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Total Synthesis of Terpenoids Employing a "Benzannulation of Carvone" Strategy: Synthesis of (−)-Crotogoudin

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Abstract

Carvone is a sustainable and readily available starting material for organic synthesis. Herein, we present the syntheses of various natural product scaffolds that rely on a novel benzannulation involving the α-methyl group (C-10) of carvone to afford a versatile tetralin. The utility of our synthetic approach is highlighted by its application to a short synthesis of the *ent*-3,4-*seco*-atisane diterpenoid (−)-crotogoudin. The 13-step enantiospecific synthesis features a regioselective double oxidative dearomatization, a Diels—Alder cycloaddition with ethylene gas (to construct the bicyclo[2.2.2]octane framework), and a final acid-mediated lactonization. The versatility of this benzannulation strategy is demonstrated by its utility in the preparation of the carbon skeleton of *ent*-3,4-*seco*-abietane diterpenoids using an intramolecular oxidative dearomatization.

A key aspiration in pursuing total syntheses of complex molecules in the modern era is to maximize sustainable practices.[1] Designing highly efficient synthesis strategies, as well as powerful methods to implement them, is paramount to realizing this objective.[2] In addition to considerations of strategies and methods, the choice of readily available and sustainable starting materials contributes substantially to achieving the goals of a modern synthesis. In this context, the pool of chiral compounds including amino acids,[3] sugars,[4] and terpenes[5] (the "chiral pool")[6] has served admirably as starting materials for many practical and inspirational total syntheses over the past century. With regard to the total synthesis of terpenoid natural products,[7] carvone has been a frequently employed starting material due to its ready availability in both enantiomeric forms, as well as the potential for the orthogonal derivatization of its functional groups.[8]

Despite the wealth of reactivity that has been established for the α-methyl (C-10), isopropenyl, and enone (i.e., double bond and carbonyl) groups of carvone (Figure 1), *we*

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Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b06823.

Experimental details and complete analytical data for all new compounds (PDF)

Crystallographic data for 14 (CIF)

Crystallographic data for 15 (CIF)

The authors declare no competing financial interest.

recognized that direct C—C bond formation involving the α-methyl group has been underexplored. Direct C—C bond formation to this methyl substituent holds significant potential in the context of natural product synthesis. Specifically, we envisioned that if benzannulation of the carvone six-membered ring could be achieved by engaging the C-10-methyl and enone carbonyl groups, the stage could be set to access myriad natural product classes. In particular, numerous natural product scaffolds could arise from benzannulation following sequential diastereoselective functionalization α to the enone carbonyl group (i.e., at C-6) of carvone.[9] For example, 3,4-*seco*-atisane natural products[10] such as agallochaol C[10a] (Figure 1A) could be accessed from (*S*)-carvone whereas 3,4-*seco*-abietanes including *seco*-hinokiol[11] or callicarpic acid A[12] (Figure 1B) could arise from (*R*)-carvone.

In this Communication, we report our initial investigations into developing this potentially unifying strategy, which has afforded the frameworks of several terpenoid secondary metabolites via short diastereoselective sequences. The virtues of this approach are borne out in a short, enantiospecific total synthesis of the *ent*-3,4-*seco*-atisane diterpenoid (−)-crotogoudin (**1**)[13] in 13 steps from (*S*)-carvone.

We commenced our studies with the preparation of benzo-fused bicycle **6** (Scheme 1A), bearing allyl and methyl groups at C-6 (carvone numbering). The methyl group is resident in many of the natural products that could arise from this benzannulated intermediate, whereas the choice of the allyl substituent was dictated by its facile introduction as well as its versatility for subsequent derivatizations. Following a well-established sequence, known carvone derivative **2** was easily prepared through a sequential methylation/allylation protocol.[9c] Conjugate reduction using L-Selectride followed by oxidative workup affords the corresponding ketone,[14] which is converted to vinyl triflate **3** upon deprotonation and treatment of the resulting enolate with Comins' reagent.[15–16] Heck reaction of **3** with ethyl acrylate as the cross-coupling partner yields an ethyl enoate (**4**), which upon saponification provides acid **5**, the substrate for benzannulation.

