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SYNTHESIS OF (±)-AVERUFANIN,† NORAVERUFANIN AND BIS-DEOXYAVERUFANIN

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Abstract—Alkylation of xanthopurpurin (8) by 2-hydroxy-6-methyltetrahydropyran (6a and 6b) produced bis-deoxyaverufanin (9). This reaction was first carried out in aqueous sodium bicarbonate solution. Use of (*S*)-(−)-proline in dimethylformamide gave a quantitative yield of 9. With this method, 1,3,6,8-tetrahydroxyanthraquinone (4) was alkylated by 2-hydroxytetrahydropyran (15). Chromatography of the reaction mixture produced noraverufanin (17) along with a dialkylation product 18. Synthesis of (±)-averufanin (12) with 42% yield was achieved.

The C_{20}-anthraquinones isolated from *Aspergillus versicolor* (Vuillemin) Tirasboschi constitute a unique class, all of them having in common a 1,3,6,8-tetrahydroxyanthraquinone nucleus[1-3] which is bound through carbon 2 to an alkyl chain with the first carbon oxygenated.‡ This O atom is either part of a hydroxy (averantin), ketone (norsolorinic acid), ether (1,3,6,8 - tetrahydroxy - 2 - (1' - methoxyhexyl)anthraquinone), cyclic ether (averufanin (12)) or cyclic ketal function (averufin). The similarities among the anthraquinone pigments can be rationalized by the following biosynthetic process (Scheme 1). A C_{20} polyketide chain *i* is produced by the acetate-polymalonate pathway. The first anthraquinone resulting from the cyclization of this chain would be a 1,3,6,8-tetrahydroxyanthraquinone *ii* containing an oxidized benzylic position. Biosynthesis of averufin and averufanin among other pigments would involve stepwise modifications of the polyketonic side-chain by reduction of the CO groups and cyclization.

An efficient method of alkylation of 1,3-dihydroxyanthraquinone has been previously reported.[4,5] This paper describes the application of (*S*)-(−)-proline catalyzed alkylation[6] in the synthesis of (±)-averufanin (12) and noraverufanin (17) and includes experimental details of the alkylation of xanthopurpurin (8) by 2-hydroxy-6-methyltetrahydropyran (6a and 6b).

Our primary interest was to develop a synthetic approach that could be used for synthesis of most of the metabolites of *Aspergillus versicolor*. Such a procedure would require a method for hydroxyalkylation of 1,3-dihydroxyanthraquinones. In a two step synthesis, Castonguay and Brassard[7,8] were able to prepare 1,3,6,8-tetramethoxyanthraquinone, a common moiety of all metabolites, on a 3 gram scale. Anthraquinone 3 was obtained in low yield by treatment of 2,6-dichlorobenzoquinone (1) with ketene dimethyl acetal (2). Total demethylation of 3 in a melted NaCl/$AlCl_3$ mixture was quantitative.[9]

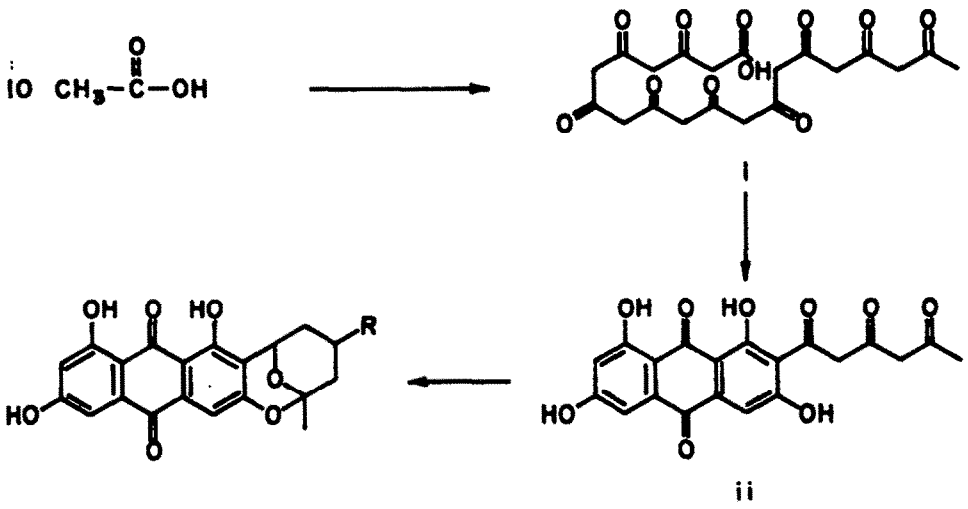
Numerous preparations of 2-hydroxy-6-methyltetrahydropyran (6a and 6b) required for the synthesis of (±)-averufanin 12 have been published.[10-14] However, most of them involved difficult multi-step syntheses and suffered from low overall yield. For example, we were unable to prepare 6a and 6b by acid hydrolysis of 2-ethoxy-6-methyltetrahydropyran (7). We then chose to work out a one-step synthesis of 6a and 6b from the commercially available glutaraldehyde 5. Freshly distilled glutaraldehyde 5 was allowed to react with an excess of methylmagnesium iodide to furnish the expected 2-hydroxy-6-methyltetrahydropyran (6a and 6b). Gas chromatography and ^{1}H NMR spectra show the presence of the two anomers 6a and 6b (ratio 3:2).

