

A SIMPLE NEW GENERAL SYNTHESIS OF MACROCYCLIC KETONES:
A NEW ENTRY TO THE SYNTHESIS OF EXALTONE AND (±)-MUSCONE¹⁾

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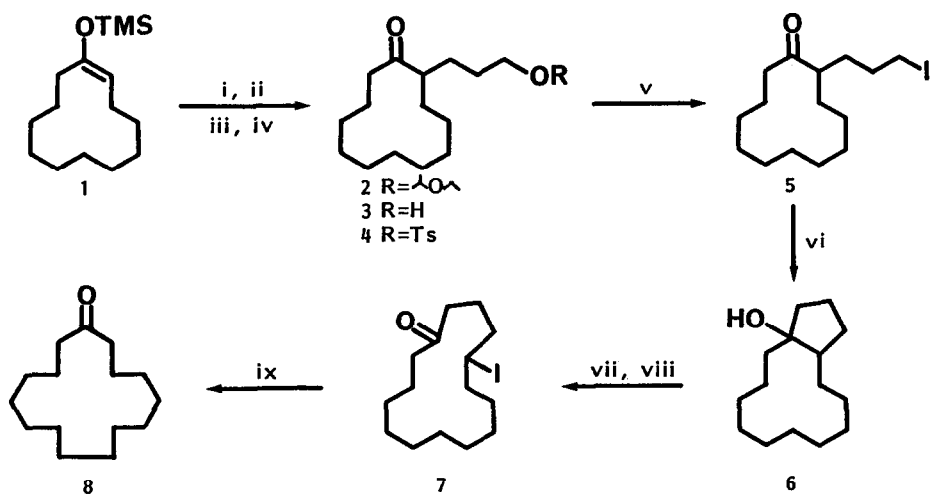
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Abstract: We describe an efficient new synthesis of 15-membered cyclic ketones, exaltone and (±)-muscone, based on a three-carbon annelation of cyclic ketones followed by the regioselective radical cleavage of the fused bond of the resulting bicyclic systems.

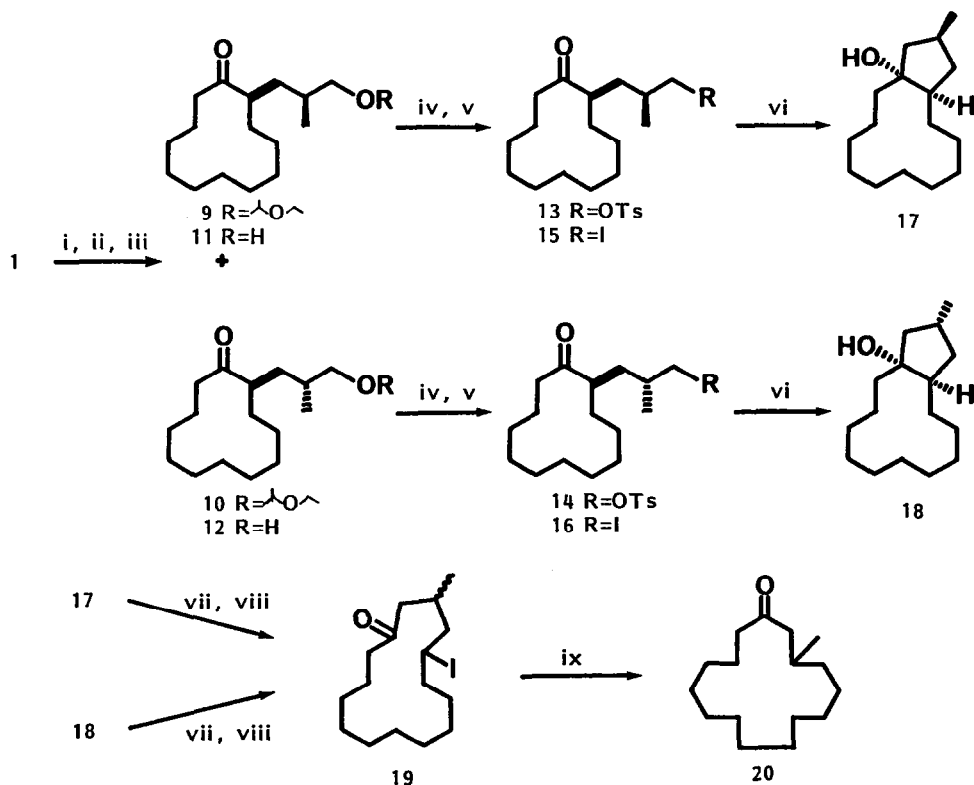
As part of our continuing program to explore the potential of the β-scission of alkoxyl radicals for organic synthesis, we have recently reported several new methods for the synthesis of cyclic ethers², cyclic sulphides³, cyclic amines³, furoquinolones⁴, furocoumarins⁵, medium-sized lactones⁶, benzohomotropones⁷, benzocyclooctenones⁸, and phthalides⁹, all of which use the regioselective β-scission of the C-C bonds of the alkoxyl radicals generated from cyclic alcohols, lactols and cyclobutenols.

