

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

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Abstract: This account presents our laboratory's latest endeavors in C_{sp3}-H activation in the context of total synthesis, as well as a historical perspective of the field of C_{sp3}-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.

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Key words: biomimetic synthesis, oxidation, pyramid, terpenoids, total synthesis

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 C_{sp3}-H functionalization in terpenoid skeletons, specifically, directed C_{sp3}-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.

2 C_{sp3}-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 C_{sp3}-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*, Scheme 1),¹¹ the earliest recognition of directed C_{sp3}-H functionalization can be traced back to A. W. Hofmann,^{12a} 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 C_{sp3}-H into a C_{sp3}-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 C_{sp3}-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 C_{sp3}-H activation until Barton (reaction *U*)² and Breslow (reaction *V*)³ in the 1960's and 1970's demonstrated directed C_{sp3}-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 C_{sp3}-H oxidation chemistry (Gif chemistry,¹⁸ reaction *A*), whereas Breslow continued to work on noncovalently-directed C_{sp3}-H functionalization (reaction *S*).^{4,19} There has since been sustained interest in research in C_{sp3}-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).²⁰ 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.²¹

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.²² 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 program²³ was initiated in our laboratory and our first attempts were undertaken in the eudesmane family of sesquiterpenoids (Figure 1).²⁴ This oxidase phase pyramid places the desired natural product (**7**)^{24b} 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**,^{24g–i} 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, dihydrojunenol (**13**)^{24h} was chosen due to its potential access to natural products **10**^{24e} and **11**^{24f} 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).²³

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 eudesmantetraol (**7**) in mind, 'level 2' eudesmanes **10** and **11** were targeted first (Scheme 2). After the trifluoroethyl carbamate directing group^{20q} was introduced, carbamate **15** was subjected to methyl(trifluoromethyl)dioxirane (TFDO)^{20k} to yield **16** 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).²⁵ Alkaline cleavage of the carbamate moiety, which served as a protecting group in this synthetic se-

Biographical Sketches



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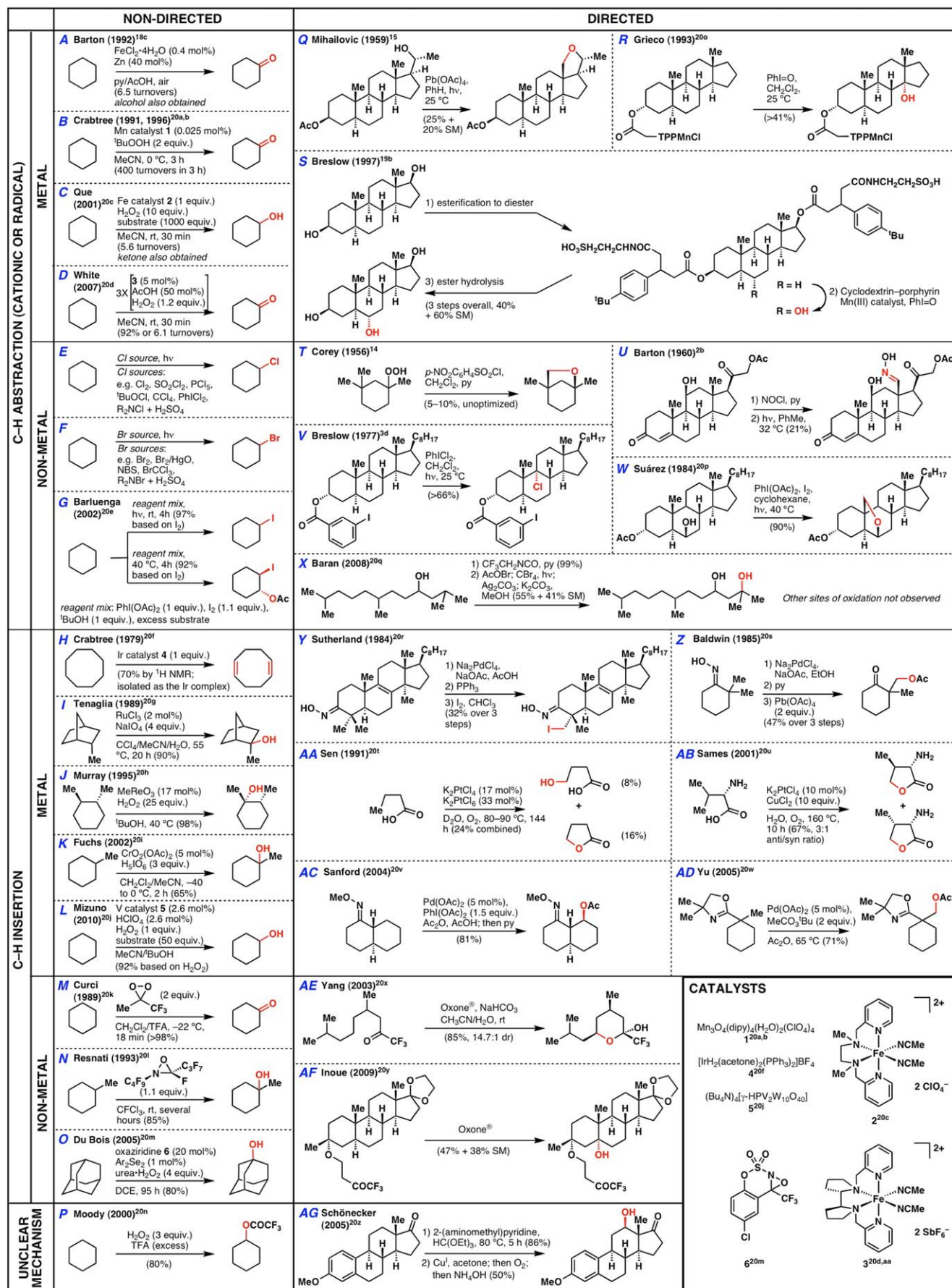
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Institute rising to the rank of Professor in 2008. His laboratory is dedicated to the study of fundamental organic chemistry through the auspices of natural product total synthesis.