Alkylation of xanthopurpurin (8) with an excess of 2-hydroxy-6-methyltetrahydropyran (6a and 6b) in the presence of two equivalents of (*S*)-(−)-proline went to completion within 15 hr. The yellow solid isolated in quantitative yield by preparative tlc was identified as bis-deoxyaverufanin (9).

Alkylation of carbon 2 is confirmed in ^{1}H NMR spectrum by the lack of aromatic proton absorption below 7.00 ppm and by assignment of the singlet at 7.53 ppm to the 4-H. Comparison of the mass spectra of 9 and of (+)-averufanin indicate that both have the same carbon backbone. As shown in Scheme 2 all fragments observed in the mass spectrum of bis-deoxyaverufanin (9) appear in the mass spectrum of (+)-averufanin but decreased by 32 units. For the eventual synthesis of (+)-averufanin (12) it was essential to elucidate the stereochemistry of the tetrahydropyran ring of anthraquinone 9. ^{1}H NMR spectrum shows that the 6'-Me absorbed as a doublet indicating the presence of only one stereoisomer. The anthraquinone nucleus was expected to occupy an equatorial rather than axial position.[9] This was confirmed by the absorption of the benzylic proton, H-2', as a doublet of doublet with coupling constants of 10.0 and 2.0 Hz. The ^{1}H NMR spectrum did not permit elucidation of the stereochemistry of 6' asymmetric center since the 6'-H absorption was a broad multiplet centered at 3.72 ppm.

†This pigment has also been named avermutin. See Ref. 1.

‡The pigment averythrin is considered as a dehydration product of averantin and desoxyaverufanone a reduction product of averufanone.

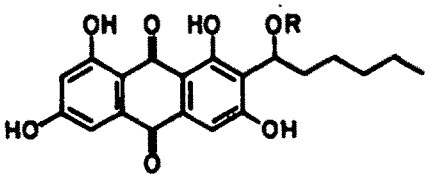


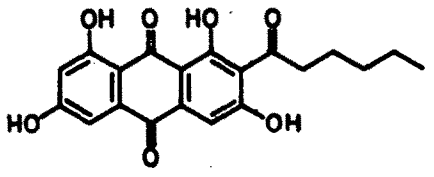
i

ii

R = H Averufin

R = OH Hydroxyaverufin



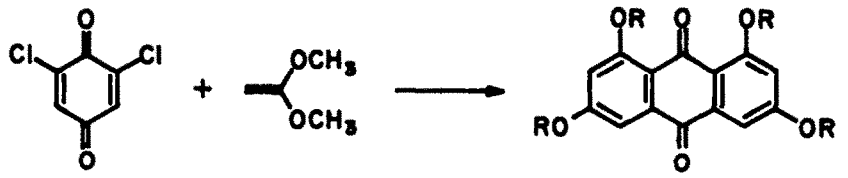


R = H Averantin

Norsolorinic Acid

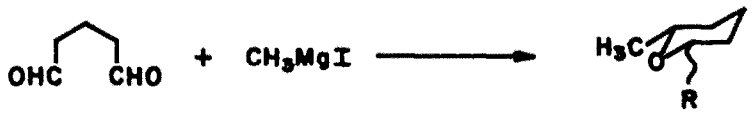
R = CH_3

Scheme 1.



