Phorbol, the flagship member of the tigliane diterpene family, has been known for over 80 years and has attracted attention from many chemists and biologists owing to its intriguing chemical structure and the medicinal potential of phorbol esters. Access to useful quantities of phorbol and related analogues has relied on isolation from natural sources and semisynthesis. Despite efforts spanning 40 years, chemical synthesis has been unable to compete with these strategies, owing to its complexity and unusual placement of oxygen atoms. Purely synthetic enantiopure phorbol has remained elusive, and biological synthesis has not led to even the simplest members of this terpene family. Recently, the chemical syntheses of eudesmanes, germacrenes, taxanes and ingenanes have all benefited from a strategy inspired by the logic of two-phase terpene biosynthesis in which powerful C–C bond constructions and C–H bond oxidations go hand in hand. Here we implement a two-phase terpene synthesis strategy to achieve enantiospecific total synthesis of (+)-phorbol in only 19 steps from the abundant monoterpene (+)-3-carene. The purpose of this synthesis route is not to displace isolation or semisynthesis as a means of generating the natural product per se, but rather to enable access to analogues containing unique placements of oxygen atoms that are otherwise inaccessible.

Tigliane diterpenes have been viewed as promising leads in many different medicinal applications including immunomodulatory, anti-viral and anti-cancer applications. The most progressed compound in this class of natural products is phorbol 12-myristate 13-acetate, which is currently in phase II clinical trials for treatment of acute myeloid leukaemia. Subtle perturbations of their structures can have a marked effect on their biological profiles, perhaps as a result of differing protein kinase C subtype selectivity. As such, phorbol esters and related terpenes have been a focus of natural products research. Our interest in this family stemmed from the anti-cancer effects of certain phorbol analogues whose access was limited. Numerous eudesmane family members have previously been accessed in a concise way via a strategy for the chemical synthesis of complex terpenes that follows the underlying logic of biosynthesis. This strategy has subsequently been successfully applied to germacrenes, complex taxanes and ingenanes. In particular, the two-phase synthesis of (+)-3-carene is only 14 steps from (+)-3-carene and has enabled access to a variety of analogues that were not accessible by any other means. Because ingenanes and tiglianes are closely related in nature, we hypothesized that intermediate 5, which is available in quantities of more than 100 g, might serve as an ideal starting point for a short route to 1. The execution of this plan depended on the invention of a simple solution to the challenge of incorporating the C12 and C13 oxygen atoms of 1; the difficulty in installing this functionality is well known in the field of organic chemistry. So far, only two total syntheses of (+)-phorbol and two formal syntheses of 1 have been reported in 40–52 steps (see Supplementary Information for a summary). In these studies, an α-oxygenated enone was prepared from a ketone and subsequently cyclopropanated to build in the C13 oxidation via a six-step sequence. Many other efforts towards 1 have also been reported (for a full listing of the 36 papers in this area, see Supplementary Information).

The route described in refs 17 and 18 is particularly instructive and illustrates the inherent challenge of using (+)-3-carene as a starting material to (+)-phorbol (1): 38 steps were required to reach a phorbol analogue lacking the C11 methyl and C13 oxygen from 6 (refs 17, 18). (Here we define a reaction step as one in which a substrate is converted to a product in a single reaction flask (irrespective of the number of transformations) without intermediate workup or purification.) Our studies, outlined below, culminated in a two-phase, 19-step synthesis of 1 that solves these problems in a concise way.

The synthesis commenced with intermediate 5 (Fig. 2), provided in large quantities using a previously described route. Installation of the C4 oxygen was accomplished using a Mukaiyama hydration and in situ silyl group installation to furnish 7 in 70% yield (gram scale). At this juncture, we pursued installation of the C12 oxygen atom, which required the selective oxidation of a methylene position in the presence of an enone, six tertiary C–H bonds and two other competing methylene sites. To choose the proper oxidant for this transformation, we analysed the structure computationally (Fig. 3a) and by

