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Total synthesis of (±)-dysidiolide

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Abstract—The total synthesis of (±)-dysidiolide was accomplished with a high level of intramolecular stereo-induction. Methylation of 6-carboethoxy-3-chloro-5-methyl-cyclohex-2-enone provided **33** bearing the 6,7-*trans*-dimethyl substitution of the C6–C11 B-ring. Diastereoselective conjugate addition upon enone **34** installed the C11 stereogenic center. Annulation then provided an A-ring enone (**23**), a substrate for a challenging conjugate addition of the branched pentenyl side chain. The combination of tri-*n*-butylphosphine, boron trifluoride etherate, and a dialkylcuprate uniquely effected conjugate addition to yield **58**. Incorporation of the hydroxybutenolide-containing side chain completed the total synthesis and established the viability of a general approach for the preparation of the isolabdanoid terpene system.

1. Introduction

Dysdiolide (Fig. 1) is a structurally unique *neo*-isolabdanoid sesterterpene isolated from the marine sponge *Dysidea etheria* de Laubenfels that was collected off the Bahamian islands.[1] The structure of dysidiolide was shown by Gunasekera et al. to possess a bicyclic dehydrodecalin core adorned with four stereogenic centers including two quaternary carbons and two unusual axially disposed appendages. The latter project from the bicyclic framework in a parallel fashion and in close spatial proximity to each other (ca. 4 Å). One extending arm is hydrophobic terminating in an isoprenyl group and the other is hydrophilic culminating with a γ-hydroxybutenolide moiety. The latter may mimic a phosphate ester.

The architectural novelty of dysidiolide is complemented by its distinction as the first known natural inhibitor of the dual specificity phosphatase enzyme cdc25A (IC_{50} 9.4 μM), causing stage specific arrest of the cell cycle at the G1/S transition and loss of the G2/M peak.[1] Although, Blanchard et al. suggested that the inhibition was probably caused by an unidentified component in the crude extract,[2] Shirai and co-workers subsequently confirmed that dysidiolide not only inhibits cdc25A (IC_{50} 35 μM) but also cdc25B (IC_{50} 87 μM).[3] In addition, Gunasekera et al. reported that dysidiolide inhibited the growth of A-549 human lung carcinoma and P388 murine leukemia cell lines with IC_{50} values of 4.7 and 1.5 μM, respectively.[1] Furthermore, Danishefsky has reported that racemic synthetic dysidiolide inhibited PC3, TSU-Pr1, DU145 prostate cancer cells and an MCF7 breast cancer cell line with IC_{50} values of 2–50 μM.[4] In the MCF 7 breast cancer cell line, dysidiolide caused the loss of G2/M peak and the accumulation of cells in G1 consistent with the inhibition of cdc25A. Consequently, dysidiolide has emerged a promising new anti-mitotic lead compound.

Due to the combination of structural novelty and biological activity, dysidiolide has become the focus of several total synthesis efforts. The groups of Corey,[5] Boukouvalas[6] and Danishefsky[4] succeeded in developing the first total syntheses of dysidiolide. The enantioselective syntheses by Corey and Boukouvalas established the absolute configuration of the natural product (−)-**1** as depicted in Fig. 1. Subsequently, total syntheses have been reported from our own laboratories,[7] as well as by Shirai et al.,[8] and Yamada and co-workers.[9] Additional synthetic efforts have also been reported,[10] including formal total syntheses by Piers[11] and Jung.[12]

The initial syntheses fall into two of the three categories of general approaches for bicyclic terpenoids outlined by Tokoroyama.[13] Corey used the Wieland–Miescher ketone as a decalin template, and Boukouvalas and Danishefsky

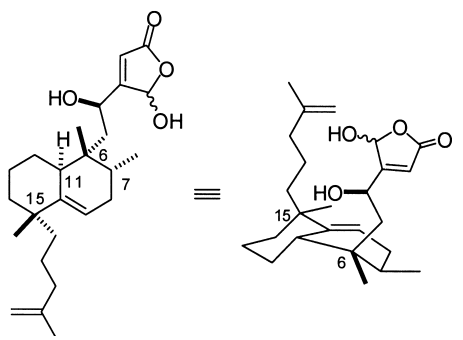

Figure 1. Structure and conformation of (−)-dysidiolide.

Keywords: total synthesis; (±)-dysidiolide; intramolecular stereo-induction.

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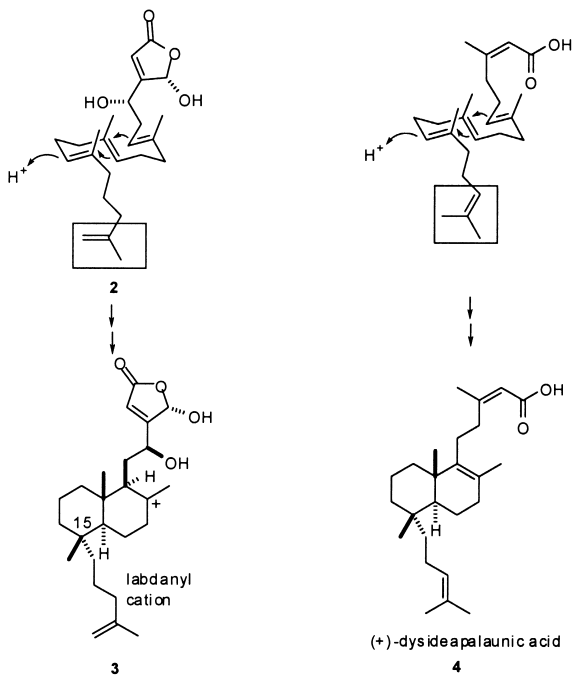
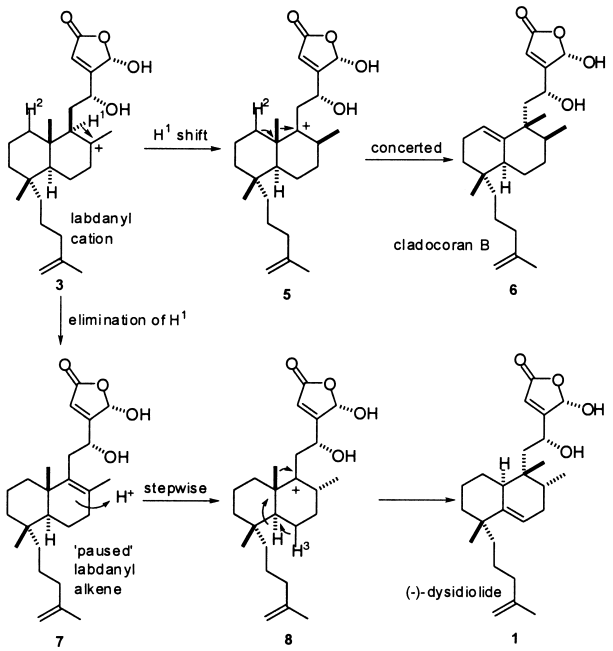
used Diels–Alder cycloadditions to construct the core bicyclic ring system. The earliest syntheses applied synthetic methods developed for the preparation of clerodane and isolabdane terpenoids with vicinal *cis*-dimethyl substitution. We sought to complement these approaches by devising a general entry into the isolabdane class, which could be modified for the synthesis of labdane and clerodane terpenoids. This approach could be placed in Tokoroyama's third and most flexible category of strategies for the synthesis of labdane, isolabdane and clerodane terpenoids.[13] Specifically, dysidiolide's bicyclic nucleus would be constructed from an initial cyclohexenone template for the B-ring (C6–C11) that bears the vicinal *trans*-dimethyl substitutents at C6 and C7.[14] The remaining stereogenic centers could be relayed from the B-ring precursor by a sequence of diastereoselective reactions. The use of independently installed stereogenic centers in the B-ring to control the creation of subsequent chirality would enable the synthesis of dysidiolide and analogues in all possible stereoisomeric combinations, as desired for thorough SAR studies. Described here are the full details of this versatile synthetic approach, culminating in the total synthesis of (±)-dysidiolide.[7]



Scheme 1. Putative biosynthetic cyclizations.



Scheme 2. Labdanyl cation partitioning.

2. Results and discussion

2.1. Structure and biosynthesis

Several structural features make dysidiolide an unusual sesterterpene. First, its biosynthetic cyclization appears to occur exclusively with the central alkenes producing a stereogenic quaternary carbon at C15 with methyl and branched pentenyl substituents (cf. **2**→**3**, Scheme 1) instead of the more common dimethyl substituted quaternary carbon. Second, this pentenyl appendage has a terminal alkene rather than a trisubstituted internal alkene. In addition, dysidiolide's *trans*-vicinal dimethyl substitution pattern at C6, C7 represents a paused cyclization of a labdanyl cation (**3**). Other natural products with similar bicyclic systems include the aldose reductase inhibitor dysideapalaunic acid (**4**, Scheme 1)[15,16] and the cladocorans A and B.[17] Comparing the skeleta of these natural products, dysideapalaunic acid has an unrearranged labdane skeleton with a pentenyl appendage that has the more common trisubstituted internal alkene. Cladocoran B (**6**, Scheme 2) is isomeric with dysidiolide differing only in the position of its core alkene and the *cis*-orientation of the vicinal methyl groups. The unusual pentenyl appendage of dysdiolide and the cladocorans may be formed in the initial stages of isoprene elongation, during the synthesis of their linear precursors.

Cationic cyclization could proceed in a concerted manner via **5** with the migration of the ring junction methyl group, producing the *cis*-dimethyl substitution pattern of cladocorans (Scheme 2). Alternatively, cyclization may pause at a labdanyl alkene (**7**) formed by the elimination of H^1 from **3**, giving rise to a structure similar to dysideapalaunic acid. Protonation of this paused alkene **7** from the β-face would reactivate the rearrangement cascade via **8** producing dysidiolide's C6,7-*trans*-dimethyl substitution and proceeding until the elimination of H^3.

