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Total synthesis of taxane terpenes: cyclase phase

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Dedicated to Professor Melanie S. Sanford on the occasion of her receipt of the Tetrahedron Young Investigator Award

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ABSTRACT

A full account of synthetic efforts toward a lowly oxidized taxane framework is presented. A non-natural taxane, dubbed 'taxadienone', was synthesized as our first entry into the taxane family of diterpenes. The final synthetic sequence illustrates a seven-step, gram-scale, and enantioselective route to this tricyclic compound in 18% overall yield. This product was then modified further to give (+)-taxadiene, the lowest oxidized member of the taxane family of natural products.

1. Introduction

Taxanes represent a large family of terpenes comprising over 350 natural products, of which many exhibit cytotoxic activity against various types of cancer and also display interesting neurological and antibacterial properties.[1] The most celebrated example of these diterpenoids, from both medicinal and structural standpoints, is Taxol® (**1**; Fig. 1).[1a,d,e] Its success as an anti-cancer drug, its densely functionalized and complex structure, and its unique mechanism of action involving the stabilization of microtubules[2] have fascinated medicinal chemists, synthetic chemists, and biologists alike. While chemical synthesis seems to be no longer needed to solve a supply problem for this particular drug, synthetic chemistry is able to modify biologically active structures in ways that synthetic biology cannot.[3] Coupled with the opportunity to invent new methods using a complex framework, this natural product appeared to us as an ideal target for an endeavor in organic synthesis.[4–7]

A general two-phase design for the construction of terpenes was recently formulated using eudesmane sesquiterpenes as a proof of concept.[8] In Nature, oxidized eudesmanes such as eudesmantetraol (**2**) most likely arise from C–H oxidation[9] of **3** or **4**, which in turn arise from farnesyl pyrophosphate (**5**). In a similar vein, a laboratory two-phase approach allowed for the simplification of target **2** into a lowly oxidized eudesmane framework such as dihydrojunenol (**6**), followed by retrosynthetic disconnections into simple starting materials such as methyl vinyl ketone and isovaleradehyde.[10] Our next objective is to target Taxol® (**1**) while retaining the same line of logic. Since Taxol® (**1**) is one of the most highly oxidized taxanes, a two-phase terpene synthesis strategy that targets Taxol® (**1**) would also generate other taxanes that are lower in oxidation level.[11] The ultimate goal is to divergently access as many 'pre-Taxol®' compounds as possible (both natural and unnatural) and to learn about the innate reactivity of the taxane framework through various C–H oxidation strategies.

Structurally, Taxol® (**1**) and other taxanes are highly functionalized diterpenes with a captivating 6–8–6 tricyclic skeleton and a bridgehead olefin. It is adorned with many acetyl and benzoyl groups, as well as a signature side chain at the C13 oxygen atom (see carbon numbering on **1**). For retrosynthetic analysis purposes, **1** is treated as if it was devoid of acyl groups and is substituted with oxygenated hydrocarbon **7**. Many oxidized taxanes have in common a C2-hydroxyl group and can be envisioned to arise from taxa-4(5),11(12)-dien-2-one, or 'taxadienone' (**10**; quotation marks in the text are removed hereinafter for brevity). This ketone represents a key intermediate for a comprehensive access to the taxane

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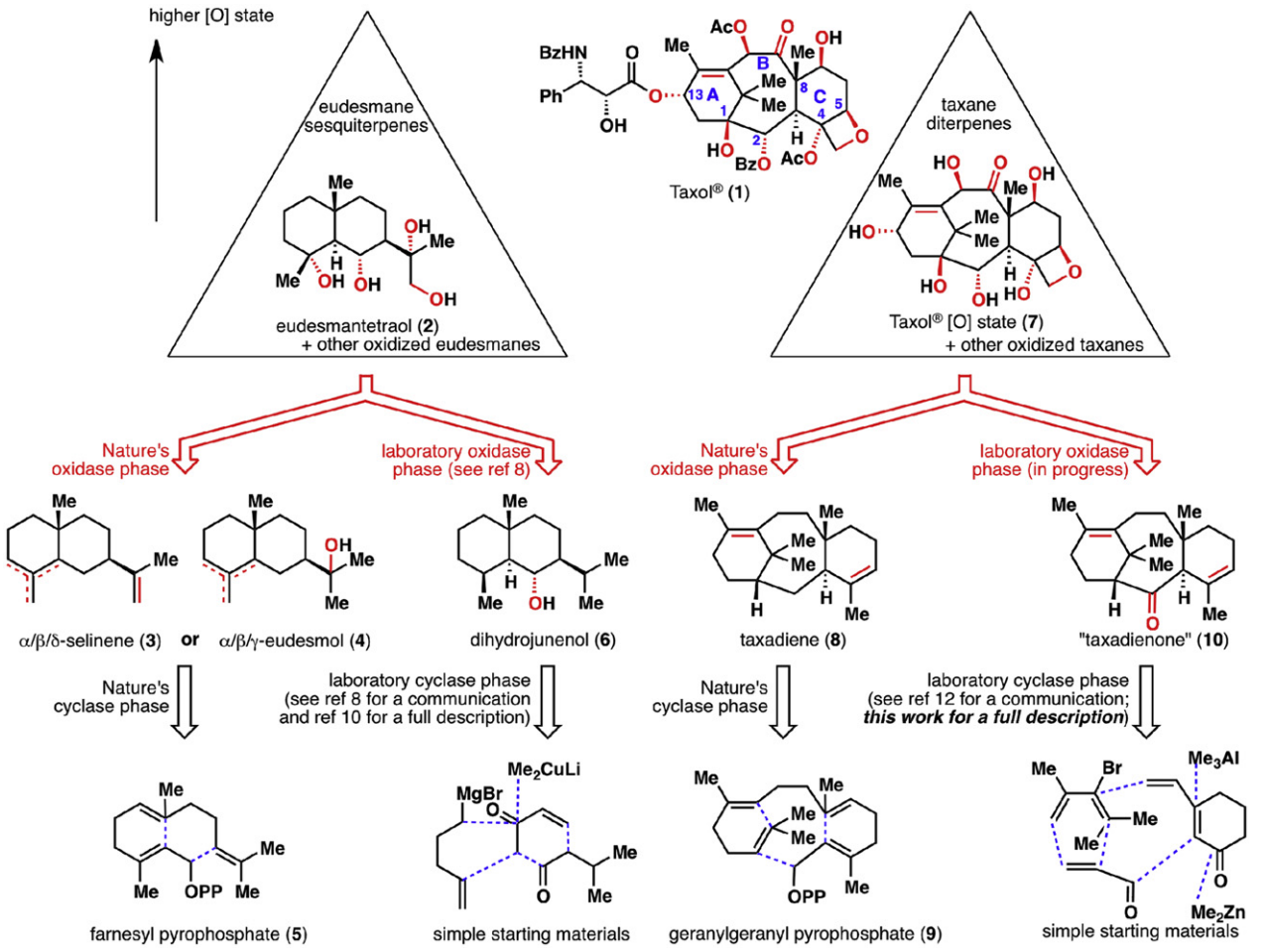

Fig. 1. A two-phase biosynthesis versus terpene synthesis in the eudesmane and taxane families of natural products. [O]=oxidation.

family because it would allow for both the natural C2α-alcohol series and the unnatural C2β-alcohol series. Furthermore, if taxadiene (**8**), the least oxidized natural product[1c] in the taxane family, was to be desired, one could simply deoxygenate **10**. Thus, taxadienone (**10**) became the target of our cyclase phase endpoint, which would serve as the diverging starting point toward polyhydroxylated taxanes. The synthesis of both taxadienone (**10**) and taxadiene (**8**) has been reported in an earlier communication[12] and is described herein as a full account.

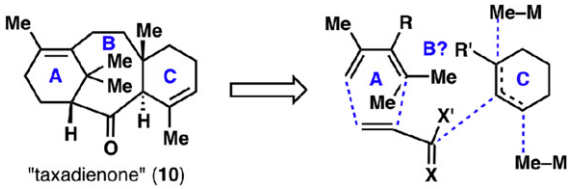

Fig. 2. Early retrosynthetic disconnections for taxadienone (**10**).

2. Results and discussion

2.1. Initial strategies and failed approaches

Considering the wealth of chemical knowledge surrounding the synthesis of the taxane framework,[4–7] there were so many retrosynthetic routes that could be followed toward the synthesis of taxadienone (**10**). While each synthesis has its strengths and weaknesses, we were particularly drawn to Nicolaou's route,[4c] which involved a Diels–Alder reaction to set the A-ring (see ring numbering on **1** in Fig. 1). For the C-ring, judging from the absence of functional groups in **10**, a simple cyclohexane-based starting material was deemed best. Numerous experimental explorations and strategy revisions then came from the synthesis of the B-ring (Fig. 2).

Many other previous attempts at making the taxane skeleton employed a Diels–Alder route for the A-ring,[6,7] possibly because of its isohypsic and atom-economical nature. These studies, as well as Nicolaou's A-ring synthesis,[4c] employed a trimethylated butadiene component for their Diels–Alder reactions. The most commonly used diene fragments, along with the number of steps it takes to make them, are shown in Fig 3A. Regarding the taxane C-ring, cyclohexane starting materials[13] that were deemed useful are listed in Fig. 3B.

With a collection of A-ring precursors and C-ring frameworks ready to use, potentially useful A-ring/C-ring coupled compounds were synthesized (Fig. 4). Many of these were generated as a mixture of inseparable diastereomers (**38**, **40**, **41**, **45**–**48**, **50**), presenting early problems in the designed routes. Furthermore, many of these steps were only feasible in low yields and were not scalable.

Despite the drawbacks in yield and diastereoselectivity in forming many of the compounds presented in Fig. 4, these intermediates were used in a number of approaches toward the B-ring, and a snapshot of many of the evaluated strategies toward taxadienone (**10**) is illustrated in Fig. 5. For example, the known

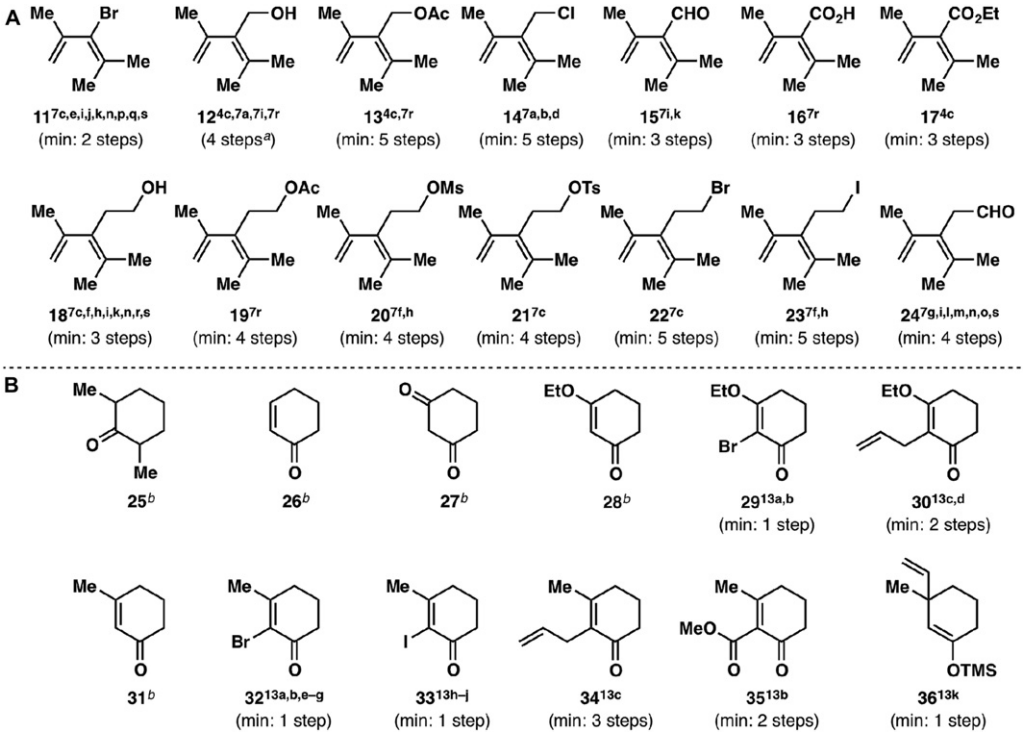

Fig. 3. (A) Dienes that have been used in various taxane core syntheses.[4c,7a–s] (B) Potentially useful cyclohexane starting materials to serve as the taxane C-ring.[13] The reported minimum number of steps to make these dienes and cyclohexanes are listed for comparison. Note: [a]Diene **12** can be made in one step from tetramethylallene and formaldehyde using a thermal ene reaction,[7a] but tetramethylallene is prohibitively expensive at >$200/g (Sigma–Aldrich, April 2013). [b]Commercially available as of April 2013.

