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The power of singlet oxygen chemistry in biomimetic syntheses

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Dedicated to the memory of Christopher S. Foote, mentor and friend

Abstract—Herein, we describe selected highlights from the successful syntheses of the litseaverticillol family of natural products and from the synthesis of the core of the prunolide molecules, using powerful $^1O_2$-orchestrated biomimetic strategies. In these syntheses, cascade reaction sequences initiated by the reaction of $^1O_2$ with a furan and the ene-reaction of $^1O_2$ with double bonds together facilitated the swift assembly of the targeted compounds from simple precursors. We also introduce our most recent $^1O_2$-facilitated synthetic strategies used in our approach to the synthesis of premnalane A. In this investigation, we explore a number of different reactivities of $^1O_2$, thus completing a brief survey of how $^1O_2$ chemistry may be fruitfully employed in the synthesis of complex secondary metabolites.

1. Introduction

There is perhaps no reagent that could be said to be more synonymous with biomimetic synthetic strategies than singlet oxygen. This situation arises because in plants and living organisms four crucial prerequisites are met, which favor the production and reaction of singlet oxygen. These criteria are: (1) the presence of natural sunlight providing visible spectrum irradiation; (2) the proliferation of photosensitizers (e.g., tannins, porphyrins, and chlorophyll) in the environment; (3) pervasive molecular dioxygen ($\approx$20% of atmospheric air); and, finally, (4) an abundance of oxidizable substrates, such as terpenes, in the immediate vicinity. Biomimetic synthetic strategies, as this special edition of Tetrahedron so aptly illustrates, are admired for their efficiency in the swift construction of molecular complexity. Of particular note, are biomimetic strategies that harness cascade reaction sequences to forge core structures rapidly from simpler precursors. Here, once again, we can see how singlet oxygen is uniquely suited to the paradigm since it willingly participates in complex domino reaction sequences. In the article that follows, we hope to convince you of the veracity of all our introductory statements by giving a brief overview of our work, both past and current, employing singlet oxygen in the field of biomimetically inspired natural product syntheses.

2. Designing biomimetic syntheses using singlet oxygen

Herein, we shall see three different reactions of $^1O_2$, namely, [4+2][1] and [2+2][2] cycloadditions, and the ene-reaction.[3] Before one can consider designing a biomimetic strategy for the synthesis of any given natural product using $^1O_2$, the chief characteristics of each of the various modes of reaction of $^1O_2$ must be fully appreciated; for knowledge about the respective rates and preferences of each reaction mode is an essential prerequisite to the design of cascades that will work smoothly. As we shall soon see, we frequently encounter substrates where each of the different $^1O_2$ modes of reaction could be envisaged as being possible, and, because, $^1O_2$ is a highly reactive electrophilic species, unless we can control the order and timing of such reactions indiscriminate oxidation and degradation are the likely result. Fortunately, the reactions of $^1O_2$ have been studied extensively in simple substrates[4] providing us with key information that may now be used to extend the use of $^1O_2$ chemistry in the synthesis of the more complex molecules. Our first example of the application of a $^1O_2$-orchestrated biomimetic strategy, to the synthesis of a family of naturally occurring sesquiterpenes, the litseaverticillols, perfectly illustrates this point as selective reaction through one reaction mode at a time and regiochemical discretion are both of pivotal importance in this instance.

3. Synthesis of the litseaverticillols

The litseaverticillols are a family of related sesquiterpenes, isolated from a Vietnamese shrub, which possess interesting

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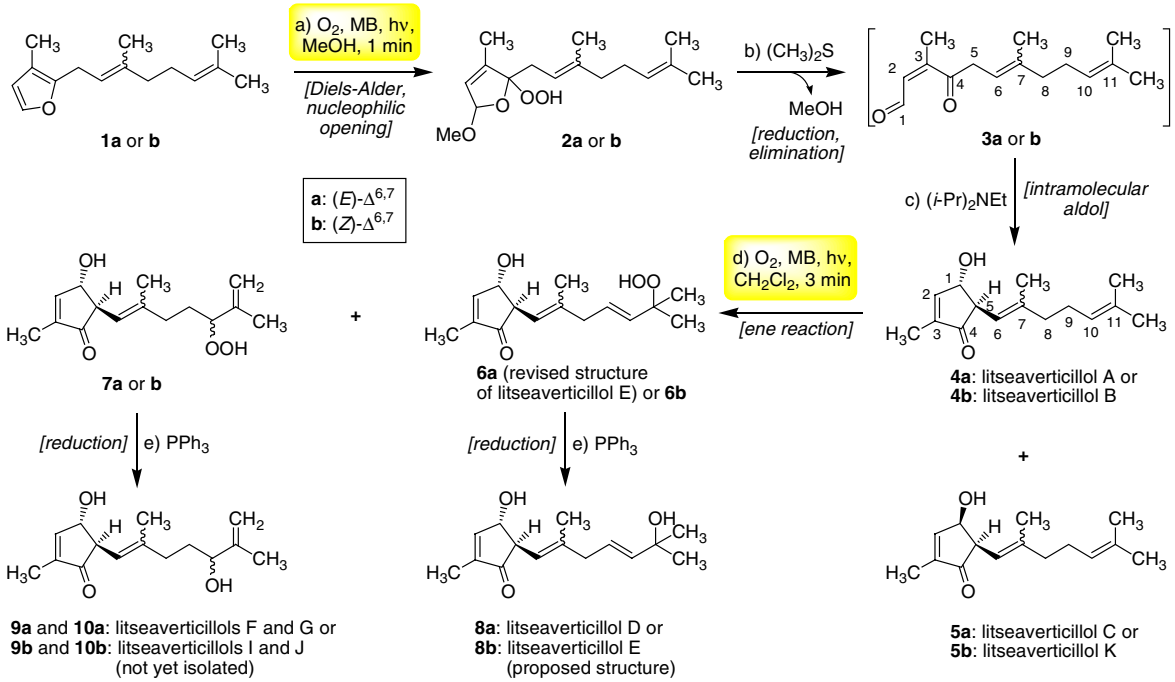
anti-HIV activity.[5] Upon close inspection of their structures, a possible biomimetic synthetic strategy presented itself to us. Our subsequent syntheses of litseaverticillols A–G, I and J[6] and the surprising structural reassignment for litseaverticillol E[7] would seem to provide ample empirical justification for the original hypothesis of their biogenesis (Scheme 1).

