

TOTAL SYNTHESIS OF THE SESQUITERPENE (\pm) β -CUPARENONE: USE OF
THREE-CARBON ANNULATION[†] IN SYNTHESIS

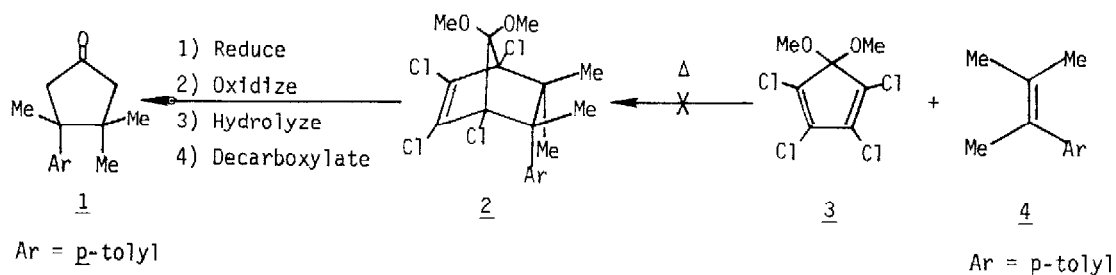
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Abstract: A total synthesis of β -cuparenone, which highlights the advantages and disadvantages of the three-carbon annulation process, is described.

The cyclopentane ring system is found in numerous naturally occurring products, including such diverse compounds as steroids, prostaglandins, and terpenes. We have recently published a new method for the formation of cyclopentanones from olefins, a process termed three-carbon annulation.² We now wish to describe the advantages and limitations of this annulation method and to report its use in the total synthesis of (\pm) β -cuparenone 1.

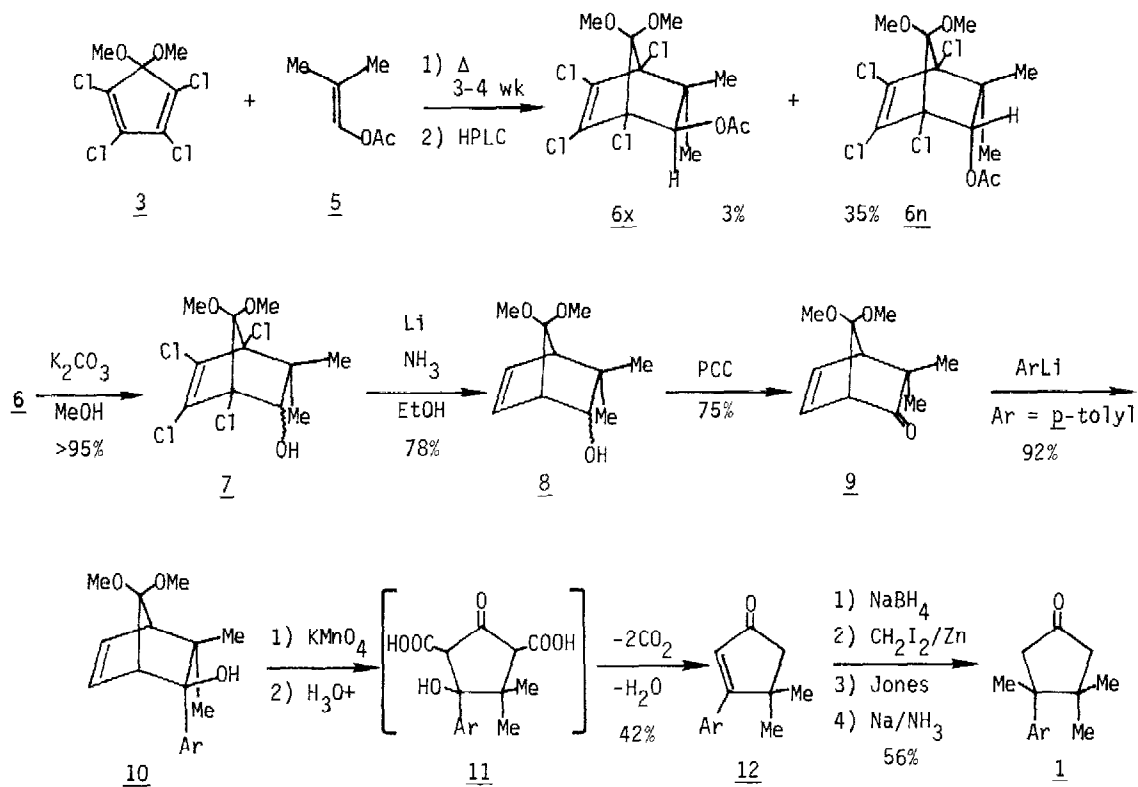
Isolated³ from the essential oil of the wood of "mayur pankhī," β -cuparenone 1 has been the target of several synthetic efforts. This interest is no doubt due to the two contiguous quaternary centers in the cyclopentanone ring, a reasonable synthetic challenge. To date five total syntheses have been described, each of which forms the cyclopentane system in a different way.⁴ A very simple approach to 1 would involve the three-carbon annulation of the tetrasubstituted olefin 4. This process must begin with the Diels-Alder reaction of the diene 3 with the olefin 4 to afford the adduct 2, which would then be transformed into 1 by the usual four-step procedure. However, under all conditions tried (e.g., heating 3 and 4 to > 200°C in a sealed tube for several days)



