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Scalable enantioselective total synthesis of taxanes

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Taxanes form a large family of terpenes comprising over 350 members, the most famous of which is Taxol (paclitaxel), a billion-dollar anticancer drug. Here, we describe the first practical and scalable synthetic entry to these natural products via a concise preparation of (+)-taxa-4(5),11(12)-dien-2-one, which has a suitable functional handle with which to access more oxidized members of its family. This route enables a gram-scale preparation of the 'parent' taxane—taxadiene—which is the largest quantity of this naturally occurring terpene ever isolated or prepared in pure form. The characteristic 6-8-6 tricyclic system of the taxane family, containing a bridgehead alkene, is forged via a vicinal difunctionalization/Diels–Alder strategy. Asymmetry is introduced by means of an enantioselective conjugate addition that forms an all-carbon quaternary centre, from which all other stereocentres are fixed through substrate control. This study lays a critical foundation for a planned access to minimally oxidized taxane analogues and a scalable laboratory preparation of Taxol itself.

Terpenes are omnipresent natural products that are found predominantly as constituents of plant oils and have long held importance as flavours and fragrances, and as poisons and medicines[1–3]. Isolation, structural elucidation and synthetic studies on this vast family of natural products were already being conducted over 100 years ago[1], providing constant challenges to chemists and thus resulting in continuous development of the field. Taxol (**1**), a successful anticancer drug, is one example that has societal and scientific merit, being one of the most famous terpenes from a medicinal standpoint and one of the most densely functionalized and complex molecules from a structural standpoint. Its unique mechanism of action, involving the stabilization of microtubules[4], has also held fascination for biologists, so extensive research efforts have been carried out around the globe by both chemists and biologists.

Taxol (**1**) is a potent anticancer drug that was originally used as a treatment for ovarian and breast cancer[5], but its versatile effects now extend to treatments of lung, liver and other types of cancer[6]. Initially isolated from the bark of the yew tree[7], substantial work in the 1980s and 1990s led to a semisynthetic route to Taxol (**1**) that reduced the accompanying detrimental effects to the yew tree population[8–10]. Currently, its commercial supply relies on cell-culture production, and it is now manufactured with plant cell-culture technology through a collaboration of Bristol-Myers Squibb and Phyton Biotech, Inc., a DFB Pharmaceuticals company. This diterpene is one of the few natural products that continues to draw worldwide attention, and tremendous efforts have already culminated in seven total syntheses[11–19] and one formal synthesis[20]. However, the inventory of man-made Taxol (**1**) produced by total synthesis is still less than 30 mg (refs 11–20), even when including the most recent approach by Takahashi in which an automated synthesis was used for the majority of the synthetic steps[20]. In contrast, the current industrial output of **1** through the use of biological machinery is on the scale of tonnes (10^9 mg), clearly indicating the magnitudes of difference between chemical and biological scales and efficiency. Closing this huge gap is not simply a matter of engineering, but rather a learning objective through which to guide chemical innovation in the tactics, strategies[21] and methods of synthesis (for a discussion of the different definitions of the terms 'strategy' and 'tactics', see ref. 21). Until the pioneering bioengineering work of Stephanopoulos in 2010, there was no access to large quantities of the less-oxidized taxane members such as taxadiene (**7**)[22]. Although not necessarily a means of supplanting its current tonne-scale production, a reexamination of Taxol (**1**) over 15 years after its first total syntheses could be of academic and medicinal merit. In this Article, we present the first scalable synthetic entry to the taxane family, setting the stage for rapid access to minimally oxidized taxane analogues and a scalable laboratory preparation of Taxol (**1**) itself.

