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STEREOCHEMICAL CORRELATION OF (-)-AVERANTIN

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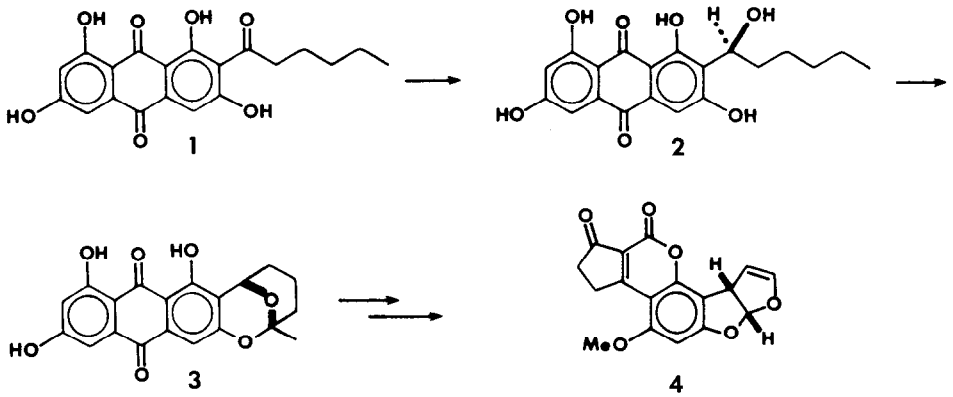
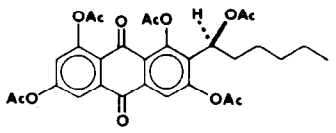
Summary: *Natural (-)-averantin has been degraded to afford a sample of (S)-(+)-2-hydroxyheptanoic acid. The absolute configuration of averantin is therefore, S in accord with recent biogenetic proposals for aflatoxin B_1.*

Proceeding from a linear six-carbon primer,[2] norsolorinic acid **(1)** is the first anthraquinone intermediate in the aflatoxin pathway.[3,4] Reduction yields averantin **(2)**, whose single asymmetric center has been proposed[5,6] to direct the stereochemical course of all subsequent transformations of the C_6-side chain to give ultimately the bisfuran of aflatoxin B_1 **(4)**. The absolute configuration of this characteristic structural feature was established in Büchi's laboratory by unambiguous chemical means.[7] We report in this Letter the degradation of natural (-)-averantin to (S)-(+)-2-hydroxyheptanoic acid. Averantin, therefore, must itself have the (S)-configuration congruent with stereochemical consequences implicit in recent biogenetic proposals.[5,6]



Averantin was isolated from mycelial mats of Aspergillus parasiticus mutant AVN-1[4] grown in standing culture (5 L in 10 2.8L Fernbach flasks) for 9 days, 774 mg, mp 231-234°C (lit.[8] mp 233-234°C, lit.[4] 232°C), but having an optical rotation lower than the reported value, $[\alpha]^{22}_{579}$ = -138° (c=0.37, EtOH), lit.[8] $[\alpha]^{22}_{579}$ = -178° (c=0.37, EtOH). Treatment of this material with Ac_2O/pyridine as described previously[8] gave the pentaacetate **5** (SiO_2 chromatography, 85% yield) as a viscous, yellow-green oil, $[\alpha]^{25}_{D}$ = -77° (c=0.85, $CHCl_3$). Ozonolysis of **5** in $CHCl_3$, MeOH or absorbed in silica gel,[9] or attempted oxidation with RuO_4[10] all failed to proceed. This lack of reactivity was attributed to the electron-withdrawing effects of the four aryl acetoxy groups. Consequently, **5** was treated with sodium bicarbonate in aqueous MeOH (75 min, r.t.) to afford (SiO_2 chromatography, $CHCl_3$:MeOH 95:5) a 10-15% yield

of tetraacetate 6 and a 60-70% yield the triacetate 7.[9] The structures of 6 and 7 were secured by spectral comparisons to 5[11] and n.O.e. measurements on the dimethyl ether **8**.



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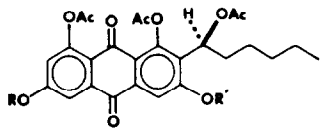
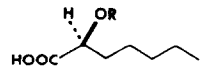


6 R=H, R'=Ac
7 R=R'=H
8 R=R'=Me



9 R=Ac
10 R=H

Treatment of triacetate **7** with a catalytic amount of RuO_4 and $NaIO_4$ (36 eq., 24 hr, r.t.) in aqueous acetonitrile[10] gave an approximately 60:40 mixture of 2-acetoxyheptanoic acid **(9)** and hexanoic acid, the latter presumably resulting from over oxidation of **9**. The two acids were largely separable by chromatography on acid-washed silica gel (Et_2O:pentane 3:1). Fractions containing pure **9** were pooled, saponified with 0.5 N methanolic KOH[12] and the 2-hydroxyheptanoic acid **(10)** so obtained was purified by chromatography on acid-washed silica gel ($CHCl_3$:MeOH, 98:2) and recrystallized from pentane: $[\alpha]_D^{25}$ = +4.8° (c=1 and c=4, $CHCl_3$); for (S)-(+)-2-hydroxyheptanoic acid: lit.[12] $[\alpha]_D^{25}$ = +6.9° (c=5.8, $CHCl_3$), lit.[13] $[\alpha]_D^{26}$ = +5.53° (c=5.8, $CHCl_3$). It may be concluded that the absolute configuration of (-)-averantin is S, consistent with that recently established for averufin **(3)**.[14]

Acknowledgements

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