Article

Two-Phase Synthesis of Taxol

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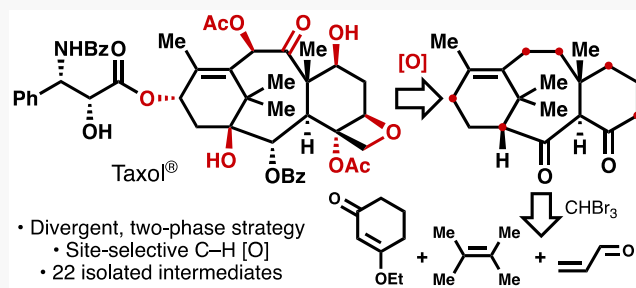
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ABSTRACT: Taxol (a brand name for paclitaxel) is widely regarded as among the most famed natural isolates ever discovered, and has been the subject of innumerable studies in both basic and applied science. Its documented success as an anticancer agent, coupled with early concerns over supply, stimulated a furious worldwide effort from chemists to provide a solution for its preparation through total synthesis. Those pioneering studies proved the feasibility of retrosynthetically guided access to synthetic Taxol, albeit in minute quantities and with enormous effort. In practice, all medicinal chemistry efforts and eventual commercialization have relied upon natural (plant material) or biosynthetically derived (synthetic biology) supplies. Here we show how a complementary divergent synthetic approach that is holistically patterned off of biosynthetic machinery for terpene synthesis can be used to arrive at Taxol.

- Divergent, two-phase strategy
- Site-selective C–H [O]
- 22 isolated intermediates

INTRODUCTION

Taxol (a brand name for paclitaxel, **1**, Figure 1) stands among the most famous terpene-based natural products to be used in a clinical setting.[1] Registering more than US$9 billion in sales between 1993 and 2002[2] for use as an anticancer agent, Taxol is still prescribed today in generic form, and alternative formulations such as Abraxane (albumin-bound) have generated more than US$5.5 billion in revenue as of January 2020.[3] Numerous other taxanes either have been approved by the FDA or are in various stages of clinical development.[4–6] The storied history of Taxol in society began in ancient times and has been narrated in numerous books and reviews.[1,7–10] After the molecule's iconic structure was fully elucidated in 1971,[11] and clarity regarding its unique mechanism of action was revealed in 1979,[12] numbers of clinicians, formulations experts, biologists, and chemists contributed to its eventual use as a life-saving medicine in 1992.[13] Taxol has stimulated research in nearly all branches of chemical science, including medicinal, natural product, engineering, chemical biology, biochemistry, and last but not least, synthetic organic. Historically, the clinical use of **1** relied exclusively on semi-synthesis,[14,15] both for the preparation of analogues (from **2**) and as the initial commercial source before the advent of a synthetic biology-based route using plant-cell cultures.[16,17]
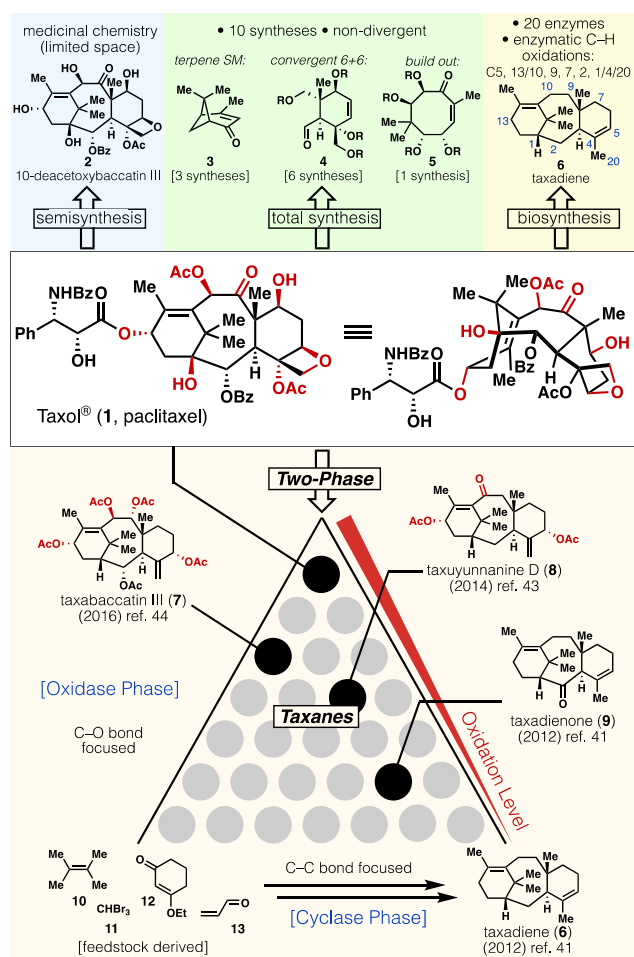
Structurally, this heavily oxygenated polycyclic diterpenoid presents a monumental challenge for total synthesis due to the dense orientation of functionality that renders precise and predictable manipulations difficult. Any route to such a molecule must address the issue of a conformationally flexible central eight-membered ring system, which makes the neighboring reactivity of various functional groups unpredict-