Inspired by nature's efficiency in creating vast numbers of complex terpene natural products, a research programme was initiated in 2007[23] to mimic the essence of the two-phase biosynthesis of terpenes[24]. In the first biogenetic phase (the cyclase phase), linear hydrocarbon building blocks are brought together and cyclized efficiently, and in the second phase (the oxidase phase), C=C and C–H bonds are oxidized in a divergent manner, thus generating structural diversity. The taxanes represent a large family of terpenes comprising over 350 natural products[25–32], for which this two-phase terpene synthesis strategy, if realized in a laboratory setting, could target not only Taxol (**1**) itself, but also related taxanes that differ in oxidation levels (Fig. 1)[23,33]. As such, this research programme has been designed to recapitulate the way that nature builds taxanes. The goal is to divergently access all 'pre-taxol' compounds (both natural and unnatural) and to unveil new insights into their chemical reactivity during an 'oxidative ascent' of the taxane pyramid. This Article outlines the completion of our artificial 'cyclase phase' for the taxane terpene family, as a prelude to a total synthesis of Taxol (**1**). Thus, the logic (including strategic and tactical concerns)[21] and execution of a concise and scalable synthesis of minimally oxidized taxanes, including nature's putative cyclase phase endpoint, taxadiene (**7**)[34], are reported.

Structurally, Taxol (**1**) is a highly oxygenated diterpene adorned with acetyl and benzoyl groups, as well as a signature taxol side chain at the C13 oxygen atom (see carbon numbering on **1**, Fig. 1a). For retrosynthetic discussion purposes, **1** is treated as if it were devoid of acyl groups, and this target is substituted with oxygenated hydrocarbon **2** (ref. 33). Placing **2** at the apex of an 'oxidase phase pyramid', the number of C–O bonds decreases as one moves down the pyramid, with taxanes **3**, **4** and **5** corresponding to the oxidation pattern of 2-acetoxybrevifoliol[25], taxinines E and J[26] and yunnanxane[27], respectively (Fig. 1b). These highly oxidized taxanes

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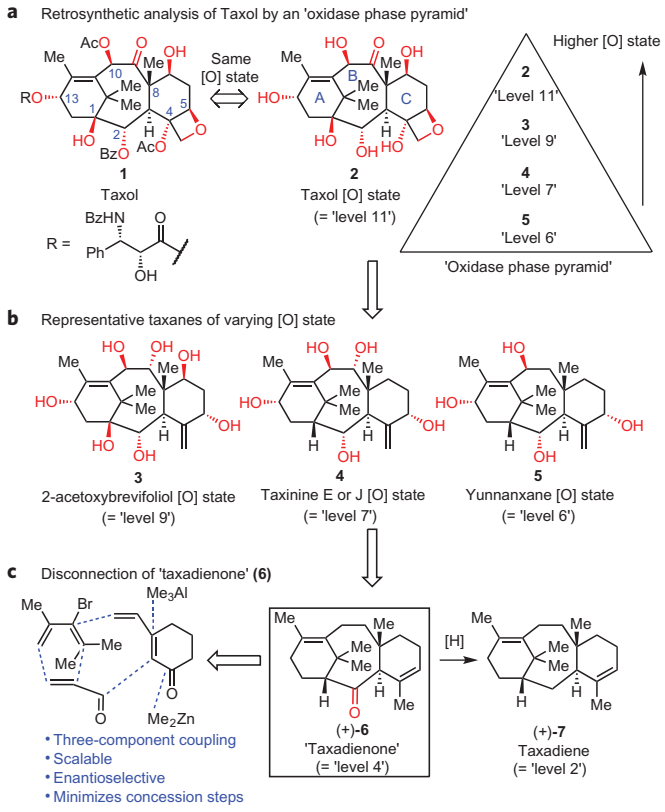

Figure 1 | Retrosynthetic analysis of Taxol (1) and other members of the taxane family. a, Partial 'oxidase phase pyramid' for the retrosynthetic planning of the taxane family, including its key member, Taxol (**1**). **b**, Representative taxanes of varying oxidation states, sharing a C2-hydroxyl group. **c**, Synthetic design for 'taxadienone' (**6**) and reduction to generate taxadiene (**7**). Sites of oxidation installed onto taxadiene (**7**) are indicated in red. The 'oxidation level' of taxanes is defined as the number of C=C and C–O bonds installed onto the taxane carbon skeleton[33].

all feature a C2-hydroxyl group and can be further simplified to taxa-4(5),11(12)-dien-2-one (**6**), dubbed 'taxadienone', which represents a benchmark intermediate for comprehensive access to the taxane family. Furthermore, if taxadiene (**7**) were desired, one could simply deoxygenate **6** to generate the least oxidized natural product in the taxane family (Fig. 1c). A full scholarly analysis of the taxane pyramid has been described previously, together with the merits in choosing a C2-oxidized taxane such as **6** (ref. 33).

