

Synthesis of Wieland–Miescher Ketone Analogues bearing an Angular Protected Hydroxymethyl Group

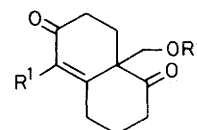
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Wieland–Miescher ketone analogues (1) and (2), bearing an angular protected hydroxymethyl group, have been prepared by alkylation of the lithiated methyl 2,6-dimethoxycyclohexa-2,5-diene-1-carboxylate.

Recent work by Mander and Hamilton¹ concerning the synthesis of the Wieland–Miescher ketone analogues bearing an angular ethoxycarbonyl group starting from methyl 2-(*t*-butyldimethylsilyloxy)-6-methoxybenzoate prompts us to report the similar results of our work on the synthesis of the derivatives (1) and (2), bearing a protected hydroxymethyl group in place of an ethoxycarbonyl group, from 2,6-dimethoxybenzoic acid.

The dihydroaromatic ester (3) was prepared in 80% yield by the Birch reduction (Na–liquid NH₃–MeOH) of 2,6-dimethoxybenzoic acid,² followed by esterification (MeI–K₂CO₃–acetone). Compound (3) was treated with 1.2 mol. equiv. of lithium di-isopropylamide in tetrahydrofuran (THF) (0 °C, 10 min) and then allowed to react with 4-bromobut-1-ene (0 °C, overnight) or 2-ethyl-4-iodobut-1-ene† (0 °C, 5 h) to give the alkylated esters (4) and (6) in 92 and 90% yields, respectively.‡§ Reduction of compounds (4) and (6) with LiAlH₄ gave quantitatively the corresponding hydroxymethyl derivatives (5) and (7), which were then protected as the (β-methoxy)ethoxymethyl (MEM) ether [for (5) and (7)] (MEMCl–Pr₁₂EtN–CH₂Cl₂),³ as the acetate [for (7)] (EtOAc, 60 °C), or as the methyl ether [for (7)] (NaH–MeI–THF, 50 °C).



- (1) R¹ = H, R² = MEM
 (2) R¹ = Me, **a**; R² = MEM
 b; R² = Ac
 c; R² = Me

MEM = MeOCH₂CH₂OCH₂

The protected alcohols were hydrolysed to give the cyclohexane-1,3-dione derivatives (8) and (9) by stirring in anhydrous acetone containing 2.5 mol. equiv. of *p*-MeC₆H₄SO₃H–H₂O or in 6 M HCl (in the case of the acetate). Thus, the cyclohexane-1,3-diones (8) (0 °C, 1 h, 90%), (9a) (0 °C, 7 h, 75%), (9b) (0 °C, 7 h, 90%), and (9c) (–20 to –5 °C, 12 h, 70%) were obtained.

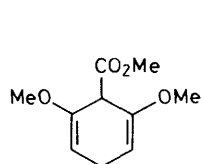
Palladium-catalysed oxidation (PdCl₂–O₂–CuCl–dimethylformamide–H₂O)⁴ of compound (8) afforded the desired oxobutyl precursor (10) in 55% yield. The oxopentyl analogues (11a–c) were readily obtained from (9) in 80–82% yield by ozonolysis in methanol (–78 °C), followed by treatment with dimethyl sulphide.

In contrast with the case of the methoxymethyl protected analogues [R² = CH₂OMe in (10) and (11)] synthesized by Mander and Hamilton,¹ the triketones (10) and (11) successfully undergo cyclisation to produce the target enones (1) and

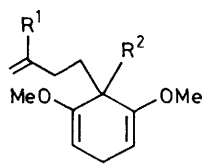
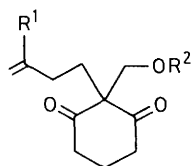
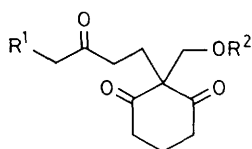
† Prepared from 2-ethylprop-2-en-1-ol through four steps.

‡ Yields are for the isolated pure products. All new compounds were characterized by combustion analysis as well as by i.r., u.v., and ¹H n.m.r. spectroscopy.

§ Reaction with 2,2-ethylenedioxy-4-iodobutane did not give the alkylated product as reported by Mander and Hamilton, ref. 1.



(3)

(4) $R^1 = H$, $R^2 = CO_2Me$ (5) $R^1 = H$, $R^2 = CH_2OH$ (6) $R^1 = Et$, $R^2 = CO_2Me$ (7) $R^1 = Et$, $R^2 = CH_2OH$ (8) $R^1 = H$, $R^2 = MEM$ (9) $R^1 = Et$ $a; R^2 = MEM$, $b; R^2 = Ac$, $c; R^2 = Me$ (10) $R^1 = H$, $R^2 = MEM$ (11) $R^1 = Me$

(2). The triketone (10) on treatment with 1 mol. equiv. of piperidinium benzoate in benzene (40 °C, 1 day), gave the keto enone (1) in 75% yield. In the case of (11), it was found that the use of an amino acid as an agent was more effective for cyclisation. Thus, treatment of (11b) and (11c) with 1 mol. equiv. of racemic phenylalanine in acetonitrile containing 0.5 mol. equiv. of 1 M $HClO_4$ (80 °C, 4 days) gave the homo-

logous keto enones (2b) and (2c) in 80 and 86% yields, respectively. The triketone (11a) gave a complex mixture, probably owing to hydrolysis of the MEM unit during the reaction. Cyclisation of (11a) to (2a) was ultimately achieved by treatment with the same amino acid in dimethyl sulphoxide (DMSO) (70 °C, 1 week). The keto enone (2a) was obtained in 30% yield.

The successful cyclisation catalysed by an amino acid is of particular interest, since the use of an optically active amino acid⁵ would be expected to yield optically active (1) and (2). In fact, the cyclisation of (10) with L-proline (DMSO, 20 °C, 1 day) or of (11b) with D-phenylalanine ($MeCN-HClO_4$, 80 °C, 4 days) gave the optically active (1) (60%), $[\alpha]_D^{20} + 76.6^\circ$ (c 0.14, $CHCl_3$), and (2b) (80%), $[\alpha]_D^{20} - 70.8^\circ$ (c 0.30, $CHCl_3$), respectively. The optical purities and absolute configurations of these products are under active investigation and will be reported in the near future.

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