1 2 3 R = CH_3

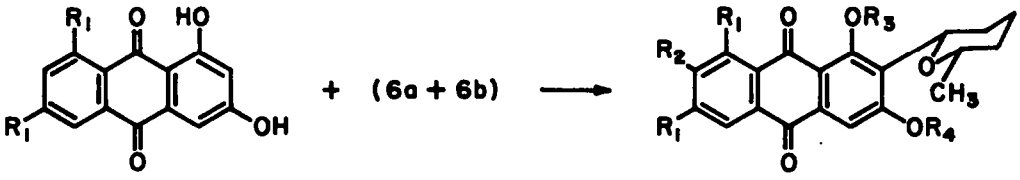
4 R = H



5 6a R = OH Axial

6b R = OH Equatorial

7 R = OC_2H_5



4 $R_1 = OH$

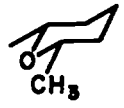
8 $R_1 = H$

9 $R_1 = R_2 = R_3 = R_4 = H$

10 $R_1 = R_2 = R_3 = H$, $R_4 = CH_3$

11 $R_1 = R_2 = H$, $R_3 = R_4 = CH_3$

12 $R_1 = OH$, $R_2 = R_3 = R_4 = H$

13 $R_1 = OH$, $R_3 = R_4 = H$, $R_2 =$ 

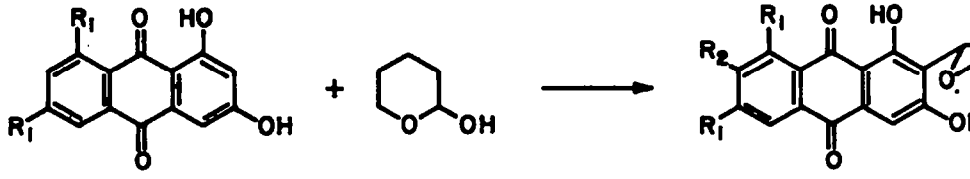
14 $R_1 = OCH_3$, $R_2 = H$, $R_3 = R_4 = CH_3$

Methylation of bis-deoxyaverufarin (9) was achieved with dimethyl sulfate and potassium carbonate in acetone. Treatment of 9 with one equivalent of dimethyl sulfate almost selectively methylated the 3-OH. The monomethyl ether 10 obtained in 87% yield was contaminated by a small amount (6%) of 1,3 - dimethoxy - 2 - (6' - methyltetrahydropyran - 2' - yl)anthraquinone (11). Refluxing 9 with an excess of dimethyl sulfate for 5.5 hr yielded 11. The similarities in the ^{13}C NMR absorptions (Table 1) of the tetrahydropyran ring of 9 and (+)-averufanin tetramethyl ether (14)[15] suggested to us that the tetrahydropyran stereochemistry was identical in both compounds, i.e. Me as well as anthraquinone groups were in equatorial positions.

The (*S*)-(−)-proline catalyzed alkylations of xanthopurpurin (8) proceed with higher yield than with the method published by Castonguay and Brassard.[16] For example, bis-deoxyaverufanin (9) was obtained with only 7% yield by treatment of the aqueous salt of xanthopurpurin with 2-hydroxy-6-methyltetrahydropyran (6a and 6b) at 100°. As observed by Castonguay and Brassard,[9] this method led to the formation of dianthraquinonylalkane; this important side product being formed from two molecules of xanthopurpurin (8) and one molecule of the aldehyde (6a and 6b). Interestingly, such compounds were not observed when using the (*S*)-(−)-proline catalyzed alkylation method.

1,3,6,8-Tetrahydroxyanthraquinone (4) has two sites susceptible to alkylation, carbon 2 and 7. We recognized that the time of reaction and the ratio of anthraquinone to aldehyde would be critical. Consequently, we decided to study the alkylation of anthraquinone 4 with commercially available 2-hydroxytetrahydropyran (15). When 4 was heated with an excess of the lactol 15 and two equivalents of (*S*)-(−)-proline for 8.5 hr, we observed by chromatography two alkylation products, 17 and 18 along with some starting material. The two anthraquinones 17 and 18 were extracted with ethyl acetate and purified by preparative tlc. Beside the presence of the molecular ion at 356 the mass spectrum of noraverufanin (17) shows many fragments (272, 285, 286, 297, 299, 310 and 311) also found in the mass spectrum of (+)-averufanin, indicating a similar fragmentation of the tetrahydropyran ring in both compounds. Such data are in agreement with previous studies[2,17] and can be rationalized as shown in Scheme 2.

(±)-Averufanin (12) was prepared by alkylation of 1,3,6,8-tetrahydroxyanthraquinone (4) with 2-hydroxy-6-



