3,4-Disubstituted 4-Alkanolides (Butyrolactones) from 5,6-Dihydro-2-pyrone

A. GUZMÁN*, S. MENDOZA

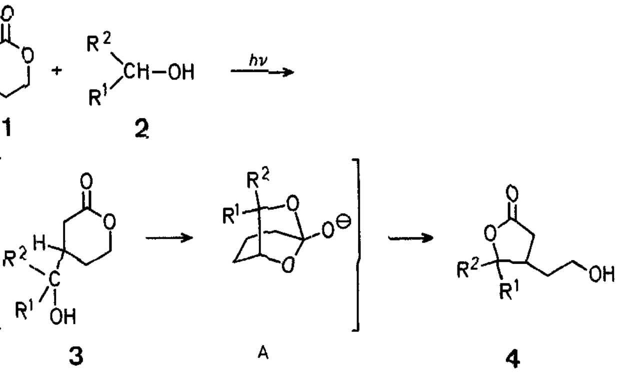
Research Laboratories, Syntex S. A., Apartado Postal 10-820, México 10, D. F.

E. DIAZ

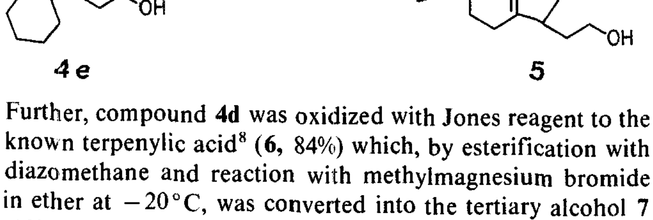
Instituto de Química, Universidad de México, Mexico

The photoinduced addition of alcohols to α-enones has been shown by Fraser-Reid et al.[1,2] to be a simple and promising method of C—C bond formation[3,4,5].

We tried the addition of ethanol to 5,6-dihydro-2-pyrone[6] (**1**), and instead of the simple addition product **3**, the substituted butyrolactone **4** was obtained. Undoubtedly, compound **4** was formed by a simple translactonization reaction of **3** through the bicyclic intermediate A. In view of the promise of this simple procedure in organic synthesis, we tried to add more complex alcohols to **1** in an equally simple experimental operation. We found that photoalkylation of the unsaturated lactone **1** may be effected by irradiating **1** in the alcohol **2** as solvent [or in cyclohexanol (**2e**)/hexane 1/1 in the synthesis of **3e**] containing benzophenone and using a 200 W low-pressure mercury lamp. In all the cases studied, the substituted 4-alkanolides (**4a–e**) were isolated in moderate yields as a mixture of stereoisomers, as determined by ^{1}H-N.M.R. spectrometry. The structure of lactones **4a–e** were confirmed by microanalysis, I.R., U.V., and ^{1}H-N.M.R. spectrometry.

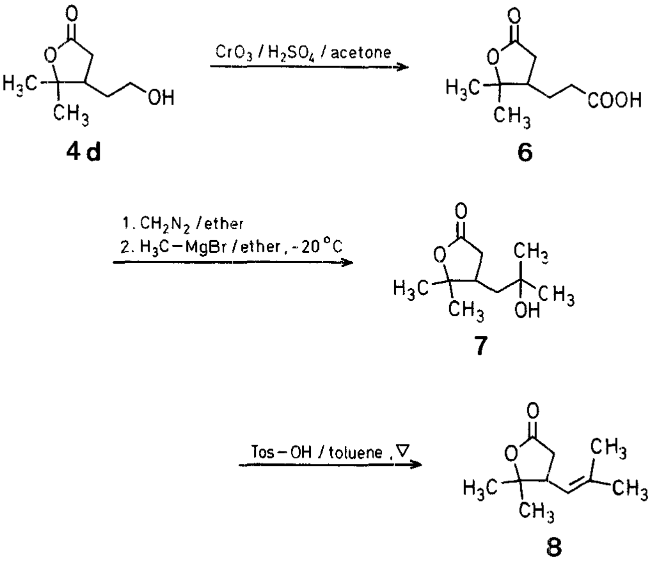


In order to show the potential utility of this method, the product 3-(2-hydroxyethyl)-4-alkanolides **4** were subjected to further, preparatively interesting conversions. Thus, the spirolactone **4e** was converted into 3-(2-hydroxyethyl)-4,5,6,7-tetrahydro-1-indanone (**5**, 62%) by acetylation followed by reaction with phosphorus(V) oxide/methanesulfonic acid[7].



