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Enantioselective synthesis of bicarbocyclic structures with an all-carbon quaternary stereocenter through sequential cross metathesis and intramolecular Rauhut–Currier reaction

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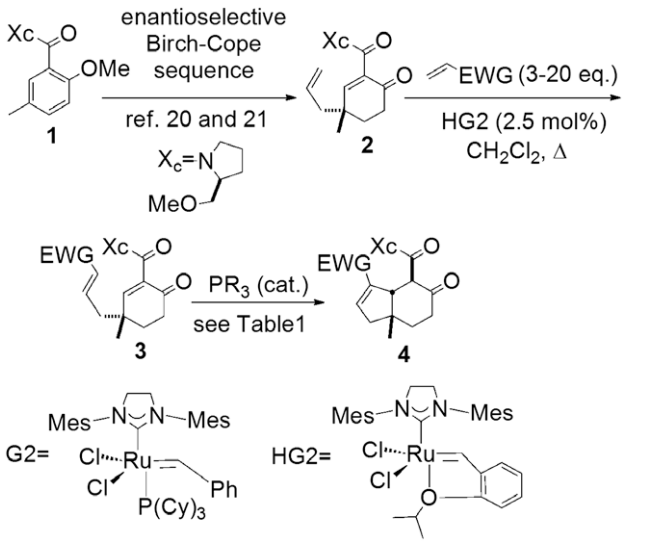
ABSTRACT

A new extension of the Birch–Cope sequence is described which allows the efficient enantioselective construction of highly functionalized, fused bicarbocyclic structures with an all-carbon quaternary stereocenter in two steps. The two-step sequence includes a cross metathesis between a terminal alkene and a polarized alkene followed by an intramolecular Rauhut–Currier reaction with a trialkylphosphine catalyst.

The enantioselective synthesis of fused bicarbocyclic structures containing all-carbon quaternary stereocenters is an important activity in organic synthesis. Due to their intriguing complex chemical architecture and their potential therapeutic applications, these structures have attracted the attention of synthetic chemists for many decades. Recent examples of bicarbocyclic structures with all-carbon quaternary stereogenic centers that have fomented synthetic activity include the cyanthiwigins,[1–6] the guanacastapenes,[7–10] and platensimycin.[11–16] One of the most common tools to enantioselectively generate these structures is the Hajos–Parrish–Eder–Sauer–Weichert reaction.[17–19] In fact, the popularity of this reaction in natural product synthesis is another indication of the demand for bicarbocyclic architectures, which can serve as key intermediates in complex molecule construction.

With the interest of developing new tools to create enantiomerically pure bicarbocyclic structures with all-carbon quaternary stereocenters in an angular position, we have extended our Birch–Cope sequence (Scheme 1)[20,21] to rapidly create several such structures with the hydrindane skeleton. The procedure selectively functionalizes the terminal alkene of the Birch–Cope sequence product **2** with a Grubbs cross metathesis reaction[22] and then performs an intramolecular Rauhut–Currier reaction with trialkylphosphine to afford **4** (Scheme 1). One-pot tandem reactions, such as the Rauhut–Currier reaction, are important for the efficient construction of complex chemical structures and therefore are an active research area in the synthetic community.[23–31] The intramolecular Rauhut–Currier reaction[32] has experienced a resurgence based on groundbreaking studies by Krische,[33] Murphy,[34,35] and Roush.[36] Under the influence of catalytic phosphine, conjugated systems can be merged to form a new ring while retaining one conjugated system for subsequent functionalization. Application of the intramolecular Rauhut–Currier reaction to the cross metathesis product **3** should afford valuable intermediates **4** on the path to a range of complex chemical architectures. Details of the successful transformation of **2**–**4** are presented herein.

The Birch–Cope sequence product **2** was subjected to cross metathesis in the presence of an alkene (3–20 equiv) and the second generation Hoveyda-Grubbs (HG2, 2.5 mol %) catalyst.



Scheme 1. Olefin cross metathesis and Rauhut–Currier reaction to bicarbocyclic structures with an all-carbon quaternary stereocenter in an angular position.

