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Skeletal diversification by C—C cleavage to access bicyclic frameworks from a common tricyclooctane intermediate†

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Abstract

Herein, the diversification of tricyclo[3.2.1.$0^{3,6}$]octane scaffolds to afford diverse bicyclic scaffolds is described. The strained tricyclooctanes are prepared in two steps featuring a blue light-mediated [2+2] cycloaddition. Strategies for the cleavage of this scaffold were then explored resulting in the selective syntheses of the bicyclo[3.1.1]heptane, bicyclo[3.2.1]octane, and bicyclo[3.2.0]heptane cores. These findings may guide future studies of C—C cleavage reactions in strained carbon frameworks and their application in complex molecule synthesis.

The structural complexity of natural products has long served as an inspiration for synthetic chemists to devise strategies and methodologies for their preparation.[1-3] Their three-dimensional topologies have also expanded the chemical space for drug and agrochemical discovery.[4-7] Our laboratory has been broadly interested in exploiting C—C cleavage reactions to forge new C—sp^3 bonds.[8-10] While not immediately obvious, the use of compounds containing more C—C bonds than a desired target compound can be greatly simplifying in synthesis—especially if the additional bonds are easily introduced en route to the target structure.[11] Cyclopropanation and [2+2] cycloaddition reactions have been a particularly effective means to arrive at intermediates of this type as these reactions can form sterically congested C—C bonds that are also highly strained and reactive.[12-15]

Strategies to accomplish manifold C—C cleavage reactions from a single substrate to access diverse targets remain underexplored.[16-19] Through selective cleavage of different bonds in a single polycyclic scaffold, a variety of substructures bearing unique topology can be accessed. While our group has explored this approach for structural diversification in the remodeling of bicyclic cyclobutanols derived from carvone,[20-27] these developments have been inherently limited. Here, we describe C—C cleavage tactics to access new chemical space using topologically complex—yet simple to synthesize—molecules that feature a cyclobutane.

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Conflicts of interest

There are no conflicts to declare.

During the course of a total synthesis, we recognized that the strained [3.2.1.$0^{3,6}$] tricycle **1**, an intermediate in our synthesis, contained distinct bicycles that corresponded to substructures of various natural products (Scheme 1). Through fragmentation of the [3.2.1.$0^{3,6}$] tricyclic skeleton, bicyclo[3.2.1]octane and bicyclo[2.2.1]heptane cores could be readily accessed through cleavage of the cyclobutane. Alternatively, bicyclo[3.1.1]- and [3.2.0]heptane scaffolds could be obtained through cleavage of other, less strained, bonds (*i.e.*, C1—C2, C1—C7 Scheme 1). As all the target bicycles are well-represented in natural product structures,[28-31] variations in C—C bond cleavage using **1** could unlock a unified strategy to these molecules.

Consistent with the extensive literature on strained ring opening reactions,[5] we reasoned that incipient charge (either positive or negative), or open shell intermediates would destabilize beta-disposed C—C bonds (Scheme 2). Introducing charge at specific positions would reduce the number of possible fragmentations in a pairwise fashion (see **2**–**5**, Scheme 2a). Selective C—C cleavage could therefore be achieved by manipulating the functional groups in **1** (Scheme 2b). For example, formation of alkoxide **6** could lead to selective fragmentation of the C1—C7 bond through a retro-aldol cleavage to give enolate **7**. Alternatively, formation of a carbon-centered radical at C7 (see **8**) could lead to the selective cleavage of the C3—C6 bond. We hypothesized that formation of more stabilized radical **9** would be reflected in the selectivity-determining transition state. Furthermore, the C1—C2 bond could be targeted through formation of alkoxy radical **10**, which could undergo β-scission to form stable tertiary radical **11**. Finally, ionization to carbocation **12** could fragment the strained cyclobutane C3—C4 bond to give tertiary carbocation **13** following rearrangement. To test these envisioned fragmentations, we commenced with the preparation of tricycle **1**.

