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A Facile Synthesis of 1,4-diketones

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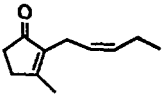
Summary: 1,4-Diketones may conveniently be synthesized by the addition of 2-methylcyclopropenyllithium to N-methoxy-N-methylcarboxamides followed by hydrolysis of intermediate cyclopropyl ketone adducts on silica gel. The new method has been applied to the synthesis of *cis*-jasmone.

A variety of methods[1-7] have been designed for the synthesis 1,4-diketones, which are important intermediates in the synthesis of many natural products, such as *cis*-jasmone (**1**), prostaglandin B_2 (**2**), the rethrolones (**3**) and cuparene (**4**).



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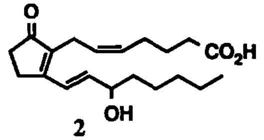

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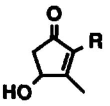

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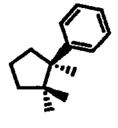

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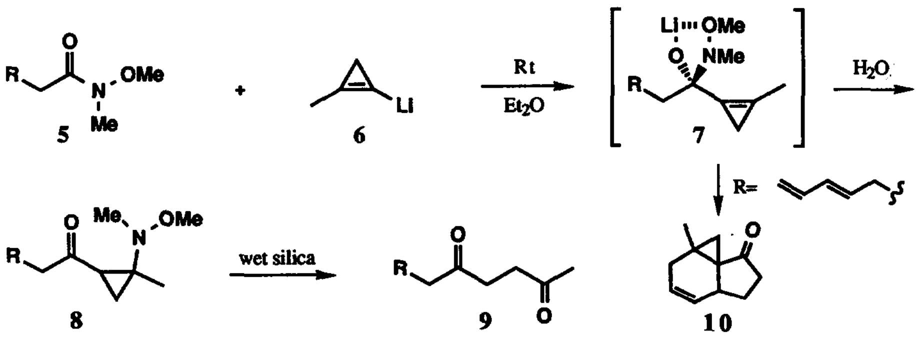
In connection with a recent total synthesis of isovelleral,[8] we studied the addition of 2-methylcyclopropenyllithium to carboxylic acid derivatives, such as acid chlorides, esters, mixed anhydrides and N-methoxy-N-methylcarboxamides.[9] We then discovered that 1,4-diketones may conveniently be obtained from the reaction of N-methoxy-N-methylcarboxamides **5** with methylcyclopropenyllithium (**6**) in ether at ambient temperature (Scheme 1). Apparently the intermediate adduct **7** eliminates N,O-dimethylhydroxylamine, which then undergoes a Michael addition to the resulting cyclopropenyl ketone with formation of the cyclopropyl ketone **8**. On contact with moist silica or alumina the latter immediately hydrolyzes to the 1,4-diketone **9**.

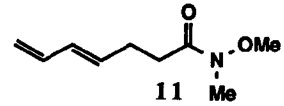
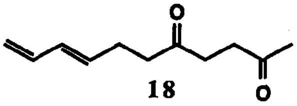
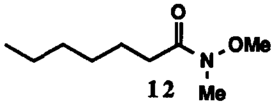
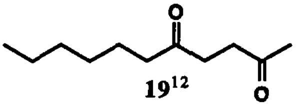
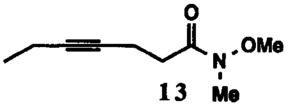
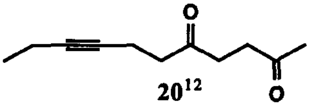
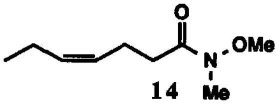
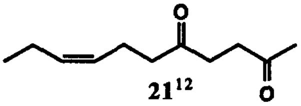
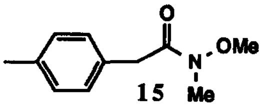
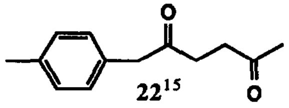
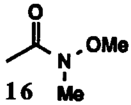
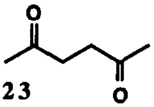
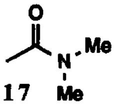
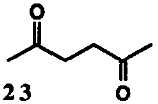
Scheme 1



To evaluate the scope of the reaction, several N-methoxy-N-methylcarboxamides were reacted with 2-methylcyclopropenyllithium. The results are shown in Table 1.

Table 1

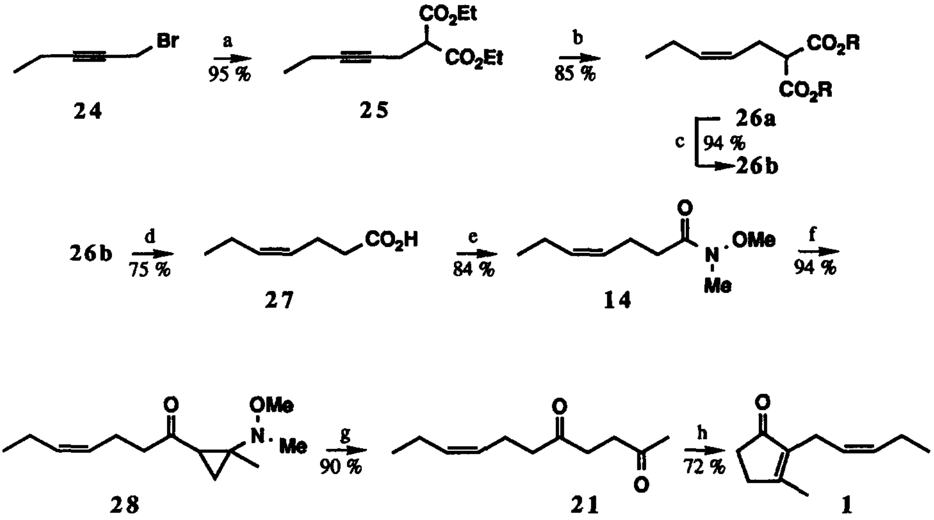
Addition of 2-methylcyclopropenyllithium to N-methoxy-N-methylcarboxamides.
Yields after flash chromatography on silica gel.

