Two-Phase Terpene Total Synthesis: Historical Perspective and Application to the Taxol® Problem

Yoshihiro Ishihara, Phil S. Baran*

Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA
Fax +1-(858)784-7375; E-mail: pbaran@scripps.edu

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Abstract: This account presents our laboratory’s latest endeavors in Csp3–H activation in the context of total synthesis, as well as a historical perspective of the field of Csp3–H activation. Our viewpoints in using a two-phase terpene synthesis strategy and how known oxidative transformations could benefit an eventual biomimetic synthesis of Taxol® are discussed.

1 Introduction

‘Biomimetic hydroxylation of saturated carbons [...] – liberating chemistry from the tyranny of functional groups’ – Breslow, 2002

Long before the current surge of studies in the field of C–H activation,¹ pioneers such as Barton² and Breslow³ had been addressing the challenge of Csp3–H functionalization in terpenoid skeletons, specifically, directed Csp3–H oxidations in steroidal substrates. Breslow’s inspiring and insightful quote written early in this century⁴ reflects an interesting and important challenge to address in the coming years. When granted the privilege to write this account on the occasion of the 2010 Thieme–IUPAC Award, we captured the opportunity to provide a unique historical perspective on the challenge of C–H activation in terpene synthesis rather than to recapitulate our studies in total synthesis since this has been done recently from the vantage points of chemoselectivity,⁵ protecting-group-free synthesis,⁶ synthesis economy,⁷,⁸ and ‘ideality’.⁹ Thus, in addition to pointing out key historical precedents and some of our preliminary studies, considerations for a proposed Taxol® synthesis will be presented as well as an extended discussion of the logic of two-phase terpene synthesis.

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2 Csp3–H Functionalization: A Historical Perspective

Advances in organic chemistry during the 20th century allow the modern chemist to maintain and to propagate pre-existing oxidized functionality in a molecule en route to a desired target. Our 2007 review of modern terpene synthesis highlights some great examples of this strategy.¹⁰ However, the chemical community is still dramatically behind the chemoselective prowess of Nature: Oxidases, one of Nature’s powerful chemical tools, can oxidize unfunctionalized Csp3–H bonds in a chemo-, regio-, and stereoselective fashion. An area of research that has been attempting to mimic this efficiency, that of C–H functionalization, has received much attention from the synthetic community over the last 10 to 15 years.¹ Despite its recent resurgence, this concept had been known from over 100 years ago, and thus a brief chronological summary is presented herein.

Although the notion of functionalizing C–H bonds has been known since the 1800’s thanks to free-radical halogenation reactions with Cl₂ or Br₂ (reactions E and F),¹¹ the earliest recognition of directed Csp3–H functionalization can be traced back to A. W. Hofmann,¹² as well as to K. Löffler and C. Freytag.¹²b Their contributions from over 100 years ago led to what is now known as the Hofmann–Löffler–Freytag reaction, a reaction that transforms a Csp3–H into a Csp3–N bond via an alkyl halide intermediate. A few reports on the use of this reaction appeared in the 1950’s,¹³ as well as isolated cases in Csp3–H activation, such as Corey’s hydroperoxy-induced methyl activation in 1956 (reaction T),¹⁴ and Mihailovic’s Pb-mediated, photochemical methyl activation in 1959 (reaction Q).¹⁵ However, no one had undertaken detailed studies in Csp3–H activation until Barton (reaction U)² and Breslow (reaction V)³ in the 1960’s and 1970’s demonstrated directed Csp3–H oxidations in steroidal substrates and carefully tuned substrate conformations to study their effects on reactivity. These two pioneers realized the impact of hydrocarbon oxidation in organic chemistry; Breslow, in particular, went further to coin terms such as ‘biomimetic chemistry’¹⁶ and ‘remote functionalization’.¹⁷

In the following decades, Barton developed nondirected Csp3–H oxidation chemistry (Gif chemistry,¹⁸ reaction A), whereas Breslow continued to work on noncovalently-directed Csp3–H functionalization (reaction S).⁵,¹⁹ There has since been sustained interest in research in Csp3–H bond
oxidation, and while the table below is not comprehensive, an attempt was made to render it extensive and to depict representative developments in this field (Scheme 1). Due to the variety of mechanisms exploited in achieving C-sp3-H functionalizations, the reactions discussed herein are categorized into hydrogen abstraction versus C–H insertion, non-directed versus directed, and metal-mediated versus non-metal-mediated; a disclaimer should also be made here, wherein C–N and C–C bond formations, bonds from carbons to other nonmetals, C-sp2-H oxidations as well as allylic and benzylic C-sp3-H oxidations are not listed.

