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TOTAL SYNTHESIS OF ARTEANNUIN AND DEOXYARTEANNUIN

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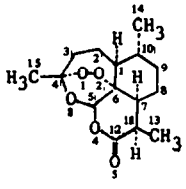
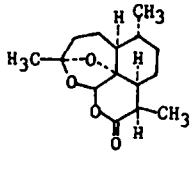
Abstract---Arteannuin 1 is a new sesquiterpene lactone containing a peroxide linkage and is an antimalarial principle isolated from Artemisia annua L. . R(+)-Citronellal 5 as a starting material for the total synthesis was converted into 11R(-)-methyl dihydroarteannuinate 12 in 14 steps. The key intermediate 4 was obtained from compound 12 in 5 steps. The introduction of hydroperoxide in 4 by photooxidation followed by acid treatment gave 1. Hydroxylation of 4 with osmium tetraoxide afforded deoxyarteannuin 2.

Arteannuin (Qinghaosu) 1 is an antimalarial active principle isolated from Qinghao (Artemisia annua L.)[1], which is a traditional Chinese herbal medicine used in treatment of malaria. Its structure was determined by us[2] and shown to be a new type of sesquiterpene lactone containing a peroxide group. The outstanding antimalarial activity and novel structure of arteannuin impelled us to study its total synthesis. Deoxyarteannuin 2 occurs in the same plant[3] and was isolated as a metabolite from the urine of patients treated with arteannuin. This paper describes the full account of our synthesis of these two naturally occurring sesquiterpene lactones starting from R(+)-citronellal 5[4].

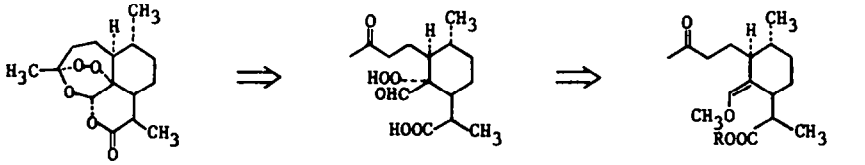


1



2

Because the arteannuin molecule can be visualized as ketal-acetal-lactone system formed from the attack on the hydroperoxy group in the molecule 3, the enol methyl ether compound 4 might be used as a key intermediate for total synthesis (scheme 1). In order to achieve the transformation of 4 to 3, which then could cyclize to 1, the key intermediate 4 was hydroperoxidized on the C_6 by photooxidation.

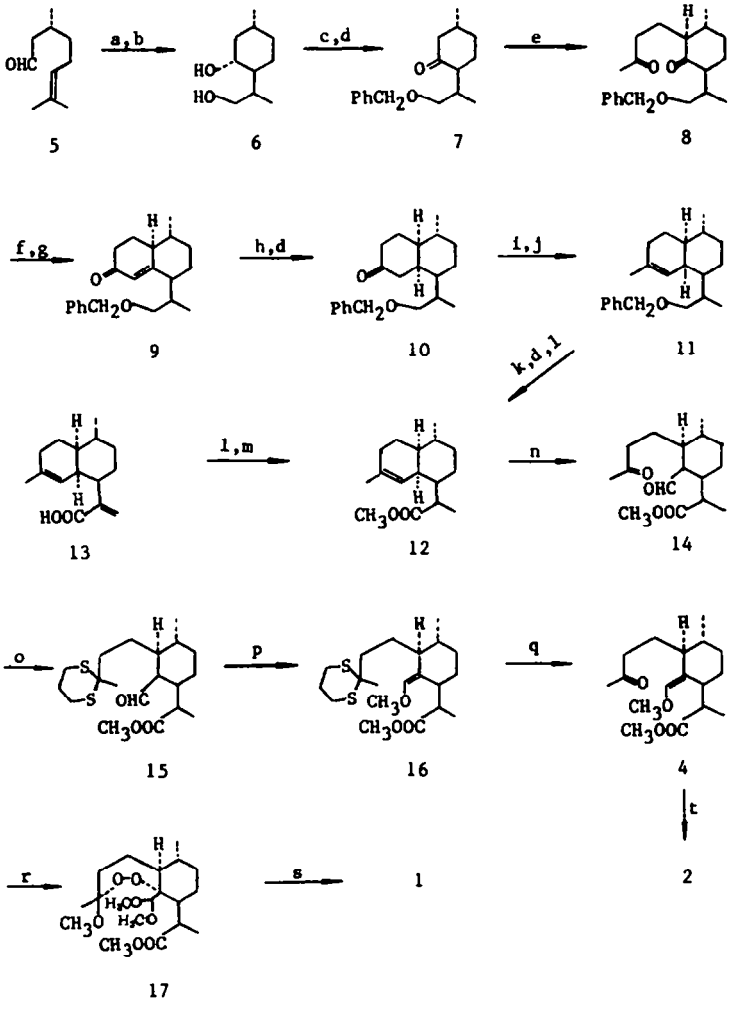


1 3 4 R=H,CH_3

(Scheme 1)

