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A Simple Strategy for Spirocyclopentannulation of Cyclic Ketones. Formal Total Synthesis of (±)-Acorone

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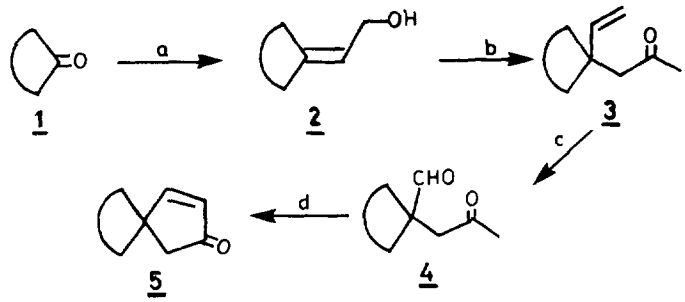
Abstract: A general and simple methodology for spirocyclopentannulation of cyclic ketones (or 4,4-disubstituted cyclopentenones from acyclic ketones) and its application in the synthesis of the spirodienone **7** via a prochiral precursor constituting a formal total synthesis of (±)-acorone (**6**), are described.

Methods for the annulation of five membered rings onto a preexisting ring, with stereo- and regiocontrol, are valuable in organic synthesis, and have received considerable attention during the last two decades.[1] However in contrast to the many procedures developed for the ring fused cyclopentannulations, very little attention was focussed on the spirocyclopentannulation. Presence of spirofused cyclopentanes, either direct or as a part of polycyclic framework is frequently encountered in a variety of natural products.[2] In continuation of our interest in the construction of spirosystems,[3] herein we describe a simple and convenient methodology for the conversion of cyclic ketones into the corresponding spirocyclopentannulated products and simple ketones into the corresponding 4,4-disubstituted cyclopentenones employing a Claisen rearrangement-ozonolysis-intramolecular aldol condensation sequence and its application in the formal total synthesis of the spirosesquiterpene acorone.

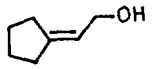
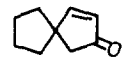
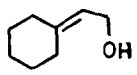
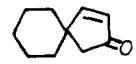
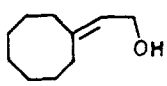
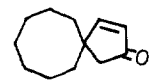
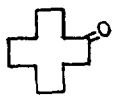
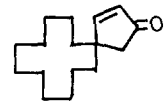
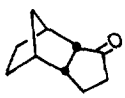
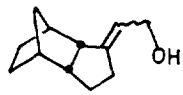
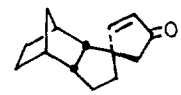
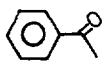
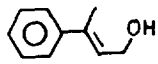
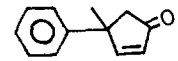
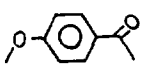
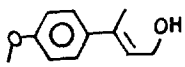
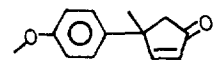
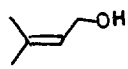
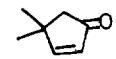
acorone (6)

The general methodology is depicted in the scheme 1. The conversion of the ketones **1a-g** into the allyl alcohols **2a-g** has been achieved[3b] in 85-90% overall yield via the Wittig-Horner-Emmons reaction using triethyl phosphonoacetate and sodium hydride in refluxing THF, followed by regiospecific reduction of the resultant α,β-unsaturated esters with lithium aluminium hydride in ether at low temperature. The one pot Claisen rearrangement of the allyl alcohols **2a-h** with 2-methoxypropene in the presence of a catalytic amount of either mercuric acetate or propionic acid generated the enones **3a-h**. Ozonolysis of the enones **3a-h** following a reductive work-up using triphenylphosphine furnished the enals **4a-h**. Finally intramolecular aldol condensation of the enals **4a-h** furnished the spirannulated products[4] **5a-h**. The conversion of various cyclic and acyclic ketones into the corresponding spirocyclopentannulated products or 4,4-



Scheme 1: (a) i. $(EtO)_2P(O)CH_2COOEt$, NaH, THF; ii. $LiAlH_4$, Et_2O, -50°C, 2h; (b) $CH_2=C(Me)OMe$, $Hg(OAc)_2$ or EtCOOH, sealed tube, 170-175°C, 24-36h; (c) i. O_3/O_2, MeOH:CH_2Cl_2 1:5, -60°C; ii. PPh_3, rt, 5h; (d) 1M KOH in MeOH, rt, 10h.