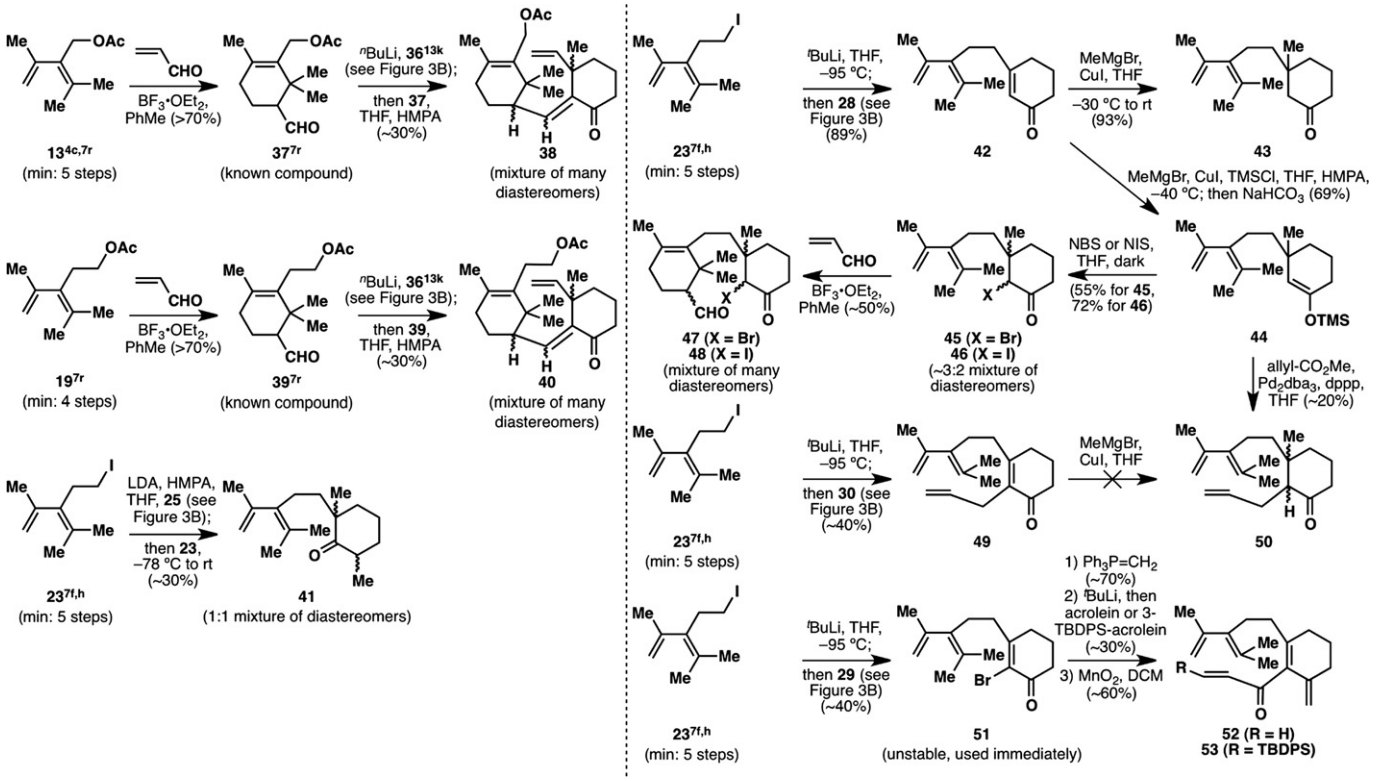

Fig. 4. Selected examples of A-ring/C-ring coupled compounds in initial studies.

difficulties in forming the taxane skeleton[4] led us to consider a ring-closing metathesis (RCM) strategy to forge the central eight-membered ring since olefin metathesis is a robust method to synthesize medium-sized rings (Fig. 5, disconnection A). However, the fact that the required substrate **54** would take many steps to build and that the stereocenters at C1 and C8 would have to be formed with two separate enantioselective reactions dissuaded us from this route. An aldol route was then conceived, partly because the required

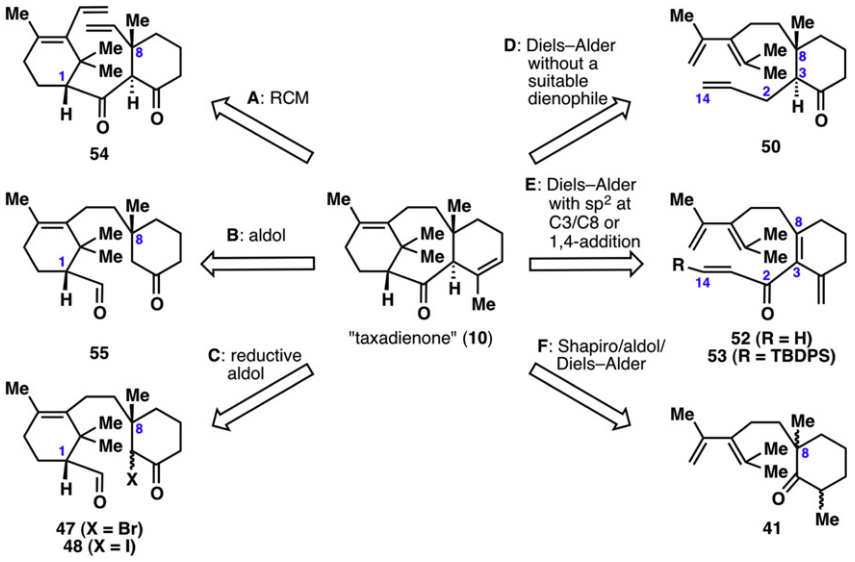

Fig. 5. Initial synthetic investigations toward the synthesis of taxadienone (**10**). Disconnection A: a ring-closing metathesis (RCM) approach would require many steps to even reach the key intermediate **54**. Disconnection B: the required aldol closure from **55** simply did not proceed. Disconnection C: the required reductive aldol closure from **47** or **48** did not proceed. Disconnection D: without a suitable dienophile (i.e., using an electronically neutral olefin), the Diels–Alder reaction did not proceed under thermal or radical cation conditions. Disconnection E: with sp^2 carbons at C3 and C8, the Diels–Alder reaction did not proceed even under radical cation conditions, and conjugate addition at C8 to install the methyl unit did not proceed because only the undesired conjugate addition onto C14 occurred. Disconnection F: a Shapiro reaction with an acrolein trap, followed by oxidation and Diels–Alder reaction, would not lead to an enantioselective synthesis of **10** because the stereochemistry at C8 could not be set selectively.

diketone **55** can be easily synthesized from ketone **43** (disconnection B). However, despite a plethora of attempted experiments using various Lewis and Brønsted acids and bases, the desired cyclization from **55** did not proceed. Similar failures were met when attempting Reformatsky-type cyclizations from **47** or **48** using reducing agents such as Zn,[14a,b] SmI_2,[14c] $CrCl_2$,[14d] $Co(PPh_3)_4$[14e] or Et_3B[14f] (disconnection C). Thereafter, closure of the AB ring by a Diels–Alder reaction was envisioned. While allylated ketone **50** does not contain a suitable dienophile for a normal-demand Diels–Alder reaction, it was hoped that a proximity-induced Diels–Alder reaction[15] of an electronically neutral dienophile would take place (disconnection D). However, thermal conditions or radical cation conditions using triarylamine hexachloroantimonate[16] did not allow closure of the B-ring. In a similar vein, Diels–Alder reaction of substrates **52** and **53** was attempted under thermal or radical-based conditions (disconnection E). These intermediates did not undergo [4+2] cyclization, likely due to the conformation engendered by the sp^2 carbons at C3 and C8. Furthermore, a methyl 1,4-addition at C8 was not possible, since reaction first occurred at the less hindered C14, even with a large *tert*-butyldiphenylsilyl group appended at C14. Lastly, ketone **41** was considered a viable intermediate toward the formation of taxadienone (**10**), since a Shapiro reaction with acrolein trap, oxidation, and Diels–Alder reaction could potentially form an isomer of **10** (disconnection F). However, ketone **41** already required six steps to construct (see Fig. 4), and the stereocenter at C8 was thought to be challenging to control despite existing methods in asymmetric enolate alkylation.[17]

During these initial studies, a convenient 1,6-addition of diene **11** onto known vinylcyclohexenone **56**[18] was found to take place in good (72%) yield on gram-scale (resulting in 1.7 g of product in one run), resulting in a diene–cyclohexane coupled compound (**42**) that was previously only feasible in six steps (Fig. 6). This reaction was initially optimized using $BF_3 \cdot OEt_2$, but was later optimized with TMSCl (vide infra). As the objective of this research project was a scalable and enantioselective synthesis of the taxane skeleton, this reaction was highly suitable unlike many of the reactions shown in Fig. 4. Efforts hereafter were therefore focused around enone **42**.

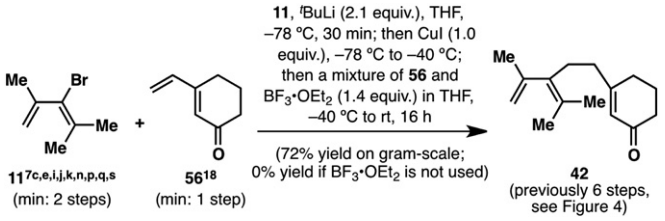

Fig. 6. A scalable 1,6-addition reaction resulting in a compound bearing both an A-ring precursor and a C-ring, which then became the focal point of this research project.

2.2. Revised strategy and further failures, followed by completion of racemic taxadienone (10)

With many grams of enone **42** in hand, the synthetic route was then revised and centered around a single strategy: methylation of the cyclohexenone, followed by a three-carbon appendage and a key Diels–Alder reaction (Fig. 7). The first methylation step was restricted to two methods, a methyl 1,4-addition[19] or a cyclopropanation,[20] because these reactions were the most likely to be amenable to enantioselective synthesis. From transient intermediate **58**, a three-carbon appendage could then take place via an S_N2 onto an allyl halide or via a 1,2-addition onto acrolein or an acryloyl halide. This three-carbon unit would then have to be oxidized accordingly, by C–H activation or otherwise, to furnish the ketone oxidation state in **60**. Finally, the key Diels–Alder reaction from **60** to **61** had good literature precedent through the work of Jenkins[7u] and Williams[6,21] whose intermediates only differed from **60** at the C4 position. The advantage of this sequence over many other possible routes was that the asymmetric construction of the 6–8–6 tricyclic skeleton would only rely on one enantioselective reaction, after which the resulting stereochemical information could be propagated to set all the other stereocenters diastereoselectively.

Based on this plan, the most efficient synthesis of **60** from **42** would be a one-step reaction: a methyl conjugate addition followed by trapping with an acryloyl halide. While the methyl 1,4-addition

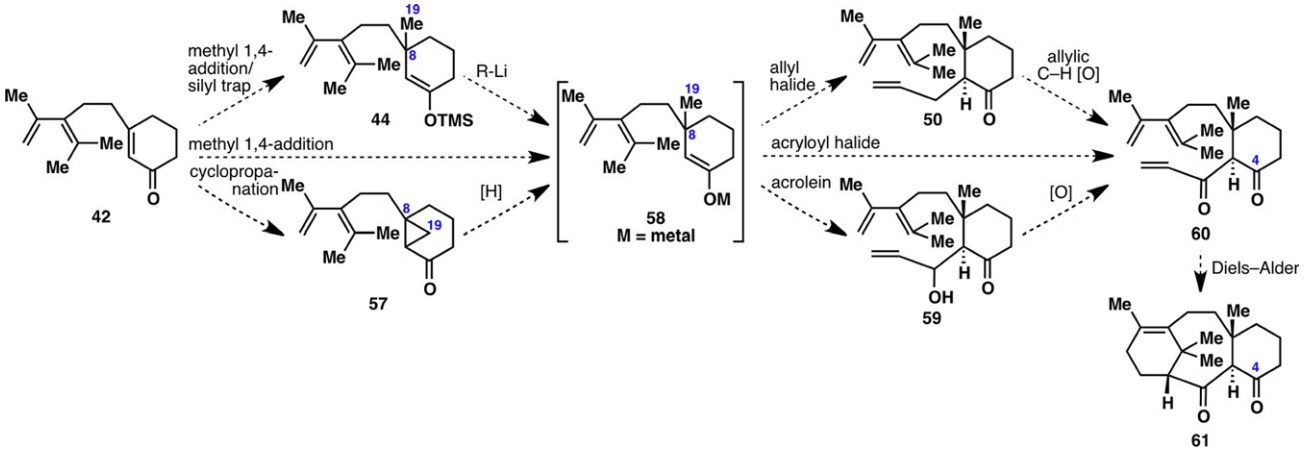

Fig. 7. Revised strategy for the synthesis of the taxane tricyclic framework. [O]=oxidation, [H]=reduction.

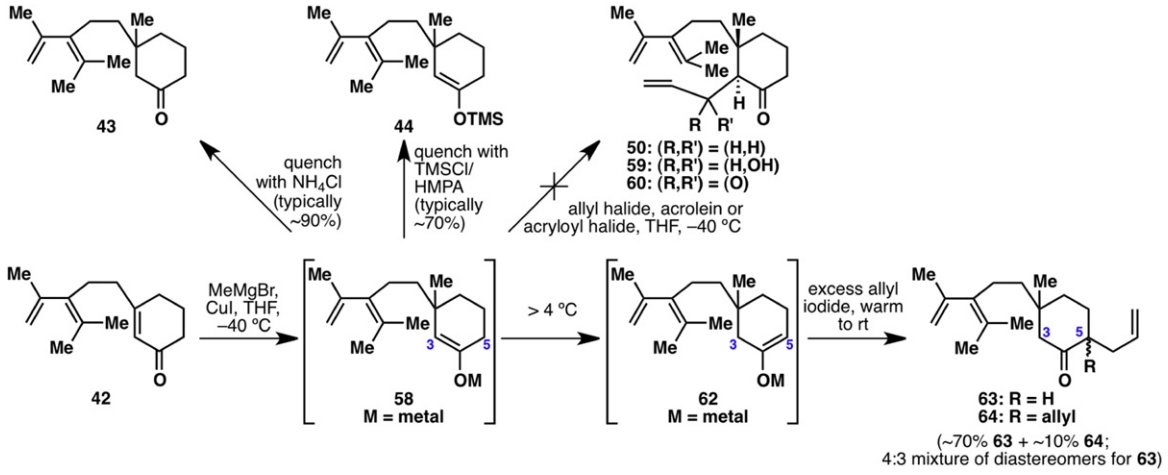

Fig. 8. Limited utility of kinetic enolate **58**, rearrangement to thermodynamic enolate **62**, and failure to allylate at C3.

step proceeded smoothly and was quenched with acid to give **43** or trapped with TMSCl to give **44**, it could not be trapped with a three-carbon unit to give **50**, **59** or **60**; only ketone **43** would result (Fig. 8). In fact, intermediate **58** was completely unreactive at C3 toward carbon-based electrophiles; while it could be trapped with deuterium oxide or halonium ions at C3 (e.g., to form **45** and **46** in Fig. 4), it would only give C5-allylated product **63** and a small amount of C5-bis-allylated product **64** when forced to react with allyl iodide. This most likely occurs because kinetic enolate **58** rearranges to thermodynamic enolate **62** at 'high' temperatures (>4 °C), and because the C5 position is less hindered than the C3 position, thus reacting more easily.

The only successful albeit inefficient and stereochemically non-selective way to place an allyl group onto the C3 position to make **50** was via Pd-catalyzed methods (see Fig. 4, **44** to **50**). However, not only did the Diels–Alder cyclization of **50** not occur (see Fig. 5), but allylic C–H oxidation also did not proceed, only resulting in decomposed material likely due to the lability of the diene moiety (Fig. 9). This result demanded that the revised strategy in Fig. 7 avoid the formation of **50**, and go through **59** or **60** instead.

In order to synthesize **59** or **60**, much effort was spent on trying to functionalize kinetic enolate **58**. Since **58** must be stored in the fridge or freezer and is not stable for much longer than a day, TMS enol ether **44** was stored in large batches to serve as a direct surrogate for **58**. Both **44** and **58** were reacted with acrolein, acryloyl chloride, and benzaldehyde (as a test substrate) under a variety of Lewis acidic conditions, only to return **44** or result in hydrolyzed ketone **43** (Fig. 10). Thinking that perhaps the lability of the trimethylsilyl group in **44** is the root of the problem in the failure of Mukaiyama-type reactions, a more robust TBS enol ether **65** was synthesized and subjected to the same set of Lewis acidic conditions. The only outcome was that the reaction of **65** was much slower than that of **44**; when submitted to a larger amount of Lewis acid for a longer period of time, **65** resulted in ketone **43** as well. Believing that trace amounts of water were hydrolyzing **44**, **58**, and **65** whenever a reaction was run, water was excluded with utmost rigor but **43** would always form.

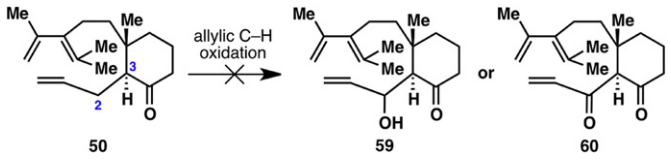

Fig. 9. Failure to oxidize allylated ketone **50** at the C2 position via allylic C–H oxidation methods.

