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ASYMMETRIC SYNTHESIS OF FURANONES

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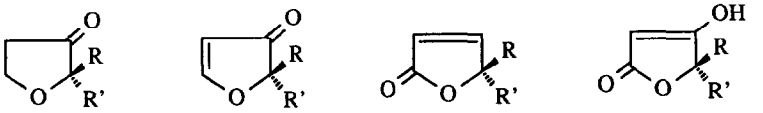
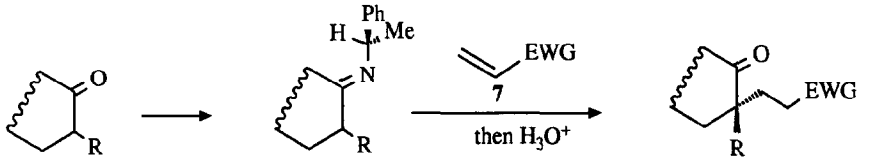
Abstract : *Addition of imine* **10** *to methyl acrylate led exclusively, after hydrolytic work-up, to furanone* **11** *(95 % stereoselectivity). By contrast, addition of this imine to MVK was not regioselective, giving a mixture of compounds* **18**, **19** *and* **20**.

Dihydrofuran-3-ones **1** are valuable starting materials in organic synthesis ; indeed, as shown in this report, they can readily be converted into naturally occuring 5-membered heterocycles 3(2H)-furanones **2** [1], $\Delta^{\alpha,\beta}$-butenolides [2(5H)-furanones] **3** [2] and tetronic acids [4-hydroxy-2(5H)-furanones] **4** [3].



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

Compounds **1** contain a single stereogenic center, namely a fully substituted carbon atom in the α-position to the carbonyl function of a cyclanone. This particular structural feature is encountered in adducts **8** resulting from the very efficient asymmetric Michael addition which we have disclosed [4], typified by equation [**5** → **8**]. Thus chiral imines **6**, derived from α-substituted cyclanones **5** and optically active 1-phenylethylamine, add to electron-deficient alkenes **7** to lead, after hydrolytic work-up, to α,α-disubstituted cyclanones **8**, with an excellent yield and with a high degree of regio- and enantioselectivity.



5 **6** **8**

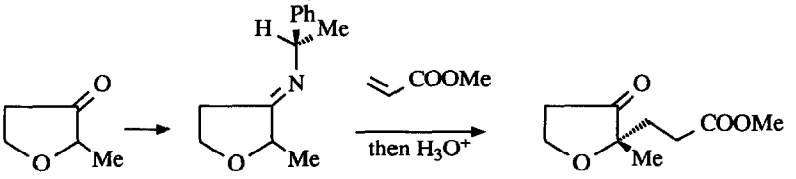
90 % chemical yield
90-95 % stereoselectivity

Such an asymmetric process might be applied successfully to the enantioselective synthesis of key dihydrofuran-3-ones **1**, provided that the presence of an oxygen atom in the α-position to the carbonyl function in the ring of the starting ketone (*e.g.* **9**) does not notably alter the two aforementioned essential features of this reaction, namely the remarkable regio- and stereoselectivity [5].

In this communication we show that the regioselectivity of the present process depends strongly on the nature of the electrophilic partner which is used. Thus, with methyl acrylate the reaction is completely regioselective (and highly stereoselective) [**10** → **11**], giving with a high yield adduct **11**, *as the sole product*, resulting from the alkylation at *the more* substituted α-side of imine **10**. By contrast, a dramatic loss of

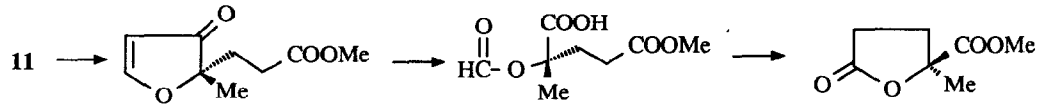
regioselectivity results from the use of methylvinylketone : in that case nearly equimolar mixtures of the two regioisomeric monoadducts **18** and **19** are invariably formed, along with substantial amounts of the bis-adduct **20**, resulting from the bis-alkylation *at the same carbon center* (*the less* substituted α-side of imine **10**).

Required imine **10** was prepared quantitatively from 2-methyl-dihydrofuran-3-one **9** [6] and *R*-(+)-1-phenylethylamine ($[\alpha]^{20}_D$ + 39.1 neat, 96 % ee), (12 h at 20 °C in cyclohexane in the presence of powdered 5 Å molecular sieves). This crude imine was added to methyl acrylate (3 eq of methyl acrylate, neat, 72 h at 60 °C, then hydrolytic work-up with AcOH/H_2O/THF at 20 °C), leading to (*S*)-adduct **11** [7] (80 % chemical yield, 91 % ee, 95 % stereoselectivity).



