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Quaternary–centre–guided synthesis of complex polycyclic terpenes

Pengfei Hu[1,2], **Hyung Min Chi**[1,2], **Kenneth C. DeBacker**[1], **Xu Gong**[1], **Jonathan H. Keim**[1], **Ian Tingyung Hsu**[1], **Scott A. Snyder**[1,*]

[1]University of Chicago, Department of Chemistry, Chicago, IL, USA

Abstract

The presence of a quaternary centre—a carbon with four other carbons bonded to it—in any given molecule can have a substantial chemical and biological impact. In many cases, it can enable otherwise challenging chemistry. For example, quaternary centres induce large rate enhancements in cyclization reactions—known as the Thorpe–Ingold effect—which has application in drug delivery for molecules with modest bioavailability[1]. Similarly, the addition of quaternary centres to a drug candidate can enhance both its activity and its metabolic stability[2]. When present in chiral ligands[3], catalysts[4] and auxiliaries[5], quaternary centres can guide reactions toward both improved and unique regio-, stereo- and/or enantioselectivity. However, owing to their distinct steric congestion and conformational restriction, the formation of quaternary centres can be achieved reliably by only a few chemical transformations[6,7]. For particularly challenging cases—for example, the vicinal all-carbon[8], *oxa*- and *aza*-quaternary centres[9] in molecules such as azadirachtin[10,11], scopadulcic acid A[12,13] and acutumine[14]—the development of target-specific approaches as well as multiple functional-group and redox manipulations is often necessary. It is therefore desirable to establish alternative ways in which quaternary centres can positively affect and guide synthetic planning. Here we show that if a synthesis is designed such that each quaternary centre is deliberately leveraged to simplify the construction of the next—either through rate acceleration or blocking effects—then highly efficient, scalable and modular syntheses can result. This approach is illustrated using the conidiogenone family of terpenes as a representative case; however, this framework provides a distinct planning logic that is applicable to other targets of similar synthetic complexity that contain multiple quaternary centres.

[*]**Correspondence and requests for materials** should be addressed to S.A.S. sasnyder@uchicago.edu.

[2]These authors contributed equally: Pengfei Hu, Hyung Min Chi.

Author contributions S.A.S. and PH. conceived the project. S.A.S. directed the research, and S.A.S., PH. and H.M.C. composed the manuscript and the Supporting Information section; all authors commented on the manuscript. P.H. and H.M.C. developed the synthesis of compound **10**. P.H. completed the syntheses of compounds **9**, **11**, **38** and **41**. H.M.C. synthesized the NHC and sulfonamide ligands and conducted the large-scale preparation of compounds **18**, **S12**, **S13** and **S14**. K.C.D. conducted large-scale racemic syntheses and reaction optimizations for compounds **18**, **19**, **20** and **S3**. X.G., J.H.K. and I.T.H. participated in material preparation and explored various alternative pathways towards the target molecules.

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Among quaternary-centre-containing molecules (Fig. 1), perhaps one of the most notable collections is terpenes such as **6**–**11**[15–21] (Fig. 1c). These natural products possess unique, polycyclic architectures that are effectively devoid of traditional reactive functional groups (such as carbonyls, alkenes and alcohols) but are relatively rich in all-carbon quaternary centres. In **8** and **9**, for instance, 20% of the carbon atoms fit such a description. Despite being 'greasy' compounds, many are highly bioactive, potentially owing to the structural rigidity enforced by their polycyclic frames. Intriguingly, that activity can change markedly depending on the positioning of their rare functional groups. For example, conidiogenone (**9**) induces conidiogenesis in the fermentation of *Penicillium cyclopium*[19], whereas conidiogenone B (**10**) has considerable antibacterial activity, including against methicillin-resistant *Staphylococcus aureus* (MRSA)[21]. A site-specifically oxidized analogue, conidiogenone C (**11**), has nanomolar cytotoxicity[20].