Just as Nature has numerous oxidases at its disposal, organic chemists are armed with several options to functionalize hydrocarbon skeletons. The next section describes a platform, based on Nature’s strategy, for the use of such methodologies in the context of a multistep total synthesis.

3 Two-Phase Terpene Synthesis: Proof of Principle

Nature creates its library of terpenes in a unified fashion by a two-phase approach, despite the diversity of architectural complexity that is generated. The first of these phases stitches together simple linear hydrocarbon phosphate building blocks by enzymatically controlled cyclizations and rearrangements (cyclase phase). In the second phase, chemo-, regio-, and stereoselective oxidation of olefins and C-sp3-H bonds results in a large array of oxidative diversity (oxidase phase). The awe-inspiring efficiency of biosynthesis that has evolved over time suggests that there might be certain advantages to conducting terpene synthesis in a similar manner. Thus, a two-phase terpene synthesis program was initiated in our laboratory and our first attempts were undertaken in the eudesmane family of sesquiterpenoids (Figure 1). This oxidase phase pyramid places the desired natural product (7) at the apex, and removes oxidized functionalities during the ‘retrosynthetic descent’ of the pyramid. This process is continued until the lowest oxidized members of the family are reached. Out of the ‘level 1’ eudesmane natural products 12–14, the most logical precursor is chosen after carefully considering the merits and drawbacks in both the preceding cyclase phase and the subsequent oxidase phase (12–14 are labeled ‘level 1’ because it is one oxidation state greater than the unfunctionalized eudesmane skeleton). In this case, dihydromenol (13) was chosen due to its potential access to natural products 10 and 11 and due to its projected efficiency in the cyclase phase. As such, the construction of 13 was feasible within nine steps and in 21% overall yield, as well as enantioselectively and in gram-scale (see Scheme 2).

After a short and scalable cyclase phase, 13 then became the ideal system for testing selectivity in C–H functionalization. With a stepwise oxidative ascent toward eudemantetraol (7) in mind, ‘level 2’ eudesmanes 10 and 11 were targeted first (Scheme 2). After the trifluoroethyl carbamate directing group was introduced, carbamate 15 was subjected to methyl(trifluoromethyl)dioxirane (TFDO) to yield selectively, in good yield (82%), and amenable to gram-scale synthesis. Only one of the five tertiary C–H bonds was oxidized (H1 on compound 15), and this selectivity was attributed in part to the release of 1,3-diaxial strain in the transition state (strain release).

Biographical Sketches

Yoshihiro Ishihara was born in Kyoto, Japan, in 1984, but was raised in Montreal, Canada. He received his B.Sc. in chemistry by a two-phase approach, despite the diversity of architectural complexity that is generated. The first of these phases stitches together simple linear hydrocarbon phosphate building blocks by enzymatically controlled cyclizations and rearrangements (cyclase phase). In the second phase, chemo-, regio-, and stereoselective oxidation of olefins and C-sp3-H bonds results in a large array of oxidative diversity (oxidase phase). The awe-inspiring efficiency of biosynthesis that has evolved over time suggests that there might be certain advantages to conducting terpene synthesis in a similar manner. Thus, a two-phase terpene synthesis program was initiated in our laboratory and our first attempts were undertaken in the eudesmane family of sesquiterpenoids (Figure 1). This oxidase phase pyramid places the desired natural product (7) at the apex, and removes oxidized functionalities during the ‘retrosynthetic descent’ of the pyramid. This process is continued until the lowest oxidized members of the family are reached. Out of the ‘level 1’ eudesmane natural products 12–14, the most logical precursor is chosen after carefully considering the merits and drawbacks in both the preceding cyclase phase and the subsequent oxidase phase (12–14 are labeled ‘level 1’ because it is one oxidation state greater than the unfunctionalized eudesmane skeleton). In this case, dihydromenol (13) was chosen due to its potential access to natural products 10 and 11 and due to its projected efficiency in the cyclase phase. As such, the construction of 13 was feasible within nine steps and in 21% overall yield, as well as enantioselectively and in gram-scale (see Scheme 2).

