A New Spiro-annelation Procedure: Intramolecular Decarboxylative Alkylation of β-Keto-esters

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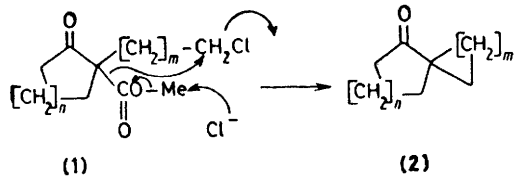
Summary A new intramolecular decarboxylative alkylation route to spirocyclic ketones, and its application to the synthesis of (±)-β-vetivone and (±)-β-vetispirene are described.

ALTHOUGH many known methods of spirocyclization involve intramolecular alkylation routes,[1] there is need for an operationally simple procedure which avoids the use of a strong base. We report herein a regiospecific intramolecular alkylation of enolates, generated *in situ* by halide-induced non-hydrolytic decarboxylation[2] of ω-halogeno-β-keto-esters (**1**), which provides a convenient route to spirocyclic ketones (**2**) (Scheme 1).



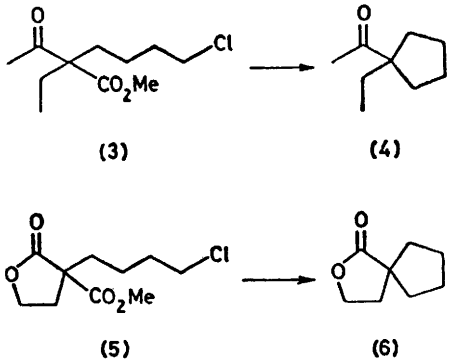
SCHEME 1.

Treating cycloalkanone carboxylates (**1**) with anhydrous lithium chloride (0·5 equiv.) in hexamethylphosphoramide at 125—140 °C provided the corresponding spiro-annelated ketones (**2**) in good yield. The results of representative experiments are summarized in the Table. Similar results were obtained with *N*-methyl-2-pyrrolidone as solvent, but dimethylformamide (DMF) was less satisfactory. Cyclization of the keto-ester (**3**) proceeded equally well, providing the acetylcyclopentane (**4**) in 80% yield. Similarly, the lactone carboxylate (**5**) gave the spirolactone (**6**) in 69% yield. This is believed to be the most direct general route to 2-spirolactones presently available.

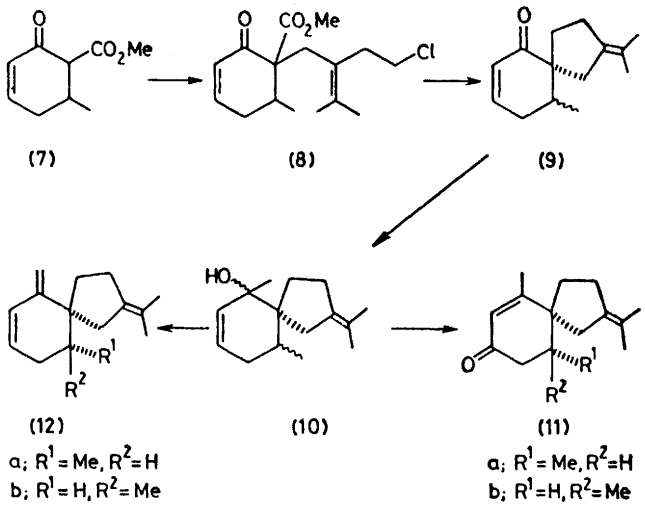
TABLE. Representative spirocyclization experiments.

Compound (**1**)	Reaction time/h	Yield of (**2**)/%[a]
a; $n = 1, m = 1$	1	64
b; $n = 1, m = 3$	1	75
c; $n = 2, m = 3$	1	68
d; $n = 3, m = 3$	1·5	70
e; $n = 8, m = 3$	1·5	71[b]

[a] Yields reported are for isolated product. [b] M.p. 64—65 °C (lit.[8] 50—52 °C).

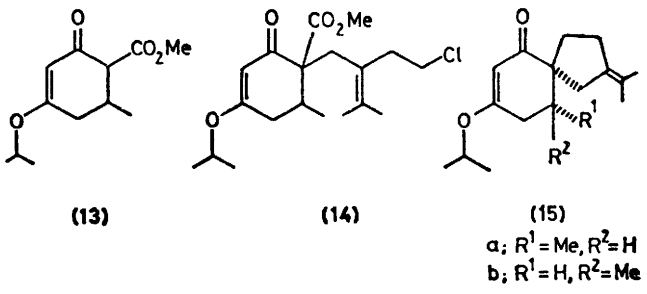


This spiro-annelation procedure has been successfully applied to the construction of the spiro[4.5]decane skeleton,[3] resulting in a new synthesis of β-vetivone and β-vetispirene, components of the oil obtained by steam distillation of the roots of *Vetivera zizanioides*. Thus, reaction of the keto-ester (**7**)[4] with 2-isopropylidene-1,4-dichlorobutane (sodium hydride–DMF, 3 h) afforded adduct (**8**) in 65% yield.† Decarboxylative spirocyclization of (**8**) gave the ketone (**9**) in 80% yield (9 : 1 mixture of epimers). Treatment of (**9**) with methyl-lithium afforded the allylic alcohol (**10**) which, without purification, was oxidized with pyridinium chlorochromate[5] to give a mixture of (±)-β-vetivone (**11a**) and (±)-epi-β-vetivone (**11b**) (ratio 9 : 1) in 72% yield from (**9**). The alcohol (**10**) was also converted (toluene-*p*-sulphonic acid at 25 °C) into a mixture of (±)-β-vetispirene[6] (**12a**) and its epimer (**12b**) (ratio 9 : 1) in 82% yield (Scheme 2).



SCHEME 2.

Application of the spirocyclization process to the Stork synthesis[7] of β-vetivone resulted in an improved overall yield. The keto-ester (**13**) was treated with 2-isopropylidene-1,4-dichlorobutane (sodium hydride–DMF) to give (**14**) in 83% yield. Lithium chloride-induced decarboxy-



† All new compounds gave satisfactory i.r. and n.m.r. spectra, and microanalytical and/or mass spectral data in agreement with the assigned structures.

lation gave the spiroketone (**15**) (98%) as a 9:1 mixture of epimers, from which (**15a**) crystallized (m.p. 77—78 °C, from hexane) in 83% yield.‡ Treating (**15a**) with methyllithium, followed by hydrolysis with 1M hydrochloric acid, gave pure racemic β-vetivone (**11a**) (m.p. 49—50 °C, from hexane) in 87% yield.

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‡ The stereochemistry of (**15a**) was confirmed by analytical h.p.l.c. comparison with an authentic sample prepared by the method of Stork.[7]

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