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TOTAL SYNTHESIS AND THE ABSOLUTE CONFIGURATION OF AUROVERTIN B, AN ACUTE NEUROTOXIC METABOLITE

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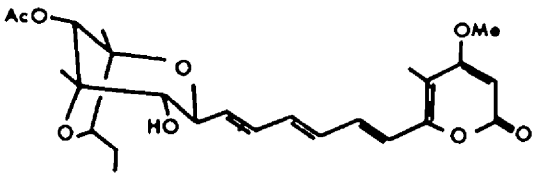
Abstract - Aurovertin B, a metabolite of Calcarisporium arbuscula, has been synthesized from D-glucose via stereospecific cyclization. Its absolute configuration has been unambiguously determined.

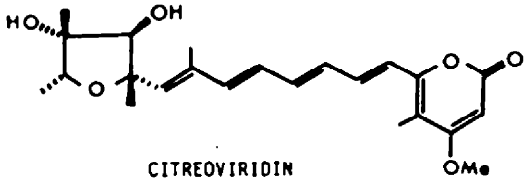
Of mycotoxins exhibiting an acute neurotoxicity, aurovertins[1], citreoviridins, and related metabolites as illustrated in Fig. I are known as an inhibitor of mitchondrial ATPase. Among metabolites of Calcarisporium arbuscula, aurovertin B (1)[1] is a main component, and the structure was established by spectroscopic manner[2] coupled with an X-ray crystallographic analysis[3]. The absolute configuration was postulated as shown in Fig. I using Helmchen's method[1,4], though the detailed results have not been published. On the basis of our extensive investigation on isolation, structural determination and synthesis of the metabolites of Penicillium citreoviride B. and related compounds including citreoviridin [5], citreoviridinols[6,8,9], neocitreoviridinols[7,8] and verrucosidin [10], aurovertin B (1) must have the same absolute configuration as those of the above mycotoxins which could be synthesized in optically active form. Moreover, good agreement was also obtained in synthetic studies on (-)-asteltoxin [11]. We describe herein full details of first total synthesis of (-)-aurovertin B, by which the absolute configuration could be unambiguously confirmed[12].

Our synthetic process to (-)-aurovertin B (1), summarized in Scheme I and II, was started from the readily accessible branched-chain sugar (2)[13]. At the outset, the tertiary hydroxyl group in 2 was benzylated in usual manner for ease of the following reactions. A benzyl ether (3) thus obtained was subjected to acid hydrolysis to yield a vicinal diol (4), which could be converted into an olefin (6) by sulfonylation and Tipson-Cohen type deoxygenation. Subsequently, selective hydrogenation of 6 using Pd on charcoal catalyst provided 7. In the next stage, 7 was successively derivatized in high yield to a conjugated ester (8) in four steps, that is, 1)80% AcOH, 2)$NaIO_4$, 3)$Ph_3P{=}C(Me)COOMe$, 4)K_2CO_3. For

Fig. I.



AUROVERTIN B (1)



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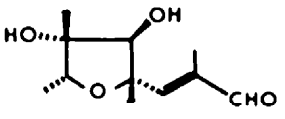
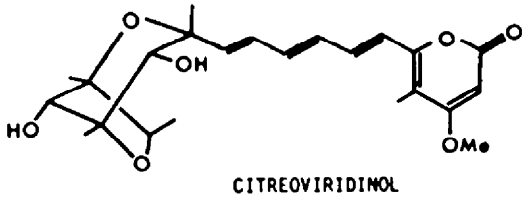


CITREOVIRAL



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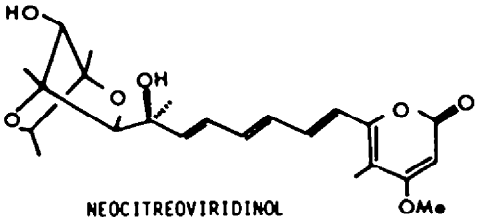

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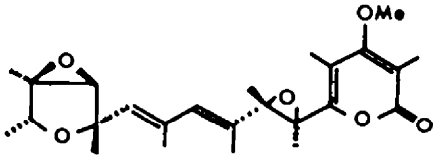
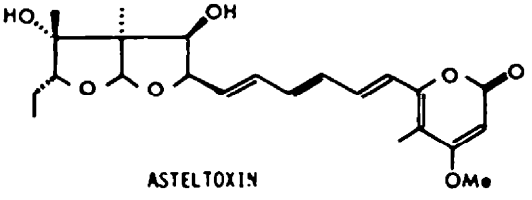