From a synthetic perspective, these molecules are strategically challenging because reactive functional groups are typically central to retrosynthetic planning[22]. As a result, the addition and eventual removal of such groups is often needed for the formation of core C–C bonds; such issues can further intersect with the broad and general challenge of quaternary centre generation. This concept is illustrated in Fig. 1d, in which a key step used in a previous study[18] to fashion one of the spirocyclic quaternary carbons of **9** proceeds with proper regiocontrol only with the added, but ultimately target-superfluous (**12**→**13**), phenylsulfide. We have also observed similar issues with other non-functionalized targets[15,16]; however, it was by reassessing those syntheses that we realized how quaternary centres could positively impact synthetic strategy. For instance, in a step in which a site-selective deprotonation of one of two axial protons was necessary, the neighbouring all-carbon quaternary centre presumably provided sufficient steric bulk to enable the requisite control[16] (**14**→**15**); similarly, in forming α-diazo ketone **17**, the highlighted quaternary centre in **16** probably blocked deprotonation at the alternative site[16]. Given their beneficial role in these steps, here we report a design in which quaternary centres are viewed as a strategic asset in synthetic planning to aid and/or direct the smooth and efficient formation of other quaternary centres without extraneous functional group manipulations, and illustrate its application (Fig. 2).

The ultimate goal is to identify the optimal order of quaternary-centre construction, building around an initial guiding quaternary carbon to then effectively generate the others without the step-count-heavy manipulations that are typical of standard designs. Although traditional retrosynthetic analysis is applied, each quaternary centre is considered, one-by-one, to determine whether it can assist in the formation of other quaternary centres. A benefit can be assessed as either: (1) blocking undesired reactivity and/or enforcing site selectivity (quaternary centre blocking); or (2) facilitating a reaction through rate acceleration (quaternary centre facilitating). In some instances, these elements might be synergistic. Furthermore, the presence of additional, temporary quaternary centres can be considered if they, too, assist in the preparation of other quaternary centres. Reaction development can, of course, be facilitated by applying the sterically encumbered nature of the quaternary carbons themselves to reveal where further advancements are needed (quaternary centre opportunity). Such analyses should look particularly for cases in which neighbouring bulk has either previously prevented reactions, or where it might enable new processes to occur as

a result of that bulk arresting the undesired reactivity that is typical of more accessible positions.

The product of that analysis for the conidiogenones has been drawn in Fig. 2 as a projected forward synthesis for clarity. Here, the light-blue-coloured quaternary centre was identified as the linchpin guiding quaternary centre, as it was the one that, after extensive retrosynthetic analysis, had the best potential to enable the formation of the other three. In the opening steps, we anticipated that its presence within cyclopentanone **18** would promote the smooth formation of **20**—first by blocking the neighbouring position from the approach of any electrophile or base in the oxidation to form **19**, and then by providing a potential Thorpe–Ingold-type accelerated ring closure leading to the new quaternary centre in **20**. Next, an additional blocking step would allow for regioselective alkylation, enabling the eventual formation of **21**. If so, the stage would be set for one of the most critical steps of the route: a palladium-catalysed ring closure. This process was expected to generate the third quaternary centre of the framework, with a 1,3-*trans* diastereoselectivity[16,23,24] of the exocyclic methyl and hydrogen groups at the carbons marked with an asterisk in both **22** and **23**—intermediates that are expected to be in equilibrium[24]. Here, the core design element was that the new quaternary centre—including the additional temporary quaternary centre within **23**—would prevent β-hydride elimination and/or any other deleterious events to enable functionalization with an external oxygen nucleophile to generate **24** as a terminal product. To our knowledge, such C—O bond formation from an unactivated C(sp^3)—Pd(II) intermediate in a Pd(0)/Pd(II) catalytic system is unprecedented (see Supplementary Figs. 1 and 2 for discussion). Thus, in this case, the quaternary centres would enable the pursuit of such unique reactivity by shunting alternative reactive pathways that would normally predominate. Finally, the remaining ring and quaternary centre were projected to arise through side-chain incorporation using a Nozaki–Hiyama–Kishi (NHK) reaction[25] to generate **25**, followed by a reductive palladium-catalysed ring closure[26] to deliver **27**. The presence of the neighbouring quaternary centre was viewed as an opportunity to improve NHK methodology, because additions onto hindered, neopentyl aldehydes are quite rare and, to our knowledge, unknown with radical mechanisms. In the cyclization, the quaternary centres would provide potential rate enhancements in the generation of the final highly congested quaternary centre, as well as blocking to enable the reduction of the C(sp^3)—Pd(II) intermediate without competing (β-hydride elimination. Changes in the oxidation state of **27** were then anticipated to finalize the synthesis of several target compounds.

