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A Radical-Polar Crossover Annulation To Access Terpenoid Motifs

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Abstract

A new catalytic radical-polar crossover annulation between two unsaturated carbonyl compounds is described. The annulation proceeds under exceptionally mild conditions and provides direct and expedient access to complex terpenoid motifs. Application of this chemistry allows for synthesis of forskolin, a densely functionalized terpenoid, in 14 steps from commercially available material.

Annulations allow for rapid increase in structural complexity and have found broad application in organic synthesis. Of particular note are transformations involving fusion of new rings via two new carbon–carbon bonds, which can dramatically simplify construction of polycarbocyclic motifs present in terpenoid and polyketide natural products.[1] Among those, Diels–Alder cycloadditions have demonstrated exceptional flexibility with respect to the accessible connectivity patterns and feature prominently in many successful syntheses.[2] A requirement for the acyclic 1,3-diene to adopt the s-*cis* conformation often imposes limitations on the presence of substituents at the terminal positions, and formation of quaternary carbons originating from the diene component is challenging in bimolecular settings.[3,4] Here we demonstrate a new annulation between two unsaturated carbonyl components that allows for construction of saturated six-membered carbocycles and is particularly well-suited for installation of fully substituted carbons (Figure 1). Development of this transformation builds on our previous efforts in the synthesis of paxilline indoloterpenoids, where a hydrogen atom transfer (HAT)-initiated radical-polar crossover polycyclization allowed for rapid assembly of the shared tricyclic scaffold and selective installation of vicinal quaternary centers.[5] The new HAT-initiated radical-polar crossover annulation proceeds under exceptionally mild conditions and provides direct and expedient access to complex terpenoid motifs, including those related to labdane and scalarane families of natural products.[6–8] We also show that application of this chemistry allows for a

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Supporting Information

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Experimental procedures and characterization data for all new compounds (PDF)

Data for $C_{16}H_{22}O_3$ (CIF)

Data for $C_{27}H_{46}Cl_2O_4$ (CIF)

Data for $C_{21}H_{32}O_6$ (CIF)

The authors declare no competing financial interest.

14-step synthesis of forskolin (**1**), a densely functionalized labdane diterpenoid, from commercially available material.

We began our studies with the annulation of γ,δ-unsaturated aldehyde **2** and methacrolein (**3**, Table 1). After considerable optimization the desired cyclohexanol **4** could be obtained in a highly diastereoselective manner and moderate levels of efficiency. This transformation likely involves HAT to the electron-rich 1,1-disubstituted alkene followed by the conjugate addition of the resulting *tert*-alkyl radical to the enal, reduction to the corresponding enolate, and subsequent aldol reaction with the pendant aliphatic aldehyde functionality.[6,9–11] Our investigations revealed that slow addition of a mixture of **3** and silane to an excess of **2** was beneficial to allow for selective engagement of the γ,δ-unsaturated carbonyl component in the HAT event and attenuation of the competing reductive aldol pathway.[8] Notably, presence of the α-substituent in **3** was required for complete propagation of the HAT-initiated cascade and only traces of the expected cyclized product were observed in the case of acrolein. Other α-substituted acroleins performed similarly to methacrolein (**3**) and cyclohexanols **5** and **6** were obtained in a highly diastereoselective manner.[12] 2-Methyl-2-cyclopentenone also participated in the annulation with good levels of disaster-eocontrol, and hexahydroindanone derivative **7** could be isolated in a synthetically useful yield.[13] At the same time, application of isopropenyl methyl ketone resulted in a nearly stoichiometric mixture of diastereomeric aldol products **8** and **9**, presumably due to unselective formation of *E* and *Z* isomers of the intermediate iron enolate. Remarkably, γ,δ-unsaturated ketones were also found to be suitable annulation partners, and products **10** and **11** were formed with high diastereoselectivity after derivatization of the intermediate hydroxyaldehydes, which proved necessary to prevent retro-aldol reactions during the chromatographic purification. Other modifications of the γ,δ-unsaturated component were tolerated and allowed for diastereoselective formation of decalin **12** and perhydrophe-nanthrene **13**, which contains the functionalized tricyclic motif found in several scalarane terpenoids.[14]

