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Enantioselective synthesis of decalin structures with all-carbon quaternary centers via one-pot sequential Cope/Rauhut-Currier reaction

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Abstract

The first example of one-pot sequential Cope/Rauhut-Currier reactions are reported and used to make functionalized decalin structures with all-carbon quaternary stereocenters. The substrates for the new sequential reaction are generated through a six-step sequence including an enantioselective Birch reduction-allylation reaction which makes the overall process asymmetric.

Keywords

sequential; Cope; Rauhut-Currier; enantioselective

In an age when most any molecular target can be synthesized, a primary focus of current synthetic organic chemistry is to increase the efficiency of synthetic transformations. Tandem or sequential reactions have been an important tool in this regard[1–12]. Herein we report a one-pot intramolecular Cope/Rauhut-Currier sequence which illustrates the potential for the efficient enantioselective construction of functionalized decalin structures (**3**, Scheme 1). Building on the Birch-Cope sequence[13–15] and Rauhut-Currier application[16] that we communicated recently, we now report the ability to conduct the Cope rearrangement and an intramolecular Rauhut-Currier reaction in one pot. There are many tandem reactions involving a Cope rearrangement[1,11,12] and there are also a collection of domino reactions involving the Rauhut-Currier reaction[17–22], but to the best of our knowledge the two have yet to be combined into a one-pot sequential process.

The new Cope-Rauhut-Currier sequence may be used to enantioselectively generate valuable functionalized decalin cores with an all-carbon quaternary center. Decalin cores with quaternary stereocenters can be found at the heart of many bioactive natural product classes, including most notably terpenoid compounds. Some recent literature examples of

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Supplementary data
General experimental details; copies of ^{1}H and ^{13}C NMR spectra, IR spectra, gas and liquid chromatographs and mass spectra for compounds **1a-d**, **3a-d**, and **5**–**9**. This material is available free of charge via the Internet at doi:.

bioactive natural produts with a decalin core include crotonolides[23], kauranes[24], crotogoudin[25], walsucochin B[26], cafestol[27], and tubingensin A[28].

Not surprisingly, given the prevalence of these structures with potentially useful therapeutic activity, there are many approaches to the enantioselective synthesis of decalin rings. Some classic common strategies employed in recent work include the Diels Alder [4+2] cycloaddition[29–33], Weiland-Miescher ketone (WMK) synthesis[34–39], and cascading polyene cyclizations[40–42]. Although these strategies have all proven successful and quite efficient, there is always a need for new tools to address the many idiosyncrasies of molecule construction. This is especially true for the particularly complex case of enantioselective synthesis of all-carbon quaternary stereocenters and the frequently used decalin structure, a common and valuable intermediate in bioactive natural product synthesis.

Development of the one-pot Cope/Rauhut-Currier sequence commenced with the synthesis of the starting materials for the Cope rearrangement in six steps (Scheme 2). Beginning with 5-iodosalicylate derivate **4**[15], a Sonogashira cross-coupling reaction appended the necessary three carbon chain. Other procedures, such as Heck cross-coupling or Wittig reactions with a 5-formyl-salicylate derivative, were attempted, but the Sonogashira procedure was the most efficient. The tetrahydropyranyl (THP) ether protected propargylic coupling partner was also the most effective in this procedure as it eliminated a polymerization side reaction. The THP group also offered a stable protecting group for the alcohol functionality in the subsequent Birch reduction-alkylation step. Catalytic hydrogenation reduced the alkyne and enantioselective Birch reduction-allylation[43,44] afforded the cyclohexadiene **7** in good yield and excellent enantioselectivity. Concomitant hydrolysis of the enol ether and the THP protecting group was followed by Dess-Martin periodinane oxidation of the primary alcohol to afford aldehyde **8**. Finally, Horner-Wadsworth-Emmons conditions were used to add the requisite polarized alkene in **1**. The six step process was accomplished in 32–49% overall yield.

Initially, Cope rearrangement and the Rauhut-Currier process were explored independently. In the case of **1a** and **1b**, the Cope rearrangement to **2a** and **2b** occurred in an unoptimized 68 and 35% yield, respectively. Disappointingly, subjecting **2a** or **2b** to the Rauhut-Currier conditions that we previously reported[16] on similar substrates were unsuccessful. Fortunately, a simple adjustment to a higher boiling alcohol solvent, 2-methyl-1-butanol, and heating the reaction to reflux temperature provided the necessary solution. In the event, **2a** was successfully converted to **3a** in the requisite Rauhut-Currier reaction with trimethylphosphine (0.3–0.6 eq., 1 M in toluene) and 2-methyl-1-butanol in 56% yield.

