REGIO- AND STEREOSELECTIVE FUNCTIONALIZATIONS OF THE WIELAND-MIESCHER KETONE DERIVATIVES AT THE C-8 POSITION

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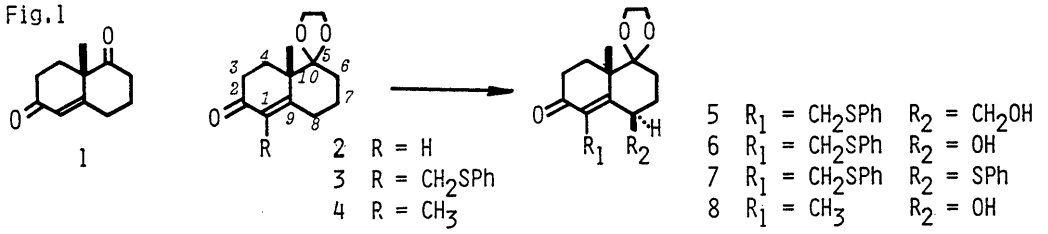
New efficient methods for stereoselective hydroxymethylation, hydroxylation, and thiophenylation at the C-8 position of the Wieland-Miescher ketone derivatives (2-4) have been developed by diverse modifications from the Kirk-Petrow reaction, which involve autoxidation for the hydroxylation.

KEYWORDS Wieland-Miescher ketone; Kirk-Petrow reaction; phenylthiomethylation; hydroxylation; hydroxymethylation; thiophenylation

Since the Wieland-Miescher ketone (1) is a convenient substrate for the synthesis of the natural products of middle or higher terpenoids, simple procedures for the regio- and stereoselective introduction of various functional groups at the specific positions of its decalin ring are essentially important. Among these, the oxidative functionalization at the C-8 position is particularly important, as there are many bioactive terpenoids containing condensed carbocyclic rings whose C-6 positions, which correspond to the C-8 of the decalin ring system, are specifically oxygenated. Typical examples are 6β-hydroxygrindelic acid[1] and a number of insect antifeedants,[2] or scoparic acid A,[3] forskolin,[4] and nagilactones[5] as cytotoxic substances.

In connection with our series of studies on biorational designs and synthesis of bioactive terpenoids, we initially detected trace amounts of several new useful derivatives, whose C-8 is stereoselectively functionalized, among the products from the Kirk-Petrow reaction[6a] applied to the ethylene ketal (2).[6b] We now report new procedures that afford the new derivatives in fair to good yields under mild conditions. This is the first report of a functionalization at the C-8 which is completely stereoselective for β-orientation.

Fig.1



The ethylene ketal(2) was primarily converted in 80% yield to the 1-phenylthiomethylated ketone (3) with HCHO, thiophenol and Et_3N in EtOH according to the protocol of Kirk-Petrow,[6] but we also found a trace of the new derivative (5)[9] which was hydroxymethylated at C-8 in addition to phenylthiomethylation at C-1. Moreover, when 2 was treated with a large excess (6 eq) of HCHO in the presence of KOAc (1.2 eq), in addition to Et_3N and thiophenol in DMF for 3 h , the 8β derivative (5) was the major product in 66% yield accompanied with a small percentage of 3. 5 was also obtained (68%) from 3 under similar conditions. The presence of the hydroxymethyl group at the C-8 in β-orientation was deduced from NMR data[9] of its new derivatives (9), (10), and (11) obtained by the procedures shown in Fig. 2, and this was confirmed by X-ray crystallography.

More interestingly,treatment of 3 with an excess of thiophenol or diphenyl disufide in the presence of Et_3N and KOAc in DMF under air for 3-6 hr gave two new derivatives (6)[9] (37%) and (7)[9] (46%). These were selectively hydroxylated or thiophenylated at the C-8 in the β-orientation with concurrent formation of the dimeric compounds (15)(Table I, entry 1 and 2). 6 and 7 were also prepared from 2 in similar yields by a one-pot procedure (entry 4). The structure of 6 was determined on the basis of the NMR data and by the chemical conversions of 6 to the diol (12), the acetate (13) and the diketone (14).[9]