With many failures en route to the taxane framework, the one compound that never failed to form was hydrolyzed ketone **43**. The accumulation of this compound in this project prompted an attempt at regenerating the potentially useful TMS enol ether **44**.

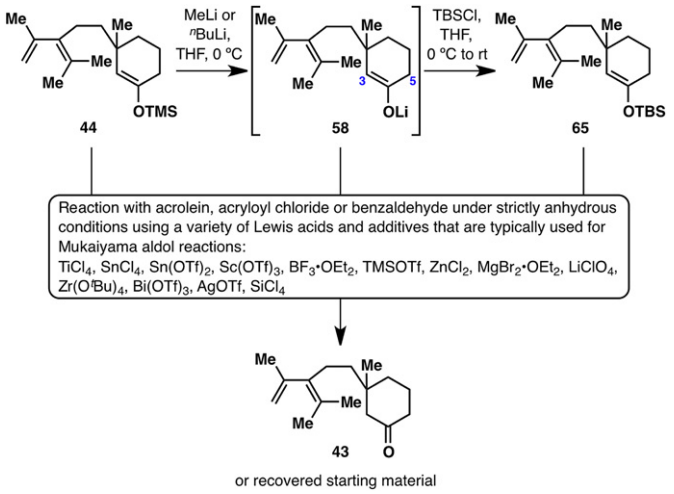

Fig. 10. Failure to functionalize the C3 position of **44**, **58**, and **65** using acrolein, acryloyl chloride or benzaldehyde.

However, ketone **43**, while bearing a carbonyl group at C4, would not allow selective functionalization at C3 because it would always deprotonate at C5 first. For example, generation of a TMS enol ether from **43** resulted in $\Delta^{4,5}$ enol ether **66**, with a diastereoselectivity of greater than 10:1 over the desired $\Delta^{3,4}$ enol ether **44**: unfortunately, **66** and **44** were inseparable and therefore this attempt at material recovery proved to be fruitless (Fig. 11). Another try at making use of ketone **43** was the formation of enone **67**, to possibly allow for C3-deprotonation. While the formation of **67** was possible through IBX oxidation of **43** or Ito–Saegusa oxidation of **66**, the resulting enone could not be deprotonated and functionalized at C3.

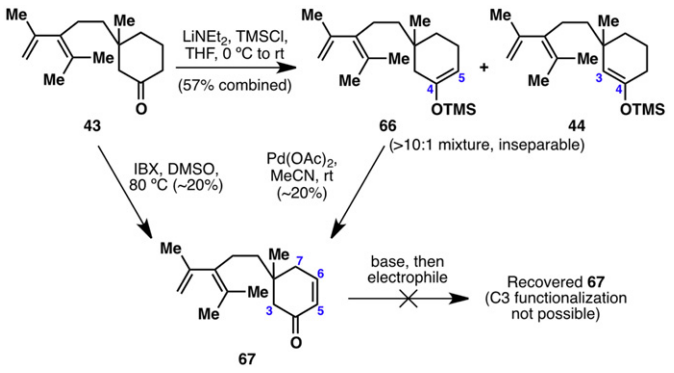

Fig. 11. Attempting to make use of hydrolyzed ketone **43**: synthesis of a TMS enol ether from **43** resulting primarily in $\Delta^{4,5}$ enol ether **66**, as well as formation of enone **67**.

Due to the accumulated failures when using intermediates **44** and **58**, a methyl conjugate addition strategy was temporarily suspended and a plan to synthesize cyclopropane **57** was put into action instead (Fig. 12A). The goal here was to append a three-carbon unit to the cyclopropane C3 position to make **68** and open the cyclopropane thereafter. After all, this method of introducing the C19 methyl group was featured in Kuwajima's successful syntheses of taxusin (**8**)[5b,c] and Taxol®(**1**).[4n,o] While Kuwajima performed a Simmons–Smith cyclopropanation on an allylic alcohol substrate, an enone moiety was present in **42** and thus a Corey–Chaykovsky cyclopropanation was carried out (Fig. 12B). As a result, cyclopropanated ketone **57** did form in low yield (~30%), but it was accompanied by side products **69**, **71**, and **72** (in a combined yield of ~30%). Aldehyde **71** and allylic alcohol **72** most likely arise from cyclopropane epoxide **70**, which results from over-methylenation; since the less reactive ketone moiety seemingly competes with the enone olefin for reaction with the Corey–Chaykovsky reagent, this suggests that access to the sterically hindered C3–C8 olefin is difficult. As for a three-carbon appendage onto ketone **57**, it was hoped that the increased s-character of the C–H bond in a cyclopropane would aid in deprotonation and functionalization.[22] However, treatment with an unhindered strong base only led to C5 deprotonation and functionalization, resulting in **73** and **74** upon allylation and **75** upon acrolein addition (Fig. 12C).

With the cyclopropane strategy now also a dead-end, it was again time to reevaluate all the synthesis routes that had been examined and to revisit failed reactions that seemingly should have worked. Since the synthesis plan laid out in Fig. 7 was still very attractive, we analyzed every failed reaction and concluded that the reaction that should have worked is the aldol reaction of **44** with acrolein to give aldol product **59**. While we had always assumed that the hydrolysis of TMS enol ether **44** to ketone **43** involved water, this time we asked ourselves the question: what would happen if we deliberately added water? Perhaps **44** actually reacts with acrolein to give **59** but suffers a fast *retro*-aldol reaction, whose rate can be slowed down by the addition of water? Thus, a bold move was made to include water in the reaction conditions, this time employing aldol conditions that only works well with water[23] (Fig. 13). This reaction of **44** to **59**, to our surprise and delight, resulted in an extension of three carbons at C3 while retaining a functional group at C2. This represented a turning point in this project, as all the 'dead ends and detours' seemed to finally give way to a successful total synthesis.[24]

With aldol product **59** in hand, a first-generation synthesis of racemic taxadienone (**10**) was not far out of reach (Fig. 14). Oxidation of the allylic alcohol under Swern conditions gave uncyclized diketone **60**, which was an inseparable mixture of diastereomers at C3 (dr ~3:2). Hoping that a Lewis acidic reaction would funnel both isomers of this mixture toward the desired diastereomer, the key Diels–Alder cyclization to **61** was accomplished using previously described acidic conditions,[6,7f,u,21] generating a 6–8–6 tricyclic framework for the first time in this project. Although the reaction yield was low and the diastereomeric ratio did not appear to improve during the cyclization, **61** was carried onward, with optimizations performed at a later time (vide infra).

Although diketone **61** appears to have two reactive carbonyl groups, the C2 carbonyl is quite hindered due to the nearby *gem*-dimethyl group, and thus addition of MeMgBr onto **61** in PhMe occurred selectively at the C4 position to give **76** as a single diastereomer. It is of note that this reaction does not occur when conducted in THF or in Et_2O. Finally, keto-alcohol **76** was dehydrated using Burgess reagent or Martin sulfurane to give the desired taxadienone (**10**) as a major product and its isomer *exo*-taxadienone (**77**) as a significant but still a minor product. Most fortunately, taxadienone (**10**) turned out to be crystalline, and an X-ray structure confirmed the connectivity and relative stereochemistry of the molecule.

Although each step in this reaction sequence was modest at best, a first-generation synthesis of the taxane framework was now complete (Fig. 15). Many more hurdles remained, however, to reach our goal of a scalable and enantioselective synthesis of taxadienone (**10**). Possible areas of improvement are noted, including the known two-step synthesis from **78** to **11** that could be shortened, the use of pyrophoric ^{t}BuLi, the asymmetry-inducing step, the use of toxic HMPA, the two-step synthesis from **44** to **60** that could be shortened and rendered scalable, the low diastereomeric ratio when forming **60**, the low yield and scalability of the Diels–Alder cyclization step, and the two-step synthesis from **61** to **10** that could be shortened, rendered scalable, and made regioselective.

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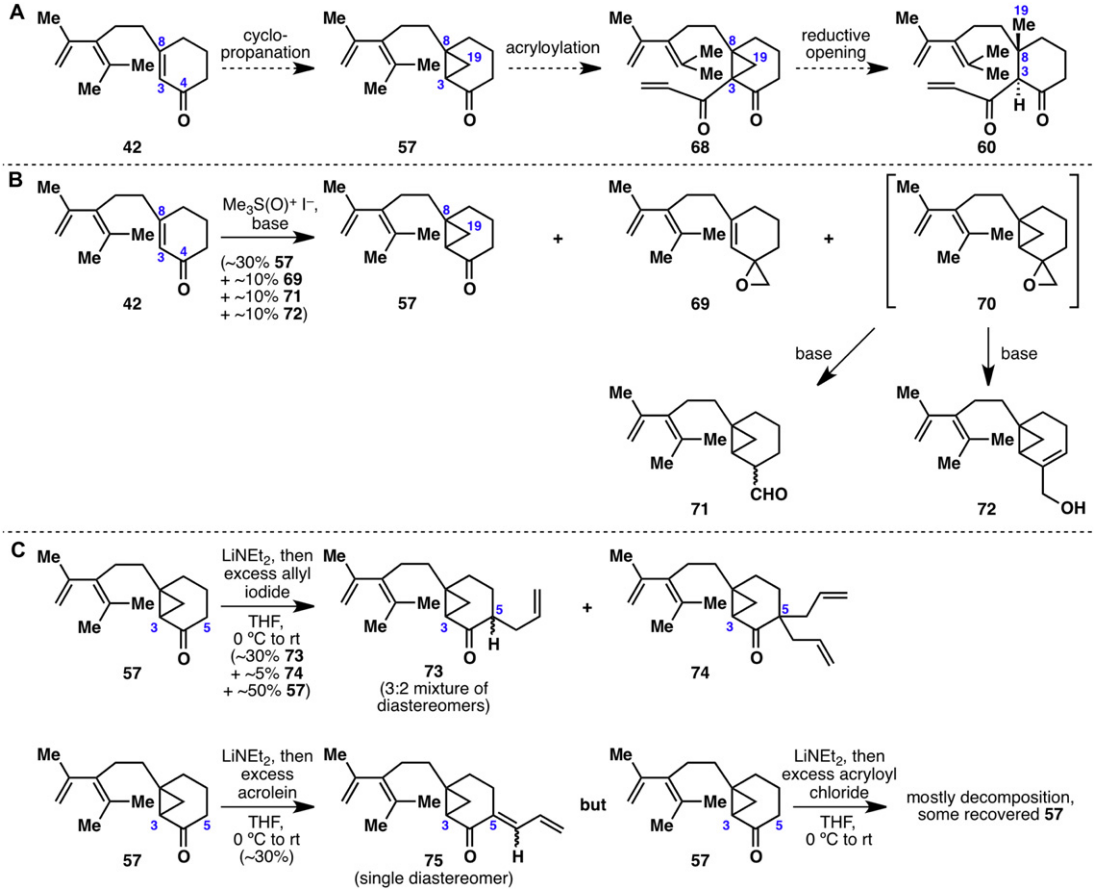

Fig. 12. (A) A cyclopropanation strategy that was (B) inefficient during the cyclopropane synthesis step and that (C) failed at cyclopropane C3 functionalization.

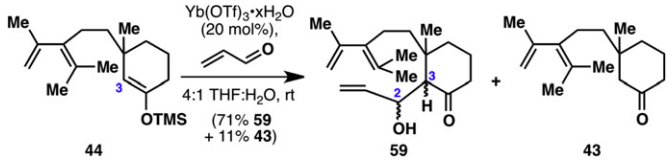

Fig. 13. The elusive aldol reaction at C3, requiring the unexpected additive: water.

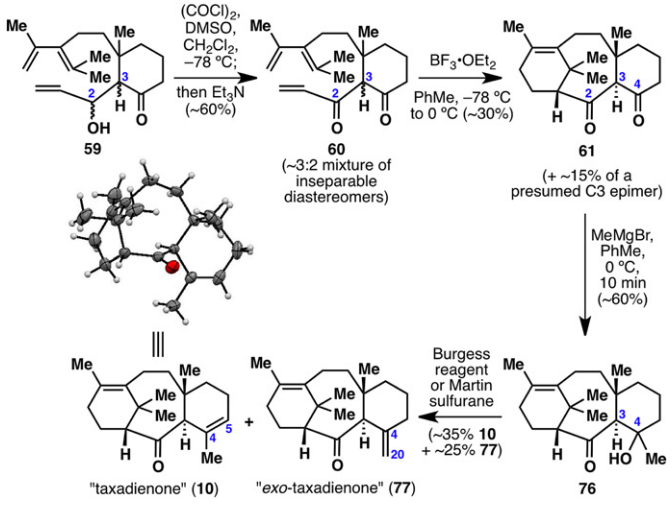

Fig. 14. Completion of racemic taxadienone (**10**).

2.3. Enantioselective route to taxadienone (10), total synthesis of taxadiene (8), and reaction optimizations from the vantage point of scalability

One of the advantages of the first route to taxadienone (**10**) described in Fig. 15 is that only one asymmetric reaction would be needed to generate enantiomerically enriched taxadienone (**10**); another is that the C8 stereocenter, once formed, is not epimerizable. Although asymmetric conjugate additions using alkyl nucleophiles are well-known,[19] early developments only involved the formation of chiral tertiary carbon centers from disubstituted enones.[19a–e] Only recently (since 2005) has there been a methodology that allows for the construction of chiral quaternary stereocenters, with only two major research groups studying the addition of methyl nucleophiles, those of Alexakis[19f–h] and Hoveyda.[19i–k] A decision was then made to employ Alexakis' chemistry simply based on the ease of preparation of both enantiomeric series of the chiral catalyst.[19h]

The plan was then to test the enantioselectivity and absolute configuration of the asymmetric addition at three stages (Fig. 16): (1) after generation of the first achiral intermediate **44**, hydrolysis would form an enantioenriched sample of **43** that could be tested against the previously synthesized racemic **43**, using chiral HPLC to obtain the enantiomeric ratio; (2) enantioenriched **44** could then be elaborated onto taxadienone (**10**), for which an attempt could be made at determining the absolute configuration using X-ray crystallography despite the absence of heavy atoms;[25] (3) enantioenriched taxadiene (**8**) could be synthesized from **10** and the sign of the optical rotation could be compared to that of the bioengineered sample of **8** (which was found to be of positive optical rotation).[26]

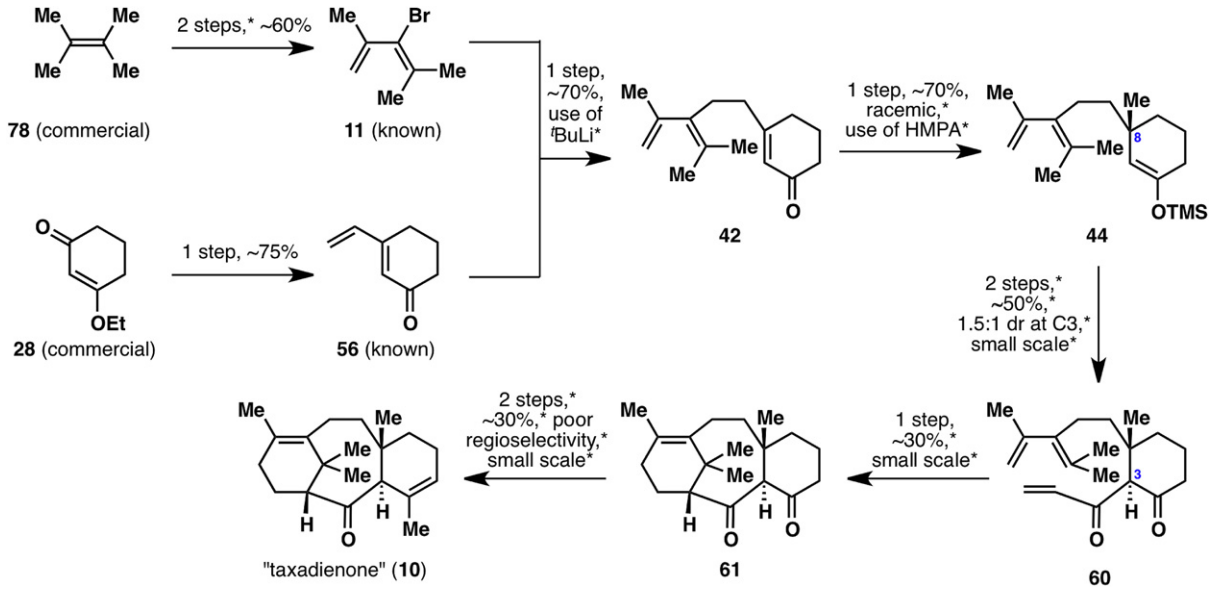

Fig. 15. A summary of the nine-step, first-generation racemic synthesis of taxadienone (**10**), with possible areas of improvement marked with *.