Strategic disconnections of **6** were built upon the landmark syntheses of **1** (refs 11–20) and the many studies geared towards the taxane framework[35–41]. Of the many possible disconnections of the 6-8-6 tricyclic backbone, one was chosen such that (i) the forward synthesis would be short, convergent and scalable[42] and (ii) its asymmetric synthesis would only rely on one enantioselective reaction, after which the resulting stereochemical information could be propagated to set all other stereocentres diastereoselectively. A vicinal difunctionalization/Diels–Alder strategy to forge the taxane AB ring system (see ring numbering in **2**, Fig. 1a) seemed to fulfil most of the above criteria. The Diels–Alder strategy has been used previously in the context of taxane synthesis by Shea[35], Jenkins[36] and Williams[37], as well as others[38–41]. In fact, Williams reported the only total synthesis of (±)-taxadiene (**7**), in 26 steps, as long ago as 1995 (ref. 37). Furthermore, the decision to implement a vicinal difunctionalization strategy was underpinned by recent developments in the asymmetric formation of all-carbon quaternary centres[43,44]. Thus, a concise, enantioselective strategy was conceived, allowing for a gram-scale access to **6** in only seven steps, as well as a gram-scale synthesis of (+)-taxadiene (**7**).

Results

In the forward direction, known compounds **10** (refs 35,40,41; made from **8** in a modified one-pot procedure; see Supplementary Information) and **11** (ref. 45; made from **9** using a one-step procedure) were combined to generate enone **12** by means of a Lewis acid-modified organocopper 1,6-addition (Fig. 2). This convergent synthesis of **12** is operationally simple and provides decagram quantities per reaction batch (86%; over 50 g of this material has been synthesized to date). This enone was deemed to be a suitable substrate for the enantioselective conjugate addition of Alexakis[43] to establish the quaternary centre (C8). However, this strategy was contingent on the feasibility of trapping the resulting aluminium enolate by trimethylsilyl chloride (TMSCl). Although Alexakis noted that isolation of such silyl enol ethers is difficult due to facile desilylation[43], a modified quenching procedure involving dilution with tetrahydrofuran (THF), addition of TMSCl, followed by addition onto Florisil in 1:10 Et_3N:hexanes, allowed the isolation of trimethylsilyl (TMS) enol ether **14** in 89% yield and in 93% e.e. (1.0 g scale; enantioselectivity measured for desilylated ketone **15** on chiral high-performance liquid chromatography (HPLC); see Supplementary Information). Only 2 mol% of CuTC and 4 mol% of chiral phosphoramidite ligand **13** were required[43], and this asymmetric reaction was routinely conducted on a gram scale (over 20 g of this material has been synthesized to date). TMS enol ether **14** was indeed quite prone to desilylation, and formation of undesired ketone **15** was often the sole reaction pathway when attempting Mukaiyama aldol reactions[46] with commonly used Lewis acids (such as $TiCl_4$, $SnCl_4$, $Sn(OTf)_2$, $Sc(OTf)_3$, $BF_3{\cdot}OEt_2$, TMSOTf, $ZnCl_2$ or $MgBr_2{\cdot}OEt_2$) or other catalysts (such as $LiClO_4$, $Zr(O^tBu)_4$, $Bi(OTf)_3$, AgOTf or $SiCl_4$), even when performed under strictly anhydrous conditions. Surprisingly, water was found to be the enabling additive that allowed for an aldol reaction with acrolein. Gratifyingly, Kobayashi conditions[47] with $Gd(OTf)_3$ in 1:10:4 H_2O:EtOH:PhMe generated the corresponding aldol product smoothly as a 2:1 mixture of diastereomers that are isomeric at C3. This aldol product was then oxidized in the same reaction pot with Jones' reagent to generate keto-enone **16** in 85% over two steps (3.2 g scale, 2:1 ratio of diastereomers at C3; this inseparable mixture of stereoisomers was carried onwards for the ensuing step). A Diels–Alder reaction to generate the 6-8-6 tricyclic skeleton has previously been demonstrated on similar systems[35–37], and mixture **16** reacted predictably with $BF_3{\cdot}OEt_2$ to furnish tricyclic compound **17** (2.3 g scale). The desired diketone **17** was obtained in 47% yield, together with its diastereomer (see Supplementary Information) in 29% yield, with complete diastereoselectivity at C1. These cyclized diketones displayed very different polarities and were thus easily separated by silica gel chromatography at this stage. Only one more carbon remained to be installed to complete the taxane framework: this was achieved via enol triflate formation followed by Negishi coupling to generate taxadienone (**6**) in 84% over two steps (2.4 g scale). This material solidified quite readily, and single-crystal X-ray analysis confirmed both the absolute and relative stereochemistry of the synthesized ABC ring system. This lowly oxidized core is the key intermediate for our future research efforts to elaborate the taxane pyramid. In summary, the total synthesis of (+)-taxadienone (**6**) was achieved in a total of 8 steps, with a longest linear sequence of 7 steps. A few grams of taxadienone (**6**) could be synthesized by one chemist over the course of 7 days, with an overall yield of 18% from **8** or 20% from **9**.

