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TRIPLE

MICHAEL ADDITION REACTION

BY

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## ABSTRACT

The consecutive Michael addition of a nucleophile to an  $\alpha$ -methylenecyclopentenone, thence to methyl acrylate, occurs readily and stereospecifically, yielding bicyclo(2.2.1)heptanone. The reaction represents the first example of a three-component triple conjugate addition process.

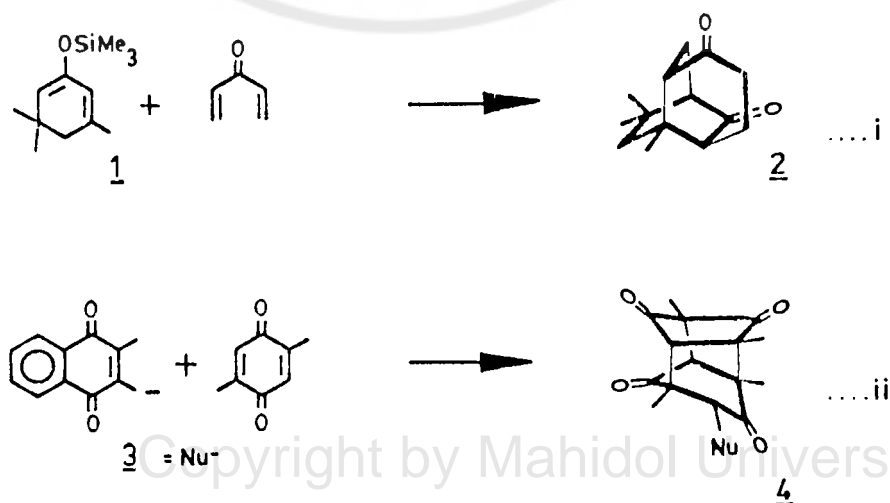
### STEREOSPECIFIC TRIPLE MICHAEL ADDITION

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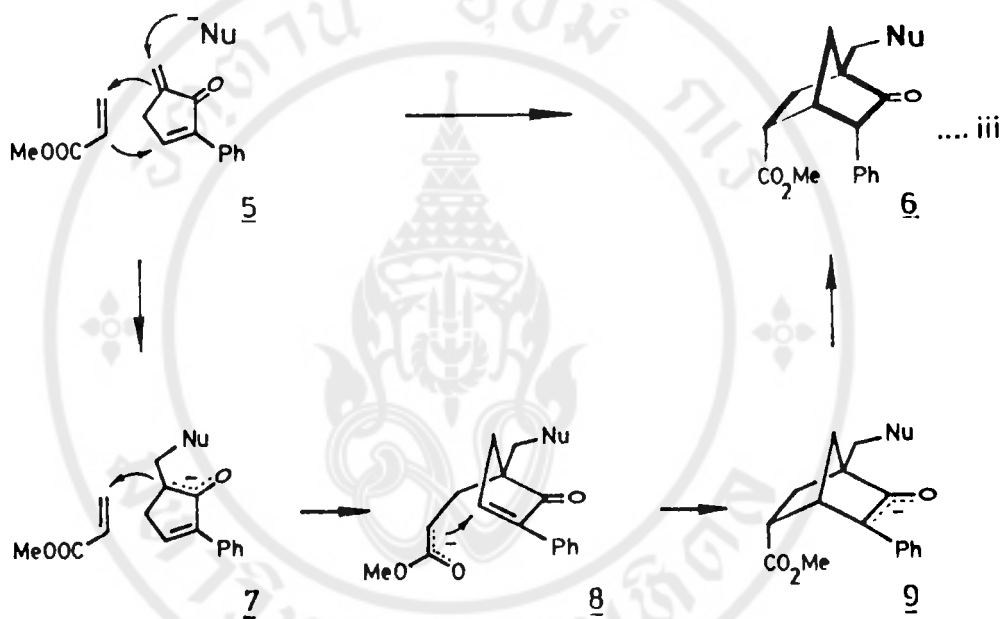
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**Abstract:** The consecutive Michael addition of a nucleophile to an  $\alpha$ -methylene cyclopentenone, thence to methyl acrylate, occurs readily and stereospecifically, yielding bicyclo-[2,2,1]-heptanone. The reaction represents the first example of a three-component triple conjugate addition process.