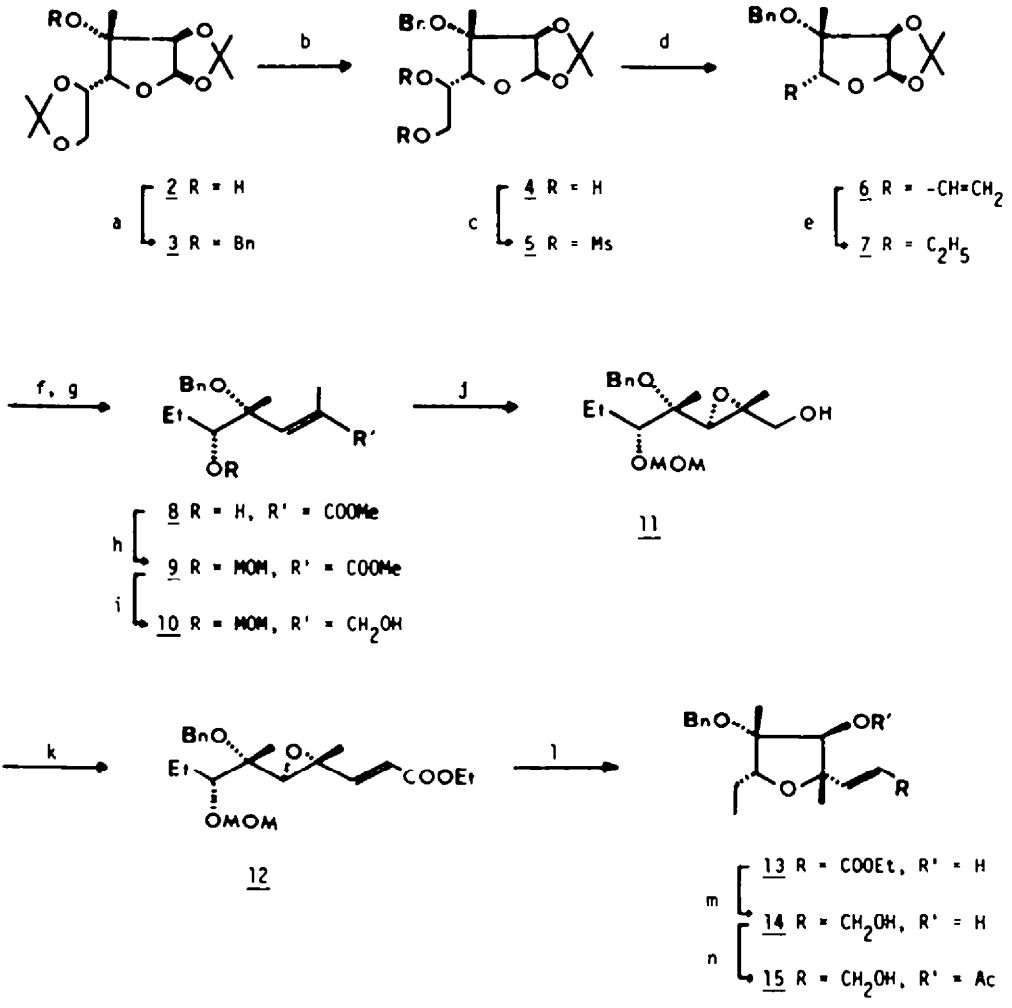
VERRUCOSIDIN



ASTELTOXIN

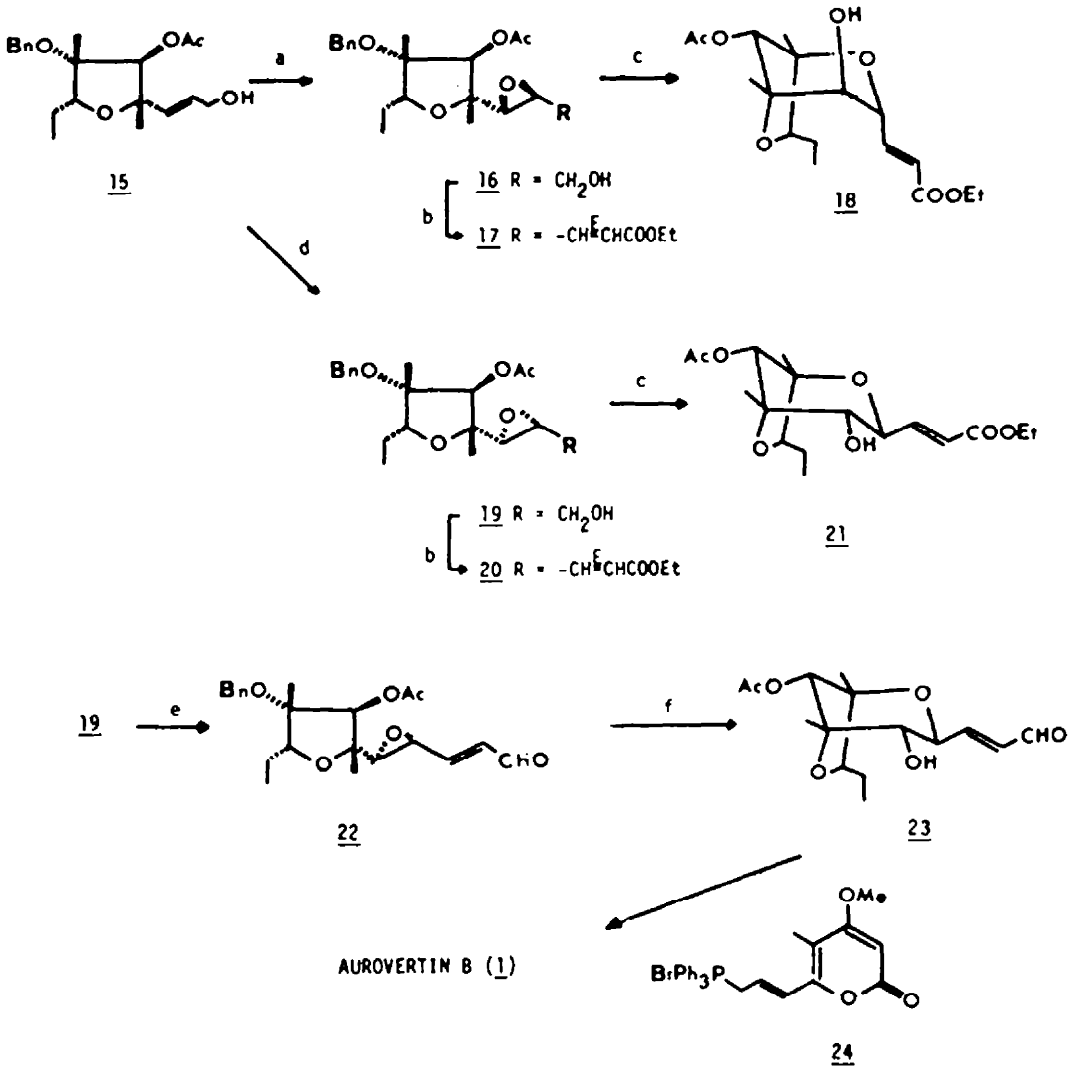
protection of the secondary alcohol in 8 with methoxymethyl group, Fujita's method [$CH_2(OMe)_2$, P_2O_5 / $CHCl_3$][14] afforded a desired MOM ether (9) in 88% yield. Then, the allyl alcohol (10) obtained by DIBAL reduction of 9 was treated with mCPBA in CH_2Cl_2 to furnish an epoxy alcohol (11) as a sole product in 90% yield. The stereochemistry of the epoxide was confirmed as depicted in Scheme I, after construction of a tetrahydrofuran (13), whose ^1H NMR spectrum was quite similar to that of citreoviral [6]. This high stereoselectivity might be derived from a chelation effect of the reagent and the benzyl ether in 10.[15] The epoxy alcohol (11) so far obtained was then subjected to Swern oxidation followed by Wittig reaction (Ph_3P=CHCOOEt) to give 93% yield of the corresponding unsaturated ester (12), which was treated with TFA in $CHCl_3$, resulting in smooth removal of the MOM group and subsequent cyclization to afford a tetrahydrofuran derivative (13)