With the key taxane **6** secured in gram quantities, taxadiene (**7**) was then targeted, primarily as a means of spectroscopic comparison to previously reported data, but also to demonstrate the feasibility

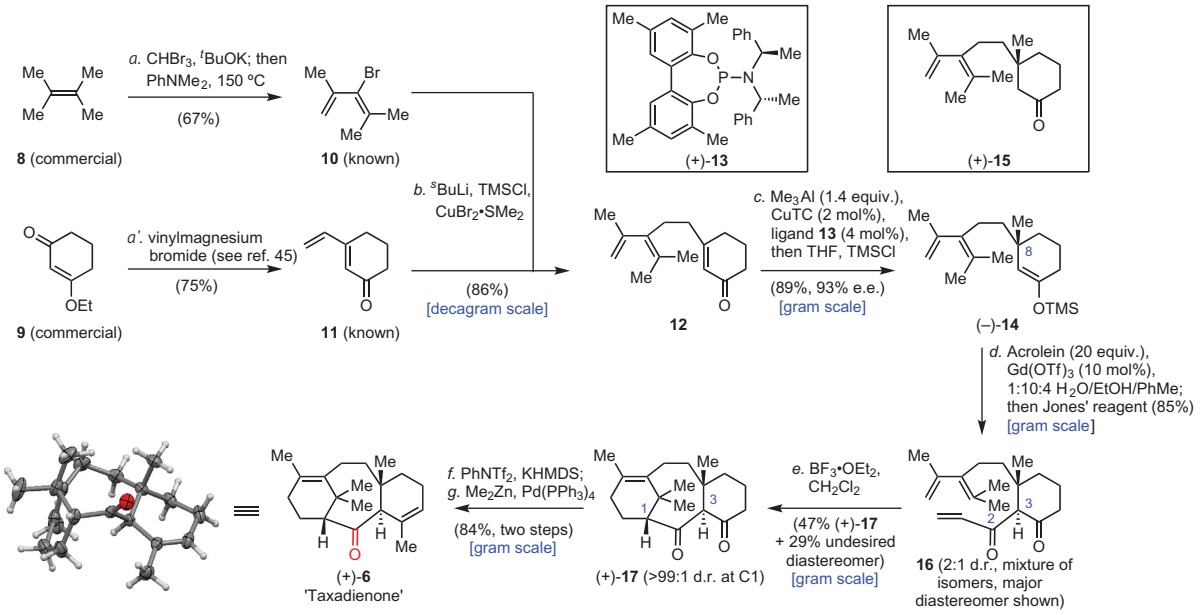

Figure 2 | Enantioselective synthesis of key taxane 6. Conditions: *a*. 2,3-dimethyl-2-butene, $CHBr_3$, potassium *tert*-butoxide, hexanes, 2 h; evaporate volatile materials, then *N*,*N*-dimethylaniline, 150 °C, 30 min (67%); *a*′. 3-ethoxy-2-cyclohexen-1-one, vinylmagnesium bromide, Et_2O, 16 h (75%)[45]; *b*. **10**, sec-butyllithium, Et_2O, –78 °C, 15 min; then $CuBr{\cdot}SMe_2$, 30 min; then TMSCl, 5 min; then **11**, 2 h; warm to room temperature, 8 h; then AcOH, 30 min; then 3 M HCl, 30 min (86%); *c*. CuTC (2 mol%), phosphoramidite **13** (4 mol%), Et_2O, room temperature, 30 min; then 2.0 M Me_3Al, enone **12**, –30 °C, 24 h; then THF, TMSCl, 0 °C to room temperature, 8 h; then Et_3N, Florisil, 2 h (89%, 93% e.e.); *d*. $Gd(OTf)_3$ (10 mol%), acrolein, 1:10:4 H_2O:EtOH:PhMe, 4 °C, 24 h; then evaporate volatiles, then Jones' reagent, acetone, 10 min (85% over two steps, 2:1 d.r. at C3, inseparable mixture of diastereomers); *e*. $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C, 6 h (47% **17** + 29% undesired diketone); *f*. 0.4 M KHMDS, $PhNTf_2$, THF, 0 °C, 1 h; *g*. 1.2 M Me_2Zn, $Pd(PPh_3)_4$ (5 mol %), THF, 0 °C to room temperature, 5 h (84% over two steps). TMSCl, trimethylsilyl chloride; CuTC, copper(I) thiophene-2-carboxylate; $PhNTf_2$, *N*-phenylbis(trifluoro methanesulfonimide); KHMDS, potassium hexamethyldisilazide; $Pd(PPh_3)_4$, tetrakis(triphenylphosphine)palladium.

of a large-scale laboratory production of enantioenriched **7**. Furthermore, taxadiene (**7**) is produced in negligible amounts in nature (less than 1 mg can be obtained from 750 kg of tree bark from *T. brevifolia*)[34] and therefore its optical rotation has never been recorded. To this end, a three-step deoxygenation sequence[48] was performed in 52% yield overall on a gram scale (Fig. 3), to generate (+)-**7**, which was spectroscopically indistinguishable from natural **7** (ref. 34), previously synthesized (±)-**7** (ref. 37) and bioengineered (+)-**7** (ref. 22). The optical rotation of $[\alpha]^D$ $(CHCl_3) = +165°$ ($c = 1.0$) is reported herein for the first time and is comparable to that obtained for a bioengineered sample of (+)-**7** (see Supplementary Information). This represents the largest quantity of pure (+)-**7** isolated to date.