4 $R_1 = OH$

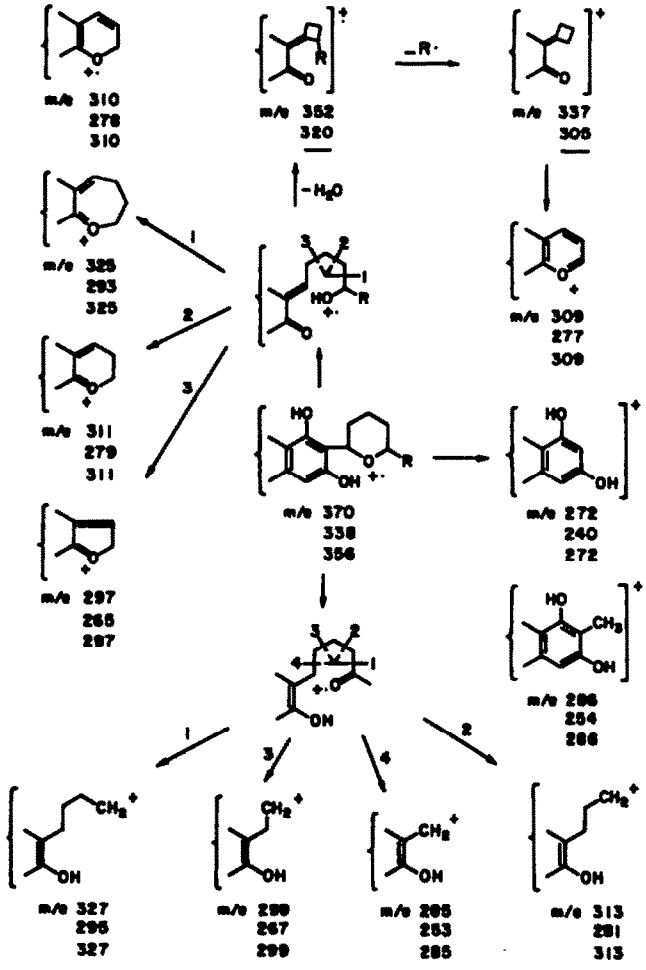
8 $R_1 = H$

15

16 $R_1 = R_2 = H$

17 $R_1 = OH$, $R_2 = H$

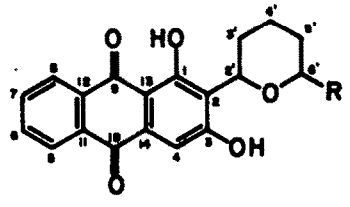
18 $R_1 = OH$, $R_2 =$ 



Scheme 2. Mass spectrometry fragmentation of (+)-averufanin, bis-deoxyaverufanin (9) and noraverufanin (17).

methyltetrahydropyran (6a and 6b). Two equivalents of (*S*)-(−)-proline were stirred with 4 and with 0.6 ml of the lactol 6a and 6b at 50°. No alkylation reaction was found to take place at first, but after 5 hr tlc showed the presence of two alkylation products. Work-up and chromatography of the reaction mixture after 7.5 hr gave 12 along with a less polar dialkylation product 13. IR, mass spectra and tlc (four solvent systems) of (±)-averufanin (12) and (+)-averufanin were found to be identical. Extended reaction time increased the amount of the dialkylation product 13 but did not increase the yield of 12. None of the products prepared so far by the (*S*)-(−)-proline promoted alkylation showed optical activity.

The different synthetic intermediates provide an occasion for the study of conformational and structural effects on the chemical shifts of ^{13}C resonances of the products. Moreover, the data contribute to the general understanding of the properties of the 9,10-anthraquinone nucleus which forms the core of many natural products. The absorption resonances of alkylated hydroxyanthraquinones as shown in Table 1 were assigned by using decoupling techniques, by comparison of the various derivatives and by comparison with the ^{13}C spectra of polyhydroxy anthraquinones[18,19] and polymethoxyanthraquinones.[18] The numbering adopted is the usual numbering of anthraquinone derivatives.



A comparison of the spectra of 16 and 17 in $(CD_3)_2SO$, and of the spectra of 10, 11, 12 and 14 indicate that the tetrahydroxyanthraquinone carbon shifts are weakly influenced by the nature of the C-2 substituent on the anthraquinone nucleus. These carbon shifts are also weakly influenced by solvent change unless the rotation of the tetrahydropyran substituent is altered. The substituent parameters for the 6'-Me obtained from 12 and 17 are characteristic of an equatorial orientation of this substituent.[20-22] Accordingly, we concluded that only the less hindered stereoisomer was obtained by (*S*)-(−)-proline alkylation.