Starting amide[10]	Product (1,4-diketone)	Yield (%)
 11	 18	79
 12	 19[12]	86
 13	 20[12]	90
 14	 21[12]	85
 15	 22[15]	75
 16	 23	55
 17	 23	17

Despite their apparent instability, the cyclopropyl ketones **8** were often obtained in good yields and with sufficient purity for ^1H NMR interpretations.[11] All attempts at further purification on liquid chromatography columns failed in our hands, but it proved possible to characterize the cyclopropyl ketone **8** obtained from diene amide **11** by GC-MS (high resolution).[11] Not unexpectedly, in a side reaction the intermediate cyclopropenyl ketone adduct **7** (from **11**) also underwent an intramolecular Diels-Alder reaction with the formation of the tricyclic ketone **10** in low yield (*ca* 5 %, Scheme 1). (An analogous cyclization was utilized in the synthesis of isovelleral.[8]) As exemplified by dimethylformamide (**17**), it was also possible to synthesize diketone **23** from a tertiary amide, but not with the same efficiency as from **16**.

The 1,4-diketones **19**, **20** and **21** are easily transformed to dihydrojasmone, dehydrojasmone and *cis*-jasmone, respectively,[12] by mild base treatment in ethanol.[13] Compound **22** is a suitable starting material for the synthesis of cuparene (**4**).[14, 15] The following procedure (Scheme 2) for the synthesis of *cis*-jasmone is typical:

Scheme 2



(a) diethyl malonate, nBu_4NHSO_4, 6M NaOH, CH_2Cl_2; (b) P-2 Ni, ethylenediamine, H_2, EtOH; (c) i) 6M NaOH, EtOH; ii) 2M HCl; (d) 170 °C, neat, 15 min, argon; (e) i) 1-chloro-N,N,2-trimethyl-1-propenylamine, CH_2Cl_2, 22 °C; ii) N,O-dimethylhydroxylammonium chloride, Et_3N, 22 °C; (f) i) 2-methylcyclopropenyllithium, Et_2O, 22 °C; ii) H_2O; (g) SiO_2, hexane-ethyl acetate 2:1; (h) NaOH, EtOH, 22 °C, 30 h, argon.

Diethyl malonate was alkylated under phase-transfer conditions[16] with 1-bromopent-2-yne[17] **24** to give the diester **25**.[18] Hydrogenation of **25** over $NaBH_4$-reduced nickel[19] (P-2 Ni) in ethanol containing ethylenediamine stereospecifically furnished the *cis*-olefinic diester **26a** (*cis*:*trans* ratio > 100:1). The P-2 Ni catalyst was superior to the classical Lindlar catalyst in this case. Hydrolysis of **26a** to the diacid **26b** (mp 155-160 °C, dec.) and thermal decarboxylation of the latter afforded *cis*-heptenoic acid **27** (bp_{15} 110-112 °C).[20] Reaction of **27** with 1-chloro-N,N,2-trimethyl-1-propenylamine[21] gave the acid chloride, which was transformed directly to the N-methoxy-N-methyl amide **14** by reaction with N,O-dimethylhydroxylamine.[9] Addition of 2-methylcyclopropenyllithium[22, 23] to **14** and quenching of the reaction with water gave the cyclopropyl ketone **28**, which underwent a retroaldol type reaction to give *cis*-8-undecene-2,5-dione **21** when chromatographed on silica gel.[24] On gentle base treatment,[13] **21** cyclized to *cis*-jasmone (yield 65 % from **28**).

The increasing availability of various substituted cyclopropenes[25] should allow variations in the cyclopropane derived part of the 1,4-diketones, thus expanding the prospective usefulness of the method.

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10. Compounds **11-17** were prepared by the general procedure of Nahm and Weinreb[9]. All gave appropriate ^{1}H NMR, ^{13}C NMR, infrared and mass spectra.
11. Spectral data for the cyclopropyl ketone **8** obtained from **11:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.3 (m, 1H), 6.07 (m, 1H), 5.07 (m, 1H), 5.08 (d, 1H, J= 16.6 Hz), 4.96 (d, 1H, J= 10.3 Hz), 4.43 (br. d, 1H, J= 2 Hz), 3.55 (s, 3H), 2.58 (dd, 1H, J= 2.0, 16.2 Hz), 2.56 (s, 3H), 2.45 (dd, 1H, J= 2.0, 16.2 Hz), 2.31 (m, 2H), 2.2 (t, 2H, J= 6.4 Hz), 1.54 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.77, 137.12, 133.98, 131.41, 115.06, 102.17, 92.26, 60.87, 39.75, 35.73, 29.64, 27.72, 24.84. GC-MS (VG ZAB HF spectrometer, 70 eV, 200 mA, 150 °C, manual peak matching) m/z 223.1575±5 ppm (M^+); $C_{13}H_{19}NO_2$ req. 223.15722.
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18. This is an improved preparation of diester **25,** *cf.* O. P. Vig, M. L. Sharma, R. Gauba, *Indian J. Chem., Sect. B,* **1985,** *24 B,* 313.
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24. Acidic work up (2M sulfuric acid) reduced the yield of **20** to less than 50 %.
25. See e.g.: A. T. Stoll, E. Negishi, *Tetrahedron Lett.,* **1985,** *26,* 5671; M. S. Baird, W. Nethercott, *Tetrahedron Lett.,* **1983,** *24,* 605.

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