Discussion

In retrospect, the forward synthesis of (+)-taxadienone (**6**) appears to be rather simple and perhaps intuitive; however, in practice, this optimized approach required many rounds of strategic and tactical revision[21]. Strategically, the retrosynthesis designed in Fig. 1c was one of many that were considered at the outset. A small snapshot of the many evaluated blueprints is presented in Fig. 4. For example, the known difficulties in forming the 6-8-6 tricyclic framework of taxanes[11–20] led us to first consider a ring-closing metathesis (RCM) strategy to close the central 8-membered ring (disconnection A). However, the realization that the required substrate **18** would take many steps to build, and the fact that the stereocentres at C1 and C8 would have to be formed with two separate enantioselective reactions, dissuaded us from pursuing this route. An aldol route was then conceived, partly due to the facile formation of **19** via ketone **15** (disconnection B). Although installation of the stereocentres at C1 and C8 might still require two independent enantioselective transformations, the hope was that the reaction conditions used for the aldol cyclization would concomitantly epimerize the C1 stereocentre into the desired configuration. However, despite a plethora of attempted experiments, the desired cyclization from **19** did not proceed. Thereafter, strategies involving closure of the AB ring by a Diels–Alder reaction were envisioned. One attempt involved the formation of ketone **20** by a sequence involving a coupling of the enolate of 2,6-dimethylcyclohexanone and a primary alkyl bromide, a Shapiro reaction onto acrolein, oxidation and Diels–Alder (disconnection C), much akin to the transformation from **14** to **17** (Fig. 2). However, ketone **20** already required many steps to construct, and the stereocentre at C8 was challenging to control, despite existing methods in asymmetric enolate alkylation[49]. Finally, enones **21** were considered as viable intermediates in the formation of **6** (disconnection D) due to our initial difficulties in forging the C2–C3 bond via the Mukaiyama aldol reaction (*vide supra*). Although enones **21** were formed in short order and already contained all but one carbon of the taxane framework, they did not undergo [4 + 2] cyclization, probably due to the rigidity of the sp^2 carbons at C3 and C8. Furthermore, a methyl 1,4-addition at C8 was not possible,