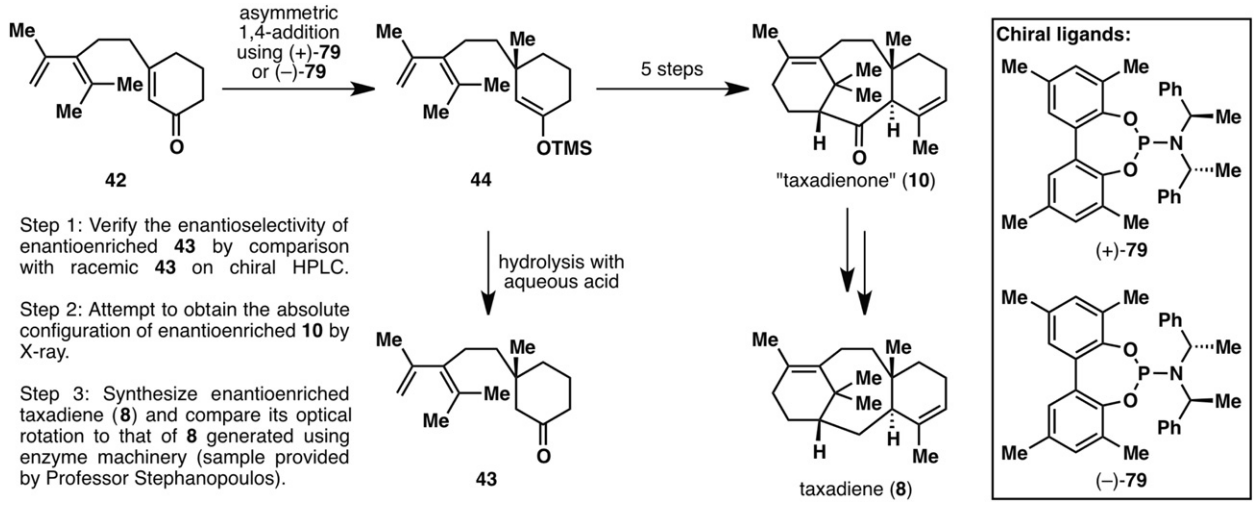

Fig. 16. Plan of action for testing the enantioselectivity and absolute configuration of the asymmetric addition step. Note: the desired enantiomeric series of products are displayed.

The absolute configuration of the asymmetric synthesis needed to be verified at two distinct stages because taxadiene (**8**), while being a natural product,[1c] was never isolated in large enough amounts for sufficient purification and analysis, and thus its optical rotation had never been recorded.

At the outset, one enantiomer of chiral ligand **79** was chosen at random, and it was decided that studies would be conducted on (−)-**79**. The first asymmetric reaction that was performed using Alexakis' conditions (2 equiv Me_3Al, 5 mol % CuTC, 10 mol % (−)-**79**, Et_2O, −30 °C, 18 h)[19h] was successful, resulting in 88% yield and 93% ee of (−)-**43** (Fig. 17). However, since Alexakis was unsuccessful in trapping the enolate intermediate with a silyl group,[19h] the synthesis and isolation of **44** indeed proved to be difficult. After some experimentation, it was found that the enolate intermediate after the conjugate addition can be silylated after dilution with THF then adding TMSCl and Et_3N, and that (+)-**44** can be isolated after high dilution with hexanes and quenching with basic alumina. After three steps from (+)-**44**, diketone (−)-**61** was obtained; unexpectedly, this compound was found to crystallize on one occasion and thus an X-ray structure was obtained. A high-precision X-ray crystallographic analysis resulted in a small enough uncertainty in the Flack parameter to allow for absolute configuration determination;[25] however, (−)-**61** turned out to have the wrong configuration. For further verification, (−)-**61** was elaborated into (−)-**10**, whereby determination of the absolute configuration by X-ray analysis again established the wrong configuration of this molecule. Having enough confidence after these two assignments, the correct enantiomeric series was then targeted, using chiral catalyst (+)-**79**.

Restarting the synthesis with (+)-**79**, TMS enol ether (−)-**44** was formed, from which (+)-**43**, (+)-**61**, and (+)-**10** were generated (i.e., Fig. 17 but with all the stereocenters inverted). While (+)-**61** could not be crystallized on this occasion, (+)-**10** reproducibly yielded crystals (from Et_2O/MeOH) and the absolute configuration was confirmed to be the desired one by X-ray crystallography (see Fig. 18). However, another method of confirmation of absolute configuration was still desired. To this end, deoxygenation studies were conducted on (+)-**10** to generate taxadiene (**8**), which was used to verify that the synthetic route also generated a sample with a positive optical rotation.[26]

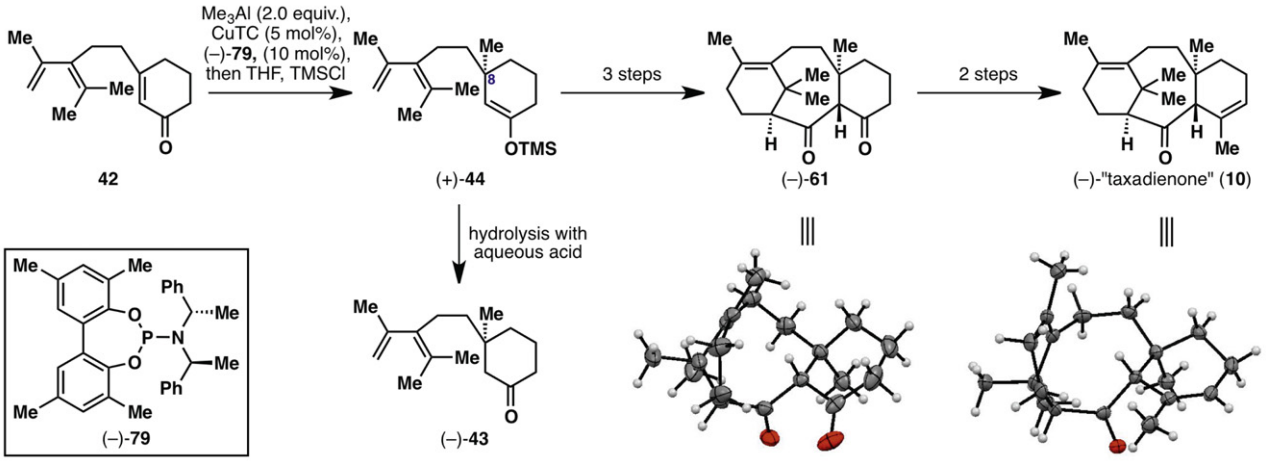

Fig. 17. Synthesis of (+)-**44**, (−)-**43**, (−)-**61**, and (−)-**10**, with X-ray structures of the latter two compounds displaying the wrong absolute configuration.

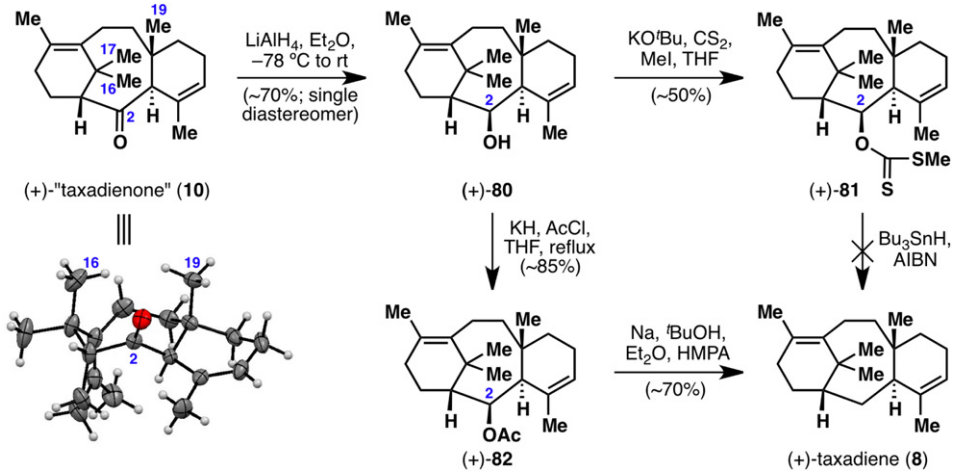

Fig. 18. X-ray structure of enantiomerically enriched (+)-taxadienone (**10**) with the correct absolute configuration and deoxygenation from (+)-taxadienone (**10**) to taxadiene (**8**).

The final stages of the synthesis of a natural taxane, taxadiene (**8**), were not simple: classic methods of ketone deoxygenation such as Clemmensen and Wolff–Kishner reductions failed (including methodology in recent reports such as Myers' method[27]), largely due to the failure of forming the requisite hydrazone (Fig. 18). The C2 carbonyl group is quite hindered at the β face due to the C16 and C19 methyl groups, which can be seen in the X-ray structure of (+)-**10**. This effect had also been observed in the inertness of the C2 carbonyl to undergo attack by a Grignard reagent in diketone **61** (see Fig. 14). It is therefore difficult for any functional group to leave from the β face as well: even if hydrazine could attack taxadienone (**10**) at its α face, a molecule of water needs to depart from the β-face, and as this is too energetically prohibited, the hydrazinohydrin intermediate expels hydrazine back from the α face to simply return the starting material **10**. Thus, we resorted to a three-step deoxygenation procedure. $LiAlH_4$ reduction of (+)-**10** proceeded smoothly to give (+)-**80**, and xanthate formation, while requiring the use of KO^{t}Bu as base, occurred in moderate yield to give xanthate (+)-**81**. However, standard Barton–McCombie deoxygenation never provided the desired taxadiene (**8**; for which authentic NMR spectra were available),[1c,6] as evidenced by NMR analysis of the crude product. At this juncture, unusual deoxygenation methods were attempted: acetylation followed by Li/$EtNH_2$,[28a] K/^{t}BuNH$_2$,[28a] or Na/HMPA;[28b] SO_3/pyridine followed by NaH/$LiAlH_4$;[28c] and $Ph_2SiHCl/InCl_3$.[28d] Out of these methods, the one that eventually led to taxadiene (**8**) was the acetylation–Na/^{t}BuOH/HMPA strategy.[28b] Thus, (+)-**80** was treated with KH and AcCl in refluxing THF (reactions using Ac_2O did not work, and KH led to a faster reaction than KHMDS or NaH) to give (+)-**82**, and Na/^{t}BuOH/HMPA in Et_2O led to taxadiene (**8**). While this synthetic sample of taxadiene (**8**) was found to have an optical rotation of +170°, that of the bio-engineered sample[26] was +135°. Despite the discrepancy in the absolute value of these optical rotations,[12] the sign of the optical rotation of these two samples matched, thereby lending further support for the use of ligand (+)-**79** to synthesize the correct enantiomeric series of the taxane skeleton.

With the enantioselective synthesis of taxadienone (**10**) and taxadiene (**8**) now complete, it was time to revisit the entire synthesis from the vantage point of reaction scalability (Fig. 19). Almost every single step of this sequence was optimized, on one occasion even resulting in a different synthetic intermediate than what was originally carried out. As a result, the nine-step synthesis of taxadienone (**10**) was reduced to a seven-step sequence, with the overall yield increasing from 1.5% to 18%. Extensive optimizations of all reactions (except for the reaction from **28** to **56**[18]) from the starting alkene **78** to enantiomerically enriched (+)-taxadienone (**10**) are shown in Fig. 20.

While the contents of Fig. 20 will not be reiterated, it is important to note that these optimization efforts have resulted in an enantioselective and scalable synthesis of a laboratory cyclase

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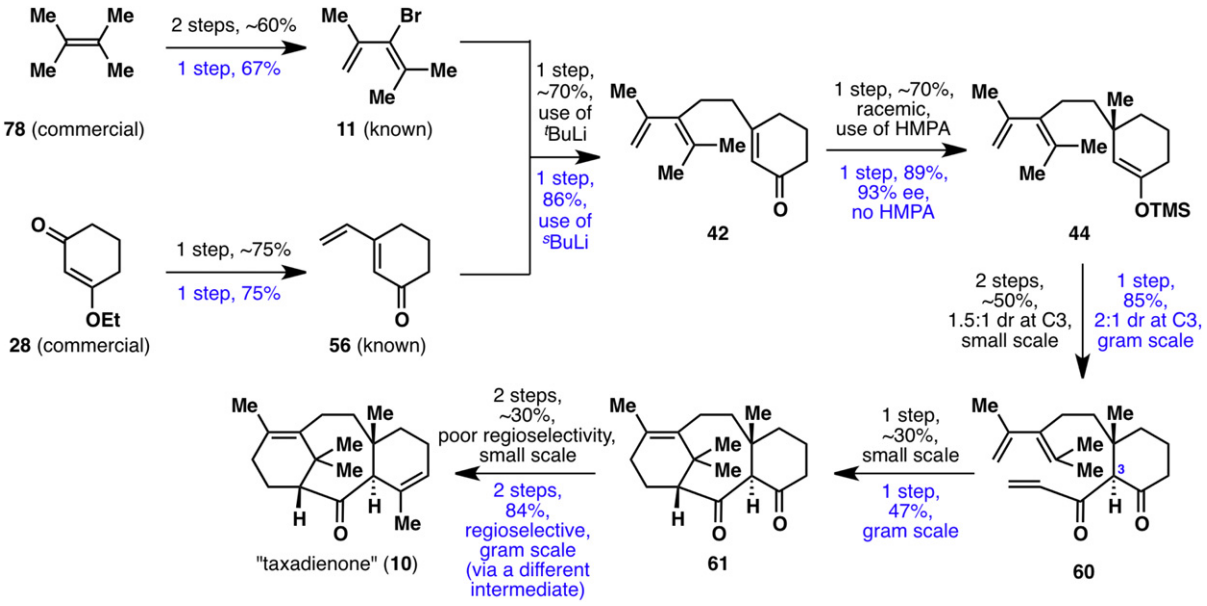


Fig. 19. The nine-step, first-generation racemic synthesis of taxadienone (**10**; shown in black) as well as its seven-step, second-generation enantioselective synthesis (shown in blue).

