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# β-Keto -δ-Valerolactone : Synthesis and Use as Methylvinylketone Anion Equivalent in Michael Additions

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*Key words : β-Keto-δ-valerolactone, Michael additions, methylvinylketone anion equivalent.*

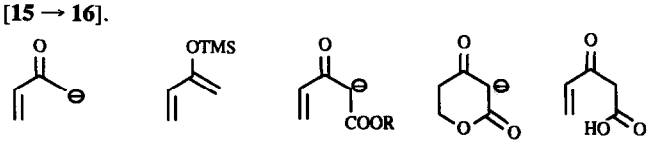
***Abstract** : β-Keto-δ-valerolactone **11** was prepared from 3-butyn-1-ol **6** in 5 steps (50 % overall yield). This lactone was added to Michael acceptors **13, 17, 19** and **25**, giving adducts **14, 18, 20** and **26** respectively.*

Formation of anion **1** by direct deprotonation of methylvinylketone is thwarted by the competitive polymerization of this enone in strongly basic medium. Though anionic species **1** can be easily generated by nucleophilic cleavage of the Si-O bond (*e.g.* by using $Bu_4NF$)[1] of 2-trimethylsilyloxy-1,3- butadiene **2**, to our knowledge there is no successful application of this anion in Michael addition reported so far[2].

A synthetic equivalent to species **1** would be the anion of the Nazarov reagents **3**, in which the β-keto-ester part would stabilize the negative charge. However, while the Nazarov reagents have been widely used as electrophilic partners in Michael additions[3], there is no reported corresponding application of these compounds as nucleophile. The masking of the double bond in anions **1** and **3** appears therefore crucial prior to their utilization in Michael additions.

In this respect anion **4**, derived from β-keto-δ-valerolactone **11**, seemed to be a valuable candidate as synthetic equivalent to species **1** and **3**. Indeed, compound **11** corresponds *formally* to the ring closure of γ-vinyl-β-keto-acid **5** (the Nazarov reagents acid moiety), *the double bond of the latter derivative being thus protected internally by lactonization.*

In this paper we actually show that lactone **11** adds to electrophiles **13**, **17**, **19** and **25**, giving the Michael adducts **14**, **18**, **20** and **26**, respectively. The "masked" vinylketone moiety in adducts **14** and **18** was then generated by acidic hydrolysis, leading in both cases to the same ketol **15** [**14** → **15** and **18** → **15**] which was next dehydrated [**15** → **16**].



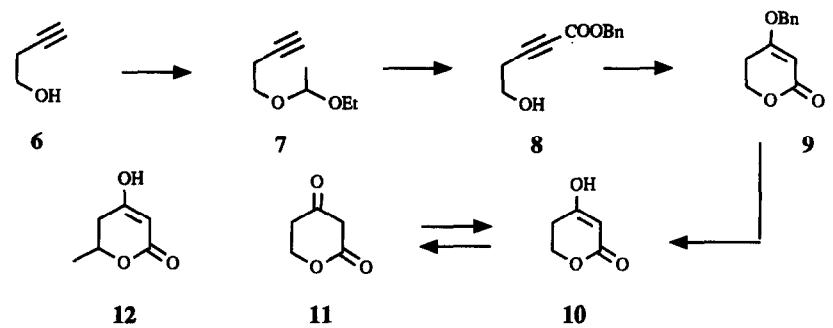

**1** **2** **3** **4** **5**

**Preparation of β-keto-δ-valerolactone 11**

Somewhat surprisingly, although the methyl derivative **12** is commercially available[4], the unsubstituted parent compound, β-keto-δ-valerolactone **11**, was unknown until the present study (since we have established that the original claim concerning this molecule is erroneous)[5]. We found that preparation of compound **11** is greatly hampered by its highly polar character, its important water-solubility, as well as its facile hydrolytic cleavage[6]. These difficulties were overcome by using, as final step of our synthetic design, the hydrogenolysis of benzyl derivative **9** which furnished quantitatively lactone **11** which was next purified by sublimation.