Figure 1 | A two-phase approach to ingenanes and tiglianes enables a concise approach to the phorbol structure.
inference of innate reactivity using NMR (Fig. 3b). Thus, we predicted the pseudo-equatorial C–H bond at C12 to be the most reactive on the basis of the following considerations: (1) steric shielding of the C6, C7, C8 and C11 positions would decrease their rate of oxidation; (2) the higher s-character of the tertiary cyclopropane C–H bonds (C13/14) makes them very difficult to oxidize; (3) of the remaining carbon centres, 13C NMR indicated that C12 is the most ‘nucleophilic’; (4) hyperconjugation from the π-like cyclopropane system should facilitate oxidation of the pseudo-equatorial C–H bond on C12; and (5) strain-release might, to a small extent, accelerate such an oxidation. Therefore, we chose the small, reactive, electrophilic oxidant methyl(trifluoromethyl)dioxirane (TFDO), owing to its straightforward preparation and success in other challenging methylene oxidations. As predicted, TFDO cleanly achieved C–H oxidation at C12 to deliver the intermediate cyclopropyl carbinol intermediate 8 (single diastereomer), which could be isolated and fully characterized on a gram scale. In practice, however, it was directly treated in the same flask with MgI2/ZnI2 to elicit a dehydrative ring opening to furnish diene 9 along with unreacted enone 7. We did not observe the anticipated tertiary iodide product, presumably owing to rapid elimination to form a diene system. The mixture of 7 and 9 was directly subjected to another Mukaiyama hydration to furnish the tertiary carbonyl 10 in 34% isolated yield from 7 along with 62% recovered 7. The addition of PPh3 to this type of reaction has not previously been reported and was found to be essential to prevent the reactive intermediate peroxide adduct from generating an unwanted by-product (see Supplementary Information for details).

With the cyclopropane ruptured, the next step was to install the C12/13 oxygenation pattern along with reclosure of the cyclopropane. This manoeuvre has no precedent, and needed to be accomplished this manoeuvre has no precedent, and needed to be accomplished this manner, the reduction of the C12/13 olefin to diketone 11 was performed by chemoselective oxidation of the pseudo-equatorial C–H bond along with enone 7. To this end, chemoselective oxidation of the C12/13 oxygenation pattern along with reclosure of the cyclopropane. This manoeuvre has no precedent, and needed to be accomplished...
of the diketone to an enediol would need to take place followed by intramolecular cyclization. Whereas attempts at acetylation of the hindered tertiary alcohol were fruitless and mesylation led to rapid elimination (as with the putative iodide intermediate in 8 → 9), treatment with trifluoroacetic anhydride smoothly led to an intermediate trifluoroacetate. This ester could be treated in the same flask with Zn to deliver an intermediate (12) whose structure was confirmed with the aid of X-ray crystallography. Although the desired reduction took place, it was accompanied by the formation of an additional, unwanted and bizarre C–C bond between C13 and the carbonyl group of the trifluoroester. Although aldol additions of enediols to aldehydes and ketones are known, there is no precedent for such reactivity with esters. We reasoned that this product originated from a highly reactive enediol intermediate (such as A; R = H) that might be regenerated under equilibrating conditions. In support of this hypothesis was the empirical observation that conversion of 11 to 12 initially resulted in the formation of an approximately 1:1 mixture of 12 along with an isomeric species tentatively assigned as the diastereomeric aldol adduct. Over 24 h this mixture equilibrated to 12 exclusively, perhaps owing to stabilizing intramolecular hydrogen bonding interactions. We evaluated various sets of conditions with the aim of reintroducing the enediol (retro aldol) in the hope that concomitant irreversible cyclopropane formation (via attack at C15) would take place. However, treatment of 12 with catalytic Sc(OTf)3 in DMF led instead to the cyclobutanone 13. Although clearly undesired, this was encouraging because 13 must have been derived from the desired hydroxy-cyclopropane B via a 1,2-shift, which in turn was produced via the enediol intermediate A (R = H). Indeed, the formation of cyclobutanones such as 13 from hydroxycyclopropanes has a precedent. To circumvent this undesired pathway, intermediate 12 was converted to hemioether 14 by simple treatment with Ac2O followed by exposure to Et3N and gentle heating to 60 °C to deliver 15. The single flask conversion of 11 to 15 can be conducted on a gram scale, and presumably succeeds owing to the in situ formation of intermediate A (R = Ac), which prevents 1,2-shift after cyclopropanation. We believe that the conversion of A to the desired cyclopropane is concerted because no elimination products were observed (see above). This reaction cascade consists of thirteen discrete events occurring in the same flask, forming two new C–C bonds, three new ring systems and three C–O bonds, along with the cleavage of one C–C bond, two ring systems and two C–O bonds. It unravels a complex polycyclic network to a kinetic endpoint using simple reagents thereby overcoming the greatest challenge posed by 1.