Scheme 1 Examples of non-directed and directed C_{sp}³–H functionalization methods to generate halides and oxygen-containing functionality; oxidations engendered by the given reaction are indicated in red.

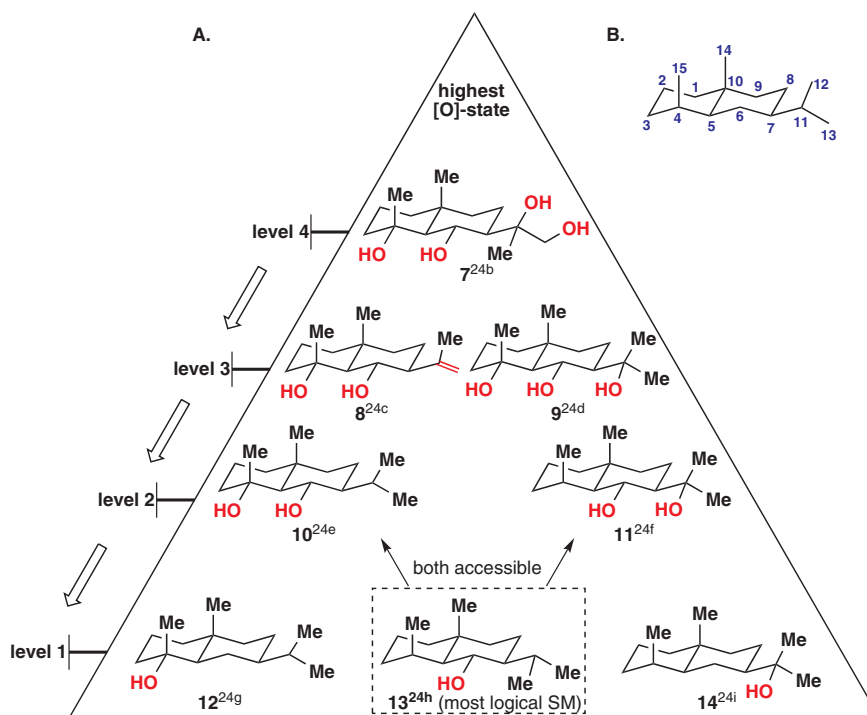
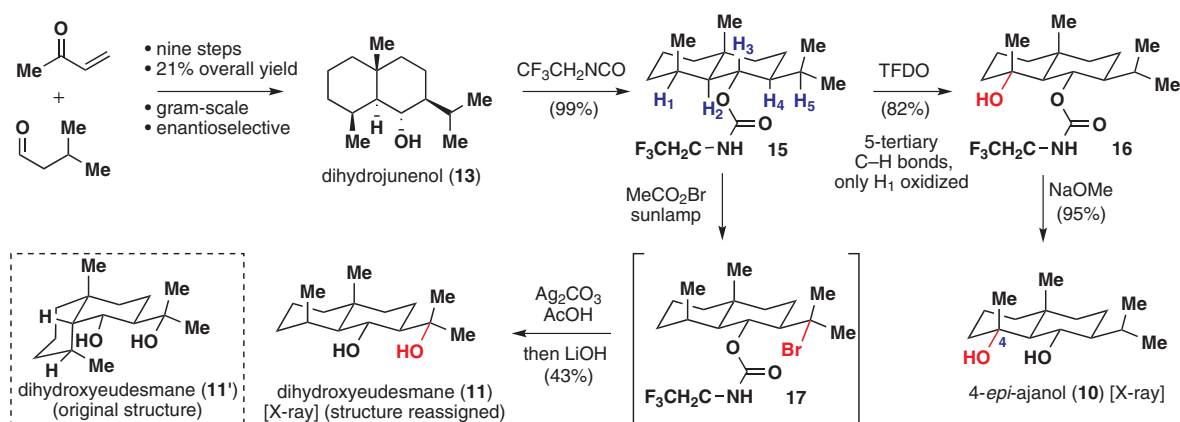


