Total Synthesis of Nine Longiborneol Sesquiterpenoids using a Functionalized Camphor Strategy

Robert F. Lusi,[1,†] Goh Sennari,[1,†,*] Richmond Sarpong[1,*]

[1] Department of Chemistry, University of California, Berkeley, CA, USA. [†]these authors contributed equally to this work. *corresponding authors, email: gohsennari@berkeley.edu, rsarpong@berkeley.edu

Abstract:

Natural product total synthesis inspires strategy development in chemical synthesis. In the 1960s, Corey and coworkers demonstrated a visionary preparation of the terpenoid longifolene, using "strategic bond analysis" to craft a synthesis route. This approach proposes that efficient synthesis routes to bridged, polycyclic, structures should be formulated to introduce the bulk of the target's topological complexity at a late stage. In subsequent decades, similar strategies have proved general for the syntheses of a wide variety of bridged, polycyclic molecules. Here, we demonstrate that an orthogonal strategy, which utilizes a topologically complex bicyclo[2.2.1] starting material accessed through a scaffold rearrangement of (*S*)-carvone, leads to a remarkably short synthesis of the longifolene-related terpenoid longiborneol. We also employ a variety of late-stage C–H functionalization tactics in divergent syntheses of many longiborneol congeners. Our strategy should prove effective for the preparation of other topologically complex natural products that contain the bicyclo[2.2.1] framework.

MAIN TEXT:

The field of natural product total synthesis has long served as a testing ground for new methods and strategies for chemical synthesis. Among the many classes of natural product targets, chemists continue to be especially fascinated by bridged, polycyclic terpenoids, in part due to the distinct synthesis challenges posed by their topologically complex frameworks.[1] Longifolene (**1**, Fig. 1a) is emblematic of this class. In their seminal synthesis of **1**,[2,3] Corey and coworkers demonstrated that a method for retrosynthetic analysis termed "strategic bond analysis" could effectively identify synthesis routes to these terpenoids.[4] For bridged polycyclic targets, this analysis begins with network analysis, which identifies the maximally bridged ring (MBR) in the molecule's framework. Retrosynthetic disconnection of each bond in the MBR is then considered, in order to determine disconnections that lead to the simplest, most synthetically accessible intermediates.[4] Corey's analysis of longifolene resulted in a visionary 15 step synthesis of longifolene, via

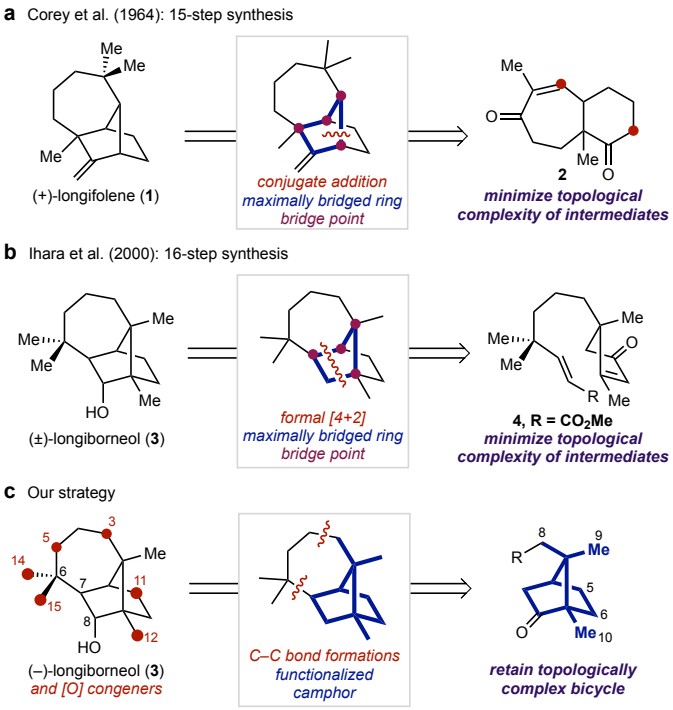

Fig. 1 | Retrosynthetic approaches to longifolene and longiborneol. a, Corey and coworkers to longifolene,[3,4] **b**, Ihara and coworkers to longiborneol,[10,11] **c**, Our approach to longiborneol and congeners. (*Note:* A comprehensive analysis of the reported syntheses of longiborneol and longifolene is provided in the Supplementary Information.)

fused bicycle **2**.[2,3] Because strategic bond analysis seeks to minimize topological complexity in the retrosynthetic direction, it implies that the most efficient synthesis of a bridged, polycyclic molecule would introduce target-relevant topological complexity at a late stage. This type of approach has been applied to other syntheses of **1**[5] and to the construction of a variety of structurally complex natural products.[6,7,8] For example, the shortest synthesis of the related natural product longiborneol[9] (**3**, Fig. 1b)—16 steps from commercial precursors—by Ihara and coworkers constructs the [2.2.1]bicyclic framework at a late stage, using a formal [4+2]cycloaddition.[10,11]

We envisioned an orthogonal strategy that could yield an even shorter synthesis of longiborneol and provide access to a wide range of related natural products. Instead of utilizing primary retrosynthetic disconnections that minimize the topological complexity of intermediates, we instead sought an easily obtained starting material that retained as much of the target molecule's topological complexity as possible

(Fig. 1c). Through this lens, functionalized camphor derivatives appeared to be ideal synthetic precursors to longiborneol, a stark contrast to cyclopentane derivatives, such as **4**, and the fused bicycles prompted by strategic bond analysis. If effective, a "functionalized camphor" strategy could also prove valuable for total syntheses of a variety of natural products, such as those shown in Fig. 2a, featuring the bicyclo[2.2.1] bornane sub-skeleton.