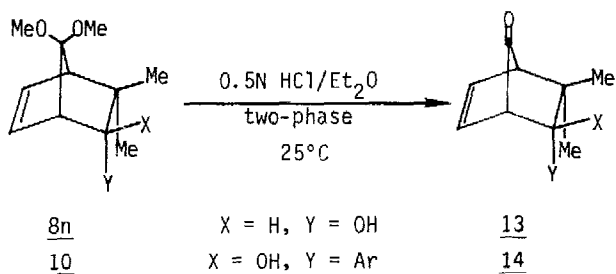
the initial Diels-Alder reaction could not be forced to occur. This is a general problem with the use of diene 3, namely that unactivated tetrasubstituted olefins react very sluggishly if at all with 3 in cycloaddition reactions, presumably due to steric hindrance.⁵

To further test the reactivity of 3 with highly substituted olefins and to thereby prepare intermediates for the synthesis of 1, the reaction of 3 with isobutenyl acetate 5 was conducted. (Scheme). Refluxing a solution of 3 and catalytic hydroquinone in excess 5 as solvent under N₂ for 3-4 weeks gave, after workup and chromatography (Prep HPLC), the two stereoisomeric adducts 6x (oil) and 6n (mp 58-9°C) in yields of 3% and 35%, respectively.⁶ The conversion of each isomer to the symmetrical ketone 9 was carried out but will be described in detail only for the endo series. Basic hydrolysis of the acetate 6n furnished the alcohol 7n (mp 139-41°C) in > 95% yield.⁶ Reduction of the tetrachloro alcohol 7n was accomplished under dissolving metal conditions (Li, NH₃, EtOH, -78°C)⁷ to afford the dechlorinated alcohol 8n in a purified yield of 78%.⁶ Oxidation of 8n by any of several methods (Jones, Collins, PCC) gave the ketone 9 in good yield (e.g., 75% for PCC oxidation).⁸ The same sequence of reactions were also used to convert 6x to the ketone 9 in comparable yields. Reaction of 9 with p-tolyllithium (formed from p-bromotoluene and n-butyllithium at -78°C) at 25°C for 1 hr furnished after chromatography a 92% yield of the alcohol 10 (mp 126-127°C).⁶ As observed previously,⁹ the dimethyl ketal blocks addition from the exo face so that only endo addition results. Oxidation of the olefin was accomplished with a buffered permanganate solution followed by treatment with aqueous acid to produce the desired enone 12¹⁰ in 42% yield. This compound is presumably formed by double decarboxylation and dehydration of the intermediate 11. The production of 12 in 7.8% overall yield from 3 completes the total synthesis of (±)β-cuparenone since the conversion of 12 into 1 has been carried out by Maldonado^{4c} in four steps in 56% overall yield.¹¹ Thus 1 is available from 3 via 10 steps in 4.3% overall yield.

We have also observed a very interesting steric acceleration of ketal hydrolysis in these systems. Norborn-2-en-7-one ketals are generally very resistant to acidic hydrolysis, presumably due to the ring strain involved in changing the hybridization of C-7 from sp³ (idealized angle of 109.5°) to sp² (120°). However, this is not the case for ketals 8n and 10, which are hydrolyzed to the corresponding ketones, 13 and 14,⁶ in high yield under very mild conditions, namely, two-phase 0.5N HCl and Et₂O at 25°C for 2 h (for 8n) or overnight (for 10). We ascribe this greatly accelerated rate of hydrolysis to steric acceleration, namely the exo-methyl group experiences a very large steric interaction with the syn-methoxy group which is eliminated as the ketal is hydrolyzed to ketone.



SCHEME



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+ There is still a discrepancy in the spelling of this term. Both variations would appear to be correct since both are derived from Latin roots meaning "ring," annulation from annulus and annelation from anellus. We prefer annulation since this spelling appears in most common English dictionaries.

REFERENCES AND NOTES

1. Camille and Henry Dreyfus Teacher-Scholar, 1978-83; Fellow of the Alfred P. Sloan Foundation, 1979-81
2. M. E. Jung and J. P. Hudspeth, J. Am. Chem. Soc., 99, 5508 (1977).
3. G. L. Chetty and S. Dev, Tetrahedron Lett., 73 (1964).
4. a) P. T. Lansbury and F. R. Hilfiker, J.C.S. Chem. Comm., 619 (1969); b) P. Leriverend, Bull. Soc. Chim. Fr., 3498 (1973); c) R. B. Mare and G. S. Krishna Rao, J. Chem. Soc. Perkin Trans. I, 1806 (1973); d) A. Casares and L. A. Maldonado, Syn. Commun., 6, 11 (1976); e) L. A. Paquette, W. E. Fristad, D. S. Dime, and T. R. Bailey, J. Org. Chem., 45, 3017 (1980).
5. The steric hindrance which greatly inhibits this intermolecular cycloaddition can be significantly diminished by causing the Diels-Alder reaction to be intramolecular, i.e., by having the diene and olefin as part of the same molecule. Some success has been already achieved in this regard and further studies are currently in progress. M. E. Jung and L. Light, unpublished results.
6. All new compounds exhibited spectral data (200 MHz ^1H NMR, ^{13}C NMR, IR, MS) in complete accord with their structure. In addition, all compounds gave correct elemental analyses or high resolution mass spectra.
7. Other alkali metals could be employed but lithium gave the best results in this case. We have found that it is preferable to work up this reduction as rapidly as possible since this technique gives significantly higher yields than the normal workup. This reduction (and that of the doubly desmethyl analogue²) is accompanied by the production of a bright green light as the alkali metal is added to the solution of the chloro compound in ammonia. We have no explanation to account for this chemiluminescence.
8. E. J. Corey and J. W. Suggs, Tetrahedron Lett., 2647 (1975).
9. M. E. Jung and J. P. Hudspeth, J. Am. Chem. Soc., 100, 4309 (1978).
10. W. Parker, R. Ramage, and R. A. Raphael, J. Chem. Soc., 1558 (1962).
11. We thank Dr. Maldonado for generously providing an authentic sample of the enone, which was shown to be identical to 12 (NMR, IR).

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