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A Concise Synthesis of the Novel Antibiotic Aranorosin§

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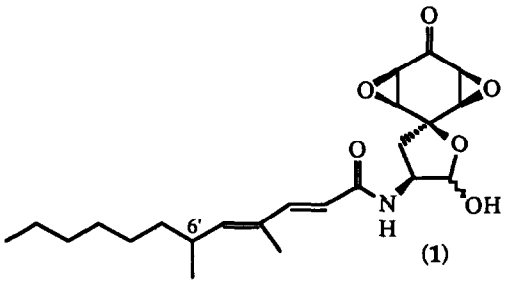
Abstract: A short synthesis of the novel antibiotic aranorosin is described which employs a novel hypervalent iodine-mediated oxidative hydroxylation of a tyrosinal derivative in the key step. A similar procedure was employed to prepare 6'-epiaranorosin, and hence establish the stereochemistry of the natural compound.

Aranorosin (**1**) was isolated from the fungal strain *Pseudoarachniotus roseus* and shown to possess a broad spectrum of biological activity, including antibiotic, antitumour and antifungal properties.[1] The gross structure of aranorosin, together with the relative stereochemistry around the tetracyclic nucleus, was determined by NMR spectroscopy, mass spectrometry and chemical studies, but the configuration of the side chain C-6' methyl substituent was not established.[1] The highly challenging structure of aranorosin, combined with its pharmaceutical potential, has attracted considerable synthetic interest, both from our group[2] and others.[3] We now wish to report a concise total synthesis of aranorosin, thereby establishing its absolute stereochemistry, together with the synthesis of 6'-epiaranorosin and several other *N*-acyl analogues of the natural compound.



(1)

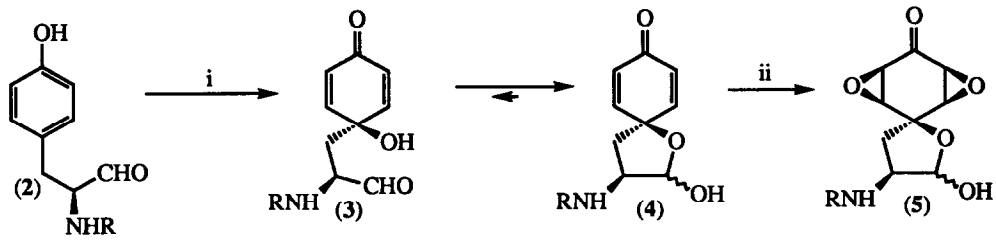
§Dedicated to Professor Alan Katritzky on the occasion of his 65th birthday.

The biogenesis of aranorosin has not been ascertained, but L-tyrosine would seem to be the most likely biosynthetic precursor, and several synthetic approaches have been based on the oxidative cyclisation of *N*-protected L-tyrosine to generate the bicyclic nucleus of the natural product in the cyclohexadienone-spirolactone oxidation level.[2a,3] This approach requires a subsequent reduction of the lactone to a hemiacetal in the presence of sensitive functionality, and while this problem can be overcome,[3b] we wished to circumvent it by devising an oxidative cyclisation procedure which led directly to the bicyclic lactol. Kita *et al.* have shown that oxidation of *N*-acyl tyramines with [bis(trifluoroacetoxy)iodo]benzene (PIFA) in alcoholic solvents gives 4-alkoxycyclohexadienones.[4] We reasoned that use of an aqueous solvent would give *p*-quinols directly, and that oxidation of *N*-acylated tyrosine aldehydes (**2**) would give the required aranorosin precursor lactols (**4**) *via* a very concise route (Scheme 1). We also anticipated that the subsequent bis-epoxidation reaction would proceed with the stereoselectivity shown in Scheme 1: this followed from a consideration of molecular models, and from model studies[2b] which indicated that the presence of a hydroxyl substituent at C-4 of cyclohexadienones [as in hydroxy aldehyde (**3**)], favoured double *cis*-epoxidation.