Tricycles of the general structure **1** were readily prepared through the [2+2] cycloaddition of enediones related to **14** (Scheme 2c). In our initial design, we sought to avoid issues of diastereoselectivity[32,33] by using achiral, symmetric enediones. The syntheses began with prenylation[34] of commercially available 2-methyl-1,3-cyclopentanedione (**15**), followed by desaturation with phenyltrimethylammonium tribromide to give **16** in 50% yield over 2 steps on multigram scale.

The key [2+2] photocycloaddition to give **17** was then investigated (see ESI† for full optimization). Irradiating **16** using 254, 310, and 350 nm light resulted in no reaction, however irradiation at 420 nm in DCM gave **17** in >95% yield. The photocycloaddition is tolerant of both air and moisture and proceeds best in aprotic solvents and notably does not require the use of a triplet sensitizer. Interestingly, the UV-vis spectrum of **16** shows strong absorption at the unreactive wavelengths of 254 nm and 310 nm, but a smaller trailing absorbance tail at 400–470 nm (visible at relatively high concentrations).[35,36] The photocycloaddition reaction performed faithfully on larger scale, with similar efficiencies observed on gram-scale, though the reaction time had to be extended significantly. Prolonged exposure to blue LED irradiation did lead to product decomposition. As such,

†Electronic supplementary information (ESI) available. CCDC 2234155 and 2234156. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d3cc00945a

careful monitoring of conversion and exposure window is crucial to success (see the ESI† for details).

With ready access to sufficient quantities of key tricycle **17**, we commenced our studies on its fragmentation. A benefit of the "reagentless" cycloaddition is that no purification or work-up procedure is necessary. We first studied anionic opening reactions (Scheme 3). Addition of TMSI, which first silylates the C7 carbonyl group to activate it toward iodide addition (see **18**), led to the selective fragmentation of the C1—C7 bond and following hydrolysis gave [3.1.1]-bicyclic acid **20** in 78% yield over the two steps.[37] Overall, functionalized [3.1.1] bicycle **20**, reminiscent of the pinane scaffold, is accessed in 4 steps (3 purifications) from commercially available material. Engaging the carboxy group of **20** in decarboxylative cross coupling reactions[38] could provide access to a wide range of unnatural "pinene-like" compounds possessing unique 3D-topology and vectors for drug discovery.

Next, we investigated the synthesis of the bicyclo[3.2.1]octane core from **17**. One-step cleavage methods (for example, ketyl radical fragmentation[39]) were unsuccessful. We then sought to form a cation or radical at C7 of **17**. Reduction of the less-hindered C7 carbonyl group using 1 equivalent of DIBAL at −78 °C yielded the corresponding alcohol in 58% as a single diastereomer. Ionization of this hydroxy group with strong acid or activating groups proved challenging, so we then explored methods for forming a radical at C7. Mesylation and displacement with sodium iodide yielded keto-iodide **21** in 43% yield over 3 steps as a single diastereomer. Radical dehalogenation reactions (AIBN, Bu_3SnH, TTMSS, photoredox, *etc.*) of **21** gave nonselective mixtures of C—C bond cleavage and dehalogenation products. Notably, dehalogenation indicated that the putative C7 radical was persistent enough to participate in a bimolecular H-atom abstraction and the competing C—C bond cleavage was unselective. Remarkably, conditions adapted from the pioneering work of Gevorgyan and coworkers for palladium (I)-mediated visible-light catalysis[40] resulted in selective cleavage of the C5—C6 bond to give diene **24**. Oxidative additions of this type are proposed to proceed through radical intermediates (**22**) and subsequent capture by Pd(I) (see **23**). Sequential β-carbon and β-hydride eliminations of **23** would then afford **24**. Notably, prior studies have shown that cyclopropenyl iodides undergo radical ring opening under these Pd(I) conditions, which contrasts with our system where the product distribution is different from that observed in the free-radical reaction.[41] Diene **24** decomposes upon prolonged exposure to blue LED and at elevated temperatures (>35 °C) potentially due to di-pi methane type rearrangements of the skipped diene. Despite these complications, [3.2.1] bicycle **24** could be isolated in 26% yield over 4 steps from **17**.

