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

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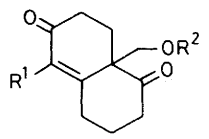
Wieland–Miescher ketone analogues (**1**) and (**2**), bearing an angular protected hydroxymethyl group, have been prepared by alkylation of the lithiated methyl 2,6-dimethoxycyclohexa-2,5-diene-1-carboxylate.

Recent work by Mander and Hamilton[1] 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 NH_3–MeOH) of 2,6-dimethoxybenzoic acid,[2] followed by esterification (MeI–K_2CO_3–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 $LiAlH_4$ 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–Pr^i_2EtN–CH_2Cl_2),[3] as the acetate [for (**7**)] (EtOAc, 60 °C), or as the methyl ether [for (**7**)] (NaH–MeI–THF, 50 °C).



(**1**) R^1 = H, R^2 = MEM

(**2**) R^1 = Me, **a**; R^2 = MEM
b; R^2 = Ac
c; R^2 = Me

MEM = $MeOCH_2CH_2OCH_2$

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*-$MeC_6H_4SO_3H$–H_2O 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.

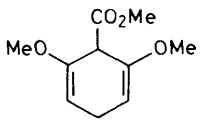
Palladium-catalysed oxidation ($PdCl_2$–O_2–CuCl–dimethylformamide–H_2O)[4] of compound (**8**) afforded the desired oxobutyl precursor (**10**) in 55% yield. The oxopentyl analogues (**11a**—**c**) were readily obtained from (**9**) in 80—82% yield by ozonolysis in methanol (−78 °C), followed by treatment with dimethyl sulphide.

In contrast with the case of the methoxymethyl protected analogues [R^2 = CH_2OMe 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

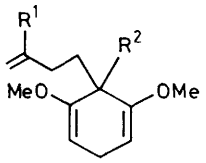
† Prepared from 2-ethylprop-2-en-1-ol through four steps.

‡ 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.

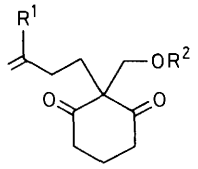
§ Reaction with 2,2-ethylenedioxy-4-iodobutane did not give the alkylated product as reported by Mander and Hamilton, ref. 1.



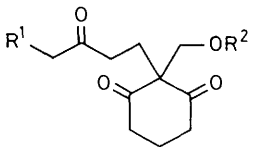
(3)



(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



(10) R^1 = H, R^2 = MEM
(11) R^1 = Me

a; R^2 = MEM, **b**; R^2 = Ac, **c**; R^2 = 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 homologous 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 acid[5] 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 ° (*c* 0.14, $CHCl_3$), and (**2b**) (80%), $[\alpha]_D^{20}$ −70.8 ° (*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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