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THE INTRAMOLECULAR MICHAEL ADDITION AS A ROUTE TO ANGULARLY SUBSTITUTED CIS-HYDRINDANES

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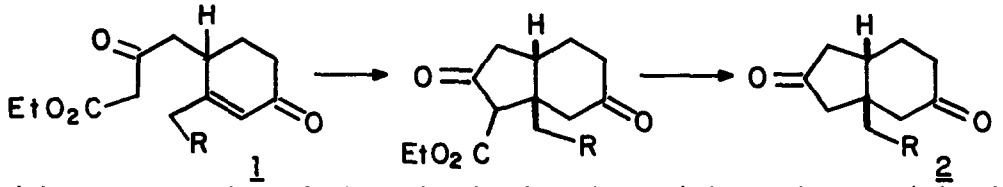
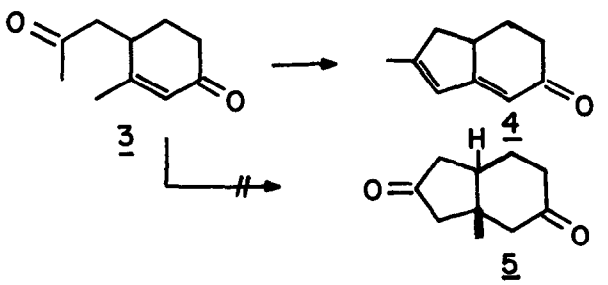
Cis-hydrindane derivatives carrying an angular substituent and suitably functionalized are of interest, inter alia, for the construction of natural products such as the gibberellic acids.

We now show that the intramolecular Michael addition of 3,4-disubstituted cyclohexenones of type 1, readily available by a previously reported synthesis,[1] is a useful stereospecific route to angularly substituted cis-hydrindan-2,5-diones 2.

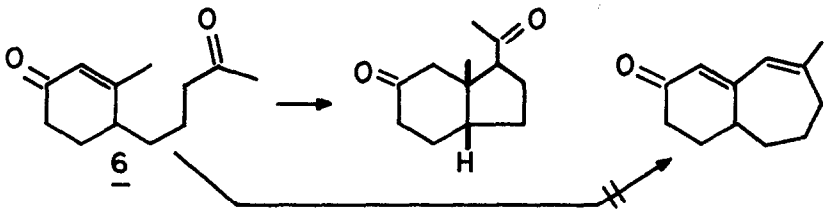


With systems such as 1 there is the formal possibilty of competition between Michael addition and vinylogous aldol cyclization. In fact, earlier studies[2] had shown that the related methyl ketone 3 undergoes only the latter reaction: treatment of 4-(2-oxopropyl)-3-methyl-2-cyclohexenone[3] with 0.2 N potassium tert. butoxide in tert. butanol (5° → room temp., 30 min.) gave, in over 75% yield, the product of aldol cyclization, the dienone 4 (homogeneous



by vpc on SE30: kugelrohr bp 102-107° (5mm); λ_{max}^{EtOH} 289 nm, ε 18,700; ir (film) 6.00, 6.15, 6.22 μ; δ ($CDCl_3$) 1.99, bs, 3H; 6.08, s 1H; 5.65 (s, 1H); 2,4-dinitrophenylhydrazone mp 204-205°). No evidence for any Michael adduct (e.g. 5) could be obtained under a variety of other basic conditions. Heating with acetic acid p-toluenesulfonic acid gave recovered 3, in addition to some decomposition.

It should be noted that in the particular case of 3, either reaction mode (Michael or aldol) would lead to the same size ring. The situation is thus different from that of a previous case[4] shown in 6 in which the competition between intramolecular Michael and aldol reaction is resolved in favor of the former.



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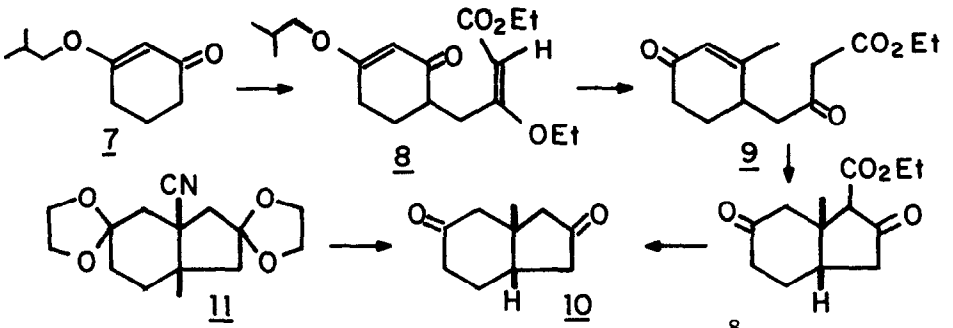
The failure of 3 to cyclize in the desired manner led us to examine the related β-keto ester 1, R = H. The previously mentioned cyclohexenone synthesis is fortunately easily adapted to produce the particular array of functionality present in molecules such as 1.