The need for even higher temperatures in the Rauhut-Currier reaction immediately suggested that the two processes might be coupled. Indeed, subjecting **1a** to the Cope conditions and then, upon completion as monitored by NMR, adding PMe_3 and 2-methyl-1-butanol and returning to 130°C, produced the identical product, **3a**, in 69% yield; a 30% improvement in yield over the two-pot, two-step process (Table 1). Subjecting the nitrile (**1b**), methyl ketone (**1c**) and ethyl ketone (**1d**) to the same conditions produced good yields of the respective products, **3b-d**. The t-butyl ester (not shown) decomposed under the Cope

reaction conditions; presumably due to the instability of the t-butyl group at higher temperatures. Attempts to extend this procedure to the synthesis of a homologated seven-member carbocyclic ring with an ethyl ester derivative also failed. The ring junction stereochemistry of **3a-d** is tentatively assigned as cis. The 2-carboxamide group is a mixture of stereoisomers and can isomerize.

In conclusion, the first example of a one-pot sequential Cope/Rauhut-Currier reaction has been accomplished. The current procedure for the synthesis of decalin cores compliments our previous work[16] which generated 6–5 bicarbocyclic structures with Rauhut-Currier reactions. The highly functionalized decalin structure that results from the one-pot sequential Cope/Rauhut-Currier reaction has the potential to be a valuable intermediate in the synthesis of complex bioactive natural products.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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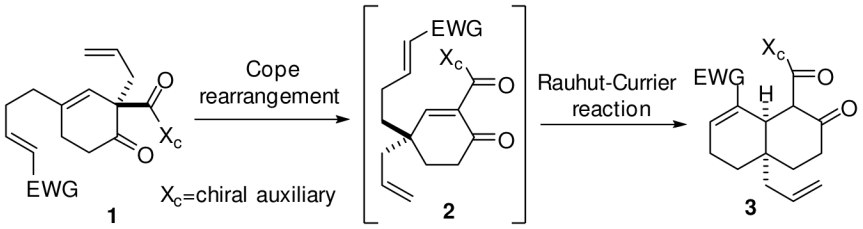
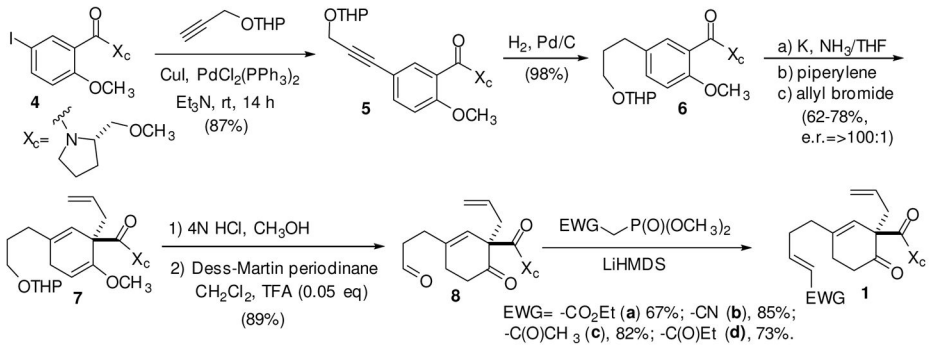


Scheme 1.

One-pot sequential Cope-Rauhut-Currier to build decalin structures.

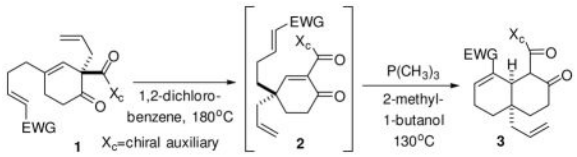


Scheme 2.

Synthesis of Cope/Rauhut-Currier reaction starting materials.

Table 1

One-pot sequential Cope/Rauhut-Currier reaction.



entry	EWG	One-pot Sequential Cope/Rauhut-Currier yield of 3
1	-CO_2Et (**a**)	69%
2	-CN (**b**)	65
3	-C(=O)CH_3 (**c**)	81
4	-C(=O)CH_2CH_3 (**d**)	76