The structural relationships among dysidiolide and its biogenetic cogeners suggested that in the course of targeting the former for total synthesis, a general entry to the synthesis of labdanes, isolabdanes and clerodanes could be developed. The dehydrodecalin cores of dysidiolide, the cladocorans, and the cacospongionolide[18–20] natural products share a common 6,7-*trans*-vicinal dimethyl substitution pattern (Fig. 2).[14] The core structures of dysidiolide and cacospongionolide F (**10**) belong to the isolabdane terpenoid class, while that of cacospongionolide E (**9**) belongs to the clerodane group. The core structures of

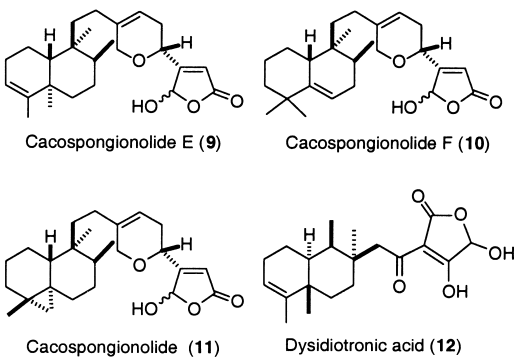
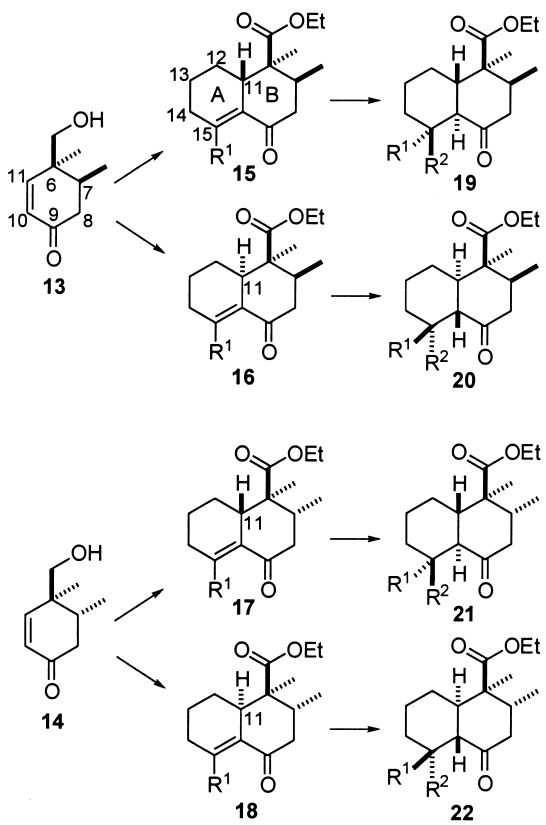


Figure 2. Structures of related sesterterpenes.

the parent cacospongionolide (**11**) and dysidotronic acid (**12**),[21] however, have not been assigned to specific skeletal classes. Cacospongionolide has an additional cyclopropane ring fused to its decalin core, and dysidotronic acid's core appears to be biosynthetically singular.

Aside from their core terpenoid skeleta, the natural products dysidiolide, cladocorans, and cacospongionolides share additional structural motifs. The most conspicuous is the presence of a hydrophilic butenolide derivative attached either directly to a hydrophobic core, or by an intervening pyranyl or geranyl spacer. These butenolide moieties display a range of oxidation states. The incorporation of these variable side chain motifs upon the decalin cores could be accomplished late in their total syntheses.

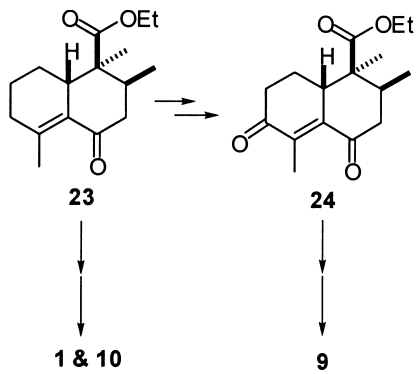


Scheme 3. Generality of the B-ring templates.

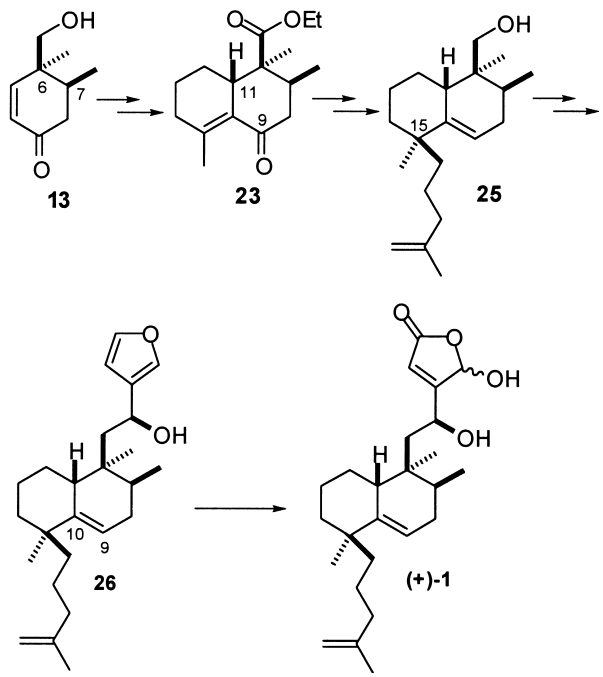
2.2. Synthetic design

2.2.1. Core strategy. It was envisioned that the vicinal *trans*- and *cis*-disubstituted cyclohexenones **13** and **14**, respectively, could serve as general B-ring (C6–C11) templates (Scheme 3).[22] A conjugate addition–annulation sequence would install the A-ring (C10–C15), in principle with either relative configuration at the C11 ring junction (**15** and **17** vs. **16** and **18**). The quaternary center at C15 could be installed by another conjugate addition of a substituent R^2 on the β-face of the decalin system. By alternating the order of introducing R^1 and R^2, either C15 epimer would be available.

Although this design may permit access to a variety of stereoisomers of the dysidiolide core (**19**–**22**), further functionalization of both rings would be required to access the labdanes, isolabdanes and clerodanes. For ring B, remaining functionalization would occur in the presence of the ketone. For ring A, bicyclic enone **23** would be converted into diketone **24**, which may permit the addition



Scheme 4. Generality of enone **23**.[22]



Scheme 5. Synthetic design for dysidiolide.[22]

of a ring junction methyl group at C10, as in cacospongionolide E (Scheme 4).

Application of this design to the total synthesis of dysidiolide would utilize the 6,7-*trans*-dimethyl cyclohexenone **13** (Scheme 5). The C11 ring junction would be set by an axial conjugate addition of an A-ring annulation precursor, using the equatorial disposition of the vicinal methyl groups to enforce the conformation of the enone and enhance the facial selectivity. Following the transformation of the adduct to the enone **23**, the quaternary center at C15 would be installed by the introduction of a branched pentenyl nucleophile on the rigid bicyclic system to provide **25**. Hydroxymethyl side chain elongation would then lead to the addition of a furan moiety to obtain **26**, as a masked form of the natural product's γ-hydroxybutenolide. Final photooxidation of the furan would complete the total synthesis of dysidiolide.

2.3. Synthesis of the decalin core

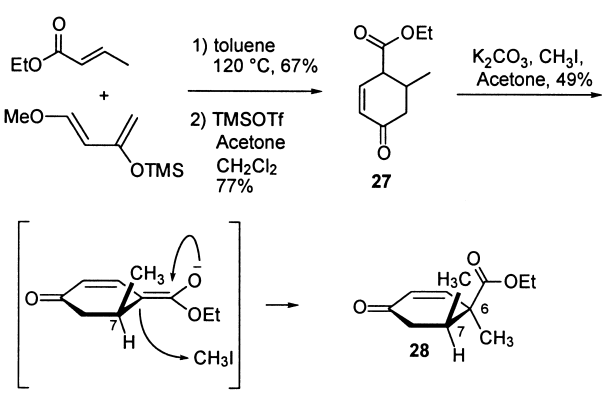
2.3.1. Synthesis of B-ring (C6–C11) enone 13. The key enone **13** with the 6,7-*trans*-vicinal dimethyl substituents was prepared by a variation of the Stork–Danheiser alkylation.[23] To establish that the requisite vicinal *trans*-dimethyl substitution could be secured by alkylation, model ester **27** was prepared using the Diels–Alder reaction of Danishefsky's diene with ethyl (*E*)-but-2-enoate (Scheme 6).[24] When the deprotected cycloadduct **27** was treated with potassium carbonate and excess methyl iodide, *trans*-dimethyl substituted ester **28** was produced as the exclusive diastereomer. The *trans* orientation of the methyl groups was established by the observed NOE enhancement of the C7 methine proton resonance upon irradiation of the C6 quaternary methyl group.

This type of *trans* selective alkylation was extended to the β-dicarbonyl compound **29** (Scheme 7), containing ester and vinylogous ester functionalities. Subsequent to alkylation, reductive carbonyl transposition would take advantage of the facile reduction of the ester functionality of **30** to an alcohol, whereas reduction of the vinylogous ester would stop at the stage of the vinylogous hemiacetal. Net enone transposition would then be completed upon acidic treatment to yield **13**.

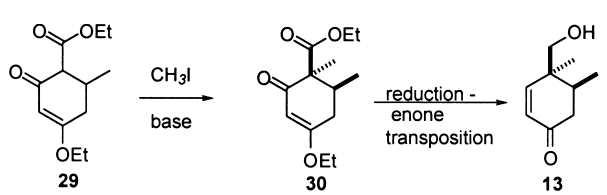
A useful synthetic equivalent to β-ketoester **29** was found to be the vinylogous acyl chloride **32**, an intermediate reported by Mukherjee (Scheme 8).[25]

Condensation of ethyl acetoacetate with ethyl crotonate provided the tricarbonyl compound **31**, which was dehydrated with phosphorus trichloride to **32**. Given the susceptibility of the vinyl chloride to conjugate addition–elimination, the alkylation required a non-nucleophilic base. Reaction of **32** with sodium hydride and methyl iodide provided a good yield of the alkylation product **33** (Scheme 8). Upon treatment of **33** with sodium ethoxide in ethanol, the vinyl chloride was quantitatively converted into the enol ether **30**.

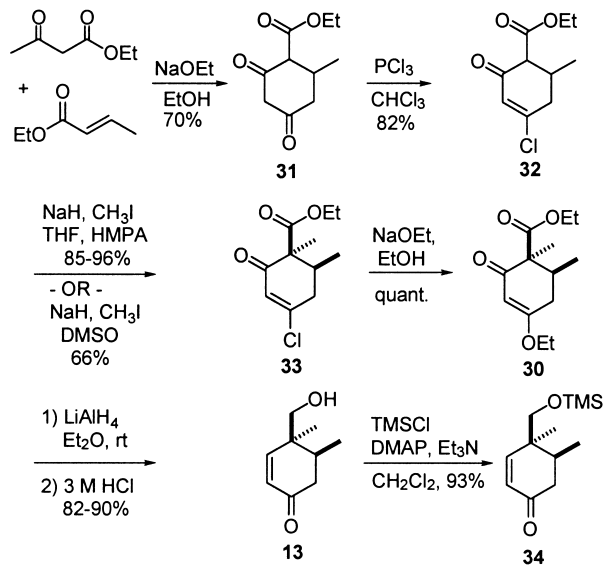
Intermediate **30** was surprisingly stable to reduction, requiring excess lithium aluminum hydride and ambient temperatures. Reduction at 0°C mainly produced an over-reduced, saturated compound. However, controlled reduction occurred when **30** was added slowly to an excess of lithium aluminum hydride at room temperature. Upon hydrolysis with 2 M HCl, the reduction product gave the expected enone **13**, which was silylated to give **34**.



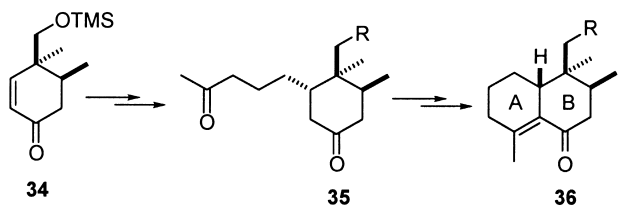
Scheme 6. Preparation of *trans*-dimethyl substitution by alkylation.



Scheme 7. Stork–Danheiser alkylation–enone transposition variation.



