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Total Syntheses of (−)-Hibiscone C and Lysergine: A Cyclization/Fragmentation Strategy

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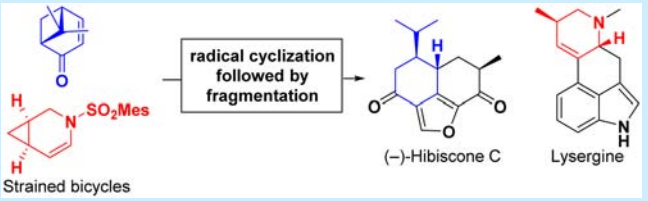
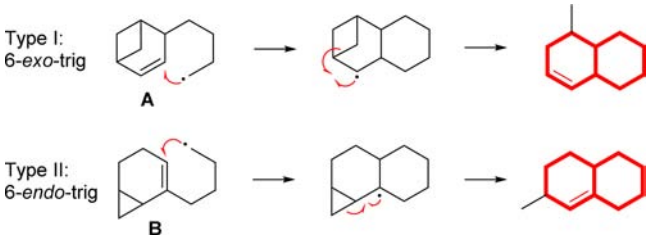
Supporting Information

ABSTRACT: The first asymmetric total synthesis of (−)-hibiscone C and a concise synthesis of ergot alkaloid lysergine are described. Both syntheses were achieved using the radical cyclization/fragmentation strategy. This cascade reaction enabled the application of the strained bicycle as a synthon for the synthesis of highly substituted decalins in an efficient and stereoselective manner.



The bicyclo[4.4.0]decane ring system, including azadecalins, is commonly found in a wide variety of small-molecule natural products.[1] To efficiently prepare multifunctionalized decalins, we envisioned a transform-based strategy[2] that combines a radical cyclization and scission of the strained ring to construct the desired skeleton (Scheme 1).[3] We

Scheme 1. Transform-Based Strategy To Construct Multifunctionalized Decalins from Strained Bicycles



reasoned that a strained bicycle, such as bicyclo[3.1.1]-heptene **A** or bicyclo[4.1.0]-heptene **B**, could serve as a template for the effective control of stereochemistry. Two modes of cyclization, either 6-*exo* or 6-*endo*, could be implemented to afford the bicyclo[4.4.0]decane ring systems with different structural figures. Herein, we substantiate these concepts via the total syntheses of (−)-hibiscone C and (±)-lysergine.

Hibiscone C (Gmelofuran) is a unique furanosesquiterpenoid first isolated from the heartwood of *Gmelina arborea*, later from the roots of *Hibiscus elatus*, and most recently from the roots of *Bombax malabarium*.[4] Even though its structure has been unequivocally determined by X-ray crystallography, the absolute configuration has not been assigned. Interestingly, two [α] values have been reported for hibiscone C, inviting an enantioselective synthesis to clear up this ambiguity.[4] There have been three reported syntheses of racemic hibiscone C, all of which used 5-isopropyl-1,3-cyclohexanedione as the starting material.[5,6] The Smith group reported the first synthesis of hibiscone C as early as 1982, in which the desired tricyclic ring system was constructed via an intramolecular [2 + 2] photocycloaddition followed by ozonolysis and acid-catalyzed dehydration.[5] The other two syntheses both relied on a formal Robinson annulation followed by redox manipulations and dehydration.[6]

For the construction of hibiscone C, **1**, in an enantioselective manner (Scheme 2a), we opted to synthesize enantiopure **2**, given racemic **2** has been successfully transformed to (±)-hibiscone C in five steps by the Smith group.[5] While **2** could be obtained from **3** via redox manipulations and furan ring formation, we hypothesized that **3** would be prepared in one step from **5** via a radical cyclization/fragmentation cascade involving ketyl radical **4** as the intermediate. Due to the steric weakening of the C8−C13 σ-bond by the *gem*-dimethyl group, ring opening of the cyclobutane would take place predominately by scission of this bond. Aldehyde **5** could, in turn, be prepared from chiral enone **6** through routine transformations, whereas the aldehyde side chain could be installed via a diastereoselective 1,4-addition due to steric hindrance of the *gem*-dimethyl group (Scheme 2a).

