Synthesis of (±)-Podorhizone *via* Intermediate α-Hydroxyalkylation of a β-Benzyl γ-Butyrolactone

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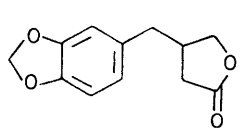
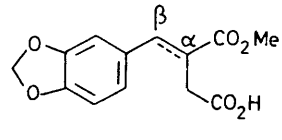
Summary α-Hydroxyalkylation of β-(3,4-methylenedioxybenzyl)-γ-butyrolactone (**1**) with 3,4,5-trimethoxybenzaldehyde, using lithium hexamethyldisilylamide as a base, affords a 1 : 1 mixture of (±)-podorhizol (**4**) and (±)-epipodorhizol (**5**); Jones's oxidation of this mixture gives (±)-podorhizone (**6**) in 63% overall yield.

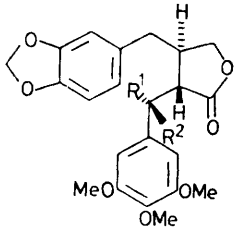
As model reactions pertaining to the total syntheses of antileukaemic lignans belonging to the bis-benzocyclo-octadiene series (steganone and analogues),[1] we considered the feasibility of direct α-hydroxyalkylation of 3-benzyl-4-butanolides such as (**1**). This reaction indeed seems almost unknown. Grieco[2] and his co-workers have described the α-hydroxymethylation of γ-butyrolactones, using lithium di-isopropylamide (LDA) as a base. α-Hydroxyalkylation of compound (**1**) by piperonal was performed in



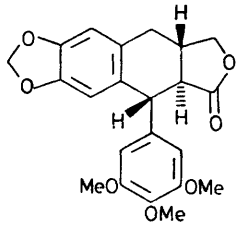
(1)



(2) αβ-double bond
(3) no αβ double bond



(4); R^1=H, R^2=OH
(5); R^1=OH, R^2=H
(6); R^1R^2=O



(7)

low yields (27%).[3] Recently, Ziegler and Schwartz[4] have carried out an efficient α-hydroxyalkylation (by means of 3,4,5-trimethoxybenzaldehyde) of the lithium enolate resulting from a Michael reaction of lithium piperonyldithian with but-2-enolide.

The ethylenic hemiester (**2**),[5] m.p. 138—139 °C (obtained in 72% yield by Stobbe condensation of methyl succinate with piperonal) was hydrogenated on 10% Pd–C in acetic acid (100 atm, 24 h, room temp.) to give the dihydrohemiester (**3**) (*ca.* 100%), m.p. 92—93 °C (Et_2O). Treatment of the potassium salt of (**3**) with calcium borohydride (prepared *in situ* from $CaCl_2$ and ethanolic $NaBH_4$) yielded the piperonyl lactone (**1**) as a thick oil, in nearly quantitative yield. This known compound had been prepared in poor yield following a more complex pathway.[3]

The lithium enolate of (**1**) was prepared in benzene at 20° C, using lithium hexamethyldisilylamide (LHDS) as a base,[6] and was subsequently treated with 3,4,5-trimethoxybenzaldehyde (reaction time 2 min). After quenching the reaction mixture with 30% HCl at −20 °C, (±)-podorhizol (**4**),[4] m.p. 126·5—128·5 °C, and (±)-epipodorhizol (**5**),[4] m.p. 136·5—137·5 °C, were obtained as a *ca.* 1:1 mixture (97%, crude). The yield of the alcohols [(**4**) + (**5**)], starting from compound (**1**), was 75% after purification by h.p.l.c., using CH_2Cl_2–Pr^iOH (99:1). In the present case, LHDS proved much more convenient to use (C_6H_6, room temp.) than LDA (tetrahydrofuran, −70 °C), and afforded much higher yields of the condensation products [(**4**) + (**5**)].

Jones's oxidation of the purified mixture of alcohols [(**4**) + (**5**)] gave (±)-podorhizone (**6**), m.p. 114·5—116 °C (MeOH), in 83% yield. The i.r. spectrum of (**6**) in CH_2Cl_2, and the corresponding spectrum of (2*S*,3*R*)-podorhizone derived from natural sources, were superimposable. The n.m.r. spectra of (**6**) in $CDCl_3$ and C_6D_6 were identical with that described by von Wartburg for this compound.[7]

(±)-Podorhizone (**6**) was reduced with $NaBH_4$ in methanol,[7] to give (±)-epipodorhizol (**5**) as the major epimer, m.p. 136·5—137·5 °C (EtOH), in 96% yield. Catalytic hydrogenation (Pd–C) of (**6**) in trifluoroacetic acid and in the presence of perchloric acid afforded an 85% yield of (±)-isodeoxypodophyllotoxin (**7**), m.p. 254—256 °C, identical with the compound prepared by Ziegler[4] by $SnCl_4$ cyclization of (±)-podorhizol (**4**). Compound (**6**) could not be obtained by treating 3,4,5-trimethoxybenzoyl chloride with the enolate of the lactone (**1**), prepared by using LDHS. Similarly, (±)-deoxypodorhizone was not obtained by alkylation of the lithium enolate with 3,4,5-trimethoxybenzyl bromide.

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