We also explored fragmentations of the southern portion of tricycle **17**. Tricycle **17** was reduced with two equivalents of DIBAL at to give diol **25** (confirmed unambiguously by X-ray crystallographic analysis).‡ Protection of the less-hindered northern hydroxy group proceeded selectively to give silyl ether **26** in 75% yield. Using mono-protected diol **26**, we explored the selective formation of an alkoxy radical from the C2 alcohol group,

‡Deposition number 2234155 (for **25**), and 2234156 (for **33**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Center.

which could undergo beta-scission to yield desired [3.2.0] bicycle **28**. Use of an iridium photocatalyst and phosphonate base presumably effected the selective activation of the O—H bond through proton coupled electron transfer (PCET)[42] to form the corresponding alkoxy radical (**27**) which underwent the β-scission to generate the tertiary alkyl radical followed by trapping with TRIP-thiol to give [3.2.0] bicyclic aldehyde. However, the resulting aldehyde group was found to be unstable during isolation and so one-pot reduction with $NaBH_4$ was undertaken. The overall sequence gave **28** in 53% yield from **26**.

At this stage, we investigated paired reactivity for C—C cleavage on the southern portion of **17**. It was hypothesized that cyclobutyl carbinyl rearrangement of a carbocation or radical at C2 would selectively cleave the more strained C3—C4 bond to form the most stable carbocation or radical. Unfortunately, all the methods for the generation of a radical at C2 (*via* the xanthate, halide, *etc.*) led mostly to decomposition, along with trace cleavage of the undesired C3—C6 bond. We also prepared pivalate **29** in anticipation of ionization of the C2 hydroxy group under strong acid; the TBS ether of **26** hydrolyzed under these reactions. We observed full conversion of **29** to amide **31** upon subjection to H_2SO_4 in MeCN at elevated temperatures. Presumably, in this case, a Ritter reaction results from desired carbocation **30**, which remains resistant to the desired fragmentation.[43] Fragmentation of **17** to afford norbornene derivatives such as **32** remain the subject of ongoing studies.

Finally, we have also explored the formation of other cycloadducts (Scheme 4). Bromo-enedione **33** (a side product of the oxidation to form **16** at higher temperature) underwent [2+2] cycloaddition under the same conditions in excellent yield to give a 1.3 :1 mixture of constitutional isomers **34** and **35**. Monosubstitution was also tolerated as allyl enedione **36** underwent cycloaddition to give tricycle **37**. The cycloaddition was found to be highly diastereoselective as phenyl substituted alkene **38** underwent cycloaddition to give adduct **39** as a single diastereomer. Bisprenyl enedione **40** also underwent [2+2] cycloaddition to give tricycle **41**, albeit at low temperature as the cycloadduct decomposed under blue LED exposure at room temperature. Tricycle **41** bears the carbocyclic core characteristic of the polyprenylated acylphloroglucinol natural product melicolone A (**42**) with an extra C—C bond that could be leveraged to construct the key oxabicycle in this compound.

In summary, we have achieved a blue-light mediated photocycloaddition of enediones to yield functionalized [$3.2.1.0^{3,6}$] tricyclooctanes. Recognizing that four distinct bicycles prevalent in natural products are embedded within this tricyclic framework, we have undertaken fragmentation reactions to access these bicycles. A readily accessible tricyclooctane (**17**) was deconstructed into several of these bicycles in a divergent and selective fashion. Some key reactions that led to selective C—C bond cleavage include visible-light palladium catalysis and PCET for the mild generation of radical intermediates. The studies reported here lay the groundwork for future studies in natural product synthesis wherein this privileged tricycle may be leveraged to achieve rapid diversification en route to different carbon skeletons. The strategic framework of divergent C—C cleavage by relying on the recognition of pairwise charge relationships at the basis of this work should aid the application of these reactions in synthesis planning.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

I B. conceived the project with guidance from R. S. I. B. conducted the substrate synthesis and fragmentation studies. J. C. T. synthesized additional cycloaddition substrates. I. B. and R. S. wrote the manuscript. R. S. is grateful to the US National Institutes of General Medical Sciences (NIGMS) for funding (R35 GM130345). The authors acknowledge 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 H. Bergman and Professor D. Tilley (UC Berkeley) for assistance with collecting UV-Vis absorbance data. The authors thank Gian Reber for experimental assistance. The authors thank N. Settineri (University of California, Berkeley) for single-crystal X-ray diffraction studies.