Figure 1 A) 'Oxidase phase pyramid' for the retrosynthetic planning of the eudesmanes using a two-phase approach; B) eudesmane carbon numbering. Notes: 1) This is not a comprehensive list of all eudesmane oxidation patterns; 2) all eudesmanes in the above diagram are found in Nature and these natural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

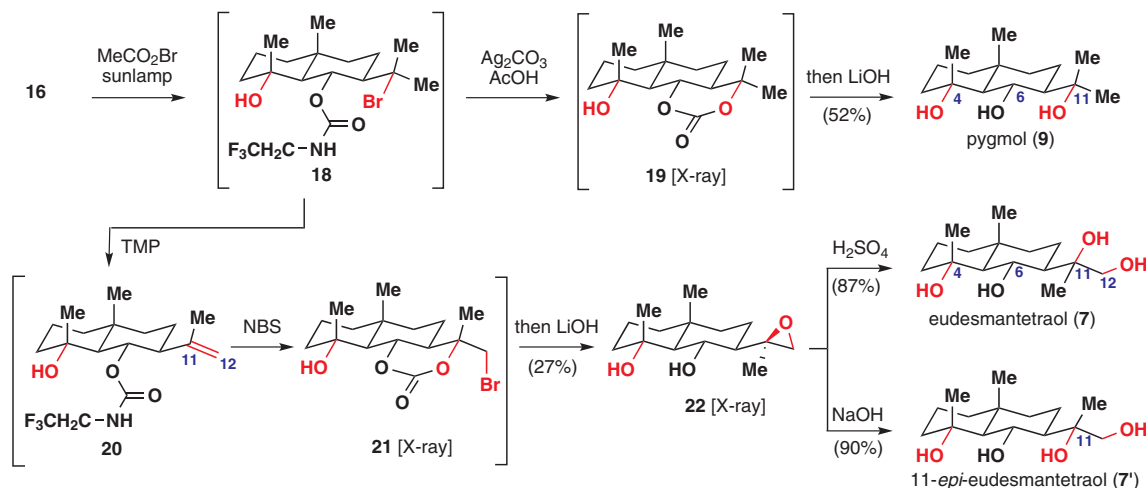
quence, yielded 4-*epi*-ajanol (**10**) in 95% yield. The carbamate moiety's primary purpose being a directing group for 1,3-diol formation,^{20q} **15** was then brought forward in an alternative synthetic pathway, generating dihydroxyeudesmane (**11**) in 43% overall yield, after photochemical C–H 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 **9**^{24d} and **7**^{24b} 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 conditions^{20q} to generate bromide **18**, which then underwent cyclization and directing group cleavage reactions to generate pygmal (**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 pygmal. 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,



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.



Scheme 3 Synthetic route toward oxidized eudesmanes pygmul (**9**), eudesmantetraol (**7**), and 11-*epi*-eudesmantetraol (**7'**); any additional oxidations installed onto eudesmane **13** are indicated in red.