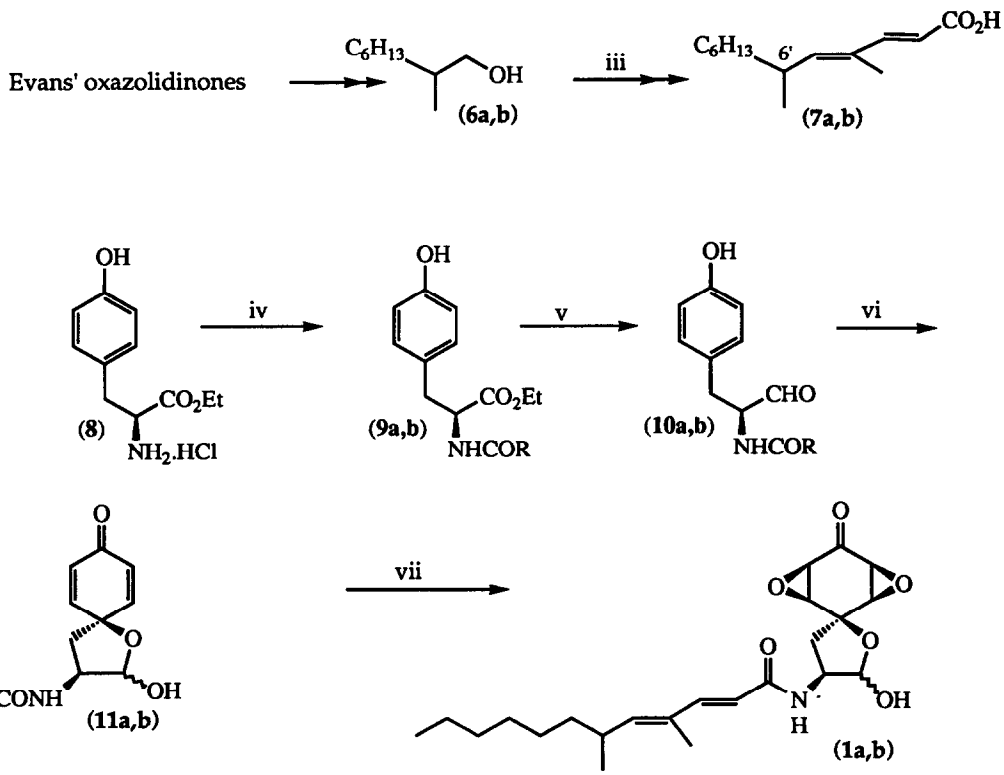
To our pleasure, on treatment with PIFA in aqueous acetonitrile, the *N*-Boc, *N*-Cbz and *N*-COPh tyrosinals (**2a-c**)[5,6] gave the dienone spirohemiacetals (**4a-c**) in 35-50 % yields. These dienones were then epoxidised using basic hydrogen peroxide to give the aranorosin analogues (**5a-c**) in acceptable yield [*e.g.* (**5a**), 43%]; the requisite all *cis*-diepoxide arrangement was confirmed by NOE studies. As expected, *N*-deprotection of these densely functionalised molecules and reacylation with simple acid chlorides proved very difficult.[7] In order to synthesise aranorosin, we therefore prepared tyrosinal (**10**), which has the unsaturated side chain of the natural product already in place (Scheme 2).