We anticipated that benzannulation would be achieved by conversion of carboxylic acid **5** to the corresponding ketene[17] (**9**, Scheme 1B) by ϵ-deprotonation in mixed anhydride intermediate **8**.[18] In turn, 6π electrocyclization of **9**, aromatization, and acylation of the resulting phenol would yield **6**, consistent with the precedent of Murali and Krishna Rao.[19] Several conditions (A–C), as outlined in Scheme 1A, were explored to effect the benzannulation. Using the conditions reported by Murali and Krishna Rao (Condition A), only a 13% yield of **6a** was isolated from a complex reaction mixture.[20] A switch to propionic anhydride as the solvent, which could be heated to 160 °C, led to a substantial increase in yield to 42% and the isolation of desired bicycle **6b** and, surprisingly, constitutional isomer **7b** in a 1:1 ratio. A Cope rearrangement[21] of 8 prior to ketene formation and electrocyclization likely explains the genesis of **7b** through conformer **8′**. Full conversion of starting material **5** was achieved by heating the reaction mixture to 180 °C for 5 days, resulting in a combined yield of 59% of **6b** and **7b** (1:1.4 ratio).

In order to obviate the competing Cope rearrangement and with an eye toward application of the benzannulated bicycle to the synthesis of the diterpenoids illustrated in Figure 1, the allyl group of ester 4 was converted to an *n*-propyl hydroxy group (Scheme 2). This was achieved

by chemoselective hydroboration of the allyl group in the presence of the isopropenyl group using Wilkinson's catalyst (1 mol % loading) and catecholborane followed by oxidation of the resulting alkylborane.[22,23] Saponification of the intermediate hydroxyester gave acid **10** in 83% yield over two steps. Benzannulated bispropionate bicycle **11** was formed in 82% yield upon heating **10** in propionic anhydride to 180 °C for 5 days.

Following procedures adapted from Kunesch and Kondo,[24] the phenyl propionate in **11** was selectively cleaved using tetramethylguanidine. This set the stage for a position selective oxidative dearomatization to afford dienone **12** (along with the corresponding *para*-quinol ether and the isomeric masked *ortho*-benzoquinone as side products in 11–13% yield, respectively).[25,23] The observed selectivity in this iodine(III)-mediated oxidative dearomatization is rather unusual and has, to the best of our knowledge, only been reported by Mal and co-workers on simpler substrates.[26] Inspired by Fukuyama's recent synthesis of (−)-lepenine,[27] a diastereoselective [4 + 2] cycloaddition of cyclohexadienone **12** with ethylene was envisioned. However, in accordance with investigations by Liu and co-workers, compound **12** did not readily undergo the desired Diels—Alder reaction.[28] Cycloaddition only proceeded under pressure and at elevated temperature (70 bar, 140 °C, 5 d) to afford tricycle **13** in 90% yield (6:1 d.r.).[29] At this stage, Wittig olefination of the ketone group followed by acid treatment removed both the propionyl group and cleaved the dimethyl ketal. The resulting primary hydroxyl was oxidized to the carboxyl group to provide *seco*-crotogoudin (**14**) in 75% yield over two steps.[30,31] Lactonization of **14** to afford (−)-crotogoudin was fraught with complicating side reactions.[23] Ultimately, conditions were identified that provided crotogoudin (**1**) in 16% yield (2.9% total yield over 13 steps), along with rearranged lactone **15** in 14% yield.[32] Current efforts are directed at identifying conditions that provide **1** more selectively and in higher yield.[33] Crotogoudin prepared using the strategy outlined here provided spectral and analytical data consistent with those obtained during its previous syntheses by Carreira[13c] and Liu[13b] as well as from its isolation by Dumontet and Rasoanaivo from croton *goudotii*.[13a]