The large deviations observed between the tetrahydropyran carbon shifts of 16 in $(CD_3)_2SO$ and in $CDCl_3$, on one hand, and between the tetrahydropyran carbon shifts of 12 in $(CD_3)_2SO$ and of 9 in $CDCl_3$, on the other hand, can be explained by the loss of the free rotation of the tetrahydropyran substituent. In $CDCl_3$, the observed deviations are a consequence of H-bonding

Table 1. ^{13}C chemical shifts (in ppm from TMS) of alkylated anthraquinones

Compound	16[c]	16	17	9	12	10	11	14	13
Solvent	$(CD_3)_2SO$	$CDCl_3$	$(CD_3)_2SO$	$CDCl_3$	$(CD_3)_2SO$	$CDCl_3$	$CDCl_3$	$CDCl_3$	$CDCl_3$
C-1	162,10	161,23 (S)	161,50	161,02	161,55(S)	163,25(S)	161,98(S)	161,37(S)	160,68
C-2	119,60	119,05 (S)	120,13	119,27	119,99(S)	122,80(S)	131,69(S)	131,64(S)	120,47
C-3	162,95	163,26 (S)	162,36	163,22	162,28(S)	162,76(S)	162,44(S)	161,58(S)	163,09
C-4	108,48	110,11 (D)	108,77	110,33	108,78(D)	103,24(D)	105,74(D)	105,05(D)	110,65
C-5	126,62	127,07 (D)	108,77	127,17	108,78(D)	127,02(D)	126,40(D)	102,23(D)	110,65
C-6	134,39	133,82 (D)	165,28	134,01	165,22(S)	133,93(D)	132,90(D)	163,58(S)	163,09
C-7	134,39	133,82 (D)	108,23	134,01	108,13(D)	133,93(D)	134,14(D)	105,48(D)	120,47
C-8	126,30	126,42 (D)	164,26	126,64	164,28(S)	126,83(D)	127,12(D)	161,76(S)	160,68
C-9	186,25	186,91 (S)	188,86	186,92	188,78(S)	186,87(S)	180,09(S)	180,59(S)	190,96[a]
C-10	181,46	182,18 (S)	181,15	182,12	181,18(S)	182,29(S)	183,08(S)	183,47(S)	181,58[a]
C-11	132,96[b]	133,37[b](S)	134,90	133,55[b]	134,91(S)	133,61(S)	132,58(S)	136,29(S)	134,32
C-12	132,64[b]	133,37[b](S)	108,74	133,55[b]	108,75(S)	133,61(S)	133,45(S)	118,60(S)	109,52[a]
C-13	108,42	109,44 (S)	108,55	109,67	108,48(S)	111,18(S)	120,39(S)	122,48(S)	109,52[a]
C-14	133,27	133,40[b](S)	133,26	133,61[b]	133,28(S)	134,14(S)	136,03(S)	134,73(S)	134,32
C-2'	73,07	76,51 (D)	72,99	76,36	73,30(D)	72,01(D)	72,59(D)	72,74(D)	76,40
C-3'	28,84	30,70 (T)	28,80	29,97	28,42(T)	27,53(T)	28,09(T)	28,01(T)	30,09
C-4'	23,19	22,97 (T)	23,16	23,28	23.42(T)	24.25(T)	24,18(T)	24,24(T)	23,24
C-5'	25,20	25,69 (T)	25,18	32,79	32,55(T)	32,99(T)	33,14(T)	33,15(T)	33,02
C-6'	68,52	69,50 (T)	68 54	75,83	74,69(D)	74,80 (D)	74,67(D)	74,68(D)	75,88
CH_3	-	-	-	22,08	21,99(Q)	22,31(Q)	22,36(Q)	22,36(Q)	22,03
OCH_3-1	-	-	-	-	-	-	63,04(Q)	63,37(Q)	-
OCH_3-3	-	-	-	-	-	56,20(Q)	56,15(Q)	56,02(Q)	-
OCH_3-6	-	-	-	-	-	-	-	55,70(Q)	-
OCH_3-8	-	-	-	-	-	-	-	56,42(Q)	-

[a] Value subject to uncertainty because of the unfavorable S/N ratio due to low concentration.

[b] Tentative assignment.

[c] Preparation of 16 is described in reference 9.

between 3-OH and 1'-O. Polar solvents like $(CD_3)_2SO$ prevent such H-bonding but do not affect the strong H-bonding between 1-OH and the carbonyl.[18,19] The preferred conformation for the 3-OH is one in which the OH group is distal to the C-2 substituent so that 4-C absorbs at a higher field in $(CD_3)_2SO$ than in $CDCl_3$. Moreover, the anisotropic effect of the anthraquinone nucleus on the tetrahydropropyran carbons is not the same in the free form as in the hindered form. The 4-C carbon of 10 absorbs at a higher field than expected from the effect of O-methylation of 9.[10] As above, this shielding is explained by the fact that the 2-C substituent interferes with the OMe group in such a way that the preferred conformation is one in which the OMe group is projected distally from the *ortho* group.