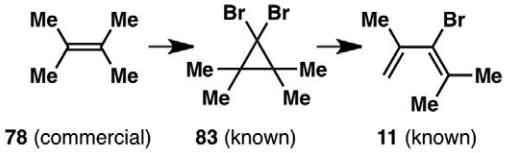
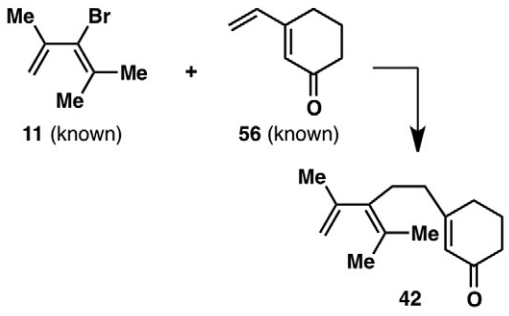
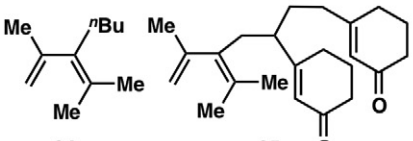
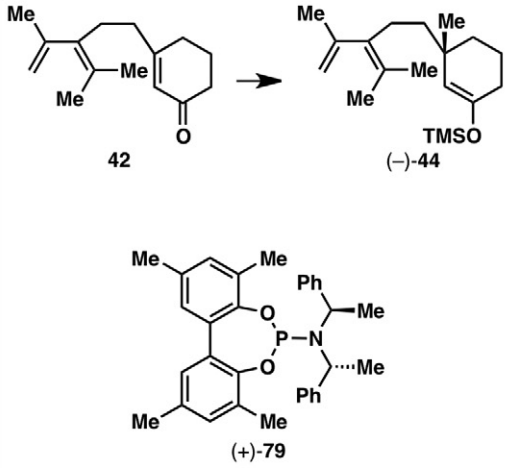
TRANSFORMATION	ORIGINAL/REVISED CONDITIONS	OTHER EXPERIMENTAL OBSERVATIONS
 78 (commercial) 83 (known) 11 (known)	Original two-step conditions: 1) **78** (1 equiv.), $CHBr_3$ (2.2 equiv.), KO^{t}Bu, pentane, 0 °C, 3 h (71%);[7n] 2) 120–140 °C (80%)[7n] or $PhNMe_2$, 140°C (82%).[7q] Revised one-step conditions: **78** (2 equiv.), $CHBr_3$ (1 equiv.), KO^{t}Bu, hexanes, 0 °C, 2 h; evaporate volatile materials, then $PhNMe_2$, 140 °C (67%).	2 equiv of **78** are needed to render this reaction into a one-pot sequence because $CHBr_3$ must not be present in the thermal step: since it is not very volatile (b.p. 151 °C), it must be consumed entirely in the cyclopropanation step using an excess of **78**. **78** is quite volatile (b.p. 73 °C), and hexanes (b.p. ~70 °C) allows for a good co-evaporation of **78**.
 11 (known) 56 (known) 42	Original conditions: **11**, ^{t}BuLi (2.1 equiv.), THF, –78 °C, 30 min; then CuI (1.0 equiv.), –78 °C to –40 °C; then a mixture of **56** and BF_3•OEt_2 (1.4 equiv.) in THF, –40 °C to rt, 16 h (72% yield on gram scale; 0% yield if BF_3•OEt_2 is not used). Revised conditions: **11**, ^{s}BuLi (1.2 equiv.), Et_2O, –78 °C, 15 min; then CuBr•SMe_2 (1.2 equiv.), –78 °C, 30 min; then TMSCl (2.0 equiv.), –78 °C, 5 min; then **56** (1.0 equiv.) in Et_2O, –78 °C, 2 h, warm to rt over 8 h; quench with AcOH then HCl (86% yield on decagram scale).	2 equiv. of ^{t}BuLi can be replaced with 1 equiv. of ^{s}BuLi without any problems; ^{n}BuLi cannot be used because it creates ^{n}BuBr as a by-product, and unproductive formation of **84** occurs. CuI and BF_3•OEt_2 were ultimately replaced with CuBr•SMe_2 and TMSCl due to the formation of variable amounts of **85**.  84 85
 42 (–)-44 (+)-79	Original racemic conditions: **42**, MeMgBr (4.0 equiv.), CuI (1.0 equiv.), TMSCl (7.0 equiv.), 4:1 THF: HMPA, –40 °C; then $NaHCO_3$ (69%). Revised racemic conditions: CuBr•SMe_2 (5 mol%), THF, 0 °C; then 2 M Me_3Al in heptane (1.2 equiv.), **42**, 0 °C to rt, 1 h; cool to 0 °C, then TMSCl (1.7 equiv), 0 °C to rt, 10 h; then pour mixture into Florisil®, Et_3N, hexanes, rt, 1 h (79%, gram scale). Revised enantioselective conditions: CuTC (2 mol%), ligand (+)-**79** (4 mol%), Et_2O, 30 min, rt; then cool to –78 °C, **42**; then 2 M Me_3Al in heptane (1.4 equiv.), –30 °C, 24 h; then THF, TMSCl (1.7 equiv.), –30 °C to rt, 10 h; then pour mixture into Florisil®, Et_3N, hexanes, rt, 1 h (89%, 93% ee, gram scale).	It was found early on that using Me_3Al as the methyl source allowed for catalytic amounts of copper to be used. Originally, the use of basic alumina was found to be the best quenching method (silica deactivated with Et_3N resulted in hydrolysis to ketone **43**), but due to irreproducible results (perhaps from the various grades of alumina available), Florisil® was used in the end. As reported by Alexakis, the enantioselective conjugate addition only takes place in good yield when Et_2O, not THF, is used.[19h] However, TMS trap of the resulting enolate only occurs when THF, not Et_2O, is used. Due to these contradictory events, the enantioselective reaction must be conducted in high concentrations in Et_2O, after which the system must be diluted with THF before trapping with TMSCl. This reaction is typically run on 1-gram scale; scaling up to 5 grams while retaining high ee requires more catalyst (4 mol% CuTC and 8 mol% **79**).

Fig. 20. Optimization of most of the steps in the enantioselective synthesis of (+)-taxadienone (**10**), resulting in more efficient reaction conditions and even going through a different synthetic intermediate.[29]

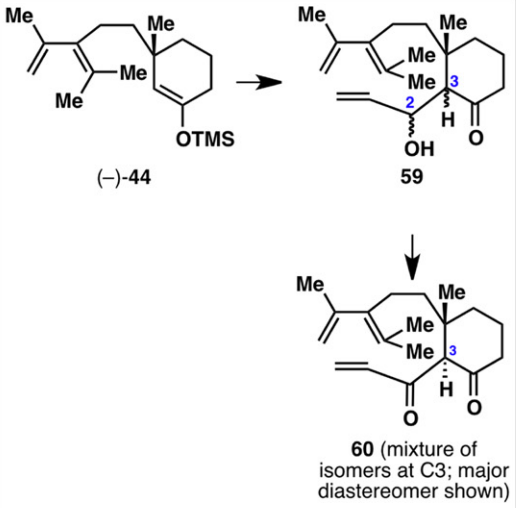
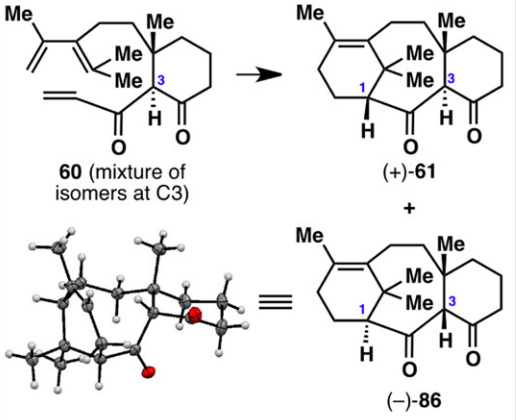
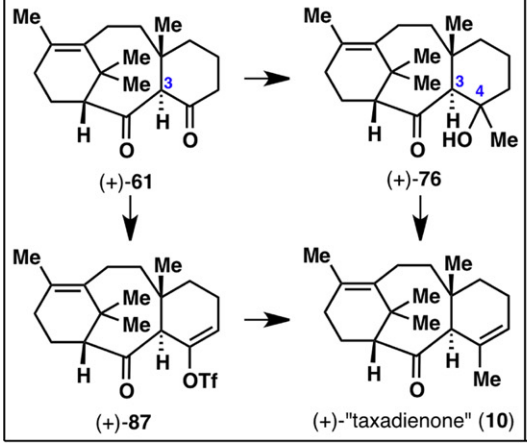
TRANSFORMATION	ORIGINAL/REVISED CONDITIONS	OTHER EXPERIMENTAL OBSERVATIONS
	Original two-step conditions: 1) **44**, acrolein (excess), $Yb(OTf)_3$ hydrate (20 mol%), 1:4 H_2O:THF, rt; 2) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C; then Et_3N (~50% overall, 1.5:1 dr). Revised one-step conditions: **44**, acrolein (20 equiv.), $Gd(OTf)_3$ (10 mol%), 1:10:4 H_2O:EtOH:PhMe, 4 °C, 24 h; evaporate volatile materials over 10 min or less; 2 M Jones' reagent (CrO_3 + H_2SO_4), acetone, 0 °C, 10 min (85% overall in gram scale, 2:1 dr).	This aldol reaction was very difficult to find at first and was equally difficult to optimize. Kobayashi's $Yb(OTf)_3$ in 1:4 H_2O:THF conditions[23a] were systematically modified. Results: 1) MeCN>THF>EtCN>DMF in terms of reaction rate when ran with H_2O as a minor co-solvent; 2) the less H_2O there is, the faster the reaction (1:24 is the fastest and 1:4 is the slowest), but some H_2O is crucial; 3) a pH of 6.0–6.4 is best for the aqueous $Yb(OTf)_3$ solution; 4) additives such as ethylene glycol, acetylacetone, BINOL, etc. do not help this reaction. Adoption of Kobayashi's ternary solvent system[23c] of 1:10:4 H_2O:EtOH:PhMe and even further optimization for reaction rate and diastereoselectivity led to these final conditions. Of note, the amount of acrolein cannot be reduced because the reaction is an equilibrium process, wherein **59** undergoes a *retro*-aldol process in the absence of acrolein. For this reason, the removal of acrolein after the first step must be conducted swiftly. Thereafter, aqueous oxidation conditions were desired, for which Jones' oxidation was most suitable.
	Original conditions: **60**, BF_3•OEt_2 (6 equiv.), PhMe, –78 °C to 0 °C (~30% + ~15% of a presumed C3 epimer that turned out to be **86**). Revised conditions: BF_3•OEt_2, DCM (to make it 0.013 M in **60**), 0 °C, slow addition of **60** over 5 h, quench by pouring it into $NaHCO_3$ solution (47% of product **61** + 29% of diastereomer **86**; exclusive diastereoselectivity was observed at C1; gram scale).	Williams' conditions[21] were modified to use DCM instead of PhMe. Furthermore, side products (presumably polymers) were suppressed by performing the reaction in high dilution and by adding **60** into the Lewis acid solution very slowly. The desired product **61** and diastereomer **86** were separable by column chromatography. Assuming that a C3-epimer of **61** was being formed as a by-product, many epimerization conditions were tried with both acids and bases. After this time, an X-ray structure was finally obtained and showed that the diastereomer in question was not a C3-epimer (see left structure). It was then imagined that the yield of **61** can be increased by stopping the cyclization reaction before completion, recovering unreacted **60** that is enriched in the undesired configuration, and then epimerizing C3; sadly, the formation of **86** is faster than that of **61**, thereby thwarting this strategy.
	Original two-step conditions: 1) **61**, PhMe, 0 °C; then MeMgBr (4.0 equiv.), 10 min (~60% on 40 mg scale). 2) Burgess or Martin sulfurane, PhH, reflux, 1 h (~35% **10** + ~25% **77**). Revised two-step conditions: 1) $PhNTf_2$ (2.0 equiv.), THF, 0 °C; then **61**, 0.4 M KHMDS (1.5 equiv.), 0 °C, 1 h; then quench with $NaHCO_3$ (carried on crude to the next step). 2) Crude **87**, THF, 0 °C; then $Pd(PPh_3)_4$, 0 °C, 5 min; then 1.2 M Me_2Zn (5.0 equiv.), 0 °C, 5 min, then warm to rt over 5 h (84% overall, gram scale).	Even though **61** is a β-diketone, it does not behave like one at all, since neither **61** nor diastereomer **86** are present in enol forms, and neither of them can be deprotonated at C3. For this reason, it was thought that triflation of **61** to give **87** would be 100% regioselective. Thus, **61** was treated with KHMDS and $PhNTf_2$ to give triflate **87** (LDA as base did not work). Coupling **87** under standard Negishi conditions using Me_2Zn led to **10** in good overall yield. Note: a one-step synthesis has been attempted, wherein the triflation reaction is not worked up and a second reaction using Fürstner's MeMgBr/$Fe(acac)_3$ conditions[29] is conducted in one-pot. While this does result in product **10**, the yields are low (<30%), possibly because the side products from the first reaction (such as PhNHTf) hinder the methyl coupling step.

Fig. 20. (*continued*)

phase endpoint that enables future efforts to elaborate the taxane pyramid. In summary, the synthesis of enantiomerically enriched (+)-taxadienone (**10**) was achieved in a total of eight steps, with a longest linear sequence of seven steps. A few grams of (+)-**10** could be synthesized by one chemist over the course of seven days, with an overall yield of 18% from **78** or 20% from **28**. Furthermore, the last three steps leading to enantiomerically enriched (+)-taxadiene (**8**) were also carried out on gram-scale, providing a scalable access to Nature's cyclase phase endpoint[1c] as well (Fig. 21). It is of note that this 10-step synthesis of (+)-taxadiene (**8**) compares favorably with the only total synthesis of (±)-**8** thus far, in 26 steps, back in 1995.[6]

Please cite this article in press as: Ishihara, Y.; et al., Tetrahedron (2013), http://dx.doi.org/10.1016/j.tet.2013.04.028

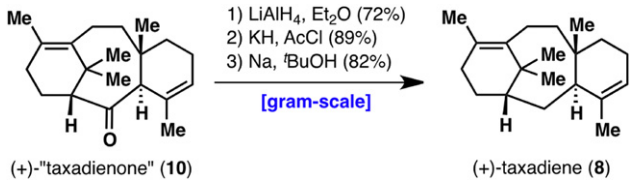


Fig. 21. Gram-scale synthesis of (+)-taxadiene (**8**) from (+)-taxadienone (**10**).