Scheme 8. Synthesis of enone **34**.

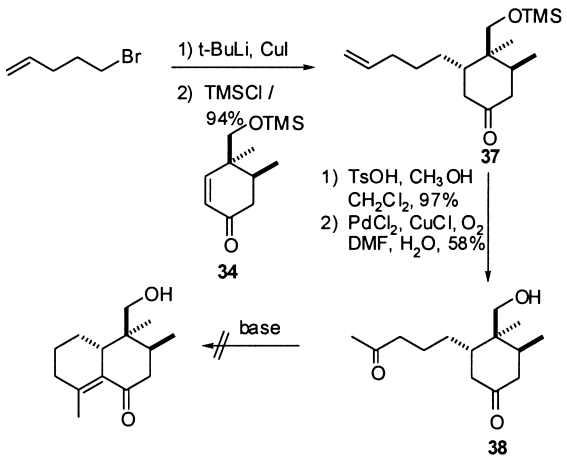


Scheme 9. Synthetic plan for bicyclic enone **36**.

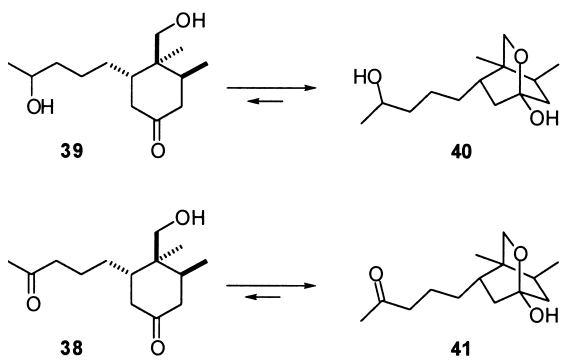
2.3.2. Synthesis of bicyclic enone 23. The B-ring intermediate **34** would serve as a substrate for a conjugate addition–annulation sequence to install the A-ring. Several nucleophiles were considered as annulation precursors for the A-ring. The required features were that the nucleophiles were five carbons long and after conjugate addition they should be easily converted into the methyl ketone **35**, which would be cyclized to the generic bicyclic enone **36** (Scheme 9).

In the first case, the cuprate reagent derived from 5-bromopent-1-ene, *tert*-butyllithium, and CuI was added to enone **34** in the presence of trimethylsilyl chloride to give the conjugate adduct **37** in 94% yield (Scheme 10). The silyl ether was cleaved and the resulting alcohol was submitted to standard Wacker oxidation[26] conditions to afford diketone **38** in 58% yield.

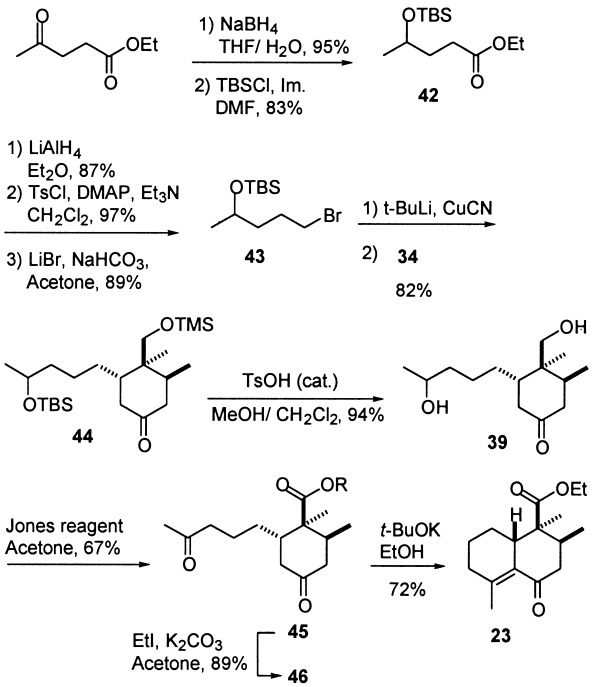
Surprisingly, diketone **38** could not be cyclized under a variety of conditions examined. In an attempt to rationalize these observations, the infrared and carbon spectra of the related keto-diol **39** suggest that this compound exists largely as a hemiketal (**40**) with the primary alcohol engaged with the cyclohexanone carbonyl group (Scheme 11). There is neither an IR absorption, nor a ^{13}C resonance in the carbonyl regions of the corresponding spectra of **40** (**39**). Instead, the ^{13}C NMR spectrum displays a hemiketal carbon resonance at 98 ppm. By analogy, diketone **38** may also exist primarily as the cyclic hemiketal **41**.



Scheme 10. Diketo-alcohol preparation.



Scheme 11. Diketone **38** as a hemiketal (**41**).



Scheme 12. Preparation of bicyclic enone **23**.

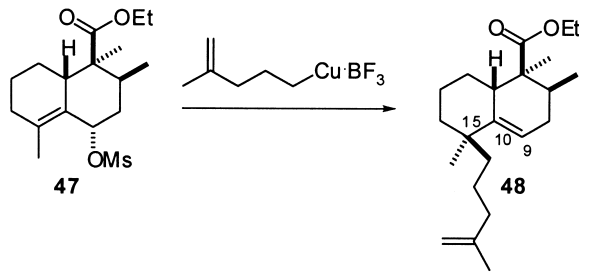
As an alternative side chain annulation precursor, 1-bromo-4-*tert*-butydimethylsilyloxypentane (**43**) was prepared from levulinic acid (Scheme 12).[27] Following literature precedent, ethyl levulinate was reduced with sodium borohydride and the resulting alcohol protected as its *tert*-butyldimethylsilylether **42**.[28] The ethyl ester was then reduced to the primary alcohol with lithium aluminum hydride. After toluenesulfonate formation, treatment with lithium bromide in the presence of sodium bicarbonate provided bromide **43**. Conjugate additions upon enone **34** of both the higher order cyanocuprate and the lower order Gilman reagent prepared from copper iodide and **43** were successful, although the use of the cyanocuprate was favored due to its more convenient preparation and handling.

Both silyl ethers of **44** were cleaved under acidic conditions and the resulting diol **45** was oxidized to the keto-acid with Jones reagent. Treatment of the keto-acid with ethyl iodide and potassium bicarbonate provided the ethyl ester **46** bearing the methyl ketone required for annulation, but without the primary alcohol of **38**.

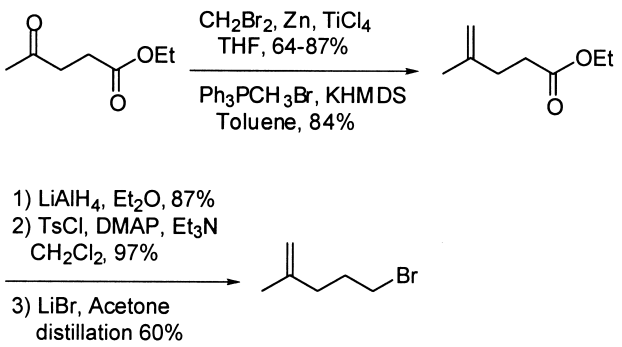
Cyclization of the 1,7-diketone **46** to afford the corresponding bicyclic enone **23** required considerable optimization. Initially, the annulation was conducted under standard conditions with 10% potassium hydroxide, but the enone was produced in less than 20% yield. Using 2–3 equiv. of potassium *tert*-butoxide, the annulation proceeded with 70–80% conversion.

2.3.3. Completion of the dysidiolide core.

2.3.3.1. Installation of the alkenyl side chain at C15. The first approach towards installing the branched pentenyl appendage was to simultaneously incorporate the Δ9,10 alkene of dysidiolide via an S_N2' displacement of an allylic methanesulfonate (**47**) with an organocopper nucleophile to



Scheme 13. Proposed Yamamoto-type S_N2' addition.

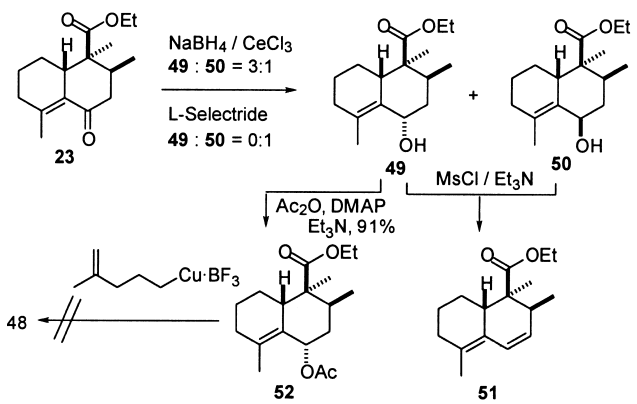


Scheme 14. Preparation of 5-bromo-2-methyl-1-pentene.

provide **48** (Scheme 13). Yamamoto has reported that the alkylcopper–boron trifluoride complex can displace allylic methanesulfonates in an S_N2' fashion to form quaternary centers.[29,30]

To attempt implementation of this approach, ethyl levulinate was converted into 5-bromo-2-methyl-1-pentene, which would serve as a precursor to the organocopper nucleophile (Scheme 14).

The targeted coupling partner of the organocopper nucleophile was the allylic methanesulfonate **47**. For this, the bicyclic enone **23** was reduced to the α-allylic alcohol **49** (Scheme 15). This was accomplished under Luche conditions,[31] which gave a 3:1 ratio of **49** to the corresponding β-allylic alcohol **50**. Alternatively, **50** could be obtained as the exclusive reduction product upon treatment of **23** with lithium tri-*sec*-butylborohydride. However, the derived methanesulfonate could not be isolated. When either the α- or β-allylic alcohols **49** or **50** were treated with methanesulfonyl chloride and triethylamine, only the conjugated diene **51** formed by the in situ elimination of the methanesulfonate could be isolated.



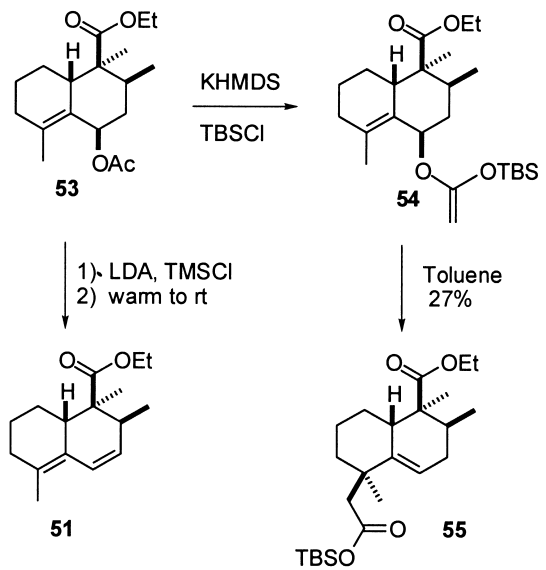
Scheme 15. Attempted S_N2' reactions.

The corresponding allylic acetates were examined briefly as an alternative to the allylic mesylates. Allylic alcohols **49** and **50** were acetylated to produce acetates **52** and **53**, respectively. Although these allylic acetates also had a tendency for elimination, they could be handled under neutral conditions. Yamamoto's reagent was prepared by treatment of 5-bromo-2-methyl-1-pentene with *tert*-butyllithium followed by 1 equiv. each of copper cyanide, or copper iodide, and $BF_3{\cdot}OEt_2$. However, attempts to react the organocopper species with the allylic acetates **52** or **53** were unproductive. The starting materials remained unchanged throughout the temperature range of −78 to 0°C.