As shown in Fig. 3, the synthesis commenced with ketone **18** (prepared enantioselectively in two steps on a decagram scale; see Supplementary Information for details)[27]. Soft enolization using trimethylsilyl trifluoromethanesulfonate and a hindered tertiary amine, 1,2,2,6,6-pentamethylpiperidine, gave **28** in quantitative yield with a regioselectivity of greater than 20:1. Subsequent oxidation using 2-iodoxybenzoic acid[28] then delivered enone **19**. Next, this intermediate was subjected to Baran's reductive coupling[29] to furnish bicyclic ketone **20** as a single diastereomer. From here, the use of Corey's hydra-zone-mediated alkylation conditions[30] with iodide **29** afforded, after acidic hydrolysis, the desired alkylated material in 66% yield and a diastereoselectivity of greater than 10:1 on >2-g scale. Again, we think that the initial quaternary centre played a critical part in that selectivity. Finally, in

advance of the first key palladium-based bond-forming cascade, that intermediate was converted regiospecifically into vinyl triflate **21**. After extensive screening, we were able to convert this new material into acetate **30** in high yield using catalytic $Pd(OAc)_2$ in the presence of *t*-BuMephos (2-di-*tert*-butylphosphino-2′-methylbiphenyl) and the highly nucleophilic *n*-Bu_4NOAc[31] as an oxygen source; no variation in these conditions afforded an effective synthesis of **30**. To our knowledge, this reaction constitutes the first example of a direct C–O bond-formation process from an unactivated C(sp^3)—Pd(II) intermediate in a Pd(0)/Pd(II) catalytic system. In practice, the incorporated acetate group could be smoothly hydrolysed in situ to afford alcohol **31** in 83% yield as a single diastereomer on a gram scale.

With three of the core quaternary centres forged, our efforts now focused on generating the final ring system and quaternary centre of the conidiogenones. We commenced with the incorporation of alkyl iodide **34** onto aldehyde **32** (derived from the oxidation of **31**), through a radical-mediated, chemoselective NHK-type reaction[25,32]. After extensive screening of the oxazoline-sulfonamide ligand (**33** was optimal) and overall loadings for all components, we could conduct this reaction on a gram scale to give—with in situ TMS-protection of the resultant alcohol—intermediate **35** in 3:1 diastereomeric ratio and 75% yield. Critically, this reaction shows a strong steric match/mismatch effect, with the absence of ligand or the alternative ligand enantiomer giving substantially lower yield and selectivity. The diastereoselectivity of the optimized outcome proved essential, in that—although this newly formed chiral centre would be ablated later—only the diastereomer shown was capable of engaging in the second reductive Heck cyclization[26], converting **35** into **36** in good yield after deprotection using *n*-Bu_4NF. Single-crystal X-ray diffraction analysis of **36** confirmed the stereochemistry of the major diastereomer. Finally, stereoselective hydrogenation delivered the unnamed natural isolate[33] **37**—although in practice **37** was oxidized in the same pot to deliver conidiogenone B (**10**) in 71% yield. As one example of the efficiency of the sequence, more than 280 mg of **10** was prepared in one batch; all the preceding steps worked on a gram scale. In addition, our 13-step synthesis of this target compares favourably to the 24-step preparation that has been achieved previously[18]. Using the chemistry from this previous study[18], **10** was then similarly converted into both conidiogenone (**9**) and conidiogenol (**38**).

