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Intramolecular Condensation via an *o*-Quinone Methide: Total Synthesis of (±)-Heliol

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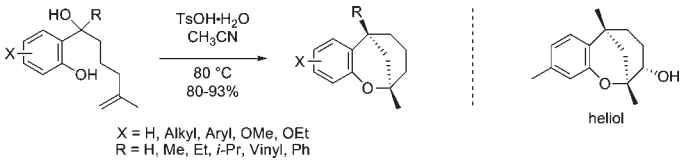
ABSTRACT

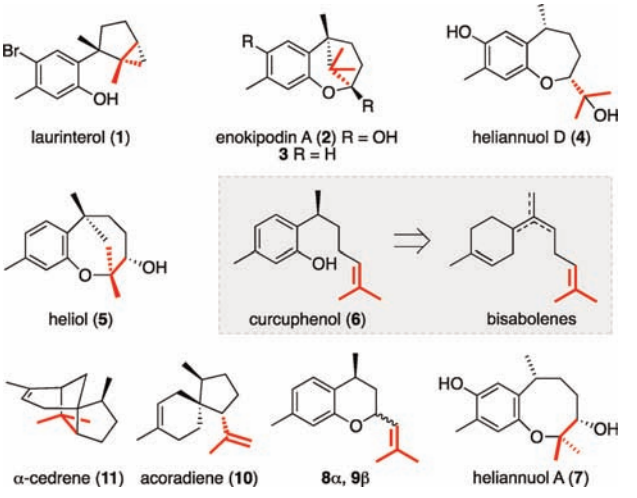


An acid-catalyzed intramolecular [4 + 2] cycloaddition of a non-natural bisabolene is reported. The key cyclocondensation was developed to access cyclic sesquiterpenes from linear phenolic precursors by generating a reactive *o*-quinone methide intermediate to initiate a cascade reaction. The new method was applied to the first total synthesis of (±)-heliol.

Nature has produced an array of cyclic natural products from the bisabolene skeleton manifested in curcuphenol (**6**) (Scheme 1).[1] The major distinction between each sesquiterpene is the resulting connectivity across the original prenyl functionality, producing an assortment of three- to eight-membered rings (**1**–**5**, **7**–**11**).[2] For some time, we have seen this array as a remarkable opportunity for chemical study in the hopes of developing new dearomatization methods that might access members of these structurally related natural products from a common linear phenolic system in a selective fashion.

One of our first studies delved into the biosynthesis of helianane, the putative *des*-hydroxy *des*-phenoxy enantiomeric antipode of heliannuol A (**7**).[3] Our attempts ultimately led to the repudiation of the entire helianane family and a new putative biosynthesis for heliannuol D (**4**) and A (**7**). The efforts also provided syntheses of the

Scheme 1. Variations of the Bisabolene Framework



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benzopyran natural products **8** and **9** and three cedrenoids from linear phenolic precursors.[4]

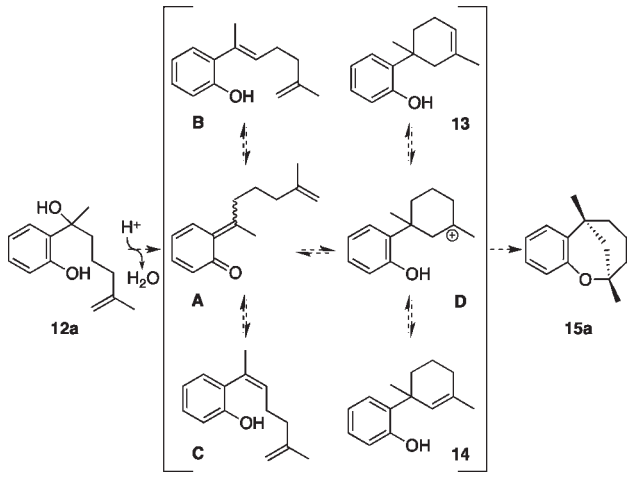
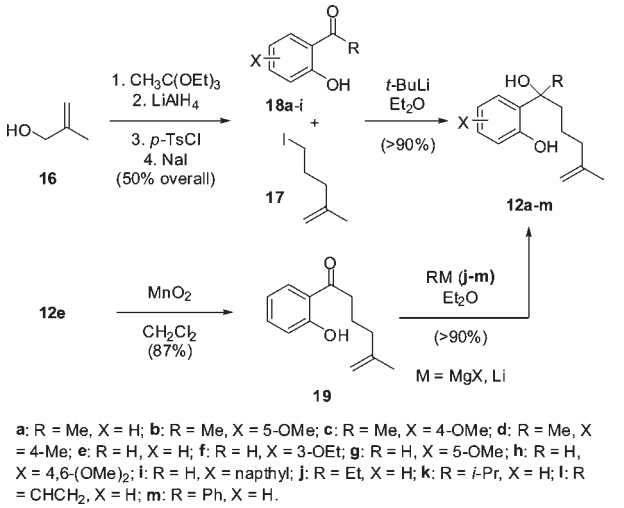


Figure 1. Proposed cyclocondensation reaction.