4-*epi*-ajanol (**10**), dihydroxyeudesmane (**11**), pygmul (**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_{sp3}-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);²⁷ for the former, its impressive anticancer activity and unprecedented mode of action sparked enthusiasm,^{27,28} and for the latter, its intriguing 6-8-6 tricyclic skeleton, *anti*-Bredt olefin and highly oxidized framework stimulated exceptional interest.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^{29a-o} and one formal synthesis,^{29p} with the first total syntheses appearing in 1994.^{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 members³⁰ (a sample of oxidized taxane frameworks is shown in Figure 2A) is gifted with a captivating tricy-

clic 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.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).³¹ The precise biological oxidation sequence of the taxane framework is still unknown, and only the first oxidation toward 5 α -hydroxytaxadiene has been confirmed (see Figure 2B for taxane numbering).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).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 fluctuations⁷ 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 synthesis²⁶ – 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 esthetics 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.

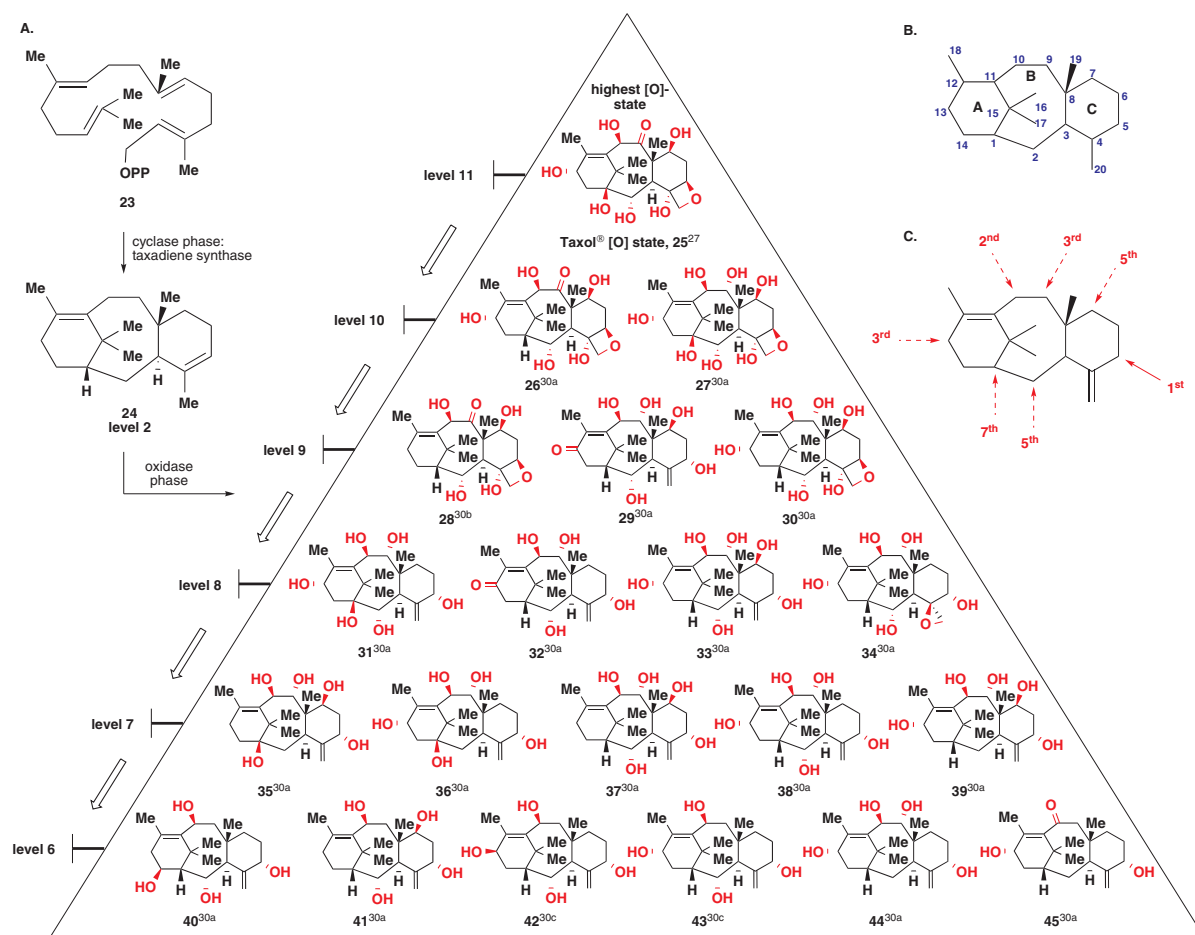


Figure 2 A) Taxane biosynthesis and ‘oxidase phase pyramid’ for the retrosynthetic planning of taxane synthesis using a two-phase approach; B) taxane carbon and ring numbering; C) assumed oxygenation sequence of taxadiene in Nature.³³ Notes: 1) This is not a comprehensive list of all taxane oxidation 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 combinatorics. It is well-known since the late 1700's that choosing one or many objects out of a set of n objects is given by the formula $C(n,k) = n!/[k!(n-k)!]$ (wherein the factorial $n!$ equals $n \times (n-1) \times (n-2) \times \dots \times 3 \times 2 \times 1$).³⁴ 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 in-

