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EFFICIENT REGIOSELECTIVE SYNTHESES OF α AND β CUPARENONES. A NEW APPROACH FOR THE CONSTRUCTION OF THE CYCLOPENTANE RING

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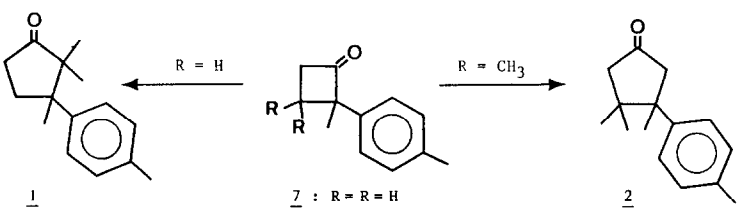
This paper discloses the regioselective synthesis of the cyclopentane ring from a carbonyl compound via two ring expension reactions.

Since their characterization by Enzel and Erdtman [1a] compounds possessing the cuparenone skeleton have been the subject of constant synthetic interest.[1,2] The synthetic challenge is associated with the steric congestion due to the presence of two contiguous quaternary centers in the cyclopentane ring.

We wish to report here a short and efficient regioselective route to α-and β-cuparenones 1 and 2, two natural compounds isolated from the essential oil of thuja orientalis [1b] and which are themselves the precursors of certain members of the series.

Key intermediates in these syntheses are the cyclobutanones 7 and 11. Transformation of the cyclobutanone 7 into α-cuparenone 1 requires formally the insertion of an isopropylidene moiety in between the carbonyl group and the disubstituted α carbon (Scheme 1). A similar insertion of a methylene group would allow the transformation of the cyclobutanone 11 into α-cuparenone 2 (scheme 1).

SCHEME 1

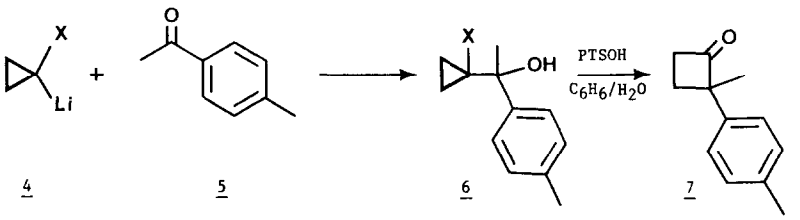


1 7 : R = R = H 11 : R = R = CH_3 2

Both cyclobutanones 7 and 11 were prepared in high yield from p-methylacetophenone 5 and 1-lithio-1-heterosubstituted cyclopropanes. The cyclopentane ring is therefore constructed by two consecutive ring enlargement reactions.

We have synthetized 2-methyl-2-p-tolylcyclobutanone 7 from β-hydroxycyclopropylselenides or sulfides, themselves prepared in high yields from 1-lithio-1-methylselenocyclopropane [3] 4a, its phenylseleno analogue [3a] 4b, and 1-lithio-1-phenylthiocyclopropane [4] 4c (X = SC_6H_5). The synthesis of the 2-methyl-2-p-tolylcyclobutanone 7 was achieved from the β-hydroxycyclopropylselenides or sulfide 6 according to published procedures (Scheme 2) [3b,4].

SCHEME 2



4 5 6 7

a	$X = SeCH_3$	ether, -78°	85	80°, 12h	80
b	$X = SeC_6H_5$	ether, -78°	81	80°, 12h	70
c	$X = SC_6H_5$	THF, -78°	88	40°, 12h	50

These results require some comments :

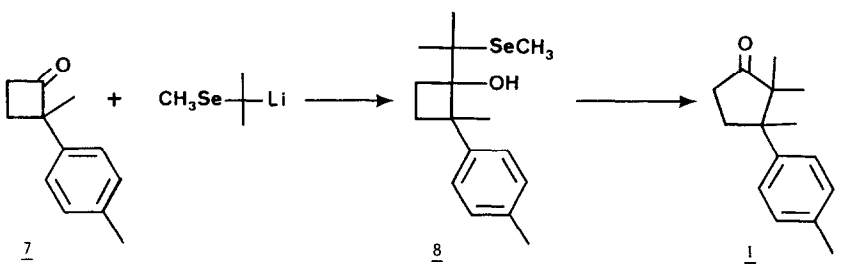
) 1-lithio 1-seleno cyclopropanes 4a and 4b and their thio analogues 4c behave similarly towards p-methylacetophenone and consequently possess a closely related nucleophilicity ; [5]

) the order of reactivity of the β-hydroxycyclopropanes 6 in acidic media is clearly in favor of the thiophenyl derivative, which completely disappears after 2 hours at 40°. However, the yield of rearranged ketone is much lower in that specific case ;

) the behaviour of the phenylseleno derivative is unusual, since analogues missing the aryl group α to the hydroxyl function (substituted by a hydrogen or an alkyl group) remain unchanged under the experimental conditions reported here. [6]

α-Cuparenone 1 was synthetized in two steps from that stage (Scheme 3).