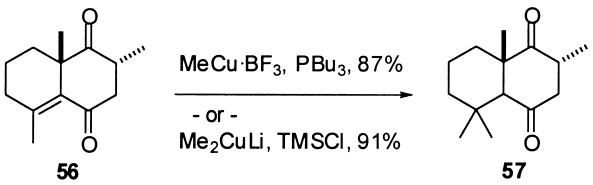
On the theme of simultaneous installation of the C15 stereogenic quaternary center with the formation of the Δ9,10 alkene, an Ireland–Claisen rearrangement was also probed.[32] It was envisioned that the allylic acetate **53** could be converted into the corresponding silyl ketene acetal **54** en route to the allylically transposed silyl ester **55** (Scheme 16). The alkenyl side chain could then be elaborated from the latter.

Following standard procedures, a solution of **53** was treated with lithium diisopropylamide and trimethylsilyl chloride then warmed to ambient temperature. Upon isolation of the products only the diene **51**, produced by elimination of the acetate, and the *C*-silylated ester were found. However, when allylic acetate **53** was treated with potassium hexamethyldisilazane in toluene followed by *tert*-butyldimethylsilyl chloride and warming to room temperature, the rearranged silyl ester **55** was isolated in 27% yield. Extensive attempts to optimize the reaction sequence led to no overall improvements in yield, however. Therefore, a stepwise sequence to introduce the side chain and Δ9,10 alkene was ultimately adopted.

Returning to enone **23**, the alkenyl side chain would be installed in its entirety via conjugate addition. Thereafter,



Scheme 16. Ireland–Claisen rearrangement.



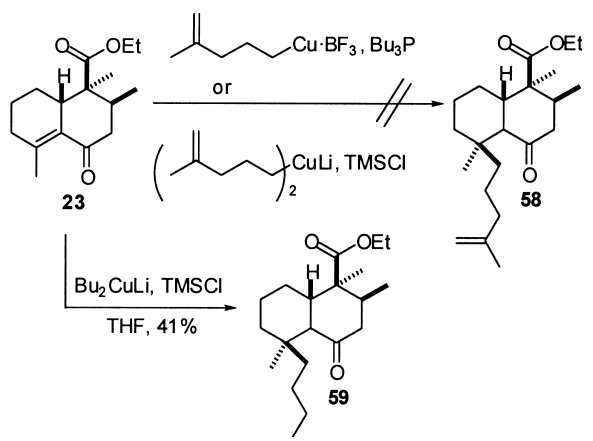
Scheme 17. Sih's conjugate addition.[33]

the resulting ketone would be serve to introduce the Δ9,10 alkene of **48**. This approach was reserved as a late alternative because β-disubstituted enone **23** is both sterically hindered and, as detailed previously, bent out of planarity by ~46°.[7]

With a somewhat similar bicyclic system, Sih and co-workers had reported the conjugate addition of a methyl group to the enone **56** (Scheme 17).[33] Whereas **56** was unreactive towards conventional organocopper reagents (Me_2CuLi or $Me_2Cu(CN)Li_2$), when treated with Yamamoto's methyl copper reagent or trimethylsilyl chloride augmented methylcuprate, high yields of the conjugate adduct were obtained.

Similarly, attempted conjugate additions upon bicyclic enone **23** of conventional organocopper species prepared from 4-methyl-4-pentenyllithium and various copper sources were unsuccessful. Attempted conjugate addition with the Yamamoto organocopper reagent, prepared from equimolar amounts of copper iodide, 4-methyl-4-pentyllithium (derived from of 5-bromo-2-methyl-1-pentene with *tert*-butyllithium) and boron trifluroide etherate, also failed to provide the anticipated product **58** (Scheme 18). Attempts to effect 1,4-addition upon **23** with a 4-methyl-4-pentenyl cuprate in the presence of trimethylsilyl chloride were similarly unproductive. However, *n*-butylcuprate, prepared from salt-free *n*-butyllithium, added to enone **23** in the presence of trimethylsilyl chloride to provide adduct **59** in 41% yield.

To enhance the success of the conjugate addition, it was reasoned that the addition of a Lewis acid such as $BF_3{\cdot}OEt_2$ might planarize the bent enone by withdrawing electron density from the carbonyl group and force allylic participation, and as a result may increase the electrophilicity of the β-carbon. Further, because the rate of conjugate addition

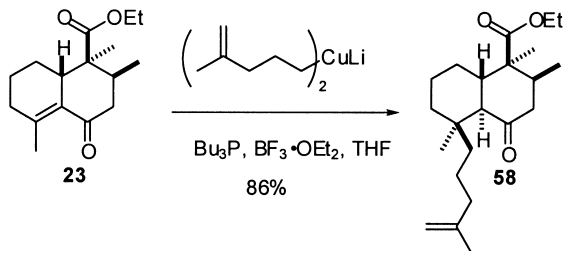


Scheme 18. Attempted conjugate additions upon enone **23**.

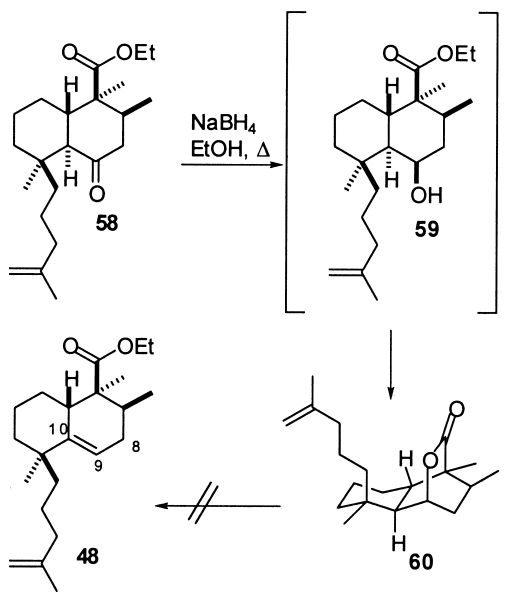
may depend upon both the electrophilicity of the enone system and the reducing potential of the alkylcuprate species, an attempt to increase the electron density of the latter was also made by the addition of tri-*n*-butylphosphine as a ligand for copper. Oppolzer had reported that addition of tri-*n*-butylphosphine to Yamamoto's alkylcopper reagent enhanced its reactivity, but this finding had apparently not been extended to alkylcuprates.[34]

In the event, lithiation of 5-bromo-2-methyl-1-pentene (4.2 equiv.) with *tert*-butyllithium in diethyl ether was followed by the addition of CuI (2.1 equiv.) and tri-*n*-butylphosphine (2.5 equiv.) in THF. To the cuprate mixture was added enone **23** (1.0 equiv.) followed by $BF_3{\cdot}OEt_2$ (4.2 equiv.). Normal quench and work up provided the anticipated adduct **58** in 86% yield (Scheme 19). This conjugate addition was reproducible, providing 80 to 90% yields of the conjugate adduct on a variety of scales.

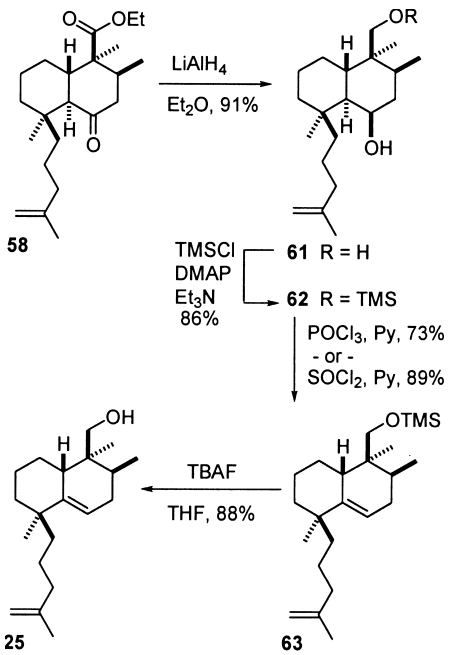
2.3.3.2. Formation of the core Δ9,10 alkene. With the successful stereoselective addition of the alkenyl side chain appendage, only formation of the Δ9,10 trisubstituted alkene remained to complete the assembly of dysidiolide's core structure. Initially, it seemed that chemoselective reduction of the C9 ketone of **58** to the alcohol **59**, followed by dehydration would produce the Δ9,10 alkene **48** (Scheme 20). But, the ketone was quite resistant to reduction with sodium borohydride at ambient temperature and when the reduction was conducted at elevated temperatures, the



Scheme 19. Successful conjugate addition upon enone **23**.



Scheme 20. Chemoselective reduction—lactonization.



Scheme 21. Global carbonyl reduction—dehydration.

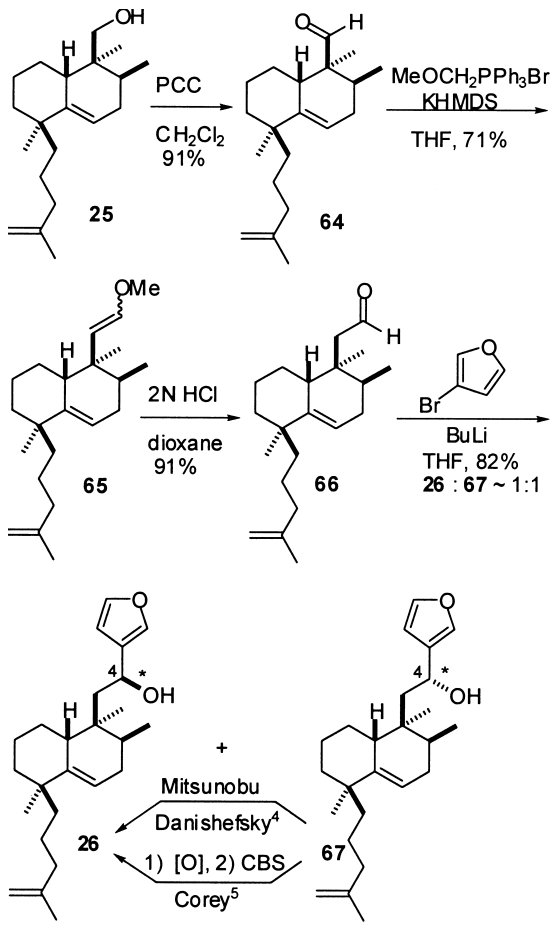
resulting alcohol readily lactonized to generate **60**. Extensive attempts to use the carboxyl moiety of the lactone **60** as a leaving group to prepare the Δ9,10 alkene of **48** were unsuccessful.

Thus, **58** was reduced with an excess of lithium aluminum hydride and the resulting diol **61** was mono-silylated at the primary alcohol to provide **62** (Scheme 21). Dehydration of **62** could be accomplished with either phosphorus oxychloride or thionyl chloride,[35] the latter being much faster. Finally, cleavage of the trimethylsilyl ether provided primary alcohol **25** bearing the core structure of dysidiolide. Attention could then be turned to the installation of the γ-hydroxybutenolide moiety and the completion of the total synthesis.

