Functionalized Five-membered Rings from Acyclic Unsaturated β-Ketoester Systems

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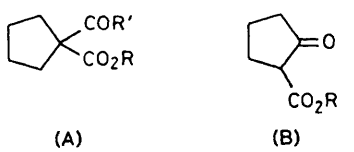
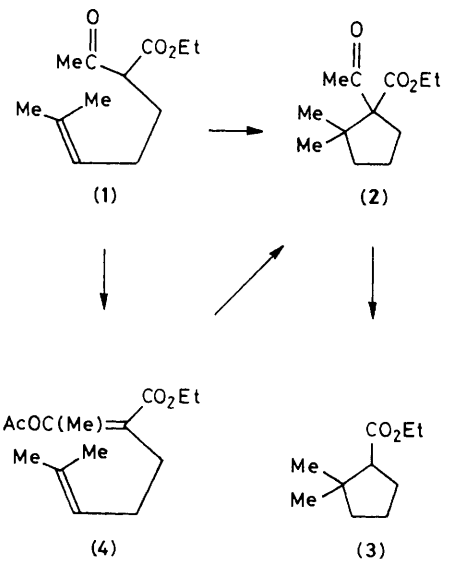
In Lewis acid-promoted cyclizations, both the ketoester (**1**) and its enol acetate (**4**) generate the cyclopentane (**2**), while the ketoester (**5**) under similar conditions does not form the carbobicycle (**6**) but is converted into the heterocycle (**7**), *via* the monocyclic ketoester (**8**).

Cyclopentanes with substituents that provide varied functional-group potential are of value in the synthesis of different substituted steroid- or tetracyclic triterpenoid-D-rings. Consequently, we assessed the cyclization of certain simple β-ketoester systems, each of which incorporates a suitably sited olefinic bond. Two general cases were investigated,[1] namely, routes to cyclopentanes with the ketone group derived from a β-ketoester, (A) attached to the ring, and (B) constituting part of the ring.

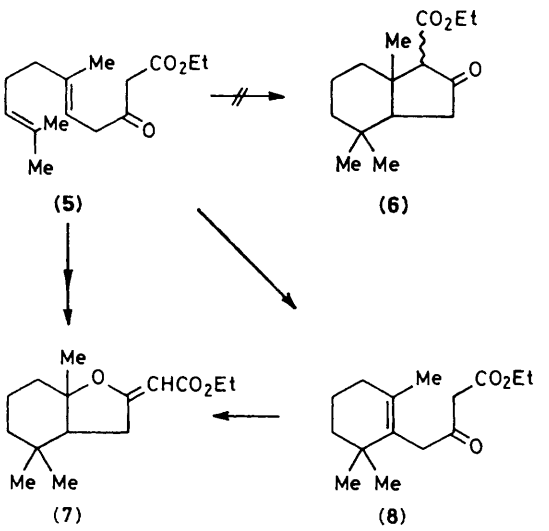
In a good example of a route to category A compounds, the acetoacetate (**1**)[2] was treated with $SnCl_4$ in dry CH_2Cl_2 (0 °C to room temp., 24 h), to give (73% g.l.c., 51% isolated yield) the *vic*-tetrasubstituted ketoester (**2**): n.m.r. (100 MHz, $CDCl_3$) δ 1.05 (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 1.29 (t, *J* 7.1 Hz, 3H, $CO_2CH_2CH_3$), 2.14 (s, 3H, CH_3CO), and 4.21 (q, *J* 7.1 Hz, 2H, $CO_2CH_2CH_3$). Structure (**2**) was confirmed by its conversion (KOH; 18-crown-6, refluxing EtOH–C_6H_6)[3] into ethyl 2,2-dimethylcyclopentanecarboxylate (**3**). Alternatively, the enol acetate (**4**) [prepared[4] from (**1**) by treatment with AcCl–Et_3N in hexamethylphosphoric triamide–tetrahydrofuran, at room temperature] was cyclized under conditions



(A) (B)



(1) (2) (4) (3)



similar to those used for (**1**), giving an improved (93% g.l.c., 70% isolated) yield of the same product (**2**) that had been obtained directly from (**1**). This reaction appears to be the first example of a 1,3-dicarbonyl enol acetate-terminated olefin cyclization.

