Synthesis of the Aglycones of the Ravidomycin Family of Antibiotics

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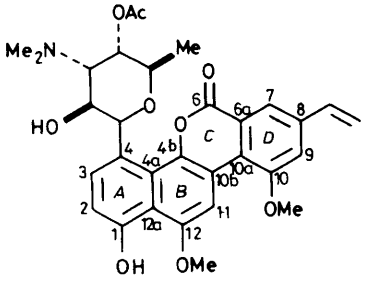
The preparation of the aglycones of the ravidomycin family of antibiotics is described, involving the palladium-catalysed coupling of appropriate stannanes with a common tetracyclic bromide (**5**), the synthesis of which involved Meerwein coupling of an aniline derivative (**13**) with 2,5-dichloro-1,4-benzoquinone followed by a directed Diels–Alder reaction.

The ravidomycin family of antibiotics has recently aroused considerable interest; these substances possess antibiotic and potent antitumour properties[1] and as such present attractive targets for synthesis.

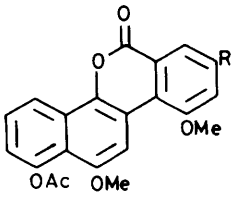
The structures of ravidomycin (**1**)[2,3] and other members of this class (toromycin,[4] albacarcin,[5] gilvocarcin,[6] virenomycin,[7] and chrysomycin[8]) may conveniently be regarded as consisting of a sugar and an aglycone. Although some of the sugars are different, the aglycones are all tetracyclic systems which differ only in the type of group attached to C-8 [structures (**2**)—(**4**)]. Defucogilvocarcin V (**4**)[9] has also been isolated as a natural product in its own right, and has recently been synthesised by Findlay *et al.*[1]

Studies on gilvocarcin,[10,11] chrysomycin,[11] and ravidomycin[11] show that the nature of the group at C-8 is crucial to antitumour activity. We have therefore chosen a synthetic route which will allow extensive manipulation at C-8 from a common precursor as the penultimate step in the synthesis, thus readily allowing preparation of analogues (especially the more potent unsaturated ones[12]) for antitumour screening.

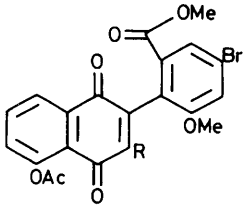
The key to our approach was the preparation of the 8-bromo compound (**5**), which would allow coupling with



(1)



(2) R = Me
(3) R = Et
(4) R = CH=CH$_2$
(5) R = Br



(6) R = Cl
(7) R = SePh

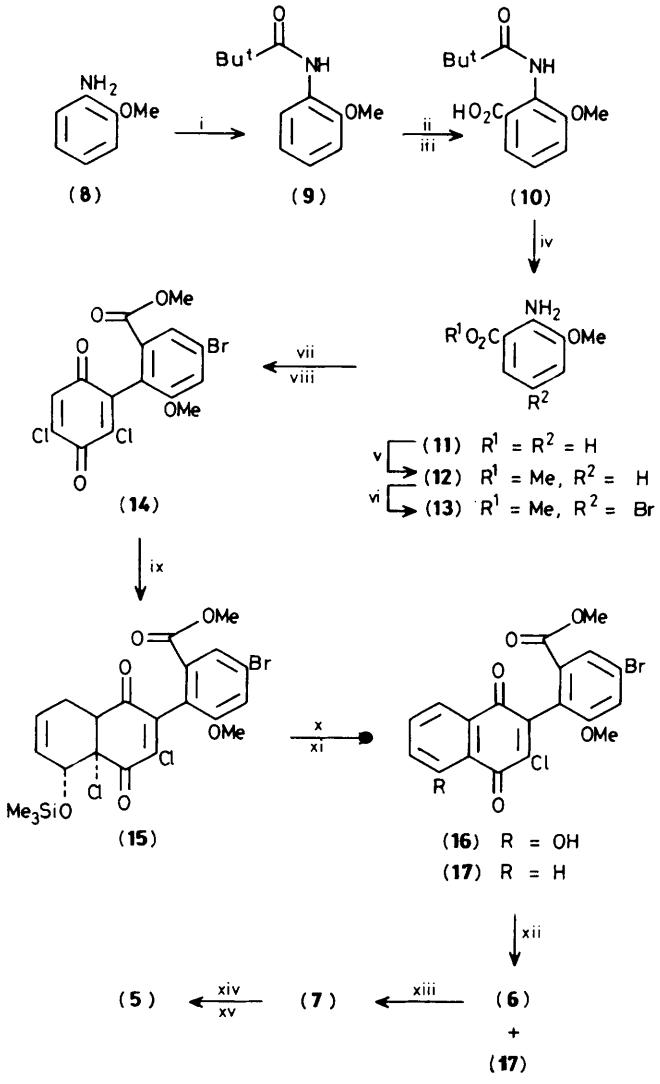
suitable stannanes in a palladium-catalysed reaction.[12,13] To demonstrate the potential of this reaction we report the preparation of the methyl, ethyl, and vinyl derivatives (the aglycones of naturally occurring compounds) and also the unnatural phenyl compound.