Finally, we sought to obtain other differentially oxidized members of the conidiogenone family, such as conidiogenones C and D (**11** and **41**, Fig. 3b). Although a late-stage C–H oxidation of **10** is not likely to be feasible (see Supplementary Fig. 4 for discussion), we took advantage of the modularity of our sequence to access **11** and **41**. We expected that, after the early introduction of the additional hydroxyl groups of these compounds, the ensuing C–C bond-forming reactions would proceed with similar yield and selectivity to those in the preparation of our earlier compounds. Indeed, by treating **19** with 3-chloroperbenzoic acid and then cyclizing with Cp_2TiCl_2 (Cp, cyclopentadienyl)[34], alcohol intermediates were obtained that—after protection with methoxymethyl ether to deliver **39** and **40**—could be separately taken through a slightly modified general sequence as described above to obtain target compounds **11** and **41** (see Supplementary Information for full details) in 16 steps each. Thus, in total, six natural products have been prepared, one of

which was obtained on a fairly large scale (greater than 250 mg). Given their scarcity in nature (between 0.21 mg and 11.2 mg of the five named conidiogenones per 100 litres of fermentation broth)[19,20], synthetic chemistry seems to be the best avenue to enable further biochemical studies.

This work provides, arguably for the first time, a formalized logic that unites many disparate observations about quaternary centres into a cohesive and unified synthetic strategy for the synthesis of complex molecules. Whether used as blocking agents, reaction rate enhancers, and/or steric differentiators capable of advancing new chemistry, as in the direct C(sp^3)-Pd(II) oxygenative functionalization illustrated here, such cohesive thinking about quaternary centres—in terms of their strategic incorporation and exploitation in generating other quaternary centres—can minimize the number of functional-group and protecting-group interconversions that are typically required when these centres are viewed in isolation. This approach can also push the boundaries of available tools, such as the NHK-type reaction achieved here, by using their distinctive steric congestion productively. We believe that the use of this design can broadly inform the synthesis of complex molecules—not just for terpenes such as the conidiogenones, but for more functionalized targets from different collections. Figure 4 provides some initial analyses along these lines. The opening projections (Fig. 4a) show how, through the successful execution of the pictured metal-mediated cascade followed by a 5-*exo*-dig cyclization, architectures bearing the three contiguous quaternary centres of certain triquinane terpenes could result quickly from a quaternary-centre-directed campaign. Perhaps more compellingly, several syntheses from our group (Fig. 4b, citations in Supplementary Information)—although uninformed by the formalized logic presented here—reflect these strategic principles. In each, a guiding quaternary centre aided in the formation of others through blocking and rate-enhancing effects (including *oxa*-quaternary centres in this analysis); in addition, reaction development opportunities and the value of temporarily incorporated quaternary centres were also illustrated. Although these three cases may not be ideal synthetic approaches, given that they were not designed directly with this planning logic in mind, their successful execution lends credence to its general potential. As such, the formal use of this approach going forward should provide substantial efficiency enhancements in the construction of quaternary-centre-based molecular complexity.

METHODS

All reactions were carried out under an argon atmosphere using dry solvents under anhydrous conditions; dry THF, toluene, benzene, diethyl ether and CH_2Cl_2 were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Yields refer to chromatographically and spectroscopically (^{1}H and ^{13}C NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were magnetically stirred and monitored by thin-layer chromatography. For full experimental details—including procedures for all reactions and characterization of all new compounds (^{1}H NMR, ^{13}C NMR, mass spectrometry, infrared spectroscopy, retention factors)—see the Supplementary Information.