Contrary to 10, the 4-C of 11 absorbs at a lower field than expected from the effect of O-methylation of 10 calculated from the spectra of 1-hydroxy-3-methoxyanthraquinone and 1,3-dimethoxyanthraquinone.[23] Similar effects are observed with 2-C and 13-C. The 1-OMe is forced out of the plane of the anthraquinone nucleus by the bulky adjacent group and the electron release by the methoxyl oxygen is significantly reduced.[24] This steric hindrance explains the upfield shift of 1-OMe of 1,3-dimethoxyanthraquinone from 56.41 ppm to 63.04 ppm.[18] The same effects were observed for (+)-averufanin tetramethyl ether (14).[15] The assignments recently reported[25] for (+)-averufanin are in agreement with our data, differences in chemical shifts being a solvent effect.

EXPERIMENTAL

M.ps were taken in capillary tubes with a Thomas–Hoover apparatus (calibrated thermometer). IR spectra were recorded with Perkin–Elmer Model 567. ^1H NMR spectra were taken with Varian A-60-A, Varian T60 or Bruker HFX-90 spectrometer; all chemical shifts are given in δ values relative to tetramethylsilane (TMS) as internal standard. ^{13}C NMR spectra were obtained with

a Bruker HFX-90 spectrometer. All chemical shifts have been converted to the δ scale relative to TMS using the following shift conversions: $(CD_3)_2SO$ $\delta = 39.60$ (TMS), $CDCl_3$ $\delta = 76.95$ (TMS). Mass spectra were obtained with a Varian Mat 112 at 70 eV. Preparative tlc was carried out on Merck 60F-254 precoated silica gel plates (thickness 2 mm). Dimethylformamide obtained from Baker was analyzed reagent grade; 2-hydroxytetrahydropyran and glutaraldehyde were purchased from Aldrich and (*S*)-(−)-proline from Eastman.

2-Hydroxy-6-methyltetrahydropyran (**6a** *and* **6b**). A soln of iodomethane (156 g) in dry ether (500 ml) was added dropwise to stirred Mg (27 g) covered with ether (200 ml). This MeMgI soln was added to freshly distilled glutaraldehyde (100 g) diluted with ether (1 l.). After 30 min, the mixture was hydrolyzed with a cold NH_4Cl aq. The decanted ether phase was dried ($MgSO_4$) and the residue obtained by evaporation of the solvent was distilled under 20 mm Hg pressure. The fraction obtained at 89–90° (25 g, 22%) contained 2 isomers of 2-hydroxy-6-methyltetrahydropyran, ν_{max} ($CDCl_3$) 3200 (hydroxyl); δ ($CDCl_3$) 1.06 (3H, 2d, J = 6.4 Hz, 6'-CH_3), 1.27–1.94 (6H, m, 3, 4, 5-H_2), 3.27–4.27 (1H, m, 6-H), 4.77, 5.27 (1H, 2d, J = 10.0 Hz, H-2), 9.80 (1H, s, 2-OH); *m/e* 99 (M^+-17) (100%), 81 (40%), 69 (3%), 57 (6%), 55 (7%), 43 (6%). By glc–MS, the 2 isomers have the same mass spectra.

1,3 - *Dihydroxy* - 2 - (6' - *methyltetrahydropyran* - 2' - *yl*) *anthraquinone* (*bis-deoxyaverufanin*) (**9**)

Method A. A soln of **8**[9] (120 mg) in DMF (1 ml) was stirred under N_2 with (*S*)-(−)-proline (115 mg) and **6a** and **6b** (0.5 ml). To the mixture heated with an oil bath (45°) was added another portion (0.5 ml) of **6a** and **6b** after 2 hr. The red soln was diluted with water after 15 hr and **9** was extracted with CH_2Cl_2 (4 × 50 ml). Preparative tlc (silica gel, benzene–EtOAc 20:1, 2 migrations) afforded **9** (170 g, 100%), m.p. 209–210° (CH_2Cl_2–hexane); λ_{max} (EtOH) 247, 280, 408 nm (log ϵ 4.37, 4.41, 3.78). ν_{max} (KBr) 3150 (OH), 1670 (quinone C = 0) and 1629 (chelated C = 0) cm^{-1}; δ ($CDCl_3$) 1.28 (3H, d, J = 6.0 Hz, 6'-CH_3), 1.20–2.20 (6H, m, 3', 4', 5'-H_2), 3.55–4.90 (1H, m, 6'-H), 5.09 (1H, dd, J = 10.0 and 2.0 Hz, 2'-H), 7.18 (1H, s, 4-H), 7.55–7.83 (2H, m, 6, 7-H), 8.00–8.30 (2H, m, 5, 8-H), 9.90 (1H, s, OH-3), 13.75 (1H, s, OH-1).