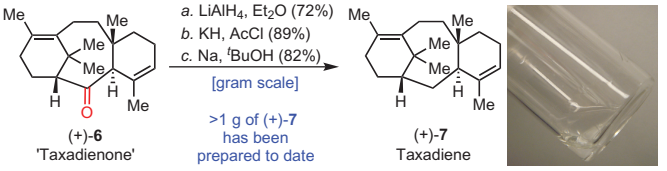

Figure 3 | Elaboration of (+)-taxadienone (6) to (+)-taxadiene (7) by a three-step reduction–deoxygenation sequence. Conditions: *a*. $LiAlH_4$ (3.0 equiv.), Et_2O, –78 °C to room temperature, 12 h (72 %); *b*. KH (7 equiv.), acetyl chloride (4 equiv.), THF, 60 °C, 18 h (89%); *c*. Na (18 equiv.), Et_2O, HMPA, ^{t}BuOH, room temperature, 40 min (82%)[48]. Sites of oxidation installed onto taxadiene (**7**) are indicated in red.

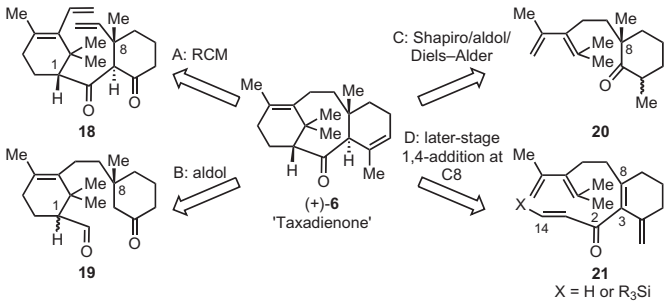

Figure 4 | Initial synthetic investigations towards the synthesis of taxadienone (6). Disconnection A: an RCM approach would require many more steps in building the taxane framework. Disconnection B: the required aldol closure simply did not proceed. Disconnection C: a Shapiro reaction, followed by aldol and Diels–Alder reactions, is strategically similar to the successful synthetic route, but the stereochemistry at C8 could not be set stereoselectively. Disconnection D: conjugate addition at C8 to install the methyl unit did not proceed, because only the undesired conjugate addition onto C14 occurred.

because reaction first occurred at the less hindered C14, even when a large *tert*-butyldiphenylsilyl group was appended at C14. After many more strategic revisions and success in forming the required C2–C3 bond from TMS enol ether **14** using $Gd(OTf)_3$, the final synthetic strategy depicted in Fig. 2 was realized.