4 was obtained from R(+)-citronellal **5** through the reaction sequence outlined in scheme 2. **5** was first converted into the dihydroxy compound **6** by known procedure[5]. Selective benzylation of the primary hydroxyl group followed by oxidation with Jones reagent gave the ketone **7** in 51% overall yield in 2 steps. Kinetic deprotonation of **7** and reaction of the resulting enolate with silylated vinyl ketone[6] provided 1,5-diketone **8** in 55% yield with simultaneous cleavage of the trimethyl silyl group. Cyclization of **8** with NaOH furnished the α,β-unsaturated ketone **9** with the inversion of configuration at C_7[7], while cyclization with $Ba(OH)_2$ followed by dehydration with 2.5%$(COOH)_2$[7] furnished mainly the α,β-unsaturated ketone **9**.The pure **9** could be obtained by crystallization in 62% overall yield in 2 steps. Reduction of **9** with $NaBH_4$-Py[8] followed by oxidation with Jones reagent afforded the ketone **10** in 47% yield. Both **9** and **10** showed a positive Cotton effect in their CD, the α-orientation of 1-H in **9** and 6-H in **10** could be assigned respectively[9]. When **10** was reacted with MeMgI followed by dehydration, the mixture of **11** and its Δ^3-isomer was obtained in 1:1 ratio in 93% yield. The pure **11** was separated by repeated flash chromatography. In order to obtain the methyl dihydroarteannuinate **12**, **11** was first treated with Na-liq.NH_3, then oxidized with Jones reagent and finally esterified with CH_2N_2 to give the desired product **12** in 72% overall yield in 3 steps. **12** can also be obtained from the arteannuinic acid **13**, which exists together with arteannuin 1 in the same plant, first through esterification with CH_2N_2, then hydrogenation with $NaBH_4$ in the presence of $NiCl_2$[10].The product was shown to be a mixture of 11R-and 11S-**12** in a ratio of 85:15 by its GC analysis. The pure 11R-**12** was obtained by flash chromatography.

Ozonization of **12** afforded aldehyde-ketone **14**. Selective protection of the ketonic carbonyl of **14** with 1,3-propanedithiol furnished the compound **15** in 55-65% yield[11]. The aldehyde carbonyl of **15** was first reacted with trimethyl orthoformate followed by the transformation of resulting acetal into the enol methyl ether by refluxing in xylene to give the compound **16**. Removal of thioketal with $HgCl_2$-$CaCO_3$ gave the key intermediate **4**. The overall yield of **4** from **12** was 33% in 5 steps. Both **16** and **4** were a mixture of two olefinic isomers shown in ^{1}H-NMR.



Reagent:a. $ZnBr_2$ b. B_2H_6;H_2O_2,OH^- c. $PhCH_2Cl$-NaH d. Jones oxidation
e. LDA,CH_2=C(Me_3Si)$COCH_3$ f. $Ba(OH)_2.8H_2O$ g. $(COOH)_2$ h. $NaBH_4$
i. CH_3MgI j. p-TsOH k. Na-liq.NH_3 l. CH_2N_2 m. $NaBH_4$,$NiCl_2.6H_2O$
n. O_3; Me_2S o. $HS(CH_2)_3SH$-$BF_3.Et_2O$ p. $HC(OMe)_3$-p-TsOH; Xylene-Δ
q. $HgCl_2$-$CaCO_3$-aq.CH_3CN r. O_2,Rose Bengal, hν' s.70% $HClO_4$
t. OsO_4;H_2S

(Scheme 2)

Photooxidation of the methanolic solution of **4** in the presence of oxygen and Rose Bengal at -78°C[12] followed by acid treatment afforded the trapping compound **17**. Acidic hydrolysis of **17** with 70% $HClO_4$ gave arteannuin **1** in 28% yield in 2 steps.The synthetic substance was found to be identical with natural arteannuin in every respect(^{1}HNMR, IR, MS, CD, $[\alpha]_D$, m.p., mixed m.p. and TLC).