stall, 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

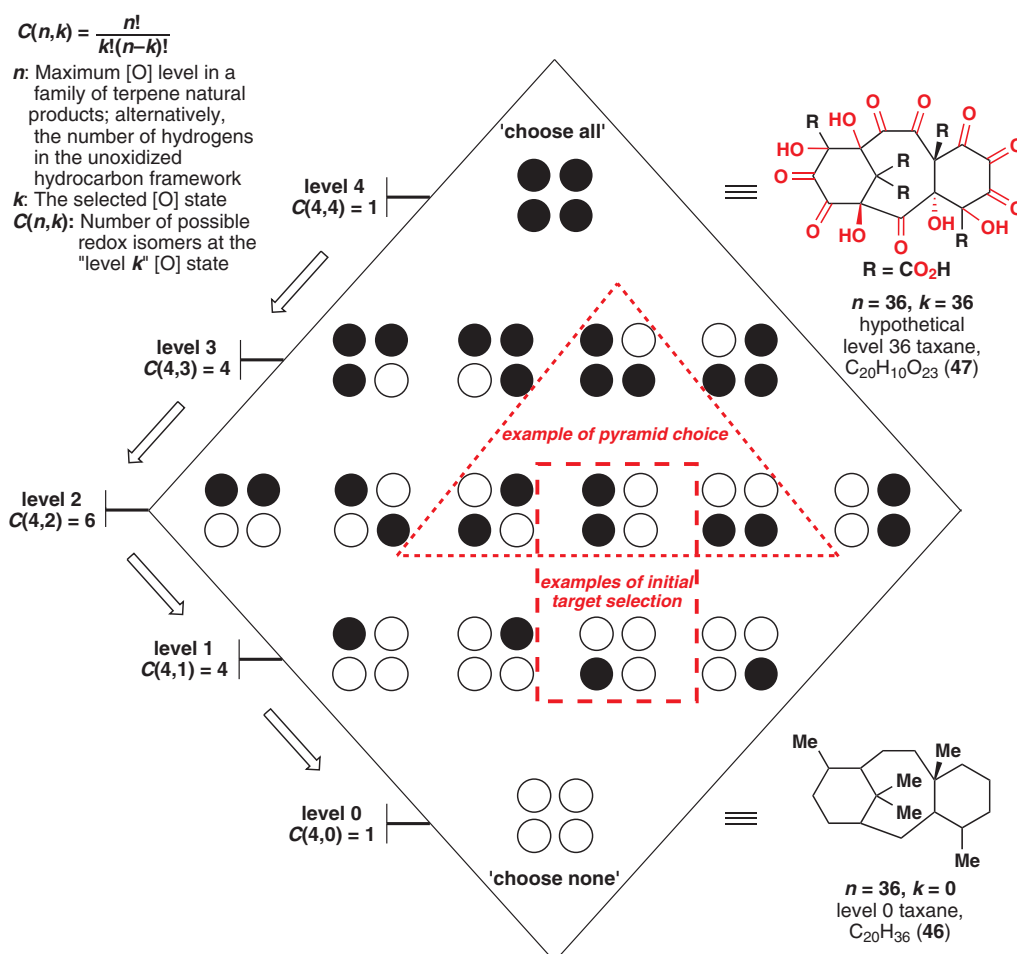


Figure 3 A 'combination diamond' and subsets indicating examples of a logical retrosynthesis pyramid and initial target selection.

