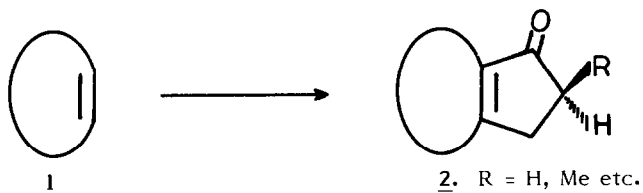


STRATEGY FOR CYCLOPENTENONE ANNULATION OF OLEFINS:  
A GENERAL PROTOCOL FOR BICYCLO [n.3.0] ENONE SYNTHESIS

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*Abstract:* Several bicyclic  $\alpha$ -chloro enones obtained through Greene annulation of cyclic olefins are shown to undergo efficient, two step, enone transposition via Luche reduction and aq. formic acid treatment. Application of this methodology to the formal synthesis of exaltone<sup>®</sup> and ( $\pm$ )-muscone is described.

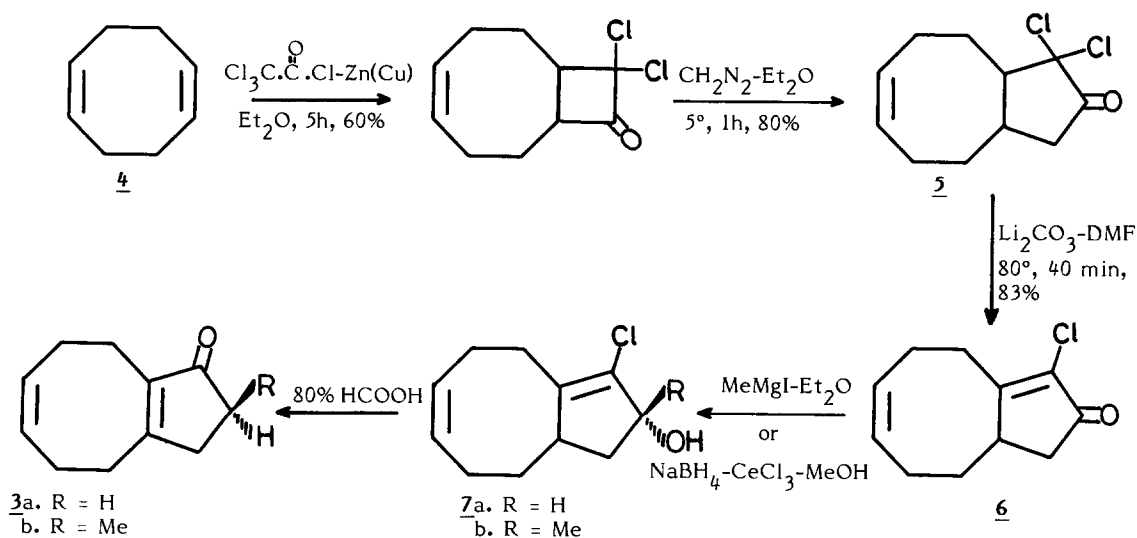
The increasing appearance of cyclopentane rings among natural products, as part of fused polycyclic frameworks, has stimulated development of many new strategies for annulating five membered rings.<sup>1</sup> In this context, a very desirable annulation sequence of considerable synthetic utility would be the direct conversion of an olefin 1 to the cyclopentenone 2.<sup>2-4</sup> The resulting cyclopentenone system 2 offers considerable latitude in terms of further synthetic manipulations, e.g., i) the endocyclic



enone double bond provides effective handle for the control of ring fusion stereochemistry as well as for the stereoselective attachment of appendages and functionalities via conjugate additions, ii) oxidative cleavage of the double bond offers a 3-carbon ring expansion sequence and iii) a wide choice in the introduction of the group R paves the way for further ring annulations. In this letter, we disclose a general methodology of significant preparative value for the realisation of 1  $\rightarrow$  2 transformation. The key step involved in this approach is the incorporation of a terminal enone transposition sequence into the versatile Greene cyclopentane annulation technology.<sup>5</sup>

The general synthetic route to bicyclo (n.3.0) enones delineated here had its origin in our quest for 3, a potent intermediate in the synthesis of 5-8 fused natural products, from readily available 1,5-cyclooctadiene 4. Scheme 1 summarises the successful attainment of 3 from 4 via dichloroketene addition and diazomethane ring expansion to 5, mono-dehydrochlorination to 6, Luche reduction<sup>6</sup> or Grignard addition to 7 and finally acid catalysed rearrangement in aq. formic acid to 3.<sup>7</sup> The satisfying outcome of the 4  $\rightarrow$  3 transformation led us to explore the generality of this methodology for

Scheme 1



cyclopentenone annulation and results with 5, 6, 7, 8 and 12 membered olefins are summarised in Table and Scheme 2. Particularly noteworthy is the formal conversion of commercially available trans, trans, cis-1,5,9-cyclododecatriene 8 to cyclopentadecanone (exaltone<sup>®</sup> 15) and ( $\pm$ )-muscone 16 as shown in Scheme 2.