The structural features that informed our analysis regarding the natural origin of the litseaverticillol family are as follow: (1) the litseaverticillols could be subdivided into two generations with the second generation compounds (litseaverticillols D, E, F, G, I, and J) conceivably arising from the first generation congeners (litseaverticillols A, B, C, and K) through regioselective $^1O_2$-mediated ene-reactions taking place at the trisubstituted $\Delta^{10,11}$ bond, most distal from the 4-hydroxycyclopentenone core, of the pendent side chains. (2) likewise, the 4-hydroxycyclopentenone core could be envisaged to have been derived via a cascade reaction sequence beginning with the [4+2]-cycloaddition between a furan precursor and $^1O_2$.[8] Notably, at least one of the proposed furan precursors, sesquirosefuran (**1a**), is a known natural product.[9] Furthermore, observations made later on during our syntheses of the litseaverticillols would suggest that this single known furan **1a** might well be the natural progenitor to all the litseaverticillols (vide infra). (3) the litseaverticillols are racemates, a relatively rare occurrence in natural products (which are usually synthesized in a homochiral fashion by enzymes), prompting us to hypothesize that the entire cascade reaction sequence, which we proposed for the synthesis of the litseaverticillol core, does not take place under the orchestration of an enzyme. In summary, it was our belief that all the litseaverticillols are derived in nature from furan precursors via sequential and selective singlet oxygen mediated non-enzymatic reactions. The best way to test and refine this postulate was by synthesizing the compounds in the laboratory and so this is what we did.[6,7]

The furan precursors (**1a** and **b**) were assembled in short order.[6,7] A one-pot, five synthetic operation, biomimetic cascade was then developed (Scheme 1) that directly and efficiently furnished the first generation litseaverticillols A (**4a**), B (**4b**), C (**5a**), and K (**5b**).[10] The biomimetic cascade begins with the [4+2]-cycloaddition between the electron rich diene of the furan **1a** (or **b**) and singlet oxygen (generated using the sensitizer methylene blue and visible light irradiation for 1 min). The resultant endoperoxide adduct is then subjected to nucleophilic attack by the solvent, in this case methanol, to afford hydroperoxide **2a** (or **b**) as a single regio- and stereoisomer (as established by NOE studies). In nature the methanol must be replaced by water, thus affording the hydroxyl-analogue of **2**. Next, reduction of the hydroperoxide **2a** (or **b**) yields the anomeric hemiketals from which methanol is eliminated to furnish the achiral keto aldehyde **3a** (or **b**). Timely addition of Hünigs base to **3a** (or **b**) then promoted an intramolecular aldol reaction to furnish the first generation litseaverticillols A (**4a**) and C (**5a**) in 55% overall yield, or B (**4b**) and K (**5b**) in 51% overall yield depending on the initial substrate. It should be noted that litseaverticillols A (**4a**) and C (**5a**) exist in equilibrium with one another (A/C 19:1), as do litseaverticillols B (**4b**) and K (**5b**, B/K 20:1), thereby attesting to the reversibility of the aldol reaction (**3a** or **b**→**4a** or **b**). Furthermore, both litseaverticillols A (**4a**) and B (**4b**) could be obtained from the reaction of furan (**1b**), especially if litseaverticillol B (**4b**) was not isolated immediately but left in the basic solution for prolonged periods (>12 h), indicating that isomerization of the $\Delta^{6,7}$ bond is facile under the mildly basic reaction conditions. This isomerization most probably occurs via the retroaldol reaction of **4b** (or **5b**) to give the C-5 anion. This process yields a stabilized and extensively conjugated anion in which rotation about the



Scheme 1. Synthesis of the litseaverticillol family using a biomimetic $^1O_2$-orchestrated cascade reaction sequence.

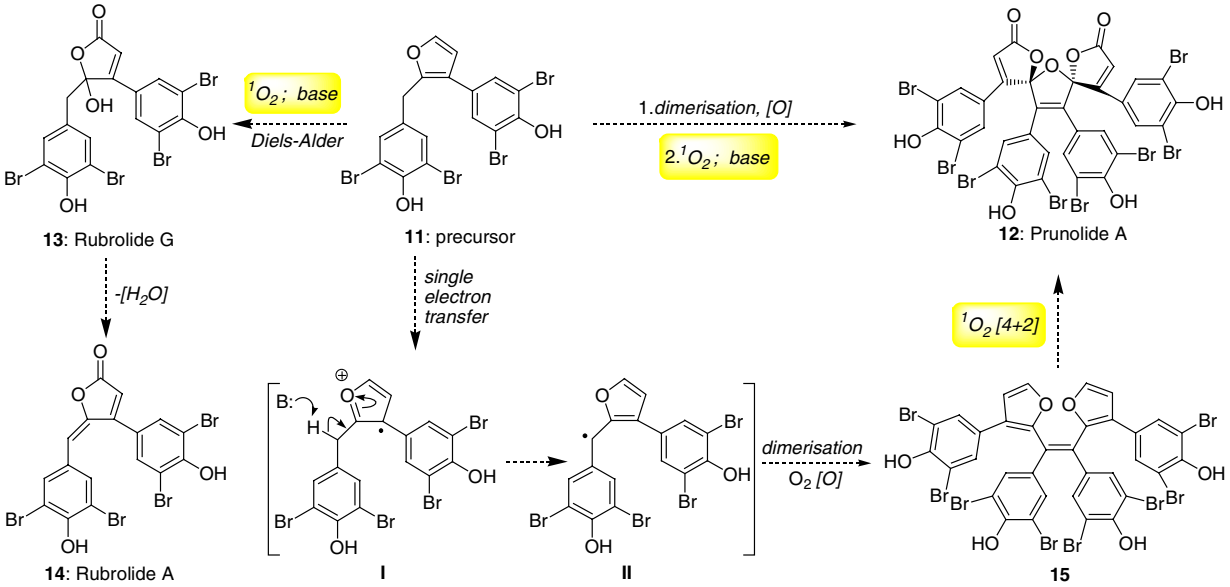
C-6/C-7 bond becomes feasible thus allowing for stereochemical scrambling. This observation is the origin of our proposed amendment of the biomimetic hypothesis to include the possibility that one furan (e.g., sesquirosefuran **1a**) could be the progenitor to all the litseaverticillols. This refinement to our proposal is in accord with the natural distribution seen for the various litseaverticillols.