Reaction of the kinetic lithium enolate of the isobutyl enol ether of dihydroresorcinol, 7, with ethyl-3-ethoxy-4-bromocrotonate[5] gave the alkylated product 8 as a waxy solid, bp 190-200° (0.5mm), in 73% yield. Addition of methyl lithium, followed by acid hydrolysis (35% aqueous perchloric acid - methylene chloride 2 hr., room temp.), neutralization (sodium bicarbonate), and silica gel chromatography (3:7 tetrahydrofuran: hexane) gave, in 54% yield from 8, the required β-ketoester 9 (1, R = H) (NMR: δ 1.30, t, 3H J = 7 Hz; 1.65 - 2.75, mb, 5H; 1.95, s, 3H; 2.65 - 3.10, bs, 2H; 3.50, s, 2H; 4.25, q, 2H, J = 7 Hz; 5.90, s, 1H).

Cyclization of 9 (2.5% potassium carbonate in ethanol, 40 hr.[6], room temp.), followed by hydrolysis and decarboxylation (hot aqueous hydrochloric acid), gave the Michael addition-derived product, cis 3a-methyl-2,5-hydrindandione 10 (45% yield, bp 115-120° (0.2mm); ir: 5.72, 5.82 μ; NMR: δ 1.25 3 H, s ; m/e 166). The structure was confirmed by comparison with the di-

one prepared from the previously reported[7] cyanodiketal 11 (via Wolff-Kishner reduction of the derived aldehyde.)



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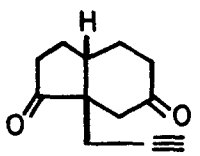
The method described here should be quite general.[8] We have used it successfully[9] in a sequence leading to the hydrindandione 12. The latter is a precursor of 13,[10] an important intermediate for possible further elaboration to gibberellic acid.



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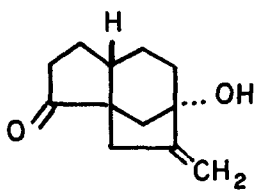

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Acknowledgement:

We thank the National Institutes of Health and the National Science Foundation for their support of this work.

References and Notes

1. G. Stork and R.L. Danheiser, J. Org. Chem., 38, 1775 (1973).

2. Michael Marx, Ph.D. thesis, Columbia University, 1966. Dissertation Abstracts 27, 42-66B (1967). C.A., 67, 116605 (1967).

3. Synthesized (ref.2) from the 3-dioxolane of 7-acetyl bicyclo 4,1,0 heptan-3-one by treatment with acid.

4. W.S. Johnson, S. Shulman, K.L. Williamson and R. Pappo, J. Org. Chem., 27, 2015 (1962); K. Yamada, M. Aratani, Y. Hayakawa, H. Nakamura, H. Nagase and Y. Hirata, J. Org. Chem., 36, 3653 (1971); see also D.H.R.

Barton, A.S. Campos-Neves, and A.I. Scott, J. Chem. Soc., 2698 (1957).

5. E.B. Reid and W.R. Ruby, J. Amer. Chem. Soc., 73, 1054 (1951).

6. The hindering effect of the β-methyl in this system is quite pronounced. Thus, the β-unsubstituted enone (prepared by sodium borohydride reduction of 8, followed by dilute acid) cyclized in one hour under the same conditions.

7. G. Stork, J.O. Gardner, R.K. Boeckman, Jr., and K.A. Parker, J. Amer. Chem. Soc., 95, 2014 (1973).

8. A related construction method has been used (A.J. Birch and J.S. Hill, J. Chem. Soc., 2324 (1966) in the decalin series. This earlier work, which used a β-diketone rather than a β-ketoester system to favor the Michael addition, suffered however from two drawbacks: low yield (∿19%), and inability to remove the activating acetyl group form the cyclized product. The β-ketoester does not suffer from these difficulties and we have, indeed, used it successfully to synthesize the decalin analog of 10.

9. This substance was first made in This Laboratory by R.K. Boeckman, Jr., starting from 11, but the construction of the latter (ref. 7), while quite stereoselective, is not stereospecific. The synthesis by the internal Michael process outlined in this paper (unpublished work in This Laboratory by D.F. Taber, W.C. Still and J. Singh) is entirely stereospecific.

10. By the method of G. Stork, S. Malhotra, H. Thompson and M. Uchibayashi J. Amer. Chem. Soc., 87, 1148 (1965). Unpublished work from This Laboratory.