Fig.2

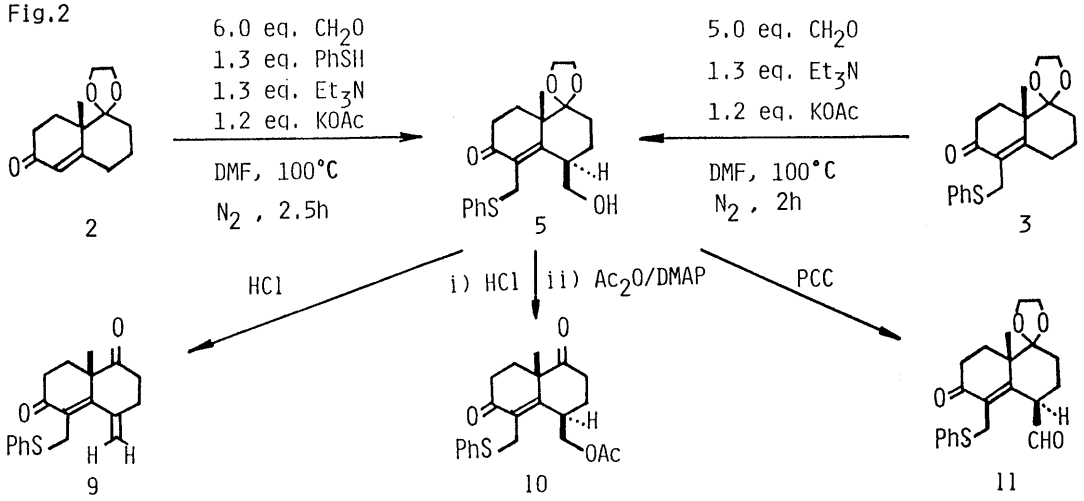


Fig.3

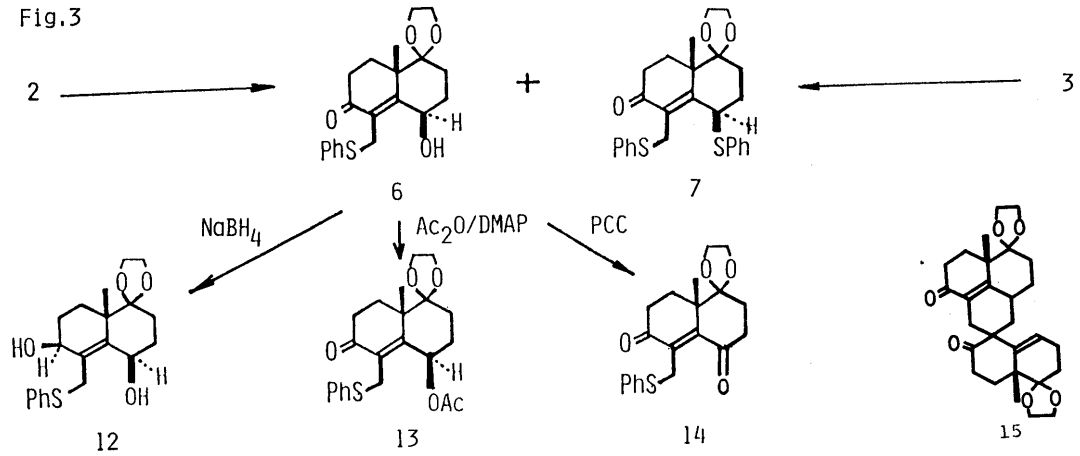


Table I. Hydroxylation and Thiophenylation of 2 and 3

Entry	SM	CH_2O(eq)	PhSH(eq)	$(PhS)_2$(eq)		Yield(%) 6	7	15
1	3	–	10	–	Air	37	18	40
2	3	–	3	6	Air	20	46	30
3	3	–	–	2	Air	15	19	62
4	2	1.4	1.4+10*	–	N_2 → Air	31	20	45

The reaction was carried out in DMF at 100°C in the presence of Et_3N(1.3eq) and KOAc(1.2eq).
*1.4 eq of PhSH was used under N_2 for 6 h ,then 10 eq of PhSH was added and air was introduced.

Fig.4

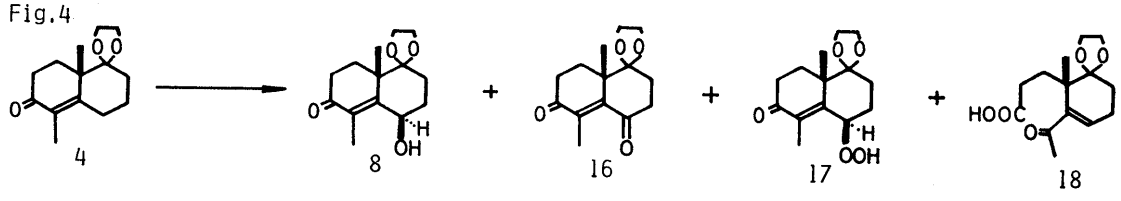


Table II. Oxidation of 4 under Air

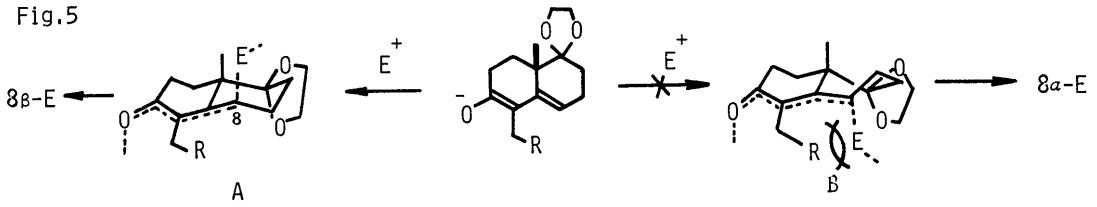
Entry	Base (eq)	Additive(eq)	Solvent	Temp.(°C)	Time(day)	Yield (%) 8	16	17	18
1	Et_3N(1.3),KOAc(1.2)	–	DMF	100	4	36	15	–	–
2	Et_3N(1.3),KOAc(1.2)	Et_3N→O(3.0)	DMF	100	4	45	9	–	–
3	KOH	–	MeOH-H_2O	65	1	70	–	–	11
4	Na_2O_2	–	EtOH-H_2O	20	0.1	49	–	8	3