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Biographical Sketches

Yoshihiro Ishihara was born in Kyoto, Japan, in 1984, but was raised in Montreal, Canada. He received his B.Sc. in chemistry under the supervision of Professor Hanadi Sleiman. He is currently a graduate student studying the total synthesis of terpenoids with Professor Phil S. Baran at The Scripps Research Institute.

Phil S. Baran was born in New Jersey, USA, in 1977 and received his undergraduate education from New York University with Professor David I. Schuster in 1997. After earning his Ph.D. with Professor K. C. Nicolaou at The Scripps Research Institute in 2001, he pursued postdoctoral studies with Professor E. J. Corey at Harvard University until 2003, at which point he began his independent career at The Scripps Research Institute rising to the rank of Professor in 2008. His laboratory is dedicated to the study of fundamental organic chemistry through the auspices of natural product total synthesis.

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Scheme 1  Examples of non-directed and directed Csp3-H functionalization methods to generate halides and oxygen-containing functionality; oxidations engendered by the given reaction are indicated in red.
sequence, yielded 4-epi-ajanol (10) in 95% yield. The carbamate moiety’s primary purpose being a directing group for 1,3-diol formation,20q 15 was then brought forward in an alternative synthetic pathway, generating dihydroxyeudesmane (11) in 43% overall yield, after photochemical C–H bond activation into bromide 17, followed by cyclization and directing group cleavage. Structures 10 and 11 were confirmed by X-ray crystallography, and for the latter, structural revision from the original assignment of 11¢ was provided.23a

Access to the more oxidized eudesmanes 924d and 724b required oxidations on both sides of the carbamate moiety, at C4 and C11 (Scheme 3). To this end, intermediate 16 was subjected to C–H oxidation conditions20q to generate bromide 18, which then underwent cyclization and directing group cleavage reactions to generate pygmol (9) directly in 52% overall yield. Divergent synthesis26 took advantage of the same intermediate 18, such that it was dehydrohalogenated and stereoselectively epoxidized via carbamate participation to yield 22, an unnatural eudesmane species of higher oxidation state than pygmol. It is of note that the intermediate olefin 20 is merely a carbamate of the natural product 8.24c Epoxide 22 then furnished two isomeric compounds after acidic or basic ring opening, generating eudesmantetraol (7) and its 11-epi derivative 7¢. In this first example that uses multiple, sequential C–H bond oxidation processes in total synthesis.

Figure 1  A) ‘Oxidase phase pyramid’ for the retrosynthetic planning of the eudesmanes using a two-phase approach; B) eudesmane carbon numbering. Notes: 1) This is not a comprehensive list of all eudesmane oxidation patterns; 2) all eudesmanes in the above diagram are found in Nature and these natural products are indicated with isolation paper references; 3) any sites of oxidations installed onto the eudesmane skeleton are indicated in red.

Scheme 2 Cyclase phase synthesis toward ‘level 1’ eudesmane dihydrojunenol (13), and oxidase phase synthesis toward ‘level 2’ eudesmanes 4-epi-ajanol (10) and dihydroxyeudesmane (11); any additional oxidations installed onto eudesmane 13 are indicated in red.
4-epi-ajanol (10), dihydroxyeudesmane (11), pygmol (9), and eudesmantetraol (7) were synthesized in 12, 12, 13, and 15 steps, with overall yields of 17, 9, 9, and 4%, respectively. It should be noted that the directing group served many pivotal roles: 1) It rendered most of the intermediates crystalline; 2) it acted as a protecting group; 3) it enabled C_{	ext{eq}}–H oxidation; and 4) it accomplished a completely stereoselective olefin functionalization (whereas other epoxidation reagents gave mixtures of isomeric products).

With the completion of a two-phase approach to the eudesmanes, the obvious question is whether such logic can be applied to one of the most famous terpenes of all time: Taxol®.