Continuing along in this direction, we imagined that access to structures resembling laurinterol (**1**), enokipodin A (**2**), **3**, or heliol (**5**) would require the development of a new procedure to render the benzylic position as an electrophile so that the prenyl residue might serve as an intramolecular nucleophile. We devised that the non-natural phenol **12a**, which possesses a terminal olefin and a tertiary benzylic alcohol, should undergo an acid-catalzyed, *stepwise*, intramolecular [4 + 2] cycloaddition to afford the desired 3,4-benzo-fused 2-oxabicyclo[3.3.1]nonane framework found in the structure **15a** (Figure 1).

The syntheses of the starting diol **12a** and various analogues are described in Figure 2. The alkyl iodide **17** was accessed by a known four-step sequence from methallyl alcohol **16**.[5] The resulting alkyllithium was added to a number of commercially available acetophenones **18a-d** (R = CH_3) and salicylaldehydes **18e**–**i** (R = H). Variation at the benzylic position was accomplished by oxidation of diol **12e** (R^1 = H, X = H) with MnO_2 followed by addition of the appropriate organolithium or Grignard reagent to ketone **19**, thereby arriving at the respective tertiary benzyl alcohols **12j**–**m**.

Next, we turned our attention toward affecting the desired intramolecular cyclization (Table 1). We found that numerous Lewis and Brønsted acids served to catalyze the desired cyclocondensation in good yields. We chose toluenesulfonic acid hydrate (TsOH·H_2O) in acetonitrile for its simplicity and ease of use. Catalytic amounts (0.1 equiv) of the acid afforded a mixture of the desired cycloadduct **15a** (35%) and cyclohexenes **13** (9%) and **14** (29%) (Table 1, entry 1). When the identical reaction was



a: R = Me, X = H; **b**: R = Me, X = 5-OMe; **c**: R = Me, X = 4-OMe; **d**: R = Me, X = 4-Me; **e**: R = H, X = H; **f**: R = H, X = 3-OEt; **g**: R = H, X = 5-OMe; **h**: R = H, X = 4,6-$(OMe)_2$; **i**: R = H, X = napthyl; **j**: R = Et, X = H; **k**: R = *i*-Pr, X = H; **l**: R = $CHCH_2$, X = H; **m**: R = Ph, X = H.

Figure 2. Synthesis of various diol precursors.

heated to 80 °C for 10.5 h, the yield of **15a** increased to 91% (Table 1, entry 2). Optimal conditions, 1.1 equiv of the acid at 80 °C, afforded the desired product in 93% yield in 15 min (Table 1, entry 4). The cyclization could be carried out in open atmosphere, and the reaction consistently afforded excellent yields on both millimolar and molar scales.

Table 1. Acid-Catalyzed Cyclocondensation

entry	TsOH·H_2O (equiv)	temp (°C)	time	product (yield, %)
1	0.1	25	30 h	**15a** (35) **14** (29) **13** (9)
2[b]	0.1	80	10.5 h	**15a** (91)
3	1.1	25	19.5 h	**15a** (91)
4[c]	1.1	80	15 min	**15a** (93)

[a] Reaction conditions: **12a** (0.05 M in CH_3CN), *p*-TsOH·H_2O, open to the atmosphere at designated temperature. [b] Catalytic procedure. [c] General procedure.

Various neutral and electron-donating substituents on the aromatic ring were tolerated under the reaction conditions (Figure 3, **15b**–**d**). Removal of the benzylic methyl substituent slightly diminished the yield to afford compounds **15e**–**i**. Ethyl, isopropyl, vinyl, and aryl substitution at the benzylic junction similarly afforded high yields of the desired cycloadducts **15j**–**m**.