The second generation litseaverticillols were then synthesized from their first generation parents using a second mode of $^1O_2$ reaction. Thus, a regioselective ene-reaction was employed to produce both of the two possible hydroperoxide-regioisomers from each substrate. A classic ene-reaction mechanism governs the formation of these two products; wherein the perepoxide intermediate forms such that the pendant oxygen atom sits preferentially over the more substituted side of the double bond, in a phenomenon known as the cis-effect,[3] it follows that there are then two positions from which a hydrogen atom can be abstracted. The ene-reaction only took place at the desired $\Delta^{10,11}$ bond, the other two, more electron deficient and/or hindered, olefins in the substrate proved to be unreactive. The hydroperoxide products were reduced to the corresponding alcohols using triphenylphosphine. Each of these so-formed alcohols represented a second generation litseaverticillol. Thus, through this two step procedure, litseaverticillol A (**4a**) fathered the tertiary alcohol litseaverticillol D (**8a**) and the diastereoisomeric secondary alcohols, litseaverticillols F and G (**9a** and **10a**, respectively). Likewise, when litseaverticillol B (**4b**) was subjected to the same two sets of reaction conditions, three new litseaverticillols were synthesized, litseaverticillols I (**9b**) and J (**10b**) [not yet isolated from natural sources, perhaps because of the low abundance of their parent, litseaverticillol B (**4b**)] and a compound possessing the structure proposed for litseaverticillol E (**8b**). In an unexpected turn of events, the spectral data we obtained for tertiary alcohol **8b** did not match those reported for litseaverticillol E.[5] After some detective work involving the reexamination of the reported spectral data for litseaverticillol E and comparison of it with spectral data for our intermediate compounds, it became obvious that the true structure of litseaverticillol E was that of the tertiary hydroperoxide **6a**.

The fact that we were able to make both the entire litseaverticillol family, systematically, and in relative ratios that reflected the natural abundance of the compounds, and reassign the structure of litseaverticillol E as being an intermediate en-route to the final products, strongly supports our biogenetic hypothesis for this sesquiterpene family. Furthermore, the two modes of reaction of $^1O_2$ that we used proved to be highly chemo- and regioselective with the [4+2]-cycloaddition occurring at a much faster rate than the subsequent ene-reaction. It is notable that other non-natural reagents (Br_2/MeOH/H_2SO_4[11] or magnesium monoperoxyphthalate[12]), known in the literature for the oxidation of furans to the corresponding (*Z*)-1,4-enediones, proved to be unselective in their reaction with our substrates, reacting both at the side chain double bonds and the furan core indiscriminately. Once again, this feature would seem to lend credence to the $^1O_2$ biogenesis hypothesis. From a practical standpoint the litseaverticillol synthesis reinforces the comment made at the beginning of this article that a good knowledge and understanding of the relative rates and selectivities for the reactions of $^1O_2$ are vital if it is to be employed successfully in complex biomimetic synthetic strategies.

4. Synthesis of the spirocyclic core of the prunolides

The prunolides are a family of architecturally beautiful cytotoxic natural products isolated in 1999 from a species of Australian colonial ascidian.[13] Our interest in these compounds was piqued not only by their compact and intricate C_2-symmetric bis-spiroketal core, but by the repeating occurrence of the butenolide moiety and by their isolation partners, the rubrolides (Scheme 2). The antibiotic rubrolide A (**14**), which was found within the same colonial ascidian extract as the prunolides, had also been isolated, along with other rubrolides, previously in 1991.[14] These latter features of interest immediately suggested a hypothesis for the



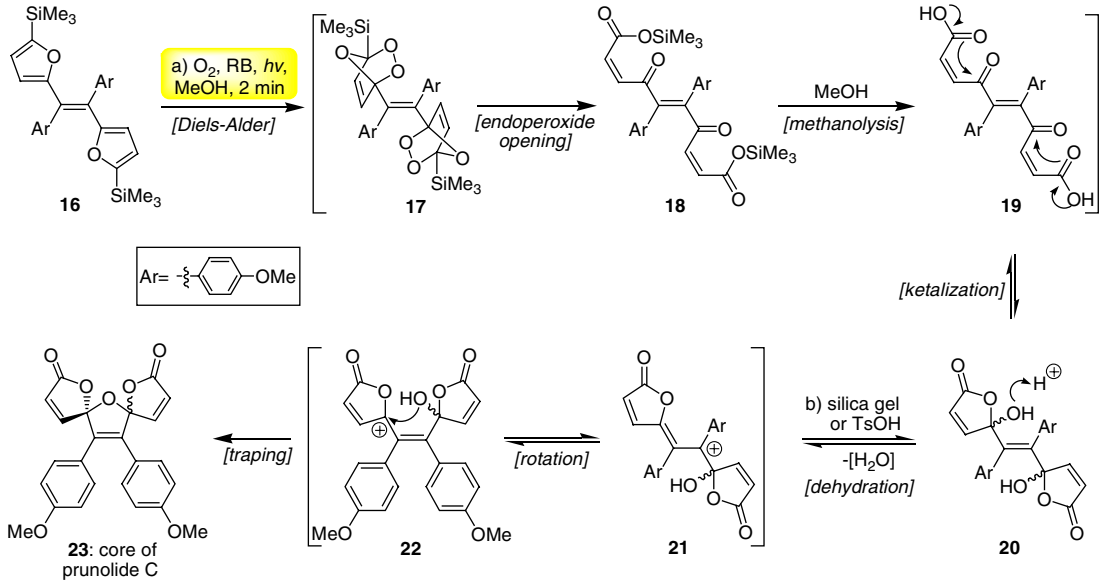
Scheme 2. Proposed biogenesis of the prunolide and rubrolide families of natural products.

prunolide/rubrolide biogenesis to us, which we intended to test through the vehicle of a laboratory synthesis.

At the heart of the biogenetic proposal lay the oxidation of furan precursors by $^1O_2$ and a key dimerization reaction that delineated the relationship, which we were proposing existed between the rubrolides and the prunolides. Thus, if we take the case of rubrolides A (**14**) and G (**13**) and prunolide A (**12**) as the example, we envisaged the existence of a common furan precursor **11** to these compounds (Scheme 2). Two different fates can reasonably be imagined for this precursor **11**. In the first, the furan moiety might be oxidized by $^1O_2$ directly to give the hydroxybutenolide rubrolide G (**13**). The production of hydroxylbutenolides from 2-substituted furans upon oxidation with $^1O_2$ is a well-known and studied reaction.[15,8b] Facile elimination of water from rubrolide G (**13**) would then furnish rubrolide A (**14**). The second possible destiny for the precursor **11** involves a single electron transfer-dimerization sequence. Thus, the furan moiety could possibly donate an electron to a single electron transfer oxidant (of which nature has an abundance) to form the radical cation intermediate I. The radical II may then form upon loss of a proton from the radical cation I. Radical II might conceivably dimerize to form a difuryl compound, which, it is reasonable to expect, might be readily oxidized by molecular dioxygen to afford the cascade precursor **15**. The envisaged cascade sequence is initiated by a double [4+2]-cycloaddition, occurring between the two furan moieties and $^1O_2$, to afford a diendoperoxide (e.g., **17**, Scheme 3) that we proposed might swiftly collapse to furnish a linear unsaturated diacid (e.g., **19**). Following double ketalisation and the elimination of a molecule of water, this diacid might yield prunolide A intact.