"Chiral pool" terpenes[1] have classically been used to prepare molecules with which they share skeletal characteristics. It is, therefore, intuitive to imagine synthesizing these functionalized camphor derivatives from camphor. However, such strategies can present challenges. For example, Kuo and Money employed 8-bromocamphor to prepare longiborneol,[12] but reported that its preparation from camphor (in three steps) was capricious and somewhat low yielding.[13] An alternative approach is to employ a different chiral pool terpene in scaffold remodeling—concise, selective series of C–C bond forming and C–C cleaving reactions that enable diverse carboskeletons to be accessed from a single starting material. This strategy allows chiral pool feedstocks to be applied to synthesis targets onto which they cannot be intuitively superimposed. We have previously shown that scaffold remodeling of (*S*)-carvone can be used to access functionalized camphor derivatives,[14] but the sequence has not been employed in complex molecule synthesis, prior to this report.

While a synthesis of longiborneol provided an opportunity to test the "functionalized camphor" strategy described above, syntheses of its various oxidized congeners (e.g., **5**–**14**, Fig. 2b)[15,16,17,18] presented an additional opportunity to probe the effectiveness of modern C–H functionalization methods in late-stage diversification. In recent years, the use of such reactions to introduce myriad oxygenation patterns on complex molecules has been of intense interest to synthetic chemists.[19,20,21,22] Determining the positional selectivities of these methods on intricate hydrocarbon frameworks is pivotal to their further development

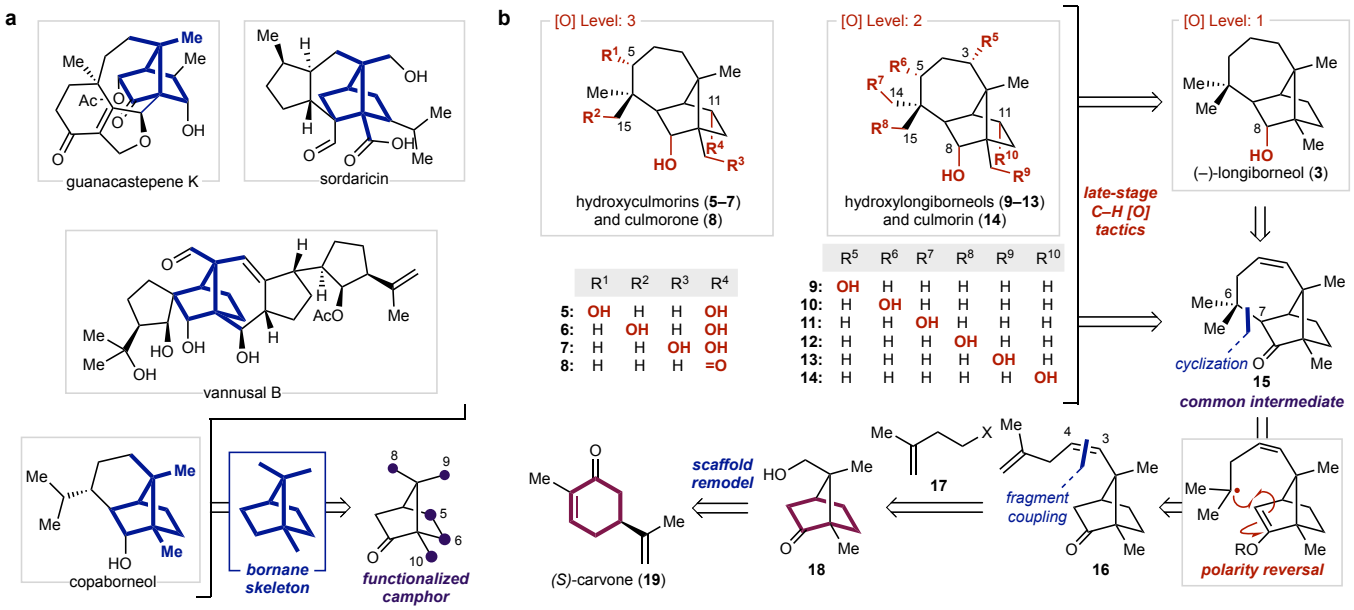

Fig. 2 | Structurally similar natural products and retrosynthesis of longiborneol. a, Natural products that contain the bornane skeleton. **b**, Our retrosynthesis of the longiborneol family of natural products. [O], oxidation.

and application. Therefore, we saw the implementation of a divergent synthesis of many longiborneol congeners as a valuable contribution to this effort.

Herein, we report a unified synthesis of nine longiborneol congeners from 8-hydroxycamphor (**18**). This key synthetic intermediate is accessed from carvone using a scaffold rearrangement process consisting of three reproducible steps.[14] An unusual, metal-mediated hydrogen atom transfer (MHAT)[23] initiated cyclization enabled rapid construction of the longiborneol skeleton around this camphor-based structural nucleus. Using this approach, longiborneol (**3**) was prepared in nine total steps from carvone — the shortest route to date.[11,12,24,25] Additionally, we leveraged a common intermediate to prepare longifolene, using a rearrangement of the longiborneol scaffold, as well as a variety of oxygenated longiborneols, through late-stage oxidation tactics.