SCHEME 3



7 8 1

ether, -78°	66	$AgBF_4/Al_2O_3/CH_2Cl_2$	69
THF, -78°	0	TlOEt/$CHCl_3$	57
		CH_3OSO_2F/ether	82

These include a) the formation of the β-hydroxyselenide 8 (as a 5/1 mixture of stereoisomers) from the particularly hindered and enolisable cyclobutanone 7 and the bulky 2-lithio-2-methylselenopropane . This was achieved in 66% yield if ether was used as the solvent; b) the rearrangement of the β-hydroxyselenide 8 to the cyclopentanone 1, which occurs on its reaction with thallium ethoxide in chloroform [6] (57%, 20°, 21h), or with silver tetrafluoroborate on alumina in methylene dichloride [7] (69%, 20°, 3hr). The cyclopentanone 1 was also obtained in particularly high yield (82%) on reaction of this β-hydroxyselenide 8 with methyl fluorosulfonate (ether/20°, 1h).

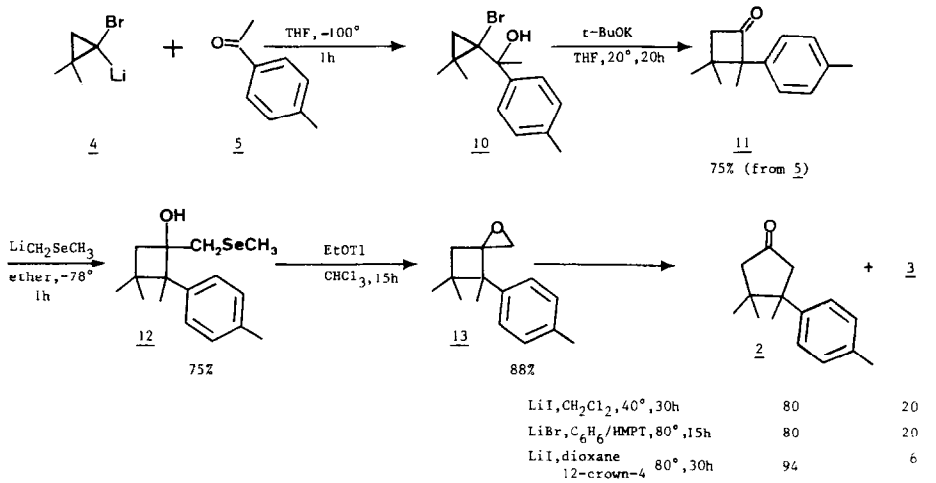
The last reaction is not general but was observed [8] when particularly hindered β-hydroxyselenides are reacted with an alkylating agent.

The synthesis of β-cuparenone 2 requires a somewhat different synthetic strategy, as β-hydroxyselenides in which the carbon atom bearing the selenium atom possesses one or two hydrogens do not lead to the ring enlargement reaction but rather to the epoxide.[6] We therefore decided to synthesize the epoxide 13 and to rearrange it later to the desired cyclopentanone 2 with lithium iodide [2h] or bromide.[9]

The cyclobutanone 2 was formed in two steps from 1,1-dibromo 2,2-dimethylcyclopropane and p-methylacetophenone using a set of reactions already disclosed by Nozaki [10] and Seebach.[11] Surprisingly, however, the cyclobutanone 11 is already present in the basic media after reaction of 10 with potassium t-butoxide and does not arise from an acidic rearrangement of the intermediate oxaspiropentane.[10,11]

The β-hydroxyselenide 12, obtained in 75% yield from ' methylselenomethyllithium and 11 in ether, does not lead to the cyclopentanone 2 on reaction with thallium ethoxide in chloroform, but, as expected [6] to the epoxide 13 (isolated in 88% yield). Treatment of that epoxide with lithium iodide in methylene dichloride [2h] (40°, 24h) or lithium bromide in benzene/HMPT [9] (80°, 15h) unexpectingly produced a mixture of α-cuparenone 2 and its regioisomer 3 in a 80/20 ratio. After several unsuccessful attemps, better selectivity (94/6) was obtained on performing the isomerization with lithium iodide in dioxan in the presence of 1 equivalent of 12-crown-4, Under these conditions, 2 is almost quantitatively isolated (95%) after TLC purification (pentane/ether 9/1 ; rf (2) : 0.25 ; rf (3) : 0.35).