With regard to the second case (B), the possible conversion of the β-ketoester (**5**) into the hydrindanone carboxylic ester (**6**) was examined. The starting material (**5**) was prepared (86%) from homogeranic acid[5] by the method of Wierenga and Skulnick.[6] Under conditions similar to those employed in case A, the ketoester (**5**) was transformed (49%) to a new substance, which exhibited none of the properties expected for structure (**6**). The product gave a negative $FeCl_3$ colour test, and the following n.m.r. data: (100 MHz, $CDCl_3$) δ 0.96 and 1.03 [s, 6H, $C(CH_3)_2$], 1.25 (t, *J* 7.14 Hz, 3H, $CO_2CH_2CH_3$), 1.48 (s, 3H, CCH_3), 2.8 and 3.4 (m, 2H, $CH_2C{=}C$), 5.14 (q, *J* 7.12 Hz, 2H, $CO_2CH_2CH_3$), and 5.2 (m, 1 H, =CH). This suggested that the product was the heterocycle (**7**), whose stereochemistry is not yet known.

After exposure to the above cyclization conditions for only one hour or on treatment with $BF_3.Et_2O$ in CH_2Cl_2 at room temperature for 24 h, the ketoester (**5**) did not give (**7**), but instead a different product, allotted structure (**8**) on the basis of its n.m.r. properties: (100 MHz, $CDCl_3$) δ 0.92 [s, 6H, $C(CH_3)_2$], 1.28 (t, *J* 7.14, 3H, $CO_2CH_2CH_3$), 1.58 (s, 3H, $=CCH_3$), 3.28 [s, 2H, $=CCH_2C(O)$–], 3.46 (s, 2H, CH_2CO_2), and 4.21 (q, *J* 7.12, 2H, $CO_2CH_2CH_3$). These results leave no doubt that monocyclic ketoester (**8**) (or a co-ordination product with $SnCl_4$) is an intermediate in the overall conversion of the acyclic ketoester (**5**) into the bicycle (**7**), which, furthermore, must be formed by attack of enolic oxygen on a cyclohexyl cation or its equivalent. No meaningful cyclization results were obtained with the enol acetate of the β-ketoester (**5**).

Conversions (**1**) → (**2**) and (**8**) → (**7**), examples of ring closure in the '*endo*'-mode (attack of initiating agent $SnCl_4$ on an incipient annular carbon), are related to the previously described[1b] '*exo*'-type cyclizations to five-membered ring systems induced by phenylselenating species. Theoretical and practical aspects of the present study will be published elsewhere.

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References

1 For the generation of cyclohexane rings by cyclization of unsaturated β-ketoesters, see (a) R. W. Skeean, G. L. Trammell, and J. D. White, *Tetrahedron Lett.*, 1976, 525; (b) W. P. Jackson, S. V. Ley, and A. J. Whittle, *J. Chem. Soc., Chem. Commun.*, 1980, 1173; (c) E. J. Corey, M. A. Tius, and J. Das, *J. Am. Chem. Soc.*, 1980, **102**, 1742.
2 C. Daessle, H. Favre, and H. Schinz, *Helv. Chim. Acta*, 1957, **40**, 2278.
3 D. H. Hunter and R. A. Perry, *Synthesis*, 1977, 37.
4 C. P. Casey and D. F. Marten, *Tetrahedron Lett.*, 1974, 925.
5 T. R. Hoye and M. J. Kurth, *J. Org. Chem.*, 1978, **43**, 3693.
6 W. Wierenga and H. I. Skulnick, *J. Org. Chem.*, 1979, **44**, 310.