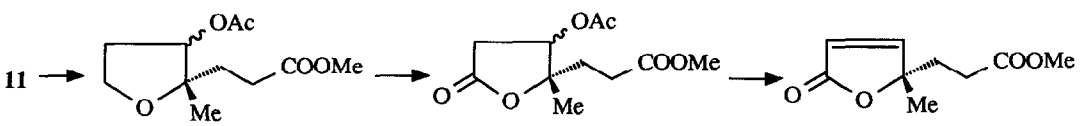
9 **10** **11**

The ee of adduct **11** was established by ^1H NMR, using $Eu(hfc)_3$ as chiral shift reagent, and its absolute configuration was determined as follows, by correlation with known (*S*)-lactone-ester **14** [9]. Compound **11** was first transformed into (*S*)-3(2H)-furanone **12** [8] (*i* : slow bromination with 1 eq of bromine at 20 °C in CH_2Cl_2, in the presence of catalytic amounts of hydrobromic acid ; *ii* : LiBr/Li_2CO_3 in DMF, 1 h at 130 °C, 75 % overall yield). Ozonolysis of this furanone (*i* : 0_3 in CH_2Cl_2/MeOH at -78 °C ; *ii* H_2O_2 in MeOH ; *iii* : heating at 60 °C under 0.1 mm Hg) gave compound **13** which was cyclized and methylated (*i* : 1 N NaOH in MeOH ; *ii* : 6 N HCl → dryness ; *iii* : CH_2N_2) to furnish lactone **14** [9].



12 **13** **14**

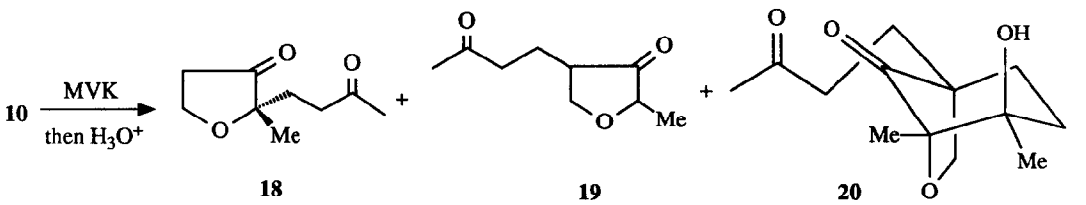
Seeing that the $\Delta^{\alpha,\beta}$ butenolide nucleus occurs in a number of natural products [2], the conversion of furanone **11** into this heterocycle [**11** → **17**] was next examined. Reduction of this furanone [$Zn(BH_4)_2$, Et_2O, 0 °C, 2 h], followed by acetylation of the resulting mixture of epimeric alcohols (Ac_2O, DMAP, Et_3N, 20 °C) led to acetate **15** (90 % overall yield). Oxidation of latter derivative ($RuCl_3$ cat, 4.5 eq of $NaIO_4$, MeCN, CCl_4, H_2O, 20 °C, 48 h) [10] gave lactone **16** with a 70 % yield. Treatment of this lactone with DBU (2 h in refluxing toluene) led finally to the desired (*S*)-butenolide **17** [11] (80 % yield).



15 **16** **17**

Furanone **11** has been also converted into tetronic acids **4** , by using a similar oxidation-elimination protocol [12].

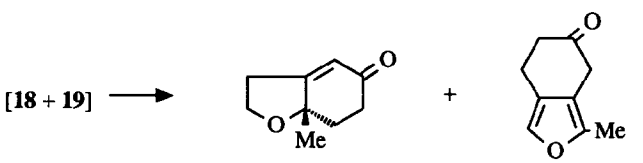
As mentioned above, addition of imine **10** to methylvinylketone (MVK) led generally to three-component mixtures [**18** + **19** + **20**]. The composition of latter mixtures depends on the operating conditions : if the formation of the bis-adduct **20** can be minimized -or even suppressed- by a careful monitoring of the reaction, unfortunately important amounts of the undesired monoadduct **19** are invariably produced, irrespective of the experimental conditions.



