Tetrahedron Vol. 46, No. 6, pp. 2035-2046, 1990
Printed in Great Britain

0040-4020/90 $3.00+.00
Pergamon Press plc

COPPER AND COBALT MEDIATED REGIOSELECTIVE ALKYLATION OF POLYKETIDE MODELS: METHYL 3,5-DIOXOHEXANOATE AND TRIACETIC ACID LACTONE[1]

JORDI CERVELLO, JORGE MARQUET* and MARCIAL MORENO-MAÑAS*
Department of Chemistry, Universitat Autònoma de Barcelona.
08193-Bellaterra. Barcelona. Spain

(*Received in UK* 19 *December* 1989)

Abstract.- Regioselective C-alkylations at the intercarbonyl positions C-4 and C-2 of the polyketide model methyl 3,5-dioxohexanoate, **1**, have been acomplished through reactions of its cobalt(II), **4a**, and copper(II), **4b**, complexes respectively. Some examples of double alkylations at both positions are presented. Cyclizations of the regioselectively substituted diketoesters so prepared gave triacetic acid lactone derivatives regioselectively alkylated at C-5 and at C-3.

INTRODUCTION

Polyketides constitute a family of natural products derived by transformation of poly-β-ketoacids or their activated forms. The chemistry of the living systems is delicate enough as to have the ability to alkylate selectively certain intercarbonyl activated positions leaving untouched other positions of nearly identical chemical reactivity. Methyl groups transferred from S-adenosylmethionine and terpenoid chains transferred from activated terpene alcohols are the most common groups found in the intercarbonyl positions of the vast array of natural products from polyketide origin. It is believed that transfers of the aforementioned radicals to the activated methylene groups of the poly-β-ketoacids do not differ mechanistically very much from the conventional alkylations of activated methylene groups of β-diketones, β-diketoesters and the like.

Alkylation of activated methylene groups of β-dicarbonyl compounds is a usual synthetic procedure in laboratory chemistry. However, synthetically useful alkylations of poly-β-carbonyl compounds is still a synthetic challenge. Were regioselective alkylations of such compounds be achieved in the bench, a new avenue in the synthesis of natural products would be opened. The presence of more than one activated position with protons of similar acidity renders the synthetic goal really difficult, adding difficulties to those commonly encountered in alkylations of simple β-dicarbonyl compounds, i.e. C- vs O-alkylation, dialkylation at the carbon atom, retro-Claisen cleavage of the β-dicarbonyl compounds and instability of the alkylating agents to the generally required basic media. Thus, the alkylation under conventional conditions of methyl 3,5-dioxohexanoate, **1**, has been reported to produce a mixture of several of the possible alkylation products.[2] The terminal methyl group is exceptional in that regioselective reactions of poly-β-ketoesters with electrophiles is possible at this position thanks to the polyanion chemistry developed by Harris.[3]

We believe that the problem of the regioselective alkylations of **1** (Scheme 1) and of the related 4-hydroxy-6-methyl-2-pyrone (triacetic acid lactone), **3**, deserves attention. Pyrone **3** is itself a natural polyketide[4] and many related pyrones with biogenetically relevant substituents at C-3 and C-5 have been isolated from natural sources. Both **3**[5] and **1**[6] can be prepared from the industrially available dehydroacetic acid, **2**, a dimer of diketene (Scheme 1) and are therefore excellent candidates for the study of regioselective alkylations.

Our group has reported alkylations of **3** at position C-3 by a thioalkylation-desulfuration sequence,[7a] by palladium catalyzed thermodynamically controlled allylation[7b] and by cobalt(II) chloride catalyzed alkylation with activated alcohols.[7c] We have also reported alkylations at C-5 by Claisen rearrangement of 6-hydroxymethyl-4-methoxy-2-pyrone[8a] and through [2.3]sigmatropic rearrangement of sulfonium ylides.[8b]

We have also developed an alkylation technique for β-dicarbonyl compounds based on the use of their cobalt(II) complexes. This method can be applied to easily dehydrohalogenable alkyl halides[9a], to non active halides such as 1-adamantyl bromide[9b] and to other special halides such as 9-bromofluorene.[9c] Many transition metal complexes of β-diketones have been tested as alkylation substrates[10] but for reasons not completely understood yet cobalt(II) is by far the most useful metal. Contrariwise, the easily accessible and more stable copper(II) complexes of β-diketones are quite inert towards alkylating agents.

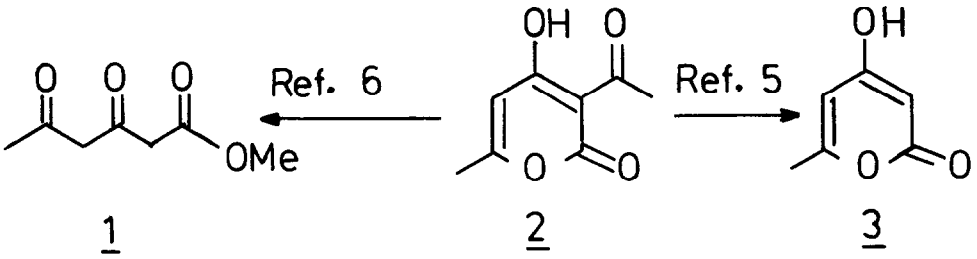
The mechanisms of the cobalt mediated alkylations are being intensively studied.[11] Two mechanisms operate simultaneously: one of them works through an electron transfer and radical initiated chain and it can be triggered by working at high concentrations or simply by driving the solutions to dryness.

With this background available we anticipated that if transition metal complexes of diketoester **1** could be formed with the metal linked at both ketone groups the cobalt(II) complex would have position C-4 activated and the copper complex would have the same position protected which would give us a chance to operate at C-2 by conventional methods.

