Biomimetic Synthesis of Sclerin

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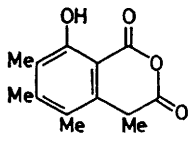
Summary A general synthesis of 3-hydroxy-homophthalates is developed and applied to the synthesis of sclerin (**1**), a compound possessing plant-growth activity; the critical step in the synthesis of (**1**) can be considered as the controlled condensation of a dicarbonyl unit with a tricarbonyl unit, in analogy to the biogensis of polyketides.

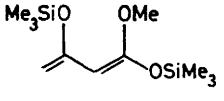
CONDENSATION of poly-β-carbonyl compounds is a major pathway for the biogenesis of aromatic natural products.[1,2] Efforts to mimic this reaction in the laboratory have met with limited success, mainly because of the difficulty of controlling the specificity of the direction of condensation.[2] Such control is particularly critical when the poly-β-carbonyl precursor is composed of mixed acetate and propionate units. We report a solution to the problem, using as an illustration the synthesis of sclerin (**1**).

Sclerin, a metabolite isolated from *Sclerotinia* fungi, possesses interesting plant growth activity.[3] Its biosynthesis has been investigated extensively by labelling experiments;[4-6] essentially, it can be considered as the condensation product of a penta-β-carbonyl precursor. A few chemical syntheses of sclerin have previously been reported,[7-9] based on conventional aromatic chemistry, often with the inherent problem of regioselection in electrophilic aromatic substitution, and gave low overall yields.

Recently we reported a novel cycloaromatisation reaction based on the regio-controlled condensation of 1,3-bis-(trimethylsiloxy)-1-methoxybuta-1,3-diene (**2**), the dianion



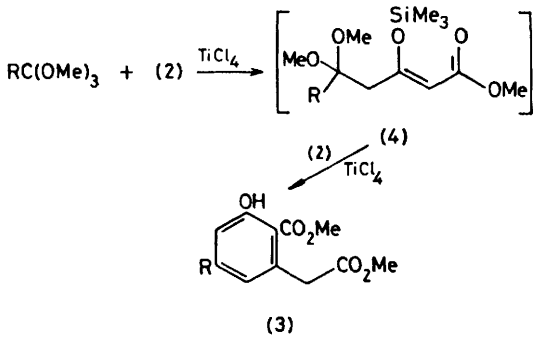
(1)



(2)

equivalent of methyl acetoacetate, with various 1,3-dicarbonyl equivalents to give substituted methyl salicylates.[10] We have now applied the reaction to a general synthesis of 3-hydroxyhomophthalates. In particular, our synthesis of sclerin has the construction of the hexa-substituted benzene ring as the critical step (Scheme 2).

Dimethyl 3-hydroxyhomophthalate (**3a**) was obtained in good yield when (**2**) (2 mol. equiv.) was condensed with methyl orthoformate (1 mol. equiv.) in the presence of titanium tetrachloride (2 mol. equiv.) (Scheme 1; Table).



SCHEME 1.

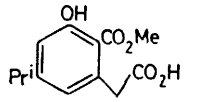
The reaction is assumed to proceed *via* the intermediate (**4**; R = H), formed by the condensation of (**2**) with methyl orthoformate. Subsequent condensation of (**4**; R = H) with 1 mol. equiv. of (**2**) then yields the product (**3a**). The same reaction with methyl orthoacetate gave (**3b**) (65%). With equimolar amounts of (**2**), methyl orthoacetate, and titanium tetrachloride, the product was a mixture of (**3b**) (36%) and the hexenoate (**5**) (31%).† Evidently, (**5**) was derived from (**4**; R = Me) during the hydrolytic work-up.

† An additional component in the product mixture was methyl 3,5-dioxohexanoate which was derived from further hydrolysis of (**5**).

$$MeC(OMe)=CH\cdot CO\cdot CH_2\cdot CO_2Me$$

(5)

The orientation of the condensation between (**4**) and (**2**) suggests that the electrophilic reactivity order is acetal > conjugate position of the β-oxy-αβ-unsaturated ester. This is verified by the observation that (**2**) does not condense intermolecularly with methyl 3-trimethylsiloxybut-2-enoate under identical conditions.