Our retrosynthesis of **3** sought to address not only this target but the collection of longiborneol-related natural products (classified by oxidation level) illustrated in Fig. 2b. We envisioned that the

disparate oxygenation patterns of these targets could be installed by exploiting strategically positioned alkene, ketone, and hydroxy groups for C–H functionalizations at a late stage. Therefore, all the targets would ultimately arise from common intermediate **15**. Disconnection of the C6–C7 bond of **15** led back to **16**. To accomplish this transformation in the forward sense, we sought a cyclization method that would effect concomitant formation of the C6–C7 bond and the C6 quaternary center. We posited that this could be achieved by polarity-reversal enol alkylation. Specifically, we recognized that metal-hydride hydrogen atom transfer (MHAT) chemistry could be used to generate a nucleophilic, tertiary radical from the terminal alkene (see **16**).[23] This radical could then add into an electrophilic enol derivative. Disconnection of the C3–C4 bond in **16** traced back to 8-hydroxycamphor and alkyl halide **17**. We envisioned coupling these two fragments using a Wittig reaction.[26] We have previously shown that **18** can be readily prepared from (*S*)-carvone (**19**) using a scaffold remodeling strategy.[14]

Results:

Our synthesis (Fig. 3a) commenced with epoxidation of (*S*)-carvone, followed by Ti(III)-mediated reductive cyclization of the epoxy-carvone to give cyclobutanol **20** in excellent yield as a 1.5:1 mixture of epimers at C7.[27] A Brønsted acid-mediated semipinacol rearrangement[28] of **20**, carried out using a modification of the conditions from our previous report,[14] yielded 8-hydroxycamphor, which was then oxidized to the corresponding aldehyde (**21**). Selective Wittig olefination of aldehyde **21**, using the phosphonium ylide derived from **22**,[29] furnished skipped-diene **16**, which contains all the carbon atoms of longiborneol and its structurally related congeners.

In order to implement the MHAT-initiated cyclization, we needed to identify a suitable olefin coupling partner—ideally one derived from the carbonyl group at C8. There are many examples of polarity-matched additions of electrophilic radicals to a variety of *O*-functionalized enol acceptors.[30,31,32] However, in our case, the planned radical donor and acceptor presented a polarity mismatch. Specifically, the

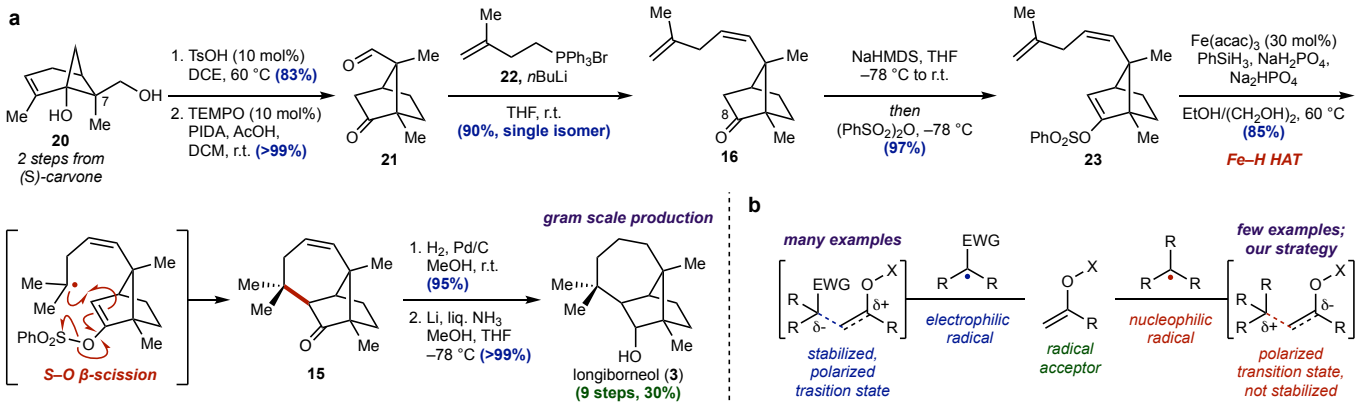

Fig. 3 | Total synthesis of longiborneol. a, Total synthesis of longiborneol. **b**, Polarity considerations in radical additions to enol derivatives. TEMPO, (2,2,6,6-tetramethylpiperidin-1-yl)oxyl; PIDA, (diacetoxyiodo)benzene; *n*BuLi, *n*-butyllithium.

proposed addition would be kinetically unfavorable because the radical donor-acceptor pair would not effectively stabilize a polarized transition state.[33] For this reason, additions of nucleophilic radicals to enol-derived acceptors are quite uncommon, and tend to be limited in scope with regard to the enol derivative (Fig. 3b).[31,32,34,35] In addition, enol derivatives are known to be competent H-atom acceptors in MHAT reactions.[36] We rationalized that these reactivity and selectivity challenges could be mitigated by using an electron poor enol-derivative. Following extensive investigation, we identified a vinyl phenylsulfonate group as the optimal acceptor coupling partner. The vinyl phenylsulfonate group was easily installed, in high yield (see **23**), by treating the corresponding ketone with sodium bis(trimethylsilyl)amide (NaHMDS) and benzenesulfonic anhydride. Subjecting **23** to optimized Fe-HAT conditions,[37,38,39] including critical buffering agents, smoothly effected cyclization to **15** in a remarkable 85% yield. A possible mechanism is illustrated in Fig. 3a. There exists a single report of addition of cyclohexyl and cyclopentyl radicals (generated by H-atom abstraction from the parent alkanes) into 1-phenyl vinyl triflate.[32] However, the cyclization of **23** to **15** is, to our knowledge, the first example of addition of a nucleophilic radical generated through MHAT into a vinyl sulfonate.

Hydrogenation of the disubstituted alkene in **15** gave longicamphor (**24**). A subsequent diastereoselective reduction of the ketone in **24**, using dissolving metal conditions, furnished longiborneol (9 total steps and 33% overall yield from (*S*)-carvone). Each step has been performed on gram scale, and over a gram of longiborneol has been synthesized in a single pass.

