2:1) to give the alcohol **22** as a colorless oil (578 mg, 86%). R_f = 0.19 (petroleum ether/ethyl acetate 2:1); $[\alpha]_D^{24}$ −8.3 (*c* 1.01, $CHCl_3$); ν_{max} ($CHCl_3$) 3436, 2979, 2949, 1707, 1640, 1622, 960, 911, 833 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47 (1H, d, *J* = 12.4 Hz), 5.26 (1H, d, *J* = 12.4 Hz), 4.99 (1H, dd, *J* = 1.4, 1.4 Hz), 4.97 (1H, br s), 4.27 (1H, dd, *J* = 7.7, 5.5 Hz), 4.15 (1H, q, *J* = 7.1 Hz), 4.14 (1H, q, *J* = 7.1 Hz), 3.70−3.63 (2H, m), 1.87−1.51 (4H, m), 1.67 (3H, s), 1.35 (1H, br s), 1.26 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 161.5, 142.8, 114.9, 98.2, 86.5, 62.5, 59.9, 29.6, 28.7, 17.1, 14.5; HRMS (CI, isobutane) *m*/*z* calcd for $C_{12}H_{21}O_4$ $[M + H]^+$ 229.1440, found 229.1441; LRMS (CI, isobutane) *m*/*z* (%

dx.doi.org/10.1021/jo302542h | J. Org. Chem. XXXX, XXX, XXX−XXX

intensity) 229.4 (100), 221.4 (10), 183.3 (8), 137.3 (10), 117.2 (80); 113.2 (50). Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.14; H, 8.83. Found: C, 62.86; H, 8.91.

(*R*)-Ethyl (*E*)-3-(5-Methyl-5-hexenal-4-yl)oxypropenoate (23). To a stirred solution of oxalyl chloride (12.7 g, 158 mmol) in dry dichloromethane (370 mL) at −78 °C was added anhydrous DMSO (25.3 g, 324 mmol) in anhydrous dichloromethane (115 mL) dropwise by cannula. The resulting solution was stirred for 30 min at −78 °C, and then the alcohol **22** (20.0 g, 87.6 mmol) in anhydrous dichloromethane (260 mL) was added dropwise by cannula. The resulting solution was stirred for a further 3 h at −78 °C and then quenched with Et_3N (44.3 g, 438 mmol). The reaction mixture was allowed to warm to rt, stirred for 30 min, and then diluted with dichloromethane (200 mL) and water (100 mL). The aqueous phase was separated and extracted with dichloromethane (3 × 200 mL). The organic extracts were combined, washed with brine (100 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash column chromatography on silica gel (petroleum ether/ethyl acetate 5:1) afforded the aldehyde **23** as a colorless oil (19.3 g, 97%). R_f = 0.41 (petroleum ether/ethyl acetate 2:1); $[\alpha]_D^{23}$ −1.9 (*c* 1.00, $CHCl_3$); ν_{max} ($CHCl_3$) 2980, 2940, 1706, 1641, 1623, 957, 912, 834 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.78 (1H, s), 7.44 (1H, d, *J* = 12.4 Hz), 5.25 (1H, d, *J* = 12.4 Hz), 5.01 (1H, br s), 4.98 (1H, s), 4.29 (1H, dd, *J* = 7.9, 5.4 Hz), 4.15 (1H, q, *J* = 7.1 Hz), 4.14 (1H, q, *J* = 7.1 Hz), 2.56−2.52 (2H, m), 2.10−1.92 (2H, m), 1.68 (3H, s), 1.26 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.2, 168.0, 161.0, 142.2, 115.2, 98.6, 85.1, 59.9, 39.8, 25.7, 17.2, 14.5; HRMS (CI, isobutane) *m*/*z* calcd for $C_{12}H_{19}O_4$ $[M + H]^+$ 227.1283, found 227.1279; LRMS (CI, isobutane) *m*/*z* (% intensity) 227.4 (100), 209.4 (5), 111.2 (59). Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.27; H, 8.04.

Ethyl [(2*R*,3*S*,6*R*)-3-Hydroxy-6-isopropenyltetrahydropyran-2-yl]acetate. To a stirred solution of the aldehyde **23** (244 mg, 1.08 mmol) and anhydrous MeOH (138 mg, 4.31 mmol) in anhydrous THF (11 mL) at rt was added a freshly prepared solution of samarium diiodide (0.1 M in THF) until the solution remained deep blue in color (approximately 4 equiv added). The resulting solution was stirred for 30 min and then quenched with ethyl acetate (5 mL) and a saturated aqueous solution of sodium thiosulfate (12 mL). The aqueous phase was separated and extracted with ethyl acetate (3 × 10 mL). The organic extracts were combined, washed with brine (15 mL), dried ($MgSO_4$), and concentrated in vacuo to yield a yellow oil. Flash column chromatography on silica gel (petroleum ether/ethyl acetate, gradient elution 4:1 → 1:1) afforded the title tetrahydropyranol (212 mg, 86%) as a yellow oil. R_f = 0.22 (petroleum ether/ethyl acetate 2:1); $[\alpha]_D^{25}$ +42.6 (*c* 1.02, $CHCl_3$); ν_{max} ($CHCl_3$) 3456, 2979, 2942, 2861, 1738, 1721, 901 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.93 (1H, s), 4.81 (1H, s), 4.15 (2H, q, *J* = 7.1 Hz), 3.74 (1H, br d, *J* = 9.7 Hz), 3.60 (1H, ddd, *J* = 9.2, 7.0, 5.0 Hz), 3.44−3.34 (1H, m), 2.81 (1H, dd, *J* = 15.1, 5.0 Hz), 2.57 (1H, dd, *J* = 15.1, 7.0 Hz), 2.19−2.12 (1H, m), 2.02−1.96 (1H, m), 1.88−1.81 (1H, m), 1.72 (3H, s), 1.56−1.48 (2H, m), 1.25 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 145.1, 110.7, 80.3, 79.0, 70.7, 60.8, 38.9, 33.2, 29.7, 19.3, 14.4; HRMS (CI, isobutane) *m*/*z* calcd for $C_{12}H_{21}O_4$ $[M + H]^+$ 229.1439, found 229.1438; LRMS (CI, isobutane) *m*/*z* (% intensity) 229.4 (100), 211.4 (5), 183.3 (10). Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.14; H, 8.83. Found: C, 62.73; H, 8.95.

Ethyl [(2*R*,3*S*,6*R*)-3-(*tert*-Butyldimethylsilyloxy)-6-isopropenyltetrahydropyran-2-yl]acetate (24). To a stirred solution of tetrahydropyranol (7.44 g, 32.6 mmol) and imidazole (4.43 g, 65.2 mmol) in anhydrous *N*,*N*-dimethylformamide (DMF) (75 mL) was added *t*-butyldimethylsilyl chloride (8.84 g, 58.7 mmol) portionwise over 5 min. The resulting solution was stirred overnight at rt and then quenched by addition of diethyl ether (300 mL) and water (600 mL). The aqueous phase was separated and the organic phase was washed with water (5 × 300 mL). The aqueous extracts were combined and extracted with diethyl ether (300 mL). The organic extracts were combined, washed with brine (200 mL), dried ($MgSO_4$), and concentrated in vacuo to give a yellow oil. Flash column chromatography on silica gel (petroleum ether/ethyl acetate 20:1) afforded the silyl ether **24** (10.7 g, 96%) as a colorless oil. R_f = 0.73 (petroleum ether/ethyl acetate 2:1); $[\alpha]_D^{24}$ +59.0 (*c* 1.03, $CHCl_3$); ν_{max} ($CHCl_3$) 2951, 2930, 2858, 1740, 898, 858, 835, 774 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.91 (1H, s), 4.78 (1H, s), 4.14 (2H, q, *J* = 7.1 Hz), 3.69 (1H, br d, *J* = 9.9 Hz), 3.65 (1H, ddd, *J* = 9.2, 9.1, 3.3 Hz), 3.40−3.32 (1H, m), 2.80 (1H, dd, *J* = 14.8, 3.3 Hz), 2.37 (1H, dd, *J* = 14.8, 9.2 Hz), 2.07−2.00 (1H, m), 1.84−1.77 (1H, m), 1.70 (3H, s), 1.56−1.48 (2H, m), 1.25 (3H, t, *J* = 7.1 Hz), 0.87 (9H, s), 0.06 (3H, s), 0.05 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 145.3, 110.3, 80.0, 79.6, 70.9, 60.4, 38.4, 33.5, 29.7, 25.9, 19.4, 18.1, 14.4, −3.9, −4.6; HRMS (CI, isobutane) *m*/*z* calcd for $C_{18}H_{35}O_4Si$ $[M + H]^+$ 343.2304, found 343.2307; LRMS (CI, isobutane) *m*/*z* (% intensity) 343.5 (100), 329.5 (11), 285.4 (15), 113 (44). Anal. Calcd for $C_{18}H_{34}O_4Si$: C, 63.11; H, 10.00. Found: C, 62.95; H, 10.07.

(2*R*,3*S*,6*R*)-3-(*tert*-Butyldimethylsilyloxy)-6-isopropenyltetrahydropyran-2-ylacetic Acid (25). To a stirred solution of ester **24** (10.2 g, 29.7 mmol) in ethanol (150 mL) and water (50 mL) was added lithium hydroxide (3.74 g, 89.2 mmol) portionwise over 5 min. The resulting solution was stirred at rt overnight and then acidified to pH 2−3 with 1 M HCl. The reaction mixture was diluted with ethyl acetate (300 mL) and water (200 mL), and the aqueous phase was then separated and extracted with ethyl acetate (3 × 150 mL). The organic extracts were combined, washed with brine (100 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash column chromatography on silica gel (petroleum ether/ethyl acetate, gradient elution 20:1 → 4:1) afforded the carboxylic acid **25** as a colorless gum (8.28 g, 89%). R_f = 0.57 (petroleum ether/ethyl acetate 3:1); $[\alpha]_D^{25}$ +67.5 (*c* 1.00, $CHCl_3$); ν_{max} ($CHCl_3$) 2951, 2930, 2887, 2859, 1715, 899, 837, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.88 (1H, br s), 4.94 (1H, s), 4.82 (1H, s), 3.80 (1H, br d, *J* = 9.6 Hz), 3.62 (1H, ddd, *J* = 8.9, 8.9, 3.2 Hz), 3.40−3.32 (1H, m), 2.86 (1H, dd, *J* = 15.6, 3.2 Hz), 2.46 (1H, dd, *J* = 15.6, 8.9 Hz), 2.08−2.02 (1H, m), 1.85−1.79 (1H, m), 1.72 (3H, s), 1.59−1.50 (2H, m), 0.87 (9H, s), 0.07 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 144.7, 111.1, 80.6, 79.1, 70.8, 37.9, 33.4, 29.7, 25.9, 19.2, 18.0, −3.9, −4.6; HRMS (CI, isobutane) *m*/*z* calcd for $C_{16}H_{31}O_4Si$ $[M + H]^+$ 315.1992, found 315.1995; LRMS (CI, isobutane) *m*/*z* (% intensity) 315.4 (100), 297.4 (12), 257.4 (20), 183.8 (55).

1-Diazo-3-[(2*R*,3*S*,6*R*)-3-(*tert*-butyldimethylsilyloxy)-6-isopropenyltetrahydropyran-2-yl]-propan-2-one (26). To a stirred solution of carboxylic acid **25** (3.00 g, 9.55 mmol) and triethylamine (1.32 g, 13.0 mmol) in anhydrous diethyl ether (120 mL) was added isobutyl chloroformate (1.64 g, 12.0 mmol) dropwise, and the resulting solution was stirred for 2.5 h (a white precipitate formed). The solution of the anhydride was filtered under suction; the residue was washed with diethyl ether and then immediately added to a freshly prepared ethereal solution of diazomethane (∼100 mmol) dropwise. The solution was stirred for 2 days and quenched by addition of glacial acetic acid (5 mL), then poured into a saturated aqueous solution of $NaHCO_3$ (200 mL) and stirred vigorously for 15 min. The aqueous phase was separated and extracted with ethyl acetate (3 × 75 mL). The combined organic extracts were washed with brine (75 mL), dried ($MgSO_4$), and concentrated in vacuo to give a yellow oil. Flash column chromatography on silica gel (petroleum ether/ethyl acetate 10:1) afforded diazo ketone **26** as a yellow oil (2.83 g, 88%). R_f = 0.51 (petroleum ether/ethyl acetate 2:1); $[\alpha]_D^{23}$ +95.7 (*c* 1.01, $CHCl_3$); ν_{max} ($CHCl_3$) 2949, 2929, 2883, 2857, 2099, 1640, 897, 835, 774 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.39 (1H, br s), 4.92 (1H, s), 4.80 (1H, s), 3.72 (1H, d, *J* = 10.1 Hz), 3.58 (1H, ddd, *J* = 9.1, 9.1, 2.4 Hz), 3.37−3.29 (1H, m), 2.77 (1H, dd, *J* = 14.3, 2.4 Hz), 2.45−2.30 (1H, m), 2.07−2.01 (1H, m), 1.83−1.77 (1H, m), 1.71 (3H, s), 1.60−1.43 (2H, m), 0.87 (9H, s), 0.06 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.8, 145.3, 110.5, 80.2, 79.9, 70.8, 55.3, 44.3, 33.6, 29.8, 25.9, 19.4, 18.1, −3.9, −4.6; HRMS (FAB) *m*/*z* calcd for $C_{17}H_{31}O_3N_2Si$ $[M + H]^+$ 339.2104, found 339.2105; LRMS (FAB) *m*/*z* (% intensity) 339.1 (100), 297.2 (18), 281.1 (99), 255.2 (25), 207.0 (37), 171.0 (62).

(1*R*,2*S*,5*Z*,8*R*)-2-(*tert*-Butyldimethylsilyloxy)-6-methyl-11-oxabicyclo[6.2.1]-5-undecen-9-one (*Z*-30) and (1*R*,2*S*,5*E*,8*R*)-2-(*tert*-Butyldimethylsilyloxy)-6-methyl-11-oxabicyclo[6.2.1]-5-undecen-9-one (*E*-30). To a stirred solution of $Rh_2(pfm)_2$ (360 mg, 0.34 mmol) in anhydrous dichloromethane (175 mL) at reflux was

dx.doi.org/10.1021/jo302542h | J. Org. Chem. XXXX, XXX, XXX−XXX

added diazo ketone **26** (5.95 g, 17.5 mmol) in anhydrous dichloromethane (880 mL) over 45 min, while vigorous reflux was maintained. The resulting solution was stirred for a further 15 min, allowed to cool, and concentrated in vacuo to give a brown solid. Rapid column chromatography on deactivated alumina (petroleum ether/ethyl acetate 15:1) allowed the removal of the catalyst. Flash column chromatography on silver(II) nitrate (10%) impregnated silica gel (petroleum ether/ethyl acetate, gradient elution 30:1 → 1:1) afforded ketone ***Z*-30** (1.20 g, 22%) as a colorless crystalline solid and ketone ***E*-30** (2.26 g 41%) as a colorless crystalline solid.

***Z*-30**: R_f = 0.56 (petroleum ether/diethyl ether 5:1); mp 88−90 °C; $[\alpha]_D^{28}$ +31.8 (*c* 1.03, $CHCl_3$); ν_{max} ($CHCl_3$) 2954, 2927, 2856, 1754, 835, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.41 (1H, dd, *J* = 11.6, 5.8 Hz), 4.23 (1H, t, *J* = 4.4 Hz), 4.17 (1H, t, *J* = 8.7 Hz), 3.42 (1H, ddd, *J* = 10.8, 8.7, 2.7 Hz), 2.81−2.68 (3H, m), 2.29 (1H, d, *J* = 17.7 Hz), 2.21 (1H, dd, *J* = 14.6, 4.4 Hz), 2.02−1.93 (1H, m), 1.86 (1H, dddd, *J* = 13.6, 10.8, 6.1, 2.7 Hz), 1.75 (3H, s), 1.69−1.58 (1H, m), 0.86 (9H, s), 0.05 (3H, s), 0.01 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.0, 132.5, 127.7, 80.4, 78.9, 75.5, 42.4, 33.5, 33.2, 26.9, 25.9, 18.0, −3.7, −4.4; HRMS (CI, isobutane) *m*/*z* calcd for $C_{17}H_{31}O_3Si$ $[M + H]^+$ 311.2042, found 311.2039; LRMS (CI, isobutane) *m*/*z* (% intensity) 311.6 (100), 253.4 (18), 179.4 (18). Anal. Calcd for $C_{17}H_{30}O_3Si$: C, 65.76; H, 9.74. Found: C, 65.78 H, 9.83.