Synthesis of lactone **10** was thus achieved in 5 steps (50 % overall yield) from 3-butyn-1-ol **6**. This alcohol was first protected as ketal derivative **7** (ethylvinyl ether) which was then converted into ester **8**[7] (*i* :

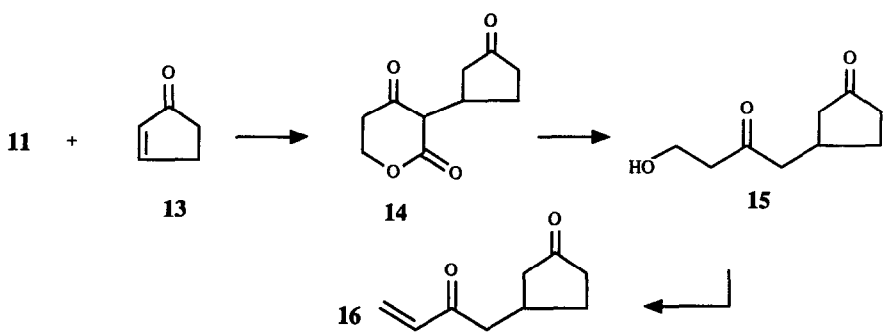
*n*BuLi -78 °C then ClCOOBn, *ii* : 0.5 N HCl/acetone, 75 % yield from **6**). Benzyloxymercuration of this ester[8] (6 eq of BnOH, 0.03 eq of HgO, 0.3 eq of $BF_3$-$Et_2O$ complex, 1 h at 60 °C, then dropwise addition of a mixture of 1 eq of **8** and 2 eq of BnOH, 0.5 h at 70 °C : exothermic reaction ! , then 24 h at 20 °C) led to lactone **9**[9] (65 % yield). Finally, hydrogenolysis of the latter derivative [$Pd(OH)_2$, iPrOH, 3.5 bar of hydrogen] gave quantitatively the desired lactone **11**[10]. In $CD_3COCD_3$ solution, this keto-lactone exhibits a *ca* 2:1 tautomeric equilibrium with the enol form **10** (by $^1H$ and $^{13}C$ NMR), while the sole enol form is observed in the solid state (by IR).



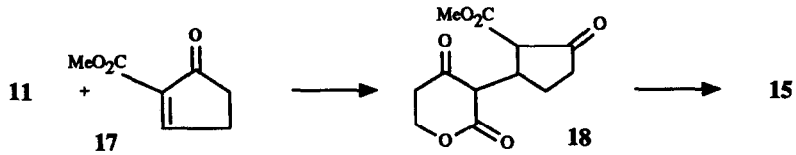

**β-Keto-δ-valerolactone 11 in Michael additions**

As suggested by its pronounced propensity to enolize, lactone **11** was found to be a rather strongly acidic compound (pKa relative to water 5.15)[6]. Owing to this acidity, its use in Michael reaction proved to be severely restricted by the competitive reversibility of the addition process. Nevertheless we discovered that when *good Michael acceptors* are employed, especially the *gem*-diactivated ones **17** and **19**, the corresponding adducts are obtained in satisfactory yields. On the other hand we have established that substoechiometric amounts of a weak base and a good proton donor solvent are required to achieve efficiently these additions, a quarter molar equivalent of *cesium hydrogen carbonate*[11] *in methanol* giving thus the best results.