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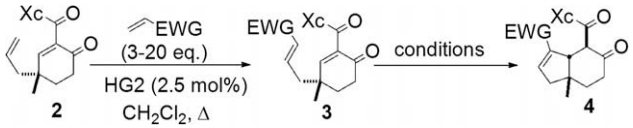
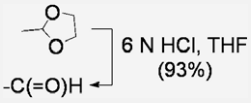
Table 1
Olefin cross metathesis and Rauhut–Currier reaction

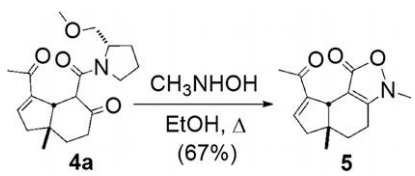


	EWG	Yield (%)	*E*/*Z* ratio	Conditions	Yield (%)
a	$-C(=O)CH_3$	87	~8.5:1	PBu_3(0.3 equiv), CH_2Cl_2, 0 °C to rt	81
b			*E* only		
c		86	~9:1	PBu_3(0.3 equiv), CH_3CN, 0 °C to rt	91
d	$-C(=O)OCH_3$	82	~30:1	PMe_3(0.4 equiv), *t*-BuOH/THF, Δ	81
e	$-C(=O)OH$	86	N.D.		no rxn
f	$-S(O)_2Ph$	41	N.D.		no rxn

Initially, the Grubbs second generation (G2) catalyst was tested, but the reaction proved more efficient with HG2. Previous reports[37,38] have described similar reactivity differences in Grubbs catalysts used for related cross metathesis examples. In all cases, an excess of alkene was essential for maximizing the conversion of **2**.[39] As has been previously reported,[22] the cross metathesis was amenable to a variety of alkenes (Table 1). Alkenes functionalized with a ketone, 1,3-dioxolane, ester, acid, and sulfone were all successful, although the sulfone was markedly less efficient. The cross metathesis reactions predominantly or exclusively formed the *E* alkene isomer.

A variety of Rauhut–Currier conditions, which modified both phosphine and solvent, were explored to determine the optimum method for conversion of **3**–**4** (Table 1).[33–36] Consistent with previously reported tendencies in the Rauhut–Currier reaction,[32] the relatively more electrophilic alkenes in **3a** and **3c** easily underwent tandem conjugate addition/Michael addition and subsequent phosphine elimination to afford the products **4a** and **4c**, respectively, in high yield. The regioselectivity of the tandem reaction in **3a** and **3c** is presumably based on both electronic and steric principles. Although the ring alkene might initially be considered the more electrophilic alkene with two carbonyl substituents, our previous studies[20,21] have shown that the C-2 amide prefers to adopt a more orthogonal conformation with respect to the ring pi system for steric reasons. Therefore, the C-2 amide is unlikely to contribute to ring alkene electron deficiency. Furthermore, the vicinal quaternary center of the ring alkene undoubtedly also contributes to a regioselective reaction at the least hindered alkene beta position. Finally, the product resulting from initial conjugate addition to the ring enone system would not be capable of eliminating phosphine after subsequent Michael addition and therefore would not generate a thermodynamically stable product.

The less electrophilic alkenes such as **3d**, **3e**, and **3f** were more problematic, as expected based on prior art. Nevertheless, **3d** was successfully transformed to **4d** with the use of the more reactive trimethylphosphine and a polar, protic solvent, *t*-BuOH. Solvent effects have been previously recognized in the Rauhut–Currier reaction with polar, protic solvents generally accelerating the reaction.[32] Interestingly, the sequential enoate, then enone order of addition witnessed in **3d** is extremely rare with only one other reported example to the best of our knowledge.[40] Failure to react in the more typical enone, then enoate order is again probably due to the steric hindrance of the ring enone and the inability of the product to eliminate phosphine. Despite repeated attempts to apply the conditions that were used with **3d**, acid **3e** and sulfone **3f** were resistant to any Rauhut–Currier annulation procedure. The products of the Rauhut–Currier reaction were epimerizable at the C-2 stereocenter, but they were not separable and simple computational studies suggest that the cis isomer is more thermodynamically stable. Equilibration between the two epimers was accomplished with heating in the presence of an acid (1:1 2 M H_2SO_4/THF).



Scheme 2. Chiral auxiliary cleavage.

Removal of the chiral auxiliary was accomplished in the standard manner previously reported[41,21] to form the isoxazolinone **5** (Scheme 2). Removal of the chiral auxiliary and formation of the isoxazolinone eliminated epimerization and allowed for easier spectroscopic and chromatographic analysis of the product.

In conclusion, a new extension of the Birch–Cope sequence is reported which allows the efficient enantioselective construction of highly functionalized hydrindane skeletons containing an all-carbon quaternary stereocenter in an angular position. The procedure couples cross metathesis and an intramolecular Rauhut–Currier procedure to generate the fused bicarbocyclic structures in two steps.

Acknowledgments

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Supplementary data

Supplementary data (general experimental details, copies of ^1H and ^{13}C NMR spectra, gas and liquid chromatographs and mass spectra for compounds **3a**–**d**, **4a**, **4c**, **4d** and **5**. COSY and HMQC for **5**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.03.026.

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