***E*-30**: R_f = 0.56 (petroleum ether/diethyl ether 5:1); mp 55−57 °C; $[\alpha]_D^{28}$ −38.7 (*c* 0.99, $CHCl_3$); ν_{max} ($CHCl_3$) 2950, 2931, 2860, 1755, 837, 774 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.35 (1H, dd, *J* = 11.9, 4.3 Hz), 4.17−4.12 (2H, m), 3.02 (1H, dd, *J* = 8.9, 7.8 Hz), 2.78 (1H, ddd, *J* = 18.0, 9.1, 1.4 Hz), 2.55−2.50 (2H, m), 2.28 (1H, br d, *J* = 18.0 Hz), 2.28−2.11 (2H, m), 1.96 (1H, dddd, *J* = 14.1, 11.8, 7.8, 3.9 Hz), 1.71 (1H, ddd, *J* = 14.1, 3.6, 3.6 Hz), 1.55 (3H, s), 0.86 (9H, s), 0.08 (3H, s), 0.03 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 217.4, 133.4, 124.8, 80.9, 78.5, 76.6, 42.1, 40.4, 35.9, 27.0, 25.9, 18.9, 18.0, −3.7, −4.6; HRMS (CI, isobutane) *m*/*z* calcd for $C_{17}H_{31}O_3Si$ $[M + H]^+$ 311.2042, found 311.2038; LRMS (CI, isobutane) *m*/*z* (% intensity) 311.6 (100), 253.4 (18), 179.4 (10). Anal. Calcd for $C_{17}H_{30}O_3Si$: C, 65.76; H, 9.74. Found: C, 65.78; H, 9.81.

1-{(1*R*,2*R*,3*S*,8*R*,10*Z*,14*S*)-14-(*tert*-Butyldimethylsilyloxy)-6-ethoxy-10-methyl-15-oxatricyclo-[6.6.1.0^{2,7}]pentadeca-6,10-dien-3-yl}ethan-1-one (*Z*-33). To a solution of bicyclic ketone ***Z*-30** (1.06 g, 3.31 mmol) and $PhN(Tf)_2$ (2.44 g, 6.82 mmol) in anhydrous THF (70 mL) at −78 °C was added sodium bis(trimethylsilyl)amide (NaHMDS; 8.53 mL of a 1.0 M solution in THF, 8.53 mmol) dropwise over 10 min. The resulting solution was stirred at −78 °C for 2 h, then quenched with water (20 mL) at −78 °C and allowed to warm to rt. The aqueous phase was separated and extracted with diethyl ether (3 × 80 mL). The organic extracts were combined, washed with brine (40 mL), dried ($MgSO_4$), and concentrated in vacuo to give the crude enol triflate ***Z*-31** as a yellow oil, which was used in the subsequent Stille reaction without further purification.

To a solution of the above crude enol triflate ***Z*-31** and $CH_2C(OEt)SnBu_3$ (3.69 g, 10.2 mmol) in anhydrous THF (70 mL) were added lithium chloride (434 mg, 10.2 mmol) and $Pd(PPh_3)_4$ (591 mg, 510 μmol), the solution was heated at reflux overnight. The reaction mixture was cooled and diluted with ethyl acetate (30 mL). The organic phase was washed with brine (20 mL), 5% aqueous solution of NH_4OH (20 mL), and brine (20 mL). The organic extracts were dried (Na_2SO_4) and concentrated in vacuo to give a yellow oil. Rapid flash column chromatography on silica gel (petroleum ether/ethyl acetate 15:1 with 1% Et_3N) afforded the highly unstable diene ***Z*-32** as a colorless oil, which was used immediately in the subsequent Diels−Alder cycloaddition reaction.

The above diene ***Z*-32** and freshly distilled methyl vinyl ketone (2.39 g, 34.1 mmol) were dissolved in anhydrous toluene (140 mL), and the mixture was heated at reflux in a sealed tube overnight. The volatiles were removed in vacuo to give a yellow oil. Flash column chromatography on silica gel (petroleum ether/ethyl acetate 15:1 with 1% Et_3N) delivered a mixture (2:1) of the Diels−Alder cycloadducts ***Z*-33** and ***Z*-34** (1.02 g, 69% over three steps) as a colorless oil.

To a solution of the mixture of cycloadducts ***Z*-33** and ***Z*-34** (1.02 g, 2.35 mmol) in methanol (25 mL) was added potassium carbonate (389 mg, 2.80 mmol), and the solution was stirred at rt overnight. The reaction mixture was diluted with a saturated aqueous solution of NH_4Cl (25 mL) and ethyl acetate (40 mL). The aqueous phase was separated and extracted with ethyl acetate (2 × 40 mL). The organic extracts were combined, washed with brine (20 mL), dried ($MgSO_4$), and concentrated in vacuo to give a yellow oil. Flash column chromatography on silica gel (petroleum ether/ethyl acetate 20:1 with 1% Et_3N) afforded the ketone ***Z*-33** as a colorless oil (929 mg, 91%). R_f = 0.40 (petroleum ether/ethyl acetate 4:1); $[\alpha]_D^{24}$ +143 (*c* 0.99, $CHCl_3$); ν_{max} ($CHCl_3$) 2951, 2928, 2855, 1714, 870, 833, 808, 772 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.36 (1H, dd, *J* = 11.5, 5.6 Hz), 4.87−4.85 (1H, m), 3.78 (2H, q, *J* = 7.0 Hz), 3.70 (1H, dd, *J* = 9.3, 2.6 Hz), 3.59−3.57 (1H, m), 3.15−3.05 (1H, m), 2.96−2.87 (1H, m), 2.82 (1H, d, *J* = 14.0 Hz), 2.35−2.16 (3H, m), 2.15 (3H, s), 2.06−1.98 (1H, m), 1.92 (1H, dd, *J* = 14.0, 4.0 Hz), 1.88−1.72 (3H, m), 1.66 (3H, s), 1.65−1.54 (1H, m), 1.26 (3H, t, *J* = 7.0 Hz), 0.88 (9H, s), 0.04 (3H, s), 0.03 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.3, 143.8, 130.5, 130.2, 119.2, 88.2, 75.2, 72.0, 63.2, 52.3, 43.5, 37.5, 32.9, 29.8, 28.4, 27.2, 26.3, 24.6, 22.1, 18.7, 15.8, −4.3, −4.4; HRMS (CI, isobutane) *m*/*z* calcd for $C_{25}H_{43}O_4Si$ $[M + H]^+$ 435.2933, found 435.2935; LRMS (CI, isobutane) *m*/*z* (% intensity); 435.5 (100), 377.4 (7).

(1*R*,2*S*,6*S*,7*R*,8*R*,9*S*,12*Z*)-6-(Propen-2-yl)-13-methyl-15-oxatricyclo[6.6.1.0^{2,7}]-12-pentadecen-3-one-9-ol (*Z*-35). To a stirred suspension of potassium *t*-butoxide (123 mg, 1.10 mmol) in anhydrous THF (5 mL) was added methyltriphenylphosphonium bromide (493 mg, 1.38 mmol) in one portion, and the solution was stirred for 30 min. A solution of the ketone ***Z*-33** (120 mg, 0.656 mmol) in anhydrous THF (2.5 mL) was then added dropwise to the solution of phosphonium ylide. The flask containing the ketone ***Z*-33** was rinsed with further anhydrous THF (2 mL), and this was added dropwise to the reaction mixture. The solution was heated to 50 °C and stirred for 2 h, then allowed to cool and quenched with aqueous 2 M HCl solution (12 mL), and the mixture was stirred for a further 3 h. The reaction mixture was diluted with ethyl acetate (20 mL). The aqueous phase was separated and extracted with ethyl acetate (2 × 20 mL). The organic extracts were combined, washed with brine (25 mL), dried, and concentrated in vacuo to yield a white solid. Flash column chromatography on silica gel (petroleum ether/ethyl acetate 4:1) afforded the diene ***Z*-35** (153 mg, 78%) as a colorless solid. R_f = 0.45 (hexane/ethyl acetate 2:1); mp 171−173 °C; $[\alpha]_D^{25}$ +2.0 (*c* 0.50, $CHCl_3$); ν_{max} ($CHCl_3$) 3621, 2926, 1704, 1644, 1602, 1455, 1380, 1324, 1266, 1087, 1053, 1004, 948, 987 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.50 (1H, dd, *J* = 11.8, 5.7 Hz), 4.91 (1H, br s), 4.89 (1H, dq, *J* = 1.5, 1.5 Hz), 4.35 (1H, ddd, *J* = 9.8, 3.3, 3.1 Hz), 3.66 (1H, d, *J* = 9.3 Hz), 3.33−3.24 (1H, m), 2.84 (1H, br d, *J* = 14.9 Hz), 2.81−2.73 (2H, m), 2.57−2.49 (2H, m), 2.45 (1H, dddd, *J* = 16.0, 4.2, 2.6, 1.5 Hz), 2.36 (1H, ddd, *J* = 12.2, 12.2, 3.0 Hz), 2.02−1.93 (2H, m), 1.91 (3H, br t, *J* = 1.3 Hz), 1.84 (1H, dd, *J* = 14.9, 3.3 Hz), 1.81−1.70 (3H, m), 1.72 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.3, 146.3, 132.8, 127.5, 113.3, 87.4, 80.8, 71.5, 52.1, 49.8, 44.6, 38.7, 35.0, 34.3, 30.5, 28.2, 26.1, 18.9; HRMS [positive electrospray ionization time-of-flight (+ESI-TOF)] *m*/*z* calcd for $C_{18}H_{26}O_3Na$ $[M + Na]^+$ 313.1774, found 313.1765.

(1*R*,2*S*,6*R*,7*R*,8*R*,9*S*,12*Z*)-6-Isopropyl-13-methyl-15-oxatricyclo[6.6.1.0^{2,7}]-12-pentadecen-3-one-9-ol (*Z*-36). To a stirred solution of the diene **35** (123 mg, 0.42 mmol) in ethyl acetate (12 mL) was added platinum(IV) oxide (9.6 mg, 42 μmol). The solution was placed under an atmosphere of hydrogen for 110 min, and the reaction was monitored by ^1H NMR to ensure that overreduction was avoided. The suspension was filtered, washed with ethyl acetate, and concentrated in vacuo to afford the desired product ***Z*-36** (120 mg, 97%) as a colorless solid. R_f = 0.45 (hexane/ethyl acetate 2:1); mp 162−165 °C; $[\alpha]_D^{25}$ +26.0 (*c* 0.50, $CHCl_3$); ν_{max} ($CHCl_3$) 3623, 2927, 2874, 1704, 1455, 1380, 1370, 1349, 1323, 1263, 1172, 1084, 1046, 1022, 1007, 986, 970, 946, 909, 866, 841 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.49 (1H, dd, *J* = 11.7, 5.6 Hz), 4.32 (1H, ddd, *J* = 9.8, 3.2, 3.0 Hz), 3.81 (1H, d, *J* = 9.2 Hz), 3.30 (1H, ddd, *J* = 9.2, 9.1, 5.6 Hz), 2.85−2.71 (3H, m), 2.50−2.34 (3H, m), 2.05−1.92 (3H, m), 1.90 (3H, s), 1.82 (1H, dd, *J* = 14.9, 3.2 Hz), 1.79−1.71 (2H,

dx.doi.org/10.1021/jo302542h | *J. Org. Chem.* XXXX, XXX, XXX−XXX

m), 1.57 (1H, ddd, J = 12.1, 11.9, 2.6 Hz), 1.47−1.37 (1H, m), 1.02 (3H, d, J = 6.9 Hz), 0.81 (3H, d, J = 6.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.1, 132.9, 127.4, 87.2, 80.8, 71.8, 52.4, 50.8, 40.5, 38.6, 35.0, 34.4, 28.2, 28.1, 26.1, 24.1, 21.9, 15.4; HRMS (+ESI-TOF) m/z calcd for $C_{18}H_{28}O_3Na$ $[M + Na]^+$ 315.1931, found 315.1930.

(1*R*,2*R*,6*R*,7*R*,8*R*,9*S*,12*Z*)-6-Isopropyl-13-methyl-3-methylidene-15-oxatricyclo[6.6.1.0^{2,7}]-12-pentadecene-9-ol (*Z*-37). To a suspension of potassium *t*-butoxide (69 mg, 0.62 mmol) in anhydrous benzene (1 mL) was added methyltriphenylphosphonium bromide (221 mg, 0.619 mmol), and the yellow mixture was heated at reflux for 1 h. To the reaction mixture was added a solution of ketone **36** (20 mg, 68 μmol) in anhydrous toluene (3 mL) dropwise, and the resulting mixture was heated at reflux for 1 h. The reaction was then quenched with water (10 mL) and diluted with ethyl acetate (10 mL). The aqueous phase was separated and extracted with ethyl acetate (2 × 10 mL). The organic extracts were combined, dried ($MgSO_4$), and concentrated in vacuo to yield a colorless solid. Flash column chromatography on silica gel (hexane/ethyl acetate 5:1) afforded diene *Z*-**37** (18 mg, 93%) as a colorless solid. R_f = 0.61 (hexane/ethyl acetate 2:1); mp 136−138 °C; $[\alpha]_D^{22}$ +47.4 (c 1.00, $CHCl_3$); ν_{max} (attenuated total reflectance, ATR) 3432, 3074, 2956, 2939, 2915, 2871, 2852, 1648, 1466, 1439, 1427, 1367, 1343, 1315, 1261, 1182, 1110, 1082, 1045, 1026. 1014, 983, 945, 889, 861, 835, 791, 770, 741, 717, 661, 561 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.51 (1H, dd, J = 11.7, 5.9 Hz), 4.80 (1H, t, J = 1.9 Hz), 4.77 (1H, t, J = 1.7 Hz), 4.14 (1H, ddd, J = 9.5, 3.1, 3.1 Hz), 3.66 (1H, d, J = 9.3 Hz), 3.44−3.36 (1H, m), 2.91−2.81 (1H, m), 2.77 (1H, br d, J = 14.9 Hz), 2.72 (1H. dd, J = 9.5, 6.5 Hz), 2.28 (1H, ddd, J = 13.6, 3.2, 3.1 Hz,), 2.17−2.08 (1H, m), 2.00 (1H, dd, J = 11.8, 6.5 Hz), 2.03−1.83 (3H, m), 1.86 (3H, s), 1.81−1.71 (3H, m), 1.39−1.30 (1H, m), 1.21 (1H, br s), 1.02 (1H, qd, J = 13.0, 3.2 Hz), 0.96 (3H, d, J = 7.0 Hz), 0.76 (3H, d, J = 6.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.0, 132.8, 127.6, 110.7, 87.5, 81.0, 71.6, 49.1, 46.5, 41.3, 34.6, 34.4, 31.6, 28.9, 28.5, 26.4, 25.5, 21.9, 15.6; HRMS (+ESI-TOF) m/z calcd for $C_{19}H_{31}O_2$ $[M + H]^+$ 291.2319, found 291.2312.

(+)-Cladiella-6*Z*,11(17)-dien-3-ol (*Z*-1).[12c,14f] To a stirred solution of alcohol *Z*-**37** (58 mg, 0.20 mmol) and pyridine (81 μL, 1.00 mmol) in anhydrous dichloromethane (4 mL) was added Dess−Martin periodinane (211 mg, 0.500 mmol) in one portion. The mixture was stirred for 1 h, and the reaction was then quenched by addition of a saturated aqueous solution of sodium thiosulfate/sodium hydrogen carbonate (5:1, 5 mL). The mixture was diluted with dichloromethane (5 mL) and water (2 mL), and the aqueous phase was separated and extracted with dichloromethane (2 × 15 mL). The organic extracts were combined, dried ($MgSO_4$), and concentrated in vacuo to give the crude ketone as a yellow oil. The ketone was used immediately in the next reaction without purification.