After we had submitted our preliminary communication[4a] to Acta Chimica Sinica, we saw the paper on the total synthesis of arteannuin published by G. Schmid and W. Hofheinz[13].

Hydroxylation of **4** with osmium tetroxide in ether at room temperature followed by treatment with hydrogen sulfide yielded deoxyarteannuin **2** in 45% yield. Synthetic and natural deoxyarteannuin were identical in every respect.

EXPERIMENTAL

All m.p. are uncorrected. $[\alpha]_D$ was measured with Autopol® III.The IR were recorded with Specord 75 spectrophotometer. The NMR were obtained with EM-360L, chemical shifts are expressed in ppm with TMS as an internal standard. MS were determined with Finnigan 4021.CD data were measured with J-500c spectropolarimeter.

TLC was performed with silica gel plate made by ourselves (Chinese made silica gel G,10-40μ), developing with petroleum ether-acetone. Chromatograms were visualized by spraying with phospho-molybdic acid and heating. The flash chromatography was carried out with TLC silica gel (Chinese made silica gel H, 10-40μ) under pressure, eluting with petroleum ether-acetone system in various different ratio.

(1R,4S,8R)-9-benzyloxy-p-menthone 7

To a suspension of 80% NaH(660mg) in DMF (20ml) was added dropwise a solution of dihydroxy compound **5** (1.72g) in DMF (15ml) and further stirred for 45 min. Then $PhCH_2Cl$ (1.39g) in DMF (5ml) was added dropwise and stirring was continued for 3 hrs. The temperature was kept at 10-15°C. The reaction mixture was poured into ice water (40ml) and extracted with ether. The ethereal solution was washed to neutrality, dried and concentrated. The residue was chromatographed to give 1.5g of the desired product. ν_{max}:3400 (br, -OH),3070, 3050, 3015 (-Ph) cm^{-1}; δ: 0.90 (3H, d, J=4Hz, 1-CH_3), 0.93 (3H, d, J=7Hz, 8-CH_3),3.16-3.63 (3H, m,9-CH_2, 3-H), 4.47 (2H, s, $PhCH_2$-), 7.38 (5H, s, C_6H_5-); m/z: 263(M^++1).

A solution of above product in acetone (15ml) was oxidized with Jones reagent at 5-10°C for 15min. The reaction mixture was worked up in the usual way to afford ketone **7**(1.32g). The overall yield was 50.8% in two steps. ν_{max}:3070,

3050, 3015 (-Ph), 1700(C=O)cm^{-1}; δ:0.90 (3H, d, J=4Hz, 1-CH_3), 0.99 (3H, d, J=7Hz, 8-CH_3), 3.41(2H,d,J=5Hz, 9-CH_2), 4.46(2H,s, $PhCH_2$-), 7.40(5H,s, C_6H_5-); m/z:260(M^+).

(1R, 2S, 4S, 8R)-2-(3'-oxobutyl)-9-benzyloxy-p-menthone 8

To -78°C solution of lithium diisopropylamide in THF prepared from 1.5M BuLi (2.4ml), diisopropylamine (0.5ml) and THF (8ml) was added dropwise a solution of ketone **7** (690mg) in THF (1ml). After stirring for 30min, 3-trimethylsilyl-3-buten-2-one (570mg) in THF (1ml) was added dropwise and stirring continued at -78°C for 1hr, then allowed to warm to 0°C and stirred at 0°C for 2.5hrs. The reaction was quenched by acidification with 10% HCl (PH~3) and stirred for 15 min, then neutralized with 5% $NaHCO_3$, extracted with ethyl acetate, washed, dried and concentrated to give the crude product, which was purified by flash chromatography to afford the 1,5-diketone **8** (480mg) in 55% yield. ν_{max}: 3070, 3050, 3015 (Ph-), 1705 (C=O)cm^{-1}; δ: 0.98 (3H, d, J=7Hz, 1-CH_3), 1.08 (3H, d, J=7Hz, 8-CH_3), 2.08 (3H, s, CH_3CO-), 3.43 (2H, d, J=5Hz, 9-CH_2), 4.52 (2H, s, $PhCH_2$-), 7.43 (5H, s, C_6H_5-); m/z: 331 (M^++1). 40% of **7** was recovered.