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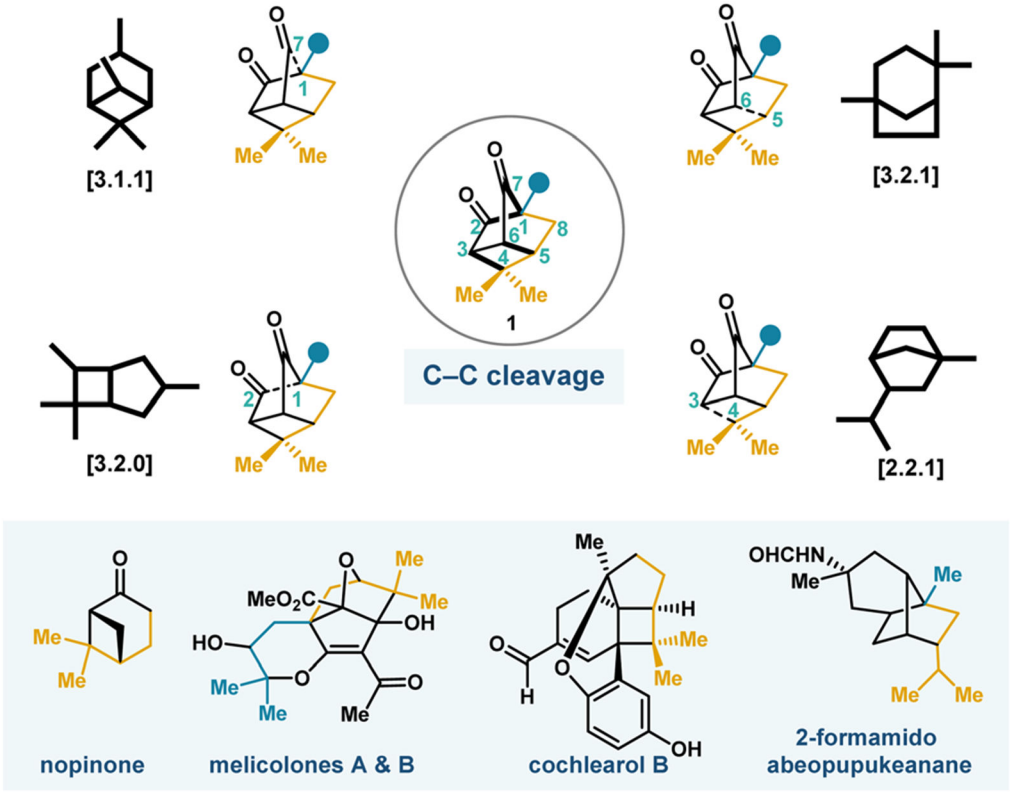
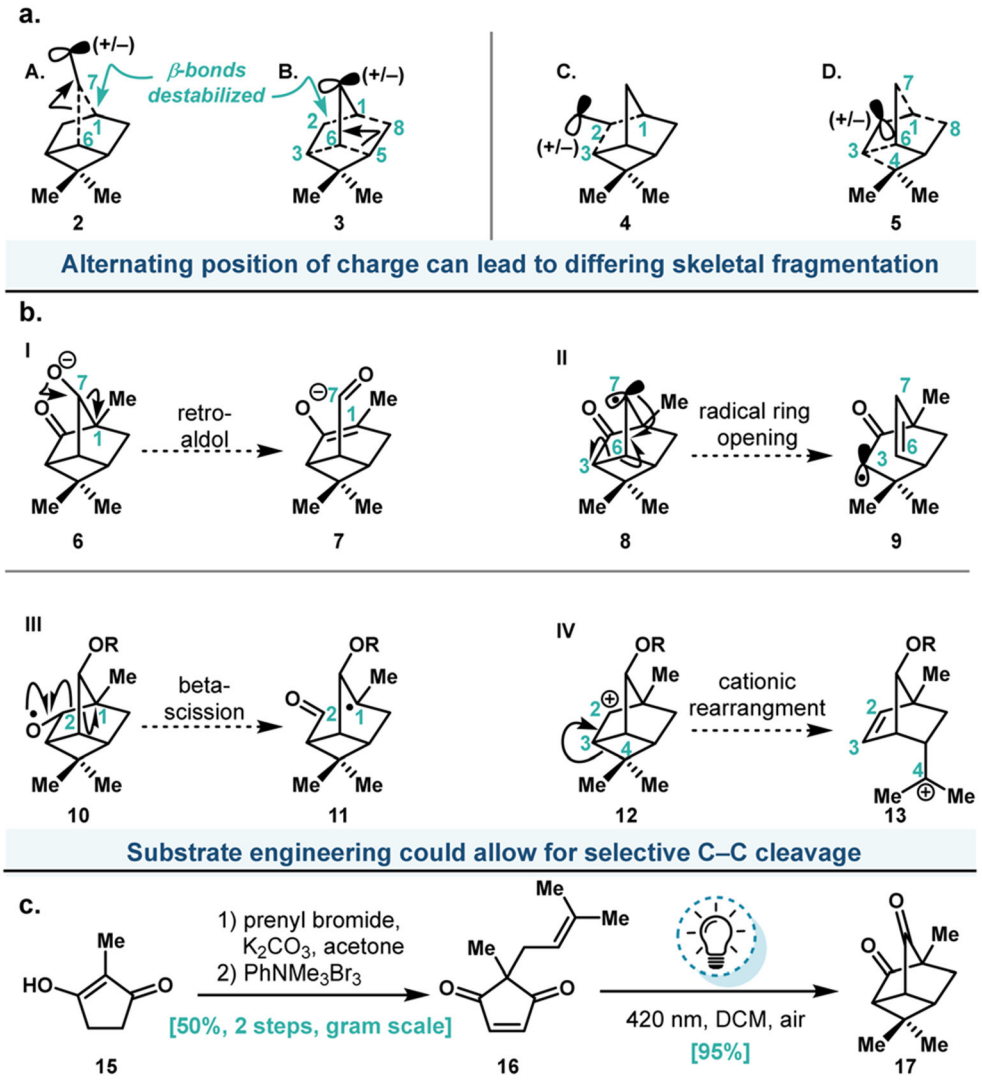