Addition of dichloroketene to the triene 8 proceeded chemoselectively to yield mono-adduct 9 which was ring expanded with diazomethane to  $\alpha, \alpha'$ -dichlorocyclopentanone 10. Mono-dehydrochlorination of 10 furnished  $\alpha$ -chloroenone 11, the common intermediate for elaboration to exaltone<sup>®</sup> 15 and ( $\pm$ )-muscone 16. Reduction of 11 using Luche's recipe, formic acid rearrangement and selective catalytic hydrogenation of disubstituted double bonds yielded bicyclo [10.3.0] pentadec-1(12)-en-13-one 12.<sup>3e,8</sup> In a complimentary sequence, the chloro enone 11 was subjected to Grignard addition and the resulting tertiary alcohol was rearranged with aq. formic acid to give methyl substituted enone 13. Selective catalytic hydrogenation led to 14. Since, 12 and 14 have been converted<sup>3f,9</sup> to 15 and 16 in a variety of ways, our arrival at 12 and 14 signifies a formal synthesis of the latter. Further examples of this new cyclopentenone annulation methodology in natural products synthesis will be described in due course.

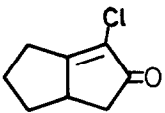
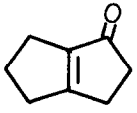
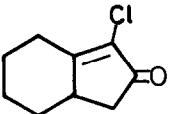
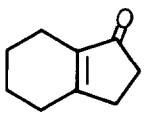
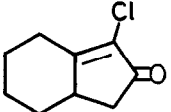
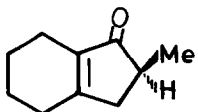
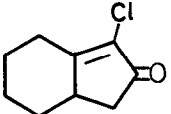
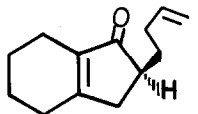
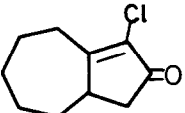
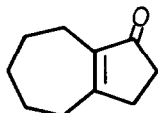
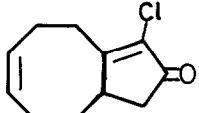
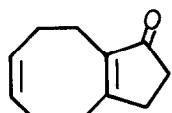
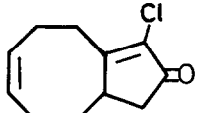
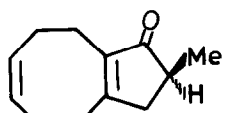
**Acknowledgement:** This research was supported by University Grants Commission, India in the form of a special assistance programme in Organic Chemistry.

**References and Notes:** 1(a) G. Mehta, J. Sci. Ind. Res. (India) 1978, 37, 256; (b) L.A. Paquette, Topics Current Chemistry, 1979, 79, 43.

2. Several methodologies for the cyclopentenone annulation of ketones have been recently described.<sup>3</sup> However, examples of direct olefin  $\rightarrow$  cyclopentenone conversion are extremely rare.<sup>4</sup>