able and substrate-dependent. In addition, the congested array of similarly reactive secondary alcohols creates a chemo-selectivity puzzle of the highest magnitude. In the early 1990s, at least 30 teams[18] competed for finishing the synthesis first, and all completed syntheses, regardless of date, have been deservedly heralded as major (even "herculean")[1] accomplishments in the annals of organic chemistry. A relatively concise totally synthetic approach to **1** has been widely viewed as impossible, with one textbook (published in 2007) declaring that "even an academic-type synthesis of **1** poses a major challenge, unlikely to be solved by a preparation under 30 or 40 steps in length".[9] This prediction had so far proven true, as 10 distinct syntheses have been disclosed (from 1994 to 2015).[19–31] Of those, seven have reported totally synthetic approaches and three have described formal syntheses that intercepted known intermediates. From a strategic perspective, three of these syntheses used naturally occurring terpene starting materials (e.g., **3**),[19,20,23,24,27] six of them fused two chemically synthesized six-membered ring systems to form the central eight-membered ring (e.g., **4**),[21,22,25,27–31] and one built out by double annulation onto an already-constructed eight-membered ring (e.g., **5**).[26] Previous approaches to **1** showed that it was feasible to create such a molecule in the lab and paved a foundation for future approaches to taxanes.

Figure 1. Approaches to the synthesis of Taxol (**1**): semi-synthesis, canonical total synthesis, biosynthesis, and two-phase synthesis (this work).

first class of enzymes (cyclases) forges C–C bonds to generate complex hydrocarbon-based frameworks in what is known as a "cyclase phase". These minimally oxidized terpenes are then processed by a second set of enzymes that install C–O bonds in what is known as an "oxidase phase". This ingenious synthetic plan, despite being linear rather than convergent, benefits strategically from near-perfect redox economy and ideality. Divergent access to analogues is encoded into this logic, as each oxidative event during the oxidase phase potentially gives rise to different bioactivity; thus, the oxidase phase represents a superb medicinal chemistry machinery from an evolutionary standpoint. It therefore stands to reason that designing a chemical synthesis patterned off this biosynthetic route for structures as complex as **1** could harbor similar divergence, in contrast to conventional abiotic approaches to **1** that have been reported to date.

In 2009, we disclosed a proof-of-concept to efficiently access highly oxidized terpenes that holistically mimics this underlying logic of biosynthesis.[34] Two-phase terpene synthesis logic, despite lacking convergency, could be applied to concise syntheses of complex systems such as ingenol,[35] phorbol,[36] thapsigargin,[37] and others.[38,39] Application of this strategy to the non-skeletally rearranged taxanes,[40] of which **1** resides at the apex of structural complexity, remained aspirational for the past decade. This can be visualized in Figure 1, with a hypothetical retrosynthetic pyramid for the two-phase synthesis of **1** requiring a chemist to navigate no less than nine different C–O bond-forming steps from a minimally oxidized taxane precursor such as taxadienone (**9**). Initial progress toward this goal was registered in 2012 with the scalable synthesis of enantiopure **9** and taxadiene (**6**) through a concise cyclase phase.[41] Although bioengineering approaches to **6** are known,[42] our laboratory has been a primary supplier of this molecule to numerous groups around the world (nine as of this writing). Extensive studies were then performed to decipher the innate reactivity of **6** toward allylic oxidation (installation of C-5, C-10, and C-13) culminating in the total synthesis of taxuyunnanine D (**8**).[43] Translating those lessons to the total synthesis of taxabaccatin III (**7**) via **9** was successful.[44] As aforementioned, the vexing arrangement of oxygenation required more than a consideration of chemo-, regio-, and stereoselectivity which Nature mastered using eons of evolution with enzymes. Scheme 1 outlines a route to **1** that overcomes such challenges.

