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STUDIES DIRECTED TOWARDS THE TOTAL SYNTHESIS OF ARANOROSIN

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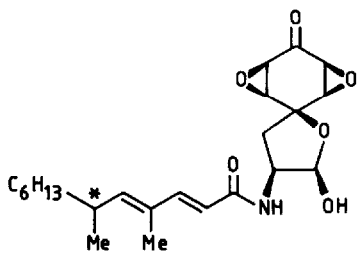
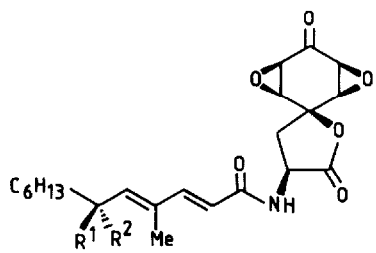
Abstract: Protocols that led to the construction of cyclohexanone bisoxirane as a part of 1-oxaspiro[4,5]decane moiety present in aranorosin, are described.

Aranorosin (**1**) is a novel antibiotic isolated[1] from the fermentation broth of Pseudo-arachniotus roseus. The anticancer, antibacterial, as well as prounced activity against yeast and filamentous fungi are some of the impressive biological profiles[2] of aranorosin. However, the most distinguished and unique architectural features are the presence of hitherto unknown[3] cyclohexanone bisoxirane fragment as a part of a 1-oxaspiro[4,5]decane system, thus endorsing this molecule as a challenging synthetic target. A concise protocol that could lead to the construction of cyclohexanone bisoxirane and 1-oxaspiro[4,5]decane ring would indeed be a useful contribution to this molecule. Due to the chemical unstability[4] of aranorosin, we have chosen the derived spirolactone derivative (**2**), in which the above mentioned structural features are unperturbed, for the first synthetic study towards aranorosin.



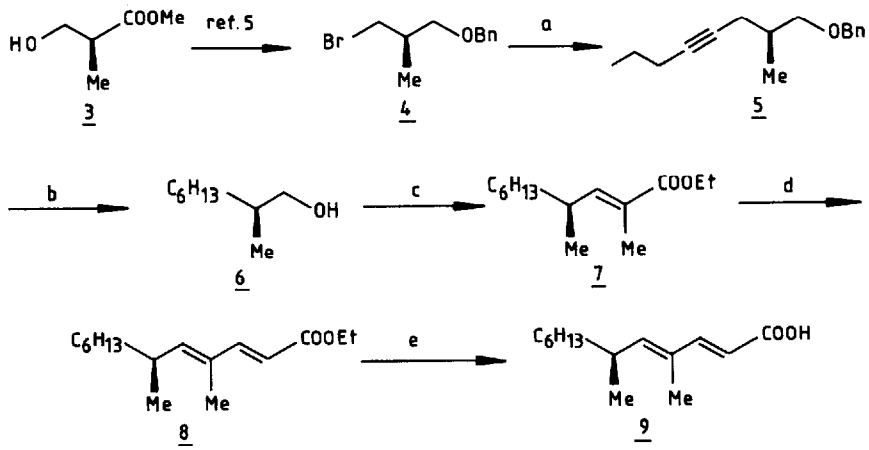
1
(* unknown)



2a R^1= Me, R^2 = H
2b R^1= H , R^2 = Me

Our immediate concern was to synthesise the C_{14} side chain (**9**) of aranorosin in an enantiomerically pure form for which the commercially available chiral building block (S)-methyl 3-hydroxy-2-methylpropionate (**3**) was considered. The known[5] bromide derivative (**4**) was coupled with 1-pentyne in the presence of n-BuLi at -78°C to form the alkylated product (**5**) (80%). Reduction of **5** over Pd-C gave (S)-2-methyloctan-1-ol (**6**). Swern oxidation of **6** followed by Wittig olefination with (carbethoxyethylidene)triphenylphosphorane afforded the E-ester (**7**). DIBAL reduction of **7** followed by Swern oxidation and Wittig reaction with (carbethoxymethylene)triphenylphosphorane afforded **8** (75%). **8** on hydrolysis with LiOH and acidification under mild conditions with citric acid gave the (S)-acid **9** (65%) confirmed by ^{1}H-NMR spectrum[6]. (Scheme 1)