Our synthesis of **15** set the stage for the preparation of many oxygenated longiborneol congeners. Because C3 and C5 are activated by the alkene group, 3-hydroxylongiborneol (**9**) and 5-hydroxylongiborneol (**10**) were envisioned to arise from **15** by a formal hydration and allylic oxidation, respectively (Fig. 4a). Indeed, a regio- and diastereoselective Mukaiyama hydration[40] of the C3–C4 double bond of **15** effectively installed a hydroxy group at C3. Subsequent dissolving metal reduction of the C8 carbonyl delivered 3-hydroxylongiborneol. Alternatively, SeO_2-mediated allylic oxidation of **15** diastereoselectively installed a hydroxy group at C5. At that stage, reduction of the alkene and C8 ketone groups yielded 5-hydroxylongiborneol.

We next sought to synthesize either 14-hydroxylongiborneol (**11**) or 15-hydroxylongiborneol (**12**) by effecting a Suárez reaction on *iso*-longiborneol (**27**).[41] However, our attempts led only to degradation of the starting material—possibly due to a kinetically favored β-scission of the strained [2.2.1]bicycle.[42] Because of the lack of other functional groups proximal to C14 or C15 in our late-stage intermediates, and a paucity of methods for undirected functionalization of primary C–H bonds, we turned to a relay oxidation strategy (Fig. 4b).[43,44] Specifically, we envisioned that oxygenation at C5, in intermediates similar to those employed in our synthesis of 5-hydroxylongiborneol, could direct subsequent hydroxylation at C14 or C15. For this purpose, oxime **25** was synthesized from **15** in a six-step sequence (see the Supplementary Information). Sanford palladium-catalyzed C–H acetoxylation[45,46] initially led to bis-acetoxylation at both C14 and C15 in the major product. While this reaction product was unproductive, it indicated that suppression of bis-acetoxylation would enable syntheses of both 14- and 15-hydroxylongiborneols. We

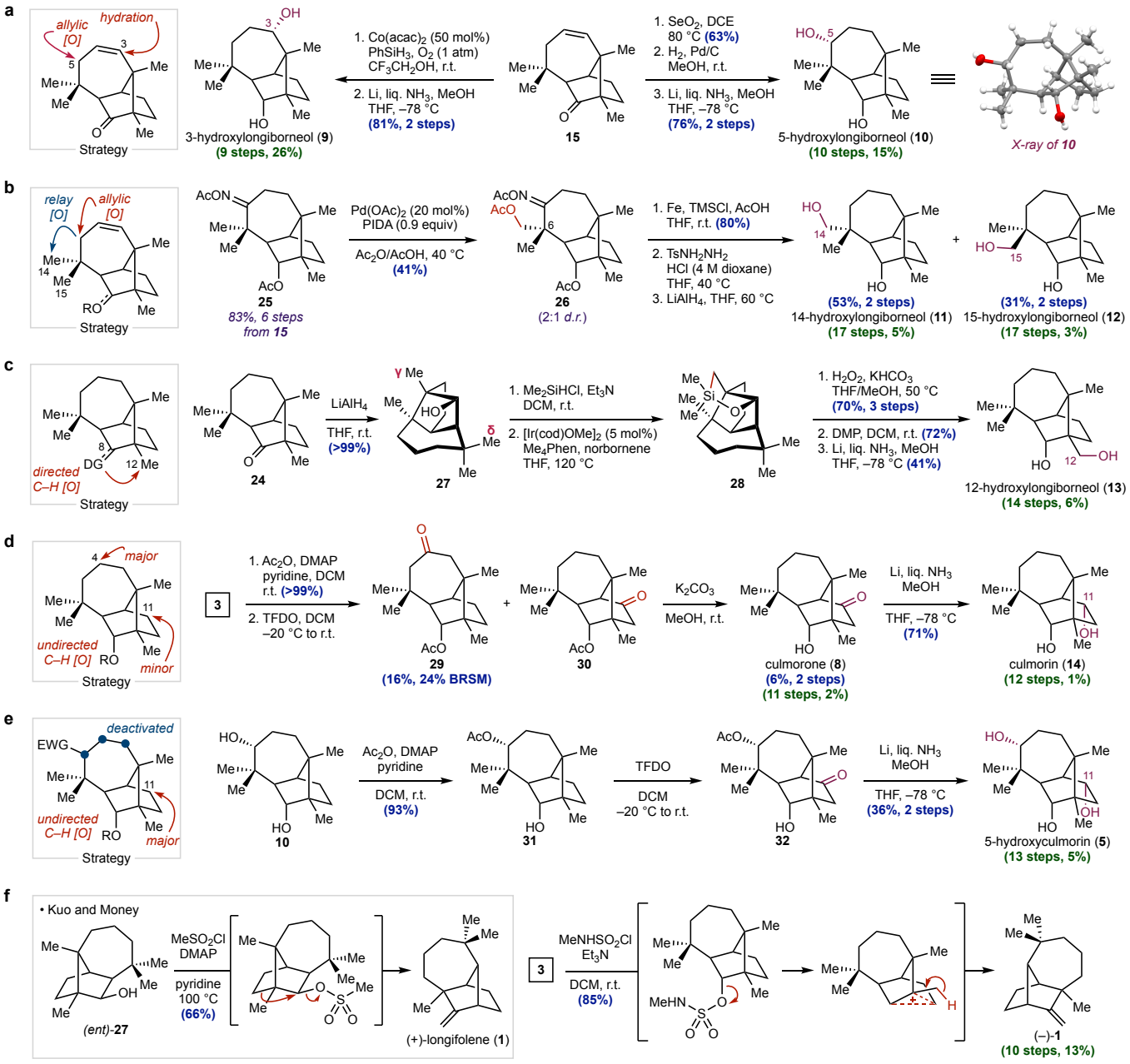

Fig. 4 | Syntheses of oxygenated longiborneol congeners. C–H oxidation strategies and final synthetic routes for: **a**, 3-hydroxylongiborneol and 5-hydroxylongiborneol, **b**, 12-hydroxylongiborneol, **c**, 14-hydroxylongiborneol and 15-hydroxylongiborneol, **d**, culmorone and culmorin, **e**, 5-hydroxyculmorin. **f**, Synthesis of longifolene from longiborneol. acac, acetylacetonate; DMAP, 4-dimethylaminopyridine; DG, directing group; Me_4Phen, 3,4,7,8-tetramethyl-1,10-phenanthroline; DMP, Dess–Martin periodinane; TFDO, trifluoromethyl-methyldioxirane.