■ TWO-PHASE SYNTHESIS OF TAXOL

Starting from simple feedstock-derived building blocks **10–13**, the cyclase phase published in 2012[41] underwent significant optimization and was initially accomplished using flow chemistry by Albany Molecular Research Inc. (AMRI) to deliver multi-gram quantities of **14**.[45] Subsequently, our collaborators (Chemveda) devised a semi-process-scale second-generation cyclase phase route through the following modifications (see the Supporting Information (SI) for full summary and graphical procedure): (i) use of alternative solvents for extracting volatile intermediates to simplify workup; (ii) replacement of s-BuLi with less expensive n-BuLi; (iii) use of a more easily accessible ligand to set the stereochemistry; (iv) development of an operationally convenient and reproducible enolate trapping sequence; (v) shorter reaction time; and (vi) development of a simple recrystallization protocol for purification. In this way, ca. 110 g of **14** was prepared in a simple batch protocol. Lessons from

However, these pioneering studies remained within the realm of academic research, as they did not form a basis for scalable chemical production of **1** or a viable medicinal chemistry campaign to explore taxane's bioactivity. Obviously, the quantity of **1** chemically synthesized by these efforts (or ours) can never match the metric ton quantities prepared yearly through plant-derived sources. Aside from efficiency, another salient feature of taxane biosynthesis is its inherent divergency and the formation of hundreds of differentially oxidized analogues. It is this feature of biosynthesis that we sought to mimic in the two-phase retrosynthetic approach. Since prior approaches followed the canonical rules of retrosynthetic analysis (e.g., maximizing convergency) to establish the feasibility of accessing specifically **1**, actual taxanes (compounds containing the full carbon skeleton) are not accessed in those syntheses until late in the sequence.

The goal of this study, initiated in 2007, was to answer to a fundamental question of whether an approach to terpene synthesis loosely patterned on the logic of biosynthesis would enable a hypothetical medicinal chemistry approach to taxanes in the absence of a viable semi-synthetic option. Herein we present the realization of our ultimate goal: a two-phase synthesis of Taxol (**1**).
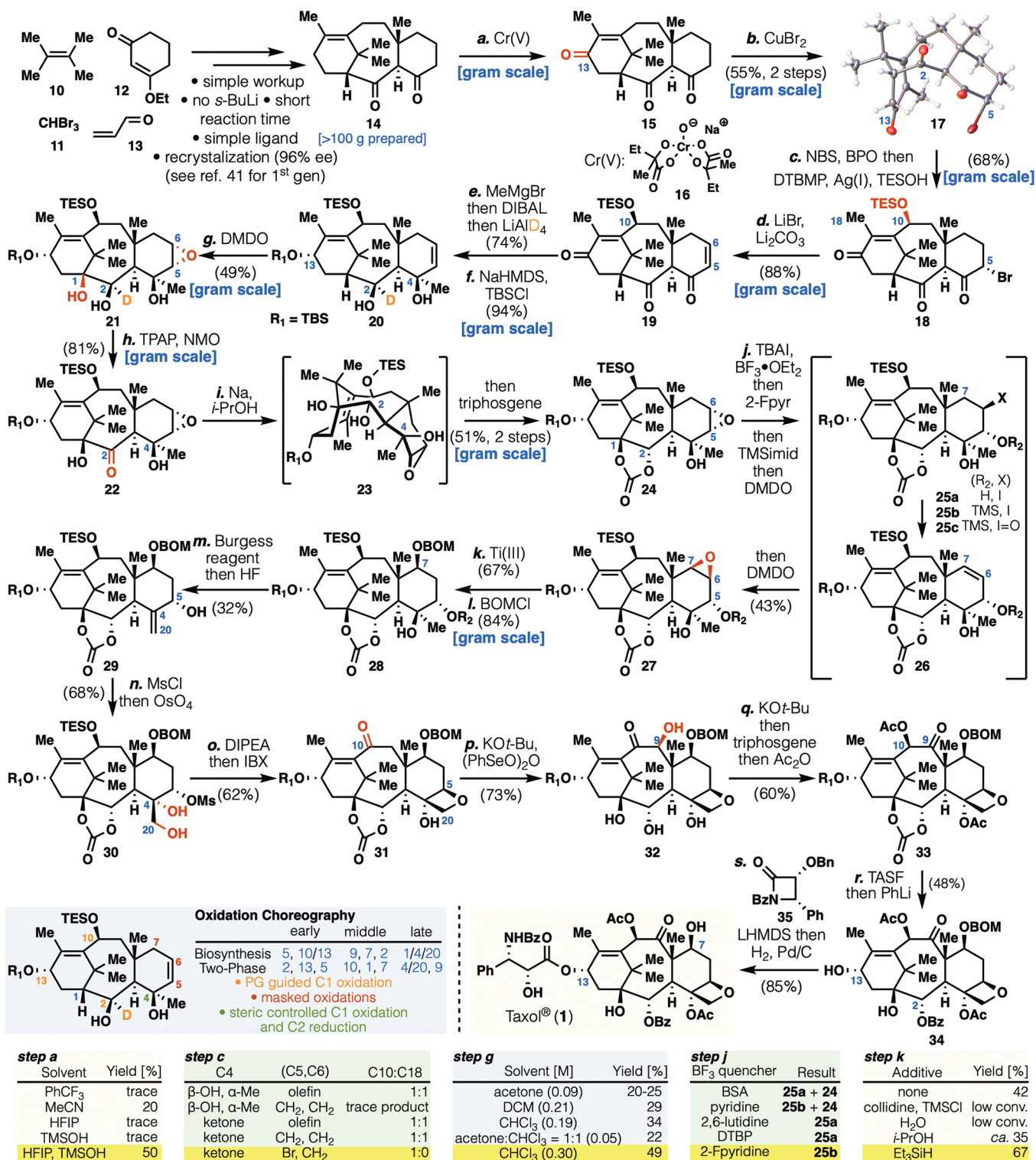
Nature's route to complex terpenes is well-documented and enlists two conceptually different types of enzymes.[32,33] The