SCHEME 4

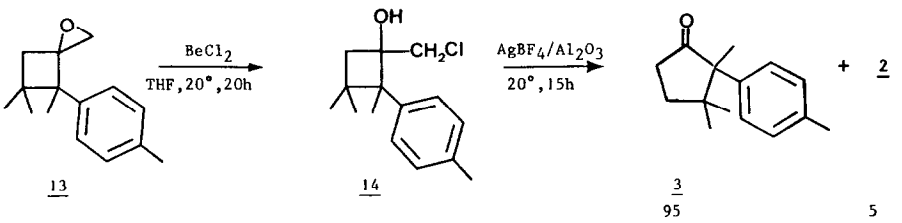


Finally, in the course of that study, we were also able to regioselectively (95/5) prepare the unwanted cyclopentanone 3 (75% overall from 13) by reaction of the epoxide 13 with beryllium chloride in ether followed by treatment of the resulting chlorohydrin 14 with silver tetrafluoroborate [12] (Scheme 5).

This paper not only discloses new reactions for the regioselective syntheses of two natural products but also provides a new regioselective route to cyclopentanones, a structure found

in several biologically active molecules.

SCHEME 5



13 14 3 (95) 5

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REFERENCES

1. a) C. Enzell, H. Erdtman , Tetrahedron, 4, 361 (1958).
   b) G.L. Chetty, S. Dev, Tet. Lett., 73 (1964) ; absolute configuration : T. Irie, T. Suzuki, S. Itô, E. Kurosawa, Tet. Lett., 3187 (1967).

2. a) W. Parker, R. Ramage, R.A. Raphael, J. Chem. Soc., 1558 (1962).
   b) P. De Mayo, R. Suau, J. Chem. Soc., Perkin I, 2559 (1974).
   c) C.W. Bird, Y.C. Yeong, Synthesis, 27 (1974).
   d) P. Leriverend, Bull. Soc. Chim. Fr., 3498 (1973).
   e) E. Wenkert, B.L. Buckwalter, A.A. Craveiro, E.L. Sanchez, S.S. Sathe, J. Amer. Chem. Soc., 100, 1267 (1978).
   f) Y. Hayakawa, F. Shimizu, R. Noyori, Tet. Lett., 993 (1978).
   g) H. Sakurai, A. Shirahata, A. Hosomi, Angew. Chem. Int. Ed. Engl., 18, 163 (1979).
   h) M.-L. Leriverend, P. Leriverend, C.R. Acad. Sci. Paris, Série C, 280, 791 (1975).
   i) P.T. Lansbury, F.R. Hilfiker, J. Chem. Soc.,Chem. Comm., 619 (1969).
   j) R.B. Mane, G.S. Krishna Rao, J. Chem. Soc., Perkin I, 1806 (1973).
   k) A. Casares, L.A. Maldonado, Syn. Comm., 6, 11 (1976).
   l) M.E. Jung, C.D. Radcliffe, Tet. Lett., 4397 (1980).
   m) L.A. Paquette, W.E. Fristad, D.S. Dime, T.R. Bailey, J. Org. Chem., 45, 3017 (1980).
   n) Y. Inouye, S. Inomata, Y. Ishihara, H. Kakisawa, Bull. Soc. Chem. Jpn., 55, 208 (1982).

3. a) S. Halazy, J. Lucchetti, A. Krief, Tet. Lett., 3971 (1978).
   b) S. Halazy, A. Krief, J. Chem. Soc., Chem. Comm., 1136 (1979).

4. B.M. Trost, D. Keeley, M.J. Bogdanowicz, J. Amer. Chem. Soc., 95, 3068 (1972) ; B.M. Trost, D.E. Keeley, H.C. Arndt, J.H. Rigby, M.J. Bogdanowicz, J. Amer. Chem. Soc., 99, 3080 (1977).

5. Surprisingly [3a], the nucleophilicity of all these species 4 towards hindered or enolisable carbonyl compounds in THF is identical as the result of competitive experiments. However, higher yields of β-hydroxyselenides are often obtained if THF is replaced by ether.[3b] Details will be presented in the full paper.

6. Unpublished results from our laboratory.

7. D. Labar, J.L. Laboureur, A. Krief, Tet. Lett., 983 (1982).

8. D. Labar, A. Krief, J. Chem. Soc., Chem. Comm., 564 (1982).

9. B.M. Trost, L.H. Latimer, J. Org. Chem., 43, 1031 (1978).

10. T. Hiyama, S. Takehara, K. Kitatani, H. Nozaki, Tet. Lett., 3295 (1974).

11. M. Braun, R. Dammann, D. Seebach, Chem. Ber., 2368 (1975).

12. The scope and limitations of this reaction are under study in our laboratory.

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