Evans' oxazolidinone methodology[8,9] was employed to prepare 2-(*S*) and 2-(*R*)-methyloctanol (**6a,b**) which were required as starting materials for the side chain synthesis. Straightforward transformations were then employed to complete the preparation of 6-(*S*)- and 6-(*R*)-4,6-dimethyldodecadienoic acids (**7a,b**).[10] These acids were separately coupled to tyrosine ethyl ester hydrochloride (**8**) using either ethyl chloroformate or diphenylphosphinic chloride to give the amides (**9a,b**). The latter procedure was preferred as the mixed anhydride method gave significant amounts of the ethyl carbamate as a byproduct. DibalH reduction of (**9a**) produced aldehyde (**10a**) which was normally oxidised immediately. Reaction with 0.95 equivalents of PIFA in 4:1 CH_3CN-H_2O gave dienone (**11a**) in <10% overall yield after chromatography. The yield could be increased to 20% by the addition of 0.5 eq. of 2,2,6,6-tetramethyl-1-piperidinyloxy radical (TEMPO), and to 39% by using chromatographically pure aldehyde. Epoxidation of the 6'-(*S*)-methyl dienone (**11a**) using H_2O_2-LiOH[11] in methanol gave 22% of the required bis-epoxide (**1a**) along with products from attack by the solvent. The use of isopropanol as solvent resulted in a much cleaner reaction and the yield of (**1a**) was increased to 31%. This reaction apparently occurred in a completely stereoselective manner, as isomeric diepoxides were not observed in the crude product mixture. The NMR spectroscopic data of (**1a**) were entirely consistent with the published values for aranorosin[1] but the optical rotation was markedly different [(**1a**), $[\alpha]_D$ +33.5° (c 0.31, $CHCl_3$); aranorosin,[1] $[\alpha]_D$ -2.42° (c 2.58, $CHCl_3$)]. We therefore repeated this sequence using the 6'-(*R*)-tyrosine derivative (**9b**) as shown in Scheme 2. Similar yields were obtained in each of the steps and the product (**1b**), obtained as a colourless solid, again displayed NMR data fully consistent with those published for aranorosin. In this case, however, the optical rotation was consistent with the published[1] value {$[\alpha]_D$ -8.2° (c 0.48, $CHCl_3$)}, as were the melting characteristics (150°C dec.). We therefore assign

Scheme 1 (a, R=Boc;b, R=Cbz; c, R=PhCO.)



Scheme 2 [a = 6'-(*S*); b = 6'-(*R*); R = *E*,*E*-$C_6H_{13}CH(CH_3)CH{=}C(CH_3)CH{=}CH$-]



Reagents

i. PIFA, CH_3CN-H_2O (4:1), 0°C.

ii. 30% H_2O_2, NaOH, MeOH, 0°C.

iii. (a) Swern oxidation; (b) $Ph_3PC(CH_3)CO_2Et$; (c) DibalH; (d) MnO_2; (e) Ph_3PCHCO_2Et; (f) LiOH

iv. (**7a,b**), Ph_2POCl, Et_3N, THF, rt (73-85%). (58-59% overall).

v. DibalH, THF, -78°C .

vi. PIFA, TEMPO, CH_3CN-H_2O (4:1), 0°C (18-31% over 2 steps).

vii. 30% H_2O_2, LiOH, ^iPrOH, 0°C (31-35%).

structure (**1b**), with the 6'-(*R*)-configuration, to aranorosin, and structure (**1a**) to its 6'-diastereomer.

We are currently optimising this synthetic route and investigating the biological activity of synthetic aranorosin analogues.

Acknowledgements

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5. Prepared by DibalH reduction of the corresponding esters [see (**9**) -> (**10**), Scheme 2].
6. All new compounds gave consistent spectral and analytical/mass spectrometric data.
7. The *N*-Cbz compound (**5b**), was converted into the corresponding methyl acetal which was *N*-deprotected (H_2-Pd/C) and acylated (PhCOCl), but the yields were low.
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10. These acids were fully characterised, although the enantiomeric excesses have yet to be conclusively determined [(**7a**), $[\alpha]_D$ +62.6° (c 0.54, CH_2Cl_2); (**7b**), $[\alpha]_D$ - 57.4° (c 0.5, CH_2Cl_2)]. The alcohols (**6a**) and (**6b**) were shown to be enantiomerically pure by NMR spectroscopy on their Mosher ester derivatives.
11. Epoxidation of (**11a**) using H_2O_2-NaOH in methanol gave *ca.* 17% of the required bis-epoxide (**1a**).

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