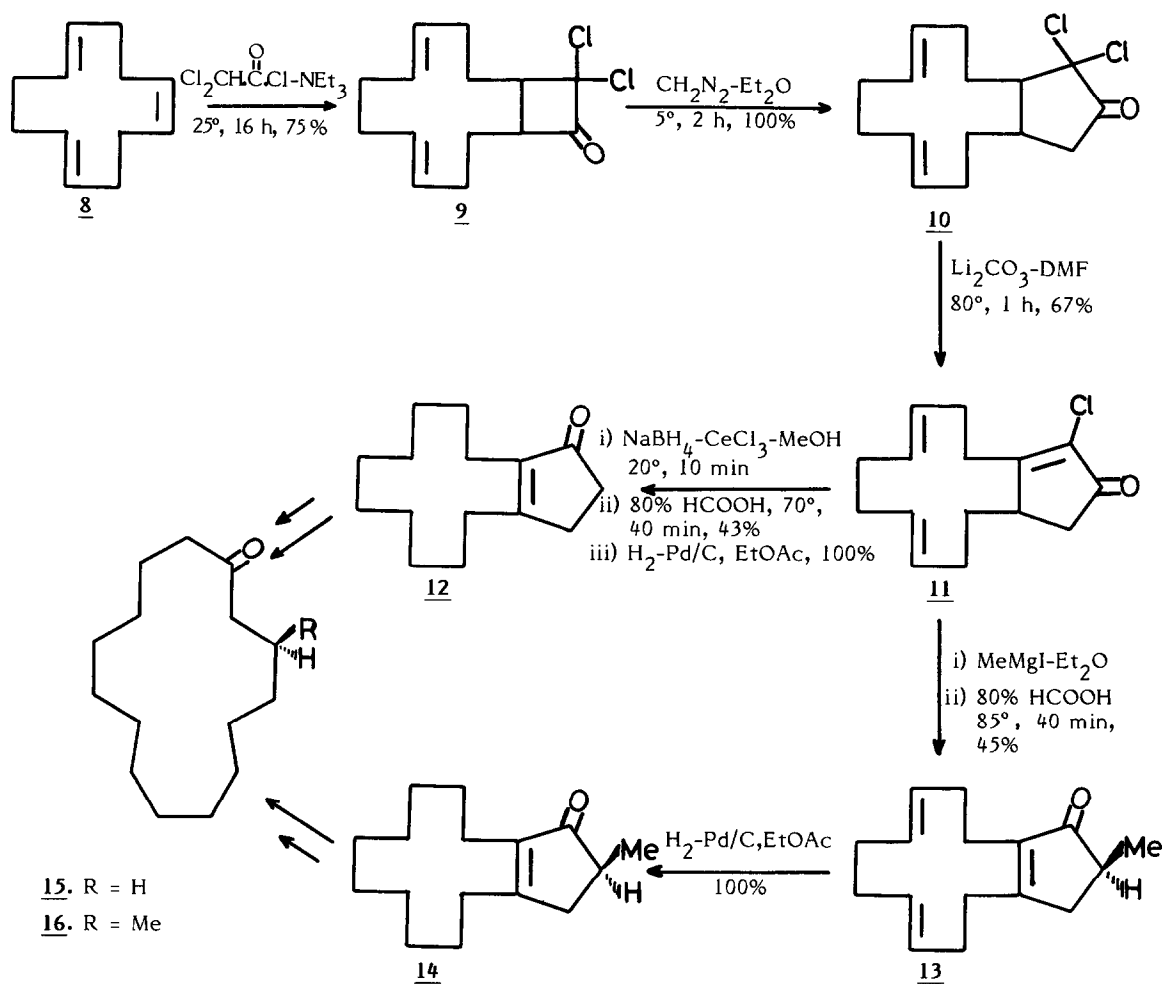
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Table

Substrate <sup>a</sup>	Reagents and Reaction Conditions	Product <sup>b</sup>	Yield
	d → [ ] <sup>c</sup> → e		35%
	d → [ ] <sup>c</sup> → e		65%
	f → [ ] <sup>c</sup> → e		50%
	g → [ ] <sup>c</sup> → e		55%
	d → [ ] <sup>c</sup> → e		45%
 <u>6</u>	d → [ ] <sup>c</sup> → e	 <u>3a</u>	40%
 <u>6</u>	f → [ ] <sup>c</sup> → e	 <u>3b</u>	60%

(a) All the  $\alpha$ -chloro enones were synthesised, along preceded lines,<sup>7</sup> from corresponding monoolefins in three steps via dichloroketene addition, diazomethane ring expansion and dehydrochlorination and were fully characterised on the basis of ir, <sup>1</sup>H nmr and <sup>13</sup>C nmr data. (b) Yields reported here are based on the pure, isolated compound and are unoptimized. (c) The intermediate hydroxy compounds were not purified. (d) NaBH<sub>4</sub>-CeCl<sub>3</sub>-MeOH, 20°, 10 min. (e) 80% HCOOH, 80-85°, 30-40 min. (f) MeMgI-Et<sub>2</sub>O, 25°, 6 h. (g) CH<sub>2</sub>=CH-CH<sub>2</sub>-CH<sub>2</sub>MgBr-THF, 25°, 6 h.

Scheme 2



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7. All new compounds reported here were fully characterized on the basis of their spectral data.
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