Scheme 1. Two-Phase Synthesis of 1[a]

Oxidation Choreography

	early	middle	late
Biosynthesis	5, 10/13	9, 7, 2	1/4/20
Two-Phase	2, 13, 5	10, 1, 7	4/20, 9

• PG guided C1 oxidation
• masked oxidations
• steric controlled C1 oxidation and C2 reduction

Taxol® (1)

step a

Solvent	Yield [%]
PhCF₃	trace
MeCN	20
HFIP	trace
TMSOH	trace
HFIP, TMSOH	50

step c

C4	(C5,C6)	C10:C18
β-OH, α-Me	olefin	1:1
β-OH, α-Me	CH₂, CH₂	trace product
ketone	olefin	1:1
ketone	CH₂, CH₂	1:1
ketone	Br, CH₂	1:0

step g

Solvent [M]	Yield [%]
acetone (0.09)	20-25
DCM (0.21)	29
CHCl₃ (0.19)	34
acetone:CHCl₃ = 1:1 (0.05)	22
CHCl₃ (0.30)	49

step j

BF₃ quencher	Result
BSA	25a + 24
pyridine	25b + 24
2,6-lutidine	25a
DTBP	25a
2-Fpyridine	25b

step k

Additive	Yield [%]
none	42
collidine, TMSCl	low conv.
H₂O	low conv.
i-PrOH	ca. 35
Et₃SiH	67