Scheme - 1

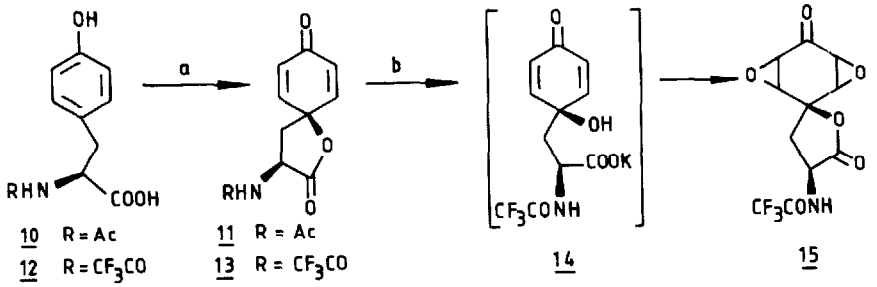


a) n-BuLi, THF, ≪, -78°C, 2h b) Pd-C, H_2, EtOH, 1atm, 18h c) i- $(COCl)_2$, DMSO, CH_2Cl_2, -78°C, Et_3N, 1h ii- $Ph_3P=C(Me)COOEt$, C_6H_6, Δ, 4h d) i- DIBAL-H, CH_2Cl_2, -78°—0°C, 1h ii- $(COCl)_2$, DMSO, CH_2Cl_2, -78°C, Et_3N, 1h iii- $Ph_3P=CHCOOEt$, C_6H_6, Δ, 4h e) LiOH, H_2O-MeOH, citric acid.

For the second phase of our synthetic plan, the spirolactone derivative of the type **11** or **13** appeared to be the most logical precursor as it contains functionalities appropriately suited for the target molecule (**2**). The electrochemical route[7] to **11** from N-acetyl-L-tyrosine (**10**) has been reported long ago but in poor yield. We therefore, felt the need to develop a chemical route by involving oxidative cyclisation reagents. For instance, N-trifluoroacetyl-L-tyrosine (**12**) underwent smooth oxidative cyclisation reaction in the presence of bis(trifluoroacetoxy)iodobenzene and pyridine in acetonitrile to give **13** in 60% yield. The structure of **13** was unambiguously determined by ^{1}H-NMR spectrum[8]. This oxidative cyclisation reaction apparently looks versatile irrespective of the N-protecting group present[9] (Scheme 2).

The creation of the cyclohexanone bisoxirane moiety turned out to be a difficult proposition. As expected compound **13** did not undergo epoxidation with reagents such as MCPBA, pertrifluoroacetic etc. This led us to suggest that alkaline-H_2O_2 may be the reagent of choice for the following reasons. Under alkaline condition the spirolactone would open up to expose the free tertiary OH group (**14**) which would be expected[10] to control the epoxidation of olefins with H_2O_2. Concomitant cyclisation of hydroxy acid salt would regenerate the spirolactone again. Thus, **13** was treated with potassium carbonate and hydrogen peroxide in aqueous THF at 0°C. The reaction mixture was acidified with citric acid, excess of peroxide was decomposed by careful addition of triphenylphosphine and consequently lactonised in the presence of DCC. The product isolated after chromatography showed in its mass spectrum, the molecular ion peak at m/z 307 (M^+) and also the fragmentation pattern expected for the structure **15**. How-

Scheme - 2



a) PhI(OCOCF3)2, Py., CH3CN, 0–10°C, 18h

b) K2CO3 (2eq), H2O (30%, 8eq.), H2O-THF, 0°C, 4h, citric acid, (pH-6), TPP, DCC (1eq).

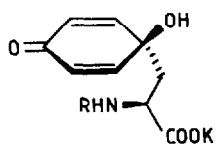


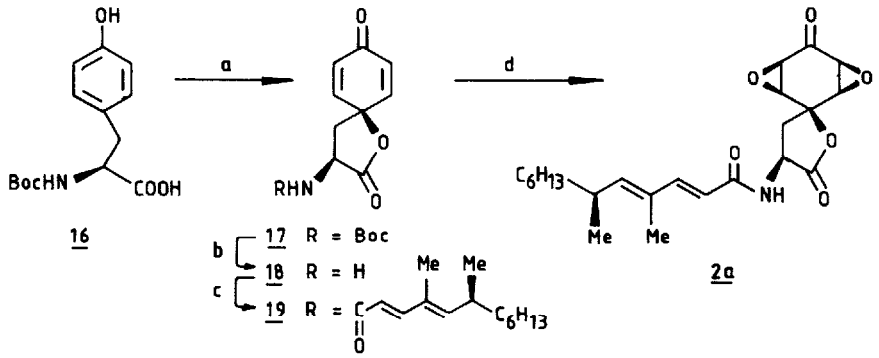
FIG. A

ever, its ^{1}H-NMR spectrum was complex particularly between 3-4 ppm, certainly due to the formation of isomeric epoxide derivatives (**15**). Although it has been claimed[10] that the stereochemical outcome of epoxide formation is dictated by the configuration of the hydroxy group, it appeared that the nitrogen[11] substituent could have also influenced the stereochemical course (Fig A). Since the separation of isomers was not possible, we felt to circumvent this problem by increasing the steric bulk on the amide group by introducing the side-chain prior to epoxidation step. The N-BOC-spirolactone derivative (**17**) was prepared[9] from **16** in 67% yield by the route described earlier. The protecting group (N-BOC) was cleaved by using trifluoroacetic acid and triflic acid (cat.) at 0°C to give the amine **18** which was not isolated but directly condensed by mixed anhydride method with **9** in the presence of ethylchloroformate to furnish **19** (65%). The structure of **19** was confirmed by ^{1}H-NMR spectrum[12].

