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TWO SIX-MEMBERED RINGS ANNELATION TO CYCLIC KETONES THROUGH TWO SEQUENTIAL DIELS-ALDER REACTIONS

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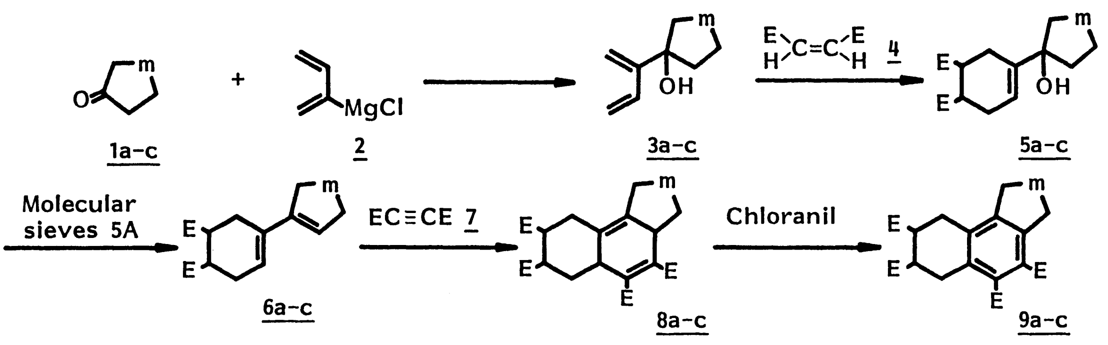
A method for the two six-membered rings annelation to cyclic ketones through two sequential Diels-Alder reactions is presented. Naphtho-annelated cycloalkanes with a variety of unsaturation are accessible by choosing the kind of dienophiles, the order of their use, and dehydrogenation.

Among the known ring-forming methods, the Diels-Alder reaction must be one of the most important and reliable ways as it makes a six-membered ring in one step in a highly stereo- and regioselective manner.1) Although the elaboration of a complex natural product frequently requires a process that forms more than one ring, such a process utilizing the Diels-Alder reaction is quite rare.2) The diene-transmissive Diels-Alder reaction becomes useful for the construction of two six-membered rings, but with a rather limited applicability.3) Quite recently we have found that a tertiary alcohol with a 2-(1,3-butadienyl) moiety reacts, as a cross-conjugated triene equivalent, with two different dienophiles under dehydrating conditions.4)

In the present communication, the synthetic utility of diene-transmissive Diels-Alder reaction of cross-conjugated triene equivalent is demonstrated with an example of new method for the two six-membered rings annelation.

Our method consists of the introduction of a 2-(1,3-butadienyl) functionality to cyclic ketones, the first cycloaddition, the second under dehydrating conditions, and if needed, dehydrogenation.

The Grignard reactions of 2-(1,3-butadienyl)magnesium chloride 2,5) readily available from chloroprene, introduced the diene functionality to three cyclic ketones 1a-c. The corresponding alcohols 3a-c formed were contaminated with unseparable 1-(2,3-butadienyl)cycloalkanols in every case.6) Only the desired alcohols 3 reacted giving quantitative yields of cycloadducts 5a-c when the alcohol mixtures were subjected to the Diels-Alder reactions with dimethyl maleate 4 (Scheme 1 and Table 1).7) The dehydration of 5 and the second Diels-Alder reactions of diene 6 were successfully performed in the same flask. Thus, the alcohols 5a-c were heated with dimethyl acetylenedicarboxylate 7 in the presence of molecular sieves 5A providing the bis-cycloadducts 8a-c in good yields.8) Although the



E=COOMe

a: m=CH_2; b: m=$(CH_2)_2$; c: m=$(CH_2)_3$

Scheme 1.

stereochemistry of 8 was not confirmed, it is clear that the second Diels-Alder reactions of 6 all proceeded in a highly stereoselective manner.9) No any stereo-

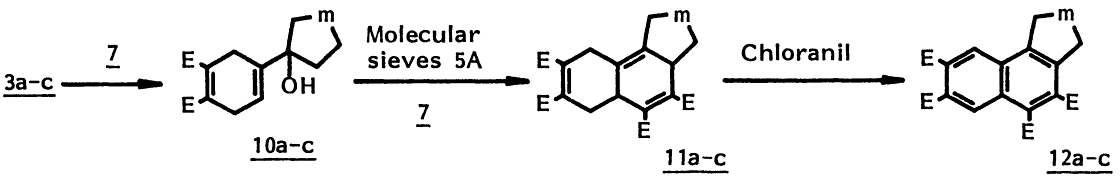
Table 1. Two six-membered rings annelation through two sequential Diels-Alder reactions

Conversion	Product	Yield/%	Mp/°C	Reaction conditions a)			
				Solvent b)	Time/h	Molar ratio c)	
3 → 5	5a	92	viscous oil	T	40	4/3 = 1.0	
	5b	93	viscous oil	T	48	1.0	
	5c	97	viscous oil	T	48	1.0	
5 → 8	8a	63 d)	130-131	B	48	7/5 = 1.0	MS/5 = 5*
	8b	83	126-127	T	43	3.2	10*
	8c	77	70-71	T	48	3.0	10*
3 → 10	10a	89	viscous oil	T	20	7/3 = 1.0	
	10b	94	viscous oil	B	48	1.0	
	10c	100	viscous oil	B	40	1.0	
10 → 11	11a	64	113-114	B	72	7/10 = 1.0	MS/10 = 10*
	11b	63	116	T	40	2.0	10*
	11c	69	128-129	T	40	2.0	10*
8 → 9	9a	100	181-182	B	24	CA/8 = 1.5	
	9b	90	159-160	T	48	1.5	
	9c	93	129-130	T	48	1.5	
11 → 12	12a	92	144-145	T	72	CA/11 = 2.5	
	12b	88	151-152	T	72	4.0	
	12c	88	120-121	T	72	4.0	

a) All the reactions were carried out under reflux. b) T: toluene; B: benzene. c) MS: molecular sieves 5A; CA: chloranil. The numbers with an asterisk show the weight-to-weight ratios. d) The unreacted diene 6a was recovered in 17% yield.

isomers other than 8 were obtained. The dehydrogenation of 8 with chloranil took place only on the secondarily formed ring affording the meta bis-annelated benzene derivatives 9a-c.