4 A Two-Phase Approach to Taxol®: Planning Stage

The discovery of Taxol® elicited a worldwide fever in both the biological and chemical communities (its oxidized carbon skeleton is depicted as 25, Figure 2A);\textsuperscript{22} for the former, its impressive anticancer activity and unprecedented mode of action sparked enthusiasm,\textsuperscript{27,28} and for the latter, its intriguing 6-8-6 tricyclic skeleton, anti-Bredt olefin and highly oxidized framework stimulated exceptional interest.\textsuperscript{29} Coupled with its scarcity in nature at the time, this natural product represented the ideal target for an endeavor in total synthesis. Tremendous effort throughout the 1980’s and 1990’s culminated in six total syntheses\textsuperscript{29a–o} and one formal synthesis,\textsuperscript{29p} with the first total syntheses appearing in 1994.\textsuperscript{29a,f,g} The impressive nature of these classic syntheses notwithstanding, we believe that a reexamination of the Taxol® problem more than 15 years later could be of merit, not as a means of supplanting the current production of Taxol®, but rather as a target of academic curiosity. The taxane family of over 300 members\textsuperscript{30} (a sample of oxidized taxane frameworks is shown in Figure 2A) is gifted with a captivating tricyclic framework that could present an unprecedented model system for testing conformational effects in C–H oxidation. A two-phase terpene synthesis strategy that targets Taxol® would also generate other bioactive taxanes that differ in oxidation levels, such as those exhibiting cytotoxic activity against various types of cancer as well as interesting neurological and antibacterial properties.\textsuperscript{30} According to the two-phase design, a taxane skeleton with minimal oxidative adornment should be first constructed during a ‘cyclase phase’, and oxidized taxanes would be targeted by C–H oxidation of this taxane hydrocarbon framework during a subsequent ‘oxidase phase’.

Nature’s taxane library synthesis commences with geranylgeranyl pyrophosphate (23) and cyclization into taxa-4,11-diene (24, Figure 2A).\textsuperscript{31} The precise biological oxidation sequence of the taxane framework is still unknown, and only the first oxidation toward 5α-hydroxytaxadiene has been confirmed (see Figure 2B for taxane numbering).\textsuperscript{32} In pioneering detective work by Williams and Croteau, based on the frequency of oxygenation at various positions in natural taxoids (this variety is expressed in the selection of taxanes in Figure 2A), the oxygenation sequence after C5 oxidation is inferred to be in the order of C10, followed by C9 and C13, then C2 and C7, and finally C1 (Figure 2C).\textsuperscript{33} In order to target many members of the taxane diterpenoids, it appears logical to follow, at least roughly, the assumed order of oxidation that Nature employs, during a ‘synthetic ascent’ of the oxidase phase pyramid. But is a pyramid really the best option for such a complex family of molecules? In the next section, some limitations and desirable aspects of this design are discussed.

5 Heuristic Value of the Oxidation Pyramid

The idea of an ‘oxidase phase pyramid’ merely aids in minimizing non-strategic oxidation state fluctuations and serves to graphically organize, in order of oxidation state,
a family of related natural products. It is of note that this retrosynthesis pyramid differs from conventional terpene retrosynthesis in that C–C bond disconnections are not made while descending the pyramid, and that sets of compounds are generated rather than one. The key stage in planning a two-phase terpene synthesis lies in the determination of the most suitable cyclase phase endpoint, before designing the sequence of C–H oxidations in the forward direction. It is imperative that the selection of this lowly oxidized molecule facilitates the forward execution of the cyclase phase and that it provides a common entry point to access many members of a family of terpenes simultaneously (if several targets are desired). The proposed cyclase phase is thus intended to be short, efficient and scalable, through innovation in synthetic strategy and tactics; the ensuing oxidase phase is expected to identify and to fill current gaps in the chemistry literature, thereby soliciting innovation in synthetic methodology.