Multiple Michael additions have long been recognized to be processes of high potential in organic synthesis. However, despite the fact that the consecutive double Michael addition is now a well known art, examples of controlled triple or quadruple conjugate additions remain extremely rare. One, very recent, is the Lewis acid assisted threefold Michael reaction of divinyl ketone with silyl enol ether 1, which gives 2,<sup>1</sup> another is the intriguing observation, by Dean,<sup>2</sup> of the formation of a cage product 4 via a fourfold Michael addition of anion 3 to 2,5-dimethylbenzoquinone. Typically, the yields from these reactions are not high, a fact probably attributable to competing polymerization processes. Here we would like to report the development of a unique three-component, stereospecific Michael addition as depicted in equation iii.



The reaction can be performed in a single operation and involves the following sequence: regioselective addition of a nucleophile to the exocyclic double bond of  $\alpha$ -methylene cyclopentenone 5<sup>3</sup> followed by trapping of the resulting enolate 7 by methyl acrylate and eventual attack of this last-formed anion 8 on the endocyclic double bond of the cyclopentenone moiety to result in, after protonation, the bicyclo-[2,2,1]-heptanone 6.<sup>3</sup>


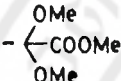
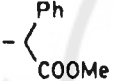
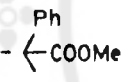



In a typical experiment a THF solution of  $\alpha$ -methylene cyclopentenone 5 was slowly added to a stirred solution of the preformed nucleophile<sup>4</sup> in THF at  $-78^{\circ}$  and the resulting mixture allowed to stir at  $-78^{\circ}$  for 1.5 hr. A 1 molar THF solution of methyl acrylate was then added and the mixture further stirred at room temperature for 2 hr. Saturated ammonium chloride work-up followed by purification by PLC finally afforded the bicyclic product 6.

An interesting feature of the stereochemistry of 6 is revealed by the chemical shift of the carbomethoxy group which appears in the region  $\delta$  2.62 - 2.84 in the  $^1\text{H}$  nmr spectrum.<sup>5</sup> This upfield shift of about 1 ppm indicates close proximity of the -OMe group to the aromatic ring, hence the endo-endo relationship of these two groups is deduced as shown. An X-ray crystal data of 6a ( Figure ) has since conclusively proved this assignment.<sup>6</sup>

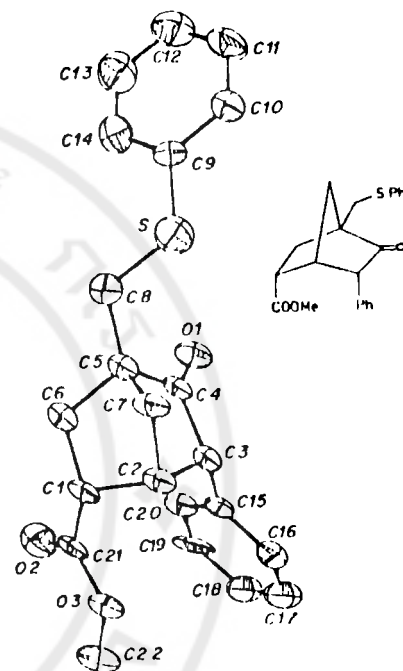
The endo-endo relationship between the ester and phenyl groups of bicycloheptanone 6 can be appreciated upon inspection of the transition state model 10. A conformation held by lithium ion chelation to the ester group and the keto-enolate or the adjacent phenyl ring is envisioned in the last Michael addition step.<sup>7</sup> Protonation on the less hindered side would thus lead to the product with the observed stereochemistry. Indeed we were able to trap the enolate 9 with electrophiles other than the proton. For example, bicyclopentanone 11, showing the carbomethoxy

TABLE

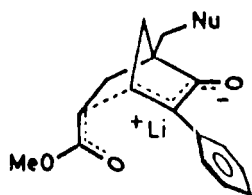
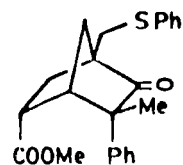
Entry	Nu <sup>-</sup>	% Yield of <u>6</u>
a	- SPh	68
b	- 	40
c	- 	25
d	- 	48 <sup>+</sup>
e	- 	41 <sup>+</sup>
f		67 <sup>+</sup>

<sup>+</sup> Two isomers were obtained due to chirality of the nucleophile.

FIGURE



peak at  $\delta$  2.84, was obtained in 61% yield by quenching the reaction of entry a) with methyl iodide.

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These findings demonstrate and emphasize the feasibility of a one-pot multiple Michael addition reaction. Clearly sequential conjugate additions can be conveniently manoeuvred to yield desired products. The usefulness of such a process is apparent and with suitably designed starting components the possibilities appear unlimited in this barely explored area.