Excited by this biogenetic proposal, we immediately set forth on a synthetic program aimed at testing its essential postulates. We begun by working with a compound unencumbered by the peripheral functionalities in order to explore the validity of the concept.[16] A McMurray coupling was chosen to mimic the oxidative coupling step of the biogenetic proposal. Thus, from the corresponding ketone monomer (synthesized rapidly from furan itself[16]), dimer **16** and its *Z*-isomer were synthesized in good yield (72%, $Z/E \approx 1{:}3$) using the standard McMurray coupling conditions. Both the isomers, which were easily separated, were then investigated in the biomimetic reaction cascade sequence, however, for ease of discussion we have chosen to represent only the more interesting (vide infra) *E*-isomer in the scheme delineating the cascade outcome (Scheme 2).

Nature certainly does not include silicon groups in her substrates for the photooxygenation reactions, so why did we? It is known that the unsubstituted furans (where H replaces $SiMe_3$) do undergo the desired [4+2]-cycloaddition reaction[8] with $^1O_2$, however, the transformation of the resultant endoperoxide into the hydroxybutenolide using base[17] is known to be problematic.[18] This problem was confirmed in our case when we first tested the unsubstituted analogue of **16** in the photooxygenation cascade sequence. As a result, we were prompted to include the trimethylsilyl groups from the start. When 1,2-difuryl alkene **16** was subjected to standard photooxygenation conditions (10^{-4} M Rose Bengal as senitizer, O_2, MeOH, and visible spectrum irradiation) for 2 min the beautiful biomimetic cascade took place just as predicted (Scheme 3). Endoperoxide **17** was rapidly transformed through **18**[19] to the linear diacid **19**. The intermediary and labile bis-hydroxybutenolides **20** were observed by ^1H NMR spectroscopy. Upon treatment of butenolides **20** with traces of acid (TsOH), or on contact with silica gel, two readily separable bis-spiroketal products **23** were obtained in high yield (80% overall from **16**). The bis-spiroketals were a mixture of the cis and trans isomers (cis/trans $\approx 1{:}2$), the trans isomer representing the fully intact prunolide core. It should be noted that the *Z*- and *E*-isomer (**16**) of the starting 1,2-difuryl alkene compound produced identical results from the cascade sequence, indicating that the central double bond of **16** is the subject of isomerization during the course of this sequence (**21**→**22**). Hence we were able to access the prunolide core with remarkable ease from a simple dimer via an oxidative



Scheme 3. Synthesis of the core of the prunolide molecules using a biomimetic $^1O_2$-mediated cascade sequence.

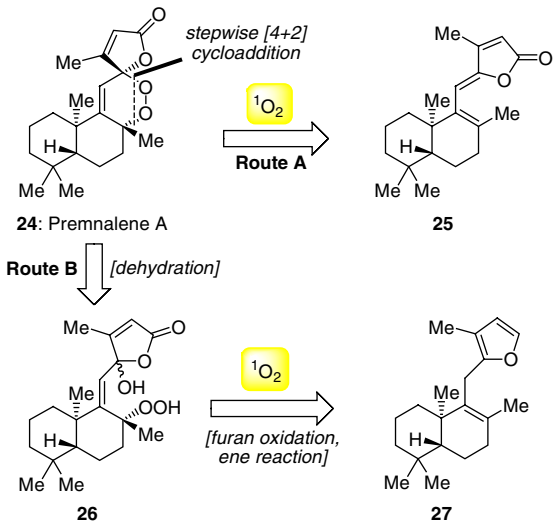
cascade sequence orchestrated by $^1O_2$ during which a linear molecule was zipped up to form this complicated bis-spiroketal core. Unfortunately, the venerable McMurray coupling has not proven to be robust enough to tolerate the more highly functionalized ketone monomers required to apply the elaborated cascade to the total syntheses of all the various prunolides. At present a modified approach to these molecules is, therefore, under investigation in our laboratories.

5. Towards the synthesis of premnalane A

Simple success stories are frequently less instructive than the analogous tales relating surprising and unpredicted results. For the latter can, and often do, inspire new approaches and strategies that otherwise would have remained unexplored. We shall now turn our attention to some recent results obtained in our laboratory, which, although not proceeding quite as planned, have thrown up some didactic observations and very useful ideas that we hope to convert into a new series of $^1O_2$ biomimetic syntheses in the near future.

Premnalane A (**24**, Scheme 4)[20] was isolated in 1991 from a shrub growing at high altitude in the Sidamo Province of Ethiopia. Its gross structure, as revealed by X-ray crystallography, was shown to be based upon an enantiomer of the known labdane skeleton. We were immediately attracted to this synthetic target because of its obvious $^1O_2$ roots. The six-membered peroxide ring bearing a spirocyclic unsaturated lactone was highly suggestive of a $^1O_2$-mediated cascade sequence. Our first retrosynthetic analysis for the key biomimetic $^1O_2$-orchestrated cascade is shown in Scheme 4 (Route A, **24**→**25**). In this analysis, we envisaged that the last step of the synthetic sequence would be a stepwise [4+2]-addition. Although rarer than their concerted cousins, stepwise [4+2]-additions are known, especially in cases where the diene partner cannot easily adopt a planar *s*-cis conformation (true of the hindered diene we were proposing).[21] The intermediate in the stepwise reaction may be either a biradical, or a bipolar species.[22] We proposed a stepwise [4+2]-addition to construct premnalane A's endoperoxide ring not only due to the hindrance of the starting diene, but also because of the trans-stereochemistry desired in the resultant endoperoxide. In order to test our hypothesis, we set forth on a program directed towards the synthesis of $^1O_2$-precursor **25**. It should be noted that it was clear to us from the beginning that a different series of $^1O_2$ reactions might be responsible for the assembly of premnalane A (Scheme 4, Route B). However, only a laboratory study of the various possibilities could shed light on which series of reactions likely to have been used by Nature herself. With this in mind we sought to introduce flexibility, at as many stages as possible, into our synthesis of the photooxygenation precursors.