Scheme I.



a. BnBr, NaH/ DMF. b. 1% aq. H_2SO_4, rt.. c. MsCl, pyr.. d. NaI/ 2-butanone, reflux. e. H_2, Pd/C in MeOH. f. 1) 80% AcOH, 80°C 2) $NaIO_4$. g. 1) $Ph_3P{=}C(Me)COOMe$/benzene, 2) K_2CO_3/ MeOH. h. $CH_2(OMe)_2$, P_2O_5/ $CHCl_3$. i. DIBAL, -78°C. j. mCPBA/ CH_2Cl_2, -30 - -20°C. k. 1) Swern Oxidation, 2) $Ph_3P{=}CHCOOEt$. l. TFA. m. DIBAL/ -78°C. n. 1) TrCl, pyr., 2) Ac_2O, pyr., 3) TsOH/MeOH.

Scheme II.



a. mCPBA, $NaHCO_3$/ CH_2Cl_2, 0°C. b. 1) H_2, Pd/black in MeOH, 2) Swern oxidation, 3) Ph_3P=CHCOOEt/ benzene. c. TsOH/ benzene. d. TBHP, D-(-)-DET, $Ti(OiPr)_4$. e. 1) H_2, Pd/black in MeOH, 2) Swern oxidation, 3) Ph_3=CHCHO/ benzene. f. CsOH/ CH_2Cl_2, rt..

in 94% yield. After DIBAL reduction of 13, the secondary alcohol in 14 was acetylated with conventional stepwise procedure [1)TrCl - pyridine, 2)Ac_2O - pyridine, 3)H^+], yielding 15 (88% yield in three steps).

In order to construct the desired dioxabicyclo[3.2.1]octane skeleton, we used two different methods for epoxidation of the allyl alcohol (15). On oxidation with mCPBA, 15 was stereoselectively converted into an epoxide (16), which was subjected to hydrogenation, Swern oxidation, and then Wittig reaction to give the corresponding ester (17). The acid-catalyzed stereospecific cyclization of 17 gave rise to a bicyclo compound (18), which was different from that of aurovertin B (1) in their ^1H NMR spectra. On the other hand, asymmetric epoxidation of the allyl alcohol (15) under Sharpless condition afforded another epoxide (19). According to the same procedure as described above, 19 was straightforwards converted into the corresponding conjugated ester (20), which was stereospecifically cyclized to give a desired bicyclo[3.2.1] compound (21) in 92% yield. At this stage, the conjugated ester (21) in hand is considered to be used as a synthetic precursor of aurovertin B (1), however, it seems difficult to convert 21, without affecting the acetoxyl group, into the corresponding aldehyde (23) which would be submitted to coupling with the pyrone segment (24). To circumvent such a difficulty, the Wittig reagent, $Ph_3P{=}CHCHO$, instead of $Ph_3P{=}CHCOOEt$ seems to promise ready access to 23, though high yield conversion of 19 into 22 is not always expected as compared with the case of 20. Thus, when treated with $Ph_3P{=}CHCHO$, the unsaturated aldehyde (22) and its cyclization product (23) were obtained in 49 and 14% yields, respectively. The aldehyde (22) so far obtained was cleanly cyclized with catalytic camphorsulfonic acid to yield 23 in high yield.

On the basis of our relevant investigation, finally, the Wittig reaction of 23 was effected with <u>in situ</u> generated phosphorane carrying the corresponding pyrone, to afford aurovertin B (1) in 22% yield, which was completely identical with natural one in all respects of spectral data (^1H NMR, ^{13}C NMR, IR, and MASS). Especially the optical rotation of the synthetic sample ($[\alpha]_D^{27}$ -57.9° (c 0.125, EtOH)) was in a good agreement with that of natural one ($[\alpha]_D^{20}$ -50.6° (EtOH))[2]. Accordingly, the absolute cofiguration of 1 was unambiguously established as depicted in Fig. I. Moreover, our synthetic strategy would also be applicable for synthesis of closely related other aurovertins[1].

EXPERIMENTAL

All the melting points were obtained on a Mitamura Riken melting point apparatus and uncorrected. IR spectra were recorded on a JASCO Model A-202 spectrophotometer. ^{1}H NMR spectra were obtained on a Varian EM-390 (90MHz) and JEOL JNM GX-400 (400MHz) NMR spectrometers in deuteriochloroform solution using tetramethylsilane as an internal standard. High resolution mass spectra were obtained on a Hitachi M-80 GC-MS spectrometer operating with an ionization energy (70eV). Optical rotations were measured on a JASCO DIP-360 polarimeter in chloroform solution, unless otherwise stated. Preparative and analytical TLC were carried out on silica gel plates (Kieselgel 60 F_{254}, E. Merck A. G. West Germany) using UV light and/or 5% molybdophosphoric acid in ethanol for detection. Katayama silica gel (K 070) was used for column chromatography.