On the other hand, lysergine **7** was first synthesized from agroclavine in the laboratory and was later isolated from ergot fungi in 1961, verifying its existence in nature.[7] Later, the other semisynthetic approach to lysergine starting from lysergic acid was reported,[8] whereas Rebek and co-workers developed a de novo synthesis of racemic lysergine starting from tryptophan in 11 steps.[9] Despite numerous strategies being disclosed for the total syntheses of ergot alkaloids,[10] we wondered whether a radical cascade transformation could be a new way to access such a characteristic tetracyclic skeleton with important pharmacological properties. Retrosynthetic analysis of lysergine **7** revealed that **8** could be a reasonable intermediate resulting from a 6-*endo*-trig cyclization followed by fragmentation (Scheme 2b). In this key step, the intramolecular radical addition to the olefin in **10**

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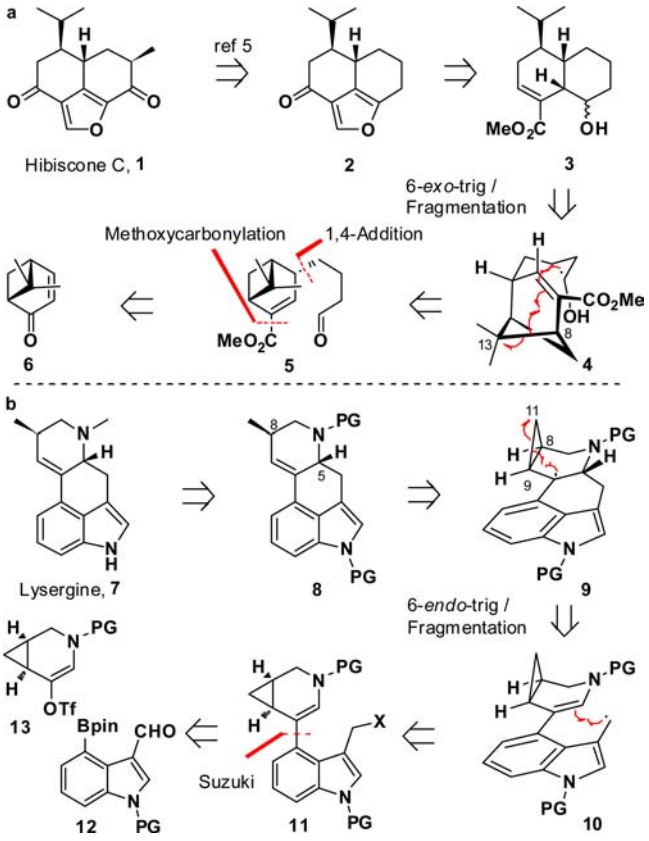
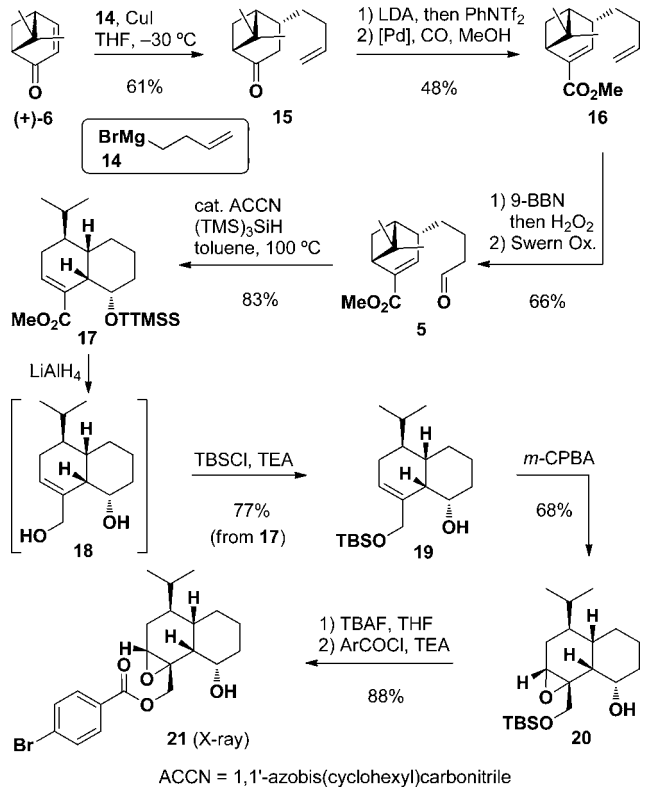
Scheme 2. Retrosynthetic Analysis of Hibiscone C (1) and Lysergine (7) Based on a Radical Cyclization/Fragmentation Strategy