18 19 20

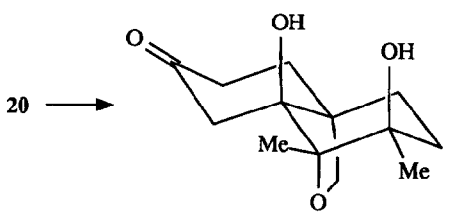
Operating conditions				Chemical yields (%)		
MVK/**10** (ratio of eq)	solvent	temperature (°C)	duration (h)	**18**	**19**	**20**
1.5	Et_2O	20	24	19	19	traces
1.6	Et_2O	20	115	15	15	25
2	Et_2O	5	140	7	28	7
1.6	cyclohexane	20	94	13	18	15
4	cyclohexane	20	24	8	18	15
3	neat	40	12	traces	traces	80

Flash chromatography on silica gel of mixture [**18** + **19** + **20**] led to isolation of pure bis-adduct **20**, along with an inseparable mixture of the two regioisomeric monoadducts **18** and **19**. The latter two-component mixture was submitted to cyclization reactions, giving the corresponding bicyclic derivatives (*S*)-**21** [13] (90 % ee) and **22** [15] (5 % KOH in MeOH, 50 °C, 2 h for an efficient preparation of **21** ; pyrrolidinium acetate in refluxing benzene, 30 min, for an efficient preparation of **22**) which were easily separated by chromatography on silica gel.

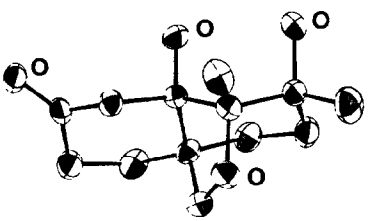


21 **22**

When the bis-adduct **20** was treated under basic conditions (5 % KOH in MeOH, 20 °C, 12 h), the tricyclic derivative **23** [16] was obtained quantitatively.



23



X-ray crystal structure of **23**

No definitive statement can, as yet, be made concerning the factors that govern the regioselectivity in the above Michael additions and related reactions [4]. Nevertheless the unprecedented lack of regioselectivity observed in the reaction [**10** + MVK] may be interpreted tentatively, invoking a competitive reversibility (retro-Michael process).

References and Notes

1. A.B. Smith, III, P.A. Levenberg, P.J. Jerris, R.M. Scarborough, Jr., P.M. Wovkulich, *J. Am. Chem. Soc.*, **103**, 1501 (1981).

2. Y.S. Rao, *Chem. Rev.*, **76**, 625 (1976).

3. L.J. Haynes, J.R. Plimmer, *Quat. Rev.*, **14**, 292 (1960).

4. (a) M. Pfau, G. Revial, A. Guingant, J. d'Angelo, *J. Am. Chem. Soc.*,**107**, 273 (1985). (b) A. Sevin, J. Tortajada, M. Pfau, *J. Org. Chem.*, **51**, 2671 (1986). (c) T. Volpe, G. Revial, M. Pfau, J. d'Angelo, *Tetrahedron Lett.*, **28**, 2367 (1987). (d) J. d'Angelo, A. Guingant, C. Riche, A. Chiaroni, *ibid.*, **29**, 2667 (1988). (e) J. d'Angelo, G. Revial, T. Volpe, M. Pfau, *ibid.*, **29**, 4427 (1988). (f) D. Desmaele, J. d'Angelo, *ibid.*, **30**, 345 (1989). (g) J. d'Angelo, G. Revial, A. Guingant, C. Riche, A. Chiaroni, *ibid.*, **30**, 2645 (1989). (h) G. Revial, *ibid.*, **30**, 4121 (1989). (i) J. d'Angelo, C. Ferroud, C. Riche, A. Chiaroni, *ibid.*, **30**, 6511 (1989). (j) H. Sdassi, G. Revial, M. Pfau, J. d'Angelo, *ibid.*, **31**, 875 (1990). (k) J. d'Angelo, D. Desmaele, *ibid.*, **31**, 879 (1990). (l) D. Desmaele, J. d'Angelo, *ibid.*, **31**, 883 (1990). (m) F. Dumas, J. d'Angelo, *Tetrahedron Asymmetry*, **1**, 167 (1990). (n) A. Sevin, D. Masure, C. Giessner-Prettre, M. Pfau, *Helv. Chim. Acta*, **73**, 552 (1990).

5. The behavior of chiral imines derived from α-alkoxycyclanones (**5**, R = OMe, OBn) toward electrophilic alkenes has been reported recently : see ref. 1f.