The bromo lactone (**5**) was prepared from the chloroquinone (**6**), in a transformation which required specific removal of the chlorine in the presence of an aryl bromide, a functionality notoriously sensitive to reducing conditions. Literature methods for removal of halogen from quinones[14,15] and other methods developed by our group[16] always also removed the bromine. However, after considerable experimentation, we have found that conversion into the phenyl selenide (**7**) allows reduction to the bromo lactone (**5**) with zinc and acetic acid.

The synthesis of (**5**) followed methodology (different from that of Findlay *et al.*[1]) already developed by our group[17] where the latent quinone functionality of ring *B* was utilized to achieve two key synthetic transformations, namely Meerwein coupling of ring *D* to ring *B* followed by creation of ring *A* *via* a directed Diels–Alder reaction. This last step would also allow attachment of the sugar moiety from a suitable precursor.

The synthesis of the bromide (**5**) (Scheme 1) starts from 1-amino-2-methoxybenzene (**8**), which was protected as its carbamate (**9**) (98%; b.p. 118 °C at 0.02 mmHg). Treatment of (**9**) with 2.4 equiv. of n-butyl-lithium gave the dianion, which was quenched with carbon dioxide, yielding the acid (**10**) (84%; m.p. 118—119 °C). Acid hydrolysis of (**10**) gave the amino acid (**11**) (87%; m.p. 165—166.5 °C), which was methylated with diazomethane to give the amino ester (**12**) (92%; m.p. 34—35 °C). Bromination of (**12**) with *N*-bromosuccinimide–dimethylformamide gave the bromide (**13**) (97%; m.p. 54.5—55 °C), the ^{1}H n.m.r. spectrum of which showed two *meta*-coupled doublets, (*J* 2.1 Hz), indicating that carbonation of the dianion of (**9**) had occurred *ortho* to the carbamate rather than *ortho* to the methoxy group.

Meerwein coupling of the diazotized derivative of (**13**) with 2,5-dichloro-1,4-benzoquinone gave the aryl quinone (**14**) (67%; m.p. 147—148 °C). The Diels–Alder reaction between

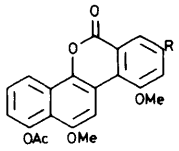


Scheme 1. *Reagents:* i, Bu^{t}COCl, aq. Na_2CO_3, CH_2Cl_2, room temp.; ii, Bu^{n}Li, THF, room temp., iii, CO_2, room temp., then dil. HCl; iv, 25% HCl, reflux; v, CH_2N_2, Me_2CO, room temp., vi, *N*-bromosuccinimide, dimethylformamide, room temp.; vii, $NaNO_2$, 20% HCl, 0 °C; viii, 2,5-dichlorobenzoquinone, H_2O, 65 °C; ix, $Me_3SiOCH{=}CHCH{=}CH_2$, THF, room temp., x, 49% HF, THF, room temp.; xi, act. MnO_2, CH_2Cl_2, reflux; xii, acetic anhydride, pyridine, 4-dimethylaminopyridine, EtOAc, room temp.; xiii, NaSePh·BH_3, THF, room temp.; xiv, Zn, acetic acid, 80 °C; xv, CH_2N_2, Me_2CO, room temp.

the quinone (**14**) and 1-trimethylsilyloxybutadiene gave (**15**) (91%; m.p. 161—162 °C) as the sole product. Desilylation with aqueous HF in tetrahydrofuran (THF) followed by aromatisation with activated manganese dioxide gave a mixture of the hydroxynaphthoquinone (**16**) (m.p. 213—215.5 °C) and the deoxygenated compound (**17**) (m.p. 237—239 °C). Exposure of the mixture to acetylation conditions allowed separation of the acetoxynaphthoquinone (**6**) (58% for three steps, m.p. 219.5—220.5 °C). Treatment with sodium phenyl selenide gave (**7**) (97%, m.p. 182—185 °C), which was reduced with zinc dust in acetic acid and then methylated to give (**5**) (73% for two steps; m.p. 260—263 °C).

Transformation of (**5**) into the aglycone acetates (**2**)—(**4**) and the phenyl derivative (**18**) was accomplished by treatment with tetrakis(triphenylphosphine)palladium and the appro-

Table 1. Product details of palladium-catalysed coupling reactions with the bromide (**5**).



Derivative	Tin reagent	% Yield[a]	M.p. (°C)	Ref.
(**2**) R = Me	Me_4Sn	61	227—229	10, 16
(**3**) R = Et	Et_4Sn	44	226—228	10
(**4**) R = CH=CH_2	$CH_2CHSnBu_3$	66	216—219	1, 10
(**18**) R = Ph	Ph_4Sn	20	261—263	

[a] Not optimised.

priate stannane, as shown in Table 1. Spectral data for (**2**)—(**4**) compared satisfactorily with those already published.[1,7,10]

Treatment of (**4**) with sodium phenyl selenide gave the deacetylated aglycone (68%; m.p. 264—267 °C), data for which also compared satisfactorily with those already published.[2]

All other new compounds gave satisfactory spectral and analytical data.

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