2.4. Side chain elaboration

2.4.1. Synthesis of *sec*-dysidiolide. Two key tasks remained to complete the synthesis of dysidiolide, extension of the hydroxymethyl substituent of **25** into a one-carbon homologated aldehyde (**66**, Scheme 22), and installation of the γ-hydroxybutenolide moiety. As stated at the outset, the butenolide moiety would be incorporated via the addition of 3-lithiofuran upon a C4 aldehyde, which would provide both a photooxidation substrate for hydroxybutenolide formation and the secondary hydroxyl group resident at C4 of **1**.

The neopentyl nature of the C6 carbon of **25** precluded the use of substitution reactions for chain homologation. Instead, a Wittig homologation was initiated via oxidation of the hydroxyl group to the corresponding aldehyde **64** with pyridinium chlorochromate. Exposure of **64** to methoxymethyltriphenylphosphorane, generated from methoxymethyltriphenylphosphonium chloride and potassium hexamethyldisilazane, provided the isomeric (*E*,*Z*)-vinyl methyl ethers **65**.[36]



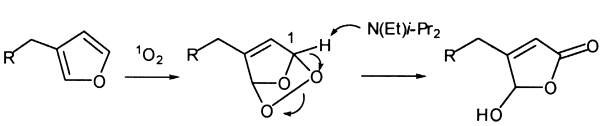
Scheme 22. Side chain elaboration.

Hydrolysis of the vinyl ethers with 2N hydrochloric acid in dioxane cleanly provided the pivotal C4 aldehyde **66**, which has been a common advanced intermediate in each of the total syntheses of dysidiolide reported to date.[4–7,9,10]

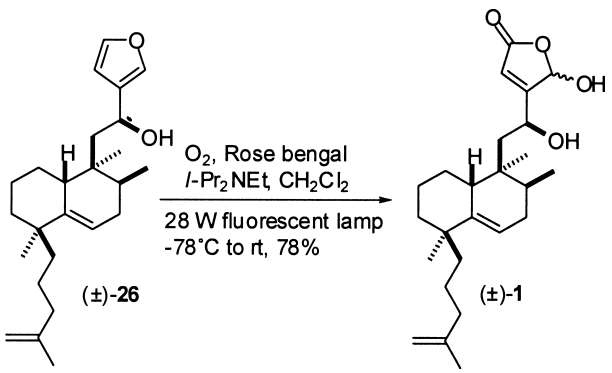
2.4.2. Furan addition. Mirroring the end-game strategy of Corey[5] and Danishefsky,[4] the masked butenolide could be installed via 3-lithiofuran, which is available by lithiation of 3-bromofuran. Because 3-lithiofuran is prone to isomerization to the thermodynamically favored 2-lithiofuran above −40°C,[37] 3-bromofuran was lithiated and the aldehyde **66** was added at −78°C. This reaction provided a ca. 1:1 ratio of epimeric alcohols **26** and **67**.[5] At this stage, diastereomer **67** bearing the unnatural relative configuration at C4 could be epimerized via either Mitsunobu inversion,[4] or an oxidation–diastereoselective reduction process.[5] Only photooxidation of the furan moiety of **26** to reveal the γ-hydroxybutenolide remained to complete the total synthesis (Scheme 23).

2.5. Furan oxidation: total synthesis of dysidiolide

Faulkner and Kernan simplified the synthesis of hydroxy



Scheme 23. Regioselective endoperoxide fragmentation.[38]



Scheme 24. Furan oxidation to dysidiolide.[22]

butenolides when they reported the regioselective oxidation of 3-alkylfurans with singlet oxygen in the presence of Hünig's base.[38] Furan precursors to hydroxy butenolides substituted at C1 with carboxylic acid, trimethylsilyl or trialkylsilyloxy groups were known to undergo directed fragmentation of the endoperoxide intermediates. Faulkner reported that the activation at C1 provided by these substituents could be replicated, in effect, by a regioselective deprotonation of a C1-unsubstituted endoperoxide with a hindered base that would discriminate between C1 and C4 endoperoxide sites. Such discrimination can be induced by substitution at C3, which leads to the 3-alkyl-5-hydroxy-butenolide isomer (Scheme 24). This process has been exploited in previous syntheses of **1**.[4,5]

Optimal conditions for the photooxidation–fragmentation were found to involve irradiation with a 28 W fluorescent bulb of a −78°C solution of **26** and diisopropylethylamine saturated with oxygen and containing Rose Bengal sensitizer. After warming the solution to ambient temperature, (±)-dysidiolide was produced and isolated in 73% yield. The synthetic dysidiolide obtained had identical ^{1}H, ^{13}C NMR, IR spectra and HPLC retention time as a sample of the natural product kindly provided by Dr Gunasekera.

3. Conclusions

The total synthesis of dysidiolide was accomplished via a flexible synthetic route that is characterized by a high level of intramolecular stereo-induction. This began with 6-carboethoxy-3-chloro-5-methyl-cyclohex-2-enone[25] (**32**) representing the B-ring and containing the priming methyl bearing stereogenic center corresponding to C7 of dysidiolide. Diastereoselecitve methylation of **32** installed the 6,7-*trans*-dimethyl substitution characteristic of dysidiolide and the cacospongionolides. Unmasking of the transposed enone system **34** led to a diastereoselective conjugate addition to install the A-ring annulation precursor. Cyclization then provided another enone system (**23**) that served as a substrate for a challenging conjugate addition to incorporate the branched pentenyl side chain at C15. The combination of tri-*n*-butylphosphine and $BF_3{\cdot}OEt_2$ in conjunction with a dialkylcuprate uniquely effected conjugate addition upon the sterically hindered and non-planar enone system of **23**. Thereafter, elaboration of the hydroxymethyl side chain intercepted the common C4 aldehyde (**66**) used in each of the total syntheses of **1** reported to date. A final regioselective photooxidation–fragmentation of an incorporated furan moiety completed the total synthesis of (±)-**1**.

This synthesis of dysidiolide establishes the viability of a general approach for the preparation of the isolabdanoid terpene system. On a final note, the key B-ring intermediate enone (±)-**13** could be resolved by treatment with vinyl acetate and lipase AK Amano 20 in hexanes to provide (6*S*,7*S*)-**13** in 93% ee, which formally allows an enantioselective entry to **1** and congeners via the general route established here.

4. Experimental

4.1. General

Unless noted otherwise, all oxygen and moisture-sensitive reactions were executed in oven-dried glassware sealed under a positive pressure of dry argon or nitrogen. Moisture-sensitive solutions and anhydrous solvents were transferred via standard syringe and cannula techniques. All commercial reagents were used as received. Organic solvents were dried under nitrogen: tetrahydrofuran (THF) and diethyl ether were distilled over Na-benzophenone; CH_2Cl_2, HMPA, triethylamine, and pyridine were distilled from CaH_2. Flash chromatography was performed using Baker Flash silica gel 60 (40 μM); analytical TLC was performed using 0.25 mm EM silica gel 60 F_{254} plates that were visualized under UV light (254 nm) or by staining with anisaldehyde reagent (450 mL of 95% ethanol, 25 mL conc. H_2SO_4, 15 mL acetic acid, and 25 mL anisaldehyde) and heating. Optical rotations were obtained using a JASCO DIP-370 digital polarimeter. IR spectra were recorded using a Perkin–Elmer 683 infrared spectrophotometer. NMR spectra were obtained using INOVA 500 and 300 MHz Varian instruments. High resolution mass spectrometric data were obtained using a VG Analytical Sector-Field mass spectrometer.

4.1.1. (±)-(5*S,6*S**)-6-Carboethoxy-3-chloro-5,6-dimethyl-cyclohex-2-enone (33).** Dry NaH (95%, 3.39 g, 134 mmol) was added to a stirred solution of 6-carboethoxy-3-chloro-5-methyl-cyclohex-2-enone[25] (**32**, 24.12 g, 111.6 mmol) in THF (372 mL) at 0°C. When the evolution of gas ceased, HMPA (38 mL, 0.22 mol) followed by iodomethane (8.35 mL, 134 mmol) were added and the mixture allowed to warm to rt and stir for 6 h. The solvent was removed in vacuo and the residue was suspended in diethyl ether (1 L) and washed with saturated aqueous NH_4Cl (100 mL) then brine (100 mL). The organic extract was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was chromatographed with silica gel (hexanes–ethyl acetate, 8:1, v/v) to give **33** (21.9 g, 94.9 mmol, 85%) as a colorless oil: R_f (hexanes–ethyl acetate, 3:1, v/v) 0.70; IR (film) ν_{max} 2983, 2939, 1736, 1676, 1623, 1454, 1375, 1357, 1307, 1277, 1247, 1231, 1193, 1133, 1108 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.27 (d, J=2.4 Hz, 1H), 4.14 (m, 2H), 2.80 (ddd, J=2.4, 11.1, 18.6 Hz, 1H), 2.56 (dd, J=4.8, 18.6 Hz, 1H), 2.23 (m, 1H), 1.41 (s, 3H), 1.23 (t, J=7.2 Hz, 3H), 1.13 (d, J=6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 194.5, 169.9, 157.5, 127.1, 61.2, 56.0, 40.1, 38.6, 18.3,

16.0, 14.1; HRMS (CI, NH_3) *m/z* calcd for $[C_{11}H_{15}ClO_3+NH_4]^+$, 248.1052; found, 248.1066.

4.1.2. (±)-(4*S* *,5*S* *)-4-Hydroxymethyl-4,5-dimethyl-cyclohex-2-enone (13). Dry NaH (95%, 2.88 g, 114 mmol) was added in small portions to a solution of **33** (21.89 g, 94.89 mmol) in absolute ethanol (500 mL) at 0°C. After 30 min the solvent was evaporated in vacuo and replaced with diethyl ether (500 mL) and triethylamine (30 mL). Vacuum filtration through a thin layer of silica gel and concentration in vacuo gave a residue (**30**, 22.84 g). This was dissolved in dry diethyl ether (250 mL) and the resulting solution was added dropwise to a suspension of $LiAlH_4$ (3.6 g, 95 mmol) in diethyl ether (750 mL) at rt. After stirring for 1 h, the mixture was cooled to 0°C and H_2O (5 mL) and 2 M aqueous HCl (250 mL) were sequentially added. The resulting mixture was warmed to rt and stirred for 30 min. The aqueous layer was removed and the organic phase was washed with saturated aqueous $NaHCO_3$ (100 mL), H_2O (100 mL), and brine (100 mL). The oranic phase was dried over Na_2SO_4 and filtered. The filtrate was concentrated in vacuo and the residual oil was chromatographed on silica gel (hexanes–ethyl acetate, 1:1, v/v) to give **13** (13.20 g, 86 mmol, 90%) as a colorless oil: R_f 0.25 (hexanes–ethyl acetate, 1:1, v/v); IR (film) ν_{max} 3444, 2964, 2879, 1669, 1457, 1377, 1285, 1257, 1049 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.60 (d, *J*=10.2 Hz, 1H), 5.91 (d, *J*=10.2 Hz, 1H), 3.67 (d, *J*=10.8 Hz, 1H), 3.44 (d, *J*=11.1 Hz, 1H), 3.29 (s, 1H), 2.50 (dd, *J*=11.7, 17.4 Hz, 1H), 2.26 (dd, *J*=4.8, 17.1 Hz, 1H), 2.01 (sept, *J*=6.9 Hz, 1H), 1.04 (s, 3H), 0.98 (d, *J*=6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 201.3, 157.4, 128.8, 66.2, 42.9, 40.9, 37.1, 22.7, 15.6; HRMS (CI, NH_3) *m/z* calcd for $[C_9H_{14}O_2+NH_4]^+$, 172.1338; found, 172.1327.

