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# Tandem Diels–Alder/Ene Reactions

## Abstract

The reactions of unsaturated aldehydes and triene **3** afford adducts via a tandem Diels–Alder/ene reaction.

## Disciplines

Chemistry | Organic Chemistry | Other Chemistry | Polymer Chemistry

## Comments

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## Tandem Diels–Alder/Ene Reactions

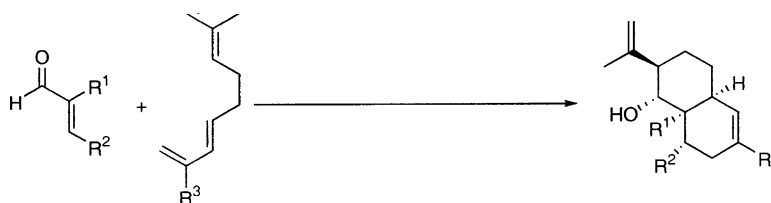
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## ABSTRACT



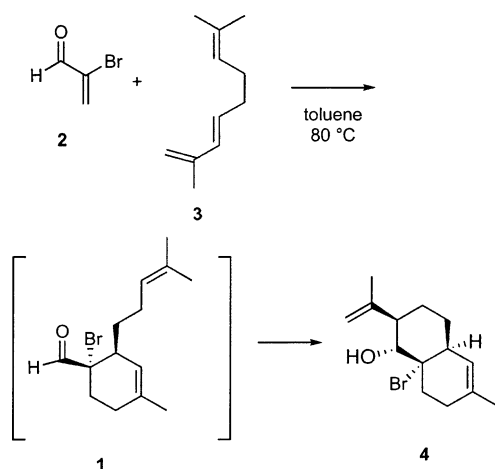
The reactions of unsaturated aldehydes and triene **3** afford adducts via a tandem Diels–Alder/ene reaction.

Tandem reactions have become a powerful tool for the synthetic chemist.<sup>1</sup> They often enable the generation of multiple stereogenic centers in a single operation. We have recently been interested in tandem Diels–Alder/radical cyclizations.<sup>2</sup> To study these reactions sequentially, we attempted to generate bromo aldehyde **1** by a Diels–Alder reaction between 2-bromoacrolein (**2**)<sup>3</sup> and diene **3**. The reaction of **2** with **3** did not yield **1** either by a thermal or a Lewis acid-catalyzed pathway. The product, alcohol **4**, was generated as a single diastereomer by a tandem Diels–Alder/ene reaction.<sup>4</sup> After searching the literature, we believe the examples described herein represent the first examples of this tandem reaction. Heathcock, in his elegant synthesis of *Daphniphyllum* alkaloids, employed a hetero-Diels–Alder/ene sequence.<sup>5</sup> There are also a few examples of tandem

Diels–Alder/Diels–Alder reactions and tandem ene/ene reactions.<sup>6</sup>

The stereochemistry of bromo alcohol **4** was determined by chemical and spectral methods. Since bromo alcohol **4** resisted epoxide formation under the conventional conditions,<sup>7</sup> the alcohol was assumed to be syn to the bromine. NOESY NMR experiments showed strong interactions between the carbinol hydrogen and the methyl of the isopropenyl group, indicating that the isopropenyl group was syn to the methine. No NOE interaction was observed between the carbinol hydrogen and the methine at the ring juncture. The structure of the adduct from 2,5-dihydrothiophene-3-carboxaldehyde and **3** was determined by X-ray crystallography. The product stereochemistries are consistent with an endo-selective Diels–Alder reaction followed by an ene reaction via a chairlike conformation.

To better understand the scope and limitations of this reaction, we reacted several substituted acroleins with trienes.



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Table 1.

