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APPROACH TO THE SYNTHESIS OF STEFFIMYCINS
PREPARATION AND ANTIBACTERIAL ACTIVITY OF (±) 8-DEMETHOXY 7-EPI (?) STEFFIMYCINONE

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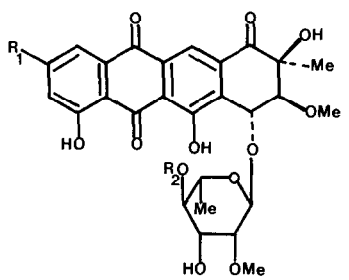
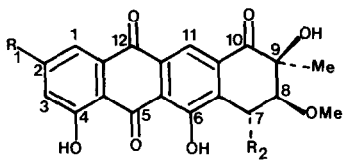
Abstract : Title compound has been prepared in five steps from the readily avalaible 3-chloro 5-hydroxy 7-methoxy 1,4-naphthoquinone, and tested for antibacterial activity.

Steffimycin A 1 first isolated in 1967 from culture of *Streptomyces steffisburgensis* exhibits antibiotic activity against gram-positive bacteria but also in vitro cytotoxic properties (KB, HERPES)[1]. Structure of 1 was proposed on the basis of spectroscopic data and chemical degradation, however stereochemistry and absolute configuration of ring A functions were not determined[2]. Interesting features of the corresponding aglycone, steffimycinone 2, are the presence of a C_{10} carbonyl and a C_8 methoxy groups together with more common functions of ring A anthracyclines : a C_9 methyl group with a C_7-C_9 diol. Moreover this 11-deoxyanthracyclinone is characterized by a relatively rare methoxy group at C_2[3].



1 R_1=OMe, R_2=H
3 R_1=OMe, R_2=Me
4 R_1=R_2=H

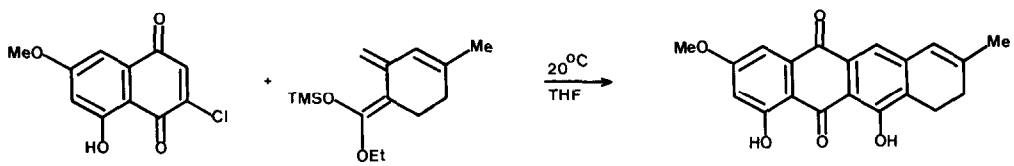


2 R_1=OMe, R_2=OH
5 R_1=R_2=H

Other closely related and biologically active compounds are steffimycin B[4] 3 (4'-O methyl steffimycin A) aranciamycin 4 (identical to SM 173 A[6]) isolated in 1970 from cultures of *Streptomyces echinatus* and SM 173 B 5[6].

The complete structure of aranciamycin has been recently secured by X-Ray analysis[7] and it may be anticipated on the basis of anthracycline biosynthesis that steffimycin A 1 is in fact 2-methoxy aranciamycin. The recent publication by Krohn[8] on the synthesis of 8-demethoxy aranciamycin leads us to describe here our own progress toward steffimycins.

Cycloaddition of the readily available ketene acetal 6[9] with 3-chloro 5-hydroxy 7-methoxy 1,4-naphthoquinone 7, itself obtained by Diels-Alder condensation of Danishefsky diene (1-methoxy 3-trimethylsilyloxy 1,3-butadiene)[10] with 2,6-dichlorobenzoquinone[11], affords after acidic hydrolysis olefin 8[12], m.p. 229-230°C, an orange powder (60%), as the only detectable regioisomer.



7 6 8

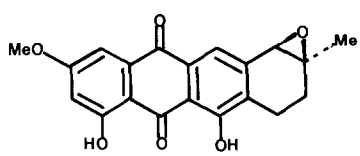
Epoxydation with metachloroperbenzoic acid (3 eq., CH_2Cl_2, 20°C) gives oxirane (±) 9 m.p. 233-234°C (70%)[12] together with some fully aromatized material.

Treatment of 9 with trifluoroacetic acid in CH_2Cl_2 at room temperature (16 hrs.) affords a mixture of cis 10a and trans 10b diols after cleavage of the intermediate trifluoroacetates with mild base ($NaHCO_3$) and, without separation, oxidation with Jones reagent (2 eq.) in acetone overnight gives (±) 11, m.p. 245-250°C as yellow powder (52% from 9)[12]. This material which may be considered as 8-demethoxy 7-deoxy steffimycinone shows similar U.V. spectrum, in ethanol, to 7-deoxy steffimycinone ($\lambda_{max.}$ 240 nm (log ε = 4.46), 285 nm (4.43) and 440 nm (4.23)[2,13].

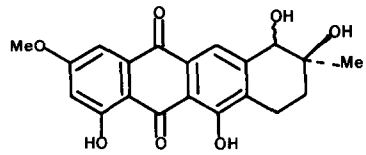
As already observed by Krohn[8] introduction of the C_7 hydroxyl group is easily carried out in this series by base treatment (Triton B, Pyridine, water) to give cis diol (±) 12, m.p. 223-225°C (61%)[12] together with variable amounts (∿ 0-6 %) of trans diol.