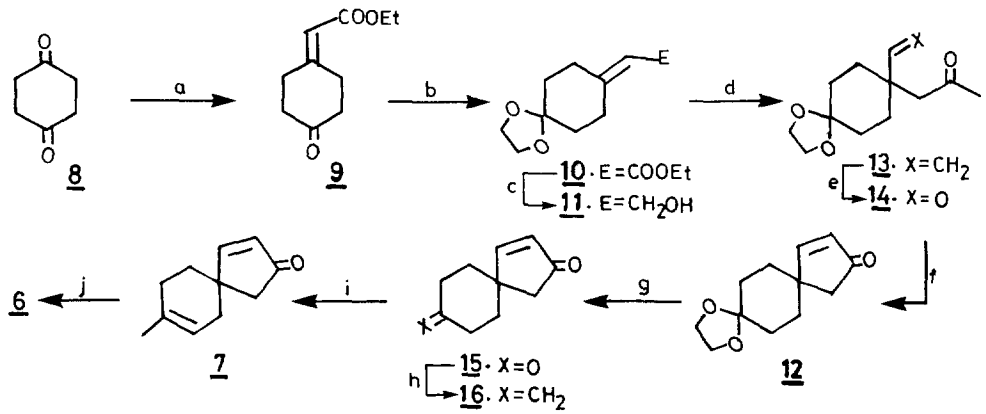
TABLE 1: Spirocyclopentannulation of ketones

entry	ketones	allyl alcohols		% yields[a] of 3a-h[b]	4a-h	5a-h	annulated products	
(a)			2a	65	72	71		5a
(b)			2b	69	71	75		5b
(c)			2c	71	72	73		5c
(d)			2d	72	73	74		5d
(e)			2e	71	72	75		5e
(f)			2f	69	73	74		5f
(g)			2g	62	72	60		5g
(h)	—		2h	95	71	70[c]		5h

(a) Yields (unoptimised) refer to isolated and chromatographically pure compounds. (b) For the Claisen rearrangement, in the entries a,b and e propionic acid was used as catalyst and in other entries mercuric acetate was used as catalyst. (c) Reaction was carried out at reflux temperature for 4h.

disubstituted cyclopentenones is summarised in Table 1. All the reactions were found to be clean. In the entry e, quite expectedly (because of the endo structure) only one isomer (by NMR) was noticed. The synthetic utility of some of the products are well established,[4] *e.g.* 4,4-dimethylcyclopentenone **5h** (entry h) is a widely used intermediate in terpene synthesis. Finally the sequence has been extended to the formal total synthesis of the spiro sesquiterpene acorone **6** via an efficient synthesis of the spirodienone **7**.

Acorone **6** first isolated[5] from the oil of Sweet Flag, *Acorus calamus L.*, is the best known member of a small group of spirocyclic sesquiterpenes having the acorane skeleton. Stereocontrolled construction of the spiroskeleton made acoranes interesting synthetic targets,[6] Synthesis of the dienone **7** starting from 1,4-cyclohexanedione (**8**) is depicted in the scheme 2. Thus selective Wittig-Horner-Emmons reaction of the dione **8** with triethyl phosphonoacetate and sodium hydride in THF furnished the keto ester **9**.[7] Protection of the ketone functionality using ethylene glycol and p-toluenesulfonic acid transformed the ketoester **9** into the ketalester **10**, which on reduction with lithium aluminium hydride in ether at low temperature furnished the allyl alcohol **11**. The allyl alcohol **11** is tranformed into the spiroenone **12** employing the spirocyclopentannulation methodology described above (scheme 1). Thus, one pot Claisen rearrangement of the allyl alcohol **11** with 2-methoxypropene in the presence of a catalytic amount of propionic acid generated the enone **13**.[8] Ozonolysis of the enone **13** followed by intramolecular aldol condensation of the resultant ketoaldehyde **14** furnished the spirannulated product **12**.[8] Acid catalysed hydrolysis of the ketal moiety transformed the enone **12** into the endione **15**.[9] Finally regioselective Wittig reaction with methylenetriphenylphosphorane followed by acid catalysed isomerisation of the exo olefin in the resultant product **16**[8] furnished the spirodienone **7**,[8] which exhibited spectral data identical to that reported in the literature. Since Martin and Chou had already converted[6b] the dienone **7** into acorone, the present sequence constitutes a formal total synthesis of acorone. It is worth mentioning that the endione **15** in the present sequence is a prochiral molecule and can serve as precursor to chiral acorone via either the enolisation or chiral elimination of a suitable leaving group using chiral lithium bases.[10]



Scheme 2: (a) $(EtO)_2P(O)CH_2COOEt$, NaH, THF, 0°C, 10 min, 92%; (b) $(CH_2OH)_2$, pTSA, C_6H_6, reflux, 10h, 90%; (c) $LiAlH_4$, Et_2O, -50°C, 2h, 92%; (d) $CH_2=C(Me)OMe$, EtCOOH, sealed tube, 175°C, 24h, 68%; (e) i. O_3/O_2, MeOH:CH_2Cl_2 1:5, -60°C; ii. PPh_3, rt, 2h, 82%; (f) 1M KOH in MeOH, rt, 10h, 88%; (g) 3N HCl, CH_2Cl_2, rt, 1.5h, 79%; (h) $Ph_3P^+CH_3\ I^-$, 1M $K^+\ O$-'Amy in 'Amy-OH, C_6H_6, rt, 1.5h, 76%; (i) p-TSA, C_6H_6, reflux, 3h, 81%; (j) reference 5b.