To a stirred solution of MeMgCl (3.0 M in THF, 667 μL, 2.00 mmol) in anhydrous THF (4 mL) at 0 °C was added a solution of ketone (58 mg, 0.20 mmol) in anhydrous THF (4 mL) dropwise. The flask containing the ketone was rinsed with further anhydrous THF (1 mL), and this was added dropwise to the reaction mixture. The solution was stirred for 1.5 h and then quenched with a saturated aqueous solution of ammonium chloride (7 mL). The reaction mixture was then diluted with ethyl acetate (7 mL) and water (5 mL). The aqueous phase was separated and extracted with ethyl acetate (2 × 25 mL). The organic extracts were combined, dried ($MgSO_4$), and concentrated in vacuo to give a yellow oil. Flash column chromatography on silica gel (hexane/diethyl ether, gradient elution 7:1 → 5:1) afforded (+)-cladiella-6*Z*,11(17)-dien-3-ol (*Z*-**1**) (45 mg, 90%) as a colorless solid. R_f = 0.28; (petroleum ether/diethyl ether 5:1); mp 91−93 °C; $[\alpha]_D^{22}$ +69.7 (c 0.60, $CHCl_3$) {lit.[12c] $[\alpha]_D^{22}$ +95.3 (c 0.40, $CHCl_3$); lit.[14f] $[\alpha]_D^{25}$ +82.2 (c 0.27, $CHCl_3$)}; ν_{max} ($CHCl_3$) 3494, 2929, 1718, 1645, 1453, 1377, 1353, 1318, 1092, 1079, 1058, 979, 945, 896 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.88 (1H, dd, J = 11.1, 6.1 Hz), 4.77 (1H, t, J = 2.0 Hz), 4.71 (1H, br s), 4.13 (1H, ddd, J = 9.8, 3.1, 3.1 Hz), 3.91 (1H, s), 3.36−3.15 (1H, m), 2.90 (1H, br d, J = 4.4 Hz), 2.84 (1H, dd, J = 9.7, 6.9 Hz), 2.28 (1H, ddd, J = 13.5, 3.2, 3.0 Hz), 2.22 (1H, dd, J = 12.0, 6.9 Hz), 2.17−2.08 (1H, m), 2.05−1.87 (3H, m), 1.89 (3H, s), 1.84−1.70 (3H, m), 1.36−1.25 (2H, m), 1.04 (1H, qd, J = 13.1, 3.2 Hz), 0.98 (3H, s), 0.97 (3H, d, J = 7.0 Hz), 0.78 (3H, d, J = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.9, 136.6, 128.8, 110.7, 91.5, 80.4, 75.5, 48.2, 47.1, 42.5, 38.9, 34.5, 31.7, 29.2, 28.8, 28.6, 27.8, 25.4, 22.1, 15.4; HRMS (+ESI-TOF) m/z calcd for $C_{20}H_{33}O_2$ $[M + H]^+$ 305.2475, found 305.2477.

(+)-Vigulariol (2).[16,33] To a stirred solution of the alcohol *Z*-**1** (10 mg, 34 μmol) in anhydrous dichloromethane (1.5 mL) at 0 °C was added a solution of *m*-chloroperoxybenzoic acid (*m*-CPBA; 0.05 M in dichloromethane, 670 μL) dropwise. The mixture was stirred for 30 min at 0 °C and then quenched by addition of a saturated aqueous solution of sodium thiosulfate (2 mL) and dichloromethane (3 mL). The aqueous phase was separated and extracted with dichloromethane (3 × 5 mL). The organic extracts were combined, washed with a saturated aqueous solution of sodium hydrogen carbonate (3 mL) and water (3 mL), dried ($MgSO_4$), and concentrated in vacuo to give a yellow oil. Flash column chromatography on silica gel (hexane/diethyl ether, gradient elution 5:1 → 2:1) afforded (+)-vigulariol (**2**) (9.8 mg, 91%) as a colorless oil: R_f = 0.35; (petroleum ether/ethyl acetate 1:1); ν_{max} ($CHCl_3$) 3601, 2961, 1715, 1601, 1458, 1376, 1064, 896 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.72 (1H, dd, J = 2.1, 2.0 Hz), 4.71 (1H, dd, J = 2.0, 1.7 Hz), 4.11−4.04 (2H, m), 3.69 (1H, t, J = 8.1 Hz), 3.65 (1H, s), 2.43 (1H, dddd, J = 11.8, 9.6, 9.3, 6.9 Hz), 2.28 (1H, dd, J = 15.1, 4.4 Hz), 2.26−2.22 (1H, m), 2.21−2.14 (2H, m), 2.10−1.96 (2H, m), 1.86 (1H, dd, J = 15.1, 2.9 Hz), 1.78 (1H, ddd, J = 12.5, 9.8, 9.6 Hz), 1.74−1.67 (2H, m), 1.53 (3H, s), 1.31−1.22 (1H, m), 1.18 (3H, s), 1.01 (1H, qd, J = 13.0, 2.9 Hz), 0.96 (3H, d, J = 6.9 Hz), 0.76 (3H, d, J = 6.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.0, 110.0, 90.1, 87.2, 85.9, 80.7, 74.6, 47.6, 45.9, 43.1, 42.3, 38.5, 31.9, 31.4, 29.1, 28.0, 25.0, 24.0, 22.0, 15.5; HRMS (+ESI-TOF) m/z calcd for $C_{20}H_{33}O_3$ $[M + H]^+$ 321.2424, found 321.2415.

1-{(1*R*,2*R*,8*R*,10*E*,14*S*)-14-(*tert*-Butyldimethylsilyloxy)-6-ethoxy-10-methyl-15-oxatricyclo[6.6.1.0^{2,7}]pentadeca-6,10-dien-3-yl}ethanone (*E*-33). To a solution of ketone *E*-**30** (1.53 g, 4.93 mmol) and $PhN(Tf)_2$ (3.52 g, 9.87 mmol) in anhydrous THF (100 mL) at −78 °C was added NaHMDS (12.4 mL of a 1.0 M solution in THF, 12.4 mmol) dropwise over 10 min. The resulting solution was stirred at −78 °C for 2 h; the reaction was then quenched with water (30 mL) at −78 °C and allowed to warm to rt. The aqueous phase was separated and extracted with diethyl ether (3 × 80 mL). The organic extracts were combined and washed with brine (60 mL), then dried ($MgSO_4$) and concentrated in vacuo to give the crude enol triflate *E*-**31** as a yellow oil.

To a solution of enol triflate *E*-**31** and $CH_2C(OEt)SnBu_3$ (5.35 g, 14.8 mmol) in anhydrous THF (100 mL) were added LiCl (628 mg, 14.8 mmol) and $Pd(PPh_3)_4$ (856 mg, 740 μmol), and the solution was heated at reflux overnight. The reaction mixture was cooled and diluted with ethyl acetate (50 mL). The organic phase was washed with brine (30 mL), 5% aqueous solution of ammonium hydroxide (30 mL), and brine (30 mL). The organic phase was dried (Na_2SO_4) and concentrated in vacuo to give a yellow oil. Rapid flash column chromatography on silica gel (petroleum ether/ethyl acetate 15:1 with 1% Et_3N) afforded the highly unstable diene *E*-**32** as a colorless oil, which was used immediately.

Diene *E*-**32** and freshly distilled methyl vinyl ketone (3.45 g, 49.3 mmol) were dissolved in anhydrous toluene (200 mL) and heated at 130 °C in a sealed tube overnight. The volatiles were removed in vacuo to give a yellow oil. Flash column chromatography on silica gel (petroleum ether/ethyl acetate 15:1 with 1% Et_3N) delivered a mixture (1.6:1) of the Diels−Alder cycloadducts *E*-**33** and *E*-**34** (1.47 g, 68% over three steps) as a colorless oil.

To a stirred solution of the mixture of cycloadducts *E*-**33** and *E*-**34** (1.44 g, 3.31 mmol) in methanol (35 mL) was added potassium carbonate (550 mg, 3.97 mmol), and the solution was stirred at rt overnight. The reaction mixture was diluted with a saturated aqueous solution of ammonium chloride (35 mL) and ethyl acetate (60 mL). The aqueous phase was separated and extracted with ethyl acetate (2 × 50 mL). The organic extracts were combined, washed with brine (30 mL), dried ($MgSO_4$), and concentrated in vacuo to give a yellow oil. Flash column chromatography on silica gel (petroleum ether/ethyl acetate 20:1 with 1% Et_3N) afforded the ketone *E*-**33** as a colorless oil

dx.doi.org/10.1021/jo302542h | J. Org. Chem. XXXX, XXX, XXX−XXX

(1.22 g, 85%). R_f = 0.30 (petroleum ether/ethyl acetate 5:1); $[\alpha]_D^{25}$ +119 (*c* 1.04, $CHCl_3$); ν_{max} ($CHCl_3$) 2951, 2927, 2856, 1713, 935, 896, 869, 836, 774 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.67 (1H, t, *J* = 8.4 Hz), 4.84 (1H, d, *J* = 6.0 Hz), 3.91 (1H, dd, *J* = 8.3, 4.9 Hz), 3.80 (1H, q, *J* = 7.0 Hz), 3.79 (1H, q, *J* = 7.0 Hz), 3.66 (1H, dd, *J* = 6.3, 4.9 Hz), 2.68−2.62 (1H, m), 2.49 (1H, dd, *J* = 13.5, 6.0 Hz), 2.35−1.96 (8H, m), 2.15 (3H, s), 1.70−1.59 (2H, m), 1.65 (3H, s), 1.23 (3H, t, *J* = 7.0 Hz), 0.92 (9H, s), 0.05 (3H, s), 0.04 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.7, 143.3, 130.6, 125.5, 121.3, 88.0, 74.7, 74.0, 63.3, 52.9, 43.5, 42.8, 30.3, 28.9, 27.1, 26.1, 24.4, 21.6, 18.5, 18.3, 15.7, −4.5, −4.6; HRMS (CI, isobutane) *m*/*z* calcd for $C_{25}H_{43}O_4Si$ $[M + H]^+$ 435.2930, found 435.2922; LRMS (CI, isobutane) *m*/*z* (% intensity) 435.7 (100), 303.6 (10), 113.3 (20). Anal. Calcd for $C_{25}H_{42}O_4Si$: C, 69.08; H, 9.74. Found C, 68.93; H, 9.73.

***tert*-Butyl({[(1*R**,6*S**,7*R**,8*R**,9*S**,12*E*)-3-ethoxy-13-methyl-6-(propen-2-yl)-15-oxatricyclo[6.6.1.$0^{2,7}$]pentadeca-2,12-dien-9-yl]oxy})dimethylsilane [(±)-39].** To a solution of methyltriphenylphosphonium bromide (1.50 g, 4.19 mmol) in anhydrous THF (20 mL) at 0 °C was added dropwise NaHMDS (3.35 mL of a 1 M solution in THF, 3.35 mmol). The resulting yellow reaction mixture was stirred for 1 h at 0 °C. A solution of ketone (±)-*E*-**33** (363 mg, 840 μmol) in anhydrous THF (10 mL) was then added dropwise to the solution of the ylide. The mixture was stirred at rt for 1.5 h before the reaction was quenched with a saturated aqueous solution of ammonium chloride (50 mL) and diluted with diethyl ether (100 mL). The aqueous phase was separated and extracted with diethyl ether (2 × 100 mL). The organic extracts were combined, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate 25:1) to afford the alkene (±)-**39** (289 mg, 80%) as a colorless solid. R_f = 0.56 (petroleum ether/ethyl acetate 4:1); mp 80−82 °C; ν_{max} ($CHCl_3$) 2949, 2926, 2854, 1709, 895, 862, 835, 773 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.71−5.63 (1H, m), 4.85 (1H, d, *J* = 6.2 Hz), 4.75 (1H, br s), 4.73−4.68 (1H, m), 3.86 (1H, dd, *J* = 8.1, 4.6 Hz), 3.84−3.74 (3H, m), 2.49 (1H, dd, *J* = 13.7, 6.2 Hz), 2.32−2.10 (5H, m), 2.06 (1H, d, *J* = 12.9 Hz), 1.93−1.69 (4H, m), 1.64 (3H, s), 1.63−1.54 (1H, m), 1.59 (3H, s), 1.23 (3H, t, *J* = 7.0 Hz), 0.92 (9H, s), 0.04 (3H, s), 0.02 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.7, 144.0, 130.4, 126.0, 122.3, 112.2, 88.2, 75.1, 74.1, 63.3, 48.8, 43.9, 43.8, 29.3, 29.1, 26.4, 24.9, 21.9, 18.8, 18.6, 18.5, 15.9, −4.2, −4.6; HRMS (CI, isobutane) *m*/*z* calcd for $C_{26}H_{45}O_3Si$ $[M + H]^+$ 433.3138, found 433.3137; LRMS (CI, isobutane) *m*/*z* (% intensity) 433.3 (100). Anal. Calcd for $C_{26}H_{44}O_3Si$: C, 72.17; H, 10.25. Found: C, 72.14; H, 10.32.

(1*R,2*S**,6*S**,7*R**,8*R**,9*S**,12*E*)-9-(*tert*-Butyldimethylsilyloxy)-13-methyl-6-(propen-2-yl)-15-oxatricyclo[6.6.1.$0^{2,7}$]pentadec-12-en-3-one [(±)-40].** To a stirred solution of enol ether (±)-**39** (26 mg, 60 μmol) in THF (6 mL) was added a 1 M aqueous solution of HCl (60 μL, 60 μmol). The solution was stirred at rt overnight and then diluted with dichloromethane (15 mL) and water (12 mL). The aqueous phase was separated and extracted with dichloromethane (2 × 15 mL). The organic extracts were combined, dried ($MgSO_4$), and concentrated in vacuo to give a colorless solid. Flash column chromatography on silica gel (petroleum ether/ethyl acetate 15:1) delivered the ketone (±)-**40** (21 mg, 87%) as a colorless solid. R_f = 0.46 (petroleum ether/ethyl acetate 4:1); mp 96−98 °C; ν_{max} ($CHCl_3$) 2949, 2930, 2887, 2859, 1707, 949, 868, 837, 810, 773 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.30 (1H, br d, *J* = 12.3 Hz), 4.87 (1H, s), 4.86−4.84 (1H, m), 4.29 (1H, dd, *J* = 10.1, 5.9 Hz), 3.70 (1H, d, *J* = 9.2 Hz), 2.98 (1H, dd, *J* = 9.2, 7.6 Hz), 2.74 (1H, dd, *J* = 10.0, 4.9 Hz), 2.60−2.50 (2H, m), 2.45−2.42 (1H, m), 2.41−2.33 (2H, m), 2.25 (1H, qd, *J* = 12.3, 3.9 Hz), 2.18−2.12 (1H, m), 2.09 (1H, d, *J* = 13.8 Hz), 1.99−1.92 (1H, m), 1.88 (3H, s), 1.86−1.63 (3H, m), 1.67 (3H, s), 0.87 (9H, s), 0.09 (3H, s), 0.02 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.9, 146.1, 134.6, 124.4, 113.8, 88.4, 80.6, 73.9, 54.2, 49.0, 44.6, 40.5, 38.6, 37.6, 30.8, 27.5, 26.2, 21.1, 19.4, 18.2, −3.8, −4.0; HRMS (CI, isobutane) *m*/*z* calcd for $C_{24}H_{41}O_3Si$ $[M + H]^+$ 405.2825, found 405.2829; LRMS (CI, isobutane) *m*/*z* (% intensity) 405.5 (100), 347.4 (20), 273.4 (56). Anal. Calcd for $C_{24}H_{40}O_3Si$: C, 71.23; H, 9.96. Found: C, 71.22; H, 10.11.