Notably, our synthesis plan affords opportunities to access other diterpenoid secondary metabolites including the atisane and abietane frameworks outlined in Figure 1. For example, ester cleavage of bispropionate bicycle **11** (Scheme 3) and subsequent intramolecular oxidative dearomatization[34] of the intermediate phenol (not shown) provided dienone **16**. Selective reduction of the less substituted double bond of the cyclohexadienone moiety of **16** to yield α,β-unsaturated ketone **17** was achieved using a combination of MAD[35] and L-Selectride.[36] A 1,2-addition of an isopropyl group using Knochel's method[37] readily delivered allylic alcohol **18**. The direct treatment of this tertiary alcohol with a proton source results in elimination to key intermediates (**19** and **20**) for the synthesis of *seco*-abietane congeners such as 9-hydroxycallicarpic acid A and *seco*-hinokiol, respectively.

In conclusion, a novel strategy for the synthesis of diterpenoids using carvone as a starting material has been developed. Several key transformations led to the success of this approach. These include (1) a benzannulation sequence that employs propionic anhydride and (2) a site-selective double oxidative dearomatization reaction that sets the stage for (3) a highly diastereoselective cycloaddition of ethylene to forge the key [2.2.2] bicycle. Our approach

has led to an enantiospecific 13-step synthesis of the diterpenoid (−)-crotogoudin and provided a platform for the synthesis of other terpenoids. The application of this plan to the syntheses of other natural products is the subject of ongoing studies in our laboratory.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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(15). For *N*-(5-chloro-2-pyridyl)triflimide, see:Comins DL; Dehghani A Tetrahedron Lett 1992, 33, 6299.

(16). A potential one-pot conversion of **2** to **3** was investigated; for carvone, see:Crisp GT; Scott WJ Synthesis 1985,1985, 335.Steric bulk conferred by the substituents at C-6 of enone **2** presumably hamper the reactivity of the intermediate enolate and result in only a poor yield of triflate **3**.

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(18). Deprotonation of the vinyl methyl ε position presumably occurs faster than at the endocyclic ε position. However, deprotonation of the latter position followed by equilibration and benzannulation cannot be ruled out.

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(20). An extensive investigation of various reaction conditions was performed. Addition of acids (2-nitrobenzoic acid, camphorsulfonic acid, pyridinium *p*-toluene-sulfonate), bases (collidine, K_2CO_3, diisopropylethylamine) or cosolvents to compound **5** in acetic anhydride did not lead to a significant improvement in the reaction outcome. Attempts to form dienylketene **9** from mixed anhydrides with either TFAA or tosyl chloride were also not successful.

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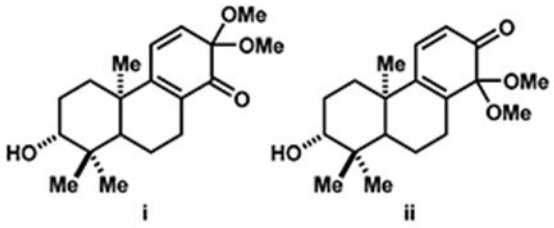
(28). In Liu's synthesis of (±)-crotogoudin [ref 13b] **i** and **ii** were reduced or hydrolyzed by reacting with ethylene (7 MPa) in CH_2Cl_2 at 70 °C for 48 h. Dienone **12** did not react under these conditions.



(29). Attempted Mukaiyama hydration of cycloadduct **13** under the conditions described by Liu and co-workers (see ref 13b) resulted in highly complex product mixtures.

(30). Epp JB; Widlanski TS J. Org. Chem 1999, 64, 293. [PubMed: 11674117]

(31). The absolute stereoconfiguration of compound **14** was unambiguously determined by single crystal X-ray analysis, and assignment of the stereocenters in cycloadduct **13** was thus inferred.

(32). Compound **15** may arise from an initial isomerization of the isopropenyl double bond to the corresponding tetrasubstituted alkene. Protonation of the endocyclic double bond in the bicyclo[2.2.2]octane and a subsequent 1,2-methyl migration will then yield an allylic cation which may be engaged by the carboxyl group to form the γ-lactone.