Data availability

Data produced in this study is available in the Supplementary Information or on request from the corresponding author.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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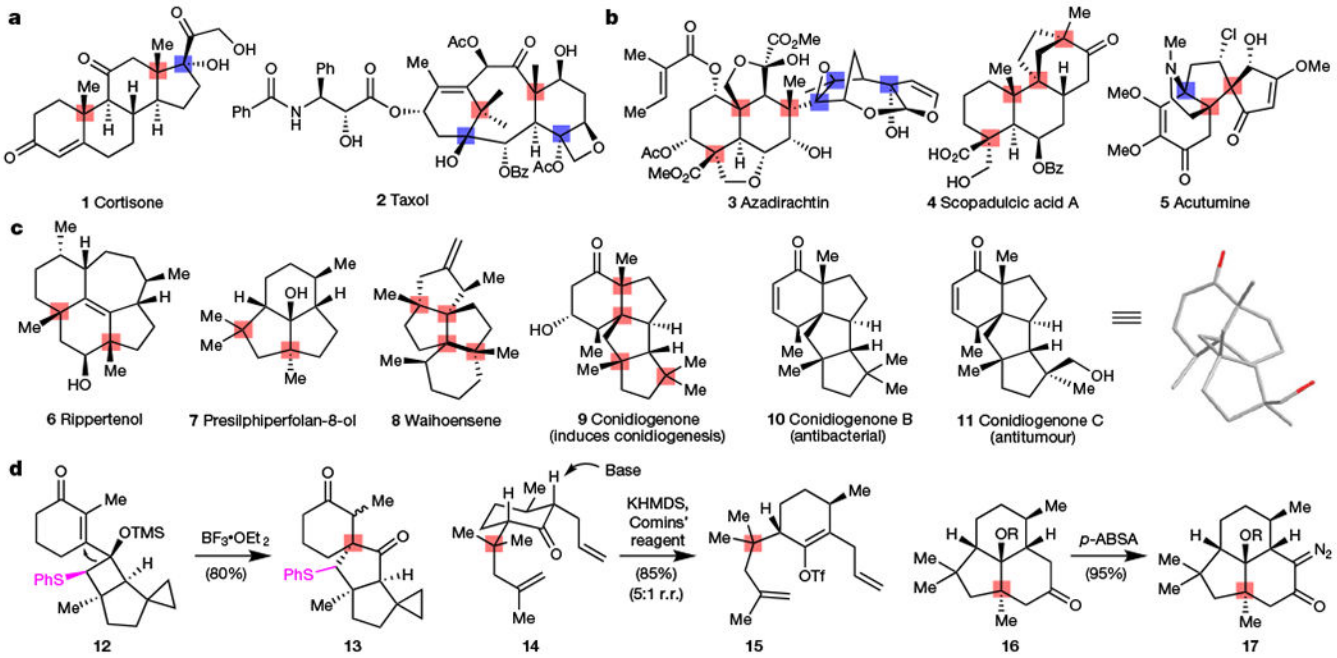

Fig. 1 |. Quaternary centres as a point of challenge and opportunity for organic synthesis.

a, Quaternary centres can be greatly beneficial, including several drugs that are natural products. All-carbon quaternary centres are highlighted in red, with *oxa*-quaternary centres highlighted in blue. **b**, Additional natural products containing quaternary carbons, noting that *oxa*- or *aza*-quaternary centres pose different challenges for laboratory synthesis compared with all-carbon quaternary centres. **c**, Unique, non-functionalized terpenes that are rich in all-carbon quaternary centres. **d**, Transformations showing the challenges and opportunities of quaternary carbons in such terpenes, with R = TMS. Comins' reagent, *N*-(5-chloro-2-pyridyl)bis(trifluoromethanesulfonimide); KHMDS, potassium hexamethyldisilazide; *p*-ABSA, 4-acetamidobenzenesulfonyl azide; r.r., regioselectivity ratio; TMS, trimethylsilyl.