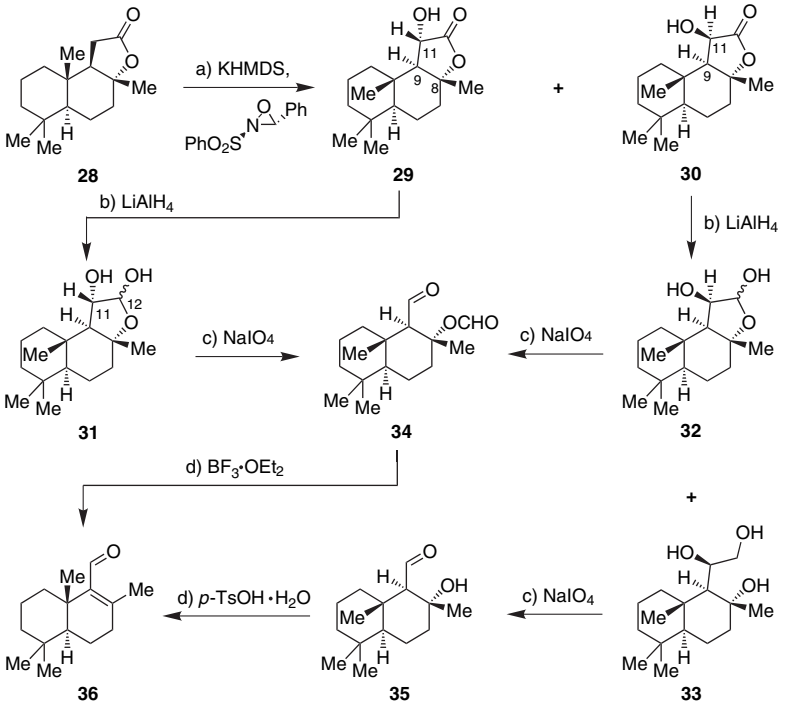
The decalin system of (+)-sclareolide (**28**), a commercially available compound, provided us with a suitable starting point for an initial investigation into our proposed biomimetic strategy for the synthesis of premnalane A. (+)-Sclareolide (**28**) possesses the enantiomeric stereochemistry at the decalin ring junction from premnalane A, but for the purposes of our initial investigations this was not important. We began with the installation of a hydroxyl group α to the



Scheme 4. Retrosynthetic analyses delineating the possible biogenetic origins for premnalane A.

lactone moiety of **28** by reaction of the enolate with Davis oxaziridine[23] (Scheme 5). This reaction proceeded in good yield (93%), with KHMDS as base, to afford a separable mixture of diastereomeric products, **29** and **30** (**29**:**30**≈1:1). The stereochemistry of **29** and **30** was assigned based on the coupling constant of the interaction between the adjacent C-9 and C-11 hydrogens, with the trans-relationship present in the more polar compound **29** having a larger value. These details proved important when we later became aware of the work of Quideau et al. in a similar system.[24] During their work towards the marine sponge metabolite, (+)-puupehenone, they took (+)-sclareolide (**28**) and first epimerized the C-8 stereocenter under acidic conditions. Following this epimerization, their attempts to introduce a hydroxyl group at C-11 (using Vedejs' $MoO_5\cdot$pyridine$\cdot$HMPA reagent system) were fraught with difficulties. LDA failed to deprotonate the precursor and they had to resort to use of magnesium bis(diisopropylamide) as base. Notably, only one C-11 hydroxyl diastereoisomer was seen in their study.

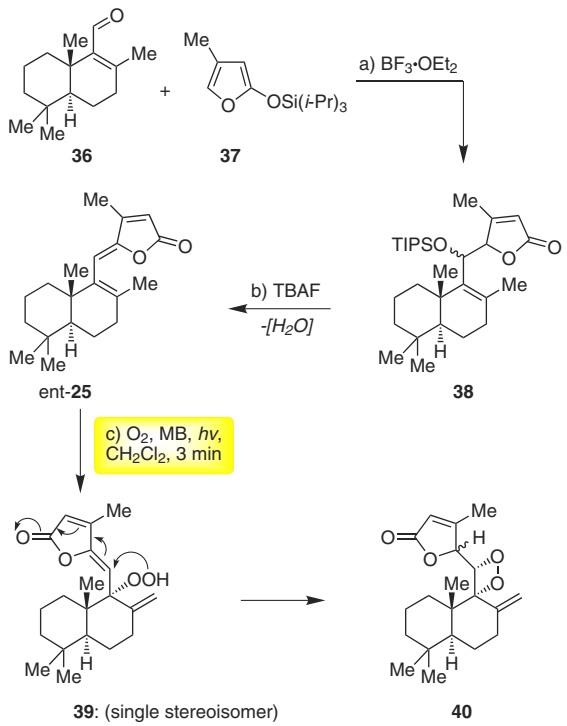
We next wished to reduce the newly acquired hydroxylactones, **29** and **30**, to triol **33** and its diastereoisomer. Surprisingly, however, upon treatment of **29** with $LiAlH_4$, diastereomeric lactols **31** were the sole products formed (H-11, H-12 trans/cis≈1.5:1). Use of excess $LiAlH_4$ had no effect on the outcome. Conversely, when hydroxylactone **30** was treated with $LiAlH_4$ a mixture of diastereomeric lactols **32** and triol **33** resulted (**32a**:**32b**:**33**≈1:1:2). The product ratio in this case was also unaffected by the amount of $LiAlH_4$ employed. Quideau et al.[24] had attempted to reduce their hydroxylactone (differing from **29** in the stereochemistry at C-8) to the corresponding triol using $LiAlH_4$, but had found that the reaction stopped at the intermediate lactol and could not be forced further. When they switched reducing agent and employed Dibal-H for the reduction a mixture of the lactol and the desired triol (lactol/triol≈1.2:1) was obtained, albeit with a low yield. We next examined the oxidative cleavages, using silica-supported $NaIO_4$,[25] of substrates **31**, **32**, and **33**. Cleavage of the lactols **31** and **32** furnished the formate **34**, whilst triol **33** afforded the aldehyde **35**. The divergence of the synthesis that we



Scheme 5. Preparation of α,β-unsaturated aldehyde **36**.

now had was of no concern to us because we were able, following the dehydration of **34** and **35** (combined with formate hydrolysis in the former case), to converge upon a single compound, the α,β-unsaturated aldehyde **36**. Furthermore, we optimized the sequence such that the mixtures obtained from the preceding reactions (installation of hydroxyl functionality and reduction) could be carried through the subsequent transformations without separation up to the dehydration step. Thus, reduction with $LiAlH_4$ of the mixture of diastereoisomers **29** and **30** afforded a mixture of **31**, **32**, and **33** (overall yield 93%) that was subjected, without separation, to oxidative cleavage using silica-supported $NaIO_4$ to furnish a mixture of **34** and **35** in 92% combined yield. Hydroxy aldehyde **35** could then be dehydrated by warming it up in toluene in the presence of catalytic *p*-TsOH to furnish α,β-unsaturated aldehyde **36** (yield 54%). In a similar fashion, formate **34** could be hydrolyzed and dehydrated using $BF_3 \cdot OEt_2$ at ambient temperature to afford **36** in excellent yield (95%).