found that this shift in product distribution could be achieved by utilizing a substoichiometric loading of the PIDA oxidant (0.9 equiv) and significantly lowering the reaction temperature (100 °C → 40 °C)

compared to the initially reported conditions.[46] Thus, we were able to obtain synthetically useful yields of acetoxylated intermediate **26** as a 2:1 mixture of epimers at C6. Reductive oxime cleavage and hydrolysis of the resulting imine, tosyl hydrazone formation, and $LiAlH_4$-mediated Caglioti reaction[47] completed syntheses of 14-hydroxylongiborneol and 15-hydroxylongiborneol through our C5→C14/C15 relay hydroxylation.

We hypothesized that 12-hydroxylongiborneol (**13**) could be prepared by directed C–H functionalization from C8 to C12 (Fig. 4c), perhaps by using an oxime derived from **15** in a directed C(sp^3)–H acetoxylation.[45,46] However, our attempts to condense oxyamines with **15** were uniformly unsuccessful––likely due to steric hindrance around the ketone group. Instead, we turned our attention to the directed C–H silylations discovered by Hartwig and coworkers.[48,49] Use of longiborneol as the starting material led to none of the desired silacycle. On the other hand, *iso*-longiborneol (**27**), synthesized by $LiAlH_4$ reduction of longicamphor, proved a more competent substrate. Treatment of **27** with chlorodimethyl silane yielded a dimethyl (hydrido)silyl ether, which, following iridium-catalyzed C–H silylation, provided silacycle **28**. Tamao–Fleming oxidation[50,51] of **28** yielded *iso*-12-hydroxylongiborneol (**S7**, not shown). Oxidation of the hydroxy groups in **S7** followed by dissolving-metal reduction of the resulting carbonyls yielded 12-hydroxylongiborneol.

Given that C11 is distal from all potential directing groups that could easily be derived from **15**, we turned to undirected C–H oxidations to prepare culmorone (**8**) and culmorin (**14**). We anticipated that undirected oxidation of the longiborneol scaffold with metal-oxo[52] or dioxirane[53] reagents would result primarily in oxidation at C4, due to its steric accessibility and distance from electron-withdrawing groups (Fig. 4d). However, we also expected competing C11 oxygenation, given that it is the only other methylene group that is not neopentyl. Following extensive experimentation, we identified methyl(trifluoromethyl)dioxirane (TFDO) as the most effective reagent for undirected C–H oxidation of

acetyl-longiborneol (**S8,** not shown). C4 oxidation accounted for the major product (**29**, 16% yield, 24% BRSM) and C11 oxidation (**30**) was also observed. In addition, C3 (6% yield; see the Supplementary Information) and C5 (see Supplementary Information) oxidation products as well as several unidentified side-products were also observed. While efforts to further optimize this sequence have thus far proven unsuccessful, a direct synthesis of culmorone was achieved upon cleavage of the acetyl group of **30**. Dissolving metal reduction of culmorone gave culmorin. Armed with a new understanding of the selectivity of the TFDO-mediated C–H oxidation of the longiborneol scaffold, we sought to employ it in syntheses of additional congeners.

Even though undirected C–H functionalization of acetyl-longiborneol was poorly selective, we anticipated that installation of additional electron-withdrawing groups on the seven-membered ring would slow the rate of oxidation at C3, C4, and C5 (Fig. 4e).[53] In line with this expectation, TFDO-mediated C–H oxidation of bis-acetylated 5-hydroxylongiborneol (**31**) resulted in a more selective oxidation at C11 (as observed by NMR analysis), leading to an efficient preparation of 5-hydroxyculmorin (**5**), following dissolving-metal reduction of the crude mixture, in 38% yield over 2 steps.

Finally, during the course of our C–H functionalization studies, we also observed the rearrangement of the longiborneol scaffold to other natural product frameworks. For example, treating longiborneol with methylsulfamoyl chloride furnished longifolene as the sole product in good yield (Fig. 4f). A related rearrangement is known via Wagner–Meerwein shift of the *iso*-longiborneol-derived mesylate.[13] Our total synthesis of longifolene proceeds in 10 linear steps from commercial precursors and is the shortest to date.

The total syntheses presented here rest on a scaffold rearrangement of carvone (Fig. 5), a versatile tactic that can provide the diverse camphor derivatives required to pursue similar synthesis strategies towards other complex molecules (see Fig. 2a). For example, we have previously reported the preparation of **18**, **35**, **36** and **37** from carvone in three steps.[14] Additionally, we have now shown that oxygenation of

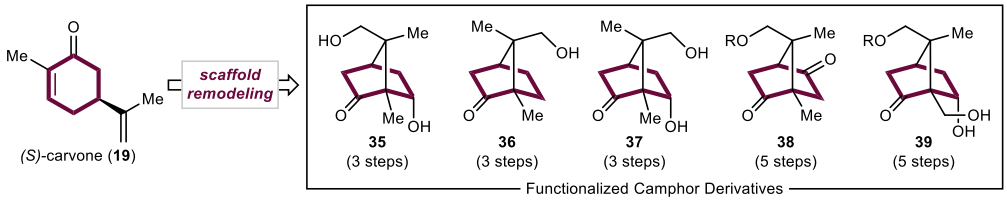

Fig. 5 | Camphor derivatives accessible by scaffold remodeling of (*S*)-carvone.

hydroxylated pinene derivative **20** (accessed from carvone), prior to the semipinacol rearrangement, ultimately affords functionalized camphor derivatives **38** and **39** (see the Supplementary Information). In this way, camphor derivatives bearing functionality at every unactivated, non-quaternary carbon can be prepared using scaffold remodeling tactics.