1α-Δ^5-10α-methyl-7β-[2'β-(1'-benzyloxy)-propyl]-decalone-4 9

To a solution of 1,5-diketone **8** (470mg) in EtOH (15ml) was added $Ba(OH)_2$. $8H_2O$ (450mg) and stirred at room temperature for 2.5 hrs. The solution was neutralized with 10% HCl and concentrated under reduced pressure, the residue was extracted with CH_2Cl_2, washed, dried and concentrated. The crude product was chromatographed to give the cyclized product (400mg.).ν_{max}: 3370 (br,-OH), 3070, 3050, 3015 (-Ph), 1705 (C=O) cm^{-1}; m/z: 331 (M^++1).

A mixture of the above cyclized product and 2.5% oxalic acid in EtOH(20ml) was refluxed for 2.5 hrs. The solution was neutralized with 5% $NaHCO_3$ and concentrated under reduced pressure. The residue was extracted with CH_2Cl_2 and worked up in the usual way to give the crude product, which was purified by chromatography to afford the α,β-unsaturated ketone **9** (275mg). The overall yield was 61.9% in two steps. Recrystallization from hexane furnished caking crystals,m.p. 75.5-77°C. $[\alpha]_D^{20}$+11.25° (c, 1.32, CH_3OH); ν_{max}: 3070, 3050, 3015 (-Ph), 1670, 1605 (α,β-unsaturated ketone)cm^{-1}; δ: 1.00-1.10 (6H,m,10-CH_3, 2'-CH_3), 3.33(2H, d, J=4Hz, 1'-CH_2), 4.38 (2H, s, $PhCH_2$-), 5.61 (1H, s, 5-H), 7.20 (5H, s, C_6H_5-); m/z: 313 (M^++1); CD: $\Delta\varepsilon^{333}$=+1.27(dioxane).

1α,10α-methyl-7β-[2'β-(1'-benzyloxy)-propyl]-decalone-4 10

To a solution of $NaBH_4$ (225mg) in Py(3ml) was added a solution of α,β-unsaturated ketone **9** (320mg) in Py(4ml).The reaction mixture was stirred at 25°C for 6 hrs,then added water (0.5ml) and stirred for 30min. The reaction mixture

was diluted with ether (30ml) and acidified with 10% HCl. The ethereal layer was separated, to which a solution of KIO_3 (2.2g) in water (45ml) was added. After stirring overnight, organic layer was separated and the aqueous layer was further extracted with ethyl acetate, the combined extract was washed successively with 10% HCl, 5% Na_2SO_3, water,dried and concentrated to give an oil product, which directly oxidized with Jones reagent in the usual way to afford the saturated ketone **10** (150mg) in 46.6% yield. Recrystallization from hexane furnished needle crystals, m.p. 63-65°C. $[\alpha]_D^{12}$+8° (c, 0.85, CH_3OH); ν_{max}: 3070, 3050, 3015 (-Ph), 1705 (C=O) cm^{-1}; δ: 0.89-1.00 (6H, m, 10-CH_3, 2'-CH_3), 3.38 (2H,d, J=3Hz, 1'-CH_2), 4.47 (2H, s, $PhCH_2$-), 7.38 (5H,s,C_6H_5-); m/z: 314 (M^+); CD: $\Delta\varepsilon^{283}$=+0.27 (CH_3OH).

1α-Δ^4-4,10α-dimethyl-7β-[2'β-(1'-benzyloxy)-propyl]-decalin 11

To a Grignard reagent prepared from Mg (560mg), CH_3I (3.6g) and ether(30 ml) was added a solution of the saturated ketone **10** (540mg) in ether (25ml). The reaction mixture was stirred at room temperature for 1.5hrs and worked up in the usual way to give an oily product (570mg). ν_{max}: 3400 (br, -OH), 3070, 3050, 3015 (-Ph)cm^{-1}.

A solution of p-TsOH (550mg) in THF (1ml) was added to a solution of the above oily product in PhH(55ml). The reaction mixture was refluxed for 1hr and worked up in the usual way to give a mixture of Δ^4-and Δ^3-compound (500mg) in 93.2% yield. GC showed that their ratio was 1:1.The pure Δ^4-compound **11** (100mg) was obtained by repeated flash chromatography. δ: 0.86 (3H, d, J=5Hz, 10-CH_3), 1.00 (3H, d, J=7Hz, 2'-CH_3), 1.64 (3H, s,4-CH_3), 2.46 (1H, br,2'-H), 3.23-3.50 (2H, m, 1'-CH_2), 4.46 (2H, s, $PhCH_2$-), 5.19 (1H, s, 5-H), 7.32 (5H, s, C_6H_5-); m/z: 312 (M^+).