Epoxidation of **19** by hydrogen peroxide-potassium carbonate as described above followed by separation of reaction mixture on preparative tlc (E Merck silica gel 0.25 mm) gave a slower moving product in 27% yield whose structure **2a** was suggested by spectral studies including mass spectroscopy. For example, the ^{1}H-NMR spectrum[13] of our sample was almost identical with the authentic spectrum provided to us by the Hoechst group. In addition proton decoupling experiments on epoxy protons substantiated the assigned structure **2a**. Although both the ^{1}H-NMR spectra were identical, due to non-availability[1-3] of the optical rotations of the side-chain or that of **2**, the stereochemistry at C_6 of the side-chain of aranorosin could not be established beyond doubt at this juncture. Further studies to prepare R isomer of **9** and the corresponding spirolactone derivative **2b** are forthcoming.

The authors wish to thank Dr B N Ganguli and his group for fruitful discussions and also for providing the ^{1}H-NMR spectrum of **2**. The financial support, in part, from NIH, Bethesda, USA, under PL-480 scheme is duly acknowledged.

Scheme - 3



a) Ph-I-(OCOCF$_3$)$_2$, Py , CH$_3$CN , 0°–10°C , 18h b) CF$_3$COOH , CF$_3$SO$_3$H (cat.) , 0°C , 5min. c) ClCOOEt , CH$_2$Cl$_2$, 9 , 0°C , 15min. d) K$_2$CO$_3$ (2eq) , H$_2$O$_2$ (30%, 8eq), H$_2$O -THF , 0°C , 4h , citric acid (pH 6) , TPP , DCC (1eq).

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1. Fehlhaber H W, Kogler H, Mukhopadhyay T, Vijaykumar E K S and Ganguli B N, J Am Chem Soc, **110**, 8242 (1988).
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3. Fehlhaber H W, Kogler H, Mukhopadhyay T, Vijaykumar E K S, Roy K, Rupp R H and Ganguli B N, J Antibio, **41**, 1785 (1988).
4. Personal Discussion.
5. Branca Q and Fischi A, Helv Chem Acta, **60**, 925 (1977).
6. ^{1}H-NMR spectral data (200 MHz, CDCl$_3$) for **9:** δ 0.91 (t, 3H, J = 7.0 Hz), 0.98 (d, 3H, J = 6.5 Hz), 1.29 (m, 10H), 1.81 (s, 3H), 2.48 (m, 1H), 5.71 (d, 1H, J = 9.5 Hz), 5.78 (d, 1H, J = 15.5 Hz), 7.36 (d, 1H, J = 15.5 Hz).
7. Meyers M B, McCapra F, Dodson P A and Scott A I, J Am Chem Soc, **85**, 3702 (1963).
8. ^{1}H-NMR spectra data (200 MHz, CDCl$_3$) for **13:** δ 2.4-2.85 (m, 2H), 5.07 (m, 1H), 6.32 (m, 2H), 7.0 (m, 2H), 8.67 (d, 1H, J = 8.0 Hz).
9. Other substituents such as N-acetyl, N-Cbz, N-BOC, N-phthalamido present on L-tyrosine undergo efficient cyclisation in 60-70% yield.
10. Carndruff J, Hafiz M, Hendrie R and Monaghan F, Tetrahedron Lett, **25**, 6033 (1984).
11. Laguzza B C and Ganem B, Tetrahedron Lett, **22**, 1483 (1981).
12. ^{1}H-NMR spectral data (200 MHz, CDCl$_3$) for **19:** δ 0.86 (t, 3H, J = 5.9 Hz), 0.96 (d, 3H, J = 6.6 Hz), 1.23 (m, 10H), 1.74 (s, 3H), 2.44 (m, 2H), 2.80 (dd, 1H, J = 9.5 and 14.3 Hz), 4.77 (m, 1H), 5.65 (d, 1H, J = 9.5 Hz), 5.75 (d, 1H, J = 15.4 Hz), 6.27 (m, 2H), 6.41 (d, 1H, J = 6.4 Hz), 6.90 (m, 2H), 7.23 (d, 1H, J = 15.4 Hz).
13. ^{1}H-NMR spectral data (200 MHz, CDCl$_3$) for **2a:** δ 0.87 (t, 3H, J = 6.0 Hz), 0.96 (d, 3H, J = 6.8 Hz), 1.25 (m, 10H), 1.75 (s, 3H), 2.52 (m, 2H), 2.81 (dd, 1H, J = 10.3 and 13.4 Hz), 3.50 (m, 2H), 3.70 (m, 1H), 3.94 (m, 1H), 4.70 (m, 1H), 5.67 (d, 1H, J = 9.5 Hz), 5.81 (d, 1H, J = 15.3 Hz), 6.75 (d, 1H, J = 6.4 Hz), 7.25 (d, 1H, J = 15.3 Hz).

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