Method B. Compound **8** (480 mg) was dissolved in $NaHCO_3$ aq (315 mg; 4.5 ml) and treated with **6a** and **6b** (1.16 g) for 23 hr at 100° (external temp.). The acidified (dil. HCl) mixture was extracted with EtOAc (3 × 100 ml). The red oil obtained by evaporation of the dried ($MgSO_4$) organic phases was chromatographed on preparative tlc (silica gel, benzene). Extraction of the yellow band (R_f = 0.55) with ether and crystallization from ether–hexane yielded **9** (46 mg, 7%) identical (IR, tlc, m.p. and mass spectra) with the previous sample.

1 - *Hydroxy* - 3 - *methoxy* - 2 - (6' - *methyltetrahydropyran* - 2' - *yl*) *anthraquinone* (**10**). Compound **9** (100 mg) in refluxing acetone (20 ml) was treated with K_2CO_3 (138 mg) and Me_2SO_4 (36 mg) for 3 hr. A yellow solid was collected by filtration of the mixture diluted with water. Two methylated derivatives were separated by preparative tlc (silica gel, benzene, 4 migrations). Extraction of the band at R_f 0.24–0.37 with EtOAc and crystallization from MeOH yielded **10** (91 mg, 87%), m.p. 186.5–188.0° (MeOH); λ_{max} (EtOH) 249, 277, 410 nm (log ϵ 4.39, 4.46, 3.79) (MeOH); ν_{max} (KBr) 1670 (quinone C = 0), 1625 (chelated C = 0) cm^{-1}; δ ($CDCl_3$) 1.27 (3H, d, J = 6.1 Hz, 6'-CH_3), 1.36–3.02 (6H, m, 3', 4', 5'-H_2), 3.43–3.76 (1H, m, 6'-H), 4.02 (3H, s, 3-OCH_3), 5.13 (1H, dd, J = 11.4 Hz, J = 2.3 Hz, H-2'), 7.38 (1H, s, 4-H), 7.70–7.85 (2H, m, 6, 7-H), 8.17–8.31 (2H, m, 5, 8-H); *m/e* 352 (M^+) (82%), 337 (7%), 334 (7%), 321 (13%), 309 (87%), 307 (15%), 306 (50%), 295 (37%), 293 (37%), 292 (10%), 291 (18%), 283 (47%), 281 (100%), 268 (88%), 267 (45%), 265 (25%), 253 (52%), 225 (73%).

Extraction of the band at R_f 0.17 with EtOAc furnished 11 (7.0 mg, 6%) identical with the product isolated from the next reaction.

1,3 - *Dimethoxy* - 2 - (6' - *methyltetrahydropyran* - 2' - *yl*) *anthraquinone* (**11**). Treatment of a boiling soln of **9** (109 mg) in acetone (5 ml) with K_2CO_3 (150 mg) and Me_2SO_4 (9 drops) for 5.5 hr gave a yellow solid after dilution with water. Preparative tlc (silica gel, benzene–EtOAc 20:1, 1 migration, benzene–EtOAc 10:1, 1 migration) of this solid and extraction of the band at R_f 0.36–0.50 with CH_2Cl_2–EtOAc 10:1 furnished **11** (114 mg, 96%) m.p. 166–167° (acetone–hexane); λ_{max} (EtOH) 242, 277, 337 nm (log ϵ 4.31, 4.57, 3.75) ν_{max} (KBr) 1670 (quinone C = 0) cm^{-1}; δ ($CDCl_3$) 1.24 (3H, d, J = 7.0, 6'-CH_3), 1.10–2.00 (6H, m, 3', 4', 5'-H_2), 3.35–3.79 (1H, m, 6'-H), 3.98, 4.02 (2 × 3H, 2s, 1, 3-OCH_3), 5.10 (1H, dd, J = 11.0 Hz, 2.0 Hz), 7.67 (1H, s, 4-H), 7.70–7.85 (2H, m, 6,7-H), 8.11–8.41 (2H, m, 5, 8-H); *m/e* 366 (M^+) (8%), 352 (14%), 351 (16%), 309 (47%), 292 (42%), 281 (72%), 279 (56%), 277 (28%), 268 (25%), 267 (25%), 255 (100%), 225 (36%).

