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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

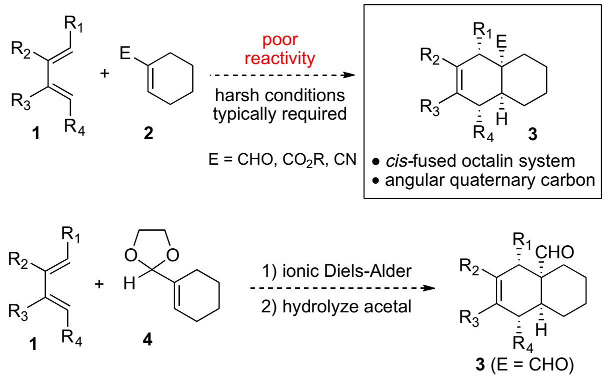
We describe herein the development of efficient and stereoselective synthetic routes to a series of *cis*-octalins possessing an all-carbon quaternary center in an angular position.

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 **2**[2,3] 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 et al. 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 allows α,β -unsaturated ketals to undergo facile ionic Diels–Alder cycloaddition, in the presence of 4.0 M $LiClO_4$ in Et_2O 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 4.0 M $LiClO_4$ in Et_2O 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, 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**, respec-



Scheme 1. A proposed route to *cis*-fused octalins bearing an angular substituent.

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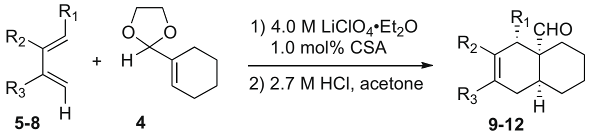
tively), in a two-step protocol, via the intermediate formation of an aldoxime function.[9] In another demonstration of the synthetic versatility of these cycloadducts, aldehydes **9** and **10** were advanced to the octalin esters, **15** and **16**, through Pinnick oxidation[10] followed by esterification of the resulting carboxylic acids.

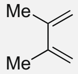
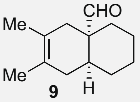
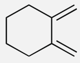
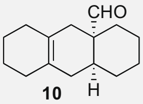
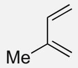
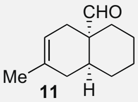
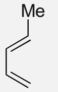
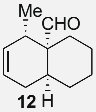
In summary, we have described herein the development of a method which is superior to those currently in use for the preparation of a series of *cis*-fused octalin derivatives containing an all-carbon quaternary stereocenter at the ring-junction carbon.

Table 1

Ionic Diels–Alder reactions and hydrolysis of the resulting acetals[a]



5-8 **4** **9-12**

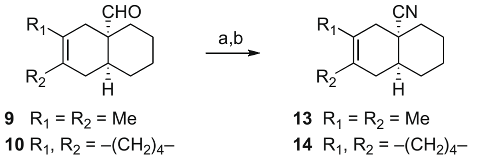
Entry	Diene	Product	Yield[b] (%)
1	 **5**	 **9**	53
2	 **6**	 **10**	58
3	 **7**	 **11**	56[c]
4	 **8**	 **12**	41[d]

[a] Diels–Alder reactions were carried out with 1.0 mmol of **4**, 5.0 mmol of diene in 4.0 M $LiClO_4$ (16.0 mmol) in Et_2O (4.0 mL), in the presence of 0.5 M CSA in THF (20 μL, 1.0 mol %) at room temperature for 15–17 h.

[b] Isolated yields of the cycloadducts over two steps.

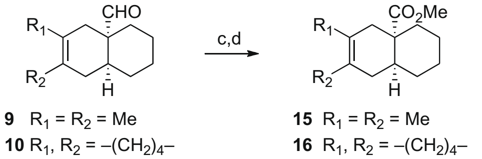
[c] *p*-Directed/*m*-directed = 4:1.

[d] *Endo*/*exo* = 10:1.



9 $R_1 = R_2 = Me$
10 $R_1, R_2 = –(CH_2)_4–$

13 $R_1 = R_2 = Me$
14 $R_1, R_2 = –(CH_2)_4–$



9 $R_1 = R_2 = Me$
10 $R_1, R_2 = –(CH_2)_4–$

15 $R_1 = R_2 = Me$
16 $R_1, R_2 = –(CH_2)_4–$

Scheme 2. Derivatization of angular aldehydes. Reagents and conditions: (a) $H_2NOH·HCl$, NaOAc, THF, reflux, 2 h; (b) $SOCl_2$, DMF, 0–23 °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), 0–23 °C, 1.5 h, 99% over two steps (*cis*-**15**), 88% over two steps (*cis*-**16**).

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.12.127.

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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, P. S.; Reddy, V. R.; Pitre, S. V.; Roy, R.; Vankar, Y. D. *Tetrahedron* **1999**, *55*, 1099–1110. and pertinent references cited therein; (b) Sammakia, T.; Berliner, M. A. *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. (a) 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. Kim, W. H.; Lee, J. H.; Aussedat, B.; Danishefsky, S. J., manuscript in preparation.; (b) Kim, W. H.; Lee, J. H.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2009**, *131*, 12576–12578.
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