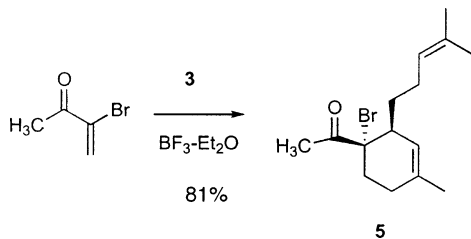
aldehyde	diene	reaction condition	product	% yield
	R <sup>3</sup> = Me	toluene 80 °C, 24 h BF <sub>3</sub> ·OEt <sub>2</sub> , Et <sub>2</sub> O 0 °C to 25 °C, 6 h		56 82
	R <sup>3</sup> = H	BF <sub>3</sub> ·OEt <sub>2</sub> , Et <sub>2</sub> O 0 °C to 25 °C, 6 h		77
	R <sup>3</sup> = Me	BF <sub>3</sub> ·OEt <sub>2</sub> , Et <sub>2</sub> O 0 °C to 25 °C, 18 h		40
	R <sup>3</sup> = Me	BF <sub>3</sub> ·OEt <sub>2</sub> , Et <sub>2</sub> O 0 °C to 25 °C, 10 h		56
	R <sup>3</sup> = Me	Et <sub>2</sub> AlCl, CH <sub>2</sub> Cl <sub>2</sub> -78 °C to 0 °C, 2 h		34
	R <sup>3</sup> = Me	BF <sub>3</sub> ·OEt <sub>2</sub> , Et <sub>2</sub> O 0 °C to 25 °C, 12 h		46
	R <sup>3</sup> = H	BF <sub>3</sub> ·OEt <sub>2</sub> , Et <sub>2</sub> O 0 °C to 25 °C, 19 h		41
	R <sup>3</sup> = Me	Et <sub>2</sub> AlCl, CH <sub>2</sub> Cl <sub>2</sub> -78 °C to 0 °C, 2 h		55

The results of this research are illustrated in Table 1. Although the reaction of **2** with **3** could be conducted using either thermal or Lewis acid-catalyzed conditions, the reactions with less reactive aldehydes needed to be conducted

using Lewis acid catalysis. It is clear from the results in Table 1 that the tandem reaction is general for substituted acroleins.

Interestingly, 2-methylbutenal, 2,5-dihydrothiophene-3-carboxaldehyde,<sup>8</sup> and cyclopentene carboxaldehyde react

with **3** to afford a single stereoisomer.<sup>9</sup> The adduct with acrolein is a 3:2:1 mixture of diastereomers. The adduct derived from methacrolein is a 2:1 mixture of diastereomers. We attempted to extend this reaction to unsaturated ketones. Unfortunately, the reaction of 3-bromobuten-2-one with triene **3** afforded only the Diels–Alder adduct **5** in 81% yield.



The tandem Diels–Alder/ene reactions create up to five stereogenic centers in a single operation. The bicyclic alcohol derived from dimethylacrolein contains the skeleton of the eremophilane sesquiterpenes. The mild reaction conditions

should be compatible with a wide variety of trienes and unsaturated aldehydes.

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**Supporting Information Available:** Spectra NMR and CMR spectra for compounds in Table 1. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL048847D

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(9) **General Procedure for Tandem Diels–Alder/Ene Reaction.** To a 0 °C solution of  $\alpha,\beta$ -unsaturated aldehyde (1.1 mmol) in Et<sub>2</sub>O (3.5 mL) was added BF<sub>3</sub>·OEt<sub>2</sub> (1.1 mmol) and the mixture stirred for 10 min at 0 °C (in the case of Et<sub>2</sub>AlCl, it was added to aldehyde at –78 °C and stirred for 10 min at –78 °C). To the resulting yellow solution was added via cannula a solution of triene (1 mmol) in Et<sub>2</sub>O (1. mL plus 0.5 mL rinse). After 1 h at 0 °C, the reaction was warmed to rt and further stirred for 6–19 h (monitored by TLC). The reaction was quenched by the addition of saturated aqueous NH<sub>4</sub>Cl (3 mL) and extracted by CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was dried over MgSO<sub>4</sub>, filtered, and concentrated in vacuo. The residue was purified via flash column chromatography to give the adduct.