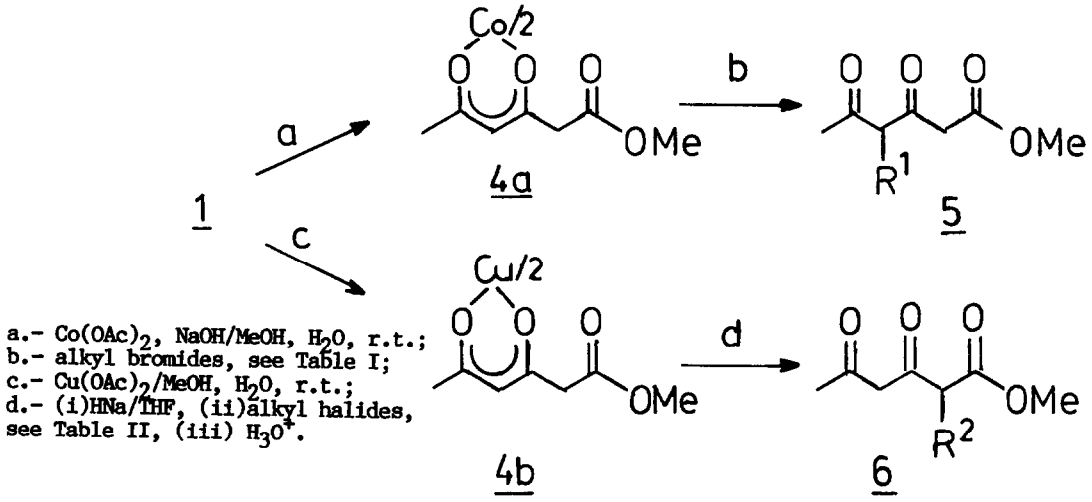
RESULTS

Alkylations of **1** at C-4. Diketoester **1** was converted into the cobalt(II) complex **4a** upon treatment with cobalt(II) acetate in methanol-water (Scheme 2). An infrared absorption at 1735 cm^{-1} was attributed to the free ester group of structure **4a**. It was not possible to perform an X-ray analysis neither of complex **4a** nor of the corresponding copper(II) complex **4b** but the synthetically useless dipyridine nickel complex (infrared absortion at 1735 cm^{-1}) gave suitable crystals for X-ray analysis that demonstrated that the nickel atom was indeed linked to both ketone oxygen atoms the ester group being free.[12]

The complex **4a** reacted with the alkyl bromides indicated in Table I to afford methyl 4-alkyl-3,5-dioxohexanoates, **5**, in reasonable yields (Scheme 2). Benzhydryl bromide and 1-bromo-3-methyl-2-butene required only refluxing in chloroform (runs 1 and 2) whereas 1-bromo-1-phenylethane (run 3) and 9-bromofluorene (run 4) needed more severe conditions. In particular the reaction of run 3 required triggering the chain mechanism in order to achieve



Scheme 1



a.- $Co(OAc)_2$, NaOH/MeOH, H_2O, r.t.;
b.- alkyl bromides, see Table I;
c.- $Cu(OAc)_2$/MeOH, H_2O, r.t.;
d.- (i)HNa/THF, (ii)alkyl halides, see Table II, (iii) H_3O^+.

Scheme 2

Table I. Alkylations at C-4 of Complex **4a**

run	alkylating agent	conditions[a]	5 (%)
1	Ph_2CH-Br	A	**5a** (62)
2	Me_2C=$CHCH_2$-Br	A	**5b** (42)
3	PhCH(Me)-Br	B	**5c** (46)
4	9-Bromofluorene	C	**5d** (33)

[a] A: Boiling in chloroform for 24 h. B: Evaporation of the chloroform and heating at 110°C for 15 min. C: Refluxing in chlorobenzene for 1h.

Table II. Alkylations at C-2 of Complex **4b**

run	alkylating agent	6 (%)
1	Et-Br	**6a** (85)
2	n-C_4H_9-I	**6b** (60)
3	CH_2=$CHCH_2$-Br	**6c** (83)
4	$PhCH_2$-Br	**6d** (73)
5	$MeOCOCH_2$-Br	**6e** (94)

synthetically useful rates. Compounds **5** exist as mixtures of enol and keto tautomers. The existence of two diastereoisomers of **5c**, each being present in keto and enol forms and the existence of enol forms of **5d** with hindered rotation render the 1H NMR spectra quite uninformative. Further evidence for the structures **5** come from cyclization to pyrones **10** (vide infra)

Alkylations of **1** at C-2. Reaction of the diketoester **1** with copper acetate in water-methanol afforded the complex **4b** (Scheme 2) which exhibits a peak at 1730 cm^{-1} in the infrared spectrum. Treatment of **4b** with sodium hydride in THF followed by primary alkyl halides and final hydrolysis afforded methyl 2-alkyl-3,5-dioxohexanoates, **6**, in high yields (Scheme 2 and Table II). The diketoesters **6** were mixtures of keto and enol tautomers. 2-Bromopropane did not react under the described conditions. This is a limitation recently overcome since allylation at C-2 has been achieved with primary, secondary and even with tertiary radicals under palladium catalysis.[13]

Alkylations of **1** at C-2 and C-4. The cobalt(II) and the copper(II) complexes of β-diketones are very different in reactivity. However, a very active halide such as benzhydryl bromide can react with both metal complexes. Thus, reaction of copper bis-pentano-2,4-dionato with benzhydryl bromide affords 3-benzhydryl-2,4-pentanedione, **7**, in 77% yield (Scheme 3). This fact suggested the idea of double alkylations of diketoester **1** at C-2 with several alkyl halides and at C-4 with benzhydryl bromide. This was acomplished (Scheme 3 and Table III) by initial alkylation at C-2 of the copper complex **4b** avoiding the hydrolysis step. The alkylated complexes **8** were in general not isolated. Instead the solvent (THF) was evaporated and replaced with chloroform after which the second alkylation step with benzhydryl bromide was performed to afford methyl 2-alkyl-4-benzhydryl-3,5-dioxohexanoates, **9**, as mixtures of diastereoisomers. Complex **8e** (R = $MeOCOCH_2$, numbering of Table II) was isolated and fully characterized.

Conversion of Diketoesters **5**, **6** and **9** to Pyrones **10** and Pyrazoles **11**. The accessibility of diketoesters regioselectively alkylated at C-2 and C-4 permitted us a new synthesis of triacetic acid lactone derivatives **10** regioselectively alkylated at C-3 and C-5. Cyclizations of polyketoacids and their esters under acid conditions[14] or in the presence of carbonyldiimidazole[15] afford pyrones. However, acid media should be avoided in our case due to the propensity of 3-allyl-4-hydroxy-6-methyl-2-pyrones to cyclize through protonation of the allyl moiety.[16] On the other hand treatment of poly-β-ketoacids and their esters under basic conditions frequently results on the formation of aromatic carbocyclic compounds.[3a,17]

We have developed a very useful and general method to cyclize diketoesters **5**, **6** and **9** to pyrones **10** regioselectively alkylated at C-3 and C-5 by using one equivalent of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in refluxing benzene. Thus, pyrones **10** (Table IV and Scheme 4) could be prepared in excellent yields but for compound **10j**. However, pyrazole **11j** was prepared by the conventional method.