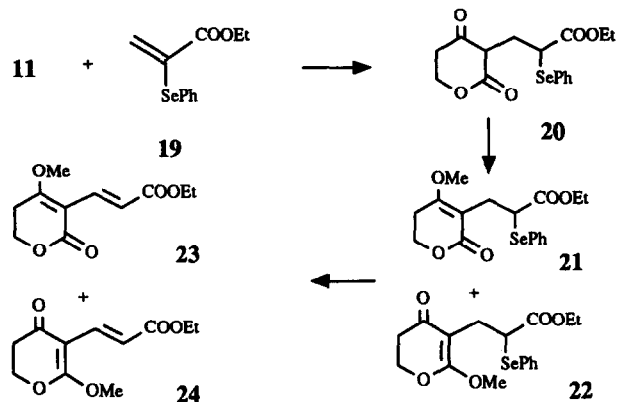
Addition of lactone **11** to cyclopentenone **13** (0.25 eq of $CsHCO_3$, MeOH, 24 h at 20 °C) gave expected adduct **14**, albeit with a low yield (30-35 %). Hydrolytic cleavage of this adduct (4 N $H_2SO_4$, 60 °C, 4 h) led to ketol **15**[12] (75 % yield) which was then converted into enone **16**[13] (3 eq of MsCl, 5 eq of $Et_3N$, catalytic amounts of DMAP, $CH_2Cl_2$, 30 min at 20 °C, 90 % yield).



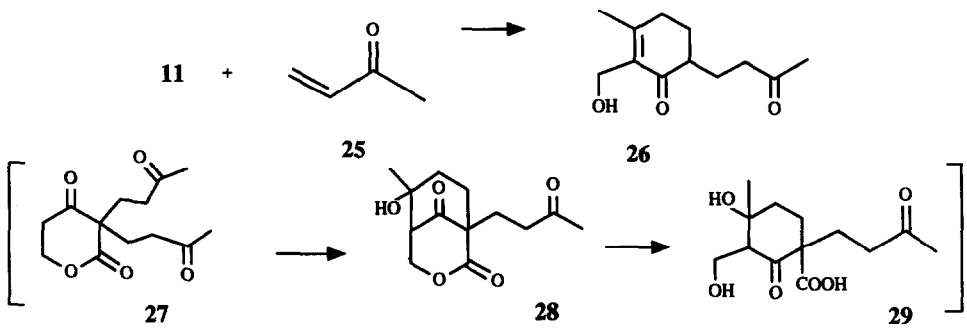

As mentioned above, replacement of cyclopentenone **13** by its "activated" equivalent **17**[14] gave a better yield in the present Michael addition. Thus, addition of lactone **11** to keto-ester **17** (0.25 eq of $CsHCO_3$, MeOH, 24 h at 20 °C), followed by hydrolytic cleavage of the resulting crude adduct **18** (4 N $H_2SO_4$, 60 °C, 12 h) led to ketol **15** with a 55 % overall yield (while the precedent conversion **11** → **14** → **15** was achieved with only 25 % overall yield).



Though all attempts of addition of lactone **11** to methyl acrylate were fruitless, the former reagent was easily added to acrylate **19**[15], "activated" by an α-phenylseleno group (0.25 eq of $CsHCO_3$, MeOH-THF, 24 h at 20 °C). The resulting unstable crude adduct **20** was then methylated ($CH_2N_2$, $Et_2O$, 20 °C), giving a nearly equimolar mixture of the methoxy derivatives **21** and **22** (75 % yield from **11**)[16]. Oxidation of the latter compounds[14] (4 eq of $NaIO_4$, $H_2O$-MeOH, 15 min, 20 °C) led next to dienic esters **23** and **24**[17] with a 50 % yield.



Addition of lactone **11** to methylvinylketone **25** led unexpectedly to cyclohexenone **26**[18] (*i* : 3 eq of MVK, 0.25 eq of $CsHCO_3$, MeOH, 24 h at 20 °C, *ii* : 1 N HCl, 1 h at 20 °C, 75 % yield). Formation of compound **26** may be rationalized as follows, invoking that a double Michael addition took place first, leading to intermediate **27**, followed by an intramolecular aldol condensation [**27** → **28**]. Hydrolysis of the lactone ring of bridged ketol compound **28** would give derivative **29** which, upon decarboxylation of the β-keto-acid function and dehydration of the tertiary ketol, would lead to cyclohexenone **26**.