With α,β-unsaturated aldehyde **36** in hand, we next sought to install the requisite unsaturated lactone moiety. This task was readily accomplished by using a $BF_3 \cdot OEt_2$-mediated Mukaiyama aldol to couple the aldehyde **36** with an excess of 2-triisopropylsilyloxyfuran **37** to give diastereoisomeric unsaturated lactones **38** (3:1 mixture of isomers) in a yield of 63% (Scheme 6). Deprotection with concomitant dehydration of **38**, under the influence of TBAF, afforded the $^1O_2$ reaction precursor diene *ent*-**25** as a single geometric isomer in high yield (89%). The stage was now set to test the hypothesis regarding the stepwise [4+2]-addition of singlet oxygen to the diene. When diene *ent*-**25** was treated with $^1O_2$, generated using methylene blue as a sensitizer and visible spectrum irradiation, in dichloromethane for 3 min, diastereomeric dioxetanes **40** were the only products (isolated yield 96%, major/minor isomer ≈ 1.5:1). Once again, just as we saw in the synthesis of the litseaverticillols (vide supra), this result underscores the importance of garnering an intricate knowledge about the relative rates and preferences of the possible modes of $^1O_2$ reaction in a given substrate. For, without this information the correct biomimetic cascade sequence toward the synthetic target cannot readily be identified. In this instance, the desired product (i.e., *ent*-

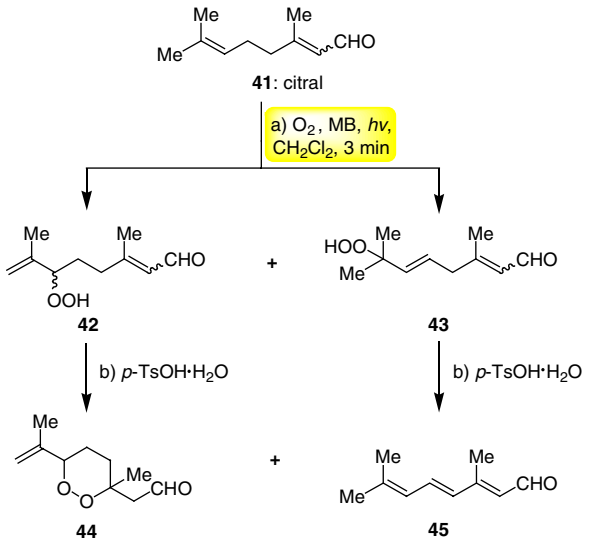


Scheme 6. Abortive attempts to synthesize *ent*-premnalane A: synthesis of dioxetane **40**.

premnalane A *ent*-**24**) was not obtained because a stereoselective ene-reaction between $^1O_2$ and the endocyclic double bond of *ent*-**25** was faster than the corresponding stepwise [4+2]-addition reaction. The product of the ene-reaction, hydroperoxide **39**, then underwent an intramolecular conjugate addition reaction to afford **40**. If the reaction was carried out in benzene at 6 °C, intermediate hydroperoxide **39** could be separated by column and analyzed by ^{1}H NMR spectroscopy, because a mixture of **39** and **40** was obtained (**39**:**40** ≈ 1:1.6).

We have now redesigned and refined our hypothesis regarding the details of the biomimetic cascade sequence, which might afford premnalane A (**24**), taking into account the new information that was revealed by our initial foray. Thus, we now believe that premnalane A (**24**) might arise in nature when a furan precursor, such as **27** (Scheme 4), is subjected to a $^1O_2$-orchestrated cascade reaction sequence. We expect based upon our litseaverticillol work that first the furan moiety of **27** will undergo a [4+2]-cycloaddition with $^1O_2$. In the presence of a base the labile endoperoxide so-formed should collapse to afford the hydroxybutenolide.[17] We then anticipate an ene-reaction might occur with the endocyclic double bond to regio- and stereoselectively form hydroperoxide **26**. It is our postulate that the negative steric interactions between the methyl group, situated at the ring junction, and the butenolide moiety of the ene-reaction substrate will force the latter group to sit above the face of the decalin system opposite to this large axial group. This confirmation will then govern the stereoselectivity of the initial addition of $^1O_2$ to the double bond through steric and electronic interactions.[3,26] Modeling and mechanistic precedent regarding the cis-effect[3] and the large group effect[27] would indicate that hydrogen abstraction from this intermediate would then occur to yield regioisomer **26** exclusively.

This new and exciting analysis of the biogenetic origins of premnalane A (**24**) has now become the subject of an investigation in our laboratory and we hope to be in a position to communicate the initial results soon. Meanwhile, the fact that we obtained isomer **40** during our first foray towards premnalane A (**24**) has prompted us to explore this type of conjugate addition further. A host of interesting and biologically active natural products contain five[28]- or six[28,29]-membered endoperoxide rings. We propose that this motif arises in nature following conjugate addition of the hydroperoxide obtained from the ene-reaction between $^1O_2$ and a specified fatty acid, or terpenoid, unsaturated precursor. We have now completed a proof of concept study for this hypothesis (Scheme 7), and, intend, in the near future, to apply it towards the synthesis of a new set of natural products.



Scheme 7. Proof of principle: synthesis of six-membered peroxide moieties using a biomimetic $^1O_2$-faciltated approach.

6. Conclusion

Herein, we have described highlights from the successful syntheses of the litseaverticillol family of natural products and from the synthesis of the core of the prunolide molecules, using powerful $^1O_2$-orchestrated biomimetic strategies. In these syntheses, cascade reaction sequences initiated by the reaction of $^1O_2$ with a furan and the ene-reaction of $^1O_2$ with double bonds proved to be crucial tools that allowed the respective molecules to be rapidly assembled from simple precursors. We also introduced our most recent $^1O_2$-facilitated synthetic strategies used in our approaches to the synthesis of premnalane A. Here we use a number of different reactivities of $^1O_2$, thus completing a brief survey of how $^1O_2$ chemistry may be fruitfully employed in the synthesis of complex secondary metabolites.