[a]Reagents and conditions: (a) Cr(V) (**16**), HFIP, TMSOH, t-BuOH, 80 °C. (b) CuBr₂, THF, rt, 55%, over two steps. (c) NBS, BPO, CCl₄, then DTBMP, AgOTf, TESOH, 4 Å MS, PhMe, rt, 68%. (d) LiBr, Li₂CO₃, DMF, 100 °C, 88%. (e) MeMgBr, DCM, 0 °C to rt, then DIBAL, −78 °C, DCM, then LiAlD₄, THF, 60 °C, 74%. (f) NaHMDS, TBSCl, THF, 0 °C to rt, 94%. (g) DMDO, 0 °C, 49%. (h) TPAP, NMO, DCM, rt, 81%. (i) Na, i-PrOH, Et₂O, rt, then triphosgene, pyr, DMAP, DCM, −78 to 0 °C. (j) TBAI, BF₃·OEt₂, DCM, −78 °C, then 2-Fpyr, −78 °C, then TMSIm, rt, then DMDO, −78 °C to rt, 43%. (k) Cp₂TiCl, Et₃SiH, THF, −78 °C to rt, 67%. (l) BOMCl, TBAI, DIPEA, DCE, 45 °C, 84%. (m) Burgess reagent, PhMe, dioxane, then HF, H₂O, pyr, MeCN, rt, 32%. (n) MsCl, pyr, 0 °C to rt, then OsO₄, THF, pyr, 0 °C to rt, 68%. (o) DIPEA, PhMe, then IBX, DMSO, H₂O, 80 °C, 62%. (p) KOt-Bu, (PhSeO)₂O, THF, H₂O, −78 to 0 °C, 73%. (q) KOt-Bu, THF, then triphosgene, pyr, DMAP, DCM, −78 to 0 °C, then Ac₂O, DMAP, pyr, rt, 60%. (r) TASF, THF, rt, then PhLi, THF, −78 °C, 48%. (s) β-Lactam (**35**), LHMDS, THF, −78 °C to rt, then Pd/C, H₂, EtOH, 80 °C, 85%. Abbreviations: HFIP, hexafluoroisopropanol; TMSOH, trimethylsilanol; NBS, N-bromosuccinimide; BPO, benzoyl peroxide; DTBMP, 2,6-di-tert-butyl-4-methylpyridine; TESOH, triethylsilanol; DIBAL, diisobutylaluminum hydride; HMDS,

Scheme 1. continued

hexamethyldisilazane; TBSCl, *tert*-butyldimethylsilyl chloride; DMDO, dimethyldioxirane; TPAP, tetrapropylammonium perruthenate; NMO, *N*-methylmorpholine *N*-oxide; pyr, pyridine; DMAP, 4-dimethylaminopyridine; TBAI, tetra-*n*-butylammonium iodide; 2-Fpyr, 2-fluoropyridine; TMSIm, *N*-(trimethylsilyl)imidazole; Cp$_2$TiCl, bis(cyclopentadienyl)titanium(III) chloride; BOMCl, benzyl chloromethyl ether; DIPEA, *N,N*-diisopropylethylamine; DCE, 1,2-dichloroethane; MsCl, methanesulfonyl chloride; IBX, 2-iodoxybenzoic acid; TASF, tris(dimethylamino)-sulfonium difluorotrimethylsilicate.

previous studies on the selective C–H functionalization of allylic C–H bonds in the taxane core suggested that oxidation at C-13 would be feasible. It was found that the solvent played a decisive role in controlling the regioselectivity (as three allylic positions can be oxidized) and conversion to enone **15** using the Cr(V)-based oxidant **16**.[43,46] As shown in the inset table for step a, a unique protic and non-nucleophilic mixture of HFIP/TMSOH (2:1) exhibited critical synergy to achieve the high C-13 selectivity over C-11 to afford **15**, which could be carried on directly to the next reaction with minimal purification. It has been speculated that the mechanism of this oxidation putatively involves a cationic intermediate.[47] This tricarbonyl-bearing scaffold was selectively brominated at C-5 rather than C-1, C-3, C-10, or C-14 using CuBr$_2$, delivering **17** (whose structure was undoubtably confirmed by X-ray crystallography) in 55% isolated yield (19 g scale). This high selectivity stemmed from the facts that C-1 and C-2 are virtually non-enolizable and the C-14 enolate would form a strained bridgehead diene. Bromination at this stage was essential, as it served as a placeholder for the eventual C-5 and C-7 oxidations and also drove subtle conformational shifts that enabled complete selectivity in the ensuing C–H allylic oxidation at C-10 (see inset table for step c, and SI for discussion). Radical-based oxidation of C-10 took place smoothly following our 2014 protocol,[43] proceeding through a dibromide (C-5/10) that could be selectively displaced at C-10 with TESOH in the presence of Ag(I) to deliver **18** in 68% isolated yield (gram scale). Elimination of the C-5 bromide under standard conditions (LiBr/Li$_2$CO$_3$) afforded dienone **19** in 88% isolated yield on gram scale. To set the stage for the pivotal C-1 oxidation, the last carbon atom of the taxane core was installed, the C-13 stereochemistry was set, and a deuterium atom was strategically placed onto C-2; that is, taxane **20** was produced from **19** by sequential addition of MeMgBr and DIBAL, and then LiAlD$_4$ (relative reactivity dictated by C-19, C-11, and C-20 methyl groups, respectively), followed by TBS installation in 67% yield over two transformations (gram scale). The remarkable site selectivity in functionalizing **19** was enabled by exploiting the unique steric and electronic features associated with each carbonyl group. A complex matrix of experiments across multiple taxanes (see SI) revealed substrate **20** to be ideally suited to chemo- and stereoselective oxidation events using DMDO in step g to deliver epoxy-triol **21** in 49% yield as a single diastereomer (gram scale).[48] The Δ^{11,12}-olefin remained intact because of the steric shielding by C-10 and C-13 substituents as well as the nature of this hyperstable olefin.[49,50] The stereoselectivity of the Δ^{5,6}-olefin epoxidation was guided by the C-19 methyl group. The solvent (CHCl$_3$, which presumably enhances the reactivity of DMDO through H-bonding) and concentration choice were essential (see inset table for step g),[51,52] as was the precise functionality expressed in taxane **20**. Thus, if C-2 bearing alcohol did not have the *β*-stereochemistry (presumably prevents C-2 from directing oxidation elsewhere)[53] and *α*-deuterium incorporation (9%