3-O-Benzyl-1,2:5,6-di-O-isopropylidene-3-C-methyl-α-D-glucofuranose (3). To a stirred solution of 1,2:5,6-di-O-isopropylidene-3-C-methyl-α-D-glucofuranose (2) (1.8 g, 6.8 mmol) in anhydrous DMF (15 ml) was added NaH (60% dispersion in oil, 0.35 g, 8.9 mmol) at 0°C under argon. After 10 min, benzyl bromide (1.1 ml, 8.9 mmol) was added to the mixture and the temperature was gradually warmed up to room temperature during 1.5 h. The resulted mixture was partitioned between water (50 ml) and EtOAc (50 ml), and the aqueous layer was further extracted with EtOAc (20 ml x 2). The combined organic extract was washed with brine (100 ml), dried over anhydrous Na_2SO_4, and then evaporated. The residue was purified on a silica gel column (100 g, hexane/EtOAc = 5/1) to afford 2.49 g (100%) of 3 as a colorless oil: $[\alpha]_D^{24}$ +4.8° (c 4.06); IR (film) 1590 and 1570cm^{-1}; 1H NMR δ 1.31 (3H, s), 1.36 (3H, s), 1.43 (3H, s),1.58 (6H, s), 3.90 - 4.04 (3H, complex), 4.37 (1H, m), 4.42 (1H, d, J= 3.6 Hz), 4.53 (1H, d, J= 11 Hz), 4.64 (1H, d, J= 11 Hz), 5.80 (1H, d, J= 3.6 Hz), and 7.32 (5H, broad s); HRMS calcd. for $C_{19}H_{25}O_6$: m/z 349.1649 (M^+-CH_3). Found: m/z 349.1634.

3-O-Benzyl-1,2-O-isopropylidene-3-C-methyl-α-D-glucofuranose (4). A solution of 3 (2.84 g, 7.8 mmol) in 1% aqueous H_2SO_4 (15 ml) and MeOH (35 ml) was stirred at room temperature for 2 days. The reaction mixture was neutralized with sat. aq. $NaHCO_3$ and evaporated to a half volume, and then extracted with EtOAc (50 ml, 20 ml x 2). The organic extracts were combined, washed with brine (100 ml), dried over anhydrous Na_2SO_4, and concentrated in vacuo to give 2.53 g (100%) of 4 as a colorless syrup: $[\alpha]_D^{24}$ + 12.6° (c 3.51); IR (film) 3450, 1600, and 1500cm^{-1}; 1H NMR δ 1.32 (3H, s), 1.53 (3H, s), 1.57 (3H, s), 3.67 - 4.20 (4H, complex), 4.47 (1H, d, J= 3.6 Hz), 4.53 (1H, d, J= 11 Hz), 4.64 (1H, d, J= 11 Hz), 5.82 (1H, d, J= 3.6 Hz), and 7.32 (5H, broad s); HRMS calcd. for $C_{17}H_{25}O_6$: m/z 325.1648 (M^++H). Found: m/z 325.1643.

3-O-Benzyl-1,2-O-isopropylidene-5,6-di-O-mesyl-3-C-methyl-α-D-glucofuranose (5). To an ice-cooled solution of 4 (2.53 g, 7.80 mmol) in pyridine (1.75 ml, 21.6 mmol) and CH_2Cl_2 (20 ml) was added mesyl chloride (1.67 ml, 21.5 mmol),and the reaction mixture was stirred at room temperature for 6 h. The resulted mixture was poured into a mixture of ice-water (100 ml) and CH_2Cl_2 (30 ml), and the aqueous layer was further extracted with CH_2Cl_2 (20 ml x 2). The combined organic layers were successively washed with 2N HCl (50 ml), sat. aq. $NaHCO_3$ (50 ml), and brine (100 ml), then dried over anhydrous Na_2SO_4. Evaporation of the solution yielded a crude product, which was purified by silica gel column chromatography (100 g, hexane/EtOAc = 2/1) to provide 5 (3.62 g, 97%): $[\alpha]_D^{24}$ + 13.2° (c 2.58); IR (film) 1600 and 1500cm^{-1}; ^{1}H NMR δ 1.32 (3H, s), 1.52 (3H, s), 1.59 (3H, s), 2.88 (3H, s), 3.09 (3H, s), 4.17 - 4.73 (6H, complex), 5.17 (1H, dt, J= 2, 6 Hz), 5.81 (1H, d, J= 3.6 Hz), and 7.33 (5H, broad s); HRMS calcd. for $C_{18}H_{25}O_{10}S_2$: m/z 465.0877 (M^+-CH_3). Found: m/z 465.0882.

3-O-Benzyl-5,6-dideoxy-1,2-O-isopropylidene-3-C-methyl-α-D-xylohexo-5-eno-furanose (6). A mixture of 5 (3.55 g, 7.4 mmol) and NaI (5.0 g, 33 mmol) in 2-butanone (50 ml) was stirred under reflux for 18 h. The reaction mixture was poured into H_2O (100 ml) and extracted with EtOAc (100, 50 ml). The combined organic extracts were washed with sat. aq. $Na_2S_2O_3$ (50 ml x 3) and brine (100 ml). After being dried over anhydrous Na_2SO_4, the solution was evaporated to give a crude oil, which on purification by passing through a short column (silica gel 30 g, hexane/EtOAc = 2/1) afforded 6 (2.01 g, 94%) as a colorless oil: $[\alpha]_D^{27}$ - 46.1° (c 5.01); IR (film) 1710, 1640, and 1600cm^{-1}; ^{1}H NMR δ 1.32 (3H, s), 1.36 (3H, s), 1.52 (3H, s), 4.25 (1H, d, J= 7.5 Hz), 4.43 (1H, d, J= 3.3 Hz), 4.53 (2H, s), 5.20 - 5.50 (2H, complex), 5.80 - 6.20 (2H, complex), and 7.30 (5H, broad s); HRMS calcd. for $C_{16}H_{19}O_4$: m/z 275.1282 (M^+-CH_3). Found: m/z 275.1302.