11R-methyl arteannuinate 12

To a mixture of liquid NH_3 (20ml) and a solution of Δ^4-**11** (90mg) in ether (3ml)was added a small piece of Na under cooling with dry ice bath and stirring. After stirring for 30min, the reaction was quenched by careful addition of some drops of aqueous NH_4Cl. The NH_3 was evaporated to dryness and the residue was extracted with ethyl acetate, washed, dried and concentrated to give solid product (64mg) in quantitative yield. Recrystallization with hexane furnished needle crystals,m.p. 80-81°C $[\alpha]_D^{11}$-8.47°(c,0.55 $CHCl_3$); ν_{max}: 3400, 3300 (br, -OH) cm^{-1}; δ: 0.90 (3H, d, J=6Hz, 10-CH_3), 1.00 (3H, d, J=7Hz, 11-CH_3), 1.68 (3H, s, 4-CH_3), 2.47 (1H, br,11-H), 3.40-3.68 (2H, m,12-CH_2), 5.21 (1H,s,5-H); m/z: 222(M^+); Calc. for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.17; H,11.91.

60mg of the above product was oxidized with Jones reagent to give an acid (55mg) in 86% yield. Recrystallization with hexane-acetone afforded needle

crystals,m.p. 137-138°C $[\alpha]_D^{10}$-12.2° (c, 1.23, $CHCl_3$); ν_{max}: 3200-2500, 1730, 1700 (-COOH) cm^{-1}; δ: 0.85 (3H, d, J=4Hz, 10-CH_3), 1.17 (3H, d, J=7Hz,11-CH_3), 1.63 (3H,s,4-CH_3), 5.08 (1H, s, 5-H); m/z: 236 (M^+); Calc. for $C_{15}H_{24}O$: C, 76.22; H, 10.24. Found: C, 76.34; H, 10.46.

To a solution of the above acid (45mg) in ether cooled to 0°C was added portionwise the ethereal solution of CH_2N_2. After standing for 5 min, the excess CH_2N_2 was removed. The ethereal solution was washed, dried and concentrated to give a crude product,which was purified by chromatography to afford the ester 12 (40mg) in 84% yield. $[\alpha]_D^{10}$-20.6° (c, 0.56, CH_3OH); ν_{max}: 1740 (-$COOCH_3$)cm^{-1}; δ: 0.85 (3H, d, J=6Hz, 10-CH_3), 1.09 (3H, d, J=7Hz, 11-CH_3), 1.64 (3H,s,4-CH_3), 3.64 (3H,s, -$COOCH_3$), 5.10 (1H, s, 5-H); m/z: 251 (M^++1).

11R-methyl arteannuinate 12 from arteannuinic acid 13

To a stirred solution of methyl arteannuinate (1g), obtained from esterification of arteannuinic acid 13 with CH_2N_2, and $NiCl_2.6H_2O$(100mg) in MeOH (20ml) cooled to -15°C was added in small portions 240mg $NaBH_4$ and further stirred for 30min. The reaction mixture was acidified with 10% HCl and stirred until the black color disappeared, then neutralized with 5% $NaHCO_3$ and concentrated under reduced pressure. The residue was worked up in the usual way to give the ester 12 shown to be a mixture of 11R-and 11S-12 in a ratio of 85:15 by GC. The pure 11R-CH_3 compound 12 was obtained by flash chromatography. Its spectral data were identical with those of 12 obtained from R(+)-citronellal 5.

Ozonization of 11R-methyl arteannuinate 12 (12⟶14)

Ozone was passed into a solution of ester 12 (500mg) in CH_3OH (1ml) and CH_2Cl_2 (15ml) at -78°C until the substrate reacted (by TLC). After purging the ozone with a stream of N_2, Me_2S(1ml) was added to the reaction solution with stirring at room temperature for 2 hrs. The solvent was removed in vacuo to give aldehyde-ketone compound 14. The pure 14 was obtained by flash chromatography. ν_{max}: 2740,1732 (-CHO), 1740 (-$COOCH_3$),1715 (C=O) cm^{-1}; δ: 0.93 (3H, d, J=5Hz,10-CH_3), 1,13(3H,d,J=7Hz, 11-CH_3),2.09(3H,s, CH_3CO-), 3.58(3H,s,-$COOCH_3$), 9.77 (1H, d, J=5Hz, -CHO); m/z : 281 (M^++1).