(33). An iodolactonization using **14** only engaged the isopropenyl group to form a seven-membered lactone. See the Supporting Information for details.

34. (a)Tamura Y; Yakura T; Haruta J; Kita Y J. Org. Chem 1987, 52, 3927.(b) Bauer RA; Wenderski TA; Tan DS Nat. Chem. Biol 2012, 9, 21. [PubMed: 23160003] (c) For a review, see:Pouysegu L; Deffieux D; Quideau S Tetrahedron 2010, 66, 2235.

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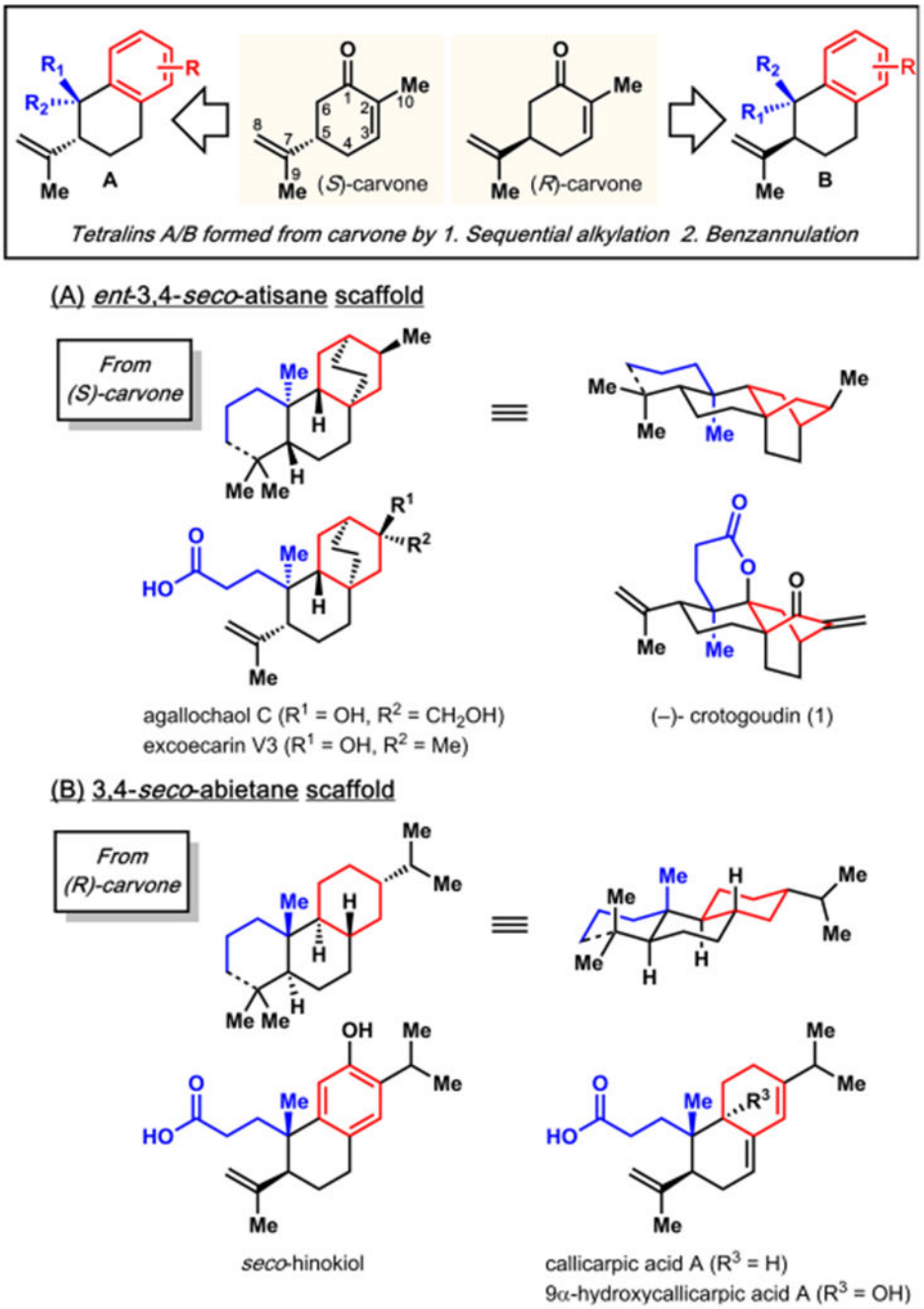
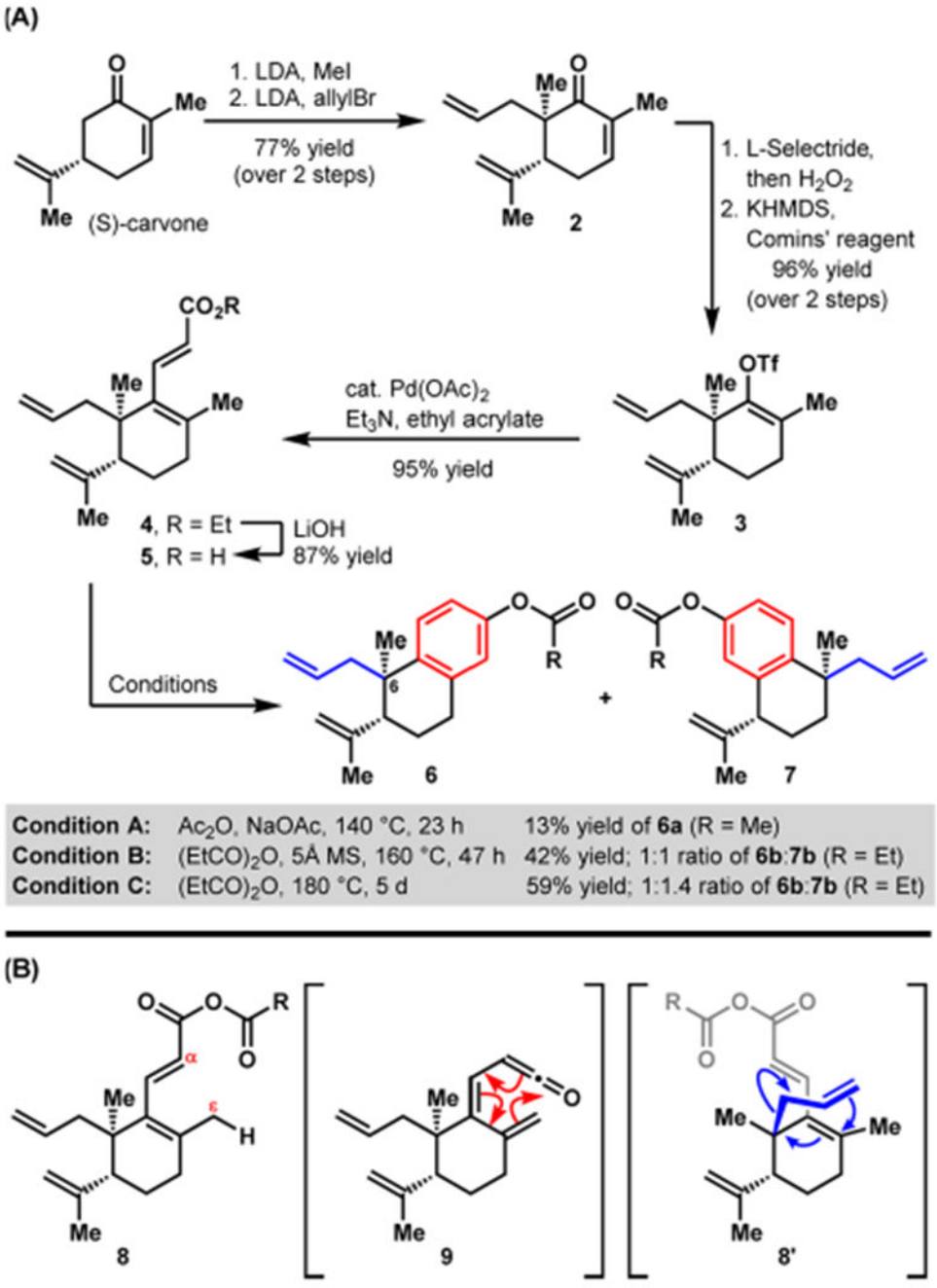
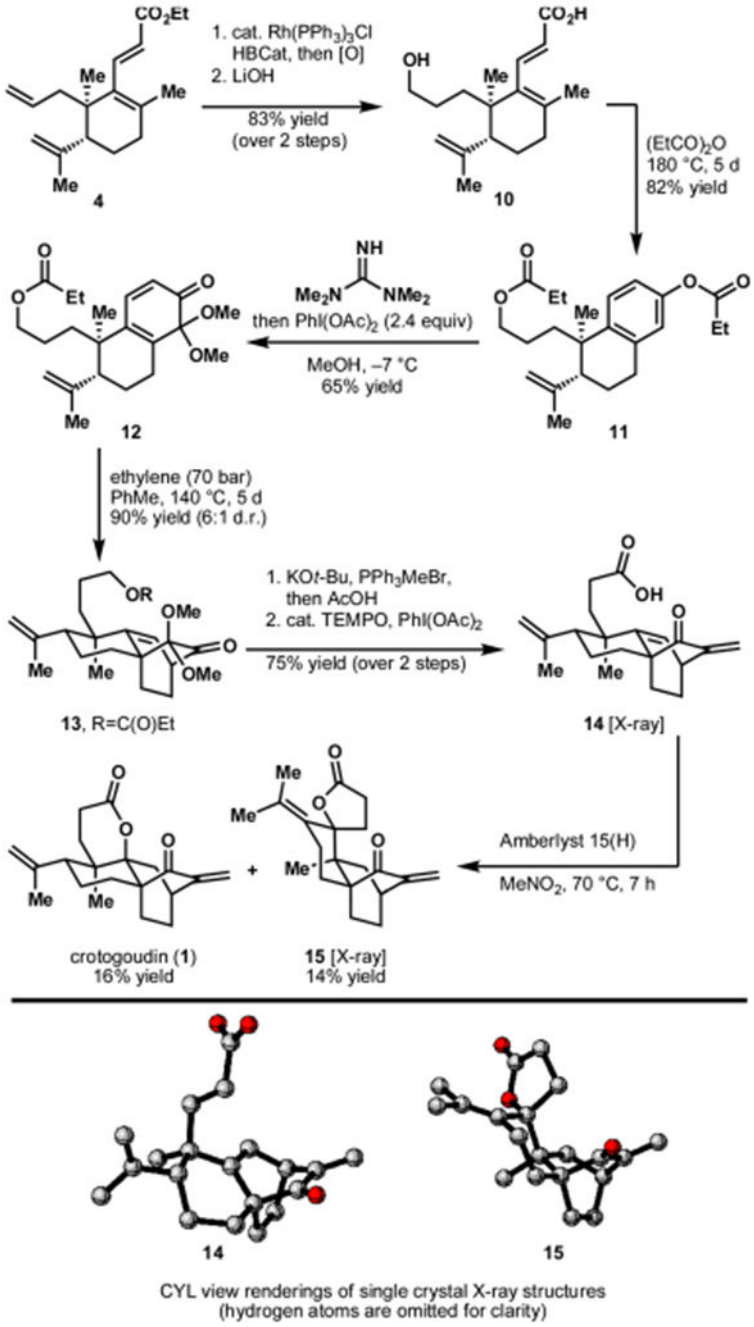