When the acetylenic dienophile 7 was employed both in the first and second Diels-Alder reactions with 3, the bis-cycloadducts 11a-c were obtained via mono-cycloadducts 10a-c (Scheme 2 and Table 1). As the bis-cycloadducts 11 have one more unsaturation on the initially formed ring, the dehydrogenation with chloranil occurred also on this ring yielding the cycloalkane-fused naphthalene derivatives 12a-c.

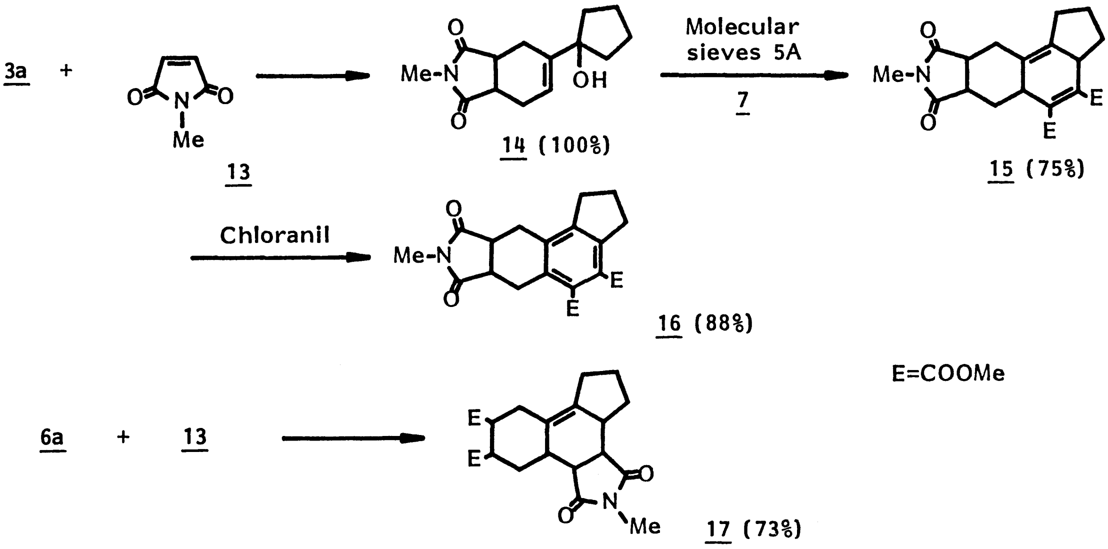


E=COOMe

a: m=CH_2; b: m=$(CH_2)_2$; c: m=$(CH_2)_3$

Scheme 2.

Not only these two six-membered rings annelation but also the annelation of more than two rings to cyclic ketones can be achieved. As shown in Scheme 3, the use of cyclic dienophiles will add some more rings to the bis-cycloadducts. The alcohol 3a was allowed to react with N-methylmaleimide 13 under reflux in toluene for 20 h forming a quantitative yield of the mono-cycloadduct 14 (bp 180 °C/1.5 mmHg (bulb-to-bulb)). It was then heated with an equivalent of 7 in the presence of molecular sieves 5A under reflux in benzene for 72 h giving the stereoselective bis-cycloadduct 15 (mp 142-143 °C) which was dehydrogenated with chloranil into a three rings-annelated product 16 (mp 192-193 °C). The other example is the Diels-



Scheme 3.

Alder reaction of the diene 6a with the cyclic dienophile 13 under reflux in toluene for 17 h leading to the stereoselective tetracyclic bis-cycloadduct 17 (mp 121-122 °C).[10]

As shown above, our annelation method has some advantages: 1) two six-membered rings can be annelated to cyclic ketones by a simple procedure using readily available chloroprene; 2) any combination of olefinic and acetylenic dienophiles can be employed providing the bis-cycloadducts with a variety of unsaturation; 3) the annelation of more than two rings is also possible; 4) a wide variety of substituents can be introduced stereoselectively.

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6) The Grignard reactions of 1a-c were carried out with an equivalent of 2 under reflux in THF for a few hours. The yields of alcohol mixtures were given as follows (purity of 3): 3a: 60% (91%); 3b: 60% (70%); 3c: 70% (71%).

7) The first Diels-Alder reactions were performed between the alcohol mixtures and the dienophiles equivalent to 3. The contaminants, 1-(2,3-butadienyl)-cycloalkanols, were quantitatively recovered unchanged after the reactions.

8) All the compounds reported herein gave satisfactory spectral data as well as analytical results.

9) A Dreiding model inspection suggests that the acetylenic dienophile 7 more likely cycloadds to the dienes 6 from the less hindered direction. This may be the same in the formation of 15.

10) The stereochemistry of 17 was hardly determined only on the basis of the spectral data. However, it was tentatively assigned as the endo cycloadduct formed through the approach of 13 from the less hindered face of the diene 6a (For the stereoselectivity of Diels-Alder reaction, see Refs. 1 and 3).

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