(1*R,2*S**,6*S**,7*R**,8*R**,9*S**,12*E*)-9-Hydroxy-13-methyl-6-(propen-2-yl)-15-oxatricyclo[6.6.1.$0^{2,7}$]pentadec-12-en-3-one [(±)-*E*-35].** To a solution of silyl ether **40** (30 mg, 74 μmol) and 4 Å molecular sieves in anhydrous THF (2 mL) was added tetra-*n*-butylammonium fluoride (TBAF; 148 μL of a 1 M solution in THF, 148 μmol). The reaction mixture was stirred at rt for 4 h and then quenched with a saturated aqueous solution of NH_4Cl (1 mL). The molecular sieves were filtered off and rinsed with ethyl acetate. The aqueous phase was separated and extracted with ethyl acetate (3 × 5 mL). The organic extracts were combined, washed with brine (5 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate, gradient elution 10:1 → 7:1 → 5:1) to deliver the alcohol (±)-*E*-**35** (16 mg, 72%) as a colorless solid. R_f = 0.30 (petroleum ether/ethyl acetate 2:1); mp 113−115 °C; ν_{max} ($CHCl_3$) 3440, 2925, 2864, 1705, 1645, 940, 898, 794 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.30 (1H, br d, *J* = 12.4 Hz), 4.89 (1H, s), 4.87−4.84 (1H, m), 4.29 (1H, dd, *J* = 9.6, 5.8 Hz), 3.60 (1H, d, *J* = 9.4 Hz), 2.93−2.90 (1H, m), 2.78 (1H, dd, *J* = 9.6, 6.7 Hz), 2.58−2.48 (3H, m), 2.45−2.36 (2H, m), 2.30 (1H, qd, *J* = 12.3, 4.3 Hz), 2.21−2.13 (1H, m), 2.10 (1H, d, *J* = 13.8 Hz), 1.99−1.86 (2H, m), 1.85 (3H, s), 1.81−1.71 (2H, m), 1.69 (3H, s), 1.26−1.18 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.4, 146.5, 133.8, 124.4, 113.5, 88.5, 80.5, 74.1, 53.6, 49.5, 44.8, 40.6, 38.5, 37.4, 30.5, 27.5, 20.8, 18.8; HRMS (CI, isobutane) *m*/*z* calcd for $C_{18}H_{27}O_3$ $[M + H]^+$ 291.1960, found 291.1959; LRMS (CI, isobutane) *m*/*z* (% intensity) 291.3 (17), 273.3 (7), 113.2 (13).

2-{(1*R*,2*R*,3*R*,8*R*,10*E*)-14-(*tert*-Butyldimethylsilyloxy)-6-ethoxy-10-methyl-15-oxatricyclo[6.6.1.$0^{2,7}$]pentadeca-6,10-dien-3-yl}propan-2-ol (42). To a solution of ketone *E*-**33** (462 mg, 1.06 mmol) in anhydrous THF (50 mL) at 0 °C was added slowly methylmagnesium bromide (2.12 mL of a 3 M solution in diethyl ether, 6.36 mmol). The reaction mixture was allowed to warm to rt and stirred for 3 h, then quenched with a saturated aqueous solution of ammonium chloride (45 mL) and diethyl ether (15 mL). The aqueous phase was separated and extracted with diethyl ether (3 × 30 mL). The organic extracts were combined, washed with brine (20 mL), dried ($MgSO_4$), and concentrated in vacuo to give the crude alcohol as a yellow oil. Flash column chromatography on silica gel (petroleum ether/diethyl ether, gradient elution 20:1 → 5:1 with 1% Et_3N) afforded the alcohol **42** as a colorless oil (373 mg, 78%). R_f = 0.39 (petroleum ether/ethyl acetate 4:1); $[\alpha]_D^{23}$ +79.3 (*c* 0.91, $CHCl_3$); ν_{max} ($CHCl_3$) 3458, 2953, 2926, 2855, 1708, 935, 899, 863, 774 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.71 (1H, br t, *J* = 8.9 Hz), 4.82 (1H, d, *J* = 5.9 Hz), 4.64 (1H, dd, *J* = 7.2, 4.6 Hz), 4.34 (1H, dd, *J* = 7.8, 4.6 Hz), 3.79 (1H, q, *J* = 7.0 Hz), 3.78 (1H, q, *J* = 7.0 Hz), 2.45 (1H, dd, *J* = 13.2, 5.9 Hz), 2.31−2.09 (6H, m), 1.94−1.82 (2H, m), 1.68−1.63 (1H, m), 1.63 (3H, s), 1.37−1.31 (2H, m), 1.28 (3H, s), 1.23 (3H, t, *J* = 7.0 Hz), 1.03 (3H, s), 0.97 (1H, s), 0.93 (9H, s), 0.06 (3H, s), 0.05 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.6, 130.3, 125.9, 123.9, 88.0, 74.6, 73.7, 71.6, 62.9, 51.6, 43.6, 43.6, 32.1, 28.7, 27.5, 26.2, 25.1, 23.7, 21.9, 18.4, 18.2, 15.7, −4.2, −4.7; HRMS (CI, isobutane) *m*/*z* calcd for $C_{26}H_{47}O_4Si$ $[M + H]^+$ 451.3243, found 451.3243; LRMS (CI, isobutane) *m*/*z* (% intensity) 451.4 (100), 433.3 (13), 319.3 (8).

(1*R,2*S**,6*S**,7*R**,8*R**,9*S**,12*E*)-9-(*tert*-Butyldimethylsilyloxy)-6-(2-hydroxypropan-2-yl)-13-methyl-15-oxatricyclo-[6.6.1.$0^{2,7}$]pentadec-12-en-3-one (43) and *tert*-Butyl-{(1*S**,2*R**,3*R**,4*S**,7*E*,10*R**,11*S**,12*R**)-12-ethoxy-8,14,14-trimethyl-13,17-dioxatetracyclo[10.2.2.$1^{3,10}$.$0^{2,11}$]heptadec-7-en-4-yl}oxidimethylsilane (44).** To a solution of enol ether (±)-**42** (96 mg, 0.21 mmol) in THF (10 mL) was added a 1 M aqueous solution of HCl (210 μL, 210 μmol). The solution was stirred at rt for 1 h and then diluted with diethyl ether (30 mL) and water (20 mL). The aqueous phase was separated and extracted with diethyl ether (3 × 20 mL). The organic extracts were combined, washed with brine (30 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate 10:1) to deliver the ketone (±)-**43** (39 mg, 43%) as a colorless oil and the tetracycle (±)-**44** (15 mg, 17%) as a colorless oil.

(±)-**43**: R_f = 0.50 (petroleum ether/ethyl acetate 1:1); ν_{max} ($CHCl_3$) 3456, 2954, 2929, 2887, 2859, 1710, 872, 837, 826, 807,

dx.doi.org/10.1021/jo302542h | J. Org. Chem. XXXX, XXX, XXX−XXX

779 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.32 (1H, br d, J = 12.3 Hz), 4.56 (1H, d, J = 9.4 Hz), 4.27 (1H, dd, J = 9.8, 6.1 Hz), 3.04 (1H, dd, J = 9.4, 7.8 Hz), 2.78−2.73 (1H, m), 2.62−2.42 (3H, m), 2.35−2.27 (1H, m), 2.25 (1H, qd, J = 12.3, 4.0 Hz), 2.18−2.11 (1H, m), 2.08 (1H, d, J = 13.8 Hz), 2.02 (1H, dddd, J = 13.5, 4.2, 4.2, 4.2 Hz), 1.96−1.87 (1H, m), 1.86 (3H, s), 1.86−1.81 (1H, m), 1.71 (1H, ddd, J = 14.2, 4.0, 2.8 Hz), 1.60 (1H, s), 1.55−1.42 (1H, m), 1.28 (3H, s), 1.17 (3H, s), 0.90 (9H, s), 0.15 (3H, s), 0.08 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.9, 134.3, 124.1, 90.5, 81.2, 76.0, 74.1, 54.6, 48.3, 45.6, 40.6, 37.6, 37.0, 29.5, 28.6, 27.1, 26.2, 25.8, 20.9, 18.0, −3.6, −4.1; HRMS (CI, isobutane) m/z calcd for $C_{24}H_{43}O_4Si$ $[M + H]^+$ 423.2931, found 423.2936; LRMS (CI, isobutane) (% intensity) 423.3 (100), 405.3 (40), 365.5 (13), 291.3 (60). Anal. Calcd for $C_{24}H_{42}O_4Si$: C, 68.20; H, 10.02. Found: C, 68.06; H, 10.06.

(±)-**44**: R_f = 0.76 (petroleum ether/ethyl acetate 1:1); ν_{max} ($CHCl_3$) 2956, 2928, 2856, 1730, 836, 772 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.24 (1H, br d, J = 8.6 Hz), 4.32−4.29 (1H, m), 3.63−3.52 (3H, m), 3.26 (1H, dd, J = 8.1, 8.1 Hz), 2.66−2.58 (2H, m), 2.44 (1H, dd, J = 11.0, 3.6 Hz), 2.30−2.18 (1H, m), 2.17−2.09 (1H, m), 2.04 (1H, d, J = 13.3 Hz), 1.92−1.75 (5H, m), 1.78 (3H, s), 1.69−1.66 (1H, m), 1.42−1.36 (1H, m), 1.29 (3H, s), 1.26 (3H, s), 1.16 (3H, t, J = 7.0 Hz), 0.87 (9H, s), 0.11 (3H, s), 0.05 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.5, 125.8, 101.3, 89.8, 81.8, 78.7, 76.6, 56.8, 50.8, 46.6, 44.7, 37.6, 37.1, 29.0, 28.7, 27.5, 26.0, 24.0, 19.8, 17.9, 17.1, 15.7, −3.5, −4.6.

(1*R*,7*R*,6*S*,8*R*,9*S*,12*E*)-3-Ethoxy-6-isopropyl-13-methyl-15-oxatricyclo[6.6.1.0^{2,7}]pentadeca-2,12-dien-9-ol (46). To a flask containing alcohol **42** (95 mg, 0.21 mmol), dimethylaminopyridine (DMAP) (135 mg, 1.11 mmol), and distilled triethylamine (561 mg, 5.54 mmol) was added freshly distilled acetic anhydride (1.13 g, 11.1 mmol). The resulting solution was heated at 40 °C for 30 min, then cooled at 0 °C and quenched with a saturated aqueous solution of ammonium chloride (3 mL) and diethyl ether (5 mL). The aqueous phase was separated and extracted with diethyl ether (3 × 5 mL). The organic extracts were combined, washed with brine (5 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was filtered through a pad of silica gel (petroleum ether/ethyl acetate 10:1 with 1% Et_3N) to afford the crude acetate **45** as a colorless oil. The crude acetate **45** was used in the following step without purification.

A small freshly cut piece of potassium (∼100 mg) was added to a solution of recrystallized 18-crown-6 (530 mg, 2.00 mmol) in freshly distilled *t*-butylamine (20 mL) at rt. The mixture was sonicated and then stirred at the same temperature until a dark blue color developed, after which anhydrous THF (20 mL) was added. A solution of the crude acetate **45** in anhydrous THF (4 mL) was added upon reappearance of the blue color at such a rate that the color did not disappear for a long time. After addition of the substrate and reappearance of the blue color, excess potassium was destroyed by addition of absolute ethanol and the resulting mixture was neutralized by addition of a saturated aqueous solution of ammonium chloride. The mixture was diluted with diethyl ether (20 mL), and the aqueous phase was separated and extracted with diethyl ether (3 × 10 mL). The organic extracts were combined, washed with brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate, gradient elution 100:1 → 30:1 with 1% Et_3N) to afford the alcohol **46** as a colorless oil (44 mg, 65% over two steps). R_f = 0.30 (petroleum ether/ethyl acetate 3:1); $[\alpha]_D^{25}$ +106 (c 1.00, $CHCl_3$); ν_{max} ($CHCl_3$) 3442, 2956, 2914, 2871, 1709, 966, 942, 895, 837, 803 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.45 (1H, tt, J = 8.8, 1.2 Hz), 4.86 (1H, d, J = 5.9 Hz), 4.05 (1H, dd, J = 8.2, 5.2 Hz), 3.95−3.88 (1H, m), 3.82 (1H, q, J = 7.0 Hz), 3.81 (1H, q, J = 7.0 Hz), 2.52 (1H, d, J = 9.5 Hz), 2.41 (1H, dd, J = 13.2, 5.9 Hz), 2.38−2.09 (6H, m), 1.91−1.85 (2H, m), 1.79 (1H, dd, J = 12.8, 6.5 Hz), 1.67 (3H, s), 1.66−1.60 (1H, m), 1.23 (3H, t, J = 7.0 Hz), 1.22−1.12 (2H, m), 0.92 (3H, d, J = 6.9 Hz), 0.72 (3H, d, J = 6.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.7, 128.8, 127.8, 122.1, 87.1, 75.2, 74.0, 62.9, 45.4, 44.0, 43.3, 28.7, 28.5, 24.9, 22.2, 21.8, 21.3, 18.3, 15.7, 15.7; HRMS (CI, isobutane) m/z calcd for $C_{20}H_{33}O_3$ $[M + H]^+$ 321.2429, found 321.2433; LRMS (CI, isobutane) m/z (% intensity); 321.5 (100).

(1*R*,2*S*,7*R*,8*R*,9*S*,12*E*)-9-Hydroxy-6-isopropyl-13-methyl-15-oxatricyclo[6.6.1.0^{2,7}]pentadec-12-en-3-one (*E*-36). To a stirred solution of enol ether **46** (33 mg, 0.10 mmol) in THF (5 mL) was added a 1 M aqueous solution of HCl (100 μL, 100 μmol), and the mixture was stirred at rt for 1 h and then diluted with diethyl ether (10 mL) and water (10 mL). The aqueous phase was separated and extracted with diethyl ether (3 × 10 mL). The organic extracts were combined, washed with brine (10 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate, gradient elution 10:1 → 7:1 → 5:1) to deliver ketone *E*-**36** (27 mg, 89%) as a colorless solid. R_f = 0.23 (petroleum ether/ethyl acetate 3:1); mp 175−177 °C; $[\alpha]_D^{24}$ −19.5 (c 1.00, $CHCl_3$); ν_{max} ($CHCl_3$) 3531, 2954, 2926, 2855, 1694, 969, 937, 896, 856, 794 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.34−5.27 (1H, m), 4.26 (1H, dd, J = 9.8, 5.7 Hz), 3.76 (1H, d, J = 9.0 Hz), 2.96 (1H, dt, J = 9.0, 6.6 Hz), 2.75 (1H, dd, J = 9.8, 7.5 Hz), 2.52 (1H, dd, J = 13.6, 5.7 Hz), 2.49−2.37 (3H, m), 2.31 (1H, dddd, 12.3, 12.3, 12.3, 4.3 Hz), 2.23−2.14 (1H, m), 2.09 (1H, d, J = 13.6 Hz), 2.02−1.87 (3H, m), 1.85 (3H, s), 1.75 (1H, ddd, J = 13.6, 3.6, 3.6 Hz), 1.64−1.58 (1H, m), 1.48−1.34 (1H, m), 1.21 (1H, d, J = 6.6 Hz), 1.00 (3H, d, J = 6.9 Hz), 0.79 (3H, d, J = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.3, 133.7, 124.5, 88.4, 80.5, 74.4, 53.9, 50.5, 40.7, 40.6, 38.4, 37.5, 28.1, 27.4, 24.1, 22.0, 20.8, 15.3; HRMS (CI, isobutane) m/z calcd for $C_{18}H_{29}O_3$ $[M + H]^+$ 293.2116, found 293.2120; LRMS (CI, isobutane) m/z (% intensity) 293.5 (100), 275.5 (9), 222.4 (11). Anal. Calcd for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 73.94; H, 9.63.