Figure 1.
Benzannulation of carvone: a unified approach toward terpenoids.



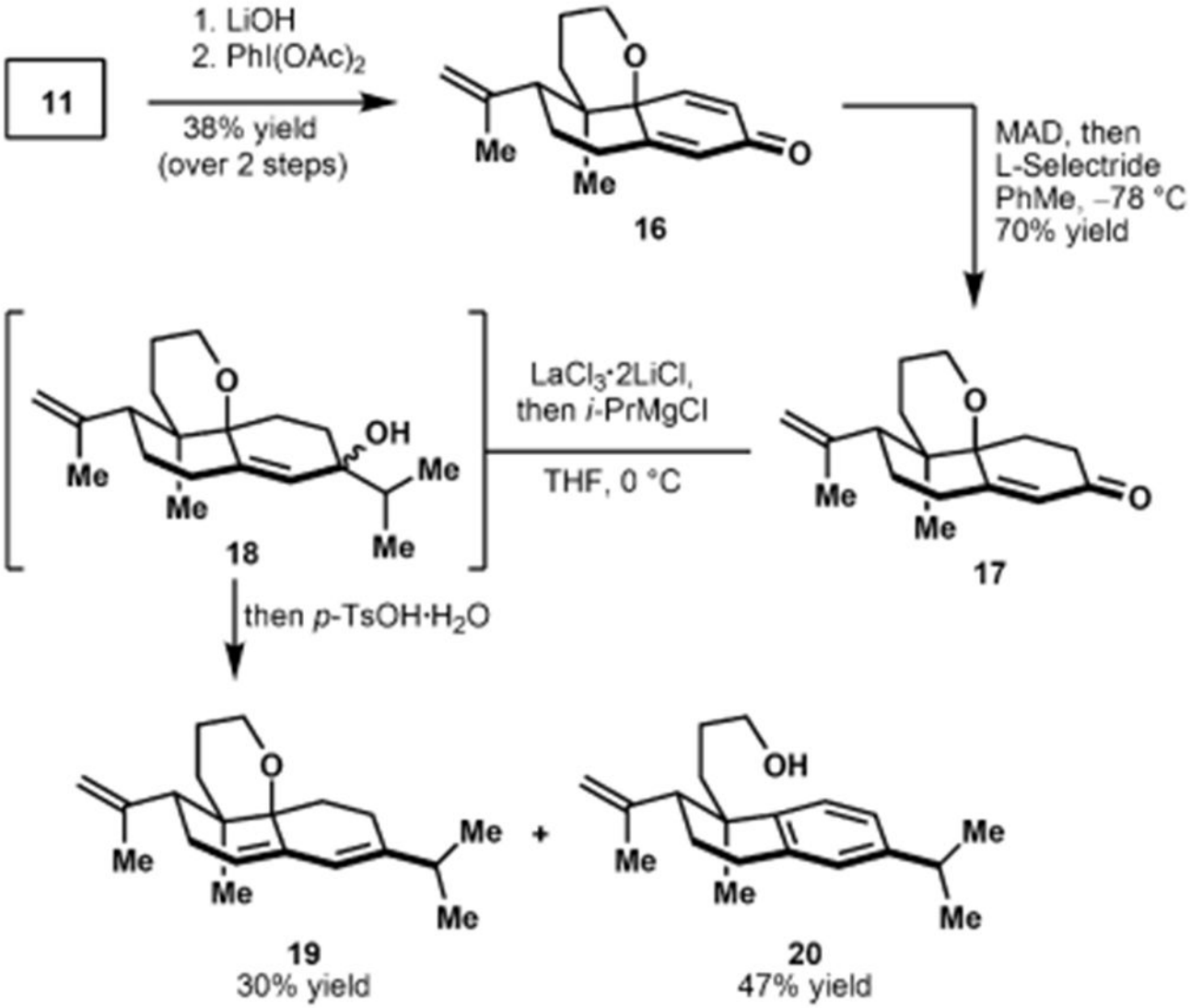
Scheme 1.

Synthesis of Hexadienoic Acid 5 and Initial Exploration of the Proposed Benzannulation



Scheme 2.

Completion of the Synthesis of Crotogoudin via a Double Oxidative Dearomatization Strategy



Scheme 3.

Synthesis of Secondary Metabolite Congeners via an Intramolecular Oxidative Dearomatization Pathway