The final eight steps of the synthesis served to install two additional oxygen atoms, one methyl group and the proper C12 and C10 stereochemistry. Attempts to install the key C10 stereocentre by way of conjugate reduction were met with failure despite extensive experimentation (see Supplementary Information for details). Thus, to achieve allylic transposition of 15, the weakest point of the synthesis from an efficiency standpoint, we used TsNHNH2 under reductive conditions, which led to 16 in 40% yield. Allylic oxidation with CrO3 (ref. 26) delivered enone 17 in 46% yield. A two-step methyl group introduction was accomplished by formation of an α-iodoenone (TMSN3, I2)22 followed by a Stille coupling28, which afforded 18 in 64% overall yield along with 33% recovered 17. Selective removal of the C7 and C9 silyl groups with the HF · pyridine complex led to a diol that could be selectively dehydrated using the Martin Sulfurane reagent to an unstable olefin that was directly oxidized using SeO2 to aldehyde 19 in 51% overall yield. The selective cleavage of the C7 and C9 silyl groups could stem from the inductive effect of the C3 carbonyl group, which could make the C4 silyl group less reactive to acids. X-ray crystallographic analysis of 19 confirmed the structural assignments made thus far. To complete the synthesis, 19 was reduced to the allylic alcohol and shielded as the acetate ester. Attempts to directly reduce the C20 aldehyde and the C12 ketone in 19 were unsuccessful, owing to the rapid rate of the C3 enone carbonyl reduction in the presence of the C20 free primary alcohol (the C20 hydroxy group is actually proximate to C3 as judged by molecular models). Stereoselective ketone reduction using NaBH(OAc)3 followed by successive treatment with fluoride and hydroxide sources (TBAF and Ba(OH)2, respectively) led to optically pure (+)-1 (synthetic, [α]26D 105.37 (c 0.23, CH3OH); natural, [α]25D 104.25 (c 0.20, CH3OH)) in 72% isolated yield (15 mg prepared by this route).

The concise route to 1 is enabled by a fundamentally different retrosynthetic approach to terpene synthesis in the laboratory, rather than by focusing on the invention of a new synthetic method; the newest method used in this synthesis is a Stille coupling, invented in the 1980s28. Although the development of new synthetic methodologies are necessary to push the field of organic chemistry forward, this work emphasizes the equal importance of strategy design in the total synthesis of complex natural products29. By holistically mimicking the biosynthesis of ingenol (2) in the laboratory6,7, we exploited the interrelationship between ingenanes and tiglianes by using the same building block for both synthetic routes. Because two-phase terpene synthesis builds the carbon skeleton with a strategically planned redox state, the majority of steps can focus on installing key oxidations rather than repositioning functional groups and C–C bonds. Access to phorbol (1) requires only five additional steps compared to ingenol (2), owing to the presence of two additional oxygen atoms (C12/13) placed at particularly challenging locations on the carbon skeleton. Successful installation of these oxygenations and two others directly or indirectly relied on the application of C–H functionalization logic to pinpoint both the location and sequence of reactions19,30. This artificial oxidase phase will enable the synthesis of analogues containing deep-seated modifications in the same fashion that has recently been reported for ingenol (2)31. Although the route, in its current concise form, cannot compete with isolation for the procurement of large quantities of phorbol (1), we argue that it could be adapted to become truly scalable if the need arose. Rather, the purpose of this synthesis is to enable rapid access to new tigliane family members with exciting bioactivity that are either difficult or impossible to access through isolation or semisynthesis.
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Supplementary Information is available in the online version of the paper.

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Author Information Metrical parameters for the structures of 12 and 19 are available free of charge from the Cambridge Crystallographic Data Centre (CCDC) under reference numbers 1434376 and 1434377. Reprints and permissions information is available at www.nature.com/reprints. The authors declare no competing financial interests. Readers are welcome to comment on the online version of the paper. Correspondence and requests for materials should be addressed to P.S.B. (pbaran@scripps.edu).