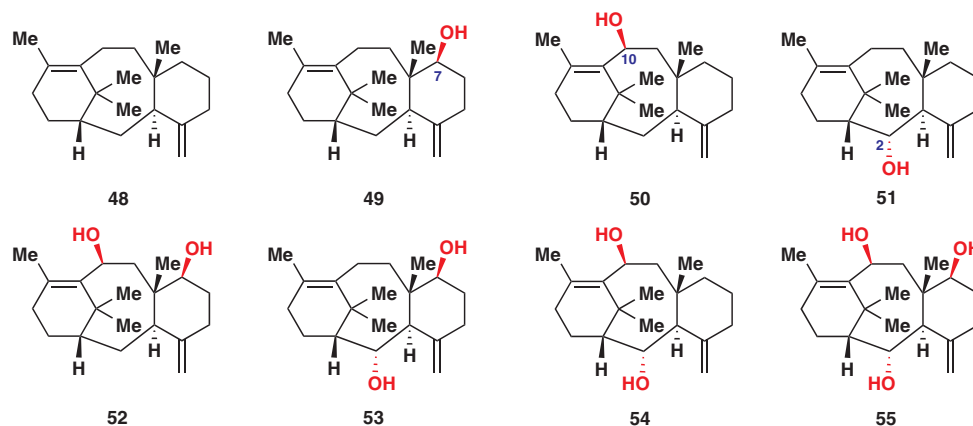


Figure 4 Potential cyclase phase endpoints for the two-phase synthesis of taxanes; any additional oxidations installed onto taxadiene **48** are indicated in red.

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.

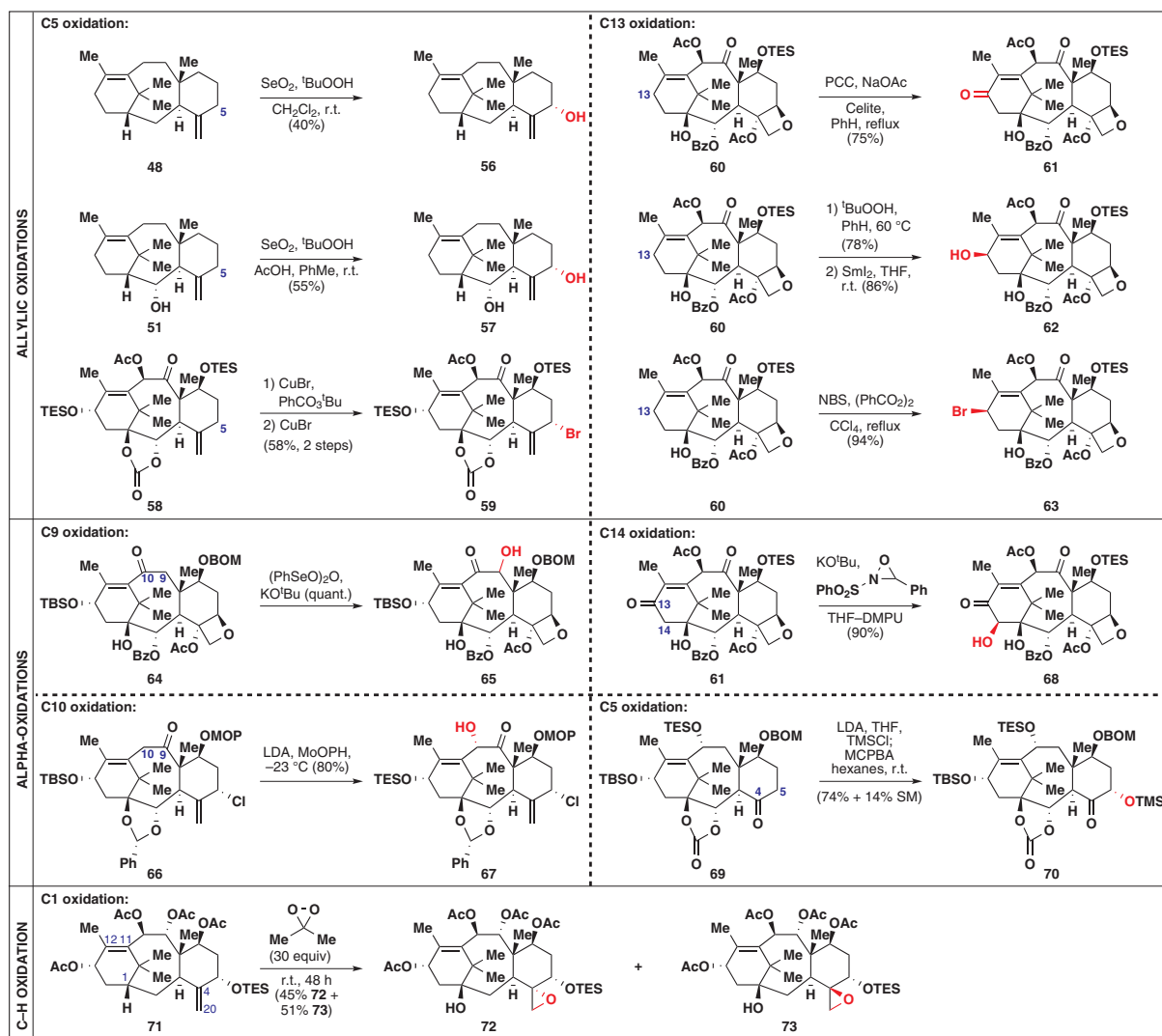
A final useful feature when generating an oxidation pyramid is that it generates short-term, yet concrete goals: a single student could approach a task as daunting as the synthesis of Taxol® by breaking it down into a series of reasonable milestones.