Further, compound **4d** was oxidized with Jones reagent to the known terpenylic acid[8] (**6**, 84%) which, by esterification with diazomethane and reaction with methylmagnesium bromide in ether at −20 °C, was converted into the tertiary alcohol **7** (38%). Compound **7** was further transformed to the known olefinic compound **8**[9] (71%) by heating in toluene in the presence of *p*-toluenesulfonic acid. The conversion of compound **8** into *trans*-chrysanthemic acid has previously been reported[9].

0039-7881/81/1232-0989 $ 03.00



3-(2-Hydroxyethyl)-4,4-(1,5-pentanediyl)-4-butanolide (4e); Typical Procedure:

A 5 l round-bottom flask fitted with a mechanical stirrer and a reflux condenser is charged with 5,6-dihydro-2-pyrone (**1**; 10.78 g, 0.11 mol), benzophenone (3.644 g, 0.02 mol), cyclohexanol (**2e**; 810 ml), and hexane (540 ml). Argon is bubbled through the solution for 15 min and the solution is then externally irradiated under an argon atmosphere with a 200 W low-pressure mercury-vapor lamp. After 2.5 h, no more starting material can be detected by T.L.C. (silica gel, ethyl acetate/hexane 60/40). The hexane is evaporated and the residual product distilled in vacuo; yield: 11.8 g (54%); b.p. 162-164 °C/0.2 torr. The product solidifies upon cooling; m.p. 91-93 °C.

3-(2-Hydroxyethyl)-4,5,6,7-tetrahydro-1-indanone (5):

3-(2-Acetoxyethyl)-4,4-(1,5-pentadiyl)-4-butanolide (*O*-Acetyl-**4e**): A mixture of lactone **4e** (600 mg), pyridine (2 ml), and acetic anhydride (1 ml) is stirred at room temperature for 1 h and then poured into cold water (50 ml). The mixture is extracted with dichloromethane (3 x 40 ml), the organic extract is successively washed with 10% hydrochloric acid (30 ml) and water (3 x 30 ml), and dried with anhydrous sodium sulfate. The solvent is evaporated to afford practically pure *O*-acetyl-**4e**; yield: 0.70 g (96%).

3-(2-Hydroxyethyl)-4,5,6,7-tetrahydro-1-indanone (**5**): A solution of crude *O*-acetyl-**4e** (560 mg, 2.33 mmol) in methanesulfonic acid/phosphorus pentoxide (10/1; 55 g) is stirred under argon for 42 h at room temperature. The mixture is then cooled and water (120 ml) is added carefully. The resultant mixture is extracted with dichloromethane (3 x 60 ml), the extract washed with saturated sodium hydrogen carbonate solution (3 x 50 ml) and water (2 x 50 ml), dried with sodium sulfate, and evaporated. The residual product is purified on silica gel using 9:1 ethyl acetate/hexane as eluent to give pure **5** as an oil; yield: 260 mg (62%).

$C_{11}H_{16}O_2$	calc.	C 73.30	H 8.95
(180.2)	found	72.96	8.70

M.S.: *m/e* = 180 (M^+); 162, 136.

I.R. ($CHCl_3$): $\nu = 3450$ (OH); 1690 (C=O); 1640 cm^{-1} (C=C).

U.V. (methanol): $\lambda_{max} = 242$ nm ($\varepsilon = 12300$).

^{1}H-N.M.R. ($CHCl_3$/TMS): $\delta = 3.7$ ppm (m, 2H, C$\underline{H}_2$—OH).

3,5-Dinitrobenzoate of **5**; m.p. 145-146 °C (from ethyl acetate/hexane).

$C_{18}H_{18}N_2O_7$	calc.	C 57.75	H 4.81	N 7.48
(374.3)	found	57.61	4.85	7.41

4-Methyl-4-pentanolide-3-acetic acid (6):

To a stirred solution of 3-(2-hydroxyethyl)-4-methyl-4-pentanolide (**4d**; 316 mg, 2.0 mol) in acetone (30 ml) Jones reagent (1 ml) is added at 0 °C and stirring is continued for 4 h. The unused reagent is destroyed by addition of isopropyl alcohol (1 ml). The mixture is diluted with water (50 ml) and extracted with dichloromethane (3 x 40 ml). The combined extract is washed with water and dried with sodium sulfate. Evaporation of the solvent gives compound **6**; yield: 290 g (84%); m.p. 89-90 °C (from acetone/ether) (Ref.[8], m.p. 89-90 °C).

$C_8H_{12}O_4$ (172.2)

M.S.: *m/e* = 173 (MH^+).

I.R. ($CHCl_3$): $\nu = 1760$ (lactone); 1715 cm^{-1} (acid).