We next set out to test the applicability of our annulation in the synthesis of terpenoids and chose forskolin (**1**, see Figure 1) as our primary target.[15] This densely functionalized diterpene exhibits allosteric stimulation of adenylyl cyclases and a derivative is currently approved for acute heart failure treatment in Japan.[16,17] Since its discovery, forskolin has been a subject of frequent inquiry by organic chemists, which culminated in several successful syntheses that expanded our understanding of the chemistry of highly oxidized labdane motifs.[18] We envisioned that the radical-polar crossover annulation would allow for construction of the C4–C5 and C1–C10 bonds of the decalin fragment. Thus, subjection of enone **14** and aldehyde **2** to our optimized conditions resulted in efficient formation of the desired polycyclic motif, albeit with low diastereoselectivity at C1 and only slight preference for desired product **16** (Scheme 1). Nevertheless, the annulation was readily scalable and allowed for production of multigram quantities of alcohol 16. Furthermore, diastereomer **15** could be converted to alcohol **16** via consecutive oxidation and reduction events in 87% yield over two steps.[19] Facile epimerization at C1 to the undesired configuration necessitated protection, which was followed by a retro-Diels–Alder reaction to reveal the enedione motif. This sequence secured access to intermediate **17** in four steps from 2,6-dimethylbenzoquinone and was rendered asymmetric by taking advantage of

oxazaborolidine catalysis in the preparation of Diels–Alder adduct **14** in 96% ee.[19,20] Notably, previous investigations employed a circuitous cycloaddition-based route that necessitated multiple functional group manipulations to obtain racemic silyl ether **17** in eight steps from commercially available material.[21]

Regio- and stereoselective addition of the lithio derivative of alkyne **18** to racemic enedione **17** followed by epimerization at C5 afforded *trans*-octalin **19** (Scheme 2).[22] Subsequent reduction of the remaining keto group and epoxidation of the alkene allowed for a highly diastereoselective production of diol **20**. We discovered that the epoxidation pathway was competing with oxidation of the secondary allylic alcohol to enone **19**, and application of tetrahydrofuran-based solvent mixtures was necessary for attenuation of this undesired pathway.[23] Intramolecular displacement of the epoxide with in situ generated monoalkylcarbonate required deprotection of the hydroxy group at C1, which proceeded under the reaction conditions and could be accelerated in the presence of cesium fluoride.[24,25] Addition of carbonyldiimidazole to the reaction solution led to formation of a mixture of cyclic carbonates **21** and **22**. Acid-catalyzed cyclization of a mixture of protected ynones **21** and **22** resulted in efficient formation of the desired dihydropyranone motif, and treatment with base resulted in hydrolysis of the carbonate moieties. Selective protection of the resulting tetraol delivered acetonide **23**, and the structure was confirmed by X-ray crystallographic studies. We found this switch of protecting groups to be necessary for achieving the desired facial selectivity during the installation of stereocenter at C13. Thus, conjugate addition to acetonide **23** delivered desired tetrahydropyranone **24** with good diastereoselectivity, while application of the corresponding dicarbonate led exclusively to the undesired configuration at C13. Acetonide **24** was readily deprotected and the penultimate tetraol could be isolated as a single diastereomer.[25] Acetylation of 7-deacetylforskolin under previously described conditions delivered the target natural product, completing the synthesis in 14 steps from commercially available starting material.[25,26]