Discussion:

In summary, we leveraged a scaffold rearrangement strategy to efficiently access a topologically complex core structure of the longiborneol scaffold, 8-hydroxycamphor, which was used to complete a short total synthesis of longiborneol. A variety of late-stage C–H functionalization tactics were employed to complete syntheses of eight additional oxygenated congeners. While the strategy used here directly contrasts traditional strategic approaches (i.e., strategic bond analysis) that prompt construction of the longiborneol [2.2.1]bicycle toward the end of the synthesis, it nonetheless led to the shortest synthesis of longiborneol and set the stage for the preparation of myriad congeners. In total, we prepared longiborneol congeners featuring oxygenation at C3, C5, C11, C12, C14, and C15 using methods including allylic oxidation, undirected dioxirane C–H oxidation, oxysilane-directed C–H silylation, and oxime-directed C–H acetoxylation on the complex sesquiterpene skeleton. Analogous strategies should prove effective for the preparation of a variety of natural products (Fig. 2a) from functionalized camphor intermediates. While scaffold remodeling is a robust strategy for the production of such derivatives, we also continue to

investigate functionalizations of camphor itself, which would provide more direct access to these versatile starting materials for synthesis.

References:

1. Brill, Z. G.; Condakes, M. L.; Ting, C. P.; Maimone, T. J. Navigating the Chiral Pool in the Total Synthesis of Complex Terpene Natural Products. *Chem. Rev.* **117**, 11753–11795 (2017).
2. Corey, E. J.; Ohno, M.; Vatakencherry, P. A.; Mitra, R. B. TOTAL SYNTHESIS OF d,l-LONGIFOLENE. *J. Am. Chem. Soc.* **83**, 1251–1253 (1961).
3. Corey, E. J.; Ohno, Masaji.; Mitra, R. B.; Vatakencherry, P. A. Total Synthesis of Longifolene. *J. Am. Chem. Soc.* **86**, 478–485 (1964).
4. Corey, E. J.; Howe, W. J.; Orf, H. W.; Pensak, D. A.; Petersson, G. General Methods of Synthetic Analysis. Strategic Bond Disconnections for Bridged Polycyclic Structures. *J. Am. Chem. Soc.* **97**, 6116–6124 (1975).
5. Boger, D. L. XIII. Synthetic Analysis and Design, D. Total Synthesis Exemplified with Longifolene. In *Modern Organic Synthesis Lecture Notes*; Garbaccio, R. M.; TSRI Press: La Jolla, CA, 1999; pp 443–460.
6. Doering, N. A.; Sarpong, R.; Hoffmann, R. W. A Case for Bond-Network Analysis in the Synthesis of Bridged Polycyclic Complex Molecules: Hetidine and Hetisine Diterpenoid Alkaloids. *Angew. Chem., Int. Ed.* **59**, 10722–10731 (2020).
7. Marth, C. J.; Gallego, G. M.; Lee, J. C.; Lebold, T. P.; Kulyk, S.; Kou, K. G. M.; Qin, J.; Lilien, R.; Sarpong, R. Network-Analysis-Guided Synthesis of Weisaconitine D and Liljestrandinine. *Nature* **528**, 493–498 (2015).
8. Haider, M.; Sennari, G.; Eggert, A.; Sarpong, R. Total Synthesis of the Cephalotaxus Norditerpenoids (±)-Cephanolides A–D. *J. Am. Chem. Soc.* (2021).
9. Matsuo, A.; Nakayama, M.; Hayashi, S. Chemical Proof of Enantiomeric (−)-Longiborneol. *Chem. Lett.* **2**, 769–772 (1973).
10. Takasu, K.; Mizutani, S.; Noguchi, M.; Makita, K.; Ihara, M. Stereocontrolled Total Synthesis of (±)-Culmorin via the Intramolecular Double Michael Addition. *Org. Lett.* **1**, 391–394 (1999).
11. Takasu, K.; Mizutani, S.; Noguchi, M.; Makita, K.; Ihara, M. Total Synthesis of (±)-Culmorin and (±)-Longiborneol: An Efficient Construction of Tricyclo[6.3.0.03,9]Undecan-10-One by Intramolecular Double Michael Addition. *J. Org. Chem.* **65**, 4112–4119 (2000).
12. Kuo, D. L.; Money, T. An Enantiospecific Synthesis of Longiborneol and Longifolene. *J. Chem. Soc., Chem. Commun.* **0**, 1691–1692 (1986).
13. Kuo, D. L.; Money, T. Enantiospecific Synthesis of Longiborneol and Longifolene. *Can. J. Chem.* **66**, 1794–1804 (1988).
14. Masarwa, A.; Weber, M.; Sarpong, R. Selective C–C and C–H Bond Activation/Cleavage of Pinene Derivatives: Synthesis of Enantiopure Cyclohexenone Scaffolds and Mechanistic Insights. *J. Am. Chem. Soc.* **137**, 6327–6334 (2015).
15. Bahadoor, A.; Schneiderman, D.; Gemmill, L.; Bosnich, W.; Blackwell, B.; Melanson, J. E.; McRae, G.; Harris, L. J. Hydroxylation of Longiborneol by a Clm2-Encoded CYP450 Monooxygenase to Produce Culmorin in Fusarium Graminearum. *J. Nat. Prod.* **79**, 81–88 (2016).
16. Ashley, J. N.; Hobbs, B. C.; Raistrick, H. Studies in the Biochemistry of Micro-Organisms: The Crystalline Colouring Matters of Fusarium Culmorum (W. G. Smith) Sacc. and Related Forms. *Biochem. J.* **31**, 385–397 (1937).
17. Alam, M.; Jones, E. B. G.; Hossain, M. B.; van der Helm, D. Isolation and Structure of Isoculmorin from the Marine Fungus Kallichroma Tethys. *J. Nat. Prod.* **59**, 454–456 (1996).

