Diethylaluminum Ethoxide Mediated Stereoselective Diels-Alder Reaction of α,β-unsaturated Ketones and Acetoxy-1,3-butadienes as Diene Components

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Stereoselective Diels-Alder reaction between several α,β-unsaturated ketones and acetoxy-1,3-butadienes is effectively performed by the promotion of diethylaluminum ethoxide under mild conditions. This reaction is successfully applied to the synthesis of optically active bicyclo[6.4.0]dodecanone **9** which corresponds to the BC ring system of 10-deoxy taxane derivatives from the 8-membered ring enone **7** and diene **2**.

Diels-Alder reaction is one of the most fundamental and powerful methods for the construction of 6-membered ring system and has been widely used in the synthesis of natural products and artificial compounds in which a conjugated diene component undergoes a stereospecific addition reaction with dienophiles.[1] In most cases, Diels-Alder reactions are carried out at relatively high temperature without using catalysts. However, there is obvious limitation in carrying out Diels-Alder reaction at such high temperature since synthetic intermediates in the multi-steps synthesis of complex molecules are often heat-sensitive. On the other hand, Yates and Eaton, as well as Fray and Robinson, reported that Lewis acid catalysts such as $AlCl_3$, $BF_3{\cdot}OEt_2$, $SnCl_4$, etc., efficiently accelerated certain Diels-Alder reactions at rather low temperatures.[2] Furthermore, other Lewis acids such as $EtAlCl_2$, Et_2AlCl, $TiCl_2(OR)_2$, $ZnCl_2$, $MgBr_2$, $Yb(OTf)_3$, $Sc(OTf)_3$ etc., were also shown to be effective for the promotion of some regio- and *endo*-selective Diels-Alder reactions.[1,3] Though the above reactions generally take place smoothly and give satisfactory yields, acid catalysts sometimes induce the polymerization of dienes and other side reactions such as isomerizations and rearrangements when substrates having acid-sensitive functionalities are employed. In order to expand the scope and limitation of this reaction, therefore, exploration of a new catalyst together with easily available dienes by which Diels-Alder reaction proceeds under mild conditions is still required.

In our previously reported total synthesis of antitumor agent Taxol®, the BC ring system, an optically active bicyclo[6.4.0] dodecanone, was constructed by stereoselective Michael addition of an alkyl copper reagent to the B ring, an 8-membered ring enone, and successive intramolecular aldol cyclization.[4] Because the C ring is a 6-membered carbocycle, Diels-Alder reaction was considered to be another useful route for the effective construction of the BC ring system.[5] Here, we would like to describe an alternative method for the synthesis of the BC ring system of 10-deoxy taxane (taxane numbering) derivatives by Diels-Alder reaction of the 8-membered ring enone by using acetoxy-1,3-butadienes as diene components.

In the first place, Diels-Alder reaction between 2-cyclooctenone (**1**) and acetoxy-5-(*t*-butyldimethylsiloxy)-1,3-pentadiene (**2**)[6] which contains functional groups at C7 and C20 positions (taxane numbering) was examined as a model study for the construction of the BC ring system of taxane derivatives (see Table 1). The cycloaddition did not proceed at all when a mixture of these compounds was stirred in a sealed tube at 180 °C nor in the presence of Lewis acids such as $ZnCl_2$, $Yb(OTf)_3$ and $Sc(OTf)_3$ at 0 °C. After screening several catalysts, however, it was found that Et_2AlOEt promoted the above reaction effectively and the deacetylated cycloadduct **3** (*endo* / *exo* = >98 / 2) was produced unexpectedly in 62% yield.