3-O-Benzyl-5,6-dideoxy-1,2-O-isopropylidene-3-C-methyl-α-D-xylohexofuranose (7). The olefin (6) (1.95 g, 6.7 mmol) was hydrogenated at room temperature for 18 h in MeOH (40 ml) in the presence of 10% palladium on charcoal. The catalyst was filtered off and the filtrate was concentrated under reduced pressure to give 7 (1.95 g, 99%) as an oil: $[\alpha]_D^{27}$ +24.8° (c 1.93); IR (film) 1710 and 1600cm^{-1}; ^{1}H NMR δ 1.05 (3H, t, J= 7.5 Hz), 1.37 (6H, s), 1.53 (3H, s), 1.70 (2H, m), 3.78 (1H, dd, J= 4.2, 9 Hz), 4.49 (1H, d, J= 3.3 Hz), 4.55 (2H, s), 5.85 (1H, d, J= 3.3 Hz), and 7.31 (5H, broad s); HRMS calcd. for $C_{16}H_{21}O_4$: m/z 277.1438 (M^+-CH_3). Found: m/z 277.1430.

Preparation of the acyclic ester (8). A solution of 7 (2.13 g, 7.3 mmol) in 80% AcOH (60 ml) was stirred at 80°C for 20 h. The reaction mixture was evaporated and co-evaporated with water to give a crude syrup, which was partitioned between sat. aq. $NaHCO_3$ and EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and then evaporated. The resulted oil was treated with K_2CO_3 (0.2 g) in MeOH (10 ml) at room temperature for 30 min. The reaction mixture was worked up in usual manner to provide 1.70 g (93%) of a desired diol.

A mixture of the diol (1.33 g, 7.9 mmol) and $NaIO_4$ (1.69 g, 7.9 mmol) in H_2O (25 ml) and MeOH (25 ml) was stirred at room temperature for 1 h. The reaction mixture was diluted with H_2O (50 ml) and extracted with EtOAc (50 ml, 20 ml x 2). The combined EtOAc extracts were washed with brine (100 ml), dried over anhydrous Na_2SO_4, and evaporated to give a crude aldehyde, which was reacted with $Ph_3P{=}C(CH_3)COOMe$ (3.66 g, 10.5 mmol) in boiling benzene (40 ml) for 20 h. The resulted mixture was evaporated and purified by preparative TLC (hexane/ EtOAc = 8/1) to furnish 1.40 g (83%) of the formate.

The formate (1.40 g) so far obtained was dissolved in MeOH (3 ml) and treated with K_2CO_3 (110 g) at room temperature for 30 min. Work-up procedure in usual manner provided the acyclic ester (8) (230 mg, 100%) as a colorless oil: $[\alpha]_D^{24}$ -19.1° (c 1.52); IR (film) 3500, 1710, and 1640cm^{-1}; ^{1}H NMR δ 1.02 (3H, t, J= 7.5 Hz), 1.40 (2H, m), 1.42 (3H, s), 2.05 (3H, d, J= 1 Hz), 3.66 (1H, m), 3.78 (3H, s), 4.30 (1H, d, J= 11 Hz), 4.43 (1H, d, J= 11 Hz), 5.59 (1H, q, J= 1 Hz), and 7.33 (5H, broad s); HRMS calcd. for $C_{17}H_{25}O_4$: m/z 293.1741 (M^++H). Found: m/z 293.1725.

Synthesis of the MOM derivative (9). To a stirred solution of 8 (103 mg, 0.35 mmol) and dimethoxymethane (0.5 ml) in $CHCl_3$ (5 ml) was added P_2O_5 (200 mg), and the mixture was stirred at room temperature for 30 min. The reaction was quenched by addition of sat. aq. $NaHCO_3$ (10 ml), and then the mixture was extracted with $CHCl_3$ (10 ml x 2). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was separated by preparative TLC (hexane/EtOAc = 7/1, three times elution) to afford 9 (104 mg, 88%), coupled with the starting material 8 (5.6 mg, 5.4%): $[\alpha]_D^{24}$ +21.7° (c 1.92) ; IR (film) 1715, 1640, and 1500cm^{-1}; ^{1}H NMR δ 0.97 (3H, t, J= 7.5 Hz), 1.42 (3H, s), 1.46 (2H, m), 2.02 (3H, d, J= 1 Hz), 3.38 (3H, s), 3.64 (1H, m), 3.74 (3H, s), 4.29 (1H, d, J= 11 Hz), 4.44 (1H, d, J= 11 Hz), 4.69 (1H, d, J= 7 Hz), 4.93 (1H, d, J= 7 Hz), 6.61 (1H, q, J= 1 Hz), and 7.28 (5H, broad s); HRMS calcd. for $C_{18}H_{26}O_4$: m/z 306.1829 (M^+-HCHO). Found: m/z 306.1818.

DIBAL reduction of 9. To a solution of 9 (1.12 g, 3.33 mmol) in THF (25 ml) was added DIBAL-H (1.5M solution in toluene, 9.96 ml, 14.9 mmol) at -78°C under argon. The reaction mixture was stirred at the same temperature for 1.5 h and then quenched by addition of sat. aq. Rochelle salt, EtOAc (30 ml), and anhydrous Na_2SO_4. The mixture was stirred vigorously for 1 h and during this period the temperature was gradually elevated to room temperature. The resulted mixture was filtered through Celite pad and the filter-cake was washed thoroughly with EtOAc. The combined organics were further dried over anhydrous Na_2SO_4 and concentrated in vacuo to afford a crude product, which on passing through a short column (silica gel 30 g, hexane/EtOAc = 1/1) to provide the allyl alcohol (10) (1.04 g, 100%): $[\alpha]_D^{24}$ +17.2° (c 3.54); IR (film) 3450, 1665, 1600, and 1495 cm^{-1}; ^{1}H NMR δ 0.98 (3H, t, J= 7.5 Hz), 1.37 (3H, s), 1.50 (2H, m), 1.82 (3H, d, J= 1 Hz), 3.40 (3H, s), 3.63 (1H, dd, J= 3, 9 Hz), 3.98 (2H, broad s), 4.30 (1H, d, J= 12 Hz), 4.43 (1H, d, J= 12 Hz), 4.71 (1H, d, J= 7 Hz), 4.97 (1H, d, J= 7 Hz), 5.31 (1H, q, J= 1 Hz), and 7.29 (5H, broad s); HRMS calcd. for $C_{17}H_{25}O_3$: m/z 277.1802 (M^+-CH_3O). Found: m/z 277.1802.