18. Kasitu, G. C.; ApSimon, J. W.; Blackwell, B. A.; Fielder, D. A.; Greenhalgh, R.; Miller, J. D. Isolation and Characterization of Culmorin Derivatives Produced by Fusariumculmorum CMI 14764. *Can. J. Chem.* **70**, 1308–1316 (1992).

19. Qiu, Y.; Gao, S. Trends in Applying C–H Oxidation to the Total Synthesis of Natural Products. *Nat. Prod. Rep.* **33**, 562–581 (2016).

20. White, M. C.; Zhao, J. Aliphatic C–H Oxidations for Late-Stage Functionalization. *J. Am. Chem. Soc.* **140**, 13988–14009 (2018).

21. Ma, X.; Kucera, R.; Goethe, O. F.; Murphy, S. K.; Herzon, S. B. Directed C–H Bond Oxidation of (+)-Pleuromutilin. *J. Org. Chem.* **83**, 6843–6892 (2018).

22. Norseeda, K.; Gasser, V.; Sarpong, R. A Late-Stage Functionalization Approach to Derivatives of the Pyrano[3,2-a]Carbazole Natural Products. *J. Org. Chem.* **84**, 5965–5973 (2019).

23. Crossley, S. W. M.; Obradors, C.; Martinez, R. M.; Shenvi, R. A. Mn-, Fe-, and Co-Catalyzed Radical Hydrofunctionalizations of Olefins. *Chem. Rev.* **116**, 8912–9000 (2016).

24. Welch, S. C.; Walters, R. L. Total Syntheses of (+)-Longicamphor and (+)-Longiborneol. *Synth. Commun.* **3**, 419–423 (1973).

25. Welch, S. C.; Walters, R. L. Stereoselective Total Syntheses of (+-)-Longicyclene, (+-)-Longicamphor, and (+-)-Longiborneol. *J. Org. Chem.* **39**, 2665–2673 (1974).

26. Wittig, G.; Schöllkopf, U. Über Triphenyl-phosphin-methylene als olefinbildende Reagenzien (I. Mitteil. *Chem. Ber.* **87**, 1318–1330 (1954).

27. Bermejo, F. A.; Fernández Mateos, A.; Marcos Escribano, A.; Martín Lago, R.; Mateos Burón, L.; Rodríguez López, M.; Rubio González, R. Ti(III)-Promoted Cyclizations. Application to the Synthesis of (E)-Endo-Bergamoten-12-Oic Acids. Moth Oviposition Stimulants Isolated from Lycopersicon Hirsutum. *Tetrahedron* **62**, 8933–8942 (2006).

28. Song, Z.-L., Fan, C.-A. & Tu, Y.-Q. Semipinacol Rearrangement in Natural Product Synthesis. *Chem. Rev.* **111**, 7523–7556 (2011).

29. Ikan, R.; Markus, A.; Bergmann, E. D. The Synthesis of 22-Trans-Cholesta-5, 22, 25-Trien-3β OL. *Isr. J. Chem.* **9**, 259–261 (1971).

30. Huang, Q.; Suravarapu, S. R.; Renaud, P. A Giese Reaction for Electron-Rich Alkenes. *Chem. Sci.* Advance Article (2021). https://doi.org/10.1039/D0SC06341J

31. **Two examples with nucleophilic radicals, low yielding and limited to acetophenone derived acceptor:** Song, H.-J.; Lim, C. J.; Lee, S.; Kim, S. Tin-Free Radical Alkylation of Ketones ViaN-Silyloxy Enamines. *Chem. Commun.* **No. 27**, 2893–2895 (2006).

32. **Nucleophilic radical examples limited to acetophenone and pyruvic ester derived acceptors:** Lee, J. Y.; Lim, K.-C.; Meng, X.; Kim, S. Radical Alkylations of Alkyl Halides and Unactivated C-H Bonds Using Vinyl Triflates. *Synlett* **2010**, 1647–1650 (2010).

33. Roberts, B. P. Polarity-Reversal Catalysis of Hydrogen-Atom Abstraction Reactions: Concepts and Applications in Organic Chemistry. *Chem. Soc. Rev.* **28**, 25–35 (1999).

34. **Single example:** Crossley, S. W. M.; Barabé, F.; Shenvi, R. A. Simple, Chemoselective, Catalytic Olefin Isomerization. *J. Am. Chem. Soc.* **136**, 16788–16791 (2014).

35. **Limited to benzyl acceptors:** Fu, M.-C.; Shang, R.; Zhao, B.; Wang, B.; Fu, Y. Photocatalytic Decarboxylative Alkylations Mediated by Triphenylphosphine and Sodium Iodide. *Science* **363**, 1429–1434 (2019).

36. Lo, J. C.; Gui, J.; Yabe, Y.; Pan, C.-M.; Baran, P. S. Functionalized Olefin Cross-Coupling to Construct Carbon–Carbon Bonds. *Nature* **516**, 343–348 (2014).