with C-2 *α*-H, see SI),[54−57] or if C-4 did not bear full substitution, then rapid oxidation back to the C-2 ketone took place with little to no observable hydroxylation at C-1 (see SI).

The second half of the synthesis began with TPAP-mediated[58] oxidation of C-2 (**22**, 85% isolated yield, gram scale). Thermodynamic reduction of the ketone using Na/*i*-PrOH[59] followed by addition of triphosgene to epoxy-triol **23** furnished carbonate **24** in 51% isolated yield (gram scale), with the C-5/6 epoxide left completely unscathed. As with the oxidation in step g, the stereochemistry and right balance of sterics at C-4 again played an important role in enabling this outcome, presumably due to its staggered conformation relative to the C-2 *α*-keto radical intermediate during the reduction. The stage was now set for a redox-relay event to stereoselectively install the C-7 oxygen atom. This maneuver was achieved without isolation of unstable intermediates in one flask through a carefully designed sequence involving the addition of orthogonally reactive and volatile reagents. In the event, taxane **24** was exposed to TBAI/BF$_3$·OEt$_2$ to regio-selectively (via stereoelectronic guidance) afford the corresponding iodohydrin **25a**, followed by addition of 2-fluoro-pyridine to sequester boron salts. As indicated in the inset table, the use of other additives and alternative bases led to low yields, stemming from incomplete reaction (**26**) and/or reformation of **24**. Immediate capping at C-5 with a TMS group (TMS-imidazole), followed by addition of DMDO, led to iodine oxidation and spontaneous *syn*-elimination of iodoso **25c** to liberate olefin **26**, which could be further stereo-selectively oxidized to epoxy-taxane **27** in 43% isolated yield.[60] Regioselective elimination through **25c** was essential, as E2 elimination of the corresponding iodide **25b** did not take place due to steric hindrance around C-7 and the C-5 *syn* hydrogen was conformationally less accessible. It is important to note that this sequential addition design proved to be essential in practice, as **25a** was found to revert to **24** upon isolation. Ti-mediated, sterically guided, regioselective reductive lysis of the epoxide in the presence of Et$_3$SiH followed by BOM installation proceeded in 56% isolated yield to furnish **28** (gram scale).[61] The use of triethylsilane as reductive quenching agent in Ti-mediated epoxide reduction is, to the best of our knowledge, without precedent, and increased both the yield and robustness of the transformation (see inset table for step k). At this juncture, **28** structurally resembled one of Holton's intermediates, and the following transformations were thus heavily inspired by their findings.[20] The tertiary alcohol at C-4, which played a pivotal role in numerous transformations, was dismantled through Burgess dehydration, followed by addition of HF·py to afford allylic alcohol **29** in 32% yield, accompanied by a C-5 ketone side product (see SI, compound **SI-13**). Next, the C-5 hydroxyl group was activated with MsCl, and the resulting allylic mesylate (which could not be isolated due to its instability) was immediately subjected to dihydroxylation using OsO$_4$ to deliver oxetane precursor diol **30** in 68% isolated yield. Oxetane formation was achieved using a hindered amine base (DIPEA), and subsequent addition of