While testing the reaction scope, we found that the monosubstituted olefin **20** failed to participate in the cyclization (Figure 4). This observation provides additional

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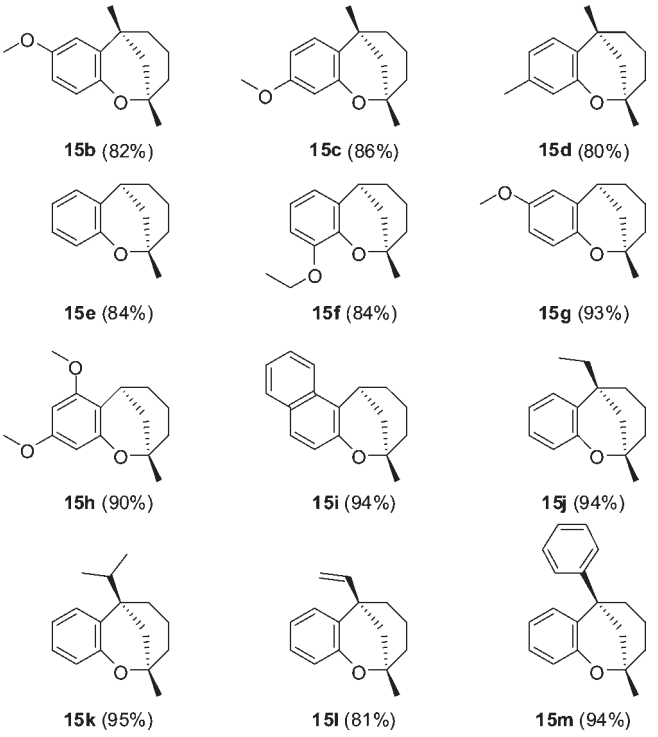

Figure 3. Analogues made from respective starting materials **12b**–**m**. Isolated yields given in parentheses.

support to the stepwise mechanism postulated within Figure 1 that involves the tertiary cationic intermediate **D**. Reduction of the tether length, as shown with diol **21**, resulted in the formation of the seven-membered ether **22** as the major product.

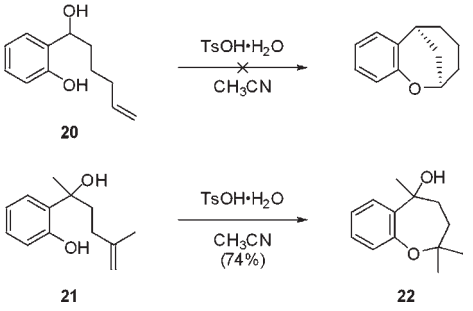

Figure 4. Observed limitations.

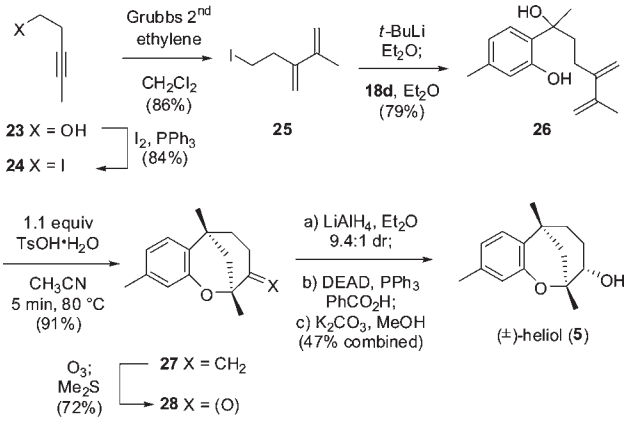

Figure 5. Total synthesis of (±)-heliol (**5**).

Application to the total synthesis of (±)-heliol (**5**) began by iodination of 3-pentyn-1-ol **23** (Figure 5). Enyne cross metathesis of this product with ethylene provided the diene **25**. Upon undergoing lithium–halogen exchange by the addition of *tert*-butyllithium to diene **25**, addition to 2-hydroxy-4-methylacetophenone **18d** afforded the diol **26**. Subjecting this material to the cyclization conditions resulted in formation of the methylenated tricycle **27** in 91% yield. Ozonolysis of the exocyclic olefin followed by reductive workup furnished ketone **28**. Reduction of the ketone with $LiAlH_4$ provided 3-*epi*-heliol as the major diastereomer. Stereochemical inversion of the secondary alcohol afforded (±)-heliol (**5**), which was identical in all spectroscopic respects to the natural product.

In conclusion, we developed an acid-catalyzed, stepwise, cyclocondensation reaction involving an *o*-quinone methide intermediate as means to access the 3,4-benzofused 2-oxabicyclo[3.3.1]nonane skeleton. We examined the scope of this cyclocondensation and demonstrated its utility with the first total synthesis of (±)-heliol (**5**).

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Supporting Information Available. Experimental procedures and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.