We wish to report here a simple new general method for the synthesis of macrocyclic ketones based on a transformation of cyclic ketones into bicyclic alcohols by the three-carbon annelation followed by the regioselective radical cleavage of their fused bond. The potential usefulness of the method is demonstrated by an efficient new synthesis of a well-known natural 15-membered cyclic ketone, muscone (20), as well as its nor-derivative, exaltone (8); the method is outlined in Schemes 1 and 2. Although muscone has been synthesized by over thirty different methods¹⁰ since its first historical synthesis by Ruzicka and by Ziegler in 1934¹¹, the present new synthesis may perhaps be one of the simplest so far reported.

The reaction of lithium enolate¹² derived from trimethylsilyl enol ether 1 of a commercially available cyclododecanone with 1-iodo-3-(1'-ethoxyethoxy)propane⁶ gave an α-alkylcyclododecanone 2 in a 55% yield. The removal of the protecting group of 2 with pyridinium p-toluenesulphonate (PPTS) in THF and water at room temperature gave 2-(3'-hydroxypropyl)cyclododecanone (3)¹³. Hydroxyketone 3 gave the corresponding tosylate 4 by the standard method; this was then transformed into the corresponding iodide 5 by treatment with sodium iodide in acetone at 50°C. The yield of iodide 5 from 2 was 59%. Iodide 5 was then transformed into a single bicyclo[10.3.0.]pentadecan-1-ol 6 either by a Grignard reagent¹⁴ or with butyllithium in THF¹⁵. The procedure for its cyclization recently developed by Molander and Etter¹⁶ that uses samarium diiodide¹⁷ has been found to give the best yield of bicyclic alcohols. We then confirmed that the addition of HMPA¹⁸



i) MeLi-DME; ii) $\text{I}-\text{CH}_2\text{CH}_2\text{OEE}-\text{THF}-\text{HMPA}$; iii) PPTS-THF- H_2O ; iv) TsCl-pyridine; v) NaI-acetone; vi) $\text{Sml}_2-\text{THF}-\text{HMPA}$ or BuLi-THF or Mg-HgCl₂-THF; vii) HgO-I₂-benzene; viii) hv; ix) Bu₃SnH-AIBN-benzene-hv. Scheme 1.



i) MeLi-DME; ii) $\text{I}-\text{CH}_2\text{CH}_2\text{OEE}-\text{THF}-\text{HMPA}$; iii) PPTS-THF- H_2O ; iv) TsCl-pyridine; v) NaI-acetone; vi) $\text{Sml}_2-\text{THF}-\text{HMPA}$; vii) HgO-I₂-benzene; viii) hv; ix) Bu₃SnH-AIBN-benzene-hv. Scheme 2.

to THF, which was used by original investigators¹⁶, appreciably improved the yield of the bicyclic alcohol 6, m.p. 63-66°C (94%). The treatment of bicyclic alcohol 6 with mercury(II) oxide-iodine in benzene followed by irradiation with a 100-W high pressure Hg arc at room temperature gave 15-membered iodoketone 7 in a 96% yield. Iodoketone 7 was transformed smoothly into exaltone 8 by the irradiation of its benzene solution containing tributyltin hydride and AIBN in an 80% yield.

The potential usefulness of the present method was further demonstrated by the synthesis of (±)-muscone through a series of reactions analogous to those used to prepare exaltone as outlined in Scheme 2. The reaction of the lithium enolate of cyclododecanone with 2-methyl-3-(1'-ethoxyethoxy)propan-1-ol tosylate in THF-HMPA gave a mixture of the stereoisomers of 2-[2'-methyl-3'-(1"-ethoxyethoxy)propyl]cyclododecanones (9) and (10) in an 86% yield. The treatment of the mixture with PPTS in THF-water at room temperature afforded a mixture of the two stereoisomeric hydroxyketones 9 and 12; these were separable by means of preparative t.l.c. to cis hydroxyketone 11 (45%) and trans hydroxyketone 12 (36%), both in the form of oily material. The trans hydroxyketone 12 was transformed into the corresponding tosylate 14 (78%) and then iodide 16 (92%), as in the case of the exaltone synthesis. The treatment of iodide 16 with samarium diiodide in THF containing HMPA gave bicyclic alcohol 18 in a 90% yield. Its ring expansion to a mixture of cis and trans 15-membered cyclic ketones 19 carrying iodine was achieved by irradiation of the benzene solution containing mercury(II) oxide and iodine at 0°C (59%). A similar series of reactions was carried out on cis-hydroxyketone 11 to give tosylate 13 (77%), iodide 15 (87%), bicyclic alcohol 17 (75%), and finally 15-membered iodoketone 19 successively. The removal of the iodine from iodoketone 19, as described in the case of the exaltone synthesis gave (±)-muscone (20) in an 82% yield.¹⁹

The present method, which consists of a three-carbon annelation of cyclic ketones and the regioselective cleavage of the fused bond of the resulting bicyclic compounds, may be used repeatedly for the ring expansions of cyclic ketones as readily available starting materials.

A further investigation of the scope of this method and its application to the synthesis of other macrocyclic ketones is being pursued and will be reported in future publications.

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