In summary, we disclose a new radical-polar crossover annulation that allows for direct and diastereoselective construction of cyclic aldol motifs. In contrast to the venerable Diels–Alder reaction, this transformation is well suited for bimolecular assembly of multiple quaternary centers, offering a complementary approach to the synthesis of six-membered carbocycles. We also demonstrate application of this chemistry to the synthesis of forskolin that allows for rapid assembly of this highly oxidized labdane diterpenoid and is readily amenable to efficient asymmetric induction. We anticipate that the radical-polar crossover annulation will be valuable in the synthesis of other functionalized terpenoids and will simplify production of natural and unnatural congeners for biological studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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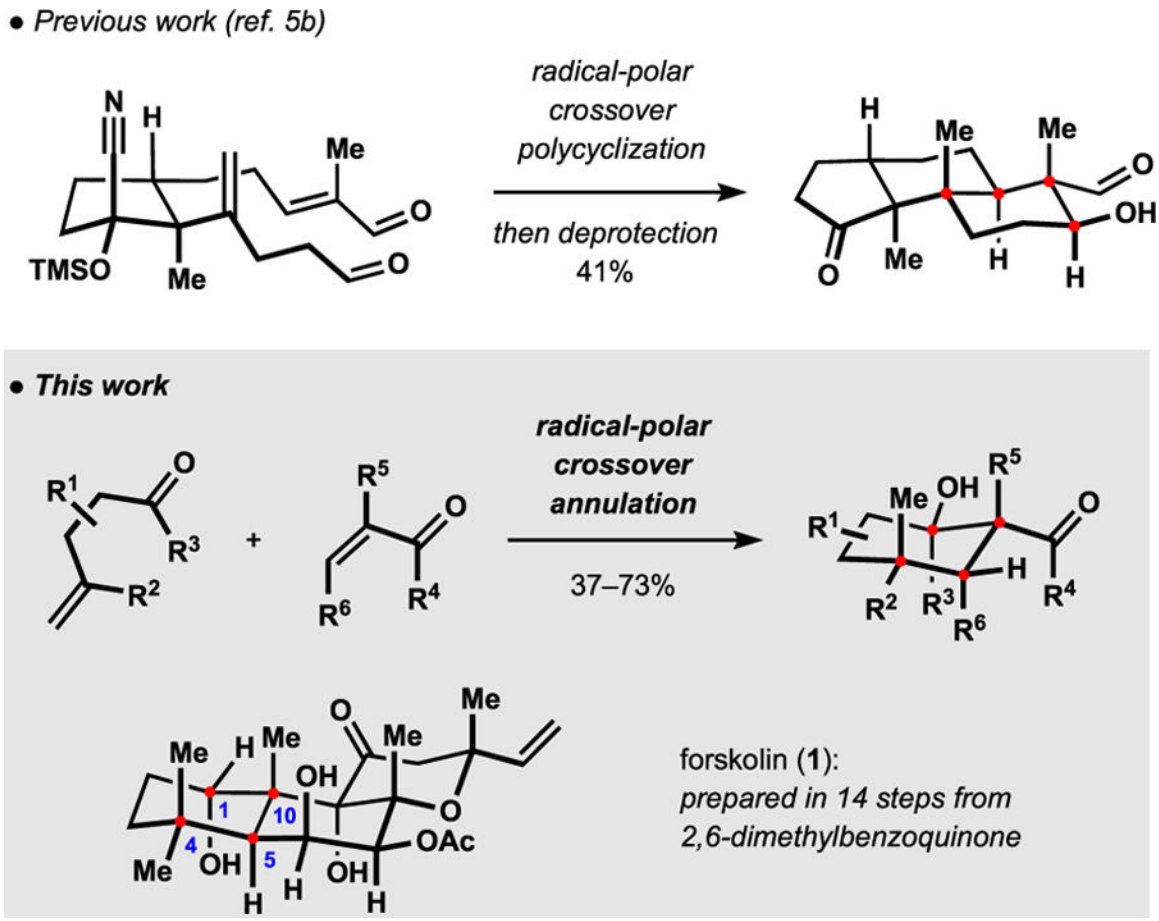
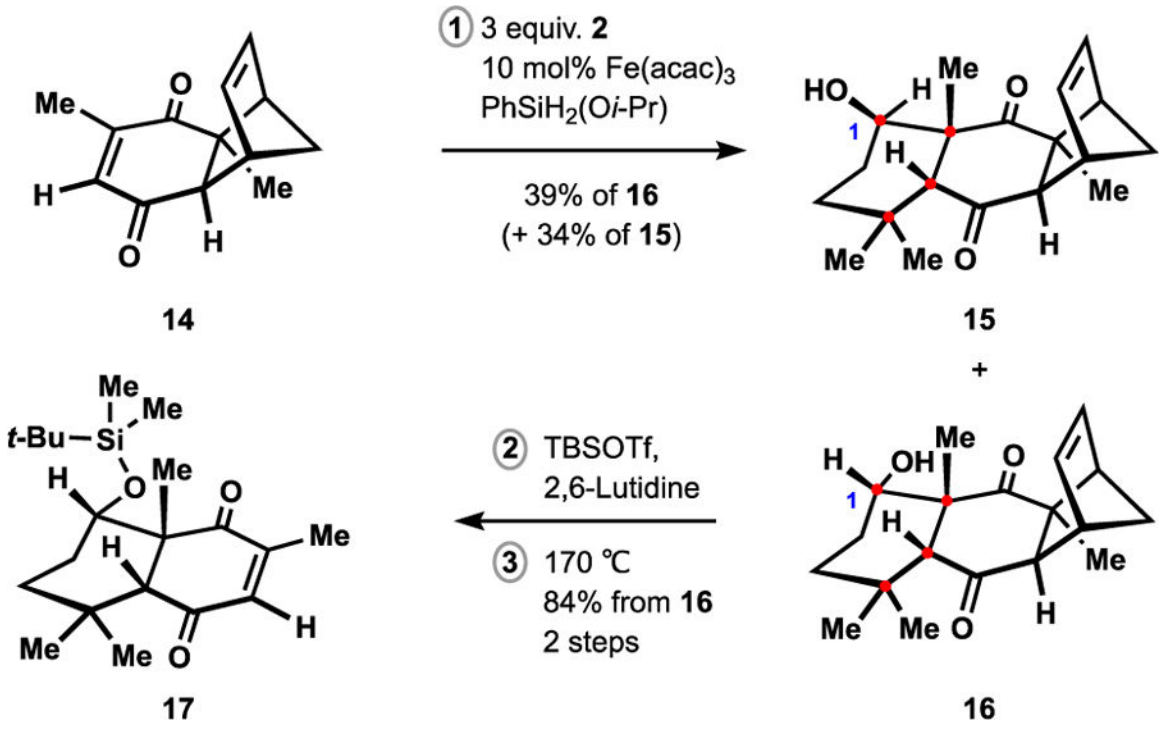
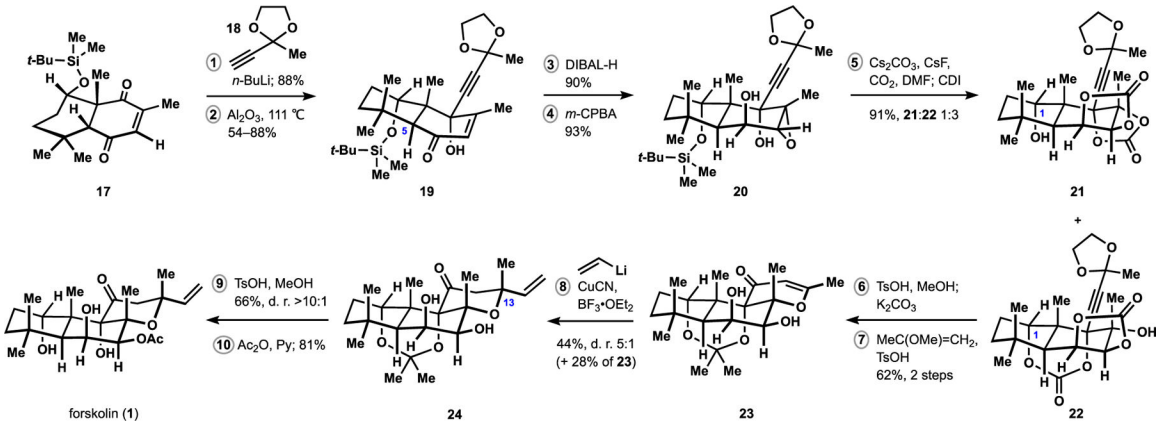