proceeded from the convex face of the 3-azabicyclo[4.1.0]hept-4-ene moiety to provide tertiary radical **9**. Given that the overlap of the orbital containing the single electron with the orbital of the C9−C11 σ-bond is better than that with the C9−C8 σ-bond, this stereoelectronic factor would lead to selective cleavage of the C9−C11 carbon−carbon bond in **9** securing a *cis*-relationship of the C5-H and the C-8 methyl group.[11] Indole **11**, the precursor for radical **10**, could be readily prepared by Suzuki coupling of **12** and **13** followed by functional group manipulations.

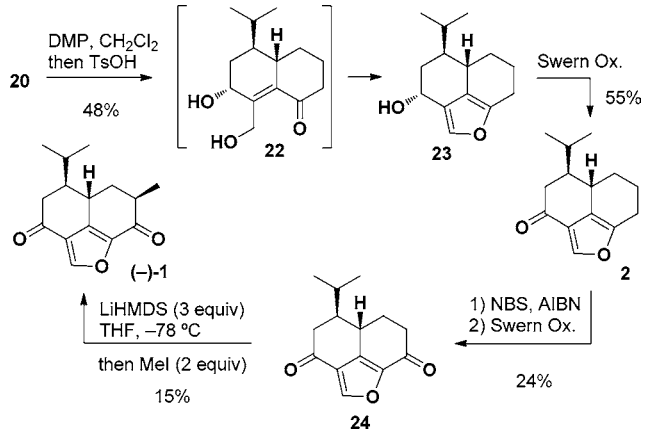
We began our studies by making (+)-apoverbenone **6** readily prepared from (−)-β-pinene in three steps.[12] Conjugate addition of **6** using Grignard reagent **14** catalyzed by copper iodide *trans* to the bridged carbon bearing the *gem*-dimethyl groups afforded ketone **15** in 61% yield as a single diastereomer (Scheme 3).[13] Converting the ketone to the enol triflate followed by Pd-catalyzed methoxycarbonylation gave rise to **16**, which underwent hydroboration and oxidation to yield the precursor for our key reaction, aldehyde **5**. Among the various methods of generating ketyl radicals, we found that tris(trimethylsilyl)silane smoothly promoted the desired transformation in the presence of a catalytic amount of 1,1′-azobis(cyclohexyl)carbonitrile (ACCN) at 100 °C, providing the cyclization/ring-ruptured product **17** as a single diastereomer in 83% yield. Reduction of **17** using $LiAlH_4$ was accompanied by the loss of the tris(trimethylsilyl)silyl group, leading to diol **18**, which was monoprotected to afford **19** in 77% yield over two steps. The hydroxyl-guided epoxidation of **19** furnished **20** in 68% yield, the structure of which was determined unambiguously by X-ray diffraction of its derivative **21**.

Scheme 3. Synthesis of Functionalized *cis*-Decalin 20



To construct the furan ring, we first oxidized alcohol **20** by DMP, and the resulting ketone was directly subjected to treatment with *p*-toluenesulfonic acid in THF/H_2O (Scheme 4). This procedure, effecting deprotection of the TBS group and

Scheme 4. Enantioselective Synthesis of (−)-Hibiscone C (1)



cyclization/aromatization in one pot, afforded tricyclic furan **23** in 48% yield presumably via intermediate **22**. Swern oxidation of **23** yielded chiral **2**, the racemic form of which was prepared in Smith's synthesis of hibiscone C.[5] Following a similar oxidation procedure reported by Smith and co-workers, we introduced the carbonyl group at the secondary allylic position of **2** to furnish diketone **24** in 24% yield over two steps. Instead of applying the existing protection/alkylation/deprotection sequence to synthesize hibiscone C,[5] we were intrigued by the possibility of converting **24** to **1** in one step via a selective methylation. Subsequently, diketone **24** was treated with excess LiHMDS

