## CYCLOBUTENE DERIVATIVES AS ISOPRENE EQUIVALENTS IN

## TERPENE SYNTHESIS: 1-CYCLOBUTENYL METHYL LITHIUM

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A common structural feature among a number of terpenoids is the terminal isoprene unit. Although the thermal ring opening of cyclobutene to 1,3 dienes (i.e.  $1 \rightarrow 2$ )<sup>1,2</sup> is a well



known process, the potential applications of this reaction to natural products synthesis has not been generally recognized.<sup>3</sup>

We describe herein a new and hopefully quite general method for the synthesis of 1-substituted cyclobutenes and illustrate its utility by a convenient two step synthesis of a sex attractant of <u>Ips confusus</u>,<sup>4</sup> a bark beetle common in ponderosa pine.

Metalation<sup>5</sup> of methylenecyclobutane  $\tilde{\lambda}$  occurs smoothly with the <u>n</u>-butyl lithium/IMEDA complex in hexane to give anion  $h^{6}$ . Reaction of this ambident anion with electrophiles  $E^{\dagger}$  leads



to mixtures of products 5 and 6 (Table I).

It has been shown<sup>7</sup> that the product ratios from allyl anions can usually be adjusted within large limits. Thus by variation of solvent, temperature and electrophile we were

able to adjust the regioner ratio from 0/100 to 61/39 in favor of the desired adduct 5 (E = CH<sub>2</sub>Ph).

Initial application of this method to terpene synthesis has thus been accomplished since cyclobutene 5 (E = CH<sub>2</sub>CH=C(CH<sub>3</sub>)<sub>2</sub>) has been previously prepared by direct irradiation of myrcene. On heating at 215°C for 3 minutes 5 (E = CH<sub>2</sub>CH=C(CH<sub>3</sub>)<sub>2</sub>) was quantitatively reconverted to myrcene.<sup>8</sup>

Entry	$Electrophile E^+$	Solvent	Temperature	% Yield <sup>a</sup>	Ratio <sup>b</sup> 5/6
1	D <sub>2</sub> 0	THF	25°	с	67/33
2	• CO <sub>2</sub>	THF	-78°	21 <sup>d</sup>	66/34
3	<u>n</u> -butyl bromide	THE	25°	22	50/50
4	(CH3)2C=CHCH2Br	hexane	25°	75	48/52
5	(CH <sub>2</sub> ) <sub>3</sub> I	THF	0°	97	50/50
6	OCH3 PhCH2Cl	hexane	<b>-</b> 78°	71	0/100
		hexane	25°	92	34/66
		hexane	70°	85	38/62
7	PhCH <sub>2</sub> Br	hexane	25°	73	50/50
8	PhCH2I	hexane	25°	43	61/39
		THF	25°	64	49/51
		DME	25°	59	36/64
9	adamantanone	THF	25°	29	22/78
10	<u>iso-valeraldehyde</u>	hexane	25°	80	30/70
		hexane	-78°	82	23/67

Table I: Reaction of 4 with Electrophiles

a. Isolated yield of isomer mixture. All new compounds possessed satisfactory analytical and spectral data.

b. Ratio determined by NMR.

c. Not isolated. Characterized by Deuterium NMR.

d. After esterification.

The application of this general method to the synthesis of a component of the <u>Ips</u> confusus pheromone is now described. The male bark beetle <u>Ips</u> confusus in ponderosa pine produces a pheromone attractive to both sexes but especially to the female. At least two components of the pheromone  $\chi$  and  $\frac{8}{2}$  are required to elicit a response in bioassay at a 1 µg level.<sup>9</sup> A convenient synthesis of one of these materials follows the general method outlined above.



Reaction of  $\frac{4}{2}$  with <u>iso</u>-valeraldehyde at room temperature gave 30% of the desired cyclobutene 9 which could be easily separated from the undesired isomer by chromatography on AgNO<sub>3</sub> impregnated Silica Gel. Compound 9 had the following spectral properties: IR: 3200-3700 cm<sup>-1.</sup> (broad). NMR: 0.9 & (6H-d, J = 6Hz), 3.88 & (1H-m), 5.85 & (1H, broad). High resolution molecular weight: 154.1343, (calculated for C<sub>10</sub>H<sub>18</sub>0: 154.1359). On heating at 150° for 4 hours 9 isomerized smoothly to 2-methyl-6-methylene-7-octen-4-ol 8 a component of the <u>Ips confusus</u> pheromone.

Further applications of this general route to the synthesis of isoprenoid natural products, as well as investigations of anions related to  $\frac{1}{2}$  will be the subject of subsequent reports.

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