When this work was well advanced we became aware that W. Oppolzer and coworkers reported one cyclization of a diketoester to the related pyrone using DBU in toluene in

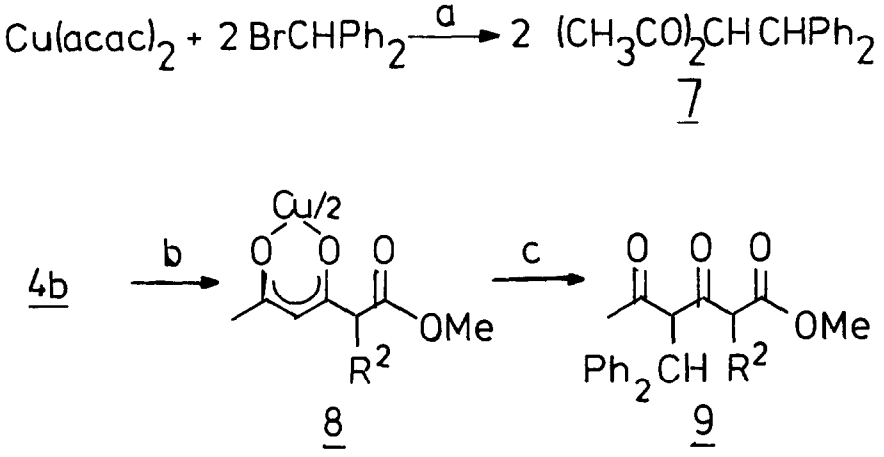
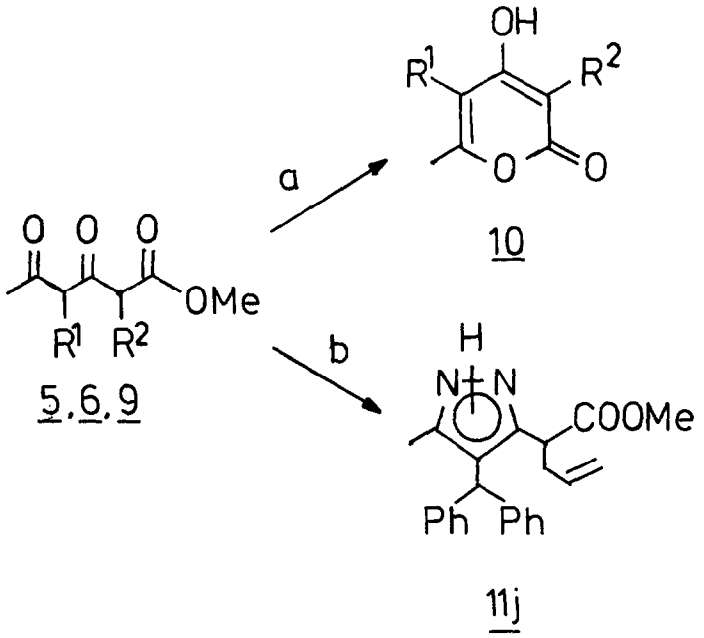


Table III. Alkylations at C-2 and at C-4 of Complex **4b**

run	R^2-Br	**9** (%)
1	CH_2=$CHCH_2$-Br	**9a** (76)
2	$PhCH_2$-Br	**9b** (79)
3	$MeOCOCH_2$-Br	**9c** (60)
4	MeOCOCH(Me)-Br	**9d** (52)

a.- $HCCl_3$, reflux; b.- (i) HNa/THF, (ii) alkyl halides, see Table III; c.- $BrCHPh_2/HCCl_3$, reflux.

Scheme 3



a.- DBU/benzene, reflux; b.- hydrazine hydrate.

Scheme 4

Table IV. Formation of Pyrones **10** and Pyrazole **11j**

run	diketoester	10 or 11 (%)	R^1	R^2
1	**5a**	**10a** (100)	Ph_2CH-	H
2	**5b**	**10b** (98)	Me_2CH=$CHCH_2$-	H
3	**5c**	**10c** (70)	$PhCH(Me)$-	H
4	**5d**	**10d** (96)	9-Fluorenyl-	H
5	**6a**	**10e** (88)	H	Et
6	**6b**	**10f** (65)	H	n-C_4H_9
7	**6c**	**10g** (100)	H	CH_2=$CHCH_2$-
8	**6d**	**10h** (73)	H	$PhCH_2$-
9	**6e**	**10i** (77)	H	$MeOCOCH_2$-
10	**9a**	**10j** (0)	Ph_2CH-	CH_2=$CHCH_2$-
11	**9b**	**10k** (79)	Ph_2CH-	$PhCH_2$-
12	**9c**	**10l** (100)	Ph_2CH-	$MeOCOCH_2$-
13	**9d**	**10m** (84)	Ph_2CH-	$MeOCOCH(Me)$-
14	**9a**	**11j** (70)	Ph_2CH-	CH_2=$CHCH_2$-

their synthesis of deoxypolypropionate structures.[18]

Evidences supporting structures **10**. These methods of regioselective alkylations of diketoester **1** rely upon the correct assignment of structure to compounds **5**, **6** and **9**. We have already mentioned the relatively uninformative character of the 1H NMR spectra of compounds **5** and **6**. However, the site of alkylation on compounds **10a-i** can be determined considering the following facts:

1.- Triacetic acid lactone, **3**, itself exhibits (in Me_2SO-d_6) two doublets (J ca. 2Hz) at 5.22 (proton at C-3) and 5.96 (proton at C-5). The difference in chemical shifts is the expected from the electron donating ability of the OH group at C-4. Other 6-alkyl-4-hydroxy-2-pyrones show similar behaviour.[19] All our reported related pyrones unsubstituted at C-3 show absortions due to the proton at C-3 in the range 5.22-5.60[19,20,21]. Also, pyrones unsubstituted at C-5 show absortions due to the proton at C-5 in the range 5.65-6.32.[7a,7b,7c,8a,19,21,22,23] Pyrones **10a-d** reported in this paper as having a substituent at C-5 exhibit absortions for the proton at C-3 in the range 5.3-5.5. On the other hand, pyrones **10e-i** substituted at C-3 show signals for the protons at C-5 in the range 5.87-6.15.

2.- The active protons at C-3 interexchange upon addition of D_2O. This is sometimes observed even in $CDCl_3$ solutions without added D_2O. We have checked this behaviour for **10b** and **10c** as indicated in the experimental part.

3.- Pyrones **10a** and **10b** exhibit signals for their protons at C-3 at 5.3 and 5.45 respectively. Their isomers substituted at C-3 with the same radicals have been reported.[7c] Their melting points are different and they show signals for their protons at C-5 at 5.8 and 6.2 respectively.

4.- Compounds **10f** and **10h** have been compared with samples previously synthesized by a different route.[7a]

5.- The assignment of structure to the doubly alkylated products **10j-m** rely upon the belief that the initial copper mediated alkylation produces always reaction at the C-2 position of the diketoester as observed for **6a-e**.

EXPERIMENTAL

All melting points are uncorrected. 1H NMR and 13C NMR spectra were recorded at 80 and 20 MHz unless otherwise stated using TMS as internal standard. Mass spectra were recorded at 70 eV; only peaks with relative intensity higher than 20 are reported unless they correspond to the molecular ion. The benzhydryl bromide used in this work was 92% pure the rest being diphenylmethane.

