

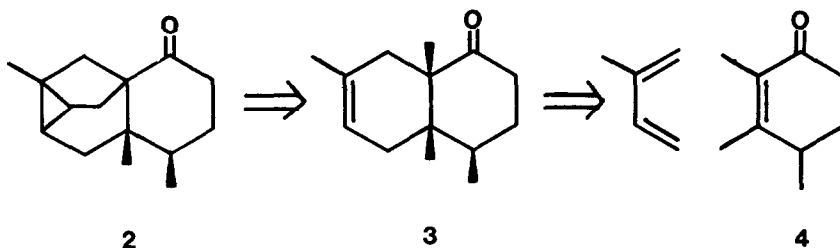
### A SHORT SYNTHESIS OF ISHWARONE

Robert M. Cory\*, Dominic M.T. Chan, Fred R. McLaren, Mary H. Rasmussen and Richard M. Renneboog

Department of Chemistry, University of Western Ontario, London, Ontario, N6A 5B7, Canada

2,3,4-Trimethyl-2-cyclohexenone can be converted to the corresponding isoprene Diels-Alder adduct by a sequence initiated by conjugate addition of lithium bis(3-methyl-3-butenyl)cuprate; the sesquiterpenoid ishwarone has been synthesized in two steps from the resulting octalone.

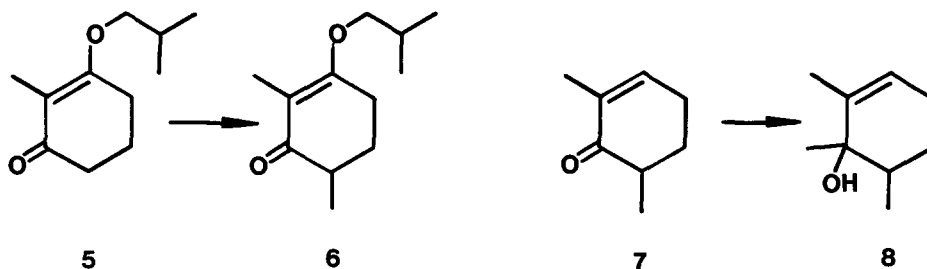
Annulation of cyclohexenones by Diels-Alder cycloaddition with conjugated dienes is a valuable method for the synthesis of functionalized decalins<sup>1</sup>, particularly<sup>2</sup> in view of the widespread occurrence of this structure in natural products. By analogy with our synthetic approach<sup>3</sup> to ishwarane (1) a logical precursor to ishwarone (2), which occurs with 1 in *Aristolochia indica*<sup>4</sup>, would be the octalone 3. The simplest dissection of 3 gives isoprene and 2,3,4-trimethyl-2-cyclohexenone (4), which would be converted to 3 by Diels-Alder reaction. Unfortun-



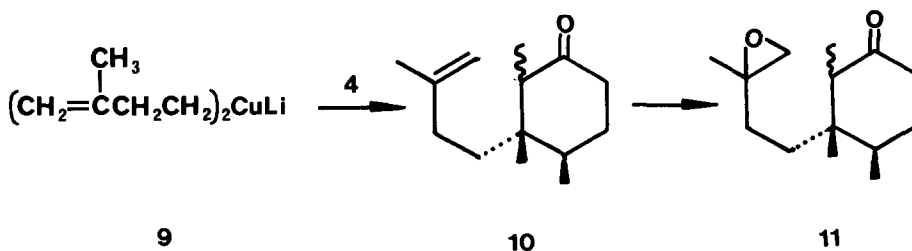
ately, this analysis is thwarted by two important limitations of the Diels-Alder synthesis: (1) the failure<sup>1</sup> of 2,3-disubstituted 2-cyclohexenones to undergo the reaction, apparently due to steric hindrance<sup>5</sup>, and (2) the regioselectivity with 2-substituted butadienes, which would be expected to give rise to the undesired regioisomer in this case<sup>6</sup>. Thus, complementary

methods are needed, and we describe herein a simple strategy which transforms 4 into 3 by forming one bond at a time, using an organocopper synthon for isoprene.