Recently, Bienaymé *et al.* reported that Diels-Alder reaction of dimethyl fumarate, dimethyl maleate, fumaronitrile and maleimide with dimethylaluminum 1,3-butadienolate proceeded to afford the corresponding cycloadducts in good yields.[7a] The above dimethylaluminum 1,3-butadienolate was generated *in situ* from trimethylsiloxy-1,3-butadiene by successive treatments with MeLi and Me_2AlCl. Also, Bienaymé reported that cycloaddition of maleimides took place rapidly with triisopropoxytitanium 3-methyl-1,3-butadienolate, prepared *in situ* from acetoxy-3-methyl-1,3-butadiene and $Ti(O^iPr)_4$, and afforded the corresponding 6-membered compounds in high yields.[7b] However, the desired cycloadduct **5** was obtained in low yield when the reactions of enone **1** and the above mentioned metal dienolates were tried according to their given conditions. Therefore, we focused our attention on developing an effective promoter for the synthesis of cycloadducts by direct reaction of α,β-unsaturated ketones with acetoxy-1,3-butadienes using the aluminum reagent.

In the next place, effect of the substituents of the aluminum reagent was examined in detail. The above Diels-Alder reaction of enone **1** with readily available acetoxy-1,3-butadiene (**4**) was tried by using organoaluminum compounds, respectively generated from trialkylaluminum and alcohol, phenol, amine or thiol. Then, it was revealed that i) the reaction proceeded slowly when the aluminum reagent having a bulky alkyl group was employed, ii) replacement of ethoxy group with alkylamino or alkylthio group caused to decrease yield of the cycloadduct and iii) trialkoxyaluminum reagents such as $Al(OEt)_3$ did not promote the above reaction. As a result, it was noted that Et_2AlOEt was the best promoter in the present Diels-Alder reaction between α,β-unsaturated ketones and acetoxy-1,3-butadienes.

Several examples of the present Diels-Alder reaction of α,β-unsaturated ketones and acetoxy-1,3-butadienes show that the desired adducts were obtained in good to high yields under mild conditions when Et_2AlOEt was used (Table 1). The reaction of cyclic α,β-unsaturated ketones with a simple diene **4** proceeded smoothly to give the corresponding products in good yields with high regio- and *endo*-selectivities (Entries 2 and 3). Since high *endo*-selectivity was observed in every case, it is suggested that the reaction proceeded by the concerted mechanism. In the meantime, the reaction of acyclic α,β-unsaturated ketones with the diene **4** proceeded slowly compared with those of cyclic α,β-unsaturated ketones and the corresponding 6-membered carbocycles were obtained in moderate yields with high regio- and *endo*-selectivities (Entries 4 and 5). Similarly, the desired cycloadducts **8** and **9** having many functionalities were exclusively obtained in high yields by the reaction of 4-benzyloxy-7-(*t*-butyldimethylsiloxy)-5-(*p*-methoxybenzyloxy)-

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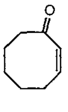
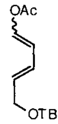
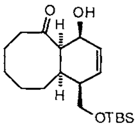
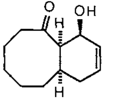
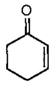
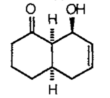
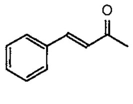
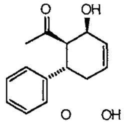
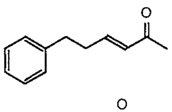
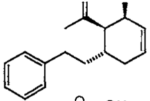
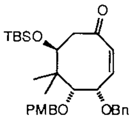
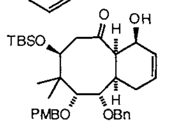
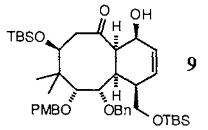
6,6-dimethyl-2-cyclooctenone (**7**), corresponding to the B ring of 10-deoxy taxane derivatives, with dienes **4** and **2** (Entries 6 and 7). While, the adduct was not obtained from dimethyl fumarate, dimethyl maleate or naphthoquinone and diene **2** or **4** under the present reaction conditions.