Methyl 3,5-dioxohexanoate, **1**, was prepared by treatment of dehydroacetic acid, **2**, with magnesium methoxide according to the method of Batelaan.[6]

Bis(Methyl 3,5-dioxohexanoate)cobalt(II) Dihydrate, **4a**

Solutions of cobalt(II) acetate (3.24 g, 16.0 mmol) in water (20 mL) and sodium hydroxide (1.25 g, 31.3 mmol) in water (5 mL) were sequentially added under argon atmosphere to a stirred solution of **1** (5.0 g, 31.6 mmol) in methanol (5 mL). The mixture was stirred at least for 10 h after which the solid was quickly filtered and dried in vacuum to afford 5.25 g (81%) of **4a**: mp 75-76ºC; IR(KBr) 1735 cm^{-1}; MS, m/e (relative intensity) 373(M, 19), 326(20), 144(26), 85(30), 69(24), 59(35), 43(100). Anal. Calcd for $C_{14}H_{22}CoO_{10}$: C, 41.08; H, 5.43. Found: C, 41.18; H, 5.36.

Bis(Methyl 3,5-dioxohexanoate)copper(II), **4b**

A solution of copper(II) acetate monohydrate (7.0 g, 35 mmol) in water (100 mL) was added into a stirred solution of **1** (10.0 g, 63 mmol) in methanol (10 mL). The immediately

formed precipitate was filtered, sequentially washed with water and with cold acetone and dried under vacuum to afford 11.0 g (92%) of **4b**: mp 201-205ºC; IR(KBr) 1730 cm^{-1}; MS, m/e (relative intensity) 377(M, 14), 221(23), 220(21), 189(23), 147(32), 85(20), 69(27), 59(54), 43(100). Anal. Calcd for $C_{14}H_{18}CuO_8$: C, 44.50; H, 4.76. Found: C, 44.62; H, 4.81.

Methyl 4-Benzhydryl-3,5-dioxohexanoate, **5a** (Run 1, Table I)

A solution of **4a** (1.0 g, 2.45 mmol) and benzhydryl bromide (1.21 g, 4.89 mmol) in chloroform (25 mL) was refluxed under magnetic stirring for 24 h. The mixture was partitioned between 1N HCl and dichloromethane. The organic layer was dried and evaporated. The residue (1.98 g) was dissolved in ether (10 mL) and pentane was added till permanent turbidity. A precipitate appeared upon cooling at -10ºC which was filtered and washed with cold pentane to afford **5a** (0.99 g, 62%): mp 86-88ºC; IR(KBr) 1740, 1720, 1700 cm^{-1}; 1H NMR($CDCl_3$) keto form δ 2.0(s, 3H), 3.3(center of a AB system, J = 16 Hz, 2H), 3.6(s, 3H), 4.8(center of a AB system J = 12 Hz, 2H), 7.2(apparent s, 10H); 13C NMR($CDCl_3$) δ 29.4, 48.5, 51.4, 52.1, 73.1, 127.0, 127.7, 128.4, 128.7, 128.8, 140.9, 166.4, 196.9, 201.8; MS, m/e (relative intensity) 324(M, 2), 281(42), 223(35), 207(53), 178(20), 167(100), 165(41), 152(22), 43(35). Anal. Calcd for $C_{20}H_{20}O_4$: C, 74.04; H, 6.23. Found: C, 74.32; H, 6.34.

Methyl 4-(3-Methyl-2-buten-1-yl)-3,5-dioxohexanoate, **5b** (Run 2, Table I)

This compound was prepared from 1-bromo-3-methyl-2-butene by the same procedure as **5a** under the experimental conditions indicated in Table I. **5b**: bp (oven temperature) 140ºC/1 mmHg; IR($HCCl_3$) 1730, 1690 cm^{-1}; 1H NMR($CDCl_3$) δ keto form predominating 1.75(apparent d, J = 7 Hz, 6H), 2.15(s, 3H), 2.55(broad t, J = 7 Hz, 2H), 3.5(s, 2H), 3.9(s overlapped with t, 4H), 5.0(m, 1H); 13C NMR δ 17.2, 25.1, 26.7, 28.7, 47.9, 51.7, 66.5, 119.3, 134.5, 166.7, 198.3, 203.1; MS m/e (relative intensity) 226(M, 0.6), 188(33), 109(38), 69(36), 43(100). Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.06; H, 8.33.

Methyl 4-(1-Phenylethyl)-3,5-dioxohexanoate, **5c** (Run 3, Table I)

This compound was prepared from 1-bromo-1-phenylethane by the same procedure as **5a** under the experimental conditions indicated in Table I. **5c**: bp (oven temperature) 110-120ºC/0.8 mmHg; MS, m/e (relative intensity) 262(M, 2), 219(20), 208(33), 193(29), 161(49), 145(22), 129(22), 115(51), 105(100), 77(29), 43(18).

Methyl 4-(9-Fluorenyl)-3,5-dioxohexanoate, **5d** (Run 4, Table I)

This compound was prepared from 9-bromofluorene by the same procedure as **5a** under the experimental conditions indicated in Table I. It was directly converted into **10d**.

Methyl 2-Ethyl-3,5-dioxohexanoate, **6a** (Run 1, Table II)

A mixture of **4b** (0.5 g, 1.26 mmol) and 50% sodium hydride (0.12 g, 2.52 mmol) in THF (20 mL) was refluxed for 5 min. Ethyl bromide (4.27 g, 39.2 mmol) was added portionwise during 7 h to the refluxing mixture which after cooling was partitioned between 1N hydrochloric acid and dichloromethane. The organic layer was washed, dried and evaporated. The residue was chromatographed through silica gel to afford **6a** (85%) upon elution with hexane-ether. **6a**: bp (oven temperature) 85-87ºC/1.1 mmHg; IR(film) 1742, 1610 cm^{-1}; 1H NMR($CDCl_3$) enol form δ 0.95(t, J = 7.6 Hz, 3H), 1.90(dq J 7.6 and 7.6 Hz, 2H), 2.07(s, 3H), 3.19(t, J = 7.6 Hz, 1H), 3.74(s, 3H), 5.60(s, 1H), 15.18(broad s, 1H); 13C NMR($CDCl_3$) δ 11.5, 22.4, 23.8, 51.8, 56.5, 99.1, 170.3, 189.3, 191.0; MS m/e (relative intensity) 186(M, 17), 87(44), 85(100), 69(25), 55(25), 43(43). Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 58.30; H, 7.97.

Methyl 2-n-Butyl-3,5-dioxohexanoate, **6b** (Run 2, Table II)

This compound was prepared from 1-iodobutane by the same procedure as **6a** after refluxing 4 h. **6b**: bp (oven temperature) 89-91ºC/1.2 mmHg; IR(film) 1740, 1610 cm^{-1}; 1H NMR($CDCl_3$) enol form δ 0.93(t, J, = 6 Hz, 3H), 1.37(m, 4H), 1.86(dt, J 8 and 8 Hz, 2H), 3.25(t, J = 8 Hz, 1H), 3.67(s, 3H), 5.57(s, 1H), 14.2(broad s, 1H); 13C NMR($CDCl_3$) δ 13.6, 22.2, 23.9, 28.9, 29.4, 52.1, 55.2, 99.2, 170.6, 189.3, 191.4; MS m/e (relative intensity) 215(M+1, 30), 214(M, 4), 87(31), 85(48), 69(23), 55(39), 43(100), 41(26). Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.50; H, 8.70.