(1*R*,2*S*,7*R*,8*R*,9*S*,12*E*)-9-(*tert*-Butyldimethylsilyloxy)-6-isopropyl-13-methyl-15-oxatricyclo[6.6.1.0^{2,7}]pentadec-12-en-3-one (*E*-41). To a solution of alcohol *E*-**36** (33 mg, 0.11 mmol) and 2,6-lutidine (35 mg, 0.33 mmol) in anhydrous dichloromethane (1 mL) at −78 °C was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf; 45 mg, 0.17 mmol). The reaction mixture was stirred at the same temperature for 1 h, then quenched by addition of a saturated aqueous solution of sodium bicarbonate (2 mL) and diluted with ethyl acetate (3 mL). The aqueous phase was separated and extracted with ethyl acetate (3 × 3 mL). The organic extracts were combined, washed with brine (5 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate 50:1) to deliver the silyl ether **41** (36 mg, 78%) as a colorless solid. R_f = 0.58 (petroleum ether/ethyl acetate 4:1); mp 108−110 °C; $[\alpha]_D^{27}$ −44.5 (c 0.99, $CHCl_3$); ν_{max} ($CHCl_3$) 2956, 2930, 2859, 1707, 837, 824, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.34−5.27 (1H, m), 4.26 (1H, dd, J = 10.0, 6.0 Hz), 3.78 (1H, d, J = 9.0 Hz), 2.96 (1H, dd, J = 9.0, 7.8 Hz), 2.69 (1H, dd, J = 10.0, 6.9 Hz), 2.51 (1H, dd, J = 13.7, 6.0 Hz), 2.50−2.43 (1H, m), 2.36 (1H, br d, J = 15.4 Hz), 2.31−2.19 (2H, m), 2.18−2.11 (1H, m), 2.07 (1H, d, J = 13.7 Hz), 2.01−1.81 (3H, m), 1.87 (3H, s), 1.70 (1H, ddd, J = 10.7, 3.3, 3.3 Hz), 1.59−1.53 (1H, m), 1.36 (1H, dddd, J = 13.2, 13.2, 13.2, 3.6 Hz), 0.99 (3H, d, J = 6.9 Hz), 0.87 (9H, s), 0.75 (3H, d, J = 6.9 Hz), 0.10 (3H, s), 0.01 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.5, 134.4, 124.2, 88.8, 80.7, 74.0, 54.4, 50.0, 40.8, 40.5, 38.2, 37.5, 27.8, 27.3, 26.0, 24.5, 22.2, 20.8, 17.9, 16.3, −4.1, −4.2; HRMS (CI, isobutane) m/z calc for $C_{24}H_{43}O_3Si$ 407.2981 $[M + H]^+$, found 407.2986; LRMS (CI, isobutane) m/z (% intensity) 407.6 (18), 113.3 (18).

(1*R*,2*R*,6*S*,7*R*,8*R*,9*S*,12*E*)-6-Isopropyl-3,13-dimethyl-15-oxatricyclo[6.6.1.0^{2,7}]pentadeca-3,12-dien-9-ol (49). To a stirred solution of ketone **41** (44 mg, 0.11 mmol) and $PhN(Tf)_2$ (78 mg, 0.22 mmol) in anhydrous THF (1.5 mL) at −78 °C was added dropwise a solution of NaHMDS (270 μL of a 1.0 M solution in THF, 0.27 mmol). The resulting mixture was stirred at −78 °C for 2 h, and the reaction was then quenched by addition of water (3 mL) at −78 °C. The mixture was allowed to warm to rt and diluted with diethyl ether (3 mL). The aqueous phase was separated and extracted with diethyl ether (3 × 5 mL). The organic extracts were combined, washed with brine (5 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was filtered through a pad of silica gel (petroleum ether/ethyl acetate 10:1) to afford crude enol triflate **47**, which was used for the next step without further purification.

dx.doi.org/10.1021/jo302542h | *J. Org. Chem.* XXXX, XXX, XXX−XXX

To a solution of the crude enol triflate **47**, lithium chloride (23 mg, 0.54 mmol) and $Pd(PPh_3)_4$ (12 mg, 11 μmol) in anhydrous THF (10 mL) was added dropwise a solution of methylmagnesium chloride (180 μL of a 3 M solution in THF, 0.54 mmol). The mixture was stirred at rt for 4 h, and the reaction was quenched at 0 °C by addition of a saturated aqueous solution of ammonium chloride (5 mL). The reaction mixture was allowed to warm to rt and diluted with diethyl ether (5 mL). The aqueous phase was separated and extracted with diethyl ether (3 × 5 mL). The organic extracts were combined, washed with brine (5 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate 100:1) to deliver the crude alkene **48** contaminated with traces of PPh_3. The crude alkene was used in the next step without further purification.

To a solution of the crude alkene **48** and 4 Å molecular sieves in anhydrous THF (2 mL) was added TBAF (220 μL of a 1 M solution in THF, 0.22 mmol). The reaction mixture was stirred at rt for 5 h and then quenched by addition of a saturated aqueous solution of ammonium chloride (1 mL). The molecular sieves were removed by filtration and rinsed with ethyl acetate. The aqueous phase was separated and extracted with ethyl acetate (3 × 5 mL). The organic extracts were combined, washed with brine (5 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate, gradient elution 100:1 → 20:1 → 10:1) to deliver alcohol **49** (21 mg, 68% yield over four steps) as a colorless oil. R_f = 0.26 (petroleum ether/ethyl acetate 5:1); $[\alpha]_D^{28}$ +16.5 (*c* 1.00, $CHCl_3$); ν_{max} ($CHCl_3$) 3416, 2955, 2928, 2894, 2867, 943, 798 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.49 (1H, br d, *J* = 4.6 Hz), 5.37−5.30 (1H, m), 3.95 (1H, dd, *J* = 9.2, 5.8 Hz), 3.78 (1H, d, *J* = 9.1 Hz), 3.13−3.06 (1H, m), 2.60 (1H, dd, *J* = 13.6, 5.8 Hz), 2.42 (1H, dd, *J* = 9.2, 7.0 Hz), 2.32 (1H, dddd, *J* = 12.2, 12.2, 12.2, 4.3 Hz), 2.23 (1H, d, *J* = 13.6 Hz), 2.22−2.16 (1H, m), 2.10−1.89 (4H, m), 1.85 (3H, s), 1.82−1.68 (2H, m), 1.75 (3H, s), 1.53−1.44 (1H, m), 1.29 (1H, br d, *J* = 6.1 Hz), 0.93 (3H, d, *J* = 6.9 Hz), 0.78 (3H, d, *J* = 6.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.5, 131.9, 124.8, 122.9, 86.0, 83.8, 74.9, 45.8, 44.8, 42.8, 37.7, 36.8, 27.5, 27.4, 23.6, 23.5, 21.6, 20.8, 14.9; HRMS (CI, isobutane) *m*/*z* calcd for $C_{19}H_{31}O_2$ $[M + H]^+$ 291.2324, found 291.2328; LRMS (CI, isobutane) *m*/*z* (% intensity) 291.5 (100), 273.4 (20).

(−)-Cladiella-6,11-dien-3-ol (5).[15,40,41] To a solution of alcohol **49** (26 mg, 90 μmol) in anhydrous dichloromethane (4 mL) were added pyridine (29 mg, 0.36 mmol) and Dess−Martin periodinane (57 mg, 0.13 mmol). The mixture was stirred at rt for 30 min and then the reaction was quenched by addition of a saturated aqueous solution of sodium thiosulfate and sodium bicarbonate (5:1, 2 mL). The mixture was diluted with diethyl ether (10 mL) and stirred vigorously for 1 h. The aqueous phase was separated and extracted with diethyl ether (3 × 5 mL). The organic extracts were combined, washed with brine (5 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was filtered through a pad of silica gel (petroleum ether/ethyl acetate 10:1) to afford crude ketone **50**, which was used without further purification in the next step.

To a solution of crude ketone **50** in anhydrous THF (3 mL) was added sodium tetrafluoroborate (100 mg, 900 μmol) at rt. The mixture was stirred at rt for 10 min and then cooled at −78 °C. A solution of methyllithium (170 μL of a 1.6 M solution in THF, 0.27 mmol) was added, and the mixture was stirred at −78 °C for 30 min. The reaction was quenched by addition of a saturated aqueous solution of sodium bicarbonate, diluted with diethyl ether (5 mL), and allowed to warm to rt. The aqueous phase was separated and extracted with diethyl ether (3 × 5 mL). The organic extracts were combined, washed with brine (5 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (*n*-hexane/ethyl acetate 15:1) to deliver (−)-cladiella-6,11-dien-3-ol (**5**) (19 mg, 69% over two steps) as a colorless solid. R_f = 0.25 (petroleum ether/ethyl acetate 4:1); mp 51−53 °C {lit.[40] 48−52 °C; lit.[41] 56−57 °C; lit.[15] 51−52 °C}; $[\alpha]_D^{26}$ −25.7 (*c* 0.30, $CHCl_3$) {lit.[40] $[\alpha]_D^{25}$ −22.7 (*c* 0.3, $CHCl_3$); lit.[41] $[\alpha]_D^{25}$ −18.1 (*c* 0.07, $CHCl_3$); lit.[15] $[\alpha]_D^{24}$ −24.4 (*c* 0.25, $CHCl_3$)}; ν_{max} ($CHCl_3$) 3423, 2956, 2921, 2868, 1697, 1459, 1367, 1259, 1071 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.56−5.48 (1H, m), 5.42−5.37 (1H, m), 4.10 (1H, dd, *J* = 5.7, 2.8 Hz), 3.82 (1H, d, *J* = 7.4 Hz), 2.50 (1H, dd, *J* = 13.8, 5.7 Hz), 2.47−2.34 (3H, m), 2.17−1.89 (5H, m), 1.82 (3H, s), 1.68 (3H, s), 1.62−1.50 (3H, m), 1.41 (3H, s), 1.06 (1H, br s), 0.96 (3H, d, *J* = 6.6 Hz), 0.84 (3H, d, *J* = 6.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 132.9, 129.4, 126.8, 121.5, 89.8, 81.0, 77.3, 47.0, 44.4, 40.3, 38.4, 36.8, 29.1, 27.5, 23.1, 22.9, 22.2, 21.7, 20.8, 19.0; HRMS (CI, isobutane) *m*/*z* calcd for $C_{20}H_{33}O_2$ $[M + H]^+$ 305.2480, found 305.2477; LRMS (CI, isobutane) *m*/*z* (% intensity) 305.5 (100), 287.5 (85).

(−)-3-Acetoxycladiella-6,11-diene (6).[41] To a flask containing (−)-cladiella-6,11-dien-3-ol (**5**) (7.2 mg, 23 μmol), DMAP (14 mg, 0.12 mmol), and distilled triethylamine (60 mg, 0.59 mmol) was added freshly distilled acetic anhydride (128 mg, 1.18 mmol). The resulting solution was heated at 40 °C for 30 min and then cooled at 0 °C, and the reaction was quenched by addition of a saturated aqueous solution of ammonium chloride (1 mL) and diethyl ether (2 mL). The aqueous phase was separated and extracted with diethyl ether (3 × 2 mL). The organic extracts were combined, washed with brine (2 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate 40:1) to afford (−)-3-acetoxycladiella-6,11-diene (**6**) (2.0 mg, 25%) as a colorless oil. R_f = 0.50 (petroleum ether/diethyl ether 1:4); $[\alpha]_D^{26}$ −28.5 (*c* 0.60, $CHCl_3$) {lit.[41] $[\alpha]_D^{25}$ −34.7 (*c* 0.5, $CHCl_3$)}; ν_{max} ($CHCl_3$) 2959, 2929, 2870, 1732, 1450, 1370, 1246, 1069, 1022, 802 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.47 (1H, dd, *J* = 11.3, 6.3 Hz), 5.41 (1H, br s), 4.07 (1H, dd, *J* = 5.5, 3.5 Hz), 4.05 (1H, d, *J* = 6.4 Hz), 2.52 (1H, dd, *J* = 13.7, 5.5 Hz), 2.44−2.33 (3H, m), 2.32−2.24 (1H, m), 2.18−2.08 (2H, m), 2.05 (1H, d, *J* = 13.7 Hz), 2.00 (1H, ddd, *J* = 13.4, 11.0, 6.2 Hz), 1.93 (3H, s), 1.93−1.90 (1H, m), 1.81 (3H, d, *J* = 1.5 Hz), 1.74 (3H, s), 1.70 (3H, s), 1.65 (1H, heptet, *J* = 6.7 Hz), 1.43−1.41 (1H, m), 0.96 (3H, d, *J* = 6.7 Hz), 0.84 (3H, d, *J* = 6.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0, 132.7, 129.7, 126.6, 121.6, 89.5, 87.9, 81.1, 46.7, 43.9, 40.7, 38.4, 32.6, 28.7, 23.1, 23.1, 23.0, 22.4, 22.1, 21.9, 20.3, 19.4; HRMS (EI+) *m*/*z* calcd for $C_{22}H_{34}O_3$ $[M]^+$ 346.2508, found 346.2506; LRMS (EI+) *m*/*z* (% intensity) 346.3 (18), 286.2 (62), 243.2 (32), 218.2 (54), 217.2 (45), 177.1 (20), 147.1 (56), 105.1 (76), 93.1 (100).

(−)-Cladiell-11-ene-3,6,7-triol (9).[9b,15,42] To a solution of (−)-cladiella-6,11-dien-3-ol (**5**) (5.0 mg, 16 μmol) in a mixture of THF and water (1 mL of a 1:1 mixture) at 0 °C were added *N*-methylmorpholine *N*-oxide (NMO; 19 μL of a 1.0 g/mL solution in water, 0.16 mmol) and OsO_4 (2 μL of a 4.0 wt % solution in water, 0.3 μmol). The mixture was stirred at 0 °C for 1 h and then allowed to warm to rt and stirred at this temperature for 1 h. The reaction was then quenched by addition of a saturated aqueous solution of sodium thiosulfate (2 mL), and the mixture was stirred vigorously for 30 min before being diluted with dichloromethane (2 mL). The aqueous phase was separated and extracted with dichloromethane (3 × 3 mL). The organic extracts were combined, washed with brine (3 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (*n*-hexane/ethyl acetate, gradient elution 2:1 → ethyl acetate 100%) to deliver (−)-cladiell-11-ene-3,6,7-triol (**9**) (3.7 mg, 66%) as colorless crystals. R_f = 0.16 (petroleum ether/ethyl acetate 1:2); mp 195−198 °C {lit.[15] 196.8−198.4 °C, lit.[9b] 205−206 °C, lit.[42] 205.5−206.0 °C}; $[\alpha]_D^{28}$ −12.1 (*c* 0.70, $CHCl_3$) {lit.[15] $[\alpha]_D^{25}$ −11.9 (*c* 0.43, $CHCl_3$), lit.[9b] $[\alpha]_D^{25}$ −12.3 (*c* 1.00, $CHCl_3$), lit.[42] $[\alpha]_D$ −16.1 (*c* 0.75, $CHCl_3$)}; ν_{max} ($CHCl_3$) 3423, 2960, 2926, 1726, 1078, 1047, 1024, 929, 883, 798, cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.44 (1H, br s), 4.56 (1H, br s), 4.34−4.28 (1H, m), 3.73 (1H, d, *J* = 6.8 Hz), 2.61 (1H, ddd, *J* = 6.8, 6.5, 4.6 Hz), 2.28 (1H, br d, *J* = 6.5 Hz), 2.21−2.13 (1H, m), 2.11−1.94 (3H, m), 1.88−1.78 (2H, m), 1.73−1.53 (6H, m), 1.66 (3H, s), 1.50−1.45 (1H, m), 1.36 (3H, s), 1.18 (3H, s), 0.97 (3H, d, *J* = 6.6 Hz), 0.87 (3H, d, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.5, 122.2, 87.0, 76.6, 76.1, 75.4, 75.1, 48.1, 46.6, 40.0, 39.6, 36.2, 30.6, 29.5, 28.9, 23.2, 22.9, 22.0, 21.5, 20.7; HRMS (CI, isobutane) *m*/*z* calcd for $C_{20}H_{33}O_3$ $[M - OH]^+$ 321.2429, found 321.2434; LRMS (CI, isobutane) *m*/*z* (% intensity) 321.4 (100), 305.4 (25), 303.4 (21), 287.4 (10).