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**³⁵ 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 retrosynthesis³⁶ would take over, in an attempt to maximize synthetic efficiency by implementing cascade reactions when possible,³⁷ and minimizing non-strategic redox manipulations^{7,8} and protecting group chemistry.⁶ The target with the most ‘ideal’ synthetic route⁹ on paper would be given primary consider-

ation 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 syntheses²⁹ and other synthetic studies³⁸ 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;^{32,38a} allylic halogenation at C5 was also performed on an advanced taxane intermediate, such as **58**.^{29m} 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**);^{29a} 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**.^{38b} 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**,^{29g} and conversely, C10 oxidation was accomplished by generating the enolate of the C9 ketone in **66**.^{29n,o} Although C14 is not oxidized in Taxol®, many taxanes are oxidized at this position,³⁰ and therefore this was achieved by making use of an enolate engendered from the C13 ketone in **61**.^{38c} An alternative method to oxidize the C5 position was shown to make use of a carbonyl group at C4,^{29g} 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 to be possible on taxane **71** by using dimethyldioxirane (DMDO); although the C4–C20 olefin was also epoxidized, it is of note that

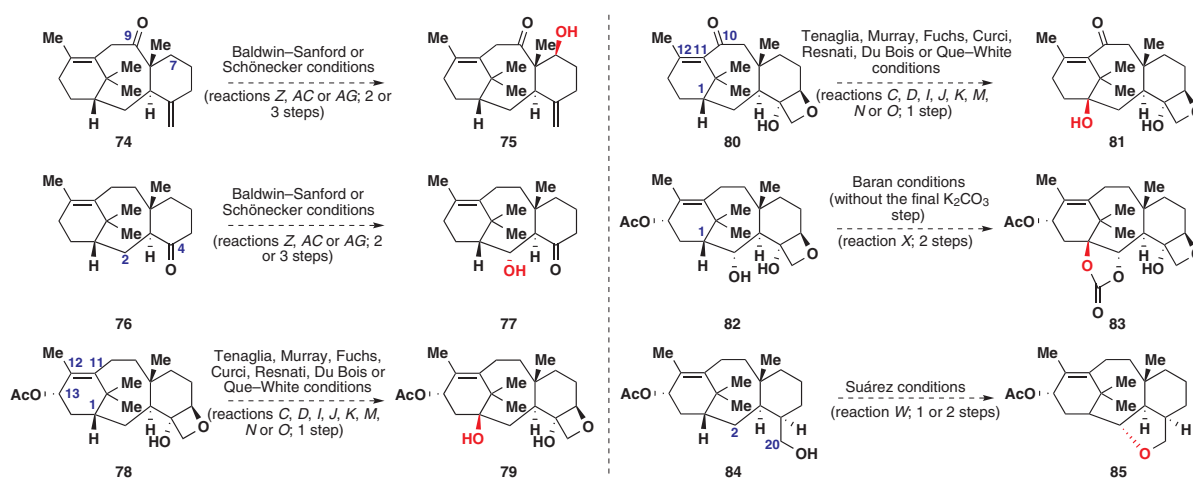


Scheme 4 Known oxidative transformations in taxanes; oxidations engendered by the given reaction are indicated in red.

epoxidation of the C11–C12 olefin could be avoided under these reaction conditions.^{38d,e}

Given the massive compilation of knowledge in C–H activation (see Scheme 1) and information garnered from