Methyl 2-Allyl-3,5-dioxohexanoate, **6c** (Run 3, Table II)

This compound was prepared from allyl bromide by the same procedure as **6a** after refluxing 1 h. **6c**: bp (oven temperature) 83-84ºC/1.2 mmHg; IR(film) 1740, 1610 cm^{-1}; 1H NMR($CDCl_3$) enol form δ 2.03(s, 3H), 2.57(dd, J = 7 and 7 Hz, 2H), 3.33(t, J = 7 Hz, 1H), 3.67(s, 3H), 4.77-6.08(m, 3H), 5.55(s, 1H), 14.4(broad s, 1H); 13C NMR($CDCl_3$) δ 23.7, 32.9, 52.0, 54.7, 99.3, 117.1, 134.0, 169.8, 189.0, 190.6; MS m/e 199(M+1, 2), 85(52), 55(23), 43(100), 41(29). Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.60; H, 7.50.

Methyl 2-Benzyl-3,5-dioxohexanoate, **6d** (Run 4, Table II)

This compound was prepared from benzyl bromide by the same procedure as **6a** after refluxing 3 h. **6d**: bp (oven temperature) 100ºC/1 mmHg; IR(film) 1740, 1600 cm^{-1}; 1H NMR($CDCl_3$) δ enol form 2.02(s, 3H), 3.18(d, J = 7 Hz, 2H), 3.55(t, J = 7 Hz, 1H), 3.69(s, 3H), 5.57(s, 1H), 7.23(aromatic, 5H), 15.18(broad s, 1H); 13C NMR($CDCl_3$) δ 23.7, 34.8, 52.1, 57.0, 99.6, 126.5, 128.3, 128.6, 137.9, 169.8, 189.0, 190.4; MS m/e 248(M, 25), 163(58), 131(80), 104(38), 103(21), 104(38), 103(21), 91(77), 85(100), 77(25), 43(85). Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.44; H, 6.59.

Methyl 3-Methoxycarbonyl-4,6-dioxoheptanoate, **6e** (Run 5, Table II)

This compound was prepared from methyl bromoacetate by the same procedure as **6a** after refluxing 20 min. **6e**: mp 61-62ºC (acetone-pentane); IR(KBr) 1735, 1720, 1615 cm^{-1}; 1H NMR($CDCl_3$) δ enol form 2.10(s, 3H), 2.92(d, J = 8 Hz, 2H), 3.67(s, 3H), 3.75(s, 3H), 3.80(t, J = 8 Hz, 1H), 5.67(s, 1H), 14.20(broad s, 1H); 13C NMR($CDCl_3$) δ 23.2, 32.3, 50.9, 51.7, 52.4, 53.9, 99.5, 169.2, 171.3, 187.6, 190.7; MS, m/e 230(M, 3), 114(47), 85(100), 55(33), 43(39); Anal. Calcd for $C_{10}H_{14}O_6$: C, 52.17; H, 6.13. Found: C, 52.29; H, 6.46.

3-Benzhydrylpentane-2,4-dione, **7**

A mixture of copper bis-pentane-2,4-dionato (1.0 g, 3.83 mmol), benzhydryl bromide (1.8 g, 7.16 mmol) and ethanol-free chloroform (20 mL) was refluxed for 70 min. The colour changed from blue to green. The mixture was partitioned between 1N HCl and dichloromethane. The organic layer was washed, dried and evaporated. The residue was taken in hot hexane and upon cooling gave 1.47 g (77%) of diketone **7**: mp 114-115ºC (lit.[9a] mp 113-115ºC).

Bis(Methyl 3-Methoxycarbonyl-4,6-dioxoheptanoate)copper(II), **8e**

50% Sodium hydride (0.121 g, 2.53 mmol) was added at 0ºC into a stirred solution of **4b** (0.54 g, 1.26 mmol) in anhydrous THF (10 mL) and the mixture kept for 2h under these conditions. Methyl bromoacetate (0.38 g, 2.52 mmol) was added and the mixture stirred at 0ºC for 3 h and at 20ºC for 10 h. Hexane (5 mL) was added and the formed precipitate was filtered off and washed with dichloromethane. The combined organic solutions were evaporated to afford a blue solid (0.801 g) which was recrystallized from THF-hexane to afford **8e** (0.545 g, 80%). A sample for elemental analysis was recrystallized from THF-cyclohexane. **8e**: mp 165-168ºC; IR(KBr) 1730 cm^{-1}; MS, m/e (relative intensity) 521(M, 0.2), 293(32), 291(30), 208(37), 169(24), 151(24), 149(63), 147(45), 146(22), 114(59), 85(100), 43(47). Anal. Calcd for $C_{20}H_{26}CuO_8$: C, 46.06; H, 4.99. Found: C, 46.09; H, 5.69.

Methyl 4-Benzhydryl-2-benzyl-3,5-dioxohexanoate, **9b** (Run 2, Table III)

50% Sodium hydride (0.243 g, 5.06 mmol) was added into a solution of **4b** (1.0 g, 2.53 mmol) in anhydrous THF (10 mL). After refluxing 5 min the colour changed from blue to green. At this moment benzyl bromide (0.86 g, 5.06 mmol) was added and the mixture refluxed for 1 h the blue colour being recovered. The solvent was evaporated under vaccum and the residue was dissolved in ethanol free chloroform (10 mL) and benzhydryl bromide (1.45g, 5.06 mmol) was added. The new mixture was refluxed for 18 h and partitioned between dichloromethane and 1N HCl. The organic layer was washed, dried and evaporated to afford 2.3 g of a residue which was chromatographed through silica gel with hexane-ether (3:2) to afford 1.65 g (79%) of **9b** as a mixture of diastereoisomers that crystallized spontaneously upon standing. A sample was recrystallized from methanol: mp 113-115ºC; IR(KBr) 1740, 1700 cm^{-1}; 1H NMR($CDCl_3$) δ 1.55(s, 3H), 2.95(d, J = 7.7 Hz, 2H), 3.35(s, 3H), 4.0(t, J = 7.7 Hz, 1H), 4.95 (center of the AB system, 2H), 7.0-7.3 (m, 15H); 13C NMR($CDCl_3$) δ 27.3, 28.1, 33.0, 33.3, 46.6, 47.7, 48.7, 49.8, 50.2, 52.2, 60.3, 62.1, 72.3, 74.7, 126.3, 126.5, 126.8, 127.5, 127.69, 127.73, 128.0, 128.3, 128.7, 137.4, 140.3, 140.5, 141.2, 167.5, 197.2, 201.9; MS m/e (relative intensity) 414(M, 4), 223(54), 207(33), 167(100), 165(22), 159(32), 91(38). Anal. Calcd for $C_{27}H_{26}O_4$: C, 78.24; H, 6.32. Found: C, 78.13; H, 6.35.