4.1.3. (±)-(4*S* *,5*S* *)-4-(Trimethylsilyl)oxymethyl-4,5-dimethyl-cyclohex-2-enone (34). Trimethylsilyl chloride (1.31 mL, 10.3 mmol) was added dropwise to a stirred solution of **13** (1.06 g, 6.9 mmol), imidazole (2.34 g, 35.0 mmol) and 4-*N*,*N*-dimethylaminopyridine (0.12 g, 1.0 mmol) in CH_2Cl_2 (35 mL) at 0°C. The solution was allowed to warm to rt and stir for 1 h. Ethyl acetate (150 mL) was added and the solution was washed with H_2O (25 mL) and brine (25 mL), then dried over Na_2SO_4 and filtered. The filtrate was concentrated in vacuo and the residue chromatographed over silica gel (hexanes–ethyl acetate, 8:1, v/v, 0.5% triethylamine) to give **34** (1.45 g, 6.4 mmol, 93%) as a colorless oil: R_f 0.52 (hexanes–ethyl acetate, 5:1, v/v); IR (film) ν_{max} 2961, 2878, 1681, 1454, 1378, 1252, 1092 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.58 (d, *J*=10.2 Hz, 1H), 6.00 (d, *J*=10.2 Hz, 1H), 3.69 (d, *J*=9.6 Hz, 1H), 3.41 (d, *J*=10.5 Hz, 1H), 2.58 (dd, *J*=11.7, 16.8 Hz, 1H), 2.33 (dd, *J*=5.1, 17.1 Hz, 1H), 2.6 (sept, *J*=4.8 Hz, 1H), 1.08 (s, 3H), 1.04 (d, *J*=6.9 Hz, 3H), 0.07 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 200.6, 156.7, 128.7, 66.3, 43.0, 40.6, 37.1, 22.8, 15.5, −0.73; HRMS (CI, NH_3) *m/z* calcd for $[C_{12}H_{22}O_2Si+NH_4]^+$, 244.1733; found, 244.1715.

4.1.4. (±)-(3*S* *,4*S* *,5*S* *)-3-(4-(*tert*-Butyldimethylsilyl)-oxy-1-*n*-pentyl)-4-(trimethylsilyl)oxymethyl-4,5-dimethyl-cyclohex-2-enone (44). To a stirred −78°C solution of 1-bromo-4-(*tert*-butydimethylsilyl)oxy-pentane (**43**,[39] 8.95 g, 32 mmol) in diethyl ether (70 mL), *tert*-butyllithium (37.5 mL of 1.7 M solution in pentane, 64 mmol) was added dropwise and the solution allowed to stir for 20 min before CuCN (1.40 g, 16 mmol) was added via a solid addition funnel. After gradual warming to −10°C, the solution was re-cooled to −78°C and a solution of enone **34** (2.97 g, 13 mmol) in diethyl ether (10 mL) was added dropwise. After stirring for 2 h, the solution was gradually warmed to −30°C. A 10% NH_4OH/saturated aqueous NH_4Cl solution (10 mL) was added and the resulting mixture was warmed to rt. Diethyl ether (400 mL) was added and the mixture was washed with H_2O (100 mL) and brine (100 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo and the residue was chromatographed on silica gel (hexanes–ethyl acetate–triethylamine 20:1:0.005, v/v/v) to give **44** (4.6 g, 11 mmol, 82%) as a colorless oil: R_f 0.61 (hexanes–ethyl acetate, 5:1, v/v); IR (film) ν_{max} 2958, 2929, 2857, 1716, 1462, 1376, 1251, 1091 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.74 (sext, *J*=6.0 Hz, 1H), 3.56 (d, *J*=9.5 Hz, 1H), 3.43 (d, *J*=9.5 Hz, 1H), 2.46–2.41 (m, 2H), 2.20–2.14 (m, 1H), 2.12–2.03 (m, 2H), 1.96–1.90 (m, 1H), 1.44–0.83 (m, 6H), 1.09 (d, *J*=6.5 Hz, 3H), 1.00 (d, *J*=3.0 Hz, 3H), 0.91 (dd, *J*=2.0, 7.0 Hz, 3H), 0.87 (s, 9H), 0.10 (s, 9H), 0.05 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 213.0, 68.5, 42.2, 39.9, 39.2, 38.5, 37.5, 29.9, 25.9, 23.9, 18.7, 18.1, 15.5, −0.7, −4.4, −4.7; HRMS (FAB) *m/z* calcd for $[C_{23}H_{48}O_3Si_2+H]^+$, 429.3220; found, 429.3191.

4.1.5. (±)-(3*S* *,4*S* *,5*S* *)-3-(4-Hydroxy-1-*n*-pentyl)-4-hydroxymethyl-4,5-dimethyl-cyclohex-2-enone (45). To a stirred rt solution of **44** (3.77 g, 8.8 mmol) in methanol (50 mL) and CH_2Cl_2 (50 mL) was added *p*-toluenesulfonic acid monohydrate (0.17 g, 0.9 mmol). After stirring for 2 h, $NaHCO_3$ (70 mg) was added and the mixture was concentrated in vacuo. The residue was chromatographed over silica gel with ethyl acetate to give **45** (2.0 g, 8.3 mmol, 94%) as a colorless oil: R_f 0.32 (hexanes–ethyl acetate, 1:1, v/v); IR (film) ν_{max} 3432, 2959, 2932, 2860, 1456, 1373, 1348, 1328, 1177, 1110 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.91 (d, *J*=15 Hz, 1H), 3.73 (q, *J*=7.5 Hz, 1H), 3.34 (dd, *J*=3.0, 15.0 Hz, 1H), 3.25 (s (br), 2H), 2.17–2.02 (m, 1H), 2.02 (brs, 1H), 1.91–1.74 (m, 2H), 1.63–1.57 (m, 1H), 1.49–0.98 (m, 7H), 1.22 (d, *J*=10.5 Hz, 3H), 0.91 (d, *J*=11.5 Hz, 3H), 0.62 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 98.6, 72.4, 67.9, 49.2, 42.3, 39.4, 36.9, 33.8, 30.7, 28.2, 23.6, 23.3, 17.6, 16.7; HRMS (CI, NH_3) *m/z* calcd for $[C_{14}H_{26}O_3+NH_4]^+$, 260.2226; found, 260.2215.

4.1.6. (±)-(3*S* *,4*S* *,5*S* *)-3-(4-Oxo-1-*n*-pentyl)-4-carboxethoxy-4,5-dimethyl-cyclohex-2-enone (46). To a stirred 0°C solution of **45** (2.20 g, 9.1 mmol) in acetone (50 mL) was added Jones reagent until a red solution persisted. The solution was allowed to stir for 30 min before 2-propanol was added until the solution was decolorized. After removal of the solvent in vacuo and addition of H_2O (20 mL), the mixture was extracted with diethyl ether (4×50 mL). The combined diethyl ether extract was washed with brine (20 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was dissolved in acetone (50 mL) and K_2CO_3 (6.27 g, 45.4 mmol) and iodoethane (2.18 mL, 27.2 mmol) were added. The mixture was heated at reflux for 1 h, cooled to rt, filtered through celite and concentrated in vacuo. The

residue was suspended in ethyl acetate (200 mL), washed with H_2O (40 mL) and brine (40 mL), dried over Na_2SO_4, and filtered. After concentration in vacuo the remaining oil was chromatographed on silica gel (hexanes–ethyl acetate, 3:1, v/v) to provide **46** (2.08 g, 7.4 mmol, 81%) as a colorless oil: R_f 0.54 (hexanes–ethyl acetate, 1:1, v/v); IR (film) ν_{max} 2961, 1716, 1457, 1419, 1364, 1273, 1212, 1163, 1118 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 4.14 (t, J=7.5 Hz, 2H), 2.52 (dd, J=5.1, 14.7 Hz, 1H), 2.45–2.36 (m, 4H), 2.27 (ddd, J=1.5, 5.5, 14.5 Hz, 1H), 2.14–2.01 (m, 2H), 2.10 (s, 3H), 1.68–1.59 (m, 1H), 1.48–1.36 (m, 2H), 1.29 (s, 3H), 1.25 (t, J=6.5 Hz, 3H), 1.08–1.00 (m, 1H), 0.88 (d, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 210.6, 208.5, 175.6, 60.5, 48.4, 44.4, 43.3, 42.2, 39.3, 38.1, 31.3, 29.9, 21.5, 18.1, 16.7, 14.2; HRMS (CI, NH_3) m/z calcd for $[C_{16}H_{26}O_4+NH_4]^+$, 300.2149; found, 300.2175.

4.1.7. (±)-(1*S* *,2*S* *,8*aS* *)-1,2-Dimethyl-4-oxo-1,2,3,4,6,7,8,8a-octahydro-naphthalene-1-carboxylic acid ethyl ester (23). Potassium *tert*-butoxide (0.67 g, 5.5 mmol) was added to a stirred solution of **46** (1.52 g, 5.38 mmol) in absolute ethanol (100 mL). The mixture was heated at reflux for 30 min, the heating source was removed, and NH_4Cl (0.3 g, 6 mmol) was added. After removing the ethanol in vacuo, ethyl acetate (300 mL) was added and the mixture was washed with H_2O (50 mL) and brine (50 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo and the residue was chromatographed on silica gel (hexanes–ethyl acetate, 10:1, v/v) to give **23** (1.03 g, 3.89 mmol, 72%) as a colorless oil: R_f 0.49 (hexanes–ethyl acetate, 5:1, v/v); IR (film) ν_{max} 2936, 1725, 1683, 1608, 1456, 1423, 1377, 1252, 1220, 1174, 1134, 1100 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 4.65 (t, J=7.5 Hz, 2H), 3.12–3.11 (m, 1H), 2.67 (dd, J=5.0, 15.5 Hz, 1H), 2.31 (dd, J=4.0, 15.5 Hz, 1H), 2.16–2.13 (m, 3H), 1.95 (d, J=2.5 Hz, 3H), 1.90–1.87 (m, 1H), 1.75–1.73 (m, 1H), 1.56–1.52 (m, 1H), 1.33–1.27 (m, 4H), 1.28 (t, J=2.5 Hz, 3H), 0.96 (d, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.5, 175.7, 148.5, 130.7, 60.4, 48.6, 45.0, 38.7, 38.5, 34.2, 24.7, 22.7, 21.4, 19.6, 19.8, 14.2; HRMS (CI, NH_3) m/z calcd for $[C_{16}H_{24}O_3+NH_4]^+$, 282.2069; found, 282.2069.