37. Ishikawa, H.; Colby, D. A.; Seto, S.; Va, P.; Tam, A.; Kakei, H.; Rayl, T. J.; Hwang, I.; Boger, D. L. Total Synthesis of Vinblastine, Vincristine, Related Natural Products, and Key Structural Analogues. *J. Am. Chem. Soc.* **131**, 4904–4916 (2009).

38. Leggans, E. K., Barker, T. J., Duncan, K. K., Boger, D. L. Iron(III)/NaBH4-Mediated Additions to Unactivated Alkenes: Synthesis of Novel 20′-Vinblastine Analogues. *Org. Lett.* **14**, 1428–1431 (2012).
39. Lo, J. C., Yabe, Y. & Baran, P. S. A Practical and Catalytic Reductive Olefin Coupling. *J. Am. Chem. Soc.* **136**, 1304–1307 (2014).
40. Isayama, S.; Mukaiyama, T. A New Method for Preparation of Alcohols from Olefins with Molecular Oxygen and Phenylsilane by the Use of Bis(Acetylacetonato)Cobalt(II). *Chem. Lett.* **18**, 1071–1074 (1989).
41. Concepción, J. I.; Francisco, C. G.; Hernández, R.; Salazar, J. A.; Suárez, E. Intramolecular Hydrogen Abstraction. Iodosobenzene Diacetate, an Efficient and Convenient Reagent for Alkoxy Radical Generation. *Tetrahedron Lett.* **25**, 1953–1956 (1984).
42. Nakazaki, M. & Naemura, K. Photolyses of Isobornyl and Bornyl Nitrites. *Bull. Chem. Soc. Jpn.* **37**, 532–535 (1964).
43. Renata, H.; Zhou, Q.; Baran, P. S. Strategic Redox Relay Enables A Scalable Synthesis of Ouabagenin, A Bioactive Cardenolide. *Science* **339**, 59–63 (2013).
44. Berger, M.; Knittl-Frank, C.; Bauer, S.; Winter, G.; Maulide, N. Application of Relay C−H Oxidation Logic to Polyhydroxylated Oleanane Triterpenoids. *Chem* **6**, 1183–1189 (2020).
45. Desai, L. V.; Hull, K. L.; Sanford, M. S. Palladium-Catalyzed Oxygenation of Unactivated Sp3 C−H Bonds. *J. Am. Chem. Soc.* **126**, 9542–9543 (2004).
46. Neufeldt, S. R.; Sanford, M. S. O-Acetyl Oximes as Transformable Directing Groups for Pd-Catalyzed C−H Bond Functionalization. *Org. Lett.* **12**, 532–535 (2010).
47. Caglioti, L.; Magi, M. The Reaction of Tosylhydrazones with Lithium Aluminium Hydride. *Tetrahedron* **19**, 1127–1131 (1963).
48. Simmons, E. M.; Hartwig, J. F. Catalytic Functionalization of Unactivated Primary C–H Bonds Directed by an Alcohol. *Nature* **483**, 70–73 (2012).
49. Li, B.; Driess, M.; Hartwig, J. F. Iridium-Catalyzed Regioselective Silylation of Secondary Alkyl C–H Bonds for the Synthesis of 1,3-Diols. *J. Am. Chem. Soc.* **136**, 6586–6589 (2014).
50. Tamao, K.; Ishida, N.; Kumada, M. (Diisopropoxymethylsilyl)Methyl Grignard Reagent: A New, Practically Useful Nucleophilic Hydroxymethylating Agent. *J. Org. Chem.* **48**, 2120–2122 (1983).
51. Fleming, I.; Henning, R.; Plaut, H. The Phenyldimethylsilyl Group as a Masked Form of the Hydroxy Group. *J. Chem. Soc., Chem. Commun.* **No. 1**, 29–31 (1984).
52. Chen, M. S.; White, M. C. A Predictably Selective Aliphatic C–H Oxidation Reaction for Complex Molecule Synthesis. *Science* **318**, 783–787 (2007).
53. Curci, R.; D'Accolti, L.; Fusco, C. A Novel Approach to the Efficient Oxygenation of Hydrocarbons under Mild Conditions. Superior Oxo Transfer Selectivity Using Dioxiranes. *Acc. Chem. Res.* **39**, 1–9 (2006).

Acknowledgements:

We are grateful to the National Institutes of Health (NIGMS MIRA R35 GM130345) for grant support as well as the Molecular Scaffold Design Collective (MSDC; Agreement No. HR00111890024) of the Defense Advanced Research Projects Agency (DARPA) for partial support of this work.

R.F.L. is grateful for fellowship support from the NSF GRFP (DGE 1752814).

G.S. thanks the Uehara Memorial Foundation for a postdoctoral fellowship.

We thank Dr. Hasan Celik and UC Berkeley's NMR facility in the College of Chemistry (CoC-NMR) for spectroscopic assistance. Instruments in the CoC-NMR are supported in part by NIH S10OD024998.

We thank Dr. Nicholas Settineri (UC Berkeley) for single-crystal X-ray diffraction studies.

Contributions:

The overall design for this project was conceptualized by G.S. with input from R.F.L. and R.S. R.F.L. and G.S. conducted the chemical reactions. G.S. and R. F. L. developed the synthesis of **15** and **3** and G.S. optimized the route. Syntheses of **5** and **10**–**14** were achieved by R.F.L. who also designed the C–H functionalization sequence with input from G.S. and R.S. Rearrangement of **3** to **1** as well as preparation of **38** and **39** were discovered by G.S. The manuscript was written and edited jointly by R.F.L., G.S. and R.S.