Methyl 5-Benzhydryl-3-methoxycarbonyl-4,6-dioxoheptanoate, **9c** (Run 3, Table III)

This compound was prepared by the same procedure as **9b** from sodium hydride (0.12 g, 2.53 mmol), **4b** (0.5 g, 1.26 mmol), anhydrous THF (10 mL), methyl bromoacetate (0.38 g, 2.53 mmol) and benzhydryl bromide (0.658 g, 2.53 mmol). **9c** was a mixture of diastereoisomers (0.60g, 60%). A sample was recrystallized from acetone-pentane: mp 120-123ºC; IR(KBr) 1750, 1745, 1700, 1500 cm^{-1}; 1H NMR($CDCl_3$) δ 2.0(s, 3H), 2.76-2.81(m, 2H), 3.47(s, 3H), 3.68(s, 3H), 4.1-4.2(m, 1H), 7.1-7.3(m, 10H); 13C NMR($CDCl_3$) δ 27.4, 31.4, 50.0, 51.4, 52.2, 54.0, 73.7, 126.2, 127.5, 128.0, 128.4, 140.3, 141.1, 166.3, 170.5, 196.1, 201.1; MS m/e (relative intensity) 396(M, 1), 223(43), 207(40), 167(100), 165(44), 152(25), 145(33), 113(47). Anal. Calcd for $C_{23}H_{24}O_6$: C, 69.68; H, 6.10. Found: C, 69.49; H, 6.16.

Methyl 5-Benzhydryl-3-methoxycarbonyl-2-methyl-4,6-dioxoheptanoate, **9d** (Run 4, Table III)

This compound was prepared by the same procedure as **9b** from sodium hydride (0.768 g, 16.0 mmol), **4b** (3.0 g, 8.0 mmol), anhydrous THF (50 mL), methyl 2-bromopropanoate (3.34 g,

20.0 mmol) and benzhydryl bromide (4.94 g, 20 mmol). **9d** was a mixture of diastereoisomers (3.40 g, 52%). A sample was recrystallized from acetone-pentane: mp 172-190ºC; IR(KBr) 1751, 1728, 1701, 1698 cm^{-1}; 1H NMR($CDCl_3$) of a sample enriched in one diastereoisomer δ 0.53(d, J = 6.9 Hz, 3H), 1.95(s, 3H), 3.05(m, 1H), 3.60(s, 3H), 3.64(s, 3H), 3.5-3.7(m, 1H), 4.9 (center of an AB system, 2H), 7.3 (10H); MS m/e (relative intensity) 410(M, 4), 367(32), 335(26), 207(76), 178(28), 167(100), 165(61), 159(27), 152(25), 127(40), 69(24), 59(23), 43(71). Anal. Calcd for $C_{24}H_{26}O_6$: C, 70.23; H, 6.38. Found: C, 70.04; H, 6.46.

Methyl 2-Allyl-4-benzhydryl-3,5-dioxohexanoate, **9a** (Run 1, Table III) and 4-Benzhydryl-3(5)-(1-methoxycarbonyl-3-buten-1-yl)-5(3)-methylpyrazole, **11j** (Run 14, Table IV)

Compound **9a** was prepared by the same procedure as **9b** from sodium hydride (0.121 g, 2.52 mmol), **4b** (0.5 g, 1.26 mmol), anhydrous THF (10 mL), allyl bromide (0.30 g, 2.52 mmol) and benzhydryl bromide (0.692 g, 2.52 mmol) to afford 1.26 g (76%) of a residue which could not be purified properly and was directly converted into **11j**. **9a**: IR(film) 1750, 1705 cm^{-1}.

Crude **9a** (0.544 g, 1.45 mmole) in dichloromethane (10 mL) was mixed with a solution of hydrazine hydrate (0.075 g, 1.149 mmol) in methanol (10 mL). The mixture was left 72 h at -10ºC and evaporated to give a residue which was chromatographed through silica gel with a mixture of hexane-ether-methanol (2.0:6.0:0.1). Pyrazole **11j** (0.37 g, 70%): mp 126-128ºC (ether-hexane); IR(KBr) 3234(broad), 1739 cm^{-1}; 1H NMR($CDCl_3$) δ 1.81(s, 3H), 2.0-2.9(m, 3H), 3.55(s, 3H), 4.65-5.65(m, 4H), 7.0-7.3(m, 10H), 9.90(broad s, 1H); 13C NMR($CDCl_3$) δ 11.7, 36.1, 42.9, 46.1, 51.8, 116.9, 117.7, 126.2, 126.3, 128.15, 128.21, 129.09, 129.14, 134.9, 142.42, 142.9, 172.8; MS m/e (relative intensity) 361(15), 360(M, 28), 259(100), 258(55), 147(86), 192(31), 167(91), 165(41), 152(22), 115(25), 91(34), 77(27), 59(22), 42(22), 41(52). Anal. Calcd for $C_{23}H_{24}N_2O_2$: C, 76.64; H, 6.71; N, 7.77. Found: C, 76.88; H, 6.65; N, 7.54.

4-Hydroxy-6-methyl-5-(3-methyl-2-buten-1-yl)-2-pyrone, **10b** (Run 2, Table IV)

A mixture of the diketoester **5b** (0.404 g, 1.79 mmol), DBU (0.28 g, 1.79 mmol) and benzene (5 mL) was refluxed for 1 h. The cooled mixture was partitioned between 1N HCl and ethyl acetate. The organic layer was washed, dried and evaporated to afford **10b** (0.34 g, 98%): mp 143-144ºC (acetone); IR(KBr) 3200-2500(broad), 1680, 1630 cm^{-1}; 1H NMR($CDCl_3$+CD_3OD) δ 1.75(br s, 6H), 2.15(s, 3H), 3.05(br d, J = 7 Hz, 2H), 5.0(t, J = 7 Hz, 1H), 5.45(s, 1H, interex. with D_2O); MS m/e (relative intensity) 194(M, 4), 151(29), 43(100). Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.10; H, 7.27. Found: C, 67.79; H, 7.42.