$^1O_2$ is a benign and environmentally sound biomimetic reagent that is extremely versatile in a synthetic capacity. Furthermore, the use of $^1O_2$ avoids unnecessary waste because protecting groups are rarely, if ever, required in $^1O_2$ reaction cascades. Despite the obvious utility of $^1O_2$, its application in natural product synthesis is rarer than might be expected. One suspects the reason being that the relative rates and chief characteristics of its various modes of reaction are not widely appreciated. We hope that our examples described herein will go some way to rectify this situation so that the beautiful and powerful chemistry of $^1O_2$ will in the future find many more applications in biomimetic natural product syntheses.

7. Experimental

7.1. Diastereomeric 11-hydroxysclareolides 29 and 30

To KHMDS (1.53 g, 7.68 mmol), in anhydrous THF (40 mL), under argon, and at −20 °C, was added dropwise a solution of sclareolide (1.20 g, 4.8 mmol) in anhydrous THF (40 mL). The reaction mixture was allowed to warm from −20 to −10 °C over 50 min. Afterwards the reaction mixture was recooled to −30 °C and a solution of Davis oxaziridine (2.13 g, 8.16 mmol) in anhydrous THF (50 mL) was added dropwise. The mixture was then allowed to warm from −30 to −10 °C over 40 min. The reaction was quenched upon addition of H_2O (4 mL), warmed to 0 °C, and Et_3N (4 mL) added. After stirring for 5 min, 5% aq HCl (150 mL) was added and stirring was continued for further 20 min. The reaction mixture was diluted with Et_2O, washed with saturated aq Na_2CO_3 and then brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexane/

EtOAc 6:1→2:1) to afford 0.59 g of the less polar epimer **30** and 0.60 g of the more polar epimer **29** (93% combined yield).

7.2. Lactols 31 and 32, and triol 33

To a solution of $LiAlH_4$ (228 mg, 6.0 mmol) at 0 °C in anhydrous THF (5 mL) was added dropwise a solution of the two diastereomeric 11-hydroxysclareolides **29** and **30** (1.04 g, 3.91 mmol) in anhydrous THF (10 mL). The reaction mixture was allowed to warm to ambient temperature with stirring over 30 min, before a few drops of EtOAc were added as a quench. The reaction mixture was diluted with EtOAc and washed two times with a saturated solution of Rochelle's salt. The combined aqueous layers were extracted with EtOAc. The combined organic layers were then dried (Na_2SO_4) and concentrated in vacuo. The crude material was employed in the next step without further purification (0.98 g, 93%).

7.3. Formate 34 and hydroxyl aldehyde 35

A suspension of silica gel-supported $NaIO_4$ reagent (7.34 g) was stirred vigorously in dry CH_2Cl_2 (18 mL). To this suspension was added a dropwise solution of the crude mixed of **31**, **32**, and **33** obtained from the previous reaction (see above) in dry CH_2Cl_2 (18 mL). The reaction mixture was stirred for 5 min. The mixture was then filtered through a sintered glass funnel to remove the silica gel, which was washed with copious quantities of EtOAc. The solvent was removed from the combined filtrates and the residue purified by flash column chromatography (silica gel, hexane/EtOAc 9:1→4:1) to afford two products—formate **34** (0.0.69 g, 71%) and hydroxyl aldehyde **35** (0.18 g, 21%).

34: ^{1}H NMR (500 MHz, $CDCl_3$): δ=9.98 (d, J=3.9 Hz, 1H), 7.91 (s, 1H), 2.55 (td, J_1=12.8 Hz, J_2=3.5 Hz, 1H), 2.49 (d, J=3.9 Hz, 1H), 1.85 (s, 3H), 1.84 (m, 1H), 1.76 (m, 1H), 1.64 (m, 2H), 1.42 (m, 3H), 1.20 (m, 2H), 1.17 (s, 3H), 0.99 (dd, J_1=12.4 Hz, J_2=2.1 Hz, 1H), 0.88 (s, 3H), 0.82 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ=204.0, 159.8, 85.6, 68.6, 54.8, 41.4, 39.7, 39.6, 38.8, 33.2, 33.0, 22.0, 21.3, 19.8, 17.9, 17.0 ppm.

35: ^{1}H NMR (500 MHz, $CDCl_3$): δ=9.98 (d, J=1.4 Hz, 1H), 3.20 (br s, OH), 2.04 (br s, 1H), 1.90 (br d, J=12.6 Hz, 1H), 1.78 (td, J_1=12.6 Hz, J_2=3.2 Hz, 1H), 1.66 (m, 2H), 1.44 (m, 3H), 1.35 (s, 3H), 1.29 (dq, J_1=12.3 Hz, J_2=3.2 Hz, 1H), 1.17 (tt, J_1=13.3 Hz, J_2=3.8 Hz, 2H), 1.08 (s, 3H), 0.93 (dd, J_1=12.2 Hz, J_2=2.0 Hz, 1H), 0.86 (s, 3H), 0.80 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ=208.0, 72.7, 71.2, 55.0, 42.7, 41.5, 39.7, 37.3, 33.2, 33.1, 25.2, 21.3, 19.8, 18.1, 17.4 ppm.

7.4. α,β-Unsaturated aldehyde 36 (from formate 34)

To a solution of formate **34** (0.43 g, 1.62 mmol) in dry CH_2Cl_2 (60 mL) was added dropwise $BF_3\cdot Et_2O$ (0.1 mL, 0.81 mmol). The reaction mixture was allowed to stir for 24 h at ambient temperature. The mixture was washed with saturated aq $NaHCO_3$, dried (Na_2SO_4), and concentrated in vacuo to afford the α,β-unsaturated aldehyde **36** (0.34 g, 95%).

7.5. α,β-Unsaturated aldehyde 36 (from hydroxy aldehyde 35)

To a solution of hydroxy aldehyde **35** (30 mg, 0.126 mmol) in toluene (2 mL) in a sealed tube was added p-TsOH·H_2O (3.0 mg, 12 mol %). The reaction mixture was allowed to stir at 50 °C for 1 h. It was then diluted with Et_2O and washed two times with saturated aq $NaHCO_3$ and with brine. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc 8:1→5:1) to afford α,β-unsaturated aldehyde **36** (15 mg, 54%).