3-Acetoxycladiellin-11-ene-6,7-diol (10).[43] To a solution of (−)-3-acetoxycladiella-6,11-diene (**6**) (3.1 mg, 8.9 μmol) in a mixture

dx.doi.org/10.1021/jo302542h | J. Org. Chem. XXXX, XXX, XXX−XXX

of THF and water (0.6 mL of a 1:1 mixture) at 0 °C were added NMO (10 μL of a 1.0 g/mL solution in water, 89 μmol) and OsO_4 (1.1 μL of a 4.0 wt % solution in water, 0.17 μmol). The mixture was stirred at 0 °C for 1 h before being allowed to warm to rt and stirred at this temperature for 1.5 h. The reaction was then quenched with a saturated aqueous solution of sodium thiosulfate (2 mL) before being stirred vigorously for 30 min and diluted with dichloromethane (2 mL). The aqueous phase was separated and extracted with dichloromethane (3 × 3 mL). The organic extracts were combined, washed with brine (3 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate, gradient elution 2:1 → 1:1 → ethyl acetate 100%) to deliver (−)-3-acetoxycladiellin-11-ene-6,7-diol (**10**) (1.1 mg, 36%) as colorless crystals. R_f = 0.23 (petroleum ether/ethyl acetate 1:2); $[\alpha]_D^{28}$ 0 (*c* 0.30, $CHCl_3$) {lit.[43] $[\alpha]_D$ −1.84 (*c* 2.17, $CHCl_3$)}; ν_{max} ($CHCl_3$) 3446, 2963, 2959, 2934, 1734, 910, 731 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.45 (1H, br s), 4.55 (1H, br s), 4.30 (1H, dt, *J* = 11.8, 3.0 Hz), 3.89 (1H, d, *J* = 6.3 Hz), 2.60 (1H, ddd, *J* = 6.3, 6.3, 6.3 Hz), 2.32 (1H, br d, *J* = 6.3 Hz), 2.25−2.09 (3H, m), 1.99 (3H, s), 1.94−1.83 (3H, m), 1.73 (1H, dd, *J* = 15.0, 3.0 Hz), 1.67 (3H, s), 1.64 (3H, s) 1.63−1.56 (4H, m), 1.39−1.35 (1H, m), 1.17 (3H, s), 0.96 (3H, d, *J* = 6.7 Hz), 0.86 (3H, d, *J* = 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 132.2, 121.9, 86.6, 86.4, 77.6, 77.3, 75.9, 48.5, 46.8, 40.3, 39.4, 31.4, 30.5, 29.1, 23.4, 22.9, 22.9, 22.5, 22.0, 21.6, 20.2; HRMS (EI) *m*/*z* calcd for $C_{22}H_{36}O_5$ $[M]^+$ 380.2565, found 380.2567; LRMS (EI) *m*/*z* (% intensity) 380.3 (7), 362.3 (5), 320.3 (50), 302.3 (55), 93.1 (100).

(1*R*,2*R*,6*S*,8*R*,9*R*,13*R*,14*R*)-2,6,10-Trimethyl-13-isopropyl-15,16-dioxatetracyclo[6.6.1.1^{2,6}.0^{9,14}]hexadec-10-ene (51).[15] To a solution of (−)-cladiella-6,11-dien-3-ol (**5**) (3.0 mg, 9.8 μmol) in anhydrous dichloromethane (300 μL) at 0 °C was added freshly distilled acetic anhydride (11 mg, 98 μmol) and a solution of trimethylsilyl trifluoromethanesulfonate (10 μL of a 1 mg/mL solution in anhydrous dichloromethane, 0.49 μmol). The reaction mixture was stirred for 30 min at 0 °C and then quenched by addition of a saturated aqueous solution of sodium bicarbonate (1 mL). The aqueous phase was separated and extracted with dichloromethane (3 × 3 mL). The organic extracts were combined, washed with brine (5 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate 10:1) to deliver the tetracyclic ether **51** (2.2 mg, 81%) as a colorless oil. R_f = 0.65 (petroleum ether/ethyl acetate 6:1); $[\alpha]_D^{25}$ +17.1 (*c* 0.73, $CHCl_3$) {lit.[15] $[\alpha]_D^{23}$ +19.0 (*c* 0.37, $CHCl_3$)}; ν_{max} 2959, 2923, 1761, 1734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.45 (1H, br d, *J* = 5.4 Hz), 4.01 (1H, td, *J* = 5.1, 1.0 Hz), 3.85 (1H, s), 2.95−2.90 (1H, m), 2.42−2.28 (2H, m), 2.21 (1H, dd, *J* = 14.4, 5.2 Hz), 1.93−1.81 (4H, m), 1.73−1.65 (1H, m), 1.66 (3H, s), 1.54−1.33 (5H, m), 1.31 (3H, s), 1.09 (3H, s), 0.93 (3H, d, *J* = 6.9 Hz), 0.77 (3H, d, *J* = 6.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.7, 121.2, 91.7, 81.4, 75.9, 74.3, 48.3, 48.2, 42.1, 39.8, 38.9, 36.3, 35.8, 28.4, 28.2, 22.6, 22.3, 22.0, 18.4, 15.6.

(1*R*,2*R*,6*R*,7*R*,8*R*,9*S*,12*E*)-6-Isopropyl-13-methyl-3-methylidene-15-oxatricyclo[6.6.1.0^{2,7}]pentadec-12-en-9-ol (*E*-37). To a flask containing alcohol **42** (265 mg, 590 μmol), DMAP (359 mg, 2.94 mmol), and distilled triethylamine (1.48 g, 14.7 mmol) was added freshly distilled acetic anhydride (3.00 g, 29.4 mmol). The resulting solution was heated at 40 °C for 30 min before being cooled at 0 °C, and the reaction was quenched by addition of a saturated aqueous solution of ammonium chloride (10 mL) and diethyl ether (20 mL). The aqueous phase was separated and extracted with diethyl ether (3 × 20 mL). The organic extracts were combined, washed with brine (20 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was filtered through a pad of silica gel (petroleum ether/ethyl acetate 10:1 with 1% Et_3N) to afford crude acetate **45** as a colorless oil, which was used without purification in the next reaction.

To a solution of crude acetate **45** in THF (30 mL) was added a 1 M aqueous solution of HCl (630 μL, 630 μmol), and the solution was stirred at rt for 1 h. The mixture was diluted with diethyl ether (30 mL) and water (30 mL), and the aqueous phase was then separated and extracted with diethyl ether (3 × 20 mL). The organic extracts were combined, washed with brine (30 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was filtered through a pad of silica gel (petroleum ether/ethyl acetate 10:1) and the solvent was removed in vacuo to deliver ketone **52**, which was used without purification in to the susequent reaction.

To a solution of methyltriphenylphosphonium bromide (1.13 g, 3.16 mmol) in anhydrous THF (10 mL) at 0 °C was added dropwise a solution of NaHMDS (0.34 mL of a 1 M solution in THF, 0.34 mmol). The resulting yellow solution was stirred for 1 h at rt. A solution of crude ketone **52** in anhydrous THF (10 mL) was added dropwise to the solution of ylide. The solution was stirred at reflux for 1 h and then cooled to rt before the reaction was quenched with a saturated aqueous solution of ammonium chloride (10 mL). The mixture was diluted with diethyl ether (20 mL), and the aqueous phase was separated and extracted with diethyl ether (2 × 20 mL). The organic extracts were combined, dried ($MgSO_4$), and concentrated in vacuo. The residue was filtered through a pad of silica gel (petroleum ether/ethyl acetate 10:1) and the solvent was removed in vacuo to give crude diene **53**, which was used without further purification in the next step.

A small freshly cut piece of potassium (∼200 mg) was added to a solution of recrystallized 18-crown-6 (780 mg, 2.95 mmol) in freshly distilled *t*-butylamine (30 mL) at rt. The mixture was sonicated and stirred at rt until a dark blue color developed, after which anhydrous THF (30 mL) was added. A solution of crude diene **53** in anhydrous THF (10 mL) was added upon reappearance of the blue color at such a rate that the color did not disappear for a long time. After addition of the substrate and reappearance of the blue color, excess potassium was destroyed by addition of absolute ethanol, and the resulting mixture was neutralized by addition of a saturated aqueous solution of ammonium chloride. The mixture was diluted with diethyl ether (30 mL), and the aqueous phase was separated and extracted with diethyl ether (3 × 20 mL). The organic extracts were combined, washed with brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate, gradient elution 100:1 → 10:1 with 1% Et_3N) to afford alcohol ***E*-37** as a colorless solid (81 mg, 47% for four steps). R_f = 0.58 (petroleum ether/ethyl acetate 2:1); mp 149−152 °C; $[\alpha]_D^{26}$ +5.95 (*c* 1.00, $CHCl_3$); ν_{max} ($CHCl_3$) 3426, 2932, 2870, 941, 895 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.37−5.30 (1H, m), 4.78 (1H, t, *J* = 1.9 Hz), 4.72 (1H, t, *J* = 1.9 Hz), 4.03 (1H, dd, *J* = 9.9, 5.9 Hz), 3.63 (1H, d, *J* = 9.2 Hz), 3.04 (1H, ddd, 9.2, 8.2, 6.5 Hz), 2.70 (1H, dd, *J* = 9.9, 6.5 Hz), 2.45 (1H, dd, *J* = 13.8, 5.9 Hz), 2.29 (1H, qd, *J* = 12.3, 4.2 Hz), 2.26 (1H, ddd, *J* = 13.5, 3.2, 3.2 Hz), 2.24−2.16 (1H, m), 2.16−2.10 (1H, m), 2.05 (1H, d, *J* = 13.8 Hz), 2.01 (1H, dd, *J* = 11.8, 6.5 Hz), 1.95−1.85 (2H, m), 1.85 (3H, s), 1.79−1.71 (2H, m), 1.41−1.32 (1H, m), 1.13 (1H, d, *J* = 6.5 Hz), 1.02−0.98 (1H, m), 0.95 (3H, d, *J* = 6.9 Hz), 0.74 (3H, d, *J* = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.7, 133.5, 124.8, 110.5, 88.2, 80.6, 74.7, 48.7, 47.5, 41.1, 39.4, 37.5, 31.2, 28.3, 27.7, 25.3, 22.0, 21.1, 15.6; HRMS (EI) *m*/*z* calcd for $C_{19}H_{30}O_2$ $[M]^+$ 290.2246, found 290.2245; LRMS (EI) *m*/*z* (% intensity) 290.2 (62), 272.3 (15), 229.2 (12), 193.2 (21), 93.1 (71), 59.1 (100).

(1*R*,2*R*,6*R*,7*R*,8*R*,9*R*,12*E*)-6-Isopropyl-9,13-dimethyl-3-methylidene-15-oxatricyclo[6.6.1.0^{2,7}]pentadec-12-en-9-ol (*E*-1). To a solution of alcohol ***E*-37** (80 mg, 0.27 mmol) in anhydrous dichloromethane (12 mL) were added pyridine (87 mg, 1.1 mmol) and Dess−Martin periodinane (175 mg, 410 μmol) at rt. The reaction mixture was stirred at this temperature for 30 min before being quenched with a saturated aqueous solution of sodium thiosulfate and sodium bicarbonate (5:1, 6 mL). The mixture was diluted with diethyl ether (20 mL) and stirred vigorously for 1 h. The aqueous phase was separated and extracted with diethyl ether (3 × 10 mL). The organic extracts were combined, washed with brine (10 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was filtered through a pad of silica gel (petroleum ether/ethyl acetate 15:1) to afford crude ketone, which was used in the next step without purification.

To a solution of the above crude ketone in THF (10 mL) was added sodium tetrafluoroborate (301 mg, 2.75 mmol) at rt. The mixture was stirred at rt for 10 min and then cooled at −78 °C. A

dx.doi.org/10.1021/jo302542h | *J. Org. Chem.* XXXX, XXX, XXX−XXX

solution of methyllithium (0.52 mL of a 1.6 M solution in THF, 0.83 mmol) was added, and the reaction mixture was stirred at −78 °C for 30 min. The reaction was quenched by addition of a saturated aqueous solution of $NaHCO_3$ (5 mL), and the mixture was diluted with diethyl ether (10 mL) and then allowed to warm to rt. The aqueous phase was separated and extracted with diethyl ether (3 × 10 mL). The organic extracts were combined, washed with brine (10 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (*n*-hexane/ethyl acetate 20:1) to deliver alcohol ***E*-1** (65 mg, 78% over two steps) as a colorless solid. R_f = 0.64 (petroleum ether/diethyl ether 1:1); mp 139−140 °C; $[\alpha]_D^{26}$ −37.6 (*c* 1.00, $CHCl_3$); ν_{max} ($CHCl_3$) 3427, 2957, 2930, 2915, 2874, 1643, 1448, 890 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.58 (1H, br s), 4.77 (1H, t, *J* = 2.0 Hz), 4.70 (1H, s), 4.01 (1H, br s), 3.74 (1H, s), 2.69 (1H, br s), 2.45 (1H, dd, *J* = 13.8, 5.4 Hz), 2.44−2.36 (1H, m), 2.25 (1H, dt, *J* = 12.9, 3.4 Hz), 2.20−2.05 (3H, m), 2.02 (1H, d, *J* = 13.8 Hz), 1.87 (3H, s), 1.86−1.80 (1H, m), 1.72 (1H, dddd, 12.9, 3.5, 3.5, 3.4 Hz), 1.70−1.63 (2H, m), 1.35−1.25 (2H, m), 1.17 (3H, br s), 1.03 (1H, qd, *J* = 12.9, 3.5 Hz), 0.95 (3H, d, *J* = 6.9 Hz), 0.75 (3H, d, *J* = 6.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.8, 132.9, 124.8, 110.4, 92.3, 80.4, 75.3, 48.1, 46.3, 42.7, 39.0, 38.7, 31.5, 29.8, 28.2, 25.4, 24.5, 22.1, 20.6, 15.5; HRMS (EI) *m*/*z* calcd for $C_{20}H_{32}O_2$ $[M]^+$ 304.2402, found 304.2401; LRMS (EI) *m*/*z* (% intensity) 304.3 (25), 286.3 (10), 243.2 (9), 219.2 (19), 179.1 (91), 59.1 (100).

(−)-Sclerophytin A (7).[12c,18,57] To a solution of alcohol ***E*-1** (4.0 mg, 13 μmol) in a mixture of THF and water (0.8 mL of a 1:1 mixture) at 0 °C were added NMO (15 μL of a 1.0 g/mL solution in water, 0.13 mmol) and OsO_4 (1.7 μL of a 4.0 wt % solution in water, 0.26 μmol). The reaction mixture was stirred at 0 °C for 1 h and then at rt for 1 h. The reaction was then quenched by addition of a saturated aqueous solution of sodium thiosulfate (2 mL), and the mixture was stirred vigorously for 30 min before being diluted with dichloromethane (2 mL). The aqueous phase was separated and extracted with dichloromethane (3 × 3 mL). The organic extracts were combined, washed with brine (3 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (*n*-hexane/ethyl acetate 4:1) to deliver (−)-sclerophytin A (**7**) (2.6 mg, 59%) as colorless crystals. R_f = 0.23 (ethyl acetate/petroleum ether 2:1); mp 186−188 °C {lit.[57] mp 187 °C, lit.[18] mp 185−186 °C}; $[\alpha]_D^{25}$ −6.2 (*c* 1.00, $CHCl_3$) {lit.[18] $[\alpha]_D^{20}$ −3.0 (*c* 1.00, $CHCl_3$), lit.[12a] $[\alpha]_D^{20}$ −2.7 (*c* 0.11, $CHCl_3$)}; ν_{max} 3415, 2962, 2927, 797, 668 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.66 (1H, br s), 4.64 (1H, br s), 4.56 (1H, br d, *J* = 5.8 Hz), 4.11 (1H, ddd, *J* = 10.8, 6.6, 3.8 Hz), 3.62 (1H, s), 2.97 (1H, dd, *J* = 7.7, 6.6 Hz), 2.30−2.21 (2H, m), 2.16 (1H, dd, *J* = 10.1, 7.7 Hz), 2.06−1.96 (2H, m), 1.90−1.75 (2H, m), 1.75−1.50 (6H, m), 1.30−1.24 (2H, m), 1.20 (3H, s), 1.15 (3H, s), 1.05 (1H, qd, *J* = 12.5, 3.0 Hz), 0.96 (3H, d, *J* = 6.9 Hz), 0.79 (3H, d, *J* = 6.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.0, 109.3, 90.6, 80.2, 78.2, 75.0, 53.1, 45.4, 45.3, 43.8, 40.1, 31.7, 30.4, 29.4, 29.2, 24.9, 23.1, 22.1, 16.1; HRMS (CI, isobutane) *m*/*z* calcd for $C_{20}H_{33}O_3$ $[M - OH]^+$ 321.2430, found 321.2433; LRMS (CI, isobutane) *m*/*z* (% intensity) 321.4 (18), 303.4 (15), 287.4 (10).