The formation of 12 is believed to arise through initial base catalyzed enolisation followed by addition of OH^- at C_7 and subsequent reoxidation to the quinone state. Standard benzylic bromination (Br_2, CCl_4, light in presence of epoxycyclohexane as HBr scavenger) affords after base treatment ($Ca(OH)_2$, THF, H_2O) a similar yield of (±) 12.

The relative stereochemistry at C_7 and C_9 in 12 has been confirmed by ^1H NMR[12] and quantitative conversion to the corresponding acetonide (2-methoxy propene, cat. PTSA, room temperature).

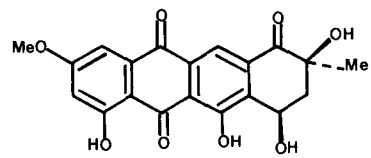


(±) 9

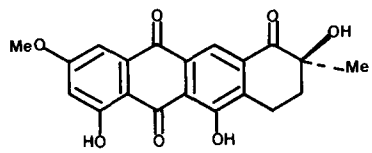


(±) 10a 10 α OH

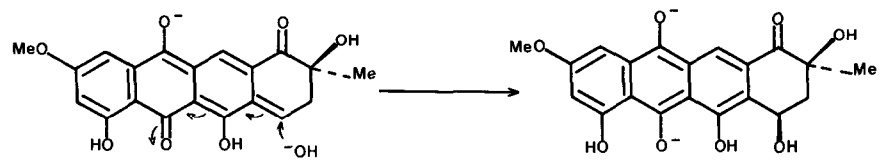
(±) 10b 10 ß OH



(±) 12



(±) 11



ANTIBACTERIAL ACTIVITY

Compound 12 has been tested against gram-positive bacteria. Preliminary results indicate activity against *Bacillus subtilis* and *Bacillus pumilus* at 100 µg/ml. No activity was observed at this high concentration level against *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginea* and *Sarcina lutea*.

The presence of a C_8 methoxy group may be important for antibacterial activity since 7-deoxy steffimycinone[13], aranciamycinone[14] and SM 173 B inhibit gram-positive bacteria at much lower concentration.

Further efforts to prepare steffimicinone are in progress and extension of this synthetic methodology to analogs may bring more information about structural parameters neccessary for antibacterial and/or antitumor activity.

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12 - All new compounds exhibit analytical data and/or high resolution M.S. in agreement with the proposed structures. Melting points were taken on a Büchi 510 apparatus and are uncorrected. M.S. : Relative percentage of each fragments are given in parentheses.

8 NMR ($CDCl_3$) : δ 2.00 (s, 3H), 2.43 (t, J=7Hz, 2H), 2.86 (t, J=7Hz, 2H), 3.91 (s, 3H), 6.23 (s, 1H), 6.61 (s, 1H), 7.16 (s, large, 1H), 7.40 (s, large, 1H), 12.27 (s, 1H) and 12.33 (s, 1H), I.R (KBr) : 3275, 3030, 1680, 1640, 1620, 1600 cm^{-1}. M.S : m/z 336 (57), 334 (91), 274 (68), 238 (100), 175 (57) and 133 (82).

9 NMR ($CDCl_3$) : δ 1.55 (s, 3H), 3.66 (s, 1H), 3.90 (s, 3H), 6.64 (d, J=2Hz, 1H), 7.33 (d, J=2Hz, 1H), 7.79 (s, 1H), 12.20 (s, 1H) and 12.43 (s, 1H). I.R (KBr) : 3300, 3280, 1680, 1620, 1605 cm^{-1}. M.S : m/z 352 (47), 337 (23), 334 (26), 324 (100), 309 (23), 284 (10), 69 (38) and 51 (61).

11 NMR ($CDCl_3$) : δ 1.42 (s, 3H), 3.96 (s, 3H), 6.74 (s,large, 1H,), 7.43 (s, large, 1H), 8.41 (s, 1H), 12.20 (s, 1H), 12.71 (s, 1H). I.R (KBr) : 3260, 3000, 1700, 1680, 1640, 1620 cm^{-1}. M.S : m/z 368 (58), 340 (52), 325 (100), 310 (17), 297 (52) and 282 (20).

12 NMR ($CDCl_3$) : δ 1.41 (s, 3H), 3.97 (s, 3H), 5.40 (t, J=6Hz, 1H), 6.76 (s, 1H), 7.43 (s, 1H), 8.44 (s, 1H), 12.08 (s, 1H), 13.14 (s, 1H). I.R (KBr) : 3360, 3020, 1710, 1680, 1620 cm^{-1}. U.V (EtOH) : 283 nm (log ε = 4.21), 240 nm (log ε = 4.38), 455 nm (log ε = 3.95). M.S. : m/z 384 (17), 368 (48), 366 (42), 350 (90), 338 (64), 324 (100), 297 (44), 277 (37) and 270 (33).

13 - R.C. Kelly, U.S. Pat. 3 976 667, Aug. 24 (1976).

14 - Interestingly aranciamycinone appears to be twice as potent against *Bacillus subtilis* (1-2 μg/ml) as the parent aranciamycin (see ref. 5).

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