36: ^{1}H NMR (500 MHz, $CDCl_3$): δ=10.04 (s, 1H), 2.55 (br d, J=12.0 Hz, 1H), 2.26 (m, 2H), 2.02 (s, 3H), 1.71 (m, 1H), 1.62 (m, 1H), 1.45 (m, 3H), 1.18 (s, 3H), 1.17 (m, 1H), 1.08 (dd, J_1=12.6 Hz, J_2=1.9 Hz, 1H), 0.97 (dt, J_1=13.2 Hz, J_2=3.7 Hz, 1H), 0.89 (s, 3H), 0.86 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ=192.6, 153.5, 143.6, 51.5, 41.5, 37.5, 36.5, 36.2, 33.4, 33.2, 21.6, 20.1, 19.1, 18.8, 18.2 ppm.

7.6. Mukaiyama aldol product 38

To a solution of α,β-unsaturated aldehyde **36** (110 mg, 0.5 mmol) in dry CH_2Cl_2 (5 mL) was added a solution of 2-triisopropylsilyloxyfuran **37** (378 mg, 1.5 mmol) in dry CH_2Cl_2 (5 mL). The reaction mixture was cooled to −78 °C and $BF_3\cdot Et_2O$ (63 μL, 0.5 mmol) was added dropwise. The resulting mixture was allowed to warm to −40 °C and it was then quenched with saturated aq $NaHCO_3$. Following this quench, the reaction mixture was allowed to warm to ambient temperature. The solution was diluted with CH_2Cl_2 and washed two times with saturated aq $NaHCO_3$ and then brine. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc 8:1→6:1) to afford the coupled product **38** (150 mg, 63%).

7.7. Diene *ent*-25

To a solution of **38** (70 mg, 0.15 mmol) at 0 °C in anhydrous THF (2 mL), under an argon atmosphere, was added TBAF (0.3 mL, 1.0 M solution in anhydrous THF). The resulting solution was allowed to warm to ambient temperature and was then stirred for a further 12 h. The solution was diluted with Et_2O and washed with brine. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc 20:1→18:1) to afford the diene *ent*-**25** (40 mg, 89%).

ent-**25**: ^{1}H NMR (500 MHz, $CDCl_3$): δ=5.89 (s, 1H), 5.75 (br s, 1H), 2.18 (s, 3H), 2.13 (br m, 2H), 1.70 (br m, 1H), 1.60 (br m, 3H), 1.53 (s, 3H), 1.43 (m, 3H), 1.20 (m, 2H), 1.02 (s, 3H), 0.90 (s, 3H), 0.85 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ=170.0, 154.4, 150.1, 134.5, 132.4, 115.7, 110.2, 50.9, 41.6, 38.5, 38.2, 33.3 (2C), 33.1, 21.7, 21.4, 20.4, 18.9, 18.6, 12.2 ppm.

7.8. Diastereomeric dioxetanes 40

A solution of diene *ent*-**25** (20 mg, 0.066 mmol) in CH_2Cl_2 (3 mL), containing methylene blue (10^{-4} M), was placed

in a test tube with O_2 gently bubbling through it. Irradiation with a Xenon Variac Eimac Cermax 300 W lamp for 2.5 min at –40 °C leads to complete tranformation of the starting material (based on TLC). The solvent was removed in vacuo to yield the diastereomeric dioxetanes **40** (21 mg, 96%).

Alternatively, the reaction could be carried out in benzene using TTP (tetraphenylporphyrin) as sensitizer. In this case, irradiation for 3 min at 6 °C afforded a mixture of **39**:**40** that could be separated and purified by column chromatography (silica gel, hexane/EtOAc 10:1→6:1)

39: ^{1}H NMR (500 MHz, $CDCl_3$): δ=8.71 (s, –OOH), 5.97 (s, 1H), 5.50 (s, 1H), 5.14 (s, 1H), 4.83 (s, 1H), 2.62 (dt, J_1=13.4 Hz, J_2=8.1 Hz, 1H), 2.35 (qd, J_1=13.4 Hz, J_2=2.3 Hz, 1H), 2.21 (d, J=1.3 Hz, 3H), 1.99 (dd, J_1=12.8 Hz, J_2=3.0 Hz, 1H), 1.75 (m, 2H), 1.50–1.13 (m, 6 H), 1.01 (s, 3H), 0.92 (s, 3H), 0.85 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ=169.0, 155.9, 149.5, 147.9, 115.8, 113.5, 110.3, 92.3, 46.0, 45.2, 41.6, 33.9, 33.8, 33.7, 32.5, 23.1, 22.5, 18.9, 18.3, 12.5 ppm.

40: ^{1}H NMR (500 MHz, $CDCl_3$): δ=5.83 (br t, J=1.4 Hz, 1H, minor), 5.79 (br t, J=1.4 Hz, 1H, major), 5.78 (d, J=9.5 Hz, 1H, minor), 5.60 (d, J=9.5 Hz, 1H, major), 5.06 (br d, J=1.5 Hz, 1H major plus 1H minor), 4.91 (br t, J=1.8 Hz, 1H, major), 4.80 (d, J=9.5 Hz, 1H, major), 4.76 (d, J=9.5 Hz, 1H, minor), 4.54 (br t, J=1.9 Hz, 1H, minor), 2.55 (qd, J_1=13.0 Hz, J_2=2.2 Hz, 1H, major), 2.50 (qd, J_1=13.0 Hz, J_2=2.2 Hz, 1H, minor), 2.15 (m, 1H, minor), 2.00 (s, 3H, minor), 1.96 (s, 3H, major), 1.79 (m, 1H major plus 1H minor), 1.68–1.06 (m, 9H major plus 8H minor), 0.99 (s, 3H major plus 3H minor), 0.89 (s, 3H, major), 0.88 (s, 3H, minor), 0.87 (s, 3H, major), 0.86 (s, 3H, minor) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, major isomer): δ=173.9, 169.0, 162.5, 144.6, 116.3, 113.4, 111.9, 83.4, 54.1, 42.4, 41.7, 37.7, 37.5, 34.2, 33.6, 23.5, 22.2, 22.1, 19.9, 14.3 ppm; ^{13}C NMR (125 MHz, $CDCl_3$, minor isomer): δ=173.5, 169.0, 161.5, 146.3, 117.1, 112.7, 112.5, 82.7, 53.2, 42.2, 41.8, 37.5, 37.2, 34.2, 33.5, 23.6, 22.8, 22.5, 21.2, 14.3 ppm.

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