3. Conclusion, strategic perspective, and future outlook

The efficiency with which the synthesis of (+)-taxadienone (**10**) was completed is partly due to the low oxidation state of the target, which was an intended objective of this study (Fig. 22). With only one heteroatom present in target **10**, protecting group chemistry was minimized,[30] side reactions were reduced, and the use of versatile but harsh organometallic reagents was enabled. The generation of ample quantities of this tricyclic terpene should enable subsequent use as a starting material in a creative exploration of C–H oxidation chemistry.

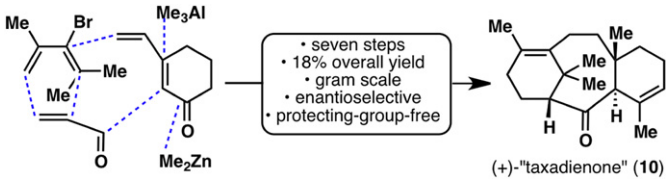


Fig. 22. Summary of the taxane cyclase phase.

With the completion of a successful cyclase phase in the laboratory, an oxidase phase can then be planned based on oxidations of olefins and C–H bonds. In this project, one functional group has been placed strategically on each of the A, B, and C rings of the taxane skeleton in taxadienone (**10**)—one heteroatom and two olefins—to propagate oxidative information in the most efficient manner (Fig. 23). This was designed because unlike in Nature, where enzymes can oxidize substrates virtually anywhere they want (for the assumed order of C–H oxidation on the taxane skeleton in Nature,[31] see **8**), long-range C–H oxidations are very limited in the laboratory. Furthermore, taxadienone (**10**) has an oxygen atom at C2, which is strategic because in principle, it would allow for the generation of a series of natural taxanes with a C2α-hydroxyl group (**89**) and a series of unnatural taxanes with a C2β-hydroxyl group (**90**) for medicinal chemistry research (Fig. 24).

A dauntingly complex, yet intriguing system on which to implement the two-phase strategy is that of the taxanes, and the value of this project lies in building upon the formidable efforts of other researchers that have spearheaded C_{sp^3}–H oxidation strategies.[11] Ultimately, we hope that future endeavors in pursuing a two-phase terpene total synthesis (on taxanes or on other terpene families) will aid in identifying gaps in current methodology and provide numerous opportunities for invention. Our laboratory is currently proceeding onward with the taxane oxidase phase and these studies will be reported in due course.

4. Experimental section

4.1. General

All reactions were carried out under an inert nitrogen atmosphere with dry solvents under anhydrous conditions unless otherwise stated. Dry acetonitrile (MeCN), dichloromethane (DCM), diethyl ether (Et_2O), tetrahydrofuran (THF), toluene (PhMe), and triethylamine (Et_3N) were obtained by passing the previously degassed solvents through activated alumina columns. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous material, unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm E. Merck silica plates (60F-254), using UV light as the visualizing agent and an acidic solution of *p*-anisaldehyde and heat, ceric ammonium molybdate and heat, or $KMnO_4$ and heat as developing

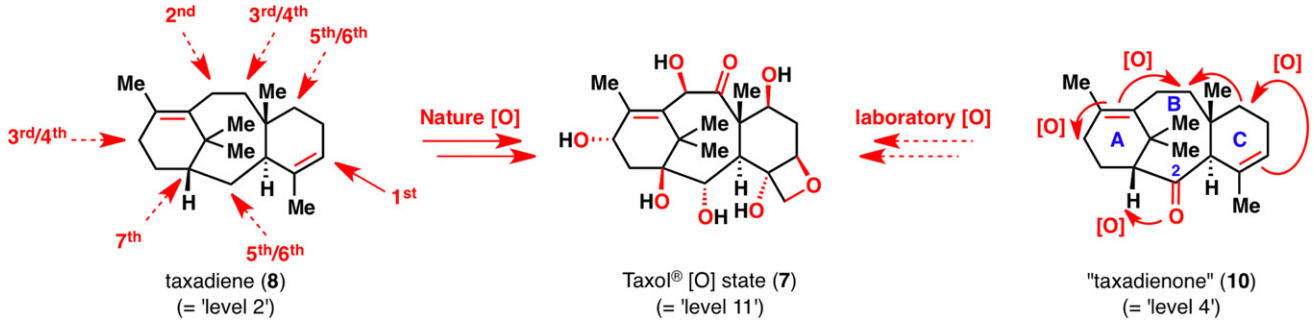


Fig. 23. Nature's presumed oxidation sequence[31] from taxadiene (**8**) and a planned propagation of oxidative information from the three functional groups of taxadienone (**10**). [O]= oxidation.

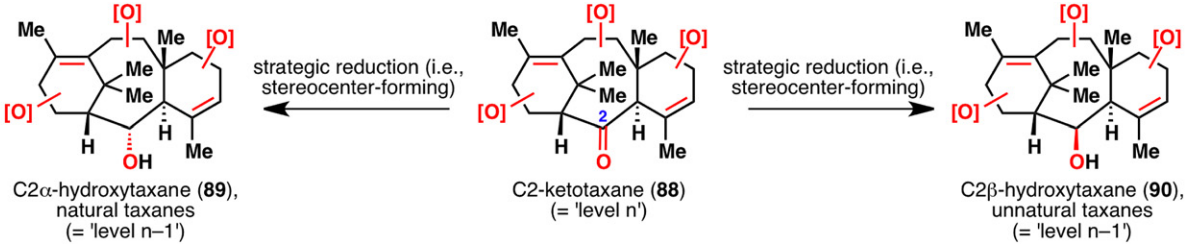


Fig. 24. Strategic advantage of having an over-oxidized functional group at C2: generating a series of natural and unnatural taxanes. [O]=oxidation.

agents. Flash silica gel chromatography was performed using E. Merck silica gel (60, particle size 0.043–0.063 mm), flash alumina chromatography was performed using Brockmann Grade 1 aluminum oxide (activated, basic, 58 Å, 60 mesh powder), and flash Florisil® chromatography was conducted using Acros magnesium silicate (activated, 60–100 mesh). Chiral HPLC was performed using a Hitachi LaChrom Elite HPLC system. NMR spectra were recorded on Bruker DRX-600 and AMX-400 instruments and were calibrated using residual undeuterated solvent as an internal reference ($CHCl_3$ at 7.26 ppm ^1H NMR, 77.2 ppm ^{13}C NMR). The following abbreviations were used to explain NMR peak multiplicities: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad. High-resolution mass spectra (HRMS) were recorded on an Agilent LC/MSD TOF mass spectrometer by electrospray ionization time-of-flight (ESI-TOF) reflectron experiments. IR experiments were recorded on a Perkin–Elmer Spectrum 100 FT-IR spectrometer. Optical rotations were obtained on a Perkin–Elmer 341 polarimeter. Melting points were recorded on a Fisher-Johns 12-144 melting point apparatus and are uncorrected.

4.2. Experimental procedures and data of synthetic intermediates

Note: Procedures and data for bromodiene **11**, vinylcyclohexenone **56**, enone **42**, TMS enol ether **44**, ketone **43**, aldol product **59**, uncyclized diketone **60**, cyclized diketone **61**, diastereomeric diketone **86**, enol triflate **87**, taxadienone (**10**), taxadienol **80**, acetoxytaxadiene **82**, and taxadiene (**8**) have been reported in the Supplementary data of Ref. 12 and will not be reiterated below.

*4.2.1. C5-Allylated ketone **63** and bis-allylated ketone **64**.* To a flame-dried 10 mL microwave vial equipped with a stir bar was added TMS enol ether (±)-**44** (31.4 mg, 0.102 mmol, 1.00 equiv) in THF (500 μL) and cooled to 0 °C. A solution of MeLi in Et_2O (1.6 M; 70 μL, 0.112 mmol, 1.10 equiv) was added dropwise and this mixture was stirred at 0 °C for 1 h. A solution of freshly prepared allyl iodide (40 μL, 0.437 mmol, 4.29 equiv) in THF (400 μL) was added and this reaction mixture was warmed to room temperature overnight. The reaction was quenched with saturated aqueous NH_4Cl (1 mL), diluted with H_2O (3 mL), and extracted with EtOAc (3×3 mL). The combined organic layers were washed with H_2O (5 mL) then brine (5 mL), dried over $MgSO_4$, and then evaporated to dryness in vacuo. Purification by silica gel flash chromatography (gradient of EtOAc/hexanes) yielded three separate compounds (in order of decreasing R_f), (±)-**64** (3.0 mg, 9% yield), (±)-**63a** (8.5 mg, 30% yield), and (±)-**63b** (11.5 mg, 39% yield). While **63a** and **63b** are C5-epimers of one another, the relative stereochemistry at C5 for **63a** and **63b** is unknown.

*4.2.1.1. Data for (±)-**63a**.* Appearance: slightly yellow oil. TLC: R_f=0.74–0.77 (silica gel, 1:3 EtOAc/hexanes). ^1H NMR (400 MHz, $CDCl_3$): δ 5.78 (dddd, *J*=17.0, 10.1, 7.8, 6.4 Hz, 1H), 5.06–4.96 (m, 2H), 4.91 (dq, *J*=3.0, 1.5 Hz, 1H), 4.53 (dq, *J*=2.7, 0.8 Hz, 1H), 2.52 (dddt, *J*=14.4, 6.7, 5.4, 1.4 Hz, 1H), 2.34–2.24 (m, 1H), 2.22 (d, *J*=12.8 Hz, 1H), 2.12 (dd, *J*=12.8, 1.6 Hz, 1H), 2.08–1.93 (m, 4H), 1.75 (dd, *J*=1.5, 0.9 Hz, 3H), 1.65 (s, 3H), 1.65 (s, 3H), 1.64–1.58 (m, 2H), 1.48 (m, 1H), 1.32 (m, 2H), 0.85 (s, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ 212.5, 146.5, 136.6, 136.4, 125.1, 116.4, 113.3, 53.5, 49.6, 43.0, 39.7, 36.1, 33.7, 28.9, 25.2, 22.9, 22.8, 21.9, 19.6 ppm. IR (neat): ν=3075, 2915, 2854, 1710, 1640, 1443, 1380, 1371, 1285, 1201, 1190, 1072, 993, 910, 893 cm^{-1}. HRMS (ESI-TOF): calcd for $C_{19}H_{30}O$ [$M+H^+$] 275.2369, found 275.2367.

*4.2.1.2. Data for (±)-**63b**.* Appearance: slightly yellow oil. TLC: R_f=0.71–0.74 (silica gel, 1:3 EtOAc/hexanes). ^1H NMR (400 MHz, $CDCl_3$): δ 5.76 (dddd, *J*=16.8, 10.1, 7.6, 6.5 Hz, 1H), 5.06–4.96 (m, 2H), 4.88 (dq, *J*=2.9, 1.5 Hz, 1H), 4.51 (dq, *J*=2.7, 0.9 Hz, 1H), 2.48 (dddt, *J*=14.7, 6.7, 5.5, 1.4 Hz, 1H), 2.32–2.22 (m, 1H), 2.22 (dd, *J*=13.2, 2.0 Hz, 1H), 2.15 (dd, *J*=13.0, 0.8 Hz, 1H), 2.06–1.86 (m, 4H), 1.77–1.69 (m, 1H), 1.73 (dd, *J*=1.4, 0.9 Hz, 3H), 1.63 (s, 3H), 1.63 (s, 3H), 1.59–1.41 (m, 2H), 1.17 (m, 2H), 0.99 (s, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ 212.3, 146.5, 136.5, 136.3, 125.2, 116.4, 113.3, 54.0, 49.2, 39.2, 36.3, 35.4, 33.8, 28.3, 27.5, 25.1, 22.9, 21.9, 19.6 ppm. IR (neat): ν=3075, 2928, 2855, 1709, 1640, 1459, 1444, 1373, 1283, 1228, 1193, 1075, 999, 909, 893 cm^{-1}. HRMS (ESI-TOF): calcd for $C_{19}H_{30}O$ [$M+H^+$] 275.2369, found 275.2374.

*4.2.1.3. Data for (±)-**64**.* Appearance: slightly yellow oil. TLC: R_f=0.77–0.79 (silica gel, 1:3 EtOAc/hexanes). ^1H NMR (400 MHz, $CDCl_3$): δ 5.76–5.56 (m, 2H), 5.10–5.00 (m, 4H), 4.90 (dq, *J*=2.9, 1.4 Hz, 1H), 4.53 (dq, *J*=2.7, 0.9 Hz, 1H), 2.38–2.23 (m, 4H), 2.24 (d, *J*=14.0 Hz, 1H), 2.14 (dd, *J*=14.0, 1.2 Hz, 1H), 2.00 (m, 2H), 1.74 (dd, *J*=1.4, 0.9 Hz, 3H), 1.73–1.66 (m, 3H), 1.65 (s, 3H), 1.64 (s, 3H), 1.28–1.18 (m, 3H), 0.90 (s, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ 214.2, 146.5, 136.3, 133.9, 133.7, 125.2, 118.3, 118.3, 113.3, 51.2, 50.6, 40.0, 39.7, 39.6, 38.7, 31.9, 31.4, 25.1, 25.1, 22.9, 21.9, 19.6 ppm. IR (neat): ν=3075, 2925, 2857, 1703, 1638, 1444, 1372, 1328, 1286, 1201, 1160, 1082, 993, 910, 893 cm^{-1}. HRMS (ESI-TOF): calcd for $C_{22}H_{34}O$ [$M+H^+$] 315.2682, found 315.2689.