5-Benzhydryl-4-hydroxy-6-methyl-2-pyrone, **10a** (Run 1, Table IV)

This compound was prepared by the same procedure as **10b** from diketoester **5a**. Pyrone **10a** (100%): mp 185-188ºC (THF); IR(KBr) 3500-2500(br), 1700, 1630 cm^{-1}: 1H NMR(Me_2SO-d_6) δ 2.0(s, 3H), 5.3(s, 1H), 5.7(s, 1H), 7.0-7.3(m, 10H); 13C NMR(Me_2SO-d_6) δ 18.9, 46.1, 89.6, 114.5, 126.8, 128.7, 128.9, 141.8, 161.6, 164.1, 170.8; MS m/e (relative intensity) 292(M, 23), 203(22), 187(25), 179(24), 178(38), 165(30), 115(22), 77(28), 51(30), 43(100), 42(59).

4-Hydroxy-6-methyl-5-(1-phenylethyl)-2-pyrone, **10c** (Run 3, Table IV)

This compound was prepared by the same procedure as **10b** from diketoester **5c**. Pyrone **10c** (70%): mp 212-215ºC; IR(KBr) 3200-2800(br), 1715, 1615 cm^{-1}; 1H NMR($CDCl_3$+CD_3OD) δ 1.7(d, J = 7 Hz, 3H), 2.1(s, 3H), 4.4(q, J = 7 Hz, 1H), 5.45(s, 1H, interex. with D_2O); MS m/e (relative intensity) 230(M, 38), 187(40), 43(100). Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.03; H, 6.13. Found: C, 73.09; H, 6.24.

5-(9-Fluorenyl)-4-hydroxy-6-methyl-2-pyrone, **10d** (Run 4, TableIV)

This compound was prepared by the same procedure as **10b** from diketoester **5d**. Pyrone **10d** (96%): mp 159-161ºC (THF-pentane); IR(KBr) 3300-2400(br), 1690, 1630 cm^{-1}; 1H NMR($CDCl_3$+CD_3OD) δ 1.15(s, 3H), 5.5(s, 1H), 5.6(s, 1H), 7.2-7.9(m, 10H); MS m/e (relative intensity) 290(M, 26), 43(100).

3-Ethyl-4-hydroxy-6-methyl-2-pyrone, **10e** (Run 5, Table IV).

This compound was prepared by the same procedure as **10b** from diketoester **6a**. Pyrone **10e** (88%): mp 188-189ºC (acetone-pentane); IR(KBr) 3200-2400(br), 1670, 1625 cm^{-1}; 1H NMR($CDCl_3$+CD_3OD) δ 1.00(t, J = 7.2 Hz, 3H), 2.11(s, 3H), 2.38(q, J = 7.2 Hz, 2H), 5.87(s, 1H); 13C NMR($CDCl_3$+CD_3OD) δ 11.8, 15.9, 18.9, 100.5, 103.9, 159.4, 165.8, 167.2; MS m/e (relative intensity) 154(M, 38), 139(38), 111(100), 85(60), 69(37), 55(21), 43(61). Anal. Calcd for $C_8H_{10}O_3$: C, 62.33; H, 6.54. Found: C, 62.34; H, 6.84.

3-n-Butyl-4-hydroxy-6-methyl-2-pyrone, **10f** (Run 6, Table IV)

This compound was prepared by the same procedure as **10b** from diketoester **6b**. Pyrone **10f** (65%): mp 132-133ºC (lit.[7a] mp 132-133ºC).

3-Allyl-4-hydroxy-6-methyl-2-pyrone, **10g** (Run 7, Table IV)

This compound was prepared by the same procedure as **10b** from diketoester **6c**. Pyrone **10g**

(100%): mp 159-160ºC (acetone-pentane): IR(KBr) 3200-2400(br); 1670-1620 cm^{-1}; 1H NMR($CDCl_3$+CD_3OD) δ 2.15(s, 3H), 3.15(d, J = 6.6 Hz, 2H), 4.77-5.20(m, 2H), 5.93(s, 1H), 5.95(br s, 1H); 13C NMR($CDCl_3$+CD_3OD) δ 19.1, 26.7, 100.2, 100.6, 114.4, 134.5, 160.1, 166.5, 167.0; MS m/e (relative intensity) 166(M, 32), 151(46), 111(21), 95(37), 85(47), 82(37), 81(23), 69(45), 55(26), 43(100). Anal. Calcd for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found: C, 65.35; H, 6.61.

3-Benzyl-4-hydroxy-6-methyl-2-pyrone, **10h** (Run 8, Table IV)

This compound was prepared by the same procedure as **10b** from diketoester **6d**. Pyrone **10h** (86%): mp 171-172ºC (acetone-pentane) (lit.[7a] mp 168ºC); IR(KBr) 3200-2400(br), 1660, 1620 cm^{-1}; 1H NMR($CDCl_3$) δ 2.20(s, 3H), 3.78(s, 2H), 6.00(s, 1H), 7.2-7.4(s, 5H).

4-Hydroxy-3-methoxycarbonyl-6-methyl-2-pyrone, **10i** (Run 9, Table IV)

This compound was prepared by the same procedure as **10b** from diketodiester **6e**. Pyrone **10i** (77%): mp 179-184ºC (acetone-pentane); IR(KBr) 3200-2300(br), 1730, 1660-1630 cm^{-1}; 1H NMR($CDCl_3$+CD_3OD) δ 2.27(s, 3H), 3.43(s, 2H), 3.68(s, 3H), 5.97(s, 1H). Anal. Calcd for $C_9H_{10}O_5$: C, 54.55; H, 5.09. Found: C, 54.79; H, 5.07.

5-Benzhydryl-3-benzyl-4-hydroxy-6-methyl-2-pyrone, **10k** (Run 11, Table IV)

This compound was prepared by the same procedure as **10b** from diketoester **9b**. Pyrone **10k** (79%): mp 148-150ºC (methanol); IR(KBr) 3400-2800(br) cm^{-1}; 1H NMR($CDCl_3$) at 60 MHz δ 1.99(s, 3H), 3.70(s, 2H), 5.6(s, 1H), 7.0-7.2(m, 15H); 13C NMR($CDCl_3$) δ 18.1, 28.8, 46.6, 103.7, 103.7, 113.1, 125.8, 126.9, 128.0, 128.3, 128.5, 138.5, 139.9, 158.5, 164.2, 164.6; MS m/e (relative intensity) 382(M, 43), 249(21), 215(23), 207(36), 179(22), 178(42), 167(27), 152(25), 91(100), 77(46), 65(24), 43(90). Anal. Calcd for $C_{26}H_{22}O_3$: C, 81.65; H, 5.80. Found: C, 81.67; H, 5.95.