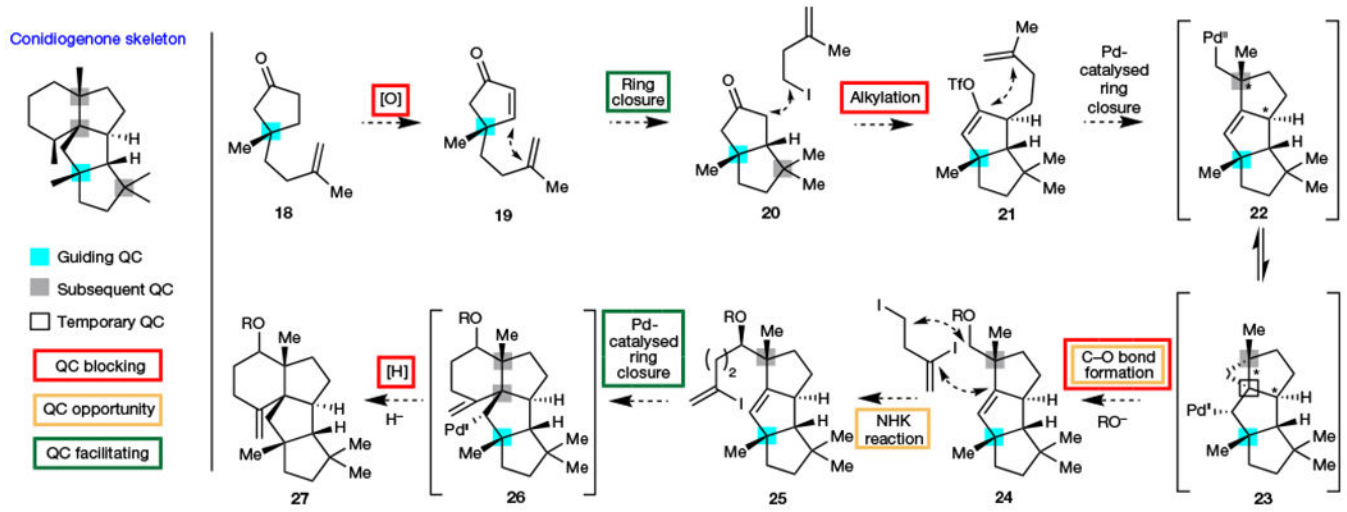

Fig. 2 |. Quaternary-centre-guided synthetic analysis of the conidiogenones.

A guiding quaternary centre (QC) is used to block and/or facilitate additional quaternary-centre formation as well as to provide opportunities along the route for reaction development, which can lead to efficient synthetic designs. [H], reduction; [O], oxidation. Reactions are highlighted in red for a quaternary centre used for steric blocking, in yellow for a synthetic opportunity, and in green for facilitating a reaction.