Selective protection of ketonic carbonyl group of 14 (14⟶15)

To a solution of crude 14 (obtained from 500mg of 12) in CH_2Cl_2(10ml) was added dropwise 1,3-propanedithiol (220mg) with stirring, then $BF_3.Et_2O$ (160mg) was added dropwise. The reaction mixture was stirred at room temperature for 3 hrs. The solution was washed successively with 5% $NaHCO_3$, water,dried and concentrated to give a crude product, which was purified by flash chromatography to afford desired product 15 (310mg). ν_{max} : 2715, 1710 (-CHO), 1730 (-$COOCH_3$) cm^{-1}; δ: 0.93 (3H, d,J=6Hz, 10-CH_3), 1.12 (3H, d, J=7Hz, 11-CH_3), 1.50 (3H, s,

4-CH_3), 2.66-2.90 (4H, m, $(SCH_2)_2$), 3.58 (3H,s, $-COOCH_3$), 9.90 (1H,d, J=5.5Hz, -CHO); m/z : 372 (M^+).

40mg of aldehydic carbonyl protected product was separated. δ: 0.87 (3H, d, J=6Hz, 10-CH_3), 1.20 (3H, d, J=7Hz, 11-CH_3), 2.09 (3H, s,CH_3CO-), 2.66-2.86 (4H, m, $(SCH_2)_2$), 3.59 (3H, s, $-COOCH_3$), 4.15 (1H, d, J=2Hz, S-CH-S).

Double protected product was also obtained. δ: 0.88 (3H,d, J=6Hz, 10-CH_3), 1.24 (3H,d,J=7Hz, 11-CH_3), 1.59 (3H, s, 4-CH_3), 2.66-2.86(8H,m,2$(SCH_2)_2$), 3.61 (3H, s, $-COOCH_3$), 4.21 (1H, d, J=2Hz, S-CH-S); m/z : 462 (M^+).

Transformation of aldehydic carbonyl group into enol methyl ether (15⟶16)

A mixture of crude **15** (obtained from 500mg of **12**), trimethyl orthoformate (200mg), CH_3OH (1ml) and catalytic amount of p-TsOH was stirred at room temperature for 2.5 hrs. Then the reaction solution was added to a boiling solution of xylene (20ml) and refluxed with a water-separator for 2 hrs. After cooling, the solution was worked up in the usual way to afford the enol ether **16**(300mg). The overall yield in 3 steps was 39%. ν_{max} : 1730 ($-COOCH_3$), 1650 (enol ether) cm^{-1}; δ: 0.91 (3H, d, J=7Hz, 10-CH_3), 1.03 (3H, d, J=7Hz, 11-CH_3), 1.55 (3H,s, 4-CH_3), 2.65-2.85 (4H, m, $(SCH_2)_2$), 3.52 (3H, s, $-OCH_3$), 3.61 (3H,s, $-COOCH_3$), 5.84, 5.77 (1H, 2s, $=\!\!\diagdown_H$); m/z: 386 (M^+).

Convertion of thioketal into the carbonyl group (16⟶4)

To a stirred solution of $HgCl_2$ (400mg) and powdered $CaCO_3$ (240mg) in 80% aqueous CH_3CN (9ml) was added at 25°C a solution of the dithiane **16**(280mg) in 80% aqueous CH_3CN (6ml). The mixture was stirred and refluxed under N_2 for 3 hrs,cooled and filtered,the filtered cake was washed with CH_2Cl_2. The organic layer was washed successively with 5M aqueous NH_4OAC and water,dried and concentrated to afford compound **4** (180mg) in 83.5% yield. ν_{max} : 1720 ($-COOCH_3$), 1710 (C=O), 1650 (enol ether) cm^{-1}; δ: 0.92 (3H, d, J=7Hz, 10-CH_3), 1.03 (3H, d,J=7Hz,11-CH_3), 2.06 (3H,s,CH_3CO-), 3.54 (3H,s, $-OCH_3$), 3.64 (3H,s,$-COOCH_3$), 5.90, 5.76 (1H, 2s, $=\!\!\diagdown_H$); m/z: 297 (M^++1).