mCPBA epoxidation of the allyl alcohol (10). To a solution of 10 (1.69 g, 5.5 mmol) in dry CH_2Cl_2 (30 ml) was added mCPBA (1.12 g, 6.5 mmol) at -30°C under argon. The mixture was stirred at the same temperature for 7 h, then at -20°C for 18 h. The resulted mixture was evaporated and the residue was diluted with EtOAc (100 ml), which was successively washed with sat. aq. $NaHSO_3$ (30 ml x 2), $NaHCO_3$ (50 ml x 2), and brine (100 ml). After being dried over anhydrous Na_2SO_4, the solution was evaporated to give a crude product, which was purified by silica gel column chromatography (150 g, hexane/ EtOAc = 2/1) to give 11 (1.60 g, 90%): IR

(film) 3450, 1600, 1580, and 1495cm^{-1}; ^{1}H NMR δ 1.01 (3H, t, J= 7.5 Hz), 1.29 (3H, s), 1.43 (3H, s), 1.72 (2H, m), 3.25 (1H, s), 3.41 (3H, s), 3.53 (3H, complex), 4.61 (2H, broad s), 4.79 (2H, broad s), and 7.30 (5H, broad s); HRMS calcd. for $C_{18}H_{29}O_5$: m/z 325.2012 (M^++H). Found: m/z 325.1982.

Synthesis of the conjugated ester (12). To a mixture of DMSO (1.03 ml, 14.5 mmol) and oxalyl chloride (0.65 ml, 7.45 mmol) in dry CH_2Cl_2 (20 ml) at -50°C under argon was added a solution of 11 (1.60 g, 4.94 mmol) in dry CH_2Cl_2 (20 ml). After being stirred at the same temperature for 15 min, Et_3N (3.41 ml, 24.5 mmol) was added ,and the reaction mixture was gradually allowed to warm to room temperature, then poured into H_2O (50 ml). The separated aqueous phase was extracted with CH_2Cl_2 (30 ml) and the combined organic extracts were washed with brine (100 ml), dried over anhydrous Na_2SO_4, and evaporated. The residue so far obtained was reacted with Ph_3P=CHCOOEt (3.43 g) in benzene (40 ml) at room temperature for 1 h. After evaporation of the mixture, the residue was purified by silica gel column chromatography (100 g, hexane/EtOAc = 3/1) to afford 12 (1.80 g, 93%): IR (film) 1720, 1650, 1600, and 1495cm^{-1}; ^{1}H NMR δ 1.01 (3H, t, J= 7.5 Hz), 1.28 (3H, t, J= 7.5 Hz), 1.35 (3H, s), 1.58 (3H, s), 1.60 (2H, m), 3.05 (1H, s), 3.40 (3H, s), 3.52 (1H, dd, J= 3, 9 Hz), 4.18 (2H, q, J= 7.5 Hz), 4.60 (2H, s), 4.71 (2H, s), 6.01 (1H, d, J= 16 Hz), 6.80 (1H, d, J= 16 Hz), and 7.34 (5H, broad s); HRMS calcd. for $C_{20}H_{27}O_5$: m/z 347.1857 (M^+-C_2H_5O). Found: m/z 347.1857.

Cyclization of the epoxy ester (12). To a solution of 12 (1.80 g, 4.5 mmol) in $CHCl_3$ (30 ml) was added TFA (10 ml) at room temperature. After 10 min, the solution was evaporated to give a brownish residue, which was diluted with $CHCl_3$ (50 ml), washed with sat. aq. $NaHCO_3$ (30 ml) and brine (50 ml), dried over anhydrous Na_2SO_4, and evaporated. Purification of the residue on a silica gel column (50 g, hexane/EtOAc = 3/1) afforded the desired tetrahydrofuran (13) (1.50 g, 94%): $[\alpha]_D^{31}$ +20.8° (c 1.33) ; IR (film) 3460, 1710, 1690, 1655, and 1495cm^{-1}; ^{1}H NMR δ 1.02 (3H, t, J= 7.5 Hz), 1.20 (3H, t, J= 7.5 Hz), 1.31 (3H, s), 1.34 (3H, s), 1.70 (2H, m), 3.73 (1H, dd, J= 4.5, 7.5 Hz), 4.08 (2H, q, J= 7.5 Hz, overlapped with 1H signal), 4.32 (1H, d, J= 11 Hz), 4.47 (1H, d, J= 11 Hz), 5.99 (1H, d, J= 16 Hz), 7.03 (1H, d, J= 16 Hz), and 7.27 (5H, broad s); HRMS calcd. for $C_{20}H_{28}O_5$: m/z 348.1935 (M^+). Found: m/z 348.1935.

Synthesis of the allyl alcohol (14). A mixture of 13 (800 mg, 2.3 mmol) and DIBAL-H (1.5 M solution in toluene, 6.12 ml, 9.2 mmol) was stirred at -78°C for 1 h under argon. The reaction was quenched by addition of 1 N HCl (30 ml) and the mixture was extracted with EtOAc (50 ml, 20 ml x 2). The combined organic extracts were washed with brine (100 ml) and dried over anhydrous Na_2SO_4. Concentration of the solution under reduced pressure provided 14 (705 mg, 100%) as a colorless oil: $[\alpha]_D^{31}$ +26.3° (c 3.11); IR (film) 3400, and 1500cm^{-1}; ^{1}H NMR δ 1.01 (3H, t, J= 7.5 Hz), 1.27 (3H, s), 1.33 (3H, s), 1.68 (2H, m), 3.71 (1H, t, J= 6 Hz), 3.95 (2H, d, J= 4 Hz), 4.06 (1H, s), 4.39 (1H, d, J= 12 Hz), 4.51 (1H, d, J= 12 Hz), 5.72 (1H, dd, J= 4, 16.5 Hz), and 7.30 (5H, broad s); HRMS calcd. for $C_{18}H_{24}O_3$: m/z 288.1724 (M^+-H_2O). Found: m/z 288.1734.