4.1.8. (±)-(1*S* *,2*S* *,4*aR* *,5*R* *8*aS* *)-1,2,5-Trimethyl-5-(4-methyl-pent-4-enyl)-4-oxo-decahydro-naphthalene-1-carboxylic acid ethyl ester (58). A solution of *tert*-butyllithium (9.4 mL, 1.7 M in pentane, 16 mmol) was added dropwise to a stirred solution of 5-bromo-2-methyl-pent-1-ene (1.30 g, 8.0 mmol) in diethyl ether (53 mL) at −78°C. After 30 min, a mixture of CuI (0.73 g, 4.0 mmol) and tri-*n*-butylphosphine (2.5 mL, 10 mmol) in THF (21 mL) was added. The mixture was stirred for 20 min before a solution of enone **23** (0.51 g, 1.9 mmol) in THF (6 mL) was added dropwise. Boron trifluoride etherate (1.0 mL, 8.0 mmol) was then added. After 4 h, saturated aqueous NH_4Cl (10 mL) was added and the mixture was warmed to rt. Diethyl ether (100 mL) was added and the separated organic solution was washed with H_2O (20 mL) then stirred with aqueous 30% H_2O_2 (2 mL) for 15 min. The resulting brown mixture was filtered through silica gel and concentrated in vacuo. The residue was chromatographed with silica gel (hexanes–ethyl acetate, 15:1, v/v) to give **58** (0.58 g, 1.7 mmol, 86%) as a colorless oil: R_f 0.56 (hexanes–ethyl acetate, 5:1, v/v); IR (film) ν_{max} 3072, 2936, 2870, 1712, 1648, 1463, 1388, 1375, 1268, 1246, 1215, 1179, 1148, 1110 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 4.65, (m, 2H), 4.14 (q, J=6 Hz, 2H), 2.65–2.60 (m, 2H), 2.10–2.04 (m, 2H), 1.97–0.82 (m, 13H), 1.71 (s, 3H), 1.37 (s, 3H), 1.25 (t, J=11.0 Hz, 3H), 1.10 (s, 3H), 0.83, (d, J=12 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 210.4, 175.6, 146.3, 109.4, 60.3, 58.7, 48.5, 45.6, 40.7, 38.7, 37.6, 35.7, 29.9, 27.4, 22.3, 21.4, 18.9, 16.5, 14.1; HRMS (FAB) m/z calcd for $[C_{22}H_{36}O_3+H]^+$, 349.2743; found, 349.2721.

4.1.9. (±)-(1*R* *,3*R* *,4*S* *,4*aS* *,8*R* *8*aR* *)-4-Hydroxymethyl-3,4,8-trimethyl-8-(4-methyl-pent-4-enyl)-decahydro-naphthalen-1-ol (61). A solution of **58** (0.10 g, 0.28 mmol) in diethyl ether (1 mL) was added dropwise to a suspension of $LiAlH_4$ (0.01 g, 0.3 mmol) in diethyl ether (3 mL) at 0°C. The mixture was allowed to warm to rt and stir for 1 h. The mixture was cooled to 0°C and H_2O (1 mL) and saturated aqueous sodium potassium tartrate (1 mL) were added sequentially. The resulting mixture was extracted with diethyl ether (3×10 mL) and the combined extract was washed with brine (5 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was chromatographed with silica gel (hexanes–ethyl acetate, 4:1, v/v) to give **61** (80 mg, 0.25 mmol, 91%) as a colorless oil: R_f 0.15 (hexanes–ethyl acetate, 5:1, v/v); IR (film) ν_{max} 3446, 2931, 1647, 1458, 1375, 1018 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 4.67 (d, J=7.5 Hz, 2H), 4.28 (d, J=3.0 Hz, 1H), 3.54 (d, J=3.5 Hz, 2H), 1.99–0.80 (m, 19H), 1.71 (s, 3H), 1.20 (d, J=7.0 Hz, 3H), 0.98 (s, 3H), 0.97 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 146.6, 109.4, 70.0, 68.1, 50.3, 40.7, 39.0, 37.7, 37.4, 36.4, 34.4, 33.4, 29.7, 27.5, 26.6, 22.6, 21.9, 20.9, 18.7, 18.3; HRMS (CI, NH_3) m/z calcd for $[C_{20}H_{36}O_2+H]^+$, 309.2794; found, 309.2791.

4.1.10. (±)-(1*R* *,3*R* *,4*S* *,4*aS* *,8*R* *8a*R* *)-4-(Trimethylsilanyloxymethyl)-3,4,8-trimethyl-8-(4-methyl-pent-4-enyl)-decahydro-naphthalen-1-ol (62). Trimethylsilyl chloride (0.11 mL, 0.86 mmol) and triethylamine (4.3 mmol) were added to a stirred 0°C solution of **61** (0.25 g, 0.81 mmol) and 4-*N*,*N*-dimethylaminopyridine (0.01 g, 0.09 mmol) in CH_2Cl_2 (5 mL). The solution was warmed to rt and stirred for 1 h. Ethyl acetate (20 mL) was added and the solution was washed with H_2O (5 mL) and brine (5 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo and the residue was chromatographed over silica gel (hexanes–ethyl acetate–triethylamine, 10:1:0.005, v/v/v) to give **62** (0.27 g, 0.70 mmol, 86%) as a colorless oil: R_f 0.68 (hexanes–ethyl acetate, 5:1, v/v); IR (film) ν_{max} 2931, 1652, 1458, 1375, 1250, 1088, 1072 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 4.68 (d, J=6.0 Hz, 2H), 4.25 (s, 1H), 3.42 (s, 1H), 1.99 (t, J=7.5 Hz, 2H), 1.95–1.86 (m, 2H), 1.76–1.67 (m, 2H), 1.72 (s, 3H), 1.63–1.57 (m, 2H), 1.50 (dt, J=2.5, 14.4 Hz, 1H), 1.46–1.41 (m, 1H), 1.34–1.28 (m, 4H), 1.14 (d, J=8 Hz, 3H), 1.13–1.06 (m, 3H), 0.98 (s, 3H), 0.92 (s, 3H), 0.87–0.83 (m, 1H), 0.08 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 146.7, 109.4, 69.2, 68.3, 50.5, 40.5, 39.1, 37.7, 37.5, 36.4, 34.0, 33.6, 29.8, 27.5, 26.7, 22.6, 21.9, 21.0, 18.8, 17.9, −0.5; HRMS (CI) m/z calcd for $[C_{23}H_{44}O_2Si+H]^+$, 381.3189; found, 381.3176.

4.1.11. (±)-Trimethyl-[(1*R* *,2*R* *,5*S* *,8*aS* *)-1,2,5-trimethyl-5-(4-methyl-pent-4-enyl)-1,2,3,5,6,7,8,8a-octahydro-naphthalene-1-ylmethoxy]-silane (63). $SOCl_2$

(0.12 mL, 1.6 mmol) was added dropwise to a stirred 0°C solution of **62** (0.12 g, 0.32 mmol) in pyridine (5 mL). The solution was stirred for 30 min. Wet diethyl ether (200 mL) was added and the resulting solution was washed with 1N HCl (70 mL), saturated $NaHCO_3$ (20 mL), H_2O (20 mL), and brine (20 mL). Drying over Na_2SO_4, filtration and concentration in vacuo gave a residue that was chromatographed over silica gel (hexanes–ethyl acetate–triethylamine, 20:1:0.005, v/v/v) to give **63** (0.10 g, 0.28 mmol, 89%) as a colorless oil: R_f 0.74 (streaky, hexanes–ethyl acetate, 15:1, v/v); IR (film) ν_{max} 2953, 1652, 1456, 1374, 1250, 1093, 881, 839 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 5.29 (t, J=2.8 Hz, 1H), 4.69 (s, 1H), 4.66 (s, 1H), 3.46 (d, J=9.5 Hz, 1H), 3.34 (d, J=9.5 Hz, 1H), 2.00–1.95 (m, 4H), 1.77–1.62 (m, 4H), 1.71 (s, 3H), 1.59–1.55 (m, 1H), 1.52–1.49 (br, 1H), 1.30–1.26 (m, 1H), 1.20–1.00 (m, 5H), 0.98 (s, 3H), 0.88 (s, 3H), 0.86 (s, 3H), 0.07 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 146.2, 116.7, 109.6, 66.0, 41.9, 40.0, 39.8, 38.7, 38.3, 37.1, 31.7, 31.6, 29.3, 26.2, 22.5, 22.4, 22.0, 20.9, 15.4, −0.54; HRMS (CI, NH_3) m/z calcd for $[C_{23}H_{42}OSi+H]^+$, 363.3083; found, 363.3058.

4.1.12. (±)-[(1*R* *,2*R* *,5*S* *,8*aS* *)-1,2,5-Trimethyl-5-(4-methyl-pent-4-enyl)-1,2,3,5,6,7,8,8a-octahydro-naphthalene-1-yl]-methanol (25). A solution of TBAF (0.2 mL of 1.0 M solution in THF, 0.20 mmol) was added to a stirred 0°C solution of **63** (61.5 mg, 0.17 mmol) in THF (2 mL). After stirring for 30 min, diethyl ether (10 mL) was added and the resulting solution was washed with water (2 mL) and brine (2 mL), dried over Na_2SO_4 and filtered. The filtrate was removed in vacuo and the residue was chromatographed over silica gel (hexanes–ethyl acetate, 8:1, v/v) to give **25** (43.3 mg, 0.15 mmol, 88%) as a colorless oil: R_f 0.48 (hexanes–ethyl acetate, 5:1, v/v); IR (film) ν_{max} 3412, 2937, 1648, 1456, 1374, 1020, 887 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 5.31 (s, 1H), 4.68 (s, 1H), 4.66 (s, 1H), 3.51 (m, 2H), 2.04 (br, 1H), 2.02 (br, 1H), 1.97 (t, J=7.5 Hz, 2H), 1.76–1.50 (m, 7H), 1.70 (s, 3H), 1.30 (m, 1H), 1.20–1.05 (m, 5H), 0.98 (s, 3H), 0.94 (s, 3H), 0.88 (d, J=6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 146.6, 116.9, 109.6, 66.5, 41.9, 40.0, 39.9, 38.7, 38.6, 38.4, 37.1, 31.7, 31.6, 29.3, 26.14, 22.40, 22.36, 20.5, 15.3; HRMS (CI, NH_3) m/z calcd for $[C_{20}H_{34}O+H]^+$, 291.2688; found, 291.2699.