(−)-Sclerophytin B (8).[12c,57] To a solution of (−)-sclerophytin A (**7**) (3.5 mg, 10 μmol) in anhydrous dichloromethane (0.5 mL) at 0 °C were added DMAP (1.3 mg, 10 μmol), distilled triethylamine (3.1 mg, 31 μmol), and distilled acetic anhydride (1.7 mg, 15 μmol). The resulting solution was stirred for 30 min before being concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (*n*-hexane/ethyl acetate 5:1) to afford (−)-sclerophytin B (**8**) (3.0 mg, 79%) as a colorless solid. R_f = 0.60 (ethyl acetate/petroleum ether 2:1); mp 186−188 °C {lit.[57] 190−192 °C}; $[\alpha]_D^{25}$ −19.4 (*c* 1.00, $CHCl_3$); ν_{max} 3434, 2935, 2960, 1707, 990 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.63 (1H, br d, *J* = 4.8 Hz), 4.65 (1H, t, *J* = 2.0 Hz), 4.61 (1H, br s), 4.13 (1H, ddd, *J* = 11.2, 7.2, 3.8 Hz), 3.68 (1H, s), 3.02 (1H, dd, *J* = 7.2, 7.2 Hz), 2.36−2.21 (3H, m), 2.15−2.00 (4H, m), 2.08 (3H, s), 1.78−1.67 (4H, m), 1.57 (1H, br s), 1.43−1.37 (1H, m), 1.34−1.24 (1H, m), 1.23 (3H, s), 1.14 (3H, s), 1.01−0.98 (1H, m), 0.96 (3H, d, *J* = 6.9 Hz), 0.78 (3H, d, *J* = 6.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 148.0, 109.5, 90.7, 85.2, 78.1, 76.1, 75.0, 53.4, 45.6, 45.5, 43.7, 40.0, 31.7, 30.4, 29.2, 28.2, 24.9, 23.9, 22.1, 21.7, 15.7; HRMS (CI, isobutane) *m*/*z* calcd for $C_{22}H_{35}O_4$ $[M - OH]^+$ 363.2535, found 363.2536; LRMS (CI, isobutane) *m*/*z* (% intensity) 363.4 (40), 321.4 (100), 303.4 (60).

(1*R*,2*R*,6*S*,8*R*,9*R*,13*R*,14*R*)-2,6-Dimethyl-13-isopropyl-10-methylidene-15,16-dioxatetracyclo[6.6.1.1^{2,6}.0^{9,14}]hexadecane (54).[12c] To a flask containing alcohol ***E*-1** (5.0 mg, 16 μmol) and *p*-toluenesulfonic acid monohydrate (12 mg, 65 μmol) was added freshly distilled isopropenyl acetate (1 mL). The mixture was stirred at rt for 3 h, and the reaction then was quenched with a saturated aqueous solution of sodium bicarbonate (1 mL). The mixture was diluted with ethyl acetate (2 mL), and the aqueous phase was separated and extracted with ethyl acetate (3 × 3 mL). The organic extracts were combined, washed with brine (3 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (petroleum ether/diethyl ether 20:1) to deliver tetracyclic ether **54** (4.5 mg, 90%) as colorless solid. R_f = 0.58 (petroleum ether/diethyl ether, 6:1); mp 101−103 °C; $[\alpha]_D^{25}$ −8.5 (*c* 1.00, $CHCl_3$) {lit.[12c] $[\alpha]_D^{20}$ −8.5 (*c* 0.07, $CHCl_3$)}; ν_{max} ($CHCl_3$) 2962, 2929, 2871, 1654, 1458, 1370, 1108, 1062, 991, 957, 884 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.65−4.63 (2H, m), 3.92−3.88 (1H, m), 3.64 (1H, s), 3.42 (1H, dd, *J* = 6.8, 6.8 Hz), 2.36 (1H, qt, *J* = 13.1, 4.0 Hz), 2.27−2.21 (2H, m), 2.13 (1H, dd, *J* = 14.3, 5.1 Hz), 1.97 (1H, br t, *J* = 13.3 Hz), 1.90 (1H, dd, *J* = 14.3, 1.0 Hz), 1.80 (1H, dddd, *J* = 13.5, 4.1, 2.8, 1.3 Hz), 1.72−1.65 (2H, m), 1.56−1.51 (1H, m), 1.48−1.33 (3H, m), 1.32 (3H, s), 1.28−1.20 (1H, m), 1.06 (3H, s), 0.96 (1H, qd, *J* = 13.0, 2.8 Hz), 0.94 (3H, d, *J* = 6.9 Hz), 0.76 (3H, d, *J* = 6.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.8, 108.6, 93.8, 81.9, 75.7, 74.5, 50.3, 46.3, 45.2, 43.9, 39.9, 36.4, 35.9, 31.5, 29.6, 27.9, 24.8, 22.1, 18.4, 15.9; HRMS (CI, isobutane) *m*/*z* calcd for $C_{20}H_{33}O_2$ $[M + H]^+$ 305.2481, found 305.2487; LRMS (CI, isobutane) *m*/*z* (% intensity) 305.5 (11), 140.3 (10).

(+)-Deacetylpolyanthellin A (11).[15,17,58,59] To a solution of tetracyclic alkene **54** (3.2 mg, 10 μmol) in a mixture of THF and water (1 mL of a 1:1 mixture) was added mercury(II) acetate (6.7 mg, 21 μmol) at rt. The mixture was stirred for 30 min, and then additional mercury(II) acetate (6.7 mg, 21 μmol) was added. The resulting mixture was stirred for 1 h, diluted with THF (2 mL), and cooled to −20 °C before successive addition of a solution of triethylborane (136 μL of a 1.0 M solution in THF, 136 μmol) and solid sodium borohydride (6.7 mg, 0.18 mmol). The resulting mixture was stirred overnight and then diluted with diethyl ether (3 mL). The aqueous phase was separated and extracted with diethyl ether (3 × 3 mL). The organic extracts were combined, washed with brine (3 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate 2:1) to deliver (+)-deacetylpolyanthellin A (**11**) (2.6 mg, 77%) as a colorless oil (10:1 mixture of diastereomers). R_f = 0.44 (petroleum ether/ethyl acetate 2:1); $[\alpha]_D^{25}$ +14.6 (*c* 0.86, $CHCl_3$) {lit.[15] $[\alpha]_D^{25}$ +18.1 (*c* 0.29, $CHCl_3$), lit.[59] $[\alpha]_D^{25}$ +19.4 (*c* 0.57, $CHCl_3$), lit.[58] $[\alpha]_D^{25}$ −11.0 (*c* 0.6, $CHCl_3$)}; ν_{max} ($CHCl_3$) 3437, 2960, 2929, 2872, 955, 813 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.87 (1H, dd, *J* = 5.3, 5.1 Hz), 3.58 (1H, s), 2.89−2.83 (1H, m), 2.42−2.29 (2H, m), 2.18 (1H, dd, *J* = 14.2, 5.1 Hz), 1.85 (1H, d, *J* = 14.2 Hz), 1.81−1.74 (1H, m), 1.68 (1H, dqd, *J* = 6.8, 6.8, 2.2 Hz), 1.55−1.33 (9H, m), 1.29 (3H, s), 1.19 (3H, s), 1.18−1.12 (1H, m), 1.06 (3H, s), 0.93 (3H, d, *J* = 6.9 Hz), 0.82 (3H, d, *J* = 6.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 93.3, 78.6, 75.6, 74.4, 70.4, 53.9, 47.7, 42.4, 41.8, 39.8, 36.6, 36.0, 33.8, 29.8, 29.7, 27.6, 22.0, 18.4, 17.5, 16.0; HRMS (CI, isobutane) *m*/*z* calcd for $C_{20}H_{35}O_3$ $[M + H]^+$ 323.2586, found 323.2583; LRMS (CI, isobutane) *m*/*z* (% intensity) 323.3 (9), 305.5 (18), 113.3 (15).

(+)-Polyanthellin A (12).[15,17,34,58,59] To a flask containing (+)-deacetylpolyanthellin A (**11**) (2.6 mg, 8.0 μmol), DMAP (5.0 mg, 40 μmol), and distilled triethylamine (41 mg, 0.40 mmol) was added freshly distilled acetic anhydride (44 mg, 0.40 mmol). The resulting solution was stirred at rt for 1 h, then cooled at 0 °C, and the reaction was quenched by addition of a saturated aqueous solution of sodium bicarbonate (1 mL) and diethyl ether (2 mL). The aqueous phase was separated and extracted with diethyl ether (3 × 2 mL). The organic extracts were combined, washed with brine (2 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by

dx.doi.org/10.1021/jo302542h | *J. Org. Chem.* XXXX, XXX, XXX−XXX

flash column chromatography on silica gel (petroleum ether/ethyl acetate 30:1) to afford (+)-polyanthellin A (**12**) (1.6 mg, 55%) as a colorless oil. R_f = 0.60 (petroleum ether/ethyl acetate 4:1); $[\alpha]_D^{24}$ +9.0 (*c* 0.40, $CHCl_3$) {lit.[15] $[\alpha]_D^{20}$ +10.5 (*c* 0.31, $CHCl_3$), lit.[59] $[\alpha]_D^{25}$ +8.9 (*c* 0.22, $CHCl_3$), lit.[58] $[\alpha]_D^{25}$ −9.9 (*c* 1.0, $CHCl_3$), lit.[34] $[\alpha]_D^{25}$ +8.0 (*c* 0.75, $CHCl_3$), lit.[17] $[\alpha]_D^{25}$ +9.9 (*c* 0.085, $CHCl_3$)}; ν_{max} ($CHCl_3$) 2952, 2927, 2896, 2875, 2363, 1731, 956 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.91−3.89 (1H, m), 3.54 (1H, s), 3.23−3.19 (1H, m), 2.45−2.40 (1H, m), 2.40−2.31 (1H, m), 2.30 (1H, dd, *J* = 10.4, 7.6 Hz), 2.19 (1H, dd, *J* = 14.3, 5.0 Hz), 2.00 (3H, s), 1.86 (1H, d, *J* = 14.3 Hz), 1.79−1.76 (1H, m), 1.69−1.62 (1H, m), 1.55−1.47 (1H, m), 1.48 (3H, s), 1.47−1.34 (4H, m), 1.33 (3H, s), 1.25−1.20 (1H, m), 1.19−1.15 (2H, m), 1.08 (3H, s), 0.92 (3H, d, *J* = 6.9 Hz), 0.80 (3H, d, *J* = 6.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 93.9, 83.3, 77.6, 75.7, 74.5, 51.2, 47.7, 42.5, 41.8, 39.8, 36.4, 35.8, 29.9, 29.8, 27.7, 24.2, 22.7, 21.8, 18.3, 17.7, 15.7; HRMS (EI) *m*/*z* calcd for $C_{20}H_{32}O_2$ $[M - AcOH]^+$ 304.2402, found 304.2398; LRMS (EI) *m*/*z* (% intensity) 304.3 (100), 261.2 (13), 243.2 (18), 219.2 (19), 179.1 (22).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Details of DFT calculations; X-ray crystallographic data for compounds (±)-**40**, **9**, and *E*-**1**; copies of ^1H and ^{13}C NMR spectra for compounds *Z*-**1**, *E*-**1**, **2**−**12**, (+)-**14**−**26**, *Z*-**30**, *E*-**30**, *Z*-**33**, *E*-**33**, *Z*-**35**−*Z*-**37**, (±)-*E*-**35**, *E*-**36**, *E*-**37**, (±)-**39**, (±)-**40**, *E*-**41**, **42**, (±)-**43**, (±)-**44**, **49**, **51**, and **54**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail stephen.clark@glasgow.ac.uk.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Dr Marc Schmidtmann for providing X-ray crystal data for compound (±)-**40**. We are grateful to EPSRC and F. Hoffmann-La Roche Ltd. for funding to support a studentship for S.T.H. We thank MSD, WestCHEM, and the University of Glasgow for financial support to fund a studentship for R.B. We acknowledge funding from EPSRC for support of this project (Grants GR/T21905/01 and/02). In addition, we thank Novartis for the award of the European Young Investigator Award to J.S.C., the funding from which partly supported this work.

■ REFERENCES

(1) (a) Kennard, O.; Watson, D. G.; Riva di Sanseverino, L.; Tursch, B.; Bosmans, R.; Djerassi, C. *Tetrahedron* **1968**, *9*, 2879. (b) Kennard, O.; Watson, D. G.; Riva di Sanseverino, L. *Acta Crystallogr.* **1970**, *B26*, 1038.

(2) Ortega, M. J.; Zubía, E.; Salvá, J. *J. Nat. Prod.* **1997**, *60*, 485.

(3) For a review of early cladiellin natural products, see Bernardeli, P.; Paquette, L. A. *Heterocycles* **1998**, *49*, 531.

(4) For a review of cladiellin natural products isolated between 1998 and 2010, see Welford, A. J.; Collins, I. *J. Nat. Prod.* **2011**, *74*, 2318.

(5) Stierle, D. B.; Carté, B.; Faulkner, D. J.; Tagle, B.; Clardy, J. *J. Am. Chem. Soc.* **1980**, *102*, 5088.

(6) (a) D'Ambrosio, M.; Guerriero, A.; Pietra, F. *Helv. Chim. Acta* **1987**, *70*, 2019. (b) D'Ambrosio, M.; Guerriero, A.; Pietra, F. *Helv. Chim. Acta* **1988**, *71*, 964.

(7) Friedrich, D.; Paquette, L. A. *J. Nat. Prod.* **2002**, *65*, 126.

(8) For a comprehensive recent review concerning the total synthesis of cladiellin natural products, see Ellis, J. M.; Crimmins, M. T. *Chem. Rev.* **2008**, *108*, 5278.

(9) (a) MacMillan, D. W. C.; Overman, L. E. *J. Am. Chem. Soc.* **1995**, *117*, 10391. (b) MacMillan, D. W. C.; Overman, L. E.; Pennington, L. D. *J. Am. Chem. Soc.* **2001**, *123*, 9033.

(10) Overman, L. E.; Pennington, L. D. *Org. Lett.* **2000**, *2*, 2683.

(11) (a) Paquette, L. A.; Moradei, O. M.; Bernardelli, P.; Lange, T. *Org. Lett.* **2000**, *2*, 1875. (b) Friedrich, D.; Doskotch, R. W.; Paquette, L. A. *Org. Lett.* **2000**, *2*, 1879.

(12) (a) Gallou, F.; MacMillan, D. W. C.; Overman, L. E.; Paquette, L. A.; Pennington, L. D.; Yang, J. *Org. Lett.* **2001**, *3*, 135. (b) Paquette, L. A. *Chem. Rec.* **2001**, *1*, 311. (c) Bernardelli, P.; Moradei, O. M.; Friedrich, D.; Yang, J.; Gallou, F.; Dyck, B. P.; Doskotch, R. W.; Lange, T.; Paquette, L. A. *J. Am. Chem. Soc.* **2001**, *123*, 9021.