5-Benzhydryl-4-hydroxy-3-methoxycarbonylmethyl-6-methyl-2-pyrone, **10l** (Run 12, Table IV)

This compound was prepared by the same procedure as **10b** from diketodiester **9c**. Pyrone **10l** (100%): mp 132-133ºC (acetone-pentane); IR(KBr) 3600-2400, 1748, 1668, 1638 cm^{-1}; 1H NMR($CDCl_3$) at 60 MHz δ 2.0(s, 3H), 2.6(s, 2H), 2.7(s,3H), 5.7(s, 1H), 7.2(m, 10H); 13C NMR($CDCl_3$) δ 18.7, 29.6, 46.2, 47.9, 49.0, 50.0, 52.4, 96.4, 114.8, 126.6, 128.4, 128.6, 140.9, 159.7, 164.9, 166.9, 173.6; MS m/e (relative intensity) 365(15), 364(M, 52), 304(100), 305(25), 233(34), 227(36), 215(21), 205(20), 199(35), 179(32), 178(46), 173(39), 167(31), 165(50), 152(39), 131(37), 129(28), 128(28), 115(24). Anal. Calcd for $C_{22}H_{20}O_5$: C, 72.57; H, 5.55. Found: C, 72.64; H, 5.39.

5-Benzhydryl-4-hydroxy-3-(1-methoxycarbonyl)ethyl-6-methyl-2-pyrone, **10m** (Run 13, Table IV)

This compound was prepared by the same procedure as **10b** from diketodiester **9d**. Pyrone **10m** (84%): mp 127-130ºC (ether); IR(KBr) 3400-2800(br), 1735, 1660 cm^{-1}; 1H NMR($CDCl_3$) δ 1.4(d, J = 7.7 Hz, 3H), 1.92(s, 3H), 3.76(s, 3H), 4.26(q, J = 7.7 Hz, 1H), 5.82(s, 1H), 7.0-7.45(m, 10H), 10.74(s, 1H); 13C NMR($CDCl_3$) δ 16.4, 18.9, 36.4, 45.8, 53.1, 100.9, 115.2, 126.5, 128.4, 128.6,141.1, 159.6, 164.0, 166.7, 179.9; MS m/e (relative intensity) 370(M, 61), 319(61), 318(100), 275(26), 213(21), 207(23), 179(27), 178(36), 173(59), 167(40), 165(36), 152(28), 131(35), 77(20), 43(54). Anal. Calcd for $C_{23}H_{22}O_5$: C, 73.00; H, 5.86. Found: C, 73.22; H, 5.97.

ACKNOWLEDGEMENTS

Financial support from CAICYT and from DGICYT (Grants 2014/83 and 0030/87) are gratefully acknowledged.

REFERENCES

1. Preliminary reports of this work have been published: (a) Cervelló, J.; Marquet, J.; Moreno-Mañas, M. J. Chem. Soc., Chem. Commun. **1987**, 644. (b) Cervelló, J.; Marquet, J.; Moreno-Mañas, M. Tetrahedron Lett. **1987**, 28, 3715.

2. Gelin, S.; Rouet, J. Bull. Soc. Chim. Fr. **1972**, 232.

3. (a) Harris, T.M.; Harris, C.M. Pure Appl. Chem. **1986**, 58, 283. (b) Hauser, C.P.; Harris, T.M. J. Am. Chem. Soc. **1958**, 80, 6360. (c) Harris, T.M.; Harris, C.M. Tetrahedron **1977**, 33, 2159.

4. Bentley, R.; Zwitkowits, P.M. J. Am. Chem. Soc. **1967**, 89, 676 and 681.
5. Collie, J.N. J. Chem. Soc. **1891**, 59, 607.
6. Batelaan, J.G. Synth. Commun. **1976**, 6, 81.
7. (a) Moreno-Mañas, M.; Pleixats, R. Synthesis, **1984**, 430. (b) Moreno-Mañas, M.; Ribas, J.; Virgili, A. J. Org. Chem. **1988**, 53, 5328. (c) De March, P.; Marquet, J.; Moreno-Mañas, M.; Pleixats, R.; Ripoll, I.; Trius, A. An. Quím. **1983**, 79C, 15.
8. (a) Bacardit, R.; Moreno-Mañas, M.; Pleixats, R. J. Heterocycl. Chem. **1982**, 19, 157. (b) De March, P.; Moreno-Mañas, M.; Ripoll, I. Chem. Ber. **1987**, 120, 1413.
9. (a) Marquet, J.; Moreno-Mañas, M. Synthesis, **1979**, 348. (b) González, A.; Marquet, J.; Moreno-Mañas, M. Tetrahedron, **1986**, 42, 4253. (c) Moreno-Mañas, M.; González, A.; Marquet, J.; Sánchez-Ferrando, F. Bull. Chem. Soc. Jpn. **1988**, 61, 1827.
10. Boya, M.; Moreno-Mañas, M.; Prior, M. Tetrahedron Lett. **1975**, 1727.
11. Marquet, J.; Moreno-Mañas, M.; Pacheco, P.; Vallribera, A. Tetrahedron Lett. **1988**, 29, 1465.
12. Vlassi, M.; Germain, G.; Cervelló, J.; Marquet, J.; Moreno-Mañas, M.; Piniella, J.F. Z. Kristallogr. in press.
13. Marquet, J.; Moreno-Mañas, M.; Prat, M. Tetrahedron Lett. **1989**, 30, 3105.
14. (a) Harris, T.M.; Harris, C.M. J. Org. Chem. **1966**, 31, 1032. (b) Harris, T.M.; Harris, C.M. Tetrahedron **1969**, 25, 2687. (c) Borsche, W.; Bodenstein, C.K. Ber. **1929**, 62, 2515. (d) Suzuki, E.; Sekizaki, H.; Inoue, S. J. Chem. Soc. (S) **1977**, 200.
15. Ohta, S.; Tsujimura, A.; Okamoto, M. Chem. Pharm. Bull. **1981**, 29, 2762.
16. Marquet, J.; Moreno-Mañas, M. Chem. Lett. **1981**, 173.
17. (a) Harris, T.M.; Carney, R.L. J. Am. Chem. Soc., **1967**, 89, 6734. (b) Howarth, T.T.; Murphy, G.P.; Harris, T.M. J. Am. Chem. Soc. **1969**, 91, 517. (c) Howarth, T.T.; Harris, T.M. J. Am. Chem. Soc. **1971**, 93, 2506.
18. Oppolzer, W.; Moretti, R.; Bernardinelli, G. Tetrahedron Lett. **1986**, 27, 4713.
19. Bacardit, R.; Moreno-Mañas, M. J. Chem. Ecol., **1983**, 9, 703.
20. De March, P.; Moreno-Mañas, M.; Ripoll, I. Synth. Commun., **1984**, 14, 521.
21. De March, P.; Moreno-Mañas, M.; Pi, R.; Ripoll, I.; Sánchez-Ferrando, F. J. Heterocyclic Chem., **1985**, 22, 1537.
22. De March, P.; Moreno-Mañas, M.; Pi, R.; Trius, A. J. Heterocyclic Chem., **1982**, 19, 335.
23. De March, P.; Moreno-Mañas, M.; Casado, J.; Pleixats, R.; Roca, J.L.; Trius, A. J. Heterocyclic Chem., **1984**, 21, 85.