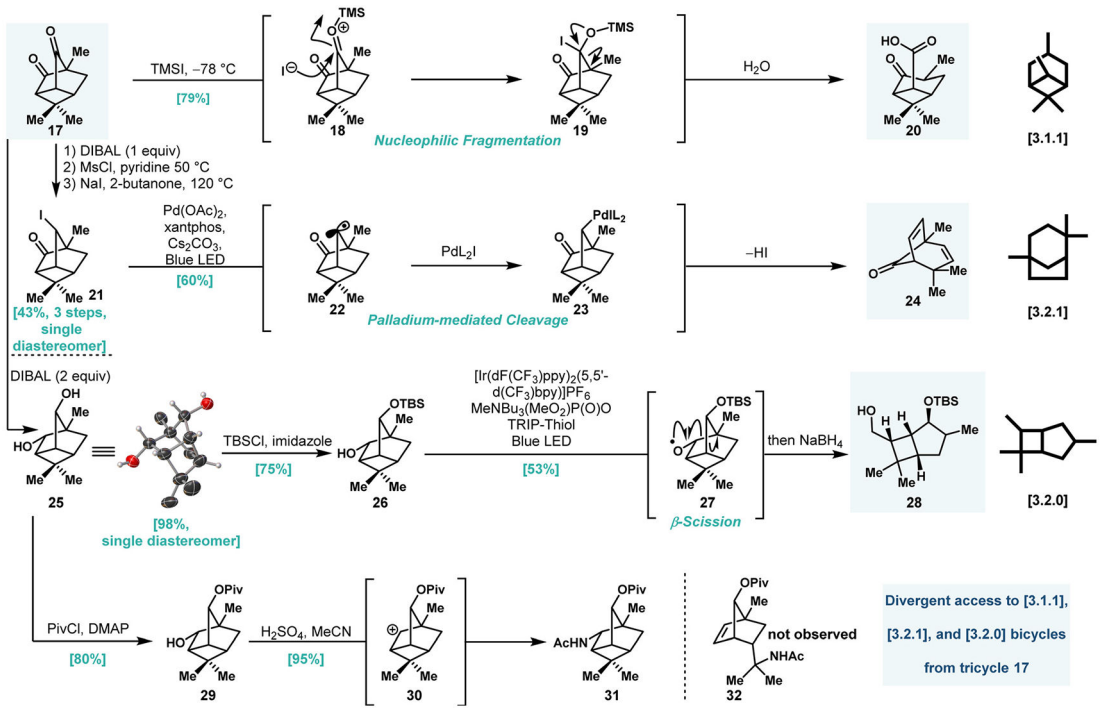
Scheme 1.