When organizing related natural products, one might ask the question, ‘why a pyramid?’ After all, Nature takes a common cyclase phase endpoint and generates an array of oxidized sites, resulting in a divergent synthesis or graphically, an inverse pyramid. However, our attempt to categorize members of a family of natural products by displaying them in pyramidal fashion goes beyond graphical aesthetics and convenience. In fact, oxidation of any hydrocarbon framework, in principle, results in a diamond array – an inverse pyramid at the bottom, and an upright pyramid at the top (Figure 3). At the lower apex lies the bare carbon framework, exemplified by the ‘level 0’ taxane 46. This type of unfunctionalized hydrocarbon may or may not be synthesized in Nature as a cyclase phase endpoint, depending on the natural product family; however, by all means, this structure is thermodynamically stable. On the contrary, at the upper apex lies a hypothetical structure with every available C–H bond oxidized maximally, that is, methyl units into carboxylic acids, methylene units into ketones, and methine units into tertiary alcohols. A molecule of such an extreme level of oxidation, exemplified by the hypothetical ‘level 36’ taxane 47, would be susceptible to an assortment of degradation, fragmentation and rearrangement pathways, including decarboxylation, retro-aldol, retro-Claisen and Grob reactions; therefore, by any means of thermodynamic assessment, these maximally oxidized molecules cannot be considered stable.

Figure 2 A) Taxane biosynthesis and ‘oxidase phase pyramid’ for the retrosynthetic planning of taxane synthesis using a two-phase approach; B) taxane carbon and ring numbering; C) assumed oxygenation sequence of taxadiene in Nature. Notes: 1) This is not a comprehensive list of all taxane oxidation patterns; 2) for clarity and discussion purposes, all side chains attached to hydroxyl groups were omitted; 3) all taxanes in the above pyramid are found in Nature, and these natural products are indicated with isolation paper references; 4) any additional oxidations installed onto taxadiene 24 are indicated in red.
This diamond array of a set of objects does not merely belong to the realm of chemistry and molecules, but is rather inherent to mathematics and combinatorials. It is well-known since the late 1700’s that choosing one or many objects or values from a greater set results in a combination in which the number of possible ways to choose \( k \) objects out of a set of \( n \) objects is given by the formula \( C(n,k) = \frac{n!}{k!(n-k)!} \) (wherein the factorial \( n! \) equals \( n \times (n-1) \times (n-2) \times \ldots \times 2 \times 1 \)). For any number \( n \), \( C(n,n) = 1 \) (there is only one possibility when choosing all objects from a set) and \( C(n,0) = 1 \) (there is also only one possibility when choosing zero objects from a set), and is greatest at \( C(n,k) \) for \( k \) closest to \( n/2 \), thus establishing the diamond arrangement (Figure 3). In the context of chemistry, \( n \) would represent the maximum oxidation level in a given family of compounds (or alternatively, the number of hydrogens the non-oxidized framework possesses), \( k \) would represent the selected oxidation level and \( C(n,k) \) would dictate the number of possible redox isomers at the ‘level \( k \)’ oxidation state. It is of note however, that the number of combinations in chemistry differs from that given by the mathematical equation due to degenerate structures lowering the number of combinations (via molecular symmetry and impossible structures, e.g., ‘isomeric’ 1,1-diols converging into aldehydes) and due to a greater variety of functional groups that chemistry can install, increasing the number of combinations (e.g., a halide or an amine is equivalent to an alcohol in terms of oxidation level).

In a total synthesis endeavor, since the terpene target can never be a fully oxidized form of a given hydrocarbon framework (e.g., ‘level 4’ array of circles, Figure 3), a less oxidized compound would be chosen as the target (e.g., ‘level 3’ array). A pyramid should be designed based on this apex, and this entire pyramid would inherently become a subset of the diamond array. From a synthetic chemist’s standpoint, the set of molecules that fills the pyramid should be restricted to natural products (but this is not required if the natural product family is small). This pyramid could then be made as small as one desires; however, the advantage of using a pyramid would become obsolete for small pyramids with one or two oxidation levels, because its simplicity would not warrant its use. Conversely, there is an inherent disadvantage in designing overly large pyramids as well, since ‘oxidation ascents’ of the pyramid would typically be performed in stepwise fashion, and an excessively large pyramid would necessarily imply a long, linear synthesis phase, which would detract from the efficiency of the preceding cyclase phase. Finally, after including one’s desired targets within the oxidation pyramid, a suitable cyclase phase endpoint.

Figure 3 A ‘combination diamond’ and subsets indicating examples of a logical retrosynthesis pyramid and initial target selection.
should be chosen. Theoretically, any molecule bearing an oxidation state equal to or less than the least oxidized targets in the pyramid is a viable cyclase phase endpoint, but for practical reasons, a lowly oxidized molecule bearing an oxidative resemblance to those in the pyramid should be selected. For example, all quartets of circles within the cartoon pyramid are blackened at the bottom left corner, and thus a logical cyclase phase endpoint would be blackened at the bottom left corner as well (Figure 3). Combining the above considerations with the projected feasibility of the cyclase phase should enable the elucidation of a logical cyclase target.