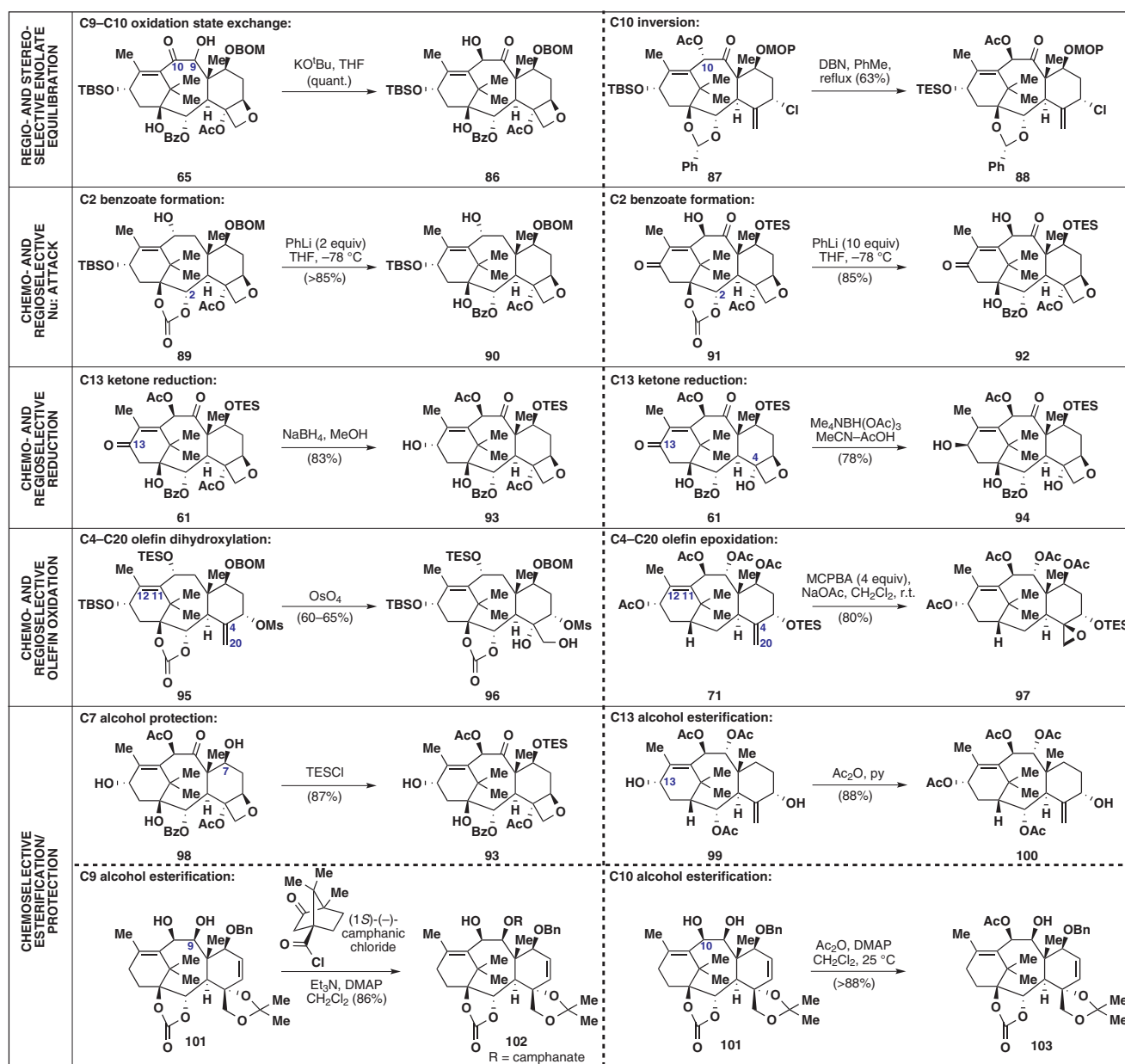
previous taxane studies (see Scheme 4), it is tempting to design possible oxidase phase transformations that could render a future Taxol® synthesis possible by way of a two-phase approach. The few reactions presented herein are



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.

speculative but are included for the sake of oxidative planning (Scheme 5). With the lessons learned from the chemistry of Baldwin,^{20s} Sanford,^{20v} and Schönecker,^{20z} 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 oxidase 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-acetoxy group seems to withdraw enough electron density from the nearby C11–C12 olefin,^{38d,e} a carbonyl group could also be installed at C10 to

prevent olefin epoxidation of **80**. In a similar vein, Tenaglia,^{20g} Murray,^{20h} Fuchs,²⁰ⁱ Curci,^{20k} Resnati,^{20l} Du Bois,^{20m} or Que-White^{20c,d,aa} 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.^{20q} 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^{20p} 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 proximity.



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 α face of the puckered molecule, resulting in a C13 β alcohol (**61** to **94**).^{38f} 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**,^{29m} and in the acetylation of **99** to **100**.^{38e} 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 cas-

es 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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