The requisite cyclohexenone (4)<sup>7</sup> was obtained by two different routes. Employing a sequence suggested by Stork and Danheiser<sup>8</sup>, the enol ether 5<sup>9</sup> was methylated (lithium diisopropylamide, THF; MeI), and the resulting dimethyl enol ether 6<sup>10</sup> was converted to 4 by treatment with methyllithium followed by acid hydrolysis. Alternatively, 2,6-dimethyl-2-cyclohexenone (7)<sup>11</sup>, obtained by chlorination-dehydrochlorination<sup>12</sup> of the corresponding saturated ketone, could be converted to 4 by the method of Dauben and Michno<sup>13</sup>. Addition of methyllithium to 7, followed by oxidation of the resulting allylic tertiary alcohol 8 with PCC (pyridinium chlorochromate) afforded 4 in 57% overall yield. Although this compares unfavorably with the 73% overall yield of 4 by the former method, it was more easily and economically carried out on a large scale.

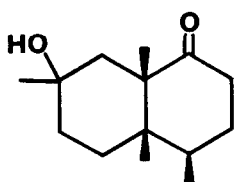


The Diels-Alder-equivalent sequence, which provides the key intermediate octalone 3 in four steps from 4, was performed as follows. To a solution of the isopentenyl cuprate 9<sup>14</sup> in diethyl ether at  $-45^\circ$  was added an ethereal solution of ketone 4. Upon aqueous work up, the conjugate adduct 10 was isolated in 60% yield. Although this product was shown to be a mixture of epimers by  $^1\text{H}$  n.m.r., trapping of the intermediate enolate with acetyl chloride gave a single enol acetate. Thus, the addition is stereoselective, as was expected from previous work<sup>15</sup>.

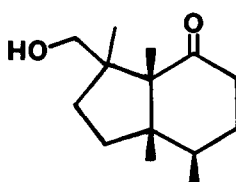


Quantitative epoxidation of enone 10 by *m*-chloroperbenzoic acid, uncomplicated by Baeyer-Villiger oxidation, was followed by base-catalyzed ( $\text{KOtBu}$ ,  $\text{tBuOH}$ ) cyclization of the resulting epoxides (11) to give alcohols 12 and 13. That the desired tertiary alcohol 12 predominated

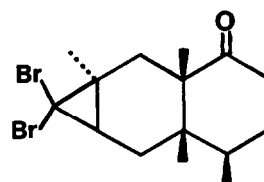
became evident after acid-catalyzed dehydration (50% aqueous  $H_2SO_4$ , cyclohexane) of the mixture, leaving the primary alcohol (13) unaffected (30% yield from 11) and providing a 40% yield (from 11) of octalone 3 (contaminated with 19% of the  $\Delta^7$ -isomer).<sup>19</sup> As the epoxide (11) is a mixture of up to four diastereomers, it is impossible at this time to speculate on the stereoelectronic factors controlling the cyclization, although the successful conversion of 3 to ishtarone, as well as spectral data, confirm the cis-ring junction in 3.



12



13



14

The synthesis was completed by addition of dibromocarbene ( $CHBr_2$ , 50% aqueous NaOH, tributylamine<sup>16</sup>) to 3, followed by treatment of the resulting dibromocyclopropane (14) with methyllithium in ether. As expected<sup>17</sup>, interference by the carbonyl group did not prevent the desired insertion, and chromatographic purification of the crude product gave racemic ishtarone (2), whose spectral properties matched those of an authentic sample of (+)-ishtarone from *A. indica*. By comparison with the previously reported synthesis<sup>18</sup> of ishtarone, which required some 22 steps from commercially available starting materials, our synthesis is much shorter (9 steps). However, there certainly is still room for improvement, and attempts to streamline this synthesis further are now in progress.<sup>20</sup>

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#### References and Notes

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- (5) We have confirmed that, in fact, cyclohexenone 4 gives no trace of Diels-Alder adduct with isoprene with or without Lewis acid catalysts even under forcing conditions.

- (6) This, however, is by no means certain: see reference 1 and H. -J. Liu and E.N.C. Browne, Can. J. Chem., 57, 377 (1979).
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- (19) As the olefinic group of the  $\Delta^7$ -octalone is too hindered to react with dibromocarbene, separation of the  $\Delta^6$  and  $\Delta^7$  isomers was not necessary for the purpose of this synthesis, but their separation could be accomplished by TLC.
- (20) A prime target for these further studies is the optimization of the overall yield for the conversion of the octalone (3) to ishwarone. The low yield of this transformation was disappointing, but no product resulting from attack on the carbonyl group could be isolated. We have so far been unsuccessful in employing our one-step "carbon atom insertion" method<sup>3</sup> in this synthesis.

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