A final useful feature when generating an oxidation pyramid is that it generates short-term, yet concrete goals: a single student could approach a task as daunting as the synthesis of Taxol® by breaking it down into a series of reasonable milestones.

6 Taxol®: Precedent and First Ruminations

Relying on the above merits and guidelines for using an oxidation pyramid, and considering the inferred order of oxidation that Nature employs, synthesizing the non-hydroxylated taxadiene 48 could be a first target (Figure 4), although this may be too low of an oxidation state to enable an efficient oxidase phase. A second line of consideration could be of one oxidation level higher, i.e., 7-hydroxytaxadiene 49, 10-hydroxytaxadiene 50, and 2-hydroxytaxadiene 51. It is of note that oxidations at C5 and C13 do not need not be incorporated into the cyclase phase due to their ease of installment, these being at allylic positions (see Scheme 4). A combination of sites of oxidation at C2, C7, and C10 (taxanes 52–55) could also provide viable cyclase phase endpoints. At this juncture, established principles in retrosynthesis would take over, in an attempt to maximize synthetic efficiency by implementing cascade reactions when possible, and minimizing non-strategic redox manipulations and protecting group chemistry. The target with the most ‘ideal’ synthetic route on paper would be given primary consideration in the laboratory, and the retrosynthetic analysis would be readjusted as necessary after new laboratory observations are obtained.

After the completion of a scalable route to one of the above cyclase phase endpoints, sequential oxidations of the taxane framework would be planned. The concept of oxidizing the taxane framework itself is not new, as the highly oxidized nature of Taxol® has compelled earlier total syntheses and other synthetic studies into finding a way to oxidize carbon sites adjacent to existing functional groups (at C5, C9, C10, C13 and C14), or in some cases, to oxidize a ‘remote’ carbon atom (at C1; Scheme 4). In biomimetic studies, taxadiene 48 and hydroxytaxadiene 51 underwent allylic oxidation at C5 using SeO₂ and t-butyl hydroperoxide; allylic halogenation at C5 was also performed on an advanced taxane intermediate, such as 58. Within the context of total synthesis, the C13 position of 60 was oxidized using PCC and the corresponding enone 61 was subsequently reduced with NaBH₄ to generate the required C13α alcohol (also see Scheme 6, 61 to 93); in later synthetic studies, direct C13 oxidation was shown to occur with opposite stereochemistry to that above to generate 13β-functionalized compounds 62 and 63. α-Oxidations have also been achieved at various positions of the taxane skeleton: C9 oxidation was secured by generating the enolate of the C10 carbonyl group in 64, and conversely, C10 oxidation was accomplished by generating the enolate of the C9 ketone in 66. Although C14 is not oxidized in Taxol®, many taxanes are oxidized at this position, and therefore this was achieved by making use of an enolate engendered from the C13 ketone in 61. An alternative method to oxidize the C5 position was shown to make use of a carbonyl group at C4, although the conversion from ketone 69 into 70 cannot be considered as an oxidase phase endeavor since it is lacking one carbon atom from a full taxane framework. Finally, in a pioneering report displaying remote oxidation in taxanes, C–H oxidation at C1 was shown be possible on taxane 71 by using dimethyldioxirane (DMDO); although the C4–C20 olefin was also epoxidized, it is of note that
known oxidative transformations in taxanes; oxidations engendered by the given reaction are indicated in red.

Given the massive compilation of knowledge in C–H activation (see Scheme 1) and information garnered from previous taxane studies (see Scheme 4), it is tempting to design possible oxidase phase transformations that could render a future Taxol® synthesis possible by way of a two-phase approach. The few reactions presented herein are

**Scheme 5** Potential applications of C–H oxidation in the taxane framework; please see Scheme 1 for reaction labeling; projected oxidations engendered by the given reaction are indicated in red.