Further applications of promising synthon **11** are currently under investigation in our laboratory.

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## REFERENCES AND NOTES


1. R.A. Olofson, J. Cuomo, *Tetrahedron Lett.*, **21**, 819 (*1980*) ; for a nickel enolate complex of MVK, see : E.R. Burkhardt, R.G. Bergman, C.H. Heathcock, *Organometallics*, **9**, 30 (*1990*).
2. However for sequential inter-intramolecular Michael additions using **2**, see : T. Mukaiyama, Y. Sagawa, S.Kobayashi, *Chem. Lett.*, 1821 (*1986*).
3. Preparation of the Nazarov reagents : R. Zibuck, J. M. Streiber, *J. Org. Chem.*, **54**, 4717 (*1989*) and references cited therein. Uses in synthesis : H. Takahata, K. Yamabe, T. Suzuki, T. Yamazaki, *Chem. Pharm. Bull.*, **34**, 4523 (*1986*) and references cited therein.
4. Compound **12** is available from Aldrich-Chimie ; see also : R. Bacardit, M. Moreno-Mañas, *Tetrahedron Lett.*, **21**, 551 (*1980*).
5. D. Gomez-Pardo, J. d'Angelo, *Tetrahedron Lett.*, this Issue, following paper.
6. Freshly prepared aqueous solutions of lactone **11** must be used to measure the pKa of this molecule, aged solutions giving erratic results.
7. **8** : oil ; *IR* (neat) 3380, 2240, 1705 $cm^{-1}$ ; *$^1H$ NMR* (90 MHz, $CDCl_3$) δ 2.27 (br s, 1H) 2.53 (t, J=6 Hz, 2H) 3.73 (t, J=6 Hz, 2H) 5.17 (s, 2H) 7.37 (m, 5H).
8. E. R. H. Jones, M. C. Whiting, *J. Chem. Soc.*, 1419 (*1949*) ; *Ibid* 1423 (*1949*).
9. **9** : solid ; mp 71°C (iPrOH) ; *MS* (70 ev) m/e 132, 92, 91, 65, 39 ; *IR* (KBr) 1720, 1620 $cm^{-1}$ ; *$^1H$ NMR* (90 MHz, $CDCl_3$) δ 2.57 (t, J=6.3 Hz, 2H) 4.36 (t, J=6.3 Hz, 2H) 4.97 (s, 2H) 5.27 (s, 1H) 7.38 (m, 5H) ; *$^{13}C$ NMR* (63 MHz, $CDCl_3$) 171.7 166.4 134.4 128.54 128.49 127.6 91.5 64.2 27.6 ; *Anal.* calcd for $C_{12}H_{12}O_3$ C 70.57 H 5.92, found C 70.85 H 5.80.
10. **10⇌11** : solid ; mp 68 °C (after sublimation at 65 °C under 0.01 Torr) ; *HRMS* calcd for $C_5H_6O_3$ m/e 114.03169, found 114.03120 ; *MS* (70 eV) m/e 114 ($M^+$, 14) 86(5) 69(3) 57(4) 56(5) 55(52) 43(20) 42(100) ; *IR* (KBr) 3400, 1660, 1580 $cm^{-1}$ ; *UV* (dioxanne) $\lambda_{max}$ 301 nm ($\epsilon$ = 75) ; *$^1H$ NMR* (250 MHz, $CD_3COCD_3$) δ *enol form* (**10**) 2.56 (t, J=6.3 Hz, 2H) 4.31 (t, J=6.3 Hz, 2H) 5.06 (s, 1H) 10.20 (br s, 1H), *keto form* (**11**) 2.70 (t, J=5.8 Hz, 2H) 3.61 (s, 2H) 4.66 (t, J=5.8 Hz, 2H) ; *$^{13}C$ NMR* (63 MHz, $CD_3COCD_3$), *enol form* (**10**) 173.2 167.5 92.8 64.9 28.1, *keto form* (**11**) 201.4 168.4 64.5 48.6 38.2.