4.1.13. (±)-(1*R* *,2*R* *,5*S* *,8*aS* *)-1,2,5-Trimethyl-5-(4-methyl-pent-4-enyl)-1,2,3,5,6,7,8,8*a*-octahydro-naphthalene-1-carbaldehyde (64). Silica gel (0.16 g) and pyridinium chlorochromate (0.15 g, 0.71 mmol) were added to a stirred solution of **25** (0.16 g, 0.54 mmol) in CH_2Cl_2 (5 mL) at rt. After 1 h, the mixture was filtered through silica gel and the solvent was removed in vacuo. The residue was chromatographed over silica gel (hexanes–ethyl acetate, 10:1, v/v) to give **64** (0.14 g, 0.49 mmol, 91%) as a colorless oil: R_f 0.70 (hexanes–ethyl acetate, 5:1, v/v); IR (film) ν_{max} 2937, 2706, 1721, 1649, 1453, 1376, 886, 812 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 9.57 (s, 1H), 5.36 (s, 1H), 4.67 (s, 1H), 4.64 (s, 1H), 2.35 (d, J=11.5 Hz, 1H), 2.26 (d, J=18.0 Hz, 1H), 1.95 (t, J=7.5 Hz, 2H), 1.89–1.85 (m, 1H), 1.82 (sext, J=6.0 Hz, 1H), 1.71–1.66 (m, 3H), 1.68 (s, 3H), 1.60–1.53 (m, 2H), 1.31–1.06 (m, 5H), 1.00 (s, 3H), 0.99 (s, 3H), 0.90 (d, J=6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 207.2, 146.1, 144.3, 116.9, 109.8, 49.9, 41.3, 39.7, 38.58, 37.2, 31.7, 31.1, 29.1, 26.1, 22.4, 22.3, 21.9, 17.7, 15.5; HRMS (CI, NH_3) m/z calcd for $[C_{20}H_{32}O+NH_4]^+$, 306.2797; found, 306.2785.

4.1.14. (1*S* *,5*R* *,6*R* *,4*aS* *)-5-[(*E*,*Z*)-2-Methoxy-vinyl]-1,5,6-trimethyl-1-(4-methyl-pent-4-enyl)-1,2,3,4,4*a*,5,6,7-octahydro-naphthalene (65). A 15% solution of KHMDS in toluene (1.10 mL, 0.73 mmol) was added dropwise to a suspension of methoxymethyltriphenylphosphonium chloride (0.25 g, 0.73 mmol) in THF (1 mL) at −78°C. The mixture stirred for 30 min. A solution of **64** (88.1 mg, 0.31 mmol) in THF (1 mL) was added dropwise and the resulting mixture was stirred for 1 h then gradually warmed to rt. After re-cooling to 0°C, wet diethyl ether (20 mL) was added and the mixture was washed with H_2O (5 mL) and brine (5 mL), dried over Na_2SO_4, and filtered. After concentration in vacuo, the residue was chromatographed over silica gel (hexanes) to give **65** (71.1 mg, 0.22 mmol, 71%) as a colorless oil: R_f 0.73 (hexanes–ethyl acetate, 10:1, v/v); ^1H NMR ($CDCl_3$, 500 MHz) δ 6.26 (d, J=13.0 Hz, 1H), 5.32 (dd, J=1.0, 5.0 Hz, 1H), 4.89 (d, J=13.0 Hz, 1H), 4.66 (s, 1H), 4.64 (s, 1H), 3.44 (s, 3H), 2.03–2.00 (m, 1H), 1.95 (t, J=7.5 Hz, 2H), 1.83–1.50 (m, 8H), 1.69 (s, 3H), 1.33–0.95 (m, 5H), 0.99 (s, 3H), 0.95 (s, 3H), 0.76 (d, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 146.6, 146.3, 117.1, 109.6, 55.6, 42.3, 39.9, 39.5, 38.6, 37.6, 37.0, 34.8, 26.1, 22.5, 22.4, 22.2, 20.0, 15.5, 15.0; HRMS (CI, NH_3) m/z calcd for $[C_{22}H_{36}O+H]^+$, 317.2844; found, 317.2857.

4.1.15. (±)-[(1*R* *,2*R* *,5*S* *,8*aS* *)-1,2,5-Trimethyl-5-(4-methyl-pent-4-enyl)-1,2,3,5,6,7,8,8*a*-octahydro-naphthalene-1-yl]-acetaldehyde (66). A 2N aqueous solution of HCl (120 μL) was added to a stirred solution **65** (71.1 mg, 0.22 mmol) in 1,4-dioxane (12 mL) at rt. After 20 min diethyl ether (50 mL) was added and the mixture was washed with H_2O (10 mL) and brine (10 mL), dried over Na_2SO_4, and filtered. The solvent was removed in vacuo and the residue was chromatographed over silica gel (hexanes–ethyl acetate, 30:1, v/v) to give **66** (61.4 mg, 0.20 mmol, 91%) as a colorless oil: R_f 0.56 (hexanes–ethyl acetate, 10:1, v/v); IR (film) ν_{max} 2936, 2724, 1719, 1649, 1445, 1374, 885, 812 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 9.90 (t, J=3.0 Hz, 1H), 5.33 (t, J=3.0 Hz, 1H), 4.67 (s, 1H), 4.64 (s, 1H), 2.33 (dd, J=2.5, 15.0 Hz, 1H), 2.24 (dd, 3.0, 14.5 Hz, 1H), 2.08–1.93 (m, 4H), 1.80 (m, 1H), 1.73–1.51 (m, 6H), 1.68 (s, 3H), 1.31–1.28 (m, 1H), 1.20–1.09 (m, 4H), 1.07 (s, 3H), 0.99 (s, 3H), 0.84 (d, J=6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 204.6, 146.3, 117.12, 109.7, 42.0, 40.0, 38.6, 37.6, 37.0, 33.0, 31.6, 29.4, 26.0, 23.0, 22.5, 22.4, 22.3, 15.0; HRMS (CI, NH_3) m/z calcd for $[C_{21}H_{34}O+H]^+$, 303.2688; found 303.2685.

4.1.16. (±)-(*R* *)-1-Furan-3-yl-2-[(1*R* *,2*R* *,5*S* *,8*aS* *)-1,2,5-trimethyl-5-(4-methyl-pent-4-enyl)-1,2,3,5,6,7,8,8*a*-octahydro-naphthalene-1-yl]-ethanol (26), and (±)-(*S* *)-1-furan-3-yl-2-[(1*R* *,2*R* *,5*S* *,8*aS* *)-1,2,5-trimethyl-5-(4-methyl-pent-4-enyl)-1,2,3,5,6,7,8,8*a*-octahydro-naphthalene-1-yl]-ethanol (67). A solution of *n*-BuLi (0.14 mL of 2.5 M in hexane, 0.34 mmol) was added to a solution of 3-bromofuran (31 μL, 0.34 mmol) in THF (5 mL) at −78°C. The resulting solution was stirred for

30 min before a solution of **66** (34.6 mg, 114 μmol) in THF (2 mL) was added dropwise. After 30 min saturated aqueous NH_4Cl (1 mL) was added and the mixture allowed to warm to rt. Diethyl ether (50 mL) was added and the resulting mixture was washed with H_2O (10 mL) and brine (10 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel (hexanes–ethyl acetate, 10:1, v/v) to yield **26** (15.7 mg, 42 μmol, 37%) and **67** (19.1 mg, 51 μmol, 45%). Characterization data for **26**: R_f 0.30 (hexanes–ethyl acetate, 8:1, v/v); IR (film) ν_{max} 3388, 2937, 1650, 1503, 1445, 1374, 1161, 1025, 874; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.33 (d, J=8.5 Hz, 2H), 6.38 (s, 1H), 5.32 (s, 1H), 4.85 (t, J=6.0 Hz, 1H), 4.66 (s, 1H), 4.59 (s, 1H), 1.90–1.03 (m, 21H), 1.65 (s, 3H), 0.97 (s, 3H), 0.88 (d, J=6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 145.9, 143.2, 142.0, 138.4, 131.1, 117.2, 113.9, 109.7, 108.7, 64.0, 41.5, 39.8, 38.5, 36.9, 36.2, 33.4, 31.8, 31.6, 29.7, 26.1, 22.5, 22.4, 22.1, 21.9, 15.0 cm^{-1}; HRMS (FAB) m/z calcd for $[C_{21}H_{34}O+Na]^+$, 393.2769; found, 393.2786. Characterization data for **67**: R_f 0.45 (hexanes–ethyl acetate, 8:1, v/v); IR (film) ν_{max} 3454, 2936, 1649, 1502, 1444, 1374, 1160, 1056, 1024, 873; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36 (s, 2H), 6.39 (s, 1H), 5.34 (s, 1H), 4.85 (s, 1H), 4.65 (s, 1H), 4.64 (s, 1H), 1.97–0.97 (m, 18H), 1.68 (s, 3H), 1.00 (s, 3H), 0.97 (s, 3H) 0.77 (d, J=6.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 146.6, 143.2, 142.0, 138.5, 131.3, 117.1, 113.8, 109.6, 108.6, 64.9, 42.9, 42.3, 40.1, 38.6, 38.2, 37.2, 35.9, 33.0, 31.8, 29.8, 26.2, 22.5, 14.9; HRMS (FAB) m/z calcd for $[C_{21}H_{34}O+Na]^+$, 393.2769; found, 393.2780.

4.1.17. (*R*,*S*)-5-Hydroxy-4-{(*R)-1-hydroxy-2-[(1*R**, 2*R**,5*S**,8*aS**)-1,2,5-trimethyl-5-(4-methyl-pent-4-enyl)-1,2,3,5,6,7,8,8*a*-octahydro-naphthalene-1-yl]-ethyl}-5*H*-furan-2-one [(±)-dysidiolide] (1).** A −78°C solution of **26** (1.3 mg, 3.5 μmol), diisopropylethylamine (10 μL, 0.06 mmol), and Rose Bengal (0.2 mg) in CH_2Cl_2 (4 mL) was irradiated with a 28 W fluorescent lamp while anhydrous oxygen was bubbled through it for 20 min. Irradiation was continued for 2 h after removal of the oxygen line. Argon was bubbled through the solution for 10 min and the solution warmed to rt. Saturated aqueous oxalic acid (0.3 mL) was added and the solution stirred until colorless. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (2×10 mL). The combined CH_2Cl_2 layers were dried over $MgSO_4$, filtered, concentrated in vacuo, and chromatographed over silica gel (CH_2Cl_2–methanol, 98:2, v/v) to provide **1** (1.1 mg, 2.8 μmol, 78%) as a white amorphous solid: R_f 0.51 (hexanes/ethyl acetate 1:1, v/v); HPLC (C-18, 5 μm, 100 Å, 250 mm×4.6 mm ID column): t_R=17.01 min (85% MeOH–15% H_2O, flow rate=0.75 mL/min); co-eluted with a sample of naturally occurring **1**, ^{1}H NMR (DMSO, 500 MHz) δ 7.84 (brd, J=6.5 Hz, 1H), 6.09 (brs, 1H), 5.92 (brs, 1H), 5.28–5.25 (br, 2H), 5.12 (s, 1H), 4.63 (s, 1H), 4.60 (s, 1H), 4.50 (s, 1H), 4.38 (br, 1H), 2.24 (br, 1H), 1.98–0.78 (m, 15H), 1.61 (s, 3H), 1.47 (brs, 3H), 0.93 (s, 3H), 0.81 (d, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 176.2, 170.9, 145.9, 142.3, 116.4, 116.0, 110.54, 98.2, 64.9, 40.5, 39.5, 38.4, 33.5, 29.9, 26.4, 22.6, 22.2, 15.4; HRMS (FAB) m/z calcd for $[C_{21}H_{34}O+H]^+$, 403.2848; found, 403.2825.

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