Numerous bicyclic terpene-like scaffolds are embedded in the tricyclic [3.2.1.$0^{3,6}$] core. Cleavage of select bonds would lead to the [3.2.1] bicyclooctane, [2.2.1] bicyclooctane, [3.2.0] bicycloheptane, and [3.1.1] bicycloheptane skeletons.



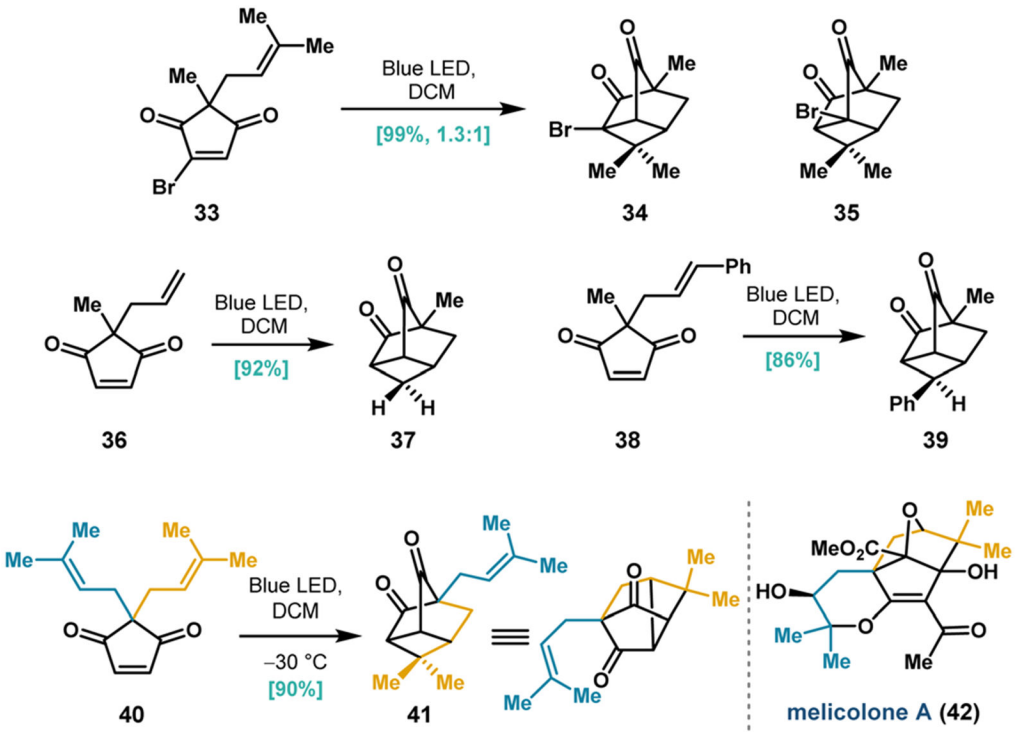
Scheme 2.

(a) Relationship between developing charge or radical and fragmentation. (b) Strategies for gaining selectivity in C—C bond cleavage. (c) tricyclooctane synthesis.



Scheme 3.

Syntheses of the embedded [3.1.1], [3.2.1], and [3.2.0] bicyclic frameworks through divergent skeletal fragmentation.



Scheme 4.
Synthesis of additional tricyclooctane substrates.