^{1}H-N.M.R. ($CHCl_3$/TMS): $\delta = 1.28$, 1.25 (s, CH_3); 2.2-3.0 ppm (m, C$\underline{H}_2$—C=O, C$\underline{H}_2$—COOH).

3-(2-Hydroxy-2-methylpropyl)-4-methyl-4-pentanolide (7):

(3-Methoxycarbonylmethyl)-4-methyl-4-pentanolide: A solution of diazomethane (excess) in ether is added to a stirred solution of acid **6** (1.3 g, 7.55 mmol) and stirring is continued for 5 min. Excess diazomethane is quenched by addition of acetic acid (0.5 ml). Evaporation of the solvent gives practically pure product; yield: 1 g (71%); m.p. 58-59 °C (from acetone/ether).

3-(2-Hydroxy-2-methylpropyl)-4-methyl-4-pentanolide (**7**): A solution of methylmagnesium bromide (from 91.12 mg of magnesium and 532.5 mg methyl bromide in 20 ml ether) is added dropwise to a stirred solution of the methyl ester of **6** (279 mg, 1.5 mmol) in ether (20 ml) at −20 °C. Stirring is continued for 3 h, then saturated ammonium chloride solution (10 ml) is added, the organic phase is separated, and the aqueous phase is extracted with ether (3 x 20 ml). The organic phases

Table. 3-(2-Hydroxyethyl)-4-alkanolides (**4**) prepared

4	R^1	R^2	Time of irradiation [h]	Yield [%]	m.p. or b.p./torr [°C]	Molecular formula[a]	M.S. *m/e*	I.R. ($CHCl_3$) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS) δ [ppm]
a	H	H	4	30	158-161°/3	$C_6H_{10}O_3$ (130.1)	(187, $M^+ - CH_3$)[b]	3450 (OH); 1770 (C=O)	1.72 (q, 2H, —C$\underline{H}_2$—CH_2—OH); 3.65 (t, C$\underline{H}_2$—OH); 3.98, 4.46 (2d, C$\underline{H}_2$—O—CO)
b	H	CH_3	3.5	63	115°/3.5	$C_7H_{12}O_3$ (144.2)	(201, $M^+ - CH_3$)[b]	3500 (OH); 1775 (C=O)	1.28 (d, CH_3); 2.5 (m, CH_2—C=O); 3.7 (t, C$\underline{H}_2$—OH); 4.69 (q, H_3C—C$\underline{H}$—O)
c	H	C_2H_5	3.5	50	166°/3.5	$C_8H_{14}O_3$ (158.2)	(215, $M^+ - CH_3$)[b]	3500 (OH); 1770 (C=O)	1.1 (t, CH_3); 2.5 (m, CH_2—C=O); 3.82 (q, C$\underline{H}_2$—OH); 4.42 (q, —C$\underline{H}$—O)
d	CH_3	CH_3	2.0	65	156-159°/4	$C_8H_{14}O_3$ (158.2)	143 ($M^+ - CH_3$)	3460 (OH); 1760 (C=O)	1.27 (s, CH_3); 1.46 (s, CH_3); 2.4 (m, CH_2—C=O); 3.65 (t, 2H, C$\underline{H}_2$—OH)
e	—$(CH_2)_5$—		2.5	54	91-93°	$C_{11}H_{18}O_3$ (198.3)	(270, M^+)[b]	3500 (OH); 1765 (C=O)	1.7 (m, 2H, C$\underline{H}_2$—CH_2—CH_2—OH); 2.5 (m, —CH_2—C=O); 3.63 (2H, C$\underline{H}_2$—OH)

[a] The microanalyses were in satisfactory agreement with the calculated values: C, ±0.34; H, ±0.10.

[b] M.S. of trimethylsilyl ether.

[c] Irradiation carried out in cyclohexanol (**2e**)/hexane (1/1).

are combined, washed with water (20 ml), and dried with sodium sulfate. The solvent is evaporated and the residue purified by preparative T.C.L. on silica gel using 6:3:1 hexane/dichloromethane/methanol as eluent; yield: 145 mg (38%, based on **6**); m.p. 104–105 °C (from acetone/hexane).

$C_{10}H_{18}O_3$	calc.	C 64.51	H 9.67
(186.3)	found	64.67	9.65

M.S.: $m/e = 187$ (MH^+).

I.R. ($CHCl_3$): $\nu = 3500$ (OH); 1765 cm^{-1} (C=O).

^{1}H-N.M.R. ($CHCl_3$): $\delta = 1.20$, 1.23, 1.25, 1.41 (s, CH_3); 2.5 ppm (m, CH_2—C=O).