IBX directly oxidized the C-10 allylic OTES group to the C-10 enone, forming **31** in 62% isolated yield. C-9 oxidation took place first, using a modification of Holton's conditions (KOt-Bu and water/(PhSeO)$_2$O) to deliver **32** (with the cyclic carbonate cleaved) in 73% yield. Redox isomerization (KOt-Bu) and quadruple acylation to reinstall the cyclic carbonate and acetylate C-4/10 proceeded smoothly to afford taxane **33**. Tandem desilylation at C-13 and addition of PhLi gave rise to baccatin III bearing a BOM group at C-7 (**34**) in 48% isolated yield.[24] The total synthesis of **1** could be completed by Ojima acylation[62] using β-lactam **35** and the Li-alkoxide of **34**, followed by hydrogenation in 85% isolated yield. The use of **35**, which has not been utilized in the context of taxane synthesis before,[63] enabled more direct access to **1**. This sequence could be performed with high reproducibility through the isolation and purification of 22 intermediates and has been used to prepare 35.2 mg of **1** in multi-batch fashion.

■ DISCUSSION

It is worth contrasting the strategy employed in Nature with the pioneering syntheses that preceded this work. As aforementioned, the biological two-phase approach to **1** is rather linear, requiring no fewer than 20 different enzymes (2 in the cyclase phase and 18 in the oxidase phase).[32,33,64] Each transformation takes place in high yield, and intermediates are individually sequestered, leading to incredible efficiency and scalability. Conventional retrosynthetic analysis would teach that a more convergent approach to **1** should be a better solution for procurement in the laboratory. Yet, as history has proven, such designs so far did not succeed in meaningfully adding to the supply of **1**. This issue stems from the sheer number of manipulations required by all syntheses (including our work). A potential approach for medicinal chemistry explorations was uncharted because prior retrosynthetic designs accessed taxanes (compounds bearing the complete carbon skeleton) late into the syntheses, a challenge the present approach overcomes. To be sure, of the 10 syntheses reported, actual taxanes are accessed half-way through[21] or near the end of the sequence.[26] Such issues cannot be resolved by creative engineering solutions or sophisticated analytical chemistry, as Takahashi has shown with the fully automated formal synthesis of **1** that delivered 0.0001 g of baccatin III after 44 machine-automated transformations.[27] While the current synthesis offers no benefit in terms of overall yield, and clearly was not developed in a vacuum and benefitted from the many pioneering syntheses that came before, it does however provide a conceptual blueprint for how a viable medicinal chemistry evaluation could take place without semisynthetic approaches. Furthermore, since multi-gram quantities of the full taxane skeleton are accessed at a very early stage (step e), this could serve as a new platform for further analogue synthesis combined with the known structure−activity relationships of **1** (as demonstrated with **6**, **7**, and **8**).[65,66] Since taxanes exhibit useful bioactivity only when a C-13 side chain is present, it is notable that our route mirrors biosynthesis in that the proper oxidation is installed at C-13 very early in the synthesis (step a) rather than at a late stage as in most of the past routes (see Scheme 1 oxidation choreography for a summary). The strategic advance of this two-phase retrosynthesis is reinforced by the fact that all of the methods employed to access **1** were, in principle, known and available to past practitioners. The robust nature of these reactions ensured that two-thirds of the transformations in this synthesis could be conducted on a gram scale.

■ CONCLUSION AND OUTLOOK

It is worth recounting some of the key lessons, tactics, and maneuvers that enabled the current route to **1**. As with the biosynthetic two-phase approach, this synthesis focuses mostly on the oxidase phase, and thus the precise choreography of O-installation was critical to access the target. C-2 was chosen for the first oxygenation not only due to the retrosynthetic simplification it enabled during the cyclase phase but also because of its critical role in bioactivity.[66] Oxidation of C-13, C-5, and C-10 gave the best material throughput in this order. These oxidations were rapidly completed based on our previous work[43,44] to set the stage for the key C-1 oxidation. The challenge of installing C-1 and C-7 could be addressed in unison through careful selection of neighboring functionality and redox relay through a C-5/6 epoxide group. The C-7 oxidation state was installed through a carefully designed redox relay originating from the C-4 ketone, the C-5 bromide, the C-5/6 epoxide, the C-6 iodide, the Δ^{6,7}-olefin, the C-6/7 epoxide, and finally to the C-7 alcohol. As the Supporting Information details, multiple generations of strategies were evaluated before finalizing this pathway. This is clearly a weakness of the two-phase design with regard to one of the most densely functionalized terpenes known. In biosynthesis, enzymatic hydroxylation events accomplished through eons of evolution do not necessitate protecting groups or functional group manipulations and are largely impervious to subtle substrate modifications. C-4 and C-20 benefited from simple dihydroxylation of an olefin, and the pioneering work of Holton[20] guided the final C-9 oxidation (and stereochemistry thereof).