Table 1. Diels-Alder reaction of various α,β-unsaturated ketones[a]

Entry	Dienophile	Diene[b]	Product[c]	Yield[d] / %
1	 1	 2	 3	62
2	1	 4	 5	82
3		4	 6	78
4		4		57
5		4		59
6	 7	4	 8	69
7	7	2	 9	78

[a]All reactions were carried out in toluene at 0 °C except entries 6 (at rt) and 7 (at 50 °C). [b]Mixtures of *trans*- and *cis*-isomers were used (**2**; *trans* / *cis* = *ca.* 2 / 1, **4**; *trans* / *cis* = *ca.* 3 / 2). The *trans*-isomers predominantly reacted.[8] [c]Relative configurations were determined by ^{1}H NMR. [d]Isolated yield.

Though a typical Diels-Alder reaction using acetoxy-1,3-butadienes generally affords the corresponding acetoxycyclohexene derivatives, deacetylated cycloadducts were afforded by the present procedure. In addition, there are no reports to our knowledge which showed that Et_2AlOEt reacted with acetoxy-1,3-butadienes to produce diethylaluminum 1,3-butadienes. Then, the following experiment was tried in order to study the reaction mechanism further. When 10-acetoxy-*cis*-bicyclo[4.4.0]decan-2-one, prepared by acetylation of C10 hydroxyl group of the cycloadduct **6**, was treated with Et_2AlOEt under ice cooling, the deacetylation reaction did not take place at all. Further, it was shown by ^{1}H NMR measurement of the reaction between diene **4** and Et_2AlOEt that the formation of ethyl acetate is accelerated in the coexistence of α,β-unsaturated ketones, which suggested that the cleavage of acetyl group in diene **4** occurred during the process of concerted cycloaddition. Therefore, the mechanism was assumed as follows: α,β-unsaturated ketones were initially activated by coordination of their carbonyl groups to aluminum reagent. Then formation of ethyl acetate and the concerted Diels-Alder reaction took place synchronously by the nucleophilic addition of the ethoxy group in Et_2AlOEt to the carbonyl groups of acetoxy-1,3-butadienes as shown in Figure 1.

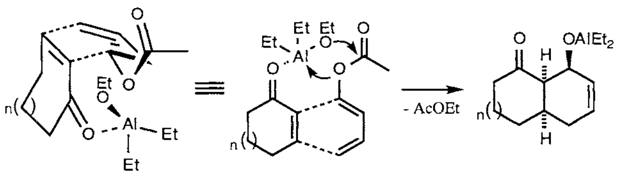


Figure 1. Proposed reaction mechanism.

A typical experimental procedure is described for the reaction of 2-cyclooctenone (**1**) and acetoxy-1,3-butadiene (**4**): To a solution of enone **1** (41 mg, 0.33 mmol) and diene **4** (150 mg, 1.33 mmol) in toluene (2.5 mL) was added Et_2AlOEt in hexane (1.0 M, 1.33 mL) at 0 °C. The reaction mixture was stirred for 1.5 h at 0 °C. After saturated aqueous potassium sodium tartrate and ethyl acetate were added to quench the reaction, the mixture was stirred for an additional 30 min at rt. By a usual work up, the crude products were chromatographed on silica gel to afford the corresponding cycloadduct **5** (53 mg, 82% yield) as a colorless crystalline solid (Table 1, Entry 2).

Thus, Et_2AlOEt mediated stereoselective Diels-Alder reaction between α,β-unsaturated ketones and acetoxy-1,3-butadienes was developed. It is noted that the above reaction affords the corresponding cyclohexenol derivatives accompanied by deacetylation of acetoxy-1,3-butadiene. This is the characteristic feature of the present reaction in contrast with typical Diels-Alder reaction using acetoxy-1,3-butadienes as diene components. Further, optically active BC ring system of 10-deoxy taxane derivatives was successfully prepared from the 8-membered ring enone and the acetoxy-1,3-butadiene in high yield by the present reaction.

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