Tactically, although quite efficient at present, most steps shown in Fig. 2 were initially difficult to scale and suffered from low and inconsistent yields. Even the first transformation from **8** to **10** (Fig. 2) was not trivial, despite it being a known two-step transformation[35,40,41]. Modifying the reaction stoichiometry and reaction times was necessary to coax this process into giving good yields consistently on a decagram scale, with eventual success as a one-pot operation. The second transformation, a merging of the two similar-sized fragments **10** and **11**, can be conducted in good yields (86%) on a decagram scale, but initially this reaction was plagued with inconsistent yields due to side-product formation: the original reaction conditions of *tert*-butyllithium, $BF_3{\cdot}OEt_2$ and CuI resulted in 1,6-addition of *tert*-butyllithium (whereas sec-butyllithium is not a very competent nucleophile for this reaction), iodination of **12** (whereas the use of $CuBr{\cdot}SMe_2$ circumvents this problem), and deconjugation of **12** to give a β,γ-unsaturated ketone (this problem was rectified by optimizing the work-up procedure; see Supplementary Information). The third, asymmetry-inducing step[43] from **12** to **14** was straightforward when run on a small scale (<100 mg) and delivered high enantioselectivity with 0.5 mol% CuTC and 1 mol% ligand loading. However, on increasing the reaction scale to a gram scale, the reaction conversion suffered significantly. Eventually, a higher catalyst loading (2 mol% CuTC and 4 mol% ligand) and precise temperature control allowed this reaction to give reliable yields and consistent enantioselectivity on a gram scale. Also worth mentioning is a modified quenching procedure that was developed to address the troublesome TMS trapping of the aluminium enolate[43] (*vide supra*).

The fourth and the most difficult reaction was the aldol reaction of **14** and acrolein, which only returned desilylated ketone **15** under most reaction conditions. A variety of Lewis acid-mediated reactions (*vide supra*), as well as anionic silicon–metal exchange reactions, never led to the desired product. This aldol reaction only proceeded when lanthanide triflates such as $Yb(OTf)_3$ or $Gd(OTf)_3$ and very specific solvent systems were used. The final challenge was a scalable Diels–Alder reaction from **16** to **17**, which has been known to proceed in moderate yields on similar substrates[35–37]. Although efficient on a small scale, the yield decreased when the reaction was conducted on a gram scale, possibly due to the formation of oligomers and polymers. This problem was solved using high dilution conditions (running the reaction at ~0.01 M) and by the slow addition of substrate **16** to the Lewis acid solution (see Supplementary Information).

Developing a scalable route to the taxane core involved the study and modification of fundamental aspects of the described chemistry, rather than a mere exercise in scaling up. The conciseness of the synthetic route is a direct result of trying to achieve a scalable synthesis, and the reliability of the yields attests to the small variability of reactions run on a larger scale[50].

Despite the efficiency of the described approach, there are two obvious limitations in the synthesis of taxadienone (**6**): (i) the single functional group manipulation from cyclized diketone **17** to the corresponding enol triflate (rendering the route 85% rather than 100% ideal)[42] and (ii) the 2:1 diastereoselectivity in the aldol reaction of **14** and acrolein. These issues are currently being addressed by (i) developing a scalable, one-step enol triflation/methyl coupling reaction and (ii) generating creative acrolein equivalents and/or reaction conditions with various additives to increase the diastereoselectivity of the aldol step.

In summary, a scalable, enantioselective entry to the taxane family of natural products was achieved in only seven steps from commercially available starting material (18–20% overall yield). This triply convergent approach to taxa-4(5),11(12)-dien-2-one (**6**) allowed for a minimization of concession steps, in which 6 of 7 steps formed skeletal (C–C) bonds. Every one of these steps was performed on a gram scale, attesting to the scalability and robustness of the sequence. Furthermore, (+)-taxadiene (**7**) was synthesized, enabling further structural confirmation, as well as the first optical rotation determination of this natural product. The simple chemical route to (+)-**7** nicely complements the recent pioneering studies of Stephanopoulos and co-workers[22], whose bioengineering strategy also delivers gram-scale quantities of (+)-**7**, albeit as a 9:1 mixture of olefin isomers (taxa-4(5),11(12)-diene (**7**) and taxa-4(20),11(12)-diene) (see Supplementary Information). Studies are currently under way to make use of the existing functional group handles in **6** to oxidize various sites on the taxane skeleton and to create a pyramid-like library of unnatural and natural taxanes en route to Taxol (**1**).

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Author contributions

A.M., Y.I. and P.S.B. conceived the synthetic route, conducted the experimental work, analysed the results and wrote the manuscript.

Additional information

The authors declare no competing financial interests. Supplementary information and chemical compound information accompany this paper at www.nature.com/naturechemistry. Reprints and permission information is available online at http://www.nature.com/reprints. Correspondence and requests for materials should be addressed to P.S.B.