*4.2.2. TBS enol ether **65**.* To a flame-dried 20 mL microwave vial equipped with a stir bar was added TMS enol ether (±)-**44** (65.0 mg, 0.212 mmol, 1.00 equiv) in THF (3 mL) and cooled to 0 °C. A solution of MeLi in Et_2O (1.6 M; 150 μL, 0.24 mmol, 1.13 equiv) was added dropwise and this mixture was stirred at 0 °C for 1 h. A solution of freshly distilled TBSCl (distilled over CaH_2; 200.0 mg, 1.327 mmol, 6.26 equiv) in THF (3 mL) was added and this reaction mixture was stirred at 0 °C for 1 h. The reaction was quenched at 0 °C with 1:1 MeOH/Et_3N (3 mL), diluted with H_2O (5 mL), and extracted with EtOAc (3×7 mL). The combined organic layers were washed with H_2O (10 mL) then brine (10 mL), dried over Na_2SO_4, and then evaporated to dryness in vacuo. Although TMS enol ether **44** is unstable on silica gel, TBS enol ether **120** is stable and can be purified by silica gel. Thus, purification by silica gel flash chromatography (hexanes) yielded (±)-**65** (40.7 mg, 55% yield). Appearance: colorless oil. TLC: R_f=0.37–0.40 (silica gel, hexanes). ^1H NMR (400 MHz, $CDCl_3$): δ 4.89 (dq, *J*=2.9 and 1.4 Hz, 1H), 4.66 (s, 1H), 4.53 (dq, *J*=2.7, 0.9 Hz, 1H), 2.02 (m, 2H), 1.95 (m, 2H), 1.75 (dd, *J*=1.4, 0.9 Hz, 3H), 1.67 (m, 2H), 1.66 (s, 6H), 1.42 (m, 1H), 1.35–1.20 (m, 3H), 0.96 (s, 3H), 0.92 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ 149.7, 146.9, 137.3, 124.5, 114.4, 112.9, 42.0, 34.7 (two carbons), 30.1, 28.0, 26.2, 25.9, 23.0, 21.9, 19.8, 19.6, 18.2, −4.1, −4.3 ppm. IR (neat): ν=3074, 2933, 2866, 1660, 1444, 1366, 1263, 1250, 1203, 1137, 963, 938, 894, 840, 752 cm^{-1}. HRMS (ESI-TOF): calcd for $C_{22}H_{40}OSi$ [$M+H^+$] 349.2921, found 349.2924.

*4.2.3. $\Delta^{4,5}$-TMS enol ether **66** (>90% pure, contains some **44**).* To a flame-dried 10 mL microwave vial equipped with a stir bar was added lithium diethylamide (2.0 M, synthesized by adding ^{n}BuLi to diethylamine; 250 μL, 0.500 mmol, 1.52 equiv) and this was cooled to 0 °C. Freshly distilled TMSCl (distilled over CaH_2; 200 μL, 1.58 mmol, 4.80 equiv) was added, followed by a solution of ketone (±)-**43** (77.0 mg, 0.329 mmol, 1.0 equiv) in THF (1 mL). The reaction mixture was stirred at 0 °C for 30 min and then warmed to room temperature over 1 h. It was then cooled to 0 °C, 1:1 MeOH/Et_3N (1 mL) was added, and this reaction mixture was warmed to room temperature over 1 h. The reaction mixture was diluted with H_2O (3 mL) and extracted with EtOAc (3×2 mL). The combined organic layers were washed with H_2O (4 mL) then brine (4 mL), dried over Na_2SO_4, and then evaporated to dryness in vacuo. Purification by Et_3N-treated silica gel chromatography (2% Et_3N in hexanes) yielded >90% pure (±)-**66** with <10% of (±)-**44** (combined: 69.0 mg,

57% yield), along with recovered (±)-**43** (27.2 mg, 35% yield). Appearance: colorless oil. TLC: R_f=0.00–0.20 (silica gel, hexanes, streaks due to decomposition when without Et_3N). ^1H NMR (400 MHz, $CDCl_3$): δ 4.89 (dq, J=2.9, 1.5 Hz, 1H), 4.82 (tt, J=3.7, 1.3 Hz, 1H), 4.53 (dq, J=2.7, 1.0 Hz, 1H), 2.08–1.98 (m, 4H), 1.86 (m, 1H), 1.75 (dd, J=1.5, 1.0 Hz, 3H), 1.70 (m, 1H), 1.66 (s, 3H), 1.65 (s, 3H), 1.27 (m, 4H), 0.91 (s, 3H), 0.17 (s, 9H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ 149.3, 146.8, 137.0, 124.6, 113.0, 103.2, 42.5, 40.4, 33.0, 32.9, 25.3, 24.0, 23.0, 21.9, 21.2, 19.6, 0.5 ppm. IR (neat): ν=3074, 2933, 2866, 1660, 1444, 1366, 1263, 1250, 1203, 1137, 963, 938, 894, 840, 752 cm^{-1}. HRMS (ESI-TOF): calcd for $C_{22}H_{40}OSi$ [M+H^+] 349.2921, found 349.2924.

4.2.4. Methylated enone ***67****.* This compound can be prepared in ~20% yield using one of two ways: from ketone **43** or TMS enol ether **66**. *From ketone* ***43***: To a flame-dried 20 mL microwave vial was added IBX (611.0 mg, 2.182 mmol, 4.87 equiv), followed by a solution of ketone **43** (105.0 mg, 0.4480 mmol, 1.00 equiv) in DMSO (4 mL). This mixture was heated to 80 °C for 8 h. The reaction mixture was cooled to room temperature, upon which it was partitioned using saturated aqueous $NaHCO_3$ (5 mL) and EtOAc (5 mL). The aqueous layer was extracted with EtOAc (2×3 mL). The combined organic layers were washed with H_2O (5 mL) then brine (5 mL), dried over $MgSO_4$, and then evaporated to dryness in vacuo. Purification by flash silica gel chromatography afforded **67** (21.0 mg, 20% yield). *From TMS enol ether* ***66***: To a flame-dried 5 mL microwave vial were added TMS enol ether **66** (42.0 mg, 0.115 mmol, 1.00 equiv), MeCN (1 mL), and $Pd(OAc)_2$ (30.0 mg, 0.134 mmol, 1.17 equiv), in that order, and this dark reaction mixture was stirred at room temperature for 16 h. This mixture was directly filtered on Celite (eluting with EtOAc). The obtained solution was evaporated in vacuo and purified by flash silica gel chromatography to afford **67** (5.4 mg, 20% yield) and ketone **43** (9.9 mg, 37%). Appearance: Yellow oil. TLC: R_f=0.57–0.59 (silica gel, 1:3 EtOAc/hexanes). ^1H NMR (400 MHz, $CDCl_3$): δ 6.86 (ddd, J=10.1, 4.6, 3.7 Hz, 1H), 6.03 (dt, J=10.1, 1.9 Hz, 1H), 4.90 (dq, J=3.0, 1.5 Hz, 1H), 4.52 (dq, J=2.7, 0.9 Hz, 1H), 2.33 (dt, J=17.8, 3.0 Hz, 1H), 2.30 (AB quartet, 2H), 2.18 (dddd, J=18.8, 4.6, 1.8, 1.1 Hz, 1H), 2.03 (m, 2H), 1.74 (dd, J=1.5, 0.9 Hz, 3H), 1.65 (s, 3H), 1.63 (s, 3H), 1.37 (m, 2H), 1.02 (s, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ 200.1, 148.4, 146.4, 136.1, 129.2, 125.4, 113.4, 50.3, 40.1, 38.2, 36.6, 25.3, 24.7, 22.8, 21.9, 19.6 ppm. IR (neat): ν=3074, 2960, 2915, 2871, 1679, 1631, 1444, 1386, 1343, 1284, 1246, 1168, 1124, 893, 733 cm^{-1}. HRMS (ESI-TOF): calcd for $C_{16}H_{24}O$ [M+H^+] 233.1900, found 233.1902.

4.2.5. Corey–Chaykovsky products ***57****,* ***69****,* ***71****, and* ***72****.* To a flame-dried 20 mL microwave vial were added trimethylsulfoxonium iodide (58.0 mg, 0.264 mmol, 1.00 equiv), DMSO (200 μL), and NaH (60% dispersion in mineral oil, ~11 mg, ~0.28 mmol, ~1.0 equiv). After stirring for 30 min at room temperature, enone **42** (57.5 mg, 0.263 mmol, 1.00 equiv) was added and the reaction mixture was stirred overnight. H_2O (1 mL) was added and then this reaction mixture was extracted with Et_2O (3×1 mL). The combined organic layers were washed with H_2O (2 mL) then brine (2 mL), dried over $MgSO_4$, and then evaporated to dryness in vacuo. Purification by flash silica gel chromatography afforded **57** (18.3 mg, 30% yield), **69** (6.2 mg, 10% yield), **71** (6.1 mg, 10% yield), **72** (6.2 mg, 10% yield).

*4.2.5.1. Data for (±)-****57****.* Appearance: slightly yellow oil. TLC: R_f=0.56–0.60 (silica gel, 1:3 EtOAc/hexanes). ^1H NMR (400 MHz, $CDCl_3$): δ 4.89 (dq, J=2.9, 1.5 Hz, 1H), 4.50 (dq, J=2.7, 0.9 Hz, 1H), 2.27 (ddd, J=18.4, 5.6, 3.1 Hz, 1H), 2.14 (t, J=8.5 Hz, 2H), 2.08–1.92 (m, 2H), 1.82–1.67 (m, 2H), 1.73 (dd, J=1.5, 0.9 Hz, 3H), 1.64 (s, 6H), 1.62 (m, 1H), 1.59 (dd, J=10.0, 4.5 Hz, 1H), 1.49–1.30 (m, 3H), 0.92 (dd, J=10.0, 5.2 Hz, 1H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ 209.7, 146.3, 135.9, 125.4, 113.4, 37.8, 36.3, 33.8, 28.6, 27.9, 25.6, 22.8, 21.8, 19.6, 18.4, 17.4 ppm. IR (neat): ν=3074, 2914, 2855, 1688, 1631, 1444, 1372, 1323, 1243, 1216, 1170, 1076, 935, 891, 871 cm^{-1}. HRMS (ESI-TOF): calcd for $C_{16}H_{24}O$ [M+H^+] 233.1900, found 233.1904.

*4.2.5.2. Data for (±)-****69****.* Appearance: slightly yellow oil. TLC: R_f=0.74–0.77 (silica gel, 1:3 EtOAc/hexanes). ^1H NMR (400 MHz, $CDCl_3$): δ 5.50 (br s, 1H), 4.91 (dq, J=3.0, 1.5 Hz, 1H), 4.54 (dq, J=2.7, 0.9 Hz, 1H), 2.69 (s, 2H), 2.30 (m, 1H), 2.23–2.13 (m, 4H), 2.11–1.92 (m, 3H), 1.75 (dd, J=1.5, 0.9 Hz, 3H), 1.68–1.58 (m, 2H), 1.66 (s, 6H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ 146.6, 136.7, 136.3, 125.4, 120.5, 113.3, 57.7, 54.4, 36.3, 36.1, 29.6, 29.5, 24.2, 22.9, 21.9, 19.7 ppm. IR (neat): ν=3074, 3034, 2915, 2855, 1631, 1442, 1399, 1371, 1291, 1175, 1040, 931, 891, 826, 790 cm^{-1}. HRMS (ESI-TOF): calcd for $C_{16}H_{24}O$ [M+H^+] 233.1900, found 233.1910.

*4.2.5.3. Data for (±)-****71*** *as a 3:2 mixture of inseparable diastereomers.* Appearance: slightly yellow oil. TLC: R_f=0.79–0.82 (silica gel, 1:3 EtOAc/hexanes). *Major diastereomer*, ^1H NMR (400 MHz, $CDCl_3$): δ 9.72 (d, J=1.3 Hz, 1H), 4.88 (m, 1H), 4.50 (m, 1H), 2.47 (m, 1H), 2.12 (m, 2H), 1.79 (m, 1H), 1.74 (dd, J=1.5, 0.9 Hz, 3H), 1.69 (m, 1H), 1.65 (s, 3H), 1.64 (s, 3H), 1.58 (m, 1H), 1.52–1.44 (m, 1H), 1.44–1.34 (m, 1H), 1.34–1.07 (m, 3H), 1.02 (ddd, J=9.4, 5.2, 1.7 Hz, 1H), 0.53 (dd, J=9.3, 4.5 Hz, 1H), 0.28 (t, J=4.9 Hz, 1H) ppm. *Minor diastereomer*, ^1H NMR (400 MHz, $CDCl_3$): δ 9.66 (d, J=1.5 Hz, 1H), 4.88 (m, 1H), 4.50 (m, 1H), 2.74 (m, 1H), 2.12 (m, 2H), 1.79 (m, 1H), 1.75 (dd, J=1.5, 0.9 Hz, 3H), 1.69 (m, 1H), 1.66 (s, 3H), 1.65 (s, 3H), 1.58 (m, 1H), 1.52–1.44 (m, 1H), 1.44–1.34 (m, 1H), 1.34–1.07 (m, 3H), 0.93 (ddd, J=9.0, 6.7, 5.6 Hz, 1H), 0.48 (dd, J=8.8, 4.8 Hz, 1H), 0.20 (t, J=5.2 Hz, 1H) ppm. *Major diastereomer*, ^{13}C NMR (151 MHz, $CDCl_3$): δ 204.1, 146.8, 136.6, 124.8, 113.0, 48.7, 40.3, 28.1, 27.6, 22.9, 22.9, 21.9, 20.3, 19.6, 19.6, 16.7, 16.4 ppm. *Minor diastereomer*, ^{13}C NMR (151 MHz, $CDCl_3$): δ 204.3, 146.8, 136.4, 124.9, 113.1, 45.6, 40.3, 28.2, 27.9, 22.9, 21.9, 20.4, 20.1, 19.6, 18.9, 16.5, 14.4 ppm. IR (neat): ν=3073, 2925, 2855, 2712, 1726, 1631, 1447, 1371, 1301, 1172, 1123, 1076, 1021, 892, 833 cm^{-1}. HRMS (ESI-TOF): calcd for $C_{17}H_{26}O$ [M+H^+] 247.2056, found 247.2048.

*4.2.5.4. Data for (±)-****72****.* Appearance: slightly yellow oil. TLC: R_f=0.50–0.53 (silica gel, 1:3 EtOAc/hexanes). ^1H NMR (400 MHz, $CDCl_3$): δ 5.39 (d, J=6.5 Hz, 1H), 4.89 (dq, J=3.0, 1.5 Hz, 1H), 4.51 (dq, J=2.7, 0.8 Hz, 1H), 4.13 (br s, 2H), 2.17 (dtd, J=26.2, 13.3, 5.3 Hz, 2H), 2.03 (dt, J=17.1, 6.5 Hz, 1H), 1.90 (dd, J=12.8, 7.2 Hz, 1H), 1.87–1.76 (m, 1H), 1.75 (dd, J=1.5, 0.9 Hz, 3H), 1.66 (s, 3H), 1.65 (s, 3H), 1.50 (td, J=12.6, 5.4 Hz, 1H), 1.45 (td, J=12.5, 6.1 Hz, 1H), 1.32 (br s, 1H), 1.26 (m, 1H), 1.00 (dd, J=8.4, 4.2 Hz, 1H), 0.80 (t, J=4.2 Hz, 1H), 0.64 (dd, J=8.4, 4.2 Hz, 1H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ 146.7, 140.6, 136.7, 124.9, 117.5, 113.0, 67.4, 38.8, 28.5, 24.2, 23.2, 22.9, 21.9, 21.6, 19.6, 19.2, 16.7 ppm. IR (neat): ν=3347 (br), 3072, 2913, 2853, 1661, 1631, 1442, 1371, 1168, 1069, 1050, 1005, 931, 892, 813 cm^{-1}. HRMS (ESI-TOF): calcd for $C_{17}H_{26}O$ [M+H^+] 247.2056, found 247.2053.