Furthermore, the 1-methyl analog (4) of 2 was converted in a moderate yield(45-49%)to the 8β-hydroxyl derivative (8)[7] with Et_3N and KOAc in the presence of $Et_3N{\rightarrow}O$ under air or with Na_2O_2 and H_2O . A better yield (70%) for 8 was attained on heating with KOH in H_2O - MeOH under air accompanied with the acid (18) (11%). None of the 8α-hyroxyl derivatives were detected in these cases (Fig.4 and Table II).

The high steric control for β-orientation of these functional groups at the C-8 of 5, 6, 7, or 8 may be explained in analogy with the mechanism proposed by Holland and Auret,[8] where the C-1H analog gives a mixture of the α- and β-substituted derivatives. We assume in our cases that an axial electrophilic attack at the thermodynamically more stable $\Delta^{2,9}$-enolate takes place under stereo-electronic control giving the intermediate(s) A and/or B (see Fig. 5); A, with a β-E group, is apparently preferred to B with an α-E group if a non-bonding interaction between the groups E and R exceeds the 1,3-diaxial interaction resulting from the E and Me group at the C-10.

In this connection, we found that the MCPBA oxidation of the dienol acetate of 4 gave a mixture of the 8α- and 8β-hydroxyl derivatives (8') and (8) in a 1 : 2.5 ratio,[8] whereas only the 8β derivatives were produced by the current procedures involving air autoxidation. The mechanism of these functionalizations in perfect steric control has not yet been clarified.

Fig.5



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6) a) D. N. Kirk and V. Petrow, *J. Chem. Soc.*, **1962**, 1091; b) A. B. Smith III and R. Mershaw, *J. Org. Chem.*, **49**, 3685 (1984).
7) The 2,5-diketone,the 5β-hydroxy-2-ketone, and the 5β-benzoyloxy-2-ketone derivatives were similarly converted in moderate (up to 40%)yields to the corresponding 8β-hydroxyl derivatives respectively under the same conditions shown in entry 2 (Table II).
8) H. L. Holland and B. J. Auret, *Can. J. Chem.*,**53**, 2041 (1975).
9) For another reference to moderate stereoselective oxidation with MCPBA, see J. B. P. A. Wijnberg, J. Vader,and A. de Groot, *J. Org. Chem.*, **48**, 4380 (1983).
10) All the new compounds (5 through 18) gave the following NMR spectra ($CDCl_3$, δ). 5: ^{1}H-NMR 1.31 (s, 3 H), 3.09 (m, 1 H), 3.6 - 4.0 (m, 4 H). ^{13}C-NMR 29.15 (t), 41.07(d),65.18 (t), 132.58 (s), 164.81 (s). 6: ^{1}H-NMR 1.55 (s,3 H), 3.61 (d,1H, J = 11.9 Hz), 4.28(d, 1H, J = 11.9 Hz), 4.80 (bt,1H, J = 2.9 Hz, H-8). ^{13}C-NMR 28.61 (t),65.56 (d), 132.53 (s), 162.60 (s). 7: 1H-NMR 1.56 (s, 3H), 3.49 (d,1H, J = 11.9 Hz), 4.14 (d, 1H, J = 11.9 Hz), 4.40 (bt,1H, $W_{1/2}$ = 7 Hz). ^{13}C NMR 29.15 (t), 46.27 (d), 133.55 (s), 161.89 (s). 8: ^{1}H-NMR 1.53 (s, 3H), 1.88 (s, 3H), 4.93 (bt, 1H, J = 2.6 Hz, H-8). ^{13}C-NMR 65.61(d). 9: ^{1}H-NMR 5.20 (bs, 1H), 5.33 (bs, 1H). 10: ^{1}H-NMR 3.34 (dddd, 1 H, J = 9.2, 6.5, 6.5 Hz, H-8). 11: ^{1}H-NMR 3.66 (d, 1 H,J = 5.9 Hz, H-8). 12: ^{1}H-NMR 1.45 (s, 3 H), 4.26 (dd, 1H, J = 13.3, 7.0 Hz, H-3), 4.66 (bt, 1H, H-8).13: ^{1}H-NMR 1.45 (s, 3H), 5.85 (t, 1H, J = 3.1 Hz, H-8). 14: ^{1}H-NMR 1.23 (s, 3H). 16:^{1}H-NMR 1.28 (s, 3H) 1.82 (s, 3H). 17: ^{1}H-NMR 1.45 (s, 3H), 5.13 (bt, 1H, J=2.6 Hz).^{13}C-NMR 79.00 (d). 18: ^{1}H-NMR 1.27(s, 3H), 2.31 (s, 3H), 6.85 (t,1H,J=3.5Hz).

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