(13) (a) Molander, G. A.; St. Jean, D. J., Jr.; Haas, J. *J. Am. Chem. Soc.* **2004**, *126*, 1642. (b) Molander, G. A.; Czakó, B.; St. Jean, D. J., Jr. *J. Org. Chem.* **2006**, *71*, 1172.

(14) (a) Crimmins, M. T.; Brown, B. H. *J. Am. Chem. Soc.* **2004**, *126*, 10264. (b) Crimmins, M. T.; Ellis, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 17200. (c) Crimmins, M. T.; Brown, B. H.; Plake, H. R. *J. Am. Chem. Soc.* **2006**, *128*, 1371. (d) Crimmins, M. T.; Ellis, J. M. *J. Org. Chem.* **2008**, *73*, 1649. (e) Crimmins, M. T.; Mans, M. C.; Rodríguez, A. D. *Org. Lett.* **2010**, *12*, 5028. (f) Crimmins, M. T.; Stauffer, C. S.; Mans, M. C. *Org. Lett.* **2011**, *13*, 4890.

(15) Kim, H.; Lee, H.; Kim, J.; Kim, S.; Kim, D. *J. Am. Chem. Soc.* **2006**, *128*, 15851.

(16) Becher, J.; Bergander, K.; Fröhlich, R.; Hoppe, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 1654.

(17) (a) Campbell, M. J.; Johnson, J. S. *J. Am. Chem. Soc.* **2009**, *131*, 10370. (b) Campbell, M. J.; Johnson, J. S. *Synthesis* **2010**, 2841.

(18) Wang, B.; Ramirez, A. P.; Slade, J. J.; Morken, J. P. *J. Am. Chem. Soc.* **2010**, *132*, 16380.

(19) Evans, M. A.; Morken, J. P. *Org. Lett.* **2005**, *7*, 3367.

(20) For our preliminary results concerning the total synthesis of cladiellin natural products, see (a) Clark, J. S.; Hayes, S. T.; Wilson, C.; Gobbi, L. *Angew. Chem., Int. Ed.* **2007**, *46*, 437. (b) Clark, J. S.; Berger, R.; Hayes, S. T.; Thomas, L. H.; Morrison, A. J.; Gobbi, L. *Angew. Chem., Int. Ed.* **2010**, *49*, 9867.

(21) (a) Pirrung, M. C.; Werner, J. A. *J. Am. Chem. Soc.* **1986**, *108*, 6060. (b) Roskamp, E. J.; Johnson, C. R. *J. Am. Chem. Soc.* **1986**, *108*, 6062.

(22) For reviews concerning metal carbenoid reactions and covering the generation of oxonium ylide-type species, see (a) Doyle, M. P. *Chem. Rev.* **1986**, *86*, 919. (b) Adams, J.; Spero, D. M. *Tetrahedron* **1991**, *47*, 1765. (c) Padwa, A.; Krumpe, K. E. *Tetrahedron* **1992**, *48*, 5385. (d) Doyle, M. P.; McKervey, M.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley: New York, 1998. (e) Clark, J. S. *Nitrogen, Oxygen and Sulfur Ylide Chemistry*; Oxford University Press: New York, 2002; Chapt. 1, pp 22−39. (f) Sweeney, J. B. *Chem. Soc. Rev.* **2009**, *38*, 1027.

(23) (a) Clark, J. S. *Tetrahedron Lett.* **1992**, *33*, 6193. (b) Clark, J. S.; Krowiak, S. A.; Street, L. J. *Tetrahedron Lett.* **1993**, *34*, 4385. (c) Clark, J. S.; Dossetter, A. G.; Blake, A. J.; Li, W.-S.; Whittingham, W. G. *Chem. Commun.* **1999**, 749. (d) Clark, J. S.; Whitlock, G.; Jiang, S.; Onyia, N. *Chem. Commun.* **2003**, 2578. (e) Clark, J. S.; Walls, S. B.; Wilson, C.; East, S. P.; Drysdale, M. J. *Eur. J. Org. Chem.* **2006**, 323. (f) Clark, J. S.; Guérot, C.; Wilson, C.; Blake, A. J. *Chem. Commun.* **2007**, 4134. (g) Clark, J. S.; Baxter, C. A.; Dossetter, A. G.; Poigny, S.; Castro, J. L.; Whittingham, W. G. *J. Org. Chem.* **2008**, *73*, 1040. (h) Clark, J. S.; Vignard, D.; Parkin, A. *Org. Lett.* **2011**, *13*, 3980.

(24) (a) Eberlein, T. H.; West, F. G.; Tester, R. W. *J. Org. Chem.* **1992**, *57*, 3479. (b) West, F. G.; Eberlein, T. H.; Tester, R. W. *J. Chem. Soc. Perkin Trans. 1* **1993**, 2857. (c) West, F. G.; Naidu, B. N.; Tester, R. W. *J. Org. Chem.* **1994**, *59*, 6892. (d) Marmsäter, F. P.; West, F. G. *J. Am. Chem. Soc.* **2001**, *123*, 5144. (e) Marmsäter, F. P.; Vanecko, J. A.; West, F. G. *Tetrahedron* **2002**, *58*, 2027. (f) Marmsäter, F. P.; Murphy, G. K.; West, F. G. *J. Am. Chem. Soc.* **2003**, *125*, 14724. (g) Marmsäter, F. P.; Vanecko, J. A.; West, F. G. *Org. Lett.* **2004**, *6*, 1657. (h) Murphy, G. K.; Marmsäter, F. P.; West, F. G. *Can. J. Chem.* **2006**, *84*, 1470. (i) Stewart, C.; McDonald, R.; West, F. G. *Org. Lett.* **2011**, *13*, 720.

(25) (a) Pirrung, M. C.; Brown, W. L.; Rege, S.; Laughton, P. *J. Am. Chem. Soc.* **1991**, *113*, 8561. (b) Brogan, J. B.; Bauer, C. B.; Rogers, R. D.; Zercher, C. K. *Tetrahedron Lett.* **1996**, *37*, 5053. (c) Brogan, J. B.; Zercher, C. K.; Bauer, C. B.; Rogers, R. D. *J. Org. Chem.* **1997**, *62*, 3902. (d) Doyle, M. P.; Ene, D. G.; Forbes, D. C.; Tedrow, J. S. *Tetrahedron Lett.* **1997**, *38*, 4367. (e) Pierson, N.; Fernández-García, C.; McKervey, M. A. *Tetrahedron Lett.* **1997**, *38*, 4705. (f) Doyle, M. P.; Peterson, C. S. *Tetrahedron Lett.* **1997**, *38*, 5265. (g) Hodgson, D. M.; Petroliagi, M. *Tetrahedron: Asymmetry* **2001**, *12*, 877. (h) Kitagaki, S.; Yanamoto, Y.; Tsutsui, H.; Anada, M.; Nakajima, M.; Hashimoto, S. *Tetrahedron Lett.* **2001**, *42*, 6361. (i) Karche, N. P.; Jachak, S. M.; Dhavale, D. D. *J. Org. Chem.* **2001**, *66*, 6323. (j) Yakura, T.; Muramatsu, W.; Uenishi, J. *Chem. Pharm. Bull.* **2005**, *53*, 989. (k) Weathers, T. M., Jr.; Wang, Y.; Doyle, M. P. *J. Org. Chem.* **2006**, *71*, 8183. (l) Hodgson, D. M.; Angrish, D.; Erickson, S. P.; Kloesges, J.; Lee, C. H. *Org. Lett.* **2008**, *10*, 5553. (m) Jackson, K. L.; Henderson, J. A.; Motoyoshi, H.; Phillips, A. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 2346. (n) Shimada, N.; Nakamura, S.; Anada, M.; Shiro, M.; Hashimoto, S. *Chem. Lett.* **2009**, *38*, 488. (o) Jaber, D. M.; Burgin, R. N.; Hepler, M.; Zavalij, P.; Doyle, M. P. *Chem. Commun.* **2011**, 7623. (p) Hodgson, D. M.; Man, S. *Chem.—Eur. J.* **2011**, *17*, 9731.

(26) Williams, D. R.; Meyer, K. G.; Shamim, K.; Patnaik, S. *Can. J. Chem.* **2004**, *82*, 120.

(27) Nicolaou, K. C.; Prasad, C. V. C.; Hwang, C.-K.; Duggan, M. E.; Veale, C. A. *J. Am. Chem. Soc.* **1989**, *111*, 5321.

(28) (a) Winterfeldt, E. *Chem. Ber.* **1964**, *97*, 1952. (b) Winterfeldt, E.; Preuss, H. *Chem. Ber.* **1966**, *99*, 450.

(29) (a) Hori, N.; Matsukura, H.; Matsuo, G.; Nakata, T. *Tetrahedron Lett.* **1999**, *40*, 2811. (b) Matsuo, G.; Kadohama, H.; Nakata, T. *Chem. Lett.* **2002**, 148. (c) Hori, N.; Matsukura, H.; Matsuo, G.; Nakata, T. *Tetrahedron* **2002**, *58*, 1853. (d) Nakata, T. *Chem. Rec.* **2010**, *10*, 159. (e) Nakata, T. *Chem. Soc. Rev.* **2010**, *39*, 1955.

(30) A large excess of diazomethane was used to ensure complete conversion and high yields; batches of diazomethane (100 mmol) were prepared from *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (Diazald) and used to prepare ~3 g batches of the diazo ketone **26** according to the procedure of Hudlický: Hudlický, M. *J. Org. Chem.* **1980**, *45*, 5377.

(31) (a) Dennis, A. M.; Korp, J. D.; Bernal, I.; Howard, R. A.; Bear, J. L. *Inorg. Chem.* **1983**, *22*, 1522. (b) Padwa, A.; Austin, D. J.; Hornbuckle, S. F.; Semones, M. A.; Doyle, M. P.; Protopopova, M. N. *J. Am. Chem. Soc.* **1992**, *114*, 1874. (c) Brown, D. S.; Elliott, M. C.; Moody, C. J.; Mowlem, T. J.; Marino, J. P., Jr.; Padwa, A. *J. Org. Chem.* **1994**, *59*, 2447. (d) Keaney, G. F.; Wood, J. L. *Tetrahedron Lett.* **2005**, *46*, 4031. (e) Hashimoto, S.; Watanabe, N.; Ikegami, S. *Tetrahedron Lett.* **1992**, *33*, 2709.

(32) Annunziata, R.; Cinquini, M.; Cozzi, F.; Gennari, C.; Raimondi, L. *J. Org. Chem.* **1987**, *52*, 4674.

(33) Su, J.-H.; Huang, H.-C.; Chao, C.-H.; Yan, L.-Y.; Wu, Y.-C; Wu, C.-C.; Sheu, J.-H. *Bull. Chem. Soc. Jpn.* **2005**, *78*, 877.

(34) Hassan, H. M.; Khanfar, M. A.; Elnagar, A. Y.; Mohammed, R.; Shaala, L. A.; Youssef, D. T. A.; Hifnawy, M. S.; El Sayad, K. A. *J. Nat. Prod.* **2010**, *73*, 848.

(35) Kwon, H. B.; McKee, B. H.; Stille, J. K. *J. Org. Chem.* **1990**, *55*, 3114.

(36) Stahl, P.; Kissau, L.; Mazitschek, R.; Huwe, A.; Furet, P.; Giannis, A.; Waldmann, H. *J. Am. Chem. Soc.* **2001**, *123*, 11586.

(37) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

(38) We thank Professor K. A. El Sayad (University of Louisiana at Monroe, USA) for providing the ^{1}H and ^{13}C NMR spectra of natural (+)-cladiella-6*Z*,11(17)-dien-3-ol (**Z-1**) for comparison purposes.

(39) We thank Professor Sheu, J.-H. (National Sun Yat-Sen University, Taiwan) for providing the ^{1}H and ^{13}C NMR spectra of natural (+)-vigulariol (**2**) for comparison purposes.

(40) Hochlowski, J. E.; Faulkner, D. J. *Tetrahedron Lett.* **1980**, *21*, 4055.

(41) Seo, Y.; Rho, J.-R.; Cho, K. W.; Shin, J. *J. Nat. Prod.* **1997**, *60*, 171.

(42) Uchio, Y.; Nakatani, M.; Hase, T.; Kodama, M.; Usui, S.; Fukazawa, Y. *Tetrahedron Lett.* **1989**, *30*, 3331.

(43) Uchio, Y.; Kodama, M.; Usui, S.; Fukazawa, Y. *Tetrahedron Lett.* **1992**, *33*, 1317.

(44) Gadwood, R. C.; Rubino, M. R.; Nagarajan, S. R.; Michel, S. T. *J. Org. Chem.* **1985**, *50*, 3255.

(45) Scott, F.; Raubenheimer, H. G.; Pretorius, G.; Hamese, A. M. *J. Organomet. Chem.* **1990**, *384*, C17−C20.

(46) (a) Pauluth, D.; Hoffmann, H. M. R. *Liebigs Ann. Chem* **1985**, 756. (b) Brown, H. C.; Murray, K. J. *Tetrahedron* **1986**, *42*, 5497.

(47) (a) Barton, D. H. R.; Hartwig, W.; Motherwell, R. S. H.; Motherwell, W. B.; Stange, A. *Tetrahedron Lett.* **1982**, *23*, 2019. (b) Singh, V.; Prathap, S.; Porinchu, M. *J. Org. Chem.* **1998**, *63*, 4011. (c) Rowlands, G. J. *Tetrahedron* **2009**, *65*, 8603.

(48) Barrett, A. G. M.; Godfrey, C. R. A.; Hollinshead, D. M.; Prokopiou, P. A.; Barton, D. H. R.; Boar, R. B.; Joukhadar, L.; McGhie, J. F.; Misra, S. C. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1501.

(49) Dye, J. L.; DeBacker, M. G.; Nicely, V. A. *J. Am. Chem. Soc.* **1970**, *92*, 5226.

(50) The reduction reaction was highly moisture-sensitive, and in order to obtain the required royal-blue solution, the crown ether had to be carefully recrystallized from acetonitrile and thoroughly vacuum-dried prior to use, and the potassium metal had to be cut and transferred into the reaction flask while coated in mineral oil.

(51) (a) Ruprah, P. K.; Cros, J.-P.; Pease, J. E.; Whittingham, W. G.; Williams, J. M. J. *Eur. J. Org. Chem.* **2002**, 3145. (b) Giuffredi, G.; Bobbio, C.; Gouverneur, V. *J. Org. Chem.* **2006**, *71*, 5361.

(52) We thank Professor Yasuto Uchio (Kagoshima University, Japan) for providing us with copies of the original ^{1}H and ^{13}C NMR spectra of (−)-cladiell-11-ene-3,6,7-triol (**9**).

(53) Procopiou, P. A.; Baugh, S. P. D.; Flack, S. S.; Inglis, G. G. A. *J. Org. Chem.* **1998**, *63*, 2342.

(54) We thank Professor Yasuto Uchio (Kagoshima University, Japan) for providing us with a copies of the original ^{1}H and ^{13}C NMR spectra of 3-acetoxycladiellin-11-ene-6,7-diol (**10**).

(55) Kazlauskas, R.; Murphy, P. T.; Wells, R. J.; Schönholzer, P. *Tetrahedron Lett.* **1977**, *18*, 4643.

(56) Ochi, M.; Futatsugi, K.; Kotsuki, H.; Ishii, M.; Shibata, K. *Chem. Lett.* **1987**, *16*, 2207.

(57) Sharma, P.; Alam, M. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2537.

(58) Ospina, C. A.; Rodríguez, A. D.; Ortega-Barria, E.; Capson, T. L. *J. Nat. Prod.* **2003**, *66*, 357.

(59) Bowden, B. F.; Coll, J. C.; Vasilescu, I. M. *Aust. J. Chem.* **1989**, *42*, 1705.

(60) Smith, W. B.; Chen, T.-K. *J. Org. Chem.* **1965**, *30*, 3095.

(61) Kang, S. H.; Lee, J. H.; Lee, S. B. *Tetrahedron Lett.* **1998**, *39*, 59.

(62) Commercially available compound.