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An Ionic Diels-Alder Route to *cis*-Fused Octalins Containing an All-Carbon Quaternary Stereocenter in an Angular Position

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Abstract

We describe herein the development of efficient and stereoselective synthetic routes to a series of *cis*-octalins possessing an all-carbon quaternary center in an angular position.

Polycyclic *cis*-fused octalin systems bearing angular quaternary carbon centers, of the type **3**, can be of considerable value in organic synthesis.¹ In principle, this type of functionality could be rapidly reached through Diels-Alder cycloaddition between a substituted butadiene (cf. **1**) and a cycloalkene dienophile, conjugated to an exocyclic activating group (E). However, we and others have observed that cyclic dienophiles of the type **22·3** generally exhibit poor reactivity in the Diels-Alder cycloaddition, necessitating exposure to harsh reaction conditions (such as high reaction temperature and prolonged reaction time) or the use of a highly reactive diene. In the course of a program underway in our laboratory, focused on the investigation of new applications of Diels-Alder strategies, we sought to gain ready access to generic octalin motifs of the type **3**.

In the light of the difficulties associated with applying the traditional Diels-Alder reaction to the problem at hand, we considered the possibility of adopting the ionic variation en route to **3**. Gassman and coworkers were the first to describe the ionic Diels-Alder reaction of α,β -unsaturated ketals, as a useful means by which to prepare cycloadducts under mild reaction conditions.⁴ More recently, Grieco et. al. developed a modified protocol, which allow α,β -unsaturated ketals to undergo facile ionic Diels-Alder cycloaddition, in the presence of 4.0M LiClO₄ in Et₂O containing 1.0 mol% camphorsulfonic acid (CSA).⁵ As described below, we sought to extend the Grieco ionic Diels-Alder protocol to encompass acetal substrates of the type **4**.⁶ The development of this capability could well be a useful method for the preparation of highly substituted, *cis*-fused octalin systems of the type **3** (Scheme 1).⁷

In the event, it was found that, upon exposure to 4.0M LiClO₄ in Et₂O and 1.0 mol% CSA, diene **5** and dienophile **4** underwent the desired ionic Diels-Alder cyclization to afford a ~3:1 mixture of the direct acetal cycloadduct and the aldehyde product (**9**), which presumably arises through hydrolysis of the acetal intermediate. In situ hydrolysis of the acetal was suppressed through the use of freshly distilled dienes in the Diels-Alder step. Subsequent hydrolysis of the acetal cycloadduct delivered the target aldehyde, **9**, in 53% yield over two steps (Table 1,

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entry 1). This protocol was readily extended to a series of acyclic dienes, as shown in Table 1, and moderate overall yields were obtained (41–58% over two steps). When diene **7**, possessing a weakly directing group at the 2-position, was investigated, moderate regioselectivity was observed (4:1, *para*: *meta*). By contrast, diene **8**, possessing substitution at the 1-position, demonstrated very high regioselectivity, and afforded adduct **12** with 10:1 *endo* selectivity. It is of note that each of the reactions presented in Table 1 were conducted at ambient temperature and pressure. A control experiment, performed in the absence of CSA, resulted only in the recovery of unreacted starting material, confirming the critical role played by Brønsted acid in the reaction sequence.⁸

In an effort to further explore the utility of this approach to *cis*-fused octalin motifs, we sought to further functionalize aldehyde adducts **9** and **10**. As shown in Scheme 2, the aldehydes were readily converted to the corresponding nitriles (**13** and **14**, respectively), in a two-step protocol, via the intermediate formation of an aldoxime function.⁹ In another demonstration of the synthetic versatility of these cycloadducts, aldehydes **9** and **10** were advanced to the octalin esters, **15** and **16**, through Pinnick oxidation¹⁰ followed by esterification of the resulting carboxylic acids.

In summary, we have described herein the development of a method which is superior to those currently in use for the preparation of a series of *cis*-fused octalin derivatives containing an all-carbon quaternary stereocenter at the ring-junction carbon

Supplementary Material

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7. To the best of our knowledge, the known acetal **4** never been utilized in any Diels-Alder Reactions. For the ionic Diels-Alder reactions of acetals of α,β -unsaturated aldehydes, see: (a) Kumareswaran R, Vankar PS, Reddy VR, Pitre SV, Roy R, Vankar YD. *Tetrahedron* 1999;55:1099–1110., and pertinent references cited therein. (b) Sammakia T, Berliner MA. *J Org Chem* 1994;59:6890–6891.

8. Diels-Alder reaction of **4** (1.0 equiv) with 2,3-dimethyl-1,3-butadiene (5.0 equiv) under thermal condition (0.5 M in toluene-*d*₈, 5.0 mol% of 2,6-di-*tert*-butyl-4-methylphenol, 150 °C, 40 h) afforded a complete recovery of the acetal **4**.
9. We note that the isonitrile adducts, **13** and **14**, have served as useful reference compounds in the context of a separate Diels-Alder related investigation. (a) Kim WH, Lee JH, Aussedat B, Danishefsky SJ. Manuscript in Preparation. (b) Kim WH, Lee JH, Danishefsky SJ. *J Am Chem Soc* 2009;131:12576–12578. [PubMed: 19685875]
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Scheme 1.

A proposed route to *Cis*-fused octalins bearing an angular substituent.

Scheme 2.

Derivatization of Angular Aldehydes.

(a) $\text{H}_2\text{NOH}\cdot\text{HCl}$, NaOAc , THF, reflux, 2 h; (b) SOCl_2 , DMF, 0 to 23 °C, 4 h, 60% over two steps (*cis*-**13**), 56% over two steps (*cis*-**14**); (c) NaClO_2 , NaH_2PO_4 , 2-methyl-2-butene, *t*-BuOH/ H_2O (4:1, v/v), 23 °C, 2.5 h; (d) TMSCHN_2 , benzene/ CH_3OH (3:1, v/v), 0 to 23 °C, 1.5 h, 99% over two steps (*cis*-**15**), 88% over two steps (*cis*-**16**).

Table 1Ionic Diels-Alder reactions and hydrolysis of the resulting acetals^a

Entry	Diene	Product	Yield ^b
1			53%
2			58%
3			56% ^c
4			41% ^d

^a Diels-Alder reactions were carried out with 1.00 mmol of **4**, 5.00 mmol of diene in 4.0 M LiClO₄ (16.0 mmol) in Et₂O (4.0 mL), in the presence of 0.5 M CSA in THF (20 μ L, 1.0 mol%) at room temperature for 15–17 h.

^b Isolated yields of the cycloadducts over 2 steps.

^c *p*-Directed/*m*-directed = 4:1.

^d *Endo/exo* = 10:1.