In conclusion, we have developed a simple and very convenient method for the conversion of cyclic ketones into the corresponding spirocyclopentannulated products (and acyclic ketones into the corresponding 4,4-disubstituted cyclopentenones). Efficient synthesis of the spirodienone **7**, a precursor to the spirosesquiterpene acorone, established the versatility of the present methodology.

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6. (a) Reference 2, pp. 284-303. (b) Martin, S.F.; Chou, T.-S, *J. Org. Chem.*, **1978**, *43*, 1027. (c) Rao, G.S.R.S.; Pramod, K. *Indian J. Chem.*, **1986**, *25B*, 783; (d) Mori, M.; Isono, N.; Kaneta, N.; Shibasaki, M. *J. Org. Chem.*, **1993**, *58*, 2972 and references cited therein.
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8. All the compounds exhibited spectral data in agreement with the structures. IR and NMR spectral data for the select compounds are as follows. For 4-(2-oxopropyl)-4-vinylcyclohexanone ethylene ketal **13**: IR (neat): ν_{max} 3080, 1710, 1630, 1360, 1105, 1035, 940 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ 5.83 (1H, dd, J=17, 12.5 Hz, CH=CH_2), 5.14 (1H, dd, J=12.5, 1.5 Hz) and 5.03 (1H, dd, J=17, 1.5 Hz) (CH=CH_2), 3.89 (4H, s, O-CH_2CH_2-O), 2.44 (2H, s, CH_2-C=O), 2.06 (3H, s, CH_3-C=O), 1.5-1.9 (8H, m). ^{13}C NMR (50 MHz, $CHCl_3$): δ 207.6 (C=O), 143.1 (CH=CH_2), 114.0 (CH=CH_2), 108.6 (O-C-O), 64.0 (2C, O-CH_2CH_2-O), 54.0 (CH_2-C=O), 38.6 (C-4), 32.8 (2C, C-2 and 6), 32.4 (CH_3-C=O), 30.8 (2C, C-3 and 5). For spiro[4,5]dec-3-en-2,8-dione 8-ethylene ketal **12**: IR (neat): ν_{max} 1710, 1670 (sh), 970, 820 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ 7.57 (1H, d, J=6.3 Hz, H-4), 6.08 (1H, d, J=6.3 Hz, H-3), 3.92 (4H, s, O-CH_2CH_2-O), 2.27 (2H, s, CH_2-C=O), 1.4-2.0 (8H, m). ^{13}C NMR (50 MHz, $CHCl_3$): δ 172.1 (C-4), 131.8 (C-3), 107.7 (O-C-O), 64.2 (2C, O-CH_2CH_2-O), 46.1 (CH_2-C=O), 44.8 (spiro C), 34.0 (2C, C-7 and 9), 32.1 (2C, C-6 and 10). For spiro[4,5]dec-3-en-2,8-dione **15**: IR (neat): ν_{max} 1705, 1590, 1100, 790 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ 7.54 (1H, d, J=6.3 Hz, H-4), 6.14 (1H, d, J=6.3 Hz, H-3), 2.4 (2H, s, CH_2-C=O), 1.6-2.7 (8H, m). For 8-methylenespiro[4,5]dec-3-en-2-one **16**: IR (neat): ν_{max} 3080, 1710, 1645, 1585, 1180, 885, 795 cm^{-1}. ^1H NMR (80 MHz, $CDCl_3$): δ 7.45 (1H, d, J=6.3 Hz, H-4), 6.0 (1H, d, J=6.3 Hz, H-3), 4.51 (2H, s, C=CH_2), 2.14 (2H, s, CH_2-C=O), 1.9-2.4 (2H, m), 1.25-1.9 (6H, m). For 8-methylspiro[4,5]deca-3,7-dien-2-one **7**:[6b,d] IR (neat): ν_{max} 1710, 1590, 1190, 790 cm^{-1}. ^1H NMR (80 MHz, $CDCl_3$): δ 7.56 (1H, d, J=6.3 Hz, H-4), 5.75 (1H, d, J=6.3 Hz, H-3), 5.05 (1H, br s, H-7), 1.9 (2H, s, H-1), 1.5 (3H, s, C_8-CH_3), 1.25-1.9 (6H, m).
9. Incidentally the compounds **12** and **15** are the intermediates in the abandoned synthesis (because of very poor yields) of acorone by Martin and Chou.[6b]
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