4.2.6. Allylated cyclopropane ketone ***73****.* To a flame-dried 10 mL microwave vial equipped with a stir bar was added ketone (±)-**57** (18.0 mg, 0.0775 mmol, 1.0 equiv) in THF (500 μL) and cooled to 0 °C. Lithium diethylamide (2.0 M, synthesized by adding ^{n}BuLi to diethylamine; 40 μL, 0.080 mmol, 1.0 equiv) was added and was stirred at 0 °C for 30 min. A solution of freshly prepared allyl iodide (30 μL, 0.33 mmol, 4.2 equiv) in THF (200 μL) was added and this reaction mixture was warmed to room temperature overnight. The reaction was quenched with saturated aqueous NH_4Cl (1 mL), diluted with H_2O (1 mL), and extracted with EtOAc (3×1 mL). The combined organic layers were washed with H_2O (2 mL) then brine (2 mL), dried over $MgSO_4$, and then evaporated to dryness in vacuo.

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Purification by PTLC (gradient of EtOAc/hexanes) yielded four separate compounds (in order of decreasing R_f), (±)-**74** (1.4 mg, 5% yield, ~90% pure), (±)-**73a** (3.6 mg, 17% yield), (±)-**73b** (2.6 mg, 12% yield) and recovered (±)-**57** (8.9 mg, 49%). While **73a** and **73b** are C5-epimers of one another, the relative stereochemistry at C5 for **73a** and **73b** is unknown.

*4.2.6.1. Data for (±)-**74**.* The full compound characterization has not been obtained. Its structure has been assigned solely by its mass analysis and an analogy to the formation of allylated products **63** and **64** (see Fig. 8). Appearance: slightly yellow oil. TLC: R_f=0.80–0.83 (silica gel, 1:3 EtOAc/hexanes). HRMS (ESI-TOF): calcd for $C_{22}H_{32}O$ [M+H$^+$] 313.2526, found 313.2520.

*4.2.6.2. Data for (±)-**73a**.* Appearance: slightly yellow oil. TLC: R_f=0.77–0.80 (silica gel, 1:3 EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.67 (ddt, *J*=17.3, 10.2, 7.2 Hz, 1H), 5.06–4.99 (m, 2H), 4.90 (dq, *J*=3.0, 1.5 Hz, 1H), 4.51 (dq, *J*=2.7, 0.9 Hz, 1H), 2.50 (dddt, *J*=13.6, 6.7, 3.9, 1.2 Hz, 1H), 2.23 (m, 1H), 2.14 (t, *J*=8.4 Hz, 2H), 2.02 (m, 1H), 1.95 (m, 1H), 1.85–1.70 (m, 2H), 1.74 (dd, *J*=1.5, 0.9 Hz, 3H), 1.65 (s, 6H), 1.61 (d, *J*=10.2, 4.5 Hz, 1H), 1.50–1.30 (m, 4H), 0.85 (dd, *J*=10.2, 5.2 Hz, 1H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ 209.9, 146.4, 136.0, 135.9, 125.5, 117.1, 113.4, 46.0, 37.6, 35.6, 33.7, 27.9, 27.7, 25.6, 22.9, 22.9, 21.9, 19.7, 15.8 ppm. IR (neat): ν=3075, 2916, 2855, 1684, 1640, 1442, 1371, 1335, 1263, 1213, 1171, 1073, 997, 910, 892 cm^{-1}. HRMS (ESI-TOF): calcd for $C_{19}H_{28}O$ [M+H$^+$] 273.2213, found 273.2210.

*4.2.6.3. Data for (±)-**73b**.* Appearance: slightly yellow oil. TLC: R_f=0.74–0.77 (silica gel, 1:3 EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.79–5.68 (m, 1H), 5.06–5.03 (m, 1H), 5.01 (t, *J*=1.2 Hz, 1H), 4.90 (dq, *J*=3.0, 1.5 Hz, 1H), 4.53–4.50 (m, 1H), 2.50–2.42 (m, 1H), 2.17–1.98 (m, 4H), 1.92–1.76 (m, 3H), 1.74 (dd, *J*=1.5, 0.9 Hz, 3H), 1.65 (s, 6H), 1.61–1.56 (m, 2H), 1.38–1.32 (m, 2H), 1.27–1.24 (m, 1H), 1.02 (dd, *J*=10.0, 5.2 Hz, 1H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ 211.2, 146.4, 136.5, 135.9, 125.5, 116.9, 113.4, 43.2, 38.5, 34.8, 33.2, 30.4, 28.1, 26.2, 24.9, 22.9, 21.9, 21.6, 19.7 ppm. IR (neat): ν=3074, 2918, 2856, 1684, 1639, 1443, 1371, 1320, 1265, 1228, 1205, 1167, 996, 909, 892 cm^{-1}. HRMS (ESI-TOF): calcd for $C_{19}H_{28}O$ [M+H$^+$] 273.2213, found 273.2213.

*4.2.7. Acroleinated cyclopropane ketone **75**.* To a flame-dried 10 mL microwave vial equipped with a stir bar was added ketone (±)-**57** (18.0 mg, 0.0775 mmol, 1.0 equiv) in THF (500 μL) and cooled to 0 °C. Lithium diethylamide (2.0 M, synthesized by adding ^{n}BuLi to diethylamine; 40 μL, 0.080 mmol, 1.0 equiv) was added and was stirred at 0 °C for 30 min. A solution of freshly distilled acrolein (distilled over $CaSO_4$; 20 μL, 0.30 mmol, 3.9 equiv) in THF (200 μL) was added and this reaction mixture was warmed to room temperature overnight. The reaction was quenched with saturated aqueous NH_4Cl (1 mL), diluted with H_2O (1 mL), and extracted with EtOAc (3×1 mL). The combined organic layers were washed with H_2O (2 mL) then brine (2 mL), dried over $MgSO_4$, and then evaporated to dryness in vacuo. Purification by PTLC (gradient of EtOAc/hexanes) yielded (±)-**75** (6.0 mg, 29%). Appearance: slightly yellow oil. TLC: R_f=0.71–0.73 (silica gel, 1:3 EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.12 (d, *J*=11.6 Hz, 1H), 6.56 (ddd, *J*=16.7, 11.6, 10.1 Hz, 1H), 5.63 (d, *J*=16.8 Hz, 1H), 5.51 (d, *J*=10.0 Hz, 1H), 4.91 (dq, *J*=3.0, 1.5 Hz, 1H), 4.52 (dq, *J*=2.7, 0.9 Hz, 1H), 2.76 (dd, *J*=17.2, 5.3 Hz, 1H), 2.25 (m, 1H), 2.15 (t, *J*=8.4 Hz, 2H), 2.05 (ddd, *J*=13.3, 5.6, 1.8 Hz, 1H), 1.82 (td, *J*=13.6, 5.6 Hz, 1H), 1.79 (dd, *J*=9.4, 4.1 Hz, 1H), 1.74 (dd, *J*=1.4, 0.9 Hz, 3H), 1.65 (s, 6H), 1.53–1.36 (m, 3H), 1.00 (dd, *J*=9.5, 5.0 Hz, 1H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ 199.1, 146.4, 136.0, 135.1, 132.2, 131.4, 125.9, 125.5, 113.4, 37.7, 33.6, 30.1, 27.9, 24.5, 22.9, 22.1, 21.9, 19.7, 17.6 ppm. IR (neat): ν=3075, 2917, 2856, 1670, 1630, 1611, 1580, 1444, 1372, 1319, 1264, 1228, 989, 892, 875 cm^{-1}. HRMS (ESI-TOF): calcd for $C_{19}H_{26}O$ [M+H$^+$] 271.2056, found 271.2055.

*4.2.8. Methylated alcohol **76**.* To a flame-dried 5 ml microwave vial was added a solution of (±)-**61** (40.0 mg, 0.139 mmol, 1.00 equiv) in PhMe (900 μL) and this was cooled to 0 °C. MeMgBr solution (2.8 M; 200 μL, 0.560 mmol, 4.03 equiv) was then added dropwise, and the reaction mixture was stirred at 0 °C for 10 min. The reaction was quenched with saturated aqueous NH_4Cl (0.5 mL), diluted with H_2O (1 mL), and extracted with EtOAc (3×1 mL). The combined organic layers were washed with H_2O (2 mL) then brine (2 mL), dried over Na_2SO_4, and then evaporated to dryness in vacuo. Purification by silica gel flash chromatography (gradient of EtOAc/hexanes) yielded (±)-**76** (25.3 mg, 60%). Appearance: slightly yellow oil. TLC: R_f=0.64–0.68 (silica gel, 1:3 EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.00 (s, 1 H, D_2O exchangeable), 2.87 (s, 1H), 2.74 (ddd, *J*=14.5, 11.5, 5.2 Hz, 1H), 2.49 (m, 1H), 2.44 (t, *J*=12.2 Hz, 1H), 2.14 (m, 1H), 2.05–1.85 (m, 1H), 1.79 (m, 1H), 1.78 (s, 3H), 1.66 (dddd, *J*=14.0, 4.1, 2.9, 1.5 Hz, 1H), 1.51 (td, *J*=13.2, 3.7 Hz, 1H), 1.39 (m, 1H), 1.29 (dt, *J*=15.2, 5.3 Hz, 1H), 1.25 (s, 3H), 1.24 (dtd, *J*=13.2, 3.5, 1.5, 1H), 1.14 (s, 3H), 1.11 (m, 1H), 1.08 (s, 3H), 1.06 (s, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ 223.6, 137.3, 129.9, 72.2, 64.8, 57.1, 42.8, 40.7, 40.4, 39.5, 38.0, 32.7, 30.2, 28.4, 26.9, 25.1, 24.7, 21.9, 18.7, 18.6 ppm. IR (neat): ν=3504, 2962, 2900, 1661, 1460, 1380, 1369, 1327, 1176, 1137, 1093, 1044, 949, 896, 732 cm^{-1}. HRMS (ESI-TOF): calcd for $C_{20}H_{32}O_2$ [M+H$^+$] 305.2475, found 305.2466.

*4.2.9. Taxadienyl xanthate (+)-**81**.* To a flame-dried 10 mL microwave vial equipped with a stir bar were added KO^{t}Bu (15.0 mg, 0.134 mmol, 2.0 equiv) and THF (1 mL). This was cooled to 0 °C, upon which taxadienol (+)-**80** (19.5 mg, 0.0676 mmol, 1.0 equiv) was added as a solution in THF (0.5 mL), and warmed to room temperature over 2 h. The reaction mixture was cooled to 0 °C, upon which freshly distilled CS_2 (100 μL, 1.66 mmol, 24 equiv) was added and stirred for 1 h at 0 °C. Finally, MeI (50 μL, 0.803 mmol, 12 equiv) was added and the reaction mixture was warmed to room temperature over 1 h. The reaction was quenched with saturated aqueous NH_4Cl (0.5 mL), diluted with H_2O (1 mL), and extracted with EtOAc (3×1 mL). The combined organic layers were washed with H_2O (2 mL) then brine (2 mL), dried over Na_2SO_4, and then evaporated to dryness in vacuo. Purification by silica gel flash chromatography (gradient of EtOAc/hexanes) yielded (+)-**81** (13.1 mg, 51%). Appearance: yellow oil. TLC: R_f=0.42–0.44 (silica gel, hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.39 (d, *J*=4.1 Hz, 1H), 5.32 (s, 1H), 3.22 (s, 1H), 2.81 (td, *J*=13.6, 5.2 Hz, 1H), 2.69 (td, *J*=14.2, 5.2 Hz, 1H), 2.60 (s, 3H), 2.34 (dd, *J*=9.3, 3.9 Hz, 1H), 2.30 (d, *J*=9.6 Hz, 1H), 2.22 (d, *J*=8.8 Hz, 1H), 2.20–2.06 (m, 2H), 2.05–1.94 (m, 2H), 1.85 (ddd, *J*=18.6, 10.5, 3.6 Hz, 1H), 1.80 (s, 3H), 1.71 (s, 3H), 1.46 (s, 3H), 1.42 (ddd, *J*=15.3, 5.0, 3.0 Hz, 1H), 1.37 (ddd, *J*=14.8, 10.6, 4.1 Hz, 1H), 1.15 (m, 1H), 1.03 (s, 3H), 0.99 (s, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ 215.2, 137.8, 136.7, 128.9, 122.4, 90.2, 46.4, 41.8, 40.3, 38.2, 38.2, 38.2, 32.4, 28.9, 26.2, 25.4, 24.8, 24.6, 23.9, 22.1, 21.4, 19.6 ppm. IR (neat): ν=3048, 3004, 2919, 2882, 2857, 1459, 1376, 1250, 1212, 1079, 1052, 963, 895, 821, 784 cm^{-1}. HRMS (ESI-TOF): calcd for $C_{22}H_{34}OS_2$ [M+H$^+$] 379.2124, found 379.2140. Optical rotation: $[\alpha]_D^{20}$ +1.4 (*c* 5.0, $CHCl_3$), taken on a 91% ee sample.

*4.2.10. Dimered enone **85**.* During the formation of enone **42** from bromodiene **11** and vinylcyclohexenone **56**, varying amounts of a bis-addition product have been observed, sometimes not at all, sometimes in large quantities of ~20% yield. This product has been characterized and was found to have the structure shown in Fig. 20. Appearance: yellow oil. TLC: R_f=0.28–0.31 (silica gel, 1:1 EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.85 (s, 1H), 5.82 (s, 1H), 4.99 (dq, *J*=2.9, 1.4 Hz, 1H), 4.54 (dq, *J*=2.7, 0.9 Hz, 1H), 2.40–2.30 (m, 4H), 2.30–2.20 (m, 7H), 2.10–2.00 (m, 2H), 2.00–1.90 (m, 4H), 1.73

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(dd, J=1.4, 0.9 Hz, 3H), 1.68 (s, 3H), 1.66 (s, 3H), 1.65 (m, 1H), 1.57 (m, 1H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ 199.9, 199.8, 168.4, 165.7, 145.3, 133.9, 128.0, 127.0, 125.7, 114.9, 46.2, 37.8, 37.4, 36.0, 34.6, 30.0, 29.1, 27.2, 23.0, 22.8, 22.6, 22.2, 20.4 ppm. IR (neat): ν=3073, 2931, 2866, 1663, 1621, 1453, 1427, 1372, 1345, 1324, 1252, 1190, 1132, 964, 886 cm^{-1}. HRMS (ESI-TOF): calcd for $C_{23}H_{32}O_2$ [M+H$^+$] 341.2475, found 341.2485.

4.3. X-ray crystallographic data

Crystallographic data for (+)-**10**, (−)-**10**, (−)-**61**, and (−)-**86** have been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained free of charge from http://www.ccdc.cam.ac.uk/products/csd/request/ with CCDC # 837815 for (+)-**10**, # 932623 for (−)-**10**, # 932622 for (−)-**61**, and # 840165 for (−)-**86**.

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