Conversion of 14 into the acetyl derivative (15). A mixture of 14 (21 mg, 0.07 mmol) and trityl chloride (29 mg, 0.1 mmol) in pyridine (0.1 ml) and CH_2Cl_2 (2 ml) was stirred at room temperature for 22 h. Concentration of the reaction mixture, followed by purification using preparative TLC (hexane/ EtOAc = 2/1) afforded a trityl ether (31 mg, 82%), coupled with recovered 14 (3.4 mg, 16%).

After acetylation of the ether (30 mg, 0.06 mmol) in usual manner, the product was stirred at room temperature for 1 h in MeOH (2 ml) in the presence of catalytic TsOH. The reaction mixture was evaporated and the residue was purified by preparative TLC (hexane/EtOAc = 2/1) to provide 15 (18 mg, 90%) as a colorless oil: $[\alpha]_D^{24}$ +28.8° (c 1.46); IR (film) 3450, 1740, and 1495cm^{-1}; ^{1}H NMR δ 1.02 (3H, t, J= 7.5 Hz), 1.19 (3H, s), 1.23 (3H, s), 1.72 (2H, m), 2.14 (3H, s), 3.70 (1H, dd, J= 4.5, 9 Hz), 3.93 (2H, broad s), 4.45 (2H, s), 5.34 (1H, s), 5.88 (2H, broad s), and 7.32 (5H, broad s); HRMS calcd. for $C_{20}H_{28}O_5$: m/z 348.1934 (M^+). Found: m/z 348.1915.

Synthesis of 16 by mCPBA oxidation of 15. A mixture of 15 (25 mg, 0.07 mmol), mCPBA (15 mg, 0.085 mmol), and $NaHCO_3$ (12 mg, 0.14 mmol) in CH_2Cl_2 (2 ml) was stirred at 0°C for 2.5 h under argon. The resulted mixture was evaporated and the residue was purified by preparative TLC (hexane/EtOAc = 1/1) to afford the epoxy alcohol (16) (24 mg, 91%): IR (film) 3450, 1740, and 1500cm^{-1}; ^{1}H NMR δ 1.01 (3H, t, J= 7.5 Hz), 1.01 (3H, s), 1.24 (3H, s), 1.64 (2H, m), 2.12 (3H, s), 3.00 (1H, m), 3.20 (1H, d, J= 2 Hz), 3.30 - 3.80 (3H, complex), 4.50 (2H, s), 5.30 (1H, s), and 7.32 (5H, broad s); HRMS calcd. for $C_{20}H_{28}O_6$: m/z 364.1883 (M^+). Found: m/z 364.1846.

Synthesis of the conjugated ester (17). Compound 16 (11 mg) was hydrogenolized at

room temperature for 1 h in MeOH (3 ml) in the presence of Pd/black catalyst. After filtration of the catalyst, the filtrate was evaporated to afford a diol (8 mg, 94%), which was added to a solution of oxalyl chloride (0.1 ml) and DMSO (0.2 ml) in CH_2Cl_2 (1.0 ml) at -60°C under argon. After the reaction mixture was stirred at the same temperature for 15 min, Et_3N (0.1 ml) was added. Stirring was continued for another 5 min, and then the mixture was allowed to warm up to room temperature. The resulted mixture was diluted with CH_2Cl_2 (10 ml) and washed with H_2O (5 ml x 2). The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo to provide a crude aldehyde. The aldehyde was reacted with Ph_3P=CHCOOEt (20 mg, 0.06 mmol) in dry benzene (3 ml) at room temperature for 1 h. The mixture was evaporated to give a brownish syrup, which on purification by preparative TLC (hexane/EtOAc = 2/1) afforded 17 (4.5 mg, 45% in 2 steps): IR (film) 3450, 1740, 1720, and 1640cm^{-1}; ^{1}H NMR δ 0.96 (3H, t, J= 7.5 Hz), 1.11 (3H, s), 1.14 (3H, s), 1.28 (3H, t, J= 7.5 Hz), 1.54 (2H, m), 2.13 (3H, s), 3.13 (1H, d, J= 2 Hz), 3.49 (1H, t, J= 6 Hz), 3.80 (1H, dd, J= 2, 7.5 Hz), 4.19 (2H, q, J= 7.5 Hz), 5.07 (1H, s), 6.16 (1H, d, J= 17 Hz), and 6.70 (1H, dd, J= 17, 7.5 Hz); HRMS calcd. for $C_{17}H_{24}O_6$: m/z 324.1571 (M^+-H_2O). Found: m/z 324.1564.

Preparation of the 2,6-dioxabicyclo[3.2.1]octane (18). A solution of the ester (17) (4.5 mg) in benzene (2 ml) in the presence of catalytic TsOH was heated under reflux for 1h and then evaporated. The residue was purified by preparative TLC (hexane/EtOAc = 2/1) to provide 16 (4.2 mg, 90%) as a colorless oil: IR (film) 3500, 1740, 1720, and 1640cm^{-1}; ^{1}H NMR δ 0.98 (3H, t, J= 7.5 Hz), 1.18 (3H, s), 1.23 (3H, s), 1.27 (3H, t, J= 7.5 Hz), 1.53 (2H, m), 2.14 (3H, s), 3.60 (2H, complex), 4.19 (2H, q, J= 7.5 Hz), 4.22 (1H, m), 5.50 (1H, s), 6.10 (1H, dd, J= 17, 2 Hz), and 6.98 (1H, dd, J= 17, 5 Hz); HRMS calcd. for $C_{17}H_{26}O_7$: m/z 342.1676 (M^+). Found: m/z 342.1654.