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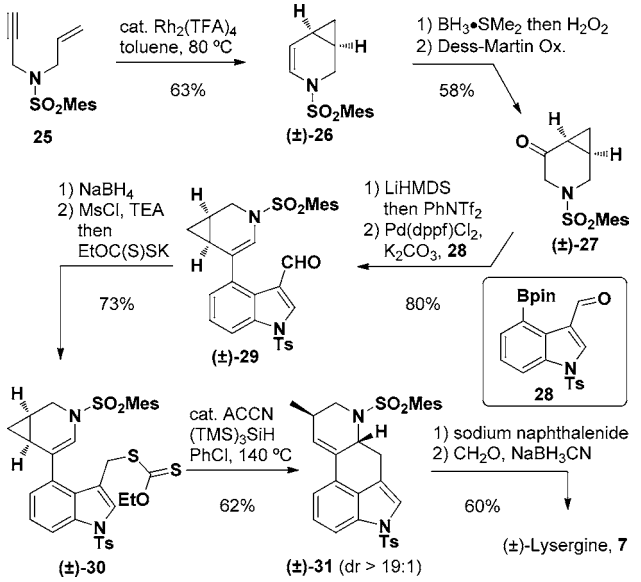
followed by MeI. Although substantial decomposition was observed, hibiscone C (**1**) was identified as the only isolable product, albeit in low yield (15%), providing an alternative way to access the natural product without the need for any protecting groups. The spectroscopic data of the synthesized sample of **1** were in good agreement with those reported for the isolated natural product.[4] By comparing the optical rotation of the synthesized sample of **1** to those reported by groups of Thomson and Xuan,[4b,c] we confirmed the absolute configuration of natural (−)-hibiscone C.

Encouraged by the total synthesis of hibiscone C, we moved on to the study of lysergine (Scheme 5). The synthesis began

Scheme 5. Total Synthesis of (±)-Lysergine (7)



with a rhodium-catalyzed cycloisomerization of 1,6-enyne **25** to afford azabicycle[4.1.0]heptene **26**.[14] The 2,4,6-trimethylphenyl sulfonyl group was chosen as the protecting group to avoid a side reaction in the late-stage radical cascade (Scheme S1; see Supporting Information for details). Regioselective hydroboration/oxidation of **26** gave bicyclic ketone **27** in 58% yield over two steps. Installation of the triflate, followed by palladium-catalyzed Suzuki coupling reaction with aldehyde **28**,[15] provided **29** in 80% yield over two steps. Aldehyde **29** was subsequently reduced to the alcohol and converted to xanthanate **30** via O-mesylation, followed by reaction with potassium ethyl xanthogenate.[16] When **30** was treated with tris(trimethylsilyl)-silane and ACCN in refluxing chlorobenzene, the desired cascade reaction took place to afford **31** in 62% yield as a single diastereomer. Eventually, removal of both sulfonamide protecting groups using sodium naphthalenide, followed by reductive amination, led to lysergine **7**. The spectroscopic data of the synthesized sample of **7** were in good agreement with those reported in the literature.[7,8]

In summary, we have accomplished the total syntheses of (−)-hibiscone C, **1**, in 15 steps and racemic lysergine, **7**, in 10 steps from enone (+)-**6** and enyne **25**, respectively. Key for both syntheses was the application of a radical cyclization/fragmentation strategy. The small ring-fused bicyclic substrates not only provided excellent stereochemical control but also enabled the strain-release fragmentation. Given that numerous potential substrates and reaction patterns can be envisaged, adopting this efficient strategy could find wide application for synthesizing complex natural products with structural and functional diversity, which is ongoing in our group and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03778.

Detailed experimental procedures, compound characterization data (PDF)
X-ray data for (−)-**21** (CIF)
X-ray data for **S12** (CIF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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