(A)

$Pr^iC(=O)CH_2C(=O)CH_2CO_2Me$

(B)

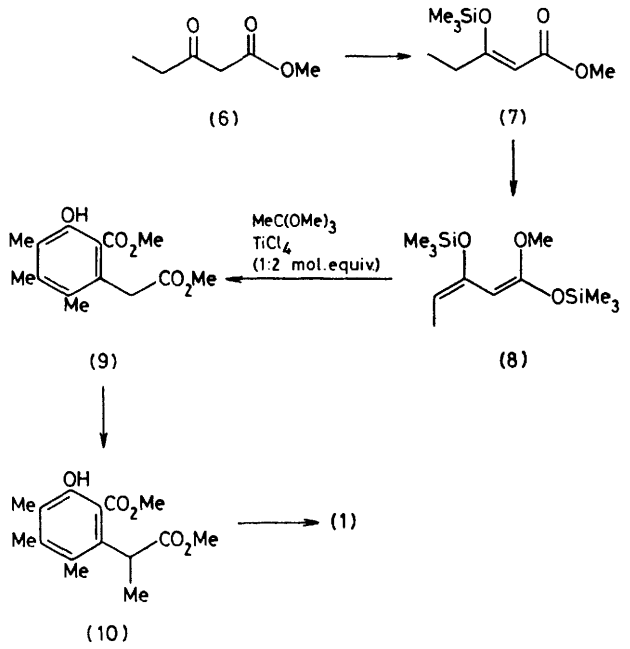
TABLE. Products of the reaction of (**2**) with various electrophiles in the presence of $TiCl_4$ (*cf.* Scheme 1).

Electrophile	Product (**3**)	% Yield	M.p./°C
$HC(OMe)_3$	(**3a**), R = H	68	53—55[a]
$MeC(OMe)_3$	(**3b**), R = Me	65	82—83[b]
$(MeCO)_2O$	,,	69	
$(PhCO)_2O$	(**3c**), R = Ph	72	109—110
$(Pr^iCO)_2O$	(A)[c]	42	165—166·5
	(B)	31	Oil
γ-Butyrolactone	(**3e**), R = $HO[CH_2]_3$–	13	Oil[d]

[a] Lit., 55—57 °C (K. Nitta, C. Takura, I. Yamamoto, and Y. Yamamoto, *Agric. Biol. Chem.*, 1963, **27**, 813). [b] Ref. 10. [c] This acid arose by hydrolysis of the initial product (**3d**) during washing with dilute NaOH. It must be emphasized that the acetate methyl group of the 3-hydroxyhomophthalates is very sensitive to base hydrolysis. [d] Purified by column chromatography.

In a similar fashion (**2**) condensed with a number of anhydrides to give dimethyl 5-substituted-3-hydroxyhomophthalates (Table). With isobutyric anhydride, the product contained a substantial amount of methyl 6-methyl-3,5-dioxoheptanoate (31%) even though 2 mol. equiv. of (**2**) were used. We presume that in this case the cycloaromatisation reaction is slow owing to the steric effect of the isopropyl group. γ-Butyrolactone can, though less effectively, serve as the acylating agent to give compound (**3e**).

Methyl 3-oxopentanoate (**6**) was converted into the trimethylsilyl enol ether (**7**) with triethylamine, a catalytic amount of zinc chloride, and trimethylchlorosilane (Scheme 2). Treatment of (**7**) with lithium di-isopropylamide (LDA) and trimethylchlorosilane gave 1,3-bis(trimethylsiloxy)-1-methoxypenta-1,3-diene (**8**) in 90% yield overall. From its n.m.r. spectrum, (**8**) appears to exist mainly as one geometric isomer, probably the *E,E* isomer. Condensation of (**8**) (2 mol. equiv.) with methyl orthoacetate in the presence of titanium tetrachloride (2 mol. equiv.) gave in 53% yield the aromatic compound (**9**) as colourless prisms, m.p. 85—85·5 °C. The structure of (**9**) is evident from its ^1H n.m.r. spectrum ($CDCl_3$) which showed three aromatic methyl peaks (δ 2·17, 2·21, and 2·25), two ester methyl peaks (δ 3·68 and 3·87), methylene hydrogens at δ 3·91, and a phenolic OH at δ 11·04. Its i.r. (3150 br, 1735, 1663, and 1599 cm^{-1} in $CHCl_3$) and mass [M^+, *m/e* 266, 83%; *m/e* 234 $(M-MeOH)^+$, 100%] spectra are also consistent with its structure. Methylation of (**9**) with 2 mol. equiv. of LDA and 1 mol. equiv. of methyl iodide gave in 80% yield dimethyl sclerinate (**10**), m.p. 113—114 °C (lit.,[11] 113—116 °C). The conversion of (**10**) into (**1**) was readily accomplished by using sodium hydroxide followed by acid.[11]



SCHEME 2.

The construction of compound (**9**) can be considered as the controlled condensation of a dicarbonyl unit with a tricarbonyl unit. In a recent review article,[2] the hope was expressed that the aesthetically pleasing route of biogenetic-type synthesis can, in selected cases, provide commercially attractive routes to natural products of economic importance. By using enol silyl ethers as the nucleophiles, various carbonyl equivalents as the electrophiles, and titanium tetrachloride as the activating agent, controlled condensation of poly-β-carbonyl compounds may be within the realm of possibility.

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