11. For a related application of $Cs_2CO_3$ as catalyst in Michael additions, see : R. Ruel, P. Deslongchamps, *Tetrahedron Lett.*, **31**, 3961 (*1990*) and references cited therein.
12. **15** : oil ; *IR* (neat) 3400, 1730, 1710 $cm^{-1}$ ; *$^1H$ NMR* (90 MHz, $CDCl_3$) δ 1.1-2.8 (m, 11H) 3.2 (br s, 1H) 3.83 (t, J=5.7 Hz, 2H) ; *$^{13}C$ NMR* (20 MHz, $CDCl_3$) 219.1 209.6 57.5 48.5 45.2 44.6 38.2 32.1 29.2.
13. **16** : oil ; *IR* (neat) 1739, 1698, 1679 $cm^{-1}$ ; *$^1H$ NMR* (250 MHz, $CDCl_3$) δ 1.45-1.89 (m, 2H) 2.09-2.41 (m, 4H) 2.45-2.59 (m, 1H) 2.59-2.83 (m, 2H) 5.89 (dd, J=1.5 Hz, J=10.1 Hz, 1H) 6.26 (dd, J=1.5 Hz, J=17.6 Hz, 1H) 6.39 (dd, J=10.1 Hz, J=17.6 Hz, 1H) ; *$^{13}C$ NMR* (63 MHz, $CDCl_3$) 219.1 199.0 136.5 128.5 44.8 44.7 38.3 32.4 29.3.
14. H. J. Reich, J. M. Renga, I. L. Reich, *J. Am. Chem. Soc.*, **97**, 5434 (*1975*).
15. G. M. Ksander, J. E. McMurry, M. Johnson, *J. Org. Chem.*, **42**, 1180 (*1977*).
16. In contrast, methylation of compound **11** by using $CH_2N_2$ is highly regioselective, giving exclusively 4-methoxy-5,6 dihydro-2H-pyran-2-one.
17. **23** + **24** : oil (unseparable mixture) ; *IR* (neat) 1704, 1659, 1615, 1585 $cm^{-1}$ ; *$^1H$ NMR* (250 MHz, $CDCl_3$) δ **23** : 1.19 (t, J=7.1 Hz, 3H) 2.54 (t, J=6.6 Hz, 2H) 3.91 (s, 3H) 4.08 (q, J=7.1 Hz, 2H) 4.56 (t, J=6.6 Hz, 2H) 6.62 (d, J=16 Hz, 1H) 7.47 (d, J=16 Hz, 1H), **24** : 1.2 (t, J=7.1 Hz, 3H) 2.78 (t, J=6.2 Hz, 2H) 3.89 (s, 3H) 4.11 (q, J=7.1 Hz, 2H) 4.26 (t, J=6.2 Hz, 2H) 6.63 (d, J=16.2 Hz, 1H) 7.56 (d, J=16.2 Hz, 1H) ; *$^{13}C$ NMR* (63 MHz, $CDCl_3$) **23+24** : 188.3 172.7 171.8 166.4 167.7 165.0 134.2 133.5 119.6 115.1 103.7 94.4 68.5 62.4 59.8 59.5 56.5 55.6 35.1 24.5 14.1 14.0.
18. **26** : oil ; IR (neat) 3440, 1710, 1660, 1630 $cm^{-1}$ ; *$^1H$ NMR* (250 MHz, $CDCl_3$) δ 1.70 (m, 2H) 1.91-2.12 (m, 2H) 1.99 (s, 3H) 2.13 (s, 3H) 2.25 (m, 1H) 2.40 (m, 2H) 2.47 (br s, 1H) 2.55 (t, J=7.5 Hz, 2H) 4.32 (s, 2H) ; *$^{13}C$ NMR* (63 MHz, $CDCl_3$) 208.8 201.8 158.3 133.6 56.6 44.9 41.1 31.8 29.8 27.6 23.8 20.7.


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