4-Methyl-3-(2-methylpropenyl)-4-pentanolide (8):

p-Toluenesulfonic acid (28 mg) is added to a solution of compound **7** (140 mg, 0.75 mmol) in toluene (20 ml) and the mixture is heated under reflux for 4 h. After cooling, the solution is washed with water and dried with sodium sulfate. The solvent is evaporated and the residue crystallized; yield: 90 mg (71%); m.p. 57–59 °C (from petroleum ether) (Ref.[9], m.p. 57–58 °C).

$C_{10}H_{16}O_2$ (168.2)

M.S.: $m/e = 168$ (M^+).

I.R. ($CHCl_3$): $\nu = 1760$ cm^{-1} (C=O).

^{1}H-N.M.R. ($CDCl_3$/TMS): $\delta = 1.23$, 1.39, 1.66, 1.73 (s, CH_3); 2.45, 2.57 (dd, CH_2—C=O); 5.02 ppm (d, CH=C).

Received: December 1, 1980
(Revised form: April 21, 1981)

---

* Address for correspondence.

[1] B. Fraser-Reid, N. L. Holder, D. R. Hicks, D. L. Walker, *Can. J. Chem.* **55**, 3978 (1977).

[2] B. Fraser-Reid, R. C. Anderson, D. R. Hicks, D. L. Walker, *Can. J. Chem.* **55**, 3986 (1977).

[3] P. Bladon, I. A. Williams, *J. Chem. Soc.* [C] **1967**, 2032.

[4] A. Guzmán, J. M. Muchowski, *Tetrahedron Lett.* **1975**, 2053.

[5] G. L. Bundy, *Tetrahedron Lett.* **1975**, 1957.

[6] M. Nakagawa et al., *Synthesis* **1974**, 510.

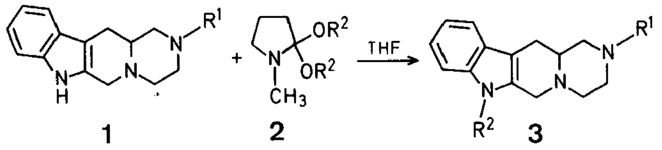
[7] P. E. Eaton, G. R. Carlson, J. T. Lee, *J. Org. Chem.* **38**, 4071 (1973).

[8] A. Takeda, S. Tsuboi, T. Sakai, *J. Org. Chem.* **39**, 2601 (1974).

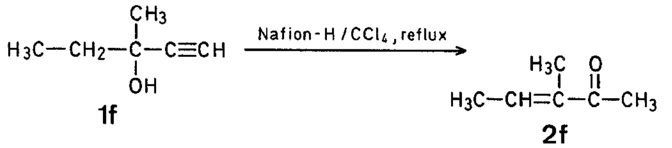
[9] M. Julia, S. Julia, C. Jeanmart, M. Langlois, *Bull. Soc. Chim. Fr.* **1962**, 2243.

0039-7881/81/1232-0991 $ 03.00

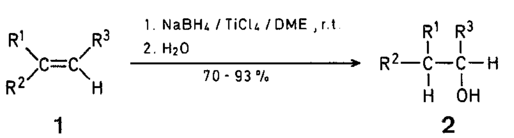
S. K. Agarwal, A. K. Saxena, N. Anand, *Synthesis* **1981** (6), 465-466:
The formula scheme (p. 465) should be:



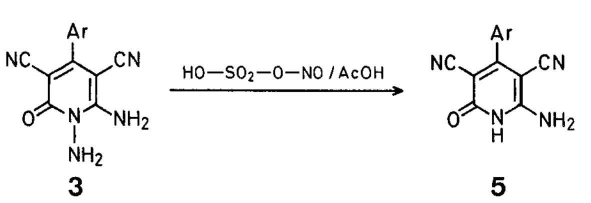
G. A. Olah, A. P. Fung, *Synthesis* **1981** (6), 473-474:
The reaction scheme **1f→2f** should be:



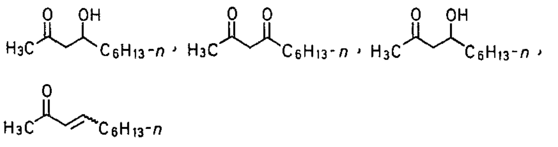
Abstract 6127, *Synthesis* **1981** (6), 498:
The formula scheme **1→2** should be:



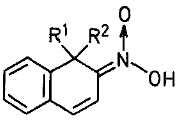
J. L. Soto, C. Seoane, P. Zamorano, F. J. Cuadrado, *Synthesis* **1981** (7), 529-530:
The reaction scheme **3→5** (p. 529) should be:



A. B. Smith, III, P. A. Levenberg, *Synthesis* **1981** (7), 567-570:
The heading for Table 1 (p. 567) should be Oxidation of 4-Hydroxy-2-decanone (**3a**) under various conditions. The structure given in the first column of Table 1 should be, respectively:

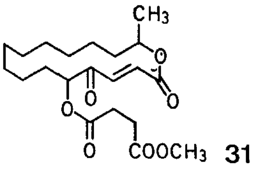


G. Bartoli, M. Bosco, A. C. Boicelli, *Synthesis* **1981** (7), 570-572:
The structure of products **4aa-cd** (p. 571) should be:



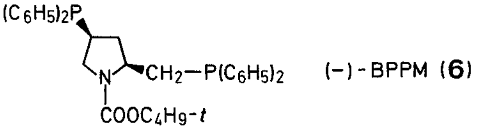
4aa-cd

Y.-H. Lai, *Synthesis* **1981** (8), 585-604:
The structure of compound **31** (p. 588) should be:

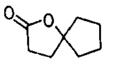


M. R. H. Elmoghayar, M. K. A. Ibraheim, A. H. H. Elghandour, M. H. Elnagdi, *Synthesis* **1981** (8), 635-637:
The title compounds **5** are thiazolo[3,2-*a*]pyridine derivatives.

A. Kleemann, J. Martens, M. Samson, W. Bergstein, *Synthesis* **1981** (9), 740-741:
The structure of compound **6** should be:

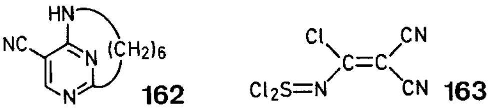


Abstract 6236, *Synthesis* **1981** (11), 922:
The structure of product **3** should be:



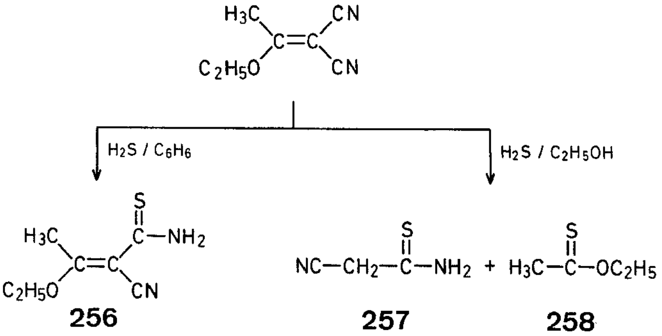
3

F. Freeman, *Synthesis* **1981** (12), 925-954:
The structures of compounds **162** and **163** (p. 937) should be:

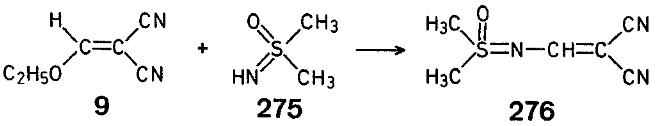


The text of the first paragraph starting on p. 943 (right-hand column) should be: Hydrogen sulfide reacts with 1-ethoxyethylidenemalononitrile, the methyl homolog of **9**, to give different products depending on the solvent used^{293}.

The following formula scheme should be:



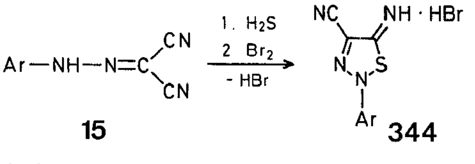
The first formula scheme on p. 944 (right-hand column) should be:



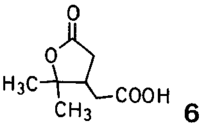
The last sentence on page 946 (left-hand column) should be: An analogous reaction with cyclopentadiene leads to the 2-azabicyclo[2.2.1]heptene (**299**) and with cyclohexadiene to 2-azabicyclo[2.2.2]octene (**301**) derivatives^{317}.

The correct names for compounds **336** and **337** (p. 949) are 5-hydroxy-2-oxo-3-phenylazo-1,2,3,7-tetrahydropyrazolo[1,5-*a*]pyrimidine (**336**) and *α*-(*N*-methylphenylhydrazono)-cyanoacetamidrazone (**337**).

The formula scheme **15→344** (p. 950) should be:



A. Guzmán, S. Mendoza, E. Diaz, *Synthesis* **1981** (12), 989-991:
The structure of compound **6** (p. 990) should be:



6

Abstract 6269, *Synthesis* **1981** (12), 1015:
The legend under the formula scheme should read: n = 1, 2, 3.