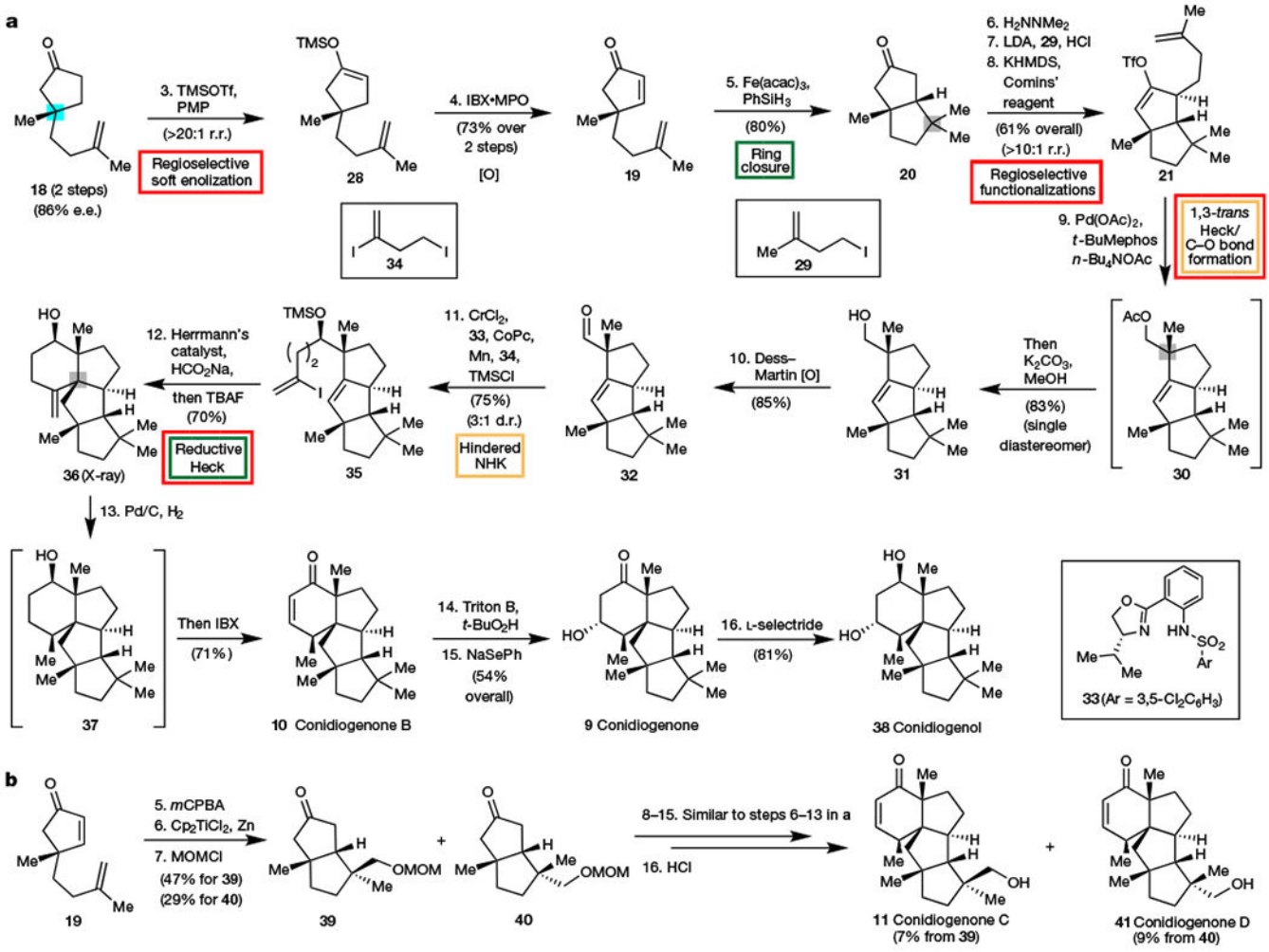

Fig. 3 |. Short, enantioselective synthesis of the conidiogenone family of natural products empowered by quaternary-centre-based synthetic planning.

a, Concise synthesis of conidiogenone B (**10**), conidiogenone (**9**) and conidiogenol (**38**), with each quaternary carbon highlighted once generated. The first 12 steps were carried out on a gram scale. 280 mg of conidiogenone B (**10**) was prepared in a single batch. The colours used to highlight the quaternary carbons and the steps are the same as in Fig. 2. **b**, Modular synthesis of conidiogenones C (**11**) and D (**41**) using key elements of the synthetic plan developed in **a**. CoPc, cobalt(II) phthalocyanine; Cp_2TiCl_2, bis(cyclopentadienyl)titanium(IV) dichloride; Dess–Martin periodinane, 1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1*H*)-one; $Fe(acac)_3$, iron(III) acetylacetonate; Herrmann's catalyst, *trans*-bis(acetato)bis[*o*-(di-*o*-tolylphosphino) benzyl]dipalladium(II); IBX, 2-iodoxybenzoic acid; LDA, lithium diisopropylamide; L-selectride, lithium tri-*sec*-butylborohydride; *m*CPBA, 3-chloroperbenzoic acid; MOMCl, chloromethyl methyl ether; MPO, 4-methylpyridine *N*-oxide; OTf, trifluoromethanesulfonate; PMP, 1,2,2,6,6-pentamethylpiperidine; TBAF, tetra-*n*-butylammonium fluoride; *t*-BuMephos, 2-di-*tert*-butylphosphino-2′-methylbiphenyl; Triton B, benzyltrimethylammonium hydroxide.