While this synthesis does employ protecting groups (C-5, C-7, C-10, and C-13), their effect was maximized by strategic selections and allocations so that analogous functional groups were well differentiated throughout the synthesis—e.g., simultaneous installation of an OTES group upon C−H oxidation (C-10) or tandem removal during oxidation (C-10) in the presence of OTBS (C-13). The silyl groups at C-13 and C-10 did play a pivotal role in shielding the bridgehead olefin from oxidation. Unconventional means of protecting functionality and directing reactivity were also employed, including the use of deuterium (kinetic isotope effect) at C-2,[67] a bromine atom at C-5, a tertiary alcohol at C-4, and an epoxide at C-5/6. The dense functionality innate to **1** enabled unique positionally selective reactions such as the reactivity of a tricarbonyl (step e), the oxidation at C-1 (step g), and the stability and reactivity of epoxide intermediates (steps h−j). Reactive intermediates (steps c, j, n, and q) could also be utilized through consecutive operations in order to achieve challenging transformations with minimal labor.

Through this unique opportunity of implementing the "pyramid-climbing" approach to one of the most densely functionalized terpenes (arguably, the most iconic known), we could reevaluate the way one approaches disconnections to other terpenes. The two-phase approach is a synthetically high-risk/high-reward strategy, as we have demonstrated with other syntheses (such as ingenol,[35] phorbol,[36] and thapsigargin[37]). As a carbon skeleton of a target terpene is built in early stage, all oxidase phase reactions are essentially a late-stage functionalization of a complex natural product. As the oxidation level ascends, there are more and more (similar) functional groups in a molecule; thereby, protecting group

manipulations and choice of substrate-compatible reagents and conditions become progressively more challenging. However, all late-stage intermediates can, in principle, be elaborated to bioactive candidates, since a carbon skeleton is already present (akin to Nature's route). Such a route might pass through a low-yielding transformation, but that is typically a minor issue when it comes to an initial medicinal chemistry campaign. This leads to the second point, that the two-phase synthesis is a useful strategy depending on the context. For example, the overall yield of Nicolaou's convergent Taxol synthesis was 0.0078%,[21] while our linear two-phase approach ended up yielding only 0.0014%. Employing either approach for a target-oriented synthesis (e.g., process chemistry) would be inappropriate and result in poor material throughput. On the other hand, under a circumstance where multiple non-specific analogues were required (e.g., medicinal chemistry), the two-phase strategy would be an extremely powerful way of achieving maximal analogue output. Lastly, we felt this aspect was enabling for navigating the dead-ends and detours often encountered in complex natural product synthesis.[68] Arrays of substrates possessing the same carbon skeleton but slightly different reactivity due to subtle differences in functional group arrangement enable facile substrate screening. In contrast, a traditional convergent synthesis might require a redesigned substrate that needs to be prepared when a particular transformation fails.

As aforementioned, we began our campaign to access Taxol (**1**) to answer a fundamental thought experiment: Would a holistically biomimetic approach enable an unified medicinal synthetic campaign involving divergent access to natural and non-natural taxanes at various oxidation patterns? In one sense, if **1** were pursued by a large pharma company in the absence of a natural supply, this route would indeed enable such a study (where milligram quantities of each analogue are needed). On the other hand, the blueprint laid out herein required deeply choreographed empirically derived manipulations unique to each substrate's reactivity. Thus, extensive effort would be required, and process chemists might choose a different path to the final target. At the end of the day, chemical synthesis to *specifically* access **1** will likely never be competitive with a fully enzymatic approach. To avoid unnecessary concession steps that beleaguer all syntheses of **1**, we predict that far more improved medicinal chemistry-based approaches to novel taxanes could be accomplished using a hybrid approach that employs synthesis to generate carbon frameworks (for example, containing unnatural motifs) and enlists synthetic biology for chemo- and site-specific oxidations.[69] In the meantime, the present synthesis demonstrates that two-phase synthesis can open the possibility of divergent access to taxanes, in contrast to classical synthetic strategies.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c03592.

Detailed experimental procedures and analytical data (PDF)

X-ray crystallographic data for **17** (CIF)

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Notes

The authors declare no competing financial interest.

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