Figure 1.
Radical-polar crossover annulation allows for rapid assembly of complex terpenoid motifs.



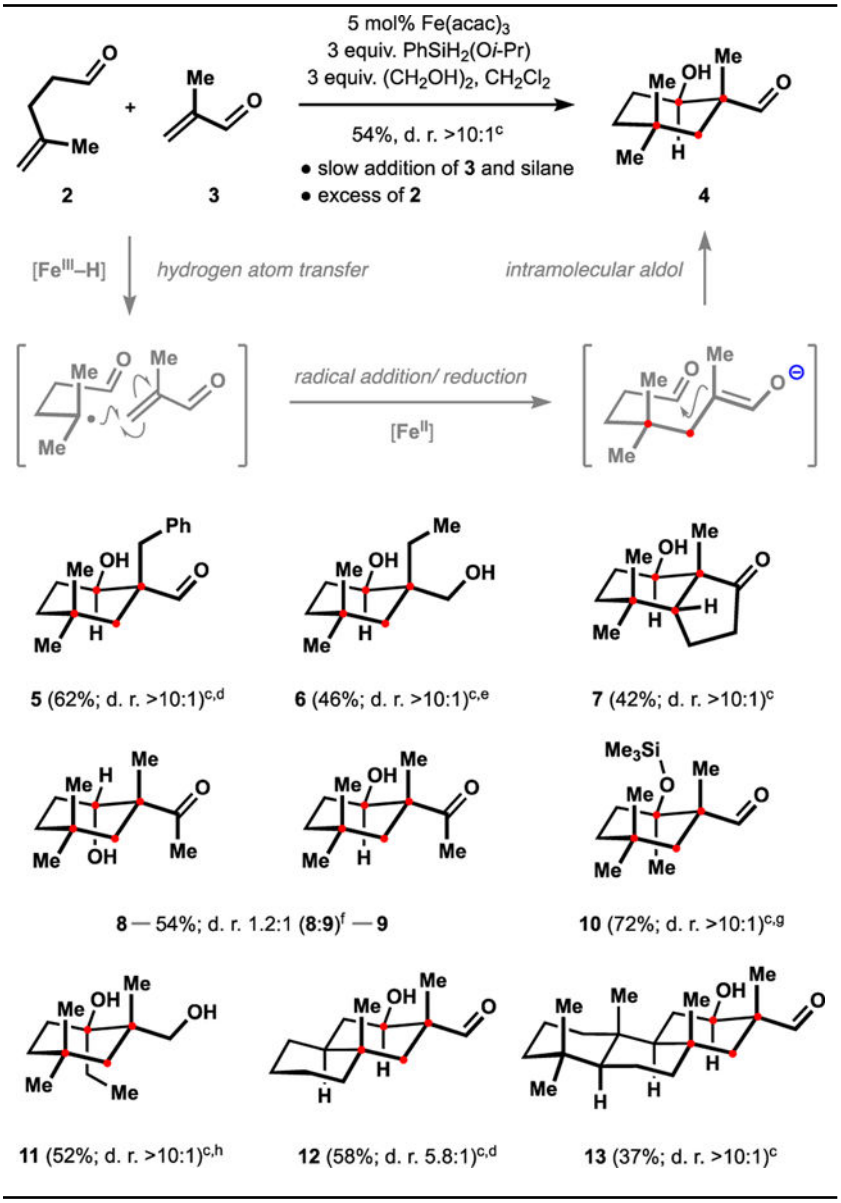
Scheme 1.
Annulation en Route to Forskolin (1)



Scheme 2.
Synthesis of (±)-Forskolin (1)

Table 1.

Radical-Polar Crossover Annulation of α,β- and γ,δ-Unsaturated Carbonyl Compounds[a,b]



[a]Typical reaction conditions: 2–3 equiv. γ,δ-unsaturated carbonyl compound, 5–50 mol % $Fe(acac)_3$, 1.5–3 equiv. $PhSiH_2(O\textit{i}\text{-Pr})$, 1–3 equiv. $(CH_2OH)_2$, 0.2 M in CH_2Cl_2; see SI for details.

[b]Diastereomeric ratios were determined by ^1H nuclear magnetic resonance analysis of crude product mixtures.

[c]Yields are reported for the depicted analytically pure isomers.

[d]Structure was confirmed by X-ray crystallographic analysis; see SI for details.

[e]After reduction and recrystallization; see SI for details.

[f] Isolated and characterized as a mixture of isomers.

[g] After silylation; see SI for details.

[h] After reduction; see SI for details.