1,3,6,8 - *Tetrahydroxy* - 2 - (*tetrahydropyran* - 2' - *yl*) *anthraquinone* (*Noraverufanin*) (**17**). Compound **15** (0.2 ml) and (*S*)-(−)-proline (92 mg) were added to a stirred soln of **4** (54 mg) in DMF (2.5 ml). The mixture was heated under N_2 with an oil bath thermoregularized at 50°. After 8.5 hr, tlc showed some substrate left along with a noticeable amount of dialkylation product. The mixture diluted with water (10 ml) was extracted with EtOAc (5 × 50 ml). The residue obtained by evaporation of the solvent was chromatographed by preparative tlc (silica gel, benzene–EtOAc 100:1, 2 migrations). A first band (R_f = 0.69) extracted with EtOAc yielded **18** (9 mg, 10%), m.p. 264–265° (CH_2Cl_2–hexane); ν_{max} (KBr) 3140 (OH), 1670 (quinone C = 0), 1610 (chelated C = 0) cm^{-1}; δ ($CDCl_3$) 1.42–2.13 (12H, m, 3', 4', 5'-H_2), 3.42–3.92 (2H, m, H-6' axial), 4.07–4.38 (2H, 2m, J_{gem} = 11.0 Hz, 6'-H equatorial), 5.07 (2H, broad d, J = 9 Hz, 2'-H axial), 7.28, 7.29 (2H, 2s, 4, 5-H); *m/e* 440 (M^+) (100%), 423 (5%), 422 (7%), 394 (9%), 381 (10%), 370 (16%), 363 (24%), 309 (26%).

Extraction of a second band (R_f = 0.31) with EtOAc and crystallization from acetone–hexane furnished **17** (19 mg, 26%), m.p. 259–262° (acetone–hexane); ν_{max} (KBr) 3480 (OH), 1660 (quinone C = 0), 1615 (chelated C = 0) cm^{-1}; δ ($(CD_3)_2SO$) 1.30–2.08 (6H, 2m, 3', 4', 5'-H_2), 2.90–3.75 (1H, m, 6'-H axial), 4.04 (1H, d, J_{gem} = 11.0 Hz, 6'-H equatorial), 4.88 (1H, d, J = 10.3 Hz, 2'-H axial), 6.55 (1H, d, J = 2.3 Hz, 7-H), 7.07 (1H, d, J = 2.3 Hz, 5-H), 7.11 (1H, s, 4-H), 12.08, 12.55 (2H, 2s, 1, 8-OH).

(±)-*Averufanin* (**12**). A soln of **4** (54 mg) in DMF (2.5 ml) was treated with (*S*)-(−)-proline (92 mg) and **6a** and **6b** (0.2 ml) at 50° (external temp.). Two more portions of **6a** and **6b** (0.2 ml each) were added after 1.5 and 4.0 hr. The mixture diluted with water (20 ml) was extracted with EtOAc (8 × 20 ml). Removal of the solvent gave a red oil that was chromatographed on preparative tlc (silica gel, benzene–EtOAc 100:3, 2 migrations). Extraction of the fast moving band (R_f = 0.72) with EtOAc furnished **13**, (9 mg, 10%), m.p. 189–190° (CH_2Cl_2); ν_{max} (KBr) 3200 (OH), 1675 (quinone C = 0), 1620 (chelated C = 0) cm^{-1}; δ ($CDCl_3$) 1.10 (6H, d, J = 7.0 Hz, 6'-CH_3), 1.00–2.00 (12H, m, 3', 4', 5'-H_2), 3.66 (2H, m, 6'-H), 5.16 (2H, m, 2'-H), 7.43 (2H, s, 4, 5-H), 9.98 (2H, s, 3, 6-OH), 12.91 (2H, s, 1, 8-OH); *m/e* 468 (M^+) (100%), 450 (23%), 440 (5%), 432 (5%), 422 (5%), 410 (14%), 408 (12%), 407 (8%), 398 (8%), 393 (8%), 390 (11%), 384 (35%), 377 (11%), 366 (22%), 351 (14%), 337 (19%), 325 (19%), 323 (22%), 313 (15%), 311 (20%), 309 (20%), 299 (14%), 285 (9%).

Extraction of the yellow band at R_f = 0.33 with EtOAc and crystallization from EtOAc gave **12** (31 mg, 42%), m.p. 258–259° (EtOAc); lit.[26] m.p. 252–254°; lit.[27] m.p. 271°; lit.[2] m.p. 258°; ν_{max} (KBr) 3490 (OH), 1675 (quinone C = 0), 1620 (chelated C = 0) cm^{-1}; δ ($(CD_3)_2SO$) 1.17 (3H, d, J = 5.8 Hz, 6'-CH_3), 1.28–2.01 (6H, m, 3', 4', 5-H_2), 2.98–3.77 (1H, m, 6'-H), 4.91 (1H, d, J = 8.5 Hz, 2'-H), 6.48 (1H, d, J = 2.3 Hz, 7-H), 6.99 (1H, s, H-4), 7.00 (1H, d, J = 2.3 Hz, H-5), 10.88 (2H, m, 3, 6-OH), 12.08, 12.66 (2H, 2s, 1, 8-OH).

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