Synthesis of the epoxy alcohol (19) by Sharpless oxidation. Compound 15 (267 mg, 0.77 mmol) was subjected to a mixture of diethyl D-tartrate (0.19 ml, 1.1 mmol), $Ti(O^iPr)_4$ (0.33 ml, 1.1 mmol), and TBHP (3.85 M in toluene, 0.65 ml, 2.5 mmol) in CH_2Cl_2 (20 ml). The mixture was stirred at -20°C for 12 h and then treated in usual manner to afford 19 (276 mg, 99%): $[\alpha]_D^{31}$ +38.5° (c 0.75); IR (film) 3450, 1740, 1600, and 1495cm^{-1}; ^{1}H NMR δ 1.01 (3H, t, J= 7.5 Hz), 1.21 (3H, s), 1.23 (3H, s), 1.72 (2H, m), 2.14 (3H,s), 3.09 (1H, d, J= 2 Hz), 3.25 (1H, complex), 3.40 - 3.70 (2H, complex), 4.53 (2H, s), 5.33 (1H, s), and 7.34 (5H, broad s); HRMS calcd. for $C_{20}H_{28}O_6$: m/z 364.1883 (M^+). Found: m/z 364.1867.

Synthesis of the conjugated ester (20). The epoxy alcohol (19) (33 mg) was treated according to the same reaction sequence as described above to furnish 20 (19 mg, 60%): IR (film) 3500, 1740, 1720, and 1650cm^{-1}; ^{1}H NMR δ 1.01 (3H, t, J= 7.5 Hz), 1.14 (3H, s), 1.17 (3H, s), 1.28 (3H, t, J= 7.5 Hz), 1.56 (2H, m), 2.13 (3H, s), 3.15 (1H, d, J= 2 Hz), 3.53 (1H, dd, J= 5, 7.5 Hz), 3.78 (1H, dd, J= 2, 7 Hz), 4.19 (2H, q, J= 7.5 Hz), 4.71 (1H, s), 6.16 (1H, d, J= 16 Hz), and 6.68 (1H, dd, J= 16, 7 Hz).

Preparation of the 2,6-dioxabicyclo[3.2.1]octane (21). Compound 20 (18 mg) was cyclized using catalytic TsOH in benzene (5 ml) at 55°C for 40 min to give 21 (16 mg, 90%) as needles: mp 112 - 114°C (hexane - EtOAc); $[\alpha]_D^{29}$ -23.0° (c 0.81); IR (film) 3500, 1740, 1720, and 1640cm^{-1}; ^{1}H NMR δ 1.05 (3H, t, J= 7.5 Hz), 1.17 (3H, s), 1.24 (3H, s), 1.27 (3H, t, J= 7.5 Hz), 1.61 (2H, m), 2.15 (3H, s), 3.28 (1H, dd, J= 8.5, 10 Hz), 3.92 (1H, t, J= 6.5 Hz), 4.19 (2H, q, J= 7.5 Hz), 4.20 (1H, m), 4.74 (1H, s), 6.13 (1H, dd, J= 2, 16 Hz), and 7.07 (1H, dd, J= 16, 4.5 Hz); HRMS calcd. for $C_{17}H_{26}O_7$: m/z 342.1676 (M^+). Found: m/z 342.1661.

Synthesis of the aldehyde (23). The epoxy alcohol (19) (42 mg, 0.15 mmol) was oxidized by the Swern method to give a crude aldehyde, which was dissolved immediately in benzene (5 ml) and reacted with Ph_3P=CHCHO (70 mg, 0.23 mmol) at room temperature for 1.5 h. The reaction mixture was evaporated to give a brownish syrup, which on purification by preparative TLC (hexane/EtOAc = 1/1) to afford 22 (22 mg, 49%) and 23 (6.2 mg, 14%).

The epoxy aldehyde (22) (19 mg) was stirred at room temperature for 3 h in CH_2Cl_2 (3 ml) in the presence of catalytic camphorsulfonic acid. After concentration of the mixture, the residue was purified by preparative TLC (hexane/EtOAc = 1/1) to provide 23 (17 mg, 92%) as needles: mp 138 - 140°C (hexane - EtOAc); $[\alpha]_D^{26}$ -45.8° (c 1.06); IR (film) 3450, 1740, and 1690cm^{-1}; ^{1}H NMR δ 1.07 (3H, t, J= 7.5 Hz), 1.19 (3H, s), 1.26 (3H, s), 1.62 (2H, m), 2.16 (3H, s), 3.33 (1H, dd, J= 8, 11 Hz), 3.93 (1H, t, J= 7 Hz), 4.32 (1H, m), 4.76 (1H, s), 6.40 (1H, ddd, J= 1.5, 8, 15.6 Hz), 6.97 (1H, dd, J= 4, 15.6 Hz), and 9.60 (1H, J= 8 Hz); HRMS calcd. for $C_{15}H_{22}O_6$: m/z 298.1415 (M^+). Found: m/z 2998.1425.

Synthesis of aurovertin B (1). A mixture of the phosphonium salt (24) (12 mg, 0.023 mmol) and NaH (60% dispersion in oil, 0.8 mg, 0.02 mmol) in THF (1 ml) was

stirred at room temperature for 1 h under argon. To this deep orange suspension was added a solution of 23 (5.3 mg, 0.018 mmol) in THF ((1.5 ml) and the resulted mixture was stirred at 40°C for 17 h. After further addition of the phosphorane prepared from 24 (38 mg, 0.07 mmol) and NaH (2.9 mg, 0.07 mmol), the mixture was continuously stirred under reflux for 28 h. The resulted mixture was diluted with EtOAc (30 ml), washed with 1N HCl and brine, dried over anhydrous Na_2SO_4, and then evaporated. The residue was purified by repeated preparative TLC using benzene/acetone = 2/1, $CHCl_3$/ EtOAc = 1/1, and $CHCl_3$/MeOH = 20/1 to provide the target aurovertin B (1) (1.8 mg, 22%); $[\alpha]_D^{20}$ -57.9° (c 0.125, EtOH).

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