Arteannuin 1

To a solution of the enol ether **4** (600mg) in CH_3OH (200mg) was added Rose Bengal (40mg). The resulting solution through which oxygen was bubbled was cooled to -78°C and irradiated, using 1% $Na_2Cr_2O_7$-H_2O as filter, with a high pressure mercury lamp (Chinese made, GCQ 200) for 4 hrs. Then the HCl gas was passed to the reaction mixture until the red solution was decolorized. After further stirring at room temperature for 1.5 hrs, the reaction solution was neutralized with 5% $NaHCO_3$ and concentrated under reduced pressure to give the crude product, which was purified by flash chromatography to afford 250mg of **17**. ν_{max} : 1720 ($-COOCH_3$),1070-1180 (R-O-CH_3) cm^{-1}; δ: 0.79 (3H, d, J=7Hz, 10-

CH_3), 1.22 (3H, d, J=7Hz, 11-CH_3), 1.20 (3H, s, 4-CH_3), 3.23 (3H, s, 4-OCH_3), 3.38, 3.45 (6H, 2s, 5-$(OCH_3)_2$), 3,57 (3H, s, -$COOCH_3$), 4.33 (1H, s, 5-H); m/z: 374 (M^+).

To a solution of 17 in ether(15ml) was added a solution of 70% $HClO_4$(1ml) and water(5ml). The mixture was stirred at 25°C for 28 hrs. The ethereal layer was separated and the aqueous layer was further extracted with ether. The combined ethereal solution was washed,dried and concentrated to obtain the target compound 1(160mg).The overall yield were 28% in 2 steps. Recrystallization from petroleum ether-isopropyl ether to give needle crystals, m.p. 151-153°C, $[\alpha]_D^{13}$ +68.6°(c, 0.58, $CHCl_3$); ν_{max}: 1740 (δ-lactone) cm^{-1}; δ: 0.95 (3H,d, J=4Hz, 10-CH_3), 1.13(3H, d, J=7Hz, 11-CH_3), 1.40 (3H, s, 4-CH_3), 3.28 (1H, qxd, J=7Hz, J=4Hz, 11-H), 5.74 (1H,s,5-H); m/z : 283 (M^++1). Calc. for $C_{15}H_{22}O_5$: C,63.81; H, 7.85. Found :C,63.92; H,7.93.

Deoxyarteannuin 2

A solution of OsO_4(340mg) in anhydrous ether(15ml) was added with stirring to a cooled (dry ice) solution of **4** (370mg) in anhydrous ether (6ml). After the addition was complete, the cooling bath was removed and the mixture allowed to stir at room temperature for 24 hrs. Then the reaction solution was saturated with gaseous H_2S and the black precipitate was filtered off. The filter-cake was washed with ether and the filtrate was evaporated to dryness. The crude product was chromatographed to give **2** (150mg) in 45% yield. Recrystallization from petroleum-ether gave plate crystals, m.p. 110-111°C, $[\alpha]_D^{10}$-136.4°(c,0.5, CH_3OH); ν_{max} : 1750 (δ-lactone)cm^{-1}; δ: 0.90 (3H, d, J=4Hz, 10-CH_3), 1.09 (3H, d, J=7Hz, 11-CH_3), 1.46 (3H,s, 4-CH_3), 3.00 (1H, qxd,J=7Hz, J=4Hz, 11-H), 5.50 (1H, s, 5-H,); m/z : 266 (M^+); Calc. for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found : C, 67.52 ; H, 8.31.

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7. Dehydration of the cyclized product of **8** with the concentrated solution of oxalic acid also partly caused the inversion of configuration at C_7, which can be discerned by ^{1}H-NMR. The ^{1}H-NMR of **9** in which the C_7 configuration was inverted by treatment with NaOH was: δ: 0.95-1.05 (6H, m,10-CH_3,2'-CH_3) 3.09(2H,d,J=4Hz,1'-CH_2), 4.27(2H,s,PhCH_2-), 5.61(1H,s,5-H),7.20(5H,s,C_6H_5-).
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11. Reaction of **14** with 1,3-propanedithiol afforded a mixture of two mono-1, 3-dithiane and one di-1,3-dithiane separable by flash chromatography, in which the mono-1,3-dithiane **15** was the major product, selective protection of the ketonic carbonyl of **14** may be considered as a result of the steric hindrance of the aldehydic carbonyl group in this molecule.
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