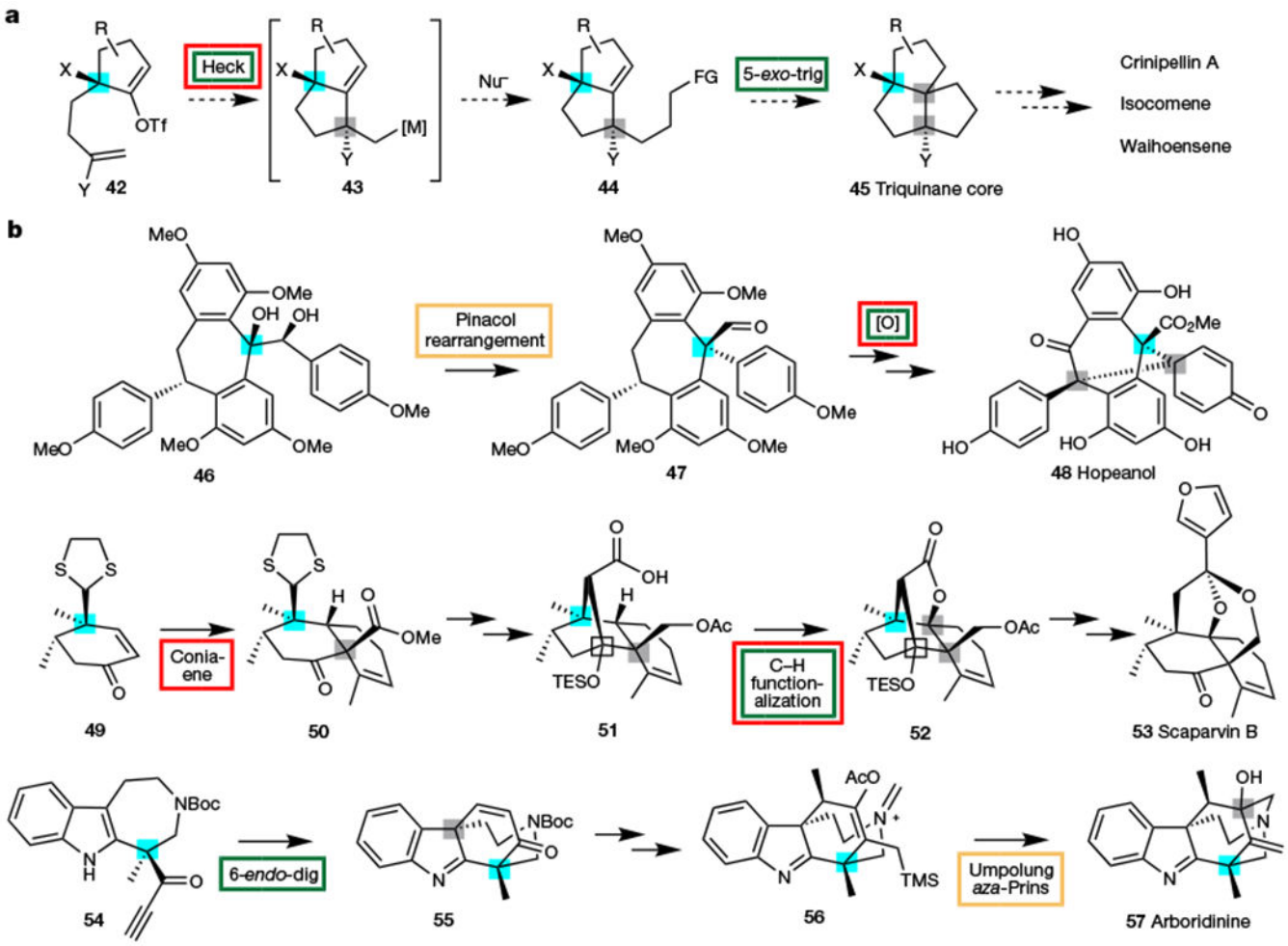

Fig. 4 |. Quaternary-centre-guided synthetic analysis can apply to diverse targets.
a, One projection for the preparation of the triquinane framework relevant to numerous targets. **b**, Re-evaluation of previous syntheses, here considering just the work of our laboratory, reveals that the logic is applicable to the synthesis of polyphenols, more highly oxidized terpenes, and alkaloids. Boc, *tert*-butyloxycarbonyl; FG, functional group; TES, triethylsilyl.