6. Prepared according to : M.A. Gianturco, P. Friedel, A.S. Giammarino, *Tetrahedron*, **20**, 1763 (1964).

7. **11** (91 % ee) : $[\alpha]^{20}_D$ -46.8 (c = 15, EtOH) ; IR (neat) 1750-1730 cm^{-1} ; ^1H NMR (250 MHz, $CDCl_3$) δ 4.17 (dt, J = 9.5 Hz, J = 7.4 Hz, 1H) 4.11 (dt, J = 9.5 Hz, J = 7.6 Hz, 1H) 3.66 (s, 3H) 2.55 (t, J = 7.5 Hz, 2H) 2.35 (m, 2H) 1.95 (m, 2H) 1.18 (s, 3H) ; ^{13}C NMR (20 MHz, $CDCl_3$) δ 216.9 173.5 80.5 61.7 51.7 36.3 30.8 28.6 20.3.

8. **12** (90 % ee) : $[\alpha]^{20}_D$ -90 (c = 7, EtOH) ; IR (neat) 1735, 1700, 1560 cm^{-1} ; ^1H NMR (250 MHz, $CDCl_3$) δ 8.14 (d, J = 1 Hz, 1H) 5.56 (d, J = 1 Hz, 1H) 3.57 (s, 3H) 2.2 (m, 2H) 2.0 (m, 2H) 1.28 (s, 3H) ; ^{13}C NMR (63 MHz, $CDCl_3$) δ 206.1 176.5 172.5 105.8 88.3 51.4 31.0 27.8 21.2.

9. **14** (90 % ee) : $[\alpha]^{20}_D$ -4.2 (c = 6, $CHCl_3$) ; lit $[\alpha]^{20}_D$ -4.7 (c = 0.8, $CHCl_3$) : H.P. Sigg, H.P. Weber, *Helv. Chim. Acta*, **51**, 1395 (1968).

10. Per. H.J. Carlsen, T. Katsuki, V.S. Martin, K.B. Sharpless, *J. Org. Chem.*, **46**, 3936 (1981).

11. **17** (90 % ee) : $[\alpha]^{20}_D$ +50.7 (c = 4.5, EtOH) ; IR (neat) 1750-1730 cm^{-1} ; ^1H NMR (90 MHz, $CDCl_3$) δ 7.3 (d, J = 6 Hz, 1H) 6.0 (d, J = 6 Hz, 1H) 3.6 (s, 3H) 2.2 (m, 4H) 1.45 (s, 3H) ; ^{13}C NMR (20 MHz, $CDCl_3$) δ 173.0 172.1 159.7 120.9 87.8 51.8 32.8 28.2 24.2.

12. D. Desmaele, unpublished results.

13. **21** (90 % ee) : $[\alpha]^{20}_D$ +55.2 (c = 3, EtOH) ; IR (neat) 1710, 1670 cm^{-1} ; ^1H NMR (200 MHz, $CDCl_3$) δ 5.80 (s, 1H) 4.08 (m, 2H) 2.98 (m, 1H) 2.78 (m, 1H) 2.46 (m, 2H) 2.15 (m, 2H) 1.38 (s, 3H) ; ^{13}C NMR (20 MHz, $CDCl_3$) δ 198.1 169.6 120.7 79.0 64.2 35.3 34.2 30.8 21.6.
Diketone **18**, precursor of compound **21**, can alternatively be prepared starting from keto-ester **11** (*i* : NaOH *ii* : MeNHOMe, DCC, DMAP [14] *iii* : $NaBH_4$, MeOH *iv* : MeLi excess, Et_2O, 0 °C *v* : Jones reagent).

14. S. Nahm, S.M. Weinreb, *Tetrahedron Lett.*, **22**, 3815 (1981).

15. **22** : IR (neat) 1710 cm^{-1} ; ^1H NMR (250 MHz, $CDCl_3$) δ 7.05 (s, 1H) 3.30 (s, 2H) 2.85 (m, 2H) 2.55 (m, 2H) 2.17 (s, 3H).

16. **23** (ca 30 % ee) : colorless solid ; mp 125 °C ; IR (KBr) : 3300 (br), 1705 cm^{-1} ; ^1H NMR (250 MHz, $CDCl_3$) δ 4.3 (br s, 2H) 4.06 (dd, J = 8.7 Hz, J = 1.1 Hz, 1H) 3.74 (d, J = 8.7 Hz, 1H) 2.67 (d, J = 14 Hz, 1H) 2.45 (m, 2H) 2.25 (m, 1H) 2.0-1.7 (m, 4H) 1.62 (m, 1H) 1.25 (m, 1H) 1.18 (s, 3H) 1.13 (s, 3H) ; ^{13}C NMR (63 MHz, $CDCl_3$) δ 210.3 83.8 81.4 76.9 70.5 47.3 42.9 37.0 34.3 28.6 28.5 25.7 12.9.
Crystallographic data of compound **23** have been deposited at the Cambridge crystallographic Data Centre, U.K.