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speculative but are included for the sake of oxidative planning (Scheme 5). With the lessons learned from the chemistry of Baldwin, Sanford, and Schönecker, we envision that carbonyl-directed acetoxylation or hydroxylation could enable oxidations at C7 or C2 of ketones 74 or 76 (it is of note, however, that the transformation from 76 to 77 cannot be considered as an oxidative phase transformation). Although C1 hydroxylation has been previously demonstrated using DMDO (71 to 72 and 73, Scheme 4), substrate 71 contained an olefin that did not survive the reaction conditions; therefore, to correct for this undesired side reaction, the oxetane moiety present in Taxol would be installed early on, such as in 78 or 80. Although the C13-acetoxyl group seems to withdraw enough electron density from the nearby C11–C12 olefin a carbonyl group could also be installed at C10 to prevent olefin epoxidation of 80. In a similar vein, Tenaglia, Murray, Fuchs, Curci, Resnati, Du Bois, or Que–White conditions should also allow this transformation to take place. Moreover, this C1 oxidation could perhaps be made possible by using directed hydroxylation conditions reported in our laboratory; although the reported substrates were typically 1,3-diols, 1,2-direction was also found to be possible. If the rigid taxane framework were to allow carbonate formation to occur after the C–H activation step, substrate 83, bearing a convenient carbonate protection (see Scheme 6), would result. Finally, it could be interesting to see if Suárez conditions would induce 1,4-direction on a substrate such as 84; models of the taxane framework in 84 dictate that the C20 alcohol and the C2 hydrogen are in proximi-

**Scheme 6** Chemo-, regio-, and/or stereoselective transformations in taxanes.
ty, and perhaps THF ring formation could occur to generate 85.

The vast amount of data accumulated in taxane studies would not only be useful in oxidizing C–H bonds, but also in efficient, selective functional group transformations (Scheme 6). Regio- and stereoselective enolate equilibration could set the stereochemistry at both C9 and C10 in one step due to an extraordinary feat of substrate control (65 to 86, and 87 to 88).29g,n,o The carbonate protecting group proved useful in many Taxol® syntheses since it allows a convenient transformation into the required tertiary alcohol–secondary benzoate motif (89 to 90, and 91 to 92).29b-g Stereoselective reduction at C13 was also an oft-used transformation in Taxol® syntheses (e.g., 61 to 93),29a,h,i,m but if the opposite stereochemistry were to be desired for medicinal chemistry purposes, a remarkable C4 alcohol-directed reduction could take place from the a face of the puckered molecule, resulting in a C13β alcohol (61 to 94).33d The C4–C20 olefin seems to be sufficiently electronically and sterically different from the C11–C12 olefin, such that chemoselective (as well as stereoselective) functionalization of the former is possible (95 to 96, and 71 to 97).29g,38e Some reagent- and substrate-controlled differentiations of functional groups were achieved in the silylation of 98 to 93,23m and in the acetylation of 99 to 100.34e Finally, a classic example of the mysteries of the taxane system reported that camphanic chloride esterification occurred at the C9 alcohol, but a simple acetylation occurred at the C10 alcohol on the same substrate 101.29d

7 Conclusions and Outlook

In this account, we have highlighted historical examples of C(sp3)−H oxidation and how it set a foundation for us to view terpene synthesis as a platform for sequential C(sp3)−H oxidations. The eudesmane total synthesis was a proof-of-concept study that allowed us to formulate guidelines for the use of an oxidation pyramid, for which a more detailed viewpoint is delineated herein. A dauntingly complex, yet intriguing system on which to implement the two-phase strategy is that of the taxanes, and we hope to build upon the formidable efforts of others in the field that have spearheaded C(sp3)−H oxidation strategies and functional group conversions specific to the taxane system. Ultimately, we hope that future endeavors in pursuing a two-phase terpene total synthesis (on taxanes or other terpene families) will aid in identifying gaps in current methodology and provide numerous opportunities for invention. Some of these opportunities for innovation include: 1) The development of a practical and versatile means of achieving controllable dehydrogenation (a synthetic desaturase); 2) new methods to override inherent C–H bond reactivity without recourse to directing groups; 3) new multipurpose directing groups, which in some cases might be more useful than a reagent-only approach; 4) strategic innovation in the design and execution of a highly practical (gram-scale), minimally oxidized hydrocarbon synthesis (cyclase phase).

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